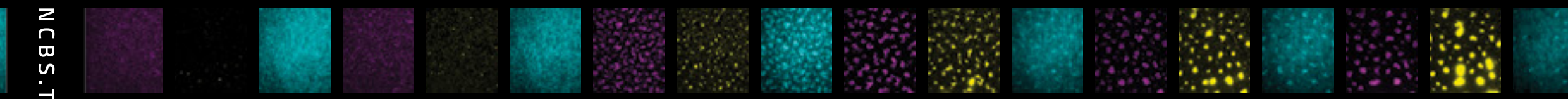
NATIONAL CENTRE FOR
BIOLOGICAL SCIENCES

TIFR



NCBS.TIFR \ REPORT \ 2012 . 2014 \

REPORT

2012 . 2014

Experiments in living cells and theoretical work have implicated energy-consuming patterning mechanisms located at the cell 's edge, the plasma membrane. These are expected to assist in reading signals from the outside world and transmitting them into the cell. An in vitro system consisting of a few ingredients involved in this mechanism is shown in the movie strip. Here protein filaments (actin; pink), motor proteins (myosin; yellow) and molecules in the membrane linked to these filaments (cyan) are capable of recreating similar patterns. This motif is also represented by the abstract collections of lines shown in the background

MANAGEMENT

***NCBS Director*, Satyajit Mayor**
Dean, NCBS Upinder S Bhalla
Head, Academic Activities Apurva Sarin
Head, Research Development Savita Ayyar
Head, Infrastructure & Construction V R Rengasamy
Head, Administration & Finance Pradip Pyne
Head, Architect U B Poornima
Head, Scientific & Engineering Services P C Gautam
Head, Purchase K V Ramanathan

MANAGEMENT BOARD

M Barma, *Director, TIFR (Chairman)*
Gautam. R. Desiraju, *Indian Institute of Science, Bangalore (till Aug 2012)*
P Balaram, *Indian Institute of Science, Bangalore (till Aug 2013)*
Utpal Banerjee, *UCLA, USA*
Mary Beckerle, *University of Utah, USA*
John Kuriyan, UCLB, USA
Satyajit Mayor, *Director, NCBS, Bangalore*
Pradip Baviskar, *Joint Secretary (R & D), Govt of India, DAE*
Upinder S. Bhalla, *Dean, NCBS, Bangalore*
Satyajit Rath, *National Institute of Immunology, New Delhi*
Anjana Rao, *La Jolla Institute for Allergy & Immunology , USA*
Benny Shilo, *WIS, Israel (from Aug 2014)*
Apurva Sarin, Head Academics, *NCBS, Bangalore (from Aug 2014)*
L.S. Shashidhara, *IISER, Pune (from Aug 2014)*
Jayant B Udgaonkar, *NCBS, Bangalore*
M.K.Bhan *(till Nov 2012)*
K VijayRaghavan, Secretary, *Department of Biotechnology,New Delhi (till Jan 2014)*
Vidita Vaidya, *DBS, TIFR,Mumbai (from Aug 2014)*
George Antony, *Registrar, TIFR, Mumbai*
Pradip Pyne, *Head Administration and Finance, NCBS, Bangalore (Non Member Secretary)*

SCIENTIFIC ADVISORS

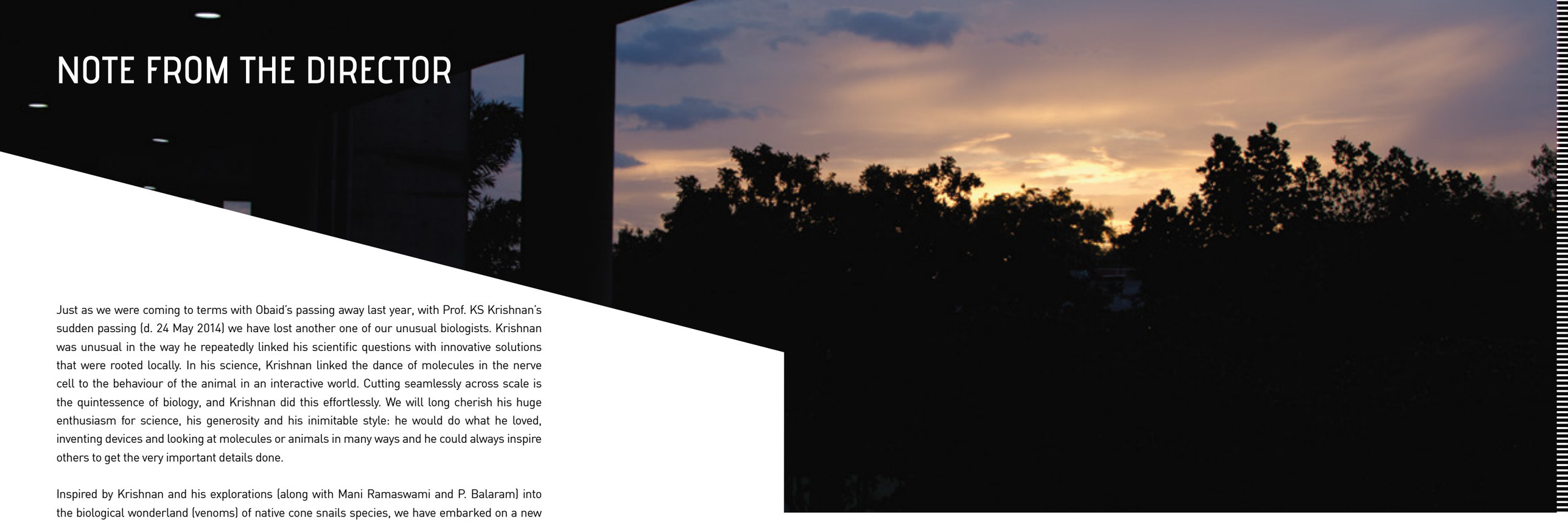
Shinichi Aizawa, *RIKEN, Japan*
Tony Hyman, *Max Planck Institute, Germany*
Albert J Libchaber, *Rockefeller University, USA*
Eve Marder, *Brandeis University, USA*
Peter H. Raven, *Missouri Botanical Garden, USA*

NCBS & CAMPUS COMMITTEE ON ADMINISTRATION & LABORATORY MANAGEMENT (N-CALM)

Satyajit Mayor, Director NCBS (Chairman)
S Ramaswamy
Sumantra Chattarji
Apurva Sarin
Upinder S Bhalla
V R Rengasamy
Pradip Pyne
T M Sahadevan
K V Ramanathan
K F James
S Ashok Rao

Post Doctoral Appointments	Students Registered for PhD	Masters Students	Junior Research Fellows	Scientific and Technical staff (including trainees)	Number of Faculty (Group Leaders /Young Investigators/ International Investigators/ Joint Faculty / Adjunct Faculty)	Administration and Auxillary (including trainees)
63	182	15	138	97	39	78

NOTE FROM THE DIRECTOR



Just as we were coming to terms with Obaid's passing away last year, with Prof. KS Krishnan's sudden passing (d. 24 May 2014) we have lost another one of our unusual biologists. Krishnan was unusual in the way he repeatedly linked his scientific questions with innovative solutions that were rooted locally. In his science, Krishnan linked the dance of molecules in the nerve cell to the behaviour of the animal in an interactive world. Cutting seamlessly across scale is the quintessence of biology, and Krishnan did this effortlessly. We will long cherish his huge enthusiasm for science, his generosity and his inimitable style: he would do what he loved, inventing devices and looking at molecules or animals in many ways and he could always inspire others to get the very important details done.

Inspired by Krishnan and his explorations (along with Mani Ramaswami and P. Balaram) into the biological wonderland (venoms) of native cone snails species, we have embarked on a new programme in Chemical Ecology. This aims to connect the scales of biology, represented on our campus from the single molecule to ecosystems. With an expanding array of field stations accessible to our researchers and the natural biodiversity that these field stations offer, our programme offers a veritable cornucopia of possibilities for original research that is locally rooted. To add to the excitement this new avenue offers we welcome our newest recruit, Shannon Olsson (Chemical Ecologist) to our campus. We also welcome P. Shivaprasad (our first card-carrying plant biologist), Ranabir Das (NMR spectroscopist), Varadha Sundarmurthy (infectious disease biologist) who have all recently joined us and will surely engage with the avenues that field biology opens up.

And as a sign of coming of age (NCBS just turned 21 last year) some of our colleagues who have been nurtured here, are testing new pastures. We bid farewell to Deepak Nair, Madhusudhan Venkadesan, and Yamuna Krishnan. Deepak moves to the Regional Centre for Biotechnology in New Delhi to head up a structural biology unit there. Madhu moves to Yale University to build up on research that started here on biomechanics and control theory, and Yamuna to the University of Chicago to expand the scope of her interactions in her domain of DNA-based sensors. Apurva Sarin also moves away from NCBS, but fortunately not too far; she takes on a big challenge as the new Dean at inStem. We wish all of them only the very best.

With our theorists colleagues now housed in their chalk-board filled digs at the Simons@NCBS complex (see page 201) and embarking on new journeys, and our new laboratory complex with its open plan architecture beginning to grow on its occupants, as well as a brand new housing complex completed, we must commend our projects and the technical services teams for making sure of the architecture and quality necessary for our research. As we rapidly fill our new building and renew our old building with new and exciting science (as you will no doubt read in this report), we also realize that we will soon have a new research block in our neighbourhood, this time built for the Institute for Stem Cell and Regenerative Medicine (inStem).

This brings up the question of our 'neighbourhood'. It is here that I believe we are forming a new ecosystem for biological research. This spans scale [from single molecules to ecosystems (at NCBS)], thematics [from basic mechanisms underlying how cells chose their fate by a complex interplay of nature and nurture to the use of stem cells in translational research (at inStem)], with the technological capabilities necessary [development of core facilities and new technology necessary for Biology and innovation (at CCAMP)]. I see huge potential of combining different modes of research, in which individual laboratory based (NCBS) and theme driven approaches (inStem) could create a heady mixture for truly exciting science.

If this potential is to be realized, we will need an enlightened mechanism to govern the interactions of this cluster of institutions, without compromising individual institutional identities, autonomies and directions. inSTEM and CCAMP were established with the explicit involvement of both NCBS's administration and scientists, to help amplify research potential on our campus. The presence of these institutions enriches our scientific environment, and opens avenues for PIs to initiate projects that transcend limitations imposed by the scale of work possible in an individual's laboratory.

Some fruits of such collaborative and theme based research are beginning to be realized, in the launching of a number of multi-institute programmes (such as Centre for Brain Development and Repair - CBDR, National Mouse Resource - NaMoR, Discovery Biology of Neuropsychiatric Syndromes - DBNS, NCBS-Max Planck Lipid Center. I believe that this ecosystem will provide us the necessary bandwidth to engage with the huge potential for human and other organismal biology that our new clinical engagements and field research offers, filling our laboratories with questions that emanate from our own local environments. We need a multi-disciplinary research environment that can support many modes of research, and this is what we must nurture our campus.

Satyajit Mayor
Director, NCBS

Biochemistry Biophysics Bioinformatics

- Jayant B Udgaonkar
- M K Mathew
- R Sowdhamini
- Aswin Sai Narain Seshasayee
- P V Shivaprasad
- Ranabir Das

Neurobiology

- Mitradas M Panicker
- Upinder S. Bhalla
- Sumantra Chattarji
- Sanjay P Sane
- Gaiti Hasan
- Vatsala Thirumalai
- Axel Brockmann
- Shannon Olsson

Theory, Simulation and Modeling of Biological Systems

- Mukund Thattai
- Madan Rao
- Shachi Gosavi
- R Sowdhamini
- Upinder S Bhalla
- Sandeep Krishna
- Madhusudhan Venkadesann

Cellular Organization and Signaling

- Sudhir Krishna
- Apurva Sarin
- Satyajit Mayor
- Madan Rao (Adjunct faculty)
- Raghu Padinjat
- Varadharajan Sundaramurthy

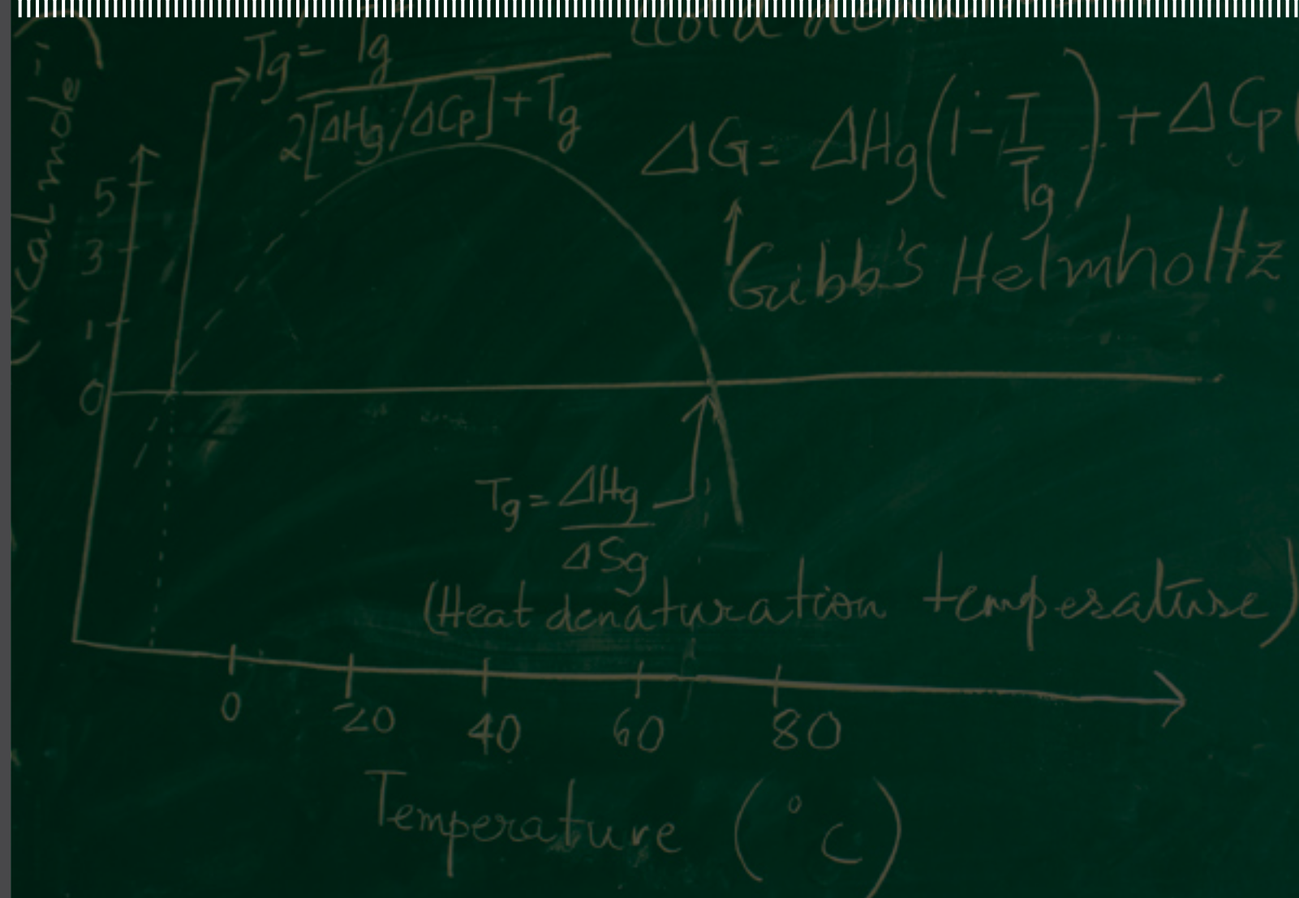
Genetics and Development

- K VijayRaghavan
- Gaiti Hasan
- Uma Ramakrishnan
- Krushnamegh Kunte
- P V Shivaprasad
- Mani Ramaswami (Adjunct faculty)

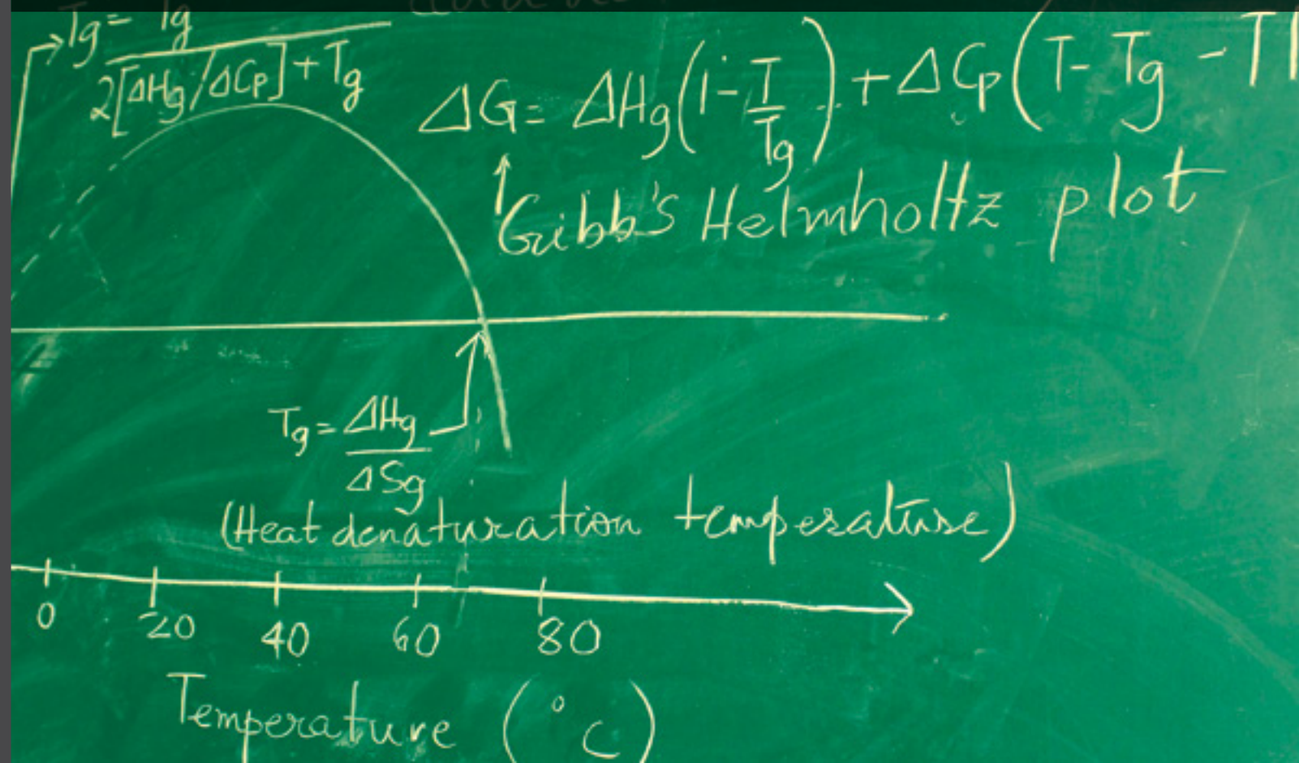
Ecology and Evolution

- Uma Ramakrishnan
- Mahesh Sankaran
- Sanjay P Sane
- Krushnamegh Kunte
- Deepa Agashe

* Several of our investigators have research interests spanning multiple areas of biology and only one of their affiliations is given here.



BIOCHEMISTRY, BIOPHYSICS & BIOINFORMATICS



The function of any protein is determined by its three-dimensional structure. We study how a polypeptide chain self-assembles into its correct conformation during folding, how the native conformation of a protein dissembles during unfolding, and how a protein forms aggregates when folding or unfolding goes wrong.

JAYANT B UDGOANKAR

How do Proteins Fold, Unfold and Misfold?

SELECTED PUBLICATIONS

Singh, J., Sabareesana, A.T, Mathew, M.K. and **Udgaonkar, J.B.** (2012). Development of the structural core and of conformational heterogeneity during the conversion of oligomers of the mouse prion protein to worm-like amyloid fibrils. *J. Mol. Biol.* 423, 217-231.

Udgaonkar, J.B. (2013). Polypeptide chain collapse and protein folding. *Arch. Biochem. Biophys.* 531, 24-33.

Ramachandran, G. and **Udgaonkar, J.B.** (2013) Mechanistic studies unravel the complexity inherent in tau aggregation leading to Alzheimer's disease and the tauopathies. *Biochemistry* 52, 4107-4126.

The polypeptide chain of a protein must bend, loop, coil, turn and twist itself in a very precise manner while folding into the unique structure that enables the protein to function in the cell. The protein folding problem is to understand how structure develops as a protein folds. It has been a long-standing, unsolved puzzle in biology, whose solution has obvious biotechnological as well as medical implications. In particular, the improper folding of some proteins, and their consequent aggregation into amyloid fibrils, are characteristic features of several neuro-degenerative diseases as well as of the prion diseases. An understanding of the mechanism of protein folding will also lead to a better understanding of the other facet of the protein folding problem, which is how to predict the functional structure of a protein from the amino-acid sequence that specifies it.

My laboratory uses several small proteins, including monellin, the SH3 domain of the PI3-kinase, barstar, tau, and the mouse prion protein as archetypical model proteins for studying how proteins fold, unfold as well as aggregate. We also study how correct folding is assisted by the chaperone GroEL. We use the tools of protein engineering and physical biochemistry. These include diverse optical spectroscopic methods such as time-resolved fluorescence, as well as mass spectrometry and nuclear magnetic resonance spectroscopy. Our kinetic measurements span the time domain of 40 microseconds to 10 hours.

Highlights of our recent work on protein folding and unfolding include (1) the demonstration that multiple pathways are available for the folding and unfolding of monellin and that switching between alternative pathways can occur with a change in folding or unfolding conditions; (2) the demonstration that the native state of the prion protein undergoes unusually high fluctuations, which makes it extremely malleable to structural change; (3) the demonstration that protein unfolding reactions can occur through intermediates with non-native interactions; and (4) the demonstration that protein unfolding proceeds through dry and wet globules and a solvated transition state. Highlights of our recent work on protein misfolding and aggregation include (1) the structural characterization of oligomeric intermediates and worm-like fibrils formed by the mouse prion protein, and the demonstration that these aggregates can perturb membrane structure; (2) the temporal dissection of the structural changes that occur during fibril formation by the prion protein; and (3) the demonstration of a secondary pathway for fibril formation by the tau protein, and the delineation of structural changes that occur during fibril formation.

Tau fibrils

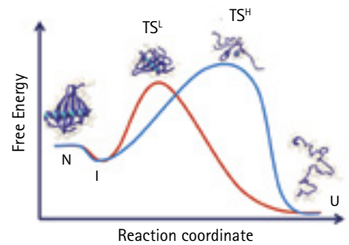
1 THE UTILIZATION OF ALTERNATIVE PATHWAYS DURING PROTEIN FOLDING AND UNFOLDING

Nilesh Aghera

Determining whether a protein utilizes multiple pathways to fold and unfold is an important goal in protein folding studies. Multiple pathways may manifest themselves by causing the dependence on denaturant concentration of the logarithm of the observed rate constant of folding and/or unfolding to have an upward curvature. This will happen when the transition states on the alternative pathways differ in their compactness and structure but not significantly in energy. Detection of multiple pathways in this manner is rare.

Upward curvatures were detected in the chevron arms for both the fast and slow phases of refolding of heterodimeric monellin. It was shown that the initial encounter complex formed by the two chains folds *via* two folding routes, one of which is populated by a productive folding intermediate. Similarly an upward curvature was observed for the unfolding of single chain monellin. For both proteins, it was shown that the folding or unfolding reaction switches from one pathway to another with a change in denaturant concentration.

Figure 1: Multiple pathways of unfolding of monellin



2 COMPLEXITY OF THE FOLDING PATHWAY OF THE SH3 DOMAIN OF PI3 KINASE

Amrita Dasgupta

Protein folding reactions often appear to be deceptively simple. The hidden complexity of the folding reaction of the apparently "two-state" folder, the SH3 domain of PI3 kinase (PI3K-SH3 domain) was revealed by the addition of a co-solute that stabilized folding intermediates. A collapsed intermediate before the rate limiting step and a more unfolded like intermediate after the rate limiting step were identified in kinetic folding and unfolding studies. A four-state mechanism for folding and unfolding was shown to be valid over the entire range of denaturant concentration studied. Very interestingly, the intermediate that forms after the rate limiting step of folding was shown to possess non-native structure.

3 CRITICAL EVALUATION OF A TWO-STATE MODEL FOR EQUILIBRIUM UNFOLDING

Megha Kishore

The probes commonly used to measure equilibrium unfolding reactions of proteins cannot detect the underlying heterogeneity inherent in the reactions, and hence these reactions are described as two-state. Time resolved fluorescence resonance energy transfer (TRFRET) measurements revealed the gradual expansion of the native state of the PI3K-SH3 domain at low denaturant concentration, and that the unfolding cannot be described by models that invoke only a few discrete states.

4 THE NATIVE STATE OF THE PRION PROTEIN HAS A CONFORMATIONALLY FLEXIBLE AND MALLEABLE NATIVE STATE

Roumita Moulick

The prion protein appears to be unusually susceptible to conformational change. Unlike most other proteins it can easily adopt alternative misfolded conformations. A complete thermodynamic

characterization of the unfolding of the mouse prion protein revealed, by measurement of heat capacity changes, that the native state undergoes substantial fluctuations in enthalpy and hence, in structure.

5 HIGH ENERGY INTERMEDIATES IN PROTEIN UNFOLDING

Pooja Malhotra

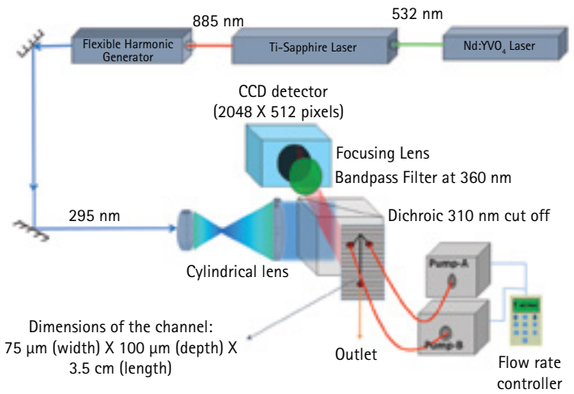
A protein unfolding reaction usually appears to be so dominated by a large free energy barrier, that identifying and characterizing high energy intermediates, and hence dissecting the unfolding reaction into multiple structural transitions, has proven to be a challenge. Native-state thiol labeling measurements were used to identify high energy intermediates as well as to delineate the barriers to the disruption of side-chain packing interactions and to site-specific solvent exposure in different regions of the small protein monellin.

6 INITIAL CHAIN COLLAPSE DURING THE FOLDING OF MONELLIN

G. Rama Reddy

A microsecond mixer capable of measuring protein folding rates as high as 25,000 s^{-1} was developed. Initial use of the mixer has shown that different regions of the protein chain undergo initial chain collapse at different rates independent of each other.

Figure 2: Schematic of microsecond mixing instrumentation



7 INITIAL STRUCTURAL CHANGES DURING THE UNFOLDING OF THE PI3K-SH3 DOMAIN

Prashant Jethva

Hydrogen exchange coupled to mass spectrometry (HX-MS) is being used to compare the unfolding of the PI3K-SH3 domain in two denaturants. Initial results showed that in the absence of denaturant, the native state transforms into an intermediate in a gradual and not in an all-or-none manner.

8 GROEL-ASSISTED REFOLDING OF HETERODIMERIC MONELLIN

Neha Nandwani

A study of the mechanism by which the chaperone GroEL assists the folding of the heterodimeric protein monellin, was begun.

9 STRUCTURAL CHARACTERIZATION OF THE TRANSFORMATION OF OLIGOMERS OF THE MOUSE PRION PROTEIN INTO WORM-LIKE AMYLOID FIBRILS

Jogender Singh and A.T. Sabareesan, in collaboration with M.K. Mathew

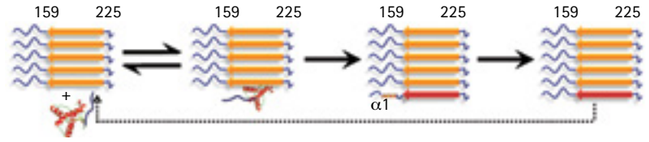
Understanding how structure develops and conformational heterogeneity manifests itself during the course of amyloid fibril formation by the prion protein is important for understanding prion diseases. HX-MS was used to delineate the structural cores of two oligomers formed by the mouse prion protein at low pH, and to understand in structural terms why only the larger oligomer and not the smaller can transform into worm-like fibrils. All three amyloid aggregates were shown to be capable of disrupting lipid membrane structure, pointing to a mechanism by which they may be toxic.

10 STRUCTURAL CHARACTERIZATION OF THE CONVERSION OF MONOMERIC PRION PROTEIN INTO AMYLOID FIBRILS

Jogender Singh

A molecular understanding of prion diseases requires an understanding of the mechanism of amyloid fibril formation by the prion protein. HX-MS was used to describe the conformational conversion of monomeric mouse prion protein into aggregated amyloid fibrils. It was shown that conformational conversion occurs in two steps after the binding of monomer to fibril, with helix 1 unfolding only after helices 2 and 3 transform into beta-sheet.

Figure 3: Conformational conversion during fibril formation by the prion protein



11 MECHANISM OF AMYLOID FIBRIL FORMATION BY HUMAN TAU AND STRUCTURAL CHARACTERIZATION OF TAU FIBRILS

Gayathri Ramachandran

Tau protein is an intrinsically disordered protein which is known to aggregate and form neurofibrillary tangles in Alzheimer's disease as well as in a wide range of other taupathies. The polyanion heparin is commonly used as an inducer in studies of tau aggregation in vitro, but its kinetic role in inducing aggregation had not been known. Similarly the kinetic role of intermediates populated during tau aggregation was not understood. Amyloid fibril formation by tau4RD, a tau four-repeat domain construct, in the presence of the inducer heparin was shown to occur by a nucleation dependent polymerization mechanism, and the kinetic role of heparin was shown to be restricted to nucleation. It was shown that rod-like protofibrils were populated during the course of aggregation but that these were off the pathway of fibril formation.

The amyloid fibril formation reaction of tauK18, another tau four-repeat construct was also studied. It was shown that not only is there a primary nucleation pathway but also a secondary pathway for fibril growth. It was shown that the dominant secondary pathway is fibril fragmentation.

HX-MS was used to show that the fibrils formed by tau4RD and tauK18 are constructed on similar structural principles, but that the tauK18 fibril has a slightly more stable core.

12 CELLULAR MODEL OF POLYGLUTAMINE AGGREGATION

Vishal Bhardwaj, in collaboration with M.M. Panicker

The aggregation of poly-glutamine rich proteins in inclusion bodies in cells is closely linked with numerous neuro-degenerative disorders, but the organization of protein in the inclusions is poorly understood. Fluorescence anisotropy based measurements were used to probe packing in inclusions at various stages of growth in live cells. It was shown, by measurement of the enhancement of the homo-FRET that accompanies inclusion growth, that the protein packing evolves and becomes tighter as the inclusion grows in size.

13 **AMYLOID FIBRIL FORMATION BY THE CHAIN B SUBUNIT OF MONELLIN**

A. T. Sabareesan

Proteins possessing very different structures, or even no structure, form fibrils that are very similar in internal structure, suggesting that they aggregate by similar mechanisms. The aggregation reaction of chain B of monellin was shown to meet all the stringent kinetic criteria of a nucleation dependent polymerization mechanism valid over a wide range of protein concentration. Off-pathway spherical oligomers were shown to form transiently during fibril formation.

14 **ARCHITECTURE OF PRION FIBRILS**

Ishita Sengupta

A study of the morphology of prion fibrils, using TRFRET spectroscopy as well as NMR spectroscopy was initiated.

15 **AMYLOID FIBRIL FORMATION BY A-SYNUCLEIN**

Pratibha Kumari

A study of the mechanism by which the dye thioflavin T modulates amyloid fibril formation by α-synuclein was begun.

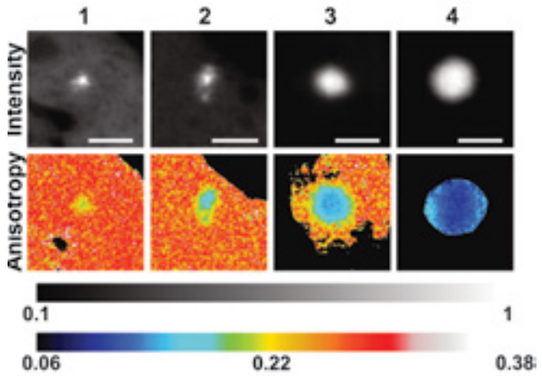


Figure 4: Steady-state intensity and anisotropy images of mammalian cells containing poly-glutamine inclusions.

Membrane transport processes contribute to survival under stressful situations. We study the role of transport processes that contribute to defensive strategies deployed by plants facing drought or salt stress. Roles played by a mitochondrial transporter in programmed cell death are also explored.

MK MATHEW

Membrane Transport: Sorting the Quick from the Dead (Or Dying)

SELECTED PUBLICATIONS

Godbole A., Mitra R., Dubey A.K., Reddy, P.S. and **Mathew, M.K.** (2011) .Bacterial Expression, Purification and Characterization of a Rice Voltage Dependent Anion-Selective Channel Isoform, OsVDAC4 *J Membrane Biol* 244, 67–80

Kavitha, P.G., Miller, T., **Mathew, M.K.** and Maathuis, F.J.M. (2012) Rice cultivars with differing salt tolerance contain similar cation channels in their root cells. *J Exp Botany* . 63, 3289–3296

Godbole, A., Dubey, A.K., Reddy, P.S., Udayakumar, M. & **Mathew, M.K.** (2013) Mitochondrial VDAC and hexokinase together modulate plant programmed cell death *Protoplasma* 250, 875–884

ENDOCYTIC MECHANISMS IN SALT TOLERANCE

Anirban Baral, in collaboration with Prof. S Mayor NCBS

Endocytosis, the internalization of plasma membrane along with embedded proteins and extracellular fluid, is a ubiquitous cellular process in metazoans. Multiple pathways of endocytosis have been identified in animal systems which vary in terms of the molecular constituents involved and also by the type of cargo that is internalized. Most studies have utilized isolated cells in culture apart from some recent studies in developing embryos of *C elegans* and *Drosophila*. The latter studies raise the possibility that endocytic processes may be differentially regulated across different cell lineages. Endocytic mechanisms may be expected to vary across cell types in an intact, functional tissue and, moreover, be subject to differential regulation in response to varying physiological conditions. The *Arabidopsis* root is a well stratified organ composed of distinct cell layers which are clearly demarcated in terms of position, shape (Fig 1A), developmental origin and gene expression profiles – and is amenable to imaging in its entirety, thus allowing the study of endocytosis in an intact functioning tissue. Exploiting the optical transparency and physical accessibility of young *Arabidopsis* roots we have explored the full panoply of endocytic mechanisms in the different cell layers. We have probed uptake mechanisms utilizing a range of probes and varied physiological conditions. We find that at least three distinct mechanisms of endocytosis operate in the root. A relatively well characterized clathrin-dynamin mediated mechanism operates across all cell layers and serves to take up transmembrane proteins. In addition, a clathrin-independent pathway operates constitutively in the epidermis – the outermost layer of the root. This pathway takes up lipid but excludes transmembrane proteins. Finally, salinity stress induces a clathrin-independent pathway in all layers of the root that is catholic in its choice of cargo, and employs molecular components that are not shared with the constitutive clathrin-independent pathway. Concomitant with the induction of this pathway, we observe the expansion of small acidic compartments into larger vacuole-like structures in inner cell layers. It may be noted that large vacuoles are a feature of the epidermis, but not seen in internal layers. Thus saline stress reprogrammes endocytic pathways and remodels a vital compartment involved in intracellular trafficking.

Mutant plants deficient in the third pathway fail to make large vacuoles in internal cell layers. They are also severely salt sensitive. We speculate that there could be a correlation between construction of mature vacuoles and the operation of the clathrin-independent endocytic pathways. In unstressed plants, the only cell layer with a well developed vacuole is the epidermis, which also has an active clathrin-independent uptake system. Under saline stress, the induction of a clathrin-independent endocytic process throughout the root correlates with the development of a vacuolar system in the inner layers. We therefore suggest that the salt-induced pathway of endocytosis contributes to the formation of large vacuoles in internal cell layers and is critical to the mounting of a successful defence against salinity stress.

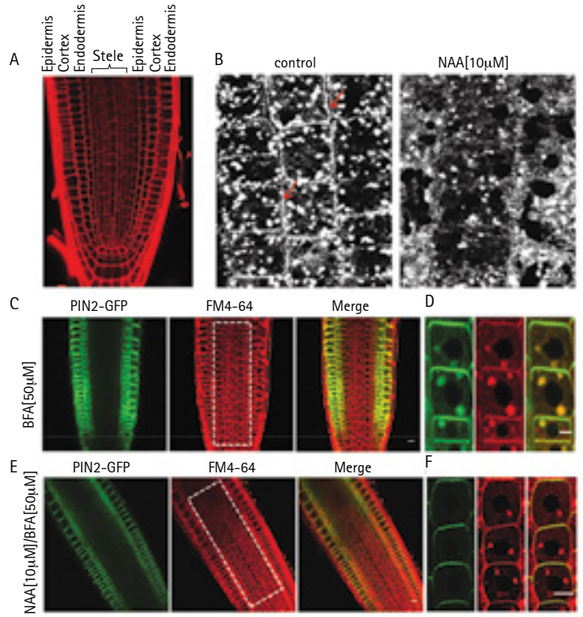


Figure 1A: Different layers of *Arabidopsis* root visualized by propidium iodide staining. The layers of the root from outside to inside are epidermis, cortex, endodermis and stele. Treatment with NAA reduces localization of clathrin localization to plasma membrane **(Fig 1B, right)** seen in control plants **(Fig 1b, left, red arrows)**. Uptake and Brefeldin-A (BFA) induced clumping of transmembrane protein PIN2-GFP and lipid probe FM4-64 **(Fig 1C and 1D)**. Pre-treatment with NAA prevents endocytosis and BFA induced clumping of PIN2-GFP but FM4-64 is still taken up in epidermal cells **(Fig1E and 1F)**, indicating operation of a clathrin–independent endocytosis in those cells. Note that, Stele cells in BFA treated roots have clumps containing FM4-64 while those pre-treated with NAA do not. **(1B and 1D, boxed area in middle)** suggesting clathrin-dependent endocytosis is predominant in those internal cell layers.

NB: BFA induced clumping of endocytosed cargo is a standard assay to monitor endocytosis in plants (Paciorek et al., 2005).

1 ROOT ARCHITECTURE AND UNDER DROUGHT AND SALINITY

Rukaya Amin, in collaboration with Prof. HE Shashidhar, University of Agricultural Sciences, GKVK Bangalore

We have studied the architecture of roots of rice plants subjected to drought and saline stress. Four cultivated *Indica* varieties were chosen – Pokkali, which grows in coastal regions and is very tolerant to salt; BI-33, a drought tolerant cultivar which was developed in UAS; IR-20, which is very sensitive to both salt and drought; and Jaya, which is intermediate in its tolerance characteristics. Roots of the four varieties differ greatly in length and number in a manner that could contribute to their tolerance characteristics. Earlier work in the lab had shown that the integrity of a waxy barrier around the endodermis is critical for restricting the entry of Na^+ into the xylem stream and hence its uptake into shoots. The ability to restrict Na^+ upate into shoots correlates with salt tolerance. The waxy barrier has breaks for passage cells which allow fluid access. We now find that xylem sap uptake into the shoot correlates with the density of passage cells. This correlation differs strikingly between control plants and those subjected to either drought or saline stress. Xylem sap uptake increases almost linearly with passage cell density in control plants. All four varieties dramatically reduced xylem sap uptake into shoots on saline stress and form a small cluster on the plot in Figure 2. On the other hand, there is a dramatic increase in passage cell number on drought stress together with a large spread in xylem sap uptake among the different varieties in response to drought. BI-33 shows a more than three-fold increase in passage cell density, which contributes to its ability to maintain high fluid uptake even under drought. The composition of the xylem sap has also been analysed. We find that Pokkali adds a large quantity of osmolytes to its xylem sap thereby compensating for the osmotic imbalance with the saline medium.

Our data indicate that BI-33 has very high xylem sap uptake in control plants, and its ability to maintain high uptake even under drought stress contributes to its survival under drought stress. BI-33 has very long roots that extend almost vertically downwards in order to tap into water reserves deep within the soil. Pokkali is very succesful in adding osmolytes to the xylem sap under saline stress and also in restricting Na^+ entry into the sap, thus maintaining reasonable xylem flow under saline conditions without subjecting the shoot to Na^+ loading.

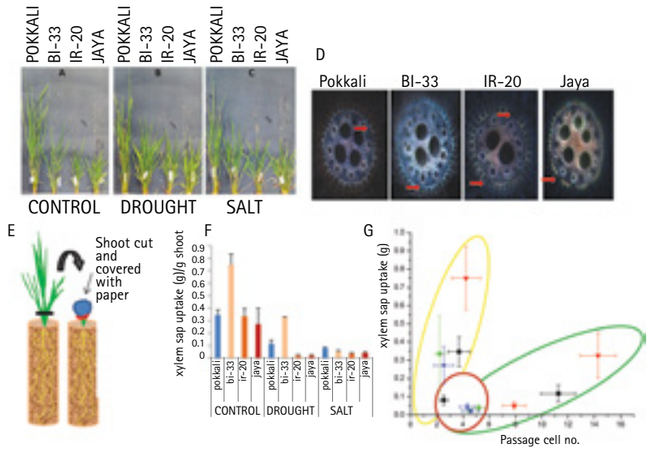


Figure 2: Shoot of different rice varieties at 45 days. Plants were subjected to **A)** control (well-watered), **B)** drought (no irrigation) and **C)** salinity (100mM) from the 38th day for one week. **D)** Passage cells. For passage cell scoring, root sections (200µm) taken from control, drought and salt stressed plants were stained with berberin hemisulphate and aniline blue. Sections were observed under fluorescent microscope using UV filter and number of cells with no tangential suberin or no suberin deposition at all, were counted. **E)** Schematic Representation of xylem sap uptake. After growing rice varieties in PVC pipes and exposing them to control (well-watered), drought (no irrigation) and salt (100mM) conditions from the 38th day, for about a week. After 45th day Shoot was cut 5cm above soil level and the stem covered first with blotting paper and then polyethylene wrapper, which was then tightly sealed with rubber band. After 12 hours, blotting paper was weighed to obtain the mass of xylem sap collected. **F)** Quantification of xylem sap uptake in control, drought and salt condition. **G)** Relation between passage cell number and xylem sap uptake in different varieties of rice (Pokkali, BI-33, IR-20 and Jaya). Data points cluster according to the treatment given and outlines have been drawn for clarity. **Yellow** – control plants, **Red** – plants subjected to salinity and **Green** – plants subjected to drought.

2 VDAC AND CELL DEATH

Ashvini Dubey & Ashwini Godbole

The voltage-dependent anion-selective channel (VDAC) is the most abundant protein in the mitochondrial outer membrane and forms the major conduit for metabolite transport across this membrane. We had earlier shown that VDAC plays a role in cell death in both plants and animals. Bcl2-family proteins that regulate mitochondrially-mediated cell death in animal cells have been shown to interact with VDAC, and this interaction has been implicated in some models of their regulation of cell death. Further, hexokinase has been suggested to modulate cell death by interacting with VDAC. We had shown earlier that heterologously expressed VDAC is initially present in the cytosol and subsequently moves to the mitochondrion. An analysis of the distribution of heterologously expressed VDAC in cells which also overexpress hexokinase or Bcl2-family proteins indicates that death correlates with the fraction of expressed VDAC that was localized in mitochondria as opposed to the cytosol. We therefore propose that one mechanism by which Bcl2-family proteins and hexokinase regulate cell death is by controlling the distribution of freshly synthesised VDAC between the cytosol – its site of synthesis – and the mitochondrion.

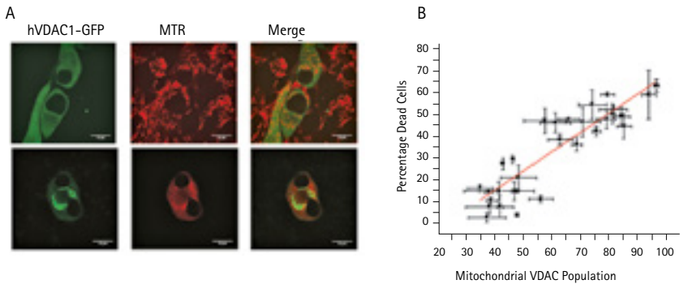


Figure 3: Subcellular distribution of VDAC is correlated with cell death. A) Localization of human VDAC 1 (hVDAC1) after overexpression in HeLa Cells. hVDAC1 is present both in cytosol and mitochondria at this time point. B) Correlation of the fraction of cells where VDAC is present in mitochondria with cell death. Data are for HeLa cells transfected with VDAC (either hVDAC1 or OsVDAC4) alone or in combination with either Hexokinase or Bcl2.

3 BIOPHYSICAL CHARACTERIZATION OF VDAC

Ashvini Dubey & Ashwini Godbole

OsVDAC4 is a rice VDAC which we have previously shown to operate in an apoptotic context in lymphocytes. OsVDAC4 protein was purified after overexpression in E coli and reconstituted into artificial membrane systems of two topologies –planar bilayer membranes which allow for electrical measurements, and spherical liposomes which are suitable for monitoring solute fluxes. We monitored liposome swelling in response to influx of polyethylene glycols of defined sizes through VDAC to estimate a pore radius of around 1.3 nm.

Electrical measurements made on single channels inserted into planar bilayers revealed a unitary conductance of 4.53 nS with several subconductance states. The probability of channel opening was maximal at 0 mV and decreased on shifts to either positive or negative potentials, with more transitions seen at positive potentials than at negative potentials. Introduction of ATP into the chamber resulted in a decrease in measured conductance (due to the decreased mobility of ATP compared to Cl^-) and an increase in noise. We also estimated the amount of ATP transported through a single channel to be around 10^7 ATP per second at -10 mV with an imposed gradient of 50 mM ATP.

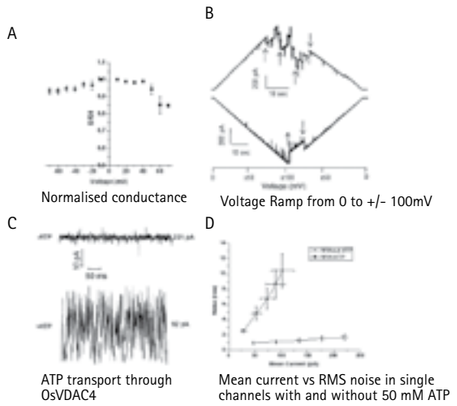


Figure 4: Electrophysiological characterization of OsVDAC4. A) Voltage dependence of OsVDAC4 conductance. Membrane conductance normalized to the conductance at +10 mV (G/G_{10}) as a function of applied membrane potential (mV) (n = 5). B) Voltage Ramp. Membrane containing 3 OsVDAC4 channels was subjected to 2 voltage ramps. In the upper trace, voltage was varied from 0mV to +100 and back to 0mV and in the lower trace from 0mV to -100 and back to 0 mV. The voltage was ramped at 5mV/sec. Transitions between sub conductance states are indicated with arrows. C) ATP transport through OsVDAC4, A representative trace at 50 mV in the absence and presence of 50 mM ATP under symmetric buffer conditions. Note the large increase in noise accompanied by a decrease in current on introduction of ATP. D) RMS noise and mean conductance through single channels in the presence and absence of 50 mM ATP and potentials ranging from +10 to +50 mV. Each point represents mean current and noise (±SE) from four independent channel recordings. Empty square: channel in the absence of ATP, Filled square: channel in the presence of 50 mM ATP.

Genome sequencing projects provide a large amount of data on sequence information of genes in various model organisms. Our laboratory is interested in enabling functional characterization of gene products and to perform in-depth studies of mechanism of action of enzymes through structural analysis.

R SOWDHAMINI

Computational Approaches to Protein Science

SELECTED PUBLICATIONS

Malhotra, S. and Sowdhamini,R. (2013). Genome-wide survey of DNA-binding proteins in Arabidopsis thaliana:analysis of distribution and fuctions. *Nucleic Acids Research*; doi:10.1093/nar/gkt505.

Eshita Mutt, Oommen K. Mathew and Sowdhamini, R. (2014). LenVarDB: Database of length-variant protein domains. *Nucleic Acid Research* 42 (D1): D246-D250.

Kaushik, S., Etchebest, C. and Sowdhamini,R. (2014). Decoding the structural events in substrate-gating mechanism of eukaryotic prolyl oligopeptidase using normal mode analysis and molecular dynamics simulations. *PROTEINS: Structure, Function and Bioinformatics* DOI: 10.1002/prot.24511.

1 IMPROVED SEARCH STRATEGY TO RECOGNIZE BEST REPRESENTATIVES IN PROTEIN SEQUENCE DOMAIN FAMILIES AND UPDATE OF 3PFDB DATABASE

Agnel P. Joseph, Prashant Shingate, Atul Upadhyay and R. Sowdhamini

Even today, nearly 50% of genome of any model organism does not have a reliable functional attribute and committed wet-biology laboratories are struggling to cope with the rapid pace of incoming data for detailed functional characterization. There remains a constant quest to connect, the "unknown", to the "known" – namely, genome sequences to protein structural entries or well-characterised sequence domain families. It can be prohibitively computationally expensive to systematically query such connections even from mere sequence information. We have employed, HMMER and an in-house motif-based search algorithm FASSM, to recognize best representatives of protein families which can drastically reduce the computational time. Subsequent to clustering of family members, an one-time computationally exhaustive procedure (Figure 1) was carried out. Such information on best representatives is now available for 13519 families and organized into 3PFDB+ database (Joseph et al., 2014). These data are in direct correspondence with PFAM v26 (Finn et al., 2009). It should be possible to perform sensitive function annotation of gene products, in one or many genomes, starting from these protein family representatives.

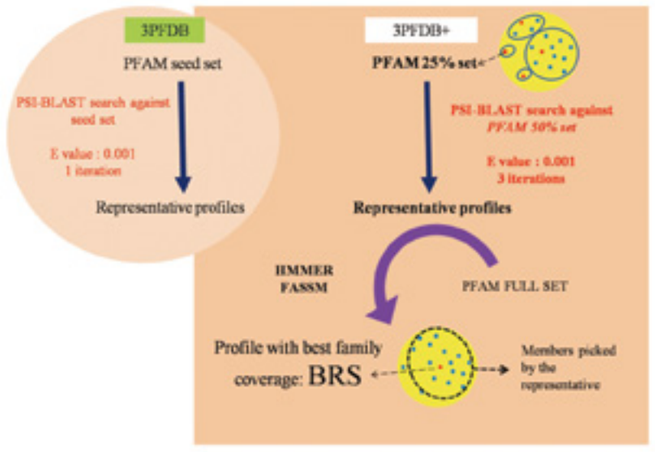


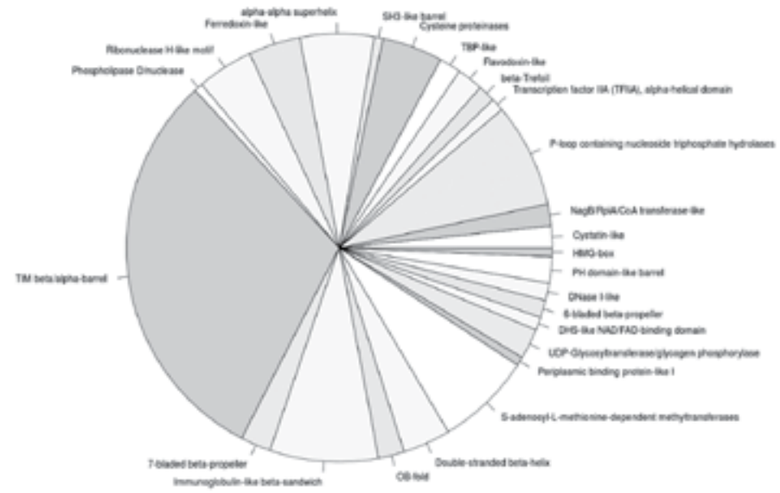
Figure 1: Workflow for the identification of best representative sequences and associated profiles in 3PFDB+ database. The portion highlighted in the circular background shows the differences in the profile generation approach in our previous study (Shameer et al., 2009).

2 STRUCTURE AND SEQUENCE FAMILIES OF DNA-BINDING PROTEIN DOMAINS AND GENOME-WIDE SURVEY IN *ARABIDOPSIS THALIANA*

Sony Malhotra and R. Sowdhamini

How easy will it to be perform genome-wide survey of say, 1000 different protein families? To address this and owing to high biological relevance, we collected 1057 protein domain families that are annotated to bind to DNA-binding proteins, both from structural and sequence databanks (Malhotra and Sowdhamini, 2012) and queried for putative members in the whole genome of *Arabidopsis thaliana*. Mathematical profiles and Hidden Markov Models were employed for the identification and validation of gene products that contain DNA-binding domains belonging to different folds (Figure 2). Such an early and broad-based analysis revealed 4471 gene products in the genome. A majority of such domains implicated in DNA repair in *Arabidopsis* could have DNA glycosylase or lyase activity (Malhotra and Sowdhamini, 2013).

Figure 2: Distribution of GO Molecular function terms associated with different SCOP folds mapped to DNA-binding function.



3 ANALYSIS OF LENGTH VARIATIONS IN PROTEIN DOMAIN SUPERFAMILIES AND INCLUSION OF SEQUENCE HOMOLOGUES

Eshita Mutt [1,2], Abhijit Mitra[2], Oommen K. Mathew[1] and R. Sowdhamini[1]

[1] National Centre for Biological Sciences, GKVK Campus, Bellary Road, Bangalore

[2] International Institute of Information Technology-Hyderabad, Gachibowli, Hyderabad

Accumulation of putative members of protein domain families and distantly related members (referred as superfamilies) by sequence searches offer a unique advantage to perform analysis of evolutionary changes when searched in not one genome, but many genomes of model organisms. We first developed a computational pipeline (Mutt et al. 2011) (Figure 3), starting from structural entries recorded in our PASS2 database (Gandhimathi et al. 2011) that selectively encourages the accumulation of homologues that retain sufficient evolutionary changes, stamped in the form of insertions and deletions. Such homologues have been carefully aligned and analysed for length

variations. A majority of insertions and deletions in enzyme superfamilies do occur distal from the active site, but still could influence the activity of enzymes by means of long-range or allosteric interactions. Information of homologous domains of variable lengths, corresponding to PASS2 database, is provided as a repository or a public domain database referred as LenVarDB (Mutt et al., 2014) for 731 domain superfamilies including 2,730,625 sequence homologues.

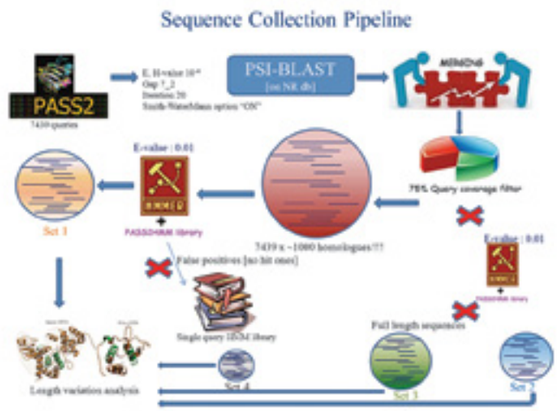


Figure 3: *Flowchart of full pipeline for collection of length-variant homologues* Initial hits for homologous sequences were obtained using PSI-BLAST against the non-redundant sequence database. Where segments of alignments had more than 50% of overlap, they were merged. Hits were validated by examining the length of alignments against the query (QCF: query coverge filter needs to be more than 75%) and association to the parent superfamily.

True positives under Set1 were the hits which associated with Hidden Markov Model (HMM) of the same superfamily as the query with significant values. Hits which have failed QCF but have successfully been validated by HMM (on PASS2HMM) were retained in Set2. Set3 hits were ones which passed these two parameters when searched against full-length of the hits, while Set4 hits were included since they could be associated with HMM of any one of the members of the PASS2 superfamily.

4 COMPUTATIONAL APPROACHES TO STUDY MECHANISM OF SUBSTRATE ENTRY IN PROLYL OLIGOPEPTIDASES

Swati Kaushik and R. Sowdhamini

Whereas large-scale sequence searches, either in the form of genome-wide survey in a single genome or genomes of multiple genomes provide an early bioinformatics overview of protein domain families, it is always useful to perform in-depth analysis and comparison of structure-function relationships on particular protein families. For this purpose, we chose prolyloligopeptidases (PoPs) to compare this enzyme from three sources, viz. human, porcine and *Arabidopsis* and reported them to have different substrate-inhibitor binding affinities (Kaushik and Sowdhamini, 2011). The functional unit of PoPs consists of a catalytic domain of the α/β hydrolase superfamily and a β-propellor domain. Despite the availability of crystal structure information of

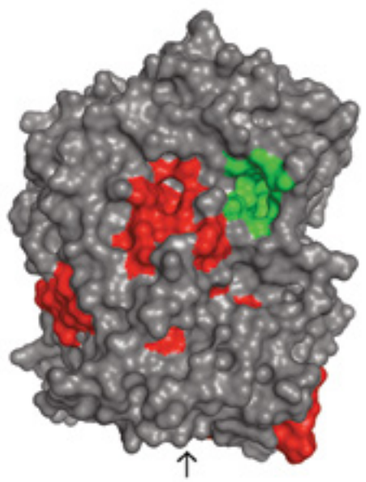


Figure 4: Structure of prolyloligopeptidase (Polgar, 2002) with active site (in green colour) and other cavities (in red colour) shown. Catalytic domain is on top and propellor domain is underneath.

several PoPs, several questions such as the substrate gating and product exit remained open. Various theories emerged – for instance, was it through the propeller domain pore or blades? Was it through inter-domain movements at the interface? Or, was it mediated by conformational changes of limited loops near the functional sites? We have performed molecular dynamics simulations and normal mode analysis (Kaushik and Sowdhamini, 2014) to explain preferred pathway for substrate entry driven by controlled conformational changes such as twisting movement of the two domains and domain opening (Figure 5) which is accompanied by inter-domain loop conformational changes as a possible mode for substrate ingestion by the enzyme.

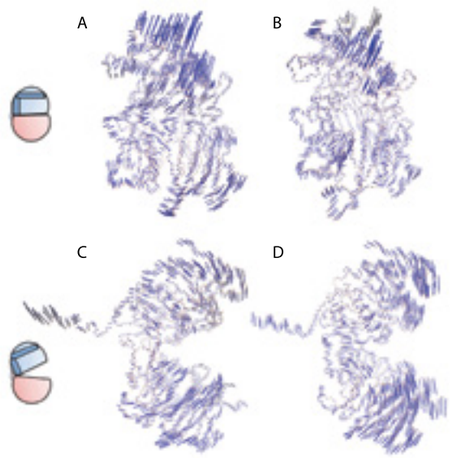


Figure 5: Motions observed in bacterial POPs. (A) Domain opening motion in bound form. (B) Domain opening motion in bound form of porcine POP. (C) Twisting of two domains in unbound form. (D) Domain opening motion in unbound form. Motion vector is represented in blue color.

Evolution has produced an overwhelming variety of biological devices that function at the nanoscale. We study the structure and dynamics of nucleic acids and translate this knowledge to create nucleic acid based nanodevices to probe living systems.

YAMUNA KRISHNAN

Nucleic Acid-Based Molecular Devices

Bionanotechnology aims to learn from nature - to understand the structure and function of biological devices and to utilise nature's solutions in advancing science and engineering. Evolution has produced an overwhelming number and variety of biological devices that function at the nanoscale or molecular level. My lab's central theme is one of synthetic biology, which involves taking a biological device, component or concept out of its natural cellular context and harnessing its function in a completely new setting so as to probe or reprogram the cell. Our research involves understanding the structure and dynamics of unusual forms of nucleic acids and translating this knowledge to create nucleic acid-based nanodevices for applications in biology.

Structural DNA nanotechnology is an emerging field that seeks to create exquisitely defined nanoscale architectures via the self-assembly of a set of carefully chosen DNA sequences. With a diameter of 2 nm and a helical periodicity of 3.5 nm, the DNA double helix is inherently a nanoscale object. The specificity and predictable affinities of Watson-Crick base pairing affords a hierarchy of molecular glues between given rods at defined locations that makes DNA an ideal nanoscale construction material. DNA nanodevices could either be rigid scaffolds in 1D, 2D or 3D that function as molecular breadboards. They could also function as switches or transducers, undergoing controlled nanomechanical motion, by exhibiting a conformational change in response to a stimulus. We create such DNA-based nanodevices for applications such as high-performance 'custom' biosensors that intercept biochemical signals, thereby interrogating and reporting on cellular processes. We are also interested in understanding naturally occuring nucleic acid based devices such as non-coding RNAs. RNA is an exciting and powerful biological medium for making genetically encoded, synthetic nucleic acid architectures that can probe and program the cell.

SELECTED PUBLICATIONS

Modi, S., Nizak, C., Surana, S., Halder, S. and **Krishnan, Y.** (2013) Two DNA nanomachines map pH of intersecting endocytic pathways. *Nature Nanotechnology*, 8, 459-467.

Chakraborty, S., Mehtab, S., Patwardhan, A.R. and **Krishnan, Y.** (2012). Pri-miR-17-92a Transcript folds into a tertiary structure and autoregulates its processing. *RNA*, 18, 1014-1028.

Bhatia, D., Surana, S., Chakraborty, S., Koushika, S.P. and **Krishnan, Y.** (2011). A synthetic, icosahedral DNA-based host-cargo complex for functional in vivo imaging. *Nature Communications*, 2, 339.

Yamuna Krishnan is now based at the University of Chicago.

https://chemistry.uchicago.edu/faculty/faculty/person/member/yamuna-krishnan.html

1 A DNA NANOMACHINE IS FUNCTIONAL IN A MULTICELLULAR LIVING ORGANISM

Sunaina Surana

DNA nanomachines are artificially designed assemblies that switch between defined conformations in response to an external cue. One of the devices made by our lab is the I-switch, which is a DNA nanomachine that undergoes a conformational change triggered by protons. Though it has proved possible to create DNA machines and rudimentary walkers, the function of such autonomous DNA-based molecular devices has not yet been achieved inside living organisms. We have recently demonstrated the operation of a pH-triggered DNA nanomachine inside the nematode *Caenorhabditis elegans*. The I-switch is uptaken by coelomocytes of *C elegans* selectively through the Anionic Ligand Binding Receptor pathway and we have followed endosomal maturation along this pathway *in vivo* using FRET (Figure 1). One can effectively map spatiotemporal pH changes associated with endocytosis in wild type as well as mutant worms, which reveals the autonomous function of the DNA nanodevice within the organismal milieu in a variety of genetic backgrounds. From this first demonstration of the independent functionality of a DNA nanomachine *in vivo*, we observe that rationally designed DNA-based molecular devices retain their *in vitro* functionality with quantitative precision. This positions DNA nanodevices as exciting and powerful tools with which to interrogate complex biological phenomena.

Collaborator: Sandhya Kaushika, previously NCBS

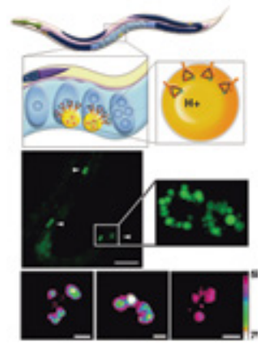


Figure 1: A) Schematic and representative image of a *C. elegans* hermaphrodite microinjected with the I-switch in the pseudocoelom (Scale bar: 50 µm). B) Upon injection, the I-switch labels the coelomocytes, where it is capable of mapping spatiotemporal pH changes accompanying endosomal maturation (Scale bar: 5 µm.)

2 MULTIPLEXING DNA NANODEVICES

Saheli Halder and Souvik Modi

Eukaryotic cell function is tuned by an orchestrated network of compartments involved in uptake and secretion of various macromolecules. These compartments are functionally connected to each other via a series of controlled fusion and fission events between their membranes. One of the crucial determinants of this functional networking is the lumenal acidity of these compartments which is maintained by proton concentration, concentrations of different counter ions, membrane ion permeabilities and various ATP-dependent proton pumps. Maintenance of intraorganellar pH homeostasis is essential for protein glycosylation, protein sorting, biogenesis of secretory granules and transport along both secretory and endocytic pathways. Lack of probes reporting multiple pathways simultaneously has impeded understanding of intesection between the endocytic pathways. Therefore we have created a palette of DNA-based pH sensors compatible to various sub-cellular organelles such as the trans Golgi network (TGN), cis Golgi (CG) and endoplasmic reticulum (ER) of living cells (Figure 2A) as, each organelle has a different

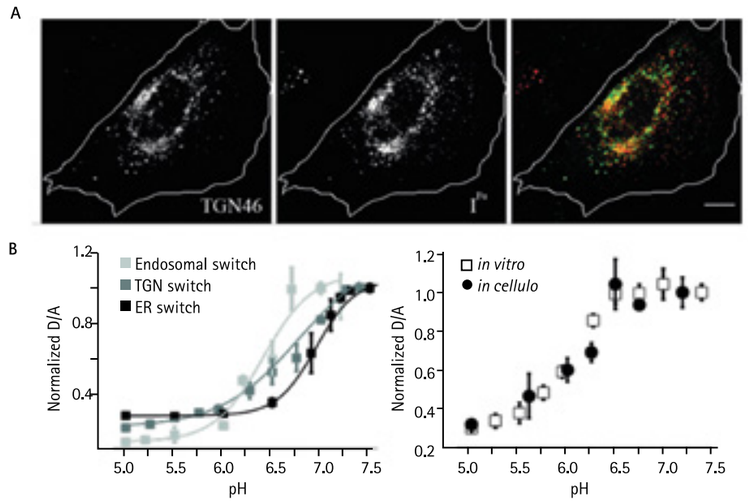


Figure 2: Targeting DNA nanodevices to secretory pathway. A) Co-localization of DNA nanodevice inside trans-Golgi network (TGN) as revealed by immunofluorescence against TGN marker TGN46. Scale Bar: 10 µm. B) *In vitro* pH response curves of various organelle specific I-switches as revealed by their Donor (D) to acceptor (A) ratios as a function of pH. C) Overlay of *in vitro* and *in cellulo* performance of DNA nanodevices when targeted to the secretory pathway.

lumenal pH e.g., pH_{ER} is 7.2, pH_{CG} is 6.6, while pH_{TGN} is 6.3. We have engineered the I-switch to tune its pH responsive regime and now have I-switches specific for the ER, the Golgi and the late endosome (Figure 2B-C) and have successfully deployed two pH sensitive DNA nanodevices in the same live cell to measure pH in two different organelles simultaneously.
Collaborator: Clément Nizak, ESPCI, Paris

3 DNA ICOSAHEDRA FOR FUNCTIONAL BIOIMAGING

Dhiraj Bhatia, Sunaina Surana, Saikat Chakraborty

3D DNA polyhedra could have applications in drug delivery given that they have hollow internal cavities in which functional macromolecules may be housed and targeted. To this end we have shown that DNA can be used to make complex polyhedra such as an icosahedron, using a novel, modular assembly based approach. The power of this approach is that it allows the efficient encapsulation of other nanoscale entities in high yields. Many peptide based drugs cannot be delivered efficiently to their target due to degradation. Thus encapsulating them in non-leaky, programmable capsules such as DNA polyhedra might solve this problem. To check this hypothesis, we chose FITC-Dextran as a model biopolymeric drug, demonstrated that it can be encapsulated inside DNA Icosahedra and delivered effectively in a targeted manner *in vivo* (Figure 3). We showed that these FITC-Dextran loaded DNA icosahedra could be targeted to specific cells in *C elegans*, and that post-encapsulation and post-delivery, cargo functionality was unaffected.
Collaborator: Sandhya Koushika, NCBS.

Figure 3: Schematic showing the encapsulation of FITC-Dextran within DNA icosahedra obtained by mixing complementary two half icosahedra in a 1:1 ratio in presence of excess of FD10 molecules. The FITC-Dextran loaded icosahedra are uptaken cell-type specifically in *C. elegans*. Scale bar: 10 µm.

4 New DNA structures: "Foldback" A-motifs

Sonali Saha

Our lab has described a new DNA structure held together by non-Watson Crick base pairs called the A-motif. The A-motif is a parallel stranded DNA duplex held together by AH^+-H^+A base pairs formed at acidic pH values by A-rich oligodeoxynucleotides. We have shown that gold nanoparticles functionalized with poly dA undergo a pH dependent change in their optical properties due to their aggregation mediated by A-motif formation under acidic conditions. This forms the basis of a colorimetric assay that reports on the efficacy of A-motif formation as revealed by mutational analysis of the associating oligo dA tracts (Figure 4). Application of this colorimetric assay to varying lengths of oligo dA tracts has yielded the first experimental evidence of longer poly dA tracts folding back upon themselves to form intramolecular A-motifs (Figure 4).

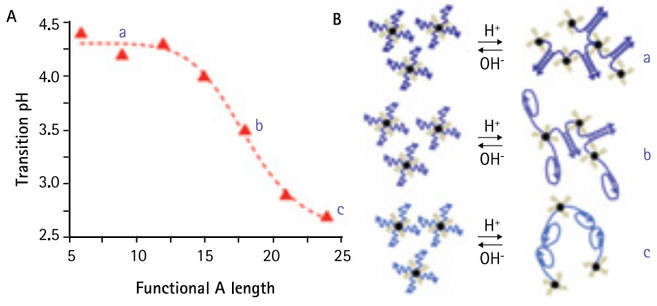


Figure 4: A) Transition pH of the pH dependent interparticle association of poly dA functionalized GNPs versus functional poly dA length B) Working models for association of poly dA functionalized GNPs at acidic pH. GNP association mediated by (a) short, (b) intermediate and (c) long poly dA segments showing the transition between two modes of interparticle association.

5 Naturally occuring Nucleic Acid Devices: Primary MicroRNA

Saikat Chakraborty and Shabana Mehtab

Our lab is also interested in naturally occuring nucleic acid based devices. Several naturally occuring nucleic acid based devices are nearly entirely composed of RNA: riboswitches, ribozymes and long non-coding RNAs to name a few. We also want to understand how some of these RNA based devices function, in the hope that we may someday be able to use the lessons learned to engineer smarter synthetic devices. MicroRNAs for example, are a class of RNAs that control gene expression by either by RNA transcript degradation or translational repression. Expressions of miRNAs are highly regulated in tissues, disruption of which leads to disease. But how this regulation is achieved and maintained is still largely unknown. MiRNAs that reside on clustered or polycistronic transcripts represent a more complex case where individual miRNAs from a cluster are processed with different efficiencies despite being co-transcribed. To shed light on the regulatory mechanisms that might be operating in these cases we considered the long polycistronic primary miRNA transcript pri-miR-17-92a that contains six miRNAs with diverse function. The six miRNA domains on this cluster are differentially processed to produce varying amounts of resultant mature miRNAs in different tissues. How this is achieved is not known. We show using various biochemical and biophysical methods coupled with mutational studies that pri-miR-17-92a adopts a specific three dimensional architecture which poses a kinetic barrier to its own processing. This tertiary structure could create suboptimal protein recognition sites on the pri-miRNA cluster due to higher order structure formation (Figure 5). Black and red. Initial rates of processing determined from kinetic traces are shown in the inset.

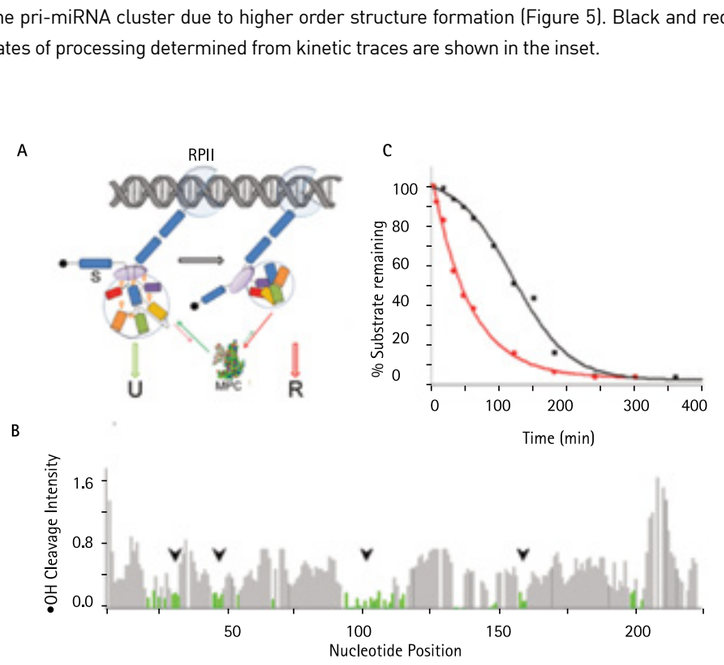


Figure 5: A) Schematic of cotranscriptional processing of pri-miR-17-92a. Unfolded pri-miR-17-92 is efficiently cleaved by MPC (Microprocessor Complex) as all single strand-double strand (ss-ds) junction are equally accessible. This leads to unregulated (U) processing. When pri-miR-17-92 adopts a tertiary structure regulated (R) processing occurs. RPII=RNA polymerase II; S = Spliceosome. B) Hydroxy radical footprinting of primiR-17-92 evidences tertiary structure with solvent protected core. Solvent inaccessible nucleotides in the folded RNA are indicated in green. C) Kinetics of processing of the full length native (pri-miR-17-92) and shuffled transcripts (pri-miR-20a-19a) are shown in

Our lab aims to understand the principles that underly the interplay between genome organization, gene function and an organism's lifestyle. Besides addressing this issue broadly using comparative genomic approaches, we investigate aspects of adaptation – by transcriptional control by combinations of global regulators, and evolution in the face of genetic and environmental stresses – on a genomic scale using *E. coli* as the model system.

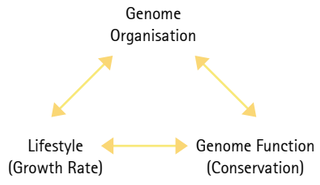
ASWIN SAI NARAIN SESHASAYEE

Genome Organization And Gene Expression In Bacteria

Organisms adapt to their circumstances either by evolving their genetic content or by altering their gene expression and activity states. Both involve complex molecular processes, and present various biochemical and evolutionary questions. Recent developments in genomics – in particular those that come under what is referred to as *functional genomics* - have catalysed rapid progress in the cataloguing and understanding of these processes. These developments have had particular impact on eukaryotic biology, with research gradually tending to move away from classical model systems to human cells.

Bacteria represent a paradigm for adaptation. Many evolutionary processes – including the extent of horizontal gene transfer and genome reduction - that underly bacterial genetic architecture came to be appreciated only after the advent of genome sequencing. In the bacterial domain, the more recent explosion of deep sequencing technologies are most apparent in *genomic epidemiology*, which involves sequencing of the genomes of a large variety of isolates of a single bacterial species, high-resolution phylogenetic analysis of variation, followed by say, the tracking of the history of an epidemic. That aside, genomic technologies – microarrays and deep sequencing – have made us aware that an understanding of fundamental molecular processes even in the studied-to-death model bacterium *Escherichia coli* is far from being a closed chapter.

The aim of our lab is to understand the principles that underly the interplay between genome organization, gene function and an organism's lifestyle. Besides addressing this issue broadly using comparative genomic approaches, we investigate aspects of adaptation – by transcriptional control by combinations of global regulators, and evolution in the face of genetic and environmental stresses – on a genomic scale using *E. coli* as the model system.



SELECTED PUBLICATIONS

Mogre A, Sengupta T, Reshma TV, Ravi P, **Seshasayee, A.S.** *Genomic analysis reveals distinct concentration-dependent evolutionary trajectories for antibiotic resistance in Escherichia coli.* DNA Research. In Press

Srinivasan, R., Chandraprakash, D., Krishnamurthi, R., Singh, P., Scolari, V., Krishna, S.and **Seshasayee, A.S.** (2013) Genomic analysis reveals a bilayered epistatic control of "expensive" genes in Escherichia coli: implications for gene silencing. *Molecular Biosystems.* 9: 2021-33.

Seshasayee, A.S., Singh, P. and Krishna, S. (2012) Context-dependent conservation of DNA methyltransferases in bacteria. *Nucleic Acids Res.* 40(15):7066-73.

1 GLOBAL GENE REGULATORY NETWORKS IN BACTERIA

Gene expression in bacteria is regulated by a complex network involving transcription factors (TF), interchangeable components of the RNA polymerase called σ-factors (SF), chromosome-shaping nucleoid-associated proteins (NAP), small molecule messengers and RNA regulators.

Bacterial transcriptional networks are best studied in *E. coli*. Much of the information on its regulatory network is derived from the literature, spanning decades of molecular work. In more recent years, genomic tools including ChIP-chip / ChIP-seq and gene expression microarrays have been applied to the study of *E. coli*'s regulatory network. Together, these types of data have accumulated a reasonable network of interactions for several TFs and SFs in *E. coli*.

Analysis of transcriptional regulatory networks in their current form have described certain organizational principles. One is that the network comprises two broad classes of regulation. The first is an on-demand activation or repression of a small set of genes that help the cell cope with that demand. This form of *local* regulation is exemplified by the control of the *lac* operon in *E. coli*. These local circuits establish a certain level of modularity in the network at a very deep level. Despite the apparent simplicity of these networks, it is remarkable that many details regarding the response kinetics of these types of interactions remain to be addressed, and efforts connecting mathematical modelling with detailed molecular experiments are underway in many labs.

The second type of regulation is called *global* gene expression control. This refers to a class of DNA-binding proteins that interact with a large number of sites on the chromosome. Binding to a subset of these sites results in a typical TF-like activity, modulating the expression of a proximal gene. Many of these interactions are also believed to influence the topology of the chromosome in as yet poorly understood ways. Genes regulated by such global networks typically belong to a broad spectrum of functions, and do not necessarily represent specific response to a signal. It is also apparent that there is much redundancy and combinatorial characteristic to these global regulatory networks. Our laboratory is interested in addressing some of these aspects:

A The degree and rationale behind *combinatorial control by global regulators*. Certain global regulators – namely the NAPs – are thought to be major components of the bacterial chromatin. How does the binding of one to the chromosome affect that of another? And how does this response vary with environmental conditions? Specifically, we are interested in epistasis between global regulators, where one has an effect on growth only in the absence of another.

B The discovery and characterisation of *parallel regulatory pathways that substitute for certain global regulatory networks* in terms of growth phenotypes. Global regulatory networks are believed to evolve rapidly. We discover and analyse pathways in which mutations help suppress fitness defects arising from loss of specific global gene regulatory systems.

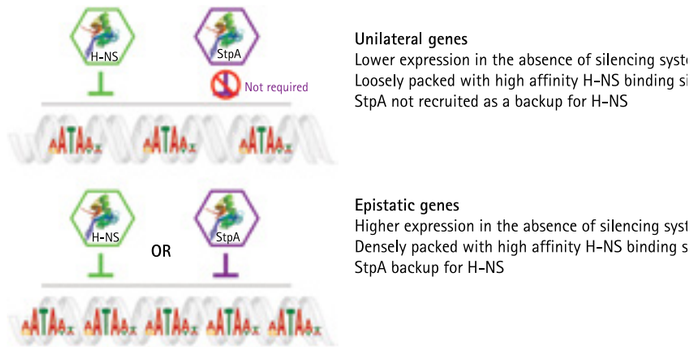
C The interplay between the *interactions of global regulators to the chromosome in the context of chromatin structure* or as TFs. We collaborate with Sankar Adhya (NCI, NIH, USA), Marco Cosentino Lagomarsino (UPMC, Paris, France) and Bianca Sclavi (ENS-Cachan, Paris, France), studying multiple aspects of the interplay between chromosome structure and genome dynamics and gene expression.

1.1 HORIZONTAL GENE TRANSFER: GENE REGULATION AND SELECTIVE PRESSURES

Horizontal gene transfer is a major mode of evolution among bacteria. It implies acquisition of blocks of DNA from the environment in the form of naked DNA (transformation), or through viral vehicles (transduction), or from fellow bacteria (conjugation). A single gene transfer event could allow the recipient bacteria to explore entirely new phenotypes and niches. Besides contributing to such dramatic phenotypic alterations, a horizontal gene transfer event could also have more protracted and subtle effects on the conserved genomic backbone. Many horizontally acquired DNA carry selfish modules, which maintain themselves in the host without providing major

selective benefits. Therefore, it is not surprising that the process of gene acquisition and its expression post-acquisition are tightly controlled processes.

Our research considers characteristics that define the combinatorial (or not) nature of a global gene silencing system that regulates the expression of horizontally acquired genes. What are the selective pressures that define the biochemical features of this silencing system, and the need for combinatorial control? How is the function of this gene silencing system modulated by environmental and genetic conditions? In the recent past, we had also investigated – computationally – the fates of restriction-modification systems, which are horizontally-acquired selfish elements, and the gene regulatory and / or mutational effects these systems might have on the host cell.



Unilateral genes
Lower expression in the absence of silencing syst
Loosely packed with high affinity H-NS binding si
StpA not recruited as a backup for H-NS

Epistatic genes
Higher expression in the absence of silencing syst
Densely packed with high affinity H-NS binding s
StpA backup for H-NS

1.2 σ-factor switching and the transition from growth to stasis

A fundamental mechanism of global gene regulation operates at the level of the composition of the RNA polymerase itself. The RNA polymerase comprises (a) the enzymatically active, but non-specific DNA-binding, core RNA polymerase; and (b) the replaceable SF (σ-factor), which recognises promoters and performs the initial DNA unwinding essential to initiate transcription. The *E. coli* genome encodes a major SF (σ^{70}) that is responsible for transcription from a majority of promoters. Also present are several alternative SFs, which are activated under specific environmental or cellular conditions, compete with the major σ^{70} for associating with the core RNA polymerase, and bind as a SF-RNA polymerase complex (referred to as Eσ) to specific target promoters. Thus, SF competition is a major factor in determining the transcriptional program of the bacterial cell.

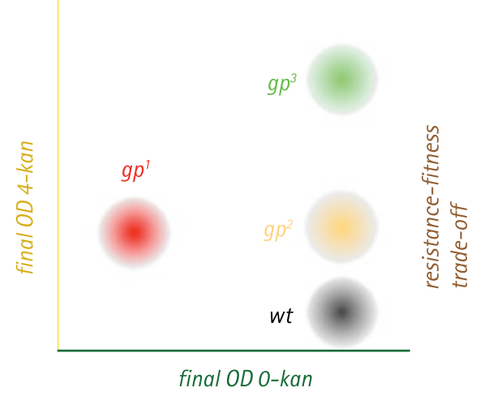
An important phenotype that is determined to some extent by SF competition is the switch between growth and stasis. Whereas growth-associated promoters are regulated by σ^{70}, those for stasis are governed by an alternative SF σ^{38}. Even during stasis, the level of σ^{38} is only a fraction of that of σ^{70}; further, the affinity of RNA polymerase to σ^{38} is much less than that to σ^{70}. Therefore, additional players are involved in sequestering either σ^{70} or $E\sigma^{70}$ to increase the chance of $E\sigma^{38}$-dependent transcription. We perform genomic experiments, alongside biochemical modelling (in collaboration with Sandeep Krishna) to examine the distinct effects that different modes of σ^{70} sequestration can have on σ-factor competition, and the transcriptional programme of *E. coli* during different stages of growth.

2 ADAPTATION TO STRESS BY MUTATION AND SELECTION

The most classical mechanism of adaptation to stress is by mutation and selection of variants best equipped to survive the stress. Identification and analysis of variants that emerge under stress is useful in many different contexts. It provides a platform to understand the biochemical processes the mutated locus is involved in; helps understand mechanisms by which the mutation affects fitness; helps understand mutational processes.

Our lab is interested in the discovery and characterisation of mutations that confer resistance to antibiotics. Bacteria gain resistance to antibiotics either by horizontal acquisition of genes that either export or detoxify the antibiotic, or by mutations in genes linked to the antibiotic targets or alternative pathways that cause cell death in the presence of the antibiotic. Since antibiotics target essential, well conserved cellular processes, many of which may tolerate mutations poorly, many resistance-conferring mutations come with a cost: i.e. the mutants fare poorer than the wildype in the absence of the antibiotic.

We are interested in mutations that confer resistance to aminoglycosides, a class of antibiotics that target the ribosome, and the tradeoff against cost in the absence of the antibiotic. What aspects of cellular function do these mutations reflect? What is the dependence of the trajectory of resistance development on the concentration of the antibiotic? Looking into the future, what are the adaptive regimes that a bacterial population would see in the face of a combination of linked or un-linked antibiotics?



We address how nucleic acid interacting proteins/ enzymes recognize and act on the genome in different physiological contexts. The biological processes under scrutiny are Replication of the Japanese Encephalitis virus genome, Stress-induced Mutagenesis/ Translesion DNA synthesis, DNA Mismatch Repair and Transcriptional Regulation.

DEEPAK T NAIR

Nucleic Acid Recognition and Metabolism

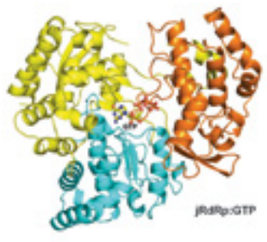
We interrogate native and mutant proteins associated with the processes under examination using structural, biochemical, biophysical tools and functional assays to elucidate the mechanism utilized by these molecules to achieve biological function.

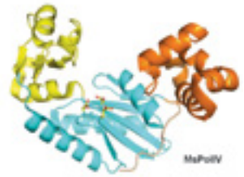
1 REPLICATION OF THE JEV GENOME

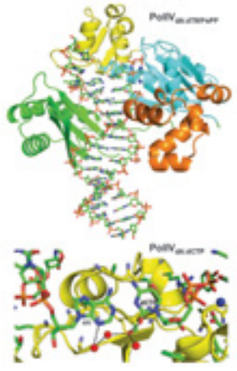
JEV is an RNA virus and is the leading cause of viral encephalitis in the world. The virally encoded NS3 and NS5 proteins form a complex that may represent the minimal replisome. The C-terminus region of NS5 houses the RNA dependent RNA polymerase (RdRp) activity that is critical for genome replication. Replication involves (i) initiation wherein the RdRP activity catalyzes *ab initio* RNA synthesis using a single-stranded RNA template to create a dinucleotide primer (ii) elongation wherein the 3'-OH on the primer is extended to generate a complement of the template strand.

Unlike DNA Polymerases, the RdRp activity of many viruses does not require a primer and can initiate synthesis *ab initio* in the presence of high concentrations of GTP. In the majority of the flaviviruses including JEV, the terminal dinucleotide sequence is 5' CU 3' and hence the requirement for GTP is surprising as GTP would be second incoming nucleotide.

The structure of JEV RdRp in complex with GTP provides a basis for the specific recognition of GTP and shows that this nucleotide binds in an unexpected conformation. Initiation and elongation assays of wt and site specific mutants of RdRp showed that the $jRdRp_{GTP}$ structure represents a previously uncharacterized pre-initiation state. In addition, binding assays showed that GTP binding reduces the affinity of RdRp for RNA but the presence of Mn^{2+} in the mix abolishes this inhibition. In the light of available data, these observations suggest that, during initiation, flaviviral RdRp molecules bind the second nucleotide GTP first, followed by RNA in the presence of Mn^{2+} and finally the first nucleotide ATP. The proposed mechanism would prevent stabilization of two nucleotides in the RdRp active site in the absence of template RNA and thus prevent non templated RNA synthesis. Thus, GTP binding may serve to temporally partition nucleotide binding on either side of RNA binding to prevent unwanted and wasteful template independent RNA synthesis that could be erroneous. The proposed mechanism will therefore enforce conservation of the terminal dinucleotide 5' CU 3' sequence. Also, the novel pre-initiation state that we have identified can be targeted by chemical therapeutics to combat the debilitating diseases caused by flaviviruses.







2 STRESS-INDUCED MUTAGENESIS AND TRANSLESION DNA SYNTHESIS

In prokaryotes, members of the Y-family of DNA Polymerases (dPols) are responsible for stress-induced and spontaneous mutagenesis. The expression of these enzymes is upregulated when the organism encounters environmental and nutrient stress. Low-fidelity DNA synthesis by these dPols generates multiple genomic templates for natural selection. This strategy allows microbes to adapt and relieve selection pressure imposed by an adverse environment. Stress-induced mutagenesis is one of the processes responsible for the appearance of multi-drug resistance strains in pathogenic bacteria. In addition to the mutator function, prokaryotic Y-family dPols can also synthesize DNA past replication-blocking damaged nucleotides (DNA lesions) and thus rescue stalled replication.

To unearth the structural and chemical strategies used by these enzymes to achieve mutagenic and translesion DNA synthesis, we are carrying out a rigorous biochemical and structural analysis of DNA Polymerase IV from *Escherichia coli* (PolIV) and *Mycobacterium smegmatis* (MsPolIV).

A. Stress-induced mutagenesis

PolIV is coded for by the *dinB* gene and is known to play an important role in stress-induced mutagenesis. It is expected that the ability of PolIV to create mutations has to be regulated to exist within an appropriate range as too many mutations can be deleterious and too few will not provide enough templates for natural selection. The structural attributes of the PolIV active site that allow calibration of mutagenesis within the correct limits are not known.

We observed that PolIV has significant propensity to incorporate the incorrect nucleotide during DNA synthesis on undamaged DNA substrates. We determined crystal structures of PolIV in its functional pre-catalytic state- in complex with substrate DNA presenting the four possible template nucleotides that are paired with the corresponding incoming nucleotide triphosphates. In addition, the structure of the ternary complex of PolIV with the dA: dCTP mismatch in the active site was also determined. These structures show that a serine residue (S42) present in the active site of PolIV forms interactions with the incoming nucleotide in the case of both matched and mismatched nascent base pairs. Biochemical experiments and functional assays showed that mutation of S42 to Ala drastically enhanced the fidelity of PolIV. Together, these experiments show that the serine residue present in the PolIV allows stabilization of the wrong nucleotide in the active in a conformation compatible with catalysis. The presence of the serine residue at a strategic location in the enzyme active represents an elegant strategy to calibrate the fidelity of PolIV to a level that will allow generation of adequate number of genomic templates for natural selection without compromising genetic viability.

B. Translesion DNA synthesis

We have determined the structure of MsPolIV in its apo- form. The experimental electron density map did not show electron density for the C-terminal domain unique to members of the Y-family– termed the PAD (Polymerase associated Domain). SDS-PAGE analysis showed that the crystals are of intact protein. The packing diagram of the crystal shows that the presence of voids and the lack of electron density suggest that the PAD region is present in these voids in multiple orientations. Consistent with this inference, dynamic light scattering and gel filtration studies showed that MsPolIV undergoes significant compaction on binding substrate DNA.

The observed conformational heterogeneity is facilitated by a flexible linker that connects the PAD to the rest of the protein. The PAD region contributes substantially to interactions with DNA as it docks into the major groove and also influences the shape of the active site housing the nascent base pair. The flexibility associated with the PAD will allow MsPolIV and its orthologs to accommodate the alterations in the width of the DNA double helix that appear due to mismatches and damaged nucleotides. The observed flexibility can thus facilitate the twin functions of translesion synthesis and adaptive mutagenesis.

SELECTED PUBLICATIONS

Surana, P., Vijaya, S. and **Nair, D. T.** (2014). RNA-dependent RNA polymerase of Japanese Encephalitis Virus binds the initiator nucleotide GTP to form a mechanistically important pre-initiation state. *Nucleic Acids Research* 42:2758

Sharma A., Kottur, J., Narayanan, N. and **Nair, D. T.** (2013). A strategically located serine residue is critical for the mutator activity of DNA Polymerase IV from *Escherichia coli*. *Nucleic Acids Research* 41:5104

Jain, D. and **Nair, D. T.** (2013). Spacing between core recognition motifs determines relative orientation of AraR monomers on bipartite operators. *Nucleic Acids Research* 41:639.

Deepak Nair is now at Regional Centre for Biotechnology, Gurgaon

http://www.rcb.res.in/index.php?param=empdetails/129

3 DNA MISMATCH REPAIR

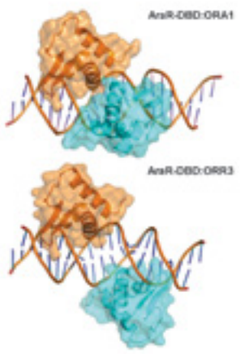
The Mismatch Repair (MMR) Pathway serves to maintain genomic integrity by correcting errors that appear during replication. In *E. coli*, the specific components of MMR are MutS, MutL and MutH. Of these proteins, MutH is a site specific endonuclease and plays a vital role in identification and creation of a nick in the newly synthesized daughter strand. The majority of bacteria and all eukaryotes lack a homolog of MutH. It is, therefore, expected that these organisms will show significant differences in MMR especially in the mechanism of strand discrimination and nick-creation.

Using the pathway from *Neisseria gonorrhoeae* as a model system, we aim to elucidate the mechanism of MMR in organisms that do not follow the *E. coli* paradigm. The MutS and MutL homologs in *Neisseria* are named NgoS and NgoL, respectively.

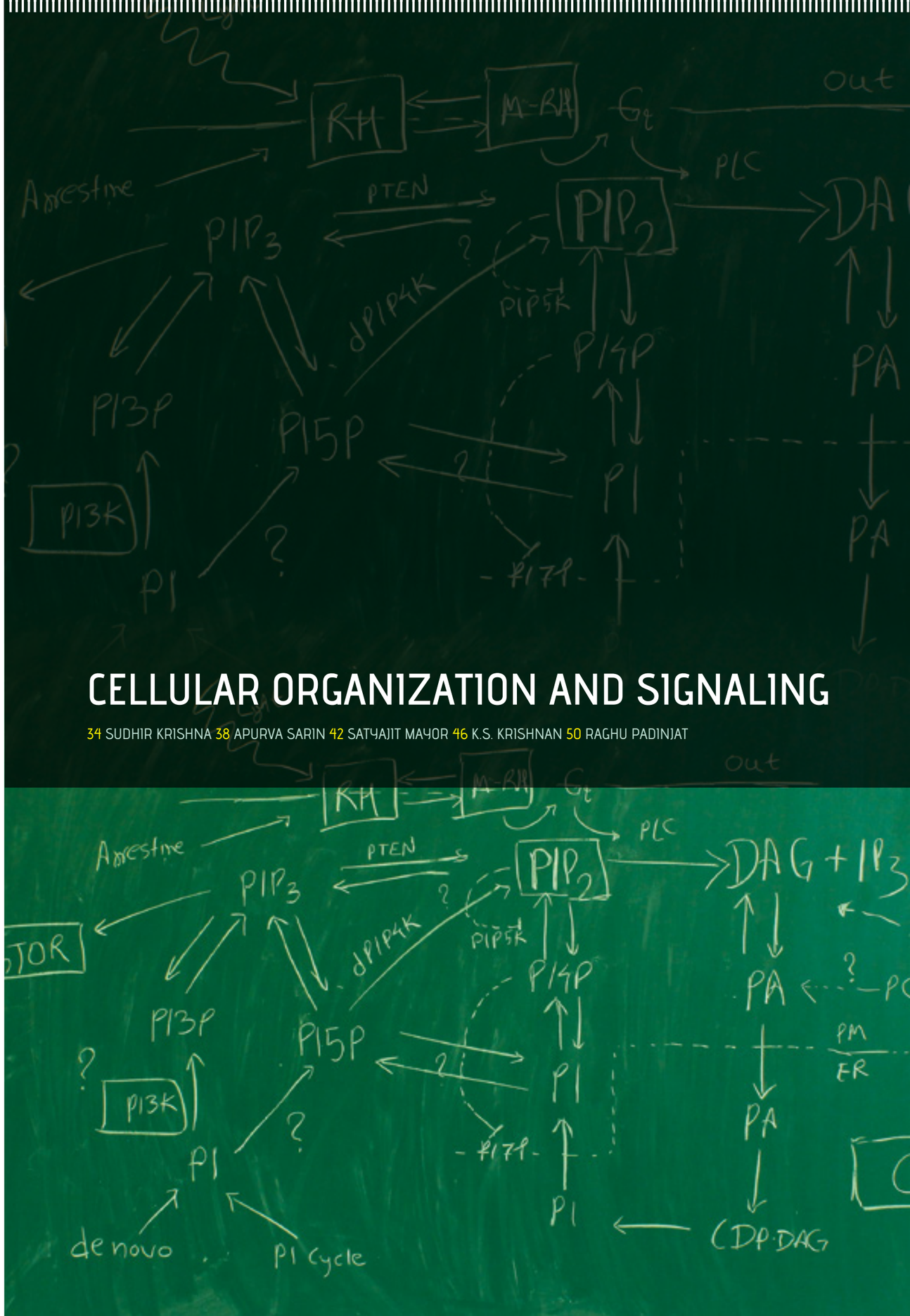
The nicking activity of NgoL is resident in its C-terminal domain. The NgoL-CTD structure enabled identification of the active site that is responsible for the creation of the nick to initiate the repair reaction. More importantly, the structure reveals that this protein forms an inverted homodimer and this dimer organization was different from that postulated for MutL-CTD. The observed arrangement of the two monomers places the two active sites on either lateral side of the protein. Homodimeric NgoL possesses two active sites but still exhibits nicking activity. The arrangement of the active sites may result in occlusion of one of them when NgoL associates with partner proteins. This will ensure that only one active site is presented to DNA. The inverted dimer arrangement will thus prevent adventitious double-stranded cleavage.

4 TRANSCRIPTIONAL REGULATION

AraR (*B. subtilis*) is a transcription factor responsible for repressing genes involved in arabinose metabolism through binding to seven different operators in the promoter region of the L-arabinose operon. AraR binds to these operators with distinct affinities that appear to be correlated with the level of repression for the corresponding gene/operon. AraR and its cognate operators provide a model system to study the relation between specificity, affinity and level of transcription modulation.



AraR binds to the two operators ORA1 and ORR3 with different affinities and the genes downstream of these operators are repressed to different levels. The crystal structures of the DNA binding domain (DBD) of AraR in complex with ORA1 and ORR3 reveal that two monomers bind to one recognition motif (T/ANG) each in the bipartite operators. The structures show that the two recognition motifs are spaced apart by either 6 bases (ORA1) or 8 bases (ORR3). This increase in the spacing between the recognition motifs results in a drastic change in the position and orientation of the AraR monomers on DNA and the shape of the nucleoprotein complex. This study suggests that variation in the spacing between core recognition motifs may be a strategy utilized by transcription modulators to optimally tune operator affinity and therefore repression of target genes.



Our current focus is on a sub-set of cd66+/Notch-high cells that are critical for the progression of human cervical cancers. We also closely work with St. John's Medical college and other medical campuses to create enabling collaborative networks in hematology and infectious diseases

SUDHIR KRISHNA

Cellular Heterogeneity and Signaling in Human Cervical Cancers

SELECTED PUBLICATIONS

Kumar, M. M., Adurthi, S., Ramachandran, S., Mukherjee, G., Joy, O., Krishnamurthy, H., **Krishna, S.**, Bafna, U. D., Uma, D. K., and Jayshree, R. S. (2013). Toll-like receptors 7, 8, and 9 expression and function in primary human cervical cancer Langerhans cells: evidence of anergy. *International journal of gynecological cancer*, 23, 184–92.

Adurthi, S., Mukherjee, G., Krishnamurthy, H., **Krishana, S.**, Bafna, U. D., Umadevi, K., and Jayshree, R. S. (2012). Functional tumor infiltrating TH1 and TH2 effectors in large early-stage cervical cancer are suppressed by regulatory T cells. *International journal of gynecological cancer*, 22, 1130–7.

Pattabiraman, C., Hong, S., Gunasekharan, V. K., Pranatharthi, A., Bajaj, J., Srivastava, S., Krishnamurthy, H., Ammothumkandy, A., Giri, V. G., Laimins, L. A., and **Krishna, S.** (2014). CD66+ Cells in Cervical Precancers Are Partially Differentiated Progenitors with Neoplastic Traits. *Cancer research*, 74, 6682–92.

Cervical cancers, a major cause of cancer associated female mortality in the developing world, is caused by high risk human papillomaviruses. Papillomavirus belong to the family of small DNA tumor viruses and the study of these agents have been extraordinarily influential in driving key concepts in cancer biology. Our laboratory for over two decades has been interested in the signals that complement the function of papillomavirus oncogenes (for review see Malliekal T. et al., Oncogene 2008) and our focus has been on the role of Notch signaling.

More recently, it is becoming increasingly clear that unique sub-sets of cells with enhanced tumorigenic functions and resistance to conventional therapy drive many tumours. The origin and nature of such cellular heterogeneity is of enormous clinical significance. However, even in extensively characterized tumours like human breast cancers, no clear consensus has emerged on the biological features including plasticity, differentiation status, mechanism of induction or evolution of metastatic characteristics in such subsets.

Our work on Notch signaling led us to identify a sub-set of cells that are CD66+ and are both dependent on this signaling pathway previous work that identified CD66+ cells as a tumorigenic subset in cervical cancers (Bajaj J. et al., Cancer Research, 2011) and has distinctive tumorigenic functions that can broadly be categorized as "cancer stem cell like". Following up on this report, we have been interested in the following questions:

i Are CD66+ cells present in human cervical pre-cancerous lesion and can we define their properties ? In particular, is there any relationship to the papillomavirus life cycle ?

ii Can the CD66+ sub-sets be further characterized by other markers and are there functional differences between these potential sub-sets that can be used to understand tumor progression and devise novel therapeutic strategies.

iii What is the role of CD66+ in radioresistance and clinical outcomes ? Can these cells be used to prognosticate or stratify human cervical cancers for therapies ?

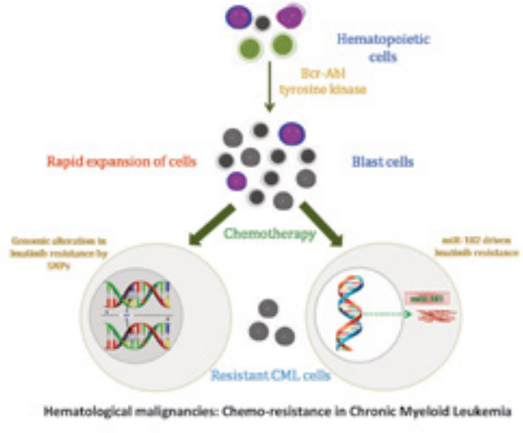
iv What is the nature of plasticity of the CD66+ sub-set ? Can we identify some of the regulators and also the relationship to pluripotency ?

Chitra Pattabiraman, A. K. Aswathy, Sweta Srivastava, Calvin Rodrigues, Leanna Rose Joy

In collaboration with Laimonis Laimin's laboratory in Chicago, we have asked if CD66+ cells are present in pre-neoplastic lesions and focused on exploring the emergence of neoplastic properties, the differentiation state of such a subset and links to the papillomavirus life cycle. In parallel we asses the induction of key regulators of keratinocyte self renewal/ differentiation by papillomavirus episomes. We have restricted our analysis in this study to HPV 31b, which belongs to the group of highly oncogenic viruses and principally use the CIN 612 cell line.

The CIN612 cell line was derived from a precursor lesion in the Laimins's laboratory and is extremely well characterized with respect to the viral life cycle and keratinocyte differentiation. The hallmark of this cell line is the ability to induce all aspects of the papillomavirus life cycle, which is differentiation dependent. Notably, this cell line has been used to define many of the cellular controls of viral replication and in addition critical cellular mechanisms to evade the immune response. Since, we were interested in using a pathophysiologically relevant reagent to ask questions about the early phase of cervical cancers, we have extensively focused this study using the CIN 612 cells.

The data in this study makes a few key observations: CD66High cells exist in early cervical precancer lesions and form the major migratory and invasive fraction of CIN612 cells. These CD66High cells also have a mixed progenitor-differentiated keratinocyte like gene expression signature. This led us to examine its relationship with the viral life cycle. We find that CD66+ cells have both higher levels of HPV DNA and a range of cellular features that have been described in cells that support viral replication including the presence of intermediate viral products such as E1^E4. The notable point in our study is that these cells are present in the basal conditions in the absence of differentiation signals. On detecting high levels of DNMT1 and Notch1, known determinants of keratinocyte self renewal, CD66High cells we find that HPV31 genomes can upregulate these molecules in primary keratinocytes. We also show a partial dependence of the neoplastic phenotypes on DNMT1. Collectively, these data link the CD66+ sub-set to the cells which selectively replicate viral replication. Based on the expression of pluripotentcy gene transcripts and the data with DNMT1 and Notch1, we speculate that these cells emerge from a reprograming mechanism.



Hematological malignancies: Chemo-resistance in Chronic Myeloid Leukemia

The other approach that we have taken principally in collaboration with the Kidwai Memorial Institute of Oncology is to analyse primary cervical cancers and cell lines. After undertaking an extensive marker analysis, we are currently focused on the relationship between CD49f in addition to CD66 in order to decipher the progressive steps to metastasis. In addition, are results are laying the foundation for improving drug therapies.

Sweta Srivastava (Research co-ordinator) and Cecil Ross

SETTING UP A BIOLOGY-MEDICINE INTERPHASE PROGRAM

- 2005 Meeting on translational research organized by S. Krishna and I. Verma (Salk Institute) initiated and supported by the Department of Biotechnology,
- 2005-2008 The planning process
- 2008-2011 Several joint courses with clinicians and scientists with a focus on hematological malignancies

BROAD GOALS:

1 Develop broad based multi-centric collaborative programs between physicians and scientists with a heavy engagement from the medical campuses. The initial effort has been to identify a broad based program in "genomics with specific relevance to hematology in the Indian context"
2 Setting up infrastructure which would allow a continuous inter-campus course structure and research program. The intermediate aim to consolidate this process would be to develop a joint PhD program with medical campuses.
3 Broaden medical research beyond the ambit of clinical trials and case studies to model organisms etc.

2011 ONWARDS:

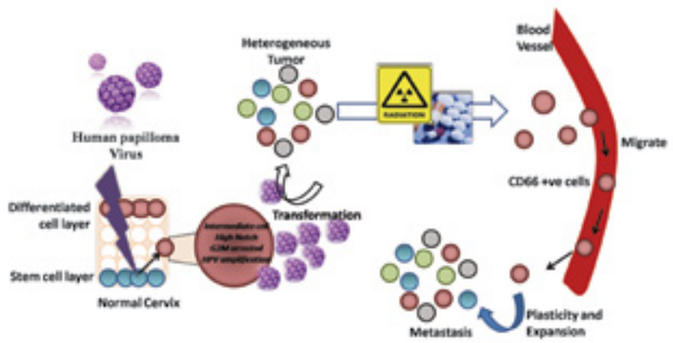
Established infrastructure for Confocal microscopy, FISH, high end flow cytometry, molecular biology and tissue culture for both research and "continuous hands on" courses in an inter-departmental setting.

HEMATOLOGICAL MALIGNANCY RESEARCH

Deepak Arya and Anita Chacko. In collaboration with R. Sowdhamini

Chronic Myeloid Leukemia has emerged as a major treatable disease using drugs such as Imatinib which are novel tyrosine kinase inhibitors. However, over time there are broadly two forms of resistance that can emerge i) due to mutations in the BCR-ABL gene and ii) abrogation of the drug response due to a possible expansion of a CML stem cell like pool.

We were interested in characterizing the stem cell like pool and also analyzing potential other mutations that might aid the generation of resistance. The two major projects underway are an analysis of microRNA 182 in the context of imatinib resistance and a longitudinal analysis of mutations using whole exome sequencing. Srinag is also engaged in a clinical platelet study in various disorders.



Human Cervical Cancer Program: CD66+ve tumorigenic subset

DEVELOPMENT OF A NATIONAL HLA REGISTRY BY NGS (DUAL SERVICE AND RESEARCH)

A major project that we have undertaken primarily with the TTK blood bank (Drs. Latha Jaganathan and Nutan Dighe) and CCAMP (Malali Gowda and colleagues) is to lay the foundation for a national HLA registry by Next Gen Sequencing. This would have a invaluable role in serving to sustain a bone marrow transplant program which is a critical need for leukemia and other therapies. In addition, this would serve to lay the stage for research in infectious disease progression, next generation vaccines etc. The NGS approach can also be used for population evolution studies and multiplexing is a useful tool to study any gene variants at a large level.

Currently, we have sequenced 80 donors with a very high quality by NGS and are aiming to lay the foundation for a one million donor registry in a multi-centric manner.

The immune system repeatedly refreshes itself, to meet new challenges, by sacrificing cells once their jobs are accomplished. We study molecular mechanisms that orchestrate decisions controlling the deletion of damaged or redundant cells, while sparing others to live on.

APURVA SARIN

Spatial Organization and Activity-Dependent Assembly of Signaling Networks

SELECTED PUBLICATIONS

Perumalsamy, L.R., Nagala, M. and **Sarin, A.** (2010). A Notch activated signaling cascade interacts with mitochondrial remodeling proteins to regulate cell survival. *Proc. Natl Acad Sci USA.* 107:6882-6887.

Perumalsamy, L.R., Marcel, N., Kulkarni, S., Radtke, F. and **Sarin, A.** (2012) Distinct spatial and molecular features of Notch pathway assembly in Regulatory T-cells. *Science Signaling5* (234), ra53. [DOI: 10.1126/scisignal.2002859]

Purushothaman, D.*, Marcel. N.*, Garg, M.*, Venkataraman, R. and **Sarin, A.** (2013) Apoptotic programs are determined during lineage commitment of CD4+ T-effectors: Selective regulation of T-effector-memory apoptosis by iNOS. *J. Immunol.* 190:97-105. *equal contribution

It is well established that cells adopt specific fates by the activation of distinct programs, but mechanisms by which cells regulate the activation of these programs in space and time to ensure tissue homeostasis are less well understood. The broad aim of my laboratory is to understand interactions between cell death and survival cues. We focus mainly (but not exclusively) on consequences to the regulation of cell number and function in mature T-cells, a cell type in the mammalian immune system. T-cells depend on extrinsic cues from growth factors and cytokine for nutrient uptake to meet metabolic needs and the integration of cytokine inputs is critical to death or survival decisions in this lineage. We employ experimental systems that recapitulate the deletion of T-cells differentiated in cell culture or following the manipulation of cells *in vivo*.

Our experiments implicate the receptor Notch in the regulation of survival with the initial analysis of ectopically expressed recombinants, suggesting that Notch signaling is initiated outside the nucleus (Perumalsamy et al., 2009). Subsequent experiments revealed that endogenous Notch assembles similar complexes in T-cell subsets protected from apoptosis triggered by metabolic stressors. Notably, Notch activity from the nucleus and the cytoplasm with distinct signaling outcomes is detected in the same cells suggesting a spatio-temporal regulation of Notch pathway assembly and activity. Our current understanding of the signaling pathway is described in the sections that follow.

1 NOTCH ACTIVITY AT THE MITOCHONDRION

Sowmya Lakshminarayanan, Lakshmi R Perumalsamy, Manjula Nagala, Nimi Marcel

The Notch proteins (3-4 isoforms in mammals) are membrane-associated receptors, which are processed, to yield signaling-competent intermediates following interactions with one of several ligands. The processed Notch intracellular domain (referred to as a NIC) localizes to the nucleus and interacts with several co-factors that regulate transcription. There is a growing appreciation from more recent experiments that Notch, like several other signaling initiators, achieves large-scale signal integration by crosstalk with other signaling hubs.

We observed Notch function at the mitochondrion in experiments where the apoptotic response triggered by a protein Bax, which activates cell death cascades, was used to report on NIC mediated anti-apoptotic activity. Bax nucleates multi-protein assemblies on mitochondria, committing cells to irrevocable mitochondrial damage. NIC-mediated anti-apoptotic activity was dependent on interactions with molecules that regulate mitochondrial remodeling and integrity, thereby revealing a novel aspect of Notch signaling (Perumalsamy et al., 2010).

Subsequent experiments using biochemical approaches suggested that Notch activity is linked to sites of association between the endoplasmic reticulum (ER) and mitochondria, referred to as ER-mitochondrial-extended structures (ERMES). Interactions between ER and mitochondria control a wide array of cellular functions and protein complexes localized at regions of proximity between the organelles are thought to mediate these interactions. This junction controls the movement of Ca^{2+} and Notch activity reduced ER (store) Ca^{2+}, thereby protecting cells from dysregulated Ca^{2+} signaling associated with cell death (Figure1). Molecules that form conduits for controlled release from ER and mitochondrial uptake of Ca^{2+} were necessary for Notch activity. Prolonged Ca^{2+} overload of mitochondria constitutes an early event in the cellular apoptotic response. We propose that as a consequence of its effect on Ca^{2+} stores, Notch activity blocked apoptotic cascades triggered by diverse stimuli. NIC mediated anti-apoptotic activity was regulated by molecules controlling functional outputs and structural integrity of the ERMES (Lakshminarayanan et al., in review). Nuclear activity of Notch was not reduced following ablation of these molecules. Taken together, these observations open up the possibility of reciprocal regulation of Notch activity in the cytoplasm and nucleus, which remain to be investigated. Modulation of the Ca^{2+} signaling landscape suggested by these experiments holds implications for Notch regulated cell-fate decisions governing differentiation

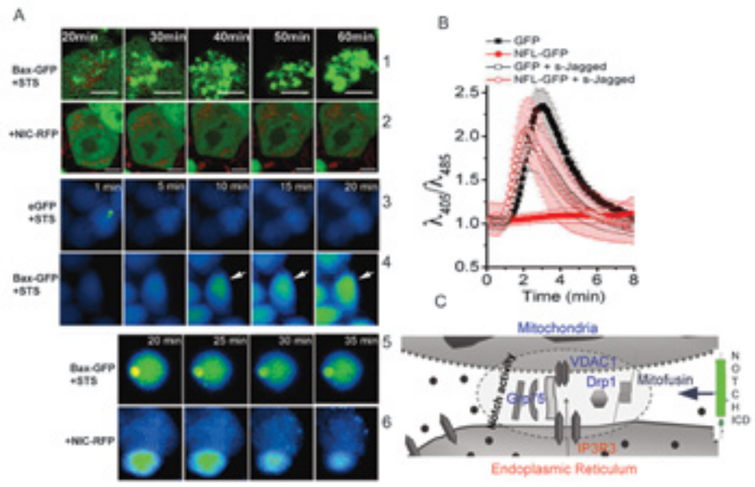


Figure 1: A, Notch regulates intracellular Ca^{2+} fluxes. Staurosporine (STS) induced oligomerization/ activation of Bax-(tagged to GFP) in HEK cells undergoing apoptosis (green in 1) is inhibited in cells co-expressing NIC (2). The Bax-induced increase in cytoplasmic Ca^{2+} (white arrows in 4 & 5), precedes Bax activation and is inhibited in cells co-expressing NIC (6). B, Passive store depletion of Ca^{2+} is inhibited in cells expressing Notch via ligand-dependent signaling. C, The schematic summarizes possible molecular interactions of NIC at mitochondria - ER contact sites, suggested by our experiments. Scale Bar 10µm

2 SPATIAL REGULATION OF NOTCH SIGNALING

Lakshmi R Perumalsamy, Nimi Marcel, Sneha Kulkarni

T-cells at all developmental stages are dependent on cytokines for the uptake of nutrients from the environment. Thus, the cellular integration of cytokine inputs is a key cell-autonomous mechanism regulating cell number in this lineage. Enforced Notch activity results in phosphorylation of the kinase Akt, and regulated cell survival in response to nutritional cues (Sade et al., 2004; Bheeshmachar et al. 2006). These studies also identified a subset of cells – T regulatory cells or Tregs - which express elevated levels of cell-surface Notch and are protected from apoptosis.

Consequently, characterization of Notch activity in activated Tregs revealed that T cell receptor (TCR) stimulation results unusually, in cytoplasmic enrichment of NIC. Essential roles for Notch activity were also indicated in mice with a targeted deletion of Notch-1 (Notch-1$^{-/-}$) in mature T-cells, (generated in the laboratory of Freddy Radtke, EPFL, Switzerland). Blocking ligand inputs attenuated survival, implicating ligand-dependent interactions in the Notch activated anti-apoptotic cascade. Intriguingly, interactions with canonical co-activators of Notch mediated transcription were not required for Notch mediated anti-apoptotic activity. Notch activity was compromised by the depletion of the nutrient sensor kinase mammalian Target Of Rapamycin (mTOR) or the protein Rictor, which constitute the mTORC2 complex. Biochemical and imaging approaches provided the first evidence of an intracellular, ligand-dependent, membrane-proximal assembly of NIC and Rictor specifically present in cell populations protected from apoptosis (Figure 2).

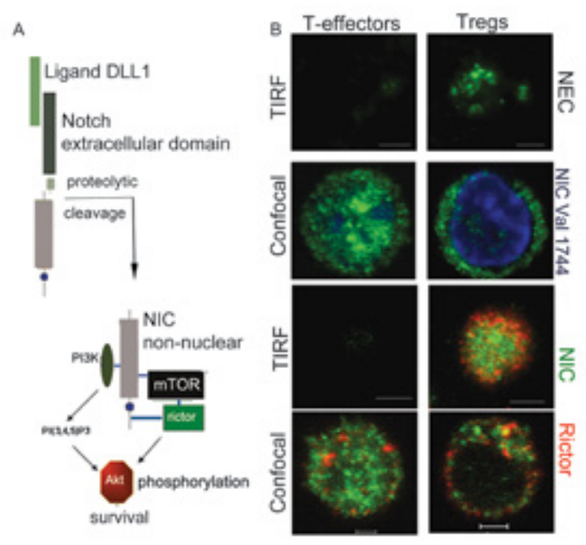


Figure 2: A, schematic summarizing non-nuclear Notch signaling in Tregs (adapted from Perumalsamy et al., 2012). B, Differences in the spatial distribution of the Notch receptor, its processed form (NIC Val1744) and associated proteins' (Rictor) in T-cell subsets. TIRF microscopy revealed membrane-proximal organization of NIC and Rictor (red) in Tregs. Confocal microscopy revealed distinct patterns of the cellular distribution of NIC, the processed intermediate (NIC Val 1744) and Rictor in the two subsets. Scale Bar 2µm

3 NOTCH - mTORC1 INTERACTIONS ACTIVATE AUTOPHAGY FOR SURVIVAL

Nimi Marcel

Autophagy is an evolutionarily conserved pathway, triggered by nutrient deprivation that results in the degradation of cytoplasmic proteins, macromolecules, and organelles and serves as a cell survival mechanism during starvation. We investigated the interaction of NIC signaling and autophagy since inhibiting autophagy by chemical or genetic intervention ablated Tregs survival. An increase in LC3II (Light Chain 3, marker of autophagy) was observed within 6 hours of cytokine withdrawal as also an increase in the Autophagy related protein 5 (ATG5) implicated in the formation of the double membrane-bound autophagosome. In contrast to the observations in Tregs, modulating autophagy did not regulate apoptosis in T-effectors although the machinery for this process is present in T-effectors. However, a non-nuclear recombinant form of activated Notch (NIC-NES) when expressed in T-effectors imparted protection from apoptosis via the activation of autophagy. To explore the consequences of the interplay between Notch signaling and autophagy, we analyzed the status of mitochondrial activity and organization in T-cell subsets undergoing nutrient stress.

Mitochondrial function and outputs are fundamentally required to provide optimal cellular bioenergetics and constitute metabolic signaling centers. Mitochondrial organization was assessed by imaging live cells by confocal microscopy or florescence recovery after photo-bleaching (FRAP) analysis of mitochondria marked using organelle-specific dyes. Tregs are characterized by tubular, contiguous mitochondria when compared to T effectors or Notch1$^{-/-}$ Tregs, which have short, discrete mitochondria. Mitochondrial architecture remained tubular and fused in Tregs following nutrient deprivation whereas this resulted in organelle fragmentation in T-effectors and Notch1$^{-/-}$ Tregs. Mitochondrial trans-membrane potential (MTP), is an indicator of organelle metabolic activity and this was compromised in Tregs treated with inhibitors of autophagy. In nutrient-replete conditions, inhibiting Notch signaling in Tregs by abrogating inputs from ligand also resulted in lower MTP, suggesting a link between Notch activity and mitochondrial function.

The nutrient sensing mTORC1 (mTOR and Raptor) complex is a well-characterized regulator of autophagy and prompted the exploration of possible integration of Notch signaling with mTORC1. Induction of autophagy in response to nutrient deprivation was preceded by Notch independent reduction of mTORC1 activity. Intriguingly, this was followed by a Notch dependent restoration of mTORC1 activity at a later time point (24 hours post neglect) in cells held in culture conditions. Further, perturbation of Notch signaling in nutrient replete conditions, abrogated mTORC1 activity. Consistently, mTORC1 activity was substantially reduced in Notch1$^{-/-}$ Tregs held in nutrient/cytokine replete conditions. These data indicate a complex interaction of the cellular nutrient-sensing machinery (mTORC1) with Notch activity.

Together, these studies reveal a coupling between the localization of Notch and diverse intracellular signaling pathways that may impinge on cellular processes accompanying development and/or self-renewal in adult tissues and the possible regulation of cellular processes by metabolic signals.

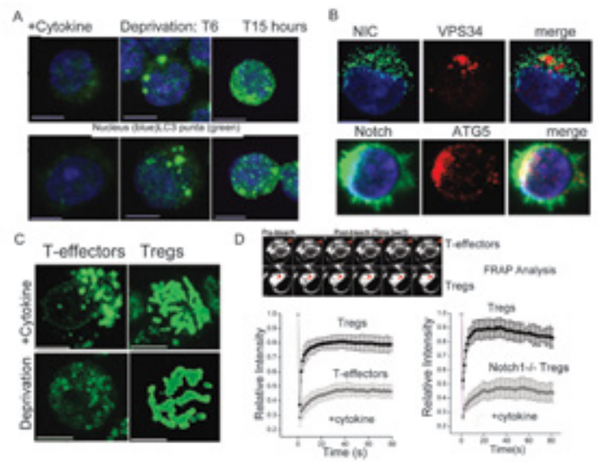


Figure 3: A, Increase in LC3 puncta over time in Tregs following cytokine withdrawal. B, The activation of autophagy is indicated by the distribution of Vps34 (probed with PX- mCherry) and induction of Atg5 in Tregs following cytokine withdrawal. Tregs were counter-stained for NIC or Notch1 in the upper and lower panel respectively. C, Mitochondria stained with an organelle-specific probe in T-cell subsets. D, FRAP analysis to assess mitochondrial contiguity in T-effectors and Tregs from wild-type and CD4^{+} Notch1$^{-/-}$ mice. Scale Bar 2µm

We study how the cell builds functional signaling complexes and responsive endocytic platforms. Our laboratory's goal is to uncover physico-chemical rules and principles that govern local regulated organization of the cell membrane, and connect this to cell and organismal physiology.

SATYAJIT MAYOR

Mechanisms of Membrane Organization and Endocytosis

To study phenomena at the cellular scale, we engage the tools of physics, chemistry and genetics to discover rules and principles governing the behavior of molecules and materials in living systems. We continue to develop numerous microscopy tools to study organization of cellular components, from the nanometer scale in specialized domains in cell membranes to the micron or larger scales prevalent in mapping endocytic pathways, and in tissue patterning.

The trajectory of this work has led us to explore the fine structure of the plasma membrane, providing for the first time an understanding of how lipidic assemblies may form in the membrane of cells, generating a new understanding of how membrane rafts are created. Our studies provide a compelling picture of the cell membrane as an active composite of the lipid bilayer and a dynamic cortical actin layer beneath, wherein, dynamic actin filaments help in controlling the local composition of membranes, and shaping endocytic trafficking.

We are now involved in several specific lines of inquiry. These include:

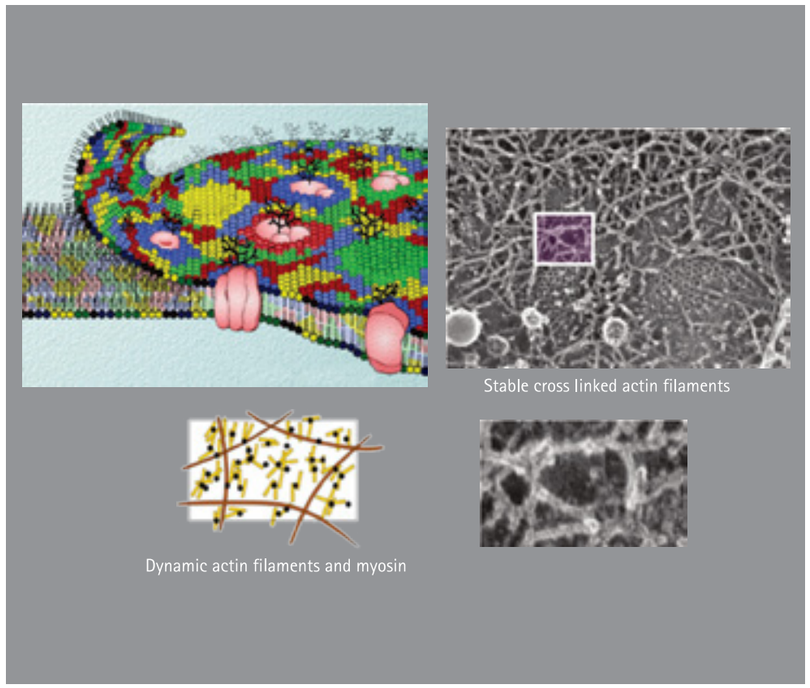
SELECTED PUBLICATIONS

Gupta, G. D., et al. (2014). "Population distribution analyses reveal a hierarchy of molecular players underlying parallel endocytic pathways." PLoS One **9**(6): e100554.

Mayor, S., R G. Parton, and J G. Donaldson, Clathrin independent pathways of endocytosis, in *Endocytosis*. Cold Spring Harb Perspect Biol. 2014 Jun 2;6(6). pii: a016758. doi: 10.1101/cshperspect.a016758.

Madan Rao and Satyajit Mayor, Active organization of membrane constituents in living cells. Curr Opin Cell Biol. 2014 Aug;29:126-32. doi: 10.1016/j.ceb.2014.05.007. Epub 2014 Jun 27.

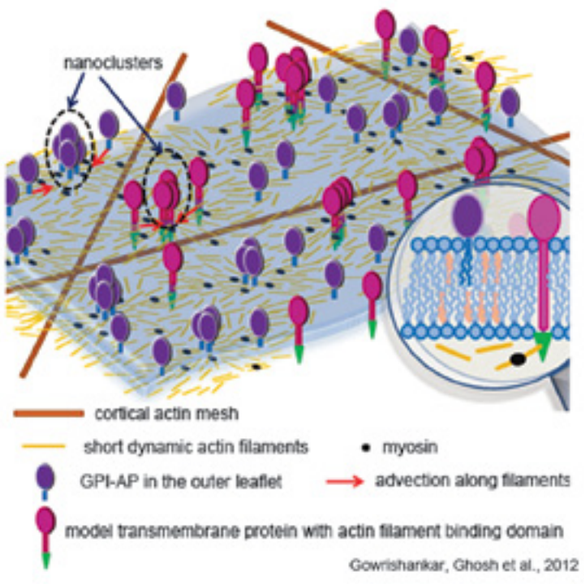
Figure 1: Cell membrane juxtaposed to dynamic cortical actin



1 EXPERIMENTAL AND THEORETICAL STUDIES ON THE FORMATION OF MEMBRANE DOMAINS IN LIVING CELLS.

In collaboration with Madan Rao (Page 116), we had shown that there is an unexpected organization of specific lipids, lipid-tethered proteins and membrane proteins at the cell surface in the form of small dynamic nanoclusters. This had suggested non-equlibrium mechanisms for their formation. The existence of nanoclusters of specific lipids and lipid-tethered proteins such as GPI-anchored proteins and the Ras family proteins depend on the composition of the membrane (cholesterol levels). In addition, nanoclusters of these molecules as well as specific transmembrane proteins require an active actin cytoskeleton at the cell cortex for their existence. We now understand this organization in terms of a theoretical framework based on active mechanics. This framework envisages the presence of dynamic filaments of actin associated with myosin motors, closely juxtaposed to the membrane, continuously applying stresses on the membrane (Figure 1). This configuration of dynamic actin results in small contractile actin platforms, which in turn pattern membrane components associated with actin (see Figure 2).

Figure 2: Contractile actin platforms (asters)

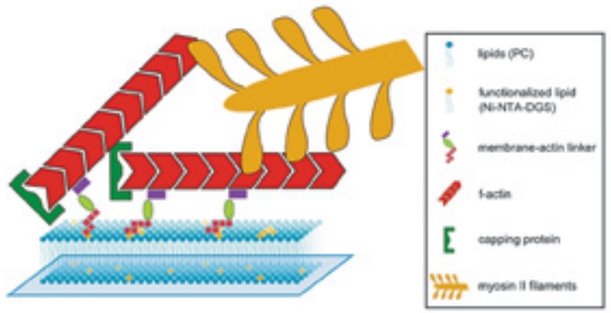


For membrane proteins that may bind actin, the connection to actin is of course, direct. For many other membrane molecules, such as GPI-anchored proteins, located at the outer leaflet there must be a transbilayer connection with molecules at the inner leaflet to link up with cytoplasmic actin. To experimentally test and validate the hypothesis of a transmembrane linkage, we collaborate with synthetic organic chemist (Ram Viswakarma at IIIM Jammu) to create synthetic variants of GPI-anchors and other lipids. To explore how molecules at the upper leaflet of the membrane bilayer connect to cytoplasmic actin and other proteins at the inner leaflet we build molecular dynamic simulations of plasma membrane lipids in asymmetric bilayers. Results from these studies, together suggest that trans-bilayer connections in membranes in the liquid disordered phase are established by the interdigitation of long acyl chain containing lipids, and by their immobilization at one or the other leaflet. Our goal here is to understand the mechanism of the transbilayer connection in living cells, and its consequence for the construction of membrane lipid domains.

2 *IN VITRO* RECONSTITUTION OF ACTIN AND MYOSIN-DRIVEN MEMBRANE COMPOSITION.

To appreciate the role of the dynamic actin filaments and myosin motors in membrane organization, as uncovered in *i)* above, we attempt to reconstruct this active composite, composed of a fluid bilayer and a thin film of active acto-myosin. Using minimal ingredients believed necessary for reconstitution of this membrane actin composite (Figure 3), we explore a rich phase space of actin and myosin configurations that result from the reconstituted membrane-linked actin filaments advected by myosin. These configurations are a function of filament concentration and length and in one specific region of this phase space support a remodeling steady state. This remarkably recapitulates key features of membrane organization that we have previously only observed at the surface of living cells. This reconstitution will also provide a link between experiments and the theoretical framework developed in *i)* above to fully develop an active composite model of the cell surface.

Figure 3: *in vitro* reconstitution of active actin membrane composite



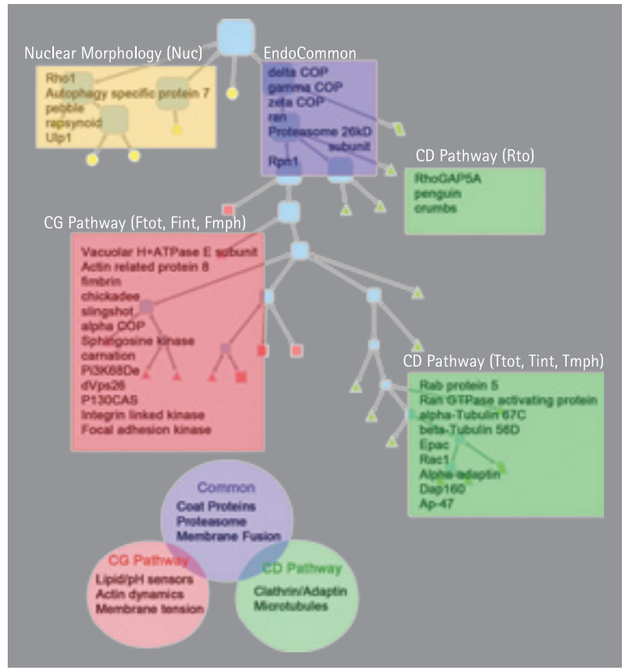
3 EXPLORING THE DYNAMICS OF MEMBRANE COMPLEXES DURING SIGNALING AND TEMPLATED DIFFERENTIATION IN MULTIPLE CELL SYSTEMS, INCLUDING STEM CELLS

We explore the construction of specific functional signaling systems such as the T Cell receptor complex (in collaboration with Ron Vale, UCSF USA), the integrin receptor and the acetylcholine receptor (in collaboration with Francisco Barrantes, Buenos Aires, Argentina). Here we study the construction of these receptor systems in experimentally tractable contexts where the ligand is presented on a controlled manner on a membrane bilayer surface to the receptor in its native cellular context. We monitor changes in signaling output in conjunction with the organization of the membrane molecules and determine their relationship(s) with both constitutive and triggered actin dynamics at the plasma membrane. Using rules and principles uncovered in *i)* and *ii)* above, we perturb these systems in specific ways to probe the logic of the changes that we are able to visualize. In the integrin-signalling system we also explore the role of these membrane mechanisms in the context of integrin function in stem cell fate determination.

4 UNCOVERING THE MOLECULAR MECHANISM OF DYNAMIN-INDEPENDENT ENDOCYTOSIS TO STUDY ITS REGULATION AND EVOLUTION

Using cell-based assays at the individual gene scale and genome wide-RNAi screening methods, we have uncovered a rich haul of molecular players that regulate clathrin-dependent (CD) versus clathrin-independent (CLIC/GEEC: CG) endocytosis (Figure 4). To study the assembly of an endocytic platform necessary for the CG pathway we have set up a TIRF based assay system that allows the detection of the endocytic event simultaneously with the recruitment of specific molecular players potentially involved in the same. These studies will contribute to a systematic understanding of the endocytic machinery responsible for the ubiquitous CG pathway. In collaboration with Mukund Thattai (Page 112), we are also using phylogenetic signatures of the set of genes that contribute to endocytosis to study the evolutionary antecedents of this pathway in the context of eukaryotic evolution.

Figure 4: Heirarchical Organization of Endocytic Players



5 UNDERSTANDING FUNCTIONAL ROLE(S) OF CLATHRIN AND DYNAMIN INDEPENDENT ENDOCYTIC PATHWAYS IN CELL AND ANIMAL PHYSIOLOGY;

The existence of a number of distinct endocytic pathways raises questions about the functional significance of these ubiquitous cellular processes at the level of cells and the context in which cells locate themselves. Given the identity of the molecular players that influence the CG pathway and the nature of the early endocytic carriers produced, we propose that this predisposes the CG pathway to act as a sensitive regulator of membrane tension or area homeostasis. We plan to verify this hypothesis in our laboratory. To examine these questions we study the effect of the physical environment (stiffness and tension) on endocytosis. To understand how the CG pathway may play a functional role in a metazoan, we also explore if this pathway is involved in the development of the wing epithelium in *Drosophila*. We find that the CG pathway plays a major role in regulating the supply of the secreted Wingless protein to its native receptor, dFrizzled. We are interested in the detailed mechanism whereby the CG pathway intersects with Wingless signaling, and examining the broader implications of these findings, considering that the CG pathways may be sensitive to a distinct set of external inputs in comparison to the CD pathway.

6 UNDERSTANDING THE SCALES OF ORGANIZATION IN THE FUNCTIONING OF LIPID-TETHERED MORPHOGENS IN PATTERNING TISSUES IN SITU

We extend our earlier work studying the organization of the dually lipid-modified Hedgehog protein (Hh), an important secreted morphogen. We had found that Hh formed nanoscale oligomers that were necessary for its long-range signal transduction. Our recent work explores the nature of the signaling vehicle that requires the formation of the Hh oligomer. Available evidence from our laboratory suggests Hh forms oligomers that enter into secreted vesicular carriers similar to *exosomes*. We visualize the nature of the particles that carry Hh, as well as study functional consequences of the perturbations we can make on the assembly of Hh into the exovesicle both in a cell culture system and in *Drosophila* wing imaginal discs where the Hh structures are involved in tissue patterning.

Our research is aimed at identifying peptides of therapeutic value from venoms of carnivorous marine cone snails and wasps as well as the skin secretions of frogs. We use a combination of molecular biology and mass spectrometry towards this end.

KS KRISHNAN

Cell Biology of the Synapse

The interest is to identify and characterise new neuro-active compounds from a variety of organisms. These include venoms of Marine cone snails, frog skin secretions and wasp venoms. The highly toxic cono-peptides from Conus, once characterised, could be exploited as pharmacological tools in neuroscience, cell biology and in search for drugs to treat many debilitating diseases. We have isolated many novel peptides from a few cone snail species collected off the shores of South Eastern India and TIFR. Mass spectrometry-based de novo sequencing of venom components combined with deep sequencing RNA from the venom glands and validation by chemical synthesis is our main thrust. We have started identifying and characterising peptides of therapeutic value from wasp venoms and frog skin secretions. We are developing several assays mainly utilising the power of *Drosophila* genetics, Oocyte expression of specific channel proteins and cell biology to establish protocols for activity dependent purification of peptides that could be drug leads. These studies are done in collaboration mainly with Prof. Balaram at IISc. I also actively collaborate with colleagues at IISc (S Sarma, Hanumae Gowd), colleagues at NCBS (MK Mathew, S. Mayor), GKVK (Chandrasekhara Krishnappa), North Orissa (Sushil Dutta) and Trinity College Dublin (Mani Ramaswami).

SELECTED PUBLICATIONS

Gupta, K., Kumar, M., Chandrashekara, K., **Krishnan, K.S.** and Balaram, P. (2012) Combined electron transfer dissociation-collision-induced dissociation fragmentation in the mass spectrometric distinction of leucine, isoleucine, and hydroxyproline residues in Peptide natural products. J Proteome Research, 11(2):515-22.

Krishnan, K.S, Ramaswami, M. and Wu, C.F. (2012) Obaid Siddiqi at 80 and neurogenetics in India. J Neurogenet. (3-4): 255-6.

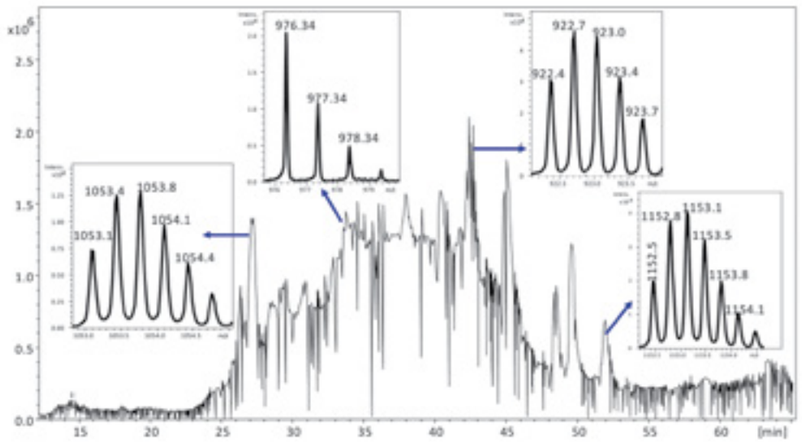
Sanyal, S. and **Krishnan, K.S.** (2012) Genetic modifiers of comatose mutations in *Drosophila*: insights into neuronal NSF (N-ethylmaleimide-sensitive fusion factor) function. J Neurogenet. (3-4):348-59.

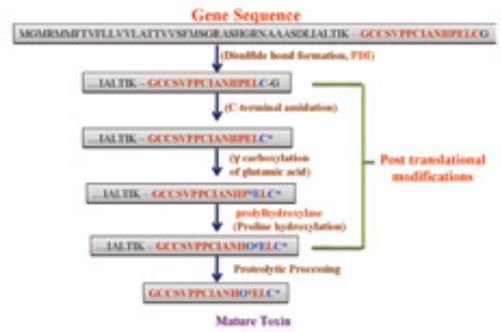
KS Krishnan passed away on 24th May 2014. His enthusiasm for science and his presence will be greatly missed, especially by the Wildlife and Chemical Ecology group for which he was a mentor.

1 DECONVOLUTION OF PEPTIDE TOXIN LIBRARIES THROUGH MASS SPECTROMETRY BASED VENOM DUCT TRACSRIPTOMICS

K S Krishnan,Sam Kuruvila,Shashank Rao (NCBS) in collaboration with P Balaram, Kallol Gupta,MV Sarathy (IISc)

Next Generation DNA Sequencing (NGS) based venom duct transcriptome analysis and mass spectrometry of crude venom have been effectively used to predict and confirm sequences of several venom peptides and their post translational modifications. NGS derived transcriptome library provides only information about the complete, unmodified, polypeptide sequence, but not the ubiquitous Post-Translational Modifications (PTMs) or di-sulphide linkages while LC–MS profile will contain masses of mature toxin peptides. Figure 1 shows LC-MS profile of crude venom from *Conus amadis* where several peptides can be easily recognized. We have used in-house developed programs to seek out di-sulphide rich cono-peptides from all the possible frames of translation of contigs from the deep sequence data. In addition using other programs developed in the lab such as "Disconnect" and "Venome" we have been able to rapidly determine more than 200 unique toxin sequences and over 150 PTM sites. Figure 2 profiles a protocol of analysis of one identified sequence and its various post-transcriptional modifications. Table 1 summarises the results of a de-convolution exercise with a single Amadis specimen.





Representative Set of Sequences Identified by Mass Spectrometry of the Venom

Gene Predicted Sequence	Found Sequences	Mass (Da)	GCCGAIWACAWAGCRPCCG	GCCGAIWACAWAGCRPC[E*]	1183.48
GCCSVPPCIANHPELCG	GCCSVPPCIANHP[ELE*]	1680.65	CCKYGWTCWLGCSPCCG	CCKYGWTCWLGCSPC[CE*]	1820.60
	GCCLVPPCIANHPELE*	1636.66	CIPQIVEPCDMLRHTCDGLCVLVC	CIPQIVEPCDMLRHTCDGLCVLV	2931.31
	GCCLVPPCIANHPELCG	1738.65	L	VCL	
	CCSVPPCIANHPELE*	1623.62		CIPQIVEQCDMLRHTCDGLCVLV	2947.30
	CCSVPPCIANHPELL*	1579.64		VCL	
DCCSRPPCRWSHPELCS	DCCSRPPCRWSHPELCS	1970.76	ALIEQICITNKYEPCDMLRHTCCT	ALIEQICITNKYEPCDMLRH	3868.66
	DCCSRPPCRWSHPELCS	2014.75	GLCVLIVEL	TCCTGL	
RPECCSHPACNVDHPEICR	RP[ECCSHQACNVDHQEIC	2124.74	TYDCGGWPCEITGCCRIIDGKEKCRE	TYDCGGWPCEITGCCRIIDGKEK	3156.39
	RP[ECCSHQACNVDHQEIC	2080.74	IDCD	CREIDCD	
	RP[ECCSHQACNVDHPEIC	2064.75	CRTVGRPCHYSAQCCSIFCAHTIS	CRTVGRPCHYSAQCCSIFCAH	3828.59
	RP[ECCSHPACNVDHPEIC	2048.75	NFYYYIKRCS	TSNYYYYIKRCS	
	RPECCSHPACNVDHPEIC	2034.76		CRTVGRQCHYSAQCCSIFCAH	3844.60
GCCPVPPCIANHPELCG	GCCPVQQCIANHPELC*	1738.65		TSNYYYYIKRCS	
GCCTVPPCIANHPELCG	GCCTVPPCIANHP[ELE*]	1695.65	GCTWWIFGRCAEDGECCSNYECDQIY	GCTWWIFGRCA[EDGECCSNS	3772.35
	GCCTVQQCIANHP[ELE*]	1742.65	YCELNAFPS	CDQIYYCELNAFQS	
RPECCDHPACNVSHPEIC	RPECCDHQACNVSHQEIC	2142.78		RGCTWWIFGRCA-EDGECCSN	3728.36
SRCCGYWLESHPCG	SRCCGYWLESHQC*	1344.44		SCDQTYYCELNAFQS	
RNCCRKWDCCG	RNCCRKWDCC*	1221.49	GHWGECKDGLTTCLAPSECCSED	GHW[GECKDGLTTCLAQSECC	3741.82
	RNCCRKWDCC	1222.48	CDGRSCAWW	TE[DCDGRSCAWW]	
RCCPITYFCDKLIGG	RCC[ITYFCDKLIG*	1344.58		GHW[GECKDGLTTCLADSECC	3697.83
	RCC[ITYFCDKLIGC	1423.60		SS[DCDGRSCAWW]	
GELELFLCPFFCIGGIGDEYCDCQE	GELELFLCPFFCIGGIGDEYCDCQE	2795.12	CKDAGESCDIFSQNCCVDTCAFRD	CKDAGESCDIFSQNCCVDTCAF	3764.88
	AGELELFLCPFFCIGGIGDEYCDCQE	2864.16	Q	ICKQ	
DDTTD-A-A-A-GELELFLCPFFCIGGIGDEYCDCQE	AAGELELFLCPFFCIGGIGDEYCDCQE	2937.19		CKDAGESCDIFSQNCCVDTCA	2808.87
	AAAGELELFLCPFFCIGGIGDEYCDCQE	3008.23		FICKQ	
	DDTDAAAGELELFLCPFFCIGGIGDEYC	3454.36		RCKDAGESCDIFSQNCCVDTCA	2920.18
	DCQE			FICKQ	
	DDTDAAAGELELFLCQFFCIGGIGDEYC	3470.36	CADQEERCNYAEIDCCETGCDNGY	NOT FOUND	
	DCQE		CKDAGESCDIFSQNCCVDTCAFRD	CKDAGESCDIFSQNCCVDTCAF	3733.88
GCEPALACAWGCRPCCG	GCCPALACAWGCRPC*	1550.51	P	ICIP	
	GCCQALACAWGCRPCC	1566.51		CKDAGESCDIFSQNCCVDTCAF	2749.87
				ICIQ	

2 CHARACTERIZATION OF BIOACTIVE PEPTIDES FROM FROG SKIN SECRETIONS

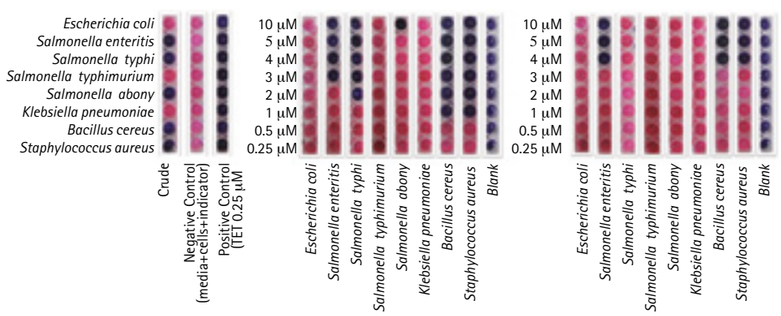
K S Krishnan, Jissa Krishna, P Balaram, IISc and Sushil Dutta, IISc

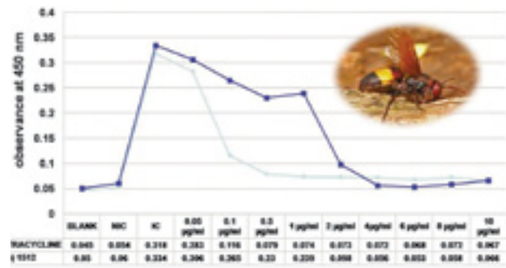
Eleven and ten residue peptides with the sequence EPQSEPRVVWA (UG1298) and DEENAVSRQD (UG1162) have been characterized from the frog *Uperodon globulosus* collected from North Orissa, after HPLC purification and Masspectrometry. The sequences of UG 1298 and UG 1162 were further confirmed by the solid phase peptide synthesis. Results of antibacterial assay with resazurin indicator are shown in Figures 1, 2 and 3.

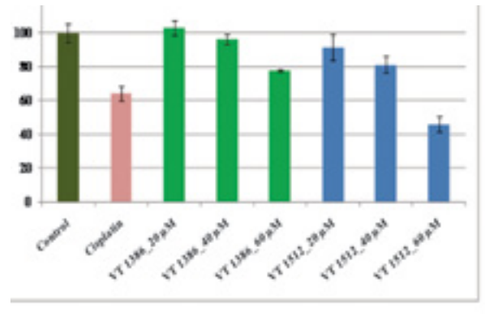
3 PEPTIDE COMPONENTS OF WASP VENOMS

K S Krishnan, Mukesh Kumar, Jissa Krishna, K Chandrasekhara

The crude venom extracts of *Vespa tropica* were subjected for purification using HPLC and MALDI and ESI MS/MS for the structural characterization. The following are the sequences isolated from *Vespa tropica*, Vt1512 INLKAIAALAKKIF-NH_2, Vt1386 FLPVIAKLLGGLF-NH_2, Vt1398 ILKAIAALAKKIF-NH_2, Vt1239 LPVIAKLLGGLF-NH_2, Vt898 INLKAIAL, Vt1013 FLPVIAKLL, Vt813 INLKAIAA, Vt900 FLPVIAKL, Vt659 FLPVIA. The sequences Vt1512 and Vt1386 were then chemically synthesized used for biological activities. Antimicrobial activity was estimated by standard *zone of inhibition* assay, against standard bacterial strains. Concentration dependent growth inhibitory assay of wasp toxin Vt1512 against *S. aureus* indicates cooperativity (Figure 1). Anticancer property of two peptides VT1512 and VT1386 against human cervical cancer cell lines, were tested by an MTT assay (Figure 2).







4 A FUNCTIONAL ASSAY FOR ANALGESIA WITH *DROSOPHILA MELANOGASTER*

(KS Krishnan, Sam Kuruvila)

We have generated UAS-SCN9A transgenic lines in the w^{1118} strain of *Drosophila melanogaster.*
A total of 10 transgenic lines were generated:
a) 2 lines with transgene insertion on the X chromosome
b) 5 lines with insertion on the 2nd chromosome
c) 3 lines with insertion on the 3rd chromosome

These transgenic lines have been crossed to Gal4 driver strains that would
1) Constitutively express the human SCN9A in the whole body of the fly (Tubulin-Gal4 driver on the 3rd Chromosome)
2) Only in the nervous system of the fly (ELAV-Gal4 drivers on the 2nd and 3rd Chromosomes)
3) Or more specifically to overlap the expression of the endogenous *para* protein (four para-Gal4 drivers on the 3rd Chromosome)

These transgenic Gal4 strains have been mated to the *para* ts1 mutant strain to score for rescue of the loss of function mutation. The results of the paralysis profiles are encouraging with some lines showing complete and others partial rescue of paralysis. These sensitized lines after they stabilize will be used for screening activity of prospective analgesic molecules.

We study cellular communication mediated by phosphoinositides. These lipid signals provide molecular control to orchestrate basic cellular behaviours such as cell division, shape changes, polarized movement and cell death. The overall goal is to understand how the architecture of this signalling cascade is designed to optimally deliver physiological outputs.

RAGHU PADINJAT

Architecture of Phosphoinositide Signaling systems

SELECTED PUBLICATIONS

Gupta, A, Sarah Toscano, S, Trivedi, D, Jones DJ, Mathre S, Clarke J, Georgiev P, Divecha N and **Raghu P**. (2013) Phosphatidylinositol 5-phosphate 4-kinase (PIP4K) regulates TOR signalling and cell growth during *Drosophila* development. *Proc.Natl.Acad.Sci.USA* Apr 9;110 (15):5963-8

Raghu, P., Yadav, S and Mallampati, N. (2012) Lipid signalling in *Drosophila* photoreceptors. Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids. Vesicular Transport. 1821(8):1154-65.

Georgiev, P., Okkenhaug, H, Drews, A, Wright, D., Flick, M, Lambert, S, Oberwinkler, J and Raghu, P (2010). TRPM channels mediate zinc homeostasis and cellular growth during *Drosophila* larval development. Cell Metabolism. 12, 386–397

Our long term scientific interest is the analysis of signalling mediated by lipid molecules generated during phosphoinositide metabolism. Phosphoinositide signals provide molecular control for key sub-cellular processes such as membrane remodelling, cytoskeletal function, transcription and translation. Through these processes, this signalling pathway orchestrates basic cellular behaviours such as cell division, shape changes, polarised movement and cell death. Therefore, this pathway plays a key role in a number of physiological processes including early embryogenesis, lymphocyte development and function as well as neuronal activity. The overall goal of our work is to understand how the architecture of this signalling cascade is designed to optimally deliver physiological outputs. We use *Drosophila* as our model system; the objective is to discover key principles of signal transduction that are likely to be conserved during evolution but are experimentally more tractable in *Drosophila*. It is hoped that in the medium term, our analysis in *Drosophila* will inform studies of equivalent signalling pathways in mammalian models with more immediate biomedical relevance.

Regulation of phosphatidylinositol 4,5 bisphosphate [PI(4,5)P_2] levels at the plasma membrane

The hydrolysis of the minor membrane lipid PI(4,5)P_2 by phospholipase C (PLC) isoenzymes is a conserved signalling mechanism used by animal cells. Despite the widespread use of PI(4,5)P_2 as a signalling substrate, its levels in animal cells are stable and demonstrable changes in PI(4,5)P_2 levels during normal cell signalling are at best minimal. In order to tightly regulate PI(4,5)P_2 levels, it is essential for cells to closely match the rate of PI(4,5)P_2 re-synthesis with its consumption by PLC activity. A major mechanism that contributes to PI(4,5)P_2 re-synthesis is the sequential phosphorylation of phosphatidylinositol (PI) by PI and phosphatidylinositol phosphate (PIP) kinases. Although the activities of the enzymes that catalyze these reactions *in vitro* have been described, relatively little is known about their activities *in vivo* and the molecular mechanisms that co-ordinate the activities of these kinases with ongoing PI(4,5)P_2 hydrolysis is obscure.

We study this question in the context of G-protein coupled PLC activity using *Drosophila* photoreceptors as a model system (Hardie and Raghu, 2001) that offer a number of specific advantages for this work. In addition to being tractable to sophisticated molecular genetics, the sensory transduction cascade in fly photoreceptors uses G-protein coupled PI(4,5)P_2 turnover to transduce the detection of light and under conditions of bright light these cells experience high levels of PLCβ activity but see limited depletion of plasma membrane PI(4,5)P_2. Thus photoreceptors offer an excellent system to study the regulation of plasma membrane PI(4,5)P_2 levels. We are using a combination of molecular genetics, live-cell imaging and electrophysiology to study *Drosophila* photoreceptors.

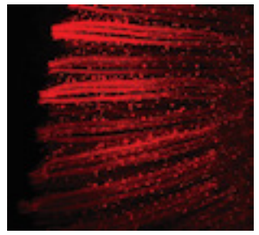


Figure 1: Longitudinal section of *Drosophila* photoreceptors stained for rhodopsin 1 showing the plasma membrane and endocytic pools of this protein.

1 UNDERSTANDING PI AND PIP KINASE FUNCTION IN PHOTOTRANSDUCTION.

My group has been focussed on identifying the PIP kinase(s) (Hinchliffe et al., 1998) that regulate PI(4,5)P_2 synthesis during *Drosophila* phototransduction. These are the enzymes that perform the last step in the synthesis of PI(4,5)P_2. The completed *Drosophila* genome contains two genes that encode phosphatidylinositol-4-phosphate 5 kinase (PIP5K) activity and one phosphatidylinositol-5-phosphate 4 kinase (PIP4K) activity. To date the contributions of these two classes of enzymes in regulating PI(4,5)P_2 turnover in the context of G-protein coupled signalling *in vivo* is unknown. Over the last five years, we have systematically generated loss-of-function mutants in all of these genes and studied their requirement for phototransduction and other PI(4,5)P_2 dependent functions in photoreceptors. Using this approach we are building a portrait of the regulation of functional PI(4,5)P_2 pools at a cellular membrane. Recently we have identified a PIP5K (dPIP5K) that specifically controls the PI(4,5)P_2 pool required for phototransduction but not other PI(4,5)P_2 dependent functions in photoreceptors. This opens the door to addressing key questions relating to how PI(4,5)P_2 levels are regulated during signalling. How are PI(4,5)P_2 levels at the plasma membrane sensed and communicated to the PIP kinase in order to regulate its activity? How is the activity of dPIP5K regulated by lipid metabolites generated during G-protein coupled PI(4,5)P_2 hydrolysis? These research themes are presently being developed.

2 REGULATION OF THE PI(4,5)P_2 CYCLE BY PHOSPHATIDIC ACID (PA)

The generation of (PA) by the action of diacylglycerol kinase (DGK) *rdgA* in *Drosophila* photoreceptors play a key role in the regulation of phototranduction [reviewed in (Raghu and Hardie, 2009)]. *In vitro*, PIP5K function can be stimulated by PA and this has led to the attractive but unproven hypothesis that PA generated in cells in a signalling capacity can regulate PI(4,5)P_2 resynthesis. As in most animal cells, photoreceptor PA can be generated by multiple pathways and recently we have established a major role for PA in regulating rhabdomere biogenesis (Raghu, 2009). In addition to phosphorylation of diacylglycerol (DAG) by DGK, PA levels can also be regulated by the activity of phospholipase D (PLD) that generates PA from phosphatidylcholine. Although a number of signalling functions have been proposed for PLD, its importance in metazoans in unknown [reviewed in (Raghu et al., 2009)]. We have generated a null mutant in the single *Drosophila* PLD gene and analysis of this mutant is being used to understand the role of PA derived through PLD activity in regulating PIP5K function.

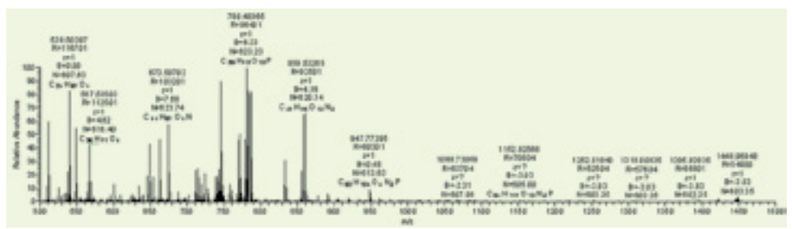


Figure 2: Mass spectrometric profile of lipids from *Drosophila* retinae. This approach allows identification of multiple molecular species of any phospholipid class.

3 THE FUNCTION OF PI TRANSFER PROTEINS IN REGULATING PI(4,5)P_2 RESYNTHESIS

The principal site of PI synthesis is the endoplasmic reticulum. In order to generate PI(4,5)P_2 by sequential phosphorylation of positions 4 and 5, PI needs to be transferred to the Golgi and/or plasma membrane where the relevant kinases are thought to operate. This function is thought to involve PI transfer proteins (PITP). *In vitro,* these proteins transfer PI from liposomes enriched in this lipid to those with low levels of PI. One class of PITPs, *rdgB*, was first isolated as a *Drosophila* mutant with a profound defect in phototransduction [reviewed in (Trivedi and Raghu, 2007)]. However, the molecular basis for these defects is unknown although it has previously been shown

that *rdgB* mutants have a profound defect in PI(4,5)P_2 resynthesis during phototransduction. We are studying the requirements for PI binding and transfer in the function of rdgB *in vivo*. The crystal structure of a mammalian PITP has been solved in complex with PI allowing the identification of residues within the protein that contact the lipid. We have generated point mutants in four such residues (PI binding mutants) in *rdgB* that abolish PI transfer in vitro. When reconstituted into *rdgB* mutant photoreceptors, these PI binding mutants fail to rescue mutant phenotypes. These findings map for the first time, the PI binding activity of the PITP domain onto *in vivo* function. Current projects involve using this system to unravel how PITPs regulate PI(4,5)P_2 synthesis.

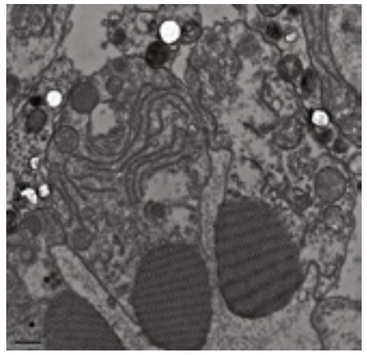
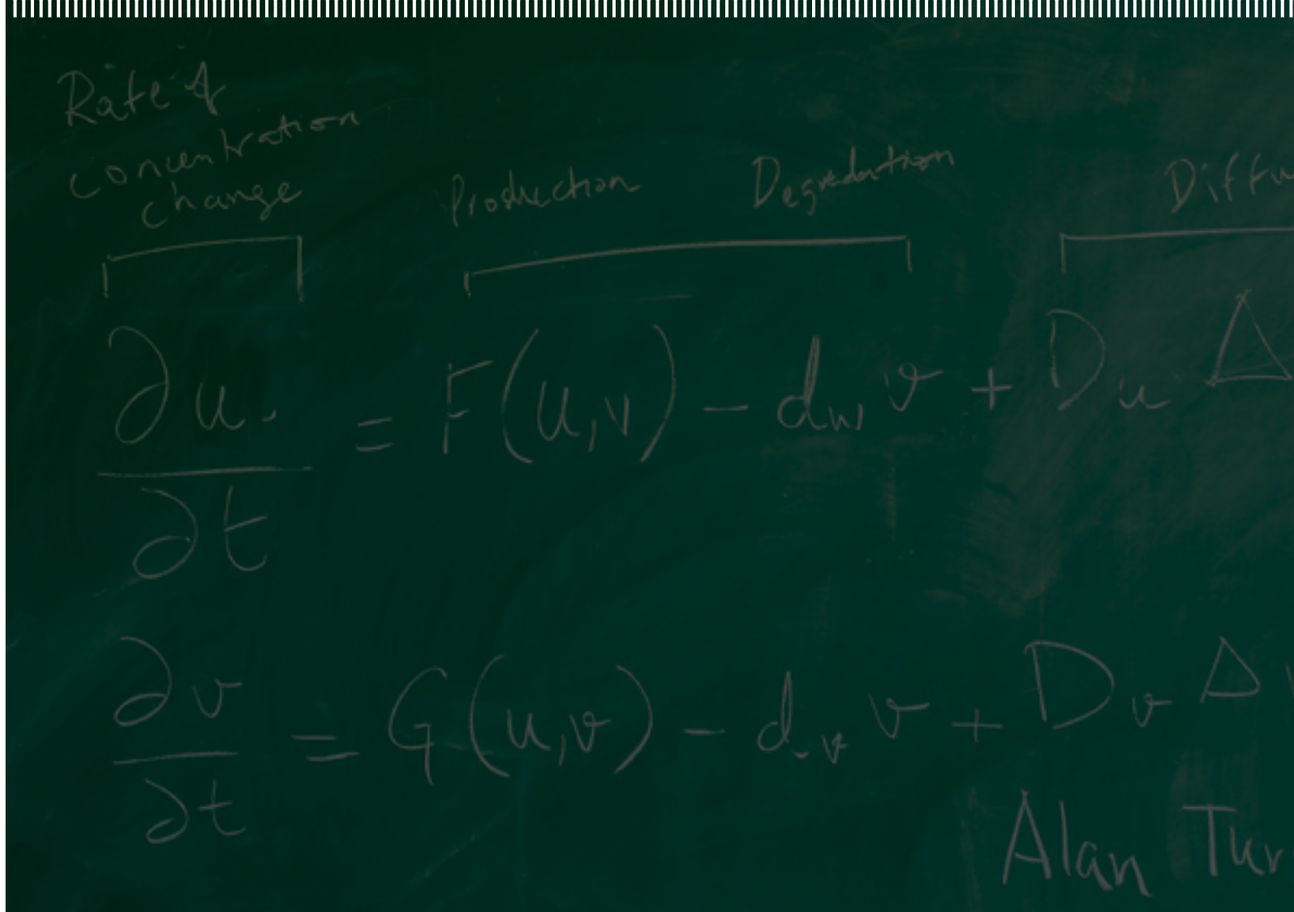


Figure 3: Transmission electron micrograph of a *Drosophila* photoreceptor outlining cellular membranes including the apical microvillar membrane.

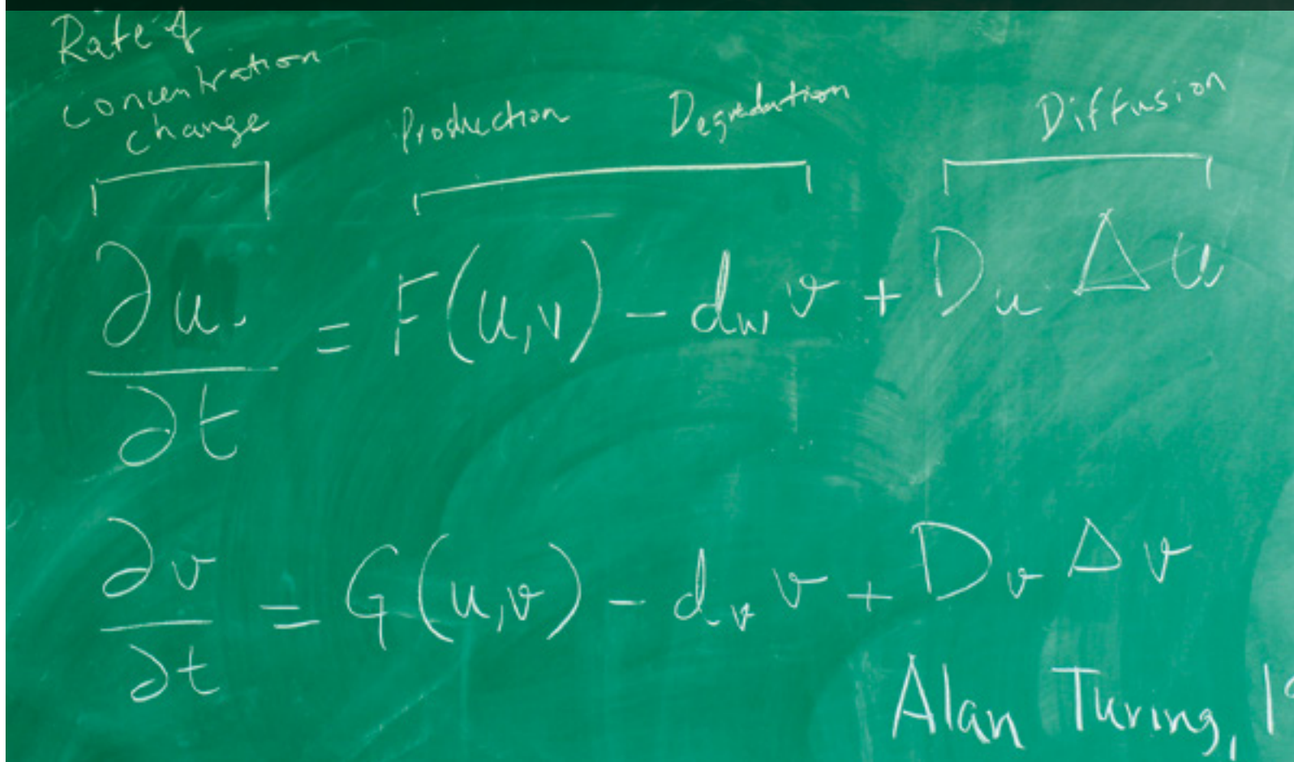
4 GROWTH CONTROL AND CELL SIZE REGULATION BY PIP4K

PIP4K are enzymes that generate a small pool of PI(4,5)P_2 by phosphorylation of PI5P at position 4 of the inositol ring. We have discovered that the principal function of this enzyme is to control PI5P levels. The absence of this enzyme results in a reduction of larval cell size and defective TOR signalling in *Drosophila*. A number of projects that seek to unravel how PI5P levels regulate cell size are being pursued. The evolutionary significance of this class of enzymes is also being analysed.

Figure 4: Larval salivary glands stained with fluorescent lipids to outline cellular membranes. The nucleus of each cell is stained in red.



ECOLOGY AND EVOLUTION



Boasting three biodiversity hotspots, the Indian subcontinent includes high mountains, deserts, tropical rainforests and scrublands. My research investigates the assembly of biodiversity in the Indian subcontinent from macro-ecological to micro-evolutionary perspectives, straddling ecology and evolution in natural systems.

UMA RAMAKRISHNAN

Deconstructing Indian Biodiversity: Evolutionary Origins and Future Prospects

India has a population of over a billion people, and around 4% of its area protected as wildlands. Yet the Indian subcontinent harbours incredible biodiversity. Do we know what this diversity is? How has this diversity come to be? How are we impacting this diversity? My research attempts to address these questions. We use biological samples collected from wild populations to generate genetic data. These genetic data are used along with ecological and behavioral observations, analyzed in population genetic and phylogenetic contexts to study the evolution, population ecology and behavior of populations.

Lek mating and courtship in black buck. This picture shows display behavior in males and females inspecting males on the Lek in Talchapper, Rajasthan.

1 BIOGEOGRAPHY OF THE INDIAN SUBCONTINENT

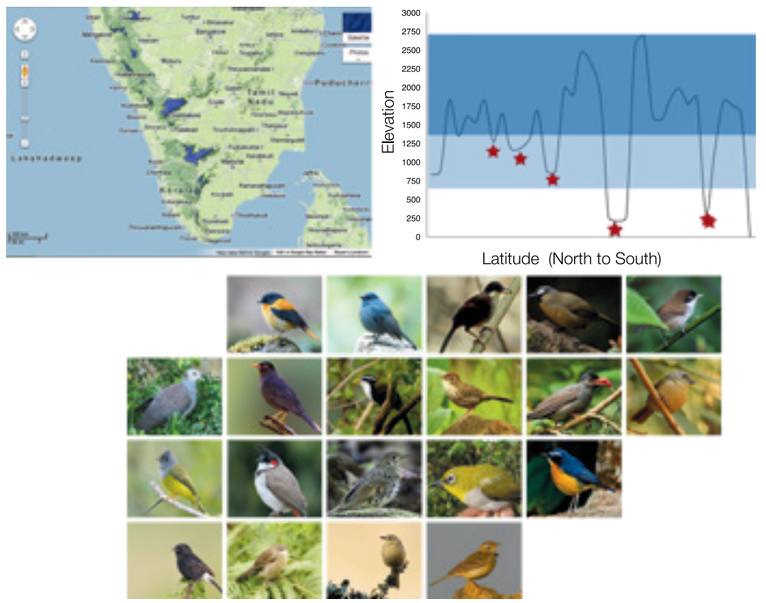
The Indian subcontinent is a fascinating place to study biogeography because of its dynamic geological history. Little research has been directed at addressing how the current bird and mammal biodiversity in the subcontinent has been assembled. How have the physical features of the subcontinent drive speciation and biodiversity? Do species' responses to these physical features vary depending on their ecologies?

What drives biodiversity, speciation and genetic variation in montane systems?

While subcontinent-wide analyses suggest low endemic diversity for mammals, we know that mountain chains should drive diversification because they serve as a barrier and result in isolation between populations on either side of the massif. Additionally, elevational gradients result in dramatic environmental change, which requires evolutionary adaptation by species that inhabit different elevations. We are characterizing biodiversity and its distribution in two Indian mountain systems, the Western Ghats and the Himalaya. We have just begun identifying the possible genetic basis of temperature sensitivity in high elevation shrubs (through transplant experiments and transcriptomics in *Primula* species: Priyadarshini Gurung, graduate student) and hypoxia in Pikas (transcriptomics of animals from an elevational gradient: collaborative project with Katie Solaris (PhD student, Stanford University) and Elizabeth Hadly).

In the Western Ghats, we (see Robin et al., 2010) have shown that deep valleys or gaps in this mountain chain drive speciation and biodiversity. However, we expect species to respond differentially to these mountain gaps based on their habitat preferences: high elevation species should be more affected by gaps compared to those that live at lower elevations (Figure 1). Intensive field sampling by NCBS fellow Robin V for the entire understory bird community (25 species) in the Western Ghats reveals that while some species follow the predicted pattern, most do not. Despite these mountains being geologically very old (~50 mya), most species that show a less than expected impact of physiography are relatively young (~2mya). Perhaps this low genetic differentiation is reflective of the relatively little time these species have had across this landscape.

Figure 1: The map shows high elevation habitats in the Western ghat, while the elevation profile reveals the expectations for different birds in the high elevation community based on their elevational limits. The birds that constitute this community are shown below.



SELECTED PUBLICATIONS

Srinivasan, U., Tamma, K. and **Ramakrishnan, U.** (2014). Past climate and species ecology drive nested species richness patterns along an east-west axis in the Himalaya. *Global Ecology and Biogeography*,23(1):52–60.

Joshi, A., Vaidyanathan, S., Mondol, S., Edgaonkar, A. and **Ramakrishnan, U.** (2013). Connectivity of Tiger (Panthera tigris) Populations in the Human-Influenced Forest Mosaic of Central India. *PloS one*, 8(11), e77980.

Mondol, S., Bruford, M. W. and **Ramakrishnan, U.** (2013) Demographic loss, genetic structure and the conservation implications for Indian tigers. *Proceedings of the Royal Society B: Biological Sciences*, 280(1762).

2 HOW DO HETEROGENOUS LANDSCAPES IMPACT GENETIC VARIATION?

As population geneticists, we conceptualize populations as discrete entities. In reality, animals traverse incredibly heterogenous landscapes to successfully disperse. How do species respond to different landscape elements? How do different species respond within the same landscape? How might landscape be important in the context of infectious disease?

Do large carnivores like tigers move across high density, human-dominated landscapes? Using landscape genetics approaches, we investigated correlations between genetic data (collected from the Central India) and resistance to movement offered by landscape features (human settlements, forest cover, roads). We showed that (1) tigers disperse very long distances (on the order of 600 km) and (2) human footprints on the landscape (such as roads, urban settlements) significantly impact recent movement of tigers across this landscape (Joshi et al., 2013).

NCBS fellow Robin V has also investigated how habitat discontinuity impacts connectivity in populations of a naturally patchily distributed species, the white-bellied shortwing. Results suggest that recently fragmented patches now behave like natural patches, both typified by low recent geneflow.

Graduate student Prachi Thatte is investigating whether body size is a factor that impacts landscape connectivity for populations of carnivores in the Central Indian highlands. We expect small-bodied carnivores (e.g. jungle cat, jackal) to have lower dispersal but higher local density while larger-bodied carnivores (e.g. leopard, tiger) will have higher dispersal, but lower local density. Local density and dispersal, through effective population size and geneflow, will impact population structure. These considerations are independent of how individual species respond to landscapes.

Postdoc Fiona Savory is investigating how landscape features impact genetic variability in a plant pathogen (foorkey) that affects large cardamom. Foorkey is a multi-partite DNA virus transmitted by aphids. Using spatial analyses, Fiona identifies hotspots for viral evolution in the Eastern Himalaya (Figure 2, Savory et al., in press, *Evolutionary Applications*). In this novel and exciting line of research, we are trying to investigate how population genetics maybe implemented in more applied contexts of vector-pathogen systems.

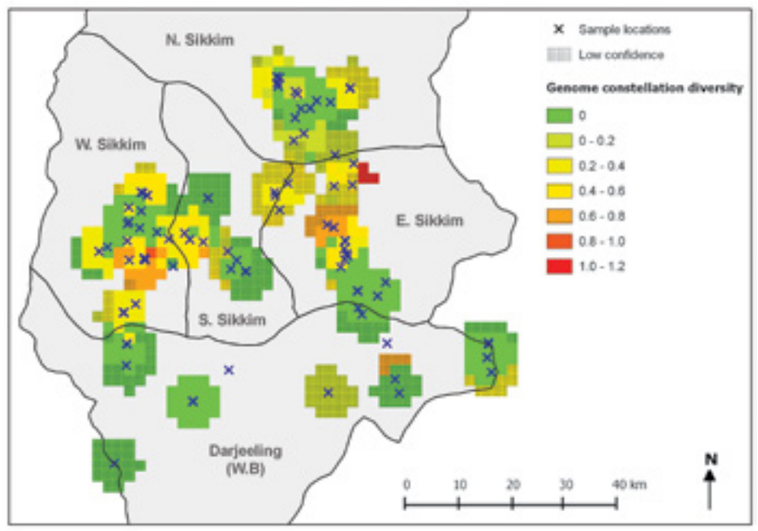


Figure 2: Spatial variation in genome constellation diversity in the North(N), East(E), South(S) and West(W) districts of Sikkim and the Darjeeling district of West Bengal (W.B). Genome constellation diversity was calculated using the median pairwise ordination distance for all isolates collected within a 5km radius of each grid point. Shaded areas represent locations where grid points were assigned a low confidence score (←5samples).

3 WHAT ARE EVOLUTIONARY CONSEQUENCES OF MATING SYSTEMS AND BEHAVIOR?

Observations of courtship and mating behaviors have guided our understanding of mating systems and variance in reproductive success. However, the presence of cryptic strategies often results in situations where social mating system is not reflective of genetic mating system, and such behavioral interactions impact the future evolution of species through effective population size.

Using long-term data from six mating seasons of fruit bats and paternity analyses, graduate student Kritika Garg revealed that social harem assemblages do not play a role in the mating system, and variance in male reproductive success is lower than expected assuming polygynous mating (Garg et al., 2012), but consistent with promiscuity. Then how do females choose their mates? Initial results suggest that females do not choose males based on body size, heterozygosity or relatedness. Our analyses reveal a post-copulatory choice by females for divergent male alleles, a process that results in increased heterozygosity in the offspring. To our knowledge, this is the first demonstration of such a process in wild terrestrial mammal populations. Kritika has investigated colony dynamics, and contrasted socio-behavioral strategies used by males and females, and her results reveal that males are more likely to be colony residents than females, and that this strategy is associated with increased reproductive payoff. Kritika has also investigated association (behavior-based) and relatedness networks in a colony of fruit bats and has identified the presence of dynamic and fluid social grouping.

In collaboration with Kavita Iswaran from IISc, graduate student Jyothi Nair is continuing to study mating systems in the lab using the behaviorally well described black buck. Males of this species display on leks (picture 1) and females choose males. Jyothi will investigate reproductive success payoff for different males.

Apart from the described research directions, members of the lab research macro-ecological patterns in the Indian subcontinent, the impacts of human-dominated environments on adaptation and speciation. Through our research, we help conserve Indian biodiversity through discovery and technology.

Can our ecosystems cope with the challenges of ever-expanding human activities? We work on understanding the dynamics of grasslands and mixed tree-grass ecosystems, their responses to changes in climate, and what this means for their future distribution and functioning.

MAHESH SANKARAN

Terrestrial Ecosystems and Community Ecology

SELECTED PUBLICATIONS

Lehmann, C., T.M. Anderson, **M. Sankaran**, S.I. Higgins, S. Archibald, W.A. Hoffmann, N.P. Hanan, R.J. Williams, R. Fensham, J. Felfili, L. Hutley, J. Ratnam, J. San Jose, R. Montes, D. Franklin, J. Russell-Smith, C. M. Ryan, G. Durigan, P. Hiernaux, R. Haidar, D. M. J. S. Bowman and W.J. Bond (2014). Savanna vegetation-fire-climate relationships differ between continents. *Science* 343: 548 – 552

Sankaran, M. Ratnam, J. and Augustine D. J. (2013). Native ungulates of diverse body sizes collectively regulate ong-term woody plant demography and structure of a semi-arid savanna. *Journal of Ecology 101: 1389 – 1399.*

Ratnam, J., Bond, W. J., Fensham, R. J., Hoffmann, W. A., Archibald, S., Lehmann, C. E. R., Andersen, M. T., Higgins, S. I. and **Sankaran, M.** (2011). When is a forest a savanna and why does it matter? *Global Ecology & Biogeography* 20: 653 - 660.

Current research in the lab is grouped around broad themes that examine

- How interactions and feedbacks between climate, biogeochemistry, fires and herbivory influence the structure, composition and stability of ecosystems and nutrient cycling.
- How global change drivers such as rising CO2, increased temperature, altered precipitation regimes, and nutrient deposition will impact ecosystem function, stability and services.

Most of our research has been carried out in savanna ecosystems in Africa and India. We have recently extended this work to encompass a wider range of ecosystems including rainforests and grasslands. Using both field surveys and experiments, we address the above questions across the gamut of natural ecosystem types in India, with the goal of bringing a comprehensive understanding of biome-scale vegetation and nutrient dynamics in the sub-continent.

1 DETERMINANTS OF SAVANNA STRUCTURE AND FUNCTION

Mahesh Sankaran, Jayashree Ratnam

Savanna ecosystems cover more than a fifth of the Earth's land surface (~33 million km^2), and support a large proportion of the world's human population, and a majority of its rangeland, livestock and wild-herbivore biomass. Savannas can be abstracted into a few components: trees, grasses, grazers and browsers, the interactions among which are mediated by climate, soil, fire and human use. Yet, despite this apparent simplicity, understanding how these different components interact to function as an integrated whole remains a challenge.

Our long-term work in Africa, and our recent initiatives in India, centre on mechanistically understanding the individual and interactive effects of 'top-down' (herbivory and fire) and 'bottom-up' forces (resource availability) in regulating savanna structure. Specifically, we are looking at how rainfall, soil nutrients, fire and herbivory interact to influence patterns of woody growth, recruitment and mortality in savannas. In addition, we are also exploring the role of competition is structuring savanna communities. Traditionally, savanna ecologists have emphasized the role of tree-grass competition, but there is a growing recognition that intra-tree competition might be equally important in regulating savanna structure. Our work looks at how competition between trees influences savanna structure across broad environmental gradients. Ultimately, these initiatives will provide us with a more nuanced picture of the role of competition, resource availability and disturbances in regulating savanna dynamics.

2 SAVANNA-FOREST TRANSITIONS IN THE INDIAN SUB-CONTINENT

Jayashree Ratnam, Vijay K. S., Chengappa, S. K.

Savannas are mixed tree-grass systems characterized by a discontinuous tree canopy in a continuous grass layer. Within the bounds of this definition, actual tree cover in the world's savannas is highly variable, ranging from sparsely 'treed' grasslands to heavily 'treed' woodlands, often along a gradient of increasing precipitation. While this definition captures structural features of savanna vegetation, it contains little information about the functional ecology or the evolution of these ecosystems. This distinction is important. At the mesic end of the savanna biome, where savannas transition into forests, distinguishing between savanna and true forest based on vegetation structure can be difficult, but we expect major functional differences between the two ecosystems. Tropical savannas, distinguished by the presence of C_4 grasses in the understorey, are characterised by frequent fires and high ambient light regimes. The opposite is true for forests that are closed and shaded habitats. These environmental differences are expected to select for major differences in the functional traits and life histories of the flora that characterise these biomes. We have developed a predictive framework to characterize savanna and forest species based on differences in functional traits, and are now working towards a functional reclassification of savanna regions across India, with implications for management and conservation of these biomes.

3 RESPONSES OF SAVANNA AND DRY FOREST ECOSYSTEMS TO GLOBAL CHANGE DRIVERS

Varun Varma, Lalitha Krishnan, Yadugiri V.T.

Since industrialization, the amount of nitrogen and phosphorous cycling through the biosphere has more than doubled. In addition, rainfall regimes are also changing, with most climate models predicting an increase in rainfall variability and the occurrence of more frequent extreme rainfall events over large areas of the globe, including India. Our research aims to understand the effects of nutrient loading and altered precipitation regimes on the early life history stages of leguminous and non-leguminous savanna and dry forest trees using fully replicated greenhouse and large-scale field experiments. Specifically, we are interested in determining what functional traits of savanna trees predispose them to performing better or worse in the face of such changes. Ultimately, the objective is to develop a framework to predict *a priori* which species will have a competitive advantage under these altered conditions.

In a further twist, we are also exploring the effects of global change drivers on plant performance via their effects on plant-fungal mutualisms. Most plants invest carbon in symbionts like arbuscular mycorrhizal fungi and endophytic fungi. These mutualists enhance plant resource access, and can thereby influence plant responses to changes in the availability of resources such as water and nutrients. Using both field-based and pot experiments, we are working to

understand the implications of these mutualistic interactions for plant responses to global change.

4 RESPONSES OF ALPINE GRASSLANDS TO WARMING

Dharmendra Lamsal

Our work on the impacts of climate change on ecosystem functioning and processes also encompasses alpine grassland ecosystems of the Himalayas. As part of this effort, we have established a warming experiment, using open-top chambers (OTCs), to look at the effects of future temperature rise on high-altitude grasslands in the Sikkim Himalaya. Replicated warming chambers and paired controls have been setup in each of 5 different elevations from 3000 m to 5000 m to investigate the role of warming on plant community shifts and nutrient cycling in grasslands, and how such effects vary across elevation gradients.

5 LAND USE AND CARBON SEQUESTRATION IN TROPICAL RAINFORESTS

M. O. Anand

Earth's tropical forests serve as important repositories of biodiversity and provide critical ecosystem services such as carbon sequestration and climate control. However, tropical forests are highly threatened. While vast extents have been clear felled and logged, many remaining areas are highly fragmented. Our work in the central Western Ghats investigates the impacts of forest fragmentation on the community structure and composition and the resulting consequences for carbon storage; an important ecosystem service. Results suggest that fragmentation reduces carbon storage through changes in tree allometry over time: trees growing in fragments are about 25% shorter at any given basal diameter than trees in contiguous forests. The size structure of forest stands in fragments also suggests that carbon storage in fragments is relatively more reliant on a few large trees, and likely to decline considerably following their eventual death. We are now examining functional traits of tree species in contiguous and fragmented forests to obtain insights into the mechanisms by which fragmentation alters species composition and carbon storage potential.

6 ECOLOGY FOR THE LONG HAUL: LONG-TERM VEGETATION DYNAMICS IN THE INDIAN SUBCONTINENT

Jayashree Ratnam, Swapna Nellaballi, H. V. Raghavendra, M. O. Anand, VijayKumar K.S., Chengappa S.K.

To date, the most in-depth understanding of forest dynamics has come from long-term monitoring plots that have been established in different forest ecosystems worldwide. However, with the exception of plots set up in the dry forests of Mudumalai in south India, we have little information on the long-term dynamics of other forest types in the Indian region. To address this lacuna, we have initiated the establishment of a network of forest monitoring plots in India, spanning a gradient from savanna and dry forests through to wet evergreen forests. We are using these plots to address fundamental questions in vegetation ecology, community dynamics, and the cycling of energy and nutrients in ecosystems. The network will enable us to better understand the factors regulating forest dynamics, and will provide critical data for both regional and global estimates of tropical vegetation responses to climate change.

7 Shola-grassland mosaics of southern India

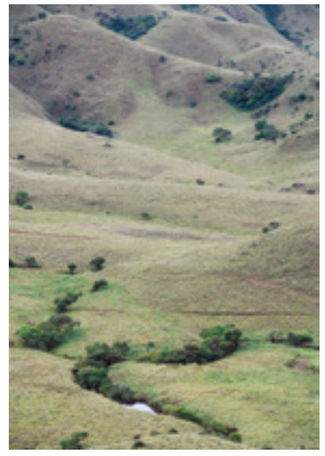
Atul Joshi, Harinandan P. V.

Forest-grassland mosaics occur on many continents across the earth, including Asia, America and Africa. In India, such mosaics occur in the high-altitude hilltops of the Western Ghats. They are characterized by stunted evergreen montane forests, locally known as 'sholas' in ridge-top depressions or valleys, set in a matrix of montane wet grasslands on surrounding hill slopes. The abrupt transitions between adjacent shola forests and grasslands in the mosaics make them model systems to study state transitions between biome types. Our work looks at the factors currently limiting tree establishment in grasslands, and how these are likely to change with changes in rainfall and temperature.

8 CURRENT AND HISTORICAL ECOLOGY OF THE GRASSES OF THE INDIAN SUBCONTINENT

Harinandan P.V., Atul Joshi, Anusree A.S.

The rise and spread of C_4 grasses and tropical savanna ecosystems during the Miocene ranks amongst the most dramatic events of biome evolution in geological history. The causes underlying the rapid expansion of C_4 grasslands, however, remain unclear. Ultimately, a resolution of this debate will require a synthesis of both current and historical data. To this end, we have initiated a program to reconstruct past climate and vegetation in select grassland and savanna regions in India from sediment cores. We have also begun work towards building a nationwide spatially explicit database of grass species distribution for India. This data set will allow us to embark on a suite of different analyses ranging from climatic and phylogenetic controls of grass species dominance to macro-ecological patterns of diversity and distribution in Indian grasses. Together, these ventures will provide a more comprehensive picture of the evolution of Indian savannas and C_4 grasslands.



Diversity is the cornerstone of life on earth. We are evolutionary biologists who study biodiversity, its organization and complexity, the selective processes that shape it, and the means to preserve it in tropical regions such as India.

KRUSHNAMEGH KUNTE

Evolution, Speciation and Morphological Diversification in Tropical Regions

Our lab has a broad interest in biology encompassing the fields of natural selection theory, genetics, population and community ecology, and conservation biology. However, we use two systems as microcosms to study a range of phenomena that fascinate us, such as morphological evolution, sexual dimorphism, geographical distribution of animals, and speciation. The first system is Batesian mimicry, which is a phenomenon whereby unprotected prey species (called "mimics") gain protection from predators by mimicking toxic or otherwise protected species (called "models"). Predators learn to avoid models based on prior experience, and subsequently avoid eating mimics due to misidentification. Batesian mimicry has been at the forefront of evolutionary research since the beginning, and we study this phenomena from ecological dynamics to molecular genetics using the latest tools and technologies. Our second research system is Indian butterflies, which, with ca 1,800 species and subspecies distributed in an interesting geographical mosaic, offer virtually unlimited opportunities to study biodiversity, biogeography, community ecology, population biology and conservation issues. Summaries of our major research projects are given below. Further information is given on our lab website (http://biodiversitylab.org/research).

1 DIVERSITY AND EVOLUTION OF BATESIAN MIMICRY

The magnificent diversity of Batesian mimicry is manifested in hundreds of mimetic butterfly species in tropical forests. There is tremendous variation in the nature of Batesian mimicry: mimicry can be sexually monomorphic, polymorphic or sex-limited within and across species. This offers an excellent system to study natural, sexual and frequency-dependent selection that shapes the evolution of sex-limited traits and polymorphism. Early evolutionists such as Charles Darwin, Alfred Russel Wallace, Henry Bates (who first proposed the theory of mimicry and in whose honor it is named) and Edward Poulton hailed Batesian mimicry as a fine example of natural selection, pointing to the often perfect resemblance between the mimics and their models. They saw this as one of the strongest demonstrations of evolution by natural selection, in this case brought about through the agency of predators such as birds. We now know many other good examples of natural selection but the interest in Batesian mimicry has persisted to this day among evolutionary biologists. This is because we have a very strong theoretical framework for Batesian mimicry, and extensive field observations as well as numerous laboratory experiments have provided rich detail of the phenomenon under a variety of ecological conditions and in a number of organisms. Building on this extensive foundation, we study: (a) how natural and sexual selection influence speciation and morphological diversification in mimetic butterflies, and (b) how different mimicry types have evolved in relation to each other. To answer these questions, we have developed: (a) a mathematical model of the selection regimes under which various mimicry types may be favored, (b) a graphical model of the evolution of mimicry types to study character state changes within a phylogenetic framework, and (c) a set of ecological methods to address how selection shapes mimicry in the field. We are testing these models with data on communities of mimetic butterflies in the Eastern Himalaya and Western Ghats, and by analyzing evolution of mimicry types on a molecular phylogeny of *Papilio* swallowtail butterflies.

Figure 1: A Batesian community involving predators, models and mimics. Image of Little Green Bee-eater (*Merops orientalis*): © Shashidhar Hiremath, used with permission.

2 WING COLOR PATTERN EVOLUTION, MIMICRY, AND SPECIATION IN *PAPILIO* SWALLOWTAIL BUTTERFLIES

Mormon swallowtails (subgenus *Menelaides*) make up a diverse group of *Papilio* with ca 50 species distributed over the Indo-Australian Region. The geographic mosaic of their distributional ranges, endemism and diversification in regional hotspots, and subspeciation at sometimes micro-spatial scales make them a promising group for studying biogeographic processes and speciation. Many of them also show a spectacular diversity of Batesian mimicry and wing patterns. We are studying speciation and morphological diversification in this model group of butterflies mainly using phylogenetic methods.

3 MOLECULAR GENETICS AND EVOLUTION OF MIMICRY IN THE *PAPILIO POLYTES* BUTTERFLY

Papilio polytes, a widely ranging Asian swallowtail, has a single non-mimetic male form and several female forms, most of which mimic locally abundant toxic *Pachliopta* butterflies. We are studying this female-limited mimetic polymorphism in *P. polytes* to understand the molecular

SELECTED PUBLICATIONS

Kunte, K., Zhang, W., Tenger-Trolander, A., Palmer, D. H., Martin, A. R., Reed, D., Mullen, S. P. and Kronforst, M. R. (2014). doublesex is a mimicry supergene. *Nature*, 507:229-232.

Lasley, R. M. Jr., Jain, A. and **Kunte, K.** (2013). Alleviating poverty in India: Biodiversity's role. *Science*, 341:840-841.

Sondhi, S., and **Kunte, K.** (2014). *Butterflies and Moths of Pakke Tiger Reserve*. Titli Trust (Dehradun), and Indian Foundation for Butterflies (Bengaluru). vi+202pp.

genetic basis of sexual dimorphism and polymorphism. We are also aiming to understand what kind of genetic changes enable major switches between wing color patterns in butterflies, and what selective pressures favor their evolution. We are studying these factors at the continental scale, covering the entire Oriental Region. This is interesting because *P. polytes* is a regionally variable species in which some female forms occur in some populations but not others. This offers an opportunity to study local adaptation and compare genomic backgrounds on which wing patterns and their genetic bases have evolved. Furthermore, there is genetic dominance hierarchy between the female forms, the non-mimetic female form being recessive to all the mimetic female forms. Thus, we also study the basis and nature of genetic dominance.

Figure 2: Female-limited mimetic *polymorphism* in the Papilio polytes swallowtail butterfly

4 POPULATION BIOLOGY OF BUTTERFLY MIGRATIONS, AND ITS EVOLUTIONARY AND GENETIC CONSEQUENCES

A spectacular natural event takes place across southern India every year: millions of butterflies migrate from the Western Ghats to the eastern plains around May, and a reverse migration takes place in October or November. These migratory swarms may contain half a dozen species, but are overwhelming dominated by two: *Tirumala septentrionis dravidarum* (Dakhan Dark Blue Tiger) and *Euploea sylvester coreta* (Double-branded Black Crow) (Nymphalidae: Danainae). This migration is quite fascinating because: (a) it is longitudinal (east-west), not latitudinal (north-south) or altitudinal like most other well-known migrations, and (b) it seems to be driven by the Indian monsoon, not by cold or drought, as is the case in many other migrations. We are currently investigating how the Indian monsoon influences population biology of these butterflies, and what are the evolutionary and genetic consequences of migratory behavior.

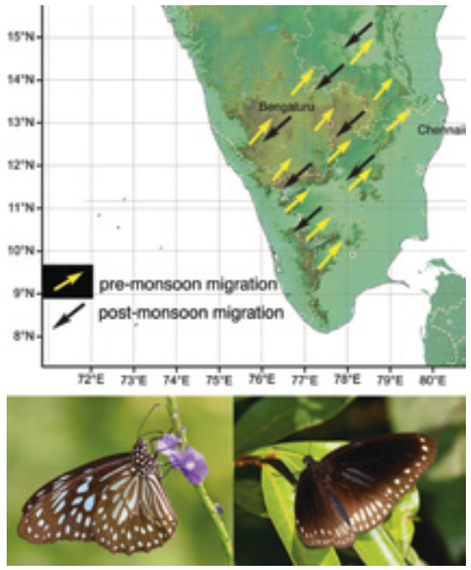


Figure 3: Butterfly migration in peninsular India

5 EVOLUTION, DIVERSIFICATION AND BIOGEOGRAPHY OF CICADAS ON THE INDIAN SUBCONTINENT

India is at the junction of Palearctic and Oriental zoogeographic regions, and is believed to have been critical in the evolution and exchange of faunal elements between these zoogeographic regions. Thus, understanding the biogeography of Indian faunas is important in constructing a more complete picture of biological diversification in the Indo-Australian Region. Using cicadas, we aim to: (a) study the origin and diversification of cicadas in India in relation to neighboring regions, (b) generate a higher-level phylogeny of Indian cicadas that will form a backbone of further studies, and (c) inventory cicada diversity.

Figure 4: A selection of Indian cicadas.

6 ECOLOGY, BIOGEOGRAPHY, PHYLOGENETICS AND CONSERVATION OF INDIAN BUTTERFLIES

One of the long-term goals of our lab is to study the ecology and patterns of diversification, endemism and evolution of Indian butterflies. Migration, seasonal population dynamics, biogeography, phylogeography, community structure and mimicry are some of the areas in which we have several ongoing projects. We have started a modern research collection of Indian butterflies, with associated geo-referenced data and DNA library, which we are using for our taxonomic, phylogenetic, phylogeographic, conservation genetics and conservation prioritization work on Indian butterflies. We are also spear-heading the development of a continually updated and expanding website on Indian butterflies (http://ifoundbutterflies.org).

7 BIODIVERSITY CONSERVATION IN INDIA

India is one of the world's most biodiverse countries, and also the world's second-most populous country with a very large population of rural and urban poor. Moreover, it has ambitions to become a major industrialized nation. As a result, India faces contradictory choices of conserving biodiversity on one hand and ramping up its use of natural resources on the other hand for developing necessary infrastructure for economic development, alleviating poverty and increasing agricultural productivity. If we are to conserve biodiversity in the Indian Region, we need a better understanding of how biodiversity has evolved in this complex natural landscape, how it is affected by human history and modern progress, and how its loss will contribute towards degradation of the quality of life and economic growth in India. Although our lab is primarily a basic research lab, we are committed to making advances in understanding natural and social issues that will be critical in biodiversity conservation in India. We do this in various ways. First, we research on topics that will shed light on the evolutionary and ecological history of biodiversity in the Indian Region, e.g., phylogenetic patterns of speciation and endemism, phylogeographic structure of populations, and ecological requirements of representative insects (our favorites). Second, we use this understanding to come up with traditional as well as novel suggestions for biodiversity conservation, and we directly communicate these to policy-makers at national and local levels. Third, we collaborate with grassroots governmental and non-governmental bodies that closely work with tribal and other rural communities whose lives are influenced the most by the presence and quality of forests and biodiversity in their neighborhood. This is with the long-term goal of informing local action that will benefit both the local human communities as well as the biodiversity.

My lab combines diverse approaches to understand the evolutionary and ecological processes underlying adaptive evolution. We often use experimental evolution of insects and bacterial systems to determine the dynamics of adaptation under new genetic and ecological selective pressures.

DEEPA AGASHE

The Evolutionary Ecology and Genetics of Adaptation

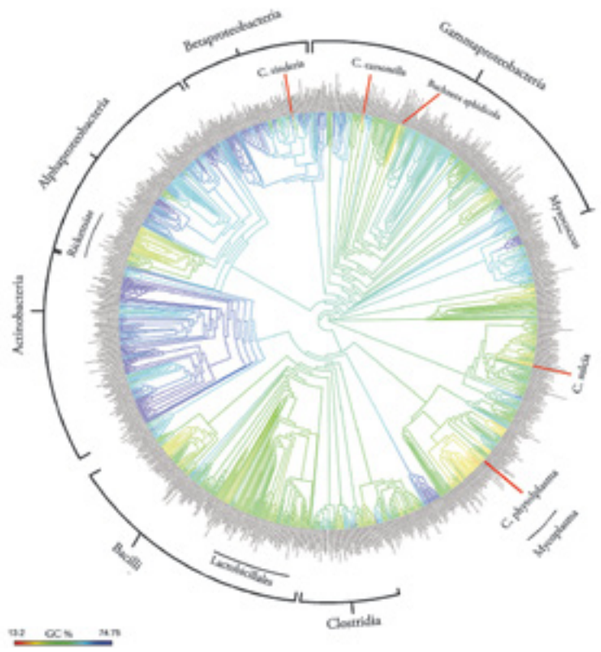
Adaptation to various ecological factors has been an important force in the evolution of the amazing array of species on earth. How does genomic structure and composition affect adaptive response to ecological selection? How does variation within and among individuals alter the genetic and phenotypic basis of adaptation to specific habitats? Understanding interactions between ecological and evolutionary processes that govern adaptation is critical to answer these questions, and forms the core of my research program.

SELECTED PUBLICATIONS

Parent CE*, **Agashe D*** and Bolnick DI (2014). Intraspecific competition reduces niche width in experimental populations. 4(20): 3878-3990 Ecology and Evolution *Equal contribution

Agashe Dand Shankar N (2014). The evolution of bacterial DNA base composition. *Journal of Experimental Zoology B* 322(7): 517-528

Agashe D, Martinez-Gomez NC, Drummond DA and Marx CJ (2013). Good codons, bad transcript: large reductions in gene expression and fitness arising from synonymous mutations in a key enzyme. *Molecular Biology and Evolution* 30(3): 549-560



Bacterial genome GC content mapped on a phylogeny (from Agashe & Shankar 2014)

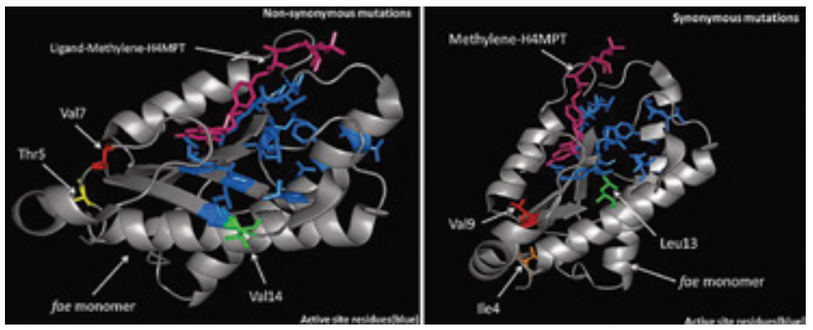
1 WHAT (MICRO)EVOLUTIONARY FORCES SHAPE BACTERIAL GENOMES?

Bacteria have enormously diverse genomes that vary widely in size, composition, and gene copy number. We are trying to understand the factors responsible for the generation and maintenance of this variation. Currently, we focus on testing the fitness impacts of synonymous codon variation (typically thought to be selectively neutral) and tRNA genes, and the evolution of genomic GC content. The forces responsible for the evolution of major genomic features such as GC content and codon usage, and their impact on adaptation, are still poorly understood. Across various taxa, the most frequently used codons in protein-coding regions tend to be the ones that are recognized by the most abundant tRNAs in the cell, approximated by each tRNA's genomic copy number. Hence, the dominant hypothesis for explaining codon bias is that these frequently used codons minimize ribosomal pausing during translation, and maximize translational efficiency (encapsulating both accuracy and speed). Population genetic models thus posit that tRNA gene copy number and codon usage co-evolve under mutation-selection-drift processes, and that the variation in observed codon bias is a result of varying selection pressures combined with mutational bias. However, this model is empirically largely untested, even though it leads to a number of testable predictions.

Mounting evidence indicates that synonymous codon changes may sometimes face quite strong selection, although it remains difficult to derive general patterns about the nature and strength of such selection. In previous work with synonymous variants of an enzyme-encoding gene of *Methylobacterium extorquens*, I showed that altering codons could be extremely deleterious. Although the exact physiological mechanism likely depends on the specific sequence, the fitness disadvantage arose from insufficient enzyme production.

Recent work from our group shows that during laboratory evolution, these synonymous variants rapidly regain fitness, often via repeatable and mutant-specific beneficial point mutations in the N-terminal region of the gene. Interestingly, none of the mutations (some of which were synonymous) caused a reversion to wild-type codons, but all of them increased focal gene and protein expression. Other putatively beneficial compensatory mutations in the genome that were associated with increased enzyme production did not involve tRNA genes. These results suggest that co-evolutionary dynamics between tRNA copy number and codon use may be unlikely in the short-term, potentially because of the existence of multiple fitness peaks. Instead, bacteria may find diverse evolutionary solutions to the immediate physiological problems caused by accumulated deleterious synonymous mutations and subsequent tRNA gene copy number changes may fine-tune global protein production in the long term. We are now testing whether similar results hold for other important, endogenous genes in bacteria.

Figure 1: The position of laboratory-evolved beneficial mutations in the formaldehyde activating enzyme of Methylobacterium extorquens AM1



GENETICS AND DEVELOPMENT

70 K VIJAYRAGHAVAN 74 GAITI HASAN 78 PV SHIVAPRASAD

2 HOW ARE BEHAVIOR, ECOLOGY, AND EVOLUTION OF NATURAL POPULATIONS CONNECTED?

An ultimate goal of biological research is to connect the genetic, phenotypic, and behavioral features of organisms; however, this remains logistically challenging for most species. To address this issue, we are analyzing over a dozen populations of a generalist insect pest (the red flour beetle *Tribolium castaneum*) collected from different parts of India. We are quantifying within- and between- population variation in a number of life history (fecundity, development, immune function and lifespan) and behavioral traits (resource choice, dispersal, and cannibalism) in different resources with varying nutritional content. We are also measuring levels of sequence variation at loci that may be evolving under selection and may contribute to the phenotypic variation we observe. Together, this will produce a rich dataset that we can use to test patterns of tradeoffs and correlations between traits important for the ecology and evolution of the species. More generally, this project promises to provide deeper understanding of how organisms evolve and diverge.

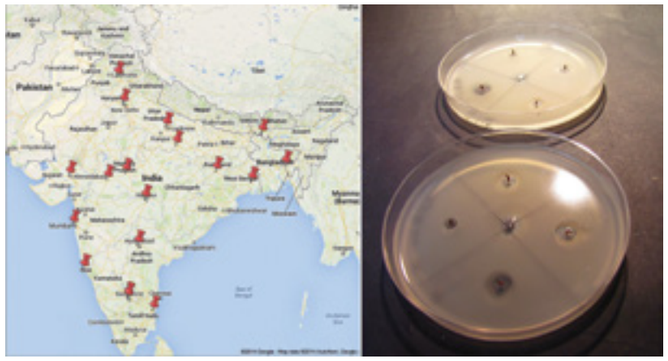


Figure 2: (A) A map of India showing collection locations for Tribolium beetles
(B) Antimicrobial activity of defensive beetle secretions

3 (HOW) DO INSECTS AND THEIR GUT MICROBIAL COMMUNITIES CO-DIVERSIFY?

Microbes associated with an organism's gut are fantastic examples of symbiotic relationships between species, with nutritional and other benefits to both partners. However, since most microbes remain uncultured and unexplored, we are only just beginning to understand the breadth and depth of such interactions using metagenomic approaches. Co-evolutionary dynamics with gut microbes are particularly interesting in host groups such as insects, which encompass a wide range of dietary, ecological, and life history variation. We are beginning to explore the ecology and evolution of gut microbial interactions with a few groups of insects across India.

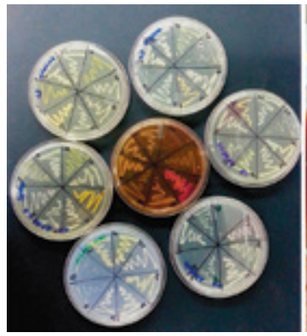


Figure 3: Bacteria isolated from dragonfly guts

Our laboratory studies how the birth, morphogenesis and connectivity of neurons and muscles translate into behaviour. We pare this complex problem to tractability by focusing on the olfactory and motor system of *Drosophila melanogaster.*

K VIJAYRAGHAVAN

The Brain and Brawn Lab: Development of Neural Circuits and Muscles and the Emergence of Behaviour

1 DEVELOPMENTAL GENETICS OF THE OLFACTORY CIRCUIT ASSEMBLY

Indu Nair, Rudra Nayan Das, Ajeet Pratap Singh, Gururaj, Ramveer Choudhary, Silvia Biagini, Sonia Sen

The olfactory circuit of *Drosophila* has a unique, highly stereotyped architecture consisting of different classes of sensory neurons (OSNs) housed on the antenna, which target the antennal lobe in the central brain to make synaptic contacts with projection interneurons (PNs) in a class-specific manner in synapse dense regions of the antennal lobe called glomeruli. Local interneurons (LNs) in the antennal lobe interconnect these glomeruli. The very precise connectivity of this circuit, sophisticated genetic tools that allow access to its individual neurons and its easy-to-assay behavioural output, make this an ideal neural circuit to study the developmental genetics of neural circuit assembly, its function and maintenance.

The OSNs, develop from sense organ precursors (SOPs) on the antenna while the PNs and LNs develop in the central brain from stem cell like precursors called neuroblasts (NBs). The development of both precursor types (SOPs and NBs) are, in part, controlled by embryonic developmental patterning genes and signaling pathways. Thus, we find that early patterning genes such as *orthodenticle* (*otd*) and *empty spiracles* (*ems*) and the transcription factor encoding gene, *jing,* and Eph-Ephrin signaling have diverse and complex roles in the different olfactory neuron cell types. Often these genes continue to be required reiteratively in these neurons. Furthermore, we find that the proper development of the olfactory circuit depends not only on genes that are expressed in olfactory neurons, which promote appropriate circuitry, but also on genes expressed elsewhere, which prevent inappropriate circuitry. Finally, in an attempt to link developmental patterning to the emergence of behavior, we are now studying the role of an identified serotonergic neuron (CSD) in odour guided navigation (figure1).

Collaborators: Heinrich Reichert, University of Basel, Switzerland.
Jing Wang, University of California, San Diego, USA.
Matthieu Louis, CRG, Barcelona, Spain.

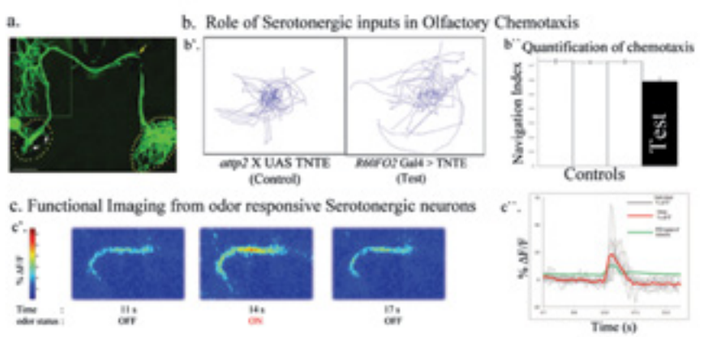


Figure 1: A pair of serotonergic neurons innervates the larval olfactory lobes (a). Silencing these neurons (by cell specific expression of tetanus toxin) results in less efficient odor driven chemotaxis as seen by the larval tracts (b', quantified in b''). Functional imaging using genetically encoded calcium sensors show these neurons to be odor responsive (c'). c'' shows enhanced calcium signal (grey line, individual animals; red line, mean response), which is correlated with the odor stimulus (green, signal from photo ionization device).

SELECTED PUBLICATIONS

Gunage, R.D., Reichert, H., **VijayRahavan, K.** (2014) Identification of a new stem cell population that generates *Drosophila* flight muscles . eLIFE 2014;3:e03126. doi: 10.7554/eLife.03126

Sudhakaran, I.P., Hillebrand, J., Dervan, A., Das, S., Holohan, E.E., Hülsmeier, J., Sarov, M., Parker, R., **VijayRahavan, K.**, Ramaswami, M. (2014). FMRP and Ataxin-2 function together in long-term olfactory habituation and neuronal translational control . PNAS, Jan 7;111(1):E99-E108. doi: 10.1073/pnas.1309543111

Sen, S., Biagini, S., Reichert, H., **VijayRahavan, K.** (2014). Orthodenticle is required for the development of olfactory projection neurons and local interneurons in *Drosophila* Biol Open, 3(8):711-7. doi: 10.1242/bio.20148524

Singh, A.P., Das, R.N., Rao, G.,Aggarwal, A., Diegelmann, S.,Evers, J.F., Karandikar, H.,Landgraf, M., Rodrigues,V., **VijayRahavan, K.** (2013).Sensory neuron-derived Ephregulates glomerular arborsand modulatory function of acentral serotonergic neuron. PloS Genetics, 9(4).doi:10.1371/journal.pgen.100345

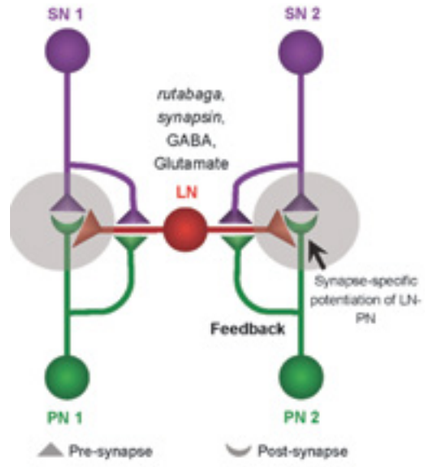


Figure 2: Circuit mechanisms of habituation: Sensory neurons (SNs), which take information from the environment, project to the primary olfactory/gustatory centers and make synapses with projection neurons (PNs) and local interneurons (LNs). For olfactory or gustatory habituation, the LN-PN synapses undergo inhibitory potentiation (GABA), which requires rutabaga-dependent cAMP signaling in the LNs and GABAA receptors (Rdl) in PNs. Glutamate release and NMDA function in LNs and PNs are respectively required for stimulus-specific behavioral response.

2 LEARNING TO IGNORE AND IGNORING TO LEARN: A CIRCUIT MECHANISM FOR HABITUATION IN *DROSOPHILA*

Ankita Chodankar, Baskar Bakthavachalu, Indulekha P Sudhakaran, Madhumala K Sadanandappa, Pushkar Paranjpe, Sudeshna Das and Swati Trisal

How do we ignore any familiar smell or taste? Brief or prolonged stimulus presentation causes reversible decrement in behavioral response. This phenomenon is referred to as habituation. Though most sensory systems habituate, as it is necessary for an organism to pay attention to salient features of the environment, the underlying molecular and neuronal mechanisms remains elusive.

Our studies in *Drosophila* olfactory and gustatory circuits suggest a general mechanism for habituation in different sensory circuits, by providing evidence for inhibitory potentiation that drives habituation (figure 2). Further, we have established that short-term habituation is not a necessary step towards long-term habituation, but they are processed in parallel. Different mRNPs and translational control molecules are known to regulate the potentiation of inhibitory synapses during long-term habituation, which is our current focus of interest.

Collaborators: Mani Ramaswami, Trinity College, Dublin, Ireland. and NCBS-TIFR, Bangalore, India Erich Buchner, University of Wurzburg, Germany. Bertram Gerber, Leibniz Institute for Neurobiology, Germany. Jayant Udgaonkar, NCBS-TIFR, Bangalore, India

3 MUSCLE DEVELOPMENT AND MAINTENANCE

Rajesh Gunage, Priyankana Mukherjee, Nagaraju Dhanyasi, M. Umashankar, Krishan Badrinath, Kunal Chakraborty

We use the indirect flight muscles (IFMs) of *Drosophila* as a model system to investigate muscle development.

A large pool of myoblasts (muscle precursors), which are specified on the developing wing disc, contribute to the different muscles required for flight. We find that these myoblasts are amplified during larval life through symmetric, followed by asymmetric modes of proliferation. This switch in division modes is regulated by Notch and Wingless signaling pathways. We are now investigating how muscle identities are determined within this common pool of precursors and the possibility of adult myogenic precursors.

Myoblasts then fuse with larval template muscles to form the adult IFMs. We have previously

identified a role for actin and actin nucleator proteins in this process. We are now performing a high resolution ultra-structural analysis of this process using transmission electron microscopy and by live imaging using confocal microscopy. We thus hope to understand the process of fusion by describing the sequence of events that occur in the wild type and comparing it with mutants that affect each of these processes.

Proper differentiation of the IFMs depends on reciprocal interactions between the muscle and its motoneuron. Surprisingly, perturbation of Hox function in the MNs has dramatic effects on the developing muscle. Conversely, perturbing levels of sphingolipid metabolites in muscles, leading to their severe malformation, results in reduced contacts between the MN and the developing IFM. We are now examining the mechanistic underpinnings of these phenotypes during development and maintenance of the IFMs.

Collaborators: Heinrich Reichert, University of Basel
Julie Saba, Children's Hospital Oakland Research Institute, USA.
Eyal Schejter and Ben-Zion Shilo, Weizmann Institute of Science, Israel

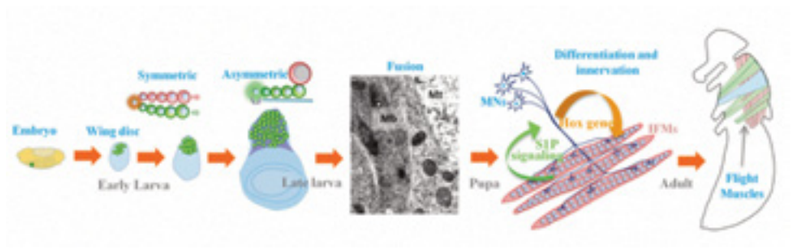


Figure 3: IFMs are derived from myoblasts associated with the wing disc. These initially proliferate symmetrically and then asymmetrically to generate the appropriate numbers. In the pupa, they fuse with templates to produce the IFM. Interactions between MNs and IFMs ensure appropriate differentiation to produce functional flight muscles in the adult fly.

4 DEVELOPMENT OF FUNCTIONAL MOTOR NEURON CONNECTIVITY IN THE WALKING AND GUSTATORY CIRCUIT

Syed Durafshan Sakeena, Ali Asgar Bohra, Aman Aggarwal

Complex motor behaviours like walking and feeding are enabled by precisely timed muscle contractions, which are regulated by motor circuits. Motor neurons (MNs) that control the legs (for walking) and those that control the proboscis (for feeding) are born in the central brain from stem cells like precursors called neuroblasts (NBs). We have previously identified the NB that give rise to the leg MNs and have found that they are organized as a 'myotopic map' in the ventral nerve cord of the central nervous system. This precise organization depends on NB lineage and the birth order of the MNs within that lineage. We find that the proboscis MNs develop very differently. They are embryonically born, and while they too are organized as myptopic map (in the suboesophageal ganglion, SOG, of the central brain), they are not associated with any known NB lineage of the SOG.

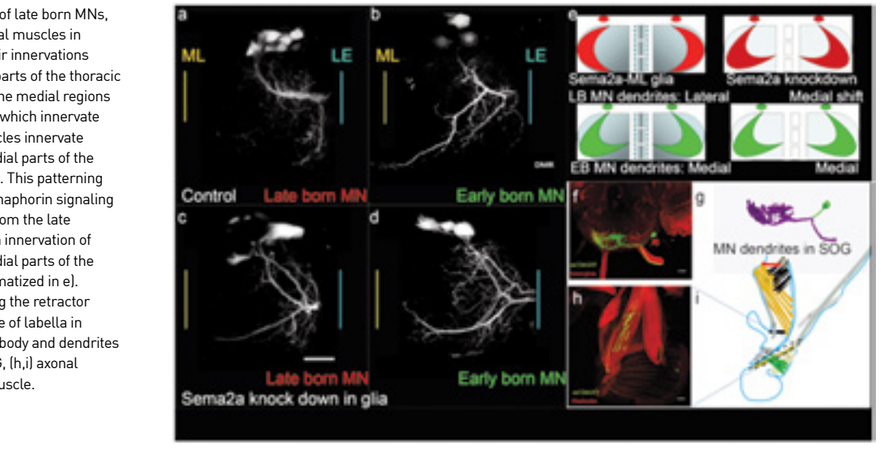


Figure 4: Dendrites of late born MNs, which innervate distal muscles in the legs, restrict their innervations towards the lateral parts of the thoracic ganglion and avoid the medial regions (a). Early born MNs, which innervate more proximal muscles innervate both lateral and medial parts of the thoracic ganglion (b). This patterning is dependent on Semaphorin signaling as loss of Sema2a from the late borm MNs results in innervation of both lateral and medial parts of the neuropile (c,d, schematized in e). (f-i) A MN innervating the retractor of paraphysis muscle of labella in proboscis. (f, g) Cell body and dendrites of the MN in the SOG, (h,i) axonal innervation of the muscle.

What are the molecular programs that instruct specificity in neuronal wiring required for the formation of these functional myotopic maps? We find that Semaphorins, and the signals to MNs from glial cells and muscles, instruct the development of functional motor neuron connectivity in the *Drosophila* walking circuit. The cross talk between glia, MNs and muscles imposes topographic order and proper positioning of the MNs in the central nervous system and the periphery so that a proper functional circuit is developed.

5 DEVELOPMENT OF COORDINATED LOCOMOTION IN LARVAL AND ADULT *DROSOPHILA*

O Venkateshwara Reddy, Swetha BM, Pushkar Paranjpe, Aman Aggarwal

Normal adult fly walking depends on well co-ordinated control of its six legs. The neural circuit and molecular mechanism of this precise inter-leg co-ordination is not understood. We have developed an assay using which we are trying to see how the circuit for inter-limb coordination is set in place prior to eclosion from the pupa. We are also developing a paradigm for free-walking flies and a highly detailed, automated analysis of acquired data for tackling this problem. We are now able to quantify walking behavior using eight basic parameters (three are depicted in figure 5). We aim to describe walking in wild type flies and in genetically perturbed backgrounds using these parameters and hope to unravel the mechanisms underlying adult fly walking. Using similar approaches we are also addressing the problem of larval locomotion.

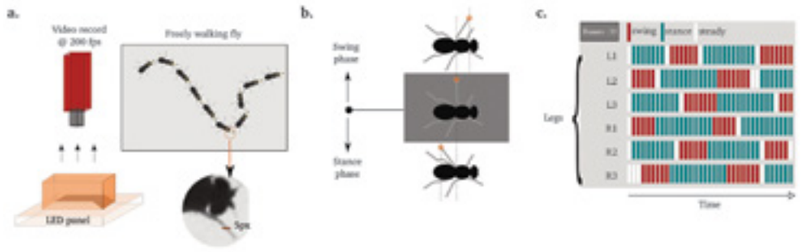


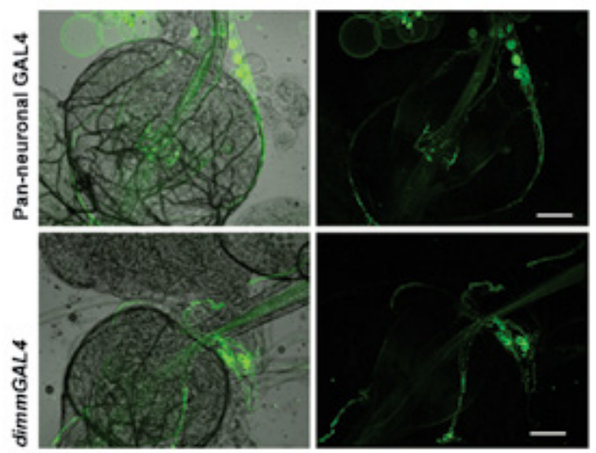
Figure 5: Automated analysis of free walking behavior of *Drosophila* using the FreeWalk platform. a) Walking behavior of a single fly is captured on a 200fps camera. b) The fly body centroid, the co-ordinates of leg-tips are used to auto-classify leg phases as swing, stance. c) Walking is summarized using a gait diagram. Each tick is 5ms in duration; red tick implies swing, turquoise tick implies stance and white tick implies steady phase.

Cellular events are often mediated by spikes of cytoplasmic calcium, sourced either externally or from internal stores. We study the mechanism and roles of the internal-stores system, focussing on how the intracellular messenger Inositol 1,4,5-trisphosphate triggers calcium release.

GAITI HASAN

Intracellular Calcium Signaling in Cellular and Systemic Physiology

Life evolved in sea water amongst a range of ions including calcium (Ca^{2+}). Primordial cells devised mechanisms that maintained a tight control on Ca^{2+} levels within them so as to prevent reactions incompatible with life such as protein aggregation and precipitation of ATP. Consequently, Ca^{2+} channels and pumps exist on cell membranes of organisms ranging from unicellular bacteria to higher animals and plants. Ca^{2+} containing intracellular compartments were formed as endo-membranes evolved and as multi-cellular organisms appeared these compartments are thought to have acquired new roles in intercellular communication, essential to manage the biological complexity of higher plants and animals. In higher animals the role of intracellular Ca^{2+} signalling in immune function is well understood. It's role in neuronal function has been proposed but not identified. Through behavioural, physiological and cellular studies of novel *Drosophila* mutants we show that signalling initiated by release of Ca^{2+} from intracellular stores co-ordinates flight and metabolism at multiple levels. These studies have broader implications for certain neurodegenerative disorders and metabolic diseases in humans



SELECTED PUBLICATIONS

Agrawal, T., Sadaf, S. and **Hasan, G.** (2013). A Genetic RNAi screen for IP_3/Ca^{2+} coupled GPCRs in *Drosophila* identifies the PdfR as a regulator of insect flight. *Plos Genet* 9: e1003849. Doi:10.1371/journal.pgen.1003849

Subramanian, M., Metya, S.K., Sadaf, S., Kumar, S., Schwudke, D. And **Hasan, G.** (2013). Altered lipid homeostasis in *Drosophila* $InsP_3$ receptor mutants leads to obesity and hyperphagia. *Dis. Model. Mech* 6 doi: 10.1242/dmm.010017.

Hasan, G. (2013). Intracellular signaling in neurons: unraveling specificity, compensatory mechanisms and essential gene function. *Current Opinion in Neurobiology,* 23:62–67http://dx.doi.org/10.1016/j.conb.2012.07.004.

1 INSULIN SIGNALING AND *DROSOPHILA* FLIGHT

Neha Agrawal, Gayatri Venkiteswaran, Sufia Sadaf

Ca^{2+} signaling is known to regulate the development, maintenance and modulation of activity in neuronal circuits that underlie organismal behavior. In *Drosophila*, intracellular Ca^{2+} signaling by the inositol 1,4,5-trisphosphate receptor and the store-operated channel (dOrai) regulates the formation and function of neuronal circuits that control flight. Here, we show that restoring $InsP_3R$ activity in insulin producing neurons of flightless $InsP_3R$ mutants (*itpr*) during pupal development can rescue systemic flight ability. Expression of the store operated Ca^{2+} entry (SOCE) regulator dSTIM in insulin producing neurons also suppresses compromised flight ability of $InsP_3R$ mutants suggesting that SOCE can compensate for impaired $InsP_3R$ function. Despite restricted expression of wild-type $InsP_3R$ and dSTIM in insulin producing neurons, a global restoration of SOCE and store Ca^{2+} is observed in primary neuronal cultures from the *itpr* mutant. These results suggest that restoring $InsP_3R$ mediated Ca^{2+} release and SOCE in a limited subset of neuro-modulatory cells can influence systemic behaviors such as flight by regulating intracellular Ca^{2+} homeostasis in a large population of neurons through a non-cell autonomous mechanism.

2 INTRACELLULAR CALCIUM SIGNALING AND LARVAL METABOLISM

Satish Kumar and Debleena Dey

Characterisation of *Drosophila* mutants for the $InsP_3R$ has demonstrated that $InsP_3$-mediated Ca^{2+} release is required in *Drosophila* larvae for growth and viability. To understand the molecular basis of these growth defects a genome wide microarray analysis has been carried out with larval RNA obtained from a strong $InsP_3R$ mutant combination in which 1504 independent genes were differentially regulated with a $\log_2$ of fold change of 1 or more and $P \leftarrow 0.05$. This was followed by similar transcript analyses from $InsP_3R$ mutants where growth defects were either suppressed by introduction of a dominant suppressor or rescued by ectopic expression of an $InsP_3R$ transgene in the *Drosophila* insulin like peptide-2 (Dilp2) producing cells. These studies show that expression of transcripts related to carbohydrate and amine metabolism is altered in $InsP_3$ receptor mutant larvae. Moreover, from a comparative analysis of genes that are regulated in the suppressed and rescued conditions with the mutant condition, it appears that the organism could use different combinations of pathways to restore a 'normal' growth state.

3 FUNCTIONAL COMPLEMENTATION OF *DROSOPHILA* IP3R BY THE RAT IP3R1

Sumita Chakraborty

The *Drosophila* inositol 1,4,5-trisphosphate receptor (IP3R) and mammalian type-1 IP3Rs have 57–60% sequence similarity and share major domain homology with each other. Mutants in the single *Drosophila* IP3R gene, itpr, and Itpr1 knockout mice both exhibit lethality and defects in motor coordination. Here the authors show that the rat type-1 IP3R, which is the major neuronal isoform, when expressed in the pan-neuronal domain in *Drosophila*, functionally complements *Drosophila* IP3R function at cellular and systemic levels. It rescues the established neuronal phenotypes of itpr mutants in *Drosophila*, including wing posture, flight, electrophysiological correlates of flight maintenance, and intracellular calcium dynamics. This is the first in vivo demonstration of functional homology between a mammalian and fly IP3R. This study also paves the way for cellular and molecular analyses of the spinocerebellar ataxias in *Drosophila*, since SCA15/16 is known to be caused by heterozygosity of human ITPR1.

4 SEROTONERGIC MODULATION OF *DROSOPHILA* FLIGHT

Sufia Sadaf

Flight is an integral component of many complex behavioral patterns in insects. The giant fiber circuit has been well studied in several insects including *Drosophila*. However, components of the insect flight circuit that respond to an air-puff stimulus and comprise the flight central pattern generator are poorly defined. Aminergic neurons have been implicated in locust, moth and

Drosophila flight. Here we have investigated the requirement of neuronal activity in serotonergic neurons, during development and in adults, on air-puff induced flight in *Drosophila*. To target serotonergic neurons specifically, a *Drosophila* strain that contains regulatory regions from the *TRH* (Tryptophan Hydroxylase) gene linked to the yeast transcription factor GAL4 was used. By blocking synaptic transmission from serotonergic neurons with a tetanus toxin transgene or by hyperpolarisation with Kir2.1, close to 50% adults became flightless. Temporal expression of a temperature sensitive Dynamin mutant transgene (*Shi^{ts}*) suggests that synaptic function in serotonergic neurons is required both during development and in adults. Depletion of IP_3R in serotonergic neurons via RNAi did not affect flight. Interestingly, at all stages a partial requirement for synaptic activity in serotonergic neurons was observed. The status of serotonergic neurons was investigated in the central nervous system of larvae and adults expressing tetanus toxin. A small but significant reduction was observed in serotonergic cell number in adult second thoracic segments from flightless tetanus toxin expressing animals.These studies show that loss of synaptic activity in serotonergic neurons causes a flight deficit. The temporal focus of the flight deficit is during pupal development and in adults. The cause of the flight deficit is likely to be loss of neurons and reduced synaptic function. Based on the partial phenotypes, serotonergic neurons appear to be modulatory, rather than an intrinsic part of the flight circuit. (Collaborator: Dr. Serge Birman, ESPCI, Paris, France).

5 OBESITY, INTRACELLULAR CALCIUM SIGNALING AND METABOLISM

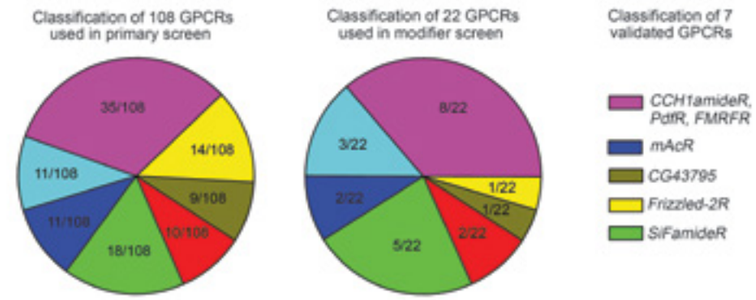
Manivannan Subramanian, Suman Kumar Metya

In recent years, there has been an alarming increase in individuals suffering from metabolic syndrome. This syndrome manifests in most cases as obesity, which arises due to an imbalance in nutritional intake and energy utilization, followed by diabetes and cardiovascular disease. Although genetic bases for metabolic syndrome are indicated, identification of susceptibility genes has been lagging. Recent studies have focused on the role of conserved signaling pathways in maintaining a healthy energy balance, in an attempt to identify causative factors underlying obesity and the associated metabolic syndrome. We show that previously well-characterized *Drosophila* melanogaster strains with mutations affecting an intracellular Ca2+-release channel, the inositol 1,4,5-trisphosphate receptor (InsP3R), are obese as adults. In contrast with most existing animal models of obesity, which require a fat enriched diet, the InsP3R mutants become obese on a normal diet. Obesity can be rescued in part by raising insulin signaling but, interestingly, the authors' data show that reduced insulin signaling in InsP3R mutants is not the primary cause of obesity. By extensive lipid profiling of mutant, wild-type and rescued *Drosophila* using mass spectrometry, they identified changes in the metabolic profile of InsP3R mutants: a higher level of storage lipids (triacylglycerides; TAGs) and a reduced level of membrane lipids. We propose that this altered metabolic profile is primarily due to reduced metabolism of long chain fatty acids. In addition, the mutant flies were found to exhibit loss of appetite control, leading to excessive feeding (hyperphagia), as well as altered transcriptional regulation of mid-gut lipases. Pharmacological inhibition of a subset of these enzymes was found to reduce obesity and TAG deposits in the InsP3R mutants. This study shows, for the first time, that mutations in InsP3R might be associated with adult-onset obesity. The *Drosophila* InsP3 mutants could prove to be a useful model for understanding the link between altered lipid metabolism and development of insulin resistance in humans. Furthermore, they can be used for the investigation of anti-obesity drugs, specifically those that target fatty-acid metabolism and TAG storage. (Collaboration: Dr. Dominik Schwudke, previously NCBS).

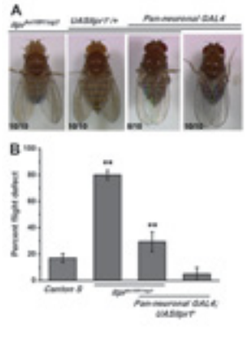
6 A GENETIC SCREEN TO IDENTIFY G-PROTEIN COUPLED RECEPTORS AFFECTING DROSOPHILA FLIGHT BEHAVIOR

Tarjani Agrawal

Insect flight is regulated by various sensory inputs and neuromodulatory circuits which function in synchrony to control and fine-tune the final behavioral outcome. The cellular and molecular bases of flight neuromodulatory circuits are not well defined. In *Drosophila melanogaster*, it is known that neuronal IP_3 receptor mediated Ca^{2+} signaling and store-operated Ca^{2+} entry (SOCE) are required for air-puff stimulated adult flight. However, G-protein coupled receptors (GPCRs) that activate intracellular Ca^{2+} signaling in the context of flight are unknown in *Drosophila*. We performed a genetic RNAi screen to identify GPCRs that regulate flight by activating the IP_3 receptor. Among the 108 GPCRs screened, we discovered 5 IP_3/Ca^{2+} linked GPCRs that are necessary for maintenance of air-puff stimulated flight. Analysis of their temporal requirement established that while some GPCRs are required only during flight circuit development, others are required both in pupal development as well as during adult flight. Interestingly, our study identified the Pigment Dispersing Factor Receptor (PdfR) as a regulator of flight circuit development and as a modulator of acute flight. From the analysis of PdfR expressing neurons relevant for flight and its well-defined roles in other behavioral paradigms, we propose that PdfR signaling functions systemically to integrate multiple sensory inputs and modulate downstream motor behavior.



Sensory	Perception of light and taste
Monoamine GABA, Glutamate, Acetylcholine Neuropeptide	Act as neurotransmitters, neuromodulators, neurohormones to regulate range of behaviors-mood, cognition, appetite, sleep, memory, courtship
Methuselah-like	Regulation of ageing, reproduction and exocytosis
Frizzled, smoothened rhomboid, roughoid	Control gene expression during morphogenesis
Not classified	Not known



7 METABOLIC CONTROL OF OBESITY THROUGH NEUROPEPTIDE SIGNALING

Siddhartha Jayakumar, Manivannan Subramanian, Shlesha Richhariya

In previous work we have shown that *Drosophila* mutants for the IP_3R (*itpr^{ku}*) become unnaturally obese as adults with excessive storage of lipids on a normal diet. While the phenotype manifests in cells of the fat body, genetic studies suggest dysregulation of a neurohormonal axis. We now show that knockdown of the IP_3R, either in all neurons or in peptidergic neurons alone, mimics known *itpr* mutant phenotypes. The peptidergic neuron domain includes, but is not restricted to, the medial neurosecretory cells as well as the stomatogastric nervous system. Conversely, expression of an *itpr^{+}* cDNA in the same set of peptidergic neurons rescues metabolic defects of *itpr^{ku}* mutants. Transcript levels of a gene encoding a gastric lipase *CG5932 (magro),* which is known to regulate triacylglyceride storage, can be regulated by *itpr* knockdown and over-expression in peptidergic neurons. Thus, the focus of observed *itpr* mutant phenotypes of starvation resistance, increased body weight, elevated lipid storage and hyperphagia derive primarily from peptidergic neurons. The present study shows that *itpr* function in peptidergic neurons is not only necessary but also sufficient for maintaining normal lipid metabolism in *Drosophila*. Our results suggest that intracellular calcium signaling in peptidergic neurons affects lipid metabolism by both cell autonomous and non-autonomous mechanisms.

Epigenetic marks superimpose underlying DNA sequence of eukaryotes and provide considerable agility is modulating gene expression. Epigenetics and small RNAs influence phenotypes of plants more likely than in animals. We are interested in understanding epigenetic and small RNA variations among plants.

PV SHIVAPRASAD

Understanding Epigenetic and Small RNA Variations

Small RNAs are the key molecules resulting from RNA silencing pathways and they regulate both transcription and translation with the help of their protein partners. Small RNAs are also important factors in initiating and maintaining heritable changes in gene expression without changes in DNA sequence (called 'epigenetics'). Small RNAs and epigenome modifications impact every aspect of eukaryotic development and disease. Contribution of individual small RNAs and epigenetic variations in phenotypes of plants are well documented but the mechanism is poorly understood. We are interested in understanding the pathways that generate small RNAs and epigenome modifications to be able to use them effectively in plants. Our laboratory uses various biochemical, genetic, bioinformatic and whole-genome approaches in a wide variety of model plants.

We use rice and its wild relatives to profile RNAs and look for variations in epigenome (such as DNA methylation and histone modifications) using whole-genome techniques. The idea is not only to generate fine map of genomic regions that show epigenetic and small RNA variations, but also to understand what contribution they have towards plant phenotypes and to understand how they are inherited. We use cauliflower, broccoli and wheatgerm to isolate native protein complexes that generate small RNAs to identify partner proteins to help us understand how they bring about changes in transcription and translation. Once the role of a small RNA/epigenome modification for a given phenotype is identified, they can be introduced to plants through transcriptional gene silencing technology that relies on viruses to alter the epigenome. Our approach should facilitate us to generate crop plants with specific, useful and predictable phenotypes.

SELECTED PUBLICATIONS

Jagtap, S., **Shivaprasad, P.V.** (2014). Diversity, expression and mRNA targeting abilities of Argonaute-targeting miRNAs among selected vascular plants. BMC Genomics 15:1049.

Shivaprasad, P.V., Ho-Ming, Patel,K., Bond,D. and Baulcombe,D. (2012). A microRNA superfamily regulates disease resistance via effects on NBS-LRR mRNAs and secondary siRNAs. Plant Cell 24: 859-874.

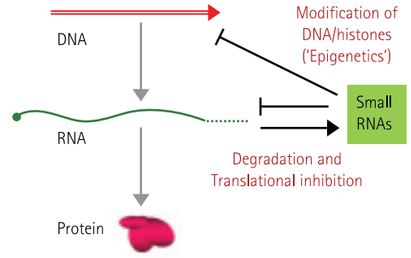
Shivaprasad, P.V., Dunn,R., Santos,B., Bassett,A. and Baulcombe, D.C. (2012). Extraordinary transgressive phenotypes of hybrids are influenced by epigenetics and small silencing RNAs. EMBO J. 31:257-266.

1 UNDERSTANDING FUNCTIONS OF RICE GENES INVOLVED IN SILENCING

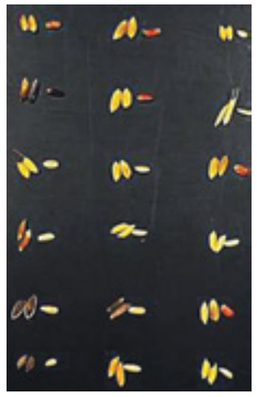
Rahul Raj Singh, Soumita Das, Anuradha Singh

Collaborator: K. Veluthambi, Madurai

Most of the understanding on plant silencing comes from Arabidopsis which is an annual dicotyledonous weedy plant. We use rice as model system to study small RNAs and epigenetics using landraces and wild relatives of rice. Rice has 3 times bigger genome than the model system Arabidopsis, but its complexity provides advantages too. For example, 4% of cytosines are methylated in Arabidopsis (genome size is 150 Mb), while 15-20% of all cytosines are methylated in rice (genome size 450 Mb) thus showing a considerable difference in genome-wide methylation. Rice has much more diverse and likely altered silencing pathways than Arabidopsis. Rice is a monocot (and model for all monocots) and a crop plant with high phenotypic variation among its landraces/varieties. However, the drawback of using rice is that there are no ready tools, such as stable knockout lines, established protocols, etc. readily available. There are 4 knockdown lines reported from China for rice genes involved in silencing, but the method used for knockdown (Inverted repeats) creates doubt about their off target effects especially since rice has multiple copies of these genes with high sequence similarity. We use artificial miRNAs, carefully designed to target individual mRNAs. Artificial miRNAs are assembled by replacing rice miRNA with an artificial one in a base plasmid (pNW55, gift from Detlef Weigel's group) and then cloned under maize Ubiquitin promoter in a binary vector that we specifically designed (pSD1). These binary vectors are being used to generate transgenic rice knockdown lines in our tissue culture facility.



Small RNA regulators influence expression of RNA at multiple levels. They regulate development, disease and genome integrity among eukaryotes.



Natural Variation among local rice landraces

2 INDUCTION AND MAINTENANCE OF EPIGENETIC VARIATIONS USING VIRAL VECTORS: CLONING AND CHARACTERIZATION OF A NEW *BEGOMOVIRUS*

Soumita Das, Supriya Khedkar

Collaborator: Aswin Seshasayee, NCBS

Viruses have been used to effectively silence genes by a method called 'Virus-induced gene silencing' (VIGS). A fragment of DNA in the viral genome is introduced and this modified virus is used for infecting plants. When the virus replicates, part of the foreign fragment is expressed and initiates silencing of the complementary endogenous host sequence. Recent data indicates that genes can be silenced using virus derived vectors targeting promoters of important host genes. This targeting not only triggers silencing of the genes, but also stimulates methylation of the promoters (transcriptional gene silencing). Quite extraordinarily, this methylation can be inherited to the next generation without the presence of the inducer (virus or transgene) to keep the gene shut off. In other words, a gene knockdown can be achieved without having any transgene/foreign DNA in the offsprings of the plants treated. This is an extremely interesting and valuable tool to avoid the GM controversy since most common technology used until now to knockdown genes is through GM technology.

We use three sets of viral vectors to achieve this. In addition to using reported viral vectors such as those derived from Tobacco rattle virus (TRV), and Rice tungro bacilliform virus (RTBV), we are evaluating if DNA viruses of *Geminiviridae* family would serve similar purpose. Geminiviruses should be better suited to induce transcriptional silencing due to their replication in the nucleus and abundant 24 nt siRNAs they generate, two key ingredients for transcriptional silencing. A geminiviral vector system (Cabbage leaf curl virus) is available with us, however it is a typical bipartite begomovirus with DNA A and DNA B with limited host range. Another version of begomovirus that has DNA β, coding for an extremely interesting protein called βC1 is highly desirable as a vector.

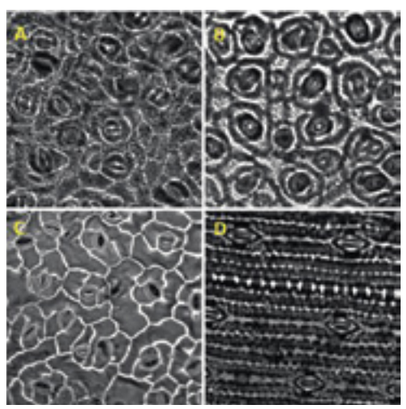
We have isolated such a virus infecting *Syndrella nodiflora* from GKVK campus that holds promise as a vector for epigenetic modification of host promoters. This virus has a typical DNA A and a DNA β molecule half the size of DNA B. The DNA A is less than 90% similar to any known begomovirus, thus it qualifies as a new species. Analysis of nucleotide and aminoacid similarities with other members of the *Geminiviridae* has shown that this virus is a recombined version of well-known Tomato leaf curl virus and some weed infecting viruses from South India and Sri Lanka.

3 MECHANISM OF SILENCING: A BIOCHEMICAL APPROACH

Soumita Das, Unnati Patel

Collaborators: David Baulcombe, University of Cambridge; Deepak Nair, NCBS

Dicer-like (DCL) proteins are RNAse III type nucleases that cleave structured RNA species to produce small RNAs. These small RNAs are incorporated into effectors called Argonautes (AGO) to target RNAs that have complementarity with the small RNAs. Most AGOs and DCLs are abundant only in floral tissues. Despite RNA silencing being discovered in plants, biochemical analyses of silencing players in plants such as *Arabidopsis* has met with little success, especially because the plant DCL complexes are huge, low abundant, have many partners and their extracts are unstable. Thus, most of the mechanistic understanding of plant silencing came from mutation studies. However, unlike animal systems, plants have diversity in Dicer genes (4 variants in *Arabidopsis*) and AGOs (10 in *Arabidopsis*), with partially redundant functions, thus taking conclusive mechanistic understanding of their functions from mutants a challenge. We use cauliflower, wheatgerm and broccoli systems, that can easily circumvent several of the practical and technical difficulties one deals with *Arabidopsis* and other model systems.



Simultaneously, it is useful to understand what kind of small RNAs/miRNAs exists in cauliflower and broccoli as those candidates can be used for detecting native ribonucleoprotein complexes. Such datasets are not available publicly. Hence we performed an Illumina HiSeq RNAs from seedlings and florets of cauliflower. The samples were prepared taking into account inverse correlation among miR172 and miR156 between seedlings and floral tissues. Several interesting observations have been made from these datasets and we are trying to understand how small RNAs influence cauliflower development.

4 STRUCTURAL AND BIOCHEMICAL STUDIES USING GEMINIVIRAL PROTEINS:

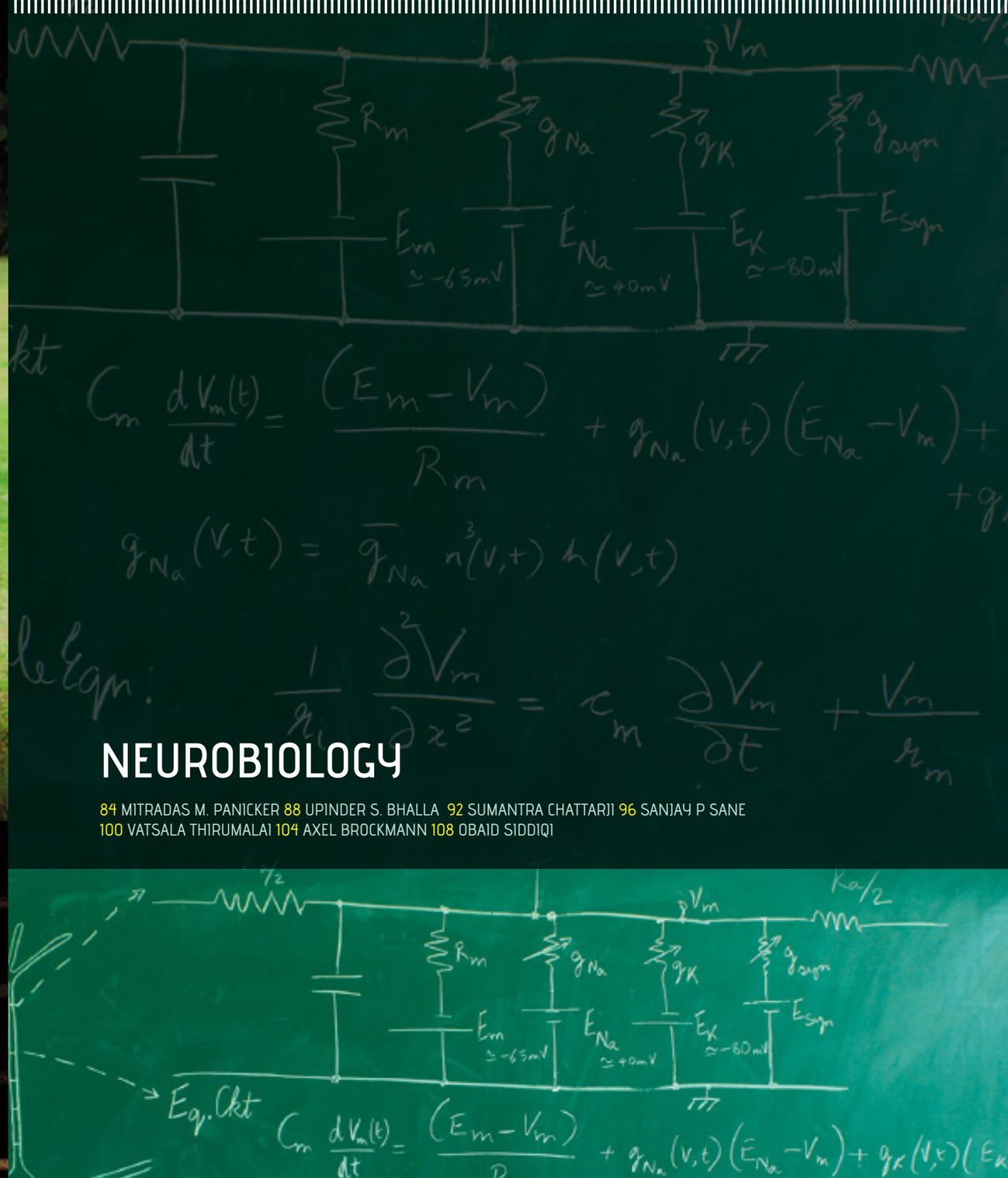
Unnati Patel

Collaborator: Deepak Nair, NCBS

Viruses and their proteins are excellent tools to understand silencing. All viruses are targets of silencing and in order to successfully infect the host, viruses must counteract silencing. Usually this suppression is brought about by 'suppressor proteins' that can interfere with multiple steps of silencing. Among RNA viruses, the strategy seems to be to bind to all small RNAs thereby protecting viral mRNAs that could be targeted for mRNA cleavage. Among DNA viruses though, the mechanism is not clear.

We are interested in structural studies of DNA viral suppressor proteins from Syndrella yellow vein virus (SYVV), the ssDNA virus that we have cloned. We have generated bacterial expression cassettes for Rep (a WT clone in pET vector has been generated as well as a tyrosine mutant), AC2 (WT) and βC1 (sole protein from the DNA β). We are currently expressing these proteins in order to purify and determine their crystal structures hoping that this will shed light on their mechanisms in silencing suppression and also the mechanism of silencing itself.

A. Rice plants in the growth chamber.
B. Regenerating rice callii



NEUROBIOLOGY

Serotonin plays important roles in the CNS and the periphery. We aim to understand its role using in vitro cellular models as well as in vivo studies. We also use in vitro cellular models using individual-specific pluripotent stem cells to study neurodegeneration.

MITRADAS M PANICKER

Roles of Serotonin in Neural and Non-neural Systems

Serotonin (5-Hydroxytryptamine – 5-HT) not only plays an important role in behavior but also in varied processes such as liver regeneration, hematopoesis, gut motility, insulin secretion etc. Most of the 5-HT is present outside the nervous system and most of its activity is driven through multiple receptor subtypes. Our laboratory has focused on the interactions of serotonin with its receptors, primarily the 5-HT_{2A} subtype. These interactions have been studied in non-neuronal and neuronal model cell lines, rodent models as well as more recently in human pluripotent stem cells and their derivatives. Modified human and rat 5-HT_{2A} receptors have been used to allow for easy visualization of the receptors within cells. These studies have led to interesting observations regarding the behavior of the receptor in the presence of serotonin, dopamine and antipsychotics – the latter being in wide clinical use. These studies have also helped us dissect some of the details of how these receptors are regulated by endogenous and exogenous ligands. We have extended some of these studies to behavior using rodents that have been genetically engineered to lack these receptors. Interesting behavioral variations have been observed with these animals when given antipsychotics.

Serotonin also seems to have a very early role in mammalian embryonic stem cells. Serotonin is localized to the mitochondria in pre-implantation mouse embryos and application of exogenous serotonin increases mitochondrial potential. Serotonin is also present in mouse and human embryonic stem cells and also in induced pluripotent stem cells, where a significant portion of it is localized to the mitochondria. Exogenous application of serotonin increases mitochondrial potential in mouse ES cells and also decreases the levels of reactive oxygen species.

SELECTED PUBLICATIONS

Bhattacharya, A., Sankar, S. and **Panicker, M.M.** (2010). Differences in the C-terminal tail contribute to the variation in trafficking between the Rat and Human 5-HT2A receptor isoforms: Identification of a primate-specific tripeptide ASK motif that confers GRK-2 and β2-Arrestin interaction. *J. Neurochem.* 112: 732-732.

Raote, I., Bhattacharyya, S. and **Panicker M.M.** (2012). Functional Selectivity in Serotonin Receptor 2A (5-HT2A) Endocytosis, Recycling and Phosphorylation. ***Mol. Pharmacol***. 83: 42-50.

Cavaliere, F., Benito-Muñoz, M., **Panicker. M.** and Matute, C. (2013). NMDA modulates oligodendrocyte differentiation of subventricular zone cells through PKC activation. *Front. Cell Neurosci.* 7: 1-7. eCollection 2013.

1 FUNCTIONAL SELECTIVITY AT SEROTONIN RECEPTORS

Ishier Raote, Shishupal Singh, Shuchita Soman, Radhika Joshi

We have determined that a number of endogenous amines, including trace amines, have been found to interact with the 5-HT_{2A} receptor. The list includes dopamine, tryptamine, tyramine, norepinephrine, epinephrine, β-phenylethylamine (PEA). We have observed that most, but not all amines, act as agonists at the 5-HT_{2A} receptor, with different potencies and efficacies. Different ligands acting at the same receptor but modulating intracellular transduction cascades to different extents is commonly referred to as 'functional selectivity'. This has obvious implications *'in vivo'* and should be helpful in determining the differing roles of the receptor in various tissues. In these studies we have determined that the phosphorylated state of the receptor is important in its recycling to the cell surface after internalization following activation by an agonist.

In addition, our studies we have continued to try and understand the interaction of the 5-HT2A receptor with antipsychotics. Our results suggest that many of these drugs not only block the interactions of the endogenous ligands with the receptor but also activate other signalling pathways. In order to characterise these interactions we have generated and characterized a 5-HT_{2A} Knockout mouse.

Collaborator: R. Sowdhamini

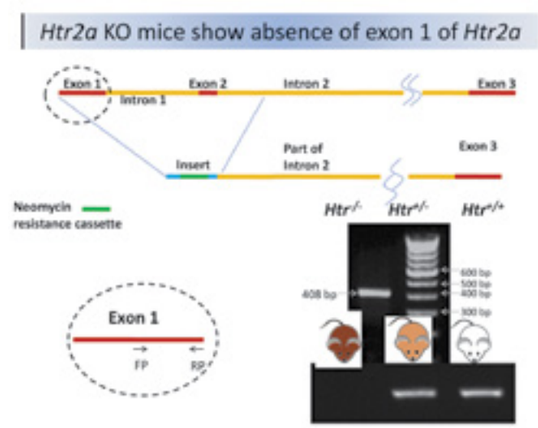
2 CHARACTERIZATION OF THE 5-HT_{2A} KNOCKOUT MOUSE

Radhika Joshi, Shuchita Soman

A 5-HT_{2A} receptor 'knockout' mouse had been generated in collaboration with Dr. Rupasri Ain. The mouse fails to express the 5-HT_{2A} receptor in the brain as well as in other tissues and serves as a global knockout model (Figure 1.). We are currently using Clozapine as a representative antipsychotic to look at the role 5-HT_{2A} in antipsychotic-mediated side effects in this strain. Clozapine is known to induce sedation in almost 30% of patients. This effect is also observed in mice and can be quantified by measuring the spontaneous locomotor activity in mice. We observe that 5-HT_{2A} knockout mice are resistant to clozapine-induced sedation in a dose-dependent manner, consistent with what has been reported in the literature, though with increases in the dose of clozapine, the knockout mice also start showing sedation. Having established the basic behavioural and molecular characteristics of the knockout strain, we are now exploring the pathways that lead to clozapine-induced sedation as well as interactions with other antipsychotics.

Collaborator: Rupasri Ain

Figure 1: Generation and Characterization of a *Htr2A* KO mouse



3 ROLE OF SEROTONIN IN EMBRYONIC AND INDUCED PLURIPOTENT STEM CELLS

Megha PB

Mouse pre-implantation embryos contain serotonin at fairly high levels which is localized to the mitochondria. Addition of exogenous serotonin increases mitochondrial potential. We have extended these studies to mammalian embryonic stem cells. Serotonin is localized to the mitochondria in both mouse and human ES cells. Addition of extracellular serotonin alters the mitochondrial potential in mouse ES cell similar to what was observed with pre-implantation embryos. In addition, extracellular serotonin decreases the levels of Reactive Oxygen Species (ROS) in ES cells. On converting mouse or human somatic cells to the pluripotent state, serotonin is synthesized and gets localized to the mitochondria significantly. Exogenous addition of serotonin also decreases the level of ROS in these cells. Mitochondrial potential has also been reported to affect the differentiation potential of ES cells. These results suggest that serotonin has a role to play in early development.

We are also examining the role of serotonin in embryonic stem cells and induced pluripotent stem cells using mouse strains that have the rate-limiting enzyme for serotonin synthesis – tryptophan hydroxylase, deleted. These studies should throw light on some of the processes involved.

Collaborators: Michael Bader (Max Delbruck Center for Molecular Medicine, Germany), Natasha Alenina (Max Delbruck Center for Molecular Medicine, Germany), Valentina Mosienko (Max Delbruck Center for Molecular Medicine, Germany.

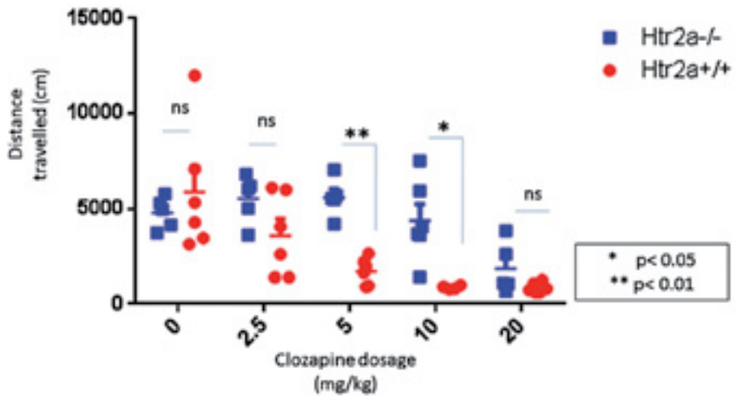


Figure 2: Behavioural Differences between *Htr2A* KO mice and Wildtype mice on Clozapine

4 HUMAN INDUCED PLURIPOTENT STEM CELLS AND DISEASE MODELS

Radhika Menon, Muthuswamy Thangaselvam, Shadan Zulfiqar, Tara Atmaram, Anu Sebin, Krithikka Ravi, Gopal Das, Ashaq Hussain, Aparna Ashok, Odity Mukherjee

Human somatic cells can be converted to pluripotent stem cells (iPSCs), very similar to embryonic stem cells, using a set of transcriptions factors identified by Shinya Yamanaka and colleagues. The iPSCs allow for the generation of individual-specific pluripotent stem cell lines, and more interestingly from individuals with disorders. These cell lines differentiate *in vitro* into specific cell types and in the case of some diseases have been shown to model some aspects of the disease, particularly when the disease is associated with a genetic disorder. They serve as an inexhaustible source for tissue-specific cells from such individuals and have begun to provide interesting results and approaches to understand these disorders.

We have generated iPS cells from individuals who suffer from early onset dementia and have differentiated them into neural stem cells and neurons. We used lymphoblastoid cell lines from different individuals and converted these into iPS cells with EBV-based plasmids using an integration-free method devised by Yamanaka and colleagues. These human iPS lines are from individuals carrying specific alleles at the ApoE locus and with a clinical history of late onset Alzheimer's disease (LOAD) or dementia. Transcriptome analysis of these lines, both undifferentiated as well as differentiated, are in progress. These cell lines are also being modified at the ApoE locus to generate a set of isogenic cell lines that carry various alleles. These cell lines and their differentiated derivatives will be used in various *in vitro* assays designed to understand and discover the processes involved at the cellular level in dementia.

The neural stem cells from the iPS cell lines are also being studied to determine the process of differentiation and the factors that can play a role. These are being used to study the role of serotonin and its receptors in neural stem cell and their proliferation.

Collaborators: Sanjeev Jain (NIMHANS) – Early Onset Dementia, Mukund Thattai, Ashwin Seshasayee, Carlos Matute (University of Pais Vasco, Spain), Fabio Cavaliere (University of Pais Vasco, Spain).

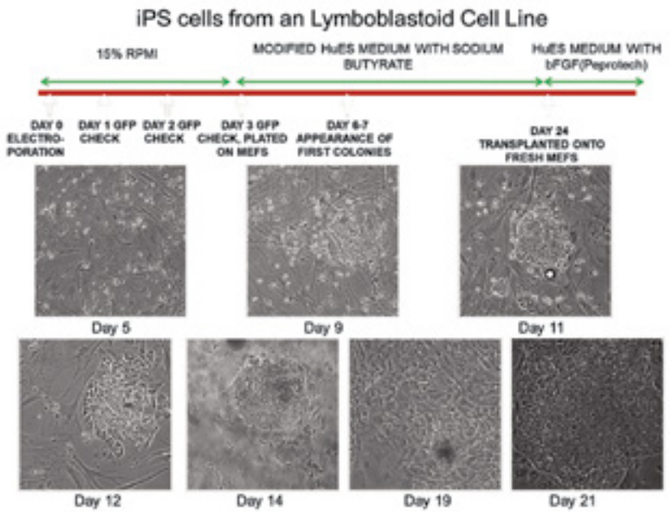


Figure 3: Derivation of iPS cells from a Lymphoblastoid Cell Line

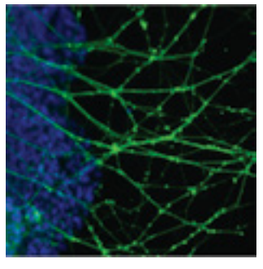
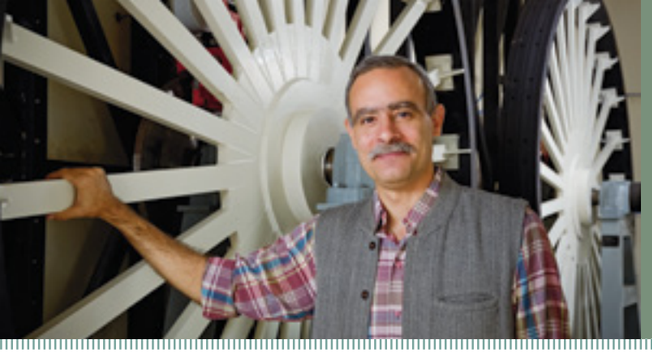


Figure 4: Neurons derived from an iPS cell line

5 CELL SUBSTRATE ADHESION AND 5-HT$_{2A}$ RECEPTORS

Joe Anand Kumar, Basudha Basu

The 5-HT$_{2A}$ receptor has been a target for antipsychotics and its interactions with these clinically used drugs can also lead to various side-effects. The receptor is expressed extensively outside the nervous system and so these observations are not too surprising. We had observed that over-expression of the 5-HT$_{2A}$ receptor in a weakly adherent non-neural cell line i.e. HEK293 increased cell substrate adhesion significantly. The adhesion was blocked by antipsychotics or antagonists, while 5-HT$_{2A}$ agonists, including partial agonists, increased cell substrate adhesion. The mechanism of adhesion is dependent on the cell type and the signalling processes that are activated. Preliminary results indicate that the adhesion process may be different between the rat and human receptor subtypes, similar to the differences in the signalling processes that we have observed between the rat and human receptor isoforms.



Molecules are the ink of experience, cells the words, and the vast networks of the brain form the rolled-up scroll of our memory. We use computer modeling and experiments to understand how experiences leave their trace through all these levels.

UPINDER S BHALLA

Watching Memories Form: Molecules, Networks and Computation

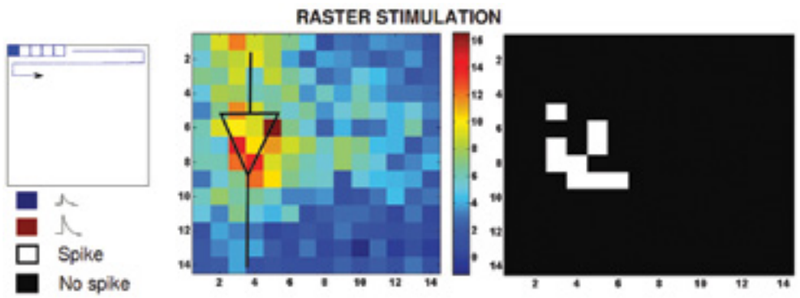
We study how memories are encoded, from molecular changes at synapses to large-scale rewiring of the brain. We also ask the complementary question: how does network activity trickle down through electrical and chemical signals, to trigger these long-term changes? Our research utilizes rodent behavior, electrophysiology, brain-activity imaging, and optogenetics to address these questions. We also develop detailed, biologically constrained computational models to understand network plasticity phenomena across scales.

SELECTED PUBLICATIONS

Modi, M.N., Dhawale, A.K. and **Bhalla, U.S.** (2014). CA1 cell activity sequences emerge after reorganization of network correlation structure during associative learning. ***eLife***.

Bhalla, U.S. (2014) Molecular computation in neurons: a modeling perspective. *Curr. Op. Neurobiol.* 25:31-37.

Parthasarathy, K, and **Bhalla, U.S.** (2013).Laterality and symmetry in rat olfactory behavior and in physiology of olfactory input. *Journal of Neuroscience*, 33(13):5750-60.



Light-sensitive map of a neuron that expresses Channel Rhodopsin 2, which converts light into electrical stimulation. Map was generated by scanning a light spot over a brain slice and recording the electrical response of the neuron.

1 WATCHING MEMORIES FORM.

Mehrab Modi, Ashesh Dhawale, Kambadur Ananthamurthy, Soumya Bhattacharjee.*

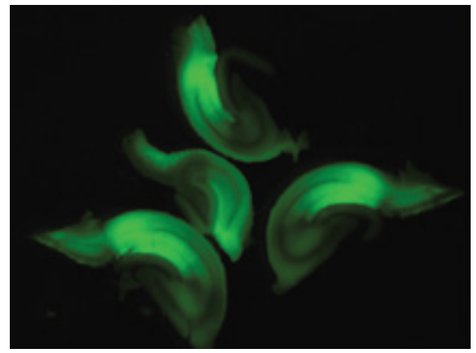
Modern imaging and optogenetic methods provide a way to literally watch brain activity. We have constructed a custom two-photon microscope and used it to record the activity of hundreds of neurons in the hippocampus, which is one of the key memory regions of the brain. Mice are exposed to a sound that comes half a second before an air puff to an eye, and soon they learn to blink in anticipation. We find that as the mice learn, neurons in their hippocampus organize their activity into a relay where one cell is active briefly, then another cell takes over, and so on. This sequence spans the interval between the sound and the puff and provides a mechanism to potentially establish the association between the stimuli. We also monitor baseline correlations between cells as a measure of network connectivity, and using this we find that the network reorganizes during this learning process. (Modi, Dhawale, and Bhalla, eLife 2014).

2 DECODING NETWORK WIRING

Aanchal Bhatia, Oliver Muthmann

We use two techniques to study connectivity, and how it changes, in brain networks. Both these methods work in brain tissue in a dish. In one approach, we put thin slices of rat or mouse hippocampus in a dish and carry out patch recordings from output neurons in the CA1 region of the hippocampus, to obtain very sensitive readouts of all inputs impinging on the cells. We then use patterned light stimuli in the upstream CA3 region, to trigger activity in cells which express a genetically-encoded light sensor. This lets us fill in 'maps' of which cells from the CA3 connect to those in the CA1 (Bhatia). We will use these maps to understand how connections change during learning, and if prior experience of the animals alters connectivity patterns. In the second approach we analyze data from collaborators who have recorded from many cells grown on an electrode array. By analyzing correlations in these activity patterns we can estimate connectivity and network activity sequences (Muthmann).

Figure 1: Sections through the hippocampus of a transgenic mouse whose cells express an optogenetic construct (Channel Rhodopsin 2), which here is visualized as green fluorescence



3 CHEMICAL COMPUTATION IN MEMORY

Pragati Jain, Sahil Moza*

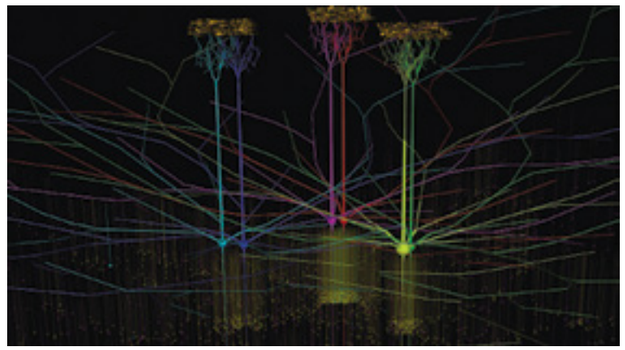
At a smaller scale than even individual cells, we have for many years examined how molecular logic can give rise to computation at the very tiny scale of connections (synapses) between cells. One important form of such logic involves the synthesis of new proteins following activity. This has two aspects, both of which we have modeled. First, local protein machinery must respond to input activity to trigger translation of mRNA (Jain and Bhalla 2009). On a longer timescale, the mRNA itself must be synthesized and transported from the nucleus. We have found that different activity patterns at the synapse can be decoded into distinct subsets of synthesized mRNA (Jain and Bhalla, in review). Once synthesized, the proteins at the synapse must store information reliably. We are investigating the kinds of chemical networks that may give rise to robust molecular memory switches, which are resistant to chemical noise (Moza). This is important to understand how nature has designed chemical memory switches to reliably store information.

4 DETAILED MODELS OF NETWORK COMPUTATION

Subhasis Ray, Aditya Gilra*

We have used detailed computer models to study how networks of neurons implement computational functions in the cortex and in the olfactory systems. To do this, we utilize data from our own experiments as well as other published work. In the cortex we have implemented a previously proposed model in MOOSE, and used this to analyze what kinds of network phenomena lead to, and suppress oscillations (Ray). We have also used this model to propose techniques for working out synaptic connectivity, which may help to guide the experimental design for decoding network wiring as described above. In the olfactory system, we have implemented a model of the olfactory bulb which is the first stage of olfactory computation. This model contains over 10,000 biophysically detailed compartmental models of mitral, granule, and periglomerular cells. (Gilra and Bhalla, in review). Having constrained the model with well-established cellular excitability properties, we are able to predict highly specific spatial connection patterns that are essential to replicate the odor encoding results.

Figure 2: Computer model of olfactory bulb



5 ODOR LOCALIZATION AND CODING

K. Parthasarathy, Urvashi Raheja, Priyanka Gupta*

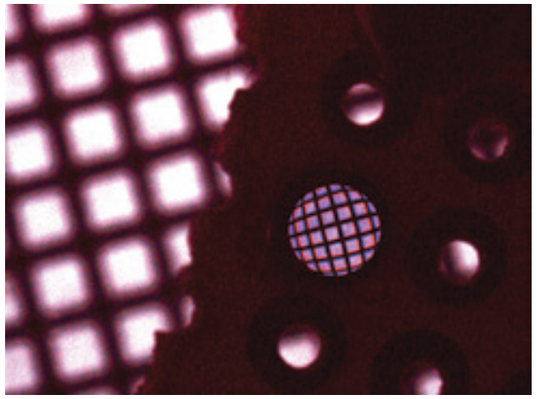
Rats are very good at localizing odorants. We have previously shown that they can sense odor direction using their two nostrils. In recent work we have shown that this translates into effective localization by virtue of very precise balance in sensitivity on the two sides, as well as well-separated pathways for odor detection. We used intrinsic signal imaging from both sides of the rat brain to show that the brain responses are also very well separated, and that these brain responses are completely sufficient to account for the ability of the animals to localize the odor (Parthasarathy and Bhalla, 2013). We have earlier examined odor tracking of surface-borne odorants, to work out the strategy employed by rats to do this (Khan, Sarangi and Bhalla 2012). In current work we have taken this to the more difficult system of air-borne odorants, and find that they employ quite different strategies (Raheja). In order to perform these remarkable odor tracking tasks, animals must encode details about *when* stimuli arrive, and *what* these stimuli were. We have used precise computer-controlled odor pulses to study how odor signals sum in time (Gupta and Bhalla, in revision). We find, surprisingly, that a simple linear summation model accounts both for summation in time and between odors, within any given concentration range.

6 ONE SIMULATOR TO RULE THEM ALL: THE MOOSE PROJECT

G.V. HarshaRani, Subhasis Ray, Aditya Gilra, Aviral Goel, Dilwar Singh, H.Chaitanya.

A large part of our research described above depends on being able to make detailed, biologically motivated models of neuronal events, from molecules up to networks. No simulator currently spans all these scales. As a major long-term project in our lab, we are building the Multiscale Object Oriented Simulation Environment, MOOSE. This is a framework for embedding many levels of biological description, and linking these to diverse numerical engines for simulations. MOOSE currently handles biophysical models incorporating channel physiology, network models of simple as well as highly detailed biophysical neurons, and a range of deterministic and stochastic methods for chemical signaling. We work closely with international efforts to develop modeling standards like SBML and NeuroML, and have incorporated these into MOOSE (HarshaRani). We are further implementing a new language for MUltiscale Models in Biology (MuMBL) which will facilitate combining SBML and NeuroML descriptions and adding diffusion detail (Singh and Bhalla). Within MOOSE, we have implemented a Python interface for model scripting (Ray and Bhalla, 2008), and a graphical interface for model development (HarshaRani, Ray, Goel). We are developing a standalone program MooGli, for display and analysis of model and experimental data in 3D (Chaitanya, Goel and Bhalla).

Figure 3: Imaging a reference grid through a Graded Refractive Index (GRIN) lens. We are developing methods to use GRIN lenses to image deep-brain structures such as the hippocampus.



Severe emotional problems are a hallmark of many stress and autism spectrum disorders. We explore the neural basis of these phenomena in the brain's emotional hub – the amygdala – from molecular and synaptic mechanisms at one end to their behavioral manifestations at the other.

SUMANTRA CHATTARJI

The Amygdala in Affective Disorders: from Molecules to Memories

Although we think of memories as rooted in the past, they have a profound influence on how we respond to events in the future. In this sense, what we learn from past experiences – our memories – not only give shape to our sense of who we are, but also how we interact with the world around us. Memories come in many different flavors – some experiences are memorable, others forgettable. Emotionally significant experiences tend to be well remembered, and the amygdala has a pivotal role in this process. But the rapid and efficient encoding of emotional memories can become maladaptive – severe stress often turns them into a source of prolonged anxiety. What are the cellular mechanisms underlying these powerful emotional symptoms? To answer these questions, we have been carrying out a range of behavioral, morphometric, electrophysiological and biochemical analyses of the neural correlates of stress-induced modulation of amygdala structure and function.

Our findings point to unique features of stress-induced plasticity in the amygdala, which are strikingly different from those seen in the hippocampus, and could have long-term consequences for behavioral symptoms seen in affective disorders. Further, the genes we inherit can also cause behavioral dysfunction. Strikingly, individuals afflicted with certain types of autism spectrum disordedrs often exhibit impaired cognitive function alongside debilitating emotional symptoms. Hence, we are extending our analyses to genetically engineered rats and mice to identify cellular and molecular targets that can be used to correct symptoms of Fragile X Syndrome, the leading genetic cause of autism.

In earlier studies, stress-induced plasticity in different brain regions was viewed as stand-alone effects manifested as properties intrinsic to individual structures. Further, function was inferred from analysis at the cellular and behavioral levels without any online readout of dynamic changes in neuronal activity in the intact animal. However, neuroanatomical data also point to extensive interconnections between the hippocampus and amygdala. This raises the intriguing possibility that some of the structural and physiological changes triggered by stress in one brain area may, at least in part, influence changes in other areas. Therefore, we are using *in vivo* recordings in freely behaving animals to explore the potential interdependence and interactions between brain areas differentially affected by stress.

SELECTED PUBLICATIONS

Ghosh, S. and **Chattarji, S.** (2014) Neuronal encoding of the switch from specific to generalized fear. *Nature Neuroscience* doi:10.1038/nn.3888.

Ghosh, S., Rao, L.T., and **Chattarji, S.** (2013) Functional Connectivity from the Amygdala to the Hippocampus Grows Stronger after Stress. *Journal of Neuroscience* 33(17):7234 –7244.

Rao, R.P., Anilkumar, S., McEwen, B.S., and **Chattarji, S.** (2012) Glucocorticoids protect against the delayed behavioral and cellular effects of acute stress on the amygdala. *Biological Psychiatry* 72 (6): 466-475

Suvrathan, A. and **Chattarji, S.** (2011) Fragile X Syndrome and the Amygdala. *Current Opinion in Neurobiology*, 21 (3): 509-515.

1 ERRING ON THE SIDE OF CAUTION: NEURONAL ENCODING OF THE SWITCH FROM SPECIFIC TO GENERALIZED FEAR

Supriya Ghosh

Fear memories are crucial for survival. However, excessive generalization of such memories, characterized by a failure to discriminate dangerous from safe stimuli, is common in anxiety disorders. Neuronal encoding of the transition from cue-specific to generalized fear is poorly understood. We identified distinct neuronal populations in the lateral amygdala (LA) of rats that signaled generalized versus cue-specific associations and determined how their distributions switched during fear generalization. Notably, the same LA neurons that were cue-specific before the behavioral shift to generalized fear lost their specificity afterwards, thereby tilting the balance of activity toward a greater proportion of generalizing neurons (Figure 1). Neuronal activity in the LA, but not the auditory cortex, was necessary for fear generalization. Furthermore, targeted activation of cAMP/PKA signaling in the LA increased neuronal excitability of LA neurons and led to generalized fear. These results provide a cellular basis in the amygdala for the alteration of emotional states from normal to pathological fear.

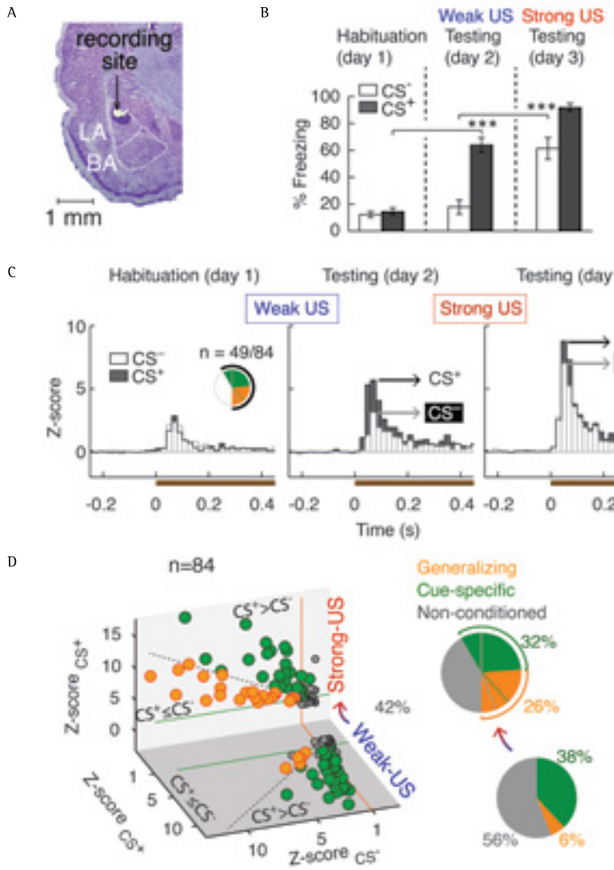


Figure 1: (A) Recording sites in the LA. **(B)** Freezing levels after weak US conditioning. During testing 1 d after conditioning, the CS^+, but not CS^-, evoked higher freezing relative to habituation and CS^-. After strong US conditioning, the same CS^- elicited a significantly higher level of freezing, thereby causing generalization of conditioned fear. **(C)** Population responses of cue-specific (green) and generalizing (orange) neurons. Weak US increased responses to CS^+, but not CS^-. After strong US, the two responses were not significantly different. **(D)** *Left*, population distribution of all three classes of neurons. *Right*, pie plots of population distribution shifted during switch to higher generalization.

2 EFFECTS OF STRESS ON FUNCTIONAL CONNECTIVITY BETWEEN THE AMYGDALA, HIPPOCAMPUS AND PREFRONTAL CORTEX

Supriya Ghosh and Mohammed Mostafizur Rahman

The cellular and molecular effects of stress on the amygdala are strikingly different compared with those in the hippocampus. Previous findings on stress-induced plasticity were based primarily on postmortem analysis within individual areas. However, little is known about how stress

affects dynamic changes and interactions in neuronal activity between the two areas. Hence, we simultaneously monitored *in vivo* activity of neuronal populations located in hippocampal areas CA1 and CA3 and the lateral amygdala (LA) in rats during and after chronic immobilization stress. The amplitude of auditory-evoked potentials (AEPs) in the hippocampus increased transiently only after a single 2 h stress but not when it was repeated for 10 d. In contrast, both acute and chronic stress caused a persistent increase in AEPs in the LA. Chronic stress also elicited a sustained increase in the LA but a decrease in the hippocampus in the evoked power of gamma and beta frequencies. Moreover, beta and gamma synchrony was reduced between areas CA1 and CA3 but enhanced between the LA and hippocampus after chronic stress. Granger causality spectra revealed a strong directional influence from the LA to area CA1 that persisted throughout and even 10 d after chronic stress (Figure 2). However, directional coupling from hippocampal area CA3 to CA1 became weaker at the end of chronic stress. Thus, our findings suggest that the growing dominance of amygdalar activity over the hippocampus during and even after chronic stress may contribute to the enhanced emotional symptoms, alongside impaired cognitive function, seen in stress related psychiatric disorders. These analyses are now being extended to study interactions with the medial prefrontal cortex.

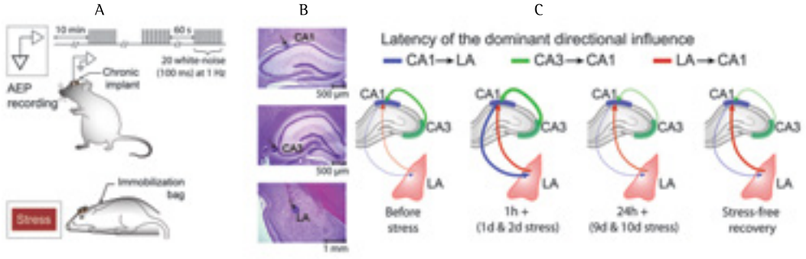


Figure 2: (**A**) Chronic *in vivo* recordings of AEPs simultaneously from hippocampal areas CA1 and CA3 and the LA, in the same animal before, during, and after chronic stress. (**B**) Histological verification of recording sites in hippocampal areas CA1 and CA3 and the LA. (**C**) Granger causality graphs depicting the modulation of directional influence during different stages of stress between the LA and areas CA1 and CA3. The strength of Granger spectral causality values are coded by the thickness of lines. Solid and dotted lines indicate presence and absence of dominant directional influence, respectively.

3 DELAYED IMPACT OF A SINGLE EPISODE OF STRESS ON THE AMYGDALA: IMPLICATIONS FOR PTSD

Dr. Kapil Saxena, Farhana Yasmin, Shobha Anilkumar, Dr. Rajnish Rao

Post-traumatic stress disorder (PTSD) is triggered by a single overwhelmingly traumatic event. Moreover, some components of the fear response in PTSD persist well beyond the original event. We aimed to capture some of the defining temporal features of PTSD by building upon our earlier findings wherein a single episode of acute immobilization stress triggered a delayed onset of anxiety-like behavior and spinogenesis in the basolateral amygdala [BLA] of rats. Using whole-cell recordings from excitatory neurons in amygdalar slices, we find that acute stress causes a significant increase in the frequency of miniature excitatory postsynaptic currents (mEPSCs) 10 days later. Targeted infusion of an NMDA-receptor antagonist into the basolateral amygdala during stress prevents both the increase in mEPSC frequency and spine-density 10 days later. Further, we have also identified a role for the endocannabinoid system by showing that oral administration of a pharmacological inhibitor of fatty acid amide hydrolase before acute stress prevents the delayed impact of acute stress on the strengthening of structural and physiological connectivity in the amygdala.

One of the most counterintuitive features of PTSD comes from clinical reports showing that cortisol treatment *reduces* the cardinal symptoms of PTSD. We have subjected our rodent model of PTSD to the challenge of replicating these clinical findings. We found that the presence of elevated levels of corticosterone at the time of acute stress confers protection against the delayed enhancing effect of stress on synaptic connectivity in the BLA and anxiety-like behavior. These observations are consistent with clinical reports on the protective effects of glucocorticoids against the development of PTSD symptoms triggered by traumatic stress. Finally, social avoidance is one of the key symptoms of PTSD. Yet, relatively little is known about the delayed impact of stress on ethologically natural social behaviors in rodents. Therefore, we analyzed the short and long-term effects of acute stress on various facets of social interaction in rats. Acute stress caused an immediate reduction in social interaction that persisted even after 10 days. In contrast, the enhancing effects of the stress on more individualistic measures of anxiety-like behavior only became evident 10 days later.

Collaborator: Bruce McEwen, Rockefeller University, New York, USA

4 EFFECTS OF CHRONIC STRESS ON HIPPOCAMPAL STRUCTURE AND FUNCTION

Anupratap Tomar & Mohammed Mostafizur Rahman

A neural circuit particularly vulnerable to the effects of stress is the hippocampus, a key component of the episodic and spatial memory system in both humans and rodents. However little is known about dynamic changes in activity that occur over the course of repeated stress. Hence, we used *in vivo* single unit recordings to characterize stress-induced modulation of the spatially receptive fields of the hippocampal CA1 'place cells' as mice explore familiar and novel tracks at the middle and at the end of 10 days of chronic immobilization stress. Place cells in stressed mice exhibit a smaller dynamic range of firing rates, leading to deficits in the experience-dependent changes in the firing of cells that occurs with familiarity and a muted response to representational changes of a novel space. Moreover, the activity of the ensemble is more rigid across contexts. These results suggest that a loss of network flexibility may underlie some of the behavioral deficits accompanying chronic stress.

We also explored the behavioral consequences of these network level changes. In the Morris Water Maze, rats exhibited only a mild deficit in the consolidation, but not acquisition, of spatial memory for the hidden platform half way through the 10-day stress. After the end of stress, however, the same animals showed a significant deficit in the Object Displacement Task. Using a 7T MRI scanner, we also found a gradual decrease in hippocampal volume over the course of chronic stress. Strikingly, the decrease in hippocampal volume even on day 3 was correlated with the eventual spatial memory deficit seen after the end of stress. This suggests that animals that were worst affected both in terms of memory deficits and hippocampal atrophy at the end of chronic stress, show relatively early signs of stress-induced impairment and continue on a trajectory of steady decline as the stress is repeated.

Collaborator: Thomas McHugh, RIKEN Brain Science Institute, Saitama, Japan; Shane O'Mara, Trinity College, Dublin, Ireland

5 CHARACTERIZATION AND REVERSAL OF SYNAPTIC DEFECTS IN THE AMYGDALA IN FRAGILE X SYNDROME

Sonal Kedia & Dr. Debarati Mukherjee

Earlier studies have identified a role for aberrant synaptic plasticity mediated by metabotropic receptors (mGluRs) in Fragile X syndrome (FXS). However, many of these observations are derived primarily from studies in the hippocampus. The strong emotional symptoms of FXS, on the other hand, are likely to involve the amygdala. Unfortunately, little is known about how exactly FXS affects synaptic function in the amygdala. Using whole-cell recordings in brain slices from adult *FMR1* knockout (KO) mice, we find mGluR-dependent long-term potentiation (LTP) to be impaired at thalamic inputs to principal neurons in the LA. Further, thalamic inputs to LA neurons also show reduced transmitter release probability. Using primary neuronal cultures from the amygdala (Figure 3), we are now probing a wide range of cell intrinsic post-synaptic and pre-synaptic mechanisms, and also analyzing potential points of difference, in terms of molecular and physiological signaling, between the amygdala and hippocampus both in normal and FXS neurons. Finally, we have succeeded in reversing many of the synaptic defects in the amygdala using chronic, *in vivo* treatment with an mGluR5-antagonist in FXS mice. This work is now part of the recently established Centre for Brain Development and Repair, an international collaborative program between NCBS, inStem and the University of Edinburgh.

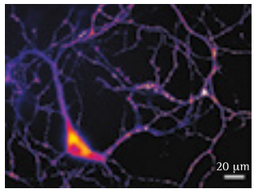


Figure 3: Amygdala cultured neurons expressing Synaptophysin-pHluorin and stimulated at 10Hz for 30 sec.

My laboratory studies insect flight from multi-disciplinary perspectives. These include the aerodynamics of flapping flight, the mechanics of their aerial manoeuvres, the neurobiology of sensory and motor processing by their nervous systems during flight, and the flight-related eco-physiological contexts.

SANJAY P SANE

The Physics, Neurobiology and Eco-physiology of Insect Flight

SELECTED PUBLICATIONS

Krishnan, A. and Sane, S.P.* (2014) Visual feedback influences antennal positioning in flying hawk moths. *Journal of Experimental Biology 217, 908-917*

Truong, T.Q., Phan, V.H., Sane S.P. and Park, HC* (2014) Pitching moment generation in an insect-mimicking flapping-wing system. *Journal of Bionic Engineering* 11 36–51

Cheng, B., Sane, S.P., Barbera, G., Troolin, D.R., Strand, T. and Deng, X.* (2013) Three-dimensional flow visualization and vorticity dynamics in revolving wings. *Experiments in Fluids* 54:1423.

During flight, insects flap their wings at frequencies that often exceed 100 Hz. which forces their nervous systems to acquire, process and respond to environmental and self-generated sensory cues at a similarly rapid rates. Yet, the flight of insects is very precisely controlled and flight-related sensory and motor systems are among the most compelling examples of evolutionary adaptations for locomotion. The fast control and stabilization of flight is a question in which my laboratory is particularly interested. To study these questions, we delve into multi-disciplinary aspects that include biology, physics and engineering. From a neurobiological perspective, we use electrophysiological and neuroanatomical tools to study how insects perceive their environment and use sensory cues from multiple modalities to gain and process information 'on the fly' and generate rapid responses from their motor neurons. From a biomechanics perspective, the motor output generated by the nervous system plays through the musculo-skeletal system to generate high-frequency wing movements, a process that critically depends on the cuticular structure and material properties. From an aerodynamics perspective, the moving wings generate flows around the wings that ultimately result in aerodynamic forces and torques. Finally, from an ecophysiological perspective, the natural contexts in which flight occurs are also very important especially because laboratory- based flight assays do not always bring out the full richness of these behaviours.

The search for interesting flight behaviours, be they territorial chases or long-distance migrations, often take us to outdoor locations where they may be observed. We can then recreate some of these behaviours in indoor or greenhouse settings. We film and measure their flight behaviours using techniques such as high-speed videography thus prompting an in-depth investigation of the various sensory modalities involved in these behaviours. How is this behaviour elicited by multi-modal sensory cues? How does the brain process these sensory cues and generate the required motor patterns and wing motion, which we recognize as a behavioural output. We are interested in the mechanistic basis of all these processes including the sensory encoding aspects of visual, mechanosensory and olfactory pathways, the musculoskeletal biomechanics in conjunction with the motor activity in flight muscles, and the aerodynamics of the wings interacting with their fluid environment. To rigorously study flight behaviour, all these aspects must be equally emphasized.

We have recently undertaken the following specific studies in diverse systems:

1 ANTENNAL FLIGHT CONTROL IN THE OLEANDER HAWK MOTH, *DAPHNIS NERII* AND HONEYBEE, *APIS MELLIFERA*

Antennae provide key mechanosensory cues to the flight control system in many insects (Sane et al, 2007). These cues are sensed by a set of mechanosensory scolopidial units that are collectively called the Johnston's organ, which is located near the base of the antennae. The Johnston's organ detects passive vibrations of the antennae and its scolopidial units are range-fractionated (Dieudonne, Daniel and Sane, 2014). Thus, they can sense a wide range of stimuli frequencies while maintaining exquisite sensitivity and speed of transduction. We seek to understand how these mechanosensory cues mediate flight control in moths, bees, and other insects. As an early step in this study, we studied how these insects position their antennae at the onset of flight. We showed that another set of mechanosensors, called the Böhm's bristles, located on the basal segments of the antennae are involved in the antennal positioning response at the onset of flight. These bristles project directly on to the antennal motor neurons and mediate very rapid corrections of the antennal position during flight. Thus, the antennal positioning response appears to be a classic sensorimotor reflex (Krishnan et al, 2012).

Additionally, we have also recently showed that antennal muscles respond to visual stimuli, thus implying that the antennal positioning response is actuated by a control system that integrates multiple sensory cues (Krishnan et al, 2014). These cues are involved in air speed sensing during free flight in honeybees which move their antennae in a specific relationship relative to ambient air flow. Future studies will delve deeper into the function and neuroanatomy of sensorimotor circuits of the Böhm's bristles and Johnston's organs. We are also keen to study how the combined visual cues from eyes and mechanosensory cues from antennae are transmitted to the flight motor system.

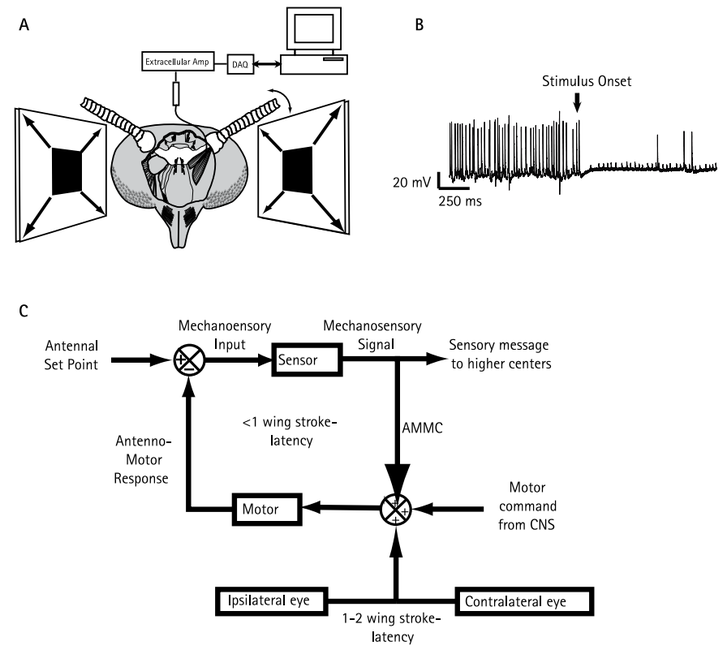


Figure 1: Visual inputs to antennal positioning behaviour (A) Experiment to study response of antennal muscles to visual stimuli displayed on LED arrays. (B) Preliminary data shows inhibition of background EMG activity by a looming visual stimulus (arrow) presented to the ipsilateral eye. (C) Summary of hypothetical negative feedback loop for antennal positioning response.

2 WING-HALTERE COORDINATION IN THE DIPTERAN FLIES

In Diptera, a mechanosensory organs called halteres provide critical information about aerial turns on a stroke-by-stroke basis. Feedback from these organs, which evolved from the hind wings

of the ancestral four-winged insects, is essential for flight control. Flies with ablated halteres are unable to properly orient when they try to fly. Halteres move with a very precise phase-relationship relative to the wings and we have recently been studying the biomechanical basis of the wing-haltere coordination. Our studies show that wings and halteres are mechanically connected *via* thoracic elements. We have been able to identify these connections and put together a model of the thorax that can explain the kinematics of the wing-haltere system.
In collaborations with Dr. Gaiti Hasan's lab, we have also begun testing some of the hypotheses emerging from this study using Drsophila genetic tools.

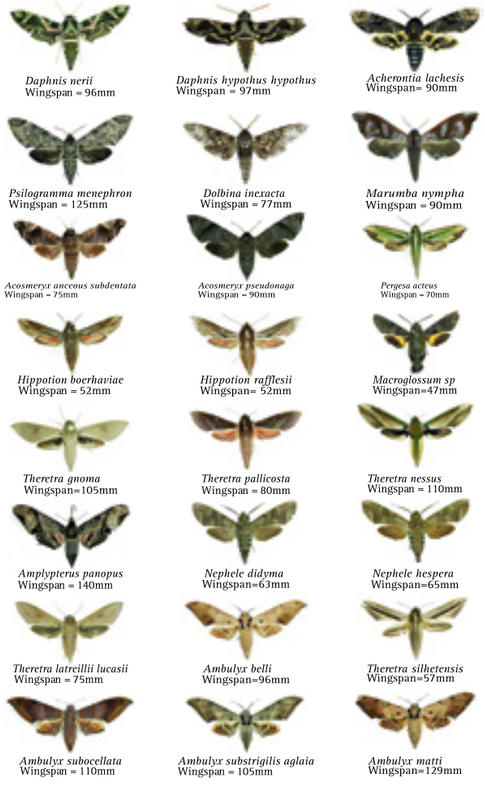
3 LOCALIZATION OF ODOUR SOURCES BY THE FRUIT FLY, *DROSOPHILA MELANOGASTER*

During foraging or ovipositioning, insects are able to pinpoint the location of odour sources using a combination of visual and olfactory cues. How do insects parse these cues and what are the rules that guide their behaviour during the precise localization of the odour sources? We study this question using *Drosophila melanogaster* as a study system. Our work shows that presence of a visual clutter elicits a search behaviour in flies as they try to match specific visual objects with odours.

4 NATURAL HISTORY OF INTERACTIONS BETWEEN HAWK MOTHS AND THEIR HOST PLANTS

One important natural context of flight, especially in many Lepidopteran insects, is the identification of host plants for ovipositioning. In the case of the Oleander hawk moth *Daphnis nerii*, this decision is crucial for the survival of the hatchlings because new hatchlings perish on a diet of mature leaves. It is therefore imperative that the female lays eggs on freshly emerged leaves.

Hawkmoths of Agumbe, Karnataka



We are studying how *Daphnis* females use visual and olfactory cues to distinguish fresh leaves from mature ones. We are also studying how plants defend themselves from insect herbivory. Recently we have begun to collect and catalogue hawk moths in the Western Ghats with an aim to identifying specific moth - plant relationships.

5 AERODYNAMIC MECHANISMS OF FLAPPING FLIGHT

In collaboration with Dr. Xinyan Deng's laboratory at the Purdue University, we have been investigating various questions related to the aerodynamics of insect flight. This work continues from a long-standing interest in the fluid mechanics of flapping flight. Initially, we developed a mechanical model of a flapping wing and used it to measure the basic forces and flow characteristics around flapping rigid wings. More recently we investigated the influence of wing flexion on flow structures and forces in flapping flight (Zhao et al, 2011). We have also been working on the measurement and quantification of 3D flow structures around the flapping wings and the biological consequences of induced flow around the insect body during flight (Cheng et al, 2013, Sane 2006).

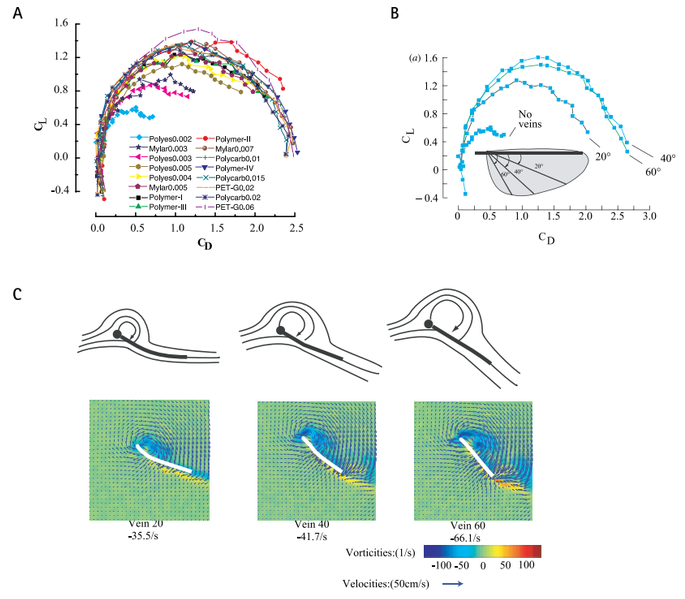


Figure 2: Effect of wing flexion on aerodynamic forces and flow.
(*A*) Aerodynamic polar plots of artificial wings with varying flexural stiffness and (B) with wing veins including a leading edge spar and one of three vein configurations. Veins are either absent or placed at either 20°, 40° or 60° with respect to the leading edge spar, enabling us to flex the wing through various angles. The corresponding flows for 20° (left), 40° (middle) or 60° (right) venation are shown along with cartoons of the associated flows. Numbers under each figure represent maximum value for leading edge vorticity, which is negative because the leading edge vortices are clockwise.

6 THE CONSTRUCTION AND MAINTENANCE OF TERMITE MOUNDS

As part of a Human Frontiers Science Program team that studies the architecture of termite mounds and its role in the physiology of the 'super-organism', we are conducting experiments to study how termites repair an injured mound. Specifically, what sensory cues convey information about mound disrepair, and how do these cues elicit recruitment and derecruitment of the termites the site of the injury. We are also able to film the termites at work within the mound and thus observe their behaviours at close quarters.

How does the developing nervous system generate locomotion in spite of undergoing constant modification? Larval zebrafish offer an excellent model system to answer this question.

VATSALA THIRUMALAI

The Assembly of Neural Networks Controlling Movement

Many species of animals are able to walk and run as soon as they are born. At these early life stages, neural pathways are still being specified, axons myelinated and synaptic connections still being forged. Yet, the immature nervous system generates locomotion that is coordinated. How do immature and mature neural circuits generate locomotion?

Vertebrate locomotion is generated by motor-pattern generating circuits located in the spinal cord, which are in turn activated by inputs from the brain via descending projections. Little is known about how these disparate circuits in the brain and spinal cord generate coordinated locomotion in the adult or in the developing vertebrate.

In my lab, we use the zebrafish (*Danio rerio*) as a model system for studying the generation of locomotion in developing and in more mature vertebrate animals. Zebrafish are small fresh water fish belonging to the subclass Teleosta and native to the Ganges and the Brahmaputra. Zebrafish embryos and early larvae are nearly transparent allowing the visual observation of neurons inside the living animal. Further, zebrafish can be easily manipulated to express any gene of interest. They develop rapidly from single-celled zygotes to independently foraging larvae in the course of five to six days. The zebrafish genome has recently been sequenced and annotated. RNAseq data for many genes at multiple life stages are also currently available at Ensembl (www.ensembl.org). We exploit these advantages to ask how locomotory behaviors are generated by neural circuits during various life stages and how these neural circuits may be put together. Our approach combines techniques in molecular genetics, electrophysiology and imaging to answer questions about the assembly of neural circuits that control movement.

SELECTED PUBLICATIONS

Thirumalai, V., Behrend, R.M., Birineni, S., Liu, W., Blivis, D. and O'Donovan, M.J. (2012). Preservation of VGLUT1 synapses on ventral calbindin-immunoreactive interneurons and normal locomotor function in a mouse model of Spinal Muscular Atrophy. *J Neurophysiol*;109(3):702-10.

Thirumalai, V. (2012). Assembling neural circuits for generating movement. *J. Ind. Inst. Sci.* 92(4), 411-426.

Jabeen, S. and **Thirumalai, V.** (2013). Distribution of the gap junction protein Connexin 35 in the central nervous system of developing zebrafish larvae. *Front Neural Circuits*. 2013;7:91.

1 GAP JUNCTIONS, DEVELOPMENT AND FUNCTION

Shaista Jabeen, Mohini Sengupta, Anubhab Khan, Bhavika Mam

Gap junctions are cytoplasmic bridges between cells formed by specialised protein assemblies called connexons. At the junction, two connexons, each made of connexin subunits come together to form a continuous pore through which ions, second messengers and other small molecules can pass from one cell to the other. In neurons, gap junctions are called electrical synapses as elecrical signals can be communicated from one neuron to another via gap junctions. We found that Connexin 35 (Cx35), a neuronal connexin isoform, is widely distributed within the central nervous system of larval zebrafish. Cx35 expression begins as early as 1 day after fertilization and continues into adulthood. Several neuropilar regions in the olfactory bulb, optic tectum and hindbrain also expressed high levels of this protein. Consistent with these results we found that low molecular weight dyes, injected into one neuron in the hindbrain, label many neurons after being transported across gap junctions (Figure 1). We are also following the appearance of Cx35 and markers for chemical synapses at various stages of development in identified circuits.

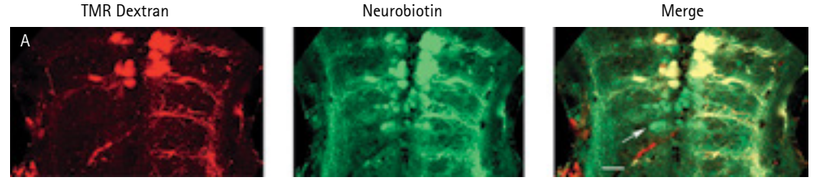


Figure 1: Dye coupling in reticulospinal neurons. A mixture of high molecular weight (TMR Dextran) and low molecular weight (Neurobiotin) tracers were pressure injected into the spinal cord. These dyes were retrogradely transported via axons to fill the cell bodies and dendrites of reticulospinal neurons. Neurons dye-coupled to reticulospinal neurons appear green in the merged picture (white arrowhead).

2 A ZEBRAFISH MODEL OF MANGANISM

Subha Bakthavatsalam, Shreya Das Sharma*

Manganese is an essential trace element, which regulates many key cellular processes. However, chronic exposure to high levels of manganese results in a set of cognitive and motor disturbances collectively called 'manganism'. Manganism symptoms include bradykinesia, loss of balance and gait dysfunction. Post mortem analyses of brains from manganism patients show that there is a high degree of neurodegeneration in many regions. Nevertheless, the loss of neurons could well signal the end stage of the disease and the appearance of manganism-related symptoms may precede the phase of neurodegeneration. To understand the neurobiological basis of manganese toxicity, we developed a zebrafish model of the disease by rearing the larvae in water containing 0.8 to 1mM $MnCl_2$. Larvae thus treated with manganese also showed reduced movements, loss of balance and altered kinematics of swimming, recapitulating many aspects of the human disease.

Next, we analyzed the effects of manganese treatment on the function of sensory, motor and neuromodulatory neurons. We found that although no neurodegeneration was seen at any of these loci, function was impaired. Importantly, dopaminergic neurons expressed lower levels of tyrosine hydroxylase, the key biosynthetic enzyme in dopamine biosynthesis. When manganese-treated larvae were supplemented with dopamine, the reduction in movements could be rescued. Motor neurons also show altered firing behavior and many of these functional impairments were reversible when the manganese was removed from the rearing medium. Our current efforts are directed at understanding the mechanisms by which manganese impairs firing behavior of neurons.

Collaborator: Dr. Ankona Datta, Department of Chemical Sciences, TIFR, Mumbai.*

3 DOPAMINE MODULATION OF DESCENDING MOTOR CONTROL

Mohini Sengupta, Lena Robra, Urvashi Jha

Dopamine is a major neuromodulator of motor circuits. Dopamine acts as a brake and inhibits swimming in young larvae; however, this inhibition is lost at later stages. Dopamine appears to

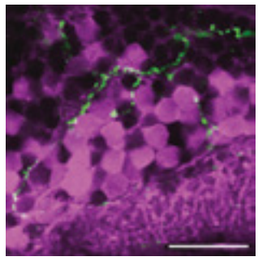


Figure 2: DARPP-32 immunoreactivity in the cerebellum of a 15 dpf larva (magenta). Tyrosine hydroxylase immunoreactivity marks catecholaminergic nerve fibers innervating the cerebellum (green).

regulate swim network activity by acting on supra-spinal motor centers. To identify neurons that receive dopaminergic input, we raised an antibody against the Dopamine and cAMP regulated phosphoprotein DARPP-32. DARPP-32 is an integrator of dopamine signaling implicated in neuronal disorders and is known to control the activity of Protein kinase A and Protein phosphatase-1. However, its physiological role is not clearly understood, nor is it known how it affects neuronal activity. The anti-DARPP32 antibody we raised binds specifically to zebrafish DARPP32 and shows clear staining in the cerebellum (Figure 2). In preliminary experiments, we find that dopamine inhibits spontaneous activity in Purkinje neurons (Figure 3). In a parallel set of experiments, we are profiling dopamine sensitivity of reticulospinal neurons using calcium imaging.

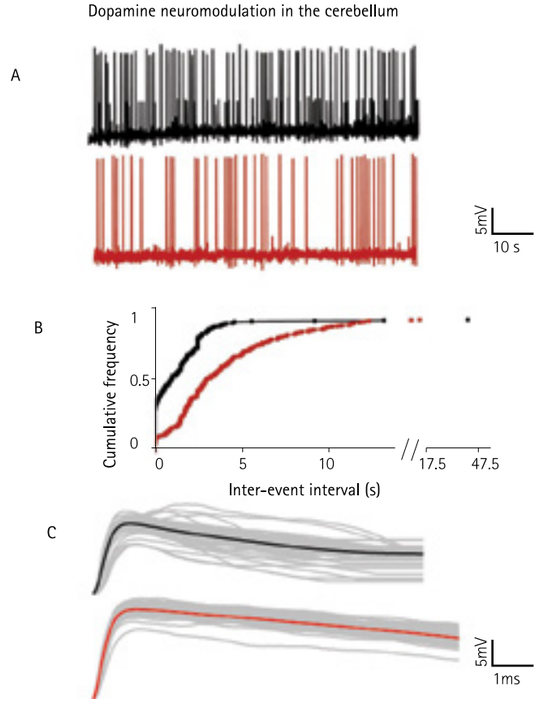


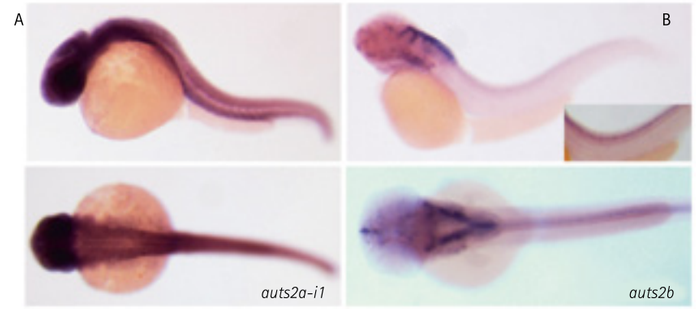
Figure 3: Dopamine decreases spontaneous activity in cerebellar Purkinje neurons without affecting spike shape. (A) Representative traces of spontaneous activity from a cell at 7 dpf in the absence (black) and presence of 100 µM Dopamine (red). (B) Cumulative distribution of inter-event interval of spontaneous activity shown in (A) with (red) and without (black) dopamine. N= 3 cells from 1 larva. (C) Superimposed traces of spikes during spontaneous activity of the cell shown in (A). The average is shown in black for control and red for 100 µM Dopamine application.

4 AUTS2 ISOFORMS DURING DEVELOPMENT

Igor Kondrychyn

Autism spectrum disorders (ASDs) are characterized by deficits in communication skills, social interaction and a presence of stereotyped and repetitive movements. More than a decade ago, a region on chromosome 7 was identified as being translocated in monozygotic twins who both had autism. The autism susceptibility candidate gene (*Auts2*) was shown to be located within this locus. Subsequent studies implicate auts2 in intellectual disability, addiction, speech disorders and developmental delay. Auts2 is a nuclear-localized protein but domain analysis shows no DNA binding domains. What function does Auts2 serve and how does its loss-of-function result in disease phenotypes? We undertook to study this question and isolated two orthologs, auts2a and auts2b in zebrafish. The auts2a gene has two transcription start sites and codes for at least nine different gene products. Auts2b on the other hand codes for a single message. Interestingly, auts2a and auts2b are expressed as early as 3 hours post fertilization and seem to be maternally deposited in the egg. While auts2b expression is limited to the central nervous system, auts2a is distributed in many tissues besides the CNS (Figure 4). We are analyzing the functional roles of atus2a and auts2b using morpholino antisense oligonucleotides and TALEN-mediated knockout approaches.

Figure 4: Auts2 expression pattern in zebrafish larvae. A. auts2a-i1 is ubiquitously expressed. B. auts2b is restricted to the central nervous system. Inset in the top panel shows auts2b expression in the spinal cord.



5 NEUROBIOLOGICAL CORRELATES OF DECISION MAKING DURING SIMPLE VISUO-MOTOR TASKS

Sriram Narayanan, Urvashi Jha

Fish larvae at 5dpf can already perform simple behaviors such as orienting towards and capturing *Paramecium* or swimming away from a looming dot. Fish also respond to high frequency acoustic stimuli by startling and swimming away. We ask how the decision to swim toward or away from a target is made by the CNS. In fish larvae expressing a genetically encoded calcium sensor in all neurons, we image different brain regions to understand the responses to startling or attractive stimuli. We image activity in multiple brain areas during these behaviors using our custom-built two-photon microscope. Simultaneously, we are also asking whether the presence of neuromodulators such as dopamine affect the kinematics of these behaviors and the responses of the neurons being imaged.

We are interested in the organization and mechanisms of animal behaviour. How do animals do what they do and what are the underlying neural and molecular mechanisms? Our study animals are honeybees and we are particularly interested in decision-making processes during social foraging and dance communication.

AXEL BROCKMANN

Honeybees and the Organization of Behaviour

We are interested in understanding mechanisms of behaviour and their neural and molecular underpinnings using honeybees. The European-African honeybee, *Apis mellifera*, has been used very successfully to study and identify sensory and behavioural capabilities of insects and animals in general. Colour vision, spatial navigation and circadian regulation of behaviour were first identified in *A. mellifera*.

Honeybees with respect to the degree of their behavioral complexity and the ease with which one can perform behavioural experiments under both natural and laboratory conditions. Although honeybee research currently lacks the sophisticated analytical tools available for genetic model organisms, in the long run honeybees are the most promising insect species to study neural and molecular mechanisms of complex behaviours in natural conditions.

Research in my lab pursues four general goals: (a) developing assays and procedures to study behaviour at the level of the individual, (b) establishing molecular techniques to detect and measure behaviourally induced molecular changes in single brains, brain parts and individually identifiable neurons, (c) performing comparative behavioural and molecular studies with Asian honeybee species, and (d) using *Drosophila* to identify candidate neural circuitry and molecular processes involved in honeybee behaviour.

SELECTED PUBLICATIONS

Streinzer M., **Brockmann A.**, Nagaraja N. and Spaethe J. (2013). Sex and caste-specific variation in compound eye morphology of five honeybee species. *PLoS One*. 8(2): e57702.

Barron A.B., **Brockmann A.**, Sen Sarma M. and Robinson G.E. (2012). Molecular dissection of honey bee dance behaviour. In "Honeybee neurobiology and behaviour – a tribute for Randolf Menzel". Eds.: D. Eisenhardt, C.G. Galizia, and M. Giurfa, Springer Verlag, Berlin Heidelberg New York.

Brockmann A., Annangudi S.P., Richmond T.A., Ament S.A., Xie F., Southey B., Rodriguez-Zas S.R., Robinson G.E. and Sweedler J.V. (2009). Brain peptide signatures of behavior with quantitative peptidomics. *Proc. Natl. Acad. Sci.* U S A. 106: 2383-8.

1 HONEYBEE DANCE COMMUNICATION

Honeybee dance communication conveys information about the reward value as well as the direction and distance of a profitable food source. In the last years my former colleagues and I started research projects to identify neural circuits and neuromodulators involved in dance behaviour. At NCBS we continue this line of research focusing on two aspects: (a) individual variation in dance activity and neuromodulatory systems involved in dance behaviour, and (b) time dynamics of processing and encoding distance information in the waggle run.

A. Individual variability and plasticity of dance behaviour

Previous experiments on dance behaviour demonstrated huge individual variations in dance activity. These experiments also indicated that most of the dances within a foraging group, i.e. all foragers visiting the same food source, are done by a few individuals (Seeley, 1994). We started studying inter-individual variation in dance activity with a focus on two questions: (1) Is the individual dance activity consistent over time? (2) Does the composition of the foraging group affect individual dance activity?

Similar to the earlier experiments, we found strong differences in dance activity among individuals of a foraging group (6 -12 foragers). Furthermore, the relative dance activity of individual foragers remained constant over the 3-5 experimental days. We then started manipulation experiments in which we remove foragers which show the highest dance activity from the foraging group. First results suggest that changes in the composition of the foraging group affect individual dance activity. Parallel to these behavioural experiments we collaborate with C-CAMP to develop mass-spectrometric procedures to measure neurotransmitter and neuromodulator titres in single honeybee brains to test whether the differences in dance behaviour correlate with differences in neuromodulator systems.

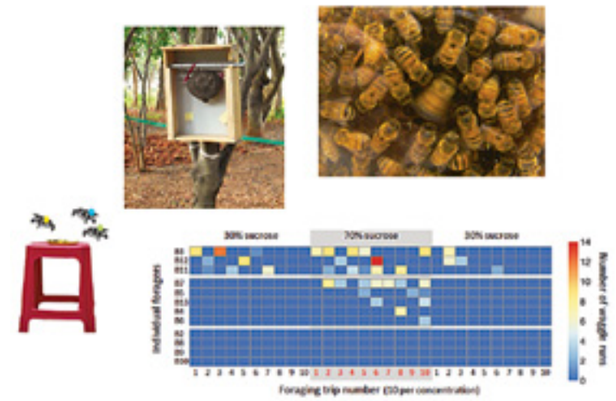


Figure 1: Experimental set up to study individual variability in dance behaviour

B. Time dynamics of processing and encoding distance information in the waggle run.

Generally, dance experiments are done using a group of bees and the duration and direction information of waggle runs are determined as a population mean. We started to do experiments in which we record all waggle runs of individual foragers and analyse the variation in duration and direction of waggle runs for each individual. Furthermore, we use this approach to monitor how individual foragers change their dance behaviour in response to changes in feeder distances. Our major question is whether honeybees instantaneously change the waggle run duration or whether they need time to process and encode the new information.

Collaborators: Gene E. Robinson (University of Illinois, USA), Kannan R (C-CAMP), Taketoshi Kiya (Kanazawa University, Japan)

2 SOCIAL FORAGING AND DECISION-MAKING

Individual foragers visit a food source over several days flying back and forth between the nest and the food source. We suggest that this foraging activity can be divided into at least six distinct sub-behaviours: (1) Leaving the hive, (2) flying towards the food source, (3) collecting food, (4) flying back home, (5) delivering the food and recruiting nest mates, and (6) resting. With respect to current ideas on behavioural decision-making we propose that the sub-behaviours of honeybee foraging are accompanied and regulated via the activity of different neuromodulator systems.

Our research pursues three goals: (a) Comprehensive analysis of changes in neuromodulators associated with the different sub-behaviours during foraging (b) developing strategies to monitor neuromodulator changes in brain regions and neuron populations, and (c) identification of the behavioural function of the candidate neuromodulators using manipulative lab assays.

Collaborators: Kannan R. (C-CAMP), Susanne Neupert and Reinhard Predel (University of Köln, Germany)

3 SEX-PHEROMONE COMMUNICATION AND IDENTIFYING NEW GENES INVOLVED IN OLFACTORY TRANSDUCTION AND SENSITIVITY

One of the most successful strategies in neuroethology is to use "natural experiments" to understand fundamental biological questions. We plan to use the sex-pheromone sensitive olfactory system of drone (male) honeybees to identify new genes and proteins involved in olfactory transduction and sensitivity. This project is based on two hypotheses. First, the male's sex-pheromone sensitive olfactory system is under strong selection to detect and rapidly respond to minute amounts of sex-pheromone. There are two basic strategies to increase olfactory sensitivity; one is to enlarge the olfactory epithelium and the other is to improve the underlying molecular transduction machinery. Second, the mating behaviour of honeybees is regulated by the circadian clock and we expect that genes and proteins involved in sex-pheromone detection are also likely to be regulated by the circadian clock. If so, then in reverse, antennal genes and proteins, which are expressed or synthesized in synchrony with mating time are highly likely involved in olfactory processing. Currently we perform preliminary experiments demonstrating circadian changes in olfactory sensitivity and antennal gene expression.

Collaborators: R. Sowdhamini (NCBS), Wolfgang Roessler and Johannes Spaethe (University of Würzburg, Germany)

4 ASIAN HONEYBEES AND THE EVOLUTION OF BEHAVIOUR

Traditionally, behavioural and neurobiological research in honeybees has focused on the European-African honeybee species, *A.mellifera*, neglecting the variability in social organization and individual behaviour among honeybee species. Worldwide there are nine species of honeybees and three of them, *A. florea*, *A. dorsata* and *A. cerana*, which represent major phylogenetic lineages, are native to India. We have started comparative research projects on the visual and olfactory systems and behaviours, as well as colony organization and division of labour. In the long run we are interested in studying neural and molecular changes underlying evolutionary changes in behaviour.

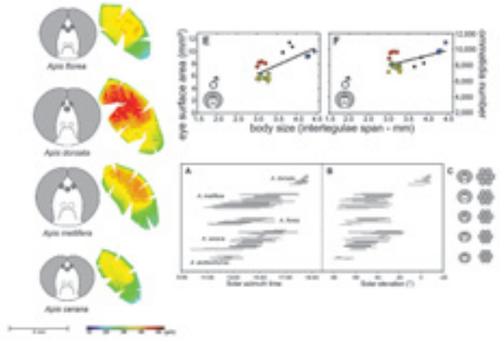


Figure 2: Variation in drone compound eye of five honeybee species

5 THE BEE CURTAIN IN OPEN-NESTING SPECIES AND THE EVOLUTION OF DIVISION OF LABOUR AMONG HONEYBEE SPECIES

Colonies of open-nesting honeybee species (e.g. *A. florea* and *A. dorsata*) build only one comb and the workers form a cluster of multiple layers, the bee curtain, which covers the whole comb. The bee curtain functions as a protective shield against unfavourable environmental conditions and predators. First studies on the bee curtain suggested that open-nesting species have a specific "curtain bee" worker caste not present in the cavity-nesting species like *A. mellifera*. Unfortunately, so far, such a worker caste has never been identified with respect to behaviour and physiology. We started a detailed analysis of the functional organization of the bee curtain and division of labour in *A. florea*. We are investigating three different aspects of the curtain: (1) Massed flight activity and the opening of the curtain, (2) string-organization of the curtain and (3) movement patterns of individual bees on the outer layer of the curtain. Our observations of massed flight activity showed that strings or chains of worker bees clinging to each other form the curtain. These string bees might be recognized as a specific worker caste and represent what other authors have described as curtain bees. Our next experiments will focus on the behavioural and molecular analysis of adult behavioural maturation and the caste status of string bees.

Figure 3: Nest organization and the bee curtain in Apis florea (Figure to section 4 Asian Honeybees and the Evolution of Behaviour)

6 STUDYING HONEYBEE BEHAVIOUR WITH *DROSOPHILA*

We establish procedures to use the fruit fly *Drosophila melanogaster* to identify neural circuits involved in honeybee behaviour, and in particular honeybee dance behaviour. Conceptually, we dissect dance behaviour or any other complex behaviour into several different simpler behaviours or behavioural modules, which can be found in *Drosophila.* For these simpler behaviours we then develop lab assays that can be performed with both fruit flies and honeybees. This research strategy follows ideas by the American entomologist Vincent Dethier who suggested, more than fifty years ago, that the relatively simple sugar-elicited search behaviour found in flies might be a solitary behaviour that has been integrated into the more complex social dance behaviour. Sugar-elicited search and dance behaviour are similar in that the initiation and intensity of both behaviours is dependent on the hunger state of the animal and the reward value (i.e. sugar concentration) of the food. We established lab assays for sugar-elicited search behaviour for honeybees and *Drosophila* and are currently investigating the modulatory systems involved in regulating this behaviour. We expect that the same modulatory systems are likely involved in the regulation of honeybee dance behaviour.

Collaborators: Teiichi Tanimura (Kyushu University, Japan)

The olfactory responses from organisms are partly inborn and partly acquired. We study how in *Drosophila*, learning occurs by experience-dependent changes after birth, in brain organization, neurophysiology and neurochemistry.

OBAID SIDDIQI

Genetic Analysis of Chemosensory Perception

PUBLICATIONS

Khurana S., **Siddiqi O.** (2013). Olfactory responses of *Drosophila* larvae. *Chem Senses* ;38 (4):315-23. doi: 10.1093/chemse/bjs144.

Chakraborty TS, **Siddiqi O.** (2011). Odor reception in antenna and antennal lobe of *Drosophila*. **Fly (Austin)** ;5(1):14-7.

Iyengar, A., Chakraborty, T.S., Goswami, S.P., Wu, C.F., **Siddiqi, O.** (2010) Post-eclosion odor experience modifies olfactory receptor neuron coding in *Drosophila*. *Proc Natl Acad Sci U S A* ;107(21):9855-60. doi: 10.1073/pnas.1003856107.

Obaid Siddiqi passed away tragically on July 26th 2013

The chemosensory system of the animals helps them to understand the surrounding chemical environment. This understanding provides these animals a better chance of survival. Our lab is using behavioral genetics and neurobiological tools to understand fundamental problems of chemosensory perception in *Drosophila* larva as well as in the imago. One of the aims of our research is to understand the magnitude of inborn chemosensory behavior compared to the acquired chemosensory behaviour. Odorants are neither intrinsically attractive nor aversive. By appropriate training attraction can be changed to aversion and vice versa. Peripheral as well as central nervous system requires multiple processes in order to form a consolidated memory. This is known as imaginal conditioning. However, imaginal conditioning is a slow process in terms of sensitization of olfactory neurons which takes from hours to days. On the other hand, rapid associative learning by reward or punishment takes place in a matter of seconds to minutes. The memory retention curves seen after electroshock training of the larvae are polyphasic which can be decomposed into three memory components; short-term, middle-term and long-term memories using kinetic analysis, treatment with memory ablating reagents and mutation studies. Single animal experiment provides information about the behavioral strategy involved in learning. The experiments are conducted in the lab on freely moving single *Drosophila* in a close odor arena to find how these animals change their orientation, upwards or downwards, in response to a local odor gradient.

The lab is also involved in exploring the correlates between the electroshock memory in the larval brain and changes in the sensitivity of olfactory receptor neurons (ORNs) after imaginal conditioning (Figure 1). In case of larvae, we have identified a number of proteins which show

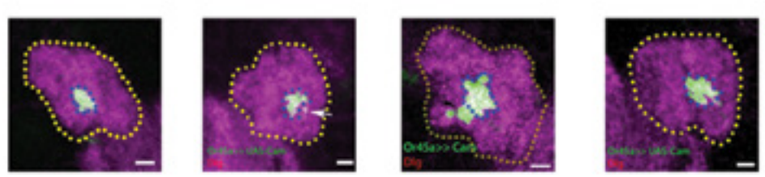
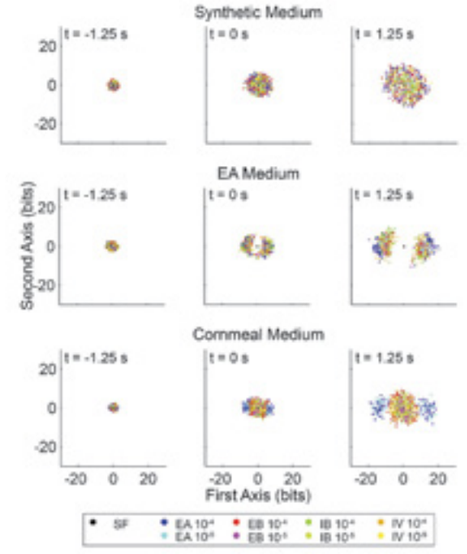


Figure 1: New projection in Or45a with time at the larval antennal lobe. The yellow dotted line marks approximately the larval antennal lobe and the blue dotted line marks approximately Or45a glomerulus. Or45a labeled in green by the expression of UAS-Cameleon 2.1 under the control of Or45a-Gal4. At three hrs after training a new projection protruding from Or45a glomerulus is observed which is indicated by white arrow. At five hrs after training, the volume of the new projection has increased (indicated by arrow) as well the entry point of Or45a neuron into larval antennal lobe. The new projection and expanded entry point of Or45a into larval antennal lobe requires new protein synthesis and it is blocked by feeding the larvae protein synthesis inhibitor cycloheximide (20mM) for 10 min before training. Scale bar is 8µm.

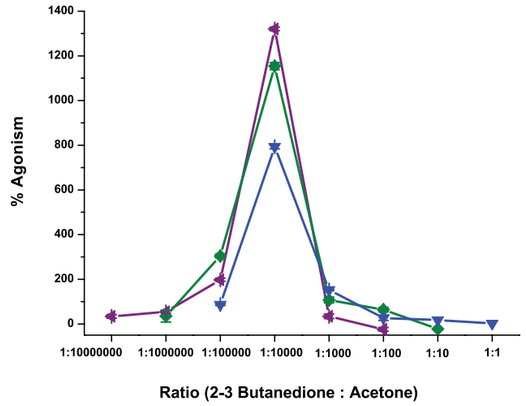
significant changes in the expression pattern upon learning. The entire process of learning is dependent on three ORNS, one for processing olfactory response, the second one for processing consolidation of memory, while the third is involved in recall of memory. Single unit recording from sensilla basiconica have shown that imaginal conditioning involves changes in threshold and sensitivity of ORNs (Figure 2). These results have been confirmed by 2-photon Ca^{+2} imaging. Psychophysical experiments show that the quality of an odor mixture is determined by its

Figure 2: Isomap showing improved discrimination with olfactory experience of odour-rich medium. Cornmeal-grown flies show maximum discriminative ability when measured by Shannon-Jenson divergence. Each colour coded point signifies the location of the particular response ensemble relative to others. The figure shows 200 bootstrapped response ensembles for each pair wise comparison. Notice that deprivation leads to poor separation.



chemical composition, particularly the ratio of the constituent chemicals. We have found that the ratio of chemicals in a mixture is represented in the ORN by peaks of agonisms and antagonisms (Figure 3).

Figure 3: Agonism shows a sharp peak at a fixed ratio of 2-3 Butanedione to Acetone independently to absolute concentration of the odorants. The peak of agonism corresponds to peak of attraction.



THEORY AND MODELING OF BIOLOGICAL SYSTEMS

We study the emergence of eukaryotic cells from prokaryotic ancestors. By combining abstract models, molecular phylogenetics, and cell biological experiments, we explore how increasing genomic complexity drove the emergence of eukaryotic organelles and vesicle traffic over two billion years ago.

MUKUND THATTAI

The Evolutionary Origins of Complex Cells

SELECTED PUBLICATIONS

Thattai, M. (2012) Using topology to tame the complex biochemistry of genetic networks. *Philosophical Transactions of the Royal Society A*, 20110548.

Brodsky, F, Thattai, M., and Mayor, S. (2012) Evolutionary cell biology: Lessons from diversity. *Nature Cell Biology* 14, 651.

Ramadas R. and Thattai, M. (2013) New organelles by gene duplication in a biophysical model of eukaryote endomembrane evolution. *Biophysical Journal* 104, 2553.

All life is made of cells, and all cells can be classified into three great groups: the bacterial and archaeal prokaryotes, and the eukaryotes. The latter include single-celled protists like ciliates, amoebae, algae and so on, as well as the cells of multi-cellular plants and animals. Proto-eukaryotes began to diverge from their prokaryotic cousins following the global oxygenation event (GOE) 2.5 billion years ago, but all living eukaryotes share a much more recent last eukaryotic common ancestor (LECA) dating from about 1.8 billion years ago. The intervening period was one of rapid innovation that has left no trace of intermediate forms: all extant eukaryotic cells have a compartmentalized structure (with nuclei, mitochondria and other membrane-bound organelles connected by vesicular traffic) whereas such features seem completely absent in prokaryotes. Except for the origin of the genetic code, in the history of life on earth there has never been a comparable jump in complexity. We want to understand this jump: to develop testable hypotheses for the emergence of the eukaryotic compartmentalized cell plan.

Broadly sampled genomic data suggest that eukaryotic genomes are a mix of bacterial and archaeal genes, which themselves have ancient origins. This is consistent with the idea that eukaryotes arose through a singular event – the acquisition of a free-living bacterium by an archaeal host cell about two billion years ago, to form mitochondria. The availability of a specialized respiratory organelle relieved constraints on host genome size, leading to a massive expansion in several gene families. This genomic expansion coincided with the development of quintessential eukaryote-specific traits, including the compartmentalized endomembrane system and vesicle traffic. The coincidence of these two patterns, one deduced from molecular phylogenetics and the other from cell fossil data, suggests a hypothesis for eukaryotic origins: that the increase in genomic complexity drove the increase in cellular complexity [Figure 1]. This hypothesis is the focus of our investigations [2].

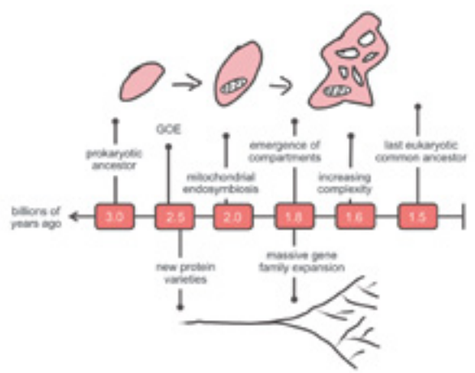


Figure 1: The acquisition of mitochondria was a watershed event, triggering massive gene family expansions and the emergence of the eukaryotic compartmentalized cell plan. Our goal is to rigorously understand how changes at the genomic level drove changes at the cellular level.

1 ABSTRACT MODELS: TOWARD STATISTICAL CELL BIOLOGY

There is a fundamental link between the endomembrane system and large gene families. If we were to extract membrane patches from different locations of a eukaryotic cell, we would find that they were all decorated with the same *types* of proteins. Cell-biological studies have identified most of these molecular players, part of the conserved vesicle traffic apparatus: they include lipids and Rab GTPases that confer membrane identity; coat and adaptor proteins that drive vesicle budding and cargo sorting from source compartments; and SNARE proteins and tethers that drive vesicle fusion into specific destination compartments. However, while two distinct membranes such as the plasma membrane and the endoplasmic reticulum might both be decorated with Rabs, coats and SNAREs, a closer analysis would reveal that each membrane had distinct *flavours* of these proteins. Thus, if a cell contains a number of membrane-bound compartments, it must encode a number of paralogs of the vesicle trafficking molecules; compartments decorated with distinct paralogs would be endowed with distinct properties, such as location, morphology, and internal chemistry; the more paralogs available, the more organelles are possible. We want to extend this basic idea, and make the connection between molecular to cellular properties more rigorous.

The compartments of a eukaryotic cell are dynamic entities whose compositions are maintained by the specific gain and loss of molecules via vesicle traffic. These cellular-level events are the consequence of various specific molecular-level interactions, including the specificity of vesicle budding and fusion. We can use computational models to go from the informational molecular scale to the geometric cellular scale. We have previously developed a detailed biophysical model of intracellular traffic using a dynamical systems framework [3]. Our results demonstrate that self-sustaining compartments can spontaneously arise from an initially disorganized state, and that the number and connectivity of these compartments depends essentially on the rules of molecular interaction. Strikingly, we find that the process of gene duplication and divergence can drive the emergence of new compartments, supporting the idea that massive expansions of traffic-related gene families prior to LECA might have driven organellar innovation. However, detailed biophysical models are limited by a lack of data about the specificity of protein interactions. Borrowing a key idea from statistical mechanics, we suggest that the solution is to develop a statistical cell biology in which we explore the behaviour of all possible models consistent with a known set of molecular and cellular constraints. To this end, we have built an abstract syntax within which we can encode infinitely many molecular models of intracellular traffic and analyze the resulting cellular dynamics [Figure 2]. Using graph theoretic techniques, we are able to place rigorous limits on the kinds of molecular interactions that are needed to specify cells with biologically relevant intracellular traffic systems. Going forward, we hope to couple statistical cell biology with mutational dynamics, to explore the robustness and discoverability of traffic systems over evolutionary timescales.

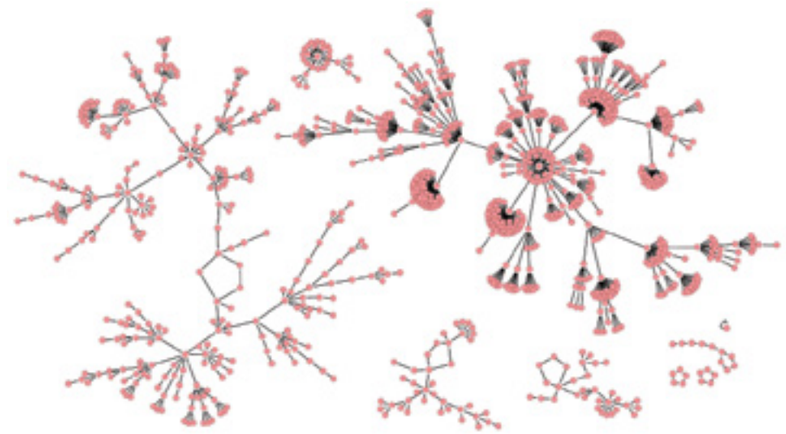


Figure 2: Abstract models of intracellular traffic allow us to rapidly search through the space of molecular rules and find those which specify interesting compartmentalized cells. This graph is a snapshot of traffic dynamics for one such rule set: cells placed in some initial state (nodes) update to other states (via arrows) and ultimately occupy periodic solutions (cycles). In this example, the bulk of initial conditions converge to a period-one solution.

2 DETAILED BIOLOGICAL DATA: CONNECTING GENE-FAMILY EXPANSIONS TO THE EMERGENCE OF NEW ORGANELLES

Cells rarely leave behind fossils, but mutation and recombination leave traces which allow us to deduce ancestral protein sequences. If it were possible to use the presence of a certain protein as a proxy for a particular cellular property, we could use ancestral protein sequences to reconstruct ancestral cell states. There are many challenges in implementing such a program. First, we have to identify the correct set of proteins to probe cell properties of interest; since we focus on membrane-bound compartments, the obvious candidates are membrane-interacting proteins. Second, we are interested in timescales beyond the billion-year horizon; standard phylogenetic techniques fail at these scales, and we are forced to develop new methods with deep resolution. Third, any predictions we make about ancestral cell states must be testable; one route is through the existence of "living fossils" – extant organism that retain ancestral protein variants. We have implemented this program for the dynamin superfamily of proteins, which are uniquely sensitive probes of the endomembrane system. Dynamins are mechano-chemical proteins that drive membrane scission, and different dynamin variants are associated with the plasma membrane, mitochondria, peroxisomes, chloroplasts, and cytokinetic cleavage sites. We have traced the history of dynamin diversification from LECA to the present day, and shown how ancient dynamin variants have been repeatedly recruited, following gene duplication and divergence, to new locations within eukaryotic cells. One of our key findings is that a few scattered eukaryotic lineages retain the same dynamin variants as LECA, including a bifunctional dynamin simultaneously capable of driving vesicle scission and mitochondrial division [Figure 3]. These organisms are therefore ideal experimental systems for exploring ancestral cell biology.

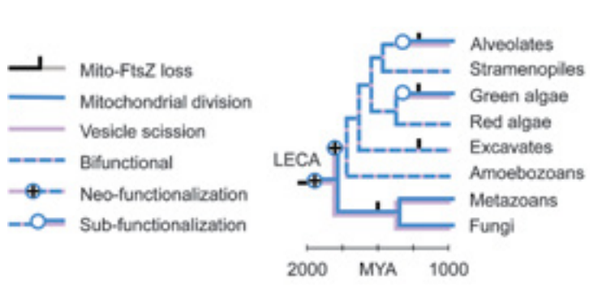


Figure 3: We can track the recruitment of duplicate gene copies to distinct locations of a cell. The last eukaryotic common ancestor (LECA) had a bifunctional dynamin which specialized into mitochondrial division and vesicle scission variants independently in multiple eukaryotic lineages. Organisms such as stramenopiles, which retain the ancestral dynamin variant, could help us understand the cell biology of LECA.

In parallel with studying the nature of ancestral traffic systems, it is important to understand how these systems change over evolutionary timescales. Our computational models suggest that the development of a new endomembrane compartment requires the simultaneous duplication and divergence of a large number of independent protein complexes. Such circumstances are rare: initially identical protein complexes, such as those which might arise following a whole-genome duplication, are typically constrained from diverging. There is, however, one scenario in which large number of non-identical duplicate protein complexes arise naturally: during the hybridization of moderately diverged species. Hybridization is common among eukaryotes, and is expected to strongly impact the traffic system, but this connection has never been examined experimentally. We have initiated a study of intracellular traffic in the lager-brewing yeast *Saccharomyces pastorianus*, which is a five-hundred-year-old hybrid between two yeast species (*Saccharomyces cerevisiae* and *Saccharomyces eubayanus*) separated by twenty million years. We have established that the hybrid organism has retained the bulk of the traffic-related machinery from both parents [Figure 4], and is therefore expected to have a traffic system distinct from either parent. This hypothesis remains to be tested; if true, it will place limits on the rate at which the vesicle traffic system can be modified, allowing us to parameterize our evolutionary models.

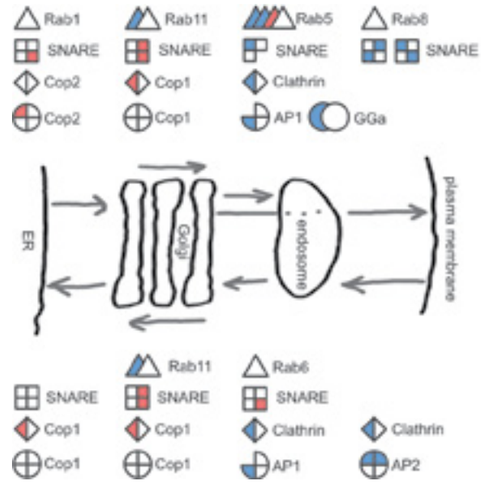


Figure 4: The vesicle traffic system of the hybrid yeast *Saccharomyces pastorianus* contains molecules inherited from *Saccharomyces cerevisiae* alone (blue), from *Saccharomyces eubayanus* alone (pink), or from both parents (white). The large number of proteins present in two copies suggests that this hybrid traffic system might have properties distinct from those of the two parent species.

Our group studies the interplay between active mechanics, molecular organization, geometry,and information processing in a variety of cellular contexts such as cell surface signaling and endocytosis, packing of chromatin within the nucleus, organelle biogenesis and tissue patterning.

MADAN RAO

Theoretical Approaches in Cell Biology: Physics of Active, Evolving Systems

The living cell is an active, self-organized medium comprising molecular processes fuelled by a steady throughput of energy. Our group is broadly interested in the organization, flow, processing and control of chemical composition, mechanical stress, energy and information in living cells and tissues. These fluxes are coupled via interconnected networks of molecules engaged in biochemical reactions played out in this active dynamical background. We are interested in unearthing new physical principles that may be unique to the living state.

These new physical principles are a consequence of the novel response of cellular systems to local active forces which maintain it away from equilibrium. These active forces arising from (i) the coupled dynamics of the cytoskeleton, motors and cytoskeletal regulatory proteins, and (ii) the active dynamics of fission and fusion of organelles, regulate the flux of composition, momentum, energy and information. We have been engaged in developing a theoretical framework, called active hydrodynamics, to address the relationship between fluxes and forces in a variety of contexts, where activity plays a significant role. Using this framework we study the mechanical response, pattern formation, symmetry breaking and hydrodynamic instabilities in both in-vivo and in-vitro reconstituted active systems. More recently our interest has turned to its implications in information processing, computation and stochastic control within the cell.

SELECTED PUBLICATIONS

Chaudhuri, A., Bhattacharya, B., Gowrishankar, K., Mayor, S. and **Rao, M.** (2011). Spatiotemporal regulation of chemical reactions by active cytoskeletal remodeling. *Proceedings of the National Academy of Sciences*, 108, 14825-14830.

Gowrishankar, K., Ghosh, S., Saha, S., Ruma, C., Mayor, S. and **Rao, M.** (2012). Active remodeling of cortical actin regulates spatiotemporal organization of cell surface molecules. *Cell*, 149, 1353-1367.

Marchetti, M.C., Joanny, J.-F., Ramaswamy, S., Liverpool, T.B., Prost, J., **Rao, M.** and Simha, R.A. (2013). Hydrodynamics of Soft Active Matter. *Reviews of Modern Physics*, 85, 1143-1189.

Dmitrieff, S., **Rao, M.** and Sens, P. (2013). Quantitative analysis of intra-Golgi transport shows intercisternal exchange for all cargo. *Proceedings of the National Academy of Sciences*, 110, 15692-15697.

Iyengar, G. and **Rao, M.** (2014). A Cellular Solution to an Information Processing Problem, *Proceedings of the National Academy of Sciences*, 111, 12402-12407.

Maitra, A., Srivastava, P., **Rao, M.** and Ramaswamy, S. (2014). Activating membranes. *Physical Review Letters*, 112, 258101.

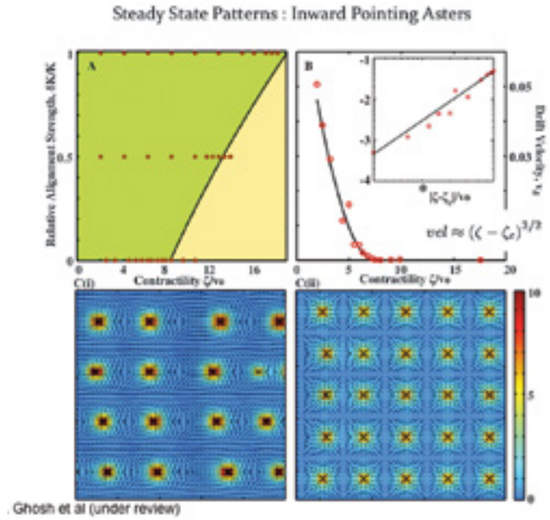
1 ACTIVE COMPOSITE CELL SURFACE : COMPOSITION, SHAPE, INFORMATION PROCESSING AND CONTROL

Kabir Husain, Amit Das, Raj Hossein, SreeKrishna, Amit Kumar

Based on years of theoretical and experimental study, we, in collaboration with Satyajit Mayor's group, have proposed a new model for the organization of the cell surface called the Active Composite Cell Surface Model (Chaudhuri et al., Gowrishankar et al.), wherein the multicomponent, asymmetric cell membrane bilayer is juxtaposed with a thin cortical actomyosin fluid layer. This actomyosin layer is complex and dynamic, with a detailed substructure that is only now beginning to be understood.

This actomyosin dynamics is primarily driven by active, energy consuming processes and and exerts active stresses and currents on the cell membrane. We showed that the contractile flows of actin filaments driven by myosin, can local control membrane composition (Gowrishankar et al.), and shape changes (Maitra et al.) of the cell membrane. We make detailed predictions about the statistics of density fluctuations, their dynamics and spatial distribution. Many of our predictions and the underlying assumptions of our theoretical have been verified in Gowrishankar et al., and in ongoing work in the lab. We have also worked out the physico-chemical details of how outer-leaflet lipid tethered proteins may link to the cortical actin using a combination of cell-based experiments and atomistic molecular dynamic simulations.

We have been studying the implications of the active composite cell surface to spatio-temporal regulation of chemical reaction kinetics, segregation and signaling (Chaudhuri et al.). We have also analyzed in great detail the effects of membrane curvature on the active dynamics of contractile actin, and showed that actin rings, cables and nodes appear naturally as steady state structure on rigid cylinders. These studies were used to understand the dynamics of actin rings in fission yeast, in collaboration with Mohan Balasubrmanian's group. We have recently studied the dynamics of a membrane juxtaposed with this cortical actomyosin (Maitra et al.) dynamics and activity the effects of these active stresses on membrane deformation and budding.



2 ACTIVE MECHANICS OF THE CYTOSKELETON

Sudipto Muhuri, Lenin Shagolsem and V.S. Gayathri

We have studied the mechanical instabilities and active stiffening of cytoskeletal filaments such as microtubules, embedded in an contractile active medium consisting of actin and myosin (Kikuchi et al, 2009). The rheological properties of this active system is rather unique showing strong departure from fluctuation-dissipation relation including negative dissipation. Our results are of relevance to the dynamics of axons and the microtubule based propulsion of neuronal

growth cones (Ehricher et al, to be submitted). We have also been studying simple physical model of bidirectional transport and a cytoskelaton-based mechanism of spontaneous cell polarity.

3 ORGANELLE REMODELING AND DYNAMICS OF INTRACELLULAR TRAFFICKING

V.S. Gayathri

We have been studying the dynamics of organelle remodeling, biogenesis, chemical identity and diffusion through compartments using techniques of non-equilibrium statistical physics. The active driving leads to a regulated flux of lipids and proteins via a process of budding, fission and fusion of transport vesicles. We have been studying these theoretical models in the context of mitochondria, golgi and endosomes.

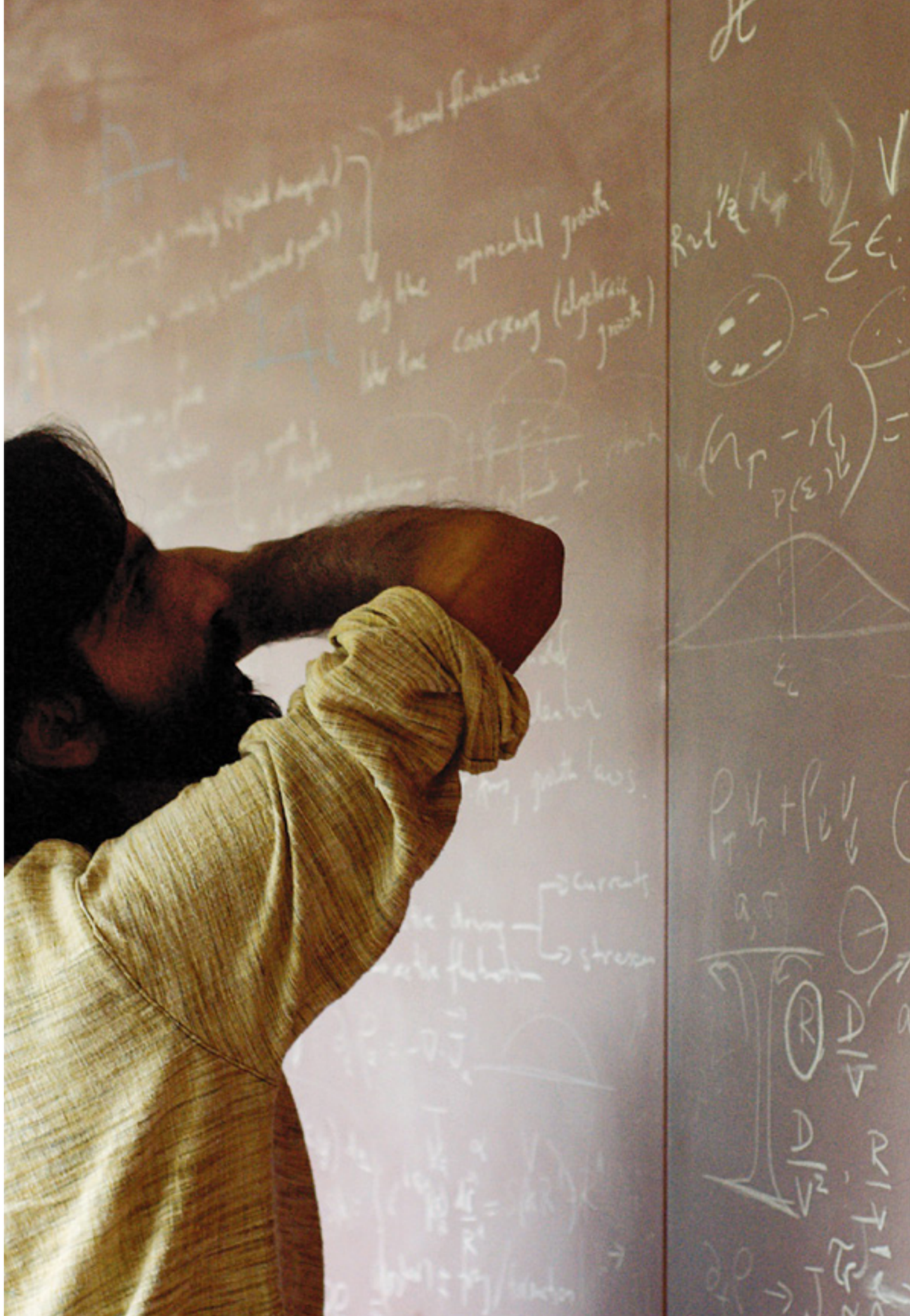
4 ACTIVE MECHANICS OF THE NUCLEUS, TISSUE

These principles can be carried over to the study of the active dynamics of chromatin in the nuclear milieu and the active rheology of the nuclear environment (in collaboration with GV Shivashankar's group) and the dynamics and patterning of the spindle.

In a more recent collaboration with M. Narasimha's group, we have been studying the dynamics of active stress patterning in the amnioserosa during dorsal closure.

5 SOFT MATTER PHYSICS

In addition we continue to work on a variety of topics on theoretical soft matter physics. These include (i) Physics of semi-flexible hetero-polymers and poly-electrolytes (ii) Phase transitions and non-equilibrium physics of membranes (iii) Competition between folding and aggregation of proteins and "in-vivo" protein folding (iv) Directed nucleation of bio-molecular assemblies. We have also been working on understanding the properties of solids which are driven far from equilibrium, both as a result of structural transformation and external stresses.



We use molecular dynamics simulations and structure-based models to understand folding-function-stability trade-offs in proteins. Several protein design principles emerge from these tradeoffs and we use these principles to develop algorithms to design both the structures and the sequences of protein scaffolds.

SHACHI GOSAVI

Computational Protein Folding and Design

SELECTED PUBLICATIONS

Yadahalli, S. and **Gosavi, S.** (2014) "Designing cooperativity into the designed protein Top7", *Proteins*, 82, 364-374,

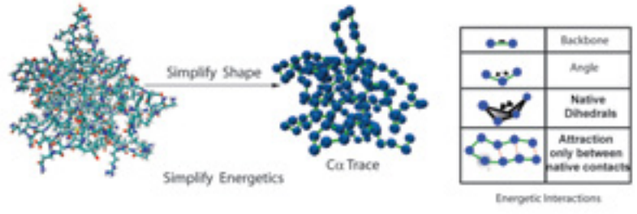
Gosavi, S. (2013) "Understanding the folding-function tradeoff in proteins", *PLOS ONE*, 8, e61222,

Capraro, D. T., Roy, M., Onuchic, J. N., Gosavi, S. and Jennings, P. A. (2012) "β-Bulge triggers route-switching on the functional landscape of interleukin-1β", *Proc. Natl. Acad. Sci.*, 109,1490-1493,

Natural proteins fold robustly because of a funnel-shaped energy landscape. This funnel shape arises because native interactions dominate the folding landscape while interactions not present in the native state (i.e., non-native interactions) contribute only in an average way. Structure-based models (SBMs) of proteins ignore non-native interactions by encoding only the folded structure of the protein into the energy function (Figure 1). This energy function is then used to perform molecular dynamics (MD) simulations. SBMs have been successfully used to understand the folding routes and the folding rates of several proteins. The advantage of SBMs is that they simplify the energy function such that large proteins can be folded and unfolded. In my group, we use purely native SBMs and variants which include some non-native interactions to understand folding-function-stability tradeoffs present in natural proteins.

Natural proteins have evolved to fold on a biologically reasonable timescale and to be as stable as is necessary to perform their function. However, selection directly acts only on the functional residues (where function could be binding, catalysis, cellular localization, etc.). These, functional residues cannot be mutated to make protein folding more efficient or protein stability greater. Given the choice of only twenty amino acids at each position, it has been hypothesized that parts of the protein which function are likely to be the least foldable or stable. Functional regions thus perturb folding from the "ideal" and we use SBMs to understand both what ideal folding is and how functional regions perturb it (Figure 2). In order to understand ideal folding, we have developed a method to extract the structure of a "function-less" protein scaffold. Using such scaffolds we would like to design protein scaffolds into which any required function can be engineered. We also study the folding of other experimentally designed scaffolds in order to understand and compare their folding with the folding of our scaffolds.

Another overarching theme in the group is to understand the design priniciples of the folding cooperativity of natural proteins. Despite the possible diversity of folding routes accessible to them, natural proteins fold cooperatively through remarkably simple folding kinetics. It has been hypothesized that this folding cooperativity reduces the population of partially folded states and guards the protein from aggregation in the crowded environment of the cell. However, different proteins achieve folding cooperativity using different sequence driven factors. We study the molecular basis of folding cooperativity (or lack thereof) in both natural (E. Coli Adenylate Kinase) and designed (Top7 has complex non-cooperative folding kinetics).



Cartoon of a coarse-grained structure-based model. The protein shape is simplified by coarse-graining it to a C_α level. The energetic terms that contribute to the potential energy function are listed in the table. The parameters for these terms are all derived from the folded state of the protein. All C_α atoms not in contact in the folded state of the protein interact through a purely repulsive interaction.

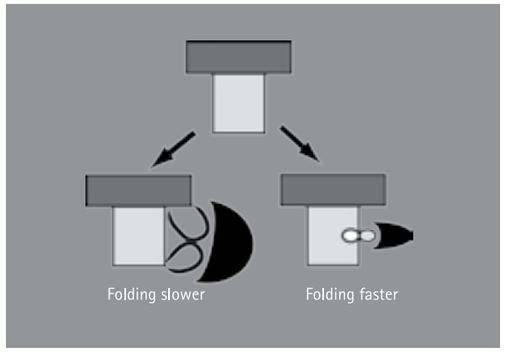


Figure 1: The folding-function tradeoff. Cartoon of an ideal β-trefoil fold (the hairpin triplet cap is shown in dark grey while the barrel is in pale grey) and two ways in which function can be introduced into it. The binding partners are shown in black. The effect of folding depends on whether function is added through extra structural elements or by reassigning fold residues.

1 TESTING PROTEIN SCAFFOLD DESIGN

Current protein design algorithms incorporate minimal backbone design. They start with the three-dimensional backbone structure of a naturally occurring protein and produce new amino-acid sequences which will likely fold to this target backbone. If the target structure has a lot of binding cavities or dynamic loops then it becomes difficult to design a sequence which will "fill" these cavities and lose the function of the original protein. This makes the target structure less designable and can also create unintended side-effects in applications. I have developed a method to design the backbones of "ideal" protein structures. I find that my scaffolds are very similar to "ideal" proteins that have already been designed and synthesized using diverse methods. However, I find that subtle differences between the packing interactions of the scaffolds that I build and the synthesized proteins result in observable changes in the computational folding of the proteins. In particular, the β-trefoil scaffold created using my method computationally folds by a completely different folding route than the naturally synthesized scaffold. We would like to incorporate these subtle changes between contact maps (and in turn folding routes) into a sequence design algorithm.

2 DEVELOPMENT OF AN ALGORITHM FOR PROTEIN SEQUENCE DESIGN

(with Hemanth G., Vishram T., Hitesh R. and Venkataramana S.) We are developing a simple, modular and scalable algorithm for sequence design. We hope to learn the design essentials of a particular fold based upon what factors (such as tertiary interactions, loop design) are necessary and sufficient to get an experimentally foldable scaffold. We intend to first test our algorithm with the β-trefoil scaffold. We also plan to compare the sequences that we generate using our algorithm with those that generated by RosettaDesign.

3 IMPLEMENTING AND TESTING COARSE-GRAINED STRUCTURE-BASED MODELS WHICH INCORPORATE NON-NATIVE INTERACTIONS

(with Shilpa Y. and Hemanth G.) The models of protein folding that we currently use (purely structure-based models) work best for evolved proteins with funneled energy landscapes. The landscapes of designed proteins are likely to be less funneled and more rugged. We are currently testing several protein models that incorporate different forms of non-native interactions. Using the protein Top7 as a test case, we have investigated the changes in the intermediate ensembles (folding routes) that occur due to the nature of the non-native interactions. We find that certain intermediates are robust to changes in model while others are specific to a particular model of non-native interactions. We expect that the robust intermediates will likely be present in experiments. Once tested, we will use these models to not only test the foldability of designed proteins but to also test the protein sequences generated using our design algorithm.

4 HOW ARE NATURAL MULTI-DOMAIN PROTEINS DESIGNED?

(with Hemanth G.) Recently, multi-domain proteins have gained biotechnological importance as a way to combine the functions of several domains. However, the design of such proteins usually occurs by trial and error. We are studying the folding of several multi-domain proteins including E.coli Adenylate kinase (AKE) and the serpin family in order to understand how their structure determines both their folding and their conformational transitions. In the three-domain protein AKE, we find that the two weakly stable domains which are required to be dynamic in order to perform conformational transitions are inserted into the more stable core domain. This domain insertion makes the entire protein more cooperatively folding and reduces partially folded states. (Figure 2). We find that weakly stable domains in T4-lysozyme and E. coli slyD are also inserted to enhance folding cooperativity. We plan to computationally fold several other proteins with inserted domains, such as the MBP-like histidine binding protein HisJ.

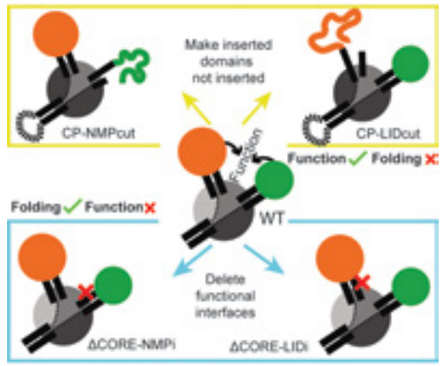


Figure 2: Domain insertion and the folding-function tradeoff in AKE. An idealization of the AKE results. Folding implies folding cooperativity and WT AKE is the most cooperative of the mutants. Function is the mechanism of conformational transitions. Domain insertion allows WT AKE to maintain folding cooperativity while accommodating the residue constraints that are placed on domain interfaces due to ligand binding.

5 UNDERSTANDING COLD AND HEAT STABILITY USING THE EXPERIMENTAL FOLDING THERMODYNAMICS AND KINETICS OF THE HYPERTHERMOPHILIC PROTEIN CTD-MK0293.

(with Hitesh R. and Prof. J. B. Udgaonkar) In order to observe if signatures of a protein's native environment can be detected in its folding, we have studied the room-temperature folding thermodynamics of the C-terminal domain of the hyperthermophilic protein MK0293 (PDB ID: 3C19) from Methanopyrus kandleri AV19. This hyperthermophilic archaeon survives upto temperatures of 110°C and its proteins may fold and unfold at even higher temperatures. We found that the protein resists unfolding upto a concentration of 4.1 M guanidinium hydrochloride (GdnHCl) at 298 K, but other than this unusual stability, showed normal "mesophile-like" two-state folding behaviour. We used isothermal GdnHCl-induced denaturation curves at different temperatures and temperature-induced melting curves at different GdnHCl concentrations in conjunction with the linear free energy model to derive various thermodynamic parameters (ΔG, ΔH, ΔS, ΔC_p) to high precision. The low temperature (cold) denaturation transition of this protein became experimentally accessible upon simultaneously varying both the temperature and the denaturant concentration, and we thermodynamically characterized it. Furthermore, we theoretically analyzed the heat and cold denaturation transitions for both Ctd-MK0293 and several other proteins using calculated solvent accessible surface areas (SASAs). We also analyzed the individual contributions of polar and non-polar SASAs to these transitions. Our calculations suggest that the extreme thermal stability of Ctd-MK0293 is achieved by better H-bonding and internal packing. In addition, in contrast to current belief but in agreement with early work of Makhatadze and Privalov we find that the hydration of polar groups plays a major role in the cold denaturation of proteins. We are currently studying the folding kinetics of this protein.

I'm interested in understanding the strategies cells use to make decisions based on incomplete and unreliable information about their environment.

SANDEEP KRISHNA

SELECTED PUBLICATIONS

Road rules for traffic on DNA—systematic analysis of transcriptional roadblocking in vivo N Hao, **S Krishna** , A Ahlgren-Berg, EE Cutts, KE Shearwin, IB Dodd (2014) Nucleic acids research 42, 8861-8872.

The effect of LacI autoregulation on the performance of the lactose utilization system in Escherichia coli S Semsey, LJ Pedersen, Z Csiszovszki, J Erd ssy, V Stéger, S Hansen, S Krishna (2013) Nucleic acids research 41, 6381-6390.

Context-dependent conservation of DNA methyltransferases in bacteria ASN Seshasayee, P Singh, **S Krishna** (2012) Nucleic acids research 40, 7066-7073.

Coexistence of phage and bacteria on the boundary of self-organized refuges S Heilmann, K Sneppen, **S Krishna** (2012) Proceedings of the National Academy of Sciences 109, 12828-12833 Inducing phase-locking and chaos in cellular oscillators by modulating the driving stimuli MH Jensen, S Krishna (2012) FEBS letters 586, 1664-1668.

The Choices of a Cell*

Cells are quintessential examples of complex systems, consisting of numerous non-identical components, interacting non-linearly and operating far from equilibrium. They are adaptive, both on shorter timescales where they respond to changes in their surroundings, and on longer timescales by evolution via natural selection.

In order to thrive and reproduce, biological cells - all the way from free-living single cell prokaryotes to eukaryotic cells in a multicellular organism - must constantly make "decisions" about how to respond to changes in their surroundings. For example, when certain viruses infect bacteria, their DNA, inserted into the bacterium, either replicates rapidly and kills the bacterium releasing a burst of hundreds of offspring, or goes into a dormant mode allowing the bacterium to live and replicate normally (Figure 1). This is perhaps the simplest example of a living system making a decision. Evidently, many factors could make one strategy better than the other: bacterial numbers, how fast they're replicating, the ratio of viruses to bacteria, etc. So it is not surprising that this decision is not made entirely randomly. For instance, when two or more lambda viruses simultaneously infect an *E. coli* bacterium it is more likely to go into the dormant mode, whereas a single infection goes more often into the killing mode [1]. A possible reason could be that multiple infections provide information that viruses outnumber bacteria in the environment [2]. Although such viruses have been studied extensively (the lambda virus has been studied for over 60 years, right from the beginnings of molecular biology) we do not completely understand when and why a virus chooses one strategy over the other. Similarly, we lack a full explanation of many other cellular decisions. An example of such a binary decision in higher organisms is when mammalian cells choose between committing suicide or turning on repair mechanisms when they are damaged by UV radiation. Discrete non-binary decisions occur often in the development of an embryo, where initially identical cells, with the same DNA,

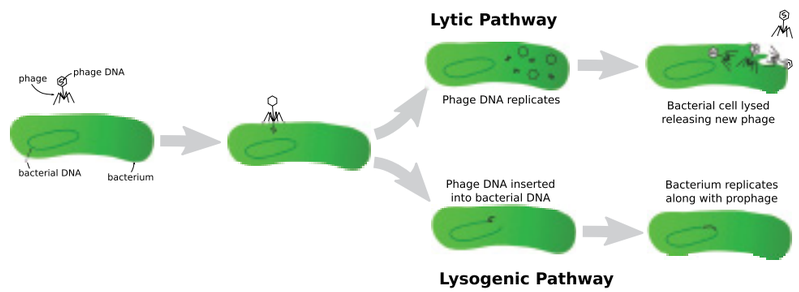


Figure 1: Lysis-lysogeny decision in temperate bacteriophage. One of the simplest examples of a cellular decision occurs when a temperate bacteriophage, a type of bacterial virus, infects a bacterium. After it's inserted, the phage DNA hijacks the cell's machinery to express its own genes. It may enter the ``lytic pathway'', where the phage DNA replicates, produces the proteins needed to package the DNA into new phage particles, and finally bursts the bacterial cell open thus killing it and releasing a large number of offspring phage. Alternatively, it enters the "lysogenic pathway", where the phage DNA inserts itself into the DNA of the bacterium and remains dormant [1,2]. Most studied bacteria contain at least one such dormant `prophage'. In this state the bacterium replicates normally, along with the embedded prophage, until some later time when a signal, such as DNA damage, switches the phage back to the lytic pathway.

* With apologies to Lewis Thomas

switch to different states; some become muscle cells, some neurons, some skin cells, and so on. More continuous decisions underlie the response of bacteria to changing environments with fluctuating food sources, physical stresses, predation and competition, etc.

A comprehensive understanding of such decisions requires investigation at many scales:

At the *molecular level* one can ask what kind of information the signalling network of a cell can obtain about the environment. Precisely what does having one, or two, or three, infections tell a virus about the ratio of virus to bacteria numbers, and how reliable can this information be? How does the concentration of sugar inside a bacterium correlate with the amount of sugar remaining in the surroundings?

These are inference problems and I use Bayesian approaches to determine the kind of information that can be reliably inferred from cellular signalling pathways. At the *population/ecosystem level* one can investigate the optimality of different strategies by combining tools from population dynamics and game theory. For example, I am studying a game of two competing viruses that can choose between a variety of strategies, some of which use information about the virus:bacteria ratio to bias the decision, and some which don't. The Nash equilibria of this game, played under different conditions, show when this information helps or hinders a virus. Similar games can be constructed for bacterial strains competing for resources, stem cells ungergoing differentiation, damaged cells committing suicide, etc.

In between is the *cellular level*, where lies the decision-making apparatus: a feedback control system that produces/degrades proteins and other cellular components depending on the environmental information it receives from the signalling network [3, 4] (Figure 2). In combination

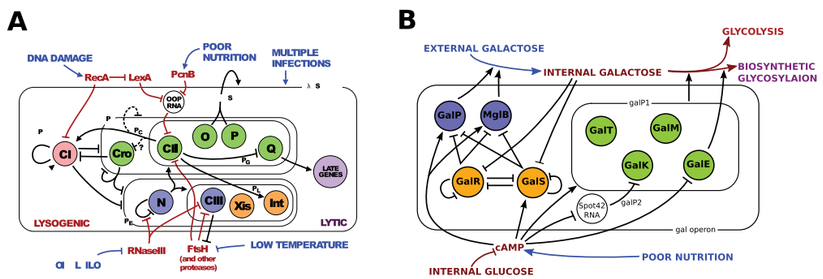


Figure 2: The complex networks that control cellular decisions. Regulatory networks that control (A) the lysis-lysogeny decision in phage lambda [1,2] (courtesy Ian Dodd and Keith Shearwin, Adelaide Univ.), and (B) the production of galactose transporters and metabolic enzymes in *E. Coli* [5,6]. The significance of this figure is not the details of the network interactions, but to show that these networks are complex and integrate diverse pieces of information about the surroundings. Our understanding of the components and their interactions is still far from complete.

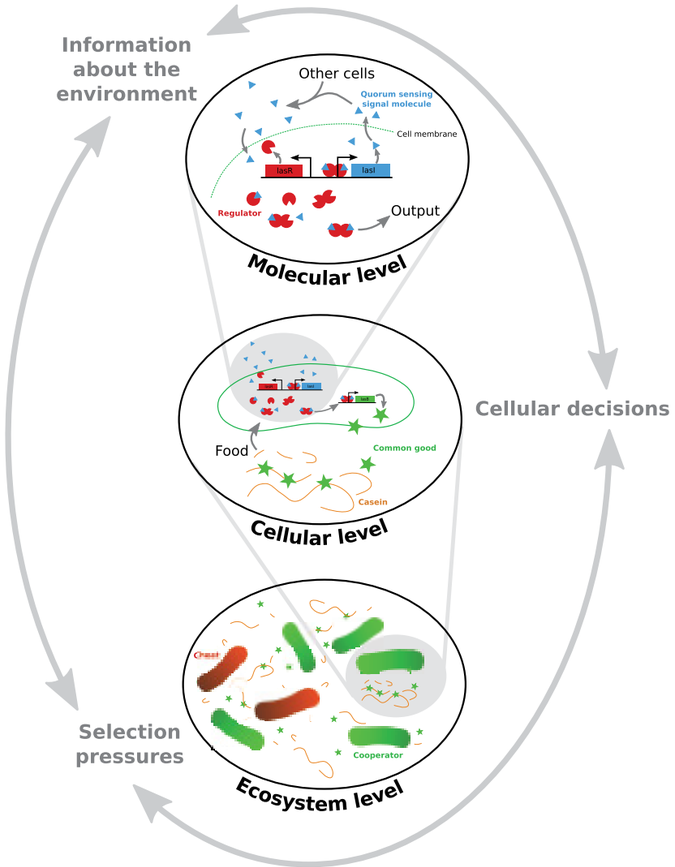
with the studies at the population and molecular levels, I use tools from control theory and nonlinear dynamics to understand how feedback loops and other control structures are designed to choose better strategies over worse ones.

This kind of multi-scale study of a decision (Figure 3) is likely to open up new experimental directions. For instance, my work with competing virus games indicates the importance of information about bacterial numbers in choosing the optimal strategy. This raises the experimentally testable question of whether viruses hook into the quorum sensing systems of bacteria (almost all bacteria secrete small molecules, whose net concentration in their vicinity they then measure and use to estimate bacterial numbers). Similarly, work on the control of galactose metabolism in bacteria indicates that it needs two regulators, one to take care of steady-states and one to control transients [5], which suggests several experiments that can test and exploit this design.

I have long-running collaborations with biologists at the Niels Bohr Institute [6, 7] and Adelaide University [1, 2], as well as some more recent collaborations with laboratories studying genetic and signalling networks and bacterial quorum sensing at NCBS, the University of Copenhagen and the University of Washington, Seattle.

With these collaborators, I design experiments to test questions that arise from the theoretical investigation of biological decisions and, in turn, use data from experiments to design further theoretical studies.

Figure 3: Towards a multi-scale understanding of biological decisions. This figure summarizes my approach to studying cellular decisions. Consider a population of *P. aeruginosa* bacteria which can produce a common good, the protease LasB [8], that breaks casein proteins into smaller digestible polypeptides. It is important for the bacteria producing the common good (cooperators, green) to carefully regulate the production so they are not out-competed by mutant bacteria (cheats, red) that obtain the benefit of the good but avoid the cost by not producing it themselves [9]. At the cellular and molecular level, the production decision uses a quorum sensing system [8], consisting of small signal molecules (blue triangles) that are secreted and diffuse around. Selection pressures at the population level (presence of cheats, casein availability, environmental conditions, etc.) determine the best physiological responses of individual cells and the kinds of information about the surroundings the molecular signalling pathways need to collect. The unavoidable uncertainties in the molecular information, in turn, constrain the possible physiological responses of the cell. We can only begin to understand such cellular decisions once we understand the connections between processes at these different length- and time-scales.



FOOTNOTE

0 Thomas L (1974) The Lives of a Cell: Notes of a Biology Watcher, The Viking Press, New York.
1 Avlund M, Dodd I, Sneppen K, Krishna S (2009) J. Mol. Biol. 394, 681–693.
2 Avlund M, Dodd I, Semsey S, Sneppen K, Krishna S (2009) J. Virol. 83, 11416–11420.
3 Krishna S, Semsey S, Sneppen K (2007) Proc. Natl. Acad. Sci. (USA) 104, 20815–20819.
4 Mengel B, Hunziker A, Pedersen L, Trusina A, Jensen MH, Krishna S (2010) Curr. Opin. Gen. Devel. 20, 656–664.
5 Semsey S, Krishna S, Erdossy J, Horvath P, Orosz L, Sneppen K, Adhya S (2009) J. Bacteriol. 191, 4487–4491.
6 Horvath P, Hunziker A, Erdossy J, Krishna S, Semsey S (2010) J. Biol. Chem. 285, 38062–38068.

We study the interactions between control and morphology in human movement and also design biologically inspired machines and control strategies. Specially, we work on the mechanics and control of the quintessential human abilities of hand dexterity, endurance running, and throwing.

MADHUSUDHAN VENKADESAN

Mechanics, Materials and Control of Machines and Animals

SELECTED PUBLICATIONS

Lieberman DE, **Venkadesan M**, Werbel WA, Daoud AI, D'Andrea S, Davis SI, Mang'eni RO, Pitsiladis Y. Foot strike patterns and collision forces in habitually barefoot versus shod runners. *Nature* (cover page) 463: 531–535 (2010).

Roach NT, **Venkadesan M**, Rainbow MJ, Lieberman DE. Elastic energy storage in the shoulder and the evolution of high-speed throwing in *Homo*. *Nature* (cover page) 498: 483–486 (2013).

Venkadesan M, Valero-Cuevas FJ. Effects of neuromuscular lags on controlling contact transitions. *Philosophical Transactions of the Royal Society A* 367: 1163–1179 (2009).

Madhusudhan has moved to Yale School of Engineering and Applied Science http://seas.yale.edu/faculty-research/faculty-directory/madhusudhan-venkadesan

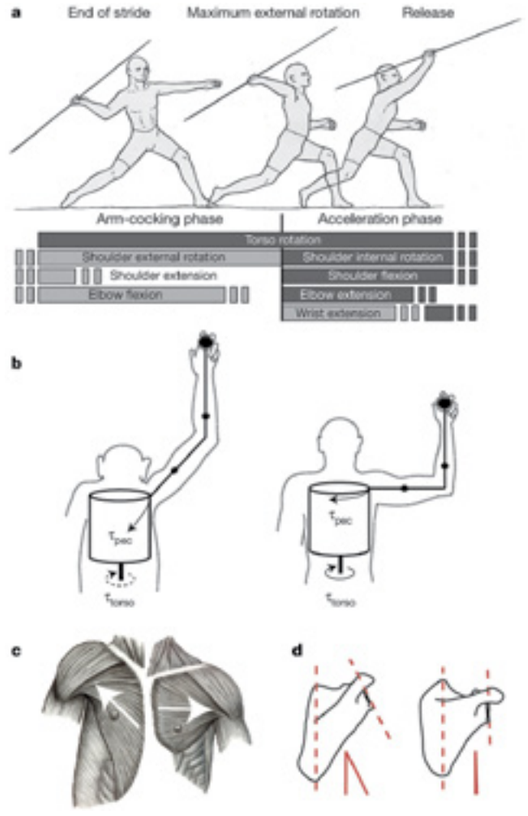
Animals routinely perform motor behaviours that are beyond the abilities of current robots. A cockroach navigates uneven terrains at speeds that are unmatched by any machine. Most humans, even with cold and numb fingers, can handle objects with far greater dexterity than the most precise robot. On the other hand, compared to animals, robotic joints are more precise, motors have higher force and power output, sensory feedback control is faster, and computations are more repeatable. How do apparently sloppy animals outperform the fast and precise robots that we build? Are animals better because of, or despite their sloppiness, i.e. how do the body's mechanics affect control? My lab's research, straddling the areas of *Mechanics*, *Control theory* and *Biology*, aims at extracting the design and control principles that underlie the deftness of animal motor behavior, and translate that to next generation actuators, robots and prostheses. Our current work with human biomechanics and motor control is focused on the quintessential human abilities of hand dexterity, endurance running, and throwing.

OVERVIEW

Through natural selection, humans have evolved to excel in endurance running [1], high-speed and accurate throwing [2] and hand dexterity [3]. Our research aims at characterizing the role of mechanics in human motor control, and at the same time generate design and control principles for actuated machines. To do this, we use a combination of human subject experiments, reduced order mathematical models, computational methods, and the fabrication of actuated mechanical devices, to identify the material properties and morphological elements of our bodies that are necessary to excel at these behaviors. The mathematical theories of animal behavior also guide the design of new actuators and body morphologies for use in robots. Applications of our current and planned future work include new designs for arms capable of throwing fast and accurately without real-time feedback, fingers capable of stable contacts without feedback, strategies for stable, energy-efficient locomotion on rough terrains, and muscle-like motors with tension dependent stiffness and damping. Our current work suggests that the bodies of animals are finely tuned through evolution to create mechanical solutions for control problems, especially in those situations where the performance is sensitive to noise and time delays.

DEXTEROUS MANIPULATION

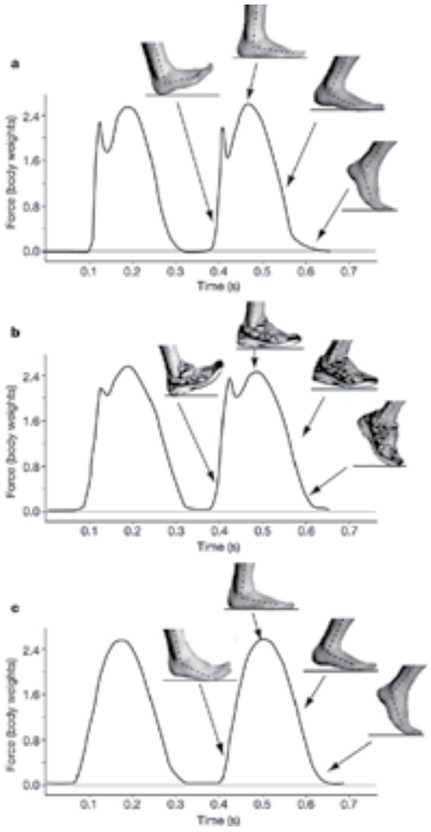
Our hands are capable of lot more than static grasping. Dexterous manipulation, involving the precise regulation of the fingers, is a skilled activity that we use every day. Such manipulation is a combination of predictive control strategies and feedback from multiple sensors such as vision, touch and proprioception. How do humans use potentially redundant information from multiple sensors? We developed an experimental task, of compressing slender springs prone to buckling, in order to measure dexterous manipulation ability. Using these measurements we showed how humans combine feedback from multiple sensors in a context sensitive manner. Vision, the slowest of the available sensory modalities, was almost unused when tactile information was reliable. But, when the quality of tactile sensation was experimentally degraded, vision became the dominant mode of feedback despite having larger time delays than proprioception. We used bifurcation theory, from nonlinear dynamics, to develop a reduced order model for this dynamic manipulation task. Using this model, we found that the globally optimal strategy for sensor fusion resembled what humans use. This work led to a clinical tool for quantifying hand function, as well as a functional MRI study to identify the neural correlates of strength and dexterity. Fundamental questions remain on how the nervous system learns to control objects with many internal degrees of freedom, and whether techniques of bifurcation detection that are employed by engineers (such as in electrical power grids) have a role to play in neural and robotic control near stability boundaries.



CONTACT CONTROL

Using our fingers, we routinely touch, press and interact with external surfaces. These interactions couple the dynamics of the finger to the object or surface being touched, and creates challenging problems for control of robotic grasping. However, the strategies that humans use in fingertip contact control was unknown prior to our studies. Using fine-wire electromyograms from all seven muscles of the index finger and biomechanical modeling, we showed that when transitioning between motion and force (finger tapping) humans precisely anticipate fingertip collisions. The torques at the finger joints rapidly switch from motion to force control just in time (< 60ms) for contact. Then using optimal control we showed that elasticity of the long tendons of the fingers, the time constant for neural excitation of muscle and frictional constraints at the fingertip are the primary mechanical and neuromuscular factors that govern the observed strategy [3]. Our investigations into contact control by humans drives some current work on muscle-like motors, and a broader theory for systematic actuator and mechanical design. Such actuators

and mechanisms are critical to alleviate the need for fast and precise feedback control on short timescales (< 10ms). This work is part of ongoing efforts in my lab and elsewhere to make use of mechanical responses for developing agile robots.



MOTOR VARIABILITY

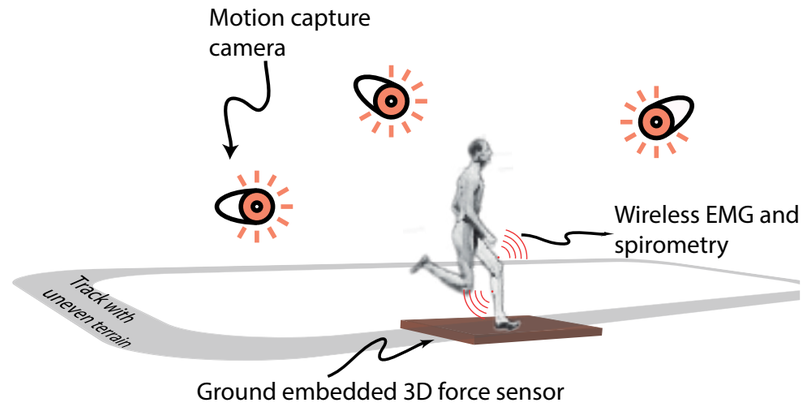
Humans appear noisy in their motor capabilities, but are not uniformly so. There is emerging evidence of underlying structure to this noise. Humans exhibit lesser variability in parameters that directly affect the outcome of the task than in task-irrelevant parameters. Can the nervous system directly alter the covariance of motor noise across multiple muscles? Until our study, it was not possible to rule out other factors such as task mechanics and fatigue driven trial-to-trial variability. Using fine-wire electromyograms recorded from all muscles of the index finger, for a static finger pressing task, we found that there is indeed neurally modulated structure to the variability of muscle output. Muscle combinations that contributed to the instructed force direction had lesser variability than those that did not. For both machines and humans, open questions remain on whether reducing variability in actuation comes at a cost, energetic, performance or otherwise. In tasks that involve working near boundaries of instability, actuator noise can play a key role in monitoring whether the system is close to failure or not. Noise reduction is therefore not always beneficial. Questions on the limits and consequences of noise reduction in actuators are part of our ongoing and future work, such as the project on dynamic manipulation.

THROWING

Some primates, including chimpanzees, occasionally throw objects such as rocks, but only humans routinely throw with high speed and accuracy. Are there morphological features that underlie the superior throwing ability of humans? If so, when in the fossil record of human ancestors are these features evident? We used experimental studies of humans throwing projectiles, and mechanical estimates of power output at joints to show that our throwing capabilities largely result from anatomical features that enable elastic energy storage and release at the shoulder [2]. These features first appear together approximately 2 million years ago in the species *Homo erectus*. Such vigorous and dynamic behaviors are unusual in robots, and high-speed throwing could be a good benchmark problem to assess the state of agile robots. Our ongoing experimental and computational work are progressing towards mechanical and control design for developing highly dynamic robotic arms.

PLANNING

Controlling the arm for pointing at targets has been the predominant paradigm to study motor learning and adaptation for several decades. However, arm pointing inextricably couples motor learning with active feedback control. To separate planning from control, we studied the problem of motor planning for accurate throwing, and found that noise propagation through the dynamics of projectile flight has a profound effect on strategy. Understanding throwing ability has implications for human evolution and for clinical evaluation of motor development in children. This leads to questions about motor learning, i.e. how to develop an experiential understanding of Newtonian mechanics from repeated observations.



ENDURANCE RUNNING

Humans are foremost among all animals at sustained running over long distances. Evolved morphological features for heat dissipation, energetic efficiency, and agile bodies are thought to underlie the human capacity for endurance running. One key problem, related to neural coordination of our bodies, is the collision at the foot that generates a force more than twice the body weight. With more than 500 foot strikes per kilometre, these impacts are postulated to be a major contributor to running injuries that afflict over 30% of endurance runners. But, how did humans run safely before the invention of the modern cushioned running shoe in the 1970s? We compared habitually barefoot versus habitually shod endurance runners from the USA and also from the Nandi district in Kenya (famous for its endurance runners). We found that the collisional impulse for barefoot runners was four to seven times smaller than for shoe-wearing runners. By modeling the collisional mechanics for a runner, we show that foot impacts in the barefoot runners were smaller because they first land on their forefoot (ball of their feet), and also maintain lower ankle stiffness than heel strikers [1]. Ongoing work in the lab studies the role of compliance in the leg and the foot for stability on rough terrains. Besides implications for the shoe industry, our work affects future studies on the biomechanics of human running, and raises questions about the role of feet in humans, animals, robots and prostheses.

ADJUNCT FACULTY

We have been privileged to have especially strong associations with a number of remarkable scientists from around the world, who form our adjunct faculty. Their roles span those of close collaborators, through to institutional mentors and people who have catalyzed entire new areas of activity on campus. **Madan Rao** from the Raman Research Institute is a close collaborator of Satyajit Mayor, and is a founding member of the theory group and Simon's centre at NCBS. His engagement with us is so complete as to have his own page in this report. **Sanjeev Jain** from the National Institute of Mental Health and Neurosciences collaborates with Mitradas Panicker on the physiological and genetic basis of psychiatric disorders, and has also been an invaluable link with the scientific and medical community in Bangalore. **Michael Bate** from Cambridge is an old NCBS collaborator, working for years with K. VijayRaghavan on development of neural control of movement.

Mani Ramaswami at Trinity College Dublin, has also been closely associated with NCBS since its founding. He collaborates with K. VijayRaghavan on fly neural development and olfactory processing. He, along with (the late) K.S. Krishnan and Uma Ramakrishnan, has been one of the key drivers of the evolving Chemical Ecology programme. **Ullas Karanth** of the Centre for Wildlife Studies has been the impetus behind the vibrant Masters programme in wildlife biology and conservation and provides us with an eminent link to the crucial conservation community in the country.

In the realm of cell biology we have **Vivek Malhotra** of the Centre for Genomic Regulation, Barcelona, who is a stimulating frequent visitor and collaborator with Raghu Padinjat and Satyajit Mayor. **James Spudich** of Stanford University has not only been a collaborator but has served as a mentor to the entire campus, with key insights that led not only to the design of our dynamic new Southern Laboratory complex, but also to the establishment of research themes at inStem. **Francisco Barrantes**, who works on acetylcholine receptors with Satyajit Mayor, is from the Beunos Aires in Argentina.

Ajit Varki and Sushma Reddy are Visiting faculty affiliated with Mukund Thattai and Satyajit Mayor, and Uma Ramakrishnan, respectively.

NEW INVESTIGATORS

SHANNON B OLSSON

Naturalist-Inspired Chemical Ecology

PUBLICATIONS

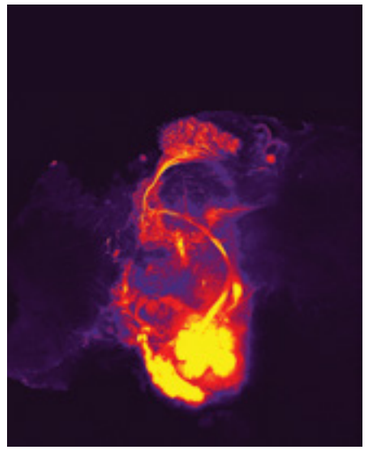
Capurro, A., Baroni, F., Kuebler, L., Kárpáti, Z., Dekker, T., Hansson, B.S., Pearce, T.C., **Olsson, S.B.** (2014). Temporal features of spike trains in the moth antennal lobe revealed by a comparative time-frequency analysis. *PlosONE, 9*, e84037.

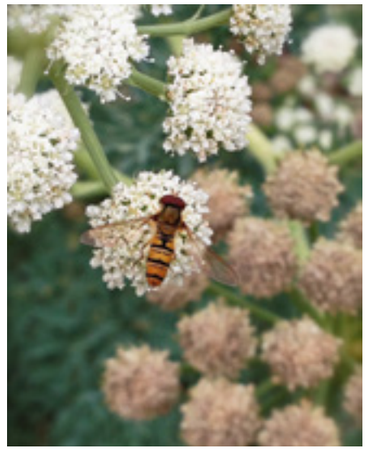
Olsson, S.B., Hansson, B.S. (2013) Electroantennogram and single-sensillum recording in insect antennae. In: *Pheromone Signaling: Methods and Protocols*, K. Touhara, ed. Springer Protocols: Totowa, NJ, 1068, 157–177.

Kuebler, L.S., Schubert, M., Karpati, Z., Hansson, B.S., **Olsson, S.B.** (2012) Antennal lobe processing correlates to moth olfactory behavior. J. Neuroscience, 32(17): 5772-5782.

Chemical interactions are ubiquitous in nature. Chemical ecology examines the role of chemical interactions between organisms and their environment. The study of chemical ecology thus offers both powerful insight into biological processes, as well as ecologically-based applications for agriculture, manufacturing, and medical industries. Our research employs a comparative approach to understand how different insects locate odor sources in complex natural environments. We take field trips, record neurons, generate models, and even build robots, all with the goal of understanding how different insects have evolved to smell "odor objects" and make decisions (i.e. select actions). We are dedicated to using advanced neuroethological techniques to understand sensory processing in the context of natural observations, and assess the response of the nervous system to ecologically-relevant stimuli. Today we are developing more and more tools to probe the genetic, molecular, and cellular basis of behavior. Still, we often use these tools to observe a phenomenon in the lab and strive to find its meaning in nature without understanding the natural behavior, or even if the phenomenon occurs in nature. Our research strives to inspire a new type of scientist who fuses a Naturalist's heart with a technician's insight.

Determining how and why animals make choices in their environment is an essential component to understanding the delicate interplay between species, preserving their ecology, and predicting the impact of invasive species, climate change, and human disturbance. To examine natural olfactory behavior, we employ an interdisciplinary mixture of: evolutionary and ecological models to understand how insect olfactory systems process complex odors, molecular and genetic tools to probe olfactory signal transduction, extra- and intracellular electrophysiology and optophysiology to assess the processing of complex odor objects, computational modeling to test our hypotheses, virtual reality behavior to assess multimodal sensory integration, and robotics and engineering to replicate our biological findings in artificial systems. Dr. Olsson is also passionate about education and outreach, and dedicated to training scientists who are as comfortable with binoculars as they are with a compound microscope and a computational model.





VARADHARAJAN SUNDARAMURTHY

Host-pathogen Interactions

PUBLICATIONS

Sundaramurthy, V., Barsacchi, R., Chernykh, M., Stoter, M., Tomschke, N., Bickle, M., Kalaidzidis, Y. & Zerial, M. (2014). Deducing the mechanism of action of compounds identified in phenotypic screens by integrating their multiparametric profiles with a reference genetic screen. *Nature protocols*, 9, 474-90.

Sundaramurthy, V., Barsacchi, R., Samusik,N., Marsico, G., Gilleron,J., Kalaidzidis, I., Meyenhofer,F., Bickle, M., Kalaidzidis,Y., & Zerial, M. (2013) Integration of chemical and genome-wide siRNA multi-parametric profiles identifies triggers of intracellular mycobacterial killing . *Cell Host and Microbe*, 13, 129-142.

Jayachandran, R.*, **Sundaramurthy,V.***, Combaluzier,B., Muller, P., Korf, H ., Huygen, K., Miyazaki, T., Albrecht, I., Massner, J. & Pieters, J. (2007) Survival of Mycobacteria in Macrophages is Mediated by Coronin 1 Dependent Activation of Calcineurin. *Cell*, 130, 37-50. (* **equal contribution**).

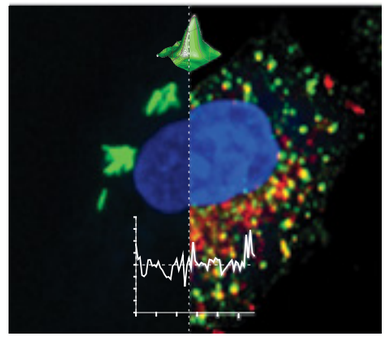
Intracellular pathogens are often considered as master cell biologists. They understand the host cells perfectly and manipulate them in subtle and non-subtle ways to ensure a successful infection. Pathogens and host cells have co-evolved for a long time and hence the host-pathogen interface offers fascinating glimpses into the forces that have shaped pathogenesis. The broad goal of our group is to understand the contours of these interactions at multiple levels across different pathogens. More specifically, we aim to study the modulation of critical host pathways by pathogens and exploit the potential of this knowledge for drug discovery.

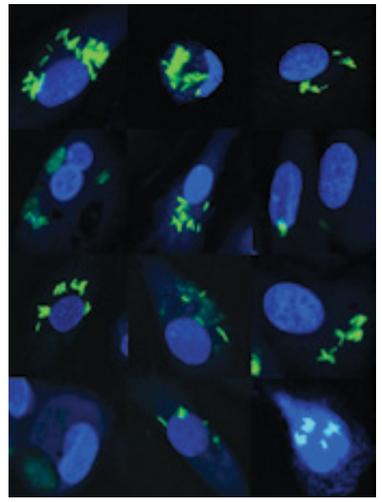
In my previous work, I have studied the host-pathogen interaction during mycobacterial infections. Our work has uncovered a new host cellular pathway, the Coronin1 mediated activation of Calcineurin, which operates specifically in mycobacteria infected cells (Jayachandran et al, Cell, 2007). More recently, we have performed a high content chemical screen to identify compounds that modulate host cellular processes that impact intracellular mycobacterial survival and used these compounds as chemical probes to identify the underlying cellular mechanisms (Sundaramurthy et al, 2013). We also captured the systems properties in multi-parametric space using quantitative image analysis and established methods to integrate disparate multi-parametric datasets to derive mechanistic insights (Sundaramurthy et al, 2013, 2014).

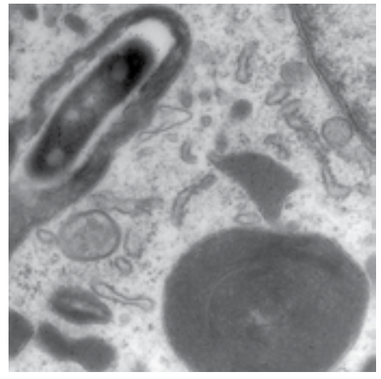
Our current interests are to understand the modulation of host trafficking pathways by two very different pathogens, namely Mycobacterium and Plasmodium, the causative agents of the deadly diseases tuberculosis (TB) and malaria. The specific topics we address fall in three broad areas:

1. Influence of intracellular mycobacterial infection on host trafficking pathways
2. Involvement of host trafficking pathways during Plasmodium infection in the liver stage of malaria
3. Protein trafficking in Plasmodium infected erythrocytes

We aim to quantify these effects at single cell resolution to capture the heterogeneities of the association and understand their biological significance. In addition, we will continue exploring the idea of targeting host cellular processes to fight against infectious agents. In these studies, we will to apply a combination of chemical genetics, quantitative image analysis and high content screening tools along with conventional cell and molecular biological approaches.







BIOCHEMISTRY BIOPHYSICS BIOINFORMATICS { rana@ncbs.res.in }

RANABIR DAS

PUBLICATIONS

Das, R., Liang, Y.H., Mariano, J., Li, J., Huang, T., King, A., Tarasov, S.G., Weissman, A.M., Ji, X. & Byrd, R.A. (2013). Allosteric regulation of E2:E3 interactions promote a processive ubiquitination machine, *EMBO J*, 32(18):2504-16.

Metzger, M.B., Liang, Y.H., **Das, R.**, Mariano, J., Li, S., Li, J., Kostova, Z., Byrd, R.A., Ji, X., Weissman, A.M. (2013). A structurally unique E2-binding domain activates ubiquitination by the ERAD E2, Ubc7p, through multiple mechanisms", *Molecular Cell*, 50(4): 516-27.

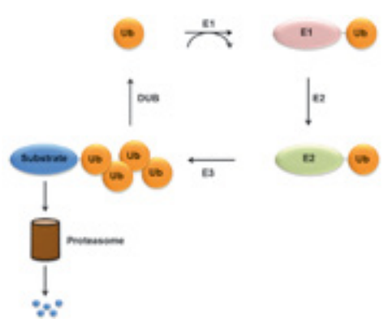
Das, R., Mariano, J., Tsai, Y.C., Kalathur, R.C., Kostova, Z., Li, J., Tarasov, S.G., McFeeters, R.L., Altieri, A.S., Ji, X., Byrd, R.A., Weissman, A.M. (2009). Allosteric activation of E2-RING finger-mediated ubiquitylation by a structurally defined specific E2-binding region of gp78, *Molecular Cell*, 34(6):674-85.

The conjugation of ubiquitin to other cellular proteins regulates a broad range of eukaryotic cell functions, including protein degradation, cell cycle regulation, DNA repair, transcription, and endocytosis. This is because ubiquitin can alter the activity of its target in a variety of ways, from targeting it to the proteasome for degradation to alter its localization or enzymatic activity. Ubiquitylation, the process that involves the covalent attachment ubiquitin to the target protein, creates a covalent isopeptide linkage in a variety of different topologies to affect these diverse processes.

Ubiquitylation is a highly regulated process involving a specific cascade of activities performed by the E1, E2, and E3 series of enzymes. E1, or ubiquitin-activating enzyme, activates ubiquitin by forming a thiol ester link between the carboxy terminus of ubiquitin and the active site cysteine of E1 in an ATP-requiring step. The activated ubiquitin is then transferred to an E2 ubiquitin-conjugating enzyme, also through a thiol ester bond between ubiquitin and the active site cysteine of E2. E2, together with E3 or ubiquitin ligase, transfers the ubiquitin to its target, forming a covalent isopeptide linkage between the carboxyl terminus Gly-76 of ubiquitin to a primary amine (usually the ε-amino group of lysine) of the target protein.

Ubiquitylation is a unique form of post-translational modification in which, beyond a single ubiquitin attachment to the target protein, that ubiquitin monomer can be further ubiquitylated to create polyubiquitin chains. Remarkably, different ubiquitin topologies or linkages between ubiquitin moieties can lead to vastly different cellular functions. For example, the canonical lysine-48 (K48)-linked polyubiquitin targets the substrate protein for proteasomal degradation; whereas lysine-63 (K63)-linked polyubiquitin is often involved in localization or signaling events. Polyubiquitin can be linked through one residue to create a homogeneous chain, or through multiple residues, forming branched ubiquitin chains.

We study the assembly and recognition of ubiquitin chains with the goal to understand how these chains affect cellular processes.



PUBLICATIONS

137 PUBLICATIONS 2012 145 PUBLICATIONS 2013 151 PUBLICATIONS 2014

PUBLICATIONS 2012

BIOCHEMISTRY, BIOPHYSICS AND BIOINFORMATICS

JAYANT B UDGOANKAR

- Aghera, N., Dasgupta, I., and **Udgaonkar, J. B.** (2012). A buried ionizable residue destabilizes the native state and the transition state in the folding of monellin. ***Biochemistry,*** 51, 9058–66.
- Dasgupta, A., and **Udgaonkar, J. B.** (2012). Transient non-native burial of a Trp residue occurs initially during the unfolding of a SH3 domain. ***Biochemistry,*** 51, 8226–34.
- Jha, A., Narayan, S., **Udgaonkar, J. B.**, and Krishnamoorthy, G. (2012). Solvent-induced tuning of internal structure in a protein amyloid protofibril. ***Biophysical Journal*** , 103, 797–806.
- Singh, J., Sabareesan, A. T., **Mathew, M. K.,** and **Udgaonkar, J. B.** (2012). Development of the structural core and of conformational heterogeneity during the conversion of oligomers of the mouse prion protein to worm-like amyloid fibrils. ***Journal of Molecular Biology,*** 423, 217–31.
- Aghera, N., and **Udgaonkar, J. B.** (2012). Kinetic studies of the folding of heterodimeric monellin: evidence for switching between alternative parallel pathways. ***Journal of Molecular Biology***, 420, 235–50.
- Dasgupta, A., and **Udgaonkar, J. B.** (2012). Four-state folding of a SH3 domain: salt-induced modulation of the stabilities of the intermediates and native state. ***Biochemistry,*** 51, 4723–34.
- Jha, S. K., Deepalakshmi, P. D., and **Udgaonkar, J. B.** (2012). Characterization of deamidation of barstar using electrospray ionization quadrupole time-of-flight mass spectrometry, which stabilizes an equilibrium unfolding intermediate. ***Protein Science,*** 21, 633–46.
- Ramachandran, G., and **Udgaonkar, J. B.** (2012). Evidence for the existence of a secondary pathway for fibril growth during the aggregation of tau. ***Journal of Molecular Biology,*** 421, 296–314.
- Wani, A. H., and **Udgaonkar, J. B.** Mass spectrometry studies of protein folding. ***Current Science,*** 102, 1–21.

MK MATHEW

- †Anil, V. S., Kavitha, P. G., Kuruvilla, S., Kumar, P., and **Mathew, M. K.** (2013). Measurements of cytosolic ion concentrations in live cells. ***Methods in Molecular Biology,*** *953*, 233–41.F Maathuis ed, published by Humana Press, USA.
- Kavitha, P. G., Miller, A. J., **Mathew, M. K.,** and Maathuis, F. J. M. (2012). Rice cultivars with differing salt tolerance contain similar cation channels in their root cells. ***Journal of Experimental Botany,*** 63, 3289–96.
- Kumar, S., Dubey, A. K., Karmakar, R., Kini, K. R., **Mathew, M. K.,** and Prakash, H. S. (2012). Inhibition of TMV multiplication by siRNA constructs against TOM1 and TOM3 genes of *Capsicum annuum.* ***Journal of Virological Methods,*** 186, 78–85.
- Singh, J., Sabareesan, A.T., **Mathew, M.K.** and **Udgaonkar, J.B.** (2012) Development of the structural core and of conformational heterogeneity during the conversion of oligomers of the mouse prion protein to worm-like amyloid fibrils. ***Journal of Molecular Biology,*** 423, 217-231.

R SOWDHAMINI

- Nagarathnam, B., Kalaimathy, S., Balakrishnan, V., and **Sowdhamini, R.** (2012). Cross-Genome Clustering of Human and *C. elegans* G-Protein Coupled Receptors. ***Evolutionary Bioinformatics Online,*** 8, 229–59.
- Shingate, P., and **Sowdhamini, R.** (2012). Analysis of domain-swapped oligomers reveals local sequence preferences and structural imprints at the linker regions and swapped interfaces. ***PloS One,*** 7, e39305.
- Gandhimathi, A., Nair, A. G., and **Sowdhamini, R.** (2012). PASS2 version 4: an update to the database of structure-based sequence alignments of structural domain superfamilies. ***Nucleic Acids Research,*** 40, D531–4.
- Harbi, D., Parthiban, M., Gendoo, D. M. A., Ehsani, S., Kumar, M., Schmitt-Ulms, G., **Sowdhamini, R.**, and Harrison, P. M. (2012). PrionHome: a database of prions and other sequences relevant to prion phenomena. ***PloS One,*** *7*, e31785.
- Syamaladevi, D. P., Sunitha, M. S., Kalaimathy, S., Reddy, C. C., Iftekhar, M., Pasha, S. N., and **Sowdhamini, R.** (2012). Myosinome: a database of myosins from select eukaryotic genomes to facilitate analysis of sequence-structure-function relationships. ***Bioinformatics and Biology Insights,*** 6, 247–54.
- Shameer, K., and **Sowdhamini, R.** (2012). Functional repertoire, molecular pathways and diseases associated with 3D domain swapping in the human proteome. ***Journal of Clinical Bioinformatics,*** 2, 8.
- Malhotra, S., and **Sowdhamini, R.** (2012). Re-visiting protein-centric two-tier classification of existing DNA-protein complexes. ***BMC Bioinformatics,*** 13, 165.
- Gandhimathi, A., Nair, A.G. and **Sowdhamini, R.** (2012). Comparison of structure based sequence alignment programs for protein domain superfamilies with multiple members. ***Advances in Computing***, 2, 23-28.

YAMUNA KRISHNAN

- Saha, S., Chakraborty, K., and **Krishnan, Y.** (2012). Tunable, colorimetric DNA-based pH sensors mediated by A-motif formation. ***Chemical Communications,***48, 2513–5.
- Bhatia, D., Chakraborty, S., and **Krishnan, Y.** (2012). Gene delivery: Designer DNA give RNAi more spine. ***Nature Nanotechnology,*** 7, 344–6.
- †Saha, S., and **Krishnan, Y.** (2012). pH sensitive DNA devices. In Fox, K.R., Brown, T (ed), ***DNA Conjugates and Sensors.,*** pp pp166–183. Royal Society of Chemistry publishing, Cambridge.
- Chakraborty, S., Mehtab, S., Patwardhan, A., and **Krishnan, Y.** (2012). Pri-miR-17-92a transcript folds into a tertiary structure and autoregulates its processing. ***RNA,*** 18, 1014–28.
- **Krishnan, Y.,** and Bathe, M. (2012). Designer nucleic acids to probe and program the cell. ***Trends in Cell Biology,*** 22, 624–33.

DEEPAK T NAIR

- Sharma, A., Subramanian, V., and **Nair, D. T.** (2012). The PAD region in the mycobacterial DinB homologue MsPolIV exhibits positional heterogeneity. ***Acta crystallographica. Section D, Biological Crystallography,*** 68, 960–7.
- Sharma, A., and **Nair, D. T.** (2012). MsDpo4-a DinB Homolog from *Mycobacterium smegmatis*-Is an Error-Prone DNA Polymerase That Can Promote G:T and T:G Mismatches. ***Journal of Nucleic Acids,*** 2012, 285481.

ASWIN SAI NARAIN SESHASAYEE

- **Seshasayee, A. S. N.,** Singh, P., and Krishna, S. (2012). Context-dependent conservation of DNA methyltransferases in bacteria. ***Nucleic Acids Research,*** 40, 7066–73.
- Kahramanoglou, C., Prieto, A. I., Khedkar, S., Haase, B., Gupta, A., Benes, V., Fraser, G. M., Luscombe, N. M., and **Seshasayee, A. S. N.** (2012). Genomics of DNA cytosine methylation in *Escherichia coli* reveals its role in stationary phase transcription. ***Nature Communications,*** 3, 886.
- Prabhakara, S., Khedkar, S., Loganathan, R. M., Chandana, S., Gowda, M., Arakere, G., and **Seshasayee, A. S. N.** (2012). Draft genome sequence of *Staphylococcus aureus* 118 (ST772), a major disease clone from India. ***Journal of Bacteriology,*** 194, 3727–8.
- Prieto, A. I., Kahramanoglou, C., Ali, R. M., Fraser, G. M., **Seshasayee, A. S. N.,** and Luscombe, N. M. (2012). Genomic analysis of DNA binding and gene regulation by homologous nucleoid-associated proteins IHF and HU in *Escherichia coli K12*. ***Nucleic Acids Research,*** 40, 3524–37.
- Martincorena, I., **Seshasayee, A. S. N.**, and Luscombe, N. M. (2012). Evidence of non-random mutation rates suggests an evolutionary risk management strategy. ***Nature***, 485, 95–8.
- Khedkar, S., Prabhakara, S., Loganathan, R.M., S Chandana, S., Gowda. M., Arakere G., **Seshasayee, A.S.(**2012). Draft genome sequence of *Staphylococcus aureus* ST672, an emerging disease clone from India***. Journal of Bacteriology,*** 194, 6946-47.

PV SHIVAPRASAD

- **Shivaprasad, P. V**, Dunn, R. M., Santos, B. A., Bassett, A., and Baulcombe, D. C. (2012). Extraordinary transgressive phenotypes of hybrid tomato are influenced by epigenetics and small silencing RNAs. ***The EMBO Journal,*** 31, 257–66.
- **Shivaprasad, P. V**, Chen, H.-M., Patel, K., Bond, D. M., Santos, B. A. C. M., and Baulcombe, D. C. (2012). A microRNA superfamily regulates nucleotide binding site-leucine-rich repeats and other mRNAs. ***The Plant Cell,*** 24, 859–74.

CELLULAR ORGANIZATION AND SIGNALING

SUDHIR KRISHNA

- Adurthi, S., Mukherjee, G., Krishnamurthy, H., **Krishna, S.**, Bafna, U. D., Umadevi, K., and Jayshree, R. S. (2012). Functional tumor infiltrating TH1 and TH2 effectors in large early-stage cervical cancer are suppressed by regulatory T cells. ***International Journal of Gynecological Cancer***, 22, 1130–7.

APURVA SARIN

- Gupta, S., Marcel, N., Talwar, S., Garg, M., Indulaxmi, R, , Perumalsamy, L. R., **Sarin, A.**, and Shivashankar, G. V. (2012). Developmental heterogeneity in DNA packaging patterns influences T-cell activation and transmigration. ***PloS One***, 7, e43718.
- Gupta, S.*, Marcel, N.*, **Sarin, A.**, and Shivashankar, G. V. (2012). Role of actin dependent nuclear deformation in regulating early gene expression. ***PloS One***, 7, e53031.
- Perumalsamy, L. R., Marcel, N., Kulkarni, S., Radtke, F., and **Sarin, A**. (2012). Distinct spatial and molecular features of notch pathway assembly in regulatory T cells. ***Science Signaling***, 5, ra53.

SATYAJIT MAYOR

- Ghosh, S., Saha, S., Goswami, D., Bilgrami, S., and **Mayor, S**. (2012). Dynamic imaging of homo-FRET in live cells by fluorescence anisotropy microscopy. ***Methods in Enzymology***, 505, 291–327.
- Brodsky, F. M., Thattai, M., and **Mayor, S**. (2012). Evolutionary cell biology: Lessons from diversity. ***Nature Cell Biology***, 14, 651.

- Gowrishankar, K., Ghosh, S., Saha, S., C, R., **Mayor, S.**, and Rao, M. (2012). Active remodeling of cortical actin regulates spatiotemporal organization of cell surface molecules. ***Cell***, 149, 1353–67.

RAGHU PADINJAT

- Badsha, F., Kain, P., Prabhakar, S., Sundaram, S., **Raghu, P.**, Rodrigues, V., and Hasan, G. (2012). Mutants in *Drosophila* TRPC channels reduce olfactory sensitivity to carbon dioxide. ***PloS One***, 7, e49848.
- Garner, K., Hunt, A. N., Koster, G., Somerharju, P., Groves, E., Li, M., **Raghu, P.**, Holic, R., and Cockcroft, S. (2012). Phosphatidylinositol transfer protein, cytoplasmic 1 (PITPNC1) binds and transfers phosphatidic acid. ***The Journal of Biological Chemistry***, 287, 32263–76.
- Georgiev, P., Toscano, S., Nair, A., Hardie, R., and **Raghu, P**. (2012). Identification of a suppressor of retinal degeneration in *Drosophila* photoreceptors. ***Journal of Neurogenetics***, 26, 338–47.
- **Raghu, P.**, Yadav, S., and Mallampati, N. B. N. (2012). Lipid signaling in *Drosophila* photoreceptors. ***Biochimica et Biophysica Acta***, 1821, 1154–65.

KS KRISHNAN

- Gupta, K., Kumar, M., Chandrashekara, K., **Krishnan, K. S.**, and Balaram, P. (2012). Combined electron transfer dissociation-collision-induced dissociation fragmentation in the mass spectrometric distinction of leucine, isoleucine, and hydroxyproline residues in Peptide natural products. ***Journal of Proteome Research***, 11, 515–22.
- ‡ **Krishnan, K. S.** (2012) The Illustrated Book of South Indian Snakes by B. Vijayaraghavan and S. R. Ganesh, ***Current Science***, 102, 923.
- **Krishnan, K. S.**, Ramaswami, M., and Wu, C.-F. (2012). Obaid Siddiqi at 80 and neurogenetics in India. ***Journal of Neurogenetics***, 26, 255–6.
- Sanyal, S., and **Krishnan, K. S**. (2012). Genetic modifiers of comatose mutations in Drosophila: insights into neuronal NSF (N-ethylmaleimide-sensitive fusion factor) functions. ***Journal of Neurogenetics***, 26, 348–59.

ECOLOGY AND EVOLUTION

UMA RAMAKRISHNAN

- Chattopadhyay, B., Garg, K. M., **Ramakrishnan, U.**, and Kandula, S. (2012). Sibling species in South Indian populations of the rufous horse-shoe bat Rhinolophus rouxii. ***Conservation Genetics***, 13, 1435–45.
- Garg, K. M., Chattopadhyay, B., Doss D, P. S., A K, V. K., Kandula, S., and **Ramakrishnan, U**. (2012). Promiscuous mating in the harem-roosting fruit bat, *Cynopterus sphinx*. ***Molecular Ecology***, 21, 4093–105.
- Mukherjee, S., Adhya, T., Thatte, P., and **Ramakrishnan, U**. (2012). Survey of the Fishing Cat *Prionailurus viverrinus* Bennett, 1833 (Carnivora: Felidae) and some aspects impacting its conservation in India. ***Journal of Threatened Taxa***, 4, 3355-61.

MAHESH SANKARAN

- Velho, N., Ratnam, J., Srinivasan, U., and **Sankaran, M**. (2012). Shifts in community structure of tropical trees and avian frugivores in forests recovering from past logging. ***Biological Conservation***, 153, 32–40.

KRUSHNAMEGH KUNTE

- **Kunte, K.**, Sondhi, S., Sangma, B. M., Lovalekar, R., Tokekar, K., and Agavekar, G. (2012). Butterflies of the Garo Hills of Meghalaya, northeastern India: their diversity and conservation. ***Journal of Threatened Taxa***, 4, 2933–92.

DEEPA AGASHE

- Falk, J.J., Parent, C.E., **Agashe, D.** And Bolnick, D.I. (2012). Drift and selection entwined: Asymmetric reproductive isolation in an experimental niche shift. ***Evolutionary Ecology Research*** 14, 403-23.
- **Agashe, D**., and Bolnick, D. I. (2012). Dietary niche and population dynamic feedbacks in a novel habitat. ***Oikos***, 121, 347–56.

GENETICS AND DEVELOPMENT

K VIJAYRAGHAVAN

- Roy, S., and **VijayRaghavan, K**. (2012). Developmental biology: taking flight. ***Current Biology***, 22, R63–5.
- Sudhakaran, I. P., Holohan, E. E., Osman, S., Rodrigues, V., **VijayRaghavan, K.**, and Ramaswami, M. (2012). Plasticity of recurrent inhibition in the *Drosophila* antennal lobe. ***The Journal of Neuroscience***, 32, 7225–31.
- Paranjpe, P., Rodrigues, V., **VijayRaghavan, K.**, and Ramaswami, M. (2012). Gustatory habituation in *Drosophila* relies on rutabaga (adenylate cyclase)-dependent plasticity of GABAergic inhibitory neurons. ***Learning & Memory (Cold Spring Harbor, N.Y.)***, 19, 627–35.
- Jain, M., Bhat, G. P., **VijayRaghavan, K.**, and Inamdar, M. S. (2012). Rudhira/BCAS3 is a cytoskeletal protein that controls Cdc42 activation and directional cell migration during angiogenesis. ***Experimental Cell Research***, 318, 753–67.
- **VijayRaghavan, K**. (2012). Obaid Siddiqi: celebrating his life in science and the cultural transmission of its values. ***Journal of Neurogenetics***, 26, 257–59.

PV SHIVAPRASAD

- **Shivaprasad, P. V**, Dunn, R. M., Santos, B. A., Bassett, A., and Baulcombe, D. C. (2012). Extraordinary transgressive phenotypes of hybrid tomato are influenced by epigenetics and small silencing RNAs. ***The EMBO Journal***, 31, 257–66.
- **Shivaprasad, P. V**, Chen, H.-M., Patel, K., Bond, D. M., Santos, B. A., and Baulcombe, D. C. (2012). A microRNA superfamily regulates nucleotide binding site-leucine-rich repeats and other mRNAs. ***The Plant Cell***, 24, 859–74.

NEUROBIOLOGY

UPINDER S BHALLA

- Parameshwaran, D., and **Bhalla, U. S.** (2012). Summation in the Hippocampal CA3-CA1 Network Remains Robustly Linear Following Inhibitory Modulation and Plasticity, but Undergoes Scaling and Offset Transformations. ***Frontiers in Computational Neuroscience,*** 6, 71.
- Khan, A. G., Sarangi, M., and **Bhalla, U. S.** (2012). Rats track odour trails accurately using a multi-layered strategy with near-optimal sampling. ***Nature Communications,*** 3, 703.

SUMANTRA CHATTARJI

- Malik, R., and **Chattarji, S.** (2012). Enhanced intrinsic excitability and EPSP-spike coupling accompany enriched environment-induced facilitation of LTP in hippocampal CA1 pyramidal neurons. ***Journal of Neurophysiology,*** 107, 1366–78.
- Lakshminarasimhan, H., and **Chattarji, S.** (2012). Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the hippocampus and amygdala. ***PloS One,*** 7, e30481.
- Rao, R. P., Anilkumar, S., McEwen, B. S., and **Chattarji, S.** (2012). Glucocorticoids protect against the delayed behavioral and cellular effects of acute stress on the amygdala. ***Biological Psychiatry,*** 72, 466–75.

- Pillai, A. G., Anilkumar, S., and **Chattarji, S.** (2012). The same antidepressant elicits contrasting patterns of synaptic changes in the amygdala vs hippocampus. ***Neuropsychopharmacology,*** 37, 2702–11.

SANJAY P SANE

- Krishnan, A., Prabhakar, S., Sudarsan, S., and **Sane, S. P.** (2012). The neural mechanisms of antennal positioning in flying moths. ***The Journal of Experimental biology***, 215, 3096–105.

GAITI HASAN

- Agrawal, N., and **Hasan, G.** (2012). *Drosophila* InsP3R mutants and their effects on cellular and systemic physiology. ***Wiley Interdisciplinary Reviews: Membrane Transport and Signaling,*** 1, 70–77. Invited review.
- Chorna, T., and **Hasan, G.** (2012). The genetics of calcium signaling in *Drosophila melanogaster*. ***Biochimica et Biophysica Acta,*** 1820, 1269–82.
- Chakraborty, S., and **Hasan, G.** (2012). IP3R, store-operated Ca2+ entry and neuronal Ca2+ homoeostasis in *Drosophila*. ***Biochemical Society Transactions,*** 40, 279–81.
- **Hasan, G.** (2012). The early years of *Drosophila* chemosensory genetics in Mumbai's Tata Institute of Fundamental Research. ***Journal of Neurogenetics,*** 26, 264–6.
- Chakraborty, S., and **Hasan, G**. (2012). Functional complementation of *Drosophila* itpr mutants by rat Itpr1. ***Journal of Neurogenetics,*** 26, 328–37.
- Badsha, F., Kain, P., Prabhakar, S., Sundaram, S., Padinjat, R., Rodrigues, V., and **Hasan, G.** (2012). Mutants in *Drosophila* TRPC channels reduce olfactory sensitivity to carbon dioxide. ***PloS One,*** 7, e49848.
- Sadaf, S., Birman, S., and **Hasan, G.** (2012). Synaptic activity in serotonergic neurons is required for air-puff stimulated flight in *Drosophila melanogaster*. ***PloS One,*** 7, e46405.

VATSALA THIRUMALAI

- **Thirumalai, V.** (2012). Assembling Neural Circuits for Generating Movement. ***Journal of the Indian Institute of Science,*** 92, 411-426.

AXEL BROCKMANN

- ‡Barron A.B., **Brockmann A.**, Sen Sarma M. and Robinson G.E. (2012). Molecular dissection of honey bee dance behaviour. ***Honeybee Neurobiology and Behaviour – a Tribute for Randolf Menzel.*** Eds.: D. Eisenhardt, C.G. Galizia, and M. Giurfa, Springer Verlag, Berlin Heidelberg New York.

THEORY, SIMULATION AND MODELING OF BIOLOGICAL SYSTEMS

MUKUND THATTAI

- Rai, N., Anand, R., Ramkumar, K., Sreenivasan, V., Dabholkar, S., Venkatesh, K. V, and **Thattai, M**. (2012). Prediction by promoter logic in bacterial quorum sensing. ***PLoS Computational Biology***, 8, e1002361.
- Brodsky, F. M., **Thattai, M**., and Mayor, S. (2012). Evolutionary cell biology: Lessons from diversity. ***Nature Cell Biology***, 14, 651.

SHACHI GOSAVI

- Capraro, D. T., Roy, M., Onuchic, J. N., **Gosavi, S**., and Jennings, P. A. (2012). β-Bulge triggers route-switching on the functional landscape of interleukin-1β. ***Proceedings of the National Academy of Sciences of the United States of America***, 109, 1490–3.
- Capraro, D. T., **Gosavi, S**., Roy, M., Onuchic, J. N., and Jennings, P. A. (2012). Folding circular permutants of IL-1β: route selection driven by functional frustration. ***PloS one***, 7, e38512.

R SOWDHAMINI

- Sunitha, M. S., Nair, A. G., Charya, A., Jadhav, K., Mukhopadhyay, S., and **Sowdhamini, R**. (2012). Structural attributes for the recognition of weak and anomalous regions in coiled-coils of myosins and other motor proteins. ***BMC Research Notes***, 5, 530.
- Harini, K., Kannan, S., Nemoto, W., Fukui, K., and **Sowdhamini, R**. (2012). Residue conservation and dimer-interface analysis of olfactory receptor molecular models. ***Journal of Molecular Biochemistry***, 1, 161-170.
- Sunitha, M. S., Mercer, J. A., Spudich, J. A., and **Sowdhamini, R**. (2012). Integrative structural modelling of the cardiac thin filament: energetics at the interface and conservation patterns reveal a spotlight on period 2 of tropomyosin. ***Bioinformatics and Biology Insights***, 6, 203–23.
- Sandhya, S., Mudgal, R., Jayadev, C., Abhinandan, K. R., **Sowdhamini, R**., and Srinivasan, N. (2012). Cascaded walks in protein sequence space: use of artificial sequences in remote homology detection between natural proteins. ***Molecular BioSystems***, 8, 2076–84.
- Malhotra, S., and **Sowdhamini, R**. (2012). Re-visiting protein-centric two-tier classification of existing DNA-protein complexes. ***BMC Bioinformatics***, 13, 165.
- Gromiha, M. M., Harini, K., **Sowdhamini, R**., and Fukui, K. (2012). Relationship between amino acid properties and functional parameters in olfactory receptors and discrimination of mutants with enhanced specificity. ***BMC Bioinformatics***, 13 Suppl 7, S1.
- Harini, K., and **Sowdhamini, R**. (2012). Molecular Modelling of Oligomeric States of DmOR83b, an Olfactory Receptor in *D. Melanogaster*. ***Bioinformatics and Biology Insights***, 6, 33–47.
- Sunitha, M. S., Nair, A. G., Charya, A., Jadhav, K., Mukhopadhyay, S., and **Sowdhamini, R.** (2012). Structural attributes for the recognition of weak and anomalous regions in coiled-coils of myosins and other motor proteins. ***BMC Research Notes***, 5, 530.

UPINDER S BHALLA

- †**Bhalla, U.S.** (2012). Still looking for the memories: Molecules and synaptic plasticity. In: ***20 Years of Computational Neuroscience***, Ed. Bower, JM. Springer, ISBN 978-1-4614-1423-0.
- †**Bhalla, U.S.** (2012). Multi-compartmental models of neurons. In: ***Computational Systems Neurobiology***, Ed. Le Novère. Springer, ISBN: 978-94-007-3857-7.

SANDEEP KRISHNA

- Li, W., **Krishna, S**., Pigolotti, S., Mitarai, N., and Jensen, M. H. (2012). Switching between oscillations and homeostasis in competing negative and positive feedback motifs. ***Journal of Theoretical Biology***, 307, 205–10.
- Jensen, M. H., and **Krishna, S**. (2012). Inducing phase-locking and chaos in cellular oscillators by modulating the driving stimuli. ***FEBS letters***, 586, 1664–68.
- Chakraborty, S., Jensen, M. H., **Krishna, S**., Mengel Pers, B., Pigolotti, S., Sekara, V., and Semsey, S. (2012). Limit-cycle oscillations and stable patterns in repressor lattices. ***Physical Review. E, Statistical, nonlinear, and Soft Matter Physics***, 86, 031905.
- Seshasayee, A. S. N., Singh, P., and **Krishna, S**. (2012). Context-dependent conservation of DNA methyltransferases in bacteria. ***Nucleic Acids Research***, 40, 7066–73.
- Mengel Pers, B., **Krishna, S**., Chakraborty, S., Pigolotti, S., Sekara, V., Semsey, S., and Jensen, M. H. (2012). Effects of growth and mutation on pattern formation in tissues. ***PloS One***, 7, e48772.
- Heilmann, S., Sneppen, K., and **Krishna, S**. (2012). Coexistence of phage and bacteria on the boundary of self-organized refuges. ***Proceedings of the National Academy of Sciences of the United States of America***, 109, 12828–33.

(† Denotes Book Chapter, ‡ Denotes Book)

PUBLICATIONS 2013

BIOCHEMISTRY, BIOPHYSICS AND BIOINFORMATICS

JAYANT B UDGOANKAR

- **Udgaonkar, J.,** and Marqusee, S. (2013). Folding and binding. ***Current Opinion in Structural Biology,*** 23, 1–3.
- **Udgaonkar, J. B.** (2013). Polypeptide chain collapse and protein folding. ***Archives of Biochemistry and Biophysics,*** 531, 24–33
- Ramachandran, G., and **Udgaonkar, J. B.** (2013). Mechanistic studies unravel the complexity inherent in tau aggregation leading to Alzheimer's disease and the tauopathies. ***Biochemistry,*** 52, 4107–26.
- Kishore, M., Krishnamoorthy, G., and **Udgaonkar, J. B.** (2013). Critical evaluation of the two-state model describing the equilibrium unfolding of the PI3K SH3 domain by time-resolved fluorescence resonance energy transfer. ***Biochemistry,*** 52, 9482–96.
- Sarkar, S. S., **Udgaonkar, J. B.**, and Krishnamoorthy, G. (2013). Unfolding of a small protein proceeds via dry and wet globules and a solvated transition state. ***Biophysical Journal,*** 105, 2392–402.
- Aghera, N., and **Udgaonkar, J. B.** (2013). The utilization of competing unfolding pathways of monellin is dictated by enthalpic barriers. ***Biochemistry,*** 52, 5770–9.
- Singh, J., and **Udgaonkar, J. B.** (2013). Dissection of conformational conversion events during prion amyloid fibril formation using hydrogen exchange and mass spectrometry. ***Journal of Molecular Biology,*** 425, 3510–21.
- Ramachandran, G., and **Udgaonkar, J. B.** (2013). Difference in fibril core stability between two tau four-repeat domain proteins: a hydrogen-deuterium exchange coupled to mass spectrometry study. ***Biochemistry,*** 52, 8787–9.

MK MATHEW

- Godbole, A., Dubey, A. K., Reddy, P. S., Udayakumar, M., and **Mathew, M. K.** (2013). Mitochondrial VDAC and hexokinase together modulate plant programmed cell death. ***Protoplasma,*** 250, 875–84.
- Kumar, S., Dubey, A.K., Karmakar, R., Kini, R.K., **Mathew, M.K** and Prakash, H.S. (2013). Inhibition of virus infection by transient expression of short hairpin RNA targeting methyltransferase domain of Tobacco mosaic virus replicase. ***Phytoparasitica,*** 41, 9–15.

R SOWDHAMINI

- Naika, M., Shameer, K., Mathew, O. K., Gowda, R., and **Sowdhamini, R.** (2013). STIFDB2: an updated version of plant stress-responsive transcription factor database with additional stress signals, stress-responsive transcription factor binding sites and stress-responsive genes in *Arabidopsis* and rice. ***Plant & Cell Physiology,*** 54, e8.
- †Naika, M., Shameer, K., Gowda, R., and **Ramanathan, S.** (2013). Analysis of protein-protein interaction network mediated by Absicisic acid induced stress-response in *Arabidopsis thaliana,* in ***Molecular Approaches for Abiotic Stress*** (Sharma, R. K. G. and P., Ed.). Centre for Agricultural Bioscience International Press, U.K
- Manoharan, M., Sankar, K., Offmann, B., and **Ramanathan, S.** (2013). Association of putative members to family of mosquito odorant binding proteins: scoring scheme using fuzzy functional templates and cys residue positions. ***Bioinformatics and Biology Insights,*** 7, 231–51.
- Sukhwal, A., and **Sowdhamini, R.** (2013). Oligomerisation status and evolutionary conservation of interfaces of protein structural domain superfamilies. ***Molecular bioSystems,*** 9, 1652–61.
- Naika, M., Shameer, K., and **Sowdhamini, R.** (2013). Comparative analyses of stress-responsive genes in *Arabidopsis thaliana:* insight from genomic data mining, functional enrichment, pathway analysis and phenomics. ***Molecular bioSystems,*** 9, 1888–908.
- Malhotra, S., and **Sowdhamini, R.** (2013). Genome-wide survey of DNA-binding proteins in *Arabidopsis thaliana:* analysis of distribution and functions. ***Nucleic Acids Research,*** 41, 7212–9.
- Mutt, E., Rani, S. S., and **Sowdhamini, R.** (2013). Structural updates of alignment of protein domains and consequences on evolutionary models of domain superfamilies. ***BioData Mining,*** 6, 20.
- Kaushik, S., Mutt, E., Chellappan, A., Sankaran, S., Srinivasan, N., and **Sowdhamini, R.** (2013). Improved detection of remote homologues using cascade PSI-BLAST: influence of neighbouring protein families on sequence coverage. ***PloS One,*** 8, e56449.

YAMUNA KRISHNAN

- Ganesh, K., and **Krishnan, Y.** (2013). Nucleic acids--chemistry and applications. ***The Journal of Organic Chemistry,*** 78, 12283–7.
- Modi, S., Nizak, C., Surana, S., Halder, S., and **Krishnan, Y.** (2013). Two DNA nanomachines map pH changes along intersecting endocytic pathways inside the same cell. ***Nature Nanotechnology,*** 8, 459–67.
- Surana, S., Bhatia, D., and **Krishnan, Y.** (2013). A method to study in vivo stability of DNA nanostructures. ***Methods,***64, 94–100.
- Banerjee, A., Bhatia, D., Saminathan, A., Chakraborty, S., Kar, S., and **Krishnan, Y.** (2013). Controlled release of encapsulated cargo from a DNA icosahedron using a chemical trigger. ***Angewandte Chemie (International ed. in English) 52***, 6854–7.
- Surana, S., and **Krishnan, Y.** (2013). A method to map spatiotemporal pH changes in a multicellular living organism using a DNA nanosensor. ***Methods in Molecular Biology,*** 991, 9–23.
- Bhatia, D., Chakraborty, S., Mehtab, S., and **Krishnan, Y.** (2013). A method to encapsulate molecular cargo within DNA icosahedra. ***Methods in Molecular Biology,*** 991, 65–80.
- †Bhatia, D., and **Krishnan, Y.** (2013). Designer Nucleic Acid-Based Devices in Nanomedicine, in ***DNA and RNA Nanobiotechnologies in Medicine: Diagnosis and Treatment of Diseases*** (Erdmann, V. A., and Barciszewski, J., Eds.). Springer Berlin Heidelberg, Berlin, Heidelberg.

DEEPAK T NAIR

- Sharma, A., Kottur, J., Narayanan, N., and **Nair, D. T.** (2013). A strategically located serine residue is critical for the mutator activity of DNA polymerase IV from Escherichia coli. ***Nucleic Acids Research,*** 41, 5104–14
- Jain, D., and **Nair, D. T.** (2013). Spacing between core recognition motifs determines relative orientation of AraR monomers on bipartite operators. ***Nucleic Acids Research,*** 41, 639–47.

ASWIN SAI NARAIN SESHASAYEE

- Prabhakara, S., Khedkar, S., Shambat, S. M., Srinivasan, R., Basu, A., Norrby-Teglund, A., **Seshasayee, A. S. N.,** and Arakere, G. (2013). Genome sequencing unveils a novel sea enterotoxin-carrying PVL phage in *Staphylococcus aureus* ST772 from India. ***PloS One,*** 8, e60013.
- Srinivasan, R., Chandraprakash, D., Krishnamurthi, R., Singh, P., Scolari, V. F., Krishna, S., and **Seshasayee, A. S. N.** (2013). Genomic analysis reveals epistatic silencing of "expensive" genes in *Escherichia coli* K-12. ***Molecular bioSystems,*** 9, 2021–33.
- Kingsley, R. A., Kay, S., Connor, T., Barquist, L., Sait, L., Holt, K. E., Sivaraman, K., Wileman, T., Goulding, D., Clare, S., Hale, C., **Seshasayee, A.** , Harris, S., Thomson, N. R., Gardner, P., Rabsch, W., Wigley, P., Humphrey, T., Parkhill, J., and Dougan, G. (2013). Genome and transcriptome adaptation accompanying emergence of the definitive type 2 host-restricted *Salmonella enterica* serovar Typhimurium pathovar. ***mBio 4***, e00565–13.
- Sasidharan, V., Lu, Y.-C., Bansal, D., Dasari, P., Poduval, D., **Seshasayee, A.** , Resch, A. M., Graveley, B. R., and Palakodeti, D. (2013). Identification of neoblast- and regeneration-specific miRNAs in the planarian *Schmidtea mediterranea.* ***RNA,*** 19, 1394–404.

CELLULAR ORGANIZATION AND SIGNALING

SUDHIR KRISHNA

- Kumar, M. M., Adurthi, S., Ramachandran, S., Mukherjee, G., Joy, O., Krishnamurthy, H., **Krishna, S.**, Bafna, U. D., Uma, D. K., and Jayshree, R. S. (2013). Toll-like receptors 7, 8, and 9 expression and function in primary human cervical cancer Langerhans cells: evidence of anergy. ***International Journal of Gynecological Cancer***, 23, 184–92.

APURVA SARIN

- Purushothaman, D., Marcel, N., Garg, M., Venkataraman, R., and **Sarin, A.** (2013). Apoptotic programs are determined during lineage commitment of CD4+ T effectors: selective regulation of T effector-memory apoptosis by inducible nitric oxide synthase. ***Journal of Immunology*** , 190, 97–105.

SATYAJIT MAYOR

- Saha, R., Verma, P. K., Rakshit, S., Saha, S., **Mayor, S.**, and Pal, S. K. (2013). Light driven ultrafast electron transfer in oxidative redding of Green Fluorescent Proteins. ***Scientific Reports***, 3, 1580.
- Pols, M. S., van Meel, E., Oorschot, V., ten Brink, C., Fukuda, M., Swetha, M. G., **Mayor, S.**, and Klumperman, J. (2013). hVps41 and VAMP7 function in direct TGN to late endosome transport of lysosomal membrane proteins. ***Nature Communications***, 4, 1361.
- **Mayor, S**. (2013). Biological research in India. An interview with Dr Satyajit Mayor, Dean at the National Centre for Biological Sciences in Bangalore, India. Interview by Barbara Pauly. ***EMBO Reports***, 14, 239–41.

RAGHU PADINJAT

- Chu, B., Liu, C.-H., Sengupta, S., Gupta, A., **Raghu, P.**, and Hardie, R. C. (2013). Common mechanisms regulating dark noise and quantum bump amplification in *Drosophila* photoreceptors. ***Journal of Neurophysiology***, 109, 2044–55.
- Gupta, A., Toscano, S., Trivedi, D., Jones, D. R., Mathre, S., Clarke, J. H., Divecha, N., and **Raghu, P.** (2013). Phosphatidylinositol 5-phosphate 4-kinase (PIP4K) regulates TOR signaling and cell growth during *Drosophila* development. ***Proceedings of the National Academy of Sciences of the United States of America***, 110, 5963–8.

KS KRISHNAN

- Vishnu, R., Kumar, V.A, Varikoden, H., **Krishnan, K. S.**, Sreekanth,T. S., Subi Symon, V. N., Murali Das, S., Mohan Kumar, G. (2013). Convective thundercloud development over the Western Ghats mountain slope in Kerala. ***Current Science,*** 104, 1506-1514.
- Ramaswami, M., **Krishnan, K.S.** (2013). Obaid Siddiqi (1932-2013), ***Current Science,*** 105, 531-533.

ECOLOGY AND EVOLUTION

UMA RAMAKRISHNAN

- Mondol, S., Bruford, M. W., and **Ramakrishnan, U**. (2013). Demographic loss, genetic structure and the conservation implications for Indian tigers. ***Proceedings. Biological sciences / The Royal Society***, 280, 20130496.
- Joshi, A., Vaidyanathan, S., Mondol, S., Edgaonkar, A., and **Ramakrishnan, U**. (2013). Connectivity of tiger (Panthera tigris) populations in the human-influenced forest mosaic of Central India. ***PloS One***, 8, e77980.
- Bay, R. A., **Ramakrishnan, U.**, and Hadly, E. A. (2013). A call for tiger management using "reserves" of genetic diversity. ***The Journal of Heredity***, 105, 295–302.

MAHESH SANKARAN

- Seabloom, E. W., Borer, E. T., Buckley, Y., Cleland, E. E., Davies, K., Firn, J., Harpole, W. S., Hautier, Y., Lind, E., MacDougall, A., Orrock, J. L., Prober, S. M., Adler, P., Alberti, J., Anderson, T. M., Bakker, J. D., Biederman, L. A., Blumenthal, D., Brown, C. S., Brudvig, L. A., Caldeira, M., Chu, C., Crawley, M. J., Daleo, P., Damschen, E. I., D'Antonio, C. M., DeCrappeo, N. M., Dickman, C. R., Du, G., Fay, P. A., Frater, P., Gruner, D. S., Hagenah, N., Hector, A., Helm, A., Hillebrand, H., Hofmockel, K. S., Humphries, H. C., Iribarne, O., Jin, V. L., Kay, A., Kirkman, K. P., Klein, J. A., Knops, J. M. H., La Pierre, K. J., Ladwig, L. M., Lambrinos, J. G., Leakey, A. D. B., Li, Q., Li, W., McCulley, R., Melbourne, B., Mitchell, C. E., Moore, J. L., Morgan, J., Mortensen, B., O'Halloran, L. R., Pärtel, M., Pascual, J., Pyke, D. A., Risch, A. C., Salguero-Gómez, R., **Sankaran, M.**, Schuetz, M., Simonsen, A., Smith, M., Stevens, C., Sullivan, L., Wardle, G. M., Wolkovich, E. M., Wragg, P. D., Wright, J., and Yang, L. (2013). Predicting invasion in grassland ecosystems: is exotic dominance the real embarrassment of richness? ***Global Change Biology***, 19, 3677–87.
- Moustakas, A., Kunin, W. E., Cameron, T. C., and **Sankaran, M**. (2013). Facilitation or competition? Tree effects on grass biomass across a precipitation gradient. ***PloS One***, 8, e57025.
- **Sankaran, M.**, Augustine, D. J., and Ratnam, J. (2013). Native ungulates of diverse body sizes collectively regulate long-term woody plant demography and structure of a semi-arid savanna. ***Journal of Ecology***, 101, 1389–99.

SANJAY P SANE

- Cheng, B., **Sane, S. P.**, Barbera, G., Troolin, D. R., Strand, T., and Deng, X. (2013). Three-dimensional flow visualization and vorticity dynamics in revolving wings. ***Experiments in Fluids***, 54, 1423.

KRUSHNAMEGH KUNTE

- Murray Lasley, R., Jain, A., and **Kunte, K**. (2013). Alleviating poverty in India: biodiversity's role. ***Science (New York, N.Y.)***, 341, 840–1.
- Zhang, W., **Kunte, K.**, and Kronforst, M. R. (2013). Genome-wide characterization of adaptation and speciation in tiger swallowtail butterflies using de novo transcriptome assemblies. ***Genome Biology and Evolution***, 5, 1233–45.
- Kumaraswamy, S., and **Kunte, K**. (2013). Integrating biodiversity and conservation with modern agricultural landscapes. ***Biodiversity and Conservation***, 22, 2735–2750.
- ‡Sondhi, S., **Kunte, K.**, Agavekar,G., Lovalekar, R. and Tokekar, K. (2013). ***Butterflies of the Garo Hills.*** Samrakshan Trust (New Delhi), Titli Trust (Dehradun), and Indian Foundation for Butterflies (Bengaluru). xvi + 200pp.

DEEPA AGASHE

- **Agashe, D.**, Martinez-Gomez, N. C., Drummond, D. A., and Marx, C. J. (2013). Good codons, bad transcript: large reductions in gene expression and fitness arising from synonymous mutations in a key enzyme. ***Molecular Biology and Evolution***, 30, 549–60.

AXEL BROCKMANN

- Streinzer, M., **Brockmann, A.**, Nagaraja, N., and Spaethe, J. (2013). Sex and caste-specific variation in compound eye morphology of five honeybee species. ***PloS One***, 8, e57702.

GENETICS AND DEVELOPMENT

K VIJAYRAGHAVAN

- **VijayRaghavan, K.**, and Rath, S. (2013). Evolution, ovulation and cancer. ***eLife***, 2, e00729.
- Singh, A. P., Das, R. N., Rao, G., Aggarwal, A., Diegelmann, S., Evers, J. F., Karandikar, H., Landgraf,M., **Rodrigues, V.**, and **VijayRaghavan, K.** (2013). Sensory neuron-derived eph regulates glomerulararbors and modulatory function of a central serotonergic neuron. ***PLoS Genetics***, 9, e1003452.
- Sen, S., Reichert, H., and **VijayRaghavan, K**. (2013). Conserved roles of ems/Emx and otd/Otx genes in olfactory and visual system development in *Drosophila* and mouse. ***Open Biology***, 3, 120177.
- Nair, I. S., **Rodrigues, V.**, Reichert, H., and **VijayRaghavan, K**. (2013). The zinc finger transcription factor Jing is required for dendrite/axonal targeting in *Drosophila* antennal lobe development. ***Developmental Biology***, 381, 17–27.
- Lee, A. S. J., Harris, J., Bate, M., **VijayRaghavan, K.**, Fisher, L., Tajbakhsh, S., and Duxson, M. (2013). Initiation of primary myogenesis in amniote limb muscles. ***Developmental Dynamics***, 242, 1043–55.
- Blanco Redondo, B., Redondo, B. B., Bunz, M., Halder, P., Sadanandappa, M. K., Mühlbauer, B., Erwin, F., Hofbauer, A., **Rodrigues, V.**, **VijayRaghavan, K.**, Ramaswami, M., Rieger, D., Wegener, C., Förster, C., and Buchner, E. (2013). Identification and structural characterization of interneurons of the *Drosophila* brain by monoclonal antibodies of the würzburg hybridoma library. ***PloS One***, 8, e75420.
- Sadanandappa, M. K., Blanco Redondo, B., Michels, B., **Rodrigues, V.**, Gerber, B., **VijayRaghavan, K.**, Buchner, E., and Ramaswami, M. (2013). Synapsin function in GABA-ergic interneurons is required for short-term olfactory habituation. ***The Journal of Neuroscience***, 33, 16576–85.
- Zirin, J., Cheng, D., Dhanyasi, N., Cho, J., Dura, J.-M., **VijayRaghavan, K.**, and Perrimon, N. (2013). Ecdysone signaling at metamorphosis triggers apoptosis of *Drosophila* abdominal muscles. ***Developmental Biology***, 383, 275–84.

UMA RAMAKRISHNAN

- Bay, R. A., **Ramakrishnan, U.**, and Hadly, E. A. (2013). A call for tiger management using "reserves" of genetic diversity. ***The Journal of Heredity***, 105, 295–302.

NEUROBIOLOGY

MITRADAS M PANICKER

- Cavaliere, F., Benito-Muñoz, M., **Panicker, M.**, and Matute, C. (2013). NMDA modulates oligodendrocyte differentiation of subventricular zone cells through PKC activation. ***Frontiers in Cellular Neuroscience***, 7, 261.
- Raote, I., Bhattacharyya, S., and **Panicker, M. M.** (2013). Functional selectivity in serotonin receptor 2A (5-HT2A) endocytosis, recycling, and phosphorylation. ***Molecular Pharmacology***, 83, 42–50.

UPINDER S BHALLA

- Parthasarathy, K., and **Bhalla, U. S.** (2013). Laterality and symmetry in rat olfactory behavior and in physiology of olfactory input. ***The Journal of Neuroscience***, 33, 5750–60.
- Parameshwaran, D., and **Bhalla, U. S.** (2013). Theta frequency background tunes transmission but not summation of spiking responses. ***PloS One***, 8, e55607.

SUMANTRA CHATTARJI

- Wijetunge, L. S., **Chattarji, S.**, Wyllie, D. J. A., and Kind, P. C. (2013). Fragile X syndrome: from targets to treatments. ***Neuropharmacology***, 68, 83–96.
- Ravinder, S., Burghardt, N. S., Brodsky, R., Bauer, E. P., and **Chattarji, S.** (2013). A role for the extended amygdala in the fear-enhancing effects of acute selective serotonin reuptake inhibitor treatment. ***Translational Psychiatry***, 3, e209.
- Ghosh, S., Laxmi, T. R., and **Chattarji, S.** (2013). Functional connectivity from the amygdala to the hippocampus grows stronger after stress. ***The Journal of Neuroscience***, 33, 7234–44.
- Udagawa, T., Farny, N. G., Jakovcevski, M., Kaphzan, H., Alarcon, J. M., Anilkumar, S., Ivshina, M.,Hurt, J. A., Nagaoka, K., Nalavadi, V. C., Lorenz, L. J., Bassell, G. J., Akbarian, S., **Chattarji, S.**, Klann,E., and Richter, J. D. (2013). Genetic and acute CPEB1 depletion ameliorate fragile X pathophysiology. ***Nature Medicine***, 19, 1473–7.

SANJAY P SANE

- Cheng, B., **Sane, S. P.**, Barbera, G., Troolin, D. R., Strand, T., and Deng, X. (2013). Three-dimensional flow visualization and vorticity dynamics in revolving wings. ***Experiments in Fluids***, 54, 1423.

GAITI HASAN

- Subramanian, M., Metya, S. K., Sadaf, S., Kumar, S., **Schwudke, D.**, and **Hasan, G.** (2013). Altered lipid homeostasis in *Drosophila* InsP3 receptor mutants leads to obesity and hyperphagia. ***Disease Models & Mechanisms***, 6, 734–44.
- Agrawal, T., Sadaf, S., and **Hasan, G.** (2013). A genetic RNAi screen for IP3/Ca2+ coupled GPCRs in *Drosophila* identifies the PdfR as a regulator of insect flight. ***PLoS Genetics***, 9, e1003849.
- **Hasan, G.** (2013). Intracellular signaling in neurons: unraveling specificity, compensatory mechanisms and essential gene function. ***Current Opinion in Neurobiology***, 23, 62–7.
- Subramanian, M., Jayakumar, S., Richhariya, S., and **Hasan, G.** (2013). Loss of IP3 receptor function in neuropeptide secreting neurons leads to obesity in adult *Drosophila*. ***BMC Neuroscience***, 14, 157.

VATSALA THIRUMALAI

- Jabeen, S., and **Thirumalai, V.** (2013). Distribution of the gap junction protein connexin 35 in the central nervous system of developing zebrafish larvae. ***Frontiers in Neural Circuits***, 7, 91.
- **Thirumalai, V.**, Behrend, R. M., Birineni, S., Liu, W., Blivis, D., and O'Donovan, M. J. (2013). Preservation of VGLUT1 synapses on ventral calbindin-immunoreactive interneurons and normal locomotor function in a mouse model of spinal muscular atrophy. ***Journal of Neurophysiology***, 109, 702–10.

MADHUSUDHAN VENKADESAN

- Roach, N. T., **Venkadesan, M.**, Rainbow, M. J., and Lieberman, D. E. (2013). Elastic energy storage in the shoulder and the evolution of high-speed throwing in *Homo*. ***Nature***, 498, 483–6.

THEORY, SIMULATION AND MODELING OF BIOLOGICAL SYSTEMS

MUKUND THATTAI

- **Thattai, M**. (2013). Using topology to tame the complex biochemistry of genetic networks. ***Philosophical Transactions. Series A, Mathematical, Physical, and Engineering Sciences***, 371, 20110548.
- Anand, R., Rai, N., and **Thattai, M**. (2013). Interactions among quorum sensing inhibitors. ***PloS One***, 8, e62254.
- Ramadas, R., and **Thattai, M**. (2013). New organelles by gene duplication in a biophysical model of eukaryote endomembrane evolution. ***Biophysical Journal***, 104, 2553–63.

SHACHI GOSAVI

- **Gosavi, S**. (2013). Understanding the folding-function tradeoff in proteins. ***PloS One***, 8, e61222.

R SOWDHAMINI

- Manoharan, M., Ng Fuk Chong, M., Vaitinadapoulé, A., Frumence, E., **Sowdhamini, R.**, and Offmann, B. (2013). Comparative genomics of odorant binding proteins in *Anopheles gambiae, Aedes aegypti,* and *Culex quinquefasciatus*. ***Genome Biology and Evolution***, 5, 163–80.
- Syamaladevi, D. P., Joshi, A., and **Sowdhamini, R**. (2013). An alignment-free domain architecture similarity search (ADASS) algorithm for inferring homology between multi-domain proteins. ***Bioinformation***, 9, 491–9.

- Kaushik, S., Mutt, E., Chellappan, A., Sankaran, S., Srinivasan, N., and **Sowdhamini, R**. (2013). Improved detection of remote homologues using cascade PSI-BLAST: influence of neighbouring protein families on sequence coverage. ***PloS One***, 8, e56449.
- Joshi, A. G., Raghavender, U. S., and **Sowdhamini, R**. (2013). Improved performance of sequence search algorithms in remote homology detection. ***F1000 Research***, 2, doi: 10.12688/f1000research.2-93.v1.

UPINDER S BHALLA

- Parthasarathy, K., and **Bhalla, U. S.** (2013). Laterality and symmetry in rat olfactory behavior and in physiology of olfactory input. ***The Journal of Neuroscience,*** 33, 5750–60

SANDEEP KRISHNA

- Sipos, L., Mengel Pers, B., Kalmár, M., Tóth, I., **Krishna, S**., Jensen, M. H., and Semsey, S. (2013). Comparative Network Analysis of Preterm vs. Full-Term Infant-Mother Interactions. ***PloS One***, 8, e67183.
- Semsey, S., Jauffred, L., Csiszovszki, Z., Erdossy, J., Stéger, V., Hansen, S., and **Krishna, S**. (2013). The effect of LacI autoregulation on the performance of the lactose utilization system in *Escherichia coli*. ***Nucleic Acids Research***, 41, 6381–90.
- Srinivasan, R., Chandraprakash, D., Krishnamurthi, R., Singh, P., Scolari, V. F., **Krishna, S**., and Seshasayee, A. S. N. (2013). Genomic analysis reveals epistatic silencing of "expensive" genes in *Escherichia coli* K-12. ***Molecular bioSystems***, 9, 2021–33.
- Singh, S., Samal, A., Giri, V., **Krishna, S**., Raghuram, N., and Jain, S. (2013). Flux-based classification of reactions reveals a functional bow-tie organization of complex metabolic networks. ***Physical Review. E, Statistical, Nonlinear, and Soft matter Physics***, 87, 052708.

MADHUSUDHAN VENKADESAN

- Roach, N. T., **Venkadesan, M.,** Rainbow, M. J., and Lieberman, D. E. (2013). Elastic energy storage in the shoulder and the evolution of high-speed throwing in *Homo*. ***Nature,*** 498, 483–6.

PUBLICATIONS 2014

BIOCHEMISTRY, BIOPHYSICS AND BIOINFORMATICS

JAYANT B UDGOANKAR

- Ramachandran, G., Milán-Garcés, E. A., **Udgaonkar, J. B.,** and Puranik, M. (2014). Resonance raman spectroscopic measurements delineate the structural changes that occur during Tau fibril formation. ***Biochemistry,*** 53, 6550–65.
- Malhotra, P., and **Udgaonkar, J. B.** (2014). High-energy intermediates in protein unfolding characterized by thiol labeling under nativelike conditions. ***Biochemistry,*** 53, 3608–20.
- Bhardwaj, V., Panicker, M. M., and **Udgaonkar, J. B.** (2014). Fluorescence anisotropy uncovers changes in protein packing with inclusion growth in a cellular model of polyglutamine aggregation. ***Biochemistry,*** 53, 3621–36.
- Milán-Garcés, E. A., Mondal, S., **Udgaonkar, J. B.,** and Puranik, M. (2014). Intricate packing in the hydrophobic core of barstar through a CH-π interaction. ***Journal of Raman Spectroscopy,*** 45, 814–821.
- Sabareesan, A. T., and **Udgaonkar, J. B.** (2014). Amyloid fibril formation by the chain B subunit of monellin occurs by a nucleation-dependent polymerization mechanism. ***Biochemistry,*** 53, 1206–17
- Moulick, R., and **Udgaonkar, J. B.** (2014). Thermodynamic characterization of the unfolding of the prion protein. ***Biophysical Journal,*** 106, 410–20.
- Dasgupta, A., **Udgaonkar, J. B.,** and Das, P. (2014). Multistage unfolding of an SH3 domain: an initial urea-filled dry molten globule precedes a wet molten globule with non-native structure. ***The Journal of Physical Chemistry,*** B 118, 6380–92.

R SOWDHAMINI

- Nagarathnam, B., Karpe, S. D., Harini, K., Sankar, K., Iftekhar, M., Rajesh, D., Giji, S., Archunan, G., Balakrishnan, V., Gromiha, M. M., Nemoto, W., Fukui, K., and **Sowdhamini, R.** (2014). DOR - a Database of Olfactory Receptors - Integrated Repository for Sequence and Secondary Structural Information of Olfactory Receptors in Selected Eukaryotic Genomes. ***Bioinformatics and Biology Insights,*** 8, 147–58.
- Malhotra, S., and **Sowdhamini, R.** (2014). Interactions Among Plant Transcription Factors Regulating Expression of Stress-responsive Genes. ***Bioinformatics and Biology Insights,*** 8, 193–8.
- Malhotra, S., Sankar, K., and **Sowdhamini, R.** (2014). Structural interface parameters are discriminatory in recognising near-native poses of protein-protein interactions. ***PloS One,*** 9, e80255
- Dharmaprakash, A., Mutt, E., Jaleel, A., **Ramanathan, S.,** and Thomas, S. (2014). Proteome profile of a pandemic *Vibrio parahaemolyticus* SC192 strain in the planktonic and biofilm condition. ***Biofouling,*** 30, 729–39.
- Mutt, E., Mathew, O. K., and **Sowdhamini, R.** (2014). LenVarDB: database of length-variant protein domains. ***Nucleic Acids Research,*** 42, D246–50.
- Joseph, A. P., Shingate, P., Upadhyay, A. K., and **Sowdhamini, R.** (2014). 3PFDB+: improved search protocol and update for the identification of representatives of protein sequence domain families. ***Database,*** 2014, bau026.
- Chacko, A.R., Mathew, O.K., Joshi, A., Raghavender, U.S. and **Sowdhamini, R.** (2014) SMOS.2: Update of database of structural motifs in superfamilies. ***Nucleic Acids Research, Database Issue***, Jan. 2014.

YAMUNA KRISHNAN

- Chakraborty, S., Mehtab, S., and **Krishnan, Y.** (2014). The predictive power of synthetic nucleic acid technologies in RNA biology. ***Accounts of Chemical Research,*** 47, 1710–9.
- Sharma, S., Zaveri, A., Visweswariah, S. S., and **Krishnan, Y.** (2014). A fluorescent nucleic Acid nanodevice quantitatively images elevated cyclic adenosine monophosphate in membrane-bound compartments. ***Small,*** 10, 4276–80.
- Ghosh, A., and **Krishnan, Y**. (2014). At a long-awaited turning point. ***Nature Nanotechnology,*** 9, 491–4.
- Modi, S., Halder, S., Nizak, C., and **Krishnan, Y.** (2014). Recombinant antibody mediated delivery of organelle-specific DNA pH sensors along endocytic pathways. ***Nanoscale,*** 6, 1144–52.

(† Denotes Book Chapter, ‡ Denotes Book)

ASWIN SAI NARAIN SESHASAYEE

- Chandraprakash, D., and **Seshasayee, A. S. N.** (2014). Inhibition of factor-dependent transcription termination in *Escherichia coli* might relieve xenogene silencing by abrogating H-NS-DNA interactions in vivo. ***Journal of Biosciences,*** 39, 53–61.

PV SHIVAPRASAD

- Jagtap, S., and **Shivaprasad, P. V.** (2014). Diversity, expression and mRNA targeting abilities of Argonaute-targeting miRNAs among selected vascular plants. ***BMC Genomics,*** 15, 1049.

CELLULAR ORGANIZATION AND SIGNALING

SUDHIR KRISHNA

- Pattabiraman, C., Hong, S., Gunasekharan, V. K., Pranatharthi, A., Bajaj, J., Srivastava, S., Krishnamurthy, H., Ammothumkandy, A., Giri, V. G., Laimins, L. A., and **Krishna, S**. (2014). CD66+ Cells in Cervical Precancers Are Partially Differentiated Progenitors with Neoplastic Traits. ***Cancer Research***, 74, 6682–92.

APURVA SARIN

- Garg, M., Ramdas, N., Vijayalakshmi, M., Shivashankar, G. V, and **Sarin, A**. (2014). The C-terminal domain (CTD) in linker histones antagonizes anti-apoptotic proteins to modulate apoptotic outcomes at the mitochondrion. ***Cell Death & Disease***, 5, e1058.
- Garg, M., Perumalsamy, L. R., Shivashankar, G. V, and **Sarin, A**. (2014). The linker histone h1.2 is an intermediate in the apoptotic response to cytokine deprivation in T-effectors. ***International Journal of Cell Biology***, 2014, 674753.

SATYAJIT MAYOR

- Manzo, C., van Zanten, T. S., Saha, S., Torreno-Pina, J. A., **Mayor, S**., and Garcia-Parajo, M. F. (2014). PSF decomposition of nanoscopy images via Bayesian analysis unravels distinct molecular organization of the cell membrane. ***Scientific Reports***, 4, 4354.
- Dey, G., Gupta, G. D., Ramalingam, B., Sathe, M., **Mayor, S**., and Thattai, M. (2014). Exploiting cell-to-cell variability to detect cellular perturbations. ***PloS One***, 9, e90540.
- Yadav, M., Raghupathy, R., Saikam, V., Dara, S., Singh, P. P., Sawant, S. D., **Mayor, S**., and Vishwakarma, R. A. (2014). Synthesis of non-hydrolysable mimics of glycosylphosphatidylinositol (GPI) anchors. ***Organic & Biomolecular Chemistry***, 12, 1163–72.
- Gupta, G. D., Dey, G., Swetha, M. G., Ramalingam, B., Shameer, K., Thottacherry, J. J., Kalappurakkal, J. M., Howes, M. T., Chandran, R., Das, A., Menon, S., Parton, R. G., Sowdhamini, R., Thattai, M., and **Mayor, S**. (2014). Population distribution analyses reveal a hierarchy of molecular players underlying parallel endocytic pathways. ***PloS One***, (Bassham, D., Ed.) 9, e100554.

KS KRISHNAN

- **Krishnan, K.S.** (2014). Remembering Obaid–One Year Later. ***Journal of Bioscience***, 39, 543-44.

ECOLOGY AND EVOLUTION

UMA RAMAKRISHNAN

- Srinivasan, U., Tamma, K., and **Ramakrishnan, U**. (2014). Past climate and species ecology drive nested species richness patterns along an east-west axis in the Himalaya. ***Global Ecology and Biogeography***, 23, 52–60.
- Savory, F. R., and **Ramakrishnan, U**. (2014). Asymmetric patterns of reassortment and concerted evolution in *Cardamom bushy dwarf virus*. ***Infection, Genetics and Evolution***, 24, 15–24.
- Savory, F. R., Varma, V., and **Ramakrishnan, U**. (2014). Identifying geographic hot spots of reassortment in a multipartite plant virus. ***Evolutionary Applications***, 7, 569–79.

MAHESH SANKARAN

- Krishnaswamy, J., Vaidyanathan, S., Rajagopalan, B., Bonell, M., **Sankaran, M**., Bhalla, R. S., and Badiger, S. (2014). Non-stationary and non-linear influence of ENSO and Indian Ocean Dipole on the variability of Indian monsoon rainfall and extreme rain events. ***Climate Dynamics***, (In press).
- Osuri, A. M., Madhusudan, M. D., Kumar, V. S., Chengappa, S. K., Kushalappa, C. G., and **Sankaran, M.** (2014). Spatio-temporal variation in forest cover and biomass across sacred groves in a humanmodified landscape of India's Western Ghats. ***Biological Conservation***, 178, 193–99.
- Osuri, A. M., Kumar, V. S., and **Sankaran, M**. (2014). Altered stand structure and tree allometry reduce carbon storage in evergreen forest fragments in India's Western Ghats. ***Forest Ecology and Management***, 329, 375–83.
- Wordley, C. F. R., Foui, E. K., Mudappa, D., **Sankaran, M**., and Altringham, J. D. (2014). Acoustic Identification of Bats in the Southern Western Ghats, India. ***Acta Chiropterologica***, 16, 213–22.
- Kohli, M., **Sankaran, M**., Suryawanshi, K. R., and Mishra, C. (2014). A penny saved is a penny earned: lean season foraging strategy of an alpine ungulate. ***Animal Behaviour***, 92, 93–100.
- Hautier, Y., Seabloom, E. W., Borer, E. T., Adler, P. B., Harpole, W. S., Hillebrand, H., Lind, E. M., MacDougall, A. S., Stevens, C. J., Bakker, J. D., Buckley, Y. M., Chu, C., Collins, S. L., Daleo, P., Damschen, E. I., Davies, K. F., Fay, P. A., Firn, J., Gruner, D. S., Jin, V. L., Klein, J. A., Knops, J. M. H., La Pierre, K. J., Li, W., McCulley, R. L., Melbourne, B. A., Moore, J. L., O'Halloran, L. R., Prober, S. M., Risch, A. C., **Sankaran, M**., Schuetz, M., and Hector, A. (2014). Eutrophication weakens stabilizing effects of diversity in natural grasslands. ***Nature***, 508, 521–25.
- Lehmann, C. E. R., Anderson, T. M., **Sankaran, M**., Higgins, S. I., Archibald, S., Hoffmann, W. A., Hanan, N. P., Williams, R. J., Fensham, R. J., Felfili, J., Hutley, L. B., Ratnam, J., San Jose, J., Montes, R., Franklin, D., Russell-Smith, J., Ryan, C. M., Durigan, G., Hiernaux, P., Haidar, R., Bowman, D. M. J. S., and Bond, W. J. (2014). Savanna vegetation-fire-climate relationships differ among continents. ***Science***, 343, 548–52.

SANJAY P SANE

- Truong, T. Q., Phan, V. H., **Sane, S. P**., and Park, H. C. (2014). Pitching Moment Generation in an Insect-Mimicking Flapping-Wing System. ***Journal of Bionic Engineering***, 11, 36–51.
- Dieudonné, A., Daniel, T. L., and **Sane, S. P**. (2014). Encoding properties of the mechanosensory neurons in the Johnston's organ of the hawk moth, *Manduca sexta*. ***The Journal of Experimental Biology***, 217, 3045–56.
- Parween, R., Pratap, R., Deora, T., and **Sane, S. P**. (2014). Modeling Strain Sensing by the Gyroscopic Halteres, in the Dipteran Soldier Fly, *Hermetia illucens*. ***Mechanics Based Design of Structures and Machines***, 42, 371–85.
- Krishnan, A., and **Sane, S. P**. (2014). Visual feedback influences antennal positioning in flying hawk moths. ***The Journal of Experimental Biology***, 217, 908–17.

KRUSHNAMEGH KUNTE

- **Kunte, K**., Zhang, W., Tenger-Trolander, A., Palmer, D. H., Martin, A., Reed, R. D., Mullen, S. P., and Kronforst, M. R. (2014). doublesex is a mimicry supergene. ***Nature***, 507, 229–32.

DEEPA AGASHE

- **Agashe, D**., and Shankar, N. (2014). The evolution of bacterial DNA base composition. ***Journal of Experimental Zoology. Part B, Molecular and Developmental Evolution***, 322, 517–28.

GENETICS AND DEVELOPMENT

K VIJAYRAGHAVAN

- Sen, S., Biagini, S., Reichert, H., and **VijayRaghavan, K**. (2014). Orthodenticle is required for the development of olfactory projection neurons and local interneurons in *Drosophila*. ***Biology Open***, 3, 711–17.
- Sudhakaran, I. P., Hillebrand, J., Dervan, A., Das, S., Holohan, E. E., Hülsmeier, J., Sarov, M., Parker, R., **VijayRaghavan, K.**, and Ramaswami, M. (2014). FMRP and Ataxin-2 function together in long-term olfactory habituation and neuronal translational control. ***Proceedings of the National Academy of Sciences of the United States of America,*** 111, E99–E108.
- Gunage, R. D., Reichert, H., and ***VijayRaghavan, K.*** (2014). Identification of a new stem cell population that generates *Drosophila* flight muscles. ***eLife***, 3, e03126. doi: 10.7554/eLife.03126.
- Mullin, A.P., Sadanandappa, M.K., Ma W., Dickman, D.K., **VijayRaghavan, K.** Ramaswami,M., Sanyal.S. and Faundez, V. (2014). Gene Dosage in the Dysbindin Schizophrenia Susceptibility Network Differentially Affect Synaptic Function and Plasticity. ***The Journal of Neuroscience,*** (In Press).
- Jameel, .S, Banerjee, U., and **VijayRaghavan, K.** (2014). Remembering Obaid - one year later. ***Journal of Bioscience***, 39, 543-4.

GAITI HASAN

- Kumaran, D., Balagopal, K., Tharmaraj, R. G. A., Aaron, S., Kuriyan, G., Muliyil, J., Sivadasan, A., Danda, S., Alexander, M. and **Hasan, G.** (2014) Genetic characterization of Spinocerebellar Ataxia 1 in a South Indian cohort. ***BMC Med Genetics*** (in press).

PV SHIVAPRASAD

- Jagtap, S., and **Shivaprasad, P. V.** (2014). Diversity, expression and mRNA targeting abilities of Argonaute-targeting miRNAs among selected vascular plants. ***BMC Genomics***, 15, 1049.

NEUROBIOLOGY

MITRADAS M PANICKER

- Muthusamy, T., Mukherjee, O., Menon, R., Megha, P. B., and **Panicker, M. M.** (2014). A method to identify and isolate pluripotent human stem cells and mouse epiblast stem cells using lipid body-associated retinyl ester fluorescence. ***Stem Cell Reports***, 3, 169–84.

UPINDER S BHALLA

- Jain, P., and **Bhalla, U. S.** (2014). Transcription control pathways decode patterned synaptic inputs into diverse mRNA expression profiles. ***PloS One,*** 9, e95154.
- Modi, M. N., Dhawale, A. K., and **Bhalla, U. S.** (2014). CA1 cell activity sequences emerge after reorganization of network correlation structure during associative learning. ***eLife,*** 3, e01982.
- **Bhalla, U. S.** (2014). Molecular computation in neurons: a modeling perspective. ***Current Opinion in Neurobiology,*** 25, 31–7.
- **Bhalla, U. S.** (2014). Multiscale modeling and synaptic plasticity. ***Progress in Molecular Biology and Translational Science***, 123, 351-86.

SUMANTRA CHATTARJI

- Ghosh, S., and **Chattarji, S.** (2014). Neuronal encoding of the switch from specific to generalized fear. ***Nature Neuroscience,*** doi: 10.1038/nn.3888. [Epub ahead of print]
- Tomar, A., Polygalov, D., **Chattarji, S.,** and McHugh, T. J. (2014). The dynamic impact of repeated stress on the hippocampal spatial map. ***Hippocampus,*** doi: 10.1002/hipo.22348
- Kedia, S., and **Chattarji, S.** (2014). Marble burying as a test of the delayed anxiogenic effects of acute immobilisation stress in mice. ***Journal of Neuroscience Methods,*** 233, 150–4.
- Suvrathan, A., Bennur, S., Ghosh, S., Tomar, A., Anilkumar, S., and **Chattarji, S.** (2014). Stress enhances fear by forming new synapses with greater capacity for long-term potentiation in the amygdala. ***Philosophical transactions of the Royal Society of London. Series B, Biological sciences,*** 369, 20130151.
- Rahman, M. M., Kerskens, C. M., **Chattarji, S.**, and O'Mara, S. M. (2014). Chronic immobilization stress occludes in vivo cortical activation in an animal model of panic induced by carbon dioxide inhalation. ***Frontiers in Behavioral Neuroscience,*** 8, 311.
- Kim, S.-Y., Burris, J., Bassal, F., Koldewyn, K., **Chattarji, S.**, Tassone, F., Hessl, D., and Rivera, S. M. (2014). Fear-specific amygdala function in children and adolescents on the fragile x spectrum: a dosage response of the FMR1 gene. ***Cerebral Cortex,*** 24, 600–13.
- Sampath, D., Sabitha, K. R., Hegde, P., Jayakrishnan, H. R., Kutty, B. M., **Chattarji, S.**, Rangarajan, G., and Laxmi, T. R. (2014). A study on fear memory retrieval and REM sleep in maternal separation and isolation stressed rats. ***Behavioural Brain Research,*** 273, 144–54.
- **Chattarji, S.**, and Rao, R. P. (2014). Blood-brain biomarkers for stress susceptibility. ***Proceedings of the National Academy of Sciences of the United States of America,*** 111, 13253–4.

SANJAY P SANE

- Krishnan, A., and **Sane, S. P.** (2014). Visual feedback influences antennal positioning in flying hawk moths. ***The Journal of Experimental Biology,*** 217, 908–17.
- Dieudonné, A., Daniel, T. L., and **Sane, S. P.** (2014). Encoding properties of the mechanosensory neurons in the Johnston's organ of the hawk moth, *Manduca sexta.* ***The Journal of Experimental Biology,*** 217, 3045–56.
- Parween, R., Pratap, R., Deora, T., and **Sane, S. P.** (2014). Modeling Strain Sensing by the Gyroscopic Halteres, in the Dipteran Soldier Fly, *Hermetia illucens.* ***Mechanics Based Design of Structures and Machines,*** 42, 371–385.
- Truong, T. Q., Phan, V. H., **Sane, S. P.**, and Park, H. C. (2014). Pitching Moment Generation in an Insect-Mimicking Flapping-Wing System. ***Journal of Bionic Engineering,*** 11, 36–51.

GAITI HASAN

- Sadaf, S., and **Hasan, G.** (2014). Serotonergic neurons of the Drosophila air-puff-stimulated flight circuit. ***Journal of Biosciences,*** 39, 575–83.
- Kumaran, D., Balagopal, K., Tharmaraj, R., Aaron, S., George, K., Muliyil, J., Sivadasan, A., Danda, S., Alexander, M., and **Hasan, G.** (2014). Genetic characterization of Spinocerebellar ataxia 1 in a South Indian cohort. ***BMC Medical Genetics,*** 15, 114.

VATSALA THIRUMALAI

- Bakthavatsalam, S., Das Sharma, S., Sonawane, M., **Thirumalai, V.**, and Datta, A. (2014). A zebrafish model of manganism reveals reversible and treatable symptoms that are independent of neurotoxicity. ***Disease Models & Mechanisms,*** 7, 1239–51.

THEORY, SIMULATION AND MODELING OF BIOLOGICAL SYSTEMS

MUKUND THATTAI

- Dey, G., Gupta, G. D., Ramalingam, B., Sathe, M., Mayor, S., and **Thattai, M.** (2014). Exploiting cell-to-cell variability to detect cellular perturbations. ***PloS One***, 9, e90540.
- Gupta, G. D., Dey, G., Swetha, M. G., Ramalingam, B., Shameer, K., Thottacherry, J. J., Kalappurakkal, J. M., Howes, M. T., Chandran, R., Das, A., Menon, S., Parton, R. G., Sowdhamini, R., **Thattai, M.,** and Mayor, S. (2014). Population distribution analyses reveal a hierarchy of molecular players underlying parallel endocytic pathways. ***PloS One***, (Bassham, D., Ed.) 9, e100554.
- **Thattai, M.,** and Peisajovich, S. G. (2014). Current approaches in evolution: from molecules to cells and organisms. ***Journal of experimental zoology. Part B, Molecular and Developmental Evolution***, 322, 465–67.

SHACHI GOSAVI

- Yadahalli, S., and **Gosavi, S.** (2014). Designing cooperativity into the designed protein Top7. ***Proteins***, 82, 364–74.
- Yadahalli, S., Hemanth Giri Rao, V. V., and **Gosavi, S**. (2014). Modeling Non-Native Interactions in Designed Proteins. ***Israel Journal of Chemistry***, 54, 1230–1240.

R SOWDHAMINI

- Kaushik, S., Etchebest, C., and **Sowdhamini, R**. (2014). Decoding the structural events in substrate-gating mechanism of eukaryotic prolyl oligopeptidase using normal mode analysis and molecular dynamics simulations. ***Proteins***, 82, 1428–43.
- Mudgal, R., **Sowdhamini, R**., Chandra, N., Srinivasan, N., and Sandhya, S. (2014). Filling-in void and sparse regions in protein sequence space by protein-like artificial sequences enables remarkable enhancement in remote homology detection capability. ***Journal of Molecular Biology***, 426, 962–79.
- Joseph, A. P., Shingate, P., Upadhyay, A. K., and **Sowdhamini, R**. (2014). 3PFDB+: improved search protocol and update for the identification of representatives of protein sequence domain families. ***Database***, 2014, bau026.
- Malhotra, S., and **Sowdhamini, R**. (2014). Interactions Among Plant Transcription Factors Regulating Expression of Stress-responsive Genes. ***Bioinformatics and Biology Insights***, 2014, 193–198.

UPINDER S BHALLA

- **Bhalla, U.S.** (2014). Multiscale modeling and synaptic plasticity. ***Progress in Molecular Biology and Translational Science***, 123, 351-86.

SANDEEP KRISHNA

- Semsey and Sandeep **Krishna, S**. (2014). Combining Theory and Experiments to Understand Sugar Regulation in Bacteria. ***Current Chemical Biology***, 7, 224-233.

(† Denotes Book Chapter, ‡ Denotes Book)

MEETINGS AND WORKSHOPS

158 MEETINGS AND WORKSHOPS 2012 160 MEETINGS AND WORKSHOPS 2013

162 MEETINGS AND WORKSHOPS 2014

The development of this program has its genesis in our realisation that students at NCBS, as well as those at other scientific institutions in India, benefit tremendously from an exposure to the best international science. The Meetings and Workshops Program also plays a role in showcasing Indian science at its best to visitors from outside the country.

SCAN THIS TO KNOW MORE ABOUT NCBS MEETINGS AND WORKSHOPS

MEETINGS AND WORKSHOPS 2012

January 2 – 4
Genes to Olfaction: 60 years in Science

January 8 - 12
Young Investigators Meeting, Pune

January 9 -10
Indo Japan Meetings

February 1 - 8
Unifying Concepts in Materials: James A Krumhansl Symposium and School

February 6 - 7
IORMC meeting

February 8 - 12
King's College London Collaborative meeting

February 20 – March 2
King's College London Collaborative meeting

February 23 – 24
Royal Society DST Inositide Meeting

April 4 - 5
NCBS-BII Workshop

April 12 - 13
JCB and EMBO editors meeting

April 26
IFOM-IEO meeting

May 11
Passion for Baroque concert

June 12 - 13
Brandeis-NCBS Collaborative Meeting
Area of Research:
Cellular Organization and Signalling & Theory and Modelling of Biological Systems, Neurobiology

July 9 - 27
Science Journalism Workshop

August 6 - 7
Curie-NCBS Collaborative Meeting

September 14
Cambridge – inStem/NCBS Collaborative Meeting

September 23 - 30
Microscopy Course

September 28
Workshop on Scholarly Publishing

October 15 - 17
International Symposium on Protein Folding and Dynamics

October 29 - November 10
Advanced Course on Genes and Behavior
Area of Research:
Genetics and Development
A workshop on evolutionary development of the nervous system and behavior

November 28 - December 2
Inositide signalling in health and disease

December 17 - 26
The Sixth Bangalore Benny Shilo Course in Developmental Biology
Area of Research:
Genetics and Development
A course to focus on connecting molecular and cellular pathways to an understanding of the mechanisms that underlie animal development.

JANUARY | FEBRUARY | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEPTEMBER | OCTOBER | NOVEMBER | DECEMBER

MEETINGS AND WORKSHOPS 2013

January 3 – 5
Control in Biological Systems

January 13 - 16
EBI - C-CAMP Next Generation Genomics Data Analysis Workshop

February 9 - 13
Young Investigator's Meeting 2013
Meeting focuses on the "how-to" of setting up research labs and conducting research with an emphasis on mentorship.

March 10 - 23
inStem Workshop on Mouse Embryology: Stem Cells to Organogenesis

April 15 - 26 ICTS short program on "Mechanical manipulations and responses at the scale of the cell and beyond"
Area of Research: Cellular Organization and Signalling & Theory and Modelling of Biological Systems
Introduces a scope of techniques to gain quantitative information of responses of the biological material (at all scales) to perturbations of a mechanical nature, and explores how the combination of theory and experiments will lead to a systematic deciphering of the physics of how living material engages with mechanical information

June 10 - 12
Conference on "Genes and Genomes"

June 10 - 21
2013 NCBS-ICTS Monsoon School: Physics of Life

July 10 - 26
The Third Annual NCBS Science Journalism Course

September 8 - 14
Bangalore Microscopy Course 2013

October 19
Cell Author Seminar

October 22 - 25
International Symposium on 'Bacterial Expressions'

November 7
Evolution Symposium: Celebrating Wallace
Area of Research: Ecology
To highlight Wallace's contributions, the symposium will include a public lecture about his life and work.

November 15 - 16
Rufford Grantees Meet

November 25 - 30
Asian otter Conservation Workshop

December 12
Launch of the Simons Centre for the Study of Living Machines, NCBS-TIFR
Area of Research: Theory and Modelling of Biological Systems
A centre to build bridges between theory and experiment, support post-doctoral fellowships, and host long-term visitors. Please join us as we celebrate this milestone.

December 22 - 24
All India Cell Bio Conference

JANUARY | FEBRUARY | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEPTEMBER | OCTOBER | NOVEMBER | DECEMBER

MEETINGS AND WORKSHOPS 2014

February 17 - 28 DST-SERB School on Chemical Ecology
Area of Research: Ecology
The SERB school on Chemical Ecology will give advanced PhD students, postdocs and young faculty a broad training in developing and addressing research questions in chemical ecology, as well as hands-on experience with various methods that can be used for such work.

February 3 - 5
NCBS-MBI Meeting on EM: Frontiers in Bio-Imaging

February 2 - 23
Advanced topics in Cell Biology for College Students

June 28- July 12
Computational Approaches to Memory and Plasticity - CAMP @ Bangalore, Summer School

August **25- 29**
Stem Cell Engineering Workshop by Shyni Varghese, UCSD

October 29 - 30
International Meeting on Neuromodulation of Behaviour
Area of Research: Neurobiology
A meeting to bring together a group of neuroscientists from India, Europe and the US with a common interest in studying how neuromodulatory inputs influence natural behaviors in a range of organisms

JANUARY | FEBRUARY | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEPTEMBER | OCTOBER | NOVEMBER | DECEMBER

January 5 – 8
Short Term Course on Bioinformatics

January 14
Annual Review & 2nd Scientific Advisory Committee Meeting

January 15 - 17
Annual Talks 2014 - Action within Cells

January 27 - 31
NCBS Glyco Course

March 20
Conference on Concepts and Mechanisms in Plant Development

May 19 -20
Workshop on Ecosystem Monitoring and Forest Census Research in India

July 25
At The Crossroads- Career Day @ NCBS

July 23 - August 7
4th Annual Science Journalism Workshop
A workshop to impart basic skills necessary for communicating science to the lay person via the written word.

July 21 - 26 Physics of Life, NCBS Annual Monsoon School, 2014
Area of Research: Theory and Modelling of Biological Systems
To expose undergraduate students from mathematics, physical sciences and engineering backgrounds to exciting problems in biology

September 21 - 28
Bangalore Microscopy Course

November 5 - 7 2nd International Symposium on Protein Folding and Dynamics
Area of Research: Biochemistry, Biophysics and Bioinformatics
Internationally recognized biologists, chemists and physicists discuss topical issues in protein folding.

ACADEMIC ACTIVITIES

165 ACADEMIC PROGRAMS 166 DEGREES AWARDED 172 LECTURES AND VISITS

183 MSc WILDLIFE PROGRAM

ACADEMIC PROGRAMS

Our academic programmes have grown to match the breadth and diversity that marks the research on our campus today. The programmes remain committed to training graduate and master's students as well as post-doctoral researchers. Rooted in interdisciplinary approaches we strive to bring a range of perspectives to build both depth and breadth in intellectual pursuits in our community of younger researchers.

The Graduate Studies programme, offers opportunity for education and research leading to the award of a PhD degree. Students may apply after the first (Bachelors) or second (Masters) undergraduate degree for the Integrated MSc-PhD or PhD programmes respectively. Selections are via a nation-wide entrance exam followed by an interview on our campus. The primary goal of this programme is to train graduate students to participate in the generation of knowledge even as they grapple with the importance of discovery. Courses form an integral part of this training and students have the option of in-house courses, as well as international schools and workshops on campus, offered by faculty from within the country and overseas.

A few years ago, we started the Fellows Programme to attract early career (post-doctoral) researchers of exceptional talent to develop programmes that complement ongoing research in our laboratories. Six Fellows and an equivalent number of Career Development Fellowships have been awarded thus far with many of our Fellows successfully competing for international funding from the AXA Research Fund, EMBO and Welcome Trust-DBT Alliance. This programme has been nurtured – like many other endeavors on this campus – by enduring partnerships with colleagues at CRG, Barcelona, IFOM Milan and Cambridge University, UK to name a few. The Fellows Programme adds to the rich repertoire of fellowships - both National and International – hosted on our campus and we look forward to growth and alumni successes in the years ahead.

The Master's Programme in wildlife biology and conservation continues to flourish, enriched by students from diverse educational backgrounds and a faculty – drawn from the best institutions worldwide - committed to training students in the many aspects of conservation science. Offering yet another example of the strength of collaborations, the programme is a joint effort of NCBS and the Centre for Wildlife Studies and has successfully attracted extramural support from the Department of Science & Technology and the Sir Dorabji Tata Trust. That its alumni continue to draw recognition for their contributions to conservation science is a matter of considerable pride for our community.

And finally, a word about our youngest colleagues! The campus hosts an active year-round Internship programme, which brings undergraduates from within the country and overseas for a year or shorter stints ranging from a few weeks to six months to our laboratories. Students must be enrolled in an undergraduate degree to qualify for this programme, which also offers our graduate students unique opportunities for mentorship and training of younger colleagues. New efforts of special note include the summer programme for Tibetan students residing in India, initiated by Ron Vale, Satyajit Mayor and LS Shashidhara; year-long internships (culminating in a Master's Dissertation Thesis) by students from Milan University, coordinated by Elisabetta Dejana and Francesco Blasi at IFOM, Milan and student exchanges funded by the DAAD programme 'New Passage to India' in partnership with the University of Würzburg.

Apurva Sarin
Head, Academic Activities

DEGREES AWARDED

2010

PhD

- **Albert Chiang** ▪ K.VijayRaghavan ▪ 06/01/2010 ▪ *TIFR Deemed University*
  The mechanisms of activity-dependent maintenance of the Drosophila olfactory sensory map
- **Gayatri. V.** ▪ Gaiti Hasan ▪ 2/12/2010 ▪ *TIFR Deemed University*
  Investigating Intracellular Neuronal Calcium Homeostasis in Drosophila
- **Sandhya Sankaran** ▪ R. Sowdhamini ▪ 25/01/2010 ▪ *Manipal University*
  Remote homology detection and Analysis of protein domain superfamilies
- **Feroz Meeran Hameed** ▪ G.V.Shivashankar ▪ 25/01/2010 ▪ *TIFR Deemed University*
  Force induced chromatin remodelling in living cells
- **Sanjeev Kumar** ▪ M.K. Mathew ▪ 04/01/2010 ▪ *TIFR Deemed University*
  Structural Transitions driven by voltage in ion channels: A case study on potassium channel
- **Santosh Kumar Jha** ▪ Jayant B. Udgaonkar ▪ 12/04/2010 ▪ *TIFR Deemed University*
  Characterization of the nature of free-energy barriers during the folding and unfolding of small proteins
- **Ajazul Hamid Wani** ▪ Jayant B. Udgaonkar ▪ 25/01/2010 ▪ *TIFR Deemed University*
  Characterization of confromational heterogeneity in protein unfoldinig using HX-MS and optical spectroscopy
- **V.S. Gayathri** ▪ Madan Rao ▪ *SASTRA*
  Fluctuation Induced Spontaenous Symmetry Breaking in Autocatalytic Cellular Systems
- **Ajeet Pratap Singh** ▪ K.VijayRaghavan ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Mechanisms underlying remodeling of an identified neuron in the CNS of Drosophila Melanogaster

INTEGRATED PhD

- **Neha Agarwal** ▪ Gaiti Hasan ▪ 16/04/2010 ▪ *TIFR Deemed University*
  Investigating the cellular basis for Drosophila Inositol 1,4,5, triphonsphate receptor mutant phenotypes
- **Ashish Kumar Patra** ▪ Jayant B. Udgaonkar ▪ 11/06/2010 ▪ *TIFR Deemed University*
  Characterization of folding unfolding and groEL assisted folding of a sweet protein monellin
- **Aparna Suvrathan** ▪ Sumantra Chattarji ▪ 30/07/2010 ▪ *TIFR Deemed University*
  Synaptic Plasticity in the amygdala - Implications for affecting disorders
- **Hyder Usman** ▪ M.K. Mathew ▪ 05/08/2010 ▪ *TIFR Deemed University*
  Characterization of KCNRG(K+Potassium CN Channel RG Regulator) as a regulator of shaker type potassium chnnels
- **Aprotim Mazumder** ▪ G.V.Shivashankar ▪ 11/06/2010 ▪ *TIFR Deemed University*
  Physical constraints due to nuclear and cytoplastic elements impose a prrestressed state on the eukaryotic cell nucleus

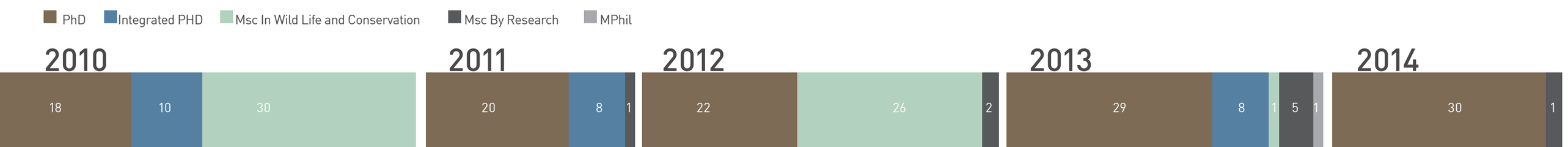
Msc IN WILD LIFE AND CONSERVATION

- **Meghna Krishnadas** ▪ Ajith Kumar ▪ 4/01/2011 ▪ *TIFR Deemed University*
  Foramgomg Strategoes amd patterns of homerange use by an obligate frugivore in relation to resources availability
- **Sachin Sridhara** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Habbit use of the indian chevrotain (Moschiola Indiaca) in someshwara wildlife sanctuary
- **Tarun Nair** ▪ Ajith Kumar ▪ 06/08/2010 ▪ *TIFR Deemed University*
  Ecological and anthropogenic coveriates influencing gharial distribution and habitat use in chambal river
- **Imran Siddiqui** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Prediciting tiger devsities based on prey abundance in disturbed forest of kawal
- **Mayuresh Satish Gangal** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Sedimentation influences resource allocation in the sea grass cymbocea serrulata
- **Nisarg Prakash** ▪ Ajith Kumar ▪ 4/01/2011 ▪ *TIFR Deemed University*
  Factors influencing the occurrence & Habitat use of small clawed otters in human modified lanscape of Western Ghats, South India
- **Shivani Vijayraj Jadeja** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Effects of intraspecific variation in balckbuck behaviour on disperasal of invasive prosopsis juliflora in a semi arid grassland
- **Girish Arjun Punjabi** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  A Multi Scale assessement of factors affecting den site selection in the indian fox in a human dominated dry grassland ecosystem in certrlindia
- **Nishant M.S.** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Determination of dry season distribution of Asian elephant in a fragmental landscope of Easten Ghats, Southern India and implications for human elephant conflict
- **Bipin C.M.** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Human Elephant impacts of landover changes along the western ghats in karnataka
- **killivalavan.R** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Assessing potential tiger habitats in vauvery wildlife sanctuary karnataka using occupancy modeling approaches
- **Aditya Suresh Joshi** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Genetic Structure and Connectivity of Tiger (Panthera tigris tigris) Population in central
- **Jayendra K. Baliga** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Heterogeneity in allogrooming networks of females in troops of bonnet macaques in a tropical deciduous in southern India
- **Rajat R. Nayak** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Effects of recurring forest fire on ground vegetation composition and soil properties in a South Indian tropical forest
- **Ipsita Raveendra Herlekar** ▪ Ajith Kumar ▪ 14/01/2011 ▪ *TIFR Deemed University*
  Effect of canopy gragmentation on patterns of habitat use of the grizzled giant squirrel cauvery wildlife sanctuary karnataka

2011

PhD

- **A. Padmanabhan** ▪ R.Sowdhamini ▪ 07/09/2011 ▪ *National Institute of Mental Health and Neuro Science*
  Molecular Mechanism of Agonist and Antagonist with 5-HT Receptors, Structural Consequences of SNP's and Evolutionary Trace Analysis of 5-HT Receptors.
- **Shameer P.K** ▪ R.Sowdhamini ▪ 05/08/2011 ▪ *Manipal University*
  Identification and analysis of domains in proteins
- **Tuhin Subra Chakraborty** ▪ Obaid Siddiqi ▪ 15/04/2011 ▪ *Manipal University*
  Neural correlates of Olfactory learning in Drosophila melanogaster
- **M. Malini** ▪ R.Sowdhamini ▪ 06/10/2011 ▪ *Manipal University*
  Genomic, structural and functional characterization of odorant binding proteins in olfaction of mosquitoes involved in infectious disease transmission
- **K. Kanagarajadurai** ▪ R.Sowdhamini ▪ 02/07/2011 ▪ *Manipal University*



Sequence and structural Analysis of Protein Domain Families and Superfamilies

- **Keshava Subramanya, M.R.** ■ Veronica Rodrigues ■ 19/02/2011 ■ *University of Mysore*
  Exploring the Structure and Development of Olfactory system in social insects: A case study of Formicine ants Camponotus sericeus and Camponotus compresses
- **Ruchika Anand** ■ V. Sriram ■ 19/01/2012 ■ *TIFR Deemed University*
  The role of NSF and L-Snap in regulation of snare druing mitochondrial remodelling
- **Jeevisha Bajaj** ■ Sudhir Krishna ■ 19/01/2012 ■ *TIFR Deemed University*
  A cancer stem like subset in human cervical cancers is maintained by Notch signaling
- **Gaurav Goyal** ■ V. Sriram ■ 14/01/2011 ■ *TIFR Deemed University*
  Mitochondrial remodeling during programmed cell death in Drosophila melanogaster
- **Anup G** ■ Sumantra Chattarji ■ 01/07/2011 ■ *TIFR Deemed University*
  Celllular mechanisms of stress and antidepressant effects inthe hippocampus and amygdala

INTEGRATED PhD

- **Amrita Sekhar** ■ Jayant B. Udgaonkar ■ 19/01/2012 ■ *TIFR Deemed University*
  Exploring the nature of protein aggregation
- **Shweta Jain** ■ Jayant B. Udgaonkar ■ 19/01/2012 ■ *TIFR Deemed University*
  Characterization of the structural events involved in mouse prion protein aggregation
- **Aditi Bhattacharya** ■ Mitradas M. Panicker ■ 01/07/2011 ■ *TIFR Deemed University*
  Dissection of the internalization and recycling of the human serotonin receptor (5HT2aR)
- **Adil Ghani Khan** ■ Upinder S. Bhalla ■ 19/01/2012 ■ *TIFR Deemed University*
  Studies of the rat olfactory system coding and neuro ethology

MSc BY RESEARCH

- **Akankshi Munjal** ■ Satyajit Mayor ■ 19/01/2012 ■ *TIFR Deemed University*
  Screening for small molecule inhibitors against HIV-I encoded NEF interaction with CD80/CD86

2012

PhD

- **Dhanya. P** ■ Upinder S. Bhalla ■ 24/01/2013 ■ *TIFR Deemed University*
  Role of Network Activity in Neuronal Summation and communication
- **Divya P.S.** ■ R. Sowdhamini ■ 24/01/2013 ■ *TIFR Deemed University*
  Structure function relationships and computational analysis of myosins and other proteins containing coiled-coils
- **Namrata Jayanth** ■ Mrinalini J. Puranik ■ 24/01/2013 ■ *TIFR Deemed University*
  Lesion Discrimination by the ecoli repair enzymes, Alkb and formamidopyrimidine glycosylase
- **Samrat Mondal** ■ Uma Ramakrishnan ■ 12/07/2012 ■ *Manipal University*
  Phylogeography and population genetics of the Bengal tiger (Panthera tigris tigris) in the Indian subcontinent
- **Abhijit Das** ■ K. VijayRaghavan ■ 15/06/2012 ■ *TIFR Deemed University*
  A study of Local Interneurions in the Antennal Lobe of Drosophila melanogaster
- **Souvik Modi** ■ Yamuna Krishnan ■ 15/06/2012 ■ *TIFR Deemed University*
  I-motif based DNA pH sensor:design, delivery and spatiotemporal pH mapping of endocytic pathways
- **M.G. Swetha** ■ Satyajit Mayor ■ 31/12/2012 ■ *TIFR Deemed University*
  Molecular mechanisms of endo-lysosomal trafficking in metazoan cells
- **Jitendra Kumar** ■ Sandhya P. Koushika ■ 15/06/2012 ■ *TIFR Deemed University*
  The C elegans kinesin motor UNC-104 gets degraded upon loss of specific binding to cargo
- **Tejas Milind Gupte** ■ V. Sriram ■ 15/06/2012 ■ *TIFR Deemed University*
  Delimeating components of the mitochondrial fussion machinery
- **Ruchi Malik** ■ Sumantra Chattarji ■ 24/01/2013 ■ *TIFR Deemed University*
  Neurophysiological correlates of the contrasting effects of enriched environment on the hippocampus and amygdala
- **Spriha Gogia** ■ Mrinalini J. Puranik ■ 15/06/2012 ■ *TIFR Deemed University*
  Distortion in HGPRT purine substrates brought about by protonation, enzyme-binding and chemical modification

MSc BY RESEARCH

- **Rohini Ramadas** ■ Mukund Thattai ■ 24/01/2013 ■ *TIFR Deemed University*
  Mathematical modeling of the eukaryotic membrane traffic system
- **Ramveer Choudhary** ■ Yamuna Krishnan ■ 24/01/2013 ■ *TIFR Deemed University*
  Genetically Encodable Sensors for Terra (Telomeric repeat containing RNA)

MSc IN WILD LIFE AND CONSERVATION

- **Anup B Prakash** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  A Study on the impacts of highways on wildlife in Bandipur Tiger Reserve
- **Arjun Sudheendra Srivathsa** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  A multi-method approach to assessing occurrence and space-use patterns of the Asiatic Wild Dog Cuon alpinus in a tropical forest landscape of Southern India
- **Ashwin Viswanathan** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Seed dispersal by avian frugivores: non-random heterogeneity at fine scales
- **Bhanu Prasanna Sridharan** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Limits of a temporary habitat: Factors affecting juvenile fish in an intertidal mangrove forest
- **Dayani Chakravarthy** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Examining spatial patterns of dispersal and post dispersal seed fate of civet dispersed seeds for Vitex pentaphylla and Prumus ceylanica
- **Deepthi Bharadwaj Chimalakonda** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Ecological and anthropogenic covariates influencing diversity of waterbirds of a wetland complex in an agriculture dominated landscape
- **Mayank Kohli** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Winter foraging strategies of bharal (Pseudois nayaur) and its implications for fintess ina liverstock grazed landscape
- **Sapna Jayaraman** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Assessing the effectiveness of a marine protected area in the andaman Islands
- **Shashank Jayshree Dalvi** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Role of brahmaputra as a biogeographic barrier for avain fauna of north east India
- **Suman Raja Jumani** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Dry season ranging and foraging behaviour of Asain elephants (Elephas maximus) in a critical habitat
- **Uddipana Kalita** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Diet selection by capped langur (Trachypithecus pileatus) in Hollongapar Gibbon Wildlife Sanctuary, Assam, Northeastern India
- **Vanjulavalli Sridhar** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Tracing the geographic origin of traded body parts of leopards using genetic tools
- **Vishnupriya Sankararaman** ■ Ajith Kumar ■ 24/01/2013 ■ *TIFR Deemed University*
  Effects of fishing on the assemblage structure of stream fishes in the tropical hills streams of pakke tiger reserve in northeast india

2013

PhD

- **Anupratap Tomar** ■ Sumantra Chattarji ■ 16/12/2013 ■ *Manipal University*
  Effects of chronic stress on encoding of space and context in the hippocampus: behavioural and in vivo electrophyslological analysis
- **Supriya Ghosh** ■ Sumantra Chattarji ■ 29/11/2013 ■ *TIFR Deemed University*
  Generalized fear, stress and the amygdala; from neurons to networks
- **Subhasri Ghosh** ■ Satyajit Mayor ■ 29/11/2013 ■ *TIFR Deemed University*
  Understanding the role of dynamic actin filaments in the organization of plasma membrane molecules
- **Abhishek Kumar** ■ G.V. Shivashankar ■ 26/11/2013 ■ *TIFR Deemed University*
  Emergence of prestressed nuclear organization and its dynamics
- **Amit Sharma** ■ Deepak T. Nair ■ 29/11/2013 ■ *TIFR Deemed University*
  Structural and Biochemical studies on the prokaryotic Y-family DNA polymerases MsDpo4 and EcDpo4

- **Shovamayee Maharana** ▪ G.V. Shivashankar ▪ 29/11/2013 ▪ *TIFR Deemed University*
  Transcription dependent chromosome organization and nucelar body dynamics
- **K. Venkatesan Iyer** ▪ G.V. Shivashankar ▪ 29/11/2013 ▪ *TIFR Deemed University*
  Functional intergration of mechano-signals to chromatn organization in living cells
- **Shefali Talwar** ▪ G.V. Shivashankar ▪ 29/11/2013 ▪ *TIFR Deemed University*
  Nuclear plasticity in stem cells and its functional implications
- **Aghera Nilesh K.** ▪ Jayant B. Udgaonkar ▪ 18/09/2013 ▪ *TIFR Deemed University*
  Studies of the folding and unfolding of monomeric and dimeric monellin
- **Priyankana Mukherjee** ▪ K. VijayRaghavan ▪ *Manipal University*
  To decipher mechanisms of actin reorganisation during myoblast fusion
- **Gayathri Ramachandran** ▪ Jayant B. Udgaonkar ▪ 29/11/2013 ▪ *TIFR Deemed University*
  Characterization of the mechanism of amyloid fibril formation by tall
- **Lakshmi Revathi P** ▪ Apurva Sarin ▪ 15/05/2013 ▪ *TIFR Deemed University*
  Notch mediated cell survival:spatial regulation of Notch activity underlies the activation of a non-canonical signaling cascade in mammalian cells
- **Dhiraj devidas Bhatia** ▪ Yamuna Krishnan ▪ 29/11/2013 ▪ *TIFR Deemed University*
  Icosahedral DNA Nano capsules for targeted, functional Bio-imaging in Cellulis and in vivo
- **Pragati Jain** Upinder S. Bhalla 23/12/2013 ▪ *Manipal University*
  Spatiotemporal modeling of neuronal protein synthesis in synaptic plasticity
- **Sonia Sen** ▪ K. VijayRaghavan ▪ *Manipal University*
  Conserved peripheral and central roles of transcription factors, empty spiracles and orthodenticle, in Drosophila olfactory system development.

INTEGRATED PhD

- **Harini. L.** ▪ Sumantra Chattarji ▪ 29/11/2013 ▪ *TIFR Deemed University*
  Molecular and behavioral corrlates of stress induced plasticity in the amygdala and hippocampus
- **Ishier Raote** ▪ Mitradas M. Panicker ▪ 29/11/2013 ▪ *TIFR Deemed University* ▪ ***Functional selectivity in serotonin receptor 2A (5-HT2a) trafficking***
- **Soumya Gupta** ▪ Apurva Sarin ▪ 29/11/2013 ▪ *TIFR Deemed University* ▪ ***Nuclear and chromatin reorganization during T-celldevelopment and activation***
- **Shilpa Ravinder** ▪ Sumantra Chattarji ▪ 07/06/2013 ▪ *TIFR Deemed University*
  Effects of the selection serotonin reputake inhibitor fluoxetine on the amygdala : cellular, circuit and behavioral analysis
- **Amrita Dasgupta** ▪ Jayant B. Udgaonkar ▪ 29/11/2013 ▪ *TIFR Deemed University*
  Characterization of sub-millisecond intermediates detected during the refolding and unfolding of the SH3 domain of PI3 kinase

MPhil

- **Suman Das** ▪ Sumantra Chattarji ▪ 18/03/2013 ▪ *TIFR Deemed University* ▪ ***Delayed effects of acute stress on generaliazation of conditioned fear in rats***

MSc BY RESEARCH

- **Megha Kishore** ▪ Jayant B. Udgaonkar ▪ 07/06/2013 ▪ *TIFR Deemed University*
  Investigation of structural heterogeneity in protein folding reactions using time-resolved fluorescence
- **Anusuya Banerjee** ▪ Mrinalini J. Puranik ▪ 07/06/2013 ▪ *TIFR Deemed University* ▪ ***Structure and UVRR vibrational spectra of aminopurines - adenine, 2-aminopurine and 2,6-diaminopurine***
- **Sunil Prabhakar** ▪ Sanjay P. Sane ▪ 18/09/2013 ▪ *TIFR Deemed University*
  The sensorimotor integration of antennal mechanosensory inputs in flying moths

MSc IN WILD LIFE AND CONSERVATION

- **Amod Mohan Zambre** ▪ Ajith Kumar ▪ 15/05/2013 ▪ *TIFR Deemed University*
  Effects of Coral Bleaching on Corallivorous Butterflyfish (Chateodontidae) communities

2014

PhD

- **Pushkar D Paranjpe** ▪ K. VijayRaghavan ▪ 11/08/2014 ▪ *TIFR Deemed University*
  Mechanisms of Habituation in Drosophila
- **Subhasis Ray** ▪ Upinder S. Bhalla ▪ 12/06/2014 ▪ *TIFR Deemed University*
  computational study of a alamocortical neuronal network
- **Saikat Chakraborty** ▪ Yamuna Krishnan ▪ 17/07/2014 ▪ *TIFR Deemed University*
  Tertiary structure of pri-miRNA 17-92aimpacts its processing
- **Sonali saha** ▪ Yamuna Krishnan ▪ 17/07/2014 ▪ *TIFR Deemed University*
  Clensor: A nucleic acid based ratiometric chloride ion sensor for intracellular applications
- **Parag Surana** ▪ Deepak T. Nair ▪ 18/08/2014 ▪ *TIFR Deemed University*
  Biochemical and Structural Studies on RNA Dependent RNA Polymerase from Japanese Encephalitis Virus
- **Kritika M. Garg** ▪ Uma Ramakrishnan ▪ *TIFR Deemed University*
  Mating Games : Lessons from the Haren-Forming fruit bat, cynopterus sphinx
- **Rajat Anand** ▪ Mukund Thattai ▪ 12/06/2014 ▪ *TIFR Deemed University*
  Feedback loops and cell communication in bacterial quorum sensing
- **Swati Kaushik** ▪ R. Sowdhamini ▪ 12/06/2014 ▪ *TIFR Deemed University*
  Remote homology detection techniques, molecular simulations & genomre-wide survey: case study using prolyl oligopeptidases
- **Mehrab N Modi** ▪ Upinder S. Bhalla ▪ 22/08/2014 ▪ *TIFR Deemed University*
  A Hippocampal Mechanism for Associating Stimuli Separated in Time
- **Anand Krishnan** ▪ Sanjay P. Sane ▪ 12/06/2014 ▪ *TIFR Deemed University*
  The neurobiology of antennal positioning in flying hawk moths
- **S. Indu Nair** ▪ K. VijayRaghavan ▪ 12/06/2014 ▪ *TIFR Deemed University*
  A study of the mechanisms of wiring of the adult olfactory circuitry of Drosophila melanogarter
- **Sudeshna Das** ▪ K. VijayRaghavan ▪ 22/03/2014 ▪ *University of Mysore*
  Mechanism of Olfactory long term habituation in Drosophila
- **Satish Kumar** ▪ Gaiti Hasan ▪ *University of Mysore*
  Transcriptional regulation in Drosophila by intracellular calcium
- **K. Parthasarathy** ▪ Upinder S. Bhalla ▪ 02/01/2014 ▪ *Manipal University*
  Neural mechanisms of stereo olfaction
- **A. Gandhimathi** ▪ R. Sowdhamini ▪ 11/04/2014 ▪ *Bharathidasan University*
  Structural Bioinformatics, Biomolecular interactions & Drug design : A case study on specific protein-protein and protein-li gand interaction systems.

M.SC. BY RESEARCH

- **Seema Sheoran** ▪ Sandhya P. Koushika ▪ 17/03/2014 ▪ *TIFR Deemed University*
  Role of UNC-16/JIP3 In Axon Regeneration

SCAN THIS TO KNOW MORE ABOUT NCBS COURSES

LECTURES AND VISITS

APURVA SARIN

2010 Adaptive & innate immune responses to neglected tropical diseases, US-Japan Cooperative Medical Science Program, San Diego, USA ◆ Dept. Biological Sciences, National University of Singapore, Singapore ◆ Department of Genetics, Trinity College, Dublin, Ireland. ◆ Indian Academy of Science, Mid-year Meeting, Indian Institute of Science.
2011 Molecular Immunology Forum. NII, New Delhi, India ◆ IFOM, Milan.
2012 Royal Society-DBT meeting on, Phosphoinositides, NCBS Bangalore
2014 Regional Centre for Biotechnology, Gurgaon.

ASWIN SAI NARAIN SESHASAYEE

2011 Department of Biophysics, Molecular biology and Bioinformatics, University of Calcutta ◆ Biotechcellence, Centre for Biotechnology, Anna University, Chennai, India ◆ Centre for DNA Fingerprinting and Diagnostics, Hyderabad, India ◆ InSTEM-CIRM meeting, Bangalore, India ◆ Biogrid, EU-India GRID, University of Cambridge, Cambridge, UK ◆ Sree Narayana College, Kannur, India ◆ SASTRA, Tanjore, India ◆ Sir M Visweswaraya Institute of Technology, Bangalore, India.
2012 Centre for Genomic Regulation, Barcelona, Spain ◆ Symposium on Systems Biology, University of Delhi South Campus, Delhi, India ◆ NCBS-BII conference, Bangalore, India.

AXEL BROCKMANN

2012 University of Würzburg, Germany ◆ Indian Institute of Science Bangalore, India ◆ Indian Institute of Science Education and Research, Thiruvananthapuram, India.
2013 Department of Biology, Faculty of Sciences, Kyushu University, Japan ◆ Department of Earth System Science, Faculty of Science, Fukuoka University, Japan ◆ Institute of Science and Engineering, Faculty of Natural System, Kanazawa University, Japan ◆ National Brain Research Centre (NBRC), Manesar, Gurgaon, India.

DEEPA AGASHE

2012 National University of Singapore , Singapore ◆ 1st Joint Congress on Evolutionary Biology, Ottawa, Canada ◆ Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India ◆ Uppsala University, Sweden School of Natural Sciences, Linnaeus University, Kalmar, Sweden ◆ University of Bielefeld, Germany.
2013 Young Investigator's Meeting, Jodhpur, India ◆ Evolution Symposium: Celebrating Wallace, Bangalore, India ◆ International conference on Bacterial Expressions, Bangalore, India.
2014 American Society of Naturalists' Conference, 21st Century Naturalists: integrating pattern and process to understand biodiversity, Pacific Grove, USA ◆ ICTS School on Population Genetics and Evolution, Bangalore, India ◆ SMBE Satellite Meeting/NIG International Symposium: Causes of Genome Evolution, Japan

DEEPAK T NAIR

2010 35th Mahableshwar Seminar on Evolution of Molecular Function and Principles of Protein Design. Mahableshwar, India.
2011 Modern Trends in Macromolecular Structures- Indo-US Workshop/Symposium, Indian Institute of Technology, Mumbai ◆ XXII International Congress of the International Union of Crystallography in Madrid, Spain ◆ The Regional Centre for Biotechnology, Gurgaon, India.
2012 The Ramanujan Fellow Meeting, Pune, India ◆ NCBS-St John's infectious diseases meeting, Bangalore, India ◆ Annual Meeting of the Society of Biological Chemists, Kolkata, India ◆ Indian Institute of Science Education and Research, Mohali, India ◆ Institute of Microbial Technology, Chandigarh, India ◆ Meeting on 'Control in Biological Systems', NCBS, Bangalore, India.
2013 National Conference on recent trends in Protein Structural Biology held at Jamia Hamdard, Delhi, India. ◆ 2nd Ramanujan Conclave held at IISER (Pune) ◆ Guha Research Conference held at Araku Valley and Vishakhapatnam, India ◆ The National Seminars in Crystallography: No. 42 (NSC42) held at Jawaharlal Nehru University, India ◆ Meeting titled 'Dundee-NCBS-inStem', Bangalore Symposium held at NCBS, Bangalore, India ◆ Workshop titled "Proteomics, Biomarkers and Diagnostics" at the Regional Centre for Biotechnology, Delhi, India ◆ Conference titled "Bacterial Expressions" held at NCBS, Bangalore, India ◆ Meeting titled "Frontiers in Modern Biology" held at the Department of Biochemistry ◆ Indian Institute of Science, Bangalore, India ◆ Meeting titled "Control in Biological Systems" held at the National Centre for Biological Sciences,Bangalore, India.
2014 The National Seminars in Crystallography-43A IISER, Mohali, India ◆ The Science Academies two-day lecture workshop titled Recent Advances in Biology held at Christ University, Bangalore, India ◆ Zing Conference on DNA polymerases in Biology, Diseases and Biomedical Applications (Cambridge, UK) ◆ Indo Us Conference And Workshop On Recent Advances In Structural Biology & Drug Discovery, at Department of Biotechnology, IIT Roorke.

GAITI HASAN

2010 Natural Sciences Colloquium, Tata Institute of Fundamental Research, Mumbai, India ◆ Confluence 2010, the Indian Academy of Research and Post Graduate Learning, Bangalore, India ◆ Francis Crick Neurosciences Symposium, Cold Spring Harbor Asia, Suzhou, China ◆ The 13th European Fly Neurobiology meeting (Neurofly), Manchester, UK ◆ CME on triplet repeat disorders, Christian Medical College, Vellore, India ◆ University of Cambridge, Cambridge, UK.
2011 Laboratoire de Neurobiologie, ESPCI ParisTech, CNRS, Paris, France ◆ Institut de Neurobiologie Alfred Fessard, CNRS,Gif-sur-Yvette, France ◆ All India Cell Biology Meeting XXXV, NISER, Bhubhaneshwar, India.
2012 Raman Research Institute Colloquium, Bangalore, India ◆ Wellcome-DBT India Alliance mini-symposium, CDFD, Hyderabad, India ◆ Inositide signaling in health and disease, Orange County, Coorg, India ◆ Genes,Circuits and the Development of Behavior, Tata Institute of Fundamental Research, Mumbai, India.

JAYANT B UDGAONKAR

2010 The 35th Mahabaleshwar Seminar on Modern Biology, Mahabaleshwar Bharathidasan University, Palkalaiperur, Tiruchirappalli ◆ The Indo-Japan workshop on 'Frontiers in Molecular Spectroscopy' from Gas Phase to Proteins; Kobe, Japan ◆ Institute of Chemical Technology, University of Mumbai, India ◆ The University –DAE Centre for Basic sciences, Univ of Mumbai, India ◆ IUPAP Council and Commission Chairs Meeting, Delhi ◆ TIFR Weizmann Meeting, TIFR, Mumbai, India ◆ Indian Institute of Technology Madras, India
2011 Chemistry Annual Talks, TIFR, Mumbai.
2012 CSIR meeting Biology 2012 and beyond, Hyderabad ◆ 2nd Annual Conference, Bio World 2012, IIT Delhi ◆ DBS@50, Mumbai ◆ International Physics of Living Systems (iPoLS), INSERM, France.
2013 Gordon Research Conference, Texas. USA ◆ R.P. Mitra Memorial Lecture, University of Delhi ◆ INSA meeting, NCL, Pune.
2014 Weizmann Institute of Science TIFR Interaction Meeting , Israel ◆ 4th Asia Pacific Protein Association (APPA2014) Conference, South Korea.

KS KRISHNAN

2010 DBS meeting, TIFR, Mumbai, India ◆ Prof. P. N. GANAPATI Centennial Commemoration, Andhra University, Visakhapatnam, India ◆ CME of Association of Pharmacologists of India, APICON, Nagpur, India.
2011 INSPIRE Camp at Kannur Kerala, India ◆ TIFR DBS Annual talks, Mumbai, India.
2012 5th SERB School in Neuroscience: NIMHANS Bangalore, India ◆ NISER Bhubaneshwar, India ◆ SERB School in Herpatology: Baripada North Orissa University, India.

K VIJAYRAGHAVAN

2010 EMBO Global Exchange & the Wellcome Trust/DBT India Alliance meeting, Barcelona, Spain ◆ Prof. C.V.Ramakrishnan lecture series,University of Baroda, Baroda, India ◆ Tata Institute Alumni Association, Science Day Public Lecture, Tata Institute of Fundamental Research ◆ Homi Bhabha Centenary Celebrations Invited Lecture, Tata Institute of Fundamental Research.
2010 The Bose Memorial Lecture at the Royal Society, London ◆ Development and Behaviour Trends and Trendsetters Biochemistry Department IISc, Mumbai ◆ Development and Behaviour National Science Day Public Lecture 2010 TIFR Alumni Association TIFR, Mumbai
2011 Bangalore-Milan workshop, Milan, Italy ◆ National Institute of Biomedical Genomics, Kolkata, India.
2012 Developmental wiring in the brain and the regulation of animal behaviour, National Inst. Of Plant Genome Research, New Delhi Foundation Day: JC Bose Lecture New Delhi.

KRUSHNAMEGH KUNTE

2014 ◆ FEBS-EMBO Meeting 2014, Paris, France ◆ Max-Planck Institute for Chemical Ecology, Jena, Germany ◆ 9th International Workshop on the Molecular Biology and Genetics of the Lepidoptera, Kolympari (Crete), Greece ◆ 7th International Conference on the Biology of Butterflies, Turku, Finland ◆ Guest lecture at the Phylogenetics Workshop organized by Dr. Praveen Karanth, CES, IIsc, Bengaluru ◆ Evolution Conference, Raleigh, North Carolina, USA . ◆ ICTS School on Population Genetics and Evolution, IISc, Bengaluru.
2013 EMBO- IndiaBioScience Young Scientist Network Meeting, Bengaluru ◆ Ashoka Trust for Research in Ecology and the Environment (ATREE), Bengaluru, India ◆ National University of Singapore, Singapore ◆ 3rd Training Programme on Taxonomy of Insects and Mites, ICAR Niche Area of Excellence Project on Capacity Building in Taxonomy of Insects and Mites, University of Agricultural Sciences, GKVK, Bengaluru ◆ Rufford India Conference, NCBS, India ◆ Evolution Symposium: Celebrating Wallace, NCBS, Bengaluru. Departmental seminar, Dept. of Biological Sciences, National University of Singapore, Singapore ◆ Indo-US Joint Workshop on Biodiversity Informatics, Ashoka Trust for Research in Ecology and the Environment, Bengaluru, India ◆ Sexual Selection: Ideas and Evidence, CES, IISc, Bengaluru.
2012 YETI (Young Ecologists Talk and Interact) Conference, Wildlife Institute of India, Dehradun, India.

MADHUSUDHAN VENKADESAN

2011 NCBS/Barcelona Collaboration Meeting, NCBS, Bangalore, India ◆ INSPIRE Science Camp, Sree Narayana College, Kannur, India ◆ Summer School on Impedance, EU FP7 meeting (STIFF and VIACTORS), Frauenchiemsee, Germany ◆ Center for Genomic Regulation (CRG), Barcelona, Spain ◆ Staff-Science Talk, NCBS, Bangalore, India ◆ Indian Institute Science, Bangalore, India.
2012 Grant-writing workshop, NCBS, Bangalore, India ◆ Centre for Genomic Regulation (CRG), Barcelona, Spain ◆ Queensland Brain Institute, University of Queensland, Australia ◆ Annual Fellows Meeting of the WellcomeTrust/DBT India Alliance, Hyderabad, India ◆ Indian National Node of Neuroinformatics / International Neuroinformatics Coordinating Facility meeting, Chennai, India ◆ Department of Chemical Engineering, Indian Institute of Science, Bangalore, India.
2013 Centre for Neuroscience, Indian Institute of Science, Bangalore, India ◆ Annual Talks, NCBS, Bangalore ◆ Natural Sciences Faculty Colloquium, Tata Institute of Fundamental Research, Mumbai, India ◆ Center for Applied Mathematics Colloquium, Cornell University, Ithaca, NY, USA ◆ Sibley School of Mechanical & Aerospace Engineering, Cornell University, Ithaca, NY, USA ◆ Department of Mechanical Engineering, Ohio State University, Columbus, OH, USA ◆ Okinawa Institute of Science and Technology Graduate University, Okinawa, Japan. ◆ Engineering, Neuroscience & Health Seminar, University of Southern California, Los Angeles, CA ◆ Institute of Perception, Action and Behaviour, School of Informatics, University of Edinburgh, Edinburgh, Scotland, UK ◆ Department of Mechanical Engineering, University of Liverpool, Liverpool, UK.

MITRADAS M PANICKER

2010 Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram ◆ The Indo-Danish Symposium on Stem Cells and Regenerative Medicine, Odense, Denmark ◆ Neuroscience Update 2010 - SDM Medical College & Hospital, Dharwad.
2011 Bader lab Retreat at Döllnsee , Max Delbruck Center of Molecular Medicin, Berlin (DST-DAAD Program visit) ◆ Wilhelms-Universitat Munster, Germany ◆ Seminars in Neuroscience series University of Pais Vasco (Indo-Spain DST Exchange) ◆ 8th Indo-Australian Biotechnology Conference on Stem Cell Biology. Bangalore, India ◆ European School of Molecular Medicine 2nd Joint Bangalore/Milan Workshop, Milan, Italy.
2012 Kishore Vigyanic Protsahan Yojana, IISCER, Pune ◆ Function at Clinical and Molecular Approached to Drug Discovery at JSS College of Pharmacy, Udhagamandalam.
2013 ISN - 24th Biennial Meeting ISN/ASN 2013 Symposia on Serotonin Receptors, Signaling and Physiology - Co-Chair Cancun, Mexico ◆ Daichi_Sankyo Life Science Research Centre in India, New Delhi ◆ Indo-German Workshop on Regenerative Medicine in Liver Diseases, Institute of Liver & Biliary Sciences (ILBS), New Delhi ◆ International Humboldt Kolleg on Bench to Bedside Translational Research Manipal University, Manipal. ◆ Queratarо Seminarios Departamento de Neurobiología Celular y Molecular, Instituto de Neurobiologia, UNAM México ◆ International Conference on REPROMICS - OMICS in Reproduction & Fertility and 22nd Meeting of ISSRF - Thiruvananthapuram.
2014 Ranbaxy Science Foundation's 20th Annual Symposium on "Regenerative Medicine – Current and Future Perspectives," New Delhi ◆ 10th Indo-Australian Workshop in Biotechnology – Epithelial Development Function and Disease – New Frontiers and Therapies Manipal University, Manipal ◆ Symposium - Stem Cells in Regenerative Medicine - School of Regenerative Medicine (SORM), Manipal University, Bangalore.

MAHESH SANKARAN

2010 Mammal Research Institute, Bialowieza, Poland.
2012 International PAGES Science Workshop, University of Southampton, UK. ◆ Ramalingaswami Re-entry Fellows Conclave, Hyderabad, India ◆ IGBP PAGES workshop, University of Oxford, UK.
2013 Research & Monitoring in the Banni Landscape, Bhuj, Gujarat, India ◆ Curtin University, Perth, Australia ◆ Okinawa Institute of Science & Technology, Okinawa, Japan ◆ Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India ◆ Indo-US Frontiers of Science Symposium, Agra, India.
2014 Jain University, Bangalore, India.

MUKUND THATTAI

2010 Kavli Institute for Theoretical Physics, UCSB, USA ◆ Physics Department Colloquium, University of California in Santa Barbara, USA ◆ I2CAM School, JNCASR, Bangalore, India. ◆ Public Seminar, Bangalore Science Forum, National College, Bangalore, India ◆ Control Theory Satellite Meeting, International Congress of Mathematicians,Hyderabad, India ◆ RIKEN Mathematical Sciences Workshop, Kamisuwa, Japan ◆ WT-DBT Fellows' Meeting Hyderabad, India.
2011 Center for Study of Science,Technology and Policy, Bangalore, India ◆ WellcomeTrust Meeting: Biomedical Science in India, Bangalore ◆ Humboldt Kolleg on Self-Organized Criticality, Bangalore, India ◆ Computational Biology Meeting, Indian Academy of Sciences, Coorg, India ◆ Isaac Newton Institute for Mathematical Sciences, Cambridge, UK ◆ Program on Emerging Paradigms in Physical Biology. NCBS Bangalore, India ◆ EUROSPIN Meeting, NCBS Bangalore, India.
2012 ICTS Discussion Meeting on Theory in Biology, International Centre for Theoretical Sciences, Bangalore, India ◆ International Conference on Mathematical and Theoretical Biology, Pune, India ◆ ICTS Program on Evolutionary Origins of Compartmentalized Cells, NCBS Bangalore, India ◆ NCBS-CRG Discussion Meeting [via video link], Center for Genomic Regulation, Barcelona ◆ Invited talk at the Discussion Meeting on Inference in the Physical Sciences, Royal Society, London ◆ Theoretical Sciences Seminar, JNCASR Bangalore, India

◆ Center for Genomic Regulation, Barcelona, Spain ◆ Meeting on Networks in Biology, Social Science and Engineering, IISc, Bangalore, India ◆ ISMB 2012 Meeting, Long Beach, California, USA ◆ Stanford Medical School, USA ◆ Bangalore Science Forum Annual Science Festival, National Pre University College, Bangalore, India ◆ School on DNA Dynamics and Life Strategies, Niels Bohr Institute, Copenhagen ◆ WT-DBT Fellows' Meeting, Hyderabad, India
2013 ICTP Winter School on Quantitative Biology, Trieste, Italy ◆ Conference on Condensed Matter and Biological Systems, BHU, Varanasi,India ◆ Gene networks in theory and practice. Bangalore India Bio 2013, Bangalore, India ◆ Accelerating Biology 2013, C-DAC,Pune, India ◆ Chemical Engineering Department, IISc Bangalore, India.

MK MATHEW

2010 2-day Joint Academies lecture workshop on ' Protein structure, dynamics and function' at Maharani Lahsmi Ammanni College, Bangalore, India ◆ Frontiers in Biology Seminars held at Sikkim Government College, Gangtok, India ◆ Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India ◆ National Institute for Interdisciplinary Science and Technology, Thiruvananthapuram, India.
2011 DBT Training Programme on "SSR markers and Plant Transformation" Biotechnology Dept UAS – GKVK Campus, bangalore , India ◆ Indian Institute of Science Education and Research, Thiruvananthapuram, India ◆ Indo-Irish Neuroscience Meeting Bangalore , India ◆ Indo-Irish Plant Meeting Bangalore ◆ Institute of Bioinformatics and Applied Biotechnology, Bangalore, India ◆ Bristol-Myers-Squibb, Bangalore, India ◆ INSPIRE Camp at Kannur, Kerala, India ◆ Jawaharlal Nehru Planetarium, Bangalore, India ◆ Analysis and Simulation of Biomolecular Structures meeting organized at the Indian Institute of Science, Bangalore, India ◆ Indian Institute of Science Education, and Research, Thiruvananthapuram, India ◆ KKG Menon Memorial Lecture held at Hindustan Unilever, Bangalore, India ◆ Biotechnology Department, University of Agricultural Sciences, Hasan, India ◆ Indian Institute of Science Education and Research, Thiruvananthapuram, India.
2012 Jubilant Biosys, Bangalore, India ◆ Indo-US Symposium on Structure Dynamics and Mechanics of Biological Membranes,Bangalore, India ◆ SERB School in Neuroscience at NISER Bhubaneswar, Orissa, India ◆ University of Sri Jayewardenepura, Sri Lanka ◆ Basic Neuroscience Course taught at IISER, Thiruvananthapuram ◆ SERC School in Neuroscience, NIMHANS Bangalore ◆ VLTP Programme in Neuroscience University of Jayawardenepura, Sri Lanka.
2013 Cotton College State University. Colloquium: Rice & Salt: Learning how Plants Cope with a Salty Diet ◆ Monsoon School, NCBS: How do Plants Survive When Fields Get Salty? ◆ Basic Neuroscience course taught at IISER, Thiruvananthapuram ◆ SERB School in Neuroscience, Central University of Hyderabad ◆ IBRO Course in Neuroscience,Center for Cognitive Neuroscience & Semantics, University of Latvia Riga, Latvia.

R SOWDHAMINI

2010 ReUnion University, ReUnion Islands ◆ Micro- and Nanotechnology Department of Technical University of Denmark,Copenhagen ◆ Institut for Elektroteknologi, Technical University of Denmark, Copenhagen ◆ The Inaugural Session of COMBIGS'10 (Computational Biology Group in SASTRA) in SASTRA University, Tanjore, India.
2011 International conference entitled "Recent Advances in Bioinformatics" in KIIT, Bhubaneswar, India ◆ Universite de la ReUnion, ReUnion Islands ◆ DTU-Elektro, Copenhagen ◆ International Conference on "Mathematical Biology", Indian Institute of Science, Bangalore, India ◆ Research Seminar in IIIT, Hyderabad, India ◆ Hematological Research between Indo-EU Investigators: Focus on Cancer, Stem Cells, Genomics and Signaling in NCBS, Bangalore, India ◆ Second Eurospin workshop held in NCBS, Bangalore, India ◆ University of Agricultural Sciences Bangalore, India ◆ Research Seminar, Department of Biophysics, University of Manchester, Manchester, U.K.
2012 Department of Biochemistry,University of Cambridge, Cambridge, U.K ◆ Macquarie University, Sydney, Australia ◆ Joint meeting on Open Source Drug Discovery held in Indian Institute of Science, Bangalore, India ◆ Conference on 'Role of High Performance Computing (HPC) in Accelerating Innovation in Biotechnology' held at Lalit Ashok Hotel, Bangalore, India ◆ REAP-Bio lectures held in Jawaharlal Nehru Planetarium, Bangalore, India ◆ Staff-Science talks in NCBS, Bangalore, India ◆ NCBS-BII workshop held in NCBS, Bangalore, India

RAGHU PADINJAT

2010 FASEB Summer Conference, Steamboat Springs, Colorado, USA ◆ EMBO meeting on Molecular biology of *Drosophila* "Crete" meeting, Kolymbari, Greece ◆ Plenary Lecture, Physiological Society of India, Bangalore India ◆ Indian Institute of Science Education and Research, Pune, India ◆ Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science
2011 CRG-Centre de Regulació Genòmica, Barcelona ◆ Indo-Japanese Cell & Developmental Biology Meeting. NCBS,Bangalore, India.
2012 CRG-Centre de Regulació Genòmica , Pompeu Fabra University, Barcelona, Spain ◆ International workshop: Inositide signalling in health and disease, Coorg, India ◆ FASEB Meeting: Phospholipid Metabolism: Disease, Signal Transduction, & Membrane ◆ Divison of Signal Transduction, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, USA ◆ National Cancer Institute, NIH, Frederick, Maryland, USA ◆ Max-Planck Institute for Cell Biology & Genetics, Dresden, Germany ◆ Department of Life Sciences, Jawaharlal Nehru University, New Delhi
2013 TIFR Colloqium, Tata Institute of Fundamental Research, Mumbai, India ◆ Department of Pharmacology, University of California, San Deigo, USA ◆ McLaughlin Research Institute, Montana, USA ◆ Human Genome Meeting 2013, Singapore ◆ Institute for Molecular and Cell Biology, Singapore ◆ Royal Society-DST Meeting on Inositide signalling. NCBS , Bangalore, India.
2014 38th Mahabaleshwar Meeting, Mitochondria, Energetics and Metabolism, Maharashtra, India ◆ Indian Institute of Science Education and Research, Pune, India ◆ Babraham Institute, Cambridge, UK ◆ Department of Pharmacology, University of Cambridge, UK ◆ Department of Physiology and Neuroscience, University College, Lonodn, UK ◆ School of Life Sciences, University of Dundee, UK ◆ FASEB Meeting:Phospholipid Cell Signaling & Metabolism in Inflammation & Cancer, Niagara Fall, USA ◆ Center for Cancer Research, National Institute of Health, Bethesda, Maryland, USA ◆ Centre for DNA Fingerprinting and Diagnostics, Hyderabad, India.

SATYAJIT MAYOR

2010 EMBO Workshop: HEDGEHOG SIGNALING: From developmental biology to anti-cancer drugs. Saint Jean Cap- Ferrat, France ◆ Gordon Research Conference:Lysosomes & Endocytosis Proctor Academy, Andover, New Hampshire, USA ◆ FASEB Summer Research Conferences: Arf Family G Proteins, Carefree, Arizona, USA ◆ Asian Science Camp – 2010. Tata Institute of Fundamental Research, Mumbai ◆ Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany ◆ Beyond the fluid-mosaic: Active construction of Membrane. Tata Institute of Fundamental Research, Mumbai ◆ 13th Carl Zeiss Sponsored International Workshop on FCS and Related Methods. National University of Singapore, Singapore ◆ ASBMB Symposium on Biochemistry of Membrane Traffic: Secretory and Endocytic Pathways, Tahoe City, California, USA ◆ Symposium on 'Stem cells in development and regeneration: From the bench to bedside and back': 76th Annual Meeting of Indian Academy of Sciences, Goa, India.
2011 ASCB 50th Annual Meeting, Philadelphia, USA ◆ ImmunanoMap Symposium, Nijmegen, The Netherlands ◆ FRET at 65: A celebration of Forster, University of Virginia, USA ◆ EMBO/ EMBL SYMPOSIUM - Seeing is Believing, Heidelberg, Germany ◆ Joining Forces Symposium: Biological Membranes, ETH Zurich Hoenggerberg, Switzerland ◆ EMBO Conference on Systems Dynamics of Intracellular Communication (Spatial 2011), Engelberg, Switzerland ◆ The Tay Hayashi Endowed Lecture. Marine Biological Laboratory, USA ◆ Protein Lipidation, Signaling, & Membrane Domains Summer Research Conference, FASEB, Saxtons River, USA.
2012 TWAS 22nd General Meeting, Trieste, Italy ◆ 2011 Annual Meeting. Denver, Colorado, USA ◆ Molecular Biology Cell Course, Institut Pasteur and I Institut Curie, Paris ◆ Keystone Symposium on Members in Motion, Tahoe City, California, USA ◆ NCBS-CRG Joint meeting, Barcelona, Spain ◆ 105th International Titisee Conference on Lipids as organizers of cell membranes, Titisee, Germany.

2013 MBL Physiology Course entitled "Modern Cell Biology using Microscopic, Biochemical and Computational Approaches" WoodsHole, USA ◆ Workshop - Membrane domains: Translating compositional complexity into biological functions Bordeaux, France. ◆ Mechanobiology Conference - Dynamic Architecture of Cells & Tissues ,Singapore ◆ ASCB - Annual Meeting, New Orleans, USA.
2014 KITP Conference : Active Process in Living and Non-living Matter Santa Barbara, USA ◆ APOCB - Congress and ASCB Workshops- Chaired by Dr.Mayor, Singapore ◆ Editorial Board Meeting of Biochemical Journal London, UK ◆ Meetings / Talk at Curie Institute-Paris, IBDM-Marseille, Max Planck Institute-Munich, Universeity Hospital, Heidelberg. Pris, Marseille, Munich, Heidelberg ◆ Marine Biological Laboratory (MBL),WoodsHole, USA ◆ Building the Cell Meeting, organised by Institut Pasteur-France, Paris.

SANJAY SANE

2010 International Conference of Intelligent Unmanned Systems, Bali, Indonesia ◆ Tata Institute of Fundamental Research, Mumbai ◆ Department of Physics, Mysore University, Mysore ◆ Umea University, Sweden ◆ ICTP Workshop on Development and Evolution of Nervous Systems- International Centre for Theoretical Physics, Trieste, Italy ◆ Wright State University, Dayton, Ohio, USA ◆ DST-INSPIRE, Hongirana Public school, Sagar, Shimoga ◆ Jawaharlal Nehru Center for Advanced Scientific Research,Bangalore ◆ Jawaharlal Nehru Planetarium, Bangalore ◆ TIFR Center for Applicable Mathematics, Bangalore ◆ Invited speaker, Gandhi Krishi Vigyan Kendra (GKVK).
2011 Insect Flight Symposium, CAnMove program, Lund University, Sweden ◆ Eglin Air Force Base, US Air Force, Florida, USA ◆ Wright-Patterson Air Force Base, Dayton, Ohio,USA
2012 Symposium: Insect flight and migration, International Conference of Entomology, Daegu, South Korea ◆ 1st Annual Ramanujan Meeting, Organized by IISER Pune, and Department of Science and Technology, Government of India, Pune ◆ Center for Excellence in Basic Sciences, University of Mumbai-DAE, Kalina Campus, Mumbai.
2014 Department of Mechanical Engineering, Purdue, University, West Lafayette, Indiana, USA ◆ Department of Biology, Case Western Reserve University, Cleveland, Ohio, USA ◆ Booz Allen Hamilton Distinguished Colloquium series, Department of Electrical Engineering and Computer Sciences, University of Maryland, USA ◆ Systems Neuroscience Seminar, Howard Hughes Medical, Institute, Janelia Farm Campus, USA ◆ Symposium on Turbulence, Bangalore, India ◆ International Union of Theoretical and Applied Mechanics international conference, Bangalore, India.

PV SHIVAPRASAD

2013 Secondary small RNA silencing in plants, Madurai Kamaraj University ◆ A miRNA superfamily regulates disease resistance in plants. Institute of Bioinformatics and Applied Biotechnology, Bangalore ◆ Artificial induction and maintenance of epigenetic variations. Dundee-NCBS-InStem symposium. ◆ Regulation of disease resistance by miRNAs. International Conference on Biotechnology and Human Welfare, Shastra University.
2014 Role of miRNAs in plant disease resistance. IISc-ETHZ-NCBS conference, February, Indian Institute of Science, Bangalore ◆ Plant Epigenetics. RNAi technology and its Applications, Maharani's College for Women, Bangalore ◆ Transcriptional silencing and epigenetics. University of Agricultural Sciences, Bangalore ◆ Role of two less conserved plant miRNAs. In 'Concepts and mechanisms in plant development' conference organized by the Fellow at NCBS, Bangalore ◆ Epigenetics and transcriptional silencing. University of Agricultural Sciences, Hassan.

SANDEEP KRISHNA

2010 Center for Neural and Cognitive Sciences, University of Hyderabad ◆ Counting genomes: the lysis-lysogeny decision in phage lambda' at CCMB, Hyderabad ◆ Workshop on Genome Maintenance and Consequences, at the Niels Bohr Institute, Copenhagen ◆ Small Systems Biology conference, Dragoer, Denmark.
2011 Workshop on Signals and Space: Spatio-temporal patterns in simple bio-systems, at the Niels Bohr Institute, Copenhagen, Denmark ◆ 'Combining theory and experiments to understand sugar regulation in bacteria' at an ICTS discussion meeting on Systems Biology/ Systems Neuroscience, Bangalore ◆ 'Counting genomes: the lysis-lysogeny decision in temperate bacteriophage' at IISER, Pune ◆ Discussion meeting on Computational Biology in India - status and prospects, Orange County, Coorg.
2012 Workshop on Dynamics and Regulation of Biomolecular Networks, Institute for Computational and Theoretical Studies, Hong Kong Baptist University ◆ Benefits of cooperation and communication in bacteria' at JNCASR, Bangalore ◆ Krogerup summer school on "DNA dynamics and life strategies" at Humlebaek,Denmark ◆ International Conference on Networks in Biology, Social Science and Engineering, Indian Institute of Science, Bangalore ◆ International Conference on Mathematical and Theoretical Biology, Pune.

SUDHIR KRISHNA

2010 International conference on cancer biology, IIT Madras, Chennai, Feb 2010 ◆ Kidwai Memorial Institute of Oncology, Bangalore, March 2010 ◆ ILBS-NIH Meeting, New Delhi, March 2010 ◆ St. John's Medical College, Bangalore, April 2010 ◆ iCeMS-InStem-NCBS mini symposium, Bangalore, August 2010 ◆ Department of Genetics, University of Cambridge, UK, September 2010 ◆ Department of Oncology, University of Cambridge, Hutchison-MRC, September 2010 ◆ St. Joseph's college, Bangalore, September 2010 ◆ The InStem Annual symposium, Bangalore, November 2010 ◆ XIX Annual conference of Association of Gynaecologists of India, Bangalore, November 2010 ◆ CME on CML, organized by BMS, Bangalore, November 2010 ◆ 79th Annual Meeting of the Society of Biological Chemists (India), Indian Institute of Science, Bangalore.
2011 International conference on frontiers in carcinogenesis and cancer prevention: scientific advances and public health initiatives, Bangalore ◆ Institute Curie, Paris, France ◆ Genentech, San Francisco, USA ◆ American Association of Cancer Research International Conference on "New Horizons in cancer research" New Delhi ◆ University of Delhi, South Campus, Delhi
2012 "NANOBIO 2012, 2nd Internatinal conference on Nanotechnology at the Bio-Medical Interface, AIMS, Kochi, Kerala ◆ 31st Annual convention of the Indian Association for Cancer Research, ACTREC, Mumbai, India ◆ Manipal Life Sciences Centre, Manipal University, India ◆ Curie-NCBS meeting, NCBS, Bangalore, India ◆ Asia Knowledge 2012 Symposium on Stem cells. Bangalore, India ◆ XXXVI Cell Biology meeting, BARC, Mumbai, India.
2013 32nd Annual convention of Indian Association for Cancer Research, Delhi, India ◆ DST INSPIRE Program, Manipal University, India ◆ Christian Medical College, Vellore, India ◆ Department of Oncology, University of Cambridge, UK ◆ Indo-UK Oncology Summit, Chennai, India ◆ IX DAE-BRNS Life Sciences Symposium, Mumbai, India.
2014 Cancercon: international conference on cancer, IIT Madras, Chennai ◆ BioAsia's drug discovery conference, Hyderabad ◆ Indo-Australian workshop on biotechnology: Epithelial development, function and disease-new frontiers and therapies, Manipal University, Manipal ◆ Centre for Cellular and Molecular Biology, Hyderabad.

SHACHI GOSAVI

2010 Workshop on School of Information Technology, JNU, Delhi ◆ Protein folding at the "Topics in Biophyiscs". Workshop at Department of Physics, Mysore University, India ◆ The "Frontiers in Molecular Spectroscopy: From Gas Phase to Proteins" conference, Kobe, Japan. ◆ The Theoretical Chemistry Symposium, IIT, Kanpur ◆ IMI, Indian Institute of Science, Bangalore, India.
2011 Series of 4 teaching lectures on "Protein folding" in the Inorganic and Physical Chemistry Dept., Indian Institute of Science, Bangalore ◆ The "Biomolecular simulations: Algorithms and Applications" conference at the JNU, Delhi,India ◆ The Bioinformatics Institute, A*STAR, Singapore ◆ International Conference on Biological Physics, San Diego, USA.
2012 NCBS-BII Workshop, National Centre for Biological Sciences, Bangalore, India ◆ The Weizmann Institute of Science, Israel.

SUMANTRA CHATTARJI

2010 Plenary Speaker, FRAXA Research Foundation Investigators Meeting, Fragile X: From Basic Neuroscience to Improved Clinical Care, Durham, NH, USA (2010)
2011 Invited Speaker: International Meeting for Autism Research (IMFAR). San Diego, USA ◆ M.I.N.D. Institute, UC Davis, USA.
2012 Invited Speaker:7th Annual Amygdala, Stress and PTSD Conference, Uniformed Services University, Bethesda, MD, USA ◆ Invited Speaker:Workshop on Brain Plasticity, Collegium Helveticum, University and ETH of Zurich, Rockefeller University, New York, USA ◆ Plenary Speaker, Dutch Endo-Neuro-Psycho (ENP) Conference, Lunteren, Holland ◆ Invited Speaker:Gordon Research Conference on "Fragile X and Autism-related Disorders", Stonehill College, MA, USA ◆ Invited Speaker:Frontiers in Stress and Cognition: From Molecules to Behavior, Ascona, Switzerland.
2013 Invited Speaker, Japanese Neuroscience Society, Kyoto, Japan ◆ Chair and Invited Speaker, MCCS-Asia Symposium, Kyoto, Japan ◆ Keynote Lecture, IUPS 2013, The Physiological Society, Birmingham, UK ◆ Keynote Address, Annual Meeting, Pavlovian Society, Austin, TX, USA ◆ Invited speaker, "Long-term potentiation: enhancing neuroscience for 40 years", Royal Society, UK ◆ Invited speaker, Neuroscience Seminar Series, University of Oxford, UK.
2014 Invited speaker, Cold Spring Harbor, Asia meeting on ""Neural Circuit basis of Behavior and its Disorders", Suzhou, China.

UMA RAMAKRISHNAN

2010 CCMB, Laboratory for Conservation of Endangered Species, Hyderabad ◆ Workshop on Conservation Genetics, Student Conservation Science Conference, Bangalore.
2011 Raffles Museum, National University of Singapore, Singapore ◆ Departmental Seminar, Biological Sciences, National University of Singapore, "Why numbers are not enough: genetic insights for tiger conservation" ◆ Invited Presentation, Singapore Zoo -" Why numbers are not enough: genetic insights for tiger conservation" ◆ Contributed Presentation, 'Phylogeography' session, International Meeting of the Society for Biogeography, Crete, Greece.
2012 Departmental Colloquium, Tata Institute of Fundamental Research, Mumbai, "Numbers versus connectivity" ◆ Plenary Talk, Society for Conservation Biology, Asia meeting. ◆ Workshop, Conservation genetics, Society for Conservation Biology, Asia meeting ◆ KVPY Science camp, IISER Pune.
2013 International Biogeography Congress, Miami ◆ Nehru Memorial Museum and Library, New Delhi Session on "Using molecular tools in conservation" as part of an international workshop on otter conservation, NCBS, Bangalore ◆ Evolution Symposium: Celebrating Wallace NCBS,Bangalore ◆ Departmental Seminar, Stanford University-"Why does the Indian subcontinent have few endemic mammals?" ◆ Young Investigator Meeting, India ◆ 'Hot Topics' session, International Meeting of the Society for Biogeography, Miami, Florida.

UPINDER S BHALLA

2010 Computational Cell Biology, Hinxton, USA ◆ Memory, smell and neuronal networks. Aberdeen, UK ◆ Multiscale models of memory: the interface between chemical and electrical signaling. Aberdeen, UK ◆ Optical probing of memory network connectivity. Delhi, India ◆ Systems Biology Centers of New York Annual Meeting, Mount Sinai School of Medicine, New York, USA ◆ CSHL Cognitive and Computational Neuroscience course, Suzhou, China ◆ Computational and Neural Systems Annual Meeting, San Antonio, Texas ◆ Modelling. Workshop on the Development of Behaviour: Emergent Properties of Nervous Systems, Trieste, Italy ◆ Biophysics. Workshop on the Development of Behaviour: Emergent Properties of Nervous Systems, Trieste, Italy ◆ Biochemistry and Multilevel Models. Workshop on the Development of Behaviour: Emergent Properties of Nervous Systems, Trieste, Italy ◆ How animals track odours: Behaviour and neuronal processing. Workshop on the Development of Behaviour: Emergent Properties of Nervous Systems,Trieste, Italy ◆ 3rd INCF Congress of Neuroinformatics, Kobe, Japan.
2011 Motifs, Molecules and Movement: states that emerge from molecular traffic. Mathematical Workshop, IISc, Bangalore, India ◆ NCBS-Edinburgh workshop, Bangalore, India ◆ Ireland-India Conference on Neuroscience. Indian Academy of Sciences, Bangalore, India ◆ Workshop and Symposium on Mathematical Physiology, IISER Pune, India ◆ Workshop on Learning and Plasticity CIEM, Manseille, France ◆ 4th INCF Congress of Neuroinformatics, 2011, Boston, USA ◆ Workshop: Ecole Polytechnique Federale De Lausanne (EPFL), Laboratory of Neural Microcircuitry (LNMC) and the Blue Brain Project (BBP) in Brain Mind Institute (BMI), Switzerland ◆ Bio Grid and Cloud Workshop, Cambridge, UK ◆ 4th DST- SERC school on Systems and Cognitive Neuroscience, NBRC, Delhi ◆ Development of Behaviour emergent properties of nervous system, Trieste, Italy.
2012 Brain science awareness workshop, Indian Statistical Institute, Bangalore, India ◆ INCF Seminar, Karolinska Institute, Stockholm, Sweden ◆ Workshop: From cellular/network models to tissue simulation, Stockholm, Sweden ◆ Computational, Neuroscience Short Course, ISI, Bangalore ◆ Erasmus Mundus Launch Meeting, Strasbourg, France.
2013 Computational and Cognitive Neurobiology, CSHL Summer School , China. ◆ Transylvanian Experimental Neuroscience Summer School, Romanian Institute of Science and Technology, Romania ◆ INCF meeting, Karolinska Institute, Stockholm, Sweden ◆ 3rd Eurospin meeting , University of Freiburg, Germany".
2014 Kavil Institute of Theoretical Physics Workshop on Neurophysics of Space , Time and Learning, Santa Barbara and COSYNE, Salt Lake city, USA ◆ Review committee meeting ,CRG Barcelona, Spain ◆ "Memory traces and sequenes" Trinity College, Dublin ◆ Eurospin Annual Meeting, Edinburgh.

VATSALA THIRUMALAI

2011 Neuromodulatory control of circuits in a developing vertebrate, NCBS-Edinburgh Workshop on Neurodevelopmental Disorders and Neuroinformatics, Bangalore ◆ An inside look at Spinal Muscular Atrophy, Harvard-inStem Collaborative Meeting, Bangalore ◆ The rhythm is gonna get you – rhythm generators in your body, Biotechcellence, Anna University, Chennai ◆ Zebrafish as a Model Organism in Biology, Workshop on Emerging Model Systems to Study Stem Cell Biology and Regenerative Medicine, inStem, Bangalore ◆ The development of neural circuits controlling movement, Second Eurospin Workshop, NCBS, Bangalore.
2012 Assembling a network: Lessons from the zebrafish motor system, Indo-Japan Meeting on Developmental Biology, NCBS, Bangalore ◆ Neuromodulation of descending motor control in a developing vertebrate, Asia-Pacific Developmental Biology Meeting, Taipei, Taiwan ◆ Neuromodulation of descending motor control in a developing vertebrate, Brandeis-NCBS collaborative meeting, NCBS, Bangalore ◆ Under construction, but in operation: strategies from the developing brain, Centre for Neural Science, IISc, Bangalore ◆ Descending motor control during development, INCF workshop, IIT and IMSc, Chennai.
2013 Development of circuits controlling swimming in zebrafish, NCBS-RIKEN Collaborative Meeting, Bangalore ◆ Annual Fellows Meeting, Wellcome Trust- DBT India Alliance, Hyderabad ◆ From Molecules to Motion: Development of Motor Circuits in the Zebrafish Model System, Annual meeting of Indian Society of Developmental Biologists, TIFR, Mumbai.
2014 Mind the gap: Gap junctions and neural circuit assembly in larval zebrafish, Symposium on 'Emergence of motor patterns in developing vertebrates', International Congress of Neuroethology, Sapporo, Japan ◆ Mind the gap: Gap junctions and neural circuit assembly in larval zebrafish, Plenary Lecture, Molecular Biophysics Unit Annual Retreat, Indian Institute of Science, Bangalore ◆ Dopamine, Manganese and Locomotion, Frontiers in Biology and Medicine, Zurich-Bangalore Workshop, Bangalore.

YAMUNA KRISHNAN

2010 Zing Nucleic acids Conference Cancun, Mexico ◆ Nucleic Acids Conference NACON-VIII, Sheffield ◆ Indo-French Seminar on Soft Interfaces, Paris ◆ Biophysical Society Meeting, San Francisco, California ◆ *ibid*: Dept of Chemistry, Carnegie Mellon University, Pittsburgh, USA ◆ *ibid*: LMU, Munich, Germany ◆ *ibid*: Dept of Physics, University of Cambridge ◆ 79th Society of Biological Chemists (India) meeting. IISc, Bangalore ◆ First Blueprint, now Bricks - DNA as construction material on the Nanoscale. TIFR Hyderabad Foundation Stone Ceremony, Hyderabad ◆ *ibid*: Public Lecture at St. Joseph's College.
2011 DNA-17, Caltech, Pasadena, USA ◆ Chemistry and Biology of Nucleic Acids Conference, Cambridge UK ◆ European Symposium on Bioorganic Chemistry, Gregynog, Wales ◆ 46th EUCHEM Conference on Stereochemistry (The Bürgenstock Conference) ◆ Brünnen, Switzerland ◆ *ibid*: Dept of Biological Sciences, National University of Singapore ◆ *ibid*: Institut Curie, Paris, France ◆ *ibid*: MRC Laboratory of Molecular Biology, University of Cambridge, UK ◆ *ibid*: RCE Mechanobiology, National University of Singapore, Singapore ◆ Indo-European Symposium on Frontiers of Chemistry, NISER, Bhubaneshwar ◆ R. A. Mashelkar Endowment Lecture, National Chemical Laboratories, Pune.
2012 Award Lecture: Young Investigator Meeting 2012, Boston, USA. ◆ FNANO-2012, 9th Annual Conference,Foundations of Nanoscience, Snowbird, Utah ◆ Miami 2012 Winter Symposium, Nanotechnology in Biomedicine. Jointly organized by Nature Nanotechnology, Nature Medicine and Nature Biotechnology ◆ International Conference on Riboregulation. Shanghai, China ◆ Zing Conference on Nucleic Acids, Cancun, Mexico ◆ *ibid*: Dept of Biological Engineering, Massachusetts Institute of Technology, Boston ◆ *ibid*: University of Frankfurt, Frankfurt, Germany ◆ *ibid*: ETH Zurich, Switzerland ◆ Karnataka Science and Technology Academy, Annual Meeting ◆ Guha Research Conference, Shillong ◆ Complex Chemical Systems. Indo German Conference, IISER Bhopal ◆ Molecular DNA devices in Living Systems. Guha Research Conference, Shillong ◆ *ibid*: ASET Colloquium, Tata Institute of Fundamental Research ◆ *ibid*: Recent Trends In Biology, University of Pune. ◆ Colloquium, BSBE Dept, Indian Institute of Technology ◆ Pfizer Symposium, Organic Chemistry Department, Indian Institute of Science ◆ Young Investigator Meeting 2012, Lonavala.
2013 Indo-German meeting on Selective Regulation, Kloster Banz, Germany ◆ Indian National Science Academy and Leopoldina Academy of Sciences, Germany, Indo ◆ German Symposium, Halle ◆ CIPSM, Scientific Oktoberfest, LMU, Munich ◆ External speaker, NMR and protein dynamics in Structural BiologyBudapest, Hungary ◆ RSC Roadshow in India, Bangalore, India ◆ The 2012 Oration, Annual Meeting of Academia Ophthalmologica Internationalis ◆ Hyderabad, India ◆ Molecular DNA devices in Living Systems; Dept of Chemistry, University of Chicago, Chicago ◆ *ibid*: Dept of Chemistry & Biochemistry, University of Maryland, Baltimore ◆ *ibid*: University of Goettingen, Goettingen, 9th May 2013 ◆ *ibid*: Dept of Biological Sciences, Columbia University, New York ◆ *ibid*: Dept of Chemistry, New York University, New York ◆ *ibid*: Institut Curie, Paris ◆ All India Cell Biology Conference,Bangalore ◆ NanoIndia, Trivandrum ◆ International Symposium on Challenges in Chemical Biology, Kolkata.
2014 Invited Speaker: Future Research Initiatives at the MPI, Max Planck Institute, Biochemistry, Martinsreid, Munich, Germany.

MSc WILDLIFE PROGRAM: MASTERS COURSE IN WILDLIFE BIOLOGY AND CONSERVATION

The Masters course in Wildlife Biology and Conservation is offered by National Centre for Biological Sciences in partnership with Centre for Wildlife Studies and Wildlife Conservation Society – India

Wildlife Program: Masters course in Wildlife Biology and Conservation (Should carry a box or statement: The Masters course in Wildlife Biology and Conservation is offered by National Centre for Biological Sciences in partnership with Centre for Wildlife Studies and Wildlife Conservation Society – India)

On any day from January to March in 2014, the MSc wildlife students would be diving in coral reefs off the coast of Andamans and Lakshadweeps, following herds of elephants and large herbivores in the Western Ghats, tracking carnivores in West Bengal, following poachers in Tamil Nadu, monitoring vulture nests in Maharashtra or catching bats in caves. This was all part of their dissertation projects, spread across 10 states and union territories. They had started preparing for this from July 2013; in fact, from the day they joined the course in July 2012, dissertation project had always been in their mind. Three semesters of coursework had prepared them for this. Twenty two papers, offered by eminent faculties from NCBS, Centre for Wildlife Studies and other institutions covered several major disciplines in ecology, mathematics, statistics and social sciences such as history, politics, policies and law that impinge on conservation. The courses also gave the students hands on experience in lab methods in conservation genetics, hormonal analysis, and GIS and remote sensing, an in science communication through professional and popular writing and presentations. Most of important of all, in every semester they spent nearly several weeks in wilderness areas.

The first such trip was to the rainforests on Periyar Tiger Reserve, where the students sharpened their natural history skills, learning to identify plants, fishes, frogs, reptiles, birds and mammals. This also provided an opportunity for them to design and implement research projects, which included posing research questions, sampling of plant and animal populations, data analysis and scientific report writing. Over a period of 20 days, the students in small groups and together

implemented five projects. Two of these were at the request of the Forest Department - on road kills of animals and impact of high-tension transmission lines through Reserve on the distribution of mammals and birds. Three other projects were on behavioral ecology of frogs, making use of their high abundance during northeast monsoon. Twenty days in Periyar Tiger Reserve helped the students immensely to contrast the concepts and theories in ecology and statistics developed in classrooms with data from the real world!

Perhaps the most exciting field visit was to Bhadra Tiger Reserve was with Dr.George Schaller, the legendary wild biologist and conservationist who has inspired several generations of wildlife biologists across the world. In Bhadra the students also spent several days practicing the estimation and analysis of animal populations using photo capture-recapture and distance sampling, guided by Dr.Ullas Karanth and his team who have pioneered these methods.

No less exciting was the course in Marine and Coastal Ecology conducted at ANET field station in Andaman Island and led by Dr.Rohan Arthur of Nature Conservation Society and Dr.Naveen Namboothri of Centre for Ecological Sciences. After completing a PADI Certificate course in open water diving, the students spent grueling 15 days, when classroom lectures and field practical followed each other from dawn to bed time. Here also students implemented research projects that involved diving into coral reefs for several hours, walking through impenetrable mangrove forests and walking several kilometers of coastline.

People are at the centre of applied conservation; therefore, the papers in Conservation in Practice and Social Science Research Methods offered by Dr. Krithi Karanth had strong field practical components. The students visited conservation landscapes which are conflict ridden to interact with forest officials and local communities. In small groups, they visited six coastal states to interview local communities and stakeholders on the status of marine fisheries.

The students began planning their dissertation projects in July 2013, with theoretical insights gained from classroom lectures and practical experience gained from project implementation in several situations. After several rounds of discussions with faculties and a public seminar to defend their proposals, they were ready with their projects in November 2013. When finalized, these projects were spread over 10 Indian states and union territories. The research topics included coral reef recovery, ecology of large herbivores such as elephants and gaur, carnivores and butterflies in human modified landscapes, nesting success in highly endangered vultures and impact of poaching on wetland bird communities. With the challenging task of obtaining research permits from 10 states completed in record two months, and with funding from the Department Science and Technology, the students left NCBS for their project sites in the last week of November 2013, and began their projects very soon. We made sure that their thesis advisors visited them soon afterwards in order to make sure that the projects had a smooth start. Nearly 30 faculties from 13 institutions are involved in guiding the students; without such a participation, 15 research projects of such geographical and topical diversity would not be possible. The students would return to NCBS in the first week of May 2014, and spend the next two months in data analysis and writing their thesis, which are due for submission in the second week of July 2014.

Continuing support to alumni is as important as support to the current students. We support them in getting their thesis published in peer reviewed journals, in grant applications and in seeking admission for higher education. Last two years saw the publication of several papers by our alumni from their Master's thesis. Out of 60 alumni that we presently have, four completed their Ph.D in 2013-14 and 20 others are doing their Ph.D. Most of the others are working with conservation organizations, and one is with the Indian Forest Service. Two of our alumni received national awards for their conservation achievements and another got a best publication award from the Journal of Applied Ecology.

In 2012-13, we also completed an external review of the Masters course by a panel consisting of Dr.Paul Krausman (Professor of Wildlife Management, University of Montana), Dr.Barry R. Noon (Professor, Department of Fish, Wildlife and Conservation Biology, Colorado State University) and Dr.Mewa Singh FASc (Professor, Department of Psychology and Animal Behavior). The Masters course continued to attract the participation of nearly 40 faculty from 20 institutions; without their support it would be impossible to offer this course.

- **Dalvi, S., Sreenivasan, R. and Price, T.** (2013) Exploitation in northeast India. Science, 339:270.
- **Kohli, M., Sankaran, M., Suryawanshi, K. and Mishra, C.** (2014) A penny saved is a penny earned: lean season foraging strategy of an alpine ungulate. Animal Behavior, 92: 93-100.
- **Nayak, R.R., Srinivas, V. and Krishnaswamy, J.** (2014). Fire and grazing modify grass community response to environmental determinants in savannas: Implications for sustainable use. Agriculture, Ecosystems and Environment, 185: 197– 207.
- **Punjabi, G., Ravi Chellam and Vanak, AT.** (2013) Importance of native grassland habitat for den-site selection of Indian foxes in a fragmented landscape. PLOS One, 8: e76410.
- **Srivathsa, A, Karanth, KK, Jathanna, D, Kumar, NS and Karanth, KU.** On a Dhole Trail: Examining ecological and anthropogenic correlates of Dhole (*Cuon alpinus*) habitat occupancy in the Western Ghats of India. PLOS One, 9: e98803.
- **Srinivasan, U., Quader, S.** (2012). Patterns of species participation across multiple mixed-species flock types in a tropical forest in northeastern India. Journal of Natural History, 46, 43–44
- **Gangal, M.S., Arthur, R., Alcoverro, T.** (2012). Structure and dynamics of South East Indian seagrass meadows across a sediment gradient. Aquatic Botany, 98, 34– 39.
- **Prakash, N., Mudappa, D., Raman, T.R.S., Kumar, A.** (2012). Conservation of the Asian small-clawed otter (*Aonyx cinereus*) in human-modified landscapes, Western Ghats, India. Tropical Conservation Science, 5, 67-78
- **Srinivasaiah N.M, Verma, S., Anand, V.D., Gopalakrishna, S.P., Avinash, K.G.** (2012). Ecology, Conservation and Management of the Asian Elephant in Bannerghatta National Park, southern India. A Rocha India/ANCF: Asian Elephant Ecology and Conservation Reference Series No.1.
- **Srinivasaiah N.M., Anand V.D., Vaidyanathan, S., Sinha, A.** (2012). Usual Populations, Unusual Individuals: Insights into the Behavior and Management of Asian Elephants in Fragmented Landscapes. PLOS ONE, 7, e42571.
- **Sridhara, S., Edgaonkar, A., Kumar, A.** (2013). Understorey structure and refuges from predators influences habitat-use by a small ungulate, the Indian chevrotain (*Moschiola indica*). Ecological Research, 28,.427-433.
- **Jadeja S.V., Prasad S., Quader, S., Isvaran, K.** (2013). Antelope mating strategies facilitate invasion of grasslands by a woody weed. Oikos, doi: 10.1111/j.1600-0706.2013.00320.x.
- **Nair, T., Thorbjarnarson,J.B., Aust, P., Krishnaswamy, J.** (2012). Rigorous gharial population estimation in the Chambal: implications for conservation and management of a globally threatened crocodilian. Journal of Applied Ecology, 49, 969-1194.
- **Nair, T., Krishna, Y.C.** (2013). Vertebrate fauna of the Chambal River Basin, with emphasis on the National Chambal Sanctuary, India. Journal of Threatened Taxa, 5, 3620-3641..
- **Choudhary, S., Dey, S., Sagar, V., Nair, T., Kelkar, N.** (2012). River dolphin distribution in regulated river systems: implications for dry-season flow regimes in the Gangetic basin. Aquatic Conservation: Marine and Freshwater Ecosystems, 22: 11–25.
- **Kohli, M., Sankaran, M., Suryawanshi, K. and Mishra, C.** (2014) A penny saved is a penny earned: lean season foraging strategy of an alpine ungulate. Animal Behavior (in press).
- **Mondol, S. Sridhar, V., Yadav, P., Gubbi, S. and Ramakrishnan, U.** (2014) Tracing the geographic origin of traded leopard body parts in the Indian subcontinent. Conservation Biology DOI: 10.1111/cobi.12393.
- **Chakravarty, R. and Isaac, S.** (2013). Observations on Gonyosoma oxycephalum (Boie, 1827) predating upon cave bats in the Andaman Islands, India. SAURIA, Berlin, 36: 55–58.
- **Joshi A., Vaidyanathan S, Mondol S, Edgaonkar A and Ramakrishnan, U.** (2013). Connectivity of tiger (Panthera tigris) populations in the human-influenced forest mosaic of Central India. PLOS One, 8: e77980.

HONORS AND AWARDS 2010-2014

APURVA SARIN

2010 Fellow, Indian Academy of Sciences, Bangalore.

ASWIN SAI NARAYAN SESHASAYEE

2011 Ramanujan Fellowship (2011)
2013 Associate of the Indian Academy of Sciences

DEEPA AGASHE

2013 INSPIRE Faculty Award, Department of Science and Technology, India

DEEPAK T NAIR

Memberships (of societies and decision-making bodies)
Society of Biological Chemists ◆ Indian Crystallographic Association ◆ Member, Guha Research Conference

GAITI HASAN

2011 Chaire Joliot visiting scientist at the ESPCI, ParisTech, CNRS, Paris, April/May, 2011.

JAYANT UDGAONKAR

2011 Prof. G N Ramachandran Gold Medal for Excellence in Biological Sciences and Technology ◆ Distinguished Alumnus Award, Indian Institute of Technology, Madras
2013 Elected Fellow,The World Academy of Sciences (TWAS) in 2013
Editors Guest Editor, Section on Folding and Binding, Curr. Opin. Struct Biol. (2013) ◆ Member, Editorial Board of Protein Engineering, Design and Selection (2003-) ◆ Member, Editorial Advisory Board of Biochemistry (2013-)

K VIJAYRAGHAVAN

2010 Fellow of TWAS, The Academy of Sciences For The Developing World
2011 Doctor of Sciences, Honoris Causa, 2011, University of Edinburgh
2012 Fellow of Royal Society
2013 Padma Shri
2014 Foreign Associate of The Us National Academy of Sciences
Memberships (of societies and decision-making bodies)
Member, Science Advisory Council to the Cabinet 2012-

KRUSHNAMEGH KUNTE

2012 Ramanujan Fellowship, 2012 – 2017

MADHUSUDHAN VENKADESAN

2011 WT-DBT India Alliance Intermediate Fellowship

MAHESH SANKARAN

2013 Kavli Frontier of Science Fellow, 2013
Editors Associate Editor, Conservation & Society

MUKUND THATTAI

2010 WT-DBT India Alliance Intermediate Fellowship
2011 Prix Ars Electronica Honorary Mention
2012 Highlight ISMB Meeting of the International Society for Computational Biology
Memberships (of societies and decision-making bodies) Member of Program Committee of the International Centre for Theoretical Studies
Editors Academic Editor for the open-access journal *PLoS ONE*

P.V. SHIVAPRASAD

2013 Ramanujan Fellowship, Department of Science and Technology, Government of India, 2013-2017.

R SOWDHAMINI

2010 Coordinator, Eighth Asia Pacific Bioinformatics Conference in Bangalore
2011 Bharat Jyoti Award and Glory India Gold Medal
2012 Indira Gandhi Excellence Award
2013 Fellow of Indian Academy of Sciences, Bangalore
Memberships (of societies and decision-making bodies)
Member, Bioinformatics Taskforce of Department of Biotechnology since 2013
Editors Academic Editors of *PLoS ONE, BMC Bioinformatics* and in the Editorial Board of *Journal of Biomolecular Structure and Dynamics, Biology Direct and International Journal of Knowledge Discovery in Bioinformatics*

RAGHU PADINJAT

2014 Cambridge-Hamied Visiting Lectureship

SANJAY P SANE

Memberships (of societies and decision-making bodies) Society of Integrative and Comparative Biology (1996-) ◆ Society of Experimental Biology (2005-) ◆ International Society of Neuroethology (2007-) ◆ Biology letters (2012- date) ◆ Frontiers in Neural Circuits (2010-date) ◆ Journal of Neurophysiology (2014- date)

SATYAJIT MAYOR

2010 TWAS Prize in Biology ◆ EMBO Global Lecturer ◆ JC Bose Fellowship, DST, 2006-2011 (renewed till 2016).
2012 Infosys Prize for Life Sciences
2013 Distinguished Alumnus of IIT Mumbai ◆ Elected EMBO Fellow
Memberships (of societies and decision-making bodies)
President , Asia Pacific Organization of Cell Biology (APOCB), 2014-2015 ◆ Invited Fellow, Royal Society of 3.Chemistry, 2014
Fellow, EMBO, 2013, Chair of Task force for Centres of Excellence, DBT, Chair of Task Force for Basic Biology, DBT
Editors Editorial Board, Biochemical and Biophysical Research Communications 2014-present ◆ Editorial Board, Cell 2008-present ◆ Editorial Board, Journal of Cell Science, 2011-present

SHACHI GOSAVI

2010 Ramanujan Fellowship

SUDHIR KRISHNA

2010 Cambridge Hamied Visiting lectureship
2012 Chairman, Cancer Task Force, Department of Biotechnology, Govt of India 2012- 2014
Memberships (of societies and decision-making bodies) 2012 - Member, Science and engineering research board, Department of Science and Technology, Govt of India: Program advisory committee of biophysics, biochemistry, molecular biology and microbiology. ◆ 2014- Member, Research Advisory Council, All India Institute of Medical Sciences,

SUMANTRA CHATTARJI

2014 Honorary Professor, School of Clinical Sciences, University of Edinburgh
Fellow, Indian Academy of Science, Bangalore
2013 Chair, Gordon Research Conference on "The Amygdala in Health and Disease"
2011 Vice Chair, Gordon Research Conference on "The Amygdala in Health and Disease" ◆ Chair, Organizing Committee, Indian-American Kavli Frontiers of Science Symposium
Memberships (of societies and decision-making bodies) Member, Professional Development Committee, Society for Neuroscience (2012) ◆ Member, Annual Meeting Advisory Group, Society for Neuroscience (2010)
Editors: Editorial Board, "Molecular Brain" (2011) ◆ Editorial Board, "Journal of Neuroscience Methods" (2011) ◆ Associate Editor, "Frontiers in Behavioral Neuroscience" (2010) ◆ Editorial Board, "Journal of Neurophysiology" (2008-present) ◆ Associate Editor, "Neural Plasticity" (2006-present)

UMA RAMAKRISHNAN

2010 Ramanujan Fellowship, Department of Science and Technology, Government of India
Member, National board for wildlife, Government of India
2011 Senior Research Visiting Fellow, Department of Biological Sciences, National University of Singapore
2012 Outstanding Scientist Award, Department of Atomic Energy
2013 INK Fellow

UPINDER S BHALLA

Memberships (of societies and decision-making bodies)
2011-2012 Member, INCF Training Committee. ◆ 2011- Member, NeuroML steering committee. ◆ 2010-2012 Member, INCF Multiscale Modeling Oversight Committee. ◆ 2010- Member, Governing Board, International Neuroinformatics Coordination Facility. ◆ 2010- Member, Program Committee, Neuroinformatics Meeting 2011 (Boston, MA). ◆ 2009-2014 Chair, Neurosciences Task Force, Department of Biotechnology

Editors Journal of Computational Neuroscience ◆ Neuroinformatics ◆ Frontiers in Neuroscience

VATSALA THIRUMALAI

2010 Wellcome Trust – DBT India Alliance Intermediate Fellowship Award 2010-2015.
Editors Editorial Board, Journal of Neurophysiology (2014-2017)

YAMUNA KRISHNAN

2010 Wellcome-Trust-DBT Alliance Senior Research Fellowship ◆ BK Bachhawat International Grant for Young Scientists.
2012 YIM-Boston Young Scientist Award ◆ RNA Society Fellowship
2013 Shanti Swarup Bhatnagar Award
2014 The AVRA Young Scientist Award (AV Rama Rao Foundation award for the best scientist under 40)
Editors Editorial Advisory Board, ChemBioChem (Wiley Interscience) 2010 ◆ Associate Editor, Nanoscale (RSC Publishing) 2013 ◆ Editorial Advisory Board, Bioconjugate Chemistry (American Chemical Society) 2013. ◆ Member, IUPAC (Division-III Biomolecular Chemistry) for 2014-15

OBAID SIDDIQI

2011 Homi Bhabha Life Time Achievement Award (2011)

SUPPORTING OUR SCIENCE

RESEARCH FACILITIES OVERVIEW

NCBS is now 32 groups strong and 22 years old. Even as we approach steady-state in numbers, we continue to strive to be nimble in our research directions. Our six research areas (htpp://www.ncbs.res.in/research_areas.htm) have all extended their horizons. The Biochemistry, Biophysics and Bioinformatics group have ventured into NMR work in a big way. The fledgling Institute for Stem Cell Biology and Regenerative Medicine (inStem), which shares the extended campus with us, has nucleated many new interactions across all our areas of research. Prominent among these are structural biology work, and many engagements with Genetics and Development, and Cellular Organization and Signaling. The Neurobiology group has participated in setting up a new theme within inStem: the Centre for Brain Development and Repair. This has been made possible through a generous donation from the Wadhwani Foundation to set up the Shanta Wadhwani Centre for Cardiac and Neural Medicine.

At a still larger scale of biological endeavor, the Ecology and Evolution group together with Neurobiology, has unleashed a new campus research effort in Chemical Ecology. The Masters program in Wild Life and Conservation is now in its sixth batch, and continues to go strong with Dr. Jayashree Ratnam joining as Deputy Course Director to help Dr. Ajith Kumar. The Theory and Modeling group have now a new epicentre, with the formation of the Simons Centre for the Study of Living Machines at NCBS. All of these groupings have enthusiastically organized workshops and meetings to attract students from ever-wider backgrounds.

Our campus laboratory space has nearly doubled with the construction of a new building, the Southern Laboratories. In a testimony to the popularity of the open and shared laboratory plan, this new building is nearly fully occupied just 2 years after opening. The building fosters many

FACILITIES AND RESOURCES

layers of interaction: between scientists across labs, between institutions such as inStem and between academia and the public, through its auditorium and large open collonnade.
The new building houses a supercomputer centre including new clusters Tiramisu and Nargis, which increase the existing campus computer power five-fold. Also within are a new SPF transgenic mouse facility and the vastly expanded home of the imaging and spectroscopy facilities. The latter, along with mass spectrometry, genomics are all run by C-CAMP which is jointly managed by NCBS and inStem.

Elsewhere on campus we now have an extensive greenhouse complex on the roof of the Eastern Laboratories, that supports organisms from butterflies to cauliflower. It has also substantially reduced the cooling costs for the building. Beyond campus, the Ecology and Evolution groups manage and utilize a wide network of field stations, from the high Himalayas to the coral reefs of the Andaman islands.

The smooth functioning of our infrastructure is the bedrock on which our science runs. This key role has been taken over by Sanjay Sane as the new Chair of the Research and Technical Services Committee, with able support from Mr. Rengasamy and his team. Beyond the huge effort to get the new Southern Laboratories up and running, they have built a new housing complex in our residential colony four kilometres north of campus. This will soon be connected by a link route through the pleasant fields of the GKVK campus.

Even as construction and physical development on the campus continue apace, our living environment has also built on the hard work of many people and committees. I specially acknowledge Raghu Padinjat for hugely strengthening our medical and counselling services with the able help of Dr. Prasad and now Dr. Patil, our Chief Medical Officers.
Our New Faculty committee (Shivaprasad, Axel and Mr. P.P. Ranjith) have done much to help our new faculty colleagues make a smooth transition to the campus.

The administrative wheel has turned bringing new people to old responsibilities even as the scale of these responsibilities has grown. Vijay, our Director for eighteen years, has expanded his scientific horizons from NCBS to the entire country in his new role as Secretary of the Department of Biotechnology. The domino effect of this is that Jitu Mayor, our Dean for the last five years, has taken over as Director, and I have become Dean of Research.

The student and postdoctoral programs under the Head of Academics, Dr. Apurva Sarin have scaled up to keep pace with all the groups and activities on campus. Attractive new postdoctoral programs (http://www.ncbs.res.in/postdoctoral_fellowships) have led to a near-doubling of our postdoctoral strength. Our joint PhD programs (http://www.ncbs.res.in/phd_program.htm) now bring in students from around the world to increase the diversity on campus.

Upinder Bhalla
Dean NCBS

Researchers at NCBS have access to several world-class research facilities, details of which can be accessed at http://www.ncbs.res.in/research_infrastructure. In addition, access is also available to several research services via the Centre for Cellular and Molecular Platforms (CCAMP - http://www.ccamp.res.in/).

Shared facilities at NCBS include a well-managed CIFF (equipped with one Transmission Electron Microscope (TEM) and an Atomic Force Microscope (AFM); confocal microscopes, one near field scanning optical microscope (NSOM), and a STED microscope, as well as six different flow cytometers), an Animal House for the generation and upkeep of transgenic mice, rats, Xenopus and Zebrafish, a Mass Spectrometry facility, a fly facility for the generation of custom transgenic Drosophila, mechanical, electrical and electronics workshops, greenhouse, X-ray crystallography and BioSAXS resources and protein NMR facilities. Also available via CCAMP are facilities for Next Generation Sequencing, Mass-Spectrometry, cell based HTS screening and others. NCBS has collaborations at several field stations around the country, ranging from the high Himalayas to the Coral reefs of the Andamans.

The NCBS library is well stocked with a comprehensive list of prominent material. Electronic subscriptions are available for online access to many major and specialized journals and journal articles from unsubscribed titles are available quickly via online purchases.

Support is provided to our researchers, both for configuring new laboratory spaces and refurbishing existing ones. A dedicated team for projects and services at NCBS helps design, plan and coordinate the activity of setting up labs, facilities, and common spaces throughout the campus. Their role is key to ensuring that NCBS can accommodate the expanding infrastructural needs of the researchers, translating user requirements into tangible structures whilst maintaining the natural beauty and aesthetics of the campus.

In addition, the team also provides comprehensive support for the maintenance of existing laboratory spaces, uninterrupted power supply, air handling, networking, multimedia and care of major equipment. These different inputs are crucial to the smooth functioning of the research enterprise at NCBS. The team also closely interact with Campus committees such as the aesthetics committee for maintaining the overall theme of the campus. The Technical services team consists of the Heating, Ventilating and Air Conditioning Services, Electrical Section, Civil Engineering Section, Internet technology and Technical support (I.T.), Instrumentation Section, NCBS Architects Team, Mechanical and Electronics workshops and the Landscaping team. The NCBS laboratories and other buildings are placed within a green 20-acre plot within the UAS campus. This is supported via groups taking care of lab support, lab kitchens, housekeeping, security, housing and hospitality. This workforce, predominantly outsourced, forms a significant fraction of the staff supporting the upkeep of the campus.

The foundation layer of much of the science on campus is also the administration, which forms several links that help the campus function efficiently. Staff from the administrative teams are also the points of connect to external organizations that are invaluable for campus activities. Diverse teams support campus research via administration including accounts, establishment, procurement and stores, Deans office, Academic Office, Directors Office, Meetings and travel and others.

SCAN THIS TO KNOW MORE ABOUT NCBS FACILITIES AND RESOURCES

FACILITIES AND RESOURCES

RESEARCH FACILITIES

- 1a 1b Central Imaging & Flow Cytometry Facility (CIFF)
  Facility Head: H Krishnamurthy
- 2 Radioactivity Lab
- 3a 3b Mass Spectrometry Facility
- 4 Biosafety
- 5 Chemcore
- 6 High-Throughput & High Content Screening Facility
- 7 Next Generation Genomics Facility (NGGF)
- 8 NMR
- 9 Structural Biology Facility
- 10 Animal House
  Facility In-charge: G H Mohan
- 11 Drosophila Facility
- 12 Greenhouse

TECHNICAL SERVICES

- 13 Mechanical & Electrical Workshops
  Facility In-charge: Karthikeyan M N
- 14 IT Section
  Facility In-charge: P K Baruah
- 15 Architect
  Facility In-charge: U B Poornima
- 16 AC
  Facility In-charge: H S Venkataramana
- 17 Instrumentation
  Facility In-charge: P C Gautam
- 18 Civil
  Facility In-charge: P C Gautam
- 19 Electrical
  Facility In-charge: Suresh Kumar A

HEALTH & WELL-BEING

- 20 Créche
- 21 Medical Facilities
  Facility In-charge: Dr. V N Patil
- 22 Sports
  Facility In-charge: Ranjith P P
- 23 Library
  Facility In-charge: Avinash D Chinchure

RDO@NCBS

The 2007-2009 period saw the genesis of inStem and CCAMP in close proximity to NCBS. The premise was that the growth of these two new entities would be supported by the dynamic NCBS administration, allowing for rapid ramp-up of exciting new research directions. At this point, a strategic decision was taken to create a single research office, to centralize all major extramural funding support to the expanding cluster.

The Research Development Office (RDO) was consequently created in July 2010. Three key priorities were identified: creating a knowledgebase of funding schemes for campus researchers (previously lacking in India), supporting the researchers on campus with their individual funding needs and facilitation of multi-institutional funding mechanisms to support campus development.

The first step was the creation of a detailed database of the Indian funding landscape. With the database in place, the team also put in place a quarterly newsletter with information on forthcoming deadlines, policy-related matters, awarded grant highlights and more. Together, these tools now serve as a primary resource for providing detailed grants advice to all the researchers at the NCBS campus.

Staff at the RDO work in close collaboration with the researchers, administration and management to facilitate funding and award management of campus grants from local and international sources. We also undertake outreach to all the funding agencies supporting campus research. Our emphasis is on enabling exceptional science in a manner that complies with both agency and campus norms.

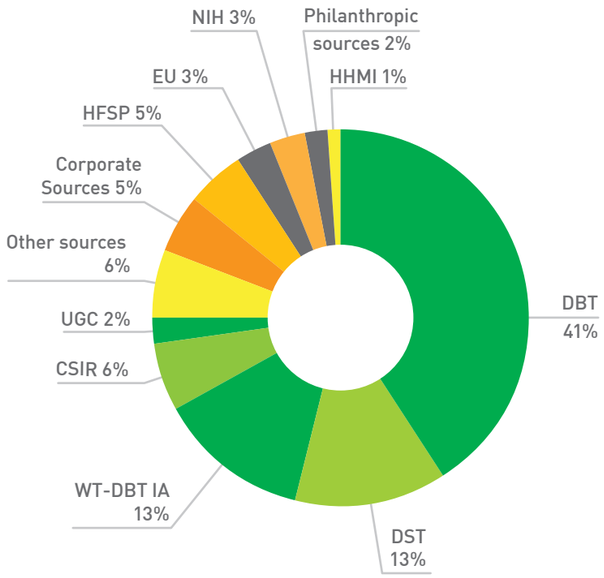
We work with our researchers to facilitate timely submissions of a gamut of grants including fellowship applications, project grants, collaborative grants, infrastructure grants and more. We also provide oversight with annual reporting to the agencies, in-depth management of the complex awards and transitions of our investigators through the lifetime of their grants.

Looking to the future, we recognize that the extended NCBS campus would be financially secure with a mixed funding portfolio and a corpus. To this end, we are now putting in place mechanisms to reach out to philanthropic donors to attract endowments and also to corporate sources to fund areas of campus research, which might have translatable outcomes. These additional means of funding campus research would add to the considerable support we receive from the Government of India and other agencies.

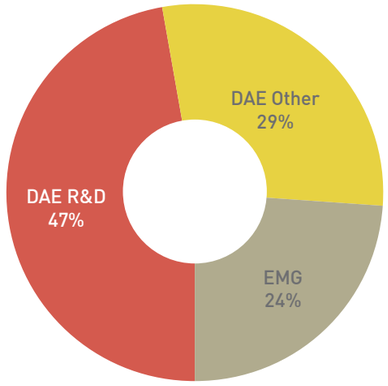
We have every expectation that there will be outstanding research here at the NCBS campus and it will be our privilege to have helped facilitate this science via the requisite funding support.

Savita Ayyar
Head, Research Development

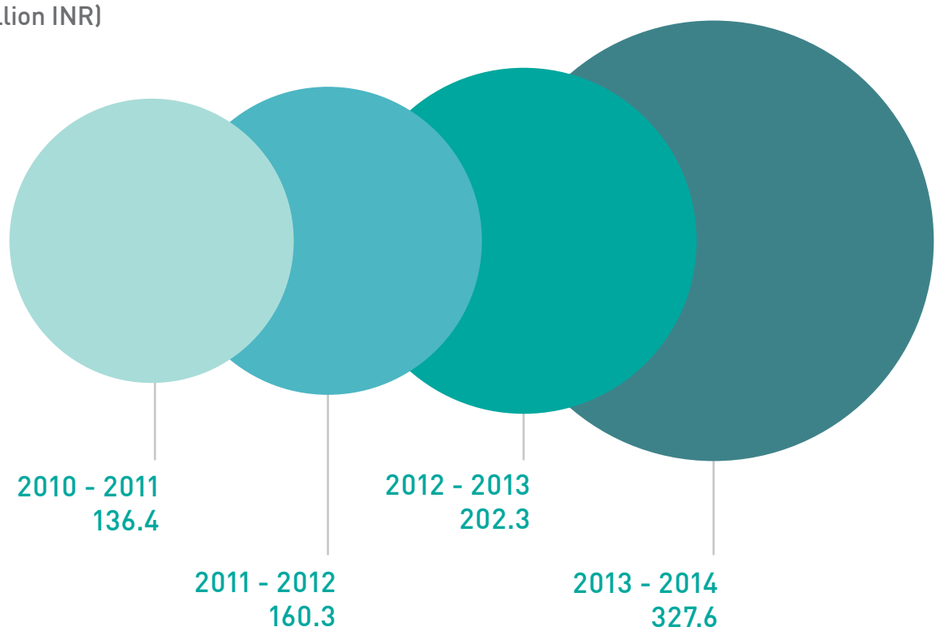
Funding portfolio for NCBS (over 2010-2014, reflecting relative contributions)



Relative contributions of intramural and extramural funding for NCBS in the financial year 2013 - 2014



Extramural support received at NCBS (in million INR)



PUBLIC ENGAGEMENT

NEWS AT NCBS

The NCBS news effort has completed 5 vibrant years communicating articles and announcements lauding research achievements amongst the scientific community on campus.

The team's focus is to convey diversity in biology in a creative and classic manner. This is important as news from campus is now accessed by a wider range of readers. Students and researchers have largely contributed to this endeavour. The team also engages with professional freelance writers by providing all key components essential for conceptualizing and developing exceptional news stories. Researchers on campus form the editorial net to ensure that each story conforms to the highest standard of quality and the essence of science is maintained.

The team now manages a diverse portfolio of publication specific articles, profile interviews, photo stories and news on outreach programs. Social media platforms and audio visual technologies are also applied to deliver news. The news page is represented in the NCBS web portal and can be accessed to view outcomes from the campus.

ANNUAL SCIENCE JOURNALISM WORKSHOP

On August 7, 2014, another edition of NCBS' annual science journalism workshop concluded successfully. NCBS has now played host to four such workshops. The first workshop, in 2011, was a dry-run: limited mainly to students from NCBS and IISc, with just one journalist from Delhi participating. The central idea behind the workshop was to introduce students keen on science journalism to the nuts-and-bolts of writing news and features, while also engaging them in broader discussions on topics such as journalistic ethics. The focus was on the written word—communicating science with simplicity, clarity and accuracy, while being engaging and entertaining, so that the layperson could find science as fascinating as the practicing scientist. The students learned how to interview scientists, parse complicated papers, and turn the information into well-crafted stories.

Science journalists Anil Ananthaswamy and Peter Aldhous taught the workshop, with Peter focusing on news and Anil on features. Geoff Hyde taught students the art of unpacking a scientific paper. The extremely positive feedback from the students signaled that NCBS had initiated something very useful, and for which there was considerable appetite.

The subsequent workshops, from 2012-2014, have drawn students from all over India, from a range of scientific disciplines, including biology, neuroscience, ecology, physics, fluid mechanics and computer science. There was even the occasional social scientist. Even some practicing journalists came for the workshop, desiring to expand their expertise to science journalism. Jessica Marshall and Rosie Mestel joined Anil as co-instructors in 2013 and 2014 respectively, while Peter came for all editions except 2013.

The workshop's primary purpose is to inspire students to become science journalists—and all signs are that the workshop is succeeding. Each year has seen 2 or 3 students (out of a batch of 10-12) taking up the challenge. They have begun writing for both Indian and foreign magazines and newspapers, including The Hindu, Down to Earth, Nature India, New Scientist, BBC Earth and Mosaic (a Wellcome Trust publication).

SCIENCE AND SOCIETY

The Science and Society Programme develops, facilitates and coordinates projects and events that bridge the sciences and the humanities to stimulate cross-disciplinary dialogue. One aim of this venture is to extend the activities within the remit of the programme beyond the confines of academia and make it accessible to the larger public. To this end, lectures, exhibitions, and theatre performances are regularly hosted, enhancing the exchange of ideas and knowledge between scholars involved with the programme and the community at large.

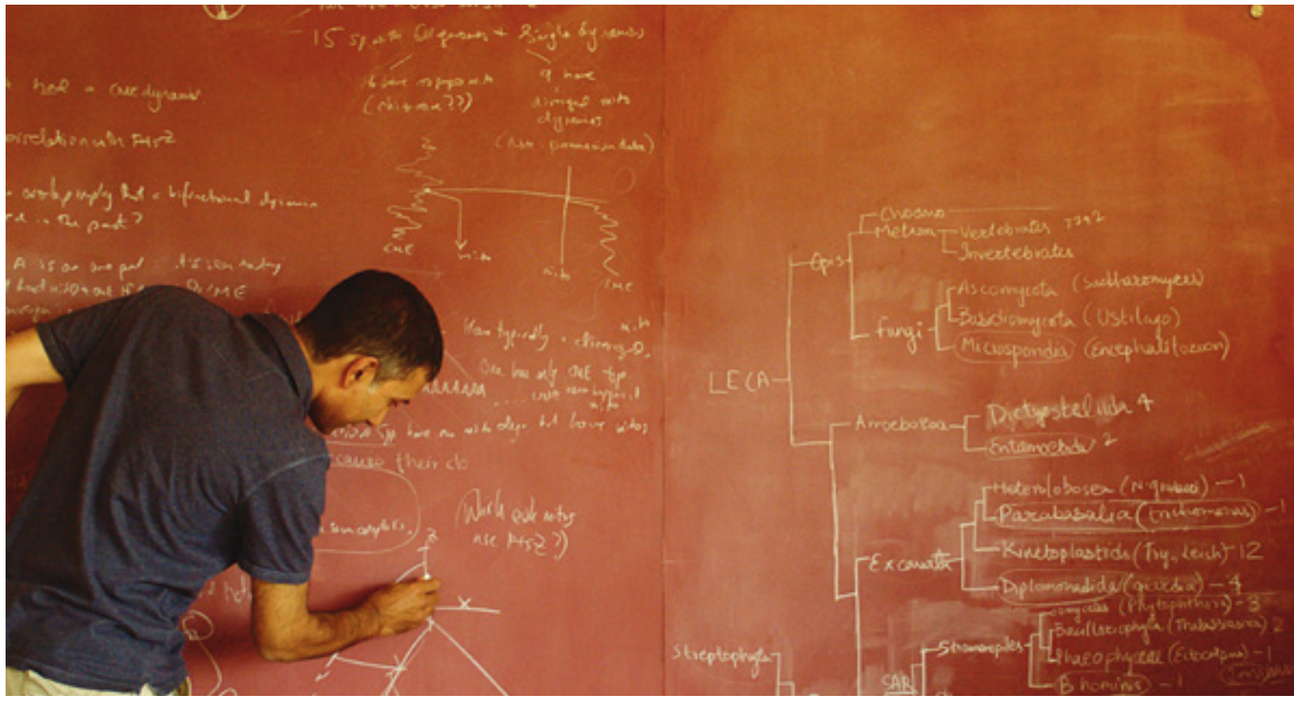
In 2013-2014, the programme sponsored a variety of events, including ten public talks, a music performance, a German film festival, two documentary film screenings, two theatre performances and an art history lecture series. The programme maintains high international visibility by bringing together participants from within and outside India. The German film festival and the art history lecture series were both the first of its kind to be presented at NCBS. With the support and encouragement of the faculty, staff and students of NCBS, the programme will continue to expand its scope and activities.

From the play, 'Serious Men'

THE SIMONS CENTRE FOR THE STUDY OF LIVING MACHINES

NCBS and the Simons Foundation partnered in 2013 to establish the Simons Centre for the Study of Living Machines. This Centre brings together five research groups at NCBS who use theoretical or computational methods, in conjunction with quantitative experiments, to address complex biological problems. The current Centre members and their research interests are: Madhu Venkadesan, biomechanics; Mukund Thattai, computational cell biology; Madan Rao, cellular biophysics; Sandeep Krishna, cellular networks and cellular decision making; Shachi Gosavi, protein dynamics. These groups are united by a common philosophy: we ask how evolutionary and physical constraints combine to determine the nature of molecules, cells and organisms, which we view as "living machines".

In addition to core research activities, the Centre aims to encourage interactions between theory and experiments; to host an international visitors program; and to support excellent post-doctoral fellows.

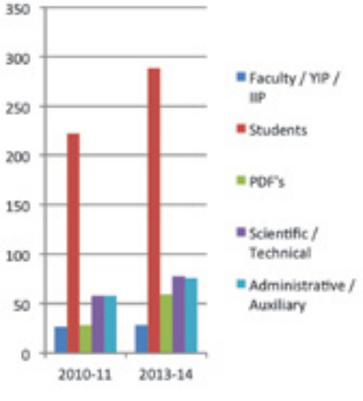


ADMINISTRATION AND FINANCE AT NCBS

NCBS currently is at a pivotal point in its development phase as it turns 25 in two years from now i.e.2017 and as it strives to enhance its excellent reputation in research, teaching, mentoring and its international presence.

Since the time of last reporting, NCBS has grown in Size and stature. The table below shows our growth both physical and financial during the last five years.

MAN POWER GROWTH



FINANCIAL PROGRESS

BUDGET & EXPENDITURE (Rupees in Millions)			
Sl. No	**Particulars**	**2010-11**	**2013-14**
1	Research & Development	147	633
2	Extra Mural Grant	136	328
3	Salaries	103	153
4	Operational Expenditure	247	252
5	Construction	432	-
	Total	**1065**	**1366**

In the process of our growth on our campus and in the vicinity we are actively involved in incubating two institutions, Institute for Stem Cell Biology & Regenerative Medicine (inStem)& Centre for Cellular & Molecular Platforms (C-CAMP). Through this process what will emerge is a cluster of institutions with NCBS which we would like to call as Bangalore Life Sciences Cluster (BLiSC).
The growth in infrastructure and facilities on our campus has brought in, new challenges and increased complexity of work flows and handling of multiple tasks, by not only individuals but also operational divisions. At this juncture, to sustain the growth path we need alignment of all resources most importantly human and financial. Also, needed is an appropriate strategy to harness the resources so that we are able to optimally deploy them in a manner that facilitates our researchers to achieve scientific excellence and fostering new research ideas.

Given the amount of investment envisaged on the campus in the next 5 years, it calls for strategic planning and management of resources particularly finance & human. It would be apt to term 'Finance' as a 'Key Result Area' (KRA) around which many functions will revolve. As the cluster evolves as an entity it is essential that it aligns with its 'scientific goals' and has to establish & develop self accounting responsible cost centers which will manage its own allocated budget. This calls for budgetary and other financial information/data to be made available on real time basis for appropriate analysis, communication and presentation for strategic decision-making.

There has to be constant oversight of the cost centers. The need for oversight emerges from the fact that the cluster will be predominantly funded by government of India and funding has become more complex and is fuelled by a changing regulatory environment, budget and resource constraints. The oversight must focus on the larger canvas and emphasize on value creation for the scientific community of the 'Cluster'. It is important to have the *'big picture'* of the cluster and the partnering institutions in perspective at each stage. In other words *the forest has to be kept in mind by not ignoring the trees.*

During the coming years we are headed for a phase that we hope will create a lasting impression in the scientific world. All we know is that the last five years have been challenging and the future holds surprises. We need to create capacity to respond to surprises. We are headed for a journey where we are committed to create value for the scientific community of the cluster.

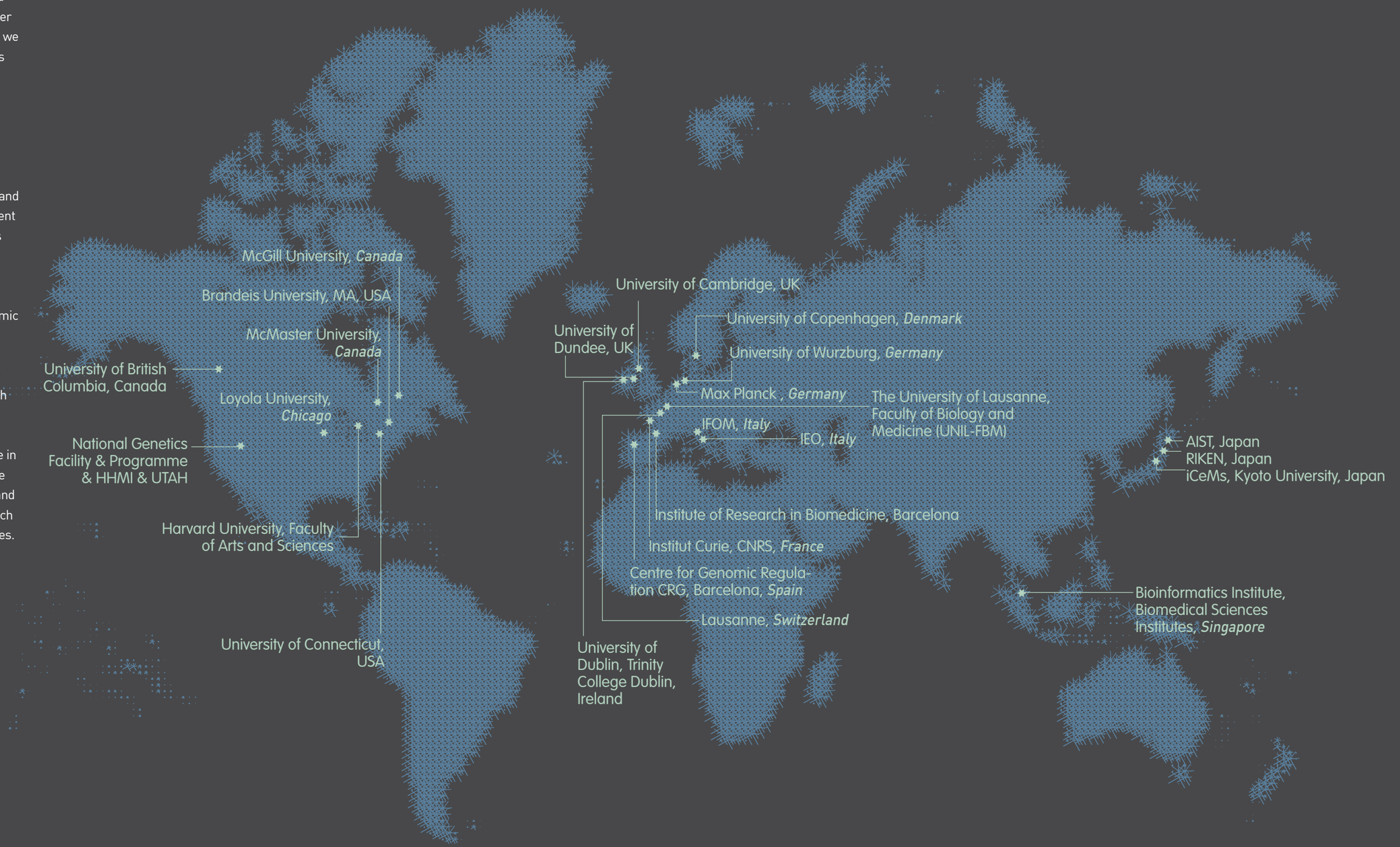
Before I end, I would like to acknowledge support of Department of Atomic Energy (DAE) in our endeavors. I would like to sincerely thank all my colleagues for their support. The support of my colleagues has helped us to work as a team without barriers of hierarchy hindering communication.

I look forward to their continued support in our journey ahead.

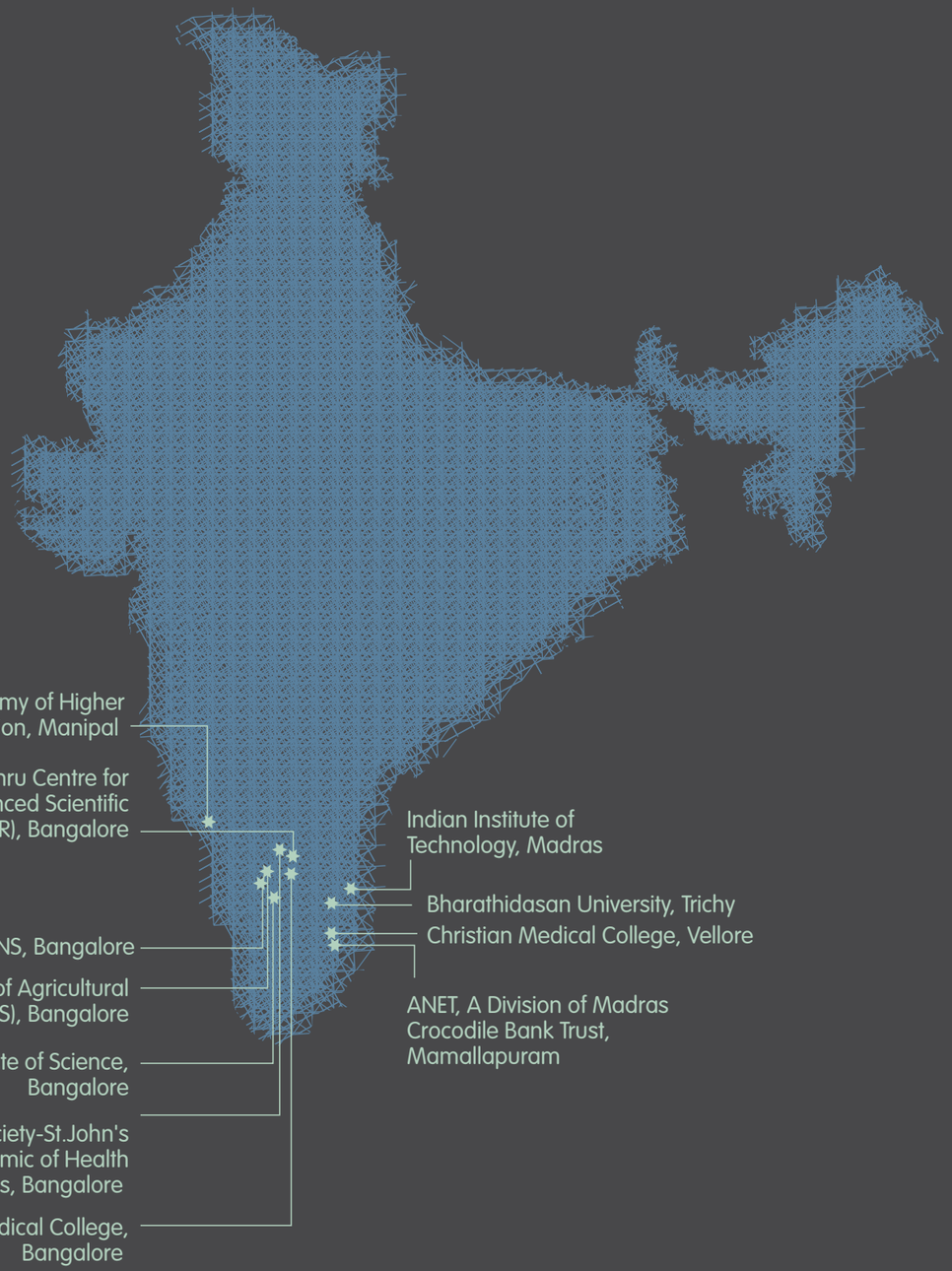
Pradip Pyne
Head Administration & Finance

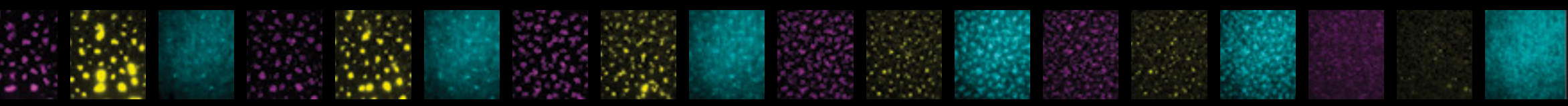
NCBS INTERNATIONAL COLLABORATIONS

Due to the tremendous breadth of research we encompass - across spatial and temporal scales necessary to grasp the complexities of biology, from molecules to ecosystems, and nanoseconds to evolutionary time - we suffer from a lack of local critical mass. However, we also have many international collaborations with a number of first-class institutes that are more specialized. For example, IFOM- Milan for their depth in cancer biology, the Gurdon Institute at Cambridge and their Department of Zoology for their understanding of regenerative biology and morphogenesis, the Kyoto iCEMS Institute and for their understanding of induced pluripotent stem cells. And there are deep connections with Stanford, MIT and the CRG, Barcelona and Harvard, with whom we have frequent exchange of ideas and people as well as several visiting faculty. We also have academic exchange programs involving partnerships with the Erasmus Mundus EUROSPIN network, the ICAM-I2CAM network and the University of Würzburg. among others. Such collaborations allow our faculty at NCBS to have access to the depth of research necessary to succeed, and are only possible in a globally connected world. As scientists we must engage across our own institutional and national borders to take advantage of the rich resource of people and talent in other locales.



NCBS NATIONAL COLLABORATIONS





Compiled and edited by Sumantra Chattarji,
Arachana Shetty and Savita Ayyar
Design: Sarita Sundar & Sybil D'Souza, Special
Illustrations: Georgie Paul
Photography: Manoj Sudhakaran
Additional photographs contributed by students
and staff
Print: www.pragati.com

National Centre for Biological Sciences
Tata Institute of Fundamental Research
GKVK, Bellary Road,
Bangalore 560065, India

Phone: +91 80 23666001 / 02 / 18 / 19
Fax: +91 80 23636662

ncbs tifr