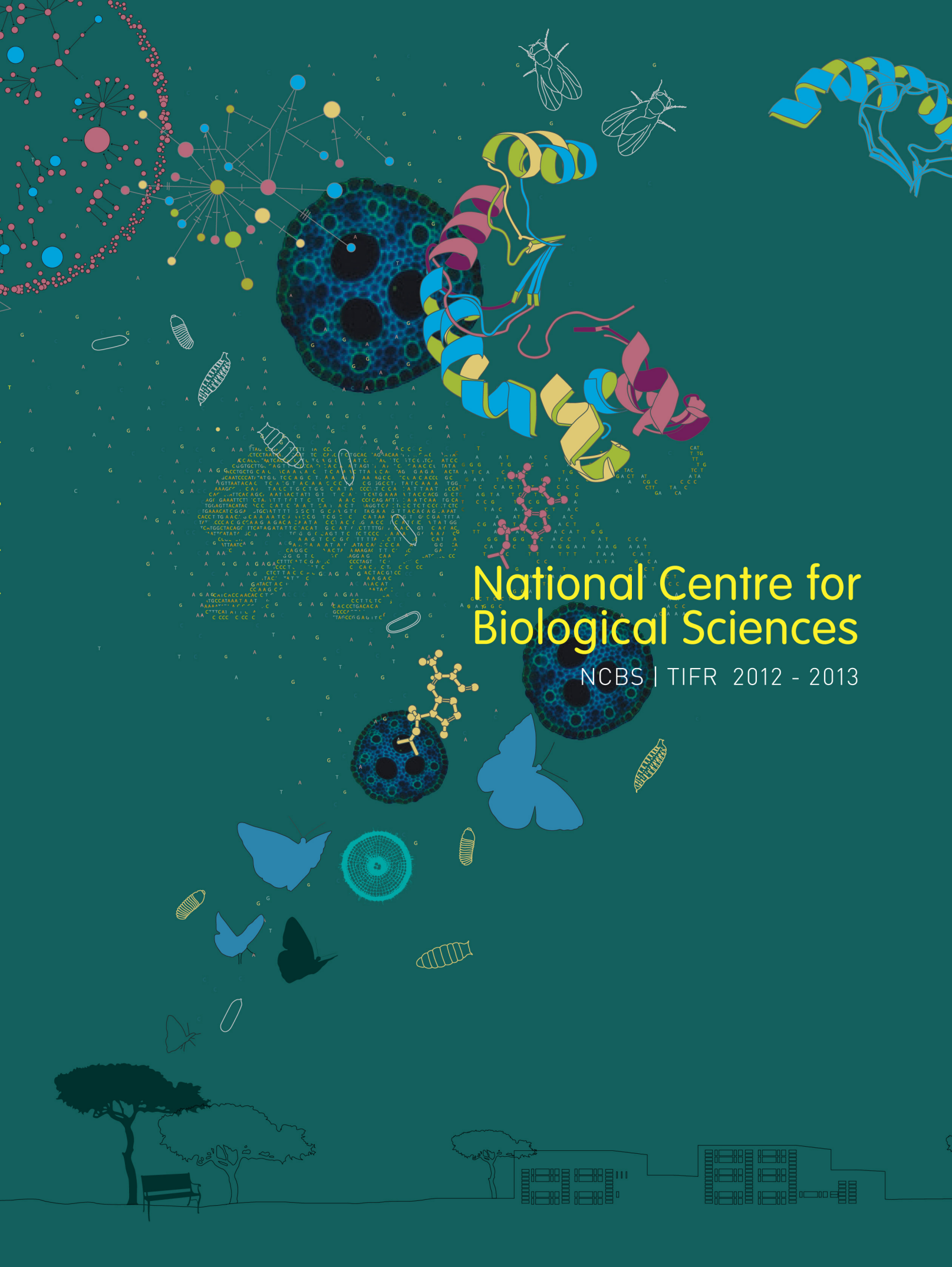

National Centre for Biological Sciences

NCBS | TIFR 2012 - 2013

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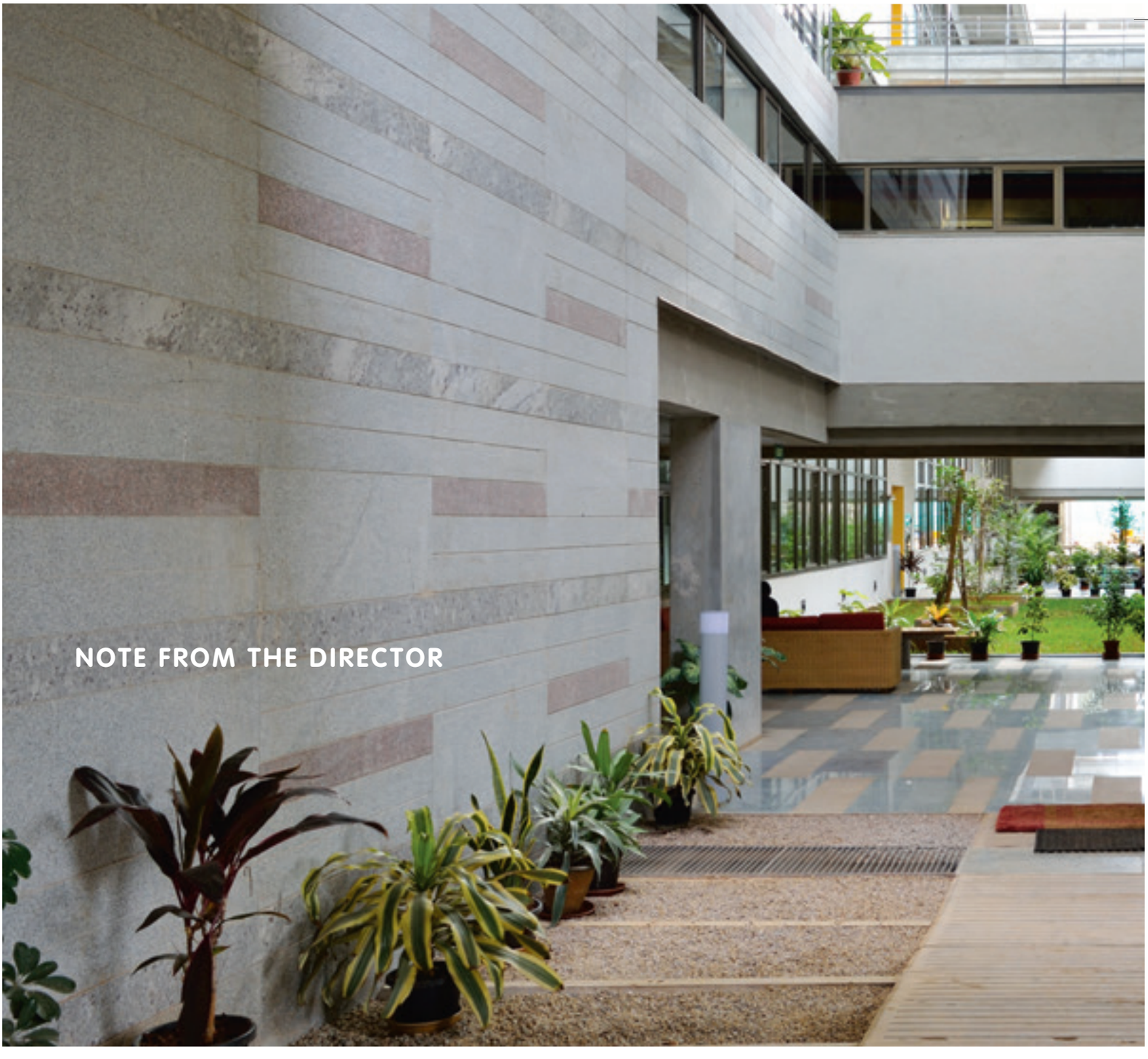
CONTENTS



NOTE FROM THE DIRECTOR

It is with a somber tone that I must begin this note. Obaid Siddiqi, Fellow of the Royal Society, Member US National Academy of Sciences, ex-President of the Indian Academy of Sciences, National Research Professor at NCBS (TIFR), passed away tragically in a freak accident on 26 July 2013. 'Obaid', as he was called by many, was the chief architect and founder of NCBS. We deeply mourn a creative scientist, a self-effacing and visionary institution builder, and a genuine humanist. Obaid has left us an example that will be hard to follow. However collectively, I believe that we can create a special place here at NCBS, that Obaid would be proud to claim as his vision.

NCBS.indd 4 04/01/14 12:13 PM

If Obaid's passing was not a sufficient jolt, the year had already begun ominously; in January, K. VijayRaghavan, Director, NCBS went missing. Fortunately, he resurfaced in New Delhi, at the portals of the Indo-Tibetan Border Police, marching in to take up office as the new Secretary of the Department of Biotechnology (DBT). It is heartening to note that someone of Vijay's caliber (much celebrated by his recent election to the Fellowship of the Royal Society and the award of a Padma Shri by the President of India) both as a scientist and an administrator is nominated, and more importantly accepts to take up the top job. Vijay appears to be thriving in this high-pressure job, and here's wishing him and Indian biosciences all the very best.

It's always hard to remain afloat when one has lost two of our main stays in such a short span; it will require all hands on the deck to keep our ship from running aground. As the new Director at NCBS, Obaid and Vijay have certainly left myself a challenging ship to steer! But with the kind of vessel that Obaid and Vijay have lovingly crafted at NCBS, I believe that we have a great place for realizing our scientific visions (and resources to boot). This ship is ours to sail to new horizons, as we continue to explore exciting destinations in Biology (read this short report for a sample of what we have done). A lot of excitement is also being generated in the assembly of a new vessel, inSTEM (www.instem.in), in our midst with support from the DBT. As the super structure of this ship is being constructed, we already have an adventurous crew at inStem being hosted in an admirably collegial fashion by many at NCBS.

Obaid Siddiqi, NCBS study

At NCBS we are now embarking on two new expeditions. Our 'Theory Space' now named Simons' Centre for the Study of Living Machines, is one of these. Here our colleagues from the theoretical sciences propose to nucleate a strong programme in understanding Biology from a theoretical perspective offered by a close engagement with Physics, Computer Science and Mathematics. The second is a Chemical Ecology Programme, where some of our colleagues hope to discover what kind of Biology (molecules, cells, cell systems and whole organisms) goes on in natural habitats, rather than what can occur in the laboratory setting. This programme will also stitch together a new fabric from our extensive network of field stations, our colleagues at the MSc Wild life programme, and our faculty.

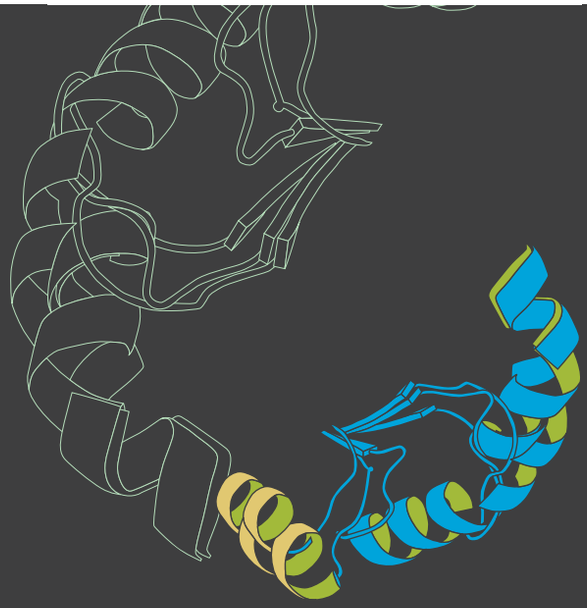
Finally, to keep Obaid's vision alive at NCBS, we plan to make his laboratory space the site for our science and history of science archive, a space for rare music that Obaid had so dearly wished existed on our campus, and a living monument to celebrate a wonderfully generous, creative and inquisitive spirit that Obaid so definitely embodied.

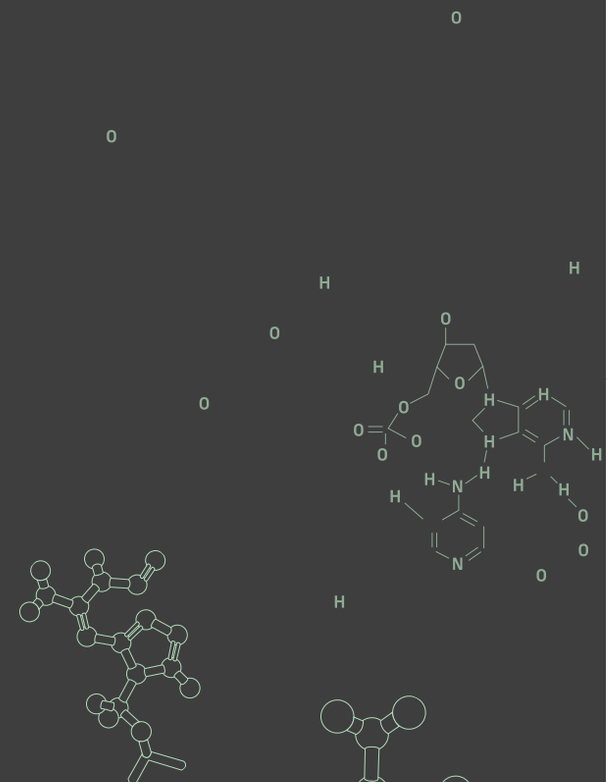
NCBS.indd 5 04/01/14 12:13 PM

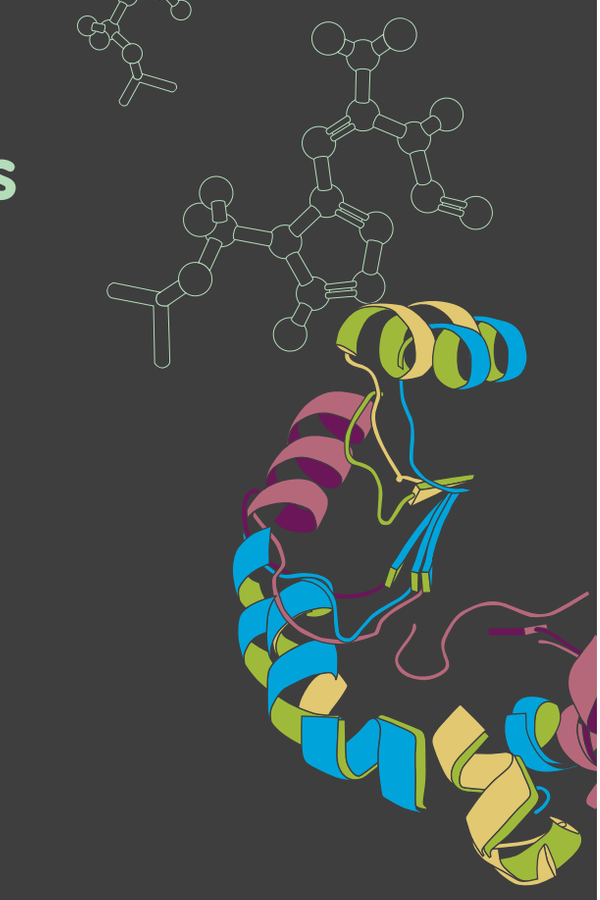
RESEARCH REPORTS

SCAN THIS TO KNOW MORE ABOUT RESEARCH AT NCBS

NCBS.indd 6 04/01/14 12:13 PM







Biochemistry, Biophysics and Bioinformatics

JAYANT B UDGAONKAR
How do proteins fold, unfold and misfold?

MK MATHEW
Crossing barriers: Studies of membrane transport

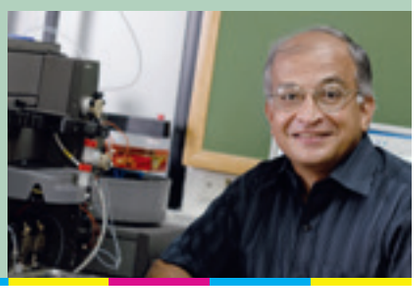
R SOWDHAMINI
Computational approaches to protein science

YAMUNA KRISHNAN
Structure and dynamics of nucleic acids

ASWIN SAI NARAIN SESHASAYEE
Computational and functional genomics of bacterial gene regulation

DEEPAK T NAIR
Genomic plasticity and integrity

NCBS.indd 7 04/01/14 12:13 PM



jayant udgaonkar

The role played by any given cellular protein depends on it having an appropriate structure. We study the folding routines by which polypeptide chains self-assemble into the correct conformation, and how unwanted proteinaceous aggregates form when folding goes wrong.

HOW DO PROTEINS FOLD, UNFOLD AND MISFOLD?

The polypeptide chain of a protein must coil, turn, bend, loop 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. How proteins fold 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 barstar, monellin, the SH3 domain of the PI3-kinase, α-synuclein, tau, and the mouse prion protein as archetypical model proteins for studying how proteins fold, unfold and 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 methods, as well as nuclear magnetic resonance spectroscopy and mass spectrometry methods. Our kinetic measurements span the time domain of 100 microseconds to 10 hours.

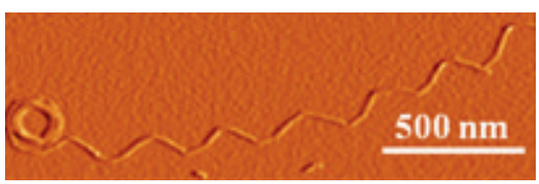
Highlights of recent work on protein folding include (1) the demonstration that the folding of the PI3K SH3 domain commences by a gradual non-specific chain collapse reaction, and (2) the demonstration that monellin folds via multiple pathways, and that folding switches between the alternative pathways upon a change in folding conditions. Highlights of recent work on protein aggregation include (1) the elucidation of the role of heparin in amyloid fibril formation by tau, and the demonstration of a secondary pathway for tau aggregation, and (2) the delineation of on-pathway and off-pathway roles for different sub-populations of oligomers in the pathway of amyloid fibril formation by the mouse prion protein.

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.

Singh, J. & **Udgaonkar, J.B.** (2013) Dissection of conformationalconversion events during prion amyloid fibril formation using hydrogen exchange and mass spectrometry. *J. Mol. Biol.* 425, 3510-3521.

Aghera, N. & **Udgaonkar, J.B.** (2013) The utilization of competing unfolding pathways of monellin is dictated by enthalpic barriers. *Biochemistry* 52, 5770-5779.

4. Sarkar, S.S., **Udgaonkar, J.B.** & Krishnamoorthy, G. (2013) Step-wise unfolding of a small protein proceeds via dry and wet molten globule intermediates and a solvent-accessible transition state. *Biophys. J.* 105, 2392-2402.



Coiled spring-like fibrils formed by the human tau protein

NCBS.indd 8 04/01/14 12:13 PM

mk mathew *Proteins called ion transporters mediate the passage of various ions across cellular membranes. We focus on two sets of transporters: a potassium ion channel central to nerve conduction; and transport systems that help plants to survive in salty soils.*

CROSSING BARRIERS: STUDIES OF MEMBRANE TRANSPORT

My laboratory studies biological membranes, which serve to enclose cells and compartments within cells. We study proteins that mediate the movement of solutes across membranes, and also processes by which membranes are moved within cells. At one level, we investigate the nuts and bolts of how transporter proteins function: we proposed atomic level mechanisms for the function of voltage-gated K^+ channels. At another level, we ask questions regarding ion movements and their regulation in trying to understand how plants survive high concentrations of salt in the soil.

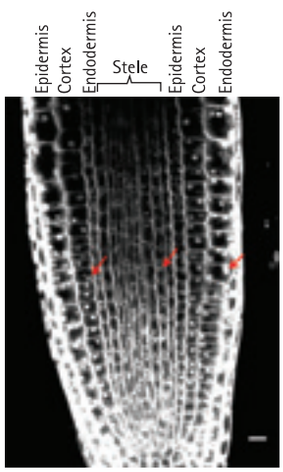
The voltage-gated K^+ channel also appears to be critical for processes as varied as cell proliferation, cell death and differentiation. We have studied proteins that regulate the trafficking of voltage-gated K^+ channels within cells. We are also studying the voltage dependent anion channel, resident in the outer membrane of mitochondria, which plays a role in some pathways of cell death. The K^+ channel is composed of α–helices, while the VDAC is a β–barrel protein.

Plants use a variety of strategies to survive in salty soil. We have earlier shown that controlling the amount of Na^+ that reaches the shoot is critical, as are cellular mechanisms for maintaining low Na+ levels in the cytoplasm. Barriers in the root which prevent external fluid from directly entering the xylem contribute to the ability of the plants to regulate what gets sent up to the shoot. We are studying these barriers in rice roots and also investigating how cells maintain low Na^+ in the cytosol even when subjected to a saline environment. For the latter objective, we look at transport across the plasma membrane and into the vacuole, and have initiated a study of endocytic mechanisms that may play a role in maintaining low cytosolic sodium.

Krishnamurthy, P., Ranathunge, K., Nayak, S., Schreiber, L. and **Mathew, M.K.** (2011) Root barriers block Na+ traffic to shoots in rice (*Oryza sativa L.*). *J. Exp. Botany* 62, 4215 – 4228.

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.



Endocytosis in different layers of Arabidopsis root.
3 day old Arabidopsis root was pulsed with endocytic tracer dye FM4-64 and then chased in presence of Brefeldin-A for 1 hour. Brefeldin-A is an ARF-GEF inhibitor which causes clumping of endocytosed cargo. Clumping of internalized FM4-64 indicates occurrence of endocytosis in all the cell layers of the root. (Scale bar : 10 micrometers)

NCBS.indd 9 04/01/14 12:13 PM

r sowdhamini *Protein sequence data accumulate at ever-increasing rates, but to understand the evolution and functional relationships of proteins, their broader structural features must be compared. We develop computational approaches to extract maximum structural information from sequence data.*

COMPUTATIONAL APPROACHES TO PROTEIN SCIENCE

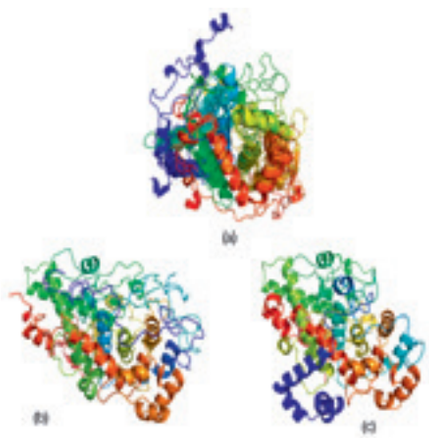
The availability of protein sequence information from whole genome sequencing projects leaves behind a lot of "unknowns" since it does not guarantee knowledge on protein structure, function, conformational changes or their response to the environment. Computational approaches for the analysis of sequences and prediction of structure and function are therefore timely and welcome. Whereas there are a limited number of folds adopted by millions of sequences, structure and function prediction of proteins are daunted by weak pattterns, fuzzy and complex data and challenges to computer algorithms in differentiating true and false positives. Our efforts in this time period have remained largely in the analysis of sequence and structural variations in proteins and how these factors might influence accurate function prediction of gene products.

We have focused our interests on extreme deviants of structurally similar proteins that have similar biological functions, namely outliers of superfamilies. We have performed in-depth studies of proteins that undergo domain swapping wherein structural segments are exchanged between two neighbouring protein subunits in a complex. We investigated the natural conformational (structural) changes adopted by some proteins by means of computer-intensive molecular dynamics simulations. When applied to prolyl oligopeptidases, for instance, it provided structural insights into some of the open questions such as substrate entry and product exit of these two-domain proteins. We have also made a systematic study of residue inserts in protein sequences to note if such inserts may be evolutionarily conserved. Finally, we have applied our experience with structural analysis of proteins to the construction of libraries of profiles of protein families, using DNA-binding proteins as an example.

Gandhimathi, A., Nair, A. and **Sowdhamini, R.** (2012) PASS2.4: An update to the database of structure-based sequence alignments of structural domain superfamilies. *Nucleic Acids Research* 2011:1–4.

Khader, S., Shingate, P.N., Manjunath, S.C.P., Karthika, M., Ganesan, P. and **Sowdhamini, R.** (2011) 3DSwap: curated knowledgebase of proteins involved in 3D domain swapping. *Database* (Oxford)

Kaushik, S. and **Sowdhamini, R.** (2011) Structural analysis of prolyl oligopeptidases using molecular docking and molecular dynamics: insights into conformational changes and ligand binding. *PLoS ONE* 6(11):e26251.



Superfamily of heme-dependent peroxidases. (a) shows the alignment of all six non-outliers. (b) and (c) are the structure of two outliers which have little conformational change with the overall core, but were hard to align due to the presence of extra residues. PFAM description for function of this superfamily domains is peroxidase activity. Outliers are animal peroxidases.

NCBS.indd 10 04/01/14 12:13 PM

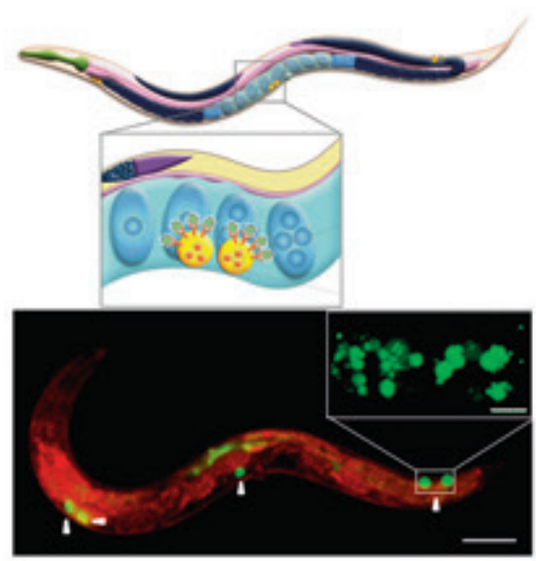
yamuna krishnan *Evolution has produced an overwhelming variety of biological devices that function at the nanoscale level. We study the structure and dynamics of nucleic acids and translate this knowledge to create nucleic acid based nanodevices to probe living systems.*

STRUCTURE AND DYNAMICS OF NUCLEIC ACIDS

Bionanotechnology aims to learn from nature to understand the structure and function of biological devices and to utilize 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 and whose performance is unsurpassed by man-made technologies. My lab uses chemical and biophysical tools to explore structure and dynamics in nucleic acid assemblies with a view to exploiting the knowledge gained for applications in biology.

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 of Watson-Crick base pairing endows oligonucleotides with unique and predictable recognition capabilities. This makes DNA an ideal nanoscale construction material. Understanding and thereby controlling structure and dynamics in designed DNA assemblies is key to realizing DNA's potential as a nanoscale building block.

We make DNA based molecular assemblies for applications as fluorescent sensors of second messengers *in cellulo and in vivo*. Another area of interest involves understanding naturally occurring RNA structural motifs and how they impact RNA processing.



Modi, S., Nizak, C., Surana, S., Halder, S., **Krishnan, Y.** (2013) Two DNA nanomachines map pH changes along intersecting endocytic pathways inside the same cell. *Nature Nanotechnology*, 8 (6): 459-467.

Banerjee, A., Bhatia, D., Saminathan, A., Chakraborty, S., Kar, S., **Krishnan, Y.** (2013) Controlled release of encapsulated cargo from a DNA icosahedron using a chemical trigger, *Angewandte Chemie International Edition*, 52 (27): 6854-6857.

Krishnan, Y., and Bathe, M. (2012) Designer nucleic acids to probe and program the cell. *Trends in Cell Biology*, 22 (12): 624-633.

Bhatia, D., Chakraborty, S., and **Krishnan, Y.** (2012) Designer DNA give RNAi more spine. *Nature Nanotechnology*, 7 (6): 344-346.

Schematic and representative image of a wild type *C. elegans* hermaphrodite microinjected with a solution of fluorescently labeled DNA icosahedron in the pseudocoelom, from where it is internalized by coelomocytes (indicated by white arrowheads, scale bar: 100µm).
Inset shows a representative confocal image of a pair of coelomocytes typically labeled with the icosahedron (Scale bar: 5µm).

NCBS.indd 11 04/01/14 12:13 PM

aswin sai narain seshasayee

Genomes of bacteria are highly economical and appear to be organised more transparently than those of eukaryotes. We exploit this in our computational studies of bacterial gene regulation, with particular focus on the environmental flexibility of these organisms.

COMPUTATIONAL AND FUNCTIONAL GENOMICS OF BACTERIAL GENE REGULATION

Bacteria, besides being agents of a variety of infectious diseases, are the most predominant form of free-living life known on Earth. Some bacteria live in stable environments, such as in a symbiotic relationship with a host; others can live across multiple habitats each presenting its own set of nutrients and adversaries. This leads to two key points, which are of interest to us:

(a) Any given bacterium should code for only those genes that would allow it to make optimal use of the conditions prevailing in its set of habitats.

(b) Regulation is critical especially to organisms that traverse multiple types of habitats, to ensure that only those genes required at any given time point are expressed.

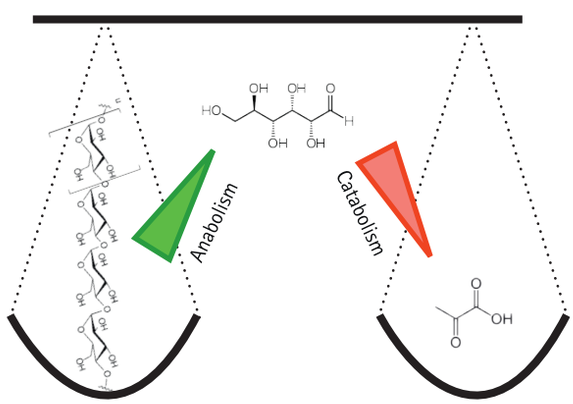
The primary focus of our research is to investigate bacterial regulatory systems from the standpoint of both their occurrence in diverse bacterial genomes and their role in achieving global and function-specific gene expression control in model bacteria such as *Escherichia coli.*

We tackle our research questions using genome-scale techniques. Genomics complements the detailed findings of reductionist molecular biology and biochemistry by describing general principles and identifying exceptions. The large-scale nature and the gaining popularity of genomic studies together generate a flood of biological data, the interpretation of which requires computational tools and expertise. Therefore, our research includes active experimental and computational components. Much of our research focuses on fundamental mechanisms in the laboratory-adapted model bacterium *Escherichia coli.* In collaboration with others, we also set up programs for research into disease-causing bacteria.

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

Prabhakara S, Khedkar S, Shambat S, Basu A, Norby-Teglund A, **Seshasayee AS,** Arakere GA. (2013) Genome sequencing reveals a novel sea enterotoxin-carrying PVL phage in *Staphylococcus aureus* ST772 from India. *PLoS ONE*. 8: e60013.

Kahramanoglou C, Prieto AI, Khedkar S, Haase B, Gupta A, Benes V, Fraser GM, Luscombe NM, **Seshasayee AS.** (2012) Genomics of DNA cytosinemethylation in *Escherichia coli* reveals its role in stationary phase transcription. *Nat Commun.* Jun 6;3:886.



Regulatory mechanisms establish a fine balance between utilisation of nutrients for energy production (catabolism) and biosynthesis of macromolecules (anabolism)

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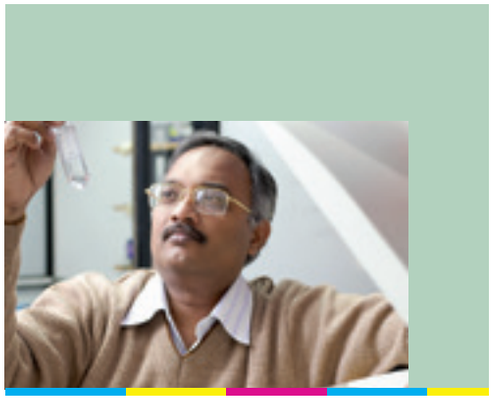

deepak t nair *The integrity of the information resident in genomic DNA has to be maintained. However, the creation and retention of error allows scope for evolution. We aim to elucidate the mechanism utilized by distinct molecules to achieve these conflicting requirements.*

GENOMIC PLASTICITY AND INTEGRITY

For all cellular processes to function optimally, the integrity of the genome has to be maintained. However, plasticity in the genome through creation and retention of error allows for evolution and will aid in relieving selection pressure imposed by an adverse environment. These two conflicting requirements have led to the presence of molecules and pathways that either prevent (e.g. DNA mismatch repair) or facilitate (e.g. error-prone polymerases) the appearance of mutations. Using a combination of structural and biochemical tools we aim to unearth the mechanism of action of these molecular determinants of genomic plasticity and integrity.

Recently, we have determined the structure of the C-terminal domain of the MutL homolog (NgoL) from *Neisseria gonorrhoeae*. The observed inverted arrangement of the monomers in NgoL-CTD was validated by mutagenesis. This configuration in the homodimer will occlude one of the active sites on association with partner proteins and prevent adventitious double stranded cleavage (Sivakumar et al., *Plos ONE*, 2010).

Y-family DNA polymerases are involved in the bypass of damaged nucleotides and enhancing the frequency of mutations to facilitate adaptive mutagenesis. We have shown that a prokaryotic member of this family – MsPolIV (*Mycobacterium smegmatis*) – can promote G:T and T:G mismatches and therefore can facilitate adaptive mutagenesis (Sharma and Nair, *J. Nuc. Acids*, 2012). Additionally, the structure of MsPolIV in conjunction with solution experiments suggests that the PAD region of this enzyme is endowed with the ability to adopt multiple orientations in the absence of substrate DNA. This could be a general feature of this class of enzymes and will allow these molecules to accommodate alterations in the width of the DNA double helix during DNA synthesis (Sharma *et al*, *Acta D*, 2012).

As part of our efforts to understand the mechanism of replication of the ssRNA genome in the case of Japanese Encephalitis Virus (JEV), we have determined the structure of JEV RNA-dependent RNA Polymerase (RdRP) in complex with the initiator nucleotide GTP. The structure and allied mutagenesis studies provide the basis for selective recognition of GTP during initiation of RNA synthesis and also allows formulation of a possible mechanism to avoid erroneous non-templated RNA synthesis.

Surana, P., Vijaya, S. and **Nair, D. T.** (2013) RNA-dependent RNA polymerase of Japanese Encephalitis Virus binds the initiator nucleotide GTP to form a mechanistically important pre-initiation state. *Nucleic Acids Research* (in press).

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.

Sharma, A., Subramanian, V. and **Nair, D. T.** (2012) The PAD region in the mycobacterial dinB homolog MsPolIV exhibits positional heterogeneity *Acta Crystallogr D Biol Crystallogr*. 68:960.

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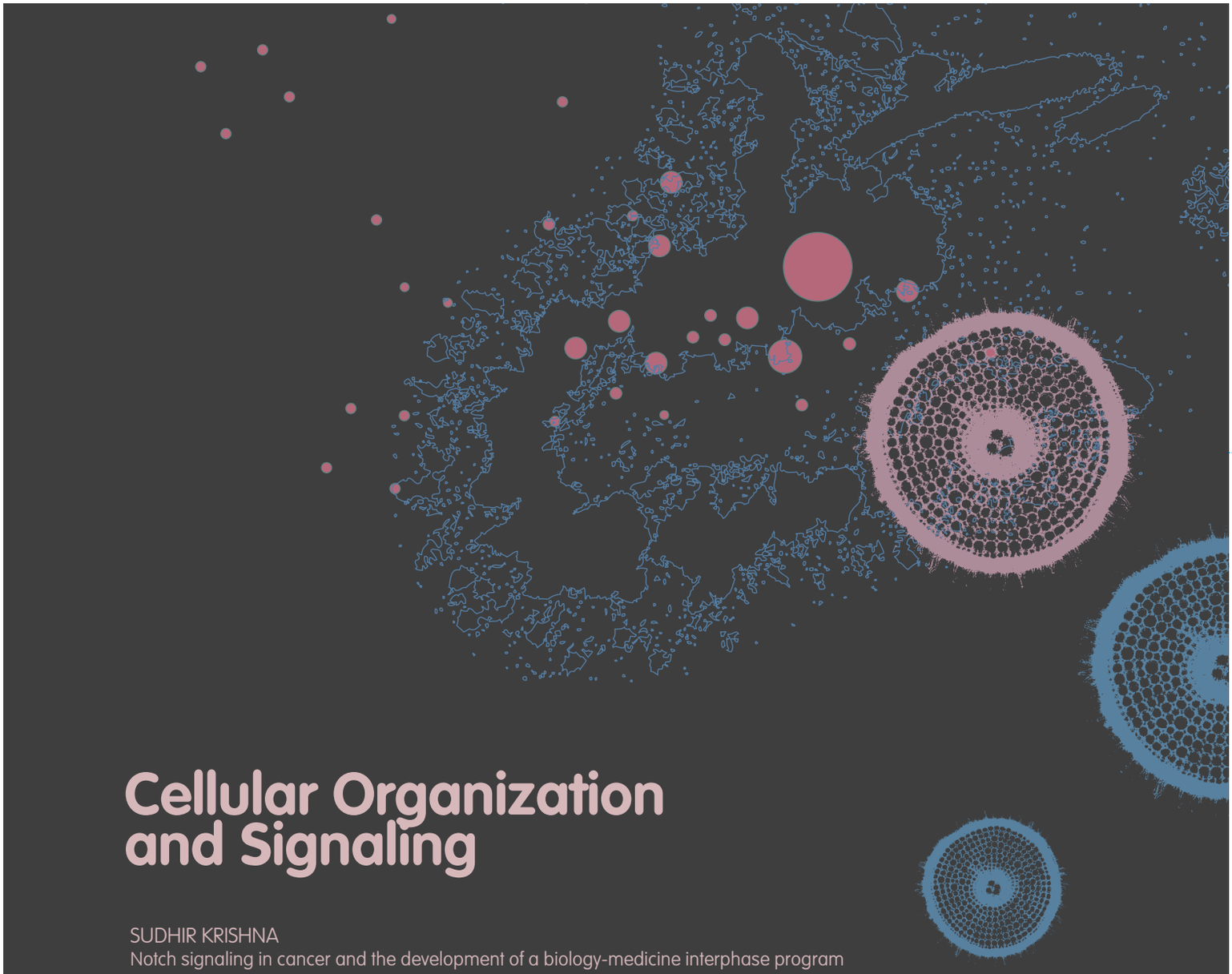


Cellular Organization and Signaling

SUDHIR KRISHNA
Notch signaling in cancer and the development of a biology-medicine interphase program

APURVA SARIN
Cellular strategies regulating survival

SATYAJIT MAYOR
Mechanisms of membrane organization and endocytosis in metazoan cells

KS KRISHNAN
Cell biology of the synapse

RAGHU PADINJAT
The architecture of phosphoinositide signaling *in vivo*

sudhir krishna *In collaboration with Kidwai Memorial Oncology Institute, we have identified and are studying a subset of CD66+ cells that is dependent on Notch signaling. Using leukemias as a pivot, we are developing a biology-medicine interphase program with St. John's Medical College.*

CELLULAR HETEROGENEITY AND SIGNALING IN HUMAN CERVICAL CANCERS

Our lab has for some time now been interested in the role of Notch signaling in human epithelial cancers. We have focussed our analysis on human cervical cancer – a tumour initiated and sustained by oncogenically high risk Human Papillomaviruses. Our recent work has led to the identification of a subset of cells (Bajaj, Maliekal et al., Cancer Research 2011) that has features of cancer stem like cells and is dependent on Notch Signaling. Our major collaborative hospital in this programe so far has been the Kidwai Memorial Institute of Oncology.

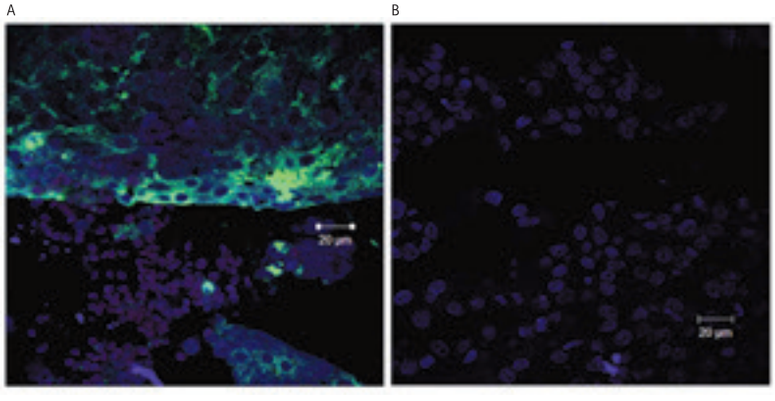
Department of Biotechnology Glue grant initative:
We have been awarded a major 5 year grant to co-develop laboratory facilities at St. John's Medical College. In addition to the existing research infrastructure in St. John's Medical College, we are developing molecular biology and tissue culture labs along with a flow cytometry and imaging facility. From NCBS, Drs. Sweta Srivastava and H. Krishnamurty are some of the key scientists involved in this program.

The St. John's Medical college program has led to a second cancer that we are studying ie: Chronic Myeloid Leukemia (CML). Our focus is on CML stem cells and our key collaborator is Cecil Ross, a senior hematologist.

Adurthi, S., Mukherjee, G., Krishnamurthy, H., **Krishna, S.,** Bafna, U.D., Uma Devi 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* In press.

Bajaj, J., Maliekal., TT., Vivien, E., Pattabiraman, C., Srivastava, S., Krishnamurty, H., Giri, V., Subramanyam, D and **Krishna, S.** (2011) Notch signaling in CD66+ cells drives the progression of human cervical cancers. *Cancer Research*, 71, 4888-97.

Srivastava, S., Ramdass, B., Nagarajan, S., Rehman, M., Mukherjee, G. and **Krishna, S.** (2010) Notch1 regulates functional contribution of RhoC to cervical carcinoma progression. *British Journal of Cancer*, 102, 196-205.



A. Immunofluorescence staining of CD66 (green) and Hoechst (blue) in a cervical SCC section showing the high level of CD66 in the edges of tumour.
B. Secondary control

AKA et.al., unpublished observations

NCBS.indd 15 04/01/14 12:13 PM

apurva sarin *The immune system must repeatedly refresh itself, to meet new challenges. Teams of T-cells, for example, are sacrificed once their jobs are accomplished. What molecular mechanisms orchestrate such suicides, and how do some T-cells live on?*

CELLULAR STRATEGIES REGULATING SURVIVAL

We study signal transduction pathways that underlie cellular decision-making. Specifically, we are interested in signal integration that results in the deletion of damaged or redundant cells while sparing healthy cells in multicellular organisms. Current research in the laboratory focuses mainly but not exclusively on understanding interactions between cell death and survival cues in the control of peripheral T-cell number in the mammalian immune system.

T-cell populations are nomadic and distributed in different tissues including blood but, their numbers show minimal changes through the lifespan of organisms and are conserved across individuals, indicating cell-autonomous programs of cell death and survival. T-cells depend on extrinsic cues from growth factors and cytokines for nutrient uptake to meet metabolic needs and the integration of these cues is critical to death or survival decisions in this lineage.

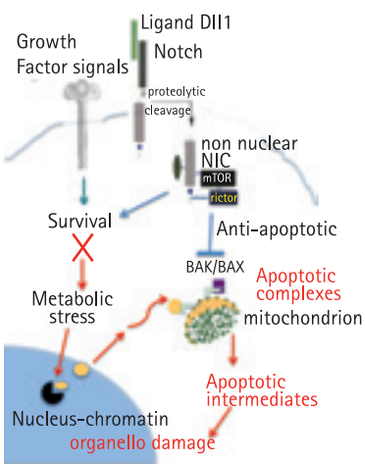
Our experiments have described a T-cell receptor (TCR)-triggered Notch-mediated signaling cascade, which maintains mitochondrial integrity and protects T-cell subsets from apoptosis triggered by cytokine withdrawal. More recent work from the laboratory suggests that nutrient sensitive histone acetylation may couple growth factor signaling inputs with the activation of apoptotic cascades in T-cells. These observations position chromatin as a site of integration of extracellular cues, culminating in an apoptotic response fuelled by mitochondrial intermediates. Thus, the spatial regulation of molecular intermediates and resultant crosstalk with other pathways revealed an hitherto unexplored coupling between their localization and signaling outputs, which we expect may be applicable in other cell lineages.

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. *Journal of Immunology 190*: 97-105.

Perumalsamy, L.R., Marcel, N., Kulkarni, K., Radtke, F., and **Sarin, A.** (2012) Distinct spatial and molecular features of Notch pathway assembly in Regulatory T-cells *Science Signaling 5 (234)*: ra53.

Gupta, S*., Marcel, N*., Talwar, S*., Garg, M., Indulaxmi, R., Perumalsamy, L., **Sarin, A.** and Shivashankar, G.V. (2012) Developmental heterogeneity in DNA packaging patterns influences T-cell activation and transmigration. *PLOS One*, *7(9)*: e43718.

*equal contribution



A schematic of pro-and anti-apoptotic signaling pathways activated in mature T-cells. Our experiments show that the spatial regulation of intracellular signaling cascades, exemplified by Notch activity, is a key mechanism governing survival in T-cell subsets. Mechanisms by which inter-organelle signaling cascades, integrated by chromatin and transducing signals to the mitochondrion, are regulated by Notch and cytokine-dependent signaling is an emerging area of research in the laboratory.

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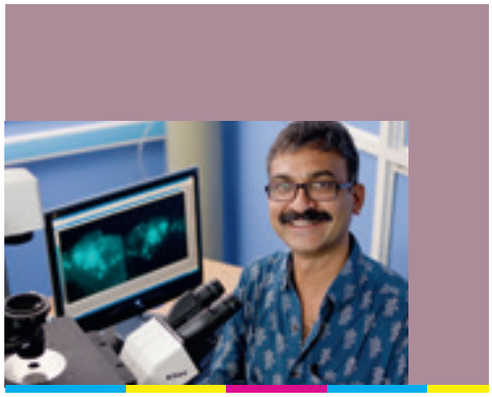


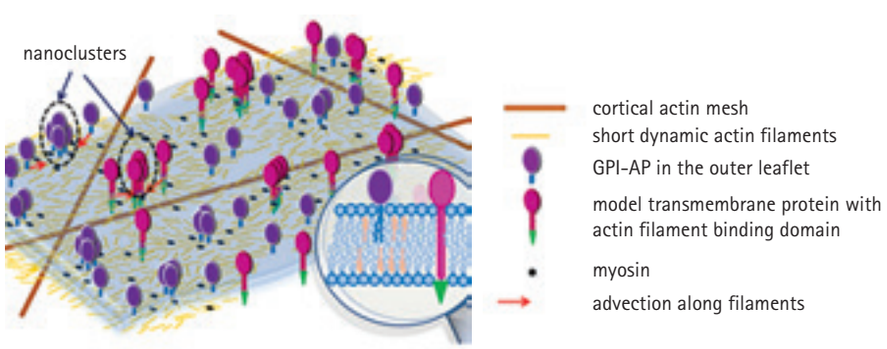
satyajit mayor *Our laboratory studies how a cell may locally regulate membrane composition and control shape to engage in fundamental cellular processes such as signaling and endocytosis, respectively. In turn we study how signaling and endocytosis control tissue patterning during development.*

MECHANISMS OF MEMBRANE ORGANIZATION AND ENDOCYTOSIS IN METAZOAN CELLS

The broad aim of my laboratory is to develop an understanding of how a cell regulates the local organization of its cell surface constituents and how it may engage in deforming its membrane in a regulated fashion. This will help in understanding how a eukaryotic cell constructs signaling complexes (local composition) and engages in membrane traffic, in particular during endocytosis. To study phenomena at the cellular scale, we utilize principles from the physical sciences to frame questions about movement of molecules and organelles inside cells. We have also developed numerous microscopy tools to study organization of cellular components, from the nanometer scale in specialized domains in cell membranes to the micron scale prevalent in mapping endocytic pathways. We also study sorting properties and endocytic pathways of a variety of molecules, including membrane proteins, lipids and lipid-tethered proteins *in vivo*. Our studies provide a new 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.

We are now involved in several specific lines of inquiry. These include; i) theoretical and experimental studies on the basis for the formation of membrane domains in living cells and *in vitro*; ii) exploring the dynamics of such membrane complexes during signaling and templated differentiation in multiple cell systems, including stem cells; iii) understanding the role(s) of scales of organization in the functioning of lipid-tethered morphogens in patterning tissues *in situ,* iv) uncovering molecular mechanism of dynamin-independent endocytosis using cell-based assays at the individual gene scale, and genome wide-RNAi screening methods to study its regulation and evolution.

The trajectory of this work has led us to explore the fine structure of the plasma membrane, providing for the first time an *in vivo* picture of lipidic assemblies challenging existing notions of membrane rafts, an understanding of the role of specialized endocytic mechanisms for the establishment of developmental gradients, and a genome-wide analysis of endocytic pathways.



Gowrishankar, K., Ghosh, S., Saha, S., Rumamol, C., **Mayor, S.** and Rao, M. (2012) Active remodeling of cortical actin regulates spatiotemporal organization of cell surface molecules. *Cell* Jun 8;149(6):1353-67.

Chaudhuri, A., Bhattacharya, B., Gowrishankar, K., **Mayor, S.** and Rao, M.(2011) Spatiotemporal regulation of chemical reactions by active cytoskeletal remodeling. *Proc Natl Acad. Sci. USA* Sep 6;108(36):14825-30.

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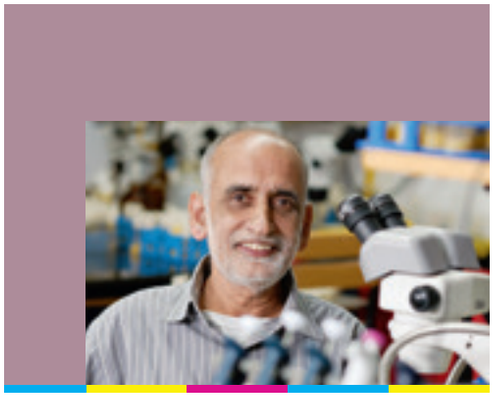

ks krishnan *Our research is aimed at identifying peptides of therapeutic value from venoms of carnivorous marine cone snails and wasps as well as the skin secretions of frogs. We use a combination of molecular biology and mass spectrometry towards this end.*

CELL BIOLOGY OF THE SYNAPSE

My current interest is to identify and characterize 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 peptides, once characterized, could be exploited as pharmacological tools in neuroscience, cell biology and in search for drugs to treat many debilitating diseases. In studies done in collaboration mainly with Prof. Balaram at IISc, 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 characterizing peptides of therapeutic value from wasp venoms and frog skin secretions. We are developing several assays mainly utilizing 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. We also actively collaborate with colleagues at IISc (S Sarma, Hanumae Gowd), colleagues at NCBS (MK Mathew, Aswin Seshasai Narayan, S. Mayor), GKVK (Chandrasekhar Krishnappa), Annamalai University (Olivia and Anthony Fernando), Andhra University (Y. P. Rao), North Orissa University (Sushil Dutta), IISER Bhopal (Vimlesh Kumar) and Trinity College Dublin (Mani Ramaswami).

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 Res.* 11, 515-522. .

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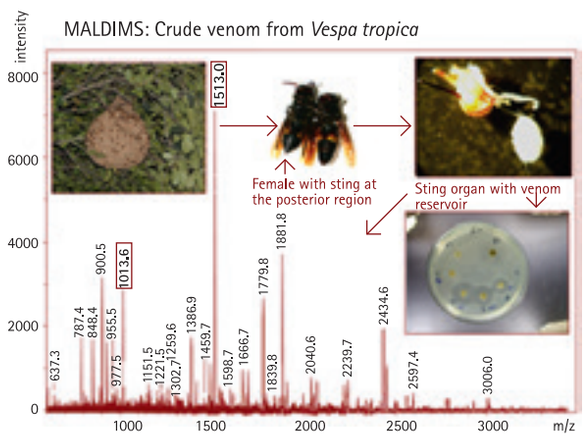

Wasp venoms are likely to have many components of value in drug discovery

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raghu padinjat *Phosphoinositide signals provide molecular control for many key sub-cellular processes. Using the fruit fly Drosophila as our model system, the overall goal is to understand how the architecture of this signaling cascade is designed to deliver optimal physiological outputs.*

THE ARCHITECTURE OF PHOSPHOINOSITIDE SIGNALING

Our long term scientific interest is the analysis of signaling mediated by lipid molecules generated during phosphoinositide metabolism. Phosphoinositide signals provide molecular control for key sub-cellular processes such as membrane remodeling, cytoskeletal function, transcription and translation. Through these processes, this signaling pathway orchestrates basic cellular behaviours such as cell division, shape changes, polarized 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 the architecture of this signaling cascade is designed to optimally deliver physiological outputs. We use *Drosophila* as our model system; the goal is to discover key principles of signal transduction that are likely to be conserved during evolution but are experimentally more tractable in *Drosophila*. Our analysis of these issues is carried out in two biological contexts: (a) Regulation of cell growth during development. (b) Understanding vesicular transport in neurons. It is hoped that in the medium term, our analysis in *Drosophila* will inform studies of equivalent signaling pathways in mammalian models with more immediate biomedical relevance.

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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

3D reconstruction of the mitochondrial network (green) and nucleus (red) in a developing *Drosophila* salivary gland. The organization of sub-cellular organelles is dynamically regulated through Signaling pathways that integrate developmental and nutritional cues. These are under analysis in this laboratory.

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Ecology and Evolution

UMA RAMAKRISHNAN
Evolutionary history of animal populations: Understanding the past and predicting the future

MAHESH SANKARAN
Terrestrial ecosystems and community ecology

KRUSHNAMEGH KUNTE
Speciation, adaptation and morphological diversification; evolution and genetics of butterfly wing patterns

DEEPA AGASHE
Evolutionary ecology of adaptation and genome evolution

uma ramakrishnan *I explore the responses of species to environmental history, climatic perturbation and human impact in the context of species ecologies, to better understand their evolution. Practically, I focus on past and present processes that drive patterns of mammalian genetic variation.*

EVOLUTIONARY HISTORY OF ANIMAL POPULATIONS: UNDERSTANDING THE PAST AND PREDICTING THE FUTURE

Natural environments around us are changing at unprecedented rates. Despite the fact that ecology and evolution are theoretical and conceptually well-developed fields, we remain unsure how the species that surround us will respond to ongoing change. Understanding how species' ecology impacts their evolution is key to predicting species' response, and this is the focus of my research. Specifically, I study the processes governing the response of species to environmental history, climatic perturbation and human impacts in the context of species ecologies, and hence gain a better understanding of their evolution. I focus on the Indian subcontinent because of its unique and dramatic geological history and rich biodiversity.

In practical terms, such research involves assembling field-collected samples, genetic data in the laboratory and conducting detailed statistical analyses. Over the past two years, we have set in motion several multi-species community-level projects for birds, small mammals and carnivores in northeastern India, the Himalaya, the Central Indian forests and the Western Ghats. Soon, we will start unraveling the demographic and evolutionary histories of these species. Using a comparative approach will allow us to discern unique and common responses, and to quantify the role of species ecology in evolution.

Joshi, A, Vaidyanathan, S, Mondol, S, Edgaonkar, A & **Ramakrishnan, U** (2013) Landscape genetics reveals that tiger reserves within an urbanized landscape are not isolated. *PLoS One* DOI: 10.1371/journal.pone.0077980

Mondol, S, Bruford, M & **Ramakrishnan, U** (2013) Demographic loss, genetic structure and the conservation implications for Indian tigers. *Proc R Soc B* 280: 20130496.

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Ochotona Macrotis from West Sikkim

21 • uramakri@ncbs.res.in

mahesh sankaran *Can our ecosystems cope with the challenges of expanding human activities? We work on understanding the dynamics of tree-grass ecosystems, their responses to changing climatic and anthropogenic drivers - and what this means for their future distribution and functioning.*

TERRESTRIAL ECOSYSTEMS AND COMMUNITY ECOLOGY

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

- How interactions and feedbacks between climate, biogeochemistry, fires and herbivory influence the structure, composition and stability of ecosystems and the cycling and sequestration of nutrients.
- How projected changes in climate such as increasing variability of rainfall, increased frequency of droughts, increasing aridity in the tropics, nitrogen and phosphorus deposition and rising CO_2 will impact ecosystem function, stability and services.

Most of our research is carried out in savanna ecosystems in Africa and India. We are now extending this work to encompass a wider range of ecosystem types including rainforests and grasslands. Our current and planned future work will employ both long and short-term experiments, as well as targeted field surveys to address the above questions across the gamut of natural ecosystem types of the Indian sub-continent, with the goal of bringing a comprehensive understanding of biome-scale vegetation and nutrient dynamics in the sub-continent.

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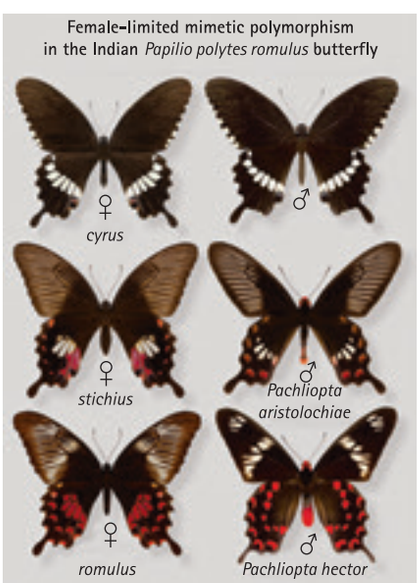
krushnamegh kunte *Biological diversity and its evolution are influenced by natural selection exerted by environmental conditions and interactions within and amongst species. Using Papilio swallowtail butterflies as a model system, we study biodiversity and its complexity at all organizational levels.*

SPECIATION, ADAPTATION AND MORPHOLOGICAL DIVERSIFICATION; EVOLUTION AND GENETICS OF BUTTERFLY WING PATTERNS

I am an evolutionary biologist interested in answering the following questions: (1) How do natural and sexual selection produce morphological complexity and novelty? (2) How do phylogenetic history and ecology impact trait evolution and speciation? (3) What is the genetic basis of adaptations? How does genetic architecture limit or facilitate evolution of adaptive traits?

To answer these questions, I study *Papilio* swallowtail butterflies, which are very diverse both in terms of wing color patterns and species, with tremendous variation in the nature of sexual dimorphism and polymorphism. My work aims to address the selective pressures that favor such variation in wing color patterning and species richness, and uncover the genetic basis of this color pattern variation. I use a variety of approaches to do this. First, I study population biology of these butterflies to understand ecological pressures under which wing color patterns and species have evolved and persist. Second, I perform behavioral experiments to study sexual and natural selection affecting morphological diversification and the formation of species. Third, I use phylogenetic approaches to trace the history of species and their wing patterns. Lastly, I use a combination of genome sequence data, RNAseq data and linkage maps in addition to more traditional genotyping techniques to study the molecular genetics and development of wing color patterns.



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Zhang, **K. Kunte,** and M. R. Kronforst (2013) Genome-wide characterization of adaptation and speciation in tiger swallowtail butterflies using de novo transcriptome assemblies. *Genome Biology and Evolution,* 5:1233-1245

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deepa agashe

Adaptation to various ecological factors has been an important force in the evolution of the amazing array of species on earth. Our lab works on understanding the dynamics and the genetic basis of adaptation, using an experimental evolution approach.

EVOLUTIONARY ECOLOGY OF ADAPTATION AND GENOME EVOLUTION

How do ecological conditions and genetic factors determine the basis and dynamics of adaptation? At the molecular level, what is the nature of selection acting on genome structure and composition? Conversely, how do these genomic characteristics affect adaptation? My favourite approach to address these questions has been experimental evolution in the lab. Using this approach, I've shown that genetic diversity can determine the dynamics of competition, population size, and extinction and adaptation in new habitats. In later work, I showed that synonymous mutations in enzyme-coding genes can affect bacterial fitness, and that these mutants follow unexpected divergent paths to increased fitness.

At my new lab at NCBS we will continue to use this powerful experimental evolution approach to understand adaptation at various levels. For instance, to understand the processes that shape a species' geographical distribution we will analyze dispersal, adaptive potential, and genetic population structure in *Tribolium* beetle populations across India. Using bacteria such as *Escherichia coli*, we also aim to understand how major genomic features such as GC content and codon usage evolve, and their impact on adaptation. With bioinformatic and phylogenetic methods, we can then test the generality of our experimental results.

Together, our projects will help us understand feedbacks between organism's genes, other individuals in their population, and the environment. Our results will be important not only for advancing evolutionary theory but also for practical applications such as predicting species' response to climate change and loss of genetic diversity; and understanding the role of evolution in clinically relevant scenarios such as emergence of drug resistance and pathogenicity.

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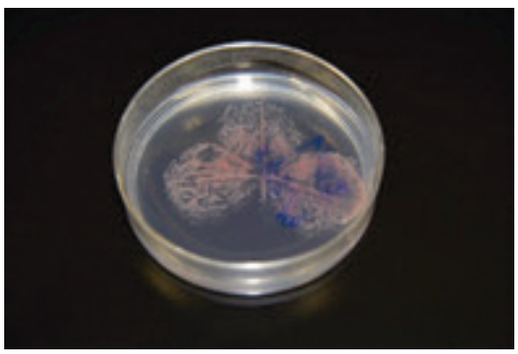

Pink *Methylobacterium* colonies from a leaf imprint, growing on an agar Petri dish

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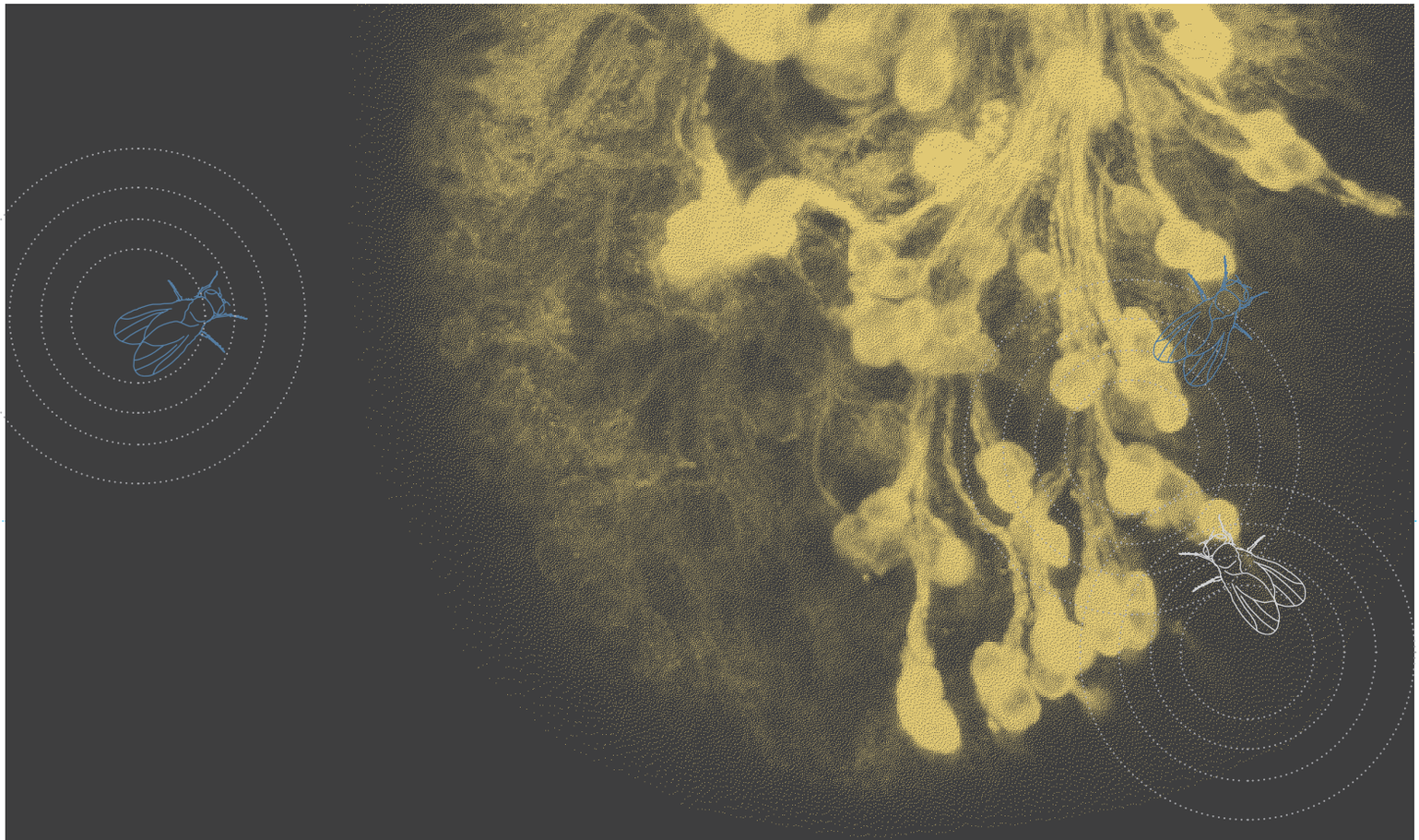

Genetics and Development

K VIJAYRAGHAVAN
Development of neural circuits underlying olfactory behaviour and locomotion

GAITI HASAN
Inositol 1,4,5-trisphosphate signaling in cellular and systemic physiology

PV SHIVAPRASAD
Plant gene silencing and epigenetics

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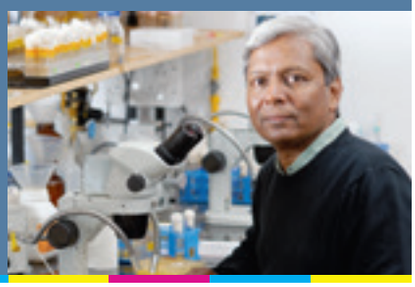


k vijayraghavan *A key problem in developmental neurobiology is deciphering how the dynamic properties of small networks of neurons, which control specific behaviours, are put in place during development. We study identified olfactory and locomotor circuits to unravel the emergence of behaviour.*

DEVELOPMENT OF NEURAL CIRCUITS UNDERLYING OLFACTORY BEHAVIOUR AND LOCOMOTION

A fly landing on a ripe banana negotiates multiple sensory inputs – from odors, its landscape, your swatter – and makes a landing. The animal's ability to deal with the outside world is assembled before it emerges from its pupal case. We examine how this developmental sophistication is achieved.

Paring a behaviour, we study how each unit develops and connects to create a coordinated marvel. Regional specialization is one unit. In the brain, for example, the building blocks are stem cells – neuroblasts – that will divide to create bundles of cells that share lineage and functional similarity and connect to other such bundles each of distinct function. Next, specialized cell-types can be examined. At the final step, we examine how the units, nerves, muscles and tendons connect to make a circuit that behaves.

We study the development of locomotion and, continuing the work of my late colleague Veronica Rodrigues, the olfactory system. Connecting nerves, muscles and the sensory system is just putting the plumbing in place. Examining how the physiology and behaviour of a circuit emerges is being done by studying how the fly walks and smells. In collaboration with Mani Ramaswami, we study robustness and plasticity in olfactory neurons.

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. *J. Neuroscience* (In press)

Brierley, D., Rathore, K., **VijayRaghavan, K.** and Williams, D. (2011) Developmental origins and architecture of *Drosophila* leg motoneurons. *J. Comp. Neurol.* doi: 10.1002/cne.23003

Guruharsha, K.G., Rual, J.F., Zhai, B., Mintseris, J., Vaidya, P., Vaidya, N., Beekman, C., Wong, C., Rhee, D.Y., Cenaj, O., McKillip, E., Shah, S., Stapleton, M., Wan, K.H., Yu, C., Parsa, B., Carlson, J.W., Chen, X., Kapadia, B., **VijayRaghavan, K.**, Gygi, S.P., Celniker, S.E., Obar, R.A. and Artavanis-Tsakonas, S. (2011) A protein complex network of *Drosophila melanogaster. Cell* 147(3):690-703

Neurons derived from an identified stem cell lineage normally connect to a part of the brain called the central complex (left). When mutant for the gene otd, these neurons now innervate the antennal lobe (right). Thus, *otd* (orange) behaves like a regulator of target specification of the neurons in this lineage.

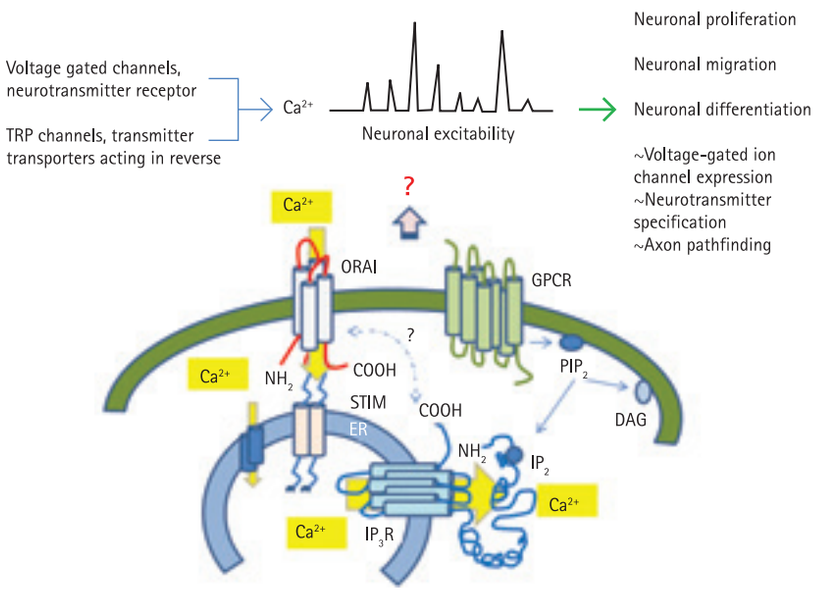
K. VijayRaghavan is currently Secretary of the Department of Biotechnology, GOI

NCBS.indd 26 04/01/14 12:13 PM

gaiti hasan *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.*

INOSITOL 1,4,5-TRISPHOSPHATE SIGNALING IN CELLULAR AND SYSTEMIC PHYSIOLOGY

Research in my group addresses systemic and cellular consequences of changes in intracellular calcium levels in animals. We are specifically interested in the second messenger Inositol 1,4,5-trisphosphate ($InsP_3$) and its receptor – the $InsP_3$ receptor. This protein exists on the membranes of intracellular calcium stores and performs the dual function of a receptor for $InsP_3$ and a channel for calcium release. We address $InsP_3$ receptor function in the model organism *Drosophila* using genetic, molecular, cellular, electrophysiological and behavioral methods. Our recent work has demonstrated that reducing $InsP_3R$ function in *Drosophila* neurons affects feeding and growth in larvae and multiple aspects of flight circuit development and function in pupae and adults. These studies have shown that restoring $InsP_3R$ function in neurons which either synthesize monoamines (like dopamine) or insulin-like peptides (ILPs) rescues $InsP_3R$ mutant defects. More recently, projects to understand how $InsP_3R$ mutants respond to changes in regulation of intracellular store Ca^{2+} and to stress conditions (S. Manivannan, S.K. Metya, submitted) have been initiated. Work from my group has demonstrated for the first time in a physiological context the requirement for store-operated calcium entry downstream of $InsP_3$ signaling in neurons. Results from these studies suggest that genetic and pharmacological methods could be used for controlling intracellular Ca^{2+} homeostasis as a possible therapeutic strategy in certain neurodegenerative and metabolic diseases. *Drosophila* model and human studies in the context of such diseases are in progress.



A model of existing and proposed pathways that contribute to spontaneous Ca^{2+} spikes and excitability in neurons.

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

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pv shivaprasad *Epigenetic marks superimpose underlying DNA sequence of eukaryotes and provide considerable agility is modulating gene expression. It appears that phenotypes of plants are more likely influenced by epigenetics than in animals. We are interested in understanding epigenetic modifications that result in gene silencing involving small RNAs in plants.*

PLANT GENE SILENCING AND EPIGENETICS

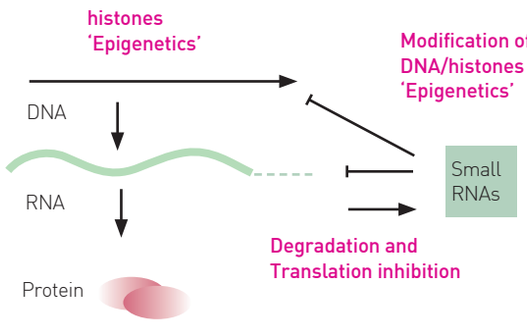
Research in our laboratory deals with molecules called small RNAs. Small RNAs are the key molecules resulting from RNA silencing pathways and they regulate both transcription and translation with the help of their protein partners. Small RNAs are also important factors in initiating and maintaining heritable 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 we really do not know how they work. 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 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 also use cauliflower 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.

Padubidri Shivaprasad, Ho-Ming, Kanu Patel, Donna Bond, and David Baulcombe (2012) A micro RNA superfamily regulates disease resistance via effects on NBS-LRR mRNAs and secondary siRNAs. *Plant Cell* 24: 859-874.

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

R. Mosher, M. Lewsey and **P.V. Shivaprasad** (2010) RNA silencing in plants: Flash report *Silence* 1:13.



A

B

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

B. Natural variation in rice landraces. How much of this appearance is due to action of small RNAs?

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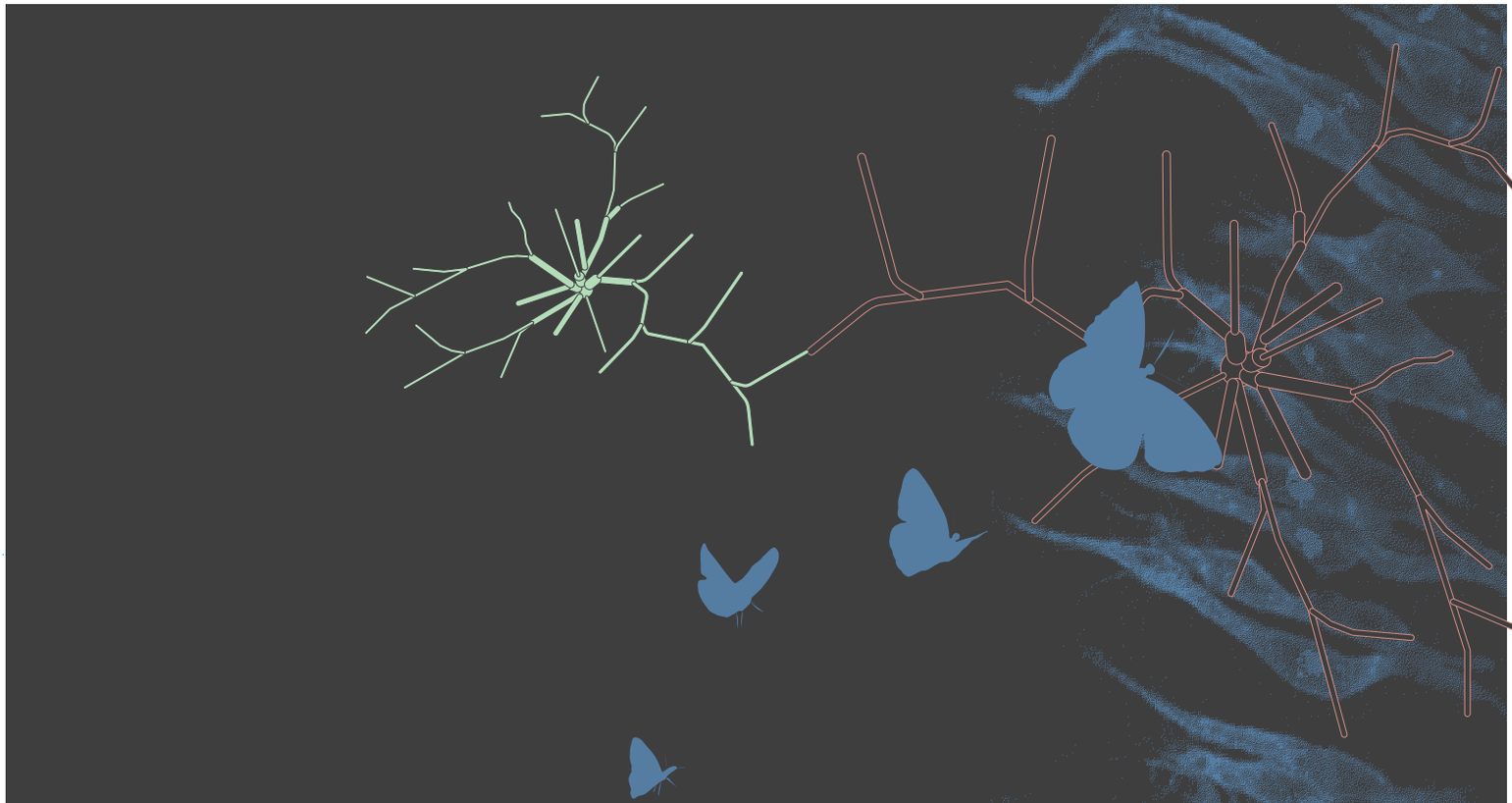

Neurobiology

OBAID SIDDIQI
Genetic analysis of chemosensory perception

MITRADAS M PANICKER
Roles of serotonin in neural and non-neural systems

UPINDER S BHALLA
Computational neuroscience and systems biology

SUMANTRA CHATTARJI
The amygdala in stress and autism spectrum disorders

SANJAY P SANE
Neural and physical basis of insect flight

VATSALA THIRUMALAI
Development and function of motor circuits

AXEL BROCKMANN
Mechanisms of behaviour in honeybees

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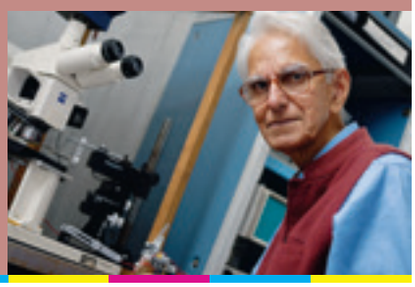


obaid siddiqi

The olfactory responses of 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.

GENETIC ANALYSIS OF CHEMOSENSORY PERCEPTION

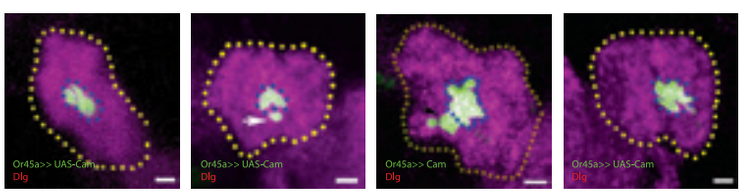
One of the aims of our research on learning and memory is to understand how much of chemosensory behaviour is inborn and how much is acquired after birth. Most odorants except perhaps a few such as CO_2, are not intrinsically attractive or repulsive. By appropriate training attraction can be changed to aversion and aversion to attraction. Previous work in our group has shown that rapid associative learning by reward or punishment takes place in seconds or minutes. Memory curves are polyphasic and can be decomposed into three components, short term, middle term and long term.

The earliest traces of olfactory learning in *Drosophila* are seen in the sensitization of the sensory neurons and altered patterns of chemoreceptor firing (Iyenger et al. 2010). Repeated aversive conditioning by electric shock lead to enhanced synthesis of a number of olfaction related proteins including olfactory and gustatory receptors (NCBS Ann. Report, 2009).

It has been found that mixtures of odorants are perceived by *Drosophila* differently from their components. We observed that the antennal response to a mixture of butanedione and acetone increases many fold at a fixed ratio of 10,000:1 of these chemicals. The duration of the ORN response is also increased. On the other hand, in a mixture of chemicals which are antagonistic, the response duration is curtailed. Binary mixture of odours are thus coded by the ratio of components independently of their absolute concentration.

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

Iyenger A., Chakraborty T.S., Wu C.F. and **Siddiqi O.** (2010) Post-eclosion odor experience modifies olfactory receptor neuron coding in *Drosophila*. *Proc. Natl Acad. Sci. USA* 107, 9855-9860.



Control | 3 hrs after training | 5 hrs after training | 5 hrs after training with cycloheximide

Or45a projection in the larval antennal lobe undergoes changes after training. This change appears after 3 hrs and saturates at 5 hrs. It also requires new protein synthesis. Arrows indicate increase GFP volume at 3 and 5 hrs after training.

Obaid Siddiqi passed away tragically July 26, 2013

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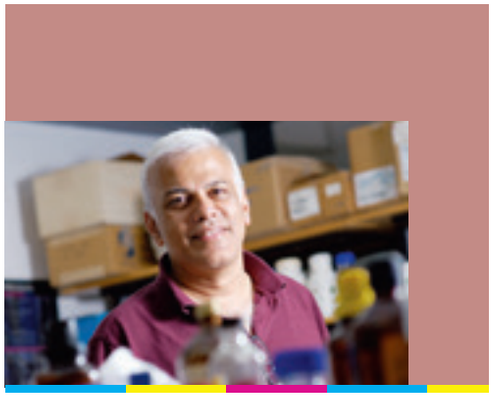


mitradas m panicker *Serotonin is an important neurotransmitter but it also has significant non-neuronal roles both during and after maturation. Our research examines how normally-occurring and introduced molecules regulate, in neuronal and non-neuronal cells, the critical serotonin receptor - 5-HT$_{2A}$.*

ROLES OF SEROTONIN IN NEURAL AND NON-NEURAL SYSTEMS

Serotonin, a well-studied neurotransmitter, has been implicated in a number of physiological processes both within and outside the nervous system. It also seems to play a role in very early development long before the nervous system begins to develop. We have been exploring the interactions of serotonin with a few of the many serotonin receptors using cell lines, cellular models from individual-derived human cell lines and transgenic mouse models.

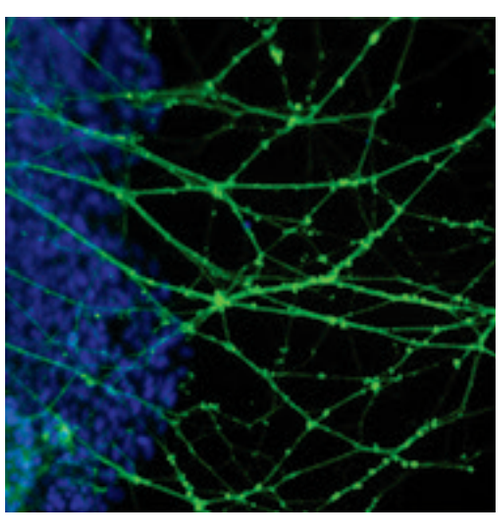
We have used the human and rat 5-HT$_{2A}$ receptors to understand some of the ligand-specific cellular signaling processes that are initiated when various agonists or antagonists bind to this receptor. This has also led to a broader query exploring the interactions of dopamine, another important neurotransmitter, with multiple serotonin receptor subtypes.

Earlier results indicated that serotonin is present in mouse pre-implantation embryos and also in human and mouse embryonic stem (ES) cells. We also have noticed its appearance in induced pluripotent stem cells i.e. when somatic cells, which lack serotonin, are converted to a more 'embryonic stem cell-like' state. Current studies indicate that serotonin seems to help ES cells survive better and seems to provide a more reduced intracellular environment. We are also looking at the role of various genes involved in neurodegenerative and psychiatric disorders in cellular models derived from induced pluripotent stem cells [iPSCs] from individuals with such disorders.

Raote I, Bhattacharyya S, **Panicker MM**. (2013) Functional selectivity in serotonin receptor 2A (5-HT$_{2A}$) endocytosis, recycling, and phosphorylation. *MolPharmacol.* 83(1):42-50.

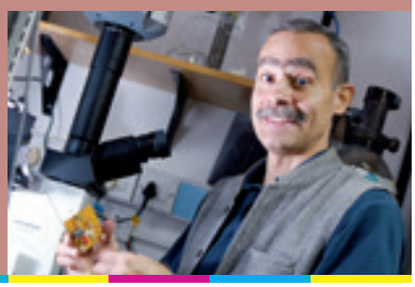
Bhattacharya A, Sankar S, **Panicker MM.** (2010) Differences in the C-terminus contribute to variations in trafficking between rat and human 5-HT$_{2A}$ receptor isoforms: identification of a primate-specific tripeptide ASK motif that confers GRK-2 and beta arrestin-2 interactions. *J Neurochem.* 112(3):723-32.

Basu B, Desai R, Balaji J, Chaerkady R, Sriram V, Maiti S, **Panicker MM.** (2008) Serotonin in pre-implantation mouse embryos is localized to the mitochondria and can modulate mitochondrial potential. *Reproduction.* 135(5):657-69.



Neurons (green) generated via iPS cells from human lymphocytes (Radhika Menon)

31 • panic@ncbs.res.in



upinder s bhalla

We study how memories form. We monitor changes in the activity of hundreds of hippocampal and olfactory bulb cells as mice learn. We then make computer models of the neural networks and subcellular chemical circuits involved in learning.

COMPUTATIONAL NEUROSCIENCE AND SYSTEMS BIOLOGY

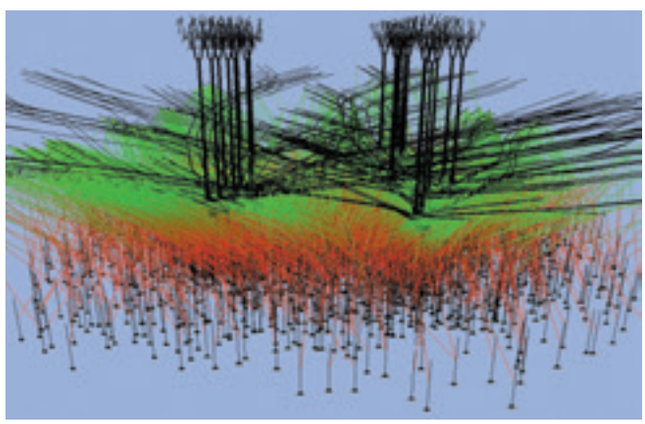
The primary areas of my research are the neurobiology of olfaction; systems biology of learning and memory; hippocampal connections and computations; and multiscale modeling. I briefly outline each below. In *neurobiology of olfaction* we study two main questions: How is odorant information represented in the early olfactory system, and, how do rats track odorants.

Using recordings from rat olfactory bulb during odorant presentation we have shown that odor responses sum linearly both between different odors, and in time. We have also used optogenetics to show that homotypic mitral cells code odors through similar average firing rates but have distinct respiration phase encoding. We have shown that rats can use the stereo signal from two nostrils to improve tracking of surface borne odorants. This analysis of tracking shows that the brain forms *predictive models* of the trajectory of the odor trail. In *Systems Biology of Learning and Memory* we study molecular and electrical signaling events in memory. We are currently modeling activity-triggered mRNA transcription, and subsequent protein synthesis. We are also investigating how structural changes arise from molecular events coupled to traffic. *Hippocampal connections and computations* is a new research topic in our lab. Here we ask how the hippocampal circuit is connected up, and how activity changes during learning. We are developing a technique for extracting network connectivity, using 2-photon recording techniques and optogenetics. We also use 2-photon microscopy to watch the activity in the hippocampus of mice given sensory stimuli, and as they learn new associations between sound and air puffs. *Multiscale Modeling* is a critical research tool for all these studies. We have developed the simulator MOOSE, which is capable of handling multiscale models involving networks, cell biophysics, structure, and molecular processes. We are involved in standardization efforts to improve model accessibility and reproducibility.

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. doi: 10.1523/JNEUROSCI.1781-12.2013

Khan, A.G., Sarangi, M., **Bhalla, U.S.** (2012) Rats track odour trails accurately using a multi-layered strategy with near-optimal sampling. *Nature Communications*. 3(703), doi:10.1038/ncomms1712,

Bhalla, U.S. (2011) Multiscale interactions between chemical and electric signaling in LTP induction, LTP reversal and dendritic excitability. *Neural Networks*. 24(9), 943-949.



Biophysically detailed simulation of the olfactory bulb

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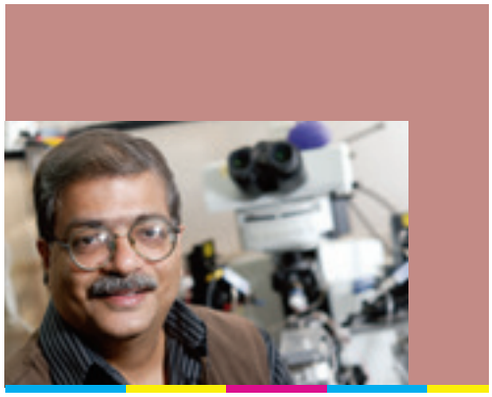
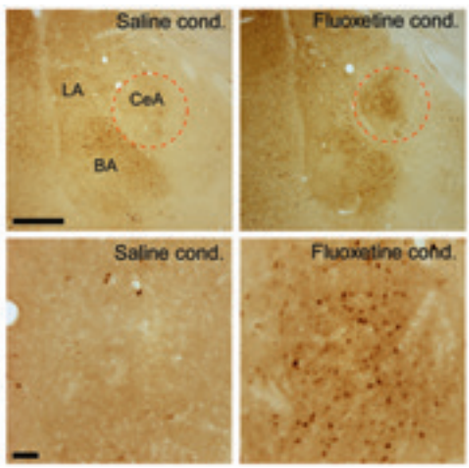


sumantra chattarji *Severe emotional problems are a hallmark of many stress and autism spectrum disorders. We explore the neural basis of these phenomena in the brain's emotional hub – the amygdala – from molecular and synaptic mechanisms at one end to their behavioral manifestations at the other.*

THE AMYGDALA IN STRESS AND AUTISM SPECTRUM DISORDERS

Memories come in different flavors, some more potent than others. Emotionally salient experiences tend to be well remembered, and the amygdala has a pivotal role in this process. But the rapid and robust encoding of emotional memories can also become maladaptive — severe stress often turns them into a source of chronic anxiety. What are the cellular mechanisms underlying these powerful emotional symptoms? To answer this question, we combine a range of behavioral, morphological, molecular and electrophysiological techniques to analyze how stress affects amygdala structure and function — from synaptic mechanisms to their behavioral consequences in rodents. Our findings point to unique features of stress-induced plasticity in the amygdala, which are strikingly different from those seen in other areas of the brain, and could have long-term consequences for pathological fear and anxiety seen in psychiatric disorders.

In addition to behavioral experience, the genes we inherit can also cause cognitive and emotional dysfunction. For instance, individuals afflicted with certain types of autism spectrum disorder often exhibit impaired cognitive function alongside debilitating emotional symptoms. Hence, we are extending our analyses to genetically engineered mice to identify cellular and molecular targets that can be used to correct symptoms of Fragile X syndrome, the leading genetic cause of autism.



Acute systemic fluoxetine treatment prior to fear conditioning leads to an increase in Arc protein expression in the central nucleus (CeA) of the amygdala. ***Upper panel***, low magnification images to show Arc protein expression in the amygdala (CeA indicated by dotted red circles) of fear conditioned rats pretreated with saline (***left***) and fluoxetine (***right***); scale bar: 500µm. Lower panel, representative images of Arc protein expression in the CeA of fear conditioned animals pretreated with saline (***left***) and fluoxetine (***right***); scale bar: 40µm.

Suvrathan, A., Sharath, B.S., Ghosh, S., Tomar, A., Anilkumar, S., **Chattarji, S.** (2013) Stress enhances fear by forming new synapses with greater capacity for LTP in the amygdala, *Philosophical Transactions of the Royal Society B* http://dx.doi.org/10.1098/rstb.2013.0151

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

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

Roozendaal, B., McEwen, B.S., and **Chattarji, S.** (2009) Stress, Memory and the Amygdala. *Nature Reviews Neuroscience* 10: 423-433

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sanjay p sane *The study of insect flight requires a complex integration of physics, physiology, behaviour and ecology. We study multiple flight-related questions in diverse insect systems to identify common underlying principles, as well as the unique capabilities of each species.*

NEURAL AND PHYSICAL BASIS OF INSECT FLIGHT

The spectacular evolutionary success of insects owes much to the evolution of flight. Insect flight is characterized by speed, control and manoeuvrability. Their wings flap at very rapid rates (typically on the order of 10-100 Hz) and hence their sensory system must acquire and process information at similar rates. How do the nervous systems of insects tackle the extraordinary challenges of acquiring, integrating and processing multimodal sensory information and generating of rapid behavioural responses to ensure stable flight? Our laboratory combines inputs from diverse disciplines such as physics, biomechanics, neurobiology, behaviour and ecology to address this question.

Broadly speaking, our approach involves the identification and measurement of interesting flight behaviours in diverse insect taxa (Diptera, Hymenoptera, Lepidoptera), and the dissection of their physical and sensorimotor machinery to understand the mechanisms underlying these behaviours. On the physical front, we combine aerodynamic studies on flapping wings with high-speed videographic measurements of wing motion to understand how flapping wings generate and modulate aerodynamic flight forces to determine their aerial trajectories. On the neurobiological front, we are investigating the combined role of vision and mechanosensation in flight control in insects, including the neural pathways. On the ecological front, we would like to know how the specific behaviours studied in the laboratory operate in their natural context, and also how they are combined and coordinated with other behaviours to enable better survival.

Krishnan, A. and **Sane, S. P.** (in press) Visual feedback influences antennal positioning in flying moths. *Journal of Experimental Biology*

Krishnan, A., Prabhakar, S., Sudarsan, S. and **Sane, S. P.** (2012) Neural mechanisms of antennal positioning in flying moths. *Journal of Experimental Biology* 215, 3096-3105

Zhao L, Huang Q, Deng X and **Sane, S.P.** (2010) Aerodynamic effects of flexibility in flapping wings. *Journal of The Royal Society* Interface 7: 485-497

Diurnal hummingbird hawk moth, *Macroglossum stellatarum*, hovering and feeding on an artificial feeder. Such preparations are very useful for the laboratory studies of flight behavior.

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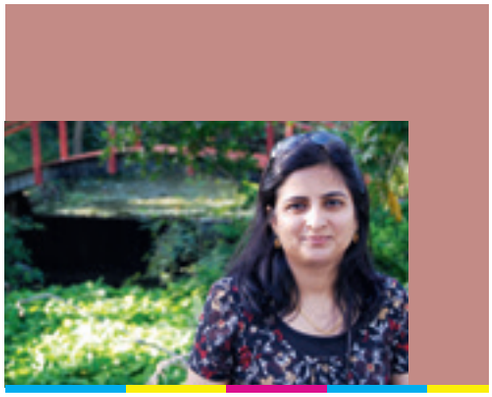


vatsala thirumalai *How does the developing nervous system generate locomotion despite undergoing constant modification? We use developing zebrafish to study this problem as these animals are virtually transparent in their early life stages and the nervous system can be directly observed.*

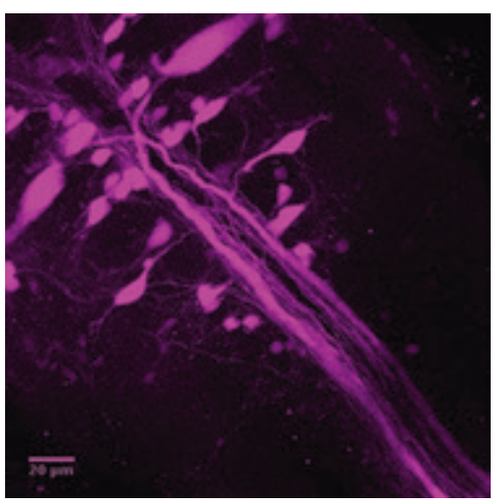
DEVELOPMENT AND FUNCTION OF MOTOR CIRCUITS

How do we move? The answer to this short question may require many more decades of research to unravel. Neural circuits that control movement are arranged in spatially distinct areas of the brain and spinal cord. However, their complex interactions and hierarchy are still not understood. My group focuses on the development and operation of neural circuits that control swimming in the zebrafish larva. Specifically we are analyzing hindbrain circuits that send direct projections to the spinal cord. These are the reticulospinal neurons and they provide the bulk of excitation to spinal motor circuits. In zebrafish, these neurons can be retrogradely labeled with fluorescent dyes and identified based on morphology, location and projection patterns. One question of interest is the neuromodulation of the reticulospinal circuitry by dopamine. Dopamine is inhibitory to swim pattern generation and this seems to be mediated via supra-spinal circuits. Our current efforts are geared towards understanding how dopamine affects the output of the reticulospinal circuit. In a separate line of investigation we are also studying the role of gap junctions in synapse formation and function using reticulospinal neurons as our model. Ultimately, our goal is to understand complex locomotory behaviors such as prey capture at the level of the neural circuit.

Jabeen S and **Thirumalai V** (2013) Distribution of the gap junction protein Connexin35 in the central nervous system of developing zebrafish larvae. *Frontiers in Neural Circuits* May 14;7:91

Thirumalai V, Behrend RM, Birineni S, Liu W, Blivis D, O'Donovan MJ (2012) Preservation of VGLUT1 synapses on ventral calbindin-immunoreactive interneurons andnormal locomotor function in a mouse model of Spinal Muscular Atrophy. *Journal of Neurophysiology* 109(3):702-10

Thirumalai V (2012) Assembling neural circuits for generating movement. *Journal of the Indian Institute of Science* 92(4), 411-426



Confocal image stack of reticulospinal neurons in a 5 day-old larval zebrafish labeled with tetra-methyl rhodamine dextran.

35 • vatsala@ncbs.res.in

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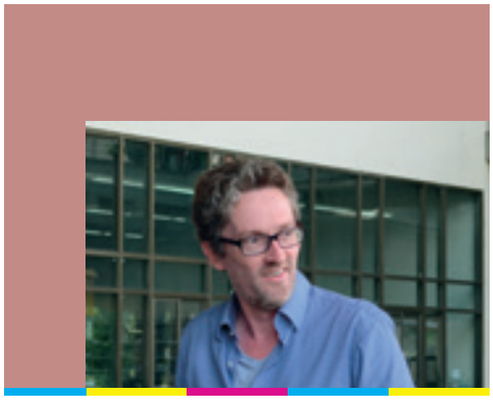


axel brockmann *Honeybees can be trained to perform a range of complex behaviors. We are developing new behavioral paradigms that can be used to analyze their underlying neural and molecular mechanisms.*

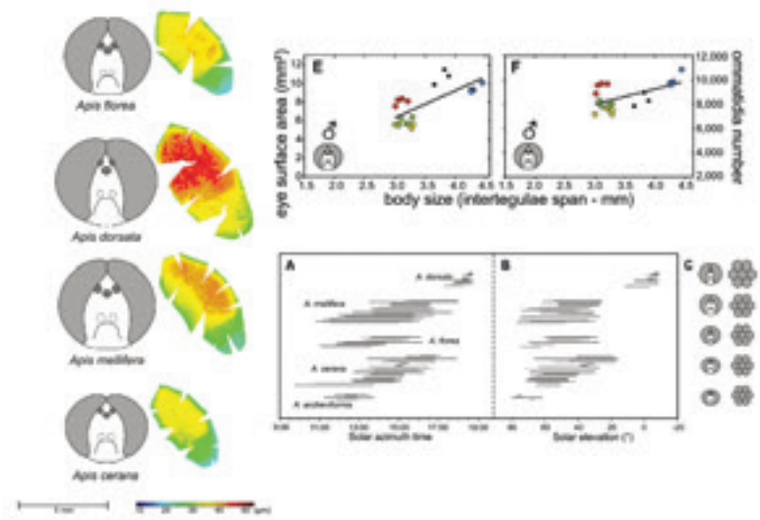
MECHANISMS OF BEHAVIOUR IN HONEYBEES

My lab uses honeybees to study mechanisms of behaviour at the level of individual behaviour, neural circuits and molecules. As a consequence of their natural behaviour honeybees can be trained to artificial feeders, which they will visit many times over a day for several consecutive days. This behaviour enables the researcher to train bees to various feeder conditions or situations, testing sensory and behavioural capabilities. K. v. Frisch successfully used this training paradigm to demonstrate colour vision, polarization vision, and the communication of navigational information. More recently the paradigm was used to test cognitive capabilities in honeybees. Although currently honeybee research lacks the sophisticated molecular tools available in genetic model organisms, in the long run honeybees are the most promising insect species to study neural and molecular mechanisms of more complex behavioural capabilities. A major goal of my lab is to develop new behavioural paradigms (e.g. sugar-elicited search behaviour) as well as new experimental strategies (e.g. peptidomics, immediate early gene activity mapping) to investigate neural and molecular mechanisms of behaviour in freely behaving honeybees.

A second line of research in my lab aims at establishing neurobiological and molecular research on Asian honeybee species (*Apis florea, Apis dorsata,* and *Apis cerana*). Traditionally behavioral research in honeybees focused on the European-African species *Apis mellifera,* unfortunately neglecting the variability in social organization and individual behavior among honeybee species. Honeybee species vary for example in colony organization, pheromone communication, dance behaviour and body size. Body size differences are interesting as they affect the size of sensory systems and the brain. Currently, research projects on Asian honeybees focus on the visual system, mating behaviour and behavioural maturation. In the long run we are interested to identify molecular and neural changes underlying changes in behaviour.

Streinzer, M., **Brockmann, A.,** Nagaraja, N., & Spaethe, J. (2013) Sex and Caste-Specific Variation in Compound Eye Morphology of Five Honeybee Species. (E. J. Warrant, Ed.) *PloS one,* 8(2), e57702. doi:10.1371/journal.pone.0057702.t001

Brockmann, A., Annangudi, S. P., Richmond, T. A., Ament, S. A., Xie, F., Southey, B. R., Rodriguez-Zas, S.R., Robinson, G.E., Sweedler, J.V. (2009) Quantitative peptidomics reveal brain peptide signatures of behavior. *Proceedings of the National Academy of Sciences of the United States of America,* 106(7), 2383–2388. doi:10.1073/pnas.0813021106



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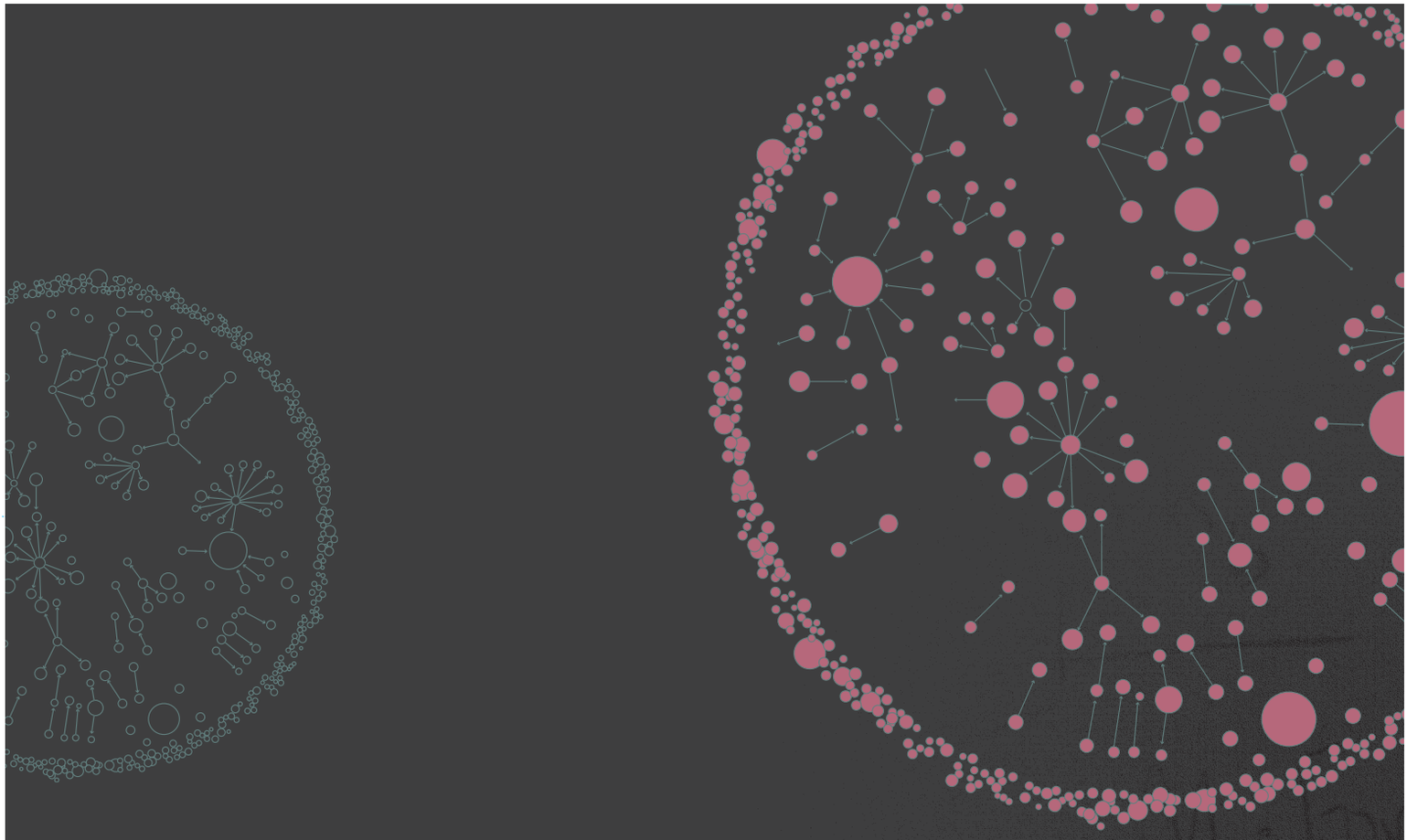


Theory and Modeling of Biological Systems

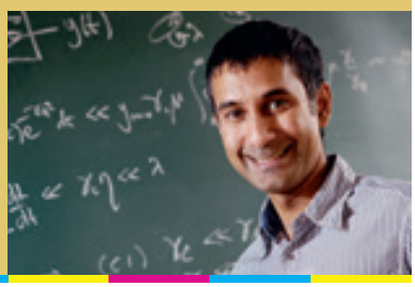
MUKUND THATTAI
The evolutionary origins of compartmentalized cells

MADAN RAO
Theoretical approaches in cell biology: Physics of active evolving systems

SHACHI GOSAVI
Computational folding and functional dynamics of proteins

SANDEEP KRISHNA
Feedback in biological response systems

MADHUSUDHAN VENKADESAN
Morphology and control in animals and machines



mukund thattai *We study the ancient origins of the eukaryotic cell plan. Using biophysical models and bioinformatic techniques, we attempt to reconstruct the emergence of eukaryotic features: the nucleus, mitochondria, compartmentalized organelles and vesicle traffic.*

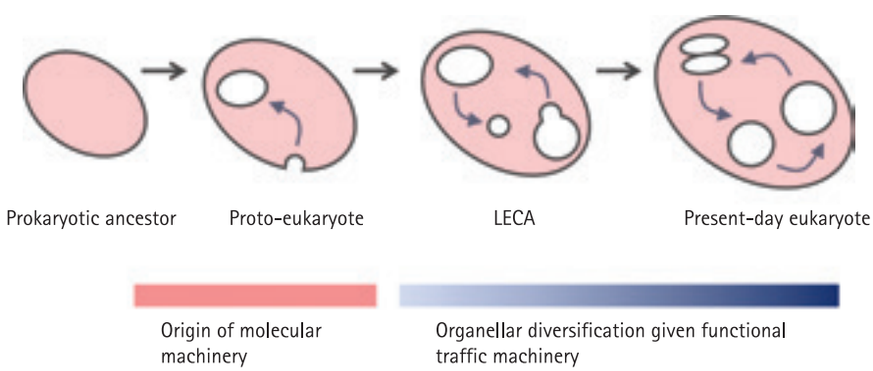
THE EVOLUTIONARY ORIGINS OF COMPARTMENTALIZED CELLS

We are interested in the ancient origins of the eukaryotic compartmentalized cell plan. Surprisingly little is known about this key phase of the evolution of life: eukaryotes began to diverge from bacteria during the global oxygenation event 2.5 billion years ago, but all living eukaryotes share a more recent common ancestor dating from about 1.5 billion years ago. Data from modern eukaryotic genomes might allow us to reconstruct the intervening billion-year period during which quintessential eukaryotic features emerged: the nucleus, mitochondria, compartmentalized organelles, the cytoskeletal machinery and vesicle traffic. In particular, we are pursuing two complementary research directions. Forward in time: we analyze potential origin scenarios using biophysical and evolutionary simulations, to uncover general principles in the evolution of compartmentalized cells. Backward in time: we study the evolution of the molecular machinery underlying compartmentalization using sequence data and phylogenetic techniques; we especially concentrate on molecules that underwent eukaryote-specific gene family expansions, including Rabs, coat proteins, and SNAREs. The population-genetic mechanisms that generated the earliest compartmentalized cells continue to drive the diversification of eukaryotes. Our evolutionary perspective might therefore shed light both on ancient events as well as on modern lineage-specific and tissue-specific elaborations of traffic systems.

M. Thattai (2013) Using topology to tame the complex biochemistry of genetic networks. Phil. Trans. Roy. Soc. A 371, 20110548

R. Ramadas & M. Thattai. (2013) New organelles by gene duplication in abiophysical model of eukaryote endomembrane evolution. *Biophys. J.* 104

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



The origins of eukaryotes can be split into two phases: In the first phase the molecular machinery underlying vesicle traffic arises, leading to the earliest compartmentalized proto-eukaryotes. In the second phase, cells with an existing traffic system undergo organellar diversification. Bioinformatic studies suggest that the 1.5 billion-year-old last eukaryotic common ancestor (LECA) was already a complex cell exhibiting all the quintessential features of modern eukaryotes.

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madan rao *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.*

THEORETICAL APPROACHES IN CELL BIOLOGY: PHYSICS OF ACTIVE EVOLVING SYSTEMS.

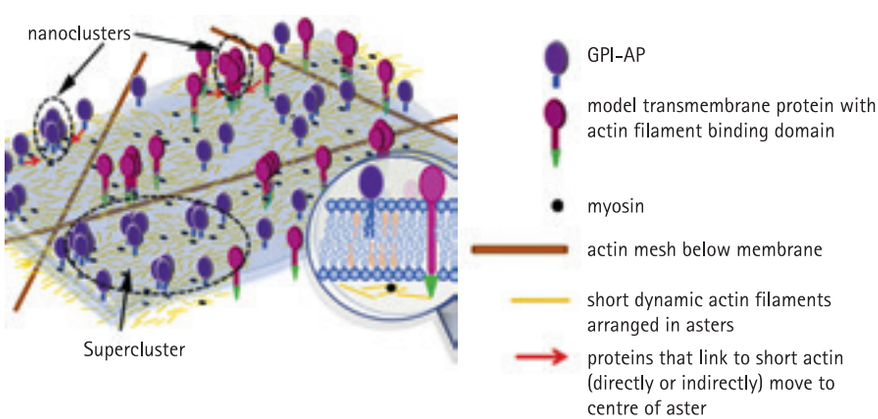
The living cell is an active, self-organized medium comprising molecular processes fuelled by a steady throughput of energy. Our group is interested in the organization, flow and processing of chemical composition, mechanical stress, energy and information in living cells and tissues. These fluxes are coupled via interconnected networks of molecules engaged in biochemical reactions played out in this active dynamical background. The structure of these networks allows for a coarse-grained approach involving new physical principles, unique to the living state. We are interested in the evolution of these molecular and force networks.

These new physical principles are a consequence of the novel response of cellular systems to local active forces which maintain them 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.

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 National Academy of Sciences (USA)*, 110: 15692-15697

Srivastava, P., Shlomovitz, R., Gov, N.S., and **Rao, M.** (2013) Patterning of polar active filaments on a tense cylindrical membrane. *Physical Review.Letters*, 110:168104



To explain the localisation of membrane proteins, it is proposed that actin filaments of a new type – short, and constantly remodeling - are arranged in asters underneath the the cell's outer membrane. If a membrane protein can bind (directly or indirectly) to these filaments, it could be carried towards the centre of an aster, leading to nanocluster formation. A cell could specify where nanoclusters form by promoting aster formation, or by boosting levels of myosin or ATP; the latter help short filaments to organise as inward-directed asters. From Gowrishankar et al., 2012 (edited)

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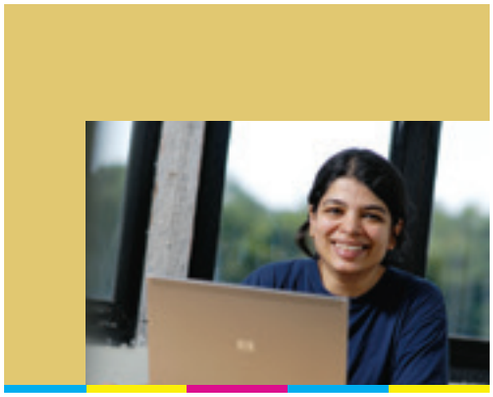


shachi gosavi *A better understanding of how proteins move, both during folding and in the context of function, would facilitate protein design. We use computational molecular dynamics of structure-based models and experiments to derive detailed descriptions of protein motion.*

COMPUTATIONAL FOLDING AND FUNCTIONAL DYNAMICS OF PROTEINS

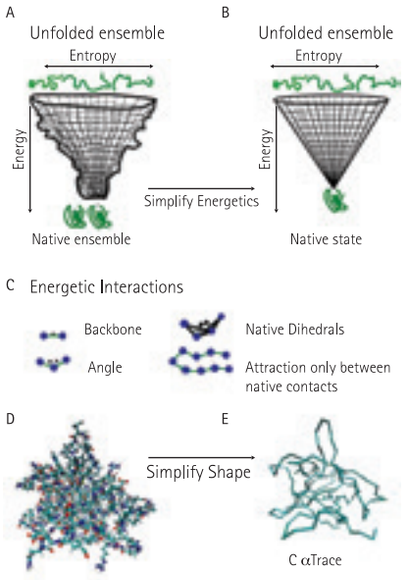
Proteins are the workers of the cell. So, it is important to be able to both predict and engineer their function, in applications ranging from drug design to nano-materials. The native or folded shape of a protein, (as seen in the crystal or NMR structure) is essential for its function. In addition, proteins are constantly in motion and these dynamics aid binding and allostery. Thus, protein motion, both folding to a unique three-dimensional structure and movement of this structure, facilitates protein function.

Computational molecular dynamics (MD) provides a detailed description of protein motion not often accessible to experiment. We use coarse-grained structure-based models of proteins and MD to understand folding as well as functionally relevant dynamics. We compare proteins which have the same fold but diverse function (e.g. the β-trefoil proteins) in order to understand how function affects folding. We study model proteins such as AKE, Top7, etc. in order to understand how sequence and structure contribute to differing folding dynamics. Finally, we also study the folding of novel proteins such at the C-terminal domain of MK0293 using experiment.

Yadahalli, S., and **Gosavi, S.** (2013) Designing cooperativity into the designed protein Top7. *Proteins*, DOI: 10.1002/prot.24393

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) beta-Bulge triggers route-switching on the functional landscape of interleukin-1beta. *PNAS 109*:1490-1493



A summary of structure-based models: (A) Energetic frustration and trapping makes the energy landscape rough. (B) Including only native interactions makes the funnel smooth. (C) The interactions on the left keep the protein polymer chain intact. The interactions depicted on the right cause the protein to fold and unfold. There are no non-native interactions in the model. (D) Full atomic picture of the protein. (E) Coarse grained Cα picture.

NCBS.indd 40 04/01/14 12:13 PM

sandeep krishna *A cell's environment is dynamic and every fluctuation can trigger internal responses that help exploit desirable conditions or counter unwanted changes. I use computational and theoretical approaches to understand the signaling networks that underpin the responsiveness.*

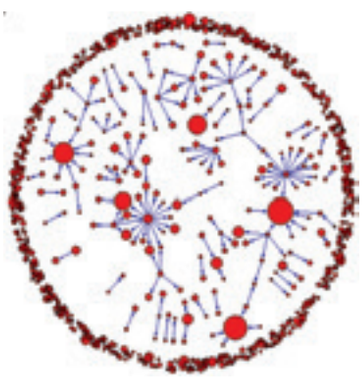
FEEDBACK IN BIOLOGICAL RESPONSE SYSTEMS

My main research interest lies in developing a theoretical framework for understanding the fascinating dynamical patterns produced by living organism as they function and reproduce in changing environments. For example, bacteriophage exhibit multiple stable states upon infection: inflammation in mammalian cells produces oscillations in important proteins; regulation of sugar uptake in prokaryotes acts to maximize the flux through the system, whereas regulation of iron metabolism prevents large fluctuations in iron levels. Feedback loops are responsible for most of this complex dynamical behavior. I use computational modeling and theoretical analyses to understand how cells' signaling networks sense information, and the advantages of different molecular implementations of these mechanisms.

Heilmann, S., Sneppen, K. and **Krishna, S.** (2012) Coexistence of phage and bacteria on the boundary of self-organized refuges., *Proc. Natl. Acad. Sci. USA* (In press)

Jensen, M. H and **Krishna, S.** (2012) Inducing phase-locking and chaos in cellular oscillators by modulating the driving stimuli. *FEBS Lett*. 586, 1664-1668

Csiszovszki, Z., **Krishna, S.**, Orosz, L., Adhya, S. and Semsey, S. (2011) Structure and function of the d-galactose network in enterobacteria. *mBio 2*, e00053-11



Modular structure of the *E coli* signaling network

41 • sandeep@ncbs.res.in

madhusudhan venkadesan

How to run stably on uneven terrains? How to throw accurately at high speeds? How to dexterously handle objects with your hands? We study the interplay between control and morphology in order to understand how animals are more versatile than their robotics counterparts.

CONTROL AND MORPHOLOGY IN ANIMALS AND MACHINES

Our lab is interested in the interaction between control and morphology in animals and machines. We seek to better understand how evolutionary pressures may have shaped the morphology of humans, and why animals often outperform their robotic counterparts in terms of robustness and versatility of motor behaviour. We combine biological, mechanical, and mathematical methods as demanded by the problem on hand. Specifically, we study the dynamics and control of the hand, arm and leg, on scales ranging from collections of muscle fibres to the whole human.

Humans are almost unparalleled in the use of our hands to pick up and handle objects of varying geometry and material properties. Do the constitutive properties of muscles and tendons help or limit our dexterous capabilities? Can this guide the design of new motors that improve the capabilities of current robotic or prosthetic hands?

What are the musculoskeletal features and control capabilities that enable humans to throw projectiles at considerably higher speeds and with better accuracy than other primates? Our studies may provide insight on how hunting as a selection pressure may have shaped certain features of our anatomy.

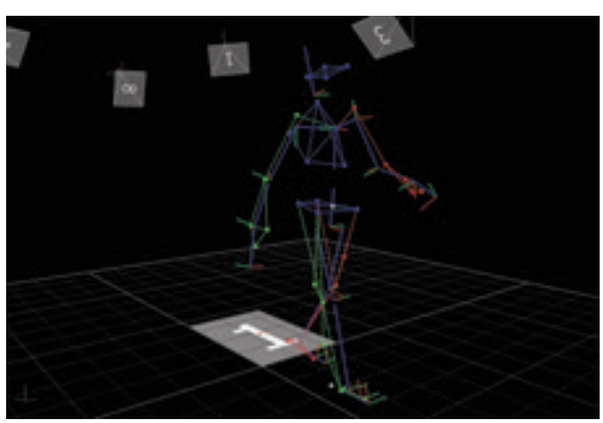
How do humans maintain stability during locomotion on uneven terrains? Does stability come at a substantial energetic cost? Are there specific musculoskeletal properties of the foot and leg that may aid in the neural control of balance?

In our projects, we seek to understand whether animals outperform their robotic counterparts because of or despite the nonlinearities and `sloppiness' inherent to biology. Have animals finely-tuned their sloppiness through evolution in order to achieve the robustness one associates with biology? How do we extract design and control principles for understanding biomechanical function, the diagnosis and treatment of disease and also for improving the state of robotics and prosthetics?

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

Lieberman, D. E., **Venkadesan, M.,** Werbel, W. A., Daoud, A. I., D'Andrea, S., Davis, I. S., Mang'eni, R. O. and Pitsiladis, Y. (2010) Foot strike patterns and collision forces in habitually barefoot versus shod runners. *Nature* 463: 531–5

Venkadesan, M. and Valero-Cuevas, F. J. (2009) Effects of neuromuscular lags on controlling contact transitions. *Philosophical Transactions of the Royal Society A: Mathematical, Physical & Engineering Sciences* 367: 1163–79



In our experiments, we use human volunteers to measure the movement of the body, the external forces acting on it (such as from the ground), the activity of muscles, and also estimate the energy consumed during the activity. Shown here is a screen capture of the software used to track movement in three dimensions with millimeter precision.

NCBS.indd 42 04/01/14 12:14 PM

ACADEMIC PROGRAMS

PhD Program

NCBS is devoted to excellence in research and teaching and our graduate program, which admits students with a Masters or Bachelors degree attracts students from diverse disciplines from all over the country and abroad. NCBS offers state-of-the art facilities for modern biology (see, Research Infrastructure at http://www.ncbs.res.in), actively fostering collaborations that span multiple disciplines. Such interactions have led to the establishment of the Integrated Biology (iBio) program, which encourages students with backgrounds in Physics, Chemistry, Mathematics, Computer Sciences and Engineering to apply their knowledge to understanding concepts in biology.

Student life at NCBS is enriched by a range of seminars, meetings and workshops, providing opportunities to interact with students and faculty from research institutions and Universities in the country and abroad. Student participation in international meetings and workshops both within the country and outside is actively encouraged. NCBS offers an in-house course program, which incorporates several international courses conducted on our campus. We also have active collaborative research programs involving student exchanges, with laboratories across the world. Our ties with the University of Agricultural Sciences on whose campus we are located remain strong with ongoing research collaborations. In addition, we offer short-term learning/training opportunities to pre-doctoral students from Universities and Colleges within India and other countries.

M. Sc. Wildlife Biology & Conservation

NCBS offers a Masters Program in Wildlife Biology & Conservation in collaboration with the Centre for Wildlife Studies, Bangalore. This 2-year program attracts exceptional students from diverse disciplines with a strong interest in wildlife and conservation issues.

The Post-doctoral & Visiting Fellows Program

NCBS has a small but vibrant program for researchers who have a PhD degree. The purpose of the research program is to bring exceptional young scientists to a stimulating intellectual environment where the best facilities are available. We expect that this will result in excellent science and the opportunity for maturing to move on to independent positions in India and abroad. Our Fellows are supported by fellowships from NCBS or national and international funding agencies. In addition, the Visiting Research Fellows/Research Associates program hosts for shorter terms, post-doctoral fellows with primary appointments in other Institutes.

Additional details on these and related programs at NCBS is available at Academic Programs at http://www.ncbs.res.in

NCBS.indd 44 04/01/14 12:14 PM



Masters program in wildlife biology and conservation

The Masters Program in Wildlife Biology and Conservation offered at the NCBS is one with a difference. Accepting candidates from multi-disciplinary backgrounds, the course's focus is to mould students with a passion for nature and conservation into biologists who have a strong grounding in sound methodology and research. Learning is not just restricted to the four walls of a classroom: an aspect that sets the program apart from many others of its kind. Theoretical lessons are located even under tree canopies in dense forests or on sun-kissed white beaches by the sea. Each semester is laden with field trips which offer invaluable hands-on experiences to students, aimed at opening their eyes to wildlife research and conservation in the real world.

Students engaging in the program have to partake in three semesters of coursework which includes the basics of biology, quantitave science and social science, incorporating allied subjects as diverse as mathematics, philosophy of science, floristics, conservation law and science communication. The final semester culminates in the development and successful completion of a field research project for the Masters thesis: where all the theory studied and practicals experienced are applied to gain an in-depth understanding of how research works. These dissertation projects traverse a range of topics – across varied ecosystems such as coffee plantations, evergreen forests and grasslands in the Western Ghats to the slopes of the snow-covered Himalaya and hill streams on north-eastern India; and across species – from elephants, snow leopards and otters to flying lizards, corals and butterflies. Although very short on duration and funding, these dissertation has so far led to nearly 50 publications in peer reviewed journals which form nearly 25% of such publications from India in the last 8 years.

Many of the course's almuni (currently more than 60 in number) are pursuing doctoral degrees in wildlife research. Others have initiated their own research projects across India – from studying insect diversity in the forests of the Western Ghats to conducting gharial surveys in the rivers of central India. Some are also working with non-governmental conservation organizations.

The Masters program is a collaboration between the NCBS, Centre for Wildlife Studies (CWS) and the Wildlife Conservation Society – India program. The Ashoka Trust for Research in Ecology and the Environment, Nature Conservation Foundation, Centre for Ecological Sciences at the Indian Institute of Science, Salim Ali Centre for Ornithology and Natural History, Foundation for Ecological Research Advocacy and Learning and the National Institute of Advanced Studies also support the course in myriad ways.

Many of the course's alumni have been recognized internationally with distinctions like the Carl Zeiss Conservation Award, AAAS Program for Excellence in Science, Scholl Research Challenge Award, Green Hero's Award and John Muir Conservation Award.

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ADJUNCT FACULTY

Adjunct faculty members have close collaborations of a long-term nature. Madan Rao, from the Raman Research Institute is at NCBS so much, and has contributed much to our theoretical understanding that it is embarrassing to call him an adjunct. Madan has a page all his own! The rest of our adjuncts are still quite impressive in their involvement, Mani Ramaswami, now at the Trinity College, Dublin has been a longtime collaborator with KS Krishnan and Veronica Rodriques. Mani's current collaborations are in understanding the cellular players and the underlying molecular mechanisms of odor-habituation. Michael Bate, from the Zoology Department at Cambridge, like Mani, takes his links with NCBS to our foetal days and he has been collaborating with K VijayRaghavan in trying to figure out how animals are set-up, during development, to move about in the real world. Pancho Barrantes, from the Bahia in Argentina, collaborates with Satyajit Mayor to study the mechanisms of acetylcholine receptor recycling. James Spudich from Stanford, who collaborates with Satyajit Mayor, was a key player in formulating the concept for inStem. Jim was also a key player in thinking through our new laboratory buildings. It's clear that we put our visitors to hard work! Sanjeev Jain from the National Institute for Mental Health and Neurosciences at Bangalore formally joined us recently as an adjunct and collaborates with Mitradas Panicker in studying the genetics of schizophrenia, bipolar disorders and Alzheimer's disease.

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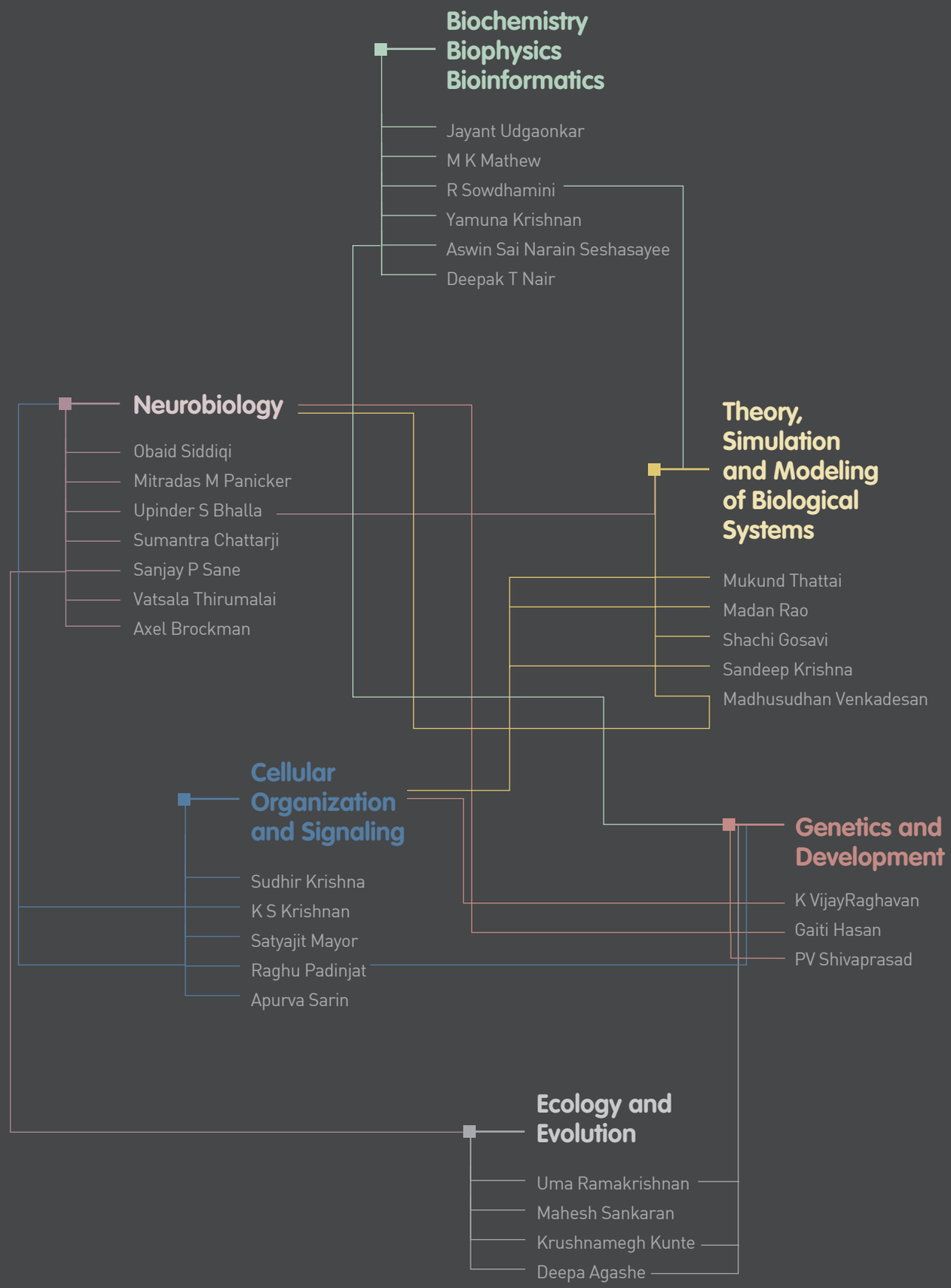

* Several of our investigators have research interests spanning multiple areas of biology and only one of their affiliations is given here.

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 MBI at Singapore for their understanding of induced pluripotent stem cells and cellular engineering principles. 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 Wisconsin-Madison (Khorana Program) 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.

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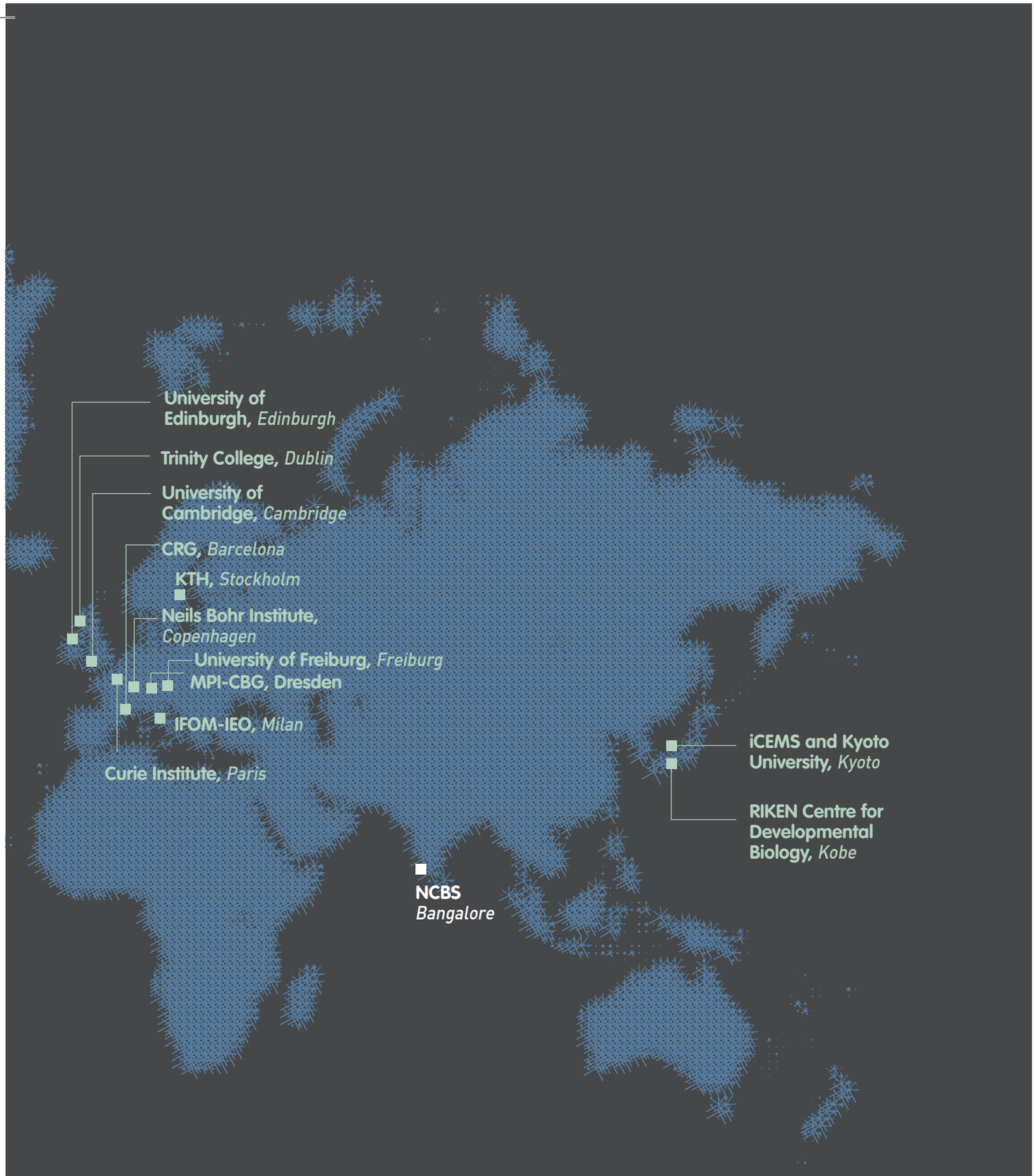

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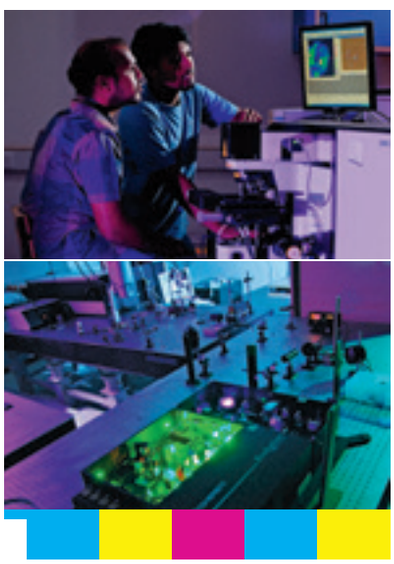
FACILITIES AND RESOURCES



Researchers at NCBS have access to several world-class research facilities, many of which are managed by the Centre for Cellular and Molecular Platforms (http://www.ccamp.res.in/).

SHARED RESOURCES: Shared facilities at NCBS include a well-managed Central Imaging and Flow cytometry Facility (CIFF; equipped with one Transmission Electron Microscope (TEM) and an Atomic Force Microscope (AFM); live cell imaging facilities at the nanoscale including 10 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 upkeep of transgenic and wildtype mice, rats, ***Xenopus*** and Zebrafish, a Mass Spectrometry facility, a Mouse genetics facility for the generation of custom transgenic mice, a transgenic fly facility for the generation of custom transgenic *Drosophila*, and mechanical, electrical and electronics workshop.

INTERNET AND COMPUTER TECHNOLOGY SUPPORT: NCBS has centralized IT support for all its personnel. IT provides services for the installation of software and hardware, maintenance of computer systems and the administration of network facilities within NCBS. Hands on technical support is available for Windows, Apple and Linux based systems and applications. In addition, Linux based high performance computing clusters are also available.

LIBRARY: The library is a large, well-lit multi-level room equipped with journal stacks and textbooks. The library holds approximately 5000 books, 9500 bound volumes, 575 CD/DVDs and subscribes to 140 scientific journals in each year. More than 200 books and 1000 bound volumes are added on average to its collection every year. 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.

FIELD STATIONS: NCBS has collaborations at two field stations of the Madras Crocodile Bank Trust, including the Andaman and Nicobar island's Environmental Team (ANET and the Agumbe Rainforest Research Station (ARRS), aimed at facilitating research and training in marine and island ecology. Under these agreements, NCBS researchers and collaborators have priority access to field facilities such as accommodation and vehicles, as well as the expertise and local knowledge resources available at each of these stations. In addition NCBS has field stations in high altitude rain forest areas of Sikkim as part of a BioResource and Monitoring program with the DBT.

SCAN THIS TO KNOW MORE ABOUT NCBS RESEARCH FACILITIES

LIFE AT NCBS

Away from the hustle and bustle of Bangalore city, NCBS is fortunate to be located within the tranquil interior of twenty acres of the post-graduate campus of the University of Agriculture Sciences. The hectic pace of our research, training and outreach programs finds quiet support from the green spaces that abound with trees, flowering plants, butterflies, dragonflies, bees and bats. Intense discussions on science are sometimes broken by a gentle slithering in the bushes and a momentary flash of color.

NCBS is a unique experience - a mix of competitive science, exposure to the arts, social debate and interactions between diverse populations of people. The campus has several spaces that allow us to host and enjoy cultural events such as music concerts ranging from vibrant jazz to sublime Sufi music and performances of Indian dance forms such as Bharatnatyam and Koodiyattam. These venues are also exploited for displays linking science and society, such as the recently curated exhibition on the life and times of the Nobel laureate Marie Curie. The walls of the institute are adorned with artwork that both celebrates our work and captures the essence of human thought. A lecture hall houses a piano, perfect for amateurs to dabble in and for adepts to rehearse. The open spaces often reverberate with sounds of music and laughter.

Also within the campus is a world of activities that supports the staff at NCBS. In addition to the main cafeteria that caters the full meals at the institute, there are terrace canteens where verdant views, endless cups of coffee and light snacks fuel animated exchanges. The sports complex is modern and well-resourced and a relaxing swim in the pool is often a great end to a hectic day. Onsite doctors ensure that NCBS staff have quick and easy access to any required healthcare. A well-run creche catering to children in the 1-10 year age-group offers immense support to working parents by providing a calm and nurturing environment for the little ones.

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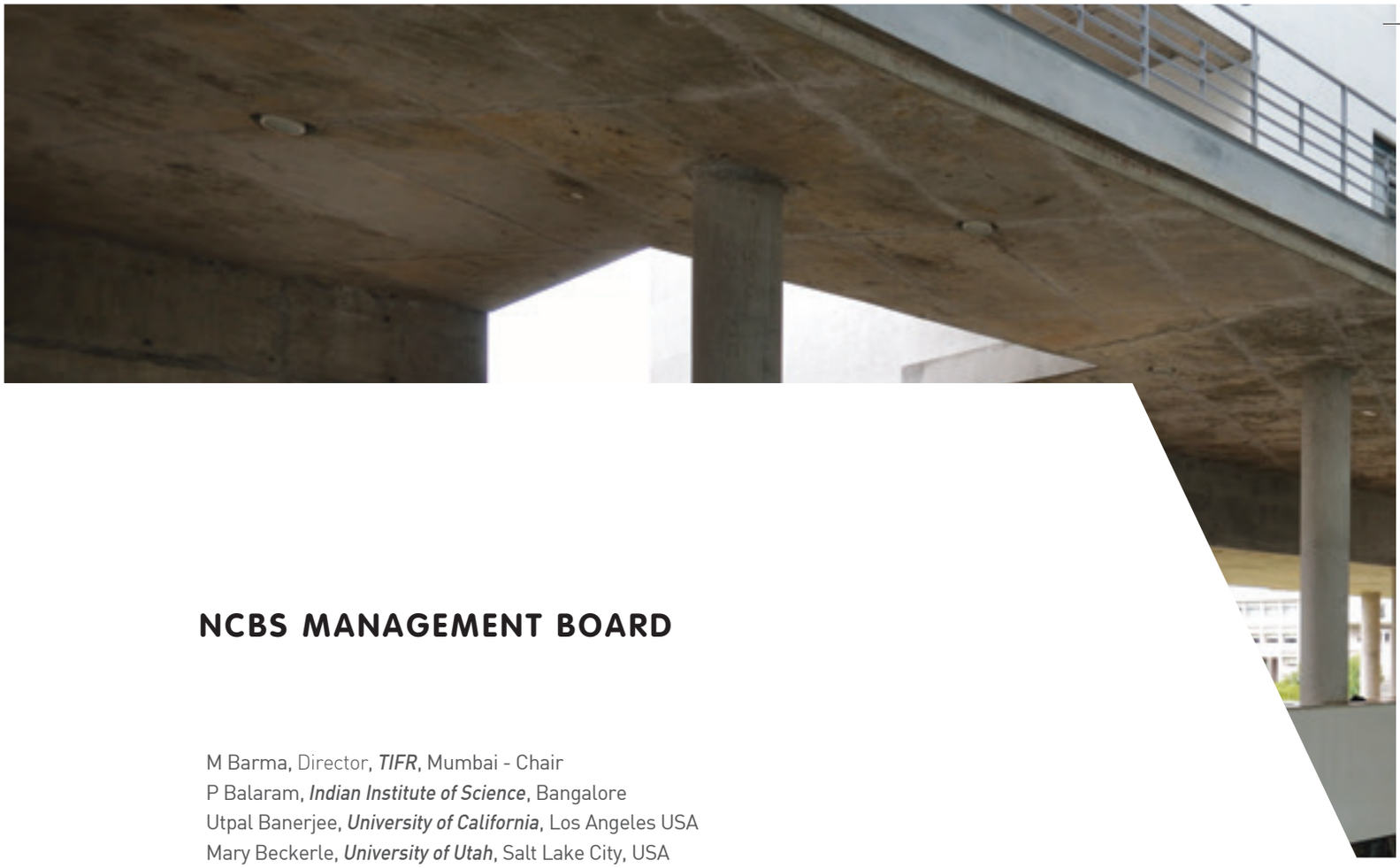

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95 Junior Research Fellows

16 MSc Wildlife Students

33 Post Doctoral Appointments

150 Students Registered for PhD

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Pradip Pyne
TM Sahadevan, ***inStem***
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S Ashok Rao

36
Faculty (Group Leaders /Young and International Investigators/ Joint and Adjunct Faculty)

72
Scientific and technical staff (including trainees)

76
Administration and Auxillary (including trainees)

NCBS Director
K VijayRaghavan (till January 2013)
Satyajit Mayor (from January 2013)

Dean, NCBS
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Head, Academic Activities
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KV Ramanathan

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Savita Ayyar

FUNDING

NCBS is part of TIFR, a major autonomous institute generously aided by the Department of Atomic Energy (DAE), Government of India. Research at NCBS is also supported in a major way through extra-mural grants raised by our investigators from sources including, amongst others, the DBT, DST, CSIR, The Wellcome DBT India Alliance, HFSP, NIH and Simons Foundation and corporate support for specific activities from MERCK, Microsoft, Pfizer, Pepsico and Sanofi-Aventis.

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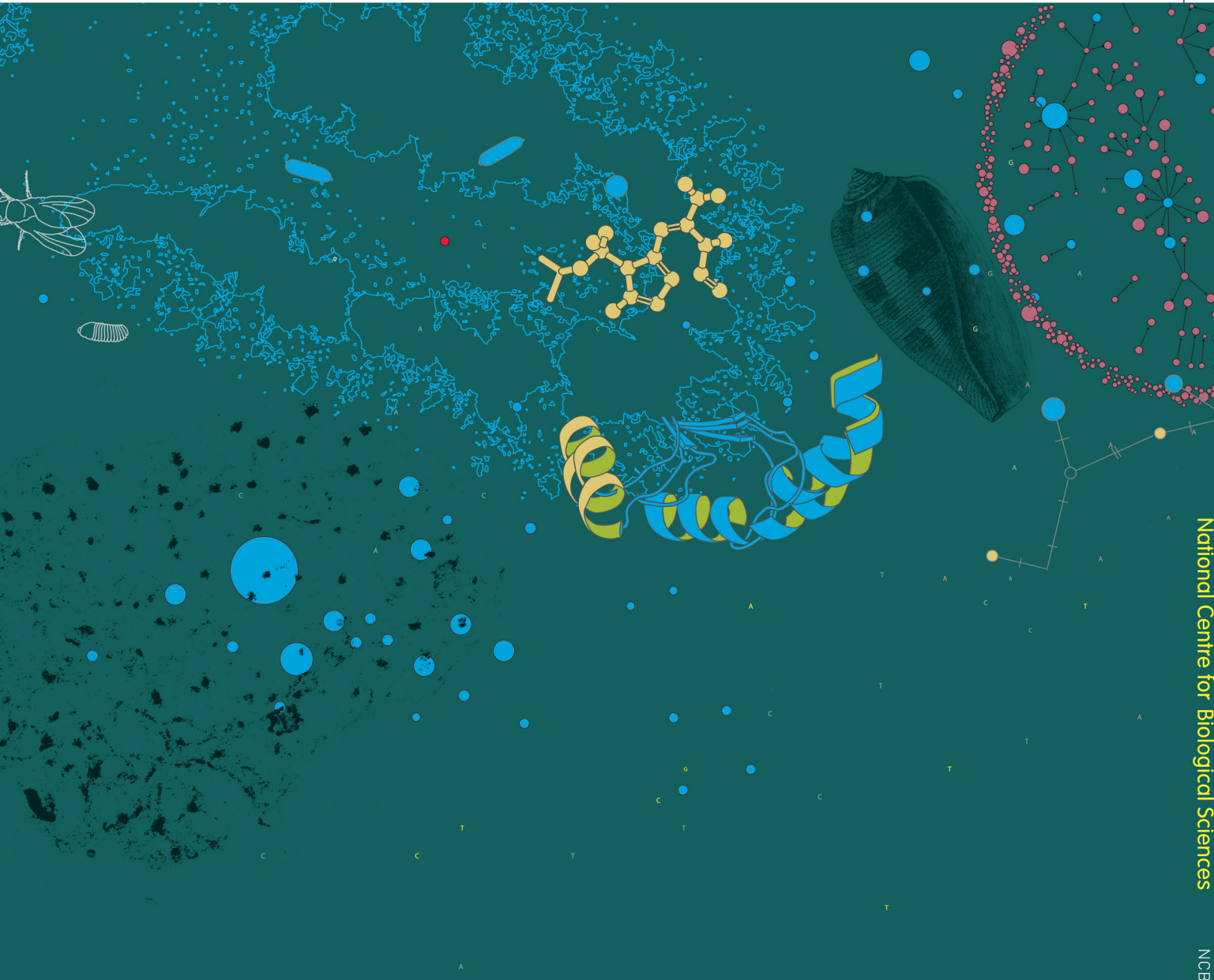

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