National Centre for Biological Sciences

NCBS | TIFR 2010 - 2012

CONTENTS

NOTE FROM THE DIRECTOR

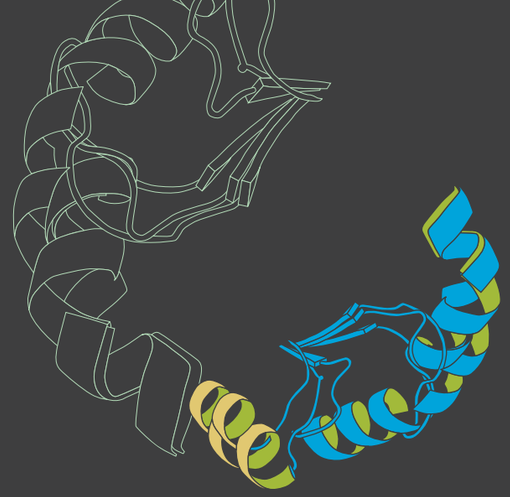
The National Centre for Biological Sciences (NCBS) of the Tata Institute of Fundamental Research (TIFR) in January 2012 celebrated 20 years of its formal existence. This was an enjoyable and stimulating scientific bash, which coincided with our celebration of the 80th birthday of our founder, Obaid Siddiqi. With about 30 investigators and over 200 researchers of various kinds, this a good time to ask what we have achieved and where we are headed.

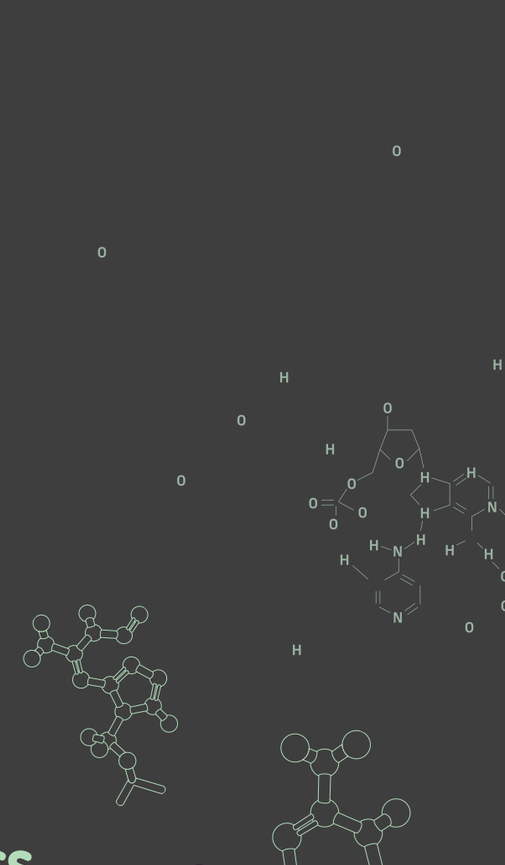
The practice of science is about thinking, doing and communicating. All too often, individuals and institutions fail at the very first step. The smoke and mirrors of perceived demands and peer pressure on what we should do with our research is not conducive to calm, interactive thinking in choosing our research directions. Individuals and institutions choose problems tailored to attract resources rather than to convince researchers that their problems are worth funding. The second step, is the doing of science upon being clear on what we want to do. While resources and facilities are indeed vital, here too its the mind rather than matter that hamstrings many a good idea from moving to fruition. While there is always much room for individual brilliance and the consequent successes of small groups, many aspects of our science today are better done by interactions and collaborations. The skewed peer-group pressure in the life sciences is a ballast against scientific curiosity and the spirit of inquiry driving science: concerns such as how credit will be apportioned to authors in a collaboration often prevent the start of interactions. Thus, while collaborations can often serve better science, the career path for those who chronically do so can appear to be fraught. Finally, in communicating our work, the sometimes crudely stated importance given to where a manuscript is published rather than what it contains can become the tail that wags the dog of science.

If there is one general success that NCBS can be proud of, in addition to building a robust foundation of scientific excellence, it is its demonstration that it is possible in today's environment - at the individual and institutional level - to focus on quality thinking, doing and communicating and not be distracted by the real and imaginary external pressures I have outlined above. You will see the results of this refreshing attitude in this, our first 'slim' report: A range of science that comes from our scientists choosing anything but the boring to work on. In doing their work, they benefit in a range of ways from interactions and collaborations of all kinds, all of which have only enhanced everyone's intellectual standing. Finally, in communicating our work, this curiosity driven science has resulted in wonderful publications of depth and value. Looking back on our 20 years, this report will give you a glimpse of the quality of science from our young median-cohort, our many very new colleagues and our tail of vigorous near 20-year residents. Lest this sound too self-congratulatory, our readers should be assured that we wake up each day and worry about the sky falling on our head: while we like to communicate our successes, we are wary of being dulled by even legitimate propaganda. Enjoy our report!

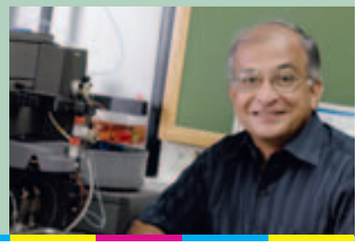
RESEARCH REPORTS

SCAN THIS TO KNOW MORE ABOUT RESEARCH AT NCBS





Biochemistry, Biophysics and Bioinformatics



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.

Jain, S. and **Udgaonkar, J.B.** (2011) Defining the pathway of worm-like amyloid fibril formation by the mouse prion protein by delineation of the productive and unproductive oligomerization reactions. *Biochemistry* 50, 1153-1161.

Aghera, N. and **Udgaonkar, J.B.** (2012) Kinetic studies of the folding of heterodimeric monellin: evidence for switching between alternative parallel pathways. *J. Mol. Biol.* 420, 235-250.

Ramachandran, G. and **Udgaonkar, J.B.** (2012) Evidence for the existence of a secondary pathway for fibril growth during the aggregation of tau. *J. Mol. Biol.* 421, 296-314.

Coiled spring-like fibrils formed by the human tau protein*

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.

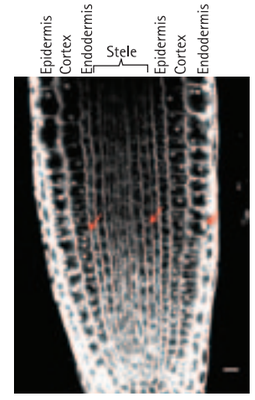
The voltage-gated K^+ channel also appears to be critical for processes as varied as cell proliferation, cell death and differentiation. We have studied proteins that regulate the trafficking of voltage-gated K^+ channels within cells. We are also studying the voltage dependent anion channel, resident 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)

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

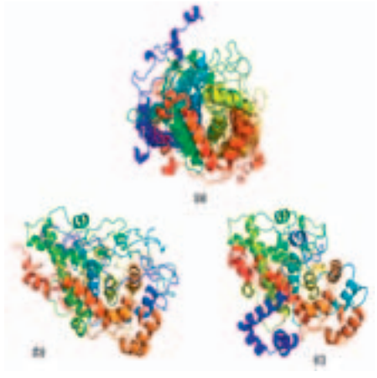
The availability of protein sequence information from whole genome sequencing projects leaves behind a lot of "unknowns" since it does not guarantee knowledge on protein structure, function, conformational changes or their response to the environment. Computational approaches for the analysis of sequences 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.

mrinalini puranik

Flexibility of proteins must impact their function but understanding this relationship is challenging. We use UV resonance Raman spectroscopy, which can detect differences in protein structure, and computational Modeling, to examine the structure and plasticity of DNA-repair proteins.

STRUCTURE AND DYNAMICS OF PROTEINS AND DNA

The extraordinary catalytic and signaling properties of enzymes are ascribed to their ability to fold into unique three dimensional structures that confer specificity of function. Paradoxically, it is also recognized that proteins are highly dynamic, flexible objects that can exist in many different structural conformations and possess motion on a wide range of timescales. Our research is aimed at understanding the role of structural plasticity of proteins in the context of their function. Flexibility of proteins is evidenced by several observations, e.g., (i) ability of enzymes to catalyze multiple substrates, (ii) presence of partially assembled active structures prior to encountering substrates, (iii) allosteric control of substrate affinities. How do these properties influence function? What is the relationship between the dynamical landscape, evolution and acquisition of new function in proteins? How do substrate and functional promiscuity come about in certain structural analogues of enzymes and not others? A challenge in the pursuit of these questions is the availability of techniques with sufficient sensitivity to detect subtle differences in protein structures in solution. We have used ultraviolet resonance Raman spectroscopy in conjunction with computational modeling to address these questions.

The relationship between structural plasticity of proteins and their function is being addressed using two distinct approaches. In one approach, we are exploiting the inherent substrate promiscuity displayed by many nucleic acid binding proteins to study how conformational flexibility plays a role in modulating the active site. We used UVRR spectra of purine substrates of the enzymes as reporters of the subtle changes in the active site environment. We obtained unprecedented, detailed information on the substrate-enzyme interaction. The enzymes under investigation are from two important cellular contexts: (1) the maintenance of genomic integrity via DNA repair in the base excision repair pathway, and (2) the salvage of purine nucleobases. We have demonstrated that the shifts in the observed Raman spectrum of the purine substrates in a nucleic acid-protein complex are an excellent probe of the local environment. The experiments have revealed subtle differences in apparently similar protein active sites. The experimental data are supported by advanced density functional theoretical calculations and hybrid quantum chemical-molecular mechanical calculations performed within our group.

In another approach we measured the dynamical response of the protein to an instantaneous perturbation and the overall conformational heterogeneity in solution. Aromatic amino acids of proteins, tyrosine and tryptophan (Trp), have a high Raman cross section in the ultraviolet region and are sensitive to interactions such as hydrogen bonding and pi-stacking. We used Trp as an intrinsic reporter of the local environment inside a protein. From analysis of the Raman band positions we have inferred the direct Trp-protein contacts. Extensive intensity analysis was then used to determine the excited state dynamics of Trp and the timescale of protein response.

Gogia, S., Balaram, H. and **Puranik, M.** (2011). HGPRT distorts the purine ring of nucleotide substrates and perturbs pKa of bound xanthosine monophosphate. *Biochemistry* 50, 4184-4193.

Jayanth, N. and **Puranik, M.** (2011) Methylation stabilizes the imino tautomer of dAMP and amino tautomer of dCMP in solution. *J. Phys. Chem. B* 115, 6234-6242.

Shanmugasundaram, M. and **Puranik, M.** (2011) Vibrational markers of structural distortion in adenine nucleobases upon DNA damage. *Phys. Chem. Chem. Phys.* 13, 3851-3862.

Currently faculty at IISER Pune
mrinalini@iiserpune.ac.in
http://www.iiserpune.ac.in/~mrinalini/

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.

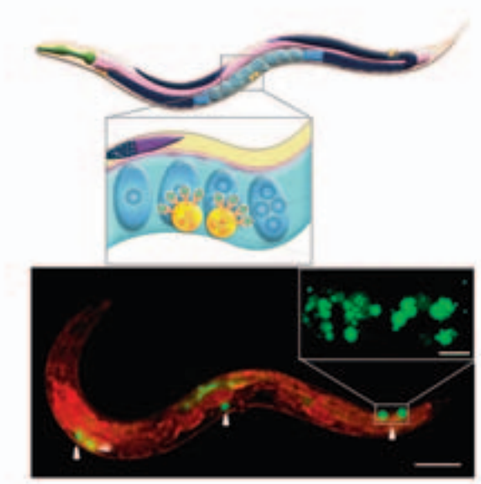
With a diameter of 2 nm and a helical periodicity of 3.5 nm, the DNA double helix is inherently a nanoscale object. The specificity of Watson-Crick base pairing endows oligonucleotides with unique and predictable recognition capabilities. This makes DNA an ideal nanoscale construction material. Understanding 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.

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

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

Saha, S., Chakraborty, K. and **Krishnan, Y.** (2012) Tunable, colorimetric DNA-based pH sensors mediated by A-motif formation. *Chem. Commun*. 48, 2513-2515.



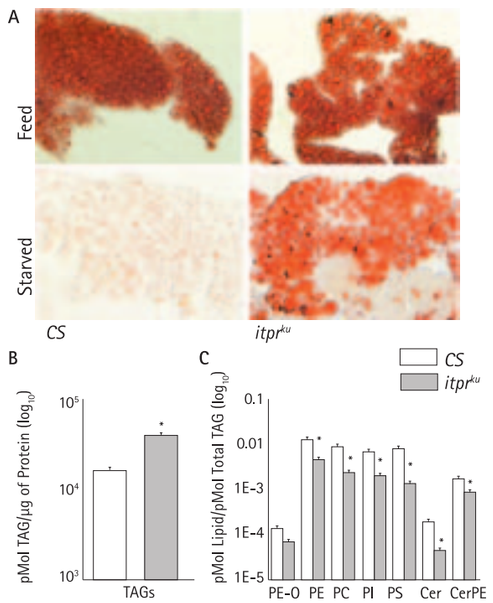
Schematic and representative image of a wild type ***C. elegans*** hermaphrodite microinjected with a solution of fluorescently labeled DNA icosahedron in the pseudocoelom, from where it is internalized by coelomocytes (indicated by white arrowheads, scale bar: 100µm).
Inset shows a representative confocal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

dominik schwudke

We use, and develop, lipidomics technologies to study nutritional and genetic control of lipid homeostasis. D. melanogaster is our model system to investigate lipid metabolism related diseases in humans.

THE INFLUENCE OF LIPID METABOLISM ON HEALTH AND DISEASE

Changes in life style and food habits have led to increasing portion of overweighed individuals in our society. Obesity itself is one of the key risk factors for developing Metabolic Syndrome which further can lead to cardiovascular diseases, hypertension and diabetes. With the development of mass spectrometry based lipidomics technologies more sophisticated diagnostic tools are available to establish the functional connection between altered lipid metabolism and the development of associated diseases. In that regard we tightly connect life science mass spectrometry with biology creating a core competence for interdisciplinary research. We have chosen *D. melanogaster* as model system because of its richness on genetic and cell biological tools and its applicability to investigate lipid metabolism related diseases in humans. We perform lipidomics of tissues, cells and cellular compartments on specific key events of the *D. melanogaster* development. A specific focus of our work is the nutritional and genetic control of lipid homeostasis. In that perspective we investigate models for neurodegeneration *bchs* (blue cheese – for Chediak Higashi Syndrome), *spin* (spinster – for Lysosomal Storage Disease) and *itpr* (inositol 1,4,5-trisphosphate receptor – for Obesity and Metabolic Syndrome) and their connection to lipid metabolism.



Lipid homeostasis is perturbed in itpr mutants inducing obesity
(A) Oil Red stained lipid droplets in wild-type (*CS*) and *itpr*^{ku} fat body cells under fed and starved conditions (B) Homeostasis of storage and membrane lipids is altered in *itpr*^{ku} pupae. The amount of TAGs per total protein was significant higher than in CS pupae (*P<0.005, ANOVA, post-hoc Bonferroni test). (C) Selected membrane lipid classes in *itpr*^{ku} pupae were significantly reduced per total TAGounts (*P<0.05 ANOVA, post-hoc Bonferroni test).

The figure is part of manuscript in cooperation with the Hasan Lab.

Graessler, J#., **Schwudke, D.#**, Schwarz, P.E.H., Herzog, R. and Shevchenko, A. Top-Down lipidomics reveals ether lipid deficiency in blood plasma of hypertensive patients. *PLoS ONE* 2009 4(7): e6261 #These authors contributed equally to this work.

Carvalho, M., **Schwudke, D.**, Sampaio, J.L., Palm, W., Riezman, I., Dey, G., Gupta, G.D., Mayor, S., Riezman, H., Shevchenko, A., Kurzchalia, T.V. and Eaton, S. (2010) Survival strategies of a sterol auxotroph. *Development* 137 (21), 3675-3685.

Herzog, R.#, **Schwudke, D.#**, Schuhmann, K., Sampaio, J.L., Bornstein, S.R., Schroeder, M. and Shevchenko, A. (2011) A novel informatics concept for high-throughput shotgun lipidomics based on the molecular fragmentation query language. *Genome Biol.* Jan 19;12(1):R8.

# These authors contributed equally to this work.

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.

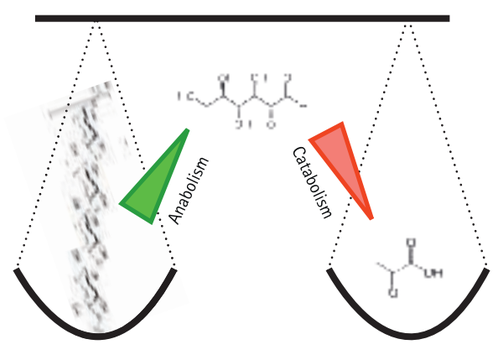
The primary focus of our research is to investigate bacterial regulatory systems from the standpoint of both their occurrence in diverse bacterial genomes and their role in achieving global and function-specific gene expression control in model bacteria such as *Escherichia coli.*

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.

Martincorena, I., **Seshasayee, A.S.N.** and Luscombe, N.M. (2012) Non-random mutation rates suggest a risk management strategy for evolution. *Nature.* 485: 95-98.

Prieto, A.I., Kahramanoglou, C., Ali, R.M., Fraser, G.M., **Seshasayee, A.S.N.** and Luscombe, N.M. (2012) Genomic analysis of DNA-binding and gene regulation by homologous nucleoid-associated proteins IHF and HU in *Escherichia coli* K12. *Nucleic Acids Research*. 40(8): 3524-3537.

Seshasayee, A.S.N., Singh, P. and Krishna, S. (2012) Context-dependent conservation of DNA methyltransferases in bacteria. *Nucleic Acids Research* 1;40(15):7066-73.



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

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.

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*. D68:960-967.

Sharma, A. and **Nair, D.T.** (2012) MsDpo4—a DinB Homolog from *Mycobacterium smegmatis*—Is an error-prone DNA polymerase that can promote G:T and T:G mismatches. *Journal of Nucleic Acids* vol. Article ID 285481, 8 pages.

Sivakumar, N., Jain, D., Kulkarni, D.S., Tabib, C.R., Friedhoff, P., Rao, D.N. and **Nair, D.T.** (2010) The C-terminal domain of the MutL homolog from *Neisseria gonorrhoeae* forms an inverted homodimer. *PLoS ONE*. Oct 28;5(10):e13726.

Cellular Organization and Signaling

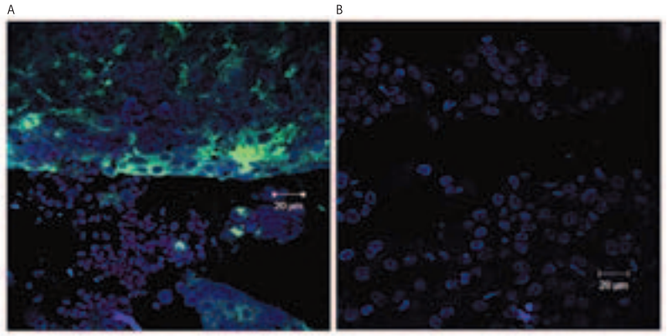
sudhir krishna *In collaboration with Kidwai Memorial Oncology Institute, we have identified and are studying a subset of CD66+ cells that is dependent on Notch signaling. Using leukemias as a pivot, we are developing a biology-medicine interphase program with St. John's Medical College.*

NOTCH SIGNALING IN CANCER AND THE DEVELOPMENT OF A BIOLOGY-MEDICINE INTERPHASE PROGRAM

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.



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

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.

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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.

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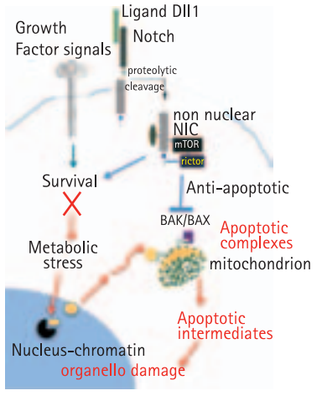


A schematic of pro-and anti-apoptotic signaling pathways activated in mature T-cells. Our experiments show that the spatial regulation of intracellular signaling cascades, exemplified by Notch activity, is a key mechanism governing survival in T-cell subsets. Mechanisms by which inter-organelle signaling 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.

satyajit mayor

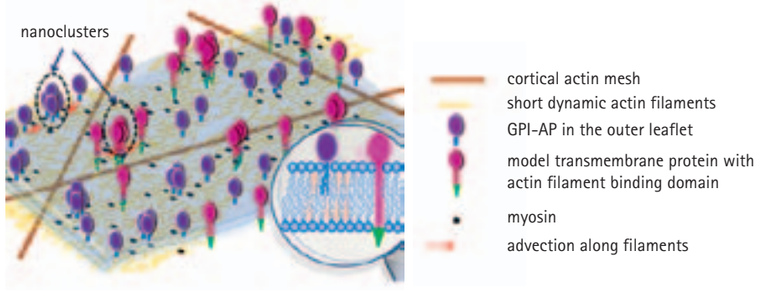
Our laboratory studies how a cell may locally regulate membrane composition and control shape to engage in fundamental cellular processes such as signaling and endocytosis, respectively. In turn we study how signaling and endocytosis control tissue patterning during development.

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.



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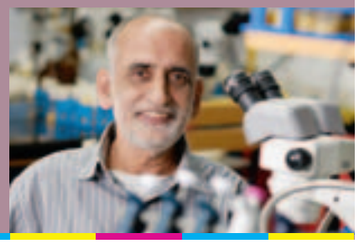

ks krishnan

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).

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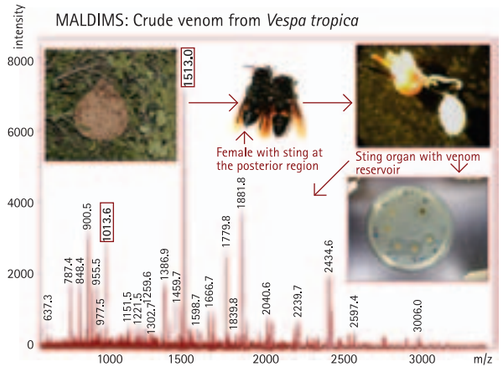

Wasp venoms are likely to have many components of value in drug discovery

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 *IN VIVO*

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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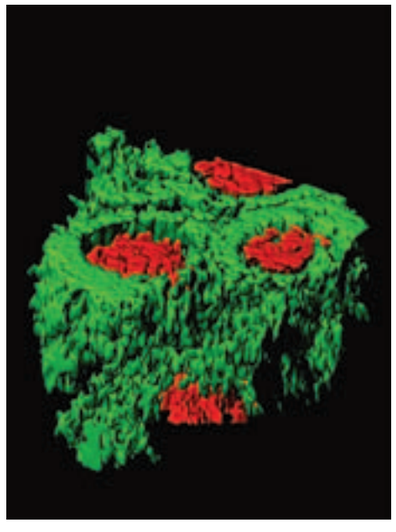

3D reconstruction of the mitochondrial network (green) and nucleus (red) in a developing *Drosophila* salivary gland. The organization of sub-cellular organelles is dynamically regulated through Signaling pathways that integrate developmental and nutritional cues. These are under analysis in this laboratory.

Ecology and Evolution

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

SUHEL QUADER
Evolutionary ecology and biodiversity conservation

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.

Garg, K.M., Chattopadhyay, B., Swami Doss, P.D., Vinoth Kumar, A.K., Kandula, S. and **Ramakrishnan, U.** (2012) Promiscuous mating in the harem-roosting fruit bat, *Cynopterus sphinx*. *Molecular Ecology*. doi:10.1111/j.1365-294X.2012.05665.x

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Mondol, S., Karanth, K.U. and **Ramakrishnan, U.** (2009) Why the Indian subcontinent holds the key to tiger recovery. *PLoS Genetics*, 5(8): e1000585. doi:10.1371/journal.pgen.1000585

Ochotona Macrotis from West Sikkim

suhel quader *Many organisms are locked into millennial struggles of one-upmanship, evolutionary arms races. We study two fascinating cases of this: female cuckoos versus the birds whose nests they lay their eggs in, and mosquito larvae versus their predators.*

EVOLUTIONARY ECOLOGY AND BIODIVERSITY CONSERVATION

Evolutionary theory unifies the biological disciplines by providing a common framework through which we can investigate both the unity and diversity of biological systems. Understanding the evolution of these systems requires an appreciation of the context in which evolution occurs. Ecology is that context. Our lab focuses on the evolutionary ecology of individuals, populations, and species.

What is the nature of coevolutionary interactions between species? To investigate this, we study the strategies of brood parasites and the defences of their hosts (Sumit Sinha); and how mosquito larvae assess and respond to predation risk (C. Karthikeyan and Sumithra Sankaran). We also look at the ecological factors influencing the outcome of mutualistic plant-pollinator relationships (Amritendu Mukhopadhyay). The consequences of habitat change can sometimes be subtle, and its effects on the details of demography can be effectively studied using birds (Umesh Srinivasan). Another area of interest is the population history and current population genetics of the invasive plant *Lantana camara* (Avik Ray).

Finally, we encourage public participation in research. Our lab runs the Citizen Science Programme at NCBS, which has two major projects. *MigrantWatch* tracks the timing of migration of birds; and *SeasonWatch* monitors the timing of flowering, fruiting, and leaf-flush of trees.

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Ray, A., Sumangala, R. C., Ravikanth, G., Uma Shanker, R. and **Quader, S.** (2011) Isolation and characterization of polymorphic microsatellite loci from the invasive plant *Lantana camara* L.. *Conservation Genetics Resources* 4:171-173.

Pomatorhinus ferruginosus (Umesh Srinivasan)

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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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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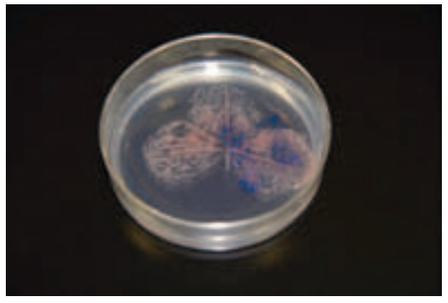
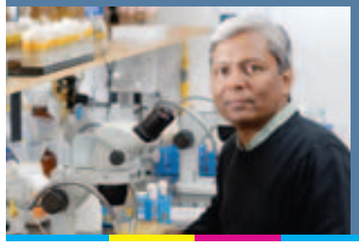


Pink *Methylobacterium* colonies from a leaf imprint, growing on an agar Petri dish

Genetics and Development



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.

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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.

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.*

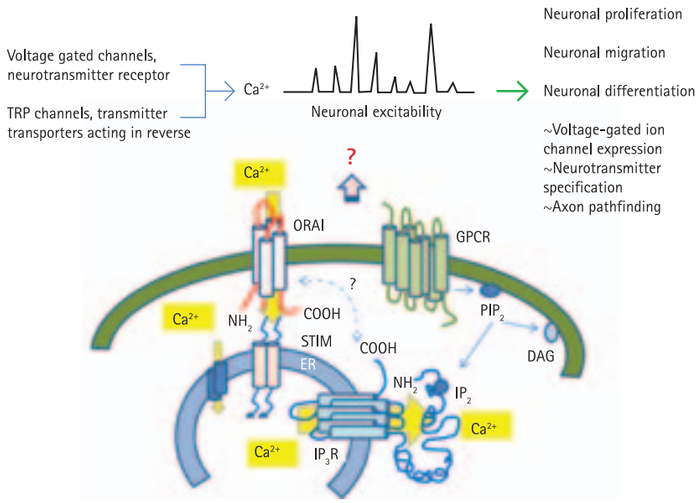
INOSITOL 1,4,5-TRISPHOSPHATE SIGNALING IN CELLULAR AND SYSTEMIC PHYSIOLOGY

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.

Kumar, S., Dey, D. and **Hasan, G.** (2011) Patterns of gene expression in *Drosophila* $InsP_3$ receptor mutant larvae reveal a role for $InsP_3$ signaling in carbohydrate and energy metabolism. *PLoS ONE*, 6(8): e24105. doi:10.1371/journal.pone.0024105

Chorna, T. and **Hasan, G.** (2011) The genetics of calcium signaling in *Drosophila melanogaster*. *Biochem. Biophys. Acta* doi:10.1016/j.bbagen.2011.11.002.

Chakraborty S. and **Hasan G.** (2012) IP_3 Receptor, store-operated calcium entry and neuronal calcium homeostasis in *Drosophila*. *Biochemical Society Transactions* 40, 279-281.



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

Neurobiology

OBAID SIDDIQI
Genetic analysis of chemosensory perception

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

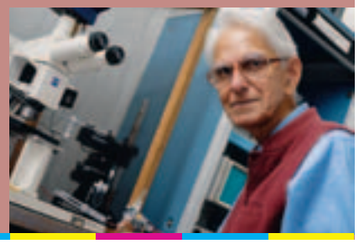
UPINDER S BHALLA
Computational neuroscience and systems biology

SUMANTRA CHATTARJI
The amygdala in stress and autism spectrum disorders

SANDHYA P KOUSHIKA
Studying the regulation of axonal transport-cellular neurobiology

SANJAY P SANE
Neural and physical basis of insect flight

VATSALA THIRUMALAI
Development and function of motor circuits



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

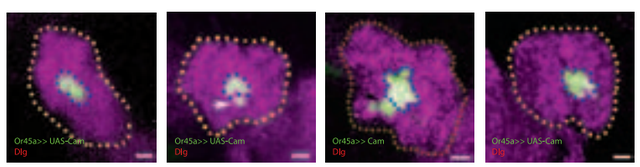
One of the aims of our research on learning and memory is to understand how much of chemosensory behaviour is inborn and how much is acquired after birth. Most odorants except perhaps a few such as CO_2, are not intrinsically attractive or repulsive. By appropriate training attraction can be changed 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.

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.

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



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.

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.

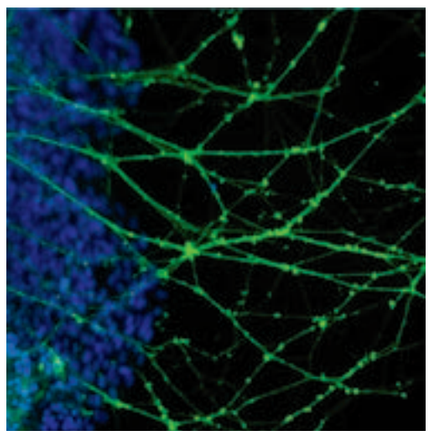
We have used the human and rat 5-HT_{2A} receptors to understand some of the ligand-specific cellular signaling processes that are initiated when various agonists or antagonists bind to this receptor. This has also led to a broader query exploring the interactions of dopamine, another important neurotransmitter,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

Basu, B., Desai, R., Balaji, J., Chaerkady,R., Sriram, V., Maiti, S., and **Panicker, M.M.** (2008) Serotonin in pre-implantation mouse embryos is localized to the mitochondria and can modulate mitochondrial potential. *Reproduction* 135: 657-65.

Kanagarajadurai, K., Manoharan, M., Bhattacharya, A., **Panicker, M.M.** and Sowdhamini, R. (2009) Molecular modeling and docking studies of human 5-hydroxytryptamine 2A (5-HT_{2A}) receptor for the identification of hotspots for ligand binding. *Molecular Biosystems* 5:1877-1888.

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



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

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

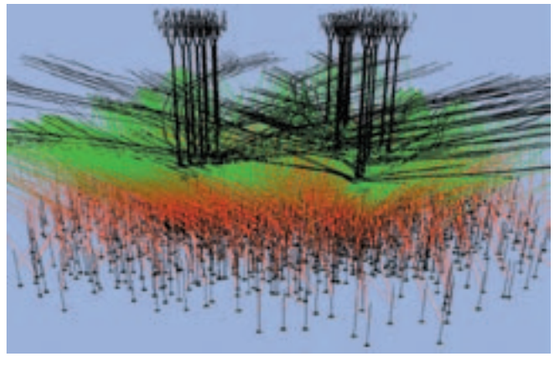
The primary areas of my research are the neurobiology of olfaction; systems biology of learning and memory; hippocampal connections and computations; and multiscale modeling. I briefly outline each below. In *neurobiology of olfaction* we study two main questions: How is odorant information represented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

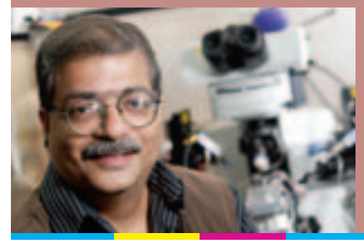
Khan, A.G., Sarangi, M. and **Bhalla, U.S.** (2012) Rats track odour trails accurately using a multi-layered strategy with near-optimal sampling. *Nature Communications* 3(703), doi:10.1038/ncomms1712.

Bhalla, U.S. (2012) Trafficking motifs as the basis for two-compartment signaling systems to form multiple stable states. *Biophys. J.* 101(1): 21-32.

Dhawale, A.K., Hagiwara, A., **Bhalla, U.S.**, Murthy, V.N. and Albeanu, D.F. (2010) Non-redundant odor coding by sister mitral cells revealed by light addressable glomeruli in the mouse. *Nature Neuroscience* 13(11):1404-12.



Biophysically detailed simulation of the olfactory bulb



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

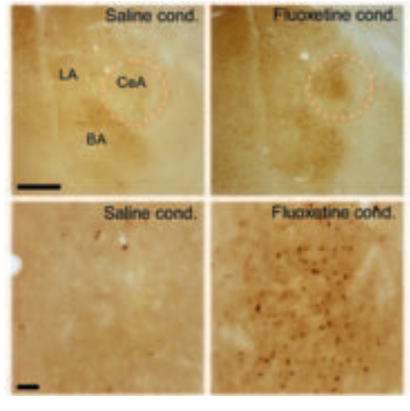
Memories come in different flavors, some more potent than others. Emotionally salient experiences tend to be well remembered, and the amygdala has a pivotal role in this process. But the rapid and robust encoding of emotional memories can also become maladaptive — severe stress often turns them into 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.

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

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

Rao, R.P., Anilkumar, S., McEwen, B.S., and **Chattarji, S.** (2012) Glucocorticoids protect against the delayed behavioral and cellular effects of acute stress on the amygdala. *Biological Psychiatry* http://dx.doi.org/10.1016/j.biopsych.2012.04.008.



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.

sandhya p koushika

Multiple cargoes produced in the cell body are transported along the axon to the synapse via a system of tracks and motors. We study motor-cargo interactions and how transport contributes to neuronal development and function.

STUDYING THE REGULATION OF AXONAL TRANSPORT-CELLULAR NEUROBIOLOGY

In neurons various cargos such as synaptic vesicles and mitochondria are carried along the axon, between the cell body and the synapse. This transport is critical for synaptic development and function. Defective axonal transport is implicated in several neurodegenerative diseases. Long-distance axonal transport is a complex process carried out by specific molecular motors that ferry cargo along microtubule tracks. Our goals are: to identify the molecules regulating axonal transport, to elucidate the mechanisms of action of these molecules in vivo and ultimately, to understand the implications for neuronal development and function. We use genetics and live imaging in the transparent model organism *C. elegans*, combined with several interdisciplinary tools and approaches.

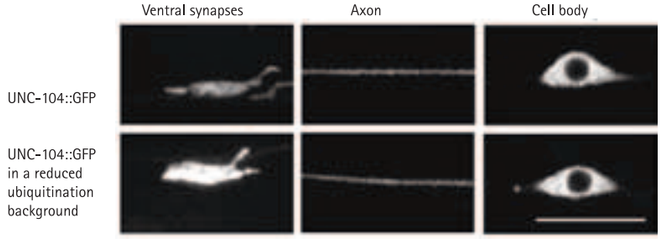
Anterograde transport of pre-synaptic vesicles is largely carried out by the conserved kinesin-3 motor UNC-104. We found that UNC-104 is degraded at synapses via the ubiquitin pathway, the first such demonstration for any anterograde motor in any model system. The motor levels in synapse rich regions of the animal directly co-relate with their ability to bind cargo. Our findings provide the first evidence for a hypothesis proposed earlier that anterograde motors may be degraded upon releasing their cargo.

To expand the use of *C. elegans* to study axonal transport we have developed several technologies: (i) An anesthetic-free microfluidic immobilization device to image in vivo cell biological events. (ii) An assay to specifically tag and follow endogenous retrograde cargo being transported from the synapse to the cell body. (iii) With Dr. Y. Krishnan, validating the use of her 'pH-sensor' DNA nanodevice in *C. elegans* to probe endocytic pathways *in vivo*.

Mondal, S., Ahlawat, S. and **Koushika, S.P.** (2012) Simple microfluidic devices for *in vivo* imaging of *C. elegans*, *Drosophila* and zebrafish. *JoVE* Accepted.

Mondal, S., Ahlawat, S., Rau, K., Venkatraman, V. and **Koushika, S. P.** (2011) Imaging in vivo axonal transport in *C. elegans* using microfluidic devices. *Traffic* [Epub] doi: 10.1111/j.1600-0854.2010.01157.x.

Kumar, J., Choudhary, B.C., Metpally, R., Zheng, Q., Nonet, M.L., Sowdhamini, R., Klopfenstein, D. and **Koushika, S. P.** (2010) The *C. elegans* kinesin-3 motor UNC-104/K1F1A is degraded upon loss of specific binding to cargo. *PLoS Genetics*, 6(11): e1001200. doi:10.1371/journal.pgen.1001200.



Motor levels increase at synapscs of the touch neurons when degradation is blocked. No changes in UNC-104 levels are observed either in the axon or the cell body upon blocking degradation. Scale bar 10 μm

Currently faculty at DBS, TIFR
spkoushika@tifr.res.in
http://www.tifr.res.in/~dbs/faculty/S_Koushika.html

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., Prabhakar, S., Sudarsan, S. and **Sane, S.P.** (2012) Neural mechanisms of antennal positioning in flying moths. *Journal of Experimental Biology* In press.

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

Sane, S.P., Dieudonne, A., Willis, M.A. and Daniel, T.L. (2007) Antennal mechanosensors mediate flight control in moths. *Science* 315, 863-866.

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.

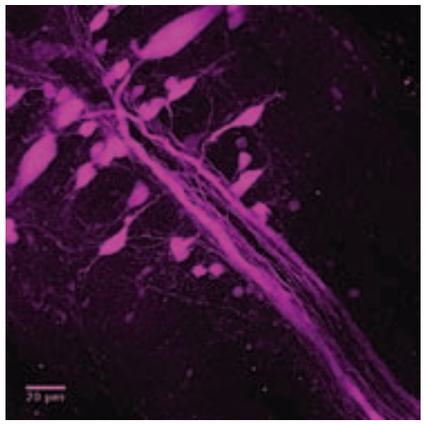
vatsala thirumalai *How does the developing nervous system generate locomotion despite undergoing constant modification? We use developing zebrafish to study this problem as these animals are virtually transparent in their early life stages and the nervous system can be directly observed.*

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.

Thirumalai, V. and Cline, H.T. (2008) A commanding control of behavior. *Nat. Neurosci.* 2008 Mar;11(3):246-8.

Thirumalai, V. and Cline, H.T. (2008) Endogenous dopamine suppresses initiation of swimming in pre-feeding zebrafish larvae. *J. Neurophysiol.* Sep;100(3):1635-48.



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

Theory and Modeling of Biological Systems

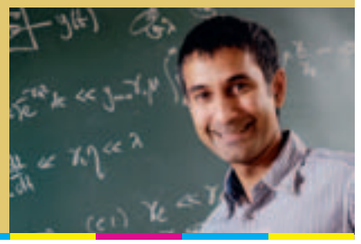
MUKUND THATTAI
The evolutionary origins of compartmentalized cells

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.*

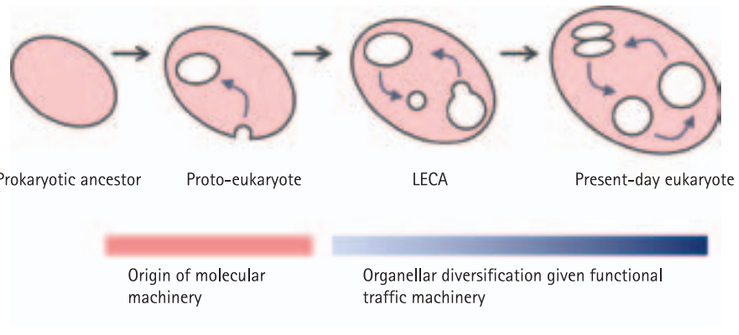
THE EVOLUTIONARY ORIGINS OF COMPARTMENTALIZED CELLS

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.

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

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

Rai, N., Anand, R., Ramkumar, K., Sreenivasan, V., Dabholkar S., Venkatesh, K.V., and **Thattai, M.** (2012) Prediction by promoter logic in bacterial quorum sensing. *PLoS Computational Biology* 8, e1002361.



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.

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.

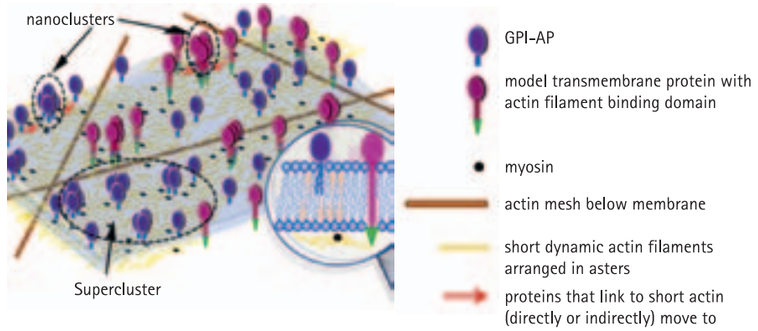
The living cell is an active, self-organized medium comprising molecular processes fuelled by a steady throughput of energy. Our group is interested in the organization, flow and processing of chemical composition, mechanical stress, energy and information in living cells and tissues. These fluxes are 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.

Gowrishankar, K. and **Rao, M.** Nonequilibrium phase transitions in active contractile polar filaments. Under review in *Phys. Rev. Lett.,* (arXiv:1201.3938 [cond-mat.soft]).

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* 149 1353-1367.

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* 108, 14825-14830.



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)

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

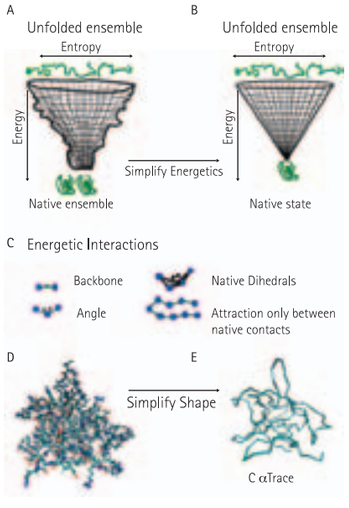
Proteins are the workers of the cell. So, it is important to be able to both predict and engineer their function, in applications ranging from drug design to nano-materials. The native or folded shape of a protein, (as seen in the crystal or NMR structure) is essential for its function. In addition, 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.

Capraro, D.T., **Gosavi, S.,** Roy, M., Onuchic, J.N. and Jennings, P.A. (2012) Folding circular permutants of IL-1β: route selection driven by functional frustration. *PLoS ONE*, 7, e38512,

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

Gosavi, S., Whitford, P.C., Jennings, P.A. and Onuchic, J.N. (2008) Extracting function from a β-trefoil folding motif. *Proc. Natl. Acad. Sci. USA* 105, 10384-10389.



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.

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.

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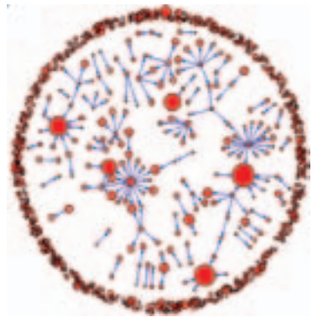
Csiszovszki, Z., **Krishna, S.**, Orosz, L., Adhya, S. and Semsey, S. (2011) Structure and function of the d-galactose network in enterobacteria. *mBio 2*, e00053-11.



Modular structure of the *E coli* signaling network

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

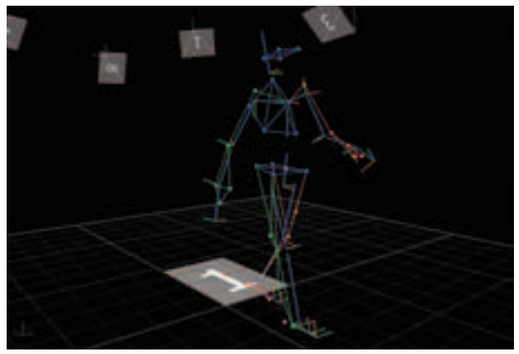
Our lab is interested in the interaction between control and morphology in animals and machines. We seek to better understand how evolutionary pressures may have shaped the morphology of humans, and why animals often outperform their robotic counterparts in terms of robustness and versatility of motor 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?



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.

Venkadesan, M. and Valero-Cuevas, F.J. (2008) Neural control of motion-to-force transitions with the fingertip. *Journal of Neuroscience*, 28(6):1366-1373.

Venkadesan, M., Guckenheimer, J. and Valero-Cuevas, F.J. .(2007) Manipulating the edge of instability. *Journal of Biomechanics* 40(8):1653–1661.

Lieberman, D.E., **Venkadesan, M.**, Werbel, W.A., Daoud, A.I., D'Andrea, S., Davis, I.S., Mang'eni, R.O., and Pitsiladis, I. (2010) Foot strike patterns and collision forces in habitually barefoot versus shod runners. *Nature* 463(7280):531–5.

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 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 schrizophrenia, bipolar disorders and Alzheimer's disease.

* 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.

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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Pradip Pyne
TM Sahadevan (inStem)
KF James (C-CAMP)
S Ashok Rao

Post Doctoral Appointments
30

Students Registered for PhD
210

Masters Students
19

Junior Research Fellows
70

Scientific and technical staff (including trainees)
89

Number of Faculty (Group Leaders /Young Investigators/ International Investigators/ Joint Faculty / Adjunct Faculty)
34

Administration and Auxillary (including trainees)
85

NCBS Director
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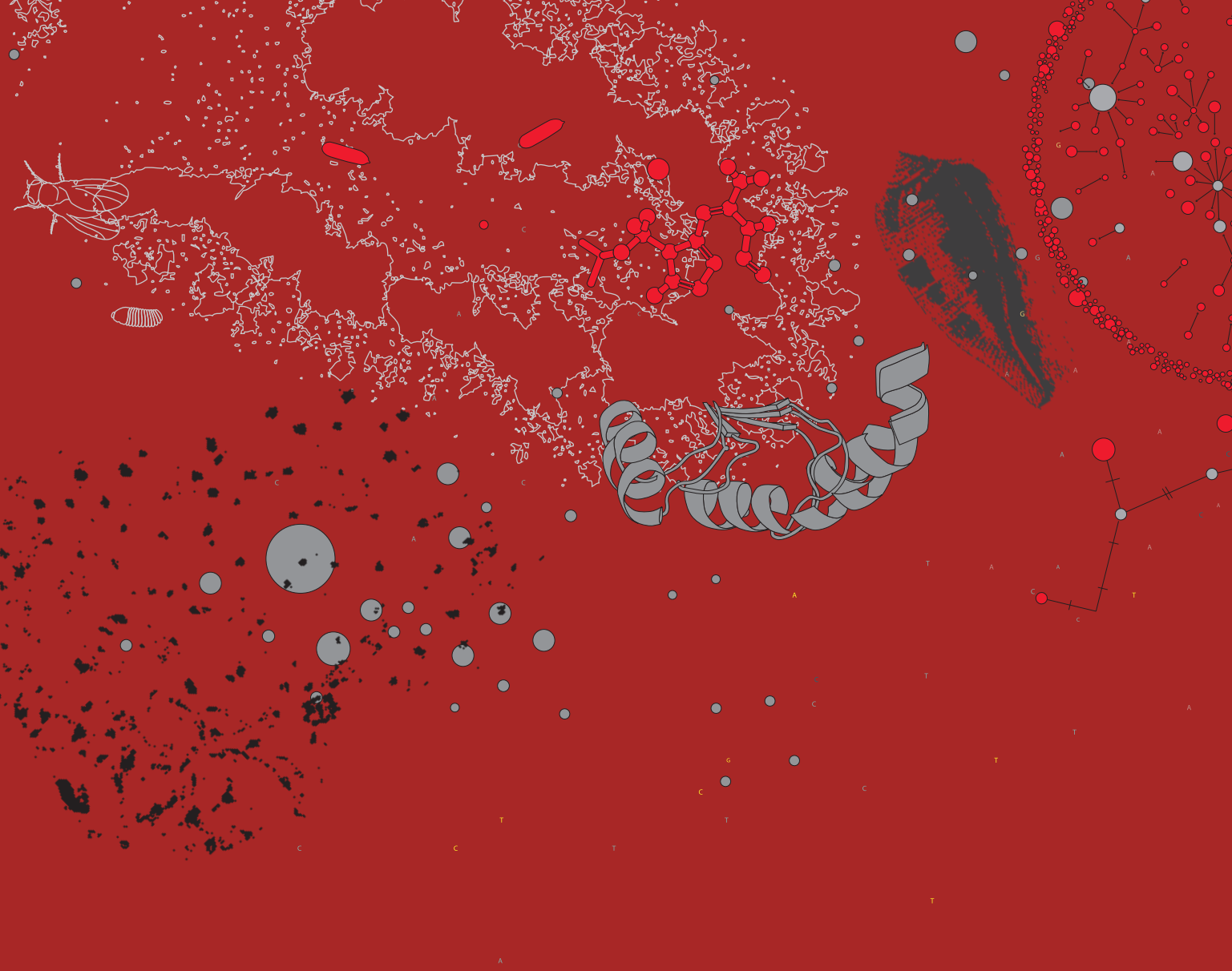

National Centre for Biological Sciences
Tata Institute of Fundamental Research

GKVK, Bellary Road
Bangalore 560065, India
T 91 80 23666001/ 02/ 18/ 19
F 91 80 23636662
www.ncbs.res.in

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