Kolkata International School cum Conference on Systems Biology

KOLSYSBIO

December 29'th 2012 to January 3'rd 2013

Venue: Auditorium, Saha Institute of Nuclear Physics, Kolkata

Abstract Book

Saha Institute of Nuclear Physics
Kolkata, INDIA

Abstracts of Conference Talks

KOLKATA INTERNATIONAL SCHOOL CUM CONFERENCE ON SYSTEMS BIOLOGY (KOLSYSBIO)

January 1, 2013 to January 3, 2013

CONVENORS:

Pradeep K Mohanty, SINP
Soumen Roy, Bose Institute

C01: What DNA teaches about evolution

James Shapiro
The University of Chicago, USA

The lecture will make nine basic points about genome change in evolution:
1.Evolution is complex, not reducible to simple formulae.
2.Evolutionary thinking has a long history full of ongoing discoveries.
3.Cell mergers are an important source of abrupt evolutionary novelty.
4.Horizontal DNA transfer is an important source of rapid evolutionary novelty.
5.Cells actively repair and restructure their genomes (the genome as a RW memory system).
6.Proteins evolve by swapping segments, not simply by changing one amino acid at a time.
7.Mobile genetic elements can rapidly modify genome function at multiple locations and establish genomic networks.
8.Inter-specific hybridization and whole genome duplications are further sources of rapid evolutionary innovation.
9.Genome restructuring (natural genetic engineering) is regulated and activated by stress, cell fusions and inter-specific hybridization.

C02: Application of structural bioinformatics in the identification of potential therapeutically vulnerable targets and their experimental validation

Prasanna Venkatraman
Advanced Centre for Treatment, Research and Education in Cancer Mumbai

High throughput genomic and proteomic studies grow at a rapid rate. But decoding information arising out of such studies to discover novel functions, build and understand communication networks and more importantly recognizing therapeutic targets remains a major challenge. One such communication network is created by protein-protein interactions. Since these interactions are rewired and new networks established in aberrant conditions like cancer they become attractive drug candidates. However in order to identify such putative targets, studies aimed at recognizing differential networks need to be coupled with residue level details of interactions. With this aim, we explore the power of structural bioinformatics to identify physiologically relevant direct interacting partners of gankyrin, an oncoprotein over expressed in several epithelial cancers. We validate our prediction by demonstrating endogenous interaction, interactions using purified proteins and confirm that the site of interaction is through predicted residues by site directed mutagenesis. We identify Hot Spot Sites in the gankyrin network and uncover interactions specific and resident in cancer cells that could be potential therapeutic targets!

C03: Identification of novel adhesins of *M. tuberculosis* H37Rv using integrated approach of multiple algorithms and experimental analysis.

Srinivasan Ramachandran
Functional Genomics Unit,
Institute of Genomics and Integrative Biology, Delhi

Bacterial cell wall biogenesis and its metabolism play crucial role in the growth of bacteria. Pathogenic bacteria interacting with eukaryotic host express adhesins on their surface. These adhesins help in bacterial attachment to the host cell receptors and aids in colonization. Characterization of *M. tuberculosis* attachment with respiratory mucosa led to identification of various adhesins, such as surface exposed heparin-binding hemagglutinin adhesin (HBHA), which is required for bacterial attachment on lung and extrapulmonary dissemination of bacterium and laminin binding protein (LBP) that is involved in cytoadherence through laminin recognition. The complete genome sequences of various species of the genus mycobacteria offer a great opportunity for detailed biological characterization of various genes and their proteins, thereby saving lot of time and resources required for experimental screening. Further, experimental screening involves precise model for setting up receptor binding interactions. This approach also results in identification of limited numbers of adhesins because of the technical setup. In the present work, computational screening of all adhesins in *M. tuberculosis* based on sequence features has been carried out on *M. tuberculosis*. We have used an integrated approach of multiple algorithms to boost the computational power and also carried out experimental testing. Initial computational screening of the whole proteome of *M. tuberculosis* using SPAAN lead to the identification of proteins with high probability of being adhesin or adhesin-like protein. Localization prediction of these proteins were predicted using various subcellular localization prediction algorithms, namely, LOCTree, PSORTb and SubLoc. Further, proteins with low molecular weight were given preferences for the ease of cloning, expression and purification of the proteins. Because our goal was to identify novel adhesins of *M. tuberculosis*, we excluded the proteins which were reported in literature. These selected proteins were cloned, expressed and purified and tested for their ability to bind to the extracellular matrix proteins using a modified ELISA method. Here we report Rv0309, Rv2599 and Rv3717 as novel potential adhesins of *M. tuberculosis* H37Rv. With the analysis of their ability to bind to proteins of extracellular ma-

trix we observed that Rv0309 binds to fibronectin, Rv2599 binds to fibronectin, laminin and collagen, whereas Rv3717 binds to both fibronectin and laminin. Our results expand the number of known adhesins of *M. tuberculosis*. This expanded information will be useful for vaccine candidate predictions.

C04: Input-output relations in biochemical networks

Vahid Shahrezaei
Department of Mathematics, Imperial College, London

Biological cells process information and make reliable decisions via biochemical signalling networks. The input-output relations in these networks are evolved to produce reliable function in spite of stochasticity present in their dynamics. Here, I present some results on mathematical modelling of a common class of biochemical signalling motifs, the phosphorylation depohosphorylation cycle. I discuss the role of enzyme saturation, multiple binding sites, diffusion-limited reactions and enzymatic complex formation. I illustrate how these networks can produce linear response, ultrasensitive response or non-monotonic response. I will also discuss the connection to yeast mating and T cell receptor signalling.

C05: Cytoskeleton dynamics, traction forces and mechanical responses investigating the interface of biochemistry and mechanics in neurons.

Aurnab Ghose
Indian Institute of Science Education and Research, Pune

Accurate growth cone-mediated axonal pathfinding is the underlying mechanism responsible for establishing the stereotyped neuronal circuitry. Growth cones are specialized tips of neurites that sense guidance cues and mediate directional translocation towards synaptic targets. Both the sensory and the motile activities of the growth cone depends on the generation of protrusive processes viz., filopodia and lamellipodia. We have investigated the role of Fmn2, a non-canonical actin nucleator, in the regulating axon guidance. Fmn2 is enriched in the developing nervous system and knockdown of Fmn2 results in guidance defects in vivo. Mechanistically, Fmn2 affects the translocation of growth cones by affecting the ability to generate traction forces. Investigations into the spatiotemporal regulation of traction forces reveal that growth cone appear to translocate using a central compression type of growth.

C06: Mitochondrial variability

Nick Jones
Department of Mathematics, Imperial College, London

A view of mitochondria as a set of static, isolated, genetically homogeneous organelles is now markedly inconsistent with data. They are a networked, fluctuating, ensemble under continuous control. I will discuss our work investigating the sources of mitochondrial variability and touch on implications for cell-to-cell variability, global gene expression, cell cycle duration and development.

C08: Systems biology approaches to drug discovery

Nagasuma Chandra
Indian Institute of Science, Bangalore

Systems biology, an emerging discipline seeks to study biochemical and biological systems from a holistic perspective, contrary to the reductionist approach that has dominated biology. Systems biology requires close co-ordination between high throughput experiment, mathematical abstractions and computational analysis. An important outcome promised by the systems level studies is an understanding of the physiology in normal health, as an integrated function of several individual components, interactions among them and their regulation. In particular, an ultimate goal is to study the effect of naturally occurring perturbations that lead to disease and explore possible ways of reversing such pathological effects through therapeutic intervention.

The science of drug discovery itself has been witnessing multiple paradigm shifts in the recent past due to several factors such as availability of genome sequences, significant growth of sequence, structure and function level databases. The omics scale experiments, development of system-level models as well as adaptation and application of computational methods to biological problems provide a further new direction to drug discovery research. Systems level understanding has the potential to address several important issues that arise in drug discovery, such as the choice of an optimal target, causes for failure of existing drugs including drug resistance, adverse effects and causes of drug toxicity. This talk will provide an overview of the principles and practices of systems biology and how it will impact all three major branches of medicine- diagnosis, treatment and prevention.

C09: Chemical chaperones assist intracellular folding to buffer mutational variations

Kausik Chakraborty
Institute of Genomics and Integrative Biology, New Delhi

Hidden genetic variations have the potential to lead to the evolution of new traits. Molecular chaperones, which assist protein folding, may conceal genetic variations in protein-coding regions. Here we investigate whether the chemical milieu of cells has the potential to alleviate intracellular protein folding, a possibility that could implicate osmolytes in concealing genetic variations. We found that the model osmolyte trimethylamine *N*-oxide (TMAO) can buffer mutations that impose kinetic traps in the folding pathways of two model proteins. Using this information, we rationally designed TMAO-dependent mutants *in vivo*, starting from a TMAO-independent protein. We show that different osmolytes buffer a unique spectrum of mutations. Consequently, the chemical milieu of cells may alter the folding pathways of unique mutant variants in polymorphic populations and lead to unanticipated spectra of genetic buffering

C10: Re-mining data to predict the future: our experience with breast cancer

Kartiki V. Desai
National Institute of Biomedical Genomics, Kolkata

Three important clinical care challenges plague breast cancer therapy, non-respons- iveness, increasing drug resistance and the presence of undesirable side effects. Clearly, better patient stratification, identification of novel prognostic/predictive markers will help devise more personalized treatments and help overcome these problems. Extracellular receptors and/or secreted growth factors that drive cancer metastasis make provocative targets as they are easily accessible on the cell surface and usually show high response rates at lower drug doses, resulting in negligible side effects. To discover novel candidate receptor/secreted oncogenes, we used a whole-genome data-mining approach that takes advantage of large microarray studies of breast tumors annotated for clinical outcomes. Based on analysis of 14 independent breast cancer cohorts (2027 patients), we identified more than 30 cell surface/secreted proteins that when expressed highly, were associated with poor patient survival across multiple cohorts. This enriched gene set offered unexplored opportunities for immunotherapy and drug development. We established a cell-based screening platform to prioritize the most clinically relevant genes, and explored pathways downstream to each candidate in order to develop assay read-outs for future drug/antibody/compound screening. Our efforts identified two genes with great translational potential: Serine protease inhibitor Kazal-type 1 (SPINK1) and Jumonji Domain Containing protein 6 (JMJD6). SPINK1 affected multiple aggressive properties in breast cancer: survival, invasiveness and chemoresistance. Because SPINK1 effects could be abrogated by neutralizing antibodies, we suggest that SPINK1 is a viable potential therapeutic target. On the other hand, JMJD6, a histone arginine demethylase emerged as a marker of tumor aggressiveness, therapy resistance and affected both cell growth as well as cell shape. Our results suggest that the extrapolation of gene-survival associations in primary tumors to phenotypic analysis *in vitro* holds promise as a platform for discovering new therapeutic targets.

C11: Systems biology at the single cell level

Calin Guet
Institute of Science and Technology, Vienna, Austria

The level of the single cell is fundamental when extracting relevant parameters for modelling endeavors. Most experimental work at the level of the single cell has been done on classic systems such as the lac operon or bacterial chemotaxis. When is it relevant to study the biology of the single cell? The mar operon will serve as a case study.

C12: Does a critical peptide fold hold the key to Alzheimers?

Sudipta Maiti
Department of Chemical Sciences,
Tata Institute of Fundamental Research, Mumbai

Aggregation of the Amyloid Beta peptide is a likely cause of Alzheimer's disease. It is believed that the peptide also changes its molecular conformation as it aggregates, though details of this process are not known. We hypothesize that folding is the critical event that turns a benign peptide into a toxic one. Understanding this process would require a simultaneous investigation of aggregation, conformation and bio-activity. We use Fluorescence Correlation Spectroscopy (FCS), Forster Resonance Energy Transfer (FRET), fluorescence quenching, and vesicle binding and cell imaging assays to address these questions in physiological buffer conditions. We show that the major conformational transition (where the peptide end-to-end FRET efficiency changes from <25 % to >50 %) takes place right at the first step of aggregation, viz. with the formation of the small oligomers. This change predominantly involves the core region of the peptide. This monomer to oligomer transition increases the affinity of Aβ for artificial lipid vesicles by at least an order of magnitude. Confocal microscopy shows that the oligomers at physiological concentrations have a strong affinity for the plasma membrane of living HEK 293T cells, while the monomers at the same concentration do not have any detectable affinity. Our results imply that the major change of molecular structure of amyloid beta occurs at the initial step of aggregation, and suggest that this plays a major role in transforming nontoxic monomers into toxic cell-adherent oligomers.

C13: Kinetics of gene regulatory networks: predicting novel interactions and understanding signal integration

Partho Sarothi Ray
Department of Biological Sciences,
Indian Institute of Science Education and Research, Kolkata

Biological networks provide insightful means to elucidate information transfer in biology and have proved useful in understanding the functioning of living systems at the whole-system level. Most biological networks such as gene regulatory networks, metabolic networks and signaling networks represent molecular interaction networks, and do not contain or represent kinetic information. However, it is crucial to understand the kinetics of the different components of the network, as it is the dynamic changes in the concentrations and the relative affinities of the network components that finally cause changes in cellular function, especially in response to stimuli. Therefore, we have endeavored to develop dynamic model simulations, based on experimental kinetic data, to describe the functioning of gene regulatory networks. We have used this methodology to investigate experimental observations in the IFN-Gamma Activated Inhibitor of Translation (GAIT) system of translation regulation of pro-inflammatory genes. Interestingly, dynamic modeling of the system predicted a novel interaction and led to the discovery of an unprecedented molecular regulatory mechanism. Therefore, incorporation of kinetic information in a gene regulatory network not only leads to better understanding of the dynamics of the network but has important predictive functions that enrich the network with more comprehensive interaction information. We are now trying to apply the methodology to address the question of signal integration at single gene level, which is a fundamental question in biological regulation, using RNA-binding protein (RBP) and microRNA-mediated regulation of translation of p53 as a model system.

C14: Interacting networks from genome-scale data with applications to complex disease genetics

Tom Michoel
The Roslin Institute, University of Edinburgh, UK

One of the central hypotheses of systems biology is that molecular networks regulate protein levels which affect physiological states. When perturbed by genetic or environmental factors, these networks may become dysfunctional, and thereby cause disease. In human populations, naturally occuring DNA variants together with environmental perturbations induce changes in mRNA expression levels from which molecular disease networks can be reconstructed. I will present mathematical and computational methods (i) to predict disease networks from integrated genetics, genomics and clinical data and (ii) to study interacting networks across regulatory levels, tissues or organisms. As an application, I will demonstrate how these methods are used to reveal the tissue distribution of inherited risk for coronary artery disease, using a dataset of more than 700 microarrays profiled in different vascular and metabolic tissues from 150 heart disease patients (the Stockholm Atherosclerosis Gene Expression (STAGE) cohort).