Krishna B S Swamy

Title: Multi-chromosomal aneuploidy is a proteotoxicity-tolerating mutation in introgressed hybrids

Complex incompatibilities involving multiple genetic loci cause proteotoxic stress due to perturbed proteostasis leading to compromised mitosis and meiosis in introgressed hybrids of Saccharomyces cerevisiae carrying one or two chromosomes from Saccharomyces var. uvarum. Such complex incompatibilities can reveal fundamental rules underlying the patterns and rate of reproductive isolation at the early stage of speciation. Experimental evolution of yeast hybrids suffering from intense proteotoxic stress indicated aneuploidy to be a primary mechanism of proteotoxicity tolerance in introgressed hybrids. Here, all the evolved lineages consistently demonstrated aneuploidy of the foreign S. uvarum chromosome, to make up for the lower protein abundance of the foreign chromosomal proteins. We also found consistent aneuploidization of specific S. cerevisiae chromosomes in the evolved lineages, probably to balance the stoichiometry of interaction partners important for the formation of functional protein complexes. We hypothesise that aneuploidy-driven whole-genome duplication as a potential speciation mechanism from introgressed hybrids.

Shraddha Karve

Title: When less is more: how protein abundance affects the evolvability of protein

Abundance is one of protein's most fundamental attributes. Abundance varies systematically across different functional classes, is high for essential genes and is known to affect protein sequence evolution. However we know surprisingly little about the role of abundance in the evolution of protein phenotype (evolvability). We perform directed evolution of green fluorescent proteins to find out. Experiments, combined with computational studies, reveal that lowly expressed proteins are under stronger selection for proper folding, which facilitates their evolvability on short evolutionary time scales. We show that this is due to a synergy between protein's scarcity and stability. The boundary conditions for such synergy are satisfied by majority of the proteins under strong selection. Hence our results can potentially explain many general observations such as why stress-responsive genes are often less abundant.

Vijay Jayaraman

Title: The "how" and "why" of biological regulation: an evolutionary and systems biological perspective

Regulatory processes are ubiquitous in biology and are needed for the maintenance of cellular homeostasis. There are myriad ways in which regulation can be achieved in biology. For instance, the activity of an enzyme can be regulated at transcriptional, translational or post-translational level. While decades of research has given us mechanistic and structural descriptions of each of these regulatory modes, the evolutionary and systems biological aspects of it are not clear. An overarching theme of my lab will be to understand “how a particular regulatory mode evolves” and “why that regulatory mode is chosen over others”. With metabolic enzymes as model systems and using directed evolution, systems biological models, and biochemical tools, my lab will address these questions. In my talk, I will introduce you to a unique regulatory mode that we discovered in B. subtilis metabolic enzyme. Following this I will present the data on both the “how” and the “why” aspects of the regulation.

Laasya Samhita

Title: Mistranslation alters the genetic basis of adaptation to antibiotics

Phenotypic variation often reflects underlying genetic variation. Additionally, non-heritable mechanisms generate RNA and protein diversity which can alter phenotype. In previous work, we showed that protein mistranslation increases phenotypic variability in growth and morphology in E. coli cells. We now find that altering the levels of mistranslation in the cell changes the genetic basis of adaptation to antibiotics. Mistranslation is known to alter bacterial resistance to lethal antibiotic concentrations under specific conditions and via unique mechanisms. We evolved strains with different levels of mistranslation in sub-MIC antibiotic concentrations to mimic environmental (and less stringent) selection pressures. We found rapid adaptation in most lines, as tested via growth rate, MIC change and survival (tolerance). Whole genome analyses via NGS showed that mistranslating cells show faster adaptation and fix mutations that are often different from the WT. Ongoing analyses will tell us how mistranslation regimes interact with genotype and environment, and what this might mean over evolutionary time.

Sabari Sankar Thirupathy

Title: The conflict between DNA replication and transcription

Conflicts between DNA replication and transcription are inevitable, as both processes concurrently traverse the same DNA template, especially in rapidly dividing bacterial cells resulting in collisions between their machinery. Depending upon the relative orientation of DNA and RNA polymerases, collisions can be either in co-directional (leading strand genes) or head-on (lagging strand genes) orientation. Both the type collisions stall replisome, cause DNA breaks and induce spontaneous mutations. The impact of collisions is more severe in the head-on orientation leading to a prominent

genome-wide co-directional gene-strand bias. Our laboratory focuses on understanding the molecular mechanisms of collision-induced mutation, and we hope to uncover collision as a fundamental mutational process that drives genome organization and evolution in bacteria.

Amitesh Anand

Title: Adaptive compensations in bacterial energetics

The bacterial lifestyle is plastic, requiring dynamic transcriptional, translational, and metabolic tailoring. These cellular processes are energy intensive; therefore, flexible energetics is requisite for adaptive plasticity.

While flexibility in bacterial energy metabolism is well appreciated, the circumstances catalyzing their evolution must be better understood. The Great Oxidation Event is one such event responsible for diversifying bioenergetics. Microbes invented a new high redox potential respiratory quinone to sustain the oxygen toxicity inflicted by the rising oxygen concentration in the environment. The absence of this respiratory quinone compromises aerobic growth and alters the flux through central carbon metabolism.

Energy generation pathways are also being explored as an avenue for the development of novel antibiotics. However, the bacterial system has a high degree of antifragility due to compensatory pathways. Identifying these compensatory features is critical to any translational development in this direction. We have performed a systems-level examination of the aerobic electron transport system and have identified some growth-potentiating mechanisms to withstand the synthetic restrictions in bacterial energetics.

Riddhiman Dhar

Title: A Journey beyond Local Fitness Landscapes

Fitness landscapes help us uncover genotype-phenotype relationships and predict evolutionary trajectories. However, empirical fitness landscapes have been limited to local neighborhoods of genotypes, except for a handful of tRNA molecules. This has greatly restricted our understanding of the evolutionary trajectories for emergence of new phenotypes, as this process often requires traversing beyond local neighborhood. In the current work, we have developed a simple molecular assembly technique that allows us to construct multi-mutant variants of a genotype, thus enabling measurement of fitness beyond local neighborhood. Using this technique, we have constructed a library of 50,000 variants of a gene containing up to twelve mutations and experimentally measured their fitness in different environments. Thus, our work opens up new directions in the study of fitness landscapes that will provide exciting insights into evolutionary trajectories, and will allow us to probe molecular interactions that determine topologies of fitness landscapes in great detail.

Nishad Matange

Title: Adaptation by Deregulation of Gene Expression: A Jekyll and Hyde story

Abstract: Many gene regulatory networks have in-built checks and balances such as negative feedback loops. However, it is unclear what evolutionary pressures lead to the evolution and maintenance of feedback. I will discuss recent work from my lab that attempts to answer this question using a bacterial two-component signaling pathway, PhoQP, in the context of antimicrobial resistance. I will show that deregulation of his gene regulatory pathway due to loss of an evolutionarily conserved negative feedback protein has adaptive value for Escherichia coli facing antibiotic pressure. However, this deregulation imposes costs to the fitness of E. coli. These costs can be traced to pervasive effects on gene expression, which are then rectified by compensatory evolution in the RpoS sigma factor. Using this example, I will attempt to formulate a generalisable idea of why regulation and deregulation represent context-dependent adaptive strategies.

Shweta Ramdas

Title: Identifying the Regulatory Architecture of Essential Genes

The search for essential genes (EG) is the quest to define a minimal set of genes for the survival of a cell or an organism. Many complementary approaches have been used to define human EGs, including assays in gene-edited cell lines and investigating human orthologs of mouse knockouts to identify genes essential for mammalian development. The resulting list of EGs (defined by either approach or a combination of approaches) includes genes that 1) show greater levels of evolutionary constraint, 2) are enriched for haploinsufficient disease genes, 3) are broadly expressed across tissues, 4) show higher levels of gene expression, and 5) are more connected in protein-interaction networks. However, the regulatory architecture of EGs is not well-understood. Using publicly available expression and epigenomic datasets, we ask if evolutionary and functional constraint on EGs is also translated into regulatory constraint, which may be defined by lower levels of context-specific regulation. We also ask if the definition of essentiality can be further sub-stratified using patterns of expression and regulation. We show that EGs are enriched in active regions of the genome and depleted in repressive regions. We also see that EGs have fewer eQTLs compared to non-essential genes (41% of expressed EGs are eGenes compared to 49% of expressed non-EGs), despite being more highly and more broadly expressed. Taken together, these two results point to a higher basal level of regulatory activity for EGs compared to context-specific regulation. Using these genome-wide analyses, we will be able to interrogate differences in regulatory features of EGs, and identify mechanistic features that can allow us to better understand biological features underlying gene essentiality.

Samay Pande

Title: Bacterial predators drive the evolution and maintenance of antibiotic resistance in complex microbial communities

Bacteria living in natural complex microbial communities use a variety of contact-dependent and contact-independent mechanisms of antagonism. Survival in such communities, therefore, requires resistance to the antimicrobial mechanisms expressed by the antagonists. Since microbial predators such as Myxococcus xanthus use a variety of antimicrobial mechanisms, we hypothesised that the arms-race between antimicrobial mechanisms (expressed by M.
xanthus) and resistance to such mechanisms (in non-myxobacterial species) might be prevalent in nature. In line with our hypothesis, we demonstrate that the presence of M. xanthus in soil samples is responsible for the abundance of antibiotic resistance. Interestingly, only M. xanthus isolates that can invade natural social communities can drive the enrichment of antibiotic resistance. Together, we demonstrate that the presence of a generalist microbial predator M.
xanthus has an influence on the maintenance of antibiotic resistance in natural microbial communities.

Supreet Saini

Title: How do genes move across species' barriers?

Movement of genes from one species to another is ubiquitous. In this work, we ask the following questions:

- Are all horizontally transferred genes functional in their new host?
- Under what circumstances might a horizontally transferred gene be non-functional in the new host?
- And finally, can we comment on the mutational spectrum which restores functionality of the horizontally transferred gene in the new host?

To answer these questions, we mimic a HGT event, where an ammonia transporter from amoeba is transferred to a yeast strain lacking ammonia transporters. From our results, we comment on the potential answers to the above questions.