STATEMENT OF RESEARCH INTERESTS

Rahul V. Kulkarni

My research interests can be broadly classified as biophysical modeling and genomics. My goal is to work closely with experimental groups to understand specific systems of biological importance, with the broader aim of discovering general principles underlying biological systems. My current projects and several future avenues of research suggested by my work are summarized below. What unifies these projects is my belief that to discover unifying principles in biology, we need to understand specific well-chosen biological systems.

Quorum sensing

Quorum sensing is the process by which bacteria communicate to regulate gene expression in response to population density. Quorum sensing allows communities of bacteria to behave as multicellular organisms; a striking example of this process is the formation of biofilms. Since biofilm infections are a serious medical problem, a deeper understanding of quorum sensing may lead to new antibiotic strategies.

In collaboration with the group of Professor Bonnie Bassler at Princeton University, I used a bioinformatic approach to discover a group of regulatory small RNAs critical to quorum sensing in *V. cholerae* and related species. This bioinformatic prediction has been experimentally verified and has led to new insights into the hierarchical nature of quorum-sensing-induced gene regulation. Furthermore, I made specific predictions for: a) new components of the input system for quorum sensing and b) a novel set of quorum sensing regulated genes which includes genes involved in biofilm formation. Experiments are currently underway in Professor Bassler's laboratory to test these predictions.

My immediate goal is to study the network of quorum-sensing regulated genes in *V. cholerae*. A related goal is to develop a model for the quorum-sensing circuit and the induced response. This work is of broad importance because quorum sensing is a model system for many fundamental processes in biology including cell signaling, information processing by integrating a multiplicity of inputs, signal transduction, and microbial development.

Regulation of small RNAs

Small, untranslated RNAs perform several regulatory functions in both prokaryotes and eukaryotes. Recent work has led to a dramatic increase in the discovery of small RNAs. For example, in *E. coli*, out of the 55 known small RNAs, 45 were discovered in the past 3 years. However the regulatory roles of most of these small RNAs are still unknown. Determining the transcription factors regulating expression of these small RNAs is an important step in discovering their regulatory function.

I performed a genome-wide analysis to associate known small RNAs with well characterized transcription factors in *E. coli* and to search for potential target genes. My results led to several novel predictions including the regulation of a known small RNA by σ^{54} and the potential role of this small RNA in nitrogen metabolism. We are currently collaborating with

several groups including the group of Professor Thomas Silhavy at Princeton University to test our predictions.

Our analysis suggests an approach to discover new small RNAs in bacteria which I plan to pursue. I am also interested in studying the mechanism by which the interaction between small RNAs and their target genes is mediated by the RNA binding protein Hfq. Understanding this mechanism will lead to an improved ability to locate target genes for small RNAs and thereby to discover their regulatory roles. Such a study will elucidate how small RNAs contribute to cell adaptation by integrating cellular responses to changing environments.

Protein-DNA interactions

The interaction of transcription factors with DNA lies at the heart of gene regulation. Characterizing how a protein recognizes binding sites is therefore crucial for understanding regulated gene expression. Such a characterization can also help in discovering genetic regulatory circuits and in understanding the evolution of these gene circuits through comparative genomics.

We studied the interaction of a specific transcription factor, the arginine repressor (ArgR), with DNA across several genomes. Using the weight-matrix approach to characterize protein-DNA interactions, we found: 1) novel genes regulated by ArgR in *E. coli* and 2) regulation of a novel metabolic pathway by ArgR in the bacteria *B. subtilis* and *B. halodurans*.

My larger goal is to understand protein-DNA co-evolution through a coordinated study of DNA binding domains in proteins, for a given family of transcription factors, and their corresponding binding sites across genomes. I believe that this study can help in discovering a code, specific to the given family of transcription factors, for protein-DNA interactions. Such a code will allow us to uncover the regulons corresponding to transcription factors and provide greater insight into the regulation of gene expression which is fundamental to most biological processes.

Protein localization

Specific targeting of proteins to subcellular locations is critical for many essential processes in bacteria such as chemotaxis and cell division. In many instances, the factors controlling proper positioning of proteins are known, however the underlying physical processes which govern targeting are unclear. Analyzing the root physical processes can thus lead to a better understanding of dynamic subcellular localization of proteins.

We studied the localization of the Min proteins: MinC, MinD, and MinE which are necessary for accurate cell division in *E. coli*. We proposed a 1D model for this system based only on the observed interactions and studied this model using analytical calculations and Monte Carlo simulations. Our results have provided an explanation for the length scale of MinD attachment zones seen in filamentous cells.

A natural extension of our work is to simulate the dynamic localization process using cellular

automata. Another application is to study the pattern of attachment of chemotaxis receptor clusters in filamentous cells. The broad goal is to carry out an integrated study, using bioinformatics tools and mathematical modeling, to understand how the physical mechanisms of targeting are coupled with regulation of gene expression to determine protein localization in bacteria.

Prion diseases

At least 16 diseases so far identified, notably Alzheimer's, the prion diseases, and Parkinson's disease, have in common that certain polypeptides or proteins accumulate in aggregates often of an amyloid character. Considerable research effort is being focused on identifying treatments based on inhibiting the aggregation process. The importance of understanding these diseases cannot be understated, given the widespread incidence of Alzheimer's disease and the public health threat posed by prion diseases.

In collaboration with the research group of Professor Daniel Cox and Professor Rajiv Singh at UC Davis, I have been studying the aggregation process in prion diseases using computer simulations and stochastic modeling. Our research connects the aggregate growth morphology to the corresponding incubation time distribution, and we provide functional forms for the incubation time distribution which can be used in epidemiology. Our approach can also be used to infer the time course of infectivity (which is difficult to measure experimentally) from the dose-incubation curve (which is a standard experimental measurement).

Our aim is to develop a model addressing the contentious issue of "strains" in prion diseases. It will also be important to extend our stochastic modeling approach to incorporate recent experimental results which suggest novel mechanisms of prion disease pathogenesis. We plan to apply the insights from our modeling to the aggregation process in other amyloid diseases, in particular Alzheimer's disease.

Network models

Many properties of complex systems can be understood by considering the network of interactions which connects their components. Hence much recent research has focused on the structure of complex networks such as genetic regulatory networks. For example, the properties of random networks have recently been used in a study of the transcription factor regulatory network of *E. coli* to discover network "motifs".

We have recently studied a class of networks called small-world networks, which have an ordered structure locally but are random on a global scale. For this class of networks, we have proved *exact* results and used them to study the scaling properties of the basic distribution function for these networks. In the limit of large system size and small disorder we have derived a functional form for this distribution function which can be used to get accurate structural information about the networks.

Our work indicates that the structural properties of various classes of random networks can be derived from a "basis set" of distribution functions. I plan to quantitatively develop this idea to create a theoretical framework for analyzing the structural properties of random

networks. My goal is to use this framework to study properties of the transcription factor regulatory network in *E. coli*. More generally, I plan to apply this framework to various classes of networks in biology such as metabolic networks and protein-protein interaction networks.

Additionally, I am interested in pursuing the following *new directions*.

Bacterial chemotaxis

The chemotaxis system of *E. coli* is considered to be one of the best-characterized signal transduction networks in biology. However, there are many significant issues in the functioning of this network which are not well understood. The recent use of techniques such as fluorescence resonance energy transfer (FRET) to monitor proteins *in vivo* has provided detailed quantitative information about network activity. These advances provide an opportunity to develop a model for bacterial chemotaxis which incorporates the new data and addresses key unresolved issues, and this is one of my goals.

Microarray data analysis

Microarray technology makes it possible to detect changes in gene expression for entire genomes. This necessitates the development of tools to infer biologically important knowledge from the data generated. I have several ideas I wish to pursue in this context. In particular, I am interested in improving existing methods and developing new techniques for inferring the underlying transcription factor regulatory network from microarray data.

Small-molecule genomics

There is an increasing trend in genomics to explore facets of cellular processes using small-molecule modulators. I plan to study the structural and electronic properties of small-molecules using the tools of Density Functional Theory (DFT). A particularly interesting problem is the specificity of the interaction of small molecules with given cellular components; minor chemical modifications significantly affect the perturbation of function due to small-molecules. Analysing small-molecules using DFT could help in identifying the corresponding signature in their electronic properties, and more generally in providing useful insights into this fast-developing field in genomics.

TEACHING STATEMENT

Rahul V. Kulkarni

I consider teaching to be an important part of my commitment to science and also a very rewarding experience. I have always enjoyed the process of sharing knowledge and communicating my enthusiasm and excitement for the subject. As a graduate student at the Ohio State University, I conducted recitations for several undergraduate physics courses including Mechanics, Electricity and Magnetism, and Modern Physics. I was also responsible for grading a graduate course on Thermodynamics and Statistical Physics. In the process, I gained considerable experience in conducting classes, interacting with students and helping them out with their difficulties. This was a very rewarding experience for me which reinforced my interest in teaching.

One of my central goals as a teacher is to foster independent thinking and enthusiasm for the subject among my students. I firmly believe that optimal learning occurs when students are ready to make the discoveries themselves. To that end, I would emphasize a thorough understanding of the basic concepts and then encourage and guide students to arrive at the derived results through independent thinking. From my own experience, I know that the process of independently deriving key results provides enormous motivation for further learning and fosters a deeper understanding of the subject. At the same time, I feel that many students learn best when they interact with other students. I would therefore encourage the formation of small groups or teams to work on class projects and assignments. My aim will be to help students experience the joy of discovery in understanding scientific concepts.

My doctoral training is in theoretical condensed matter physics. As a doctoral student, I studied and conducted research on a broad range of topics in physics. In the course of my postdoctoral research, I have increasingly focused on problems of biological importance and I'm currently involved in an active collaboration with molecular biologists at Princeton University. Therefore my educational and research background is quite broad and equips me to teach a number of basic and specialized courses in physics and biophysics. Besides all areas of undergraduate physics, I can teach most basic graduate courses as well as advanced courses in statistical mechanics and condensed matter physics. I am also excited about the prospect of developing a new interdisciplinary course in biological physics. This would involve teaching how statistical physics concepts can be fruitfully applied to current research in molecular biology and genomics. I would like the classes to be participatory, with students actively involved in small projects that introduce them to the frontiers of research.

My personal teaching style will depend on the nature of the course as well as the background of the students. In all cases, I plan to illustrate the concepts using concrete examples which the students will find interesting and which they can relate to the material being covered. I will also endeavor to be very accessible to students and will greatly appreciate their feedback. Incorporating their feedback into my teaching methods will help me become a more effective teacher. Finally, I hope to instill in my students a sense of excitement about the subject and to inspire them to discover the beauty of science.