Northwestern University

The Feinberg School of Medicine
Department of Pathology
Ward Memorial Building
303 East Chicago Avenue
Chicago, Illinois 60611-3008

NORTHWESTERN UNIVERSITY

Radu Dobrin
Northwestern University
Department of Pathology
303 E. Chicago, Ward 6-118
Chicago, IL 60611
E-mail: dobrin@pa.msu.edu
Phone: 312-503-1260

Biocomplexity Search Committee
Prof. Rob de Ruyter van Stevenick
Indiana University
Biocomplexity Institute
Swain Hall West 117
Bloomington, IN 47405-7105

October 31, 2003

Dear Search Committee,

Please consider my enclosed curriculum vitae and supporting materials in application for the tenure-track assistant professor position.

My references are:

Dr. P.M. Duxbury (Michigan State University)
Biomedical and Physical Science Building,
Michigan State University
East Lansing, MI 48824-1116.
Phone:517-355-9200 ext.2301
Fax: (517) 353-0690
E-mail: duxbury@pa.msu.edu

Dr. S.D. Mahanti (Michigan State University)
Biomedical and Physical Science Building,
Michigan State University
East Lansing, MI 48824-1116.
Phone: 517-355-9200 ext.2303
Fax: (517) 353-0690
E-mail: mahanti@pa.msu.edu

Northwestern University

The Feinberg School of Medicine
Department of Pathology
Ward Memorial Building
303 East Chicago Avenue
Chicago, Illinois 60611-3008

NORTHWESTERN
UNIVERSITY

Dr. Z.N. Oltvai (Northwestern University)
Northwestern University
Department of Pathology
Feinberg School of Medicine
Ward Bldg. 6-204, W127
303 E. Chicago Ave.
Chicago, IL 60611
Phone: (312) 503-1175
Fax: (312) 503-8240
E-mail: zno008@nwu.edu

Please inform me if you would like to see other documents or supporting materials.

Thank you for considering my application. I look forward to meeting you.

Sincerely,
Radu Dobrin

Research Statement

Radu Dobrin

Northwestern University

The most striking success of 20th century biology was the identification and characterization of the molecules of life. A major challenge of 21th century biology will be to understand how these molecules interact to produce the complex biological processes that ultimately create a living cell. What do we need to know to have this understanding? To what degree can detailed knowledge of individual molecules and their interactions provide predictive understanding of a complex biological process as it occurs in a living cell? In our mind, a major key to these questions lies in the need for the identification of the fundamental logic and derivative constraints that limit cell behavior. In this respect, it is by now well-appreciated that essentially all biological function is embedded into a complex cellular network of molecular interactions, in which function in part represent emergent properties as a consequence of complex interactions among the various constituents.

Understanding such complexity can be approached from various perspectives. However, biological functions are thought to be achieved primarily through the activity of functional modules (e.g., receptor complexes, signaling cascades), whose local organization may be a prime determinant of such activities. Therefore, in the present application we concentrate on the identification and characterization of such local modules, and to understand their dynamic behavior in the context of the network as a whole.

During the latter half of the 20th century, biology has been dominated by reductionist approaches that have provided a wealth of knowledge about individual cellular components and their functions. Despite the enormous success of the reductionist approach, a discrete biological function can only rarely be attributed to an individual molecule. Indeed, most biological functions arise from complex interactions among its various components (individual proteins, nucleic acids, small molecules, etc.). The need for more comprehensive approaches that address the full complexity of a biological system is now well-appreciated, largely due to the emergence of Genomics, in which the entire DNA sequences for a number of organisms now allows the definition of their gene portfolios. In turn, extrapolation between genomes has accelerated the definition of what amounts to a "parts catalog" of cellular components in a large number of organisms. Also, large-scale efforts for studying the effects of systematic gene disruptions and for measuring expression levels of all genes under different conditions by microarray and proteomics approaches for entire genomes are well underway.

Due to these advances, one of the major challenges will be to understand how

these molecules interact to produce the complex biological processes that ultimately create a living cell. What do we need to know to have this understanding? To what degree can detailed knowledge of individual molecules and their interactions provide predictive understanding of a complex biological process as it occurs in a living cell? The key to these questions lies in the need for the identification of the fundamental logic and derivative constraints that limit cell behavior. While the datasets available to us are far from being complete, they do offer a critical mass and coherency to begin such analysis, and for the subsequent capacity for experimentation, model development and prediction through simulation of the ensuing model.

It is increasingly appreciated that the robustness of various cellular processes is rooted in the dynamic interactions among its many constituents, such as proteins, DNA, RNA, and small molecules. The existence of complex interactions among various components of a cell or simple microorganisms has long been appreciated, but in the absence of large-scale databases and a sufficiently developed theoretical framework, no meaningful analysis of these interactions was deemed possible. However, recent large-scale sequencing projects coupled with systematic two-hybrid analysis have provided complete sequence information for a number of genomes, and also allowed the development of protein interaction and integrated pathway-genome databases that provide organism-specific connectivity maps of metabolic and, to a lesser extent, various other cellular networks. Yet, due to the large number and the diversity of the constituents and reactions forming such networks, these maps are extremely complex, offering only limited insight into the organizational principles of these systems. Our ability to address in quantitative terms the structure of these cellular networks, however, has benefited from recent advances in understanding the generic properties of complex networks. Until recently, complex networks have been modeled using the classical random network theory. On the other hand, recent empirical studies on the structure of the World-Wide Web, Internet, and social networks have demonstrated that these systems are described by scale-free networks. With this well-developed theoretical framework in hand and with the availability of detailed databases, we are now in position to initiate the analysis of cellular networks. Some of the first questions we asked included the following: What is the topological structure of metabolic and other cellular networks? What are the biologically and topologically relevant quantities that characterize them? Are there generic and common structural characteristics that apply to all cells, including both procaryotes and eucaryotes?

The scale-free topology of cellular networks results in tolerance of random node removal. The metabolic network is also modular, with the majority of its nodes predominantly involved in the regulation of a specific pathway. However, the small-scale structure of the networks still awaits better understanding. It has been shown that certain connectivity patterns (motifs) appear over-represented in biological networks and disappear as a result of network randomization. The proper definition of motifs within the network dynamics are still unsolved questions. In contrast to the route taken to understand network topology (top to bottom), the route to understand the dynamics of biological networks will be from bottom up. Thus, it is important to examine the characteristics of various motifs and their relationship to topological modules and the whole network, with the aim of identifying salient features that may delineate distinct functional elements. By using the previously examined transcriptional regulatory and metabolic network of E. coli, we examine the

postulate that within an overall hierarchically modular topological framework highly interconnected motifs may combine into larger, less cohesive structures that may overlap with functionally distinct modules. We first identify all significant motifs in both networks. We will then show, properties of the nodes (operons or metabolic substrates) within these motifs such as co-expression of their genes, essentiality of their corresponding gene products, and co-localization on the E. coli chromosome.

Revealing the topological structure of the transcriptional regulatory or metabolic network of E. coli is an important step for uncovering the functional details. However, in order to gain a better insight we will develop a dynamical model on the superstructures formed by the motifs. At this moment, the motifs are thought to perform only simple functions such as rejection of rapid variation, lacking in experimental confirmation. Naturally we will develop the model using the generated experimental data based on quantitative RT-CPR on motif superstructures and DNA microarray experiments following perturbations. Two types of perturbations will be employed: (i) environmental stress (change of medium from rich to restrictive, change of conditions from aerobic to anaerobic); (ii) direct intracellular perturbation of gene expression by a plasmid containing a toggle switch. The main challenge is to approximate as much as possible the experiment aiming at understanding the motif function within the superstructure.

The main goal of this proposal is to combine the results and modeling tools to develop a model that offers a multi layered representation and modeling of E. coli metabolism. This will be a semi-quantitative model, that, by making maximal use of the robust and relatively simple rules uncovered, will aim to make experimentally testable prediction regarding biological behavior and function. Finally, the validation and the testing of our modeling effort will be also performed, the ultimate goal being to simulate the molecular and phenotype effects of perturbing the E. coli metabolic network through individual gene deletions.

Teaching Statement

Radu Dobrin

Northwestern University

"The secret to education is respecting the pupil"
RALPH WALDO EMERSON

Learning is the most important ability we posses. Starting with our first breath we learn either from the environment or from teachers in a more structured and professional way. And who doesn't remember the good teacher, who made us think that understanding is effortless and of course the bad one, who made us wonder if there is light at the end of the tunnel. Teaching is an art, and the artist skill-measure is not much in the material universe, but rather a sum of quanta, where quantum is defined as "Now, I understand".

I have been trained to be a teacher in college, were we studied everything from Psychology, to Methods of Teaching Physics and Pedagogy. However the most important part is to be able to apply in practice everything you know, and to get the students to learn how to think as a physicist. My commitment to my students means that I must help them construct every kind of useful knowledge that I can. Physics is a way to teach us much of that knowledge. But learning physics is much more than just manipulating equations and experimental procedures. It is also knowing how to think as a scientist. Students of physics should have the opportunity to learn how to reason critically about their own knowledge, how to justify it experimentally or logically, and how to evaluate the knowledge of others. With these thinking skills, students will be prepared not only for current and future science classes, but also for life beyond the classroom and beyond their chosen careers.

Still, conceptual understanding and problem-solving skills are important for students of physics to learn. Research in science education has shown, and my own experience confirms, that what works best is some form of active learning. Students are not blank slates, ready to receive knowledge by transmission; they have prior knowledge that they must engage and then synthesize with new experiences from the classroom and laboratory to create new knowledge. My role as a teacher is to create an environment in which students can explore, evaluate, and refine their own knowledge in light of new experiences.

Elements of active learning strategies that have been shown to improve conceptual understanding include interactive lecture demonstrations, cooperative group problem solving, evaluation tasks, and guided inquiry. Many of these activities are easily implemented in large lecture classes, and have been used with great success. Combining these active-learning strategies with regular self-reflection of students knowledge and

learning can also facilitate the development of students scientific thinking skills. I would welcome the opportunity to implement these teaching methods in any undergraduate class were we have to develop a sharper thought process and also to enrich their physics knowledge.

In addition to teaching standard graduate and undergraduate physics courses, I would be interested in developing a number of graduate or undergraduate special courses related to my area of expertise. I have envisioned a "Disordered Systems" class, where in order to expose different problems encountered in this field, the main accent will be on projects. A similar class, "The Physics Behind Random Networks" could be designed for either the graduate or undergraduate level, focusing on the interdisciplinary aspect. Both of these classes could be of great appeal to undergraduate students, the projects developing additional skills in areas like computer science or biology. When teaching science courses for non-scientist I believe that the ultimate goal is to broaden the students understanding and perspective of science. One would then, expect a Physics sequence for non-scientists to free students from their misconceptions about science by exposing them to the questions that are asked in Physics and the methods used to find the answers. Such a course would convey to the students both, the limitations and the enormous power of Physics, through an overview of the problems that can be addressed and those that can't within Physics.

I am a sensitive teacher, always eager to help my students develop their knowledge. In doing so, I strive to learn from them about my own teaching, to evaluate it constantly, and to grow as a teacher and as a person.