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From: Ivan V. Maly [mailto:maly@MIT.EDU]
Sent: Wednesday, November 12, 2003 4:24 PM
To: deruyter@indiana.edu
Subject: application for faculty position in biological modeling

Dear Professor deRuyter,

I wish to apply for a tenure-track faculty position in biological modeling, as announced in a message from Prof. Glazier that was forwarded to me by Prof. Borisy. As a faculty member, I plan to establish a research program in integrative computational modeling of cell polarization via interaction of the cytoskeleton and cell signaling system. To this end, I will be taking advantage of the dual expertise I gained modeling the cytoskeleton dynamics for my dissertation, and signaling networks as a postdoctoral trainee. I will rely on my biological education and research experience in experimental biology to establish fruitful collaborations with experimentalists. I will be happy to teach introductory, cellular or molecular biology. Also, I would like to develop an advanced course with the emphasis on quantitative models of cellular processes. Thank you for your consideration of my application. Please find attached my curriculum vitae, a statement of research and teaching interests, and a list of references.

Sincerely yours,

Ivan V. Maly, Ph.D.

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Ivan V. Maly

Interests

I am interested in understanding of the self-organization of molecular ensembles that results in the emergence of life at the cellular level. My approach is theoretical. It is based on integration of the empiric knowledge by means of mechanistic, quantitative modeling. The models are meant to provide a rigorous framework for further experimentation, and predict novel mechanisms of supramolecular self-organization. I am particularly interested in explaining the spatial organization of the cell in terms of the kinetics of molecular interactions. So, I have developed models of spatial self-organization in the dynamic microtubule and actin cytoskeletons for my doctoral dissertation, and a model of self-organization in a spatially-distributed signaling network as my postdoctoral work. A problem on which I plan to concentrate my independent research is the kinetic origin of cell polarity, which results from the interaction of the cytoskeleton and cell signaling.

My studies of the self-organization of the cytoskeleton have been based on a rigorous quantitative formulation of relatively simple theoretical principles that I proposed for it. So, our analysis suggested (Maly and Borisy, 2001) that the orientational distribution of branching actin filaments is shaped by the same kinetic principles of natural selection that underlie Darwinian evolution at the higher levels of biological organization. We also established a connection between the phenomena of treadmilling and self-organization into a polar array of non-centrosomal microtubules by showing, in a kinetic-geometric model, that treadmilling results in polarization of a microtubule population (Maly and Borisy, 2002). Remarkably, in both cases it was possible to find such a viewpoint on the problem that either the relevant quantitative parameters describing the assembly combined into a single, bounded control parameter, permitting a full numerical analysis, or an analytical and parameter-independent solution could be obtained. My own experience therefore demonstrates that even in the face of today's

problems of biological complexity it is possible, and expedient, to look for simple governing principles.

In my studies of cell signaling I am taking advantage of the modern computers that make it possible to demonstrate the physical, quantitative consistency of novel mechanisms of spatial self-organization when an analytical solution, full numerical analysis, or even a conventional mathematical formulation of a detailed model is unreachable. So, I was able to demonstrate by computational analysis of a multicomponent, high-connectivity, spatially distributed signaling network that the autocrine system of epidermal growth factor receptor is capable of spatial self-organization, and to predict which of the parameters, such as protein expression levels, are likely to be responsible for it (Maly, Wiley and Lauffenburger, 2003). I believe that much of the biological research will benefit from a combination of these principle-based and computation-based theoretical approaches.

The problem that I would like to put in the center of my independent research is the origin of cell polarity. To perform their functions, such as, for instance, directed locomotion, cells must acquire an asymmetric polarized shape and distribution of their components. This requires, most prominently, the cell achieving a specific arrangement of the cytoskeleton as its major structural determinant. The cytoskeleton rearrangement involves regulation by the cell signaling system, which coordinates the cytoskeleton dynamics with extracellular cues and couples the microtubule and actin parts of the cytoskeleton. I plan to establish a research program in modeling of cell polarization that will integrate the dynamics of the cytoskeleton and the signaling system.

To that end, I will first develop models of spatial regulation of the two major components of the cytoskeleton, namely microtubules and actin filaments, by the signaling system. Of particular interest is the spatial regulation by Rho-family GTP-ases: of the microtubule assembly via the PAK-stathmin pathway and of the actin assembly via the WASP-Arp2/3 pathway. These models will form the basis for the next level of modeling where I plan to account for the effects of the cytoskeleton on signaling and the ensuing feedback interactions that lead to self-organization of polarity. Here I am particularly interested in analysis of the self-organization capability of systems that

involve microtubule-guided transport of signaling proteins, such as Asef, the activator of a Rho-family member, Rac.

These models are expected to explain, at the quantitative physico-chemical level, the polarization response of the microtubule and actin cytoskeleton to an extracellular signal, as well the intrinsic self-polarization capacity of cells. They will provide a quantitatively consistent framework for basic phenomena of cell polarization, grounded in the present empirical knowledge, and expose the problems of such an explanation, pointing to the critical gaps in the existing knowledge. They are also likely to identify which of the current intuitive speculations are physically implausible or logically inconsistent, and, conversely, what molecular mechanisms are feasible and deserve to be tested experimentally. In either case, I am determined to present my findings in a manner compelling to experimentalists, to positively influence, through application of the theoretical and computational methods, the development of this field of biology.

As the integrative modeling of the cell becomes more and more important for the advancement of biology, biotechnology, and biomedicine, learning the already established elements of the quantitative view of the cell will be a necessity for future researchers, as well as for students specializing in various related subjects. This perspective, and also my own experience as an undergraduate student greatly influenced by such a course, is what makes me especially interested in creating a novel course in cell biology with the emphasis on quantitative models of cellular processes. The more established models of processes like transport through biological membranes, and cytoskeleton assembly may, for the benefit of the future researchers, be complemented in this course by an adequate exposition of how models are used to advance our understanding of more controversial problems like mechanisms of molecular motors and reaction-diffusion processes in cell signaling. I believe that such a course will be of great interest to graduate and advanced undergraduate students of biology and related curricula. In addition, I will be happy to teach an introductory or a more advanced course in cell biology, which was at the center of my education, or a general biology course.

To summarize, in the view of my goals, I am deeply interested in becoming a part of, and in helping to develop an interdisciplinary environment for research and teaching.