Proposal for a 2005 Aspen Center for Physics Workshop

Spatial effects in signal transduction

Organizers:

Wouter-Jan Rappel   Department of Physics and Center for Theoretical Biological Physics
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92037
Tel.: (858) 822-1357
rappel@physics.ucsd.edu
Contact person and responsible for working to ensure diversity

Yuhai Tu                   IBM T. J. Watson Research Center
P. O. Box 218
Yorktown Heights, NY 10598
Tel.: (914) 945-2762
yuhai@us.ibm.com

Duration:    Three weeks

Both W-JR and YT are available from August 1 until September 3.
Preferred dates: August 8-26.

1 Topic and goal of the workshop

The study of signal transduction pathways has become an active field of interdisciplinary research. With the help of genetic and biochemical tools, these networks are getting mapped out in ever greater detail. The resulting complexity is typically addressed by bioinformatical techniques which assume that cells, the environment in which the pathway functions, can be modeled as a zero-dimensional object. However, in reality, cells are geometrically complex objects containing multiple localized components including scaffolds, vesicles, filaments and microdomains. Thus, representing the cell as a point particle or a well-stirred homogeneous bag of chemicals is a gross oversimplification. In fact, recent experimental techniques that probe intracellular events provide clear evidence that spatial effects in signal transduction play an important role in a variety of processes including signal transduction specificity and signal gain.

The modeling of these intracellular events is challenging as it can involve complex spatially extended geometries, can encompass a large number of components and might require the use of stochastic algorithms. Nonetheless, we feel that the time is ripe to start addressing the role of spatial effects through modeling efforts in several biological systems. Building on experience from previous biophysics workshops at the Center, we propose to bring together a combination of experimentalists and theorists, coming from a diverse set of disciplines. The goal of the
workshop is to help identify problems that are suitable for a combined experimental/theoretical approach and to foster future collaborations across disciplinary boundaries.

We readily admit that the title of our workshop is very broad. We have thus decided to organize the workshop around three main topics. These topics are, we believe, most ready for significant contributions from modeling minded scientists. Furthermore, these topics distinguish themselves by having a large experimental community using techniques that permit the visualization of intracellular events.

A: Signaling in myocytes

The second messenger calcium plays an essential role in the excitation-contraction coupling in cardiac myocytes. Following the depolarization of the t-tubules, invaginations of the cell membrane, a limited number of calcium ions enters the cell. This initial calcium signal is dramatically increased by additional calcium release from the sarcoplasmic reticulum, where calcium is stored at elevated concentrations. The release is regulated by calcium sensitive receptors, located close to the t-tubules and on the sarcoplasmic surface. The resulting large influx of calcium into the cytosol is then used to contract the cell and, consequently, the heart muscle. Mishandling of the calcium signaling machinery can have dire consequences, including death.

The calcium signal pathway involves a number of cytosolic proteins, typically highly localized within the cell, as demonstrated in recent experiments using fluorescent markers. When combined with the highly complex geometry of the myocyte, it becomes clear that spatial effects need to be accounted for. This, however, is a challenging task, best tackled using an interdisciplinary approach as it requires developing powerful computational tools, combined with physical insights and experimental knowledge.

B: Chemotaxis in eukaryotic cells

Chemotaxis, which is characterized by directed movement of cells up a chemical gradient, is a key component in a multitude of biological processes, including neuronal patterning, wound healing, embryogenesis, and angiogenesis. Our understanding of the mechanisms that control chemotaxis have taken major leaps forward in the past 5 years. We are at a period in the pathway discovery process in which many, but certainly not all, of the key signaling components have been identified and have been placed in both genetic and biochemical pathways. In some cases, the protein-protein interaction networks have been mapped and the pathways are sufficiently worked out that we can write an almost complete flow diagram from receptor activation to a downstream cellular behavior. This growing understanding now places us in an ideal situation in which we can investigate, in detail, the timing and coordination of these processes.

Particularly exciting from a physics point of view is the discovery that cells can respond to a signal in an asymmetric fashion. When stimulated from a point source, the cell initiates an integrated set of responses at the side of the cell closest to the source (leading edge). This polarized cell is characterized by a unique subset of signaling and cytoskeletal components that have become localized in the anterior and posterior of the cell. Further, our understanding of the flow diagrams combined with the enzymatic functions of many of the components now allows us
to develop detailed mathematical models capable of making predictions that can be tested experimentally.

C: Bacterial signaling

Spatial effects in signal transduction are not limited to eukaryotic cells but are also present in bacteria. For example, intracellular organization of several proteins plays a crucial role in the cell division process in e coli and other bacteria. In bacterial chemotaxis, the chemoreceptors are known to form spatially extended structures (receptor clusters). These structures play an important role in signal amplification, presumably through conformational spread within the spatially extended receptor cluster. Again, our ability to model these systems is greatly aided by the recent advance of sophisticated intracellular visualization techniques. The in vivo formation of the receptor cluster involves both the linker protein CheW and the Histidine kinase CheA, which together forms the spatially extended receptor complex. The structures of CheW, CheA and the cytoplasmic domains of the receptor are known, and there are a number of in vitro and in vivo experiments studying the binding and activities of the receptor complex for different external and internal conditions. However, the detailed process of the cluster formation, e.g., the stoichiometry of the complex and how the cluster structure affects the function (kinase activity of CheA) are still unknown. The receptor complex cluster also contains other members of the bacterial chemotaxis signaling pathway, such as the methylation enzyme CheR and the phosphotase CheZ. How such spatial localization of the regulatory molecules affect the signaling function is still a mystery. With the advent of high-resolution single cell measurements, all these questions may be explored and answered with the help of quantitative modeling techniques.

2 Organization

We plan to hold a three week workshop in August 2005 with roughly 40 participants. The workshop will be divided into three one-week blocks, with each week devoted to one of the three main topics. This allows bench scientists, who typically have stricter time constraints than physicists, to attend the week of their choice.

Since we believe that the most fruitful collaborations come from informal conversations among participants we plan to have only one or two seminars per day. These will be held in the morning, leaving ample time for discussion during the remainder of the day. Furthermore, we plan to have one colloquium per week. These talks will be less specialized than the seminars and will be given by one of the participants. The goal of these colloquia is to introduce the participants of the workshop as well as other physicists present at the Center to the "topic of the week".

3 Participants

One of the most important prerequisites of organizing a cross disciplinary workshop like ours is to have a critical mass of leading scientists from all involved fields. While we believe it will not be difficult to attract leading physicists to our workshop, this might not be the case for scientists from biology and biomedical fields. We have thus enlisted the help of a premier experimental biologist in each of the three subtopics: Howard Berg, the Herchel Smith Professor of Physics
and Professor of Molecular and Cellular Biology, Harvard University (signaling in bacteria), William Loomis, Professor of Biology, UC San Diego (chemotaxis in eukaryotic cells) and Donald Bers, Professor and Chairman of Cellular & Molecular Physiology, Loyola University, Chicago (signaling in myocytes). Their primary task is to assist us in inviting the experimental scientists.

In addition, the following people have been contacted and have expressed interest in attending: Elizabeth Cherry (Hofstra University), Flavio Fenton (Hofstra University), Pablo Iglesias (Johns Hopkins), Alain Karma (Northeastern University), Herbert Levine (UCSD), Andrew Rutenberg (Dalhousie University), Yohannes Shiferaw (UCLA), Jim Weiss (UCLA), Tom Shimizu (Harvard University), Ady Vaknin (Harvard), Victor Sourjik (University of Heidelberg, Germany), Bernardo Mello (Catholic University, Brazil)

The following people are among those who have not yet been contacted but who would contribute to the workshop: Martin Howard (Imperial College London), Karsten Kruse (Max Planck Institut, Germany), Boris Shraiman (Rutgers), Hans Westerhoff (University of Amsterdam), Ned Wingreen (Princeton), Dennis Bray (Cambridge University), Jeff Stock (Princeton)

This document was read and approved by both organizers.