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## Mathematical Models in Signaling Systems - June 16-18, 2004

### ***Cellular Models and Spatial Complexity***

#### *Mathematical Model of the Spatio-Temporal Dynamics of Second Messengers in Visual Transduction*

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#### ***Abstract:***

It is becoming increasingly clear from recent investigations that the control of signal transduction in cells occurs by precise, highly-regulated localization of key enzymes in sub-compartments in cells. The classical methods used to describe signal transduction processes (Michaelis-Menten kinetics) assume a well-stirred aqueous environment, and the most common mathematical modeling approaches use ordinary differential equations whose solutions average concentrations within the volume of the cell. These methods are inadequate to describe the precisely regulated signal transduction processes emanating from the highly-organized cellular structures that control signaling processes. Our goal is to apply appropriate mathematical models of signal transduction processes leading to cellular responses. The models take into account both the spatial localization in the cell of each component of the signaling pathway, as well as the temporal changes in state and include diffusion processes. Partial differential equations describe the spatio-temporal aspects have been implemented using the mathematical techniques of homogenized limits and concentrated capacity into computable forms, and the numerical output of the computable models have been compared with known biological data.

The first system this modeling approach has been tested on is visual transduction in rod outer segments. It embodies key processes common to a variety of signaling systems, and it is one of the best understood signal transduction processes, for which there is a wealth of experimental data. The highly ordered structure of rod disk membranes and the spatial separation of the transduction apparatus and the output channels is an appropriate test bed for modeling. Here, the signal is light, its receptor is rhodopsin, and the cellular response is a change in voltage at the photoreceptor's plasma membrane. Mathematical models of this process have already been applied to this system, but the localization of the enzymes on the membrane and the diffusion of the two key second messengers, cGMP and Ca<sup>2+</sup> within the cytosol has been neglected in these models based on ordinary differential equations.

We have used partial differential equations to model this signal transduction pathway. Phenomena such as the interactions of cytosolic cGMP with its membrane-bound degradative enzyme phosphodiesterase, which physically occur on the surface of the discs, have been correctly modeled as flux sources located on the discs. Similarly, the evolution of Ca<sup>2+</sup> is effected by influx through cGMP-gated channels, and as such is described by source terms supported on the lateral boundary of the rod cell. This results in a system of evolution partial differential equations with non-linear boundary conditions on the boundary of the outer segment and on each of the internal discs. The complex geometry of the rod outer segment (about 800 disk membranes, of diameter 11 microns, 14 nm apart from each other) presents mathematical and, especially, numerical difficulties for diffusion in the cytosol. The mathematical techniques of homogenized limits and limits of concentrated capacity, have been used to effectively replace the

diffusion problem with one in a much simpler "homogenized" geometry, for which computation becomes much easier and efficient. Such a homogenized limit and the limit of concentrated capacity present challenging mathematical difficulties of interest in their own right. Since the boundary contributions are not homogeneous, it is not obvious what the correct topology is in which to take such a limit. We have simulated numerically the diffusion problem in both geometries in order to compare the two, and assessed the effectiveness of the simpler homogenized problem as a substitute for the actual one.

We believe homogenization methods similar to those described here can be applied to other complex geometries of many cell types, allowing us to precisely model the particular spatial locations in cells of the elements of signaling pathways, as well as their spatial and temporal evolution, a dramatic improvement from the current models. There are complex networks of interactions among the multiple signal transduction pathways. The level of complexity that is unfolding will make mathematical models of signal transduction necessary for critical evaluation of the data and for quantitative understanding of the processes, as well as useful tools for designing discriminating experiments. Single signal transduction modules may be able to be built up together to describe multiple signal transduction pathways interacting in ways known from biological experimentation or predicted from the model. It should be possible to use these modeling approaches to eventually build up a realistic signal transduction networks to test specific hypotheses of signal cross-talk, integration and decision-making.