UNIVERSITY OF HEIDELBERG - BIOMS – BIOQUANT – WORKSHOP

on

Transport, Signaling and Structure Formation in Cellular Systems: Mathematics Meets Experiments

Saturday, JULY 14, 2007

BIOQUANT, INF 267, Seminar Room 041, Ground Floor

Organizers: Prof. Willi Jäger and Prof. Angela Stevens

PROGRAM:

9:00 – 9: 45	**Prof. Richard James (Minneapolis/Leipzig)** **Lessons on Structure from the Structure of Viruses**
9:45 – 10:15	Coffee Break
10:15 – 11:00	**Prof. Heidi Hamm (Vanderbilt)** **Modeling G-protein Signaling Pathways Downstream of PAR Receptors in Endothelial Cells**
11:15 – 12:00	**Prof. David Kinderlehrer (Pittsburgh)** **Transport in Small Systems with a Look at Motor Proteins**
12:15 – 14:00	Lunch
14:00 – 14:45	**Prof. Hans Othmer (Minneapolis)** **Mathematical Models for Spatial Patterning in Drosophila Melanogaster**
14:45 – 15:15	Coffee Break
15:15 – 16:00	**Prof. Emmanuele DiBenedetto (Vanderbilt)** **Variability of the Single Photon Response in Vertebrate Phototransduction**
16:15 – 17:00	**Prof. Bob Eisenberg (Chicago)** **Mathematics of Ions in Channels and Solutions**

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Abstracts

Lessons on structure from the structure of viruses

Richard D. James (MPI-MIS and the University of Minnesota)

Abstract: As the most primitive organisms, occupying the gray area between the living and nonliving, viruses are the least complex biological system. One can begin to think about them in a quantitative way, while still being at some level faithful to biochemical processes. We make some observations about their structure, formalizing in mathematical terms some rules-of-construction discovered by Watson and Crick and Caspar and Klug. We call the resulting structures objective structures. It is then seen that objective structures include many of the most important structures studied in science today: carbon nanotubes, the capsids, necks, tails and other parts of many viruses, the cilia of some bacteria, DNA octahedra, buckyballs, actin and collagen and many other common proteins, and certain severely bent and twisted beams. The rules defining them relate to the basic invariance group of quantum mechanics. We give simple formulas for all such structures. Some of the nonperiodic structures revealed by the formulas exhibit beautifully subtle relations of symmetry. This common mathematical structure paves the way toward many interesting calculations for such structures: simplified schemes for exact molecular dynamics of such structures (objective MD), phase transformations between them (as in bacteriophage T4), new x-ray methods for direct determination of structure not relying on crystallization, and their growth by self-assembly.

Modeling G protein signaling pathways downstream of PAR receptors in endothelial cells.

Heidi E. Hamm (Vanderbilt Univ. Med. Center)

Abstract: Thrombin, a serine protease, is a key mediator of endothelial repair responses. Many of thrombin's actions are mediated through activation of a family of proteinase activated receptors (PARs), G protein coupled receptors. PARs are known to couple to multiple G proteins including Gi, Gq, and G12 family members. Thrombin activates the protease-activated receptor-1 (PAR-1) by cleavage of the amino-terminus to unmask a tethered ligand. Though peptide analogs of the tethered ligand can activate PAR-1, agonist peptides signal in a manner which differs from thrombin activation. Human microvascular endothelial cells form monolayers in culture, and activation of PAR-1 leads to barrier permeability. To study the signaling regulating barrier function, we have compared the ability of thrombin and agonist peptide to cause intracellular Ca^{2+} mobilization and barrier dysfunction. Thrombin induced endothelial monolayer dysfunction and mobilized intracellular calcium with EC50 values of 0.1 and 1.7 nM, respectively. The opposite order of activation was observed for agonist peptide (SFLLRN-CONH2 or TFLLRNKPDK) activation. Addition of inactivated thrombin did not affect agonist peptide signaling suggesting that the differences in activation mechanisms are intramolecular in origin. Though activation of PAR-1 or PAR-2 by agonist peptides induced calcium mobilization, only PAR-1 activation affected barrier function. Induced-barrier permeability is likely to be Gα12/13-mediated as neither chelation of Gαq-induced intracellular calcium with BAPTA-AM, pertussis toxin inhibition of Gαi/o nor matrix-metalloproteinase inhibition by GM6001 had any effect while inhibition of the Gα12/13-induced Rho effector, Rho kinase, with Y-27632 abrogated the response. Similarly, calcium mobilization is Gαq-mediated and independent of Gα12/13 and Gαi/o, as pertussis toxin and Y-27632 had no effect while inhibition of PLC-β by U-73122 blocked the response. It is therefore likely that changes in permeability reflect Gα12/13 activation and changes in calcium reflect Gαq activation, implying the differences observed between thrombin and agonist peptide activation of PAR-1 are likely to be differences in the ability of the receptor, activated by different means, to activate Gα12/13 or Gαq.
Mathematical models used to characterize this system estimate the binding affinities of the thrombin receptor for the G proteins activated by free activating peptide would have to differ by ~833-fold in favor of Gαq activation.

Transport in small systems with a look at motor proteins

David Kinderlehrer (Carnegie Mellon University, Pittsburgh)

Abstract: Motion in small live systems has many challenges. Prominent environmental conditions are high viscosity and warmth. It difficult to move and maintaining a course is rendered difficult by immersion in a highly fluctuating bath. This holds especially for the motor proteins responsible for much of eukaryotic cellular traffic. The situation falls under the rubric of diffusion mediated transport, Brownian motors, and molecular rachets. We give some brief historical notes, the work of many distinguished scientists, and then turn to an approach based on the Monge transport problem (1787) and its modern version, Monge-Kantorovich Theory. We arrive at a precipice: does this help? Can we say anything about the behavior of the cellular process? An exciting venue for math in the natural world.

Mathematical Models for Spatial Patterning in Drosophila melanogaster

Hans Othmer (University of Minnesota)

Abstract: Much is known about the molecular components involved in signal transduction and gene expression in a number of systems, and the focus is now shifting to understanding how these components are integrated into networks, and how these networks transduce the inputs they receive and produce the desired pattern of gene expression. Gene expression during embryonic development is not a cell-autonomous process, because a cell's fate in a multicellular embryo usually depends on the cell's location. Pattern formation in development refers to the spatially- and temporally-organized expression of genes in a multicellular array, and frequently pattern formation results from the response of individual cells to a spatial pattern of chemicals called morphogens. Drosophila is one of several model systems for which a number of morphogens have been identified, and for which many of the components of the signal transduction and gene control networks involved in patterning are known. However, less is known about how these networks produce the desired spatio-temporal pattern of gene expression. In this talk we will use mathematical models to address this issue in several stages of Drosophila development, and show how these models can give insights that help to guide experimental work.

Variability of the Single Photon Response in Vertebrate Phototransduction

Bob Eisenberg (Rush University Medical Center, Chicago)

Abstract: An important class of biological molecules – proteins called ionic channels – conduct ions (spherical charges like Na^+ , K^+ , Ca^{2+}, and Cl^- with diameter ~ 0.2 nm) through a narrow tunnel of fixed charge ('doping') with diameter ~ 0.6 nm. Ionic channels control the movement of electric charge and current across biological membranes and so play a role in biology as significant as the role of transistors in computers: a substantial fraction of all drugs used by physicians act on channels. Channels can be studied in the tradition of physical science. Poisson - drift diffusion equations familiar in physics form an adequate model of current voltage relations in many types of channels under many conditions, and can be extended to describe 'chemical' phenomena like selectivity with some success. Ionic channels are studied with the powerful techniques of molecular biology in hundreds of laboratories. Atoms (and thus charges) can be substituted a few at a time and the location of every atom can be determined in favorable cases. Ionic channels are one of the few living systems of great importance whose natural biological function can be well described by a tractable set of equations.