Michael I. Monine - Research interests

Modeling combinatorial complexity in signal transduction systems
(Theoretical Biology and Biophysics group, Los Alamos National Laboratory, PIs: Drs. B. Goldstein and W. Hlavacek)

The focus of my current research is the development of novel computational methods in cell biology. There is growing appreciation for the need for predictive mathematical (computational) models that could enable the engineering of cellular behavior. Computational modeling aids in the design of new and more effective drugs, prediction of the functioning of cells and understanding of mechanisms of disease development at molecular level. Molecular changes that affect signal-transduction systems in cells are responsible for a number of diseases. Therefore, it is important to understand how to manipulate these systems to reverse the effects of deleterious molecular changes.

Modeling of signal-transduction systems is challenging, in part because the molecular interactions occurring in these systems have the potential to generate large numbers of molecular complexes. Multivalent protein-protein interactions can produce myriad protein complexes and post-translational modifications. Because of the problem of combinatorial complexity, manual specification of reaction schemes or sets of corresponding equations is impractical. An alternative approach to model specification is to use reaction rules to represent biochemical interactions. A number of software tools have been recently developed to enable a rule-based formalism of biochemical networks (see [1] for references). However, some of these tools are either inherently inefficient or designed for only specific types of interactions.

My research efforts aim for development of stochastic methods that allow for easier specification and processing of reaction networks in terms of rules. We have recently developed a rule-based kinetic Monte Carlo (RBKMC) method [1], which introduces a general framework for more efficient implementation of the well-known Gillespie's method. Although Gillespie's method had been originally proposed for simulating well-mixed compartments, our method accounts for the spatial structure of multimolecular complexes that can arise from multivalent molecular interactions, and the effects of steric constraints on spatial configurations of complexes. In the RBKMC method, rules describe how reactivity depends on the identity of interacting sites, the local context of interacting molecules (e.g., the binding or modification states of neighboring sites), and whether the reactants are in solution (well-mixed) or tethered to a membrane (diffusion-limited interactions).

The specific system that I am currently studying computationally involves the interaction of a multivalent ligand (antigen) with a bivalent cell-surface receptor (FcεRI-IgE complexes). Crosslinking of cell-surface receptors by extracellular antigens initiates cascades of signaling reactions in cells. Downstream intracellular reactions determine the immune response of the whole organism (human). Mast cells (a type of tissue cells) and basophils (a type of white blood cells) are the examples of cells, in which such ligand-receptor interactions are vital. Both these types of cells play a functional role in allergic

reactions. When activated by ligand, these cells secrete regulatory molecules (histamine). Experimentally, the interaction of a synthetic ligand with IgE antibody bound to FcεRI on the surface of rat basophilic leukemia (RBL) cells was studied using the flow-cytometry technique (R. Posner's lab, Northern Arizona University and TGen). The RBKMC model applied to this system predicts the formation of large receptor clusters within an interval of ligand concentrations, which correspond to a maximum secretory response. Extended analysis of steric effects on kinetic and equilibrium behavior yields insights that could potentially explain how the ligand is able to activate cells while apparently inducing large receptor aggregates, which are generally believed to be inhibitory [1,2]. My computational results also shows that dynamics of receptor aggregation may play a dominant role in initiating cellular responses.

Another system of interest is clustering of the transmembrane protein, linker for the activation of T-cells (LAT), at the inner leaflet of a cell membrane. Clustering of LAT, which is a scaffolding protein, is mediated by binding of a complex of cytosolic proteins (Grb2-SOS1-Grb2). Scaffolds promote signaling by providing binding sites for the assembly of signaling complexes. Preliminary studies of LAT oligomerization were performed with an equilibrium theory, which was derived based on a partition function for concentrations of all possible complexes, and verified with the RBKMC method, which was extended to account for Grb2 and SOS1 interactions in solution and binding of Grb2 to LAT at a membrane [3]. Using the computational model, we show that the valence of LAT is a critical factor in determining both the nature and extent of aggregation. When the valence of LAT is switched from two to three, there is a dramatic rise in oligomerization, a phenomenon we call valence switching, because the valence is controlled by the extent of phosphorylation of specific LAT sites.

A potential application area of the RBKMC model is associating polymers that play an important role in biological tissues. This method can also be applied to study aggregation phenomena in other fields of physical science, e.g., colloidal ferrofluids that undergo a self-assembly process and can form linear chains or isotropic aggregates.

Modeling diffusion-limited reactions in cell signaling

(2005-2006, PI: Prof. J. Haugh, NCSU; 2004, PI: Prof. S. Shvartsman, Princeton University)

During the earlier stages of my work, I contributed to the development of off-lattice spatial simulation methods. Among problems studied were extracellular and intracellular diffusion-limited interactions at cell membranes.

I have developed a two-dimensional Brownian Dynamics (BD) model of the interactions between receptors, membrane-bound proteins and cytosolic enzymes in an intracellular compartment of a platelet-derived growth factor (PDGF) receptor [4,5]. In this system, enzymes, such as GAP (GTPase activating protein), Grb2-SOS1 (guanine-nucleotide exchange factor, GEF) and PI-3 kinase (PI3K), are recruited from the cell cytoplasm to membrane-associated Ras proteins and cell surface receptors. Ras proteins belong to a class of G proteins; these molecules switch between two conformations:

inactive guanosine diphosphate (GDP) and active guanosine triphosphate (GTP) bound states. Transition of Ras-GDP to Ras-GTP is catalyzed by GEF, whereas the reverse reaction is facilitated by GAP. Ras proteins and PI3K are involved in the most important signaling pathways governing cell proliferation and survival. Dysregulation of these pathways figures prominently in cancer progression. The purpose of my computational study was to explore conditions for spatial coupling, i.e., the first step that initiates crosstalk between Ras and PI3K pathways. In the BD model, diffusion of membrane-associated Ras molecules was modeled by the first-passage-time algorithm; probabilities for interactions between Ras molecules and receptor-associated enzymes were described by one-dimensional propagators for the absorbing/reflective boundaries. Binding of enzymes from the cytoplasm and activation/inactivation of Ras were modeled as Poisson processes assuming a well-mixing approximation. The major conclusion withdrawn from the analysis using the BD model is that the diffusion-controlled capture of active Ras and Ras/PI3K complexes released from the receptor complex is the main mechanism by which many signaling pathways are propagated and spatially coordinated for efficient crosstalk between them. Spatial coupling between GEF and PI3K recruitment by the same receptor scaffold enhances Ras/PI3K crosstalk.

I have also built a macroscopic hybrid model of dermal wound healing. This model accounts for the PDGF gradient sensing mechanism in fibroblasts (tissue cells) [6]. Our hybrid modeling approach treats fibroblasts stochastically as discrete objects endowed with heterogeneous properties, namely expression levels of PDGF receptors, PI3K and other enzymes. Analysis of the model suggests that cell-to-cell variability results in a significantly higher rate of wound invasion as compared with the case of non-distinct cells, in a manner that depends on how individual cell properties are sampled or inherited upon cell division.

Another project I worked on was simulation of autocrine binding assays. Autocrine signaling is a form of extracellular signaling, in which a cell secretes a ligand that signals the same cell in response to external stimuli. This type of signaling occurs in epidermal growth factor (EGF) receptor systems. The key aspect of my study was derivation of the survival probability for a single secreted particle (ligand) assuming boundary homogenization [7]. The developed approximation has been tested by three-dimensional BD simulations and compared against recent experiments involved cell culture assays.

I also contributed to a methodological study of systems, in which diffusing particles are trapped by surfaces covered by randomly or regularly located traps [8,9]. These problems are abundant in heterogeneous catalysis, cell biology, membrane technology, etc. To make the analysis of such systems more tractable, a homogenization approach has been proposed. The idea behind the homogenization is that nonuniformity of the boundary manifests itself only near the surface. The memory about local properties of the boundary decays with the distance from the boundary and the fields of fluxes and concentrations become uniform in lateral directions. We have proposed approximate expressions for the effective trapping rate of traps placed in random, triangular, square and hexagonal arrangements on a reflective surface, and validated these approximations by BD simulations and finite difference solutions.

Pattern formation in heterogeneous catalysis
(1997-2003, advisor: Prof. L. Pismen, Technion, Haifa, Israel)

During my PhD research, I studied theoretically heterogeneous catalytic reactions [10-15]. Heterogeneous catalytic reactions represent nonlinear systems that can demonstrate reaction rate instabilities, oscillations and spatio-temporal chaos. Many reactions of this type, for example, carbon monoxide (CO) oxidation and nitrogen monoxide (NO) reduction, are widely used in industry. These reactions are also vital in our everyday life, because they occur in automotive exhaust systems, where toxic combustion products, CO and NO, are converted to non-toxic substances, CO_2 and N_2. Understanding of kinetic mechanisms that cause instabilities in these reactions is of great importance to pollution control. The most effective catalysts for the $CO+O_2$ and $NO+H_2$ reactions are rhodium (Rh) and platinum (Pt). The fact that these metals are very precious imposes additional concerns for optimal design of catalytic converters.

This work was done in close collaboration with our experimental colleagues, the group of Prof. R. Imbihl (University of Hannover, Germany). We have developed a number of models based on phenomenological equations of the FitzHugh-Nagumo and time-dependent Ginzburg-Landau types and the realistic Langmuir-Hinshelwood mechanism to provide qualitative and quantitative description of the experiments. One of the systems of interest was the $CO+O_2$/Pt(110) reaction conducted under low-pressure conditions. In this system, the mechanism of rate oscillations and spatio-temporal instabilities, which are also referred to as pattern formation, is based on adsorbate-induced surface phase transition of the catalytic surface. The surface phase transition is controlled by critical adsorbate coverage (CO). The clean Pt(110) surface exhibits a stable missing “row-structure”, whereas CO adsorption shifts Pt(110) surface atoms to the close-packed configuration, which is characterized by higher catalytic activity. The $CO+O_2$ reaction removes CO from the surface, prompting the reverse reconstruction. Interplay between CO adsorption/removal, fast CO diffusion and slow surface phase reconstruction causes a hysteretic behavior. My contribution to this research was to explore a role of the Pt(110) surface phase transition in pattern formation at both macroscopic and nanoscopic scales [10,11]. To bridge the gap between the phenomenological macroscale description of the Pt catalytic surface and its atomic-scale representation, a realistic kinetic Monte Carlo model of the surface phase transition has been proposed [11-13]. The model I have developed describes the atomic structure of Pt(110) catalytic surface and takes into account surface atom energies, which are assumed to be dependent on the occupancy of the nearest sites of the surface lattice. Pt atoms are allowed to hop between lattice sites. Binding energies of Pt atoms are modified by CO adsorption; parameters for Pt-Pt and Pt-CO interactions have been extracted from recent experimental data and density function calculations. My simulations using the Monte Carlo model have shown that defect formation, roughening and faceting of the Pt(110) surface dominate kinetics of the surface phase transition [11]. In particular, the front between alternative phases, i.e., the close-packed configuration of the CO-covered Pt(110) surface and the missing-row structure of the clean Pt(110) surface, disintegrates due to effects of roughening. A spatial extension of the model, which includes the $CO+O_2$ reaction coupled to a nonuniform distribution of

CO (diffusion of CO is fast compared to diffusion of Pt atoms), reveals local synchronization of surface states and formation of traveling waves [11]. My simulation results also qualitatively agree with the experimental observations showing that the rate oscillations may stop spontaneously, resulting in relaxation to the higher CO_2 production rate [13]. The simulations clearly demonstrate that repeated transition of Pt atoms leads to a stable facet structure, which is catalytically efficient. A regular facet pattern obtained in the simulations is similar to that detected in scanning tunneling microscopy experiments.

Other systems studied, both experimentally and theoretically, included O_2+H_2 and NO+H_2 reactions conducted on the Rh(111) catalytic surface (14,15). Since the Rh(111) surface is stable, these reactions are non-oscillatory. However, even in these systems, one can observe spatial organization phenomena. Experimentally, the fronts in the O_2+H_2/Rh(111) reaction have been observed to be either isotropic or triangular depending on the conditions of saturation of the Rh bulk by oxygen as well as on temperature and hydrogen pressure (see references in [14]). Anisotropy of the reaction front arises due to release of oxygen from the bulk, the crystalline structure of which has a face-centered cubic lattice. To simulate this system, I have developed a hybrid model that describes the coupling between an isotropic hydrogen diffusion front on the surface with an anisotropic front of oxygen release from the bulk. In this hybrid model, the hydrogen coverage is modeled by a PDE, whereas the local oxygen coverage is modeled by an ODE, which depends on the presence of subsurface oxygen in the bulk. The oxygen transition from the bulk to the surface is modeled with the help of a Lagrangian algorithm based on the local equation of boundary motion [10,14]. Depending on the reaction conditions, the slower process determines the morphology of the resulting front. By fitting parameters describing the propagation of the phase transition front, its anisotropy and its coupling to the reaction-diffusion front on the surface, the model quantitatively reproduces the experimental observations [14].

References

1. J. Yang, **M. I. Monine**, J. R. Faeder, W. S. Hlavacek. “Kinetic Monte Carlo method for rule-based modeling of biochemical networks”. *Phys. Rev. E.* **78**, 031910 (2008).
2. **M. I. Monine**, R. G. Posner, P. B. Savage, J. R. Faeder, and W. S. Hlavacek. “Modeling multivalent ligand-receptor interactions with steric constraints on configurations of cell-surface receptor aggregates”. *Submitted to Biophys. J.*
3. A. Nag, **M. I. Monine**, J. R. Faeder, and B. Goldstein. “Aggregation of Membrane Proteins by Cytosolic Cross-Linkers: Theory and Simulation of the LAT-Grb2-SOS1 System”. *Accepted to Biophys. J., in press*.
4. **M. I. Monine**, J. M. Haugh. “Signal transduction at point-blank range: simulation and analysis of spatially coupled crosstalk”. *Biophys. J.* **95**, 2172 (2008).
5. **M. I. Monine**, J. M. Haugh. “Reactions on cell membranes: comparison of continuum theory and Brownian dynamics simulations”. *J. Chem. Phys.*, **123**, 74908 (2005).
6. **M. I. Monine**, J. M. Haugh. “Cell population-based model of dermal wound invasion

with heterogeneous intracellular signaling properties". *Cell Adhesion and Migration*, **2**, 137 (2008).

7. **M. I. Monine**, A. M. Berezhkovskii, E. J. Joslin, H. S. Wiley, D. A. Lauffenburger, S. Y. Shvartsman. "Ligand accumulation in autocrine cell cultures". *Biophys. J.*, **88**, 2384 (2005).
8. A. M. Berezhkovskii, Yu. Makhnovskii, **M. I. Monine**, V. Zitserman, S. Y. Shvartsman. "Boundary homogenization for trapping by patchy surfaces". *J. Chem. Phys.*, **121**, 11390 (2004).
9. A. M. Berezhkovskii, **M. I. Monine**, C. B. Muratov, S. Y. Shvartsman. "Homogenization of boundary conditions for surfaces with regular arrays of traps". *J. Chem. Phys.*, **124**, 36103 (2006).
10. L. M. Pismen, R. Imbihl, B. Y. Rubinstein, **M. I. Monine**. "Two-tier symmetry-breaking model of patterns on a catalytic surface". *Phys. Rev. E*, **58**, 2065 (1998).
11. **M. I. Monine**, L. M. Pismen. "Reconstruction and roughening of a catalytic Pt(110) surface coupled to kinetic oscillations". *Phys. Rev. E*, **66**, 051601 (2002).
12. **M. I. Monine**, L. M. Pismen. "Realistic kinetic Monte Carlo study of the surface phase reconstruction". *Phys. Rev. E*, **69**, 21606 (2004).
13. **M. I. Monine**, L. M. Pismen, R. Imbihl. "Realistic kinetic Monte Carlo simulation of the faceting of a Pt(110) surface under reaction conditions". *J. Chem. Phys.*, **121**, 11332 (2004).
14. **M. I. Monine**, L. M. Pismen, M. Baer, M. Or-Guil. "Modeling triangular titration fronts in the O_2+H_2 reaction on a catalytic Rh(111) surface". *J. Chem. Phys.*, **117**, 4473 (2002).
15. **M. I. Monine**, A. Schaak, B. Y. Rubinstein, R. Imbihl, L. M. Pismen. "Dynamics of subsurface oxygen formation in catalytic water formation on a Rh(111) surface – experiment and simulation". *Cat. Tod.*, 70, **321** (2001).