

CENTER FOR THE STUDY OF BIOCOMPLEXITY

Workshop on Applications of Methods of Stochastic Systems and Statistical Physics in Biology

October 28 - 30, 2005
University of Notre Dame

Organizers:

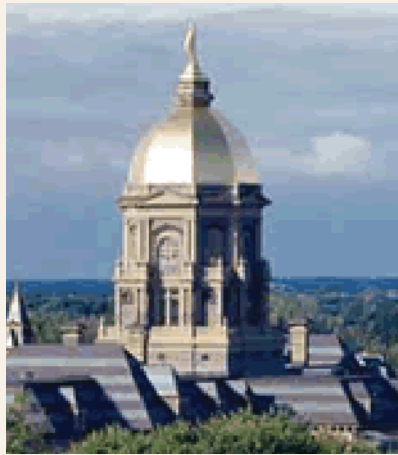
Mark Alber (Notre Dame)

Albert-Laszlo Barabasi (Notre Dame)

Holly Goodson (Notre Dame)

Yi Jiang (Los Alamos)

James Glazier (IU Bloomington)



Sponsors:

- National Science Foundation
- Department of Energy
- Indiana 21st Century Research and Technology Fund
- Los Alamos National Laboratory
- University of Notre Dame:
 - Interdisciplinary Center for the Study of Biocomplexity
 - Graduate School
 - Department of Mathematics
 - Department of Physics
 - Center for Applied Mathematics
- Biocomplexity Institute, Indiana University, Bloomington

KEYNOTE ADDRESS:

Dennis Bray, Cambridge University, UK

"Intercellular Signalling in a Molecular Jungle: Insights from Bacterial Chemotaxis"

MILLER LECTURE IN BIOPHYSICS:

Albert Libchaber, Rockefeller University

"Towards an Artificial Cell"

PUBLIC LECTURE:

Alan Perelson, Los Alamos National Laboratory

"New Developments in Modeling the Dynamics of Viral Infections"

SPECIAL LECTURE IN MATHEMATICAL BIOLOGY:

Avner Friedman, Mathematical Biosciences Institute, Ohio State University

"Tumor Proliferation is Affected by the Material Properties of its Surroundings"

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Introduction

The Notre Dame Interdisciplinary Workshop on Applications of Methods of Stochastic Systems and Statistical Physics in Biology <http://www.nd.edu/~icsb/wrkshp2005.html> was held from October 28-30, 2005. It was jointly organized by the Interdisciplinary Center for the Study of Biocomplexity (ICSB) at the University of Notre Dame, and Los Alamos National Laboratory, in cooperation with the Society of Industrial and Applied Mathematics (SIAM).

There were 47 invited talks by researchers from the USA, Canada and Europe and 50 posters. The total number of participants was 150. The meeting consisted of a public lecture, 3 keynote addresses, 9 sessions of talks and a poster session. The meeting was followed by two satellite Workshops on Limb Morphogenesis and Molecular Dynamics with 25 participants each.

This meeting was important and timely because recent years have revealed an increasing interest in studying biological problems using stochastic simulations. One of the driving forces in these developments has been the analysis of random and hierarchical effects that arise naturally in many classes of problems of complex biological systems. The applications of stochastic methods in biological modeling are even more justified based on the complexity of biological subunits and more sophisticated local rules compared with exploration of nonliving systems. In recognition of this significance, the National Science Foundation, Department of Energy and Indiana 21st Century Research and Technology Fund have sponsored the Workshop.

The Workshop brought together researchers in many disciplines (including mathematics, experimental and theoretical biology, physics, chemistry, bioengineering, and computer science) to discuss current and future applications of methods of stochastic systems and statistical physics to problems ranging from single molecular biophysics to HIV immunology and cardiac electrophysiology. One of the goals of the Workshop was to provide a forum for junior faculty and graduate and undergraduate students to interact with a wide range of experts and attract new researchers to the field of biological modeling. Each 3 hour session contained 20 minute talks by young researchers. Each plenary talk was designed in such a way as to provide new viewpoints to the established methods and theories, as well as to assist junior investigators and students to identify specific areas of emphasis for their future research. These talks were followed by extended discussions on different aspects of biological modeling.

Summaries of all Workshop presentations and posters have been compiled into a booklet provided to all participants. These will be also made available electronically on the ICSB website: <http://www.nd.edu/icsb>. Material from several talks will be used for developing several tutorials which will be posted on the ICSB web cite and will be used in teaching graduate and undergraduate courses on computational and mathematical biology, biophysics and biochemistry.

Participants of the Workshop were invited to contribute to the special Issue of the Journal of Statistical Physics (JSP) (Springer). The ICSB has already put together Special Issue on Applications to Biology of the SIAM Journal of Multiscale Modeling and Simulations, Volume 3, Number 2, 2005, and a Special Issue of Biofilms, Volume 1, Number 4, 2004 (Cambridge University Press).

DAILY SCHEDULE OF EVENTS

Friday October 28, 2005 - McKenna Hall Auditorium

7:30 – 8:15 Registration (Main Desk, McKenna Hall)
8:15 – 8:30 Opening Address: Joseph Marino, Dean, College of Science

SESSION I

Chair: Mark Alber

8:30 – 9:10 L. Glass (McGill University, Canada)
9:10 – 9:50 H. Levine (University of California – San Diego)
9:50 – 10:05 BREAK
10:05 – 10:45 B. Goldstein (Los Alamos National Laboratory)
10:45 – 11:45 Plenary Lecture: D. Bray (Cambridge University, UK)
11:45 – 1:15 LUNCH

SESSION II

Chair: Stuart Newman

1:15 – 1:45 D. Kaiser (Stanford University)
1:45 – 2:15 M. Swat (Indiana University - Bloomington)
2:15 – 2:45 Z. Toroczka (Los Alamos National Laboratory)
2:45 – 3:15 T. Lipniacki (Polish Academy of Sciences)
3:15 – 3:45 B. Birnir (University of California – Santa Barbara)
3:45 – 4:00 BREAK

SESSION III

Chair: Yi Jiang

4:00 – 4:20 J. Peng (University of Notre Dame)
4:20 – 4:40 R. De Ruyter (Indiana University – Bloomington)
4:40 – 5:00 B. Schmittmann (Virginia Polytechnic Institute and State University)
5:00 – 5:20 P. Atzberger (Rensselaer Polytechnic Institute)
5:20 – 5:40 P. Kramer (Rensselaer Polytechnic Institute)
5:40 – 6:00 A. Madzvamuse (Auburn University)
6:00 – 6:20 T. Glimm (Western Washington University)
6:20 – 6:40 D. Milutinovic (Utrecht University, The Netherlands)
7:00 – 9:00 POSTER SESSION AND RECEPTION
Lower Level Dining Room – McKenna Hall

Saturday October 29, 2005 -102 DeBartolo Hall

7:45 – 8:30 Coffee and Bagels

SESSION I

Chair: James Glazier

8:30 – 9:10 A. Levchenko (Johns Hopkins University)
9:10 – 9:50 S. Panfilov (Utrecht University, The Netherlands)
9:50 – 10:05 BREAK
10:05 – 10:45 A. Garcia (Rensselaer Polytechnic Institute)
10:45 – 11:45 Miller Lecture in Biophysics: A. Libchaber (Rockefeller University)
11:45 – 1:15 LUNCH
Lower Level Dining Room – McKenna Hall

SESSION II

Chair: Dale Kaiser

1:15 – 1:45D. Odde (University of Minnesota)
1:45 – 2:15 J. Pearson (Los Alamos National Laboratory)
2:15 – 2:45 U. Tauber (Virginia Polytechnic Institute and State University)

2:45 – 3:15 H. Hentschel (Emory University)

3:15 – 3:30 BREAK

SESSION III

Chair: James Keener

3:30 – 3:50 S. Schnell (Indiana University – Bloomington)
3:50 – 4:10 G. Huber (University of Connecticut Health Center)
4:10 – 4:30 I. Derenyi (Eotvos University, Hungary)
4:30 – 4:50 F. Alexander (Los Alamos National Laboratory)
4:50 – 5:10 D. Anderson (Duke University)
5:10 – 5:30 L. Sander (University of Michigan)

5:30 – 6:30 RECEPTION

Notre Dame Room, Morris Inn

6:30 – 7:30 PUBLIC LECTURE: A. Perelson (Los Alamos National Laboratory)
102 DeBartolo Hall

8:00 ND CONCERT – Dawn Upshaw and Eighth Blackbird
Leighton Concert Hall, DeBartolo Performing Arts Center

Sunday October 30, 2005 -102 DeBartolo Hall

7:45 – 8:30 Coffee and Bagels

SESSION I

Chair: Alan Perelson

8:30 – 9:10 H. Othmer (University of Minnesota)
9:10 – 9:50 A. Mogilner (University of California – Davis)

9:50 – 10:05 BREAK

10:05 – 10:45 J. Keener (University of Utah)
10:45 – 11:45 Special Lecture in Mathematical Biology: A. Friedman
(Mathematical Biosciences Institute, Ohio State University)

11:45 – 1:15 LUNCH
Lower Level Dining Room – McKenna Hall

SESSION II

Chair: Holly Goodson

1:15 – 1:45 D. Sumners (Florida State University)
1:45 – 2:15 Y. Kevrekidis (Princeton University)
2:15 – 2:45 A. Deutsch (Technical University Dresden, Germany)
2:45 – 3:15 T. Newman (Arizona State University)
3:15 – 3:45 G. Forgacs (University of Missouri – Columbia)

3:45 – 4:00 BREAK

SESSION III

Chair: Alex Panfilov

4:00 – 4:20 I. Kosztin (University of Missouri – Columbia)
4:20 – 4:40 T. van Erp (Ecole Normale Supérieure de Lyon, France)
4:40 – 5:00 P. Borowski (Max Planck Institute for the Physics of Complex
Systems, Germany)
5:00 – 5:20 V. Krstic (University of Zagreb, Croatia)
5:20 – 5:40 R. Etienne (University of Groningen, The Netherlands)

Friday October 28, 2005
McKenna Hall Auditorium

8:30am – 9:10am

Leon Glass

Centre for Nonlinear Dynamics
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Title: *Stochastic Aspects of Cardiac Arrhythmias*

Abstract: Many cardiac arrhythmias have a haphazard appearance. They may start and stop suddenly, and there can be complex rules governing the mix of normal and abnormal heartbeats. For example, in an arrhythmia called concealed bigeminy, over extended times of many minutes, there are an odd numbers of normal beats occurring between two abnormal beats. Although many mechanisms have been proposed to account for various cardiac arrhythmias, it is sometimes difficult to associate a particular mechanism with a given record. In this talk I will suggest that subcellular events associated with the stochastic opening and closing of individual ion channels might be manifest in gross phenomenological statistical features of some arrhythmias. I review experimental and theoretical analyses that demonstrate the role of stochastic processes in resetting of aggregates of spontaneously beating heart cells, and argue that similar phenomena may be involved in the generation of irregularity of arrhythmias. I discuss how paroxysmal bursting rhythms may arise as a consequence of basic physiological properties of heart cells. Finally, I will discuss include analyses of cardiac arrhythmias in people. This talk is based on work with a number of colleagues including Claudia Lerma, Verena Schulte-Frohlinde, Trine Krogh-Madsen, Gil Bub, Gene Stanley, Michael Guevara, Alvin Shrier, and Ary Goldberger.

9:10am – 9:50am

Herbert Levine

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Title: *Gradient Detection by Dictyostelium Cells*

Abstract: Dictyostelium amoebae use chemoattractant-mediated motion to aggregate as a response to starvation. Recent experiments have focused attention on the signaling mechanisms underlying this behavior and on the threshold for gradient detection. This talk

reviews the current experimental situation and then compares and contrasts several conceptual models put forth to understand how the system works. A particular interesting question concerns the role of receptor noise in limiting the accuracy of the response, and some preliminary results regarding this issue will be presented.

10:05am – 10:45am

Byron Goldstein

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Title: *Modeling Immune Receptor Signaling and the Problem of Combinatorial Complexity*

Abstract: The process of signaling through cell surface receptors involves highly connected networks of interacting components. I will focus on the application of mathematical models to understanding signaling through immune recognition receptors which trigger a variety of immune responses. Simple models, like kinetic proofreading and serial engagement, which ignore the details of the signaling machinery, have provided considerable insight into how ligand-receptor binding properties affect signaling outcomes but are unable to make contact with the vast majority of cell signaling data. After reviewing these models and discussing their strengths and weaknesses, I will look at the problems that the modeler is confronted with when he or she tries to deal with the details of a signaling cascade. I illustrate with a model for the early signaling events mediated by the high affinity receptor for IgE, Fc RI, a receptor that plays a key role in allergic reactions.

10:45am – 11:45am

Plenary Lecture: Dennis Bray

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Title: *Intracellular Signalling in a Molecular Jungle: Insights from Bacterial Chemotaxis*

Abstract: The set of biochemical reactions by which an E. coli bacterium detects and responds to distant sources of attractant or repellent molecules is probably the simplest and best understood example of a cell signaling pathway. The pathway has been saturated

genetically and all of its protein components have been isolated, measured biochemically, and their atomic structures determined. We are using detailed computer simulations, tied to experimental data, to ask how the pathway works as an integrated unit. Increasingly we find that the physical location of molecular components within the molecular jungle of the cell interior is crucial for an understanding of their function. Signal amplification, for example, appears to depend and the propagation of activity across clusters of receptors and associated molecules.

A suite of algorithms (called Smoldyn - for Smoluchowski Dynamics) was developed by Steven Andrews to track the diffusive trajectory and chemical reactions of individual molecules in three dimensions. Karen Lipkow is now using this program to explore the movements of CheY - the only freely diffusing protein in the bacterial chemotaxis pathway - through the bacterial cytoplasm. We are addressing such questions as how quickly CheY diffuses from the receptors to the flagellar motors? What gradients of CheY are set up and how will they depend on external stimuli? We are particularly interested in how the intracellular location of particular proteins is determined and whether this is modulated by environmental stimuli.

1:15pm – 1:45pm

Dale Kaiser

Developmental Biology
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Title: *Pattern Formation in Myxobacteria*

Abstract: Myxobacteria are single cells that organize several multicellular patterns. To gather food for growth, cells swarm outward at constant rate for weeks. When the swarm exhausts its food supply, the cells stop spreading outward and begin moving inward. Finally they form fruiting bodies of 100,000 cells whose shape is species specific. Spores differentiate within the fruiting body. The genome of *Myxococcus xanthus* has been sequenced; its genes can readily be manipulated, and individual cells can be tracked.

Early in the process of building fruiting bodies, waves of high cell density sweep across the swarm. Small traffic jams arise within a field of waves from cells that converge on the same focus from several directions. Such foci enlarge as cells stream over and around them in circular orbits. The streams constitute a set of concentric spherical shells, like the skins of an onion. Slow dissolution of the traffic jam at the center of the onion hollows it. The resulting spherical aggregate is capable of fusing with others of its kind until the aggregate reaches fruiting body size (1). Both the waves and aggregation depend on a morphogen, a 17 kDa,

surface-bound protein called the C-signal. Several mathematical models of cell movement and signaling in the traveling waves has been developed that agree with the recorded trajectories of single cells (2, 3). Moreover, the model has been extended to explain the position and form of the aggregates (4). The model depends on signaling by cell-cell contact, C-signal is not diffusible.

[1] Kaiser D and Welch R (2004) Dynamics of fruiting body morphogenesis. *J Bacteriol.* **186**: 919-27.

[2] Welch R and Kaiser, D. (2001) Cell behavior in traveling wave patterns of myxobacteria. *Proc. Natl. Acad. Sci. USA* **98**: 14907-14912.

[3] Igoshin O, Welch R, Kaiser D, and Oster G (2004) Waves and aggregation patterns in Myxobacteria. *Proc. Natl. Acad. Sci. USA* **101** 15760-15765.

[4] Sozinova, O., Jang, Y., Kaiser, D., and Alber, M.S. (2005) Three-dimensional model of myxobacterial aggregation by contact-mediated interaction. *Proc Natl Acad Sci USA* **102**: 11308-11312.

1:45pm – 2:15pm

Maciej Swat

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Title: *CompuCell3D Progress and Roadmap*

Abstract: TBA

2:15pm – 2:45pm

Zoltan Toroczkai

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Title: *Steric Constraint Networks and Protein Folding*

Abstract: The Levinthal's paradox of protein folding basically contrasts the time that a uniform random sampling of the configuration space for an N-monomer protein would take (which is on the order of 10^N and would take astronomical times even for peptides) with the actual observed times for folding from a denaturated state to the native state (which ranges from nano-seconds to minutes). Recent studies have taken a networks approach to protein folding by identifying secondary structures with nodes, and folding through small-energy barriers between two such configurations as links (Rao and Caflisch, 2004). Molecular Dynamics simulations show that the protein folding network is a scale-free graph (Albert and Barabasi, 1999) with an exponent of -2, that seems to be independent on the ordering of the monomers in the chain. Here we introduce the notion of gradient flow networks as directed substructures on graphs generated by following

the gradients of a scalar field distributed on the nodes of this graph. We then show that in general these gradient networks have a scale-free degree distribution, with an exponent that depends on the correlations between the scalars (energies) at nodes and local graph properties such as degree and clustering. This formalism then allows us to give a simple resolution to the Levinthal paradox and recover the measurements obtained via MD simulations.

2:45pm – 3:15pm

Tomasz Lipniacki

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Title: *Stochasticity in Early Immune Response*

Abstract: Living cells may be considered noisy or stochastic biochemical reactors. In eukaryotic cells, in which the number of protein or mRNA molecules is relatively large, the stochastic effects originate primarily in regulation of gene activity. Transcriptional activity of a gene can be initiated by trans-activator molecules binding to the specific regulatory site(s) in the target gene. The stochasticity of activator binding and dissociation is amplified by transcription and translation, since target gene activation results in a burst of mRNAs molecules, and each copy of mRNA then serves as a template for numerous protein molecules. In the present paper, we reformulate our model of the NF- κ B regulatory module (Lipniacki et al., 2004. J. Theor. Biol. 228: 195-215) in order to analyze a single cell regulation. Ordinary differential equations, used for description of fast reaction channels of processes involving a large number of molecules, are combined with a stochastic switch to account for activity of genes involved. The stochasticity in gene transcription causes simulated cells to exhibit large variability. Moreover none of them behave like an "average" cell. Although the average mRNA and protein levels remain constant prior to TNF stimulation, and stabilize following a prolonged TNF stimulation, in any single cell these levels oscillate stochastically in the absence of TNF and keep oscillating under the prolonged TNF stimulation. However in short period of about 90 minutes, most cells are synchronized by the TNF signal, and exhibit similar kinetics. We hypothesize that this synchronization is crucial for proper activation of early genes controlling inflammation. Our theoretical predictions of single cell kinetics are supported by recent experimental studies of oscillations in NF- κ B signaling made on single cells (Nelson et al., 2004 Science 306: 704-708 and 2005, Science 308: 52b).

3:15pm – 3:45pm

Bjorn Birnir

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Title: *Stick-slip and H-stability in Stochastic Simulations of Schools of Fish*

Abstract: The dynamics of a school of fish with noise are simulated both for applications to pelagic species of fish and as a model for a primitive organism. Methods from statistical mechanics and simulations are used to compute the potential in the associated Fokker-Plank equation for the density. Stick-slip behavior is observed for some parameter values whereas for others H-stability yields either attraction or repulsion in the school.

4:00pm – 4:20pm

Jeffrey Peng

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Title: *Biomolecular Motion and Recognition: Insights from Magnetic Resonance*

Abstract: Living systems rely on networks of protein interactions, and there is intense interest in understanding the molecular factors that govern the specificity and strength of these interactions. This has driven a nearly singular focus on protein structure to correlate structure and recognition. However, proteins and their ligands are dynamical systems. To gain a predictive understanding of protein interactions, we must further account for their inherent motions. Solution nuclear magnetic resonance (NMR) provides a uniquely powerful approach for investigating the motions of these protein machines to atomic resolution. We will provide an overview of the latest NMR approaches for relating the recognition properties of proteins with their dynamics using examples from our own research.

4:20pm – 4:40pm

Rob de Ruyter

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Title: *Optimal Processing of Natural Visual Input*

Abstract: As an animal moves through the world, the array of its photoreceptors typically receives a complicated, fluctuating spatiotemporal pattern of stimuli, which is corrupted by photon shot noise, and blurred by the optics. It is the brain's job to make sense of this complex high-dimensional data stream. We are interested in how the fly's brain performs this job, and, more specifically, in the design principles underlying its computations. With motion estimation as an example of a neural computation I will present two approaches to this question:

1) Using a simple custom-built camera coupled to a rotation sensor, we sample the joint statistics of rotational motion and visual input during a walk in a natural environment. From these data we obtain directly the conditional probability distribution describing the distribution of rotational velocities conditional on visual input. The conditional mean of that distribution defines an optimal velocity estimator for natural visual input signals. This estimator is biased: For example, it underestimates velocity if visual contrast is low. We compare its predictions to responses of H1, a motion sensitive neuron in the blowfly visual system. In laboratory experiments we find that H1 gives a biased readout of velocity very reminiscent of the bias in the optimal estimator.

2) We quantify how accurately H1 represents motion in natural conditions by recording from this cell with the fly spinning on a motor outdoors. For behaviorally relevant visual stimuli, H1 increases the precision of motion estimation if the statistical quality of the visual input improves: For example, at noon the neural response is much more reproducible than around sunset. Even a relatively small decrease in light intensity produces a measurable decrease in information transmission, suggesting that H1's precision is limited by photon shot noise.

Both these findings indicate that motion estimation by the fly's brain approaches an optimal strategy within the context of real world visual statistics. This interpretation unifies two disparate models of motion estimation, namely the Reichardt correlator model and the gradient model. These models should be seen as extremes on a continuum, the first being optimal at low, the second at high signal to noise ratio of the visual input.

4:40pm – 5:00pm

Beate Schmittmann

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Title: *From Asymmetric Exclusion Processes to Protein Synthesis*

Abstract: Asymmetric exclusion processes, with periodic or open boundaries, have been studied extensively in the mathematics and statistical physics communities, as paradigm models for stochastic particle transport far from equilibrium. Though significant progress was made only recently, the original model was actually introduced decades ago to model protein synthesis.

In this presentation, we describe recent efforts to develop a comprehensive theory for protein synthesis, building on asymmetric exclusion processes with extended objects, modeling ribosomes covering multiple

codons. We discuss the effects of ribosome size and local hopping rate on density profiles and current-density relationships. The latter translate directly into synthesis rates for the corresponding protein. Turning to more realistic scenarios, we also investigate the competition of multiple mRNAs for a finite supply of ribosomes and a-tRNAs.

5:00pm – 5:20pm

Paul Atzberger

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Title: *A Stochastic Immersed Boundary Method Incorporating Thermal Fluctuation: Toward Modeling Membrane Dynamics of the Cell*

Abstract: The dynamics of biomembranes play an important role both mechanically and chemically in many cellular processes from the protrusions generated in cell motility to the functioning of complex organelles such as the golgi apparatus. To a first approximation a membrane can be regarded as a mutable elastic sheet which interacts with a fluid. For macroscopic systems the immersed boundary method has been successfully applied in modeling many problems in which elastic structures interact with a fluid. These include blood flow in the heart, lift generation in insect flight, and wave propagation in the cochlea. In this talk the framework of the immersed boundary method is extended to model biomembranes. At the length scale of cells and cell organelles thermal fluctuations become significant and are incorporated in the immersed boundary method through appropriate stochastic forcing terms in the fluid equations. A practical simulation method is presented overcoming stiffness in the governing equations by making use of techniques from stochastic calculus. The numerical scheme allows for long time steps by under-resolving the fastest degrees of freedom associated with the fluid while accounting for their statistical contributions over the time step. Simulations of membrane sheets and vesicles are then discussed along with preliminary results for a model of the golgi apparatus.

5:20pm – 5:40pm

Peter Kramer

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Title: *Stochastic Mode Reduction with Metastability in Biomolecular Modeling*

Abstract: One approach to accelerating biomolecular simulations is to simulate explicitly only certain slow degrees of freedom of interest, incorporating the effects

of the remaining "fast" variables through effective stochastic models. We illustrate a systematic multi-scale stochastic mode reduction procedure on a simple model problem with metastability -- a high potential energy barrier separating different conformational states. Metastability is a prevalent feature in biomolecular systems. We show in particular how the metastability can lead to various effective stochastic equations for the slow degrees of freedom depending on the relations between the physical parameters and properties of the potential energy landscape. This work is in collaboration with Jessika Walter, Christof Schuette, Carsten Hartmann, and Wilhelm Huisinga at the Free University of Berlin.

5:40pm – 6:00pm

Anotida Madzvamuse

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Title: *Implications of Mesh Structure to Solutions of Reaction-Diffusion Systems on Fixed and Growing Domains*

Abstract: Reaction-diffusion systems have been widely used in developmental biology and most of these systems comprise of nonlinear reaction terms which makes it difficult to find closed form solutions. It therefore becomes convenient to look for numerical solutions: finite difference, finite elements, finite volume and spectral methods are typical examples of the numerical methods used.

In this talk, we present the implications of mesh structure to solutions of reacting and diffusing systems on fixed and growing domains. We illustrate computationally that the finite difference scheme imposes symmetry to solutions if regular mesh elements are used on regular domains. Such solutions are not observed if, for example, asymmetric mesh or randomly chosen mesh elements are used.

We compare our results to those obtained by use of the finite and moving grid finite element method on unstructured triangular elements.

6:00pm – 6:20pm

Tilman Glimm

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Title: *Continuous Limit of a Chemotaxis Model*

Abstract: Rea The Cellular Potts Model (CPM) is a stochastic energy minimization method which is popular as a framework for modeling multicellular behavior. It has been used to simulate various phenomena such as fruiting body formation of the slime mold *Dictyostelium*

discoideum, angiogenesis, chondrogenesis in embryonic vertebrate limbs, and many others. In contrast to PDE models, which can only yield information at a macroscopic scale (e.g. information about the cell density), the CPM models behavior at a microscopic scale (i.e., on the scale of single cells) as well. However, it is clear that at a macroscopic scale, the results of CPM simulations should correspond to the results obtained by certain PDEs. While this link is conceptually clear, there is so far little knowledge in detail about the exact correspondences. In this talk, we present the results of recent advances in these questions, namely we derive a PDE for the temporal development of the probability distribution of a one-dimensional Potts model describing the chemotactic motion of cells in a substrate. We present numerical validations of this formal continuous limit and derive expressions for the effective diffusion coefficient and chemotaxis coefficient as functions of the Potts parameters, such as cell-substrate interaction energy coefficient, volume constraint parameter and chemosensitivity parameter. This talk is based on joint work with M. Alber and N. Chen (Notre Dame).

6:20pm – 6:40pm

Dejan Milutinovic

Department of Theoretical Biology
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Title: *Fitting the LCMV CD8+ Data Based on Measurement and Process Noise Models*

Abstract: Mathematical modeling of immunological data can be a very powerful tool for understanding the immune system dynamics. Although it is reasonable to assume that the nature of the inter-cellular interactions is stochastic, usually, deterministic models are fitted to experimental data. We analyze the experimental data of lymphocytic-chorimeningitis virus (LCMV) infected mice. To explain the stochastic variation of the data, we use different stochastic measurement error models and we find that the intensity of the errors is quite high regardless of the model. Using the Gillespie simulation, we are able to show that the intensity of the process noise is not negligible in comparison to the variation seen in the experimental data. This suggests that the process noise of the underlying dynamics must be included in parameter estimation procedures, and considered separately from stochastic measurement errors. This work is a part of a larger research project leading to the system theory approach for modeling immunological data and corresponding sources of uncertainties. This work is developed in collaboration with Prof. Rob De Boer.

Saturday October 29, 2005
102 DeBartolo Hall

8:30am – 9:10am

Andre Levchenko

The Whitaker Institute for Biomedical Engineering
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Title: *A Stochastic Model of Pattern Development in Yeast Colonies*

Abstract: Unlike lab strains, wild type yeast colonies develop into complex shapes that presumably facilitate their nutrient absorption and waste secretion. Here I will present a stochastic model and its analysis that capture the behavior of yeast colonies on a single cell level. The computational results will be contrasted with experiments performed at our lab.

9:10am – 9:50am

Sasha Panfilov

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Title: *Modelling in Electrophysiology Using Anatomically Accurate Models of the Heart*

Abstract: Modeling in cardiology gives an exciting example of application of methods of applied and computational physics to medicine and biology. One of the most important applications of such modelling is understanding the mechanisms of cardiac arrhythmias and sudden cardiac death, accounting for about 1 death in 10 in industrialized countries. In my talk I will review the basic regimes of abnormal wave propagation in cardiac tissue leading to the arrhythmias. Then, I will talk about one of the most promising recent approaches in cardiac modelling: development of anatomically accurate models of the heart and will present in details our model of human ventricles which features accurate geometry (with a 0.2 mm resolution) and anisotropic intramural fibrous structure. Dynamics of cardiac cells is described using an ionic 16 variable ODE model. I will show our recent results on modelling of different cardiac arrhythmias and on 3D organization of ventricular fibrillation in human heart and discuss possible future developments in this area.

10:05am – 10:45am

Angel Garcia

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Title: *Temperature and Pressure Effects on Folding/Unfolding of Proteins*

Abstract: High hydrostatic pressures change the energy landscape of proteins, affecting the thermodynamics and kinetics of folding. Proteins denature at high hydrostatic pressures, implying that the unfolded proteins in aqueous solution have lower volume than the folded state. A model that explains pressure unfolding requires water to penetrate the protein interior and disrupt the protein hydrophobic core. I will explore the energetics of water penetration and the effect of pressure on hydrophobic interactions. I will also describe molecular simulations of the reversible folding/unfolding equilibrium as a function of density and temperature of solvated peptides that can form alpha helices (the AK peptide) and beta hairpins (the C terminal domain of protein G). I will characterize the structural, thermodynamic and hydration changes as a function of temperature and pressure. To study protein folding equilibrium thermodynamics we use an extension of the replica exchange molecular dynamics (REMD) method that allows for density and temperature Monte Carlo exchange moves.

10:45am – 11:45am

Miller Lecture in Biophysics: Albert Libchaber

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Title: *Towards an Artificial Cell*

Abstract: We show first how a temperature gradient can lead to giant DNA accumulation by thermophoresis and to DNA sequence amplification in a convection set-up. Non-equilibrium thermodynamics can thus help to solve some nagging problems of critical concentration and sequence selection in a prebiotic soup.

We show that a vesicle bioreactor can function for many days in an homeostatic state producing proteins. This is a first necessary step to artificial cells. The next step will be vesicle replication.

1:15pm –1:45pm

David Odde

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Title: *Stochastic Mechanics of the Mitotic Spindle*

Abstract: Chromosome segregation is mediated by the dynamic interplay of microtubule assembly and molecular motors, which act in concert to stretch sister chromosome pairs. Failure to develop chromosome tension is characteristic of improperly attached chromosomes, and is sensed by checkpoint and error correction mechanisms to prevent chromosome missegregation. How do chromosomes develop proper tension? Through integration of quantitative fluorescence microscopy and stochastic computer simulation of the dynamics of kinetochore microtubules (kMTs) in budding yeast, we have identified two primary influences on kMT plus end assembly. First, net assembly depends on kMT plus end position within the spindle, such that assembly is favorable near the poles and unfavorable near the equator. By itself, this situation establishes a "barrier" to assembly that tends to prevent MT plus ends from crossing the equator, thereby establishing the rudiments of a bipolar spindle with sister plus ends generally constrained to their respective half-spindles. Second, increased tension between sister plus ends, mediated via elastic chromatin stretching, promotes net assembly. Together with the spatial gradient effect, tension-dependent assembly serves as an error-correcting mechanism that promotes kMT disassembly in the rare instances when a plus end crosses the equator. In this case, tension on the chromosome is low, which leads to kMT disassembly. Finally, since chromosome mechanical properties are important to the tension-dependent assembly, and spindle mechanics generally, we developed a model for chromatin stretching in budding yeast. We predict that the chromatin is sufficiently stretched so that nucleosomal release is driven by the tension. We developed a stochastic simulation of chromatin stretching that accounts for nucleosomal release, and find that a stochastic stress-strain relationship can be established.

1:45pm –2:15pm

John Pearson

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Title: *Equivalence and Identification of Markov Models for Ion Channel Kinetics*

Abstract: Deducing plausible reaction schemes from single channel current traces is time consuming and difficult. The goal is to find the simplest possible scheme, but there are many ways to connect even a small number of states (more than 2.5 million schemes with four open and four closed states). Many of those schemes make identical predictions and even an exhaustive search over model space does not address the problem of how to represent the many equivalent schemes that may result. We have found a canonical form that can express all reaction schemes for binary channels. This form has the minimal number of rate constants unlike other canonical forms such as the well-established "uncouples" scheme. For many models proposed in the literature our form has dramatically fewer links than the uncoupled form. The new form, which is based on the number of independent open-closed transitions, leads naturally to new strategies for searching for the simplest model.

2:15pm –2:45pm

Uwe Tauber

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Title: *The Role of Stochastic Fluctuations and Spatio-Temporal Correlations in Lattice Models for Predator-Prey Interactions*

Abstract: We have studied different variants of two-species predator-prey models defined on a lattice. Introducing spatial degrees of freedom and allowing for stochastic fluctuations generically invalidate the classical Lotka-Volterra mean-field picture. Moreover, site occupation constraints, modeling locally limited resources, lead to the emergence of either a continuous active-to-absorbing state transition or to a first-order phase transition. In the former case, the universal critical properties near the extinction threshold are governed by the directed percolation universality class. In the active state, where predators and prey coexist, the classical limit cycles or centers are replaced by either nodes or foci, and the system displays complex and correlated spatio-temporal patterns of competing fronts of activity. Finite systems near stable foci are characterized by irregular population number oscillations, whose features are determined by the intrinsic interaction rates rather than initial conditions. In the thermodynamic limit, however, the densities of predators and prey exhibit damped oscillatory behavior. We illustrate these general issues by considering in detail ecologically motivated models with nearest-neighbor interactions, as well as

other variants with nearest and next-nearest neighbor interactions.

2:45pm –3:15pm

H.G.E. Hentschel

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Title: *Dynamical Mechanisms for Axon Guidance in the Presence of Skeletal Elements*

Abstract: Diffusible and contact chemoattractants have been implicated in the establishment of connections between neurons and their targets in a developing nervous system. We will describe simulations of these mechanisms for a whole sequence of events including nerve guidance, bundling, pathfinding, and debundling of axons with specific reference to the influence of internal skeletal structures on their growth and form.

3:30pm –3:50pm

Santiago Schnell

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Title: *Lesson from the Computational Modeling of Reaction Kinetics in Intracellular Environments*

Abstract: The experimental evidence has clearly illustrated the fundamental difference between cytoplasmic and test tube. It has also showed that the classical reaction kinetics approaches, such as the law of mass action, breakdown in in vivo conditions. As a consequence the attention of theoretical biochemists has focused in discovering the rate laws controlling reactions in vivo. In recent years, theoreticians have been using computational frameworks to extract rate laws or empirical equations of reactions from direct numerical simulations. In this talk we will discuss some of the simulation techniques which we have been using to explore reactions in in vivo conditions. We will pay special attention is paid to the strengths and limitations of these modeling techniques and appropriate conditions under which each can be used.

3:50pm –4:10pm

Greg Huber

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Title: *Dominos, First-Passage Problems, and Dynamic Binding in Flagellar Motor Statistics*

Abstract: The flagellar motor of bacteria is perhaps the most elaborate stoichiometric molecular machine engineered by evolution. It harnesses the chemical energy associated with a proton (or sodium) gradient for its rotation (typically hundreds of Hz), while, at longer time scales, stochastically switching between clockwise (CW) and counterclockwise (CCW) rotations. And while the switching of the rotational direction of the flagellar motor plays a crucial role in bacterial chemotaxis, its mechanism remains poorly understood. Here, I'll present recent work on the switch statistics of the flagellar motor of *Caulobacter crescentus*. I'll show how the interval distribution of the CW and CCW rotation provides insight into the switching, and describe a model that combines first-passage-time theory and domino toppling to explain the switching mechanism. The model accounts for the motor's dependence on CheYp concentration, and predicts that dynamic binding of CheYp to the switch-complex proteins is the key to the signal amplification of the motor. Joint work with Guanglai Li, Qi Wen, and Jay Tang.

4:10pm –4:30pm

Imre Derenyi

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Title: *Uncovering the Overlapping Community Structure of Complex Networks in Nature and Society*

Abstract: Many complex systems in nature and society can be described in terms of networks capturing the intricate web of connections among the units (proteins, genes, people, etc.) they are made of. A question of great current interest is how to interpret the global organization of such networks as the coexistence of their structural sub-units (communities) associated with more densely interconnected groups of nodes. Identifying these communities is crucial to the understanding of the structural and functional properties of networks. The existing methods used for large networks find separated communities, however, in most real networks the communities are believed to overlap with each other at a great extent. Here we introduce a new approach to determine the interwoven sets of overlapping communities of large real networks. Among other examples, we demonstrate the power of our method by identifying the communities of proteins in the protein-protein interaction network of yeast, which then, for example, allows us to make predictions for yet unknown functions of some proteins.

G. Palla, I. Derenyi, I. Farkas, and T. Vicsek, *Nature* 435, 814 (2005).

4:30pm –4:50pm

Francis Alexander

CCS-3
Los Alamos National Laboratory
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Title: *Hybrid Numerical Algorithms*

Abstract: The construction of hybrid particle/continuum algorithms for multi-scale modeling of complex, dynamical phenomena will be explained. Applications to diffusion, reaction, phase transitions and flow will be presented. The impact and importance of fluctuations will be emphasized.

4:50pm –5:10pm

David Anderson

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Title: *Propagation of Fluctuations in Biochemical Systems*

Abstract: We consider biochemical reaction systems equipped with an input subjected to (possibly large) ongoing stochastic fluctuations and study how the input fluctuations propagate through the system. In particular, we consider how different geometric properties of reaction diagrams and different asymptotic limits in the kinetics of systems suppress, magnify, or otherwise shape the fluctuations.

By adding fluctuations to a biochemical system one is confronted with a complicated set of nonlinear stochastic differential equations. A natural first step is to prove that there is a unique stationary measure on Euclidean space to which the distribution of any solution of the SDEs will converge as time goes to infinity. This puts a restriction on the type of system we consider because it is an open question as to how to categorize all systems for which a unique stationary measure exists. If such a measure does exist, however, the solution to the SDEs with distribution given by that measure becomes the natural object to consider when asking questions about how the variances of different concentrations and fluxes vary based on the different geometric and asymptotic properties of the system.

The work presented represents the beginning stages of an avenue possibly rich with both pure mathematical questions (for example, questions of convergence to a unique stationary measure) and serious applications. One such application, numerical calculations of fluctuations used to study long range control mechanisms in methionine metabolism, will be briefly discussed.

5:10pm –5:30pm

Leonard Sander

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Title: *A Stochastic Model for Wound Healing*

Abstract: We present a discrete stochastic model which represents many of the salient features of the biological process of wound healing. The model describes fronts of cells invading a wound. We have numerical results in one and two dimensions. In one dimension we can give analytic results for the front speed as a power series expansion in a parameter, p , that gives the relative size of proliferation and diffusion processes for the invading cells. In two dimensions the model becomes the Eden model for p near 1. In both one and two dimensions for small p , front propagation for this model should approach that of the Fisher-Kolmogorov equation. However, as in other cases, this discrete model approaches Fisher-Kolmogorov behavior slowly. Work done with T. Callaghan, E. Khain, and R. M. Ziff.

6:30pm –7:30pm

Public Lecture: Alan Perelson

Theoretical Biology and Biophysics
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Title: *New Developments in Modeling the Dynamics of Viral Infections*

Abstract: I will present a general overview of the problem of modeling viral infections in vivo. The point of view that I will take is that models should be useful for giving insights into the treatment of human disease. From this perspective, I will discuss two examples: HIV infection and hepatitis C virus (HCV) infection. I will show how viral dynamic models can provide insights into both the basic biological processes underlying infection as well as treatment with drug or vaccine. I will also discuss aspects of the immune response to these infections.

Sunday October 30, 2005
102 DeBartolo Hall

8:30am – 9:10am

Hans Othmer

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Title: *Stochastic Analysis of Chemical Reaction Networks*

Abstract: In this talk we will first briefly describe a complete analytical solution for low-order moments of linear reaction networks, with or without diffusion. We will then describe a new reduction method for removing fast kinetic steps and compare the method with existing methods. Finally, we will discuss a stochastic model of actin dynamics that includes fragmentation, annealing, and a variety of control molecules.

9:10am – 9:50am

Alex Mogilner

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Title: *Monte Carlo Simulations and Probabilistic Analysis Shed Light on how Microtubules Search in Space*

Abstract: Mitosis is the process of segregation of chromosomes before cell division. Before the chromosomes can be moved, they have to be attached to the opposite poles of the cell through microtubules, dynamic polymers that grow and shrink rapidly and repeatedly probing space and searching for the chromosomes. Attachment to the chromosomes stabilizes microtubules and is a basis for the proper cell division. This process, termed Search and Capture, is time consuming and is often the bottleneck for the cell division. In this work, using mathematical modeling and stochastic simulations, we show that without any bias toward the chromosomes, Search and Capture is not efficient enough to explain experimentally measured mitosis duration. We propose that a spatial chemical gradient stabilizes microtubules in the vicinity of the chromosomes, therefore introducing a bias in the Search and Capture process. We show mathematically that the biased Search and Capture is efficient enough to explain experimental results. To test model predictions, we

measured the mitosis duration in mutant cells. Our experimental results confirm the model predictions. The model also suggests that the cell fine-tunes a number of parameters to optimize the process, and that the time for Search and Capture depends little on the chromosome number. The last conclusion has important implication for cancer cells.

10:05am – 10:45am

James Keener

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Title: *A Model for Length Control of Flagellar Hooks of Salmonella Typhimurium*

Abstract: The construction of flagellar motors is a carefully regulated genetic process. Among the structures that are built is a U-joint-like structure called the hook. The length of the hook is tightly regulated. The question that will be addressed in this talk is how Salmonella detects and regulates the length of these structures. This is related to the more general question of how physical properties (such as size or length) can be detected by chemical signals and what those mechanisms are.

In this talk, I will present mathematical models for the length regulation of the hook structure by Salmonella Typhimurium. Some of the details are as follows: Under the assumption that the molecular constituents are translocated into the nascent filament by an ATP-ase and then move by molecular diffusion to the growing end, where they polymerize into the growing tube, we find that there is a detectable transition from secretion limited growth to diffusion limited growth. We propose that this transition can be detected by the secretant FliK, allowing FliK to interact with FlhB thereby changing the secretion target of the type III secretion machinery and terminating the growth of the hook.

10:45am – 11:45am

**Special Lecture in Mathematical Biology:
Avner Friedman**

Mathematical Biosciences Institute
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Title: *Tumor Proliferation is Affected by the Material Properties of its Surrounding*

Abstract: We consider a mathematical model of a spherical tumor within a tissue whose material properties are either similar to a porous medium, or to a fluid. When the proliferation rate increases and the cell-to-cell adhesiveness decreases, the tumor will become unstable, and its spherical shape will change, producing several protrusions, say N . We prove that whereas for a tumor in a porous medium N is just 2, for a tumor in fluid tissue N may be arbitrarily large depending on the size of the original tumor's radius. Mathematically, the model deals with a bifurcation problem for a system of PDEs with a free boundary. This is a joint work with Bei Hu.

1:15pm – 1:45pm

De Witt Summers

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Title: *Monte Carlo vs Experiment: DNA Knots Reveal Chiral Packing of DNA in Viral Phage Capsids*

Abstract: Bacteriophages are viruses that infect bacteria. They pack their double-stranded DNA genomes to near-crystalline density in viral capsids and achieve one of the highest levels of DNA condensation found in nature. Despite numerous studies some essential properties of the packaging geometry of the DNA inside the phage capsid are still unknown. Although viral DNA is linear double-stranded with sticky ends, the linear viral DNA quickly becomes cyclic when removed from the capsid, and for some viral DNA the observed knot probability is an astounding 95%. This talk will discuss comparison of the experimentally observed viral knot spectrum with Monte Carlo simulations of knots in confined volumes, concluding that the packing geometry of the DNA inside the capsid is non-random and writhed.

1:45pm – 2:15pm

Yannis Kevrekidis

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Title: *Equation-Free Computations for Stochastic Models: Biological Applications*

Abstract: In current modeling, the best available descriptions of a system often come at a fine level (atomistic, stochastic, microscopic, individual-based) while the questions asked and the tasks required by the modeler (prediction, parametric analysis, optimization and control) are at a much coarser, averaged, macroscopic level. Traditional modeling approaches

start by first deriving macroscopic evolution equations from the microscopic models, and then bringing an arsenal of mathematical and algorithmic tools to bear on these macroscopic descriptions. Over the last few years, and with several collaborators, we have developed and validated a mathematically inspired, computational enabling technology that allows the modeler to perform macroscopic tasks acting on the microscopic models directly. We call this the "equation-free" approach, since it circumvents the step of obtaining accurate macroscopic descriptions. The backbone of this approach is the design of (computational) experiments. Ultimately, what makes it all possible is the ability to initialize computational experiments at will. Short bursts of appropriately initialized computational experimentation through matrix-free numerical analysis and systems theory tools like variance reduction and estimation-bridges microscopic simulation with macroscopic modeling in general (and bifurcation computations in particular). I will briefly discuss the approach and present a selection of illustrative examples arising in a biological modeling context, ranging from coarse molecular dynamics to coarse kinetic Monte Carlo and agent-based simulations.

2:15pm – 2:45pm

Andreas Deutsch

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Title: *Cellular Automaton Modeling of Biological Pattern Formation*

Abstract: Examples of biological pattern formation are life cycles of bacteria and social amoebae, embryonic tissue formation, wound healing or tumor growth. Thereby, development of a particular spatio-temporal "multi-cellular" pattern may be interpreted as cooperative phenomenon emerging from an intricate interplay of local (e.g. by adhesion) and non-local (e.g. via diffusing signals) cell interactions. What are cooperative phenomena in interacting cell systems and how can they be studied?

Mathematical models are required for the analysis of cooperative phenomena. Typical modeling attempts focus on a macroscopic perspective, i.e. the models (e.g. partial differential equations) describe the spatio-temporal dynamics of cell concentrations. More recently, cell-based models have been suggested in which the fate of each individual cell can be tracked. Cellular automata are discrete dynamical systems and may be utilized as cell-based models.

Here, we analyze spatio-temporal pattern formation in cellular automaton models of interacting discrete cells. We introduce lattice-gas cellular automata and a cellular automaton based on an extended Potts model that

allows us to consider cell shapes. Model applications are bacterial pattern formation and tumor growth.

2:45pm – 3:15pm

Timothy Newman

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Title: *Modeling Multicellular Systems Using Many-Body Theory*

Abstract: Robust multicellular structures and processes are crucial for the construction and function of higher organisms. In these systems large numbers of cells communicate through short and long-ranged interactions in order to achieve large-scale coherence. In this talk I will present a general framework for describing these systems, which is similar in spirit to many-body theory, which has been so successful in understanding coherent structures in physical systems. The framework provides some analytical insights into the behavior of multicellular systems, and also allows the construction of optimized off-lattice computer algorithms. If time allows, I will illustrate the latter in the context of early stages of chick embryogenesis, in particular the dynamics of primitive streak formation.

3:15pm – 3:45pm

Gabor Forgacs

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Title: *The Role of Physical Mechanisms in Biological Self Organization*

Abstract: Organs form during morphogenesis, the process that gives rise to specialized biological structures of specific shape and function in early embryonic development. Morphogenesis is under strict genetic control, but shape evolution itself is a physical process. Here we report the results of experimental and modeling biophysical studies on in vitro biological structure formation. Experimentally, by controlling the interaction between cells and their embedding matrices, we were able to build living structures of definite geometry. The experimentally observed shape evolution was reproduced by Monte Carlo simulations using a statistical mechanical model of the cellular system, which also shed light on the biophysical basis of the process. Our work suggests a novel way to engineer biological structures of controlled shape.

4:00pm – 4:20pm

Ioan Kosztin

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Title: *Fluctuation Driven Active Molecular Transport in Passive Channel Proteins*

Abstract: Living cells interact with their extracellular environment through the cell membrane, which acts as a protective permeability barrier for preserving the internal integrity of the cell. However, cell metabolism requires controlled molecular transport across the cell membrane, a function that is fulfilled by a wide variety of transmembrane proteins, acting as either passive or active transporters. In this talk it is argued that, contrary to the general belief, in active cell membranes passive and spatially asymmetric channel proteins can act as active transporters by consuming energy from nonequilibrium fluctuations fueled by cell metabolism [1]. This assertion is demonstrated in the case of the E. coli aquaglyceroporin GlpF channel protein, whose high resolution crystal structure is manifestly asymmetric. By calculating the glycerol flux through GlpF within the framework of a stochastic model, it is found that, as a result of channel asymmetry, glycerol uptake driven by a concentration gradient is enhanced significantly in the presence of non-equilibrium fluctuations. Furthermore, the enhancement caused by a ratchet-like mechanism is larger for the outward, i.e., from the cytoplasm to the periplasm, flux than for the inward one, suggesting that the same non-equilibrium fluctuations also play an important role in protecting the interior of the cell against poisoning by excess uptake of glycerol. Preliminary data on water and sugar transport through aquaporin and maltoporin channels, respectively, are indicative of the universality of the proposed nonequilibrium-fluctuation-driven active transport mechanism.

This work was supported by grants from the University of Missouri Research Board, the Institute for Theoretical Sciences and the Department of Energy (DOE Contract W-7405-ENG-36).

[1] I. Kosztin and K. Schulten, Fluctuation-Driven Molecular Transport Through an Asymmetric Membrane Channel, *Phys. Rev. Lett.* 93, 238102 (2004).

4:20pm – 4:40pm

Titus van Erp

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Title: *Can One Predict DNA Transcription Start Sites by Studying Bubbles?*

Abstract: It has been speculated that bubble formation of several base-pairs due to thermal fluctuations is indicative for biological active sites. Recent evidence, based on experiments and molecular dynamics (MD) simulations using the Peyrard-Bishop-Dauxois model [1,2], seems to point in this direction [3,4]. However, sufficiently large bubbles appear only seldom which makes an accurate calculation difficult even for minimal models. In this talk, I introduce a new method that is orders of magnitude faster than MD. Using this method we are able to show that the present evidence is unsubstantiated [5].

[1] M. Peyrard and A. R. Bishop, Phys. Rev. Lett. 62, 2755 (1989).

[2] T. Dauxois, M. Peyrard, and A. R. Bishop, Phys. Rev. E 47, 684 (1993).

[3] C. H. Choi, G. Kalosakas, K. O. Rasmussen, M. Hiromura, A. R. Bishop, A. Usheva, Nucl. Acid Res. 32, 1584 (2004).

[4] G. Kalosakas, K. O. Rasmussen, A. R. Bishop, C. H. Choi, A. Usheva, Eur. Phys. Lett. 68, 127 (2004).

[5] T. S. van Erp, S. Cuesta-Lopez, J.-G. Hagmann, and M. Peyrard, accepted for publication in Phys. Rev. Lett.

4:40pm – 5:00pm

Peter Borowski

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Title: *Signal Transduction in Olfactory Cilia: Fluctuations, Correlations and Response in the Presence of Feedback*

Abstract: We study the stochastic kinetics of Ca^{2+} ion channels in the olfactory cilium, with special focus on the negative feedback by which Ca^{2+} regulates its influx by increasing the closing rate of the channel. This coupling between the channel and the Ca^{2+} makes the channel evolution strongly non-Markovian. We develop a path-integral formulation of the two-state (open/close) process for a single channel, based on the temporal statistics of its state-flips. The feedback effect is built into the model in a systematic way in the form of a weak perturbation. Analytic results are obtained for the open probability of the channel as well as the auto-correlation and response functions (both for the channel variable Ca^{2+} and the Ca^{2+} concentration). Monte Carlo simulations are performed which support the analytical predictions in the weak feedback limit and provide results beyond linear perturbation theory.

5:00pm – 5:20pm

Vladimir Krstic

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Title: *Min-Protein Oscillations in E. Coli: 3D Off-Lattice Stochastic Reaction-Diffusion Model*

Abstract: Division site in the rod-shaped bacterium *E. coli* is partially regulated by pole-to-pole oscillations of the Min-family proteins: MinC, MinD, and MinE. Only MinD and MinE proteins are required to obtain oscillations. MinC proteins are recruited to the membrane by MinD, and hence follow the same oscillatory pattern. MinC when attached to the membrane (in the form of MinD-MinC complex) inhibits septum formation. As time-averaged distributions of the membrane associated MinD/MinE/MinC proteins have minimum in the central region of the cell, this region is strongly favored division site. We introduce 3D off-lattice stochastic reaction-diffusion model to describe MinD/MinE dynamical structures. The model simulates: (1) MinD/MinE diffusion (2) MinD - membrane interaction (3) MinD - MinE interaction (4) MinE driven ATP hydrolysis (5) transformation of MinD:ADP into MinD:ATP by nucleotide exchange. In addition, we assume that each membrane associated MinD protein can form up to three bonds with adjacent membrane associated MinD molecules and that MinE induced hydrolysis strongly depends on the number of bonds MinD has established.

Each of approximately 5000 molecules are explicitly tracked within our 3D simulation. This is extremely time consuming job. We have speeded up our simulation by using adaptive time steps: in our stochastic system one can use much longer time steps when the molecule tracked is in the region far from the membrane than when the molecule is in the region near the membrane. Our model reproduces many different experimentally observed phenomena using a small number of "free" parameters (many analytical models can do the same), but we think our model is step forward because it enables one to attack the problem of Min-oscillations from the microscopic point of view.

[1] K.C. Huang, Y.Meir, and N.S. Wingreen, Dynamic structures in *Escherichia coli*: Spontaneous formation of MinE rings and MinD polar zones, Proc. Natl. Acad. Sci. USA 100, 12724 (2003).

[2] S.S. Andrews and D. Bray, Stochastic simulation of chemical reactions with spatial resolution and single molecule detail Phys. Biol. 1, 137 (2004).

[3] N. Pavin, H. Cipcic Paljetak, V. Krstic, Min Oscillations in *Escherichia coli* with Spontaneous Formation of Two-Stranded Filaments in 3D Stochastic Reaction-Diffusion Model, <http://arxiv.org/abs/q-bio.SC/0505051> (submitted to PRL).

5:20pm – 5:40pm

Rampal Etienne

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Title: *Stochasticity in Community Ecology: the Neutral Model and a Dispersal-Limited Sampling Formula*

Abstract: Most models describing the structure of ecological communities are deterministic. An exception is the now famous (or infamous) neutral theory of biodiversity by S.P. Hubbell which he launched in his 2001 book. He makes two assumptions: all species are equivalent and the community has constant size. He put these two assumptions into action in a stochastic individual-based model with the basic ecological processes of birth, death, speciation and dispersal, and was able to explain observed patterns such as the species-abundance distribution and the species-area relationship. While Hubbell obtained most of his results by simulations, others (mostly physicists) have tried to find analytical expressions. One of these is a new sampling formula I derived for the probability that a particular species abundance distribution is observed. Here I summarize the model, the controversy it has caused, and I outline the approach to derive the new sampling formula (that views dispersal as a sampling effect), and I discuss the prospects of neutral (stochastic) theory in community ecology.

Poster Session Titles and Abstracts

Oleg Bakunin

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Title: *Small Cluster Statistics and Levy Size Distributions*

Abstract: There exists a large variety of models describing cluster growth in biological system [1]. In the present paper, we consider the statistical properties of small cluster system. There are several conventional methods to describe aggregation, but at the same time, it is difficult to find a suitable equation to describe properties of small clusters systems, which play an important role in biology. Thus, the Smoluchowski aggregation equation appears to be the well-known method to analyze the kinetics of growth processes. However, the character of its solution depends significantly on the form of integral equation kernel. Another drawback of this equation is the neglect of density fluctuations [1]. These fluctuations can be considerable on the initial stage of growth in the system with rare growth centers. The same reasons prevent to use the diffusive Zeldovich approximation [1].

The initial stage of growth has the fluctuation character, hence in such a system the number of "events" can be small, and the diffusion form of the equation is often incorrect. A number of modifications of the conventional diffusive equations were suggested in anomalous transport theory [2,3] to describe the non-diffusive character of a process in terms of fractional differential equations and scalings [4]. In the framework of this approach, it is possible to obtain the power form distribution based on statistical properties of a system.

The new functional equation is obtained from the probabilistic consideration of the transition to cluster-cluster aggregation in small cluster systems. The solution of this equation is based on using the model correlation functions [5]. In the Poisson dependence, the new nontrivial solution for cluster size distribution is obtained as follows:

$$n(s) = \frac{Const}{s^\alpha} \exp\left(-\frac{s_0}{s}\right)$$

This function is non-analytical with $s \rightarrow 0$. Therefore, it cannot be obtained by the asymptotic technique from the Fokker-Planck type equations. The fluctuation character of the model is related to using the waiting time distribution approach. The transformation of equations

for the case of large number of growth centers is analyzed. It was demonstrated that the dependence for cluster size distribution $n(s)$ in the Levy form with $\alpha=3/2$ could be found [5]. The difference between the Levy solution of the non-local Einstein-Smoluchowski equation and randomization approach is discussed.

References:

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Title: *Stochastic Dynamics of Calcium Ion Motion and Channel Gating in the Cardiac Dyad during Excitation-contraction Coupling*

Abstract: Excitation-contraction (EC) coupling in the cardiac ventricular myocyte occurs in a highly localized microdomain known as the dyad. During EC coupling, the opening of individual L-type calcium channels, which are located in the t-tubule membrane, triggers the release of calcium from the sarcoplasmic reticulum (SR) via activation of a cluster of calcium release channels known as ryanodine receptors (RyRs). The RyRs are located directly across the dyad in the SR membrane, in close proximity to the L-type channels. Previous computational models of the cardiac dyad are based on reaction-diffusion equations which describe the dynamics of calcium concentration inside the restricted volume of a single dyad. In such models, L-type channel and RyR gating kinetics are coupled to local changes of calcium concentration. In this study, we have constructed a detailed stochastic model of calcium dynamics based on the Smoluchowski- Poisson-Boltzman (SPB) description of ion diffusion in the dyadic space. The algorithm recently described by Xing, Wang, and Oster (2005, *Biophys J.*) is applied to convert the continuous SPB equation into a continuous-time Markov chain which is then coupled to kinetic models of the L-type calcium channel and RyR in order to form a complete model of local EC coupling in the cardiac dyad. Model results demonstrate the roles of noise in stochastic calcium dynamics, electrostatic interactions, and structures of dyadic proteins in modulating EC coupling. These simulations provide an important link between deterministic models based on sets of ordinary

differential equations and models that capture fine details using molecular dynamics calculations.

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Title: *Structure Formation of Mechanically Active Cells*

Abstract: Predicting cellular structure formation is much more complicated than for passive particles because cells are informed by internal instructions and fueled by metabolic energy. However, for special cases extreme principles might apply which then allow us to predict active structure formation in analogy to classical systems of passive particles. Here we show that mechanical active cells in soft environments, which can be modeled as force dipoles, behave in a similar way as electrostatic dipoles: they align with external fields, their interaction is long-ranged and anisotropic, and favors the formation of strings. We show analytically that due to screening, the effective interaction between strings decays exponentially, with a decay length only determined by geometry. Both for positionally disordered and ordered arrangements of cells, we predict novel phase transitions from paraelastic to ferroelastic and anti-ferroelastic phases as a function of material properties of the environment. These predictions can be tested experimentally using the elastic substrate method.

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Title: *Model of Intracellular Ca Oscillations Due to Negative Feedback*

Abstract: We present a mathematical model for calcium oscillations and fast adaptation in the cilia of olfactory sensory neurons. Stoichiometric network analysis is used for analyzing the kinetic equations and finding the oscillatory regime. The underlying mechanism is based on direct negative regulation of cyclic nucleotide-gated channels by calcium/calmodulin, and does not require any autocatalysis such as calcium-induced calcium release. Results of the model using physiological parameter values agree quantitatively with experiment, both with respect to oscillations and to fast adaptation. The bifurcation diagram of the model is calculated to make predictions regarding the occurrence of oscillations.

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Title: *Estimation Strategies in "Equation Free Methods*

Abstract: An important component of many multiscale simulations is the ability to accurately and efficiently extract derivatives from atomistic simulations. We obtain system information by proposing a local parametric diffusion model and then obtain the drift and diffusion coefficients by observing output of a stochastic process run for a short amount of time then maximizing the associated likelihood function. The parametric fit utilizes the likelihood expansion of Ait-Sahalia in order to get closed form expressions for the transition density for both scalar and vector processes. The driving processes are both kinetic Monte Carlo (kMC) and stochastic differential equations (SDE's) corresponding to mass action kinetics systems, however all of our local models are diffusion models that have affine drift and diffusion functions. The unknown drift and diffusion coefficients of the true process are allowed to be nonlinear, but for our method to be applicable the unknown functions do need to have a high degree of smoothness. The derivative information obtained is then used in classical numerical methods. Here we use the methodology proposed to carry out Newton Raphson fixed point iterations and to numerically integrate (both explicit and implicit schemes) a Michaelis-Menten type system in both stiff and non-stiff parameter regimes. Another application presented is how to apply the information contained in the local models in order to do variational calculations; specifically we calculate the monodromy matrix of the Brusselator. We also numerically explore model reduction and various methods of quantifying model uncertainty when a parametric diffusion model is used to locally model the output of a stochastic simulation.

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Title: *Patterns of Mesenchymal Condensation in a Multiscale, Quasi-3D Cellular Automaton Model*

Abstract: We present a biological lattice gas model for high-density cultures of precartilidge mesenchymal cells derived from the embryonic vertebrate limb. This model resolves some artifactual aspects of an earlier model by representing cells as extended, multipixel objects that change shape in the plane and "round up" by moving pixels into a virtual third dimension, condense without denuding the regions surrounding condensations centers, and implement two different grids of different scales that are used for cell and molecular dynamics. Results reproduce the formation of precartilidge condensation patterns through calibration of simulation

parameters with experimentally determined values. Also, our simulations disclosed two regimes of behavior in the reaction-diffusion system of morphogens; one regime is characterized by steady-state behavior, and the other regime has an oscillatory behavior. While both regimes produced patterns of condensation statistically similar to experimentally measured values, the second did so with a better fit, and it provides a natural explanation for apparent oscillatory effects of limb precartilaginous cell responses to TGF-beta seen in previous experimental studies.

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Title: *CompuCell3D, A Framework for Three-Dimensional Simulation of Morphogenesis*

Abstract: CompuCell3D is a software framework for running morphogenesis simulations in three dimensions. The framework employs biologically relevant models to simulate processes such as cell clustering, growth, and interaction with chemical fields. The framework has been carefully designed using software design patterns for easy extensibility to encapsulate new biological models, flexibility, and addressing the issues of speed and memory consumption. CompuCell3D has been verified using a three-dimensional simulation of avian limb bud growth and can also run simulations of basic cell sorting, amoeba migration, and Dictyostelium Discoideum. Finally, the framework has been interfaced to a GUI for interactive visualization.

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Title: *Self-Sorting of Mixture of Particles in a Double-Well Potential*

Abstract: We consider the self-sorting of binary mixture of Brownian particles having different diffusion constants assisted by the thermal kick they get while crossing the barrier in a double-well potential. We find that the segregating process is better accomplished when the temperature in the well in which the mixture is initially put is hotter than the temperature of the other well as compared to the case where the temperature is uniform, which actually is due to the enhancement of the effective diffusion constant (and hence the escape rate) from the hotter well to the colder one. Two criteria for optimization are introduced and it will be shown that the optimized segregation is closely related to the behavior of the escape rates from either of the wells as a function of the parameters defining the model. We also investigate how the entropy of mixing evolves with time in such a segregation process.

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Title: *Quantitative in vitro Measurements of Embryonic Cardiac Tissue Physiologically Validate Novel Tissue Engineering Concepts*

Abstract: At the onset of valvulogenesis cushion tissue (hyaluronic acid rich mesenchyme) forms between the endocardium and myocardium within the outflow tract and atrio-ventricular (AV) region of the developing avian heart. These cushions swell and eventually fuse to form the septum and the valvular leaflets of the mature adult heart. This morphogenetic process is developmentally regulated through the control of the biomechanical properties of these tissues. The *in vitro* methods of explant tensiometry, coalescence, and migration were used to quantitatively measure the surface tension, viscosity, and migratory potential of tissue explants from different stages of development: Hamburger Hamilton stage 23 (HH23) before AV cushion tissue fusion, (HH27) during fusion, and (HH30) after fusion. The results indicate that as the septum develops from the cushions the tissue becomes more cohesive and viscous with a lower migratory potential, thus preserving the emerging architectural patterns of the heart. The methods presented here are sensitive enough to detect differences in the biomechanical properties of AV cushion tissue during septum morphogenesis. They may be employed to study the mechanisms governing tissue fusion and pattern preservation. The fact that the AV cushion tissues fuse *in vivo* during natural development and explants of this tissue fuse *in vitro* proves that tissue fusion is possible and physiologically validates the concept that tissue fusion may be applied towards the engineering of replacement tissues.

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Title: *Using Stochastic Models to Disentangle Mechanisms of Population Change*

Abstract: Stochastic models are increasingly important for understanding ecological systems. Recent work has shown how they can be combined with observational and experimental data to make inferences about mechanisms of population change. We used this approach with a stochastic nonlinear pure death model to make inferences about density independent and density dependent mortality in our data. The data consists of a time series of post-reproduction population counts during a single season. The data in question is fit poorly by Poisson survival models, suggesting that different mechanisms are operating at different points in

the population trajectory. Using two separate Poisson rate parameters improves the fit dramatically, but implies that the mortality rate changes phenomenologically as a function of time. We know, however, that competition and predation are important sources of mortality and so instead use nonlinear pure death models that allow us to include intraspecific competition mechanistically. Because there is a many-to-one mapping between process and pattern, we cannot simultaneously estimate predation mortality and the effects of intraspecific competition. We therefore used independent estimates of predation mortality and fit the remaining parameters, density independent and density dependent mortality, to the data. The density dependent parameter provides insight into the importance of intraspecific competition on the mortality rate, while the density independent parameter provides information about mortality at zero density. This, in turn, can be used with fecundity estimates to generate estimates of r , the intrinsic rate of population growth.

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Title: *The Role of Chemical Plant Volatiles in Host Plant Discrimination for Rhagoletis Flies*

Abstract: TBA

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Title: *Determining The Speed of Myxococcus xanthus Cells with Partial A-Motility by Photomicroscopy and Video Analysis*

Abstract: Knockout mutations in several genes involved in slime secretion for A-motility in *Myxococcus xanthus* cells unexpectedly led to the finding of partially motile mutants. Partially motile mutants have a slower swarm rate and a lower elasticotaxis coefficient than fully motile (A+S-) strains. This could result from differing cellular interaction, an altered reversal frequency, or a slower cell speed. To distinguish these possibilities, videos of partially motile mutants and A+S- mutants were analyzed with imaging software to determine the speed of cells in hopes of relating the speed of individual cells to the swarm rate. A+S- cells (DK10410) mean speed was determined to be 1.4 with a standard error of ± 0.3 $\mu\text{m}/\text{min}$. The partially motile mutants pglB and pglE exhibited mean speeds of $1.1 \pm 0.2 \mu\text{m}/\text{min}$ and $1.2 \pm 0.3 \mu\text{m}/\text{min}$, respectively. This shows a statistically significant difference in speed of the partially motile mutants that might explain the reduced swarm rate. Analysis herein of the distribution of speeds for partially

motile mutants gives further insight into the mechanisms of gel formation in the slime secretion engines used for A-Motility and the effect of cell speed on swarm rate.

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Title: *Ecological Models in which "Metabolic Codes" Appear*

Abstract: We define and study systems in which individuals are characterized by a metabolic type and a receptor type. When two individuals meet, their receptors govern the probability that they interact; if they do interact, their metabolic types govern the outcome of their interaction, in terms of gain or loss of mass. We say that a population abides to a code if each metabolic type appears only associated with a single receptor type and vice-versa, that is, if there exists a de facto convention binding metabolic types to receptor types. We show how real-world situations may be modeled by such systems and study the conditions under which a population asymptotically abides to a code and conditions under which it does not.

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Title: *Power-Law Scaling for Coupling Strength and Complexity during Stereotypic and Intentional Body Movements*

Abstract: This study examined the dynamics of body rocking and sitting still in both mentally retarded adults and healthy age-matched controls. Intentional and stereotypical body rocking possessed similar dynamics, but differences were revealed during maintenance of still sitting postures. When sitting still, healthy controls exhibited more complex dynamics of their center of pressure (COP) motions on both mediolateral and anteroposterior axes of motion. A power-law scaling was found between coupling strength for the two axes of COP motion (measured by information entropy of their relative phase) and complexity (approximate entropy, ApEn) of the oscillations on each individual axis. This scaling was found across both populations and encompassed both stereotypical and intentional body rocking as well as sitting still. These results are suggestive of a scale invariant process that drives both posture and intentional and stereotypical movements.

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Title: *Latrunculin A: a Candidate Cryoprotective Agent*

Abstract: Finding cryopreservation techniques that yield higher survival rates in oocytes and better developmental competence represents a major challenge.

The first objective of this study was to quantify the changes in the oocyte cytoskeletal network induced by cryopreservation. We characterized fresh and cryopreserved (frozen-thawed) oocytes in terms of cytoplasmic viscoelastic coefficients by intracellular magnetic tweezers experiments. We found that cryopreservation altered the viscoelastic parameters of the oocytes. The relaxation time was longer in the frozen-thawed eggs than in the fresh, unfrozen ones. All viscoelastic parameters (viscosity and elasticity) were significantly smaller in frozen thawed eggs than in fresh ones.

Based on this finding, we hypothesized that the reversible disassembly of the cytoskeletal network prior to cryopreservation prevents it from being damaged uncontrollably during freezing. We evaluated the effect of Latrunculin A (LATA) pretreatment on cryopreserved oocytes by using the viscoelastic parameters as a marker of cytoskeletal integrity. We found that the relative numbers of oocytes surviving cryopreservation was 20% higher in the LATA pretreated group. The viscoelastic parameters in LATA pretreated survivors were similar to the ones found in fresh oocytes.

Finally, we tested the fertilization and developmental competence of frozen and thawed oocytes having been pretreated with LATA, and compared the results to oocytes having been frozen without exposure to LATA. Of all the oocytes frozen and thawed, nearly twice as many having been exposed to LATA prior to cryopreservation reached the blastocyst stage compared to untreated oocytes.

In connection with our findings, we conclude that the cytoskeletal integrity, as assessed by viscoelastic determinations could be used to assess the effect of the cryopreservation procedure. LATA is a candidate drug for improving both cryosurvival and developmental competence in cryopreserved oocytes.

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Title: *A Stochastic Reaction-Diffusion Method for Studying the Control of Gene Expression in Eukaryotic Cells*

Abstract: A method is developed for incorporating diffusion of chemicals in complex geometries into stochastic chemical kinetics simulations. Systems are modeled using the reaction-diffusion master equation, with jump rates for diffusive motion between mesh cells calculated from the discretization weights of an embedded boundary method. Since diffusive jumps between cells are treated as first order reactions, individual realizations of the stochastic process can be created by the Gillespie Method. A spatial model of transcription, nuclear export, translation, nuclear import, and gene regulation in eukaryotic cells is presented to demonstrate the feasibility of the method in studying biological processes in which spatial localization and molecular noise are simultaneously of importance.

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Title: *Three-Dimensional Functional Tissue Structures Via Directed Self-Assembly of Multicellular Spheroids*

Abstract: Embryonic development represents a sequence of spectacular morphogenetic transformations involving intense cellular rearrangements. Although developmental patterning is under genetic control, a living organism acquires its final form through physical shape transformations, a particular one being based on the apparent liquid-like properties of tissues composed of adhesive and motile cells (e.g. embryonic tissues). The Differential Adhesion Hypothesis (DAH) provides the molecular basis for these properties, which in turn provide the biophysical basis for a number of morphogenetic processes (e.g. sorting, epithelial folding, convergent extension, etc.).

In the present study we exploit these self-organizing properties to build functional 3D tissue constructs of prescribed shape. Spherical cell aggregates were embedded contiguously into biocompatible gels creating templates for geometric configurations encountered in living organisms. Depending on the properties of the gels and the initial arrangements, upon incubation the aggregates fused into toroidal, tubular and planar configurations. Model simulations based on DAH reproduced the observed shapes, the only control parameter being the cell-gel interfacial tension. The lifetime of the experimentally observed constructs depends on the magnitude of cell-cell and cell-gel interactions, thus long-lived tissue structures can be built.

The results of these proof of concept experiments were employed in the development of a rapid prototyping technique, "bioprinting". Due to their liquid like properties aggregates can be regarded as "bioink" droplets. We developed a protocol and a special cutting device to produce standard aggregate size and customized the

hardware and software of the bioprinter to improve the accuracy of embedding. Primary cell cultures of different types were used as multicolor bioink to create functional, living tissue constructs mimicking their native histological arrangements.

Our experiments and modeling efforts represent a novel approach to tissue engineering, an important step toward building complex organ modules via biological self-assembly.

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Title: *Non-equilibrium Studies of Voltage-Gated Ion Channels*

Abstract: Ion channels are proteins specializing in transport of certain ions across cellular membranes. They play a crucial role in physiological processes such as: excitability of brain or cardiac cells, cell volume control, messenger ion flow. Understanding and control of the ion channel functioning (their gating and selectivity) is one of the major goals of cellular biophysics. Ion channels are studied using molecular biology and electrophysiology techniques. Among the latter a standard method is patch clamping where currents across a whole cell membrane or a patch of it, sometimes containing only one channel, are recorded. These currents reveal changes in membrane conductance due to changes in gating variables. In our lab we study voltage-gated ion channels. We develop a new electrophysiological technique that involves applying specially designed, rapidly fluctuating voltage waveforms to the cell membrane, thus driving the channel molecules far from equilibrium. The method probes new details of the channel kinetics inaccessible to the standard techniques. It aids the development of new mathematical models of the ion channel gating and the testing and refinement of existing models.

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Title: *Physics of Secondary Tumor Formation: Effects of Cell-Cell Adhesion*

Abstract: Formation of dense secondary tumor from a low density suspension of randomly located mobile cells is investigated using a discrete 2-D stochastic lattice model. Tumor growth is associated with the formation and growth of cell clusters. First, small-size clusters that contain several cells are formed from the homogenous state as a result of non-zero cell-cell adhesion. Then these clusters start growing; for subcritical adhesion

parameter, the growth is entirely determined by proliferation (the first scenario) and for supercritical adhesion parameter, there is also a phase separation between high density clusters of cells and low density "gas" of cells (the second scenario). In the case of a sufficiently small proliferation rate, the dynamics in the second scenario can be dictated by the coarsening process, where larger clusters (tumors) grow at the expense of smaller ones.

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Title: *Traffic of Molecular Motors*

Abstract: Molecular motors which move along cytoskeletal filaments exhibit movements on several length scales. We discuss several transport phenomena related to large-scale movements of molecular motors: (i) The motor walks which arise from the repeated unbinding from and rebinding to filament, (ii) the large-distance transport of cargoes by several motors, and (iii) collective traffic phenomena due to the mutual exclusion of motors from binding sites of the filaments.

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Title: *Min-protein Oscillations in E. Coli: 3D Off-lattice Stochastic Reaction-Diffusion Model*

Abstract: Division site in the rod-shaped bacterium *E. coli* is partially regulated by pole-to-pole oscillations of the Min-family proteins: MinC, MinD, and MinE. Only MinD and MinE proteins are required to obtain oscillations. MinC proteins are recruited to the membrane by MinD, and hence follow the same oscillatory pattern. MinC when attached to the membrane (in the form of MinD-MinC complex) inhibits septum formation. As time-averaged distributions of the membrane associated MinD/MinE/MinC proteins have minimum in the central region of the cell, this region is strongly favored division site. We introduce 3D off-lattice stochastic reaction-diffusion model to describe MinD/MinE dynamical structures. The model simulates: (1) MinD/MinE diffusion (2) MinD - membrane interaction (3) MinD - MinE interaction (4) MinE driven ATP hydrolysis (5) transformation of MinD:ADP into MinD:ATP by nucleotide exchange. In addition, we assume that each membrane associated MinD protein can form up to three bonds with adjacent membrane associated MinD molecules and that MinE induced hydrolysis strongly depends on the number of bonds MinD has established.

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Title: *Networks of Three Identical Coupled Systems*

Abstract: Homogeneous three-cell networks are networks of three identical coupled systems of ODE's. We consider networks where each system of ODE's has at least two couplings. We show that there are 34 distinct homogeneous three-cell networks as opposed to only three such two-cell networks. We also classify the kinds of transitions from a synchronous equilibrium that can occur as we vary one parameter and we show that they are determined by the coupling structure of the network.

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Title: *Dynamics, Rectification and Fractionalization for Colloids on Flashing Substrates*

Abstract: We show that a rich variety of dynamic phases can be realized for mono- and bidisperse mixtures of interacting colloids under the influence of a symmetric flashing periodic substrate. With the addition of dc or ac drives, phase locking, jamming, and new types of ratchet effects occur. In some regimes we find that the addition of a non-ratcheting species increases the velocity of the ratcheting particles. We show that these effects occur due to the collective interactions of the colloids.

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Title: *Interplay of Molecular and Biophysical Mechanisms in Tumor Invasion*

Abstract: Tumor invasion requires the acquisition of migratory capacity by the constituent cells, established through by the competition of cell-cell and cell-matrix interactions. To study the contribution of these factors, adhesive and invasive properties of nine human brain tumors were investigated, using molecular and

biophysical approaches. The biomolecular analysis entailed to measuring the expression level of N-cadherin (predominant cell adhesion molecule in these cells), along with the mRNA level of proteins involved in matrix degradation (i.e. matrix metalloproteases and their inhibitors). Biophysically, cell adhesion strength was quantified in terms of surface tension, a physical parameter related to tissue cohesivity, as well as through the surface morphology of three-dimensional cell aggregates using scanning electron microscopy. Strict quantitative correlation between the measured quantities (N-cadherin level, tissue cohesivity, MMP level and invasive capacity) was observed. We discovered striking variation in the invasive patterns of the different tumors that can only be interpreted by the competition of the measured factors.

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Title: *Thermodynamics and Kinetics of Pausing in Bacterial Transcription: Predicting the Motion of the Molecular Motor RNA Polymerase*

Abstract: Transcription is the first step in gene expression and it is at this stage that most of genetic regulation occurs. Once bound to a DNA template the enzyme RNA polymerase (RNAP) creates an RNA transcript at a highly non-uniform rate. RNAP will pause or arrest at specific sites on the DNA template. These pauses and arrests are known to have a regulatory function and thus the prediction of their position is of much interest. No consensus sequences have been found for these events. We examine intrinsic pauses, one of the major classes of pauses, where it is thought that the RNAP will move backwards along the DNA template without changing the length of the RNA transcript. We present a thermodynamic and a kinetic model based on the known structural models of the bacterial elongation complex (EC). We include changes in the co-transcriptional RNA secondary structure which forms behind the RNAP and fluctuations in the configuration of the EC. Our thermodynamic approach is to find the sequence dependent steady state elongation rate for each position of the RNAP along the DNA template. When this method is applied to 100 experimental pauses on 10 DNA templates we find that positions with a low steady state elongation rate correspond very well with backtracked pauses. There are no free parameters in this model. We also present a kinetic model for the recovery of backtracked pauses. This is a Markov chain model where kinetic barriers to backtracking are formed as a result of steric clashes between the RNAP and RNA secondary structure. The predictions of this model agree well with the experimental pause positions. The separation of timescales between the movement of the RNAP and global changes in the RNA secondary structure is seen

to be crucial for the maintenance of elongation competent ECs.

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Title: *Geant4 Simulation of a Fiber Based Scintillating Detector for Brachytherapy Treatment (GESIB)*

Abstract: Uniformity of radioactive sources is vital in delivering accurate doses in brachytherapy. To determine source uniformity, a fiber based scintillating beta detector was developed at the Center for Advanced Medical Instrumentation (CAMI) at Hampton University. To understand and optimize the capabilities of the beta detector, a Geant4 Monte Carlo simulation of the detector system was developed. It consisted of 32 scintillating fibers with cross sections of 1mm², coupled to two Hamamatsu (H6568) photomultiplier tube for photon to current conversion. The fibers consisted of a polystyrene based core and polymethylmethacrylate (PMMA) cladding. The brachytherapy sources (90Sr/90Y and 32P) were simulated using the General Particle Source (GPS), and sandwiched between the fibers. Uniform and non-uniform sources were simulated and compared.

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Title: *A Multi-Scale Evolutionary Model for Bone Adaptation using Cellular Automata*

Abstract: Modeling biological materials is an increasingly important topic in optimization. Bone is of particular interest, as local bone structure is continually remodeled during the bone lifetime. Simulations of bone functional adaptation can improve our understanding of age-related bone tissue generation and can be used in the design of tissue-engineered devices. A novel methodology has been developed to simulate the hierarchical bone remodeling process, known as Hybrid Cellular Automata (HCA). This methodology makes use of finite element analysis, cellular automaton (CA) computing paradigm, control and structural optimization techniques. The hierarchical HCA method, developed for mesostructural simulation of bone remodeling, allows for decomposition of the bone structure into smaller sub-models in which HCA is applied locally to determine local trabecular and/or cortical microstructural features. This method has been shown to be effective in producing trabecular-like structures in an application of this technique to a two-dimensional model of a femoral head. In addition, preliminary analyses have been conducted on the application of time-dependent relations

in the remodeling process to incorporate changes in bone structure due to remodeling activity.

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Title: *Chick Limb Growth using CompuCell3D*

Abstract: A central question in developmental biology is: what controls the behavior of cells so highly organized structures can emerge? To answer this question, we study the growth of the chick limb bud, using the Cellular Potts Model, a grid-based stochastic framework designed to simulate cell interactions and movement. We show that diffusion of growth factors through the extracellular matrix, and mechanical properties of the apical ectodermal ridge, are responsible for the proper shape of the bud. It has also been shown that differential adhesion of cells, together with chemo- and haptotaxis, leads to density-dependent patterns consistent with experiment. We need to combine the two mechanisms, in order to obtain a realistic cartilage pattern in the chick limb.

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Title: *Modeling Swarming of Myxococcus Xanthus*

Abstract: *Myxococcus xanthus* is a Gram-negative soil bacteria that has an interesting life cycle. *M. Xanthus* is a model organism for understanding how multicellular processes occur in bacteria. This work focuses on the beginning of a colony. Once agar has been inoculated with *M. Xanthus*, the colony begins to expand radially. This is a cooperative process with cells interacting with one another via physical collisions and slime. A modified lattice gas cellular automata model of this process was developed. Cells are represented as particles, and interact with a local neighborhood. The expansion rates of wild type cells and that of several mutants were investigated. A comparison of our results with those of experiments will be presented. This model should provide the basis for further investigations of the developmental process of *M. Xanthus*.

Paolo Rocchi

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Title: *A Proposal for the Calculus of the Cell Growth*

Abstract: The empirical Gompertz law, the best statistical model for biological growth, has not been

satisfactory explained in relation to the cell kinematics. This paper puts forward a structural model for the cell and the stochastic entropy that calculates this structure. The present mathematical method assumes five constraints for the cell growth and brings evidence that the growth trend follows the Compertz law.

Monica Skoge

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Title: *Receptor-receptor Coupling in Bacterial Chemotaxis: Evidence for Strongly Coupled Clusters*

Abstract: Recently Sourjik and Berg [Sourjik, V. and Berg, H.C, 2002 PNAS (99) 123-7] measured dose-response curves for a variety of E. coli adaptation mutants using fluorescence resonance energy transfer (FRET). They measured receptor activity in living cells in response to steps of chemoattractant. We have studied receptor activity for different models of receptor coupling. We model receptors as two-level systems coupled either in an extended lattice or in isolated clusters. We find the SB data is inconsistent with lattice models, but rather suggests that receptors form strongly coupled clusters.

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Title: *Mathematical Model For Effects of Weather on Asthma Patients*

Abstract: It is known that weather conditions, seasonal changes could be used to predict the severity of an asthmatic's asthma symptoms. We have collected the data of asthma patients. Correlation and regression analyses were performed on the collected data using a statistical technique. The simulation is used to predict asthma. We have built a simple mathematical model that relates asthmatic effects and allergy.

Temperatures were found to influence the asthma. Although asthmatics accurately predicted the seasons in which their symptoms were the best and the worst, they were, on the average, unable to guess which individual weather factors influenced their symptoms the most. Formulas based upon multiple linear regression were constructed which could be used by an asthmatic sufferer to predict the severity of asthma. Finally, rather than complex mathematical models, a personalized asthma model was constructed using a computer program to easily predict asthmatic severity.

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Title: *A Stochastic Three-Dimensional Model of Myxobacterial Aggregation and Fruiting Body Formation*

Abstract: Myxobacteria are social bacteria that provide one of the simplest models of cell-cell interaction and organized cell movement. Under starvation rod-like, motile myxobacteria cells change their movement pattern from outward spreading to inward concentration; they form aggregates that become fruiting bodies. Cells inside fruiting bodies differentiate into round, non-motile, environmentally resistant spores. While cell aggregation has traditionally been considered as a result of chemotaxis, growing evidence shows that myxobacterial aggregation is the consequence of direct cell-cell interaction. We present 3D stochastic lattice-gas cellular automata model and computer simulations of different stages of cell aggregation: formation of traffic jam (early asymmetric aggregate), which serves as an initial seed for further cell accumulation, mature symmetric aggregate (3D hemispherical mound), cell sporulation and, finally, fruiting body growth.

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Title: *The Effect of Cholesterol on Cell Mechanical Properties*

Abstract: There is growing consensus that the plasma membrane of eukaryotic cells is a patchwork of domains, with varying concentrations of membrane proteins and lipids. Cholesterol plays an indispensable role in regulating the properties of the cell membrane of mammalian cells. In particular, lipid rafts, specific membrane domains, which are thought to be required for a number of cell functions, such as receptor-mediated signaling and membrane trafficking, are dispersed when cell cholesterol is extracted. In this study, we investigated the effect of cellular cholesterol on membrane mechanical properties of bovine aortic

endothelial cells (BAECs). To compare the mechanical properties of the cells with different cholesterol content, we measured the forces needed to extract nanotubes (tethers) from their membranes, using atomic force microscopy (AFM). Our observations show that, in contrast to the known effect of cholesterol on membrane stiffness of lipid bilayers, cholesterol depletion of BAECs results in significant decrease of membrane deformability, indicating that cholesterol-depleted cells are stiffer than normal (control) cells. An increase in cellular cholesterol to a level higher than that in normal cells, had no effect on the stiffness of BAECs, but significantly decreased the surface viscosity of their membranes. This finding implies that the cell membrane of BAECs becomes more fluid-like upon cholesterol enrichment. While cholesterol depletion and enrichment had no apparent effect on the intensity of F-actin specific fluorescence, disrupting F-actin with latrunculin A abrogated the observed effects. This result suggests that cholesterol affects membrane mechanical properties by altering the properties of the cortical F-actin network and/or its attachment to the membrane. As a complementary method, fluorescence recovery after photobleaching (FRAP) experiments were also performed, to measure the lateral mobility (diffusion constant) of a lipid probe (DiI16) at different cholesterol contents. The results of the two different methods are compared and discussed.

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Title: *Graded Calcium Release in a Stochastic Model of Cardiac Muscle*

Abstract: The bulk of calcium required for contraction of ventricular cardiac muscle is released from the sarcoplasmic reticulum (SR) via the calcium-induced calcium-released mechanism. This mechanism exhibits high-gain, meaning that the amount of calcium released is much larger than the trigger calcium influx through the cell membrane. The response would appear to be all or none: high-gain and positive feedback would cause all SR calcium to be released. However, experimental observation indicates a graded response. That is, the amount of calcium released is proportional to the trigger influx amount. This poses a paradox. We explore this phenomenon by analyzing a fire-diffuse-fire model of calcium release in which release times are considered random variables. A graded response is obtained only when the calcium uptake rate is high or the distance between release sites is far apart. This observation helps resolve the paradox mentioned above. Graded calcium release is due to local control. A single trigger can only cause release from a localized region or release unit. While positive feedback can occur within this unit, it does not spread to neighboring units. Graded response with high-gain results from statistical

recruitment of release units. We explore the effect of varying the geometry of the release unit to study situations occurring in diseased myocytes. Additionally, we discuss possible extensions of the model to study voltage dependence of calcium transients.

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Title: *Effects of Sequence Disorder on Cyclization and Looping of DNA*

Abstract: The theoretical study of the effects of sequence disorder on looping and cyclization of DNA will be presented. We demonstrate that the presence of random intrinsic curvature and inhomogeneous bending modulus lead to substantial enhancement of the cyclization probability, compared to the classical disorder-free theory by Shimada and Yamakawa. This helps us to explain the inconsistency between the existing experiment and that theory. We also predict the looping probability to be a strongly sequence-dependent quantity, whose distribution may span over several orders of magnitude even for an ensemble of completely random sequences.

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Title: *Stochastic Modeling of Natural Organic Matter Degradation*

Abstract: Degradation of natural organic matter (NOM) is a major geochemical process occurring in essentially all environments near the Earth's surface. NOM mineralization constitutes a substantial component of the terrestrial carbon cycle, and products of NOM degradation and alteration affect the physical and chemical properties of soils, sediments, and surface and subsurface waters. Any given quantity of NOM has widely distributed chemical properties (such as molecular weight, concentrations of specific functional groups, proton binding affinities, etc.). Hence, the chemical properties of NOM are reasonably modeled using continuously distributed probability functions. In particular, molecular weight distributions of dissolved NOM can be measured using size exclusion chromatography (SEC) as a function of degradation and alteration progress.

We use monte carlo simulations to model the changes in molecular weight distributions of dissolved NOM induced by either ^{60}Co gamma radiolysis or 640 kHz sonolysis, two processes destructive of NOM *via* hydroxyl radical ($\bullet\text{OH}$) reactions. Specific hypotheses of the

transformation mechanisms are simulated in the model and tested against experimental observation. Some hypothetical mechanisms are rejected outright as not constituting major contributions to the alteration process. However, other mechanisms, such as indiscriminant destruction of organic carbon and decrease in molecular size, appear to be important processes in the alteration of this NOM by gamma radiolysis and sonolysis, respectively.

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Title: *Mathematical Modeling of the Formation of the Primitive Streak in the Chick Embryo*

Abstract: The body plan of all higher organisms is laid down during gastrulation. Gastrulation results from the integration of cell proliferation, differentiation and migration. In the chick embryo gastrulation starts with the formation of the primitive streak, the site of invagination of mesoderm and endoderm cells, from cells overlaying Koller's Sickle. Using the cellular Potts model we analyse possible mechanisms underlying the formation of Koller's Sickle and the primitive streak in the chick embryo. Computations show that the formation of the primitive streak may result from guided (chemotactic) movement of a subpopulation of Sickle cells that will give rise to Hensen's node, while that of all the other cells in the epiblast is governed by contact-following. The combination of these two mechanisms, chemotaxis and contact-following, gives rise to the large scale cell flows experimentally observed during streak formation. The calculations show that streak formation can result from chemo-attraction as well as from chemo-repulsion. The calculations further suggest that the manner in which two streaks in the same embryo interact allows discrimination between attraction and repulsion. We conclude that the most likely mechanism of streak extension involves the repulsion of cells in the tip of the streak by other cells in the streak.

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Title: *Learning from Sequences Utilizing the Synergy of Computational Intelligence Algorithms and Biophysical Characterizations*

Abstract: Advent of high throughput genome sequencing technology has led to an exploration of sequence data available. Learning from the protein sequences coded for by genomes is a difficult task, because data is noisy, could be high-dimensional, has unbalanced classes, and has multiply-labeled instances.

We designed and implemented automated approaches using synergy of computational intelligence algorithms and biophysical properties in order to increase predictors' accuracies and their explanatory powers. We developed optimal methods that combines supervised and unsupervised machine learning and utilizes feature generation, feature selection, biophysical characterization, data mining and Ensemble Method techniques for automated structural predictions and functional annotations.

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Title: *Modeling in Genetic Regulatory Systems in the Presence of Colored Noises*

Abstract: To capture the stochastic feature of genetic transcription, we incorporate the more general colored noises into the kinetic model of genetic regulatory system proposed by Smolen et al. [Am. J. Physiol. 274, C531 (1998)]. As far as a single colored noise is concerned, the memory effect due to the colorness promotes resistance of the system to shift away from its steady states. When two noises with sufficiently large cross-correlation strength are present, an increase in the correlation time of either noise or the cross-correlation time can elicit a switch.

In addition, the color effect of the auto-correlation can induce a sharper twice-switch in which the system goes from one steady state to another and switch back again, whereas the color effect of the cross-correlation hinders the switch processes. From these results, a better understanding of the noisy transcription process and its implications in engineered cellular control are anticipated.

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Title: *Atomistic Simulation of Structure and Dynamics of Columnar Phases of Hexabenzocoronene Derivatives*

Abstract: We study the solid columnar discotic and liquid crystalline phases formed by the alkyl-substituted hexabenzocoronene mesogens based on atomistic MD simulations. Correlations between the molecular structure, packing, and dynamical properties of these materials are established.

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Title: *Biomolecular Modeling with Poisson-Boltzmann Equation*

Abstract: Biomolecular simulation is playing an increasingly important role in understanding the molecular structure, dynamics and function. The energetic description of a molecule involves both bond and non-bond forces. Coulomb force, or the electrostatic interaction is a type of nonbond force and contributes significantly to the molecular interaction at all length scales. The effects of solvent on the electrostatic interactions has to be included as the real biomolecules are always in solution environment. Explicit modeling of the solvent considers a large number of solvent molecules surrounding which substantially increases the computational complexity. On contrast, the implicit modeling treats the solvent as a structure-less dielectric media. The biomolecule immersed inside has partial charge distribution and a different dielectric constant. The electrostatic potential induced by these partial charges and the free ions in the solvent is governed by a single Poisson-Boltzmann (PB) equation. The discontinuity of the dielectric constant on the molecular interface reduces the convergence of many popular numerical methods and therefore is one of the most important mathematical issues associated with the implicit solvent modeling. In this work we are proposing a novel high order interface method to improve both the accuracy and the efficiency of the solution of PB equation.

Information on Submission of Papers for the Special Issue of the Journal of the Statistical Physics

We would like to invite you to submit a paper to the Special Issue on Applications to Biology of the Journal of Statistical Physics (JSP).

Special Issue Editors are Mark Alber, Raymond Goldstein, Erwin Frey, Leah Edelstein-Keshet. Joel L. Lebowitz is an Editor-in-Chief of the Journal.

The deadline for submissions is February 1, 2006. We plan to move very quickly with the editorial process after that. All papers will be refereed in accordance with the JSP policies.

Please be informed that Journal of Statistical Physics has an electronic manuscript submission and tracking-system that will greatly speed up the editorial process.

In order to provide you with the benefit of the electronic system, we would kindly ask you to submit your manuscript by using Editorial Manager. You can find the Editorial Manager at:

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We look forward to receiving your paper.

Sincerely,

Mark Alber

Special Issue Editor

Journal of Statistical Physics

Special Issue on Multiscale Modeling in Biology

Mark Alber, Thomas Hou, James A. Glazier, Yi Jiang, Guest Editors

Abstract.

This special issue of *Multiscale Modeling and Simulation: A SIAM Interdisciplinary Journal*, on multiscale modeling in biology, stems from the workshop "Biocomplexity V: Multiscale Modeling in Biology," held August 14-17, 2003, at the University of Notre Dame and organized jointly by the Interdisciplinary Center for the Study of Biocomplexity at the University of Notre Dame, the Biocomplexity Institute at Indiana University, and Los Alamos National Laboratory, in cooperation with the Society for Industrial and Applied Mathematics. The workshop took place in conjunction with the Notre Dame Conference on Partial Differential Equations with Applications.

Modeling and simulation are becoming central research tools in biology. The most advanced of these efforts have focused on single levels or scales, e.g., genomic/proteomic, cellular, tissue, organ, whole body, behavioral, and population. We now need to develop the software tools and mathematical approaches to integrate models from micro-scales to macro-scales in a seamless fashion. Such multiscale models are essential if we are to produce quantitative, predictive models of complex biological behaviors such as embryonic development, cancer, cytoskeletal function, and ecosystems. At the same time, developing the abstractions to integrate between scales will lead to a much deeper understanding of the universal or generic features of biological phenomena.

This special issue of *MMS* presents a state-of-the-art view of the multiscale approach to modeling in biology. The papers in this collection combine theoretical and computational approaches to model a variety of important multiscale biological phenomena in areas ranging from immunology to pattern formation to cytoskeletal dynamics and calcium wave propagation.

As the papers in this issue illustrate, researchers in this interdisciplinary field have developed a rich variety of techniques and applied them to a variety of biological problems at multiple scales. In certain applications, such as the study of intracellular calcium cycles (Tsaneva-Atanasova, Shuttleworth, Yule, Thompson, and Sneyd), subcellular results have explained behaviors at larger scales, e.g., experimentally observed cell and tissue behaviors. Excitable medium and pattern formation methodologies apply to a wide spectrum of tissue behaviors (ten Tusscher and Panfilov). Continuum models for excitable media have the attraction of being amenable to both analytical and numerical methods. Population models (Doering, Sargsyan, and Sander) that describe ecosystem scales in terms of agents and smaller-scale variables are similarly rich and immediately apply to the study of epidemics and their control through drugs. The paper by Murray and Perelson also includes genetic behaviors to study the population-level effects of various drugs and mutations on HIV.

Clearly, addressing multiple biological scales requires a heterogeneous model framework; Gammack, Ganguli, Marino, Segovia-Juarez, and Kirschner integrate discrete and continuum models to explore the immune response to tuberculosis. Biological cells provide an obvious integration level between subcellular and molecular scales on the one hand, and tissues and organs on the other. Jonsson and Levchenko explain the behaviors of yeast colonies using a model for single cells that considers the cell-level phenomena of growth and division. Chemical signals usually mediate cell responses; Erban and Othmer discuss the role this microscale plays in the resulting macroscopic behavior of embryonic spatial pattern formation. Banks and Pinter present a probabilistic model for hysteresis and shear waves at the tissue scale and its possible medical applications, another case requiring heterogeneous models and approaches to treat multiple biological scales.

The hybrid models typical of systems biology tend to mix continuous, discrete, deterministic, and probabilistic approaches to address important questions in morphogenesis and regeneration. Recent advances in developing a three-dimensional hybrid framework for modeling morphogenesis, the pattern of structural development of an organism or its organs, promise a truly integrated approach to multiscale biological processes. Morphogenesis involves differentiation, growth, death, and migration of cells as well as changes in the shapes of cells and tissues and the secretion and absorption of extracellular materials. Rubinstein, Jacobson, and Mogilner provide a good example of this philosophy in their multiscale model of lamellopodia; their composite model ranges from the molecular scale of actin machinery to the micron-scale lamellopodium itself, to illustrate the many model extensions and modifications that moving from one-dimensional to three-dimensional models requires. Alarcon, Byrne, and Maini take a similar approach to tumor growth.

One key area for future research is the integration of genomic and macroscopic approaches to produce more complete models which include both genetic and generic phenomena.

We would like to express our special thanks to Dr. James M. Hyman, for the idea of a conference volume and help in every step of creating this special issue. We also want to thank Dr. Leah Edelstein-Keshet for her advice and help in preparing this issue.

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Limb Morphogenesis Workshop
Center for the Study of Biocomplexity
University of Notre Dame
Monday October 31, 2005
Mc Kenna Hall Building (CCE), Room 100/104

Begin 9 AM

10-15 minute summary talks of work related to Biocomplexity

- | | |
|--|------------------|
| 1. 2D Reactor-Diffusion pattern formation system for the limb | Tilman Glimm |
| 2. Mathematical considerations of 2D reactor-diffusion system | Mark Alber |
| 3. CompuCell 3D; properties, potential | Jesus Izaguirre |
| 4. Extensions of limb R-D model to 3D; necessary simplifications, etc. | Rajiv Chaturvedi |
| 5. Implications of limb model for development and evolution | Stuart Newman |

Discussion over lunch

Begin 12:30 pm

10-15 minute talks, with discussion, of approaches to modeling of limb outgrowth, shaping, and integration with Reaction-Diffusion pattern formation mechanism.

- | | |
|--|-------------------|
| 1. Description of limb outgrowth, shaping; experimental background | Stuart Newman |
| 2. Adhesion between cells and diffusion of growth factors produce the paddle shape of the growing chick limb bud | Nikodem Poplawski |
| 3. Theoretical considerations of viscoelastic modeling of the growing limb | George Hentschel |
| 4. Mesenchymal viscoelasticity--experiment and theory | Gabor Forgacs |
| 5. Computational modeling of growing tissues with natural shapes | Jesus Izaguirre |

End approx. 2:30 pm.

**Midwest Molecular Dynamics Workshop
November 3rd 2005
University of Notre Dame**

Objectives:

To discuss and devise a consistent interface for algorithmic development and MD simulation. A current proposal calls for a Python based front end which uses existing computational libraries.

Two levels of detail are proposed –

1. Simulation level
What would a simulation script look like in Python assuming it makes library calls to objects like integrators, MC steppers, file readers, file writers, force types, etc...?
2. Step level
What will one step of an integrator look like in Python assuming library routines that calculate parts of the overall force, instantaneous kinetic temperature, instantaneous pressure, and other observables?

Accelerating the simulation process –

It has been argued that a high level scripting interface could efficiently couple the simulation processes (minimization, equilibration, simulation, post processing) in addition to accelerating algorithm development. These potential benefits will be discussed.

Logistics:

All events will take place at the University of Notre Dame Center for Continuing Education (CCE), Room 202, McKenna Hall; unless otherwise noted. Directions and maps can be found at <http://cce.nd.edu/travelers.shtml>. Please feel free to contact us for any additional information or accommodations that you may require. Please note that Notre Dame, IN operates on Eastern Standard Time as opposed to Eastern Daylight Savings Time. On Sunday Oct 30th EDST adjusted one hour backward thus EST and EDST will be equivalent on the day of our workshop.

MDL Prototype:

The MDL Prototype can be reviewed and downloaded from the following site:
<http://www.nd.edu/~lcls/mdl>.

MDX:

The MDX libraries and tools can be found at:
<http://www.ks.uiuc.edu/Development/MDTools/mdx/>.

Acknowledgments:

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**Midwest Molecular Dynamics Workshop
November 3rd 2005
University of Notre Dame**

Timetable:

All events will take place at the University of Notre Dame Center for Continuing Education (CCE), Room 202, McKenna Hall; unless otherwise noted. The Morris Inn is conveniently located across the street from the CCE.

8:30-9:30am	Breakfast Morris Inn	Notre Dame Campus
9:30-11:00	Preliminary Discussion Technical Demonstration Setup	
11:00-11:30	Opening Remarks	<i>Robert D. Skeel</i> Computer Science and Mathematics, Purdue University
11:30-12:30	Scripting Proposal – MDL	<i>Jesus A. Izaguirre</i> Computer Science and Engineering, Notre Dame
12:30-1:30	Lunch Morris Inn	Notre Dame Campus
1:45-2:30	Scripting Proposal - MDX	<i>David Hardy</i> Computer Science and Beckman Institute University of Illinois at Urbana- Champaign
2:30-2:45	Coffee Break	
2:45-3:45	Wish List Discussions 20 minute talks	<i>Qun Marc Ma</i> Computer Science, New Jersey Institute of Technology <i>Eric Barth</i> Mathematics, Kalamazoo College <i>Stephen Bond</i> Computer Science University of Illinois at Urbana- Champaign
3:45-4:00	Coffee Break	
4:00-5:00	Wish List Discussions Continued 20 minute talks	<i>Christopher Sweet</i> Computer Science and Engineering, Notre Dame <i>Santanu Chatterjee</i> Computer Science and Engineering, Notre Dame <i>Paul Brenner</i> Computer Science and E Engineering, Notre Dame
5:00-5:45	Workshop Products: Composite Critique for Each Proposal Recommended Path Forward	
6:30pm	Dinner Location TBA	