

Statement of Research Interests

My research focuses on *complex adaptive behavior* arising in biological systems ranging from biochemical networks within living cells to networks of neurons in the central nervous systems. I use numerical and analytical techniques to investigate *principles of biological computation* in a wide variety of model systems.

I am currently pursuing two related lines of research, one in *computational neuroscience* and the other in *computational cell biology*. In collaboration with experimental electrophysiologists at the Salk Institute I am investigating biophysical entrainment mechanisms underlying the precision and reliability of patterns of electrical discharge produced by single nerve cells and populations of nerve cells in response to time-varying inputs [1, 2]. In collaboration with cell biologists at UCSD I am developing numerical and analytic methods for studying signal transduction in spatially-distributed stochastic biochemical networks [3, 4]. My interest in mathematical biology originated at the University of Chicago, where as a student of Prof. Jack Cowan I studied models of pattern formation in the development of the visual cortex [5]. Along with P. Bressloff (U. Utah) and M. Golubitsky (U. Houston) we continue collaborating on developmental modeling, emphasizing the role of symmetries in cortical pattern formation [6, 7, 8, 5, 9].

Computation and Communication in Biochemical Networks

All cells, from nerve cells in the brain to single-celled microorganisms, communicate with other cells and with their environments via networks of biochemical interactions known as *signal-transduction networks*. Discovering the properties and functions of biochemical networks is fundamental to understanding biological systems ranging from the immune system to learning and memory.

In collaboration with Prof. William Loomis (UCSD Biology) and Prof. Herbert Levine and Wouter-Jan Rappel (UCSD Center for Theoretical Biological Physics) I have constructed a numerical platform based on *finite-element analysis* for solving general boundary-coupled reaction-diffusion partial differential equations in arbitrary two-dimensional geometries [3]. This platform is applicable to any signal-transduction system; we have used it to understand the mechanism by which eukaryotic cells such as the social amoeba *Dictyostelium discoideum* choose a direction of movement in a chemoattractant gradient.

Building on this numerical platform, my current work addresses two fundamental problems in modeling biochemical networks: *stochasticity* and *principled reduction of complexity*.

Although biochemical networks involve familiar laws of chemical kinetics, it has become clear that classical analytical methods, based on ordinary differential equations, are inadequate for understanding their function. Unlike reagents in a test tube, reactants in living cells are often

localized to small subvolumes in a cell. The finite-element method naturally accommodates spatially heterogeneous chemical reactions; such heterogeneities play a key role in establishing a eukaryotic cell's orientation for directed motility.

In addition to nonuniform spatial distribution of reactants, cellular biochemical systems may contain as few as dozens of interacting particles, leading to significant *statistical fluctuations and randomness* in the chemical dynamics. For example, the polymerization reaction required for bacterial cell division involves cooperative stochastic dynamics of approximately 15,000 single units of a bacterial cytoskeleton protein. In a project funded by the Mellon foundation, I am cosupervising a student project developing Monte Carlo codes to study this system, along with Prof. Laura Romberg (Oberlin College Biology).

Combining stochastic and spatially distributed chemical systems, I am now extending the finite-element method to include the effects of fluctuations. I use a master-equation formulation in which transitions between finite elements and transitions between chemical states have an equal footing. This approach to stochastic partial differential equations bridges the classical ODE analysis of chemical systems and the molecular dynamics codes that track each ion and molecule individually but are too computationally costly for modeling an entire cell.

The rapidly accumulating data characterizing biochemical signaling pathways reveal an enormous complexity of chemical components, many of which can exist in multiple active or inactive states. By viewing a stochastic chemical reaction system as a flow of probability on a graph, one can reduce the descriptive complexity of the system by aggregating multiple chemically distinct states into a smaller number of effective or "coarse-grained" chemical states. I am developing a principled approach to simplifying complex reaction networks, based on error-minimization techniques borrowed from the communications engineering.

The application of information theory to neural behavior has yielded insights into the organization of information processing in sensory systems such as vision, audition and olfaction. In collaboration with communications engineers at UCSD's school of engineering we are developing an analogous treatment of signal-transduction in simple biochemical networks from an information-theoretic perspective [4]. In collaboration with Prof. Harihara Baskaran (Case Chemical Engineering and Bioengineering) I am applying these techniques to quantify the chemical information available to a eukaryotic cell performing chemotaxis (chemically directed cell movement) in a microfabricated fluidic device.

Establishing principles of computation in biological systems should shed light on the mechanisms governing a range of biochemical control systems, including eukaryotic chemotaxis, plasticity of synaptic connections in the brain, and other important signaling networks.

Computation and Communication in Neural Networks

How do networks of nerve cells collectively represent sensory information about the world, selectively process and transmit it, and compute appropriate responses? Multielectrode techniques and multi-neuron imaging techniques (voltage-sensitive dyes, Ca^{2+} fluorescence indicators) are improving our ability to look under the hood of the computational engine that creates our perceptual world. Rhythms, correlations and fluctuations within the network of inputs received by a cell influence the pattern of spikes it communicates to its targets. Despite intrinsic and extrinsic sources of “noise” individual nerve cells can produce reliable, precise patterns of action potentials in response to a given input signal.

In collaboration with electrophysiologists Prof. Jean-Marc Fellous (Duke Bioengineering) and Dr. Klaus Stiefel (Salk Institute), I am currently investigating the biophysical mechanisms underlying robust patterns of activity in pyramidal neurons driven in vitro by stereotyped current input waveforms. These patterns reveal a dynamical structure quite different from the sort of random renewal process (Poisson process) often used to imitate neural discharges. We are developing tools for quantifying the unique structure found within neural spike trains. The existence of discrete spike-time patterns induces a natural partition of the space of input signals, providing fundamental building blocks for neural encoding. We are interested in careful characterization of the effects of fluctuations (noise) and multi-frequency rhythms (as seen for example in EEG) on entrainment phenomena in driven neurons [1, 2].

I am currently supervising a student research project analyzing the structure of multielectrode collections of spike train data from Prof. Bruce McNaughton (U. Arizona’s Center for Neural Systems, Memory and Aging). Collaborations with experimental labs allows access to “real data” which allow quantitative assessment of models and hypotheses. In addition, I am currently collaborating with Prof. Hillel Chiel (Case Biology) on an dynamical systems analysis of multineuron firing patterns involved in decision making and motor control of the sea slug *Aplysia californica*.

A fundamental problem in the conceptual foundations of computational neuroscience is the reconciliation of the two principal approaches to understanding neural circuitry, namely the probabilistic framework of statistical learning theory and machine intelligence, and the dynamical framework of biophysical modeling of neural behavior. Mathematically, the intersection of these two realms is stochastic nonlinear dynamical systems, an exciting area within applied mathematics requiring new tools, new concepts and new theorems. A long-range goal of my research in theoretical neuroscience is to develop these tools into a unified explanatory framework.

References

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Statement of Teaching Interests

The avalanche of quantitative biological data becoming available from new experimental techniques in genomics, proteomics and microscopy demands invigorated communication between the mathematical and biological communities. The next generation of biologists will need fundamental skills in analytic and computational techniques that bridge the traditional disciplines of biology and mathematics. I look forward to designing interdisciplinary courses to introduce young biologists to cutting-edge techniques in computational biology, numerical simulation and complex systems analysis, as well as teaching more traditional quantitative courses in applied and computational mathematics.

I will bring **over eight years of teaching experience** to a position on the faculty. Throughout my career I have taught mathematics and the physical sciences to students whose primary interests lay in biology and other fields as well as mathematics, chemistry and physics.

Following graduation from college I entered *Teach for America*, the national teacher corps of recent college graduates committed to teaching in public schools in low-income communities across the country. As a TFA corps member I taught introductory physics and chemistry at the Baton Rouge Magnet High School for the Arts in Baton Rouge, Louisiana (1990-1992). After completing my two-year teaching commitment in Baton Rouge, I entered graduate school at the University of Chicago, where I had the opportunity both to assist and to teach a wide variety of courses in the Department of mathematics.

I built on my earlier experience making the sciences exciting and accessible to a non-science-oriented audience as a teaching assistant in the “math for poets” mathematical sciences sequence (1993-1994). This innovative course included quarters devoted to mathematical logic, statistics (applied for example to authenticating newly discovered Shakespearean verse) and mathematical modeling of population growth and disease dynamics.

Beginning in 1995 I was responsible for my own courses as a graduate instructor. I taught the non-math-major introductory calculus sequence, the sequence in multivariate calculus for the biological and social sciences, and linear algebra (1995-8). Because economics majors made up the lion’s share of the students in the multivariate calculus sequence, I persuaded the department to supplement the standard textbook for the course with a text on fundamentals of mathematical economics. Subsequently I served as teaching assistant for the University of Chicago’s Master’s program in financial mathematics, teaching students about stochastic processes, numerical solutions of partial differential equations, neural networks and other approaches to modeling the financial markets.

I am currently teaching teaching traditional applied mathematics courses (differential equations and linear algebra). I have expanded the traditional curriculum to include numerical methods

and computer simulation exercises (in the MATLAB programming language) while retaining rigorous methods (e.g. series methods, vector spaces, bifurcation theory) needed for careful analysis of complex systems. I have recently been named a recipient of a curriculum development grant for a course bridging the mathematical and biological curriculae for incoming students at Oberlin College, and I look forward to pioneering an advanced undergraduate course in mathematical methods for computational neuroscience in the spring of 2005.

As a faculty member at Indiana I look forward to the opportunity to train the coming generation of mathematically sophisticated biologists and complex systems analysts, as well as students from chemistry, physics, computer science and applied mathematics who wish to apply their quantitative skills to the study of complex adaptive systems.