

## Peter J. Thomas

*Applied Mathematics & Computational Biology*

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Biocomplexity Faculty Search Committee  
c/o Prof. Rob de Ruyter  
Department of Physics  
Swain West 117  
727 East Third Street  
Indiana University  
Bloomington, IN 47405-7105

11/29/2003

Dear Members of the Search Committee:

I am writing to apply for the tenure-track position in Biocomplexity at Indiana University, Bloomington, at the rank of assistant professor.

I am currently a postdoctoral fellow with Prof. Terrence Sejnowski in the Computational Neurobiology Laboratory at the Salk Institute for Biological Studies. My research concerns biophysical mechanisms of computation, communication and control in biological systems ranging from biochemical signal-transduction networks to biological neural networks.

As a postdoctoral fellow in computational neurobiology I have had the opportunity for extensive interaction with the neuroscience and cell biology communities both here and at the Scripps Research Institute and the University of California, San Diego (UCSD). This environment has provided the background for two major projects. The first concerns the biophysics of single neurons driven by realistically fluctuating input currents. In close collaboration with experimental neurophysiologist Jean-Marc Fellous I have studied mechanisms for *precise and reliable timing of action potentials* in real and model neurons, and their implications for encoding, transmission and decoding of information in the nervous system.

My second project concerns the mechanisms of information processing in intracellular signal-transduction networks, for example the biochemical network controlling chemotaxis in the social amoeba *Dictyostelium discoideum*. In collaboration with cell biologists and theoretical biophysicists at UCSD I have developed a numerical platform to simulate arbitrary systems of boundary-coupled reaction-diffusion equations representing the network of chemical reactions comprising a

eukaryotic cell's "brain", with results published in the *Biophysical Journal*. I am now extending this platform to incorporate the effects of small-numbers noise endemic to reaction networks in subcellular volumes, and to study the implications of intrinsic chemical noise for cell-to-cell communication. We are actively developing an information theoretic framework for the investigation of biochemical signal-transduction networks, with preliminary results to appear in the *Neural Information Processing Systems* conference.

My work draws on nonequilibrium statistical mechanics, dynamical systems, critical phenomena, numerical modeling and simulation of complex systems, entrainment of nonlinear oscillators and analysis of spontaneous pattern formation to study fundamental biophysical problems in developmental and cellular biology and computational neuroscience. Areas of active research include pattern formation in the visual cortex, the control of eukaryotic chemotaxis, and the structure of dynamical attractors in patterns of neural activity. (For further details, see the attached statement of Research Interests).

The environment for biophysics at Indiana University would be an outstanding place to continue this interdisciplinary research. In addition to the University's substantial investment in Informatics, within biophysics there is strength in developmental biology and the biophysics of pattern formation (Prof. Glazier), computational neurobiology (Profs. de Ruyter and Beggs), and biophysics of cell signaling (Prof. Setayeshgar).

As a faculty member at Indiana University I will arrive with eight years of previous teaching experience at the secondary, college and graduate levels. I look forward to supervising Ph.D., M.S. and undergraduate research projects in computational biophysics, computational biological modeling, cellular systems biology, computational neuroscience and complex systems, as well as teaching in these areas and in mainstream physics areas such as statistical mechanics and thermodynamics, mathematical methods for physicists and introductory physics.

I obtained my Bachelor's degree in Physics and Philosophy from Yale University (1990) and my Ph.D. in mathematics under Prof. Jack Cowan at the University of Chicago (2000).

Thank you for your consideration, and I look forward to hearing from you.

Sincerely,

Peter J. Thomas, Ph.D.

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## Statement of Research Interests

My research focuses on the biophysical basis of *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 theoretical biophysics 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 in my thesis, *Order and Disorder in Visual Cortex: Spontaneous Symmetry-Breaking and Statistical Mechanics of Pattern Formation in Vector Models of 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], with additional results to appear in *Physical Review Letters* [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. 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]. 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,  $\text{Ca}^{2+}$  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 Jean-Marc Fellous and Klaus Stiefel in the Sejnowski lab, 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].

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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- [6] Paul C. Bressloff, Jack D. Cowan, Martin Golubitsky, Peter J. Thomas, and Matthew C. Wiener. What geometric visual hallucinations tell us about the visual cortex. *Neural Computation*, 14(3):473–491, March 2002.
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- [9] Peter J. Thomas and Jack D. Cowan. Symmetry induced coupling of cortical feature maps. *Physical Review Letters*, to appear.

## Statement of Teaching Interests

As a teacher I have amassed eight years of experience in secondary, collegiate and graduate instruction, teaching both service and research-oriented courses in mathematics, chemistry and physics. I look forward to teaching both fundamental physics courses, such as introductory physics, statistical mechanics and thermodynamics, and mathematical methods, and research-oriented theoretical biophysical courses such as computational neuroscience and biophysical cell biology.

I strongly believe that undergraduates can contribute to and benefit from cutting-edge research in applied mathematics and mathematical biology. As a postdoctoral fellow at the Salk Institute, I have been fortunate to have the opportunity to mentor undergraduates from the University of California San Diego's Jacobs School of Engineering. My students' hard work has already yielded interesting new results that have been accepted for publication (*The Diffusion-Limited Biochemical Signal-Relay Channel*, see publication list).

For example, some of the projects in which I could immediately involve *undergraduates* include:

- *Computational Neuroscience*  
Effects of noise-induced transitions on the trajectories of nonlinear oscillator neuron models in the vicinity of a dynamical instability (bifurcation), with applications to the problem of the “neural code.”
- *Computational Cell Biology*  
Simulation of a bacterial random walk in a field of chemoattractant, comparing the survival value of different model internal biochemical networks.
- *Critical Phenomena*  
Numerically simulated vortex dynamics in a spatially extended mixed Ferro-Antiferromagnetic Heisenberg XY spin lattice, with applications to the development of the visual cortex.

The avalanche of quantitative biological data becoming available from new experimental techniques in genomics, proteomics and microscopy demands invigorated communication between the biophysical and biological communities. I am committed to developing appropriate curricular materials (textbooks, web-based tools, research projects) to support interdisciplinary teaching that provides students of physics and biology a common language through which to interact.

My eight years of teaching experience – first as a high school physics and chemistry instructor, later as a college instructor of beginning and advanced calculus, and later as a teaching assistant in a financial mathematics M.S. program – have taught me the importance of engaging my students and preparing multiple approaches to the subject matter. Some students are adept at memorizing and applying formulae; others respond best to graphic illustrations of concepts; still others benefit most from hands-on “learning by doing”. Some of my most successful lessons as a high school physics teacher involved improvised laboratory experiments, or hands-on demonstrations. It was especially gratifying to watch a class of high school juniors grasp the second law of thermodynamics upon playing a coin-tossing game that implemented the diffusion operator for fake currency stamped with a likeness of Boltzmann. A “hands-on” approach at the graduate level could mean creating a research-oriented atmosphere by emphasizing open problems and encouraging collaborative work by teams of students on modeling projects.

At both the introductory and the advanced level, I find that teaching deepens my own understanding of a subject and my appreciation for its unity and scope. Teaching the coming generation of talented undergraduates from both the physical and biological sciences will provide the opportunity to lay the foundations for the bridges that will span these disciplines.