Statements Concerning Research, Teaching and Service

Peter J. Thomas

Assistant Professor of Mathematics, Biology, and Cognitive Science

Department of Mathematics

Case Western Reserve University

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As a mathematical biologist, I study communication and control within complex adaptive biological systems. My choice of problems is guided by a desire to identify and extend the boundaries of mathematical knowledge, as well as to advance biological understanding. To illustrate the interplay of biology and mathematics in my work, I will discuss: (1) control of rhythmic behavior in a central pattern generator, (2) entrainment and synchronization of noisy neural oscillators, and (3) application of information theory to biology. My work has been continuously supported, since 2007, by the National Science Foundation’s Mathematical Biology program, in the Division of Mathematical Sciences.

Mathematical Neuroscience: Control of Rhythmic Oscillatory Behavior. Oscillations underly a wide range of biological functions. Biological oscillators must be both robust (i.e. stable) and flexible (i.e. adaptable to changing inputs or external conditions). How real systems balance these objectives is not well known. Models of rhythmic behavior typically take the form of a continuous-time dynamical system with an orbitally stable limit cycle (LC) solution. The sensitivity of the limit cycle to small instantaneous perturbations is captured by the infinitesimal phase response curve (iPRC). The iPRC is defined as the directional derivative (in the direction of the perturbation) of the asymptotic phase function, $\phi(x)$, giving the phase of that point on the limit cycle with which a trajectory started from a given initial condition $x$ eventually converges. The iPRC is available in simple closed form in only a few cases, e.g. for the topological normal forms of the Andronov-Hopf and saddle-node-on-invariant-circle bifurcations. In [23] we constructed a novel one-parameter family of piecewise linear planar dynamical systems possessing limit cycle solutions for which the iPRC can be calculated exactly. Our construction was motivated by the desire to understand control of the central pattern generator (CPG) circuit underlying rhythmic feeding motions in the marine mollusk *Aplysia californica*, a model organism for motor control studied in the laboratory of my collaborator H. Chiel (CWRU Biology). Experimental evidence suggests the feeding CPG may be controlled by passage of a limit cycle trajectory near a sequence of equilibrium points, i.e. the system operates near a heteroclinic orbit. Phase response curves for limit cycles near heteroclinic bifurcations have not been extensively studied, although heuristic calculations for the (closely related) iPRC near a homoclinic orbit appear in [7], §3.1.3 and [13] p.483. In the heteroclinic limit, the limit cycle period diverges, and the asymptotic phase and iPRC are no longer well defined. From the analytic solution, however, we obtained the limiting behavior of the iPRC as the system approaches the heteroclinic in our model system. In [7] it was claimed that, for perturbations parallel to the stable eigendirection, the iPRC is identically zero. However, we proved in [23] the existence of a critical phase $\phi_c$ with the following property: in the heteroclinic limit, perturbations at phases $\phi < \phi_c$ give vanishing phase response, consistent with [7], but perturbations at $\phi \geq \phi_c$ give divergent phase response. This result suggests a testable biological hypothesis: that systems with limit-cycle like trajectories passing near fixed points may show great sensitivity to perturbations timed to coincide with specific phases of the oscillation. The existence of phases at which the response switches between hyper- and insensitivity may, in the long run, help understand how organisms modulate ongoing rhythmic behavior. Future Work: Extending [7], we are studying iPRCs for limit cycles near a saddle-homoclinic bifurcation in the Morris-Lecar equations, a physiologically motivated oscillator. Surprisingly, we find that the peak sensitivity occurs at phases farther from the equilibrium point, near the point of closest approach of the equilibrium’s stable and unstable manifolds. Further analysis should indicate the generality of this paradoxical sensitivity. Simultaneously, we are investigating near-equilibrium-transits in more detailed physiological models, and examining electrophysiological recordings for analogous behavior. In related work, I am collaborating with electrophysiologist C. Wilson (CWRU Pediatrics) on models of the CPG regulating mammalian breathing, to ask how rhythmic activity is adaptively controlled in the brainstem.

Mathematical Neuroscience: Stochastic Neural Oscillators. Noisy dynamics arise from ion channel fluctuations and barrages of synaptic activity, complicating analysis of entrainment and synchronization in neural oscillators. Inspired by Mainen and Sejnowski’s demonstration of precise, reliable spiking in intrinsically noisy mammalian neurons [16] I began studying entrainment phenomena as a student [10, 12, 29], and continued through collaboration with Sejnowski and others [15, 24, 30, 31]. Rigorous analysis of entrainment in noisy oscillators requires techniques from both dynamical systems and stochastic processes. For example, consider a periodically forced, noisy, leaky integrate-and-fire (LIF) neuron, described by the (Itô) stochastic differential equation, $dV = (-V + \alpha + \beta h(t)) \, dt + \sigma dW(t)$ with initial condition $V(T_0) = v_0$, threshold $v_{th}$, mean injected current $\alpha$ and injected current fluctuation $\beta h(t)$, with $h$ a bounded, measurable, zero-mean, deterministic function with period $T$. The trajectory $V(t)$ is “reset” to $v_0$ at each threshold crossing $T_{k+1} = \inf\{t > T_k : V(t) \geq v_{th}\}$. Equivalently, $V(t)$ is a periodically forced Ornstein-Uhlenbeck
process (OUP) with threshold reset. For \( \alpha > v_{th} > v_0 \) this model represents a nerve cell receiving periodic suprathreshold input and firing at times \( T_k \). The phases \( \phi_k = (T_k \mod T)/T \in S^1 \) obey a stochastic circle map. The question, Will the nerve cell synchronize to the input? asks for the existence of a unique invariant measure on \( S^1 \). While the affirmative answer may be obvious to any electrophysiologist, a proof is not available even in this simplified case. In [25] I took a step towards obtaining a proof by deriving the first strictly positive lower bound on the first passage time (FPT) density for the time homogeneous OUP. The proof exploits Doob's representation of the OUP along with construction of a piecewise linear boundary region. **Future Work:** In collaboration with P. Kramer (Rensselaer Polytechnic Institute) and J. Mattingly (Duke University) I am developing a proof of the existence of a unique invariant measure for the periodically forced case, using Girsanov’s change of measure for Brownian motions, and building on [25]. Subsequently, I plan to investigate the relationships between the frequency spectrum of the stimulus, the noise amplitude, and the degree of synchronization of the neuronal firing pattern. More broadly, I will investigate the consequences of noise for nonlinear oscillators. In systems with attracting heteroclinic cycles, adding noise creates “statistical” limit cycles even when the deterministic system does not have periodic solutions. How should one define “phase resetting” in such cases? Ion channel noise arises fundamentally from a system of jump Markov velocity processes [6, 18], which are a generalization of random evolution processes [19, 20]. What governs synchronization of periodically forced jump Markov processes? I am developing an approach to these problems based on spectral analysis of Kolmogorov evolution operators.

**Information Theory in Biology.** Shannon’s *Mathematical Theory of Communication* [22] provided a framework for understanding functional organization of biological systems, e.g. sensory neural networks [3, 5]. However, classical information theory does not quantify the significance of different signals, limiting its applicability to biology. For an organism, the importance of information is state dependent. When hungry, information about food is more salient; when thirsty, information about water is more important. In [2] we challenge the widely assumed that optimal information processing per se is a necessary aspect of optimal behavior. We constructed a model system comprising an organism exploring a finite space \((Z_N)\) in search of food. We found an exact coarse graining of the full state space, \(Z_N \times Z_N \times P(\mathbb{R}^N)\) (where \(P\) is the probability simplex), to a Markov chain on three states. Analysis of the invariant measures on the reduced system allowed us to prove that conditions exist in which pursuing the information-theoretically optimal strategy would lead to suboptimal performance for the organism, in terms of utility or survival. **Future work:** Diffusion-mediated communication is ubiquitous in biology, but information-theoretic analysis of biological signaling systems is in its infancy [26]. With Andrew Eckford (York University), I recently obtained results on the capacity of a discrete time, discrete state communication channel based on the interaction of signaling molecules with receptor proteins [27]. My interest in information theory in biological systems began as a postdoc, with work aimed at understanding how cells communicate with one another through biochemical signal transduction networks [14, 21, 28]. This work has continued through a series of MS theses [1, 8, 11] and jointly with H. Baskaran (Chemical Engineering) [32], R. Snyder (Biology) and Eckford.

**Further Biological Applications.** In some instances, creative application of routine mathematics can lead to advances in otherwise difficult biological problems. FtsZ, an important structural protein in bacteria, exhibits cooperative polymerization even though it is single- rather than multi-stranded. In [17] we resolved this important “paradox” by providing an allosteric assembly model, analyzed using geometric series of matrices. Using even more elementary methods, in [4, 9] we dramatically improved the accuracy of diagnosis for malaria field samples by exploiting a simple change of variables to align the analysis with intrinsic geometric properties of the data. **Future work:** In collaboration with P. Zimmerman (CWRU) we are using elementary probabilistic reasoning to interpret high-volume data from so-called *Next Generation Sequencing* techniques, with application to monitoring naturally occurring genotypic diversity in malaria.

**Future Prospects.** I am continually fascinated by the interplay of stochastic phenomena with nonlinear dynamics, and the limits of communication and control in biological systems. I plan to continue developing a variety of analytical approaches, including ordinary and stochastic differential equations, analysis of Markov processes in discrete and continuous time, and in discrete and continuous spaces, as well as numerical simulations, to gain mathematical and biological insights into a wide variety of biological model systems.
References


Teaching Statement

My goal as a teacher and mentor is to create the conditions under which my students can reach their fullest potential as scholars, and to communicate my enthusiasm for mathematics, regardless of whether the students are mathematics majors, undergraduates from the sciences and engineering, or mathematics graduate students. In the classroom, I teach a range of courses spanning the discipline of mathematics, from classical elementary analysis (Math 321-322) to applied mathematics courses cross-listed in the departments of biology, neuroscience, and physiology (Math 319, Math 378/478). I enjoy teaching at the graduate level (Math 435, Math 478) at the service level (Math 223-224), and core courses in the major (Math 321-322). From 2006-2012 I have taught sixteen semester courses, with a total of 353 students enrolled in that time.

Before coming to Case, I was on the faculty of Oberlin College, a highly rated four-year liberal arts college, where excellence in teaching was the faculty’s first priority. While at Oberlin I learned that successful teaching requires thorough preparation, frequent assessment of student learning, and sensitivity to the backgrounds and abilities present in a given class. As a faculty member at Case I have kept these lessons in mind, while making the most of the high level of technical sophistication which is a hallmark of Case’s student body.

In teaching service level courses (Math 223: Calculus for Science and Engineering III; Math 224: Ordinary Differential Equations) I find that students benefit when I regularly engage them in hands-on problem solving in addition to traditional lecture. For Math 223 I have developed a series of original problems for each topic in the textbook, and about half of most class meetings is devoted to students working together on these problems in teams of three or four. For example, when working with vectors and angles in spherical coordinates, I ask students: Which city is farther from Cleveland: Tehran or Tokyo? Another popular problem is: Estimate how many golf balls can fit into a 1m × 1m × 1m crate? For Math 224, I find that giving regular short quizzes gives students a strong motivation to keep current with the reading for the course. The daily quiz requires time to grade (I can usually finish one day’s quizzes on my train ride home) and students initially grumble about the frequent assessments. However, by the time of the first midterms, students find them indispensable, and I am able to intervene earlier when I see that a student is not catching on to basic concepts. At the same time that I hold the students to high expectations through homework and exams, I try to leaven the course with unexpected allusions that the students will appreciate. When discussing the forward and inverse Laplace transform, for instance, I illustrate the idea of an invertible functional transformation by showing drawings from Dr. Suess’ story The Sneetches. When discussing constrained optimization in Math 223 I show the illustration from Roald Dahl’s James and the Giant Peach in which James explores the corners of his fenced yard as remote as possible from his Aunts’ cottage.

Some of these techniques carry over successfully to more advanced courses as well. For instance, I used frequent short quizzes while teaching Analysis (Math 321-322), a course notorious among mathematics majors for its difficulty. When I surveyed student attitudes towards the course during the fifth week of the fall term, a large majority urged me to continue the quizzes; students said the quizzes positively impacted their comprehension. Although the short quiz takes some time away from lecture, I typically was able to use one as a springboard for the other. For example, when discussing differentiation, the quiz question was: Give an example of a function f : R → R that is continuous everywhere, and which is differentiable everywhere except at the n points x_1 < x_2 < ... < x_n. Immediately following the quiz, we reviewed the students’ answers. During the ensuing discussion, exploring the (mistaken) reasoning leading to the incorrect answers was particularly valuable. This approach helps expose and clear up common confusions quickly, which I found to be a helpful supplement to the traditional lecture. Students responded positively: in 2010-11 students from Math 321-322 nominated me for the Carl F. Wittke Award for Excellence in Undergraduate Teaching, for which I was one of twelve finalists.

In addition to standard service and core mathematics courses, I have had the opportunity to introduce or redesign two courses integrating teaching and research through a combination of traditional lectures, hands-on computational modeling exercises, and team research projects. Math 378/478 (Computational Neuroscience)
introduces students to mathematical modeling of dynamical systems in neuroscience at both a theoretical level and through computational tools such as the NEURON programming environment, Ermentrout’s XPP phase plane analysis package, and Matlab. Students in Math 478 met for additional sessions during which we worked through parts of Ermentrout and Terman’s graduate textbook, *Mathematical Foundations of Neuroscience*. Math 319 (Applied Probability and Stochastic Processes for Biology) introduces students to practical aspects of stochastic modeling in discrete and continuous time and space. The course draws from Pinsky and Karlin’s text *An Introduction to Stochastic Modeling* as well as Wilkinson’s book *Stochastic Modelling for Systems Biology*. In 2011 I was honored to receive a T. Keith Glennan Fellowship, a CWRU program recognizing tenure track faculty for leadership in both teaching and scholarship; the fellowship allowed me to expand the hands-on computational component of Math 319. The computer exercises introduce students to computational aspects of biological random walks using both Matlab and the MCell simulation platform. Both Math 319 and Math 378/478 integrate teaching and research by incorporating current research topics into lectures and exercises as well as through students’ course projects. Two student projects from these courses developed into work that was presented publicly. A. Boxerbaum presented a poster at the 2008 Society for Neuroscience meeting based on work in Math 378; D. M. Ackermann coauthored a paper with me appearing in 2011 in the Journal of Neural Engineering, that grew out of his Math 319 course project.

The teaching mission of the University is not limited to traditional classroom instruction, but includes mentoring of research students at the undergraduate, graduate and postdoctoral levels. During 2006-2012, I have directly supervised research projects for ten undergraduate students, ranging from one semester to multiple years. Several students who began working with me ultimately became coauthors on refereed journal articles (including Drew Kouri, David Kent, Edward Agarwala, and Young-Min Park). In the same interval, I have directed Masters theses in Applied Mathematics for four students, some of whom began working with me as undergraduates and continued to complete a BS/MS program. The titles and dates of the MS theses are as follows:


I am currently supervising two postdoctoral fellows, co-mentoring one MD/PhD student, advising two MS students, and supervising four undergraduate research students. Casey Diekman is a postdoctoral fellow at the Mathematical Biosciences Institute (MBI) at The Ohio State University. C. Wilson (CWRU School of Medicine) and I co-mentor Dr. Diekman through MBI’s external mentoring program. Dr. Diekman is working with us on mathematical modeling of biological rhythms in the mammalian brainstem that underly breathing. In addition, R. Snyder (CWRU Biology) and I co-mentor Deena Schmidt, who is supported by our joint NSF grant. Dr. Schmidt is working with us to find optimal reduction techniques for stochastic processes on complex biological networks. As of the summer of 2012 I will begin working with two students embarking on MS thesis work: Margaret Callahan, who will work with me and Prof. Zimmerman (CWRU School of Medicine) on data mining problems associated with next-generation-sequencing analysis of malaria genomes; and Abdulaziz Alsenafi, who will work with me and Prof. Chiel (CWRU Biology) on stochastic dynamical systems models of rhythmic motor control systems. Along with Prof. Chiel, I also co-mentor Kendrick Shaw, an MD/PhD student working on combined experimental, computational, and mathematical studies of motor control in the feeding central pattern generator of the marine mollusk *Aplysia californica*. Undergraduate students Young-Min Park (dynamical systems and *Aplysia* motor control) and Alex White (biological networks) will continue ongoing research projects; John Henry (malaria data mining) and Casey Bennett (interspike interval variability) will begin new projects with me, during the summer of 2012.
Service Statement

During 2006-2012 I have been active in service at the national, university, and departmental levels. The CV provides full details; here I present some highlights of my service activities.

Conference Organizing: I have organized seven minisymposia as parts of larger scientific meetings, including a minisymposium on Stochastic Biochemical Systems at the joint meeting of the International Council for Industrial and Applied Mathematics (ICIAM) and the Society for Industrial and Applied Mathematics (SIAM) in Zurich in 2007; and a special session on Applications of Stochastic Processes in Neuroscience at the Joint Mathematics Meetings in New Orleans in 2011. I am currently co-organizing, with Eric Shea-Brown (U. Washington), a Virtual Working Group (VWG) on Master Equations and Neural Dynamics, to be hosted by the Mathematical Biosciences Institute (MBI) at The Ohio State University during 2012-13. The VWG is a new effort by MBI aimed at supporting sustained scholarly interaction through videoconferencing technology.

Editorial Service: I served as co-Guest Editor (with H. Chiel), of a special issue of the Journal of Neural Engineering, dedicated to the topic of Applied Dynamics: From Neural Dynamics to Neural Engineering, which appeared in 2011.

Scholarly Review: I have provided peer review for over a dozen scholarly journals including the Bulletin of Mathematical Biology, BMC-Systems Biology, the Journal of Computational Neuroscience, the SIAM Journal on Scientific Computing, Proceedings of the National Academy of Sciences, and Science. I regularly provide peer review for the National Science Foundation, through service on panels and through mail review.

STEM Education: During 2011-2012 I helped Teach For America (TFA), the national teacher corps, convene an advisory board composed of TFA alumni active in Science, Technology, Engineering and Mathematics (STEM). As chair of the board’s working group on recruitment, I am contributing to efforts to strengthen recruitment of recent college graduates majoring in STEM disciplines into the teaching workforce.

University Service: From August 2007 through December 2011 I served as co-Director, with Prof. R. Snyder (Biology), of RIBMS, Case Western Reserve University’s undergraduate program in Research at the Interface of the Biological and Mathematical Sciences. This interdisciplinary undergraduate research program, funded by the National Science Foundation through a grant proposal I cowrote with Prof. Snyder, supported teams of undergraduates from the mathematical and biological sciences conducting year-long research projects under the mentorship of interdisciplinary teams of faculty. A total of 25 students participated in year-long research projects, which involved sixteen faculty members.

Departmental Service: In addition to serving, at various times, on the Department’s Colloquium Committee and the Undergraduate Committee, I have been the lead organizer, since 2007, of the Mathematical Life Sciences Seminar (originally the Biomathematics Research Forum). This biweekly forum serves as a gathering point for faculty and students with interests at the intersection of the mathematical and the biological sciences. From 2007-2012 participants have come from over a dozen departments across the College of Arts and Sciences, the School of Medicine and the School of Engineering, with a mixture of internal speakers and external speakers from institutions ranging from Rensselaer Polytechnic Institute to The University of Chicago.