Overview

My research includes both (a) answering mathematical questions in stochastic processes, dynamical systems, and analysis and (b) using mathematics to answer biological questions. The mathematical questions that I work on typically arise from biological questions.

I have extensively studied stochastic hybrid systems. I have proven that ODEs with randomly switching right-hand sides can exhibit surprising behavior [14]. I have also developed theoretical machinery for analyzing PDEs with randomly switching boundary conditions [15]. These results have important implications both for the mathematical study of stochastic hybrid systems and for biological applications.

I have also used mathematical modeling to address the arsenic poisoning crisis in Bangladesh [13], [16]. This ongoing project is a collaboration between myself and one other mathematician, one biologist, one biochemist, one epidemiologist, and two undergraduates.

1. Stochastic Hybrid Systems

Stochastic hybrid systems are a type of stochastic process that are used in many areas of biology (for example, molecular biology [6], ecology [24], epidemiology [9]) and many other applied areas outside of biology [23]. The word "hybrid" is used because these processes involve both continuous dynamics and discrete events. One example is a dynamical system whose right-hand side randomly switches between elements of a collection of vector fields. The continuous dynamics in this example are the different right-hand sides of the dynamical system, and the discrete events are when the right-hand side switches.

In general, a stochastic hybrid system is a continuous-time stochastic process with two components: a continuous component $(X_t)_{t\geq 0}$ and a jump component $(J_t)_{t\geq 0}$. The jump component J_t is a jump process on a finite set, and for each element of its state space we assign some continuous dynamics to X_t. In between jumps of J_t, the component X_t evolves according to the dynamics associated with the current state of J_t. When J_t jumps, X_t switches to following the dynamics associated with the new state of J_t.

1.1. **Stochastically switched linear ODEs.**

Consider the stochastic process driven by an ordinary differential equation whose right-hand side randomly switches between a collection of different linear terms. Explicitly, consider the process (X_t, J_t) where $X_t \in \mathbb{R}^d$ solves

$$\dot{X}_t = A_{J_t} X_t$$

with J_t a continuous-time Markov jump process on a finite set E and $\{A_j\}_{j\in E}$ a set of real matrices. Despite their apparent simplicity, my co-authors and I have proven that these systems can have surprising behavior.

In [14], my co-authors and I constructed planar examples that switch between two matrices where the individual matrices and the average of the two matrices are all stable (all eigenvalues have strictly negative real part), but nonetheless the process goes to infinity at large time for certain values of the switching rate. To state our result precisely, let r scale the rate at which the right-hand side switches by letting J_t have generator rQ, and define the average matrix $\bar{A} := \sum_{j\in E} A_j \pi_j$ where π is the invariant measure of J_t.

Theorem 1. There exist matrices $A_0, A_1 \in \mathbb{R}^{2\times 2}$ so that A_0, A_1, and $\bar{A}$ are each stable, but nonetheless $||X_t|| \to \infty$ almost surely as $t \to \infty$ for some switching rate r.

We further constructed examples in higher dimensions where again A_0, A_1, and $\bar{A}$ are all stable, but $||X_t||$ has arbitrarily many transitions between converging to ∞ and converging to 0 as the switching rate varies:

Theorem 2. For any positive integer n, there exist matrices A_0, A_1 and n non-overlapping intervals $\{(a_k, b_k)\}_{i=1}^n$ so that

(1) A_0, A_1, and $\bar{A}$ are each stable.
(2) If the switching rate $r \notin \bigcup_{i=1}^n (a_i, b_i)$, then $||X_t|| \to 0$ almost surely as $t \to \infty$.
(3) For every $i \in \{1, \dots, n\}$, $||X_t|| \to \infty$ almost surely as $t \to \infty$ for some switching rate $r \in (a_i, b_i)$.

Our results are part of a broad literature on ODE switching systems. Our work is a stochastic counterpart to the extensive work done by control theorists in the past decade on deterministically switched linear ODEs (see [18] for a review). In [4], the authors consider stochastically switched linear ODEs with two stable matrices and show that the process may go to infinity at large time as long as the average of the two matrices has a positive eigenvalue. Thus, our results show that their assumption on the average matrix is not necessary to ensure a blowup.

Our work in [14] also has important implications for the general study of stochastic hybrid systems. [8], [5], [3], and [1] all study invariant measures for stochastic hybrid systems. Our work shows that the existence of invariant measures may depend on the switching rates in a complicated way. In [10], [11], and [2], the authors provide conditions under which their randomly switched systems behave according to the individual systems for slow switching and according to the average system for fast switching. In [14], we prove that stochastically switched linear ODEs also obey this principle by proving that if the individual matrices are each stable, then $\lim_{t\to\infty} ||X_t|| = 0$ for sufficiently slow switching rate and if the average matrix is stable, then $\lim_{t\to\infty} ||X_t|| = 0$ for sufficiently fast switching rate. However, our Theorem 2 above shows that the transition between the slow and fast switching regimes can be arbitrarily complicated.

1.1.1. *Future work.* I conjecture that the large time behavior of stochastically switched linear ODEs depends solely on the spectrum of a (possibly infinite) sum of nested commutators of the matrices $\{A_j\}_{j\in E}$ and that this sum is given explicitly by the Baker-Campbell-Hausdorff formula. The Baker-Campbell-Hausdorff formula is a classical result in group theory that can be used to represent the logarithm of a product of exponentiated matrices in terms of a (possibly infinite) sum of nested commutators of those matrices [20]. My conjecture is consistent with numerical simulations and all the results in [4] and [14]. Indeed, this conjecture was the motivation for the examples in [14].

Verifying this conjecture would lend insight to more complicated ODE switching problems. For example, in [1] the authors study ODEs with right-hand sides that randomly switch between possibly non-linear elements of a collection of vector fields. In that paper, the authors provide conditions on the Lie brackets of the vector fields that ensure uniqueness and absolute continuity of an invariant measure. Thus the commutators in my conjecture give context to these conditions on the Lie brackets. Furthermore, confirming this conjecture would provide Lyapunov exponents for products of a large family of random matrices. Finally, this conjecture can be seen as providing higher order terms to the finite-dimensional case of the main result in [12].

1.2. **Infinite-dimensional systems and random PDEs.** I have developed general mathematical machinery for analyzing stochastic hybrid systems [15]. This machinery combines techniques from various fields of mathematics, including probability, ergodic theory, and functional analysis, to yield explicit formulae for important statistics of these processes. My methods are particularly useful for infinite-dimensional processes, such PDEs with randomly switching boundary conditions.

This machinery examines stochastic hybrid systems from the viewpoint of iterated random maps on abstract spaces. Consider a stochastic hybrid system $(X_t, J_t) \in \mathcal{X} \times E$ with $\mathcal{X}$ a complete separable metric space and E a finite set. For each $j \in E$, define $\Phi_j^t : \mathcal{X} \to \mathcal{X}$ to be the flow map for the continuous dynamics associated with state j. Thus X_t is constructed by repeatedly applying the flow maps according to the evolution of the jump component J_t.

If J_t does not depend on X_t and the flow maps Φ_j^t are contracting in some average sense, then I have proven that X_t converges in distribution as $t \to \infty$. Furthermore, I have shown that this limiting distribution is invariant under applications of the flow map Φ_ξ^τ for random variables τ and ξ chosen appropriately. This invariance property is the main tool that yields explicit formulae for statistics of the process.

We are able to cast many stochastic hybrid systems into this framework. Applying these tools to parabolic PDEs with randomly switching boundary conditions yields explicit formulae for expectations, variances, and covariances of the Fourier coefficients of the solution. In Section 1.3 below, I apply these tools to the heat equation with a randomly switching boundary condition.

1.2.1. *Future work.* My current results only hold under the assumption that the jump component is independent of the continuous component. Motivated both by biological applications and purely mathematical interest, I aim to generalize my current machinery to remove this assumption. A biological example requiring this generalization is a membrane channel whose stochastic opening and closing is correlated to internal state variables such as membrane potential.

If we allow the jump rates to depend on X_t, and if we assume this dependence is Lipschitz and make appropriate contractive assumptions on the flow maps Φ_j^t, then X_t converges in distribution. Furthermore, it follows from similar arguments to those in [15] that this limiting distribution is invariant under applications of the flow map Φ_ξ^τ for some random variables τ and ξ. The difficulty now lies in finding the distributions of τ and ξ, but once these are obtained, then formulae for statistics of the process as in [15] follow quickly.

1.3. **Insect respiration.** My work analyzing PDEs with randomly switching boundary conditions was prompted by various biological questions, including questions in cell polarization, neuroscience, and immunology. I have devoted the most effort to a question concerning insect respiration.

Essentially all insects breathe via a network of tubes that allows oxygen and carbon dioxide to diffuse to and from their cells [22]. Air enters and exits this network through valve-like holes (called spiracles) in the exoskeleton. These spiracles regulate air flow by opening and closing. Surprisingly, spiracles have three distinct phases of activity, each typically lasting for hours. There is a completely closed phase, a completely open phase, and a flutter phase in which the spiracles rapidly open and close [17].

Insect physiologists have proposed at least five major hypotheses to explain the purpose of this behavior [7]. In order to address these competing hypotheses, physiologists would like to understand how much cellular oxygen uptake decreases as a result of the spiracles closing.

To answer this question, I began with the following prototype model. I represent a tube by the interval $[0, L]$ and model the oxygen concentration at a point $x \in [0, L]$ at time t by the function $u(x, t)$. As diffusion is the primary mechanism for oxygen movement in the tubes (see [19]), the function u satisfies the heat equation with some diffusion coefficient D. I impose an absorbing boundary condition at the left endpoint of the interval to represent cellular oxygen absorption where the tube meets the insect tissue. The right endpoint represents the spiracle, and since the spiracle opens and closes, the boundary condition here switches between a no flux boundary condition, $u_x(L, t) = 0$ (spiracle closed) and a Dirichlet boundary condition, $u(L, t) = c > 0$ (spiracle open).

My mathematical machinery for analyzing PDEs with randomly switching boundary conditions yields an explicit formula for the average oxygen intake to the tissue as a function of the spiracle opening and closing [15]. To illustrate, suppose that the spiracle switches from open to closed and from closed to open with exponential rates r_0 and r_1 respectively. If we let $\rho = r_0/r_1$ and $\gamma = L\sqrt{(r_0 + r_1)/D}$, then the expected oxygen flux to the cells at large time is given by

$$\frac{cD}{L}\left(1 + \frac{\rho}{\gamma}\tanh(\gamma)\right)^{-1}.$$

1.3.1. *Future work.* I will apply this theoretical result to the real problem of insect respiratory tubes. This will entail taking into account the geometry and other properties of the tubular network. My preliminary results indicate that the flutter phase does not reduce oxygen uptake as much as previously thought. Thus, hypotheses that posit spiracular control as a means of avoiding oxygen toxicity (such as in [7]) may need revision.

2. Arsenic Detoxification

Chronic ingestion of arsenic from contaminated drinking water is a health hazard in over 70 countries. The problem is most disastrous in Bangladesh after an attempt in the 1970's to improve drinking water backfired. This well-intentioned effort led to what the World Health Organization has called "the largest mass poisoning of a population in history" [21].

I have used mathematical modeling to address this crisis. I have developed a model of arsenic detoxification that was used to interpret clinical data from Bangladesh and evaluate nutritional supplements aimed at increasing arsenic detoxification [13]. More recently, I have used modeling to elucidate the biochemical pathway of arsenic detoxification and suggest new supplementation strategies for increasing arsenic detoxification [16]. In both cases, the models consist of a system of ODEs that we solve numerically.

This interdisciplinary project is an ongoing collaboration with a nutritional biochemist at Columbia University, Mary Gamble, an epidemiologist at Columbia University, Megan Hall, a biologist at Duke University, Fred Nijhout, and a mathematician at Duke University, Michael Reed. A pair of Duke undergraduates, Molly Cinderella and Jina Yun have been instrumental to our work.

I am excited to mentor undergraduates in research projects. Modeling projects such as this are ideal for undergraduates since they require only ODEs. Furthermore, undergraduates enjoy projects like this because they can help alleviate pressing public health problems.

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