Research Statement
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My interests lie in applied dynamical systems and ordinary and partial differential equations (ODEs and PDEs). In particular, I am interested in employing techniques in dynamical systems and PDEs to model and analyze biological and physical phenomena. In recent years, an increase in the amount and variety of biological data has combined with efforts to increase our quantitative understanding of biological systems to cement mathematical biology as an essential interdisciplinary effort.

What is Mathematical Biology?

Mathematical Biology is an interdisciplinary field of research which connects mathematics with biology, neuroscience, and medicine. The aims are to describe a biological process by a mathematical model, analyze that model by either analytical or numerical means, compare the results to experimental data, and predict more biological phenomena based on the outcome of the model. Mathematicians typically employ probability theory, graph theory, combinatorics, algebraic geometry, topology, dynamical systems, and partial differential equations to model biological systems. I am particularly interested in employing ordinary and partial differential equations to describe biological processes. Studying the behavior of the solutions of the equations, describes how the biological system behaves either over time or at equilibrium.

In what follows, I will elaborate on my main research programs and discuss some of my future plans.

Research Programs

The analysis of synchrony in networks of coupled systems is a long-standing problem in different fields of science and engineering as well as in mathematics. In biology, the synchronization phenomenon can be observed at both individual physiological level and the overall population level. For example, synchronization phenomenon is exhibited in neuronal interactions, in generation of circadian rhythms, in the emergence of organized bursting in pancreatic beta-cells, and in the simultaneous flashing of fireflies. In engineering, one finds applications of synchronization ideas in areas as varied as robotics or autonomous vehicles. In the human brain, synchronization at the neuronal or regional level can be beneficial, allowing for production of a vast range of behaviors, or detrimental, causing disorders such as Parkinson’s disease and epilepsy. In particular, I am interested in networks of diffusively coupled neuronal oscillators which can be described either by nonlinear systems of ODEs or by reaction-diffusion PDEs. In biology, reaction-diffusion PDEs describe the change in space and time of abundances of different types of individuals (particles, chemical species, etc.) that can react instantaneously and can diffuse due to random motion. In Section 1, I study synchronization phenomena in networks of diffusively coupled systems, modeled by ODEs and reaction-diffusion PDEs, using the methods of contraction theory and algebraic graph theory.

As a real application of synchronization in biological settings, in particular in neuroscience, I study synchronous behavior in central pattern generators (CPGs). CPGs are networks of neurons that produce rhythmic motor patterns such as walking, swimming, flying, without any rhythmic inputs from peripheral nervous system. CPGs are sophisticated circuits that can generate complex locomotor
behaviors and even switch between very different gaits while receiving only simple input signals. The theory of dynamical systems can help in designing CPGs. For instance, the theory can help in identifying when synchronization occurs in a system of coupled oscillators depending on parameters such as coupling weights and intrinsic frequencies. In Section 2, using some techniques from dynamical systems, I study the mechanism of gait transition in an oscillator model of CPGs in insects.

1. Synchronization in Networks of Diffusively Coupled Systems

Problem Statement and Previous Work. The objective is to understand the synchronization behavior in networks where individual nodes may have identical or different intrinsic nonlinear dynamics. Many different theoretical methods, based on Lyapunov exponents, master stability functions, graph theory, and Lyapunov functions, have been employed to approach the problem of synchronization. Another useful method to show synchronization, which I have employed in my research, is contraction theory. Contraction theory is a powerful tool for understanding synchronization phenomena in networked systems. The proper tool for characterizing contractivity for nonlinear systems is provided by the matrix measures of the Jacobian of the vector field, evaluated at all possible states. Let $Q$ be a positive definite matrix and for any $1 \leq p \leq \infty$, let $\|x\|_{p,Q}$ be a $Q$-weighted $L^p$ norm on $\mathbb{R}^n$, defined by $\|x\|_{p,Q} = \|Qx\|_p$. The matrix measure $\mu_{p,Q}(\cdot)$ induced by $\|\cdot\|_{p,Q}$ is defined as the directional derivative of the matrix norm, that is,

$$
\mu_{p,Q}[A] = \lim_{h \to 0^+} \sup_{\|x\|_{p,Q} = 1} \frac{\|(I + hA)(x)\|_{p,Q} - 1}{h},
$$

where $I$ is the identity operator on $X$.

For homogenous systems, synchronization results based on techniques from contraction theory, typically employing measures derived from $L^2$ or weighted $L^2$ norms, have been already well studied, see for example [1, 2, 3, 4, 5, 6]. In contrast, for heterogeneous systems, even measures derived from $L^2$ or weighted $L^2$ norms are not well studied.

New Results. My main contribution on contraction theory and its application to synchronization problem is threefold:

1. In homogeneous systems, I extended contraction theory specifically for (weighted) $L^p$ norms, $1 \leq p \leq \infty$. The reason that I was interested in $L^p$ norms rather than just $L^2$ norms is that I was motivated by a desire to understand an important biological system, for which contractivity holds for (weighted) $L^1$ norms, but not with respect to (weighted) $L^p$ norms, for any $1 < p \leq \infty$.

2. I also extended contraction theory to a setting where systems may have heterogeneous intrinsic dynamics and the network satisfies a cluster-input-equivalence condition. Using this extension, I proved new sufficient conditions for cluster synchronization in a network of heterogeneous systems.

3. Moreover, motivated by important biological systems, I extended contraction theory for $L^p$ norms in reaction-diffusion PDEs and studied spatially uniform behavior of their solutions.

Synchronization of homogeneous coupled systems

In [6, 7, 8], we study the global convergence of the solution of a network of $N$ compartments (nodes) $x_1, \ldots, x_N, x_i \in \mathbb{R}^n$, with identical dynamics $\dot{x}_i = f_i(x_i, t) = f(x_i, t)$, which are diffusively connected.
through an undirected, connected graph with (graph) Laplacian $L$. The following system of ODEs describe the evolution of the $x_i$’s in the network:

$$\dot{x} = F(x, t) - L \otimes Dx,$$

where $x$ is the column of $x_i$’s and $F(x, t)$ is the column of $f(x_i, t)$, $\otimes$ denotes the Kronecker product of two matrices, and $D$ is the diffusion matrix.

The goal is to find conditions on $f$ and $D$ such that $x_i(t) - x_j(t) \to 0$, as $t \to \infty$, $\forall i, j$, namely the system synchronizes. See Fig. 1 for a graphical illustration.

![Figure 1: (Left) The behavior of 6 individual compartments that are isolated. (Right) The behavior of the 6 compartments that are now connected through a complete graph.](image)

We say that the system (1) is contractive if any two solutions of the network converge to each other exponentially and with no overshoot. In [7], we provided conditions on (only) $f$ that guarantee contractivity of the system (1):

**Theorem 1.** Consider the system (1) and let $c = \sup_{(x,t)} \mu_{p,Q}[J_f(x,t)]$, where $\mu_{p,Q}$ is the logarithmic norm induced by the $Q$-weighted $L^p$ norm, $\| \cdot \|_{p,Q}$, on $\mathbb{R}^n$ defined by $\|x\|_{p,Q} := \|Qx\|_p$, and $Q$ is a positive diagonal matrix. Then for any two solutions $u, v$ of (1), we have

$$\|u(t) - v(t)\|_{p,Q} \leq e^{ct} \|u(0) - v(0)\|_{p,Q}.$$

In particular, when $c < 0$, the system (1) is contractive.

Although the “contractivity” condition provided in Theorem 1, $c < 0$, guarantees synchrony of Equation (1), we are interested in a weaker condition. In [9, 10, 11], we showed that for special graphs (e.g., complete, star, linear) if, $\sup_{(x,t)} \mu_{p,Q}[J_f(x,t) - \lambda D] < 0$, where $\lambda > 0$ is the smallest nonzero eigenvalue of the (graph) Laplacian, then the system synchronizes. An abstract synchronization theorem, [11, Theorem 1], is proved for an arbitrary graph. Although the theorem is very interesting mathematically and the results for arbitrary graphs are direct applications of the abstract theorem, the condition is not easy to check for arbitrary graphs. A direction for future research would be to generalize the synchronization condition $\sup_{(x,t)} \mu_{p,Q}[J_f(x,t) - \lambda D] < 0$ to arbitrary graphs.

**Cluster synchronization of heterogenous coupled systems**

In realistic networks with heterogeneous nodes and nonuniform coupling structure, complex patterns of synchronization emerge. Under certain conditions, it is possible to partition the network into clusters of nodes that are synchronized within clusters but not across clusters. This is called cluster synchronization.

In [12, Theorem 1], we studied the synchronous behavior of Equation (1), where $f_i$’s are non-identical, i.e., a network of heterogenous systems. We assumed that there exists $K \leq N$ groups of nodes that
have identical intrinsic dynamics, and for any system in each group, we assumed “cluster-input-equivalence condition” which means the sum of the edge weights from the systems in group $j$ to system $k$ in group $i$ is equal to the sum of the edge weights from the systems in group $j$ to system $l$ in group $i$. Let $G$ denote the network graph, $G_i$ denotes the subgraph for the nodes in group $i$, and $\bar{G} = G - \cup G_i$ be the graph describing connections among the clusters, and assume that

$$\mu := \max_{i=1,...,K} \sup_{(x,t)} \mu_{2,Q} \left[ J_{f_{ci}}(x,t) - (\lambda_{ci} + \bar{\lambda})D \right] < 0,$$

where $\lambda_{ci} > 0$ and $\bar{\lambda}$ are the smallest nonzero eigenvalue of the Laplacian of graph $G_i$ and $\bar{G}$, respectively. Then the systems in each group synchronize exponentially with rate $\mu$. See Fig. 2 for a graphical illustration.

![Figure 2: Cluster synchronization in a network of 17 heterogeneous Fitzugh-Nagumo oscillators.](image)

We have detailed an approach to find sufficient conditions for synchronization independent of oscillator model and network structure. However, the cluster-input-equivalence condition limit the amount of heterogeneity in the oscillator dynamics and asymmetry in the network. Future generalizations of this work will include relaxations of the complete synchronization requirement which would allow for more complex and realistic network configurations to be studied.

### Spatially uniform behavior in systems of reaction-diffusion PDEs

In the twentieth century, the Hodgkin-Huxley equations and Turing’s paper on morphogenesis inspired research in reaction-diffusion equations and pattern formation. In biology, reaction-diffusion PDEs of the form $\partial u_i/\partial t(\omega,t) = F_i(u(\omega,t),t) + d_i \Delta u_i(\omega,t)$, for $i = 1, \ldots, n$, describe individuals of $n$ different types, with respective abundances $u_i(\omega,t)$ at time $t$ and location $\omega$. The elements of the system can react instantaneously, guided by interaction rules encoded into the vector fields $F_i$, and can diffuse due to random motion, described by $d_i \Delta$. As in the discrete case, I am interested in finding conditions that guarantee synchronous behavior of the solutions of reaction-diffusion PDEs.

Consider the following reaction-diffusion PDEs defined on $\Omega \times [0, \infty)$ for a smooth domain $\Omega \subset \mathbb{R}^m$, and subject to Neumann boundary conditions:

$$\frac{\partial u_i}{\partial t}(\omega,t) = F_i(u(\omega,t),t) + d_i \Delta u_i(\omega,t), \quad i = 1, \ldots, n,$$

$$\frac{\partial u_i}{\partial n}(\xi,t) = 0 \quad \forall \xi \in \partial \Omega, \ \forall t \in [0, \infty).$$

In this case, we want to obtain conditions on $F = (F_1, \ldots, F_n)^T$ and $D = \text{diag}(d_1, \ldots, d_n)$ such that $u(\omega,t) - u(\nu,t) \to 0$ as $t \to \infty$ for all $\omega, \nu \in \Omega$ (understood in an appropriate topology), namely the system synchronizes. See Fig. 3 for a graphical illustration.
An analogous result to Theorem 1 for the system (2) is the following theorem proved in [7]:

**Theorem 2.** Consider the PDE (2) and let \( c = \sup_{(x,t)} \mu_{p,Q}[J_F(x,t)], \) for some \( 1 \leq p \leq \infty, \) and some positive, diagonal matrix \( Q. \) Then for every two solutions \( u, v \) of the PDE (2) and all \( t \in [0,T) \):

\[
\|u(t) - v(t)\|_{p,Q} \leq e^{ct} \|u(0) - v(0)\|_{p,Q}.
\]

Similar to Theorem 1, Theorem 2 guarantees synchrony of reaction diffusion PDE system (2), namely when \( \sup_{(x,t)} \mu_{p,Q}[J_F(x,t)] < 0, \) any solution \( u, \) converges to a uniform solution \( \bar{u}(\omega,t) = \bar{u}(t). \)

In a compelling extension of this work, we are looking for a weaker condition which depends on the structure of the space \( \Omega \) and the diffusion matrix \( D. \) In [13], we found such a condition for 1-dimensional space and for \( L_1 \) norms: If \( \sup_{(x,t) \in \Omega \times [0,T)} \mu_{1,Q} [J_F(x,t) - \pi^2/L^2] < 0, \) then (2) synchronizes. The problem is still open for higher dimensions and arbitrary norms.

**Future Research.** I hope to complete the project by generalizing the synchronization problem in homogeneous systems to arbitrary graphs in discrete case, and to arbitrary spaces and norms in continuous case. Generalizing contraction theory for non-\( L_2 \) norms in heterogenous systems is also an interesting research topic.

Analogue to the cluster synchronization in ODE systems, studying cluster synchronization or pattern formation in reaction diffusion PDEs, specifically using the methods of contraction theory, is one of my future research programs.

In addition, I am interested to investigate generalization of the results to the stochastic systems which represent more realistic models of biological and physical phenomena.

In modeling networks, a direct communication between nodes is often assumed. In our studies, we considered such communications. However, there are many natural examples that nodes rather to communicate through the environment than direct communication. Quorum sensing is an example of this kind of communication. I am interested in extending our techniques to such networks.

### 2. Central Pattern Generators and Patterns of Locomotion

**Problem Statement and Previous Works.** Legged locomotion involves various gaits. It has been observed that fast running insects (cockroaches) employ a tripod gait with three legs lifted off the ground simultaneously in swing, while slow walking insects (stick insects) use a tetrapod gait with two legs lifted off the ground simultaneously. Fruit flies use both gaits and exhibit a transition from tetrapod to tripod at intermediate speeds. In [14], we studied the effect of stepping frequency on gait transition from tetrapod to tripod in an ion-channel bursting neuron model, developed in [15], in
which each leg represents a hemi-segmental thoracic circuit of the central pattern generator (CPG). CPGs are networks of neurons in invertebrate thoracic ganglia that are responsible for generating locomotive activities (Figure 4). CPGs for rhythmic movements are reviewed in e.g. [16, 17]. A periodic orbit which contains a sequence of spikes (burst) followed by a quiescent phase describes the swing and stance durations of each step, respectively. In the bursting neuron model, represented by 24 ordinary differential equations, a couple of parameters stand for the speed of insects; i.e., when the parameters increase, the period of the periodic orbit decreases, and therefore the speed of the insect increases.

**New Results.** A simulation of 24 ODEs shows gait transition from tetrapod to tripod as speed increases (Figure 5); in tetrapod, 2 legs swing together; in tripod, 3 legs swing together. Colored bars indicate right and left leg swing phases.

Assuming weak coupling and employing phase reduction, we collapsed the network of bursting neurons represented by 24 ordinary differential equations to 6 coupled nonlinear phase oscillators, each corresponding to a sub-network of neurons controlling one leg. Assuming that the left and right legs maintain constant phase differences (contralateral symmetry), we reduced from 6 equations to 3, allowing analysis of a dynamical system with 2 phase differences between front-to-middle legs ($\theta_1$) and between hind-to-middle legs ($\theta_2$). We analyzed the gait transitions on the reduced toroidal phase space (Figure 6, left and right). We also computed bifurcation diagrams showing branches of gaits vs. speed (Figure 6, middle). Bifurcations occur from multiple stable tetrapod gaits to a unique stable tripod gait as speed increases. Finally, we considered gait transitions in two sets of data fitted to freely walking fruit flies. We showed that coupling data from fruit flies supports our theory.

Figure 4: Network of CPGs

Figure 5: Interconnected bursting neuron model: gait transitions from tetrapod to tripod as speed increases. Width of horizontal bars indicate swing durations. R1, R2, R3 (resp. L1, L2, L3) denote right (resp. left) front, middle, and hind legs.

Figure 6: (Left & Right) Gait transition from multiple stable tetrapod to stable tripod (green dots) through a degenerate bifurcation (combination of pitchforks) and a saddle node bifurcation (middle), as speed increases.
Future Research. This work can be improved mathematically in many different ways. To analyze the model rigorously, and motivated by some experimental data, we simplified the model by reducing the number of parameters and showed gait transition through a very degenerate bifurcation. Then, using singular perturbation theory, we analyzed the degeneracy and showed the existence of a saddle node bifurcation and a less degenerate bifurcation, as Figure 6 (middle) depicts. One can unfold the system further and analyze the degenerate bifurcation shown in Figure 6 (middle). Gait transition in insects occurs in a noisy environment. So far, we studied a deterministic model of CPG. Currently, I am working on investigating gait transition from tetrapod to tripod in the presence of noise.

A “half center oscillator” consists of two neurons that do not fire individually, but produce rhythmic outputs when they are coupled. Parallel to our work, A. Yeldesbay, T. Tóth, and S. Daun have been working on a “half center oscillators” model of CPGs in stick insects and have been using this model to study their gait transitions. An interesting project would be to compare these two models (the bursting neuron and half centre oscillator models) and study different features of each model.

Other Interesting Projects

I addition, I have also explored other projects with applications to a diverse range of systems. Specifically, I worked on the following two projects, which are engaged with human diseases and therapies.

1. PDEs for Chemotaxis

Chemotaxis is important in biological processes as well as in ecology. For example, when a bacterial infection invades the body it may be attacked by movements of cells towards the source as a result of chemotaxis. Convincing evidence suggests that leukocyte (white blood) cells, which are responsible for protecting the body against infectious disease, move towards a region of bacterial inflammation by moving up a chemical gradient caused by the infection.

In [18, 19], we studied the chemotaxis behavior of E. coli. In order to respond to an external signal in the environment, which is usually nutrient, bacteria change their frequency of turning (tumbles) and move directly toward (or away from) the signal (run). A transport (Fokker-Planck) equation describes the motion of individuals whose velocity changes are governed by a Poisson process, at a microscopic level. Since it is difficult to study the solutions of this equation mathematically, it is of great interest to study the movement of bacteria at macroscopic levels and to derive an equation for the density of the population of bacteria starting from microscopic equations. We showed that, in a one dimensional space and in the presence of an exponential gradient, under an appropriate parabolic scaling of space and time, the asymptotic behavior of solutions of such macroscopic equations can be approximated by the solution of an advection-diffusion equation obtained via a regular perturbation expansion. The solution of the advection-diffusion equation matches well with the results from agent-based simulation and data as shown below, [18].

Future Research. Studying macroscopic behavior of bacteria such as E. coli is also a way of studying group behavior in complex systems that I am interested in. In order to refine and extend the above results, it would be interesting to generalize this work to higher dimensions (2 and 3), find a better error estimate, and study the equation that approximates the solution of the Fokker-Planck equation in the presence of a linear gradient.
2. Cancer Modeling

In practice, almost all chemotherapeutic agents lead to drug resistance, but it is a challenge to clinically determine whether resistance arises prior to, or as a result of, cancer therapy. Many different mechanisms can be adopted by cancer cells to resist treatment. These mechanisms can broadly be divided into intrinsic (intracellular) causes and extrinsic (microenvironmental) causes. In [20] we have developed a hybrid discrete-continuous mathematical model wherein cancer cells described through a particle-spring approach respond to dynamically changing oxygen and DNA damaging drug concentrations described through reaction diffusion partial differential equations. We thoroughly explored the behavior of our self-calibrated model under the following common conditions: a fixed layout of the vasculature, an identical initial configuration of cancer cells, the same mechanism of drug action, and one mechanism of cellular response to the drug. We considered one set of simulations in which drug resistance existed prior to the start of treatment, and another set in which drug resistance is acquired in response to treatment. This allowed us to compare how both kinds of resistance influence the spatial and temporal dynamics of the developing tumor, and its clonal diversity. We show that both pre-existing and acquired resistance can give rise to three biologically distinct parameter regimes: successful tumor eradication, reduced effectiveness of drug during the course of treatment (resistance), and complete treatment failure. When a drug resistant tumor population forms from cells that acquire resistance, we find that the spatial component of our model (the microenvironment) has a significant impact on the transient and long-term tumor behavior. On the other hand, when a resistant tumor population forms from pre-existing resistant cells, the microenvironment has only a minimal transient impact on treatment response. Finally, we present evidence that the microenvironmental niches of low drug/sufficient oxygen and low drug/low oxygen play an important role in tumor cell survival and tumor expansion. This may play a role in designing new therapeutic agents or new drug combination schedules.

Future Research. Our model can also be extended to address other important aspects of tumor resistance. In the future, we will investigate different drug scheduling schemes including typical clinical protocols, as well as metronomic and adaptive schedules. Beyond the drug schedule, we can expand the model from considering DNA damaging drugs to considering other drugs with different killing mechanisms, including anti-mitotic drugs or drugs activated in specific microenvironmental conditions (low oxygen or high acidosis). This allows us to further extend our model to study the effects of combinations of drugs. This is especially important, because, in clinical practice, the
treatment is often changed to another therapeutic agent when the tumor cells become resistant to a given drug. However, it has been observed that resistance to one drug is accompanied by resistance to other drugs whose structures and mechanisms of action may be completely different (multiple drug resistance). This poses interesting questions. If the hypothesis of a pre-existing population of resistant cells is true, what mechanisms enable those cells to resist the drug action of the often multiple chemotherapeutic treatments that may be given to a patient sequentially or in parallel? If the hypothesis of gradual emergence of drug resistance is true, what factors contribute to the development of acquired drug resistance? The mathematical framework developed here has the potential to address such multiple aspects of drug resistance in solid tumors and test methods for increasing efficacy of drug combinations.

References


