I am an applied mathematician and mathematical biologist. I am particularly motivated by problems where an underlying spatial structure contributes to the self-organization of a given system. This interest was originally born from a delight in beautiful patterns, but has developed into a desire to understand how the underlying interplay of structure and movement creates self-organization – often in surprising ways. In my work, I have primarily pursued problems in biological applications because these systems are a fruitful source of inspiration where these mathematical motifs arise again and again, and in turn they lead to the development of new mathematics.

Because of these interests, much of my work thus far is motivated by intracellular transport mechanisms. While proteins can be passively transported via diffusion in the cell body, the localization of proteins necessitates a more direct method of transport. To this end, cells also use filament structures called microtubules as avenues for active transport. Proteins are able to bind and unbind to these structures and thus travel directionally along a microtubule. Intracellular transport is crucial for proper cell functionality; malfunctions in intracellular transport have been implicated in a variety of neurodegenerative disorders, including Alzheimer’s disease, Huntington’s disease, and other dementias [AH00, MJ13]. These same intracellular transport mechanisms can also be exploited by harmful viruses in order to travel to the nucleus and replicate [DNS05]. In my doctoral work, I have been focusing on three projects that fall under the broad themes of transport and structure:

1. I have analyzed pattern formation in a partial differential equation model based on two interacting proteins that are undergoing passive and active transport, respectively. This work is inspired by a longstanding problem in identifying a biophysical mechanism for the control of synaptic density in C. elegans [RK99] and leads to a novel mathematical formulation of Turing-type patterns in intracellular transport [BB16, BB17].

2. Together with Sean Lawley and Marie Tuft, we derived an effective stochastic differential equation to describe the motion of a particle that is randomly switching between diffusion and active transport. In particular, we illustrate how our method can be used to describe the intermittent transport of a virus infecting a host cell [LTB15].

3. I am involved in a collaboration to model the spread of parasites on a dynamic social network. We compare agent-based simulations to differential equation models to show that the dynamic nature of a network nontrivially affects the parasite distribution, and that this behavior cannot be captured by the continuous deterministic model.

To investigate these problems, I employ tools from both applied mathematics and theoretical physics, including linear and weakly nonlinear analysis, perturbation theory, adiabatic reduction, symmetric bifurcation theory, and stochastic processes.

**Project 1: Turing pattern formation with active and passive intracellular transport**

*Motivation: Turing mechanisms provide an elegant biophysical explanation for the spatial organization of interacting particles, but existence of these pattern formation mechanisms has gone largely unexplored in the context of intracellular transport.*

The dynamical processes underlying the establishment of synaptic connections during neural development are thought to be critical in learning and memory. Since the proteins and transport mechanisms that regulate synaptic development are conserved across multiple species, considerable insights can be obtained by studying simpler organisms such as the nematode worm Caenorhabditis elegans, see Figure 1. During development, the density of synapses containing the glutamate receptor GLR-1 is maintained despite significant changes in length [RK99]. It is known that this maintenance also requires the protein kinase CaMKII, which regulates the active transport and delivery of GLR-1 to synapses [HMB+13, HWM+15, RK99]. However, a long outstanding problem has been identifying a possible physical mechanism involving diffusing CaMKII molecules and motor-driven GLR-1 that leads to the control of synaptic density [RK99].
Although the above problem arises within the context of neural development, it raises a more general issue regarding self-organization in systems of actively and passively transported particles. That is, the formation of a regularly spaced distribution of synapses at an early stage of development is suggestive of some form of Turing-like pattern formation. The traditional mechanism for spontaneous pattern formation due to Turing [Tur52] is the interaction of two or more passively diffusing chemical species undergoing nonlinear reaction kinetics and having different rates of diffusion [KM94, Mur01]. In joint work with Paul Bressloff, I have proposed an alternative pattern-forming mechanism [BB16], involving the interaction between a slowly diffusing species (e.g. CaMKII) and a rapidly advecting species (e.g. GLR-1) switching between anterograde and retrograde motor-driven transport (bidirectional transport).

To investigate the proposed pattern formation mechanism, we developed a model of three partial differential equations on a 1-dimensional domain with no flux boundary conditions. Our main results are as follows:

1. Using linear stability analysis, we derive the conditions for the emergence of patterns on a 1-dimensional domain of fixed length. This allows us to derive analytic conditions on the parameter $\gamma$, which is the ratio of switching rate and diffusion coefficient to active transport velocity. We find an expression for the critical value of $\gamma$ below which instabilities arise. This is analogous to the previous results obtained in reaction-diffusion equations, where pattern formation requires fast (long-range) inhibition.

2. Pattern formation arises outside of the fast switching parameter regime, i.e. when bidirectional switching rate $\alpha = O(\epsilon^{-1})$. It would be natural to suppose that patterns arise in this transport mechanism because the bidirectional switching in some sense "acts like" diffusion. However, this is not the case: in the adiabatic limit, this system reduces to a reaction-diffusion equation that does not satisfy the necessary conditions for pattern formation.

3. This pattern formation mechanism is robust to asymmetries in transport velocities. There is a growing literature on pattern formation in 1D reaction-diffusion-advection equations, where one typically considers a finite or semi-infinite domain with some form of forcing at one end [SS00, SM00, SMM00, SMM01]. The combination of forcing, advection, diffusion and nonlinear reactions can lead to so-called stationary flow-distributed structures (FDS). We have derived analytical conditions under which the biased version of our model supports the analog of an FDS, yielding patterns that persist in time.

4. If the domain grows isotropically, this system can continue to self-organize and stripes can be inserted to maintain patterns. Following the work of Crampin et al. [CGM99], we derive evolution equations for the growing domain by rewriting spatial position using a Lagrangian coordinate description and applying Reynolds's transport theorem. Under this transformation, the domain growth can be interpreted as time-dependent diffusion and velocity coefficients, representing dilution and local flow. In this formulation, we then show that this mechanism supports pulse insertion on the growing domain.

With biologically relevant parameter values, our model produces 4 evenly distributed peaks of GLR-1 in a 10 $\mu$m segment of ventral cord, which matches what is observed in the biological data. The density of the GLR-1 peaks is also maintained under slow logistic growth of the domain (Figure 2). Thus, we hypothesize that the C. elegans system is regulated via the Turing-type mechanism we describe, and our model can provide experimentally testable predictions of this mechanism, particularly with regard the spacing of synapses. More precisely, linear stability analysis can determine the wavelength of emerging patterns as a function of various biophysical parameters such as the diffusivity of CaMKII and the speed and switching rates of molecular motors. Our model predicts that manipulation of these parameters should change the synaptic spacing, but the insertion of new synapse sites should persist.
Future directions.

1. Linear stability analysis allows us to derive conditions to understand when and how patterns arise in a particular system, but it does not give us any information about the selection and stability of these patterns - these features are determined by the nonlinearities of the system. In order to investigate the stability of the periodic patterns that arise in the 1-dimensional model, we can perform a weakly nonlinear stability analysis. Using the method of multiple scales, one can derive an amplitude equation to describe the slow timescale evolution of patterns. It is important to note that, since patterns do not arise in the fast switching limit, this analysis must be applied to the full model.

2. We will explore whether Turing-type instabilities can arise with a 2-dimensional version of this hybrid transport model, where it is necessary to consider the microtubular network configuration. If we assume that the microtubule network is locally disordered and sufficiently dense, we can make the simplifying homogenization assumption that all velocity directions are possible independent of position. Alternatively, one can suppose that the microtubules are arranged in a dense mesh in the plane, which is formed by a regular planar lattice. For a given lattice type (e.g. square or hexagonal), there will be a corresponding group generated by the rotations and reflections that preserve the lattice. We can exploit this group structure to study the bifurcations of the solutions. In general, unlike the classical reaction-diffusion models, the full hybrid reaction-transport equations has an oriented structure which explicitly breaks \(O(2)\) symmetry. However, we can exploit the existing shift-twist symmetries of the system to understand selection and stability of patterns in higher dimensions. The same shift-twist Euclidean group action occurs within the context of continuum neural field models of primary visual cortex, where non-local interactions are mediated by axonal connections between neurons that are tuned to respond to oriented visual stimuli [BCG01, BCGT01, TC04]. These symmetries have not yet been explored in the context of transport models.

Project 2: Effective stochastic differential equation for virus trafficking

Motivation: Random switching introduces interesting dynamics into intracellular transport, and careful mathematical analysis is required to capture how domain geometry affects stochastic processes.

Cells rely on the transport structures to ensure proper cell function. However, these transport mechanisms can also be exploited by viruses. Viruses lack cellular structure and metabolism, and thus are unable to replicate themselves; they rely on the infrastructure of infected host cells for this purpose. In order for a virus to replicate itself successfully within its host, it needs to navigate to the cell’s nucleus, all without any of its own locomotion mechanisms [DNS05]. Single particle tracking experiments [AGK06, SRE01] show that viral motion alternates between passive diffusion in the cytosol and ballistic transport along microtubules. This erratic, alternating motion behavior makes quantitative analysis difficult.

Most of the mathematical work on this topic takes an effective stochastic differential equation as a starting point for study of these processes [Hol07, LDH09]. There exists a previous reduction of the full process to an SDE due to Lagache and Holcman [LH08], but this method is only applicable for 2 dimensional cell geometries. Furthermore, their method captures only the mean first passage time for the virus to reach the nucleus and not the mean first passage time distribution.
In this work, joint with Sean Lawley and Marie Tuft, we developed a method to derive an effective stochastic differential equation (SDE) that encapsulates the switching transport dynamics and captures several important features of the associated probability distributions when compared to Monte Carlo simulations of the full process (See Figure 3 for an illustration of this process cell modeled by a 2-dimensional disk). In order to write down an SDE with the correct drift and diffusion coefficients, we need to know the probability that the virus is on a microtubule given its radial position. By partitioning (or ‘coarse-graining’) the space between the microtubules and approximating diffusion as a Markov jump process on this partition, we are able to use the adiabatic limit to approximate the proportion of time spent on a microtubule.

Our primary results are as follows:

1. Our effective SDE matches the empirical first passage time distributions generated by numerical simulations of the full intermittent process (Figure 4). This is in contrast to previous work by other groups, which only matched mean first passage times. We also show that the distribution of viral position $x$ at various times $t$ corresponds well with the full process for all geometries that we explored.

2. Due to the generality, our coarse-graining method can be applied to a variety of cell geometries. In particular, we have derived an effective SDE for virus trafficking in a 3-dimensional spherical cell as well as a 3-dimensional cylindrical cell, in addition to the 2-dimensional disk model described above.

Future directions.

1. Incorporating detailed biophysics of particular viruses into this method would allow biologists and theoreticians to better understand the dynamics of specific viral infections. We have not yet considered the biochemical interactions a particular virus undergoes during its journey through the cell, and this has potential for a fruitful collaboration to understand how the transport of particular viruses are affected. This also provides potential to consider physical extensions to the model, such as bidirectional transport and alternate microtubule lattice structures.
2. This method allows us to explore other applications with intermittent transport. For example, this method can be applied to animal transport models in ecological systems. In the Alberta Boreal forests, oil and gas exploration has led to a number of linear cuts through the forest called “seismic lines”. GPS data show that wolves are using these seismic lines to travel more efficiently through the forest, thus increasing their ability to locate and kill endangered caribou [LLBB11, MLM09]. In collaboration with Mark Lewis, we intend to extend our method to develop an SDE to explore how the density of seismic lines affects wolf transport, i.e. by investigating their first passage time to reach a particular site.

**Project 3: Parasite spread on dynamic social networks**

Motivation: Dynamic network structure plays a crucial role in resulting distributions, and parasite spread is tied explicitly to the structure of the network.

A population’s evolutionary fitness is inherently tied to its social structure. On one hand, social animals experience group fitness benefits such as predator protection or increased ability to locate resources. However, due to close contact, these social groups may be more susceptible to infection from pathogens or parasites. Previous work has shown that different social systems yield different epidemic burdens for pathogens, which raises the interesting question of whether pathogen spread is a result of complex social network structure or whether such structures evolved to mitigate the effects of pathogens [HF12]. As yet, no such studies have examined the results of parasite infection in dynamic social networks, despite the fact that parasite transmission and infection is deeply intertwined with social behaviors like allogrooming.

This collaboration with Nina Fefferman, Maryann Hohn, Candice Price, Ami Radunskaya, Suzanne Sindi, Nakeya Williams, and Shelby Wilson examines how parasites alter the optimal social strategies for a population’s evolutionary fitness. We have developed an agent-based simulation of a dynamic social network which organizes according to various social metrics. In particular, we focus on networks that self-organize based on degree (the number of nodes to which a node is connected), closeness (a measure of the average path length between nodes), and betweenness (the percentage of shortest paths from one node in the network to another node). We will use these simulations to explore how pathogen spread differs on networks for each particular measure. This agent-based model also allows us to explore how system parameters such as parasite reproduction and grooming effectiveness alter the infection burden of the population, and whether certain individuals are more influential in determining population risk because of their social standing.

Concurrently with the agent-based model, we have developed a model of ordinary differential equations to represent parasite infection load in a population. By subdividing the population into individuals with various levels of parasite load, we can analyze the steady-state behaviors and gain insight into which model parameters are most influential. Preliminary results show that this continuous deterministic model does not yield the same results as the full agent-based network model. This suggests that the dynamic nature of the network structure plays a critical role in the parasite distribution, and the full spread of parasites in the population cannot be captured by considering homogeneous transmission dynamics alone.

**References**


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