Research Statement

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1 Introduction

My primary interest is analysis and applications of delay differential equations (DDEs). These types of equations are often given less attention by mathematicians due to their unavoidable complexity. Unlike ODEs and PDEs, the presence of delayed arguments makes the associated differential operators nonlocal in time. Intuitively, progressing the solution requires knowledge of the solution's history over an interval rather than just its value at a single point. I chose to study DDEs because there is a solid foundation of knowledge to build upon, but a great richness of unexplored territory to try and uncover.

Furthermore, delays are common and natural in many areas of application, including physics, chemistry, biology, and engineering. A better understanding of this class of equations can improve the interdisciplinary power of mathematical modeling for these fields. My dissertation research specifically focuses on a model of mitochondrial fission that was created in concert with our biology collaborators in the department of internal medicine and cardiology. Our project seeks to examine the essential parameters that regulate a Hopf bifurcation in the rate of mitochondrial fission. This model can be interpreted as a DDE. That is why my research focuses on understanding delay differential equations, their complexities, and and their applications.

2 Dissertation Work

2.1 Mitochondrial Fission

Mitochondria are organelles that provide energy to cells in many living species. Mitochondria, like a whole cell, are capable of splitting themselves into a pair of functioning daughter organelles through a fission process. When stressed, mitochondria can begin to fission rapidly, creating large numbers of small mitochondria. This hyperfission process has been linked to cancer, metabolic disorders, heart disease, and neuro-degenerative diseases including Alzheimer's and Parkinson's[1,4,5,7,9,10]. Thus, it is critical to understand the process of fission in health and disease.

My work at the University of Iowa began with a mathematical model of mitochondrial fission. It was developed by Dr. Anna Leinheiser and my advisor Dr. Colleen Mitchell in concert with our collaborator in the department of internal medicine and cardiology, Dr. Chad Grueter[6]. When exploring the fission process using the Leinheiser et al model it was discovered the model exhibits a Hopf bifurcation. The large jumps in total fission rate in the highly oscillatory regions of parameter space were exactly the kind of rapid fission that could cause health issues. However, due to the complexity of the model, the bifurcation was difficult to study. My goal with this system was to investigate the Hopf bifurcation structure that Dr. Leinheiser numerically approximated in her 2024 paper. A graph illustrating the bifurcation can be found in Panel A of Figure 1.

2.2 Simplified Model

I created a simplification to the Leinhesier et al model that would still have the same qualitative bifurcation structure. The model is as follows:

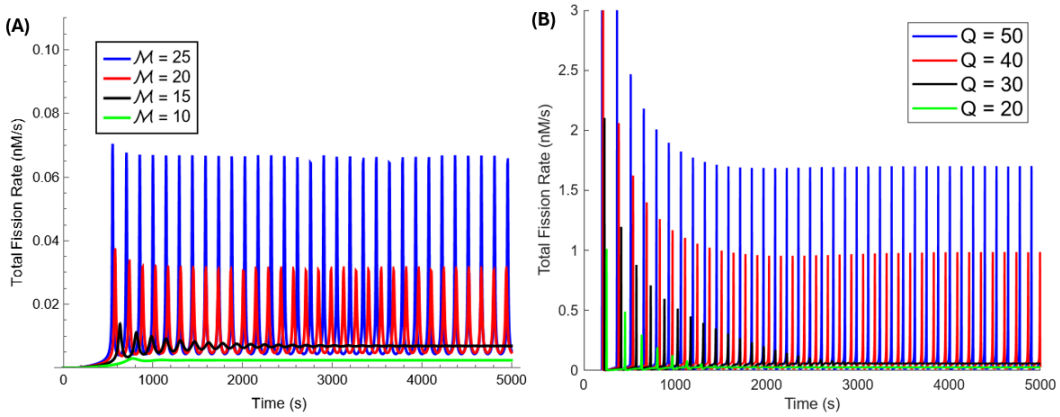

Figure 1: (A) Numerical Simulations of the Leinheiser et al model[6] with parameters $k_+ = 5$, $k_- = .1$, $\ell = 25$, $a = 5$, $k_1 = 1$, $k_{-1} = 0.02$, $\mathcal{T} = 20$, $\gamma = 0.01$, and $N = 30$, showing the transition from stable steady state to stable oscillation as the pool of available fission proteins passes the Hopf bifurcation. (B) Numerical Simulations of the Continuous-Size DDE with parameters $\ell = 25$, $a = 5$, $k = 1$, $k_1 = 1$, and $b = .01$, with varying Q, showing qualitatively similar behavior.

$$\dot{M} = f(i)\sum_{i=1}^{\infty} iC_i - k_1 M$$

$$\dot{C}_1 = k_1 M - bC_1 - k\left(C_1^2 + \sum_{i=1}^{\infty} C_1 C_i\right)$$

$$\dot{C}_i = kC_1C_{i-1} - kC_1C_i - f(i)C_i \quad i \geq 2$$

$$\text{where} \quad f(i) = \begin{cases} b & i < \ell \\ a & i \geq \ell \end{cases}$$

A reaction schematic for this model can be found in Figure 2. In the simplification, the separate concentrations of dynamin-related protein 1 (DRP1) and mitochondrial fission factor (MFF) will be combined into a concentration of "material" represented by M. This is a reasonable approximation when one of the two is in excess so the effective material is governed only by the limiting substrate. Next, the dissociation rate between sizes of oligomers on the outer mitochondrial membrane, k_-, was replaced with an ejection parameter b. At rate b, oligomers of any size can "eject" all of their material back to the material pool. A model with neither k_- nor b did not have the same qualitative behavior as the Leinheiser et al. model and approaches a trivial equilibrium with no fission. Lastly, there is no size cap on oligomers. This is because the original model finds that concentrations of large oligomer sizes quickly go to zero.

2.3 Oligomer size as a continuous variable

Even after these simplifications, the resulting model is unwieldy. I therefore considered a version of the model with oligomer size as a continuous variable. To retain the mathematical structure through this transformation, I had two goals for the resulting continuous-size system: 1. preserve the qualitative behavior including the Hopf bifurcation and 2. retain a conserved quantity analogous to total DRP1 concentration. To do this, I let $\Theta(s,t)$ be the evolving density of oligomers of size s at time t defined for $s > 1$ and $t > 0$.[2] That is, $\Theta(i,t) = C_i(t)$ for $i \geq 1$. For notation's sake I denoted the boundary condition $C_1(t) = \Theta(1,t)$ as simply $C(t)$. One such continuous-size PDE model is:

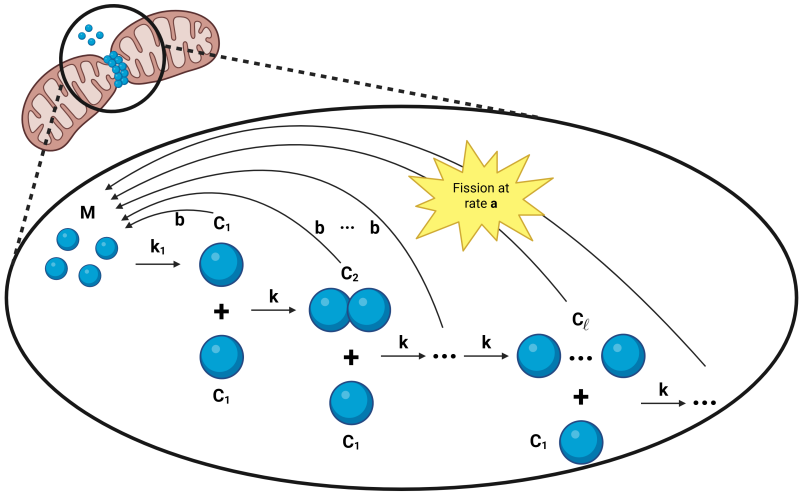

Figure 2: Reaction Schematic for the simplified version of the Leinheiser et al Mitochondrial Fission model.

$$\dot{M} = \int_1^\infty f(u)u\Theta(u,t)du - k_1 M$$
$$\dot{C} = k_1 M - kC^2 - kC\int_1^\infty \Theta(u,t)du$$
$$\frac{\partial \Theta}{\partial t} = -kC\frac{\partial \Theta}{\partial s} - f(s)\Theta(s,t)$$
$$\text{where} \quad f(i) = \begin{cases} b & i < \ell \\ a & i \geq \ell \end{cases}$$

The first term corresponds to the material returned through ejection, while the second is material returned through the fission of active fission complexes. In this set up, we observe that the quantity

$$Q = M + C + \int_1^\infty u\Theta(u,t)du$$

is conserved and strictly positive. In the simulations and transformation below, we consider an initial condition with no oligomers, $C(0) = \Theta(s,0) = 0$ and an instantaneous addition of material $M(0) = Q$. An example $\Theta(s,t)$ surface with these initial conditions can be seen in Figure 3. Such a system is mathematically rich by its form alone. The equation for $\dot{C}(t) = \frac{\partial \Theta(1,t)}{\partial t}$ acts as a boundary condition on the PDE, but contains multiple terms with non-local information about $\Theta(s,t)$. Further, the velocity in the advection term is proportional to this boundary condition.

2.4 Transformation to state-dependent, threshold delay system

To spotlight the relevance of the inherent delay, the system will be transformed into a state dependent threshold delay system. The first step is to replace the integral terms with new variables: $n_1(t) = \int_1^\ell \Theta(u,t)du$, and $n_2(t) = \int_\ell^\infty \Theta(u,t)du$ (the total concentration of oligomers of non-fission and ready-to-fission sizes respectively, denoted n_i for number), as well as $m_1(t) = \int_1^\ell u\Theta(u,t)du$, and $m_2(t) = \int_\ell^\infty u\Theta(u,t)du$ (the total concentration of the building blocks that make up the oligomers of non-fission and ready-to-fission sizes respectively, denoted m_i for mass or moment). Using integration by parts to calculate the derivatives of these new variables introduces terms containing $\Theta(\ell,t)$. However, we can solve for $\Theta(\ell,t)$ explicitly using the method of characteristics because $kC > 0$ for all time. Tracing back along characteristics leads to either

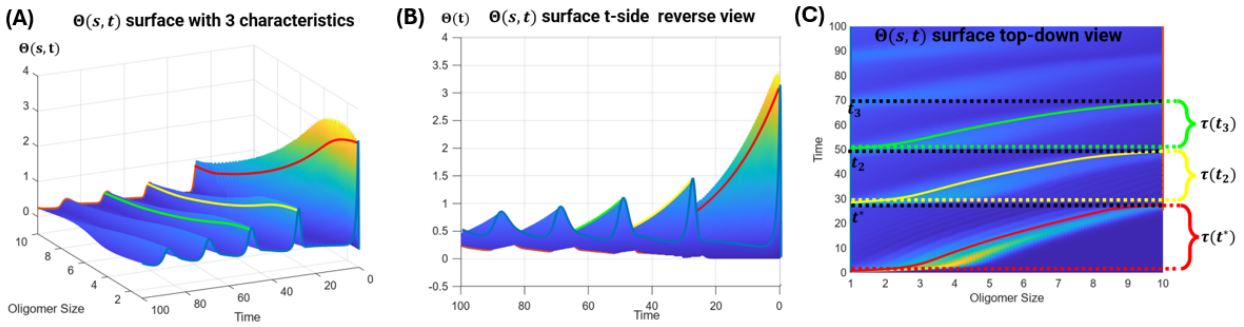

Figure 3: (A) Numerical simulation of the $\Theta(s,t)$ surface created by simulating $C(t)$ using the DDE form of the system and then using that $C(t)$ as a prescribed boundary condition for the PDE equation. The DDE was solved using the parameter set: $\ell = 10$, $a = 5$, $k = 1$, $k_1 = 1$, $b = .05$, and $Q = 20$. Three characteristics are graphed on top of the surface. (B) The same surface from a side-on perspective. Note that to make the characteristics visible, the graph is reversed, with time 100 on the left side and time 0 on the right. From this perspective, the exponential decay behavior along the characteristics is clear. (C) The same surface from a top-down perspective. At time t_i one can see the corresponding characteristic intersects size $\ell = 10$. Following the characteristics back through size and time, the associated $\tau(t_i)$ is revealed as the time in the past where the characteristic intersects size 1.

the initial condition of $\Theta(s,0)$ for $t < t^*$ or to the evolving boundary condition $C(t) = \Theta(1,t)$. This allows us to define $\Theta(\ell,t) = C(t-\tau)e^{-b\tau}$ for $t > t^*$[8]. Example characteristics are shown in Figure 3. This delay, τ, is defined by the time it takes a cohort of oligomers to grow from size 1 to size ℓ. The equation for this is $\int_{t-\tau(t)}^{t} kC(u)du = \ell - 1$. Since $C(t)$ changes over time, $\tau(t)$ also changes over time and can be viewed as an additional state variable in the delay system. A delay of this form is called a threshold delay; it describes the time it takes an oligomer to reach the threshold size.

$$
\begin{aligned}
\dot{M} &= bm_1 + am_2 - k_1 M \\
\dot{C} &= k_1 M - kC^2 - kC(n_1 + n_2) \\
\dot{n}_1 &= -kC(\Theta_\ell - C) - bn_1 \\
\dot{m}_1 &= -kC(\ell\Theta_\ell - C - n_1) - bm_1 \\
\dot{n}_2 &= kC\Theta_\ell - an_2 \\
\dot{m}_2 &= kC(\ell\Theta_\ell + n_2) - am_2 \\
\Theta_\ell &= \begin{cases} 0 & t < t^* \\ C(t-\tau)e^{-b\tau} & t \geq t^* \end{cases} \\
\int_{t-\tau}^{t} kC(u)du &= \ell - 1
\end{aligned}
\tag{1}
$$

Theorem: System 1 undergoes a Hopf bifurcation.

Proof Outline: The complications introduced by the delayed form of this system require a unique approach to finding the areas of parameter space where a Hopf bifurcation occurs. Due to the $e^{-b\tau}$ term, the equations for the steady states of system 1 are transcendental equations, and must be solved numerically. This means a parameter scheme must be selected *before* the steady states can be calculated. After linearizing about the numerically calculated steady state, one can solve for the eigenvalues of the linearization as in a usual bifurcation investigation. The proof is completed by showing all the steps in the calculation process are continuous and applying the Intermediate Value Theorem to prove the bifurcation must occur between two particular parameter schemes. For example, by performing these steps with $a = 5$, $k = 1$, $b = .01$, $k_1 = 1$, $\ell = 25$, and $Q = 38$ one finds the eigenvalues with the largest real part to be $-0.000088 \pm 0.119i$. Repeating the calculation process with the same parameters except $Q = 39$, one will find the eigenvalues

with largest real part to be $0.000112 \pm 0.12i$. This example bifurcation can be seen in Figure 1 Panel B.

3 Future Directions

The transformation studied in my dissertation can be applied to any model of a similar form to the Leinheiser et al model. For similar polymerization models, the inherent delay structure may already provide insight. Other problems in cellular physiology can be considered, such as microtubule catastrophe[3]. I conjecture that the delay dynamics will lead to oscillations whenever the return to a material pool is sufficiently faster in larger polymers. I can work on a generic transformation from ODE to DDE for the class of Becker-Doring polymerization models.

This project has ample space for undergrad research projects. The specifics of the transformation require many steps and calculations, but are not too daunting as long as an example is provided. If I am given the opportunity, I would love to set up an undergraduate researcher with several tweaks to the method and allow them to perform the transformation and investigate the properties of the resulting systems.

One of the critical simplifications that was made to the Leinheiser et al. model to allow the transformation to the DDE above was the removal of the k_- term for dissociation of building blocks one at a time. When attempting the transformation on a model with k_- included, the resulting PDE equation includes both a diffusion term and an advection velocity that may be positive or negative. This means the straightforward method of characteristics described above cannot be applied, I can investigate other similarity solutions or approximate solutions to this full system.

The Leinheiser et al. model has a constant fission rate, a, for all active fission complexes. I kept this form of the fission term for my simplified model. I propose to study more general models that have fission functions that are not step functions. In the simplest PDE version, this can be written

$$u_t + v(u_0)u_s = b(s)u,$$

$$\text{with boundary condition} \quad u(0,t) = u_0 \text{ where } {u_0}' = g\Big(u_0, \int sb(s)u(s,t)ds, \int u(s,t)ds\Big).$$

This novel formulation will be studied in the context of existence, uniqueness and stability of solutions.

As with any mathematical endeavor, the limits of this work don't stop at biology. Delays are common in the natural world and in many other sciences. Further study of the mathematical structure of delay equations is crucial to improving the interdisciplinary power of mathematical modeling. That is why my research focus is analysis and applications of DDEs across any relevant field.

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