A Nonlocal Model for the Segregation of Axonal Microtubules and Neurofilaments in Neurodegenerative Diseases

A Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Mathematical Sciences in the Graduate School of The Ohio State University

By

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Abstract

Both the shape and function of an axon depend critically on the organization of its cytoskeleton, which is a dynamic system of intracellular polymers including microtubules, neurofilaments and actin microfilaments. Under normal conditions, microtubules and neurofilaments align longitudinally in axons and are interspersed in axonal cross-sections. However, in many neurodegenerative disorders, they separate radially with microtubules clustered centrally and neurofilaments located near the periphery. This striking polymer segregation proceeds to focal accumulations of neurofilaments and/or organelles that are early hallmarks of nerve degeneration. A recent stochastic model of the phenomena suggests that this segregation is a consequence of the disruptions of neurofilament transport along microtubules, and in the absence of neurofilament transport, axonal organelles pull microtubules to the center and displace neurofilaments to the periphery. Motivated by these results, we develop a nonlocal PDE model for the cross-sectional distribution of axonal microtubules and neurofilaments in this thesis, and use it to systematically analyze how different balances of organelle transport and neurofilament transport affect the cross-sectional organization of microtubules and neurofilaments. Results of the PDE model agree tightly with the results of the stochastic model and experimental data. Through modeling we highlight the importance of incorporating cargo interactions in addressing biological questions related to axonal transport.
Acknowledgments

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Chapter 1: Introduction

1.1 Motivation

An axon is a long thin projection of a neuron that allows rapid electrochemical communications with other cells over long distances. The ability of an axon to maintain its shape and function is critically dependent on its cytoskeleton — a dynamic system of intracellular polymers including microtubules, neurofilaments and actin microfilaments.

Microtubules are long polarized polymers that align axially along the axon, with plus end pointing away from the cell body. They form an overlapping array from the cell body to the axon terminal [20, 22], and serve as highway tracks for the long-range transport of membraneous organelles and macromolecular proteins called axonal transport [4, 9]. Axonal transport is powered by kinesin and dynein molecular motors, which move cargo towards the plus and minus ends of microtubules respectively [11].

Neurofilaments are the intermediate filaments of neurons. They are long non-polarized polymers that function as space-filling structures to increase the axonal caliber [18], and occupy most of the axonal volume in large axons [7]. In addition to their structural role, they also undergo infrequent bidirectional transport along microtubules, which consists of short bouts of movements interrupted by prolonged pauses [3, 24]. This is different from the axonal transport of organelles which is usually more frequent and more persistent [4].
In healthy axons, microtubules and neurofilaments align along the axon and are interspersed in axonal cross-sections [12, 19, 22]. However, in many toxic neurodegenerative disorders these two polymers separate from each other, with microtubules and organelles located near the center of the axon and neurofilaments displaced to the periphery near the axonal membrane, as illustrated in Figure 1.1. For further information, please see [25] for a comprehensive list of references.

This striking polymer separation has been studied most extensively in axons treated by the toxin 3,3’-iminodiproprionitrile (IDPN). Systematic administration of IDPN to rats causes selective impairment of neurofilament transport, massive focal accumulations of neurofilaments, and neurological symptoms similar to amyotrophic lateral sclerosis (ALS) in humans [14, 15, 17]. Microtubules and neurofilaments have been observed to segregate within hours after IDPN injection, preceding local accumulations of neurofilaments and axonal swelling by hours or days. Moreover, the segregation has been shown to be reversible, as has the disruption of neurofilament transport [17].

These phenomena were discovered over 30 years ago, but the underlying mechanisms are still largely unexplored. One specific question regards the relation between impairment of neurofilament transport and their segregation from microtubules. It is clear that if neurofilaments are separated from microtubules, then they can not be transported along microtubule tracks. However, it is not known if extra mechanisms are needed to explain the polymer segregation.

To address this question, a stochastic particle-based model for the cross-sectional distribution of microtubules, neurofilaments and organelles in a circle representing a cross-section of an axon was recently developed [25]. It incorporates the stochastic motor cross-bridges between microtubules and engaged cargoes, i.e., organelles or neurofilaments, as elastic spring forces between the particle pairs. It describes the longitudinal transport of
Figure 1.1: Segregation of microtubules and neurofilaments in experiments. (A) Schematic drawing that illustrates the normal distribution of microtubules (large black dots), neurofilaments (small grey dots) and organelles (cyan disks) in untreated axons. (B) Schematic drawing that illustrates the segregated components in IDPN-treated axons. (C) In normal axons microtubules, neurofilaments and organelles are interspersed in axonal cross-section. Big dots: microtubules; small dots: neurofilaments; objects: organelles. (D) In axons treated by neurotoxin IDPN these components segregate radially, with microtubules and organelles located in the center and neurofilaments migrated to the periphery. The black region outside of the axon is the myelin sheath. The scale bars are 1 $\mu$m. Adapted from [17]. Originally published in Journal of Cell Biology, 91:866-871.

these particles as random additions and removals. It also includes volume exclusion and Brownian motion of all the particles. Simulations of the model demonstrated that in the absence of neurofilament transport, organelles can pull microtubules together and segregate them from neurofilaments within hours, in a similar way as observed in experiments. The
model also predicted that (1) the extent and rate of microtubule-neurofilament segregation depends on the flux rate and size of the moving organelles; and (2) during the segregation process, microtubules form small clusters which eventually merge into a single big cluster over time. Because particle binding, unbinding, addition and removal occur on a time scale of seconds or shorter, the model has to be simulated on a time scale of milliseconds to ensure accuracy. Because polymer segregation occurs on a time scale of hours, the model is computationally expensive.

In this paper, we develop a continuum model for the microtubule-neurofilament segregation phenomena, based on insights gained from the stochastic model in [25]. The model consists of a system of two nonlocal PDEs that describe the densities of microtubules and neurofilaments, and the “zippering effect” of organelle transport is included implicitly as a means of indirect microtubule-microtubule interaction. We use the model to systematically analyze how different balances of organelle transport and neurofilament transport affect the distribution of microtubules and neurofilaments. The nonlocal integrals comes from the fact that particle interactions occur within a capturing radius.

1.2 Organization of this Thesis

The remainder of this thesis is organized as follows.

Chapter 2 will introduce the basic biological background necessary for future chapters as well as provide a description of the biological problem to be studied and the prior models used to study it.

Chapter 3 will introduce the model used to study the problem that is based on previous stochastic models along with the results of recent papers. The parameters used to populate the model along with its non-dimensionalization will also be introduced.
Chapter 4 will analyze the model in the 1D case using linear stability analysis. Numerical simulations of the model using both periodic and no-flux boundary conditions will also be presented to highlight both key behaviors and the effects of the boundary on the system.

Chapter 5 will then consider the 2D case of the model on a square domain with periodic boundary conditions using both linear stability analysis and numerical simulations to determine whether dimension has a significant effect on the behavior of the model.

Chapter 6 summarizes the main results of the thesis, and considers possible directions of future work.
In this chapter we shall introduce the information necessary to understand the biological problem posed, as well as the models previously used to study similar behaviors.

2.1 Biological Background

How are axons structured? As the foundation of the nervous system, neurons are able to communicate rapidly with one another in networks that can span vast distances in response to sensory input using a combination of chemical and electrical signals. While the finer details of the structure can vary to some degree, all neurons possess a similar overall form, as shown in Figure 1. The large, roughly circular object forming the center of the neuron is the cell body, and it contains the neuron’s nucleus, a portion of its organelles, along with the many of the other cellular components shared among eukaryotic cell types. The small projections away from the cell body are dendrites; they serve as the cell’s receivers, as they house the chemical receptors that allows the neuron to receive chemical signals sent by nearby neurons using neurotransmitters. While similar in visual form to the dendrite, the long, winding appendage to the cell is called the axon, and its function is to transmit outgoing information away from the cell body in the form of rapid short electrical impulses towards the axon terminal which will then be converted into a chemical messages and sent to nearby neurons [5].
What are axonal polymers? As the axon is the most significant pathway through which outgoing information is delivered, its structure is of utmost importance to the proper functioning of the neuron as a whole. The axon’s rigid, tubular structure, as shown in Figure 2.2 (a), is given to it by the dynamic scaffolding called the cytoskeleton, which is composed of microtubule, neurofilament and smaller actin microfilaments polymers, each of which is composed of smaller protein subunits. Microtubules are the largest of these three polymers, and as shown in Figure 2.2 (b), are polarized, hollow helical tubes of protofilaments approximately 25nm in diameter. In addition to maintaining the axon’s shape, microtubules act as scaffolding for molecular motors to bind onto and serve as highways for the flow of intra-axonal transport [26]. Neurofilaments, a subclass of intermediate filaments, are smaller than microtubules at a diameter of approximately 10nm and are un-polarized. As
seen in Figure 2.2 (c), neurofilaments share a common structure of protein subunits forming α-helix backbone and that backbone being attached to numerous smaller amino acid sidearms. Neurofilaments do not participate directly in axon transport beyond serving as cargo, instead they play a crucial role in providing tensile strength to the axon and allow it to maintain its tubular shape in the presence of outside mechanical pressure [6]. Microfilaments, the smallest of the polymers, are composed of linear strands of actin proteins and have a diameter of approximately 6-7nms. Microfilaments provide the cytoskeleton with much needed motility due to naturally rapid binding and unbinding behavior of actin.

Figure 2.2: (A) A schematic diagram of an axon showing its structural components. Not pictured: actin filaments. Adapted from [3]. (B) A schematic diagram of microtubule structure showing its approximate diameter. Adapted from [23]. (C) A schematic diagram of a neurofilament showing its structure and appendages.

**What is axonal transport?** While organelles and proteins are required by every part of the neuron, they are only produced in the soma. In order to remedy this, cells employ
the aid of molecular motors to transport cargo throughout the cell along microtubules in a process collectively called axon transport. These molecular motors can be divided into kinesins and dyneins, with kinesin motors carrying cargo away from the axon body and dynein motors carrying cargo towards it. The process of axon transport itself is jerky, with motors frequently switching between rapid movement forward and backward and periods of rest in which no forward or backward movement occurs. The relative balance of these two actions is what separates fast axon transport from slow axon transport. Fast axon transport, which can move cargo at a rate of up to 20cm per day and is characterized by long periods of rapid movement and relatively few periods of inactivity. The organelles’ ability to bind to multiple motors which each then bind to separate microtubules is what allows organelles to have a ‘zippering’ effect upon microtubules. By contrast, slow axon transport moves cargo such as neurofilaments and other collections of cytoskeletal proteins at rates below as 1mm per day [21]. While the forward movement in slow axon transport is no less rapid than in fast axon transport, the molecular motors enter the inactive phase much more often, reducing the average rate of travel. While neurofilaments are presumed to be physically able to bind with multiple molecular motors simultaneously, the presumed rate of multiple bindings occur is so low that they are ignored in the model [25].

**How does this relate to neurodegenerative disease?** In healthy neurons, neurofilaments and microtubules align themselves in parallel along the length of the entire axon and form roughly uniform and randomly dispersed mixtures when viewed cross-sectionally with some slight clustering of microtubules near large organelles. This allows for the widest dispersal of neurofilaments and thus maximizes both the diameter and tensile strength of the axon’s shape. This is in sharp contrast to the situation in many neurodegenerative diseases such as Charcot-Marie-Tooth disease and amyotrophic lateral sclerosis, as one of
the defining qualities of these diseases is the radial segregation of microtubules and neurofilaments, with organelles and microtubules forming clusters near the center of the axon and neurofilaments pushed towards the edges. This is presumed to lead to high levels of neurofilaments and organelles accumulating locally, which is a presumed source of axonal swelling that leads to nerve degeneration. While this behavior is able to be induced both reliably and reversibly in the laboratory setting using chemicals — the most common of which is 3′-iminodiproprionitrile (IDPN), a compound related to food poison — the mechanisms behind it are, despite recent work in the area, still rather poorly understood [25].

2.2 Prior Mathematical Models

In [25], the authors created a 2d stochastic multi-scale individual cell-based model to describe the process of axonal polymer segregation. In this model the movement of individual polymers is governed by the system of equations

\[ \frac{dx^k_i}{dt} = \frac{F^k_i}{\mu^k} dt + \sigma_k dW^k_i, \]

where \( x^k_i \) indicates polymer \( i \) of type \( k \) of either microtubule, neurofilament or organelle, \( F^k_i \) indicates the net sum of volume exclusive and molecular motor forces from axon transport, \( \mu^k \) is a drag coefficient for the forces, and \( \sigma_k dW^k_i \) describes Brownian motion. Repulsive volume exclusive force takes the form of

\[ R^{kl}_{ij} = (-\epsilon(L_r/d_{ij}^{kl} - 1) + \epsilon_{ij}^{kl}, \]

where \( R^{kl}_{ij} \) is the force between particles \( i \) and \( j \) of types \( k \) and \( l \), \( \epsilon \) is a force prefactor, \( L_r \) is the maximum binding radius, \( d_{ij}^{kl} \) is the distance between particles, \((x)_+ = \max(x, 0)\), and \( \epsilon_{ij}^{kl} \) is the vector pointing between particles. This allows the repulsive force to point in the direction between particles, allows that force to increase to infinity as the distance shrinks to 0, and allows the force to continuously decay to zero as the distance approaches the
maximum interaction radius $L_r$. For molecular motor forces, the authors’ model uses linear spring force equations given by

$$G_{i,j}^{k,l} = -G_{i,j}^{l,k} = \kappa^k d_{ij} e^{k,l},$$

where $\kappa^k$ is a spring force constant. These equations, when taken to their macroscopic limit form the basis for the continuous PDE model described in Chapter 3. By simulating over the timespan of several hours, the authors are able to show that the model displays reversibly segregative behavior when axon transport for neurofilaments is inhibited, as well as the existence of intermediate states between full segregation and uniformly mixed populations.

In [1], the authors present a continuous 2D PDE model to study the effects of cell-cell adhesion and cell sorting, processes quite similar to axonal polymer segregation. The authors include the effects of standard diffusion as well both intra-population and cross-population adhesion terms, which touches upon everything except for the repulsive volume exclusion force in the general model in Chapter 3. The authors were able to successfully replicate the cell sorting behavior previously observed experimentally in the laboratory, a feat previously reserved for discrete models.
Chapter 3: The Mathematical Model

3.1 The Model

We developed a continuous PDE model analagous to the stochastic one used in [25] to investigate the relationship between the strength and frequency of the formation of intercellular bonds between cytoskeletal polymers and the behaviors of their populations in aggregate. As illustrated in Figure 3.1, we started with a section of an axon that is modeled by a cylinder in 3D, and then restricted the domain of our focus, $\Omega$, to a single cross section of an axon. In this case that cross section $\Omega$ takes the form of a circle of fixed radius. As the aggregate behavior of molecules is our focus, we denote the two variables in $\Omega$, $u(x, t)$ and $v(x, t)$, to be the densities of microtubules and neurofilaments respectively. As the volume fraction of organelles is very small compared with the fraction of microtubules and neurofilaments, we do not track their density explicitly and instead include their effects on microtubules and neurofilaments implicitly.

Under these assumptions the equations for $u$ and $v$ will have the following form:

\[
\begin{align*}
    u_t &= -\nabla \cdot J_u, \\
    v_t &= -\nabla \cdot J_v,
\end{align*}
\]
Figure 3.1: A schematic of the 2D domain $\Omega$. A cross section of a cylindrical 3D axon results in $\Omega$ being a circle of fixed radius.

where $J_u$ and $J_v$ are the fluxes of $u$ and $v$ in $\Omega$ respectively. It is worth noting that this flux is in the $x-y$ directions within $\Omega$, and not the longitudinal $z$ direction. The above equations follow the principle of conservation of mass and can be derived using standard control volume methods.

The three main contributors to the movement of microtubules in $\Omega$ are the elastic spring forces generated by molecular motors that bridge microtubules and their cargo during axon transport, volume exclusive forces generated by other particles, and random Brownian motion. Thus we can decompose the flux $J_u$ into

$$J_u = J_u^D + J_u^{VE} + J_u^A,$$
where $J^D_u$ is a passive flux due to diffusion, $J^{VE}_u$ is a passive flux due to particle crowding, and $J^A_u$ is an active flux due to microtubule-cargo binding.

We describe the diffusion passive flux $J^D_u$ as

$$J^D_u = -D_1 \nabla u$$

using Fick’s law with an effective diffusion coefficient $D_1$. The volume exclusive passive flux $J^{VE}_u$ can be described either using the results from [25] as

$$J^{VE}_u = \varepsilon_r \int_{\Omega \cap B_{r_0}(x)} (y - x) \left( u(y, t) + v(y, t) \right) dy$$

where $\varepsilon_r$ is a force prefactor and $r_0$ is the maximum interaction radius for volume exclusive forces, or $J^{VE}_u$ can be described as

$$J^{VE}_u = -\eta_1 u \nabla (u + v)$$

using the results formally derived for interacting particle systems with repulsive potentials in [2], where the flux is proportional to the gradient of the total density of microtubules and neurofilaments. For the purposes of this thesis we shall use the second form of the volume exclusive flux.

To describe the active flux $J^A_u$, we first note that both organelles and neurofilaments are moved as cargo along microtubules via kinesin and dynein motors. As organelles can interact with several microtubules simultaneously due to their large size [8], they can draw nearby microtubules closer together as they move axially [27]. This mechanism provides a means of indirect interaction between microtubules, which, as illustrated in Figure 3.2, can be described using spring forces between microtubule pairs within a set interaction distance. Taking this into account, we represent the net spring forces $K^a_u$ acting on microtubules at a position $x$ by summing the per-particle spring force at each location $y$ in the domain multiplied by the total density of particles of that type at $y$. In integral form, $K^a_u$ will take the form:
Figure 3.2: A schematic of the indirect MT-MT interaction force. The forces between MTs and organelles are projected onto the direction between MTs and MTs.

\[
K_u^v(u, v) = k_1 \int_\Omega G_{r_1}(y - x)u(y, t)dy + k_2 \int_\Omega G_{r_2}(y - x)v(y, t)dy, \tag{3.3}
\]

where the force functions \(G_{r_i}\) are taken to be linear spring force functions proportional to the distance between particles within a maximum binding radius, and are thus given by

\[
G_{r_i}(x) = x\chi_{|x|<r_i} \quad i = 1, 2. \tag{3.4}
\]

Here \(k_1\) and \(k_2\) are spring constants for the molecular motor bridges between microtubule-microtubule and microtubule-neurofilament pairs multiplied by the average fraction of time these particle pairs are engaged, and \(r_1\) and \(r_2\) are the maximum interaction radii determined by the length of the motors and size of the respective cargo. As the movement of
microtubules is viscous-dominated, the active flux $J^A_u$ can be described as

$$J^A_u = uK^a_u(u,v)/\mu_1,$$

where $\mu_1$ is the drag coefficient of a microtubule in the lateral direction.

In summary, the equation for the microtubule density has the form

$$\frac{\partial u}{\partial t} = D_1 \Delta u + \nabla \cdot (\eta_1 u \nabla (u+v)) - \frac{1}{\mu_1} \nabla \cdot \left[ uK^a_u(u,v) \right],$$

with $K^a_u$ given in 3.3. The equation for neurofilament density can similarly be written as

$$\frac{\partial v}{\partial t} = D_2 \Delta u + \nabla \cdot (\eta_2 v \nabla (u+v)) - \frac{1}{\mu_2} \nabla \cdot \left[ vK^a_v(u,v) \right],$$

with

$$K^a_u(u,v) = k_2 \int_{\Omega} G_{r_2}(y-x)u(y,t)dy,$$

where $\mu_2$ and $D_2$ are the drag and diffusion coefficients of neurofilaments and $\eta_2$ measures the repulsive forces for volume exclusion. As there is currently no known mechanism for cross-bridging two neurofilaments, the active flux for neurofilaments only incorporates microtubule-neurofilament interactions.

As the uniform steady state $(u,v) = (u_0,v_0)$ exists for the system, the initial conditions for the system can always be represented as some perturbation away from the uniform steady state. Thus it is reasonable to represent our initial conditions as

$$u(x,0) = u_0 + \eta u_1(x), \quad v(x,0) = v_0 + \eta v_1(x) \quad \text{in} \quad \Omega.$$

While the axonal membrane is selectively permeable to certain compounds such as calcium ions used in signal propagation, in general it is relatively non-porous. Thus the most natural boundary conditions for our domain $\Omega$ are no-flux boundary conditions, which are examined in Chapter 4 and are given by

$$\left( - D_1 \nabla u - \eta_1 u \nabla (u+v) + \frac{1}{\mu_1} uK^a_u(u,v) \right) \cdot n = 0,$$

$$\left( - D_2 \nabla v - \eta_2 v \nabla (u+v) + \frac{1}{\mu_2} vK^a_v(u,v) \right) \cdot n = 0.$$
For numerical simplicity and ease of computation, in most cases periodic boundary conditions will be used in the analysis.

### 3.2 Parameters

When it comes to parameters, this model experiences a slight advantage over others in that the parameters used have estimates that have been narrowed down to a reasonable degree in previous literature [10, 13, 25]. The exceptions to this are the microtubule-neurofilament binding constant $k_2$ which can be inhibited both chemically and through disease, the radius for microtubule binding $r_1$ which varies with the size of adjacent microtubules, and the microtubule-microtubule binding constant $k_1$, which varies based on the flux rate of organelles in the axon. In subsequent sections we shall choose 200nm as a conservative estimate for $r_1$, while $k_1$ and $k_2$ will be the parameters of interest and will thus be allowed to vary within a reasonable range. The parameters have been summarized in Table 3.1.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Values</th>
<th>Notes and Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_1$</td>
<td>MT diffusion coefficient</td>
<td>$8.02 \times 10^{-6} \mu m^2/s$</td>
<td>Based on Brownian motion; $D_1 = k_B T/\mu_1$</td>
</tr>
<tr>
<td>$D_2$</td>
<td>NF diffusion coefficient</td>
<td>$5.59 \times 10^{-5} \mu m^2/s$</td>
<td>$D_2 = k_B T/\mu_2$</td>
</tr>
<tr>
<td>$\mu_1$</td>
<td>MT drag coefficient</td>
<td>512 pN $\cdot$ s/µm</td>
<td>[25]</td>
</tr>
<tr>
<td>$\mu_2$</td>
<td>NF drag coefficient</td>
<td>73.5 pN $\cdot$ s/µm</td>
<td>[25]</td>
</tr>
<tr>
<td>$\eta_1$</td>
<td>volume exclusion parameter</td>
<td>2.5161 $\times 10^{-6} \mu m^4/s$</td>
<td>See $\eta_i$ Calculations</td>
</tr>
<tr>
<td>$\eta_2$</td>
<td>volume exclusion parameter</td>
<td>1.7527 $\times 10^{-5} \mu m^4/s$</td>
<td>See $\eta_i$ Calculations</td>
</tr>
<tr>
<td>$r_1$</td>
<td>Max radius for MT-MT binding via organelles</td>
<td>120 – 400 nm</td>
<td>[10, 25]</td>
</tr>
<tr>
<td>$r_2$</td>
<td>Max radius for MT-NF binding via molecular motors</td>
<td>100 nm</td>
<td>[10, 25]</td>
</tr>
<tr>
<td>$k_1$</td>
<td>Spring constant for organelle-MT binding $\times$ fraction of time bound</td>
<td>0.9pN/nm $\times \alpha$, a small variable-rate factor</td>
<td>The variable rate depends on organelle flux [25]</td>
</tr>
<tr>
<td>$k_2$</td>
<td>Spring constant for MT-NF binding $\times$ fraction of bound</td>
<td>either 0.18pN/nm $\times 1/15$ in the normal case, or 0 if inhibited</td>
<td>[25]</td>
</tr>
</tbody>
</table>

Table 3.1: Full Model Parameter Values
3.2.1 \( \eta_i \) Calculations

Based on the results in [2], \( \eta_i \) will take the form \( \eta_i = \int_{\mathbb{R}^2} V(x)\,dx/\mu_i \), where \( V(x) \) is defined to be the repulsion potential that goes to 0 as \( x \) goes to infinity. Thus in order to calculate \( \eta_i \), the value \( \eta_i = \int_{\mathbb{R}^2} V(x)\,dx \) must be known. As \( V(x) \) is the repulsion potential, it can be calculated as the integral of the repulsion force, which for our model is governed by \( F_{r_0}(x) = -\left( \frac{r_0}{|x|} - 1 \right)_+ e_x \), where \( r_0 \) is the maximum interaction radius and \( e_x \) is the elementary vector pointing at \( x \). Under this condition, the repulsion potential will have the form

\[
V(r) = \begin{cases} 
-r_0 \log\left( \frac{r}{r_0} \right) - (r_0 - r) & r < r_0 \\
0 & r > r_0.
\end{cases} \tag{3.10}
\]

If we integrate this function over \( \mathbb{R}^2 \), we get:

\[
\int_{\mathbb{R}^2} V(x)\,dx = \frac{\pi r_0^3}{6}.
\]

3.3 Nondimensionalization

As the choice of units for time, space and density can all potentially have a significant effect on the behavior of the models, we use the technique of non-dimensionalization on the systems to remove such effects. To do this, we select a length scale \( L_0 = 200 \text{nm} \), a time scale \( T = 1 \), a force scale of \( F = 1 \text{pN} \), and a density scale \( U \) using an estimated average density of 10 polymers per \( \mu m^2 \) for microtubules and neurofilaments in the axon and rescale our variables according to

\[
t' = \frac{t}{T}, \quad x' = \frac{x}{L_0}, \quad y' = \frac{y}{L_0}, \quad u' = \frac{u}{U}, \quad v' = \frac{v}{U}.
\]
If we plug in our new variables into (3.5), we get
\[
\frac{U}{T} \frac{\partial u'}{\partial t'} = D_1 \frac{U}{L_0^2} \Delta u' + \frac{1}{L_0} \nabla \cdot \left( \eta_1 u' \frac{1}{L_0} \nabla (U u' + U v') \right) - \frac{F}{\mu_1} \frac{1}{L_0} \nabla \cdot \left[ U u' K_u^0 (U u, U v) \right]
\]

⇒ \frac{\partial u'}{\partial t'} = D_1 T \frac{L_0^2}{\Delta u'} + \nabla \cdot \left( \eta_1 \frac{U}{L_0} u' \nabla (u' + v') \right) - \frac{F T}{\mu_1} \nabla \cdot \left[ u' K_u^0 (U u, U v) \right].

(3.11)

If we plug in our new variable to (3.3), we get
\[
K_u^a (U u', U v') = k_1 \int_{\Omega} \frac{L_0}{F} G_{r_1} \left( y' - x' \right) U u(y', t) L_0^3 dy' + k_2 \int_{\Omega} \frac{L_0}{F} G_{r_2} \left( y' - x' \right) U v(y', t) L_0^3 dy',
\]
\[
= k_1 \frac{UL_0^3}{F} \int_{\Omega} G_{r_1} \left( y' - x' \right) U u(y', t) dy' + k_2 \frac{UL_0^3}{F} \int_{\Omega} G_{r_2} \left( y' - x' \right) U v(y', t) dy'.
\]

(3.12)

If we choose new parameters such that
\[
D'_1 = \frac{T}{L_0^2} D_1, \quad \eta'_1 = \frac{U}{L_0^2} \eta_1, \quad \mu'_1 = \frac{L_0}{F} \mu_1, \quad r'_1 = \frac{r_1}{L_0}, \quad k'_1 = \frac{UL_0^3}{F} k_1, \quad i = 1, 2,
\]
our new equations will have the same form as (3.5). The equation for \( v \) can be rescaled in a similar manner. As both equations retain their forms under nondimensionalization, for simplicity of notation we shall drop the prime symbols for the remainder of this thesis and instead use the rescaled parameters summarized in Table 3.2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_1 )</td>
<td>0.7218</td>
<td>( D_2 )</td>
<td>5.031</td>
</tr>
<tr>
<td>( \mu_1 )</td>
<td>( 2.844 \times 10^{-2} )</td>
<td>( \mu_2 )</td>
<td>( 4.0834 \times 10^{-3} )</td>
</tr>
<tr>
<td>( \eta_1 )</td>
<td>2.2645</td>
<td>( \eta_2 )</td>
<td>15.774</td>
</tr>
<tr>
<td>( r_1 )</td>
<td>( 0.6 - 2 )</td>
<td>( r_2 )</td>
<td>0.5</td>
</tr>
<tr>
<td>( k_1 )</td>
<td>( 72 \times \alpha )</td>
<td>( k_2 )</td>
<td>( 14.4 \times 1/15 )</td>
</tr>
</tbody>
</table>

Table 3.2: Non-Dimensional Parameters
Chapter 4: The Model in 1D

In this chapter, we examine a 1D abstraction of the model. As illustrated in Figure 4.1, in this abstraction we assume that the axon is a 2D rectangle rather than a 3D cylinder. Thus a cross section of the axon takes the form of a line of fixed length $L$.

![Diagram of 1D Model Domain and 2D Axon](image)

Figure 4.1: A schematic of the 1D domain $\Omega$. A cross section of a rectangular 2D axon results in $\Omega$ being a line of fixed length.
In this 1D abstraction, the equations of our model can be written as

\[
\frac{\partial u}{\partial t} = D_1 \frac{\partial^2 u}{\partial x^2} + \frac{\partial}{\partial x} \left( \eta_1 u \frac{\partial}{\partial x} (u + v) \right) - \frac{1}{\mu_1} \frac{\partial}{\partial x} \left( uK_u^a(u, v) \right) \quad \text{in } [0, L]
\]

\[
\frac{\partial v}{\partial t} = D_2 \frac{\partial^2 v}{\partial x^2} + \frac{\partial}{\partial x} \left( \eta_2 v \frac{\partial}{\partial x} (u + v) \right) - \frac{1}{\mu_2} \frac{\partial}{\partial x} \left( vK_v^a(u, v) \right) \quad \text{in } [0, L].
\]

(4.1)

We choose to further simplify calculations through the use of periodic boundary conditions. As shown in Figure 4.2, this further abstraction takes the endpoints of the domain, which biologically represent the membrane of the axon, and assumes that they occupy the same point in space. As a simplification, this allow us to eliminate any effects of the geometry and boundary of the domain on the model itself as well as reduce both the analytical and numerical complexity of the calculations. Once we have examined the 1D model analytically, we will compare it to numerical simulations of the 1D model under both periodic and no-flux boundary conditions to illustrate both the key behaviors of the system and the effects of boundary on the system.

4.1 Linear Stability Analysis of the 1D Uniform Steady State

According to classical differential equations theory, the overall stability or lack of stability near a stationary point can be classified based on the eigenvalues of the system that has been linearized around that particular stationary point. By knowing the stability of a system near its stationary point, we can gain insight into the general behavior of the system for points close to the stationary point. In practice, the linearization for linear stability analysis involves building a first order linear approximation of the system around the known quantity of the system’s stationary point.

For our model, there exists a known stationary point at the uniform steady state (USS) \((u, v) = (u_0, v_0)\), thus allowing us to apply the method of linear stability analysis. Let us define new domain variables \(\tilde{u} = u - u_0, \tilde{v} = v - v_0\) in relation to this USS. If we linearize
Figure 4.2: A schematic of periodic boundary conditions. Space is stretched so that the two endpoints of the domain representing the axon membrane become the same point.

our system by plugging in our new variables into (4.1) and ignoring terms of higher order than first order, we obtain the following equations for $\bar{u}$ and $\bar{v}$:

\[
\frac{\partial \bar{u}}{\partial t} = D_1 \frac{\partial^2 \bar{u}}{\partial x^2} + \eta_1 u_0 \frac{\partial^2}{\partial x^2} (\bar{u} + \bar{v}) - \frac{u_0}{\mu_1} \frac{\partial}{\partial x} \left( K_u(\bar{u}, \bar{v}) \right) \quad \text{in } [0, L]
\]

\[
\frac{\partial \bar{v}}{\partial t} = D_2 \frac{\partial^2 \bar{v}}{\partial x^2} + \eta_2 v_0 \frac{\partial^2}{\partial x^2} (\bar{u} + \bar{v}) - \frac{v_0}{\mu_2} \frac{\partial}{\partial x} \left( K_v(\bar{u}, \bar{v}) \right) \quad \text{in } [0, L].
\]

(4.2)

It is worth noting for the calculations for this conversion that the attractive nonlocal terms have kernels that are odd functions. In the remainder of this section, we drop the bars for simplicity of notation.

To begin, we can express both $u$ and $v$ using a discrete Fourier transform as

\[
u = \sum_{q \neq 0} \psi_q(t) e^{iwx}, \quad \psi_q(t) e^{iwx},
\]

(4.3)
with \( w_q = 2q\pi/L \). Using basic rules of partial derivatives, we can then obtain that

\[
\frac{\partial u}{\partial t} = \sum_{q \neq 0} \phi_q'(t)e^{iw_qx}, \quad \frac{\partial v}{\partial t} = \sum_{q \neq 0} \psi_q'(t)e^{iw_qx},
\]

\[
\frac{\partial^2 u}{\partial x^2} = -\sum_{q \neq 0} \phi_q(t)w_q^2e^{iw_qx}, \quad \frac{\partial^2 v}{\partial x^2} = -\sum_{q \neq 0} \psi_q(t)w_q^2e^{iw_qx}.
\]

If we wish to also express our nonlocal integrals in this form, we can note that

\[
\int G_{r_1}(y-x)u(y,t)dy = \sum_{q \neq 0} \phi_q(t) \int G_{r_1}(y-x)e^{iw_qy}dy
\]

\[
= \sum_{q \neq 0} \phi_q(t) \left( \int G_{r_1}(y-x)e^{iw_q(y-x)}dy \right) e^{iw_qx}
\]

\[
= \sum_{q \neq 0} \phi_q(t) \left( \int G_{r_1}(y)e^{iw_qy}dy \right) e^{iw_qx}
\]

\[
= \sum_{q \neq 0} \phi_q(t) \hat{G}_{r_1,q} e^{iw_qx},
\]

where we let

\[
\hat{G}_{r_1,q} = \int G_{r_1}(y)e^{iw_qy}dy. \quad (4.4)
\]

Thus we can factor \( \phi_q(t)e^{iw_qx} \) from every term in \( G_{r_1} \). Using a similar line of reasoning, we can also express the remaining nonlocal integrals as

\[
\int G_{r_2}(y-x)u(y,t)dy = \sum_{q \neq 0} \phi_q(t) \hat{G}_{r_2,q} e^{iw_qx},
\]

\[
\int G_{r_2}(y-x)v(y,t)dy = \sum_{q \neq 0} \psi_q(t) \hat{G}_{r_2,q} e^{iw_qx},
\]

where

\[
\hat{G}_{r_2,q} = \int G_{r_2}(y)e^{iw_qy}dy. \quad (4.5)
\]

Thus we can express all of the nonlocal integrals as the sum of terms either involving \( \phi_q(t)e^{iw_qx} \) or involving \( \psi_q(t)e^{iw_qx} \). As every term of (4.2) has been expressed as an infinite sum of terms involving the factors \( \phi_q(t)e^{iw_qx} \) and \( \psi_q(t)e^{iw_qx} \), if we plug in our new expressions into (4.2), cancel the \( e^{iw_qx} \) that is common amongst all terms and assume the
equation holds for each individual \( q \), we arrive at a system of differential equations for each \( \phi_q \) and \( \psi_q \) given by

\[
\phi'_q = \left[ - (D_1 + \eta_1 u_0) w_q^2 - \frac{u_0}{\mu_1} (i w_q) \left( k_1 \hat{G}_{r_1,q} \right) \right] \phi_q + \left[ - \eta_1 u_0 w_q^2 - \frac{u_0}{\mu_1} (i w_q) \left( k_2 \hat{G}_{r_2,q} \right) \right] \psi_q,
\]
\[
\psi'_q = \left[ - \eta_2 v_0 w_q^2 - \frac{v_0}{\mu_2} (i w_q) \left( k_2 \hat{G}_{r_2,q} \right) \right] \phi_q + \left[ - (D_2 + \eta_2 v_0) w_q^2 \right] \psi_q,
\]

or in a more condensed matrix format,

\[
\begin{pmatrix}
\phi_q \\
\psi_q
\end{pmatrix}' = A_q
\begin{pmatrix}
\phi_q \\
\psi_q
\end{pmatrix},
\]

(4.6)

with

\[
A_q = -
\begin{pmatrix}
(D_1 + \eta_1 u_0) w_q^2 + \frac{w_0}{\mu_1} (i w_q) \left( k_1 \hat{G}_{r_1,q} \right) & \eta_1 u_0 w_q^2 + \frac{w_0}{\mu_1} (i w_q) \left( k_2 \hat{G}_{r_2,q} \right) \\
\eta_2 v_0 w_q^2 + \frac{v_0}{\mu_2} (i w_q) \left( k_2 \hat{G}_{r_2,q} \right) & (D_2 + \eta_2 v_0) w_q^2
\end{pmatrix}
\]

(4.7)

In order to further simplify our matrix \( A_q \), we can draw again upon the fact that the kernel functions \( G_{r_1} \) and \( G_{r_2} \) are odd functions in space, and thus \( \hat{G}_{r_2,q} \) and \( \hat{G}_{r_2,q} \) must be imaginary numbers. Recall from (4.4) that the function \( G_{r,i,x} \) can be rewritten as

\[
\hat{G}_{r_j,q} = \int G_{r_j} (x) e^{i w_q x} dx
= 2i \int_0^{r_j} x \sin(w_q x) dx
= \frac{2i}{w_q^2} \left( \sin(w_q r_j) - w_q r_j \cos(w_q r_j) \right)
= 2i r_j^2 H(w_q r_j),
\]

(4.8)

where

\[
H(z) = \frac{\sin(z) - z \cos(z)}{z^2}.
\]

(4.9)

is used to simplify the notation. For reference, \( H(z) \) is plotted for \( z > 0 \) in Figure 4.3.

We can further simplify our notation by denoting \( h_{j,q} \) as

\[
h_{j,q} = w_q r_j^2 H(w_q r_j), \quad j = 1, 2,
\]
and then substitute (4.8) into (4.7) using the above notation to obtain a more useful form of the matrix $A_q$:

$$A_q = \begin{pmatrix}
-(D_1 + \eta_1 u_0)w_q^2 + 2 \frac{u_0}{\mu_1} \left( k_1 h_{1,q} \right) & -\eta_1 u_0 w_q^2 + 2 \frac{u_0}{\mu_1} \left( k_2 h_{2,q} \right) \\
-\eta_2 v_0 w_q^2 + 2 \frac{v_0}{\mu_2} \left( k_2 h_{2,q} \right) & -(D_2 + \eta_2 v_0)v_q^2
\end{pmatrix}. \tag{4.10}$$

Now that we have simplified our linear system’s matrix as much as possible, we can determine the stability of the system by looking at the eigenvalues of the matrix $A_q$. If there exists a single $q$ such that $A_q$ has an eigenvalue with a positive real part, then small initial perturbations away from the stationary point will grow in time and thus the system will be classified as linearly unstable at the stationary point. As the calculation of all of the eigenvalues of a matrix can be lengthy process, it is useful to recall a result from linear algebra that if $\lambda_1$ and $\lambda_2$ are the eigenvalues of a matrix $A$, then $\text{Tr}(A) = \lambda_1 + \lambda_2$ and $\text{Det}(A) = \lambda_1 \lambda_2$. This tells us that if we want to know when $\lambda_1 > 0$ or $\lambda_2 > 0$ occur, this
is equivalent to finding out when $\text{Tr}(A) > 0$ or $\text{Det}(A) < 0$ occur. Thus we can determine the stability of $A_q$ solely by looking at $\text{Tr}(A)$ and $\text{Det}(A)$. In the most general case, the trace and determinant are given by:

$$\text{Tr}(A_q) = -(D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0) w_q^2 + 2 \frac{u_0}{\mu_1} \left( k_{1,h_1,q} \right),$$

(4.11)

$$\text{Det}(A_q) = \left[ D_1 D_2 + D_1 \eta_2 v_0 + D_2 \eta_1 u_0 \right] w_q^4 - 2 \frac{u_0}{\mu_1} k_1 \left( D_2 + \eta_2 v_0 \right) h_{1,q} w_q^2$$

$$+ 2u_0 v_0 k_2 \left[ \frac{\eta_1}{\mu_2} + \frac{\eta_2}{\mu_1} \right] h_{2,q} w_q^2 - 4 \frac{u_0 v_0}{\mu_1 \mu_2} \left( k_2 h_{2,q} \right)^2.$$  (4.12)

As even the reduced model in full is quite complicated, it is difficult to sort out the individual contributions from all of the different mechanisms. To rectify this we will first consider the special case in which there are no special interactions between particles and then slowly build up the complexity of the system by adding different types of interactions until all interaction types are present so that we can get the clearest understanding as to the contribution of each mechanism.

**Case I:** $\eta_i = k_1 = k_2 = 0$. This case corresponds to the assumption that there are no interactions between microtubules and neurofilaments through either repulsive volume exclusion forces or attractive spring forces, i.e., $k_1 = k_1 = \eta_i = 0$. This case is trivial, as the interaction between particles is through standard diffusion. As we have all terms involving $\eta_1, \eta_2, h_{1,q}$ and $\phi_{2,1}$ equal to 0 for all $q$, our matrix (4.10) reduces to

$$A_q = \begin{pmatrix} -D_1 w_q^2 & 0 \\ 0 & -D_2 w_q^2 \end{pmatrix}.$$  (4.13)

As this matrix is triangular, its eigenvalues are its diagonal elements. As $w_q^2 > 0$ and $D_i > 0$, both of these eigenvalues are negative, ensuring that the USS is stable. This result is biologically reasonable as no aggregation should occur in the absence of attractive forces.
**Case II:** $\eta_i \neq 0, k_1 = k_2 = 0$. This case corresponds to a system in which there are only pairwise repulsive forces but no attractive interactions between particles through molecular motors. Thus we have $k_1 = k_2 = 0$, but $\eta_i \neq 0$. Under this assumption our matrix (4.10) reduces to

$$A_q = \begin{pmatrix} - (D_1 + \eta_1 u_0) w_q^2 & - \eta_1 u_0 w_q^2 \\ - \eta_2 v_0 w_q^2 & -(D_2 + \eta_2 v_0) w_q^2 \end{pmatrix} \quad (4.14)$$

As the only $q$-dependent term $w_q^2$ is a positive constant affecting every term of the matrix, the stability of the matrix does not depend on $q$. We can thus examine the stability of the similar but easier to work with matrix

$$A = \begin{pmatrix} - (D_1 + \eta_1 u_0) & - \eta_1 u_0 \\ - \eta_2 v_0 & -(D_2 + \eta_2 v_0) \end{pmatrix}. \quad (4.15)$$

As we have $D_i \geq 0$, $\eta_i \geq 0$ and $u_0v_0 \geq 0$, the following properties hold:

$$\text{Tr}(A) = -(D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0) < 0 \quad (4.16)$$

$$\text{Det}(A) = D_1D_2 + D_1\eta_2 v_0 + d_2 \eta_1 u_0 > 0. \quad (4.17)$$

As these are the two conditions for the stability of a matrix, our uniform steady state must be stable and thus no aggregation can occur. As aggregation was not possible in Case I where no interactions beyond diffusion were present, it is also biologically reasonable that the introduction of additional repulsive forces would not detract from the stability of the uniform steady state.

**Case III:** $\eta_i, k_2 \neq 0, k_1 = 0$. This case corresponds to a system in which we have the repulsive volume exclusion of all particles and attractive interaction through molecular motors only between neurofilaments and microtubules, but not between microtubules and
microtubules. As we only have $k_1 = 0$ and $k_2, \eta_i \neq 0$, our matrix will take the form

$$A_q = \begin{pmatrix} -(D_1 + \eta_1 u_0)w_q^2 & -\eta_1 u_0 w_q^2 + 2 \frac{u_0}{\mu_1} (k_2 h_{2,q}) \\ -\eta_2 v_0 w_q^2 + 2 \frac{v_0}{\mu_2} (k_2 h_{2,q}) & -(D_2 + \eta_2 v_0)w_q^2 \end{pmatrix}, \quad (4.18)$$

and simple calculations will lead to the trace and determinant being given by

$$\text{Tr}(A_q) = -(D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0)w_q^2 < 0$$

$$\text{Det}(A_q) = (D_1 D_2 + D_1 \eta_2 v_0 + D_2 \eta_1 u_0)w_q^4 + 2u_0 v_0 k_2 \left[ \frac{\eta_1}{\mu_2} + \frac{\eta_2}{\mu_1} \right] w_q^2 h_{2,q} - 4 \frac{u_0 v_0}{\mu_1 \mu_2} k_2^2 h_{2,q}^2. \quad (4.19)$$

As the trace of the matrix is always negative, the stability or lack thereof will be determined by the determinant. If we recall that $\eta_i = \int_{R^2} V(x) dx / \mu_i$, we must also have that $\frac{\eta_i}{\mu_i} = \frac{\eta_j}{\mu_j}$ holds true, which allows us to simplify (4.19) into

$$\text{Det}(A_q) = \left[ - 4 \frac{u_0 v_0}{\mu_1 \mu_2} h_{2,q}^2 \right] k_2^2 + \left[ 4u_0 v_0 \frac{\eta_1}{\mu_2} w_q^2 h_{2,q} \right] k_2$$

$$+ (D_1 D_2 + D_1 v_0 \eta_2 + D_2 \eta_1 u_0)w_q^4. \quad (4.20)$$

If we fix all other variables as constant then $\text{Det}(A_q)$ can be viewed as a quadratic function of $k_2$ with negative concavity. Thus as $\text{Det}(A_q) > 0$ for $k_2 = 0$, there must exists a critical value $k_2^*$ for the spring interaction $k_2$ for which $\text{Det}(A_q) > 0$ for $k_2 \in [0, k_2^*)$ and $\text{Det}(A_q) < 0$ for $k_2 > k_2^*$. This can be interpreted to mean that if the spring force interaction strength is below the critical value, the system will be stable and no segregation can occur.

**Case IV:** $\eta_i, k_1 \neq 0, k_2 = 0$. This case corresponds to a system in which there is volume exclusion between all particles and long-range attractive interactions between microtubules through organelles and molecular motors, but no interaction between microtubules and neurofilaments. This case is similar to axons that have been treated with the compound
IDPN in nature. As we only have $k_2 = 0$ and all other terms $k_1, \eta_i \neq 0$, our matrix $A_q$ will condense into

$$A_q = \begin{pmatrix} - (D_1 + \eta_1 u_0)w_q^2 + 2 \frac{u_0}{\mu_1} k_{1,q} & - \eta_1 u_0 w_q^2 \\ - \eta_2 v_0 w_q^2 & -(D_2 + \eta_2 v_0)w_q^2 \end{pmatrix}$$  \hspace{1cm} (4.21)$$

and our trace and determinant will be given by

$$\text{Tr}(A_q) = -(D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0)w_q^2 + 2 \frac{u_0}{\mu_1} k_{1,q}$$

$$\text{Det}(A_q) = (D_1 D_2 + \eta_1 u_0 + \eta_2 v_0)w_q^4 - 2 \frac{u_0}{\mu_1} (k_{1,q})(D_2 + \eta_2 v_0)w_q^2.$$  \hspace{1cm} (4.22)$$

In this scenario we have the possibility of both a positive trace and negative determinant, thus if either of

$$k_1 > \frac{\mu_1}{2 u_0 h_{1,q}} (D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0)w_q^2,$$

$$k_1 > \frac{\mu_1}{2 u_0 h_{1,q}} (D_1 + \frac{D_2 \eta_1 u_0}{D_2 + \eta_2 v_0})w_q^2$$

hold true, the eigenvalues of the system will be positive and initial perturbations will grow unbounded. As $D_2, u_0, v_0, \eta_1, \eta_2 > 0$, we know

$$\frac{D_2 \eta_1 u_0}{D_2 + \eta_2 v_0} < \eta_1 u_0 < D_2 + \eta_1 u_0 + \eta_2 v_0,$$

which implies

$$\frac{\mu_1}{2 u_0 h_{1,q}} (D_1 + \frac{D_2 \eta_1 u_0}{D_2 + \eta_2 v_0})w_q^2 < \frac{\mu_1}{2 u_0 h_{1,q}} (D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0)w_q^2,$$

and thus

$$k_1 > \frac{\mu_1}{2 u_0 h_{1,q}} (D_1 + \frac{D_2 \eta_1 u_0}{D_2 + \eta_2 v_0})w_q^2$$

is the inequality that determines instability. A simple way to interpret this condition is that there exists a critical threshold for the microtubule-microtubule interaction strength given by the weaker of these two inequalities above which aggregation of microtubules can occur and below which it cannot.
**Case V:** $\eta_i, k_1, k_2 \neq 0$. This is the most general simplified case in which we have the repulsive volume exclusion force between all particles along with the attractive force between both microtubules and neurofilaments and microtubules and microtubules via organelles. As calculated earlier, our full matrix $A_q$ is

$$A_q = \begin{pmatrix}
-(D_1 + \eta_1 u_0) w_q^2 + 2 \frac{u_0}{\mu_1} (k_1 h_{1,q}) & -\eta_1 u_0 w_q^2 + 2 \frac{u_0}{\mu_1} (k_2 h_{2,q}) \\
-\eta_2 v_0 w_q^2 + 2 \frac{v_0}{\mu_2} (k_2 h_{2,q}) & -(D_2 + \eta_2 v_0) w_q^2
\end{pmatrix} \quad (4.23)$$

where

$$\text{Tr}(A_q) = -(D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0) w_q^2 + 2 \frac{u_0}{\mu_1} (k_1 h_{1,q}), \quad (4.24)$$

$$\text{Det}(A_q) = \left[ D_1 D_2 + D_1 \eta_2 v_0 + D_2 \eta_1 u_0 \right] w_q^4 - 2 \frac{u_0}{\mu_1} k_1 (D_2 + \eta_2 v_0) h_{1,q} w_q^2 + 2 u_0 v_0 k_2 \left[ \frac{\eta_1}{\mu_2} + \frac{\eta_2}{\mu_1} \right] h_{2,q} w_q^2 - 4 \frac{u_0 v_0}{\mu_1 \mu_2} (k_2 h_{2,q})^2. \quad (4.25)$$

As $\text{Tr}(A_q)$ is the same in Case V as it is in Case IV, we will again have a critical point of instability in $k_1$ determined by the inequality

$$k_1 > \frac{\mu_1}{2 u_0 h_{1,q}} (D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0) w_q^2, \quad (4.26)$$

For $\text{Det}(A_q)$, we have shifted the equation from Case IV by the terms

$$2 u_0 v_0 h_{2,q} k_2 \left[ \left( \frac{\eta_2}{\mu_1} + \frac{\eta_1}{\mu_2} \right) w_q^2 - 2 \frac{h_{2,q}}{\mu_1 \mu_2} k_2 \right],$$

which is a quadratic function of $k_2$ with negative concavity. As $k_2 = 0$ and

$$k_2 = \frac{(\mu_1 \eta_1 + \mu_2 \eta_2) w_q^2}{2 h_{2,q}} > 0$$

are the roots of this term, there is a interval $k_2 \in [0, \frac{(\mu_1 \eta_1 + \mu_2 \eta_2) w_q^2}{2 h_{2,q}}]$ where if all else is fixed then $k_2$ will add stability to the system and outside of which it will detract from it. Biologically this result tells us that for low to medium levels of MT-NF interaction strength,
the overall system will have more stability and aggregations will have more difficulty occurring, but if the interaction strength is too strong then additional instabilities will be introduced.

Overall, the 1D analytical results tell us that the parameters $k_1$ and $k_2$, which affect the binding strength of the microtubule-microtubule and microtubule-neurofilament interactions, are driving forces behind the stability of the overall system. In the event that these interactions are too weak, no aggregations of polymers are possible and the system will tend towards a uniform mixture of microtubules and neurofilaments.

4.2 Numerical Results of the 1D Model

Having confirmed the possibility of the model to exhibit instability analytically, it remains to show that the 1D model can exhibit this behavior in the form of aggregative and segregative behavior. To show this we simulated the system in MATLAB using the numerical scheme described in the next section over a domain of length 1 µm. Time integration uses MATLAB’s multi-step stiff ODE solver ode15s. Non-dimensional model parameters are chosen from Table (3.2) with $r_1 = 1$ and $\alpha = 1/800$, while the initial conditions are chosen to be either

$$u(x, 0) = (18 + 15 \sin(4\pi x))(0.2)^2$$
$$v(x, 0) = (115 - 15 \sin(4\pi x))(0.2)^2$$

(4.27)

in the sinusoidal perturbation case, and

$$u(x, 0) = (18 + 15u_1(x))(0.2)^2$$
$$v(x, 0) = (115 - 15v_1(x))(0.2)^2$$

(4.28)

where $u_1$ and $v_1$ are uniformly distributed random variables on $[-1, 1]$ in the uniformly distributed perturbation case that more closely mimics white noise. Results using sinusoidal perturbations are plotted in Figure 4.4, Figure 4.5 and Figure 4.8 while results using random
perturbations are plotted in Figure 4.6 and Figure 4.7. Results were run using both periodic and no-flux boundary conditions to determine the effects of boundary on the system.

(A)

(B)

Figure 4.4: (A): 1D simulation with no MT-NF interaction ($k_2$ zero), sinusoidal initial perturbation and periodic boundary condition. (B): 1D simulation under same conditions except for no-flux boundary conditions. Results are plotted in hours.

From the above analytical analysis we expect to see a windows of values for $k_1$ above which segregating behavior occurs, below which the USS is stable and in the middle of which the results depend on the strength of the stabilizing effect of $k_2$. In Figure 4.4 we see the time evolution of the density of microtubules and neurofilaments with a fixed strength of
Figure 4.5: (A): 1D simulation with both MT-MT and MT-NF interactions ($k_2$ non-zero), sinusoidal initial perturbation and periodic boundary condition. (B): 1D simulation under same conditions except for no-flux boundary conditions. Results are plotted in log-hours.

microtubule-microtubule interaction corresponding to a bound:unbound rate in axon transport of 1:800 and no microtubule-neurofilament interaction under both periodic boundary conditions and no-flux boundary conditions. In both situations we see rapid accumulations of microtubules around the center of the domain on the time scale of hours with the neurofilament population displaced from the associated area of the domain. In the periodic boundary case this occurs by approximately $t = 6$ hours, while in the no-flux boundary
case this process is complete by \( t = 3 \) hours with a wider peak, indicating that segregation can occur much more rapidly in the no-flux boundary case. It is worth noting that in both cases the mass of microtubules is initially concentrated around multiple small peaks in density, all but one of which quickly disperses their mass, which then accumulates around the one remaining peak in a process similar to the transition from fully formed intermediate peaks to a smaller number of peaks observed in [25]. In Figure 4.5 we see a time evolution of microtubule and neurofilament density under the same conditions as 4.4 except that the microtubule-neurofilament interaction coefficient \( k_2 \) is set at its standard non-zero level derived from previous literature. With microtubule-neurofilament interaction - and thus axon transport of neurofilaments - restored, in both cases of the boundary condition we do not see substantial aggregate growth, indicating that the uniform steady state is stable. In both of the boundary cases this process occurs prior to \( t = 1 \) hour, though it appears to occur slightly faster in the periodic boundary case, indicating the possibility that the restricting the flow of particles can reduce the rate of dispersion.

As the previous figures used a sinusoidal perturbation from the uniform steady state as their initial condition, their results were thus representative of the behavior of a select Fourier mode. In order to get a more general idea of the behavior of the system, the simulations were repeated in Figures 4.6 and 4.7 using the random perturbations listed above that contain all of the Fourier modes. In Figure 4.6 we see a time evolution of polymer density using the same conditions as in Figure 4.4 except for the initial condition. We see instability surface in the form of a single peak in microtubule density and matching single valley in neurofilament density, though we do not see the formation of the initial intermediate peaks, which indicates that intermediate peaks may be specific to each Fourier mode. In the periodic case the aggregate can form around any point in the domain depending on the initial random perturbations, but in the no-flux boundary conditions the aggregate appears
Figure 4.6: (A): 1D simulation with no MT-NF interaction ($k_2$ zero), white noise initial perturbation and periodic boundary condition. A single aggregate peak of microtubules forms by $t = 6$ hours. (B): 1D simulation under same conditions except for no-flux boundary conditions. The single aggregate peak forms by $t = 5$ hour. Results for both are plotted in hours.

to center around $x = 2.5$. Similar to Figure 4.4, segregation is evident at a earlier time in the no-flux boundary case than in the periodic boundary case, though the difference is less pronounced. In Figure 4.7 we see a time evolution of the density of microtubules and neurofilaments under the same conditions as in Figure 4.5 except for the initial condition. Aggregations do not appear to occur, indicating that the uniform steady state is still stable.
Figure 4.7: (A): 1D simulation with both MT-MT and MT-NF interaction ($k^2_{2}$ non-zero), white noise initial perturbation and periodic boundary condition. Initial perturbations do not appear to grow in time. (B): 1D simulation under same conditions except for no-flux boundary conditions. The initial perturbations appear to disperse much more evenly. Results for both are plotted in log-hours.

In the no-flux boundary condition case, the decay appears to be much more even than in the periodic boundary case.

In Figure 4.8, the system is first simulated under the same conditions as Figure 4.6 with $k^2_{2}$ set to zero until time $t = 10$ hours, after which the conditions are changed to the same as in Figure 4.7 where $k^2_{2}$ is non-zero, and the system is then simulated until $t = 12$ hours.
Figure 4.8: (A): 1D simulation with no MT-NF interaction ($k_2$ zero) before $t = 10$ hours when peak forms and non-zero interaction after $t = 10$ hours, with a random initial perturbation. Aggregations quickly disperse when MT-NF interaction is restored. (B) 1D simulation under similar conditions except for no-flux boundary conditions. $k_2$ is restored at $t = 10$ hours to allow for peak formation. The initial aggregate is quicker to form and more closely held together. Aggregates disperse more evenly when $k_2$ is restored. Results for both are plotted in hours.

to see the immediate behavior of polymer aggregates. When $k_2$ is switched on we see an immediate change in the dynamics of the system as the single peak in microtubule density
and valley in neurofilament density quickly disperses to a near-uniform level. This indicates that the model in 1D is able to successfully mimic the reversibility of the aggregative behavior induced by the inhibition of microtubule-neurofilament interaction that was found in [25]. Similarly to Figure 4.4 and Figure 4.5, in the no-flux boundary condition case we see a fully formed aggregate by $t = 4$ hour rather than $t = 9$ hours in the periodic case. Dispersion after $t = 10$ appears to occur slower in the no-flux case, as there are still areas below a density of 0.5 by $t = 12$ in the no-flux case but not in the periodic boundary case. Overall this indicates that restricting the flow of polymers at the boundaries has the effect of drawing microtubules to the center of the domain and dampening their ability to disperse to the periphery, thus adding to the process of segregation.

4.2.1 1D Numerical Method Used

To simulate this system, we first used the method of lines to discretize the space $[0, 5]$ into $N$ equally spaced points $x_j = jh$ for step size $h$ and $0 \leq j < N$, and discretized time with time step $\delta t$ such that $t_n = n\delta t$ for $n \geq 0$. If we let $U^n_j$ be the approximation of $u(x, t)$ at point $x = x_j$ and time $t = t_n$, and $V^n_j$ approximate $v(x, t)$ under the same conditions, then we can approximate our time derivative using the forward difference formula

$$\frac{\partial v}{\partial t} \approx \frac{1}{\delta t} (V^{n+1}_j - V^n_j).$$

For standard diffusion we can use the second order central difference approximation $\frac{\partial^2 v}{\partial x^2} \approx \frac{1}{h^2} (V^n_{j+1} - 2V^n_j + V^n_{j-1})$. For our nonlinear diffusion term, we can use a central difference formula staggered halfway between the spatial mesh and use linear interpolation to approximate the function values there. Thus we have

$$\frac{\partial}{\partial x} (\eta_2 v \frac{\partial}{\partial x} (u + v)) \approx \frac{\eta_2}{h^2} [\frac{1}{2}(V^n_{j+1} + V^n_j)((U^n_{j+1} + V^n_{j+1}) - (U^n_j + V^n_j)) - \frac{1}{2}(V^n_j + V^n_{j-1})((U^n_{j} + V^n_{j}) - (U^n_{j-1} + V^n_{j-1}))].$$

(4.29)

To calculate the non-local integral $v \int_\Omega G_{r_2}(y - x)u(y, t)dy$, we first create a periodic extension by extending our domain from $[0, 1]$ to $[-1, 2]$ and letting $v(x, t) = v(x + 1, t)$ for
\( x \in [-1, 0] \) and \( v(x, t) = v(x - 1, t) \) for \( x \in [1, 2] \), with \( u \) is defined similarly. We then create a new variable \( G_2 V_j^n = \sum_{i=-N}^{2N-1} G_{r_2}(x_i - x_j)v_i^n \) where \( G_{r_2} \) is defined as in (3.4).

We can then apply central differencing to approximate the spatial derivative, so we have

\[
\frac{1}{\mu_2 \partial x} \left( v^{K_1}(u, v) \right) \approx \frac{k_2}{2\mu_2 h} \left[ G_2 V_{j+1}^n - G_2 V_{j-1}^n \right].
\]

Our initial conditions are imposed directly as \( V_j^0 = v(x_j, 0) \), while periodic boundary conditions are imposed using the ghost point \( x_N \) outside the mesh, where \( V_N^1 = V_0^n \). The equation for \( u(x, t) \) is discretized in a similar manner.

To impose no-flux boundary conditions, we note that in 1D the boundary conditions are given by:

\[
\begin{align*}
( -D_1 u_x - \eta_1 u(u + v)x + \frac{1}{\mu_1} u^{K_1}(u, v) )|_{x=0, x=L} &= 0, \\
( -D_2 v_x - \eta_2 v(u + v)x + \frac{1}{\mu_2} v^{K_1}(u, v) )|_{x=0, x=L} &= 0.
\end{align*}
\]

(4.30)

Using the above discretization of space and central difference approximations for the first derivatives, we get

\[
\begin{align*}
\left[ -\frac{D_1}{2h}(U_{j+1} - U_{j-1}) - \frac{\eta_1}{2h} U_j(U_{j+1} + V_{j+1} - U_{j-1} - V_{j-1}) + \frac{1}{\mu_1} U_j^{K_1}(U_j, V_j) \right] &= 0, \\
\left[ -\frac{D_2}{2h}(V_{j+1} - V_{j-1}) - \frac{\eta_2}{2h} V_j(U_{j+1} + V_{j+1} - U_{j-1} - V_{j-1}) + \frac{1}{\mu_2} V_j^{K_1}(U_j, V_j) \right] &= 0.
\end{align*}
\]

(4.31)

at \( j = 0 \) and \( j = N \). Isolating \( U_{j+1} \) and \( V_{j+1} \) on one side yields

\[
\begin{align*}
\left[ D_1 + \eta_1 U_j \right] U_{j+1} + \left[ \eta_1 U_j \right] V_{j+1} &= D_1 U_{j-1} + \eta_1 U_j(U_{j-1} + V_{j-1}) + \frac{2h}{\mu_1} U_j^{K_1}(U_j, V_j), \\
\left[ \eta_2 V_j \right] U_{j+1} + \left[ D_2 + \eta_2 V_j \right] V_{j+1} &= D_2 V_{j-1} + \eta_2 V_j(U_{j-1} + V_{j-1}) + \frac{2h}{\mu_2} V_j^{K_1}(U_j, V_j).
\end{align*}
\]

(4.32)

We can solve the matrix equation associated with this linear system to find \( U_{j+1} \) and \( V_{j+1} \), which are our ghost points on the right boundary when \( j = N \).

If we isolated \( U_{j-1} \) and \( V_{j-1} \) in the (4.31) instead, we would get:
\[
\begin{align*}
[D_1 + \eta_1 U_j] U_{j-1} + [\eta_1 U_j] V_{j-1} &= D_1 U_{j+1} + \eta_1 U_j (U_{j+1} + V_{j+1}) - \frac{2h}{\mu_1} U_j K_u^a(U_j, V_j), \\
[\eta_2 V_j] U_{j-1} + [D_2 + \eta_2 V_j] V_{j-1} &= D_2 V_{j+1} + \eta_2 V_j (U_{j+1} + V_{j+1}) - \frac{2h}{\mu_2} V_j K_v^a(U_j, V_j).
\end{align*}
\]

(4.33)

Solving the matrix equation associated with this linear system for \( U_{j-1} \) and \( V_{j-1} \) will find the ghost points at the left boundary when \( j = 0 \).

For time integration, MATLAB’s multi-step stiff ode solver \textit{ode15s} is used.
Chapter 5: The Model in 2D with Periodic Boundary Conditions

While the 1D analysis of the model in Chapter 4 was useful in illustrating some of the key ideas of the model, the effects of the boundary, it ignores the effects of dimension and geometry. To determine what, if any, effects that dimension may have on the system, we will first study the simplified model in 2D on a square domain with periodic boundary conditions using linear stability analysis, then numerically simulate the system on a square domain to see if dimension has altered the way in which instability is manifest.

To begin, it is useful for reference to examine the 2D model on a square domain, which is given by

\[
\begin{align*}
\frac{\partial u}{\partial t} &= D_1 \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + \nabla \cdot \left( \eta_1 u \nabla (u + v) \right) - \frac{1}{\mu_1} \nabla \cdot \left[ uK_u^a(u, v) \right] \quad \text{in} \ [0, L_x] \times [0, L_y] \\
\frac{\partial v}{\partial t} &= D_2 \left( \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} \right) + \nabla \cdot \left( \eta_2 u \nabla (u + v) \right) - \frac{1}{\mu_2} \nabla \cdot \left[ vK_v^a(u, v) \right] \quad \text{in} \ [0, L_x] \times [0, L_y].
\end{align*}
\]

(5.1)

5.1 Linear Stability Analysis of the 2D Uniform Steady State

As the uniform steady state \((u, v) = (u_0, v_0)\) is a steady state of both the general full model and general simplified model, it will also be a stationary point for the 2D simplified system around which we can perform linear stability analysis. Let \(\bar{u} = u - u_0, \bar{v} = v - v_0\). Using the same linearization techniques from previous chapters for (5.1) around the USS,
we obtain the following equations for $\bar{u}$ and $\bar{v}$ in $[0, L_x] \times [0, L_y]$,

$$\frac{\partial \bar{u}}{\partial t} = D_1 \left( \frac{\partial^2 \bar{u}}{\partial x^2} + \frac{\partial^2 \bar{u}}{\partial y^2} \right) + \eta_1 u_0 \left( \frac{\partial^2 \bar{u}}{\partial x^2} + \frac{\partial^2 \bar{u}}{\partial y^2} + \frac{\partial^2 \bar{v}}{\partial x^2} + \frac{\partial^2 \bar{v}}{\partial y^2} \right) - \frac{u_0}{\mu_1} \nabla \cdot \left[ K^u_\theta(u, v) \right]$$

$$\frac{\partial \bar{v}}{\partial t} = D_1 \left( \frac{\partial^2 \bar{v}}{\partial x^2} + \frac{\partial^2 \bar{v}}{\partial y^2} \right) + \eta_2 v_0 \left( \frac{\partial^2 \bar{u}}{\partial x^2} + \frac{\partial^2 \bar{u}}{\partial y^2} + \frac{\partial^2 \bar{v}}{\partial x^2} + \frac{\partial^2 \bar{v}}{\partial y^2} \right) - \frac{v_0}{\mu_2} \nabla \cdot \left[ K^v_\theta(u, v) \right].$$

(5.2)

To obtain the above linear system, we again used the property that the kernels in the nonlocal terms are odd functions. As in the previous chapters, we will drop the bars for simplicity of notation for the remainder of the chapter.

As we have moved to 2D, we can consider the equivalent 2D Fourier transforms for $u$ and $v$ given by

$$u = \sum_{q_1, q_2 \neq 0} \phi_{q_1, q_2} e^{iw_{q_1} x + iw_{q_2} y}, \quad v = \sum_{q_1, q_2 \neq 0} \psi_{q_1, q_2} e^{iw_{q_1} x + iw_{q_2} y},$$

(5.3)

assume that we have a square domain i.e. $L_x = L_y = L$, and set $w_{q_i} = 2q_i \pi / L$. Under these conditions the nonlocal integrals will be given by

$$\int G_{r_1}(y - x) u(y, t) dy = \sum_{q_1, q_2 \neq 0} \phi_{q_1, q_2} \hat{G}_{r_1, q_1, q_2} e^{iw_{q_1} x + iw_{q_2} y},$$

$$\int G_{r_2}(y - x) u(y, t) dy = \sum_{q_1, q_2 \neq 0} \phi_{q_1, q_2} \hat{G}_{r_2, q_1, q_2} e^{iw_{q_1} x + iw_{q_2} y},$$

$$\int G_{r_2}(y - x) v(y, t) dy = \sum_{q_1, q_2 \neq 0} \psi_{q_1, q_2} \hat{G}_{r_2, q_1, q_2} e^{iw_{q_1} x + iw_{q_2} y},$$

where

$$\hat{G}_{r_j, q_1, q_2} = \int \int G_{r_j}(x, y) e^{i(w_{q_1} x + w_{q_2} y)} dx dy, \quad j = 1, 2.$$

As the kernel functions $G_{r_1}$, $G_{r_2}$ are also odd functions in two dimensional space, we can again draw upon the fact that $\hat{G}_{r_2, q_1, q_2}$ and $\hat{G}_{r_2, q_1, q_2}$ must be imaginary numbers. For simplicity of analysis, we assume that polymers can interact with one another within a square radius $r_j$ rather than a circular radius. In this situation, we can simplify the terms $G_{r_j, q_1, q_2}$ further as
\[
\hat{G}_{r, q_1, q_2} = \int_{-r_j}^{r_j} \int_{-r_j}^{r_j} G_r(x, y)e^{i w_{q_1} x + i w_{q_2} y} \, dx \, dy
\]

\[
= \int_{-r_j}^{r_j} \int_{-r_j}^{r_j} \left( x, y \right) e^{i w_{q_1} x + i w_{q_2} y} \, dx \, dy
\]

\[
= \left( \int_{-r_j}^{r_j} x e^{i w_{q_1} x} \, dx \int_{-r_j}^{r_j} e^{i w_{q_2} y} \, dy \right) + \left( \int_{-r_j}^{r_j} e^{i w_{q_1} x} \, dx \int_{-r_j}^{r_j} y e^{i w_{q_2} y} \, dy \right)
\]

\[
= r_j^2 \left( \frac{1}{w_{q_2}} H(w_{q_1} r_j)(e^{i w_{q_2} r_j} - e^{-i w_{q_2} r_j}) \right) + \left( \frac{1}{w_{q_1}} H(w_{q_2} r_j)(e^{i w_{q_1} r_j} - e^{-i w_{q_1} r_j}) \right)
\]

\[
= 2i r_j^2 \left( \frac{1}{w_{q_2}} H(w_{q_1} r_j)(\sin(w_{q_2} r_j)) \right) + \left( \frac{1}{w_{q_1}} H(w_{q_2} r_j)(\sin(w_{q_1} r_j)) \right)
\]

with

\[
H(z) = \frac{\sin(z) - z \cos(z)}{z^2}.
\]

In order to further simplify our notation, let us denote

\[
h_{j, q_i} = w_{q_i}^2 r_j^2 H(w_{q_i} r_j), \quad i, j = 1, 2.
\]

If we draw again on the basic rules of partial derivatives to calculate \( \frac{\partial}{\partial t}, \frac{\partial^2}{\partial x^2} \) and \( \frac{\partial^2}{\partial y^2} \) for both \( u \) and \( v \), then as before we will have expressed all of the pieces of the 2D model in terms of \( \phi_{q_1, q_2} \) and \( \psi_{q_1, q_2} \). This allows us to create a system of ODEs in terms of our new variables for every combination of \( q_1 \) and \( q_2 \), which will be

\[
\phi'_{q_1, q_2} = \left[ -(D_1 + \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2) + \frac{2 u_0 k_1}{\mu_1 w_{q_1} w_{q_2}} \left( h_{1, q_1} \sin(w_{q_2} r_1) + h_{1, q_2} \sin(w_{q_1} r_1) \right) \right] \phi_{q_1, q_2}
\]

\[
+ \left[ -(\eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2) + \frac{2 u_0 k_2}{\mu_1 w_{q_1} w_{q_2}} \left( h_{2, q_1} \sin(w_{q_2} r_2) + h_{2, q_2} \sin(w_{q_1} r_2) \right) \right] \psi_{q_1, q_2},
\]

\[
\psi'_{q_1, q_2} = \left[ -(\eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) + \frac{2 v_0 k_2}{\mu_2 w_{q_1} w_{q_2}} \left( h_{2, q_1} \sin(w_{q_2} r_2) + h_{2, q_2} \sin(w_{q_1} r_2) \right) \right] \phi_{q_1, q_2}
\]

\[
+ \left[ -(D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) \right] \psi_{q_1, q_2},
\]

\[
(5.5)
\]
or in more succinct matrix format,

\[
\begin{pmatrix}
\phi_{q_1,q_2} \\
\psi_{q_1,q_2}
\end{pmatrix}' = A_{q_1,q_2} \begin{pmatrix}
\phi_{q_1,q_2} \\
\psi_{q_1,q_2}
\end{pmatrix},
\]

(5.6)

where

\[
A_{q_1,q_2} = -\begin{pmatrix}
a_{11} & a_{12} \\
a_{21} & a_{22}
\end{pmatrix}
\]

(5.7)

with elements given by

\[
\begin{align*}
a_{11} &= (D_1 + \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2) - \frac{2u_0 k_1}{\mu_1 w_{q_1} w_{q_2}} \left( h_{1,q_1} \sin(w_{q_2} r_1) + h_{1,q_2} \sin(w_{q_1} r_1) \right) \\
a_{12} &= \eta_1 u_0 (w_{q_1}^2 + w_{q_2}^2) - \frac{2u_0 k_2}{\mu_1 w_{q_1} w_{q_2}} \left( h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2) \right) \\
a_{21} &= \eta_2 v_0 (w_{q_1}^2 + w_{q_2}^2) - \frac{2v_0 k_2}{\mu_2 w_{q_1} w_{q_2}} \left( h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2) \right) \\
a_{22} &= (D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2).
\end{align*}
\]

To check whether there are any significant changes in the stability of the system that were introduced by a change in geometry, we will examine cases of building complexity in the same order as in Chapter 4. In each case we will determine if \(\operatorname{Tr}(A_{q_1,q_2}) < 0\) and \(\operatorname{Det}(A_{q_1,q_2}) > 0\) hold for all choices of \(q_1\) and \(q_2\) as the conditions for stability of the overall system.

**Case I: \(\eta_i = k_1 = k_2 = 0\).** We start with the trivial case, in which only standard diffusion of MTs and NFs is present in the cross-section of the axon, and we have all terms involving \(\eta_1, \eta_2, h_{1,q_i}, \) and \(h_{2,q_i}\) for all \(q_i\) set to zero. This allows us to reduce (5.7) to

\[
A_{q_1,q_2} = \begin{pmatrix}
-(D_1 + \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2) & 0 \\
0 & -(D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2)
\end{pmatrix}
\]

(5.8)

which similarly to the 1D case, has eigenvalues \(\lambda_1^q = -(D_1 + \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2) < 0\) and \(\lambda_2^q = -(D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) < 0\). As both eigenvalues have negative real parts, the uniform steady state must be stable.
**Case II:** $\eta_i \neq 0$, $k_1 = k_2 = 0$. In this case we allow for a non-zero pairwise repulsive force on top of the conditions of Case I, but keep all attractive interactions between particles through molecular motors restricted. As we have all terms involving $h_{1,qi}$ and $h_{2,qi}$ set to zero for all $q_i$, we can simplify our initial matrix into

$$A_{q_1,q_2} = \begin{pmatrix} - (D_1 + \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2) & -\eta_1 u_0(w_{q_1}^2 + w_{q_2}^2) \\ -\eta_2 v_0(w_{q_1}^2 + w_{q_2}^2) & -(D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) \end{pmatrix}.$$  \hspace{1cm} (5.9)

As this matrix only depends on $q_1, q_2$ through $(w_{q_1}^2 + w_{q_2}^2) > 0$ that is present in every term, the stability of the matrix will not depend on $q_1$ or $q_2$, and will have the same stability as the simpler matrix

$$A = \begin{pmatrix} -(D_1 + \eta_1 u_0) & -\eta_1 u_0 \\ -\eta_2 v_0 & -(D_2 + \eta_2 v_0) \end{pmatrix}$$

which was found to be stable in the 1D case. Thus the USS is again stable.

**Case III:** $\eta_i, k_2 \neq 0$, $k_1 = 0$. This case builds upon Case II by adding in microtubule-neurofilament interactions via molecular motors through a non-zero $k_2$ value. Thus as only terms involving $h_{1,qi}$ are zero, our matrix $A_{q_1,q_2}$ becomes

$$A_{q_1,q_2} = - \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$$

where

$$a_{11} = (D_1 + \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2)$$

$$a_{12} = \eta_1 u_0(w_{q_1}^2 + w_{q_2}^2) - \frac{2u_0 k_2}{\mu_1 w_{q_1} w_{q_2}} \left( h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2) \right)$$

$$a_{21} = \eta_2 v_0(w_{q_1}^2 + w_{q_2}^2) - \frac{2v_0 k_2}{\mu_2 w_{q_1} w_{q_2}} \left( h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2) \right)$$

$$a_{22} = (D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2)$$
and our determinant and trace are given by

\[
\text{Tr}(A_{q_1,q_2}) = -(D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) < 0, \tag{5.10}
\]

\[
\text{Det}(A_{q_1,q_2}) = \left[-\frac{4u_0v_0}{\mu_1\mu_2 w_{q_1}^2 w_{q_2}^2} (h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2))^2\right] k_2^2
\]
\[
+ \left[\frac{2u_0 v_0}{w_{q_1} w_{q_2}} \left( \frac{\eta_1}{\mu_2} + \frac{\eta_2}{\mu_1} \right) (h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2))(w_{q_1}^2 + w_{q_2}^2) \right] k_2
\]
\[
+ (D_1 D_2 + D_1 \eta_2 v_0 + D_2 \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2)^2.
\tag{5.11}
\]

Similarly to the 1D case, as all of our parameters are either positive or involve in a squared term, \(\text{Det}(A_{q_1,q_2})\) will be a quadratic function of \(k_2\) with negative concavity. Thus if there is a sufficiently large spring interaction, indicated by a sufficiently large \(k_2\), we will encounter \(\text{Det}(A_{q_1,q_2}) < 0\), and the uniform steady state will no longer be stable.

**Case IV: \(\eta_i, k_1 \neq 0, k_2 = 0\).** Thus case also builds upon Case II, but instead by adding in MT-MT long-range interactions via organelles and molecular motors through a non-zero \(k_1\) value. This leaves only terms involving \(h_{2,q_i}\) equal to zero. Under these conditions, the matrix \(A_q\) becomes

\[
A_{q_1,q_2} = -\begin{pmatrix}
a_{11} & a_{12} \\
a_{21} & a_{22}
\end{pmatrix}
\tag{5.12}
\]

with

\[
a_{11} = (D_1 + \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2) - \frac{2u_0 k_1}{\mu_1 w_{q_1} w_{q_2}} (h_{1,q_1} \sin(w_{q_2} r_1) + h_{1,q_2} \sin(w_{q_1} r_1))
\]

\[
a_{12} = \eta_1 u_0 (w_{q_1}^2 + w_{q_2}^2)
\]

\[
a_{21} = \eta_2 v_0 (w_{q_1}^2 + w_{q_2}^2)
\]

\[
a_{22} = (D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2).
\]
This matrix has trace and determinant given by

\[
\begin{align*}
\operatorname{Tr}(A_{q_1, q_2}) &= -(D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) \\
&\quad + \frac{2u_0}{\mu_1 w_{q_1} w_{q_2}} \left( h_{1,q_1} \sin(w_{q_2} r_1) + h_{1,q_2} \sin(w_{q_1} r_1) \right) k_1 \\
\operatorname{Det}(A_{q_1, q_2}) &= (D_1 D_2 + D_1 \eta_2 v_0 + D_2 \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2)^2 \\
&\quad - \frac{2u_0}{\mu_1 w_{q_1} w_{q_2}} (D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) \left( h_{1,q_1} \sin(w_{q_2} r_1) + h_{1,q_2} \sin(w_{q_1} r_1) \right) k_1,
\end{align*}
\]

(5.13) (5.14)

where similarly to the 1D system, \(\operatorname{Tr}(A_{q_1, q_2})\) and \(\operatorname{Det}(A_{q_1, q_2})\) are linear functions of \(k_1\).

As the trace and determinant classify the system as stable when \(k_1 = 0\), \(\frac{\partial \operatorname{Tr}(A_{q_1, q_2})}{\partial k_1} > 0\) and \(\frac{\partial \operatorname{Det}(A_{q_1, q_2})}{\partial k_1} < 0\), we can conclude that there are critical points in the range of \(k_1 > 0\) where both \(\operatorname{Tr}(A_{q_1, q_2}) > 0\) or \(\operatorname{Det}(A_{q_1, q_2}) < 0\) can occur, though these critical points of instability could be shifted from their analogous counterparts in Case IV of the 1D simplified model.

**Case V:** \(\eta_i, k_1, k_2 \neq 0\). By adding in all possible interactions, we arrive at the most general case for the simplified 2D system. As all terms are non-zero, our matrix will be as we calculated earlier, which is

\[
A_{q_1, q_2} = -\begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}
\]

with

\[
\begin{align*}
a_{11} &= (D_1 + \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2) - \frac{2u_0 k_1}{\mu_1 w_{q_1} w_{q_2}} \left( h_{1,q_1} \sin(w_{q_2} r_1) + h_{1,q_2} \sin(w_{q_1} r_1) \right) \\
a_{12} &= \eta_1 u_0(w_{q_1}^2 + w_{q_2}^2) - \frac{2u_0 k_2}{\mu_1 w_{q_1} w_{q_2}} \left( h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2) \right) \\
a_{21} &= \eta_2 v_0(w_{q_1}^2 + w_{q_2}^2) - \frac{2v_0 k_2}{\mu_2 w_{q_1} w_{q_2}} \left( h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2) \right) \\
a_{22} &= (D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2)
\end{align*}
\]
where

\[
\begin{align*}
\text{Tr}(A_{q_1,q_2}) &= -(D_1 + D_2 + \eta_1 u_0 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) \\
&\quad + \frac{2u_0}{\mu_1 w_{q_1} w_{q_2}} \left( h_{1,q_1} \sin(w_{q_2} r_1) + h_{1,q_2} \sin(w_{q_1} r_1) \right) k_1 \\
\text{Det}(A_{q_1,q_2}) &= (D_1 D_2 + D_1 \eta_2 v_0 + D_2 \eta_1 u_0)(w_{q_1}^2 + w_{q_2}^2)^2 \\
&\quad + \left[ \frac{2u_0v_0}{w_{q_1} w_{q_2}} \left( \frac{\eta_1}{\mu_2} + \frac{\eta_2}{\mu_1} \right)(w_{q_1}^2 + w_{q_2}^2) \left( h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2) \right) \right] k_2 \\
&\quad - \left[ \frac{4u_0v_0}{\mu_1 \mu_2 w_{q_1}^2 w_{q_2}^2} (h_{2,q_1} \sin(w_{q_2} r_2) + h_{2,q_2} \sin(w_{q_1} r_2))^2 \right] k_2^2 \\
&\quad - \frac{2u_0}{\mu_1 w_{q_1} w_{q_2}} (D_2 + \eta_2 v_0)(w_{q_1}^2 + w_{q_2}^2) \left( h_{1,q_1} \sin(w_{q_2} r_1) + h_{1,q_2} \sin(w_{q_1} r_1) \right) k_1.
\end{align*}
\] (5.15)

As the trace is the same function of \(k_1\) as in Case IV, we can draw the same conclusion that there is a hard upper limit on the microtubule-microtubule interaction strength above which the system is unstable and instability can occur. We can view \(\text{Det}(A_{q_1,q_2})\) as the sum of the negatively sloped linear function of \(k_1\) from Case IV and a quadratic function of \(k_2\) of negative concavity similar to the determinant in Case III. Thus the microtubule-neurofilament interaction strength \(k_2\) can have a stabilizing effect - by requiring a higher value of \(k_1\) before instability occurs - if \(k_2\) is in the window for which the quadratic function is positive, and a destabilizing effect - by lowering the value of \(k_1\) required for instability - if \(k_2\) is above this range. As the overall behavior of the matrices for the two dimensional simplified system in each of these cases is quite similar to the behavior of their one dimensional counterparts, we can conclude that the potential impacts of dimension on the system are likely to be found in shifts in the levels of the parameters required to destabilize the system and the system’s behavior once destabilized rather than a change in the system’s overall potential to destabilize.
5.2 Numerical Results of the 2D Model

To further understand the effects of a change in dimension, we solve the 2D system numerically on a $1\mu m \times 1\mu m$ domain using the numerical method described in the next section. Similarly to the 1D case, periodic boundary conditions are imposed for numerical simplicity, while non-dimensional model parameters are chosen from Table (3.2) with $r_1 = 1$ and $\alpha = 1/800$. The initial conditions are randomly generated perturbations away from the uniform steady state. Results are shown in Figure 5.1, Figure 5.2, and Figure 5.3.

We can see that the behavior of the system varies quite wildly, particularly with the choice for the strength of microtubule-microtubule interaction parameter $k_1$ but also for the microtubule-neurofilament cross population interaction term $k_2$. The columns in the figures demonstrate the time evolution of the behavior of the two populations with high (Figure 5.1), low (Figure 5.2), and zero (Figure 5.3) cross-population interaction under a fixed value of microtubule-microtubule interaction corresponding to a bound to unbound relation $\alpha$ of $1/800$. With $k_2$ at a non-zero level in line with previous literature in Figure 5.1, the initial perturbations for both microtubules and neurofilaments rapidly decay and by $t = 2$ hours the system is approximately at equilibrium at its uniform steady state. When the value of $k_2$ is decreased by half in Figure 5.1, initial perturbations appear to die off by $t = 2$, after which the microtubule population then proceeds to coalesce into one low dispersed peak while the neurofilament population forms a shallow valley in the corresponding location. This indicates that for this parameter set the system is unstable, though that instability is unable to manifest as full segregation of polymer populations. When $k_2$ is set to zero and there is no microtubule-neurofilament interaction we see signs of the formation of two peaks in the microtubule population by $t = 4$, but these peaks are not
Figure 5.1: 2D numerical results with full MT-NF interaction strength over 2 hours. The left column indicates microtubule density while the right column indicates neurofilament density. Density remains relatively constant after 2 hours.

completely formed until $t = 7$ when they reach approximately 10 times their initial densities in height while the neurofilament population forms valleys in their density levels in the corresponding spatial locations. Together these figures confirm that for the given value
of microtubule-microtubule interaction strength, changes to the strength of microtubule-
neurofilament interaction can not only change the stability of the system, but also change
the way instability is manifested. When compared to the 1D simulations with a periodic
boundary in Chapter 4, aggregations occur on a slightly faster time scale, though dispersal
rates and the the overall behavior patterns appear to be similar. It is additionally worth
noting that the edges of the microtubule aggregates begin to lose their circular shape when
beyond the radius of microtubule-microtuble interaction $r_1$. This is likely to be an issue
related the accuracy of using the trapezoidal rule to approximate the circular non-local in-
tegrals. While the error can be mitigated to some degree through the refinement of the
spatial mesh, the use of an alternative numerical method with radial symmetry similar to
the one used in [16] can be a potential avenue for further research.

5.2.1 2D Numerical Method Used

To simulate this system, we first discretized the space $[0, L] \times [0, L]$ into $N \times N$ equally
spaced grid points

$$x_i = L/Ni, \quad y_j = L/Nj, \quad 0 \leq i \leq N, \quad 0 \leq j \leq N,$$

and let $F_{i,j}$ denote the numerical approximation of $f$ at point $(x_i, y_j)$. For the Laplace
operator in standard diffusion we use a second order central difference approximation

$$\Delta f(x, y) = f_{xx} + f_{yy} \approx \frac{1}{h^2} (F_{i+1,j} - 2F_{i,j} + F_{i-1,j}) + \frac{1}{h^2} (F_{i,j+1} - 2F_{i,j} + F_{i,j-1}).$$

For the nonlinear diffusion term, we use the following conservative central difference
scheme

$$\nabla \cdot (uf) \approx \frac{1}{h_x^2} [u_{i+1/2,j}(F_{i+1,j} - F_{i,j}) - u_{i-1/2,j}(F_{i,j} - F_{i-1,j})]$$

$$+ \frac{1}{h_y^2} [u_{i,j+1/2}(F_{i,j+1} - F_{i,j}) - u_{i,j-1/2}(F_{i,j} - F_{i,j-1})]$$

(5.17)
where
\[u_{i+1/2,j} = \frac{u_{i+1,j} + u_{i,j}}{2}, \quad u_{i-1/2,j} = \frac{u_{i1,j} + u_{i-1,j}}{2},\]
and \(u_{i,j+1/2}\) and \(u_{i,j-1/2}\) are defined similarly.

As our non-local integrals are all characterized by the integration of a function \(f(x, y)\) on a circle \(\Omega_r\) of radius \(r\), it is useful to note that these integrals will take the form
\[
\int_{\Omega_r} f(x, y) \, dx \, dy = \int_{-r}^{r} \int_{-\sqrt{r^2-y^2}}^{\sqrt{r^2-y^2}} f(x, y) \, dx \, dy = \int_{-r}^{r} g(y) \, dy,
\]
where \(g(y) = \int_{-\sqrt{r^2-y^2}}^{\sqrt{r^2-y^2}} f(x, y) \, dx\). We can thus approximate this 2D integral using the trapezoidal rule applied successively to two 1D integrals as follows:

First, let \(M_x = \lfloor r/h \rfloor\) denote the number of vertical grid points above the center of the circle, and \(r_y = r - M_y h\) denote the residual distance between the furthest grid point and the boundary of the circle. For every \(-M_y \leq \bar{j} \leq M_y\), we approximate \(g(y_j)\) by solving for the number of grid points in the \(x\) direction that fall within the circle, half of which is given by \(M_x = \lfloor (\sqrt{r^2 - (\bar{j}h)^2})/h \rfloor\), along with the residual distance between the furthest grid point within the circle and the circle boundary, \(r_x = \sqrt{r^2 - (\bar{j}h)^2} - M_x h\). For grid points in the \(x\)-direction fully within the circle, we use the trapezoid rule
\[
\int_{x_i}^{x_{i+1}} f(x) \, dx \approx \frac{1}{2} [f(x_i) + f(x_{i+1})] h
\]
to approximate the integral. To approximate the integral between the boundary of the circle and the first grid point within the circle, \(x_1\), we first extend the domain of \(f\) to encompass \(x_0\), the first grid point beyond the circle. With the function at \(x_0\) and \(x_1\), i.e. \(f(x_0)\) and \(f(x_1)\), known we can calculate the slope between the two points as \(m = \frac{(f(x_1) - f(x_0))}{h}\), and thus we can approximate the function value at \(x^* = \sqrt{r^2 - (\bar{j}h)^2}\), the boundary of the circle using the linear interpolation method:
\[
f(x^*) \approx f(x_1) + \left( -\frac{f(x_1) - f(x_0)}{h} \right) (x_1 - x^*).\]
As \((x_2 - x^*)\) was already calculated to be \(r_x\), this becomes:

\[
  f(x^*) \approx f(x_1) + r_x\left(\frac{f(x_0) - f(x_1)}{h}\right).
\]

With \(f(x^*)\) known, we can approximate the integral from \(x^*\) to \(x_1\) as

\[
  \frac{(f(x^*) + f(x_1)}{2} r_x = \left(f(x_1) + r_x\left(\frac{f(x_0) - f(x_1)}{2h}\right)\right) r_x.
\]

As the area near the right-boundary can be calculated using a similar method, we can get a full approximation for \(g(y_j) = \int_{\sqrt{r^2 - y_j^2}}^{\sqrt{r^2 - y_j^2}} f(x, y) \, dx\). To calculate the outer integral, we can again use linear interpolation to approximate the value of \(g\) at both boundaries of the circle, then apply the trapezoid rule at all grid points, thus achieving an approximation of the 2d integral.

Our initial conditions are imposed directly as \(F_{i,j}^{0} = f(x_i, y_j, 0)\), and periodic boundary conditions are imposed as the conditions \(F_{N_x,j}^{n} = F_{0,j}^{n}\) and \(F_{i,N_y}^{n} = F_{i,0}^{n}\). A forward Euler method is used for time integration.
Figure 5.2: 2D numerical results with half MT-NF interaction strength over 9.5 hours. The left column indicates microtubule density while the right column indicates neurofilament density. Density remains relatively constant after 9.5 hours.
Figure 5.3: 2D numerical results with no MT-NF interaction over 7 hours. The left column indicates microtubule density while the right column indicates neurofilament density. Aggregate density remains relatively constant after 7 hours.
Chapter 6: Discussion, Contributions, and Future Work

The ability for the axon to properly transduce signals depends on its ability to maintain its shape, which in turn depend critically on the organization of its cytoskeleton. While microtubules and neurofilaments mix roughly uniformly in axonal cross-sections under normal circumstances, in many neurodegenerative disorders they separate radially with microtubules clustered centrally and neurofilaments located near the periphery. This distinct polymer segregation is an early hallmark of nerve degeneration, yet the mechanics behind it are still relatively poorly understood. Quantitative descriptions of the segregation process can thus lead to a better understanding of the mechanics of segregation and consequently a deeper understanding of a vital link in the nerve degeneration process.

We used a non-local PDE model developed based upon the macroscopic limit of a recent stochastic individual-cell model to study the cross-sectional distribution of axonal microtubules and neurofilaments, all of which are subject to Brownian motion, volume exclusion and interact with one another either directly or indirectly through axon transport. We use linear stability analysis and numerical simulations in both 1D and 2D with a focus on the spring interaction parameters encapsulating axon transport to determine the effect that changes in the rate of axon transport can have on the axon.

In Chapter 4 we successfully show that our model is able to replicate the segregative behavior seen in the previous stochastic model and in experimental data. Additionally we show that there exists a window in the strength of the fast axon transport of organelles,
encompassed by our microtubule-microtubule interaction parameter, above which segre-
gation is guaranteed to occur, below which segregation cannot occur, and inside of which
the behavior of the system will depend on the strength of stabilizing effect generated by
the slow axon transport of neurofilaments and other cargo. As a change from periodic to
no-flux boundary conditions had a similar effect to, all else held equal, an increase in the
microtubule-microtubule interaction parameter, the ratio of the strength of fast axon trans-
port to slow axon transport throughout the axon is likely to be a determining factor in the
behavior of the cytoskeleton distribution.

In Chapter 5 we extend our analysis to 2D, show that the model is consistent with earlier
results in 2D, and show that the behavior of the system under unstable conditions where
segregation is possible will still depend critically upon the flux rate of the fast axon transport
of organelles. Additionally, as segregation appears to occur slightly faster in 2D compared
with 1D, increased dimension appears to have a destabilizing on the system. This is po-
tentially related to the destabilizing effect of increasing domain size found in the 1D linear
stability analysis. As the mesh used for the 2D simulations was relatively coarse compared
to the size of the circles involved with the non-local integrals, their approximation using
the trapezoidal method may have suffered. The accuracy of the simulation could poten-
tially be improved either using a significantly finer mesh, or by switching the numerical
method used for the non-local integrals to the one described in [16]. The overall similarity
in results in both 1D and 2D indicate that any insights generated through the study of the
1D model are likely to carry over into the 2D model. As the computational cost of running
numerical simulations in 1D are relatively low, this can be viewed as a major advantage of
this continous PDE model over previous computationally expensive stochastic models of
the same phenomena.
There are several avenues through which further improvements to the model could be made, such as modifying the parameters involving axon transport of organelles to vary in time. As size and shape vary from organelle to organelle, it would be reasonable to assume that the radius in which the average organelle can interact with other polymers will depend on the current distribution of organelles in the axon, and thus will vary in time. Varying organelle sizes could also be incorporated by splitting our microtubule-microtubule interaction non-local integral term into several non-local integrals, with each non-local integral representing the indirect effect that organelles of a particular discrete set of sizes have on microtubules. Additionally as neurofilaments are transported laterally through the axon, in a fixed cross-section of an axon neurofilaments would appear stochastically throughout the domain, and thus an additional stochastic term for neurofilament density would be most natural.

A possible long-term extension for the model would be the extension to 3D using a fixed cylindrical domain to model a section of the axon. This would have the advantage of confirming whether the destabilizing effect of dimension carries over to 3D as well. Additionally, a fully 3D domain would allow us to model the effects of longitudinal transport, which are currently ignored for the purpose of the model.

As the model also currently ignores the effects of axonal swelling in order to focus on the segregation process, an extend model that includes the effects of swelling would help to develop a more complete understanding of the neurodegenerative disease process as a whole. As axon caliber translates to the model’s domain size, this could be accomplished by extending our PDE model to a model with a free boundary.

Lastly, as the analysis and simulations of the model in 2D used a square domain and periodic boundary conditions, further research could be done regarding the effects of a circular domain and no-flux boundary conditions - which better capture the shape of the axon.
and relative impermeability of the axon membrane - on the model’s behavior. This behavior can be explored through the study of numerically simpler radially symmetric solutions, which are solutions on a disk $\Omega$ of fixed radius that depend only on the radius $r$ from the center of the domain.
Bibliography


