USING CONTINUOUS LIMIT TECHNIQUES AND STOCHASTIC
COMPUTATIONAL MODELING TO PREDICT THE BIOLOGICAL
BEHAVIOR OF AGGREGATING CELLS.

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by

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USING CONTINUOUS LIMIT TECHNIQUES AND STOCHASTIC COMPUTATIONAL MODELING TO PREDICT THE BIOLOGICAL BEHAVIOR OF AGGREGATING CELLS.

Abstract

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Mathematical modeling and computational simulations can be used to predict the average behavior of many cell-cell interactions. In this thesis, results on modeling the predatory bacteria *myxococcus xanthus* and the slug forming amoeba *dictyostelium discoideum* are presented as well as results on random placement of non-overlapping cells in an individual based model, and continuous limits of discrete stochastic systems.

Periodic reversals in systems of self-propelled rod shaped bacteria can lead to ordering of cells, thus enabling them to effectively resolve traffic jams formed during swarming and maximize their swarming rate. A connection is described between a one dimensional cell-based stochastic model of reversing non-overlapping bacteria and a non-linear diffusion equation in [35] and this thesis. Boltzmann-Matano analysis is used to determine the nonlinear diffusion equation corresponding to the specific reversal frequency. It is shown that cell populations with high reversal frequencies are able to spread out effectively at high densities. If the cells rarely reverse then they are able to spread out at lower densities but are not able to spread out at higher densities.
The amoeba Dictyostelium is able to sense the location of other members of its species and aggregate, using chemotaxis. During aggregation, the amoeba creates and follows the gradient of a diffusive chemical. Through local behavioral chemotactic rules, the cells are able to cluster together and create slugs. PDE equations describing this behavior have been derived in [78]. Existence, uniqueness and boundedness of solutions of this equation are proven in [5] and this thesis. The 1D steady state solutions and their stability are also analyzed. It is predicted that stable solutions correspond to biologically realizable aggregates, and conditions for determining whether or not certain amoeba aggregation patterns will occur in nature are presented.
To my loving wife Sonje, whose encouragements have made this possible.
CHAPTER 5: DETERMINATION OF THE NONLINEAR DIFFUSION COEFFICIENT FOR MYXOBACTERIA MOTION

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CHAPTER 1

INTRODUCTION

Biological experimentation typically involves a large amount of trial and error as various parameters are tested and examined. This involves the expenditure of a lot of time and resources. Mathematical modeling and computer simulations can help predict the results of experiments and thereby guide biological experiments toward useful channels. This work develops new tools towards this goal. These tools are used to create new insights for guiding experimentation. We do this by examining simulation results and deriving mathematical continuous-limit equations. The equations are then analyzed to develop important insights about properties such as existence, uniqueness, boundedness, stability, and geometric structure of solutions to the equations.

The usual cycle for modeling biological problems is well known. A biological question arises that we attempt to answer by simplifying biological assumptions and by developing a computational or mathematical model. The choice of the model depends on the nature of the biological problem. The model is used for simulations or analysis that lead to predictions. These predictions are tested and compared to real world data. The results of these experiments are then used for validating or refining the model.

In this thesis, a specific approach to the modeling cycle is taken. Biological observations motivate the problems studied in this thesis. We start with generally
accepted rules governing specific biological system. These rules are formalized as an algorithm that drives stochastic computational models. The simulation results are used to develop analytical models, which is a very novel idea in mathematical biology. This idea drives this thesis. This is in the same spirit as traditional lab results being used to develop analytical models. Stochastic simulations are used because experimental data is not always available. Thus the simulation results replace lab experimental results. A Partial Differential Equation (PDE) is then derived from the simulation data using a specific approach to be described below or by using continuous limits. Finally, the PDE itself is analyzed and understood to make predictions that lead back to the biology. Another use of stochastic simulation results is to provide initial insights on what biological experiments might produce novel and interesting results concerning the behavior of the system.

There are two main ideas which we emphasize in this thesis:

1. The combination of stochastic computational models and PDEs yields a multiscale modeling environment which combines features at micro and macro scales.

2. Derivation of continuous limits of stochastic models, in the form of PDEs allows us to connect microscopic behavior with macroscopic observations. For example, in this thesis we demonstrate how reversal frequency of individual bacteria are used to calculate the nonlinear diffusion coefficient for a PDE describing hundreds of thousands of bacterial cells.

In Chapter 2, we review what is known about the observed biological behavior of myxococcus bacteria and slime-mold forming amoeba *dictyostelium*. In Chapter 3, past computational models for these systems are discussed with emphasis placed on what the models have predicted.
Next, in Chapter 4 we discuss continuous limit PDEs that describe the evolution of the discrete microscopic systems. Specifically, we review the literature on derivation of continuous limits using various model assumptions, and a data dependent method for numerically approximating diffusion coefficients. The later method is called Boltzmann-Matano Analysis. In Chapter 5, we use this method to approximate the nonlinear diffusion coefficient for reversing myxobacteria cells. A connection is drawn between the type of non-linear diffusion the system demonstrates and the reversal period. This work will also appear in [35].

The final two Chapters, 6 and 7, are on the analysis of a PDE equation modeling amoeba aggregation. Our new results on existence, uniqueness and boundedness of the solutions are discussed in Chapter 6, which justifies numerically solving equations describing aggregation of cells with chemotaxis (see [5]). Additional new results in Chapter 7 and in [34] present a classification of the 1D steady states, an analysis of the stability of the patterns, and when the solutions can be classified as spikes or plateaus. These results allow us to predict the type of non-trivial patterns that will form, which ones we predict will appear in nature, and some basic results on whether the pattern will qualitatively resemble a spike or a plateau.

In the Appendix A we derive the Transient Differential Chapman-Kolmogorov equation, which is a more general version of the well known Differential Chapman-Kolomogorov Equation (TDCK). In Appendix B, an application of the TDCK is presented where a continuous limit is taken to derive a new algorithm for random placement of non-overlapping cells according to a given probability density distribution.
2.1 Myxobacteria

Many species of bacteria spread rapidly over surfaces by the process of swarming. By aligning together and achieving directional movement, the cells work together and collectively travel at a faster rate than if they were aligned against each other. For certain species under starvation conditions, chemical signals are transmitted telling the cells to aggregate together and form biofilms. Biofilms protect the species and allow it to survive until conditions for growth are satisfied. Such biofilms can be found in a variety of places from the plaques formed on a person’s teeth to the interior of water drainage pipes. Both biofilms and swarming are demonstrated in both innocuous carbon-cycle organisms as well as harmful pathogens such as *Pseudomonas aeruginosa*. Understanding how these bacteria swarm and form biofilms will allow us to predict their ability to aggregate together and form these protective barriers, and prevent this from happening.

This chapter introduces and reviews two innocuous model organisms that are capable of swarming and generating patterns. The first is myxobacteria, a group of bacteria that consists of gram negative predatory delta proteobacteria that are capable of swarming, aggregating, and forming fruiting bodies. The second is
**dictyostelium discoideum**, an amoeba that is capable of swarming together into slugs which then moves towards sunlight before forming into a fruiting body. In both cases, the ecology and life cycle will be discussed and special attention will be directed towards the mechanisms for movement and swarming. Exposition in this review follows from [17, 21, 27, 41, 62, 63, 68, 99, 111].

### 2.1.1 Ecology of Myxobacteria

Myxobacteria are found predominantly in soil or the topmost layer of soil and decaying plant material [91]. However myxobacteria spores, dormant and non-reproductive structures, can be found everywhere from Antartica to the tropics, even in large bodies of fresh water. In many of the more extreme cases, it is possible that the cells may not naturally live in these places, but have been blown there from a hospitable habitat. They are obligate aerobe bacteria, but under sporulation their temperature and desiccation resistant myxospores allow them to survive in inhospitable habitats for over 20 years. While the cells may survive near the edge of salt water environments, large concentrations of salt will desiccate and kill the spores.

Myxobacteria’s primary food source consists are prey bacteria, but they are also reported to lyse green algae, yeast and fungus [91]. Myxobacteria is capable of aligning itself with the slime trails formed from other bacteria. It will then track down the prey bacteria by following the slime trail [21]. Finally, it will swarm around the prey bacteria before consuming it [63].

Under starvation conditions, the cells engage in a developmental process. The cells exhibit rippling patterns before aggregating into mound shaped fruiting bodies [58]. Cells in the mound then either lyse or undergo sporulation. Once con-
Figure 2.1. Myxobacteria life cycle including vegetation, rippling, aggregation, fruiting body formation and spore development taken from [58].
ditions are viable for the cells, the spores turn into individual cells, and the cycle begins again (see Figure 2.1).

2.1.2 Cell Motility

Myxobacteria cells are rods with rounded ends, about $1\mu m$ wide and $8 - 10\mu m$ long [20, 41]. When clustered with other cells, the cells line up together and produce long, thin, delicate swarm structures (see Figure 2.2). These structures allow for efficient movement of the cells with minimal collisions. By comparing the swarming patterns formed by knock-out mutants, biologists were able to distinguish between two different engines for cellular movement [47]. The engines and their motility type were subsequently named $A$ and $S$ where $A$ stands for adventurous motility and $S$ stands for social motility [63].

While wild type cells are able to effectively spread out, cells with only the $A$ engine, $A^+S^-$, produce long and strung out swarms [47]. In contrast, cells with only the $S$ engine, $A^+S^-$, create short and stubby swarms. In all cases, the swarms contain cells that move individually and in groups, suggesting that the cells swarming mechanism does not rely on just one method of motility but on general behavioral rules.

Unlike many other bacteria, myxobacteria do not have flagella to facilitate swimming [62]; instead the cell’s glide on a surface in the direction of the cells long axis [43, 63]. Wild type gliding cells are covered in slime and effuse most of the slime from over a hundred pores located at one end of the cell [114]. The slime then combines together in ribbons that stream away from the cell (see Figure 2.3). The calculated force generated from the slime propulsion is consistent with the amount of force necessary to propel gliding bacteria forward. This and the noticeable
Figure 2.2. Myxobacteria aligned together in a small cluster. Picture obtained with permission from Shrout lab Notre Dame.

Figure 2.3. Image of A and S motility engines in *Myxococcus xanthus* taken from [58]. The A-engine secretes slime and acts as a 'pusher' engine, while the S-engine projects and retracts type IV pili and acts as the 'puller' engine. Both engines are unipolar and coordinate with each other. Slime pores and basal pili proteins are present at both ends, but in wildtype are active at only one end.
connection between defects in slime production and changes in A-motility when certain genes are knocked out, has led researchers to infer that slime propulsion is responsible for the gliding motility of individual cells [65, 119].

Experiments show that individual $A^-S^+$ mutants extrude slime from both ends of the cell rather than a single end, and are thus unable to demonstrate directional movement [65, 119]. In particular, one type of $A^-S^+$ mutant is observed to oscillate rapidly back and forth [102]. With each oscillation, the cell travels less than one-fifth of the cell’s length. It is believed that the variation in speed of the oscillating bacteria is due to changes in the number of nozzles that are working at a specific time [62].

In addition to emitting slime from one end, type IV pili are observed at the polar opposite end of the cell [63]. These pili are long retractile hairs that are capable of extending out and grabbing onto fibrils that surround neighbouring cells. Once these pili grab on to fibrils, they retract and pull the cell towards its neighbour. Unlike slime, the pili are seen to emerge from a single pole of the cell but never from both ends at once [61]. Furthermore, the pili are never observed to emerge from the sides of the cell. The fibrils themselves are filaments that are responsible for the cohesion between cells [11, 12]. They only appear on cells in high density situations.

The $A$ and $S$ engines work together in a synergistic manner [116]. The $A$-engines allow the cells to work cooperatively since cells with this engine will follow the slime trails of other cells [21, 63]. The $S$-engines allows cells to interact and stay close to one another using the pulling action of the pili. Cells with both engines swarm at a maximum rate of $1.6\mu m/min$ while cells with one engine swarm at $1.0\mu m/min$ [64]. This observation has led researchers to posit that the
S and A engines occupy opposite poles of the cells.

It has been observed that in agar, myxobacteria are able to locate and find stationary objects that do not interact with the surrounding environment. When a sterile glass bead or a washed and incinerated polystyrene latex bead was placed in an agar plate containing myxobacteria, the swarm was able to consistently locate the beads [29, 63]. This form of movement is called "elasticotaxis", and has been linked to the cells ability to align themselves with compressed chains of amino acids. *Coralloccus exiguus* myxobacteria cells have been observed to align themselves with streaks in the agar, as well as perpendicular to lines of stress in compressed agar. [58, 103]. Elasticotaxis is linked to gliding behavior of the cells [32]. It requires A-motility to occur, and S-motility inhibits this form of movement.

It has been suggested that elasticotaxis can explain the cells ability to following a slime trail [58]. By aligning themselves with the amino acids created by prey bacteria, myxobacteria swarms are capable of following and hunting prey bacteria over a variety of surfaces. By aligning themselves with the slime trails of other myxobacteria, they are able to interact and communicate necessary signals for their development.

2.1.3 Reversals

Myxobacteria are observed to periodically reverse their direction of motion [60, 63]. This behavior is very counter-intuitive since individual bacteria want to move outwards in search of nutrients. Without the ability to reverse direction, the cells are unable to swarm together and can at best produce mounded shape colonies with sharp edges [104]. The cells do not reverse randomly in time and each
cell appears to have its own reversal clock [51]. On average, each cell reverses its gliding direction every eight minutes [113, 116], but other factors such as genotype and starvation conditions of the cell have been suggested to alter the reversal rate [54, 55].

The synergism between A and S motility suggests that not only do the A and S engines occupy opposite ends of the bacteria, but that reversals between engines are highly correlated [63, 100]. During a reversal, the cell will always stop for 1 minute to switch head and tail roles, but it should be noted that not all stops lead to reversals [55, 100] (also see [102] for interesting examples on stopping behavior).

The mechanism for reversals is governed by a complex biochemical clock [62]. The clock itself is believed to be regulated by the amount of C signal that the cell is exposed to due to the connection between how reversal period changes depending on cell density which is correlated to the amount of C-signal transmitted. Under starvation conditions, the behavior of wild type bacteria changes as they start producing C-signal. Exposure above a threshold of C-signal results in traveling waves of cells, where the cells are able to demonstrate rippling waves [50–52]. These waves are interesting because they travel at a constant velocity, and can pass through each other without any change in the amplitude. During rippling, the cell’s oscillation frequency has been observed to increase.

After about 6 hours of starvation, there is a transition from rippling to streaming - the reversals slow down before stopping altogether and the cells follow one another in streams [54, 56]. During streaming, bacteria that were near aggregation mounds were observed to have a decreased cell speed, lower stopping time and a decreased oscillation frequency suggesting that with enough C-signal the oscillation frequency will eventually decrease [55, 56]. Finally during aggregation,
the oscillation frequency vanishes as the cells no longer reverse and instead join the mound.

In a similar manner, it has been suggested that phosphatidylethanolamine, which is found on the cells outer membrane, may serve as an attractant during fruiting body formation since this chemical changes reversal frequency [66].

2.1.4 Colony Growth and Spreading

Cell growth happens slowly and only under non-starvation conditions when the swarm is expanding outwards. When a cell does eventually decide to divide, it produces two identical daughter cells where each one inherits a different motility engine from the parent [62]. The result of this is the initial polarity of the daughter cells will be identical to the parent. Cells reverse on average total of 20 times before reproducing once [113], giving an average of at least 2 hours and 40 minutes before a reproduction event.

In order to catch prey bacteria, it is important that the cells move fast. Individual wild type cells are capable of moving between $1 - 20 \mu m/min$ with an average velocity of $4.4 \mu m/min$, depending on the agar concentration and cell density [101, 102]. Cells less than $0.5 \mu m$ apart tended to move fast with an average velocity of $5.0 \mu m/min$ and in some cases around $20 \mu m/min$. In contrast, separated cells move slower at about $3.8 \mu m$. Only an eighth of this velocity can be attributed to cell growth [63, 64]. In order to determine the effect that growth has on swarming rate, non motile $A^-S^-$ cells have a colony that expands one-eighth the rate of the motile $A^+S^+$ due to colony growth [63, 64].

In order for the cells to travel faster at higher density than at lower densities, not only is alignment of the cells expected to occur, but there needs to be cell
to cell interactions that allows them spread out faster. As will be shown in later chapters, reversals and volume exclusion can be shown to cause this result.

2.1.5 Fruiting Body Formation and Cell Signaling

Myxobacteria under starvation conditions are capable of producing fruiting bodies. Limitation on any essential or nonessential amino acid, carbon, energy or phosphorous induces fruiting body formation [63, 80]. Single celled colonies are not prone to fruiting body formation. Only when hundreds of thousands of cells cooperate in starvation conditions are fruiting bodies readily formed. Within the fruiting body, vegetative cells are converted into desiccation-resistant myxospores that are capable of surviving harsh, inhospitable conditions [91].

Of the various mutants incapable of creating fruiting bodies, two of them, labeled A and C mutants, experienced mutations that define the extracellular signals that are exchanged between cells. The signalling mechanisms themselves are called A and C type signalling [63].

Under starvation conditions, two options are open to myxobacteria - either the cells can slow down their growth rate in hopes of not running out of nutrient, or it can initiate fruiting body development so cells can turn a few cells into myxospores [111]. Empirically fewer than one percent of the cells actually are converted to myxospores during fruiting body formation, so judging and projecting nutrient availability is important to a colony’s survival.

In particular, A-signalling has been found to help assess the availability of nutrients by activating after a build up of (p)ppGpp in the presence of limited resources [97]. This build up is believed to occur due to a lack of amino-acylated tRNA that require amino acids, energy and phosphorous [59]. In response to
extracellular A-signal, fruiting body formation is initiated if a certain density dependent concentrations are achieved - thus giving the cells a mechanism for quorum sensing before fruiting body initiation.

A second type of signalling found in myxobacteria is C-signalling. Like the A-signal, C-signal activity only occurs under starvation conditions [69]. However, it is also known that C-signal requires cells to be motile and occurs between cells with end to end contact [70]. The C-signal itself is a morphogen that ultimately manages cell movement and sporulation [62]. Low levels of C-signaling are capable of increasing their oscillation frequency [51, 93]. Once a moderate threshold of C-signalling molecules is achieved, cells maintain their reversal frequency and increase their speed (thereby increasing the distance between reversals) [55, 56, 62]. Such cells tend to form a chains or steams of end to end cells which ultimately leads to streaming and rotational behavior. When the C-signal molecules reach a second threshold, reversal are stopped altogether and the cells continue their pathway to sporulation.

2.2 *Dictyostelium Discoideum*

In order to understand how cells behave, model organisms are often used and studied. In particular, the amoeba *Dictyostelium discoideum* is easy to acquire and work with; and it is capable of demonstrating cell to cell communication and multicellular morphogenesis.

*Dictyostelium discoideum* is ubiquitous throughout the world, commonly found in soil and decaying leaves. They are most abundant in cool and temperate forests where there is organic matter and sufficient moisture to support them [22]. They commonly prey upon a wide variety of bacteria and yeast and under starvation
conditions are capable of forming fruiting bodies.

They experience competition for bacteria prey with and predation from nematodes which, when food is scarce, will rip out patches of the amoebas membrane [68]. While in an aggregate slug form, the amoeba develops a mucopolysaccharide-cellulose sheath that prevents the nematodes from penetrating it. During fruiting body formation, the *Dictyostelium* is able to rise above the larval stages of the nematode. However, the dauerlarva nematode form is able to climb the fruiting body stalk, into the spore mass, and cause the spore mass to slide down the stalk. Adult nematodes are then able to ingest the spores. The spores pass harmlessly through the gut and are dispersed simultaneously with bacteria spores up to 6cm by the motile worms.

Cells that are able to sense the approach of starvation continually synthesize and secrete prestarvation factor (PSF) that accumulates outside the cells in proportion to the cell density [17, 90]. PSF regulates the expression of genes responsible for aggregation. PSF is inhibited by the presence of bacteria [26]. When there is a large PSF/bacteria ratio, the cells will start expressing genes necessary for aggregation.

Under starvation conditions, the amoeba cease dividing, PSF production declines, and the cells secrete conditioned medium factor (CMF) [17, 68]. CMF is used as a quorum sensor that signals that continues the cells developmental program [53, 120]. The secretion rate of CMF is density development, and when a threshold of CMF is reached aggregation is permitted.

Between 5-10 hrs after starvation, the cells aggregate using cAMP as a chemoattractant [14]. The cells form large streams that break up into groups of around 20,000 cells [17]. These groups form slugs that will then crawl to the light. In
Figure 2.4. Image of *Dictyostelium* life cycle by David Brown and Joan E. Strassmann on DictyBase, http://www.dictybase.org. Cycle shows that cells can either undergo mitosis, form fruiting bodies, or create a macrocyst.
brightly lit, dry, open areas they then develop fruiting bodys which are a mass of spore cells supported by a 2mm high stalk. Approximately 20 percent of the cells vacuolate to become stalk cells and the rest are in the spore mass (see Figure 2.4).

Besides mitotic division, and fruiting body formation, cells are able to express a third cycle by creating a macrocyst [68]. As part of a sexual cycle, when two mating types are present in starvation conditions, cells fuse together to form a giant cell with two or more nuclei. The structure attracts other amoeba by chemotaxis with cAMP. These cells are cannibalized by the structure via endocytosis, and eventually the giant cell produces meiotic offspring (see Figure 2.4). 

While the macrocyst achieves aggregation in a similar manner as fruiting body formation, it does not have the characteristic slug formation and movement or the distinguishing of cell-types between spore and stalk cells.

There are many benefits for using *dictyostelium* as a model organism: it is how easy for biologists to work with, they can be grown in room temperature, cell division time is 8hrs making time lapse an option, cell can be grown to $10^{10}$ cells/liter, and the organism is accessible to high schools and researchers with limited budgets[17]. Also, strains of cells can be stored for long periods through lyophilization or in silica desiccation of the spores. Finally, a vast amount of sequencing information is available for researchers to analyze. In particular, online bioinformatics information and gene sequences can be found at http://dictybase.org/.
3.1 Markov Chain Monte Carlo Models (MCMC)

A Markov chain Monte Carlo method is a method for modeling realizations of a stochastic process, $X(t)$, using the generation of (pseudo)random numbers and the Markov assumption [13]. When the transition probability from one state to any other state is known, sample paths can be generated using knowledge of the current state. The literature on Markov modeling is quite vast, and well developed. For an introduction and information on theoretical results concerning Markov processes see [6, 13, 38] and the references therein.

By the definition of a Markov process, the finite time transition probability from one state to another can be completely determined by the given state without any additional knowledge of the past states. For a process with a countable state space, this translates to the equation

$$P(X(t_{n+1}) = a_{n+1}|X(t_1) = a_1, \ldots, X(t_n) = a_n) = P(X(t_{n+1}) = a_{n+1}|X(t_n) = a_n)$$

(3.1)

The Markov assumption allows one to move from state to state without any past knowledge. In the discrete time case, we can define the transition probabilities $P_{ij}(t)$ which is the probability of transitioning from state $i$ to $j$ at time $t$. If the
process is continuous in time one has

\[ P(X(t + h) = j | X(t) = i) = q_{ij}h + o(h) \] (3.2)

where \( q_{ij} \) is the transition rate from state \( i \) to \( j \), and \( o(h) \) is some function such that \( \lim_{h \to 0} o(h)/h = 0 \).

Since the transitions between states are countable, it is possible to order them by index, and generate a cumulative distribution. For a given realization up to time \( t \), one determines the state at the next time step by generating a pseudo-random number between 0 and 1, and based on where this number falls on the cumulative distribution will determine the chosen transition that the process accepts.

It should be noted that using stochastic modeling, such as Markov Chain Monte Carlo (MCMC) modeling, for determining statistical distributions can take a lot of computational time. For example, in order to determine the probability distribution that a random walker occupies an interval, \( I = [x, x + dx) \), at a given time step, \( t \), one would need to run thousands of simulations. By counting the number of instances that the walker is found in the interval and dividing by the total number of simulation runs, \( N \), we can get a probability for this event to occur. However, according to the central limit theorem, the rate of convergence for this process is \( O(\sqrt{N}) \) \([13]\), which means if we want to increase the accuracy of our probability measure by a single significant digit, we would need to run 100 times as many simulations. In such cases, accurate measurements quickly become intractable beyond at most a couple of significant figures.

It is possible to define Markov processes for non-discrete state spaces using
filtrations and stopping times (see [28] and the references therein), but since numerical simulations that are always discretized either due to placement on a grid or restrictions due to numerical accuracy, this refinement is not needed for our purposes.

3.1.1 Metropolis-Hastings Algorithm

In many situations, one does not know the transition probability itself, but instead knows a desired stationary distribution as well as a distribution that is proportional to the probability density by a normalization constant. This probability mass density distribution could be integrated to determine the normalization constant, but doing so would require sampling all possible transitions which is not always computationally feasible.

In such cases, one can utilize the Metropolis-Hastings algorithm, a Markov chain Monte Carlo method for sampling a probability distribution when given a probability mass density distribution, $q(x, y)$, as well as the stationary distribution, $\Pi^*$. The algorithm itself was first given by Nicholas Metropolis and his co-authors [81], and was extended by Hastings to include more general cases [42].

Given a current state $x$, the algorithm makes the transition to state $y$ with probability

$$p(x, y) = q(x, y) \min(1, \frac{\pi(y)q(y, x)}{\pi(x)q(x, y)}) \quad x \neq y \quad (3.3)$$

$$p(x, x) = q(x, x)\alpha(x, x) + 1 - \sum_{y \in S} q(x, y)\alpha(x, y) \quad (3.4)$$

where $S$ is a finite state space and $\pi(x)$ and $\pi(y)$ are stationary probabilities of states $x, y \in S$. 
It is important to note that this process satisfies detailed balance with the distribution $\Pi^*$, and so has stationary distribution $\Pi^*$ [13]. Furthermore, if the chain is irreducible, then the empirical distribution of many Metropolis-Hastings runs converges to $\Pi^*$. The dynamics will cause this Markov chain to behave as one would expect a Markov chain with the given stationary distribution to behave.

### 3.1.2 Gibbs Sampling

Often we can assign an energy, $E$ to the system, in which case we may assume that the stationary distribution of the system follows a Boltzmann distribution on the state space $S$. In this special case, $\pi(x) = e^{-E(x)/(k_B T)}$, for some given $k_B$ and $T$. Given that a state $x$ may have $n(x)$ neighboring states that it may transition to, it is possible to assume that each of the states is equally likely to be selected and define $d(x, y) = 1/(n(x))$ if $y$ is a neighbor of $x$, and 0 otherwise. In such a case

$$p(x, y) = \frac{1}{n(x)} \min(1, \frac{n(x)}{n(y)} e^{-\Delta E/(k_B T)}) \quad x \neq y \quad (3.5)$$

where $\Delta E = E(y) - E(x)$.

In many cases, symmetry allows us to see that the number of neighboring transitions is invariant to the current state or can be approximated as such with, $n(x) = n(y)$. This sort of assumption is common when modeling cell behavior, since a cell will theoretically be able to move, stretch, bend, or otherwise deform itself the same ways independent of location and how it is already deformed. We can model this algorithmically. Given the current state is $x$, we randomly choose a neighboring state, $y$. If $\Delta E < 0$ we set our state to $y$. Otherwise, we accept the state $y$ with probability $e^{-\Delta E/(k_B T)}$ and maintain state $x$ otherwise.
It is important to note, that this algorithm is local in nature. One does not need to calculate the stationary probability of every state, but only a randomly chosen neighboring state in order to proceed to the next step. As a result, this algorithm is very fast in comparison to a traditional Markov approach which requires computing every transition probability. In the case where one models the cell deformations, it is not uncommon to sample state spaces that are of the order $10^{15}$.

3.2 Review of Previous Computational Models and Simulation Results

In this section we review some of the literature on computational models of bacteria and amoeba behavior. We pay particular attention to what these algorithms were able to biologically predict and make some comments concerning their implementation.

Cell swarming is very important for the collective movement. If the cells are unable to align together, then they jam and cannot move. A computational off lattice model to approximate the swarming rates of cells swarming under various conditions was developed in [116, 117]. The model itself represents each cell as three nodes connected by springs. It has the head of the cell move with constant velocity and in case of collision applies a collision resolution algorithm to allow the cells to stall and align. The other two nodes of the cell are then updated using the Metropolis selection algorithm where the energy is determined by the amount of bending, and stretching the cell experiences. This model was able to show that cells can achieve a constant swarming rate over long periods of time and demonstrate how different engines influence the swarming rate in a synergistic manner [116].

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An interesting aspect of myxobacteria behavior is their ability to reverse. It is known that cells that cannot reverse cannot swarm effectively [104]. In order to find out why this is as well as what affect the reversal period has on the swarming rate, cells swarming was modelled using different reversal rates. It was shown that there is an optimal swarming rate and an optimal orientation correlation when the reversal rate is 8 minutes [117]. This optimal reversal rate is within the range of the observed reversal rate of wild type bacteria. While this is by no means a proof, it does suggest that the biochemical circuit governing reversal frequency in wild type myxobacteria has evolved under selection pressures to optimize swarming rate and alignment.

Rippling can be shown to occur as a consequence of increasing the reversal frequency as a cell experiences collisions using a variety of models and a variety of definitions of what a collision is. Using Lattice Gas models, rippling behavior was demonstrated as a result of collisions [1], where a collision occurs if two anti-parallel cells overlap in the interaction neighborhood of the cells. Furthermore, as the refractory period, the period where collisions do not influence cell behavior, increases, so does the characteristic wavelength of the rippling pattern.

A more general definition of collisions has the number of collisions a given cell experiences set as the number of neighboring particles whose direction is opposite to the current cell, i.e. has a negative dot product with respect to the direction of the current cell. Assuming cells reverse on collision, it is possible to use a simple individual based model of gliding cells to demonstrate rippling behavior [15]. Allowing instead that cell collisions increase the internal clock till the next reversal period, it is possible to also replicate the qualitative double peak in reversal times that was observed experimentally [16, 113]. Furthermore, since
having cells exhibit a refractory period was not necessary for rippling behavior, cells were able to ripple with no refractory period.

Efforts to model rippling behavior using continuous descriptions also exist. Recently, an advanced partial differential equation model has been developed that describes the evolution of cell densities that fall in five different classes: aligned with local slime gradient and moving, unaligned and moving, aligned and in its refractory period, unaligned and refractory, or stalled due to the collisions [52]. The model was constructed using phenomenological Markovian transition rates to determine how cells move from one class to another. C-signalling is incorporated by setting the reversal rate to increase at higher densities of motile cells. Under these conditions, the system is able to demonstrate rippling behavior consistent with experimentally observed ripples (see Figure 3.1). In particular, the waves are capable of passing through each other. When reversal rates are decreased in the presence of high density motile cells, the system displays the beginning aggregate of a fruiting body.

Figure 3.1. Rippling simulation results using a P.D.E. from [52] of a) ripples with constant distance between waves and b) the presence of planar waves with concentric and spiral waves.
Computational Models have also been developed that demonstrate aggregation. A Monte Carlo Markov Chain lattice gas model was developed where the cells preferentially align themselves with maximum C-signal transmission due to collisions [2, 71]. This has the effect of causing cells to follow one another in streams. These streams then are able to combine together into large stable aggregates that resemble those observed experimentally. If the aggregates are small or nearby other aggregates, they can dissipate back into streams and merge with nearby aggregates.

Recently, a 3D computational model demonstrating rippling and fruiting body formation has been introduced [48, 49]. Using Monte Carlo dynamics coupled with Metropolis-Hastings selection, the authors were able to demonstrate sufficient conditions for bacterial aggregation into three dimensional fruiting bodies (see Figure 3.2) as a natural consequence of cell behavior without centralised coordination. The energy term they used included stretching, alignment, bending, propulsion, slime, climbing, gravity, collision, and adhesion. Reversals are included and the
reversal rate is decreased in the presence of C-signal which is calculated based on the number of colliding cells. Unlike other models, their model does not use pili, but rather includes an alignment term to allow the cells to align. A climbing energy based on the number of nearby collisions is introduced to allow the cells to go over each other, and a gravity term to keep the cells grounded. Also, adhesion terms are included to simulate the effects of the extracellular polysaccharide in the biofilm allow the cells to remain close to each other. Without this term the cells escape the aggregate. A step-function collision energy is included to prevent cells from getting too close. In order to ensure the fruiting body does not dissipate over time, the model requires a constant influx of new cells from outside the boundary.

Early models of bacteria motion assume that myxobacteria cells exhibit chemotaxis and mitigate cell interactions by allowing cells to overlap [85, 105–107]. While these assumptions are incorrect for myxobacteria, the models do provide some interesting results for other bacteria and other cells that are chemotactic. By only allowing cells to follow slime trails, with no chemotaxis, simulations of cell motion show the cells are able to create transient aggregates [85]. Adding diffusion to the chemical causes the patterns to become stable. Diffusion is capable of smoothing out aggregates to make mound like clusters rather than spikes in the system [107]. Adding chemical decay increases the occurrence of smoothed aggregation centers.

By modeling the motion of a single cell as a biased random walk with persistence, it is possible to take a continuous limit and derive a Fokker-Planck equation and the corresponding SDE for this model [105]. Particles that follow this or similar chemotactic SDE will, in a weak sense, satisfy a Keller-Segal equation governing their distribution [106]. However, the Keller-Segal equation is known to display blow-up behavior by going to infinite density in finite time [46, 118].
Blow-up behavior is consistent with the spikes seen in the individual based models, but this behavior is not biologically realistic indicating a problem in one of the assumptions. In later chapters, an equation will be presented which was derived with volume exclusion constraints and it will be shown that it does not blow-up infinite time [78].
CHAPTER 4

CONTINUOUS LIMITS AND OTHER PDE DERIVATIONS

Discrete-time stochastic equations often rely on many simulations over a wide range of parameters in order to yield meaningful results. Computer modeling is severely limited by the computational power available. In contrast, if the limit PDE which approximates the discrete stochastic model were available (e.g. [78]), results would immediately be in reach. To determine sensitivity to parameter variation by simulation, we could, for example, try every single possible combination of parameters, or randomly choose different patterns. This can prove to be quite a daunting task, as it involves searching through a high-dimensional vector space (see [94] for information on this topic). When using stochastic simulations, bifurcations or phase transitions due to changes in one or more parameters may remain elusive to simple searches using numerical methods. In comparison, a PDE can be readily analyzed for transitions between stable and unstable steady states through linear stability analysis. PDEs are also helpful when modeling a very large number of cells. Where there are a large enough number of cells, stochastic simulations become unfeasible.

Hence, it is very useful to derive a PDE describing either the deterministic behavior of the cells, or the evolution of the probability density over time. These derivations often take the form of a continuous limit of the discrete stochastic dynamical system governed by basic discrete rules.
There are many approaches to deriving a PDE equation from a stochastic process. The first main approach involves taking the Taylor expansion of the probability density function, and removing higher order terms. It is applicable to situations where we know how the probability density function of a single or a few agents changes in time. The second major approach is to utilize the Differential Chapman-Kolmogorov (DCK) equation [33, 110]. It can applied to the same situations as the first approach, but one only needs to know the first few moments of the transition probabilities. In case one can describe a single particle’s evolution using a Stochastic Differential Equation (SDE), it is possible to use the equivalence between an SDE and the Fokker-Planck PDE [28, 33, 84]. In the case where there are many interacting agents, it is sometimes possible to take scaling or hydrodynamic limits where it is assumed that number of cells goes to infinity. In many situations, this is not possible since it is not obvious how to take such a limit. In these cases, numerical methods can provide data driven methods for deriving the underlying macroscopic limit PDE.

While Taylor expansions and the Differential Chapman-Kolmogorov equation are very useful for converting many stochastic processes to PDEs, they both assume the underlying probability distribution to be of the \( C^1 \) class with respect to time and \( C^2 \) class with respect to space. This assumption can be quite restrictive when dealing with discontinuous probability densities. Furthermore, in certain situations one wants to consider the evolution of a probability distribution over a subset of measure less than or equal to unity. In which case the probability density over the domain may fluctuate, something that is not allowed for in the DCK.

To address these issues, the novel Transient Differential Chapman-Kolomogorov
equation is introduced in this chapter and derived in appendix A as an extension of the DCK. This result allows us to take continuous limits on probability density distributions that are functionals over $C^2$. Also, we consider the evolution of the probability density in a subset, and allow for the local probability density to decrease or increase from an outside flow. As an example of its usage, the TDCK results will be used in appendix B to help establish an algorithm for random placement of non-overlapping cells.

Since knowing the various methods behind continuous limits is important, we discuss each of the above methods. First we demonstrate the classical result of deriving Brownian Motion using Taylor expansion. Rather than restate the commonly used Differential Chapman-Kolmogorov Equation, the more general Transient Differential Chapman-Kolmogorov equation is derived. The equivalence between SDEs and Fokker Planck equations is then shown. Comments concerning hydrodynamics/scaling limits are mentioned. Finally, we discuss the well known Boltzmann-Matano experimental method for deriving the non-linear diffusion coefficient.

4.1 Continuous Limits and a Classical Derivation of Brownian Motion Using Taylor Expansion

In general, continuous-limit equations are found by taking the limit of a family of equations describing the evolution of the discrete processes as a specified scaling factor goes to zero. In this case, we consider a single discrete equation and assume that the process’s probability distribution is sufficiently smooth that a Taylor expansion can be taken. Higher order terms are ignored when we take the limit as a specified scaling factor goes to zero. The resulting equation is a PDE whose
solution approximates the original discrete process

We review the classical example of a diffusion process being derived from the discrete random walk [6, 33]. This diffusion processes is one way to derive Brownian motion, and serves as the motivation for the differential Chapman-Kolmogorov Equation derived below. Consider a simple biased random walker on the set the infinite one-dimensional spacing $\Delta x$, $\Omega = \{0, \pm \Delta x, \pm 2\Delta x, \ldots \}$. We let $X(t)$ be a discrete time Markov Chain where $t \in \{0, \Delta t, 2\Delta t, \ldots \}$ with $X(t) \in \Omega$ and define the probability distribution $u(x, t) = P(X(t) = x)$. At each time step, we assume the walker randomly decides to move either left or right. Assuming he moves right with probability $p$, and left with probability $q$, with the condition that $p + q = 1$. This gives

$$u(x, t + \Delta t) = pu(x - \Delta x, t) + qu(x + \Delta x, t). \quad (4.1)$$

As described above, we assume that $u(x, t)$ is of class $C^{2,1}$ and is defined for all $x \in (-\infty, \infty)$ and $t \in [0, \infty)$. Performing a Taylor expansion we have

$$u(x, t + \Delta t) = \left[ u(x, t) - \partial_x u(x, t) \Delta x + \partial_{xx} u \frac{(\Delta x)^2}{2} + O((\Delta x)^3) \right]$$

$$+ q \left[ u(x, t) + \partial_x u(x, t) \Delta x + \partial_{xx} u \frac{(\Delta x)^2}{2} + O((\Delta x)^3) \right] \quad (4.2)$$

$$= u(x, t) + (q - p)\partial_x u(x, t) \Delta x + \partial_{xx} u \frac{(\Delta x)^2}{2} + O((\Delta x)^3) \quad (4.3)$$

Subtracting $u(x, t)$ from both sides, and dividing by $\Delta t$ gives

$$\frac{u(x, t + \Delta t) - u(x, t)}{\Delta t} = \frac{1}{\Delta t} \left[ (q - p)u_x(x, t) \Delta x + u_{xx} \frac{(\Delta x)^2}{2} + O((\Delta x)^3) \right] \quad (4.4)$$

In order to take the limit as $\Delta t, \Delta x \to 0$, we assume that the following scaling
conditions are satisfied:
\[
\frac{(\Delta x)^2}{\Delta t} \xrightarrow{\Delta t, \Delta x} D,
\]
and
\[
\frac{\Delta x}{\Delta t} (p - q) \xrightarrow{\Delta t, \Delta x} c.
\]

The former assumes that in the limit we have \( \Delta x^2 \propto \Delta t \), and the latter assumes for \( c \neq 0 \) in the limit the scaling \( p - q \propto \Delta x \). It is straightforward to observe this happens if and only if as the time and space step decreases, \( p, q \xrightarrow{\Delta t, \Delta x} \frac{1}{2} \). This condition is satisfied if \( p = \frac{1}{2} + c\Delta x + O(\Delta x^2) \) and \( q = \frac{1}{2} - c\Delta x + O(\Delta x^2) \).

Taking the limit yields
\[
\partial_t u = -c\partial_x u + \frac{D}{2} \partial_{xx} u \tag{4.5}
\]
for \( x \in (-\infty, \infty) \).

If we assume the partial is located at \( x_0 \) at time \( t = 0 \), i.e. the probability density at \( t = 0 \) can be described by the dirac-delta function \( u(x, 0) = \delta(x - x_0) \) and \( X(0) = x_0 \), then this partial differential equation has solution
\[
u(x, t) = \frac{1}{\sqrt{2\pi Dt}} e^{-\frac{(x - x_0 - ct)^2}{2Dt}}.
\]

For \( c = 0 \), the probability distribution is a Gaussian distribution, which is the distribution for Standard Brownian motion, or the Wiener processes. It is often used to describe how moving particles experience random perturbations or how heat spreads along a metal rod. Here it describes the probability density for where the walker will be at a given time step.

It should be noted that for fixed \( t \), the resulting probability distribution is
uniquely defined by its mean $x_0 + ct$ and variance $Dt$. This indicates that on average the walker drift $ct$ units, but its standard deviation grows proportionally to $\sqrt{t}$. As such, we expect the random walker to be modelled by the random variable $x_0 + ct + N(0, \sqrt{Dt})$ where $N(0, \sigma)$ is the Gaussian Distribution with mean 0 and variance $\sigma$. In the following section, we will show how the Differential Chapman-Kolmogorov equation can determine the appropriate continuous limit given the mean and variance.

In order to take the Taylor expansion above, we need the underlying probability distribution to be $C^1$ class with respect to time and $C^2$ class with respect to space. As we will see in the next section, it is sufficient to assume the probability distribution is a $C_0^\infty$ distribution with respect to space which allows for more general probability distributions to be described.

4.2 Differential Chapman-Kolmogorov Equation and extensions

Rather than taking a Taylor Expansion and cancelling out terms every time, it is possible to create a general result for the limiting process as the volume and time go to zero. This result is known as the Differential Chapman-Kolmogorov Equation [33] and it requires that one only needs to understand the limits of the first and second moments of the transition probabilities for a stochastic Markov process that is discrete in time. See appendix A for details.

4.3 Stochastic Differential Equation (SDE) equivalence to a PDE

In many cases, one can describe their process in terms of how a particle fluctuates under a variety of forces both deterministic and stochastic. Common examples include Brownian motion in a gravitational well, or a deterministic particle’s
trajectory with noise added to it. Such systems are traditionally represented in the physics literature with a Langevin equation of the form

\[ \frac{dx}{dt} = a(x, t) + b(x, t)\eta(t) \]  \hspace{1cm} (4.6)

where \( \eta \) is white noise with the properties:

\[ \langle \eta(t) \rangle = 0 \]  \hspace{1cm} (4.7)
\[ \langle \eta(t)\eta(t') \rangle = \delta(t - t'). \]  \hspace{1cm} (4.8)

This can be formulated as the more rigorously defined stochastic differential equation (SDE)

\[ dx(t) = a(x, t)dt + b(x, t)dW(t) \]  \hspace{1cm} (4.9)

In this section, we offer a formal argument that the evolution of the probability density for the stochastic differential equation satisfies a Fokker Plank equation. This establishes a connection between the PDE description for how the probability density evolves and the random trajectory of a single particle.

As in the derivation of the TDCK, we assume the process observes specific types of boundary conditions that allow us to ignore the effects of boundary terms later. Situations where it is viable to discard the boundaries include infinite boundary conditions or absorbing boundary conditions, where the probability density goes to zero, or periodic boundary conditions when the boundary terms cancel.

The derivation is similar to the one found in [33, 110]. For a more rigorous derivation of these results using measure theory and martingale properties, see 34.
[28, 30].

Let $x(t)$ be a random variable that satisfies (4.9). We now consider the time development of an arbitrary function, $f(x(t))$ and use Ito’s formula to describe its evolution.

$$df(x) = (a(x,t)\partial_x f(x) + \frac{1}{2} b(x,t)^2 \partial_x^2 f(x))dt + b(x,t)\partial_x f dW(t)$$  \hspace{1cm} (4.10)

Let $< \cdot >$ be the average value or expectation with respect to the transitional probability $p(x,t|x_0,t_0)$. With this, and the observation that

$$< \int_0^t b(x,s)\partial_x f dW(s) >= 0,$$

we have that

$$\frac{d}{dt} < f(x(t)) >= a(x,t)\partial_x f + \frac{1}{2} b(x,t)^2 \partial_x^2 f$$ \hspace{1cm} (4.11)

$$= \int (a(x,t)\partial_x f + \frac{1}{2} b(x,t)^2 \partial_x^2 f)p(x,t|x_0,t_0)dx$$ \hspace{1cm} (4.12)

By construction, we also have

$$\frac{d}{dt} < f(x(t)) = \frac{d}{dt} \int f(x)p(x,t|x_0,t_0)dx$$ \hspace{1cm} (4.13)

$$= \int f(x)\partial_t p(x,t|x_0,t_0)dx$$ \hspace{1cm} (4.14)

Equating (4.11) and (4.13), we can use integration by parts and assuming the
process is such that we can discard the boundary terms, we can get

\[
\int f(x) \partial_t p(x, t|x_0, t_0) dx = \int f(x) (-\partial_x [a(x, t)p(x, t|x_0, t_0)] + \frac{1}{2} \partial_x^2 [b(x, t)^2 p(x, t|x_0, t_0)]) dx \quad (4.15)
\]

Since \(f(x)\) is arbitrary, using standard arguments using cut-off functions it holds that

\[
\partial_t p(x, t|x_0, t_0) = -\partial_x [a(x, t)p(x, t|x_0, t_0)] + \frac{1}{2} \partial_x^2 [b(x, t)^2 p(x, t|x_0, t_0)] \quad (4.16)
\]

With this equivalence between SDEs and the Fokker-Planck PDE, it is both possible to solve for the probability density of the stochastic processes using the PDE description and it is possible to get statistics about the PDE but numerically integrating the SDE. More importantly, we can view the process in two different ways in terms of how single realizations behave versus how the probability density evolves.

4.4 Hydrodynamic Equations

Difficulties arise when one considers processes with many cell-cell interactions. While a particle moving stochastically along a force gradient is straightforward to describe, the situation becomes tricky when the force gradient is generated from many particle-particle interactions. In this case, one needs to be careful in how limits are taken since adding an infinite number of interacting particles could cause the force to diverge.

In such cases, one often uses more rigorous methods of determining the continuous limit which often fall under the category of the so-called hydrodynamic
or scaling limits. In this method, one starts off with a stochastic Markov process, generally an interacting particle system where particles are allowed to move on a discrete lattice. Then one assumes the existence of a family of scaled Markov processes where each element corresponds to a different scaling that contains more particles and lattice sites. The goal is to prove that for each fixed time, the empirical measure of the scaled Markov processes converges in probability to a diffusion process that can be described using a PDE. Generally these proofs use Prohorov’s criterion to show that the sequence is relatively compact, so that there are convergent subsequences, and then show that all subsequences converge to the same limit. The limits and the solutions to the partial differential equations are all done in a weak sense and the conclusions can often be extended to stochastic processes on exotic domains, so the results are much more general. However the machinery is quite involved and the results are often hard to prove for general stochastic Markov processes. The methods that mention the convergent PDE often times require constructing an appropriate martingale based on foreknowledge of the desired PDE the system will converge to. [28, 30, 72, 76, 77]

In many cases, one needs to be careful how they take the continuous limit. It is not always obvious how to take the continuous limit of a stochastic process with many particle-particle interactions either because the rules governing the microscopic behavior are completely unknown, they are complicated, or a naive continuous limit might give a deceptive answer. In particular, consider adding the volume exclusion conditions where the cells cannot overlap to a known process. Even a process as simple as a simple random walk can have ambiguous continuous limits when we include volume exclusion. Taking the approach of keeping the density constant by assuming that the particle size goes to zero as the number of
particles goes to infinity creates a process identical to the process with no volume exclusion [76, 77, 96]. A biased random walk creates a viscous Burger’s type equation with constant diffusion,

\[ \partial_t u = D \partial_x^2 u - a \partial_x (u(1-u)), \]  

which matches individual based models, where \( u(x,t) \) is the density and \( D \) and \( a \) be constants derived from the limit [96]. However, it is also possible to keep cell volume size constant and calculate the second moment using the average amount of time it takes for two cells to separate the expected separation distance of a given density. Using this method, a nonlinear diffusion equation demonstrating shock waves has been derived. In contrast, by assuming the cells follow a random walk and looking at the moments for two cells interacting, it is possible to derive a completely different diffusion term for the random walk (see [5, 78], and Chapter 6). It should be noted that this equation was derived in the case of chemotactic interactions, so here we consider the equation with no chemotaxis.

Both derivations assume a random walk with volume exclusion, but result in very different behaviors. When a chemotaxis term is added to each equation, the former demonstrates blow-up indicating that all cell density is concentrating on a single location [46, 118] and the later equation has bounded solutions for all finite time,[5] and Chapter 6. This is most likely due to the application of volume exclusion in the derivation.
Various particle-particle interactions such as cell overlap, non-local interactions, or time dependent cell behavior often make calculating the continuous limit very difficult. In such cases it is often times best to use numerical methods to measure the diffusion beforehand to provide an insight for future mathematical calculations. In this section, we go over a couple of different ways for measuring the numerical diffusion coefficient which best work for infinite boundary conditions and periodic boundary conditions respectively.

The Boltzmann-Matano analysis is a method for solving for the nonlinear diffusion coefficient that was originally solved by Boltzmann in 1894 and empirically derived by Matano in 1933. Here we review how the Boltzmann Matano Analysis is performed in a similar manner as [40]. We consider the evolution of the non-linear diffusion equation, but we assume initially the solution is a heavy side function on an infinite 1D domain and has boundary conditions $u(-\infty) = u_L$ and $u(\infty) = u_R$ with $u_L > u_R$. Assuming the density distribution of the process can be described by the diffusion equation

$$u_t = [D(u)u_x]_x \quad \text{(4.18)}$$

and motivated by the self similarity of solution of the heat equation, it is possible to consider a change of variables $\zeta = (x-x_M)/t^{1/2}$ where $x_M$ is a variable representing the Matano Interface that will be calculated later using a consistency condition. Since
\[
\frac{\partial}{\partial t} = -\frac{1}{2} \zeta \frac{\partial}{\partial \zeta} \\
\frac{\partial}{\partial x} = \frac{1}{t^{1/2}} \frac{\partial}{\partial \zeta}
\]

we get

\[-\frac{\zeta}{2} u_\zeta = \left[ D(u) u_\zeta \right]_\zeta. \tag{4.19}\]

Assuming that the density distribution evolves from a diffusion equation, it follows that for any given fixed time \( u \) is invertible with respect to \( x \) due to the monotonicity of the density profile. Here and later we abuse notation and let \( x(\cdot) := u^{-1}(\cdot) \). At this point, we integrate both sides of (4.19) with respect to \( \zeta \) to get

\[-\frac{1}{2t^{1/2}} \int_{u_L}^{u} (x(u) - x_M) du = D(u) u_\zeta \]

where the left hand side follows from

\[
\int_{-\infty}^{\zeta} \zeta u_\zeta d\zeta = \int_{u_L}^{u} \zeta(u) du = \frac{1}{t^{1/2}} \int_{u_L}^{u} (x(u) - x_M) du.
\]

Since \( \frac{\partial u}{\partial \zeta} = t^{1/2} \frac{\partial u}{\partial x} \), we rewrite the equation as

\[
D(u) = -\frac{1}{2t} \left[ \frac{\partial u}{\partial x} \right]^{-1} \int_{u_L}^{u} (x(u) - x_M) du, \tag{4.20}
\]

which gives us the Boltzmann description of the diffusion equation.

Now we calculate the appropriate value of the interface, \( x_M \), to ensure that the diffusion calculation is consistent. Specifically since mass diffuses from the left
to the right across the interface, there is a mass conservation equation where the
mass lost on the left of the interface should equal the mass gained on the right of
the interface,
\[ \int_{-\infty}^{x_M} (u_L - u(x))dx = \int_{x_M}^{\infty} (u(x) - u_R)dx. \]
Again inverting \( u(x) \), we can calculate the area under of the integrals in terms of
\( x(u) \) to get the following equivalent expression
\[ \int_{u_M}^{u_L} (x(u) - x_M)du = \int_{u_R}^{u_M} (x_M - x(u))du, \]
which simplifies to
\[ \int_{u_L}^{u_R} (x(u) - x_M)du = 0. \]
Mass conservation occurs precisely when
\[ x_M = \frac{\int_{u_R}^{u_L} x(u)du}{u_L - u_R}. \] (4.21)
Since we cannot physically evolve a system on an infinite domain, it is worth noting
that the above assumptions can be approximated when we start the process on
a heavy side distribution with long domain. However, boundary conditions will
influence the results of the diffusion calculation, so the analysis is only accurate for
short times when boundary effects are minimal. Similarly, by evolving the system
on a wide hat within an significantly wider domain and then ignoring one half of
the resulting distribution, we get a step function that has experienced minimal
boundary effects. This is important if it is not easy to initialize cells of finite
length near a no-flux boundary.

In short, to get the diffusion coefficient, all one needs to do is evolve the heavy
side function for enough time that diffusion occurs, but short enough time that boundary effects are negligible, and then solve (4.21) and (4.20) using the resulting distribution.

In Chapter 5, we consider the example of cells that glide and reverse at a deterministic time. Due to the time dependant reversals, and the prevention of cells from overlapping, the system is not Markov if one does not keep track of the reversal time. However, by numerically analysing the average behavior of the system using Boltzmann-Matano analysis, it is possible to see that the cell density can be predicted using a non-linear diffusion equation.

While there are alternate methods for calculating the diffusion coefficient [57, 73], Boltzmann-Matano is sufficient and traditionally reliable.
CHAPTER 5

DETERMINATION OF THE NONLINEAR DIFFUSION COEFFICIENT FOR MYXOBACTERIA MOTION

5.1 Introduction

Many bacteria including species found in diverse soil and water environments are able to spread rapidly over surfaces by the process of swarming which is the collective motion of many thousands of cells. The bacteria capable of swarming span the gamut of utility and range from innocuous carbon-cycle organisms to harmful pathogens. Swarming can be achieved by directional movement from pulling with type IV pili and either propulsion from rotating flagella or pushing with secretions of slime [60]. In certain cases, these mechanisms work together and allow the cells to swarm at a rate faster than each individual type of motility [64, 116].

For example, *Myxococcus xanthus*, ubiquitous bacteria found in soil, are very efficient swarmers. These bacteria have elongated rod-type shapes (about 7µm in length and 0.5µm in width) and move by gliding over a surface in the direction of their longer axis [60, 116, 117, 119]. They align and travel together in the same direction (see Figure 5.1a) as well as reverse direction about every eight minutes [60, 82, 117]. Mutant species of Myxobacteria that are unable to reverse are also unable to swarm [63, 117].
Figure 5.1. a) Swarm of \textit{M. Xanthus}, picture taken by Lotte Jelsbak. The edge of the swarm displays a single layer of cells that are spreading outwards away from the cell center [60]. b) Distribution of cells at the swarm edge [117]. The multicellular structures slime trails, mounds, and rafts are labeled. The swarm is expanding in the radial direction, which is to the right of the image.

The expansion rate of a wild type \textit{M. xanthus} (A+S+) (with pili VI and slime engine) swarm is $\sim 1.4 \mu m/min$ while the average velocity of individual myxobacteria is $\sim 4 \mu m/min$ [117]. It has been shown that a reversal period of $8.8 \text{min}$ maximizes the expansion rate for a given average cell velocity of $4 \mu m/min$ [117]. Also, large aspect ratio of cells and their ability to bend promote bacteria alignment which also increases swarming. Velocities of mutant (A-S+ and A+S+) are equal to the velocity of the wild type bacteria (A+S+).

Experimental observations suggest that their capacity to swarm depends less on the motility engine employed by individual cells and instead on the behavioral algorithms that enhance the flow of densely packed cells [60, 117]. Because of that we focus in this chapter on the study of self-propelled motion of rod shaped bacteria without specifying motility engines. We use behavior rules of \textit{M. xanthus} for setting a model for studying basic mechanism of swarming that results from
cell-cell collisions (jams) and regular cell reversals.

After an agar plate is inoculated in the center with myxobacteria, they start growing and moving, and the swarm expands. 90% of the expansion is caused by cell movement and only 10% by growth [64]. On the average every 8 minutes each one of them stops and starts moving in the opposite direction. Such motion is limited by new cells moving out from the center. Therefore, a cell in many cases can not move full 8 minutes in the direction towards the center. When encountering a cell moving in opposite direction cell stops and waits till it is time to start moving again away from the center. The swarm grows symmetrically in all directions (see Figure 5.1a). The symmetry dictates that there is net movement only in radial directions.

Recently, an off-lattice two-dimensional (2D) microscopic stochastic model (MSM) described in [116] has been able to predict optimal reversal rates for specific bacteria velocities, reversals frequencies and aspect ratios leading to maximal swarming rates of the colony by allowing cells to align better and resolving traffic jams which was confirmed in the experiments [117]. That model takes into account shape and direction of motion of each Myxobacteria in the colony as well as two motility mechanisms: pili VI and slime production. Such detailed description is computationally intense and makes any analytical description difficult.

This chapter focuses on studying the basic phenomenon of swarming by modeling a small part of colony near the edge of the swarm where motion of bacteria is nearly one-dimensional in the radial direction (see Fig. 5.1). We assume that cells cannot climb onto each other and that no more than one cell could be located at any moment of time at specific space (excluded volume constraint). The cells are modeled as self-propelled rods gliding on slime on the substrate with the
same constant velocity and reversing direction of their motion periodically in time which serve as a mechanism for diffusion. We do not incorporate the directional effects of slime, nor the social motility governed by pili in the model. Our model addresses only the basic effect of reversals and does not include any mechanism for growth of cells or details related to specific motility engines that would be necessary to recreate specific swarming behavior.

Our main result is that we establish a connection between one-dimensional (1D) microscopic and macroscopic models and relate their parameters to each other, to study swarming of bacteria reversing at different frequencies. Microscopic 1D discrete stochastic model is a 1D simplified version of the full 2D model [116]. 1D macroscopic model is a nonlinear diffusion equation for cellular density describing dynamics of self-propelled non-overlapping rods with regular reversals.

Although, only few models based on biological cell behavior exist which take cell volume into account and prevent cells from overlapping, such models are more biologically relevant and can provide novel insights. Recently continuous limit models describing dynamics of cellular density were derived from the microscopic motion of randomly moving cells exhibiting volume exclusion and chemotaxis [3, 4, 78]. In particular, the reference [78] describes a nonlinear diffusion equation model with chemotactic term of amoeba aggregation without blow up of solution in finite time [5]. This is in sharp contrast with the standard but biologically less realistic Keller-Segel equation (sometimes also called Patlak-Keller-Segel equation) with constant diffusion coefficient [67, 87] which neglects the size of bacteria resulting in solution (bacterial density) having a blow up (collapse) in finite time [19, 79].

Another 1D continuous limit equation was recently derived from a model of cells that interact using Hooke’s Law [83]. This equation also displays nonlinear
fast diffusion, and looks similar to the porous medium equation but with a negative exponent. This model agrees well with the discrete system from which it is derived and it is capable of effectively making biological predictions for cells that can be modeled as stiff springs.

This chapter is organized as follows. In Section 5.2 we introduce the Microscopic Stochastic Model (MSM) of cellular dynamics as 1D motion of self-propelled rods with periodic in time reversal of the direction of their motion. In Section 5.3 we describe the general settings for MSM simulations. We perform multiple MSM simulations of 1D the dynamics of initially localized distributions of bacterial colonies. In Section 5.4 we introduce a nonlinear diffusion equation of the general form

$$\partial_t p = \partial_x \left[ D(p) \partial_x p \right], \quad (5.1)$$

where $p(x)$ is a local cell density (measured in units of volume fraction, i.e. the ratio of volume occupied by cells to the total volume of space), $x$ is the spatial coordinate and $D(p)$ is the nonlinear diffusion coefficient determined using Boltzmann-Matano (BM) analysis [40] on the ensemble of averaged MSM simulations of bacteria motion with different reversal frequencies. The equation (5.1) describes the macroscopically averaged dynamics of cellular density vs. microscopic description of MSM model. We compare the dynamics of cellular density from MSM simulations with the simulations of the equation (5.1) for different reversal frequencies and find very good agreement between these two types of simulations for $p > p_0$. This confirms that the dynamics of cellular density is indeed of a nonlinear diffusion type (5.1). In section 5.5, we provide additional testing of the accuracy of Boltzmann-Matano for cellular distributions of finite
size. Finally, in Section 5.6 we discuss our main results and future directions.

5.2 Microscopic Stochastic Model of Cell Motion

In this section, we introduce the computational model of cellular dynamics as 1D motion of self-propelled rods that reverse their direction periodically in time. Namely, we use a discrete microscopic stochastic model (MSM) on a 1D lattice.

We simulate a constant number of cells of length \( L \) that move back (left) and forth (right) in a spatial domain along the coordinate \( x \) with periodic boundary conditions, a fixed reversal period \( T \), and a velocity \( v \). In dimensionless units we assume that \( L = 1 \) and \( v = 1 \). Each cell is represented by a finite number of lattice sites on 1D grid. For typical simulations, each cell includes 10 lattice sites, i.e. the distance between lattice sites is \( \Delta x = 0.1 \) (see Figure 5.2 a). Respectively, the time step in dimensionless units is 0.1. However we also ran separate simulations to make sure that increasing number of lattice sites per cell (but keeping \( L = 1 \) and decreasing the time step to keep \( v = 1 \)) does not significantly change our results so that a particular grid size of a lattice is not important. For \( \Delta x > 0.05 \), the results are qualitatively similar. For \( \Delta x \) around 0.01, the density and resulting diffusion description shows larger diffusion around 0.3, and smaller diffusion at larger densities. Running simulations at this lattice size is computationally expensive so unless stated otherwise, we set \( \Delta x = 0.1 \).

Unless otherwise specified, we choose \( T = 8 \). Each cell has an assigned reversal phase, \( \phi \), between 0 and 2\( T \) corresponding to the time when cell reverses from moving to the right to the motion to the left (i.e. cell reverses from right-directed motion to the left-directed at times \( t = \phi, 2T + \phi, 4T + \phi, \ldots \)). Reversal in the opposite direction occurs at at times \( t = \phi, T + \phi, 3T + \phi, \ldots \).
The following two dimensionless parameters completely determine the dynamics of cells. First parameter is \( vT/L \), which is the ratio of distance traveled by cells between reversals and the cell length. That parameter is \( vT/L = 8 \) for the typical value \( T = 8 \). The second dimensionless parameter is the local cellular density \( p(x) \) measured in units of volume fraction \( p \), i.e. the ratio of volume occupied by cells to the total volume of space (in 1D, volume is simply the length).

For example, we can choose the velocity, the reversal period and the cellular length as \( v_{\text{dim}} = 10 \mu m/min, \ T_{\text{dim}} = 8 \text{min} \text{ and } L_{\text{dim}} = 10 \mu m \), respectively, as dimensional units. This gives \( v_{\text{dim}}T_{\text{dim}}/L_{\text{dim}} = 8 \) similar to the typical dimensionless values we chose above. This choice is consistent with cell lengths and reversal period used in previous computational models [116, 117] and observed in experiments [63].

At each time step the model determines cell movement based on the occupancy of the next lattice site in the direction the cell is moving (direction is determined by \( \phi \) at the given time \( t \)). If the next lattice site is free, the cell is moved 1 lattice site in that direction (keeping constant length \( L = 1 \)). If the location is not free, the cell does not move and is considered jammed.

The model itself is stochastic. During each time step, a sequence of \( N \) randomly chosen cells are attempted to move one at a time, where \( N \) is the total number of cells. It is possible that the same cell may move more than once during a time step, and as a result some other cells may not move at all. Also, note that random selection of cells may create gaps between cells that are following each other (see Figures 5.2b and 5.2c for examples of possible cellular movement). Creation of such gaps is equivalent to the additional diffusion each cell experiences in addition to the directed motion with the speed \( v \). That diffusion is an artefact.
Figure 5.2. a) Diagram of a single cell with marks designating absolute location versus lattice index. b) Sample movement in a single time step where one cell is chosen twice and the other is not chosen at all. c) Sample movement of three cells where each cell is chosen exactly once.
of the finite width $\Delta x$ of each lattice site and it vanishes as $\Delta x \to 0$. We checked in simulations that reduction of $\Delta x$ from 0.1 to 0.001 gives only small changes for the cellular density dynamics shown below.

The additional diffusion from finite value of $\Delta x$ can be interpreted as independent fluctuations of the reversal period $T$ of each cell near the average value $T$. We also studied the role of noise in the reversal period by explicitly introducing fluctuations of $T$. We ran simulations by generating the next reversal time as a Gaussian random variable of mean $T = 8$ and small standard deviations, re-sampling if the next reversal time is negative. For standard deviations less than 2 the dynamics of cellular density did not noticeably change and the diffusion curves appear invariant. For larger standard deviations, the diffusion coefficients begin to flatten out (see Figure 5.3).

![Figure 5.3. Diffusion coefficient for different variances in the chosen Gaussian reversal period](image)

Figure 5.3. Diffusion coefficient for different variances in the chosen Gaussian reversal period
Fluctuations of $T$ are possible for Myxobacteria but experiments typically have only small fluctuations of the reversal time so their probability is sharply peaked near average reversal period $T$ [113]. Combined with our simulations it appears that fluctuations of the reversal time are not important for swarming. We have verified in simulations that noise in $T$ does not change the outcome even for considerable levels which also consisted with previous work [117].

Unless otherwise specified, the simulations are run on a one-dimensional lattice domain of length 4,000 centered at $x = 0$ using an initial top-hat distribution of cells of width 1,000 also centered at $x = 0$ (i.e. density of cells is approximately constant $p \equiv p_{max}$ for $-500 < x < 500$ and zero everywhere else). See curve for $t = 0$ in Figure 5.4a as example of top-hat boundary conditions. Because the domain is symmetric between $x$ and $-x$ it replicates no-flux boundary condition at $x = 0$ after averaging over the statistical ensemble of simulations. Generally we choose lattice domain of length large enough to have no influence of the periodic boundaries (i.e. to have zero cellular density at both right and left boundaries).

5.3 MSM Simulations

We performed multiple MSM simulations of 1D the dynamics of initially localized distributions of bacterial density and made ensemble averaging over these simulations. That ensemble serves to approximate the outward radial movement of the cells. We choose the ”top-hat” initial distribution (constant density around the center of the domain and zero density to the left and to the right of the center). Initial top-hat density profile was typically obtained by densely initial packing of bacteria in the domain of width 1000 around $x = 0$. Typical size of statistical ensemble was 20,000. We determined the cellular density (volume frac-
tion) by calculating the average number of times the given location was occupied (see Figure 5.4a). Qualitatively, the cell densities spread out symmetrically away from the center of the top hat. For later times a steep slope develops around density $p_0 = 0.2$, which implies that the rate at which the density spreads out depends on the local cell density. The cells’ movement frequently causes them

![Figure 5.4](image_url)

Figure 5.4. Results of stochastic simulations of rods reversing every $T=8$ performed 20,000 times. a) Average cell density at different times, b) Expected cluster frequencies for different times, i.e. the average number of clusters of a given size obtained in the simulations, c) Average cluster size over time on a log-log scale d) Expected cluster frequencies at end time 1 million for constant density simulations, where the vertical bars signify the average cluster size.
to collide with each other. When two cells are trying to move into each other’s space, they stall (jam) until at least one reverses. This stalling shifts the mean location of their oscillatory movement away from the location at which they stall. If no other cells are nearby, the cells stay far enough away from each other and never collide again. If other cells are nearby, these outer cells have their mean location shifted outwards while the original cells’ mean locations are shifted closer together. Through these shifts, the cells steadily spread away from each other.

In highly packed situations, the cells cluster together. Two cells can jam together forming two-cell cluster, and if another cell is moving in a direction of a that two-cell cluster then it may join the cluster forming three-cell cluster etc. To measure the amount of clustering, we calculated the frequencies of cluster sizes at different moments of time which is shown in log-log plots in Figure (5.4b). It is seen that the average cluster size decreases over time as initially densely packed cells expand. Figure (5.4c) shows that this decrease follows a power law decay over time with calculated exponent $-0.4965$.

This suggests that during early times, many of the cells are found in large clusters where they cannot move. At later times, the large clusters rapidly break up into smaller clusters allowing cells to move. Also, the individual cells near the boundaries spend a significantly greater percentage of their time moving.

It is seen from Figure 5.4a that the dynamics of the cellular density is smooth and slow compare with the velocity $v = 1$ of individual cell motion. This suggests that the ensemble of averaged distribution of cells at each moment in time and each point in space is in statistical quasi-equilibrium. Below we study such quasi-equilibrium as a functions of local cellular density, cellular collision times and cluster sizes. We also perform a second type of MSM simulations with pe-
periodic boundary conditions and uniform average densities to study the statistical equilibrium of cellular motion.

5.4 Macroscopic Nonlinear Diffusion Model vs. MSM simulations

If collisions are frequent and the distribution of the reversal phases and initial position of cells is random, then we expect that collective dynamics of cells is diffusion-like described by the general equation of the type (5.1). In this section we look for the numerical approximation of the diffusion coefficient \( D(p) \) in (5.1) to match the results of MSM simulations. The calculation is done by running MSM simulations with a top-hat initial distribution and using Boltzmann-Matano (BM) analysis [40] on the right half of the domain to determine the diffusion coefficient. A description of the BM analysis is given in Chapter 4.

Unavoidably, the results of MSM simulations have noise due to the finite size of stochastic ensemble used to determined cellular densities. BM analysis relies on calculating derivatives of density and we applied a Gaussian filter to the MSM density data to smooth both \( p \) and all its derivatives.

Typically, to perform BM analysis we run MSM using an initial top-hat distribution of length 1,000 in a domain of size 4,000 (see the end of Section 5.2 for more detail). For most of our simulations this choice of top-hat is wide enough so that during simulation time the density at the middle of the domain remains close to the initial density \( p_{\text{max}} \) (in most simulations \( p_{\text{max}} = 1 \)). It means that cellular dynamics occurs mostly near the the boundary of initial top-hat distribution while at the middle of domain cellular density is almost constant. This allows us to ignore the left half of the domain and treat the cells as if they were were on a step-wise distribution with an infinite domain. This is necessary in order
to perform BM analysis which is exact for infinite spatial interval with step-wise initial conditions only. Below we study the accuracy of BM analysis for a finite width of top-hat initial conditions and established its accuracy.

Another limitation of BM analysis is that it requires calculating $(dp(x)/dx)^{-1}$. Due to the presence of the regions where the density is constant, singularities of $(dp(x)/dx)^{-1}$ may be generated in the calculation of the non-linear diffusion coefficient near the end of the diffusion curves where $p$ is about 0 or $p_{\text{max}}$. These singularities are purely artificial ones and result from a loss of numerical precision near singularity of $(dp(x)/dx)^{-1}$. To avoid that loss of numerical precision we only perform BM analysis in the neighborhood of the interface that encompasses the initial step of top-hat rather than the entire right half of the domain. We also reform a cubic spline interpolation from MSM simulation data to obtain $D(p)$ for all values of $p$.

Since the Boltzmann-Matano approach for calculating the diffusion coefficient assumes that the non-linear diffusion equation is solved on an infinite domain, there will be errors in calculating the diffusion coefficient if there is significant density near the boundary due to boundary conditions. So if we choose a time that is too large, the analysis will fail. If we choose a time that is too small, then not enough cells reverse to generate diffusion. We found that any time between $t = 125$ and $t = 10,000$ appears sufficient for generating reasonably universal diffusion curves as seen Figure 5.5a. Unless otherwise specified below we use $t = 500$ to generate the diffusion curves. The curves at this time period are very similar to later times and it is an early time which is important for the purposes of being able to predict densities at large times like $t = 10,000$. The differences between the curves are most likely due to using an insufficient ensemble size even
Figure 5.5. (a) Diffusion coefficient $D(p)$ generated by BM analysis at different time periods for $T = 8$, (b) $D(p)$ generated by BM analysis for varying reversal periods $T$ for curves taken at $t = 500$, (c) Density profiles from MSM simulations vs. PDE density profiles (solutions of (5.1)) at $t = 64$ and $t = 30,000$ obtained using diffusion coefficients from (a) at $t = 500$ and $t = 10,000$. Very good fit between these two types of density profiles is demonstrated except region of small density $p < p_0 = 0.2$. 

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with an ensemble size of 20,000, but using a larger ensemble sizes for long times would be computationally expensive. To see that the there is little difference in the resulting PDE (partial differential equation) solution of (5.1) by choosing the diffusion coefficient $D(p)$ based on BM analysis from $t = 500$ versus $t = 10,000$, we compare the resulting numerical solutions with the densities from the microscopic stochastic model (see Figure 5.5c). For both times, a good fit is demonstrated with the microscopic stochastic model density curves obtained using stochastic simulations. Furthermore, the difference between the numerical solutions of the nonlinear diffusion equation and stochastic simulation results are negligible.

Diffusion terms for different reversal periods were calculated (see Figure 5.5b). Large reversal periods $T$ produce high diffusion at low densities, and low diffusion at high densities. Small reversal periods produce low diffusion at low densities and high diffusion at high densities. In the former case the cells move left or right until they collide and they stay jammed for a long time. In the later case, the cells rapidly oscillate left and right. Once the cells spread out, collisions become infrequent.

To test that the diffusion curves in Figure 5.5b actually predict the diffusion in the stochastic model, we compare the results of the numerical solutions to the diffusion equation (5.1) with $D(p)$ derived from BM analysis of MSM simulations with different reversal periods at an early and a later time (see Figure 5.6). Very good matching is demonstrated for $p > p_0$, where $p_0$ is the critical density, below which cells are not expected to interact, and is defined as

$$p_0 := \frac{L}{L + vT/2}. \quad (5.2)$$
For $p < p_0$ there are practically no jams between cells and subsequently there is no diffusion (some occasional jams are still possible only because cells are not in fully quasi-equilibrium). The nonzero values of $D(p)$ for $p < p_0$ in Figures 5.5a and b are nothing more than the artefact of the BM method. In fact there is no average macroscopic motion of cells for $p < p_0$. MSM simulations indicate that by the sharp drop of density for $p < p_0$. That drop is not completely vertical because of finite size of cells in MSM. In addition, macroscopic averaging requires also taking into account a finite spatial width of that sharp drop of density. In contrast, BM analysis assumes that $D(p)$ is a smooth function so it replaces a drop of $D(p)$ from finite value at $p \to p_0 + 0$ to the zero value at $p \to p_0 - 0$ by a smooth function clearly seen in Figures 5.5a and b. So the difference between MSM and PDE curves in Figure 5.5c for $p < p_0$ is due to that lack of applicability of BM analysis for $p < p_0$.

To test whether the stochastic system is consistently well approximated by the diffusion equation, independently of initial density, we compared the numerics
Figure 5.7. Solution of the diffusion equation using the derived curve above compared to the MSM results using different initial densities.

For the diffusion equation with MSM simulations for $T = 8$ reversal period and different initial conditions. For this comparison, we first generated random initial conditions with constant average density and periodic boundary conditions and allowed the cells to evolve in MSM simulations for $t = 5,000$ to reach an a statistical equilibrium. After that, we inserted the equilibrium distribution as the top part of top-hat initial conditions and run MSM simulations for these spatially nonuniform initial conditions. Figure 5.7 shows good matching for these simulations with the results of the nonlinear diffusion equation simulations. Not as good matching is seen for smaller densities due to the lack of diffusion for $p < p_0$ as explained above.

Since the cells move on a discrete grid on discrete time steps, we test convergence of the system to a continuous description of cell movement by decreasing the length between each lattice index, i.e. the pixel size, and by scaling the lengths and time steps appropriately. Decreasing the pixel size of the stochastic simulations produced negligible changes in the density curves suggesting that the discrete system closely approximates what happens for continuously moving cells.
Looking at the diffusion curve $D(p)$ for different reversal periods, we conclude that diffusion peaks shift to smaller densities with increase of $T$. Thus cell populations with high reversal frequencies (low $T$) are able to spread out effectively at high densities. If the cells rarely reverse ($T$ is large) then they are able to spread out at lower densities but less efficient to spread out at higher densities. It can also be seen at density profiles in Figure 5.6 that low density tail spread much faster for $T = 16$ compare with smaller $T$ while high density region propagate more efficiently for $T = 4$.

5.5 Accuracy of Boltzmann-Matano Analysis

BM analysis, described in Chapter 4, is defined on infinite spatial interval with step-wise initial conditions only. Assume now that we apply BM analysis for top-hat initial conditions as described in Section 5.2. In that case BM analysis is only an approximation because initial conditions include spatial scale $x_{\text{width}}$, which is the spatial width of top-hat and a finite domain. The solution is only approximately valid in the neighborhood of each of two steps of top-hat. Because of spatial symmetry, it is enough to consider any of these two steps. To estimate the accuracy of BM analysis in that case we note that if the density at $x = 0$ (middle of top-hat) remains nearly constant then BM analysis is still applicable (except small unavoidable corrections because for any $t > 0$ density is never exactly constant). Assuming that the diffusion coefficient $D(p) \sim 1$, we roughly estimate that the width of initial top-hat doubles with time when $D(p)t_0/x_{\text{width}}^2 \sim 1$ which gives $t_0 \sim 10^6$ for $x_{\text{width}} = 1000$. For $t \ll t_0$ a change of density in the middle of top-hat is small in agreement with Figure 5.5. A similar limitation of BM analysis is that the total spatial width of the simulation domain must exceed the width.

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Figure 5.8. a) Diffusion for different initial MSM top-hat widths in different domains. b) Diffusion from PDE for top hat of width 600 using the density at time $t = 1,000$ versus diffusion derived from MSM. c) Comparison of BM analysis with Boltzmann analysis from PDE.
of top-hat in several times to make sure that the cellular density remains low at boundaries as seen in Figure 5.5.

As additional test of BM analysis we varied the domain length and width of the initial top-hat distribution calculating diffusion coefficient by BM analysis from MSM simulations (Figure 5.8a) and PDE (5.1) simulations (Figure 5.8b). We see that the diffusion curves are the same regardless of the width of the top-hat, so long as the top hat is sufficiently wide to have minimal boundary effects and no noticeable density decrease in the center of the top-hat. Also Figure 5.8b shows that BM analysis from MSM and PDE data gives the same result indicating that our statistical ensemble in MSM simulations is large enough to avoid influence of noise in the data on the diffusion curve. We also tested MSM data with and without the Gaussian filter and obtained the same diffusion curves. Larger widths were also tested and proven to match very well, but the results are not displayed here. From these observations, we can conclude that the generated diffusion curves are independent of the width of the top hat used if the top hat is sufficiently long enough in such a way that the center and boundaries have constant density. As a consistency check for the diffusive behavior of the stochastic system, we also found that the large width density profiles displayed characteristic $x^2/t$ scaling property of diffusion processes by matching the MSM density curves with those at later times with larger domains. These results are also not displayed here.

To avoid confusion, we would like to point out that we need BM analysis only to determine the diffusion curves at reasonably small times ($t \ll t_0$). After that, we run PDE simulations with these diffusion curves for much longer time (when density is changing both at the middle of top-hat and at boundaries). For these much larger times we also see very good agreement between MSM simulations and
PDE simulations (see e.g. Figures 5.4 and 5.6).

As discussed in Section 5.4, another limitation of BM analysis is the loss of numerical precision near \( p(x) = \text{const} \) because BM analysis requires calculating \((dp(x)/dx)^{-1}\). Many Figures (5.5 and 5.8) have jumps of \( D(p) \) near \( p = 1 \) which is due to the loss of numerical precision which can be fixed by the polynomial extrapolation. That is however not necessary because these jumps do not change results of PDE simulations in any any significant way.

We also tested BM analysis vs. Boltzmann analysis. Although we know \( x_M \) from top-hat initial conditions, but for finite width of top-hat we can ask if allowing \( x_M \) to be located not exactly at the step of top-hat could improve the accuracy of BM analysis to determine \( D(p) \). In that sense we can consider \( x_M \) as additional fitting parameter to accommodate finiteness of top-hat width. Figure 5.8c compares diffusion curves obtained from BM and Boltzmann analysis vs. exact diffusion curve. We see that difference in accuracy between BM and Boltzmann analysis is very small and it appears the advantage of using BM analysis vs. Boltzmann analysis is not significant in our case.

5.6 Conclusion and Discussion

In this chapter, we have developed a stochastic model to simulate microscopic motion of reversing self-propelled rod-shaped cells and have established a connection with a nonlinear diffusion equation for describing macroscopic behavior of the system. We found that macroscopically (ensemble) averaged stochastic dynamics is in very good agreement with the nonlinear diffusion equation (5.1) with the diffusion coefficient obtained from BM analysis. We also identified that the nonlinear diffusion is not applicable for small densities \( p < p_0 \), where the criti-
cal density $p_0$ is determined (5.2) from the condition of vanishing jams between cells. It remains however a quite challenging problem in the future to develop a full statistical theory of 1D self-propelled rod dynamics which is applicable for all densities. Such theory would require a detailed description of multiple formation and interaction of large cellular clusters.

The nonlinear diffusion coefficient $D(p)$ used to describe the process changes depending on the reversal period. Small and large reversal periods correspond to diffusion coefficients that favor high and low density diffusion respectively as it is seen from Figure 5.6. Since dynamics of the system is determined by the dimensionless parameters $vT/L$ (the ratio of distance traveled by cells between reversals and the cell length) and $p$ then increasing the speed at which the cells move is equivalent to increasing the reversal period. Thus cell populations with small $T$ are able to spread out effectively at high densities while large $T$ promotes cell population swarming at smaller densities.

We also studied the role of noise in the reversal period. We ran simulations by generating the next reversal time as a Gaussian random variable of mean $T = 8$ and small standard deviation, and found that the cellular density dynamics did not noticeably change. This is consistent with the results of Ref. [117], that adding small noise to the reversal period in the two-dimensional model of Myxobacteria swarming do not have a significant influence on the order parameters describing level of alignment.

We are currently working on extending the results to the 2D case. Essentially, the only type of structure we see in 1D at large density is the jammed cluster. Because of the strict topological constraints in 1D (e.g. cells cannot go around each other), we do not expect to see rafts that are normally found in 2D pictures[117].
Rafts consist of a bunch of cells aligned along their longer axis with close reversal phases. They serve as efficient means of synchronized transport of Myxobacteria. The main question to be addressed for future work will be determination of the optimum choice of reversal time $T$ to maximize the orientation of the Myxobacteria colony using nonlinear diffusion equation similar to the results of [117] obtained using a stochastic computational model.
CHAPTER 6

EXISTENCE, UNIQUENESS, AND BOUNDEDNESS OF AN EQUATION
MODELING NON-OVERLAPPING CELLULAR MOTION

6.1 Introduction

Continuous limits of microscopic models of biological systems based on point-wise cell representations were extensively studied over the last 30 years. In particular, the classical Keller-Segel PDE model has been derived from a discrete model with point-wise cells undergoing random walk in chemotactic field [67]. This model was studied among others in [7, 85]. It is known that in this model, under certain conditions, a blow up of a solution may occur in finite time [18, 44]. To avoid this, various modifications of the Keller-Segel model have been introduced (see, e.g. [86, 112, 115] and the references therein). A new system of macroscopic nonlinear reaction-diffusion equations has been derived recently in [78] from the stochastic discrete cellular Potts model (CPM) with extended cell representation. This system can be written in the form:

\begin{align}
\partial_t u &= \nabla \cdot [\Gamma(u) \nabla u] - \chi_0 [u \nabla v] \\
\partial_t v &= d \nabla^2 v + au - \gamma v .
\end{align}

(6.1)

(6.2)
Here $u$ is the fraction of volume occupied by cells and $v$ denotes the concentration of the chemical, whereas

$$\Gamma(u) = \frac{1 + u}{1 - u + u \log(u)} \quad .$$

(6.3)

The constants $\chi_0, d, a$ and $\gamma$ have the obvious physical interpretation. This system is considered in a bounded domain $\Omega \subset \mathbb{R}^2$ with $\partial \Omega \in C^{2+\eta}, \eta \in (0, 1)$, subject to the initial and boundary conditions

$$(u(0, x), v(0, x)) = (u_0(x), v_0(x)), \quad x \in \Omega, \quad \frac{\partial u}{\partial \nu}(x) = \frac{\partial v}{\partial \nu}(x) = 0, \quad x \in \partial \Omega$$

(6.4)

where $\nu = \nu(x)$ denotes the outward unit normal to $\partial \Omega$. Let us note that the coefficient $\Gamma(u) \nearrow \infty$ as $u \nearrow 1$. We will show that this prevents the blow up of solutions. A very good agreement was shown in [78] between Monte Carlo simulations of the microscopic CPM and numerical solutions of equations (6.1)-(6.2). Combination of microscopic and macroscopic models like system (6.1)-(6.2) can be used to simulate growth of structures similar to early vascular networks [78]. In this thesis we show the global in time existence of classical solutions to a generalization of system (6.1)-(6.2). This provides a mathematical justification for using numerical solutions of the system (6.1)-(6.2) for biological modeling. The proof is based (modulo slight modifications) on the method described in [25].
6.2 Global Existence of Solutions

In this section we show the existence, uniqueness and boundedness of global in time solutions for the following system

\begin{align}
\partial_t u &= \nabla \cdot [\Gamma(u) \nabla u] - \nabla [\chi(u, v) \nabla v] + g(u, v) \\
\partial_t v &= \nabla : [d(v) \nabla v] + f(u, v)
\end{align}

(6.5)

in $\Omega \times [0, T)$, where $\Omega$ is a bounded domain in $\mathbb{R}^n$, with the initial-boundary conditions

\[(u(0, x), v(0, x)) = (u_0(x), v_0(x)), \quad x \in \Omega, \quad \frac{\partial u}{\partial \nu}(x) = \frac{\partial v}{\partial \nu}(x) = 0, \quad x \in \partial \Omega.\]

(6.7)

H0 $n \geq 1$. $\partial \Omega$ is of $C^{2+\eta}$ class, $\eta \in (0, 1)$

H1 Let $\mathcal{D} := [0, 1] \times [0, \infty)$. Let $\chi : \mathcal{D} \to [0, \infty)$ be of $C^2$ class, and $\chi(0, v) = 0$ for $v \geq 0$

H2 $g : \mathcal{D} \to \mathbb{R}$ is of $C^2$ class. $g(u, v) \leq M_g(1 - u)$, $g(0, v) \geq 0$ for all $(u, v) \in \mathcal{D}$, $M_g \geq 0$;

$f : \mathcal{D} \to \mathbb{R}$ is of $C^2$ class. $f(u, v) < 0$ for all $v \geq V > 0$, $f(u, 0) \geq 0$ for all $u \in [0, 1]$;

$d : [0, \infty) \to [d_1, d_2)$ is of $C^2$ class, $0 < d_1 < d_2 < \infty$

H3 $u_0, v_0 \in C^{2+\eta}(\overline{\Omega})$, $0 \leq u_0(x) < 1$, $0 \leq v_0(x)$ for $x \in \overline{\Omega}$

and $\frac{\partial u_0}{\partial \nu}(x) = 0$, $\frac{\partial v_0}{\partial \nu}(x) = 0$ for $x \in \partial \Omega$

H4 $\Gamma : [0, 1) \to (0, \infty)$ is of $C^2$ class. There exist positive numbers $\epsilon_1 > 0$, $\epsilon_2 > 0$ and $\epsilon_3 > 0$ such that $\Gamma(u) > \epsilon_1$ for all $u \in [0, 1]$ and $\Gamma(u) \geq \epsilon_2 (1 - u)^{-\alpha}$ for
\[ u \in [1 - \epsilon_3, 1) \text{ and } \alpha \geq 2 \]

As one can see from assumptions H1-H4, system (6.5)-(6.6) is more general than the system considered in the paper [25]. Among others, it includes a nonlinear term \( g(u, v) \) describing cell proliferation.

**Lemma 1.** Assume H4. Then there exists a constant \( K > 0 \) such that, for all \( u \in [0, 1) \), \( \Gamma(u) \geq K \frac{1}{(1 - u)^{\alpha}} \).

**Proof.** Let \( \epsilon_4 = \inf_{u \in (0, 1 - \epsilon_3)} \Gamma(u)(1 - u)^{\alpha} \). If \( K = \min\{\epsilon_4, \epsilon_2\} \) then the thesis of the lemma holds. \( \square \)

**Lemma 2.** (See Lemma 3.1 in [25].) Let hypotheses H0-H4 hold. Then

1. There exists a positive constant \( T_0 \) depending on initial data \((u_0, v_0)\) such that system (6.5)-(6.6) with initial-boundary conditions (6.7) has a unique maximal solution \((u, v)\) in the space \( C^{1+\eta/2,2+\eta}(0, T_0) \times \bar{\Omega}; \mathbb{R}^2 \) with \( u(t, x) \geq 0 \) and \( v(t, x) \geq 0 \).

2. If \( u \) is bounded away from 1 for each finite time \( t > 0 \), then \( T_0 = \infty \), namely, the solution is a global classical solution of system (6.5)-(6.6),(6.7).

**Proof.** Let \( \omega = (u, v) \). Then system (6.5)-(6.6),(6.7) can be written as

\[
\partial_t \omega = \nabla \cdot (A(\omega) \nabla \omega) + \mathcal{F}(\omega), \quad \omega(0, \cdot) = (u_0, v_0) \quad \text{in} \quad \Omega, \\
[\Gamma(u) \nabla u - \chi(u, v) \nabla v] \cdot \nu = 0, \quad [d(v) \nabla v] \cdot \nu = 0 \quad \text{on} \quad \partial \Omega
\]  

(6.8)

where \( A \equiv A_{ij}, i, j = 1, 2, A_{11} = \Gamma(u), A_{12} = -\chi(u, v), A_{21} = 0, A_{22} = d(v), \mathcal{F} = (g(u, v), f(u, v))^T \). We can extend all the considered functions to the set \( \mathcal{G} = \{(u, v) \in (-\delta, 1) \times (-\delta, \infty)\}, \delta > 0 \), in \( C^2 \) class in such a way that \( \Gamma(u) > \Gamma_0 > 0 \) and \( d(v) > d_0 > 0 \) for all \((u, v) \in \mathcal{G}\). Thus the local existence and conditions
for the global existence of solutions to this system follow e.g. from Theorem 7.3 and Corollary 9.3 in [9], Theorem 5.2 in [8] or Theorem 14.6 in [10]. The solution exists globally if \((u(t, x), v(t, x))\), \(x \in \overline{\Omega}\), does not reach the boundary of \(\mathcal{G}\) for any finite \(t > 0\). According to H1-H3 we can prove that, as long as the solution exists, \(u(t, x) \geq 0\) and \(v(t, x) \geq 0\) for all \(x \in \overline{\Omega}\). To do this, we can either use the comparison principle for diagonal parabolic systems (if we treat the function \(v\) in the equation for \(u\) as given, due to the fact that \(\chi_{\nu}(0, v) = 0\)) or use Theorem 15.1 of [10] as in [112]. Moreover, according to H2, \(v(t, x)\) is bounded from above, as long as \(\|u\|_{L^\infty} \leq 1\), by a constant \(c_v = \max\{\sup_{x \in \Omega} v_0(x), V\}\). Thus the sufficient condition for the existence of the global classical solution is that \(u\) is bounded away from 1.

**THEOREM 1.** Let the conditions H0 to H4 hold. Then there exists a unique global solution \((u, v)\) to system (6.5)-(6.6), (6.7) such that \(u\) and \(v\) are in \(C^{1+\eta/2+\eta/2}([0, \infty) \times \overline{\Omega})\). Moreover, there exists a constant \(c_v \geq 0\) such that \(0 \leq v(t, x) \leq c_v\) and \(0 \leq u(t, x) < 1\) for all \(x \in \overline{\Omega}\) and all \(t > 0\).

**Proof.** It is easy to note that by appropriate scaling we can obtain a system in a region \(\Omega\) satisfying \(|\Omega| = 1\) and such that \(\Gamma(u) \geq (1 - u)^{-\alpha}\) for \(u \in [0, 1]\). The proof of the theorem is based on the proof of Theorem 1.1 from [25]. Let us consider the auxiliary scalar equation

\[
\begin{align*}
\partial_t u &= \nabla \cdot \left[ \Gamma(u) \nabla u \right] - \nabla \cdot b(t, x) + G(u, t, x), \quad (t, x) \in [0, T) \times \Omega \\
u(0, x) &= u_0(x), \quad x \in \Omega, \quad \frac{\partial u}{\partial v}(x) = 0 \quad x \in \partial \Omega
\end{align*}
\]  

(6.9)

where \(b \in L^\infty((0, \infty) \times \Omega)\) is a given function. Below, we will use the following lemma.
Lemma 3. (See Theorem 1.1 in [25]) Let \( 0 \leq u_0(x) < 1 \) for \( x \in \Omega \). Let \( \|b\|_{L^\infty((0,\infty)\times\Omega)} = M_b \) and \( \|G(u,\cdot,\cdot)\|_{L^\infty((0,\infty)\times\Omega)} \leq M_g(1-u) \) for \( u \in [0,1] \). Let us assume that \( u \) is a classical solution to Eq.(6.9) and \( 0 \leq u(t,x) < 1 \) for \( (t,x) \in Q_T = [0,T) \times \Omega \). Then there exists a constant \( \delta_T \) such that \( u(t,x) < 1 - \delta_T \) for all \( (t, x) \in Q_T \). The constant \( \delta_T \) depends only on \( M_b \) and \( \delta = \|1-u_0\|_{L^\infty(\Omega)} \).

So suppose to the contrary that the classical solution does not exist globally. According to Lemma 2, it follows that there exists finite \( T_0 > 0 \) such that \( \|u(t,\cdot)\|_{L^\infty(\Omega)} \to 1 \) as \( t \to T_0 \) and \( \|u(t,\cdot)\|_{L^\infty(\Omega)} < 1 \) for any \( t < T_0 \). However, as \( v(t,x) \leq c_v \), due to Theorem 6.49 in [75], \( \|v\|_{C^{(1+\eta)/2,1+\eta}(\Omega)} \leq W_{T_0}(\|v_0\|_{C^{1+\eta}(\Omega)} + 1) \). Then, \( b = [\chi(u,v)\nabla v] \) is bounded on \( [0,T_0] \times \Omega \), so according to Lemma 3, for any \( t < T_0 \), we would have \( u(t,x) < 1 - \delta_t \), where \( \delta_t \) does not tend to 0 as \( t \to T_0 \).

We thus arrive at a contradiction as the solution could be prolonged for \( t > T_0 \).

This concludes the proof of Theorem 1.

Proof of Lemma 3. Multiplying both sides by \( p(1-u)^{-p-1} \) and integrating we obtain

\[
\frac{d}{dt} \int_{\Omega} (1-u)^{-p} dx = p \int_{\Omega} (1-u)^{-p-1} u_t dx
\]

\[
= p \int_{\Omega} (1-u)^{-p-1} \nabla \cdot [\Gamma(u)\nabla u - b] dx + p \int_{\Omega} (1-u)^{-p-1} G(u,t,x) dx
\]

\[
= -p(1+p) \int_{\Omega} \left\{ \Gamma(u)(1-u)^{-(p+2)}|\nabla u|^2 - \frac{\nabla u \cdot b}{(1-u)^{p+2}} \right\} dx + \int_{\Omega} p G(u,t,x) \frac{1}{(1-u)^{p+1}} dx
\]

\[
\leq -p(1+p) \int_{\Omega} \left\{ \frac{|\nabla u|^2}{(1-u)^{-(\alpha+p+2)}} - \frac{\nabla u \cdot b}{(1-u)^{p+2}} \right\} dx + \int_{\Omega} M_g(1-u)^{-p} dx \tag{6.10}
\]

where the last inequality follows from the fact that \( \Gamma(u) \geq (1-u)^{-\alpha} \) and the assumption concerning the function \( G \). Let \( w_p = (1-u)^{-\frac{\alpha+p}{2}} \). Then, we can

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proceed, as in [25] to obtain

\[
\frac{d}{dt} \int_{\Omega} (1 - u)^{-p} dx - p \int_{\Omega} M_g (1 - u)^{-p} dx \\
\leq \frac{p(1 + p)}{\alpha + p} \left( - \frac{4}{\alpha + p} \int_{\Omega} |\nabla w_p|^2 dx + 2 \int_{\Omega} \frac{\nabla w_p \cdot b}{(1 - u)^{(p+2-\alpha)/2}} dx \right) \\
\leq \frac{p(1 + p)}{\alpha + p} \left( - \frac{4}{\alpha + p} \int_{\Omega} |\nabla w_p|^2 dx + 2 M_b \int_{\Omega} \frac{|\nabla w_p|}{(1 - u)^{(p+2-\alpha)/2}} dx \right) \\
\leq \frac{p(1 + p)}{\alpha + p} \left( - \frac{2}{\alpha + p} \int_{\Omega} |\nabla w_p|^2 dx + \frac{M^2_b (\alpha + p)}{2} \int_{\Omega} \frac{1}{(1 - u)^{p+2-\alpha}} dx \right)
\]

(6.11)

where we have used the Young’s inequality. According to the assumptions of the lemma, \(0 \leq u(t, x) < 1\) and \(\alpha \geq 2\), we obtain the inequality

\[
\frac{d}{dt} \int_{\Omega} (1 - u)^{-p} dx \leq \frac{p(1 + p)}{\alpha + p} \left( - \frac{2}{\alpha + p} \int_{\Omega} |\nabla w_p|^2 dx + \frac{M^2_b (\alpha + p)}{2} \int_{\Omega} \frac{1}{(1 - u)^p} dx \right)
\]

(6.12)

where \(M^2 = M^2_b + M_g\). The rest of the proof of the lemma can be carried out exactly as the proof of Lemma 2.4 in [25]. This is due to the fact that the concrete form of the coefficient \(\Gamma\) is not used in the subsequent considerations. \(\square\)

**THEOREM 2.** Let \(u_0, v_0 \in C^{2+\eta}\) be non-negative. Then there exists a unique global solution \((u, v)\) to the system (6.1)-(6.2), (6.4) such that

\((u, v) \in C^{1+\eta/2, 2+\eta}([0, \infty) \times \bar{\Omega}; \mathbb{R}^2)\). Moreover, there exists a constant \(c_v\) such that

\(0 \leq v(t, x) \leq c_v\) and \(0 \leq u(t, x) < 1\) for all \(x \in \bar{\Omega}\) and all \(t > 0\).

**Proof.** Due to Theorem 1, one has only to show that H4 is satisfied, i.e. \(\Gamma(u) \geq 1/(1 - u)^2\). This can be easily done. \(\square\)
6.3 Conclusion

We proved existence of global in time classical solutions of the system (6.5)-(6.6), generalization of both system (6.1)-(6.2) and system considered in [112]. This demonstrates that these systems can not have a blow up of solutions in finite time and justifies usage of numerical solutions of the macroscopic model of early vascularization suggested in [78].
CHAPTER 7

CLASSIFICATION, STABILITY AND GEOMETRIC STRUCTURE FOR INHOMOGENOUS STATIONARY SOLUTIONS OF AN EQUATION MODELING NON-OVERLAPPING CELLULAR MOTION

7.1 Introduction

A wide range of microscopic organisms, including both innocuous amoeba and harmful pathogenic bacteria, are able to use a combination of cell to cell interactions and chemical signals to aggregate into mounds as an initial step towards biofilm formation. These mounds are stable structures in the sense that if they are disturbed, the micro-organisms will sense this disturbance and reform themselves into another mound like structure.

*Dictyostelium discoideum* is an amoeboid that is capable of demonstrating swarming behavior under starvation conditions. The amoeba releases a chemical to signal to other amoebas where it is, and follows the local chemical gradient to find other amoebas. Through this procedure, the amoebas are able to aggregate together to form a slug.

In [78] an equation with the following form was derived to model the density
of the amoebae under excluded volume conditions:

\[ \partial_t u = \nabla \cdot [\Gamma(u) \nabla u] - \chi \nabla [u \nabla v] \]

(7.1)

\[ \partial_t v = D \nabla^2 v + \alpha u - \gamma v. \]

(7.2)

where \( u \) and \( v \) represent the cell and chemical densities respectively. \( \Gamma(u) \) has a singularity which allows the equation to demonstrate so called fast diffusion where the diffusion approaches infinity for large enough cell density. It is known that (7.1)-(7.2) demonstrates non-trivial non-homogenous patterns and that a similar 2D equation is capable of demonstrating aggregates which have been reported to have similar structure to blood vessels [78]. It is also known that linear stability analysis can be used to analyse the stability of the homogeneous steady state under small perturbation, in particular see [46].

In this chapter, we attempt to analyse the structure and stability of non-homogeneous patterns in a spatially one-dimensional case in order to understand whether or not structures resembling mounds will occur and whether or not they are stable to perturbations. In particular, we establish that multi-stepped patterns will start out unstable, but as the domain becomes larger highly oscillatory non-trivial patterns emerge and under certain conditions will become stable. Often times stability can also be determined by whether the or not the solutions can be described as spikes or plateaus, as defined in [45] and [46]. Qualitatively, there is no obvious distinction between plateaus and mounds, but it should be noted that the former is a mathematical characterization and the later is an observed quality. In our case, we are able to show that a certain class of unstable solutions are spikes, and for a specific parameter range all plateaus are stable.
In the first section, we perform phase plane analysis to categorize when the constant steady state solution(s) are saddles or centers. Then we describe the non-homogeneous stationary solutions as single or multi-stepped patterns using a Hamiltonian framework in a similar manner as [89]. We then use the Hamiltonian to describe how single and multi-stepped solutions bifurcate from a steady state when the steady state is a center. In the following section, we implement a Lyapunov functional similar to the one described in [23] to classify several conditions for instability. The existence of a bounded Lyapunov functional says that the solution in time will converge to an asymptotically stable attractor that is contained in the union of all functions that are local minimum values of the functional. These functions coincide with the stationary solutions. By determining when stationary solutions are not local minima, it is possible to determine which patterns are unstable. Several conditions for instability and stability are established using various inequalities. In particular, we determine the conditions for when multi-stepped solution can be constructed, and establish that each k-step solution, with given parameter values discussed below, becomes stable or unstable as the domain length goes to infinity. In the final section, numerics are performed to show the existence of stable multi-step patterns.

7.2 Classification of Stationary Solutions

For the rest of the chapter, we will primarily consider the following system
on the interval \((0, L), L > 0,\) satisfying the boundary conditions

\[
u_x(0) = v_x(0) = u_x(L) = v_x(L) = 0.
\] (7.5)

It is shown in [5] that this system admits unique globally bounded nonegative solutions \(u, v \in C^{2,1}([0, L], [0, \infty))\) for sufficiently smooth initial conditions satisfying compatibility conditions. We now proceed to characterize the stationary behaviour of the system through a series of manipulations leading up to a Hamiltonian formulation of the steady state. Thanks to such a formulation, we can express \(v\) as a function of \(u\).

First we set the left hand side of (7.3) to zero and integrate from 0 to \(x\) to get

\[
D \frac{1 + u^2}{(1-u)^2} u_x = \chi uv_x
\] (7.6)

where we set the integration constant to zero in order to satisfy the boundary conditions. Dividing both sides by \(\chi u(x)\) and then integrating from 0 to \(x\), we get
v(x) = \int_0^x \frac{D}{\chi u(\zeta)} \frac{1 + u(\zeta)^2}{[1 - u(\zeta)]^2} u_x(\zeta) d\zeta + v(0). \quad (7.7)

Evaluating the integral gives the following system for the stationary solutions

\begin{align}
v &= Q(u) - K \\ D_x v_{xx} &= -\gamma v + \alpha u
\end{align} \quad (7.8, 7.9)

where

\[ Q(u) := \frac{D}{\chi} \left[ \ln(u) + \frac{2}{1 - u} \right] \]

and

\[ K = Q(u(0)) - v(0). \quad (7.10) \]

Let us note that \( Q'(u) > 0 \) for \( u \in (0, 1) \) with \( \mathcal{R}(Q) = (-\infty, \infty) \), so by the inverse function theorem (7.8) is invertible. For bounded stationary solutions and fixed \( K \), we can define the inverse \( f : (-\infty, \infty) \to (0, 1) \), and using the definition \( u(v) := f(v) \). \( f(v) \) will be used extensively when we define the Hamiltonian for stationary solutions. Also, let us note that if

\[ M := \frac{1}{L} \int_0^L u(x) dx, \quad (7.11) \]
then

\[ K = \frac{D}{\chi L} \int_0^L \left[ \ln(u(x)) + \frac{2}{1 - u(x)} \right] dx - \frac{\alpha M}{\gamma}. \quad (7.12) \]

As \( u \) depends on \( v \), then we will write \( K = K[v] \). In the case when \( u \) and \( v \) are constant, we have

\[ K = Q(M) - \frac{\alpha M}{\gamma}. \quad (7.13) \]

### 7.2.1 Phase Plane Analysis

To analyse the properties of spatially inhomogeneous steady state solutions we construct a new system of equations. To do so, we treat \( K[v] \) as a given constant, substitute \( u = f(v) \) into (7.8)-(7.9) and set \( w := v_x \). The stationary solution can then be described with the 2D system of autonomous ODEs:

\[ v_x = w \quad (7.14) \]

\[ w_x = \frac{1}{D_c} (\gamma v - \alpha f(v)) \quad (7.15) \]

\[ v_x(0) = v_x(L) = 0. \quad (7.16) \]

This is a system of Hamiltonian equations with the Hamiltonian
\[ H = -\frac{w^2}{2} + \frac{\gamma v^2}{2D_c} - \frac{\alpha F(v)}{D_c} \]  

(7.17)

where \( \frac{dF(v)}{dv} = f(v) \). Looking at the Jacobian of the system at a fixed point reveals that the trace is zero and so all fixed points are either saddles or centers.

Alternatively, we can formulate a Hamiltonian in terms of \( u \). By substituting \( v = Q(u) - K \) into (7.15) and multiplying by \( Q(u)_x \) to get

\[ 0 = D_cQ(u)_{xx}Q(u)_x - \gamma Q(u)_xQ(u) + \gamma KQ(u)_x + \alpha Q(u)_xu \]

and taking the integral with respect to \( u \) gives

\[ \tilde{H} = D_c \frac{Q(u)^2}{2} - \frac{\gamma Q(u)^2}{2} + \gamma KQ(u) - \alpha B(u) + \alpha Q(u)u \]  

(7.18)

where \( B(u) \) is the integral of \( Q(u) \):

\[ B(u) := \frac{D}{\chi} [\ln(u) - u - 2\ln(1 - u)] \]  

(7.19)

The system (7.14-7.15), (7.16) has fixed points \( (v, w) = \left( \frac{\alpha f(v)}{\gamma}, 0 \right) \) and its dynamics depend not only on the parameters but also on the value of \( K[v] \). The system has fixed points \( (v, w) = \left( \frac{\alpha f(v)}{\gamma}, 0 \right) \) and its dynamics depend not only on the parameters but also on the value of \( K[v] \). Since \( Q(u) - K : [0, 1] \to [-\infty, \infty] \) is monotonically increasing, the inverse, \( f(v) \) is sigmoid in shape with asymptotes \( f(-\infty) = 0 \) and \( f(\infty) = 1 \). Typically, the equation \( v = \frac{\alpha f(v)}{\gamma} \) has either one or three roots, \( v_i \), which correspond to fixed points \( S_i \) of system (7.14)-(7.15). This
Figure 7.1. With $K = \frac{D_c}{\gamma} (\log(u(0)) + \frac{2}{1-u(0)}) - v(0)$, where $(u(0), v(0))$ are calculated from a steady state solution of the PDE with $\alpha = 20$, $\chi = 0.5$, and $\gamma = D_c = D = 1$, the equation $v = \frac{\alpha f(v)}{\gamma}$ demonstrates (a) one root for $(u(0), v(0)) = (0.25, 0.5)$ or (b) three roots for $(u(0), v(0)) = (0.0499, 0.9971)$ can be observed by numerically solving for solutions to the PDE system (see numerics section below) with $\alpha = 20$, $\chi = 0.5$, and $\gamma = D_c = D = 1$. We can achieve $(u(0), v(0)) = (0.25, 0.5)$ and $(u(0), v(0)) = (0.0499, 0.9971)$ which correspond to steady state solutions to the PDE system for $L = 20$ and $L = 40$ respectively. Using (7.10) and the definition of $f$ we can examine how many roots exist for $\frac{\alpha f(v)}{\gamma} - v$ for these two choices of $(u(0), v(0))$ (see Figure 7.1). The $v_i$ generally have to be numerically solved for in order to determine their values. This can be accomplished by inverting $f$ back and solving $Q(\alpha v/\gamma) - K = v$.

Lemma 7.2.1. If (7.14)-(7.15) has a single fixed point, it is a saddle. If it has three fixed points with $v_1 < v_2 < v_3$, then $v_2$ is a center and the other two fixed points are saddles.

Proof. Taking the trace and determinant of the Jacobian of the system, we see
the eigenvalues of the fixed points can be determined from the equations

\[ \nu_+ + \nu_- = 0 \] (7.20)

\[ D_c \nu_+ \nu_- = \alpha f'(v_i) - \gamma. \] (7.21)

Consider a fixed point \( v_i \). If \( f'(v_i) < \frac{2}{\alpha} \) then the fixed point is a saddle, and if \( f'(v_i) > \frac{2}{\alpha} \) then the fixed point is a center. Note that if we have \( f'(v_i) > \frac{2}{\alpha} \) then at \( v_i \) we can use the fact that \( f(v) - \frac{2v}{\alpha} \) is increasing and the asymptotic behaviour of \( f(v) \) to deduce that there are saddles \( v_1 \) and \( v_3 \) such that \( v_1 < v_i < v_3 \). In other words, in the case of one root, we must always have a saddle. Also if we have three roots, we have center along with two saddles since the slope of the middle root is larger than the slope of the line (see Figure 7.1b).

As will be seen later, inhomogeneous patterns can only occur if we have a center and so we will consider the case where we have three roots \( v_1 < v_2 < v_3 \).

### 7.2.2 Hamiltonian Characterization

Additional information about the structure of the steady state solutions of (7.14)-(7.16) can be gained by examining the Hamiltonian (7.17). In particular, since the Hamiltonian is independent of \( x \)-variable, for fixed Hamiltonian constant \( H \), we can examine the Hamiltonian curves and solve for \( w \) as a function of \( v \) to get

\[ w = \pm \sqrt{2(-\alpha \frac{F(v)}{D_c} + \gamma \frac{v^2}{2D_c} - H)}. \] (7.22)
The plus and minus signs correspond to the positive and negative solutions for \( w \). It is also seen that \( v \) is symmetric across the \( w = 0 \) axis and we are free to choose which sign we examine. Unless otherwise specified, from now on we only consider the positive part of the curve where \( w \geq 0 \). In this case, with \( w = v_x \), we can solve for \( x \) as a function of \( v \) along the positive curve by inverting both sides of equation (7.22) and integrating with respect to \( v \). Doing this we get

\[
x = \int_{v(0)}^{v(x)} \frac{dv}{\sqrt{2(-\alpha \frac{F(v)}{D_c} + \gamma \frac{v^2}{2D_c} - H)}}. \tag{7.23}
\]

(7.23) describes the \( x \)-location where the phase point occurs for given Hamiltonian energy \( H \). The minimal and maximal values of \( v \) occur at the turning points, when \( w = 0 \), which can be solved for from the equality:

\[
0 = -\alpha \frac{F(v)}{D_c} + \gamma \frac{v^2}{2D_c} - H. \tag{7.24}
\]

If we instead use the alternate Hamiltonian, we use the chain rule and similarly solve for

\[
x = \int_{u(0)}^{u(x)} \frac{Q'(u)du}{\sqrt{\frac{2}{D_c}(\tilde{H} + \gamma (Q(u)^2/2 - KQ(u)) + \alpha (B(u) - uQ(u)))}}. \tag{7.25}
\]

where we use the fact that \( Q'(u) > 0 \) on the domain and the minimal and maximal values of \( u \) occur at the turning points, when the denominator evaluates to 0. If
we use \(v_{\text{min}}\) as a parameter, then

\[
H = -\alpha \frac{F(v_{\text{min}})}{D_c} + \gamma \frac{v_{\text{min}}^2}{2D_c},
\]

(7.26)

and \(v_{\text{max}}\) can also be found from (7.24). Furthermore the "duration" of the half curve, \(\mathcal{T}(v_{\text{min}})\), satisfies

\[
\mathcal{T} = \int_{v_{\text{min}}}^{v_{\text{max}}} \frac{dv}{\sqrt{2\left(-\alpha \frac{F(v)-F(v_{\text{min}})}{D_c} + \gamma \frac{v^2-v_{\text{min}}^2}{2D_c}\right)}}
\]

(7.27)

Duration will become important as we link solutions to the Hamiltonian equation to solutions satisfying the boundary value problem of (7.14)-(7.16).

These results can be put in a more concrete form with the following theorem

**Theorem 7.2.2.** For any given \(u(0) > 0\), and \(v(0) > 0\), then \(f(v) \in C^1([-\infty, \infty])\) is well defined and \(F(v) \in C^2([-\infty, \infty])\) is defined up to a constant. Suppose that the equation \(f(v) - \frac{2}{\alpha}v = 0\) has three distinct roots, \(v_1\), \(v_2\), and \(v_3\). We assume that the constant \(H\) can be chosen in such a way that Eq.(7.24) has positive roots \(v_{\text{min}}, v_{\text{max}}\) satisfying \(v_1 < v_{\text{min}} < v_2 < v_{\text{max}} < v_3\).

1. It is possible to define \(w(v) \in C^2([v_{\text{min}}, v_{\text{max}}])\) by (7.22) and \(v(x) \in C^2((0, L))\) implicitly by (7.23).

2. \((v(x), w(x))\) are non-homogenous single-step solutions to the ODE described in (7.14)-(7.15) and there is a unique \(\mathcal{T}\) such that \((v(x), w(x))\) also satisfy the boundary conditions described in (7.16) using the chosen domain length \(L = \mathcal{T}\).
3. We can define \( u(x) = f(v(x)) \) to get step like solutions \((u(x), v(x))\) that are unique steady state solutions to (7.3), (7.4) satisfying boundary conditions (7.5) with the specified \( T \).

4. The reflection of \((u, v)\) over the domain is also a steady state solution to (7.3), (7.4) that satisfies the boundary conditions (7.5) with the specified \( T \).

**Proof.** Given \((u(0), v(0))\), we define \( K \) using (7.10). With \( K \), it is possible to define \( f(v) \) as the inverse of (7.8) by the inverse function theorem. Since \( f(v) \) is \( C^1 \) class, the improper integral \( F(v) \) is well defined up to a constant of integration and is \( C^2 \) class.

We can assume without loss of generality that \( v_{\text{min}} := v(0) \) and using the assumption that \( f - \frac{\gamma}{\alpha} \) has three roots we have,

\[
f(v) - \frac{\gamma}{\alpha} v < 0 \text{ for } v \in (v_1, v_2)
\]

\[
f(v) - \frac{\gamma}{\alpha} v > 0 \text{ for } v \in (v_2, v_3)
\]

Integrating the function \( 1/D_c (\alpha f(v) - \gamma v) \) with respect to \( v \) and defining \( H \) using (7.26), we see that is possible to define \( w : (v_{\text{min}}, v_{\text{max}}) \rightarrow R_+ \) by choosing the positive sign in (7.22). Also from the above statements, it follows the \( w \) is \( C^2 \) class in \((v_{\text{min}}, v_{\text{max}})\).

Since \( w \geq 0 \) for \( v \in (v_{\text{min}}, v_{\text{max}}) \), we can define \( x(v) \), where \( D(x) = (v_{\text{min}}, v_{\text{max}}) \) and \( R(x) = (0, x(v_{\text{max}})) \) using (7.23). \( x(v) \) is well defined since for \( v_{\text{min}} < v < v_{\text{max}} < \infty \), we have for some constant \( \tilde{C} > 0 \):
\[ x = \int_{v_{\min}}^{v} \frac{dv}{\sqrt{2(-\alpha \frac{F(v)}{D_c} + \gamma \frac{v^2}{2D_c} - H)}} \] (7.28)

\[ \leq \int_{v_{\min}}^{v} \frac{dv}{\sqrt{\tilde{C}(v - v_{\min})(v_{\max} - v)}} < \infty. \] (7.29)

Note that the second line follows from the fact that the roots of \(-\alpha \frac{F(v)}{D_c} + \gamma \frac{v^2}{2D_c} - H\) at \(v_{\min}\) and \(v_{\max}\) are simple. The derivative of this function is \((-\alpha f(v) + \gamma v)/D_c\), which by the above statements and assumptions is not zero at the roots because \(v_{\min}, v_{\max} \neq v_1, v_2, v_3\). Otherwise, our trajectory would be just a fixed point.

Since \(x(v)\) is monotonically increasing, it has a monotonically increasing inverse \(V(\eta) = v(\eta)\) where \(x(V(\eta)) = \eta\). Replacing \(\eta\) with \(x\) establishes part 1.

We now define the pull back \(w(x) := w(v(x))\) using a slight abuse of notation. Taking the derivative of (7.23) and inverting it, it is straightforward to see that

\[ \frac{dv(x)}{dx} = w(x). \]

Furthermore, taking the derivative of the positive sign of (7.22) we get that \(w\) satisfies (7.15). Since \(v_{\max} < \infty\), there is a unique \(T\) such that \(v(T) = v_{\max}\). In this case

\[ w(v_{\min}) = w(v_{\max}) = 0 \]

and

\[ v_{\min} = v(0) \text{ with } v_{\max} = v(L) \]

satisfying the boundary conditions.

Part 3 follows from the fact that we can define \(u(x) = f(v(x))\), and taking the
derivative of $u(x)$ gives

$$u_x = f'(v)v_x$$

$$= \frac{X}{D} \left( \frac{u(1-u)^2}{1+u^2} \right).$$

This equation is equivalent to (7.6) which we can take the derivative of to get (7.3) with $u_t = 0$ and (7.4) follows from part 2. The boundary conditions for $u$ are satisfied using (7.6) and are satisfied for $v$ by part 2. Uniqueness follows from [5], establishing part 3.

Using a change of variables, $x \to -x + L$, it is possible to see that the reflection of the solution across the domain also satisfies the stationary equation to (7.3), (7.4) with the caveat that $w$ changes sign. This yields part 4.

Remark 7.2.3. If $v_{\text{min}}$ or $v_{\text{max}}$ equals either $v_1$, $v_2$, or $v_3$, then it is instead possible to define $v(x)$ as the appropriate constant function, $u = \gamma v/\alpha$, and $w = 0$ which satisfies the conditions of being a stationary solution.

Corollary 7.2.4. All positive non-homogenous steady state solutions to (7.3) satisfying boundary conditions (7.5) are a sequence of single-steps alternating between specific values of $v_{\text{min}}$ and $v_{\text{max}}$.

Proof. Given a positive non-homogenous bounded solution $(u(x), v(x))$, let $x_1 > 0$ be the first point after $x = 0$ where either $u_x$ or $v_x$ is zero. By (7.6) if $v_x = 0$, then $u_x = 0$. If $u_x = 0$, then $v_x = 0$ or $u = 0$ where the later result is ruled out by positivity. We can therefore restrict the domain to $[0, x_1]$ with $(u(x), v(x))$ as the unique step solution to the restricted boundary value problem. At this point, we
see from the Hamiltonian dynamics given in the phase plane analysis that having a non-constant steady state solution means that \( f(v) - \frac{\alpha}{\delta}v \) is sigmoid with three roots. In order to satisfy the boundary conditions, \( w(v) \) must have two roots. By the above theorem, since we have \( K = Q(u(0)) - v(0) \) and by uniqueness we must have \( v(x_1) \) either be \( v_{\text{max}} \) or \( v_{\text{min}} \). In either case, if \( x_1 = L \) we are done. Otherwise, we can repeat the argument for the next critical point, \( x_2 \). Notice that \( K \) stays the same for the restricted solution with domain \([x_1, x_2]\) since \( K \) is an integration constant with \( K = Q(u(x)) - v(x) \) and \( x_1 \) is in both the first and second domains. Furthermore since \( K \) stays the same, we have the same \( v_{\text{min}} \) and \( v_{\text{max}} \), and their corresponding \( u \) values are also the same. By part 4 of the theorem, the second step must be a reflection of the previous step because the steps share the same minimum, maximum, and \( K \) value. Also note that the second step has the same single step length with \( x_2 = x_1 + T \). Repeating this argument until \( x_n = L \) for some \( n > 0 \) gives \( T \) divides \( L \) and the steps must alternate between reflections of the first step.

### 7.2.3 Generation of Multi-Stepped Solutions

To get spatially non-homogenous solutions along the center manifold that corresponds to stationary solution of (7.3), we need the trajectory to begin and end at \( w = 0 \) after ‘duration L’ by the boundary conditions \( w(0) = w(L) = 0 \). Note that this condition cannot be satisfied if we only had a single saddle as a fixed point. Using the symmetry of \( v \) across the \( w \)-axis, it is possible to see that this gives the condition \( L = kT \) for some integer \( k \). To parametrize possible curves, let us vary the point of intersection on the \( w \)-axis, \((v_{\text{max}}, 0)\), where \( v_2 \leq v_{\text{max}} \leq v_3 \) and let \( T \) be the duration of the half curve that ends at \((v_{\text{max}}, 0)\). As \( v_{\text{max}} \) increases,
the curves move away from the fixed point. Eventually we will approach either a heteroclinic orbit connecting \( S_1 \) and \( S_3 \) or a homoclinic orbit connecting one of the roots to itself. Using (7.24), it may or may not be possible to solve for \( v \neq v_1 \) such that

\[
0 = \alpha \frac{F(v)}{D_c} - \gamma \frac{v^2}{2D_c} - \alpha \frac{F(v_1)}{D_c} + \gamma \frac{v_1^2}{2D_c}.
\]

If no such \( v \) exists then the Hamiltonian curve containing \( S_1 \) does not connect back to the \( w \)-axis which occurs when \( S_3 \) has a homoclinic orbit connecting to itself. If such an \( v \) exists, then we either have a heteroclinic orbit with \( v = v_3 \) or a homoclinic connecting \( S_1 \) to itself with \( v < v_3 \). In all of these cases, for large enough \( v_{\text{max}} \), the duration of the half curve approaches \( \infty \).

In order to calculate how the duration behaves as \( v_{\text{max}} \) approaches \( v_2 \), we linearize (7.14)-(7.15) around \((v, w) = S_2\). Solving the linearized system using the matrix exponential method yields that the function is periodic with half-period \( T^* \) if \( T^*|_{\nu_k} = \pi k \). This gives us the limiting 'duration'

\[
\lim_{v_{\text{max}} \to v_2} T(v_{\text{max}}) = T^* = \frac{\pi}{\sqrt{\frac{1}{D_c}(-\gamma + \alpha f'(v_2))}} \tag{7.30}
\]

where \( T(v) \) is the length of the half circle that ends at \( v \). We will later show that given a domain of length \( L > T^* \), there is at least one non-homogenous solution. For \( L < T^* \), we cannot rule out the possibility of non-homogenous solutions existing as we cannot establish the monotinicity of \( T(v_{\text{min}}) \).

In order to describe the generation of multi-step solutions, we first recall that \( L = kT \), where \( k \) is the number of half cycles, or steps, the solution contains.
Multi-stepped stationary solutions of (7.14) – (7.16) for \( k \geq 1 \) can only exist with duration, \( T = L/k \). So the generation of new stationary solutions corresponds to when the first inhomogenous solution of (7.14)-(7.16) with domain length \( kT \) appears. This is equivalent to satisfying the linearized condition

\[
T^* = L/k = \frac{\pi}{\sqrt{\frac{1}{D_c}(-\gamma + \alpha f'(v_2))}}.
\]

This process of bifurcating new periodic solutions due to changes in domain length relates to the generation of new eigenvalues of an elliptic operator. For further information on branching solutions see [24].

In general \( f'(v_2) \) is hard to determine since we have to solve for \( v_2 \). However for the constant solution \( v = \alpha \tilde{M}/\gamma \) we have,

\[
f'(v_2) = \frac{\chi}{D} \left[ \frac{\tilde{M}(1 - \tilde{M})^2}{1 + \tilde{M}^2} \right], \quad (7.31)
\]

where \( \tilde{M} \) satisfies \( 0 = Q(\tilde{M}) - \frac{\alpha \tilde{M}}{\gamma} - K \) from (7.13).

We now use chemical production as a parameter and the fact that in the limit of zero amplitude oscillations we can substitute (7.31) into (7.30) to get the following result

**Lemma 7.2.5.** Assuming the same conditions as theorem 7.2.2, a \( k \)-step stationary solution to (7.3) exist for \( \alpha > \alpha_k \) when

\[
\alpha_k = \frac{D(1 + \tilde{M}^2)(D_c\left(\frac{k\pi}{L}\right)^2 + \gamma)}{\chi \tilde{M}(1 - \tilde{M})^2}. \quad (7.32)
\]

**Proof.** Recall that by the assumptions, the system (7.14) – (7.15) is Hamiltonian with a center and two saddles. The phase plane contains Hamiltonian curves that
connect the \( w = 0 \) axis to itself. By the above calculation in (7.30), there are curves whose duration is arbitrarily close to the duration \( T^\ast \) for given \( \alpha \) and since there is either a heteroclinic or homoclinic orbit connecting \( v = \sigma_1 \in [v_1, v_2) \) to \( v = \sigma_2 \in (v_2, v_3] \), there is a curve whose duration is unbounded.

The function (7.27) is continuous with respect to \( v_{\text{min}} \in (\sigma_1, v_2) \) due to the continuity of the integrand. So for any duration \( T \in (T^\ast, \infty) \), there exists at least one corresponding Hamiltonian curve with that duration. Since each Hamiltonian curve satisfies the boundary conditions for some domain length \( L \), it remains to show there is a duration \( T_k = L/k > T^\ast \) for there to exist a \( k \)-step solution on domain length \( L \). Let \( \alpha = \alpha_k + R, R > 0 \), and using (7.30), (7.31) and \( f'(v_2) > 0 \) we have,

\[
T^\ast = \frac{\pi}{\sqrt{\frac{1}{D_c}(-\gamma + \alpha f'(v_2))}} \\
= \frac{\pi}{\sqrt{\left(\frac{k\pi}{L}\right)^2 + \frac{Rf'(v_2)}{D_c}}} \\
\leq \frac{\pi}{\sqrt{\left(\frac{k\pi}{L}\right)^2}} \\
\leq \frac{\pi}{\sqrt{\left(\frac{\pi}{L}\right)^2}} \\
= L/k = T_k
\]

We note that there is a unique correspondence between our choice of \( K \) and the value of \( \tilde{M} \) since \( \tilde{M} = \frac{\gamma v_2}{\alpha} \). This correspondence allows us to switch the roles of \( \tilde{M} \) and \( K \), making \( \tilde{M} \) a parameter for determining the dynamics of the system.

Notice that (7.32) can also be used to count the number of stationary solutions
that the given parameters can produce. Given $\alpha_k < \alpha < \alpha_{k+1}$ there are $k$ known
curves that satisfy the conditions for the given the given $\tilde{M}$. However, if we were
to try and leave $\tilde{M}$ arbitrary then we can not at this time discount the possibility
for multiple $k$-step solutions with the same value of $\tilde{M}$.

7.3 Stability Analysis of Solutions

7.3.1 Lyapunov Stability Condition

In order to analyse the stability of multiple stepped equations, we will define a
Lyapunov functional and describe the conditions when the stationary solutions
are local minimums. Here we consider the system

\[ \rho_t = (h(\rho)\rho_x)_x + (g(\rho)\Phi_x)_x \]  
\[ \Phi_t = D_c \Phi_{xx} - \beta(\Phi) - \alpha \rho \]  
\[ \rho_x(0) = \Phi_x(0) = \rho_x(L) = \Phi_x(L) = 0. \]

Note that by denoting $\rho = u$ and $\Phi = -v$ system (7.3)-(7.4) changes to (7.33)-(7.34), with $h(\rho) = \Gamma(u)$, $g(\rho) = \chi u$, and $\beta(\Phi) = -\gamma v$

We define a generalized entropic functional

\[ S = - \int_0^L C(\rho(x))dx \]  

where $C(\rho)$ is the convex function determined by the equality:
\[ C''(\rho) = \frac{h(\rho)}{g(\rho)}. \quad (7.37) \]

Let us note that the function \( C(\cdot) \) is defined only up to a term \( c_1 \rho + c_2 \). However, integration of this term over space gives a constant independent of \( t \) due to the mass conservation \((L)^{-1} \int \rho(x,t)dx = M\). For definiteness, we will take \( c_1 = c_2 = 0 \) here. Let us also define the generalized free energy

\[ F = \int_0^L D_{\alpha}(\Phi_x)^2 + \frac{1}{\alpha} B(\Phi)dx + \int_0^L \rho \Phi dx + \int_0^L C(\rho)dx \quad (7.38) \]

where \( B(\Phi) \) is the antiderivative of \( \beta(\Phi) \) with integration constant 0.

**Theorem 7.3.1.** If \( \rho \in (\rho_{\text{min}}, \rho_{\text{max}}) \), where \( 0 < \rho_{\text{min}} < \rho_{\text{max}} < g(\rho) > 0 \), \( h(\rho) \geq 0 \), \( \Phi \leq 0 \), and \( \beta(\rho) \) is monotonically increasing. Then \( F \) is bounded below and is a Lyapunov functional for the system (7.33)-(7.34).

**Proof.** Since \( \rho_{\text{min}} < \rho < \rho_{\text{max}} \), \( \Phi \leq 0 \), and both \( \beta \) and \( B \) are monotonic, it follows that \( \frac{B(\Phi)}{\alpha} + \rho \Phi \) reaches a critical point equal to equal to \( \frac{B(\beta^{-1}(-\alpha \rho))}{\alpha} + \rho \beta^{-1}(-\alpha \rho) \) when \( \Phi = \beta^{-1}(-\alpha \rho) \) and this critical point is a minimum since the second derivative yields \( \beta'(\beta^{-1}(-\alpha \rho))/\alpha > 0 \).

Since \( C''(\rho) \geq 0 \), it follows that \( C(\rho) \geq 0 \). As a consequence, the functional is bounded below by
\[ F(\rho) \geq \frac{B(\beta^{-1}(-\alpha \rho))}{\alpha} + L\rho \beta^{-1}(-\alpha \rho) \quad (7.39) \]

\[ \geq \inf_{\rho} \frac{B(\beta^{-1}(-\alpha \rho))}{\alpha} + L\rho \beta^{-1}(-\alpha \rho) \quad (7.40) \]

Note that for (7.3)-(7.4), the functional is bounded below by \(-\frac{L\alpha \rho_{\text{max}}}{\alpha} + \text{const.}\).

Taking the time derivative, it is possible to show that for non-stationary \(\rho\) and \(\Phi\), the free energy

\[ F = \int_{0}^{L} \frac{D_{\alpha}}{2\alpha} (\Phi_{x})^{2} + \frac{1}{\alpha} B(\Phi) dx + \int_{0}^{L} \rho \Phi dx + \int_{0}^{L} C(\rho) dx \]

is decreasing with respect to time. We assume that \(g(\rho), \alpha > 0\) and have

\[ \frac{dF}{dt} = \int \frac{D_{\alpha}}{\alpha} \Phi_{x} \Phi_{tx} + \frac{\beta(\Phi)}{\alpha} \Phi_{t} dx + \int \rho_{t} \Phi + \rho \Phi_{t} dx + \int C'(\rho) \rho_{tx} dx \quad (7.41) \]

\[ = \int \left( -\frac{D_{\alpha}}{\alpha} \Phi_{xx} + \frac{\beta(\Phi)}{\alpha} + \rho \right) \Phi_{t} dx + \int (\Phi + C'(\rho)) \rho_{t} dx \quad (7.42) \]

\[ = -\int \frac{(\Phi_{t})^{2}}{\alpha} dx + \int (\Phi + C'(\rho))(h(\rho)\rho_{x} + g(\rho)\Phi_{x})_{x} dx \quad (7.43) \]

\[ = -\int \frac{(\Phi_{t})^{2}}{\alpha} dx + \int (\Phi + C'(\rho))(h(\rho)\rho_{x} + g(\rho)\Phi_{x})_{x} dx \quad (7.44) \]

\[ = -\int \frac{(\Phi_{t})^{2}}{\alpha} dx - \int (\Phi_{x} + C''(\rho)\rho_{x})(h(\rho)\rho_{x} + g(\rho)\Phi_{x}) dx \quad (7.45) \]

\[ = -\int \frac{(\Phi_{t})^{2}}{\alpha} dx - \int g(\rho)(\Phi_{x} + C''(\rho)\rho_{x})^{2} dx \quad (7.46) \]

\[ \leq 0 \quad (7.47) \]

where we used integration by parts and the no-flux boundary conditions on the second line and fourth lines, and substitution with (7.33) on the third line. The
last line follows from the positivity of $g(\rho)$. Notice that $\dot{F} = 0$ if and only if $\Phi_t = 0$ and $g(\rho)\Phi_x + h(\rho)\rho_x = 0$. The later condition implies $\rho_t = 0$. If $\rho_t = 0$ we have that $g(\rho)\Phi_x + h(\rho)\rho_x = \text{const}$ and by boundary conditions, we must have the constant be zero. $\dot{F} < 0$ if and only if the $(\rho, \Phi)$ are not stationary solutions. 

This forms an H-theorem in the canonical ensemble. The free energy is always decreasing and it is bounded below, its minimums correspond to stationary solutions. Moreover, the existence of this functional indicates that over time, the solutions will converge to one of these stationary solutions.

In order to determine the stability of the minimum values of the functional $F$, we look at the first and second variational derivatives. Taking the first and second variational derivatives of $F$ gives

$$
\delta F = \frac{1}{\alpha} \int_0^L D_c \Phi_x \delta \Phi_x + \beta(\Phi) \delta \Phi dx + \int_0^L \rho \delta \Phi + \delta \rho \Phi dx + \int_0^L C'(\rho) \delta \rho dr \quad (7.48)
$$

$$
\delta^2 F = \frac{1}{\alpha} \int_0^L D_c (\delta \Phi_x)^2 + \beta'(\Phi)(\delta \Phi)^2 dx + 2 \int_0^L \delta \rho \delta \Phi dx + \int_0^L C''(\rho) (\delta \rho)^2 dx.
\quad (7.49)
$$

If we find a perturbation $\delta \rho$ and $\delta \Phi$ such that at a fixed point, $\delta^2 F(\delta \rho, \delta \Phi) > 0$, then the fixed point is unstable under this perturbation. With this goal in mind, we consider perturbations that preserve the total amount of chemical density and

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that satisfy the boundary conditions. Assuming that

\[ \delta \rho = A_k \cos(k \pi x / L) \]  \hfill (7.50)

\[ \delta \Phi = C_l \cos(l \pi x / L) \]  \hfill (7.51)

\[ \delta \Phi = C_l \cos(l \pi x / L) \]  \hfill (7.52)

where \( k \) and \( l \) are positive integers numbers, it is possible to see

\[ \frac{1}{\alpha} \int_0^L D_c(\delta \Phi x)^2 dx = LD_c \mu_l^2 \frac{C_l^2}{2\alpha} \]  \hfill (7.53)

\[ \int_0^L \frac{\beta'(\Phi)}{\alpha} (\delta \Phi)^2 dx = \frac{C_l^2}{\alpha} \mathcal{J}[\Phi] \]  \hfill (7.54)

\[ 2 \int_0^L \delta \rho \delta \Phi dx = \delta_{k,l} L A_k C_k \]  \hfill (7.55)

\[ \int_0^L (\delta \rho)^2 C'' dx = A_k^2 \mathcal{K}[\rho] \]  \hfill (7.56)

where \( \delta_{k,l} \) is the Kronecker delta, \( \mu_k = (\frac{\pi k}{L}) \), and

\[ \mathcal{J}[\Phi] = \int_0^L \cos((\mu_l)x)^2 \beta'(\Phi) dx. \]  \hfill (7.57)

\[ \mathcal{K}[\rho] = \int_0^L \cos((\mu_k)x)^2 C'' dx. \]  \hfill (7.58)

Now \( (\delta F)^2(\delta \rho, \delta \Phi) < 0 \) when

\[ 0 > A_k^2 \frac{\mathcal{K}[\Phi]}{L} + A_k C_l \delta_{k,l} + (D_c \mu_l^2 \frac{C_l^2}{2\alpha} + \frac{\mathcal{J}[\Phi]}{\alpha L})C_l^2. \]  \hfill (7.59)
Since $A_k$ and $C_l$ are constants we are free to choose, we can minimize the right hand side of the equation with respect to $C_l$. Notice that the critical points that occur must be minimums. Since $\beta$ is increasing, we must have $J > 0$ and so the second derivative yields $D_c \frac{\mu^2}{\alpha} + 2\frac{J[\Phi]}{\alpha L} > 0$.

These critical points occur when

$$A_k \delta_{k,l} + (D_c \frac{\mu^2}{\alpha} + 2\frac{J[\Phi]}{\alpha L})C_l = 0$$

Or

$$C_l = -\frac{\alpha A_k \delta_{k,l}}{D_c \mu^2 + 2\frac{J[\Phi]}{L}}$$

Since this critical point is the minimum, we have that if instability will occur then it will occur for this choice of $C_k$. Furthermore, since the $C_l = 0$ choices are always stable, if instability will occur, it will occur for the choice of $k = l$ and

$$C_k = -\frac{\alpha A_k}{D_c \mu^2 + 2\frac{J[\Phi]}{L}}.$$ 

Substituting this choice in for the unstable case gives

$$0 > A_k^2 \frac{\mathcal{K}[\rho]}{L} - A_k^2 \frac{\alpha}{D_c \mu^2 + 2\frac{J[\Phi]}{L}} + A_k^2 \frac{\alpha}{2(D_c \mu^2 + 2\frac{J[\Phi]}{L})}$$

$$= A_k^2 \left[ \frac{\mathcal{K}[\rho]}{L} - \frac{\alpha}{2(D_c \mu^2 + 2\frac{J[\Phi]}{L})} \right].$$

If instability will occur for the prescribed perturbations, it will occur when the
stationary solution satisfies the condition

\[
\mathcal{K}[\rho] < \frac{\alpha L}{2(Dc\mu_k^2 + 2\frac{2\beta'(\Phi)}{L})}. \tag{7.62}
\]

In a similar fashion, more general choices of \(\delta\Phi\) and \(\delta\rho\) that still preserve total chemical density can be written as linear combinations of cosines. The general instability condition becomes

\[
\int_0^L C''(\rho(x))\delta\rho(x)^2 \, dx < \sum_{k>0} \frac{A_k^2 \alpha L}{2(Dc\mu_k^2 + 2\frac{2\beta'(\Phi)}{L})} \int_0^L \cos((\mu_k x)^2) \beta'(\Phi) \, dx. \tag{7.63}
\]

Since the instability condition holds if and only if the prescribed perturbation is unstable with respect to the stationary solution, if for arbitrary concentration preserving perturbations we have

\[
0 > \sup_{\delta\rho} \sum_{k>0} A_k^2 \frac{\alpha L}{2(Dc\mu_k^2 + 2\frac{2\beta'(\Phi)}{L})} - \int_0^L C''(\rho(x))\delta\rho^2 \, dx \tag{7.64}
\]

then the stationary solution is stable.

This condition is equivalent to all \(n \times n\) matrices of the form

\[
\mathcal{R} - \mathcal{Q}
\]

having negative eigenvalues bounded below some \(\delta < 0\), where \(\mathcal{R}\) is a diagonal
matrix with
\[ R_{ri} = \frac{\alpha L}{2(D_c\mu_i^2 + \frac{2}{L} \int_0^L \cos(\mu_i x)^2 \beta(\Phi) dx)} \]
\[ Q_{i,j} = \int_0^L C''(\rho(x)) \cos(\mu_i x) \cos(\mu_j x) dx. \]

In general it seems that this expression has to be evaluated numerically in order to determine the stability of the solution. However, we can state a few estimates about this equation. From now on, assume \( \beta(\Phi) = \gamma \Phi \). If we choose \( A_1 = 1 \) and \( A_k = 0 \) for \( k \neq 1 \), then using Holder’s inequality we see instability will occur if

\[ ||C''||_{L^\infty} < \frac{\alpha}{D_c(\frac{\pi}{L})^2 + \gamma}, \quad (7.65) \]

For the stability condition we note that

\[ \sup_{\Delta \rho} \sum_{k>0} A_k^2 \frac{\alpha L}{2(D_c\mu_k^2 + \gamma)} - \int_0^L C''(\rho(x)) \delta \rho^2 dx \]
\[ \leq \sup_{\Delta \rho} \sum_{k>0} A_k^2 \frac{\alpha L}{2(D_c\mu_k^2 + \gamma)} - \int_0^L C''(\rho(x)) \delta \rho^2 dx \quad (7.66) \]
\[ \leq \sup_{\Delta \rho} \frac{\alpha L}{2(D_c\mu_1^2 + \gamma)} \sum_{k>0} A_k^2 - \int_0^L C''(\rho(x)) \delta \rho^2 dx \quad (7.67) \]
\[ \leq \sup_{\Delta \rho} \frac{\alpha}{D_c\mu_1^2 + \gamma} ||\delta \rho||_{L^2}^2 - \int_0^L C''(\rho(x)) \delta \rho^2 dx \quad (7.68) \]
\[ \leq \sup_{\Delta \rho} \frac{\alpha}{D_c\mu_1^2 + \gamma} ||\delta \rho||_{L^2}^2 - \inf C''(\rho(x)) \int_0^L \delta \rho^2 dx \quad (7.69) \]
\[ \leq \sup_{\Delta \rho} ||\delta \rho||_{L^2}^2 \left[ \frac{\alpha}{D_c\mu_1^2 + \gamma} - \inf C''(\rho(x)) \right] \quad (7.70) \]

where the first inequality follows from \( \mu_k > \mu_1 \), and the third and fifth lines from
the observation that

$$ ||\delta \rho ||^2_{L^2} = \int_0^L \delta \rho^2 \, dx = \int_0^L (\sum_{k>0} A_k \cos(\mu_k x))^2 \, dx = \frac{L}{2} \sum_{k>0} A_k^2. $$

Using (7.70) and (7.64), we have stability if

$$ \frac{\alpha}{D_c \mu_1^2 + \gamma} < \inf C''(\rho(x)) $$

(7.71)

These results lead to the following theorem.

**Theorem 7.3.2.** Assuming the hypothesis found in theorem 7.3.1, stationary solutions to the system (7.33)-(7.34) when \( \beta(\Phi) = \gamma \Phi \) are known to be stable if they satisfy

$$ \inf C'' > \frac{\alpha}{D_c (\frac{\pi}{L})^2 + \gamma} $$

(7.72)

and are unstable solutions if

$$ ||C''||_{L^\infty} < \frac{\alpha}{D_c (\frac{\pi}{L})^2 + \gamma}. $$

(7.73)

7.3.2 Limiting Behaviour of Domain Length

For this section, we will consider the system described by (7.3),(7.4), and (7.5).

We know \( ||\beta'(\Phi)||_{L^\infty} = \gamma \) and using Corollary 7.2.4 along with the definition of \( C'' \),

$$ ||C''||_{L^\infty} = \frac{D}{\chi} \max \left( \frac{1 + \rho_{\min}^2}{\rho_{\min}(1 - \rho_{\min})^2}, \frac{1 + \rho_{\max}^2}{\rho_{\max}(1 - \rho_{\max})^2} \right). $$

(7.74)
When a new non-homogeneous solution emerges from the fixed point, \( \alpha = \alpha_k + \epsilon \), we can asymptotically approximate the solutions \( \rho = M + \epsilon \rho_1 + O(\epsilon^2) \) and \( \Phi = -\alpha M/\gamma + \epsilon \Phi_1 + O(\epsilon^2) \). Substituting these expansions into (7.32 and 7.62), we notice that

\[
1 < \frac{D_c \mu_k^2 + \gamma}{D_c \mu_k^2 + \gamma} + O(\epsilon) \tag{7.75}
\]

when \( l < k \), we get that \( l > 1 \) implies \( \delta \rho = \cos(\mu_1 x) \) is an unstable perturbation. So all non-single step perturbations start out unstable.

Note an interesting phenomena happens if we allow the domain length, \( L \), to increase. For a given \( K \), as \( L \) approaches infinity the points \((v_{\text{min}}, 0)\) and \((v_{\text{max}}, 0)\) stay finite and approach the seperatrix at \( S_1, S_3 \), or both. As a result, \( ||C'||_{L^\infty} \) stays bounded for large \( L \).

Looking at (7.32), we see that as \( L \) becomes unbounded every multi-step solution will eventually emerge. Previous phase plane analysis and (7.64) indicates that if a solution with \( k \)-step emerges and is stable in the limit, then all \( l \)-step solutions, with \( l < k \), will also become stable. In particular the single-step solutions will always stay or become stable if a given \( k \)-step solution becomes stable.

Also note that since \( C'' \) has a minimum at 0.295598 with \( C'' \) evaluating to 7.41375 at this value, if

\[
7.41375 > \frac{\alpha}{D_c (\frac{\pi}{L})^2 + \gamma}
\]

then all multi-step solutions will be stable.

### 7.3.3 Plateaus vs. Spikes

In this section, we consider the following general system.
\[ u_t = (h(u)u_x)_x - (g(u)v_x)_x \] (7.76)

\[ v_t = D_v v_{xx} + \beta(-v) + \alpha u \] (7.77)

\[ u_x(0) = v_x(0) = u_x(L) = v_x(L) = 0. \] (7.78)

and assume that \( g, h, \) and \( \beta \) are chosen such that unique solutions exist and \( u(v) \) is well defined in a similar way as (7.8). As described in [45], a one dimensional pattern can be characterized as a spike or plateau by calculating the sign of its fourth derivative at the peak of the pattern. Here we attempt to classify any patterns of (7.76) as spike or plateaus. Notice that from the above inversion calculation, spikes in \( u \) correspond to spikes in \( v \). Consider a point \( x_0 \) where

\[ u_x(x_0) = v_x(x_0) = 0, \quad u_{xx}(x_0) < 0, \quad v_{xx}(x_0) < 0, \]

and note the stability equations yield

\[ 0 = (h(u)u')' - (g(u)v')' \] (7.79)

\[ 0 = D_v v'' + \alpha u' + \beta(-v). \] (7.80)

Taking the two derivatives on the top and bottom gives:

\[ 0 = (hu')''' - (g(u)v')''' \] (7.81)

\[ 0 = D_v v^{IV} + \alpha u'' + \beta v(-v)(v')^2 - \beta_v(-v)v''. \] (7.82)
Observe that since

\[ h' = \partial_u h \partial_x u \quad (7.83) \]

\[ h'' = \partial_u u h \partial_x u + \partial_u h \partial_{xx} u, \quad (7.84) \]

we can evaluate (7.79) and (7.80) at \( x_0 \) which allows us to remove the first order derivatives of \( u \) and \( v \) to get

\[ u''(x_0) = g v'' / h \quad (7.85) \]

\[ v''(x_0) = (-\alpha u - \beta (-v)) / D_c. \quad (7.86) \]

Similarly evaluating (7.81) and (7.82) at \( x_0 \) allows us to get

\[ u^{IV}(x_0) = (-3 \partial_u h(u'')^2 + 3 g_u u'' v'' + g u^{IV}) / h \quad (7.87) \]

\[ v^{IV}(x_0) = (-\alpha u'' - \beta v v(-v)(v')^2 + \beta v(-v) v'' / D_c. \quad (7.88) \]

Substituting (7.85) and (7.86) into (7.88) we get

\[ v^{IV}(x_0) = (-\alpha g h + \beta v (-v(x_0))) \frac{v''}{D_c}. \]

Since \( v''(x_0) < 0 \), we have \( v^{IV}(x_0) \) is and a spike if and only if
\[ \frac{g(u(x_0))}{h(u(x_0))} \beta_v(-v(x_0)) \]  

(7.89)

For (7.3) and (7.4), this is equivalent to

\[ \frac{u(x_o)(1 - u(x_0))^2}{(1 + u(x_0)^2)} > \frac{\gamma D}{\alpha \chi}, \]

and the maximum of the left hand side evaluates as 0.134884. So if \( \frac{\gamma D}{\alpha \chi} > 0.134884 \), we can be sure any non-trivial patterns will be plateaus, otherwise it depends on the maximum value of the solution we are examining. Notice that the spike condition

\[ \frac{(1 + u(x_0)^2)}{u(x_o)(1 - u(x_0))^2} < \frac{\alpha \chi}{\gamma D}, \]

is similar to the condition that the solution becomes unstable as \( L \) goes to infinity. In fact, it is clearly seen that if a periodic solution is a spike, then on a long enough domain it will become unstable. Furthermore, it is possible to use Theorem 7.3.2 to see

**Corollary 7.3.3.** All solutions to the system described in (7.76) and that satisfy the instability conditions in Theorem 7.3.2 are spikes.

**Proof.** Let \( v = -\Phi \), and \( u = \rho \). Use theorem 7.3.2 and the fact that the condition on \( ||C'||_L^\infty \) is easier to satisfy than the inequality of (7.89) to get the result. \( \square \)

7.4 Numerics

To demonstrate the existence of stable multi-step solutions we use numerics to evaluate the various expressions as well as solve the PDE. Specifically, we use
MATLAB’s pdepe code which uses Skeel and Berzin’s method for discretizing the spatial domain [98] in order to apply the method of lines coupled with MATLAB’s variable-order stiff ode solver, ode15s. For this section, we assume $\alpha = 20$, $\chi = 0.5$, $M = 0.25$, and $\gamma = D_c = D = 1$.

First we wish to examine what $C''(u)$ looks like. Graphing it we see a concave up function with two singularities, with the steeper singularity at $u = 0$ (see Figure 7.2a).

Notice that not every value of $T$ achieves two fixed seperatrix points (see Figure 7.2b), as we would expect for large values of $T$ which result in a single saddle node in the $(v, w)$ phase space.

We set as the initial conditions for $u$ and $v$ to be linear combination of cos and sin waves, and allow the function to evolve until time $t = 10^{15}$. For small $L$ the PDE converges to a constant steady state solution, e.g. $L = 20$. For larger $L$, the PDE converges to a stable single step. For large $L$, we get convergence to a multi-step pattern that is not a single step. See Figure 7.3 for single and double step plots.
Figure 7.3. Surface Plots of $u$ and $v$ over time with a) a stable single step at $L=40$ b) a stable multi-step at $L=100$ with same initial conditions up to scaling
Here, the Transient Differential Chapman-Kolmogorov (TDCK) equation is found by first extending the derivation from in Gardiner [33] to include the case where the transition probabilities can be represented by distribution functionals rather than just functions. This allows us to include dirac deltas and discontinuous functions. Then we look use this to examine the case where the total probability density over a subset is decreasing over time. In Appendix B we use the TDCK to derive a new algorithm for approximating the probability density that results when cells are randomly placed on a grid according to a given inhomogenous distribution.

Gardiner [33] includes jump terms, or instantaneous transition probabilities that correspond to jumps in the stochastic process, in the Differential Chapman-Kolmogorov, a weak formulation of these results is not proven. In contrast, a weak formulation for the convergence to diffusion is given in [28, 108], but do not allow for instantaneous transition probabilities. The TDCK allows for both, but assumes the process takes place on a compact subset of $\mathbb{R}^n$. Proof of this theorem follows [33], with some modifications, and uses his notation for consistency.

**Theorem A.0.1.** Let $\Omega$ be an arbitrary measurable subset of $X \subset \mathbb{R}^n$, $X$ is compact, and $p(\cdot, t|\bar{y}, t') \in [C_0^\infty(X)]^*$ be a family of bounded positive linear functionals
parametrized by $t' > 0$, $\bar{y} \in X$, and differentiable with respect to time, $t \geq t'$. Let there be an inner product,

$$< p(\bar{x}, t|\bar{y}, t'), f(x) >_X = \int_X f(\bar{x})p(\bar{x}, t|\bar{y}, t')d\bar{x}, \quad (A.1)$$

for arbitrary $f \in C^\infty_0(X)$, smooth with compact support. Also, let the near instantaneous transition probability have total density represented by

$$< p(\bar{x}, t+\Delta t|\bar{z}, t), 1 >_X = 1, \quad (A.2)$$

and $p(\cdot, t|\bar{y}, t')$ satisfies the modified Chapman-Kolmogorov condition such that for any $f \in C^\infty(X)$,

$$< p(\bar{x}, t_1|\bar{y}, t_3), f(\bar{x}) >_X = < p(\bar{x}, t_2|\bar{y}, t_3), < p(\bar{x}, t_1|\bar{z}, t_2), f(\bar{x}) >_X \quad (A.3)$$

where $t_3 \leq t_2 \leq t_1$

Then if the stochastic process with transition probabilities $p(\cdot, t|\bar{y}, t')$ fulfills the following limit conditions for all $\epsilon > 0$:

$$\lim_{\Delta t \to 0} \frac{1}{\Delta t} < p(\bar{x}, t + \Delta t|\bar{z}, t), f(\bar{x}) >_{X-B_\epsilon(\bar{z})} = < W(\cdot|\bar{z}, t), f(\bar{x}) >_{X-B_\epsilon(\bar{z})} \quad (A.4)$$

for all $f \in C^\infty_0$ \quad (A.5)

$$\lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{|\bar{x} - \bar{z}| < \epsilon} (x_i - z_i)p(\bar{x}, t + \Delta t|z, t)d\bar{x} = A_i(\bar{z}, t) + O(\epsilon) \quad (A.6)$$

$$\lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{|\bar{x} - \bar{z}| < \epsilon} (x_i - z_i)(x_j - z_j)p(\bar{x}, t + \Delta t|z, t)d\bar{x} = B_{i,j}(\bar{z}, t) + O(\epsilon) \quad (A.7)$$

where $A_i, B_{i,j} \in L^1_{loc}$ and $W(\cdot|\bar{z}, t) \in [C^\infty_0(X)]^*$, then the density profile of the
process is a weak solution to the local P.D.E.

\[
\partial_t p(\vec{z}, t|y, t') = - \sum_i \frac{\partial}{\partial z_i} [A_i(\vec{z}, t)p(\vec{z}, t|\vec{y}, t')] + \frac{1}{2} \sum_{i,j} \frac{\partial^2}{\partial z_i \partial z_j} [B_{i,j}(\vec{z}, t)p(\vec{z}, t|\vec{y}, t')] \\
+ \lim_{\epsilon \to 0} \int_{X-B_\epsilon(\vec{z})} [W(\vec{z}|\vec{x}, t)p(\vec{x}, t|\vec{y}, t')] \\
- W(\vec{x}|\vec{z}, t)p(\vec{z}, t|\vec{y}, t')] d\vec{z} \tag{A.8}
\]

where \( B_\epsilon(\vec{z}) \) is an open ball of radius \( \epsilon \) around \( \vec{z} \).

Note that the condition

\[
< p(\vec{x}, t_1|\vec{y}, t_3), f(\vec{x}) >_\Omega = < p(\vec{z}, t_2|\vec{y}, t_3), < p(\vec{x}, t_1|\vec{z}, t_2), f(\vec{x}) >_\Omega >_X \tag{A.9}
\]

is satisfied whenever the Chapman-Kolmogorov equation

\[
p(\vec{x}, t_1|\vec{y}, t_3) = \int_X p(\vec{x}, t_1|\vec{z}, t_2)p(\vec{z}, t_2|\vec{y}, t_3)d\vec{z} \tag{A.10}
\]

holds true.

**Proof.** To prove the theorem we examine the time evolution of the expectation of a bounded function \( f(\vec{z}) \in C_0^\infty(X) \). Given \( \Omega \) is an arbitrary measurable subset of \( \mathbb{R}^n \), we now find the limiting behavior.
\[ \partial_t < p(\vec{x}, t|\vec{y}, t'), f(\vec{x}) > \] (A.11)
\[
= \lim_{\Delta t \to 0} \frac{1}{\Delta t} < p(\vec{x}, t + \Delta t|\vec{y}, t') - p(\vec{x}, t|\vec{y}, t'), f(\vec{x}) >_X 
\] (A.12)
\[
= \lim_{\Delta t \to 0} \frac{1}{\Delta t} < p(\vec{z}, t|\vec{y}, t') < p(\vec{x}, t + \Delta t|\vec{z}, t), f(\vec{x}) >_X>_X 
- < p(\vec{z}, t|\vec{y}, t'), f(\vec{z}) >_X 
\] (A.13)

where the first equality holds by bilinearity and the definition of the derivative and
the second follows from our modified Chapman Kolmogorov Equation condition
and a change of variables. Since \( f \in C^\infty_0(X) \), we can use Taylor’s expansion to
get

\[
f(\vec{x}) = f(\vec{z}) + \sum_i \frac{\partial f(\vec{z})}{\partial \vec{z}_i} (\vec{x}_i - \vec{z}_i) + \sum_{i,j} \frac{1}{2} \frac{\partial^2 f(\vec{z})}{\partial \vec{z}_i \partial \vec{z}_j} (\vec{x}_i - \vec{z}_i)(\vec{x}_j - \vec{z}_j) 
- |\vec{x} - \vec{z}|^2 R(\vec{x}, \vec{z}) 
\] (A.14)

where \( |R(\vec{x}, \vec{z})| \to 0 \) as \( |\vec{x} - \vec{z}| \to 0 \). We substitute the expansion of \( f \) into
(A.13) and split the domain two regions. One region is within radius \( \epsilon \) of \( \vec{z} \), and
the other outside. We get
\[ \partial_t < p(\vec{x}, t|\vec{y}, t'), f(\vec{x}) >_X = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \]

\[ + < p(\vec{z}, t|\vec{y}, t'), < p(\vec{x}, t + \Delta t|\vec{z}, t), f(\vec{z}) >_{B_t(z)} >_X \]

\[ + < p(\vec{z}, t|\vec{y}, t'), < p(\vec{x}, t + \Delta t|\vec{z}, t), \left( \sum_i \frac{\partial f(\vec{z})}{\partial z_i} (\vec{x}_i - \vec{z}_i) \right) >_{B_t(z)} >_X \]

\[ + \sum_{i,j} \frac{1}{2} \frac{\partial^2 f(\vec{z})}{\partial z_i \partial z_j} (\vec{x}_i - \vec{z}_i)(\vec{x}_j - \vec{z}_j) ) >_{B_t(z)} >_X \]

\[ + < p(\vec{z}, t|\vec{y}, t'), < p(\vec{x}, t + \Delta t|\vec{z}, t), f(\vec{x}) >_{X - B_t(z)} >_X \]

\[- < p(\vec{z}, t|\vec{y}, t'), f(\vec{z}) >_X \] \hspace{1cm} (A.15)

Notice that since the probability densities are continuous with respect to time, we have by the assumptions

\[ \lim_{\Delta t \to 0} \frac{1}{\Delta t} < p(\vec{z}, t|\vec{y}, t'), < p(\vec{x}, t + \Delta t|\vec{z}, t), \left( \sum_i \frac{\partial f(\vec{z})}{\partial z_i} (\vec{x}_i - \vec{z}_i) \right) >_{B_t(z)} >_X \]

\[ + \sum_{i,j} \frac{1}{2} \frac{\partial^2 f(\vec{z})}{\partial z_i \partial z_j} (\vec{x}_i - \vec{z}_i)(\vec{x}_j - \vec{z}_j) ) >_{B_t(z)} >_X \] \hspace{1cm} (A.16)

\[ = < p(\vec{z}, t|\vec{y}, t'), \sum_i A_i(\vec{z}) \frac{\partial f(\vec{z})}{\partial z_i} + \frac{1}{2} \sum_{i,j} B_{i,j} \frac{\partial^2 f(\vec{z})}{\partial z_i \partial z_j} + O(\epsilon) >_X . \] \hspace{1cm} (A.17)

We can simplify of the remainder term by using the boundedness of the operator, with operator bound 1. Using the Riesz-Markov theorem, there are positive
measures $\mu_1(t, \bar{y}, t')$ and $\mu_2(t + \Delta t, \bar{z}, t)$ such that

$$\lim_{\Delta t \to 0} \left| < p(\bar{z}, t|\bar{y}, t'), \frac{1}{\Delta t} < p(\bar{x}, t + \Delta t|\bar{z}, t), |\bar{x} - \bar{z}|^2 R(\bar{x}, \bar{z}) > \mathcal{B}(\bar{z}) > X > \right |$$

$$= \lim_{\Delta t \to 0} \left| \int_X \left( \int_{\mathcal{B}(\bar{z})} |\bar{x} - \bar{z}|^2 R(\bar{x}, \bar{z}) \mu_2(t + \Delta t, \bar{z}, t)) \mu_1(t, \bar{y}, t') \right|$$

(A.18)

$$\leq \lim_{\Delta t \to 0} \left| \int_X \left( \int_{\mathcal{B}(\bar{z})} |\bar{x} - \bar{z}|^2 \mu_2(t + \Delta t, \bar{z}, t)) \right|$$

(A.19)

$$\times ||R(\bar{x}, \bar{z})||_{L^\infty(\mathcal{B}(\bar{z}))} \mu_1(t, \bar{y}, t')|$$

$$\leq | \int_X \left( \sum_i B_{i,i} + O(\epsilon) \right) ||R(\bar{x}, \bar{z})||_{L^\infty(\mathcal{B}(\bar{z}))} \mu_1(t, \bar{y}, t')|$$

(A.20)

$$\leq | < p(\bar{z}, t|\bar{y}, t'), (\sum_i B_{i,i} + O(\epsilon)) ||R(\bar{x}, \bar{z})||_{L^\infty(\mathcal{B}(\bar{z}))} > X >$$

(A.21)

Recall that since $R(\bar{x}, \bar{z})$ goes to 0 as $\epsilon \to 0$ and the transition probabilities are continuous, this term will vanish.

Finally, observing that the total transition probability is equal to 1 we have,

$$<p(\bar{z}, t|\bar{y}, t'), f(\bar{z}) > X$$

$$= < p(\bar{z}, t|\bar{y}, t'), f(\bar{z})(< p(\bar{x}, t + \Delta t|\bar{z}, t), 1 > X > X >$$

(A.22)

$$= < p(\bar{z}, t|\bar{y}, t'), < p(\bar{x}, t + \Delta t|\bar{z}, t), f(\bar{z}) > X >$$

where the second equality follows since the inner inner product is with respect to $\bar{x}$, and not $\bar{z}$, and by linearity.
This allows us to evaluate

\[
\frac{1}{\Delta t} \left[ < p(\vec{z}, t|\vec{y}, t'), < p(\vec{x}, t + \Delta t|\vec{z}, t), f(\vec{z}) >_{B_r(\vec{z})} >_X + < p(\vec{z}, t|\vec{y}, t'), < p(\vec{x}, t + \Delta t|\vec{z}, t), f(\vec{z}) >_{X-B_r(\vec{z})} >_X - < p(\vec{z}, t|\vec{y}, t'), f(\vec{z}) >_X \right]
\]

(A.23)

\[
= \frac{1}{\Delta t} \left[ < p(\vec{z}, t|\vec{y}, t'), < p(\vec{x}, t + \Delta t|\vec{z}, t), f(\vec{z}) >_{X-B_r(\vec{z})} >_X + < p(\vec{z}, t|\vec{y}, t'), < p(\vec{x}, t + \Delta t|\vec{z}, t), f(\vec{z}) >_{X-B_r(\vec{z})} >_X \right]
\]

If we take the limit as \( \Delta t \to 0 \), then we get

\[
< p(\vec{z}, t|\vec{y}', t'), < W(\vec{x}|\vec{z}, t), f(\vec{z}) >_{X-B_r(\vec{z})} >_X - < p(\vec{z}, t|\vec{y}', t'), < W(\vec{x}|\vec{z}, t), f(\vec{z}) >_{X-B_r(\vec{z})} >_X
\]

\[
= < p(\vec{x}, t|\vec{y}', t'), \int_{|\vec{z} - \vec{x}| > \epsilon} f(\vec{z})W(\vec{z}|\vec{x}, t) d\vec{z} >_X - < p(\vec{z}, t|\vec{y}', t'), \int_{|\vec{z} - \vec{x}| > \epsilon} f(\vec{z})W(\vec{z}|\vec{x}, t) d\vec{z} >_X
\]

(A.24)

where we use the convergence assumption of \( < p(\vec{x}, t + \Delta t|\vec{z}, t)/\Delta t, f(x) >_{X-B_r(\vec{z})} \).

Replacing \( \vec{x} \) with \( \vec{z} \) on the left hand side of the equality of (A.15) and taking \( \epsilon \to 0 \) gives
\[ \partial_t < p(\vec{z}, t|\vec{y}, t'), f(\vec{z}) >_X (A.25) \]

\[ = < p(\vec{z}, t|\vec{y}', t'), \sum_i A_i(\vec{z}) \frac{\partial f(\vec{z})}{\partial \vec{z}_i} + \frac{1}{2} \sum_{ij} B_{ij}(\vec{z}) \frac{\partial^2 f(\vec{z})}{\partial \vec{z}_i \partial \vec{z}_j} >_X \]

\[ + \lim_{\epsilon \to 0} < p(\vec{x}, t|\vec{y}, t'), \int_{|\vec{z} - \vec{x}| > \epsilon} f(\vec{z}) W(\vec{z}|\vec{x}, t) d\vec{z} >_X \]

\[ - < p(\vec{z}, t|\vec{y}, t'), \int_{|\vec{z} - \vec{x}| > \epsilon} f(\vec{z}) W(\vec{x}|\vec{z}, t) d\vec{z} >_X (A.26) \]

Integrating by parts allows us to write the equation as an inner product with respect to \( f \) plus some boundary terms. Since \( f(\vec{z}) \) is an arbitrary \( C^\infty_0 \) test function, we can choose \( f \) such that it vanishes on the boundary. Also because \( f \) is arbitrary, we can remove the inner product and see the weak formulation for the P.D.E:

\[ \partial_t p(\vec{z}, t|\vec{y}', t') = - \sum_i \frac{\partial}{\partial \vec{z}_i} \left[ A_i(\vec{z}, t)p(\vec{z}, t|\vec{y}, t') \right] \]

\[ + \sum_{i,j} \frac{1}{2} \frac{\partial^2}{\partial \vec{z}_i \partial \vec{z}_j} \left[ B_{ij}(\vec{z}, t)p(\vec{z}, t|\vec{y}, t') \right] \]

\[ + \lim_{\epsilon \to 0} \int_{X-B_{ij}(\vec{z})} W(\vec{z}|\vec{x}, t)p(\vec{x}, t|\vec{y}', t') - W(\vec{x}|\vec{z}, t)p(\vec{z}, t|\vec{y}, t') d\vec{x} \] (A.27)

Boundary conditions still need to be calculated, and depend on the nature of the stochastic process. Dirchlet and periodic boundary conditions in the stochastic processes carry over quite easily to the PDE description, other boundary conditions require further analysis.

**Corollary A.0.2 (Transient Differential Chapman-Kolmogorov).** If we assume
all the above assumptions and that there is also an open subset $U \subset X$ such that
the total near instantaneous transition probability from $U$ to $U$ is $\leq 1$, and of the form

$$0 \leq p(\vec{x}, t + \Delta t | \vec{z}, t), 1 > U = 1 - M(\vec{z}, t)\Delta t + O(\Delta t^2) \leq 1,$$

(A.28)

for $\vec{z} \in U$, and $p(\vec{x}, t + \Delta t | \vec{z}, t), 1 > U = 0$ for $\vec{z} / \in U$,

then the probability density on $U$ is a weak solution to the local P.D.E.

$$\partial_t p(\vec{z}, t | y, t') = - M(\vec{z}, t)p(\vec{z}, t | \vec{y}, t') - \sum_i \frac{\partial}{\partial z_i}[A_i(\vec{z}, t)p(\vec{z}, t | \vec{y}, t')]$$

$$+ \sum_{i,j} \frac{1}{2} \frac{\partial^2}{\partial z_i \partial z_j}[B_{i,j}(\vec{z}, t)p(\vec{z}, t | \vec{y}, t')]$$

$$+ \lim_{\epsilon \to 0} \int_{X - B_\epsilon(\vec{z})} [W(\vec{z}|\vec{x}, t)p(\vec{x}, t | \vec{y}, t')]d\vec{x}$$

(A.29)

Proof. To prove this, we will restrict the problem to a subset, calculate $W$ in the
subset, and appear to the density dependent differential Chapman-Kolmogorov
equation proved above.

First, we observe that since $U$ is measurable, can we consider the restriction
$p(\cdot, t + \Delta t | \vec{z}, t)|_U$, with the property that

$$p(\cdot, t + \Delta t | \vec{z}, t) = p(\cdot, t + \Delta t | \vec{z}, t)|_U + p(\cdot, t + \Delta t | \vec{z}, t)|_{X - U}.$$
Now since
\[< p(\bar{x}, t + \Delta t | \bar{z}, t), 1 >_U = 1 - M(\bar{z}, t) \Delta t + O(\Delta t^2), \]
we have that
\[< p(\bar{x}, t + \Delta t | \bar{z}, t), 1 >_{X-U} = M(\bar{z}, t) \Delta t + O(\Delta t^2) \]

Since there are transitions from $X-U$ to $U$ with probability 0, we can change
the transition probabilities from $X-U$ to $U$ as long as we preserve the above
quantities. From this it is possible to see that this restricted distribution can be
rewritten by the constant function, so for $\bar{z} \in U$,
\[p(\cdot, t + \Delta t | \bar{z}, t) |_{X-U} = M(\bar{z}, t) \Delta t / \mu(X-U) + O(\Delta t^2) \]

where $\mu(X-U)$ is the Lebesgue measure of $X-U$. Thus for $\bar{z} \in U$

\[\lim_{\Delta t \to 0} \frac{1}{\Delta t} [< p(\bar{x}, t + \Delta t | \bar{z}, t), f(x) >_{X-B_{\epsilon}(\bar{z})}] = \lim_{\Delta t \to 0} \frac{1}{\Delta t} [< p(\bar{x}, t + \Delta t | \bar{z}, t), f(x) >_{U-B_{\epsilon}(\bar{z})} + < p(\bar{x}, t + \Delta t | \bar{z}, t), f(x) >_{X-U(\bar{z})}] + O(\Delta t) \]
\[= < W(\bar{x}|\bar{z}, t), f(x) >_{U-B_{\epsilon}(\bar{z})} + < \frac{M(\bar{z}, t)}{\mu(X-U)}, f(x) >_{X-U(\bar{z})} \quad (A.30) \]
\[\quad (A.31) \]

Similarly, if $\bar{z} \notin U$, we have
\[\lim_{\Delta t \to 0} \frac{1}{\Delta t} [< p(\bar{x}, t + \Delta t | \bar{z}, t), f(x) >_{X-B_{\epsilon}(\bar{z})}] = < W(\bar{x}|\bar{z}, t), f(x) >_{U-B_{\epsilon}(\bar{z})} \quad (A.32) \]
since $< p(\bar{x}, t + \Delta t | \bar{z}, t), 1 >_U = 0$.

Therefore we can calculate that,

$$\int_{X-B_r(\bar{z})} W(\bar{z}|\bar{x}, t)f(\bar{x})d\bar{x} = \int_{U-B_r(\bar{z})} W(\bar{z}|\bar{x}, t)f(\bar{x})d\bar{x} \quad (A.33)$$

and likewise for $\bar{z} \in U$,

$$\int_{X-B_r(\bar{z})} W(\bar{x}|\bar{z}, t)f(\bar{z})d\bar{x} = \int_{U-B_r(\bar{z})} W(\bar{x}|\bar{z}, t)f(\bar{z})d\bar{x} + M(\bar{z}, t)f(\bar{z}) \quad (A.34)$$

Finally, by the density dependent differential Chapman Kolmogorov equation, we have $\bar{y}, \bar{z} \in U$, that the density is a solution to the following PDE

$$\partial_t p(\bar{z}, t|\bar{y}, t') = -\sum_i \frac{\partial}{\partial \bar{z}_i} [A_i(\bar{z}, t)p(\bar{z}, t|\bar{y}, t')]$$

$$+ \sum_{i,j} \frac{1}{2} \frac{\partial^2}{\partial \bar{z}_i \partial \bar{z}_j} [B_{i,j}(\bar{z}, t)p(\bar{z}, t|\bar{y}, t')]$$

$$+ \lim_{\epsilon \to 0} \int_{U-B_r(\bar{z})} W(\bar{z}|\bar{x}, t)p(\bar{x}, t|\bar{y}, t') - W(\bar{x}|\bar{z}, t)p(\bar{z}, t|\bar{y}, t')d\bar{x}$$

$$- M(\bar{z}, t)p(\bar{z}, t|\bar{y}, t') \quad (A.35)$$
APPENDIX B

AN EXAMPLE OF CONTINUOUS LIMITS: THE DERIVATION OF AN ALGORITHM FOR RANDOM PLACEMENT OF NON-OVERLAPPING CELLS AT LOW DENSITIES MATCHING AN INHOMOGENOUS DISTRIBUTION

B.1 Introduction to the Problem of Random Initialization

Stochastic simulations often times call for random initial conditions where the cells are assumed to be evenly spaced out or are set to fit some given distribution on average. Unfortunately, current algorithms for generating random initial conditions with overlap explicitly excluded will at best, create bias and at worst, fail completely. Setting up the good initial conditions for a simulations with no-overlap conditions is not an obvious task.

We consider the problem of generating random cell placement patterns that mimic given patterns on average. We note that our target pattern is a spatial cell-density distribution function (SCDDF). It is intuitively similar to a probability density function, but is not strictly so, since, as we will see, it does not integrate to unity over the domain. This problem can be described using the literature on random sequential adsorption (RSA) with nearest neighbour exclusions, where a stochastic process places particles randomly with uniform probability. Particles that will overlap other particles cannot adsorb and are assumed to be carried
Particles that will not overlap adsorb, and depending on the model, may then either desorb or stay. In several physical and chemical systems the time scale is small enough that desorption is often times assumed not to occur and therefore can be ignored [95]. Excellent reviews are available on the subject [31, 95, 109].

There is an extensive body of work utilizing excluded volume type models in a variety of application areas: from physical chemistry to theater seating [36, 109]. However, there is no obvious way to place rectangular cells resulting in a given inhomogeneous initial distribution such that no pair of cells overlap. Most work assumes a uniform initial distribution of cell densities. As an example, in the 1D case, Gillespie places cells using a Monte Carlo algorithm that uses the well ordering of uniformly distributed rods to calculate subsequent locations [37]. Lampoudi, Gillespie, and Petzold place cells randomly until they achieve a uniformly distributed configuration where no cells overlap in the 2D cases [74]. Procedurally, recent RSA results tend to focus either on calculating the expected percentage of sites that contain a particle in finite domains, sometimes with non-trivial objects, (e.g. [39]), or on proving that the probability that a given site is empty for infinite domains is well defined in the limit and in some cases can be approximated (e.g. [88], [36]).

In this chapter, we derive a novel algorithm to randomly place cells along a one dimensional segment in a way that approximates a given stochastic cell-density distribution function (SCDDF) on average. The algorithm is the repeated application of random cell placement based on an appropriately chosen probability density function. The procedure we follow to derive the algorithm can be summarized as follow. We start with a discrete stochastic process that describes the random placement of cells using a simple-step function. We then take the con-
tinuous limit as the cell size goes to zero and the number of cells increases in constant ratio with respect to cell size. This results in a family of partial differential equations with respect to the number of steps as well as the heights of simple function. The pointwise limit is then taken over this family to get the probability that a single location is filled in the given limit. This algorithm has applications in initialization for microscopic stochastic model (SMS) simulations, as well as extending RSA to accurately generate non-trivial patterns. The algorithm easily extends to multi-dimensional analogues, and one such pattern is tested in this chapter.

B.2 Algorithm for Generating Inhomogenous Random Initial Conditions

Given an arbitrary spatial cell density distribution, \( u(x) \in L^2(0,L) \) where \( \int_0^L u(x) dx = N \), where \( N \) is the number of cells and \( L \) is the domain length, it is possible that this distribution is not achievable by any RSA algorithm. For instance if \( u(x)l \), where \( l \) is the length of the object in 1D, is equal to or greater than the jamming limit for randomly placed cells, the expected maximal density achievable by RSA, then with high probability, it is not possible to place the cells with no overlap. With this in mind, given an achievable distribution \( u(x) \) with domain length \( L \) and volume fraction \( \rho = Nl/L \), we can perform the following algorithm to achieve this distribution on average:

1. Solve for \( \alpha \) from the normalization condition

\[
\frac{1}{L} \int_0^L \frac{\ln(1-\alpha u(x))}{\ln(1-\rho)} dx - 1 = 0 \tag{B.1}
\]
2. Calculate

\[ h(x) = \frac{1}{L} \ln \left( 1 - \alpha u(x) \right) \ln \left( 1 - \rho \right) \]  

(B.2)

3. Assign a range to each grid element based on which values the cumulative distribution of \( h(x) \) fall on.

4. Calculate a random number between 0 and integral of \( h(x) \).

5. Use binary search to find the grid element which contains the respective range that the number falls in.

6. If empty, place the cell in the grid element.

7. If not empty, repeat steps 4-7.

8. Repeat steps 4-8 for cell until the desired percentage of cells, \( \rho \), is filled.

The inside of the \( \ln \) function cannot be either less than 0, which is undefined, or greater than 1, which will result in negative probability distributions. As a result, Newton’s method is not a good choice and for solving the root, \( \alpha \), as it sometimes will go outside the desired domain. In this chapter the bisection method was used to solve for the root in the domain \((0, 1/\max(u))\).

Since the algorithm is derived as a continuous limit that approximates the desired cell placement rather than an exact calculation, we test the algorithm according to several desired probability distributions. We consider a grid with 500 sites, and seed it with 175 cells to achieve \( \rho = 0.35 \). We perform 10,000 simulations of the algorithm to see how well the algorithm is able to produce the desired distributions.
1. Consider a simple function $u(x) = 0.5$ for $x \in [0, .25)$, $u(x) = 1.4$ for $x \in [.25, .75)$, and $u(x) = 0.7$ for $x \in [.75, 1]$

2. $u(x) = \frac{1}{Z}(3\cos(5\pi x) + 2\sin(2\pi x) + 5)$, where $Z = \int_0^1 3\cos(5\pi x) + 2\sin(2\pi x) + 5$

3. A normalized gaussian with mean 0.5, std. dev. 0.1

4. A normalized gaussian with mean 0.5, std. dev. 0.5

![Figure B.1. a) Algorithm applied to a simple function and b) on a sum of cos and sin functions](image_url)

In the first two cases, the algorithm is able to construct the desired distributions with little error (see Figure 1). However, in the Gaussian case, the algorithm is unable to construct the desired distribution as the result is a flattened curve instead of a smooth Gaussian function (see Figure 2a). In this case neither adding
more sites in, while keeping \(\rho\) constant, nor averaging more simulations help. In the 1D case, it is known by a result from Rényi [92] that the packing fraction is 0.7476. To achieve this packing fraction, we need \(u(x)lN < 0.7476\), which for given cell length \(l = 1/500\), occurs if \(N < 93\) violates our assumption and suggests that the distribution is not achievable for the given packing density. Decreasing \(u(x)\) by widening the Gaussian curves alleviates the problem (see Figure 2b); but if we want to get the original Gaussian distribution, then we need to decrease the volume fraction. Trying again with \(N = 90\) and 50, yields a distribution that is close to the desired curve as we no longer grossly exceed the jamming limit (see Figure 2c and d).

B.3 Multi-Dimensional Extensions

Without loss of generality, it is easy to extend the derivation of the algorithm and the algorithm itself from 1D to higher dimensions by replacing the integral of length with a volume integral over domain \(\Omega\) and the length scaler with a volume scaler, \(|\Omega|\). The analysis proceeds exactly as before by converting the matrix of acceptable grid elements to a vector. The algorithm also proceeds as before, but now we have to solve for the root of

\[
\frac{1}{|\Omega|} \int_{\Omega} \frac{\ln(1 - \alpha u(\vec{x}))}{\ln(1 - \rho)} d\vec{x} - 1 = 0 \quad (B.3)
\]

and our equation for \(h\) becomes,

\[
h(\vec{x}) = \frac{1}{|\Omega|} \frac{\ln(1 - \alpha u(x))}{\ln(1 - \rho)}. \quad (B.4)
\]

As a sample check, we use a reasonably complicated image from [78] and see
Figure B.2. Algorithm applied to gaussians with mean, $\mu = 0.5$ and a) $\sigma = 0.1, \rho = 0.35$ b) $\sigma = 0.5, \rho = 0.35$ c) $\sigma = 0.1, \rho = 0.18$ d) $\sigma = 0.1, \rho = 0.1$
Figure B.3. a) Image taken from [78] b) Ensemble average of algorithm applied to image with $\rho = 0.2$
if we can replicate it on average. For this test, we choose \( \rho = 0.2 \) and average the resulting random distributions for 2000 simulations according to the probability densities given by the image and described by the algorithm.

B.4 Derivation of the Random Placement Algorithm

Rather than ask what function \( h(x) \) is needed to get the desired probability density \( u(x) \), we start with a given \( h(x) \) and calculate the probability that \( x \) is occupied using the initial placement with excluded volume algorithm described above. Assume for now that \( h(x) \) is approximated by discrete simple function with \( m \) steps, and each step has \( n \) boxes.

\[
 h(x) = \sum_{i=0}^{m-1} \chi_i(x)h_i \quad x \in 0/nm, 1/nm, \ldots, (L-1)/nm
\]  

(B.5)

where \( \chi_i(x) = 1 \) if \( i/m \leq x < (i+1)/m \) and 0 otherwise. We also assume that when the algorithm is finished \( \rho \) percent of the domain will be filled.

Without loss of generality, we want to calculate the probability that after filling \( \rho \) percent of the \( nm \) boxes we have filled the first box which has height \( h_0 \). Let \( c_i \) be the number of boxes filled in step \( i \). Let \( p(c_0, c_1, \ldots, c_{m-1}) \) be the probability we have not yet filled box 0, where we filled \( c_0 \) boxes of step 0, \( c_1 \) boxes of step 1, and so on. Also \( s = \sum_{i=0}^{m-1} c_i \) is the total number of choices made.

In which case, the discrete master equation for the probability of having a certain choice selection at given time is determined by the relative number of remaining boxes as compared to the remaining boxes and their heights. It can be
calculated as:

\[
p(c_0, c_1, \ldots, c_{m-1}, s + 1) = \sum_{i=1}^{m-1} \frac{(n - c_i + 1)h_i}{\sum_{j=0}^{m-1}(n - c_j)h_j + h_i} p(c_0, \ldots, c_{i-1}, c_i - 1, c_{i+1}, \ldots, c_{m-1}, s) + \frac{(n - c_0)h_0}{\sum_{j=0}^{m-1}(n - c_j)h_j + h_0} p(c_0 - 1, c_1, \ldots, c_{m-1}, s)
\]

(B.6)

If we let \(e_i\) be the elementary vector that is 1 at index \(i\) and zero elsewhere, we also have transition probabilities

\[
p(\vec{c} + e_i|\vec{c}) = \frac{(n - c_i)h_i}{\sum_{j=0}^{m-1}(n - c_j)h_j} \quad \text{for } i \neq 0
\]

(B.7)

\[
p(\vec{c} + e_0|\vec{c}) = \frac{(n - c_i - 1)h_i}{\sum_{j=0}^{m-1}(n - c_j)h_j}
\]

(B.8)

Or with \(\delta\) being the dirac delta distribution in \(R^m\),

\[
p(\vec{c}'|\vec{c}) = \sum_{i=1}^{m-1} \frac{(n - c_i)h_i}{\sum_{j=0}^{m-1}(n - c_j)h_j} \delta(c'_i - c_i - e_i) + \frac{(n - c_0 - 1)h_0}{\sum_{j=0}^{m-1}(n - c_j)h_j} \delta(c'_0 - c_0 - e_0)
\]

(B.9)

Let us now define new spatial and temporal variables:

\[
(x_1, \ldots, x_{m-1}) = (c_1 - c_0, \ldots, c_{m-1} - c_0) \Delta x
\]

(B.10)

\[
t = (c_0 + c_1 + \cdots + c_{m-1}) \Delta t
\]

(B.11)

where \(\Delta x\) is currently free for us to choose and we set \(\Delta t = 1/mn\). Doing so gives at time \(t = \rho\), \(\rho\) percent of the boxes are occupied. At time \(t = 1\), we have filled all of the boxes.
With the above definition of $\bar{x}$ and $t$, we have:

\[
\begin{pmatrix}
  c_0 \\
  c_1 \\
  \vdots \\
  c_{m-1}
\end{pmatrix} =
\begin{pmatrix}
  -1/m & -1/m & -1/m & \ldots & -1/m & 1/m \\
  -1/m + 1 & -1/m & -1/m & \ldots & -1/m & 1/m \\
  -1/m & -1/m + 1 & -1/m & \ldots & -1/m & 1/m \\
  \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
  -1/m & -1/m & \ldots & \ldots & -1/m + 1 & 1/m \\
\end{pmatrix}
\begin{pmatrix}
  \frac{x_1}{\Delta x} \\
  \vdots \\
  \frac{x_{m-1}}{\Delta x} \\
  \frac{t}{\Delta t}
\end{pmatrix}
\]

(B.12)

i.e.

\[
c_0 = \frac{t}{m\Delta t} - \sum_{j=1}^{m-1} \frac{x_j}{m\Delta x}
\]

(B.13)

\[
c_i = \frac{t}{m\Delta t} - \sum_{j=1}^{m-1} \frac{x_j}{m\Delta x} + \frac{x_i}{\Delta x}
\]

(B.14)

Also by letting $n = \frac{1}{m\Delta t}$, this transformation gives us the transition probabilities in new coordinates as

\[
p(z, t + \Delta t | x, t) = \sum_{i=1}^{m-1} \frac{1}{\Delta t} \frac{1}{m\Delta x} \frac{1}{m\Delta x} \sum_{k=1}^{m-1} \frac{x_k}{m\Delta x} \delta(z - x - \Delta x e_i)
\]

(B.15)
Since the transition probabilities sum up to

$$
\int_{\mathbb{R}^m} p(\tilde{z}, t + \Delta t|\tilde{x}, t) \, dz = 1 - M(\tilde{z}, t) \Delta t 
$$

(B.16)

$$
= 1 - h_0 \sum_{j=0}^{m-1} \left( \frac{1}{m \Delta t} - \frac{t}{m \Delta t} + \sum_{k=1}^{m-1} \frac{x_k}{m \Delta x} \right) h_j - \sum_{j=1}^{m-1} \frac{x_j}{\Delta x} h_j 
$$

(B.17)

we can use the transient differential Chapman-Kolmogorov equation to get a continuous expression for the above equation.

As can be seen, in order to get nice convergence, we assume that $\Delta t = \Delta x$, i.e. that they converge to zero at the same rate. This makes sense because doing so gives the transition probabilities as

$$
p(z, t + \Delta t|x, t) = \sum_{i=1}^{m-1} \frac{(1/m - t/m + \sum_{j=1}^{m-1} x_j/m) h_i}{\sum_{j=0}^{m-1} (1/m - t/m + \sum_{k=1}^{m-1} x_k/m) h_j - \sum_{j=1}^{m-1} x_j h_j} \delta(z - x - \Delta t e_i) + \frac{(1/m - t/m + \sum_{j=1}^{m-1} x_j/m - \Delta t) h_0}{\sum_{j=0}^{m-1} (1/m - t/m + \sum_{k=1}^{m-1} x_k/m) h_j - \sum_{j=1}^{m-1} x_j h_j} \delta(z - x + \Delta t e_0) 
$$

(B.18)

(B.19)

Using the taxicab norm, if $||x - z|| > \epsilon$ we can appeal to the Transient Differential Chapman-Kolmogorov Equation by calculating the appropriate limits:

1. 

$$
\lim_{\Delta t \to 0} \int_{||x - z|| \geq \epsilon} \frac{p(z, t + \Delta t|x, t)}{\Delta t} \, dz = 0 
$$

(B.20)

where the last expression follows since for $\Delta t < \epsilon$ the integral is 0.
2.

\[ A_i := \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{||z-x||<\epsilon} (z_i - x_i)p(z, t + \Delta t|x, t)dz \quad (B.21) \]

\[
= \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{||z-x||<\epsilon} (z_i - x_i) \times \left( \sum_{i=1}^{m-1} \frac{x_i}{m} - x_i \right) h_i \delta(z - x - \Delta t \epsilon_i)dz \\
+ \frac{1}{\Delta t} \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} - x_j \right) h_j \delta(z - x - \Delta t)h_0 \\
+ \frac{1}{\Delta t} \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} - x_j \right) h_j - \sum_{j=1}^{m-1} x_j h_j \\
+ \frac{1}{\Delta t} \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} - x_j \right) h_j - \sum_{j=1}^{m-1} x_j h_j \\
+ \frac{1}{\Delta t} \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} - x_j \right) h_j - \sum_{j=1}^{m-1} x_j h_j \\
= \lim_{\Delta t \to 0} \frac{1}{\Delta t} \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} - x_j \right) h_j - \sum_{j=1}^{m-1} x_j h_j \\
= \lim_{\Delta t \to 0} \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} - x_j \right) h_j - \sum_{j=1}^{m-1} x_j h_j \\
\]

3.

\[ B_{i,j} := \lim_{\Delta t \to 0} \int_{||x-z||<\epsilon} (x_i - z_i)(x_j - z_j)p(z, t + \Delta t|x, t)dz \quad (B.25) \]

\[
= \lim_{\Delta t \to 0} \Delta t \left[ \frac{1}{m} - \frac{t}{m} + \sum_{i=1}^{m-1} \frac{x_i}{m} - x_i \right] h_i \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} - x_j \right) h_j \\
- \frac{1}{m} - \frac{t}{m} + \sum_{j=1}^{m-1} \frac{x_j}{m} - \Delta t)h_0 \\
- \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} - x_j \right) h_j - \sum_{j=1}^{m-1} x_j h_j \right] \\
= 0 \quad (B.27) \]

Let \( p = p(z, t|x, s) \), then the Transient Chapman-Kolmogorov Equation says
the probability density can be approximated by the solution of the limit PDE

\[
\partial_t p = - \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} \right) h_j - \sum_{j=1}^{m-1} x_j h_j
\]

\[
- \sum_i \frac{\partial}{\partial x_i} \left[ \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} \right) h_j - \sum_{j=1}^{m-1} h_j x_j \right] p
\] (B.28)

Solving this equation is equivalent to solving the backward Fokker Planck,

\[
\partial_s p = - \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} \right) h_j - \sum_{j=1}^{m-1} h_j x_j \frac{\partial p}{\partial x_i}
\] (B.29)

This is a first order PDE, so we apply the method of characteristics where

\[
\dot{x}_i = - \frac{1}{m} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} \right) (h_i - h_0) - x_i h_i
\] (B.30)

\[
\dot{p} = - \sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{t}{m} + \sum_{k=1}^{m-1} \frac{x_k}{m} \right) h_j - \sum_{j=1}^{m-1} h_j x_j \frac{\partial p}{\partial x_i}
\] (B.31)

The first equation can be rewritten as:

\[
0 = \sum_{j=0}^{m-1} (1 - t + \sum_{k=1}^{m-1} x_k) h_j - m \sum_{j=1}^{m-1} h_j x_j \dot{x}_i + (1 - t + \sum_{j=1}^{m-1} x_j)(h_i - h_0) - m x_i h_i
\] (B.32)

Theoretically we could solve this ODE and get an exact answer to \( x \). Instead notice that for \( m \) large and \( x = 0 \), we can set \( \epsilon = \frac{1}{m} \) and derive an asymptotic expansion for \( x \) in terms of \( \epsilon \), as \( \epsilon \) goes to 0..

First define \( \bar{h} = \sum h \), \( \bar{x} = \sum x = \bar{x}^0 + \epsilon \bar{x}^1 + \epsilon^2 \bar{x}^2 + O(\epsilon^3) \), and \( \bar{x} h = \sum h x \). We rewrite out equation of \( x \) as
\[
\dot{x}_i = -\left(\frac{1}{m^2} - \frac{1}{m^2} + \frac{\bar{x}}{m}\right)(h_i - h_0) - \frac{\bar{x}_h}{m}
\]
\[
= -\frac{(\epsilon^2 - t\epsilon^2 + \bar{x}\epsilon)(h_i - h_0) - x_i h_i}{(\epsilon - t\epsilon + \bar{x})h - xh}.
\] (B.33)

Expanding out, we get

\[
\dot{x}_0^0 + \epsilon \dot{x}_1^1 + \epsilon^2 \dot{x}_2^2
\]
\[
= -\epsilon\frac{(\epsilon - t\epsilon + \bar{x}^0 + \epsilon\bar{x}^1 + \epsilon^2\bar{x}^2)(h_i - h_0) - x_i^0 h_i - \epsilon x_1^1 h_i - \epsilon^2 x_2^2 h_i}{(\epsilon - t\epsilon + \bar{x}^0 + \epsilon\bar{x}^1 + \epsilon^2\bar{x}^2)h - x^0 h - \epsilon x^1 h - \epsilon^2 x^2 h} + O(\epsilon^3)
\] (B.36)

\[
x_i^0(0) = x_i^1(0) = x_i^2(0) = 0.
\] (B.37)

Summing over \(i\) gives

\[
\dot{\bar{x}} = -\frac{(\epsilon^2 - \epsilon^2 t + \epsilon\bar{x})(\bar{h} - \frac{1}{\epsilon} h_0) - \epsilon\bar{x}h}{(\epsilon - t\epsilon + \bar{x})\bar{h} - x\bar{h}}.
\] (B.38)

Let \(\bar{x} = \bar{x}^0 + \epsilon \bar{x}^1 + \epsilon^2 \bar{x}^2 + O(\epsilon^3)\), then

\[
\dot{\bar{x}}^0 = -\frac{-\bar{x}^0 h_0}{(\epsilon - t\epsilon + \bar{x})\bar{h} - h\bar{x}^0}
\] (B.39)
\[
\dot{\bar{x}}^1 = -\frac{\bar{x}^0 h_0 - \bar{x}^1 h_0 - \epsilon h\bar{x}^1}{(\epsilon - t\epsilon + \bar{x})h - xh}
\] (B.40)

Using the initial condition, \(\bar{x}^0(0) = \bar{x}^1(0) = \bar{x}^2(0) = 0\), we have \(\bar{x} = O(\epsilon)\), and we will soon see that we have \(\bar{x}^1 = 0\) as well. Using (B.35),
\[
\dot{x}_i = -\epsilon \frac{(\epsilon - t\epsilon + O(\epsilon))(h_i - h_0) - x_i h_i}{(\epsilon - t\epsilon + O(\epsilon))h - xh}
\]

(B.41)

Expanding out \( x_i = x_i^0 + \epsilon x_i^1 + \epsilon^2 x_i^2 + O(\epsilon^3) \), we use the initial conditions to get \( x_i^0 = 0 \), and so \( \bar{x}h \) is \( O(\epsilon) \) and \( \bar{x}^1 = 0 \). Likewise from (B.40) it is possible to see \( x_i^1 = 0 \). So using (B.36) for large \( m \), \( x_i = O(\frac{1}{m^2}) \).

In this case, the characteristic equation (B.31) can be written as

\[
\dot{p} = -\frac{h_0 p}{\sum_{j=0}^{m-1} \left( \frac{1}{m} - \frac{1}{m^2} \right) h_j} + O(\epsilon)
\]

(B.42)

Since the \( h_i \)'s are step functions that approximate the function \( h(x) \), we can increase \( m \) to get a better and better approximation of our function. As \( m \to \infty \), the discrete average converges in the Lebesgue integral sense to the continuous average \( \sum_{j=0}^{m-1} h_j / m \to \int_0^L h(x) dx / L \) where \( L \) is the user specified length of the continuous domain.

From this we get:

\[
\dot{p} = -\frac{L h_0 p}{(1 - t) \int h(x) dx}
\]

(B.43)

Which can be solved given \( t_0 = 0 \) to be

\[
p(t) = e^{\frac{L h_0}{\int h(x) dx} \ln(1 - t)}
\]

(B.44)

\[
= (1 - t)^{\frac{L h_0}{\int h(x) dx}}
\]

(B.45)

Now \( p(t) \) was the probability that the first box of the first step was not chosen, the probability that it is chosen is \( 1 - p(t) \). Since the box’s position is arbitrary we
can repeat the proof for an arbitrary box with height \( h(x) \) to get the probability it will be occupied:

\[
(1 - (1 - \rho)\frac{Lh(x)}{\int h(x)dx}).
\] (B.46)

Since the total cell density increases linearly with respect to time, starting with no cells at time 0, and full occupation at time \( t = 1 \), we use \( t = \rho \) where \( \rho \) is the volume fraction or percentage of boxes that are occupied. Finally, because the probability that a location is occupied is proportional to the resulting probability density, \( u(x) \), then for the algorithm to work, there must be some \( \alpha \) such that \( \alpha u(x) \) equals the right hand side of (B.46). Inverting the function gives

\[
h(x) = \frac{1}{L} \frac{ln(1 - \alpha u(x))}{ln(1 - \rho)} \] (B.47)

B.5 Discussion

In this chapter, we have derived an algorithm that is capable of seeding non-overlapping cells in sites such that, on average, their probability distribution fits a desired curve. The algorithm can be used to initialize non-trivial distributions as initial conditions for stochastic simulations. It is also possible to set up equilibrium simulations when the equilibrium distribution is known and the cells are known to have the excluded volume property. This has applications in individual based modeling as well as stochastic simulations where excluded volume principles come into play.

The algorithm can also be used to find out what the resulting distribution, \( u(x) \), is when we randomly place cells according to a distribution \( h(x) \).
occupying certain sites changes the probability that other sites will or will not be
occupied, without the algorithm it is not obvious what the resulting distribution
will be by just randomly placing cells according to so probability density. Using
this algorithm, we can at least have a reasonable prediction for what the resulting
distribution, \( u(x) \), will be. Also, we need to be careful that the given \( u(x) \) is
achievable by random placement of cells. This can be tested by measuring the
jamming limit and ensuring that the distribution never violates this limit.

Since the algorithm is an approximation of a limiting process as the cell size
goes to zero, it works best for cells that are small with respect to length of the
approximating step functions. In cases where the desired distribution cannot be
approximated by simple functions with large widths, the algorithm is not guaran-
teed to work. For every simulation that this algorithm is used, it is recommended
that the programmer checks whether or not the resulting distribution of randomly
placed cells matches the input distribution. This word of caution is especially im-
portant for any extensions that include cells with non-trivial shapes where the
jamming limit is still unknown since the derivation of the algorithm assumes sym-
metry in the cell shape.

The algorithm itself is derived in 1D dimension, but the derivation has a simple
extension into multi-dimensional analogues by taking the integral over volume
elements instead of length. We have also tested a 2D extension of the algorithm
in this chapter, and found that with small error, the algorithm still works in
generating distributions true to the passed image.
BIBLIOGRAPHY


