Keller-Segel models for chemotaxis

by

Jessica Ann Hulzebos

A Creative Component submitted to the graduate faculty in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Applied Mathematics

Program of Study Committee:
Jue Yan, Major Professor
Hailiang Liu
Pablo Raúl Stinga

Iowa State University
Ames, Iowa
2017

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DEDICATION

To my parents, Mike and Mary, for your love, unwavering support, and encouragement.

And to my sister, Paige.
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ACKNOWLEDGEMENTS

First and foremost, I would like to thank my advisor, Dr. Jue Yan, for her guidance, insight and extreme patience throughout the completion of this work. I would also like to thank all of the friends I have found in my fellow graduate students, I would not have made it through these last two years without you.
Two known motivators of cell movement are diffusion and chemotaxis. Biological experiments investigating cell movement have been conducted by various scientists. Initially a Keller-Segel system was proposed to mathematically model the cell movement seen in these experiments. However, biological experiments by Budrene and Berg resulted in cell movement and pattern formations that could not be accurately modeled with the initial Keller-Segel system. In this creative component, we largely follow the work of Tyson (1996), who developed the liquid and semi-solid models that accurately recovered the experimental results seen in Budrene and Berg’s experiments. We study two second order finite difference methods to solve the Keller-Segel models. One finite difference scheme is the Upwind scheme and the other is a Lax-Frierichs scheme. We carry out truncation error analysis to show it is a second order method with suitable CFL restriction on the time step size. We then apply the second order Lax-Friedrichs scheme to simulate the liquid and semi-solid models. The pattern formations observed are consistent to those found in Tyson (1996).
CHAPTER 1. INTRODUCTION

Whether it be on a macroscopic or microscopic level, living organisms are rarely motionless. At any point in time, the vast amount of cells inside your body are moving about, carrying out important tasks necessary to sustain life. Due to its extreme importance in a large number of biological phenomena, the process and motivation of cellular movement is the focus of much research study.

Two known motivators of cell movement are diffusion and chemotaxis. Diffusion classifies cellular movement away from areas of high cell density. Chemotaxis is defined by cell movement toward the gradient of a chemical (Murray (2002)). In this case the chemical is called a chemoattractant. This process was documented for the first time in bacterial experiments carried out by T W. Engelmann and W.F. Pfeffer in the 1880’s. Nearly a century later came one of the first mathematical models of chemotaxis, known as the Keller-Segel model (Horstmann (2003)). A general form of this model can be written out as follows,

\[
\begin{align*}
    u_t &= \nabla \cdot (k_1(u, c)\nabla u - k_2(u, c)u\nabla c) + k_3(u, c) \\
    c_t &= D_c \Delta c + k_4(u, c) - k_5(u, c)c,
\end{align*}
\]

where \( u \) is cell density and \( c \) is chemoattractant concentration. In order, the functions \( k_1(u, c) - k_5(u, c) \) represent: diffusivity of cells, chemotactic sensitivity, cell growth and death, chemoattractant production and chemoattractant degradation (Hillen and Painter (2009)).

Keller-Segel models have been proven to simulate experimentally observed pattern formation in E. Coli bacterial cells. However, there are some experiments that this model does not fit. Lab experiments carried out by Budrene and Borg revealed far more interesting pattern formation than those ever seen before. In order to model these results, the classic Keller-Segel model must be advanced and modified, we refer to Tyson’s thesis on this topic study (Tyson
In this thesis we study two finite difference methods solving equation (1.1). Specifically we derive second order Upwinding scheme and second order Lax-Friedrichs scheme for the convection terms and combine with second order central scheme for the diffusion term to complete the spatial discretization. We apply Forward Euler scheme for time discretization. With suitable restrictions on the time step size the whole scheme is of second order.

We carry out accuracy tests on the two schemes and obtain second order for both schemes. The cell aggregation/concentration phenomena are captured well. We further apply the Lax-Friedrichs scheme to study the liquid and semi-solid models. Pattern formations are observed and our numerical results are consistent to those in literature. In this thesis we follow the studies in (Tyson (1996)) regarding the liquid and semi-solid models. The parameters of the Keller-Segel equations of both models are also taken from (Tyson (1996)).

The organization of the thesis is the following. In Chapter 2 we begin by describing Budrene and Borg’s lab experiments. We then review chemotaxis models formed by Tyson (1996) which are proposed to accurately model pattern formation observed in Budrene and Borg’s experiments. Both a liquid and semi-solid model are studied. In chapter 3 we describe details of the two second order finite difference schemes solving the model Keller-Segel equation (1.1). We discuss local truncation errors and perform a sequence of numerical tests. In Chapter 4 we apply Lax-Friedrichs scheme to the liquid model and semi-solid model. Steady state solutions are obtained and pattern formations are well observed. Our numerical tests match the analysis results and are consistent to the experimental data. Chapter 5 is reserved for conclusions.
CHAPTER 2. CHEMOTAXIS MODELS

The bacteria studied in Budrene and Burg’s experiments are Escherichia coli (E. coli) and Salmonella typhimurium (S. typhimurium). These bacteria move in either runs, a forward motion, or tumbles, a stationary spin. The bacteria’s hair-like appendages called flagella are what allow them to move (Murray (2003)).

These bacteria have been observed to form interesting patterns during laboratory experiments, see Figures 2.1 and 2.2 for reprinted images. One and two dimensional experiments have been carried out to observe the bacteria’s response when food, specifically a chemoattractant, was placed in their environment. The patterns observed differed depending on whether the food distribution was uniform and how many foods were placed. These pattern formations were hypothesized and proved to be due to the bacteria’s chemotactic response to the foods placed. The bacteria moved from their initial location towards the food placed, leaving behind a traveling pulse (one dimensional case) or an expanding ring (two dimensional case) (Budrene and Berg (1995)).

When patterns are formed by bacterial cell density and chemoattractant concentrations, diffusion competes with the chemotactic response of the cells and determines if the pattern will remain. Some other factors important to pattern formation are proliferation of the bacterial cells and any nutrient intake that could be occurring.

In the first section of the chapter we discuss a simple model Keller-Segel equation for the chemotaxis. In Section 2.2 we explain Budrene and Berg’s experiments and lab observations. In Section 2.3 we advance the Keller-Segel model to incorporate the lab experiments and study the so-called liquid and semi-solid models.
2.1 Keller-Segel model

The first model to attempt to represent the biological phenomena of the bacteria observed in experiments was created by Keller and Segel. Their model was able to replicate the traveling pulse of bacteria that was observed in the one dimensional experiment. The simple model is composed of two equations. In the model equation (2.1) below the variable $n$ represents the bacterial density and $c$ represents the chemoattractant concentration. The parameter $\alpha$ represents the chemotaxis of cells, $D_n$ the diffusion of cells and $\kappa$ the consumption of the chemoattractant. The model is given by the following partial differential equation system, see also in (Murray (2002)),

$$\begin{cases}
\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} - \alpha \frac{\partial}{\partial x} \left[ n \frac{\partial c}{\partial x} \right] \\
\frac{\partial c}{\partial t} = -\kappa n.
\end{cases}$$

(2.1)

The first equation of the system (2.1) can be broken down as follows: The left hand side represents the rate of change for cell density. The first term on the right hand side represents diffusion. The second term represents chemotaxis which models the movement of the cell toward the gradient of the chemoattractant variable.

The second equation in the system (2.1) simply represents the rate of change of the chemoattractant concentration which depends on the consumption of chemoattractant by the cells. Here $\kappa$ is positive so the presence of chemoattractant diminishes. What is not taken into account in this model is the diffusion of the chemoattractant itself (Tyson (1996)).

The parameters used in the model were approximated according to previous biological experiments. Existence and well-posedness of the solution were studied over time, we skip the long list of reference here. Years after this model was created came a new lab experiment by Budrene and Berg. This experiment could not be modeled by the simple Keller-Segel system. Thus a new model was required to describe the biological phenomena seen in the experiment.

2.2 Lab experiments with observations and hypothesis

In Budrene and Berg’s experiment the bacteria were exposed to elements of the tricarboxylic acid (TCA) cycle which resulted in unique and exciting patterns that were not seen in previous
Figure 2.1: Liquid Experimental Results (courtesy of Tyson (1996))

lab experiments. The TCA substance is referred to as the stimulant and the bacteria were not chemotactic towards it. Instead, the bacteria itself produced a potent chemoattractant called aspartate (Budrene and Berg (1991)). The biological experiment was further classified into two types: liquid and semi-solid experiments.

**Liquid Experiments**

The patterns observed in the liquid experiments were quite simple and formed within minutes. They continued to remain visible for about half an hour before they were erased by the process of diffusion. See select reprinted images from (Tyson (1996)) in Figure 2.1. The liquid experiments were characterized by two types:

**Type 1:** In the first type of liquid experiment, the stimulant and bacteria were distributed uniformly throughout their environment. The pattern started as a small clump of bacteria and spread into clumps of similar size, eventually covering the whole domain.

**Type 2:** In the second type of liquid experiment, bacteria distribution was kept uniform while the stimulant was added locally at some chosen origin. This resulted in a ring centered at the stimulant origin with a random bacteria distribution inside the ring.

**Semi-Solid Experiments**
In the semi-solid experiments (see Murray (2003)), bacteria were placed in a .24% water agar solution. This type of experiment produced more interesting patterns. To begin, the food source of the bacteria was uniformly distributed throughout the environment in larger quantities. The bacteria were given more time to form patterns, so cell proliferation is a relevant factor.

Depending on the type of bacteria observed, the pattern formations were quite different. Bacteria named S. typhimurium exhibited patterns formed by concentric rings that were either continuous or broken up into clumps, see reprinted images from (Tyson (1996)) in Figure 2.2a. Bacteria named E. coli exhibited more interesting patterns such as radial spots or ‘sunflower spirals’, see reprinted images from Murray (2003) in Figure 2.2b.

It is interesting to note that the patterns observed in the liquid experiments could not be explained by cell proliferation. This is due to the short time frame of the experiment, which prohibited cell reproduction. Furthermore, the patterns could not be explained by fluid dynamics. As mentioned previously, the bacteria were not chemotactic towards the initial stimulant, but instead produced their own chemoattractant. This lead Budrene and Berg to the hypothesis: the formulated patterns were a product of interaction between diffusion and
chemotaxis to the bacteria’s own self-secreted chemoattractant. So not only could chemotaxis guide the bacteria to a food source, but it could also act as a signaling mechanism. This hypothesis lead to the development of the more biologically accurate mathematical models that are introduced in the next section, see details from Tyson (1996).

2.3 Semi-solid and liquid models

Tyson proposed the following Keller-Segel equations to model the semi-solid experiments,

\[
\begin{aligned}
\frac{\partial n}{\partial t} &= D_n \nabla^2 n - \nabla \left[ \frac{k_1 n}{(k_2 + c)} \nabla c \right] + k_3 n \left( \frac{k_4 s^2 k_9 + s}{k_9 + s} - n \right) \\
\frac{\partial c}{\partial t} &= D_c \nabla^2 c + k_5 s \frac{n^2 k_6 + n^2}{k_6 + n^2} - k_7 n c \\
\frac{\partial s}{\partial t} &= D_s \nabla^2 s - k_8 n \frac{s^2}{k_9 + s^2},
\end{aligned}
\]

where \( n \) is the cell density, \( c \) is the concentration of chemoattractant and \( s \) is the concentration of stimulant. Constants \( D_n, D_c \) and \( D_s \) are all corresponding diffusion coefficients. We refer to Tyson (1996) regarding the biological meanings of parameters \( k_1 - k_9 \) and their relation to the model.

The first equation of the system (2.2) describes the rate of change of the cell density as a function of time. The terms on the right hand side correspondingly represent the diffusion process of cell density, chemotaxis of cells towards the chemoattractant and the growth/death of the cells.

The second equation of (2.2) describes the rate of change of chemoattractant concentration variable. The terms on the right hand side correspondingly involve the diffusion process of the chemoattractant, the production of chemoattractant by the cells and consumption of chemoattractant by the cells.

The third equation of (2.2) is regarding the rate of change of the stimulant concentration variable in time. The terms on the right hand side again involve the diffusion process of the stimulant and consumption of the stimulant by the cells.

The diffusion terms in (2.2) is called Fickian diffusion. Fickian diffusion models how a population of bacteria diffuse over time (Berg (1983)). The coefficients \( D_n, D_c \) and \( D_s \) are
constants and their effects are similar to those of regular diffusion process. A larger coefficient on a diffusion term will cause the wave to diffuse at a higher rate of speed, while a smaller coefficient will cause waves to diffuse slower.

The chemotaxis term in equation one of (2.2) depends on a unique interaction between the cells, the chemoattractant and the chemoattractant gradient. In general this term is given by the divergence of the chemotactic flux

$$\nabla(J_t) = \nabla \cdot (\chi(n,c) \nabla c),$$

where $J_t$ is the chemotactic flux with respect to time. The function $\chi(n,c)$ is an unknown chemotaxis response function. Depending on the model, the function may be chosen to embody a macroscopic scale or even one with receptor level detail. For the model (2.2), Tyson chose the function $\chi(n,c) = \frac{k_{11}n}{(k_2+c)^2}$ according to a macroscopic scale.

The third term in equation one of (2.2) is a proliferation term that encompasses growth and death of the bacteria. Similar to a logistic growth term, it has a carrying capacity dependent on the nutrient. When the bacteria population is below the carrying capacity of the nutrient the bacteria will continue to proliferate. However once the bacteria population surpasses the carrying capacity of the nutrient, the bacteria population will begin to decline.

In (2.2) the second term of equation three is corresponding to the consumption of the stimulant by the cells. The consumption of the stimulant should be proportional to the birth rate of the cells thus $k_8n\frac{s^2}{k_9+s^2}$ is the chosen consumption term. The third term in equation two is a consumption term for chemoattractant. The bacteria cells do not depend on the chemoattractant for growth and it is assumed the chemoattractant is consumed by the bacteria anytime the two come in contact. Thus the chemoattractant consumption term is much simpler and represented by $k_{7}nc$.

The last term of (2.2) to be explained is the second term in equation two. This term represents the production of chemoattractant. This requires a function where an increase of stimulant concentration leads to an increase in production of chemoattractant. Once a certain cell density is reached the function needs to decrease to zero. The choice of function $k_5s\frac{n^2}{k_6+n^2}$ satisfies these conditions.
Liquid Model

The model for the liquid experiment is merely a simplified version of the semi-solid model. Murray and Tyson proposed the modified version of (2.2) as below to study the liquid model,

\[
\begin{align*}
\frac{\partial n}{\partial t} &= D_n \nabla^2 n - \nabla \cdot \left[ \frac{k_1 n}{(k_2 + c)^2} \nabla c \right] \\
\frac{\partial c}{\partial t} &= D_c \nabla^2 c + k_5 s \frac{n^2}{k_6 + n^2} \\
\frac{\partial s}{\partial t} &= D_s \nabla^2 s.
\end{align*}
\] (2.3)

The liquid experiments were run for periods of time which were not long enough to allow growth, chemoattractant decay or stimulant consumption to be factors. Thus those terms are removed from the semi-solid model to form the liquid model. In the simplest liquid experiment case, the concentration of the stimulant is uniform. Thus equation three can be removed from (2.3).

In the next chapter we derive two second order finite difference schemes to solve the model Keller-Segel equations. We further study the liquid and semi-solid models in Chapter 4. We obtained similar patterns with our numerical simulations and our results are consistent to the lab experiments.
CHAPTER 3. SECOND ORDER FINITE DIFFERENCE SCHEMES

In order to analyze and explore these biological models we endeavor to find their solutions. Finding an analytical solution to a system of partial differential equations is not trivial, and may not always be intuitively revealing. Thus we seek numerical approximations to the PDEs. Before we delve into the more complicated biological models covered in Chapter 2, we develop and analyze second order finite difference methods to solve the following Keller-Segel model equations

\[
\begin{align*}
    u_t + (c_x u)_x &= u_{xx} + f(u, c), \quad x \in [a, b], \quad t > 0 \\
    c_t &= c_{xx} + g(u, c).
\end{align*}
\]  

(3.1)

A finite difference method replaces partial derivatives with approximations, which creates a finite dimensional system that can be solved using a computer. There are various finite difference schemes with different orders of accuracy. In this chapter we focus on two second order methods: the Upwind method and the Lax-Friedrichs method.

We analyze certain properties of the scheme, such as local truncation error. We carry out a sequence of numerical tests to validate the second order of accuracy. For simplicity of presentation, in this chapter we focus on the periodic boundary condition case.

3.1 Upwind Scheme

Falling under the larger umbrella of finite difference methods, an Upwinding scheme is typically used to solve hyperbolic partial differential equations. The scheme is characterized by using one-sided data which is determined by the sign of propagation.

Before we introduce the finite difference scheme formulation, we set up the mesh partition and notation. The spatial domain \([a, b]\) is divided into \(N\) total uniform subintervals \(I_j =...\)
The numerical scheme for the general system (3.1) in the case where \( \{u^n_j, c^n_j\} \) as the collection of finite difference point value approximation to the exact solution of cell density \( u(x_j, t_n) \) and chemical concentration \( c(x_j, t_n) \) at \( x_j \) and time level \( t_n \). Time step size is denoted as \( \Delta t = t_{n+1} - t_n \). We consider Euler Forward for time discretization. For spatial discretization we consider central scheme for the diffusion term and one-sided second order Upwinding scheme for the convection term.

**Time discretization with Euler forward:**

\[
 u_t(x_j, t_n) \approx \frac{u(x_j, t_{n+1}) - u(x_j, t_n)}{\Delta t}
\]

**Central scheme:**

\[
 u_{xx}(x_j, t_n) \approx \frac{u(x_{j+1}, t_n) - 2u(x_j, t_n) + u(x_{j-1}, t_n)}{\Delta x^2}
\]

\[
 c_x(x_j, t_n) \approx \frac{c(x_{j+1}, t_n) - c(x_{j-1}, t_n)}{2\Delta x}
\]

We introduce the extra variable \( p(x, t) = c_x(x, t) \). Thus we have

\[
 p(x_j, t_n) \approx \frac{c(x_{j+1}, t_n) - c(x_{j-1}, t_n)}{2\Delta x}
\]

**Upwind Scheme:**

Suppose the wind is blowing from the left and we have \( p(x_j, t_n) \geq 0 \). Then we have the following one-sided Upwind scheme given below

\[
 (c_x u)(x_j, t_n)_x \approx \frac{3}{2} p(x_j, t_n) u(x_j, t_n) - 2 p(x_{j-1}, t_n) u(x_{j-1}, t_n) + \frac{1}{2} p(x_{j-2}, t_n) u(x_{j-2}, t_n)
\]

If we have \( p(x_j, t_n) \leq 0 \) then

\[
 (c_x u)(x_j, t_n)_x \approx \frac{3}{2} p(x_j, t_n) u(x_j, t_n) - 2 p(x_{j+1}, t_n) u(x_{j+1}, t_n) + \frac{1}{2} p(x_{j+2}, t_n) u(x_{j+2}, t_n)
\]

We introduce the notation \( u(x_j, t_n) \approx u^n_j \) as our finite difference point value approximation.

The numerical scheme for the general system (3.1) in the case where \( p(x_j, t_n) \geq 0 \) is

\[
 \begin{align*}
 u_j^{n+1} &= u_j^n - \Delta t \left[ u_j^n - \frac{3}{2} p_j^n u_j^n - 2 p_{j-1}^n u_{j-1}^n + \frac{1}{2} p_{j-2}^n u_{j-2}^n \right] + \frac{\Delta t}{\Delta x} \left[ u_{j+1}^n - 2 u_j^n + u_{j-1}^n \right] + \Delta t \cdot f(u_j^n, c_j^n) \\
 c_j^{n+1} &= c_j^n + \frac{\Delta t}{\Delta x^2} \left[ c_{j+1}^n - 2 c_j^n + c_{j-1}^n \right] + \Delta t \cdot g(u_j^n, c_j^n)
\end{align*}
\]

(3.2)
3.2 Local truncation error analysis

Local truncation error is the error introduced by replacing the partial differential equation with a finite difference scheme. We will denote local truncation error as \( \tau_{j,n}(h) \). After calculating the truncation error we are then able to determine the order of accuracy of the scheme. We begin by analyzing a constant coefficient case of (3.1) given below as

\[
\begin{cases}
  u_t = u_{xx} + (au)_x + f(u, c), & a \geq 0 \\
  c_t = c_{xx} + g(u, c)
\end{cases}
\]  

(3.3)

Here \( f(u, c), g(u, c) \) are two arbitrary functions. We begin by carrying out the truncation error of the second equation of the model. The scheme we use to approximate this equation is Forward Euler in time and central in space:

\[
\frac{u(x, t_{n+1}) - u(x, t_n)}{h} = \frac{u(x, t_{n+1}) - 2u(x, t_n) + u(x, t_{n-1})}{h^2} + f(x, t_n),
\]

where time spacing is \( k = \Delta t \) and grid spacing is \( h = \Delta x \). We Taylor expand about the point \((x, t_n)\) to obtain

\[
\frac{1}{k} \left[ c(x, t_n) + c_t(x, t_n) + \frac{1}{2} k^2 c_{tt}(x, t_n) - c(x, t_n) \right] = \frac{1}{h^2} \left[ c(x, t_n) - h c_x(x, t_n) + \frac{1}{2} h^2 c_{xx}(x, t_n) \right] - \frac{1}{6} h^3 c_{xxx}(x, t_n) + \frac{1}{24} h^4 c_{xxxx}(x, t_n) + \frac{1}{2} k^2 c_{tt}(x, t_n) + \frac{1}{6} h^3 c_{xxx}(x, t_n) + \frac{1}{24} h^4 c_{xxxx}(x, t_n) + g(x, t_n).
\]

After distributing we have,

\[
\frac{1}{k} c(x, t_n) + \frac{1}{k} c_t(x, t_n) + \frac{k}{2} c_{tt}(x, t_n) = \frac{2}{h^2} c(x, t_n) - \frac{2}{h^2} c(x, t_n) - \frac{1}{h} c_x(x, t_n) + \frac{1}{h} c_x(x, t_n) + c_{xx}(x, t_n) - \frac{h}{6} c_{xxx}(x, t_n) + \frac{h}{6} c_{xxx}(x, t_n) + \frac{h^2}{24} c_{xxxx}(x, t_n) + \frac{h}{6} c_{xxx}(x, t_n) + \frac{h^2}{24} c_{xxxx}(x, t_n) + g(x, t_n).
\]

After the cancellation of various terms we are left with

\[
c_t(x, t_n) + \frac{k}{2} c_{tt}(x, t_n) = c_{xx}(x, t_n) \frac{h^2}{12} c_{xxx}(x, t_n) + g(x, t_n).
\]  

(3.4)

The exact solution of (3.3) is then subtracted from (3.4)

\[
c_t(x, t_n) + \frac{k}{2} c_{tt}(x, t_n) - c_t(x, t_n) = c_{xx}(x, t_n) + \frac{h^2}{12} c_{xxx}(x, t_n) + g(x, t_n) - c_{xx}(x, t_n) - g(x, t_n).
\]  

(3.5)
The local truncation error of (3.5) can be written as
\[
\tau_{j,n}(h) = \frac{k}{2} c_{tt}(x_j, t_n) - \frac{h^2}{12} c_{xxxx}(x_j, t_n) + O(k^2, h^4).
\] (3.6)

Based on the truncation error leading terms, we find that the scheme for equation two of system (3.3) is first order accurate in time and second order accurate in space. With CFL restriction on time step size the whole scheme overall is second order with mesh size $h$ refined.

We repeat the same method for the first equation from our system (3.3). To approximate this equation we use Forward Euler in time and central in space. Since $a \geq 0$ we use a right-side Upwind scheme for the convection term. The scheme is given below as
\[
\frac{u(x_j, t_{n+1}) - u(x_j, t_n)}{k} = \frac{u(x_{j-1}, t_n) - 2u(x_j, t_n) + u(x_{j+1}, t_n)}{h^2} + a\left[\alpha u(x_j, t_n) + \beta u(x_{j+1}, t_n) + \gamma u(x_{j+2}, t_n)\right] + f(x_j, t_n). \tag{3.7}
\]

We start by determining the coefficients of $\alpha, \beta,$ and $\gamma$ by Taylor expanding the convection term in (3.7) about the point $(x_j, t_n)$ to obtain
\[
a\left[\alpha u(x_j, t_n) + \beta \left(u(x_j, t_n) + hu_x(x_j, t_n) + \frac{h^2}{2} u_{xx}(x_j, t_n) + \frac{h^3}{6} u_{xxx}(x_j, t_n)\right)\right] + \gamma \left(u(x, t_n) + 2hu_x(x_j, t_n) + 2h^2 u_{xx}(x_j, t_n) + \frac{4h^3}{3} u_{xxx}(x_j, t_n)\right).
\]

Terms are grouped together in the following manner
\[
u(x_j, t_n)\left[aa + a\beta + a\gamma\right] + u_x(x_j, t_n)\left[ah\beta + 2ah\gamma\right] + u_{xx}(x_j, t_n)\left[a\frac{h^2}{2}\beta + 2ah^2\gamma\right] + u_{xxx}(x_j, t_n)\left[a\frac{h^3}{6}\beta + \frac{4h^3}{3}a\gamma\right]. \tag{3.8}
\]

From (3.8) we create the matrix
\[
\begin{pmatrix}
1 & 1 & 1 & 0 \\
0 & h & 2h & 1 \\
0 & \frac{h^2}{2} & 2h^2 & 0 \\
0 & \frac{h^3}{6} & \frac{4h^3}{3} & 0
\end{pmatrix}
\]
which we then row reduce to get

\[
\begin{pmatrix}
1 & 1 & 1 & 0 \\
0 & 1 & 2 & \frac{1}{h} \\
0 & 0 & 1 & -\frac{1}{2h} \\
0 & 0 & 0 & 1
\end{pmatrix}.
\]

The above matrix yields the equations

\[
\begin{align*}
\alpha + \beta + \gamma &= 0 \\
\beta + 2\gamma &= \frac{1}{h} \\
\gamma &= -\frac{1}{2h}.
\end{align*}
\]

Thus the coefficients are

\[
\begin{align*}
\alpha &= \frac{3}{2h} \\
\beta &= \frac{2}{h} \\
\gamma &= -\frac{1}{2h}.
\end{align*}
\]

We substitute the coefficients found for \( \alpha, \beta, \) and \( \gamma \) into (3.7) to obtain

\[
\frac{u(x_j, t_{n+1}) - u(x_j, t_n)}{k} = \frac{u(x_{j-1}, t_n) - 2u(x_j, t_n) + u(x_{j+1}, t_n)}{h^2} \\
+ a \left[ \frac{3}{2h}u(x_j, t_n) + \frac{2}{h}u(x_{j+1}, t_n) + \frac{1}{2h}u(x_{j+2}, t_n) \right] + f(x_j, t_n). \tag{3.9}
\]

Taylor expansion for the whole scheme about the point \((x_j, t_n)\) gives

\[
\frac{1}{k} \left[ u(x_j, t_n) + u_t(x_j, t_n) + \frac{1}{2} h^2 u_{tt}(x_j, t_n) - u(x_j, t_n) \right] = \frac{1}{h^2} \left[ u(x_j, t_n) - hu_x(x_j, t_n) + \frac{1}{2} h^2 u_{xx}(x_j, t_n) \right] \\
- \frac{1}{6} h^3 u_{xxx}(x_j, t_n) + \frac{1}{24} h^4 u_{xxxx}(x_j, t_n) \right] + \frac{1}{h^2} \left[ -2u(x_j, t_n) \right] \\
+ \frac{1}{h^2} \left[ u(x_j, t_n) - hu_x(x_j, t_n) + \frac{1}{2} h^2 u_{xx}(x_j, t_n) + \frac{1}{6} h^3 u_{xxx}(x_j, t_n) + \frac{1}{24} h^4 u_{xxxx}(x_j, t_n) \right] \\
+ a \frac{3}{2h} u(x_j, t_n) + \frac{2}{h} \left[ u(x_j, t_n) + hu_x(x_j, t_n) + \frac{h^2}{2} u_{xx}(x_j, t_n) + \frac{h^3}{6} u_{xxx}(x_j, t_n) \right] \\
+ \frac{1}{2h} \left[ u(x, t_n) + 2hu_x(x_j, t_n) + 2h^2 u_{xx}(x_j, t_n) + \frac{4h^3}{3} u_{xxx}(x_j, t_n) \right] + f(x_j, t_n).
\]
After a large amount of simplifying we obtain
\[ u_t(x_j, t_n) + \frac{k}{2} u_{tt}(x_j, t_n) = u_{xx}(x_j, t_n) \frac{h^2}{12} u_{xxxx}(x_j, t_n) + \frac{3h^2 + 3}{2h} au(x_j, t_n) - \frac{h^2}{3} au_{xx}(x_j, t_n) \]
\[ - \frac{3h^3}{4} au_{xxxx}(x_j, t_n) + f(x_j, t_n). \]

We subtract the exact solution of equation two in (3.3) to get
\[ \tau_{j,n}(h) = \frac{k}{2} u_{tt}(x_j, t_n) - \frac{h^2}{12} u_{xxxx}(x_j, t_n) + \frac{3h^2 + 3}{2h} au(x_j, t_n) - \frac{h^2}{3} au_{xx}(x_j, t_n) \]
\[ - \frac{3h^3}{4} au_{xxxx}(x_j, t_n) + O(k^2, h^4). \]

This shows that equation one of (3.3) is also first order accurate in time and second order accurate in space, therefore the whole scheme is (3.3) is \( O(\Delta t + \Delta x^2) \). The order of accuracy of the Upwind scheme is unchanged when extended to the system (3.1).

### 3.3 Upwind scheme numerical tests

In this section we carry out two numerical tests, one for accuracy and the other for cell concentration phenomena.

**Example 1: Accuracy Test**

We consider the following Keller-Segel equation system
\[
\begin{align*}
  u_t + (c_x u)_x &= u_{xx} + f(x, t) \\
  c_t &= c_{xx} + u - c,
\end{align*}
\]  
(3.10)

with periodic boundary conditions. The exact solutions are given as \( u(x, t) = c(x, t) = e^{-t} \cos x \). The right hand side function is given as \( f(x, t) = e^{-2t} \cos(2x) \).

We run the Upwind scheme (3.2) for this system until time \( t = 1 \). The spatial domain is set to be \([a, b] = [0, 2\pi]\). The time step size used is \( \Delta t = \frac{1}{4} \Delta x^2 \). The tests were run for \( N = 10, 20, 40, 80 \) grid points. According to the truncation error analysis from the previous section we expect the scheme to be second order accurate in space. To determine the order of accuracy we calculate the order as,
\[
\text{Order} = \frac{\ln \left( \frac{\| \text{error}(\Delta x) \|}{\| \text{error}(\frac{\Delta x}{2}) \|} \right)}{\ln 2},
\]
where error (\(\Delta x\)) is the difference between the numerical solution and the exact solution for choice of \(\Delta x\).

Although we expect second order accuracy, we do observe order loss at the extrema. In Table 3.1 and Table 3.2 given below we list the \(L^\infty\) and \(L^2\) errors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=10</th>
<th>N=20</th>
<th>Order</th>
<th>N=40</th>
<th>Order</th>
<th>N=80</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>u</td>
<td>.0981</td>
<td>.0272</td>
<td>1.85</td>
<td>.0094</td>
<td>1.53</td>
<td>.0033</td>
<td>1.51</td>
</tr>
<tr>
<td>c</td>
<td>.0690</td>
<td>.0181</td>
<td>1.93</td>
<td>.0073</td>
<td>1.27</td>
<td>.0026</td>
<td>1.49</td>
</tr>
</tbody>
</table>

Table 3.1: \(L^\infty\) error for Upwind scheme

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=10</th>
<th>N=20</th>
<th>Order</th>
<th>N=40</th>
<th>Order</th>
<th>N=80</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>u</td>
<td>.1819</td>
<td>.0390</td>
<td>2.22</td>
<td>.0141</td>
<td>1.47</td>
<td>.0061</td>
<td>1.21</td>
</tr>
<tr>
<td>c</td>
<td>.1220</td>
<td>.0268</td>
<td>2.19</td>
<td>.0105</td>
<td>1.35</td>
<td>.0042</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Table 3.2: \(L^2\) error for Upwind scheme

**Example 2: Cell Concentration**

In this example we simulate the cell density concentration phenomena. The Keller-Segel equations are given as

\[
\begin{cases}
  u_t + (c_x u)_x = u_{xx} \\
  c_t = c_{xx} + u - c,
\end{cases}
\]

(3.11)

with initial conditions \(u(x, t = 0) = 840e^{-84x^2}\) and \(c(x, t = 0) = 420e^{-42x^2}\). The spatial domain is set to be \([a, b] = [-\frac{1}{2}, \frac{1}{2}]\). The time step size used was \(\Delta t = \frac{1}{4}\Delta x^2\). We simulate the Upwind scheme (3.2) until final time \(t=.0002\) with mesh size \(N = 51\).

The chemical variable is concentrated at the domain center thus the cell density is accumulated at the domain center. The results can be seen in Figure 3.1 for various times \(t\). We do observe the cell density is highly concentrated with large amplitude at the domain center \(x = 0\). The results we obtain match those in literature.
Figure 3.1: Cell concentration phenomena (Numerical output for cell density $u$ in blue and chemical concentration $c$ in green)
3.4 Lax-Friedrichs scheme

In this section we consider to derive second order Lax-Friedrichs finite difference scheme to solve the Keller-Segel model (3.1)

\[
\begin{cases}
    u_t + (c_x u)_x = u_{xx} + f(u, c), \quad x \in [a, b], \quad t > 0 \\
    c_t = c_{xx} + g(u, c).
\end{cases}
\]

Again we have Forward Euler for time discretization and central scheme for spatial discretization of the diffusion term. For the spatial discretization of the convection term we now consider the second order Lax-Friedrichs scheme. We simplify the discussion with the following nonlinear scalar conservation law,

\[ u_t + f(u)_x = 0. \]  \hspace{1cm} (3.12)

With Forward Euler in time and central approximation in space we have,

\[ \frac{u(x_j, t_{n+1}) - u(x_j, t_n)}{\Delta t} + \frac{f(u(x_{j+\frac{1}{2}}, t_n)) - f(u(x_{j-\frac{1}{2}}, t_n))}{\Delta x} = 0. \]  \hspace{1cm} (3.13)

Since neither \( u(x_{j+\frac{1}{2}}, t_n) \) or \( u(x_{j-\frac{1}{2}}, t_n) \) are available, they must be approximated with the available point values, for example the point set of \( \{u_i^n\}_{i=j-2}^{i=j+2} \) will be used for a second order approximation. We introduce the numerical flux \( \hat{f}_{j+\frac{1}{2}} \approx f(u(x_{j+1/2}, t_n)) \). We obtain the following Lax-Friedrichs type finite difference scheme for (3.12) as follows,

\[ \frac{u_{j}^{n+1} - u_{j}^{n}}{\Delta t} + \frac{\hat{f}_{j+\frac{1}{2}} - \hat{f}_{j-\frac{1}{2}}}{\Delta x} = 0. \]  \hspace{1cm} (3.14)

where

\[ \hat{f}_{j+\frac{1}{2}} = \hat{f}(u_{j-\frac{1}{2}}^{-}, u_{j+\frac{1}{2}}^{+}) = \frac{1}{2} \left[ f(u_{j-\frac{1}{2}}^{-}) + f(u_{j+\frac{1}{2}}^{+}) - \alpha (u_{j+\frac{1}{2}}^{+} - u_{j-\frac{1}{2}}^{-}) \right]. \]  \hspace{1cm} (3.15)

Shoulder notation of + indicates an approximation from the right and − indicates an approximation from the left. To approximate \( u_{j+\frac{1}{2}}^{+} \) we construct the second order Lagrange interpolating polynomial \( P_1^+(x) \). Using two points \( x_{j+1} \) and \( x_{j+2} \) to the right of \( x_{j+1/2} \) we have the following

\[ P_1^+(x) = u_{j+1} \frac{x - x_{j+2}}{x_{j+1} - x_{j+2}} + u_{j+2} \frac{x - x_{j+1}}{x_{j+2} - x_{j+1}}. \]
We then evaluate the Lagrange interpolating polynomial at $x_{j+1/2}$

$$P_1^+(x_{j+1/2}) = u_{j+1} \frac{-3}{2} \Delta x + u_{j+2} \frac{-1}{2} \Delta x,$$

which simplifies to

$$P_1^+(x_{j+1/2}) = \frac{3u_{j+1} - u_{j+2}}{2}.$$ 

Thus we have

$$u_{j+\frac{1}{2}}^+ = P_1^+(x_{j+1/2}) = \frac{3u_{j+1} - u_{j+2}}{2}. \quad (3.16)$$

We move on to approximate $u_{j+\frac{1}{2}}^-$ by constructing the second order Lagrange interpolating polynomial $P_1^-(x)$. Using two points $x_j$ and $x_{j-1}$ to the left of $x_{j+1/2}$ we have the following

$$P_1^-(x) = u_j \frac{x - x_{j-1}}{x_j - x_{j-1}} + u_{j-1} \frac{x - x_j}{x_{j-1} - x_j}.$$ 

We evaluate the Lagrange interpolating polynomial at $x_{j+1/2}$ to get

$$P_1^-(x_{j+1/2}) = \frac{3u_j - u_{j-1}}{2}.$$ 

Thus we have

$$u_{j+\frac{1}{2}}^- = P_1^-(x_{j+1/2}) = \frac{3u_j - u_{j-1}}{2}. \quad (3.17)$$

The Lagrange interpolating polynomials for approximating $u_{j+\frac{1}{2}}^+$ and $u_{j-\frac{1}{2}}^-$ are constructed in a very similar manner. To complete the scheme definition of (3.14), we simply plug in $u_{j+\frac{1}{2}}^-$ and $u_{j-\frac{1}{2}}^+$ from (3.17) and (3.16) into the numerical flux definition given in (3.15). For the choice of $\alpha$ we use the definition

$$\alpha = \max |f'(u_j^n)|,$$

to have the local or global Lax-Friedrichs scheme.

We now apply this numerical scheme to (3.1). Recall Forward Euler is used for time discretization, central scheme is used for spatial discretization of the diffusion term, and the second order Lax-Friedrichs scheme is used for spatial discretization of the convection term. Recall the previously defined central approximation

$$p_j^n = (c_x)_j \approx \frac{c^n_{j+1} - c^n_{j-1}}{2\Delta x}.$$
For system (3.1) our convection term is \( f(u) = c \partial_x u \), thus \( \hat{f}_{j + \frac{1}{2}} \) is given by

\[
\hat{f}_{j + \frac{1}{2}} = \frac{1}{2} \left[ p_{j + \frac{1}{2}} u^{-}_{j + \frac{1}{2}} + p_{j + \frac{1}{2}} u^{+}_{j + \frac{1}{2}} - \alpha \left( u^{+}_{j + \frac{1}{2}} - u^{-}_{j + \frac{1}{2}} \right) \right].
\] (3.18)

Approximations for \( u^{-}_{j + \frac{1}{2}} \) and \( u^{+}_{j + \frac{1}{2}} \) are again given by (3.17) and (3.16), respectively. Thus our second order Lax-Friedrichs scheme for (3.1) is given by,

\[
\begin{aligned}
u_{n+1} &= u_n - \Delta t \Delta x \left[ \hat{f}_{j + \frac{1}{2}} - \hat{f}_{j - \frac{1}{2}} \right] + \frac{\Delta t}{\Delta x^2} \left[ u^n_{j+1} - 2u^n_j + u^n_{j-1} \right] + \Delta t f(u^n_j, c^n_j) \\
c_{n+1} &= c^n_j + \frac{\Delta t}{\Delta x^2} \left[ c^n_{j+1} - 2c^n_j + c^n_{j-1} \right] + \Delta t g(u^n_j, c^n_j).
\end{aligned}
\] (3.19)

### 3.5 Lax-Friedrichs scheme numerical tests

#### Example 1: Accuracy Test

For this example focus is on the system (3.11), approximated by the new second order Lax-Friedrichs scheme (3.19). The scheme was run under the same conditions that were used in Section 3.3 Example 1. From the definition of the scheme, we expect this method to be second order accurate in space. An error analysis shows the \( L^\infty \) and \( L^2 \) errors converging to an order of two, as can be seen in Table 3.3 and Table 3.4 given below. Thus the Lax-Friedrichs scheme (3.19) achieves its expected order of accuracy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>(N=10)</th>
<th>(N=20)</th>
<th>Order</th>
<th>(N=40)</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>(u)</td>
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<td>.0404</td>
<td>2.06</td>
<td>.0084</td>
<td>2.27</td>
</tr>
<tr>
<td>(c)</td>
<td>.0867</td>
<td>.0214</td>
<td>2.02</td>
<td>.0045</td>
<td>2.25</td>
</tr>
</tbody>
</table>

Table 3.3: \( L^\infty \) error for Lax Friedrichs scheme

<table>
<thead>
<tr>
<th>Variable</th>
<th>(N=10)</th>
<th>(N=20)</th>
<th>Order</th>
<th>(N=40)</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>(u)</td>
<td>.2132</td>
<td>.0508</td>
<td>2.07</td>
<td>.0106</td>
<td>2.26</td>
</tr>
<tr>
<td>(c)</td>
<td>.1684</td>
<td>.0397</td>
<td>2.08</td>
<td>.0082</td>
<td>2.28</td>
</tr>
</tbody>
</table>

Table 3.4: \( L^2 \) error for Lax Friedrichs scheme

#### Example 2: Cell Concentration

For our second example, we use the same system (3.11) and the same conditions outlined in section 3.3 Example 2. The only difference is the choice of Lax-Friedrichs scheme. The results
of numerical tests can be seen in Figures 3.2a and 3.2b. We observe almost the exact same behavior of the numerical solutions that we did using an Upwind scheme.

Now that we have examined and carried out tests for two second order finite difference methods on simple systems, we move on to applying these methods to the more advanced biological systems from Tyson (1996)
CHAPTER 4. APPLICATIONS TO PATTERN FORMATION

In this chapter we apply the second order Lax-Friedrichs scheme (3.19) to simulate the liquid model and semi-solid model and investigate the pattern formation phenomena found in Tyson (1996).

4.1 Liquid model

We begin our application by starting with the simplest liquid experiment model, which is model (2.3) but with the third equation omitted,

\[
\begin{aligned}
\frac{\partial n}{\partial t} &= D_n \nabla^2 n - \nabla \cdot \left[ \frac{k_1 n}{(k_2 + c)^2} \nabla c \right] \\
\frac{\partial c}{\partial t} &= D_c \nabla^2 c + k_5 s \frac{n^2}{k_6 + n^2}.
\end{aligned}
\] (4.1)

In order to run numerical tests on this model we must first non-dimensionalise it. To do this we follow the process from Tyson (1996). We denote new variables

\[
\begin{aligned}
u = \frac{n}{n_0} & \quad \quad c^* = \frac{c}{k_2} & \quad \quad w = \frac{s}{s_0} \\
t^* = \frac{k_5 s_0}{k_2} t & \quad \quad (\nabla^*)^2 = \left( \frac{D_c k_2}{k_5 s_0} \right)^2 \nabla^2 \\
d_u = \frac{D_n}{D_c} & \quad \quad \alpha = \frac{k_1}{D_c k_2} & \quad \quad \mu = \frac{k_6}{n_0^2}
\end{aligned}
\]

where \(n_0\) and \(s_0\) are the average initial values of cell density and stimulant, respectively. Now we can rewrite (4.1) in terms of new variables \(u\) and \(c^* = c\) under a one dimensional setting as,

\[
\begin{aligned}
\frac{\partial u}{\partial t^*} &= d_u u_{xx} - \alpha \left[ \frac{u}{(1+c)^2} c_x \right]_x \\
\frac{\partial c^*}{\partial t^*} &= c_{xx} + w \frac{u^2}{\mu + u^2}.
\end{aligned}
\] (4.2)
Again \( u \) represents cell density, \( c \) represents the chemoattractant concentration and \( w \) represents the nutrient concentration. This simple liquid model implies a uniform distribution of the stimulant, which remains constant throughout the experiment, thus we have \( w = 1 \). As for the parameters introduced, \( \alpha \) is the chemotaxis coefficient, \( \mu \) is the saturation level of chemoattractant production and \( d_u \) is the diffusion ratio between cells and chemoattractant (Tyson (1996)).

Similar to the Lax-Friedrichs scheme (3.19), the second order Lax-Friedrichs scheme of (4.2) is given as,

\[
\begin{align*}
&u^n_{j+1} = u^n_j - \alpha \frac{\Delta t}{\Delta x} \left[ \hat{f}_{j+\frac{1}{2}} - \hat{f}_{j-\frac{1}{2}} \right] + \frac{d_u \Delta t}{\Delta x^2} \left[ u^n_{j+1} - 2u^n_j + u^n_{j-1} \right] \\
&c^n_{j+1} = c^n_j + \frac{\Delta t}{\Delta x} \left[ c^n_{j+1} - 2c^n_j + c^n_{j-1} \right] + \Delta t \left( \frac{(u^n_j)^2}{\mu + (u^n_j)^2} \right).
\end{align*}
\] (4.3)

where the numerical flux defined at \( x_{j+1/2} \) is,

\[
\hat{f}_{j+\frac{1}{2}} = \frac{1}{2} \left[ f(u^+_j) + f(u^-_j) - \alpha_j \left( u^+_j - u^-_j \right) \right].
\] (4.4)

Notice that the liquid model (4.2) is different to the model Keller-Segel equation (3.11). Previously we have \( f(u) = cxu \), where as in system (4.2) we now have

\[
f(u) = \frac{cx}{(1 + c)^2} u.
\]

This results in the following changes for the left and right fluxes in (4.4):

\[
f(u^-_j) \approx \frac{P_{j+\frac{1}{2}}}{\left(1 + c_{j+\frac{1}{2}}\right)^2} u^-_{j+\frac{1}{2}},
\]

\[
f(u^+_j) \approx \frac{P_{j-\frac{1}{2}}}{\left(1 + c_{j-\frac{1}{2}}\right)^2} u^+_{j+\frac{1}{2}},
\]

where we have,

\[
P_{j+\frac{1}{2}} = \frac{(cx)_j - (cx)_{j+1}}{2},
\]

\[
c_{j+\frac{1}{2}} = \frac{c_j + c_{j+1}}{2}.
\]

The corresponding values for \( p_{j+\frac{1}{2}} \) and \( c_{j+\frac{1}{2}} \) are found in a similar manner. The approximations to \( u^- \) and \( u^+ \) remain unchanged, given in (3.17) and (3.16) respectively. We consider local
Lax-Friedrichs scheme with coefficient taken as,

\[ \alpha_{j+\frac{1}{2}} = \max\{|f'(u)| = \left| \frac{(c_x)_{j+\frac{1}{2}}}{1 + (c_{j+1})^2} \right| \] .

Instead of periodic boundary conditions we now enforce zero Neumann boundary conditions. We have \( x \in [a, b] \) as the spatial domain. Thus the boundary conditions take the form,

\[ u_x(a, t) = u_x(b, t) = 0 \]

\[ (c_x)_{j=1} = (c_x)_{j=N+1} = 0. \]

We apply first order differentiation approximation at the very left and the right end of the domain. In a word, we apply \( u_x(x = a, t) \approx \frac{u_2 - u_1}{\Delta x} = 0 \) and \( u_x(x = b, t) \approx \frac{u_{N+1} - u_N}{\Delta x} = 0 \) therefore at all time level we apply the following zero Neumann boundary condition,

\[ u_{N+1} = u_N, \quad u_1 = u_2. \]

Similarly we have \( c_{N+1} = c_N, c_2 = c_1 \) for the chemotaxis variable.

### 4.2 Liquid model numerical results

We execute one numerical test on the liquid model (4.2) with the Lax-Friedrichs scheme (4.3). The initial condition for the cell density is taken as \( u(x, 0) = u_0 + r_p \) with \( u_0 = 1 \) and randomized perturbation of size \( r_p = 10^{-1} \). The initial condition for the chemical concentration is \( c(x, 0) = 0 \). We run the test with our scheme (4.3) up to time \( t=6 \), pausing along the way at various times. The computational domain is \([a, b] = [0, 10] \). The time step size used is \( \Delta t = \frac{1}{4} \Delta x^2 \) with total mesh points \( N = 166 \). The parameter values used in system (4.2) are \( \alpha = 50, \mu = 1, \) and \( d_u = .33 \). Initial conditions and parameter values were taken from Tyson (1996). The MATLAB code for this simulation can be found in Appendix A.

The results of this simulation can be seen in Figure 4.1. Since the cells are randomly distributed throughout the domain, we initially see many peaks and troughs in cell density, see Figure 4.1a. At this point the cells have just begun to secrete chemoattractant.

As time moves on the cells continue to produce chemoattractant. In Figure 4.1b we see that the many initial peaks in cell density have quickly given way to a lesser number of peaks with
increased amplitudes. The difference in amplitudes can be explained by competition between the cell groups. A group of cells with higher density will produce more chemoattractant than a group of cells with lower density, thus attracting cells to the higher density group at a faster rate.

As time continues to move on, we see a reduction in the number of peaks in cell density, as seen in Figure 4.1c. While the populations of high cell density continue to produce high levels of chemoattractant, diffusion is working against them, dissipating the concentrations of chemoattractant. If a group of cells is not producing enough chemoattractant to overpower the diffusion process that group will start to lose cell population to a group of cells whose chemoattractant production surpasses the diffusion rate. Thus we see a reduction in the number of populations with high cell density.

In Figure 4.1d we see the further effects of competition between groups of cells. Again the number of populations of high cell density is reduced, with one group out-pacing the other in...
cell density.

Since the amount of chemoattractant in the dish has no way to dissipate, eventually cells saturate and their movement is no longer governed by chemotaxis. The process of diffusion will then take over, meaning cells will travel down the concentration gradient to areas of lesser cell density. Thus over time the pattern of high cell density concentrations disappear (Tyson (1996)).

In the next section we move on to investigate applications of the semi solid model.

4.3 Semi-solid model

To begin our applications to the semi-solid model we must again start by non-dimensionalizing the system (2.2). Again the process was followed directly from Tyson (1996). We introduce new variables

\[
\begin{align*}
    u &= \frac{n}{n_0} \\
    c^* &= \frac{c}{k_2} \\
    w &= \frac{s}{\sqrt{k_0}} \\
    t^* &= k_7 n_0 t \\
    (\nabla^*)^2 &= \frac{D_c}{k_7 n_0} \nabla^2 \\
    d_u &= \frac{D_n}{D_c} \\
    d_w &= \frac{D_s}{D_c} \\
    \alpha &= \frac{k_1}{D_c k_2} \\
    \mu &= \frac{k_6}{n_0^2} \\
    \kappa &= \frac{k_8}{k_7 \sqrt{k_9}} \\
    \beta &= \frac{k_5}{k_7 k_2 n_0} \\
    \delta &= \frac{k_4}{n_0} \\
    \rho &= \frac{k_3}{k_7} \\
\end{align*}
\]

Now we can rewrite (2.2) in terms of the new variables \( u \) and \( c^* = c \) under one dimensional setting as,

\[
\begin{align*}
    \frac{\partial u}{\partial t^*} &= d_u u_{xx} - \alpha \left[ u \frac{c}{(1+c)} c_x \right]_x + \rho u \left( \delta \frac{w^2}{1+w^2} - u \right) \\
    \frac{\partial c}{\partial t^*} &= c_{xx} + \beta w \frac{u^2}{\mu+u^2} - uc \\
    \frac{\partial w}{\partial t^*} &= d_w w_{xx} - \kappa u \frac{w^2}{1+w^2}. \\
\end{align*}
\]

As we did with the liquid model simulation, we consider the case where the effect of nutrients dynamics is negligible, thus the model is further simplified as below,

\[
\begin{align*}
    \frac{\partial u}{\partial t^*} &= d_u u_{xx} - \alpha \left[ u \frac{c}{(1+c)} c_x \right]_x + \rho u \left( \delta \frac{w^2}{1+w^2} - u \right) \\
    \frac{\partial c}{\partial t^*} &= c_{xx} + \beta w \frac{u^2}{\mu+u^2} - uc. \\
\end{align*}
\]
The new parameters introduced are $d_w$, diffusion ratio of chemoattractant and nutrient, $\beta$, the chemoattractant production rate, $\delta$, the carrying capacity, $\kappa$, consumption rate of nutrient, and $\rho$, the rate of growth of cell. Recall $\alpha$ is the chemotaxis coefficient, $\mu$ is the saturation level of chemoattractant production and $d_u$ is the cell diffusion coefficient (Tyson (1996)).

Before running simulations on the model, we refer to the linear and nonlinear analysis in Tyson (1996). The linear analysis indicates the parameter ranges for where it is possible for patterns to form. The nonlinear analysis indicates which patterns are likely to form in specific parameter domains.

For the analysis purpose, it is required we use a small domain with periodic boundary conditions and initial conditions are taken as small perturbations around some concentration.

In Figure 4.2 we reprint the results from Tyson (1996) of nonlinear analysis on the system (4.5). We roughly have three groups of parameters, see region K, I and G in Figure 4.2. In our simulations we attempt to recover different pattern formations with the parameters falling in region of K, I, and G separately.
4.4 Semi-solid model numerical results

For the simulations of the semi-solid model (4.5) we apply our Lax-Friedrichs scheme (4.3). The minor change is on the zero-th order terms that involve function values of $u$ and $c$ at $x_j$ and time level $t_n$, so the details will not be revisited. Since we only focus on one-dimensional cases in this thesis, we must compare the one-dimensional plots to the profiles of the two-dimensional plots. We find that the results of our simulations are similar to those obtained in Tyson’s thesis. All initial conditions and parameter values in this section are also taken directly from Tyson (1996).

Striped Simulation

In this case we take our parameter values from the set G in Figure 4.2 and we expect to obtain a stripe pattern formulation. We start with initial conditions $c(x,0) = .3797$ and $u(x,0) = 4.6 + r_p$. We ran this scheme until a steady state was reached at time $t=6.9$. The spatial domain is taken as $[a,b] = [0, 1.213]$. The time step size used was $\Delta t = \frac{1}{4} \Delta x^2$. In this example we ran numerical tests for $N=50$ grid points. Our parameter values are taken as $\alpha = 90, \mu = 100, d_u = .25, \rho = 8.5133, \beta_w = 10, \delta \frac{w^2}{1+w^2} = 4.6$ in the semi-solid simplified model (4.5). Results can be seen in Figure 4.3a, with the comparison of Tyson’s results in 2D found in Figure 4.3b.

Spot Simulation

For this simulation we expect to obtain a spot pattern using parameter values from the set I on Figure 4.2, thus we choose parameters $\beta_w = 10, \delta \frac{w^2}{1+w^2} = 5.5$. The other parameter values are taken as $\alpha = 90, \mu = 100, d_u = .25$ and $\rho = 7.139$. The initial conditions are set as $c(x,0) = .4233$ and $u(x,0) = 5.5 + r_p$. The spatial domain is set as $[a,b] = [0, 1.159]$. This simulation was run until $t=40.98$ when a steady state was reached. Results can be seen in Figure 4.3c, with the comparison of Tyson’s results in 2D found in Figure 4.3d.

Indeterminate Simulation

For this simulation we use parameter values from the region K on Figure 4.2 where parameters are taken as $\beta_w = 10$ and $\delta \frac{w^2}{1+w^2} = 6.6$. The other parameter values are taken as $\alpha = 90, \mu = 100, d_u = .25$ and $\rho = 5.1210$. The initial conditions are chosen as $c(x,0) = .4597$
and \( u(x, 0) = 5.1210 + r_p \). The domain is taken as \([a, b] = [0, 1.15]\). This simulation was run until a steady state was reached. For this simulation we expect the pattern to be undetermined. Results can be seen in Figure 4.3e, with the comparison of Tyson’s results in 2D found in Figure 4.3f.

From these numerical simulations we recover different pattern formations which are consistent to the nonlinear analysis. However the initial conditions required for carrying out the nonlinear analysis are different from those used in the biological experiments. In the next example we switch to more experimentally accurate initial conditions.

**Semi-Solid Model Experimental Numerical Results**

For this simulation we attempt to reproduce results for the parameter set used in the Stripe Simulation but with initial conditions that better represent the experimental data. The initial conditions we have are \( c(x, 0) = 0 \) and \( u(x, 0) = 1 + r_p \) with the cell density \( u \) perturbed on a fairly large scale. The boundary conditions are once again zero Neumann boundary condition. The parameters used are \( \alpha = 90, \mu = 100, d_u = .25 \) and \( \rho = 8.5133, \beta = 10.5, \delta = 4.6 \). The domain is set to be \([0, 15]\) and the simulation was run up to time \( t = 1.8 \). Experimental evidence suggests that parameters from the stripes region should appear as a sequence of propagating pulses. When this simulation was run we do not obtain the pattern expected. However if \( \rho = 1 \) we achieve the desired pattern for the cell density, as seen in Figure 4.4. Again, all parameter values and initial conditions are taken from Tyson (1996).
(a) Stripe Simulation, parameters from G region

(b) Stripe Pattern Comparison in 2D, reprinted from Tyson

(c) Spot Simulation, parameters from I region

(d) Spot Pattern Comparison in 2D, reprinted from Tyson

(e) Indeterminant Pattern Simulation, parameters from K region

(f) Indeterminant Pattern Comparison in 2D, reprinted from Tyson

Figure 4.3: Various Pattern Formation Simulations Compared to 2D Results from Tyson
Figure 4.4: Stripe Pattern Simulation with Experimental Initial Conditions
In this thesis we intensively study the topic of chemotaxis with the Keller-Segel models. We derived two finite difference schemes to numerically solve the Keller-Segel system. The first method is an Upwind scheme and the second is Lax-Friedrichs scheme. We use Taylor expansion to carry out local truncation error analysis to verify it is second order scheme. We further apply the Lax-Friedrichs scheme to study the liquid and semi-solid models in Tyson (1996). We recovered the images of different patterns with our numerical scheme. Our results are consistent to those in Tyson (1996).
BIBLIOGRAPHY


APPENDIX A. MATLAB CODE

The following code is the second order Lax-Friedrichs scheme given in (4.3) and was used to generate Figure 4.1.

```matlab
1 clear all
2 close all
3 %solving \{u_t=D\cdot u_{xx}-a((u/(1+c)^2)\cdot c_x)_x
4 % \{c_t=c_{xx} + w(u^2/(\mu+u^2)) \} with Lax Friedrichs scheme
5
6 %model comes from Tyson's thesis, equation 3.2 page 31
7 %follows example from Chapter 3 of thesis, parameters taken
8 %from Figure 3.12 page 48
9 %in this case both mu and w are 1
10
11
12 N = 166; %mesh points
13 xmin = 0;
14 xmax = 10;
15 dx = (xmax-xmin)/N; %mesh spacing
16 x = xmin:dx:xmax;
17 t = 0;
18 tmax = 1; %maximum time
19
20 CFL = .25;
21 dt = CFL*(dx^2); %ensures stability of scheme
22 t_current = t;
23
24 %D is coefficient d_u and a is coefficient alpha from Figure 3.12
```
D = .33;
a = 50;

%specifies range for perturbation values to form $u_0$
c = -.5;
e = .5;

%forms $u_0$ and $c_0$. In this example $u_0$ is a small random perturbation about 1 and $c_0$ is 0

for i=1:N+1

    unew(i) = 1 + .1*(e-c).*rand(1,1)+c;
    cnew(i) = 0;

end

r = (dt/dx);
s = dt/(dx^2);

while (t_current<tmax)

    if(t_current+dt<tmax)
        dt = dt;
    else dt = tmax-t_current;
    end

    uold = unew;
    cold = cnew;

%Central scheme for c (equation 2 of system)

    for j = 2:N
        cnew(j) = cold(j)+s*(cold(j+1)-2*cold(j)+cold(j-1))+...
                   dt*((uold(j)^2)/(1+(uold(j))^2));
    end

    cnew(1) = cnew(2); %enforce Neumann BC
cnew(N+1) = cnew(N); %enforce Neumann BC

%Calculates c \( \times \)
for j = 2:N
    p(j) = (cold(j+1)-cold(j-1))/(2*dx);
end
p(1) = p(2);
p(N+1) = p(N);

%Calculates c \( j+1/2 \)
for j = 2:N
    v(j) = (cold(j)+cold(j+1))/2;
end
v(1) = v(2);
v(N+1) = v(N);

%Calculates alpha vector for L-F scheme by finding maximum absolute
%value of the "nonlinear term"
for j = 1:N+1
    alpha(j) = max(abs(p(j)/((1+v(j))^2)));
end

%Construct f left and u left
for j = 2:N
    uminus(j) = (1/2)*(3*uold(j)-uold(j-1));
end
uminus(1) = uminus(2);

for j = 2:N
    fuminus(j) = ((p(j)+p(j+1))/2)*uminus(j)*(1/(1+v(j))^2);
end
fuminus(1) = fuminus(2);

%Construct f right and u right
for j = 2:N-1
uplus(j) = \((1/2)*(3*u_{old}(j+1)-u_{old}(j+2))\);

end

uplus(1) = uplus(2);

uplus(N) = \((1/2)*(3*u_{old}(N+1)-u_{old}(2))\);

for j = 2:N
    fuplus(j) = \(((p(j)+p(j+1))/2)*uplus(j)*(1/(1+v(j))^2)\);
end

fuplus(1) = fuplus(2);

%Construct f hat
for j = 1:N
    fhat(j) = \((1/2)*(fuminus(j)+...\)
    fuplus(j)-alpha(j)*(uplus(j)-uminus(j)))\);
end

%Lax Friedrichs scheme for u
for j = 2:N
    u_{new}(j) = u_{old}(j) - a*r*(fhat(j) - fhat(j-1)) +...
    D*s*(u_{old}(j+1)-2*u_{old}(j)+u_{old}(j-1));
end

u_{new}(1) = u_{new}(2);
u_{new}(N+1) = u_{new}(N);

\texttt{t.current = t.current+dt};

end
plot(x,u_{new},'bo-','markerfacecolor', 'b')
axis([0 10 0 10])
xlabel('x','fontsize',16)
ylabel('U(t,x)', 'fontsize',16)
title(sprintf('time = %1.6f',tmax), 'fontsize',16)