GENERATION OF BIOLOGICAL PATTERNS BASED ON AN APPROXIMATION MODEL

by

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Declaration

I hereby declare that this submission is my own work towards the MSc degree and that, to the best of my knowledge, it contains no material previously published by another person or material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

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Abstract

Since the begining of pattern formations, various people have come out with experimental data for different modes. All the modes considered so far are all even modes. In this thesis, we looked at the various experimental data from Bentil and Murray. Based on their experimental data we came out with our experimental data that involved both even and odd modes.

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CHAPTER 1

Introduction

1.1 Application of Mathematics to Biological Systems.

The application of Mathematics to Biological Systems has had a significant effect on Biology and this has fostered a new development of Mathematics. The application of Mathematics to Biology may seem surprising because of the different natures of Mathematics and Biology. Mathematics is precise and rigorous in nature. Mathematical facts are immutable and successful Mathematical theories have lifetimes of hundreds or thousands of years. But most Biological facts evolve rapidly. Upon all these differences, their interaction have produced spectacular results.

The application of Mathematics to Biology can be divided into two categories. Application of existing Mathematical techniques to Biological problems and when the existing Mathematical Methods are inadequate and new Mathematical techniques are developed within the convectional frameworks.

The interaction of Mathematics and Biology in not new, Robert Brown, a Botanist discovered what is now called Brownian motion while watching pollen grains in water. Today, the Mathematical description of such motion is central

to probability theory.

The following are a few Mathematical methods that have been applied to Biology

1. Statistics
2. Stochastic Processes
3. Dynamical Systems Theory
4. Nonlinear Partial Differential Equation
5. Topology
6. Geometry

1.1.1 Statistics

Statistics is the most widely used and oldest Mathematical technique on Biology. During the early stages of it's application, it was basically used to determine the chances of an event happening. But down the line it was developed from chances to calculus of probabilities and also from Least Squares to Regression Analysis.

The quantitative study of Biological inheritance and evolution is another aspect of application of Statistics to Biology. With all these applications of Statistcs to Biology, a new trend of Mathematics has evolved, which is called Biometry.

Biometry is the application of Statistics to biological, medical, agricultural

and pharmaceutical sciences. The subject is concerned with the designs of experiments and surveys, the organisation and analysis of data and the interpretation of the results. Individuals with a training in biometry play a central role in industry and public sector research organisation and are involved in, for example, the design and analysis of clinical trials, the assessment of links between environmental exposures and diseases, field trials of new crop varieties, modeling in population and medical genetics, to mention but a few.

1.1.2 Stochastic processes

A Stochastic process is a process in which its outcome is non-deterministic. It states are determined both by the process of predictable actions and by a random element. Stochastic processes are complex systems in which the experts in this field acknowledge that the outcome results from both known and unknown causes. The classical example of this is in medicine.

A doctor can administer the same treatment to multiple patients suffering from the same symptoms, however the patients may not all react to the treatment the same way. This makes medicine a stochastic process.

Pressure in a gas is a stochastic process. It was modeled by Norbert Wiener. Even though each molecule is moving in a deterministic path, the motion of a collection of them is computationally and practically unpredictable. A large enough set of molecules will exhibit stochastic characteristic, such as filling the container, exerting equal pressure and diffusing along concentration gradients.

In biological systems, introducing stochastic 'noise' has been found to help improve the signal strength of the internal feedback loops for balance and other vestibular communication. It has been found to help diabetic and stroke patients with balance control.

1.1.3 Dynamical Systems Theory

Dynamical systems theory is an area of applied mathematics used to describe the behaviour of complex systems, usually by employing differential equations or difference equations. When differential equations are employed, the theory is called continuous dynamical systems and when difference equations are employed, the theory is called discrete dynamical systems. This theory deals with the solutions to partial differential equations that arise in biology.

The main aim of dynamical systems theory is to describe the fixed points, or steady states. These are values of the variable which will not change over time. Some of these fixed points are attractive, meaning that if the system starts out in a state, it will converge towards the fixed point. There is also periodic points which are values of the variable of the system that repeat themseves after several time steps. Periodic points can also be attractive. Dynamical systems theory may exhibit random, completely unpredictable behaviour that is called 'chaos'.

Dynamical systems theory has been used to model athletic performance. From a dynamical systems perspective, the human movement system is a highly

intricate network of co-dependent sub-systems (eg, respiratory, circulatory, nervous) that are composed of a large number of interacting components (eg blood cells, oxygen molecules, muscle tissue, metabolic enzymes, connective tissue and bone). In dynamical systems theory, movement patterns emerge through generic processes of self-organization found in physical and biological systems.

Dynamical system theory has recently emerged in the field of cognitive development. It is believed that cognitive development is best represented by physical theories rather than theories based on syntax and artificial insemination (AI). It is believed that differential equations are the most appropriate tool for modeling human behavior. Thes equations are interpreted to represent an agent's cognitive trajectory through state space. In other words, scientist argue that psychology should be the description (via differential equations) of the cognitions and behaviors of an agent under environmental and internal pressures.

1.1.4 Topology

Topology is the branch of Mathematics that studies the properties of a space that are preserved under continuous stretching, twisting and deformations of objects. Topology was develop from Geometry. It is concerned about shape and structure of an object and it has metric properties such as the distance between points. Unlike Geometry, Topology is concerned about the properties of a space that assembles that particular space.

Some properties of Topology

1. Connectedness
2. Orientability
3. Compactness
4. Continuous
5. Convergence

Deformations under Topology is called homeomorphisms.Homeomorphisms are functions that stretches a space without tearing it apart or sticking distinct parts together. Under Topology there is also Topological Space and it is define as Let X be any set and let T be a family of subsets of X. Then T is a topology on X if the following axioms are satisfied

1. Both the empty set and X are elements of T
2. Any union of arbitrary many elements of T is an element of T
3. Any intersection of finitely many elements of T is an element of T

If T is a topology on X, then X together with T is called a topological space

A function from one topological space to another is called continuous if the inverse image of any open set is open, then the functions maps the real numbers

to real numbers, This definition of continuous is equivalent to the definition of continuous in calculus. If a continuous function is one-to-one and onto and if the inverse of the function is also continuous, then the function is called homeomorphism and the domain of the function is said to be homeomorphic to the range. [Two spaces are homeomorphic if they have identical topological properties]. A topological property is a property of spaces that is invariant under homeomorphisms. To prove that two spaces are not homeomorphisms, it is sufficient to find a topological property which is not shared by them.

Example

1. The cube and the sphere are homeomorphic
2. Coffee cup and doughnut are homeomorphic
3. Circle is not homeomorphic to doughnut

Application of Topology as a Mathematical tool on Biology

Topology deals with the sets of numbers and the shape of items. Because of the nature of topology one can apply topology on Biology. The type of topology that has been used on Biology is the three-dimensional topology. The theorems under this type of topology deals with topological invariant of curves and ribbons in three-space. One can use these theorems to study structures of closed circular DNA. It can also be applied on supercoiling in closed DNA, topoisomerases, nucleosome winding, the free energy accompany with supercoiling and the binding between proteins and DNA.

Another application of topology on biology is the use of random knots in topology to study solutions of micromolecules. Tangle calculus is used to study the mechanism of enzyme in the human body and also in DNA.

The study of enzyme in food processing industries and the breweries is done by applying tangle calculus. Embedding invariant graph in topology is used to study topoisomers. Topoisomers or topological isomers are molecules with the same chemical formula and stereochemical bond connectivities but different topologies.

Examples of molecules for which there exists topoisomers include DNA, which can form knots and catenanes. DNA poisomers can be interchanged by enzymes called topoisomerases.

1.2 Aims and Objectives

1. To derive the model
2. To compare Bentil's experimental data with Murray and other scientists who started patterns formation.
3. To use a programing language call Matlab to implement the model.
4. To use the solution of the model to forecast some experimental data which may be useful.

1.3 Methodology

1. In 1986, Murray and other scientist came out with some experimental data for patterns formation using nonlinear least square.

   Below was the result

   Table 1.1: **Murray's experimental data**

mode	τ	μ	β	λ	D	α	s
2	2.30	1.00	0.015	0.12	0.001	0.001	57.32
4	10.2	0.022	0.0021	1.96	0.200	0.260	177.8
6	1.01	1.00	0.001	0.12	0.001	0.001	100.0
8	1.65	1.00	0.001	0.12	0.001	0.001	400.0

2. In 1990, Bentil also came out with a new experimental data for patterns formation using optimisation technique called logical parameter search method.

   Below was the result

   Table 1.2: **Bentil's experimental data**

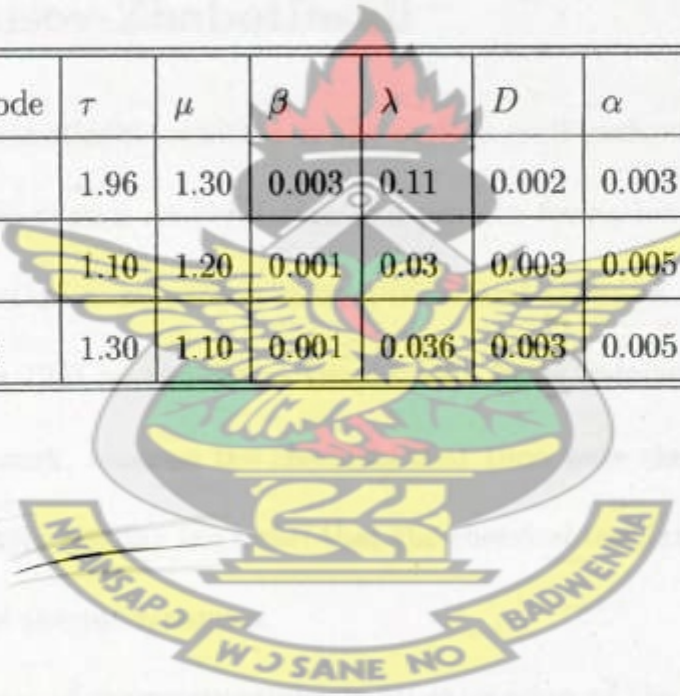
mode	τ	μ	β	λ	D	α	s
2	1.50	0.80	0.020	0.05	0.003	0.004	40.00
4	1.00	0.70	0.005	0.11	0.001	0.002	100.0
6	1.65	1.20	0.002	0.10	0.003	0.004	380.0
8	1.15	1.20	0.001	0.10	0.002	0.003	420.0

3. We used a program written in Matlab to come out with some other experimental data.

Below was the result

Table 1.3: **Dontwi and Oppong's experimental data**

mode	τ	μ	β	λ	D	α	s
5	1.96	1.30	0.003	0.11	0.002	0.003	395
9	1.10	1.20	0.001	0.03	0.003	0.005	720.0
10	1.30	1.10	0.001	0.036	0.003	0.005	965



CHAPTER 2

Background and Literature Review

2.1 Belousov-Zhabotinskii

The Belousov-Zhabotinskii reaction is the earliest well-understood example of a chemical system that is an oscillation and pattern formation. The Belousov-Zhabotinskii reaction is actually a system of several chemical reactions, which was discovered in 1951 by the Soviet Biophysicist Boris Belousov. But he could not publish his work, because the chemists that time were skeptical about his reaction. They were holding the belief that the chemical oscillator would violate the second law of thermodynamics.

The second law of thermodynamics is an expression of the universal law of increasing entropy, stating that the entropy of an isolated system which is not in equilibrium will tend to increase over time, approaching a maximum value at equilibrium.

They believed that all chemical concentration in a reaction must move directly towards equilibrium. They compared his reaction to a damped pendulum, which passes through its equilibrium position during each oscillation and eventually comes to rest. A chemical system that did this would indeed violate the second law of thermodynamics. Passing through the equilibrium point and then moving

away from it would require an increase in Gibbs free energy, which must always decrease.

However, the Belousov-Zhabotinskii reaction (like all other chemical oscillators) does not reach its equilibrium point until after the oscillations are finished. Because of all these misconceptions, Belousov was unable to get his work published.

A decade later, another Soviest scientist named Anatol Zhabotinskii reproduced Belousov's experiment and successfully persuaded more chemists to accept the idea of chemical oscillators.

Belousov's original experiment studied only temporal oscillations in a well-stirred solution, however much more interesting is the formation of spatial patterns in an unstirred solution. In these cases, if the reaction begins at a given point, the concentrations of inter-mediates will propagate in the adjacent regions. This is known as a trigger wave. Periodically the reaction will reinitiate at the nucleation point resulting in successive bonds (ina one-dimensional test tube reaction) or concentric rings (in a two-dimensional petri dish reaction). When certain reactants are combined, an "induction" period of inactivity is followed by sudden oscillation n colour from red to blue. In spatially non-homogeneous systems (such as a simple petri dish), the red and blue oscillations propagate as a spiral wave fronts. This will go on for sometime and eventually, the reaction will stop oscillating and approaches an equilibrium state. The colour changes are caused by alternating oxidation-reactions in which cerium changes it's oxidation

state from Ce(iii) producing a magenta solution to Ce(iv) producing a blue solution or vice versa. Because of this, we call the Belousov-Zhabotinskii reaction an "oscillating reacton", this simply means a reaction in which there is a regular periodic change in the concentration of one or more reactants.

Systems of chemical oscillators are of great importance in Biological systems. For example, the senatorial noge, the heart's pacemaker, causes trigger waves which though electrical in nature, propagate in much the same way as the Belousov-Zhabotinskii reaction trigger waves. The generation of cyclicadenosine monophosphate in aggregating dictyosteliumdiscoideum slime mold colonies creates spiral patterns nearly identical to those of the Belousov-Zhabotinskii reaction. RNA has been found to self-replicate with fronts of increase RNA concentration moving outward via diffusion.

In 1972, three researches at the University of Oregon, Field, Koros and Noyes published a complete mechanism describing the Belousov-Zhabotinskii reaction, known as the Field, Koros and Noyes(FKN) mechanism.

Table 2.1: **A recipe for the BZ reaction**

Species	Concentration
Malonic acid	0.2M
Sodium bromate	0.3M
Sulfuric acid	0.3M
Ferroin	0.005M

Table 2.2: **Abbreviated FKN mechanism governing the BZ reaction**

	Reaction	Rate constant
(R1)	$Br^- + HOBr + H^+ \rightarrow Br_2 + H_2O$	$K_{R1} = 8 \times 10^9 M^{-2} s^{-1}$
(R2)	$HbrO_2 + Br^- + H^+ \rightarrow 2HOBr$	$K_{R2} = 10^6 M^{-2} s^{-1}$
(R3)	$BrO_3^- + Br^- + 2H^+ \rightarrow HBrO_2 + HOBr$	$K_{R3} = 2M^{-3} s^{-1}$
(R4)	$2HBrO_2 \rightarrow BrO_3^- + HOBr$	$K_{R4} = 2 \times 10^3 M^{-1} s^{-1}$
(R5)	$BrO_3^- + HBrO_2 + H^+ \rightarrow 2BrO_2 + H_2O$	$K_{R5} = 10M^{-2} s^{-1}$
(R6)	$BrO_2 + Ce(iii) + H^+ \rightarrow HBrO_2 + Ce(iv)$	$K_{R6} = 6 \times 10^5 M^{-2} s^{-1}$

Table 2.3: **Abbreviated FKN mechanism governing the BZ reaction**

	Reaction	Rate consta
(C1)	$CH_2(COOH)_2 \rightleftharpoons (HO)_2C = CHCOOH$	see 14
(C2)	$(HO)_2C = CHCOOH + Br_2 \rightarrow BrCH(COOH)_2 + H^+ + Br^-$	see 14
(C3)	$2Ce(iv) + CH_2(COOH)_2 + BrCH(COOH)_2 \rightarrow fBr^- + otherproducts$	see 14

2.1.1 Mechanism of the Belousov-Zhabotinskii reaction

The FKN mechanism for the Belousov-Zhabotinskii reaction can be described in three concurrent processes

- Process 1: This process consists of three steps which reduce bromate to bromine

- Process 2: In this process, there is an introduction of hypobromous acid acting as a reducing agent for bromate

- Process 3: The products from processes 1 and 2 react

PROCESS ONE

In this process, we have the reaction of bromate $[BrO_3]$ to bromine by the reducing agent bromine Br. This process consists of the first three steps of the FKN Mechanism. The product of these three processes is bromomalonic BrMA. As a result the concentration of bromide which is acting as reducing agent eventually falls below some critical level. Br^-

PROCESS TWO

It is at this stage that process two begins to dominate process one. The hypobromous acid $HBrO_2$ begins to compete with the bromide to reduce the bromate. As a result, the concentration of hypobromous acid $HBrO_2$ increases and Ce(iv) is produced.

Reaction (R5) and (R6) constitute a two-step autocatalytic sequence.

This process causes the solution to change suddenly from red to blue (in the presence of a ferroin indicator)

PROCESS THREE

As process one and two cycle back and forth depending on whether Br^- is above or below Br^-. The products from process one which is bromomalonic BrMA and

process two which is Cerium-4(Ce(IV)) react. The process causes the solution to change from blue to red(in the presence of a ferroin indicator). As a result, it moves back to process one and the whole cycle repeats itself again. The change in colour from red to blue and blue to red is term as oscillation and this is why the Belousov-Zhabotinskii reaction is called the chemical oscillator. As the whole process cycle back and forth, patterns are formed

Two-dimensional spatial patterns can be form as a result of the reactions. When the reaction nucleates at a point, diffusion brings bromide from the surrounding region into the nucleation point. This facilitates the resetting mechanism at the nucleation point, while simultaneously allowing process(2) to dominate in the surrounding region,oxidizing the metal ion catalyst and perpetuating the front of bromide concentration. In this manner, a circular wave will progress outward from the nucleation point. If the conditions are such that oscillations will continue, a second circular wave will begin at the nucleation point and the end result will be many concentric rings in a 'target pattern'. If the nucleation point does not continue to oscillate, a single wave front will expand until it is annihilated at the edge of the container.

Field and Noyes (1972) discovered experimentally that the wave front velocity is given by

$$V = 0.04 cm^2 sec^{-1} m^{-1} ([H^+][BrO_3])^{\frac{1}{2}}$$

The curvature of the wave dependence on the velocity. For very small target

patterns, the curvature is relatively high and this slows the reaction's progress because diffusion from a point is less than diffusion from a line. The dependence is given by the eikonal equation

$$V^{\bullet} = V + DK$$

where D is the diffusion constant

K is the curvature (positive for a contracting circle and negative for an expanding circle)

V is the propagation velocity for the reaction at zeros curvature.

2.1.2 Mathematical Analysis

Let $X = [HBrO_2](hypobromousacid)$

$Y = [Br^-](bromide)$

$Z = [Ce(IV)](Cerium - 4)$

$A = [BrO_3](bromate)$

$B = [Org](Organic \quad species)$

$P = [HOBr]$

The table below shows the Oregonator Scheme. The Oregonator is derived from the FKN Mechanism and it is as follows:

(O1) is equivalent to reaction (R3) of the FKN Mechanism

(O2) is equivalent to reaction (R2) of the FKN Mechanism

(O3) is the autocatalytic sequence of the FKN Mechanism and is given by (R5)+2(R6)

(O4) is equivalent to reaction (R4) of the FKN Mechanism

(O5) is the organic species species in process three

Table 2.4: **The Oregonator Scheme**

	Reaction	Rate
(O1)	$A + Y \rightarrow X + P$	$K_3 = K_{R3}[H^+]^2 AY$
(O2)	$X + Y \rightarrow 2P$	$K_2 = K_{R2}[H^+]XY$
(O3)	$A + X \rightarrow 2X + 2Z$	$K_5 = K_{R5}[H^+]AX$
(O4)	$2X \rightarrow A + P$	$K_4 = K_{R4}X^2$
(O5)	$B + Z \rightarrow fY$	$K_O = BZ$

The law of mass action is used to convert the Oregonator to 3×3 system of nonlinear ordinary differential equations. The law of mass action states that the rate of a reaction is proportional to the product of the reactant concentrations.

The rate of reaction for $X = [HBrO_2]$(hypobromous acid) is derive as follows, From(O1) Reaction

$$\frac{dX}{dt} \propto AY \tag{2.1}$$

Using the constant rate of proportion of K_3 and also hypobromous acid produces

$$\frac{dX}{dt} = K_3 AY \tag{2.2}$$

From(O2) Reaction

$$\frac{dX}{dt} \propto XY \tag{2.3}$$

Using the constant rate of proportion of K_2 and also hypobromous acid is being absorbed or used, we have

$$\frac{dX}{dt} = -2K_2XY \tag{2.4}$$

From(O3) Reaction

$$\frac{dX}{dt} \propto AX \tag{2.5}$$

Using the constant rate of proportion of K_5 and also hypobromous acid is being absorbed or used, we have

$$\frac{dX}{dt} = -K_5AX \tag{2.6}$$

$$\frac{dX}{dt} \propto 2AX \tag{2.7}$$

Using the constant rate of proportion of K_5 and also hypobromous acid is being produced, we have

$$\frac{dX}{dt} = 2K_5AX \tag{2.8}$$

From(O4) Reaction

$$\frac{dX}{dt} \propto 2X^2 \tag{2.9}$$

Using the constant rate of proportion of K_4 and also hypobromous acid is being absorbed or used, we have

$$\frac{dX}{dt} = -2K_4X^2 \tag{2.10}$$

From(O5) Reaction

We have no rate of reaction for the hypobromous acid because neither hypobromous acid is being produced or used in this particular chemical equation. Putting equations (2.1) to (2.10) together we have

$$\frac{dX}{dt} = K_3AY - K_2XY + K_5AX - 2K_4X^2 \tag{2.11}$$

The rate of reaction for $Y = [Br^-]$(bromide) is derive as follows

From(O1)Reaction

$$\frac{dY}{dt} \propto AY \tag{2.12}$$

Using the constant rate of proportion of K_3 and also hypobromous acid is being absorbed or used, we have

$$\frac{dY}{dt} = -K_3AY \tag{2.13}$$

$$\frac{dY}{dt} \propto XY \tag{2.14}$$

Using the constant rate of proportion of K_2 and also hypobromous acid is being absorbed or used, we have

$$\frac{dY}{dt} = -K_2XY \tag{2.15}$$

From(O3)Reaction

We have no rate of reaction for the bromide because neither bromide is being produced or used in this particular chemical equations.

From(O4)Reaction

We have no rate of reaction for the bromide because neither bromide is being produced or used in this particular chemical equation.

From(O5)Reaction

$$\frac{dY}{dt} \propto \frac{1}{2} f B Z \tag{2.16}$$

Using the constant rate of proportion of K_0 and also bromide is being produced, we have.

$$\frac{dY}{dt} = \frac{1}{2} f K_0 B Z \tag{2.17}$$

Putting equations (2.12) to (2.17) together we have

$$\frac{dY}{dt} = -K_3 A Y - K_2 X Y + \frac{1}{2} f K_0 B Z \tag{2.18}$$

The rate of reaction for $Z = [Ce(iv)]$(Cerium-4) is derive as follows

No reaction for Cerium-4 in equation (O1),(O2) and (O4)

From(O3)Reaction

$$\frac{dZ}{dt} \propto 2AX \tag{2.19}$$

Using the constant rate of proportion of K_5 and also Cerium-4 is being produced, we have

$$\frac{dZ}{dt} = 2K_5 A X \tag{2.20}$$

From(O5)Reaction

$$\frac{dZ}{dt} \propto BZ \tag{2.21}$$

Using the constant rate of proportion of K_0 and also Cerium-4 is being absorbed or used, we have

$$\frac{dZ}{dt} = -K_0BZ \tag{2.22}$$

Putting equations (2.20) and (2.22) together we have

$$\frac{dZ}{dt} = 2K_5AX - K_0BZ \tag{2.23}$$

Putting equations (2.11), (2.18) and (2.23) together we have a 3×3 system of nonlinear ordinary differential equations.

$$\frac{dX}{dt} = K_3AY - K_2XY + K_5AX - 2K_4X^2 \tag{2.24}$$

$$\frac{dY}{dt} = -K_3AY - K_2XY + \frac{1}{2}fK_0BZ \tag{2.25}$$

$$\frac{dZ}{dt} = 2K_5AX - K_0BZ \tag{2.26}$$

Putting the system (2.24) to (2.26) in dimensional form and using the change of variables [Tyson][6]

Let

$$x = \frac{X}{X_0}, \quad y = \frac{Y}{Y_0}, \quad z = \frac{Z}{Z_0}, \quad \tau = \frac{t}{T_0} \tag{2.27}$$

Where

$$X_0 = \frac{K_5A}{2K_4}, \quad Y_0 = \frac{K_5A}{K_2}, \quad Z_0 = \frac{(K_5A)^2}{K_0B}, \quad T_0 = \frac{1}{K_0B}$$

From equation(2.27)

$$X = xX_0, \quad Y = yY_0, \quad Z = zZ_0, \quad t = \tau I_0'$$

$$X = x\frac{K_5A}{2K_4} \tag{2.28}$$

$$Y = y\frac{K_5A}{K_2} \tag{2.29}$$

$$Z = z\frac{(K_5A)^2}{K_0B} \tag{2.30}$$

$$t = \frac{\tau}{K_0}B \tag{2.31}$$

Differentiating equations (2.28) with respect to t on both sides of the equation

$$\frac{dX}{dt} = \frac{K_5A}{2K_4}\frac{dx}{dt} \tag{2.32}$$

Differentiating equation (2.31) with respect to τ

$$\frac{dt}{d\tau} = \frac{1}{K_0B} \tag{2.33}$$

$$dt = \frac{d\tau}{K_0B} \tag{2.34}$$

Combining equations (2.32) and (2.34), we have

$$\frac{dX}{dt} = \frac{K_0BK_5A}{2K_4}\frac{dx}{d\tau} \tag{2.35}$$

Putting equations (2.28), (2.29) and (2.35) into equation (2.24), we have

$$\frac{K_0BK_5A}{2K_4}\frac{dx}{d\tau} = \frac{K_3AyK_5^2A^2}{K_2} - \frac{K_2yK_5A}{2K_4K_2} + \frac{K_5AxK_5A}{2K_4} - \frac{2K_4x^2K_5^2A^2}{4K_4^2} \tag{2.36}$$

Doing a little algebra we have

$$\frac{K_0B}{K_5A}\frac{dx}{d\tau} = \frac{2K_2K_4}{K_2K_5}y - xy + x - x^2 \tag{2.37}$$

Let

$$\varepsilon = \frac{K_0 B}{K_5 A}, \quad and \quad q = \frac{2K_3K_4}{K_2K_5}$$

$$\varepsilon \frac{dx}{d\tau} = qy - xy + x - x^2 \tag{2.38}$$

$$\varepsilon \frac{dx}{d\tau} = qy - xy + x(1-x) \tag{2.39}$$

Differentiating equation (2.29) with respect to t on both sides of the equation

$$\frac{dY}{dt} = \frac{K_5 A}{K_2} \frac{dy}{dt} \tag{2.40}$$

Combining equations (2.34) and (2.40) we have

$$\frac{dY}{dt} = \frac{K_0 K_5 BA}{K_2} \frac{dy}{d\tau} \tag{2.41}$$

Putting equations (2.38), (2.29), (2.30) and (2.41) into equation (2.25) we have

$$\frac{K_0 K_5 BA}{K_2} \frac{dy}{d\tau} = -\frac{K_2 A y K_5 A}{K_2} - \frac{K_2 x y K_5 A K_5 A}{2K_4 K_2} + \frac{1}{2} f K_0 B Z \frac{(K_5 A)^2}{K_4 K_0 B} \tag{2.42}$$

Doing a little algebra we have

$$\frac{2K_0 K_4 B}{K_2 K_5 A} \frac{dy}{d\tau} = -\frac{2K_3 K_4}{K_2 K_5} y - xy + fz \tag{2.43}$$

$$\delta \frac{dy}{dt} = -qy - xy + fz \tag{2.44}$$

Where

$$\delta = \frac{2K_0 K_4 B}{K_2 K_5 A}, \quad and \quad q = \frac{2K_3 K_4}{K_2 K_5}$$

Differentiating equation (2.30) with respect to t on both sides of the equation

$$\frac{dZ}{dt} = \frac{(K_5 A)^2}{K_4 K_0 B} \frac{dz}{dt} \tag{2.45}$$

Combining equations (2.34) and (2.45) we have

$$\frac{dZ}{dt} = \frac{(K_5A)^2}{K_4}\frac{dz}{d\tau} \tag{2.46}$$

Putting equations (2.28), (2.30) and (2.46) into equation (2.26) we have

$$\frac{(K_5A)^2}{K_4}\frac{dz}{d\tau} = \frac{2K_5AxK_5A}{2K_4} - \frac{K_0BZ(K_5A)^2}{K_4K_0B} \tag{2.47}$$

Doing a little algebra, we have

$$\frac{dz}{d\tau} = x - z \tag{2.48}$$

Putting equations (2.39), (2.44) and (2.48) together we have

$$\varepsilon\frac{dx}{d\tau} = qy - xy + x(1-x) \tag{2.49}$$

$$\delta\frac{dy}{dt} = -qy - xy + fz \tag{2.50}$$

$$\frac{dz}{d\tau} = x - z \tag{2.51}$$

Equations (2.49), (2.50) and (2.51) becomes

$$\frac{dx}{d\tau} = \frac{1}{\varepsilon}(qy - xy + x(1-x)) \tag{2.52}$$

$$\frac{dy}{dt} = \frac{1}{\delta}(-qy - xy + fz) \tag{2.53}$$

$$\frac{dz}{d\tau} = x - z \tag{2.54}$$

respectively

Table 2.5: **Initial Concentrations**

Species	Initial concentration
hypobromous acid	0.3M
bromide	0.05M
cerium-4	0.004M

The maximum time considered was 40 seconds.

$f = \frac{2}{3}$ and it is the stoichiometric factor

The oscillatory nature of the diagrams below shows a system of this sort oscillates.

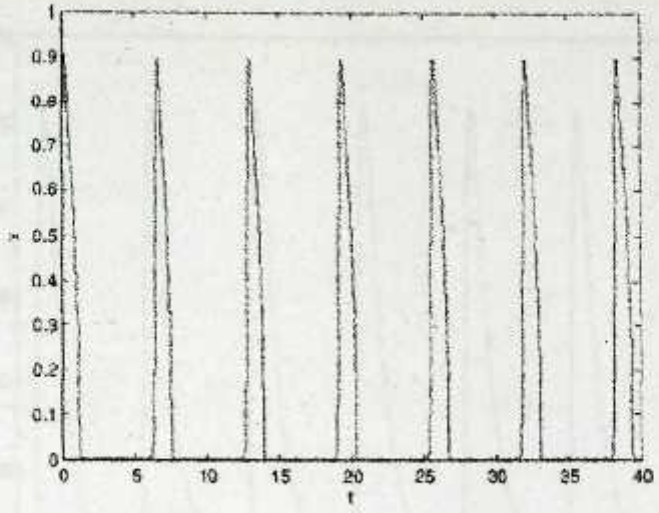


Figure 2.1: The dimensionless time-state for hypobromous acid

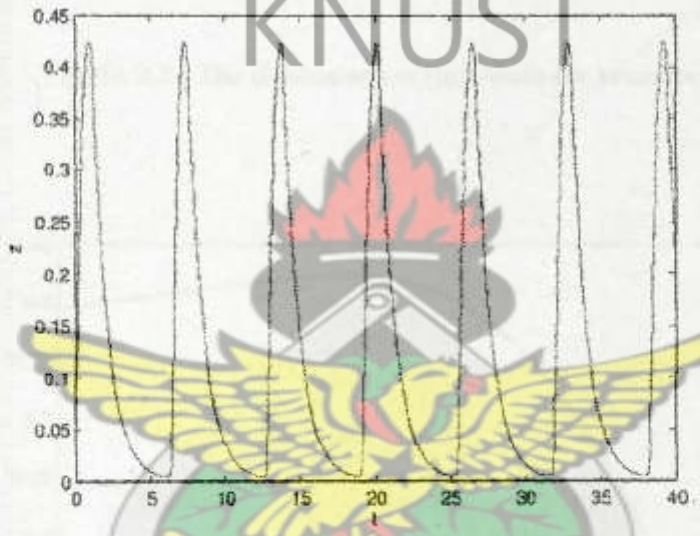


Figure 2.2: The dimensionless time-state for cerium-4

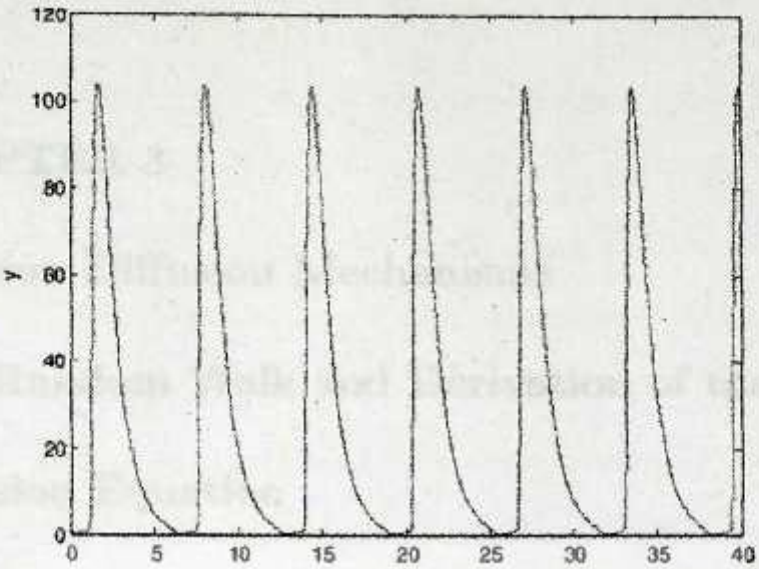


Figure 2.3: The dimensionless time-state for bromide

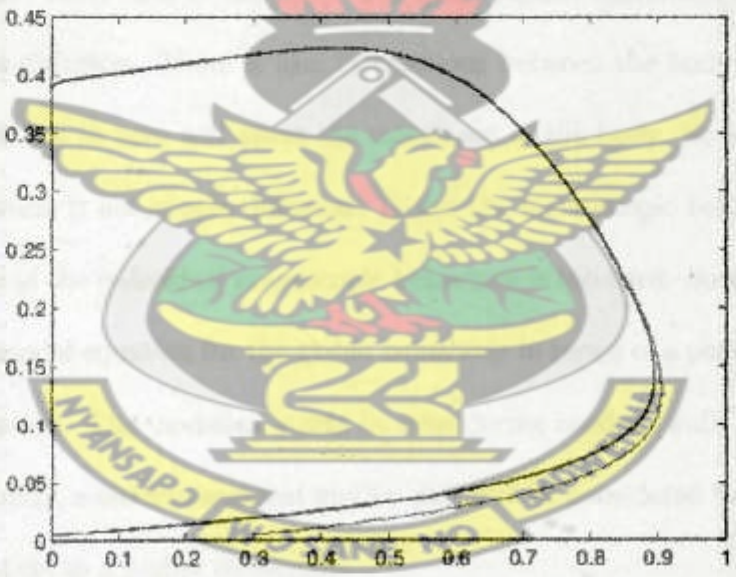


Figure 2.4: The dimensionless time-state for cerium-4 and hypobromous acid

CHAPTER 3

Reaction Diffusion Mechanisms

3.1 Random Walk and Derivation of the Diffusion Equation

Bodies such as cells, bacteria, chemicals, animals etc usually move around in a random way. The various particles are composed of individual thinner particles. These thinner particles move irregular about and their movement result in the overall regular movement of the body. The gross regular movement of the body is termed as diffusion. There is also interactions between the body and its environment which in turn will affect the movement of the body. So actually, the gross movement is not simple diffusion. To get the macroscopic behaviour from a knowledge of the individual microscopic behaviour is too hard. So we derived a continuum model equation for the global behaviour in terms of a particle density or concentration. The modeling starts by considering random walk which deals with probability, a one-dimensional motion case will be considered first and then a generalisation to a higher dimension.

Suppose a particle moves randomly back and forward along a line in a fixed steps Δx that are taken in a fixed time Δt. If the motion is unbiased then it has equal probability to take a step to the right or left. After time $N\Delta t$, the particle

can be anywhere from $-N\triangle x$ to $N\triangle x$. If the starting point of the particle is taken to be the origin, the spatial distribution is clearly not going to be uniform if we release a group of particle about $x = 0$. Since the probability of a particle reaching $x = N\triangle x$ after N steps is very small compared with that for x nearer $x = 0$ we want the probability p(m,n) that particle reaches a point m space steps to the right (that is $x = m\triangle x$) after n time steps (that is after a time $t = n\triangle t$).

Let us suppose that to reach $m\triangle x$ it has moved a step to the right and b to the left. Then $m = a - b$ and $a + b = n$

From these we have $a = \frac{n+m}{2}$ and $b = n - a$

The number of possible paths that a particle can reach this point $x = m\triangle x$ is

$$\frac{n!}{a!b!} = \frac{n!}{a!(n-a)!} = C_a^n$$

where C_a^n is a binomial coefficient.The total number of possible n-steps path is 2^n. The probabilty p(m,n) of the particle reaching the point $x = m\triangle x$ is

$$p(m,n) = \frac{1}{2^n}\frac{n!}{a!(n-a)!} \tag{3.1}$$

where $a = \frac{n+m}{2}$ We also consider the Stirling's formula when n becomes large

$$n! \sim (2\pi n)^{\frac{1}{2}} n^n e^{-n} \tag{3.2}$$

as $n \to \infty$ Putting equation(3.2) into equation(3.1) we have

$$p(m,n) = [\frac{2}{\pi n}]^{\frac{1}{2}} exp[\frac{-m^2}{2n}] \quad m \gg 1, n \gg 1 \tag{3.3}$$

which is the normal or Gaussian probability distribution

Now we consider $m\triangle x = x$ and $n\triangle t = t$

where x and t are space and time variables respectively.

If we let $m \to \infty, n \to \infty$.

Then $\triangle x \to 0$ and $\triangle t \to 0$ which means x and t are finite. It is not appropriate to have p(m,n) as the quantity of interest since the probability must tend to zero. The relevant dependent variable is more appropriate if we divides p(m,n) by $2\triangle x$ Let

$$u(x,t) = \frac{p(m,n)}{2\triangle x}$$

$$m = \frac{x}{\triangle x}, \quad n = \frac{t}{\triangle x} \tag{3.4}$$

$$p(m,n) = [\frac{2}{\pi n}]^{\frac{1}{2}} exp[\frac{-m^2}{2n}] \quad m \gg 1, n \gg 1 \tag{3.5}$$

Putting equation(3.4) into equation(3.3) we have

$$u(x,t) = \frac{p(m,n)}{2\triangle x} = \frac{[\frac{2}{\pi(\frac{t}{\triangle x})}]}{2\triangle x}$$

where D is the diffusion coefficient or diffusivity of the particles. It has dimensions $(length)^2/(time)$. It is a mensure of how efficiently the particles disperse from a high to a low density. For example in blood,haemoglobin molecules have a diffusion coefficient of the order of $10^{-7}cm^2sec^{-1}$ while that for oxygen in blood is of the order of $10^{-5}cm^2sec^{-1}$.

We now relate the result above to the classical approach to diffusion. We look at the Fickian diffusion which states that the flux, J of material, which can be cells, amount of chemical, number of animals is proportional to the gradient of the concentration of the material.

$$J \propto -\nabla c$$

$$J = -D\nabla c$$

In one dimension, we have

$$J = -D\frac{\partial c}{\partial x} \tag{3.6}$$

where c(x,t) is the concentration of the species and D is the diffusion coefficient. The minus sign simply indicates that diffusion transports matter from a high to a low concentration.

We also consider the general conservation equation which says that the rate of change of the amount of material in a region is equal to the rate of flow across the boundary plus any that is created within the boundary. If the region is $x_0 < x < x_1$ and no material is created,

$$\frac{\partial}{\partial t}\int_x c(x,t)dt = J(x_0,t) - J(x_1,t)$$

$$\int_x \frac{\partial}{\partial t}c(,t)dt = J(x_0,t) - J(x_1,t) \tag{3.7}$$

We take $x_1 = x_0 + \Delta x$ and take the limit as $\Delta x \to 0$ and differentiate equation(3.7) with respect to x. We have

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} \tag{3.8}$$

We now put equation(3.6) into equation(3.8)

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \tag{3.9}$$

where D is the diffusion coefficient.

3.2 Reaction Diffusion Equation

Let S be an arbitrary surface enclosing a volume V. The general conservation equation says that the rate of change of the amount of material in V is equal to the rate of flow of material across S into V plus the material created in V.

Thus

$$\frac{\partial}{\partial t}\int_V c(x,t).dV = -\int_S J.dS + \int_V f.dV \tag{3.10}$$

where J is the flux of material and f represents the source and is a function of (c,x,t). Applying the divergence theorem to the surface integral, we have

$$\int_V \tfrac{\partial}{\partial t}c(x,t)dV = -\int_V \nabla.JdV + \int_V f.dV$$

$$\int_V [\tfrac{\partial}{\partial}c(x,t) + \nabla.J - f]dV = 0$$

Differentiating with respect to V, we have

$$\tfrac{\partial}{\partial t}c(x,t) + \nabla.J - f = 0$$

$$\frac{\partial c}{\partial t} = f - \nabla.J \tag{3.11}$$

Putting equation (3.6) into equation(3.11) we have

$$\frac{\partial c}{\partial t} = f + \nabla(D\nabla.C) \tag{3.12}$$

where D is a function of x and c and f is a function of (c,x,t).

For example the source term f in an ecological context could represent the birth-death process.

With logistic population growth $f = rn(1 - \frac{n}{k})$, where r is the linear reproduction rate, n is the population density and k is the carrying capacity of the environment. The resulting equation will be

$$\frac{\partial n}{\partial t} = rn(1 - \frac{n}{k}) + D\nabla^2 n \tag{3.13}$$

where D is constant

The equation above is known as the Fisher Equation.

We further generalise equation (3.13) to the situation in which there are several interactions among species or chemicals.

$$\frac{\partial u}{\partial t} = f + \nabla.(D\nabla u) \tag{3.14}$$

where now D is a matrix of the diffusivities and ∇u is a tensor so $\nabla.(D\nabla u)$ is a vector.

Equation (3.14) is the reaction diffusion system

CHAPTER 4

Approximation Model

4.1 Derivation of the Approximation Model

Morphogenesis is part of developmental biology which controls cell growth and cellular differentiation. It is concerned with the shapes of tissues, organs and entire organisms and the positions of the various specialized cell types. Cell growth and differentiation can take place in cell culture or inside the tumor cell masses without the normal morphogenesis that is seen in an intact organism. The study of morphogenesis involves an attempt to understand the processes that control the organized spatial distribution of cells that arises during the embryonic development of an organism and that give rise to the characteristic forms of tissues, organs and overall body anatomy. In the human embryo, the change from a cluster of nearly identical cells at the blastula stage to a post-gastrulation embryo with structured tissues and organs is controlled by the genetic and can also be used to describe the development of unicellular life forms that do not have an embryonic stage in their life cycle or to refer to the evolution of a body structure within a taxonomic group.

Morphogenetic responses may be induced in organisms by hormones or by environmental chemicals ranging from substances produced by other organisms

to toxic chemicals or radionuclides released as pollutants. Development of spatial pattern and formation is one of the central issues in embryology. The formation of structure in embryology is known as morphogenesis. Pattern generation models are generally grouped together as morphogenetic models. These models provide the embryologist with possible scenarios as to how pattern is laid down and how the embryonic form might be created. Although, genes play a crucial role in the control of pattern formation, genetics say nothing about the actual mechanism involved or how the vast range of pattern and form that we see evolve from a homogeneous mass of dividing cells.

There are two views of pattern generation

1. Chemical pre-pattern approach
2. Mechanochemical approach

The mechanochemical approach of modeling pattern formation, will be considered. Also the role that mechanical forces play in the process of morphogenetic pattern formation wil be looked into. The two approaches are basically different.

In the chemical pre-pattern approach, pattern formation and morphogenesis take place one after the other. First, the chemical concentration pattern is laid down, the cells interpret this pre-pattern and differentiate accordingly. So in this approach, morphogenesis is essentially a slave process which is determined once the chemical pattern has been established. Mechanical shaping of form which occurs during embryogenesis is not addressed in the chemical theory of morphogenesis. The elusiveness of these chemical morphogens is proving a considerable

drawback in the acceptance of such a theory of morphogenesis. There is however, on doubt that chemical plays a crucial role in development.

In the mechanochemical approach, pattern formation and morphogenesis go on simultaneously as a single process. Here, the chemical patterning and the form-shaping movements of the cells and the embryological tissue interact continuosly to produce the observed spatial pattern. Another important aspect of this approach is that the models associated with it are formulated in terms of measurable quantities such as cell densities, forces, tissue deformation, chemical gradient etc. This focuses attention on the morphogenetic process itself and in principle is more amenable to experimental investigation. The principal use of any theory is its predictions and even though each theory might be able to create similar patterns, they are mainly distinguished by the different experiments they suggest.

The advantage of the simultaneous development is its ability for self-correction. Embryonic development is usually a very stable process with the embryo capable of adjusting to many outside disturbances. The process whereby a pre-pattern exists and then morphogenesis takes place is effectively an open loop system. These are potentially unstable processes which make it difficult for the embryo to make the necessary adjustment to such disturbances as development proceeds.

The model has three field variables

1. $n(x,t)$ =density of mesenchymal cells at position x at time t
2. $\rho(x,t)$ =density of extracellular matrix(ECM) at position x at time t
3. $u(x,t)$ =displacement at time t of a material point of the ECM initially at x

The model consists of motile cells immigrating through an elastic medium. The elastic medium is known as extracellular matrix(ECM). As the motile cells move through the elastic medium, the motile cells exert force on the elastic medium. This traction forces of the motile cell deforms the extracellular medium. As the elastic medium deforms, it induces an isotropy which affects the movement of the motile cells. The Mathematical model for these movement and traction forces consists of the following equations.

1. The cell density
2. The mechanical balance of forces between the cell traction and the matrix.
3. The balance law governing the matrix material

We starts the model with the cell density equation

4.2 The Cell Density Equation

Let n(x,t) be cell density function at time t per unit volume at position x. This cell density equation is modeled by making use of the conservation law.

Conservation law states that a particular mesurable property of an isolated physical system does not change as the system evolves.

Using the conservation law we equate the rate of change of the cell density at x to the various terms which affects the cell movement through the extracellular matrix. The Mathematical form of this is

$$\frac{\partial n}{\partial t} = -\nabla . J + M \tag{4.1}$$

where J is the flux of cells per unit area and M is the mitotic rate. Mitosis is the division of cells.

4.2.1 Random Dispersal

As the motile moves through the extracellualr matrix it exhibit a random movement or diffuse and it is termed random dispersal. The random dispersal term has two components.

1. Local or short random motion
2. Nonlocal or long range random motion

The local or short range random motion

If the mesenchymal cels simply move or diffuse in a homogeneous isotropic matrix then according to Fick's Law the flux is given as

$$J = -D\nabla n$$

Where D is the diffusion coefficient of the mesenchymal cells in the medium. If D is a constant then this term in the conservation equation has the usual Laplacian form: $D\nabla^2 n$. The Laplacian operator is the difference between the value of the density function $n(x,t)$ at position x and its local average.

The Non-local or long range random motion

Mesenchymal cells are quite densely packed. The mesenchymal cells possess long filopodia which extend beyond their nearest neighbours. Which means they can sense and respond to conditions beyond their immediate neighbourhood. A cell which can sample their environment will respond not only to the local value of the concentration gradient but also to the average value, that is n_{av} in that neighbourhood. As the cell responds to the non-local in their neighbourhood, a time will come that the non-local will have major influence in their behavior. If this happens then we must augment this situation by adding an additional term which is called harmonic diffusion. $D_2\nabla(\nabla^2 .n)$

There are several ways of modeling long range interactions. Cohen and Murray in 1980 modeled a population system by using a Landau-Ginzberg approach in which spatial gradient contributes to the interaction energy. Biharmonic diffusion was added to the equation(4.1). The flux expression appropriate for diffusing objects which responds to local average and non-local average of the concentration gradient is given by

$$J = -D_1\nabla n + D_2\nabla(\nabla^2 n) \tag{4.2}$$

where D_1 is the harmonic diffusion coefficient for the local or short range effect in the random dispersal.

D_2 is the biharmonic diffusion coefficient for the non-local or the long range effect in the random dispersal. The dimension for D_1 is $[(length)]^2/[time]$ and it is a mesure of the short range effect in the random dispersal. The dimension for D_2 is $[(length)]^4/[time]$ and it is a measure of the long range effect in the random dispersal.

4.2.2 Haptotaxis

As the cell moves through the extracellular matrix it exerts force on the path it moves, while exerting force on the surrounding area of the extracellular matrix. This force exerted by the cell deforms the extracellular locally and non locally.

Local Haptotaxis

At the local front as the extracellular matrix deforms it generate gradients in the matrix density $\rho(x,t)$. These density gradients are sites for cell attachment. The cells migrate within an adhesive gradient will tend to move up the gradient. (Gustafson and Wolpert, 1965, 1967). This directionality comes about because of the nature of cell motion. Each side of a cell forms adhesions to the substratum and engages in a tug-of-war. The net displacement occurs in the direction of the side with the strongest pull and the firmest attachments to the substratum. The simplest model for haptotactic transport, assume that the cell flux is proportional to this matrix gradient and to the density cells whose traction are deforming the

matrix. The cell traction coefficient τ is the compressive stress exerted per cell on a unit mass of matrix.

$$J = \alpha n \nabla \rho \tag{4.3}$$

where α is the harmonic diffusion coefficient for the traction on the extracellular matrix locally.

Non-local Haptotaxis

For the non-local traction, as the cell moves through the extracellular matrix it exerts force on the medium and it deforms the extracellular matrix locally and non-locally. That is, it also exerts force on the surroundings of the extracellular matrix. The deformation of the extracellular matrix generate gradient externally in the matrix density. The gradient that are produced serves as a site for cell attachment.

$$J = \alpha \alpha' n \nabla^2 \rho \tag{4.4}$$

where α is the harmonic diffusion coefficient for the traction on the extracellular matrix locally and where α' is the biharmonic diffusion coefficient for the non-local traction on the extracellular matrix.

Putting equations(4.3) and (4.4) together, we have

$$J = \alpha n \nabla \rho + \alpha \alpha' n \nabla^3 \rho \tag{4.5}$$

$$J = \alpha n \nabla (\rho + \alpha' \nabla^2 \rho) \tag{4.6}$$

4.2.3 Convection

As the cell migrate through the extracellular matrix, it exerts force on the medium and the medium also exerts equal and opposite force on the cell. As this goes on the cell moves passively on the extracellular matrix and we have convection. Convection is the product of the cell density(n) and the local matrix velocity $(\frac{\partial u}{\partial t})$

$$J = n(\frac{\partial u}{\partial t}) \tag{4.7}$$

Putting equations (4.2), (4.6) and (4.7) together, we have

$$J = -D_1\nabla n + D_2\nabla(\nabla^2 n) + \alpha n\nabla[\rho + \alpha'\nabla^2\rho] + n(\frac{\partial u}{\partial t}) \tag{4.8}$$

$$J = -D_1\nabla n + D_2\nabla^3 n + \alpha[n\nabla\rho + \alpha' n\nabla(\nabla^2\rho)] + n(\frac{\partial u}{\partial t}) \tag{4.9}$$

But

$$\frac{\partial n}{\partial t} = -\nabla.J + M$$

Therefore putting equation (4.9) into equation (4.2), we have

$$\frac{\partial n}{\partial t} = -\nabla(-D_1\nabla n + D_2\nabla^3 n + \alpha[n\nabla\rho + \alpha' n\nabla(\nabla^2\rho)] + (\frac{\partial u}{\partial t}) + M \tag{4.10}$$

$$\frac{\partial n}{\partial t} = D_1\nabla^2 n - D_2\nabla^4 - \alpha\nabla[n\nabla\rho + \alpha' n\nabla(\nabla^2\rho)] - \nabla n(\frac{\partial u}{\partial t}) + M \tag{4.11}$$

4.2.4 Mitosis

Mitosis is the division of cells and because of this we represent this term by the logistic growth model. Where the growth rate is r and the maximum density is N. Folkman and Mascona (1978) showed that the mitotic rate dependence on the cell shape. Therefore in our modele the mitotic rate will depend on the displacement u. So the growth of the cells is formulated as

$$M = rn(N - n) \tag{4.12}$$

where r is the growth rate and N is the carry capacity or the maximum density. Putting equation (4.12) into equation (4.11)

Our model for the cell equation becomes

$$\frac{\partial n}{\partial t} = D_1\nabla^2 n - D_2\nabla^4 - \alpha\nabla[n\nabla\rho + \alpha' n\nabla(\nabla^2\rho)] - \nabla n(\frac{\partial u}{\partial t}) + rn(N - n) \tag{4.13}$$

We assume that the maximum density to be 1 that is $N = 1$

Then we have

$$\frac{\partial n}{\partial t} = D_1\nabla^2 n - D_2\nabla^4 - \alpha\nabla[n\nabla\rho + \alpha' n\nabla(\nabla^2\rho)] - \nabla n(\frac{\partial u}{\partial t}) + rn(1 - n) \tag{4.14}$$

$$\frac{\partial n}{\partial t} - D_1\nabla^2 n + D_2\nabla^4 + \alpha\nabla[n\nabla\rho + \alpha' n\nabla(\nabla^2\rho)] + \nabla n(\frac{\partial u}{\partial t}) - rn(1 - n) = 0 \tag{4.15}$$

4.3 Cell-Matrix Interaction

The extracellular matrix in which the cells migrate is compose of complex fibrous. The fibrous of the extracellular matrix changes as the cell moves through it. We are only interested in the mechanical interaction between the cells and the extracellular matrix. We first assume that the extracellular matrix will be modeled to first order and also because of the fluid nature of the extracellular matrix and the traction, we also assume isotropic viscoelastic continuum. The time scale for the embryonic motions is very long hours and the spatial scale is very small that is millimeters. So we consider very low Reynolds number (Purcell, 1977, Odell, et al, 1981). We assume the traction produced by the cells are in equilibrium with the restoring forces exerted by the extracellular matrix.

The equilibrium equation is given by the composite material[cells+matrix]. We also modify the expression for the viscoelastic stress tensor (Landau and Lifshitz, 1970)

$$\sigma = [\mu_1 \frac{\partial \varepsilon}{\partial t} + \mu_2 \frac{\partial \theta}{\partial t} I] + [\frac{E}{1+\nu}(\varepsilon + \frac{\nu}{1-2\nu}\theta I)] \tag{4.16}$$

where $\theta = \nabla . u$ is the dilation of the matrix material,

μ_1 is the shear viscosity,

μ_2 is the bulk viscosity,

E is the Young's modulus,

ν is the Poisson ratio,

I is the unit tensor,

We modify the above constitutive relation to account for the following

1. The fibrous nature of the extracellular matrix
2. The effects of the external forces on the system
3. The cell traction to the elastic properties

4.3.1 Stress Alignment

The extracellular matrix is isotropic in the absence of cell tractions, so in the presence of cell traction the extracellular matrix can no longer be modeled by a 2-parameter isotropic constitutive relation like the Hooke's law. For example, when a fibrous material is strained the fibers tend to align in the directions of the principal stresses and the effective elastic modulus in the direction of strain increases. Since an initially isotropic material when strained is no longer isotropic and so equation(4.16) cannot be use in the modeling. However, we shall for mathematical simplicity, eschew a more complex constitutive relation for the extracellular matrix and proceed with the following approximation. The principle macroscopic effect of fiber alignment is to strengthen the material in the direction of the strain. Thus we can incorporate some aspects of fiber alignment by making the elastic modulus an increasing function of the dilation θ. This is, of course an approximation to a constitutive relation that has a separate elastic constants in each principle direction (cf, Christiansen, 1979). We emphasize that this may be, but one representative effect of matrix nonlinearities which influence cell behavior. Nevertheless we shall proceed with the 2-parmeter description

of the extracellular matrix and model the elastic behavior of the extracellular matrix. The effect of fiber alignment in the extracellular matrix is to stiffen the material as it is strained. Therefore the stress-strain behavior can be modeled. The effective elastic modulus (the slope of the curve) increases as the material is stretched ($\varepsilon > 0$), until the yield point is reached where upon the curve levels off and falls as the fibers commence to tear. The extracellular matrix is very weak in compression,however eventually the composite material [cells+matrix] is in compressible and so the curve must drop off to $-\infty$ as $\varepsilon \to -1$. All this goes on at the local front and we have

$$\frac{E(\theta)}{1+\nu}(\varepsilon + \nu'\theta I) \tag{4.17}$$

where

$$\nu' = \frac{\nu}{1-2\nu}$$

Then at the nonlocal front the fibrous materials are charaterised by nonlocal elastic interactions. This is because the fibers can transmit stress between matrix nodes which are quite far apart. Thus the stress at a point is a function of the strain averaged over a region on the order of an internodal fiber length. By an argument identical to that which led to the biharmonic diffusion term we can alter the local law to include nonlocal effects.

$$\varepsilon \to \varepsilon + \beta_1 \nabla^2 \varepsilon \tag{4.18}$$

$$\nu'\theta I \to \nu'\theta I + \nu'\beta_2 \nabla^2 \theta I \tag{4.19}$$

Putting equations (4.18) and (4.19) into equation (4.17), we have

$$\frac{E(\theta)}{1+\nu}[\varepsilon + \beta_1\nabla^2\varepsilon + \nu'\theta I + \nu'\beta_2\nabla^2\theta I] \tag{4.20}$$

$$\frac{E(\theta)}{1+\nu}[\varepsilon + \beta_1\nabla^2\varepsilon + \nu'(\theta I + \beta_2\nabla^2\theta)I] \tag{4.21}$$

where

$$\nu' = \frac{\nu}{1-2\nu} \quad \text{and} \quad \beta_1 < 0, \beta_2 < 0$$

However, since the distance between the nodes of the extracellular matrix is much less than a typical cell diameter the nonlocal effects of fiber elasticity are probably small. So we assume that $\beta_1 = 0$ and $\beta_2 = 0$

Then we have

$$\frac{E(\theta)}{1+\nu}(\varepsilon + \nu'\theta I) \tag{4.22}$$

where

$$\nu' = \frac{\nu}{1-2\nu}$$

4.3.2 Cell Tractions

The contribution of the cell tractions to the stress tensor can be modeled by assuming that the force generated per cell per unit mass of matrix is a saturating function of cell density

$$\tau(n) = \frac{\tau}{1+\lambda n^2}$$

where τ, λ are both positive, so that the contribution of cell tractions to the stress tensor is

$$\sigma_{cell} = [\frac{\tau \rho n}{1+\lambda n^2}]I \tag{4.23}$$

where $\tau[dyne - cm/gm]$ is characteristic of the cell types. Typical experimental values for τ are in the $range = 10^{-3}$dyne/μm of cell edge-a-sizeable force (Harris et al,1981). If the filopodia with which cells attach to the extracellular matrix extend beyond nearest neighbours then it is reasonable to include a nonlocal effect.

$$\sigma_{cell} = [\frac{\tau}{1+\lambda n^2}]\rho(n + \gamma\nabla^2 n)I \tag{4.24}$$

where $\gamma > 0$ measures the magnitude of the long range cell interactions

Equation (4.25) applies to the situation where cells interact with one another via filopodia which may extend further than nearest neighbours, this is typical in chondrogenic condensations. In other situation, where the cells are more loosely packed, the nonlocal effect is primarily between cells and the extracellular matrix. So we ignore the interaction between cells and consider the interaction of cells and the extracellular matrix.

$$\sigma_{cell} = [\frac{\tau}{1+\lambda n^2}]n(\rho + \beta\nabla^2\rho)I \tag{4.25}$$

where $\beta > 0$ measures the magnitude of the long range interactions between the cells and the extracellular matrix.

Putting equation(4.16), (4.22) and (4.26) together, we have the force been exerted by the cells as they move through the medium is

$$\nabla([\mu_1\frac{\partial\varepsilon}{\partial t}+\mu_2\frac{\partial\theta}{\partial t}I]+[\frac{E}{1+\nu}(\varepsilon+\frac{\nu}{1-2\nu}\theta I)]+[\frac{\tau}{1+\lambda n^2}]n(\rho+\beta\nabla^2\rho)I \quad (4.26)$$

4.3.3 Body Forces

The cell and the matrix material is generally attached elastically to an external substratum, usually an epithelial layer. As this goes on there is a body force that is produced. The body force is proportional to the displacement of the matrix material from its unstrained position.

$$F \propto u\rho$$

$$F = su\rho \quad (4.27)$$

where s is the elastic constant characterising the substratum to which the extracellular matrix is attached.

Using the Newton third law of motion that states that action and reaction are equal and opposite.

We have

$$\nabla([\mu_1\frac{\partial\varepsilon}{\partial t}+\mu_2\frac{\partial\theta}{\partial t}I]+[\frac{E}{1+\nu}(\varepsilon+\frac{\nu}{1-2\nu}\theta I)]+[\frac{\tau}{1+\lambda n^2}]n(\rho+\beta\nabla^2\rho)I=su\rho$$

$$\nabla([\mu_1\frac{\partial\varepsilon}{\partial t}+\mu_2\frac{\partial\theta}{\partial t}I]+[\frac{E}{1+\nu}(\varepsilon+\frac{\nu}{1-2\nu}\theta I)]+[\frac{\tau}{1+\lambda n^2}]n(\rho+\beta\nabla^2\rho)I-su\rho=0 \tag{4.28}$$

4.4 Matrix Density Equation

The conservation equation for the matrix material $\rho(x,t)$ is

$$\frac{\partial\rho}{\partial t}=-\nabla J+S(n,u,\rho) \tag{4.29}$$

where S is the secretion rate of matrix material by the cells. Secretion and degradation of matrix material is thought to play an important role in mesenchymal cell organisation.

J is the flux of the matrix material per unit area. As the cells move through the medium,the cells will exert force on the medium which will deform the medium, but the medium will react to this force by also exerting equal and opposite force on the cell. As this goes on the energy that comes out is the convection energy. Convection energy is the tansfer of heat energy through a gas or liquid by movement of currents. The convection on the matrix material is simply the product of the matrix density (ρ) and the local matrix velocity ($\frac{\partial u}{\partial t}$). As the exchange of forces goes on, the matrix material will move from one point to another and actually you can find the velocity as the distance move with respect to time.

$$J = \rho(\frac{\partial u}{\partial t}) \tag{4.30}$$

Putting equation (4.31) into (4.30), we have

$$\frac{\partial \rho}{\partial t} = -\nabla\rho(\frac{\partial u}{\partial t}) + S(n, u, \rho) \tag{4.31}$$

As this goes on, the matix material will secret a liquid substance and this liquid sunstance at a time will affect the movement of the matrix material itself. The rate of secretion of liquid substance in plants is higher than that in animals. The model we are looking at is considering the medium as the one in animal. So we ignore the secretion rate by setting $S = 0$

$$\frac{\partial \rho}{\partial t} = -\nabla\rho(\frac{\partial u}{\partial t}) \tag{4.32}$$

$$\frac{\partial \rho}{\partial t} + \nabla\rho(\frac{\partial u}{\partial t}) = 0 \tag{4.33}$$

Putting equations (4.15), (4.29) and (4.34) together.

We have our approximation model

$$\frac{\partial n}{\partial t} - D_1\nabla^2 n - D_2\nabla^4 + \alpha\nabla[n\nabla\rho + \alpha' n\nabla(\nabla^2\rho)] + \nabla n(\frac{\partial u}{\partial t}) - rn(1-n) \tag{4.34}$$

$$\nabla([\mu_1\frac{\partial \varepsilon}{\partial t} + \mu_2\frac{\partial \theta}{\partial t}I] + [\frac{E}{1+\nu}(\varepsilon + \frac{\nu}{1-2\nu}\theta I)] + [\frac{\tau}{1+\lambda n^2}]n(\rho + \beta\nabla^2\rho)I - su\rho = 0 \tag{4.35}$$

$$\frac{\partial \rho}{\partial t} + \nabla\rho(\frac{\partial u}{\partial t}) = 0 \tag{4.36}$$

Dimensionaless Equations

In order to examine the importance of the various effects and to deal with limiting conditions as one of the parameters tend to zeros. We nondimensionalize the model equations with a general length scale L and time T.

We define the following dimensionless parameters:

$$x^* = x/L \qquad D_2^* = D_2 T/L^4$$

$$t^* = t/T \qquad D_1^* = D_1 T/L^2$$

$$u^* = u/L \qquad \alpha^* = \alpha\rho_0 T/L^2$$

$$\nabla^* = L\nabla \qquad r^* = rNT$$

$$\theta^* = \theta\nabla \qquad \mu_i = \mu_i(1+\nu)/ET, i = 1,2$$

$$\varepsilon^* = \varepsilon \qquad \tau^* \tau\rho_0 N(1+\nu)/E$$

$$\rho^* = \rho/\rho_0 \qquad s^* = 2s\rho_0 L^2(1+\nu)/E$$

$$n^* = n/N \qquad E^* = E$$

$$\gamma^* = \gamma/L^2 \qquad \lambda^* = \lambda N^2$$

$$\alpha^{*'} = \alpha'/L^2 \qquad \beta^* = \beta/L^2$$

where ρ_0 i the initial matrix denstiy. With these definitions the dimensionless system becomes.

4.5 The Approximation Model

$$\frac{\partial n}{\partial t} - D_1\nabla^2 n - D_2\nabla^4 + \alpha\nabla[n\nabla\rho + \alpha' n\nabla(\nabla^2\rho)] + \nabla n(\frac{\partial u}{\partial t}) - rn(1-n) \quad (4.37)$$

$$\nabla([\mu_1\frac{\partial \varepsilon}{\partial t} + \mu_2\frac{\partial \theta}{\partial t}I] + [\frac{E}{1+\nu}(\varepsilon + \frac{\nu}{1-2\nu}\theta I)] + [\frac{\tau}{1+\lambda n^2}]n(\rho + \beta\nabla^2\rho)I - su\rho = 0 \quad (4.38)$$

$$\frac{\partial \rho}{\partial t} + \nabla\rho(\frac{\partial u}{\partial t}) = 0 \quad (4.39)$$

where E is the Young's modulus

μ_1 and μ_2 are the shear and bulk viscosities respectively

ν is the Poisson ratio, it measures the transverse compression of the matrix when it is stretched.

I is the unit tensor

$\varepsilon = (\nabla u + \nabla u^T)/2$ is the linear strain tensor

$\theta = \nabla.u$ is the dilation

E measures the passive elastic modulus of the matrix

The function τ is the traction gencrated by the motile cells.

D_1, D_2 are the diffusion coefficients

α, α' are the haptotactic coefficients

r is a constant related to the maximum mitotic rate

N is the maximum cell density

s is an elastic parameter characterising the extracellular matrix attachments to the cells.

β is the long range traction effect.

4.6 Model Analysis

Steady State Analysis

The stationary states of the system are

1. $n = 0, \quad u = 0, \quad \rho = 0$

2. $n = 1, \quad u = 0, \quad \rho = 1$

Assumptions

We set $r > 0, n \equiv n - 1, \rho \equiv \rho - 1, \rho = 1, n = 1, \theta = \nabla.u$

Putting the assumptions into the system, we have

$$\frac{\partial n}{\partial t} - D_1\nabla^2 n + D_2\nabla^4 n + \alpha\nabla^2\rho + \alpha\alpha'\nabla^4\rho + \nabla\frac{\partial u}{\partial t} + rn = 0 \tag{4.40}$$

$$\nabla.([\mu_1\frac{\partial \varepsilon}{\partial t} + \mu_2\nabla\frac{\partial u}{\partial t}I] + \frac{E}{1+\nu}(\varepsilon + \frac{\nu}{1-2\nu}\nabla.uI) + (\frac{\tau}{1+\lambda}\rho + \frac{\tau}{1+\lambda}n + \frac{\tau}{1+\lambda}\beta\nabla^2\rho)I) - su = 0 \tag{4.41}$$

$$\frac{\partial \rho}{\partial t} + \nabla\frac{\partial u}{\partial t} = 0 \tag{4.42}$$

To determine what spatial patterns might arise as a result of the cell movement and extracellular matrix deformation. We first consider the model in one dimension.

$$\frac{\partial n}{\partial t} - D_1\frac{\partial^2 n}{\partial x^2} + D_2\frac{\partial^4 n}{\partial x^4} + \alpha\frac{\partial^2\rho}{\partial x^2} + \alpha\alpha'\frac{\partial^4\rho}{\partial x^4} + \frac{\partial^2 u}{\partial x\partial t} + rn = 0 \tag{4.43}$$

$$\mu_1\frac{\partial^2\varepsilon}{\partial x\partial t}+\mu_2\frac{\partial^3 u}{\partial x^2\partial t}+\frac{\partial\varepsilon}{\partial x}+\frac{\nu}{1-2\nu}\frac{\partial^2 u}{\partial x^2}+\frac{\tau}{1+\lambda}\frac{\partial n}{\partial x}+\frac{\tau}{1+\lambda}\frac{\partial\rho}{\partial x}+\frac{\tau}{1+\lambda}\beta\frac{\partial^3\rho}{\partial x^3}-su=0 \tag{4.44}$$

$$\frac{\partial\rho}{\partial t}+\frac{\partial^2 u}{\partial x\partial t}=0 \tag{4.45}$$

4.6.1 Linear Analysis

$$F=\frac{\partial n}{\partial t}-D_1\frac{\partial^2 n}{\partial x^2}+D_2\frac{\partial^4 n}{\partial x^4}+\alpha\frac{\partial^2\rho}{\partial x^2}+\alpha\alpha'\frac{\partial^4\rho}{\partial x^4}+\frac{\partial^2 u}{\partial x\partial t}+rn \tag{4.46}$$

$$G=\mu_1\frac{\partial^2\varepsilon}{\partial x\partial t}+\mu_2\frac{\partial^3 u}{\partial x^2\partial t}+\frac{\partial\varepsilon}{\partial x}+\frac{\nu}{1-2\nu}\frac{\partial^2 u}{\partial x^2}+\frac{\tau}{1+\lambda}\frac{\partial n}{\partial x}+\frac{\tau}{1+\lambda}\frac{\partial\rho}{\partial x}+\frac{\tau}{1+\lambda}\beta\frac{\partial^3\rho}{\partial x^3}-su \tag{4.47}$$

$$H=\frac{\partial\rho}{\partial t}+\frac{\partial^2 u}{\partial x\partial t} \tag{4.48}$$

The linear stability of the system is study by making n,ρ,u proportional to $exp(\sigma t+ikx)$

$$n\propto e^{(\sigma t+ikx)} \qquad \rho\propto e^{(\sigma t+ikx)} \qquad u\propto e^{(\sigma t+ikx)}$$

$$n=\psi e^{(\sigma t+ikx)} \qquad \rho=\psi e^{(\sigma t+ikx)} \qquad u=\psi e^{(\sigma t+ikx)}$$

where ψ is the constant of proportionality k is the wave vector and σ is the growth rate to obtain the dispersion relation.

We start the linearisation by first considering equation (4.47)

$$F=\frac{\partial n}{\partial t}-D_1\frac{\partial^2 n}{\partial x^2}+D_2\frac{\partial^4 n}{\partial x^4}+\alpha\frac{\partial^2\rho}{\partial x^2}+\alpha\alpha'\frac{\partial^4\rho}{\partial x^4}+\frac{\partial^2 u}{\partial x\partial t}+rn \tag{4.49}$$

We differentiate n with respect to x and t in equation (4.47), holding ρ and u constant.

$$n = \psi e^{(\sigma t + ikx)} \tag{4.50}$$

$$\frac{\partial n}{\partial t} = \sigma \psi e^{(\sigma t + ikx)} \tag{4.51}$$

$$\frac{\partial n}{\partial x} = ik\psi e^{(\sigma t + ikx)} \quad \frac{\partial^2 n}{\partial x^2} = i^2 k^2 \psi e^{(\sigma t + ikx)} = -k^2 \psi e^{(\sigma t + ikx)}$$

Therefore

$$\frac{\partial^2 n}{\partial x^2} = -k^2 \psi e^{(\sigma t + ikx)} \tag{4.52}$$

$$\frac{\partial^3 n}{\partial x^3} = -ik^3 \psi e^{(\sigma t + ikx)}$$

$$\frac{\partial^4 n}{\partial x^4} = -i^2 k^4 \psi e^{(\sigma t + ikx)} = k^4 \psi e^{(\sigma t + ikx)}$$

Therefore

$$\frac{\partial^2 n}{\partial x^2} = k^4 \psi e^{(\sigma t + ikx)} \tag{4.53}$$

Because ρ and u are held constant, if you differentiate them with respect to x or t it will gives you zero.

$$F_n' = \sigma \psi e^{(\sigma t + ikx)} - D_1(-k^2 \psi e^{(\sigma t + ikx)}) + k^4 \psi e^{(\sigma t + ikx)} + r\psi e^{(\sigma t + ikx)}$$

$$F_n = \sigma \psi e^{(\sigma t + ikx)} + D_1(k^2 \psi e^{(\sigma t + ikx)}) + k^4 \psi e^{(\sigma t + ikx)} + r\psi e^{(\sigma t + ikx)}$$

Factorising $\psi e^{(\sigma t + ikx)}$ out,we have

$$F_n = (\sigma + D_1 k^2 + D_2 k^4 + r)\psi e^{(\sigma t + ikx)} \tag{4.54}$$

We differentiate ρ with respect to x and t in the same equation and also holding n and u constant.

$$\rho = \psi e^{(\sigma t + ikx)}$$

$$\frac{\partial \rho}{\partial x} = ik\psi e^{(\sigma t + ikx)}$$

$$\frac{\partial^2 \rho}{\partial x^2} = i^2 k^2 \psi e^{(\sigma t + ikx)} = -k^2 \psi e^{(\sigma t + ikx)}$$

Therefore

$$\frac{\partial^2 \rho}{\partial x^2} = -k^2 \psi e^{(\sigma t + ikx)} \tag{4.55}$$

$$\frac{\partial^3 \rho}{\partial x^3} = -ik^3 \psi e^{(\sigma t + ikx)}$$

$$\frac{\partial^4 \rho}{\partial x^4} = -i^2 k^4 \psi e^{(\sigma t + ikx)} = k^4 \psi e^{(\sigma t + ikx)}$$

Therefore

$$\frac{\partial^4 \rho}{\partial x^4} = k^4 \psi e^{(\sigma t + ikx)} \tag{4.56}$$

Because n and u are held constant, if you differentiate them with respect to x or t it will gives you zero

$$F_\rho = -\alpha k^2 \psi e^{(\sigma t + ikx)} + \alpha\alpha' k^4 \psi e^{(\sigma t + ikx)}$$

Factoring $\psi e^{(\sigma t + ikx)}$ out, we have

$$F'_\rho = (-\alpha k^2 + \alpha\alpha' k^4)\psi e^{(\sigma t + ikx)} \tag{4.57}$$

We differentiate u with respect to x and t in the same equation and hold ρ and n constant.

$$u = \psi e^{(\sigma t + ikx)} \tag{4.58}$$

$$\frac{\partial u}{\partial t} = \sigma \psi e^{(\sigma t + ikx)}$$

$$\frac{\partial^2 u}{\partial x \partial t} = i\sigma \psi e^{(\sigma t + ikx)} \tag{4.59}$$

Because ρ and n are held constant, if you differentiate them with respect to x or t it will gives you zero

$$F_u = i\sigma \psi e^{(\sigma t + ikx)} \tag{4.60}$$

The next equation from the model is

$$G = \mu_1 \frac{\partial^2 \varepsilon}{\partial x \partial t} + \mu_2 \frac{\partial^3 u}{\partial x^2 \partial t} + \frac{\partial \varepsilon}{\partial x} + \frac{\nu}{1-2\nu} \frac{\partial^2 u}{\partial x^2} + \frac{\tau}{1+\lambda} \frac{\partial n}{\partial x} + \frac{\tau}{1+\lambda} \frac{\partial \rho}{\partial x} + \frac{\tau}{1+\lambda} \beta \frac{\partial^3 \rho}{\partial x^3} - su \tag{4.61}$$

We differentiate n with respect to x and t in equation (4.48) and holding ρ and u constant.

$$n = \psi e^{(\sigma t + ikx)}$$

$$\frac{\partial n}{\partial x} = ik\psi e^{(\sigma t + ikx)} \tag{4.62}$$

Because ρ and u are held constant, if you differentiate them with respect to x or t it will gives you zero

$$G_n = i\tau k\psi e^{(\sigma t+ikx)} \tag{4.63}$$

We differentiate ρ with respect to x and t in equation (4.48) and holding n and u constant.

$$\rho = \psi e^{(\sigma t+ikx)}$$

$$\frac{\partial \rho}{\partial x} = ik\psi e^{(\sigma t+ikx)} \tag{4.64}$$

$$\frac{\partial^2 \rho}{\partial x^2} = i^2k^2\psi e^{(\sigma t+ikx)} = -k^2\psi e^{(\sigma t+ikx)}$$

Therefore $\frac{\partial^2 \rho}{\partial x^2} = -k^2\psi e^{(\sigma t+ikx)}$

$$\frac{\partial^3 \rho}{\partial x^3} = -ik^3\psi e^{(\sigma t+ikx)} \tag{4.65}$$

Because n and u are held constan, if you differentiate them with respect to x or t it will give you zero.

$$G_\rho = \frac{\tau}{1+\lambda}ik\psi e^{(\sigma t+ikx)} - \frac{\tau}{1+\lambda}\beta ik^3\psi e^{(\sigma t+ikx)}$$

Factoring $\psi e^{(\sigma t+ikx)}$ out, we have

$$G_\rho = (\frac{\tau}{1+\lambda}ik - \frac{\tau}{1+\lambda}\beta ik^3)\psi e^{(\sigma t+ikx)} \tag{4.66}$$

We differentiate u with respect to x and t in equation (4.48) and holding ρ and n constant.

$$u = \psi e^{(\sigma t+ikx)}$$

$$\frac{\partial u}{\partial x} = ik\psi e^{(\sigma t + ikx)}$$

$$\frac{\partial^2 u}{\partial x^2} = i^2 k^2 \psi e^{(\sigma t + ikx)} = -k^2 \psi e^{(\sigma t + ikx)}$$

Therefore

$$\frac{\partial^2 u}{\partial x^2} = -k^2 \psi e^{(\sigma t + ikx)}$$

$$\frac{\partial u}{\partial t} = \sigma \psi e^{(\sigma t + ikx)}$$

The next equation from the model is

$$\frac{\partial \rho}{\partial t} + \frac{\partial^2 u}{\partial n \partial t} = 0 \tag{4.67}$$

We differentiate n with respect to x and t in equation (4.66) and holding ρ and u constant.

$$n = \psi e^{(\sigma t + ikx)}$$

$$\frac{\partial n}{\partial t} = 0$$

$$H_n = 0 \tag{4.68}$$

We differentiate ρ with respect to x and t in equation (4.66) and holding n and u constant

$$\rho = \psi e^{(\sigma t + ikx)}$$

$$\frac{\partial \rho}{\partial t} = \sigma \psi e^{(\sigma t + ikx)}$$

Because n an u are held constan, if you differentiate them with respect to x or t it will give you zero.

$$H_\rho = \sigma\psi e^{(\sigma t+ikx)} \tag{4.69}$$

We differentiate u with respect to x and t in equation (4.66) and holdingρ and u constant

$$u = \psi e^{(\sigma t+ikx)}$$

$$\frac{\partial u}{\partial t} = \sigma\psi e^{(\sigma t+ikx)}$$

$$\frac{\partial^2 u}{\partial x \partial t} = ik\sigma\psi e^{(\sigma t+ikx)}$$

$$H_u = ik\sigma\psi e^{(\sigma t+ikx)} \tag{4.70}$$

The jacobian matrix

$$\begin{pmatrix} (\sigma+D_1k^2+D_2k^4+r)\psi e^{(\sigma t+ikx)} & (-\alpha k^2+\alpha\alpha' k^4)\psi e^{(\sigma t+ikx)} & i\sigma\psi e^{(\sigma t+ikx)} \\ i\frac{\tau}{1+\lambda}k\psi e^{(\sigma t+ikx)} & (\frac{\tau}{1+\lambda}ik-\frac{\tau}{1+\lambda}\beta ik^3)\psi e^{(\sigma t+ikx)} & (-\mu_2k^2\sigma\psi-\frac{\nu}{1-2\nu}k^2\psi-s\psi)e^{(\sigma t+ikx)} \\ 0 & \sigma\psi e^{(\sigma t+ikx)} & ik\sigma\psi e^{(\sigma t+ikx)} \end{pmatrix}$$

We find the determinant of the jacobian matrix

$$\begin{vmatrix} (\sigma+D_1k^2+D_2k^4+r)\psi e^{(\sigma t+ikx)} & (-\alpha k^2+\alpha\alpha' k^4)\psi e^{(\sigma t+ikx)} & i\sigma\psi e^{(\sigma t+ikx)} \\ i\frac{\tau}{1+\lambda}k\psi e^{(\sigma t+ikx)} & (\frac{\tau}{1+\lambda}ik-\frac{\tau}{1+\lambda}\beta ik^3)\psi e^{(\sigma t+ikx)} & (-\mu_2k^2\sigma\psi-\frac{\nu}{1-2\nu}k^2\psi-s\psi)e^{(\sigma t+ikx)} \\ 0 & \sigma\psi e^{(\sigma t+ikx)} & ik\sigma\psi e^{(\sigma t+ikx)} \end{vmatrix} = 0$$

Factorising $\psi e^{(\sigma t+ikx)}$ out, we have

$$\begin{vmatrix} (\sigma+D_1k^2+D_2k^4+r) & (-\alpha k^2+\alpha\alpha' k^4) & i\sigma \\ i\frac{\tau}{1+\lambda}k & (\frac{\tau}{1+\lambda}ik-\frac{\tau}{1+\lambda}\beta ik^3) & (-\mu_2k^2\sigma-\frac{\nu}{1-2\nu}k^2-s) \\ 0 & \sigma & ik\sigma \end{vmatrix} \psi e^{(\sigma t+ikx)} = 0$$

Dividing through by $\psi e^{(\sigma t+ikx)}$, we have

$$\begin{vmatrix} (\sigma + D_1k^2 + D_2k^4 + r) & (-\alpha k^2 + \alpha\alpha' k^4) & i\sigma \\ i\frac{\tau}{1+\lambda}k & (\frac{\tau}{1+\lambda}ik - \frac{\tau}{1+\lambda}\beta ik^3) & (-\mu_2k^2\sigma - \frac{\nu}{1-2\nu}k^2 - s) \\ 0 & \sigma & ik\sigma \end{vmatrix} = 0$$

$$(\sigma + D_1k^2 + D_2k^4 + r)\begin{vmatrix} (i\frac{\tau}{1+\lambda}k - i\frac{\tau}{1+\lambda}\beta k^3) & (-\mu_2k^2\sigma - \frac{\nu}{1-2\nu}k^2 - s) \\ \sigma & ik\sigma \end{vmatrix}$$

$$-(-\alpha k^2 + \alpha\alpha' k^4)\begin{vmatrix} (i\frac{\tau}{1+\lambda}k) & (-\mu_2k^2\sigma - \frac{\nu}{1-2\nu}k^2 - s) \\ 0 & ik\sigma \end{vmatrix}$$

$$+ik\sigma\begin{vmatrix} (i\tau k) & (i\frac{\tau}{1+\lambda}k - i\frac{\tau}{1+\lambda}\beta k^3) \\ o & \sigma \end{vmatrix} = 0$$

$$(\sigma+D_1k^2+D_2k^4+r)[ik\sigma(i\tfrac{\tau}{1+\lambda}k-i\tfrac{\tau}{1+\lambda}\beta k^3]-(-\alpha k^2+\alpha\alpha' k^4(-\tfrac{\tau}{1+\lambda}k^2\sigma)+ik\sigma(i\tau k\sigma)$$

$$(\sigma + D_1k^2 + D_2K^4 + r)[i^2\tfrac{\tau}{1+\lambda}k^2\sigma - i^2\tfrac{\tau}{1+\lambda}\beta k^4\sigma + \mu_2k^2\sigma^2 + \tfrac{\nu}{1-2\nu}k^2\sigma + s\sigma] +$$

$$(\alpha K^2 - \alpha\alpha' k^4)(-\tfrac{\tau}{1+\lambda}k^2\sigma) + i^2\tfrac{\tau}{1+\lambda}k^2\sigma^2 = 0$$

$$(\sigma + D_1k^2 + D_2k^4 + r)[i^2\tfrac{\tau}{1+\lambda}k^2\sigma - i^2\tfrac{\tau}{1+\lambda}\beta k^4\sigma + \mu_2k^2\sigma^2 + \tfrac{\nu}{1-2\nu}k^2\sigma + s\sigma] -$$

$$\tfrac{\tau}{1+\lambda}\alpha K^4\sigma + \tfrac{\tau}{1+\lambda}\alpha\alpha' k^6\sigma + i^2\tfrac{\tau}{1+\lambda}k^2\sigma^2 = 0$$

$$(\sigma + D_1k^2 + D_2k^4 + r)[-\tfrac{\tau}{1+\lambda}k^2\sigma + \tfrac{\tau}{1+\lambda}\beta k^4\sigma + \mu_2k^2\sigma^2 + \tfrac{\nu}{1-2\nu}k^2\sigma + s\sigma] -$$

$$\tfrac{\tau}{1+\lambda}\alpha K^4\sigma + \tfrac{\tau}{1+\lambda}\alpha\alpha' k^6\sigma - \tfrac{\tau}{1+\lambda}k^2\sigma^2 = 0$$

$$\sigma[-\tfrac{\tau}{1+\lambda}k^2\sigma + \tfrac{\tau}{1+\lambda}\beta k^4\sigma + \mu_2k^2\sigma^2 + \tfrac{\nu}{1-2\nu}k^2\sigma + s\sigma] + D_1k^2[-\tfrac{\tau}{1+\lambda}k^2\sigma + \tfrac{\tau}{1+\lambda}\beta k^4\sigma +$$

$$\mu_2k^2\sigma^2 + \tfrac{\nu}{1-2\nu}k^2\sigma + s\sigma] + D_2k^4[-\tfrac{\tau}{1+\lambda}k^2\sigma + \tfrac{\tau}{1+\lambda}\beta k^4\sigma + \mu_2k^2\sigma^2 + \tfrac{\nu}{1-2\nu}k^2\sigma + s\sigma] +$$

$$r[-\tfrac{\tau}{1+\lambda}k^2\sigma + \tfrac{\tau}{1+\lambda}\beta k^4\sigma + \mu_2k^2\sigma^2 + \tfrac{\nu}{1-2\nu}k^2\sigma + s\sigma] = 0$$

$$-\tfrac{\tau}{1+\lambda}K^2\sigma^2 + \tfrac{\tau}{1+\lambda}\beta k^4\sigma^2 + \mu_2k^2\sigma^3 + \tfrac{\nu}{1-2\nu}k^2\sigma^2 + s\sigma^2 - D_1\tfrac{\tau}{1+\lambda}k^4\sigma + D_1\tfrac{\tau}{1+\lambda}\beta k^6\sigma +$$

$$D_1\mu_2k^4\sigma^2 + D_1\tfrac{\nu}{1-2\nu}k^4\sigma^2 + D_1k^2s\sigma - D_2\tfrac{\tau}{1+\lambda}k^6\sigma + D_2\tfrac{\tau}{1+\lambda}\beta k^8\sigma + D_2\mu_2k^6\sigma^2 +$$

$$D_2\tfrac{\nu}{1-2\nu}k^6\sigma + D_2k^4s\sigma - r\tfrac{\tau}{1+\lambda}k^2\sigma + r\tfrac{\tau}{1+\lambda}\beta k^4\sigma + r\mu_2k^2\sigma^2 + r\tfrac{\nu}{1-2\nu}k^2\sigma + rs\sigma -$$

$$\tfrac{\tau}{1+\lambda}\alpha k^4\sigma + \tfrac{\tau}{1+\lambda}\alpha\alpha' k^6\sigma - \tfrac{\tau}{1+\lambda}k^2\sigma^2 = 0$$

$$\mu_2 k^2\sigma^3 + \tfrac{\tau}{1+\lambda}\beta k^4\sigma^2 - \tfrac{\tau}{1+\lambda}k^2\sigma^2 - \tfrac{\tau}{1+\lambda}k^2\sigma^2 + \tfrac{\nu}{1-2\nu}k^2\sigma^2 + s\sigma^2 + D_1\mu_2 k^4\sigma^2 +$$

$$D2\mu_2 k^5\sigma^2 + r\mu_2 k^2\sigma^2 + D_2\tfrac{\tau}{1+\lambda}\beta k^8\sigma + D_2\tfrac{\nu}{1-2\nu}k^6\sigma - D_2\tfrac{\tau}{1+\lambda}k^6\sigma + \tfrac{\tau}{1+\lambda}\alpha\alpha' k^6\sigma +$$

$$D_1\tfrac{\tau}{1+\lambda}\beta k^6\sigma + r\tfrac{\tau}{1+\lambda}\beta k^4\sigma + D_1\tfrac{\nu}{1-2\nu}k^4\sigma + D_2 k^4 s\sigma - \tfrac{\tau}{1+\lambda}\alpha k^4\sigma - D_1\tfrac{\tau}{1+\lambda}K^4\sigma +$$

$$D_1 k^2 s\sigma - r\tfrac{\tau}{1+\lambda}k^2\sigma + r\tfrac{\nu}{1-2\nu}k^2\sigma + rs\sigma = 0$$

let

$$\mu_2 = \mu \quad \text{and} \quad \tfrac{\nu}{1-2\nu} = 1$$

$$\mu k^2\sigma^3 + \tfrac{\tau}{1+\lambda}\beta k^4\sigma^2 - 2\tfrac{\tau}{1+\lambda}k^2\sigma^2 + k^2\sigma^2 + s\sigma^2 + D_1\mu k^4\sigma^2 + D_2\mu_2 k^6\sigma^2 + r\mu k^2\sigma^2 +$$

$$D_2\tfrac{\tau}{1+\lambda}\beta k^8\sigma + D_2 k^6\sigma - D_2\tfrac{\tau}{1+\lambda}k^6\sigma + \tfrac{\tau}{1+\lambda}\alpha\alpha' k^6\sigma + D_1\tfrac{\tau}{1+\lambda}\beta k^6\sigma + r\tfrac{\tau}{1+\lambda}\beta k^4\sigma +$$

$$D_1 k^4\sigma + D_2 k^4 s\sigma - \tfrac{\tau}{1+\lambda}\alpha k^4\sigma - D_1\tfrac{\tau}{1+\lambda}K^4\sigma + D_1 k^2 s\sigma - r\tfrac{\tau}{1+\lambda}k^2\sigma + rk^2\sigma + rs\sigma = 0$$

$$\mu k^2\sigma^3 + D_2\mu k^6\sigma^2 + k^4[\tfrac{\tau}{1+\lambda}\beta + D_1\mu]\sigma^2 + k^2[1 + r\mu - 2\tfrac{\tau}{1+\lambda}]\sigma^2 + s\sigma^2 +$$

$$D_2\tfrac{\tau}{1+\lambda}\beta k^8\sigma + k^6[D_2 - D_2\tfrac{\tau}{1+\lambda} + \tfrac{\tau}{1+\lambda}\alpha\alpha' + D_1\tfrac{\tau}{1+\lambda}\beta]\sigma + k^4[r\tfrac{\tau}{1+\lambda}\beta + D_1 + D_2 s -$$

$$\tau \alpha - d_1 \tfrac{\tau}{\quad}]\sigma + k^2[D_1 s - r\tfrac{\tau}{\quad} + \tfrac{\tau}{\quad}]\sigma + rs\sigma = 0$$

4.6.2 Dispersion relation

$$\mu k^2\sigma^2 + b(k^2) + c(k^2) = 0$$

where

$$b(k^2) = \mu D_2 k^6 + k^4[\mu D_1 + \beta\tfrac{\tau}{1+\lambda}] + k^2[1 + \mu r - 2\tfrac{\tau}{1+\lambda}] + s$$

$$c(K^2) = \tfrac{\tau}{1+\lambda}\beta D_2 k^8 + k^6[\tfrac{\tau}{1+\lambda}(\beta D_1 + \alpha\alpha' - D_2 0 + D_2] + k^2[r + sD_1 - r\tfrac{\tau}{1+\lambda}] + rs$$

The spatially heterogeneous solutions of the linear equations are characterised by a dispersion relation $\sigma(k^2)$ which exhibits a range of unstable modes when $Re(\sigma) > 0$ but it will exhibits a range of stable modes $Re(\sigma) < 0$. The most essential parameter in the dispersion relation is the cell traction τ.

We assume that there is no long range cell interactions

That is $D_2 = 0 \quad and \quad \alpha' = 0$ And also letting $D_1 = D$

we have

Dispersion relation

$$\mu K^2\sigma^2 + b(k^2)\sigma + c(k^2) = 0$$

where $b(k^2) = k^4\left(\mu D + \tfrac{\beta\tau}{1+\lambda}\right) + k^2\left(1 - \tfrac{\tau}{1+\lambda}\left[2 - \tfrac{2\lambda}{1+\lambda}\right] + \mu r\right) + s$

$$c(k^2) = \tfrac{\tau\beta D}{1+\lambda}k^6 + k^4\left(D + \tfrac{\tau}{1+\lambda}\left[r\beta - D - \alpha\left(1 - \tfrac{2\lambda}{1+\lambda}\right)\right]\right) + K^2\left(r + sD - \tfrac{r\tau}{1+\lambda}\right) + rs$$

4.6.3 Patterns Formation

To get the patterns that are form from this dispersion relation. We wrote a matlab program and use the experimental data from Murray and Bentil. Relationship between the mode(m) and the wave number(k) is given as

$k = m \times \pi$

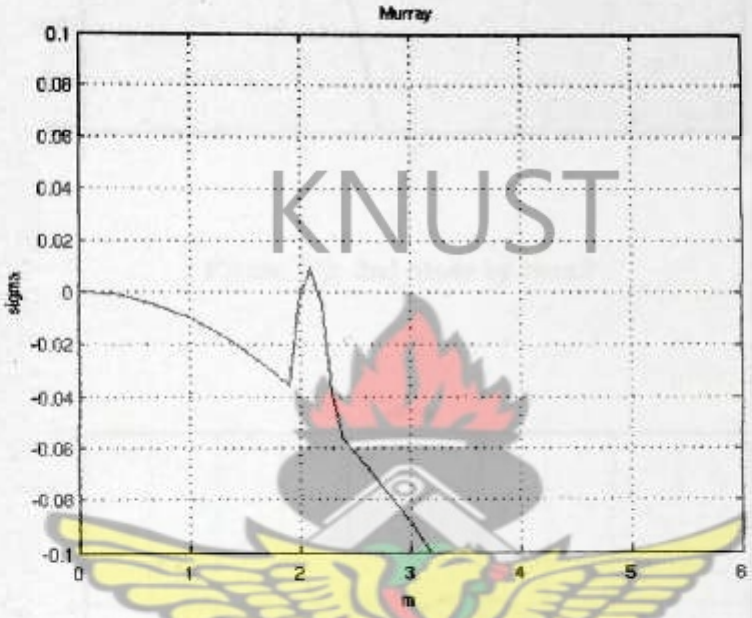


Figure 4.1: 2nd Mode by Murray and Co

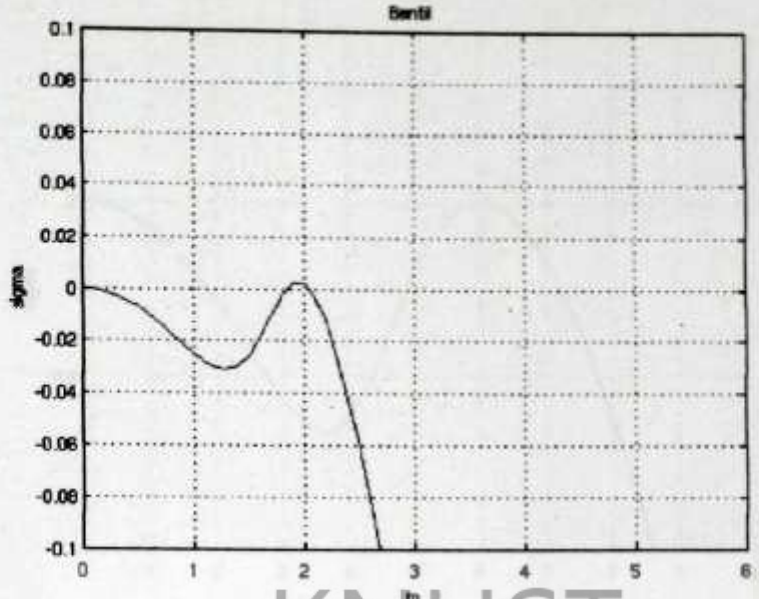


Figure 4.2: 2nd Mode by Bentil

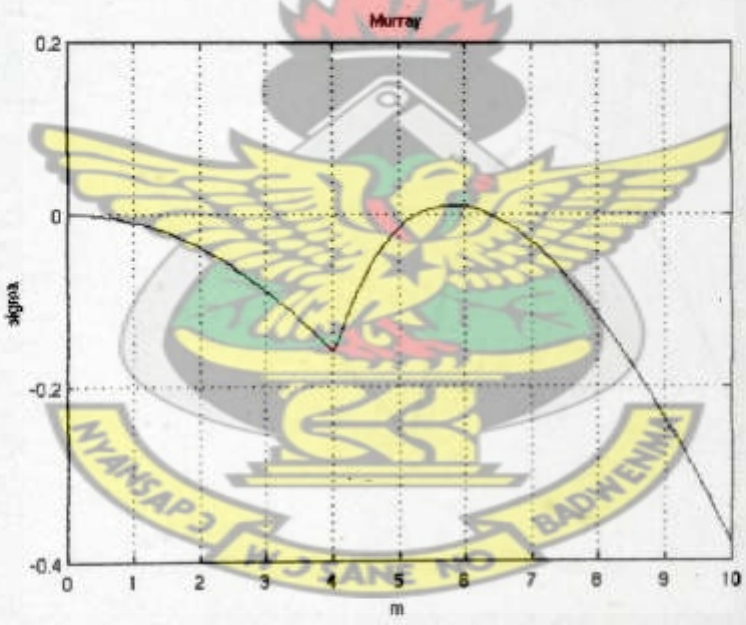


Figure 4.3: 6th Mode by Murray and Co

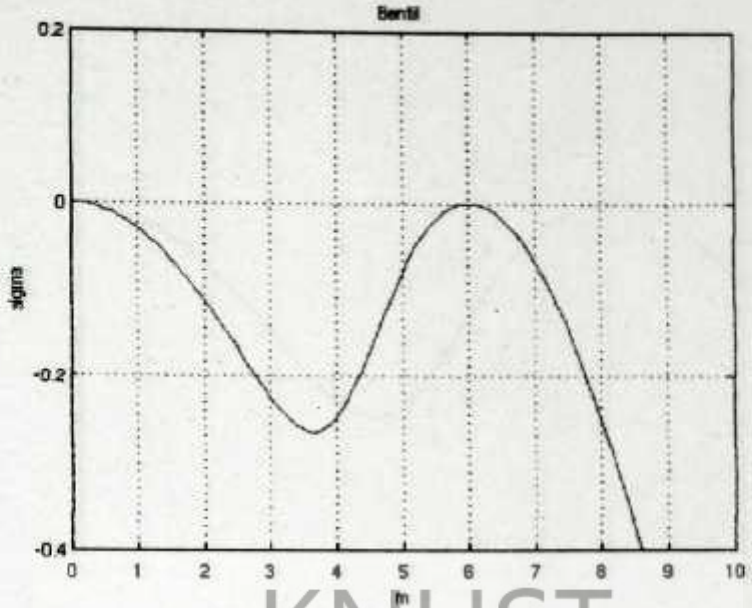


Figure 4.4: 6th Mode by Bentil

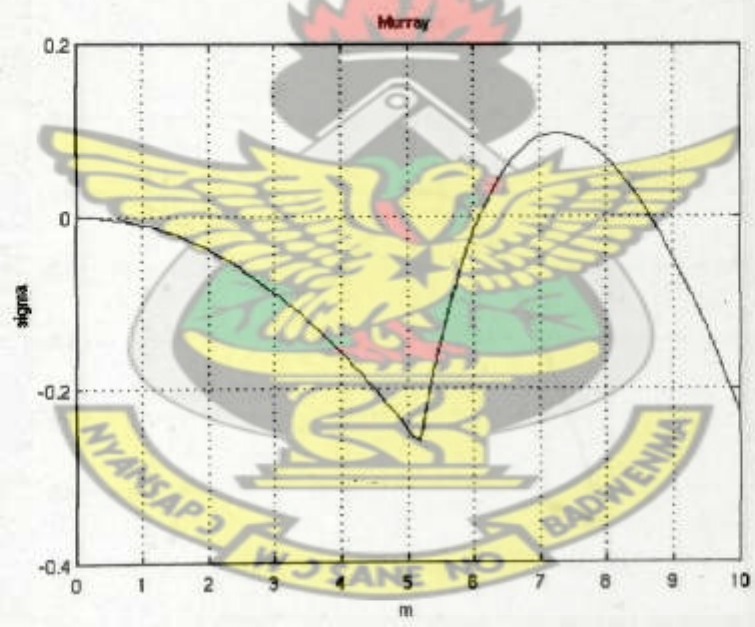


Figure 4.5: 8th Mode by Murray and Co

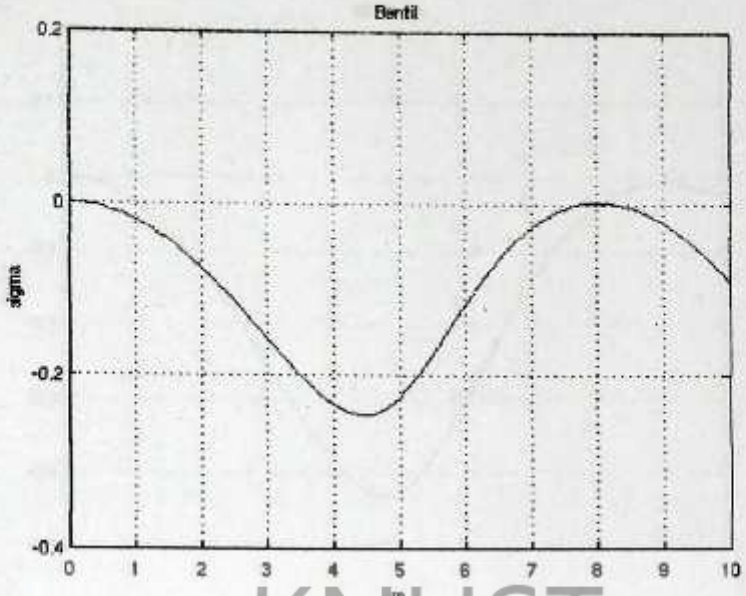


Figure 4.6: 8th Mode by Bentil

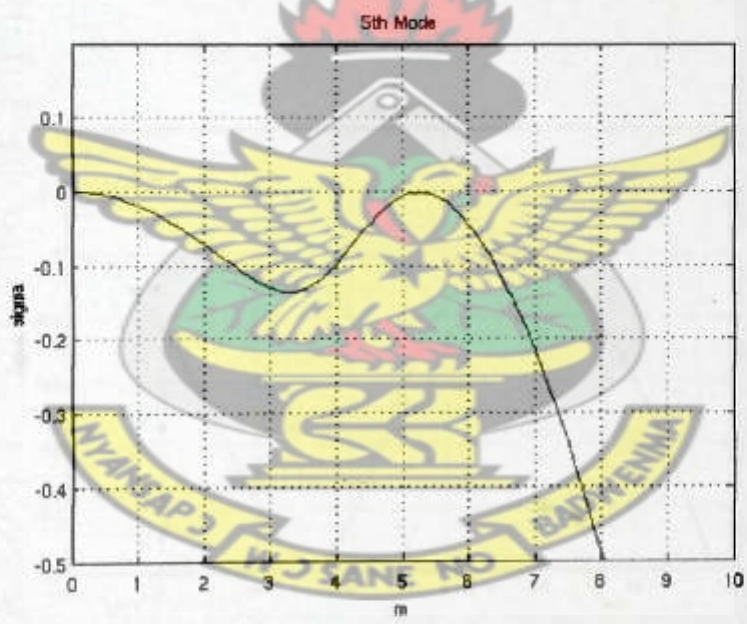


Figure 4.7: 5th Mode by Dontwi and Oppong

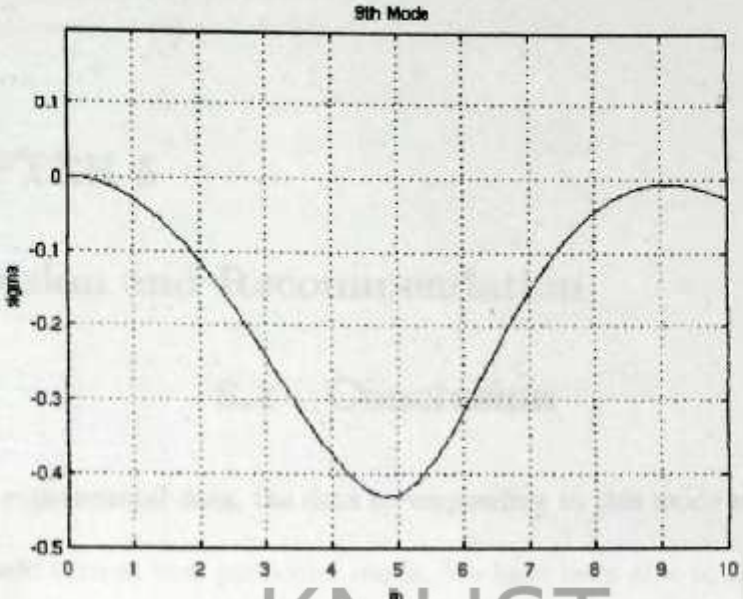


Figure 4.8: 9th Mode by Dontwi and Oppong

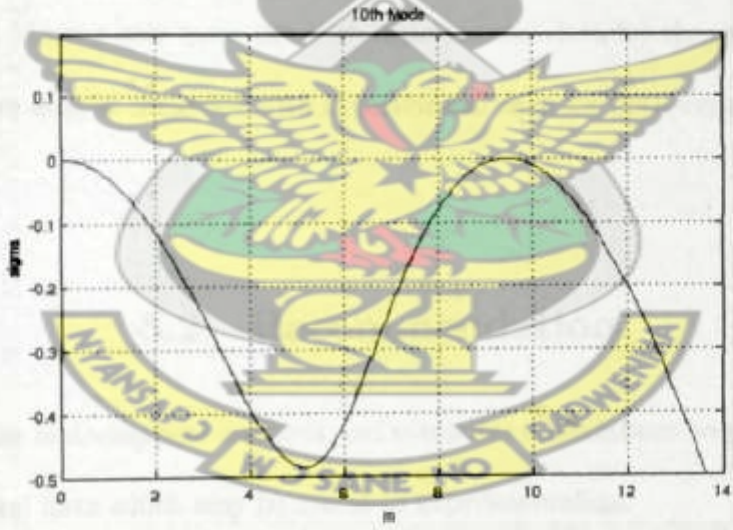


Figure 4.9: 10th Mode by Dontwi and Oppong

CHAPTER 5

Conclusion and Recommendation

5.1 Conclusion

From the experimental data, the data corresponding to this mode means the graph should turn at that particular mode. We have been able to derive the Aproximation Model and also showed that Bentil's experimental data were giving us better results than Murray who started biological pattern formation. We were able to come out with experimental data for the 5th, 9th and 10th modes which was not considered in Bentil's and Murray's experimental data. Bentil and Murray only came out with experimental data for the even modes but we were able to come out with experimental data for both even and odd modes.

5.2 Recommendation

One can use mathematical methods and computer stimulations to generate the experimental data which may be useful to experimentalists.

Using mathematical modeling one can predict what will happen in real life situation.

Bibliography

1. Dan Hill and Timothy Morgan. *Pattern Formation and Wave Propagation in the Belousov-Zhabotinskii Reaction*

2. I.R Epstein and J.A Pojman. *Introduction to Nonlinear Chemical Dynamics, Oscillations, Waves, Patterns and Chaos.* Oxford UP. New York: 1998.

3. Richard J. Field and Richard M. Noyes. *Oscillations in Chemical Systems. V. Quantitative Explanation of Band Migration in the Belousov-Zhabotinskii Reaction.* Journal of the American Chemical Society, 96:7:2001-2006, 1974

4. Stephen K.Scott. *Oscillations, Waves and Chaos in Chemical Kinetics.* Oxford UP. New York: 1994

5. Bassam Z. Shakhashiri. *Chemical Demonstrations: A Handbook for Teachers of Chemistry.* University of Wisconson Press. Madison, Wisconson: 1983

6. John J. Tyson. *The Belousov-Zhabotinskii Reaction.* Springer-Verlag. New York: 1976

7. Casey R.Gray. *An Analysis of the Belousov-Zhabotinskii Reaction*

8. G.W.Beeler and H.Reuter, *Reconstruction of the action potential of ventricular myocardial fibers*, Journal of Physiology 268(1977), 177-210

9. O.Benini, R.Cervellati and P.Fetto, *The BZ reaction: experimental and model studies in the physical chemistry laboratory*, Journal of Chemical Education 73 (1996), 865-868

10. I.R. Epstein, *The role of flow systems in far-from-equilibrium dynamics*, Journal of Chemical Education 66 (1989), 191-195

11. R.J.Field, E. Koros and R.M. Noyes *Oscillations in chemical systems*, Part 2. Thorough analysis of temporal oscillations in the bromate-cerium-malonic acid system, Journal of the American Chemical Society 94 (1972), 8649-8664

12. R.J. Field and F.W Schneider, *oscillating chemical reactions and nonlinear dynamics*, Journal of Chemical Education 66 (1989), 195-204

13. R. Fitzhugh, *Impulses and physiological states in theoretical models of nerve membrane*, Biophysical Journal 1 (1961), 445-466

14. P.Gray and S.K Scott, *Chemical Oscillations and Instabilities: Nonlinear Chemical Kinetics*, Oxford Science Publications, Oxford, 1990

15. A.L Hodgkin and A.F Huxley, *A quantitative description of membrane current and its application to conduction and excitation in nerve*, Journal of Physiology 116 (1952), 500-544

16. S.Hollis, *Differential Equations with Boundary Value Problems*, Prentice Hall, Upper Saddle River, 2001

17. J.E Marsden and M.McCracken, *The Hopf Bifurcation and Its Applications*, Springer-Verlag, New York, 1976

18. J.L Martiel and A. Golbeter *A model based on receptor desensitization for cyclic AMP signaling in DIctyostelium cells*, Biophysical Journal 52 (1987), 807-828

19. J.D Murray, *Mathematical Biology*, Springer-Verlag, New York, 1993

20. J.S Nagumo, S.Arimoto and S.Yoshizawa, *An active pulse transmission line simulating nerve axon*, Proceedings of IRE 50 (1962), 2061-2071

21. R.M Noyes,*Some models of chemical oscillators*, Journal of Chemical Education 66 (1989), 190-191

22. S.K Scott, *Oscillations, Waves and Chaos in Chemical Kinetics*, Oxford Science Publications, Oxford, 1994

23. M.M Slinko and N.I Jaeger, *Oscillating Heterogeneous Catalytic Systems*, Elsevier, Amsterdam, 1994

24. J.J Tyson, *The Belousov-Zhabotinskii Reaction* ,Springer-Verlag, New York, 1976

25. V.K Vanag and I.R Epstein, *Inwardly rotating spiral waves in a reaction-diffusion system*, Chemical and Engineering News 79 (2001), 835-837

26. A.T Winfree, The prehistory of the Belousov-Zhabotinskii Oscillator, Journal of Chemical Education 61 (1984), 661-663

27. http://www.musc.edu/ alievr/rubin.html

28. http://www.clubtre.sky.net.ua/denis/recipes.html

29. http://neon.chem.ox.ac.uk/vrchemistry/FilmStudio/oscillating/HTML/page03.htm

30. *http : //www.chem.leeds.ac.uk/People/SKS/sks_research/sks_group_page.htm*

31. *http : //genchem.chem.wisc.edu/demonstrations/Gen_Chem_Pages/12kineticpage/*

32. http:/hopf.chem.brandeis.edu/anatol.htm

33. D.E Bentil and J.D Murray, *Pattern Selection in Biological Pattern Formation Mechanisms* (1990)

34. J.J More. *The Levenberg-Marquart algorithm: Implementation and theory*, G.A Watson (Ed), *Numerical Analysis*, Proceedings,Dundee 1977, Springer, (1978)

35. J.D Murray, *Mathematical Biology*, Springer-Verlad, Hiedelberg, (1989)

36. G.F Oster, J.D Murray and A.K Harris, *Mechanical aspects of mesenchymal morphogenesis*, J.Embryo.Exp.Morph. 78, 83-125 (1983)

37. J.D Murray and G.F Oster, *Cell traction models for generating patterns and form*, J.Math.Biol.19, 265-279 (1984)

38. A.S Perelson, P.K Maini, J.D Murray, J.M Hyman and G.F Oster, Nonlinear pattern selection in a mechanochemical model for morphogenesis, J.Math,Biol.24, 525-541 (1986)

39. J.D Murray, Parameter space for Turing instability in reaction-diffusion mechanisms: A comparison os models, J.Theor.Biol.98, 143-163 (1982)

Appendix A

Matlab Programe

A.1 Belousov-Zhabotinskii reaction and phase diagrams

1. *Belousov-Zhabotinskii reaction and phase diagrams*
2. *Using Matlab Ode*
3. $T = 40$*: maximum time*
4. $h = 0.3$*:Initial concentration of hypobromous acid*
5. $k = 0.05$*:Initial concentration of bromide*
6. $l = 0.004$*:Initial concentration of cerium-4*
7. $x0 = [h, k, l]$
8. .....*execution*.....
9. $[t, x] = Ode23(@fun[0T], x0);$
10. .....*graphical output*.....
11. *plot3(x(:,1),x(:,2),x(:,3))*

12. *plot(t,x(:,1))*

13. *xlabel('t');ylabel('x')*

14. *plot(t,x(:,3))*

15. *xlabel('t');ylabel('x')*

16. *plot(t,x(:,2))*

17. *xlabel('t');ylabel('x')*

18. *plot(x(:,1),x(:,3))*

19. *grid off*

20. .....*function*.....

21. $function[y] = fun(t, x);$

22. $[y] = zeros(3, 1);$

23. $ess = 4e^{-2};$

24. $delta = 4e^{-4};$

25. $q = 8e^{-4};$

26. $f = \frac{2}{3};$

27. $y(1) = (\frac{1}{ess}) * (q * (x(2) - x(1) * x(2) + x(1) * (1 - x(1)));$

28. $y(2) = (\frac{1}{delta} * (-q * x(2) - x(1) * x(2) + f * x(3));$

29. $y(3) = x(1) - x(3)$;

Appendix B

Matlab Programe

B.1 Pattern phase diagrams

1. *function dispatterns*
2. $taw = 1.02$
3. $mew = 0.022$
4. $beta = 0.0021$
5. $lambda = 0.96$
6. $D = 0.200$
7. $alpha = 0.260$
8. $s = 177.8$
9. $r = 0$
10. $m = [0 : 0.1 : 10]$
11. $k = m * pi$
12. $k2 = k.^2$

13. $k4 = k.^4$

14. $k6 = k.^6$

15. $a = mew * k2$

16. $lambda1 = 1 + lambda$

17. $lambda2 = (beta * taw)/lambda1$

18. $b1 = (mew * D + lambda2) * k4$

19. $f1 = (2 * taw)/lambda1^2$

20. $b2 = (1 - f1 + mew * r)$

21. $b3 = b2 * k2 + s$

22. $b = b1 + b3$

23. $f2 = D * lambda2$

24. $c1 = f2 * k6$

25. $lambdac = 1 - lambda$

26. $f3 = lambdac/lambda1$

27. $f4 = r * beta - D - alpha * f3$

28. $f5 = (f4 * taw)/lambda1$

29. $f6 = D + f5$

30. $c2 = f6 * k4$

31. $f7 = (r * taw)/lambda1$

32. $f8 = s * D + r - f7$

33. $c3 = f8 * k2 + r * s$

34. $c = c1 + c2 + c3$

35. $b12 = b.^2$

36. $f9 = 4 * a$

37. $f10 = f9. * c$

38. $f11 = b12 - f10$

39. $f12 = sqrt(f11)$

40. $f13 = 2 * a$

41. $f14 = -b + f12$

42. $f15 = f14./f13$

43. *plot(m,f15)*

44. *grid on*

45. *axis on*

46. *xlabel('m')*

47. *ylabel('sigma')*

48. *title('Bentil')*

49. *axis([0,10,-10,5])*

50. *end*