Oscillations, Chaos, and Crises in a Model For Cell Replication

by

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ABSTRACT

In this thesis, the dynamics of a mathematical model for cell replication in which there is simultaneous proliferation and maturation is studied. The cell population dynamics are described by a first order nonlinear partial differential equation (PDE) in which there is retardo delay (delay) in both the temporal and maturation variables. The solution behaviour of this model is investigated for two different initial conditions $\varphi(x) = x^n$ for $n = 1$ and $n = 2$ where $x$ is the maturation variable. When $n \gg 1$, the solutions are travelling waves whose velocities are primarily dependent on the value of $n$ and of the delay. Increasing the delay also causes oscillations to appear near the wave front. This type of solution behaviour can be associated with solitons. When $n = 1$ and other parameters are varied, the temporal solution goes through a period doubling route to chaos and exhibits crises and multistability while the spatial solution becomes increasingly structured.
RÉSUMÉ

Dans ce mémoire, le comportement dynamique d'un modèle mathématique de cellules qui se reproduisent et mûrissent simultanément est étudié. Le comportement dynamique des populations de cellules est décrit par une équation nonlinéaire du premier ordre aux dérivées partielles avec arguments retardés dans le temps et dans l'espace. Le comportement dynamique est examiné en détail pour deux conditions initiales différentes \( \varphi(x) = x^n \) pour \( n >> 1 \) et \( n = 1 \) où \( x \) représente la maturité. Pour \( n >> 1 \), le comportement dynamique consiste en fronts mobiles dont la vitesse dépend surtout de la valeur de \( n \) et du retard. Une augmentation de ce retard provoque des oscillations au voisinage du front. Ce type de solution est associé aux solitons. Quand \( n = 1 \) et que certains paramètres sont variés, la solution temporelle suit la cascade de dédoublement de période vers le chaos, manifestant des crises et de la multistabilité pendant que la solution spatiale devient de plus en plus structurée.
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INTRODUCTION

Dynamic systems have been studied since ancient times but it is only since the middle of the twentieth century that scientists, other than astronomers and physicists, have become interested in modelling dynamic systems. This surge of interest was brought about by the development of computers which have greatly facilitated the study of dynamic systems. Before the advent of computers, the analytic study of dynamic systems was considered to be extremely difficult since it mainly consisted of using power series and special functions which can only yield solutions to the simplest of problems. Numerical methods were also used to solve dynamic systems however they were toilsome and prone to error. With the arrival of computers, numerical methods have become more practical and dynamic systems have seen some remarkable developments.

Linear systems have been used for a long time to model a variety of phenomena and the subject of linear systems is rich with theoretical work. However it has become clear in the last 30 years that most phenomena can only realistically be modelled using nonlinear dynamics. Hardly any theoretical work has been done in the field of nonlinear dynamics which has mainly been studied through special cases in the literature. The advent of computers has helped to develop the study of nonlinear dynamics and numerical methods have permitted nonlinear differential equations to be used as modelling tools.
In the past decade computers have become bigger, faster, cheaper and more accessible. However, progress in computer technology has not reduced the study of dynamic systems to routine computations. Instead, computers have shown that a simple system of ordinary differential equations can behave in an erratic fashion known as chaos. Chaotic behaviour was first observed by Henri Poincare in the early part of this century but this arcane knowledge did not, at the time, spread to the rest of the general scientific community and it wasn’t until the meteorologist, Lorenz, rediscovered chaotic behaviour through the computer study of a simple nonlinear system in the early sixties that the scientific community took note. Since then, dynamical systems have become a “hot” topic with Mandelbrot’s discovery of fractals and the study of chaotic dynamics.

Traditional users of dynamical models are astronomers, physicists, mathematicians, demographers and engineers. In last few years, biologists have become interested in dynamical systems as a tool to understand the underlying mechanisms involved in the biological processes. This recent interest has given rise to the new and exciting field of mathematical biology. Mathematical biology is a fast growing subject and mathematical models have already been studied in many areas of biology including epidemiology, development biology, population ecology, evolution, and physiology.

In this thesis, the dynamics of a mathematical model for cell replication in which there is simultaneous proliferation and maturation is studied. The cell population dynamics are described by a first order nonlinear partial differential equation in which there is retardation in both the temporal and maturation variables. This model is novel because not only have other models of cell replication rarely taken into account age structure but also because a dynamical system with retardation in both time and space has not, to my knowledge, been previously studied. The solution dynamics
of the model, as will be shown in this thesis, are extremely diverse and interesting ranging from stationary solution to highly erratic solutions.

The plan of this thesis is as follows. In Chapter 1, some background material is given in cell biology, numerical methods, and delay differential equations and the mathematical model for cell population in which there is simultaneous proliferation and maturation is derived. In Chapter 2, the resulting first order nonlinear partial differential equation for the cell density $u(t, x)$ in which there is retardation in both the temporal ($t$) and maturation ($x$) variables is studied for the initial condition $\varphi(x) = x^n$ where $n \gg 1$. This type of initial condition gives rise to left traveling waves which display very interesting behaviour as the delay is increased. In Chapter 3, the same first order nonlinear partial differential equation is studied for the initial condition $\varphi(x) = x$. First, an introduction to steady states, bifurcations, and chaos is given using the logistic map as an example. Then, previous results obtained by Rey and Mackey [31, 32] for the same model and the same initial condition are presented. Finally the dynamics of the temporal and spatial solutions are studied past the Hopf bifurcation. These solutions are very rich and display oscillations, chaotic attractors, and multistability. In conclusion, a brief summary of the results and their relation to biology is given. Areas which need further study and a different approach are also suggested.

The results in Chapter 2 and in Chapter 3, Section 4 are new results.
Chapter 1

1.1 INTRODUCTION

As described in the Introduction, the purpose of this thesis is to study the dynamics of a model for cell replication in which the cells are both proliferating and maturing simultaneously. In this chapter, the model, as well as the necessary background to understand the model, is introduced. First, a brief description of the biology behind the model is given with an introduction to cell structure and cell division in Section 1.2. Then, in Section 1.3, the methods of solution, the Galerkin finite elements method and the method of characteristics, are presented. This is followed by the construction of the model and an introduction to differential delay equations in Sections 1.4 and 1.5. In Section 1.6, some pertinent mathematical results are stated.

1.2 THE BIOLOGY BEHIND THE MODEL

In order to understand the origin of the mathematical model, it is first necessary to have a basic knowledge of the biology. This section provides the required knowledge through a brief introduction to blood cells [1].

7
1.2.1 The Eucaryotic Cell.

In Figure 1.1, one can find a sketch of a eucaryotic cell where the main components of the cell are represented. A cell is a small compartment (ca. 10μ diameter) bounded by a plasma membrane containing a concentrated chemical solution. A eucaryotic cell, or animal cell, has special features such as many internal membranes and a nucleus (as opposed to procaryote cells, such as bacteria, which have no nucleus) which contains most of the cell's DNA. Membranes surround the nucleus separating it from the rest of the cell which contains cytoplasm where the various organelles of the cell reside. Some of these organelles are formed by internal membranes such as endoplasmic reticulum, where the lipids and proteins of cell membranes as well as material to be exported from the cell are synthesized, and the Golgi apparatus, where synthesis and transport of other organic molecules occur. Other organelles, such as mitochondria which carry out the terminal oxidation of food, are surrounded
Figure 1.2: A diagram of the successive phases of a proliferating eucaryotic cell.

by membranes. The human body contains millions of cells. Cells get damaged or get old and hence die off. In order to keep the same amount of cells in the body, cells must divide. A cell produces two daughter cells by going through two phases, an interphase and a division phase. Each daughter cell must contain the same components as its parent cell, therefore, in order for a cell to divide, it needs to duplicate all of its contents and double its mass. This occurs during the interphase. The interphase is divided into three phases $G_1$, $S$, and $G_2$. During the $G_1$ phase, the cell increases its rate of biosynthesis before entering the $S$ phase during which the cell synthesizes its DNA and duplicates the contents of its nucleus. The cell then goes through the $G_2$ phase before entering the division phase or M phase and dividing via mitosis and cytokinesis. A diagram of the different phases is shown in Figure 1.2.
1.2.2 The Pluripotent Stem Cell and Blood Cells.

Most differentiated cell populations in humans evolve through death and renewal. Some cell populations renew themselves through simple duplication, a cell producing two identical daughter cells which will perform the same function as their parent cell. Other cell populations are renewed by stem cells. The three main properties of the stem cell are:

1. It is not terminally differentiated (i.e. it can still proliferate).

2. It can divide almost indefinitely.

3. Its daughter cells can become stem cells or can become terminally differentiated.

Thus, of the two daughter cells that a stem cell produces through division, on average one daughter will become a stem cell like its parent and the other daughter, after a few divisions, will become terminally differentiated and hence perform a different role than its parent.

The blood contains many different types of cells, classified into white or red blood cells, which all arise from the same type of stem cell in the bone marrow. These stem cells are called pluripotent stem cells since their progeny will become committed to different lines of differentiation which will eventually produce different types of blood cells. A diagram of a pluripotent hematopoietic stem cell’s progeny is shown in Figure 1.3.

1.2.3 The Production of an Erythrocyte.

The development from a daughter cell of a pluripotent stem cell to an erythrocyte occurs in the following way [24]. The first generation of the pluripotent stem cells are stem cells which are committed to producing one type of blood cell. Once a
stem cell is committed to an erythrocyte line of differentiation it (and its progeny) becomes sensitive to the hormone erythropoietin. Erythropoietin is a regulator of the production of erythrocytes. A decrease in hemoglobin (an oxygen binding protein) causes an increase in erythropoietin which leads to an increase in the rate of division in the erythrocyte precursors. This eventually induces an increase in erythrocytes and a stabilization of the hemoglobin content in the blood. During its successive divisions, the erythrocyte precursor accumulates hemoglobin. After about four divisions, the precursor extrudes its nucleus as well as most of its other organelles and becomes terminally differentiated. This type of cell is full of hemoglobin and can be considered a mature erythrocyte. After the extrusion of its nucleus it will leave the bone marrow to pass into the circulation. The maturity of the erythrocyte can be measured by its content of hemoglobin.
1.3 METHODS OF SOLUTION

Two methods of solution are implemented to integrate the partial differential equation which describes the model. This model will be described in the next section. Some boundary value problems have exact solutions which can be found using exact methods such as the method of characteristics. However, for most boundary value problems, the solution cannot be found analytically, thus the need for numerical schemes such as the Galerkin Finite Elements Method (GFEM). These two methods of solution are implemented to integrate the partial differential equation which describes the model. In this section these methods are briefly described.

1.3.1 The Galerkin Finite Elements Method.

The GFEM [3, 8, 18] is a numerical scheme which constructs an approximate solution to a boundary value problem. It is a version of the weighted residual method- a numerical scheme often used in the engineering and physical sciences. The main idea behind the GFEM is to discretize the domain in which the equation is to be solved into a finite number of simple shapes (triangles, squares...) called elements. The solution is then approximated in each of the elements by an interpolating polynomial.

In more detail, the GFEM assumes that given a nonlinear partial differential equation \( L(U) = 0 \) (where \( L \) is a nonlinear differential operator) in a domain \( D \), with boundary conditions in \( D \), \( U \) can be accurately represented by an approximate solution \( U_a \):

\[
U_a(x) = \sum_{j=1}^{N} U_j \varphi_j(x) \tag{1.1}
\]

where \( U_j, j = 1, \ldots, N \) are undetermined coefficients, and \( \varphi_j, j = 1, \ldots, N \), are known basis functions which are defined on each of the elements. Substituting \( U_a \) into the
nonlinear partial differential equation yields the nonzero residual, or error, \( R \):

\[
R = L(U_a) = L \left( \sum_{j=1}^{V} U_j \varphi_j \right).
\]

Since \( U_a \) is just an approximate solution, \( R \) cannot be null. However, in order for \( U_a \) to be as accurate as possible, the residual needs to be minimized. This is achieved by forcing \( R \) to zero in the following way. A set of weighting functions is chosen; in the GFEM this set is the same as the set of basis functions \( \varphi_j \) for \( j = 1, \ldots, N \) in (1.1). These basis functions are required to be the first \( N \) terms of a complete set. The inner product

\[
F_K = (R, \varphi_K) = \int_{D} R \varphi_K \, dx = 0, \quad \text{for} \quad K = 1, \ldots, N
\]

is then formed. Thus the residual is made orthonormal to the complete set of functions \( \varphi_k \). \( F \) is known as the weighted residual. The boundary conditions are then applied and the resulting set of nonlinear algebraic equations is solved for the \( N \) undetermined coefficients using an iterative root solver.

1.3.2 The Method of Characteristics.

The method of characteristics [34, 35] is applicable to quasilinear partial differential equations and yields an exact solution. The main idea behind the method of characteristics is to transform the partial differential equation into a set of ordinary differential equations which one can then solve exactly using the initial condition(s).

More precisely, given a quasilinear partial differential equation

\[
a(x, t, u) \frac{\partial u}{\partial t} + b(x, t, u) \frac{\partial u}{\partial x} = c(x, t, u),
\]

and an initial curve \( C \), the problem reduces to finding a surface in \((x, t, u)\)-space which satisfies (1.2) and which contains the initial curve. The vector \([a, b, c]\) determines a
direction, called the characteristic direction, at each point \((x, t, u)\). Thus, a family of curves can be constructed which have the characteristic direction at each point \((x, t, u)\). Let the family of curves be parametrized such that \(x = x(s), t = t(s), \) and \(u = u(s)\) then (1.2) can be rewritten as the set of ordinary differential equations

\[
\frac{dx}{ds} = a(x, t, u) \quad \frac{dt}{ds} = b(x, t, u) \quad \frac{du}{ds} = c(x, t, u)
\]  

(1.3)

The equations in (1.3) are called the characteristic equations of (1.2). In order to solve these characteristic equations, an initial condition of the form \(u(x(l), t(l)) = u(l)\) is necessary. The initial condition can be parametrized to define an initial curve \(x = x(l), t = t(l), u = u(l)\). In general, it is assumed that on the initial curve \(s = 0\) and \(x = l\). Hence, solutions of (1.3) will be functions of two parameters \(s\) and \(l\) with varying values of \(l\) corresponding to different points of intersection of the characteristic equations with the initial curve. The solution thus obtained is in general unique unless the initial curve is also a characteristic curve. The theorem stated below outlines the conditions that guarantee uniqueness of the solution of (1.3).

**Theorem 1.1**: Let \(a, b, \) and \(c\) in (1.2) have continuous partial derivatives in all three variables. Suppose the initial curve \(C\) given parametrically as \(x=x(l), t=t(l), \) and \(u=u(l)\) has a continuous tangent vector and that

\[
\Delta(l) \equiv \frac{dt}{dl} a[x(l), t(l), u(l)] - \frac{dx}{dl} b[x(l), t(l), u(l)] \neq 0,
\]

on \(C\). Then there exists one and only one solution \(u=u(x,t)\) defined in some neighborhood of the initial curve \(C\), that satisfies (1.2) and the initial condition \(u(x(l), t(l)) = u(l)\).

In this thesis, the method of characteristics is used as both an analytic and numerical tool.
1.4 THE MODEL

With the background from Sections 1.2 and 1.3, the model for cell replication in which the cells are both proliferating, maturing, and dying can now be constructed. This model was developed by Rey and Mackey [31, 32].

1.4.1 The Parameters.

Cells are actively proliferating if they are in the G1/S/G2/M cycle described in Section 1.2.1 and if they are committed to replicating their DNA and continuing through mitosis and cytokinesis to produce two daughter cells. Let \( a \) denote the cell age, i.e. the position of the cell in the cell cycle, with \( a \) ranging from \( a = 0 \), at the point of commitment, to \( a = \tau \), at the point of cytokinesis.

As well as proliferating, most cells also mature. The level of maturation is measured in different ways for different cells. In the case of the cells committed to the erythrocyte line of differentiation, the maturity of the cell can be measured by the hemoglobin content in the cell as explained in Section 1.2.3. Let \( x \) represent the maturation variable. The range of the values of \( x \) is taken from \( x = 0 \) to \( x = 1 \) without loss of generality. Since cells can mature at different rates (for instance in the case of cells in the erythrocyte line of differentiation the rate of maturity is controlled by the hormone erythropoietin (cf. Section 1.2.3)), a rate of maturation variable, \( r \), is also introduced. Here, the velocity of maturation is taken to be \( V(x) = rx \).

A cell can disappear at any time during its life. This death can be due to many reasons, for instance the cell might die of old age, be lost during a hemorrhage, or become diseased. Let \( \gamma \) denote the rate at which cells die. \( \gamma \) is positive and is assumed to be independent of the age or the maturation level of the cell.
Figure 1.4: A visualization of a proliferating and maturing cell.

The simultaneous proliferation and maturation of the cell can be visualized in Figure 1.4. Here the vertical axis represents the level of maturation ranging from $x = 0$ to $x = 1$ and the azimuthal axis represents the age of the cell ranging from $a = 0$ to $a = \tau$. Thus a cell’s trajectory, after entering the cell has entered the cylinder, can be visualized as a “spiral” curve going down and around the cylinder.

More precisely, a new born cell, in the case of an erythrocyte precursor, a cell born from a pluripotential stem cell, enters the cylinder. The cell then starts the $G_1/S/G_2/M$ cycle which is represented by going once around the cylinder. Each time a cell goes through this cycle it produces two daughter cells who are more mature than their parent. These daughters start their cycle closer to the bottom of the cylinder than their parent. The cell is ejected from the cylinder once it can no longer proliferate, in the case of the erythrocyte this occurs once the cell has extruded its nucleus. The cell is then considered mature.
1.4.2 Construction of the Model.

Let \( U(t, x, a) \) denote the density of proliferating cells, where \( x \) and \( a \) are as described in Section 1.4.1 and \( t \) is time, then

\[
\frac{\partial U}{\partial t} + \frac{\partial U}{\partial a} + \frac{\partial [a U]}{\partial x} = -\gamma U \tag{1.4}
\]

is the conservation equation for \( U(t, x, a) \) with initial condition

\[
U(0, x, a) = \Gamma(x, a) \quad \text{for} \quad (x, a) \in [0, 1] \times [0, \tau].
\]

The total number of proliferating cells is given by

\[
u(t, x) = \int_0^1 U(t, x, a) \, da \tag{1.5}
\]

and the boundary conditions for the system are

\[
U(t, x, 0) = \partial U(t, x, \tau) = \mathcal{F}(u(t, x)). \tag{1.6}
\]

The first equality reflects the fact that two daughter cells generated at \( a = \tau \), i.e. at the end of the cycle, constitute the input flux for the cell cycle at \( a = 0 \). The second equality states that the input flux \( \mathcal{F} \) is a function of the total number of proliferating cells at a given maturation level.

Equation (1.4) can be rewritten as

\[
\frac{\partial U}{\partial t} + \frac{\partial U}{\partial a} + r x \frac{\partial U}{\partial x} = -[\gamma + r] U \tag{1.7}
\]

The general solution of (1.7) can be calculated using the method of characteristics described in Section 1.3.2. The characteristic equations are:

\[
\frac{\partial t}{\partial s} = 1 \quad \frac{\partial a}{\partial s} = 1 \quad \frac{\partial x}{\partial s} = r x \quad \frac{\partial U}{\partial s} = -[\gamma + r] U
\]
which, after integration, give the set of parametric equations

\[ t(s) = s + t_0 \quad a(s) = s + a_0 \quad x(s) = x_0 e^{rs} \quad U(s) = U_0 e^{-[r+r]s}. \]

In order to obtain an explicit solution, two cases are considered: \( 0 \leq t \leq a \) and \( a < t \).

For \( 0 \leq t \leq a \), the initial condition \( U(0, x, a) = \Gamma(x, a) \) is used. Thus, \( t = s = 0 \) on the initial curve and

\[ t = s \quad a = t + a_0 \quad x = x_0 e^{rs} \quad U = U_0 e^{-[r+r]t}, \]

which gives

\[ U(t, x, a) = \Gamma(xe^{-rt}, a-t)e^{-[r+r]t} \quad 0 \leq t \leq a. \]

For \( a < t \), \( U(t, x, a) = U(t, x, 0) \). Thus, \( a = s = 0 \) on the initial curve and

\[ t = a + t_0 \quad a = s \quad x = x_0 e^{ra} \quad U = U_0 e^{-[r+r]a}, \]

which gives

\[ U(t, x, a) = U(t - a, xe^{-ra}, 0)e^{-[r+r]a} \quad a < t. \]

Hence,

\[ U(t, x, a) = \begin{cases} \Gamma(xe^{-rt}, a-t)e^{-[r+r]t} & 0 \leq t \leq a, \\ U(t - a, xe^{-ra}, 0)e^{-[r+r]a} & a < t \end{cases}. \quad (1.8) \]

Equation (1.7) can also be integrated over the age variable \( a \) which, in conjunction with (1.5), gives

\[ \frac{\partial u}{\partial t} + rx \frac{\partial u}{\partial x} = -[\gamma + r]u - \{U(t, x, \tau) - U(t, x, a)\}. \quad (1.9) \]

After applying the boundary conditions (1.6) and using the general solution (1.8), equation (1.9) becomes

\[ \frac{\partial u}{\partial t} + rx \frac{\partial u}{\partial x} = -[\gamma + r] + \begin{cases} \Gamma(xe^{-rt}, \tau-t)e^{-[r+r]t} & 0 \leq t \leq \tau, \\ F(u(t - \tau, xe^{-r\tau}))e^{-[r+r]r} & \tau < t \end{cases}. \quad (1.10) \]
The interesting case to study is when \( \tau < t \), i.e. when

\[
\frac{\partial u}{\partial t} + r x \frac{\partial u}{\partial x} = -[\gamma + r] \mathcal{F}(u(t - \tau, xe^{-r\tau}))e^{-(\gamma + r)\tau},
\]

(1.11) since one is mainly interested in the long time behaviour of the solution. As described above, the input flux \( \mathcal{F} \) is a function of the total number of proliferating cells at a given maturation level. The total number of proliferating cells is equivalent to the product of the proliferation rate and the cell density \( u \). The proliferation rate is a linearly decreasing function and is taken to be \((1 - u)\). \( \mathcal{F} \) is graphed in Figure 1.5.

Let

\[
\delta = \gamma + r \quad \text{and} \quad \lambda = ce^{-(\gamma + r)\tau} \quad \text{and} \quad \mathcal{F} = u(1 - u)
\]

then (1.11) becomes
Both the nonlocality \((xe^{-\tau})\) and the temporal \((t - \tau)\) retardation are clearly represented in (1.12). As will be seen in the next two chapters, these two features make the study of (1.11) extremely interesting. Furthermore, the study of systems with both nonlocality and temporal retardation have only previously been explored by Rey and Mackey [31, 32].

The following initial condition is prescribed

\[ IC : u(t - \tau, x) = \varphi(x). \]

The initial condition represents the cells entering the cylinder in Figure 1.4 from the pluripotent stem cell. If \(\varphi(0) = 0\), then the boundary condition

\[ BC : u(t, x = 0) = 0 \]

is also imposed.

### 1.5 DIFFERENTIAL DELAY EQUATIONS

#### 1.5.1 Introductory Remarks.

There is a game in the Boston Museum of Science which tests the speed at which you can respond to a visual signal. The idea of the game is to press a button as soon as a light appears on the screen in front of you. At the end of the game, the screen displays the time it took between the appearance of the light and the pressing of the button.
No matter how many times one tries, one cannot reduce the time to zero. This is because there is a time lag in between the visual message being transferred to the brain and the brain sending a message to your hand to press the button. Time lags appear in a large number of physiological processes and in many other systems. Thus when modelling most type of systems, since instantaneous transmission of information is virtually impossible, the time lag must be explicitly taken into account.

Systems in which the time lag is to be taken into account are modelled using differential delay equations (DDE). Ordinary differential equations (ODE) model systems whose future behaviour depends only on the present. Thus, given an ODE

$$\frac{dx(t)}{dt} = F(x(t))$$

(1.13)

where F can be a linear or nonlinear function of x, it suffices to specify an initial value for x at time $t = 0$ in order to predict the values of x for all times, $t > 0$.

DDE’s, on the other hand, model systems whose future behaviour depends on the present as well as on the past. Thus, given a DDE

$$\frac{dx(t)}{dt} = F(x(t), x(t - \tau)),$$

(1.14)

where $\tau$, the delay, is a parameter, one needs to specify an initial function on $[-\tau, 0]$ in order to predict the values of x for all times, $t > 0$. There are two types of possible delays. The discrete delay which implies that the present rate of change is affected by the value of some variable at time $t - \tau$; (1.14) is a DDE with discrete delay. A continuous delay implies that the present rate of change is affected by an integral over all the past values of some variable;

$$\frac{dx(t)}{dt} = F \left( x(t), \int_{-\infty}^{t} w(t - s)x(s)ds \right)$$

(1.15)

is a DDE with continuous delay. $w(t)$ is a weighting factor which says how much emphasis should be given to x at earlier times to determine the present effect. The
initial condition, in the case of a continuous delay, needs to be prescribed on the interval \((-\infty, 0]\).

It is interesting to note that if \(w(t)\) approximates the Dirac function \(\delta(\tau - t)\) then (1.15) reduces to (1.14):

\[
\frac{dx(t)}{dt} = F\left(x(t), \int_{-\infty}^{t} \delta(t - s)x(s)ds\right) = F(x(t), x(t - \tau)).
\]

Differential delay equations have recently been used to model various systems in many different areas ranging from control theory to economics. In the biological sciences, DDE's have been used to model the pupil light reflex [21, 20], blood cell dynamics [23], the control of respiration [9], population growth [28], and age structured models [36] to cite just a few. DDE's were first formulated in the late eighteenth century but it is only in the last half of this century that the subject of DDE's has been developed [14]. The recent interest in DDE's is not only due to the increase in demands for models of delayed feedback control loops but also to the diversified dynamics displayed by DDE's. For instance, a simple linear DDE [30] can exhibit oscillatory behaviour, such as stable limit cycle periodic solutions, where as this type of behaviour could never be expected from a single ODE such as (1.13). The complexity of the solution behaviour exhibited by DDE's stems partially from the fact that DDE's are infinite dimensional dynamical systems. Since it is necessary to specify an initial condition on an interval \([-\tau, 0]\) in the case of discrete delay, \((-\infty, 0]\) in the case of unbounded continuous delay), a DDE's phase space is a normed function space.
1.5.2 Two Examples of Biological Phenomena Modelled with a DDE.

The control of a physiological variable $u$ is often given by an equation of the form

$$\frac{du}{dt} = \text{production} - \text{destruction} = \alpha f(u(t - \tau)) - \beta u \quad (1.16)$$

where $f$ is a nonlinear function and $\alpha$ and $\beta$ are positive constants. Occasionally the nonlinear function $f$ is instead multiplied by $\beta$ and thus

$$\frac{du}{dt} = \text{production} - \text{destruction} = \alpha u - \beta f(u(t - \tau)).$$

The above model (1.12) is a variation of (1.16) and in fact can be reduced to (1.16) using the method of characteristics as will be shown in Chapter 3. In this section two other examples from physiology which can be modelled using a variation of (1.16) are given.

The first example is a model given by Glass and Mackey [25] for the control of carbon dioxide ($CO_2$) elimination. $CO_2$ is produced by body tissues at a constant rate $\zeta$ and is then released via ventilation. The levels of arterial $CO_2$, $u(t)$, is monitored by receptors situated in the brain stem. These receptors determine the level of ventilation. Since the blood needs to travel from the brain stem to the lungs for the $CO_2$ to be released, the ventilation, $V$, is a monotonic increasing function of arterial $CO_2$ levels at some time $\tau$ in the past and is described by

$$V = \frac{V_{\text{max}} u_\tau^n}{\theta^n + u_\tau^n}$$

where $V_{\text{max}}$ is the maximum ventilation and $\theta$ and $n$ are parameters used to describe the $CO_2$ response curve. It is assumed that the $CO_2$ is removed from the blood at a rate proportional to the product of the ventilation and the level of $CO_2$ in the blood.
Thus the fluctuations of the level of CO$_2$ in the blood can be modelled by

$$\frac{du(t)}{dt} = \zeta - \beta u(t) \frac{V_{max}u^n}{\theta^n + u^n}.$$

Glass and Mackey found that lengthening the delay or increasing the steepness of the CO$_2$ response curve causes the same breathing pattern observed in patients with Cheyne-Stokes respiration. Cheyne-Stokes respiration is a respiratory ailment characterized by regular waxing and waning of the ventilation separated by periods of apnea.

The second example is a model for the human pupil light reflex derived by Longtin and Milton [21, 20]. The pupil dilates and constricts depending on the intensity of the light source: the higher the intensity the smaller the pupil becomes. If $u(t)$ represents the size of the pupil and $\beta$, the intensity of the light source then the constrictions of the pupil can be modelled as

$$\frac{du(t)}{dt} = \alpha(u_0 - u) - \beta f(u(t - \tau)) - I$$

where $u_0$ is the maximum size of the pupil, $f$ is a piecewise constant function representing the feedback of the pupil to the light flux, $\alpha$ is the reciprocal of the time it takes for the pupil to constrict or dilate and $I$ is a forcing term. In this example, the delay represents the neural conduction time. Longtin and Milton found that the dynamics displayed by this model agreed with the experimental results and thus this model could be used as a tool to understand the causes of disease in the pupil light reflex pathways.

### 1.5.3 A Linear Stability Analysis of a Generic DDE.

As stated above, DDE's are infinite dimensional systems. For an ODE it is possible to obtain an analysis of the stability and bifurcations of steady states [15]. However,
the information obtained from this analysis is only sufficient to give a complete description of the global topological organization of the dynamics for one-dimensional ODE's. For higher dimensional ODE's, it is very difficult to obtain proofs of the topological properties of their solutions such as stability. One technique is to find a Lyapunov function. Given a differential equation, one tries to find a non-negative functional (called a Lyapunov function) of the solution which has a nonpositive derivative. The solution of the differential equation will then stay in the area described by the functional and the initial conditions. It is often very difficult to find a Lyapunov function. Similarly, for DDE's, although one can perform a linear stability analysis and occasionally find a Lyapunov function, knowledge of the global stability can most often only be obtained through numerical simulations.

A linear stability analysis for a DDE is carried out in the following way [10]. Consider the DDE (1.14)

\[
\frac{dx(t)}{dt} = F(x(t), x(t-\tau))
\]

with initial condition

\[ x(s) = G(s) \quad \text{for} \quad s \in [-\tau, 0]. \]

The steady states \( x^* \) of (1.14) are defined implicitly by \( F(x^*, x^*) = 0 \). A linear stability analysis is supposed to provide information about the stability of the steady states. Thus, one is interested in the perturbations about the steady states. Expanding (1.14) in a Taylor series in the neighborhood of \( x^* \) and ignoring all higher order terms, gives

\[
\frac{dm}{dt} = A m + B m_{t}, \quad (1.17)
\]

where

\[
m = x - x^* \quad A = \left. \frac{\partial F}{\partial x} \right|_{x^*} \quad B = \left. \frac{\partial F}{\partial x_{t}} \right|_{x^*}.
\]
Studying the local stability of (1.14) around the steady state $x^*$ is the same as studying the local stability of (1.17) around $m = 0$. Thus, one looks for solutions of the type $m(t) = ce^{\sigma t}$ which in conjunction with (1.17) gives

$$\sigma = A + Be^{-\sigma \tau}.$$  

Equation (1.18) is a transcendental equation whose solutions are the eigenvalues $\sigma$. These eigenvalues are in general complex, $\sigma = \mu \pm i\omega$. Since one is interested in the stability of $m = 0$, only the case where $Re(\sigma) < 0$ is considered (when $Re(\sigma) > 0$, $m$ grows exponentially with time and is thus unstable).

It is interesting to note that the transcendental equation (1.18) has infinitely many solutions and thus the DDE (1.14) also has infinitely many solutions. First note that there is a $\mu_0$ such that all solutions of (1.18) satisfy $Re(\sigma) < \mu_0$ (if $Re(\sigma)$ was not bounded then $|\sigma| \to \infty \Leftrightarrow e^{-\mu \tau} \to \infty \Leftrightarrow \mu \to -\infty$). One can now apply Picard’s theorem [26].

**Theorem 1.2 (Picard)**: Let $g$ have an essential singularity at $z_0$ and let $U$ be any deleted neighborhood of $z_0$. Then for all $w \in C$, except perhaps at one value, the equation $g(z) = w$ has infinitely many solutions $z$ in $U$.

In the generic DDE (1.17) if $z = 1/\sigma$ then (1.18) is equivalent to $g(z) = 0$ where

$$g(z) = A + Be^{-\tau z} = w$$

and thus $g(z)$ has an essential singularity at $z = 0$. Hence for all $w \in C$ except when $w = A$, $g(z)$ has infinitely many solutions $z$ in a deleted neighborhood of $z = 0$.

Going back to the stability analysis, in order to determine the range of $\tau$ for which $\mu < 0$, first consider the case where $\mu \equiv 0$ or $\sigma = i\omega$ is purely imaginary. Thus, (1.18) becomes

$$i\omega = A + Be^{-i\omega \tau}$$
or

\[ i \omega = A + B \cos \omega \tau - \omega B \sin \omega \tau. \]  \hfill (1.19)

Equating real and imaginary parts of (1.19) gives the following two equations

\[ B \cos \omega \tau = -A \quad \omega = -B \sin \omega \tau. \]

Squaring both these equations and adding them gives

\[ \omega = (B^2 - A^2)^{1/2}. \]

One can also obtain an expression for the delay at \( \mu \equiv 0 \). Since \( \omega \tau = \cos^{-1}(-A/B) \),

\[ \tau = \frac{\cos^{-1}(-A/B)}{(B^2 - A^2)^{1/2}}. \]

These results match those obtained by El'sgol'ts [6] who showed, using the amplitude-phase method, that if \( \mu \leq 0 \) then the steady state \( x^* \) of (1.14) will be locally stable if

\[ |A| > |B| \]

or

\[ |A| < |B| \quad \text{and} \quad \tau = \frac{\cos^{-1}(-A/B)}{(B^2 - A^2)^{1/2}}. \]

The model (1.12) which is to be studied in this thesis is a partial differential delay equation (PDDE). Thus to study the local stability of its steady states it is first necessary to reduce it to an ODE using the method of characteristics. This linear stability analysis will be done in Chapter 3. Reducing a PDDE to a DDE in order to perform a linear stability analysis is one way of obtaining some insight into the global behaviour. It is also sometimes possible to find a Lyapunov function which implies uniform asymptotic stability for all delay \( \tau \) [14]. In the case of the model (1.12), due not only to the fact that partial differential equations as well as differential delay equations are infinite dimensional systems but also to the retardation in both time
and space, very few analytical results can be obtained. The only previous work on systems like (1.12) has been done by Rey and Mackey [31, 32], whose results are mainly numerical. However some analytical results have been obtained for systems like (1.12) with no delay. The stability and uniqueness results obtained by Lasota [19] are especially pertinent. In the next section, a brief summary of these results is given.

1.6 SOME PERTINENT MATHEMATICAL RESULTS

Lasota considered the following partial differential equation

\[
\frac{\partial u}{\partial t} + c(t,x) \frac{\partial u}{\partial x} = f(t,x,u) \quad \text{for} \quad (t,x) \in D
\]  (1.20)

with initial condition

\[ u(0,x) = v(x) \quad \text{for} \quad x \in \Delta. \]  (1.21)

In (1.20) and (1.21), \( \Delta = [0,1] \), \( D = [0,\infty) \times \Delta \) and \( c(t,x) \) and \( f(t,x,u) \) are given continuously differentiable functions defined for \( (t,x) \in D \) and \( u \geq 0 \) and satisfying the following conditions

\[
c(t,x) \geq 0 \quad \text{for} \quad (t,x) \in D
\]

\[
f(t,x,0) \geq 0 \quad \text{for} \quad (t,x) \in D
\]

\[
f(t,x,u) \leq k_1(t)u + k_2(t) \quad \text{for} \quad (t,x) \in D, \quad u \geq 0
\]  (1.22)

where \( k_1 \) and \( k_2 \) are continuous coefficients.
1.6.1 Uniqueness and Stability Criteria for the Nonautonomous Equation.

The first result gives the conditions for which the solution of equation (1.20) with the initial condition (1.21) is unique. Let $C^1_+(D)$ and $C^1_+(\Delta)$ denote the space of all nonnegative continuously differentiable functions defined on $D$ and $\Delta$ respectively.

**Theorem 1.3 (Lasota):** Suppose that $c$ and $f$ satisfy (1.22) and, in addition, $c$ satisfies

$$c(t,x) = 0 \quad \text{for} \quad t \geq 0. \quad (1.23)$$

Then for each $v \in C^1_+(\Delta)$ equation (1.20) with (1.21) has a unique solution $u \in C^1_+(D)$. Conversely, if for one $v \in C^1_+(\Delta)$ equation (1.20) with (1.21) has a unique solution $u \in C^1_+(D)$ then $c$ satisfies (1.23).

In order to state the stability criteria for the nonautonomous equation (1.20), the following conditions are necessary.

$$c(t,x) \geq c_0(x) > 0 \quad \text{for} \quad (t,x) \in D, \quad x > 0, \quad (1.24)$$

where $u > 0$ is a given number, $c_0$ is a continuous function, and $f_0$ is a continuous bounded function such that

$$f_0(x,0) \leq 0, \quad f_0(0,u) < 0 \quad \text{for} \quad x \in \Delta, \quad u > 0. \quad (1.25)$$

**Theorem 1.4 (Lasota):** Suppose that $c$ and $f$ satisfy conditions (1.23) and (1.24). Then for each $v \in C^1_+(\Delta)$, $v(0) > 0$ the solution $u$ of (1.20) with (1.21) satisfies

$$\lim_{t \to \infty} u(t,x) = u_0 \quad \text{uniformly for} \quad x \in \Delta.$$
1.6.2 Uniqueness and Stability Criteria for the Autonomous Equation.

The results in this section are for the autonomous case of equation (1.20). Thus, consider the partial differential equation

$$\frac{\partial u}{\partial t} + c(x)\frac{\partial u}{\partial x} = f(x, u) \quad \text{for} \quad (t, x) \in D = [0, \infty) \times \Delta \quad (1.26)$$

with initial condition

$$u(0, x) = v(x) \quad \text{for} \quad x \in \Delta = [0, 1]. \quad (1.27)$$

Both $c$ and $f$ are continuously differentiable and satisfy the following conditions.

$$c(0) = 0, \quad c(x) > 0 \quad \text{for} \quad 0 < x \leq 1,$$

$$f_u(0, u_0) < 0, \quad f(0, u)(u - u_0) < 0 \quad \text{for} \quad u > 0, \quad u \neq u_0$$

$$0 \leq f(x, 0), \quad f(x, u) \leq k_1 u + k_2 \quad \text{for} \quad x \in \Delta \quad u \geq 0,$$  

where $k_1$ and $k_2$ are positive constants and $u_0 > 0$.

**Theorem 1.5 (Lasota):** Suppose that $c$ and $f$ satisfy (1.28) and that $v(0) > 0 \ (v \in C^+(\Delta))$. Then the solution $u$ of (1.26) with (1.27) satisfies

$$\lim_{t \to \infty} u(t, x) = w_0(x) \quad \text{uniformly for} \quad x \in \Delta,$$

where $w_0(x)$, which is differentiable for $0 < x \leq 1$ and continuous for $x \in \Delta$, is the unique solution of the initial value problem

$$c(x)\frac{dw}{dx} = f(x, w), \quad 0 < x \leq 1, \quad w(0) = u_0.$$

The most interesting result of [19] has to do with the lack of stability of the solution $u$ of (1.20). In order to present this result, some terminology must first be introduced.
Consider the solutions of (1.26) with (1.27) as the trajectories of the semi-dynamical system \( \{S_t\}_{t \geq 0} \) defined by

\[(S_tv)(x) = u(t, x).\]

Each \( S_t \) is a continuous map from \( C_+(\Delta) \) into itself and

\[S_0v = v \quad S_{t_1}(S_{t_2}v) = S_{t_1} + S_{t_2} \quad \text{for } t_1, t_2 \geq 0, \quad v \in C_+(\Delta).\]

Also, define the two sets

\[V_0 = \{v \in C_+(\Delta) : v(0) = 0\}\]

and

\[V_w = \{v \in V_0 : v(x) < w_0(x) \quad \text{for} \quad x \in \Delta\}.
\]

Let \( \{S_t\}_{t \geq 0} \) denote an arbitrary semidynamical system acting on an arbitrary metric space \( V \). A point \( v \in V \) is called stable if for any sequence \( v_n \in V \) the condition \( v_n \to v \) as \( n \to \infty \) implies \( S_tv_n \to S_tv \) uniformly for all \( t \geq 0 \). The system \( \{S_t\} \) is called chaotic if

1. every point \( v \in V \) is unstable
2. there exists \( v \in V \) such that the trajectory \( \{S_tv : t \geq 0\} \) is dense in \( V \).

With the above definitions in mind, the important theorem can now be stated.

**Theorem 1.6 (Lasota)**: Suppose that \( c \) and \( f \) satisfy (1.28) and

\[f(0, 0) = 0.\]

Then the semidynamical system \( \{S_t\}_{t \geq 0} \) generated by the initial value problem of equation (1.26) with (1.27) is chaotic in \( V_w \).
1.7 CONCLUSION

In this chapter the model (1.12), whose study will be the focus of this thesis, was introduced. Its interesting and unusual features, such as the temporal retardation and the spatial nonlocality, were pointed out and the difficulties in obtaining insight into the dynamics of such a DDE were discussed. The results on the existence and stability of solutions of systems like (1.12) with no delay were also presented. The stability of solutions, the effects of changing the initial condition and the potential existence of chaotic solutions in the system (1.12) will be investigated in the next two chapters.
Chapter 2

2.1 INTRODUCTION

In this chapter the dynamics of the model for proliferating and maturing cellular populations, described in Chapter 1, are studied for a specific initial condition, \( \varphi(x) = x^n \) for \( n >> 1 \). The effect of the model parameters on the solution behaviour is investigated using both the Galerkin Finite Elements Method and the method of characteristics to integrate the partial differential delay equation.

Recall that the model is described by

\[
\frac{\partial u}{\partial t} + r x \frac{\partial u}{\partial x} = -\delta u + \lambda u_r(l - u_r),
\]

(2.1)

where the input flux \( \mathcal{F} \) has been taken as

\[
\mathcal{F}(u) = u(1 - u),
\]

\( \delta \) and \( \lambda \) are given by

\[
\delta = \gamma + r \quad \text{and} \quad \lambda = ce^{-(\gamma+r)r},
\]

and \( \gamma \) is the rate at which cells die. The maturation velocity is given by \( rx \) with \( r > 0 \). \( c \) is a constant. \( u_r \) is defined as

\[
u_r(t, x) \equiv u(t - \tau, xe^{-\tau}).\]
In this chapter, the following initial and boundary conditions are imposed:

\[ IC : u(t, x) = x^n \quad (t, x) \in [-\tau, 0] \times [0, 1] \text{ and } n >> 1 \]

\[ BC : u(t, x = 0) = 0 \quad t \in [-\tau, \infty]. \]

2.2 NUMERICAL METHODS OF SOLUTION

The non delayed partial differential equation is integrated analytically in Section 2.3. In this section, the two numerical methods, the GFEM and the method of characteristics, used to integrate the delayed partial differential equation are described.

2.2.1 The Galerkin Finite Elements Method.

Following the GFEM described in Chapter 1, assume an approximate solution \( u_a(t, x) \) of the form

\[ u_a(t, x) = \sum_{j=1}^{N} u_j(t) \varphi_j(x), \]

where \( N \) is the number of nodes in the spatial discretization, and form the residual \( R \):

\[ R = \frac{\partial u_a}{\partial t} + r x \frac{\partial u_a}{\partial x} + \delta u_a - \lambda u_{ar}(1 - u_{ar}). \]

Forcing \( R \) to zero yields the set of \( N \) nonlinear ordinary differential equations:

\[ F_i = \int_0^1 \left[ \frac{\partial u_a}{\partial t} + r x \frac{\partial u_a}{\partial x} + \delta u_a - \lambda u_{ar}(1 - u_{ar}) \right] \varphi_i dx \quad i = 1, \ldots, N. \]

A time discretization is then implemented using a finite difference scheme and the resulting set of nonlinear algebraic equations can be solved using an iterative root finder.
The Jacobian $J$ is calculated:

$$J_{ij} = \frac{\partial F_i}{\partial a_j}, \quad i = 1, \ldots, N \quad j = 1, \ldots, N$$

or

$$J_{ij} = \int_0^1 \left[ \frac{\varphi_i}{\Delta t} + r x \frac{d\varphi_j}{dx} + \delta \varphi_i \varphi_j - \lambda [\varphi_j(1 - u_{ar}) - u_{ar} \varphi_j] \varphi_i \right] dx$$

and the following Newton Raphson iteration scheme, to solve for $u_j$, is implemented

$$0 = F + J \cdot [u_{\text{new}} - u_{\text{old}}]$$

or

$$u_{\text{new}} = u_{\text{old}} - (J^{-1}F)_{u_{\text{old}}}.$$

The code for the GFEM is written in FORTRAN and can be found in Appendix A. Linear basis and weighting functions are used with a uniform mesh of 400-600 elements ($N=401-601$). The time integration scheme is a first order implicit predictor corrector method with fixed time step. With no delay the time step is $h = 1/50$, and with delay the time step is $h = \tau/50$.

2.2.2 The Method of Characteristics.

Following the method of characteristics described in Chapter 1, (2.1) is integrated with respect to time along its characteristics.

The $x$ characteristics are given by $x(t) = \varepsilon e^{\tau t}$. Along these characteristics, (2.1) is rewritten as

$$\frac{du}{dt} = -\delta u + \lambda u_r (1 - u_r)$$

where

$$u(t, x(t)) \equiv u(t, \varepsilon e^{\tau t})$$
and

\[ u_r(t, x(t)) \equiv u(t - \tau, x e^{r(t-\tau)}) \]

The code for the integration along characteristics is written in C and can be found in Appendix B. A fourth order Runge Kutta method is used with a constant time step of \(10^{-5}\).

\[ 2.3 \] RESULTS FOR \( \tau=0 \).

The system with no delay is given by

\[ \frac{\partial u}{\partial t} + r x \frac{\partial u}{\partial x} = -\delta u + \lambda u(1 - u) \] \hfill (2.2)

where

\[ \delta = \gamma + r \quad \text{and} \quad \lambda = c \]

and the initial and boundary conditions are:

\[ IC: u(0, x) = x^n \quad x \in [0, 1] \]

\[ BC: u(t, x = 0) = 0 \quad t \in \mathbb{R}^+. \]

An analytic solution can be obtained using the method of characteristics. The characteristic equations of (2.2) are

\[ \frac{dt}{ds} = 1 \quad \frac{dx}{ds} = r x \quad \frac{du}{ds} = -\delta u + \lambda u(1 - u), \]

which, after integration, become

\[ t = s + t_0, \quad x = x_0 e^{rs}, \quad \text{and} \quad u = \frac{\lambda - \delta}{\lambda - u_0 e^{-s(l-\delta)}}. \] \hfill (2.3)

The initial function, \( \varphi(x) = x^n \), can be parametrized as
Figure 2.1: The three types of long term behaviour for \( \varphi = x^n \) with \( \delta = 1, \lambda = 3 \).

\[
x(l) = l \quad t(l) = 0 \quad u(l) = l^n.
\]

Applying this initial condition to (2.3) gives

\[
s = t, \quad l = xe^{-rs}, \quad \text{and} \quad u_0 = \lambda - \frac{\lambda - \delta}{(xe^{-r})^n},
\]

so the final solution is

\[
u(t, x) = \frac{\left[ \frac{\lambda - \delta}{\lambda} \right] (xe^{-rt})^n e^{t(\lambda - \delta)}}{(xe^{-rt})^n(e^{t(\lambda - \delta)} - 1) + \left[ \frac{\lambda - \delta}{\lambda} \right]}.
\] (2.4)

For \( \tau = 0 \), Lasota [19] showed that the solution of systems like (2.1), with \( \varphi(0) = 0 \), are chaotic in a function space in the sense that the long term behaviour of \( u(t, x) \) is sensitively dependent on the initial function \( \varphi(x) \). This result was stated at the end of Chapter 1. It is illustrated by the long term behaviour of the analytic solution
\[ (2.1) \text{ as follows:} \]
\[ \lim_{t \to \infty} u(t, x) = \begin{cases} 
0 & 0 < \lambda - \delta < nr \\
\frac{(\lambda - \delta)x^n}{\lambda - \delta + \lambda x^n} & \lambda - \delta = nr \\
\frac{\lambda - \delta}{\lambda} & \lambda - \delta > nr
\end{cases}. \] \hspace{1cm} (2.5)

These three types of solution behaviour are illustrated in Figure 2.1. The case where

\[ \lim_{t \to \infty} u(t, x) = \frac{\lambda - \delta}{\lambda} \text{ for } nr < \lambda - \delta \]

will be considered in the remainder of this section.

The solution behaviour obtained for \( nr < \lambda - \delta \), when \( n \) is taken to be sufficiently large, is that of moving fronts. Front solutions, as defined by Collet and Eckman [4], "interpolate between two (different) stationary solutions at \( x = \pm \infty \); in addition, they move with a certain speed in the laboratory frame". Here, this definition is slightly modified. Since \( x \) is only considered in the interval \([0, 1]\), the front solution interpolates between two stationary solutions, namely the trivial solution, at \( x = 0 \), and the solution \( \frac{\lambda - \delta}{\lambda} \), at \( x = 1 \). The requirement that the front solution be a smooth differentiable curve is also added.

The solution behaviour of moving fronts is illustrated in Figures 2.2 and 2.3 where the analytically computed cell densities for different values of \( n \) and \( r \) (remember \( \tau = 0 \)) are shown. The fronts appear at early times and move from right to left until they encounter an impermeable boundary created by the imposed boundary condition which does not allow the solution to go pass \( x = 0 \). The solution starts, for small \( x \), as the trivial solution and, as \( x \) increases from 0 to 1, undergoes a smooth transition from this trivial solution to the steady solution, \( \frac{\lambda - \delta}{\lambda} \). As \( t \) is increased, the slopes of the part of the solution connecting the two steady states become steeper as the long time solution takes over from the trivial solution. By the time the front has hit the impermeable boundary, the trivial solution has completely disappeared, except at \( x = 0 \) where it is imposed by the boundary condition.
2.3.1 Effect of Varying $n$.

As shown in Figure 2.2, as $n$ is increased the speed at which the front propagates towards the impermeable boundary decreases. Also, the slope of the part of the solution connecting the two steady states becomes steeper. This increase in steepness is caused by the initial condition, i.e. the solution at time $t = 0$, since as $n$ is increased, the slope of the initial condition becomes steeper.

2.3.2 Effect of Varying $r$.

As shown in Figure 2.3, as $r$ is increased the change in speed at which the front propagates towards the impermeable boundary is hardly noticeable. One can observe a small decrease in the speed as $r$ increases from $r = 0.01$ to $r = 0.1$. $r$
Figure 2.3: Effect of varying $r$ on the solution behaviour for $n=5$, $\delta=1$, $\lambda=3$. cannot be increased past $r=1$ with the parameters chosen in Figure 2.3 since this would bring on a change in stability ($nr$ would become greater than $\lambda-\delta$ and hence $\lim_{t\to\infty} u(t,x)=0$).

With the delay $\tau=0$, increasing $n$ or increasing $r$ slows down the rate at which the solution arrives at its long time behaviour, and hence reduces the speed at which the front propagates towards the impermeable boundary. A clearer way of seeing how the parameters affect the speed of propagation is in a graph of the velocities for different parameter values.

One can calculate the velocity of these fronts from the analytic solution (2.4). First rewrite (2.4) as a function of $x$:

$$x = \frac{(\lambda - \delta)u(t, x)e^{rt}}{\{\lambda[1 - u(t, x)] -\delta\}e^{(\lambda-\delta)} + \lambda u(t, x)}.$$  \hspace{1cm} (2.6)

The speed of the front can be calculated from the speed of one point, $x^t$. Pick $x^t$ so
Figure 2.4: Spatial dependance of the moving front velocities for different values of $n$ with $r = 0.01$, $\delta = 1$ and $\lambda = 3$.

that $u = u_{\text{avg}}$ where $u_{\text{avg}} = \frac{\lambda - \delta}{2\lambda}$ (which is the value of $u$ midway between the trivial solution 0 and the steady state solution $\frac{\lambda - \delta}{\lambda}$). Then for each $t$ there will be an $x = x^t$ such that

$$u_{\text{avg}}(t, x^t) = \frac{\left[\frac{\lambda - \delta}{\lambda}\right](x^t e^{-rt})^n e^{t(\lambda - \delta)}}{(x^t e^{-rt})^n (e^{t(\lambda - \delta)} - 1) + \left[\frac{\lambda - \delta}{\lambda}\right]},$$

hence, by (2.6),

$$x^t = \frac{(\lambda - \delta)u_{\text{avg}}(t, x^t) e^{rt}}{\{\lambda [1 - u_{\text{avg}}(t, x^t)] - \delta\} e^{t(\lambda - \delta)} + \lambda u_{\text{avg}}(t, x^t)}.$$

Therefore, the velocity of the front is given by

$$\frac{dx^t}{dt} = \left[re^{rt} - \frac{(\delta - \lambda[1 - u_{\text{avg}}])(\lambda - \delta)e^{t(\lambda - \delta + r)}}{n\{(\delta - \lambda[1 - u_{\text{avg}}])e^{t(\lambda - \delta)} - u_{\text{avg}}\lambda\}}\right] \times \left[\frac{(\delta - \lambda)u_{\text{avg}}}{(\delta - \lambda[1 - u_{\text{avg}}])e^{t(\lambda - \delta)} - u_{\text{avg}}\lambda}\right]^{1/n}$$

(2.7)
Figure 2.5: Spatial dependence of the moving front velocities for different values of $r$ with $n = 5$, $\delta = 1$, and $\lambda = 3$.

The analytically calculated velocities are shown in Figures 2.4 and 2.5 for different values of $n$ and $r$ respectively. The velocities are plotted in Figures 2.4 and 2.5 as a function of $x$ and it is interesting to note that the velocities $\frac{dx^t}{dt}$, which are represented by lines of negative slope starting at 0, are linear functions of $x^t$. The values of the velocities are all negative since the fronts are moving from right to left. The results of the velocity profiles are in accord with the behaviour shown in Figures 2.2 and 2.3.
There is no known method with which to obtain an analytic solution of (2.1). With certain initial conditions one can obtain insight into the local stability of the steady states of a delayed partial differential equation [10]. However, this is not possible with a nonlinear initial condition such as $\varphi = x^n$. Hence all the results obtained in this section are numerical. The accuracy of these results was checked in three ways.

1. The numerical solutions obtained with $\tau = 0$ were compared to the analytic solution (2.4).

2. In the GFEM, the number of elements were doubled and quadrupled to check for changes in the solution behaviour. These results are shown in Figure 2.6.
where the maximum difference between the solution behaviour obtained with N elements and the solution behaviour obtained with N/2 elements is plotted versus the number of elements. This figure shows that no significant change in solution occurs after N=200.

3. The solutions obtained with the GFEM were compared to those obtained numerically using the method of characteristics for $\tau > 0$.

The results obtained from all of these checks indicate that the code is correct in the sense that the numerically determined solutions match the analytic ones. Throughout this section $\delta = 1$, $\lambda = 3$, $r = 0.01$, and $n = 20$.

2.4.1 Effect of Increasing $\tau$.

The effect of increasing $\tau$ is illustrated in Figure 2.7. When $\tau$ is close to 0, the solution is similar to the solution for $\tau = 0$, i.e. the solution for small $x$ starts at the trivial solution, and as $x$ increases towards 1, smoothly approaches the $\frac{1-\delta}{\lambda}$ solution. However, the speed at which the front moves towards the impermeable boundary has decreased. Comparing the graph of $n = 20$ in Figure 2.2c, where $\tau = 0$, to the graph of $\tau = 0.1$ in Figure 2.7a, one can see that the solution for $t = 10$ for $\tau = 0.1$ is noticeably above the trivial solution at $x \approx 0.4$, while the solution at the same time, for $\tau = 0$, is already noticeably above the trivial solution at $x \approx 0.3$. This decrease in speed continues as $\tau$ is increased until the front completely disappears for a critical value of $\tau = \tau_c$ at which point the solution is no longer attracted to the $\frac{1-\delta}{\lambda}$ solution. As shown in Figure 2.7, this transition appears between $\tau = 4$ (Fig. 2.7e) and $\tau = 4.75$ (Fig. 2.7f).

Another change in the solution behaviour occurs as $\tau$ is increased from 0 to $\tau_c$. Although the solution still starts out at the trivial solution for small $x$, as $x$ increases,
Figure 2.7: Effect of increasing $\tau$ on the solution behaviour for $n = 20$, $r = 0.01$, $\delta = 1$, and $\lambda = 3$. 
Figure 2.8: Spatial dependance of the moving front velocities for different values of \(\tau\) for \(n = 20\), \(r = 0.01\), \(\delta = 1\), and \(\lambda = 3\).

Instead of making the transition smoothly to the \(\frac{\lambda - \delta}{\lambda}\) solution, the solution approaches \(\frac{\lambda - \delta}{\lambda}\) in an oscillatory fashion. The amplitude of these oscillations increases as \(\tau\) increases. This is clearly observed, in Figure 2.7, by the change in solution behaviour between \(\tau = 0.5\) (Fig. 2.7b) and \(\tau = 4\) (Fig. 2.7e).

### 2.4.2 Effect of \(\tau\) on the Velocity of the Front Solutions.

As observed in Figure 2.7, when \(\tau\) is increased from 0 to a \(\tau_c\), the speed at which the front propagates towards the impermeable boundary decreases. This is further illustrated in Figure 2.8 where the velocity profiles for different values of \(\tau\) are plotted. The velocity for \(\tau = 0\) was calculated from the analytic solution (2.7), while the velocities for \(\tau > 0\) are calculated using a difference scheme. Due to the computer
Figure 2.9: A change in solution behaviour as $\tau$ is increased for $n = 20$, $r = 0.01$, $\delta = 1$, and $\lambda = 3$.

limitations, it was necessary to smooth the velocities obtained with the difference scheme. This was done using linear regression. As in Figures 2.4 and 2.5, the velocities for the different values of $\tau$ are represented by lines of negative slope starting at 0 and the values of the velocities are all negative since the fronts are moving from right to left. Thus even with the delay greater than zero, the velocities remain linear functions of $x$. The results in Figure 2.8 indicate that the more $\tau$ is increased the smaller the difference in the velocities become, i.e. $|velocity_{\tau=1} - velocity_{\tau=0}| > |velocity_{\tau=2} - velocity_{\tau=1}|$. Thus, the more $\tau$ is increased the smaller the decreases in speed at which the front propagates towards the impermeable boundary become.

2.4.3 A New Solution when $\tau > \tau_c$. 

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Figure 2.10: Oscillations in the solution behaviour for $t \approx 100$ for various values of $\tau$ with $n = 20$, $r = 0.01$, $\delta = 1$, and $\lambda = 3$.

In Figure 2.7, it was observed that for $\tau > \tau_c$ the solution $u(t, x)$ is no longer attracted to $\frac{\lambda - \delta}{\lambda}$. This is further illustrated in Figure 2.9 where one can see that after $\tau \approx 4.5$ the solution is attracted to the trivial solution. This bifurcation in solution behaviour is due to the fact that the long time behaviour switches from the $\frac{\lambda - \delta}{\lambda}$ solution, for $\tau < \tau_c$ to the trivial solution when $\tau > \tau_c$. This switch is the same that Lasota [19] predicted analytically for $\tau = 0$ when $nr > \lambda - \delta$ (cf Equation (2.5)).

2.4.4 An Oscillating Solution Around $\frac{\lambda - \delta}{\lambda}$.

In Figure 2.7, it was observed that oscillations appeared with a small visible peak for $\tau = .5$ and that as $\tau$ was increased the amplitude of the oscillations became larger. This is further illustrated in Figure 2.10 where the solution behaviour is shown for
Figure 2.11: Oscillations in the solution behaviour for \( \tau = 3 \) for various times with \( n = 20, \tau = 0.01, \delta = 1 \) and \( \lambda = 3 \).

\( t \approx 100 \) with various values of \( \tau \). The amplitude of the oscillations, observed in Figure 2.10, decreases as \( x \) increases; these oscillations are therefore damped oscillations. Further, as \( \tau \) is increased the wave length increases. Hence, the results shown in Figure 2.10 indicate that the oscillations in the solution behaviour are damped with increasing wave length as \( \tau \) is increased. To illustrate the solution behaviour for a fixed \( \tau \), the solution at \( \tau = 3 \) for various times is plotted in Figure 2.11. The results indicate that the leading peak for each time attains the same height as do the successive peaks. Thus, time does not modify the amplitude of the oscillation. However, the wave length decreases as time increases.

Thus, \( \tau \) affects both the amplitude and the wave length of the oscillations while time affects only the wave length.
Figure 2.12: Phase-plane diagrams of the solution behaviour for various values of $\tau$ with $n = 20$, $r = 0.01$, $\delta = 1$, $\lambda = 3$.

To obtain further insight into these phenomena, the $(u, u_x)$ phase-plane diagrams of the solution behaviour are shown in Figures 2.12 and 2.13 where $du(t,x)/dx$ is plotted versus $u(t,x)$. The phase-plane diagram for $\tau = 0$ was obtained using the analytic solution (2.4):

$$
\frac{du}{dx} = \frac{[(\lambda - \delta) / \lambda]^2 (xe^{-rt})^n re^{(\lambda - \delta)}}{[(xe^{-rt})^n (e^{(\lambda - \delta)} - 1) + [(\lambda - \delta) / \lambda]^2] x}.
$$

The phase diagrams for $\tau > 0$ were obtained using a difference scheme. The phase-plane diagrams are not completely smooth for $\tau > 0$ because of computational limitations.

In the phase diagrams, the increase in the steepness of the front is shown by the increase in the values of $du/dx$. For instance, comparing the phase diagrams in...
Figure 2.13: Phase-plane diagrams of the solution behaviour for $\tau = 3$ for various times with $n = 20$, $r = 0.01$, $\delta = 1$, and $\lambda = 3$.

Figure 2.12 for $\tau = 0$ (Fig. 2.12a) and $\tau = 1$ (Fig. 2.12b), one can see that the change in steepness of the front is not as great between times $t = 10$ and $t = 30$. This is due to the fact that the speed of propagation of the front is slower for $\tau = 1$ than for $\tau = 0$. Further, the appearance of the oscillations is reflected in the curl around the point $u(t, x) = \frac{\lambda - \delta}{\lambda}$. The differences in the curls for $\tau = 1$ (Fig. 2.12b) and for $\tau = 3$ (Fig. 2.12c) illustrate that, as $\tau$ is increased, the amplitude and the wave length of the oscillations become greater.

The interesting behaviours observed above led to a literature search to see if the change from a monotone front to an oscillatory front had previously been observed. Although no one seems to have observed this change in solution behaviour in DDE's, it has been observed in the solution behaviour of the Kdv Burger’s equation [16].
The Kdv Burger's equation is given by

\[ u_t + uu_x - \mu u_{xx} + \beta u_{xxx} = 0 \]  \hspace{1cm} (2.8)

where \( \beta \) is a dispersive parameter and \( \mu \) is a dissipative parameter. By letting

\[ u(t, x) = u(x - Wt) \]

(2.8) can be rewritten as the ordinary differential equation

\[ \beta u'' - \mu u'' + u'(u - W) = 0 \]  \hspace{1cm} (2.9)

which, with the condition

\[ u = u' = u'' = 0 \quad \text{as} \quad x \to \infty \]

and after integration, gives

\[ \beta u'' - \mu u' + \frac{1}{2} u^2 - W u = 0. \]  \hspace{1cm} (2.10)

The solution of (2.10) is a shock wave of velocity \( W \). The nature of the structure of the shock wave depends on the relation between the dispersive parameter \( \beta \) and the dissipative parameter \( \mu \). For \( \beta > 0 \) and large \( \mu \) the solution is that of a moving front propagating from left to right with velocity \( W \). This is the same behaviour observed for \( \tau = 0 \) in Figures 2.2 and 2.3, except that the wave was moving from right to left. As \( \mu \) is decreased to a very small value oscillations appear at the wave front, dying out as they move away from the front. This is the same behaviour observed in Figures 2.7 and 2.10 when \( \tau \) is increased. The first few oscillations in both the biological model and Kdv Burger's equation are similar to solitons. In the case of the Kdv Burger's equation the solitons are moving with velocity \( W \). Solitons, as defined by Lamb \[17\], "take the form of localized disturbances, or pulses, that retain their shape even after interaction among themselves, and thus act somewhat like particles."
The value of $\mu$ for which oscillations appear can be calculated analytically. However, the value for $\tau$ at which oscillations appear cannot because no analytic solution and no insight into the steady states is obtainable for the delayed partial differential equation with a nonlinear initial condition. Furthermore, this value of $\tau$ cannot be calculated numerically since oscillations might be present but not picked up due to the lack of precision of the computer.

2.5 CONCLUSION

The numerical study of (2.1), with initial condition $\varphi(x) = x^n$ for $n \gg 1$, leads to some very interesting solution behaviour. The solution with no delay is a propagating wave front. The parameters $n$ and $r$ vary the speed at which the front propagates and can also lead to a change in stability. The solution with delay is also that of a propagating front. However as the delay is increased, oscillations appear near the wave front. This type of solution can be associated with solitons. As the delay is increased past a critical delay, there is a change in stability, and the long term behaviour becomes that of the trivial solution.
Chapter 3

3.1 INTRODUCTION

In Chapter 2, the dynamics of the model for proliferating and maturing cellular populations, described in Chapter 1, were studied for the initial function $\varphi(x) = x^n$. In this chapter, the dynamics of the model are studied for a special case of this initial condition, namely $n = 1$ so, $\varphi(x) = x$. With this initial condition, varying the parameters of the model can lead to different types of dynamics ranging from a single stationary steady state to turbulent solution behaviour. In order to present this behaviour, an introduction to steady states, stability analysis and bifurcations is first given in Section 3.2. In Section 3.3, the previous results obtained by Rey and Mackey [31, 32] for $\varphi(x) = x$ are summarized before presenting some new results in Section 3.4.

As in Chapter 2, the numerical methods used to integrate the partial differential delay equation are the Galerkin finite elements method and the method of characteristics. The analytic results obtained for $\tau = 0$ and $\varphi(x) = x^n$ in Section 2.3 clearly hold for $\varphi(x) = x$ with $n = 1$. Recall that the model is described by

$$\frac{\partial u}{\partial t} + r_x \frac{\partial u}{\partial x} = -\delta u + \lambda u_r(1 - u_r), \quad (3.1)$$
where $u_r$ is defined by

$$u_r(t, x) \equiv u(t - \tau, xe^{\tau r}).$$

In this chapter, $\tau$ is to be 1 without loss of generality.

### 3.2 THE LOGISTIC MAP

In Section 2.2.2, the method of characteristics was used to rewrite (3.1) as

$$\frac{du}{dt} = -\delta u + \lambda u_r(1 - u_r) \quad (3.2)$$

where

$$u(t, x(t)) \equiv u(t, xe^{\tau t})$$

and

$$u_r(t, x(t)) \equiv u(t - \tau, xe^{\tau(t-\tau)}).$$

Equation (3.2) can be rewritten as

$$\frac{1}{\delta} \frac{du}{dt} = -u + \lambda \frac{u_r}{\delta}(1 - u_r).$$

If $\delta \rightarrow \infty$ and $\frac{u_r}{\delta}$ is held constant, (3.2) becomes the logistic map, given by the first order nonlinear difference equation

$$x_{t+1} = \tilde{\lambda}x_t(1 - x_t), \quad x_t \in [0, 1] \quad 0 \leq \tilde{\lambda} \leq 4 \quad (3.3)$$

where $\tilde{\lambda} = \frac{\lambda}{\delta}$ and $x_t$ refers to the $t^{th}$ value of $x$ for $x \in [0, 1]$. In the following equations $\lambda = \tilde{\lambda}$.

The logistic map has been used, amongst other things, to model population growth [28]. In this context, the map creates a relation between the population $x_{t+1}$ in generation $t + 1$ and the population $x_t$ in generation $t$. The relation is simple and
basically states that if the population in generation $t$ is small then the population in generation $t+1$ will be larger but if the population in generation $t$ is large then it will decrease in generation $t+1$.

The quadratic nonlinearity in the map produces a growth curve with a hump, the steepness of which depends on the variable $\lambda$. This growth curve has a maximum at $x_t = .5$ for which value $x_{t+1} = \lambda/4$ and crosses the $x$-axis at $x_t = 0$ and $x_t = 1$. Thus for the logistic map to realistically model population growth we must have $0 \leq \lambda \leq 4$ and $0 \leq x_t \leq 1$.

Even though the logistic map is simple and deterministic, it exhibits very interesting dynamical behaviour ranging from stable points to bifurcations to “chaotic” fluctuations as $\lambda$ is varied. The map will be described in the rest of this section to provide an introduction to different types of bifurcations and dynamical behaviour some of which are also found in the solution behaviour of (3.1).

The logistic map is a difference equation and a typical difference equation has the form

$$x_i(t + 1) = f_i(\lambda, x_t) \quad \text{for } i = 1, \ldots, N$$

(3.4)

where $f_i$ can be non-linear (as in the case of the logistic map) and $\lambda$ is a parameter. Difference equations can be solved by iteration and thus their numerical solution is less time consuming than that of differential equations. Difference equations can also be solved graphically. This technique is often useful to obtain insight into the dynamical behaviour of the map.

In the case of the logistic map one can graphically iterate the difference equation in the following way (see Figure 3.1). First pick a value for $\lambda$, plot the quadratic map and the diagonal $x_{i+1} = x_i$. Then pick an initial point $x_0 = a$. The first point, $x_1$, is given by the intersection of the line $x_0 = a$ and the quadratic curve. The second point, $x_2$, is found by moving laterally to the diagonal and then vertically to meet
3.2.1 Steady States and their Stability.

Although the map is iterated twenty times in Figure 3.1, only three iterations, \( x_1, x_2, x_3 \), appear on the graph. This is because for \( t > 3 \), \( x_t = x_3 = 0.6 \). The value \( x^* = 0.6 \) is called a steady state. Graphically, in the logistic map, the steady states are found at the intersection of the quadratic map and the diagonal. They can be calculated analytically by solving the equation

\[
x_{t+1} = x_t = x^*.
\]
The steady states of the logistic map are given by

\[ x_t = \lambda x_t(1 - x_t) = x^*, \]

thus

\[ x_1^* = 0 \quad \text{for} \quad 0 \leq \lambda \leq 4 \]
\[ x_2^* = \frac{\lambda - 1}{\lambda} \quad \text{for} \quad 1 \leq \lambda \leq 4. \]

Steady states can either be stable or unstable. If the steady state \( x^* \) is stable the solution will always return to \( x^* \) as \( t \to \infty \) after small perturbations away from the steady state. However if the steady state \( x^* \) is unstable the solution will not return to \( x^* \) after a small perturbation away from \( x^* \).

The stability of the steady states for a nonlinear difference equation such as (3.4) can be determined graphically or analytically. To determine the stability of the steady states analytically one linearizes the map in the neighbourhood of the steady state \( x^* \)

\[ x_{t+1} = A(x_t - x^*), \]

where \( A \) is an \( N \times N \) matrix whose elements are given by

\[ a_{ij} = \frac{\partial f_i}{\partial x_j} \bigg|_{x^*}. \]

The eigenvalues \( p \) of \( A \) are then found by solving

\[ \det(A - pI) = 0. \]

The steady state \( x^* \) is locally stable if all the eigenvalues lie inside the unit circle otherwise it is locally unstable. Graphically, the stability of the steady states can be determined by the slope of the tangent to the quadratic at the steady state. If the slope of the tangent is between 1 and \(-1\) the steady state is locally stable; if it is greater than 1 or less than \(-1\) the steady state is locally unstable.
Figure 3.2: Return map and time series for $\lambda = 2.9$ (a,b) and $\lambda = 3.1$ (c,d) showing the change in solution from a single steady state to a cycle of period 2.

The logistic map is a one dimensional map, so $\lambda$ is just a number. Linearizing (3.3) gives

$$x_{t+1} = \lambda(x_t - x^*).$$

Hence, the steady state $x^*_1 = 0$ is locally stable or an attractor for all $\lambda < 1$ and the steady state $x^*_2 = (\lambda - 1)/\lambda$ is locally stable if

$$|2 - \lambda| < 1 \quad \text{or if} \quad 1 \leq \lambda < 3$$

and is locally unstable or a repellor if

$$|2 - \lambda| > 1 \quad \text{or if} \quad \lambda > 3.$$
3.2.2 Bifurcations in Solution Behaviour.

For the logistic map, at $\lambda = 1$, the stable steady state $x_1^* = 0$ loses stability and the steady state $x_2^* = (\lambda - 1)/\lambda$ starts to exist and is locally stable. Also, at $\lambda = 3$, the locally stable steady state $x_2^* = (\lambda - 1)/\lambda$ loses stability and becomes locally unstable for $\lambda > 3$. The point at which there is a transition from a stable to an unstable steady state or at which the number of steady states changes is called a bifurcation point.

Figure 3.2 shows the graphical iteration (Figs. 3.2a and 3.2c) as well as the time series (Figs. 3.2b and 3.2d) of the solution for $\lambda = 2.9$ (Figs. 3.2a and 3.2b) and $\lambda = 3.1$ (Figs. 3.2c and 3.2d). Before the bifurcation point, the solution (for $\lambda = 2.9$) converges as $t \to \infty$ to the steady state $x_1^* = (\lambda - 1)/\lambda$ at the intersection of the diagonal and the quadratic map. However after the bifurcation point, the solution (for $\lambda = 3.1$) no longer converges to a single point but instead oscillates between two points $x = 0.558$ and $x = 0.765$ on the quadratic curve so that $x_{t+2} = x_t$. This type of oscillation forms a cycle of period 2.

A cycle of period $n$ arises if

$$x_{i+n}^* = x_i^* \quad \text{with} \quad x_{i+j}^* \neq x_i^* \quad \text{for} \quad 1 \leq j < n.$$  

The local stability of the cycle is determined by the value of $|p|$, where

$$p = \left. \frac{df^n(x)}{dx} \right|_{x = x_i^*} = \prod_{i=1}^{n} \left. \left( \frac{\partial f}{\partial x} \right) \right|_{x = x_i^*} . \tag{3.5}$$

Here $f$ is the map defined in (3.4) and $f^n$ is the $n$th iteration of the map. For $|p| < 1$ the periodic cycle is locally stable. At $|p| = 1$ there is a bifurcation of the periodic cycle and the periodic cycle becomes locally unstable for $|p| > 1$.

The logistic map has two possible bifurcations depending on the value of $p$. Let $\lambda_c$ be a critical value of $\lambda$ at which a bifurcation occurs. As $\lambda$ increases past $\lambda_c$ and
$p = -1$, a transition from a locally stable cycle of period $n$ to a locally stable cycle of period $2n$ and a locally unstable cycle of period $n$ occurs. This type of transition is called a period doubling bifurcation (or a pitchfork bifurcation). The bifurcation which occurs at $\lambda = 3$ is a period doubling bifurcation. In the bifurcation diagram of Figure 3.3 one can clearly see the transition from a locally stable steady state, or a locally stable cycle of period 1, to a periodic oscillation, or a locally stable cycle of period 2 and a locally unstable cycle of period 1. The locally unstable cycle of period 1 does not appear on the graph, nor does the locally unstable steady state $x^* = 0$. A bifurcation diagram is obtained by iterating the map at least a thousand times and omitting the first several hundred iterates from the plot.

The bifurcation diagram for the logistic map from the onset of periodic solution behaviour, at $\lambda = 3$, to $\lambda = 4$ is given in Figure 3.4. As one can see, another period
doubling occurs at $\lambda_c \approx 3.445$ so that $x_{t+4}^* = x_t^*$ and yet another one at $\lambda_c \approx 3.543$ so that $x_{t+8}^* = x_t^*$. In fact an infinite number of bifurcations occur as $\lambda$ approaches $\lambda = 3.569944...$. If the first bifurcation occurs at $\lambda_1$, the second at $\lambda_2$, the third at $\lambda_3$, and so on, it is possible to approximately calculate when all the future bifurcations will occur. This discovery was made by Feigenbaum [7], who showed that the ratio between the consecutive values of $\lambda_c$ approaches a constant (the Feigenbaum number)

$$\lim_{k \to \infty} \frac{\lambda_k - \lambda_{k-1}}{\lambda_{k+1} - \lambda_k} = 4.669201609102...$$

The type of period doubling described above is one route to “chaos”. “Chaos” is the name given to the irregular and unpredictable time evolution of many nonlinear systems. A system exhibiting chaotic behaviour does not repeat its past behaviour, thus a chaotic system cannot be periodic. Also, systems which exhibit chaotic dynamics have a unique characteristic. Given two initial conditions which are close

Figure 3.4: The logistic map bifurcation diagram.
together, as \( t \) increases, the subsequent trajectories will grow linearly apart if the system is not chaotic. However if the system is chaotic the subsequent trajectories will grow apart exponentially.

The transition from regular to irregular solution behaviour (or from periodic to chaotic solution behaviour) occurs for the logistic map at \( \lambda \approx 3.569941 \ldots \). For \( \lambda > 3.569 \) there are an infinite number of different periodic cycles and an infinite number of fixed points with different periodicity. In Figure 3.4 one can see that this chaotic behaviour is interrupted by intervals of periodic solution behaviour called windows.

The largest window for the logistic map occurs for \( \lambda \approx 3.83 \). The appearance of this window is brought about by a tangent bifurcation. The tangent bifurcation is the second type of bifurcation which can occur for the logistic map. As \( \lambda \) increases past \( \lambda_c \) and \( p = 1 \) (where \( p \) is defined in (3.5)), there is a transition from no periodic cycle to two cycles of period \( n \), one locally stable and one locally unstable. This solution behaviour is represented in Figure 3.5 where the bifurcation diagram in Figure 3.4 has been magnified for values between \( \lambda = 3.82 \) and \( \lambda = 3.86 \). Just before \( \lambda \approx 3.8282 \) there is no recognizable periodic cycle. As \( \lambda \) increases past \( \lambda \approx 3.8282 \) two cycles of period 3 appear one locally stable (solid line) and one locally unstable (dashed line).

### 3.2.3 Crises in the Solution Behaviour.

In the bifurcation diagram in Figure 3.4 the chaotic behaviour ends abruptly at \( \lambda = 4 \). This is due to the fact that for \( \lambda > 4 \) the solution diverges to \(-\infty \) as mentioned before. The abrupt ending of the chaotic behaviour coincides with the intersection of the unstable steady state \( x^* = 0 \) (plotted as a dashed line) and the chaotic band. This type of collision between a chaotic attractor and a coexisting unstable steady state or periodic cycle has been named a crisis by Grebogi et al. [11]. The crisis
Figure 3.5: The logistic map bifurcation diagram for $3.82 < \lambda < 3.86$.

occurring at $\lambda = 4$ is a boundary crisis since $x^* = 0$ is on the boundary of all initial conditions which will converge as $t \to \infty$ to an attractor of the solution (this region is also called a basin of attraction.)

Another type of crises occurs in Figure 3.5. In this case the locally unstable cycle of period 3 (plotted as dashed curves), which appears at the beginning of the periodic window, intersects with three distinct chaotic bands at $\lambda \approx 3.856$. The intersection causes the three distinct chaotic bands to widen and form a single band. This phenomenon is called an interior crisis.

Thus crises can cause sudden destruction of a chaotic attractor or sudden changes in the size of the chaotic attractor. The destruction of a chaotic attractor can also be due to subduction. Subduction is a term given by Grebogi et al. [11] to describe the appearance of a non-chaotic attractor within a chaotic attractor causing the
chaotic attractor to be replaced by the nonchaotic attractor. Subduction occurs in Figure 3.5 where 2 cycles of period 3, one locally stable and one locally unstable, appear in the chaotic attractor and lead to its destruction at $\Lambda \approx 3.8282$. Subduction is not considered to be a crisis since the appearance of the two cycles of period three do not destroy the basin of the chaotic attractor.

Greboji et al. [11] conjecture that almost all sudden destruction or creation of chaotic attractors and almost all sudden changes in the size of a chaotic attractor are due to crises.

### 3.3 PREVIOUS RESULTS

Now that some background material on steady states and bifurcations has been given, previous results obtained by Rey and Mackey [31, 32] can be summarized. Rey and Mackey studied the dynamics of the model (3.1) for two initial conditions $\phi(x) = x + c$ and $\phi(x) = x$. In this section, their results for $\phi(x) = x$ will be briefly presented.

It was shown in Chapter 2 that the long time behavior or steady states for (3.1) with $\gamma = 0$ and $0 < \delta < \lambda$ with $\phi(x) = x$ are

$$
\lim_{t \to \infty} u(t, x) = \begin{cases} 
0 & 0 < \lambda - \delta < r \\
\frac{(\lambda-\delta)x}{\lambda - \delta + \lambda x} & \lambda - \delta = r \\
\frac{\lambda-\delta}{\lambda} & \lambda - \delta > r 
\end{cases}
$$

(recall that in this section only the case for $n=1$ will be considered). In order to study the stability of these steady states following the method described in Section 3.2.2, the model (3.1) is rewritten as

$$
\frac{du}{dt} = -\delta u + \lambda u_r (1 - u_r) 
$$

(3.6)
where
\[ u(t, x(t)) \equiv u(t, \varepsilon e^{\tau t}) \]
and
\[ u_\tau (t, x(t)) \equiv u(t - \tau, \varepsilon e^{\tau(t-\tau)}) \]
using the method of characteristics presented in Section 2.3. Using this method it is possible to determine the local temporal and spatial stability of the steady states separately.

Letting \( \tau = 1 \) and linearizing (3.6) around the trivial solution, Rey and Mackey showed that there is an \( r = r_c \) which determines the local stability of the three solutions when subjected to linear spatial perturbations. For \( r > r_c \), the trivial solution is locally stable and the two other solutions are locally unstable. For \( r < r_c \) the \( (\lambda - \delta)/\lambda \) solution is locally stable while the other two are locally unstable. While for \( r \equiv r_c \), the only solution which is locally stable is the \( [(\lambda - \lambda q x)]/(\lambda - \delta + \lambda x) \) solution. This solution is locally stable when \( \lambda = (\delta + r)e^\tau \).

The occurrence of a temporal Hopf bifurcation can be determined by the method described in Chapter 1. Linearizing (3.6) around \( (\lambda - \delta)/\lambda \) gives
\[
\frac{dz}{dt} = -\delta z + (2\delta - \lambda) z_\tau \tag{3.7}
\]
where \( z = u - [(\lambda - \delta)/\lambda] \). Since a transition from a single steady state to a periodic cycle is expected, one looks for solutions of the type \( z = e^{(\mu + \omega)t} \). Substituting this \textit{ansatz} back into (3.7) gives
\[
\mu + i\omega = -\delta + (2\delta - \lambda)e^{-\mu}e^{-i\omega},
\]
which after separating real and imaginary parts can be written as
\[
\mu = -\delta + (2\delta - \lambda)e^{-\mu}cos\omega \]
\[
\omega = -(2\delta - \lambda)e^{-\mu}sin\omega.
\]
Figure 3.6: Diagram of the three possible scenarios for which spatial Hopf bifurcations occur.

Thus, the steady state \((\lambda - \delta)/\lambda\) is locally stable when

\[
\sqrt{(2\delta - \lambda)^2 - \delta^2} < \cos^{-1}\left(\frac{\delta}{2\delta - \lambda}\right)
\]

and locally unstable when the inequality is reversed. The point

\[
\sqrt{(2\delta - \lambda)^2 - \delta^2} = \cos^{-1}\left(\frac{\delta}{2\delta - \lambda}\right)
\]

defines a bifurcation point marking the transition from a single locally stable solution to a locally stable periodic cycle.

There are three possible spatial Hopf bifurcations depending on the relationship between the line composed of the \((\lambda, \delta)\) values satisfying

\[
\sqrt{(2\delta - \lambda)^2 - \delta^2} = \cos^{-1}\left(\frac{\delta}{2\delta - \lambda}\right)
\]
which represents the temporal Hopf bifurcation (denote this line by THB) and the line composed of the \((\lambda, \delta)\) values satisfying \(\lambda = (\delta + r)e^r\) for which the \([(\lambda - \delta)x]/(\lambda - \delta + \lambda x)\) solution is stable. Denote this line by SS.

If the line THB is always above the line SS (this occurs when \(0 < r < .7455\)) there is a simultaneous spatial and temporal Hopf bifurcation occurring when the \((\lambda - \delta)/\lambda\) solution loses its stability. The temporal bifurcation leads to periodic solution behaviour while the spatial bifurcation leads to left traveling waves.

If the line SS crosses the line THB (this occurs when \(.7455 < r < 1.0986\)) there is a spatial Hopf bifurcation occurring when the \([(\lambda - \delta)x]/(\lambda - \delta + \lambda x)\) solution loses its stability. This Hopf bifurcation induces slow left traveling waves.

If the line SS is always above the line THB (this occurs when \(r > 1.0986\)) there is a spatial Hopf bifurcation also occurring when the \([(\lambda - \delta)x]/(\lambda - \delta + \lambda x)\) solution loses its stability. In this situation the Hopf bifurcation leads to chaotic traveling waves. These results are summarized in Figure 3.6.

### 3.4 NEW RESULTS

In this section the case where \(r << .7455\) is considered. For these values of \(r\), a simultaneous temporal and spatial Hopf bifurcation occurs when the relationship

\[
\sqrt{(2\delta - \lambda)^2 - \delta^2} = \cos^{-1}\left(\frac{\delta}{2\delta - \lambda}\right)
\]

is satisfied. The changes in solution behaviour of (3.1) will be studied as the parameter \(\lambda\) is increased.
3.4.1 Solution Behaviour Along the $x$ Characteristics.

As $\lambda$ is increased and all the other parameters are kept constant, the relationship

$$\sqrt{(2\delta - \lambda)^2 - \delta^2} = \cos^{-1}\left(\frac{\delta}{2\delta - \lambda}\right)$$

is no longer satisfied and instead

$$\sqrt{(2\delta - \lambda)^2 - \delta^2} > \cos^{-1}\left(\frac{\delta}{2\delta - \lambda}\right).$$

Increasing $\lambda$ in the logistic map created a period doubling route to chaos (cf. Section 3.2.2), thus one might expect a similar period doubling route to chaos in the solution of (3.1).
3.4.2 Temporal Bifurcations Occuring After the Hopf Bifurcation.

The bifurcation diagram for (3.1) is shown in Figure 3.7. This bifurcation diagram is obtained by calculating the solution along the characteristics given by (3.6) and plotting the local extrema of the solution \( u(t,x) \) as a function of \( \lambda \) (the \( \lambda \)'s are incremented by \( 10^{-5} \)) for \( 700 < t < 750 \). In all cases \( \delta, \epsilon \) and \( r \) are held constant and have the following values \( \delta = 1, \epsilon = .1, r = .01 \). The Hopf bifurcation occurs at \( \lambda \approx 4.25 \) which concurs with the analytic results given by the local stability analysis. A period doubling bifurcation occurs at \( \lambda \approx 5.812 \). At \( \lambda \approx 5.793 \) there is a jump in

Figure 3.8: Magnification of the bifurcation diagram in Figure 3.7 for \( 5.79 < \lambda < 5.87 \).
the solution and a new cycle of period 8 occurs. As \( \lambda \) is increased past 5.793 the cycle of period eight gives rise to a turbulent solution which appears to be chaotic. This turbulent solution ends abruptly at \( \lambda \approx 5.854 \) at which point a new cycle of period 2 occurs.

In order to attempt to understand what is happening in the region from the first jump in the solution from a period 4 cycle to a period 8 cycle to the second jump in the solution from a turbulent solution to a period 2 cycle, the solution is magnified for \( 5.79 < \lambda < 5.87 \) and is shown in Figure 3.8.

Figure 3.8b shows a period doubling route to chaos. The period doublings occur at smaller intervals of \( \lambda \) as \( \lambda \) is increased until the period doublings are no longer distinguishable and the solution becomes chaotic at \( \lambda \approx 8.194 \). Figure 3.8b–c shows that there are periodic windows in the chaotic attractor. These windows are caused by the appearance of periodic cycles in the chaotic attractor which destroy the chaotic attractor via subduction. As for the logistic map, the chaotic attractor reappears through new period doubling routes to chaos and then widens when interior crises occur. The largest window occurs when \( 5.8356 < \lambda < 5.8372 \). The cycle is of period 12 in this window.

In Figure 3.8d the chaotic attractor suddenly disappears and a new cycle of period 2 appears. By the conjecture of Grebogi et al. [11], the destruction of this chaotic attractor is most probably caused by the collision of an unstable orbit with the chaotic attractor. It is not possible to determine from this figure where the unstable orbit which causes the destruction is located.
Figure 3.9: a. Solution along the $x$ characteristics using the solution at $\lambda = 5.79$ as initial condition. b. Magnification of the bifurcation diagram in Figure 3.7 for $5.79 < \lambda < 5.89$.

3.4.3 Multistability of the Solution Along the $x$ Characteristics.

The sudden jump from a period 4 cycle to a period 8 cycle is an indication that there are two coexisting attractors of the solution. Each attractor must have a basin of attraction such that given an initial condition in the basin of attraction the solution converges to the attractor as $t \to \infty$. There has been quite an extensive study of the geometry of basins of attraction and of their boundaries in nonlinear return maps obtained from ordinary differential equations [2, 12, 29]. These basins of attraction can be extremely complicated and in some cases are fractal in nature. Sensitivity to initial conditions has previously been studied for DDE's and it has been shown
that DDE's can possess multistable solutions [5, 22]. In order to determine whether the model (3.1) has two coexisting attractors the solutions obtained along the $x$ characteristic at $\lambda = 5.79$ and at $\lambda = 5.81$ are taken as initial conditions. (Recall that at $\lambda = 5.79$ the solution consists of a cycle of period 4 and at $\lambda = 5.81$ the solution consists of a cycle of period 8, cf. Figure 3.7.)

The solution for which the initial condition is the solution at $\lambda = 5.79$ is shown in Figure 3.9a. The jump to a period 8 cycle as well as the subsequent period doublings and chaotic bands have completely disappeared and instead there is a smooth transition from the cycle of period 4 to the cycle of period 2 at $\lambda \approx 5.82$. Call the attractor shown in Figure 3.9a attractor A. In Figure 3.9b, the solution obtained

Figure 3.10: a. Solution along the $x$ characteristics using the solution at $\lambda = 5.81$ as initial condition. b. Magnification of the bifurcation diagram in Figure 3.7 for $5.79 < \lambda < 5.89$. 
Figure 3.11: Solution behaviour when attractor A is replaced by attractor B.

in Figure 3.7 is magnified for $5.7 < \lambda < 5.9$. Comparing Figure 3.9a and Figure 3.9b, one sees that attractor A becomes unstable in Figure 3.9b for $5.793 < \lambda < 5.854$. The solution for which the initial condition is the solution at $\lambda = 5.8$ is shown in Figure 3.10a. Instead of a jump in solution at $\lambda \approx 5.793$ from a period 4 cycle to a period 8 cycle, there is a jump in solution from a period 4 cycle to a new period 4 cycle at $\lambda \approx 5.732$. The new period 4 cycle then gives rise to the period 8 cycle at $\lambda \approx 5.788$. The period doubling route to chaos as well as the periodic windows and the destruction of the chaotic attractor occur as before. Call the attractor shown in Figure 3.10a attractor B. In Figure 3.10b, the solution obtained in Figure 3.7 is again magnified for $5.7 < \lambda < 5.9$. Comparing Figure 3.10a and Figure 3.10b, one sees that attractor B is unstable in Figure 3.10b for $5.732 < \lambda < 5.793$.

One can determine the range of values of $\lambda$, for which the initial conditions (which
are given by the solution at \( \lambda \) give rise to solutions which converge to attractor B as \( t \to \infty \), very precisely. If the initial condition is given by the solution for a value of \( \lambda \) such that 5.79265 < \( \lambda \) < 5.85408, then the solution converges to attractor B as \( t \to \infty \). If the initial condition is given by a solution for \( \lambda = 5.79265 \) or \( \lambda = 5.85408 \) then the solution converges to attractor A as \( t \to \infty \). Thus \( \lambda = 5.85408 \) and \( \lambda = 5.79265 \) are on the boundary of the basin of attraction. In Figure 3.11 the solution is shown for 5.7315 < \( \lambda \) < 5.7319 with the initial condition taken as the solution at \( \lambda = 5.792654 \). The solution is plotted for 500 < \( t \) < 600 and the \( \lambda \)'s are incremented by \( 10^{-7} \). This figure shows what happens when one attractor is replaced by another attractor.

Due to the appearance of a new cycle of period 4 and to the rounding at the extremities of the branches right at the beginning of the new cycle of period 4 in

Figure 3.12: Potential unstable cycle of period 4.
Figure 3.9a and Figure 3.11, one could postulate that at the value of $\lambda$ ($\lambda \approx 5.79265$), at which the new cycle of period 4 appears, a tangent bifurcation occurs creating a stable and unstable cycle of period 4. One can further postulate that the unstable cycle of period 4 collides with the chaotic attractor at $\lambda \approx 5.85408$ causing the destruction of the chaotic attractor. This postulate would agree with Grebogi's et al. conjecture [11]. Figure 3.12 shows the postulated unstable cycle of period 4 (plotted as dashed curves).

### 3.4.4 Spatial Solution Behaviour Occurring after the Hopf Bifurcation.

In Figures 3.13 - 3.16 the solution is shown as a function of $x$ ($x$ is the spatial component of the DDE (3.1)). In the top left hand corner of each of these figures the temporal bifurcation diagram is shown. In the top right hand corner the solution is shown as a function of $t$ along the $x$ characteristics. The four other plots are spatial solutions. These solutions were obtained using the method of characteristics. $\delta$ and $r$ were held constant and had the values $\delta = 1$ and $r = .0001$. Each solution was calculated for a given $t$ on 700 characteristics equidistant from each other on the interval $[0,1]$.

In Figure 3.13 the solutions are shown for $\lambda = 4.5$. Since $r << .7455$ the spatial and temporal Hopf bifurcation occur simultaneously. Thus in both cases the solution is just above the Hopf bifurcation. The length of the temporal period is approximately 3.1. The spatial solutions shown span the whole length of the temporal period and thus the solution at $t = 400.4$ is identical to the solution at $t = 403.5$.

In Figure 3.14 the solutions are shown for $\lambda = 5.5$. The temporal solution has undergone a period doubling and the length of the period is approximately 6.55.
Figure 3.13: Temporal and spatial solution for $\lambda = 4.5$.

The spatial solutions shown again span the length of the period and the solution at $t = 400.4$ is identical to the solution at $t = 406.95$. Comparing Figure 3.14 to Figure 3.13 one sees that the amplitude of the spatial solution has increased and the solution has become much more structured.

In Figure 3.15 the solutions are shown for $\lambda = 5.8$. The temporal solution has undergone a jump from a cycle of period 4 to a cycle of period 8. The length of the period is now approximately 8.2. The spatial solutions shown again span the whole
Figure 3.14: Temporal and spatial solution for $\lambda = 5.5$.

Length of the period; however this time, as one can see by comparing the plots for $t = 400.4$ and $t = 408.6$ in Figure 3.15, the solution at $t = 400.4$ is not identical to the solution at $t = 408.6$ (this difference in solution is not decreased by improving the precision of the length of the period). It is not yet clear why this is so and further work is needed to clarify this point. However one could postulate that the switch from attractor A to attractor B is the cause. Comparing Figure 3.15 to Figure 3.14 shows that the spatial solution has become even more structured.
In Figure 3.16 the solutions are shown for $\lambda = 6$. The temporal solution has undergone a reverse bifurcation and is again a cycle of period 2. The length of the period is approximately 3.35. The spatial solutions shown span the length of the period and the solution at $t = 400.4$ is identical to the solution at $t = 403.75$ (note that for $\lambda = 6$, attractor A has regained its stability). The spatial solution has become extremely structured. It is not yet clear why increasing the parameter $\lambda$ causes the spatial solution to become increasingly structured. The increase in structure in the
solution as a parameter is varied has been studied extensively by Sharkovsky et al. [33] for the logistic map. Let \( f \) denote the logistic map defined in Equation (3.3) and \( f^n \) denote the \( n \)th iteration of the map. Sharkovskiy et al. showed that the structure of the solution as \( n \to \infty \) depends on the relationship between the periodic return map (if for a certain value of \( \lambda \) the solution is of period 3 then the periodic return map is \( x_{t+3} = f^3 \) at that value of \( \lambda \)) and the line \( y = x \).

An interesting feature in the spatial plots in Figure 3.13 is the sharp reversal of
Figure 3.17: Spatial solutions just above the Hopf bifurcations for four values of $\lambda$ and ten times.

slope at approximately $x = .8$. In Figure 3.17 the spatial solution for various values of $\lambda$ is plotted. Each plot shows the solution for ten times (the times are incremented by .1).

The plot for $\lambda = 4.2$ in Figure 3.17 shows the solution just above the Hopf bifurcation. The amplitude of the solution very close to the Hopf bifurcation is small. This plot is magnified in Figure 3.18 where one can see that the solution has a node at $x \approx 0.77$ which corresponds to $u(t, x) = .7619$. The value of $u(t, x)$ at this node is the value of the steady state $(\lambda - \delta)/\lambda$ for $\lambda = 4.2$ and $\delta = 1$. Thus the node is created when the solution for various times simultaneously attain the value of the steady state $(\lambda - \delta)/\lambda$. 

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As λ is slowly increased and the solution moves away from the Hopf bifurcation the node becomes a line which lengthens as the amplitude of the solution increases. This is illustrated in Figure 3.17. Further work is needed to explain this phenomenon.

3.5 CONCLUSION

The nonlinear partial differential delay equation

\[ \frac{\partial u}{\partial t} + rx \frac{\partial u}{\partial x} = -\delta u + \lambda u_r(1 - u_r), \]

where \( u_r(t, x) \equiv u(t - \tau, xe^{-\tau}) \), has an extremely rich array of solution behaviour.

As λ is varied the temporal solution undergoes a period doubling route to chaos. The chaotic band thus obtained contains periodic windows whose behaviour can be
explained by the presence of crises. It was also shown that the temporal solution has two coexisting attractors and hence is multistable.

The spatial solution becomes more structured as \( \lambda \) is increased and at \( \lambda = 6 \) is extremely turbulent. The spatial solution displays two interesting phenomena.

1. The spatial solution at \( \lambda = 5.8 \) does not repeat itself after one time period.

2. There is a node at the steady state \( (\lambda - \delta)/\delta \) for spatial solutions just past the Hopf bifurcation. As the solution moves further away from the Hopf bifurcation, the node becomes a static front.

Further work is needed in order to fully understand both of these phenomena.
CONCLUSION

This thesis explores the dynamics of a model for cell replication, in which there is simultaneous proliferation and maturation, for two different initial conditions.

In Chapter 1, some background in cell biology is given in order to understand the different parameters in the model. The two different methods of numerical integration, the Galerkin finite elements method and the method of characteristics, are also introduced. The model is then derived and results in a first order nonlinear partial differential equation with retardation in both the temporal and maturation variables. This model is novel the dynamics of a system with retardation in two of the variables has not, to my knowledge, been previously investigated. Finally, an introduction to delay differential equations and some pertinent mathematical results of Lasota [19] are presented. Lasota’s results show that first order partial differential equations of the same class as the one that describes the model with no delay and with initial condition \( \varphi(x) = x^n \) for all \( n \) are chaotic in a function space.

In Chapter 2, the solution behaviour of the partial differential equation describing the model is studied for the initial condition \( \varphi(x) = x^n \) for \( n >> 1 \). The solutions with this initial condition are left moving fronts which hit an impermeable boundary at \( x = 0 \). The study of the dynamics of the model with no delay shows that increasing \( n \) or increasing the rate of maturation decreases the speed at which the moving fronts hit the impermeable boundary. The velocity of the fronts for different values
of $n$ and the rate of maturation are found to be linear functions of the maturation variable. Keeping $n$ and the rate of maturation fixed and increasing the value of the delay causes a sharp decrease in the speed at which the front travels towards the impermeable boundary. Further increasing the value of the delay causes the appearance of oscillations near the wave front which resemble solitons. Increasing the delay does not change the fact that the velocity is a linear function of the maturation variable.

In Chapter 3, the solution behaviour of the partial differential equation describing the model is studied for the initial condition $\varphi(x) = x$. First, an introduction to steady states, bifurcations, chaos, and crises is given using the logistic map. Then, the previous results obtained by Rey and Mackey [31, 32] for the same model and the same initial condition are given. The most important of these results, for the purpose of this thesis, is, that for a rate of maturation less than a critical rate of maturation, there is a simultaneous temporal and spatial Hopf bifurcation for a certain value of the parameter set. The temporal and spatial solution behaviour of the model are then studied past the Hopf bifurcation. The temporal solution undergoes a period doubling route to chaos. The chaotic band thus obtained contains periodic windows whose behaviour can be explained by the presence of crises. Also the temporal solution has two coexisting attractors and hence the system is multistable. The spatial solution becomes increasingly structured as the solution moves further away from the Hopf bifurcation.

There are many areas of further study left in order to fully understand the solution behaviour of the first order nonlinear delayed partial differential equation describing the model. In order to obtain some theoretical results, Lasota’s theorems, for the first order nonlinear partial differential equation which were presented in Chapter 2, should be extend to include the case with delay. Areas which need more numerical
work in order to understand all the solution behaviour presented in Chapter 3 were suggested in that chapter. Further insight could also be obtained by using an analytic technique previously presented by an der Heiden and Mackey. This technique consists of approximating the nonlinear input flux function with a piecewise constant function and studying the solution behaviour analytically in each of the different intervals defined by the piecewise constant function.

The initial conditions \( \varphi(x) = x \) and \( \varphi(x) = x^n \) for which the model for cell replication was studied is equivalent to a null output flux of red blood cell precursors from the pluripotent stem cells. This physiological phenomenon can happen in humans after chemotherapy or a bone marrow transplant. Although there does not seem to be any published literature on the subject, some of the dynamics displayed by the model have been observed in the recovery data from post chemotherapy or bone marrow transplant patients. After chemotherapy the circulating number of cells is extremely low. For the first few days, the number of circulating cells show low level fluctuations. In the next phase of recovery, the amplitude and number of fluctuations increase and can become quite erratic. If, during this phase, the amplitude becomes too high and thus the cell count too low the patient might not recover. After this transient phase the number of circulating cells stabilizes.

Some of the results presented in this thesis suggests that certain phenomena which were previously attributed to experimental error could in fact be real phenomena. For instance, experimentalists have tried to assess the number of cells at different levels of maturation from a sample of the bone marrow. They have found huge variations in the number of cells and mostly attributed this to experimental error. However, the results in Chapter 3 show that there are huge fluctuations in the number of cells at different levels of maturation. Similarly, the phenomenon of multistability could counter the belief that, if an experimentalist obtains different results for the same
experiment under the same conditions, this difference is caused by experimental error. To check these postulations would require a histologist with a lot of dedication, time, and funding.
APPENDIX A

In this Appendix the code for the Galerkin finite elements method is given. This code was used to generate the data for most of the figures in Chapter 1. This code was written for a project in a class on Galerkin Finite Elements given by Dr. Rey at McGill. The part of the code that deals with the delay was written by Dr. Rey.

```
CC-------------------------------------------------------------
CC SPECIFICATIONS
CC-------------------------------------------------------------
CC GALERKIN FINITE ELEMENTS METHOD
CC-------------------------------------------------------------
CC PURPOSE OF THE CODE
CC-------------------------------------------------------------
CC THIS CODE SOLVES THE FOLLOWING EQUATIONS
CC DU/DT + R*X*DU/DX = -C1*U + C2*U(1 - U)
CC IC: V(X) = X^2  , BC: U(0, T) = 0
CC
CC THE CODE
CC-------------------------------------------------------------
```

88
DECLARE VARIABLES AND SET UP ARRAYS

PARAMETER (NK=801)
IMPLICIT REAL *8 (A-H, O-Z)
INTEGER GU, JK
DIMENSION SF(NK), SJ(NK, NK), X(NK), U(NK), UP(NK), UO(NK)
DIMENSION W(3), GP(3), PHI(2), PHI(2)
DIMENSION C(NK), D(NK), Z(NK)

CC DELAY PARAMETERS
DIMENSION XS(NK), UO(NK), UR(NK), UAN(NK)

CC OPEN TESTFILE

OPEN(7, FILE='TESTFILE800', STATUS='OLD')

CC WHAT THINGS ARE

NE=# OF ELEMENTS PER EQUATION
N=# OF NODES PER EQUATION
DT=TIME STEP
TAU=DELAY
GP=GAUSS POINTS
GU=POWER OF INITIAL FUNCTION
W=WEIGHTS

DATA GP/0.1127016654D0, 0.50D0, 0.8872983346D0/
DATA W/0.2777777778D0, 0.4444444444D0, 0.2777777778D0/

CC MESH

89
NE=800
N=NE+1
DO 10 I=1,N
X(I)=FLOAT(I-1)/FLOAT(NE)
XS(I)=X(I)**DEXP(-TAU*R)
10 CONTINUE

INPUT INITIAL CONDITIONS
JL=0
T=0.0d0
C1=1.0d0
C2=3.0d0
TAU=5.0d0
R=.010d0
S=50.0d0
DT=TAU/S
GU=5
NS=51
DO 11 I=1,N
U(I)=X(I)**GU
UD(I)=X(I)**GU
11 CONTINUE
GO TO 29

DELAY PROCEDURE

DO 1001 I=1,NS
DO 1000 J=1,N
UR(I,J)=XS(J)**GU
1000 CONTINUE
1001 CONTINUE
GO TO 29
1002 IF (T .GT. 0.0) GO TO 1004
DO 1003 I1=1,N
WRITE (7,15) X(I1),T,U(I1)
1003 CONTINUE
1004 DO 1006 K=2,WS
DO 1005 I=1,N
     UR(K-1,I)=UR(K,I)
1005 CONTINUE
1006 CONTINUE
DO 1009 I=2,N
LS=I
DO 1007 J=1,N
LS=LS-1
IF(XS(I) .GT. X(LS)) GO TO 1008
1007 CONTINUE
1008 DIVIS= X(LS+1)-X(LS)
JJ=LS
LI=LS+1
LI=I
1009 UR(NS,I)=(U(LI)-U(LI-1))/DIVIS*(XS(I)-X(JJ))+U(LI-1)
UR(NS,1)=U(1)
DTO=DT
T=T+DTO
JL=JL+1
ICL= JL /10
JCL=ICL*10
TE=DT*FLOAT(JCL)
DIFT=T-TE
IF( DIFT .LT. 1.D-6 ) GO TO 97
GO TO 29
DO 311 I=1,N
ERROR= U(I)-UAN(I)
CC*****************************************************************
CC PRINT
CC*****************************************************************
12 CONTINUE
DO 13 I=1,N,4
WRITE(7,15) T,X(I),U(I)
13 CONTINUE
15 FORMAT(3(F10.5,1X))
CC
CC*****************************************************************
CC UPDATE TIME
CC*****************************************************************
28 CONTINUE
T=T+DT
CC*****************************************************************
CC TIME CONTROL
CC*****************************************************************
IF(T.GT.20.000) GO TO 300
CC*****************************************************************
CC PREDICTOR STEP WHEN CONVERGED SOLUTION IS ACCEPTED
CC*****************************************************************
29 CONTINUE
DO 30 K=1,N
UP(K)=U(K)+DT* (U(K)-UO(K))/DT
UO(K)=U(K)
U(K)=UP(K)
30 CONTINUE
CC*****************************************************************************
CC INITIALIZE NEWTON RAPHSON COUNTER AND MATRICES
CC*****************************************************************************
JK=0
35    CONTINUE
DO 40 I=1,N
SF(I)=0.000
DO 40 J=1,N
40    SJ(I,J)=0.000
C*****************************************************************************
C    FILL THE MATRICES GRAND LOOP
C*****************************************************************************
DO 100 I=1,NE
CC NE=#OF ELEMENTS
DO 100 J=1,3
DX=X(I+1)-X(I)
CC DX=ELEMENT PACING
CALL TFUNCT (GP(J),DX,PHI,PHIX)
CC TFUNCT CALCULATES PHI AND ITS DERIVATIVES AT GAUSS POINTS
X1=X(I) + DX*GP(J)
UI=C.000
UNO=O.000
UNX=O.000
DO 90 L=1,2
L1=   (I-1)+L
UN=UN +U(L1)*PHI(L)
UNX=UNX +U(L1)*PHIX(L)
UNO=UNO+UO(L1)*PHI(L)
90    CONTINUE
DU=(UN-UNO)/DT
DO 100 L=1,2
L1=   (I-1)+L
SF(L1)=SF(L1)-W(J)*DX*(DU*PHI(L)/R +
&X1*UNX*PHI(L)+CI*UN*PHI(L)/R +
&-C2* UN*(1.000-UN)*PHI(L)/R)
93
DO 100 M=1,2
MI= (I-1) + M
SJ(L1,M1)=SJ(L1,M1)+W(J)*DX*(PHI(L)*PHI(M))/DT/R+
&+C1*PHI(L)*PHI(M)
&+C1*PHI(L)*PHI(M)/R -C2/R*((PHI(M)*(1.0DO-UN)
&- UN*PHI(M))
&+PHI(L)))
100 CONTINUE

CC APPLY BOUNDARY CONDITIONS
CC SF(1) =0.0DO
DO 110 I=1, M1
110 SJ(I,1)=0.0DO
SJ(1,1)=1.0DO

CC MATRIX INVERSION
CC
CC
CC HK1=H-1
D(1)=SJ(1,1)
E(1)=SJ(1,2)
DO 120 I=2, M1
C(I)=SJ(I,I-1)
D(I)=SJ(I,1)
E(I)=SJ(I,I+1)
120 CONTINUE
C(N)=SJ(N,N-1)
D(N)=SJ(N,N)
CALL DGTSL (N,C,D,E,SF,INFO)

CC INCREMENT NEWTON-RAPHSON COUNT
CC******************************************************************
JK=JK+1
CC******************************************************************
CC CONVERGENCE CRITERIA FOR NEWTON RAPHSON
CC******************************************************************
DEC=0.0D0
DO 130 K=1,N
U(K)=U(K) + SF(K)
130 DEC=DEC + SF(K)**2
DEC=DSQRT(DEC)
IF (DEC .LT. 1.0D-6) GO TO 12
IF (JK .LE 100) GO TO 35
WRITE (6,140) JK
140 FORMAT(//,5X,'IT DOES NOT CONVERGE IN ',I2,' ITER',/)
300 CONTINUE
999 STOP
END
CC******************************************************************
C SUBROUTINES
CC******************************************************************
SUBROUTINE TFUNCT(GP,DX,PHI,PHIX)
CC
CC THIS SUBROUTINE WILL CALCULATE PHI AND ITS
CC DERIVATIVES AT GAUSS POINTS
CC GP:GAUSS POINTS
CC DX:ELEMENT SPACING
CC PHI
CC PHIX:dPHI/dX
CC NOTE: DX MAYBE CONSTANT OR VARYING DEPENDING ON MESH
CC
IMPLICIT REAL *8 (A-H,O-Z)
DIMENSION PHI(2),PHIX(2)
PHI(1)=1.0D0-GP
PHI(2)=GP
PHIX(1)=-1.0D0 /DX
PHIX(2)=1.0DC /DX
RETURN
END

SUBROUTINE DGTSL(N, C, D, E)
INTEGER N,INFO
DOUBLE PRECISION C(1),..,D,N

DGTSL GIVEN A GENERAL TRIDIAGONAL MATRIX AND A RIGHT HANDSIDE WILL FIND THE SOLUTION.

ON ENTRY

N INTEGER
IS THE ORDER OF THE TRIDIAGONAL MATRIX.
C DOUBLE PRECISION(N)
IS THE SUBDIAGONAL OF THE TRIDIAGONAL MATRIX.
C(2) THROUGH C(N) SHOULD CONTAIN THE SUBDIAGONAL.
ON OUTPUT C IS DESTROYED.
D DOUBLE PRECISION(N)
IS THE DIAGONAL OF THE TRIDIAGONAL MATRIX.
ON OUTPUT D IS DESTROYED.
E DOUBLE PRECISION(N)
IS THE SUPERDIAGONAL OF THE TRIDIAGONAL MATRIX.
E(1) THROUGH E(N-1) SHOULD CONTAIN THE SUPERDIAGONAL.
ON OUTPUT E IS DESTROYED.

B DOUBLE PRECISION(N) IS THE RIGHT HAND SIDE VECTOR.

ON RETURN

B IS THE SOLUTION VECTOR.

INFO INTEGER

= 0 NORMAL VALUE.

= K IF THE K-TH ELEMENT OF THE DIAGONAL BECOMES EXACTLY ZERO. THE SUBROUTINE RETURNS WHEN THIS IS DETECTED.

LINPACK. THIS VERSION DATED 08/14/78.

JACK DONGARRA, ARGONNE NATIONAL LABORATORY.

NO EXTERNALS

FORTRAN DABS

INTERNAL VARIABLES

INTEGER K, KB, KP1, NM1, NM2

DOUBLE PRECISION T

BEGIN BLOCK PERMITTING ... EXITS TO 100

INFO = 0

C(1) = D(1)

NM1 = N - 1

IF (NM1 .LT. 1) GO TO 40

D(1) = E(1)
E(1) = 0.0
E(N) = 0.0
DO 30 K = 1, NM1
KP1 = K + 1
CC
CC FIND THE LARGEST OF THE TWO ROWS
CC
IF (DABS(C(KP1)) .LT. DABS(C(K))) GO TO 10
CC
CC INTERCHANGE ROW
CC
T = C(KP1)
C(KP1) = C(K)
C(K) = T
T = D(KP1)
D(KP1) = D(K)
D(K) = T
T = E(KP1)
E(KP1) = E(K)
E(K) = T
T = B(KP1)
B(KP1) = B(K)
B(K) = T
10 CONTINUE
CC
CC ZERO ELEMENTS
CC
IF (C(K) .NE. 0.000) GO TO 20
INFO = K
CC ..............EXIT
GO TO 100
20 CONTINUE
T = -C(KP1)/C(Y)
C(KP1) = D(KP1) + T*D(K)
D(KP1) = E(KP1) + T*E(K)
E(KP1) = 0.0D0
B(KP1) = B(KP1) + T*B(K)
30  CONTINUE
40  CONTINUE
IF (C(N) .NE. 0.0D0) GO TO 50
INFO = N
GO TO 90
50  CONTINUE
CC BACK SOLVE
CC NM2 = N - 2
B(N) = B(N)/C(N)
IF (N .EQ. 1) GO TO 80
B(NM1) = (B(NM1) - D(NM1)*B(N))/C(NM1)
IF (NM2 .LT. 1) GO TO 70
DO 60 KB = 1, NM2
K = NM2 - KB + 1
B(K) = (B(K) - D(K)*B(K+1) - E(K)*B(K+2))/C(K)
60  CONTINUE
    70  CONTINUE
80  CONTINUE
90  CONTINUE
100 CONTINUE
CC
RETURN
END
APPENDIX B

In this Appendix the code which generates the data for the model’s bifurcation diagrams in Chapter 3 is given. This code uses the method of characteristics. A variation of this code is used to generate the data for all the other figures in Chapter 3. Olivier Georg and I wrote this code.

```
#include "stdio.h"
#include "math.h"
define r 0.1
define x1 .1
define tau 1.0
define dt .01
define prec .001 /* precision = .001 */
double v[4000000], /* where we store the signal*/ umax, /* max(u) on tmin -> tmax */
umin, /* min(u) on tmin -> tmax */
u, /* value of the signal at time t */
uPeak, /* interpolated value of the signal at a peak*/
u0, /* value of the signal at t0 */
middle, /* (umin+umax)/2 */
vInterpolated; /* interpolated value of v at time t*/
```
double amplitude, /* peak to peak amplitude of the signal on*/
/* tmin -> tmax */
periodN; /* N times the calculated period of the signal */
double diff1,
diffN,
eps;
double delta,
lambdamin,
lambdamax,
dlambda,
lambda;
double n=5, /* exponent for a birth rate function */
N = 5,
double t,
t0, /* approximate time when u first crosses*/
/* 'u=middle', upwards */
tN, /* = t0 + N*period */
tmin, /* beginning of the scanning for peaks*/
tmax; /* end of the scanning for peaks*/
int 1,
i0, /* index for t0 */
i1, /* index for t0 + period */
iN, /* index for tN */
i1i, /* index used when verifying the period (1st period) */
i1N, /* index used when verifying the period (Nth period) */
j, k, l, m, /* general purpose indexes */
i1min, /* index fot t1min */
i1max; /* index for tmax */
int di11,
diN;
double 1Peak, /* interpolated fractional index when the signal has a peak */
di11,
int idelay;
int GotThePeriod; /* =1 if the period was found and verified*/
int PrecisionIsOk; /* =1 if the diff. in signal over the periods */
  /* is within 'eps' */
int TooFarApart; /* =1 if the signal crosses 'u=middle' after 5*/
  /* periods is more*/
  /* than 3 steps apart from the expected crossing*/
int uTooBig; /* =1 if u diverges. */
int BelowDeltaEqLambda; /* =1 if lambda<delta ( => u(t) -> 0 ) */
double deg3[6][6] = { { 0, 0, 0, 0, 0, 0},
                      { 0, -1.0, 3.0, -3.0, 1.0},
                      { 0, 3.0, -6.0, 3.0, 0.0},
                      { 0, -2.0, -3.0, 6.0, -1.0},
                      { 0, 0.0, 6.0, 0.0, 0.0} };
double a[5];
char *fnameDiag;
FILE *fptr;
double f(),
itotO,
integstep(),
sqrt();
int ttO1();
main(argc, argv)
argc;
{
  printf("input delta :"); scanf("%lf", &delta);
  printf("input lambdamin :"); scanf("%lf", &lambdamin);
  printf("input lambdamax :"); scanf("%lf", &lambdamax);
  printf("input dlambda :"); scanf("%lf", &dlambda);
}
printf("min. time :"); scanf("%lf", &tmin);
printf("max. time :"); scanf("%lf", &tmax);
/* fname=argv[1] */
fptr = fopen("diag.dat", "w");
ldelay = ttoi(tau);
for(lambda = lambdamin; lambda <= lambdamax; lambda += dlamba)
{
  /* printf("delta=%f, lambda=%f", delta, lambda); */
  /* # initialization: time period: -tau -> 0, ##.## */
  /* # index period: 0 -> ttoi(tau) #.## */
  for(i=0; i<=ldelay; i++)
    v[i] = x1; /* v[i] = x1 */
  if (lambda<=delta)
    BelowDeltaEqLambda = 1;
  else
    BelowDeltaEqLambda = 0;
  uTooBig = 0;

  /* # calculation: time period: tmin -> tmax, #.*/
  /* # -------------- index period: ttoi(tau) -> */
  /* # ttoi(tmax+tau)##### */
  /* # integrate, and #.## */
  /* # save in v[] */
  iimin = ttoi(tmin+tau);
  imax = ttoi(tmax+tau);
  k = 1;
  for(i=k; (i<=imax) && (uTooBig==0) && (BelowDeltaEqLambda==0); i++)
  {
    if (v[i] < -10.0) uTooBig=1;
    if ( (v[i]-v[i-1])*(v[i-1]-v[i-2])<0) && (i>iimin)
    {
      /* it went up between (i-2) and (i-1) and down */
    }
  }
/* between (i-1) and (i), or the opposite */
{
  if ( (v[i-2]<v[i-1]) && (v[i-2]<v[i]) ||
       (v[i-2]>v[i-1]) && (v[i-2]>v[i]) )
    /* if (/\ AND ")" OR (\ AND "."), we need one more */
    /* point to have the peak between (i-1) and (i-2) */
    {
      i++;
      v[i] = integerstep(v, i, 1delay);
    }
  for(l=1; l<=4; l++) /* formation of the coefficients */
  { /* of the 3rd degree polynomial */
    a[l] = 0; /* used for the interpolation */
    for(m=1; m<=4; m++)
      a[l] += deg3[l][m]*v[i-4+m]/6;
  }  
  iPeak = - a[2]/3/a[1]*( 1-sqrt(1-3*a[1]*a[3]/(a[2]*a[2]))) ;
  /* position of the peak in time */
  /* interpolated value of u at the peak */
  fprintf(fptr, "%.f %.f %.f\n", delta, lambda, uPeak);
  }  
}  

int ttoi(t)
double t;
{
  return ( (int)(t/dt) );
}
double lolol(l)
{ return ( (double)i*dt ); }
double f(x,n)
double x, n;
{ return ( x * (1-x) ); }
double integstep(v, i, idelay)
double *v;
int i, idelay;
{ double k1, k2, k3, k4;
double um2, um1, um0, u, du;
  um2 = v[1-idelay-2];
  um1 = v[1-idelay-1];
  um0 = v[1-idelay ]; /* =u(t-tau) */
  u = v[i-2 ];
  /* ## here we take a time step 2dt, so that we dont have to interpolate ## */
  /* ## v[i-idelay-.5] that we need for k2 and k3 ## */
  k1 = 2*dt * ( -delta*u + lambda*f(um2) ) ;
  k2 = 2*dt * ( -delta*(u+k1/2) + lambda*f(um1) ) ;
  k3 = 2*dt * ( -delta*(u+k2/2) + lambda*f(um1) ) ;
  k4 = 2*dt * ( -delta*(u+k3) + lambda*f(um0) ) ;
  du = (k1+2*k2+2*k3+k4)/6;
  return ( u + du );
}
Bibliography


