1. INTRODUCTION

In this Chapter, the characteristics of the regulation and production of blood cells in hematological diseases are briefly presented. The analytical features of the use of granulocyte-colony stimulating factor (G-CSF) for treating low blood counting levels of white blood cells are also introduced.

1.1 HEMATOLOGICAL DISEASES

Dynamic hematological diseases are characterized by oscillatory behaviors in one or more cell lines. It has been intensively modeled due to their interesting dynamical nature. The basic characteristics of four periodic hematological disorders are reviewed and the role of mathematical modeling and numerical simulations which have played in the understanding of the origin of these diseases and in the regulation of hematopoiesis is examined.

Periodic hematological diseases are particularly interesting from a modeling point of view, due to their dynamical behaviors. Mathematical models of periodic hematological disorders have contributed substantially to the understanding of general regulatory principles of hematopoiesis and also provided insight into clinically relevant treatment strategies. Some of the mathematical models that have been developed over the years are reviewed and their applications are recounted. The normal aspects of the regulation and production of blood cells as well as the basic characteristics of some periodic hematological disorders are reviewed. Different mathematical tools that are typically useful for modeling in hematology are presented. DDEs were used for the modeling four periodic hematological diseases, namely periodic auto-immune hemolytic anemia (AIHA), cyclical thrombocytopenia (CT), cyclical neutropenia (CN) and periodic chronic myelogenous leukemia (PCML). For each of these diseases, the mathematical models as well as the knowledge of the disease gained from our mathematical analysis are reviewed.
1.1.1 Normal Hematopoiesis

Hematopoiesis is the term used to describe the production of blood cells. This process is initiated in the bone marrow by the hematopoietic stem cells (HSCs). These cells are self-replicating, and produce all types of blood cells. The HSC can produce partially differentiated progenitor cells, which can then differentiate into committed cells that give rise to one of the cell lineages: thrombocytes (platelets), erythrocytes (red blood cells (RBC)) or leucocytes (white blood cells (WBC)). Although all blood cells originate from this common source, the mechanisms that regulate their production are not completely clear. Nevertheless, the production of erythrocytes and platelets appears to be regulated by specific cytokines via negative feedback mechanisms whereas granulopoiesis is perhaps more complicated and thus less clearly understood.

The growth factor mainly involved in the regulation of erythrocyte production is erythropoietin (EPO). EPO production adjusts to the demand for oxygen in the body such that if there is a decrease in the O$_2$ levels in tissues, there will be an increase in EPO levels. This, in turn, will trigger increased production of primitive erythrocytes precursors (colony-forming units-erythroid (CFU-E)) partially mediated by interfering with apoptosis in these cells [1 –3]. These cells will mature and after a maturation delay produce new erythrocytes. As a result, the erythrocyte population will be increased and so will the oxygen carrying capacity of the blood. Hence, EPO mediates a negative feedback such that an increase in the number of erythrocytes leads to a decrease in erythrocyte production and vice versa. The regulation of platelet production involves similar feedback mechanisms mediated by the cytokine thrombopoietin. If the circulating platelets count is decreased, it triggers thrombopoietin production which then stimulates maturation of the platelet progenitor cells. This eventually leads to an increase in platelet production, again partially mediated by a decrease in megakaryocyte apoptosis [4].

There are three types of leucocytes, namely the lymphocytes, the granulocytes and the monocytes. So the main focus will be on production of granulocytes and more specifically on neutrophils, which constitutes the most abundant type of granulocyte. Cyclical neutropenia is the periodic hematological disease on which the greatest amount of published clinical procedure exists. The
mechanisms regulating granulopoiesis involve the cytokine G-CSF, which is the main regulator of neutrophil production [5]. It stimulates the formation of neutrophils from hematopoietic stem cells, accelerates the formation of neutrophils in the bone marrow and stimulates their release from the bone marrow into the blood. Although the exact mechanisms by which G-CSF acts are still unclear, it has been shown to decrease the transit time through the neutrophil post mitotic pool and increase maturation rate while interfering with apoptosis [6–8]. Several studies have shown an inverse relationship between the serum levels of G-CSF and the number of circulating neutrophils [9–12].

1.1.2 Dynamical Hematological Diseases

Periodic hematological disorders are classical examples of dynamical diseases [13, 14]. Because of their dynamical properties, they offer unique opportunity for understanding the nature of the regulatory processes involved in hematopoiesis. Periodic hematological disorders are characterized by oscillations in the number of one or more of the circulating blood cells with periods on the order of days to months [15]. The clinical aspects of four periodic hematological disorders are briefly reviewed. The first two, AIHA and CT, involve oscillations in only one cell lineage. In the other two diseases, CN and PCML, there is cycling in all of the major blood cell groups. This suggests that these disorders may involve a dynamic destabilization at the stem cell level, leading to oscillations in all cell lineages.

1.1.2.1 AIHA

AIHA results from an abnormality of the immune system that produces auto-antibodies, which attack red blood cells as if they were substances foreign to the body. It leads to an abnormally high destruction rate of the red blood cells. AIHA is a rare form of hemolytic Anemia in humans characterized by oscillatory erythrocyte numbers about a depressed level [16]. The origin of the disease is unclear. Periodic AIHA, with a period of 16 to 17 days in hemoglobin and reticulocyte counts, has been induced in rabbits by using red blood cell auto-antibodies.
Platelets are blood cells whose function is to take part in the clotting process, and CT denotes a reduced platelet count. In CT, platelet counts oscillate generally from very low values (\(1 \times 10^9\) cells/L) to normal (150 – 450 \(\times 10^9\) platelets/L) or above normal levels (2000 \(\times 10^9\) cells/L) [17 – 25]. These oscillations have been observed with periods varying between 20 and 40 days [19]. In addition, patients may exhibit a variety of clinical symptoms indicative of impaired coagulation such as purpura, petechiae, epistaxis, gingival bleeding, menorrhagia, easy bruising, possibly premenstrual, and gastrointestinal bleeding [18]. There are two proposed origins of CT. One is of auto-immune origin and most prevalent in females. The other is of a megakaryocytic origin, more common in males. It is characterized by a shortened platelet lifespan at the time of decreasing platelet counts [20]. This is consistent with normal to high levels of bone marrow megakaryocytes and with an increased destruction rate of circulating platelets [18]. Autoimmune CT has also been postulated to be a rare form of Idiopathic Thrombocytopenic Purpura (ITP) [20].

The megakaryocytic form of CT is characterized by oscillations in bone marrow megakaryocytes preceding the platelet oscillations [21 – 24]. In this second type of CT, platelet oscillations are thought to be due to a cyclical failure in platelet production [19, 22 – 26]. The platelet lifespan is usually normal and antibodies against platelets are not detected [25]. Although it has been suggested that the failure of platelet production could arise at the stem cell level, it is generally thought that the cycling originates at the megakaryocyte level [23, 25, 27]. In [18, 28], a more detailed review of CT can be found. It has been hypothesized that autoimmune and a megakaryocytic CT has a different dynamic origin [28]. It is supported that the patient's diagnosed as having the autoimmune CT generally have shorter periods (13-27 days) than those classified as a megakaryocytic (27-65) [18]. Moreover, it was reported that autoimmune patients typically show platelet oscillations from low to normal levels, whereas megakaryocytic subjects generally show oscillations from above normal to below normal levels of platelets.
1.1.2.3 CN

In a normal individual, the number of circulating neutrophils is relatively constant with an average of about \(2.0 \times 10^9\) cells/L. Neutropenia is a term that designates a low number of neutrophils, thus indicating that the individual is less effective at fighting infections. CN is characterized by oscillations in the number of neutrophils from normal to very low levels (less than \(0.5 \times 10^9\) cells/L). The period of these oscillations is usually around 3 weeks for humans, although periods up to 45 days have been observed [29]. The period in which the absolute neutrophil count (ANC) is very low usually lasts for about a week in humans. This period is associated with symptoms such as mouth ulcers, periodic fever, pharyngitis, sinusitis, otitis and other infections, some of which can sometimes be life-threatening. Fortunately, CN is effectively treated with daily administration of the growth factor G-CSF, which has the effect of reducing the period of the oscillations and increasing both the oscillation amplitude and the value of the ANC base. This has the overall effect of decreasing the period of severe neutropenia. In chapter 4–6, mathematical modeling has been used to design cheaper and more effective G-CSF treatment strategies.

Understanding of CN has been greatly aided by the existence of a similar disease in grey collies (street dogs) [30, 31]. The canine disorder shows the same characteristics as in humans, except that the period of the oscillations is usually between 11 and 15 days. The existence of this animal model has allowed the collection of a variety of data that would have been difficult, if not impossible, to obtain in humans. A major characteristic of CN is that the oscillations are not only present in neutrophils, but also in platelets, monocytes and reticulocytes, which is the reason CN is sometimes referred to as periodic hematopoiesis [31]. This observation suggests that the source of the oscillations may lie in the stem cell compartment. Although it is a rare disorder, CN is probably the most extensively studied periodic hematological disorder. The availability of an animal model and its dynamical properties makes it suitable for mathematical modeling and several modeling studies have indeed aided the understanding of the basic mechanisms of this disease.
1.1.2.4 PCML

Leukemia is a cancer of the blood or bone marrow. It is characterized by an abnormal proliferation of blood cells. It is also usually called as leucocytes. Chronic myelogenous leukemia (CML) is distinguished from other leukemias. The presence of a genetic abnormality in blood cells, also called as Philadelphia chromosome, which is a translocation between chromosomes 9 and 22 that leads to the formation of the fusion protein [26, 27]. This protein is thought to be responsible for the dysfunctional regulation of myelocyte growth and other features of CML [32]. A dynamical disease of particular interest is PCML, characterized by oscillations in circulating cell numbers that occur primarily in leucocytes, but may also occur in the platelets and reticulocytes [33]. The leucocyte count varies periodically, typically between values of 30 and $200 \times 10^9$ cells/L, with a periods ranging from 40 to 80 days. In addition, oscillation of platelets and reticulocytes may occur with the same period as the leucocytes, around normal [34]. As in CN, the hypothesis that the disease originates from the stem cell compartment is supported by the presence of oscillations in more than one cell lineage.

1.2 MATHEMATICAL MODELS OF HEMATOLOGY

Mathematical models used for modeling biological processes for decades. With the advancement of technology and the increasing amount of available data, mathematical models and simulation techniques provide ways of better understanding the underlying mechanisms of biological processes. In hematological modeling, several mathematical tools and computational methods are used [35]. The choice of the mathematical tools often depends on the desired level of description of the model. For instance, one could model processes at small scale, or on a larger scale. Mathematical models of hematopoietic regulatory systems using a stochastic formulation have not been extensively developed, primarily because the lack of corresponding data for stems cells and their progeny [36]. In this section, the focus will be on models that use differential equations: ordinary differential equations (ODE), partial differential equations (PDE), or delay differential equations (DDE). The different types of delay differential equations and the reduction of DDE systems to an ODE system using the linear chain trick are discussed. Second, a typical setting for a model, based on biological aspects of hematopoiesis is presented and shows that
this could be modeled by an age-structured model. The PDE model can be reduced to a DDE model.

1.2.1 DDE Models

Delay-differential equations are a large and important class of dynamical systems. It often arises in biological systems where time events naturally occur. In particular, in hematology several processes are controlled through feedback loops and these feedbacks are generally operative only after a certain time, thus introducing a delay in the system feedback [37]. The general form of a DDE for \( x(t) \in \mathbb{R}^n \) is

\[
\frac{dx}{dt} = f(t, x(t), x_{\tau})
\]

(1.1)

where \( x_{\tau} \) is the delayed variable \( (x(t - \tau)) \) and \( f \) is a functional operator in \( \mathbb{R} \times \mathbb{R}^n \times C^1 \).

1.2.1.1 DDE with Constant Delays

Delay differential equations with constant delays take the form

\[
\frac{dx}{dt} = f(x(t), x(t - \tau_1), x(t - \tau_2), ..., x(t - \tau_n)),
\]

where the quantities \( \tau_i, i = 1, 2, ..., n \) are positive constants. For simplicity, consider the DDE with a single constant delay:

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

(1.2)

To obtain a solution of Equation (1.2) for \( t > 0 \), one needs to specify a history function on \([-\tau, 0]\). Indeed, recall that for an ODE system with \( n \) variables, one would only need to specify the initial values \( x(0) \) for each of the \( n \) state variables. In order to solve a DDE, one needs to specify not only the value at \( t = 0 \), but also all the past values of \( x(t) \) over the interval \([-\tau, 0]\). Since one needs to specify an “infinite” number of values, DDEs are often viewed as infinite-dimensional systems [38]. Constant delay differential equations are often used in modeling in hematology. For example, let \( X(t) \) represent the circulating cell population of a certain type of blood cell, assume that \( \rho \) is the random rate of loss of cells in the circulation and \( F \) is the flux of cells from the previous compartment. Then, the dynamics of the number of circulating cells will have the generic form
\[
\frac{dx}{dt} = -\gamma X + F(X(t - \tau))
\]

Where \(\tau\) is the average length of time required to go through the compartment (time delay). Typically, \(F\) is taken to be a monotone decreasing function of \(X\) to mimic the negative feedback loops of the system.

### 1.2.1.2 DDE with Distributed Delays

A distribution of delays is more appropriate and the DDE becomes an integro-differential equation of the form:

\[
\frac{dx}{dt} = f(x(t), \int_{-\infty}^{t} x(\tau)G(t - \tau)d\tau)
\]

(1.3)

The density \(G(u)\) of the distribution function is referred to as the memory function or the kernel and is normalized,

\[
\text{i.e. } \int_{0}^{\infty} G(u)du = 1
\]

This type of model can also be interpreted as allowing for a stochastic element in the duration of the delay [37]. Also, it can be seen that for some densities \(G(u)\), it can be equivalently viewed as a system of ordinary differential equations.

### 1.2.1.3 DDE with State dependent Delays

Another type of delay differential equation occurs when the delay depends on a state variable. For example, one could imagine that the maturation time for a blood cell depends on the amount of growth factor in the circulation as, for example, is the case with the maturation time of neutrophil precursors in humans. An example of a model with a state-dependent delay can be found, but it is fair to say that models of hematopoietic regulation with state dependent delays have not appeared because of the paucity of data for the analytic variation of delays with respect to state variables [39].

### 1.2.2 ODE Models

For some forms of delays, the so-called linear chain trick enables the model to be written as an equivalent finite-dimensional system of ordinary differential equations [37]. Consider the following DDE system with a distributed delay:
\[
\frac{dx_1}{dt} = f(x_1(t), \int_{-\infty}^{t} x_1(\tau)G(t-\tau)d\tau),
\]

with the special choice of the density of the gamma distribution for the memory function

\[
G(u) = G_p^p(u) = \frac{a^{p+1}u^p}{p!}e^{-au},
\]

where ‘a’ is a positive number and ‘p’ is a positive integer or zero. Note that the function G(u) has a maximum at \( u = p/a \) and that, as a and p increase, keeping p/a fixed, the kernel approaches a delta function and the distributed delay approaches the discrete time delay with \( \tau = p/a \). Moreover, it is clear that the following three properties are satisfied:

\[
\lim_{u \to \infty} G_p^p(u) = 0, G_p^p(0) = 0 \forall p \neq 0, G_p^p(0) = a
\]

The central idea of the method is to replace the distributed delay by an extension of the set of variables. Define \( p + 1 \) new variable as

\[
x_{j+1} = \int_{-\infty}^{t} x_1(\tau)G_{j-1}^p(t-\tau)d\tau, \quad j = 1, 2, \ldots, p + 1
\]

\[
x_{p+2} = \int_{-\infty}^{t} x_1(\tau)G(t-\tau)d\tau,
\]

Then, using the properties of G one can show that these new variables satisfy a sequence of linear ODE. Solving the following system is thus equivalent to solving the DDE problem (1.3), given that the new variables are given appropriate initial values:

\[
\frac{dx_1}{dt} = f(x_1, x_{p+2})
\]

\[
\frac{dx_{j+1}}{dt} = a(x_j - x_{j+1}), \quad j = 1, 2, \ldots, p + 1
\]

\[
\frac{dx_{p+2}}{dt} = a(x_{p+1} - x_{p+2})
\]

The linear chain trick could be useful for numerical computations since it reduces the problem to an ODE system, for which several numerical methods are available.
1.2.3 Linear Chain Trick

The derivation of the ODE system obtained using the linear chain trick is presented [37]. Consider the following DDE system with a distributed delay:

\[
\frac{dx_1}{dt} = f\left(x_1(t), \int_{-\infty}^{t} x_1(\tau) G(t-\tau) d\tau\right),
\]

\[
\frac{dx_i}{dt} = f(x_i, x_{p+2})
\]

Next, the expression for \(\frac{dx_{j+1}}{dt}\), \(j = 1, ..., p + 1\) is derived from the Leibniz integral rule. We have

\[
\frac{dx_{j+1}}{dt} = d\left(\int_{-\infty}^{t} x_i(\tau) G^{j+1}_a(t-\tau) d\tau\right) = x_i(t) G^{j+1}_a(0) + \lim_{u \to -\infty} G^{j+1}_a(u) + \int_{-\infty}^{t} x_i(\tau) \frac{d}{dt} G^{j+1}_a(t-\tau) d\tau.
\]

From the three properties of \(G^{j+1}_a(u)\) presented above, the first and second terms on the right hand side vanish, except for the case \(j = 1\) where the first term is equal to \(ax_1\). Also, one can easily show that the derivatives of \(G^{j+1}_a(t-\tau)\) are given by

\[
\frac{d}{dt} G^0_a(t-\tau) = -aG^0_a(t-\tau),
\]

\[
\frac{d}{dt} G^{j+1}_a(t-\tau) = a\left[G^{j+2}_a(t-\tau) - G^{j+1}_a(t-\tau)\right].
\]

The required set of differential equations for \(x_j, j = 2, 3, ... p + 2\) are obtained:

\[
\frac{dx_2}{dt} = ax_1 - a \int_{-\infty}^{0} x_i(\tau) \frac{d}{dt} G^0_a(t-\tau) d\tau = ax_1 - ax_2,
\]

\[
\frac{dx_{j+1}}{dt} = a \int_{-\infty}^{t} x_i(\tau) \left(G^{j+2}_a(t-\tau) - G^{j+1}_a(t-\tau)\right) d\tau = ax_j - ax_{j+1}.
\]

1.2.4 Age-Structured Models

This is a PDE model used in several applications. Indeed, a cell starts from the hematopoietic stem cell and then its progeny go through a number of stages before being released into the circulation. Let \(x(t, \alpha, \beta)\) be the cell density at time \(t\), age \(\alpha\) and rate of production \(\beta\) in a generic compartment and that cells disappear (die) at a rate \(\gamma(t)\). Further it is also assumed that the cells in the compartments \(\alpha \& \beta\) with
velocities $V(t)$ & $U(t)$ and that a cell enters a compartment at $\beta = 0$ and exit this compartment at $\beta = \tau$. Let $x(t, \alpha, \beta)$ satisfy the following delay differential equation:

$$\frac{\partial x}{\partial t} + V(t) \frac{\partial x}{\partial \alpha} + U(t) \frac{\partial x}{\partial \beta} = -\gamma(t)x, \ t > 0, \ \alpha, \beta \in [0, \tau]$$  \hspace{1cm} (1.4)

with boundary condition:

$$x(t, \alpha, 0) = \psi(t)$$  \hspace{1cm} (1.5)

and initial condition

$$x(0, \alpha, \beta) = \varphi(E)$$  \hspace{1cm} (1.6)

$$\int_0^\tau \frac{\delta x(t, \alpha, \beta)}{\delta t} \ d\beta + \int_0^\tau V(t) \frac{\delta x(t, \alpha, \beta)}{\delta \alpha} \ d\beta + \int_0^\tau U(t) \frac{\delta x(t, \alpha, \beta)}{\delta \beta} \ d\beta = -\int_0^\tau \gamma(t)x(t, \alpha, \beta) \ d\beta$$

$${\frac{dx}{dt}} + V(t)[x(t, \alpha, \tau) - x(t, \alpha, 0)] + U(t)[x(t, \alpha, \tau) - x(t, \alpha, 0)] = -\gamma(t)X(t)$$

$${\frac{dx}{dt}} + [V(t) + U(t)][x(t, \alpha, \tau) - x(t, \alpha, 0)] = -\gamma(t)X(t)$$  \hspace{1cm} (1.7)

where $X(t)$ is the total number of cells.

$$X(t) = \int_0^\tau x(t, \alpha, \beta) \ d\beta$$

It can substitute the B.C $x(t, \alpha, 0) = \psi(t)$

$$(1.7) \Rightarrow \frac{dx}{dt} = [V(t) + U(t)][\psi(t) - x(t, \alpha, \tau)] - \gamma(t)X(t)$$  \hspace{1cm} (1.8)

Let $x(s) = x(t(s), \alpha(s), \beta(s))$

$${\frac{dx}{ds}} = \frac{\partial x}{\partial t} \frac{dt}{ds} + \frac{\partial x}{\partial \alpha} \frac{d\alpha}{ds} + \frac{\partial x}{\partial \beta} \frac{d\beta}{ds} = -\gamma(t)x$$  \hspace{1cm} (1.9)

This defines a set of four ODEs for $t > 0$ and $\alpha, \beta \in [0, \tau]$ as follows.

$${\frac{dt}{ds}} = 1 \Rightarrow t(s) = t(0) + s$$  \hspace{1cm} (1.10)

$${\frac{d\alpha}{ds}} = V(t) \Rightarrow \alpha(s) = \alpha(0) + \int_0^s V(w) \ dw$$  \hspace{1cm} (1.11)

$${\frac{d\beta}{ds}} = U(t) \Rightarrow \beta(s) = \beta(0) + \int_0^s U(w) \ dw$$  \hspace{1cm} (1.12)
\[
\frac{dx}{ds} = -\gamma(t)x \Rightarrow x(s) = x(0)\exp \left( -\int_0^s \gamma(t(w),\alpha(w),\beta(w))dw \right) \quad (1.13)
\]

Denote by C the curve emanating from the point \((t,\alpha,\beta) = (0,0,0)\), and separating the \(t - \alpha\) & \(t - \beta\) plane into two distinct regions \(R_1\& R_2\). The curve C is defined by

\[
C = \left\{ (t,\alpha,\beta) : t(s) = s, \alpha(s) = \int_0^s V(w)dw, \beta(s) = \int_0^s U(w)dw, s \in [0,s_T] \right\} \quad (1.14)
\]

where the values of \(s_T\) corresponds to the value of \(s\) required to reach \(a = E = \tau\), thus \(s_T\) must satisfy

\[
\tau = \int_0^{s_T} V(w)dw \quad \text{and} \quad \tau = \int_0^{s_T} U(w)dw \quad (1.15)
\]

the solution \(x(t,\alpha,\beta)\) takes a different from depending on whether it lies in region \(R_1\) or \(R_2\).

Recall that the general solution is given by (1.13)

\[
x(s) = x(0)\exp \left( -\int_0^s \gamma(t(w),\alpha(w),\beta(w))dw \right)
\]

Therefore, we need to find an expression for \(x(0)\) and \(s\) as a function of \(\alpha,\beta\) & \(t\) in order to obtain the expression

\[
x(t,\alpha,\beta) = x(t(s),\alpha(s),\beta(s)). \quad (1.16)
\]

We are interested in the value \(x(t,\alpha,\tau)\). If \((t(0),\alpha(0),\beta(0)) \in R_1\), then \(t(s) = s\) and \(\beta(s) = \beta(0) + \int_0^s U(w)dw\) with \(0 < \beta(0) < \tau\). Using the initial condition (1.6)

\[
x(0) = \varphi \left( E - \int_0^t U(w)dw \right) \quad (1.17)
\]

\[
x(t,\alpha,\tau) = \varphi \left( E - \int_0^t U(w)dw \right) \exp \left( -\int_0^t \gamma(w)dw \right)
\]

If \((t(0),\alpha(0),\beta(0)) \in R_2\), then it has \(\beta(0) = 0\) and thus \(\beta(s) = \int_0^s U(w)dw\) and \(t(s) = t(0) + s\). Hence using the boundary condition

\[
(1.5) \Rightarrow x(0) = \varphi(t-s) \quad (1.18)
\]
\[ \beta(s) = \int_{0}^{s} U(t(w)) \, dw = \int_{0}^{s} U(t(0) + w) \, dw = \int_{(0)}^{s} U(\sigma) \, d\sigma \]  
(1.19)

Let us define by \( T \) the time needed for the \( \beta \) variable to go from 0 to \( \tau \)
\[ \tau = \int_{0}^{T} U(w) \, dw = \int_{t-T}^{t} U(w) \, dw \]  
(1.20)

\[ x(t, \alpha, \tau) = \varphi(t - s) \exp \left( - \int_{0}^{\tau} \gamma(w) \, dw \right) \]  
(1.21)

The method of characteristics the solution \( x(t, \alpha, \tau) \) is
\[ x(t, \alpha, \tau) = \begin{cases} 
\varphi(t - \int_{0}^{t} U(w) \, dw) \exp(-\int_{0}^{\tau} \gamma(w) \, dw), (t, \beta) \in \mathbb{R}_1 \\
\psi(t - T) \exp(-\int_{0}^{\tau} \gamma(w) \, dw), (t, \beta) \in \mathbb{R}_2 
\end{cases} \]  
(1.22)

Substituting in eqn. (1.8)
\[ \frac{dX}{dt} = \left[ V(t) + U(t) \right] \left[ \psi(t) - \psi(t - T) \exp \left( - \int_{0}^{\tau} \gamma(w) \, dw \right) - \gamma(t) X(t) \right] \]  
(1.23)

Eqn. (1.23) reduces to
\[ \frac{dX}{dt} = \left[ V(t) + U(t) \right] \left[ \psi(t) - \psi(t - T) e^{-\gamma T} - \gamma X(t) \right], \]  
(1.24)

In addition, if the erythrocyte population velocity is constant \( (U(t) = U) \), it follows that \( T \) satisfies
\[ \tau = \int_{t-T}^{t} U \, dw = UT \]  
(1.25)

\( T = \tau / U \). Hence if \( \gamma \) and \( U \) are constant, it obtains the following DDEs with constant delay
\[ \frac{dX}{dt} = \left[ V(t) + U(t) \right] \left[ \psi(t) - \psi(t - T) e^{-\gamma T / U} \right] - \gamma X(t). \]  
(1.26)
1.3 SCOPE OF THE THESIS

Efficient methods to execute parameter estimation have been explored in the previous study, the model to perform G-CSF reduction are shown. This work uses a FFT simulation model. The main bottleneck of soft computing algorithms is time consumption and its work dependency like neutrophil counts and reduction of the target system. Since the parameters effects are modeled separately, it could study in more detail the accurate value. FFT simulations for this subject could then predict the possible outcomes of different treatment schemes. Future studies will provide novel insights and help to better value the system. The models presented would have to be modified accordingly, as this is part of the simulation of mathematical modeling. The analysis of the precise mechanism that generates oscillation in the necessary mathematical model on the kinetics of stem cell populations in the bone marrow to allow the new model to extend the original work. An alternative method to reduce the G-CSF value is by using a FFT model, and this method is studied in this research work.

1.4 CONTRIBUTION OF THE THESIS

The contribution of this thesis is investigated as follows.

1. The analysis of CN lies in destabilization of the combined HSC and neutrophil control system. This analysis presents the CN oscillations in general. The CN oscillations also present the platelets and reticulocytes. In this study, it will only consider the reduction of drug. Since oscillations are also present in platelets and red blood cell precursors in CN, the addition of this two compartments model for subcutaneous injections of G-CSF made the model more realistic by taking into account the time needed for G-CSF to go from the tissue compartment to the blood as well as its degradation rate. In the two compartment models, HSC compartment was used and to hide the dynamic behavior of the hematopoietic system under G-CSF treatment, the neutrophil count could be stabilized or to show large amplitude oscillations.

2. G-CSF is a hematopoietic growth factor that stimulates the bone marrow to increase the production of neutrophils. Thus, this is the treatment of choice for neutropenia. It is produced naturally in the body, but recombinant forms of G-CSF
are used as drugs to accelerate recovery from neutropenia. The alternative G-CSF treatment strategies for cyclical neutropenia using a combination of analytical and numerical tools were proposed. This model G-CSF treatment schemes are effective while using less G-CSF. The results were that three of the models parameters were identified as the most crucial in simulating the effects of CN and its treatment with G-CSF: the amplification in the proliferating neutrophil precursors, the rate of apoptosis in the proliferating HSCs, and the maximal rate of differentiation from the HSCs into the neutrophil line.

3. The FFT simulation analysis allowed quality variations in the dynamics of hematopoiesis in the GC, in particular in the neutrophils and the platelets. The present modeling study suggests that the peripheral feedback controlling granulocytosis is responsible for the distortion of the oscillations observed in the ANC. FFT model suggests that two different types of response can be obtained by G-CSF administration. A large neutrophil become a greater level and followed by a smaller ANC in high level is found. It remains stable and does not go to lower levels. Indeed, the idea of using a mathematical approach to study different G-CSF administration schemes originates from a previous study. It was estimated a normal blood neutrophil count higher than previous work.

4. From a mathematical point of view, many factors influence the response of the model, among which the historical values of all variables as well as the choice of parameters. It is used a first order DDE model that includes neutrophils and stem cells. If the solution has a discontinuity in a derivative somewhere, there are discontinuities in the rest of the interval at a spacing given by the delays. Such discontinuities are not unusual for ODEs, but it is almost always present for DDEs. In particular, the stability model developed general necessary and sufficient conditions for the existence of delay-induced instability in systems of two or three first order delay differential equations.

5. Three parameters were modified to mimic the effects of treatment: the amplification in the proliferating neutrophil precursors, the rate of apoptosis in the proliferating hematopoietic stem cells, and the maximal rate of differentiation from the HSCs into the neutrophil line. The goal was to study different treatment strategies through numerical simulations of the model.
1.5 CONTRIBUTION OF AUTHOR

The contribution of author and areas investigated in this research work are summarized.


1.6 CHAPTER-WISE DESCRIPTION

The remainder of this thesis is structured as follows.

In chapter 2 we give some brief Hematological diseases and literature survey to motivate the development of a G-CSF reduction model. In chapter 3 we make some preliminary remarks and observations about the solutions of a generalization of the DDE and nonlocal partial differential equation derived and prove our main theorem connecting the global solution behavior of this associated differential delay equation with the local and global solution behavior of the partial differential equations. In chapter 4 we introduce the parameter estimation model obtained from the delay differential equation by ignoring the maturation variable and neurophil count. In chapter 5 we state and prove a result that guarantees the local stability of the numerical simulation, which is a necessary ingredient for the use of the cure rate of the diseases. In chapter 6 we specifically consider the amount of reducing the G-CSF drug considered to illustrate the applicability of our results. Chapter 7 concludes the thesis with a brief consideration of the G-CSF drug in which the model solution is reduced.