Understanding and Treating Cytopenia Through Mathematical Modeling

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Abstract

In this chapter we briefly review how the study of dynamic hematological diseases with mathematical modeling tools has led to a better understanding of the origin of some types of cytopenia and to improved treatment strategies. Dynamical hematological diseases include a wide range of diseases that are characterized by predictable oscillations in one or more cellular elements of the bloods. The dynamics of the hematopoietic system have been instrumental in guiding the development of a multiplicity of mathematical models. This chapter introduces a set of delay differential equation models obtained from an age-structured model by the characteristic line method. This set of equations describe the dynamics of four cell linages, including the hemopoietic stem cells and three differentiated cell lines, leukocytes, erythrocytes, and platelets. Applications of this model to the study of cyclical neutropenia (CN) are extensively reviewed. In particularly, origin of CN, chemotherapy induced CN, and G-CSF administration in the treatment of CN induced by chemotherapy are discussed. Discussions in the chapter show that mathematical models have offer a potentially exciting opportunity to insight from mathematics to better the delivery of medical care for those needing it.

Keywords: neutropenia, thrombocytopenia, anemia, chemotherapy, granulocyte colony stimulating factor, thrombopoietin

1. Introduction

All blood cells arise from a common origin in the bone marrow, the hematopoietic stem cells (HSC). HSC are morphologically undifferentiated cells which can either proliferate or differentiate to produce all types of blood cells (erythrocytes, neutrophils and platelets). The proliferation of stem cells and progenitor cells is controlled by a negative feedback system mediated by hematopoietic cytokines. Erythropoietin (EPO) is the hormone that mediates the red blood cell (RBC) production, granulocyte colony stimulating factor (G-CSF) controls the regulation

of neutrophils, and thrombopoietin (TPO) known as c-mpl ligand or megakaryocyte growth and development factor, is the primary regulator of thrombopoiesis.

Hematopoiesis is a homeostatic system and, consequently, most disorders of its regulation lead to transient or chronic failures in the production of either all or only one blood cell type. Among the wide rage of diseases affecting the blood cell populations, there are some which are characterized by predictable oscillations in one or more cellular elements of the blood. They are called periodic or dynamical diseases [1]. The investigation of their dynamic character offers an opportunity to enrich our knowledge about the regulatory processes controlling blood cell production and can suggest better therapeutic strategies [2]. Cyclical neutropenia [3, 4, 5, 6], periodic chronic myelogenous leukemia [3, 7], periodic autoimmune hemolytic anemia [8] and cyclical thrombocytopenia [9, 10] are some of classical examples of dynamical hematological diseases. Diseases like periodic chronic myelogenous leukemia (PCML) and cyclical neutropenia (CN), which involve fluctuations in all major blood cell lines with the same period on a given subject, are believed to arise in the stem cell compartment in the bone marrow. Since in cyclical thrombocytopenia (CT) or periodic autoimmune hemolytic anemia besides oscillations in one type of cell count the patient hematological profile have been consistently normal, a destabilization of a peripheral control mechanism might play an important role in the genesis of these disorders.

2. Dynamic hematological disease

2.1. Cyclical neutropenia

Neutrophils are critical for the immune response, and low absolute neutrophil counts in the blood can lead to infections. Neutropenia is a term that designates a low number of neutrophils, thus indicating that the individual is less effective at fighting infections. The severity of neutropenia in patients can be classified based on the absolute neutrophil count (ANC) [11]: mild neutropenia ($1.0 \leq ANC < 1.5 \times 10^9$cells/L) with minimal risk of infection, moderate neutropenia ($0.5 \leq ANC < 1.0 \times 10^9$cells/L) with moderate risk of infection, and severe neutropenia ($ANC < 0.5\times10^9$cells/L) with severe risk of infection. Patients with severe neutropenia are often seen with symptoms such as mouth ulcers, fever, pharyngitis, sinusitis, otitis and other infections, some of which can sometimes be life-threatening.

Cyclical neutropenia (CN) is characterized by oscillations in the number of neutrophils from normal to very low levels (less than 0.5×10^9cells/L, also called severe neutropenia). The period of these oscillations is usually around 3 weeks for humans, although periods up to 45 days have been observed [6]. One major

characteristic of CN is that the oscillations are not only present in neutrophils, but also in platelets, monocytes and reticulocytes [4]. For CN patients, the period of severe neutropenia usually lasts for about 3-5 days within every 3 week period [5, 12].

Cyclical neutropenia also occurs in grey collies with the same characteristics as in humans and with oscillation periods on the order of 11 to 16 days [4, 6, 13]. This animal model has provided extensive experimental data that would be difficult, if not impossible, to obtain in humans.

Cyclical neutropenia was first reported as an inherited disease by Reimann [14], and later confirmed in the study of Australian families by Morley et al. [15]. In these families, the severity of symptoms and the severity of neutropenia vary among each other. Furthermore, the disease is more severe in children and is ameliorated by unknown factors as they grow older [16]. Through family studies and linkage analysis, mutations in the gene encoding neutrophil elastase (ELA2) are recognized as a trigger causing cyclic neutropenia [17].

2.1.1. Cyclical thrombocytopenia

Platelets are blood cells whose function is to take part in the clotting process, and the term thrombocytopenia denotes a reduced platelet (thrombocyte) count. In cyclical thrombocytopenia (CT), platelet counts oscillate generally from very low values (1×10^9cells/L) to normal ($150-450\times10^9$ platelets/L blood) or above normal levels (2000×10^9 cells/L) [9]. These oscillations have been observed with periods varying between 20 and 40 days [18]. 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 premenstrually, and gastrointestinal bleeding [9]. There are two proposed origins of cyclical thrombocytopenia. One is of autoimmune origin and most prevalent in females. The other is of amegakaryocytic origin, more common in males.

Autoimmune cyclical thrombocytopenia is characterized by a shortened platelet lifespan at the time of decreasing platelet counts [19]. This is consistent with normal to high levels of bone marrow megakaryocytes and with an increased destruction rate of circulating platelets [9]. Autoimmune CT has also been postulated to be a rare form of idiopathic (immune) thrombocytopenic purpura (ITP) [19].

The amegakaryocytic form of CT is characterized by oscillations in bone marrow megakaryocytes preceding the platelet oscillations [20, 21, 22, 23]. In this second type of CT, platelet oscillations are thought to be due to a cyclical failure in

platelet production [18, 21, 22, 23, 24, 25]. The platelet lifespan is usually normal [25] and antibodies against platelets are not detected [24]. Although it has been suggested that the failure of platelet production could arise at the stem cell level [26], it is generally thought that the cycling originates at the megakaryocyte level [22, 24]. For a more detailed review of CT, see [9, 27].

It has been hypothesized that autoimmune and amegakaryocytic cyclical thrombocytopenia have different dynamic origins [27]. This is supported by Swinburne and Mackey [9], who noted that the patients diagnosed as having the autoimmune CT generally have shorter periods (13-27 days) than those classified as amegkaryocytic (27-65 days). Moreover, they reported that autoimmune patients typically show platelet oscillations from low to normal levels, whereas amegakaryocytic subjects generally show oscillations from above normal to below normal levels of platelets.

2.2. Periodic anemia

Examples of periodic anemia are relatively rare in clinical literatures, though there are a few well documented examples [28, 29]. Although periodic fluctuations of erythroid precursors in the bone marrow are well documented in cyclical neutropenia and some cases of periodic leukemia (see below), the rarity of reports of actual periodic anemia is presumably due to the extremely long lifespan of circulating erythrocytes in humans. There are, however, well documented examples of cyclical anemia in mice following either the administration of a single dose of ^{89}Sr [30, 31, 32] or after whole body irradiation [33, 34].

Autoimmune hemolytic anemia (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. Periodic AIHA is a rare form of hemolytic anemia in humans characterized by oscillatory erythrocyte numbers about a depressed level [28]. The origin of this 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 [35]. Mackey showed that the laboratory characteristics of this induced disorder were consistent with model predictions using a mathematical formulation like those explored in Section 3 [36].

2.3. Periodic leukemia

Leukemia is a cancer of the blood or bone marrow characterized by an abnormal proliferation of blood cells, usually leucocytes. Chronic myelogenous leukemia

(CML) is distinguished from other leukemias by the presence of a genetic abnormality in blood cells, called the Philadelphia chromosome, which is a translocation between chromosomes 9 and 22 that leads to the formation of the BcrAbl fusion protein [37]. This protein is thought to be responsible for the dysfunctional regulation of myelocyte growth and other features of CML [38]. (For more details about CML, see [39]).

A dynamical disease of particular interest is periodic chronic myelogenous leukemia (PCML), characterized by oscillations in circulating cell numbers that occur primarily in leucocytes, but may also occur in the platelets and reticulocytes [7]. The leucocyte count varies periodically, typically between values of 30 and 200×10^9 cells/L, with a periods ranging from 40 to 80 days. In addition, oscillations of platelets and reticulocytes may also occur with the same period as the leucocytes, around normal or elevated numbers [7, 40]. As in cyclical neutropenia, the hypothesis that the disease originates from the stem cell compartment is supported by the presence of oscillations in more than one cell lineage.

3. Mathematical model development

As is clear from the preceding section describing the periodic cytopenias, the hematopoietic system is capable of displaying interesting dynamical properties in pathophysiological situations. These dynamics have been instrumental in guiding the development of a multiplicity of mathematical models of hematopoietic dynamics. Many of these have been reviewed in [41] and [42].

3.1. Model description

Although the regulation of blood cell production is complicated [4, 43], and its understanding constantly evolving, the broad outlines are clear. Figure 20.1 contains a cartoon representation of hematopoiesis.

There are four linages, including the hemopoietic stem cells and three differentiated cell lines, leukocytes, erythrocytes, and platelets.

Hemopoietic stem cells are classified as either proliferating or resting-phase [45]. The proliferating stem cells undergo mitosis at a fixed time after entry into proliferating state, and are lost randomly during the proliferation [46]. Each normal cell generates two resting-phase cells at the end of mitosis. The resting-phase cells can either re-enter the proliferative phase at a rate involving a negative feedback, or develop to mixed myeloid progenitor cell, which further differentiate into precursors of any of the three cell lines, leukocytes (white blood cells (WBC)), erythrocytes (red blood cells (RBC)), or thrombocytes (platelets).

The rates of differentiation into these three lines depend on the numbers of circulating cells of the relevant type that encapsulate the feedback between the circulating cell numbers and the production. The feedback is always negative so when the number of circulating mature cells of a given line falls, the relevant differentiation rate has a corresponding compensatory increase.

There are two stages for each of the circulating cell lines after the differentiation, first the amplification/maturation of precursor cells in the bone marrow, and next circulation of mature cells throughout the whole body. In the stage of amplification/maturation, the precursor cells undergo many stages of cell division and randomly die so that the number of precursors increases rapidly in a period: one stem cell is capable of producing about 106 mature blood cells after 20 cell divisions [47]. In the circulation stage, mature blood cells are removed randomly at a fixed rate. In additional, the circulating erythrocytes and platelets are actively destroyed at a fixed time from the entry into the circulating compartment [48, 49].

The proliferation and differentiation of hematopoietic cells and the function of mature blood cells are regulated by a variety of cytokines, including erythropoietin (EPO) [50], which mediates the regulation of erythrocyte production, granulocyte colony stimulating factor (G-CSF) [51], which regulates neutrophil number, and thrombopoietin (TPO) [52, 53], which regulates production of platelets and other cell lineages.

For the red blood cells, EPO mediates a negative feedback loop that helps to regulate erythrocyte production [50, 54]. A decrease in the numbers of circulating erythrocytes leads to a decrease in tissue pO_2 levels, which in turn triggers the production and release of EPO by renal macula cells. This elevation of EPO increases the net production of primitive erythroid precursors (CFU-E) and, ultimately, an increase in the number of circulating erythrocytes and hence the tissue pO_2 levels.

The regulation of platelet production (thrombopoiesis) involves similar feedback mechanisms mediated by TPO [55]. A decrease in circulating platelet counts results in an increased level of thrombopoietin, which then stimulates maturation of the platelet progenitor cells (colony-forming units-megakaryocyte (CFU-Meg)), and eventually leads to an increase in platelet production.

There are three types of leucocytes, namely the lymphocytes, the granulocytes and the monocytes. Here we focus on granulopoiesis (production of granulocytes) and more specifically on neutrophils. The mechanisms of regulating granulopoiesis involve G-CSF, which is the main regulator of neutrophil production [56]. It stimulates the formation of neutrophils from hematopoietic stem cells, accelerates

the formation of neutrophils in bone marrow and stimulates their release from the bone marrow into the blood. Although the exact mechanisms by which G-CSF acts is still unclear, it has been shown that the neutrophils regulate their own production through a negative feedback [51]: An increase (decrease) in the number of circulating neutrophils would induce a decrease (increase) in the production of neutrophils through the adjustment of the granulocyte colony stimulating factor levels. Several studies have shown an inverse relationship between the serum levels of G-CSF and the number of circulation neutrophils [57, 58, 59, 60].

3.2. Formulation

In the last several decades, different mathematical tools have been used in hematological modeling, including differential equations (partial, ordinarily or delay), stochastic processes, Boolean networks, Bayesian theory, multivariate statistics, decision trees, etc. For reviews, see [41, 61, 62]. The choice of the mathematical tools often depends on the desired level of description of the model. Here, we focus on models that originate from age-structured models, which offer a natural way to model hematopoietic dynamics, and are widely used in the study of dynamical blood diseases [3, 10, 44, 63, 64, 65].

3.2.1. Age-structured model

We refer the model illustrated in Figure 20.1. Variables used in the following equations and typical values for hematologically normal individuals are summarized in Table 20.1.

Let $Q(t)$ (cells/kg) denotes the population of resting-phase stem cells, and $s(t,a)$ (cells/kg) the population of stem cells in the proliferating phase, with age $a=0$ for their time of entry into the proliferative state. For the other three cell lines, let $n(t,a)$, $r(t,a)$, and $p(t,a)$ (cells/kg) represent the populations of leukocytes, erythrocytes, and platelets, respectively, with age $a=0$ for the time point of differentiating from stem cells. Let

$$N(t)=\int_{\tau_N}^{+\infty} n(t,a)da,\ \ R(t)=\int_{\tau_R}^{\tau_{Rsum}} r(t,a)da,\ \ P(t)=\int_{\tau_P}^{\tau_{Psum}} p(t,a)da, \qquad (1)$$

which are the populations of circulating cells. Hereinafter we set $\tau_{Rsum}=\tau_R+\tau_{RS},\ \tau_{Psum}=\tau_P+\tau_{PS}$. Moreover, the differentiation rates κ_N, κ_R and κ_P

are assumed depending on circulating cell populations through negative feedback functions denoted by $\kappa_N(N)$, $\kappa_R(R)$ and $\kappa_P(P)$, respectively.

Using the above notations, the age-structured model of hematopoiesis is then described by the following partial differential equations [44]

$$
\begin{aligned}
\nabla s(t,a) &= -\gamma_S(t)s(t,a) && (t>0, 0\le a\le \tau_S)\\
\frac{dQ}{dt} &= 2s(t,\tau_S)-(\beta(Q)+\kappa_N(N)+\kappa_R(R)+\kappa_P(P))Q && (t>0)\\
\nabla n(t,a) &= \begin{cases} \eta_N(t,a)n(t,a) & (t>0, 0\le a\le \tau_N)\\ -\gamma_N(t,a)n(t,a) & (t>0, \tau_N\le a)\end{cases} && (2)\\
\nabla r(t,a) &= \begin{cases} \eta_R(t,a)r(t,a) & (t>0, 0\le a\le \tau_R)\\ -\gamma_R(t,a)r(t,a) & (t>0, \tau_R\le a\le \tau_{Rsum})\end{cases}\\
\nabla p(t,a) &= \begin{cases} \eta_P(t,a)p(t,a) & (t>0, 0\le a\le \tau_P)\\ -\gamma_P(t,a)p(t,a) & (t>0, \tau_P\le a\le \tau_{Psum})\end{cases}
\end{aligned}
$$

Where $\nabla = \frac{\partial}{\partial t}+\frac{\partial}{\partial a}$. The negative feedback functions are represented by Hill functions [64]:

$$
\kappa_N(N)=f_0\frac{\theta_1^{s_1}}{\theta_1^{s_1}+N^{s_1}},\ \beta(Q)=k_0\frac{\theta_2^{s_2}}{\theta_2^{s_2}+Q^{s_2}},\ \kappa_R(R)=\frac{\overline{\kappa}_r}{1+K_rP^{s_3}},\ \kappa_P(P)=\frac{\overline{\kappa}_p}{1+K_pP^{p_4}}. \qquad (3)
$$

Typical parameter values are given in Table 20.2.

The boundary conditions at $a=0$ are given by

$$
\begin{aligned}
s(t,0) &= \beta(Q(t))Q(t),\\
n(t,0) &= \kappa_N(N(t))Q(t),\\
r(t,0) &= \kappa_R(R(t))Q(t),\\
p(t,0) &= \kappa_P(P(t))Q(t),
\end{aligned}
\qquad (t\ge 0) \qquad (4)
$$

according to the negative feedback loops. Moreover, we have

$$
\lim_{a\to\infty} n(t,a)=0. \qquad (5)
$$

The initial conditions are

$$\begin{aligned} s(0,a) &= g_S(a), \quad (0 \le a \le \tau_S) \\ Q(0) &= Q_0 \\ n(0,a) &= g_N(a), \quad (0 \le a \le +\infty) \\ r(0,a) &= g_R(a), \quad (0 \le a \le \tau_{Rsum}) \\ p(0,a) &= g_P(a), \quad (0 \le a \le \tau_{Psum}) \end{aligned} \tag{6}$$

where $g_S(a), g_N(a), g_R(a)$ and $g_P(a)$ give the initial population distributions of proliferating-phase stem cells, and the precursors of neutrophils, erythrocytes, and platelets, respectively.

The equations (1)-(6) define the initial-boundary value problem for the age-structured model of hematopoietic regulation, and is the basis of the following simplified model and analysis.

3.2.2. Delay differential equation model

In hematological modeling, we are mainly interested at the dynamics of circulating blood cell populations $N(t), R(t)$ and $P(t)$. This can be modeled by delay differential equations obtained from the above age-structured model. We assume the apoptosis rates $\gamma_N, \gamma_R, \gamma_P$ are constants. Applying the method of characteristic line to model equation (2), and using the boundary conditions (4) and (5), we obtain the following equations when $t > \tau_{\max} = \max\{\tau_S, \tau_N, \tau_{Rsum}, \tau_{Psum}\}$:

$$\begin{aligned} \frac{dQ}{dt} &= 2e^{-\tau_S \hat{\gamma}_S (t-\tau_S)} \beta(Q_{\tau_S}) Q_{\tau_S} - (\beta(Q) + \kappa_N(N) + \kappa_R(R) + \kappa_P(P))Q, \\ \frac{dN}{dt} &= -\gamma_N N + e^{\tau_N \hat{\eta}_N (t-\tau_N)} \kappa_N(N_{\tau_N}) Q_{\tau_N}, \\ \frac{dR}{dt} &= -\gamma_R R + e^{\tau_R \hat{\eta}_R (t-\tau_R)} \kappa_R(R_{\tau_R}) Q_{\tau_R} - e^{-\gamma_R \tau_{RS}} e^{\tau_R \hat{\eta}_R (t-\tau_{Rsum})} \kappa_R(R_{\tau_{Rsum}}) Q_{\tau_{Rsum}}, \\ \frac{dP}{dt} &= -\gamma_P P + e^{\tau_P \hat{\eta}_P (t-\tau_P)} \kappa_P(P_{\tau_P}) Q_{\tau_P} - e^{-\gamma_P \tau_{PS}} e^{\tau_P \hat{\eta}_P (t-\tau_{Psum})} \kappa_P(P_{\tau_{Psum}}) Q_{\tau_{Psum}}, \end{aligned} \tag{7}$$

where

$$\hat{\gamma}_S = \frac{1}{\tau_S}\int_0^{\tau_S} \gamma_S(t+s)ds, \quad \hat{\eta}_k(t) = \frac{1}{\tau_k}\int_0^{\tau_k} \eta_k(t+s,s)ds, \quad (k = N, R, P). \tag{8}$$

Here, the subscripts on the dependent variables indicate delayed arguments, i.e., $Q_{\tau_S} = Q(t-\tau_S)$.

The delay differential equations (7) determine the dynamic behaviour for the circulating blood cell populations. Here we note that when $t < \tau_{\max}$ the equation (7) is not equivalent to the original age-structured model equation (2). In this case, the initial conditions (6) have to be involved into the dynamical equation. Refer to [44] for a detailed discussion of this point.

For hematologically normal individuals, we assumed the apoptosis rate γ_S and amplification rates $\eta_k, (k = N, R, P)$ are constants, and hence $\hat{\gamma}_S = \gamma_S, \hat{\eta}_k = \eta_k$, $(k = N, R, P)$. Thus, we obtain the following delay differential equations

$$\begin{aligned}
\frac{dQ}{dt} &= 2e^{-\tau_S\gamma_S}\beta(Q_{\tau_S})Q_{\tau_S} - (\beta(Q) + \kappa_N(N) + \kappa_R(R) + \kappa_P(P))Q, \\
\frac{dN}{dt} &= -\gamma_N N + e^{\tau_N\eta_N}\kappa_N(N_{\tau_N})Q_{\tau_N}, \\
\frac{dR}{dt} &= -\gamma_R R + e^{\tau_R\eta_R}(\kappa_R(R_{\tau_R})Q_{\tau_R} - e^{-\gamma_R\tau_{RS}}\kappa_R(R_{\tau_{Rsum}})Q_{\tau_{Rsum}}), \\
\frac{dP}{dt} &= -\gamma_P P + e^{\tau_P\eta_P}(\kappa_P(P_{\tau_P})Q_{\tau_P} - e^{-\gamma_P\tau_{PS}}\kappa_P(P_{\tau_{Psum}})Q_{\tau_{Psum}}).
\end{aligned} \tag{9}$$

The equations (9) were first presented in [64], and have been used to study different types of dynamical blood diseases [3, 10, 44, 64].

In order to study the effects of clinical treatments, such as chemotherapy and G-CSF administration, which are known to affect hematopoiesis in the bone marrow, we further divide the amplification/maturation compartment of each cell line into two sub-compartments, corresponding to amplification and maturation, respectively. Let

$$\tau_k = \tau_{kP} + \tau_{kM}, \quad (k = N, R, P) \tag{10}$$

where τ_{kP} are durations of the amplification stages, and τ_{kM} are durations for the maturation stages. The amplification rates $\eta_k, (k = N, R, P)$ are defined separately within the two stages:

(11)

$$\eta_k(t,a) = \begin{cases} \eta_{kP}(t) & 0 \le a \le \tau_{kP} \\ -\gamma_{kM}(t) & \tau_{kP} \le a \le \tau_k \end{cases} \qquad (k = N, R, P)$$

where η_{kP} are amplification rates in the amplification stage, and γ_{kM} are apoptosis rates in the maturation stage, and are assumed to be independent to the age a. Therewith, $\hat{\eta}_k$ defined by equation (8) can be rewritten as

$$\hat{\eta}_k = \frac{1}{\tau_k}\left[\int_0^{\tau_{kP}} \eta_{kP}(t+s)ds - \int_{\tau_{kP}}^{\tau_k} \gamma_{kM}(t+s)ds\right]. \tag{12}$$

For hematologically normal individuals whose rates η_{kP} and γ_{kM} are constants, we have

$$\eta_k = (\eta_{kP}\tau_{kP} - \gamma_{kM}\tau_{kM})/\tau_k, \quad (k = N, R, P). \tag{13}$$

Parameters for the neutrophil compartment can be referred to [66], and parameters for the erythrocyte compartment and platelet compartment are not known yet.

4. Cyclical neutropenia

4.1. Modeling of cyclical neutropenia

Although it is a rare disorder, cyclical neutropenia is probably the most extensively studied periodic hematological disorder due to its interesting dynamics and its clinical and laboratory manifestations. A number of mathematical models have been put forward in an attempt to understand this disorder, and these fall into two major categories according to the origin of cyclical neutropenia (see Figure 20.1 to place them in perspective). For other reviews, see [4, 41, 67, 68, 69].

The first group of models identifies the origin of cyclical neutropenia with a loss of stability in the peripheral control loop. Typical examples are [70, 71, 72, 73, 74,

75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85], all of which have postulated an alteration in the feedback on immature precursor production from the mature cell population number. However, the work of [86] cast doubt on this explanation, by showing that any alternations of parameters in the peripheral control system consistent with the extant laboratory and clinical data on cyclical neutropenia are unable to reproduce either the characteristics of clinical cyclical neutropenia or its laboratory counterpart in grey collies [43, 86].

The second group of models builds upon the existence of oscillations in many of the peripheral cellular elements (neutrophils, platelets, and erythroid precursors, see Figure 20.1) and postulates that the origin of cyclical neutropenia is in the common hematopoietic stem cell (HSC) population. Mackey has suggested that the oscillations originate in a loss of stability in the HSC [45]. This hypothesis allowed the quantitative calculation of the period of oscillation when the stability was lost due to an abnormally large cell apoptosis rate within the proliferating compartment. Some mathematical models coupled a stem cell compartment with the peripheral loop for granulocytes [4, 6, 87], whereas others present a more complex model showing the stem cells coupled to all major cell lines [3, 44, 88]. For recent reviews, see [65] and [67].

Here, we introduce several models, from simple to sophisticated, that have given significant insights into the origin and dynamical features of cyclical neutropenia. Then we show how these models have been used to understand and improve the effects of CN treatments.

4.1.1. Origin of cyclical neutrophenia

Mackey presented the following delay differential equation [45]

$$\frac{dQ}{dt} = -(\beta(Q) + \kappa)Q + 2e^{-\gamma_S \tau_S}\beta(Q_{\tau_S})Q_{\tau_S} \tag{14}$$

for the resting phase HSC populations, which is obtained from equation (9) by omitting the cell lines of neutrophil, erythrocyte, and platelet, and writing κ the total HSC differentiation rate.

The equation (14) is sufficiently simple that it is possible to perform a complete bifurcation analysis [45]. There are two possible steady states. One corresponds to the state of no cells ($Q_0 = 0$) and is stable if it is the only steady state. The other one is a positive steady state Q_* and exists for small HSC apoptosis rate γ_S. The

stability of the positive steady state depends on the value of γ_S. When $\gamma_S = 0$, this steady state cannot be destabilized to produce oscillatory dynamics of cyclical neutropenia. For $\gamma_S > 0$, increases in γ_S lead to a decrease in the hematopoietic stem cell numbers, and destabilize the steady state when a critical value of $\gamma_S = \gamma_{crit,1}$ is reached and a supercritical Hopf bifurcation occurs. When γ_S is further increased, a reverse bifurcation occurs at a critical value $\gamma_S = \gamma_{crit,2}$, where the positive steady state becomes stable, and approaches the zero steady state as γ_S increases. For all values of γ_S satisfying $\gamma_{crit,1} < \gamma_S < \gamma_{crit,2}$, there is a periodic solution of equation (14) whose period is in good agreement with those seen in cyclical neutropenia [45]. These results suggest that cyclical neutropenia might be related to defects, possibly genetic, within the hematopoietic stem cell population, that lead to an abnormal apoptotic loss of cells from the proliferative phase in cell cycle.

Bernard et al. [87] presented a two variables delay differential equation model that couples the above HSC population model with the neutrophil compartment dynamics:

$$\begin{aligned} \frac{dQ}{dt} &= 2e^{-\tau_S \gamma_S} \beta(Q_{\tau_S}) Q_{\tau_S} - (\beta(Q) + \kappa_N(N)) Q, \\ \frac{dN}{dt} &= -\gamma_N N + e^{\tau_N \eta_N} \kappa_N(N_{\tau_N}) Q_{\tau_N}, \end{aligned} \tag{15}$$

where

$$\kappa_N(N) = f_0 \frac{\theta_1^{s_1}}{\theta_1^{s_1} + N^{s_1}}, \qquad \beta(Q) = k_0 \frac{\theta_2^{s_2}}{\theta_2^{s_2} + Q^{s_2}}.$$

This model is derived from equation (9) by simply neglecting the compartments for the erythrocytes and platelets. First, we note that this model has a unique positive steady state for Q and N if

$$f_0 < k_0(2e^{-\gamma_S \tau_S} - 1). \tag{16}$$

This condition states that the rate of HSC differentiation must be smaller than the increase rate due to cell division [87]. Using a combination of mathematical

analysis and computations, [87] showed that the origin of cyclical neutropenia is probably due to an increased apoptosis rate in the stem cell compartment (γ_S) and in the neutrophil precursors (which leads to a decrease in η_N), leading to a destabilization of the hematopoietic stem cell compartment through a supercritical Hopf bifurcation. Consequently, oscillations in the HSC population are generated. This result was in accordance with previous modeling studies [6] and agrees with experimental data on grey collies. Moreover, numerical analysis showed that the equations (15) have bistability, i.e., coexistence of a stable steady state and a stable oscillatory solution when γ_S and η_N take values from a certain range. This bistability is essential for understanding the diverse effect of G-CSF treatment on cyclical neutropenia as we can see in the next section.

A more sophisticated model developed by [3, 64] includes not only the neutrophils and HSC, but also the platelets and red blood cells (Figure 20.1). This model combines a number of compartmental models: the stem cell and neutrophil dynamics [87], and the erythrocyte and platelet compartment models [48, 89]. The circulating cells couple to each other via their common origin in the stem cell compartment. This model consists of a set of four coupled delay differential equations as given by equation (9).

In [3], the authors used an approach of simulated annealing to fit clinical and laboratory data (from both humans and dogs) to estimate the model parameters that can reproduce the CN characteristics. The results supported the hypothesis on the origin of CN proposed in [87] that realistic CN oscillations in neutrophils and platelets are originated from an increased apoptosis rate in the neutrophil precursors. Furthermore, in order to mimic the data, it was also necessary to decrease the differentiation rate of HSC into the neutrophil line, and changes of the apoptosis rate of stem cells in the proliferative phase.

In [44], the authors further investigate the model numerically for possible solutions of the model equations 9 with respect to changes in parameters as well as initial conditions. The results confirmed the findings in [3] that decreasing the proliferation rate of neutrophil precursors or increasing the stem cell death rate are two possible mechanisms to induce CN, and the periods of the resulting oscillations are independent of the changed parameters. In particular, these results suggested that either decreasing the neutrophil precursor proliferation rate to 3-15% less than the normal value or increasing the HSC apoptosis rate to 40-100% larger

than the normal value it is possible to induce oscillations reminiscent of those in CN patients. Furthermore, simulations with varying initial conditions showed that the hematopoietic system possesses multistability over a wide range of parameter values, including typical values representing a healthy state. In this parameter region of multistability, the hematopoietic system can display coexistence of a stable steady state along with an oscillatory state. This result is crucial for understanding the effects of CN patient treatment. Because of the multistability, CN originated from changes in system parameters may not recover to the healthy state even if the changed parameters are taken back to their normal values by therapy, for example through G-CSF treatment.

4.1.2. Modeling of chemotherapy induced cyclical neutropenia

Before introducing models for studying different G-CSF treatment strategies for CN in the next section, we show how a simple model can be used to explore neutrophil dynamics in response to chemotherapy.

Chemotherapy is frequently accompanied by hematopoietic side effects due to the myelosuppressive character of the drugs used. These side effects commonly include neutropenia and, to a lesser extent, thrombocytopenia and/or anemia. In [66] and [90], the authors presented a two compartment mathematical model of the combined dynamics of the HSC and the differentiated neutrophil progeny, modified from the model in [87] for the stem cell and neutrophil dynamics.

The model equations in [66] and [90] contain the HSC compartment and the neutrophil compartment. The neutrophil compartment is further divided into three sub-compartments corresponding to proliferating, maturating, and circulating neutrophils, respectively. The erythrocytes and platelets are not included but assume a total rate κ_δ (days) of differentiating HSCs into these two cell lines.

An illustration of this model is showed in Figure 20.2. The equations describing the cell dynamics can be obtained from equations (7) and (12), and are given below:

$$\begin{aligned} \frac{dQ}{dt} &= -(\beta(Q)+\kappa_N(N)+\kappa_\delta)Q + A_Q(t)\beta(Q_{\tau_S})Q_{\tau_S}, \\ \frac{dN}{dt} &= -\gamma_N N + A_N(t)\kappa_N(N_{\tau_N})Q_{\tau_N} \end{aligned} \tag{17}$$

and

$$
\begin{aligned}
\kappa_N(N) &= f_0 \frac{\theta_1^{s_1}}{\theta_1^{s_1} + N^{s_1}}, \\
\beta(Q) &= k_0 \frac{\theta_2^{s_2}}{\theta_2^{s_2} + Q^{s_2}}, \\
A_Q(t) &= 2\exp\left[-\int_0^{\tau_S} \gamma_S(t - \tau_S + s)ds\right], \\
A_N(t) &= \exp\left[\int_0^{\tau_{NP}} \eta_{NP}(t - \tau_N + s)ds - \int_{\tau_{NP}}^{\tau_N} \gamma_{NM}(t - \tau_N + s)ds\right], \\
\tau_N &= \tau_{NP} + \tau_{NM}.
\end{aligned}
$$

Chemotherapy increases apoptosis in both proliferative HSCs and proliferative neutrophil precursors leading to an increase in γ_S and a decrease in η_{NP} [91]. Chemotherapy is often administered with a fixed period T (days) so that the rates $\gamma_S(t)$ and $\eta_{NP}(t)$ are periodic functions and dependent on the protocol of chemotherapy administration. There are many different chemotherapeutic drugs currently in use, and therefore different methods for modeling the pharmacokinetics. Here we present the simple model as in [90] in which the effect of chemotherapy is maintained for one day, and assume square wave temporal functions for the apoptosis rate γ_S and the neutrophil precursor proliferative rate η_{NP} of the following form:

$$
\gamma_S(t) = \begin{cases} \gamma_S^{\max} & \text{if } 0 \le t - kT < 1, \\ \gamma_S & \text{otherwise}. \end{cases} \tag{18}
$$

and

$$
\eta_{NP} = \begin{cases} \eta_{NP}^{\min} & \text{if } T_1 \le t - kT < 1, \\ \eta_{NP} & \text{otherwise}. \end{cases} \tag{19}
$$

Here k is an integer, and $t = 0$ for the starting time of the first chemotherapy period. An expanded model with more realistic chemotherapy dynamics is presented in [66].

Using a combination of simulation and mathematical analysis, Zhuge et al. [90] studied the neutrophil response to chemotherapy as a function of the period T.

Simulations showed that the neutrophil amplitude varies with the period T of chemotherapy, with a peak at $T = 21$ days, and the neutrophil nadir has a minimum at the same period (Figure 20.3). Figure 20.3b shows a computed time series for the neutrophils at two different periods of chemotherapy administration. The model predicts substantial differences in the dynamic response of the system as severe neutropenia was produced in the model at $T = 21$ days but not at $T = 18$ days.

According to [90], a possible reason for the occurrence of a significant peak in the amplitude and minimum in the nadir at a specific T is the resonance between the periodic perturbation to the system and the intrinsic characteristic frequency in the neutrophil production dynamics. This hypothesis is confirmed by comparing the amplitude response with the frequency response function obtained analytically from the linearizing the model equation (17) around the steady state (shown by a solid line in Figure 20.3a). The frequency response function has a maximum at $T = 21.8$ days in agreement with the simulation results. Furthermore, an analysis of the linear response function predicts that the resonant period for the model is given by twice the average neutrophil lifetime (defined as the average time τ_N spent in marrow proliferation and maturation following commitment from the HSC plus the average lifetime γ_N^{-1} in the circulation). If this simple relationship is found to hold clinically then it offers a way to tailor chemotherapy for individuals. Namely using the techniques employed by [51] to determine τ_N and γ_N for a specific patient and then compute the resonant period T to be avoided in any delivery of myelosuppressive agents.

We note that in Figure 20.3a, there is a peak in the amplitude response and minimum in the nadir at $T = 4$ days that cannot be explained by resonance. The mechanism for the occurrence of this peak remains unknown.

4.1.3. Modeling of G-CSF administration

Cyclical neutropenia in humans is often treated using G-CSF [92], which is known to interfere with apoptosis [93, 94, 95, 96], and it has the overall effect of decreasing the period of severe neutropenia by increasing the nadir and the amplitude of the oscillations as well as decreasing their period [4]. However, G-CSF is expensive (about $40,000 per year for a 70 kg adult treated daily) and may cause undesirable side effects [97, 98]. In this section, we show how

mathematical modeling can illuminate the effects of different G-CSF treatment schemes. For another review, see [65].

In [87], five parameters in the model equation (15) are modified to mimic the effects of G-CSF in CN: decreased apoptosis in both the HSC (decrease γ_S) and in the neutrophil precursor compartment (decrease η_N), decrease in the duration of both the proliferative and differentiating phases (τ_N and τ_S) as well as increasing the parameter θ_1 in the feedback function. Interesting dynamical features of the model were found. The bifurcation analysis agreed with the clinical aspects of G-CSF administration in that G-CSF can result in an increase of amplitude and a decrease in the period of neutrophil oscillations [6, 92]. In clinical observations, some cases have been reported that G-CSF treatment can abolish significant oscillations [4, 5, 92]. This is also seen in the model of [87], in which a stable steady state (corresponding to annihilation of oscillations) coexists with a stable large amplitude oscillation. This bi-stability is interesting since it suggests that it is possible to stabilize the neutrophil count by properly designing the treatment administration scheme and could potentially reduce the amount of G-CSF required in treatment.

In [2], the model of [87] was explored to consider different G-CSF treatment protocols. The authors showed that, depending on the starting time of G-CSF treatment, the neutrophil count could either be stabilized or show large amplitude oscillations. This is also seen in the comprehensive model given by equation 9 that includes erythrocyte and platelet dynamics [44, 88]. Simulations showed that other G-CSF treatment schemes (such as administering G-CSF every other day) could be effective while using less G-CSF, hence reducing the cost of treatment and side effects for patients.

In [88], the authors studied the comprehensive model as in [3] coupled with a two-compartment model for G-CSF pharmacokinetics. They fitted their model simulation with clinical data for neutrophils and platelets and explored the effects of different treatment schedules. The results showed that different initial conditions or temporary interventions may lead to dramatically different long-term behaviors.

G-CSF is frequently used to deal with neutropenia induced by chemotherapy [65, 97]. However, the clinical administration schedule of G-CSF after chemotherapy is typically determined by trial and error and it is not clear if there is an optimal

way of giving G-CSF [99, 100]. In [65], the authors present a delay differential equation model for the regulation of neutrophil production that accounts for the effect of G-CSF. Using a combination of analysis and numerical simulations, the authors applied this model to study the effects of delivering G-CSF treatment following chemotherapy for two recombinant forms of G-CSF (filgrastim and pegfilgrastim). Simulations suggested that varying the starting day or the duration of G-CSF treatment can lead to different qualitative responses in the neutrophil count.

In [90], the authors presented a simple model based on equation (17) that coupled changes in γ_S, γ_{NM}, η_{NP} and τ_{NM} due to one day G-CSF administration. They found that the neutrophil dynamics response to G-CSF is highly variable, depending on the time of G-CSF delivery after chemotherapy at each cycle. In particular, there are specific times in the chemotherapy cycle when G-CSF can have positive effects in terms of ameliorating or even eliminating severe neutropenia. However, there are also broad ranges of administration times that will lead to a worsening by G-CSF of the neutropenia induced by the chemotherapy. These results are in general agreement with results presented in [65], but await confirmation until more realistic G-CSF kinetic are included in the modeling (for example, refer to [66]).

In summary, these studies have showed complicated dynamical properties of hematopoiesis after G-CSF treatment. Understanding the effects of G-CSF is difficult since G-CSF is known to affect the neutrophil maturation time in the bone marrow, whose detailed dependence is unknown, and further clinical investigations are needed to characterize this important facet of neutrophil regulation.

5. Discussion

Here we have given a brief survey of how the study (using mathematical models) of dynamic hematological diseases in which there is a period cytopenia has given insight into not only the physiological origin of these diseases but also afforded investigators an opportunity to see how to better treat these diseases. As an unexpected by-product of these investigations which have extended over some four decades, mathematical biologists in collaboration with hematologists and oncologists are now starting to address the important question of “How can the severe side effects of myelosuppressive therapy on the hematopoietic system be either mitigated or avoided altogether?” This later question is, in our minds, one of the more important by-products of the modeling venture and offers a potentially

exciting opportunity to use insight from mathematics to better the delivery of medical care for those needing it.

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Table 20.1: Variables used in the model equations and typical value for hematologically normal individuals (44).

Variable	Definition	Value	Unit
Stem cell compartment			
$Q(t)$	Population of resting-phase stem cells	1.12	10^6 cells/kg
$s(t,a)$	Population of proliferating-phase stem cells	–	cells/kg
β	Rate of re-entering the proliferative phase	0.0433	day^{-1}
τ_S	Duration of mitosis	2.83	days
γ_S	Apoptosis rate of proliferating stem cells	0.1013	day^{-1}
Neutrophil compartment			
$n(t,a)$	Population of neutrophils	–	cells/kg
$N(t)$	Population of circulating neutrophils	5.59	10^8 cells/kg
κ_N	Differentiation rate from stem cells to neutrophils	0.0077369	day^{-1}
η_N	Amplification rate of neutrophil precursor cells	2.2887	day^{-1}
τ_N	Duration of neutrophil precursor amplification/maturation	12.6	days
γ_N	Apoptosis rate of circulating neutrophils	2.4	day^{-1}
Erythrocyte compartment			
$r(t,a)$	Population of erythrocytes	–	cells/kg
$R(t)$	Population of circulating erythrocytes	3.5	10^{11} cells/kg
κ_R	Differentiation rate from stem cells to erythrocytes	0.005271	day^{-1}
η_R	Amplification rate of erythrocyte precursor cells	2.2	day^{-1}
τ_R	Duration of erythrocyte precursor amplification/maturation	6	days
γ_R	Apoptosis rate of circulating erythrocytes	0.001	day^{-1}
τ_{RS}	Life time of circulating erythrocytes	120	days
τ_{Rsum}	$\tau_R + \tau_{RS}$	126	days
Platelet compartment			
$P(t,a)$	Population of platelets	–	cells/kg
$P(t)$	Population of circulating platelets	1.3924	10^{10} cells/kg
κ_P	Differentiation rate from stem cells to platelets	0.0087074	day^{-1}
η_P	Amplification rate of platelet precursor cells	1.79	day^{-1}
τ_P	Duration of platelet precursor amplification/maturation	7	days
γ_P	Apoptosis rate of circulating platelets	0.15	day^{-1}
τ_{PS}	Life time of circulating platelets	9.5	days
τ_{Psum}	$\tau_P + \tau_{PS}$	16.5	days

Table 20.2: Parameters for the Hill functions equation 3 (44).

Parameter Name	Value	Unit
Function $\beta(Q)$		
k_0	8.0	day^{-1}
θ_2	0.0826	10^6 cells/kg
s_2	2	(none)
Function $\kappa_N(N)$		
f_0	0.154744	day^{-1}
θ_1	0.2942	10^8 cells/kg
s_1	1	(none)
Function $\kappa_R(R)$		
$\overline{\kappa}_r$	1.23744	day^{-1}
K_r	0.0382	$(10^{11}\ \text{cells/ kg})^{-S_3}$
s_3	6.96	day^{-1}
Function $\kappa_P(P)$		
$\overline{\kappa}_p$	0.2802	day^{-1}
K_p	20.343	$(10^{10}\ \text{cells/ kg})^{-S_4}$
s_4	1.29	day^{-1}

Figure legends

Figure 20.1: A cartoon representation of the age-structured model of hematopoiesis. See text for details and notations. Adapted from (44).

Figure 20.2: A cartoon representation of the model of neutrophil production investigated here. The model dynamics include those of the hematopoietic stem cells (HSC) as well as differentiated cells committed to the neutrophil line. Quiescent (resting phase) HSCs can either remain in Q,exit into the proliferative HSC phase at a rate β, or differentiate into the committed neutrophil compartment at a rate κ_N, or into the combined megakaryocyte/erhthrocyte lines at a rate κ_δ. Cells in the HSC proliferative phase are assumed to undergo apoptosis at a rate γ_S and the duration of the proliferative phase is taken to be τ_S. Cells in the neutrophil pathway are amplified by successive divisions for a time τ_{NP}, and then enter a purely maturation (no proliferation) compartment for a period of time τ_{NM} before they enter the circulation. The circulating neutrophils (N) die at a random rate γ_N so their average lifespan is γ_N^{-1}. The differentiation rate of HSC to neutrophils is controlled by the circulating neutrophil population through the differentiation rate κ_N, while the HSC proliferation is controlled by the resting HSC population with proliferation rate β. Adapted from (90).

Figure 20.3: Numerical simulation results for the neutrophil compartment model with chemotherapy alone. (a) The amplitude (left hand ordinate) in neutrophil response (blue squares connected with a dashed blue line) as well as the nadir (right hand ordinate and green circles connected with a dashed green line) as a function of the period T of chemotherapy. The horizontal green dash-dot line indicates the level for severe neutropenia (0.63×10^8 cells/kg). Note that the major peaks in the amplitude coincide with the minima in the nadir. The solid blue line is

the computed linear frequency response function (refer (90)) (rescaled to compare with the amplitude). (b) Simulated neutrophil levels from equation 17 in response to chemotherapy with a period of either $T = 18$ days or 21 days. Neutrophil levels are in units of 108 cells/kg, the dashed-dot horizontal line again indicates the level for severe neutropenia, and the arrow shows the first neutrophil nadir. Adapted from (90).