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Dynamic hematological disease: a review

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Abstract We review the basic characteristics of four periodic hematological disorders (periodic auto-immune hemolytic anemia, cyclical thrombocytopenia, cyclical neutropenia and periodic chronic myelogenous leukemia) and examine the role that mathematical modeling and numerical simulations have played in our understanding of the origin of these diseases and in the regulation of hematopoiesis.

Keywords Dynamical hematological diseases · Mathematical modeling

Mathematics Subject Classification (2000) 92B05 · 37N25

1 Introduction

Based on the analysis of simple mathematical models for Cheyne–Stokes respiration and periodic hematological diseases, Mackey and Glass [70] speculated that there were dynamical diseases ". . . characterized by the operation of a basically normal physiological control system in a region of physiological parameters that produces pathological behavior." Their work suggested ". . . the following approaches: (i) demonstrate the onset of abnormal dynamics in animal models by gradual tuning of control parameters;" (ii) gather sufficiently detailed experimental and clinical data to determine

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whether sequences of bifurcations ... actually occur in physiological systems; and (iii) attempt to devise novel therapies for disease by manipulating control parameters back into the normal range." This programme has been especially successful within a hematological context over the past three decades.

Periodic hematological diseases are particularly interesting from a modeling point of view, due to their dynamical behaviors. Mathematical models (and their numerical simulations) 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. In this paper, we review some of the mathematical models that have been developed over the years and recount how they have been of use. In Sect. 2, we first review the normal aspects of the regulation and production of blood cells as well as the basic characteristics of some periodic hematological disorders. Then, in Sect. 3, we present the different mathematical tools that are typically useful for modeling in hematology. Section 4 reviews the approaches used for modeling four periodic hematological diseases, namely periodic auto-immune hemolytic anemia (AIHA), cyclical thrombocytopenia (CT), cyclical neutropenia (CN) and periodic chromic myelogenous leukemia (PCML). For each of these diseases, we review the mathematical models as well as the knowledge of the disease gained from their mathematical analysis. The paper concludes with a discussion in Sect. 5.

2 Normo- and pathophysiological hematopoiesis

In this section, we briefly review normal hematopoiesis and provide a short description of some hematological diseases that have helped to elucidate the regulatoiry mechanisms of hematopoiesis.

2.1 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 (assayted by the colony-forming units (CFU-Mix)), 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)) (see Fig. 1). Although all blood cells originate from this common source, the mechanisms that regulate their production are not completely clear. Nevertheless, the production of erythrocytes (erythropoiesis) and platelets (thrombopoiesis) appears to be regulated by specific cytokines via a negative feedback mechanisms whereas granulopoiesis is perhaps more complicated and thus less clearly understood. We briefly present these processes below.

The growth factor (cytokine) mainly involved in the regulation of erythrocyte production is erythropoietin (EPO). EPO production adjusts to the demand of 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

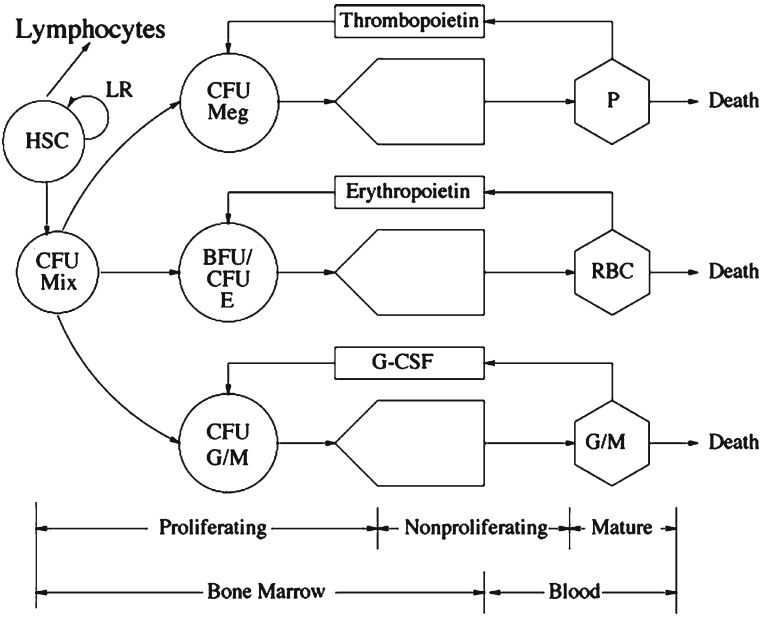

Fig. 1 Schema of the hematopoietic system, giving a schematic representation of the architecture and control of platelet (*P*), red blood cell (*RBC*), and monocyte (*M*) and granulocyte (*G*) (including neutrophil, basophil and eosinophil) production. Presumptive control loops mediated by thrombopoietin (*TPO*), erythropoietin (*EPO*), and the granulocyte colony stimulating factor (*G-CSF*) are indicated, as well as a local regulatory (*LR*) loop within the pluripotent hematopoietic stem cell (*HSC*) population. CFU (*BFU*) refers to the various colony (burst) forming units (Meg = megakaryocyte, Mix = mixed, E = erythroid, and G/M = granulocyte/monocyte) which are the in vitro analogs of the in vivo committed stem cells (CSC). Taken from Haurie et al. [47] with permission

mediated by interfering with apoptosis in these cells [45,58]. These cells will mature and eventually (after a maturation delay) produce new erythrocytes. As a result, the erythrocyte population will be increased and so will be the oxygen carrying capacity of the blood. Hence, EPO mediates a negative feedback such that a decrease (increase) in the number of erythrocytes leads to an increase (decrease) in erythrocyte production.

The regulation of platelet production (thrombopoiesis) 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 (colony-forming units-megakaryocyte (CFU-Meg)). This eventually leads to an increase in platelet production, again partially mediated by a decrease in megakaryocyte apoptosis [89].

There are three types of leucocytes, namely the lymphocytes, the granulocytes and the monocytes. We will focus our attention on granulopoiesis (production of granulocytes) and more specifically on neutrophils, which constitute the most abundant type of granulocyte, since cyclical neutropenia is the periodic hematological disease on which the greatest amount of published clinical data exists. The mechanisms regulating granulopoiesis involve the cytokine granulocyte-colony stimulating factor (G-CSF), which is the main regulator of neutrophil production [53]. It stimulates the

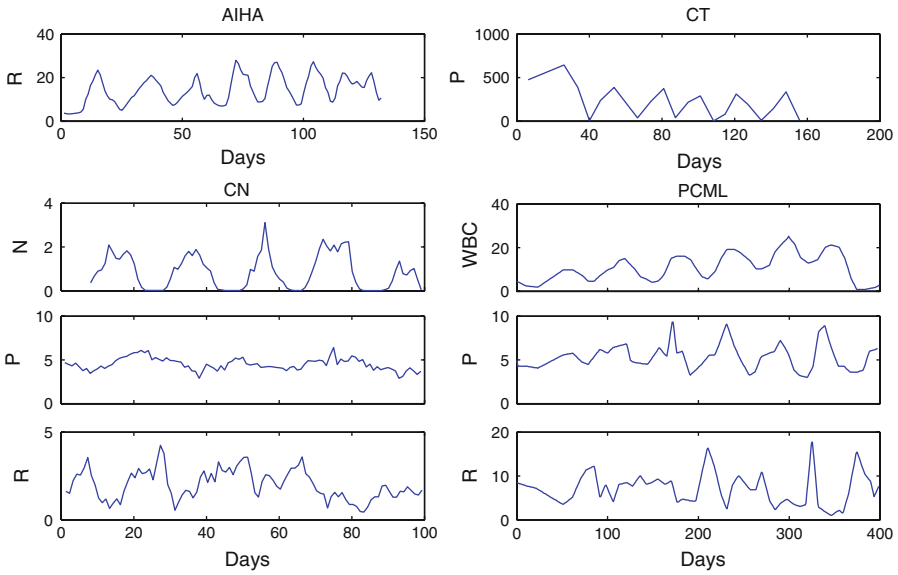

Fig. 2 Examples of data for four hematological diseases. AIHA: Reticulocyte numbers ($\times 10^4$ cells/μL) in an AIHA subject. Adapted from [80] with permission. *CT* cyclical fluctuations in platelet counts ($\times 10^3$cells/μL). From [112]. *CN* circulating neutrophils ($\times 10^3$cells/μL), platelets ($\times 10^5$cells/μL) and reticulocytes ($\times 10^4$cells/μL) in a cyclical neutropenic patient. From [42] with permission. *PCML* White blood cell (*top*) ($\times 10^4$cells/μL), platelet (*middle*) ($\times 10^5$cells/μL) and reticulocyte (*bottom*) ($\times 10^4$cells/μL) counts in a PCML patient. From [20] with permission

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 postmitotic pool and increase maturation [63,84] while interfering with apoptosis [10]. Several studies have shown an inverse relationship between the serum levels of G-CSF and the number of circulating neutrophils [55,74,103,108].

2.2 Dynamical diseases in hematology

Periodic hematological disorders are classical examples of dynamical diseases [39,70]. Because of their dynamical properties, they offer an almost 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 [47]. In this section, we briefly review the clinical aspects of four periodic hematological disorders (see Fig. 2 for examples of experimental data for each disease). The first two, periodic auto-immune hemolytic anemia (AIHA) and cyclical thrombocytopenia (CT), involve oscillations in only one cell lineage. In the other two diseases, cyclical neutropenia (CN) and periodic chronic myelogenous leukemia (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.

2.2.1 Periodic auto-immune hemolytic anemia

Auto-immune hemolytic anemia (AIHA) results from an abnormality of the immune system that produces autoantibodies, 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 [87] characterized by oscillatory erythrocyte numbers about a depressed level. The origin of the disease is unclear. Periodic AIHA, with a period of 16–17 days in hemoglobin and reticulocyte counts, has been induced in rabbits by using red blood cell auto-antibodies [80].

2.2.2 Cyclical thrombocytopenia

Platelets are blood cells whose function is to take part in the clotting process, and thrombocytopenia denotes a reduced platelet (thrombocyte) count. In cyclical thrombocytopenia (CT), platelet counts oscillate generally from very low values (1×10^9 cells/L) to normal ($150-450 \times 10^9$ platelets/L blood) or above normal levels (2000×10^9 cells/L) [102]. These oscillations have been observed with periods varying between 20 and 40 days [21]. 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 [102]. 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 [18]. This is consistent with normal to high levels of bone marrow megakaryocytes and with an increased destruction rate of circulating platelets [102]. Autoimmune CT has also been postulated to be a rare form of idiopathic (immune) thrombocytopenic purpura (ITP) [18].

The amegakaryocytic form of CT is characterized by oscillations in bone marrow megakaryocytes preceding the platelet oscillations [9,13,27,33]. In this second type of CT, platelet oscillations are thought to be due to a cyclical failure in platelet production [13,21,27,33,52,60]. The platelet lifespan is usually normal [60] and antibodies against platelets are not detected [52]. Although it has been suggested that the failure of platelet production could arise at the stem cell level [56], it is generally thought that the cycling originates at the megakaryocyte level [27,52]. For a more detailed review of CT, see [92,102].

It has been hypothesized that autoimmune and amegakaryocytic cyclical thrombocytopenia have a different dynamic origin [92]. This is supported by [102], 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). 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.

2.2.3 Cyclical neutropenia

In a normal individual, the number of circulating neutrophils is relatively constant with an average of about 2.0×10^9 cells/L. Neutropenia is a term that designates a low number of neutrophils, thus indicating that the individual is less effective at fighting infections. Cyclical neutropenia is characterized by oscillations in the number of neutrophils from normal to very low levels (less than 0.5×10^9 cells/L). The period of these oscillations is usually around 3 weeks for humans, although periods up to 45 days have been observed [46]. The period in which the absolute neutrophil count (ANC) is very low (also called severe neutropenia) 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 nadir. This has the overall effect of decreasing the period of severe neutropenia. We will see in Sect. 4.3.2 that mathematical modeling has been used to design cheaper and more effective G-CSF treatment strategies.

Our understanding of CN has been greatly aided by the existence of a similar disease in grey collies [49]. 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 for 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 [47], which is the reason CN is sometimes referred to as periodic hematopoiesis [83]. This observation suggests that the source of the oscillations may lie in the stem cell compartment. Although it is a rare disorder, cyclical neutropenia 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 our understanding of the basic mechanisms of this disease, as we review in Sect. 4.3.

2.2.4 Periodic chronic myelogenous 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 Bcr–Abl fusion protein [79]. This protein is thought to be responsible for the dysfunctional regulation of myelocyte growth and other features of CML [73] (For more details about CML, see [41]).

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 [38]. 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, oscillation of platelets and reticulocytes may occur with the same period as the leucocytes, around normal or elevated numbers [38,51]. 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 models of hematopoiesis

Mathematical models have been used for modeling biological processes for decades. With the advances in 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: differential equations (partial, ordinary or delay), stochastic processes, Boolean networks, Bayesian theory, multivariate statistics, decision trees, etc. For a review, see [90] and [105]. 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 (e.g. at the molecular or the cellular levels), or on a larger scale (model the whole system). Mathematical models of in vivo hematopoietic regulatory systems using a stochastic formulation have not been extensively developed, primarily because of the lack of corresponding data for stem cells and their progeny. Since they are widely used, we focus in this paper on models that use differential equations: ordinary differential equations (ODE), partial differential equations (PDE), or delay differential equations (DDE).

In this section, we first discuss the different types of delay differential equations and show how some DDE systems could be reduced to an ODE system using the linear chain trick. Second, we present a typical setting for a model, based on biological aspects of hematopoiesis and show that this could be modeled by an age-structured model (PDE). We then show that this PDE model can be reduced to a DDE model. Finally, we briefly comment other types of models in Sect. 3.4.

3.1 DDE models

Delay-differential equations (DDEs) are a large and important class of dynamical systems. They often arise in biological systems where time lags naturally occur [65]. 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. The general form of a DDE for $x(t) \in R^n$ is

$$\frac{dx}{dt} = f(t, x(t), x_t), \tag{1}$$

where x_t is the delayed variable and f is a functional operator in $R \times R^n \times C^1$. There are different kinds of delay-differential equations: with discrete fixed delays, with distributed delays and with state-dependent delays. In this section, we briefly discuss these different types of DDEs and give some examples of how they have arisen in modeling hematological problems.

3.1.1 DDE with constant delays

Delay differential equations with constant delays take the form

$$\frac{dx}{dt} = f(x(t), x(t-\tau_1), x(t-\tau_2), \ldots, x(t-\tau_n)), \tag{2}$$

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

$$\frac{dx}{dt} = f(x(t), x(t-\tau)). \tag{3}$$

To obtain a solution of Eq. 3 for $t > 0$, one needs to specify a history function on $[-\tau, 0]$. Indeed, recall that for an ordinary differential equation (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 on specify an "infinite" number of values, DDEs are often viewed as infinite-dimensional systems.

Constant delay differential equations are often used in modeling in hematology [14,17,47,69]. For example, let $X(t)$ represent the circulating cell population of a certain type of blood cell, assume that γ 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

$$\frac{dX}{dt} = -\gamma X + F(X(t-\tau)), \tag{4}$$

where τ 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.

3.1.2 DDE with distributed delays

Delays arise in biological systems because of properties inherent to the different processes (time lag due to maturation, transmission of an impulse, etc.). Although constant delays may be an excellent approximation of the time lag involved, one might want to account for the distribution of time delay. Indeed, in a real system, it is much more likely that events related to the delay (maturation time for example) are distributed with a density that is not a delta function. A distribution of delays is then be more

appropriate and the DDE becomes an integro-differential equation of the form

$$\frac{dx}{dt} = f\left(x(t), \int_{-\infty}^{t} x(\tau)G(t-\tau)\,d\tau\right). \tag{5}$$

The density $G(u)$ of the distribution function is referred to as the memory function or the kernel and is normalized, 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 [65]. Examples of such models in hematology are found in [19], [46] and [50]. Also, we will see in Sect. 3.2 that for some densities $G(u)$, Eq. 5 can be equivalently viewed as a system of ordinary differential equations.

3.1.3 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 [84]. An example of a model with a state-dependent delay can be found in [71], 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.

3.2 ODE models

Delay differential equations naturally arise in modeling biological systems. However, since DDEs are infinite-dimensional systems, they are difficult to analyze analytically and handle numerically. For some forms of delays, the so-called linear chain trick [65] enables the model to be written as an equivalent finite-dimensional system of ordinary differential equations. Next, we present a simple example of this method which is a specific example of the more general considerations of Fargue [34,35].

Consider the following DDE system with a distributed delay:

$$\frac{dx_1}{dt} = f\left(x_1(t), \int_{-\infty}^{t} x_1(\tau)G(t-\tau)\,d\tau\right), \tag{6}$$

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

$$G(u) = G_a^p(u) = \frac{a^{p+1}u^p}{p!}e^{-au}, \tag{7}$$

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:

1. $\lim_{u\to\infty} G_a^p(u) = 0$,
2. $G_a^p(0) = 0$ for $p \neq 0$,
3. $G_a^0(0) = a$.

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

$$x_{j+1} = \int_{-\infty}^{t} x_1(\tau) G_a^{j-1}(t-\tau)\, d\tau \quad j = 1, 2, \ldots, p+1, \tag{8}$$

and set

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

Then, using the properties of G one can show that these new variables satisfy a sequence of linear ODEs (see the Appendix for a detailed derivation). Solving the following system is thus equivalent to solving the DDE problem 6, given that the new variables are given appropriate initial values:

$$\begin{aligned} \frac{dx_1}{dt} &= f(x_1, x_{p+2}) \\ \frac{dx_{j+1}}{dt} &= a(x_j - x_{j+1}) \quad j = 1, 2, \ldots, p+1, \\ \frac{dx_{p+2}}{dt} &= a(x_{p+1} - x_{p+2}). \end{aligned} \tag{9}$$

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. However, this method cannot be used for all sort of delays (for more details about the method and some examples, see [65]). Within a hematological context Hearn et al. [50] were unable to use this technique in their model of neutrophil production because the estimated value of p in the experimentally determined distribution of delays was not an integer. Other models [61,62,94–97] have used constructs somewhat analogous to the system [50].

Introducing a delay in a system could be thought of as a way of including age-structure in the model. For instance, one could think setting up a detailed model in which the population dynamics is described by several maturation stages. If enough detail is known about the time spent in each stage, one could then associate a differential equation (ordinary or delayed) with each stage. However, detailed data such as these are often (usually) not available. Alternatively, one could lump together all the stages and reduce the model to only one DDE where the delay is the total maturation time. Another option would be to use partial differential equations, as we will discuss in the next section.

3.3 Age-structured models

We now present a typical PDE model used in several applications. Based on Fig. 1, one can see that the production of any of the cell types takes many steps. 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. One could model this process by associating a partial differential equation for the cell density function with each stage, which describes the population in the compartment as a function of the variables age a and time t [91]. The model also contains feedback control elements (rate of apoptosis, rate of production, etc.) that regulate the release of cells from one compartment to the other. The number of compartments depends on the data available which determines the maximum level of detail appropriate for the model. For instance, a model of erythropoiesis could have one compartment for each recognizable stage of erythrocytes precursors, or alternatively merge some of the compartments together and thus reduce the model dimensions. In the following, we will present some results using only a generic compartment. The treatment for a larger model is the same. We then show that by partial integration we can express this problem as a delay differential equation model. Age-structured models provide a means of understanding the regulation of hematopoiesis. Examples in the literature can be found in [1,6,7,12,30,66,71,81,82,91] and [92].

Let $x(t, a)$ be the the cell density at time t and age a in a generic compartment. We assume that cells disappear (die) at a rate $\gamma(t)$. We also assume that the cells in the compartment age with a velocity $V(t)$ and that a cell enters a compartment at age $a = 0$ and exits this compartment at age $a = \tau$. Therefore, the equation satisfied by $x(t, a)$ is an time–age equation (advection, or reaction–convection, equation):

$$\frac{\partial x}{\partial t} + V(t)\frac{\partial x}{\partial a} = -\gamma(t)x \quad t > 0, \ \ a \in [0, \tau], \tag{10}$$

The right hand side in this equation represents the rate at which cells in the age interval a to $a + \delta a$ disappear at time t. To represent the manner in which new cells enter the compartment, we define the boundary condition (B.C.) $x(t, 0) = H(t)$. Finally, to fully represent the problem, we specify the initial condition (I.C.) $x(0, a) = \phi(a)$. In the Appendix, we show that by partial integration of Eq. (10), we can reformulate this problem as a delay differential equation. Using the method of characteristics [109],

we obtain the following delay differential equation:

$$\frac{dX}{dt} = V(t)\left[H(t) - H(t-T_\tau)\exp\left(-\int_0^{T_\tau}\gamma(w)\,dw\right)\right] - \gamma(t)X(t), \quad (11)$$

where $X(t)$ is the total number of cells ($X(t) = \int_0^\tau x(t,a)\,da$) and T_τ satisfies $\tau = \int_{t-T_\tau}^{t} V(w)\,dw$. Note that if γ is a constant, Eq. (11) reduces to

$$\frac{dX}{dt} = V(t)\left[H(t) - H(t-T_\tau)e^{-\gamma T_\tau}\right] - \gamma X(t). \quad (12)$$

In addition, if the aging velocity is constant ($V(t) = V$), we have that T_τ satisfies

$$\tau = \int_{t-T_\tau}^{t} V\,dw = VT_\tau,$$

which implies that $T_\tau = \tau/V$. Hence, if γ and V are constant, we obtain a delay differential equation with constant delay:

$$\frac{dX}{dt} = V(t)\left[H(t) - H(t-\tau/V)e^{-\gamma\tau/V}\right] - \gamma X(t). \quad (13)$$

3.4 Other models

In this section, we briefly discuss some other types of mathematical models. As mentioned above, several approaches have been used for modeling hematopoiesis (for example DDE, ODE or PDE models). However, it is sometimes appropriate to combine these approaches in one model as in [104]. In this work, the authors used a PDE model which includes a distributed delay for the compartment transition time and a constant delay for the cell cycle duration. Others have included probabilistic aspects in the model, as in [59] where the authors used a probabilistic approach to model to cellular maturation of proliferative cells.

Besides the PDE models presented in Sect. 3.3, other types of partial differential equations have been used. For instance, a reaction–diffusion model for leukemia is proposed in [15]. This type of model accounts for spatial variables, which are not considered ODEs, DDEs and in the previously discussed PDE models. In [28], they proposed a reaction–diffusion system of equations in a porous medium to describe the evolution of leukemia in the bone marrow. They showed the existence of two stationary solutions, one of them corresponds to the normal case and another one to the pathological case.

Finally, a different technique has recently been used in [16]. In this work, the authors used a multi agent approach and created a software to study hematopoiesis at the cell population level with the individually based approach. This computational model is

aimed at studying different features of hematopoiesis and may be useful as an interface between theoretical work on population dynamics and experimental observations.

4 Modeling periodic hematological diseases

Based on the dynamical properties of the periodic hematological diseases, a number of mathematical models have been put forward to better understand the mechanisms responsible for the onset of the observed oscillations in blood cell counts. This mathematical modeling of periodic hematological diseases has helped our understanding of the mechanisms of hematopoiesis.

These models fall into two major categories and reference to Fig. 1 will help place these in perspective. The first broad group identifies the origin of the oscillations as a destabilization of the peripheral control loops. In this case, the cell production is adjusted relative to the number of mature cells in the blood and mediated by one the three cytokines (EPO, TBO and G-CSF). The second group of models focuses on the existence of oscillations in many of the peripheral cell lineages (neutrophils, platelets and erythroid precursors, see Fig. 1). It assumes that oscillations arise in the common stem cell populations through a loss of stability in the stem cell population that is hypothesized to be independent of feedback from peripheral circulating cell types. Thus, this would represent a relatively autonomous oscillation driving the three major lines of differentiated hematopoietic cells [22].

In this section, we review a number of mathematical models of the hematopoietic system and show how dynamical disorders have helped understanding the mechanisms involved. First, we review modeling of erythropoiesis guided by the dynamics of periodic auto-immune hemolytic anemia, and then turn to a consideration of thrombopoiesis drawing on the features of cyclical thrombocytopenia. Recall that each of these two disorders only involve oscillations in one cell line. Then, we turn to a review of large scale models drawing inspiration from the data and characteristics of cyclical neutropenia and periodic chronic myelogenous leukemia.

4.1 Modeling periodic autoimmune hemolytic anemia

In an early model of erythropoiesis, Mackey [69] examined the role of peripheral erythrocyte destruction rate on the onset of AIHA using a simple constant delay differential equation model for the regulation of erythrocyte production. The model defines the rate of change of the circulating density of erythrocytes (E (cells/kg)) by

$$\frac{dE}{dt} = -\gamma E + \beta(E_\tau), \tag{14}$$

where β is the cellular production rate in the early erythroid series cells and γ (day^{-1}) is the peripheral erythrocyte destruction rate. The delay τ represents the total average number of days between the entrance of a cell into the erythroid series and the release of a mature erythrocyte into the blood. As mentioned in Sect. 2, erythropoiesis is regulated by a negative feedback mediated by the cytokine erythropoietin (EPO). This

is modeled by using a monotone decreasing Hill function for the production rate β:

$$\beta(E) = \beta_0 \frac{\theta^n}{\theta^n + E^n}, \tag{15}$$

where β_0 (cells/kg day^{-1}) (the maximum production rate), θ (cells/kg), and n are parameters (Hill functions are often used for regulatory feedback expressions since they frequently can be fit to existing clinical or laboratory data, and offer a form that is easy to deal with analytically). Mackey [69] performed a linear stability analysis of this model and showed that a supercritical Hopf bifurcation occurs when the death rate of circulating erythrocytes is increased above a certain critical value. This transition from damped to stable oscillations would characterize the onset of periodic AIHA and account for the experimentally observed characteristics of AIHA.

In their study, Bélair et al. [12] developed an age-structured model that incorporates the fact that the population of precursor cell matures at differing rates depending on the EPO concentration, which itself varies according to the amount of oxygen carried in blood. They developed a PDE model similar to the one presented in Sect. 3. They assumed constant maturing velocity and were then able to reduce their model to a threshold-type DDE with two constant delays, using the method we presented in Sect. 3.

Even though the bifurcation analysis performed on this model agreed surprisingly well with experimental observations in an induced autoimmune hemolytic anemia, this model was less than satisfactory in predicting the response of a normal patient to a blood loss as in a blood donation. In their paper, Mahaffy et al. [71] expanded the previous model of [12] to account for the active degradation of older cells and to include the possibility of significant apoptosis. Next, we present the equations of this extended age-structured model for hematopoiesis that includes apoptosis and active degradation of the oldest mature cells.

The precursor cells begin from a pool that have differentiated into a self-sustaining population which eventually leads to the production of mature erythrocytes. The model considers two populations of cells: the precursor cells, denoted by $p(t, \mu)$ (see below), and the mature non-proliferative cells, denoted by $m(t, u)$. Figure 3 shows a cartoon representation of the model.

Let $p(t, \mu)$ denote the population of precursor cells at time t and age μ, and let $V(E)$ be the velocity of maturation, which may depend on the hormone (EPO) concentration, E. If $S_0(E)$ is the number of cells recruited into the proliferating precursor population, then the entry of new precursor cells into the age-structured model will satisfy the boundary condition

$$V(E)p(t, 0) = S_0(E). \tag{16}$$

Let the birth rate for proliferating precursor cells be $\beta(\mu, E)$ and $\alpha(\mu, E)$ represent the death rate through apoptosis. Let $h(\mu - \bar{\mu})$ be the density of the distribution of maturity levels of the cells when released into the circulating blood, where $\bar{\mu}$ represents

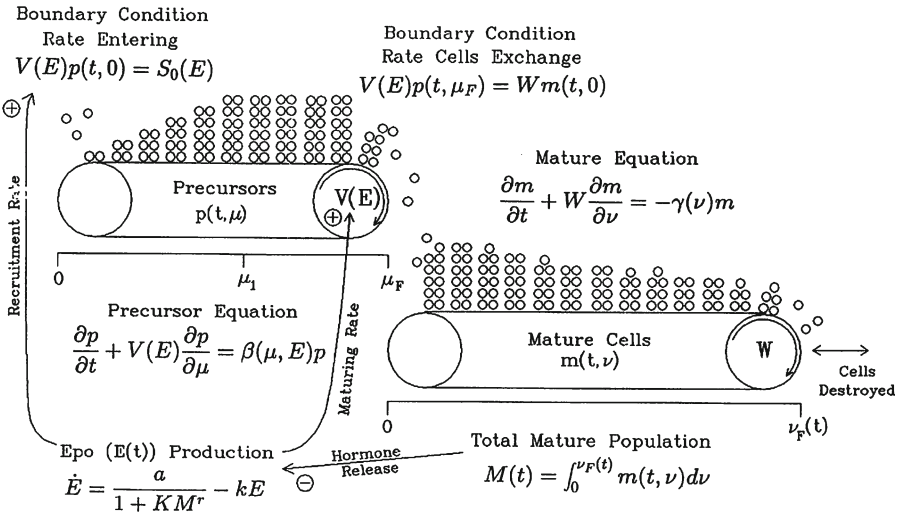

Fig. 3 Schematic representation of the age-structured model of erythropoiesis, taken from [71] with permission

the mean age of mature precursor cells and

$$\int_0^{\mu_F} h(\mu - \bar{\mu})d\mu = 1.$$

The disappearance rate function is given by:

$$H(\mu) = \frac{h(\mu - \bar{\mu})}{\int_\mu^{\mu_F} h(s - \bar{\mu})ds}.$$

With these conditions the age-structured model for the population of precursor cells with $t > 0$ and $0 < \mu < \mu_F$ satisfies:

$$\frac{\partial p}{\partial t} + V(E)\frac{\partial p}{\partial \mu} = V(E)[\beta(\mu, E)p - \alpha(\mu, E)p - H(\mu)p]. \tag{17}$$

Now, let $m(t, \nu)$ be the population of mature non-proliferating cells at time t and age ν. Assume that the mature cells age at a rate W, which is considered to be a constant for erythropoiesis since the aging process appears to depend only on the number of times that an erythrocyte passes through the capillaries. From the disappearance rate function, the boundary condition for cells entering the mature population is given by

$$Wm(t, 0) = V(E)\int_0^{\mu_F} h(\mu - \bar{\mu})p(t, \mu)d\mu, \tag{18}$$

where the maturity level μ_F represents the maximum age for a cell reaching maturity.

The authors assumed that destruction of erythrocytes occurs by active removal of the oldest cells. The immune system recognizes erythrocytes that are no longer efficient and tags them with special markers, which then signals macrophages (white blood cells) to degrade them. For erythrocytes, if one assumes either a finite source of markers or a fixed number of macrophages, then there is a constant flux of the oldest erythrocytes that are dying. From a modeling point of view, this results in a moving boundary condition with the age of the oldest erythrocyte, $\nu_F(t)$, varying in t. The boundary condition is then given by

$$(W - \dot{\nu}_F(t))m(t, \nu_F(t)) = Q, \tag{19}$$

where Q is the fixed erythrocyte removal rate (for a full derivation, see [71]). If $\gamma(\nu)$ is the death rate of mature cells (depending only on age), then the partial differential equation describing $m(t, \nu)$ is given by:

$$\frac{\partial m}{\partial t} + W\frac{\partial m}{\partial \nu} = -W\gamma(\nu)m, \quad t > 0, \quad 0 < \nu < \nu_F(t), \tag{20}$$

where the maximum age, $\nu_F(t)$, is determined by (19).

As in the simple DDE model of [69], the EPO level E is governed by a differential equation with a negative feedback, depending on the total population of mature cells, $M(t)$, defined by

$$M(t) = \int_0^{\nu_F(t)} m(t, \nu)d\nu. \tag{21}$$

The differential equation for E is thus:

$$\frac{dE}{dt} = \frac{a}{1 + KM^r} - kE, \tag{22}$$

where k is the decay constant for the hormone and the rate of EPO production is given by a monotone decreasing Hill function.

The partial differential equations and their boundary conditions given by Eqs. (16)–(20) describe the age-structured model for erythropoiesis. The hormone EPO exerts control in the model through the boundary conditions, the birth and death of precursor cells, and the velocity of aging. Using the method of characteristics and the techniques presented in Sect. 3, one can reduce this system of equations to a system of threshold delay equations. Moreover, if one make some simplifying assumptions (see [71] for the details), it further reduces this system to a system of delay differential equations with a fixed delay and one state dependent delay and it transform the constant flux boundary condition (19) to

$$Q = (1 - \dot{\nu}_F(t))e^{\beta\mu_1}e^{-\gamma\nu_F(t)}S_0(E(t - T - \nu_F(t))). \tag{23}$$

The following system of delay differential equations with a fixed delay T and a state dependent delay occurring in the equation governing the age at which mature cells die is obtained:

$$\begin{aligned}\frac{dM(t)}{dt} &= e^{\beta\mu_1} S_0(E(t-T)) - \gamma M(t) - Q,\\ \frac{dE(t)}{dt} &= f(M(t)) - kE(t),\\ \frac{dv_F(t)}{dt} &= 1 - \frac{Qe^{-\beta\mu_1} e^{\gamma v_F(t)}}{S_0(E(t-T-v_F(t))}.\end{aligned} \tag{24}$$

Analysis of the characteristic equation for the linearized model demonstrated the existence of a Hopf bifurcation when the destruction rate of erythrocytes is increased, as in the previous models by [12] and [69]. Parameters of the model have been estimated from experimental data. Numerical simulations were performed for both periodic auto immune hemolytic anemia in rabbits and blood donation in humans and compared with experimental data. Even though the extension of the model presented in [71] leads to the same conclusion about the origin of periodic AIHA, the moving boundary condition has the advantage of better capturing the physiological reality of apoptosis in circulating cells. Moreover, the model is sufficiently general to characterize other hematopoietic lines. In particular, a similar age-structured model has been used for modeling cyclical thrombocytopenia, as we will see in the next section.

4.2 Modeling cyclical thrombocytopenia

A number of studies have presented models for the regulation of thrombopoiesis. Some considered only a simple thrombopoiesis feedback [11,40,107] whereas other models are more physiologically detailed [8,31,43,110]. Nevertheless, they all assume that the production of platelets is regulated by a negative feedback loop mediated by thrombopoietin (TPO). In their study, [107] suggested that the normal platelet control system was biased close to a stability boundary and that this was the origin of the oscillatory platelets counts observed in some normal individuals [75]. Bélair and Mackey [11] specifically considered the case of cyclical thrombocytopenia. Based on the analysis of their model, they hypothesized that an increased destruction rate of circulating platelets could give rise to the characteristic oscillations in the circulating platelet counts seen in CT, an hypothesis that has recently been modified in [8] using a more comprehensive model. In [92], they developed an age-structured model for the regulation of platelet production that we briefly present.

The development of the mathematical model for thrombopoiesis from [92] follows an earlier age-structured mathematical models for erythropoiesis [12], bearing in mind that the primary difference between the processes of erythropoiesis and thrombopoiesis is in the development of the precursor cells. In erythropoiesis, the stem cells undergo rapid proliferation and differentiation until they reach the stage of reticulocytes, where the cells simply mature to become circulating erythrocytes. In

thrombopoiesis, the stem cells proliferate, then become megakaryocytes that no longer proliferate, but undergo nuclear endoreduplication. These megakaryocytes have different ploidy values at maturation and release differing numbers of platelets. In order to simplify calculations and based on the relative frequencies of megakaryocytes in various ploidy classes, the authors chose to divide the megakaryocyte populations into three classes, denoted by $m_i(t, \mu), i = 0, 1, 2$. As before, t represents time and μ represents the age of the megakaryocyte.

The partial differential equations describing the development of the megakaryocytes are given by:

$$\frac{\partial m_0}{\partial t} + \frac{\partial m_0}{\partial \mu} = -k_0(T)m_0, \tag{25}$$

$$\frac{\partial m_1}{\partial t} + \frac{\partial m_1}{\partial \mu} = k_0(T)m_0 - k_1(T)m_1, \tag{26}$$

$$\frac{\partial m_2}{\partial t} + \frac{\partial m_2}{\partial \mu} = k_1(T)m_1, \tag{27}$$

where $k_i(T)$ is the transfer rate from ploidy class i to ploidy class $i + 1$. The domain for these partial differential equations is $t > 0$ and $0 < \mu < \mu_F$.

Relevant boundary conditions for each population were included. The remaining equations for the circulating platelets $p(t, \mu)$ and its boundary condition are similar to the ones presented in Sect. 4.1 for erythrocytes and will not be presented here. They used a constant flux boundary condition as derived in [71] and a negative feedback ODE for regulation of thrombopoietin.

Despite some difficulties in estimating parameters of this age-structured model, the model numerically reproduced the normal human response to a bolus injection of TPO. They also reproduced the dynamic characteristics of the autoimmune version of cyclical thrombocytopenia if the rate of platelet destruction in the circulation is elevated to more than twice the normal value. They hypothesized that the amegakaryocytic version of cyclical thrombocytopenia, with its longer periods and different dynamic clinical presentation could potentially find an explanation in considerations of the dynamics of the hematopoietic stem cell.

Recently, a more comprehensive mathematical model was used to understand the clinical data of patients with cyclical thrombocytopenia [8]. This model is based on the work of [26] (presented in Sect. 4.3 and Fig. 5) and accounts for all cell lineages (erythrocytes, leucocytes and platelets). The authors found that it was not possible to induce oscillations in the platelet compartment without destabilizing the neutrophil compartment using the model of [26]. They found that using a constant platelet differentiation rate (instead of a rate depending on the circulating platelet levels), the hematopoietic model was then able to generate oscillations in platelets while maintaining the other cells lines at their steady state values. Their model successfully duplicates the platelets counts in CT patients and agrees qualitatively with clinical data. However, it supports only partially the conclusions drawn from the previous modeling study of [92], where CT was hypothesized to be due to an increased platelet destruction rate. Indeed, their numerical experiments showed that more than one parameter had to be modified to

reproduce clinical data. Using a simulated-annealing method, they concluded that a variation in the megakaryocyte maturity, a slower relative growth rate of megakaryocytes, as well as an increased random destruction of platelets are the critical elements generating the platelet oscillations in CT. Moreover, the authors believe that both types of CT are due to a Hopf bifurcation in the platelet dynamics, but that the parameter change inducing the bifurcation might depend on the type of cyclical thrombocytopenia. Their model raises a number of clinical issues that will have to be resolved in the future.

4.3 Modeling cyclical neutropenia

Due to its interesting dynamics and its clinical and laboratory manifestations, cyclical neutropenia is probably the most studied periodic hematological disease. A number of mathematical models have been put forward to attempt to model this disorder, and they fall into two major categories (see Fig. 1 to place them in perspective). For other reviews, see [22,29,36,47].

The first group of models identifies the origin of CN with a loss of stability in the peripheral negative feedback control loop. Typical examples of models of this type which have specifically considered CN are [54,57,64,76–78,88,93–97,99,106], and [111].

The second group of models builds upon the existence of oscillations in many of the peripheral cellular elements (neutrophils, platelets, and erythroid precursors, see Fig. 1) and postulates that the origin of CN is in the common hematopoietic stem cell (HSC) population. A loss of stability in the stem cell population is hypothesized to be independent of feedback from peripheral circulating cell types and would thus represent a relatively autonomous oscillation driving the three major lines of differentiated hematopoietic cells. In their study, [50] concluded that there is no consistent way in which a destabilization of the peripheral loop alone can give rise to the characteristics of CN. It seemed more likely that the oscillations of CN originate from the hematopoietic stem cell population as was originally proposed in earlier work by Mackey [67,68]. Some mathematical models coupled a stem cell compartment with the peripheral loop for granulocytes [14,46,50] whereas others present a more complex model showing the stem cells coupled to all major cell lines [23,26]. For a complete review, see [22].

We present two of these models that have given significant insight into the origin of cyclical neutropenia. Then, we show how these models have been used to improve existing treatment for CN.

4.3.1 Origin of CN

Bernard et al. [14] presented a two variable delay differential equation (DDE) system that has negative feedback loops in both the peripheral loop and the stem cell loop. Figure 4 illustrates the two compartments of the model: the hematopoietic stem cell (HSC) compartment (denoted S) and the neutrophil compartment (denoted N). The HSCs are assumed to be self-renewing, and thus cells in the resting (G_0) phase can

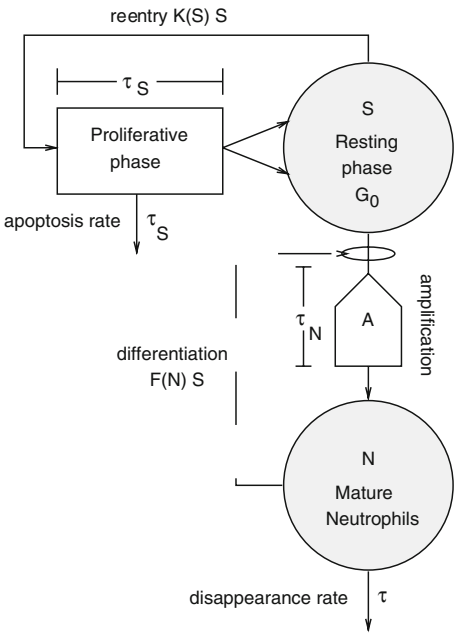

Fig. 4 Schematic representation of the mathematical model of [14]. Two feedback loops control the entire process through the proliferation rate $K(S)$ and the differentiation rate $F(N)$. Taken from Bernard et al. [14] with permission

either enter the proliferative phase at rate $K(S)$ or differentiate into neutrophils (N) at rate $F(N)$. As the neutrophil precursors differentiate, their numbers are amplified by a factor A, which accounts for both successive divisions and cell loss due to apoptosis. It is also assumed that apoptosis occurs during the proliferative phase at rate γ_s and that mature neutrophils die at rate α. As can be seen in Fig. 4, the system is controlled by two negative feedback loops. The first one regulates the rate $K(S)$ of reentry of HSCs to the proliferative cycle, and it operates with a delay τ_s (the cell cycle time) that accounts for the time required to produce two daughter cells from one mother cell. The second loop regulates the rate $F(N)$ of HSC differentiation into mature neutrophils. It operates with a delay τ_N that accounts for the transit time through the neutrophil precursor compartment.

Mathematically, this model translates into the following two variable delay differential equation (DDEs) form. The equations for the two variables N and S can be derived from a time–age maturation formulation, or written directly from consulting Fig. 4. For the compartment N, the loss is the efflux to death αN and the production of mature neutrophils is equal to the influx $F(N)S$ from the HSC compartment times the amplification A. Since one needs to take into account the transit time τ_N, the total production of mature neutrophils is $AF(N(t-\tau_N))S(t-\tau_N)$, or equivalently $AF(N_{\tau_N})S_{\tau_N}$ (recall that $N_{\tau_N} = N(t-\tau_N)$). This leads to the total rate of change of N given by

$$\frac{dN}{dt} = -\alpha N + AF(N_{\tau_N})S_{\tau_N}. \tag{28}$$

For the second variable, the loss from the compartment S is the flux reentering the proliferative phase, $K(S)S$, plus the efflux going into differentiation, $F(N)S$. The production of S is equal to the flux of cells reentering and surviving the proliferative phase, given by $K(S_{\tau_S})S_{\tau_S}e^{-\gamma_S\tau_S}$, times the cell division factor 2. The dynamics of S is then described by

$$\frac{dS}{dt} = -F(N)S - K(S)S + 2K(S_{\tau_S})S_{\tau_S}e^{-\gamma_S\tau_S}. \tag{29}$$

The feedback functions $F(N)$ and $K(S)$ are monotone decreasing Hill functions, similar to the one used in [69]:

$$F(N) = f_0\frac{\theta_1^n}{\theta_1^n + N^n}, \tag{30}$$

and

$$K(S) = k_0\frac{\theta_2^s}{\theta_2^s + S^s}. \tag{31}$$

$F(N)$ controls the number of neutrophils (N) while $K(S)$ regulates the level of HSCs (S).

This model was sufficiently simple that it was possible to perform a complete bifurcation analysis that highlighted the dynamical features of CN [14]. Using a combination of mathematical analysis and computational tools, Bernard et al. [14] showed that the origin of cyclic neutropenia is probably due to an increased apoptosis rate in the recognizable and committed neutrophil precursors, leading to a destabilization of the hematopoietic stem cell compartment through a supercritical Hopf bifurcation. This has the effects of generating oscillations in the HSC population. This result was in accordance with previous modeling studies [46] and agrees with experimental data on grey collies. This model could also be used to study the effects of G-CSF treatment on CN, as we will see in the next section. First we present a more sophisticated model of the hematopoietic system that has also been used to study cyclical neutropenia.

As mentioned, CN is characterized by oscillations in all major cell lines (neutrophils, reticulocytes and platelets). This motivated the development of a comprehensive mathematical model that includes not only the neutrophils and HSC, but also the platelets and red blood cells. This allowed a more realistic approach since one could then study the response of the hematopoietic system when considering all cell lines. In addition, the model simulations could thus be compared with data for platelets and erythrocytes. Colijn and Mackey [25] developed a comprehensive model that contains four compartments: the HSC (Q), the neutrophils (N), the erythrocytes (R) and the platelets (P). This model combines a number of compartmental models we have reviewed in previous sections: the stem cell and neutrophil dynamics are based on the model in Bernard et al. [14], and the erythrocyte and platelet compartment are simplified models based on [71] and [92] respectively. The circulating cells are coupled to each other via their common origin in stem cell compartment. Regulatory

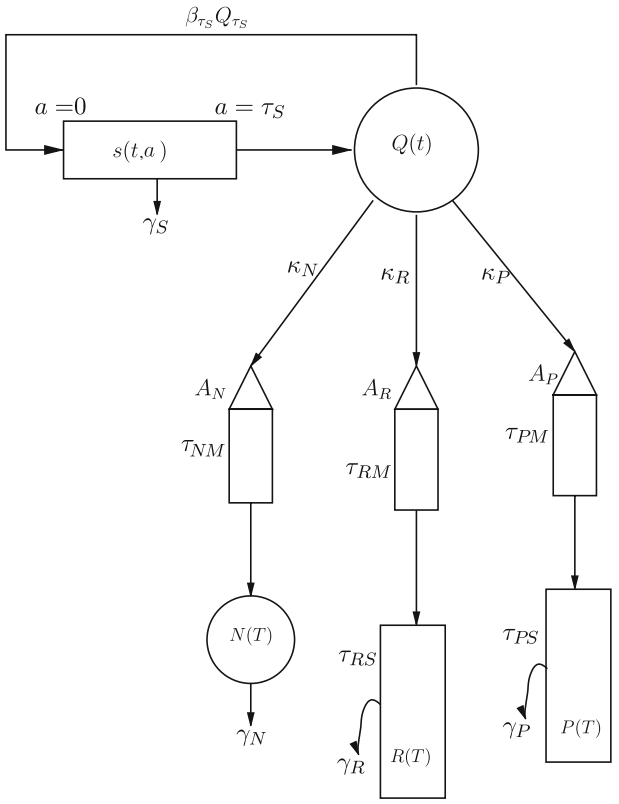

Fig. 5 Schematic representation of the comprehensive mathematical model of [26] including the HSC and the three differentiated cell lines. Each cell lineage is controlled by a negative feedback loop. Taken from [26] with permission

negative feedback loops determine how much differentiation from the stem cells each cell line will undergo. Since it takes several days to produce a mature cell from a newly differentiated cell, time delays appear in the equations. The model consists of a set of four coupled delay differential equations. Their derivation is similar to Eqs. (28) and (29) from Bernard et al.'s model [14] and is based on Fig. 5:

$$\begin{aligned}
\frac{dQ}{dt} &= -\beta(Q)Q - (\kappa_N + \kappa_R + \kappa_P)Q + 2e^{-\gamma_S \tau_S}\beta(Q_{\tau_S})Q_{\tau_S}, \\
\frac{dN}{dt} &= -\gamma_N N + A_N \kappa_N(N_{\tau_N})Q_{\tau_N}, \\
\frac{dR}{dt} &= -\gamma_R R + A_R\left\{\kappa_R(R_{\tau_{RM}})Q_{\tau_{RM}} - e^{-\gamma_R \tau_{RS}}\kappa_R(R_{\tau_{RM}+\tau_{RS}})Q_{\tau_{RM}+\tau_{RS}}\right\}, \\
\frac{dP}{dt} &= -\gamma_P P + A_P\left\{\kappa_P(P_{\tau_{PM}})Q_{\tau_{PM}} - e^{-\gamma_P \tau_{PS}}\kappa_P(P_{\tau_{PM}+\tau_{PS}})Q_{\tau_{PM}+\tau_{PS}}\right\}.
\end{aligned} \tag{32}$$

Analogous to Eqs. (30) and (31) we have

$$\begin{aligned} \beta(Q) &= k_0 \frac{\theta_2^s}{\theta_2^s + Q^s}, \quad \kappa_N(N) = f_0 \frac{\theta_1^n}{\theta_1^n + N^n}, \\ \kappa_P(P) &= \frac{\bar{\kappa}_p}{1 + K_p P^r}, \quad \kappa_R(R) = \frac{\bar{\kappa}_r}{1 + K_r R^{m_e}}, \end{aligned} \tag{33}$$

where the first two functions are the same as in [14]. For a complete derivation, see [25]. This model was applied to both PCML (Sect. 4.4) and CN.

The authors used a simulated annealing approach and clinical data from dogs and humans to estimate the model parameters. The model supported the hypothesis on the origin of CN put forward in [14] and showed that realistic CN oscillations in neutrophils and platelets can result from an increased apoptosis rate in the neutrophil precursors. Interestingly, in order to mimic clinical data, it was also necessary to decrease the rate of differentiation into the neutrophil line and the maximal rate of re-entry of the stem cells into the proliferative phase.

A bifurcation analysis was performed on this model. This analysis predicted that changes in the platelet compartment can have long-term effects on the nature of the oscillations. Simulations show that temporarily increasing the platelet amplification factor A_P will often induce the simulations to jump from an oscillating solution to the coexisting stable solution. Oscillations were thereby abolished. While there are limitations to the clinical applicability of these results because of the difficulties in administering a drug such as thrombopoietin, the ability of the platelet dynamics to affect the long-term behavior of the whole hematopoietic system is theoretically intriguing.

In the next section, we show how both Bernard et al. [14] and Colijn and Mackey's models [25] could be used to explore different G-CSF treatment strategies for CN.

4.3.2 Treatment of CN with G-CSF

Treatment for cyclical neutropenia typically involves daily G-CSF administration. This is an effective treatment since 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 [47]. However, G-CSF is expensive (about $40,000 per year for a 70 kg adult treated daily) and may cause undesirable side effects (see Sect. 2). In this section, we show how mathematical modeling can illuminate the effects of different G-CSF treatment schemes.

Foley et al. [37] used the model of Bernard et al. [14], presented earlier, to analyze alternate G-CSF treatment schemes. Even though the effects of G-CSF have been included implicitly in the model through the feedback function $F(N)$, it can be shown that by using physiologically relevant parameter values, this model can replicate the characteristics of CN and the effects of G-CSF administration. Mimicking CN can be achieved by increasing the rate of apoptosis for the neutrophil precursors, i.e. decreasing the amplification parameter A (which accounts for cell death). To simulate the effects of G-CSF in CN the authors modified five of the eleven parameters of

the model: decrease apoptosis in both the HSC (decrease γ_s) and in the neutrophil precursors compartment (increase A), decrease 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. This yields two sets of parameters of interest (for untreated CN and CN under G-CSF treatment). Assuming that the five parameters vary linearly between the untreated CN state and the G-CSF treated values, the authors expressed the five relevant parameters as a function of a new parameter T, in such a way that $T = 0$ corresponds to untreated CN and $T = 1$ corresponds to the treated state. Increasing T was therefore associated with increasing G-CSF concentration. A complete bifurcation analysis was then performed using this G-CSF parameter (T).

Interesting dynamical features of the model were found. The bifurcation analysis agreed with the clinical aspects of G-CSF administration (increased amplitude and decreased period of the oscillations [48,49]), as expected. However, some cases have been reported in the literature in which G-CSF treatment abolished significant oscillations [44,47,48]. Interestingly, the model also accounts for this effect of G-CSF administration. Indeed, for $T = 1$ (G-CSF treatment), a stable steady state (corresponding to annihilation of oscillations) coexists with a stable large amplitude oscillation. This bi-stability in the system is interesting since it suggests that by properly designing the treatment administration scheme, one might stabilize the neutrophil count to a desirable level and could potentially reduce the amount of G-CSF required in treatment. In Foley et al. [37], the authors exploited this bi-stability and showed that, depending on the starting time of the G-CSF treatment, the neutrophil count could either be stabilized or show large amplitude oscillations. Using computer simulations, they also 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.

The model of Bernard et al. [14] grasped the essential features of the system while being simple enough to carry out the detailed analysis and simulations presented in Foley et al. [37]. It gave insight into the dynamics of the system but it had two major shortcomings. First, the model included neither erythrocyte nor platelet dynamics even though clinical data indicates oscillations in those cell lines in CN patients. Thus it is not known if the results would be consistent with observed platelet and reticulocyte data. Second, G-CSF kinetics are implicitly included in the model and are based on a pseudo-equilibrium assumption on the kinetics of G-CSF clearance, which is a simplification. Therefore, the simulations did not take into account the pharmacokinetics of G-CSF.

In [23], the authors used the comprehensive model of [26] and they coupled it with a two-compartment model for G-CSF pharmacokinetics. They fitted their model with clinical data for neutrophils and platelets and explored the effects of different treatment schedules in this new model. They found that the bi-stability of periodic solutions and stable solution observed in [37] was preserved when the G-CSF pharmacokinetics was taken into account. In fact, due to the complexity of the model, there are a number of coexisting stable solutions for a given set of parameters. Hence, different initial conditions or temporary interventions may lead to dramatically different long-term behaviors. In particular, in Colijn et al. [23], the authors explore changing the period of G-CSF treatment (daily, every other day, and every third day). They also explore

changing *only* the time at which treatment is first initiated. They found that both can significantly change the nature of the oscillations. In particular, there was one dog for whom varying only the time within the neutropenic cycle that treatment was initiated significantly reduced the amplitude of oscillations.

In summary, both of the studies [23] and [37] indicate that the dynamical properties of the comprehensive mathematical model system could be used to design new efficient and cheaper G-CSF treatment strategies for cyclical neutropenia.

4.4 Modeling periodic chronic myelogenous leukemia

As for cyclical neutropenia, periodic chronic myelogenous leukemia (PCML) is an interesting dynamical disease of the hematopoietic system in which oscillating levels of circulating leukocytes, platelets and/or reticulocytes are observed. Typically all of these three differentiated cell types have the same oscillation period, but the relation of the oscillation mean and amplitude to the normal levels is variable. The hypothesis that oscillations originate in the stem cells is related to the fact that oscillations of the same period occur in different cell lines. However, in several mathematical models, only one cell line, or one line coupled to the stem cells, is represented. In particular, [85] explored how long-period oscillations (as seen in PCML) could arise within the context of a G_0 stem cell model. They used a two-dimensional DDE model and they performed a careful mathematical analysis. They studied when stability was lost and oscillations occur, and how various parameters modify the period of these oscillations. They also considered a limiting case of the original model in order to compute an explicit solution and give an exact form of the period and the amplitude of oscillations. They showed that the main parameters controlling the period are the cellular loss (the differentiation rate δ and the apoptosis rate γ), while the cell regulation parameters (proliferation rate β and cell cycle duration τ) mainly influenced the amplitude. In [86], the authors used the same model and determined the local stability conditions and showed under what conditions a Hopf bifurcation may occur. They interpreted the role of each parameter in the loss of stability, and then examined a simpler model to try to deduce possible changes at the stem-cell level that might be responsible for the characteristics of PCML.

In these papers, the models assumed a constant cell cycle duration, leading to a system of nonlinear differential equations with discrete delays. In [3] and [5], the authors assumed that all cells do not divide at the same age, introducing a distributed delay in the two-dimensional nonlinear differential equation system. The dynamics and stability of this model was analyzed in [3–5]. In particular, the authors showed the existence of a Hopf bifurcation and applied their results to periodic chronic myelogenous leukemia. They showed that their model can display long periods of peripheral cell oscillations (as seen in PCML) for relatively short cell cycle duration. Adimy et al. [5] studied the action of growth factors on the hematopoietic system using a DDE model. They assumed growth factors act on the rate of introduction in the proliferative phase and applied their model to PCML. Then, in [2] they considered the action of growth factors on apoptosis using a three-dimensional DDE system with distributed delay, concluding that the action of growth factors can lead to the existence of oscillating solutions in the stem cell population.

All these models only consider one cell line coupled with the stem cells and did not include platelet and erythrocyte regulation. Thus, it was not clear whether their hypothesis would be consistent with observed platelet and erythrocyte data in PCML. For this reason, the comprehensive model for the regulation of the hematopoietic system [25] presented in Sect. 4.3 was used to examine the possible origins of of PCML. Based on estimates of parameters for a typical normal human, the authors systematically explored the changes in some of these parameters necessary to account for the quantitative data on leukocyte, platelet and reticulocyte cycling in 11 patients with PCML, using two different fitting procedures (the Marquardt–Levenberg procedure as well as simulated annealing). Both methods gave qualitative and quantitative agreement with the published data on PCML in reproducing the period, amplitudes and mean values of the oscillating cell types as well as the relative phase differences between them. This indicates that the model is capable of duplicating the overall features of the coupled oscillations of the different cell lines.

Based on their analysis and numerical simulations, the oscillatory nature of PCML could be generated through a bifurcation in the dynamics of the coupled HSC compartment and the regulation of differentiated leukocytes. The critical model parameter changes required to simulate the periodic chronic myelogenous leukemia patient data were the amplification in the leukocyte line (A_N), the differentiation rate from the stem cell compartment into the leukocyte line (f_0), and the rate of apoptosis in the stem cell compartment (γ_S). In particular, their model system was very sensitive to changes in γ_S, suggesting that changes in the numbers of proliferating stem cells might be important in generating PCML. Note also that a high-frequency oscillation on top of the typical long time periods oscillations was often seen in their numerical simulations. In [24], they analyzed a two-compartment DDE model for stem cell and neutrophil populations and showed how such oscillations can be understood in the context of slow periodic stem cell oscillations. They suggested that these observed intermittent high frequency oscillations are likely to be partially due to the system dynamics, and not simply result from noise and fluctuations in the biological parameters.

5 Discussion

Due to their interesting dynamical characteristics, hematological periodic diseases are good candidates for using mathematical modeling and bifurcation theory to better understand the underlying mechanisms of hematopoiesis and even to potentially understand how clinical treatment affects dynamics.

We have reviewed four dynamical diseases and presented different mathematical models that have aided our understanding of the origin and features of these diseases. Several types of mathematical models have been used and the choice typically depends on the availability of data and the overall objective of the study. Due to advances in measurement technology, an increasing amount of cellular and molecular data is being generated. Their analysis and the complexity of the underlying mechanisms require the contribution of mathematical models and computational methods. Indeed, mathematical modeling and simulation techniques contribute to the discovery of regulatory principles and may also provide clinical predictions. In particular,

we illustrated how one could use mathematical models to optimize standard G-CSF treatment for cyclical neutropenia. The same ideas may be used for other diseases if enough clinical data are made available for appropriate parameter estimations. Indeed, despite major advancement in new technologies, some quantities are still difficult to measure or estimate, making the parameter estimation a limitation for mathematical modeling.

In conclusion, we also mention three other recent studies who have used computational methods for specific clinical applications. First, Engel et al. [32] used an ODE model for studying the effects of ten different multi-cycle poly-chemotherapies on leucocytes in lymphoma patients. Their model provides quantitative predictions for different G-CSF chemotherapy schedules [32,98]. Second, the PDE model in Ostby et al. [81,82] was successfully applied to clinical results for granulocyte reconstitution after high-dose chemotherapy with stem cell and G-CSF support in breast cancer patients. Finally, we mention the work of Skomorovski et al. [100,101], who developed a computer tool that simulates thrombopoietin (TPO) administration schedules on the platelets number and on the cell counts of different bone marrow compartments. This tool is aimed at suggesting improved drug protocols for patients suffering from low blood platelet levels. In our opinion, these are other examples that clinical biology and dynamical modeling should not be regarded as independent fields, but rather as complementary parts of biology.

We hope that readers of this paper will appreciate that mathematical modeling is a process that constantly evolves as the predictions of the models are iterated against data and clinical findings, and the results of the past three decades in modeling of dynamical hematological diseases is an example of this. For example, the original model for PCML in [70] bears little resemblance to the more recent model of [25] and indeed the original model of [70] is inconsistent with the currently available clinical data. Likewise, the earlier model of [67] identified apoptosis within the stem cell compartment as the likely culprit in the generation of the oscillations of CN. This led, in turn, to laboratory and clinical investigations that did, indeed, identify significantly higher than normal levels of apoptotic cells in the bone marrow *but the apoptosis was occurring in the committed neutrophil precursors*! This model has been revisited a number of times [11,14,25,26,66,72,85,86,92] as knowledge improved, and conclusions drawn from subsequent models has led to an evolution of our understanding of this disease as well as the treatment of it using G-CSF.

The reader will, no doubt, also realize that each model has its positive and negative aspects. The level of detail of the model depends on the availability and quality of the data and also on the questions we want to address. The more detail, the more complicated the model will be. A mathematical analysis might then be hard to undertake and the conclusions may only be based on numerical experiments which many, including us, find less than satisfactory. On the other hand, a simple model may be easier to analyze and mathematical analysis can give more insights into the dynamical properties or the underlying system, but it may oversimplify and fail to capture some important features of the reality.

The issue of model complexity is intimately tied to the issue of the dimensionality of the parameter space, and this is tied directly to one of the quandaries that faces every modeler. The more complex the model, the more parameters that must be estimated.

It is a virtual truism in mathematical biology that one is almost never able to obtain all of the parameters in a model from the same laboratory or clinical setting using the same procedures and techniques and subjects. So, as mathematical model construction is something of an art in itself the same can be said for parameter estimation. The experience of the senior author (MCM) based on over 45 years of experience in mathematical biology suggests that the hardest part of the modeling exercise is in obtaining decent parameter estimations.

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Appendix

Method for converting a PDE model into a DDE model

As presented in Sect. 3.3, we consider the cell density $x(t, a)$ at time t and age a in a generic compartment. We assume that $x(t, a)$ satisfies the following time–age equation (advection, or reaction–convection, equation):

$$\frac{\partial x}{\partial t} + V(t)\frac{\partial x}{\partial a} = -\gamma(t)x \quad t > 0, \ \ a \in [0, \tau], \tag{34}$$

with boundary condition (B.C.):

$$x(t, 0) = H(t) \tag{35}$$

and initial condition (I.C.)

$$x(0, a) = \phi(a). \tag{36}$$

Next, we show that by partial integration of Eq. (34), we can reformulate this problem as a delay differential equation.

Integrating with respect to the age variable a, we obtain

$$\int_0^\tau \frac{\partial x(t, a)}{\partial t}\, da + \int_0^\tau V(t)\frac{\partial x(t, a)}{\partial a}\, da = -\int_0^\tau \gamma(t)x(t, a)\, da$$

$$\Longrightarrow \quad \frac{dX}{dt} + V(t)\,[x(t, \tau) - x(t, 0)] = -\gamma(t)X(t),$$

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

$$X(t) = \int_0^\tau x(t,a)\,da.$$

We can then substitute the boundary condition $x(t,0) = H(t)$ to give

$$\frac{dX}{dt} = V(t)[H(t) - x(t,\tau)] - \gamma(t)X(t). \tag{37}$$

We next need to find an expression for $x(t,\tau)$. This can be done by directly solving Eq. (10) using the method of characteristics. We define a new (dummy) independent variable s and let $x(s) = x(t(s), a(s))$. Thus, we obtain

$$\frac{dx}{ds} = \frac{\partial x}{\partial t}\frac{dt}{ds} + \frac{\partial x}{\partial a}\frac{da}{ds} = -\gamma(t)x.$$

This defines a set of three ODEs for $t > 0$ and $a \in [0,\tau]$ as follows:

$$\frac{dt}{ds} = 1 \quad \Longrightarrow \quad t(s) = t(0) + s \tag{38}$$

$$\frac{da}{ds} = V(t) \quad \Longrightarrow \quad a(s) = a(0) + \int_0^s V(w)\,dw \tag{39}$$

$$\frac{dx}{ds} = -\gamma(t)x \quad \Longrightarrow \quad x(s) = x(0)\exp\left(-\int_0^s \gamma(t(w), a(w))\,dw\right). \tag{40}$$

Denote by $\mathcal{C}$ the curve emanating from the point $(t,a) = (0,0)$, and separating the $t-a$ plane into two distinct regions $\mathcal{R}_1$ and $\mathcal{R}_2$ (cf. Fig. 6). The curve $\mathcal{C}$ is defined by

$$\mathcal{C} = \left\{(t,a)|t(s) = s \text{ and } a(s) = \int_0^s V(w)\,dw \text{ for } s \in [0, s_T]\right\}, \tag{41}$$

where the value of s_T corresponds to the value of s required to reach age $a = \tau$. Thus, s_T must satisfy

$$\tau = \int_0^{s_T} V(w)\,dw. \tag{42}$$

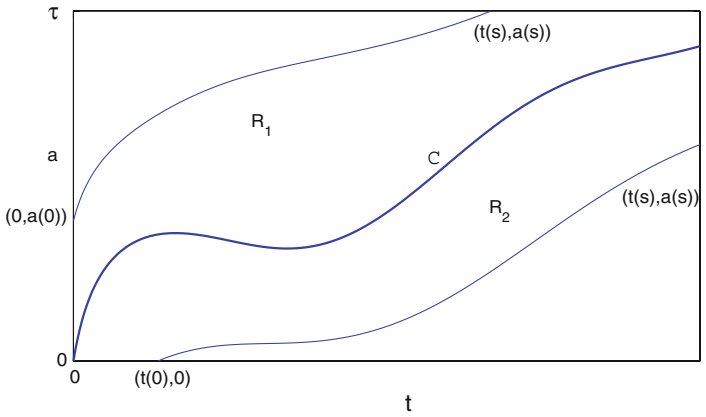

Fig. 6 Generic example of the curve $\mathcal{C}$ that separates the $a - t$ plane into regions $\mathcal{R}_1$ and $\mathcal{R}_2$

The solution $x(t, a)$ takes a different form depending on whether it lies in region $\mathcal{R}_1$ or region $\mathcal{R}_2$. Recall that the general solution is given by Eq. (40)

$$x(s) = x(0) \exp\left(- \int_0^s \gamma(t(w), a(w))\, dw \right).$$

Therefore, we need to find an expression for $x(0)$ and s as a function of a and t in order to obtain the expression for $x(t, a) := x(t(s), a(s))$. Recall also that we are interested in the value $x(t, \tau)$.

1. *If* $(t(0), a(0)) \in \mathcal{R}_1$*:* Then, it can be seen from Fig. 6 that $t(0) = 0$. Hence, we have $t(s) = s$ and $a(s) = a(0) + \int_0^s V(w)\, dw$ with $0 < a(0) < \tau$. Using the initial condition (36), this implies that $x(0) = \phi\left(a - \int_0^t V(w)\, dw\right)$ and therefore, we obtain

$$x(t, \tau) = \phi\left(\tau - \int_0^t V(w)\, dw\right) \exp\left(- \int_0^t \gamma(w)\, dw \right).$$

2. *If* $(t(0), a(0)) \in \mathcal{R}_2$*:* Then, from Fig. 6, one can see that $a(0) = 0$ and thus $a(s) = \int_0^s V(w)\, dw$ and $t(s) = t(0) + s$. Hence, using the boundary condition (35), we have $x(0) = H(t - s)$. Now, we need to find an expression for s. This is defined implicitly using the expression for $a(s)$. Indeed, we have that s represents the time required for age a to increase from 0 to $a(s)$. Moreover,

$$a(s) = \int_0^s V(t(w))\, dw = \int_0^s V(t(0) + w)\, dw = \int_{t(0)}^{t(0)+s} V(\sigma)\, d\sigma.$$

Recall also that we are interested in $x(t,\tau)$. Thus, let us define by T_τ the time needed for the age variable to go from 0 to τ, i.e.:

$$\tau = \int_0^{T_\tau} V(w)\,dw. = \int_{t-T_\tau}^{t} V(w)\,dw. \tag{43}$$

Therefore, the expression for $x(t,\tau)$ reads as follows:

$$x(t,\tau) = H(t-T_\tau)\exp\left(-\int_0^{T_\tau}\gamma(w)\,dw\right),$$

where T_τ satisfies Eq. (43).

Therefore, from the method of characteristics the solution $x(t,\tau)$ is

$$x(t,\tau) = \begin{cases} \phi\left(\tau - \int_0^t V(w)\,dw\right)\exp\left(-\int_0^t \gamma(w)\,dw\right) & \text{if } (t,a)\in\mathcal{R}_1 \\ H(t-T_\tau)\exp\left(-\int_0^{T_\tau}\gamma(w)\,dw\right) & \text{if } (t,a)\in\mathcal{R}_2, \end{cases}$$

with T_τ satisfying $\tau = \int_{t-T_\tau}^{t} V(w)\,dw$. Since we are interested in long term behaviour, we consider only the case where $(t,a)\in\mathcal{R}_2$ (from Fig. 6, one can see that region $\mathcal{R}_2$ includes the t-axis whereas $\mathcal{R}_1$ is bounded by $a=\tau$). We obtain

$$x(t,\tau) = H(t-T_\tau)\exp\left(-\int_0^{T_\tau}\gamma(w)\,dw\right).$$

Substituting in Eq. (37), this yields the general solution for $X(t)$

$$\frac{dX}{dt} = V(t)\left[H(t) - H(t-T_\tau)\exp\left(-\int_0^{T_\tau}\gamma(w)\,dw\right)\right] - \gamma(t)X(t). \tag{44}$$

Note that if γ is a constant, Eq. 44 reduces to

$$\frac{dX}{dt} = V(t)\left[H(t) - H(t-T_\tau)e^{-\gamma T_\tau}\right] - \gamma X(t). \tag{45}$$

In addition, if the aging velocity is constant ($V(t)=V$), we have that T_τ satisfies

$$\tau = \int_{t-T_\tau}^{t} V\,dw = VT_\tau,$$

which implies that $T_\tau = \tau / V$. Hence, if γ and V are constant, we obtain the following delay differential equation with constant delay:

$$\frac{dX}{dt} = V(t)\left[H(t) - H(t - \tau/V)e^{-\gamma\tau/V}\right] - \gamma X(t). \tag{46}$$

The linear chain trick

In this section, we present the derivation of the ODE system obtained using the linear chain trick (see [65] for more details and examples). Consider the following DDE system with a distributed delay:

$$\frac{dx_1}{dt} = f\left(x_1(t), \int_{-\infty}^{t} x_1(\tau)G(t-\tau)\,d\tau\right), \tag{47}$$

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

$$G(u) = G_a^p(u) = \frac{a^{p+1}u^p}{p!}e^{-au}, \tag{48}$$

where a is a positive number and p is a positive integer or zero. It can be shown that the following three properties are satisfied:

1. $\lim_{u\to\infty} G_a^p(u) = 0$,
2. $G_a^p(0) = 0$ for $p \neq 0$,
3. $G_a^0(0) = a$.

Let us define $p + 1$ new variables as

$$x_{j+1} = \int_{-\infty}^{t} x_1(\tau)G_a^{j-1}(t-\tau)\,d\tau \quad j = 1, 2, \ldots, p+1, \tag{49}$$

and set

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

Next, we show that using these definitions, we can express the DDE problem (47) as the following (p+2)-dimensional ODE system:

$$\begin{aligned}\frac{dx_1}{dt} &= f(x_1, x_{p+2})\\ \frac{dx_{j+1}}{dt} &= a(x_j - x_{j+1}) \quad j = 1, 2, \ldots, p+1,\\ \frac{dx_{p+2}}{dt} &= a(x_{p+1} - x_{p+2}).\end{aligned} \tag{50}$$

First, substituting the definition of x_{p+2} into Eq. (47) directly leads to the first differential equation

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

Next, we derive the expression for $\frac{dx_{j+1}}{dt}$, $j = 1, \ldots, p+1$. From the Leibniz integral rule, we have that

$$\begin{aligned}\frac{dx_{j+1}}{dt} &= \frac{d}{dt}\left(\int_{-\infty}^{t} x_1(\tau) G_a^{j-1}(t-\tau)\, d\tau\right)\\ &= x_1(t) G_a^{j-1}(0) + \lim_{u\to\infty} G_a^{j-1}(u) + \int_{-\infty}^{t} x_1(\tau) \frac{d}{dt} G_a^{j-1}(t-\tau)\, d\tau.\end{aligned} \tag{51}$$

From the three properties of $G_a^{j-1}(u)$ 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 $G_a^{j-1}(t-\tau)$ are given by

$$\begin{aligned}\frac{d}{dt} G_a^0(t-\tau) &= -a G_a^0(t-\tau),\\ \frac{d}{dt} G_a^{j-1}(t-\tau) &= a\left[G_a^{j-2}(t-\tau) - G_a^{j-1}(t-\tau)\right] \quad (j = 2, 3, \ldots, p+2).\end{aligned}$$

Hence, substituting in Eq. (51) and using definition (49), we obtain the required set of differential equations for x_j ($j = 2, 3, \ldots, p+2$):

$$\frac{dx_2}{dt} = ax_1 - a\int_{-\infty}^{0} x_1(\tau) G_a^0(t-\tau)\, d\tau = ax_1 - ax_2, \tag{52}$$

$$\frac{dx_{j+1}}{dt} = a\left[\int_{-\infty}^{t} x_1(\tau)\left(G_a^{j-2}(t-\tau) - G_a^{j-1}\right) d\tau\right] = ax_j - ax_{j+1}. \tag{53}$$

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