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Some Existence, Uniqueness, and Stability Results for a Human Erythropoiesis Model with Iterative Terms

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Abstract

Some Existence, Uniqueness, and Stability Results For a Human Erythropoiesis Model with Iterative Terms

During six decades, many scholars have highlighted the significance of the investigation on blood cell dynamics for grasping fundamental biological processes and developing new diagnostic and therapeutic approaches. In this thesis, we present some qualitative and quantitative results for the solutions to a first order delay differential equation with iterative terms that describes the production of red blood cells in humans. Using the Banach and Schauder fixed-point theorems as well as the Green's functions method, we discuss the existence, uniqueness, and continuous dependence on parameters of positive periodic solutions for the proposed equation.

Keywords. Continuous dependence on parameters, erythropoiesis model, existence, fixed point theorem, Green's function, iterative differential equation, uniqueness.

Abstract in French

Certain résultats d'existence, d'unicité et de stabilité d'un modèle d'érythropoïèse humaine avec des termes itératifs

Au cours des six dernières décennies, de nombreux chercheurs ont souligné l'importance de l'étude de la dynamique des cellules sanguines pour comprendre les processus biologiques fondamentaux et pour développer de nouvelles approches diagnostiques et thérapeutiques. Dans ce mémoire, nous présentons des résultats qualitatifs et quantitatifs concernant les solutions d'une équation différentielle retardée du premier ordre avec des termes itératifs, décrivant la production de globules rouges chez les humains. En utilisant les théorèmes du point fixe de Banach et de Schauder ainsi que la méthode des fonctions de Green, nous étudions l'existence, l'unicité et la dépendance continue par rapport aux paramètres des solutions périodiques positives de l'équation proposée.

Mots-clés. Dépendance continu par rapport aux paramètres, modèle d'érythropoïèse, existence, théorème du point fixe, fonction de Green, équation différentielle itérative, unicité.

Abstract in Arabic

بعض نتائج الوجود، الوحدانية والاستقرار لنموذج تكون كريات الدم الحمراء لدى البشر بحدود التكرارية

على مدار ستة عقود، سلّط العديد من الباحثين الضوء على أهمية البحث في ديناميكيات خلايا الدم لفهم العمليات البيولوجية الأساسية وتطوير مناهج تشخيصية وعلاجية جديدة. في هذه المذكرة، نعرض بعض النتائج النوعية والكمية لحلول معادلة تفاضلية تأخيرية من الدرجة الأولى ذات حدود تكرارية تصف إنتاج خلايا الدم الحمراء لدى البشر. باستخدام نظريات النقطة الثابتة لبانـاخ وشودر، بالإضافة إلى طريقة دوال غرين، نناقش الوحدانية و الاعتماد المستمر على المعلمات للحلول الدورية الموجبة للمعادلة المقترحة.

الكلمات المفتاحية. الاعتماد المستمر على المعلمات، نموذج عملية تكون الكريات الدموية الحمراء، الوجود، نظرية النقطة الثابتة، دالة جرين، معادلة تفاضلية تكرارية، الوحدانية.

Dedication

To those who were the guiding light throughout my journey of knowledge and work...

To my dear parents, thank you for your unwavering prayers and constant support.

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To all of you, I dedicate this thesis as a token of loyalty and gratitude, hoping that it reflects even a fraction of what you deserve.

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Acronyms

Abbreviation	Meaning
RBCs	Red blood cells
WBCs	White blood cells
HSCs	Hematopoietic stem cells
BM	Bone marrow
CMPs	Common myeloid progenitors
HSCs	Hematopoietic stem cells
CML	Chronic myeloid leukemia
SCF	Stem cell factor
IL-3, IL-5,...	Interleukins which are a group of signaling proteins (cytokines)
CSFs	Colony-stimulating factors
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
M-CSF	Macrophage Colony-Stimulating Factor
IGF-I	Insulin − like growth factor − 1
EPO	Erythropoietin
TPO	Thrombopoietin

List of symbols

Sets and numbers

$\mathbb{R}$: the set of real numbers (1-dimensional real Euclidean space).

$\mathbb{R}^*$: the set of all non-zero real numbers

$\mathbb{R}_+^* = (0, +\infty)$: the set of all non-zero positive real numbers

$\mathbb{R}^n$: n-dimensional real Euclidean space

$\mathbb{N}$: the set of all natural numbers

$[a, b]$: the interval of numbers between a and b, including a and b

$(a, b) =]a, b[$: an open interval

$\mathcal{C}(E) := \mathcal{C}(E, E)$ is the space of continuous functions from E into itself

$\mathcal{C}(E, F)$ is the space of continuous functions from E into F

$\mathcal{C}^1(E, F)$: space of continuously differentiable functions from E into F

τ : a delay

T : a period

Functions

$|\cdot|$: absolute value

$\|.\|_{\mathbb{X}}$: a norm on $\mathbb{X}$

$\|x\|_{\infty}$ or $\|x\|$: the uniform norm defined by $\sup_{t\in\mathbb{R}} |x(t)|$

$x^{[n]}(t)$: the composition of the function $x(t)$ with itself n times or the n^{th} iterate of the function $x(t)$

Id_E : Identity mapping on a set E

$\sum_{i=1}^{n}$: the summation from index $i = 1$ to $i = n$

$\lim_{n\longrightarrow n_0}$: limit as n approaches n_0

$\approx$: approximately equal to

$x'(t) := x^{(1)}(t) := \dfrac{dx(t)}{dt}$: the first derivative of the function $x(t)$ with respect to t

$x''(t) := x^{(2)}(t) := \dfrac{d^2x(t)}{dt^2}$: the second derivative of the function $x(t)$ with respect to t

$x^{(n)}(t) := \dfrac{d^nx(t)}{dt^n}$: the n-th derivative of the function $x(t)$ with respect to t

sup : the supremum

max : the maximum

min : the minimum

$\exp M$: the exponential function of M

$G(t,s)$: a *Green's* function

Other notations will be clarified upon their initial occurrence.

General Introduction

Human hematopoiesis is a complex and highly regulated process that starts with the differentiation of hematopoietic stem cells (HSCs) into all mature blood cell types, including red blood cells (RBCs), white blood cells (WBCs), and platelets. Due to its inherent complexity, the study of both normal and malignant hematopoiesis requires the application of a diversity of techniques and somewhat complex procedures. The investigation of blood cell dynamics, particularly those of red blood cells is crucial for grasping how these cells move, deform, and interact within the circulatory system. It provides insights into various diseases and conditions. Indeed, it helps in comprehending the process itself, the homeopathy[1], and the various blood disorders that result from either excessive destruction or impaired production of certain blood cells, including aplastic anemia[2], cyclical neutropenia[3],

[1] Homeopathy is a system of alternative medicine based on the idea that a substance that causes symptoms in a healthy person can be used in diluted form to treat similar symptoms in an ill person.

[2] Aplastic anemia is a condition that happens when your bone marrow stops making enough new blood cells.

[3] Neutropenia involves having low levels of neutrophils in the blood.

myeloproliferative neoplasms[4], or myeloid leukemia[5]. Moreover, models that are based on experimental data can serve as useful tools in clinical decisions such as, but not limited to, the prediction of the effectiveness of a treatment or a blood harvesting. It provides also an assistance in developing novel therapy strategies to deal with diseases, anemia, and even the progression of cancers and the adjustment of the dosage of the chemotherapy treatments.

Certain blood disorders can impact the function or quantity of healthy blood cells, even when hematopoiesis is taking place. For instance, white blood cell cancers like leukemia and lymphoma can disrupt normal white blood cell levels in the bloodstream. Additionally, tumors in blood-forming tissues such as the bone marrow can interfere with normal blood cell production. Furthermore, as people age, the bone marrow tends to accumulate more fat, which can hinder its ability to generate new blood cells. When the body requires more blood cells such as during illness the marrow may struggle to meet the demand. This can lead to anemia, a condition marked by a deficiency of hemoglobin due to a reduced number of red blood cells. The issues related to the study of periodic oscillations occurring in certain blood diseases quickly attracted the interest of mathematicians, whose models made it possible to suggest potential causes for the oscillations in the quantities of mature blood cells over time. In 1970, King-Smith and Morley [31] suggested, using simulations, that the oscillations occurring in the case of cyclic neutropenia could be explained by the presence of regulatory mechanisms. In 1977, Michael Mackey and Leon Glass [38] set up three physiological models, with realistic parameters extracted from the literature,

[4]Myeloproliferative neoplasms are a group of rare blood cancers where the bone marrow produces too many blood cells

[5]Myeloid leukemia is a type of cancer that occurs when the bone marrow produces abnormal myeloid cells.

based on delay-differential equations which were not yet in wide use in modeling biological phenomena and processes at that time. One of them for respiratory control, and two variants for the control of hematopoiesis and the description of oscillatory phenomena observed in certain hematological disorders, particularly the aplastic anemia and the periodic forms of chronic myeloid leukemia. Each model was defined by a single differential equation with a constant delay representing the time needed before the blood from the lungs reaches the brainstorm in the first model and the duration between the detection of a deficiency in a circulating population, and the appearance of new cells in the bloodstream in the hematopoiesis models. The erythropoiesis model which describes the red blood cell production, was given as follows:

$$x'(t) = -ax(t) + \frac{b}{1 + x(t-\tau)}.$$

In biological terms, $x(t)$ denotes the density of mature circulating RBCs in the bloodstream over time, $ax(t)$ is the mortality rate where the circulating erythrocytes are removed from the circulation at a rate depicted by the death rate $a > 0$, $\frac{b}{1 + x(t-\tau)}$ which depends on the cell density of mature RBCs at an earlier time, stands for the red blood cell production where $b > 0$ represents the rate of RBC production and the delay $\tau > 0$ is the maturation lag that represents the time it takes for red blood cells to mature and enter the circulation.

In 1979, Mackey and Glass [21] published another paper where they investigated in detail these hematopoiesis models and other dynamical disorders [6] such as cardiac arrhythmias, psychological disorders, and cancer, among others. Since then and throughout the past sixty years, many scholars have

[6] A dynamical disease occurs when a normally functioning control system operates within an abnormal range of parameters, leading to dysfunctional or pathological outcomes.

investigated numerous hematopoiesis models (see [5, 6, 16, 17, 18, 19, 24, 25, 26, 27, 34] and references therein).

This work is dedicated to investigate a first-order differential equation with iterative terms, describing the formation of red blood cells in humans. It is primarily driven by the need to address the following research questions:

(i) Under what conditions does at least one positive periodic solution exist?

(ii) Is the solution to the proposed equation unique?

(iii) Does the unique solution depend on the parameters of the model?

The technique employed to answer these questions is one of the most important instruments to tackle such problems since it combines the fixed point theory with the Green's functions method. To be more precise, it involves converting the given equation into a fixed point problem through a series of steps. In the first step, we choose of an appropriate Banach space and a subsets of it, which form the foundation for applying fixed point theorems, controlling the iterative terms, and satisfying certain biological and mathematical requirements. The next step involves transforming the equation at hand into an equivalent Fredholm integral equation with a Green's kernel. Ultimately, the application of the fixed point theorems of Schauder, and Banach, along with some properties of the obtained Green's function, is a key ingredient in the proof of the existence, uniqueness, and stability of positive periodic solutions.

This thesis revolves around the captivating theme of the dynamics of red blood cells in humans. It commences with a general introduction that sheds light on the essence of the topic, some background information, the objectives of the study, the methodology being used to establish the main results as well

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as the layout of the thesis. It concludes with a short summary and provides insights into future perspectives. The manuscript is thoughtfully divided into three chapters.

The first chapter is a preliminary chapter that introduces some fundamental definitions and necessary results that are addressed throughout this thesis. More precisely, It provides a quick glance at the Arzelà-Ascoli theorem, the Green's function and iteration concepts, and the Banach and Schauder fixed point theorems.

The second chapter serves as a doorway into understanding hematopoiesis and its pioneering mathematical models. In other words, it delves into some biological facts related to the production of blood cells in humans and the history of its mathematical modeling.

The third chapter of the thesis presents recent results published in [26]. It investigates the following first order delay functional differential equation with iterative terms which describes the production of erythrocytes in humans in the presence of a harvesting strategy:

$$x'(t) = -a(t)\,x(t) + \frac{b(t)}{1 + x^{[2]}(t)} - h\left(t, x(t - \tau(t)), x^{[2]}(t)\right),$$

where $x^{[2]}(t)$ denotes the second iterate of $x(t)$, and the functions $a, b, \tau \in \mathcal{C}(\mathbb{R}, (0, +\infty))$ are T-periodic. The function $h \in \mathcal{C}(\mathbb{R}^3, (0, +\infty))$ is also a T-periodic function in its first argument and satisfies the Lipschitz condition with respect to its second and third arguments. Indeed, feedback mechanisms from hormones, other signaling molecules, or fluctuating oxygen level could be described by a time-varying death rate. For example, lower oxygen levels might lead to a higher death rate of RBCs. Seasonal variations in temperature or food availability could lead to a time-varying the production rate of RBCs. Our focus lies on proving the existence, uniqueness, and continuous dependence on parameters of positive periodic solutions for the

proposed equation by means of a hybrid technique based on the Banach and Schauder fixed point theorems and the Green's functions method. The last section is devoted to present two examples that show the validity of the main outcomes.

CHAPTER 1

Preliminaries

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This preliminary chapter is devoted to introduce some notations, definitions, and fundamental results that are used in the remainder of the thesis.

1.1 Arzelà-Ascoli Theorem

Let $\mathbb{X}$ be a compact subset of a normed vector space over $\mathbb{F}$ and let $\mathcal{C}(\mathbb{X})$ denote the normed vector space consisting of all real-valued continuous functions defined on $\mathbb{X}$, equipped with the supremum norm

$$\|f\|_\infty = \sup_{x\in\mathbb{X}} |f(x)|.$$

Let $\mathcal{F}$ be a collection of functions in $\mathcal{C}(\mathbb{X})$.

Definition 1.1 [9] The family $\mathcal{F}$ is called equicontinuous if, for every $\varepsilon > 0$ there exists a constant $\delta > 0$ such that for all functions $f \in \mathcal{F}$ and for all points $x, y \in \mathbb{X}$ with $\|x - y\|_{\mathbb{X}} < \delta$, it holds that $|f(x) - f(y)| < \varepsilon$.
In other words:

$$\forall \varepsilon > 0,\ \forall x \in \mathbb{X}, \exists \delta > 0,\ \forall y \in \mathbb{X}, [\|x - y\|_{\mathbb{X}} < \delta] \Longrightarrow [\forall f \in \mathcal{F},\ \ |f(x) - f(y)| < \varepsilon].$$

Definition 1.2 [9] The collection $\mathcal{F}$ is called uniformly bounded if there exists a constant $M \geq 0$ such that for every function $f \in \mathcal{F}$ we have $\|f\|_\infty = \sup_{x\in\mathbb{X}} |f(x)| \leq M$, i.e.,

$$\exists M \geq 0 : \|f\|_\infty = \sup_{x\in\mathbb{X}} |f(x)| \leq M,\ \forall f \in \mathcal{F}.$$

Theorem 1.1 *[9] If $\mathcal{F}$ is a set of $\mathcal{C}(\mathbb{X})$ which is both uniformly bounded and equicontinuous, then $\mathcal{F}$ is relatively compact in $\mathcal{C}(\mathbb{X})$; that is, the closure of $\mathcal{F}$ is compact in the sup-norm topology.*

1.2 Green's Functions

Green's functions are named after the British mathematician George Green, who introduced them as a method for solving Poisson's equation for electric

potential:

$$\frac{\partial^2 v}{\partial x^2}+\frac{\partial^2 v}{\partial y^2}+\frac{\partial^2 v}{\partial z^2}=0.$$

The Green's function are not special functions such as Bessel functions, Weber function, Airy function, etc. But Green's functions can be considered as a powerful method for solving nonhomogeneous linear ordinary or partial differential equations of the form $Ly(t)=f(t)$ with specified initial conditions or boundary conditions. This approach can also transform such differential equations into integral equations, where the Green's function acts as the kernel of the inverse operator L^{-1}.

1.2.1 Green's Functions for Nonhomogeneous Linear Differential Equations

Consider the following $n-th$ order linear differential equation:

$$a_0(t)\,x^{(n)}(t)+a_1(t)\,x^{(n-1)}(t)+...+a_n(t)\,x(t)=f(t),\ \forall t\in[c,d], \quad (1.1)$$

where a_0, a_1,..., a_n, and f are continuous functions over the interval $[c,d]$ with $a_0(t)\neq 0$ for all $t\in[c,d]$. This equation is accompanied by the following boundary conditions:

$$\begin{cases} \alpha_1 x(c)+\alpha_1^{(1)}x'(c)+...+\alpha_1^{(n-1)}x^{(n-1)}(c)+\beta_1 x(d)+...+\beta_1^{(n-1)}x^{(n-1)}(d)=0 \\ \alpha_2 x(c)+\alpha_2^{(1)}x'(c)+...+\alpha_2^{(n-1)}x^{(n-1)}(c)+\beta_2 x(d)+...+\beta_2^{(n-1)}x^{(n-1)}(d)=0 \\ ..... \\ ..... \\ ..... \\ \alpha_n x(c)+\alpha_n^{(1)}x'(c)+...+\alpha_n^{(n-1)}x^{(n-1)}(c)+\beta_n x(d)+...+\beta_n^{(n-1)}x^{(n-1)}(d)=0. \end{cases} \quad (1.2)$$

The corresponding homogeneous equation of (1.1) is

$$a_0(t)\,x^{n}(t)+a_1(t)\,x^{n-1}(t)+...+a_n(t)\,x(t)=0,\ \forall t\in[c,d]. \quad (1.3)$$

We assume that the rank of the below Δ is n.

$$\Delta = \begin{vmatrix} \alpha_1 & \alpha_1^{(1)} & \dots & \beta_1 & \dots & \beta_1^{(n-1)} \\ \alpha_2 & \alpha_2^{(1)} & \dots & \beta_2 & \dots & \beta_2^{(n-1)} \\ \dots & \dots & \dots & \dots & \dots & \dots \\ \alpha_n & \alpha_n^{(1)} & \dots & \beta_n & \dots & \beta_n^{(n-1)} \end{vmatrix}. \tag{1.4}$$

Theorem 1.2 [39]

a If the homogeneous equation of (1.1) with the boundary conditions (1.2), has only the trivial solution, then the Green's function $G(t,s)$ for this boundary value problem exists and it is unique.

b Suppose that the aforementioned conditions are satisfied, then the nonhomogeneous equation (1.1) with the boundary conditions (1.2) admits a unique solution given by the following integral expression:

$$x(t) = \int_c^d G(t,s) f(s) ds. \tag{1.5}$$

1.2.2 Finding Green's Functions

We aim to solve the differential equation $Lx(t) = f(t)$ with homogeneous boundary conditions, by determining the inverse operator L^{-1}. This allows us to express the solution as $x(t) = L^{-1}(f(t)) = \int G(t,s) f(s) ds.$. We assume that the corresponding homogeneous equation of (1.1) with the boundary conditions (1.2) has only the trivial solution $x(t) = 0$, which guarantees the existence and uniqueness of the Green's function $G(t,s)$. The problem now is how to construct $G(t,s)$. Actually there are four necessary ingredients.

Definition 1.3 [39] We say that the Green's function of equation (1.1) with the boundary conditions (1.2), the function $G(t,s)$ that can be quickly constructed via the following properties:

1− $G(t,s)$ satisfies the homogeneous differential equation for any $t \neq s$.

2− For all fixed s in $(c,d) =]c,d[$, the function $G(t,s)$ satisfies the boundary conditions of the problem.

3− The *Green*'s function $G(t,s)$ must be continuous.

4− For all fixed s in $]c,d[$, $\dfrac{\partial G}{\partial t}(s^+,s) - \dfrac{\partial G}{\partial t}(s^-,s) = \dfrac{1}{a_0(s)}$ (jump in derivative or jump discontinuity of $\dfrac{\partial G}{\partial t}$ at $t = s$).

Remark 1.1 Since G depends on the main part of the differential equation, but not on the source term f, once G is found we can immediately solve the more general problem for any arbitrary source term.

Example 1.1 We seek to find the *Green's* function of the following problem:

$$\frac{d^2x(t)}{dt^2} = r(t), \tag{1.6}$$

for all $t \in]0,1[$ with the two boundary conditions

$$\begin{cases} x(0) = 0 \\ x(1) = 0. \end{cases}. \tag{1.7}$$

First and foremost, we must check that the rank of

$$\Delta = \begin{vmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{vmatrix},$$

is 2. Indeed, the first and the third columns ensure that the rank equals 2. Solutions of the homogeneous differential equation

$$\frac{d^2x(t)}{\partial t^2} = 0,$$

are of the form

$$x(t) = A\,t + B,$$

where A and B are constants. The boundary conditions (1.7) give $A = 0$ and $B = 0$, which guarantees the existence of a unique *Green's function. Therefore*

1) On $]0, s[$,

$$G(t,s) = A(s)\,t + B(s),$$

and on $]s, 1[$,

$$G(t,s) = C(s)\,t + D(s).$$

2) We must have $G(0,s) = 0$, then $B(s) = 0$ and we must also have $G(1,s) = 0$ i.e.,

$$C(s) + D(s) = 0.$$

3) Since G is continuous, then

$$G\left(s^-, s\right) = \lim_{t\uparrow s} G(t,s) = \lim_{t\downarrow s} G(t,s) = G\left(s^+, s\right),$$

this implies that

$$A(s)\,s + B(s) = C(s)\,s + D(s).$$

4)

$$\frac{\partial G}{\partial t}\left(s^+, s\right) = C(s), \quad \frac{\partial G}{\partial t}\left(s^-, s\right) = A(s).$$

Consequently

$$C(s) - A(s) = 1.$$

$A(s)$, $B(s)$, $C(s)$ and $D(s)$ are solution of

$$\begin{cases} B(s) = 0 \\ C(s) + D(s) = 0 \\ s\left[A(s) - C(s)\right] + B(s) - D(s) = 0 \\ A(s) - C(s) + 1 = 0, \end{cases}$$

which gives

$$\begin{cases} A(s) = s - 1 \\ B(s) = 0 \\ C(s) = s \\ D(s) = -s. \end{cases}$$

We have the *Green*'s function:

$$G(t,s) = \begin{cases} t(s-1) & \text{if } 0 \leqslant t \leqslant s \\ s(t-1) & \text{if } s \leqslant t \leqslant 1. \end{cases}$$

Finally, the solution of the problem (1.6)-(1.7) is

$$\begin{aligned} y(t) &= \int_0^1 G(t,s)\, r(s)\, ds \\ &\quad \int_0^t t(s-1)\, r(s)\, ds + \int_t^1 s(t-1)\, r(s)\, ds. \end{aligned} \tag{1.8}$$

1.3 Iterations

Definition 1.4 The composition $x \circ y$ of the function x with the function y is

$$(x \circ y)(t) = x(y(t)),$$

where the domain of $x \circ y$ is the set of all t in the domain of y such that $y(t)$ is in the domain of x.

Definition 1.5 For $x : E \longrightarrow E$, the n^{th} iterate of function x, denoted by $x^{[n]}$ for some nonnegative integer n, is defined recursively as follows:

$$x^{[0]} = Id_E,$$

and

$$x^{[n+1]} = x \circ x^{[n]},$$

where Id_E represents the identity function on the set E.

1.4 Fixed Point Theorems

Fixed point theory provides a powerful framework for analyzing and solving various types of equations encountered across many disciplines.

Definition 1.6 [47] Let $(\mathbb{X}, \|.\|_{\mathbb{X}})$ be a normed vector space. A fixed point of a mapping $\mathcal{A} : \mathbb{X} \to \mathbb{X}$ is an element $x \in \mathbb{X}$ such that:

$$\mathcal{A}(x) = x.$$

1.4.1 Schauder Fixed Point Theorem

The Schauder fixed point theorem relies on the compactness of the operator.

Theorem 1.3 *[47] Let $\mathbb{M}$ be a non-empty, bounded, closed, and convex subset of a Banach space $(\mathbb{X}, \|.\|)$, and let $\mathcal{A} : \mathbb{M} \longrightarrow \mathbb{M}$ be a compact mapping. Then, $\mathcal{A}$ has at least one fixed point in $\mathbb{M}$.*

An alternative formulation of the Schauder fixed point theorem is as follows:

Theorem 1.4 *[47] If $\mathbb{M}$ is a non-empty, compact, convex subset of a Banach space $(\mathbb{X}, \|.\|)$ and let $\mathcal{A} : \mathbb{M} \longrightarrow \mathbb{M}$ be a continuous mapping, then $\mathcal{A}$ has a fixed point in $\mathbb{M}$.*

1.4.2 Banach Fixed Point Theorem

The Banach fixed point theorem, also known as the contraction mapping principle, is a widely used result for establishing the existence and uniqueness of solutions.

Theorem 1.5 *[47] Let $(\mathbb{X}, \|.\|_{\mathbb{X}})$ be a Banach space, and let $\mathcal{A} : \mathbb{X} \to \mathbb{X}$ be a contraction on $\mathbb{X}$. Then there exists a unique fixed point $x \in \mathbb{X}$ such that*

$$\mathcal{A}(x) = x.$$

Theorem 1.6 *If $\mathbb{M}$ is a nonempty closed subset of a Banach space $(\mathbb{X}, \|.\|_{\mathbb{X}})$ and $\mathcal{A} : \mathbb{M} \to \mathbb{M}$ is a contraction mapping on $\mathbb{M}$, i.e.,*

$$\exists C \in [0, 1[: \|\mathcal{A}x - \mathcal{A}y\|_{\mathbb{X}} \leq C \|x - y\|_{\mathbb{X}}, \ \forall x, y \in \mathbb{M},$$

then $\mathcal{A}$ has a unique fixed point $x \in \mathbb{M}$.

CHAPTER 2

Hematopoiesis and its Mathematical Models

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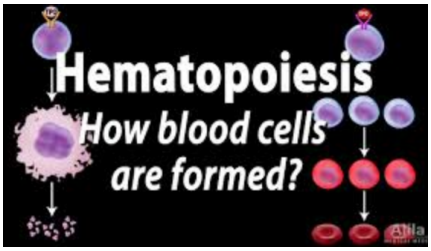
The aim of this chapter is to provide the necessary biological background for understanding human hematopoiesis and its mathematical models.

2.1 Hematopoiesis

Hematopoiesis is derived from two Greek words: Haîma which means blood and Poiēsis which means to make something. So, hematopoiesis refers to the biological process by which the body generates all of the cellular components of blood and blood plasma including red blood cells (erythrocytes), white blood cells (leukocytes), and platelets.



Every day, the human hematopoietic system produces roughly 200 billion blood cells in a hierarchical manner from a limited pool of hematopoietic stem cells (HSCs), which have the ability to both self-renew and differentiate into all types of mature blood cells. Indeed, each of these cells begins with the transformation of HSCs into cells called common myeloid progenitors (CMPs). Trilineage hematopoiesis describes the process by which the body produce 10 distinct types of cells, which can be grouped into three main categories: red blood cells, white blood cells, and platelets. Hence the building blocks of the blood are

1. **Red blood cells (RBCs):** Red blood cells, also known as erythrocytes, transport oxygen from the lungs to various organs in the body. They also help remove carbon dioxide by carrying it back to the lungs, where it is expelled through exhalation. Among all the types of blood cells, red blood cells are the most abundant.

2. **White blood cells (WBCs):** White blood cells, also known as leukocytes, help fight infections and defend the body against harmful invaders like

germs. Additionally, they destroy abnormal or damaged cells. They include various subtypes:

– Lymphocytes: Such as T cells, B cells, and natural killer cells which target viruses and tumors.

– Neutrophils: Defend against bacterial and fungal infections.

– Eosinophils: Involved in inflammation and combat certain parasites.

– Basophils: Release histamines that trigger inflammatory responses.

– Macrophages: Remove cellular debris and pathogens by engulfing and digesting them.

3. **Platelets (thrombocytes):** Crucial for blood clotting.

Remark 2.1 Neutrophils, basophils and eosinophils have similar functions and can be grouped together and called granulocytes. The other types of white blood cells are monocytes and lymphocytes.

Different Types of Blood cell Death

The death of a blood cell can take two forms: apoptosis or necrosis.

(i) Apoptosis occurs under normal physiological conditions when the cell participates in its own death like a kind of suicide. This suicide can happen at any stage of the cell's life.

(ii) The other form of cell death is necrosis. It occurs when the cell is exposed to extreme changes in physiological conditions, such as hypothermia or hypoxia (a decrease in oxygen in the tissues). Unlike apoptosis, necrosis triggers an inflammatory response.

2.2 Process of Hematopoiesis

The rate of hematopoiesis is determined according to the body's needs. New blood cells are constantly produced to replenish old ones. About 1% of the

body's blood cells are replaced daily. Red blood cells can survive for approximately 120 days, platelets survive for about five to nine days whereas white blood cells have the shortest lifespan, often living only a few hours to a few days. The process of forming blood cells involves several stages and compartments where it starts when hematopoietic stem cells (HSCs) develop into common myeloid progenitors (CMPs), which then give rise to these blood cell lineages. CMP cells change five times before finally becoming red blood cells and transform into three different cell types before becoming platelets. In addition, all leukocytes initially transform from CMP cells into to myeoblasts. After that, the process is as follows: First, before becoming a neutrophil, eosinophil, or basophil, a myeoblast goes through four further stages of development. Second, to become a macrophage, a myeoblast has to transform three more times. Finally, a second pathway of hematopoiesis produces T and B cells in which MHCs transform into cells called common lymphoid progenitors, which then become lymphoblasts. Lymphoblasts differentiate into infection-fighting T cells and B cells. Some B cells differentiate into plasma cells after exposure to infection. Generally, models that can be used to describe hematopoiesis, involves four main compartments:

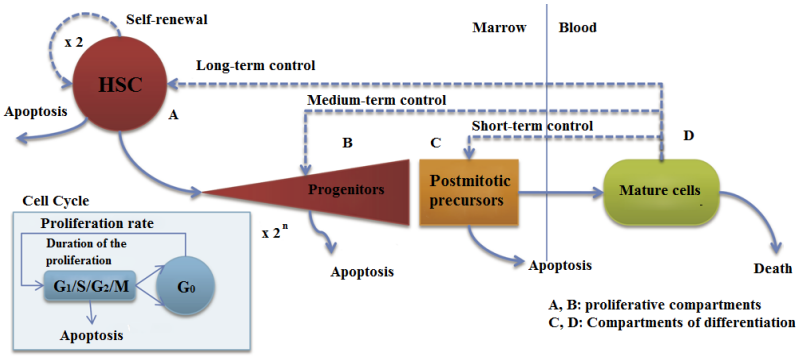
1. **Compartment A (Stem Cells)**: Pluripotent hematopoietic stem cells (HSCs) have three potential fates; they can self-renew, differentiate into progenitor cells in Compartment B, or undergo programmed cell death (apoptosis).

2. **Compartment B (Progenitor Cells)**: Progenitors may either die or differentiate into precursor cells in Compartment C. If cells do not undergo programmed cell death, their numbers is multiplied by 2^n (n divisions into 2 daughter cells). Self-renewal is also possible in this compartment.

3. **Compartment C (Precursors or Blast Cell)**: Cells in this com-

partment can no longer divide but continue their maturation. Their only fate is limited to either dying or reaching the bloodstream.

4. **Compartment D (Bloodstream or Circulating Blood)**: Cells in the bloodstream can exert regulatory feedback on earlier compartments (A, B, and C), modulating their activity over short-, medium-, or long-term time scales via control loops (depicted as dotted lines).



2.3 Common Sites of Blood Cell Production

Before Birth and Throughout Pregnancy

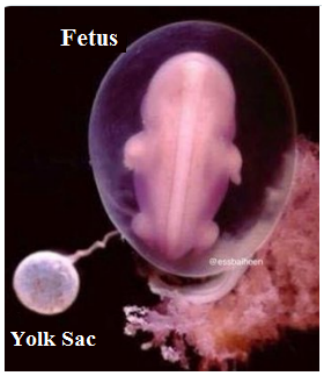
Hematopoiesis begins during the first weeks of embryonic development. It takes place in the hematopoietic system, which consists of organs and tissues like the blood islands of the yolk sac, as well as the liver and spleen during pregnancy.

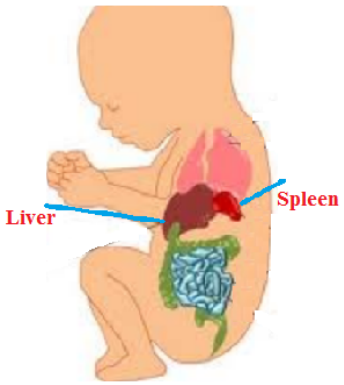
Week 3: In the yolk sac, an early form of red blood cell, less mature than those produced in adulthood, begins to develop.

Months 2 and 3: The liver and spleen become the primary sites for producing red blood cells and platelets. Meanwhile, white blood cells are formed in the liver, spleen, and thymus.

Month 5: Blood cell production shifts mainly to the bone marrow. However, the thymus, spleen, and other lymphatic tissues continue to produce

certain types of white blood cells.





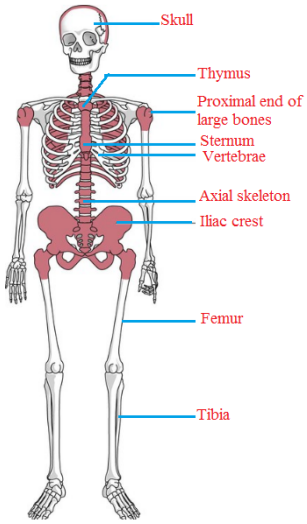
After Birth and Throughout Early Infancy

During early infancy, hematopoiesis mainly takes place in the bone marrow of long bones like the femur and tibia. Diseases can cause exceptions to the usual process. If a condition hinders the bone marrow from producing enough blood cells, hematopoiesis may revert to the sites used before birth. In such cases, blood cell production can occur in the liver, spleen, or lymph nodes.

Adulthood

Medullary hematopoiesis occurs within the bone marrow of the pelvis, skull, vertebrae, and sternum, while extramedullary hematopoiesis happens outside the bone marrow in organs such as the liver, spleen, thymus, and

lymph nodes.

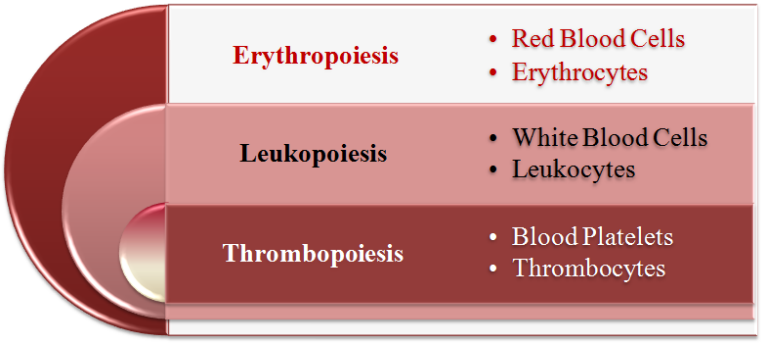


2.4 Types of Hematopoiesis

Hematopoiesis is broadly categorized into

- **Erythropoiesis**: Red blood cell production.
- **Leukopoiesis**: White blood cell production.
- **Thrombopoiesis**: Platelet production.

These processes are vital for maintaining a healthy immune system and ensuring proper oxygen transport.



2.5 Hematopoiesis Disorders

The body carefully regulates the production of blood cells to maintain proper balance. However, certain health conditions can interfere with this process, leading to an abnormal increase or decrease in blood cell counts. Such imbalances can result in various symptoms and medical issues.

2.5.1 Red Blood Cells Disorders

Many conditions can affect the production, components, and abilities of RBCs. For example, a low number of healthy RBCs is known as anemia, which can lead to fatigue or weakness due to insufficient oxygen delivery to tissues. On the other hand, an excess of red blood cells, known as erythrocytosis, can cause discomfort in mild cases, and in severe cases, can thicken the blood and raise the risk of heart attacks or strokes.

2.5.2 White Blood Cells Disorders

A reduced white blood cell count is called leukopenia, which weakens the immune system and increases the risk of infections. An elevated count, known as leukocytosis, often signals an infection but may also point to a blood disorder or cancer.

2.5.3 Platelets Disorders

Low platelet levels, or thrombocytopenia, can lead to excessive bruising and prolonged bleeding. Conversely, high platelet levels, referred to as thrombocytosis, can heighten the risk of dangerous blood clots.

2.6 Hematopoietic Growth Factors and Hormones

In healthy individuals, white and red blood cells counts can fluctuate, increasing or decreasing due to various factors. and also depending on some situations. For instance, leukocyte production increases, known as leukocytosis, quickly during infections or inflammations while leukopenia, a low white blood cell count, can signal a weakened immune system, bone marrow issues, or other underlying conditions. Furthermore, a low RBC count, known as anemia, can result from blood loss, decreased production (e.g., due to nutritional deficiencies or bone marrow disorders), or increased destruction of RBCs. Conversely, a high RBC count, or erythrocytosis, can be caused by dehydration, smoking, high altitude, certain lung or heart conditions, or conditions like polycythemia vera. For this, the production of red and white blood cells is tightly controlled by specific growth factors. A central factor in the development and renewal of hematopoietic cells is stem cell factor (SCF), which activates the c-kit receptor on hematopoietic stem cells (HSCs). SCF is vital for survival, as its absence is fatal. Several other important glycoprotein growth factors, such as interleukins IL-2, IL-3, IL-6, and IL-7, also support cell proliferation and maturation. Additionally, a group of molecules known as colony-stimulating factors (CSFs) promote the growth of specific, committed blood cell types. These include granulocyte-macrophage CSF (GM-CSF), granulocyte CSF (G-CSF), and macrophage CSF (M-CSF), which primarily encourage the development of granulocytes and act on both early progenitor cells and fully differentiated cells. Erythropoietin (EPO) is essential for guiding myeloid progenitor cells into becoming erythrocytes, while thrombopoietin (TPO) directs them to differentiate into

megakaryocytes, the cells that produce platelets.

2.7 Some Mathematical Models of Hematopoiesis

2.7.1 Malthusian Model

The familiar Malthusian Model describing the growth of a single population that predicts exponential growth ($r > 0$) or exponential decline ($r < 0$), is given by

$$\frac{dx(t)}{dt} = bx(t) - dx(t) = (b - d)\, x(t) = rx(t), \tag{2.1}$$

where $x(t)$ stands for the population size at time t, b denotes the birth rate, d denotes the death rate $r > 0$ is the intrinsic growth rate of the population.

2.7.2 Logistic Equation

Such a population growth, due to Malthus, may be valid for a short period, but it cannot go on forever. Taking into account the fact that resources are limited, Verhulst proposed the logistic equation

$$\frac{dx(t)}{dt} = rx(t)\left(1 - \frac{x(t)}{K}\right), \tag{2.2}$$

to resolve the Malthusian dilemma of unbounded growth where $K > 0$ is the carrying capacity of the environment.

2.7.3 Delayed Logistic Equation

In 1931, Volterra wrote a fundamental book on the role of hereditary effects on models for the interaction of species. This motivated Hutchinson to consider certain delays in the following equation that describes the growth of a

single population:

$$\frac{dx(t)}{dt} = r\ x\,(t)\left[1 - \frac{x(t-\tau)}{K}\right], \tag{2.3}$$

where r and K have the same meaning as in the logistic equation and τ is a positive constant that can represent fecundity rates, necessary time for the resources to recover, gestation period, maturation period,...

2.7.4 Pioneering Hematopoiesis Models

Throughout more than 60 years of the mathematical modelling of problems arising in hematology, a quite large amount of hematopoiesis models have been investigated by many authors (see [32, 38, 43, 46, 49]). They have been interested in the study of normal and malignant hematopoiesis to predict the effectiveness chemotherapy treatment, to provide assistance in developing novel therapy strategies, and to understand the process itself and the different blood diseases caused by an excess of destruction or a defect in the production of certain blood cells such as homeopathy, aplastic anemia, cyclical neutropenia, myeloproliferative neoplasms, or myeloid leukemia. The prime movers behind the research in this direction are the models of Lajtha , Oliver, Gurney, Bell, Anderson, Rubinow, Burns, and Tannock.

Lasota-Wazewska Equation

In 1976, Andrzej Lasota and his colleague Maria Wazewska-Czyzewska had published one of the most important milestones in the history of mathematical modelling of erythropoiesis (see [49]). It is an interesting paper that was aimed at modelling and getting better understanding of the survival of red

blood cells in an animal.

Maria and Andy had used the method of characteristics to drive the delay differential equation (2.4) from a time-age partial differential equation.

$$x'(t) = -ax(t) + b\exp(-\gamma x(t-\tau)), \tag{2.4}$$

where $x(t)$ stands for the density of mature red blood cells in the blood circulation at time t, $a > 0$ is the death rate of red blood cells, $\gamma > 0$, $b > 0$ are related to the production of red-blood cells per unit time, and τ denotes the time delay required to produce a mature red blood cell for release in circulating bloodstream.

Mackey-Glass Equations

In 1973 Mackey from McGill University attended the Gordon Research Conferences on Theoretical Biology and Biomathematics at Proctor Academy in New Hampshire where he met Leon Glass from the University of Chicago who had carried out some unpublished simulations in which time delays were inserted into ordinary differential equation models of negative feedback sys-

tems.

They had also met Sol Rubinow who had been very encouraging of their ideas to look at cyclical blood disease, and respiratory control with respect to Cheyne-Stokes respiration.

In the late fall of 1975, Leon moved to McGill, where they started discussions, and then a collaboration focussed on induced periodic dynamics in physiological systems, and if they might be playing a role in some of the complex rhythms observed in pathophysiological situations.

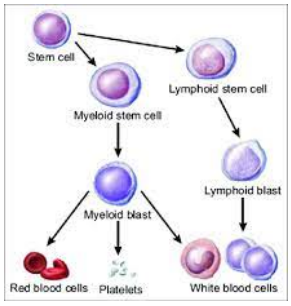
Based on the cell-cycle model of Burns and Tannock [10] and aimed to understand the regulation of blood cell production and hence the periodic leukemia and the aplastic anemia, Mackey and Glass were working with the following pioneering delay differential equations [38]:

$$x'(t) = -ax(t) + \frac{b\,x(t-\tau)}{1+x^n(t-\tau)}, \tag{2.5}$$

and

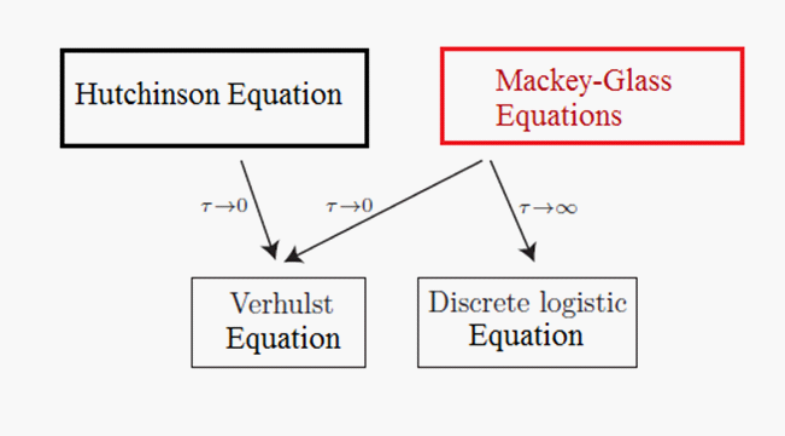
$$x'(t) = -ax(t) + \frac{b}{1+x(t-\tau)}, \tag{2.6}$$

where $x(t)$ stands for the density of mature leukocytes over time in equation (2.5) and mature erythrocytes in equation (2.6), a is the death rate, b is the maximal production rate, and τ denotes the time delay needed to produce mature blood cells in the bone marrow.



Model (2.6) was shown, by numerical simulation, to have a regime with a stable equilibrium point, and an oscillatory regime at larger values of the delay that were related to periodic hematological diseases, specifically to cyclical neutropenia and to one particular clinical presentation of chronic

granulocytic leukemia[1]. [45].



The aforementioned article which was written in three pages, was not detailed enough. For this, Mackey and Glass published in 1979 an another paper to offer a detailed study of these hematopoiesis models and other dynamical disorders including cardiac arrhythmias, psychological disorders, and cancer, among others. They published also a Book entitled " From Clocks to Chaos [20], to shed light on the importance of concept of a dynamical disease.

Derivation of the Model Equation

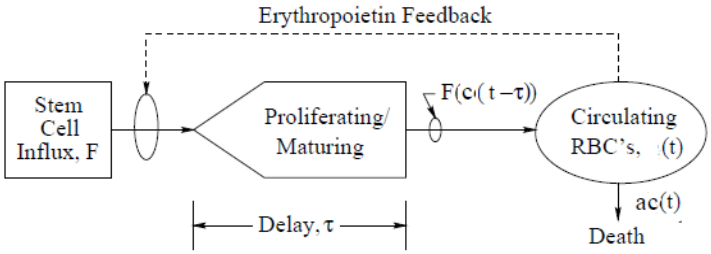
To formulate the sequence of physiological processes in a the mathematical model of hematopoiesis, we will make the following notations:

- Let $c(t)$ be the concentration of cells (the population species) in the circulating blood and let us assume that the cells are lost at a rate proportional to their concentration, say, $ac(t)$ where a is the loss rate of red blood cells in the circulation.

[1] chronic granulocytic leukemia is an indolent (slow-growing) cancer in which too many myeloblasts are found in the blood and bone marrow.

- Since the reduction in cells in the blood stream needs about a 6 days delay before the marrow releases further cells to replenish the deficiency, we assume that the flux of cells into the blood stream depends on the cell concentration at an earlier time, $c(t-\tau)$ where τ is the time required to pass through recognizable precursors.

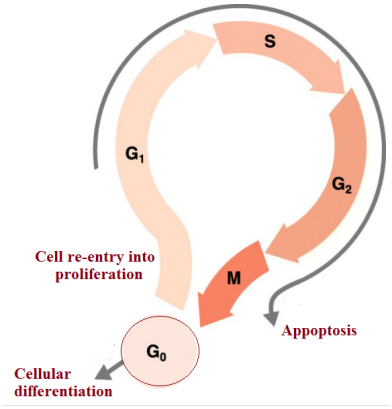
- F stands for the cell influx from erythroid colony forming units, under erythropoietin control.



Using these notations, we can write a balance equation stating that the rate of change of erythrocyte number is a balance between their production and their destruction

$$\frac{dc(t)}{dt} = \text{production} - \text{destruction} = F(c(t-\tau)) - ac(t) \qquad (2.7)$$

The changes that occur at time t were actually initiated at a time $t-\tau$ in the past. The next step in the construction of the model is to define some appropriate form for the production function F. In vivo measurements of erythrocyte production rates F in humans indicate that the feedback function saturates at low erythrocyte numbers and is a decreasing function of increasing red blood cell levels (i.e., negative feedback).



A convenient function that captures this behaviour, and which has sufficient flexibility to be able to fit the data, as well as easily handled analytic properties, is given as follows:

$$\frac{dc\left(t\right)}{dt}=\overbrace{F_0\,\frac{\theta^n}{\theta^n+c^n\left(t-\tau\right)}}^{F(x(t-\tau))}-ac\left(t\right), \tag{2.8}$$

where F_0 is the maximal red blood cell production rate that the body can approach at very low circulating red blood cell numbers. Furthermore, $n>0$ is a positive exponent, and $\theta>0$ is a shape parameter(adjusted to fit the experimental data). Let $x\left(t\right)=\theta c\left(t\right)$, we get

$$\frac{dx\left(t\right)}{dt}=-ax\left(t\right)+\frac{b}{1+x\left(t-\tau\right)},$$

with an initial condition in the form of a function defined for a period of time equal to the duration of the time delay.

2.7.5 Long-Term Impact

In the early 1980s, Loeffler and Wichmann [37] also proposed a model of hematopoietic stem cell dynamics that differed from Mackey's one. They

considered a complete model of hematopoiesis, including a stem cell compartment, a progenitor compartment, and a mature cell compartment.

The aforementioned models, which initially proposed to describe the dynamics of hematopoietic stem cells, had very significant influence. Since then, there have been innumerable contributions trying to unravel and understand the hematopoiesis and its mechanisms. For this, we find in the literature a great diversity of models such as structured models, models for proliferation-quiescence, space competition models, stochastic models, and compartment models.

In 1989, Kulenovic et al. [33] studied the following generalized Wazewska-Lasota model:

$$x'(t) = -ax(t) + \sum_{i=1}^{m} b_i e^{-\gamma x(t-\tau_i)}, \ t \geq 0, \ m \geq 1. \tag{2.9}$$

In 2005, the authors of [34] used the continuation theorem of Gaines and Mawhin to investigate the below Lasota-Wazewska model with time-varying parameters and delay:

$$x'(t) = -a(t)x(t) + b(t)e^{-\gamma(t)x(t-\tau(t))}. \tag{2.10}$$

In 2006, by means of the fixed point theory, the authors of [36] derived the existence and global attractivity of the unique positive periodic solution of the following Lasota-Wazewska model with time-varying parameters and several variable delays:

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} b_i(t)e^{-\gamma_i(t)x(t-\tau_i(t))}. \tag{2.11}$$

In 2006, the authors of [18] investigated a delay Lasota-Wazewska model with a discontinuous harvesting term of the form

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} b_i(t)e^{-\gamma_i(t)x(t-\tau_i(t))} - q(t)H(t), \tag{2.12}$$

where H is a discontinuous function.

In 2007, Liu and his co-authors [35] used fixed point theorem in cone for establishing suitable conditions that guarantee the existence, uniqueness and global attractivity of positive periodic solution for the following erythropoiesis model:

$$x'(t) = -a(t)\,x(t) + \sum_{i=1}^{n} \frac{p_i(t)}{1 + x^m(t - \tau_i(t))}. \tag{2.13}$$

In 2007, the authors investigated the existence of positive periodic solutions of the following Mackey-Glass model with periodic parameters and a time varying delay:

$$x'(t) = -a(t)\,x(t) + \frac{b(t)\,x(t - \tau(t))}{1 + x^n(t - \tau(t))}. \tag{2.14}$$

In 2010, by employing the fixed point theorem in cone, the authors of [48] and [50] discussed the existence, non existence and uniqueness of positive almost periodic solutions for the above equation.

The existence of positive almost periodic solutions of the below first-order differential equation with multiple time-varying delays.

$$x'(t) = -a(t)\,x(t) + \sum_{i=1}^{N} \frac{b_i(t)\,x^m(t - \tau_i(t))}{1 + x^n(t - \tau_i(t))}, \tag{2.15}$$

has also been considered by many investigators.

CHAPTER 3

Existence, Uniqueness, and Stability of Solutions for an Iterative Human Erythropoiesis Model

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3.6 Examples 49

In this chapter, our main objective is to establish some criteria under which solutions of the studied equation exist and they are unique and continuously dependent on parameters.

3.1 The Studied Equation

The study of human erythropoiesis models was initiated in 1978 by Mackey and Glass. Currently the literature of this model and its modifications is extensive, for instance

In [35], Liu et al. employed a fixed point theorem in cone for proving the existence, uniqueness and global attractivity of positive periodic solutions for the following erythropoiesis model:

$$x'(t) = -a(t)\,x(t) + \sum_{i=1}^{n} \frac{p_i(t)}{1 + x^m(t - \tau_i(t))}.$$

In [19], Faria and Oliveira discussed the global asymptotic stability of the following periodic erythropoiesis model with multiple time-dependent delays:

$$\begin{cases} x'(t) = -a(t)\,x(t) + \sum_{i=1}^{n} \dfrac{p_i(t)}{1 + x^m(t - \tau_i(t))}, & 0 \le t \ne t_k, \\ x\left(t_k^+\right) - x(t_k) = b_k x(t_k), & k \in \mathbb{N}, \end{cases}$$

where $m \in \mathbb{N}$, $n \in (0, \infty)$, $(t_k)_{k\in\mathbb{N}}$ and $(b_k)_{k\in\mathbb{N}}$ are $T-$periodic real sequences and $a, p_i : \mathbb{R} \to [0, \infty)$ are continuous and $T-$periodic, for $i = \overline{1, m}$.

In [5], Bouakkaz used the Schauder fixed point theorem and the Green's method to establish the existence of positive periodic solutions for the following erythropoiesis model:

$$x'(t) = -a(t)\,x(t) + \sum_{i=1}^{n} \frac{p(t)}{1 + x^{[i]}(t)},$$

where $x^{[1]}(t) = x(t)$, $x^{[2]}(t) = x(x(t))$, $x^{[3]}(t) = x(x(x(t)))$ with $x^{[n]}(t)$ refers to the composition of the function $x(t)$ with itself n times.

In this chapter, we study the following first order delay differential equation with iterative terms which describes the production of red blood cells in human:

$$x'(t) = -a(t)\,x(t) + \frac{b(t)}{1 + x^{[2]}(t)} - h\left(t, x(t - \tau(t)), x^{[2]}(t)\right). \tag{3.1}$$

Here, $x^{[2]}(t)$ denotes the second iterate of $x(t)$, and the functions a, b, and $\tau \in \mathcal{C}(\mathbb{R}, (0, +\infty))$ are T-periodic. The function $h \in \mathcal{C}(\mathbb{R}^3, (0, +\infty))$ is also a T-periodic function in its first argument and satisfies the Lipschitz condition with respect to its second and third arguments. To be more precise, there exist positive constants ρ_0, ρ_1 such that

$$|h(t, x_1, x_2) - h(t, z_1, z_2)| \leq \rho_0 |x_1 - z_1| + \rho_1 |x_2 - z_2| . \tag{3.2}$$

In biological terms

- $x(t)$ represents the density of mature red blood cells in blood circulation at time t.
- $a(t)\, x(t)$ denotes the death term.
- $a(t)$ describes the rate of lost cells from the circulation.
- $\dfrac{b(t)}{1 + x^{[2]}(t)}$ is the production term.
- $b(t)$ is the production rate of mature red blood cells.
- $\tau(t)$ denotes a harvesting time-lag.
- h stands for the harvesting function which is a common procedure for controlling diseases whether by the blood specimen collection, stem cells collection, wet cupping therapy or even by blood donation.
- $x^{[2]}(t)$ arises from a delay of the form $\tau_0(t, x(t))$ that describes the cell cycle duration.

This dependence on the density of mature red blood cells results from the fact that some growth factors and hormones play a crucial role in regulating red blood cell production. Specifically, the hormone erythropoietin (EPO),

primarily produced by the kidneys, is a key regulator of red blood cell formation. EPO stimulates the bone marrow to produce more red blood cells when the body needs them, such as in response to low oxygen levels (hypoxia) or bleeding. Although, EPO is the main regulator, other factors and hormones like insulin-like growth factor-1 (IGF-I) can also influence red blood cell production, especially in specific contexts like development or disease.

This chapter is devoted to discuss the existence, uniqueness, and continuous dependence on parameters of positive periodic solutions for equation (3.1) by means of the Banach and Schauder fixed point theorems together with the Green's functions method. Finally, two examples are provided to show the efficiency and validity of the main results.

3.2 Preliminaries

We construct an appropriate Banach space along with a suitable subset of it to apply the chosen fixed point theorems on one hand and to ensure that the iterates are well-defined as well as they fulfill some mathematical and biological facts on the other. Let $d_1 \geq 0$ and $T, d_2, d_3 > 0$. Define the set

$$\Omega = \{x \in \mathbb{X},\ d_1 \leq x(t) \leq d_2,\ \ |x(t_2) - x(t_1)| \leq d_3 |t_2 - t_1|,\ \forall t_1, t_2 \in \mathbb{R}\},$$

as a closed, convex, and bounded subset of the following Banach space (which consists of all continuous, T-periodic functions):

$$\mathbb{X} = \{x \in \mathcal{C}(\mathbb{R}, \mathbb{R}),\ x(t+T) = x(t),\ \forall t \in \mathbb{R}\},$$

equipped with the supremum norm

$$\|x\| = \sup_{t \in \mathbb{R}} |x(t)| = \sup_{t \in [0,T]} |x(t)|.$$

Remark 3.1 The set Ω is compact. This follows from the fact that, the condition $d_1 \leq x(t) \leq d_2$ guarantees that Ω is uniformly bounded whereas the inequality $|x(t_2) - x(t_1)| \leq d_3 |t_2 - t_1|$, for all $t_1, t_2 \in \mathbb{R}$ ensures that Ω is equicontinuous. Therefore, by the Arzelà–Ascoli theorem, the closed set Ω is compact.

To simplify the study, we will use the following notations:

$$\delta = \sup_{t\in[0,T]} a(t), \ \lambda_1 = \inf_{t\in[0,T]} b(t), \ \lambda_2 = \sup_{t\in[0,T]} b(t),$$
$$\rho_2 = \sup_{t\in[0,T]} h(t,0,0), \ \Lambda = (\rho_0 + \rho_1(1+d_3))\, d_2 + \rho_2,$$
$$\ell_1 = \frac{Tm_2\lambda_2}{1+d_1}, \ \ell_2 = T\left(\frac{m_1\lambda_1}{1+d_2} - m_2\Lambda\right),$$
$$\ell_3 = m_2(2+T\delta)\left(\frac{\lambda_2}{1+d_1} + \Lambda\right),$$
$$\beta = Tm_2\left(\frac{\lambda_2(1+d_3)}{(1+d_1)^2} + \rho_0 + \rho_1(1+d_3)\right),$$
$$m_1 = \frac{\exp\left(-\int_0^T a(v)\,dv\right)}{\exp\left(\int_0^T a(v)\,dv\right) - 1}, m_2 = \frac{\exp\left(\int_0^T a(v)\,dv\right)}{\exp\left(\int_0^T a(v)\,dv\right) - 1}.$$

Lemma 3.1 *[52] We have*

$$\Omega = \{x \in \mathbb{X}, \ d_1 \leq x(t) \leq d_2, \ |x(t_2) - x(t_1)| \leq d_3 |t_2 - t_1|, \ \forall t_1, t_2 \in [0,T]\}.$$

Additionally, for any $x_1, x_2 \in \Omega$, the following inequality:

$$\left\| x_1^{[2]} - x_2^{[2]} \right\| \leq (1+d_3)\|x_1 - x_2\|,$$

holds.

Remark 3.2 Based on the Lipschitz condition (3.2) and the result established in Lemma 3.1, we infer that

$$\left|h\left(t, x(t), x^{[2]}(t)\right)\right| \leq \Lambda. \tag{3.3}$$

Indeed, we have

$$\begin{aligned}\left|h\left(t,x\left(t\right),x^{[2]}\left(t\right)\right)\right| &= \left|h\left(t,x\left(t\right),x^{[2]}\left(t\right)\right)-h\left(t,0,0\right)+h\left(t,0,0\right)\right| \\ &\leq \left|h\left(t,x\left(t\right),x^{[2]}\left(t\right)\right)-h\left(t,0,0\right)\right|+\left|h\left(t,0,0\right)\right| \\ &\leq \left(\rho_0+\rho_1\left(1+d_3\right)\right)d_2+\sup_{t\in[0,T]}h\left(t,0,0\right) \\ &= \Lambda.\end{aligned}$$

3.3 Conversion of the Equation (3.1) into an Integral Equation

In this section, we show that equation (3.1) with the periodic boundary conditions is equivalent to a Fredholm integral equation with a Green's kernel.

Lemma 3.2 *$x\in\Omega\cap C^1\left(\mathbb{R},\mathbb{R}\right)$ is a solution of equation (3.1) if and only if $x\in\Omega$ is a solution of the following integral equation:*

$$x\left(t\right)=\int_t^{t+T}G\left(t,s\right)\left(\frac{b\left(s\right)}{1+x^{[2]}\left(s\right)}-h\left(s,x\left(s-\tau\left(s\right)\right),x^{[2]}\left(s\right)\right)\right)ds, \quad (3.4)$$

where the kernel $G\left(t,s\right)$ is given by

$$G\left(t,s\right)=\frac{\exp\left(\int_t^s a\left(v\right)dv\right)}{\exp\left(\int_0^T a\left(v\right)dv\right)-1}. \quad (3.5)$$

Proof. Assume that $x\in\Omega\cap\mathcal{C}^1\left(\mathbb{R},\mathbb{R}\right)$ is a solution of equation (3.1). Multiplying both sides of the last equation by $\exp\left(\int_0^t a\left(v\right)dv\right)$, we obtain

$$\begin{aligned}&\left(x'\left(t\right)+a\left(t\right)x\left(t\right)\right)\exp\left(\int_0^t a\left(v\right)dv\right) \\ &=\left(\frac{b\left(t\right)}{1+x^{[2]}\left(t\right)}-h\left(t,x\left(t-\tau\left(t\right)\right),x^{[2]}\left(t\right)\right)\right)\exp\left(\int_0^t a\left(v\right)dv\right).\end{aligned}$$

The integration of both sides of the last equation from t to $t+T$ gives

$$\int_t^{t+T} \left(x'(s) + a(s)\,x(s)\right) \exp\left(\int_0^s a(v)\,dv\right) ds$$
$$= \int_t^{t+T} \left(\frac{b(s)}{1+x^{[2]}(s)} - h\left(s, x(s-\tau(s)), x^{[2]}(s)\right)\right) \exp\left(\int_0^s a(v)\,dv\right) ds.$$

In view of the periodicity of x, the left-hand side of the above equation becomes

$$x(t)\left(\exp\left(\int_0^{t+T} a(v)\,dv\right) - \exp\left(\int_0^t a(v)\,dv\right)\right),$$

which can be rewritten as

$$\exp\left(\int_0^t a(v)\,dv\right)\left(\exp\left(\int_t^{t+T} a(v)\,dv\right) - 1\right) x(t).$$

This leads to

$$x(t) = \int_t^{t+T} \left(\frac{b(s)}{1+x^{[2]}(s)} - h\left(s, x(s-\tau(s)), x^{[2]}(s)\right)\right) \times \frac{\exp\left(\int_0^s a(v)\,dv\right)}{\exp\left(\int_0^t a(v)\,dv\right)\left(\exp\left(\int_t^{t+T} a(v)\,dv\right) - 1\right)} ds,$$

where

$$\frac{\exp\left(\int_0^s a(v)\,dv\right)}{\exp\left(\int_0^t a(v)\,dv\right)\left(\exp\left(\int_t^{t+T} a(v)\,dv\right) - 1\right)} = \frac{\exp\left(\int_0^s a(v)\,dv\right)\exp\left(-\int_0^t a(v)\,dv\right)}{\exp\left(\int_0^T a(v)\,dv\right) - 1}$$
$$= \frac{\exp\left(\int_t^s a(v)\,dv\right)}{\exp\left(\int_0^T a(v)\,dv\right) - 1}$$
$$= G(t,s).$$

Therefore

$$x(t) = \int_t^{t+T} \left(\frac{b(s)}{1+x^{[2]}(s)} - h\left(s, x(s-\tau(s)), x^{[2]}(s)\right)\right) G(t,s)\,ds.$$

Conversely, if $x \in \Omega$ satisfies the integral equation (3.4), then the differentiation of each side with respect to t shows that $x \in \Omega \cap \mathcal{C}^1(\mathbb{R},\mathbb{R})$ and satisfies the original differential equation (3.1). ■

3.3.1 Certain Properties of the Obtained Green's Function

1) The obtained *Green*'s function is sandwiched between two constants as follows:

$$0 < m_1 \leq G(t,s) \leq m_2. \tag{3.6}$$

2) By applying the mean value theorem, we obtain the following estimate:

$$\int_{t_1}^{t_1+T} |G(t_2,s) - G(t_1,s)|\, ds \leq T\delta m_2 |t_2 - t_1|, \tag{3.7}$$

for $t_1, t_2 \in [0,T]$.

3.3.2 The Integral Operator

We will now convert equation (3.1) with the periodic boundary conditions into a fixed point problem. For this end, we introduce an integral operator A: $\Omega \to \mathbb{X}$ defined by

$$(\mathcal{A}x)(t) = \int_t^{t+T} G(t,s)\left(\frac{b(s)}{1+x^{[2]}(s)} - h\left(s, x(s-\tau(s)), x^{[2]}(s)\right)\right) ds. \tag{3.8}$$

According to Lemma 3.2, the fixed points of the operator $\mathcal{A}$ correspond exactly to the solutions of equation (3.1), and the converse also holds true.

3.4 Existence Results

In this section, we apply the Schauder fixed point theorem and we use certain properties of the obtained Green's function to prove the existence of positive and periodic solutions for equation (3.1). We now present and prove the following lemmas, which are crucial for establishing the existence of solutions.

Lemma 3.3 *The operator $\mathcal{A}: \Omega \to \mathbb{X}$ is well defined and continuous.*

Proof. First, it is not hard to prove that the operator $\mathcal{A} : \Omega \to \mathbb{X}$ is well defined. Indeed, this is due to the periodicity of x which gives $(\mathcal{A}x)(t) \in \mathbb{X}$ for any $x \in \Omega$. Next, we will prove the continuity of $\mathcal{A}$. So, for any $x_1, x_2 \in \Omega$, we get

$$\begin{aligned}
|(\mathcal{A}x_2)(t) - (\mathcal{A}x_1)(t)| \leq & \int_t^{t+T} G(t,s)\, b(s) \left| \frac{1}{1+x_2^{[2]}(s)} - \frac{1}{1+x_1^{[2]}(s)} \right| ds \\
& + \int_t^{t+T} G(t,s) \Big| h\left(s, x_2(s-\tau(s)), x_2^{[2]}(s)\right) \\
& - h\left(s, x_1(s-\tau(s)), x_1^{[2]}(s)\right) \Big| ds \\
\leq & \int_t^{t+T} G(t,s)\, b(s) \frac{\left| x_2^{[2]}(s) - x_1^{[2]}(s) \right|}{\left(1+x_2^{[2]}(s)\right)\left(1+x_1^{[2]}(s)\right)} ds \\
& + \int_t^{t+T} G(t,s) \Big| h\left(s, x_2(s-\tau(s)), x_2^{[2]}(s)\right) \\
& - h\left(s, x_1(s-\tau(s)), x_1^{[2]}(s)\right) \Big| ds.
\end{aligned}$$

Using (3.2), (3.6), and Lemma 3.1, we derive the below estimate.

$$\begin{aligned}
|(\mathcal{A}x_2)(t) - (\mathcal{A}x_1)(t)| \leq & \, T m_2 \lambda_2 \frac{(1+d_3)}{(1+d_1)^2} \|x_2 - x_1\| \\
& + T m_2 \left(\rho_0 + \rho_1 (1+d_3)\right) \|x_2 - x_1\|,
\end{aligned}$$

which can be written as follows:

$$\begin{aligned}
|(\mathcal{A}x_2)(t) - (\mathcal{A}x_1)(t)| &\leq T m_2 \left(\frac{\lambda_2 (1+d_3)}{(1+d_1)^2} + \rho_0 + \rho_1 (1+d_3) \right) \|x_2 - x_1\| \\
&= \beta \|x_2 - x_1\|.
\end{aligned}$$

This shows that $\mathcal{A}$ is Lipschitz continuous, which in turn guarantees its continuity. ■

Lemma 3.4 *If $\ell_1 \leq d_2$, $\ell_2 \geq d_1$, and condition (3.2) is satisfied, then for every $x \in \Omega$, the following inequality holds:*

$$d_1 \leq (\mathcal{A}x)(t) \leq d_2. \tag{3.9}$$

Proof. Let $x \in \Omega$, so we have

$$\begin{aligned}(\mathcal{A}x)(t) &= \int_t^{t+T} G(t,s)\left\{\frac{b(s)}{1+x^{[2]}(s)} - h\left(s, x(s-\tau(s)), x^{[2]}(s)\right)\right\} ds \\ &\leq \int_t^{t+T} G(t,s)\frac{b(s)}{1+x^{[2]}(s)} ds.\end{aligned}$$

By using the Green's property (3.6) and the assumption $\ell_1 \leq d_2$, we arrive at

$$(\mathcal{A}x)(t) \leq Tm_2\frac{\lambda_2}{1+d_1} = \ell_1 \leq d_2,$$

Similarly, by applying the Green's property (3.6) again as well as the condition $\ell_2 \geq d_1$, we obtain

$$(\mathcal{A}x)(t) \geq T\left(\frac{m_1\lambda_1}{1+d_2} - m_2\Lambda\right) = \ell_2 \geq d_1.$$

Hence, for all $x \in \Omega$, it follows that

$$d_1 \leq (\mathcal{A}x)(t) \leq d_2.$$

This completes the proof. ■

Lemma 3.5 *If $\ell_3 \leq d_3$, and condition (3.2) is satisfied, then for any $x \in \Omega$ and $t_1, t_2 \in \mathbb{R}$, the following inequality:*

$$|(\mathcal{A}x)(t_2) - (\mathcal{A}x)(t_1)| \leq d_3|t_2 - t_1|, \tag{3.10}$$

holds.

Proof. Let $t_1, t_2 \in [0, T]$. We have

$$\begin{aligned}
|(\mathcal{A}x)(t_2) - (\mathcal{A}x)(t_1)| \leq & \int_{t_2}^{t_1} \frac{b(s)}{1 + x^{[2]}(s)} G(t_2, s)\, ds \\
& + \int_{t_1}^{t_1+T} \frac{b(s)}{1 + x^{[2]}(s)} |G(t_2, s) - G(t_1, s)|\, ds \\
& + \int_{t_1+T}^{t_2+T} \frac{b(s)}{1 + x^{[2]}(s)} G(t_2, s)\, ds \\
& + \int_{t_2}^{t_1} h\left(s, x(s - \tau(s)), x^{[2]}(s)\right) G(t_2, s)\, ds \\
& + \int_{t_1}^{t_1+T} h\left(s, x(s - \tau(s)), x^{[2]}(s)\right) |G(t_2, s) - G(t_1, s)|\, ds \\
& + \int_{t_1+T}^{t_2+T} h\left(s, x(s - \tau(s)), x^{[2]}(s)\right) G(t_2, s)\, ds.
\end{aligned}$$

From (3.3), (3.6), and (3.7), we get

$$\begin{aligned}
|(\mathcal{A}x)(t_2) - (\mathcal{A}x)(t_1)| \leq & \frac{2m_2\lambda_2}{1 + d_1} |t_2 - t_1| + \frac{\lambda_2}{1 + d_1} T\delta m_2 |t_2 - t_1| \\
& + 2m_2\Lambda |t_2 - t_1| + \Lambda T\delta m_2 |t_2 - t_1|.
\end{aligned}$$

Thus

$$\begin{aligned}
|(\mathcal{A}x)(t_2) - (\mathcal{A}x)(t_1)| &\leq \left(\frac{m_2\lambda_2}{1 + d_1} (2 + T\delta) + m_2\Lambda (2 + T\delta) \right) |t_2 - t_1| \\
&= \ell_3 |t_2 - t_1|.
\end{aligned}$$

Since $\ell_3 \leq d_3$, Lemma 3.1 implies that

$$|(\mathcal{A}x)(t_2) - (\mathcal{A}x)(t_1)| \leq d_3 |t_2 - t_1|,$$

for any $x \in \Omega$ and $t_1, t_2 \in \mathbb{R}$. ■

Corollary 3.1 *If $\ell_1 \leq d_2$, $\ell_2 \geq d_1$, $\ell_3 \leq d_3$, and condition (3.2) is satisfied, then the operator $\mathcal{A}$ maps Ω into itself.*

Proof. From Lemmas 3.4 and 3.5, it follows that $(\mathcal{A}x) \in \Omega$ for every $x \in \Omega$. Therefore, the operator $\mathcal{A}$ maps Ω into itself. ■

Now, based on the previously stated lemmas, we present the first existence theorem along with its proof.

Theorem 3.1 *If $\ell_1 \leq d_2$, $\ell_2 \geq d_1$, $\ell_3 \leq d_3$, and condition (3.2) is satisfied, then equation (3.1) admits at least one positive periodic solution within the set Ω.*

Proof. According to Lemma 3.3, $\mathcal{A}$ is well defined and continuous. In addition, Corollary 3.1 guarantees that the operator $\mathcal{A}$ maps the compact and convex subset Ω into itself. Therefore, all the conditions of the Schauder fixed point theorem are fulfilled. As a result, $\mathcal{A}$ has at least one fixed point in Ω, i.e. there exists at least $x \in \Omega$ such that $\mathcal{A}x = x$. By virtue of Lemma 3.2, equation (3.1) admits at least one positive periodic solution in Ω. ■

3.5 Existence, Uniqueness, and Stability Results

3.5.1 Existence and Uniqueness Result

We will establish the existence of a unique positive periodic solution by using the Banach fixed point theorem.

Theorem 3.2 *Suppose assumptions stated in Theorem 3.1 are fulfilled, If we also suppose that $\beta < 1$, then equation (3.1) admits a unique positive periodic solution $x \in \Omega$.*

Proof. By pursuing the same steps as in the proof of Lemma 3.3, we get

$$\|\mathcal{A}x_1 - \mathcal{A}x_2\| \leq \beta \|x_1 - x_2\|.$$

Because $\beta < 1$, the operator $\mathcal{A}$ is a contraction. Therefore, by the Banach fixed point theorem, $\mathcal{A}$ has a unique fixed point, which is exactly the unique positive periodic solution of equation (3.1). ■

3.5.2 Continuous Dependence on Parameters Result

Now, we will demonstrate that the unique solution of equation (3.1) continuously depends on the harvesting function h, the production rate b, and the mortality rate a. This means that for the aforementioned parameters, there is one and only one solution, and that solution changes smoothly as the parameters are varied. In other words, small changes in the parameters lead to small changes in the solution which allows us to make reliable predictions based on the model.

Theorem 3.3 *Assuming the conditions of Theorem 3.2 hold, then the unique solution of equation (3.1) depends continuously on parameters a, b, and h.*

Proof. On one hand, let x be a solution of equation (3.1), so it must satisfy the corresponding integral equation (3.4), that is

$$x(t) = \int_t^{t+T} G(t,s) \left\{ \frac{b(s)}{1 + x^{[2]}(s)} - h\left(s, x(s - \tau(s)), x^{[2]}(s)\right) \right\} ds.$$

On the other hand, we consider $\widetilde{x}$ as a solution of the perturbed equation with small perturbations in the parameters h, b and a. Furthermore, if we assume that all conditions of Theorem 3.2 are satisfied, then $\widetilde{x}$ satisfies the following perturbed integral equation:

$$\widetilde{x}(t) = \int_t^{t+T} \widetilde{G}(t,s) \left\{ \frac{\widetilde{b}(s)}{1 + \widetilde{x}^{[2]}(s)} - \widetilde{h}\left(s, \widetilde{x}(s - \tau(s)), \widetilde{x}^{[2]}(s)\right) \right\} ds,$$

where $\widetilde{h}$, $\widetilde{b}$, $\widetilde{a}$ are the perturbed functions, and

$$\widetilde{G}(t,s) = \frac{\exp\left(\int_t^s \widetilde{a}(v)\, dv\right)}{\exp\left(\int_0^T \widetilde{a}(v)\, dv\right) - 1}.$$

Now, we estimate the absolute value of the difference between $x(t)$ and $\widetilde{x}(t)$

$$
\begin{aligned}
&|\widetilde{x}(t)-x(t)| \\
&\leq \int_t^{t+T} \widetilde{G}(t,s)\left|\frac{\widetilde{b}(s)}{1+\widetilde{x}^{[2]}(s)}-\frac{b(s)}{1+x^{[2]}(s)}\right| ds+\int_t^{t+T}\frac{b(s)}{1+x^{[2]}(s)}\left|\widetilde{G}(t,s)-G(t,s)\right| ds \\
&+\int_t^{t+T}\widetilde{G}(t,s)\left|\widetilde{h}\left(s,\widetilde{x}(s-\tau(s)),\widetilde{x}^{[2]}(s)\right)-h\left(s,x(s-\tau(s)),x^{[2]}(s)\right)\right| ds \\
&+\int_t^{t+T} h\left(s,x(s-\tau(s)),x^{[2]}(s)\right)\left|\widetilde{G}(t,s)-G(t,s)\right| ds.
\end{aligned}
$$

This implies that

$$
\begin{aligned}
|\widetilde{x}(t)-x(t)| \leq & \int_t^{t+T} G(t,s)\left|\widetilde{b}(s)-b(s)\right| ds+\int_t^{t+T} G(t,s)\left|\widetilde{b}(s)x^{[2]}(s)-b(s)\widetilde{x}^{[2]}(s)\right| ds \\
&+\int_t^{t+T} b(s)\left|\widetilde{G}(t,s)-G(t,s)\right| ds \\
&+\int_t^{t+T}\widetilde{G}(t,s)\left|\widetilde{h}\left(s,\widetilde{x}(s-\tau(s)),\widetilde{x}^{[2]}(s)\right)-h\left(s,x(s-\tau(s)),x^{[2]}(s)\right)\right| ds \\
&+\int_t^{t+T} h\left(s,x(s-\tau(s)),x^{[2]}(s)\right)\left|\widetilde{G}(t,s)-G(t,s)\right| ds.
\end{aligned}
$$

From Lemma 3.1, we have the following estimate:

$$
\left|\widetilde{b}(s)x^{[2]}(s)-b(s)\widetilde{x}^{[2]}(s)\right| \leq \left\|\widetilde{b}\right\|(1+d_3)\|\widetilde{x}-x\|+d_2\left\|\widetilde{b}-b\right\|. \tag{3.11}
$$

The application of the Mean Value Theorem gives

$$
\int_t^{t+T}\left|\widetilde{G}(t,s)-G(t,s)\right| ds \leq \sigma\|\widetilde{a}-a\|, \tag{3.12}
$$

where

$$
\sigma=\left(\frac{T^2\exp\left(T\max\left\{\|a\|,\|\widetilde{a}\|\right\}\right)}{\exp\left(\int_0^T\widetilde{a}(v)\,dv\right)-1}\right)\left(1+\frac{\exp\left(T\|a\|\right)}{\exp\left(\int_0^T a(v)\,dv\right)-1}\right).
$$

Condition (3.2) leads to

$$
\begin{aligned}
&\left|\widetilde{h}\left(s,\widetilde{x}(s-\tau(s)),\widetilde{x}^{[2]}(s)\right)-h\left(s,x(s-\tau(s)),x^{[2]}(s)\right)\right| \\
\leq\ & (\rho_0+\rho_1(1+d_3))\|\widetilde{x}-x\|+\left\|\widetilde{h}-h\right\|.
\end{aligned} \tag{3.13}
$$

By taking into account inequalities (3.3), (3.6), (3.11),(3.12), and (3.13), we infer that

$$\begin{aligned}|\widetilde{x}(t)-x(t)| \leq\ & Tm_2(1+d_2)\left\|\widetilde{b}-b\right\| \\ & + Tm_2\left\|\widetilde{h}-h\right\| + \sigma(\|b\|+\Lambda)\|\widetilde{a}-a\| \\ & + Tm_2\left((1+d_3)\left(\left\|\widetilde{b}\right\|+\rho_1\right)+\rho_0\right)\|\widetilde{x}-x\|.\end{aligned}$$

Thus,

$$\begin{aligned}&\|\widetilde{x}-x\|\left(1-Tm_2\left((1+d_3)\left(\left\|\widetilde{b}\right\|+\rho_1\right)+\rho_0\right)\right) \\ &\leq Tm_2(1+d_2)\left\|\widetilde{b}-b\right\| + Tm_2\left\|\widetilde{h}-h\right\| + \sigma(\|b\|+\Lambda)\|\widetilde{a}-a\|.\end{aligned}$$

Finally, we conclude that

$$\begin{aligned}\|\widetilde{x}-x\| \leq\ & \frac{Tm_2(1+d_2)}{1-\beta}\left\|\widetilde{b}-b\right\| \\ & + \frac{Tm_2}{1-\beta}\left\|\widetilde{h}-h\right\| \\ & + \frac{\sigma(\|b_1\|+\Lambda)}{1-\beta}\|\widetilde{a}-a\|.\end{aligned}$$

The proof is completed. ■

3.6 Examples

Here we provide two illustrative examples to demonstrate the accuracy of the conditions of the theoretical findings.

Example 3.1 Consider the following first order delay differential equation

with iterative terms (a revisited Erythropoiesis model):

$$\begin{aligned} x'(t) &= -\left(0.005+0.001\sin^2\frac{2\pi}{15}t\right)x(t)+\frac{\left(0.006+0.0001\sin^4\frac{2\pi}{15}t\right)}{1+x^{[2]}(t)} \\ &\quad -\left(\frac{1}{111\pi^{19}}+\frac{x(t-\tau(t))}{113\pi^{19}(1+x(t-\tau(t)))}+\frac{z^{[2]}(t)}{115\pi^{19}(1+z^{[2]}(t))}\right), \end{aligned} \tag{3.14}$$

within the compact, convex set

$$\Omega_1=\left\{x\in\mathbb{X},\ \frac{1}{2}\le x(t)\le 0.78,\ \ |x(t_2)-x(t_1)|\le\frac{11}{100}|t_2-t_1|,\forall t_1,t_2\in\mathbb{R}\right\}.$$

The parameter values are given by

$$T=15 \text{ days},\ \delta=0.006,\ \lambda_2=0.0061,\ \lambda_1=0.006,\ \rho_2=\frac{1}{111\pi^{19}},\ \rho_1=\frac{1}{113\pi^{19}},$$
$$\rho_0=\frac{1}{115\pi^{19}},\ m_2\approx 12.628,\ m_1\approx 10.707,\ \Lambda\approx 8.4016\times 10^{-12}.$$

The solution bounds are estimated as follows:

$$\begin{aligned} \ell_1\approx 0.77031 &\le d_2=0.78, \\ \ell_2\approx 0.54137 &\ge d_1=\frac{1}{2}, \\ \ell_3\approx 0.10733 &\le d_3=\frac{11}{100}. \end{aligned}$$

Additionally, we find that

$$\beta\approx 0.57003<1.$$

Hence, all the hypotheses of Theorem 3.2 are satisfied which imply that equation (3.14) admits a unique, positive periodic solution in Ω_1. Moreover, this solution depends continuously on a, b, and h.

Example 3.2 Let us consider equation (3.14) with the same period $T = 15$ days, but within a new subset

$$\Omega_2 = \left\{ x \in \mathbb{X},\ 0.05 \leq x\left(t\right) \leq 1.2,\ \ \left|x(t_2) - x(t_1)\right| \leq \frac{4}{25}\left|t_2 - t_1\right|, \forall t_1, t_2 \in \mathbb{R} \right\},$$

where $\Lambda \approx 1.1378 \times 10^{-11}$. The estimated bounds of the solutions are

$$\begin{aligned} \ell_1 &\approx 1.1004 \leq d_2 = 1.2, \\ \ell_2 &\approx 0.43801 \geq d_1 = 0.05, \\ \ell_3 &\approx 0.15333 \leq d_3 = \frac{4}{25}. \end{aligned}$$

However, the value of β is approximately

$$\beta \approx 1.2157 > 1.$$

This means that the additional condition of Theorem 3.2 is not satisfied. Nevertheless, all conditions of Theorem 3.1 are met. Therefore, equation (3.14) admits at least one positive periodic solution in Ω_2, but this solution is not necessarily unique.

General conclusion and perspectives

The study of Erythropoiesis models has received a significant amount of attention in the last six decades, highlighting its importance in gaining insights into the process of the production of erythrocytes, the homeopathic treatments, as well as various medical conditions and diseases.

This thesis presents a study of an erythropoiesis model that incorporates an iterative production term, as well as a delayed and iterative harvesting term. The method employed herein is a hybrid technique that combines the fixed point theory and the Green's functions method. We summarize the main steps of this technique as follows: Firstly, an appropriate Banach space and a closed convex and bounded subset of it, were constructed to ensure specific biological and mathematical facts and also to help easily apply the chosen fixed point theorems. Secondly, the proposed periodic boundary value problem was then converted into an equivalent Fredholm integral equation with a Green's kernel. Thirdly, some sufficient conditions for the existence of at least one positive periodic solution were established using the Schauder fixed point theorem and certain useful properties of the obtained Green's function. Fourthly, the existence, uniqueness and continuous dependence on parameters of positive periodic solutions were demonstrated with the help

of the Banach fixed point theorem. Finally, two examples are carried out to support the theoretical findings.

Here are some potential directions for further research on erythropoiesis models.

- The technique used here can also be employed in studying other erythropoiesis models such as structured models, models for proliferation-quiescence, space competition models, stochastic models, compartment models,...

- Numerical simulation of this kind of equations help to visualize their dynamics and refine theoretical outcomes.

- Studying the existence of almost-periodic, pseudo-almost-periodic, or anti-periodic solutions of such problems seems to be of significant importance.

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