الجمهورية الجزائرية الديمقراطية الشعبية
PEOPLE'S DEMOCRATIC REPUBLIC OF ALGERIA
وزارة التعليم العالي والبحث العلمي
MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH

20 août 1955 University – Skikda
Faculty of Sciences
Department of Mathematics

جامعة 20 أوت 1955 - سكيكدة
كلية العلوم
قسم الرياضيات

Master's Thesis

Field : Mathematics and Computer Science
Program : Mathematics
Option : Applied Functional Analysis

Subject

Positive Periodic Solutions for an Iterative Model of Erythropoiesis in Animals

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Publicly defended on: 01/07/2025

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Academic Year: 2024/2025

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Abstract

Positive Periodic Solutions for an Iterative Model of Erythropoiesis in Animals

The primary aim of this work is to study the existence, uniqueness, and continuous dependence on parameters of positive periodic solutions for a first-order delay differential equation with an iterative term, describing the dynamics of red blood cell populations in animals. Using the Krasnoselskii fixed point theorem combined with the Green's functions method, we prove the existence of at least one positive periodic solution for the given equation. Furthermore, by virtue of the Banach fixed point theorem, we also investigate the existence and the continuous dependence on parameters of the unique positive periodic solution.

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

Abstract in French

Solutions périodiques positives d'un modèle d'érythropoïèse itératif chez les animaux

L'objectif principal de ce travail est d'étudier l'existence, l'unicité et la dépendance continue aux paramètres de solutions périodiques positives pour une équation différentielle à retard du premier ordre avec un terme itératif, décrivant la dynamique des populations de globules rouges chez l'animal. En utilisant le théorème du point fixe de Krasnoselskii combiné avec la méthode des fonctions de Green, nous prouvons l'existence d'au moins une solution périodique positive pour l'équation donnée. De plus, grâce au théorème du point fixe de Banach, nous étudions également l'existence et la dépendance continue aux paramètres de l'unique solution périodique positive.

Mots clés. Dépendance continue aux paramètres, équation différentielle à retard, érythropoïèse, existence, théorème du point fixe, fonction de Green, équation différentielle itérative, unicité.

Abstract in Arabic

الحلول الدورية الموجبة لنموذج تكون كريات الدم الحمراء التكراري لدى الحيوانات

الهدف الرئيسي لهذا العمل هو دراسة الوجود، الوحدانية والاعتماد المستمر على المعلمات للحلول الدورية الموجبة لمعادلة تفاضلية تأخيرية من الدرجة الأولى ذات حد تكراري تصف ديناميكيات مجتمعات من خلايا الدم الحمراء لدى الحيوانات. باستخدام نظرية النقطة الثابتة لكراسنوسلسكي وطريقة دوال غرين، أثبتنا وجود حل دوري موجب واحد على الأقل للمعادلة المطروحة. علاوة على ذلك، وبفضل نظرية النقطة الثابتة لباناخ، درسنا الوجود والاعتماد المستمر على المعلمات للحل الدوري الموجب الوحيد.

كلمات مفتاحيه. الاعتماد المستمر على المعلمات، معادلة تفاضلية تأخيرية، عملية تكون كريات الدم الحمراء، الوجود، نظرية النقطة الثابتة، دالة غرين، معادلة تفاضلية تكرارية، الوحدانية.

Dedication

To those whose prayers lit my path through the darkness of fatigue,

To those who carried me on wings of love from the very beginning...

To my father **SALEH**, my first support and teacher in patience and dignity,

And to my mother **HAFIDA**, the wellspring of tenderness and the source of strength, who taught me that nothing is impossible with faith and prayer.

And to my beloved brothers **wail** and **Ayoub**, my pillars in every moment, and my pride and joy

To my dear sisters **Maissa** and **Souzane**, the flowers of our home and my companions in this journey,

To my kind grandmother, whose prayers wrapped me in protection,

And to my aunts **Samira** and **Fatima** who showered me with love and support at every turn.

And to every teacher and professor who once looked at me with eyes of encouragement — from the early days of primary school to the gates of university...

To all of you, I dedicate this work — the fruit of years of effort, sleepless nights, and a heart driven by unstoppable ambition.

Acknowledgements

First and foremost, I would like to express my deepest gratitude to **God Almighty**, the Merciful and Powerful, who supported me during the darkest moments of my academic journey. At a time when I was about to give up on my studies — and on everything — it was through prayer and faith that I found the strength to rise again, stronger than ever.

My sincere thanks go to my supervisor *Dr. Ahleme Boukkaz*, who stood by my side with calm and kindness throughout this journey. Her moral support and constant encouragement were of great value to me.

My gratitude extends to the members of the jury, for the honor of accepting to evaluate and discuss my work.

I would also like to express my heartfelt appreciation to *Pr. Rabah khemis*, for his valuable help, patience, and the outstanding quality of his guidance.

I would also like to warmly thank the Head of the Mathematics Department, *Dr. Fatah Sassi*, at the **University of August 20, 1955-Skikda,** for his support and for ensuring favorable conditions throughout our academic path.

Thank you all...

Acronyms

Abbreviation	**Meaning**
ODE	Ordinary differential equation
PDE	Partia ldifferential equation
DDE	Delay differential equation
FDE	Functional differential equation
IDE	Iterative differential equation
RBC	Red blood cell
WBC	White blood cell
HSC	Hematopoietic stem cell
HGF	Hematopoietic growth factor
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
PMNs	Polymorphonuclear leukocytes
TPO	Thrombopoietin
EPO	Erythropoietin
NK	Natural killer cells
CSFs	Colony-stimulating factors

Abbreviation	Meaning
IL-3, IL-5,...	Interleukins which are a group of signaling proteins (cytokines)
LT	Long-term
ST	Short-term
SCF	Stem cell factor
DNA	Deoxyribonucleic Acid

List of symbols

Sets and numbers

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

$\mathbb{R}_+^* = (0, +\infty)$: 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 closed interval of numbers between a and b, including a and b

(a, b) : an open interval

$[a, b)$: the left-closed, right-open interval

$[a, +\infty)$: left-closed and right–unbounded interval

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

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

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

$\overline{\mathbb{M}}$: the closure of the set $\mathbb{M}$

τ : a delay

T : a period

Functions

$|\cdot|$: the absolute value

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

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

Id : the identity function

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

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

$\lim_{t\longrightarrow t_0} x(t)$: the limit of the function $x(t)$ as t approaches t_0

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

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

sup : the supremum

inf : the infimum

exp : the exponential function

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

Other notations will be clarified upon their initial occurrence.

General Introduction

During the past six decades of the mathematical modelling of hematopoiesis, a substantial number of hematopoiesis models have been developed to take deep dives into the blood cell dynamics and to unveil the ambiguities surrounding hematological disorders. The first chapter of the history of such models begun in the late 1970s with the pioneering works of Lasota, Wazewska, Mackey, and Glass. In 1976 and based on experimental findings, Andrzej Lasota and Maria Wasewska [32] proposed a pioneering model for describing the survival of red blood cells (RBCs) in an animal. To be more precise, the basic model is a delay differential equation (DDE) resulting from a partial differential equation (PDE) by using the method of characteristics. It includes terms for cell death and cell production, often with time delays representing the maturation time of cells. It was the following delay differential equation which was considered as one of the major turning points in the history of modelling hematopoiesis:

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

where $x(t)$ denotes the density of mature red blood cells in the bloodstream at time t, the recruitment function is defined by a Ricker function, $a > 0$ is

the rate of red blood cell death, $b > 0$ is the production rate of red-blood cells, refers to the maximum density of red blood cells that the body can produce, and τ is a positive constant stands for the time it takes for a new red blood cell to be produced. It's worth mentioning here that his model was introduced originally in the context of human erythropoiesis, but was based on experimental data obtained from rats. In essence, the Lasota-Wazewska model provides a framework for understanding how red blood cell populations are maintained and how they respond to changes in the body's environment or internal processes. This model has attracted the attention of many researchers during the last sixty years (see for example [14], [23], [24], [25] and references therein). Using variable coefficients in the Lasota-Ważewska model makes it more realistic and adaptable to real-world situations. By allowing parameters to change over time, the model can capture the complexities of how RBC populations respond to various influences and feedback loops in the body. This can lead to a better understanding of how diseases, environmental changes, or medical treatments affect RBC levels and potentially help in developing more effective treatments.

Iterative differential equations (IDEs) are often challenging to study. Although there are numerous methods for dealing with functional differential equations (FDEs), these techniques frequently fall short when it comes to investigating those with iterative terms. The key task of this work is to study a first order delay differential equation with an iterative term that describes the production and destruction of red blood cells (RBCs) in animals. The primary motivation behind this work is to address the following fundamental research questions:

(i) What are the conditions under which at least one positive periodic solution exists?

(ii) Does the proposed equation have a unique solution?

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

The technique used here lies in transforming the equation at hand into a fixed point problem by pursuing many steps. We first construct an appropriate Banach space and a suitable subset of it that lay the path for employing the chosen fixed point theorems and guarantee some mathematical and biological facts. We next transform the proposed problem into an equivalent integral equation whose kernel is a Green's function. Then, under some suitable criteria, the Schauder and Banach fixed point theorems, the Arzelà–Ascoli theorem, and certain properties of the Green's kernel help efficiently prove the existence, uniqueness, and continuous dependence on parameters of positive periodic solutions.

The current manuscript is planned as follows. In the first chapter, we briefly introduce some basic mathematical concepts and results that are required to grasp the main outcomes including Banach spaces, convex subsets, some topological notions in normed spaces, Banach and Schauder's fixed point theorems, and Green's functions for boundary value problems. The second chapter is dedicated to present the biological background of the topic as well as the pioneering mathematical models in this direction. In the third chapter which is the core of the thesis, we present findings published in [17]. We use the Banach and Schauder fixed point theorems together with sone useful properties of a Green's function to discuss the existence, uniqueness, and stability of positive periodic solutions of the following first-order delay functional differential equation with an iterative term:

$$x'(t) = -a(t)\,x(t) + b(t)\,e^{-\gamma x^{[2]}(t)} - h(t, x(t-\tau)),$$

where $a, b \in C([0,T],(0,+\infty))$, $h \in C([0,T]\times\mathbb{R},(0,+\infty))$ are T-periodic

functions with respect to the time variable t, γ is a positive constant, $x^{[2]}(t)$ is the second iterate of $x(t)$, h is the harvesting term and $\tau > 0$ is a harvest lag. Moreover, we provide three illustrative examples that support the theoretical outcomes.

CHAPTER 1

Preliminary Concepts

Contents

In this chapter, we introduce some notations, definitions and preliminary results that are used in the remainder of the thesis.

1.1 Banach Spaces

Definition 1.1 Let $\mathbb{B}$ be a vector space over a field $\mathbb{F}$. $\mathbb{B}$ is called a Banach space if every Cauchy sequence in $\mathbb{B}$ converges.

Example 1.1 For $T > 0$, the space of all $T-$periodic and continuous functions

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

endowed with the supremum norm

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

is a Banach space.

1.2 Convex Subsets in Vector Spaces

Definition 1.2 Let $\mathbb{B}$ be a vector space over a field $\mathbb{F}$ and let $\mathbb{M}$ be a subset of $\mathbb{B}$. $\mathbb{M}$ is considered convex if for any two points within the set $\mathbb{M}$, the straight line segment connecting those points lies entirely within $\mathbb{M}$. i.e., $\forall$ $x, y \in \mathbb{M}$, $\forall \lambda \in [0,1]$

$$\lambda x + (1-\lambda) y \in \mathbb{M}.$$

Example 1.2 For $T, \ell_1, \ell_2, \ell_3 > 0$, the set

$$\Omega = \{x \in \mathbb{X},\ 0 < \ell_1 \leq x(t) \leq \ell_2,\ \ |x(t_2) - x(t_1)| \leq \ell_3 |t_2 - t_1|,\ \forall t_1, t_2 \in \mathbb{R}\},$$

is a convex set of the Banach space $\mathbb{X}$ defined in Example 1.1. Indeed, let $\lambda \in [0,1]$ and $x_1, x_2 \in \Omega$. It is obvious that $\lambda x_1(t) + (1-\lambda) x_2(t) \in \mathbb{X}$. On one hand

$$\lambda \ell_1 \leq \lambda x_1(t) \leq \lambda \ell_2,$$

and

$$(1-\lambda)\,\ell_1 \leq (1-\lambda)\,x_2(t) \leq (1-\lambda)\,\ell_2.$$

So

$$\lambda\ell_1 + (1-\lambda)\,\ell_1 \leq \lambda x_1(t) + (1-\lambda)\,x_2(t) \leq \lambda\ell_2 + (1-\lambda)\,\ell_2.$$

Then

$$\ell_1 < \lambda x_1(t) + (1-\lambda)\,x_2(t) \leq \ell_2.$$

On the other hand

$$\begin{aligned}
&|(\lambda x_1 + (1-\lambda)\,x_2)(t_2) - (\lambda x_1 + (1-\lambda)\,x_2)(t_1)| \\
&= |\lambda\,(x_1(t_2) - x_1(t_1)) + (1-\lambda)\,(x_2(t_2) - x_2(t_1))| \\
&\leq \lambda\,|x_1(t_2) - x_1(t_1)| + (1-\lambda)\,|x_2(t_2) - x_2(t_1)| \\
&\leq \lambda\ell_3\,|t_2 - t_1| + (1-\lambda)\,\ell_3\,|t_2 - t_1| \\
&= \ell_3\,|t_2 - t_1|\,,
\end{aligned}$$

which proves that $\lambda x_1(t) + (1-\lambda)\,x_2(t) \in \Omega$ and hence Ω is convexe.

1.3 Topological Notions in Normed Spaces

Let $(\mathbb{B}, \|.\|_{\mathbb{B}})$ be a normed vector space over a field $\mathbb{F}$.

1.3.1 Bounded, Closed, and Compact Sets

Definition 1.3 A subset $\mathbb{M} \subset \mathbb{B}$ is said to be bounded if there exists a constant $C > 0$ such that

$$\|x\|_{\mathbb{B}} \leq C,\ \forall x \in \mathbb{M}.$$

Similarly, a sequence $(x_n)_{n\in\mathbb{N}}$ is called bounded if

$$\sup_{n\in\mathbb{N}} x_n < \infty.$$

Example 1.3 The subset Ω defined in Example 1.2 is bounded. Indeed,

$$\|x\| = \sup_{t\in[0,T]} |x(t)| \leq \ell_2, \ \forall x \in \Omega.$$

So Ω is bounded.

Theorem 1.1 *A set $\mathbb{M} \subseteq \mathbb{B}$ is closed if and only if for all sequences $(x_n)_{n\in\mathbb{N}} \subseteq \mathbb{M}$ which are convergent such that $x_n \to x$ in $\mathbb{M}$, then the limit x must be in $\mathbb{M}$.*

Example 1.4 The subset Ω defined in Example 1.2 is closed. Indeed, if $(x_n)_{n\in\mathbb{N}} \subset \Omega$ is a convergent sequence such that $x_n \longrightarrow x$, then

$$\ell_1 \leq \lim_{n\to\infty} x_n \leq \ell_2,$$

which implies that

$$\ell_1 \leq x \leq \ell_2.$$

Furthermore

$$\begin{aligned} |x(t_2) - x(t_1)| &= |x(t_2) - x_n(t_2) + x_n(t_2) - x_n(t_1) + x_n(t_1) - x(t_1)| \\ &\leq |x(t_2) - x_n(t_2)| + |x_n(t_2) - x_n(t_1)| + |x_n(t_1) - x(t_1)|. \end{aligned}$$

As n approaches infinity, then

$$\begin{aligned} |x(t_2) - x(t_1)| &\leq |x_n(t_2) - x_n(t_1)| \\ &\leq \ell_3 |t_2 - t_1|. \end{aligned}$$

So $x \in \Omega$ and hence Ω is closed.

Definition 1.4 (Sequential compactness) A set $\mathbb{M} \subseteq \mathbb{B}$ is called compact if every sequence in $\mathbb{M}$ has a convergent subsequence that converges to a point within $\mathbb{M}$ itself, i.e., for all sequences $(x_n)_{n\in\mathbb{N}}$ in $\mathbb{M}$ there exists a convergent subsequence $(x_{n_k})_{k\in\mathbb{N}}$ such that $\lim_{k\to\infty} x_{n_k} \in \mathbb{M}$.

Definition 1.5 The closure of a set $\mathbb{M} \subset \mathbb{B}$ (denoted by $\overline{\mathbb{M}}$) is the smallest closed set that contains the original set $\mathbb{M}$. It is $\mathbb{M}$ plus all its limit points (or accumulation points). In other words, it is the intersection of all closed supersets of $\mathbb{M}$, i.e.,

$$\overline{\mathbb{M}} = \bigcap_{F \subset \mathbb{M},\ F \text{ closed}} F.$$

Theorem 1.2 *Let $\mathbb{M} \subset \mathbb{B}$. Then $x \in \overline{\mathbb{M}}$ if and only if there exists a sequence $(x_n)_{n \in \mathbb{N}}$ in $\mathbb{M}$ such that $x_n \longrightarrow x$ in $\mathbb{B}$.*

Definition 1.6 A set $\mathbb{M} \subseteq \mathbb{B}$ is called relatively compact if its closure $\overline{\mathbb{M}}$ is compact.

Corollary 1.1 *A set $\mathbb{M} \subseteq \mathbb{B}$ is relatively compact if and only if every sequence in $\mathbb{M}$ has a subsequence that converges to a point in $\mathbb{B}$.*

1.3.2 Arzelà-Ascoli Theorem

The Arzelà-Ascoli theorem is a foundational result that gives necessary and sufficient conditions for a family of continuous functions defined on a closed and bounded interval to be relatively compact.

Theorem 1.3 *[8] Let $-\infty < a < b < +\infty$ and let $\mathcal{F} \subset \mathcal{C}\left(\left([a,b], \mathbb{R}\right)\right)$ such that*

1. $\mathcal{F}$ is uniformly bounded. Equivalently, there exists $M > 0$ such that

$$|f(x)| \leq M,\ \forall x \in [a,b],\ f \in \mathcal{F}.$$

2. $\mathcal{F}$ is equicontinuous. Equivalently, for each $\varepsilon > 0$, there is a $\delta > 0$ (which depends only on ε) such that for x, $y \in [a,b]$ such that

$$|x - y| < \delta \Longrightarrow |f(x) - f(y)| \leq \varepsilon,\ \forall f \in \mathcal{F}.$$

Then $\mathcal{F}$ is a relatively compact subset of $\mathcal{C}([a,b])$.

Example 1.5 The subset Ω defined in Example 1.2 is compact. Indeed, it follows form Example 1.3 that Ω is uniformly bounded and from the condition

$$|x(t_2) - x(t_1)| \leq \ell_3 |t_2 - t_1|, \ \forall t_1, t_2 \in [0, T],$$

Ω is equicontinuous. So, all conditions of the Arzelà-Ascoli theorem are satisfied which proves that Ω is a relatively compact subset of $\mathbb{X}$. Since Ω is closed, we deduce that it is compact.

1.3.3 Continuous and Compact Operators

Let $(\mathbb{B}, \|.\|_{\mathbb{B}})$ and $(\mathbb{Y}, \|.\|_{\mathbb{Y}})$ be two normed vector spaces over $\mathbb{F}$.

Definition 1.7 An operator $\mathcal{S} : \mathbb{B} \longrightarrow \mathbb{Y}$ is called continuous at $x_0 \in \mathbb{B}$ if

$$\lim_{x \longrightarrow x_0} \mathcal{S}x = \mathcal{S}x_0,$$

which is equivalent to

$$\forall \varepsilon > 0, \ \exists \delta > 0, \ \forall x \in \mathbb{B}, \ \ (\|x - x_0\|_{\mathbb{B}} < \delta) \Longrightarrow (\|\mathcal{S}x - \mathcal{S}x_0\|_{\mathbb{Y}} < \varepsilon).$$

The operator $\mathcal{S}$ is called continuous on $\mathbb{B}$, or simply continuous, if it is continuous at every point within $\mathbb{B}$. This means that

$$\forall \varepsilon > 0, \ \forall x \in \mathbb{B}, \ \exists \delta > 0, \ \forall y \in \mathbb{B}, \ \ (\|x - y\|_{\mathbb{B}} < \delta) \Longrightarrow (\|\mathcal{S}x - \mathcal{S}y\|_{\mathbb{Y}} < \varepsilon).$$

As we will see in the following theorem, compactness is preserved under continuous maps.

Theorem 1.4 *Let $(\mathbb{B}, \|.\|_{\mathbb{B}})$ and $(\mathbb{Y}, \|.\|_{\mathbb{Y}})$ be two normed vector spaces over the same field $\mathbb{F}$, $\mathbb{M} \subseteq \mathbb{B}$ is compact, and $\mathcal{S} : \mathbb{B} \longrightarrow \mathbb{Y}$ is continuous, then the image of $\mathbb{M}$ under $\mathcal{S}$, i.e., the set*

$$\mathcal{S}(\mathbb{M}) = \{\mathcal{S}x, \ x \in \mathbb{M}\},$$

is compact.

Definition 1.8 A map $\mathcal{S} : \mathbb{B} \longrightarrow \mathbb{Y}$ is called *Lipschitz continuous* if there is a positive constant C such that

$$\forall x, y \in \mathbb{B} : \|\mathcal{S}x - \mathcal{S}y\|_{\mathbb{Y}} \leq C \|x - y\|_{\mathbb{B}} .$$

If $C \in [0, 1[$, $\mathcal{S}$ is called a contraction mapping.

Remark 1.1 If $\mathcal{S} : \mathbb{B} \longrightarrow \mathbb{Y}$ then

$\mathcal{S}$ is a contraction $\Longrightarrow$ $\mathcal{S}$ is Lipschitz continuous $\Longrightarrow$ $\mathcal{S}$ is continuous on $\mathbb{B}$.

Theorem 1.5 *A continuous function on a closed bounded interval is bounded and attains its bounds.*

Remark 1.2 The above theorem is hidden in the proof of many theorems and lemmas in the rest of this thesis where we integrate a continuous function over a compact interval.

Definition 1.9 A map $\mathcal{S} : \mathbb{B} \longrightarrow \mathbb{Y}$ is said to be compact if and only if $\mathcal{S}$ maps bounded sets into relatively compact sets, i.e.,

$$[\mathcal{S} \text{ compact}] \Longleftrightarrow \left[\forall M \subset E, \ \ (M \text{ bounded}) \Longrightarrow \left(\overline{\mathcal{S}(M)} \text{ compact}\right)\right] .$$

Equivalently, $\mathcal{S}$ is compact if and only if for every bounded sequence $(x_n)_{n\in\mathbb{N}}$ in $\mathbb{B}$, the sequence $(\mathcal{S}x_n)_{n\in\mathbb{N}}$ has a convergent subsequence in $\mathbb{Y}$.

1.3.4 Iterations

Definition 1.10 The composition $x \circ y$ of the function x with the function y is

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

The domain of $x \circ y$ is a subset of the domain of y, consisting of those t for which $y(t)$ is in the domain of x.

Definition 1.11 Let E be a set and $x : E \longrightarrow E$ be a function, the n^{th} iterate of the function x, which is denoted by $x^{[n]}$ for some nonnegative integer n, is defined recursively by

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

$$x^{[1]} = x,$$

and

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

where Id_E is the identity function on E.

Lemma 1.1 *Let Ω be the set defined in Example 1.2. If $x, y \in \Omega$, then*

$$\left\|x^{[k]} - y^{[k]}\right\| \leq \sum_{j=0}^{k-1} \ell_3^j \|x - y\|, \quad k = 1, 2, ...$$

where $x^{[k]} = x \circ x \circ ... \circ x$ (k times).

Proof. We will prove this inequality by induction. So, the proof will now proceed in two steps:

The basis step: For $k = 1$, we have

$$\|x - y\| \leq \|x - y\|,$$

then, the inequality holds for $k = 1$

The inductive step: Now, we assume that the inequality holds for a given $k = m$ and we want to show that it also holds for $k = m + 1$. Suppose that

$$\left\|x^{[m]} - y^{[m]}\right\| \leq \sum_{j=0}^{m-1} \ell_3^j \|x - y\|,$$

then

$$\begin{aligned} \left|x^{[m+1]}(t) - y^{[m+1]}(t)\right| &\leq \left|x\left(x^{[m]}(t)\right) - x\left(y^{[m]}(t)\right)\right| + \left|x\left(y^{[m]}(t)\right) - y\left(y^{[m]}(t)\right)\right| \\ &\leq \ell_3 \left|x^{[m]}(t) - y^{[m]}(t)\right| + \left|x\left(y^{[m]}(t)\right) - y\left(y^{[m]}(t)\right)\right|, \end{aligned}$$

so

$$\begin{aligned}\left\|x^{[m+1]}-y^{[m+1]}\right\| &\leq \ell_3\left\|x^{[m]}-y^{[m]}\right\|+\|x-y\| \\ &\leq \ell_3\sum_{j=0}^{m-1}\ell_3^j\|x-y\|+\|x-y\| \\ &\leq \left(\sum_{j=0}^{m-1}\ell_3^{j+1}+1\right)\|x-y\| \\ &\leq \sum_{j=0}^{m}\ell_3^j\|x-y\|\,.\end{aligned}$$

By induction we deduce that

$$\left\|x^{[m]}-y^{[m]}\right\|\leq\sum_{j=0}^{m-1}\ell_3^j\|x-y\| \qquad \forall m\in\mathbb{N}\,,$$

which finishes the proof. ■

Corollary 1.2 *It follows from Lemma 1.1 that*

$$\left\|x^{[2]}-y^{[2]}\right\|\leq(1+\ell_3)\|x-y\|\,,$$

for all $x,y\in\Omega$.

1.4 Fixed Point Theorems

Fixed-point theorems offer a strong pillar for dealing with linear and nonlinear problems that arise in many fields like physics, engineering, economics, and life sciences.

Definition 1.12 [31] Let $(\mathbb{B},\|.\|_{\mathbb{B}})$ be a normed vector space over a field $\mathbb{F}$. A fixed point of a mapping $\mathcal{S}:\mathbb{B}\to\mathbb{B}$ is an $x\in\mathbb{B}$ which is mapped onto itself, that is

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

1.4.1 Banach Fixed Point Theorem

One of the very helpful tools which is broadly applicable in proving the existence and uniqueness of solutions, is the well-known Banach fixed point theorem (also known as the contraction mapping theorem or contractive mapping theorem).

Theorem 1.6 *[31] Let $(\mathbb{B}, \|.\|_{\mathbb{B}})$ be a Banach space and let $\mathcal{S} : \mathbb{B} \to \mathbb{B}$ be a contraction on $\mathbb{B}$. Then $\mathcal{S}$ has a unique fixed point $x \in \mathbb{B}$ such that*

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

Theorem 1.7 *[31] If $\mathbb{M}$ is a closed subset of a Banach space $\mathbb{B}$ and $\mathcal{S} : \mathbb{M} \to \mathbb{M}$ is a contraction, then $\mathcal{S}$ has a unique fixed point in $\mathbb{M}$.*

1.4.2 Krasnoselskii Fixed Point Theorem

Theorem 1.8 *(Krasnoselskii's fixed point theorem) [31] Let $\mathbb{M}$ be a nonempty, closed, and convex subset of a Banach space $(\mathbb{B}, \|.\|)$. Suppose that A and B map $\mathbb{M}$ into $\mathbb{B}$ such that*

(i) For all $x, y \in \mathbb{M}$, $A_1 x + A_2 y \in \mathbb{M}$,

(ii) The mapping A_1 is continuous and compact,

(iii) The mapping A_2 is a contraction with constant $\alpha < 1$.

Then there is a $z \in \mathbb{M}$ such that $A_1 z + A_2 z = z$.

1.5 Green's Function

The importance of the Green's functions in mathematics lies mainly in solving certain types of non-homogeneous boundary value problems. There are many

books and papers where the reader can consult the basic theory of Green's functions. In this section we shall follow the exposition in [9].

1.5.1 Green's Functions for a Bboundary Value Problem

We will consider two-point nth-order linear boundary value problems of the form

$$\begin{cases} L_n x(t) = \sigma(t), \ t \in I \equiv [a,b], \\ U_i(x) = \gamma_i, \ i = \overline{1,m}, \end{cases} \tag{1.1}$$

where

$$L_n x(t) = a_0(t) x^{(n)}(t) + a_1(t) x^{(n-1)}(t) + ... + a_{n-1}(t) x'(t) + a_n(t) x(t),$$

and

$$U_i(x) = \sum_{j=0}^{n-1} \left(\alpha_j^i x^{(j)}(a) + \beta_j^i x^{(j)}(b) \right), \ i = \overline{1,m}, \ m \leq n,$$

where α_j^i, β_j^i and ξ_i are real constants for all $i = \overline{1,m}$ and $j = \overline{0,n-1}$, σ and a_k are continuous real functions for all $k = \overline{0,n}$, and $a_0(t) \neq 0$ for all $t \in I$.

Theorem 1.9 *[9] The problem*

$$\begin{cases} L_n x(t) = 0, \ t \in I \equiv [a,b], \\ U_i(x) = \gamma_i, \ i = \overline{1,n}, \end{cases} \tag{1.2}$$

(where the number n of boundary conditions equals the order of the linear equation) has a unique solution if and only if the associated homogeneous problem

$$\begin{cases} L_n x(t) = 0, \ t \in I \equiv [a,b], \\ U_i(x) = 0, \ i = \overline{1,n}, \end{cases}$$

has only the trivial solution.

Definition 1.13 [9] We say that G is a Green's function for problem (1.1) if it satisfies the following properties:

(**G1**) G is defined on the square $I \times I$.

(**G2**) For $k = \overline{0, n-2}$, the partial derivatives $\dfrac{\partial^k G}{\partial t^k}$ exist and they are continuous on $I \times I$.

(**G3**) $\dfrac{\partial^{k-1} G}{\partial t^{k-1}}$ and $\dfrac{\partial^k G}{\partial t^k}$ exist and are continuous on the triangles $a \leq s < t \leq b$ and $a \leq t < s \leq b$.

(**G4**) For each $t \in (a, b)$ there exist the lateral limits

$$\frac{\partial^{n-1} G}{\partial t^{n-1}}\left(t, t^{+}\right),$$

and

$$\frac{\partial^{n-1} G}{\partial t^{n-1}}\left(t, t^{-}\right),$$

(i.e., the limits when $(t, s) \to (t, t)$ with $s > t$ or with $s < t$) and, moreover

$$\frac{\partial^{n-1} G}{\partial t^{n-1}}\left(t, t^{+}\right) - \frac{\partial^{n-1} G}{\partial t^{n-1}}\left(t, t^{-}\right) = -\frac{1}{a_0(t)}.$$

(**G5**) For each $s \in (a, b)$, the function $t \to G(t, s)$ is a solution of the differential equation $L_n x = 0$ on $t \in [a, s)$ and $t \in (s, b]$. That is,

$$a_0(t)\frac{\partial^n G}{\partial t^n}(t, s) + a_1(t)\frac{\partial^{n-1} G}{\partial t^{n-1}}(t, s) + \ldots + a_{n-1}(t)\frac{\partial G}{\partial t}(t, s) + a_n(t) G(t, s) = 0,$$

on both intervals.

(**G6**) For each $s \in (a, b)$, the function $t \to G(t, s)$ satisfies the boundary conditions

$$\sum_{j=0}^{n-1}\left(\alpha_j^i \frac{\partial^j G}{\partial t^j}(a, s) + \beta_j^i \frac{\partial^j G}{\partial t^j}(b, s)\right) = 0, \ i = \overline{1, m}.$$

Theorem 1.10 *[9] Let G be a Green's function of problem (1.1). Then, for each continuous function σ, we have that*

$$x\left(\left(t\right)\right) = \int_a^b G\left(t,s\right)\sigma\left(s\right)ds, \tag{1.3}$$

is a solution of the following problem

$$\begin{cases} L_n x\left(t\right) = \sigma\left(s\right), \ t \in I \equiv \left[a,b\right], \\ U_i\left(x\right) = 0, \ i = \overline{1,m}. \end{cases}$$

Theorem 1.11 *Let us suppose that the homogeneous problem (1.2) has only the trivial solution. Then there exists a unique Green's function, related to (1.2). Moreover, for each continuous function σ, the unique solution of problem*

$$\begin{cases} L_n x\left(t\right) = \sigma\left(t\right), \ t \in I \equiv \left[a,b\right], \\ U_i\left(x\right) = 0, \ i = \overline{1,n}, \end{cases}$$

is given by expression (1.3).

CHAPTER 2

Mathematical Models of Hematopoiesis

Contents

This chapter is devoted to present a brief biological introduction to hematopoiesis and its pioneering mathematical models.

2.1 Biological Background

2.1.1 Human Hematopoiesis

Human Hematopoiesis and its Compartments

Human hematopoiesis is the process that leads to the regulated production of all types of blood cells, namely red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes). The production of erythrocytes, leukocytes, and platelets is known as erythropoiesis, leukopoiesis, and thrombopoiesis respectively. They proceed in a stepwise, hierarchical fashion from hematopoietic stem cells (HSCs) to mature blood cells. The specific compartments are:

1. **Hematopoietic Stem Cell Compartment**

Pluripotent hematopoietic stem cells (HSCs), located in the bone marrow, occupy the highest level in the hematopoietic hierarchy. These master cells have the ability to self-renew and differentiate, which helps sustain their population and replenish all types of hematopoietic cells. There are two types of hematopoietic stem cells: long-term (LT) and short-term (ST), each with distinct self-renewal and differentiation abilities. LT-HSCs are the long-lasting, self-renewing cells in the bone marrow with minimal reaction to physiologic stress. In contrast, ST-HSCs can boost their production and differentiation in response to various pathological states.

2. **Progenitor Cell Compartment**

HSCs differentiate into progenitor cells, which are committed to specific lineages (e.g., myeloid or lymphoid) but are not yet fully specialized.

3. **Precursor Cells Compartment**

Progenitor cells further develop into precursor cells, which are more mature and closer to becoming functional blood cells.

4. **Mature Blood Cell Compartment**

Mature Blood Cells are the fully functional blood cells divides into three lineages before releasing into the bloodstream, including erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets). More precisely

Erythrocytes

Erythrocytes, also known as red blood cells, are a type of blood cell that carries oxygen from the lungs to the rest of the body and returns carbon dioxide to the lungs.

Leukocytes

Leukocytes, also known as red blood cells, which participate in the body's specific defenses, are divided into several cell categories, including:

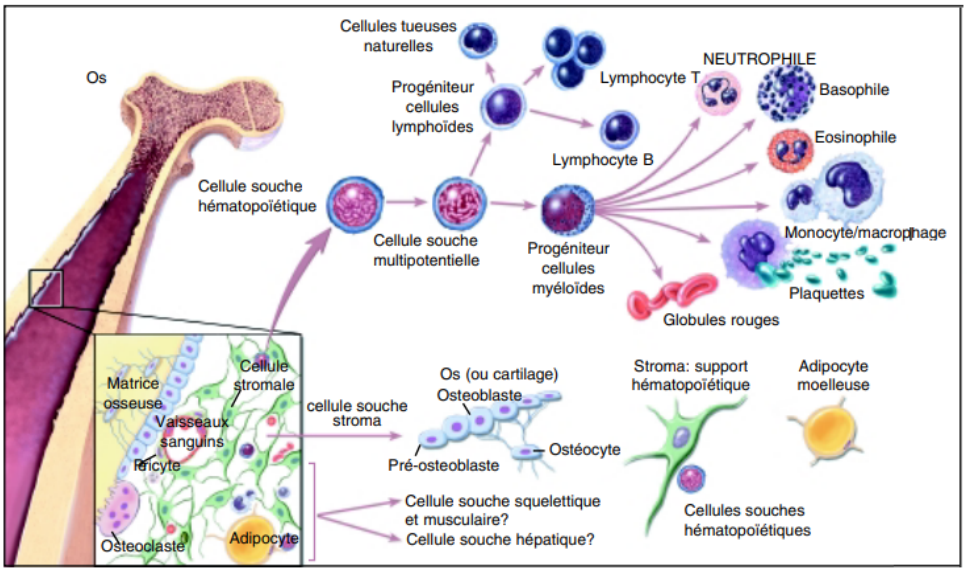
- Polymorphonuclear leukocytes (PMNs), also known as granulocytes: they are a crucial part of the innate immune system, playing a vital role in fighting infections and inflammation. Common types of granulocytes include neutrophils, eosinophils, and basophils

- Monocytes: they play a crucial role in both the body's surveillance system, patrolling for threats, and in orchestrating immune responses to infections and inflammation by engulfing and destroying pathogens (like bacteria and viruses) and cellular debris.

- Lymphocytes: they play a crucial role in the immune system, helping the body fight off infections and diseases. They are a key component of both the innate and adaptive immune responses. There are three types: B lymphocytes, which produce antibodies that help neutralize or destroy invading pathogens like bacteria and viruses, the T lymphocytes which have various functions, including killing infected or cancerous cells, and coordinating the overall immune response, and finally the Natural Killer cells (NK).

Platelets

Platelets, also known as thrombocytes, are small, colorless cell fragments in the blood that play a crucial role in homeostasis, the process of stopping bleeding. They are not complete cells but rather pieces of larger cells called megakaryocytes found in the bone marrow. Their primary function is to form blood clots at the site of injury to prevent excessive bleeding.



Stages of Hematopoiesis

Hematopoiesis occurs in distinct stages throughout life. In early embryogenesis, hematopoiesis originates in the yolk sac and then transitions to the fetal liver and spleen and finally, before birth, it settles in the bone marrow. In adults, it primarily occurs in the bone marrow. Specifically, it's located within the spongy tissue inside of bones. Whereas, hematopoiesis in children also takes place in long bones of the limbs, other organs like the spleen and liver may also play a role, especially in early childhood, but as they mature, it becomes more concentrated in certain areas like the skull, pelvis, vertebrae, and the ends of long bones.

2.1.2 Hematopoiesis in Animals

Hematopoiesis in Animals and its Compartments

Hematopoiesis in most animals, which encompasses the production of red blood cells, white blood cells, and platelets from hematopoietic stem cells, occurs in specific locations throughout development and adulthood, ensuring a continuous supply of blood cells for essential functions like oxygen transport, immunity, and blood clotting. Hematopoietic Stem cells keep dividing throughout an animal's life. Some of these cells stay as pluripotent stem cells, which are stored in the bone marrow to guarantee a steady supply of stem cells. They further differentiate into five distinct types of immature blood cells, called precursor cells or blast cells, namely:

- Proerythroblast to form RBCs
- Myeloblast to form neutrophils, eosinophils, and basophils
- Monoblast to form monocytes
- Lymphoblast to form lymphocytes
- Megakaryoblast to form platelets.

2.1.3 Comparison between Human an Animal Hematopoiesis

This process shares fundamental similarities between humans and other animals, but also exhibits key differences in location, timing, and regulation. In both, it involves the differentiation of hematopoietic stem cells (HSCs) into various blood cell types, including red blood cells, white blood cells, and platelets. However, the specific sites of hematopoiesis and the regulation of HSC behavior can vary across species, particularly during development.

Some Similarities

Although humans and animals may look different, they have some similarities in producing blood such as

- In both humans and animals, hematopoiesis originates from HSCs.

- Both humans and the majority of animals produce a similar array of blood cell types, including erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets).

- In adult humans and most adult animals, hematopoiesis primarily occurs in the bone marrow.

Some Differences

While both humans and animals undergo hematopoiesis, there are key differences in the process, particularly

- In humans, hematopoiesis begins in the yolk sac and then transitions to the fetal liver and finally the bone marrow. In animals, the specific sites and timing can vary. For example, zebrafish hematopoiesis involves distinct waves of blood cell formation in the intermediate cell mass and rostral blood island.

- Human HSCs are generally more quiescent (less frequently dividing) compared to some animals such as mouse HSCs. Additionally, the response to DNA damage, such as irradiation, differs between human and mouse HSCs, with human HSCs more likely to undergo apoptosis (programmed cell death) rather than DNA repair.

- While mouse models are commonly used to study hematopoiesis, they may not perfectly replicate human hematopoiesis due to differences in HSC behavior and other factors. Human HSCs have been studied in immuno-

compromised mice[1] and in fetal sheep models to better understand human hematopoiesis.

- While both species maintain a constant production of blood cells to replenish those that die off, the rate and magnitude of cell turnover can differ. For example, the total amount of murine and human myeloid and erythroid cells produced each day are roughly the same order of magnitude, despite the larger overall number of red blood cells in humans, likely due to the shorter lifespan of murine cells.

- The produced RBCs in humans and animals share the same primary function of carrying oxygen, but they differ in size, shape, and nuclear presence. Humans have biconcave, disk-shaped RBCs that lack a nucleus in their mature form. Many animals also have enucleated RBCs, but some, like camels and llamas, have oval-shaped RBCs that retain a nucleus.

- The produced WBCs in humans and animals share fundamental roles in the immune system, but there are notable differences in their types, numbers, and responses to various stimuli. Humans and animals both have granulocytes (neutrophils, eosinophils, basophils) and mononuclear cells (lymphocytes, monocytes) as major WBC types. However, some species have unique WBCs, like heterophiles in rabbits, guinea pigs, birds, and reptiles, which are functionally similar to neutrophils but have different granule characteristics. Furthermore, the total number and ratios of WBC types can vary significantly between species, with larger animals often having more WBCs and a higher proportion of neutrophils and monocytes.

- The produced platelets in humans and animals share the fundamental function of stopping bleeding, but here are differences in their size, lifespan,

[1]Immunocompromised mice refer to the mice with defects in one or more immune components (such as T, B, NK cells) in the immune system.

and certain functional aspects across various species. For example, platelets in mammals are not complete cells but rather small, anucleated fragments (around 2-3 μm in diameter) of larger cells called megakaryocytes. Other vertebrate classes like birds and reptiles have nucleated thrombocytes and mouse platelets, for example, are smaller than human platelets and have a shorter lifespan.

Blood Cells in Vertebrates vs. Blood Cells in Invertebrates

Here, we will see the three blood cells in vertebrates, including human, and invertebrates

White Blood Cells in Vertebrates

Vertebrates have five main types of white blood cells, also known as leukocytes: neutrophils, eosinophils, basophils, lymphocytes, and monocytes. These cells are crucial for the immune system, each playing a distinct role in defending the body against pathogens and other threats.

White Blood Cells in Invertebrates

Invertebrates do not have white blood cells in the same way vertebrates do, but they do have cells within their hemolymph (the invertebrate equivalent of blood) that carry out similar immune functions. These cells, called hemocytes, are responsible for phagocytosis (engulfing and destroying pathogens), encapsulation, and other immune responses.

Red Blood Cells in Vertebrates

Red blood cells (RBCs), also known as erythrocytes, are a key component of vertebrate blood, primarily responsible for carrying oxygen and carbon dioxide throughout the body. They are highly specialized cells, with their defining feature being the presence of hemoglobin, an iron-containing protein that binds to and transports oxygen. So, all vertebrates except for

some Antarctic icefish have red blood cells (RBCs) containing hemoglobin. The Antarctic icefish, specifically the blackfin icefish, are the only known vertebrates that lack red blood cells and hemoglobin. These fish have evolved to live in the extremely cold, oxygen-rich waters of Antarctica without relying on RBCs for oxygen transport. Instead, oxygen is freely dissolved in their blood. More precisely, in mammals, the life cycle of red blood cells is the same as in humans. Red blood cells are also the same; they are shaped like discs with a hollow center, lack a nucleus, and use hemoglobin to transport oxygen and carbon dioxide. In birds, the production of red blood cells, which retain a non-active nucleus, takes place, as in mammals, in the bone marrow. In non-mammalian vertebrates, red blood cells are larger and have retained their nuclei, and, like in mammals, use hemoglobin to bind oxygen and carbon dioxide.

An icefish

Red Blood Cells in Invertebrates

Red blood cells seem to be an exception in invertebrates (arthropods, octopuses, spiders, molluscs). Instead of hemoglobin (which contains iron and is found in red blood cells of vertebrates), many of these invertebrates use copper-based protein called hemocyanin which appears blue when it binds to oxygen, leading to the slightly blue-grey or even colorless appearance of their blood, rather than the red color seen in animals with iron-based hemoglobin.

In arthropods, air is brought directly to the organs by a system of tra-

cheae; therefore, no means of transporting oxygen is necessary. However, the "blood" is called hemolymph, which is a fluid that circulates around the body, bathing the tissues. Hemolymph contains cells called hemocytes, which are involved in immune responses, wound healing, and nutrient transport. Unlike vertebrate blood, arthropod hemolymph does not contain hemoglobin and does not play a major role in oxygen transport, though some larvae may use it for this purpose.

The blood of Octopuses, spiders, and many molluscs is blue due to the presence of a hemocyanin, which is freely dissolved in a fluid called hemolymph instead of red blood and contains copper and turns blue when it binds to oxygen. Despite the fact that the circulatory system of many molluscs, including cephalopods like octopuses is more developed than that of spiders, with a heart and some vessels, and although recent studies on octopuses that have shown the existence of different types of hemocytes (blood cells) involved in their immune response, hemocyanin still plays the key role in oxygen transport. However, there are exceptions within molluscs. For example, some air-breathing snails like the Planorbidae use iron-based hemoglobin.

Planorbidae

Platelets in Vertebrates

In vertebrates, platelets are cell fragments responsible for blood clotting. In mammals, platelets are derived from megakaryocytes in the bone marrow, while other vertebrates like birds and amphibians utilize nucleated cells called thrombocytes for similar functions. These cells play a crucial role in homeostasis (stopping bleeding) and tissue repair.

Platelets in Invertebrates

Invertebrates do not have platelets in the same way mammals do (anucleate cell fragments). Instead, they have the aforementioned hemocytes that circulate in the hemolymph and perform functions similar to both platelets and leukocytes in vertebrates. These hemocytes are involved both in homeostasis (blood clotting) and immune responses.

2.1.4 Hematopoietic Growth Factors

Hematopoietic growth factors (HGFs) in humans and animals are a group of glycoproteins that share the fundamental role by acting as messengers to regulate the growth, differentiation, and function of blood cells in both humans and animals. These factors can act as endocrine hormones, paracrine hormones, or through cell-to-cell contact, influencing specific stem cells, progenitor cells, or precursor cells. The key hematopoietic growth factors are

1. **Erythropoietin (EPO)**: Erythropoietin is a hormone primarily produced in the kidneys, with the liver also contributing, especially during fetal development. Primarily, it regulates red blood cell production (erythropoiesis). Human EPO shares 91% similarity with monkey EPO, 85% with cat and dog EPO, and 80% to 82% with EPO from pigs, sheep, mice, and rats. Invertebrates, however, lack the same type of erythropoietic system and don't produce EPO in the same way. Instead, they may have EPO-like signaling pathways that play a role in tissue protection and regeneration,

particularly in the nervous system, and can even activate mammalian EPO receptors.

2. **Thrombopoietin (TPO):** In humans, TPO is a glycoprotein hormone primarily produced in the liver and kidney , and stimulates and maturation of megakaryocytes, the cells that produce platelets. While the general function of TPO is similar across vertebrates, there are some differences in its structure and the details of its interactions with the TPO receptor. Invertebrate animals, while also having a TPO-like function, utilize different signaling pathways and may not have an exact homologous protein to human TPO.

3. **Granulocyte colony-stimulating factor (G-CSF):** Granulocyte colony-stimulating factor (G-CSF) plays a similar role in both humans and invertebrate animals, primarily regulating the production and function of granulocytes (especially neutrophils). However, there are differences in the specific mechanisms and evolutionary pathways. In humans, G-CSF is a well-characterized cytokine crucial for neutrophil development, survival, and function, and its role in infection and disease. In invertebrates, while a G-CSF homolog has been identified and its function in immune responses has been demonstrated, the precise details of its structure, signaling pathways, and evolutionary relationships are still being investigated.

4. **Granulocyte-macrophage colony-stimulating factor (GM-CSF)**: In humans, Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine that stimulates the production and maturation of granulocytes

and macrophages, playing a key role in immune responses. Invertebrate animals, lacking a bone marrow and adaptive immune system, have analogous factors with similar, though not identical, functions in regulating immune cell development and function.

5. **Interleukins (IL-3, IL-5, etc.):** Interleukins (ILs) are a group of cytokines involved in cell-to-cell communication, particularly within the immune system. While well-characterized in humans and other mammals, their presence and function in invertebrates are more complex and less understood. In vertebrates, interleukins like IL-3 and IL-5 are crucial for hematopoiesis and immune cell development. Invertebrates, however, possess simpler immune systems with different mechanisms of defense, and while some studies suggest the presence of IL-1-like molecules, the extent of interleukin diversity and function in invertebrates remains an active area of research.

6. **Stem cell factor (SCF):** Stem cell factor (SCF), also known as Kit ligand or Steel factor, plays a similar but not identical role in both human and invertebrate animal systems. In humans, SCF is crucial for the development and function of hematopoietic stem cells, mast cells, melanocytes, and germ cells. It acts by binding to the c-Kit receptor, a tyrosine kinase receptor, initiating downstream signaling pathways that regulate cell survival, proliferation, and differentiation. Invertebrate animals also utilize SCF or SCF-like molecules in stem cell regulation, though the specific mechanisms and the complexity of the signaling pathways can vary significantly.

2.2 Mathematical Growth Models in Cell Populations

2.2.1 Exponential Growth in Cell Populations

The familiar Malthusian Model representing the growth of a single predicts exponential growth or exponential decline. The exponential growth in cell populations can particularly be found in well-controlled single-species experiments. In such settings, daily dilutions can be used to maintain the culture in the exponential, or "log," phase of growth. This phase gets its name because growth rates often estimated using linear regression of logarithmic plots of cell growth.

$$\frac{dx(t)}{dt} = rx(t), \tag{2.1}$$

where $x(t)$ denotes the number of cells and $r = b - d$ with b is the birth rate and d is the death rate, is the population growth rate. This Malthusian Model assumes that the population rate of change is proportional to the population size $x(t)$. The integration of both sides of equation (2.1) gives the number of cells in the population as a function of time t and growth rate, i.e.,

$$x(t) = x_0 \ \exp(rt),$$

where x_0 is the initial number of cells in the population.

2.2.2 Delayed Exponential Growth in Cell Populations

The Delayed Malthusian Model incorporates time delays into the classic Malthusian growth model to reflect more realistic scenarios where population growth is influenced by delayed effects, such as the time lag between a

stimulus and its effect on the cell population. It is given by

$$\frac{dx(t)}{dt} = r\ x(t-\tau). \tag{2.2}$$

The term $r\ x(t-\tau)$ refers to the population growth rate at time t, which depends on the population size at a previous time $t-\tau$ where τ can denote cell maturation, the time it takes for a treatment to become effective, or the delay in the immune response,...

Another version of the Malthusian model divides the population into two groups: adults and juveniles. Let $x(t)$ denote the adult population density at time t. The model assumes that individuals spend a fixed time period τ in the juvenile stage before becoming adults. Adults reproduce at a rate of b per capita and die at a rate of d. Furthermore, it is assumed that newborns survive to reach adulthood at a rate of p. Based on these assumptions, the dynamics of the adult population can be modeled using the following differential equation:

$$\frac{dx(t)}{dt} = bp\ x(t-\tau) - dx(t). \tag{2.3}$$

The first term of this equation contains a delay term which can represent a time lag, for example the time needed for cells to become mature provided that they survive the interphase stage which is the period where a cell grows and prepares for division.

2.2.3 Logistic Growth in Cell Populations

A key drawback of modeling growth as an exponential process is that, in biologically realistic conditions, the exponential phase is relatively short, representing just one stage in the overall growth of cell populations. Additionally, single-species populations rarely exist in isolation in nature, making it uncertain how well exponential growth models apply to competitive interaction

studies. Logistic growth models were originally introduced by Verhulst in 1838. Since then, variations of the logistic model have been extensively used in diverse areas, including investigations into how autophagy affects yeast cell populations under starvation, as well as evolutionary analyses of cancer. Similar to the exponential growth model, the logistic model characterizes how population size evolves over time as follows:

$$\frac{dx(t)}{dt} = r\ x(t) - \frac{r\ x^2(t)}{K} = rx(t)\left(1 - \frac{x(t)}{K}\right), \tag{2.4}$$

where x^2 represents the pairwise interactions between the cells and captures interaction effects such as competition for resources and space, among other factors. The negative sign before this term is important because it mirrors the hypothesis that these interactions diminish the total population rate of change. $K > 0$ is the carrying capacity of the environment which represents the maximum number of cells that a specific environment can sustainably support. Once the population reaches or approaches this level, the growth rate approaches zero, and the population stabilizes around K. In other words, this model describes how a cell population's growth rate slows down as it approaches the carrying capacity of its environment. Initially, the population may grow rapidly (exponentially), but as resources, like nutrients, oxygen, and space to grow, and divide become limited and competition increases, the growth rate decreases, eventually stabilizing around the carrying capacity.

2.2.4 Delayed Logistic Growth in Cell Populations

In reality, cells do not respond instantaneously to changes in their environment. There is often a time delay before they react to factors like resource depletion or increased competition. So, delayed logistic growth in cell populations also known as Hutchinson equation, refers to a mathematical model

that describes how cell populations grow when there is a lag in their response to factors like resource availability or competition. It is represented as

$$\frac{dx(t)}{dt} = r\ x\,(t)\left[1 - \frac{x(t-\tau)}{K}\right], \tag{2.5}$$

where r and K have the same meaning as in the logistic equation and delay τ is a positive constant that can describe the time it takes for cells to replicate, the time it takes for a cell to mature, or the time it takes for the immune system to respond.

2.2.5 Lasota-Wazewska Model for Animal Erythropoiesis

In 1976 and in one of the earliest contributions, the Polish mathematician Andrzej Lasota and Wazewska proposed the following delay differential equation:

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

which aimed to discuss the existence of periodic solutions of this erythropoiesis model in mice. In this model which describes the survival of red blood cells, $x\,(t)$ denotes the density of mature red blood cells in the bloodstream at time t, $a > 0$ is the rate of red blood cell death, b is the production rate of red-blood cells, $\frac{1}{\gamma}$ represents the maximum density of red blood cells that the body can produce, and τ is a positive constant stands for the time delay required to produce a red blood cell for releasing into the bloodstream. The Ricker function within the Lasota-Ważewska model provides a biologically plausible way to represent how red blood cell production changes with the size of the cell population, including the effects of both stimulation and inhibition as the population grows.

Derivation of the Delay Differential Equation from the Transport Equation

To derive the Lasota-Wazewska delay differential equation from the McKendrick-Von Foerster transport equation, we start with the partial differential equation (PDE) describing the evolution of red blood cell density $n\,(t,a)$ over time t and age a

$$\frac{\partial n(t,a)}{\partial t}+\frac{\partial n\,(t,a)}{\partial a}=-\lambda(a)n(t,a)$$

This equation is complemented with a boundary condition representing the production of new red blood cells:

$$n(t,0)=p(t)$$

and an integral condition modeling the delayed feedback in the production process:

$$p(t)=\rho\gamma\int_0^\infty h(a)e^{-\gamma a}n(t-a,a)da$$

Using the method of characteristics, which transforms the PDE into ordinary differential equations (ODEs) along characteristic curves where$t-a$ =constant, we find a general solution of the form:

$$n(t,a)=p(t-a)e^{\int_0^a\lambda(s)}$$

This allows us to compute the total number of red blood cells:

$$N(t)=\int_0^\infty n(t,a)da$$

Taking the time derivative of $N\,(t)$, and using the transport equation, we obtain:

$$\frac{\partial N(t)}{\partial t}=p(t)-\mu(t)N(t)$$

Substituting the expression for $p\,(t)$ leads to the final delay differential equation:

$$\frac{\partial N(t)}{\partial t}=-\mu N(t)+\rho\gamma N(t-h)$$

This equation captures the dynamics of red blood cell concentration in the bloodstream, accounting for both cell death and the delayed production response.

The model which has been applied to study various hematological disorders and treatments, has been influential in the study of blood cell dynamics and has been extended and generalized by numerous researchers. Researchers have extended the model to incorporate various factors, such as multiple time-varying delays, impulsive effects, patch structures, and harvesting strategies.

2.2.6 Mackey-Glass Models for Human Hematopoiesis

In 1978, the Canadian scientists Michael Mackey and Leon Glass introduced two models of hematopoiesis in humans, which they applied in particular to the study of periodic hematopoiesis and some hematological disorders,like the periodic forms of chronic myelogenous leukemia [2]and the aplastic anemia[3].

They proposed two pioneering models describing the dynamics of populations of hematopoietic stem cells (HSCs) with a constant delay of the form:

$$x'(t) = -ax(t) + \frac{b\, x(t-\tau)}{1 + x^n(t-\tau)}, \tag{2.7}$$

and

$$x'(t) = -ax(t) + \frac{b}{1 + x^n(t-\tau)}. \tag{2.8}$$

Equation (2.7) was developed to model leukopoiesis, which is defined as the production of leukocytes (white blood cells or WBCs) from hematopoietic

[2]Chronic myelogenous leukemia is a rare type of cancer that affects the bone marrow and white blood cells.

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

stem cells located in the bone marrow.

Equation (2.8) was set up to describe the erythropoiesis in humans or what it is called the production of erythrocytes, also known as red blood cells (RBCs), which is crucial for carrying oxygen throughout the body. They are produced in the bone marrow and contain hemoglobin, a protein that binds to oxygen in the lungs and releases it to the body's tissues. Red blood cells are essential for maintaining proper oxygen levels in the body and removing carbon dioxide.

Red Blood Cells

CHAPTER 3

Positive Periodic Solutions of an Iterative Erythropoiesis Model in Animals

Contents

In this chapter, we investigate the existence, uniqueness, and stability of positive periodic solutions for a first-order delay differential equation with an iterative term, describing the survival of red blood cells in animals.

3.1 The Studied Equation

The Lasota-Wazewska model originally describes the survival of red blood cells in an animal. It uses the first-order nonlinear delay differential equation (2.6) to represent the dynamics of red blood cell population. Although it was first introduced by Wazewska-Czyzewska and Lasota in 1976 to model erythropoiesis in animals, it was generalized to study human red blood cell dynamics. This, its generalization involved adapting the parameters and potentially adding complexity to the model to account for the specific characteristics of human red blood cells. It has been generalized by many researchers where the generalizations often incorporate more complex factors like multiple delays, variable delays, variable parameters, and harvesting strategies. For instance

Thirteen years later, Kulenović and his collaborators [23] generalized this model to incorporate multiple time delays:

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

In [24], the authors employed the continuation theorem by Gaines and Mawhin to establish the existence and global attractivity of positive periodic solutions in a Lasota-Wazewska-type model with time-dependent parameters and delays:

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

Similarly, in [25], fixed point theory was applied to prove the existence and global attractivity of a unique positive periodic solution to a model with variable coefficients and multiple time-varying delays:

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

Concerning models that incorporate harvesting terms, Duan et al. [14] studied the following Lasota-Wazewska model:

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

where $H(t)$ represents a discontinuous harvesting function.

Consider the following first-order delay differential equation with an iterative term:

$$x'(t) = -a(t)\,x(t) + b(t)\,e^{-\gamma x^{[2]}(t)} - h(t, x(t-\tau)), \tag{3.1}$$

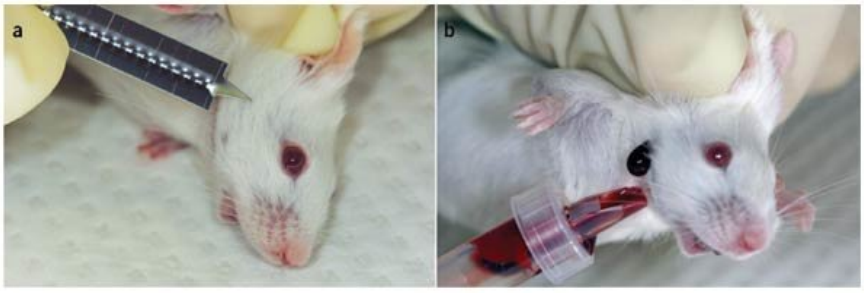
where $a, b \in C([0,T],(0,+\infty))$, $h \in C([0,T]\times\mathbb{R},(0,+\infty))$ are T-periodic functions with respect to the time variable t, γ is a positive constant, $x^{[2]}(t)$ is the second iterate of $x(t)$, h is the harvesting term and $\tau > 0$ is a harvest lag.

Equation (3.1) which can describe the dynamics of red blood cell population in the bloodstream of an animal, involves a constant delay in the harvesting function and an iterative production term. Many biological processes, including red blood cell production and death, are influenced by external factors that vary over time. Variable coefficients allow the model to capture these time-dependent changes and allow it to be adapted to different situations, such as simulating the effects of seasonal changes, disease outbreaks, or other time-dependent perturbations on red blood cell dynamics. For instance, a variable death rate can account for factors like aging of RBCs, effects of disease, especially when the body gets rid of abnormal cells by apoptosis or what it is called the programmed cell death, or even changes in the body's environment that affect how long RBCs survive. Also, a production rate means that the rate at which the body produces new RBCs can change due to factors like hormonal changes, oxygen levels, or other

regulatory mechanisms.

In medical terms

- $x(t)$ denotes the number of mature red blood cells in the blood circulation of an animal at time t.
- $a(t)$ represents the death or clearance rate of red blood cells. It represents the rate at which red blood cells are naturally removed from circulation (e.g., by spleen, aging, or damage).
- $\frac{1}{\gamma}$ represents the maximum density of red blood cells that the body can produce.
- $b(t)\, e^{-\gamma x^{[2]}(t)}$ is the flux of red blood cells in the blood circulation.
- $b(t)$ stands for the production rate of new RBCs.
- $h(t, x(t-\tau))$ represents the harvesting function with a constant lag which depends on past number of erythrocytes. It describes the blood cell harvesting such collecting blood samples for various purposes, including research, diagnostics, and the production of blood products.



- τ denotes a harvesting delay.
- $x^{[2]}(t)$ arises from a variable delay $\tau_1(t, x(t))$ that depends on both the time t and the density of mature red blood cells $x(t)$, representing the time required for a red blood cell to mature or be produced.

The dependence of the lag $\tau_1(t, x(t))$ on $x(t)$ is essentially a consequence of the fact that several growth factors and hormones contribute significantly to controlling the division of hematopoietic stem cells (HSCs) and stimulating red blood cell maturation in animals. Key regulators include erythropoietin (EPO), which is produced by the kidneys in response to low oxygen levels, and stem cell factor (SCF). These factors promote the differentiation and proliferation of erythroid progenitor cells, ultimately leading to the production of mature red blood cells. In the converse case, when the number of mature erythrocytes is large, they suppress the division of the HSCs and repress the RBC maturation.

In this chapter, we investigate the existence, uniqueness, and stability of solutions for equation (3.1). The existence of positive periodic solutions is shown using Krasnoselskii's fixed point theorem and the Green's functions method. In addition, under an extra criterion, the Banach fixed point theorem ensures the existence, the uniqueness, and the continuous dependence on parameters of positive periodic solutions. Three examples are given to demonstrate the validity of the theoretical results.

3.2 Preliminaries

Let $\mathbb{X}$ be the Banach space of all $T-$periodic and continuous functions defined as in Example 1.1 endowed with the norm

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

and let Ω, as defined in Example 1.1, be a bounded, closed, compact, and convex subset of $\mathbb{X}$, as demonstrated in Examples 1.2, 1.3, 1.4, and 1.5.

To simplify the exposition, we use the following notations:

$$\sup_{t\in[0,T]} a(t) = a_2, \quad \inf_{t\in[0,T]} b(t) = b_1 =$$

$$\sup_{t\in[0,T]} b(t) = b_2, \quad \sup_{\theta\in[0.T]} h(\theta,0) = h_2,$$

$$\frac{\exp\left(-\int_0^T a(v)dv\right)}{\exp\left(\int_0^T a(v)dv\right)-1} = \rho_1, \quad \frac{\exp\left(\int_0^T a(v)dv\right)}{\exp\left(\int_0^T a(v)dv\right)-1} = \rho_2.$$

Moreover, we assume the following hypotheses:

($\mathbf{H}_1$) The function $h(t,x)$ is globally Lipschitz with respect to the second variable x; that is, there exists a positive constant μ such that

$$|h(t,x(t)) - h(t,y(t))| \leq \mu |x(t) - y(t)|. \tag{3.2}$$

($\mathbf{H}_2$) The following estimates are satisfied:

$$T\rho_2 b_2 \leq \ell_2, \tag{3.3}$$

$$T\left(\rho_1 b_1 e^{-\gamma\ell_2} - (\mu\ell_2 + h_2)\rho_2\right) \geq \ell_1, \tag{3.4}$$

$$\rho_2 (2 + Ta_2)(b_2 + h_2 + \mu\ell_2) \leq \ell_3, \tag{3.5}$$

and

$$T\rho_2\mu < 1. \tag{3.6}$$

Remark 3.1

a) From hypothesis ($\mathbf{H}_1$), we obtain

$$|h(\theta, x(t))| \leq \mu\ell_2 + h_2. \tag{3.7}$$

Indeed, we have

$$\begin{aligned} |h(\theta,x(t))| &= |h(\theta,x(t)) - h(\theta,0) + h(\theta,0)| \\ &\leq |h(\theta,x(t)) - h(\theta,0)| + |h(\theta,0)| \\ &\leq \mu\ell_2 + h_2. \end{aligned}$$

b) Thanks to Lemma 1.1, we get

$$\left|e^{-\gamma x^{[2]}(\theta)} - e^{-\gamma y^{[2]}(\theta)}\right| \leq \gamma\left(1+\ell_3\right)\|x-y\|. \tag{3.8}$$

Indeed, the application of the Mean Value Theorem to the function $f(s) = \exp(-\gamma s)$ over the interval $\left[x^{[2]}(\theta), y^{[2]}(\theta)\right]$ where $x, y \in \Omega$, leads to

$$e^{-\gamma x^{[2]}(\theta)} - e^{-\gamma y^{[2]}(\theta)} = -\gamma e^{-\gamma\zeta(\theta)}\left(x^{[2]}(\theta) - y^{[2]}(\theta)\right),$$

such that $\zeta(\theta)$ is between $x^{[2]}(\theta)$ and $y^{[2]}(\theta)$.

Since $\gamma > 0$ and $0 < \ell_1 \leq \zeta(\theta) \leq \ell_2$, then $\left|e^{-\gamma\zeta(\theta)}\right| = e^{-\gamma\zeta_2(\theta)} < 1$ and

$$\begin{aligned}\left|e^{-\gamma x^{[2]}(\theta)} - e^{-\gamma y^{[2]}(\theta)}\right| &= \left|-\gamma e^{-\gamma\zeta(\theta)}\left(x^{[2]}(\theta) - y^{[2]}(\theta)\right)\right| \\ &= |-\gamma|\left|e^{-\gamma\zeta(\theta)}\right|\left|x^{[2]}(\theta) - y^{[2]}(\theta)\right| \\ &\leq \gamma\left|x^{[2]}(\theta) - y^{[2]}(\theta)\right|.\end{aligned}$$

Thanks to Lemma 1.1, we obtain

$$\left|e^{-\gamma x^{[2]}(\theta)} - e^{-\gamma y^{[2]}(\theta)}\right| \leq \gamma\left(1+\ell_3\right)\|x-y\|.$$

3.3 Associated Integral Equation

Now, we will present and prove the next lemma which has a pivotal role in transforming the studied equation (3.1) with the periodic properties into a fixed point problem.

Lemma 3.1 *A function $x \in \Omega \cap \mathcal{C}^1(\mathbb{R},\mathbb{R})$ is a solution to equation (3.1) if and only if $x \in \Omega$ satisfies the following nonlinear integral equation:*

$$x(t) = \int_t^{t+T} G(t,\theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta - \int_t^{t+T} h\left(\theta, x(\theta-\tau)\right) G(t,\theta)\, d\theta, \tag{3.9}$$

where

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

Proof. Suppose that $x \in \Omega \cap \mathcal{C}^1(\mathbb{R}, \mathbb{R})$ is a solution of equation (3.1), then

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

By integration from t to $t+T$, we obtain

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

The periodic properties, give

$$\begin{aligned}
&x(t) \left(\exp\left(\int_t^{t+T} a(v)\, dv\right) - \exp\left(\int_0^t a(v)\, dv\right)\right) \\
&= \exp\left(\int_0^t a(v)\, dv\right) \left[\exp\left(\int_t^{t+T} a(v)\, dv\right) - 1\right] x(t) \\
&= \int_t^{t+T} \left(b(\theta)\, e^{-\gamma x^{[2]}(\theta)} - h\left(\theta, x(\theta-\tau)\right)\right) \exp\left(\int_0^\theta a(v)\, dv\right) d\theta.
\end{aligned}$$

Consequently

$$\begin{aligned}
x(t) &= \int_t^{t+T} \left(b(\theta)\, e^{-\gamma x^{[2]}(\theta)} - h\left(\theta, x(\theta-\tau)\right)\right) \frac{\exp\left(\int_0^\theta a(v)\, dv\right) \exp\left(-\int_0^t a(v)\, dv\right)}{\exp\left(\int_0^T a(v)\, dv\right) - 1} d\theta \\
&= \int_t^{t+T} \left(b(\theta)\, e^{-\gamma x^{[2]}(\theta)} - h\left(\theta, x(\theta-\tau)\right)\right) \frac{\exp\left(\int_t^\theta a(v)\, dv\right)}{\exp\left(\int_0^T a(v)\, dv\right) - 1} d\theta \\
&= \int_t^{t+T} \left(b(\theta)\, e^{-\gamma x^{[2]}(\theta)} - h\left(\theta, x(\theta-\tau)\right)\right) G(t, \theta)\, d\theta.
\end{aligned}$$

Conversely, equation (3.1) can be easily derived by differentiating equation (3.9) with respect to t. ■

Lemma 3.2 *The obtained Green's kernel $G(t, \theta)$ is bounded as follows:*

$$0 < \rho_1 \leq G(t, \theta) \leq \rho_2. \tag{3.10}$$

Lemma 3.3 *For all $t_2, t_1 \in [0,T]$ with $t_1 < t_2$ we have*

$$\int_{t_1}^{t_1+T} |G(t_2,\theta) - G(t_1,\theta)|\, d\theta \leq \rho_2 T a_2 |t_2 - t_1|. \tag{3.11}$$

3.4 Existence Results

In this section, we will use the Krasnoselskii fixed-point theorem together with certain properties of the Green's function to demonstrate the existence of at least one fixed point of the integral operator A.

Now, we convert the integral equation (3.9) to be applicable to fixed point theorems

To do this, we introduce an operator A, which can be expressed as the sum of two operators, A_1 and A_2 as follows: $A = A_1 + A_2 : \Omega \longrightarrow \mathbb{X}$ where $A_1, A_2 : \Omega \longrightarrow \mathbb{X}$ are given by

$$(A_1 x)(t) = \int_t^{t+T} G(t,\theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta, \tag{3.12}$$

and

$$(A_2 x)(t) = -\int_t^{t+T} h(\theta, x(\theta-\tau))\, G(t,\theta)\, d\theta. \tag{3.13}$$

According to Lemma 3.1, the fixed points of A are the solutions of equation (3.1) and vice versa.

Remark 3.2 Operators A_1 and A_2 are well defined.

In the sequel, we prove the existence of positive periodic solutions by using two distinct fixed-point theorems and the *Green*'s function method.

Lemma 3.4 *Assume that conditions (3.3)-(3.5) hold, then*

$$(A_1 x) + (A_2 y) \in \Omega,$$

for all $x, y \in \Omega$.

Proof. Let $x, y \in \Omega$, then

$$\begin{aligned}(A_1x)(t) + (A_2y)(t) &= \int_t^{t+T} G(t,\theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \\ &\quad - \int_t^{t+T} h(\theta, y(\theta-\tau))\, G(t,\theta)\, d\theta \\ &\leq \int_t^{t+T} G(t,\theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta.\end{aligned}$$

It follows from (3.10) and (3.3) that

$$\begin{aligned}(A_1x)(t) + (A_2y)(t) &\leq T\rho_2 b_2 \\ &\leq \ell_2.\end{aligned}$$

Using (3.10), (3.7), and (3.4), we get

$$\begin{aligned}(A_1x)(t) + (A_2y)(t) &\geq T\rho_1 b_1 e^{-\gamma\ell_2} - (\mu\ell_2 + h_2) T\rho_2 \\ &\geq T\left[\rho_1 b_1 e^{-\gamma\ell_2} - (\mu\ell_2 + h_2)\rho_2\right] \\ &\geq \ell_1.\end{aligned}$$

Consequently,

$$\ell_1 \leq (A_1x)(t) + (A_2y)(t) \leq \ell_2, \tag{3.14}$$

for all $x, y \in \Omega$.

Now, let $t_1, t_2 \in [0, T]$, then

$$\begin{aligned}|(A_1x + A_2y)(t_2) - (A_1x + A_2y)(t_1)| &\leq |(A_1x)(t_2) - (A_1x)(t_1)| \\ &\quad + |(A_2y)(t_2) - (A_2y)(t_1)|.\end{aligned}$$

We have

$$\begin{aligned}|(A_1x)(t_2) - (A_1x)(t_1)| &= \left| \int_{t_2}^{t_2+T} G(t_2,\theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \right. \\ &\quad \left. - \int_{t_1}^{t_1+T} G(t_1,\theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \right|.\end{aligned}$$

Then

$$\begin{aligned}|(A_1x)(t_2)-(A_1x)(t_1)| = &\left|\int_{t_2}^{t_1} G(t_2,\theta)\,b(\theta)\,e^{-\gamma x^{[2]}(\theta)}d\theta\right.\\ &+\int_{t_1}^{t_1+T} G(t_2,\theta)\,b(\theta)\,e^{-\gamma x^{[2]}(\theta)}d\theta\\ &+\int_{t_1+T}^{t_2+T} G(t_2,\theta)\,b(\theta)\,e^{-\gamma x^{[2]}(\theta)}d\theta\\ &\left.-\int_{t_1}^{t_1+T} G(t_1,\theta)\,b(\theta)\,e^{-\gamma x^{[2]}(\theta)}d\theta\right|.\end{aligned}$$

So

$$\begin{aligned}|(A_1x)(t_2)-(A_1x)(t_1)| \le &\int_{t_2}^{t_1} G(t_2,\theta)\,b(\theta)\,e^{-\gamma x^{[2]}(\theta)}d\theta\\ &+\int_{t_1+T}^{t_2+T} G(t_2,\theta)\,b(\theta)\,e^{-\gamma x^{[2]}(\theta)}d\theta\\ &+\int_{t_1}^{t_1+T} |G(t_2,\theta)-G(t_1,\theta)|\,b(\theta)\,e^{-\gamma x^{[2]}(\theta)}d\theta.\end{aligned}$$

According to (3.10) and (3.11), we get

$$\begin{aligned}|(A_1x)(t_2)-(A_1x)(t_1)| &\le 2\rho_2 b_2\,|t_2-t_1| + b_2\rho_2 T a_2\,|t_2-t_1|\\ &= \rho_2 b_2\,(2+Ta_2)\,|t_2-t_1|\,.\end{aligned} \tag{3.15}$$

On the other hand, we have

$$\begin{aligned}|(A_2y)(t_2)-(A_2y)(t_1)| &= \left|\int_{t_2}^{t_2+T} h(\theta,y(\theta-\tau))\,G(t_2,\theta)\,d\theta\right.\\ &\quad\left.-\int_{t_1}^{t_1+T} h(\theta,y(\theta-\tau))\,G(t_1,\theta)\,d\theta\right|\\ &= \left|\int_{t_2}^{t_1} h(\theta,y(\theta-\tau))\,G(t_2,\theta)\,d\theta\right.\\ &\quad+\int_{t_1}^{t_1+T} h(\theta,y(\theta-\tau))\,G(t_2,\theta)\,d\theta\\ &\quad+\int_{t_1+T}^{t_2+T} h(\theta,y(\theta-\tau))\,G(t_2,\theta)\,d\theta\\ &\quad\left.-\int_{t_1}^{t_1+T} h(\theta,y(\theta-\tau))\,G(t_1,\theta)\,d\theta\right|.\end{aligned}$$

So

$$\begin{aligned}|(A_2y)(t_2)-(A_2y)(t_1)| \leq & \int_{t_2}^{t_1} h(\theta, y(\theta-\tau))\, G(t_2,\theta)\, d\theta \\ & + \int_{t_1+T}^{t_2+T} h(\theta, y(\theta-\tau))\, G(t_2,\theta)\, d\theta \\ & + \int_{t_1}^{t_1+T} |G(t_2,\theta)-G(t_1,\theta)|\, h(\theta, y(\theta-\tau))\, d\theta.\end{aligned}$$

Using now (3.10), (3.11), and (3.7), we deduce that

$$\begin{aligned}|(A_2y)(t_2)-(A_2y)(t_1)| &\leq 2\rho_2(\mu\ell_2+h_2)|t_2-t_1| \\ &\quad + (\mu\ell_2+h_2)\rho_2 T a_2 |t_2-t_1| \\ &= \rho_2(\mu\ell_2+h_2)[2+Ta_2]|t_2-t_1|. \qquad (3.16)\end{aligned}$$

By virtue of (3.5), (3.15), and (3.16), we obtain

$$|(A_1x+A_2y)(t_2)-(A_1x+A_2y)(t_1)| \leq \ell_3|t_2-t_1|, \qquad (3.17)$$

for all $x, y \in \Omega$ and $t_1, t_2 \in [0,T]$.

Finally, from (3.14) and (3.17), we conclude that

$$(A_1x)+(A_2y) \in \Omega.$$

Thus, the lemma is proved. ■

Lemma 3.5 *Suppose that condition (3.6) holds, then A_2 is a contraction.*

Proof. For all $x, y \in \Omega$, we have

$$\begin{aligned}&|(A_2x)(t)-(A_2y)(t)| \\ \leq & \int_t^{t+T} G(t,\theta)\,|h(\theta, x(\theta-\tau))-h(\theta, y(\theta-\tau))|\, d\theta.\end{aligned}$$

It follows from (3.10) and the hypothesis $(\mathbf{H}_1)$ that

$$\|A_2x-A_2y\| \leq T\rho_2\mu\|x-y\|. \qquad (3.18)$$

Inequality (3.6) implies that A_2 is a contraction. ■

Lemma 3.6 *A_1 is a completely continuous operator on Ω.*

Proof. Since Ω is a compact subset of $\mathbb{X}$ and since any continuous operator maps every compact set into compact one, it suffices to show that A_1 is continuous instead of its compactness.

For all $x, y \in \Omega$, we have

$$|(A_1x)(t) - (A_1y)(t)| = \int_t^{t+T} G(t,\theta)\, b(\theta) \left| e^{-\gamma x^{[2]}(\theta)} - e^{-\gamma y^{[2]}(\theta)} \right| d\theta.$$

In view of the Green's function property (3.10) and the estimate (3.8), we get

$$\|A_1x - A_1y\| \leq T\rho_2 b_2 \gamma (1 + \ell_3) \|x - y\|. \tag{3.19}$$

Consequently, the operator A_1 is Lipschitz continuous, and therefore, it is continuous. ■

Now, we are ready to state and prove the following existence theorem:

Theorem 3.1 *Suppose that conditions (3.2)-(3.6) hold, then equation (3.1) has at least one positive periodic solution in Ω.*

Proof. From Lemma 3.1, we see that equation (3.1) has at last a solution x in Ω if and only if the operator $A = A_1 + A_2$ has a fixed point. From Lemmas 3.4-3.6 all conditions of the Krasnoselskii fixed point theorem are satisfied. Consequently, A has a fixed point in Ω which is a solution of equation (3.1).

■

3.5 Existence, Uniqueness, and Stability Results

In this section, we aim to establish results on the existence, uniqueness, and continuous dependence on parameters of periodic positive solutions for

equation (3.1) by applying the Banach fixed point theorem.

Theorem 3.2 *Suppose conditions (3.2)-(3.5) hold. If*

$$T\rho_2\left(b_2\gamma\left(1+\ell_3\right)+\mu\right)<1, \tag{3.20}$$

then equation (3.1) has a unique positive periodic solution in Ω.

Proof. Similarly as in the proof of previous lemmas, we infer that A maps Ω into itself and

$$\|Ax-Ay\| \leq T\rho_2\left(b_2\gamma\left(1+\ell_3\right)+\mu\right)\|x-y\|,$$

for all $x, y \in \Omega$. According to condition (3.20), A is a contraction and thereby we conclude by the Banach fixed point theorem that A has a unique fixed point in Ω , which is exactly the unique solution of equation (3.1). ■

Here, we establish the continuous dependence of the unique solution upon the production rate b and the harvesting function h.

Theorem 3.3 *Under the hypotheses of Theorem 3.2, the unique solution of equation (3.1) depends continuously on parameters* b *and* h.

Proof. Let x be the unique solution of equation (3.1), so x is a solution of the integral equation

$$x(t)=\int_t^{t+T} G(t,\theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta-\int_t^{t+T} h(\theta, x(\theta-\tau))\, G(t,\theta)\, d\theta,$$

and let $\widetilde{x}$ be a solution of the perturbed equation with small perturbations in b and h which fulfil the requirements of Theorem 3.2. So, $\widetilde{x}$ is a solution of the following integral equation:

$$\widetilde{x}(t)=\int_t^{t+T} G(t,\theta)\, \widetilde{b}(\theta)\, e^{-\gamma \widetilde{x}^{[2]}(\theta)} d\theta-\int_t^{t+T} \widetilde{h}(\theta, \widetilde{x}(\theta-\tau))\, G(t,\theta)\, d\theta.$$

where $\widetilde{b}$ and $\widetilde{h}$ are the perturbed parameters.

We have

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

This gives

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

Further, it follows from (3.10), (3.8), and hypothesis $(\mathbf{H}_1)$ that

$$\begin{aligned}
|x(t)-\widetilde{x}(t)| \leq & T\rho_2 \|b\| \gamma (1+\ell_3) \|x-\widetilde{x}\| + T\rho_2 \left\|b-\widetilde{b}\right\| \\
& + T\rho_2 \left\|h-\widetilde{h}\right\| + T\rho_2 \mu \|x-\widetilde{x}\| \\
& = T\rho_2 (\|b\| \gamma (1+\ell_3)+\mu) \|x-\widetilde{x}\| \\
& + T\rho_2 \left\|b-\widetilde{b}\right\| + T\rho_2 \left\|h-\widetilde{h}\right\|.
\end{aligned}$$

Therefore

$$\|x-\widetilde{x}\| (1-T\rho_2 (\|b\| \gamma (1+\ell_3)+\mu)) \leq T\rho_2 \left(\left\|b-\widetilde{b}\right\| + \left\|h-\widetilde{h}\right\|\right).$$

Using now condition (3.20), we deduce that

$$\|x-\widetilde{x}\| \leq \frac{T\rho_2}{\left(1-T\rho_2\left(\|b\|\gamma\left(1+\ell_3\right)+\mu\right)\right)}\left(\left\|b-\widetilde{b}\right\|+\left\|h-\widetilde{h}\right\|\right).$$

This completes the proof. ■

3.6 Examples

In this section, we give three examples to corroborate the feasibility of the main theoretical findings.

Example 3.1 Consider the following first order delay differential equation with an iterative term:

$$x'(t) = -\left(0.02+0.009\left(\sin^2\frac{2\pi}{11}t\right)\right)x(t)+\left(0.01+0.04\left(\sin^2\frac{2\pi}{11}t\right)\right)\exp\left(-\frac{1}{5}x^{[2]}(t)\right) - \left(\frac{1}{17\pi^5}+\frac{1}{19\pi^5}\frac{x(t-\tau)}{1+x(t-\tau)}\right). \tag{3.21}$$

Let

$$\Omega_1 = \left\{x\in\mathbb{X},\ 0.13\leq x(t)\leq 2.35,\ \ |x(t_2)-x(t_1)|\leq\frac{1}{2}|t_2-t_1|,\ \forall t_1,t_2\in\mathbb{R}\right\},$$

where the period is 11 days. Here $\left(0.02+0.009\left(\sin^2\frac{2\pi}{11}t\right)\right)$ stands for the lost rate of erythrocytes, $\left(0.01+0.04\left(\sin^2\frac{2\pi}{11}t\right)\right)$ denotes the production rate of erythrocytes and $\left(\frac{1}{17\pi^5}+\frac{1}{19\pi^5}\frac{x(t)}{1+x(t)}\right)$ is the harvesting term h.
We have

$$a_2=0.029,\ b_1=0.01,\ b_2=0.05,\ \rho_1\approx 2.4692,\ \rho_2\approx 4.233,$$
$$\gamma=\frac{1}{5},\ \mu=\frac{1}{19\pi^5}\text{ and }h_2=\frac{1}{17\pi^5}.$$

Moreover

$$\begin{aligned}
&T\rho_2 b_2 \approx 2.3282 \leq \ell_2 = 2.35,\\
&T\left(\rho_1 b_1 e^{-\gamma \ell_2} - (\mu \ell_2 + h_2)\,\rho_2\right) \approx 0.14199 \geq \ell_1 = 0.13,\\
&\rho_2\,(2 + Ta_2)\,(b_2 + \mu\ell_2 + h_2) \approx 0.49667 \leq \ell_3 = \frac{1}{2},\\
&T\rho_2\mu \approx 0.0080083 < 1.
\end{aligned}$$

The extra condition in Theorem 3.2

$$T\rho_2\,(b_2\gamma\,(1+\ell_3)+\mu) \approx 0.70645 < 1,$$

is satisfied. We infer that all hypotheses of Theorem 3.2 hold. So equation (3.21) has a unique positive periodic solution in Ω_1.
Furthermore, let x be the unique solution of equation (3.21) and let $\widetilde{x}$ be a solution of the perturbed equation with the perturbed parameters $\widetilde{b}$ and $\widetilde{h}$. We get

$$\|x - \widetilde{x}\| \leq (158.62)\left(\left\|b - \widetilde{b}\right\| + \left\|h - \widetilde{h}\right\|\right).$$

We conclude that the unique positive periodic solution of equation (3.21) depends continuously on the production rate b and the harvesting term h.

Example 3.2 Consider the following first order delay differential equation with an iterative term:

$$\begin{aligned}
x'(t) = &-\left(0.01 + 0.009\left(\cos^4\frac{2\pi}{19}t\right)\right)x(t) + \left(0.02 + 0.03\cos^2\frac{2\pi}{19}t\right)e^{-\frac{1}{20}x^{[2]}(t)}\\
&-\left(\frac{1}{\pi^9} + \frac{1}{3\pi^9}\frac{x(t-\tau)}{1+x(t-\tau)}\right).
\end{aligned} \tag{3.22}$$

Let

$$\Omega_2 = \left\{x \in \mathbb{X},\ 0.8 \leq x(t) \leq 4.25,\ \ |x(t_2) - x(t_1)| \leq \frac{6}{10}\ |t_2 - t_1|,\ \forall t_1, t_2 \in \mathbb{R}\right\},$$

where the period is 19 days. We have

$$a_2 = 0.019,\ b_1 = 0.02,\ b_2 = 0.05,\ \rho_1 \approx 2.6806,\ \rho_2 \approx 4.4562,$$
$$\gamma = \frac{1}{20},\ \mu = \frac{1}{3\pi^9} \text{ and } h_2 = \frac{1}{\pi^9}.$$

So

$$T\rho_2 b_2 \approx 4.2334 \leq \ell_2 = 4.25,$$
$$T\left(\rho_1 b_1 e^{-\gamma \ell_2} - (\mu \ell_2 + h_2)\,\rho_2\right) \approx 0.816\,76 \geq \ell_1 = 0.8,$$
$$\rho_2\,(2 + Ta_2)\,(b_2 + \mu\ell_2 + h_2) \approx 0.526\,91 \leq \ell_3 = 0.6,$$
$$T\rho_2\mu \approx 0.0009467\,8 < 1.$$

The condition (3.20) in Theorem 3.2

$$T\rho_2\,(b_2\gamma\,(1 + \ell_3) + \mu) \approx 0.33962 < 1,$$

is satisfied. In addition, if x is the unique solution of equation (3.22) and if $\widetilde{x}$ is a solution of the perturbed equation with the perturbed parameters $\widetilde{b}$ and $\widetilde{h}$, then we get

$$\|x - \widetilde{x}\| \leq (128.21)\left(\left\|b - \widetilde{b}\right\| + \left\|h - \widetilde{h}\right\|\right).$$

Thus the unique positive periodic solution x depends continuously upon the production rate b and the harvesting term h.

The last example highlights the power of Theorem 3.1 to establish an existence result even when Banach contraction principle cannot be used.

Example 3.3 Consider the same differential equation (3.22) in

$$\Omega_3 = \left\{x \in \mathbb{X},\ 0.8 \leq x\,(t) \leq 4.25,\ \ |x(t_2) - x(t_1)| \leq \frac{38}{10}\ |t_2 - t_1|\,,\ \forall t_1, t_2 \in \mathbb{R}\right\},$$

with the same period 19 days. We have

$$T\rho_2\,(b_2\gamma\,(1 + \ell_3) + \mu) \approx 1.017 > 1.$$

Therefore, the extra condition (3.20) is not satisfied and hence Theorems 3.2 and 3.3 cannot be applied here. However, all requirements of Theorem 3.1 are fulfilled which means that the solution of equation (3.22) exists but it is not necessarily unique and we cannot get any information about the continuous dependence on parameters.

General Conclusion and Perspectives

In this thesis, we studied a nonlinear first order functional differential equation that describes the dynamics of red blood cells in the bloodstream of an animal. The revisited Lasota-Wazewska model includes an iterative recruitment term and a nonlinear delayed harvesting one. To fulfill certain biological and mathematical facts, we first defined an appropriate Banach space and a closed, convex, and bounded subset of it that satisfied all the necessary requirements and provided the foundation for an easy application of the chosen fixed point theorems. Next, we transformed the equation at hand with the periodic boundary conditions into an equivalent Fredholm integral equation whose kernel is a Green's function. Then, by virtue of a hybrid technique that combines the Krasnoselskii and Banach fixed point theorems and the Green's functions method, some sufficient conditions were established to guarantee the existence, uniqueness, and continuous dependence on parameters of periodic positive solutions. The theoretical outcomes are supported by three illustrative examples.

The technique used in this work serves as a valuable reference for tackling various forms of functional differential equations. Let us mention here some perspectives for future researches.

- The technique employed in this work could be effectively adopted to deal with higher-order iterative differential equations or fractional iterative differential equations.

- It would be worthwhile to investigate the existence of anti-periodic, almost-periodic, and pseudo-almost-periodic solutions for such equations that involve delays and iterative terms.

- Applying numerical methods or software could prove essential for obtaining approximate solutions and providing numerical simulations to illustrate the theoretical results.

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