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Thesis

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Option: ***Numerical Analysis, PDEs and Applications***

Existence results for certain delay differential equations

Presented by:

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Publicly discussed:

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CONTENTS

Abstract in English

The objective of this thesis is to study the existence, uniqueness and stability of positive, periodic and bounded solutions for four first order delay differential equations with iterative terms.

For achieving our target, we convert each problem into an equivalent integral equation whose kernel is a *Green's* function, and then we apply the *Krasnoselskii* or *Schauder* fixed point theorems with the help of some properties of the obtained kernel and some functional analysis tools in order to establish the existence results. Whereas the uniqueness and continuous dependence results are obtained by using the *Banach* contraction mapping principle. In addition, many illustrative examples are exhibited to demonstrate the validity of our theoretical findings which are novel and complement some existing results in the literature.

Keywords: Continuous dependence on parameters, existence, fixed point theorem, *Green*'s function, hematopoiesis model, iterative differential equation, periodic solution, positive solution, uniqueness.

Abstract in French

L'objectif de cette thèse est d'étudier l'existence, l'unicité et la stabilité de solutions positives, périodiques et bornées pour quatre équations différentielles à retard du premier ordre avec des termes itératifs.

Pour atteindre notre objectif, nous convertissons chaque problème en une équation intégrale équivalente dont le noyau est une fonction de *Green*, puis nous appliquons les théorèmes du point fixe de *Krasnoselskii* ou de *Schauder* à l'aide de certaines propriétés du noyau obtenu et de quelques outils de l'analyse fonctionnelle afin d'établir les résultats d'existence. Tandis que les résultats d'unicité et de dépendance continue sont obtenus en utilisant le principe de l'application contractante de *Banach*. En outre, plusieurs exemples illustratifs sont exposés pour démontrer la validité de nos résultats théoriques qui sont nouveaux et complètent certains résultats existants dans la littérature.

Mots-clés: Dépendance continue aux paramètres, existence, théorème du point fixe, fonction de *Green*, modèle d'hématopoïèse, équation différentielle itérative, solution périodique, solution positive, unicité.

Abstract in Arabic

الهدف من هذه الأطروحة هو دراسة وجود، وحدانية و استقرار الحلول الدورية الموجبة و المحدودة لأربع معادلات تفاضلية من الرتبة الأولى ذات حدود تكرارية.

لتحقيق هدفنا، نقوم بتحويل كل مسألة إلى معادلة تكاملية مكافئة نواتها دالة غرين، بعد ذلك نطبق إحدى نظريتي النقطة الثابتة لكراسنوسيلسكي أو شودر بمساعدة بعض خصائص النواة المتحصل عليها وبعض أدوات التحليل الدالي لغرض إثبات نتائج وجود الحلول الدورية. في حين يتم الحصول على نتائج الوحدانية و الارتباط المستمر باستخدام نظرية النقطة الثابتة لباناخ.

علاوة على ذلك، تم تقديم العديد من الأمثلة التوضيحية لإثبات صحة نتائجنا النظرية و التي تعتبر جديدة ومكملة لبعض النتائج الموجودة في الأدبيات.

الكلمات المفتاحية. الارتباط المستمر على المعاملات، الوجود، نظرية النقطة الثابتة، دالة غرين، نموذج تكون الدم، المعادلة التفاضلية التكرارية، حل دوري، حل موجب، وحدانية.

Dedication

This dissertation is dedicated

- To my father ***Abde Elhafid****, mother* ***Fedjria*** *and dearest grandmother* ***Yamina****, your belief in my abilities and your endless sacrifices to provide me with the best education have shaped me into the person I am today. I am profoundly grateful for your unending support.*

- To my dearest sister ***Malak****, for her constant encouragement, understanding and unwavering support.*

- To all my family, for their love and inspiration.

- To all those who have supported and inspired me throughout my doctoral journey. Without their unwavering encouragement, guidance, and belief in my abilities, this achievement would not have been possible.

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To all my family and friends. Your love and understanding sustained me through the challenges, and for that, I am profoundly grateful.

This dissertation stands as a collective effort, and to all those who, in various capacities, have contributed to its realization, I express my sincere thanks. May this work contribute positively to the academic community and beyond.

Acronyms

Abbreviation	**Meaning**
DDEs	Delay differential equations
SDDEs	State-dependent delay differential equations
RBCs	Red blood cells
WBCs	White blood cells
HSCs	Hematopoietic stem cells
BM	Bone marrow
DNA	Deoxyribonucleic Acid
RNA	Ribonucleic Acid
EPO	Erythropoietin
HGFs	Hematopoietic growth factors
CNS	Central nervous system
G-CSF	Granulocyte-colony stimulating factor
DHEA	Dehydroepiandrosterone
a.e.	Almost everywhere
EMH	Extramedullary hematopoiesis
MPNs	Myelo proliferative neoplasms

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

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

(a, b) : an open interval

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

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

$\mathcal{C}(\mathbb{R}^{n+1}, (0, +\infty))$ is the space of continuous functions from $\mathbb{R}^{n+1}$ into $(0, +\infty)$

$\mathcal{C}([a, b], (0, +\infty))$ is the space of continuous functions from $[a, b]$ into $(0, +\infty)$

$\mathcal{C}^1(\mathbb{R}^{n+1}, (0, +\infty))$: space of continuously differentiable functions from $\mathbb{R}^{n+1}$ into $(0, +\infty)$

τ : a delay

w : a period

P_w : the *Banach* space of all continuous and $w-$periodic functions

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

$\mathcal{CB}(\sigma_1, k) = \{M \in P_w,\ 0 \leq M \leq \sigma_1, |M(t_2) - M(t_1)| \leq k |t_2 - t_1|,\ \forall t_1, t_2 \in [0, w]\}$

Functions

$|\cdot|$: absolute value

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

$\|f\|_{\infty}$: the uniform norm defined by $\sup|f(M)|$

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

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

$\lim_{M \longrightarrow M_0}$: limit as M approaches M_0

$\approx$: approximately equal to

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

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

sup : the supremum

max : the maximum

min : the minimum

$\exp M$: the exponential function of M

$\mathcal{G}(t,\theta)$: the *Green's* function

Other notations will be clarified upon their initial occurrence.

CHAPTER 1

General introduction

Contents

1.1 Introduction

The present dissertation focuses on the study of delay differential equations (DDEs for short) that modelize the production and regulation of blood cells in humans and animals.

Delay differential equations which depend on previous states, now occupy an increasingly preponderant place in the literature. They have long played a crucial role to understand, model, and predict the future of several phenomena encountered in life sciences, physical sciences, economic sciences, etc.

The interpretation of the delay that can be discrete, time varying, state dependent, or even distributed, differs from one model to another depending on the studied phenomenon. In life sciences, the delay can represent the duration of the cell cycle, the duration of the transformation of one type of cells into another or the time necessary for the maturation of cells in the dynamics of cell populations, the gestation period, the developmental time, the juvenile phase, the life cycle duration or the period of maturation in the dynamics of human, animal or even plant populations or the incubation period of a contagious disease in epidemiology, etc.

To the best of our knowledge, retarded differential equations have an ancient history dating back to the early of the 18th century. The first attempts have been made by J. Bernoulli, L. Euler, J.L. Lagrange, P. Laplace, S. Poisson, but unfortunatly, equations of this kind have been ignored at that time. This can be due to many factors, including limitation of the theory and mathematical tools that can help deal with these equations and also the fact that the introduction of delays may further complicate the dynamics or may affect the stability of the system.

They had their moment of glory in the 20th century which has been marked by an explosion of scientific researches on this topic in this era. The first flame of the passion for investigating delayed real phenomena has grown during the International Congress of Mathematicians in 1908 when Picard has revealed the importance of taking into account the effect of the delays in modelling physical phenomena.

An important type of delay differential equations that have recently gained considerable momentum, is the class of state-dependent delay differential equations (SDDEs for short) in which delays depend on the state variable itself. Although the fact that the origins of these equations go back to the early 19th century and despite they appear in the modelling of a growing number of phenomena various fields such as electrodynamics, biology, epidemiology and medicine, etc., their theory is not yet well developed.

Iterative functional differential equations which involve derivatives and iterates of the unknown functions can be regarded as a special type of functional differential equations with delays depending on both the time and the state variable itself. We encounter these equations in the modelling of miscellaneous natural phenomena in various domains such as, population dynamics models in ecology, models of hematopoiesis in hematology, models of infectious diseases in epidemiology, two-body equations of motion in classical electrodynamics, and so on (see [3], [9], [12] and [64]).

The origin of iterative differential equations goes back to the early nineteenth century when *Babage* set up his famous equation but the theory was slowly developed due to the distinctive characteristics of such equations. However, in last decade, there has been a great resurgence of interest in investigating them. One of the main reasons behind the study of these equations, despite some difficulties inherent in such investigations, is the fact that equations of this kind can be found in the modelling of many natural phenomena, this reason was the driving force behind a valuable but limited list of publications in the literature of this emergent theory which has not yet been fully developed. The complexity of this type of equations lies usually in the iterative terms that may create some obstacles when studying these equations (see [3, 25], [7]-[12], [15]-[18], [28]-[35], [64] and [66]).

The present dissertation was devoted to study four first order delay and iterative differential equations appearing in the modelling of the formation and regulation of blood cells in human beings and animals. Our approach is based on the fixed point theory together with the *Green* functions method. The key idea here aims to diminish some of the difficulties resulting from the iterative terms by constructing the foundation stones of the study which are an appropriate *Banach* space and two subsets of it on the one hand, and utilizing an attractive hybrid technique based on combining the fixed point theory and the *Green* function method with the help of some functional analysis tools, on the other hand.

1.2 Hematopoiesis and mathematical models

Hematopoiesis (or haematopoiesis; sometimes also haemopoiesis or hemopoiesis), a term derived from two ancient Greek words: haima (blood) and poiēsis (to produce or make) which simply means "to make blood". It stands for the lifelong process of producing blood cellular components, that is erythrocytes, leukocytes, and platelets and through which the body makes new blood cells to replace old ones and hence to guarantee a healthy supply of blood cells that will be needed for the tissue oxygenation, the fight against infections, and the blood coagulation. Every day, the hematopoietic system in the human body produces 10^{11} to 10^{12} mature blood cells in a hierarchical manner from a small population of young parent cells called hematopoietic stem cells (HSCs) which multiply for making copies of themselves and give rise to all lineages of blood cells. The most common sites of blood cell production are specialized bone marrow regions called "niches" as well as other hematopoietic organs and tissues. More precisely, hematopoiesis begins in the blood islands of the yolk sac and then transitions to the liver and spleen during pregnancy. After birth, and throughout early infancy, it occurs primarily in the marrow of long bone such as the femur and tibia. During adulthood, the medullary hematopoiesis takes place in the bone marrow of the pelvis, cranium, vertebrae, and sternum whereas the sites of extramedullary hematopoiesis (EMH) are outside of the bone marrow like liver, spleen, thymus, and lymph nodes.

Broadly, hematopoiesis can be divided into three major categories:

Erythropoiesis: Red blood cell (RBC, or erythrocyte) production.

Leukopoiesis: White blood cell (WBC, or leukocytes) production like monocytes, lymphocytes, neutrophils, basophils and eosinophils .

Thrombopoiesis: Platelet production.

Steps of hematopoiesis

Hematopoiesis which is characterized by the rapid proliferation of HSCs, which then differentiate to produce mature blood cells, has undergone four compartments:

I. **Proliferation compartments**

a/ **Hematopoietic stem cell compartment:** Hematopoiesis begins with the hematopoietic stem cell compartment in which the primitive HSCs sitting at the apex of hematopoiesis will choose one of the two pathways: on one hand they can self-renew to maintain primitive state, and on the other hand they can differentiate towards the progenitor compartment or die by apoptosis (cellular suicide).

b/ **Progenitor compartment:** In the progenitor compartment, there are two types: lymphoid progenitors, which form two types of lymphocytes T and B, and myeloid progenitors which form the rest of the blood cells (Granulocytes, Erythrocytes, Platelets). Progenitors gradually lose their capacity for self-renewal and they may die or differentiate towards the precursor compartment.

II. **Differentiation compartments**

a/ **Precursor compartment:** In the precursor compartment, the cells only continue to mature for giving rise to the four major blood cell lineages: red cells, phagocytic cells, megakaryocytes, and lymphocytes.

b/ **Mature blood cells compartment**: In the mature blood cells compartment**,** the cells become functional cells in order to release in the bloodstream.

Mathematical modelling of hematopoiesis dynamics is the process of describing, giving a better understanding, predicting, and controlling of the production of blood cells, its disorders and hematologic malignancies in mathematical terms. Indeed, the mathematical models have the potential to provide insights into the production of blood cells, and ultimately for future advances in treating various hematologic disorders and hence can help bridge the gap between risk and recovery.

Many scholars have been interested in the study of normal and malignant hematopoiesis to predict the effectiveness chemotherapy treatments, 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 hemopathy, aplasia, cyclical neutropenia, myeloproliferative neoplasms (MPNs), or myeloid leukemia.

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. To our knowledge, the sixties of the past century can be regarded as a watershed in the history of the modelling of blood cell kinetics but the first timid attempts were focused on dealing with quite complex models.

To our knowledge, first models of hematopoiesis dynamics have been proposed by *Bell* and *E. C. Anderson* who were among the first ones to study the dynamics of a cell population structured in age and size in 1967. After a year, *Rubinow* put forward a model of maturity structured population dynamics. In 1978 and inspired by the works of *Lajtha* (1959) and *Bruns Tonnack* (1970), *Mackey* proposed two mathematical models of HSC dynamics. Then models of structured populations have been studied by various researchers. *Swick* in 1980, *Marcati* in 1981, *Gyllenberg* and *Webb* and *Bélair* in 1997, *Diekmann*, *Heijmans*, *Thieme*, *Heijmans*, *Webb* and *Grabosch*...

Starting from 1990, these models saw a significant increase in interest translated by an exponential increase in both quantity and quality of publications on this topic.

Let us now cite what we consider as remarkable contributions to this field because these works have provided a benchmark of excellence in the modelling of physiological control systems including respiratory dynamics as well as hematopoiesis in human and animal whether in health and disease.

The end of the following decade witnessed two turning points, the first work carried out by *Wazewska* and *Lasota* in 1976 and the other done by *Mackey* and *Glass* in the following year.

In the end of the seventies of the past century and in one of the earliest papers in this topic which was and still is one of the most important milestones in the history of mathematical modelling of erythropoiesis, *Wazewska-Czyzewska* and *Lasota* introduced, the following delayed differential equation with one constant delay:

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

where they were interested in the problem of the existence of periodic solutions to this erythropoiesis model which was aimed at modelling and getting better understanding of the survival of red blood cells in an animal. In medical terms $x(t)$ 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, the positive constants γ and b are related to the production of red-blood cells per unit time and the time delay required to produce a mature red blood cell for release in circulating bloodstreams is denoted by the positive constant τ.

In 1977, the Canadian physiologists *Leon Glass* and *Michael Mackey* [45] proposed two other pioneering works that have provided some surprising insight into the formation of hematopoietic cells and hence have broken a new ground in mathematical modelling of blood cell production as well as the regulation and control mechanisms of hematologic diseases, are the following famous delay differential equations with a constant delay, which are known as the *Mackey-Glass* equations:

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

and

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

for modelling and getting a better understanding of the erythropoiesis and leukopoiesis. In medical terms, $x(t)$ (cells/kg) represents the density of mature circulating red or white blood cells in the blood circulation at time t,

$\alpha x(t)$ (cells/day) is the death term, $\alpha > 0$ (days^{-1}) is called the death rate of blood cells in the circulation, $\dfrac{b}{1+x(t-\tau)}$ and $\dfrac{bx(t-\tau)}{1+x(t-\tau)}$ (cells/kg-day) which depend on the cell density at an earlier time, stands for the blood cells reproduction, $b > 0$ (units cells/kg-day) describes the maximal blood cells production rate that the body can approach when the density of blood cells in the circulation falls below normal and $\tau > 0$ (days) denotes the maturation delay.

As a result, many considerations towards *Wazewska-Lasota* and *Mackey-Glass* models and their generalizations had been made (see [2, 9, 23, 24, 37, 38, 39, 44]).

1.3 Problem statement

In the current thesis, we deal with four functional differential equations with delays and iterative terms that describe the hematopoiesis with harvesting strategies in human beings and animals.

Unfortunately, although iterative differential equations have appeared widely in many applications such as models arising in epidemiology, biology and electrodynamics and although they have also fascinated many authors and hence gained much momentum recently, their study is not always an easy task. Their unpopularity is partly due to the fact that their iterative terms that involve compositions of the unknown function with itself, may create some difficulties both when studying them and when applying the well-known methods or may lead in many cases to a dead end.

This is what motivates us, in turn, to investigate this topic and contribute to make up for this deficiency and hence to diminish some of these difficulties where the following fundamental research questions must be answered:

(i) How to control the iterative terms?

(ii) Does the problem have at least one solution?

(iii) Does the problem have a unique solution?

(iv) Does the unique solution, if it exists, depends on model parameters?

1.4 Motivation

The prime movers behind our investigation are multiple but the most important ones are on one hand their crucial role in describing many real world phenomena especially in epidemiology, life sciences and physics, and on the other hand, the fact that these kind of equations have been avoided by the majority of scholars and accordingly this reason gave us a major impetus to contribute in the literature of this emergent theory which has not yet been fully developed. Indeed, the difficulty of studying them stems usually from their iterative terms that are not generally easy to control and often hamper the application of the most known methods or may impede or hinder the ability to achieve the desired results.

Motivated by these aforementioned reasons and inspired by some excellent works on delay and iterative differential equations and hematopoiesis models, we have studied four first order delay differential equations with iterative terms that describe the production of blood corpuscles in human beings and animals.

1.5 Purpose of research

The main object of this manuscript lies in highlighting the usefulness of the hybrid technique that combines the fixed point theory and the *Green* functions methods where we are interested in the following issues: the existence, uniqueness, positivity, boundedness, periodicity and continuous dependence on parameters of the sought solutions. To be more precise, the current work principally probes into the existence, uniqueness and continuous dependence on parameters of positive periodic solutions for four classes of first order functional differential equations with delays and iterative terms. The first equation is a first order functional differential equations with a constant delay and iterative terms that models the survival of red blood cells in an animal with a harvesting strategy. The second one, is a first-order iterative differential equation with a time varying delay which describes the erythropoiesis with a harvesting strategy in human adults, by which red blood cells are produced in the marrow of certain bones for releasing them in the bloodstream. The third one is a first-order neutral differential equation including a time dependent delay and iterative terms which describes the same process as the second equation. Finally, the last equation is a first-order functional differential equation involving iterative terms that models the leukopoiesis with a harvesting strategy in human adults, by which white blood cells are created in the bone marrow.

1.6 Research methodology

Firstly, we construct the cornerstones of our hybrid approach, which are a suitable *Banach* space and a closed convex and bounded subset of it with a threefold purpose: For biological realism, they should ensure the periodicity, positivity and boundedness of the sought solution if there exists, to pave the way for the application of the fixed point theorems, and also they should help us to control the iterative terms to avoid any unexpected hitches in our investigation. Secondly, we convert our periodic boundary value problems into equivalent integral equations for transforming these problems into fixed point ones. So, fixed points of the constructed integral operators are solutions of the periodic boundary value problems and vice versa. Finally, we focus on two main issues:

(i) the establishment of a set of sufficient criteria that guarantee the existence of at least one positive periodic solution of our equations with the periodic boundary conditions by the aid of the *Krasnoselskii* and *Schauder* fixed point theorems and some properties of the obtained *Green*'s kernel in the second step. For this, the integral operators need to satisfy the requirements of the used fixed-point theorems.

(ii) the addition of some suitable conditions under which the contraction mapping principle can be applied and hence the positive periodic solution of each given problem becomes unique as well as the reveal of the impact of the harvesting strategy on the solution and also we prove that small changes in the parameters of the proposed equations lead to small variations of the obtained findings.

1.7 Contributions

The salient features of our contribution are fourfold.

(i) We have proposed revisited versions of *Lasota-Wazewska* model and *Mackey-Glass* models that involve iterative terms resulting in many cases from delays depending on both the time and the state variables and describing the durations of the life cycles. Moreover, due to the important impact of the harvesting strategies on the population dynamics, we have added a harvesting function in each equation that may be considered in some cases as a common procedure for controlling diseases whether by the blood specimen collection, stem cells collection, wet cupping therapy or even by blood donation, to name a few. Indeed, harvesting blood cells is more than merely a reduction of blood cells but it is of prime interest to gain insight into the dynamical properties of the model of whether a healthy or malignant hematopoiesis.

(ii) New sufficient criteria that ensure the existence, uniqueness, and continuous dependence on parameters of positive periodic solutions for the proposed equations are established where the hybrid technique used here can be a useful tool to study other higher-order iterative problems.

(iii) The findings here might generalize, to some extent, some previous results where the equations were without iterative terms or the ones that have ignored the impact of the harvesting strategy on the cell population dynamics.

(iv) Our main contribution comes from our motivation to contribute even a little to enriching the literature of iterative differential equations which their theory is still emerging, and not very well developed yet.

1.8 Layout of the thesis

The basic frame of this manuscript is planned in six chapters; the first two chapters are introductory and the other chapters that constitute the main parts of this thesis, expose some recent results published in four international established and reputable journals.

The first chapter is a general introduction that presents the theme, a brief biological and historical background of modelling hematopoiesis, the purpose of research, the methodology, the motivation, the contributions of our works, the layout of the manuscript which is divided into six chapters, a general conclusion, some perspectives for the future, a list of our published papers, and finally ends with a reference list.

The second chapter is dedicated to introduce some primary notions and tools that will be used through this thesis, including some functional analysis concepts, the *Schauder*, *Banach* and *Krasnoselskii* fixed point theorems and the concept of the *Green* function.

The third chapter seeks to present some results about the existence, uniqueness and continuous dependence on parameters of positive periodic solutions for the following first order iterative differential equation:

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

where $a, b \in C([0,w], (0,+\infty))$, $h \in C([0,w] \times \mathbb{R}, (0,+\infty))$ are w-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 the harvest lag. The method applied here is based upon the *Krasnoselskii* and *Banach* fixed point theorems along with the *Green* functions method.

In the fourth chapter, we mainly focus on the following erythropoiesis model with an iterative production term and a nonlinear harvesting term involving iterations and a time varying delay:

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

where $x^{[2]}(t)$ is the second iterate of $x(t)$, $a, p, \tau \in \mathcal{C}(\mathbb{R}, (0,+\infty))$ are w-periodic functions and $f \in \mathcal{C}(\mathbb{R}^3, (0,+\infty))$ is a w-periodic function with respect to the first variable and satisfies the *Lipschitz* condition with respect to the other variables. Under certain conditions and by the *Schauder* fixed point theorem, we show that the existence of positive periodic solutions can be guaranteed and based upon the *Banach* contraction principle, we establish the existence as well as the continuous dependence on parameters theorems of the unique positive periodic solution.

The fifth chapter is devoted to deal with the following the following neutral *Mackey-Glass* equation with iterative production and harvesting terms:

$$\frac{d}{dt}\left[x\left(t\right)-\lambda x\left(t-\tau\left(t\right)\right)\right]=-a\left(t\right)x\left(t\right)+\sum_{i=2}^{n}\frac{\eta\left(t\right)}{1+x^{[i]}\left(t\right)}-k\left(t,x\left(t\right),...,x^{[n]}\left(t\right)\right),$$

where $x\left(t\right)$ is the nth iterate $x^{[n]}\left(t\right)$ stands for the composition of $x\left(t\right)$ with itself n times, $\tau,a,\eta\in C(\mathbb{R},(0,\infty))$ are common w-periodic functions, $\lambda\in(0,1)$, $\tau\left(t\right)$ denotes a transit time needed for the liberation of erythrocytes into the bloodstream and $k\in C\left(\mathbb{R}^{n+1},(0,\infty)\right)$ is the harvesting function. which is assumed globally *Lipschitz* in $y_1,y_2,...,y_n$.

The main objective of the last chapter is to study the existence, uniqueness and stability of positive periodic solutions for the following first-order differential equation with iterative terms which models the regulation of white blood cell production under a harvesting strategy.

$$\varphi'(t)=-a\left(t\right)\varphi(t)+\sum_{i=1}^{N}b_i\left(t\right)\frac{\left(\varphi^{[i]}(t)\right)^m}{1+\left(\varphi^{[i]}(t)\right)^n}-h\left(t,\varphi(t),\varphi^{[2]}(t),...,\varphi^{[N]}(t)\right),$$

where $1<m\leq n$, $t\in[0,w]$, $\varphi^{[N]}\left(t\right)$ denotes the $n-$th iterate of $\varphi\left(t\right)$ such that $\varphi^{[2]}(t)=\varphi(\varphi\left(t\right))$ and $\varphi^{[N]}\left(t\right)$ is obtained by composing the function φ with itself N times, $a,b_i\in\mathcal{C}(\mathbb{R},(0,+\infty))$ are w-periodic functions and $h\in\mathcal{C}\left([0,w]\times\mathbb{R}^N,(0,+\infty)\right)$ stands for the harvesting function such that h is w-periodic with respect to the first variable t and globally *Lipschitz* with respect to the other arguments. We prove the existence of at least one positive periodic solution with the help of the *Krasnoselskii* fixed point theorem together with some properties of a *Green*'s function. Furthermore, by employing the *Banach* contraction principal we discuss the existence of

one and only one positive periodic solution that depends continuously on parameters.

CHAPTER 2

Preliminary notions

Contents

This preliminary chapter aims to provide the fundamental background for a better understanding of the chapters which follow and some necessary concepts that will come in handy later on.

In this chapter, we review the essential notions, several fundamental results, definitions, lemmas and powerful functional analysis tools that will be utilized throughout the remaining chapters. Additionally, we present some well known fixed point theorems that will play a crucial role in deriving our desired results. We conclude this chapter by providing the concept of the *Green's* function.

2.1 Preliminaries and background materials

In this section, we recall some basic concepts from functional analysis including necessary tools, definitions, lemmas and so on.

2.1.1 Convex subset in a vector space

Let $\mathbb{Y}$ be a vector space over a field $\mathbb{F}$.

Definition 2.1 [19] A convex subset of $\mathbb{Y}$ is a subset $\Omega\subseteq \mathbb{Y}$ such that for every pair of points $M, N \in \Omega$, and for every $\alpha \in [0,1]$ we have that

$$\alpha M + (1-\alpha)\, N \in \Omega.$$

Elements of the form $\alpha M + (1-\alpha)\, N$ are called *Convex Combinations* of M and N.

2.1.2 Bounded, closed and compact subset in a normed vector space

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

Definition 2.2 [53] A subset Ω of $\mathbb{Y}$ is called bounded if there exists $c > 0$ such that

$$\|M\|_{\mathbb{Y}} \leq c, \forall M \in \Omega.$$

Theorem 2.1 *[53] A set $\Omega \subseteq Y$ is closed if and only if, whenever $(M_n)_{n\in\mathbb{N}}$ is a sequence in Ω which converges to an element $M \in Y$, then $M \in \Omega$.*

Definition 2.3 [53] A set $\Omega \subseteq \mathbb{Y}$ is called compact if every sequence in Ω has a subsequence that converges to a point in Ω.

Definition 2.4 [53] The closure of a set $\Omega \subseteq \mathbb{Y}$ (denoted by $\overline{\Omega}$) is the smallest closed set that contains Ω.

Definition 2.5 [53] A set $\Omega \subseteq \mathbb{Y}$ is said to be relatively compact if its closure $\overline{\Omega}$ is compact.

Corollary 2.1 *[53] A set $\Omega \subseteq \mathbb{Y}$ is relatively compact if and only if every sequence in Ω has a subsequence that converges to a point in $\mathbb{Y}$.*

2.1.3 Continuous, Lipschitz continuous and compact operators in a normed vector space

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

Definition 2.6 [20] An operator $\mathcal{A} : \mathbb{Y} \longrightarrow \mathbb{Z}$ is said to be continuous at a point $M_0 \in \mathbb{Y}$ if

$$\lim_{M \longrightarrow M_0} \mathcal{A}M = \mathcal{A}M_0.$$

The continuity at $M_0 \in \mathbb{Y}$ could be characterized as follows:

$$\forall \varepsilon > 0, \exists \eta > 0, \forall M \in \mathbb{Y}, \; (\|M - M_0\|_{\mathbb{Y}} < \eta) \Longrightarrow (\|\mathcal{A}M - \mathcal{A}M_0\|_{\mathbb{Z}} < \varepsilon).$$

If $\mathcal{A}$ is continuous at every point of $\mathbb{Y}$, then $\mathcal{A}$ is said to be continuous on $\mathbb{Y}$. The continuity on $\mathbb{Y}$ could be characterized as follows:

$$\forall \varepsilon > 0, \forall M \in \mathbb{Y}, \exists \eta > 0, \forall N \in \mathbb{Y}, (\|M - N\|_{\mathbb{Y}} < \eta) \Longrightarrow (\|\mathcal{A}M - \mathcal{A}N\|_{\mathbb{Z}} < \varepsilon) .$$

Definition 2.7 [55] A map $\mathcal{A} : \mathbb{Y} \longrightarrow \mathbb{Z}$ is said to be *Lipschitz continuous* if there is a positive constant c such that

$$\forall M, N \in \mathbb{Y} : \|\mathcal{A}M - \mathcal{A}N\|_{\mathbb{Z}} \leq c \|M - N\|_{\mathbb{Y}} .$$

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

Remark 2.1 If $\mathcal{A} : \mathbb{Y} \longrightarrow \mathbb{Z}$ then

$\mathcal{A}$ is a contraction $\Longrightarrow$ $\mathcal{A}$ is *Lipschitz* continuous $\Longrightarrow$ $\mathcal{A}$ is continuous on $\mathbb{Y}$.

Theorem 2.2 *[53] A continuous function on a closed bounded interval is bounded and attains its bounds.*

Remark 2.2 The above theorem is essential in obtaining the proof of many theorems and lemmas in the remaining chapters of this thesis.

Definition 2.8 A map $\mathcal{A} : \mathbb{Y} \longrightarrow \mathbb{Z}$ is called compact if and only if $\mathcal{A}$ maps bounded sets into relatively compact sets, i.e.,

$$[\mathcal{A} \text{ compact}] \Longleftrightarrow \left[\forall \Omega \subset \mathbb{Y}, \ (\Omega \text{ bounded}) \Longrightarrow \left(\overline{\mathcal{A}(\Omega)} \text{ compact}\right)\right] .$$

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

2.1.4 Completely continuous operator in a Banach space

Let $(\mathbb{Y}, \|.\|_{\mathbb{Y}})$ and $(\mathbb{Z}, \|.\|_{\mathbb{Z}})$ be two *Banach* spaces over the same field $\mathbb{F}$ and Ω a subset of $\mathbb{Y}$.

Definition 2.9 A continuous map $\mathcal{A} : \Omega \subset \mathbb{Y} \longrightarrow \mathbb{Z}$ is said to be completely continuous if and only if $\mathcal{A}$ maps bounded sets of Ω into relatively compact sets, i.e.,

$$[\mathcal{A} \text{ is completely continuous}] \Longleftrightarrow \left[\forall F \subset \Omega, \ \ (F \text{ bounded}) \Longrightarrow \left(\overline{\mathcal{A}(F)} \text{ compact}\right)\right].$$

2.1.5 Arzelà-Ascoli theorem

Let $\mathbb{Y}$ be a compact subset of a normed vector space over $\mathbb{F}$ and let $\mathcal{C}(\mathbb{Y})$ be the normed vector space of real valued continuous functions on $\mathbb{Y}$ with the *sup*-norm

$$\|f\|_\infty = \sup_{M \in \mathbb{Y}} |f(M)|.$$

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

Definition 2.10 [13] The collection $\mathcal{F}$ is said to be equicontinuous if for every $\varepsilon > 0$ there exists $\eta > 0$ so that for all $f \in \mathcal{F}$ and $M, N \in \mathbb{Y}$ with $\|M - N\|_{\mathbb{Y}} < \eta$ we have $|f(M) - f(N)| < \varepsilon$, i.e.,

$$\forall \varepsilon > 0, \ \forall M \in \mathbb{Y}, \exists \eta > 0, \ \forall N \in \mathbb{Y}, [\|M - N\|_{\mathbb{Y}} < \eta] \Longrightarrow [\forall f \in \mathcal{F}, \ \ |f(M) - f(N)| < \varepsilon].$$

Definition 2.11 [13] The collection $\mathcal{F}$ is said to be uniformly bounded if there is an $C \geq 0$ so that $\|f\|_\infty = \sup_{M \in \mathbb{Y}} |f(M)| \leq C$ for all $f \in \mathcal{F}$, i.e.,

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

Theorem 2.3 *[13] If $\mathcal{F}$ is a collection of uniformly bounded and equicontinuous functions in $\mathcal{C}(\mathbb{Y})$, then $\mathcal{F}$ is relatively compact in $\mathcal{C}(\mathbb{Y})$.*

2.1.6 Periodic functions

Let f be a function defined on a set I, and let w be a non-zero real constant.

Definition 2.12 The function f is said to be w-periodic function if

$$f(t+w) = f(t).$$

for all $t \in I$.

Corollary 2.2 *The derivative of a w-periodic function is also a w-periodic function.*

Remark 2.3 The antiderivative of a w-periodic function is not necessarily a w-periodic function.

Remark 2.4 Let f be $w-$periodic function, then

$$\int_t^{t+w} f(t)\,dt = \int_0^w f(t)\,dt.$$

for $t \in \mathbb{R}$.

2.1.7 The Banach space of continuous periodic functions

Theorem 2.4

For $w > 0$, the set

$$P_w = \{x \in \mathcal{C}(\mathbb{R}, \mathbb{R}),\ x(t+w) = x(t)\},$$

of all continuous and $w-$periodic functions endowed with the supremum norm

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

is a *Banach* space.

Remark 2.5 For $d_1 \geq 0$, $d_2, d_3 > 0$, let

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

1) $P_w(d_1, d_2, d_3)$ is a closed convex and bounded subset of P_w.
2) It follows from conditions $d_1 \leq x(t) \leq d_2$ and $|x(t_2) - x(t_1)| \leq d_3 |t_2 - t_1|$ in the definition of $P_w(d_1, d_2, d_3)$ that this subset is equicontinuous and uniformly bounded. Hence, as an outcome of *Arzelà-Ascoli* theorem we conclude that the closed subset $P_w(d_1, d_2, d_3)$ is compact.

2.1.8 Iterations

Definition 2.13 The composition $M \circ N$ of the function M with the function N is

$$(M \circ N)(t) = M(N(t)),$$

The domain of $M \circ N$ is the set of all t in the domain of N such that $N(t)$ is in the domain of M.

Definition 2.14 For $M : E \longrightarrow E$, the n^{th} iterate of function M, denoted by $M^{[n]}$ for some nonnegative integer n, is defined recursively by

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

and

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

where Id_E is the identity map on E.

Now, we state and prove a crucial lemma that will be employed in the proofs of our achievements.

Lemma 2.1 *[66] If $M, N \in P_w(d_1, d_2, d_3)$, then*

$$\left\| M^{[k]} - N^{[k]} \right\| \leq \sum_{j=0}^{k-1} d_3^j \left\| M - N \right\|, \; k = 1, 2, ...$$

where $M^{[k]} = M \circ M \circ ... \circ M$ k times.

Proof. We will demonstrate this estimate by induction. So, the proof can be given in two steps:

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

$$\left\| M - N \right\| \leq \left\| M - N \right\|.$$

then, the estimate holds for $k = 1$

The inductive step: Now, we suppose that the estimate holds for a given $k = s$ and we want to prove that it also holds for $k = s + 1$. Assume that

$$\left\| M^{[s]} - N^{[s]} \right\| \leq \sum_{j=0}^{s-1} d_3^j \left\| M - N \right\|,$$

then

$$\begin{aligned} \left| M^{[s+1]}(t) - N^{[s+1]}(t) \right| &\leq \left| M\left(M^{[s]}(t)\right) - M\left(N^{[s]}(t)\right) \right| + \left| M\left(N^{[s]}(t)\right) - N\left(N^{[s]}(t)\right) \right| \\ &\leq d_3 \left| M^{[s]}(t) - N^{[s]}(t) \right| + \left| M\left(N^{[s]}(t)\right) - N\left(N^{[s]}(t)\right) \right|, \end{aligned}$$

so

$$\begin{aligned} \left\| M^{[s+1]} - N^{[s+1]} \right\| &\leq d_3 \left\| M^{[s]} - N^{[s]} \right\| + \left\| M - N \right\| \\ &\leq d_3 \sum_{j=0}^{s-1} d_3^j \left\| M - N \right\| + \left\| M - N \right\| \\ &\leq \left(\sum_{j=0}^{s-1} d_3^{j+1} + 1 \right) \left\| M - N \right\| \\ &\leq \sum_{j=0}^{s} d_3^j \left\| M - N \right\|. \end{aligned}$$

By induction we infer that

$$\left\| M^{[s]} - N^{[s]} \right\| \leq \sum_{j=0}^{s-1} d_3^j \left\| M - N \right\|, \quad \forall s \in \mathbb{N},$$

which finishes the proof. ■

Remark 2.6 The above lemma remains true if we replace the subset $P_w(d_1, d_2, d_3)$ by the following subset of P_w:

$$\mathcal{CB}(\sigma_1, k) = \{\varphi \in P_w,\ 0 \leq \varphi(t) \leq \sigma_1, |\varphi(t_2) - \varphi(t_1)| \leq k\,|t_2 - t_1|\,,\ \forall t, t_1, t_2 \in [0, w]\}\,,$$

where $k \geq 0$ and $\sigma_1 > 0$. Furtheremore, $\mathcal{CB}(\sigma_1, k)$ is a convex and compact subset of P_w.

2.2 Fixed point theory

The fixed point theory is a versatile and fundamental branch of mathematics that has applications in various areas. It provides powerful tools for proving the existence and uniqueness of solutions to different types of equations, especially nonlinear ones.

In this section, we state some fixed point theorems which will be applied in proving the desired findings (see [28, 29, 30, 31]). But before that, let us first define what we mean by a fixed point of a mapping.

Definition 2.15 [55] Let $(\mathbb{Y}, \|.\|_{\mathbb{Y}})$ be a normed vector space over $\mathbb{F}$. A fixed point of a mapping $\mathcal{A} : \mathbb{Y} \to \mathbb{Y}$ of $\mathbb{Y}$ into itself is an $M \in \mathbb{Y}$ which is mapped into itself, that is

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

2.2.1 Banach's fixed point theorem

Banach's fixed point theorem (also known as the contraction mapping theorem or contractive mapping theorem), is a powerful mathematical tool used to guarantee the existence and uniqueness of solutions.

Theorem 2.5 *[55] Let $(\mathbb{Y}, \|.\|_{\mathbb{Y}})$ be a Banach space and let $\mathcal{A} : \mathbb{Y} \to \mathbb{Y}$ be a contraction on $\mathbb{Y}$. Then $\mathcal{A}$ has a unique fixed point $M \in \mathbb{Y}$ such that*

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

Theorem 2.6 *[26] If Ω is a closed subset of a Banach space $\mathbb{Y}$ and $\mathcal{A} : \Omega \to \Omega$ is a contraction, then $\mathcal{A}$ has a unique fixed point in Ω.*

2.2.2 Schauder's fixed point theorem

The *Schauder* fixed point theorem is applicable to a compact mapping in a *Banach* space.

Theorem 2.7 *[55] Let Ω be a non-empty bounded closed convex subset of a Banach space $(\mathbb{Y}, \|.\|_{\mathbb{Y}})$ and let $\mathcal{A} : \Omega \longrightarrow \Omega$ be a compact mapping. Then $\mathcal{A}$ has a fixed point in Ω.*

An alternative version of the *Schauder* fixed point theorem can be expressed as follows:

Theorem 2.8 *[55] Let Ω be a non-empty compact convex subset of a Banach space $(\mathbb{Y}, \|.\|_{\mathbb{Y}})$ and let $\mathcal{A} : \Omega \longrightarrow \Omega$ be a continuous mapping. Then $\mathcal{A}$ has a fixed point in Ω.*

2.2.3 Krasnoselskii's fixed point theorem

The *Krasnoselskii* fixed point theorem is applicable to a mapping that can be expressed as a sum of two maps, a contraction and a completely continuous mapping in a *Banach* space.

Theorem 2.9 *[55] Let Ω be a non-empty closed convex bounded subset of a Banach space $(\mathbb{Y}, \|.\|_{\mathbb{Y}})$ and let $\mathcal{A}_1, \mathcal{A}_2 : \Omega \rightarrow \mathbb{Y}$ be two maps such that*

i) $\mathcal{A}_1 M + \mathcal{A}_2 N$ *for all* $M, N \in \Omega$,

ii) $\mathcal{A}_1$ *is continuous and compact,*

iii) $\mathcal{A}_2$ *is a contraction mapping,*

Then $\mathcal{A}_1 + \mathcal{A}_2$ has a fixed point in Ω.

Remark 2.7 Note that if $\mathcal{A}_1 = 0$, the theorem becomes *Banach*'s theorem and if $\mathcal{A}_2 = 0$ then the theorem is not other than *Schauder*'s theorem.

2.3 Green's functions for boundary value problems

The theory of *Green's* functions is a valuable tool in the analysis of differential equations. Particularly, in solving nonhomogeneous boundary value problems for ordinary differential equations where the inverse of the differential operator is an integral operator whose kernel is a *Green*'s function.
We consider two-point n^{th}-order linear boundary value problem of the form

$$\begin{cases} L_n x(t) = g(t), \ t \in I = [a, b], \\ U_i(x) = \gamma_i, \ i = 1, ..., m. \end{cases} \tag{2.1}$$

where

$$L_n x(t) = c_0(t) x^{(n)}(t) + c_1(t) x^{(n-1)}(t) + ... + c_{n-1}(t) x^{(1)}(t) + c_n(t) x(t),$$

and

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

being α_j^i, β_j^i and γ_i real constants for all $i = 1, ..., m$ and $j = 0, ..., n-1$, g and c_k continuous real functions for all $k = 0, ..., n$, and $c_0(t) \neq 0$ for all $t \in I$.

Definition 2.16 [14] We call homogeneous problem associated with (2.1), the problem (2.2) defined by

$$\begin{cases} L_n x(t) = 0, \; t \in I = [a, b], \\ U_i(x) = 0, \; i = 1, ..., m. \end{cases} \tag{2.2}$$

Remark 2.8 [14] The homogeneous problem (2.2) is said to be k-compatible, $0 \leq k \leq n$, if its set of solutions has dimension equals to k.

Theorem 2.10 *The problem*

$$\begin{cases} L_n x(t) = g(t), \; t \in I = [a, b], \\ U_i(x) = \gamma_i, \; i = 1, ..., n. \end{cases} \tag{2.3}$$

where the number of boundary conditions equals the order of the linear differential equation, has a unique solution if and only if the homogeneous problem associated with (2.3) has only the trivial solution.

Definition 2.17 [14] We say that $\mathcal{G}$ is a Green's function for problem (2.2) if it satisfies the following properties:

($\mathbf{G}_1$) $\mathcal{G}$ is defined on the square $I \times I$.

($\mathbf{G}_2$) For $k = 0, 1, ..., n-2$, the partial derivatives $\frac{\partial^k \mathcal{G}}{\partial t^k}$ exist and they are continuous on $I \times I$.

(G$_3$) $\frac{\partial^{n-1}\mathcal{G}}{\partial t^{n-1}}$ and $\frac{\partial^{n}\mathcal{G}}{\partial t^{n}}$ exist and are continuous on the triangles $a \leq \theta < t \leq b$ and $a \leq t < \theta \leq b$.

(G$_4$) For each $t \in (a,b)$ there exist the lateral limits

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

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

$$\frac{\partial^{n-1}\mathcal{G}}{\partial t^{n-1}}\left(t,t^{+}\right) - \frac{\partial^{n-1}\mathcal{G}}{\partial t^{n-1}}\left(t,t^{-}\right) = -\frac{1}{c_0\left(t\right)}.$$

(G$_5$) For each $\theta \in (a,b)$, the function $t \to \mathcal{G}\left(t,\theta\right)$ is a solution of the differential equation $L_n x = 0$ on $t \in [a,\theta)$ and $t \in (\theta, b]$. That is,

$$c_0\left(t\right)\frac{\partial^{n}\mathcal{G}}{\partial t^{n}}\left(t,\theta\right) + c_1\left(t\right)\frac{\partial^{n-1}\mathcal{G}}{\partial t^{n-1}}\left(t,\theta\right) + \ldots + c_{n-1}\left(t\right)\frac{\partial\mathcal{G}}{\partial t}\left(t,\theta\right) + c_n\left(t\right)\mathcal{G}\left(t,\theta\right) = 0,$$

on both intervals.

(G$_6$) For each $\theta \in (a,b)$, the function $t \to \mathcal{G}\left(t,\theta\right)$ satisfies the boundary conditions $U_i\left(\mathcal{G}\left(.,\theta\right)\right) = 0$, $i = 1,\ldots,m$:

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

Theorem 2.11 *[46]*

i) Assume $c_0\left(t\right) \neq 0$, $\forall t \in [a,b]$.

If the homogeneous problem associated with (2.1) has only the trivial solution, then the Green function for this boundary value problem exists and is unique.

ii) If the above conditions are assumed to be satisfied, then the solution of the nonhomogeneous boundary value problem is unique and given by

$$x\left(t\right) = \int_a^b \mathcal{G}\left(t,\theta\right)\; g\left(\theta\right) d\theta, \tag{2.4}$$

where the kernel $\mathcal{G}\left(t,\theta\right)$ *is a Green's function.*

Remark 2.9 There are several methods to finding particular solutions of nonhomogeneous equations such as the method of variation of parameters, integrating factor method, and the *Green* function method, to name a few. According to the superposition principle the general solution can be found as the sum of the general solution to the homogeneous equation and a particular solution of the nonhomogeneous equation. So, if the homogeneous problem (2.2) has only the trivial solution and the n^{th}-order boundary value problem (2.1) is linear. Then, the unique solution obeying nonhomogeneous boundary conditions is simply the obtained particular solution.

Definition 2.18 The problem is said to be regular if in addition to the previous conditions, we have

1) c_0 is nonzero (except perhaps at a finite number of isolated points).
2) The homogeneous problem (2.2) has only the trivial solution.

Remark 2.10 Since $\mathcal{G}$ depends on the main part of the differential equation, but not on the source term g, once $\mathcal{G}$ is found we can immediately solve the more general problem for any arbitrary source term.

Example 2.1 We aim to find the *Green function for the following* two-point second order boundary value problem*:*

$$\begin{cases} x^{(2)}(t) = g(t), \; t \in I = (0,1), \\ x(0) = x(1) = 0. \end{cases} \tag{2.5}$$

First, 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

$$x(t)=A_1t+A_2,$$

where A_1 and A_2 are constants. The boundary conditions of the problem (2.5) give $A_1=0$ and $A_2=0$, which ensures the existence of a unique *Green's function. Consequently*

1) On $(0,\theta)$,

$$\mathcal{G}(t,\theta)=A_1(\theta)\,t+A_2(\theta),$$

and on $(\theta,1)$,

$$\mathcal{G}(t,\theta)=B_1(\theta)\,t+B_2(\theta).$$

2) We must have $\mathcal{G}(0,\theta)=0$, then $A_2(\theta)=0$ and we must also have $\mathcal{G}(1,\theta)=0$ i.e.,

$$B_1(\theta)+B_2(\theta)=0.$$

3) Since $\mathcal{G}$ is continuous, then

$$\mathcal{G}\left(\theta^-,\theta\right)=\lim_{t\to\theta^-}\mathcal{G}(t,\theta)=\lim_{t\to\theta^+}\mathcal{G}(t,\theta)=\mathcal{G}\left(\theta^+,\theta\right),$$

this implies that

$$A_1(\theta)\,\theta+A_2(\theta)=B_1(\theta)\,\theta+B_2(\theta).$$

4)

$$\frac{\partial\mathcal{G}}{\partial t}\left(\theta^+,\theta\right)=B_1(\theta),\ \frac{\partial\mathcal{G}}{\partial t}\left(\theta^-,\theta\right)=A_1(\theta).$$

Therefore

$$B_1(\theta)-A_1(\theta)=1.$$

$A_1(\theta)$, $A_2(\theta)$, $B_1(\theta)$ and $B_2(\theta)$ are solution of

$$\begin{cases} A_2(\theta) = 0 \\ B_1(\theta) + B_2(\theta) = 0 \\ \theta\left[A_1(\theta) - B_1(\theta)\right] + A_2(\theta) - B_2(\theta) = 0 \\ A_1(\theta) - B_1(\theta) + 1 = 0, \end{cases}$$

which gives

$$\begin{cases} A_1(\theta) = \theta - 1 \\ A_2(\theta) = 0 \\ B_1(\theta) = \theta \\ B_2(\theta) = -\theta. \end{cases}$$

We have the *Green* function:

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

Finally, the solution of the problem (2.5) is

$$\begin{aligned} x(t) &= \int_0^1 \mathcal{G}(t,\theta)\, g(\theta)\, d\theta \\ &= \int_0^t t(\theta-1)\, g(\theta)\, d\theta + \int_t^1 \theta(t-1)\, g(\theta)\, d\theta. \end{aligned} \tag{2.6}$$

CHAPTER 3

Iterative Lasota-Wazewska model with a delayed harvesting term

Contents

This chapter is concerned with the existence, uniqueness and stability results of an iterative survival model of red blood cells (named also erythrocytes, erythroid cells, RBCs) in the bone marrow of animals.

3.1 Introduction

A quite large amount of hamatopoiesis models, which possesses a rich history of more than 60 years (see [36, 51, 54]), have been considered by many investigators. To the best of our knowledge, the end of the seventies of the past century witnessed two turning points in the history of the modelling of problems arising in hematology, the first work done by *Lasota* and *Wazewska* [59] in 1976 and the other carried out by *Mackey* and *Glass* [45] in the following year.

Among the contributions that have been interested in investigating the survival of red blood cells in the bone marrow of an animal, we cite some of them which are related to what we are studying in this chapter.

In the end of 1970s and in one of the earliest papers in this topic, *Lasota* and *Wazewska* [59] have set down the following differential equation with one constant delay:

$$x'(t) = -ax(t) + be^{-\gamma x(t-\tau)},$$

where they were focused on the problem of the existence of periodic solutions to this erythropoiesis model which was directed towards modelling and getting a better understanding of the survival of RBCs of an animal. In biological terms, $x(t)$ is the density of mature red blood cells (erythrocytes, erythroid cells, RBCs) in the blood circulation at time t, $a > 0$ denotes the lost rate of RBCs, γ and b are positive constants related to the production of erythrocytes per unit time and the time delay needed to produce a mature erythroid cell for releasing in bloodstreams is denoted by the positive constant τ.

Thirteen years later, in 1989, *Kulenovic* and his collaborators [37] discussed the positive equilibrium of the following generalized *Wazewska-Lasota* model:

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

In [38], the authors used the continuation theorem of *Gaines* and *Mawhin* to prove the existence and global attractivity of positive periodic solutions of the below *Lasota-Wazewska* model with time-varying parameters and delay:

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

While in [44], by means of the fixed point theory, the authors derived the existence and global attractivity of the unique positive periodic solution of the *Lasota-Wazewska* model with time-varying parameters and several variable delays:

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

It is now well known that the harvesting of blood cells plays a significant role in the blood cell population dynamics since it is more than merely a reduction of blood cells by cupping therapy, blood sampling or a blood donation, to name a few but it is of prime interest to gain insight into the dynamical properties of the problem. For any further and detailed information of the effect of the harvesting strategy in the population dynamics and the management of biological renewable one can see [12], [57] and references therein. Concerning, the *Lasota-Wazewska* models with harvesting term, we refer the readers to the paper [23] where the authors investigated a delay *Lasota-Wazewska* model with a discontinuous harvesting term of the form

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

where H is a discontinuous function.

Inspired by the discussion above and taking into account the effect of the harvesting strategy which can exhibit many delayed reactions and retarded responses to stimuli, we investigate the following first order iterative differential equation:

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

where $t \in [0, w]$, $x(0) = x(w)$, $a, b \in C([0, w], (0, +\infty))$, $h \in C([0, w] \times \mathbb{R}, (0, +\infty))$ are w-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 the harvest lag.

It is noteworthy that $x^{[2]}(t)$ results from a delay $\tau_1(t, x(t)) = t - x(t)$ depending upon both the time and the density of mature RBCs which describes the time duration between the division of hematopoietic stem cells (HSC) residing the bone marrow niche and their maturation for releasing in circulating bloodstreams. We can explain this dependence on the density of mature blood cells by the fact that some growth specific factors and hormones control the production and maturation of blood cells by playing an activator or inhibitor role as needed. Indeed, when the density of mature erythrocytes is low, the erythropoietin (EPO) produced by the kidneys with the aid of some other growth factors and some hormones such as thyroxine, sex steroids and pituitary hormones stimulate and accelerate the red blood cell division by increasing the synthesis of DNA, RNA, and hemoglobin in the cells and in the converse case, the division will be suppressed and slowed down.

It should be mentioned that the first-order iterative differential equation (3.1) which is a special kind of the class of differential equations including time and state dependent delays, has not been discussed till now.

Alas, contributions that deal with such equations remain somewhat rare and this is mainly due to the fact that their iterative terms that involve compositions of the unknown function with itself, may create some difficulties both when investigating them and when using the well-known methods. Our main idea to overcome some of these difficulties lies in choosing an appropriate *Banach* space and its subset on the one side, and applying an effective technique based on the fixed point theory, some functional analysis tools as well as the *Green* functions method, on the other side.

More specifically, the present work is primarily concerned with the existence, uniqueness and continuous dependence on parameters of positive periodic solutions for equation (3.1). For this aim, we outline the key steps of this chapter as follows:

Firstly, we construct a *Banach* space and a closed convex and bounded subset of it with a twofold raison: They should help us to control the iterates in equation (3.1) by making them well defined, also, they should guarantee, for biological realism, the periodicity, positivity and boundedness of the solution if there exists.

Secondly, we transform our periodic boundary value problem into a fixed point problem by converting it into an integral equation where the kernel is a *Green's* function and then apply the *Krasnoselskii* and *Banach* fixed point theorems along with the use of some properties of the obtained *Green's* function such that the fixed points obtained are the solutions of our given problem.

Finally, we focus on two main issues:

(1) the establishment of a set of sufficient conditions that ensures the existence of at least one positive periodic solution of equation (3.1) with the periodic boundary conditions by the help of the *Krasnoselskii* fixed point theorem and some properties of the obtained *Green's* kernel in the second

step. For this, the integral operator needs to satisfy the requirements of the used fixed-point theorem and we need especially to express it as a sum of two operators, one of them is completely continuous while the other is a contraction.

(2) the addition of some suitable conditions under which the *Banach* fixed point theorem can be utilized and hence the positive periodic solution of the given problem becomes unique as well as the reveal of the impact of the harvesting strategy on the solution and also we prove that small variations in the harvesting term h or the production rate b lead to small changes of the obtained unique solution.

The remainder of this chapter is as follows. In section 2, we present some preliminary mathematical material that will be used throughout this chapter. In section 3, we look into the existence, uniqueness and continuous dependence on parameters of positive periodic solutions. In section 4, we give three examples to support the desired findings. Finally, we draw a brief conclusion at the end of this chapter.

3.2 Essential preliminaries

Let us start this section by defining an appropriate *Banach* space and a subset of its.

Let P_w the *Banach* space of all $w-$periodic continuous functions endowed with the norm

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

defined in Therem 2.4, and let $P_w(d_1, d_2, d_3)$ the convex and compact subset of P_w defined in Remark 2.5

For ease of exposition, let us adopt the following notations:

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

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

$$A_1 = \frac{\exp\left(-\int_0^w a(v)dv\right)}{\exp\left(\int_0^w a(v)dv\right) - 1}, \; A_2 = \frac{\exp\left(\int_0^w a(v)dv\right)}{\exp\left(\int_0^w a(v)dv\right) - 1}.$$

Throughout this chapter, we impose the following hypotheses:

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

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

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

$$wA_2b_2 \leq d_2, \tag{3.3}$$

$$w\left(A_1b_1e^{-\gamma d_2} - (\mu d_2 + h_2)A_2\right) \geq d_1, \tag{3.4}$$

$$A_2(2 + wa_2)(b_2 + h_2 + \mu d_2) \leq d_3, \tag{3.5}$$

and

$$wA_2\mu < 1. \tag{3.6}$$

Remark 3.1 It follows from Lemma 2.1 that

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

for all $x, y \in P_w(d_1, d_2, d_3)$.

Remark 3.2 From hypothesis ($\mathbf{Q}_1$), we obtain

$$|h(\theta, x(t))| \leq \mu d_2 + h_2. \tag{3.7}$$

Moreover, by applying the mean value theorem to the function $f(z) = \exp(-\gamma z)$ over the interval $\left[x^{[2]}(\theta), y^{[2]}(\theta)\right]$, we get

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

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

Since $\gamma > 0$ and $0 < d_1 \leq \zeta(\theta) \leq d_2$, 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 the Remark 3.1, we get

$$\left|e^{-\gamma x^{[2]}(\theta)} - e^{-\gamma y^{[2]}(\theta)}\right| \leq \gamma(1 + d_3)\|x - y\|, \tag{3.8}$$

for all $x, y \in P_w(d_1, d_2, d_3)$.

3.3 Main findings

Before proceeding with the main findings of this section we will transform our periodic boundary value problem into a nonlinear integral equation where the kernel is a *Green's* function.

Lemma 3.1 *$x \in P_w(d_1, d_2, d_3) \cap \mathcal{C}^1(\mathbb{R}, \mathbb{R})$ is a solution of equation (3.1) if and only if $x \in P_w(d_1, d_2, d_3)$ solves the following nonlinear integral equation:*

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

where

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

Proof. Assume that $x \in P_w(d_1, d_2, d_3) \cap \mathcal{C}^1(\mathbb{R}, \mathbb{R})$ is a solution of equation (3.1) then

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

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

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

In view of periodic properties, we arrive at

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

Thus

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

Conversely, it is easy to obtain equation (3.1) by a direct derivation of (3.9) with respect to t. ■

Remark 3.3 The obtained Green's kernel $\mathcal{G}(t,\theta)$ it is bounded as follows:

$$0 < A_1 \leq \mathcal{G}(t,\theta) \leq A_2, \tag{3.10}$$

Furthermore, for all $t_2, t_1 \in [0, w]$ with $t_1 < t_2$ we have

$$\int_{t_1}^{t_1+w} |\mathcal{G}(t_2, \theta) - \mathcal{G}(t_1, \theta)|\, d\theta \leq A_2 w a_2 |t_2 - t_1|. \tag{3.11}$$

The proof of the property (3.10) can be found in [27] whereas the proof of the property (3.11) is given by Lemma 2.11 in [33].

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

To this end, we define an operator T that can be written as a sum of two operators T_1 and T_2 as follows: $T = T_1 + T_2 : P_w(d_1, d_2, d_3) \longrightarrow P_w$ where $T_1, T_2 : P_w(d_1, d_2, d_3) \longrightarrow P_w$,

$$(T_1 x)(t) = \int_t^{t+w} \mathcal{G}(t, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta, \tag{3.12}$$

and

$$(T_2 x)(t) = -\int_t^{t+w} h(\theta, x(\theta - \tau))\, \mathcal{G}(t, \theta)\, d\theta. \tag{3.13}$$

From Lemma 3.1, the fixed points obtained of the integral operator T are the solutions of our given problem.

Remark 3.4 The integral operators T_1 and T_2 are well defined.

In the following, we establish the existence and uniqueness as well as continuous dependence on parameters of positive periodic and bounded solutions by virtue of two different fixed point theorems and the *Green* functions method.

3.3.1 Existence of positive periodic solutions

In this subsection, we shall employ the *Krasnoselskii* fixed point theorem along with using some useful properties of an obtained *Green's* function to prove the existence of at least one fixed point of the integral operator T which is the solution of our given problem.

Lemma 3.2 *Suppose that conditions (3.3)-(3.5) hold, then*

$$(T_1 x) + (T_2 y) \in P_w (d_1, d_2, d_3),$$

for all $x, y \in P_w (d_1, d_2, d_3)$.

Proof. Let $x, y \in P_w (d_1, d_2, d_3)$, then

$$\begin{aligned}(T_1 x)(t) + (T_2 y)(t) &= \int_t^{t+w} \mathcal{G}(t, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \\ &- \int_t^{t+w} h(\theta, y(\theta - \tau))\, \mathcal{G}(t, \theta)\, d\theta \\ &\leq \int_t^{t+w} \mathcal{G}(t, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta.\end{aligned}$$

According to (3.10) and (3.3), we obtain

$$\begin{aligned}(T_1 x)(t) + (T_2 y)(t) &\leq w A_2 b_2 \\ &\leq d_2.\end{aligned}$$

From (3.10), (3.7) and (3.4), we conclude that

$$\begin{aligned}(T_1 x)(t) + (T_2 y)(t) &\geq w A_1 b_1 e^{-\gamma d_2} - (\mu d_2 + h_2)\, w A_2 \\ &\geq w \left[A_1 b_1 e^{-\gamma d_2} - (\mu d_2 + h_2)\, A_2\right] \\ &\geq d_1.\end{aligned}$$

Therefore

$$d_1 \leq (T_1 x)(t) + (T_2 y)(t) \leq d_2, \tag{3.14}$$

for all $x, y \in P_w (d_1, d_2, d_3)$.

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

$$|(T_1x + T_2y)(t_2) - (T_1x + T_2y)(t_1)| \leq |(T_1x)(t_2) - (T_1x)(t_1)| + |(T_2y)(t_2) - (T_2y)(t_1)|.$$

We have

$$\begin{aligned}|(T_1x)(t_2) - (T_1x)(t_1)| &= \Big| \int_{t_2}^{t_2+w} \mathcal{G}(t_2, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \\ &\quad - \int_{t_1}^{t_1+w} \mathcal{G}(t_1, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \Big| \\ &= \Big| \int_{t_2}^{t_1} \mathcal{G}(t_2, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \\ &\quad + \int_{t_1}^{t_1+w} \mathcal{G}(t_2, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \\ &\quad + \int_{t_1+w}^{t_2+w} \mathcal{G}(t_2, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \\ &\quad - \int_{t_1}^{t_1+w} \mathcal{G}(t_1, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \Big|.\end{aligned}$$

So

$$\begin{aligned}|(T_1x)(t_2) - (T_1x)(t_1)| \leq & \int_{t_2}^{t_1} \mathcal{G}(t_2, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \\ & + \int_{t_1+w}^{t_2+w} \mathcal{G}(t_2, \theta)\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta \\ & + \int_{t_1}^{t_1+w} |\mathcal{G}(t_2, \theta) - G(t_1, \theta)|\, b(\theta)\, e^{-\gamma x^{[2]}(\theta)} d\theta.\end{aligned}$$

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

$$\begin{aligned}|(T_1x)(t_2) - (T_1x)(t_1)| &\leq 2A_2b_2 |t_2 - t_1| + b_2A_2wa_2 |t_2 - t_1| \\ &= A_2b_2 (2 + wa_2) |t_2 - t_1|. \qquad (3.15)\end{aligned}$$

On the other side, we have

$$\begin{aligned}
|(T_2y)(t_2) - (T_2y)(t_1)| &= \left| \int_{t_2}^{t_2+w} h(\theta, y(\theta-\tau))\, \mathcal{G}(t_2,\theta)\, d\theta \right. \\
&\quad \left. - \int_{t_1}^{t_1+w} h(\theta, y(\theta-\tau))\, \mathcal{G}(t_1,\theta)\, d\theta \right| \\
&= \left| \int_{t_2}^{t_1} h(\theta, y(\theta-\tau))\, \mathcal{G}(t_2,\theta)\, d\theta \right. \\
&\quad + \int_{t_1}^{t_1+w} h(\theta, y(\theta-\tau))\, \mathcal{G}(t_2,\theta)\, d\theta \\
&\quad + \int_{t_1+w}^{t_2+w} h(\theta, y(\theta-\tau))\, \mathcal{G}(t_2,\theta)\, d\theta \\
&\quad \left. - \int_{t_1}^{t_1+w} h(\theta, y(\theta-\tau))\, \mathcal{G}(t_1,\theta)\, d\theta \right|.
\end{aligned}$$

So

$$\begin{aligned}
|(T_2y)(t_2) - (T_2y)(t_1)| \le \int_{t_2}^{t_1} & h(\theta, y(\theta-\tau))\, \mathcal{G}(t_2,\theta)\, d\theta \\
&+ \int_{t_1+w}^{t_2+w} h(\theta, y(\theta-\tau))\, \mathcal{G}(t_2,\theta)\, d\theta \\
&+ \int_{t_1}^{t_1+w} |\mathcal{G}(t_2,\theta) - \mathcal{G}(t_1,\theta)|\, h(\theta, y(\theta-\tau))\, d\theta.
\end{aligned}$$

From (3.10), (3.11) and (3.7), we arrive at

$$\begin{aligned}
|(T_2y)(t_2) - (T_2y)(t_1)| &\le 2A_2(\mu d_2 + h_2)|t_2 - t_1| \\
&\quad + (\mu d_2 + h_2) A_2 w a_2 |t_2 - t_1| \\
&= A_2(\mu d_2 + h_2)[2 + w a_2]|t_2 - t_1|. \qquad (3.16)
\end{aligned}$$

Thanks to (3.5), (3.15) and (3.16), we get

$$|(T_1x + T_2y)(t_2) - (T_1x + T_2y)(t_1)| \le d_3 |t_2 - t_1|, \qquad (3.17)$$

for all $x, y \in P_w(d_1, d_2, d_3)$ and $t_1, t_2 \in [0, w]$.

Finally, it follows from (3.14) and (3.17) that $(T_1x) + (T_2y) \in P_w(d_1, d_2, d_3)$.

■

Lemma 3.3 *Suppose that condition (3.6) holds, then T_2 is a contraction.*

Proof. For all $x, y \in P_w(d_1, d_2, d_3)$, we have

$$\begin{aligned} & \left|(T_2x)(t) - (T_2y)(t)\right| \\ \leq & \int_t^{t+w} \mathcal{G}(t,\theta)\left|h(\theta, x(\theta-\tau)) - h(\theta, y(\theta-\tau))\right| d\theta. \end{aligned}$$

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

$$\|T_2x - T_2y\| \leq wA_2\mu \|x-y\|. \tag{3.18}$$

(3.6) implies that T_2 is a contraction. ■

Lemma 3.4 *T_1 is completely continuous operator on $P_w(d_1, d_2, d_3)$.*

Proof. Since $P_w(d_1, d_2, d_3)$ is a compact subset of P_w and since any continuous operator maps every compact set into compact one, then to prove that T_1 is a compact operator it is enough to prove that it is continuous.
For all $x, y \in P_w(d_1, d_2, d_3)$, we have

$$\left|(T_1x)(t) - (T_1y)(t)\right| = \int_t^{t+w} \mathcal{G}(t,\theta)\, b(\theta)\left|e^{-\gamma x^{[2]}(\theta)} - e^{-\gamma y^{[2]}(\theta)}\right| d\theta.$$

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

$$\|T_1x - T_1y\| \leq wA_2b_2\gamma(1+d_3)\|x-y\|, \tag{3.19}$$

and accordingly operator T_1 is *Lipschitz* continuous and hence continuous. Consequently, T_1 is continuous and compact which means that it is a completely continuous operator. ■

By virtue of the above lemmas, one can conclude the following existence theorem.

Theorem 3.1 *If conditions (3.2)-(3.6) are satisfied, then equation (3.1) has at least one positive periodic solution in $P_w(d_1, d_2, d_3)$.*

Proof. It follows from Lemmas 3.2-3.4 that all the criteria of the *Krasnoselskii* fixed point theorem are met, so there exists at least fixed point $x \in P_w(d_1, d_2, d_3)$ such that $x = T_1x + T_2x$ which is a solution of equation (3.1). ■

3.3.2 Existence, uniqueness and stability

This subsection is devoted to derive existence, uniqueness and stability results by using *Banach* fixed point theorem.

Theorem 3.2 *If conditions (3.2)-(3.5) and*

$$wA_2(b_2\gamma(1 + d_3) + \mu) < 1, \tag{3.20}$$

hold, then equation (3.1) has one and only one positive periodic solution.

Proof. First, we can observe that under the same hypotheses of Lemma 3.2 and by utilizing the same technique as that in its proof, we can show that T maps subset $P_w(d_1, d_2, d_3)$ into itself.

Next, from (3.18) and (3.19) we obtain

$$\|Tx - Ty\| \leq wA_2(b_2\gamma(1 + d_3) + \mu)\|x - y\|,$$

for all $x, y \in P_w(d_1, d_2, d_3)$.

It follows from (3.20) that T is a contraction and thereby by virtue of the contraction principle, T has a unique fixed point in $P_w(d_1, d_2, d_3)$, which is the unique positive periodic solution of equation (3.1). ■

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

Proof. Let x be the unique solution of equation (3.1), so x solves the integral equation (3.9) i.e.,

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

and let $\widetilde{x}$ be a solution of the perturbed equation with small perturbations in the harvesting term and the production rate which satisfy the requirements of Theorem 3.3. So, $\widetilde{x}$ solves the following integral equation:

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

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

We have

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

So

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

By (3.10), (3.8) and hypothesis ($\mathbf{Q}_1$) that

$$\begin{aligned}|x(t)-\widetilde{x}(t)| &\leq wA_2\|b\|\gamma(1+d_3)\|x-\widetilde{x}\|+wA_2\left\|b-\widetilde{b}\right\| \\ &+wA_2\left\|h-\widetilde{h}\right\|+wA_2\mu\|x-\widetilde{x}\| \\ &= wA_2(\|b\|\gamma(1+d_3)+\mu)\|x-\widetilde{x}\| \\ &+wA_2\left\|b-\widetilde{b}\right\|+wA_2\left\|h-\widetilde{h}\right\|.\end{aligned}$$

Hence

$$\|x-\widetilde{x}\|(1-wA_2(\|b\|\gamma(1+d_3)+\mu))\leq wA_2\left(\left\|b-\widetilde{b}\right\|+\left\|h-\widetilde{h}\right\|\right).$$

Using condition (3.20), we arrive at

$$\|x-\widetilde{x}\|\leq\frac{wA_2}{(1-wA_2(\|b\|\gamma(1+d_3)+\mu))}\left(\left\|b-\widetilde{b}\right\|+\left\|h-\widetilde{h}\right\|\right).$$

Thus, the Theorem 3.3 is proved. ■

3.4 Examples

To illustrate our findings of the previous subsections, we provide the following examples:

Example 3.1 Consider the following iterative *Lasota-Wazewska* differential equation:

$$\begin{aligned}\frac{dx}{dt} &= -\left(0.02+0.009\left(\sin^2\frac{2\pi}{11}t\right)\right)x(t)+\left(0.01+0.04\left(\sin^2\frac{2\pi}{11}t\right)\right)\exp\left(-\frac{1}{5}x^{[2]}(t)\right) \\ &-\left(\frac{1}{17\pi^5}+\frac{1}{19\pi^5}\frac{x(t-\tau)}{1+x(t-\tau)}\right),\end{aligned} \tag{3.21}$$

in the set $P_w(d_1,d_2,d_3)=P_{11}\left(0.13,2.35,\frac{1}{2}\right)$.

Here $\left(0.02+0.009\left(\sin^2\frac{2\pi}{11}t\right)\right)$ is the lost rate of RBCs, $\left(0.01+0.04\left(\sin^2\frac{2\pi}{11}t\right)\right)$ is related to the production of RBCs per unit time and $\dfrac{1}{17\pi^5}+\dfrac{1}{19\pi^5}\dfrac{x\left(t\right)}{1+x\left(t\right)}$ is the harvesting term h.

We have

$$\begin{aligned}
&a_2=0.029,\ b_1=0.01,\ b_2=0.05,\ A_1\approx 2.4692,\ A_2\approx 4.233,\\
&\gamma=\frac{1}{5},\ \mu=\frac{1}{19\pi^5}\text{ and } h_2=\frac{1}{17\pi^5}.
\end{aligned}$$

Thus

$$\begin{aligned}
&wA_2b_2\approx 2.3282\leq d_2=2.35,\\
&w\left(A_1b_1e^{-\gamma d_2}-\left(\mu d_2+h_2\right)A_2\right)\approx 0.14199\geq d_1=0.13,\\
&A_2\left(2+wa_2\right)\left(b_2+\mu d_2+h_2\right)\approx 0.49667\leq d_3=\frac{1}{2},\\
&wA_2\mu\approx 0.0080083<1.
\end{aligned}$$

The extra condition in Theorem 3.2

$$wA_2\left(b_2\gamma\left(1+d_3\right)+\mu\right)\approx 0.70645<1,$$

is satisfied. We conclude by Theorem 3.2 that equation (3.21) possesses one and only one periodic positive solution in $P_{11}\left(0.13,2.35,\dfrac{1}{2}\right)$.
Moreover, 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 obtain

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

Since all conditions of Theorems 3.2 and 3.3 are fulfilled, equation (3.21) admits a unique positive periodic solution in $P_{11}\left(0.13,2.35,\dfrac{1}{2}\right)$ that depends continuously on the harvesting term h and the production rate b.

Example 3.2 Consider the following iterative *Lasota- Wazewska* differential equation:

$$\frac{dx}{dt} = -\left(0.01 + 0.009\left(\cos^4 \frac{2\pi}{19}t\right)\right) x(t) + \left(0.02 + 0.03\cos^2 \frac{2\pi}{19}t\right) e^{-\frac{1}{20}x^{[2]}(t)}$$
$$-\left(\frac{1}{\pi^9} + \frac{1}{3\pi^9}\frac{x(t-\tau)}{1+x(t-\tau)}\right), \tag{3.22}$$

in the set $P_w(d_1, d_2, d_3) = P_{19}(0.8, 4.25, 0.6)$.

We choose a period of 19 days since the period can vary from a few weeks up to few months.

We have

$$a_2 = 0.019,\ b_1 = 0.02,\ b_2 = 0.05,\ A_1 \approx 2.6806,\ A_2 \approx 4.4562,$$
$$\gamma = \frac{1}{20},\ \mu = \frac{1}{3\pi^9} \text{ and } h_2 = \frac{1}{\pi^9}.$$

So

$$wA_2b_2 \approx 4.2334 \leq d_2 = 4.25,$$
$$w\left(A_1b_1e^{-\gamma d_2} - (\mu d_2 + h_2)A_2\right) \approx 0.81676 \geq d_1 = 0.8,$$
$$A_2(2 + wa_2)(b_2 + \mu d_2 + h_2) \approx 0.52691 \leq d_3 = 0.6,$$
$$wA_2\mu \approx 0.00094678 < 1.$$

The extra condition (3.20) in Theorem 3.2

$$wA_2(b_2\gamma(1 + d_3) + \mu) \approx 0.33962 < 1,$$

is satisfied. Furthermore, 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 arrive at

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

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

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 iterative *Lasota- Wazewska* differential equation (3.22) with the same period in the subset $P_w(d_1, d_2, d_3) = P_{19}(0.8, 4.25, 3.8)$. We have

$$wA_2(b_2\gamma(1+d_3)+\mu) \approx 1.017 > 1.$$

So, the additional condition (3.20) in Theorem 3.2 is not met while all hypotheses of Theorem 3.1 are fulfilled. Hence equation (3.22) in this case admits at least one positive periodic solution in $P_{19}(0.8, 4.25, 3.8)$ which is not necessarily unique.

3.5 Conclusion

In this chapter, we revisited a survival red blood cells model with an iterative term and a nonlinear delayed harvesting one by assuming that the harvesting function and the coefficients in the model are positive, continuous and common periodic. Using a powerful technique including *Krasnoselskii's* fixed point theorem, *Arzelà- Ascoli* theorem and some useful properties of an obtained *Green's* function, we succeeded in constructing a set of sufficient conditions that ensures the existence results. In addition, under an extra condition and by virtue of the *Banach* fixed point theorem, the existence, uniqueness and stability results are proved. the derived theoretical findings were justified by three demonstrative examples.

CHAPTER 4

Delay model of erythropoiesis with iterative production and harvesting terms

Contents

In this chapter, we are interested in studying a delay model of human erythropoiesis with an iterative production term and an iterative harvesting one involving a time varying delay.

4.1 Introduction

Almost half a century ago, the Canadian physiologists *Leon Glass* and *Michael Mackey* [45] proposed the following first order differential equation with a constant delay:

$$N'(t) = -cN(t) + \frac{p\theta^n}{\theta^n + N^n(t-\tau)}.$$

This equation which is now known as *Mackey-Glass* model describes a highly complex process, called erythropoiesis, by which red blood cells (named also erythrocytes, erythroid cells, RBCs) are produced in the marrow of certain bones for releasing them in the bloodstream.

Here, $N(t)$ (cells/kg) is the density of circulating mature human erythrocytes, $cN(t)$ (cells/kg-day) denotes the death term, $c > 0$ (days^{-1}) stands for the mortality rate of RBCs, $\frac{p\theta^n}{\theta^n+N^n(t-\tau)}$ (cells/kg-day) is the erythroid cells reproduction where $p > 0$ (units cells/kg-day) describes the maximal erythrocytes production rate, $n, \theta > 0$ are positive constants and $\tau > 0$ (days) is the time duration of the maturational phase.

Since then, this model has provided a benchmark of excellence in the modelling of physiological control systems including respiratory dynamics as well as hematopoiesis whether in health and disease. As a result, many mathematical models of hematopoiesis had been extensively investigated where recent years showed a growing interest towards this model and its generalizations (see [2, 9, 24, 39]). For instance

In [39], *Liu* and his co-authors 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:

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

In [24], the authors derived the global asymptotic stability of a periodic erythropoiesis model with multiple time-dependent delay and linear impulses of the form:

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

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

Recently, *Bouakkaz* in her paper [9] utilized the *Schauder* fixed point theorem to investigate the existence of positive periodic solutions for a modified erythropoiesis model of the form:

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

where $x^{[1]}(t) = x(t)$, $x^{[2]}(t) = x(x(t))$, $x^{[3]}(t) = x(x(x(t)))$ and $x^{[n]}(t)$ stands for the composition of the function $x(t)$ with itself n times. The iterates $x^{[i]}(t)$ where $i = 2, ..., n$ result from implicit delays of the form $\tau_i(t, x(t))$ that depend upon both the time t and the density of mature erythrocytes $x(t)$.

Inspired by the aforementioned works, we propose a new iterative erythropoiesis model of humans which involves a nonlinear iterative harvesting term that includes a time varying delay. More specifically, this chapter discusses the following first-order differential equation with iterative terms:

$$x'(t) = -a(t)x(t) + \frac{p(t)}{1 + x^{[2]}(t)} - f\left(t, x(t - \tau(t)), x^{[2]}(t)\right), \tag{4.1}$$

where $x^{[2]}(t)$ is the second iterate of $x(t)$, $a, p, \tau \in \mathcal{C}(\mathbb{R}, (0, +\infty))$ are w-periodic functions and $f \in \mathcal{C}(\mathbb{R}^3, (0, +\infty))$ is a w-periodic function with respect to the first variable and satisfies the *Lipschitz* condition with respect to the other variables, namely, there exist two positive constants ρ_0, ρ_1 such that

$$|f(t, x_1, x_2) - f(t, z_1, z_2)| \leq \rho_0 |x_1 - z_1| + \rho_1 |x_2 - z_2|. \tag{4.2}$$

It should be pointed out that many investigations revealed that harvesting blood cells 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, provides more complicated dynamics. In addition, the most realistic harvesting strategy is the one that involves multiple delays especially variable ones. Concerning the main delay which represents the time duration needed for the maturation of erythrocytes in the bone marrow, it should be depended upon both the time t and the density of mature erythrocytes $x(t)$ since delays of this kind are the most realistic ones in describing life sciences phenomena. Actually, according to the density of RBCs, some hematopoietic growth factors (HGFs) and hormones such as erythropoietin (EPO), thyroxine, sex steroids and pituitary hormones impact and encourage the proliferation of hematopoietic stem cells (HSCs), along with the maturation and production of red blood cells. As a consequence, the duration of the proliferative phase is notoriously variable and, more precisely, it should depends on time and the density of mature RBCs which justifies the appearance of the iterative terms in equation (4.1).

The complexity of dealing and controlling the iterative terms in equation (4.1) could be the main raison behind the less investigations in this direction. For this, we will utilize a hybrid technique that combines the fixed point theory, *Green's* functions method and some functional analysis tools, for reaching our targets. Here we would like to mention that our foundation stone is the establishment of the *Banach* space and its subset that help us on one hand to pave the way for the application of our technique and, on the other hand, to ensure some basic biological facts as the periodicity, boundedness, continuity and positivity of the sought solutions.

This chapter endeavors to contribute to the emerging literature of iterative differential equations. More precisely, it aims to

- introduce a revisited *Mackey-Glass* delay differential equation which shows more complex dynamic behavior than previous models that have been investigated in the literature. Indeed, this model with an iterative production term and a nonlinear harvesting one that includes two different variable delays, the first one is a time varying delay while the other one which caused the second iterate to appear in equation (4.1), is a complex delay depending on both the time and the current density of mature erythrocytes.

- establish the existence, uniqueness, stability, periodicity, boundedness and positivity of solutions for the proposed model.

- study and discuss the effect of the harvesting strategy on the population dynamics.

The plan of this chapter is as follows. In section 2, we introduce essential preliminaries which will be included throughout the remaining part of this chapter. In section 3, we derive our main results on the existence, uniqueness and stability of positive periodic solutions. In section 4, we demonstrate the effectiveness of our theoretical findings through two examples followed by concluding remarks in section 5.

4.2 Essential preliminaries

In order to make the iterates well defined, we define a suitable *Banach* space and subset of it. To this end, Let P_w the *Banach* space of all $w-$periodic continuous functions defined in Therem 2.4, and let $P_w(d_1, d_2, d_3)$ the convex and compact subset of P_w defined in Remark 2.5

Remark 4.1 By virtue of the *Arzela-Ascoli* theorem that the closed subset $P_w(d_1, d_2, d_3)$ is compact.

For the sake of simplicity, we will introduce the following notations:

$$\begin{aligned}
\lambda_1 &= \inf_{t\in[0,w]} p(t), \ \lambda_2 = \sup_{t\in[0,w]} p(t), \\
\rho_2 &= \sup_{t\in[0,w]} f(t,0,0), \ \Lambda = (\rho_0 + \rho_1(1+d_3))\, d_2 + \rho_2, \\
\ell_1 &= \frac{wA_2\lambda_2}{1+d_1}, \ \ell_2 = w\left(\frac{A_1\lambda_1}{1+d_2} - A_2\Lambda\right), \\
\ell_3 &= A_2(2+wa_2)\left(\frac{\lambda_2}{1+d_1} + \Lambda\right), \\
\beta &= wA_2\left(\frac{\lambda_2(1+d_3)}{(1+d_1)^2} + \rho_0 + \rho_1(1+d_3)\right),
\end{aligned}$$

Lemma 4.1 *[65]It holds*

$$P_w(d_1, d_2, d_3) = \{x \in P_w, \ d_1 \le x(t) \le d_2, \ |x(t_2) - x(t_1)| \le d_3 |t_2 - t_1|, \forall t_1, t_2 \in [0,w]\}.$$

Moreover, if $x_1, x_2 \in P_w(d_1, d_2, d_3)$, *then*

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

Remark 4.2 It follows from the Lipschitz condition (4.2) and Lemma 4.1 that

$$\left| f\left(t, x(t), x^{[2]}(t)\right) \right| \le \Lambda. \tag{4.3}$$

4.3 Main findings

We begin this section by establishing an equivalence between equation (4.1) with the periodic boundary conditions and an equivalent *Freedholm* integral equation with a *Green's* function type kernel.

Lemma 4.2 *The following assertions are equivalent:*

1) $x \in P_w(d_1, d_2, d_3) \cap C^1(\mathbb{R}, \mathbb{R})$ *is a solution of equation (4.1).*

2) $x \in P_w(d_1, d_2, d_3)$ *is a solution of the following integral equation:*

$$x(t) = \int_t^{t+w} \mathcal{G}(t, \theta) \left(\frac{p(\theta)}{1 + x^{[2]}(\theta)} - f\left(\theta, x(\theta - \tau(\theta)), x^{[2]}(\theta)\right) \right) d\theta, \quad (4.4)$$

where $\mathcal{G}(t, \theta)$ *is defined in Lemma 3.1.*

Proof. Suppose that $x \in P_w(d_1, d_2, d_3) \cap \mathcal{C}^1(\mathbb{R}, \mathbb{R})$ is a solution of equation (4.1). By multiplying both sides of equation (4.1) by $\exp\left(\int_0^t a(v)\, dv\right)$, we have

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

and if we integrate both sides of the above equation from t to $t+w$, we obtain

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

In view of the periodic properties, we get

$$\begin{aligned} &x(t) \left(\exp\left(\int_0^{t+w} a(v)\, dv\right) - \exp\left(\int_0^t a(v)\, dv\right) \right) \\ &= \exp\left(\int_0^t a(v)\, dv\right) \left[\exp\left(\int_t^{t+w} a(v)\, dv\right) - 1 \right] x(t) \\ &= \int_t^{t+w} \left(\frac{p(\theta)}{1 + x^{[2]}(\theta)} - f\left(\theta, x(\theta - \tau(\theta)), x^{[2]}(\theta)\right) \right) \exp\left(\int_0^\theta a(v)\, dv\right) d\theta. \end{aligned}$$

Thus

$$\begin{aligned} x(t) = \int_t^{t+w} &\left(\frac{p(\theta)}{1 + x^{[2]}(\theta)} - f\left(\theta, x(\theta - \tau(\theta)), x^{[2]}(\theta)\right) \right) \\ &\times \frac{\exp\left(\int_0^\theta a(v)\, dv\right)}{\exp\left(\int_0^t a(v)\, dv\right) \left(\exp\left(\int_t^{t+w} a(v)\, dv\right) - 1 \right)} d\theta. \end{aligned}$$

Since

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

Consequently

$$x(t) = \int_t^{t+w} \left(\frac{p(\theta)}{1+x^{[2]}(\theta)} - f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right)\right)\mathcal{G}(t,\theta)\,d\theta.$$

Conversely, suppose that $x \in P_w(d_1,d_2,d_3)$ solves the integral equation (4.4), by differentiating equation (4.4) with respect to t we get that $x \in P_w(d_1,d_2,d_3) \cap \mathcal{C}^1(\mathbb{R},\mathbb{R})$ solves equation (4.1). ■

Now, we will transform the equation (4.1) with periodic boundary conditions into a fixed point problem.

For this aim, we define an integral operator $\mathcal{T} : P_w(d_1,d_2,d_3) \to P_w$ as follows:

$$(\mathcal{T}x)(t) = \int_t^{t+w} \mathcal{G}(t,\theta)\left(\frac{p(\theta)}{1+x^{[2]}(\theta)} - f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right)\right)d\theta. \tag{4.5}$$

It follows from Lemma 4.2 that fixed points of operator $\mathcal{T}$ are solutions of equation (4.1) and vice versa.

4.3.1 Existence of positive periodic solutions

In this subsection, we will utilize *Schauder's* fixed point theorem and some properties of the *Green* kernel to establish the existence of positive periodic and bounded solutions of equation (4.1).

Lemma 4.3 *The operator $\mathcal{T} : P_w(d_1, d_2, d_3) \to P_w$ is continuous.*

Proof. Thanks to the periodic properties, we obtain $(\mathcal{T}x)(t) \in P_w$ for any $x \in P_w(d_1, d_2, d_3)$. Additionally, if $x_1, x_2 \in P_w(d_1, d_2, d_3)$, then

$$\begin{aligned}
|(\mathcal{T}x_2)(t) - (\mathcal{T}x_1)(t)| \leq & \int_t^{t+w} \mathcal{G}(t,\theta)\, p(\theta) \left| \frac{1}{1 + x_2^{[2]}(\theta)} - \frac{1}{1 + x_1^{[2]}(\theta)} \right| d\theta \\
& + \int_t^{t+w} \mathcal{G}(t,\theta) \Big| f\left(\theta, x_2(\theta - \tau(\theta)), x_2^{[2]}(\theta)\right) \\
& - f\left(\theta, x_1(\theta - \tau(\theta)), x_1^{[2]}(\theta)\right) \Big| d\theta \\
\leq & \int_t^{t+w} \mathcal{G}(t,\theta)\, p(\theta) \frac{\left| x_2^{[2]}(\theta) - x_1^{[2]}(\theta) \right|}{\left(1 + x_2^{[2]}(\theta)\right)\left(1 + x_1^{[2]}(\theta)\right)} d\theta \\
& + \int_t^{t+w} \mathcal{G}(t,\theta) \Big| f\left(\theta, x_2(\theta - \tau(\theta)), x_2^{[2]}(\theta)\right) \\
& - f\left(\theta, x_1(\theta - \tau(\theta)), x_1^{[2]}(\theta)\right) \Big| d\theta.
\end{aligned}$$

In view of (4.2), (3.10) and Lemma 4.1, we get the following estimate:

$$|(\mathcal{T}x_2)(t) - (\mathcal{T}x_1)(t)| \leq wA_2 \left(\frac{\lambda_2 (1 + d_3)}{(1 + d_1)^2} + \rho_0 + \rho_1 (1 + d_3) \right) \|x_2 - x_1\|.$$

Therefore

$$|(\mathcal{T}x_2)(t) - (\mathcal{T}x_1)(t)| \leq \beta \|x_2 - x_1\|,$$

which proves that $\mathcal{T}$ is a *Lipschitz* continuous and hence its continuity. ■

Now we state and prove the following lemmas which are essential for the existence results:

Lemma 4.4 *If $\ell_1 \leq d_2$, $\ell_2 \geq d_1$ and condition (4.2) hold, then*

$$d_1 \leq (\mathcal{T}x)(t) \leq d_2, \tag{4.6}$$

for any $x \in P_w(d_1, d_2, d_3)$.

Proof. Let $x \in P_w(d_1, d_2, d_3)$, we have

$$\begin{aligned}(\mathcal{T}x)(t) &= \int_t^{t+w} \mathcal{G}(t,\theta)\left\{\frac{p(\theta)}{1+x^{[2]}(\theta)} - f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right)\right\} d\theta \\ &\leq \int_t^{t+w} \mathcal{G}(t,\theta)\frac{p(\theta)}{1+x^{[2]}(\theta)} d\theta.\end{aligned}$$

In view of (3.10) and $\ell_1 \leq d_2$, we get

$$(\mathcal{T}x)(t) \leq wA_2\frac{\lambda_2}{1+d_1} = \ell_1 \leq d_2,$$

and thanks to (3.10) once again and $\ell_2 \geq d_1$, we arrive at

$$(\mathcal{T}x)(t) \geq w\left(\frac{A_1\lambda_1}{1+d_2} - A_2\Lambda\right) = \ell_2 \geq d_1.$$

From which we conclude that

$$d_1 \leq (\mathcal{T}x)(t) \leq d_2,$$

for any $x \in P_w(d_1, d_2, d_3)$. ■

Lemma 4.5 *If $\ell_3 \leq d_3$ and condition (4.2) hold, then*

$$|(\mathcal{T}x)(t_2) - (\mathcal{T}x)(t_1)| \leq d_3 |t_2 - t_1|. \tag{4.7}$$

for any $x \in P_w(d_1, d_2, d_3)$ and $t_1, t_2 \in \mathbb{R}$.

Proof. Let $t_1, t_2 \in [0, w]$, we have

$$\begin{aligned}|(\mathcal{T}x)(t_2) - (\mathcal{T}x)(t_1)| \leq &\int_{t_2}^{t_1} \frac{p(\theta)}{1+x^{[2]}(\theta)}\mathcal{G}(t_2,\theta)\, d\theta \\ &+ \int_{t_1}^{t_1+w} \frac{p(\theta)}{1+x^{[2]}(\theta)} |\mathcal{G}(t_2,\theta) - \mathcal{G}(t_1,\theta)|\, d\theta \\ &+ \int_{t_1+w}^{t_2+w} \frac{p(\theta)}{1+x^{[2]}(\theta)}\mathcal{G}(t_2,\theta)\, d\theta \\ &+ \int_{t_2}^{t_1} f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right)\mathcal{G}(t_2,\theta)\, d\theta \\ &+ \int_{t_1}^{t_1+w} f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right)|\mathcal{G}(t_2,\theta) - \mathcal{G}(t_1,\theta)|\, d\theta \\ &+ \int_{t_1+w}^{t_2+w} f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right)\mathcal{G}(t_2,\theta)\, d\theta.\end{aligned}$$

By taking into account (4.3), (3.10) and (3.11), we get

$$\begin{aligned}
\left|(\mathcal{T}x)(t_2)-(\mathcal{T}x)(t_1)\right| &\leq \frac{2A_2\lambda_2}{1+d_1}\left|t_2-t_1\right|+\frac{\lambda_2}{1+d_1}wa_2A_2\left|t_2-t_1\right| \\
&+2A_2\Lambda\left|t_2-t_1\right|+\Lambda wa_2A_2\left|t_2-t_1\right| \\
&=\frac{\lambda_2A_2}{(1+d_1)}\left(2+wa_2\right)\left|t_2-t_1\right| \\
&+A_2\Lambda\left(2+wa_2\right)\left|t_2-t_1\right| \\
&=\ell_3\left|t_2-t_1\right|.
\end{aligned}$$

Since $\ell_3 \leq d_3$, and from Lemma 4.1 we get

$$\left|(\mathcal{T}x)(t_2)-(\mathcal{T}x)(t_1)\right| \leq d_3\left|t_2-t_1\right|,$$

for any $x \in P_w(d_1,d_2,d_3)$ and $t_1,t_2 \in \mathbb{R}$. ∎

Corollary 4.1 *If $\ell_1 \leq d_2$, $\ell_2 \geq d_1$, $\ell_3 \leq d_3$ and condition (4.2) hold, then operator $\mathcal{T}$ maps $P_w(d_1,d_2,d_3)$ into itself.*

Proof. It follows from Lemmas 4.4 and 4.5 that $(\mathcal{T}x) \in P_w(d_1,d_2,d_3)$ for all $x \in P_w(d_1,d_2,d_3)$. Hence, the operator $\mathcal{T}$ maps $P_w(d_1,d_2,d_3)$ into itself. Indeed, the operator $\mathcal{T}$ from $P_w(d_1,d_2,d_3)$ to P_w is well defined and if condition (4.2) is satisfied, then Lemma 4.4 ensures that for each $t \in \mathbb{R}$, $x \in P_w(d_1,d_2,d_3)$, $d_2 \geq \ell_1$ and $0 \leq d_1 \leq \ell_2$, we get

$$d_1 \leq (\mathcal{T}x)(t) \leq d_2,$$

which shows the boundedness of $(\mathcal{T}x)(t)$ where the lower bound is d_1 and the upper bound is d_2. Further, under the same condition (4.2), Lemma 4.5 guarantees that for all $x \in P_w(d_1,d_2,d_3)$, $t_1,t_2 \in \mathbb{R}$ and any $d_3 \geq \ell_3$, we have

$$\left|(\mathcal{T}x)(t_2)-(\mathcal{T}x)(t_1)\right| \leq d_3\left|t_2-t_1\right|,$$

which shows that $\mathcal{T}x$ is *Lipschitz* continuous at t.
Finally, we infer that if $x \in P_w(d_1, d_2, d_3)$, then $\mathcal{T}x$ is *Lipschitz* continuous where the *Lipschitz* constant is d_3, bounded above by d_2 and bounded below by d_1. Thus $\mathcal{T}x \in P_w(d_1, d_2, d_3)$. ∎

Now, as a consequence of the above mentioned lemmas, we set our first existence theorem and its proof.

Theorem 4.1 *If $\ell_1 \leq d_2$, $\ell_2 \geq d_1$, $\ell_3 \leq d_3$ and condition (4.2) hold, then equation (4.1) has at least one positive periodic and bounded solution in $P_w(d_1, d_2, d_3)$.*

Proof. In view of Corollary 4.1, operator $\mathcal{T}$ maps the compact and convex subset $P_w(d_1, d_2, d_3)$ into itself and since Lemma 4.3 ensures the continuity of operator $\mathcal{T}$. Then all criteria of *Schauder's* fixed point theorem are fulfilled. Therefore, $\mathcal{T}$ has at least one fixed point in $P_w(d_1, d_2, d_3)$, i.e. there exists $x \in P_w(d_1, d_2, d_3)$ such that $\mathcal{T}x = x$. As a consequence of Lemma 4.2, equation (4.1) admits at least one positive periodic and bounded solution in $P_w(d_1, d_2, d_3)$. ∎

4.3.2 Existence, uniqueness and stability

In this subsection, we shall prove the existence of a unique positive, periodic and bounded solution by means of *Banach* fixed point theorem.

Theorem 4.2 *In addition to the assumptions of Theorem 4.1, if we suppose further that $\beta < 1$, then equation (4.1) has a unique positive periodic and bounded solution $x \in P_w(d_1, d_2, d_3)$.*

Proof. First, we notice that by utilizing the same technique as that in the proof of Lemmas 4.4 and 4.5, we can prove that the operator $\mathcal{T}$ maps

$P_w(d_1, d_2, d_3)$ into itself and arguing as before in the proof of Lemma 4.3 we obtain

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

Since $\beta < 1$, then $\mathcal{T}$ is a contraction operator. So, we deduce by the *Banach* fixed point theorem that $\mathcal{T}$ admits a unique fixed point which is the unique positive periodic and bounded solution of equation (4.1). ■

In our last theorem, we show that the unique solution proved in Theorem 4.2 depends continuously on functions a, p and f even without adding any additional condition.

Theorem 4.3 *Under the same assumptions of Theorem 4.2, the unique solution of equation (4.1) depends continuously on parameters a, p and f.*

Proof. Since x is a solution of equation (4.1), then it solves the integral equation (4.4) i.e.,

$$x(t) = \int_t^{t+w} \mathcal{G}(t,\theta) \left\{ \frac{p(\theta)}{1 + x^{[2]}(\theta)} - f\left(\theta, x(\theta - \tau(\theta)), x^{[2]}(\theta)\right) \right\} d\theta,$$

and let $\widetilde{x}$ be a solution of the perturbed equation with small perturbations in the harvesting term f, the maximal production rate p and the mortality rate a which satisfies all conditions of Theorem 4.2. So, $\widetilde{x}$ solves the following integral equation:

$$\widetilde{x}(t) = \int_t^{t+w} \widetilde{\mathcal{G}}(t,\theta) \left\{ \frac{\widetilde{p}(\theta)}{1 + \widetilde{x}^{[2]}(\theta)} - \widetilde{f}\left(\theta, \widetilde{x}(\theta - \tau(\theta)), \widetilde{x}^{[2]}(\theta)\right) \right\} d\theta,$$

where $\widetilde{f}, \widetilde{p}, \widetilde{a}$ are the perturbed parameters and

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

Estimating the difference between $x(t)$ and $\widetilde{x}(t)$, we have

$$
\begin{aligned}
&|\widetilde{x}(t) - x(t)| \\
&\leq \int_t^{t+w} \widetilde{\mathcal{G}}(t,\theta) \left| \frac{\widetilde{p}(\theta)}{1+\widetilde{x}^{[2]}(\theta)} - \frac{p(\theta)}{1+x^{[2]}(\theta)} \right| d\theta + \int_t^{t+w} \frac{p(\theta)}{1+x^{[2]}(\theta)} \left| \widetilde{\mathcal{G}}(t,\theta) - \mathcal{G}(t,\theta) \right| d\theta \\
&+ \int_t^{t+w} \widetilde{\mathcal{G}}(t,\theta) \left| \widetilde{f}\left(\theta, \widetilde{x}(\theta-\tau(\theta)), \widetilde{x}^{[2]}(\theta)\right) - f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right) \right| d\theta \\
&+ \int_t^{t+w} f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right) \left| \widetilde{\mathcal{G}}(t,\theta) - \mathcal{G}(t,\theta) \right| d\theta \\
&\leq \int_t^{t+w} \mathcal{G}(t,\theta) \left|\widetilde{p}(\theta) - p(\theta)\right| d\theta + \int_t^{t+w} \mathcal{G}(t,\theta) \left|\widetilde{p}(\theta) x^{[2]}(\theta) - p(\theta)\widetilde{x}^{[2]}(\theta)\right| d\theta \\
&+ \int_t^{t+w} p(\theta) \left| \widetilde{\mathcal{G}}(t,\theta) - \mathcal{G}(t,\theta) \right| d\theta \\
&+ \int_t^{t+w} \widetilde{\mathcal{G}}(t,\theta) \left| \widetilde{f}\left(\theta, \widetilde{x}(\theta-\tau(\theta)), \widetilde{x}^{[2]}(\theta)\right) - f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right) \right| d\theta \\
&+ \int_t^{t+w} f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right) \left| \widetilde{\mathcal{G}}(t,\theta) - \mathcal{G}(t,\theta) \right| d\theta.
\end{aligned}
$$

As a result of Lemma 4.1, we deduce that

$$
\left|\widetilde{p}(\theta) x^{[2]}(\theta) - p(\theta)\widetilde{x}^{[2]}(\theta)\right| \leq \|\widetilde{p}\| (1+d_3) \|\widetilde{x} - x\| + d_2 \|\widetilde{p} - p\|. \tag{4.8}
$$

Using the mean value theorem, we obtain

$$
\int_t^{t+w} \left| \widetilde{\mathcal{G}}(t,\theta) - \mathcal{G}(t,\theta) \right| ds \leq \sigma \|\widetilde{a} - a\|, \tag{4.9}
$$

where

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

And by taking into account condition (4.2) we get

$$
\begin{aligned}
&\left| \widetilde{f}\left(\theta, \widetilde{x}(\theta-\tau(\theta)), \widetilde{x}^{[2]}(\theta)\right) - f\left(\theta, x(\theta-\tau(\theta)), x^{[2]}(\theta)\right) \right| \\
\leq\ & (\rho_0 + \rho_1(1+d_3)) \|\widetilde{x} - x\| + \left\|\widetilde{f} - f\right\|. \qquad (4.10)
\end{aligned}
$$

In view of (4.3), (3.10), (4.8),(4.9) and (4.10), we get

$$\begin{aligned} |\widetilde{x}(t) - x(t)| &\leq wA_2 (1+d_2) \|\widetilde{p} - p\| \\ &+ wA_2 \left\| \widetilde{f} - f \right\| + \sigma (\|p\| + \Lambda) \|\widetilde{a} - a\| \\ &+ wA_2 ((1+d_3)(\|\widetilde{p}\| + \rho_1) + \rho_0) \|\widetilde{x} - x\| . \end{aligned}$$

From which we infer that

$$\begin{aligned} &\|\widetilde{x} - x\| (1 - wA_2 ((1+d_3)(\|\widetilde{p}\| + \rho_1) + \rho_0)) \\ &\leq wA_2 (1+d_2) \|\widetilde{p} - p\| + wA_2 \left\| \widetilde{f} - f \right\| + \sigma (\|p\| + \Lambda) \|\widetilde{a} - a\| . \end{aligned}$$

Finally, since $\beta < 1$, then

$$\begin{aligned} \|\widetilde{x} - x\| &\leq \frac{wA_2 (1+d_2)}{1-\beta} \|\widetilde{p} - p\| \\ &+ \frac{wA_2}{1-\beta} \left\| \widetilde{f} - f \right\| \\ &+ \frac{\sigma (\|p_1\| + \Lambda)}{1-\beta} \|\widetilde{a} - a\| . \end{aligned}$$

The proof is completed. ■

4.4 Examples

This section is dedicated to demonstrate the feasibility and effectiveness of our achievements by constructing the following illustrative examples:

Example 4.1 Consider the following iterative erythropoiesis model:

$$\begin{aligned} x'(t) &= -\left(0.005 + 0.001 \sin^2 \frac{2\pi}{15} t\right) x(t) + \frac{\left(0.006 + 0.0001 \sin^4 \frac{2\pi}{15} t\right)}{1 + x^{[2]}(t)} \\ &- \left(\frac{1}{111\pi^{19}} + \frac{x(t-\tau(t))}{113\pi^{19}(1 + x(t-\tau(t)))} + \frac{z^{[2]}(t)}{115\pi^{19}(1 + z^{[2]}(t))}\right) \end{aligned} \tag{4.11}$$

in the compact and convex subset

$$P_w(d_1,d_2,d_3)=\left\{x\in P_w,\ \frac{1}{2}\leq x(t)\leq 0.78,\ |x(t_2)-x(t_1)|\leq\frac{11}{100}|t_2-t_1|,\forall t_1,t_2\in\mathbb{R}\right\}.$$

Here

$$w=15,\ a_2=0.006,\ \lambda_2=0.0061,\ \lambda_1=0.006,\ \rho_2=\frac{1}{111\pi^{19}},\ \rho_1=\frac{1}{113\pi^{19}},$$
$$\rho_0=\frac{1}{115\pi^{19}},\ A_2\approx 12.628,\ A_1\approx 10.707,\ \Lambda\approx 8.4016\times 10^{-12}.$$

We have

$$\ell_1\approx 0.77031\leq d_2=0.78,$$
$$\ell_2\approx 0.54137\geq d_1=\frac{1}{2},$$
$$\ell_3\approx 0.10733\leq d_3=\frac{11}{100}.$$

Further

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

Thus, all conditions of Theorem 4.2 are fulfilled which means that equation (4.11) has one and only one positive periodic and bounded solution in $P_w(d_1,d_2,d_3)$ that depends continuously on the harvesting term f, the maximal production rate p and the mortality rate a.

Example 4.2 Consider the same equation (4.11) given in the previous example with the same period $w=15$ days in the new subset

$$P_w(d_1,d_2,d_3)=\left\{x\in P_w,\ 0.05\leq x(t)\leq 1.2,\ |x(t_2)-x(t_1)|\leq\frac{4}{25}|t_2-t_1|,\forall t_1,t_2\in\mathbb{R}\right\},$$

where $\Lambda\approx 1.1378\times 10^{-11}$.

We have

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

But

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

So, the additional condition in Theorem 4.2 is not fulfilled. However, all requirements of Theorem 4.1 are satisfied. Consequently equation (4.11) has at least one positive periodic and bounded solution in $P_w(d_1, d_2, d_3)$ which is not necessarily unique.

4.5 Conclusion

In this chapter, an erythropoiesis model with an iterative production term and under the assumption of a retarded and iterative harvesting term is discussed. First, seeking to achieve some biological and mathematical objectives, we have chosen an appropriate *Banach* space and a closed convex and bounded subset of it that have satisfied all our desired targets. Next, we have transformed our periodic boundary value problem into an equivalent *Freedholm* integral equation where the kernel is a *Green's* function. Then, some sufficient criteria for the existence of at least one positive periodic and bounded solution have been established via the *Schauder* fixed point along with some useful properties of the obtained kernel. After that, the existence and the stability of the unique positive periodic and bounded solution have been proven by the aid of the *Banach* fixed point theorem. Finally, our theoretical findings which improve and complete existing studies in the literature, have been validated by two illustrative examples.

In conclusion, its our belief that our obtained outcomes is of paramount importance, because

- For the first time, a model of human erythropoiesis with an iterative production term and an iterative delayed harvesting one is studied.

- Until now, the effect of harvesting red blood cells in human with a time varying lag and an other time and state dependent delay leading to the appearance of iterations has not been investigated.

- Our model generalizes the ones addressed in [39] and [24] where the delays were depending only on time and also the ones treated in [9] and [39] which did not take into account the harvesting strategy while the harvesting lag of the considered animal model of erythropoiesis in chapter 3 [29] was constant.

- A new set of sufficient criteria that guarantees the existence, uniqueness, stability, positivity, boundedness and periodicity of solutions of the addressed model are derived.

CHAPTER 5

Neutral erythropoiesis model with iterative production and harvesting terms

Contents

The main objective of this chapter is to discuss the existence, uniqueness and stability of positive periodic solutions for a neutral model of human erythropoiesis with iterative terms.

5.1 Introduction

In this chapter, we revisited the *Mackey-Glass* differential equation by assuming that the mortality and maximal production rates are time varying parameters and taking into account the blood cell harvesting such as wet cupping, blood sampling or blood donation which plays a crucial role in the blood cell population dynamics and the management of biological renewable resources. More precisely, this chapter considers the following neutral *Mackey-Glass* equation with iterative production and harvesting terms:

$$\frac{d}{dt}x(t)-\lambda\frac{d}{dt}x(t-\tau(t)) = -a(t)x(t)+\sum_{i=2}^{n}\frac{\eta(t)}{1+x^{[i]}(t)}-k\left(t,x(t),...,x^{[n]}(t)\right), \tag{5.1}$$

where $x(t)$ is the nth iterate $x^{[n]}(t)$ stands for the composition of $x(t)$ with itself n times, $\tau, a, \eta \in C(\mathbb{R},(0,\infty))$ are common w-periodic functions, $\lambda \in (0,1)$, $\tau(t)$ denotes a transit time needed for the liberation of erythrocytes into the bloodstream and $k \in C(\mathbb{R}^{n+1},(0,\infty))$ is the harvesting function. which is assumed globally *Lipschitz* in $x_1, x_2, ..., x_n$, that is to say there exist n positive constants $L_1, L_2, ..., L_n$ such that

$$|k(t,x_1,...,x_n)-k(t,z_1,...,z_n)| \leq \sum_{i=1}^{n} L_i |x_i - z_i|. \tag{5.2}$$

It is worth mentioning here that the iterates $x^{[i]}(t)$ in equation (5.1) result from $(n-1)$ delays of the form $\tau_i(t,x(t))$ that describe the mean time durations between the division of multipotent hematopoietic stem cells (HSCs) in the bone marrow and the formation and maturation of erythrocytes. Indeed, these delays should depend on both the time and the current density of mature RBCs $x(t)$ and this is essentially due to the fact that some growth factors and hormones such as the renal erythropoietin (EPO), thyroid and pituitary hormones and sex steroids control the division of the HSCs and stimulate RBC maturation. In other words, when the number of mature erytrocytes is large, the aforementioned hormones with the aid of other growth factors suppress the division of the HSCs and repress the RBC maturation, and in the converse case, they will promote and stimulate them. So, equation (5.1) which is a first order iterative differential equation originates from a neutral differential equation with two types of delays, the first one is a time varying lag and the other ones depend on both the state and the time variables.

We would like to point out that our work is one of the first work that investigate the existence, uniqueness and continuous dependence on parameters of positive periodic solutions for a neutral *Mackey-Glass* equation with iterative monotone production and harvesting terms. The approach adopted is based on the fixed point theorem with the *Green* functions method along with some useful functional analysis tools.

We organize the remainder of this chapter as follows. In section 2, some essential preliminaries are stated. In section 3, the existence, uniqueness and stability of positive periodic and bounded solutions are proved. As an application of our theoretical achievements, two illustrative examples are given in section 4. Finally, the chapter ends with a brief conclusion recapitulating the main outlines of the method adopted.

5.2 Essential preliminaries

This section is dedicated to present some notations and assumptions that will be employed in establishing our main outcomes.

Let P_w the *Banach* space of all $w-$periodic continuous functions defined in Therem 2.4, and let $P_w(d_1, d_2, d_3)$ the convex and compact subset of P_w

defined in Remark 2.5.

Throughout this chapter, we shall use the following notations:

$$\inf_{t\in[0,w]} \eta(t) = \eta_1, \quad \sup_{t\in[0,w]} \eta(t) = \eta_2, \quad \sup_{\theta\in[0,w]} |k(\theta, 0, ..., 0)| = L_0,$$
$$L_0 + d_2 \sum_{i=1}^{n} L_i \sum_{j=0}^{i-1} d_3^j = L, \;\; \lambda a_2 + \eta_2 \sum_{i=2}^{n} \sum_{j=0}^{i-1} d_3^j + \sum_{i=1}^{n} L_i \sum_{j=0}^{i-1} d_3^j = d,$$

Besides, the following conditions are supposed to be true:

$$(n-1) A_2 w \eta_2 \leq (1-\lambda) d_2, \tag{5.3}$$
$$(n-1) A_1 w \frac{\eta_1}{1+d_2} - A_2 w (\lambda a_2 d_2 + L) \geq (1-\lambda) d_1, \tag{5.4}$$

and

$$A_2 (2 + w a_2) ((n-1) \eta_2 + \lambda a_2 d_2 + L) \leq d_3 - \lambda d_3 (d_3 + 1). \tag{5.5}$$

5.3 Main findings

Our foremost concern in this section is to give the main results about the existence, uniqueness and continuous dependence on parameters of positive, periodic and bounded solutions.

For this purpose, we show an equivalence between equation (5.1) and an integral equation.

Lemma 5.1 *There is an equivalence between the following two assertions:*
1) $x \in P_w(d_1, d_2, d_3) \cap \mathcal{C}^1(\mathbb{R}, \mathbb{R})$ is a solution of (5.1).
2) $x \in P_w(d_1, d_2, d_3)$ satisfies the following nonlinear integral equation:

$$\begin{aligned} x(t) &= \int_t^{t+w} \mathcal{G}(t,\theta) \left\{ \left(\sum_{i=2}^{n} \frac{\eta(\theta)}{1 + x^{[i]}(\theta)} \right) - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) \right. \\ &\quad \left. - \lambda a(\theta) x(\theta - \tau(\theta)) \right\} d\theta + \lambda x(t - \tau(t)), \end{aligned} \tag{5.6}$$

where $\mathcal{G}(t,\theta)$ is defined in Lemma 3.1.

Proof. Suppose $x \in P_w(d_1, d_2, d_3) \cap \mathcal{C}^1(\mathbb{R}, \mathbb{R})$ satisfies the equation (5.1). Then, by multiplying both sides of equation (5.1) by $\exp\left(\int_0^t a(v)\,dv\right)$, we have

$$\begin{aligned} &\left(\frac{d}{dt}x(t) - \lambda\frac{d}{dt}x(t-\tau(t))\right)\exp\left(\int_0^t a(v)\,dv\right) \\ = &\left(-a(t)x(t) + \sum_{i=2}^{n}\frac{\eta(t)}{1+x^{[i]}(t)} - k\left(t, x(t), ..., x^{[n]}(t)\right)\right)\exp\left(\int_0^t a(v)\,dv\right). \end{aligned}$$

The integration from t to $t+w$ leads to

$$\begin{aligned} &\int_t^{t+w}\left(x'(\theta) + a(\theta)x(\theta)\right)\exp\left(\int_0^\theta a(v)\,dv\right)d\theta \\ &-\lambda\int_t^{t+w}\frac{d}{d\theta}\left(x(\theta-\tau(\theta))\right)\exp\left(\int_0^\theta a(v)\,dv\right)d\theta \\ &=\int_t^{t+w}\left(\sum_{i=2}^{n}\frac{\eta(\theta)}{1+x^{[i]}(\theta)} - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right)\right)\exp\left(\int_0^\theta a(v)\,dv\right). \end{aligned}$$

Since

$$\begin{aligned} \frac{d}{dt}\left(x(t-\tau(t))\right)\exp\left(\int_0^t a(v)\,dv\right) &= \frac{d}{dt}\left(x(t-\tau(t))\exp\int_0^t a(v)\,dv\right) \\ &\quad - a(t)x(t-\tau(t))\exp\left(\int_0^t a(v)\,dv\right). \end{aligned}$$

Then

$$\begin{aligned} &\int_t^{t+w}\left(x'(\theta) + a(\theta)x(\theta)\right)\exp\left(\int_0^\theta a(v)\,dv\right)d\theta \\ &-\lambda\int_t^{t+w}\frac{d}{d\theta}\left(x(\theta-\tau(\theta))\exp\int_0^\theta a(v)\,dv\right)d\theta \\ &=\int_t^{t+w}\left(\sum_{i=2}^{n}\frac{\eta(\theta)}{1+x^{[i]}(\theta)} - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) - \lambda a(\theta)x(\theta-\tau(\theta))\right) \\ &\times\exp\left(\int_0^\theta a(v)\,dv\right)d\theta. \end{aligned}$$

Hence

$$\int_t^{t+w} \frac{d}{d\theta}\left((x(\theta) - \lambda x(\theta - \tau(\theta))) \exp \int_0^{\theta} a(v)\,dv \right) d\theta$$
$$= \int_t^{t+w} \left(\sum_{i=2}^{n} \frac{\eta(\theta)}{1 + x^{[i]}(\theta)} - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) - \lambda a(\theta)\, x(\theta - \tau(\theta)) \right)$$
$$\times \exp\left(\int_0^{\theta} a(v)\,dv \right) d\theta.$$

The property $x(t) = x(t+w)$ implies that

$$(x(t) - \lambda x(t - \tau(t))) \left(\exp\left(\int_t^{t+w} a(v)\,dv \right) - \exp\left(\int_0^{t} a(v)\,dv \right) \right)$$
$$= \exp\left(\int_0^{t} a(v)\,dv \right) \left(\exp\left(\int_t^{t+w} a(v)\,dv \right) - 1 \right) (x(t) - \lambda x(t - \tau(t)))$$
$$= \int_t^{t+w} \left(\sum_{i=2}^{n} \frac{\eta(\theta)}{1 + x^{[i]}(\theta)} - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) - \lambda a(\theta)\, x(\theta - \tau(\theta)) \right)$$
$$\times \exp\left(\int_0^{\theta} a(v)\,dv \right) d\theta.$$

Thus

$$x(t) = \int_t^{t+w} \left(\sum_{i=2}^{n} \frac{\eta(\theta)}{1 + x^{[i]}(\theta)} - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) \right.$$
$$\left. - \lambda a(\theta)\, x(\theta - \tau(\theta)) \right) \frac{\exp\left(\int_0^{\theta} a(v)\,dv \right) \exp\left(- \int_0^{t} a(v)\,dv \right)}{\exp\left(\int_0^{w} a(v)\,dv \right) - 1} d\theta$$
$$+ \lambda x(t - \tau(t)).$$

Therefore

$$x(t) = \int_t^{t+w} \left(\sum_{i=2}^{n} \frac{\eta(\theta)}{1 + x^{[i]}(\theta)} - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) \right.$$
$$\left. - \lambda a(\theta)\, x(\theta - \tau(\theta)) \right) \mathcal{G}(t, \theta)\, d\theta + \lambda x(t - \tau(t)).$$

Conversely, let x be a solution of the integral equation (5.6) that belongs to $P_w(d_1, d_2, d_3)$, then by differentiating equation (5.6) with respect to t we obtain that $x \in P_w(d_1, d_2, d_3) \cap \mathcal{C}^1(\mathbb{R}, \mathbb{R})$ is a solution of equation (5.1). ■

To this aim, let us denote the right hand side of equation (5.6) by $(\mathcal{Z}x)(t)$ where $\mathcal{Z}$ can be written as $\mathcal{Z} = \mathcal{S}_1 + \mathcal{S}_2$ such that $\mathcal{S}_1, \mathcal{S}_2 : P_w(d_1, d_2, d_3) \to P_w$ are given as follows:

$$\begin{aligned}(\mathcal{S}_1 x)(t) \;\; = \;\; & \int_t^{t+w} \mathcal{G}(t,\theta) \left\{ \left(\sum_{i=2}^{n} \frac{\eta(\theta)}{1 + x^{[i]}(\theta)} \right) - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) \right. \\ & \left. -\lambda a(\theta) x(\theta - \tau(\theta)) \right\} d\theta, \qquad (5.7)\end{aligned}$$

and

$$(\mathcal{S}_2 x)(t) = \lambda x(t - \tau(t)). \qquad (5.8)$$

Clearly, solutions of equation (5.1) are fixed points of operator $\mathcal{Z}$ and vice versa.

Remark 5.1 It follows from condition (5.2) and [[66], Lemma 1] that

$$\left| k\left(\theta, x^{[1]}(\theta), x^{[2]}(\theta), ..., x^{[n]}(\theta)\right) \right| \leq L. \qquad (5.9)$$

5.3.1 Existence of positive periodic solutions

In this portion, we study the existence of at least one positive periodic solution by means of *Krasnoselskii's* fixed point theorem. So, we must show that $\mathcal{S}_2$ is a contraction, $\mathcal{S}_1$ is continuous and compact and $\mathcal{S}_1 x + \mathcal{S}_2 z \in P_w(d_1, d_2, d_3)$, for all $x, z \in P_w(d_1, d_2, d_3)$.

Lemma 5.2 *Let $\tau \in P_w(d_1, d_2, d_3)$. Suppose that conditions (5.2), (5.3)-(5.5) hold. Then*

$$\mathcal{S}_1 x + \mathcal{S}_2 z \in P_w(d_1, d_2, d_3), \qquad (5.10)$$

for all $x, z \in P_w(d_1, d_2, d_3)$.

Proof. Let $x, z \in P_w(d_1, d_2, d_3)$, $t \in \mathbb{R}$. By (3.10) and (5.3) we have

$$\begin{aligned}(\mathcal{S}_1 x)(t) + (\mathcal{S}_2 z)(t) &\leq \sum_{i=2}^{n} \int_t^{t+w} \mathcal{G}(t,\theta) \frac{\eta(\theta)}{1+x^{[i]}(\theta)} d\theta + \lambda z(t-\tau(t)) \\ &\leq (n-1) A_2 w \eta_2 + \lambda d_2 \\ &\leq d_2 \end{aligned} \tag{5.11}$$

On the other side, from (3.10) and (5.9) we get

$$\begin{aligned}&(\mathcal{S}_1 x)(t) + (\mathcal{S}_2 z)(t) = \int_t^{t+w} \mathcal{G}(t,\theta) \left(\left(\sum_{i=2}^{n} \frac{\eta(\theta)}{1+x^{[i]}(\theta)} \right) \right. \\ &\left. -k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) - \lambda a(\theta) x(\theta - \tau(\theta)) \right) d\theta + \lambda z(t-\tau(t)) \\ &\geq (n-1) A_1 w \frac{\eta_1}{1+d_2} - A_2 w (\lambda a_2 d_2 + L) + \lambda d_1 .\end{aligned}$$

By taking into account (5.4), we get

$$(\mathcal{S}_1 x)(t) + (\mathcal{S}_2 z)(t) \geq d_1, \ \forall x, z \in P_w(d_1, d_2, d_3), \ \forall t \in \mathbb{R}. \tag{5.12}$$

Let $t_1, t_2 \in \mathbb{R}$ (with $t_1 < t_2$), using (3.10), (3.11) and (5.9), we obtain

$$\begin{aligned}&\left|(\mathcal{S}_1 x)(t_2) - (\mathcal{S}_1 x)(t_1)\right| \\ \leq &\int_{t_2}^{t_1} \left(k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) + \lambda a(\theta) x(\theta - \tau(\theta)) + \sum_{i=2}^{n} \frac{\eta(\theta)}{1+x^{[i]}(\theta)} \right) \\ &\times \mathcal{G}(t_2, \sigma) d\theta \\ &+ \int_{t_1+w}^{t_2+w} \left(k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) + \lambda a(\theta) x(\theta - \tau(\theta)) + \sum_{i=2}^{n} \frac{\eta(\theta)}{1+x^{[i]}(\theta)} \right) \\ &\times \mathcal{G}(t_2, \theta) d\theta \\ &+ \int_{t_1}^{t_1+w} \left(k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) + \lambda a(\theta) x(\theta - \tau(\theta)) + \sum_{i=2}^{n} \frac{\eta(\theta)}{1+x^{[i]}(\theta)} \right) \\ &\times \left|\mathcal{G}(t_2, \theta) - \mathcal{G}(t_1, \theta)\right| d\theta \\ \leq & A_2 (2 + w a_2) ((n-1) \eta_2 + \lambda a_2 d_2 + L) |t_2 - t_1| ,\end{aligned} \tag{5.13}$$

and

$$\left|(\mathcal{S}_2 z)(t_2) - (\mathcal{S}_2 z)(t_1)\right| \leq \lambda d_3 (d_3 + 1) |t_2 - t_1| . \tag{5.14}$$

It follows from (5.5),(5.13), (5.14) and [[66], Lemma 4] that

$$\left|\left(\mathcal{S}_1 x+\mathcal{S}_2 z\right)(t_2)-\left(\mathcal{S}_1 x+\mathcal{S}_2 z\right)(t_1)\right| \leq d_3\left|t_2-t_1\right|. \tag{5.15}$$

Finally, in view of (5.11), (5.12) and (5.15), we infer that $\left(\mathcal{S}_1 x\right)(t)+\left(\mathcal{S}_2 z\right)(t) \in P_w\left(d_1, d_2, d_3\right)$, for all $x, z \in P_w\left(d_1, d_2, d_3\right)$ and $t \in \mathbb{R}$. ■

Lemma 5.3 *If the condition (5.2) is valid, operator $\mathcal{S}_1$ is continuous and compact.*

Proof. Let $x, z \in P_w\left(d_1, d_2, d_3\right)$. From (5.2) and (3.10), we have

$$\begin{aligned}\left|\left(\mathcal{S}_1 x\right)(t)-\left(\mathcal{S}_1 z\right)(t)\right| \leq A_2 \eta_2 & \sum_{i=2}^n \int_t^{t+w}\left|x^{[i]}(\theta)-z^{[i]}(\theta)\right| d\theta \\ & +A_2 \sum_{i=1}^n \int_t^{t+w} L_i\left|x^{[i]}(\theta)-z^{[i]}(\theta)\right| d\theta \\ & +\lambda A_2 a_2 w\|x-z\| .\end{aligned}$$

Thanks to [[65], Lemma 1], we obtain

$$\left\|\mathcal{S}_1 x-\mathcal{S}_1 z\right\| \leq A_2 w d\|x-z\|,$$

That is to say that $\mathcal{S}_1$ is *Lipschitz* continuous and therefore it is continuous. The compactness of $P_w\left(d_1, d_2, d_3\right)$ implies that $\mathcal{S}_1$ is compact. ■

As a consequence of the aforementioned Lemmas, one can infer the following existence theorem.

Theorem 5.1 *Let $\tau \in P_w\left(d_1, d_2, d_3\right)$ and assume that conditions (5.2),(5.3)-(5.5) are satisfied. Then equation (5.1) has a positive periodic solution in $P_w\left(d_1, d_2, d_3\right)$.*

Proof. Since $\lambda<1$, then $\mathcal{S}_2$ is a contraction. So, it follows from Lemmas 5.2 and 5.3 that all requirements of the *Krasnoselskii* fixed point theorem are fulfilled. Therefore, $\mathcal{Z}$ has a fixed point in $P_w\left(d_1, d_2, d_3\right)$ which is a solution of equation (5.1). ■

5.3.2 Existence, uniqueness and stability

To show the existence of a unique positive periodic solution, we utilize *Banach* contraction mapping principle.

Theorem 5.2 *Let $\tau \in P_w(d_1, d_2, d_3)$. If conditions (5.2),(5.3)-(5.5) and*

$$A_2 w d + \lambda < 1, \tag{5.16}$$

are fulfilled, then equation (5.1) admits a unique solution that belongs to $P_w(d_1, d_2, d_3)$.

Proof. Similarly as in the proof of Lemmas 5.2 and 5.3, we get that $\mathcal{Z}$ maps $P_w(d_1, d_2, d_3)$ into itself and

$$\|\mathcal{Z}x - \mathcal{Z}z\| \le (A_2 w d + \lambda) \|x - z\|.$$

So, from (5.16), $\mathcal{Z}$ is a contraction mapping and hence equation (5.1) has one and only one positive periodic solution in $P_w(d_1, d_2, d_3)$. ■

Now, we prove that the unique solution obtained of equation (5.1) depends continuously on parameters a, η and k.

Theorem 5.3 *The unique solution obtained in Theorem 5.2 depends continuously on the functions a, η and k.*

Proof. Let x be the unique solution of equation (5.1), so x satisfies the integral equation (5.6) i.e.

$$x(t) = \int_t^{t+w} \mathcal{G}(t,\theta) \left(\sum_{i=2}^{n} \frac{\eta(\theta)}{1 + x^{[i]}(\theta)} - k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) \right.$$
$$\left. -\lambda a(\theta) x(\theta - \tau(\theta)) \right) d\theta + \lambda x(t - \tau(t)),$$

and let $\widetilde{x}$ be a solution of the perturbed equation with a small perturbation in the harvesting term k, the maximal production rate η and the mortality rate

a, that satisfies all conditions of Theorem 5.2. So, $\widetilde{x}$ satisfies the following integral equation:

$$\widetilde{x}(t) = \int_t^{t+w} \widetilde{\mathcal{G}}(t,\theta)\left(\sum_{i=2}^{n} \frac{\widetilde{\eta}(\theta)}{1+\widetilde{x}^{[i]}(\theta)} - \widetilde{k}\left(\theta, \widetilde{x}(\theta), ..., \widetilde{x}^{[n]}(\theta)\right)\right.$$
$$\left. -\lambda\widetilde{a}(\theta)\widetilde{x}(\theta-\tau(\theta))\right) d\theta + \lambda\widetilde{x}(t-\tau(t)),$$

where

$$\mathcal{G}(t,\theta) = \frac{\exp\left(\int_t^\theta a(v)\,dv\right)}{\left(\exp\left(\int_0^w a(v)\,dv\right)\right)-1} \text{ and } \widetilde{\mathcal{G}}(t,\theta) = \frac{\exp\left(\int_t^\theta \widetilde{a}(v)\,dv\right)}{\left(\exp\left(\int_0^w \widetilde{a}(v)\,dv\right)\right)-1},$$

and $\widetilde{k}, \widetilde{a}, \widetilde{\eta}$ are the perturbed parameters.

By virtue of (3.10) and [[66], Lemma 1] we get

$$\left|\widetilde{\eta}(\theta)x^{[i]}(\theta) - \eta(\theta)\widetilde{x}^{[i]}(\theta)\right| \leq d_2\|\widetilde{\eta}-\eta\| + \|\widetilde{\eta}\|\sum_{j=0}^{i-1} d_3^j\|\widetilde{x}-x\|, \tag{5.17}$$

and the mean value theorem gives us the following estimate:

$$\int_t^{t+w}\left|\widetilde{\mathcal{G}}(t,\theta) - \mathcal{G}(t,\theta)\right| d\theta \leq \sigma\|\widetilde{a}-a\|, \tag{5.18}$$

where σ is defined in the proof of Theorem 4.3.

We have

$$\begin{aligned}
&|\widetilde{x}(t) - x(t)| \\
&\leq \left|\sum_{i=2}^{n}\left(\int_t^{t+w}\widetilde{\mathcal{G}}(t,\theta)\frac{\widetilde{\eta}(\theta)}{1+\widetilde{x}^{[i]}(\theta)}d\sigma - \int_t^{t+w}\mathcal{G}(t,\theta)\frac{\eta(\theta)}{1+x^{[i]}(\theta)}d\theta\right)\right| \\
&+ \left|\int_t^{t+w}\widetilde{\mathcal{G}}(t,\theta)\widetilde{k}\left(\theta,\widetilde{x}(\theta),...,\widetilde{x}^{[n]}(\theta)\right)d\theta\right. \\
&\left.- \int_t^{t+w}\mathcal{G}(t,\theta)k\left(\theta,x(\theta),...,x^{[n]}(\theta)\right)d\theta\right| \\
&+ \left|\int_t^{t+w}\widetilde{\mathcal{G}}(t,\theta)\lambda\widetilde{a}(\theta)\widetilde{x}(\theta-\tau(\theta))\,d\theta\right. \\
&\left.- \int_t^{t+w}\mathcal{G}(t,\theta)\lambda a(\theta)x(\theta-\tau(\theta))\,d\theta\right| \\
&+ |\lambda\widetilde{x}(t-\tau(t)) - \lambda x(t-\tau(t))|.
\end{aligned}$$

It follows from (3.10), (5.17) and (5.18) that

$$\begin{aligned}
&\left|\sum_{i=2}^{n}\left(\int_{t}^{t+w}\widetilde{\mathcal{G}}(t,\theta)\frac{\widetilde{\eta}(\theta)}{1+\widetilde{x}^{[i]}(\theta)}d\theta-\int_{t}^{t+w}\mathcal{G}(t,\theta)\frac{\eta(\theta)}{1+x^{[i]}(\theta)}d\theta\right)\right| \\
&\leq \sum_{i=2}^{n}\int_{t}^{t+w}\widetilde{\mathcal{G}}(t,\theta)\left|\frac{\widetilde{\eta}(\theta)}{1+\widetilde{x}^{[i]}(\theta)}-\frac{\eta(\theta)}{1+x^{[i]}(\theta)}\right|d\theta \\
&+\sum_{i=2}^{n}\int_{t}^{t+w}\frac{\eta(\theta)}{1+x^{[i]}(\theta)}\left|\widetilde{\mathcal{G}}(t,\theta)-\mathcal{G}(t,\theta)\right|d\theta \\
&\leq \sum_{i=2}^{n}\int_{t}^{t+w}\widetilde{\mathcal{G}}(t,\theta)\left|\widetilde{\eta}(\theta)x^{[i]}(\theta)-\eta(\theta)\widetilde{x}^{[i]}(\theta)\right|d\theta \\
&+\sum_{i=2}^{n}\int_{t}^{t+w}\widetilde{\mathcal{G}}(t,\theta)\left|\widetilde{\eta}(\theta)-\eta(\theta)\right|d\theta \\
&+\sum_{i=2}^{n}\int_{t}^{t+w}\eta(\theta)\left|\widetilde{\mathcal{G}}(t,\theta)-\mathcal{G}(t,\theta)\right|d\theta.
\end{aligned}$$

So

$$\begin{aligned}
&\left|\sum_{i=2}^{n}\left(\int_{t}^{t+w}\widetilde{\mathcal{G}}(t,\theta)\frac{\widetilde{\eta}(\theta)}{1+\widetilde{x}^{[i]}(\theta)}d\theta-\int_{t}^{t+w}\mathcal{G}(t,\theta)\frac{\eta(\theta)}{1+x^{[i]}(\theta)}d\theta\right)\right| \\
\leq\ & (n-1)\,wA_2\,(1+d_2)\,\|\widetilde{\eta}-\eta\|+wA_2\,\|\widetilde{\eta}\|\sum_{i=2}^{n}\sum_{j=0}^{i-1}d_3^j\,\|\widetilde{x}-x\| \\
&+\sigma\,(n-1)\,\|\eta\|\,\|\widetilde{a}-a\|\,. \qquad (5.19)
\end{aligned}$$

Using (5.2) and [[65], Lemma 1], we arrive at

$$\left|\widetilde{k}\left(\theta,...,\widetilde{x}^{[n]}(\theta)\right)-k\left(\theta,...,x^{[n]}(\theta)\right)\right|\leq\left\|\widetilde{k}-k\right\|+\sum_{i=1}^{n}L_i\sum_{j=0}^{i-1}d_3^j\,\|\widetilde{x}-x\|\,. \qquad (5.20)$$

Since

$$\begin{aligned}
&\left|\int_{t}^{t+w}\widetilde{\mathcal{G}}(t,\theta)\,\widetilde{k}\left(\theta,\widetilde{x}(\theta),...,\widetilde{x}^{[n]}(\theta)\right)d\theta-\int_{t}^{t+w}\mathcal{G}(t,\theta)\,k\left(\theta,x(\theta),...,x^{[n]}(\theta)\right)d\theta\right| \\
&\leq\int_{t}^{t+w}\widetilde{\mathcal{G}}(t,\theta)\left|\widetilde{k}\left(\theta,\widetilde{x}(\theta),...,\widetilde{x}^{[n]}(\theta)\right)-k\left(\theta,x(\theta),...,x^{[n]}(\theta)\right)\right|d\theta \\
&+\int_{t}^{t+w}k\left(\theta,x(\theta),...,x^{[n]}(\theta)\right)\left|\widetilde{\mathcal{G}}(t,\theta)-\mathcal{G}(t,\theta)\right|d\theta.
\end{aligned}$$

It follows from (3.10), (5.9), (5.18) and (5.20) that

$$\begin{aligned} & \left| \int_t^{t+w} \widetilde{\mathcal{G}}(t,\theta) \widetilde{k}\left(\theta, \widetilde{x}(\theta), ..., \widetilde{x}^{[n]}(\theta)\right) d\theta - \int_t^{t+w} \mathcal{G}(t,\theta) k\left(\theta, x(\theta), ..., x^{[n]}(\theta)\right) d\theta \right| \\ \leq & \ \ \sigma L \|\widetilde{a} - a\| + wA_2 \left\|\widetilde{k} - k\right\| + wA_2 \sum_{i=1}^{n} L_i \sum_{j=0}^{i-1} d_3^j \|\widetilde{x} - x\|. \end{aligned} \tag{5.21}$$

On the other side, we have

$$\begin{aligned} & \left| \int_t^{t+w} \lambda \widetilde{\mathcal{G}}(t,\theta) \widetilde{a}(\theta) \widetilde{x}(\theta - \tau(\theta)) d\theta - \int_t^{t+w} \lambda \mathcal{G}(t,\theta) a(\theta) x(\theta - \tau(\theta)) d\theta \right| \\ & \leq \lambda \int_t^{t+w} \widetilde{\mathcal{G}}(t,\theta) \left|\widetilde{a}(\theta) \widetilde{x}(\theta - \tau(\theta)) - a(\theta) x(\theta - \tau(\theta))\right| d\theta \\ & + \lambda \int_t^{t+w} a(\theta) x(\theta - \tau(\theta)) \left|\widetilde{\mathcal{G}}(t,\theta) - \mathcal{G}(t,\theta)\right| d\theta. \end{aligned}$$

But

$$\left|\widetilde{a}(\theta) \widetilde{x}(\theta - \tau(\theta)) - a(\theta) x(\theta - \tau(\theta))\right| \leq \|\widetilde{a}\| \|\widetilde{x} - x\| + d_2 \|\widetilde{a} - a\|. \tag{5.22}$$

So, from (3.10), (5.18) and (5.22), we get

$$\begin{aligned} & \left| \int_t^{t+w} \widetilde{\mathcal{G}}(t,\theta) \lambda \widetilde{a}(\theta) \widetilde{x}(\theta - \tau(\theta)) d\theta - \int_t^{t+w} \mathcal{G}(t,\theta) \lambda a(\theta) x(\theta - \tau(\theta)) d\theta \right| \\ \leq & \ \ \lambda A_2 w \|\widetilde{a}\| \|\widetilde{x} - x\| + d_2 \lambda (\sigma \|a\| + A_2 w) \|\widetilde{a} - a\|. \end{aligned} \tag{5.23}$$

We have also

$$\left|\lambda \widetilde{x}(t - \tau(t)) - \lambda x(t - \tau(t))\right| \leq \lambda \|\widetilde{x} - x\|. \tag{5.24}$$

Thus, it results from (5.19), (5.21), (5.23) and (5.24) that

$$\begin{aligned} \|\widetilde{x} - x\| \leq & \ A_2 w \left(\lambda \|\widetilde{a}\| + \|\widetilde{\eta}\| \sum_{i=2}^{n} \sum_{j=0}^{i-1} d_3^j + \sum_{i=1}^{n} L_i \sum_{j=0}^{i-1} d_3^j \right) \|\widetilde{x} - x\| \\ & + (\sigma (n-1) \|\eta\| + \sigma L + \lambda d_2 (A_2 w + \sigma \|a\|)) \|\widetilde{a} - a\| \\ & + (n-1) w A_2 (1 + d_2) \|\widetilde{\eta} - \eta\| + wA_2 \left\|\widetilde{k} - k\right\|. \end{aligned}$$

Finally, in view of condition (5.16), we infer that

$$\|\widetilde{x}-x\| \leq \frac{1}{1-(A_2wd+\lambda)}\{(\sigma(n-1)\|\eta\|+\sigma L+\lambda d_2(A_2w+\sigma\|a\|))\|\widetilde{a}-a\| + (n-1)wA_2(1+d_2)\|\widetilde{\eta}-\eta\|+wA_2\left\|\widetilde{k}-k\right\|\}.$$

This finishes the proof. ■

5.4 Examples

This subsection involves two examples demonstrating the effectiveness of our theoretical outcomes.

Example 5.1 Let us consider the following neutral *Mackey-Glass* equation with iterative terms:

$$\frac{d}{dt}\left[y(t)-\lambda y\left(t-0.01-0.08\sin^4\frac{2\pi}{11}t\right)\right] = -\left(\frac{1}{20}+\frac{1}{20}\cos^4\frac{2\pi}{11}t\right)y(t) - \left(\frac{1}{15\pi^7}+\frac{1}{17\pi^7}\left(\cos^4\frac{2\pi}{11}t\right)y^{[1]}(t)+\frac{1}{19\pi^7}\left(\sin^2\frac{2\pi}{11}t\right)y^{[2]}(t)\right) + \frac{0.0027+0.0003\sin^2\frac{2\pi}{11}t}{1+y^{[2]}(t)}, \tag{5.25}$$

where $P_w(d_1,d_2,d_3) = P_{11}(8,0.0025,0.1)$, $\lambda = 0.002$, $n = 2$, $L_0 = \frac{1}{15\pi^7}$, $L_1 = \frac{1}{17\pi^7}$, $L_2 = \frac{1}{19\pi^7}$, $L \approx 3.9704\times 10^{-5}$, $a_2 = 0.1$, $\eta_1 = 0.0027$, $\eta_2 = 0.003$, $A_1 \approx 0.41532$, $A_2 \approx 1.8847$, $d \approx 2.7376\times 10^{-2}$.

In this case, all conditions of Theorem 5.2 are satisfied, so (5.25) has one and only one positive periodic solution in $P_{11}\left(8, 0.0025, \frac{1}{10}\right)$ that depends continuously on parameters a, η and k.

Example 5.2 Let us consider the following neutral *Mackey-Glass* equation with iterative terms:

$$\begin{aligned}
&\frac{d}{dt}\left[x(t)-\lambda x\left(t-0.3-0.05\sin^4\frac{2\pi}{11}t\right)\right]\\
&=-\left(0.02+0.005\cos^2\frac{2\pi}{11}t\right)x(t)+\frac{0.027+0.003\sin^2\frac{2\pi}{11}t}{1+x^{[2]}(t)}\\
&-\left(\frac{1}{5\pi^7}+\frac{1}{7\pi^7}\left(\cos^4\frac{2\pi}{11}t\right)x^{[1]}(t)+\frac{1}{9\pi^7}\left(\sin^2\frac{2\pi}{11}t\right)x^{[2]}(t)\right),\quad(5.26)
\end{aligned}$$

where $P_w(d_1,d_2,d_3)=P_{11}(2,0.2,1.6)$, $\lambda=0.02$, $n=2$, $L_0=\frac{1}{5\pi^7}$, $L_1=\frac{1}{7\pi^7}$, $L_2=\frac{1}{9\pi^7}$, $L\approx 3.1848\times 10^{-4}$, $a_2=0.025$, $\eta_1=0.027$, $\eta_2=0.03$, $A_1\approx 2.7803$, $A_2\approx 4.561$, $d\approx 9.0658\times 10^{-2}$.

So, the extra condition (5.16) in Theorem 5.2 is not satisfied while all conditions of Theorem 5.1 are fulfilled. So the *Mackey-Glass* equation (5.26) in this case has a positive periodic solution in $P_{11}(2,0.2,1.6)$ which is not necessarily unique.

5.5 Conclusion

This chapter has mainly studied a neutral erythropoiesis model including iterative production and harvesting terms where we have shown that the impact of the harvesting strategy does not go beyond reducing the density of RBCs, as such, it does not lead to their extinction. Under sufficient conditions and by means of a technique based on *Banach* and *Krasnoselskii's* fixed point theorems along with the *Green* functions method, we have established the existence, uniqueness and continuous dependence findings in where the desired solutions have been expressed as fixed points of an appropriate integral operator satisfying all criteria of the used fixed point theorems. One of the key step has lied in choosing an appropriate subset of a suitable *Banach* space which on the one hand have allowed us to control the iterative terms and, on the other hand, they have ensured, for the biological realism, the periodicity, positivity and boundedness of the solutions. Another prominent step has lied in deriving some useful properties of the obtained *Green's* kernel which is not always an easy task but not an impossible one.

CHAPTER 6

Leukopoiesis model with iterative production and harvesting terms

Contents

The primary focus of this chapter is to provide some sufficient conditions for the existence, uniqueness and continuous dependence results of a human model of leukopoiesis with iterative terms.

6.1 Introduction

One of the pioneering works that broke new horizons in mathematical modelling of blood cells production as well as the regulation and control mechanisms of hematologic diseases, is the following famous delay differential equation with unimodal production function:

$$x'(t) = -ax(t) + \frac{bx(t-\tau)}{\vartheta^n + x^n(t-\tau)}.$$

It has been put forward at the end of 1977 by *Mackey* and *Glass* [45] for describing the process by which the body produces white blood cells (also known as leukocytes or WBCs). Biologically, the variable of interest $x(t)$ describes the density of mature WBCs over time where cells are assumed to be lost from the circulation at a rate a and they are deemed to be produced at a rate b, the term $\frac{bx(t-\tau)}{\vartheta^n+x^n(t-\tau)}$ stands for the flux of blood cells and τ represents the time delay needed to produce a mature white blood cell in the bone marrow.

A large number of scholars have been focused on this kind of models and as an outcome of this interest there have been several significant contributions to the study of leukopoiesis models. Let us cite some of these remarkable works.

In [60], the authors investigated the existence of positive periodic solutions of the following *Mackey-Glass* model with periodic parameters and a time varying delay:

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

In [58], employing fixed point theorem in cone, the authors discussed the existence, non existence and uniqueness of positive almost periodic solutions for the last model.

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

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

has also been considered by many investigators (see [21], [22] and [40]).

In [9], via *Schauder's* fixed point theorem, *Bouakkaz* got some sufficient conditions of the existence of positive periodic solutions of a first-order iterative functional differential equation with applications to three hematopoiesis models including the following one:

$$x'(t) = -a(t)x(t) + b(t)\sum_{i=2}^{3} \frac{x^{[i]}(t)}{1+x^{[i]}(t)}.$$

On the other side, due to the important impact of the harvesting strategies on the population dynamics of healthy and malignant hematopoiesis cells, the authors of [2] discussed the following *Mackey-Glass* model with a nonlinear harvesting term and several time-varying delays:

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

where they derived some sufficient criteria that guaranteed the existence and the exponential stability of the pseudo almost periodic solutions using the *Banach* fixed point theorem and an appropriate *Lyapunov* functional.

In [10], the authors utilized the *Banach* and *Schauder* fixed point theorems to prove the existence, uniqueness, and stability of positive periodic solutions of the following leukopoiesis model:

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

For some other recent publications on hematopoiesis models, we refer the interested reader to papers [24, 28, 29, 30, 39, 63] and references therein.

Inspired and motivated by the above works and by taking into account the importance impact of the harvesting strategy in population dynamics, this chapter studies the following first-order differential equation with iterative production and harvesting terms:

$$\varphi'(t) = -a(t)\varphi(t) + \sum_{i=1}^{N} b_i(t) \frac{\left(\varphi^{[i]}(t)\right)^m}{1 + \left(\varphi^{[i]}(t)\right)^n} - h\left(t, \varphi(t), \varphi^{[2]}(t), ..., \varphi^{[N]}(t)\right), \tag{6.1}$$

where $1 < m \leq n$, $t \in [0, w]$, $\varphi^{[N]}(t)$ denotes the $n-$th iterate of $\varphi(t)$ such that $\varphi^{[2]}(t) = \varphi(\varphi(t))$ and $\varphi^{[N]}(t)$ is obtained by composing the function φ with itself N times, $a, b_i \in \mathcal{C}(\mathbb{R}, (0, +\infty))$ are w-periodic functions and $h \in \mathcal{C}\left([0, w] \times \mathbb{R}^N, (0, +\infty)\right)$ stands for the harvesting function such that h is w-periodic with respect to the first variable t and globally *Lipschitz* with respect to the other arguments, i.e.,

$$h\left(t + w, \varphi(t), \varphi^{[2]}(t), ..., \varphi^{[N]}(t)\right) = h\left(t, \varphi(t), \varphi^{[2]}(t), ..., \varphi^{[N]}(t)\right),$$

and there exist N positive constants $\mu_1, \mu_2, ..., \mu_N$ such that

$$\left|h(t, \varphi_1, ..., \varphi_N) - h(t, \psi_1, ..., \psi_N)\right| \leq \sum_{i=1}^{N} \mu_i \left|\varphi_i - \psi_i\right|. \tag{6.2}$$

We would like to mention here that the appearance of the iterates in equation (6.1) may be due to many delays that depend upon both the time t and the current density of mature WBCs $\varphi(t)$. In fact, the production of WBCs, which is a sub-process of hematopoiesis, initiates in the bone marrow and are controlled by certain organs such as the spleen, the liver, the kidneys, the adrenal cortex, the gonads, and the central nervous system (CNS). The dependence of the duration of the cell cycle on the current density $\varphi(t)$ is essentially an outcome of this fact because, depending on the density of leukocytes in the body, some growth factors, interleukins and hormones such as -to name but a few- estrogen and granulocyte-colony stimulating factor (G-CSF) stimulate stem cells of the bone marrow to increase the production of leukocytes and also induce a rapid maturation of them whereas others, such as the steroid hormone dehydroepiandrosterone (DHEA), inhibit leukocyte recruitment.

The main aim of this chapter lies in deriving certain sufficient conditions that ensure the existence, uniqueness, and continuous dependence on parameters of positive periodic solutions for equation (6.1) by applying the *Banach* and the *Krasnoselskii* fixed point theorems combined with the *Green* function method. The main idea here consists to transform equation (6.1) with the periodic boundary conditions into a fixed point problem. Then we define an appropriate integral operator for utilizing the aforementioned fixed point theorems that help us to derive our desired findings.

The key contributions that this work makes are threefold. (i) We propose a revised version of *Mackey-Glass* model with an unimodal production function and harvesting that involve iterative terms; (ii) A new sufficient criteria that ensure the existence, uniqueness, and continuous dependence on parameters of positive periodic solutions for a leukopoiesis model with iterative production and harvesting terms are established; (iii) Our results might extend; to some extent the ones of [9, 21, 22, 40, 58, 60] where the delays were assumed to be depending only on the time variable and also the ones of [2] which were ignored the impact of the harvesting strategy on the cell population dynamics while the authors of [10], have considered a model that includes only the second iterate of the unknown variable; (iv) our work aims to contribute in the literature of iterative differential equations where their theory is still emerging, and not very well developed yet. In details, one can see the recent contributions on this topic [1], [7]-[12], [15]-[18], [28]-[35], [25, 41, 48, 56, 65] and [66].

This chapter is organized as follows. In the next section, we present some notations, necessary estimates and preliminary results that will be needed for the rest of the chapter. The existence, uniqueness, and continuous dependence on parameters of positive periodic solutions will be demonstrated in the third section. Moreover, two examples are considered to illustrate our main theoretical outcomes in the fourth section. At last, the fifth section contains the conclusion.

6.2 Essential preliminaries

In this section, we present certain notations, essential estimates and preliminary results needed in the remainder of the chapter.

Let P_w the *Banach* space of all $w-$periodic continuous functions defined in Therem 2.4, and let $\mathcal{CB}(\sigma_1, k)$ the convex and compact subset of P_w defined in Remark 2.6.

For the sake of simplicity, we use the following notations:

$$\inf_{t\in[0,w]} a(t) = a_1, \quad \sup_{\theta\in[0,w]} |h(\theta, 0, ..., 0)| = \mu_0,$$

$$\omega A_2 \left(m (\sigma_1)^{m-1} + (n-m) (\sigma_1)^{m+n-1} \right) \sum_{i=1}^{N} \sup_{t\in[0,w]} (b_i(t)) \sum_{j=0}^{i-1} k^j = J,$$

$$\frac{1}{\exp\left(\int_0^w a(v)dv\right) - 1} = A_0,$$

$$\Psi(x(\theta), y(\theta)) = \sum_{i=1}^{N} b_i(\theta) \frac{\left(x^{[i]}(\theta)\right)^m}{1 + \left(x^{[i]}(\theta)\right)^n} - h\left(\theta, y(\theta), y^{[2]}(\theta), ..., y^{[N]}(\theta)\right).$$

Lemma 6.1 *[66] If $\varphi, \psi \in \mathcal{CB}(\sigma_1, k)$, then*

$$\left\| \varphi^{[\ell]} - \psi^{[\ell]} \right\| \leq \sum_{j=0}^{\ell-1} k^j \left\| \varphi - \psi \right\|, \ \ell = 1, 2, ... \tag{6.3}$$

Thanks to the previous lemma, the condition (6.2) and the mean value theorem we obtain the following essential estimates:

$$\left|h\left(\theta,\varphi^{[1]}\left(\theta\right),\varphi^{[2]}\left(\theta\right),...,\varphi^{[N]}\left(\theta\right)\right)\right| \leq \mu_0 + \sigma_1 \sum_{i=1}^{N} \mu_i \sum_{j=0}^{i-1} k^j, \tag{6.4}$$

and

$$\left|\left(\varphi^{[i]}\left(\theta\right)\right)^{\ell} - \left(\psi^{[i]}\left(\theta\right)\right)^{\ell}\right| \leq \ell\left(\sigma_1\right)^{\ell-1} \sum_{j=0}^{i-1} k^j \left\|\varphi-\psi\right\|, \tag{6.5}$$

for all $\varphi,\psi \in \mathcal{CB}\left(\sigma_1,k\right)$.

6.3 Main findings

We begin this section by the following lemma which establishes the equivalence between equation (6.1) and a nonlinear integral equation.

Lemma 6.2 *$\varphi \in \mathcal{CB}\left(\sigma_1,k\right) \cap \mathcal{C}^1(\mathbb{R},\mathbb{R})$ is a solution of equation (6.1) if and only if $\varphi \in \mathcal{CB}\left(\sigma_1,k\right)$ is a solution of the following integral equation:*

$$\begin{aligned} \varphi\left(t\right) &= \sum_{i=1}^{N} \int_t^{t+w} \left(b_i\left(\theta\right) \frac{\left(\varphi^{[i]}(\theta)\right)^m}{1+\left(\varphi^{[i]}(\theta)\right)^n}\right) \mathcal{G}\left(t,\theta\right) d\theta \\ &\quad - \int_t^{t+w} h\left(\theta,\varphi(\theta),\varphi^{[2]}(\theta),...,\varphi^{[N]}(\theta)\right) \mathcal{G}\left(t,\theta\right) d\theta, \end{aligned} \tag{6.6}$$

where $\mathcal{G}\left(t,\theta\right)$ is defined in Lemma 3.1.

Proof. The proof of the above lemma is close to the proof of the Lemmas 3.1 and 4.2 in the previous chapters. ■

Remark 6.1 The kernel $\mathcal{G}\left(t,\theta\right)$ satisfies the following properties:

$$0 < A_0 \leq \mathcal{G}(t,\theta) \leq A_2, \tag{6.7}$$

Now we will construct two well defined mappings before applying the *Krasnoselskii* fixed point theorem for a sum of two mappings to prove the existence of at least one fixed point which is the positive periodic solution of our equation (6.1).

In order to achieve our objectives and from Lemma 6.2, let us define an operator $\digamma$ that can be written as a sum of two operators $\digamma_1$ and $\digamma_2$ as follows:

$$\digamma = \digamma_1 + \digamma_2 : \mathcal{CB}(\sigma_1, k) \to P_w,$$

where $\digamma_1, \digamma_2 : \mathcal{CB}(\sigma_1, k) \to P_w$,

$$(\digamma_1\varphi)(t) = \sum_{i=1}^{N} \int_t^{t+w} \left(\frac{b_i(\theta)\left(\varphi^{[i]}(\theta)\right)^m}{1 + \left(\varphi^{[i]}(\theta)\right)^n} \right) \mathcal{G}(t,\theta)\, d\theta, \tag{6.8}$$

and

$$(\digamma_2\varphi)(t) = -\int_t^{t+w} h\left(\theta, \varphi(\theta), \varphi^{[2]}(\theta), ..., \varphi^{[N]}(\theta)\right) \mathcal{G}(t,\theta)\, d\theta. \tag{6.9}$$

Based on the periodic properties, we see that $(\digamma_1\varphi)(t) \subset P_w$ and $(\digamma_2\varphi)(t) \subset P_w$ for all $\varphi \in \mathcal{CB}(\sigma_1, k)$, so the operators $\digamma_1$ and $\digamma_2$ are well defined.

6.3.1 Existence of positive periodic solutions

In this portion, we will use the *Krasnoslskii* fixed point theorem to prove the existence of at least one positive periodic and bounded solution of equation (6.1).

Lemma 6.3 *If $\Psi(\varphi(\upsilon), \psi(\upsilon)) > 0$ and if the following condition*

$$wA_2(\sigma_1)^{m-1} \sum_{i=1}^{N} \sup_{t\in[0,w]} (b_i(t)) \leq 1, \tag{6.10}$$

holds, then

$$0 < (\digamma_1\varphi)(t) + (\digamma_2\psi)(t) \leq \sigma_1,$$

for all $\varphi, \psi \in \mathcal{CB}(\sigma_1, k)$.

Proof. Let $\varphi, \psi \in \mathcal{CB}(\sigma_1, k)$. On one hand, it follows from the fact that $\Psi(\varphi(v), \psi(v)) > 0$ and the property of the *Green* function (3.10), we can promptly and effortlessly verify that $(F_1\varphi)(t) + (F_2\psi)(t) > 0$. On the other hand, we have

$$\begin{aligned}(F_1\varphi)(t) + (F_2\psi)(t) &= \sum_{i=1}^{N} \int_t^{t+w} b_i(\theta) \frac{\left(\varphi^{[i]}(\theta)\right)^m}{1 + \left(\varphi^{[i]}(\theta)\right)^n} \mathcal{G}(t,\theta)\, d\theta \\ &\quad - \int_t^{t+w} h\left(\theta, \psi(\theta), \psi^{[2]}(\theta), ..., \psi^{[N]}(\theta)\right) \mathcal{G}(t,\theta)\, d\theta \\ &\leq \sum_{i=1}^{N} \int_t^{t+w} b_i(\theta) \left(\varphi^{[i]}(\theta)\right)^m \mathcal{G}(t,\theta)\, d\theta.\end{aligned}$$

In view of (3.10) and (6.10), we get

$$\begin{aligned}(F_1 x)(t) + (F_2 y)(t) &\leq w A_2 (\sigma_1)^m \sum_{i=1}^{N} \sup_{t\in[0,w]} (b_i(t)) \\ &\leq \sigma_1.\end{aligned}$$

Thus,

$$0 < (F_1\varphi)(t) + (F_2\psi)(t) \leq \sigma_1,$$

for all $\varphi, \psi \in \mathcal{CB}(\sigma_1, k)$. ■

Lemma 6.4 *If the following condition:*

$$A_2(2 + a_2 w)\left((\sigma_1)^m \sum_{i=1}^{N} \sup_{t\in[0,w]} (b_i(t)) + \left(\mu_0 + \sigma_1 \sum_{i=1}^{N} \mu_i \sum_{j=0}^{i-1} k^j\right)\right) \leq k, \tag{6.11}$$

holds, then

$$\left|(F_1\varphi + F_2\psi)(t_2) - (F_1\varphi + F_2\psi)(t_1)\right| \leq k\,|t_2 - t_1|,$$

for all $\varphi, \psi \in \mathcal{CB}(\sigma_1, k)$ *and* $t_1, t_2 \in \mathbb{R}$.

Proof. Let $t_1, t_2 \in [0, w]$ (with $t_1 < t_2$), then

$$\begin{aligned}\left|\left(\digamma_1\varphi+\digamma_2\psi\right)(t_2)-\left(\digamma_1\varphi+\digamma_2\psi\right)(t_1)\right| &\leq \left|\left(\digamma_1\varphi\right)(t_2)-\left(\digamma_1\varphi\right)(t_1)\right| \\ &+\left|\left(\digamma_2\psi\right)(t_2)-\left(\digamma_2\psi\right)(t_1)\right|.\end{aligned}$$

We have

$$\begin{aligned}&\left|\left(\digamma_1\varphi\right)(t_2)-\left(\digamma_1\varphi\right)(t_1)\right| \\ &\leq \sum_{i=1}^{N}\int_{t_2}^{t_1} b_i(\theta)\left(\varphi^{[i]}(\theta)\right)^m \mathcal{G}(t_2,\theta)\,d\theta+\sum_{i=1}^{N}\int_{t_1+w}^{t_2+w} b_i(\theta)\left(\varphi^{[i]}(\theta)\right)^m \mathcal{G}(t_2,\theta)\,d\theta \\ &+\sum_{i=1}^{N}\int_{t_1}^{t_1+w}\left|\mathcal{G}(t_2,\theta)-\mathcal{G}(t_1,\theta)\right| b_i(\theta)\left(\varphi^{[i]}(\theta)\right)^m d\theta,\end{aligned}$$

and

$$\begin{aligned}&\left|\left(\digamma_2\psi\right)(t_2)-\left(\digamma_2\psi\right)(t_1)\right| \\ &\leq \int_{t_2}^{t_1} h\left(\theta,\psi(\theta),\psi^{[2]}(\theta),...,\psi^{[N]}(\theta)\right)\mathcal{G}(t_2,\theta)\,d\theta \\ &+\int_{t_1+\omega}^{t_2+\omega} h\left(\theta,\psi(\theta),\psi^{[2]}(\theta),...,\psi^{[N]}(\theta)\right)\mathcal{G}(t_2,\theta)\,d\theta \\ &+\int_{t_1}^{t_1+\omega}\left|\mathcal{G}(t_2,\theta)-\mathcal{G}(t_1,\theta)\right| h\left(\theta,\psi(\theta),\psi^{[2]}(\theta),...,\psi^{[N]}(\theta)\right)d\theta.\end{aligned}$$

Green's function properties (3.10), (3.11) and the estimate (6.4), imply that

$$\begin{aligned}\left|\left(\digamma_1\varphi\right)(t_2)-\left(\digamma_1\varphi\right)(t_1)\right| &\leq \left(2A_2\sigma_1^m\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(b_i(t)\right)\right)\left|t_2-t_1\right| \\ &+\left(\omega A_2 a_2\left(\sigma_1\right)^m\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(b_i(t)\right)\right)\left|t_2-t_1\right| \\ &\leq A_2\left(\sigma_1\right)^m\left(2+a_2 w\right)\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(b_i(t)\right)\left|t_2-t_1\right|,\end{aligned}$$

and

$$
\begin{aligned}
\left|\left(\digamma_2\psi\right)(t_2)-\left(\digamma_2\psi\right)(t_1)\right| &\leq 2\left(\mu_0+\sigma_1\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)A_2\left|t_2-t_1\right| \\
&+\left(\mu_0+\sigma_1\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)wA_2a_2\left|t_2-t_1\right| \\
&\leq A_2\left(\mu_0+\sigma_1\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)\left(2+wa_2\right)\left|t_2-t_1\right|.
\end{aligned}
$$

Therefore

$$
\begin{aligned}
&\left|\left(\digamma_1\varphi+\digamma_2\psi\right)(t_2)-\left(\digamma_1\varphi+\digamma_2\psi\right)(t_1)\right| \\
&\leq A_2\left(\sigma_1\right)^m\left(2+a_2w\right)\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(b_i(t)\right)\left|t_2-t_1\right| \\
&+A_2\left(\mu_0+\sigma_1\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)\left(2+wa_2\right)\left|t_2-t_1\right| \\
&=A_2\left(2+a_2w\right)\left(\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(b_i(t)\right)\left(\sigma_1\right)^m+\left(\mu_0+\sigma_1\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)\right)\left|t_2-t_1\right|.
\end{aligned}
$$

Thanks to (6.11), we get

$$
\left|\left(\digamma_1\varphi+\digamma_2\psi\right)(t_2)-\left(\digamma_1\varphi+\digamma_2\psi\right)(t_1)\right|\leq k\left|t_2-t_1\right|,
$$

for all $\varphi,\psi\in\mathcal{CB}\left(\sigma_1,k\right)$ and $t_1,t_2\in[0,w]$. ■

Corollary 6.1 *From Lemmas 6.3 and 6.4, we infer that*

$$
\digamma_1\varphi+\digamma_2\psi\in\mathcal{CB}\left(\sigma_1,k\right),
$$

for all $\varphi,\psi\in\mathcal{CB}\left(\sigma_1,k\right)$.

Lemma 6.5 *Under the following condition:*

$$
wA_2\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j<1, \tag{6.12}
$$

$\digamma_2$ *is a contraction operator.*

Proof. Let $\varphi, \psi \in \mathcal{CB}(\sigma_1, k)$, then

$$
\begin{aligned}
&\left|(\digamma_2\varphi)(t) - (\digamma_2\psi)(t)\right| \\
&= \left| \int_t^{t+w} h\left(\theta, \varphi(\theta), ..., \varphi^{[N]}(\theta)\right) \mathcal{G}(t,\theta)\, d\theta \right. \\
&\left. - \int_t^{t+w} h\left(\theta, \psi(\theta), ..., \psi^{[N]}(\theta)\right) \mathcal{G}(t,\theta)\, d\theta \right| \\
&\le \int_t^{t+w} \mathcal{G}(t,\theta) \left| h\left(\theta, \varphi(\theta), ..., \varphi^{[N]}(\theta)\right) - h\left(\theta, \psi(\theta), ..., \psi^{[N]}(\theta)\right) \right| d\theta.
\end{aligned}
$$

The *Lipschitz* condition (6.2) and Lemma 6.1 lead to

$$
\begin{aligned}
\left|(\digamma_2\varphi)(t) - (\digamma_2\psi)(t)\right| &\le wA_2 \sum_{i=1}^{N} \mu_i \left|\varphi^{[i]} - \psi^{[i]}\right| \\
&\le wA_2 \sum_{i=1}^{N} \mu_i \sum_{j=0}^{i-1} k^j \left\|\varphi - \psi\right\|.
\end{aligned}
$$

In view of condition (6.12), we conclude that operator $\digamma_2$ is a contraction. ■

Lemma 6.6 *The operator $\digamma_1$ is completely continuous.*

Proof. Since $\mathcal{CB}(\sigma_1, k)$ is a compact subset of P_w and since any continuous operator maps every compact set into compact one, then to prove that $\digamma_1$ is a compact operator it is enough to demonstrate its continuity. For $\varphi, \psi \in \mathcal{CB}(\sigma_1, k)$, we have

$$
\begin{aligned}
&\left|(\digamma_1\varphi)(t) - (\digamma_1\psi)(t)\right| \\
\le\ & \sum_{i=1}^{N} \int_t^{t+w} b_i(\theta)\, \mathcal{G}(t,\theta) \left| \frac{\left(\varphi^{[i]}(\theta)\right)^m}{1 + \left(\varphi^{[i]}(\theta)\right)^n} - \frac{\left(\psi^{[i]}(\theta)\right)^m}{1 + \left(\psi^{[i]}(\theta)\right)^n} \right| d\theta,
\end{aligned}
$$

which gives

$$
\begin{aligned}
&\left|\left(\digamma_1\varphi\right)(t)-\left(\digamma_1\psi\right)(t)\right| \\
&\leq \sum_{i=1}^{N}\int_t^{t+w} b_i(\theta)\,\mathcal{G}(t,\theta)\left(\left|\left(\varphi^{[i]}(\theta)\right)^m-\left(\psi^{[i]}(\theta)\right)^m\right|\right. \\
&+\left.\left|\left(\varphi^{[i]}(\theta)\right)^m\left(\psi^{[i]}(\theta)\right)^m\left(\psi^{[i]}(\theta)\right)^{n-m}-\left(\psi^{[i]}(\theta)\right)^m\left(\varphi^{[i]}(\theta)\right)^m\left(\varphi^{[i]}(\theta)\right)^{n-m}\right|\right)d\theta \\
&\leq \sum_{i=1}^{N}\int_t^{t+w} b_i(\theta)\,\mathcal{G}(t,\theta)\left(\left|\left(\varphi^{[i]}(\theta)\right)^m-\left(\psi^{[i]}(\theta)\right)^m\right|\right. \\
&+\left.\left(\varphi^{[i]}(\theta)\right)^m\left(\psi^{[i]}(\theta)\right)^m\left|\left(\psi^{[i]}(\theta)\right)^{n-m}-\left(\varphi^{[i]}(\theta)\right)^{n-m}\right|\right)d\theta.
\end{aligned}
$$

From (3.10), (6.5) and Lemma 6.1, we get

$$
\begin{aligned}
&\left|\left(\digamma_1\varphi\right)(t)-\left(\digamma_1\psi\right)(t)\right| \\
&\leq wA_2\left(m\left|\varsigma_i(\theta)\right|^{m-1}+\left(\sigma_1\right)^{2m}(n-m)\left|\varsigma_i(\theta)\right|^{n-m-1}\right)\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(b_i(t)\right)\sum_{j=0}^{i-1}k^j\left\|\varphi-\psi\right\| \\
&\leq wA_2\left(m\left(\sigma_1\right)^{m-1}+\left(\sigma_1\right)^{2m}(n-m)\left(\sigma_1\right)^{n-m-1}\right)\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(b_i(t)\right)\sum_{j=0}^{i-1}k^j\left\|\varphi-\psi\right\| \\
&\leq wA_2\left(m\left(\sigma_1\right)^{m-1}+(n-m)\left(\sigma_1\right)^{m+n-1}\right)\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(b_i(t)\right)\sum_{j=0}^{i-1}k^j\left\|\varphi-\psi\right\| \\
&= J\left\|\varphi-\psi\right\|,
\end{aligned}
$$

which shows that the operator $\digamma_1$ is *Lipschitz* continuous. Hence, $\digamma_1$ is continuous and compact which means that it is a completely continuous operator. ■

As an outcome of the previous lemmas, we state our first theorem and its proof.

Theorem 6.1 *If* $\Psi(\varphi(\upsilon),\psi(\upsilon))>0$ *and if conditions (6.10)-(6.12) hold then equation (6.1) admits at least one positive periodic solution in* $\mathcal{CB}(\sigma_1,k)$.

Proof. We conclude by Corollary 6.1, Lemmas 6.5 and 6.6 that all conditions of the *Krasnoselskii* fixed point theorem are fulfilled, so $\digamma = \digamma_1 + \digamma_2$ has at least one fixed point $\varphi \in \mathcal{CB}(\sigma_1, k)$ such that $(\digamma_1 + \digamma_2)(\varphi) = \varphi$, which means that φ is a positive periodic solution to equation (6.1). ■

6.3.2 Existence, uniqueness and stability

In this subsection, we show the existence and continuous dependence on parameters of the unique solution via *Banach* fixed point theorem.

Theorem 6.2 *Let $\Psi(\varphi(v), \psi(v)) > 0$. If conditions (6.10), (6.11) and*

$$J + wA_2 \sum_{i=1}^{N} \mu_i \sum_{j=0}^{i-1} k^j < 1, \tag{6.13}$$

are satisfied, then equation (6.1) admits a unique positive periodic solution in $\mathcal{CB}(\sigma_1, k)$.

Proof. Similar to the proof of the Lemmas 6.3, 6.4 and 6.6, we can prove that the operator $\digamma$ maps the compact and bounded subset $\mathcal{CB}(\sigma_1, k)$ into itself and that

$$\|\digamma\varphi - \digamma\psi\| \leq \left(J + wA_2 \sum_{i=1}^{N} \mu_i \sum_{j=0}^{i-1} k^j \right) \|\varphi - \psi\|,$$

for all $\varphi, \psi \in \mathcal{CB}(\sigma_1, k)$.

Using condition (6.13), this last inequality implies that $\digamma$ is a contraction. Consequently, we infer by the *Banach* contraction principal that $\digamma$ has a unique fixed point which is the unique positive periodic solution of equation (6.1). ■

Theorem 6.3 *Under the assumptions of Theorem 6.2, the unique solution of equation (6.1) depends continuously on the functions a, b_i for $i = 1 : N$ and also on the harvesting function h.*

Proof. Let φ be the unique solution of equation (6.1) that satisfies the integral equation (6.6) and let $\widetilde{\varphi}$ be a solution of the perturbed equation with small perturbations in the harvesting function, the rate of loss of white blood cells from the circulation and the production rate which satisfy all requirements of Theorem 6.2. So, $\widetilde{\varphi}$ satisfies the following integral equation:

$$\widetilde{\varphi}(t) = \sum_{i=1}^{N} \int_t^{t+w} \left(\widetilde{b}_i(\theta) \frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n} \right) \widetilde{\mathcal{G}}(t,\theta)\, d\theta - \int_t^{t+w} \widetilde{h}\left(\theta, \widetilde{\varphi}(\theta), \widetilde{\varphi}^{[2]}(\theta), ..., \widetilde{\varphi}^{[N]}(\theta)\right) \widetilde{\mathcal{G}}(t,\theta)\, d\theta,$$

where

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

Estimating the difference between $\varphi(t)$ and $\widetilde{\varphi}(t)$, we get

$$\begin{aligned}
&\left|\varphi(t) - \widetilde{\varphi}(t)\right| \\
&\le \left| \sum_{i=1}^{N} \int_t^{t+w} \left(b_i(\theta) \frac{\left(\varphi^{[i]}(\theta)\right)^m}{1+\left(\varphi^{[i]}(\theta)\right)^n} \mathcal{G}(t,\theta) - \widetilde{b}_i(\theta) \frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n} \widetilde{\mathcal{G}}(t,\theta) \right) d\theta \right| \\
&+ \left| \int_t^{t+w} \left(h\left(\theta, \varphi(\theta), ..., \varphi^{[N]}(\theta)\right) \mathcal{G}(t,\theta) - \widetilde{h}\left(\theta, \widetilde{\varphi}(\theta), ..., \widetilde{\varphi}^{[N]}(\theta)\right) \widetilde{\mathcal{G}}(t,\theta) \right) d\theta \right|.
\end{aligned}$$

We have

$$\begin{aligned}
&\left| \sum_{i=1}^{N} \int_t^{t+w} \left(b_i(\theta) \frac{\left(\varphi^{[i]}(\theta)\right)^m}{1+\left(\varphi^{[i]}(\theta)\right)^n} \mathcal{G}(t,\theta) - \widetilde{b}_i(\theta) \frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n} \widetilde{\mathcal{G}}(t,\theta) \right) d\theta \right| \\
&\le \sum_{i=1}^{N} \int_t^{t+w} \mathcal{G}(t,\theta) \left| b_i(\theta) \frac{\left(\varphi^{[i]}(\theta)\right)^m}{1+\left(\varphi^{[i]}(\theta)\right)^n} - \widetilde{b}_i(\theta) \frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n} \right| d\theta \\
&+ \sum_{i=1}^{N} \int_t^{t+w} \widetilde{b}_i(\theta) \frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n} \left| \mathcal{G}(t,\theta) - \widetilde{\mathcal{G}}(t,\theta) \right| d\theta.
\end{aligned}$$

Therefore

$$\left|\sum_{i=1}^{N}\int_{t}^{t+w}\left(b_i(\theta)\frac{\left(\varphi^{[i]}(\theta)\right)^m}{1+\left(\varphi^{[i]}(\theta)\right)^n}\mathcal{G}(t,\theta)-\widetilde{b}_i(\theta)\frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n}\widetilde{\mathcal{G}}(t,\theta)\right)d\theta\right|$$
$$\leq\int_{t}^{t+w}\mathcal{G}(t,\theta)\left(\varphi^{[i]}(\theta)\right)^m\sum_{i=1}^{N}\left|b_i(\theta)-\widetilde{b}_i(\theta)\right|d\theta$$
$$+\sum_{i=1}^{N}\int_{t}^{t+w}\mathcal{G}(t,\theta)\,\widetilde{b}_i(\theta)\left|\frac{\left(\varphi^{[i]}(\theta)\right)^m}{1+\left(\varphi^{[i]}(\theta)\right)^n}-\frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n}\right|d\theta$$
$$+\sum_{i=1}^{N}\int_{t}^{t+w}\widetilde{b}_i(\theta)\frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n}\left|\mathcal{G}(t,\theta)-\widetilde{\mathcal{G}}(t,\theta)\right|d\theta,$$

and

$$\left|\int_{t}^{t+w}\left(h\left(\theta,\varphi(\theta),...,\varphi^{[N]}(\theta)\right)\mathcal{G}(t,\theta)-\widetilde{h}\left(\theta,\widetilde{\varphi}(\theta),...,\widetilde{\varphi}^{[N]}(\theta)\right)\widetilde{\mathcal{G}}(t,\theta)\right)d\theta\right|$$
$$\leq\int_{t}^{t+w}\mathcal{G}(t,\theta)\left|h\left(\theta,\varphi(\theta),...,\varphi^{[N]}(\theta)\right)-\widetilde{h}\left(\theta,\widetilde{\varphi}(\theta),...,\widetilde{\varphi}^{[N]}(\theta)\right)\right|d\theta$$
$$+\int_{t}^{t+w}\widetilde{h}\left(\theta,\widetilde{\varphi}(\theta),...,\widetilde{\varphi}^{[N]}(\theta)\right)\left|\mathcal{G}(t,\theta)-\widetilde{\mathcal{G}}(t,\theta)\right|d\theta$$
$$\leq\int_{t}^{t+w}\mathcal{G}(t,\theta)\left|h\left(\theta,\varphi(\theta),...,\varphi^{[N]}(\theta)\right)-h\left(\theta,\widetilde{\varphi}(\theta),...,\widetilde{\varphi}^{[N]}(\theta)\right)\right|d\theta$$
$$+\int_{t}^{t+w}\mathcal{G}(t,\theta)\left|h\left(\theta,\widetilde{\varphi}(\theta),...,\widetilde{\varphi}^{[N]}(\theta)\right)-\widetilde{h}\left(\theta,\widetilde{\varphi}(\theta),...,\widetilde{\varphi}^{[N]}(\theta)\right)\right|d\theta$$
$$+\int_{t}^{t+w}\widetilde{h}\left(\theta,\widetilde{\varphi}(\theta),\widetilde{\varphi}^{[2]}(\theta),...,\widetilde{\varphi}^{[N]}(\theta)\right)\left|\mathcal{G}(t,\theta)-\widetilde{\mathcal{G}}(t,\theta)\right|d\theta.$$

The Lemma 6.1 and estimate (6.5) imply that

$$\left|\frac{\left(\varphi^{[i]}(\theta)\right)^m}{1+\left(\varphi^{[i]}(\theta)\right)^n}-\frac{\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m}{1+\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n}\right|$$
$$\leq\left|\left(\varphi^{[i]}(\theta)\right)^m-\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m\right|+\left|\left(\varphi^{[i]}(\theta)\right)^m\left(\widetilde{\varphi}^{[i]}(\theta)\right)^n-\left(\widetilde{\varphi}^{[i]}(\theta)\right)^m\left(\varphi^{[i]}(\theta)\right)^n\right|$$
$$\leq\left(m(\sigma_1)^{m-1}+(n-m)(\sigma_1)^{m+n-1}\right)\sum_{j=0}^{i-1}k^j\left\|\varphi-\widetilde{\varphi}\right\|. \tag{6.14}$$

Thanks again to Lemma 6.1 and condition (6.2), we get

$$\left|h\left(\theta,\varphi(\theta),\varphi^{[2]}(\theta),...,\varphi^{[N]}(\theta)\right)-h\left(\theta,\widetilde{\varphi}(\theta),\widetilde{\varphi}^{[2]}(\theta),...,\widetilde{\varphi}^{[N]}(\theta)\right)\right|$$
$$\leq\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\left\|\varphi-\widetilde{\varphi}\right\|. \tag{6.15}$$

In view of the mean value theorem, we have

$$\int_t^{t+w}\left|\mathcal{G}\left(t,\theta\right)-\widetilde{\mathcal{G}}\left(t,\theta\right)\right|d\theta\leq\rho\left\|a-\widetilde{a}\right\|, \tag{6.16}$$

where

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

In view of (6.14),(6.15) and (6.16) we obtain

$$\left|\varphi\left(t\right)-\widetilde{\varphi}\left(t\right)\right|\leq wA_2\left(\sigma_1\right)^m\sum_{i=1}^{N}\left\|b_i-\widetilde{b}_i\right\|+J\left\|\varphi-\widetilde{\varphi}\right\|$$
$$+\left(\sigma_1\right)^m\rho\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(\widetilde{b}_i\left(t\right)\right)\left\|a-\widetilde{a}\right\|+wA_2\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\left\|\varphi-\widetilde{\varphi}\right\|$$
$$+wA_2\left\|h-\widetilde{h}\right\|+\left(\mu_0+\sigma_1\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)\rho\left\|a-\widetilde{a}\right\|.$$

This last inequality implies that

$$\left(1-\left(J+wA_2\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)\right)\left\|\varphi-\widetilde{\varphi}\right\|$$
$$\leq wA_2\left(\sigma_1\right)^m\sum_{i=1}^{N}\left\|b_i-\widetilde{b}_i\right\|+wA_2\left\|h-\widetilde{h}\right\|$$
$$+\rho\left(\left(\mu_0+\sigma_1\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)+\left(\sigma_1\right)^m\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(\widetilde{b}_i\left(t\right)\right)\right)\left\|a-\widetilde{a}\right\|.$$

Finally, from condition (6.13) we obtain

$$\left\|\varphi-\widetilde{\varphi}\right\| \leq \frac{1}{1-\left(J+wA_2\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)}\left\{wA_2\left(\sigma_1\right)^m\sum_{i=1}^{N}\left\|b_i-\widetilde{b}_i\right\|+wA_2\left\|h-\widetilde{h}\right\|\right.$$
$$\left.+\rho\left(\left(\mu_0+\sigma_1\sum_{i=1}^{N}\mu_i\sum_{j=0}^{i-1}k^j\right)+\left(\sigma_1\right)^m\sum_{i=1}^{N}\sup_{t\in[0,w]}\left(\widetilde{b}_i\left(t\right)\right)\right)\left\|a-\widetilde{a}\right\|\right\}.$$

The proof is completed. ■

6.4 Examples

In this section, we furnish two illustrative examples to demonstrate the effectiveness of the derived results.

Example 6.1 Let $N=n=m=2$. We consider the following first-order iterative differential equation:

$$\begin{aligned}\varphi'(t) &= -a\left(t\right)\varphi(t)+b_1\left(t\right)\frac{\left(\varphi^{[1]}(t)\right)^2}{1+\left(\varphi^{[1]}(t)\right)^2}+b_2\left(t\right)\frac{\left(\varphi^{[2]}(t)\right)^2}{1+\left(\varphi^{[2]}(t)\right)^2}\\ &\quad -h\left(t,\varphi(t),\varphi^{[2]}(t)\right),\end{aligned} \tag{6.17}$$

where

$$\begin{aligned}&a\left(t\right)=0.005+0.001\cos^2\left(\frac{2\pi t}{15}\right),\ \ b_1\left(t\right)=0.35+0.05\sin^4\left(\frac{2\pi t}{15}\right),\\ &b_2\left(t\right)=0.2+0.05\cos^2\left(\frac{2\pi t}{15}\right),\\ &h\left(t,\varphi(t),\varphi^{[2]}(t)\right)=\frac{1}{36\pi^{12}}\left(\sin^2\frac{2\pi t}{15}\right)+\frac{1}{38\pi^{12}}\left(\sin^2\frac{2\pi t}{15}\right)\varphi^{[1]}(t)\\ &\qquad+\frac{1}{42\pi^{12}}\left(\sin^4\frac{2\pi t}{15}\right)\varphi^{[2]}(t),\end{aligned}$$

and let

$$\begin{aligned}\mathcal{CB}\left(\sigma_0,\sigma_1,k\right) &= \{\varphi\in P_w,\ 0\leq\sigma_0\leq\varphi\leq\sigma_1,\\ &\quad \left|\varphi\left(t_2\right)-\varphi\left(t_1\right)\right|\leq k\left|t_2-t_1\right|,\ \forall t_1,t_2\in[0,w]\},\end{aligned}$$

where

$$w = 15, \ \sigma_0 = 0.0005, \ \sigma_1 = 0.0078, \ k = 0.011.$$

In this case, we obtain

$$\begin{aligned} \mu_0 &= \frac{1}{36\pi^{12}}, \ \mu_1 = \frac{1}{38\pi^{12}}, \ \mu_2 = \frac{1}{42\pi^{12}}, \ A_0 \approx 11.628, \\ A_2 &\approx 12.628, \ J \approx 1.9288, \end{aligned}$$

and

$$\begin{aligned} & wA_2\sigma_1 \sum_{i=1}^{2} \sup_{t\in[0,w]} (b_i(t)) \approx 0.96036 \leq 1, \\ & \min_{\varphi,\psi\in\mathcal{CB}(\sigma_0,\sigma_1,k)} \Psi(\varphi(\theta), \psi(\theta)) \approx 1.0701 \times 10^{-7} > 0, \\ & A_2(2 + a_2 w) \left((\sigma_1)^2 \sum_{i=1}^{2} \sup_{t\in[0,w]} (b_i(t)) + \left(\mu_0 + \sigma_1 \sum_{i=1}^{2} \mu_i \sum_{j=0}^{i-1} k^j \right) \right) \\ & \qquad \approx 0.0010445 \leq k, \\ & wA_2 \sum_{i=1}^{2} \mu_i \sum_{j=0}^{i-1} k^j \approx 0.000010326 < 1. \end{aligned}$$

So, all conditions of Theorem 6.1 are fulfilled. Therefore, equation (6.17) has at least one positive periodic solution in $\mathcal{CB}(\sigma_0, \sigma_1, k)$.

Moreover, we have

$$wA_2 \sum_{i=1}^{2} \mu_i \sum_{j=0}^{i-1} k^j \approx 0.000010326 < 1,$$

and

$$J + wA_2 \sum_{i=1}^{2} \mu_i \sum_{j=0}^{i-1} k^j \approx 1.9288 > 1,$$

which shows that the requirements of Theorems 6.2 and 6.3 are not satisfied. So, the solution of equation (6.17) exists but it is not necessarily unique.

Example 6.2 We consider the same equation of the previous example with

$$\mathcal{CB}(\sigma_0, \sigma_1, k) = \mathcal{CB}(0.0005, 0.00078, 0.011).$$

In this case, we obtain $J \approx 0.19288$ and

$$wA_2\sigma_1 \sum_{i=1}^{2} \sup_{t\in[0,w]} (b_i(t)) \approx 0.096036 \leq 1,$$

$$\min_{\varphi,\psi\in\mathcal{CB}(\sigma_0,\sigma_1,k)} \Psi(\varphi(\theta),\psi(\theta)) \approx 1.074 \times 10^{-7} > 0,$$

$$A_2(2+a_2w)\left((\sigma_1)^2 \sum_{i=1}^{2} \sup_{t\in[0,w]} (b_i(t)) + \left(\mu_0 + \sigma_1 \sum_{i=1}^{2} \mu_i \sum_{j=0}^{i-1} k^j\right)\right) \approx 0.000011232 \leq k,$$

$$J + wA_2 \sum_{i=1}^{2} \mu_i \sum_{j=0}^{i-1} k^j \approx 0.19289 < 1.$$

So, all conditions of Theorems 6.2 and 6.3 are fulfilled. Hence, equation (6.17) has one and only one positive periodic solution in $\mathcal{CB}(0.0005, 0.00078, 0.011)$ that depends continuously on the rates of loss of white blood cells from the circulation and the production as well as the harvesting function.

6.5 Conclusion

In this chapter, we have investigated a leukopoiesis model with iterative production and harvesting terms. Firstly, we have applied the *Krasnoselskii* fixed point theorem with the help of some *Green's* function properties and certain functional analysis tools to demonstrate the existence of at least one positive periodic solution for equation (6.1) which is not necessarily unique. Secondly, by supposing that the same conditions of the existence theorem have been hold except for the last one, which has been substituted with another condition, the *Banach* fixed point theorem has guaranteed the existence of a unique positive periodic solution for equation (6.1). Thirdly, without having to fulfill any further conditions, we have derived the continuous dependence on parameters result.

General conclusion and perspectives

The key goal of the research carried out and presented in the current thesis is to investigate four delayed differential equations with iterative terms describing different types of blood cell production with harvesting strategies in human beings and animals that is, three human and animal models of erythropoiesis and a model of human leukopoiesis.

In the first chapter we have given a brief overview of the topic. Additionally, we presented some biological facts and the pioneering mathematical models where we tried to be careful with references for providing the most remarkable ones in order to allow the reader to deepen and pool his/her knowledge on the subject. The intent of the second chapter has been the presentation of some useful concepts, tools and preliminary results that played an important role in establishing our main outcomes. While our foremost concern in the third, fourth, fifth and sixth chapters has been the establishment of the sufficient conditions for proving the existence, uniqueness, and continuous dependence on parameters of positive periodic and bounded solutions. Furthermore, we have illustrated our theoretical outcomes with many examples.

Our approach can be considered as a hybrid technique since it has combined the fixed point theory with the *Green* function method. At first glance, this technique appears as if it does not require too much effort to achieve the desired results, but in fact it needs to undertake some important preparatory works before applying the fixed point theorems. The red thread of this technique has been the good choice of the *Banach* space and its subsets which lay the foundations for applying the fixed point theorems, controlling the iterative terms and ensuring some biological facts. The second step has been the conversion of the iterative problems into equivalent integral equations with *Green*'s kernels where the sought solutions has been expressed as fixed points of suitable integral operators fulfilling all conditions of the chosen fixed point theorems. Finally, by the aid of the *Krasnoselskii*, *Schauder* and *Banach* fixed point theorems as well as some useful properties of the obtained *Green*'s kernel we have succeeded in reaching the sought results that have been published in well-established journals.

In conclusion, it is our belief that our works offer many research perspectives. For instance,

- The obtained findings can extend many results where the delays have been supposed to be depending only on the time variable and also the ones which have ignored the impact of the harvesting strategy on the cell population dynamics (see for example [6] and [28]).

- The technique used here can be applied successfully for doing more in-depth research on various generalizations of leukopoiesis, erythropoiesis or *Lasota–Wazewska* models, neural networks models and models for fisheries where the delays depend on both the time and the state variable (see for more details on these models [4, 5, 29, 52, 61, 62]),

- There is a potential for adopting our technique to deal with various iterative differential equations of higher order and iterative fractional differential equations.

- It would seem preferable to use numerical approaches or software to solve this kind of equations or give numerical simulations to them.

_ It would appear crucial to study the existence of almost-periodic, pseudo-almost-periodic, or anti-periodic solutions for delayed or iterative hematopoiesis models.

In the end, we hope that the results presented in this manuscript, will contribute even a little to enriching the emerging theory of iterative differential problems especially in life sciences.

List of publications

1. Khemis, M., Bouakkaz, A.: Existence and uniqueness results for a neutral erythropoiesis model with iterative production and harvesting terms. Bol. Soc. Parana. Mat (3). **41**, 1–9 (2023).

2. Khemis, M., Bouakkaz, A., Khemis, R.: Existence, uniqueness and stability results of an iterative survival model of red blood cells with a delayed nonlinear harvesting term. J. Math. Model. **10**(3), 515–528 (2022).

3. Khemis, M., Bouakkaz, A., Khemis, R.: Positive periodic solutions for a delay model of erythropoiesis with iterative terms. Appl. Anal. **103**(1), 340–352 (2024).

4. Khemis, M., Bouakkaz, A., Khemis, R.: Positive periodic solutions of a leukopoiesis model with iterative terms. Bol. Soc. Mat. Mex. **30**(1), 1–20, (2024).

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