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Existence and Uniqueness Results for a Neutral Erythropoiesis Model with Iterative Production and Harvesting Terms

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ABSTRACT: The main objective of this work is to study the existence, uniqueness and stability of positive periodic solutions for a first-order neutral differential equation with iterative terms which models the regulation of red blood cell production under a harvesting strategy. Benefiting from the Krasnoselskii's fixed point theorem as well as some properties of an obtained Green's function, we establish the existence of the solutions and taking advantage of the Banach fixed point theorem, we prove that the proposed equation has exactly one solution that depends continuously on parameters. Finally, two examples are exhibited to show the efficiency and application of our findings which are completely new and enrich the existing literature.

Key Words: Green's function, fixed point theorem, neutral differential equation, periodic solution.

Contents

1. Introduction

In 1977, the Canadian scientists Michael Mackey and Leon Glass [11] introduced the following hematopoiesis model with a monotone production rate and a constant delay:

$$x'(t) = -\gamma x(t) + \frac{\delta\theta^n}{\theta^n + x^n(t-\tau)},$$

for modeling and getting a better understanding of the erythropoiesis. In biological terms, $x(t)$ (cells/kg) denotes the density of mature circulating erythrocytes (red blood cells, RBCs) in the blood circulation at time t, $\gamma x(t)$ (cells/day) is the mortality term, $\gamma > 0$ (days^{-1}) is called the mortality rate of RBCs in the circulation, $\frac{\delta\theta^n}{\theta^n + x^n(t-\tau)}$ (cells/kg-day) which depends on the cell density at an earlier time, describes the RBCs reproduction under erythropoietin control, $\delta > 0$ (units cells/kg-day) is the maximal RBC production rate that the body can approach when the density of RBCs in the circulation falls below normal, $\theta > 0$ (units cells/kg) is a shape parameter, n is a positive exponent and $\tau > 0$ (days) stands for the maturation delay.

By letting $n = 1$ and $x(t) = \theta y(t)$, we can rewrite the above Mackey-Glass equation as follows:

$$y'(t) = -\gamma y(t) + \frac{\delta}{1 + y(t-\tau)}.$$

In this work, we revisit this 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

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sampling or blood donation which plays a significant role in the blood cell population dynamics and the management of biological renewable resources. So, we consider the following neutral Mackey-Glass equation with iterative production and harvesting terms:

$$\frac{d}{dt}y(t)-\lambda\frac{d}{dt}y(t-\tau(t))=-\gamma(t)y(t)+\sum_{i=2}^{n}\frac{\delta(t)}{1+y^{[i]}(t)}-k\left(t,y(t),...,y^{[n]}(t)\right), \tag{1.1}$$

where the nth iterate $y^{[n]}(t)$ denotes the composition of $y(t)$ with itself n times, $\tau,\gamma,\delta\in C(\mathbb{R},(0,\infty))$ are common periodic functions, $\lambda\in(0,1)$, $\tau(t)$ stands for a transit time needed for the liberation of RBCs into the bloodstream and $k\in C\left(\mathbb{R}^{n+1},(0,\infty)\right)$ is the harvesting function which is supposed globally Lipschitz in $y_1,y_2,...,y_n$, that is to say there exist n positive constants $\ell_1,\ell_2,...,\ell_n$ such that

$$|k(t,y_1,...,y_n)-k(t,z_1,...,z_n)|\leq\sum_{i=1}^{n}\ell_i|y_i-z_i|. \tag{1.2}$$

It is worth noting here that the iterates $y^{[i]}(t)$ in equation (1.1) result from $(n-1)$ delays of the form $\tau_i(t,y(t))$ that describe the time durations between the division of multipotent hematopoietic stem cells (HSCs) in the bone marrow and the formation of mature RBCs. Actually, these delays depend on both the time and the current density of mature erytrocytes $y(t)$ and this is essentially a consequence of 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 (1.1) 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. Alas, despite their applications in describing real phenomena especially in epidemiology, biology and classical electrodynamics (see [1], [2], [3] and [12]) and despite the fact that the last decade showed a growing interest towards such equations (see [1]- [10], [12] and [13]), they have been avoided by the majority of scholars and hence their theory is not fully developed yet. The difficulty of studying them stems from their iterative terms that are not generally easy to control and often hamper the use of the most known methods.

We would like to mention that, as far as we know, up until now, there are no results in the literature that addressed neutral Mackey-Glass equation with iterative monotone production and harvesting terms. So, our work is the first to study the existence and uniqueness of positive periodic solutions for this iterative model by means of the fixed point theory together with the Green's functions method as well as some useful functional analysis tools.

The organization of this manuscript is now briefly described. In the next section, we introduce some preliminary results while our foremost concern in the third and fourth Sections is to investigate the existence, uniqueness and stability of positive periodic solutions for equation (1.1). In the fifth Section, we provide two examples to check the validity of the derived key results. Finally, the paper ends with a brief conclusion recapitulating the main outlines of the technique used.

2. Mathematical background

For $\alpha\geq0$ and $\beta,\mu,T>0$, we consider the following compact and convex subset:

$$E=\{y\in\mathbb{Y},\alpha\leq y(t)\leq\beta,|y(t_2)-y(t_1)|\leq\mu|t_2-t_1|,\forall t_1,t_2\in\mathbb{R}\},$$

of the Banach space

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

furnished with the usual supremum norm.

The next lemma shows the equivalence between equation (1.1) and an integral equation.

Lemma 2.1. *There is an equivalence between the following two assertions:*
(A_1) $y \in E \cap \mathcal{C}^1(\mathbb{R},\mathbb{R})$ is a solution of (1.1).
(A_2) $y \in E$ satisfies the following integral equation:

$$y(t) = \int_t^{t+T} \mathcal{G}(t,\sigma) \left\{ \left(\sum_{i=2}^{n} \frac{\delta(\sigma)}{1 + y^{[i]}(\sigma)} \right) - k\left(\sigma, y(\sigma), ..., y^{[n]}(\sigma)\right) \right.$$
$$\left. -\lambda\gamma(\sigma)\, y(\sigma - \tau(\sigma)) \right\} d\sigma + \lambda y(t - \tau(t)), \tag{2.1}$$

where

$$\mathcal{G}(t,\sigma) = \frac{\exp\left(\int_t^{\sigma} \gamma(u)\,du\right)}{\left(\exp\left(\int_0^T \gamma(u)\,du\right)\right) - 1}. \tag{2.2}$$

We will use in the sequel the following notations:

$$\sup_{t\in[0,T]} \gamma(t) = a, \quad \inf_{t\in[0,T]} \delta(t) = b_0, \quad \sup_{t\in[0,T]} \delta(t) = b_1, \quad \sup_{\sigma\in[0,T]} |k(\sigma,0,...,0)| = \ell_0,$$
$$\ell_0 + \beta \sum_{i=1}^{n} \ell_i \sum_{j=0}^{i-1} \mu^j = \ell, \;\; \lambda a + b_1 \sum_{i=2}^{n} \sum_{j=0}^{i-1} \mu^j + \sum_{i=1}^{n} \ell_i \sum_{j=0}^{i-1} \mu^j = d,$$
$$\frac{\exp\left(-\int_0^T \gamma(u)\,du\right)}{\exp\left(\int_0^T \gamma(u)\,du\right) - 1} = A, \;\; \frac{\exp\left(\int_0^T \gamma(u)\,du\right)}{\exp\left(\int_0^T \gamma(u)\,du\right) - 1} = B.$$

We assume the following hypotheses that will be used throughout this paper:

$$(n-1)\, BTb_1 \le (1-\lambda)\,\beta, \tag{2.3}$$
$$(n-1)\, AT\frac{b_0}{1+\beta} - BT(\lambda a\beta + \ell) \ge (1-\lambda)\,\alpha, \tag{2.4}$$

and

$$B(2 + Ta)\left((n-1)\, b_1 + \lambda a\beta + \ell\right) \le \mu - \lambda\mu(\mu+1). \tag{2.5}$$

Remark 2.2. *Let $\mathcal{G}$ be the Green's function which is given by the expression (2.2). Then for all $t, \sigma \in \mathbb{R}$, we have*

$$\mathcal{G}(t+T, \sigma+T) = \mathcal{G}(t,\sigma), \;\; \forall t,\sigma \in \mathbb{R}, \tag{2.6}$$
$$0 < A \le \mathcal{G}(t,\sigma) \le B, \tag{2.7}$$

and it follows from the mean value theorem that

$$\int_{t_1}^{t_1+T} |\mathcal{G}(t_2,\sigma) - \mathcal{G}(t_1,\sigma)|\, d\sigma \le TBa\,|t_2 - t_1|, \;\; \forall t_1, t_2 \in \mathbb{R}. \tag{2.8}$$

3. Existence of positive periodic solutions

Now, we will need to construct an operator $\mathcal{Z}$ satisfying the requirements of the Krasnoselskii's fixed point theorem. To this aim, let us denote the right hand side of equation (2.1) by $(\mathcal{Z}y)(t)$ where $\mathcal{Z}$ can be written as $\mathcal{Z} = \mathcal{S}_1 + \mathcal{S}_2$ such that $\mathcal{S}_1, \mathcal{S}_2 : E \to \mathbb{Y}$ are given as follows:

$$(\mathcal{S}_1 y)(t) = \int_t^{t+T} \mathcal{G}(t,\sigma) \left\{ \left(\sum_{i=2}^{n} \frac{\delta(\sigma)}{1 + y^{[i]}(\sigma)} \right) - k\left(\sigma, y(\sigma), ..., y^{[n]}(\sigma)\right) \right.$$
$$\left. -\lambda\gamma(\sigma)\, y(\sigma - \tau(\sigma)) \right\} d\sigma, \tag{3.1}$$

and

$$(\mathcal{S}_2 y)(t) = \lambda y(t - \tau(t)). \tag{3.2}$$

Thereby fixed points of $\mathcal{Z}$ are solutions of (1.1) and vice versa. So, we must show that $\mathcal{S}_2$ is a contraction, $\mathcal{S}_1$ is continuous and compact and $\mathcal{S}_1 y + \mathcal{S}_2 z \in E$, for all $y, z \in E$.

Remark 3.1. *It follows from condition* (1.2) *and [[13], Lemma 1] that*

$$\left|k\left(\sigma,\psi^{[1]}(\sigma),\psi^{[2]}(\sigma),...,\psi^{[n]}(\sigma)\right)\right|\leq\ell. \tag{3.3}$$

Lemma 3.2. *Let $\tau\in E$. Assume that conditions* (1.2), (2.3)-(2.5) *hold. Then*

$$\mathcal{S}_1 y+\mathcal{S}_2 z\in E, \tag{3.4}$$

for all $y,z\in E$.

Proof. Let $y,z\in E$, $t\in\mathbb{R}$. From (2.7) and (2.3) we have

$$\begin{aligned}(\mathcal{S}_1 y)(t)+(\mathcal{S}_2 z)(t)&\leq\sum_{i=2}^{n}\int_t^{t+T}\mathcal{G}(t,\sigma)\frac{\delta(\sigma)}{1+y^{[i]}(\sigma)}d\sigma+\lambda z(t-\tau(t))\\&\leq(n-1)BTb_1+\lambda\beta\\&\leq\beta.\end{aligned} \tag{3.5}$$

On the other hand, in view of (2.7) and (3.3) we obtain

$$\begin{aligned}(\mathcal{S}_1 y)(t)+(\mathcal{S}_2 z)(t)=&\int_t^{t+T}\mathcal{G}(t,\sigma)\left(\left(\sum_{i=2}^{n}\frac{\delta(\sigma)}{1+y^{[i]}(\sigma)}\right)-k\left(\sigma,y(\sigma),...,y^{[n]}(\sigma)\right)\right.\\&\left.-\lambda\gamma(\sigma)y(\sigma-\tau(\sigma))\right)d\sigma+\lambda z(t-\tau(t))\\\geq&(n-1)AT\frac{b_0}{1+\beta}-BT(\lambda a\beta+\ell)+\lambda\alpha.\end{aligned}$$

Using (2.4), we obtain

$$(\mathcal{S}_1 y)(t)+(\mathcal{S}_2 z)(t)\geq\alpha,\ \forall y,z\in E,\ \forall t\in\mathbb{R}. \tag{3.6}$$

Let $t_1,t_2\in\mathbb{R}$ (with $t_1<t_2$), it follows from (2.7), (2.8) and (3.3) that

$$\begin{aligned}&|(\mathcal{S}_1 y)(t_2)-(\mathcal{S}_1 y)(t_1)|\\&\leq\int_{t_2}^{t_1}\mathcal{G}(t_2,\sigma)\left(k\left(\sigma,y(\sigma),...,y^{[n]}(\sigma)\right)+\lambda\gamma(\sigma)y(\sigma-\tau(\sigma))+\sum_{i=2}^{n}\frac{\delta(\sigma)}{1+y^{[i]}(\sigma)}\right)d\sigma\\&+\int_{t_1+T}^{t_2+T}\mathcal{G}(t_2,\sigma)\left(k\left(\sigma,y(\sigma),...,y^{[n]}(\sigma)\right)+\lambda\gamma(\sigma)y(\sigma-\tau(\sigma))+\sum_{i=2}^{n}\frac{\delta(\sigma)}{1+y^{[i]}(\sigma)}\right)d\sigma\\&+\int_{t_1}^{t_1+T}\left(k\left(\sigma,y(\sigma),...,y^{[n]}(\sigma)\right)+\lambda\gamma(\sigma)y(\sigma-\tau(\sigma))+\sum_{i=2}^{n}\frac{\delta(\sigma)}{1+y^{[i]}(\sigma)}\right)\\&\times|\mathcal{G}(t_2,\sigma)-\mathcal{G}(t_1,\sigma)|\,d\sigma\\&\leq B(2+Ta)((n-1)b_1+\lambda a\beta+\ell)|t_2-t_1|,\end{aligned} \tag{3.7}$$

and

$$|(\mathcal{S}_2 z)(t_2)-(\mathcal{S}_2 z)(t_1)|\leq\lambda\mu(\mu+1)|t_2-t_1|. \tag{3.8}$$

Using (2.5), (3.7), (3.8) and [[13], Lemma 4], we get

$$|(\mathcal{S}_1 y+\mathcal{S}_2 z)(t_2)-(\mathcal{S}_1 y+\mathcal{S}_2 z)(t_1)|\leq\mu|t_2-t_1|. \tag{3.9}$$

Finally, from (3.5), (3.6) and (3.9), we infer that $(\mathcal{S}_1 y)(t)+(\mathcal{S}_2 z)(t)\in E$, for all $y,z\in E$ and $t\in\mathbb{R}$. $\square$

Lemma 3.3. *If the hypothesis* (1.2) *is satisfied, operator $\mathcal{S}_1$ is continuous and compact.*

Proof. Let $y, z \in E$. In view of (1.2) and (2.7) we have

$$\begin{aligned}\left|\left(\mathcal{S}_1 y\right)(t)-\left(\mathcal{S}_1 z\right)(t)\right| \leq & B b_1 \sum_{i=2}^n \int_t^{t+T}\left|y^{[i]}(\sigma)-z^{[i]}(\sigma)\right| d \sigma \\ & +B \sum_{i=1}^n \int_t^{t+T} \ell_i\left|y^{[i]}(\sigma)-z^{[i]}(\sigma)\right| d \sigma \\ & +\lambda B a T\|y-z\| .\end{aligned}$$

By using [[13], Lemma 1], we get

$$\left\|\mathcal{S}_1 y-\mathcal{S}_1 z\right\| \leq B T d\|y-z\|,$$

which shows that $\mathcal{S}_1$ is Lipschitz continuous and therefore it is continuous. Thanks to the compactness of E, $\mathcal{S}_1$ is compact. □

Theorem 3.4. *Let $\tau \in E$ and assume that the hypotheses (1.2), (2.3)-(2.5) are fulfilled. Then equation (1.1) has a positive periodic solution in E.*

Proof. Since $\lambda < 1$, then $\mathcal{S}_2$ is a contraction. So, it follows from Lemmas 3.2 and 3.3 that all conditions of the Krasnoselskii's fixed point theorem are satisfied. Consequently, $\mathcal{Z}$ has a fixed point in E which is a solution of equation (1.1). □

4. Uniqueness and Continuous dependence

Theorem 4.1. *Let $\tau \in E$. If conditions (1.2), (2.3)-(2.5) and*

$$BTd + \lambda < 1, \tag{4.1}$$

hold, then equation (1.1) has a unique solution that belongs to E.

Proof. Similarly as in the proof of Lemmas 3.2 and 3.3, we obtain that $\mathcal{Z}$ maps E into itself and

$$\|\mathcal{Z}y-\mathcal{Z}z\| \leq (BTd+\lambda)\|y-z\|.$$

So, from (4.1), $\mathcal{Z}$ is a contraction and hence equation (1.1) has a unique positive periodic solution in E. □

Theorem 4.2. *The unique solution obtained in Theorem 4.1 depends continuously on the functions γ, δ and k.*

Proof. Let y_1 be the unique solution of equation (1.1), so y_1 satisfies the integral equation (2.1) i.e.

$$\begin{aligned} y_1(t)=\int_t^{t+T} & \mathcal{G}_1(t, \sigma)\left(\sum_{i=2}^n \frac{\delta_1(\sigma)}{1+y_1^{[i]}(\sigma)}-k_1\left(\sigma, y_1(\sigma), \ldots, y_1^{[n]}(\sigma)\right)\right. \\ & \left.-\lambda \gamma_1(\sigma) y_1(\sigma-\tau(\sigma))\right) d \sigma+\lambda y_1(t-\tau(t)),\end{aligned}$$

and let y_2 be a solution of the perturbed equation with a small perturbation in the harvesting term k, the maximal production rate δ and the mortality rate γ, that satisfy all conditions of Theorem 4.1. So, y_2 satisfies the following integral equation:

$$\begin{aligned} y_2(t)=\int_t^{t+T} & \mathcal{G}_2(t, \sigma)\left(\sum_{i=2}^n \frac{\delta_2(\sigma)}{1+y_2^{[i]}(\sigma)}-k_2\left(\sigma, y_2(\sigma), \ldots, y_2^{[n]}(\sigma)\right)\right. \\ & \left.-\lambda \gamma_2(\sigma) y_2(\sigma-\tau(\sigma))\right) d \sigma+\lambda y_2(t-\tau(t)),\end{aligned}$$

where

$$\mathcal{G}_1(t,\sigma)=\frac{\exp\left(\int_t^\sigma \gamma_1(u)\,du\right)}{\left(\exp\left(\int_0^T \gamma_1(u)\,du\right)\right)-1} \text{ and } \mathcal{G}_2(t,\sigma)=\frac{\exp\left(\int_t^\sigma \gamma_2(u)\,du\right)}{\left(\exp\left(\int_0^T \gamma_2(u)\,du\right)\right)-1},$$

and k_2, γ_2, δ_2 are the perturbed parameters.
In view of (2.7) and [[13], Lemma 1] we obtain

$$\left|\delta_2(\sigma)\,y_1^{[i]}(\sigma)-\delta_1(\sigma)\,y_2^{[i]}(\sigma)\right| \le \beta\left\|\delta_2-\delta_1\right\|+\left\|\delta_2\right\|\sum_{j=0}^{i-1}\mu^j\left\|y_2-y_1\right\|, \tag{4.2}$$

and the mean value theorem gives us the following estimate:

$$\int_t^{t+T}\left|\mathcal{G}_2(t,\sigma)-\mathcal{G}_1(t,\sigma)\right|d\sigma \le \varrho\left\|\gamma_2-\gamma_1\right\|, \tag{4.3}$$

where

$$\varrho=\frac{T^2 e^{T\max\{\|\gamma_1\|,\|\gamma_2\|\}}}{\exp\left(\int_0^T \gamma_2(u)\,du\right)-1}\left(1+\frac{e^{T\|\gamma_1\|}}{\exp\left(\int_0^T \gamma_1(u)\,du\right)-1}\right).$$

We have

$$\begin{aligned}
|y_2(t)-y_1(t)| \le{}& \left|\sum_{i=2}^{n}\left(\int_t^{t+T}\mathcal{G}_2(t,\sigma)\frac{\delta_2(\sigma)}{1+y_2^{[i]}(\sigma)}d\sigma-\int_t^{t+T}\mathcal{G}_1(t,\sigma)\frac{\delta_1(\sigma)}{1+y_1^{[i]}(\sigma)}d\sigma\right)\right| \\
&+\left|\int_t^{t+T}\mathcal{G}_2(t,\sigma)\,k_2\left(\sigma,y_2(\sigma),\ldots,y_2^{[n]}(\sigma)\right)d\sigma\right. \\
&\left.-\int_t^{t+T}\mathcal{G}_1(t,\sigma)\,k_1\left(\sigma,y_1(\sigma),\ldots,y_1^{[n]}(\sigma)\right)d\sigma\right| \\
&+\left|\int_t^{t+T}\mathcal{G}_2(t,\sigma)\,\lambda\gamma_2(\sigma)\,y_2(\sigma-\tau(\sigma))\,d\sigma\right. \\
&\left.-\int_t^{t+T}\mathcal{G}_1(t,\sigma)\,\lambda\gamma_1(\sigma)\,y_1(\sigma-\tau(\sigma))\,d\sigma\right| \\
&+\left|\lambda y_2(t-\tau(t))-\lambda y_1(t-\tau(t))\right|.
\end{aligned}$$

By using (2.7), (4.2) and (4.3) we get

$$\begin{aligned}
&\left|\sum_{i=2}^{n}\left(\int_t^{t+T}\mathcal{G}_2(t,\sigma)\frac{\delta_2(\sigma)}{1+y_2^{[i]}(\sigma)}d\sigma-\int_t^{t+T}\mathcal{G}_1(t,\sigma)\frac{\delta_1(\sigma)}{1+y_1^{[i]}(\sigma)}d\sigma\right)\right| \\
&\le\sum_{i=2}^{n}\int_t^{t+T}\mathcal{G}_2(t,\sigma)\left|\frac{\delta_2(\sigma)}{1+y_2^{[i]}(\sigma)}-\frac{\delta_1(\sigma)}{1+y_1^{[i]}(\sigma)}\right|d\sigma \\
&+\sum_{i=2}^{n}\int_t^{t+T}\frac{\delta_1(\sigma)}{1+y_1^{[i]}(\sigma)}\left|\mathcal{G}_2(t,\sigma)-\mathcal{G}_1(t,\sigma)\right|d\sigma \\
&\le\sum_{i=2}^{n}\int_t^{t+T}\mathcal{G}_2(t,\sigma)\left|\delta_2(\sigma)\,y_1^{[i]}(\sigma)-\delta_1(\sigma)\,y_2^{[i]}(\sigma)\right|d\sigma \\
&+\sum_{i=2}^{n}\int_t^{t+T}\mathcal{G}_2(t,\sigma)\left|\delta_2(\sigma)-\delta_1(\sigma)\right|d\sigma \\
&+\sum_{i=2}^{n}\int_t^{t+T}\delta_1(\sigma)\left|\mathcal{G}_2(t,\sigma)-\mathcal{G}_1(t,\sigma)\right|d\sigma.
\end{aligned}$$

So

$$\begin{aligned}&\left|\sum_{i=2}^{n}\left(\int_t^{t+T}\mathcal{G}_2(t,\sigma)\frac{\delta_2(\sigma)}{1+y_2^{[i]}(\sigma)}d\sigma-\int_t^{t+T}\mathcal{G}_1(t,\sigma)\frac{\delta_1(\sigma)}{1+y_1^{[i]}(\sigma)}d\sigma\right)\right|\\&\le(n-1)TB(1+\beta)\|\delta_2-\delta_1\|+TB\|\delta_2\|\sum_{i=2}^{n}\sum_{j=0}^{i-1}\mu^j\|y_2-y_1\|\\&+\varrho(n-1)\|\delta_1\|\|\gamma_2-\gamma_1\|.\end{aligned}\tag{4.4}$$

Thanks to (1.2) and [[13], Lemma 1], we arrive at

$$\left|k_2\left(\sigma,...,y_2^{[n]}(\sigma)\right)-k_1\left(\sigma,...,y_1^{[n]}(\sigma)\right)\right|\le\|k_2-k_1\|+\sum_{i=1}^{n}\ell_i\sum_{j=0}^{i-1}\mu^j\|y_2-y_1\|.\tag{4.5}$$

Since

$$\begin{aligned}&\left|\int_t^{t+T}\mathcal{G}_2(t,\sigma)k_2\left(\sigma,y_2(\sigma),...,y_2^{[n]}(\sigma)\right)d\sigma-\int_t^{t+T}\mathcal{G}_1(t,\sigma)k_1\left(\sigma,y_1(\sigma),...,y_1^{[n]}(\sigma)\right)d\sigma\right|\\&\le\int_t^{t+T}\mathcal{G}_2(t,\sigma)\left|k_2\left(\sigma,y_2(\sigma),...,y_2^{[n]}(\sigma)\right)-k_1\left(\sigma,y_1(\sigma),...,y_1^{[n]}(\sigma)\right)\right|d\sigma\\&+\int_t^{t+T}k_1\left(\sigma,y_1(\sigma),...,y_1^{[n]}(\sigma)\right)|\mathcal{G}_2(t,\sigma)-\mathcal{G}_1(t,\sigma)|d\sigma.\end{aligned}$$

It results from (2.7), (3.3), (4.3) and (4.5) that

$$\begin{aligned}&\left|\int_t^{t+T}\mathcal{G}_2(t,\sigma)k_2\left(\sigma,y_2(\sigma),...,y_2^{[n]}(\sigma)\right)d\sigma-\int_t^{t+T}\mathcal{G}_1(t,\sigma)k_1\left(\sigma,y_1(\sigma),...,y_1^{[n]}(\sigma)\right)d\sigma\right|\\&\le\varrho\ell\|\gamma_2-\gamma_1\|+TB\|k_2-k_1\|+TB\sum_{i=1}^{n}\ell_i\sum_{j=0}^{i-1}\mu^j\|y_2-y_1\|.\end{aligned}\tag{4.6}$$

On the other hand, we have

$$\begin{aligned}&\left|\int_t^{t+T}\lambda\mathcal{G}_2(t,\sigma)\gamma_2(\sigma)y_2(\sigma-\tau(\sigma))d\sigma-\int_t^{t+T}\lambda\mathcal{G}_1(t,\sigma)\gamma_1(\sigma)y_1(\sigma-\tau(\sigma))d\sigma\right|\\&\le\lambda\int_t^{t+T}\mathcal{G}_2(t,\sigma)|\gamma_2(\sigma)y_2(\sigma-\tau(\sigma))-\gamma_1(\sigma)y_1(\sigma-\tau(\sigma))|d\sigma\\&+\lambda\int_t^{t+T}\gamma_1(\sigma)y_1(\sigma-\tau(\sigma))|\mathcal{G}_2(t,\sigma)-\mathcal{G}_1(t,\sigma)|d\sigma.\end{aligned}$$

But,

$$|\gamma_2(\sigma)y_2(\sigma-\tau(\sigma))-\gamma_1(\sigma)y_1(\sigma-\tau(\sigma))|\le\|\gamma_2\|\|y_2-y_1\|+\beta\|\gamma_2-\gamma_1\|.\tag{4.7}$$

So, by using (2.7), (4.3) and (4.7), we obtain

$$\begin{aligned}&\left|\int_t^{t+T}\mathcal{G}_2(t,\sigma)\lambda\gamma_2(\sigma)y_2(\sigma-\tau(\sigma))d\sigma-\int_t^{t+T}\mathcal{G}_1(t,\sigma)\lambda\gamma_1(\sigma)y_1(\sigma-\tau(\sigma))d\sigma\right|\\&\le\lambda BT\|\gamma_2\|\|y_2-y_1\|+\beta\lambda(\varrho\|\gamma_1\|+BT)\|\gamma_2-\gamma_1\|.\end{aligned}\tag{4.8}$$

We have also

$$|\lambda y_2(t-\tau(t))-\lambda y_1(t-\tau(t))|\le\lambda\|y_2-y_1\|.\tag{4.9}$$

Thus, it follows from (4.4), (4.6), (4.8) and (4.9) that

$$\begin{aligned}\|y_2-y_1\| &\leq BT\left(\lambda\|a_2\|+\|\delta_2\|\sum_{i=2}^{n}\sum_{j=0}^{i-1}\mu^j+\sum_{i=1}^{n}\ell_i\sum_{j=0}^{i-1}\mu^j\right)\|y_2-y_1\| \\ &\quad+\left(\varrho\left(n-1\right)\|\delta_1\|+\varrho\ell+\lambda\beta\left(BT+\varrho\|\gamma_1\|\right)\right)\|\gamma_2-\gamma_1\| \\ &\quad+\left(n-1\right)TB\left(1+\beta\right)\|\delta_2-\delta_1\|+TB\|k_2-k_1\|.\end{aligned}$$

Finally, by virtue of the condition (4.1), we conclude that

$$\begin{aligned}\|y_2-y_1\| \leq \frac{1}{1-\left(BTd+\lambda\right)}&\left\{\left(\varrho\left(n-1\right)\|\delta_1\|+\varrho\ell+\lambda\beta\left(BT+\varrho\|\gamma_1\|\right)\right)\|\gamma_2-\gamma_1\|\right. \\ &\left.+\left(n-1\right)TB\left(1+\beta\right)\|\delta_2-\delta_1\|+TB\|k_2-k_1\|\right\}.\end{aligned}$$

This finishes the proof. □

5. Examples

Example 5.1. *We consider the following neutral Mackey-Glass equation with iterative terms:*

$$\begin{aligned}&\frac{d}{dt}\left[y\left(t\right)-\lambda y\left(t-0.01-0.08\sin^4\frac{2\pi}{11}t\right)\right] \\ &\quad=-\left(\frac{1}{20}+\frac{1}{20}\cos^4\frac{2\pi}{11}t\right)y\left(t\right)+\frac{0.0027+0.0003\sin^2\frac{2\pi}{11}t}{1+y^{[2]}\left(t\right)} \\ &\quad-\left(\frac{1}{15\pi^7}+\frac{1}{17\pi^7}\left(\cos^4\frac{2\pi}{11}t\right)y^{[1]}\left(t\right)+\frac{1}{19\pi^7}\left(\sin^2\frac{2\pi}{11}t\right)y^{[2]}\left(t\right)\right),\end{aligned}\tag{5.1}$$

where $E=P_{11}\left(8,0.0025,0.1\right)$, $\lambda=0.002$, $n=2$, $\ell_0=\dfrac{1}{15\pi^7}$, $\ell_1=\dfrac{1}{17\pi^7}$, $\ell_2=\dfrac{1}{19\pi^7}$, $\ell\simeq 3.9704\times10^{-5}$, $a=0.1$, $b_0=0.0027$, $b_1=0.003$, $A\simeq 0.41532$, $B\simeq 1.8847$, $d\simeq 2.7376\times10^{-2}$.
In this case, all conditions of Theorem 4.1 are satisfied, so (5.1) has a unique positive periodic solution in $P_{11}\left(8,0.0025,\dfrac{1}{10}\right)$ *that depends continuously on the functions* γ, δ *and* k.

Example 5.2. *We consider the following neutral Mackey-Glass equation with iterative terms:*

$$\begin{aligned}&\frac{d}{dt}\left[y\left(t\right)-\lambda y\left(t-0.3-0.05\sin^4\frac{2\pi}{11}t\right)\right] \\ &\quad=-\left(0.02+0.005\cos^2\frac{2\pi}{11}t\right)y\left(t\right)+\frac{0.027+0.003\sin^2\frac{2\pi}{11}t}{1+y^{[2]}\left(t\right)} \\ &\quad-\left(\frac{1}{5\pi^7}+\frac{1}{7\pi^7}\left(\cos^4\frac{2\pi}{11}t\right)y^{[1]}\left(t\right)+\frac{1}{9\pi^7}\left(\sin^2\frac{2\pi}{11}t\right)y^{[2]}\left(t\right)\right),\end{aligned}\tag{5.2}$$

where $E=P_{11}\left(2,0.2,1.6\right)$, $\lambda=0.02$, $n=2$, $\ell_0=\dfrac{1}{5\pi^7}$, $\ell_1=\dfrac{1}{7\pi^7}$,
$\ell_2=\dfrac{1}{9\pi^7}$, $\ell\simeq 3.1848\times10^{-4}$, $a=0.025$, $b_0=0.027$, $b_1=0.03$, $A\simeq 2.7803$, $B\simeq 4.561$, $d\simeq 9.0658\times10^{-2}$.
So, the condition (4.1) in Theorem 4.1 is not fulfilled while all conditions of Theorem 3.4 are satisfied. So the Mackey-Glass equation (5.2) in this case has a positive periodic solution in $P_{11}\left(2,0.2,1.6\right)$ *which is not necessarily unique.*

6. Conclusion

This work mainly dealt with a neutral erythropoiesis model involving iterative production and harvesting terms where we proved that the effect of the harvesting strategy does not go beyond reducing the density of red blood cells and, as such, it does not lead to their extinction. Under some sufficient criteria and by virtue of a technique based on Banach and Krasnoselskii's fixed point theorems as well as the Green's functions method, we derived the existence, uniqueness and stability results in where the sought solutions were expressed as fixed points of a suitable integral operator fulfilling all conditions of the chosen fixed point theorems. 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 an important preparatory work before applying our fixed point theorems. For instance, one of the key preparatory steps is to choose a suitable subset of an appropriate Banach space which on the one hand will enable us to control the iterative terms and, on the other hand, will guarantee, for the biological realism, the periodicity, positivity and boundedness of the solutions. Another preparatory step lies in establishing some useful properties of the obtained Green's kernel which is not always an easy task but not an impossible one.

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