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On multi-periodicity in a delayed model of hematopoiesis

Lian Duan[1,2,3*], Shimin Chen[1], Hang Xiao[1] and Xianwen Fang[1]

*Correspondence: lianduan0906@163.com
[1] School of Mathematics and Big Data, Anhui University of Science and Technology, Huainan, P.R. China
[2] School of Mathematics and Statistics, Central South University, Changsha, P.R. China
Full list of author information is available at the end of the article

Abstract

In this paper, we study a periodic model of hematopoiesis with a time-varying delay. Some new criteria are established to ensure that there are at least two positive periodic solutions by applying Krasnoselskii's fixed point theorem, which are essentially new and complement some existing ones. Moreover, numerical simulations are performed to substantiate the effectiveness of the theoretical analysis.

MSC: 34G20; 34K13

Keywords: Hematopoiesis; Multi-periodicity; Krasnoselskii's fixed point theorem

1 Introduction

In order to describe some physiological control systems in the classic study of population dynamics, Mackey and Glass in [1] initially proposed the following model of hematopoiesis (cell production):

$$x'(t) = -ax(t) + \frac{bx^m(t-\tau)}{1+x^n(t-\tau)}, \tag{1.1}$$

where $x(t)$ denotes the density of mature cells in blood circulation, a is the rate at which cells are lost from the circulation, the flux $g(x(t-\tau)) = \frac{bx^m(t-\tau)}{1+x^n(t-\tau)}$ of the cells into the circulation from the stem cell compartment depends on $x(t-\tau)$ at time $t-\tau$, and τ is the time delay between the production of immature cells in the bone marrow and their maturation for release in circulating bloodstreams.

In recent years, the model of hematopoiesis has been extensively and intensively studied due to its theoretical and practical significance. A very basic and important dynamics problem is the existence and uniqueness of positive (almost) periodic solutions associated with the study of the following non-autonomous model (1.1) in (almost) periodic environments:

$$x'(t) = -a(t)x(t) + \frac{b(t)x^m(t-\tau(t))}{1+x^n(t-\tau(t))}. \tag{1.2}$$

To name a few, when $m = 0$, Liu et al. studied the existence and global attractivity of periodic solution for Eq. (1.2) by using a fixed point theorem in cone and the oscillatory theory. Alzabut et al. in [2] were concerned with the existence and global exponential

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stability of almost periodic solutions by applying Banach's contraction mapping principle and Gronwall–Bellman's inequality. When $m = 1$, Zhou et al. and Wang et al. respectively studied the existence and uniqueness of periodic solution for Eq. (1.2), the methods used therein were mainly based on the exponential dichotomy theory, Mawhin coincidence degree, together with the Lyapunov functional method, see [3, 4]. Wang and Zhang in [5] investigated the existence and uniqueness of almost periodic solution for Eq. (1.2) by establishing a new fixed point theorem in cones free of compactness conditions. For other interesting theoretical results for this model, we refer to [6–12] and the references therein.

However, it is noteworthy that when $0 < m < n$, the flux function in model (1.2) has stronger nonlinearity than the cases of $m = 0$ or $m = 1$, and thus it may show more complex and rich dynamic behaviors. On the other hand, the aforementioned periodic solution (can be regarded as a special case of almost periodic solution) is unique, as mentioned by May in [13] that a large number of empirical observations shows that many natural communities have a multiplicity of stable states. The multiplicity of periodic solutions is an interesting problem in the qualitative study of delay differential equations, and such an issue of Eq. (1.2) has been seldom considered up to now. Motivated by the above discussions, in this paper we aim to establish some sufficient conditions ensuring that Eq. (1.2) has at least two positive T-periodic solutions. Our approach is based on Krasnoselskii's fixed point theorem.

The structure of the remaining part of this paper is as follows. In Sect. 2, we present some necessary lemmas. In Sect. 3, some sufficient conditions are established to guarantee that Eq. (1.2) has at least two positive periodic solutions. In Sect. 4, we demonstrate the validity of these theoretical results with numerical simulations. Finally, some conclusions are made and future directions are pointed out in Sect. 5.

2 Preliminaries

In this section, we first introduce some notations and recall well-known Krasnoselskii's fixed point theorem.

Let $h \in C(\mathbb{R}, \mathbb{R})$ be a T-periodic function, we denote

$$h^+ = \max_{t\in[0,T]} h(t), \qquad h^- = \min_{t\in[0,T]} h(t), \qquad \overline{h} = \frac{1}{T}\int_0^T h(t)\,ds.$$

On the other hand, let $g(x) = \frac{x^m}{1+x^n}$, if $0 < m < n$, we can easily verify that $g(x)$ increases strictly on $[0, \sqrt[n]{\frac{m}{n-m}}]$ and decreases on $[\sqrt[n]{\frac{m}{n-m}}, \infty)$. Thus, there exists a unique $c_0 \in (\sqrt[n]{\frac{m}{n-m}}, \infty)$ such that $g(c_0) = g(\rho\sqrt[n]{\frac{m}{n-m}})$, where $0 < \rho < 1$.

Definition 2.1 Let X be a Banach space, and let P be a closed, nonempty subset of X. P is a cone if

(i) $\alpha x + \beta y \in P$ for all $x, y \in P$ and all $\alpha, \beta \geq 0$;

(ii) $x, -x \in P$ imply $x = 0$.

Lemma 2.1 (see [14, 15]) *Let X be a Banach space, and let $P \subset X$ be a cone in X. Assume that Ω_1, Ω_2 are open bounded subsets of X with $0 \in \Omega_1 \subset \overline{\Omega}_1 \subset \Omega_2$, and let*

$$\Phi : P \cap (\overline{\Omega}_2 \setminus \Omega_1) \to P$$

be a completely continuous operator such that either

(i) $\|\Phi x\| \leq \|x\|, \forall x \in P \cap \partial\Omega_1$ *and* $\|\Phi x\| \geq \|x\|, \forall x \in P \cap \partial\Omega_2$;

or

(ii) $\|\Phi x\| \geq \|x\|, \forall x \in P \cap \partial\Omega_1$ *and* $\|\Phi x\| \leq \|x\|, \forall x \in P \cap \partial\Omega_2$.

Then Φ *has a fixed point in* $P \cap (\overline{\Omega}_2 \setminus \Omega_1)$.

Let

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

and

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

Then X is a Banach space equipped with the above norm $\|\cdot\|$. If $x(t) \in X$ is a solution of Eq. (1.2), then

$$\left[x(t)\exp\left(\int_0^t a(s)\,ds\right)\right]' = \exp\left(\int_0^t a(s)\,ds\right)\frac{b(t)x^m(t-\tau(t))}{1+x^n(t-\tau(t))}. \tag{2.1}$$

Integrating both sides of (2.1) over $[t, t+T]$, we have

$$x(t) = \int_t^{t+T} G(t,s)\frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds,$$

where

$$G(t,s) = \frac{\exp(\int_t^s a(s)\,ds)}{\exp(\int_0^T a(s)\,ds) - 1}.$$

It is easy to see that, for any $t \leq s \leq t+T$,

$$N := \frac{1}{e^{\bar{a}T}-1} \leq G(t,s) \leq \frac{e^{\bar{a}T}}{e^{\bar{a}T}-1} := M, \quad \text{and} \quad 0 < \rho = \frac{N}{M} < 1. \tag{2.2}$$

Now, choose the cone defined by

$$P = \{x(t) \in X : x(t) \geq \rho\|x\|\}$$

and define an operator $\Phi : X \to X$ by

$$(\Phi x)(t) = \int_t^{t+T} G(t,s)\frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds. \tag{2.3}$$

Obviously, to show that Eq. (1.2) has a T-periodic solution, it suffices to prove that Φ has a fixed point on X. To establish the main results, we also make the following assumptions:

(H1) $a, b, \tau \in C(\mathbb{R}, (0,\infty))$ are all T-periodic functions;

(H2) $Nb^- Tg(c_0) > c_0$.

Lemma 2.2 *The mapping Φ maps P into P, that is, $\Phi P \subset P$.*

Proof For any $x \in P$, we have from (2.2) and (2.3) that

$$\|\Phi x\| \leq M \int_t^{t+T} \frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds \tag{2.4}$$

and

$$(\Phi x)(t) \geq N \int_t^{t+T} \frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds. \tag{2.5}$$

Combining (2.4) with (2.5) gives

$$(\Phi x)(t) \geq \frac{N}{M}\|\Phi x\|.$$

Hence, $\Phi P \subset P$. The proof is completed. □

Lemma 2.3 *$\Phi : P \to P$ is completely continuous.*

Proof Denote

$$g(x_t) = \frac{x^m(t-\tau(t))}{1+x^n(t-\tau(t))}.$$

First, we show that Φ is continuous. For any $L > 0$ and $\varepsilon > 0$, there exists $\delta > 0$ such that, for $\varphi, \psi \in X$, $\|\varphi\| \leq L$, $\|\psi\| \leq L$, and $\|\varphi - \psi\| < \delta$ imply

$$\max_{s\in[0,T]} \left|g(\varphi_s) - g(\psi_s)\right| \leq \frac{\varepsilon}{b^+MT}. \tag{2.6}$$

If $x, y \in X$ with $\|x\| \leq L$, $\|y\| \leq L$, and $\|x - y\| < \delta$, then we have from (2.2), (2.3), and (2.6) that

$$\begin{aligned}\|\Phi x - \Phi y\| &\leq \int_t^{t+T} \left|G(t,s)\right| b^+ \left|g(x_s) - g(y_s)\right|\,ds \\ &\leq Mb^+ \int_0^T \left|g(x_s) - g(y_s)\right|\,ds \\ &\leq \varepsilon.\end{aligned}$$

Thus, Φ is continuous.

Next, we show that Φ is compact. Let $B > 0$ be any constant, and let $\mathscr{T} = \{x \in X : \|x\| \leq B\}$ be a bounded set . For any $x \in \mathscr{T}$, it follows from (2.2) and (2.3) that

$$\begin{aligned}\|\Phi x\| &\leq M \int_t^{t+T} \frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds \\ &\leq MTb^+ g\left(\sqrt[n]{\frac{m}{n-m}}\right).\end{aligned}$$

Again, from (2.3), we have

$$\begin{aligned}\left|\left[(\Phi x)(t)\right]'\right| &\le a(t)\left|(\Phi x)(t)\right| + b(t)\left|\frac{x^m(t-\tau(t))}{1+x^n(t-\tau(t))}\right| \\ &\le \left(a^+MT+1\right)b^+g\left(\sqrt[n]{\frac{m}{n-m}}\right),\end{aligned}$$

which implies that $\Phi\mathscr{T}\subset\mathscr{T}$ is a family of uniformly bounded and equi-continuous functions. According to the well-known Ascoli–Arzela theorem, the operator Φ is compact, and so it is completely continuous. The proof is completed. □

3 Main results

We are now in a position to state and prove our main results of this paper.

Theorem 3.1 *Let* $0 < m < n$ *and* (H1)–(H2) *hold. Then Eq.* (1.2) *has at least two positive* T*-periodic solutions.*

Proof By virtue of $\lim_{x\to 0}\frac{b(t)x^m}{1+x^n} = \lim_{x\to\infty}\frac{b(t)x^m}{1+x^n} = 0$, for any $t\in[0,T]$, for any sufficiently small $\varepsilon > 0$ such that $MT\varepsilon < 1$, there exist two constants c_1, c_2 ($c_1 < \sqrt[n]{\frac{m}{n-m}} < c_0 < c_2$) such that

$$\frac{b(t)x^m}{1+x^n} \le \varepsilon c_1, \quad (t,x)\in[0,T]\times[0,c_1], \tag{3.1}$$

and

$$\frac{b(t)x^m}{1+x^n} \le \varepsilon x, \quad (t,x)\in[0,T]\times[c_2,\infty]. \tag{3.2}$$

Define

$$\begin{aligned}&\Omega_1 = \left\{x\middle|x\in X, \|x\| < c_1\right\}, &&\Omega_2 = \left\{x\middle|x\in X, \|x\| < \sqrt[n]{\frac{m}{n-m}}\right\}, \\ &\Omega_3 = \left\{x\middle|x\in X, \|x\| < c_0\right\}, &&\Omega_4 = \left\{x\middle|x\in X, \|x\| < c_3\right\},\end{aligned}$$

where

$$c_3 = \max\left\{c_2 + \sqrt[n]{\frac{m}{n-m}}, \frac{M\mathcal{G}T}{1-MT\varepsilon}\right\}, \qquad \mathcal{G} = \max_{t\in[0,T],x\in[0,c_2]}\left\{\frac{b(t)x^m}{1+x^n}\right\}.$$

If $x = x(t)\in P\cap\partial\Omega_1$, then $\|x\| = c_1$, and $x(t)\ge\rho c_1$. From (2.2), (2.3), and (3.1), we have

$$(\Phi x)(t) \le M\int_t^{t+T}\frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds \le MT\varepsilon c_1 < c_1,$$

which means that $\|\Phi x\| < \|x\|$ for $x\in P\cap\partial\Omega_1$.

If $x = x(t) \in P \cap \partial\Omega_2$, then $\|x\| = \sqrt[n]{\frac{m}{n-m}}$ and $x(t) \geq \rho\sqrt[n]{\frac{m}{n-m}}$. In view of (2.2)–(2.3), (H2) and the fact that $\min_{x\in[\rho\sqrt[n]{\frac{m}{n-m}},\sqrt[n]{\frac{m}{n-m}}]} g(x) = g(\rho\sqrt[n]{\frac{m}{n-m}}) = g(c_0)$, we have

$$\begin{aligned}(\Phi x)(t) &\geq N\int_t^{t+T}\frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds\\ &\geq Nb^-\int_t^{t+T} g(x_s)\,ds\\ &\geq Nb^-\int_t^{t+T} g\left(\rho\sqrt[n]{\frac{m}{n-m}}\right)ds\\ &= Nb^-Tg(c_0)\\ &> c_0 > \sqrt[n]{\frac{m}{n-m}},\end{aligned}$$

which implies that $\|\Phi x\| > \|x\|$ for $x \in P\cap\partial\Omega_2$.

If $x = x(t) \in P \cap \partial\Omega_3$, then $\|x\| = c_0$, and $x(t) \geq \rho c_0 > \rho\sqrt[n]{\frac{m}{n-m}}$. Combining (2.2)–(2.3), (H2), and the fact that $\min_{x\in[\rho c_0,c_0]} g(x) = g(c_0)$ produces

$$\begin{aligned}(\Phi x)(t) &\geq N\int_t^{t+T}\frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds\\ &\geq Nb^-\int_t^{t+T} g(x_s)\,ds\\ &\geq Nb^-\int_t^{t+T} g(c_0)\,ds\\ &= Nb^-Tg(c_0)\\ &> c_0,\end{aligned}$$

and hence $\|\Phi x\| > \|x\|$ for $x \in P\cap\partial\Omega_3$.

If $x = x(t) \in P \cap \partial\Omega_4$, then $\|x\| = c_3$, and $x(t) \geq \rho c_3$. Due to (2.2) and (2.3), we obtain

$$\begin{aligned}(\Phi x)(t) &\leq M\int_t^{t+T}\frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds\\ &\leq M\int_{\Lambda_1}\frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds + M\int_{\Lambda_2}\frac{b(s)x^m(s-\tau(s))}{1+x^n(s-\tau(s))}\,ds\\ &\leq M\mathcal{G}T + MT\varepsilon c_3 < c_3,\end{aligned}$$

and so $\|\Phi x\| < \|x\|$ for $x \in P\cap\partial\Omega_4$, where $\Lambda_1 = \{s|s\in[t,t+T], 0 \leq x(s-\tau(s)) \leq c_2\}$ and $\Lambda_2 = \{s|s\in[t,t+T], c_2 < x(s-\tau(s)) \leq c_3\}$.

Obviously, Ω_i $(i = 1,2,3,4)$ are open bounded subsets of X with $0 \in \Omega_1 \subset \overline{\Omega}_1 \subset \Omega_2 \subset \overline{\Omega}_2 \subset \Omega_3 \subset \overline{\Omega}_3 \subset \overline{\Omega}_4$. Since $\Phi(P) \subset P$ and Φ is a completely continuous operator on X, we conclude from Lemma 2.1 that Φ has one fixed point $x_1 \in P\cap(\overline{\Omega}_2\setminus\Omega_1)$ and another fixed point $x_2 \in P\cap(\overline{\Omega}_4\setminus\Omega_3)$, that is, $x_i(t) = (\Phi x_i)(t)$, $i = 1,2$, and $x_1(t) \geq \rho c_1 > 0$ and $x_2(t) \geq \rho c_0 > 0$, i.e., $x_1(t)$ and $x_2(t)$ are two positive T-periodic solutions of Eq. (1.2). The proof is completed. □

Remark 3.1 The method in this paper can be used to study the model of hematopoiesis with periodic coefficients and infinite distributed delay as follows:

$$x'(t) = -a(t)x(t) + b(t)\int_0^\infty p(s)\frac{x^m(t-s)}{1+x^n(t-s)}\,ds, \tag{3.3}$$

where the delay kernel $p:(0,\infty)\to(0,\infty)$ is assumed to be integrable and normalized such that $\int_0^\infty p(s)\,ds = 1$. Then the following statements can be obtained immediately.

Theorem 3.2 *Let* $0 < m < n$ *and* (H2) *hold. Then Eq.* (3.3) *has at least two positive* T*-periodic solutions.*

4 A numerical example

In this section, we give a numerical example with simulations to illustrate the feasibility of our main results.

Example 4.1 Consider the following 2π-periodic model of hematopoiesis with a time-varying delay:

$$x'(t) = -(0.4 + 0.2\cos t)x(t) + (280 + \sin t)\frac{x(t-\cos t)}{1+x^2(t-\cos t)}. \tag{4.1}$$

Here, $a(t) = 0.4 + 0.2\cos t$, $b(t) = 280 + \sin t$, $\tau(t) = \cos t$, $m = 1$, $n = 2$. It is easy to see that $N = \frac{1}{e^{0.8\pi}-1}$, $M = \frac{e^{0.8\pi}}{e^{0.8\pi}-1}$, and so $\rho = \frac{N}{M} = e^{-0.8\pi} \approx 0.081$, $c_0 \approx 12.345$. A straightforward calculation shows that

$$Nb^- Tg(c_0) \approx 12.434 > 12.345.$$

Thus we have verified all the assumptions of Theorem 3.1 and hence Eq. (4.1) has at least two positive 2π-periodic solutions, see Fig. 1.

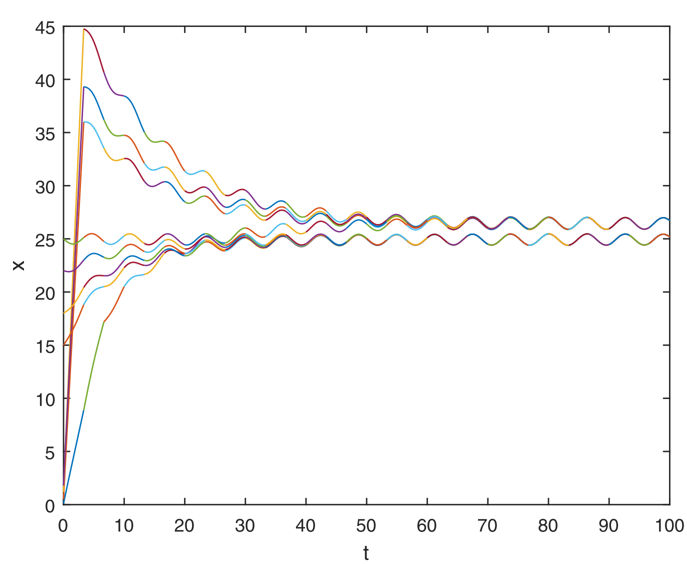

Figure 1 Equation (4.1) has two 2π-periodic solutions

Remark 4.1 In recent years, by using the continuation theorem, the existence of multiple periodic solutions of delayed population models has widely been studied (see [16, 17] and the references therein), and the multiplicity is heavily dependent on the harvesting term. It is readily seen that our methods are quite different from the previous works and the considered model is without the harvesting term. On the other hand, to the best of authors' knowledge, there is no research work concerning the multiplicity of periodic solutions of Eq. (1.2). Therefore, the results established in this paper are essentially new and complement some existing ones.

5 Conclusion

In this paper, we have studied the multiplicity of periodic solutions for a delayed model of hematopoiesis, a new set of criteria ensuring the existence of at least two periodic solutions have been derived. The effectiveness of the theoretical results has been demonstrated by a numerical example.

It is known that almost periodic problem is a hot research topic in science [18, 19] and engineering [20, 21]. However, it would be more difficult to find the sufficient condition for the multiplicity of almost periodic solutions than the periodic case since the compact condition fails the almost periodic function family, and then Krasnoselskii's fixed point theorem controlled by compact conditions cannot be used to solve the existence of almost periodic solutions. Therefore, interesting problems of the existence and stability of multiple almost periodic solutions for the kinds of models described by delay differential equations are still open, and we leave them as our future research work.

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Competing interests
The authors declare that they do not have any competing interests in this manuscript.

Authors' contributions
All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

Author details
[1]School of Mathematics and Big Data, Anhui University of Science and Technology, Huainan, P.R. China. [2]School of Mathematics and Statistics, Central South University, Changsha, P.R. China. [3]Hunan Provincial Key Laboratory of Mathematical Modeling and Analysis in Engineering, Changsha, P.R. China.

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