Existence regions of positive periodic solutions for a discrete hematopoiesis model with unimodal production functions

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Abstract

A discrete model describing the increase and decrease of blood cells is considered in this paper. This hematopoiesis model is a discretization of a delay differential equation with unimodal production function whose coefficients and delay are periodic discrete functions with ω-period. This paper is concerned with the existence of positive ω-periodic solutions. Our results are proved by using the well-known continuation theorem of coincidence degree theory. The existence range of the positive ω-periodic solutions is also clarified. A concrete example and its simulation are also given to illustrate our result. Finally, we examine how positive numbers and coefficients making up our model influence the upper and lower limits of blood cell counts.

Key words: Discrete hematopoiesis model; Unimodal production function; Positive periodic solutions; Existence Region; Continuation theorem
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1. Introduction

As is well known, blood cells are responsible for supplying oxygen and nutrients to the cells in our body and for discharging carbon dioxide outside the body. In addition, blood cells have immune action to protect the body from pathogenic bacteria and foreign bodies. Thus, blood cells are extremely important in vivo tissues.

Immature young cells that will become blood cells in the future are produced one after another in the bone marrow. This immature cell is called (multipotential) hematopoietic stem cell. In the bone marrow, hematopoietic stem cells follow a process that changes into mature cells that can play the original role of blood. Hence, in the bone marrow, hematopoietic stem cell, blood cells at various stages that it is proliferating and differentiating, and a variety of blood cells that have just been completed are coexisted. Hematopoietic stem cells differentiate into myeloid progenitor cells and lymphoid progenitor cells as an intermediate stage in order to become various blood cells in the future. Each of

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the differentiated progenitor cells will further differentiate and eventually become mature blood cells. Blood cells that have been differentiated in the bone marrow are transported through the peripheral vessels to tissues in vivo.

It is necessary for a certain amount of time for hematopoietic stem cells to repeat differentiation and become mature blood cells in bone marrow; namely, time lag occurs. Also, each blood cell has an inherent life span, and aged blood cells are eaten and processed by macrophages in the spleen, etc. For the basic knowledge of the hematopoietic process, for example, see the book [1, Chap. 18].

Mackey and Glass [2] proposed mathematical models to describe hematopoietic process by using the first-order differential equations with time delay. They divided their models into two types according to the characteristics of the production function. Since regulatory mechanisms in hematopoiesis have not yet been elucidated, they assumed that the production function is monotonically decreasing or unimodal due to simplification. Their hematopoiesis model with monotone production function is

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

with $n > 0$. On the other hand, their hematopoiesis model with unimodal production function is

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

with $n > 1$. Here, the variable x is the density of mature blood cells in the blood circulation; the constant a is the rate of blood cells lost by the circulation; the second term of the right-hand side of (1.1) or (1.2) is the influx of blood cells into the circulation from hematopoietic stem cells; the constant b is positive; the number τ is the time delay that immature cells made in the bone marrow are released into the circulating blood stream as mature cells. In equations (1.1) and (1.2), the production function f_n is defined by

$$f_n(u) = \frac{1}{1 + u^n} \quad \text{for } u \ge 0 \tag{1.3}$$

and

$$f_n(u) = \frac{u}{1 + u^n} \quad \text{for } u \ge 0, \tag{1.4}$$

respectively. The former production function is monotonically decreasing and tends to zero as $u \to \infty$. The latter increases monotonically at the beginning and then decreases monotonically. Hence, it has only one peak.

It is unnatural to think that the environment remains constant. As is well known, periodic seasonal changes have a major impact on the weather, temperature, food supply and sexual activity of organisms. Studies have been made from old times that the population density of organisms and the constituents inherent in organisms also change due to changes in various environments surrounding living organisms and behaviors of organisms. For example, Nicholson [3] gave a detailed report focusing on the relationship between periodic change in climate and the population densities of animals.

Regarding blood cells which are important components inherent in organisms, Satué *et al.* [4] mentioned that the hematological profile of Carthusian broodmares is affected by changes in temperature, the degree of physical activity, the composition of the grass that horses eat, and the amount of water intake, which are subjected to seasonal changes. From experimental data, they demonstrated that (i) red blood cell counts of Carthusian broodmares from May to August reached higher values; (ii) platelet counts in July and August were significantly higher than in other months; (iii) white blood cell counts were highest in the coldest month from February to May, and there was a significant difference from other months. Also, Maes *et al.* [5] measured hematological variables of normal humans such as number of red blood cells and platelets in detail, and pointed out that they undergo seasonal fluctuations. As another clinical evidence suggesting the periodic changes of blood cell counts, we can cite studies of white blood cell count and platelet count in patients with chronic myelogenous leukemia. By using time series data of white blood cell counts and platelet counts of patients with chronic myelogenous leukemia, which were published in many publications, Fortin and Mackey [6] found evidence that these two values change periodically with period ranging from 37 to 83 days (see also [7]). Hence, in clinical experiments, there are many evidences showing that periodic behavior of blood cell counts can actually be detected.

External factors of periodic environmental changes due to seasonal variations cannot be considered for autonomous differential equations with constant coefficients and constant time delays such as models (1.1) and (1.2). From the above-mentioned experimental points of view, it is reasonable and realistic to assume that coefficients and time lags in the hematopoiesis model are represented by periodic functions with the same period. Periodic environmental changes can be taken into account by making a modified hematopoiesis model described with a non-autonomous delay differential equation.

A large number of attempts have been made on the asymptotic behavior of solutions of the hematopoiesis models (1.1), (1.2) and their modifications. We divide hematopoiesis models into two types depending on the property of the production function. A hematopoiesis model with the monotonically *decreasing* production function (1.3) and a hematopoiesis model with the *unimodal* production function (1.4) are called *D-type* and *U-type*, respectively. We can refer to [8, 9, 10, 11, 12, 13, 14, 15, 16, 17] and [9, 10, 11, 13, 18, 19, 20, 21, 22] for the study of hematopoiesis models of D-type and of U-type, respectively. The main themes of those studies are as follows:

(i) existence and uniqueness of positive periodic solutions;

(ii) oscillation and nonoscillation of solutions around a positive equilibrium or a positive periodic solution;

(iii) global asymptotic stability of a positive equilibrium;

(iv) convergence to a periodic solution of all positive solutions.

Let us introduce each one of typical results on the hematopoiesis D-type model and the hematopoiesis U-type model.

Wang and Li [15] considered the hematopoiesis D-type model

$$x'(t) = -a(t)x(t) + \frac{b(t)}{1 + x^n(t - \tau(t))} \tag{1.5}$$

with $n > 0$, where $a,\ b : [0,\infty) \to (0,\infty)$ and $\tau : [0,\infty) \to [0,\infty)$ are continuous and ω-periodic functions with $\omega > 0$; namely,

$$a(t) = a(t+\omega), \quad b(t) = b(t+\omega) \quad \text{and} \quad \tau(t) = \tau(t+\omega) \tag{1.6}$$

for $t \geq 0$. They presented a sufficient condition for the existence and uniqueness of positive ω-periodic solutions by applying the fixed point theorem in normal cones (see Guo [23]). Their result is as follows:

Theorem A. *Assume that* (1.6) *holds. If* $n > 1$ *and*

$$\frac{\exp\left(\int_0^\omega a(t)dt\right)}{\exp\left(\int_0^\omega a(t)dt\right) - 1} \int_0^\omega b(t)dt \leq \sqrt[n]{\frac{1}{n-1}},$$

then equation (1.5) *has a unique positive ω-periodic solution.*

On the other hand, as a result of hematopoiesis U-type models, we can cite a work of Wu *et al*. [22]. They considered the hematopoiesis model which is a generalization of (1.2),

$$x'(t) = -a(t)x(t) + \frac{b(t)x(t - \tau(t))}{1 + x^n(t - \tau(t))} \tag{1.7}$$

with $n > 1$ under the assumption (1.6), and obtained the following sufficient condition for the existence of positive ω-periodic solutions by using the continuation theorem given by Gaines and Mawhin [24].

Theorem B. *Assume that* (1.6) *holds. If* $n > 1$ *and*

$$a(t) < b(t) \quad \text{for } t \in [0,\omega],$$

then equation (1.7) *has at least one positive ω-periodic solution.*

Wu *et al*. [22] proved that Theorem B is true even if $0 < n \leq 1$. However, this section is limited to the case that $n > 1$, because the production function $bu/(1+u^n)$ does not become unimodal if $0 < n \leq 1$. The case that $0 < n \leq 1$ will be discussed in Appendix of this paper.

Although blood cells in a human or a horse are discrete entities, since its number is enormous, it is reasonable to treat it like a continuum and express the hematopoiesis model with a differential equation with time delay. However, red blood cells, white blood cells, etc. play a role one by one, and they are represented by the number contained in one microliter of blood. They are never a continuum. In that sense, to examine the increase and decrease in the number of blood cells, it can be said that a discrete model is more suitable than a continuous model such as equation (1.5) or (1.7). Based on this thought, many researchers have studied discrete models of hematopoiesis concerning the same theme as a continuous model such as (i)–(iv) above. For example, refer to [25, 26, 27, 28, 29, 30, 31, 32] and the references cited therein. In those studies, there seems to be many analogies between the results of continuous model and discrete model. We will explain with one example.

Yao [31] discretized (1.5) and considered the following hematopoiesis D-type model

$$\Delta x(k) = -a(k)x(k) + \frac{b(k)}{1 + x^n(k - \tau(k))} \tag{1.8}$$

with $n > 0$, where $\Delta x(k) = x(k+1) - x(k)$, and $a\colon \mathbb{Z} \to (0,1)$, $b\colon \mathbb{Z} \to (0,\infty)$ and $\tau\colon \mathbb{Z} \to \mathbb{Z}^+ \overset{\text{def}}{=} \mathbb{N} \cup \{0\}$ are ω-periodic discrete functions with $\omega \in \mathbb{N}$; namely,

$$a(k) = a(k+\omega), \quad b(k) = b(k+\omega) \quad \text{and} \quad \tau(k) = \tau(k+\omega) \tag{1.9}$$

for all $k \in \mathbb{Z}$. We can state a result of Yao [31] as follows (note that this is not the original form):

Theorem C. *Assume that* (1.9) *holds. If* $0 < n \le 1$ *or*

$$n > 1 \quad \text{and} \quad \frac{1}{1 - \prod_{k=1}^{\omega}(1 - a(k))} \sum_{k=1}^{\omega} b(k) \le \sqrt[n]{\frac{1}{n-1}},$$

then equation (1.8) *has a unique positive* ω*-periodic solution.*

Theorem C is proved by applying the same fixed point theorem used to prove Theorem A. Because of use of the fixed point theorem, we can obtain the uniqueness theorem for positive ω-periodic solutions. Unfortunately, however, the location of the only solution cannot be estimated in Theorems A and C.

It is clear that assumption (1.9) corresponds to assumption (1.6) and

$$\frac{\exp\left(\int_0^{\omega} a(t)dt\right)}{\exp\left(\int_0^{\omega} a(t)dt\right) - 1} = \frac{1}{1 - \exp\left(-\int_0^{\omega} a(t)dt\right)}.$$

Since $\int_0^{\omega} a(t)dt$ is approximated to $\sum_{k=1}^{\omega} a(k)$, we see that

$$\exp\left(-\int_0^{\omega} a(t)dt\right) \approx \exp\left(-\sum_{k=1}^{\omega} a(k)\right) = e^{-a(1)}e^{-a(2)}\cdots e^{-a(\omega)} \approx \prod_{k=1}^{\omega}\left(1 - a(k)\right).$$

Similarly, $\int_0^{\omega} b(t)dt$ is approximated to $\sum_{k=1}^{\omega} b(k)$. Hence, it is safe to say that there is an analogy between Theorems A and C.

By using the same discretization from (1.5) to (1.8), we can obtain the hematopoiesis U-type model

$$\Delta x(k) = -a(k)x(k) + \frac{b(k)x(k-\tau(k))}{1+x^n(k-\tau(k))} \tag{1.10}$$

which corresponds to (1.7). Blood cells are transported to the whole body while drifting in the plasma. They are divided into three types: erythrocyte (red blood cell), leukocyte (white blood cell) and thrombocyte (platelet). Among them, leukocytes are mainly composed of neutrophils, basophils, eosinophils, lymphocytes, and monocytes. In clinical studies, it has confirmed that neutrophils mature in bone marrow in about 2 weeks and are released into the bloodstream after 2 days (see [33]). Also, basophils differentiate and mature in the bone marrow during 7 days (see [34, 35]). These clinical results suggest that at least two types of leukocytes take different time to enter the bloodstream. It is therefore meaningful to consider a hematopoietic model with multiple production functions that are dominated by different time delays.

For the reason above, we discuss the discrete model of hematopoiesis,

$$\Delta x(k) = -a(k)x(k) + \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))}, \tag{1.11}$$

which is a realistic modification of (1.10). Here, m is a natural number; n is a real number greater than 1; $a:\mathbb{Z}\to(0,1)$, $b_i:\mathbb{Z}\to(0,\infty)$ and $\tau_i:\mathbb{Z}\to\mathbb{Z}^+(1\le i\le m)$ are ω-periodic discrete functions. Since τ_i $(1\le i\le m)$ are ω-periodic, there exists the maximum value $\overline{\tau}$ of the sequences $\{\tau_1(k)\}$, $\{\tau_2(k)\}$, …, $\{\tau_m(k)\}$; namely,

$$\overline{\tau} = \max_{1\le i\le m}\left\{\max_{1\le k\le\omega}\tau_i(k)\right\}\in\mathbb{Z}^+.$$

Let $\phi(-\overline{\tau})$, $\phi(-\overline{\tau}+1),\dots,\phi(0)$ be arbitrary $(\overline{\tau}+1)$ given constants. Since $0<a(k)<1$ for $k\in\mathbb{Z}$, if $\phi(-\overline{\tau})$, $\phi(-\overline{\tau}+1),\dots,\phi(0)$ are positive, then equation (1.11) has a unique positive solution satisfying the initial condition

$$x(k)=\phi(k)>0 \quad \text{for } k\in[-\overline{\tau},0]\cap\mathbb{Z}. \tag{1.12}$$

Since equation (1.11) is a biological model, it is natural to assume that $\phi(k)>0$ for $k\in[-\overline{\tau},0]\cap\mathbb{Z}$.

The purpose of this paper is to give a sufficient condition for the existence of positive ω-periodic solutions of (1.11). To state our results simply, we denote the maximum value of $b_i(1), b_i(2),\dots,b_i(\omega)$ by

$$\overline{b}_i = \max_{1\le k\le\omega} b_i(k) \quad \text{for } 1\le i\le m.$$

Theorem 1. *Suppose that a, b_i and τ_i $(1\le i\le m)$ are positive ω-periodic. If there exists a $\gamma>1$ such that*

$$\gamma a(k) < \sum_{i=1}^{m} b_i(k) \quad \textit{for } k=1,2,\dots,\omega, \tag{1.13}$$

then equation (1.11) *with* $n > 1$ *has at least one positive* ω*-periodic solution located in the region* $[A, B]$, *where*

$$A \le \min\left\{ \sqrt[n]{\gamma - 1},\ \frac{\gamma \underline{a}^{n-1} \sum_{i=1}^{m} \overline{b}_i}{\underline{a}^n + \left(\sum_{i=1}^{m} \overline{b}_i\right)^n} \right\} \quad \text{and} \quad B = \frac{1}{\underline{a}} \sum_{i=1}^{m} \overline{b}_i,$$

in which $\underline{a} = \min_{1 \le k \le \omega} a(k)$.

Note that if

$$a(k) < \sum_{i=1}^{m} b_i(k) \quad \text{for } k = 1, 2, \ldots, \omega,$$

then condition (1.13) is inevitably satisfied. In fact, let

$$\gamma = \frac{1 + \min\limits_{1 \le k \le \omega} \left\{ \dfrac{\sum_{i=1}^{m} b_i(k)}{a(k)} \right\}}{2}.$$

Then, by the periodicities of a and b_i $(1 \le i \le m)$, we have

$$\gamma < 2\gamma - 1 = \min_{1 \le k \le \omega} \left\{ \frac{\sum_{i=1}^{m} b_i(k)}{a(k)} \right\} \le \frac{\sum_{i=1}^{m} b_i(k)}{a(k)} \quad \text{for } k = 1, 2, \ldots, \omega;$$

namely, condition (1.13).

In the special case that $m = 1$, Jiang *et al.* [27] already showed that the condition

$$a(k) < b(k) \quad \text{for } k = 1, 2, \ldots, \omega$$

is a sufficient condition for the existence of positive ω-periodic solutions of (1.10) under the assumption (1.9). Unfortunately, however, the region of existence was not clarified. We will prove Theorem 1 by using the the continuation theorem of Gaines and Mawhin [24]. The advantage of using the continuation theorem is that the existence range of the positive ω-periodic solutions of (1.11) can be evaluated.

Remark 1. In Theorem 1, we assume that the coefficients a, b_i and the time delays τ_i $(i = 1, 2, \ldots, m)$ have the same period ω. However, this assumption is for the sake of convenience and is not essential. In the case that these periods are different, Theorem 1 holds for their least common multiple $\omega \in \mathbb{N}$. If any coefficient or time delay is a constant (that is, if there is no period), then we may regard its period as 1.

Remark 2. Under the assumptions of Theorem 1, even if there are two or more positive ω-periodic solutions, they exist in the same range $[A, B]$.

2. Priori bounds for parametric delay difference equation

Consider the parametric delay difference equation

$$\Delta x(k) = -\lambda a(k)x(k) + \lambda \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))} \tag{2.1}$$

for each parameter $\lambda \in (0,1)$. First of all, we give the following result which is essential to prove Theorem 1.

Proposition 2. *Suppose that a, b_i and τ_i $(1 \le i \le m)$ are positive ω-periodic. If condition* (1.13) *holds, then every positive ω-periodic solution x of* (2.1) *with $n > 1$ satisfies that*

$$A < x(k) < B \quad \text{for } k = 1, 2, \ldots, \omega,$$

where A and B are constants given in Theorem 1.

Proof. Let x be any positive ω-periodic solution of (2.1) with the initial condition (1.12). For convenience, let

$$\overline{x} = \max_{1\le k\le\omega} x(k) \quad \text{and} \quad \underline{x} = \min_{1\le k\le\omega} x(k).$$

Since b_i $(1 \le i \le m)$ and x are positive ω-periodic, we see that $0 < b_i(k) \le \overline{b}_i$ for all $k \in \mathbb{Z}$ and $\underline{x} \le x(k) \le \overline{x}$ for all $k \in \mathbb{Z}^+$. Equation (2.1) can be rewritten to

$$x(k+1) = (1-\lambda a(k))x(k) + \lambda \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))}. \tag{2.2}$$

Hence, it follows from the periodicities of a, b_i and τ_i $(1 \le i \le m)$ that

$$\begin{aligned}
\overline{x} &= \max_{1\le k\le\omega} \{x(k+1)\} \\
&\le \max_{1\le k\le\omega} \{(1-\lambda a(k))x(k)\} + \lambda \max_{1\le k\le\omega} \left\{ \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))} \right\} \\
&\le \max_{1\le k\le\omega} \{(1-\lambda a(k))\} \max_{1\le k\le\omega} \{x(k)\} + \lambda \max_{1\le k\le\omega} \left\{ \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))} \right\} \\
&\le (1-\lambda \underline{a})\overline{x} + \lambda \max_{1\le k\le\omega} \left\{ \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))} \right\},
\end{aligned}$$

where $\underline{a}$ is a constant given in Theorem 1. Hence, we have

$$\overline{x} \le \frac{1}{\underline{a}} \max_{1\le k\le\omega} \left\{ \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))} \right\}. \tag{2.3}$$

Since $0 < \lambda < 1$ and $0 < a(k) < 1$ for all $k \in \mathbb{Z}$, we see that $1 - \lambda a(k) > 0$ for $k \in \mathbb{Z}$. Multiply both sides of (2.2) by $\prod_{r=0}^{k} 1/(1-\lambda a(r))$ to obtain

$$x(k+1)\prod_{r=0}^{k}\frac{1}{1-\lambda a(r)} - x(k)\prod_{r=0}^{k-1}\frac{1}{1-\lambda a(r)} = \lambda\sum_{i=1}^{m}\frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))}\prod_{r=0}^{k}\frac{1}{1-\lambda a(r)}. \tag{2.4}$$

Let k_1 be a natural number such that

$$\overline{\tau} \le k_1 \le \overline{\tau} + \omega - 1 \quad \text{and} \quad x(k_1) = \underline{x}.$$

Summing both sides of (2.4) over k ranging from k_1 to $k_1 + \omega - 1$ and using $x(k_1 + \omega) = x(k_1) = \underline{x}$, we get

$$\underline{x}\prod_{r=0}^{k_1-1}\frac{1}{1-\lambda a(r)}\left(\prod_{r=k_1}^{k_1+\omega-1}\frac{1}{1-\lambda a(r)} - 1\right) = \lambda\sum_{s=k_1}^{k_1+\omega-1}\left(\sum_{i=1}^{m}\frac{b_i(s)x(s-\tau_i(s))}{1+x^n(s-\tau_i(s))}\prod_{r=0}^{s}\frac{1}{1-\lambda a(r)}\right).$$

Since a is a positive ω-periodic function, we see that

$$\prod_{r=k_1}^{k_1+\omega-1}(1-\lambda a(r)) = \prod_{r=0}^{\omega-1}(1-\lambda a(r)). \tag{2.5}$$

Hence, we have

$$\begin{aligned}
\underline{x} &= \frac{\lambda\prod_{r=0}^{k_1+\omega-1}(1-\lambda a(r))}{1-\prod_{r=k_1}^{k_1+\omega-1}(1-\lambda a(r))}\sum_{s=k_1}^{k_1+\omega-1}\left(\sum_{i=1}^{m}\frac{b_i(s)x(s-\tau_i(s))}{1+x^n(s-\tau_i(s))}\prod_{r=0}^{s}\frac{1}{1-\lambda a(r)}\right)\\
&= \frac{\lambda\prod_{r=0}^{k_1+\omega-1}(1-\lambda a(r))}{1-\prod_{r=0}^{\omega-1}(1-\lambda a(r))}\sum_{s=k_1}^{k_1+\omega-1}\left(\sum_{i=1}^{m}\frac{b_i(s)x(s-\tau_i(s))}{1+x^n(s-\tau_i(s))}\prod_{r=0}^{s}\frac{1}{1-\lambda a(r)}\right)\\
&= \frac{\lambda}{1-\prod_{r=0}^{\omega-1}(1-\lambda a(r))}\sum_{s=k_1}^{k_1+\omega-1}\left(\sum_{i=1}^{m}\frac{b_i(s)x(s-\tau_i(s))}{1+x^n(s-\tau_i(s))}\prod_{r=s+1}^{k_1+\omega-1}(1-\lambda a(r))\right).
\end{aligned} \tag{2.6}$$

Note that we have not used the condition that $n > 1$ so far. Using (2.3) and (2.6), we will estimate the upper bound $\overline{x}$ and the lower bound $\underline{x}$. Since $n > 1$, we see that

$$u < u^n < 1 + u^n \quad \text{for } u > 0.$$

Hence, it follows from (2.3) that

$$\overline{x} < \frac{1}{\underline{a}}\max_{1\le k\le\omega}\left\{\sum_{i=1}^{m} b_i(k)\right\} \le \frac{1}{\underline{a}}\sum_{i=1}^{m}\overline{b}_i = B.$$

Recall that the function f_n defined by $f_n(u) = u/(1+u^n)$ for $u \ge 0$ is a unimodal function. Since $\underline{x} \le x(k) \le \overline{x}$ for all $k \in \mathbb{Z}^+$, it turns out that

$$\frac{x(s-\tau_i(s))}{1+x^n(s-\tau_i(s))} \ge \min\left\{f_n(\underline{x}),\ f_n(\overline{x})\right\} \quad \text{for } s \ge \overline{\tau}.$$

Note that $k_1 \geq \overline{\tau}$. Then, by using (1.13), (2.5) and (2.6), we obtain

$$
\begin{aligned}
\underline{x} &\geq \frac{\lambda \min\left\{f_n(\underline{x}),\, f_n(\overline{x})\right\}}{1-\prod_{r=0}^{\omega-1}(1-\lambda a(r))} \sum_{s=k_1}^{k_1+\omega-1}\left(\sum_{i=1}^{m} b_i(s) \prod_{r=s+1}^{k_1+\omega-1}(1-\lambda a(r))\right)\\
&> \frac{\lambda \min\left\{f_n(\underline{x}),\, f_n(\overline{x})\right\}}{1-\prod_{r=0}^{\omega-1}(1-\lambda a(r))} \sum_{s=k_1}^{k_1+\omega-1}\left(\gamma a(s) \prod_{r=s+1}^{k_1+\omega-1}(1-\lambda a(r))\right)\\
&= \frac{\gamma \min\left\{f_n(\underline{x}),\, f_n(\overline{x})\right\}}{1-\prod_{r=0}^{\omega-1}(1-\lambda a(r))} \sum_{s=k_1}^{k_1+\omega-1}\left(\lambda a(s) \prod_{r=s+1}^{k_1+\omega-1}(1-\lambda a(r))\right)\\
&= \frac{\gamma \min\left\{f_n(\underline{x}),\, f_n(\overline{x})\right\}}{1-\prod_{r=0}^{\omega-1}(1-\lambda a(r))} \sum_{s=k_1}^{k_1+\omega-1}\left(\Big(1-(1-\lambda a(s))\Big) \prod_{r=s+1}^{k_1+\omega-1}(1-\lambda a(r))\right)\\
&= \frac{\gamma \min\left\{f_n(\underline{x}),\, f_n(\overline{x})\right\}}{1-\prod_{r=0}^{\omega-1}(1-\lambda a(r))} \sum_{s=k_1}^{k_1+\omega-1}\left(\prod_{r=s+1}^{k_1+\omega-1}(1-\lambda a(r)) - \prod_{r=s}^{k_1+\omega-1}(1-\lambda a(r))\right)\\
&= \frac{\gamma \min\left\{f_n(\underline{x}),\, f_n(\overline{x})\right\}}{1-\prod_{r=0}^{\omega-1}(1-\lambda a(r))} \left(\prod_{r=k_1+\omega}^{k_1+\omega-1}(1-\lambda a(r)) - \prod_{r=k_1}^{k_1+\omega-1}(1-\lambda a(r))\right).
\end{aligned}
$$

Since $\prod_{r=k_1+\omega}^{k_1+\omega-1}(1-\lambda a(r))$ can be regarded as 1, we can conclude that

$$
\underline{x} > \gamma \min\left\{f_n(\underline{x}),\, f_n(\overline{x})\right\}. \tag{2.7}
$$

Here, we divide the argument into two cases to be considered: (i) $f_n(\underline{x}) \leq f_n(\overline{x})$; (ii) $f_n(\underline{x}) > f_n(\overline{x})$.

Case (i): It follows from (2.7) that $\underline{x} > \gamma f_n(\underline{x})$; namely,

$$
\underline{x} > \sqrt[n]{\gamma - 1}.
$$

Case (ii): The function f_n has the only peak value at $1/\sqrt[n]{n-1}$, and f_n is monotone increasing on $\left[0, 1/\sqrt[n]{n-1}\right)$ and monotone decreasing on $\left(1/\sqrt[n]{n-1}, \infty\right)$. Hence, we see that $\overline{x} > 1/\sqrt[n]{n-1}$. In fact, if $\overline{x} \leq 1/\sqrt[n]{n-1}$, then $f_n(\underline{x}) \leq f_n(\overline{x}) \leq f_n(1/\sqrt[n]{n-1})$. This is a contradiction. Since $\overline{x} > 1/\sqrt[n]{n-1}$, it follows from (2.7) that

$$
\underline{x} > \gamma f_n(\overline{x}) > \gamma f_n(B) = \frac{\gamma \underline{a}^{n-1} \sum_{i=1}^{m} \overline{b}_i}{\underline{a}^n + \left(\sum_{i=1}^{m} \overline{b}_i\right)^n}.
$$

Thus, in both cases, we can estimate that

$$
\underline{x} > \min\left\{\sqrt[n]{\gamma - 1},\ \frac{\gamma \underline{a}^{n-1} \sum_{i=1}^{m} \overline{b}_i}{\underline{a}^n + \left(\sum_{i=1}^{m} \overline{b}_i\right)^n}\right\} \geq A.
$$

Thus, every positive ω-periodic solution x of (2.1) satisfies

$$
A < \underline{x} \leq x(k) \leq \overline{x} < B
$$

for all $k \in \mathbb{Z}^+$. The proof is now complete. □

3. Preparation for proving

In the next section, we will prove Theorem 1 by using the continuation theorem. To introduce the continuation theorem, we give some definitions.

Let X be a Banach space and $L\colon \operatorname{Dom} L \subset X \to X$ a linear mapping. The mapping L is said to be a *Fredholm mapping of index zero* if

(a) $\dim \operatorname{Ker} L = \operatorname{codim} \operatorname{Im} L < +\infty$,

(b) $\operatorname{Im} L$ is closed in X.

If L is a Fredholm mapping of index zero and P, $Q\colon X \to X$ are continuous projectors such that

$$\operatorname{Im} P = \operatorname{Ker} L;$$

$$\operatorname{Ker} Q = \operatorname{Im} L = \operatorname{Im}(I - Q),$$

where I is the identity mapping from X to X, then the restriction $L_P\colon \operatorname{Dom} L \cap \operatorname{Ker} P \to \operatorname{Im} L$ is invertible. We denote the inverse of the restriction by $K_P\colon \operatorname{Im} L \to \operatorname{Dom} L \cap \operatorname{Ker} P$. Let $N\colon X \to X$ be a continuous mapping and Ω an open bounded subset of X. The mapping N is said to be *L-compact* on $\overline{\Omega}$ if

(a) $QN(\overline{\Omega})$ is bounded,

(b) $K_P(I - Q)N\colon \overline{\Omega} \to X$ is compact.

Now we are ready to state the continuation theorem (for example, see [24, 36, 37]).

Lemma 3. *Let L be a Fredholm mapping of index zero and let N be L-compact on $\overline{\Omega}$. Suppose that*

(i) *for each parameter $\lambda \in (0,1)$, every solution x of $Lx = \lambda Nx$ satisfies $x \notin \partial\Omega$;*

(ii) *$QNx \neq 0$ for each $x \in \partial\Omega \cap \operatorname{Ker} L$ and*

$$\deg\{QN, \Omega \cap \operatorname{Ker} L, 0\} \neq 0.$$

Then the equation $Lx = Nx$ has at least one solution staying in $X \cap \overline{\Omega}$.

We will apply the above continuation theorem to prove Theorem 1. To this end, we define a Banach space X by

$$X = \{x \in C(\mathbb{Z}^+, \mathbb{R})\colon x(k + \omega) = x(k)\}.$$

It is clear that X is endowed with the maximum norm $\|x\| = \max_{1 \le k \le \omega} |x(k)|$. Also, we define two mappings L and N by

$$Lx = x(k + 1) - x(k)$$

and

$$Nx = -a(k)x(k) + \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))}.$$

If $x \in X$, then

$$Lx(k+\omega) = x(k+\omega+1) - x(k+\omega) = x(k+1) - x(k) = Lx(k)$$

for all $k \in \mathbb{Z}^+$. This means that $Lx \in X$. Let x_1, $x_2 \in X$ and c_1, $c_2 \in \mathbb{R}$. Then

$$\begin{aligned} L(c_1x_1 + c_2x_2) &= (c_1x_1 + c_2x_2)(k+1) - (c_1x_1 + c_2x_2)(k) \\ &= c_1(x_1(k+1) - x_1(k)) + c_2(x_2(k+1) - x_2(k)) \\ &= c_1Lx_1(k) + c_2Lx_2(k). \end{aligned}$$

Hence, L is a linear mapping from X to X. Since a, b_i and τ_i $(1 \le i \le m)$ are positive ω-periodic, if $x \in X$, then

$$\begin{aligned} Nx(k+\omega) &= -a(k+\omega)x(k+\omega) + \sum_{i=1}^{m} \frac{b_i(k+\omega)x(k+\omega-\tau_i(k+\omega))}{1+x^n(k+\omega-\tau_i(k+\omega))} \\ &= -a(k)x(k) + \sum_{i=1}^{m} \frac{b_i(k)x(k+\omega-\tau_i(k))}{1+x^n(k+\omega-\tau_i(k))} \\ &= -a(k)x(k) + \sum_{i=1}^{m} \frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))} = Nx(k) \end{aligned}$$

for all $k \in \mathbb{Z}^+$. Hence, N is a continuous mapping from X to X.

4. Proof of Theorem 1

From the definition of L it turns out that

$$\operatorname{Ker} L = \{x \in X : x(k) \equiv c \in \mathbb{R}\}$$

and

$$\operatorname{Im} L = \left\{ x \in X : \sum_{k=1}^{\omega} x(k) = 0 \right\}.$$

In fact, if $Lx(k) = 0$ for all $k \in \mathbb{Z}^+$, then $x(k+1) \equiv x(k)$. Let $x \in X$. Then

$$\sum_{k=1}^{\omega} Lx(k) = x(\omega+1) - x(1) = 0.$$

It is clear that $\dim \operatorname{Ker} L = 1 = \operatorname{codim} \operatorname{Im} L < +\infty$ and $\operatorname{Im} L$ is closed in X. Hence, L is a Fredholm mapping of index zero.

Define $P: X \to X$ by

$$Px = \frac{1}{\omega}\sum_{k=1}^{\omega} x(k),$$

and let $Q = P$. Then P and Q are continuous projectors. For any $x \in X$,

$$\begin{aligned} Px(k+1) - Px(k) &= \frac{1}{\omega}\sum_{k=1}^{\omega} x(k+1) - \frac{1}{\omega}\sum_{k=1}^{\omega} x(k) \\ &= \frac{1}{\omega}\sum_{k=2}^{\omega+1} x(k) - \frac{1}{\omega}\sum_{k=1}^{\omega} x(k) = \frac{1}{\omega}(x(\omega+1) - x(1)) = 0 \end{aligned}$$

for all $k \in \mathbb{Z}^+$. Hence, $\operatorname{Im} P = \operatorname{Ker} L$. It is clear that $x \in \operatorname{Ker} Q \subset X$ if and only if $\sum_{k=1}^{\omega} x(k) = 0$; namely, $x \in \operatorname{Im} L$. For any $x \in \operatorname{Im} L$,

$$y(k) = x(k) - \frac{1}{\omega}\sum_{k=1}^{\omega} x(k) = x(k)$$

for all $k \in \mathbb{Z}^+$. Hence, $x = y \in \operatorname{Im}(I - Q)$. Conversely, for any $y \in \operatorname{Im}(I - Q)$, there exists an $x \in X$ such that

$$y(k) = x(k) - \frac{1}{\omega}\sum_{k=1}^{\omega} x(k)$$

for all $k \in \mathbb{Z}^+$. Hence, we have

$$\begin{aligned} \sum_{k=1}^{\omega} y(k) &= \sum_{k=1}^{\omega}\left(x(k) - \frac{1}{\omega}\sum_{k=1}^{\omega} x(k)\right) = \sum_{k=1}^{\omega} x(k) - \frac{1}{\omega}\sum_{k=1}^{\omega} x(k)\sum_{k=1}^{\omega} 1 \\ &= \sum_{k=1}^{\omega} x(k) - \sum_{k=1}^{\omega} x(k) = 0. \end{aligned}$$

This means that $y \in \operatorname{Im} L$. Thus, we see that $\operatorname{Ker} Q = \operatorname{Im} L = \operatorname{Im}(I - Q)$.

From the relations have shown in the immediately preceding paragraph, the restriction $L_P: \operatorname{Dom} L \cap \operatorname{Ker} P \to \operatorname{Im} L$ has the inverse $K_P: \operatorname{Im} L \to \operatorname{Dom} L \cap \operatorname{Ker} P$. The inverse K_P is given by

$$K_P x = \sum_{s=0}^{k-1} x(s) - \frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s} x(r)$$

for $x \in \operatorname{Im} L$. In fact, since

$$\begin{aligned} K_P x(k+\omega) - K_P x(k) &= \sum_{s=0}^{k+\omega-1} x(s) - \frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s} x(r) - \sum_{s=0}^{k-1} x(s) + \frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s} x(r) \\ &= \sum_{s=k}^{k+\omega-1} x(s) = \sum_{s=0}^{\omega-1} x(s) = 0 \end{aligned}$$

for all $k \in \mathbb{Z}^+$, it follows that $x \in \operatorname{Im} L$ implies $K_P x \in \operatorname{Dom} L$. It also turns out that

$$\begin{aligned} PK_P x &= \frac{1}{\omega}\sum_{k=1}^{\omega} K_P x(k) = \frac{1}{\omega}\sum_{k=1}^{\omega}\left(\sum_{s=0}^{k-1} x(s) - \frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s} x(r)\right) \\ &= \frac{1}{\omega}\left(\sum_{k=1}^{\omega}\sum_{s=0}^{k-1} x(s) - \frac{\omega}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s} x(r)\right) = \frac{1}{\omega}\left(\sum_{k=1}^{\omega}\sum_{s=0}^{k-1} x(s) - \sum_{k=1}^{\omega}\sum_{r=0}^{k-1} x(r)\right) = 0. \end{aligned}$$

Hence, $x \in \operatorname{Im} L$ implies $K_P x \in \operatorname{Ker} P$. For any $x \in \operatorname{Im} L$, we have

$$\begin{aligned} L_P K_P x &= K_P x(k+1) - K_P x(k) \\ &= \sum_{s=0}^{k} x(s) - \frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s} x(r) - \sum_{s=0}^{k-1} x(s) + \frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s} x(r) \\ &= x(k) = Ix. \end{aligned}$$

In addition, for any $x \in \operatorname{Dom} L \cap \operatorname{Ker} P$, we have

$$\begin{aligned} K_P L_P x &= K_P(x(k+1) - x(k)) \\ &= \sum_{s=0}^{k-1}(x(s+1) - x(s)) - \frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s}(x(r+1) - x(r)) \\ &= x(k) - x(0) - \frac{1}{\omega}\sum_{s=0}^{\omega-1}(x(s+1) - x(0)) = x(k) - \frac{1}{\omega}\sum_{s=1}^{\omega} x(s). \end{aligned}$$

Since $x \in \operatorname{Ker} P = \operatorname{Ker} Q = \operatorname{Im} L$, we see that $\sum_{s=1}^{\omega} x(s) = 0$. Hence, $K_P L_P x = x(k) = Ix$. We therefore conclude that $K_P = L_P^{-1}$.

We next show the mapping N defined above is L-compact on $\overline{\Omega}$, where

$$\Omega = \{x \in X : A < x(k) < B\}.$$

To this end, we will check that

(a) $QN(\overline{\Omega})$ is bounded,

(b) $K_P(I - Q)N : \overline{\Omega} \to X$ is compact.

By a straightforward calculation, we obtain

$$QNx = \frac{1}{\omega}\sum_{k=1}^{\omega}\left(-a(k)x(k) + \sum_{i=1}^{m}\frac{b_i(k)x(k-\tau_i(k))}{1 + x^n(k-\tau_i(k))}\right)$$

and

$$\begin{aligned}K_p(I-Q)Nx = &\sum_{s=0}^{k-1}\left(-a(s)x(s)+\sum_{i=1}^{m}\frac{b_i(s)x(s-\tau_i(s))}{1+x^n(s-\tau_i(s))}\right)\\&-\left(\frac{k}{\omega}-\frac{\omega+1}{2\omega}\right)\sum_{s=1}^{\omega}\left(-a(s)x(s)+\sum_{i=1}^{m}\frac{b_i(s)x(s-\tau_i(s))}{1+x^n(s-\tau_i(s))}\right)\\&-\frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s}\left(-a(r)x(r)+\sum_{i=1}^{m}\frac{b_i(r)x(r-\tau_i(r))}{1+x^n(r-\tau_i(r))}\right)\end{aligned}$$

for $x \in X$. Since

$$\sum_{k=1}^{\omega}\left(-a(k)x(k)+\sum_{i=1}^{m}\frac{b_i(k)x(k-\tau_i(k))}{1+x^n(k-\tau_i(k))}\right) < \sum_{k=1}^{\omega}\left(\sum_{i=1}^{m}b_i(k)\right) = \omega\sum_{i=1}^{m}\overline{b}_i$$

for $x \in \overline{\Omega}$, the mapping QN is bounded on $\overline{\Omega}$. Hence, the above sentence (a) is true.

To show that the sentence (b) is also true, from the definition of the compactness of mappings, we have only to prove that $K_P(I-Q)N(E)$ is relatively compact for any bounded subset $E \subset \overline{\Omega} \subset X$. As a matter of fact, we can even show that it is compact.

Since E is a subspace of a finite dimensional Banach space X, we see that E is closed. Hence, E is compact. Note that a metric space is compact if and only if it is sequentially compact. Hence, E is sequentially compact; namely, every infinite sequence in E contains a convergent subsequence $\{x_j\}_{j\in\mathbb{N}}$ whose limit x_* belongs to E. Let $y_* = K_P(I-Q)Nx_*$. Since $\lim_{j\to\infty} x_j = x_* \in E$, it turns out that

$$\begin{aligned}\lim_{j\to\infty} K_p(I-Q)Nx_j = &\lim_{j\to\infty}\sum_{s=0}^{k-1}\left(-a(s)x_j(s)\right)+\lim_{j\to\infty}\sum_{s=0}^{k-1}\sum_{i=1}^{m}\frac{b_i(s)x_j(s-\tau_i(s))}{1+x_j^n(s-\tau_i(s))}\\&-\left(\frac{k}{\omega}-\frac{\omega+1}{2\omega}\right)\lim_{j\to\infty}\sum_{s=1}^{\omega}\left(-a(s)x_j(s)\right)\\&-\left(\frac{k}{\omega}-\frac{\omega+1}{2\omega}\right)\lim_{j\to\infty}\sum_{s=1}^{\omega}\sum_{i=1}^{m}\frac{b_i(s)x_j(s-\tau_i(s))}{1+x_j^n(s-\tau_i(s))}\\&-\frac{1}{\omega}\lim_{j\to\infty}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s}\left(-a(r)x_j(r)\right)\\&-\frac{1}{\omega}\lim_{j\to\infty}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s}\sum_{i=1}^{m}\frac{b_i(r)x_j(r-\tau_i(r))}{1+x_j^n(r-\tau_i(r))}\\=&\sum_{s=0}^{k-1}\left(-a(s)\lim_{j\to\infty}x_j(s)\right)+\sum_{s=0}^{k-1}\sum_{i=1}^{m}\frac{b_i(s)\lim_{j\to\infty}x_j(s-\tau_i(s))}{1+\lim_{j\to\infty}x_j^n(s-\tau_i(s))}\\&-\left(\frac{k}{\omega}-\frac{\omega+1}{2\omega}\right)\sum_{s=1}^{\omega}\left(-a(s)\lim_{j\to\infty}x_j(s)\right)\end{aligned}$$

$$
\begin{aligned}
&-\left(\frac{k}{\omega}-\frac{\omega+1}{2\omega}\right)\sum_{s=1}^{\omega}\sum_{i=1}^{m}\frac{b_i(s)\lim_{j\to\infty}x_j(s-\tau_i(s))}{1+\lim_{j\to\infty}x_j^n(s-\tau_i(s))}\\
&-\frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s}\left(-a(r)\lim_{j\to\infty}x_j(r)\right)\\
&-\frac{1}{\omega}\sum_{s=0}^{\omega-1}\sum_{r=0}^{s}\sum_{i=1}^{m}\frac{b_i(r)\lim_{j\to\infty}x_j(r-\tau_i(r))}{1+\lim_{j\to\infty}x_j^n(r-\tau_i(r))}\\
=\;& K_p(I-Q)N\lim_{j\to\infty}x_j=K_p(I-Q)Nx_*=y_*.
\end{aligned}
$$

Hence, $K_p(I-Q)N(E)$ is compact.

Next, we check that the assumption (i) of Lemma 3 is satisfied. From the definitions of L and N, we see that any ω-periodic solution of (2.1) corresponds one-to-one to a solution of $Lx=\lambda Nx$ with $\lambda\in(0,1)$. Proposition 2 shows that every positive solution of $Lx=\lambda Nx$ stays in the open bounded sebset Ω. Let y be an element of $\partial\Omega$. Suppose that y is a solution of $Lx=\lambda Nx$. Of course, $y\in X$. Then, we can find a $k^*\in\{1,2,\dots,\omega\}$ so that $y(k^*)=\min_{1\le k\le\omega}y(k)$. There are three cases to be considered. If $y(k^*)>A$, then y is a positive solution of $Lx=\lambda Nx$. Hence, we see that $A<y(k)<B$ for $k=1,2,\dots,\omega$. It turns out from the fact that there exists a neighborhood of y whose all elements belong to Ω. This contradicts the fact that $y\in\partial\Omega$. If $0<y(k^*)\le A$, then y is a positive solution of $Lx=\lambda Nx$. However, this contradicts the conclusion of Proposition 2. If $y(k^*)\le 0$, then there exists a neighborhood of y whose all elements do not belong to Ω. This also contradicts the fact that $y\in\partial\Omega$. Hence, if $y\in\partial\Omega$, then y is never any solution of $Lx=\lambda Nx$. This means that the assumption (i) holds.

Finally, we check that the assumption (ii) of Lemma 3 is also satisfied. If $x\in\partial\Omega\cap\operatorname{Ker}L$, then $x(k)=A$ or $x(k)=B$ for all $k\in\mathbb{Z}^+$. Let x_1 and x_2 be sequences satisfying $x_1(k)\equiv A$ and $x_2(k)\equiv B$, respectively. Then, by (1.13) we have

$$
QNx_1=\frac{1}{\omega}\sum_{k=1}^{\omega}\left(-Aa(k)+\frac{A}{1+A^n}\sum_{i=1}^{m}b_i(k)\right)>\frac{A}{\omega}\left(\frac{\gamma}{1+A^n}-1\right)\sum_{k=1}^{\omega}a(k).
$$

Since $A\le\sqrt[n]{\gamma-1}$, we see that $QNx_1>0$. Recall that

$$
\overline{b}_i=\max_{1\le h\le\omega}b_i(k)\quad\text{and}\quad B=\frac{1}{\underline{a}}\sum_{i=1}^{m}\overline{b}_i.
$$

Then we obtain

$$
\begin{aligned}
QNx_2&=\frac{1}{\omega}\sum_{k=1}^{\omega}\left(-Ba(k)+\frac{B}{1+B^n}\sum_{i=1}^{m}b_i(k)\right)\le-\frac{B}{\omega}\sum_{k=1}^{\omega}a(k)+\frac{B}{1+B^n}\sum_{i=1}^{m}\overline{b}_i\\
&<-\frac{B}{\omega}\sum_{k=1}^{\omega}a(k)+\sum_{i=1}^{m}\overline{b}_i\le-\underline{a}B+\underline{a}B=0.
\end{aligned}
$$

We therefore conclude that $QNx \neq 0$ for each $x \in \partial\Omega \cap \operatorname{Ker} L$. To seek the degree $\deg\{QN, \Omega \cap \operatorname{Ker} L, 0\}$, we define a continuous mapping $H : \Omega \cap \operatorname{Ker} L \times [0,1] \to X$ by

$$H(x,\mu) = -\mu\left(Ix - \frac{A+B}{2}\right) + (1-\mu)QNx.$$

It is clear that H connects two continuous mappings QN, $-I + (A+B)/2 : \Omega \cap \operatorname{Ker} L \to X$. Recall that the elements of $\partial\Omega \cap \operatorname{Ker} L$ are only two sequences x_1 and x_2 satisfying $x_1(k) \equiv A$ and $x_2(k) \equiv B$, respectively. We have

$$H(x_i,\mu) = -\mu\left(Ix_i - \frac{A+B}{2}\right) + (1-\mu)QNx_i = (-1)^i\mu\left(\frac{A-B}{2}\right) + (1-\mu)QNx_i$$

for $i = 1,2$ and $\mu \in [0,1]$. Since $A < B$ and $QNx_2 < 0 < QNx_1$, we see that $H(x_2,\mu) < 0 < H(x_1,\mu)$. Hence, $H(x,\mu) \neq 0$ for all $(x,\mu) \in \partial\Omega \cap \operatorname{Ker} L \times [0,1]$, and therefore, H is a homotopic mapping. Since the mappings QN and $-I + (A+B)/2$ are homotopy equivalent, it turns out that

$$\deg\{QN, \Omega \cap \operatorname{Ker} L, 0\} = \deg\left\{-I + \frac{A+B}{2}, \Omega \cap \operatorname{Ker} L, 0\right\} = 1 \neq 0.$$

Hence, the assumption (ii) holds.

Since all assumptions of Lemma 3 are satisfied, the equation $Lx = Nx$ has at least one solution lying in $X \cap \overline{\Omega}$. In other words, equation (1.11) has at least one positive ω-periodic solution located in the region $[A,B]$. The proof is now complete. □

5. How to apply Theorem 1

We first give a concrete example to illustrate Theorem 1.

Example 1. Consider the equation

$$\Delta x(k) = -a(k)x(k) + \frac{b_1(k)x(k-\tau_1(k))}{1+x^2(k-\tau_1(k))} + \frac{b_2(k)x(k-\tau_2(k))}{1+x^2(k-\tau_2(k))}, \tag{5.1}$$

where

$$a(k) = \begin{cases} 1/2 & \text{if } k=0, \\ 5/6 & \text{if } k=1, \\ 1/4 & \text{if } k=2, \\ 1/5 & \text{if } k=3, \end{cases} \tag{5.2}$$

$$b_1(k) = \begin{cases} 3/2 & \text{if } k=0, \\ 1/2 & \text{if } k=1, \\ 2 & \text{if } k=2, \\ 1/4 & \text{if } k=3, \end{cases} \qquad b_2(k) = \begin{cases} 1 & \text{if } k=0, \\ 7/6 & \text{if } k=1, \\ 5/8 & \text{if } k=2, \\ 3/4 & \text{if } k=3, \end{cases} \tag{5.3}$$

$$\tau_1(k) = 6 + 2\cos\left(\frac{\pi}{2}k\right) = \begin{cases} 8 & \text{if } k = 0, \\ 6 & \text{if } k = 1, \\ 4 & \text{if } k = 2, \\ 6 & \text{if } k = 3, \end{cases} \quad \tau_2(k) = 5 + 3\sin\left(\frac{\pi}{2}k\right) = \begin{cases} 5 & \text{if } k = 0, \\ 8 & \text{if } k = 1, \\ 5 & \text{if } k = 2, \\ 2 & \text{if } k = 3, \end{cases} \tag{5.4}$$

and $a(k) = a(k+4)$, $b_i(k) = b_i(k+4)$, $\tau_i(k) = \tau_i(k+4)$ for $k \in \mathbb{Z}$ and $i = 1,2$. Then equation (5.1) has at least one positive 4-periodic solution.

It is clear that $\omega = 4$, and a, b_i and τ_i $(i = 1,2)$ are ω-periodic discrete functions satisfying $0 < a(k) < 1$, $b_i(k) > 0$ and $\tau_i(k) > 0$ for $k \in \mathbb{Z}$ and $i = 1,2$. Let

$$\gamma = \frac{1 + \min\limits_{1 \le k \le 4}\left\{\dfrac{b_1(k) + b_2(k)}{a(k)}\right\}}{2} = \frac{3}{2} > 1.$$

Then it is easy to check that condition (1.13) is satisfied. Hence, from Theorem 1 it turns out that equation (5.1) has at least one positive 4-periodic solution under the assumptions (5.2)–(5.4).

The advantage of Theorem 1 is that we can evaluate the existence range of the positive ω-periodic solutions of (1.11). In this example, since $m = n = 2$, $\gamma = 3/2$,

$$\underline{a} = \min_{1 \le k \le \omega} a(k) = 1/5, \quad \overline{b}_1 = \max_{1 \le k \le \omega} b_1(k) = 2 \quad \text{and} \quad \overline{b}_2 = \max_{1 \le k \le \omega} b_2(k) = \frac{7}{6},$$

we can calculate as follows:

$$\sqrt{\gamma - 1} = \frac{1}{\sqrt{2}}, \quad \sum_{i=1}^{m} \overline{b}_i = \frac{19}{6} \quad \text{and} \quad \frac{\gamma \underline{a}^{n-1} \sum_{i=1}^{m} \overline{b}_i}{\underline{a}^n + \left(\sum_{i=1}^{m} \overline{b}_i\right)^n} = \frac{45}{511}.$$

Hence, Theorem 1 shows that positive 4-periodic solutions locate in the region

$$[A, B] = \left[\frac{45}{511}, \frac{95}{6}\right].$$

In fact, we can find a positive 4-periodic solution by using hand calculations. As mentioned in Section 1, to seek a concrete solution of (5.1), we need to choose a set of initial points $\phi(-\overline{\tau})$, $\phi(-\overline{\tau}+1), \ldots, \phi(0)$, where

$$\overline{\tau} = \max_{1 \le i \le 2}\left\{\max_{1 \le k \le 4} \tau_i(k)\right\} = 8.$$

Let

$$\phi(k) = \begin{cases} 1/2 & \text{if } k = -8, \\ 1/2 & \text{if } k = -7, \\ * & \text{if } k = -6, \\ 1/2 & \text{if } k = -5, \end{cases} \quad \text{and} \quad \phi(k) = \begin{cases} 2 & \text{if } k = -4, \\ 2 & \text{if } k = -3, \\ 1 & \text{if } k = -2, \\ 2 & \text{if } k = -1, \\ 2 & \text{if } k = 0, \end{cases} \tag{5.5}$$

where $*$ can be any positive real number. Then we have

$$\begin{aligned}
x(1) &= (1-a(0))x(0) + \frac{b_1(0)x(0-\tau_1(0))}{1+x^2(0-\tau_1(0))} + \frac{b_2(0)x(0-\tau_2(0))}{1+x^2(0-\tau_2(0))} \\
&= \left(1-\frac{1}{2}\right)\times 2 + \frac{3}{2}\times\frac{x(-8)}{1+x^2(-8)} + 1\times\frac{x(-5)}{1+x^2(-5)} = 2, \\
x(2) &= (1-a(1))x(1) + \frac{b_1(1)x(1-\tau_1(1))}{1+x^2(1-\tau_1(1))} + \frac{b_2(1)x(1-\tau_2(1))}{1+x^2(1-\tau_2(1))} \\
&= \left(1-\frac{5}{6}\right)\times 2 + \frac{1}{2}\times\frac{x(-5)}{1+x^2(-5)} + \frac{7}{6}\times\frac{x(-7)}{1+x^2(-7)} = 1, \\
x(3) &= (1-a(2))x(2) + \frac{b_1(2)x(2-\tau_1(2))}{1+x^2(2-\tau_1(2))} + \frac{b_2(2)x(2-\tau_2(2))}{1+x^2(2-\tau_2(2))} \\
&= \left(1-\frac{1}{4}\right)\times 1 + 2\times\frac{x(-2)}{1+x^2(-2)} + \frac{5}{8}\times\frac{x(-3)}{1+x^2(-3)} = 2, \\
x(4) &= (1-a(3))x(3) + \frac{b_1(3)x(3-\tau_1(3))}{1+x^2(3-\tau_1(3))} + \frac{b_2(3)x(3-\tau_2(3))}{1+x^2(3-\tau_2(3))} \\
&= \left(1-\frac{1}{5}\right)\times 2 + \frac{1}{4}\times\frac{x(-3)}{1+x^2(-3)} + \frac{3}{4}\times\frac{x(1)}{1+x^2(1)} = 2, \\
x(5) &= (1-a(4))x(4) + \frac{b_1(4)x(4-\tau_1(4))}{1+x^2(4-\tau_1(4))} + \frac{b_2(4)x(4-\tau_2(4))}{1+x^2(4-\tau_2(4))} \\
&= \left(1-\frac{1}{2}\right)\times 2 + \frac{3}{2}\times\frac{x(-4)}{1+x^2(-4)} + 1\times\frac{x(-1)}{1+x^2(-1)} = 2, \\
x(6) &= (1-a(5))x(5) + \frac{b_1(5)x(5-\tau_1(5))}{1+x^2(5-\tau_1(5))} + \frac{b_2(5)x(5-\tau_2(5))}{1+x^2(5-\tau_2(5))} \\
&= \left(1-\frac{5}{6}\right)\times 2 + \frac{1}{2}\times\frac{x(-1)}{1+x^2(-1)} + \frac{7}{6}\times\frac{x(-3)}{1+x^2(-3)} = 1, \\
x(7) &= (1-a(6))x(6) + \frac{b_1(6)x(6-\tau_1(6))}{1+x^2(6-\tau_1(6))} + \frac{b_2(6)x(6-\tau_2(6))}{1+x^2(6-\tau_2(6))} \\
&= \left(1-\frac{1}{4}\right)\times 1 + 2\times\frac{x(2)}{1+x^2(2)} + \frac{5}{8}\times\frac{x(1)}{1+x^2(1)} = 2, \\
x(8) &= (1-a(7))x(7) + \frac{b_1(7)x(7-\tau_1(7))}{1+x^2(7-\tau_1(7))} + \frac{b_2(7)x(7-\tau_2(7))}{1+x^2(7-\tau_2(7))} \\
&= \left(1-\frac{1}{5}\right)\times 2 + \frac{1}{4}\times\frac{x(1)}{1+x^2(1)} + \frac{3}{4}\times\frac{x(5)}{1+x^2(5)} = 2,
\end{aligned}$$

and so on (see Figure 1). Certainly, the solution x is positive and 4-periodic satisfying

$$A = \frac{45}{511} < 1 \le x(k) \le 2 < \frac{95}{6} = B$$

for all $k \in \mathbb{Z}^+$. Note that the initial points $\phi(k)$ $(-8 \le k \le 0)$ have no periodicity.

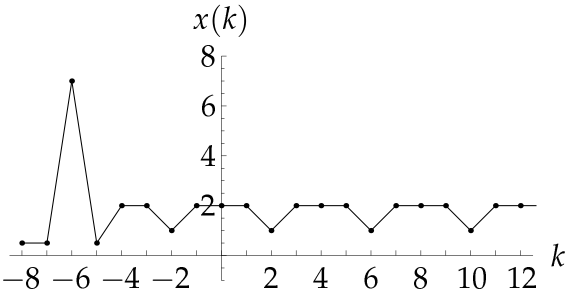

Figure 1: A graph of the solution of (5.1) with (5.2)–(5.4) satisfying the initial condition (5.5)

In Example 1, for the given positive numbers m, n, the coefficients a, b_i and the time delays τ_i ($i = 1, 2, \ldots, m$), we estimated the existence range $[A, B]$ of the positive periodic solutions of (1.11). Conversely, for the given value A and B, we can choose the positive numbers m, n, the coefficients a, b_i and the time delays τ_i so that the positive periodic solutions of (1.11) exist in the range $[A, B]$. We will explain this situation below.

It is reported that the number of red blood cells per microliter is different depending on sex and race, even for healthy humans. The lower and upper limits of the measured value are slightly different depending on health agencies. For example, according to the guidelines for clinical examination (JSLM2012) by Japanese Society of Laboratory Medicine, the standard value of red blood cells is 4.1×10^6 to 5.3×10^6 per $1\mu\ell$ for adult males, 3.8×10^6 to 4.8×10^6 per $1\mu\ell$ for adult females. Let A be the lower limit and let B be the upper limit. In the case of Japanese people, even if A and B are regarded as 3.6×10^6 and 6.0×10^6 per $1\mu\ell$ respectively, there would be no big difference from the reality. Of course, it is also possible to change the values A and B.

It is known that red blood cells start as immature cells in the bone marrow and after about 7 days of maturation they are released into the bloodstream (see [38, Sect. 1]). For this reason, we assume that time lag is 7 days; namely, $\tau_i(k) = 7$ for $i = 1, 2, \ldots, m$ and $k = 1, 2, \ldots, \omega$. To simplify hand calculations, we set $m = 2$ and $\omega = 7$.

Example 2. Let $A = 3.6 \times 10^6$ and $B = 6.0 \times 10^6$. If

$$a(k) = \begin{cases} 0.60 & \text{if } k = 0, \\ 0.66 & \text{if } k = 1, \\ 0.60 & \text{if } k = 2, \\ 0.72 & \text{if } k = 3, \\ 0.66 & \text{if } k = 4, \\ 0.60 & \text{if } k = 5, \\ 0.66 & \text{if } k = 6, \end{cases} \tag{5.6}$$

$$b_1(k) = \begin{cases} 0.8\times 10^6 & \text{if } k=0, \\ 0.5\times 10^6 & \text{if } k=1, \\ 0.6\times 10^6 & \text{if } k=2, \\ 0.8\times 10^6 & \text{if } k=3, \\ 0.7\times 10^6 & \text{if } k=4, \\ 0.2\times 10^6 & \text{if } k=5, \\ 0.6\times 10^6 & \text{if } k=6, \end{cases} \qquad b_2(k) = \begin{cases} 2.2\times 10^6 & \text{if } k=0, \\ 2.8\times 10^6 & \text{if } k=1, \\ 2.4\times 10^6 & \text{if } k=2, \\ 2.8\times 10^6 & \text{if } k=3, \\ 2.6\times 10^6 & \text{if } k=4, \\ 2.8\times 10^6 & \text{if } k=5, \\ 2.7\times 10^6 & \text{if } k=6, \end{cases} \tag{5.7}$$

and $a(k) = a(k+7)$, $b_1(k) = b_1(k+7)$, $b_2(k) = b_2(k+7)$ for $k \in \mathbb{Z}$. Then the equation

$$\Delta x(k) = -a(k)x(k) + \frac{b_1(k)x(k-7)}{1+x^{1.02}(k-7)} + \frac{b_2(k)x(k-7)}{1+x^{1.02}(k-7)} \tag{5.8}$$

has at least one positive 7-periodic solution x satisfying

$$A \le x(k) \le B \quad \text{for } k \in \mathbb{Z}^+.$$

In the case that $n > 1$, the production function f_n given by

$$f_n(u) = \frac{u}{1+u^n} \quad \text{for } u \ge 0$$

has the maximum value

$$\left(\frac{(n-1)^{n-1}}{n^n}\right)^{1/n}$$

at $u^* = \sqrt[n]{1/(n-1)}$. As n approaches 1, the maximum value $f_n(u^*)$ increases and converges to 1, and the value u^* diverges to ∞. Hence, we can find $n > 1$ so that $f_n(B) > A/B$, because $A/B < 1$. In the case that $A = 3.6\times 10^6$ and $B = 6.0\times 10^6$, we can choose n as 1.02. In fact,

$$f_{1.02}(6.0\times 10^6) = \frac{6.0\times 10^6}{1+(6.0\times 10^6)^{1.02}} = 0.7318\cdots > 0.6 = \frac{A}{B}.$$

Next, we choose a γ satisfying

$$\gamma \ge \max\left\{\frac{A}{f_n(B)},\ A^n+1\right\}.$$

Since $n = 1.02$, $A = 3.6\times 10^6$ and $B = 6.0\times 10^6$, we see that $A/f_n(B) = 4{,}918{,}872\cdots$ and $A^n + 1 = 4{,}868{,}875\cdots$. Hence, we can choose γ as 4.95×10^6.

It is clear that a, b_1 and b_2 are 7-periodic discrete functions satisfying $0 < a(k) < 1$, $b_1(k) > 0$ and $b_2(k) > 0$ for $k \in \mathbb{Z}$. Since $\underline{a} = 0.60$, $\overline{b}_1 = 0.8\times 10^6$ and $\overline{b}_2 = 2.8\times 10^6$, it turns out that

$$B = 6.0\times 10^6 = \frac{1}{0.6}(0.8\times 10^6 + 2.8\times 10^6) = \frac{1}{\underline{a}}\left(\overline{b}_1 + \overline{b}_2\right).$$

From (5.6) and (5.7), we see that condition (1.13) holds for $\gamma = 4.95$, $m = 2$ and $\omega = 7$. Hence, Theorem 1 ensures that equation (5.8) has at least one positive 7-periodic solution located in the region $[A, B]$ under the assumptions (5.6) and (5.7).

6. Conclusions

Needless to say, red blood cells that carry nutrients and oxygen to whole body cells and carry out carbon dioxide and waste products, leucocytes that are responsible for immunity related to biological defense, and platelets that work to stop bleeding are extremely important in vivo tissues. It is well known that abnormality in the number of such blood cells causes disease and leads to death. However, it is not enough only to know that the number of blood cells in a healthy organism is within the normal range. It is necessary to know how the number of blood cells repeats increase and decrease within the normal range. Hence, it is important not only in mathematics but also in medicine to analyze periodic dynamic behavior of the number of blood cells.

In general, mathematical hematopoiesis models consists of an extinction part and a production part concerning blood cells. Mackey and Glass [2] incorporated a time delay into the production part and proposed two kind of hematopoiesis models according to the property of the production functions. For convenience, we decided to call these two kind of hematopoiesis models given by Mackey and Glass as D-type and U-type, respectively,

In this paper, we focused on a hematopoietic model considering periodic seasonal changes. As Satué *et al*. [4], Maes *et al*. [5] and Fortin and Mackey [6] point out, periodic seasonal changes greatly affect the hematopoietic process of horses and humans. It is also well known that in clinical studies, a certain time (time delay) is required for the process in which hematopoietic stem cells change to mature cells and are released into the bloodstream (for example, see [33, 34, 35]). According to their clinical studies, time lags are different depending on the type of blood cell. Since the regulatory mechanism of the hematopoietic process is thus complicated, it seems difficult to elucidate the dynamics of blood cells using a single production function. Moreover, it can be said that discrete models are more suitable than continuous models to investigate the increase and decrease of the number of blood cells, which are separate entities even if the number is enormous.

Based on these facts and ideas, in order to analyze the dynamics of the hematopoietic process more properly and accurately, the hematopoietic model discussed in this paper was described by a first-order nonlinear difference equation with multiple production functions having coefficients and time delays being periodic discrete functions. We clarified periodic behavior of the number of mature blood cells by using the continuation theorem of coincidence degree theory. Our main conclusions can be summarized as follows:

(i) We obtained a straightforward sufficient condition which guarantees the existence of positive periodic solutions. It is easy to check whether this sufficient condition holds or not. In order to confirm that this sufficient condition holds, we have only to show that the ratio of a variable coefficient of the extinction part to the sum of variable coefficients of the production part is less than 1.

(ii) A significant advantage of the continuation theorem of coincidence degree theory that we utilized in this paper is that it is able to determine the region where periodic solutions located in. For that reason, we were also able to present the existence region of positive periodic solutions. As a result, appropriate variable coefficients of our model can be determined from clinical data.

(iii) From the obtained result, we found that the lower limit A and the upper limit B of blood cell counts change depending on the selection of the positive numbers m, n, γ and the variable coefficients a, b_i $(i = 1, 2, \ldots, m)$. To be exact, the upper limit B becomes larger if any of the following holds: (a) the minimum value of $a(k)$ $(k = 1, 2, \ldots, \omega)$ becomes smaller becomes smaller; (b) the maximum value of $b_i(k)$ $(i = 1, 2, \ldots, m$ and $k = 1, 2, \ldots, \omega)$ becomes larger; (c) the number m becomes larger. The lower limit A becomes smaller if any of the following holds: (d) the number γ becomes smaller; (e) the number n approaches 2.

It may be necessary to explain only (e) of (iii). As already mentioned, the production function f_n has the maximum value

$$\left(\frac{(n-1)^{n-1}}{n^n}\right)^{1/n}.$$

Since

$$\frac{d}{dx}g(x) \overset{\text{def}}{=} \frac{d}{dx}\left(\frac{(x-1)^{(x-1)/x}}{x}\right) = \frac{(x-1)^{(x-1)/x}}{x^3}\ln(x-1),$$

the function g has the minimum vable 1/2 at $x = 2$.

Although the standard value of white blood cell counts of human vary depending on age and gender and there is a slight discrepancy depending on each clinical laboratory, it can be considered that both adult male and female are in the range of 3000 to 9000 $1\mu\ell$. Outside this range, there is a suspected case of blood disease. For example, in leukemia, which is a cancer of white blood cells, it is not uncommon for white blood cell counts to become from several times to ten times than the standard value. Leukemia is divided into many types. In any leukemia, suddenly or after a certain stage of progression, the immature hematopoietic stem cells stop maturing on the way of differentiation and growth, leukemia cells having no function continue to increase rapidly. For this reason,the mechanism for making normal white blood cells is impaired, and in many cases, the number of red blood cells and platelets also decrease. Conversely, the reduction of white blood cell counts have been reported in systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD) which are types of collagen disease, and Sjögren's syndrome (SjS).

The above clinical facts can be explained by changing the positive numbers m, n, γ and the coefficients a, b_i $(i = 1, 2, \ldots, m)$ of our hematopoiesis model (1.11), that is, the fact that genes in blood cells are scratched by some cause in the middle of the hematopoietic process and it becomes impossible to adjust normal differentiation and maturation can be interpreted that the positive numbers m, n, γ and the variable coefficients a, b_i have been changed.

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Appendix

When $0 < n \le 1$, the production function $bu/(1+u^n)$ is monotonically increasing. This means that as blood cells increase, the rate of increase of blood cells also increases. Since it fails to apply the brakes to increase of blood cells, it seems not suitable as a mathematical model describing the hematopoietic process. Hence, in our main result, we have only dealt with the case that $n > 1$, in which equation (1.11) has unimodal production functions. However, from pure mathematical side, it is worth considering the case that $0 < n \le 1$.

Theorem 4. *Suppose that a, b_i and τ_i $(1 \le i \le m)$ are positive ω-periodic. If condition* (1.13) *holds, then equation* (1.11) *with* $0 < n \le 1$ *has at least one positive ω-periodic solution located in the region* $[C, D]$, *where*

$$C = \sqrt[n]{\gamma - 1} \quad \textit{and} \quad D = \sqrt[n]{\frac{\omega \sum_{i=1}^{m} b_i^*}{\underline{a}} - 1},$$

in which γ and $\underline{a}$ are constants given in Theorem 1 *and* $b_i^* = \left(\sum_{k=1}^{\omega} b_i(k)\right)/\omega$ *for* $1 \le i \le m$.

By using Lemma 3, we can show that Theorem 4 holds in the same way as the proof of Theorem 1. To apply Lemma 3 to the proof of Theorem 4, it is only necessary to show the following proposition (leave the details to the reader).

Proposition 5. *Suppose that a, b_i and τ_i $(1 \le i \le m)$ are positive ω-periodic. If condition* (1.13) *holds, then every positive ω-periodic solution x of* (2.1) *with* $0 < n \le 1$ *satisfies*

$$C < x < D,$$

where C and D are constants given in Theorem 4.

PROOF. As in the proof of Proposition 2, we can show that the inequalities (2.3) and (2.6) hold. Since $0 < n \le 1$, the function f_n defined by $f_n(u) = u/(1+u^n)$ is increasing for $u \ge 0$. Hence, it follows from (2.3) that

$$\begin{aligned}
\overline{x} &\le \frac{1}{\underline{a}} \max_{1 \le k \le \omega} \left\{ \sum_{i=1}^{m} b_i(k) f(x(k - \tau_i(k))) \right\} \\
&\le \frac{f(\overline{x})}{\underline{a}} \max_{1 \le k \le \omega} \left\{ \sum_{i=1}^{m} b_i(k) \right\} \le \frac{f(\overline{x})}{\underline{a}} \sum_{i=1}^{m} \overline{b}_i \\
&< \frac{\omega f(\overline{x})}{\underline{a}} \sum_{i=1}^{m} b_i^*.
\end{aligned}$$

Arranging this inequality, we obtain

$$\overline{x} < \sqrt[n]{\frac{\omega \sum_{i=1}^{m} b_i^*}{\underline{a}} - 1} = D.$$

From (1.13) and (2.6) it turns out that

$$\begin{aligned}
\underline{x} &= \frac{\lambda}{1 - \prod\limits_{r=0}^{\omega-1}(1-\lambda a(r))} \sum_{s=k_1}^{k_1+\omega-1} \left(\sum_{i=1}^{m} b_i(s) f_n(x(s-\tau_i(s))) \prod_{r=s+1}^{k_1+\omega-1} (1-\lambda a(r)) \right) \\
&\geq \frac{\lambda f_n(\underline{x})}{1 - \prod\limits_{r=0}^{\omega-1}(1-\lambda a(r))} \sum_{s=k_1}^{k_1+\omega-1} \left(\sum_{i=1}^{m} b_i(s) \prod_{r=s+1}^{k_1+\omega-1} (1-\lambda a(r)) \right)
\end{aligned}$$

$$\begin{aligned}
&> \frac{\gamma f_n(\underline{x})}{1 - \prod\limits_{r=0}^{\omega-1}(1-\lambda a(r))} \sum_{s=k_1}^{k_1+\omega-1} \left(\lambda a(s) \prod_{r=s+1}^{k_1+\omega-1} (1-\lambda a(r)) \right) \\
&> \frac{\gamma f_n(\underline{x})}{1 - \prod\limits_{r=0}^{\omega-1}(1-\lambda a(r))} \left(1 - \prod_{r=0}^{\omega-1}(1-\lambda a(r)) \right) = \gamma f_n(\underline{x}).
\end{aligned}$$

Hence, we can estimate that

$$\underline{x} > \sqrt[n]{\gamma - 1} = C.$$

We therefore conclude that

$$C < \underline{x} \leq x(k) < \overline{x} < D$$

for all $k \in \mathbb{Z}^+$. This completes the proof of Proposition 5. ☐

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