



A Mathematical Approach to Oscillation of a Discrete Hematopoiesis Model with Positive and Negative Coefficients

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Abstract

In this paper, we investigate a mathematical model of hematopoiesis, a process responsible for the regular replacement of circulating blood cells. Since differential delay equations are difficult to control analytically, numerous studies have considered the models as difference equations. The main objective of this work is to provide the necessary and sufficient conditions for oscillation. We address our problem mainly on the basis of oscillatory behavior. Moreover, the latest findings on the qualitative behavior of the biological mathematical model of discrete hematopoiesis are taken into account. More specifically, we explain the mathematical differential equation of discrete hematopoiesis. Moreover, certain significant, necessary and sufficient criteria for the solution of this discrete problem are found, which guarantee either the convergence of the non-oscillating solutions towards zero or the oscillation of all solutions of the discrete hematopoiesis model to the nonlinear lag difference with positive and negative coefficients. Some numerical examples are also given to illustrate the most important results.

Keywords: oscillation, delay differential equations, difference equations, delay differential equations, hematopoiesis model.

1. Introduction

The oscillatory behavior of difference equations' and dynamic equations' solutions has recently been the subject of a lot of research. Numerous recent works have been focused on oscillations of delay differential equation (DDE) solutions among these investigations [1-12]. This discovery has garnered a lot of interest since it has numerous practical applications in mathematical models of biology, ecology, and the transmission of various infectious diseases in people, and other areas. The reader can turn to [13-22] and the references therein for more details on this study. The behavior of the solutions for DDE has received a lot of attention in relation to the study of the oscillations of the analytical solutions. To the best of our knowledge, there have been very few studies that address the oscillations of nonlinear DDE solutions. In our work, we focus on this subject. An equation or a system of equations used to describe a natural occurrence is known as a mathematical model. Numerous scholars investigate how nonlinear delay mathematical models behave qualitatively in single species as well as in species that interact.



There has been a great deal of research done on the qualitative analysis of delay models with constant coefficients (autonomous models). We are aware that a variety of biological and ecological dynamical systems heavily depend on the environment. For instance, consider the physical environment's elements, like temperature and humidity, as well as the accessibility of resources like food, water, and other essentials, typically change with time on a seasonal or daily basis. Therefore, nonautonomous systems would have more accurate representations [2,20]. Studying the oscillation and non- oscillation of a certain kind of nonautonomous hematopoiesis delay model in biology is one of the goals of our work. Many authors looked for sufficient conditions to ensure oscillatory properties for different differential equations. Hematopoiesis refers to the process of producing blood cells. In 1978, Mackey and Glass proposed the first mathematical models of hematopoiesis dynamics [23]. In Saker, S. H. [24], consider the following equation of the hematopoiesis model with positive and negative coefficients:

$$\mathcal{H}'(t) = \frac{\beta(t)}{1 + \mathcal{H}^m(t - \tau)} - \delta(t)\mathcal{H}(t), \quad t \geq 0. \tag{1}$$

where $\beta(t), \delta(t) \in C([0, \infty), R^+), \tau \in [0, \infty), m \in N$. Equation (1) has a unique positive equilibrium point K , and satisfies the equation

$$\frac{\beta}{1 + K^m} = \delta K. \tag{2}$$

Since differential delay equations are challenging to control analytically, numerous studies have looked at the models as difference equations. So, there are a number of analytical results concerning the oscillation, global attractivity, and periodicity of Equation (1) [20,23]. The corresponding nonlinear first order delay difference equation with positive and negative coefficients of Equation (1) in the discrete hematopoiesis model is:

$$\Delta H_n + \delta_n H_n - \beta_n G(H_{n-l}) = f_n. \tag{3}$$

Where δ_n, β_n and f_n are infinite sequences of real numbers and Δ is the forward difference operator. And $G(H_n) = \frac{1}{1+H_n^m} \in (R, R)$ is a flux function that depends on the size of cells H_n and H_{n-l} at times n and $n - l$, respectively, and l is the time of maturation, such as that $H_n G(H_n) > 0$. There are some studies on the discrete hematopoiesis model, for instance. Wang et. al. (2013) [23]: With the assistance of two θ -methods, it was possible to discuss the conditions under which the numerical solutions fluctuate for the nonlinear delay differential equations in the hematopoiesis model. Additionally, it has been established that every non-oscillatory numerical solution tends to an equilibrium point of (3). [25]: established sufficient conditions for the existence of at least three positive T-periodic solutions for a discrete delay hematopoiesis model. Wei Li and Xianyi Li (2018) [15]: They derived a semi-discrete system for a nonlinear model of blood cell production. In [15], the authors discovered a few prerequisites for the oscillation of all $\Delta Y(n) + p(n)Y(\tau(n)) = 0$ solutions of the linear difference equation with varying delays. Every solution of first order linear difference equations with positive and negative coefficients of the form is given sufficient conditions to oscillate [26].

$$\Psi_{n+1} - \Psi_n + \mathcal{R}\Psi_{n-k} - Q\Psi_{n-l} = 0, \quad n \in N. \tag{4}$$

Every solution to Equation (4) oscillates if $Q(k - l) < 1$ and $\frac{(\mathcal{R} - Q)(k + 1)^{k+1}}{k^k} > 1$. The authors discovered sufficient conditions for the oscillation of each solution of first-order linear difference equations with multiple positive and negative coefficients in [27], extending the findings from [26].

$$\Psi_{n+1} - \Psi_n + \sum_{i=1}^m \mathcal{R}_i \Psi_{n-k_i} - Q_i \Psi_{n-l_i} = 0, n \in N_0. \tag{5}$$

It is proved that if $\sum_{i=0}^m Q_i(k_i - l_i) < 1$ and $\sum_{i=0}^m \frac{(\mathcal{R}_i - Q_i)(k_i + 1)^{k_i+1}}{k_i^{k_i}} > 1$, then every solution of Equation (5) oscillates. According to Mohamad (2015) [4], all of the solutions to the first-order neutral difference equation with positive and negative coefficients will oscillate if the necessary and sufficient requirements are satisfied. The authors of [28] provided sufficient conditions to ensure that all solutions to Equation (4) are oscillatory or tend to zero. The oscillations and global attractivity of Equation (3) with periodic time coefficients were investigated by Agarwal and Saker [24]. A mathematical model of hematopoietic stem cell dynamics is also proposed and investigated in [29], which considers the dynamics of two cell populations: an immature population and a mature population.

Our study includes recent findings on the qualitative behavior of a biological mathematical model of discrete hematopoiesis. Let's introduce an invariant oscillation transformation based on the analogous procedure in [20].

$$H_n = U_n - K, \tag{6}$$

where K is the unique positive equilibrium point of Equation (1). Then Equation (3) can be reduced to

$$\Delta U_n + \delta_n U_n - \beta_n V(U_{n-l}) = \xi_n, \tag{7}$$

Where $V(U_n) = \frac{1}{1+(U_n+K)^m}$ and $\xi_n = f_n - \delta_n K$. Then H_n oscillates about K if and only if U_n oscillates about zero. The following arguments are established in this article:

$$A_1: \sum_{n=0}^{\infty} \beta_n < \infty.$$

$$A_2: \frac{V(\zeta_n)}{\zeta_n} \leq \lambda_2.$$

$$A_3: \text{There exists a sequence } F_n \text{ such that } \Delta F_n = \xi_n \text{ and } \lim_{n \rightarrow \infty} F_n = 0.$$

$$A_4: \sum_{n=n_*}^{\infty} \delta_n < \infty, \quad n_* \geq n_0.$$

For the conditions produced A_1, A_2, A_3 is the assertion that there is no non-oscillating solution that achieves the equation of hematopoiesis or the resulting inequality from it. In return, the biological interpretation of these conditions is like the doses that are given to blood cells in order to control the number of cells produced. A sequence, U_n satisfying Equation (7) for $n > 0$ is referred to as a solution of Equation(7). If there is $n > n_j$ such that, $U_n \cdot U_{n+1} > 0$, then a nontrivial solution, U_n . is said to be oscillatory (oscillating about zero). Otherwise, it is argued that the solution is nonoscillatory [30]. In this work, several new necessary conditions are found to cause oscillations or convergence to equilibrium K in the solutions and bounded solutions of Equation (3). The theoretical results are supported by a few examples.

2. Background

Definition 1 [30] A point K in the domain of H_n is said to be an equilibrium point of (3) if it is a fixed point of H_n , that is, $H_n(K) = K$.

Definition 2 [20] If a solution to Equation (3), H_n oscillates around equilibrium K , then $H_n - k$ oscillate about zeros. If not, H_n is regarded as non-oscillatory. When $K = 0$, we say that H_n simply oscillates or oscillates about zero.

Based on Theorem 1 in [4], the result follows.

3. Results and Discussion

In this section, some sufficient conditions are established for the oscillation of all solutions to Equation (3). It is simple to demonstrate that H_n oscillates about K if and only if U_n . We just need to take into account the oscillations of Equation (3) in order to investigate the oscillations of Equation (7).

Let the sequence Z_n be defined as

$$Z_n = U_n + \sum_{i=n}^{n+l-1} \beta_i V(U_{i-l}) - F_n . \tag{8}$$

The following lemma helps to demonstrate the main findings.

Lemma 1. suppose, $\delta_n - \beta_{n+l}\lambda_2 \geq 0$ and assume that $(A_1) - (A_3)$ hold. Let H_n be a nonoscillatory solution to K of Equation (3). Then, $Z_n \geq 0$ and a nonincreasing sequence.

Proof. Let H_n be a nonoscillatory solution to K of Equation (3), that is $H_n > K, n \geq n_0$, (the proof of the case $0 < H_n < K$ is similar and will be omitted), hence $U_n > 0$ eventually. From Equation (8), we obtain

$$\Delta Z_n = -\delta_n U_n + \beta_{n+l} V(U_n) \leq -(\delta_n - \beta_{n+l}\lambda_2) U_n \leq 0 . \tag{9}$$

Hence, Z_n is a nonincreasing sequence, and $\lim_{n \rightarrow \infty} Z_n = L$, where $-\infty \leq L < \infty$. We claim that $L \geq 0$. Otherwise $L < 0$, so there exists $n_1 \geq n_0$ and $\alpha < 0$, such that $Z_n \leq \alpha < 0$ for $n \geq n_1$. From Equation (8), we get

$$\begin{aligned} U_n &= Z_n - \sum_{i=n}^{n+l-1} \beta_i V(U_{i-l}) + F_n , \\ U_n &\leq \alpha - \sum_{i=n}^{n+l-1} \beta_i V(U_{i-l}) + F_n , \\ U_n &\leq \alpha + F_n < \alpha + \varepsilon, \quad \varepsilon > 0, \quad n \geq n_2 \geq n_1. \end{aligned} \tag{10}$$

Since ε is arbitrary, then Equation (10) leads to $U_n \leq \alpha$ which is a contradiction since U_n is positive. So, since our claim has been proven, $L \geq 0$, or $Z_n \geq 0$, follows.

Theorem 1. Assume $\delta_n - \beta_{n+l}\lambda_2 \geq 0$ and let $(A_1) - (A_3)$ hold, and

$$\limsup_{n \rightarrow \infty} \sum_{i=n_*}^{n-1} \delta_i = \infty, \quad n_* \geq n_0 . \tag{11}$$

Then every solution of Equation (3) either oscillates about a unique equilibrium K or nonoscillatory tends to K as $t \rightarrow \infty$.

Proof. Assume that Equation (3) posse nonoscillatory solution H_n about K , Let $H_n > K, n \geq n_0$, hence $U_n > 0$ eventually. Then by Lemma 1:

$Z_n \geq 0$ and $\Delta Z_n \leq 0$, hence $\lim_{n \rightarrow \infty} Z_n = L$, where $-\infty \leq L < \infty$. We look at two situations:

Case 1. If U_n is unbounded. So there exists a subsequence n_j of n such that

$\lim_{j \rightarrow \infty} n_j = \infty, \lim_{j \rightarrow \infty} U_{n_j} = \infty$ and $U_{n_j} = \max \{U_s: n_0 < s < n_j\}$. By using (A_4) , we obtain from Equation (8);

$$Z_{n_j} = U_{n_j} + \sum_{i=n_j}^{n_j+l-1} \beta_i V(U_{i-l}) - F_{n_j} .$$

$$\geq U_{n_j} - F_{n_j}$$

Hence $\lim_{j \rightarrow \infty} Z_{n_j} = \infty$ leads to a contradiction.

Case 2. If U_n is bounded. From Equation (9) and condition (A_2) , we have $\Delta Z_n \leq -(\delta_n - \beta_{n+l}\lambda_2)U_n$.

Let $\liminf_{n \rightarrow \infty} U_n = l \geq 0$. By taking summation to both sides of the above inequality, it yields:

$$\sum_{i=n_0}^{n-1} \Delta Z_i \leq -\sum_{i=n_0}^{n-1} (\delta_i - \beta_{i+l}\lambda_2)U_i .$$

Then

$$Z_n - Z_{n_0} \leq -\sum_{i=n_0}^{n-1} (\delta_i - \beta_{i+l}\lambda_2)U_i . \tag{12}$$

We claim that $l = 0$, otherwise if $l > 0$, then there exists $n_1 \geq n_0$ large enough such that $U_n \geq l, n \geq n_1$.

From Equation (12), we have

$$Z_n - Z_{n_0} \leq -l \sum_{i=n_1}^{n-1} (\delta_i - \beta_{i+l}\lambda_2).$$

Let $n \rightarrow \infty$, in virtue of Equation (11) and A_1 , the last inequality leads to $\lim_{n \rightarrow \infty} Z_n = -\infty$ which is a contradiction. Hence, $\liminf_{n \rightarrow \infty} U_n = 0$, then there exists a subsequence n_j such that $\lim_{j \rightarrow \infty} U_{n_j} = 0$.

From equation (8), it can be easily got $Z_n \geq U_n, n \geq n_2 \geq n_0$. So from Equation (8), it follows

$$Z_n \leq U_n + \sum_{i=n}^{n+l-1} \beta_i \lambda_2 U_{i-l} - F_n ,$$

$$\leq U_n + \lambda_2 \sum_{i=n}^{n+l-1} \beta_i Z_{i-l} - F_n ,$$

Therefore

$$Z_{n_j} \leq U_{n_j} + \lambda_2 Z_{n-l} \sum_{i=n}^{n+l-1} \beta_i - F_{n_j} \leq U_{n_j} + \mu_2 \sum_{i=n}^{n+l-1} \beta_i - F_{n_j} .$$

Where $\lambda_2 Z_{n-l} \leq \mu_2$. Then by A_1 and A_3 , we obtain

$$\lim_{j \rightarrow \infty} Z_{n_j} \leq \lim_{j \rightarrow \infty} U_{n_j} = 0$$

Thus, $\lim_{n \rightarrow \infty} Z_n = 0$ implies that $\lim_{n \rightarrow \infty} U_n = 0$ that is $\lim_{n \rightarrow \infty} H_n = K$. The proof is finished.

In the next result, the sequence W_n will be used:

$$W_n = U_n + \sum_{i=n-l}^{n-1} \delta_i U_i - F_n . \tag{13}$$

Lemma 2: Assume, $\beta_n \lambda_2 - \delta_{n-l} \leq 0$ and suppose that $(A_1) - (A_3)$ hold. Let H_n be a nonoscillatory solution to K of Equation (3). Then, $W_n \geq 0$ and a nonincreasing sequence.

Proof. Let H_n be a nonoscillatory solution to K of Equation (3). Let $H_n > K, n \geq n_0$. From Equation (13) and Equation (3), we have

$$\Delta W_n = \beta_n V(U_{n-l}) - \delta_{n-l} U_{n-l} \leq (\beta_n \lambda_2 - \delta_{n-l}) U_{n-l} \leq 0 . \tag{14}$$

Hence, W_n is a nonincreasing sequence and $\lim_{n \rightarrow \infty} W_n = L$, where $-\infty \leq L < \infty$. We claim that

$L \geq 0$. Otherwise, $L < 0$, and then there exists $n_1 \geq n_0$ and $\alpha < 0$, such that $W_n \leq \alpha < 0$ for $n \geq n_1$. From Equation (13), we get

$$U_n = W_n - \sum_{i=n-l}^{n-1} \delta_i U_i + F_n \leq \alpha + F_n ,$$

$$U_n < \alpha + \varepsilon, n \geq n_2 \geq n_1, \varepsilon > 0.$$

Since ε is arbitrary, the last inequality leads to $U_n \leq \alpha$. This is a contradiction in terms of the fact

that U_n is positive. So, since our claim has been proven, $L \geq 0$ or $W_n \geq 0$.

Theorem 2 Assume $\beta_n \lambda_2 - \delta_{n-l} \leq \gamma < 0$ and let $(A_1) - (A_4)$ hold. Then, every solution of Equation (3) either oscillates about a positive equilibrium K or nonoscillatory tends to K as $t \rightarrow \infty$.

Proof. Let H_n be a nonoscillatory solution to K of Equation (3); assume $H_n > K$ eventually, hence $U_n > 0, n \geq n_0$. From Lemma 2, it yields $W_n \geq 0$ and decreasing sequence. This means W_n is a bounded sequence. Hence, from Equation (13), it follows that there exists $n_1 \geq n_0$ such that $W_n \geq U_n, n \geq n_1$. (15)

which means U_n is bounded. Let $\liminf_{n \rightarrow \infty} U_n = l \geq 0$. We claim that $l = 0$ otherwise $l > 0$. Then, there exists $n_1 \geq n_0$ large enough, such that $U_n \geq l, n \geq n_1$. Taking summation to both sides of Equation (14), we get

$$\sum_{i=n_0}^{n-1} \Delta W_n \leq \sum_{i=n_0}^{n-1} (\beta_i \lambda_2 - \delta_{i-l}) U_{i-l},$$

$$W_n - W_{n_0} \leq \sum_{i=n_0}^{n-1} (\beta_i \lambda_2 - \delta_{i-l}) U_{i-l}. \tag{16}$$

From Equation (16), we have

$$W_n - W_{n_0} \leq l \sum_{i=n_0}^{n-1} (\beta_i \lambda_2 - \delta_{i-l}) \leq l \gamma (n - 1).$$

As $n \rightarrow \infty$, the last inequality leads to $\lim_{n \rightarrow \infty} W_n = -\infty$ which is a contradiction. Hence, $\liminf_{n \rightarrow \infty} U_n = 0$. Therefore, there exists a subsequence n_j such that $\lim_{j \rightarrow \infty} U_{n_j} = 0$. Let $\lim_{n \rightarrow \infty} W_n = L$.

From Equation (13), it follows

$$U_n = W_n - \sum_{i=n-l}^{n-1} \delta_i U_i + F_n,$$

$$\geq W_n - \sum_{i=n-l}^{n-1} \delta_i W_i - F_n,$$

$$U_{n_j} \geq W_{n_j} - W_{n_j-l} \sum_{i=n_j-l}^{n_j-1} \delta_i - F_{n_j},$$

$$\lim_{j \rightarrow \infty} W_{n_j} \leq \lim_{j \rightarrow \infty} U_{n_j} = 0.$$

Thus, $\lim_{n \rightarrow \infty} W_n = 0$ implies that $\lim_{n \rightarrow \infty} U_n = 0$, that is $\lim_{n \rightarrow \infty} H_n = K$ and the proof is finished.

We provide examples to discuss and illustrate the previous results. In the following, we discuss the accuracy of the numerical solution and the oscillatory behavior of Equation (17) and (18). Therefore, in comparison to the exponential θ -method in [25], our results have higher accuracy.

Example 1 Consider the nonlinear first-order difference equation

$$\Delta U_n + \frac{n}{64} U_n - 6 \left(\frac{1}{e}\right)^{n+4} \frac{1}{1 + U_{n-2}} = 2(-1)^n 3^{n-2} e^{-2n}, n \geq 1. \tag{17}$$

Where

$$l = 2, \delta_n = \frac{n}{64}, \beta_n = 6 \left(\frac{1}{e}\right)^{n+4}, V(U_n) = \frac{1}{1+U_n}, \lambda_2 = 2, f_n = 2(-1)^n 3^{n-2} e^{-2n}.$$

To show that all conditions of theorem 1 are satisfying:

$$(\delta_n - \beta_{n+l} \lambda_2) = \frac{n}{64} - 12 \left(\frac{1}{e}\right)^{n+6} > 0, n \geq 1.$$

$$\limsup_{n \rightarrow \infty} \sum_{i=n_0}^{n-1} \delta_i = \lim_{n \rightarrow \infty} \sum_{i=n_0}^{n-1} \frac{i}{64} = \infty.$$

That is, the analytic solutions of Equation (17) are **oscillatory** about 0 as $t \rightarrow \infty$ which is illustrated in **Figure 1** since all conditions of theorem 1 holds. So, all the solutions of the corresponding hematopoiesis model of equation (17) are oscillatory around equilibrium K as $t \rightarrow \infty$. The MATLAB solver ode23 that allows to numerically solve delay differential Equation (17) is used to perform the numerical result.

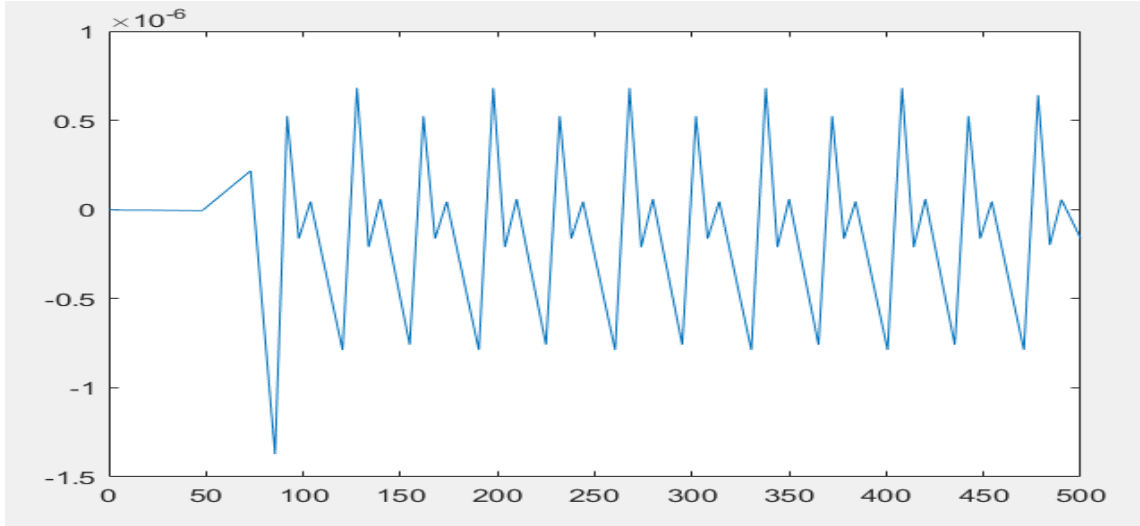


Figure 1. The solution of Equation (17) is oscillatory about 0 as $t \rightarrow \infty$.

Example 2 Consider the nonlinear Hematopoiesis difference equation

$$\Delta H_n + 3 \left(\frac{1}{e}\right)^{n+4} H_n - n(1 + 3e + e^3) \frac{1}{1 + H_{n-2}} = \frac{2}{9} \left(\frac{1}{2}\right)^n \cdot \left(\frac{-3}{2}\right)^n . \tag{18}$$

Where

$$L=2, \lambda_2 = 1, \delta_n = 3 \left(\frac{1}{e}\right)^{n+4}, \beta_n = n(1 + 3e + e^3), f_n = -e \left(\frac{1}{e}\right)^n \cdot \left(\frac{-1}{e}\right)^n, G(H_n) = \frac{1}{1+H_{n-2}}.$$

It's easy to show that all condition of theorem 2 are satisfies:

$$(\beta_n \lambda_2 - \delta_{n-l}) = 3 \left(\frac{1}{e}\right)^{n+2} - n(1 + 3e + e^3) < 0.$$

$$\limsup_{n \rightarrow \infty} (\beta_n) = \limsup_{n \rightarrow \infty} (n(1 + 3e + e^3)) = \infty.$$

Since all conditions of theorem 2 hold, the solution is non-oscillatory and tends to equilibrium $K = 10$, as $t \rightarrow \infty$, as illustrated in **Figure 2**. The MATLAB solver ode23 that allows to numerically solve delay differential Equation (18) is used to perform the numerical result.

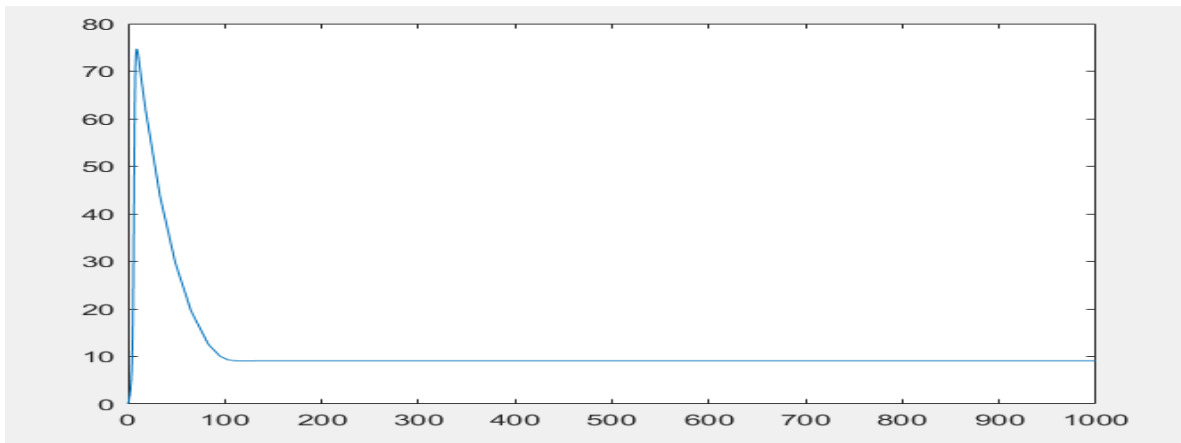


Figure 2. Non-oscillatory solution for example2 of (18) tends to equilibrium $K=10$ as $t \rightarrow \infty$.

The Matlab program is used to illustrate the numerical oscillation solutions of Equations (17) and (18).

5. Conclusions

Homeostasis is a reasonably stable internal state of physical and chemical conditions that is regulated by living systems through a self-regulating mechanism, despite the changes necessary for existence. The blood maintains homeostasis. Part of this process that allows us to adapt to change and maintain life are negative feedback loops. Mathematically, homeostasis is the stability of a state of equilibrium or oscillation. The discrete hematopoiesis model (1), which has positive and negative coefficients oscillating around the equilibrium K , has the primary purpose of identifying appropriate conditions for this oscillation. The hematopoiesis model is therefore analyzed as a difference equation (3). Its oscillation is guaranteed by sufficient conditions, which is a new discovery for the oscillatory behavior of the presented model. It is also necessary to find suitable conditions to guarantee the convergence of non-oscillating solutions to the equilibrium K . We also show that non-oscillatory numerical solutions, as shown in Example 2, can retain the associated properties of the analytical solutions. It is clear that the technique used here can be applied to models that are periodic or nearly periodic as long as a positive nearly periodic solution exists.

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Conflict of Interest

“Conflict of Interest: The authors declare that they have no conflicts of interest.”

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