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Mathematical Model of Leukocyte Formation with Delays

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Abstract. Leukopoiesis is the process of forming and developing different types of leukocyte in the bone marrow of adults and hematopoietic organs of the fetus. The process of leukopoiesis starts from inactivated stem cells originating from hematopoietic. When the process of differentiation of blood cells occurs, the sub-process of leukocyte production becomes slow-down. This can lead to serious illnesses such as cyclic neutropenia. For this purpose, the mathematical model for leukocyte formation with two consecutive delays proposed using more general continuous function as feedback control functions. The apoptosis rate of the neutrophil precursor also being replaced by a non-constant reduction function. The asymptotic stability of the equilibrium point is proved. The numerical simulation showed the illustration of solution behavior over time. We can conclude that the population of HSC daughter cells in the proliferation process tends to diverge in some critical cases.

Keywords: leukopoiesis, leukocyte, delay differential equation

INTRODUCTION

Hematopoiesis is the process that describes the synthesis of various kinds of blood cells from Hematopoietic Stem Cells (HSC). Various complicated subprocess takes place in the hematopoietic superprocess that controls the balance of each other. Almost all of the subprocesses involved in the hematopoiesis poses the feedback-control-based regulations. Proper understanding of these regulations controls plays an important role in medicine and technological-based therapy for blood disease. Various mathematical models of hematopoiesis had been extensively studied for that purpose (see [3] and [4]). However, the study of the leukocyte synthesis process which is called leukopoiesis was difficult to understand. Hence, the mathematical model of leukopoiesis required more effort to accomplish.

Leukopoiesis process had been observed through a blood disease called Cyclical Neutropenia (CN). CN provides a tractable pattern so that the control of regulation processes can be understood. Cyclical Neutropenia is a consequence of slowing down in the leukocyte production subprocess which is usually identified as a serious illness. The cyclical neutropenia characterized by the periodic pattern in the count of neutrophils. Many researchers have put various assumptions to analyze the cause of this pathological process. The latest mathematical model in [1] assumed a destabilization of the HSC proliferation process as the main cause of CN. The destabilization of HSC proliferation could be identified when the apoptosis rate of the HSC immature daughter cells during the proliferation process increased.

Many mathematical models have been constructed to describe the regulation of the HSC proliferation process under the assumption of the linear apoptosis rate of the HSC daughter cells. The model constructed by [5] has become a good foothold in the construction of several good models (see [1, 6-9]). Furthermore, the model constructed by [1] which involves two nonlinear differential equations with two consecutive delays had been discussed widely among researchers. Particularly, Adimy, et al. [2] provided a strong analytical resolution of the

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equilibrium points stability without significant simplification in the control terms, improving Bernard [1] that used a nonrealistic linear simplification of the control terms. Both [2] and [1] assumed constant apoptosis rate, hence providing a good simplification of the model. Yet, this assumption vanish some information related to the behavior of the population of proliferative HSC. In this study, the model in [2] was reconstructed by replacing the feedback control functions with a general continuous function. Further, the rate of apoptosis was generalized to be continuously decreasing reduction functions which also depended on the dependent variables.

Non-constant assumption of the apoptosis rate in the desired model was made to fit the principal assumption that the rate of apoptosis has to follow the logistic-type pattern since it must decrease when the crisis of neutrophil occurs, and elevate to a negligible level when the HSC level exceeds optimal level. The analytical discussion in this study is adopting the approach in [2] with the delays being maintained. Using this approach, the characteristics of bifurcations that occur under certain control functions and apoptosis function will be recovered. Also, we will use a similar method as [8] to guarantee the existence and uniqueness of the equilibrium point. Later, the theorems about some critical conditions that change the asymptotic stability will be proven. To deal with the possibility of bifurcations occurrence, a powerful theorem which later rules out this possibility will also be proven. In the final part, the numerical simulation has shown up to identify any bifurcation which possibly occurs.

THE MODEL AND EQUILIBRIUM POINTS

Hematopoietic Stem Cells (HSC) are separated into proliferative and non-proliferative cells. Proliferative cells prioritize the synthesis of DNA leading to cell division, while the non-proliferative cells are the cells produced by the division process. The compartment of the non-proliferative cells will be identified as a G_0 phase. The cells in the G_0 phase are free to live their whole lives if no differentiation needed. According to [2], this phase is the stationary phase in the cell cycle concerning growth and maturation. The duration of the proliferation process is assumed to be uniformly distributed with average value τ_S.

On the other hand, the non-proliferative stem cells are partly programmed to do the differentiation process into the neutrophil compartment. This differentiation process is controlled by the apoptosis of neutrophil precursors following a certain control function. The differentiation process of HSC into the neutrophil compartment proceeds with average duration τ_N which includes the time consumed by the neutrophil precursor to doing the maturation process. The model in this article is described as the following.

The population of non-proliferative HSC, which is denoted by $S(t)$, is controlled via negative-feedback control function Λ by the population of proliferative HSC. The proliferation activity of the stem cells takes a period τ_S which turns out to be the delay in the resulting equation in the model. Along with the proliferative phase, the population of proliferative HSC is reduced by apoptosis, and the proportion of surviving cells is calculated via the HSC apoptotic function F which is assumed to be continuously-decreasing. On the other hand, a portion of non-proliferative HSC is programmed to differentiate into Neutrophil, which we denote by $N(t)$. The differentiation activity and maturation of the non-proliferative HSC into the neutrophils take a period τ_N, which is assumed to be constant for all cells, and it appears as the second delay in the resulting equation in the model. Along the process of neutrophil differentiation, the neutrophil precursors are reduced by apoptosis, and the proportion of surviving cells is calculated via neutrophil apoptotic function G. Function G is a continuously-decreasing function. At the edge of the regulation process, the mature neutrophils are reduced by natural death with the death rate γ. The process mentioned above is the Leukopoiesis process which is illustrated as a compartment diagram in Figure 1.

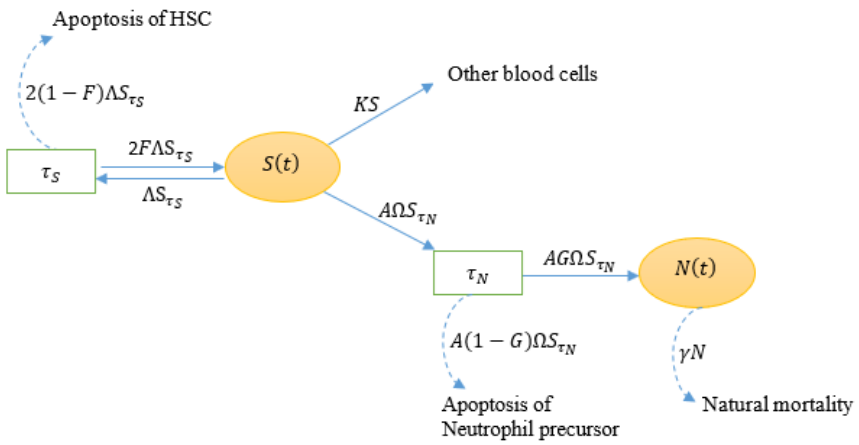


FIGURE 1. Compartment Diagram of Leukopoiesis

The apoptosis process appearing on the proliferative phase and the neutrophil-precursor regulation is represented by the function called reduction function, which is made to be precise in the following definition.

Definition 1. *A function* $F(x_1, \dots, x_n)$ *is called a reduction function if* $\max_{x_1,\dots,x_n} F = 1$, *and* $\min_{x_1,\dots,x_n} F = 0$.

Using the former compartment and above definition, the generalized version of the model constructed by [1] is written as the following

$$\begin{cases} \dfrac{dS}{dt} = -\left[K + \Omega\big(N(t)\big) + \Lambda\big(S(t)\big)\right]S(t) + 2F(S,N)\Lambda\left(S_{\tau_S}(t)\right)S_{\tau_S}(t) \\ \dfrac{dN}{dt} = -\gamma N(t) + AG(S,N)\Omega\left(N_{\tau_N}(t)\right)S_{\tau_N}(t) \end{cases} \tag{1}$$

where $S_{\tau_i}(t)$ represent the delay function $S(t-\tau_i)$, and $N_{\tau_i}(t)$ represent the delay function $N(t-\tau_i)$, where $\Lambda(S)$, $\Omega(N)$, is a continuous function, and $F(S,N)$, $G(S,N)$ are positive-continuous reduction functions. To get into the heuristics of the model, the reduction functions F, and G must represent the reduction effect of apoptosis which depends on the level of HSC and circulating neutrophil. This reduction effect must be amplified when the level of the population in the frame of reference exceeds the optimal level. Since the increase of population $S(t)$ stimulates the increase of population $N(t)$, the functions F and G are assumed to be a continuously-differentiable decreasing function of $S(t)$ and $N(t)$. These functions also assumed to be correspondingly-delay-dependent, that is, they depend on its corresponding delay. For the function F, this assumption is made following the fact that the process of apoptosis happens along with the proliferation phase with duration τ_S, hence decreasing the time interval τ_S is equivalent with decreasing the apoptosis process duration, which turns out to decrease the apoptosis rate F at a certain fixed time interval. The reason for the function G is similar.

Level of $\Omega(N)$ and the level of recognition $\Lambda(S)$ describe negative feedback which depends on the level of HSC $S(t)$ and the population of white blood cells in the circulation $N(t)$, respectively. Therefore, we assume that Λ and Ω are positive monotonous decrease functions, which tends to zero as the population of S and N cells tends to be infinite.

The equilibrium point of system (1) is (S^*, N^*) satisfying

$$\left.\frac{dS}{dt}\right|_{(S=S^*,N=N^*)} = 0 \quad \text{and} \quad \left.\frac{dN}{dt}\right|_{(S=S^*,N=N^*)} = 0 \tag{2}$$

The presence of the nonlinear term $F(S,N,t)\Lambda\left(S_{\tau_S}(t)\right)$ prevents us to obtain the simple analytical expression of equilibrium points. Regardless, we have that the fixed point (S^*,N^*) is the solution of nonlinear equation

$$\begin{cases} K+\Omega(N^*) = (2F(S^*,N^*)-1)\Lambda(S^*) \\ \gamma N^* = AG(S^*,N^*)\Omega(N^*)S^* \end{cases} \tag{3}$$

In any case, we are just interested to find out the analytical properties of equilibrium points. The following theorem states the existence and uniqueness of equilibrium points of system (1).

Theorem 2. *Let τ_S and τ_N are fixed. If the following conditions hold*

i. $0 < K+\Omega(0) < \Lambda(0)(2F(0,0)-1)$

ii. $\Omega'(N)(F(S,N)-1) > \left(K+\Omega(N)\right)\frac{\partial}{\partial N}F(S,N)$

for all $t \in [0,T]$ then there exists a unique equilibrium point of system (1) for all $t \in [0,T]$.

Proof. Let $S = S^*$ (to be found later). Define $f_{S^*}: [0,\infty) \to [0,\infty)$, by

$$f_S(N) = \frac{A}{\gamma}G(S,N)\Omega(N)\Lambda^{-1}\left(\frac{K+\Omega(N)}{2F(S,N)-1}\right)$$

By use condition (i), we get

$$f_{S^*}(N) - 0 > 0$$

Since

$$\Omega'(N)(F(S,N)-1) > \left(K+\Omega(N)\right)\frac{\partial}{\partial N}F(S,N)$$

the function f_{S^*} is strictly decreasing. Hence $f_{S^*}(0)$ is the maximum value of f on $(0,\Lambda(0)]$. By choosing

$$N = f_{S^*}(0) + 1$$

we have

$$f_{S^*}(N) - N < 0$$

Since F, G, Λ are continuous, $g(N) = f_{S^*}(N) - S$ is a strictly-decreasing-continuous function. According to the mean value theorem, there is a unique N_0 such that $g(N_0) = 0$. But this is equivalent to

$$N^* = \frac{A}{\gamma}G(S^*,N^*)\Omega(N^*)\Lambda^{-1}\left(\frac{K+\Omega(N^*)}{2F(S^*,N^*)-1}\right)$$

which satisfied the system (2). Later, S^* is calculated in terms of N^*.

■

Remark 3. As the explanation to the previous result and to make clear some notions, here are several remarks:

i. From Theorem 2, the decreasing behavior of function $f_S(N)$ guarantees the existence and uniqueness of the equilibrium point

ii. If function $f_S(N)$ non-increasing function, we get only the existing properties of the equilibrium point.

Based on Theorem 2, we can guarantee the existence of the equilibrium point if function $f_S(N)$ is continuously-non increasing function. Further, all the factors of $f_S(N)$, except Λ^{-1} function are a continuous-decreasing function. Condition (ii) in Theorem 2 guaranteed decreasing behavior of function Λ^{-1}.

THE STABILITY OF EQUILIBRIUM POINTS AND BIFURCATION OF THE MODEL

Since system (1) is nonlinear, the stability of the system is difficult to be considered purely-analytically. We use the linearization of the system (1) to recover the information about the behavior of the variable in the system around the equilibrium point. Let (S^*,N^*) be the equilibrium point of the system (2). According to Theorem 2, assuming

that the control functions and apoptosis-reduction functions in the system satisfy conditions (i) and (ii) in Theorem 2, this equilibrium point is unique. Define

$$\Gamma_1 = -[K + \Omega(N^*) + \Lambda(S^*)]$$
$$\Gamma_2 = 2\Lambda(S^*)S^* \left(\frac{\partial}{\partial S} F(S,N)\Big|_{(S^*,N^*,\cdot)} \right)$$
$$\Gamma_3 = 2\Lambda(S^*)S^* \left(\frac{\partial}{\partial N} F(S,N)\Big|_{(S^*,N^*,\cdot)} \right)$$
$$\Gamma_4 = A\Omega(N^*)S^* \left(\frac{\partial}{\partial S} G(S,N)\Big|_{(S^*,N^*,\cdot)} \right)$$
$$\Gamma_5 = A\Omega(N^*)S^* \left(\frac{\partial}{\partial N} G(S,N)\Big|_{(S^*,N^*,\cdot)} \right)$$
$$\Gamma_6 = \Lambda'(S^*)S^* + \Lambda(S^*)$$

Calculating the jacobians of the system (1) with respect to (S,N) at the point (S^*,N^*) give us $\boldsymbol{J}_1$ matrix as

$$\boldsymbol{J}_1 = \begin{bmatrix} \Gamma_1 - S^*\Lambda'(S^*) + \Gamma_2 & -\Omega'(N^*)S^* + \Gamma_3 \\ \Gamma_4 & -\gamma + \Gamma_5 \end{bmatrix}$$

Denoted $\boldsymbol{J}_2$ as jacobians of the system (1) with respect to $\left(S_{\tau_S}, N_{\tau_S}\right)$ evaluated at the point (S^*,N^*) as

$$\boldsymbol{J}_2 = \begin{bmatrix} 2F(S^*,N^*)\Gamma_6 & 0 \\ 0 & 0 \end{bmatrix}$$

Matrix Jacobi of the system (1) with respect to $\left(S_{\tau_N}, N_{\tau_N}\right)$ evaluated at the point (S^*,N^*) defined as

$$\boldsymbol{J}_3 = \begin{bmatrix} 0 & 0 \\ AG(S^*,N^*)\Omega(N^*) & AG(S^*,N^*)\Omega'(N^*)S^* \end{bmatrix}$$

The characteristic equation of the linearized system is

$$\det\left(\boldsymbol{I}\lambda - \boldsymbol{J}_1 - \boldsymbol{J}_2 e^{-\tau_S\lambda} - \boldsymbol{J}_3 e^{-\tau_N\lambda}\right) = 0$$

which can be written as the following characteristic equation

$$\begin{vmatrix} \lambda - (\Gamma_1 - S^*\Lambda'(S^*) + \Gamma_2) - 2F\Gamma_6 e^{-\tau_S\lambda} & \Omega'(N^*)S^* - \Gamma_3 \\ -\Gamma_4 - AG\Omega(N^*)e^{-\tau_N\lambda} & \lambda + \gamma - \Gamma_5 - AG\Omega'(N^*)S^* e^{-\tau_N\lambda} \end{vmatrix} = 0 \quad (4)$$

Information related to the asymptotic stability and bifurcation of the system around the equilibrium point obtained using the method of [2] with a slight modification.

Theorem 4. *Assume that all the hypotheses in Theorem 2 are satisfied, and (S^*,N^*) is the equilibrium point of system (1). Let F, G be a time-invariant-continuously-decreasing function, and let Λ, Ω, be a continuously-decreasing function such that, for $\tau_N = \tau_S = 0$, the following hold:*

i. $K + \left(1 - 2F(S^*,N^*)\right)\frac{d}{dS}(\Lambda(S)S)\Big|_{S=S^*} > \left|\frac{\Omega(N^*)S^*}{G(S^*,N^*)}\left(\frac{\partial G}{\partial S}\Big|_{(S^*,N^*)}\right)\right|$

ii. $\gamma - A\Omega(N^*)S^*\left(\frac{\partial}{\partial N}G(S,N)\Big|_{(S^*,N^*,\cdot)}\right) < -AG(S^*,N^*,)\Omega'(N^*)S^*$

Then, there is $\tau_N^* > 0$ such that (S^*,N^*) is asymptotically stable for $\tau_S = 0$ and $\tau_N \in [0,\tau_N^*)$, and stable for $\tau_S = 0$ and $\tau_N = \tau_N^*$ i.e. there is Hopf bifurcation at $\tau_N = \tau_N^*$.

Proof. Let (S^*, N^*) be the equilibrium point of system (1). According to Theorem 2, this equilibrium point is unique. Furthermore, since F, G are time-invariant, this equilibrium point does not change as time goes to infinity. Define

$$\begin{aligned}
\beta_1 &= S^*\Lambda'(S^*) - \Gamma_1 - \Gamma_2 - 2F\Gamma_6 + \gamma - \Gamma_5 \\
\beta_2 &= (\Omega'(N^*)S^* - \Gamma_3)\Gamma_4 + (S^*\Lambda'(S^*) - \Gamma_1 - \Gamma_2 - 2F\Gamma_6)(\gamma - \Gamma_5) \\
\beta_3 &= -AG\Omega'(N^*)S^* \\
\beta_4 &= (\Gamma_1 - S^*\Lambda'(S^*) + \Gamma_2 + 2F\Gamma_6)AG\Omega'(N^*)S^* + (\Omega'(N^*)S^* - \Gamma_3)AG\Omega(N^*)
\end{aligned}$$

Assuming $\tau_S = 0$, we have the following characteristic equation

$$\lambda^2 + \beta_1\lambda + \beta_2 + (\beta_3\lambda + \beta_4)e^{-\tau_N\lambda} = 0 \tag{5}$$

The fixed point (S^*, N^*) satisfies equation (3). Note that the function $F(S^*, N^*)$ is the reduction function for the apoptotic process working in the proliferative phase with work duration τ_S. Hence the admissible choice of function F must attain its maximum when the duration process of proliferative phase τ_S is made to be 0. That is

$$F(S^*, N^*)|_{\tau_S=0} = \max F(S^*, N^*) = 1$$

Hence we have

$$\begin{cases} K + \Omega(N^*) = \Lambda(S^*) \\ \gamma N^* = AG(S^*, N^*)\Omega(N^*)S^* \end{cases} \tag{6}$$

Furthermore, since $F(S^*, N^*)$ is maximum at $\tau_S = 0$ and cannot exceed 1 (see the definition of reduction function), $F(S^*, N^*)|_{\tau_S=0}$ is identically 1 for all (S^*, N^*). Since the derivative of a constant function is 0, we get $\Gamma_2 = \Gamma_3 = 0$. Exploiting this fact, we obtain

$$\begin{aligned}
\beta_1 &= S^*\Lambda'(S^*) - \Gamma_1 - 2F\Gamma_6 + \gamma - \Gamma_5 \\
\beta_2 &= \Omega'(N^*)S^*\Gamma_4 + (S^*\Lambda'(S^*) - \Gamma_1 - 2F\Gamma_6)(\gamma - \Gamma_5) \\
\beta_3 &= -AG\Omega'(N^*)S^* \\
\beta_4 &= \left(\Gamma_1 - S^*\Lambda'(S^*) + 2F\Gamma_6 + \Omega(N^*)\right)AG\Omega'(N^*)S^*
\end{aligned}$$

Based on the first inequality in the hypothesis of the theorem, we have $\beta_1 > 0$. Furthermore, we also have

$$\beta_2 > 0, \qquad \beta_3 > 0$$

Write the eigenvalues as a complex numbers $\lambda = \phi + i\theta$, we have the following real and imaginary part of the characteristic equation

$$\begin{cases} \phi^2 - \theta^2 + \beta_1\phi + \beta_2 + (\beta_3\phi\cos(\tau_N\theta) + \beta_3\theta\sin(\tau_N\theta) + \beta_4\cos(\tau_N\theta))e^{-\tau_N\phi} = 0 \\ 2\phi\theta + \beta_1\theta + (-\beta_3\phi\sin(\tau_N\theta) + \beta_3\theta\cos(\tau_N\theta) - \sin(\tau_N\theta))e^{-\tau_N\phi} = 0 \end{cases} \tag{7}$$

Assume that $\phi = 0$, then we have

$$\begin{cases} -\theta^2 + \beta_2 + \beta_3\theta\sin(\tau_N\theta) + \beta_4\cos(\tau_N\theta) = 0 \\ \beta_1\theta + \beta_3\theta\cos(\tau_N\theta) - \beta_4\sin(\tau_N\theta) = 0 \end{cases} \tag{8}$$

Solving the above system for $\cos(\tau_N\theta)$ and $\sin(\tau_N\theta)$, we obtain

$$\cos(\tau_N\theta) = \frac{(\beta_4 - \beta_1\beta_3)\theta^2 - \beta_2\beta_4}{\beta_3^2\theta^2 + \beta_4^2}, \qquad \sin(\tau_N\theta) = \frac{\beta_3\theta^3 + (\beta_1\beta_4 - \beta_2\beta_3)\theta}{\beta_3^2\theta^2 + \beta_4^2}$$

Adding the square of both equation and rearranging the terms in the resulting equation, we have

$$\frac{\theta^4 + (\beta_1^2 - 2\beta_2 - \beta_3^2)\theta^2 + \beta_2^2 - \beta_4^2}{\beta_3^2\theta^2 + \beta_4^2} = 0 \tag{9}$$

Denoting θ^2 by ω, the above equation is equivalent to

$$\omega^2 + (\beta_1^2 - 2\beta_2 - \beta_3^2)\omega + \beta_2^2 - \beta_4^2 = 0 \tag{10}$$

By the second inequality in the hypothesis of the theorem, we have $\beta_4^2 > \beta_2^2$. Hence equation (10) has at least one positive real solution, say ω^*. Hence there are two solutions of equation (9), say $\theta_1^* = \sqrt{\omega^*}$, and $\theta_2^* = -\sqrt{\omega^*}$. Since θ_1^*, θ_2^* are also the solution of system (8), so are $\theta_1^* + 2n\pi$, and $\theta_2^* + 2n\pi$ for every $n \in \mathbb{N}$. Without loss of generality, we proceed this case by making the following sequences of solution.

$$(\theta_1^{*n}) = (\theta_1^* + 2n\pi), \qquad (\theta_2^{*,n}) = (\theta_2^* + 2n\pi)$$

Define the set $\Theta = \{\theta : \theta \in (\theta_1^{*n})$ or $\theta \in (\theta_2^{*,n})\}$, and define

$$\tau_N^* = \min\{\tau > 0 : \ \beta_1\theta + \beta_3\theta\cos\tau\theta - \beta_4\sin\tau\theta = 0, \ \ \theta \in \Theta\}$$

Then $\tau_N = \tau_N^*$ is the minimum delay that guarantees the existence of solution θ of the system (8), hence is the minimum delay such that equilibrium point (S^*, N^*) is locally stable. It is easy to check that if we set $\tau_N = 0$, then the equilibrium point (S^*, N^*) is asymptotically stable. Using this fact, we conclude that equilibrium point (S^*, N^*) is asymptotically stable for $\tau_N \in [0, \tau_N^*)$.

■

The asymptotic stability of system (1) for $\tau_S = 0$ and $\tau_N > 0$ gives the insight about the stability of the system (1) with delay $\tau_S > 0$. The stability of system (1) for the case $\tau_S, \tau_N > 0$ is stated in the following theorem.

Theorem 5. *Assume that all the hypotheses in Theorem 2 and Theorem 4 are satisfied. Then, there is* $\tau_S^*, \tau_N^* > 0$ *such that* (S^*, N^*) *is asymptotically stable for* $\tau_S \in [0, \tau_S^*)$ *and* $\tau_N \in [0, \tau_N^*)$.

Proof. Using the same argument as in theorem 4, denoting

$$\begin{aligned}
\beta_1 &= S^*\Lambda'(S^*) - \Gamma_1 - \Gamma_2 + \gamma - \Gamma_5 \\
\beta_2 &= (\Omega'(N^*)S^* - \Gamma_3)\Gamma_4 + (S^*\Lambda'(S^*) - \Gamma_1 - \Gamma_2)(\gamma - \Gamma_5) \\
\beta_3 &= -AG\Omega'(N^*)S^* \\
\beta_4 &= (\Gamma_1 - S^*\Lambda'(S^*) + \Gamma_2 + 2F\Gamma_6)AG\Omega'(N^*)S^* + (\Omega'(N^*)S^* - \Gamma_3)AG\Omega(N^*) \\
\beta_5 &= -2F\Gamma_6(\gamma - \Gamma_5) \\
\beta_6 &= -2F\Gamma_6 e^{-\tau_S\lambda}
\end{aligned}$$

We can find a minimum value $\tau_S'(\tau_N)$ that guarantee the existence of a pure imaginary solution $\lambda = i\theta$ of the characteristic equation

$$\lambda^2 + \beta_1\lambda + \beta_2 + (\beta_3\lambda + \beta_4)e^{-\tau_N\lambda} + (\beta_4\lambda + \beta_5)e^{-\tau_S\lambda} = 0$$

By setting $\tau_S^* = \min_{\tau_N}\{\tau_S'(\tau_N)\}$, the proof is completed.

Remark 6. Note that the left-hand side of equation (8) is continuing to both τ_N and λ. Hence the solution λ of equation (8), if there is any, is a continuous complex-valued function of τ_N.

To deal with a more general case where the bifurcation may occur for the change of time, we assume that all the control functions are time-varying, that is, we deal with the following model

$$\begin{cases} \dfrac{dS}{dt} = -[K + \Omega(N(t), t) + \Lambda(S(t), t)]S(t) + 2F(S, N, t, \tau_S)\Lambda\big(S_{\tau_S}(t), t\big)S_{\tau_S}(t) \\ \dfrac{dN}{dt} = -\gamma N(t) + AG(S, N, t, \tau_N)\Omega\big(N_{\tau_N}(t), t\big)S_{\tau_N}(t) \end{cases} \tag{11}$$

Note that, when the equilibrium point of system (11) may change over time. This obstacle forces us to double-observing the bifurcation of the system as the delay change and, at the same time, the change of equilibrium point of system (11). The bifurcation analysis for the change of delay will be analyzed later in this chapter. Regardless, the following theorem states the existence and evolution of the equilibrium point of system (11).

Theorem 7. *Fix τ_S, τ_N, assume that, for all admissible value of S, N, for all $t \in [0, T]$, all of the following conditions hold:*

i. $0 < K + \Omega(0, t) < \Lambda(0)(2F(0,0, t, \tau_S) - 1)$

ii. $\Omega'(N, t)(F(S, N, t, \tau_S) - 1) > \big(K + \Omega(N, t)\big)\frac{\partial}{\partial N}F(S, N, t, \tau_S)$

Then, there exists a unique equilibrium point for the system (12) *for all* $t \in [0, T]$.

Proof. The proof is similar to that of Theorem 2.

Dynamical stability and bifurcation analysis of system (1) for τ_S and τ_N as being described by Theorem 4 and Theorem 5 is limited up to the interval $\tau_S \in [0, \tau_S^*(\tau_N)]$, $\tau_N \in [0, \tau_N^*]$. We can consider τ_S^*, and τ_N^* as the minimum critical delay in the sense that, we strict our consideration of stability up to the minimum value of τ_S, and τ_N at which the stability strictly changes to guarantee that there is no bifurcation along the interval $[0, \tau_S^*(\tau_N)]$ and $[0, \tau_N^*]$ which potentially disturb the stability of the system. To extend the observation beyond that critical value, on which any type of stability-disturbing bifurcation might occur, we have to use a more advanced concept of bifurcation. The following theorem describes the sufficient conditions which might rule out some types of bifurcations from the system (1).

Theorem 8. Assume that all the hypotheses in Theorem 2 and Theorem 4 are satisfied. If the following conditions hold:

i. $\left.\frac{\partial G}{\partial \tau_N}\right|_{\tau_N = \tau_N^*} = -G(S^*, N^*)$

ii. $\Lambda'(S^*)S^* > -\Lambda(S^*)$

iii. $\left.\frac{\partial^2 G}{\partial \tau_N \partial N}\right|_{(S^*, N^*, \tau_N = \tau_N^*)} > 0, \left.\frac{\partial^2 G}{\partial \tau_N \partial S}\right|_{(S^*, N^*, \tau_N = \tau_N^*)} > 0,$ *and* $\left.\frac{\partial F}{\partial \tau_N}\right|_{(S^*, N^*, \tau_N = \tau_N^*)} < 0$

for an appropriate choice of functions F and G, then the equilibrium point of system (1) *remains unique for $\tau_S = 0$ and $\tau_N > \tau_N^*$.*

Proof. Assume contrary that the equilibrium point is splitting up as the delay traces beyond τ_S^* and τ_N^*, then, there must be two different types of stability for each equilibrium point. One of the equilibrium points remains stable while the other one is not. Let consider the stable one, say (S^*, N^*), and without loss of generality consider the case for $\tau_S = 0$. Then, it indicates that the equilibrium point (S^*, N^*) is remaining asymptotically stable for τ_N beyond $[0, \tau_N^*]$. Hence, the real part of the solution λ of equation (7) is negative for $\tau_N > \tau_N^*$. We already know that the real part of the solution λ of equation (7) is negative for $\tau_N \in [0, \tau_N^*)$, and zero when $\tau_N = \tau_N^*$. Hence the real part of the solution λ of equation (7) attains its maximum at $\tau_N = \tau_N^*$. That is

$$\mathrm{Re}\left\{\left.\frac{d\lambda}{d\tau_N}\right|_{\tau_N = \tau_N^*}\right\} = \left.\frac{d}{d\tau_N}\mathrm{Re}\{\lambda\}\right|_{\tau_N = \tau_N^*} = 0 \tag{12}$$

Denote $\lambda'(\tau_N^*) = \left.\frac{d\lambda}{d\tau_N}\right|_{\tau_N=\tau_N^*}$, and $\beta_j'(\tau_N^*) = \left.\frac{d\beta_j}{d\tau_N}\right|_{\tau_N=\tau_N^*}$, $j \in \{1,2,3,4\}$. Differentiating the whole terms in (7) with respect to τ_N and evaluate at $\tau_N = \tau_N^*$ results the following

$$\begin{aligned} 2\lambda(\tau_N^*) + \beta_1\lambda'(\tau_N^*) + \beta_1'(\tau_N^*)\lambda(\tau_N^*) + \beta_2'(\tau_N^*) + \left(\beta_3\lambda'(\tau_N^*) + \beta_3'(\tau_N^*)\lambda(\tau_N^*) + \beta_4'(\tau_N^*)\right)e^{-\tau_N^*\lambda(\tau_N^*} \\ + (\beta_3\lambda(\tau_N^*) + \beta_4)e^{-\tau_N^*\lambda(\tau_N^*)}\left(\lambda(\tau_N^*) + \tau_N^*\lambda'(\tau_N^*)\right) = 0 \end{aligned} \tag{13}$$

Since the real part of the solution λ of the above equation is zero when $\tau_N = \tau_N^*$, we have

$$\mathrm{Re}\{\lambda(\tau_N^*)\} = 0 \tag{14}$$

Hence, the real part of equation (13) is

$$\begin{aligned} 2\mathrm{Re}\{\lambda(\tau_N^*)\} + \beta_1\mathrm{Re}\{\lambda'(\tau_N^*)\} + \beta_1'(\tau_N^*)\mathrm{Re}\{\lambda(\tau_N^*)\} + \beta_2'(\tau_N^*) \\ + \left(\beta_3\mathrm{Re}\{\lambda'(\tau_N^*)\} + \beta_3'(\tau_N^*)\mathrm{Re}\{\lambda'(\tau_N^*)\} + \beta_4'(\tau_N^*)\right)\cos(\tau_N^*\mathrm{Re}\{\lambda(\tau_N^*)\}) \\ - (\beta_3\mathrm{Im}\{\lambda'(\tau_N^*)\} + \beta_3'(\tau_N^*)\mathrm{Im}\{\lambda'(\tau_N^*)\})\sin(\tau_N^*\mathrm{Im}\{\lambda(\tau_N^*)\}) \\ + (\beta_3\mathrm{Re}\{\lambda(\tau_N^*)\} + \beta_4)(\mathrm{Re}\{\lambda(\tau_N^*)\} + \tau_N^*\mathrm{Re}\{\lambda'(\tau_N^*)\})\cos(\tau_N^*\mathrm{Re}\{\lambda(\tau_N^*)\}) \\ + (\beta_3\mathrm{Im}\{\lambda(\tau_N^*)\})(\mathrm{Im}\{\lambda(\tau_N^*)\} + \tau_N^*\mathrm{Im}\{\lambda'(\tau_N^*)\})\cos(\tau_N^*\mathrm{Re}\{\lambda(\tau_N^*)\}) \\ - (\beta_3\mathrm{Re}\{\lambda(\tau_N^*)\} + \beta_4)(\mathrm{Im}\{\lambda(\tau_N^*)\} + \tau_N^*\mathrm{Im}\{\lambda'(\tau_N^*)\})\sin(\tau_N^*\mathrm{Im}\{\lambda(\tau_N^*)\}) \\ - (\beta_3\mathrm{Im}\{\lambda(\tau_N^*)\})(\mathrm{Re}\{\lambda(\tau_N^*)\} + \tau_N^*\mathrm{Re}\{\lambda'(\tau_N^*)\})\sin(\tau_N^*\mathrm{Im}\{\lambda(\tau_N^*)\}) = 0 \end{aligned}$$

Simplifying the above equation using equation (12) and (14), we obtain

$$\begin{aligned} \beta_2'(\tau_N^*) + \beta_4'(\tau_N^*) - \left(\beta_3 + \beta_3'(\tau_N^*)\right)\mathrm{Im}\{\lambda'(\tau_N^*)\}\sin(\tau_N^*\mathrm{Im}\{\lambda(\tau_N^*)\}) \\ + (\beta_3\mathrm{Im}\{\lambda(\tau_N^*)\} - \beta_4\sin(\tau_N^*\mathrm{Im}\{\lambda(\tau_N^*)\}))(\mathrm{Im}\{\lambda(\tau_N^*)\} + \tau_N^*\mathrm{Im}\{\lambda'(\tau_N^*)\}) = 0 \end{aligned}$$

As explained in the previous theorem, $\Gamma_2 = \Gamma_3 \equiv 0$ for $\tau_S = 0$, and using the same method, it is easy to show that $\Gamma_4 = \Gamma_5 \equiv 0$ for $\tau_N = 0$. Since

$$\frac{d\Gamma_1}{d\tau_N} = \frac{d\Gamma_6}{d\tau_N} = \frac{d\Lambda}{d\tau_N} = \frac{d\Omega}{d\tau_N} \equiv 0$$

We have

$$\begin{aligned} \beta_2'(\tau_N^*) &= \Omega'(N^*)S^*A\Omega(N^*)S^*\left.\frac{\partial^2 G}{\partial\tau_N\partial S}\right|_{(S^*,N^*,\tau_N=\tau_N^*)} + 2\Gamma_6\left.\frac{\partial F}{\partial\tau_N}\right|_{(S^*,N^*,\tau_N=\tau_N^*)}(\gamma-\Gamma_5) \\ &\quad -(S^*\Lambda'(S^*) - \Gamma_1 - 2F\Gamma_6)A\Omega(N^*)S^*\left.\frac{\partial^2 G}{\partial\tau_N\partial N}\right|_{(S^*,N^*,\tau_N=\tau_N^*)} < 0 \\ \beta_4'(\tau_N^*) &= AG\Omega'(N^*)S^*2\Gamma_6\left.\frac{\partial F}{\partial\tau_N}\right|_{\tau_N=\tau_N^*} < 0 \end{aligned}$$

Also, from condition (1) in the hypothesis, we have

$$\beta_3 + \beta_3'(\tau_N^*) = 0$$

Based on the above results and the hypothesis of the theorem, the equation (7) has no solution λ. This result contradicts the initial assumption, hence the proof of the theorem is completed.

■

APPLICATIONS OF THE MAIN RESULTS AND NUMERICAL SIMULATIONS

To apply our results in the previous chapters, we take a sample model from the references to be tested using our theorem and make a direct conclusion based on the theorem. We use a model from [2], which can be written as the following

$$\begin{cases} \dfrac{dS}{dt} = -\left[K + \dfrac{\beta_0}{1+S^n} + \dfrac{k_0}{1+N^m}\right] S + 2e^{-\gamma_1 \tau_S} \dfrac{\beta_0 S_{\tau_S}}{1+S_{\tau_S}^n} \\ \dfrac{dN}{dt} = -\gamma N + A \dfrac{k_0 S_{\tau_N}}{1+N_{\tau_N}^m} \end{cases} \tag{15}$$

with parameters $\beta_0 = 1.77$ days^{-1}, $k_0 = 1.4$ days^{-1}, $n = 3$, $m = 2$, $\gamma_1 = 0.02$ days^{-1}, $\gamma = 0.4$ days^{-1}, $K = 0.02$ days^{-1}, and $A = 20$. In the seek of accomplishment of Theorem 2, the first attempt of this model is evaluated with delays $\tau_S = 1$, and $\tau_N = 2$ obtaining $\Omega(0) = 2.4$, $\Lambda(0) = 1.77$, $F(S,N,t) = e^{-\gamma_1 \tau_S} = e^{0.02(1)} \approx 0.98$, $G(S,N,t) = 1$ for all value of S, N, and

$$\Omega(N) = \frac{1.4}{1+N^2}, \qquad \Omega'(N) = -\frac{2.8N}{(1+N^2)^2}$$

Hence, we have

$$K + \Omega(0) = 1.42 < 1.77(1.96 - 1) = \Lambda(0)(2F(0,0,t) - 1)$$

Since $F(S,N,t)$ in this case, is constant with respect to N, we have $\frac{\partial}{\partial N} F(S,N,t) = 0$. It is then sufficient to check only that $\Omega'(N)(F(S,N,t) - 1) > 0$. Observe that

$$\Omega'(N)(F(S,N,t) - 1) = -\frac{2.8N}{(1+N^2)^2}(0.98 - 1) > 0$$

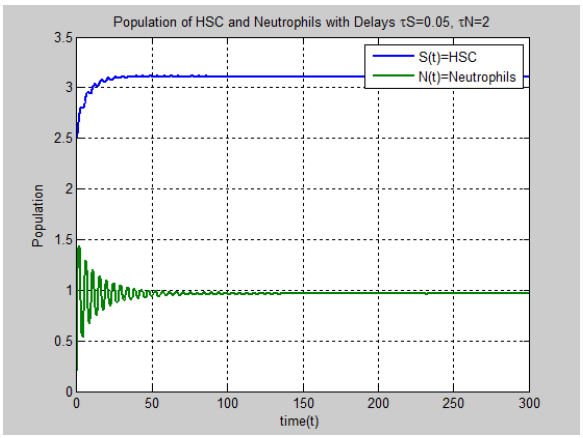
for all $N > 0$. Hence, using Theorem 2, there exists a unique equilibrium point of system (15) with parameters as mentioned above. Next, it has been shown that using a computer, we found the fixed point $S^* = 3$. In the seek of accomplishment of hypotheses in Theorem 4, since

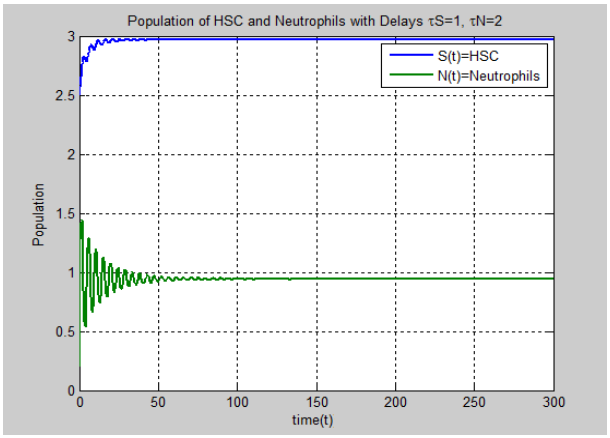
$$\left.\frac{\partial G}{\partial S}\right|_{(S^*,N^*)} = 0$$

it is sufficient to show that

$$\begin{aligned} K + \left(1 - 2F(S^*,N^*,t)\right)\frac{d}{dS}(\Lambda(S)S)\Big|_{S=S^*} &= 0.02 + (1 - 1.96)\frac{1.77(1+S^2-2S^2)}{(1+S^2)^2}\Big|_{S=S^*} \\ &= 0.02 + (-0.96)\frac{1.77(-8)}{100} \\ &\approx 0.155 \\ &> 0 \end{aligned}$$

It is easy to check that the second inequality in the hypotheses of Theorem 2 is also satisfied. Hence, the equilibrium point (S^*, N^*) for the system (15) is asymptotically stable. For this example, by observing the following numerical simulation, it is clear that the oscillation vanishes as time goes on, and the solution becomes a steady state. This behavior is caused by the low value of the delay (see Figure 2).

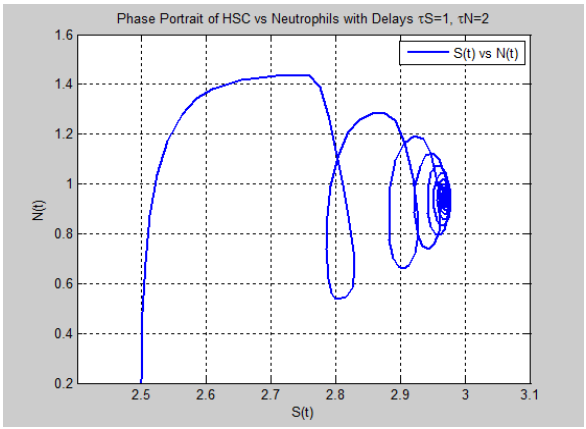


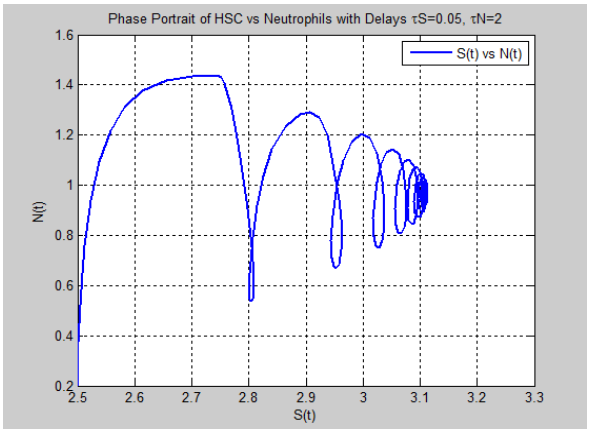


(a) $\tau_S = 0.02$ and $\tau_N = 2$ (b) $\tau_S = 1$ and $\tau_N = 2$

FIGURE 2. Solution of $S(t)$ and $N(t)$ with different delay value

The phase portrait corresponding to the equilibrium point (S^*, N^*) above is the following (see Figure 3). The equilibrium point for the system corresponding to the first delay is different from the one corresponding to the second delay. This fact indicates that the change in the value of the delay changes the equilibrium point. It can be observed that the curve is repeatedly intersecting itself. This phenomenon can only happen when the model in consideration has a higher dimension than 2. It is clear that the variables with the delay attach to it poses as the extra variables and generates an extra dimension for the equation. It is then strongly indicated that the equilibrium point change over τ_N and τ_S.





(a) $\tau_S = 0.02$ and $\tau_N = 2$ (b) $\tau_S = 1$ and $\tau_N = 2$

FIGURE 3. Phase Portrait of $S(t)$ and $N(t)$ using, $\gamma = 3$ and $K = 0.01$

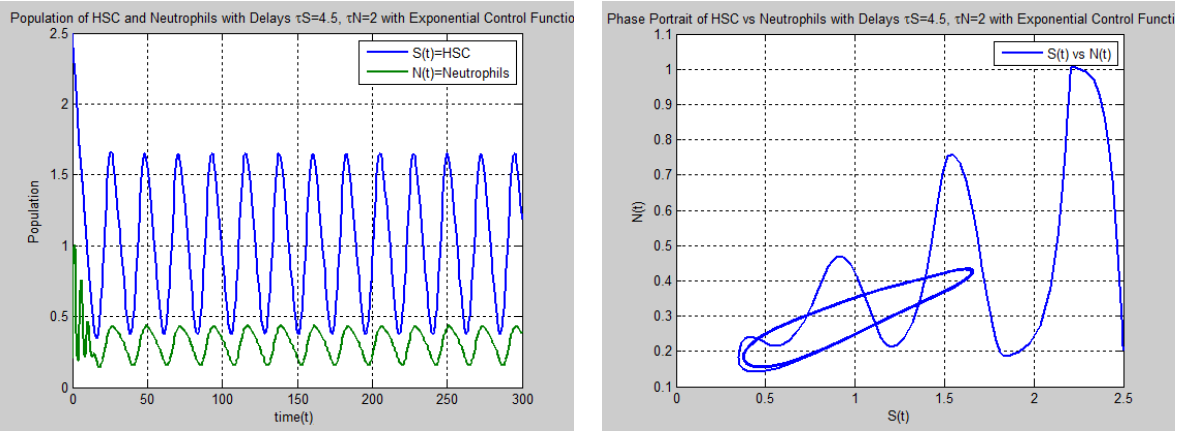
If we change one of the functions in the above example, say, we redefine the function Λ to be exponentially decaying function. For example, for the same parameters as before, we examine the following model.

$$\begin{cases} \dfrac{dS}{dt} = -[K + \beta_0 e^{-nS} + k_0 e^{-mN}]S + 2e^{-\gamma_1 \tau_S} \beta_0 e^{-nS_{\tau_N}} S_{\tau_S} \\ \dfrac{dN}{dt} = -\gamma N + A k_0 e^{-mN_{\tau_N}} S_{\tau_N} \end{cases}$$

It is easy to show that this model satisfies all of the hypothesis in Theorem 2, hence there is a unique equilibrium point, say (S^*, N^*). For the seek of accomplishment of the hypotheses in Theorem 4, we obtain

$$K + \left(1 - 2F(S^*, N^*, t)\right)\frac{d}{dS}(\Lambda(S)S)\Big|_{S=S^*} = 0.02 + (1 - 2e^{-\gamma_1 \tau_S})1.77e^{-3S}|_{S=S^*} > 0$$

It can be observed that this system requires higher τ_S for the same parameters to guarantee the asymptotic stability of its equilibrium point. In fact, for $\tau_S = 4.5$, this solution tends to a periodic solution (Figure 4).



(a) (b)

Figure 4. Time series plot and Phase Portrait of $S(t)$ and $N(t)$, stable center if delays $\tau_S = 4.5$, $\tau_N = 2$, with reduction functions $F = e^{-0.001}$, and $G = 1$, with control functions $\Lambda(x) = 1.77e^{-3x}$, $\Omega(x) = 0.09e^{-2x}$, with parameters $A = 20$, $\gamma = 3$, and $K = 0.01$

The current exponential function replacing the previous control function is more rapid in the decay. This implies that the proliferation process has a logistic-type property, that is, the proliferation process will be highly corrected as the population of S getting higher. This forces the process to behave like an oscillatory process until the minimum delay is reached to prevent the degradation process from the control function.

DISCUSSION

The analysis of the model in this article uses the approach made by [2] with some generalization. The model in this article generates a pure transcendental function equation which can only be overcome by several assumptions made in the theorem. Using the assumption in the stability theorem, we can make clear several notions about the existence of solution of the characteristic equation which in turn guarantees the pure-imaginary property of eigenvalue of the system in some critical delays. We use the continuity assumption of the functions to make clear that the real part of the eigenvalue will not arrive at some robustness which potentially makes a rapid change in the stability along with interval $[0, \tau_N^*]$. To deal with bifurcation beyond this interval, we are interested to seek for the contradictory conclusion for the trivial cases of splitting fixed points. It leads us to seek the conditions by which we can undoubtedly ensure that there is no possible way to arrive at these cases.

This research finds that the duration of differentiation activity and maturation of the non-proliferative HSC into the neutrophils τ_N and period for proliferation activity of the stem cells τ_S have a significant role in the dynamics of the population of non-proliferative HSC and Neutrophil. To get more applicable results, all of the parameters must be estimated using a real data experiment. We are inspired by the work from Colijn and Mackey (see [3], [4]) dealing with the whole system in which the Hematopoiesis take a role. To understand the more general model describing the population dynamics of the leukocyte, we have to use more advanced mathematical tools. This approach is made to prevent later difficulty if there is a new model with quite different control functions, or with extra factors. To make a clear resolution about bifurcation analysis of the system, it is important to know the crucial properties of the control functions, and any additional functions taking a role in the process.

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