

Periodical Bifurcation Analysis of a Type of Hematopoietic Stem Cell Model with Feedback Control

Suqi Ma

Department of Mathematics, China Agricultural University, Beijing, China

Email: caumasuqi@163.com

How to cite this paper: Ma, S.Q. (2023) Periodical Bifurcation Analysis of a Type of Hematopoietic Stem Cell Model with Feedback Control. *International Journal of Modern Nonlinear Theory and Application*, 12, 18-29.

<https://doi.org/10.4236/ijmnta.2023.121002>

Received: November 29, 2022

Accepted: March 20, 2023

Published: March 23, 2023

Copyright © 2023 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

The delay feedback control brings forth interesting periodical oscillation bifurcation phenomena which reflect in Mackey-Glass white blood cell model. Hopf bifurcation is analyzed and the transversal condition of Hopf bifurcation is given. Both the period-doubling bifurcation and saddle-node bifurcation of periodical solutions are computed since the observed floquet multiplier overpass the unit circle by DDE-Biftool software in Matlab. The continuation of saddle-node bifurcation line or period-doubling curve is carried out as varying free parameters and time delays. Two different transition modes of saddle-node bifurcation are discovered which is verified by numerical simulation work with aids of DDE-Biftool.

Keywords

Bifurcation, Saddle-Node Bifurcation, Period-Doubling Bifurcation, Hopf Bifurcation, Time Delay

1. Introduction

The complex dynamical phenomena arise since different dynamical transition mechanisms underlying delay feedback control become the focused topic in the scientific application field with highly nonlinear dynamics. The researchers try to introduce time delay with state feedback control to produce scenarios of bifurcation phenomena in delay differential systems. Our work is mainly dependent on the artificial technology work of DDE-Biftool [1] [2] [3], which overcomes the most difficult problems of stability analysis and Codimension 1 and Codimension 2 singularity work of equilibrium bifurcation and periodical solutions bifurcation. The aim of our work is the stability transition phenomena of

periodical solutions with DDE-Biftool software.

The observed dynamical phenomena of the Mackey-Glass equation which model the production of white blood cell have been focused on paper [4] [5] [6] [7]. The pioneer work has discussed chaos phenomena in the system and the scenarios of bifurcation phenomena of the periodical solution produced by delay windows. In their work, the period-doubling bifurcation of the periodical solution is produced due to the system's high nonlinearity and delay effects. If a new bifurcation mechanism underlying delay feedback control arises, like saddle-node bifurcation of limit cycles or new branch bifurcation of periodical solutions?

With delay feedback control, the governed delay differential equations of Mackey-Glass system in paper [7] [8] [9] are written as

$$\dot{Q} = \frac{aQ(t-\tau)}{1+Q(t-\tau)^c} - bQ + K(Q(t-\tau) - Q(t)) \quad (1)$$

herein, x denotes the concentration of white blood cells, a, c are hill coefficients, and b is the death rate. With given parameter values $a = 0.2, b = 0.1, c = 10$ and $\tau = 16.5$, the period-doubling bifurcation of periodical solution since Hopf bifurcation is computed by DDE-Biftool software, as shown in **Figure 1**. With varying free parameter b , the continuation of periodical solution from Hopf point is drawn in **Figure 1(a)**. The module of flouquet multiplier attains -1 on the threshold value of period-doubling bifurcation when it crosses the unit circle, hence, the stability property of the periodical solution is changed and the new bifurcating periodical solutions which prolong the period of unstable periodical solutions to be double times [2] [10]. This verifies that longer period of period solutions of hematological stem cells is observed as varying free parameters. The coexistence of periodical solutions after period-doubling bifurcation point is also simulated as shown in **Figure 1(b)**. In **Figure 1(a)**, the bifurcating period-doubling solutions occurs at $b = 0.1262$, then disappears at $b = 0.0862$. The maximal magnitude of periodical solutions versus varying free parameter b and the minimal magnitude of periodical solutions versus b is respectively drawn in **Figure 1(a)**, while the pink curve denotes the bifurcating period solutions from Hopf point and the blue curve denotes the bifurcating period-doubling periodical solutions occurs at period-doubling bifurcation point. As varying time delay τ , the continuation of bifurcating periodical solutions and period-2 solutions are drawn in **Figure 1(c)**. It can be seen, the magnitude of bifurcating period-2 solution becomes bigger as varying time delays. The coexistence of time series solution at $\tau = 18.02$ is drawn in **Figure 1(d)**.

In this paper, the simple version of Mackey-Glass equation with multiple delay feedback control is listed as

$$\begin{aligned} \dot{Q} = & \frac{aQ(t-\tau_1)}{1+Q(t-\tau_1)^c} - bQ + K_1(Q(t-\tau_1) - Q(t)) \\ & + K_2(Q(t-\tau_2) - Q(t-\tau_1)) + K_3(Q(t-\tau_3) - Q(t-\tau_2)) \end{aligned} \quad (2)$$

With $K_1 = -0.02, K_2 = -0.04, K_3 = -0.08, \tau_1 = 16.5, \tau_2 = 8, \tau_3 = 4$. As the view

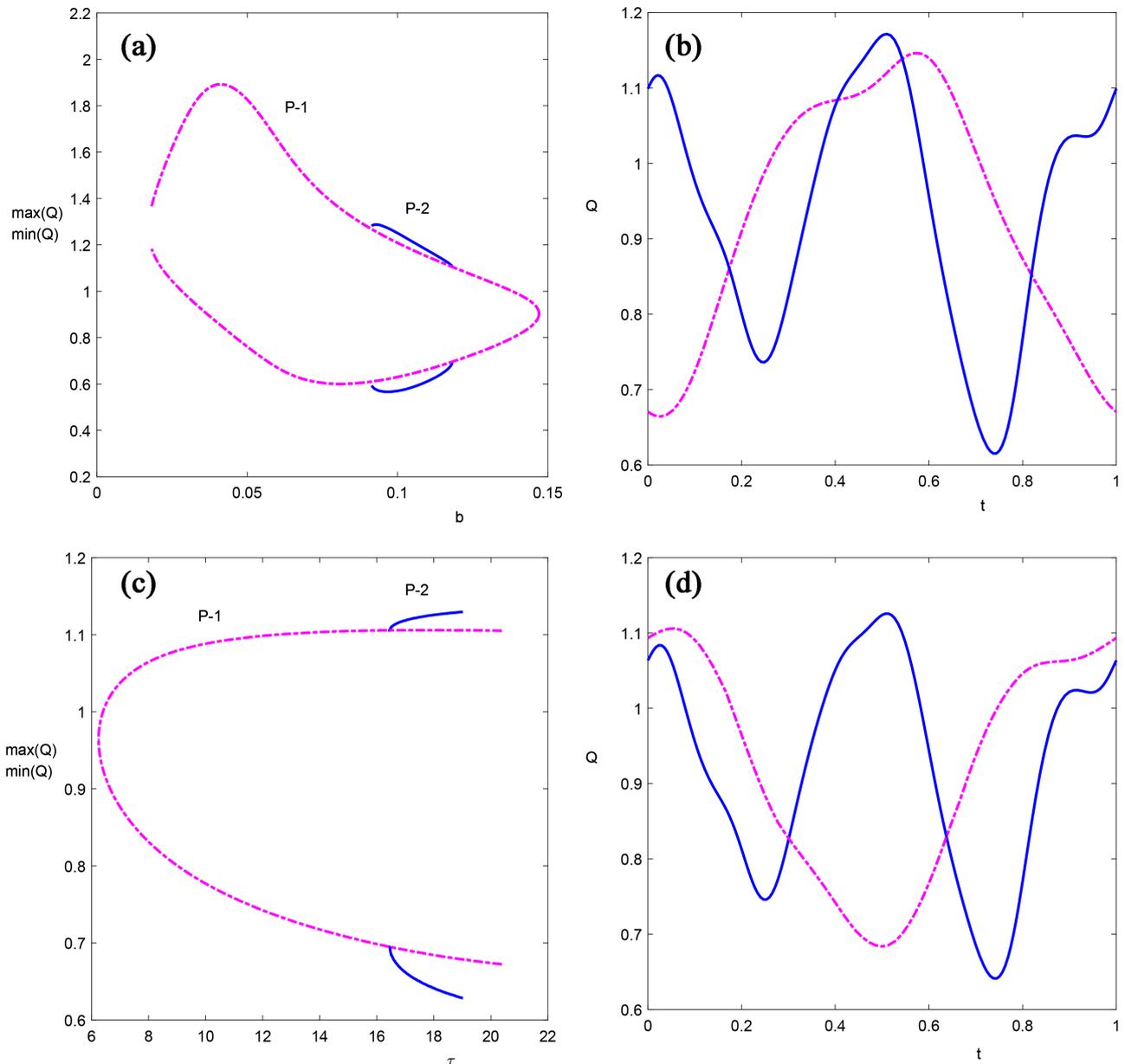


Figure 1. The dynamics of hematopoietic stem cell model (1) with $K = -0.2$. (a) The continuation of periodical solutions and period-2 solutions as varying free parameter b while choosing $\tau_1 = 16.5$; (b) The time evolution of the coexisted periodical solutions within one mesh at $b = 0.117, \tau_1 = 16.5$; (c) The continuation of periodical solutions and period-2 solutions as varying time delay τ_1 while choosing $b = 0.12$; (d) The coexistence of time series solutions with $b = 0.12, \tau_1 = 17.5$.

point in paper [7], delay feedback controls change the stability property of equilibrium solution to produce new bifurcation behavior, or produce new periodical oscillation behavior by Condimension 1 bifurcation of the limit cycles. On another respect, delay feedback control focuses on the discussion of mathematical perturbation by state difference which carries out to reflect the regulation function in system components throughout model analysis.

As the imaginary roots cross the imaginary axis from one-half plane to another to change the number of complex characteristic roots with positive real parts,

Hopf bifurcation occurs to produce new bifurcating periodical solutions. The stability analysis work and the track of imaginary roots always use algebra analysis technique, Sturm sequence analysis and geometrical scheme, the related work can see paper [11] [12] [13] [14] for reference. The fundamental theory can see [15] for reference. Herein we also use DDE-Biftool to analyze the stability property of the equilibrium solution and to track the imaginary curves by continuation of Hopf bifurcation points. In general, the stability regimes are partitioned from the unstable regimes via Hopf bifurcation curves, and the periodical solution arises on the margin of “stability to instability” regimes, and then diminished on the margin of “instability to stability” regimes, which is called the stability switching inducing periodical oscillation phenomena. The stability switching phenomena mainly depend on the transversal condition of Hopf bifurcation since the bifurcating direction of periodical solutions is determined to be “inward” or “outward” on the margins.

The stability property of periodical solutions is changed as the floquet multiplier crosses the unit circle. As is well known, the period of periodical oscillation solution of hematopoietic stem cells is varying from shortly few days to longer several months, and which is a typical phenomenon in human hematopoietic diseases. Therefore, the bifurcation of periodical solution becomes ubiquitous in dynamical analysis of periodical oscillation behavior of hematopoietic stem cell system. The authors in paper [10] have analyzed the bifurcation behavior of periodical solution in a simple version of scalar stem cells model, and both the saddle-node bifurcation and period-doubling bifurcation are discovered and the continuous work of bifurcation curve is carried out in parameter plane as varying free parameter and time delay. We aim to analyze the stability property of periodical solutions by computing the floquet multiplier with the application of DDE-Biftool software [1] [2]. Both the period-doubling bifurcation and saddle-node bifurcation is discovered underlying feedback control with multiple time delay. Besides, the two bifurcation modes of saddle-node bifurcation of periodical solutions are discovered in the continuation of periodical solutions, that is, the Codimension 1 saddle-node bifurcation and new branch bifurcation of limit cycle.

The whole paper is organized as follows, the imaginary roots curves and Hopf bifurcation are simulated by DDE-Biftool software and the transversal condition is assisted by geometrical scheme in Section 2. The continuation of periodical solutions underlying Hopf bifurcation is carried out by DDE-Biftool software in Section 3, the different modes of saddle-node bifurcation of periodical solution are detected relying on delay feedback control and high nonlinearity effects on coefficient c . In Section 4, the floquet multiplier is computed by DDE-Biftool and further work of continuation of Codimension 1 bifurcation of periodical solution is carried out by varying free parameter b and time delay τ_1 .

2. Hopf Bifurcation

DDE-Biftool can compute the rightmost characteristic roots with real parts ei-

ther positive or negative, and Hopf bifurcation occurs as a pair of imaginary roots cross over the imaginary axis from left half plane to right half plane. With Q^* being the positive equilibrium solution of system (2), doing the axis transformation $x = Q - Q^*$, one gets

$$\begin{aligned} \dot{x} = & -ax(t - \tau_1) \frac{-1 + Q^*(c-1)}{(1 + Q^*)^{1+c}} - bx + K_1(x(t - \tau_1) - x(t)) \\ & + K_2(x(t - \tau_2) - x(t - \tau_1)) + K_3(x(t - \tau_3) - x(t - \tau_2)) \end{aligned} \tag{3}$$

Hence, the corresponding characteristic equation is obtained as

$$\Delta(\lambda, b, \tau_1, \tau_2, \tau_3) = Ae^{-\lambda\tau_1} + B - \lambda + Ce^{-\lambda\tau_2} + De^{-\lambda\tau_3} \tag{4}$$

with

$$A = -a \frac{-1 + Q^*(c-1)}{(1 + Q^*)^{1+c}} + K_1, \quad B = -b - K_1, \quad C = K_2 - K_3, \quad D = K_3 \tag{5}$$

Using DDE-Biftool, the imaginary roots with $\tau_1 = 16.5, c = 10$ are listed. In the following, we introduce the lemma referred from paper [12]. Set $S = \omega\tau_1$ and $\lambda = i\omega$, then by Equation (4), one gets

$$\begin{aligned} \cos(S) = & -\frac{1}{A} \left(C \cos\left(S \frac{\tau_2}{\tau_1}\right) + D \cos\left(S \frac{\tau_3}{\tau_1}\right) + B \right), \\ \sin(S) = & -\frac{1}{A\tau_1} \left(C \sin\left(S \frac{\tau_2}{\tau_1}\right)\tau_1 + D \sin\left(S \frac{\tau_3}{\tau_1}\right)\tau_1 + S \right) \end{aligned} \tag{6}$$

Hence, we have

$$B = \frac{1}{\tau_1} \left(-C \cos\left(S \frac{\tau_2}{\tau_1}\right)\tau_1 - D \cos\left(S \frac{\tau_3}{\tau_1}\right)\tau_1 \pm \sqrt{HH} \right) \tag{7}$$

with

$$\begin{aligned} HH = & C^2 \cos^2\left(S \frac{\tau_2}{\tau_1}\right)\tau_1^2 - 2CD \sin\left(S \frac{\tau_2}{\tau_1}\right)\sin\left(S \frac{\tau_3}{\tau_1}\right)\tau_1^2 + D^2 \cos^2\left(S \frac{\tau_3}{\tau_1}\right)\tau_1^2 \\ & + A^2\tau_1^2 - C^2\tau_1^2 - 2C \sin\left(S \frac{\tau_2}{\tau_1}\right)S\tau_1 - D^2\tau_1^2 - 2D \sin\left(S \frac{\tau_3}{\tau_1}\right)S\tau_1 - S^2 \end{aligned} \tag{8}$$

Hopf bifurcation curve is plotted by Equation (6), with varying time delay τ_1 . However, we have to verify the corresponding transversal condition to be satisfied. Differentiate Equation (4) with respect to time delay τ_1 , one gets

$$Ae^{-\lambda\tau_1} \left(-\tau_1 \frac{d\lambda}{d\tau_1} - \lambda \right) - \frac{d\lambda}{d\tau_1} + Ce^{-\lambda\tau_2} \left(-\tau_2 \frac{d\lambda}{d\tau_1} \right) + De^{-\lambda\tau_3} \left(-\tau_3 \frac{d\lambda}{d\tau_1} \right) = 0 \tag{9}$$

Hence, we get

$$Re \frac{d\lambda}{d\tau_1} = Re \frac{1}{\frac{d\lambda}{d\tau_1}} = \frac{Ae^{-\lambda\tau_1}(-\tau_1) - 1 + Ce^{-\lambda\tau_2}(-\tau_2) + De^{-\lambda\tau_3}(-\tau_3)}{Ae^{-\lambda\tau_1}\lambda} \tag{10}$$

However, substitute $b = b(S), \tau_1 = \tau_1(S)$ into the characteristic Equation (4)

with the assumption $S = \omega\tau_1$, then differentiate Equation (4) with respect to S to get

$$\left(Ae^{-i\omega\tau_1}(-\tau_1) - 1 - \tau_2 Ce^{-i\omega\tau_2} - De^{-i\omega\tau_3} \tau_3 \right) (i\omega'(S)) = i\omega Ae^{-i\omega\tau_1} \tau_1'(S) + b'(S) \quad (11)$$

Substitute Equation (11) into Equation (10), then we have

$$Re \frac{d\lambda}{d\tau_1} = Re \left\{ \frac{-i\omega Ae^{-iS} \tau_1'(S) + b'(S)}{Ae^{-iS} (\omega\omega'(S))} \right\} = Re \frac{b'(S)}{Ae^{-iS} (\omega'(S))}$$

Lemma 1. Set $S = \omega\tau_1$, the transversal condition at Hopf point is listed as

$$\delta(D) = signRe \left\{ \left. \frac{d\lambda}{d\tau_1} \right|_{\lambda=i\omega} \right\} = signb'(S) sign\omega'(S) signRe \{ Ae^{iS} \} \quad (11)$$

If $\delta(S) < 0$, then a pair of imaginary roots cross imaginary axis from left half plane to right half plane as increasing time delay if $\delta(S) > 0$, either from right half plane to left half plane if $\delta(S) < 0$.

3. Continuation of Codimension 1 Bifurcation of Periodical Solutions

As shown in **Figure 1**, period-doubling bifurcation of periodical solution is explored as varying free parameter b . With feedback control of multiple time delay in system (2), the period-doubling bifurcation brings forth period-2 oscillation solutions lying inside $[0.115, 0.138]$ with $\tau_1 = 16.502$, as shown in **Figure 2(a)**. We also draw the time series solution of the coexistence periodic solution with about $b = 0.119$ in **Figure 2(b)**. However, the arising saddle-node bifurcation changes the stability property of periodical solutions which brings forth more complex dynamics. As shown in **Figure 2(c)**, by varying time delay τ_1 , the continuation of period solution and the bifurcating period-2 oscillation solutions are simulated. And the coexistence of two different period solutions is plotted with time evolution in one period with mesh $[0, t/T]$, as shown in **Figure 2(d)**.

As simulation work shown in **Figure 2(a)**, both the saddle-node bifurcation and the period-doubling bifurcation of Codimension 1 singularity of periodical solutions is observed. The work is mainly dependent on the computation of floquet multiplier following, as shown in **Figure 3**. It is observed, the floquet multiplier attains at 1 as crossing unit circle at saddle-node bifurcation point. The saddle-node bifurcation point is denoted by SN and four SN listed. We also find PD point which represents period-doubling bifurcation point whereas the observed floquet multiplier crossing unit circle in the direction marked by -1 .

Based on the above discussion of Codimension 1 bifurcation which is listed as SD or PD bifurcation, further we continue Codimension 1 bifurcation line as varying free parameter b and time delay τ_1 . As shown in **Figure 4(a)**, the period-doubling bifurcation curve which enclose the period-2 oscillation solution is simulated. The oscillation period of stable period solutions prolongs 2 times longer as crossing period-doubling bifurcation curve whereas Codimension 1 bifurcation

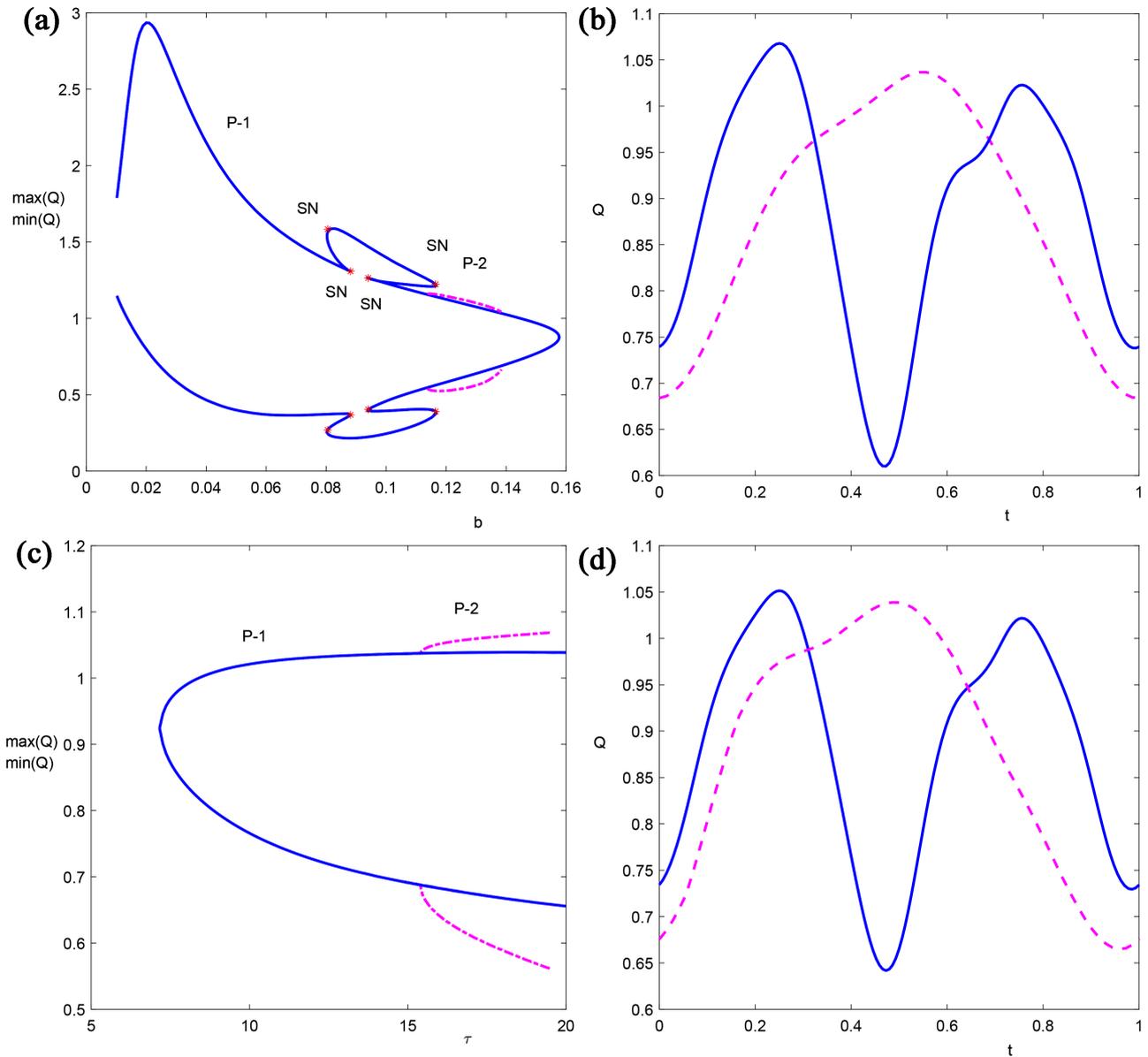


Figure 2. The periodical solutions of stem cell model (2). (a) The continuation of periodical solutions and period-2 solutions as varying free parameter b while choosing $\tau_1 = 16.5$; (b) The time evolution of the coexisted periodical solutions within one mesh at $b = 0.126, \tau_1 = 16.5$; (c) The continuation of periodical solutions and period-2 solutions as varying time delay τ_1 while choosing $b = 0.12$; (d) The coexistence of time series solutions with $b = 0.12, \tau_1 = 17.5$.

arise. The continuation of the saddle-node bifurcation curve is also simulated on (b, τ_1) parameter plane, as shown in **Figure 4(b)**. The dynamics manifests that two limit cycles collide on the saddle-node bifurcation curve then disappear, hence after, the hysteresis phenomena of limit cycle occurs underlying saddle-node bifurcation. The two different transition modes of period oscillation solutions are explored underlying saddle-node bifurcation, as shown in **Figure 4(b)**. One inner circle of saddle-node bifurcation curve is continued.

The discussion of saddle-node bifurcation of periodical solutions follows the simulation results shown in **Figure 4(b)**. The jump of stable periodical solutions

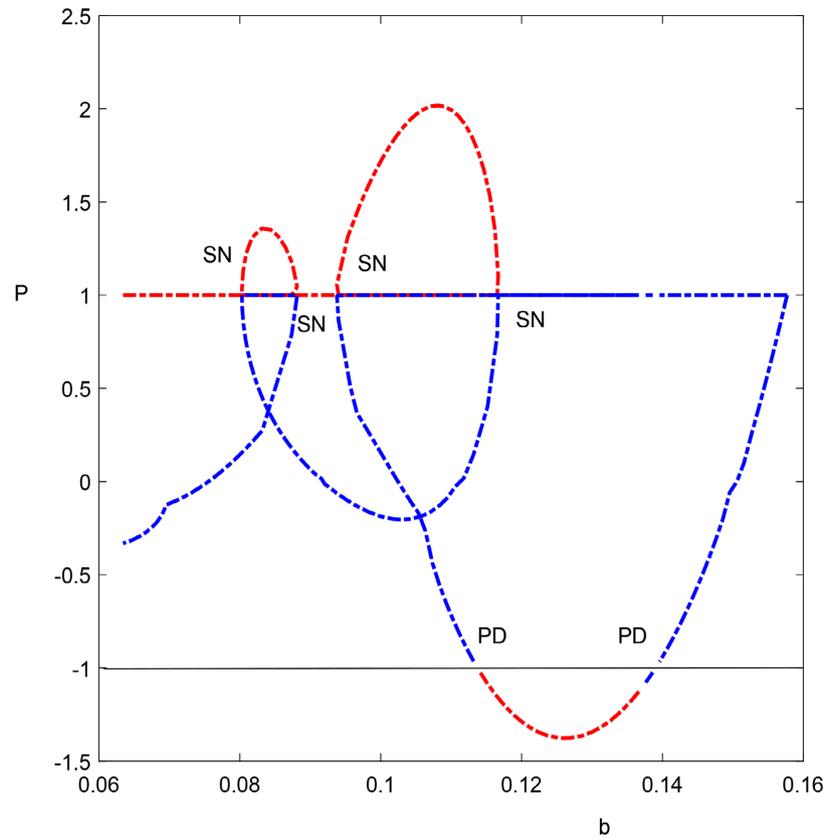


Figure 3. The floquet multiplier of system as varying free parameter b . SN denotes saddle-node bifurcation and PD represents period-doubling bifurcation of periodical solutions respectively.

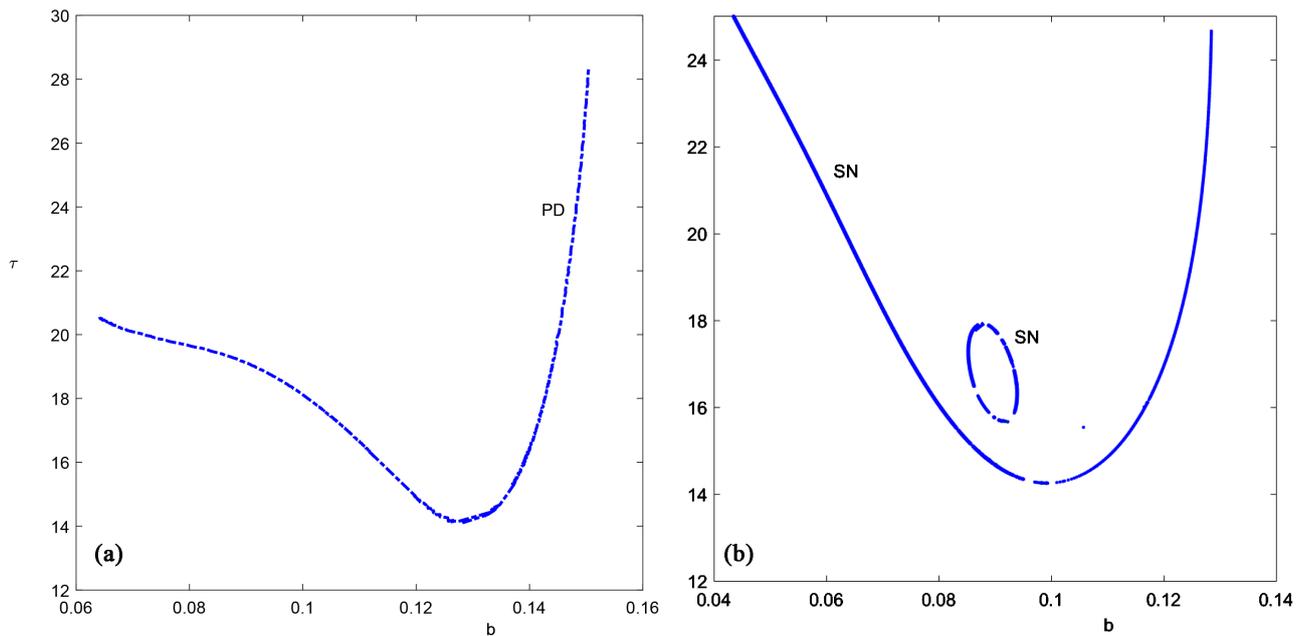


Figure 4. The bifurcation line of periodical solutions in (b, τ_1) -plane. (a) The period-doubling bifurcation line on which the period-2 solution arising inward; (b) The saddle-node bifurcation line and the saddle-node bifurcation circle in parameter plane. Two different transition modes are given as varying time delay τ_1 .

underlying hysteresis transition phenomena is observed as varying free parameter b with chosen $\tau_1 \in [15.8, 18.02]$. However, when τ_1 lying outside this interval, the continuation of periodical solutions exhibits very different transition modes which are called as the second saddle-node bifurcation mode. Underlying the second transition mode, replacing the jump phenomena of stable periodical solutions, between two saddle-node bifurcation points, an isolated “periodical oscillation island” is formed, which unattached to the continuation branch originating from Hopf point. As shown in **Figure 5(a)**, the left below stable periodic

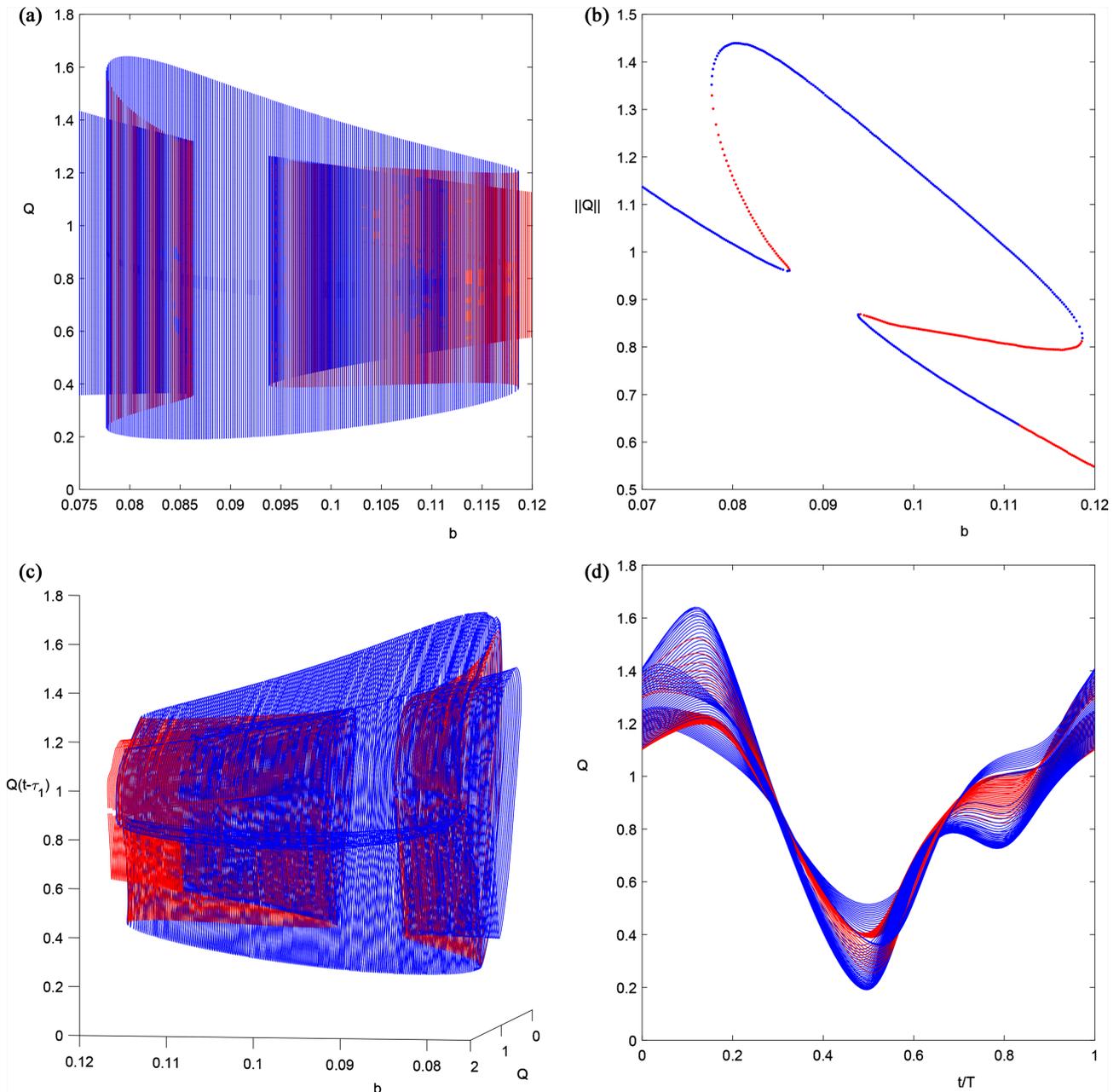


Figure 5. The continuation of period solutions as varying free parameter b with $\tau = 16.502$, the hysteresis phenomena of periodical solutions are observed. (a) The projection onto X - Y plane; (b) The magnitude of Q versus free parameter b ; (c) The view on X - Y - Z space; (d) The time series solution of continuation solutions.

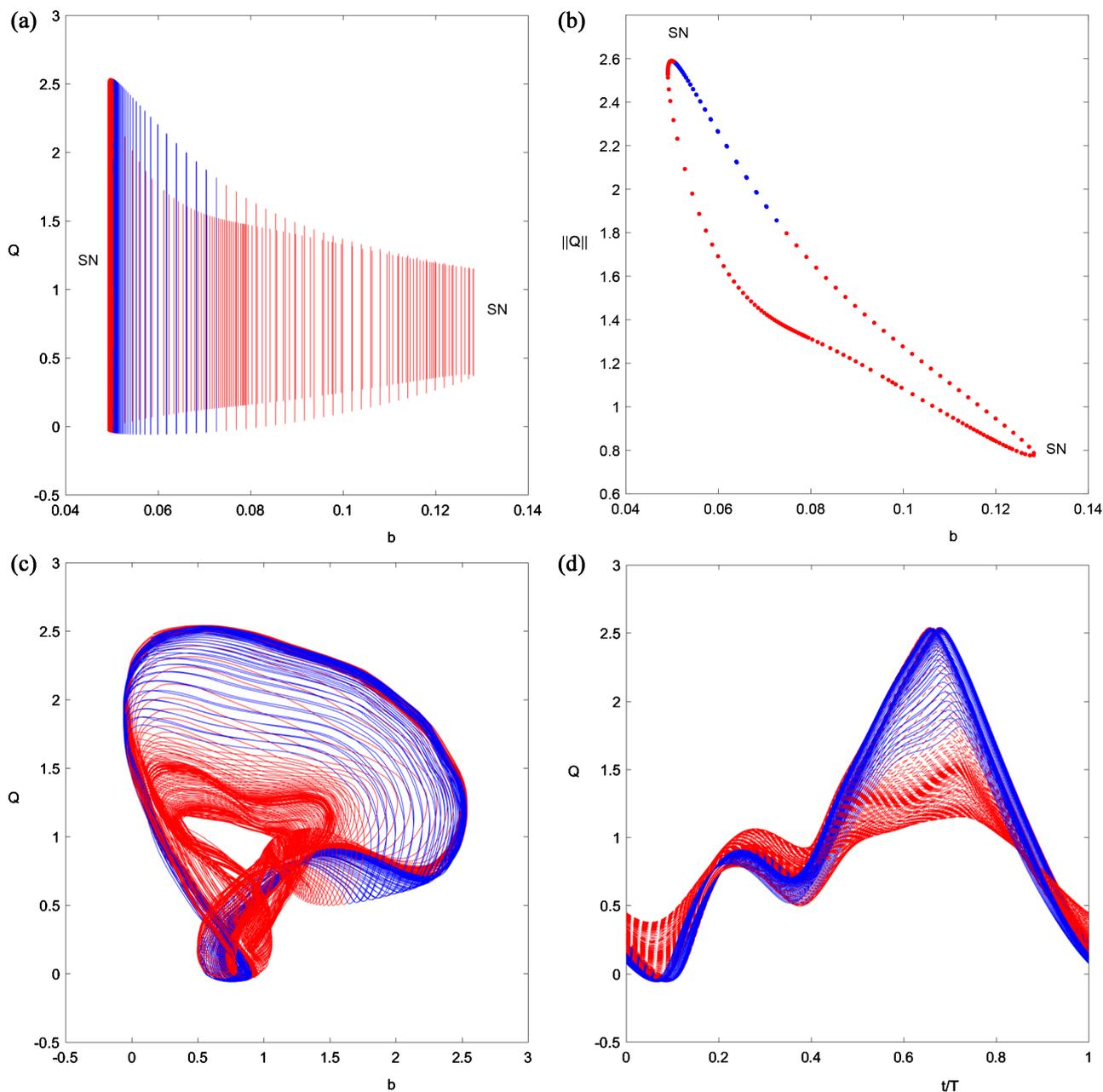


Figure 6. The continuation of periodical solutions born with saddle-node bifurcation while choosing $\tau = 23.6228$. (a) The continuation solutions in X - Y plane; (b) The magnitude versus free parameter b ; (c) The continuation solution in X - Z plane; (d) The time evolution solution within one mesh as varying b .

solution can jump to the upper stable periodic solution when increasing free parameter b to transpass over saddle-node bifurcation point. When keeping on increasing b , the upper stable period solutions transition to the below stable period-2 solution happens again when parameter transpass over next saddle-node bifurcation. Therefore, the hysteresis phenomena of stable periodical solutions are explained as shown in **Figures 5(a)-(d)**. The picture in **Figure 5(a)** and **Figure 5(c)** produces the continuation periodical solutions respectively by different views and the projection onto X - Y , X - Y - Z is shown, and the correspond-

ing time series solutions is locked as shown in **Figure 5(d)**, which use the boundary problem solving method as displaying DDE-Biftool software in Matlab. The second saddle-node transition mode exhibits continuation of periodic solutions that are also respectively shown in **Figures 6(a)-(d)**. The “island” phenomena shown in **Figure 6(b)** are in coincidence with the collision phenomena manifested by “left to right” saddle-node bifurcation points. The difference between two different transition modes manifested by saddle-node bifurcation is seen in **Figure 5(b)** and **Figure 6(b)**. The projections onto X - Y and X - Z plane of continuation solutions are respectively shown in **Figure 6(a)** and **Figure 6(c)**, and the corresponding time series solutions are shown in **Figure 6(d)**.

4. Conclusion

The delay feedback control may bring forth saddle-node bifurcation of periodical solutions. Two different transition modes of saddle-node bifurcation are discovered in Mackey-Glass model with multiple time-delay feedbacks. With hysteresis phenomena, the stable limit cycle can jump to the upper continuation branch of stable periodical oscillation by varying free parameters; however, the “oscillation island” of periodical solutions is formed between two saddle-node points underlying the second transition mode. Mathematically, the state feedback control leads to different attractors which significantly transit periodical oscillation solution to new bifurcation behavior.

Acknowledgements

Sincere thanks to the members of IJMNTA for their professional performance, and special thanks to managing editor for a rare attitude of high quality.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

- [1] Engelborghs, K., Luzyanina, T. and Samae, G. (2001) DDE-BIFTOOL, a Matlab Package for Bifurcation Analysis of Delay Differential Equations. Technical Report TW330.
- [2] Sieber, J., Engelborghs, K., Samae, G. and Roose, D. (2015) DDE-BIFTOOL Manual—Bifurcation Analysis of Delay Differential Equations. ArXiv: 1406.7144. <https://arxiv.org/abs/1406.7144>
- [3] Verheyden, K., Luzyanina, T. and Roose, D. (2004) Location and Numerical Preservation of Characteristic Roots of Delay Differential Equations by LMS Methods. Technical Report TW382.
- [4] Haurie, C., Dale, D.C. and Mackey, M.C. (1998) Cyclical Neutropenia and Other Periodic Hematological Disorders: A Review of Mechanisms and Mathematical Models. *Blood*, **92**, 2629-2640. https://doi.org/10.1182/blood.V92.8.2629.420a35_2629_2640
- [5] Bernard, S., Bélair, J. and Mackey, M.C. (2004) Bifurcation in a White-Blood-Cell

- Production Model. *Comptes Rendus Biologies*, **327**, 201-210.
<https://doi.org/10.1016/j.crv.2003.05.005>
- [6] Pujo-Menjouet, L. and Mackey, M.C. (2003) Contribution to the Study of Periodic Chronic Myelogenous Leukemia. *Comptes Rendus Biologies*, **327**, 235-244.
<https://doi.org/10.1016/j.crv.2003.05.004>
- [7] Ma, S.Q. (2021) Stability and Bifurcation Analysis of a Type of Hematopoietic Stem Cell Model, Springer Monographs in Mathematics. *International Journal of Modern Nonlinear Theory and Application*, **10**, 13-27.
<https://doi.org/10.4236/ijmnta.2021.101002>
- [8] Mackey, M.C. (1978) United Hypothesis for the Origin of Aplastic Anemia and Periodic Hematopoiesis. *Blood*, **51**, 941-956.
<https://doi.org/10.1182/blood.V51.5.941.bloodjournal515941>
- [9] Mackey, M.C., Pujo-Menjouet, L. and Wu, J. (2006) Periodic Oscillations of Blood Cell Populations in Chronic Myelogenous Leukemia. *SIAM Journal on Mathematical Analysis*, **38**, 166-187. <https://doi.org/10.1137/04061578X>
- [10] Daniel, C. and Humphries, A.R. (2017) Dynamics of a Mathematical Hematopoietic Stem-Cell Population Model. *SIAM Journal on Applied Dynamical Systems*, **18**, Article ID: 1165086.
- [11] Beretta, E. and Kuang, Y. (2002) Geometric Stability Switch Criteria in Delay Differential Systems with Delay Dependend Parameters. *SIAM Journal on Mathematical Analysis*, **33**, 1144-1165. <https://doi.org/10.1137/S0036141000376086>
- [12] Ma, S.Q. (2019) Hopf Bifurcation of a Type of Neuron Model with Multiple Time Delays. *International Journal of Bifurcation and Chaos*, **29**, Article ID: 1950163.
<https://doi.org/10.1142/S0218127419501633>
- [13] Wang, Z.H. and Hu, H.Y. (2000) Stability Switches of Time Delayed Dynamic Systems with Unknown Parameters. *Journal of Sound and Vibration*, **233**, 215-233.
<https://doi.org/10.1006/jsvi.1999.2817>
- [14] Xu, J. and Chung, K.W. (2003) Effects of Time Delayed Position Feedback on a Van der Pol-Duffing Oscillator. *Physica D: Nonlinear Phenomena*, **80**, 17-39.
[https://doi.org/10.1016/S0167-2789\(03\)00049-6](https://doi.org/10.1016/S0167-2789(03)00049-6)
- [15] Hale, J.K. and Lunel, S.M.V. (1993) Introduction of Functional Differential Equations. In: Bloch, A., Charles, L., Epstein, A.G. and Greengard, L., Eds., *Applied Mathematical Sciences*, Vol. 99, Springer, New York, 1-10.
<https://doi.org/10.1007/978-1-4612-4342-7>