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Hopf Bifurcation of a Minimal Mathematical Model of Glucose-Insulin Kinetics

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Abstract: ***This paper deals with Hopf bifurcation of the minimal mathematical model of glucose-insulin kinetics. This mathematical model consists of a system of nonlinear differential equations with time delays of the glucose-insulin. Different set of parameters used in order to match the real biological conditions. Numerical simulation are done using Matlab package. The results show that the critical delays periodic oscillations occurred and Hopf bifurcation has been token place at this level. For lower delays than critical the dynamical system deals with the stability while the values greater than critical delays it is unstable.***

Keywords: Hopf bifurcation, Stable, Unstable, Linearization, Nonlinear differential equation, Characteristic equation, Critical delays.

1. Introduction

Most nutrients such as proteins and fats are used to build and repair tissues through metabolism. These nutrients will be converted into glucose by a hormone produced by pancreas called insulin. Glucose-insulin kinetics may expect to occur in the dynamics with a given number of parameters allowed to vary. Diabetes mellitus, commonly known as diabetes is a syndrome of disordered metabolism. It is usually due to different causes but the important are a combination of hereditary and environmental causes. Those results in abnormally high levels of blood sugar known as hyperglycemia (When the blood sugar exceeds the normal range i.e. 80-110 mg/dl). It is a disease of glucose-insulin endocrine disorder where hyperglycemia is resulting from imbalance in insulin secretion, insulin in action or both. The two most common forms of diabetes are known. The first is due to a diminished production of insulin and it is called type-1 diabetes. When response by the body to insulin is diminished the diabetes is known as type-2. Another type of diabetes can occur in pregnant women who have never had diabetes before but have a high blood glucose level during pregnancy. It is called Gestational diabetes. The first approach to measure the insulin sensitivity in vivo has been introduced by Himsworth and Ker [1] in 1939. For a good understanding of the behavior of different biological and ecological system, many of the researchers have developed different mathematical. The study of glucose insulin interaction started during early sixties where in mid of 1960 DrsRosevear and Molnar of the Mayo- clinic and Ackerman and Gatewood [2] (University of Minnesota) discovered a fairly reliable criterion for interpreting the results of a glucose tolerance test (GTT). The mathematical model they proposed describes the blood glucose regulatory system during a GTT. A mathematical model governed by ordinary differential equation has been developed by Bolie in 1961 to estimate the glucose disappearance and insulin glucose dynamics in general [3]. The real first mathematical modelling of ‘glucose insulin dynamics’ was started with the so called ‘minimal model’ proposed by the team of Bergman and Cobelli in the early eighties [4]. This minimal model is the most widely used model to analyse the intravenous glucose tolerance test (IVGTT) [4]. In the survey described by Makroglou et al [5], several mathematical models have been derived. In a review by Boutayeb and Chetouni [10] for the dynamics of glucose-insulin presented intravenous glucose tolerance test (IVGTT), oral glucose tolerance tests (OGTT), and frequently sampled intravenous glucose tolerance test (FSIVGTT). Most of all the existing models were based on two variables only: glucose and insulin. From glucose-insulin mathematical model, De Gaetano and Arino proposed a delay differential model called Dynamical model [6]. From this minimal mathematical model, we introduce bordering methods to continue Hopf bifurcation in two parameters. In this approach, the function that defines bifurcation used in the minimal model is computed by solving the nonlinear differential equation. The study of the stability of Hopf bifurcation can be also be carried out through linearization, following a very simple idea suggested by Poincare´-Andronov [7]. The paper aims to provide the researchers with both a solid basis in dynamical systems theory and the necessary understanding of the approaches, methods results, and terminology used in mathematics. Hopf bifurcation is also common in physical problems that a symmetry. In such cases, fixed points tend to appear and disappear in symmetrical pairs. Fortunately there are only two situations in which the long term behavior of solutions near an equilibrium point of the nonlinear system and its linearization can differ [8]. One is when the linearized system is a center, the other is when the linearized system has zero as eigenvalue [8]. In dynamical system, the linearization occurs when the critical equilibrium has one zero eigenvalue. The stability of nonlinear differential equation depends on the roots of the characteristic polynomial. Notice that the Hopf bifurcation is determined by the stability of the equilibrium at the critical delay values [9]. Hopf bifurcation of phase portraits of two dimensional systems has been studied in great detail by Andronov in [7]. The theory behind on numerical Hopf bifurcation is vast and grows rapidly, together with computer software (Matlab packages) developed to support the analysis of dynamical systems. This work is organized as follows. The section 2 deals with setting on mathematical equation. The linearization and characteristics equation is presented in the section 3, whereas the section 4 focuses on numerical test and discussion. The concluding remarks are presented in section 6.

2. Setting on Mathematical Equations

In this section, we focused on mathematical model that shows a relationship between insulin and glucose. The most widely used model in physiological research on the metabolism of glucose-insulin is then so-called ''minimal model'' [10]. In 2001, J. Li, Y. Kuang and B. Li adopted the minimal model given by the following system of nonlinear differential equations of the glucose-insulin [11].

$$\frac{dG(t)}{dt} = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t)+1} + b_7, G(0) = G_0 \qquad (1)$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + b_6 G(t), I(0) = I_0. \qquad (2)$$

Where $G(t)$ in $[mg/dl]$ is the blood glucose concentration at time $t[\min]$, $I(t)$ in $[1UI/ml]$ is the blood insulin concentration and $b_1, b_2, b_3, b_4, b_6, b_7$ are the positive parameters associated to the function $G(t)$ and $I(t)$.

Considering two delays for the above equations, the system (1)-(2) gives us the following equations

$$\frac{dG(t)}{dt} = -b_1 G(t) - \frac{b_4 I(t-\tau_1) G(t)}{\alpha G(t)+1} + b_7, G(0) = G_0 \qquad (3)$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + b_6 G(t-\tau_2), I(0) = I_0. \qquad (4)$$

The set of parameters is used in the simulation and the results showing that the model can interpret the wide variation of glucose-insulin kinetics at the delays time τ_1 and τ_2. In this work we study nonlinear differential equations with time delays of the glucose-insulin kinetics, and discuss its stability properties. We analyze equilibrium and Hopf bifurcation at different time delays, and simulate the solutions of the glucose-insulin with different time delays.

3. Linearization and Characteristic Equation

Considering the system (3)-(4), is obtained by setting

$$\begin{cases} G(t) = G(t-\tau_2) = G_0, \\ I(t) = I(t-\tau_1) = I_0. \end{cases}$$

Let (G^*, I^*) be an equilibrium point of the model, the right hand sides of (3)-(4) becomes

$$\begin{cases} -b_1 G^* - \dfrac{b_4 I^* G^*}{\alpha G^* + 1} + b_7 = 0 \\ -b_2 I^* + b_6 G^* = 0. \end{cases} \qquad (5)$$

After the calculation yields

$$G^* = \frac{(\alpha b_7 - b_1) \pm \sqrt{(\alpha b_7 - b_1)^2 + 4\left(\alpha b_1 + \dfrac{b_4 b_6}{b_2}\right) b_7}}{2\left(\alpha b_1 + \dfrac{b_4 b_6}{b_2}\right)}$$

and

$$I^* = \frac{b_6 G^*}{b_2}.$$

Setting

$I_{\tau_1}(t) = I(t-\tau_1)$ and $G_{\tau_2}(t) = G(t-\tau_2)$,

and

$$\begin{cases} \dot{G}(t) = F_1(G, I_{\tau_1}) \\ \dot{I}(t) = F_2(I, G_{\tau_2}), \end{cases} \qquad (6)$$

where

$$F_1(G, I_{\tau_1}) = -b_1 G(t) - \frac{b_4 I_{\tau_1}(t) G(t)}{\alpha G(t)+1} + b_7,$$

and

$$F_2(I, G_{\tau_2}) = -b_2 I(t) + b_6 G_{\tau_2}(t).$$

The Taylor expansion of order one around the equilibrium point (G^*, I^*) of (6) becomes

$$\begin{cases} \dot{G}(t) = \dfrac{\partial F_1(G^*, I^*)}{\partial G}(G - G^*) + \dfrac{\partial F_1(G^*, I^*)}{\partial I_{\tau_1}}(I_{\tau_1} - I^*) + \ldots \\ \dot{I}(t) = \dfrac{\partial F_2(G^*, I^*)}{\partial I}(I - I^*) + \dfrac{\partial F_2(G^*, I^*)}{\partial G_{\tau_2}}(G_{\tau_2} - G^*) + \ldots \end{cases}.$$

Hence calculations of the linearized system are written as follows:

$$\begin{cases} \dot{G}(t) = \left(-b_1 - \dfrac{b_4 I^*}{(\alpha G^* + 1)^2}\right)(G - G^*) + \left(-\dfrac{b_4 G^*}{\alpha G^* + 1}\right)(I_{\tau_1} - I^*) \\ \dot{I}(t) = -b_2(I - I^*) + b_6(G_{\tau_2} - G^*). \end{cases}$$

Which can be written in matrix form as follows?

$$\begin{pmatrix} \dot{G}(t) \\ \dot{I}(t) \end{pmatrix} = \begin{pmatrix} -b_1 - \dfrac{b_4 I^*}{(\alpha G^* + 1)^2} & 0 \\ 0 & -b_2 \end{pmatrix} \begin{pmatrix} G - G^* \\ I - I^* \end{pmatrix} + \begin{pmatrix} 0 & -\dfrac{b_4 G^*}{\alpha G^* + 1} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} (G_{\tau_2} - G^*) \\ (I_{\tau_1} - I^*) \end{pmatrix} + \begin{pmatrix} 0 & 0 \\ b_6 & 0 \end{pmatrix} \begin{pmatrix} (G_{\tau_2} - G^*) \\ (I_{\tau_1} - I^*) \end{pmatrix}. \qquad (7)$$

That is

$$\begin{cases} \dot{Y}(t) = AY(t) + B_1 Y(t-\tau_1) + B_2 Y(t-\tau_2) \\ Y(t) = Y_0, -\tau \le t \le 0, \end{cases} \qquad (8)$$

where

$$Y(t) = \begin{pmatrix} G - G^* \\ I - I^* \end{pmatrix}, A = \begin{pmatrix} -b_1 - \dfrac{b_4 I^*}{(\alpha G^* + 1)^2} & 0 \\ 0 & -b_2 \end{pmatrix} \qquad (9)$$

and

$$B_1=\begin{pmatrix}0 & -\dfrac{b_4G^*}{\alpha G^*+1}\\ 0 & 0\end{pmatrix}, B_2=\begin{pmatrix}0 & 0\\ b_6 & 0\end{pmatrix}. \tag{10}$$

To find the characteristic polynomial of (8) we assume that its solution can be written as

$$Y(t)=K(t)e^{\lambda t}, \tag{11}$$

where

$$K(t)=Y_0 .$$

Differentiating the equation (11), we obtain:

$$\dot{Y}(t)=\left(\dot{K}(t)+\lambda K(t)\right)e^{\lambda t}. \tag{12}$$

Replacing the equations (11) and (12) into the equation (8) we obtain:

$$\dot{K}(t)e^{\lambda t}+\lambda K(t)e^{\lambda t}=AK(t)e^{\lambda t}+B_1K(t)e^{\lambda(t-\tau_1)}+B_2K(t)e^{\lambda(t-\tau_2)},$$

$$\dot{K}(t)e^{\lambda t}=(A+B_1e^{-\lambda\tau_1}+B_2e^{-\lambda\tau_2}-\lambda I)K(t)e^{\lambda t}.$$

The eigenvalue λ is obtained by solving the characteristic equation

$$\left|\lambda I-A-\sum_{i=1}^{2}B_ie^{-\lambda\tau_i}\right|=\det\left(A+B_1e^{-\lambda\tau_1}+B_2e^{-\lambda\tau_2}-\lambda I\right)\equiv 0$$

(13)

that is

$$\lambda^2+\left(b_1+b_2+\frac{b_4I^*}{(\alpha G^*+1)^2}\right)\lambda+\frac{b_2b_4I^*}{(\alpha G^*+1)^2}+\frac{b_4b_6G^*}{\alpha G^*+1}e^{-\lambda(\tau_1+\tau_2)}=0.$$

(14)

Recall that the equilibrium point (G^*,I^*) is stable if and only if all the eigenvalues of the equation (14) have negative part. The Hopf bifurcation occurs at $\lambda=iw$ where $w>0$ and i denotes the complex number that satisfies $i^2=-1$. At unique equilibrium point (G^*,I^*) of equation (14) there exists a Hopf bifurcation for a value of λ which is found by computing the real w such that $P(iw)=0$. Furthermore we separate two main parts of $P(iw)$ by taking

$$F(w,\tau_1,\tau_2)=\mathrm{Re}\left(P(iw)\right)$$

and

$$G(w,\tau_1,\tau_2)=\mathrm{Im}\left(P(iw)\right)$$

respectively real and imaginary parts of $P(iw)$. Then bifurcation parameters are obtained by solving the system

$$\begin{cases}F(w,\tau_1,\tau_2)=0\\ G(w,\tau_1,\tau_2)=0.\end{cases} \tag{15}$$

Now, we are able to apply this theory to our case.

Let $\lambda=iw\left(w\in\mathbb{R}, with\, w>0\right)$ and substitute it into (13) we obtain

$$A+B_1e^{-iw\tau_1}+B_2e^{-iw\tau_2}-\lambda I=0, \tag{16}$$

since

$$e^{-iw\tau}=\cos(w\tau)-i\sin(w\tau).$$

Then the equation (16) becomes

$$A+B_1(\cos(w\tau_1)-i\sin(w\tau_1))+B_2(\cos(w\tau_2)-i\sin(w\tau_2))-iwI=0,$$

$$A+B_1\cos(w\tau_1)+B_2\cos(w\tau_2)-i(wI+B_1\sin(w\tau_1)+B_2\sin(w\tau_2))=0,$$

where

$$F(w,\tau_1,\tau_2)=A+B_1\cos(w\tau_1)+B_2\cos(w\tau_2)$$

and

$$G(w,\tau_1,\tau_2)=B_1\sin(w\tau_1)+B_2\sin(w\tau_2)+wI.$$

From (15) yields

$$\begin{cases}B_1\cos(w\tau_1)+B_2\cos(w\tau_2)+A=0\\ B_1\sin(w\tau_1)+B_2\sin(w\tau_2)+wI=0\end{cases},$$

which allows us to get the bifurcation parameters τ_1^* and τ_2^*. For any assumptions on functions F and G, there exists a point $\tau^*=(\tau_1^*,\tau_2^*)$ and a real $w^*=w^*(\tau_1^*,\tau_2^*)$ such that $\lambda^*=iw^*$ is a solution of the equation (13). According to our model in the case where the two time delays are different $(\tau_1\neq\tau_2)$, Hopf bifurcation can be found. Hopf bifurcation is characterized by the couple of the real part of complex conjugate eigenvalues. Consequently, from the characteristic equation (14) and setting

$$\tau_1+\tau_2=\tau$$

then it is written as follows

$$\lambda^2+\left(b_1+b_2+\frac{b_4I^*}{(\alpha G^*+1)^2}\right)\lambda+\frac{b_2b_4I^*}{(\alpha G^*+1)^2}+\frac{b_4b_6G^*}{\alpha G^*+1}e^{-\lambda\tau}=0. \tag{17}$$

Since $\lambda=iw$, then the equation (17) becomes

$$-w^2+i\left(b_1+b_2+\frac{b_4I^*}{(\alpha G^*+1)^2}\right)w+\frac{b_2b_4I^*}{(\alpha G^*+1)^2}+\frac{b_4b_6G^*}{\alpha G^*+1}(\cos(w\tau)-i\sin(w\tau))=0. \tag{18}$$

Separating the real and imaginary parts of (18) we get

$$\begin{cases}-w^2+\dfrac{b_2b_4I^*}{(\alpha G^*+1)^2}+\dfrac{b_4b_6G^*}{\alpha G^*+1}\cos(w\tau)=0,\\ \left(b_1+b_2+\dfrac{b_4I^*}{(\alpha G^*+1)^2}\right)w-\dfrac{b_4b_6G^*}{\alpha G^*+1}\sin(w\tau)=0.\end{cases} \tag{19}$$

Squaring and adding the parts of the system (19) we obtain

$$\left(-w^2+\frac{b_2b_4I^*}{(\alpha G^*+1)^2}\right)^2+\left(b_1+b_2+\frac{b_4I^*}{(\alpha G^*+1)^2}\right)^2w^2=\left(\frac{b_4b_6G^*}{\alpha G^*+1}\right)^2, \tag{20}$$

equivalently to

$$w^4+\left[\left(b_1+b_2+\frac{b_4I^*}{(\alpha G^*+1)^2}\right)^2-\frac{2b_2b_4I^*}{(\alpha G^*+1)^2}\right]w^2+\left(\frac{b_2b_4I^*}{(\alpha G^*+1)^2}\right)^2-\left(\frac{b_4b_6G^*}{\alpha G^*+1}\right)^2=0.$$

(21)

After solving the (21) we have

$$w=\pm\sqrt{\frac{-\rho+\sqrt{\rho^2+4\eta}}{2}},$$

where

$$\rho=\left(b_1+b_2+\frac{b_4I^*}{(\alpha G^*+1)^2}\right)^2-\frac{2b_2b_4I^*}{(\alpha G^*+1)^2},$$

and

$$\eta=\left(\frac{b_2b_4I^*}{(\alpha G^*+1)^2}\right)^2-\left(\frac{b_4b_6G^*}{\alpha G^*+1}\right)^2.$$

We find τ in terms of arctangent when we solve the equation (19) that is

$$\begin{cases}\dfrac{b_4b_6G^*}{\alpha G^*+1}\sin(w\tau)=\left(b_1+b_2+\dfrac{b_4I^*}{(\alpha G^*+1)^2}\right)w\\ \dfrac{b_4b_6G^*}{\alpha G^*+1}\cos(w\tau)=w^2-\dfrac{b_2b_4I^*}{(\alpha G^*+1)^2},\end{cases} \quad (22)$$

where the ratio between the two equations of the system (22) give us

$$\tan(w\tau)=\frac{\left((b_1+b_2)(\alpha G^*+1)^2+b_4I^*\right)w}{(\alpha G^*+1)^2w^2-b_2b_4I^*}, \quad (23)$$

from equation (23) we get

$$\tau=\frac{1}{w}\arctan\left(\frac{\left((b_1+b_2)(\alpha G^*+1)^2+b_4I^*\right)w}{(\alpha G^*+1)^2w^2-b_2b_4I^*}\right).$$

Note that at equilibrium point τ is equal to the critical delay that is $\tau=\tau^*$ and in this case $w=w^*$.

4. Numerical Test

We are interested in describing some of the basic techniques used in the numerical analysis of our given dynamical system. The numerical simulation is done using Matlab packages where mathematical model governed by delay differential equations are solved using a solver $dde23$ command which is built in function of Matlab. We consider for the initial condition $G(0)=30$ and $I(0)=20$ and we deal mainly with analysis of Hopf bifurcation according to the critical delays cases and give only brief remarks on the time τ. In the characteristic equation (14), we take the values of parameters:

$b_1=0.226, b_2=0.01262, b_4=2.94\times10^{-3}, b_5=0.04, b_6=2.94, b_7=1.93,$ and $\alpha=0.00751$.

Using the parameters taken we obtain $G^*=71.056$ and $I^*=46.65$. The numerical simulation results are shown in the figure 1, 2, and 3 after executing the Matlab program.

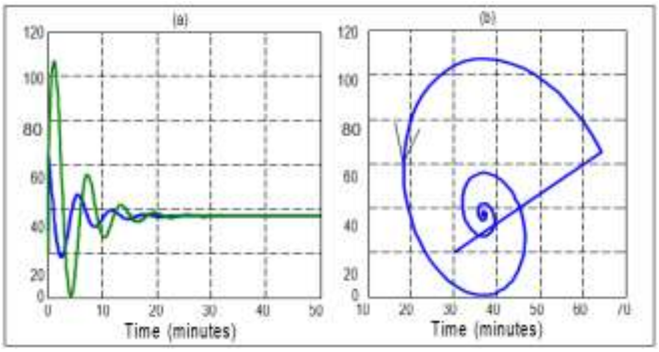

Figure 1: Variation of glucose and insulin (a) where the solid line represents glucose concentration and dashed line denotes insulin concentration in time, and its phase portrait (b) in the case of stability.

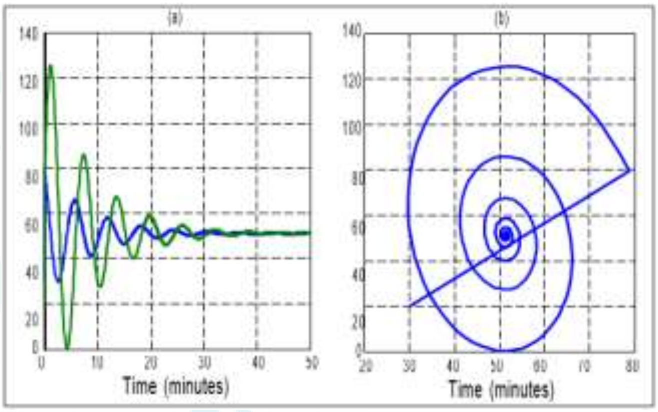

Figure 2: Oscillation of glucose and insulin (a) where solid line represents glucose concentration and dashed line denotes insulin concentration, and phase portrait (b) in the case of Hopf bifurcation.

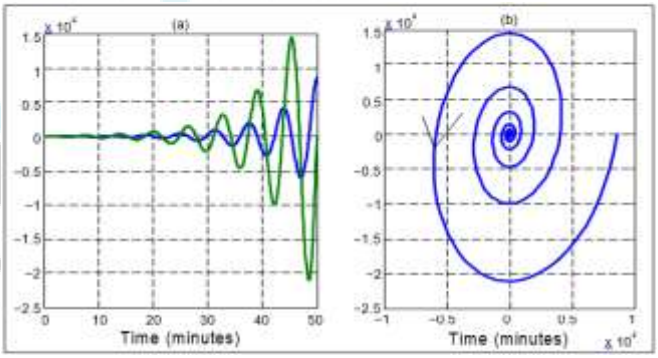

Figure 3: Variation of glucose and insulin (a) where solid line represents glucose and dashed line denotes insulin, and phase portrait of glucose and insulin (b) in the case of instability.

5. Discussion of Results

Hopf bifurcation points are shown by numerical simulation of our dynamical system of a two delays mathematical model during 50 days. It is known that Hopf bifurcation is intermediate behavior between stability and instability for dynamical system. For a mathematical model where delay τ is taken as its parameters, Hopf bifurcation occurs at a critical value of delay τ^*. The dynamical system is stable for values below τ^* whereas it is instable for the values greater than τ^*. This bihaviour happens for our simulated mathematical model. The figure 1 shows the case of stability where the glucose $G(t)$ and insulin $I(t)$ concentration are in their normal variation as curves the values less than to the critical delays. Furthermore the figure illustrates the waveform (Figure 1(a) and phase portrait 1 (b) which is a stable spiral). The two functions are varying out of the normal range since values of delays are lying beyond of τ. The values of delays taken for this asymptotic stability case are $\tau_1 = 0.16$ and $\tau_2 = 0.000549$. This situation occurs in the figure 3 that illustrates the waveform (Figure 3(a) and phase portrait 3 (b) whose the shape is divergent spiral). This case is simulated using values of delays $\tau_1 = 0.82$ and $\tau_2 = 0.0102549$. The figure 2 shows the periodic oscillations of $G(t)$ and $I(t)$ respectively that is Hopf bifurcation. Moreover, the two functions oscillate at the critical delays $\tau_1^* = 0.32$ and $\tau_2^* = 0.004549$.

6. Concluding Remarks

As a conclusion, the nonlinear differential equation glucose-insulin of minimum mathematical model with time delays and parameters. The minimum model has a Hopf bifurcation. We examine this one at equilibrium point. Certain results, such as Hopf bifurcation in two-dimensional systems, are presented in great summary, including the proofs. Simple graphs are obtained by plotting a significant state variable of a dynamical system as a function of the bifurcation parameter. The obtained graphs are called solution diagrams and can be efficiently built with parameter continuation software (Matlab). Special attention is given to numerical implementation of the developed techniques. Glucose-insulin kinetics is one of the example, mainly from mathematical biology, is used as illustrations. We discuss the results according to the values of critical delays. At these ones the periodic oscillations occurred and Hopf bifurcation has been token place at this level. For the values less than to critical delays the given dynamical system was presenting the stability and for the higher values than critical delays the system has been showing instability.

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