



# Control of Pyragas Applied to a Coupled System with Unstable Periodic Orbits

Pablo Amster<sup>1,2</sup> · Carlos Alliera<sup>1</sup>

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## Abstract

We apply a Pyragas-type control in order to synchronize the solutions of a glycolytic model that exhibits an aperiodic behavior. This delay control is used to stabilize the orbits of ordinary differential nonlinear equations systems. Inspired by several works that studied the chaotic behavior of diverse systems for the enzymatic reactions in the presence of feedbacks, the control to two of these models is analyzed.

**Keywords** Delayed differential equation · Control theory · Glycolysis · Bifurcation

## 1 Introduction

In nonlinear dynamic systems, the instability of the trajectories can occur in a variety of ways, one of which is the presence of chaos. In many cases, the existence of chaos is evidenced by the appearance of unstable orbits, irregular oscillations that never repeat (or of infinite period) and that produce strange attractors. According to Montero and Morán (1992): *By chaos is meant the aperiodic dynamic behavior, which occurs under totally deterministic conditions and presents great sensitivity to the initial conditions.* Other aspects are expressed by Decroly and Goldbeter (1982): *Evolution to chaos appears to be a universal way by which periodic behavior loses its regularity and becomes unpredictable, although governed by deterministic laws.*

Chaos usually appears in the most varied contexts (MacKey and Glass 1977), and it is not always indicative of dysfunction or bad behavior. For example, chaotic brain waves are associated with normal behavior as evidenced by electroencephalograms, whereas periodicity is typical during epilepsy attacks (Montero and Morán 1992;

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✉ Carlos Alliera  
calliera@dm.uba.ar

Pablo Amster  
pamster@dm.uba.ar

<sup>1</sup> Universidad de Buenos Aires, Buenos Aires, Argentina

<sup>2</sup> IMAS-CONICET, Ciudad Universitaria, Pabellón I, 1428 Buenos Aires, Argentina

Torres 1991). Also, the heart beats have a tenuous aperiodicity, necessary for adaptation to the changes in the environment, and the loss of this aperiodicity in the heartbeat is a sign of heart attack. There are classical experiments widely quoted in the literature (Balanov et al. 2005; Chen and Yu 1999; Morse 1976; Strogatz 1994) in which chaos appears in chemical reactions (Belousov–Zhabotinskii model), electronic circuits (see Chua and Moina 1999 the Chua circuit or Bharti and Yuasa 2010 for the Ueda oscillator), the Feigenbaum or Hénon map for the discrete case, and the famous Lorenz and Rössler models.

Moreover, there are trajectories that are not classified as chaotic, although at first glance seem to have an aperiodic behavior. This is the case, for example, of the quasi-periodic orbits, which are often confused with chaos because oscillations of this kind may never repeat.

### 1.1 The Glycolytic Model

Oscillations (or rhythmic behaviors) are found at all levels of biological organization. From a thermodynamic perspective, such cycles represent dissipative structures.

According to the definition of Nelson and Cox (2017), glycolysis (from the Greek *glykys*: sweet, *lysis*: degradation) is an ancient metabolic pathway in evolutionary terms consisting of a sequence of reactions that convert one molecule of glucose into two of pyruvate with the concomitant net production of two molecules of ATP (adenosine triphosphate). Pyruvate can be converted into a form of lactate (lactic fermentation) or ethanol (alcoholic fermentation). It is an anaerobic process, and it does not require oxygen, since it dates from a stage in which the atmosphere had not accumulated much O<sub>2</sub> and evolved with this character .

In various tissues and cells of mammals (erythrocytes, kidney, brain, and sperm), glucose is the main source of metabolic energy. This is also observed in some plant tissues (potato tubers). Although the original model of glycolysis contains ten enzymes, a simplified pathway of two enzymes is studied, those involved in generations of oscillations: phosphofructokinase (PFK) and pyruvate kinase (PK), linked in cycle by the common metabolites ADP and ATP (Torres 1991; Montero and Morán 1992). The system is maintained open by the external and periodic injection of fructose-6-phosphate (F6P) and phosphoenolpyruvate (PEP), the final products of the reaction being fructose 1,6-diphosphate (FDP) and pyruvate.

In the process of regulation of enzyme level, there exist two instability generating mechanisms: substrate inhibition (negative feedforward) and product activation (positive feedback).

Glycolytic oscillations are observed in cases such as those of the pancreas cells (see Makroglou et al. 2006; Westermack and Lansner 2003), in yeast or in muscles. The origin of these oscillations lies in the regulatory properties of the enzymes (see Kar and Ray 1994), particularly phosphofructokinase, which is activated by the ADP product.

The simplified model of 2 enzymatic reactions that shall be analyzed in this work represents a prototype of a self-regulated metabolic pathway. Clearly, this condition yields only four possibilities when two instability generators couple in series (Figs. 1, 2).

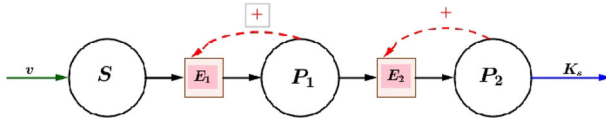


Fig. 1 Model M1

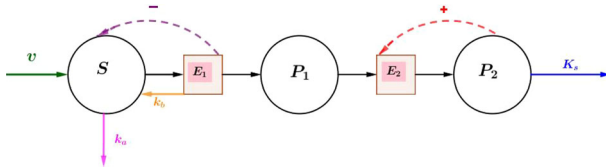


Fig. 2 Model M2

In what follows, for both models  $x, y, z$  shall denote the rescaled concentrations of substrate  $S$  and the products  $P_1$  and  $P_2$

$$x(t) := \frac{[S](t)}{K_{m1}}, \quad y(t) := \frac{[P_1](t)}{K_{P1}}, \quad z(t) := \frac{[P_2](t)}{K_{P2}},$$

where  $K_{P_j}$  are the Michaelis constants for products  $P_j, j = 1, 2$ .

### 1.1.1 Model $M_1$

For convenience, a brief description of the model is presented. The substrate  $S$  is synthesized at a constant rate  $v$ , and its transformation is catalyzed by an allosteric enzyme  $E_1$ , which is activated by the product  $P_1$ . A second allosteric enzyme  $E_2$  uses  $P_1$  as substrate and is activated by its product  $P_2$ . The removal rate of  $P_2$  shall be denoted by  $K_s$ .

The system reads

$$\begin{cases} \frac{dx}{dt} = \kappa - \sigma_1 \Phi(x, y), \\ \frac{dy}{dt} = q_1 \sigma_1 \Phi(x, y) - \sigma_2 \eta(y, z), \\ \frac{dz}{dt} = q_2 \sigma_2 \eta(y, z) - K_s z \end{cases} \quad (1)$$

where

1. The functions  $\Phi, \eta : \mathbb{R}^2 \rightarrow \mathbb{R}$  are given as in Decroly and Goldbeter (1982); Letellier (2002) by

$$\Phi(x, y) := \frac{x(1+x)(1+y)^2}{L_1 + (1+x)^2(1+y)^2}, \quad \eta(y, z) := \frac{y(1+dy)(1+z)^2}{L_2 + (1+dy)^2(1+z)^2},$$

where  $L_1$  and  $L_2$  are the allosteric constants of  $E_1$  and  $E_2$ , respectively, and  $d$  is defined below.

2.  $v$  denotes the constant input of substrate  $S$ .
3.  $\frac{v}{K_{m1}} = \kappa$ , where  $K_{m1}$  is the Michaelis constant for  $E_1$ .
4.  $\sigma_1$  and  $\sigma_2$  are the maximum activities of enzymes  $E_1$  and  $E_2$ , respectively.
5.  $q_1 = \frac{K_{m1}}{K_{P1}}$  and  $q_2 = \frac{K_{P1}}{K_{P2}}$ .
6.  $d = \frac{K_{P1}}{K_{m2}} = \frac{\Delta}{\Delta + 1}$  where  $K_{m2}$  is the Michaelis constant of  $E_2$  for substrate  $P_1$  and  $\Delta$  is defined following in Xian et al. (1984) as the asymmetry coefficient for the breakdown of the enzyme-substrate complex  $E_2P_1$ . It is supposed that the breakdown is mainly in the direction in which  $P_2$  is produced (that is  $K_{P1} \ll K_{m2}$ ); thus,  $\Delta$  is considerably small.
7. The parameter  $K_s$  represents the apparent first-order rate for removal of  $P_2$ . Decroly and Goldbeter (1982) use it as a bifurcation parameter, because the variation in  $K_s$  could result from a continuous change in enzyme activity.

### 1.1.2 Model $M_2$

This model was studied by Xian et al. (1984), who considered a physiologically more realistic model, because the coupling of enzymes occurs between a positive and a negative feedback (feedforward). Unlike in the preceding case, a substrate inhibition is observed, which makes of  $M_2$  a more complete system since it exhibits all known patterns of temporal self-organization.

Some distinctive aspects of model  $M_2$  are the following: The substrate  $S$  can also flow to another pathway through a first-order reaction with constant rate  $k_a$ . Besides, the intermediate product  $P_1$  can in turn activate the production of substrate  $S$  through first-order reaction with constant rate  $k_b$ . Thus, the model is governed by the following system of ordinary differential equations:

$$\begin{cases} \frac{dx}{dt} = \kappa - \sigma_1\Psi(x) - k_ax + k_b\frac{y}{q_1}, \\ \frac{dy}{dt} = q_1\sigma_1\Psi(x) - k_by - \sigma_2\eta(y, z), \\ \frac{dz}{dt} = q_2\sigma_2\eta(y, z) - K_s z \end{cases} \tag{2}$$

where

1. The function  $\Psi : \mathbb{R} \rightarrow \mathbb{R}$  is defined by:

$$\Psi(x) := \frac{x}{K_A + x + K''_A x^2},$$

where  $K_A, K''_A$  are the allosteric constants.

2.  $k_a$  is the first-order constant that represents the rate at which the  $S$  substrate flows out of the system.
3. The reaction according to which  $P_1$  reproduce the substrate  $S$  has rate  $k_b$ .
4. The remaining parameters and functions are defined as in the model  $M_1$ . We recall that  $K_s$  was used in Xian et al. (1984) as bifurcation parameter.

## 2 The Pyragas Method

The effect of chaos on dynamic systems is usually undesirable if one wants to predict the behavior of the variables. Several techniques have been developed to control the chaos and thus eliminate the instability of a trajectory by making slight time-dependent perturbations in the form of feedbacks, which are understood as the response of a receiver to the signal sent by an issuer. As many strange attractors store within them myriads of unstable trajectories, methods such as those developed by Ott et al. (1990) and Pyragas (1992) allow this attractor to be split into a large number of periodic trajectories. To fix ideas, let us consider the system

$$\begin{aligned}\dot{X}(t) &= F(X(t)) \\ X(t_0) &= X_0\end{aligned}\tag{3}$$

where  $X = (x_1, \dots, x_n)$  is the states vector (for instance, each coordinate  $x_j(t)$  represents a concentration depending on time) and assume that (3) has an unstable trajectory.

The Pyragas method, also known as *time-delay autosynchronization*, is part of a general class of methods called “closed loop” or “feedback” methods. It introduces a time-delayed continuous feedback by using an external control force  $\mathcal{D} : \mathbb{R}^n \rightarrow \mathbb{R}^n$  which consists in the difference between the variable to be controlled and its delayed counterpart, namely  $\mathcal{D}(S) := S(t) - S(t - \tau)$ , whose intensity is practically zero as the system evolves close to the chosen periodic orbit but increases when it drifts away from it. This force is further multiplied by a matrix  $\mathcal{K} \in \mathbb{R}^{n \times n}$ , in which the coefficients represent the weight of the perturbation added by the control. By selecting the matrix  $\mathcal{K}$ , stabilization can be achieved (see Boccaletti et al. 2000; Fourati et al. 2010; Hövel 2010; Pyragas 1992).

### 2.1 Applying the Control

Let us consider a system with same conditions of (3), which presents chaotic behavior near an unstable equilibrium (*steady state*)  $P_0 \in \mathbb{R}^n$ , according to the definition of Pyragas (1992),

$$X'(t) = F(X(t)) + \mathcal{K}(X(t) - X(t - \tau))\tag{4}$$

where  $F : \mathbb{R}^n \rightarrow \mathbb{R}^n$  corresponds to the system under study, as before  $X(t) = (x_1(t), x_2(t), \dots, x_n(t))$  is the state vector of the model,  $\tau \geq 0$  is a fixed delay (see Erneux 2009) and the control matrix  $\mathcal{K} \in \mathbb{R}^{n \times n}$ . We denote by  $A := J_F(P_0)$  the Jacobian matrix of  $F$  at the equilibrium.

Assume that  $P_0$  is an unstable equilibrium of (3) due to the fact that some eigenvalue of  $A$  has strictly positive real part. We shall choose the control matrix  $\mathcal{K}$  in such a way that all the eigenvalues of the matrix  $A + \mathcal{K}$  have strictly negative real part. This choice is based on the fact that the characteristic equation

$$P(\lambda, \tau) = \det(\lambda I - (A + \mathcal{K}) + \mathcal{K}e^{-\lambda\tau}) = 0 \tag{5}$$

satisfies

$$\limsup_{\tau \rightarrow +\infty} \max_{P(\lambda, \tau)=0} \Re(\lambda) \leq 0.$$

Indeed, it is well known that for each  $\tau \geq 0$  and each  $\mu \in \mathbb{R}$  the set  $\mathcal{S}_\mu := \{\lambda : P(\lambda, \tau) = 0, \Re(\lambda) \geq \mu\}$  is finite and, furthermore, if  $\mu > 0$ , then  $\mathcal{S}_\mu$  is empty for  $\tau$  large enough. The latter claim is due to the following facts:

1.  $|e^{-\lambda\tau}| = e^{-\Re(\lambda)\tau} \leq e^{-\mu\tau} \rightarrow 0$  as  $\tau \rightarrow +\infty$ .
2.  $\min_{\Re(\lambda) \geq \mu} |\det(\lambda I - (A + \mathcal{K}))| > 0$ .

We shall look for a minimum delay  $\tau_c > 0$  such that all solutions of (5) have non-positive real part, that is:

$$\tau_c = \min\{\tau > 0 \text{ such that } P(\lambda, \tau) = 0 \wedge \Re(\lambda_j) \leq 0 \forall j\}. \tag{6}$$

The existence of this critical delay will depend on the choice of the matrix  $\mathcal{K}$ . Numerical examples in the next sections will be devoted to find, for appropriate  $\mathcal{K}$ , a range  $(\tau_c, \tau_c + \delta)$  of values of  $\tau$  such that all the solutions of (5) have strictly negative real part. For simplicity, we shall consider constant matrices only and, as shown in the examples, sparse matrices when possible.

### 3 Decroly–Goldbeter Coupled Model (M1)

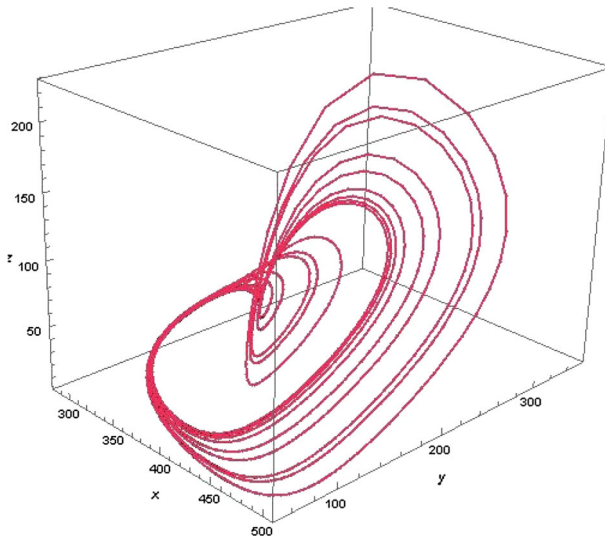
The biochemical model of glycolysis analyzed in Decroly and Goldbeter (1982) is proposed in order to observe the effect of two mechanisms generating instability within the same system. This instability produces a periodicity based on the positive feedbacks between the enzymes (whose oscillations may have periods of several minutes) and the successive substrates and products of the chain. When studying this model coupled in series, it was observed that the continuous variation of certain parameters of the system gives rise to a wide range of mechanisms of self-organization ranging from simple oscillations, birhythmicity to chaos.

#### 3.1 A Chaotic Model

According to Decroly and Goldbeter (1982), a strange attractor can be obtained by varying the coefficients of the system. For example, taking

$$\begin{aligned} \kappa &= 0, 45, & \sigma_1 &= \sigma_2 = 10, & d &= 0, \\ q_1 &= 50, & q_2 &= 0, 02, & L_1 &= 5 \times 10^8, & L_2 &= 100, \end{aligned} \tag{7}$$

the attractor of Fig. 3 can be observed for  $K_s = 2$ .



**Fig. 3** Strange attractor of system (1) with parameters (7)

Based on Chen and Yu (1999), we will apply a control type of Pyragas (1992) to study models of this kind. Under the previous choice of the parameters, the system has the following equilibrium points:

$$\begin{aligned}
 P_0 &= (x^*, y^*, z^*) = (31.2138; 152.188; 0.225) \\
 P_1 &= (x^{**}, y^{**}, z^{**}) = (-32.1667; 152.188; 0.225)
 \end{aligned}
 \tag{8}$$

Recalling the fact we are working with concentrations, for the subsequent analysis we shall focus on the first of these points, which has positive coordinates.

In order to propose a control matrix  $\mathcal{K}$ , let us observe that, since feedbacks occur between  $P_1$  and  $P_2$ , it is expected that the equation corresponding to  $S$  does not require any control. For this reason, we shall consider a matrix of the form:

$$\mathcal{K} := \begin{pmatrix} 0 & 0 & 0 \\ 0 & k_1 & k_2 \\ 0 & k_3 & k_4 \end{pmatrix}$$

We remark that different types of matrices may be suitable, according to the different models and the presence of delays. Since each nonzero coefficient of  $\mathcal{K}$  represents a new term which is added to the original system (3), it proves convenient to choose  $\mathcal{K}$  with a small number of nonzero entries.

### 3.1.1 Looking for a Critical Delay

In the first place, consider the linearized system:

$$X'(t) = AX(t)$$

where the Jacobian matrix of (1) at  $P_0$  is given by

$$A := J_{\Phi}(P_0) = \begin{pmatrix} -0.0270884 & -0.0056023 & 0 \\ 1.35442 & 0.132271 & -36.1916 \\ 0 & 0.00295688 & -1.27617 \end{pmatrix}.$$

The eigenvalues of  $A$  are given by

$$\Lambda_A = \{0.0125038 \pm 0.080875i, -1.19599\}$$

Thus, the controlled linearized system reads:

$$X'(t) = AX(t) + \mathcal{K}(X(t) - X(t - \tau)). \tag{9}$$

For example, we may take the following sparse matrix:

$$\mathcal{K} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 3 \\ 0 & 1 & 0 \end{pmatrix}$$

which yields the following eigenvalues of  $A + \mathcal{K}$ :

$$\Lambda_{A+\mathcal{K}} = \{-0.571805 \pm 5.72724i, -0.0273747\}$$

Hence, we obtain the following controlled system for (1):

$$\begin{cases} x'(t) = 0, & 45 - \frac{10(x(t)(x(t)+1)(y(t)+1)^2)}{5 \cdot 10^8 + (x(t)+1)^2(y(t)+1)^2}, \\ y'(t) = -\frac{10(y(t)(z(t)+1)^2)}{(z(t)+1)^2 + 100} + \frac{500((x(t)+1)(y(t)+1)^2x(t))}{5 \cdot 10^8 + (x(t)+1)^2(y(t)+1)^2} + 3(z(t) - z(t - \tau)), \\ z'(t) = \frac{0.2(y(t)(z(t)+1)^2)}{(z(t)+1)^2 + 100} - 2z(t) + (y(t) - y(t - \tau)), \\ x(t) = 31.214, \quad y(t) = 152.2, \quad z(t) = 0.22, \quad t < 0 \end{cases} \tag{10}$$



With the idea in mind of keeping near the equilibrium for all  $t \geq 0$ , let us fix the initial condition close to  $P_0$ . When  $\tau = 0$ , a chaotic behavior is observed, so we propose an analysis similar to that of Murray (2001, pp 246–252), Cao and Yu (2007), Xu (2011) and Xu and Liao (2010) for a model with three equations, in order to find a critical time lag by looking at the roots of the characteristic function (see Hale 1977; Ruan and Wei 2003), namely

$$P(s) := -s^3 - 1.17099s^2 + 30.1827se^{-s\tau} + 3se^{-2s\tau} + 0.817601e^{-s\tau} + 0.0812651e^{-2s\tau} - 33.1595s - 0.906876.$$

In order to find a critical delay, we shall find conditions for the existence of roots  $s = \omega_0 i$ :

$$\begin{aligned} P(\omega_0 i) = & -0.906876 - 33.1595i\omega_0 + 1.17099\omega_0^2 + i\omega_0^3 + 0.817601 \cos(\tau_c \omega_0) \\ & + 30.1827i\omega_0 \cos(\tau_c \omega_0) + 0.0812651 \cos(2\tau_c \omega_0) \\ & + 3i\omega_0 \cos(2\tau_c \omega_0) - 0.817601i \sin(\tau_c \omega_0) + 30.1827i\omega_0 \sin(\tau_c \omega_0) \\ & - 0.0812651i \sin(2\tau_c \omega_0) + 3i\omega_0 \sin(2\tau_c \omega_0) = 0 \end{aligned} \quad (11)$$

Following the ideas in Ruan and Wei (2003), we split real and imaginary parts in the previous equation and obtain two families of solutions:

$$\begin{aligned} \omega_{01} = \pm 0.0608661 \wedge \tau_{c1} = 0.027402336 + 32.859k\pi, \quad k \in \mathbb{Z} \\ \omega_{02} = \pm 7.68649 \wedge \tau_{c2} = -0.36112741 + 0.260197k\pi, \quad k \in \mathbb{Z}, \end{aligned}$$

We search for a minimum critical delay according to (6). For each group of solutions, we get:

$$\tau_{c1} = 0.0274023, \quad \tau_{c2} = 0.456302.$$

We claim that  $\tau_{c1} = 0.0274023$  is the critical delay, for which the desired stability conditions are verified. Using bifurcation diagrams, we shall demonstrate that the real parts of the characteristic values of the system remain negative in all cases for a range  $(\tau_c, \tau_c + \delta)$ . Moreover, we shall obtain a picture of the trajectories for the controlled model under this range of delays.

The corresponding bifurcation diagrams for each solution show how the equilibrium of system (10) changes for  $0 \leq \tau \leq 0.05$ . Unstable behavior is observed for small values of  $\tau$ , and stabilization occurs from  $\tau_c$  (Figs. 4, 5, 6).

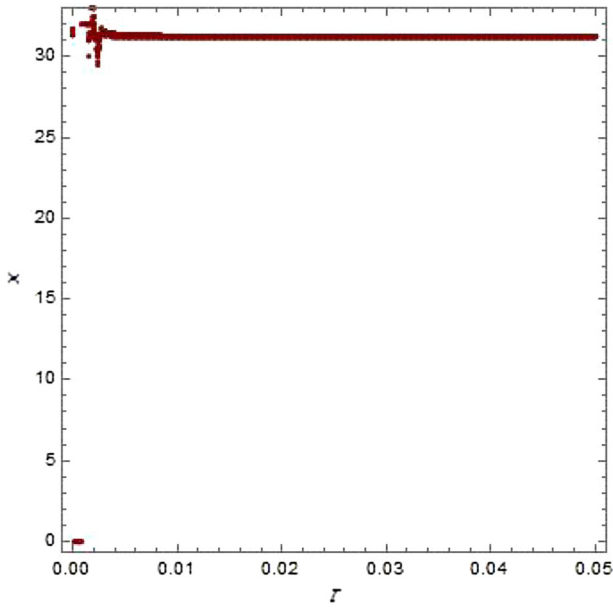


Fig. 4 Bifurcation for  $x(t)$  with  $0 < \tau < 0.05$

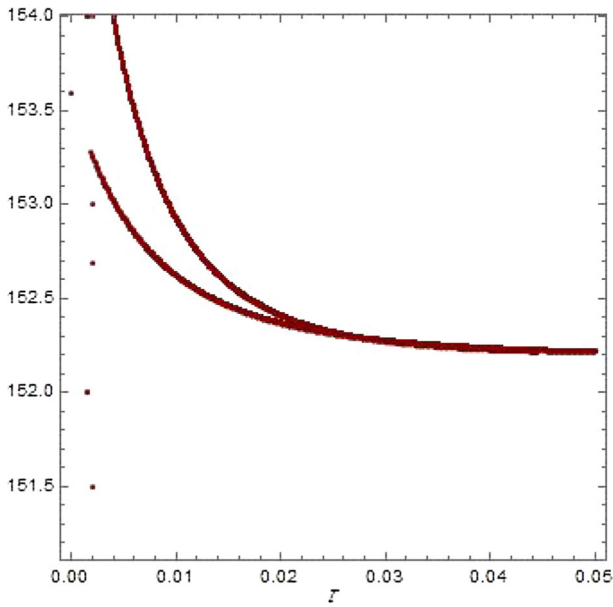


Fig. 5 Bifurcation for  $y(t)$  with  $0 < \tau < 0.05$

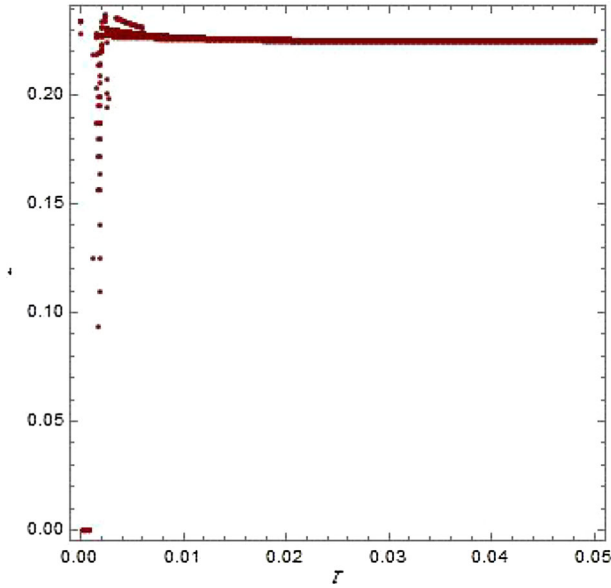


Fig. 6 Bifurcation for  $z(t)$  with  $0 < \tau < 0.05$

Next, we shall consider the evolution of each of the characteristic values as the value of  $\tau$  increases and passes through  $\tau_c$ . In all cases, we took values of  $\tau$  between 0 and 0.035 (Figs. 7, 8).

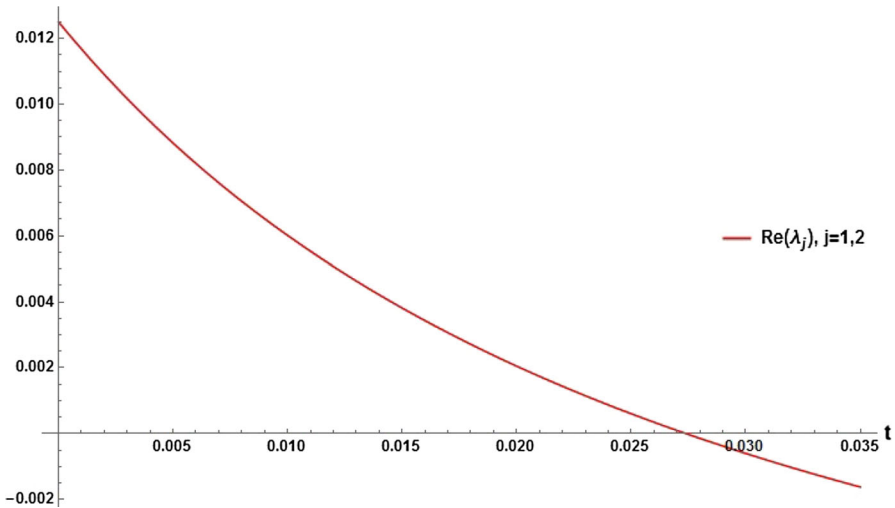


Fig. 7 Real part of  $\lambda_1$  and  $\lambda_2$

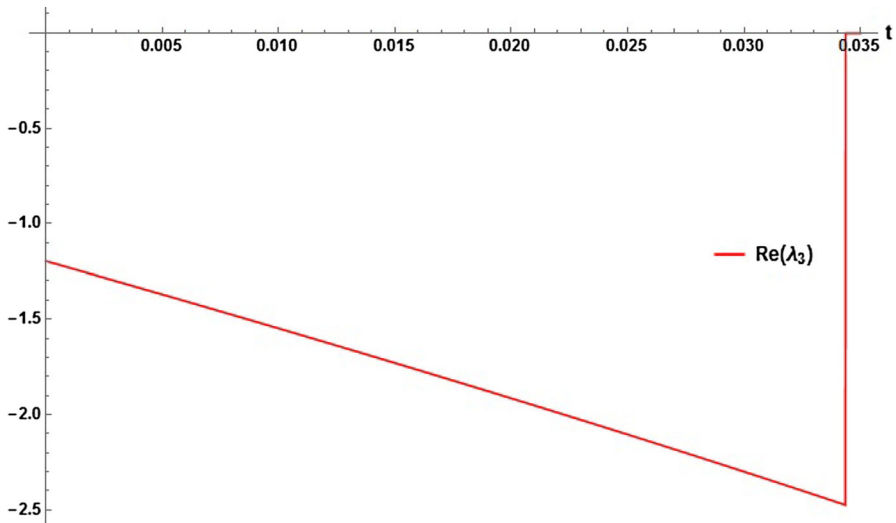


Fig. 8 Real part of  $\lambda_3$

It is observed that the real part of the characteristic values is strictly decreasing in a neighborhood of the critical delay  $\tau_c$ ; thus, there exists  $\delta > 0$  such that all the characteristic values have (strictly) negative real part when  $\tau \in (\tau_c, \tau_c + \delta)$ .

A more theoretical approach follows from the fact that, since the roots of  $P(\cdot, \tau_c)$  are simple then, by the implicit function theorem, for  $\tau$  close to  $\tau_c$  the characteristic values  $\lambda_j$  for  $j = 1, 2, 3$  can be obtained as functions of  $\tau$ . Furthermore,

$$\lambda'_j(\tau) = -\frac{\frac{\partial P}{\partial \tau}}{\frac{\partial P}{\partial \lambda}}(\lambda_j(\tau), \tau) \quad j = 1, 2, 3,$$

which yields

$$\begin{aligned} \lambda'_1(\tau_c) &= -\frac{\frac{\partial P}{\partial \tau}}{\frac{\partial P}{\partial \lambda}}(\lambda_1, \tau_c) = -0.241571 + 0.502175i \\ \lambda'_2(\tau_c) &= -\frac{\frac{\partial P}{\partial \tau}}{\frac{\partial P}{\partial \lambda}}(\lambda_2, \tau_c) = -0.241571 - 0.502175i \\ \lambda'_3(\tau_c) &= -\frac{\frac{\partial P}{\partial \tau}}{\frac{\partial P}{\partial \lambda}}(\lambda_3, \tau_c) = -38.9662. \end{aligned}$$

It is observed, in all cases, that the real part decreases and, consequently it is strictly negative over some interval  $(\tau_c, \tau_c + \delta)$ . The following figure illustrates the trajectories obtained for different values of  $\tau$  (Figs. 9, 10, 11, 12).

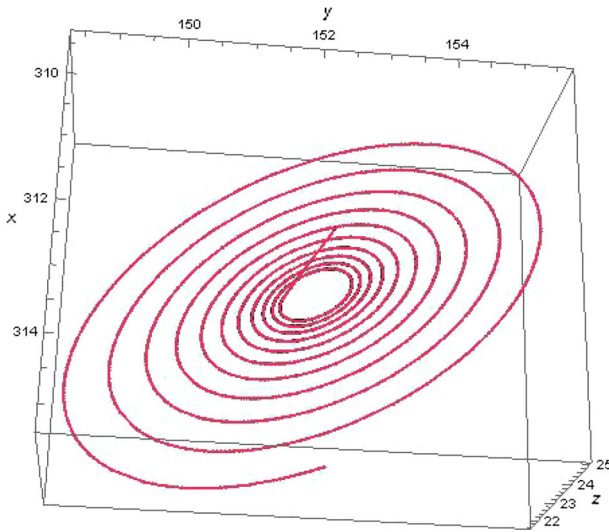


Fig. 9 Unstable trajectory for  $\tau = 0.02 < \tau_c, 0 \leq t \leq 1000$

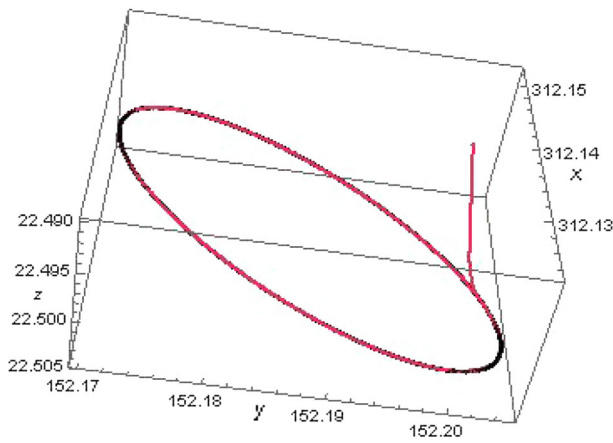


Fig. 10 Limit cycle if  $\tau = 0.0274023 \approx \tau_c, 0 \leq t \leq 2600$

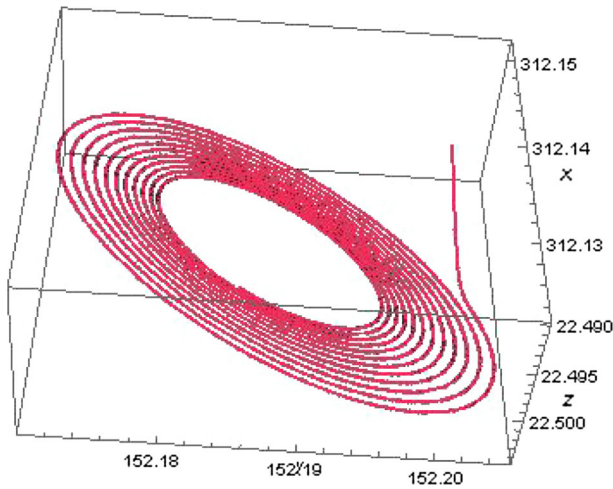


Fig. 11 Stable trajectory when  $\tau = 0.03 > \tau_c$ ,  $0 \leq t \leq 1200$

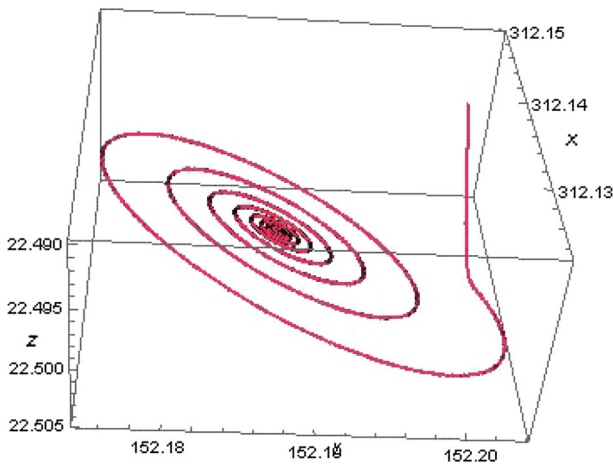


Fig. 12 Stable trajectory when  $\tau = 0.05 > \tau_c$ ,  $0 \leq t \leq 1200$ . The convergence is faster than in the case  $\tau \approx \tau_c$  (Fig. 3)

#### 4 Second Example: A Coupled Enzyme-Catalyzed System

The parameters of the model proposed in Xian et al. (1984) are the following:

$$\kappa = \frac{v}{K_{m1}} = 200 s^{-1}, \quad \sigma_1 = 40000, \quad \sigma_2 = 8 s^{-1}, \quad d = 0, \quad L_2 = 1000$$

$$q_1 = 1.5, \quad q_2 = 0,065, \quad k_a = 0.85, \quad k_b = 1.32, \quad K'_A = 1000, \quad K''_A = 0.3 \tag{12}$$

For  $K_S = 1.92$  is observed the following attractor (Fig. 13).

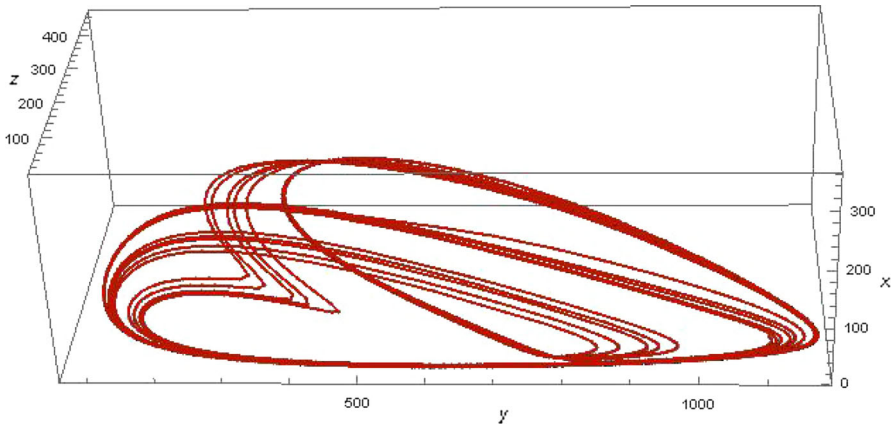


Fig. 13 Unstable path model (2) for the parameters given by (12) with  $50 < t < 200$

The resulting steady states are:

$$\begin{aligned}
 P_1 &= (x^*, y^*, z^*) = (13.2691; 351.295; 9.5835) \\
 P_2 &= (x^{**}, y^{**}, z^{**}) = (169.749; 722.885; 2.82917) \\
 P_3 &= (x^{***}, y^{***}, z^{***}) = (229.243; 607.287; 0.261201)
 \end{aligned}
 \tag{13}$$

Unlike the previous model, all the equilibria have positive coefficients, the first two of them are unstable and the latter is stable. Without loss of generality, we shall apply the method to the first equilibrium point.

### 4.1 Application of Control

As in the previous section, we shall look for a matrix  $\mathcal{K}$  such that  $J_\Phi(P_1) + \mathcal{K}$  has all its eigenvalues with negative real part. At the equilibrium  $P_1$ , the Jacobian matrix reads:

$$A := J_\Phi(P_1) = \begin{pmatrix} -34.1853 & 0.88 & 0 \\ 50.003 & -2.12582 & -48.1065 \\ 0 & 0.0523785 & 1.20692 \end{pmatrix}$$

with eigenvalues :

$$\Lambda_A = \{0.198408 \pm 1.18841i, -35.501\}$$

Hence, we may take

$$\mathcal{K} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & -7 & -3 \\ -2 & 7 & -1 \end{pmatrix}$$

since the eigenvalues of  $A + \mathcal{K}$  are:

$$\Lambda_{A+\mathcal{K}} = \{-3.88891 \pm 18.1533i, -35.3264\}$$

Thus, the controlled system reads:

$$\left\{ \begin{array}{l} \frac{dx}{dt} = 200 - 40000 \frac{x}{1000 + x + 0.3x^2} - 0.85x + 1.32 \frac{y}{1.5}, \\ \frac{dy}{dt} = 60000 \frac{x}{1000 + x + 0.3x^2} - 1.32y - 8 \frac{y(1+z)^2}{1000 + (1+z)^2} \\ \quad - 7(y(t) - y(t-\tau)) - 3(z(t) - z(t-\tau)), \\ \frac{dz}{dt} = 0.52 \frac{y(1+z)^2}{1000 + (1+z)^2} - 1.92z - 2(x(t) - x(t-\tau)) \\ \quad + 7(y(t) - y(t-\tau)) - (z(t) - z(t-\tau)), \\ x(t) = 13, \quad y(t) = 352, \quad z(t) = 9.58, \quad t < 0 \end{array} \right. \tag{14}$$

Hence, we obtain the corresponding characteristic function.

$$P(\lambda, \tau) = -\lambda^3 + 8\lambda^2 e^{-\lambda\tau} - 43.1042\lambda^2 + 660.062\lambda e^{-\lambda\tau} - 28\lambda e^{-2\lambda\tau} \\ + 13076e^{-\lambda\tau} - 951.909e^{-2\lambda\tau} - 619.427\lambda - 12175.8$$

As before, in order to find a critical  $\tau_c$ , we establish necessary conditions for the existence of a purely imaginary root of  $P$ :

$$P(\lambda, \tau_c) = 8i\omega^2 \sin(\tau_c\omega) + 660.062\omega \sin(\tau_c\omega) - 28\omega \sin(2\tau_c\omega) \\ - 13076.1i \sin(\tau_c\omega) + 951.909i \sin(2\tau_c\omega) + 660.062i\omega \cos(\tau_c\omega) \\ - 28.i\omega \cos(2\tau_c\omega) - 619.427i\omega - 8\omega^2 \cos(\tau_c\omega) + 13076.1 \cos(\tau_c\omega) \\ - 951.909 \cos(2\tau_c\omega) + i\omega^3 + 43.1042\omega^2 - 12175.8 = 0$$

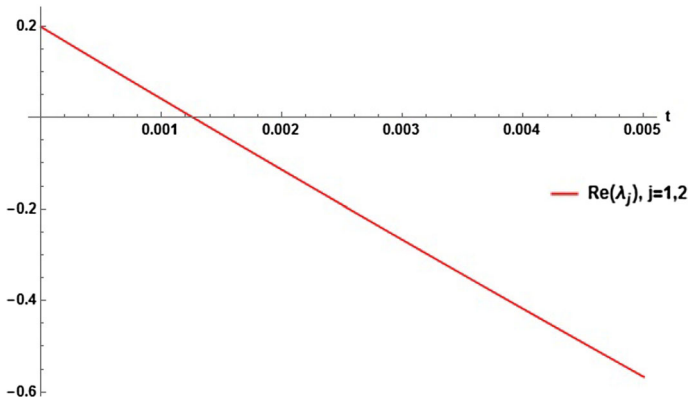
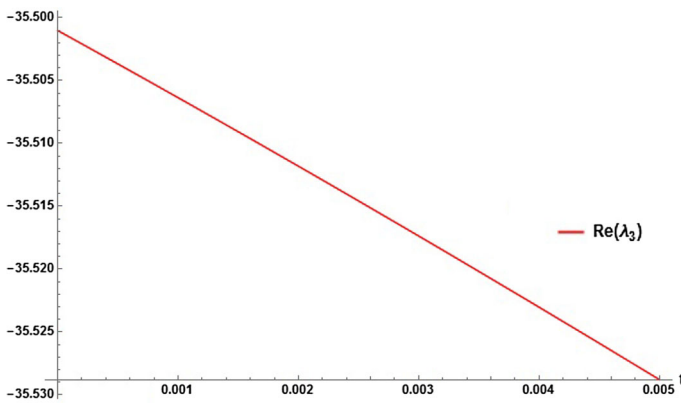
As before, two sets of solutions are obtained:

$$\omega_1 = \pm 26.9559 \quad \tau_{c1}(k) = -0.08052813 + 0.0741952k\pi \\ \omega_2 = \pm 1.19884, \quad \tau_{c2}(k) = 0.00126086 + 1.668276k\pi, \quad k \in \mathbb{Z}$$

The smallest  $\tau_c > 0$  is obtained for  $\omega_2$  with  $\tau_c = 0.00126086$ .

As before, we analyze the evolution of the characteristic values of system (14) with respect to  $\tau$  in a range containing the critical delay. The first two eigenvalues are complex conjugates:  $\lambda_2 = \bar{\lambda}_1$  (Figs. 14, 15).



Fig. 14 Real part of  $\lambda_1, \lambda_2$ Fig. 15 Real part of  $\lambda_3$ 

In all cases, we took values  $\tau \in [0; 0.005)$ . It is observed that the real part of each characteristic value decreases. We shall confirm this fact by computing the following implicit derivatives:

$$\lambda'_1(\tau_c) = -\frac{\frac{\partial P}{\partial \tau}}{\frac{\partial P}{\partial \lambda}}(\lambda_1, \tau) = -155.793 - 4.64371i$$

$$\lambda'_2(\tau_c) = -\frac{\frac{\partial P}{\partial \tau}}{\frac{\partial P}{\partial \lambda}}(\lambda_2, \tau) = -155.793 + 4.64371i$$

$$\lambda'_3(\tau_c) = -\frac{\frac{\partial P}{\partial \tau}}{\frac{\partial P}{\partial \lambda}}(\lambda_3, \tau) = -5.42631$$

The following figures show the behavior for different values of  $\tau$  (Figs. 16, 17, 18, 19).

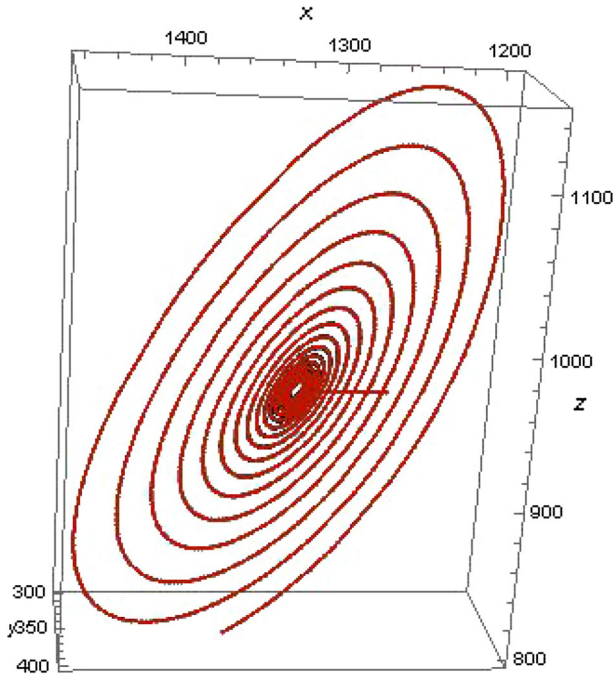


Fig. 16 Unstable path for  $\tau = 0.001 < \tau_c$  with  $0 < t < 90$

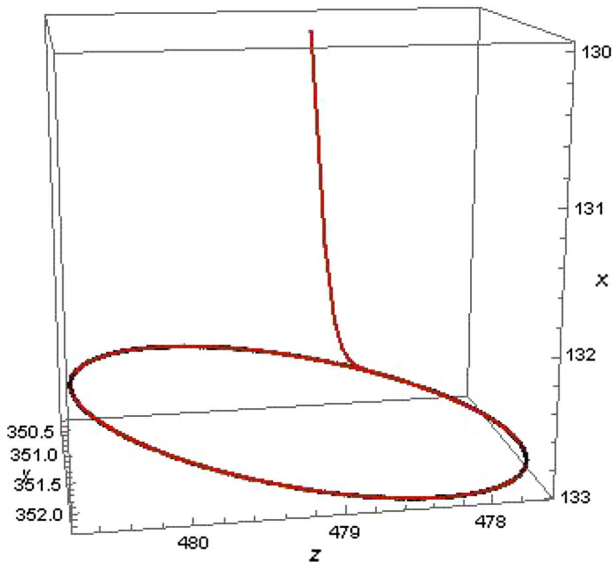
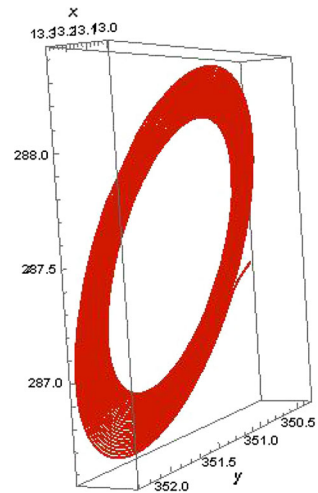
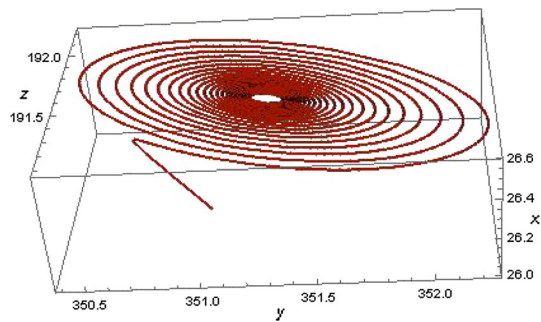


Fig. 17 Limit cycle for  $\tau = 0.00126086 \approx \tau_c$  with  $0 < t < 90$

**Fig. 18** Stable trajectory for  $\tau = 0.00128 > \tau_c$ . Slow convergence to equilibrium is observed for  $0 < t < 120$



**Fig. 19** Stable trajectory for  $\tau = 0.0014 > \tau_c$ . Faster convergence to equilibrium is observed for  $0 < t < 120$  (see Fig. 8)



## 5 Conclusions

After studying the concentrations in the controlled model starting near the equilibrium  $P_0$ , different behaviors for different delay values  $\tau > 0$  with respect to a critical delay  $\tau_c > 0$  are observed.

It is known that for  $\tau < \tau_c$  instability and even chaos is observed [the case  $\tau = 0$  already studied by Decroly and Goldbeter (1982) and Xian et al. (1984)], making unclear the fact that the concentrations behave in a predictable way or tend to a balance.

For  $\tau \approx \tau_c$ , periodic behavior is observed, in which the variables describe orbits around the equilibrium  $P_0$ . When  $\tau \in (\tau_c, \tau_c + \delta)$  for some  $\delta > 0$ , the variables (concentrations) converge to the equilibrium point  $P_0$ .

In the above-described examples, the control of Pyragas allows to synchronize the behavior of the solutions, which is in principle, aperiodic. The addition of a term that links a previous stage of concentrations  $x$ ,  $y$ ,  $z$  mathematically resolves the chaotic behavior observed in cited works. It remains to see the biochemical meaning, if any, of this control term that allows to correct the instability of the original model.

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