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Bifurcations of a one-loop circadian rhythm model

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Abstract. A four-variable circadian rhythm model is studied from the bifurcation point of view. Using the parametric representation method we give the bifurcation diagram, that is, we divide the parameter plane into regions where the number and the stability of stationary points are the same.

AMS Subject Classifications: 37N25, 37G10, 37G15

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1. Introduction

Several living beings have improved endogenous roughly-24-hour rhythm to fit the environment. These circadian rhythms exist in constant light or darkness and are relatively independent of temperature. Many models have been developed to investigate this phenomenon. One of these models is the mixed feedback loop (MFL) model introduced by François and Hakim [1]. The MFL model can be applied to describe the circadian rhythm of *Neurospora Crassa* [2]. In the present article we study the MFL model from the bifurcation point of view. Here we justify the results obtained by the simplification of the MFL [1] and consider the case not studied in [2]. For this purpose the parametric representation method (PRM) is used. This is a useful tool if the parameter dependence of the system is simpler than the dependence on the state variables. In Section 2 the main theorems of the PRM are summarized. The MFL [1] model is also introduced here. In Section 3 the discriminant curve is determined in the plane of two control parameters, that is, we divide the parameter plane into regions, where the number of stationary points is constant. In Section 4 we determine the region, where the stability of the stationary points is the same, that is, the H-curve is given. In Section 5 we construct the bifurcation diagrams for different values of parameters.

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2. The method and the model

In this section we give a summary of the PRM and refer to [4, 5] for details. Let us consider the equation

$$\dot{X}(t) = \mathcal{F}(X(t), u), \tag{2.1}$$

where $\mathcal{F} : \mathbb{R}^n \times \mathbb{R}^2 \to \mathbb{R}^n$ is a differentiable function, $X \in \mathbb{R}^n$ is the vector of state variables and $u \in \mathbb{R}^2$ is the vector of parameters.

Let us suppose that the system of equations $\mathcal{F}(X, u) = 0$ giving the stationary points can be reduced to a single equation. We assume that the control parameters u_1 and u_2 are involved linearly in the right-hand side of the reduced equation. Hence we can write the reduced equation into the form

$$f(x, u_1, u_2) = f_0(x) + f_1(x)u_1 + f_2(x)u_2 = 0. \tag{2.2}$$

The implicit function theorem states that the number of solutions of equation (2.2) can change if $f(x, u_1, u_2) = 0$ and $f'(x, u_1, u_2) = 0$, where prime denotes the differentiation with respect to x. We introduce the saddle-node bifurcation set S : $S = \{u \in \mathbb{R}^2 : \exists x \in \mathbb{R},\ f(x, u_1, u_2) = f'(x, u_1, u_2) = 0\}$, which can be given by the PRM as a curve parameterized by x. Hence S can be easily constructed and the solutions belonging to a given parameter pair can be determined by a simple geometric algorithm.

Let us solve the system of equations $f(x, u_1, u_2) = 0$ and $f'(x, u_1, u_2) = 0$ for (u_1, u_2). This solution defines the D-curve: $D : \mathbb{R} \to \mathbb{R}^2$, $x \mapsto (D_1(x), D_2(x))$, $D_1(x) := u_1$, $D_2(x) := u_2$. Using this curve we can determine the number and the value of the solutions x of (2.2), because the following lemmas hold [4].

Lemma 2.1. (Tangential property) *The number $x \in \mathbb{R}$ is a solution of equation (2.2) for the parameter values u_1 and u_2 if and only if a tangent line can be drawn from the point (u_1, u_2) to the D-curve at the point $D(x)$.*

Lemma 2.2. (Convexity property) *The D-curve consists of convex arcs that join with common tangent or asymptote. The convexity of the separate arcs means that they lie on one side of the tangent line belonging to any point of the arc.*

Lemma 2.3. (Cusp point) *Let $b(x) = f_0''(x) + f_1''(x)D_1(x) + f_2''(x)D_2(x)$. If $b(x)$ changes its sign at x_0, then the D-curve has a cusp point at x_0. (The formal definition can be found in [4].)*

The D-curve can be plotted in the $u_1 - u_2$ plane. Let $(u_1^\star, u_2^\star)$ be a parameter pair that is moved in the parameter plane. If $(u_1^\star, u_2^\star)$ crosses the D-curve, the number of stationary points of (2.2) changes by two (see Figure 1). The following lemma and its proof can be found in [3].

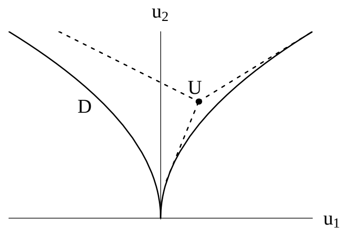

Figure 1: Schematic figure of a D-curve (solid line) with a cusp point at the origin and tangents drawn from point $U(u_1^\star, u_2^\star)$ (dashed lines).

Lemma 2.4. *Let J be the Jacobian of $\dot{X}(t) = \mathcal{F}(X(t), u)$, where $\mathcal{F} : \mathbb{R}^4 \times \mathbb{R}^k \to \mathbb{R}^4$ is a differentiable function, $X \in \mathbb{R}^4$ is the vector of state variables and $u \in \mathbb{R}^k$ is the vector of parameters. Let $P(\cdot)$ denote the characteristic polynomial of J, $P(\lambda) = c_0 + c_1\lambda + c_2\lambda^2 + c_3\lambda^3 + \lambda^4$. The matrix J has two pure imaginary eigenvalues if and only if*

$$c_0 c_3^2 - c_1 c_2 c_3 + c_1^2 = 0 \quad \textit{and} \quad c_1 c_3 > 0. \tag{2.3}$$

We can investigate the stability of a stationary point using Lemma 2.4. We define the H-curve by equations (2.2) and (2.3). The H-curve can be plotted in the $u_1 - u_2$ plane. Let $(u_1^\star, u_2^\star)$ be a parameter pair that is moved in the $u_1 - u_2$ plane. If $(u_1^\star, u_2^\star)$ crosses the H-curve, the stability of the stationary points changes.

In what follows we introduce the mixed feedback loop model. The MFL consist of two proteins (A and B) coded by their genes (g_a and g). We assume that g_a is constant and A supposed to be produced at a given rate. Variable r denotes the transcripts rate for g. Introducing dimensionless variables we have four equations describing the MFL [1]:

$$\dot{g} = \tilde{\theta}\left[(1-g) - g\frac{A}{A_0}\right] \tag{2.4}$$

$$\dot{r} = \rho_0 g + \rho_1(1-g) - r \tag{2.5}$$

$$\dot{B} = \frac{1}{\delta}(r - AB) - d_b B \tag{2.6}$$

$$\dot{A} = \frac{1}{\delta}(1 - AB) + \mu\tilde{\theta}\left[(1-g) - g\frac{A}{A_0}\right] - d_a A. \tag{2.7}$$

Transforming of the equations into dimensionless form, the parameters lose their biological meaning, hence we only mention that parameters $\tilde{\theta}$, A_0, ρ_0, ρ_1, d_a, d_b, δ, μ are positive constants, and we refer to [1] for the detailed description. Equation (2.4)–(2.7) can model the circadian rhythm of *Neurospora Crassa*. In this case, A stands for the protein frequency (FRQ), and B for the white-collar complex (WCC) [2].

3. The D-curve

Let us determine the stationary points of the system (2.4)–(2.7). From equation (2.4) we have g in terms of A:

$$g = A_0(A + A_0)^{-1}. \tag{3.1}$$

Using (3.1) from (2.5) and (2.6) we have

$$r = (\rho_0 A_0 + \rho_1 A)(A + A_0)^{-1},\ B = (\rho_0 A_0 + \rho_1 A)((A + A_0)(A + \delta d_b))^{-1}. \tag{3.2}$$

Let us substitute (3.1)-(3.2) into (2.7). Introducing

$$f_0 = \delta d_a A - 1 \tag{3.3}$$
$$f_1 = A^2((A + A_0)(A + \delta d_b))^{-1} \tag{3.4}$$
$$f_2 = A_0 A((A + A_0)(A + \delta d_b))^{-1} \tag{3.5}$$

we reduced the system of equations for the stationary points to a single equation of the form of (2.2)

$$0 = f_0 + \rho_1 f_1 + \rho_0 f_2 = f(A, \rho_1, \rho_0). \tag{3.6}$$

Since the state variables denote concentrations in (2.4)–(2.7), we investigate stationary points only with positive coordinates. The number of such stationary points is equal to the number of positive solutions of (3.6). If A is a positive solution of (3.6), we can see from (3.1)–(3.2) that g, r, B are positive as well. In what follows we consider A as a positive real number. Now we solve the $f(A, \rho_1, \rho_0) = 0$ and $f'(A, \rho_1, \rho_0) = 0$ system of equations to have ρ_1 and ρ_0. The solution gives us the parametric form of the D-curve:

$$\rho_1 = 1 - 2d_a\delta A - \frac{A_0 d_b \delta}{A^2} - A_0 d_a \delta - d_a d_b \delta^2 \tag{3.7}$$
$$\rho_0 = 1 + \frac{A^2 d_a \delta + d_b \delta}{A_0} + \frac{2 d_b \delta}{A} - d_a d_b \delta^2. \tag{3.8}$$

Using *Mathematica* we plotted the D-curve numerically in the $\rho_1 - \rho_0$ plane (see Figure 2). The other parameters were fixed at the values given in [1] as follows:

$$\delta = 0.003,\ d_a = d_b = 0.33,\ A_0 = 4,\ \mu = 0.31,\ \tilde{\theta} = 1.33. \tag{3.9}$$

Our numerical investigation shows that the value of the parameters in (3.9) does not change the D-curve qualitatively. However, if δ is large enough then there is no part of the D-curve lying in the positive quadrant (see Figure 3). More precisely the following lemmas hold.

Lemma 3.1. *The D-curve of the system (2.4)–(2.7) has a cusp point at* $A = \sqrt[3]{\frac{A_0 d_b}{d_a}}$.

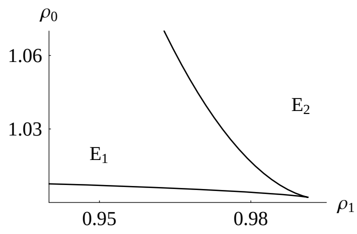

Figure 2: The D-curve

Proof: In order to prove the existence of a cusp point we show, that $b(A) = f_0''(A) + f_1''(A)\rho_1(A) + f_2''(A)\rho_0(A)$ changes its sign at $A = A^c = \sqrt[3]{A_0 d_b d_a^{-1}}$ (Lemma 2.3). Using (3.3)–(3.5) straightforward calculation shows, that

$$b(A) = -\frac{2\delta(A_0 d_b - A^3 d_a)}{A^2(A + A_0)(A + \delta d_b)}.$$

It is easy to see that if $A < A^c$ then $b(A) < 0$, and if $A > A^c$ then $b(A) > 0$. $\square$

Lemma 3.2. *If $\rho_1(A^c) > 0$, then the D-curve divides the positive quadrant into two regions, see Figure 2.*

- *If $(\rho_1^\star, \rho_0^\star) \in E_1$, then (2.4)–(2.7) with parameters $\rho_1^\star$, $\rho_0^\star$ has three stationary points.*
- *If $(\rho_1^\star, \rho_0^\star) \in E_2$, then (2.4)–(2.7) with parameters $\rho_1^\star$, $\rho_0^\star$ has one stationary point.*

Proof: Let us notice, that $\rho_1 < \rho_0$ for all $A \in \mathbb{R}^+$. $\rho_1(A^c) > 0$ thus $\rho_0(A^c) > 0$, hence the cusp point is in the positive quadrant. We are finishing our proof by using the tangential property in Lemma 2.1 and the convexity property in Lemma 2.2 (see Figure 1). $\square$

Lemma 3.3. *If $\rho_0(A^c) < 0$, then the system (2.4)–(2.7) has one stationary point.*

Proof: $\rho_0(A^c) < 0$ implies $\rho_1(A^c) < 0$. The cusp point lies in the 3rd quadrant, hence the positive quadrant is a proper subset of region E_1 (see Figure 3). $\square$

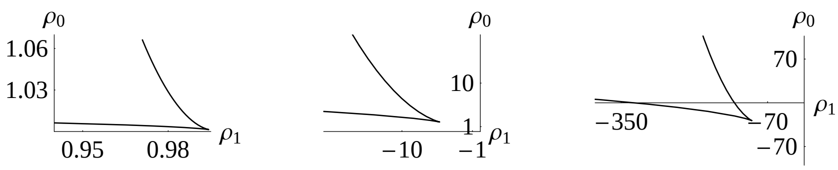

Figure 3: The D-curve for $\delta = 0.002$, $\delta = 2$ and $\delta = 20$, respectively.

4. The H-curve

The Jacobian of the system (2.4)–(2.7) can be written as follows:

$$J = \begin{pmatrix} -\alpha & 0 & 0 & -\beta \\ \rho_0 - \rho_1 & -1 & 0 & 0 \\ 0 & \epsilon & -\kappa & -B\epsilon \\ -\mu\alpha & 0 & -A\epsilon & -\gamma \end{pmatrix},$$

where $\alpha = \tilde{\theta}\left(1 + \frac{A}{A_0}\right)$, $\beta = \frac{\tilde{\theta} g}{A_0}$, $\epsilon = \frac{1}{\delta}$, $\gamma = B\epsilon + \mu\beta + d_a$, $\kappa = A\epsilon + d_b$. The characteristic polynomial $P(\cdot)$ of J is: $P(\lambda) = \lambda^4 - \mathrm{Tr}J\lambda^3 + C_2\lambda^2 - C_1\lambda + \mathrm{Det}J$, where $\mathrm{Tr}J$ and $\mathrm{Det}J$ denotes the trace and the determinant of J, respectively, and $C_2 = \alpha(1 - \beta\mu + \gamma + \kappa) + \kappa + \gamma + \gamma\kappa - AB\epsilon^2$, $C_1 = \sum_{i=1}^{4} J_{ii}$, where J_{ii} is the corresponding minor of J.

As we have seen in Section 2, we define the H-curve by equations (2.3) and (3.6) in the following way: $H : \mathbb{R} \to \mathbb{R}^2$, $\mathbb{R}^+ \ni A \mapsto (H_1(A), H_2(A))$. That is, the parametric form of the H-curve is $H_1(A) := \rho_1$, $H_2(A) := \rho_0$, where ρ_1, ρ_0 are determined by the system

$$\begin{aligned} 0 &= f_0 + \rho_1 f_1 + \rho_0 f_2 \\ 0 &= \mathrm{Det}J \cdot (\mathrm{Tr}J)^2 - C_1 \cdot C_2 \cdot \mathrm{Tr}J + {C_1}^2, \quad 0 < C_1 \cdot \mathrm{Tr}J. \end{aligned}$$

We solved this system of equations numerically and plotted the H-curve in the $\rho_1 - \rho_0$ parameter plane using *Mathematica*. The other parameters were fixed at the values given in (3.9). See Figure 4. We found that if $(\rho_1, \rho_0) \in E_2$, then the stationary point is stable. If $(\rho_1, \rho_0) \in E_3$, then the system (2.4)–(2.7) has one unstable stationary point and a stable limit cycle. Our numerical investigation shows that the qualitative shape of the H-curve does not change when the parameters in (3.9) vary.

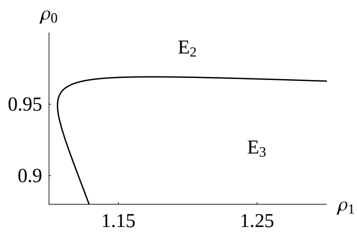

Figure 4: The H-curve for $\delta = 0.003$

5. Conclusion

In this section we give the bifurcation diagram of the MFL model for $\delta = 0.003$ and $\delta = 20$, which sum up our results shown in Section 3 and 4. See Figure 5. We found, that if δ is large, then the H-curve is in the 4th quadrant, hence there are no such ρ_1, ρ_0 parameters in the positive quadrant where a stable limit cycle exists.

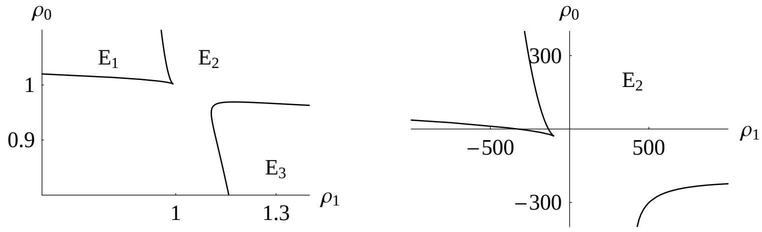

Figure 5: The bifurcation diagrams for $\delta = 0.003$ and $\delta = 20$. For the description of E_1, E_2 and E_3, see Section 3 and 4.

In this article the mixed feedback loop model is investigated from the bifurcation point of view. We verified the results of [1] and studied the case when δ is large. The bifurcation diagrams for different values of parameter δ are also given.

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