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Comparison of the bifurcation curves of a two-variable and a three-variable circadian rhythm model

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Abstract

Two dynamical systems describing the circadian fluctuation of two proteins (PER and TIM) in cells are compared. A simplified model with two variables has already been investigated. Detailed study of the possible bifurcation has been carried out. Periodic solutions of the differential equations with 24-h period have been obtained numerically. Here the general, more realistic model having three variables is investigated. The possible phase portraits and local bifurcations are studied in detail. The saddle-node and Hopf-bifurcation curves are determined in the plane of two parameters by using the parametric representation method. Using these curves the number and the type of the stationary points can be determined. The relation of the two bifurcation curves and the Takens–Bogdanov bifurcation points are also studied. The bifurcation curves are compared to those obtained for the simplified two-variable system.
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1. Introduction

Several organisms show circadian rhythms of physiology and behavior. It is entrained to the 24-h cycle of light and darkness, but it persists under constant conditions. Later discoveries show that there is an internal biological clock at molecular level. Two proteins (PER and TIM) are thought to be responsible for this mechanism.

A model for this phenomenon was introduced by [1]. Tyson et al. [2] introduced a new positive feedback loop into the original model, which consist of six state variables. The six variables are concentrations of *per* and *tim* mRNAs, PER and TIM monomers and PER/TIM dimers in the cytoplasm and nucleus. Similar time courses appear in the concentration of PER and TIM and the concentration of their mRNAs. The concentration of dimer in the cytoplasm and in the nucleus are in rapid equilibrium, thus the six-variable model

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can be reduced to three differential equations in which the state variables are the concentration of mRNA (M), the protein (P_1) and the dimer (P_2) [2]:

$$\dot{M} = \frac{v_m}{1 + \left(\frac{P_2}{P_c}\right)^2} - k_m M, \tag{1}$$

$$\dot{P}_1 = v_p M - \frac{k_1 P_1}{J_p + P_1 + r P_2} - k_3 P_1 - 2k_a P_1^2 + 2k_d P_2, \tag{2}$$

$$\dot{P}_2 = k_a P_1^2 - k_d P_2 - \frac{k_2 P_2}{J_p + P_1 + r P_2} - k_3 P_2. \tag{3}$$

Eq. (1) includes the inhibition of the mRNA transcription by the dimer, and we have the degradation of the mRNA. The reaction constants $k_1,\ k_2,\ k_3$ are related to the phosphorylation and the reaction constants $k_a,\ k_d$ belong to the dimerization process. The Michaelis–Menten kinetics is used for the DBT (kinase encoded by the double-time gene) catalyzed phosphorylation process for both monomer and dimer. The ratio of enzyme substrate dissociation constant is r.

Supposing that the dimerization reaction is fast, the monomer (P_1) and the dimer (P_2) are in equilibrium with each other, that is $P_2 = KP_1^2$. With notations

$$p = P_1 + 2P_2, \quad m = M, \qquad K = k_a/k_d, \quad r = 2$$

and using the approximation $k_1 \approx k_1 - k_2$ the system can be reduced to the following two differential equations [2,3]:

$$\dot{m} = \hat{h}_1(p) - k_m m, \tag{4}$$

$$\dot{p} = v_p m - k_1 \hat{h}_2(p) - \hat{h}_3(p), \tag{5}$$

where m and p are the concentrations of mRNA and protein, respectively; $\hat{h}_1(p),\ \hat{h}_2(p),\ \hat{h}_3(p)$ are functions of p, as defined in [3].

This two-variable model was studied by Simon and Volford in detail in [3]. They made systematic numerical investigations to determine the saddle-node and Hopf-bifurcation curves, and using these the number and the type of the stationary points. The period of the limit cycles for different values of parameters was studied there as well. They also determined the global bifurcation diagram, which is a system of bifurcation curves that divides the parameter plane into regions according to topological equivalence of global phase portraits.

Our system (1)–(3) consists of three variables and 11 parameters. To investigate the model we will apply the parametric representation method (PRM) [4,5], hence two appropriate parameters, v_p and k_1 – involved linearly – will be used as control parameters, the other nine will be fixed. The values of the parameters are taken from [2]. We will give the D- and H-curves in parametric form by the PRM [4,5] in Sections 2 and 3. We will also determine the qualitative shape of these curves and determine how the curves change if the parameters are varied. We also discuss the connection between these curves, especially the common points of the two curves the Takens–Bogdanov bifurcation points will be determined. In Section 4 we study the number and type of the stationary points. In Section 5 the two and the three-variable model are compared from the bifurcation point of view.

2. The *D*-curve

Let us determine the stationary points of the system (1)–(3). From Eq. (3) we can get the following quadratic equation for P_2

$$r(k_d + k_3)P_2^2 + h_0(P_1)P_2 - (J_p + P_1)k_a P_1^2 = 0, \tag{6}$$

where

$$h_0(P_1) = -k_a r P_1^2 + (k_d + k_3)(J_p + P_1) + k_2.$$

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