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ANALYSIS OF THE BIFURCATION BEHAVIOR OF SIMPLE BIOLOGICAL PRODUCTION-DEGRADATION SYSTEM WITH SWITCHINGS

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ABSTRACT

Among wide range of possible applications of switching systems, modelling of biological systems seems to be especially justified. Dynamics of single protein can be modelled by one-dimensional differential equation with a switchng in the model parameter values, which are related to differences in protein production rates. We propose a one-dimensional model of protein level containing production and degradation. The protein production rate is dependent on the protein level. Different values of the degradation rate result in differences in the existence and localization of the steady points. Different types of the response are observed.

INTRODUCTION

Hybrid systems are getting increasing interest due to its capability to exhibit simultaneously several kinds of dynamic behaviour. There are plenty of different applications of such systems, *e.g.* automotive industry, air traffic control and switching power converters [1]. In our work we focus on the switched systems, which combine a set of continuous-time subsystems and a rule that defines switchings between them. Switching in the parameter value induces rapid change in the system dynamics and consequently even relatively simple model can properly reconstruct dynamics of a complicate system [2].

Modelling of the biological processes is very challenging because of their high complexity. Generally all intracellular processes are regulated by many different feedback loops, both types: positive and negative. Moreover the rates of the processes inside a cell usually depend on the concentration of the regulatory molecules called enzymes. Such regulation results in highly nonlinear dynamics such as Michaelis-Menten or Hill dynamics. High rate of the process is a consequence of its rapid activation and saturation due to biologic limitations [3]. The most popular approach in systems biology is application of highly nonlinear functions to model sigmoid rate of the processes [4,5]. Nevertheless there where attempts to use the hybrid systems for this group of models. The piece-wise linear differential equation (PLDE) models are based on the assumption that for a specified state of the system reactions rate are in the steady state. When the state of the system is changed, reaction rates can be switched and the system will go to the new steady state. Consequently switching of the reaction rates may be modelled by the step change of the model

parameters. Step changes of the parameter values are dependent only on the state of the system, precisely on proteins levels [6, 7]. Comparison of the nonlinear and piece-wise linear model for biological system shows that the essential dynamic is similar [8].

MODEL

Generally, variables in biological model stand for proteins and their dynamics are described by the processes like production and degradation. Proteins production is a multi-stage process. First, the corresponding gene has to be activated by attaching transcription factors to its promoter region, then mRNA polymerase may attach. As a result mRNA is produced and then can be used as a matrix for protein production. Gene inactivation may be spontaneous or caused by other proteins. This means that the protein production rate usually depends on the system state. Proper activity of the biological system is assured by the self-regulation which usually requires additional proteins. Examples of the positive and negative regulation may be found in our previous work [4]. Negative feedback couples protein NFκB and IκBα because the first one is a transcription factor of the second, which in turn decouples its own transcription factor from the promoter region. Positive regulation is present in the ATM-p53 relation in which p53 is a transcription factor of ATM and ATM activate p53, enhancing its ability to attach to the promoter region.

To investigate the possibility of the bifurcation behaviour in the simple production-degradation system with switching we propose one-dimensional piece-wise linear differential equation model of protein level. To simplify the model we omit mRNA production/degradation processes assuming their constant rate and gene activation/deactivation, taking into account that the changes in gene activity are transmitted through mRNA level to the protein production rate and are reflected by its changes. This simplification results in highly nonlinear dependency between transcription factor level and protein production rate which we model by the switch of the production rate. As a result, the threshold value for the variable $x = \theta$ divides the system into two subsystem with different values of the protein production rate. Additionally we assume that the degradation rate does not depend on the system state.

The general model equation is presented below:

$$\frac{d\,x}{d\,t} = \begin{cases} b_1 - a \cdot x(t) & if \quad x < \theta \\ b_2 - a \cdot x(t) & if \quad x \geq \theta \end{cases} \tag{1}$$

where x is the protein level, a is the degradation rate and b_1 and b_2 are production rates, where all parameter values are positive ($a, b_1, b_2 > 0$). For both regions we can examine the local stability by comparison the derivatives to zero. In this system steady points can be calculated for both region and the appropriate formulas are as follows:

$$x_1 = \frac{b_1}{a} \qquad if \quad x < \theta \tag{2}$$

$$x_2 = \frac{b_2}{a} \qquad if \quad x \geq \theta \tag{3}$$

If the steady point is not included in the specified region, the system will reach the threshold and the switch will occur. Depending on the parameters b_1, b_2, a and the threshold value θ the steady points can exist in different localizations and thus different behaviour will be observed.

There are two possible cases for the proposed system, which should be considered. The first case is when $b_1 < b_2$, which means that in a system with low protein level, protein production rate is smaller. After increase of the protein concentration, the production rate is also increased. Such case can be related to proteins which induce its own production and such simple dependency can refer to positive autoregulation as for example between ATM and p53 [4]. The second case occurs when $b_1 > b_2$. In such system high protein level induces low protein production, so after increase

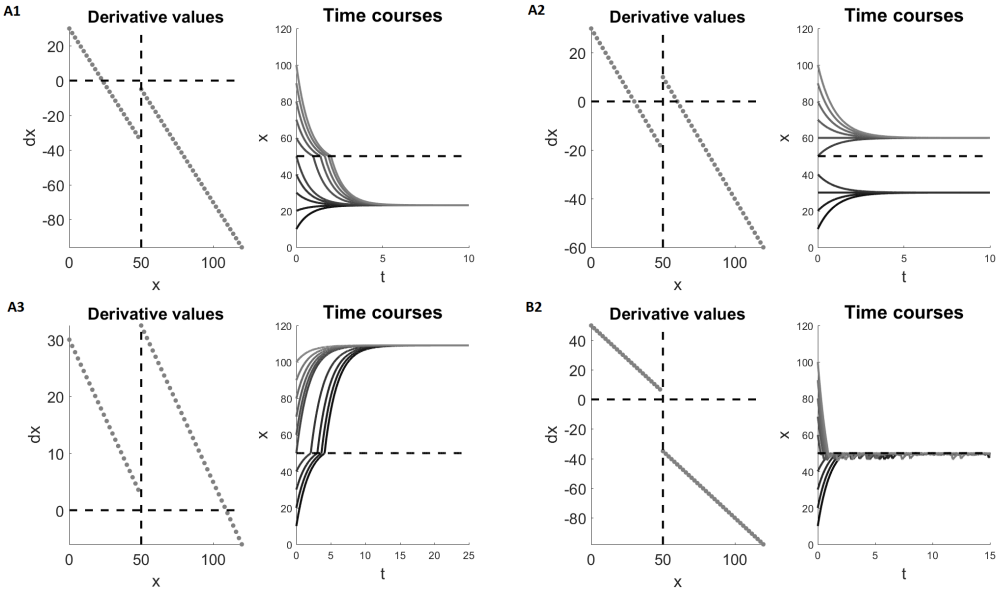

Figure 1. Derivative values and time courses in different cases. A1: $\mathbf{b_1/a < b_2/a < \theta}$ A2: $\mathbf{b_1/a < \theta < b_2/a}$. A3: $\mathbf{\theta < b_1/a < b_2/a}$. B2: $\mathbf{b_2/a < \theta < b_1/a}$.

of protein concentration, the rate of its production is decreased, that can be referred to the negative autoregulation as for example between NF-κB and IκBα [4].

RESULTS

In our model a rate of production depends on the system state and can change between b_1 and b_2. We examine how the change of the degradation parameter a effects the system response for assumed threshold value θ. In our analysis we take into account two possible cases. All the parameter values are collected in the table 1.

Case A: $\mathbf{b_1 < b_2}$ In the case with parameter b_1 smaller than b_2, three different types of response can be observed for different values of the parameter a.

Subcase 1: $\mathbf{b_1/a < b_2/a < \theta}$: For big values of the parameter a we have only one steady point in the system in the region where $x < \theta$. Time derivative of x is equal to 0 only for the steady point x_1 (Fig. 1 A1 left). There is a step change of the derivative due to the switch in the parameter values. Trajectories, that start from initial conditions from both regions, lead to the steady point in the region $x < \theta$ (Fig. 1 A1 right).

Subcase 2: $\mathbf{b_1/a < \theta < b_2/a}$: For the parameter a included in the range defined by the production parameters: $a \in (b_1/\theta, b_2/\theta)$ we can observe two steady points, one in each region. In both region there are points where the derivative is equal to 0 (Fig. 1 A2 left). All trajectories started in specific domain go to the steady point in that domain. Figure 1 A2 right presents the time courses of such system for different initial conditions.

Subcase 3: $\mathbf{\theta < b_1/a < b_2/a}$: For the parameter a smaller than b_1/θ and b_2/θ similarly as in the first case we have only one steady point, which is localized in the region with $x > \theta$ (Fig. 1 A3 left). The exemplary trajectories are presented on the Fig. 1 A3.

Case B: $\mathbf{b_1 > b_2}$: In the second case the values of the protein production are higher in the system with smaller protein level, which can be denoted by $b_1 > b_2$. Similarly to the previous case, depending on the value of the parameter a, which stands for protein degradation, we can observe three different types of the system response.

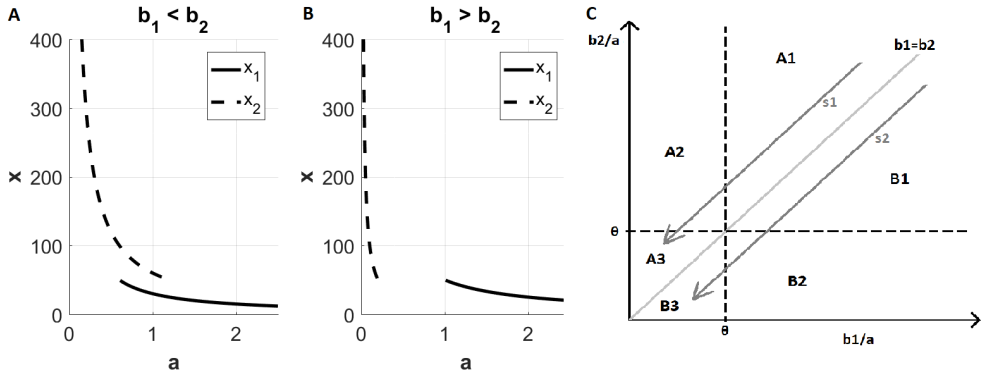

Figure 2. A: Localization of the steady points for $b_1 < b_2$. B: Localization of the steady points in for $b_1 > b_2$. C: Bifurcation diagram for different values of parameter a.

Subcase 1: $\mathbf{b_2/a < b_1/a < \theta}$: For the parameter a greater than b_2/θ and consequently b_1/θ a single steady point exists in the system in the region with $x < \theta$. Thus it is similar to Fig. 1 A1 left. The possible trajectories are similar to Fig. 1 A3.

Subcase 2: $\mathbf{b_2/a < \theta < b_1/a}$: For the parameter a smaller than b_1/θ but greater than b_2/θ there are no steady points. The reason is that for each domain the localization of the prospective steady point is included in the opposite region. As a result, trajectories in each domain aim to the threshold but right after the switch they aim to the previous region and so on. As one can notice on Fig. 1 B2 left there are no points for the derivative equal to 0. On the time course we see sliding on the border as a result of numerical calculations (Fig. 1 B2 right).

Subcase 3: $\mathbf{\theta < b_2/a < b_1/a}$: With an decrease of the value of the parameter a, the steady point from the region with $x < \theta$ is moved to the region with $x > \theta$. For the parameter a value $a \in (b_1/\theta, \inf)$ only one steady point exists in the region $x > \theta$. The diagrams of derivative localization and time courses of such system are similar to the case with $\theta < b_1/a < b_2/a$ (see Fig. 1 A3).

Bifurcation diagram

Increase of the parameter a has different effect on the system response depending on the ratio between parameters b_1 and b_2. In the case when $b_1 < b_2$, for the small value of the bifurcation parameter a, we can observe single steady point with high value of x so it is in the domain $x > \theta$ (see Fig. 2A). With the increasing a value, localization of the steady point moves to smaller x. With further increase of a bifurcation occurs and the second steady point appears, one in the same domain and second in the domain $x < \theta$. When a increases, localization of this points moves to smaller x and second bifurcation point is reached. Steady point in domain $x > \theta$ disappears so only one steady point exists in the domain $x < \theta$.

In the case when $b_1 > b_2$, for the small value of the bifurcation parameter a we can, similarly to the previous case, observe single steady point in the domain $x > \theta$ (see Fig. 2B). As a increases, localization of the steady point moves to smaller x until bifurcation point is reached and steady point disappears. Then we have a region of a in where all trajectories are sliding on the threshold. With further increase of a second bifurcation point is reached in which another steady point appears, but in the domain $x < \theta$.

On the figure 2C we present, how the proportion between parameter values influences the results - the type of response. We have marked 6 regions in relation to the cases described in the sections A and B, however the response in the section A1 and B1 and in section A3 and B3 are particularly the same. The only difference is proportion between production parameters b_1 and b_2. In the section A2 two steady points exist, and in the section B2 we do not have any stable steady

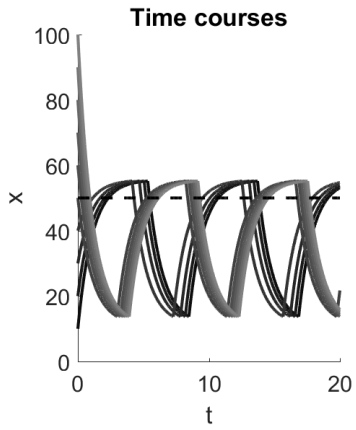

Figure 3. Time courses of the sample trajectories in the system B2 with delay.

Parameter	A ($b_1 < b_2$)	B ($b_1 > b_2$)
a (1)	1.3	1.5
a (2)	1	0.9
a (3)	0.55	0.18
b_1	30	50
b_2	60	10
θ	50	50
h	-	3

Table 1. Values of parameters

points. With $b_1 < b_2$ increase of the parameter a induces moving the system from the region A1, through the region A2 to the region A3 (Fig. 2C arrow s_1). In the opposite case ($b_1 > b_2$), the increase of the parameter a induces change of the system response from one steady point, by region without steady point to region with one steady point (Fig. 2C arrow s_2). When the parameters b_1 and b_2 are equal, the switch does not exist and any bifurcation cannot be observed.

Influence of the delay in the switching on the system response

In the real biological systems instant switchings dependent on the protein number are not possible. For example increase of the protein production requires nuclear import of the transcription factor, then its attachment to the promoter region, transcription and translation of the final protein, which takes time. Similarly after gene deactivation there still exist previously produced mRNAs, which constitute a matrix for new proteins and as long as they do not degrade (*e.g.* spontaneously), the protein is produced. This may have the significant impact on the results, especially in the case when without delays we do not have steady point. To consider this case we modify our model adding the delay h to the production terms. The new model is presented below:

$$\frac{d\,x}{d\,t} = \begin{cases} b_1 - a \cdot x(t) & if \quad x(t-h) < \theta \\ b_2 - a \cdot x(t) & if \quad x(t-h) \geq \theta \end{cases} \tag{4}$$

As expected received results differ significantly only in the case $b_2/a < \theta < b_1/a$. There still is no steady point in the system but because of the delay in the production rates, after crossing threshold, the trajectories have enough impact to move inside the new domain before they will be stopped and turned back. The interesting finding is that the trajectories starting in the domain $x > \theta$ have phase shift in time courses of half of the period in relation to the trajectories starting in the domain $x < \theta$ (see Fig. 3).

CONCLUSION

Models of intercellular protein levels have to include at least two elements: production and degradation. Moreover all the biological models are positive, cause number of molecules can not be negative. In our work the rapid change in the intercellular processes rate is modelled by the switchings in the model parameters. Even in the simple one-dimensional protein production-degradation model we can observe bifurcations. They are very important for the normal cells

existence as they induce bistability which allows the cell to make decision such as proliferation or apoptosis. In biological systems bifurcations are normally induced by the positive feedback loops which works as a switch. Many diseases, especially with genetical background, such as cancers are connected with the changes in bifurcation diagrams (see [9]). This changes, as far as p53 signalling pathway is considered, may be overcome by the Mdm2 mRNA targeted siRNA [10] or chemical [11] based drugs. In our case the bifurcations are induced by the switching of the protein production rate but the model is very simple. It may be interesting to investigate interplay between switching induced and positive feedback induced bifurcations in the more complicated models which we intend to do in the future.

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