Title

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ISBN

9781467357173

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Publication Date

2013-12-01

DOI

10.1109/cdc.2013.6760514

Peer reviewed

On the Stability of Hybrid Limit Cycles and Isolated Equilibria in a Genetic Network with Binary Hysteresis

Qin Shu and Ricardo G. Sanfelice

***Abstract*— A mathematical model for a two-gene regulatory network is derived and several of its properties are analyzed. Due to the presence of continuous dynamics and binary hysteresis, we propose a hybrid system model. Binary hysteresis with different thresholds captures the interaction between the genes. We analyze properties of the solutions and asymptotic stability of equilibria in the system as a function of its parameters. Our analysis reveals the presence of limit cycles for a certain range of parameters, a behavior that is associated with the presence of binary hysteresis. The set of points defining the limit cycle is characterized and its asymptotic stability properties are studied. Numerical simulations are presented to illustrate some of the results.**

I. Introduction

Several mathematical models have been proposed in the literature for the study of genetic regulatory networks; see [1] for a survey. In particular, boolean models are typically used to capture the dynamics of discrete switches in such networks. As introduced by Glass and Kauffman in [2], Boolean regulation functions, typically modeled as sigmoidal or step functions, can be combined with linear system models to enforce certain logic rules. The properties of such a class of piecewise linear models have been studied in the mathematical biology literature, e.g., [3], [4], [5], [6]. Snoussi presented a discrete mapping approach in [3] to study the qualitative properties of the dynamics of genetic regulatory networks. In his work, the properties of a discrete mapping were studied to determine stable isolated steady states as well as limit cycles. In [4], Gouzé and Sari employ the concept of Filippov solution to study piecewise linear models of genetic regulatory networks with discontinuities occurring on hyperplanes defined by thresholds on the variables. Chaves and coauthors [5] studied the robustness of Boolean models of gene control networks. In [6], de Jong and coauthors presented a method for qualitative simulation of genetic regulatory networks based on the piecewise linear model of [2]. Genetic regulatory networks with continuous dynamics coupled with switching can be written as a hybrid system. In [7] and [8], the authors apply hybrid systems tools to model a variety of cell biology problems.

Although it is an important phenomenon present in genetic regulatory networks, hysteresis behavior is not usually included in models of such networks. Hysteresis is characterized by behavior in which, for instance, once a gene has been inhibited due to the concentration of cellular protein reaching a particularly low value, a higher value of cellular protein concentration is required to express it. In his survey paper on the impact of genetic modeling on tumorigenesis and drug discovery [9], Huang stated that "*hysteresis is a feature that a synthetic model has to capture.*" Through experiments, Das and coauthors [10] demonstrated the existence of hysteresis in lymphoid cells and the interaction of continuous evolution of some cellular proteins. Hysteresis was also found to be present in mammalian genetic regulatory networks; see, e.g., [11], [12]. More importantly, hysteresis is a key mechanism contributing to oscillatory behavior in biological models [13], [14].

In this paper, we propose a hybrid system model that captures both continuous and discrete dynamics of a genetic regulatory network with binary hysteresis. We combine the methodology of piecewise linear modeling of genetic regulatory networks with the framework of hybrid dynamical systems in [15], and construct a hybrid system model for a genetic network with two genes; see Section II. Unlike piecewise linear models, our model incorporates hysteresis explicitly. We prove existence of solutions to the genetic network, a property that is typically overlooked or difficult to prove due to the discontinuity in the dynamics introduced by boolean variables. In Section III, we compute the equilibria of the system in terms of its parameters. We analyze the asymptotic stability of the isolated equilibrium points and determine conditions under which a limit cycle exists. It is found that, for a particular set of parameters, hysteresis is the key mechanism leading to oscillations, as without hysteresis, the limit cycle converges to an isolated equilibrium point (cf. [3]). The stability of the limit cycle is established using a novel approach consisting of measuring the distance between solutions of hybrid systems (rather than the distance to the limit cycle as in classical continuous-time systems). In Section IV, simulations validating some of our results are presented.

II. A Hybrid Systems Model for Genetic Regulatory Networks with Hysteresis

Models of genetic regulatory networks given by piecewise-linear differential equations have been proposed in [8], [16]. Such models take the form [1]

$$\dot{x} = f(x) - \gamma x, \qquad x \geq 0, \tag{1}$$

[1]The notation $x \geq 0$ is equivalent to $x_i \geq 0$ for each i.

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where $x = [x_1, x_2, \ldots, x_n]^\top$ and x_i represents the concentration of the protein in the i-th cell, $f = [f_1, f_2, \ldots, f_n]^\top$ is a function, $\gamma = [\gamma_1, \gamma_2, \ldots, \gamma_n]^\top$ is a vector of constants, and $1 \leq i \leq n$. For each i, f_i is a function representing the rate of synthesis, while γ_i represents the degradation rate constant of the protein. The function f_i is typically defined as the linear combination $f_i(x) = \sum_{\ell \in L} k_{i\ell} b_{i\ell}(x)$ where $k_{i\ell}$ is the nonzero and nonnegative growth rate constants, $b_{i\ell}$ is a Boolean regulation function that describes the gene regulation logic, and $L = \{1, 2 \ldots, n\}$ is the set of indices of regulation functions.

The modeling strategy for the Boolean regulation functions b_{il} is a key element that captures the behavior of a particular genetic regulatory network. A major feature of a genetic regulatory network is the presence of threshold-like relationships between the system variables, i.e., if a variable x_i is above (or below) a certain level, it could cause little or no effect on another variable x_j, whereas if x_i is below (or above) this certain value, the effect on x_j would become more significant (for example, it may increase the value of x_j or inhibit the growth of the value of x_j). Boolean regulation functions can be modeled by sigmoidal or step functions, an approach that was first proposed by Glass and Kauffmann [2]. When modeling as a step function, the functions $b_{i\ell}$ are given by the combination (linear or nonlinear) of

$$s^+(x_i, \theta) = \begin{cases} 1 & \text{if } x_i \geq \theta \\ 0 & \text{if } x_i < \theta \end{cases}, \quad s^-(x_i, \theta) = 1 - s^+(x_i, \theta), \tag{2}$$

where $s^+(x_i, \theta)$ represents the logic for gene expression when the protein concentration exceeds a threshold θ, while $s^-(x_i, \theta)$ represents the logic for gene inhibition.

To illustrate this modeling approach, let us consider the genetic regulatory network shown in Figure 1. Genes *a* and *b* encode proteins *A* and *B*, respectively. When the concentration of protein *A* is below certain threshold, it will inhibit gene *b*. Similarly, protein *B* inhibits gene *a* when the concentration of protein *B* is above certain threshold. In this way, a set of piecewise-linear differential equations representing the behavior in Figure 1 is given by

$$\dot{x}_1 = k_1 s^-(x_2, \theta_2) - \gamma_1 x_1, \quad \dot{x}_2 = k_2 s^+(x_1, \theta_1) - \gamma_2 x_2, \tag{3}$$

where x_1 is representing the concentration of protein *A*, while x_2 is the concentration of protein *B*. The constants θ_1, θ_2 are the thresholds associated with concentrations of protein *A* and *B*, respectively. In this model, gene *a* is expressed at a rate k_1 when x_2 is below the threshold θ_2. Similarly, gene *b* is expressed at a rate k_2 when x_1 is above the threshold θ_1. Degradations of both proteins are assumed to be proportional to their own concentrations, a mechanism that is captured by $-\gamma_1 x_1$ and $-\gamma_2 x_2$, respectively.

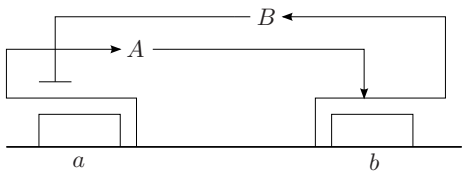


Fig. 1. *A genetic regulatory network of two genes (a and b), each encoding for a protein (A and B). Lines ending in arrows represent genetic expression triggers, while lines ending in flatheads refer to genetic inhibition triggers.*

Note that the model in (3) capturing the interaction between gene *a* and gene *b* does not incorporate binary hysteresis. Furthermore, due to the discontinuities introduced by the Boolean regulation functions, it is not straightforward to argue that solutions to (3) exist from every initial value of x. In order to overcome such limitations, we propose a hybrid system with hysteresis for this two gene genetic regulatory network, to which hybrid systems tools for analysis of existence of solutions and asymptotic stability can be applied.

We model the genetic network in (3) as a hybrid system $\mathcal{H}$ within the formalism of [17], [15], where hybrid systems are given in terms of a flow map F, a flow set C, a jump map G, and a jump set D, and solutions are parameterized by flow time t and jump time j. To this end, two discrete logic variables, q_1 and q_2, are introduced. The dynamics of these variables depend on the thresholds, θ_1 and θ_2, respectively. As one of our goals is to introduce binary hysteresis in the model in (3), we define hysteresis level constants h_1 and h_2 associated with gene *a* and gene *b*, respectively. In this way, q_i is governed by dynamics such that the evolution in Figure 2 holds.

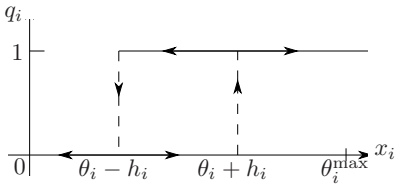


Fig. 2. *The update mechanism of q_i as a function of x_i and previous values of q_i.*

The state of the hybrid system is defined as

$$z = [x_1, x_2, q_1, q_2]^\top,$$

where $z \in \mathcal{Z} := \mathbb{R}^2_{\geq 0} \times \{0, 1\}^2$; x_1, x_2 are (nonnegative) continuous states representing protein concentrations; and q_1, q_2 are discrete variables. Here, $\mathbb{R}_{\geq 0} := [0, +\infty)$. We specify constants θ_1 and θ_2, usually inferred from biological data, satisfying $0 < \theta_1 < \theta_1^{\max}, 0 < \theta_2 < \theta_2^{\max}$, where $\theta_1^{\max}$ and $\theta_2^{\max}$ are the maximal value of the concentration of protein *A* and of the protein *B*, respectively.

To define the continuous dynamics of the hybrid system capturing the evolution of (3), we rewrite the piecewise-linear differential equation (3) by replacing the s^+ term with the logic variables q_i, and the s^- term with the complement of the logic variable q_i, i.e., $1 - q_i$. Note that the discrete logic variables q_i only change at jumps, i.e., they are constants during flows. Then, $\dot{q}_i = 0$. In this way, the continuous dynamics are governed by the differential equation

$$\dot{x}_1 = k_1(1 - q_2) - \gamma_1 x_1, \qquad \dot{x}_2 = k_2 q_1 - \gamma_2 x_2,$$
$$\dot{q}_1 = \dot{q}_2 = 0,$$

from where we obtain the flow map

$$F(z) = \begin{bmatrix} k_1(1-q_2) - \gamma_1 x_1 \\ k_2 q_1 - \gamma_2 x_2 \\ 0 \\ 0 \end{bmatrix}. \quad (4)$$

Now, we describe the discrete update of the state vector z, i.e., we define G and D. To illustrate this construction, we explain how to model the mechanism in Figure 2 for q_1. When

$$q_1 = 0 \quad \text{and} \quad x_1 = \theta_1 + h_1$$

the state q_1 is updated to 1. We write this update law as

$$q_1^+ = 1.$$

When

$$q_1 = 1 \quad \text{and} \quad x_1 = \theta_1 - h_1,$$

then the state q_1 is updated to 0, i.e.,

$$q_1^+ = 0.$$

It follows that the mechanism of q_1 in Figure 2 can be captured by triggering jumps when z belongs to

$$\{z : q_1 = 0, x_1 = \theta_1 + h_1\} \cup \{z : q_1 = 1, x_1 = \theta_1 - h_1\}.$$

Note that the update mechanism for q_2 is similar to that of q_1 just discussed.

We can define the flow and jump sets in a compact form by defining functions

$$\eta_1(x_1, q_1) := (2q_1 - 1)(-x_1 + \theta_1 + (1 - 2q_1)h_1)$$

$$\eta_2(x_2, q_2) := (2q_2 - 1)(-x_2 + \theta_2 + (1 - 2q_2)h_2).$$

In this way, the flow set is given by

$$C := \{z \in \mathcal{Z} : \eta_1(x_1, q_1) \leq 0, \eta_2(x_2, q_2) \leq 0\} \quad (5)$$

and the jump set is given by

$$D = \{z \in C : \eta_1(x_1, q_1) = 0\} \cup \{z \in C : \eta_2(x_2, q_2) = 0\} \quad (6)$$

To define the jump map, first note that at jumps, the continuous states x_1 and x_2 do not change. Then, we conveniently define

$$g_1(z) := \begin{bmatrix} x_1 \\ x_2 \\ 1 - q_1 \\ q_2 \end{bmatrix}, \quad g_2(z) := \begin{bmatrix} x_1 \\ x_2 \\ q_1 \\ 1 - q_2 \end{bmatrix},$$

so that the jump map G is given by

$$G(z) := \begin{cases} g_1(z) & \text{if } \eta_1(x_1, q_1) = 0, \eta_2(x_2, q_2) < 0 \\ g_2(z) & \text{if } \eta_1(x_1, q_1) < 0, \eta_2(x_2, q_2) = 0 \\ \{g_1(z), g_2(z)\} & \text{if } \eta_1(x_1, q_1) = 0, \eta_2(x_2, q_2) = 0. \end{cases} \quad (7)$$

The above definitions determine a hybrid system for (3), which is given by

$$\mathcal{H} : z \in \mathcal{Z} \begin{cases} \dot{z} = F(z) = \begin{bmatrix} k_1(1-q_2) - \gamma_1 x_1 \\ k_2 q_1 - \gamma_2 x_2 \\ 0 \\ 0 \end{bmatrix} & z \in C \\ z^+ \in G(z) & z \in D, \end{cases} \quad (8)$$

where C is in (5), G is in (7), and D is in (6). Its parameters are given by the positive constants k_1, k_2, γ_1, γ_2, θ_1, θ_2, h_1, h_2, which satisfy $\theta_1 + h_1 < \theta_1^{\max}$, $\theta_2 + h_2 < \theta_2^{\max}$, $\theta_1 - h_1 > 0$, $\theta_2 - h_2 > 0$.

III. Dynamical Properties of the Two-Gene Hybrid System Model

A. Existence of solutions

A solution z to $\mathcal{H}$ is said to be nontrivial if $\operatorname{dom} z$ contains at least two points, complete if $\operatorname{dom} z$ is unbounded, Zeno if it is complete and the projection of $\operatorname{dom} z$ onto $\mathbb{R}^n_{\geq 0}$ is bounded, and maximal if there does not exist another solution z' to $\mathcal{H}$ such that $\operatorname{dom} z'$ is a proper subset of $\operatorname{dom} z$, and $z'(t, j) = z(t, j)$ for all $(t, j) \in \operatorname{dom} z$.

Proposition 3.1: From every point in $C \cup D$, there exists a nontrivial solution for the hybrid system $\mathcal{H}$ in (8)*. Furthermore, every maximal solution is complete and the projection of its hybrid time domain on $\mathbb{R}_{\geq 0}$ is unbounded, i.e., every solution is not Zeno.*

The proof of this result uses the conditions for the existence of solutions to $\mathcal{H}$ in [15] for general hybrid systems.

B. Characterization of equilibria

We compute the set of isolated equilibrium points z^* as well as (nonisolated, dense) sets of equilibria for the hybrid system $\mathcal{H}$ in (8). For general hybrid systems, isolated equilibrium points are points that are an isolated equilibrium point of $\dot{z} \in F(z), z \in C$ or of $z^+ \in G(z), z \in D$. On the other hand, an equilibrium set (not necessarily an isolated equilibrium point) for a hybrid system $\mathcal{H}$ is defined as a set that is (strongly) forward invariant.

Definition 3.2 (Equilibrium set): A set $S \subset C \cup D$ is an equilibrium set of $\mathcal{H}$ if for every initial condition $z(0, 0) \in S$, every solution z to $\mathcal{H}$ satisfies $z(t, j) \in S$ for all $(t, j) \in S$.

The following results determine the equilibria of (8) for a range of parameters of the system.

Proposition 3.3: The equilibria of the hybrid system $\mathcal{H}$ in (8) *is given in Table I in terms of the positive constants k_1, k_2, γ_1, γ_2, θ_1, $\theta_1^{\max}$, θ_2, $\theta_2^{\max}$, h_1, and h_2 satisfying the conditions therein. The set $S \subset C \cup D$ in case 5 is an equilibrium set and is given by*

$$S = \bigcup_{i=1}^{4} S_i, \quad (9)$$

where[2]

$$
\begin{aligned}
S_1 &:= \left\{ x \in \mathbb{R}^2 : x = \begin{bmatrix} \frac{k_1}{\gamma_1} - \left(\frac{k_1}{\gamma_1} - p_0(1)\right)\exp(-\gamma_1 s) \\ p_0(2)\exp(-\gamma_2 s) \end{bmatrix}, \right. \\
&\quad \left. s \in [0, t_1']\right\} \times \{(0,0)\} \\
S_2 &:= \left\{ x \in \mathbb{R}^2 : x = \begin{bmatrix} \frac{k_1}{\gamma_1} - \left(\frac{k_1}{\gamma_1} - p_1(1)\right)\exp(-\gamma_1 s) \\ \frac{k_2}{\gamma_2} - \left(\frac{k_2}{\gamma_2} - p_1(2)\right)\exp(-\gamma_2 s) \end{bmatrix}, \right. \\
&\quad \left. s \in [0, t_2']\right\} \times \{(1,0)\} \\
S_3 &:= \left\{ x \in \mathbb{R}^2 : x = \begin{bmatrix} p_2(1)\exp(-\gamma_1 s) \\ \frac{k_2}{\gamma_2} - \left(\frac{k_2}{\gamma_2} - p_2(2)\right)\exp(-\gamma_2 s) \end{bmatrix}, \right. \\
&\quad \left. s \in [0, t_3']\right\} \times \{(1,1)\} \\
S_4 &:= \left\{ x \in \mathbb{R}^2 \ : \ x = \begin{bmatrix} p_3(1)\exp(-\gamma_1 s) \\ p_3(2)\exp(-\gamma_2 s) \end{bmatrix}, s \in [0, t_4'] \right\} \\
&\quad \times \{(0,1)\}
\end{aligned}
$$

and $p_0, p_1, p_2, p_3 \in \mathbb{R}^2$ *are the vertices of the set* S*, where*

$$
t_1' = \ln\left[\frac{\frac{k_1}{\gamma_1} - p_0(1)}{\frac{k_1}{\gamma_1} - (\theta_1 + h_1)}\right]^{\frac{1}{\gamma_1}}, t_2' = \ln\left[\frac{\frac{k_2}{\gamma_2} - p_1(2)}{\frac{k_2}{\gamma_2} - (\theta_2 + h_2)}\right]^{\frac{1}{\gamma_2}},
$$

$$
t_3' = \ln\left[\frac{p_2(1)}{\theta_1 - h_1}\right]^{\frac{1}{\gamma_1}}, t_4' = \ln\left[\frac{p_3(2)}{\theta_2 - h_2}\right]^{\frac{1}{\gamma_2}},
$$

and

$$
p_0 = \begin{bmatrix} (\theta_1 - h_1)\left(\frac{\theta_2 - h_2}{p_3(2)}\right)^{\frac{\gamma_1}{\gamma_2}} \\ \theta_2 - h_2 \end{bmatrix},
$$

$$
p_1 = \begin{bmatrix} \theta_1 + h_1 \\ (\theta_2 - h_2)\left(\frac{\frac{k_1}{\gamma_1} - (\theta_1 + h_1)}{\frac{k_1}{\gamma_1} - p_0(1)}\right)^{\frac{\gamma_2}{\gamma_1}} \end{bmatrix},
$$

$$
p_2 = \begin{bmatrix} \frac{k_1}{\gamma_1} - \left(\frac{k_1}{\gamma_1} - (\theta_1 + h_1)\right)\left(\frac{\frac{k_2}{\gamma_2} - (\theta_2 + h_2)}{\frac{k_2}{\gamma_2} - p_1(2)}\right)^{\frac{\gamma_1}{\gamma_2}} \\ \theta_2 + h_2 \end{bmatrix},
$$

$$
p_3 = \begin{bmatrix} \theta_1 - h_1 \\ \frac{k_2}{\gamma_2} - \left(\frac{k_2}{\gamma_2} - (\theta_2 + h_2)\right)\left(\frac{\theta_1 - h_1}{p_2(1)}\right)^{\frac{\gamma_2}{\gamma_1}} \end{bmatrix}.
$$

Moreover, the period of the limit cycle is given by

$$
T = t_1' + t_2' + t_3' + t_4'.
$$

[2] $p_i(j)$ is the j-th component of p_i.

TABLE I

EQUILIBRIA OF THE HYBRID SYSTEM (8).

	Conditions on constants	Equilibria
1	$\theta_1 + h_1 < \frac{k_1}{\gamma_1} < \theta_1^{\max}$ $0 < \frac{k_2}{\gamma_2} < \theta_2 + h_2$	$z_1^* := \begin{bmatrix} \frac{k_1}{\gamma_1} & \frac{k_2}{\gamma_2} & 1 & 0 \end{bmatrix}^\top$
2	$0 < \frac{k_1}{\gamma_1} < \theta_1 - h_1$	$z_2^* := \begin{bmatrix} \frac{k_1}{\gamma_1} & 0 & 0 & 0 \end{bmatrix}^\top$
3	$\theta_1 - h_1 < \frac{k_1}{\gamma_1} < \theta_1 + h_1$ $0 < \frac{k_2}{\gamma_2} < \theta_2 + h_2$	z_1^* or z_2^*
4	$\theta_1 - h_1 < \frac{k_1}{\gamma_1} < \theta_1 + h_1$ $\theta_2 + h_2 < \frac{k_2}{\gamma_2} < \theta_2^{max}$	z_2^*
5	$\theta_1 + h_1 < \frac{k_1}{\gamma_1} < \theta_1^{\max}$ $\theta_2 + h_2 < \frac{k_2}{\gamma_2} < \theta_2^{\max}$	equilibrium set S defined in (9)

C. Stability analysis

For convenience in the following analysis, we rewrite the flow set C as $C = \bigcup_{i=1}^4 C_i$, where

$$
\begin{aligned}
C_1 &:= \{z \in \mathcal{Z} : q_1 = 0, q_2 = 0, x_1 \le \theta_1 + h_1, \\
&\qquad\qquad x_2 \le \theta_2 + h_2\}, \\
C_2 &:= \{z \in \mathcal{Z} : q_1 = 1, q_2 = 0, x_1 \ge \theta_1 - h_1, \\
&\qquad\qquad x_2 \le \theta_2 + h_2\}, \\
C_3 &:= \{z \in \mathcal{Z} : q_1 = 1, q_2 = 1, x_1 \ge \theta_1 - h_1, \\
&\qquad\qquad x_2 \ge \theta_2 - h_2\}, \\
C_4 &:= \{z \in \mathcal{Z} : q_1 = 0, q_2 = 1, x_1 \le \theta_1 + h_1, \\
&\qquad\qquad x_2 \ge \theta_2 - h_2\}.
\end{aligned}
$$

1) Asymptotic stability of isolated equilibrium points: The following propositions determine the stability properties of the isolated equilibrium points in Table I.

Proposition 3.4: For case 1, 2, and 4 in Table I, the corresponding equilibrium points to $\mathcal{H}$ *in* (8) *are globally asymptotically stable.*

Proposition 3.5: For case 3 in Table I, if $z(0,0) \in C_2$*, then we have that* $\lim_{t+j\to\infty} z(t,j) = z_1^*$*; if* $z(0,0) \in C_1$ *or* $z(0,0) \in C_4$*, then* $\lim_{t+j\to\infty} z(t,j) = z_2^*$*. If* $z(0,0) \in C_3$*, then* $\lim_{t+j\to\infty} z(t,j) = z_1^*$ *or* z_2^**. Furthermore,* z_1^* *and* z_2^* *are stable.*

2) Stability properties of the limit cycle: Now, we determine conditions on the parameters under which the limit cycle S defined in (9) is asymptotically stable. As shown in Figure 3(b), the natural metric (shown in dashed line) defined by the distance between the trajectories z of $\mathcal{H}$ and the set S is not necessarily decreasing, even though Figure 3(a) shows that the trajectory converges to S. In fact, as depicted in the figures, the trajectory x approaches S for some time and then gets far away from it (around the corners), until a jump to a new value of q occurs.

To overcome this issue, we augment the hybrid system $\mathcal{H}$ with a state $\zeta \in \mathbb{R}^2$ and with continuous dynamics governed by a flow map given by a copy of the one for x, that is,

$$
\dot{\zeta} = \begin{bmatrix} k_1(1 - q_2) - \gamma_1 \zeta_1 \\ k_2 q_1 - \gamma_2 \zeta_2 \end{bmatrix}.
$$

The discrete dynamics of ζ are chosen so that jumps occur when jumps of $\mathcal{H}$ occur and, at such jumps, ζ is updated via the difference inclusion

$$\zeta^+ \in \widetilde{G}(x, q, \zeta).$$

To define the jump map $\widetilde{G}$, we consider the case $\gamma_1 = \gamma_2$ and we extend to $\mathbb{R}^2$ the set of points S_i, $i \in \{1, 2, 3, 4\}$, that is, we define the (unbounded) set

$$\widetilde{S} = \bigcup_{i=1}^{4} \widetilde{S}_i, \tag{10}$$

where
$\widetilde{S}_1 = \{x \in \mathbb{R}^2 : x_2 = m_1 x_1 - m_1 p_1(1) + p_1(2)\} \times \{(0,0)\}$,
$\widetilde{S}_2 = \{x \in \mathbb{R}^2 : x_2 = m_2 x_1 - m_2 p_1(1) + p_1(2)\} \times \{(1,0)\}$,
$\widetilde{S}_3 = \{x \in \mathbb{R}^2 : x_2 = m_3 x_1 - m_3 p_3(1) + p_3(2)\} \times \{(1,1)\}$,
$\widetilde{S}_4 = \{x \in \mathbb{R}^2 : x_2 = m_4 x_1 - m_4 p_3(1) + p_3(2)\} \times \{(0,1)\}$. The constants m_i are defined as

$$\begin{aligned} m_1 &= \frac{p_0(2) - p_1(2)}{p_0(1) - p_1(1)}, \quad m_2 = \frac{p_2(2) - p_1(2)}{p_2(1) - p_1(1)}, \\ m_3 &= \frac{p_2(2) - p_3(2)}{p_2(1) - p_3(1)}, \quad m_4 = \frac{p_0(2) - p_3(2)}{p_0(1) - p_3(1)} \end{aligned} \tag{11}$$

During flows, the set $\widetilde{S}$ is forward invariant for the state component ζ (both during flows and jumps) along the dynamics of q governed by $\mathcal{H}$. This is the reason we restrict ζ to belong to $\widetilde{S}$ for the current value of q. Then, due to the stability properties of the error system with state $\zeta - x$, the distance between x and ζ strictly decreases during flows. With this useful property of the trajectories while flowing, at jumps due to $\mathcal{H}$, which occur when $(x(t,j), q(t,j)) \in D$ and map $q(t,j)$ to $q(t, j+1)$ (following the definition of G in (7)), the jump map $\widetilde{G}$ is constructed to map the state ζ to satisfy $(\zeta(t, j+1), q(t, j+1)) \in \widetilde{S}$ such that, if $(\zeta(t,j), q(t,j)) \in \widetilde{S}_{q(t,j)}$ before the jump, then $(\zeta(t, j+1), q(t, j+1)) \in \widetilde{S}_{q(t,j+1)}$ and with the property that

$$\text{dist}(x(t, j+1), \zeta(t, j+1)) \leq \text{dist}(x(t,j), \zeta(t,j))$$

where dist is the Euclidean distance between two points in $\mathbb{R}^2$. In this way, the new value of ζ at jumps can be determined for each $x \in \mathbb{R}^2$, from the set
$\widetilde{G}(x, q, \zeta) :=$
$\left\{\zeta' : \text{dist}(x, \zeta') \leq \text{dist}(x, \zeta), (\zeta', q') \in \widetilde{S}_{q'}, (x, q') \in G(x, q)\right\}$
(when it is not empty). Since the distance between x and ζ decreases during flows, asymptotic stability of $\widetilde{S}$ can be established when $\widetilde{G}(x, q, \zeta)$ is nonempty since this guarantees that the distance between x and ζ is nonincreasing. The following result imposes conditions on the parameters guaranteeing that $\widetilde{G}$ is nonempty and, furthermore, extends the attractivy property to the set S.

Theorem 3.6: For positive constants k_1, k_2, γ_1, γ_2, θ_1, $\theta_1^{\max}$, θ_2, $\theta_2^{\max}$, h_1, and h_2 such that

$$\gamma_1 = \gamma_2 = \gamma, \tag{12}$$
$$|m_1| \leq \min\{|m_2|, |m_4|\}, \tag{13}$$
$$|m_3| \leq \min\{|m_2|, |m_4|\}, \tag{14}$$

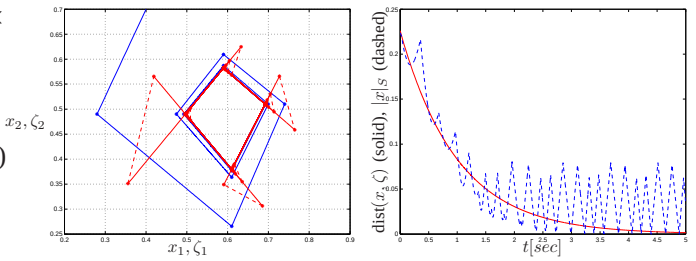
where, for each $i \in \{1, 2, 3, 4\}$, m_i are given in (11)*, the following holds:*

1) *The set $\widetilde{S}$ is globally asymptotically stable for $\mathcal{H}$. In particular, each maximal solution to $\mathcal{H}$ satisfies*

$$\begin{aligned} d((x(t,j), q(t,j)), \widetilde{S}) \leq \\ \exp(-\gamma t) d((x(0,0), q(0,0)), \widetilde{S}) \end{aligned} \tag{15}$$

for all $(t,j) \in \text{dom}(x, q)$, where $d((x,q), \widetilde{S}) = \min_{(\zeta,q) \in \widetilde{S}} |x - \zeta|$.

2) *The set S in case 5 of Table I is globally attractive for $\mathcal{H}$, i.e., every solution to $\mathcal{H}$ converges to S.*



(a) Trajectories x and ζ on the plane.

(b) Distance between trajectory x and ζ (solid), and distance between x and S (dashed).

Fig. 3. *Trajectories x and ζ on the plane, and distance between x and ζ compared to distance between x and the set S (dashed).*

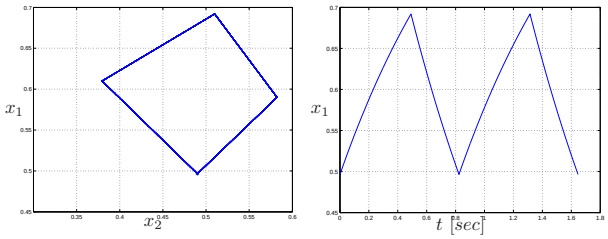
Figure 3 shows trajectories x and ζ as well as the distance between them obtained from the hybrid system augmented with the state ζ. As Figure 3(b) indicates, this distance (solid) decreases to zero while, as pointed out earlier, the natural distance between x and S (dashed) does not.

Due to the regularity properties of the data of $\mathcal{H}$, the asymptotic stability guaranteed by Theorem 3.6 is robust to small perturbations.

IV. Numerical results

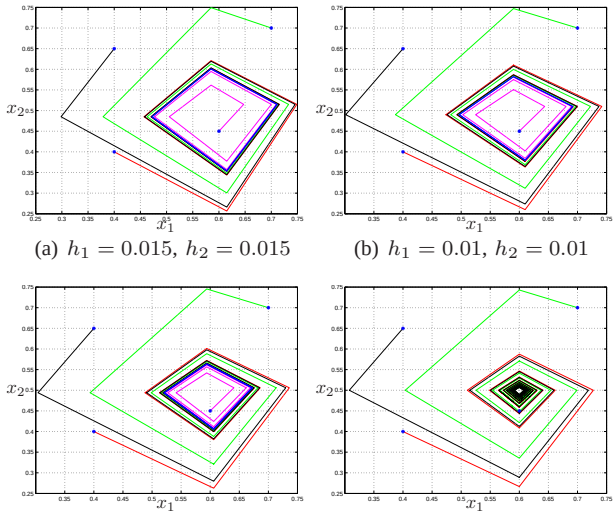
We illustrate numerically the more interesting case when the parameters lead to a limit cycle.

When the parameters are in the region $\theta_1 + h_1 < \frac{k_1}{\gamma_1} < \theta_1^{\max}, \theta_2 + h_2 < \frac{k_2}{\gamma_2} < \theta_2^{\max}$, the set of points S in (9) defines the equilibria. First, we compute this set of points for $k_1 = k_2 = 1$, $\gamma_1 = \gamma_2 = 1$, $\theta_1 = 0.6$, $\theta_2 = 0.5$, $h_1 = h_2 = 0.01$. Figure 4(a) shows the set of points S projected to $\mathbb{R}^2$ for these parameters. For the same parameter values, the period of the limit cycle obtained from Proposition 3.3 is $T = 0.8230$ sec, where $t_1' = 0.2552$ sec, $t_2' = 0.2359$ sec, $t_3' = 0.1594$ sec, $t_4' = 0.1724$ sec. Figure 4(b) confirms this result.



(a) S (b) x_1 component

Fig. 4. *Set S for parameters $k_1 = k_2 = 1$, $\gamma_1 = \gamma_2 = 1$, $\theta_1 = 0.6$, $\theta_2 = 0.5$, $h_1 = h_2 = 0.01$.*



(a) $h_1 = 0.015,\ h_2 = 0.015$ (b) $h_1 = 0.01,\ h_2 = 0.01$

(c) $h_1 = 0.006,\ h_2 = 0.006$ (d) $h_1 = 0,\ h_2 = 0$

Fig. 5. *Solutions approaching the set S with different initial conditions of z and parameters $\theta_1 = 0.6$, $\theta_2 = 0.5$, $\gamma_1 = \gamma_2 = 1$, $k_1 = k_2 = 1$.*

Figure 5 shows simulations with several initial conditions and common parameters $\theta_1 = 0.6, \theta_2 = 0.5, \gamma_1 = \gamma_2 = 1, k_1 = k_2 = 1$, but decreasing h_1, h_2. Each solution converges to the limit cycle S. The size of the limit cycle is reduced as h_1, h_2 gets smaller. From our results we know that the size of the limit cycle depends on the value of hysteresis parameters. When the magnitude of hysteresis tends to zero, the set S approaches a point, which is given by (θ_1, θ_2) (see similar case shown in Figure 5(d).)

Finally, Figure 6 shows the case when $\gamma_1 \neq \gamma_2$. In this case, the trajectories approach the limit cycle given in (9).

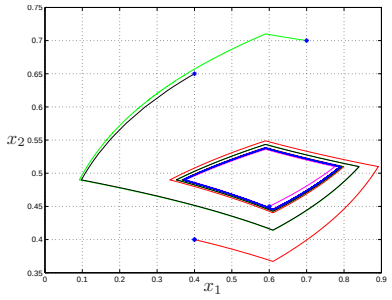


Fig. 6. *Solutions approaching the set S with different initial conditions of x_i and fixed parameters. Values of parameters: $\theta_1 = 0.6, \theta_2 = 0.5, \gamma_1 = 5, \gamma_2 = 1, k_1 = 5, k_2 = 1, h_1 = 0.01, h_1 = 0.01$. The blue line is the set S. The symbols $*$ denote the initial points.*

V. Conclusion

In this paper, a mathematical model of a genetic regulatory network has been developed under the formalism of hybrid dynamical systems. The model presented in this paper permits a quantitative analysis of the cellular protein dynamics under the influence of protein concentration thresholds and initial conditions. The analysis of the hybrid model with two genes determines conditions guaranteeing the existence of solutions, the equilibria of the system, and the stability properties of the equilibria (and its robustness). In particular, we have revealed conditions on the parameters that, when hysteresis is present, the interaction between the concentrations of two proteins leads to oscillatory behavior. Such a behavior is impossible in a two-gene network without hysteresis.

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