Dynamical properties of a two-gene network with hysteresis ☆

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Motivated by the recent development of advanced experimental techniques in molecular biology, this paper focuses on the study of the dynamical properties of a two-gene regulatory network. A mathematical model for a two-gene regulatory network is derived and several of their properties are analyzed. Due to the presence of mixed continuous/discrete dynamics and hysteresis, we employ hybrid systems models to capture the dynamics of the system. The proposed model incorporates binary hysteresis with different thresholds capturing the interaction between the genes. We analyze properties of the solutions and asymptotic stability of equilibria in the system as a function of their parameters. As a difference to previous efforts employing piecewise-linear models, the analysis of our hybrid system model reveals the presence of limit cycles for a certain range of parameters, a behavior that is associated with the presence of hysteresis. The set of points defining the limit cycle is characterized and its asymptotic stability properties are studied. Furthermore, we determine conditions under which the stability properties of the limit cycle are robust to changes of parameters. Numerical simulations are presented to illustrate the findings.

1. Introduction

1.1. Mathematical modeling of genetic regulatory networks

In recent years, the development of advanced experimental techniques in molecular biology has led to a growing interest in mathematical modeling methods for the study of genetic regulatory networks; see [1] for a literature review. A number of gene regulatory network models have been proposed to capture their main properties [2–8]. Boolean models capture the dynamics of the discrete switch in genetic networks. As introduced by Glass and Kauffman in [3], 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., [4,5,2,6]. Snoussi presented a discrete mapping approach in [4] to study the qualitative properties of the dynamics of genetic regulatory networks. In this work, the properties of the discrete mapping were studied to determine stable isolated steady states as well as limit cycles. In [5], 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 [2] studied the robustness of Boolean models of gene control networks. de Jong and coauthors [6] presented a method for qualitative simulation of genetic regulatory networks based on the piecewise linear model of [3].

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. More recently, hybrid models have been used in [9] for the study of molecular interactions. It is important to note that hysteresis behavior, which is typically present in genetic regulatory networks, has not been considered in the models mentioned above.

1.2. The role of hysteresis in genetic regulatory networks

Hysteresis is an important phenomenon in genetic regulatory networks. It 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 [10], Huang stated that "*hysteresis is a feature that a synthetic model has to capture.*" Through experiments, Das and coauthors [11] 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., [12,13]. More importantly, it has been observed that hysteresis is a key mechanism contributing to oscillatory behavior in computational biological models [14,15]. On the other hand, it is well known that hysteresis is one of the key factors that makes a system robust to noise and parametric uncertainties [16,17].

1.3. Contributions and organization of the paper

Our work is motivated by the following facts:

1. *Piecewise linear models do not incorporate hysteresis, although it plays a key role in the dynamics of genetic regulatory networks. In fact, as we establish in this paper, hysteresis leads to oscillatory, robust behavior in two-gene networks.*
2. *The discontinuities introduced by the Boolean regulation functions yield a non-smooth dynamical system, for which classical analysis tools cannot be applied to study existence of solutions, stability, robustness, etc.*

Motivated by these two limitations, we propose a hybrid system model that captures both continuous and discrete dynamics of genetic regulatory networks with hysteresis behavior. We combine the methodology of piecewise linear modeling of genetic regulatory networks with the framework of hybrid dynamical systems in [18], and construct a hybrid system model for a genetic network with two genes. Our model incorporates hysteresis explicitly, which we found leads to limit cycles. We prove existence of solutions and compute the equilibrium points in terms of parameters for the system. We analyze the stability of the isolated equilibrium points and determined conditions under which a limit cycle exists. It is found that hysteresis is the key mechanism leading to hysteresis, as without hysteresis, the limit cycle converges to an isolated equilibrium point (cf. [4]). The stability of the limit cycle is established using a novel approach consisting of measuring distance between solutions of hybrid systems (rather than the distance to the limit cycle as in classical continuous-time systems). Moreover, we show that the asymptotic stability of the limit cycle is robust to small perturbations.

The remainder of this paper is organized as follows. In Section 2, a mathematical framework of hybrid dynamical system is introduced and then applied to model a two-gene network. The analysis of existence of solutions, stability, and robustness are presented in Section 3. Section 4 presents simulations validating our results. Proofs of some of the results that due to space limitations are not included here can be found in [19].

2. 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 [8,20]. Such models take the form[1]

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

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 $1 \leqslant i \leqslant n$. 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

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