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Mathematical modeling of the lambda switch: A fuzzy logic approach

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ABSTRACT

Gene regulation plays a central role in the development and functioning of living organisms. Gaining a deeper qualitative and quantitative understanding of gene regulation is an important scientific challenge.

The Lambda switch is commonly used as a paradigm of gene regulation. Verbal descriptions of the structure and functioning of the switch have appeared in biological textbooks. We apply fuzzy modeling to transform one such verbal description into a well-defined mathematical model.

The resulting model is a piecewise-quadratic second-order differential equation. It demonstrates functional fidelity with known results while being simple enough to allow a rather detailed analysis. Properties such as the number, location, and domain of attraction of equilibrium points can be studied analytically. Furthermore, the model provides a rigorous explanation for the so-called stability puzzle of the Lambda switch.

1. Introduction

Gene regulation plays a fundamental role in the development and evolution of organisms. Understanding gene regulation within living cells is a major scientific challenge in the post-genome era. Indeed, the analysis of gene regulating networks may have important implications in many fields of science, including biology and gene therapy. It may also lead to methods of synthesizing artificial networks with applications in biotechnology and biocomputing (Gardner et al., 2000).

The λ *switch* (Ptashne, 2004) is a relatively simple gene regulating network that controls two alternative patterns of gene expression in the bacterial virus λ. This epigenetic switch ensures an efficient change from one pattern to the other in response to suitable environmental cues. Bistable switches are common motifs in gene regulation networks, and the λ switch provides a convenient test case, as the virus is one of nature's simplest organisms. In a recent survey paper, Zhu et al. (2007) point out that the λ switch "has indeed established itself as one of the fundamental elements in biological processes and as a paradigm for both experimental and theoretical studies in biology."

As noted in Zhu et al. (2007), biological theories are often of a descriptive nature. In other words, they consist of descriptions and explanations stated in *natural language*. Science can greatly benefit from transforming these verbal descriptions into well-defined mathematical models. Indeed, mathematical models summarize and interpret the empirical data, and are indispensable when we wish to rigorously analyze a dynamic system. This raises the following problem:

Problem 1. How can one convert a given verbal description into a well-defined mathematical model?

This problem was already addressed in the field of *artificial expert systems* (AESs). These are algorithms that imitate the human expert's functioning (Siler and Buckley, 2004; Kandel, 1992). In many cases, AESs are based on the knowledge of a human expert, stated in *natural language*. The problem then is how to transform this verbal information into a well-defined algorithm.

Fuzzy modeling (FM) is routinely used for constructing AESs, as it provides a simple yet highly efficient approach for addressing Problem 1. More generally, FM plays an important role in the fields of artificial intelligence and computational intelligence (Zadeh, 1994; Klir and Yuan, 1995). The real power of fuzzy logic lies in its ability to handle and manipulate linguistic information based on perceptions (Dubois et al., 1998; Margaliot and Langholz, 1999; Zadeh, 1996; Novak, 2005; Kolman and Margaliot, 2009).

Recently, FM has been used in the modeling and analysis of *biological phenomena* and, in particular, in deriving mathematical models of animal behavior (Tron and Margaliot, 2004, 2005; Bajec et al., 2005; Rashkovsky and Margaliot, 2007; Rozin and Margaliot, 2007; Margaliot, 2007). This application of FM is somewhat different than the typical approach applied in the construction of AESs. The motivation is not to replace the human expert with an automatic algorithm, but rather to assist a human expert in transforming his/her knowledge concerning a biological

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phenomenon, stated in words, into a well-defined mathematical model.

Application of FM in this context consists of four steps: (1) identifying the state variables; (2) restating the given verbal descriptions as a set of fuzzy rules relating these variables; (3) defining the fuzzy terms using suitable membership functions; and (4) inferring the fuzzy rule-base to obtain a well-defined mathematical model.

The close connection between the initial verbal description and the resulting mathematical model provides several unique advantages (Margaliot, 2008). The knowledge about the system is represented in three different forms in parallel: (1) the initial verbal descriptions and explanations; (2) the fuzzy rule-base; and (3) the mathematical model obtained by inferring the rules. This provides a synergistic view of the system. For example, simulations and analysis of the mathematical model can be used to check whether the model's behavior is congruent with that actually observed in nature. When this is not the case, it is sometimes possible, due to the If–Then structure of the fuzzy rules, to determine which rule should be altered and how. Inferring the modified rule-base yields a modified mathematical model, and so on. Furthermore, any modification in the rule-base can also be interpreted as a change in the initial verbal description, suggesting directions for further research of the original natural phenomenon.

In this paper, we apply FM to transform a verbal description of the molecular mechanisms underlying the λ switch into a well-defined mathematical model. The state variables are the amounts of two regulatory proteins. The resulting model is a piecewise-quadratic second-order differential equation.

Simulations indicate that the model demonstrates qualitative and quantitative fidelity with experimental evidence. A major advantage of the new model is that, unlike previous models (see the review in Section 2.4 below), it is also simple enough to allow a rather detailed analysis. In particular, we show that properties such as the number and location of equilibrium points and their domains of attraction can be analyzed analytically.

Furthermore, the model provides for the first time a *rigorous* explanation of the so-called stability puzzle of the λ switch. This explanation is similar to the one suggested by Santillan and Mackey (2004) based on numerical analysis of bifurcations that appear when the value of a certain parameter is increased. However, the latter model is a fourth-order differential equation with time-delays and was studied via simulations only. Our model is a piecewise-quadratic second-order differential equation. It is thus simple enough to allow a rigorous analysis of the behavior of the equilibrium points for various values of the parameters.

The remainder of this paper is organized as follows. Section 2 briefly reviews the genetic switch. Section 3 applies FM to derive a mathematical model for the λ switch. Simulations and a rigorous analysis of the mathematical model are presented in Sections 4 and 5.

2. Gene regulation and the λ switch

2.1. Gene regulation

All the cells of an individual organism contain the same DNA, that is, the same genetic information. Yet, during the development of the organism from a fertilized egg, very different types of cells appear. The reason for this variety is that different genes are expressed or "turned on" in different cells. The information encoded in these genes is decoded into proteins. These proteins determine the structure and properties of the cell. Ptashne (2004) states: "At various stages, depending in part on environmental signals, cells choose to use one or another set of genes, and thereby to proceed along one or another developmental pathway."

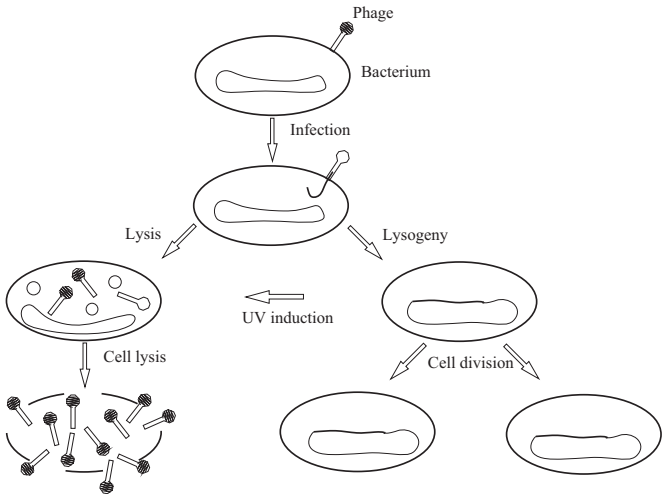

Fig. 1. Two developmental pathways: lysogenic and lytic. UV radiation may trigger lytic growth.

The controlled on/off switching of sets of genes is called *gene regulation*. Analyzing the gene regulation process in high-level organisms is very difficult. This is due to the large number of genes in the *DNA* and the intricate interactions between the genes. For example, the human genome contains 20,000–25,000 protein-coding genes; the *Drosophila melanogaster*, commonly known as the *fruit fly*, has approximately 14,000 protein-coding genes. It is thus natural that scientists turned their attention to gene regulation in simpler organisms. In particular, the λ phage virus, which has about 50 genes, became a prototype for studying gene regulation (Ptashne, 2004). The λ phage has been studied intensely over the last 50 years and almost all its components are now known in great detail. It is believed that developing a better understanding of the gene regulation process in the λ phage may also shed light on developmental and epigenetic processes in higher organisms (Ptashne, 2004).

2.2. λ phage life cycle

The λ phage is a virus that grows on a bacterium. The phage has a single DNA molecule. Upon infection of the bacteria, the phage injects its chromosome into the bacteria cell. The virus can then follow one of two different pathways: *lysogeny* or *lysis*.[1] In the lysogenic state, the phage integrates its genome into the bacteria's DNA and replicates as a part of the host bacterium. In the lytic state, the phage's DNA is extensively replicated, new phages are formed within the bacterium, and about 45 min after infection the bacterium lyses and releases about 100 new phages (see Fig. 1).

The two possible pathways are the result of expressing different sets of genes. The phage may switch from the lysogenic state to the lytic state. This is a kind of *SOS* response initiated when the host cell experiences DNA damage. This happens, for example, if the bacteria is exposed to ultraviolet (UV) light.

The molecular mechanism responsible for the lysogeny/lysis decision is known as the λ *switch*. This mechanism has two important and striking properties. First, it is exceptionally stable. Once the lysogenic state is established, it remains intact for very

[1] From the Greek, *Lysis*, act of loosening. *Lysogenic*, capable of producing or undergoing lysis.