CONTROL THEORETIC MODELING OF A GENETIC SWITCH

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ABSTRACT

The paper explores a control-theoretic approach to the modeling of a genetic switch associated with bacteriophage λ. The approach consists in modeling the underlying gene regulation mechanisms through the use of control theoretic abstractions of experimentally verified patterns and pathways of gene expression and repression, without resorting to the inclusion of detailed reaction kinetics. The proposed model is not intended to provide predictions of biochemical variables. Instead, the objective is to build a system-centric model of gene regulation dynamics that may be more suited for the analysis and understanding of biological functions. The reported simulation results provide an encouraging illustration of the stated objective's attainability.

Index Terms— Gene Regulation, Genetic Switch, Control Theoretic Model

1. INTRODUCTION

The last decade has seen an unprecedented and massive amount of genomic, transcriptomic, proteomic, metabolic, and pathway data sets becoming available to biological research. This has emboldened the emergence of the new discipline of systems biology to fill the consequent need for system-level abstractions and integration methods of biological knowledge/data. The purpose of this new way of studying biological systems is to elucidate how the dynamic interactions between genes and their products lead to biological functions [1]. This discovery quest requires a framework for system level modeling of gene regulation and related biological processes. Such framework may be provided by control system theory whose mature set of system-centric foundations could contribute to the modeling and analysis of biological regulation mechanisms in synch with the vision of systems biology. Control theoretic models of biological regulations would be amenable to system-level analysis using tools and methods such as robustness analysis, bifurcation theory, frequency response and spectral analysis. Applying these methods would greatly enhance the capacity of gene regulation models to provide relevant insight about the research questions under consideration and potentially guide experimental biology.

The paper discusses a proposed control theoretic approach to the modeling of gene regulation for the particular case of bacteriophage λ genetic switch. The nature of the explored modeling approach consists in the use of control-theoretic concepts such as feedback, state adaptation, and robust control to capture an abstraction of the information processing logic and relevant dynamics of gene regulation. This strategy enjoys a support from the evidence that biological robustness is the result of biological feedback control loops operating in a fashion not too dissimilar to robust control of a complex engineered systems such as the Boeing 777 [2].

Bacteriophage λ is one of the most studied model organisms in biology. A considerable amount of biological knowledge has been accumulated about this bacteriophage, including detailed kinetic models of its decision circuit [1, 3-5]. These models are critical to the study of gene regulation mechanisms and the underlying biochemistry. However, they are computationally forbidding and not scalable to large regulatory networks [1]. The proposed control theoretic model of gene regulation, on the other hand, seeks to provide a system level abstraction for the study of the interactions between genes, their products and regulatory elements. As such, its purpose is complementary to that of the models based on detailed reaction kinetics. Furthermore, the system-centric philosophy of the proposed modeling strategy has an inherent capacity for the integration and composition of large models from basic subsystems. This may hold the key to achieving models of gene regulatory networks that are both scalable and computationally feasible.

The proposed approach uses elementary control theoretic building blocks connected through a structure intended to achieve robustness of the model's functional behavior for wide ranges of parameter values. Consequently, the proposed modeling strategy may have the potential to yield models that capture the robustness property of biological systems as exemplified by the case of bacteria chemotaxi [6, 7]. Indeed, the robustness observed for bacteria chemotaxi was corroborated by an analysis, using robust control theory, of the ability of biochemical network to maintain a desired output under varying protein concentrations and variable input [8]. The result of this analysis further motivates the proposed control theoretic modeling approach and its potential to yield adequate models of gene regulation

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without involving a detailed consideration of reaction kinetics.

The paper is organized as follows. Section II provides a description of the biological elements involved in the bacteriophage lambda genetic switch. Section III describes and discusses the proposed model. Section IV provides a brief discussion with some concluding remarks.

2. BACTERIOPHAGE λ

Bacteriophage λ (or simply phage λ) are viruses that infect and replicate in Escerichia coli (E. coli) bacteria. The genes of the λ phage are located on a single chromosome-wrapped DNA molecule. After infecting the host bacteria, λ may follow one of two infection cycles: lytic or lysogenic. Considerable amount of knowledge has been accumulated to answer, with reasonable details, how λ decides which infection pathway to take [3]. In the lytic cycle the phage λ is extensively replicated into new phage particles which lyses (burst) the bacterium host and release about 100 progeny phage in less than an hour after infection [3]. For the lysogenic pathway, the λ DNA is integrated in the host chromosome and is quiescently replicated thereafter and passed on to the progeny of the host bacteria which grow and divide normally [3]. This process is rarely interrupted unless the phage λ senses a signal warning about the eminent demise of the host bacterium – which may be caused by DNA damage resulting from UV radiation. This warning signal induces the E. coli SOS response, the bacterial protective mechanism. This response includes the expression of the E. coli gene **recA** whose product leads phage λ to switch from the lysogenic state to the lytic state [3] [9]. This genetic switch is the focus of the modeling research effort reported in this paper. In the following, we briefly describe the biological components of the switch and how they interact to produce the experimentally observed switching behavior. The description is limited in its scope and depth to the context at hand. The reader is referred to the comprehensive treatments of the subject in [10] [9] [3, 11] .

DNA (Deoxyribonucleic acid) is an organic molecule composed of two associated chains. These chains (strands) are built using four types of unit molecules called nucleotides. These nucleotides are: Adenine (**A**), Guanine (**G**), Cytosine (**C**), and Thymine (**T**). A sequence of nucleotides such as **AACTGGCTTA** makes up the genetic code held by the DNA molecule that contains it. This DNA code contains, among other things, the "program" for making proteins. Proteins are long chains of amino acids and are essentially the workhorses necessary for the life of an organism. A DNA sequence can be viewed as a map of distinct regions endowed with different purposes. The regions that encode proteins are called genes. Other sites regulate/promote gene expression (synthesis of the protein product encoded by the gene). The path from genes to proteins follows the so called central dogma [12], whereby genes are transcribed into RNA which are than translated into proteins (Figure 1). RNA (Ribonucleic Acid) is a single strand built with the same nucleotides as the ones used for the DNA with the exception of Thymine being replaced by Uracil (**U**).

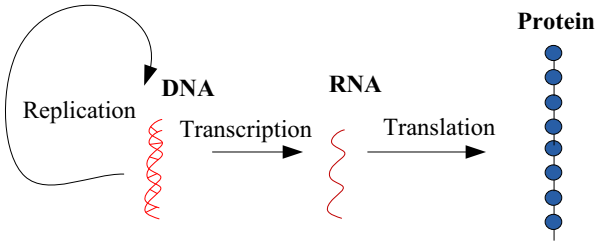

Figure 1. Central Dogma of Molecular Biology

The components of the phage λ genetic switch are the λ DNA, the Repressor and CRO proteins which are the products of phage λ genes **cI** and **cro** respectively, and the RNA polymerase of the host. RNA polymerase is an enzyme that transcribes a gene into RNA to be translated into protein. The λ DNA region of interest to our context includes three operators that control the expression of genes **cI** and **cro** respectively (Figure 2).

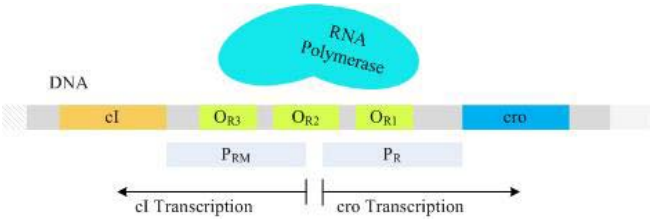

Figure 2. Components of the Switch

The RNA polymerase has to bind to the DNA at the start of the P_R region and must travel rightward and unobstructed to express **cro** which leads to the synthesis of the CRO protein. Similarly, the RNA polymerase has to bind to the beginning of the P_{RM} region and travel leftward to induce the expression of **cI** and the consequent synthesis of the Repressor protein. In the lysogenic state of λ, **cI** is expressed maintaining the synthesis of a sufficient concentration of Repressor proteins that bind $OR2$ and keep **cI** activated. During this lysogenic state, Repressor is also bound to $OR1$ to keep **cro** repressed (not activated). When the bacterial host is subjected to UV radiation, its gene **recA** becomes activated. This leads to the synthesis of RECA proteins which subsequently cleave the Repressor proteins making $OR1$ and $OR2$ clear from Repressor binding. As a result gene **cI** loses its activated state and the gene **cro** becomes activated. At this point the switch is thrown and the

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bacteriophage enters the lytic state. To keep **cI** repressed (not activated) during the lytic state, the CRO protein (products of **cro**) binds to $OR3$ and effectively prevents RNA polymerase from transcribing **cI**. The λ DNA has a set of left operators: $OL3$, $OL2$, $OL1$ which are not discussed in this paper, although the cooperative involvement of both left and right operators contributes to the switch remarkable stability.

3. A CONTROL-THEORETIC MODEL OF BACTERIOPHAGE λ GENETIC SWITCH

The concentrations of the proteins CRO, and Repressor are the driving signals of the switch. These concentrations will be denoted by $C_{cro}(t)$ and $C_{\lambda}(t)$ respectively, where t represents time. $C_{cro}(t)$ and $C_{\lambda}(t)$ are assumed to be the net values resulting from the difference between synthesis and degradation. During the lysogenic state $C_{\lambda}(t)$ must be maintained at a stable level to ensure $OR2$ and $OR1$ are bound by the Repressor proteins keeping as a result **cI** activated and **cro** repressed. Furthermore, at sufficiently high concentration, Repressor proteins bind to $OR3$ and repress **cI** to limit the level of its expression (i.e. $C_{\lambda}(t)$). On the other hand, $C_{\lambda}(t)$ must steadily decline as a reaction to any external stimuli that triggers a bacterial SOS response and the ensuing cleaving action of RECA proteins.

The proposed control-theoretic model is shown in Figure 3. The portion of the model that deals with the regulation of $C_{\lambda}(t)$ is a variable structure controller in a closed loop with an integrator plant. The synthesis rate of the Repressor can be arbitrarily adjusted using the time constant $1/K_a K_b$, while the choice $1/K_b$ specifies the steady state concentration level. The cleavage of the Repressor by RECA is modeled by attenuating $C_{\lambda}(t)$ with a rate of $K_{recA} < 1$. The regulation of $C_{cro}(t)$ is modeled using a control loop similar to that used for the synthesis of $C_{\lambda}(t)$. The ***OpRule*** logical module models the state of Repressor and CRO proteins binding to $OR1$, $OR2$, and $OR3$ based on their respective concentrations and in a accordance to the rules illustrated in Figure 4. These rules are the result of a first attempt at rendering, in a simplified and coarse fashion, the information about binding order and affinity provided in [3]. In this respect, the rules in question require future analysis as to their alignment with experimental evidence. The above qualification applies equally to the utilized rules relating gene activation to CRO and Repressor binding to the operators. In particular, it is assumed that **cI** is activated if the Repressor is bound to $OR2$, and repressed if either Repressor or CRO are bound to $OR3$. The gene **cro** is activated if both $OR1$ and $OR2$ are free of Repressor and CRO, and suppressed if Repressor is bound to $OR1$.

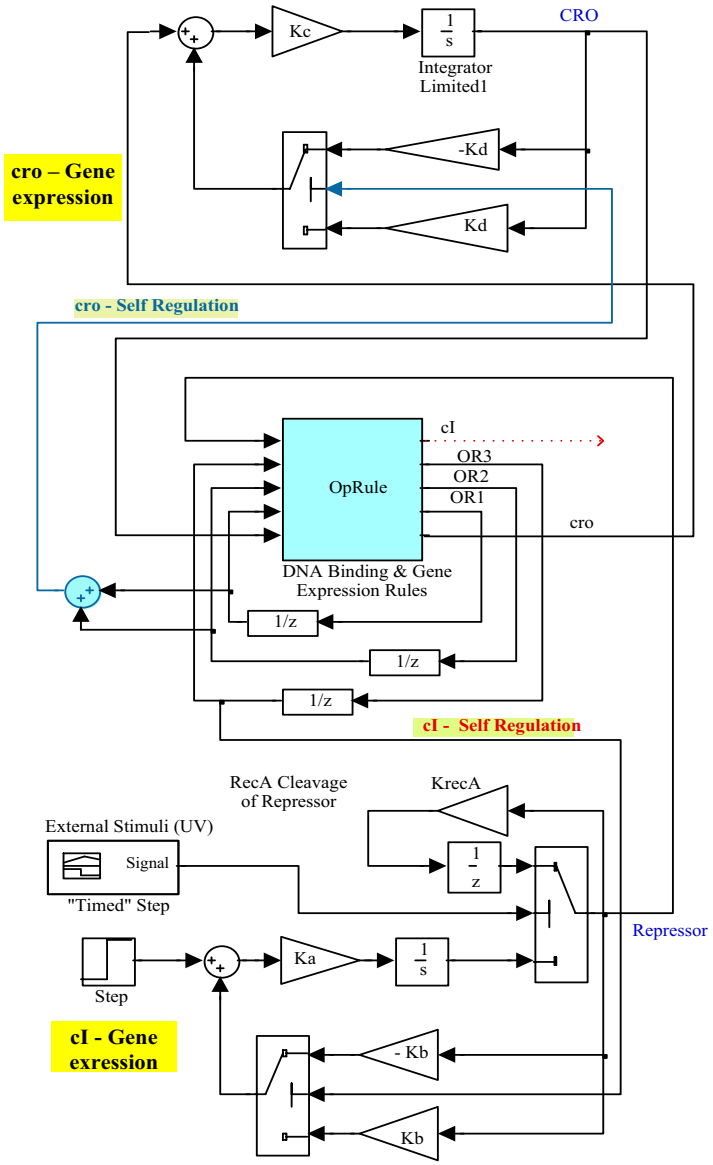

Figure 3. A Model of the Lambda Genetic Switch

The simulation results (Figure 5) illustrate the model's ability to provide a functioning abstraction of the switch operation. One may assert, based on the simulation, that the informational logic required for the switching from the lysogenic to the lytic state is adequately captured and exhibited by the model. Furthermore, the simulation results indicate that the model achieved the desired regulation of **cI** expression by its Repressor product. This behavior was accomplished by the model through feedback binding to $OR3$. Similar simulation results are achieved for the regulation of **cro** expression through the feedback binding of

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CRO to $OR1$ and $OR2$. The steady state fluctuation of $C_{cro}(t)$ is due to **cro** regulation by its own CRO product.

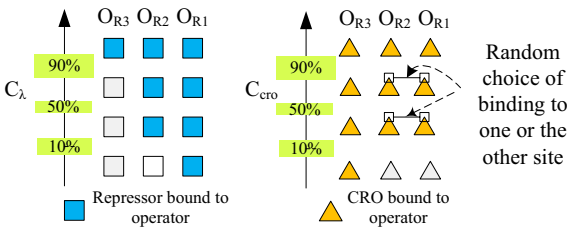

Figure 4. Rules of Binding to Operators

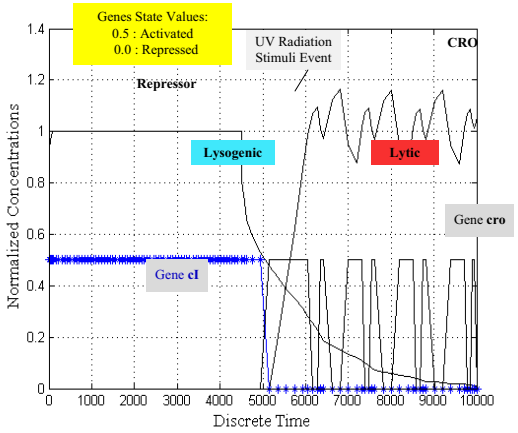

Figure 5. Simulation of the Switch Model

The proposed model maintains a similar functional behavior for a wide range of parameter values (gains). This parameter in-sensitivity may suggest that control theoretic systems have the capacity to model biological regulation mechanisms with uncertain knowledge of kinetic parameters. Investigating such potential may contribute to the development of models that internalize the observed robustness property of biological systems without requiring for their development the availability of precise values for biochemical parameters, such as enzyme levels and rate constants [2, 13, 14]. Extensive research is certainly needed to analyze these types of models and their ability to capture and predict system-level dynamics of gene regulation mechanisms.

The simplicity of the used modeling components and their connection protocols (basic signal feedback, signal feed-forward, Boolean logic rules, etc…) leads to models that are less computationally demanding compared to complex differential equations of reaction kinetics. For large gene regulatory networks this distinction may be accentuated.

4. DISCUSSION AND CONCLUDING REMARKS

The proposed control-theoretic model of phage λ gene regulation process reproduces the desired functional behavior of the genetic switch under consideration. Despite the basic nature of the regulatory building blocks being used, the proposed approach may hold a key innovation for the benefit of gene regulation modeling. This is meant in the sense that the proposed approach may have the potential to yield models that are robust towards value uncertainty of biochemical parameters. Furthermore, the system centric nature of the proposed approach may provide this last with a degree of intrinsic alignment with the needs of biological research as articulated through the emerging discipline of systems biology.

The proposed modeling approach enables the mature and rigorous analysis methods of control systems theory to be brought into context. These may consequently be leveraged towards the analysis of central biological properties such as robustness. Finally, the simplicity of the utilized modeling blocks and interaction protocols could translate into models that are computationally less demanding compared to others built around complex systems of differential equations.

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