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Exploring Model Integration through Quantized Information Flow

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Abstract

The paper explores the integration of coarse-grained model abstractions using feedback of quantized information flow. The modeling and simulation of the lytic induction cycle of lambda phage is used as an illustrative example. The simulation results show that the model, with its modest complexity, has the capacity to internalize the relevant transcription regulatory logic and replicate the salient dynamics of the lytic induction cycle.

Keywords

Quantized Information Flow; Hierarchical Feedback; Coarse-grained Abstraction;

I. INTRODUCTION

Modeling frameworks based on system-wide abstractions and integration of knowledge are needed to absorb and leverage the information content of the ever increasing size of Omics datasets into models that serve biomedical research and medicine. In this respect, a framework was contributed to address the challenges associated with the modeling of living organisms [1]. The applicability of the abstraction and integration constructs of this proposed framework is explored through the modeling of the lytic induction cycle of bacteriophage λ . The modeling results are expected to contribute towards the development of computationally feasible and analytically accessible system centric models of biological complexity. Indeed, the computer simulations reported in this short communication show that the developed model, although modest in complexity, has the capacity to internalize the relevant transcription regulatory logic and replicate the salient dynamics of the lytic induction cycle.

II. LYTIC INDUCTION MODEL OF λ PHAGE

The model is comprised of three contextual layers, namely: protein synthesis, transcription regulation, and the phage life cycle dynamics (see Fig. 1). This organization is inspired by the biological plausibility of the distinction between the biological functions carried out within these contexts. The dynamic process of protein synthesis is inevitably determined by the kinetics of the relevant biochemical reactions. The space-time distributions of protein concentrations make up the principal information about the state of the system within this model layer. The discrete time-dependent protein concentrations for CRO and Repressor are represented by the output $y_p(t)$ of the following lumped parameter model:

$$y_p(t) = \sigma(x_p(t)) + \xi(t) \quad (1)$$

$$x_p(t) = x_p(t-1) + v_p(t) \cdot \alpha_p - u_p(t) \cdot \beta_p \quad (2)$$

The subscript p is either *cro* or *rep* referencing CRO and Repressor proteins respectively. $x_p(t)$ represents the noise-free protein concentration at time t . $\sigma(\cdot)$ is a signal amplitude limiter function, $\xi(t)$ is a uniformly distributed random expression noise, and α_p and β_p are the concentration increments of protein synthesis and degradation respectively. $v_p(t)$ represents the control exerted by the transcriptional regulation layer on protein synthesis while $u_p(t)$ represents a protein degradation signal such as a UV stimulus. Both $v_p(t)$ and $u_p(t)$ are discrete-valued signals. The quantized protein CRO and Repressor concentrations drive the dynamics of λ phage life cycle state machine model which spans the states: Lytic, Lysogenic and Neutral respectively (Fig. 2). The quantization scheme given in Table I¹ is inspired from the experimentally observed CRO and Repressor respective levels of affinity and binding patterns to the right operators OR1, OR2 and OR3 detailed in [2]. The Neutral state of the phage life cycle is an approximation of the transition period during which the phage DNA is being integrated into or excised from the host's DNA. The feedback from the phage life cycle dynamics to protein synthesis is mediated by the transcription regulatory logic which provides the binary-valued control signals $v_{rp}(t)$ and $v_{cro}(t)$ for Repressor and CRO respectively:

¹Based on percentage levels of maximum steady state concentrations.

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$$v_{rp}(t) = Lys(t - 1) - O3(t - 1) \tag{3}$$

$$v_{cro}(t) = 1 - Lys(t - 1) - 0.25 * (O1(t - 1) + O2(t - 1)) \tag{4}$$

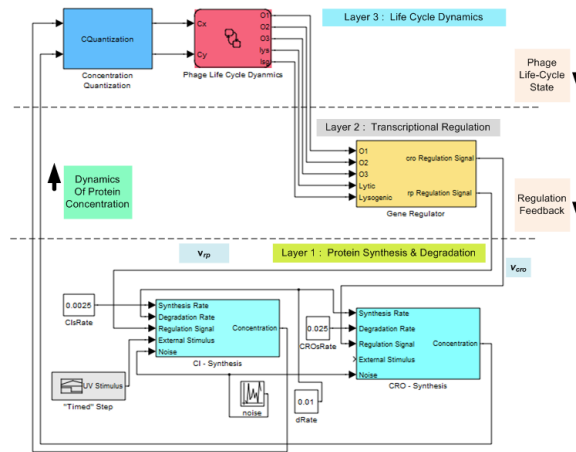


Figure 1. Model of Phage Lytic Induction (in MATLAB®).

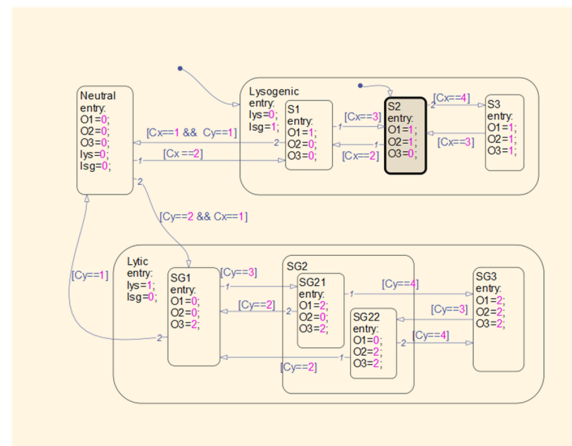


Figure 2. Phage Lambda Life Cycle Dynamics . The occupancy states of the operators OR1, OR2, OR3 are represented by the variables O1, O2 and O3 respectively. These variables take the values 0 (non-occupancy) , 1 (occupied by Repressor), or 2 (occupied by CRO). The binary values of lys and lysg defined the Lytic, Lysogenic and Neutral states.

The regulation rules specified by the above equations are inspired by the experimentally deduced correlations between the occupancy states, by CRO and Repressor proteins, of the promoters PR and PRM and the expressions of the *cro* and *cI* (repressor) genes respectively [2]. The discretization of protein concentrations establishes an information connector to the state machine model which provides a biologically plausible abstraction of the phage state dynamics. The resulting coarse-grained information about the phage and protein-operator binding flows to the transcription regulatory logic which controls the protein synthesis process, closing hence the causal loop of the model. The model's architecture is conceived to seek biological plausibility by approximating the biological organization that integrates the identified functional contexts of protein synthesis, transcription regulation and life cycle dynamics. The coarse-grained modeling applied to protein synthesis and life cycle dynamics and the modulation of the resolution of information flow through quantization were envisioned to limit the model's complexity. The objective is to achieve computational feasibility while maintaining a sufficient degree of biological plausibility and representational resolution to reenact the principle dynamics of the phage lytic induction. The simulation results given in Fig.3 illustrate the model's emulation of the UV induced lysis process, whereby the UV-triggered

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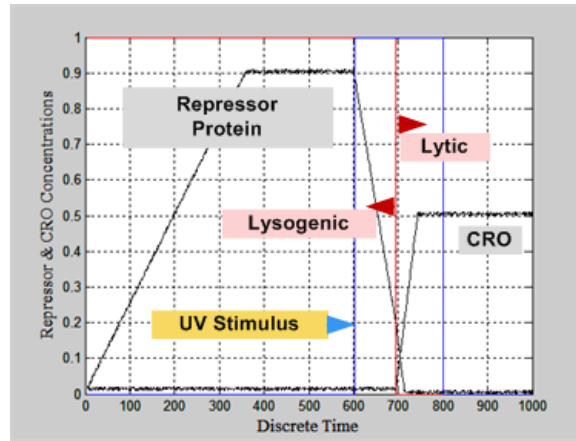


Figure 3. Simulation of λ Phage Lytic Induction Dynamics. The UV stimulus occurs at $t=600$. The UV stimulus occurs at $t=600$. The UV stimulus occurs at $t=600$. The range of the uniformly distributed expression noise is $[0, 0.01]$. The maximum levels of protein concentration represent the highest expression capacity of the genes. They are arbitrarily set using the limiter function of the protein synthesis model.

Table I
QUANTIZED SCHEME.

CRO	Cy	Repressor	Cx
0-10%	1	0-20%	1
10%-50%	2	20%-50%	2
50%-90%	3	50%-90%	3
90%-100%	4	90%-100%	4

cleavage of Repressor leads to loosening its hold on operator OR3, hence allowing the binding of CRO. This in turn prevents the expression of cI and promotes the expression of cro , leading ultimately to cell lysis. Based on the simulation results it may be concluded that the proposed coarse-grained model of protein synthesis and phage life cycle dynamics and the quantization of protein concentrations enabled an information flow of sufficient resolution to integrate the three distinct contextual layers and replicate the induction dynamics.

III. CONCLUSION

The proposed model provides an illustration of the potential utility of the modeling philosophy introduced in [1]. Coarse-grained modeling and quantization of information flow was shown to yield an analytically approachable and computationally feasible model that reproduces the essential dynamics of the lytic induction cycle of λ phage.

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