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PII: S0022-5193(17)30116-9
DOI: http://dx.doi.org/10.1016/j.jtbi.2017.03.004
Reference: YJTBI8997

To appear in: *Journal of Theoretical Biology*

Received date: 12 October 2016
Revised date: 6 February 2017
Accepted date: 7 March 2017

Cite this article as: Wolfgang Halter, Jan Maximilian Montenbruck, Zoltan A Tuza and Frank Allgöwer, A resource dependent protein synthesis model for evaluating synthetic circuits, *Journal of Theoretical Biology* http://dx.doi.org/10.1016/j.jtbi.2017.03.004

A resource dependent protein synthesis model for evaluating synthetic circuits

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Abstract

Reliable *in silico* design of synthetic gene networks necessitates novel approaches to model the process of protein synthesis under the influence of limited resources. We present such a novel protein synthesis model which originates from the Ribosome Flow Model and among other things describes the movement of RNA-polymerase and ribosomes on mRNA and DNA templates, respectively. By analyzing the convergence properties of this model based upon geometric considerations, we present additional insights into the dynamic mechanisms of the process of protein synthesis. Further, we demonstrate how this model can be used to evaluate the performance of synthetic gene circuits under different loading scenarios.

Keywords: Synthetic biology, host-circuit interactions, resource dependence, genetic regulatory networks, normally hyperbolic manifolds

1. Introduction

One of the major issues in the field of synthetic biology is the gap between the computationally predicted performance of a synthetic circuit and the performance observed in its implementation *in vitro*. This problem mainly stems from the fact that assumptions made during the modeling process are oversimplifying the dynamics of the biological processes under study. Genetic regulatory networks usually have been described focusing on the direct interactions between genes and their products, neglecting the fact that there exist significant indirect couplings between all genes, including the ones not modeled. Some of these couplings originate from the usage of shared resources of the transcriptional and translational machinery. The influence of such limited pools of resources has been addressed just recently by Gyorgy et al. (2015); Weiße et al. (2015); Gorochowski et al. (2016), where both experimental and computational approaches are being discussed. For the purpose of describing interactions of several genes and their products, the stated works mainly use Hill-kinetics to phenomenologically describe protein production depending on the concentration of certain transcription factors. The process of protein synthesis however can be described and modeled on various levels of detail, and a more mechanistic approach would be beneficial in order to understand the system on a microscopic level and better evaluate the degrees of freedom for possible modifications in terms of the design of synthetic gene circuits. Particularly, considering translational control as an additional mechanism for genetic interactions may yield one possible strategy to avoid negative effects of limited pool resources. A suitable protein synthesis model should therefore allow for the implementation of different genetic control mechanisms such as transcriptional and translational control, but also incorporate limitations of available resources within the cell. Therefore, the process of protein synthesis can be described as a sequence of several steps, which in turn are described on a low level of detail: transcription initiation, mRNA elongation, translation initiation and protein elongation. Post-translational modification will be neglected for simplicity. This way the resulting model satisfies the just stated requirements while remaining computationally tractable. It is also in accordance with the results of Ben-Tabou de Leon & Davidson (2009), in which the authors claim that there are only two factors limiting the transcription rate: transcription initiation rate and RNA polymerase (RNAP) translocation rate. This is due to the fact that RNAP needs to proceed a certain length before the next RNAP can bind. The length of a gene then determines the dead time and transcription rate for one bound RNAP. The initiation rate on the other hand mainly depends on the strength of promoter as well as the presence of certain transcription factors. In case of translation, the physical mechanisms are assumed to be similar. Instead of RNAP, the translocation of ribosomes and initiation of translation, which is now dependent on the strength of the ribosome binding site, are the rate limiting factors. Particularly, Raveh et al. (2016) offer an approach to model the process of translation on this desired level of mechanistic detail. While they consider the flow of ribosomes on several mRNA templates coupled to a pool of ribosomes; however, an extension to capturing both transcription and translation is desired and will be presented in the remainder of this work.

After introducing this novel model, we study its convergence properties based on geometric considerations in order to shed some light on the system theoretic proper-

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