Design principles of bacterial chromosome organization

J. Christian J. Ray[1,2] and Oleg A. Igoshin[1,3]

Short Abstract — **In bacteria, genes encoding interacting proteins in a given network are often co-transcribed from a single operon, and frequently subject to feedback regulation. These two aspects of chromosome organization are shown to affect network functionality by influencing network dynamics and noise levels. Here we aim to characterize evolutionary design principles for chromosomal gene linkage in bacteria – rules relating the organization with network performance. We examine two-component systems, which are frequently expressed from single operons and subject to response regulator feedback. A model predicts that feedback improves the dynamic performance of this system while co-transcription shapes the stochasticity levels.**

Keywords — **chromosome organization, operon, gene regulation, evolutionary design principles, mathematical model**

I. Introduction

Operons in bacterial chromosomes frequently link functionally related genes for co-transcription from a single promoter. However, this is not always the case. For example, while most two-component systems are expressed from a single operon, examples of response regulators uncoupled from sensor kinases are notable [c.f. 1]. This raises the question of what functional aspects of biological networks may have driven the organization of related genes such that some are co-transcribed on the chromosome while others are not.

We explore two aspects of how chromosomal organization interacts with biochemical system performance in bacteria. First, many genes are subject to feedback regulation, raising the question of how this affects overall system performance when multiple functionally relevant genes are co-transcribed versus when they are not. Second, the low number of mRNA molecules transcribed from a gene results in stochasticity in gene regulation, resulting in fluctuations of concentration ratios for gene products depending on co-transcription.

Preliminary results from a stochastic model predict that organization of genes into operons substantially reduces variance in signal-response relationships of several feedback-regulated biochemical circuits in individual cells. We therefore hypothesize that chromosomal organization in bacteria is shaped in part by the noise characteristics of the regulatory network to optimize dynamic responses of biochemical circuits.

II. Methods and Results

We are exploring this possibility in several archetypal circuits with one or more steps in a pathway regulated by multiple gene products. We compare predicted gene expression dynamics for simulated differences in chromosomal organization to deduce optimal designs based on different network architectures.

First, we are studying a class of two-component systems with a deterministic mathematical model based on previously published models [2, 3]. We extend the model to include autoregulatory transcriptional feedback by the activated response regulator represented with functions based on the thermodynamics of protein-DNA interactions [4].

Depending on the parameter regime, transcriptional feedback may be positive or negative. In contrast to previous studies on feedback in dynamic responses [e.g. 5], our model predicts that positive feedback is capable of speeding the response time, depending on the stoichiometric relationship between sensor kinase and response regulator.

Based on this result, studies are ongoing to determine the role of noise shaping chromosomal organization of two-component system genes. We are exploring the effects of chromosomal organization on classes of metabolic pathways, and testing hypothesized design rules using methods of *in silico* evolution.

References

[1] Kanehisa M *et al*. (2008) KEGG for linking genomes to life and the environment. Nucleic Acids Res 36 D480-D484.
[2] Batchelor E and Goulian M. (2003) Robustness and the cycle of phosphorylation and dephosphorylation in a two-component regulatory system. PNAS 100(2): 691-696.
[3] Igoshin OA, Alves R, and Savageau MA. (2008) Hysteretic and graded responses in bacterial two-component signal transduction. Mol Microbiol doi:10.1111/j.1365-2958.2008.06221.x
[4] Saiz L, Vilar JM. (2008) *Ab initio* thermodynamic modeling of distal multisite transcription regulation. Nucleic Acids Res 36(3): 726-731.
[5] Savageau MA. (1974) Comparison of classical and autogenous systems of regulation in inducible operons. Nature 252: 546-549

[1]Department of Bioengineering, Rice University, Houston TX.
[2]E-mail: jjray@rice.edu
[3]E-mail: igoshin@rice.edu