Nonlinear dependence in gene expression on gene copy number in regulatory network motifs

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***Short Abstract* — Gene copy number can vary significantly within organisms [1] and can cause significant changes in patterns of gene expression [2]. We develop a theoretical model of how gene copy number impacts gene expression dynamics in simple genetic circuits known as network motifs [3]. Under certain conditions, we show that small-scale variation in gene copy number can cause gene expression to change by orders of magnitude, leading to qualitatively distinct dynamics [4]. To test our predictions, we present preliminary experimental results on the effect of varying the copy number of synthetic circuits expressed in *E. coli*.**

***Keywords* — gene regulation, gene copy number, network motifs, synthetic circuit.**

I. Introduction

Copy number variation (CNV) is an important and widespread component of genetic variation [1]. The copy number of genes and genetic motifs can vary over physiological to evolutionary time scales, often conveying significant changes in phenotype. [2]. For example, CNV can change enzyme concentrations associated with nutrient intake in humans [5]. Similarly, the copy number of viral genomes undergoes dynamical changes during co-infection of host cells and may lead to alternative modes of exploitation [6,7]. Here, we present a combined theoretical and experimental approach to measuring the effect of gene copy number variation on gene expression dynamics. First, we model how gene expression dynamics in simple network motifs varies with balanced [4] and imbalanced changes in copy number (in prep). Next, we present preliminary experimental results on the relationship between gene expression and gene copy number for synthetic gene circuits analyzed in *E. coli*.

II. Modeling CNV in network motifs

Gene regulatory networks include common subgraphs known as network motifs [4], which are building blocks of complex transcription regulatory networks. To quantify the expression dynamics for different gene copy numbers, we analyze the expression dynamics of three network motifs: positive feedback, bistable feedback and toggle switch motifs. Under certain conditions, change of a few copies can lead to orders of magnitude change in gene expression. We also analyze a three-gene motif with successive inhibition, known as the represillator. Small changes in represilator copy number can lead to a qualitative switch between oscillatory and equilibrium dynamics. In all cases, both the quantitative and qualitative change in gene expression is due to the nonlinear nature of transcriptional feedback. In particular, we predict that large differences between basal and activated transcription are necessary for sensitivity of a motif to copy number changes.

III. Development of synthetic genetic circuits

To test our model predictions, we describe an experimental synthetic biology approach utilizing E. coli that is designed to manipulate the copy number of common genetic motifs while concurrently measuring the consequence of CNV for gene expression dynamics. We focus our attention on copy number variable positive feedback circuits and present preliminary experimental results on the sensitivity of the positive feedback loop to copy number variation given different ratios of enhanced to basal transcription rates.

IV. Conclusion

We demonstrate that gene copy number is a key control parameter in the gene expression dynamics of simple network motifs.

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