

Phenotypic Differences Among Seven Synthetic Oscillator Designs

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Short Abstract — Synthetic biology has proved useful in uncovering basic principles that advance our understanding of biological clocks. The mechanistic bases underlying these clocks involve specific motifs of feedback control with common circuit architectures. However, there are numerous differences that remain poorly understood. Here, we analyze seven synthetic circuit designs and compare them using mathematical and computational methods. Our results predict a novel design that has yet to be constructed, which is more realizable and robust than the alternatives. These results can aid in the design of novel synthetic oscillators and potentially provide insight into the operation of natural circuits.

Keywords — Circuit architecture, dynamic phenotypes, mathematically controlled comparison, mode of transcription control, system design space.

I. INTRODUCTION

CIRCADIAN rhythms are fascinating phenomena that are essential to diverse groups of organisms. Underlying these rhythms are genetic and biochemical clocks that are responsible for producing robust and reliable oscillations. Utilizing synthetic biology to uncover basic principles of simpler circuits is a way to advance understanding of natural biological systems [e.g., 1-4].

Recent studies have made considerable progress in identifying and characterizing component parts of genetic oscillators. However, there are numerous differences that are poorly understood and several factors that may or may not be critical to their operation. Nonlinear interactions among components are sufficiently complex that mathematical models are required to elucidate their elusive integrated behavior.

Here, we study synthetic oscillators using mathematical models to address the following questions: What are the implications of different architectures for the phenotypic repertoire of genetic oscillators? Are there designs that are more realizable or robust?

II. METHODS AND RESULTS

We analyze synthetic oscillators involving one of three architectures and four modes of transcriptional control using carefully controlled comparisons. We formulate mechanistic

models of the designs consisting of nonlinear ordinary differential equations that are compared under ideal conditions that maximize their potential for sustained oscillation.

We apply mathematical and computational tools that include the analytical system design space methodology, numerical simulations and Fourier analysis to address the difficult genotype-phenotype problem. Our system design space methodology (1) provides an efficient means of obtaining a global perspective on the behavioral repertoire of synthetic as well as natural systems, (2) allows detailed analysis of the local behaviors, and (3) focuses computational effort on testing specific predictions [5].

Through this three-part strategy we identify designs for genetic oscillators that are more promising than alternative designs because the range of parameter values that allows for their realization is larger. In particular, our results reveal distinctive phenotypes for several designs that have been studied experimentally as well as a best design among the alternatives that has yet to be constructed and tested.

III. CONCLUSION

We have recently developed a novel strategy for deconstructing intractable nonlinear models into a series of simpler models that can be readily analyzed and the results efficiently reassembled to characterize the global repertoire of the original system. We have previously applied this method to elucidate the design of a number of natural systems. In the current application to synthetic oscillator designs we have provided insight into the realization of robust oscillations for seven distinct designs involving two transcriptional regulators. Our results show generic differences, or design principles, that can be utilized to aid in the design of novel synthetic oscillators and to provide insight into the operation of natural circuits.

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Acknowledgements: This work was supported in part by a grant from the US Public Health Service (RO1-GM30054).

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