4dg Advanced Integrative Approaches for Designing and Constructing Control Circuits in Synthetic Biology

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Advances in molecular biology and the reduced costs in genetic modifications promoted the emergence of synthetic biology and gene circuit engineering over the last decade. In principle, these approaches can be applied on system level design for specific biological behavior through rewiring natural connectivity in the regulatory network. However, reality suggests otherwise: design and implementation of simple gene circuits for engineering dynamics such as oscillation has been proven to be extremely difficult. Most designs strategies are *ad hoc* , rather than systematic or strategic. One of my career goals is to devise a framework for designing large scale control circuits in synthetic biology. Such framework shall enable a robust and efficient computer-aided design for gene circuit engineering that is applicable for biomolecular or biomedical applications. My postdoctoral experience as a NIH postdoctoral fellow provided me with experience and knowledge in both synthetic biology and system biology, both of which are helpful for achieving my career goal. In this poster, I will present two projects in these areas.

Design and construction of a synthetic gene-metabolic oscillator

Our group constructed a synthetic bio-oscillator by integrating a gene circuit along the central metabolic pathway of *Escherichia coli K12* [1]. Based on a physicochemical model, we depicted the design principles and controllability of the circuit by constructing phase diagrams that map out the locus where steady state solutions lost their stability through Hopf bifurcation. The second stage of this project involves the elucidation of design principles in synthetic bio-oscillators in general, which will be partially presented on this poster. We compared synthetic oscillators that are based on transcriptional control with our synthetic gene-metabolic oscillator. Specifically, we compared these oscillators by considering the dependence of period and robustness of oscillation through both deterministic and stochastic approaches. These characterizations provide additional guidelines for designing synthetic bio-oscillations and new insights for oscillations occurred in nature.

Development and applications of network component analysis

I have been also involved heavily in the development and applications of network component analysis during my postdoc [2,3]. Network component analysis (NCA) is the first computational approach that enables an essentially unique decomposition of large scale gene expression data into transcription factor activities (TFA) and their associated control strengths. I am interested in using NCA as a reduced-order model for discovering pharmaceutical agents. Specific in this poster, I will present results in the application of NCA for identifying transcription factors that may involved in the TOR (Targets of Rapamycin) pathway in *Saccharomyces cerevisiae* . TOR is an evolutionally conserved protein that controls eukaryotic growth and proliferation. In addition, it is linked to pathogenesis and treatment of human diseases, including cancer, diabetes and graft rejection. Identifying putative transcription factors involved in the TOR pathway shall provide new insights in the cell biology involving TOR.

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