Design of Synthetic Gene-Metabolic Circuits

James C. Liao

Department of Chemical and Biomolecular Engineering,
University of California, Los Angeles

The design approach in engineering has created industrial revolution and modern civilization. The basis of design is the understanding of key principles underlying the system of interest. Such an approach has not been explored in biology until recently. While much remained unknown in the cell, key functional paradigms and many molecular components have been extensively characterized. The design approach can now be used in the cell to explore possible applications of biological components beyond their natural configurations, much like the design of analog computers using well characterized modules. In addition, the design approach provides an alternative method to explore design principles used by nature.

However, application of complex design scenarios in the cell has proved challenging, with the perturbation of cellular networks remaining a concern. Recently, several synthetic circuits, such as oscillators, toggle switches and feedback loops were designed and implemented experimentally to function independently from cellular metabolism and physiology. To enhance control capabilities and create novel functionalities, another dimension can be added to the synthetic circuit architecture by integrating both transcriptional and metabolic controls. Implementation of such a design would require extensive knowledge of an organism's physiology. To this end, we chose *E. coli* as the host due to the extensive knowledge of its metabolic pathways, metabolic control and transcriptional regulation. We have engineered an intracellular dynamic feedback controller that senses metabolic state and allows separation of growth phase and metabolite production phase to improve lycopene production; we have constructed a gene-metabolic network for artificial cell-cell communication using acetate as the signalling molecule, thus enabling coordinated population level control. Recently, we have built a synthetic gene metabolic oscillator that creates autonomous oscillation between two pools of metabolites. The success of these circuits demonstrated that the key features in physiological regulation were correctly captured in the design considerations.

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