ACS SyntheticBiology

In This Issue

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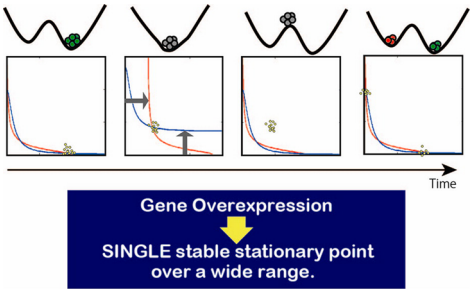
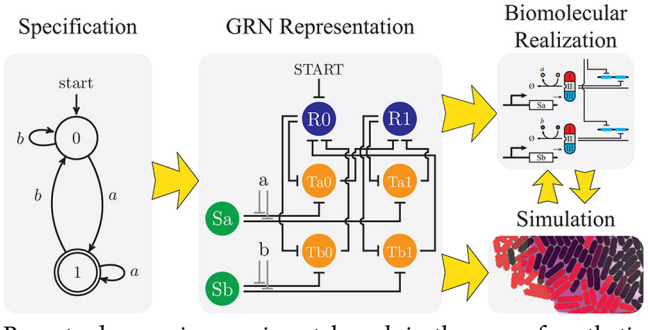
SYNTHETIC GENE-OVEREXPRESSION FOR CELL-TYPE RATIO CONTROL VIA REPROGRAMMING



Mathematical modeling-based understanding of the reprogramming of differentiated cells into a multipotent state, at which cells can differentiate into multiple cell types, is an important challenge in fields such as cell engineering and regenerative medicine. The ideal synthetic circuit for the cell differentiation model is the toggle switch, which is theoretically designed so a cell can show one of two possible phenotypes (types A and B). Now, Ishimatsu *et al.* (DOI: 10.1021/sb400102w) have expanded this standard model.

The authors added a gene overexpression system in order to reprogram the cell states into a multipotent state. As designed theoretically, the overproduction of the proteins governing the toggle switch altered the cell state to the multipotent state. Furthermore, regulation of the overproduction levels generated targeted ratios of cell-types A and B, upon cessation of the overproduction. Combining the basic ideas of cell differentiation and gene overexpression will have broad applications.

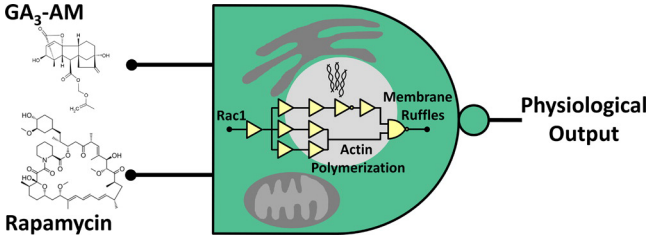
FRAMEWORK FOR ENGINEERING FINITE STATE MACHINES



Recent advances in experimental work in the area of synthetic transcription factors and engineerable gene networks demonstrate the beginnings of an engineering approach to sequential logic control of cell fate. However, a general constructive framework has yet to emerge. Here, Oishi and Klavins (DOI: 10.1021/sb4001799) introduce a design method that, in theory, produces gene regulatory networks (GRNs) from finite state machine (FSM) specifications.

The design method proposed here uses a few simple classes of parts such as repressing transcription factors, nominally "on" promoters, and small molecule sensing. This paper presents a "FSM compiler" of sorts, one that takes an FSM specification as input and automatically generates a GRN.

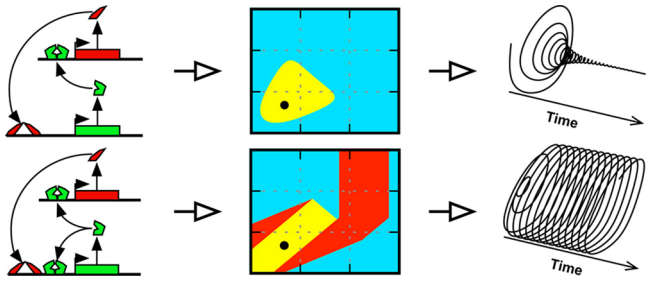
SIGNALING CIRCUITS WITH SYNTHETIC, POST-TRANSLATIONAL, NEGATING BOOLEAN LOGIC DEVICES



There has been an increasing demand for interchangeable parts from natural biology that can be assembled into systems to function in artificial settings, in a programmed manner. In this paper, Razavi *et al.* (DOI: 10.1021/sb500222z) aim to generate a computer using biomolecules.

Using a novel design principle that relies on precise control of molecular localization in cells via a chemically inducible dimerization technique, the authors devised a set of functional negating logic gates. These logic gates also engage with endogenous signaling circuits in living cells on a time scale of just a minute. The time scale is several hundred times faster than conventional logic devices consisting of gene circuits. The work described here has the potential to facilitate the construction of biomolecular computers as well as several biomedical devices.

STRATEGY REVEALING PHENOTYPIC DIFFERENCES AMONG SYNTHETIC OSCILLATORS



Advances in synthetic biology have allowed the assembly of well-characterized molecular components into simple networks of genes that exhibit sustained oscillations. This approach holds the promise of revealing fundamental principles that will advance understanding of natural circadian clocks. However, it is a challenge to identify the repertoire of potential behaviors that are latent in any particular circuit design. Now, Lomnitz and Savageau (DOI: 10.1021/sb500236e) introduce and apply a novel methodology to efficiently obtain a global perspective on the behavioral repertoire of biological systems, to perform detailed local analyses of each qualitatively distinct behavior,

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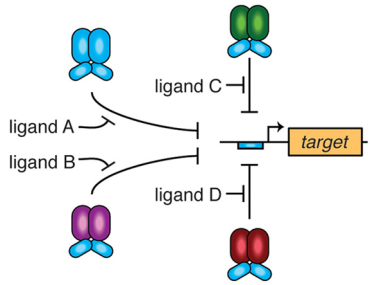
and to focus computational effort on testing specific predictions.

Through this three-part strategy, the authors compare seven genetic oscillator designs for their potential to realize robust oscillations. The results identify a new design that is most promising among the alternatives. This approach can facilitate the rational design of novel synthetic gene circuitry and provide a deeper understanding of more complex natural circuits.

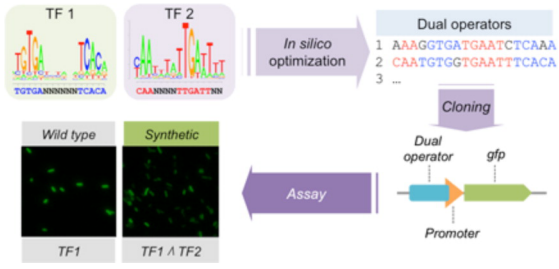
MODULAR, MULTI-INPUT TRANSCRIPTIONAL LOGIC GATING



Transcriptional logic gating is the process by which multiple signals are combined to determine the expression level of a target gene. For synthetic biologists, transcriptional logic gating provides the means to program complex cellular behaviors. In this manuscript, Shis *et al.* (DOI: 10.1021/sb500262f) describe a novel method for creating modular and tightly regulated transcriptional logic gates in *E. coli*.

The authors utilized and created new chimeric transcription factors that combine a ligand-binding domain from the LacI/GalR family of proteins with orthogonal DNA binding domains. This modular approach allowed for complex logic gates that can be programmed to respond to a number of sugars as inputs. Overall, this work provides synthetic biologists powerful new tools with which to engineer synthetic gene circuits.

EXPANDING THE LOGIC OF BACTERIAL PROMOTERS



Regulation of gene expression is a central process in all domains of life. Within this process, promoter elements are the main players in the integration of physicochemical signals and the transformation of that information into a transcriptional response. Thus, the understanding of the mechanisms related to signal integration at target promoters is fundamental both to improve our knowledge about how cells respond to changes in the environment, and to provide new tools to engineer new-to-nature systems. Here, Guazzaroni and Silva-Rocha (DOI: 10.1021/sb500084f) provide new information for the model organism *E. coli* on the relationship between the organization of binding sites for regulatory proteins at target promoters and the process of signal integration during gene regulation.

Furthermore, the investigation of mechanisms associated with the combinatorial control of gene expression allowed authors to design new regulatory sequences that were functional in *E. coli*, with potential impact for circuit engineering.

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