ACS SyntheticBiology

In This Issue

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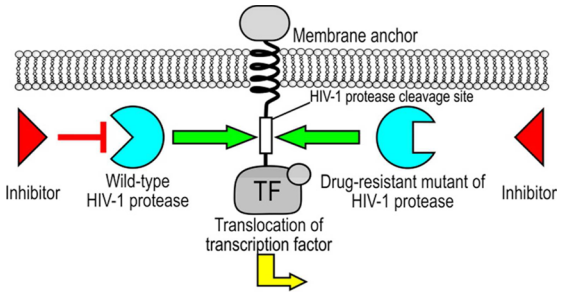
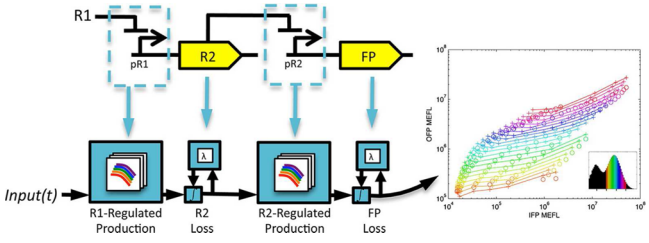
A FUNCTION-BASED, MUTATION-RESISTANT, SYNTHETIC SIGNALING DEVICE



Treatment of the human immunodeficiency virus type 1 (HIV-1) has posed several challenges to researchers due to its high mutation rate. Mutations occur with high frequency, change the sequence of the HIV-1 proteins and, thus, render a large percentage of chemical inhibitors or antibodies useless. Now, Majerle *et al.* (DOI: 10.1021/sb5002483) describe an approach to detect the presence of viral infection in host cells on the basis of specific viral function rather than a specific viral protein.

The authors describe a device, consisting of a membrane anchor connected to a transcription factor, by a peptide linker containing a specific HIV-1 protease cleavage site, which can activate transcription of specific genes in the presence of HIV-1 protease activity. HIV-1 protease activity causes the transcription factor to be released into the nucleus, where it can activate protein expression. The authors also demonstrate that luciferase expression is activated even in the presence of HIV-1 protease mutants commonly associated with drug resistance, and that the effects of several protease inhibitors could be detected between the wild type and mutant proteases.

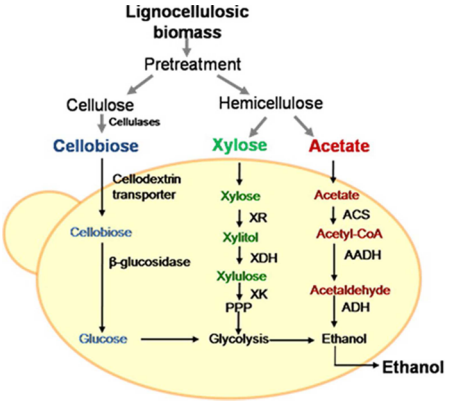
ACCURATE PREDICTIONS OF GENETIC CIRCUIT BEHAVIOR



A long-standing goal in the field of synthetic biology is the ability to be able to accurately predict the behavior of artificial genetic circuits. This capability has important applications in many areas, including precision control of endogenous gene expression, improved quantitative study of cellular events in systems biology, and ensuring safety of cell-based medical treatments. Here, Davidsohn *et al.* (DOI: 10.1021/sb500263b) address this issue of accurately predicting the behavior of a regulatory network from models of its component elements.

While previous methods have relied on biochemical models that often use imprecise parameter estimation and do not account for significant interactions with the cellular context, the authors propose a novel hybrid phenotypic/mechanistic framework instead. They use mechanistic models for those portions of the system where experimental data constrains these models well and phenotypic models for portions where existing models fit poorly or are under-constrained by experimental data. The approach detailed here favors incorporation of significant observable phenomena into computational models over the use of potentially inaccurate mechanistic models, ensuring that every parameter of the model is directly grounded in experimental data. Thus, this hybrid framework is able to achieve unprecedented accuracy and precision for predicting the behavior of transcriptional cascades implemented in mammalian cells.

BIOFUEL PRODUCTION BY AN ENGINEERED YEAST PLATFORM



Next generation biofuels produced from renewable lignocellulosic biomass are promising and sustainable energy sources. However, the inability of fermenting microorganisms to efficiently use mixed carbon components derived from lignocellulosic biomass, and the toxic nature of acetic acid released from hemicellulose have hampered the development of economically viable cellulosic biofuels. Here, Wei *et al.* (DOI: 10.1021/sb500364q) describe the integration of the fermentation pathways of both hexose and pentose sugars, and an acetic acid reduction pathway, into a *Saccharomyces cerevisiae* strain for the first time.

The authors present an innovative metabolic engineering strategy whereby multiple substrate consumption pathways can be integrated, in a synergistic way, for enhanced bioconversion. Integration of these different heterologous pathways into one microbial platform could result in unique benefits unachievable by single pathways alone, such as enhanced overall yield, increased productivity by simultaneous consumption of the mixed substrates, and *in situ* detoxification by acetic acid reduction.

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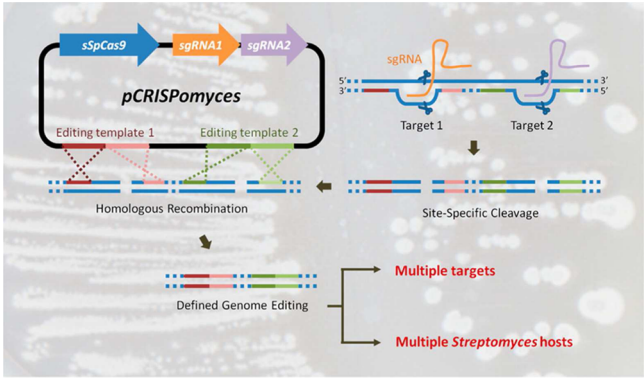
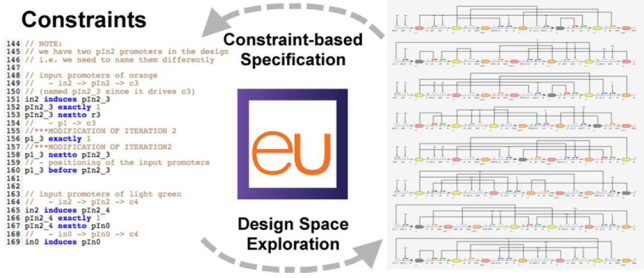
HIGH-EFFICIENCY MULTIPLEX GENOME EDITING OF *STREPTOMYCES* USING ENGINEERED CRISPR/CAS



Actinobacteria of the genus *Streptomyces* are among the most prolific and well-studied producers of diverse secondary metabolites including natural products used as anticancer compounds, herbicides, and antibacterials. While they remain invaluable for the discovery of these natural products and the engineering of the biosynthetic pathways that produce them, the genetic manipulation of these bacteria is often time-consuming and labor intensive. In this paper, Cobb *et al.* (DOI: 10.1021/sb500351f) describe an engineered CRISPR/Cas system for rapid multiplex genome editing of *Streptomyces* strains.

The authors develop this high-efficiency multiplex genome-editing platform by engineering a CRISPR/Cas system from *Streptomyces pyogenes*. This system allows rapid plasmid construction *via* Golden Gate assembly and isothermal assembly (or traditional digestion/ligation) to target any genomic locus of interest. Using this system, the authors also demonstrated targeted chromosomal deletions, of various sizes, in three different *Streptomyces* species, with efficiency ranging from 70 to 100%.

WEB-BASED SOFTWARE TOOL FOR CONSTRAINT-BASED DESIGN SPECIFICATION OF SYNTHETIC BIOLOGICAL SYSTEMS



Combinatorial design is emerging as one potential design paradigm for synthetic biology. The ability to combine individual libraries of biological parts to create designs promises to be a powerful approach since relatively small libraries can encode many possible designs. In this Technical Note, Oberortner and Densmore (DOI: 10.1021/sb500352b) describe how to use *mini*Eugene, a web-based software tool that provides computational support for solving combinatorial design problems. *mini*Eugene enables users to specify and enumerate designs for novel biological systems based on sets of biological constraints. Provided here is a brief tutorial on *mini*Eugene and a step-by-step guide to specify the design of a classical synthetic biological system, the genetic toggle switch.

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