Multiobjective Strain Design: A Framework for Modular Cell Engineering

Background

- Whole-cell catalysis can be used to produce several value-added chemicals, but strain design can be both time consuming and expensive.
- New methods focused on modular cell design enable rapid generation of optimal production strains by systematically assembling modular cells that can be combined with exchangeable production module(s) to produce target molecules efficiently with minimal optimization.

Approach

- We used a multi-objective optimization approach to formulate design schema for modular cell engineering, capturing the competing nature of diverse biochemical pathways.
- Generalized metabolic engineering phenotypes based on mass balance of genome-scale metabolic models, including growth-coupled to product synthesis and stationary phase product synthesis, were used as design objectives.

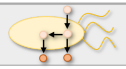
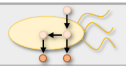
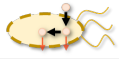
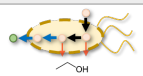
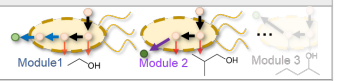
Outcome

- We developed a novel computational platform (ModCell2), based on multi-objective optimization and mass balance analysis of cellular metabolism, to guide modular cell design that can be used to modulate large-scale metabolic networks and is applicable to a library of products in any organism.
- Successfully applied ModCell2 to design highly compatible, modular *E. coli* strains capable of producing a variety alcohols, organic acids and esters.
- Showed modular cells exhibit minimal tradeoffs between modularity, performance, and robustness.

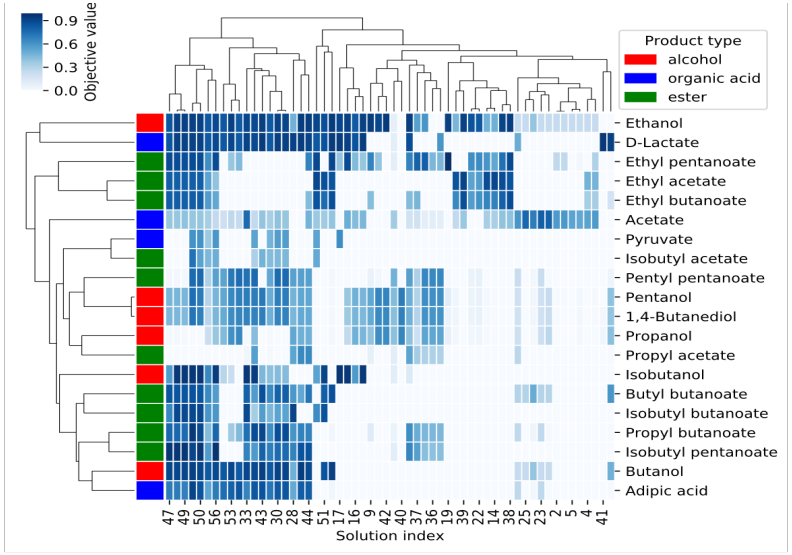
Significance

- ModCell2 is a new powerful tool that can be used to guide modular cell engineering, enabling rapid generation of optimal production strains in a plug-and-play fashion for efficient synthesis of a large library of molecules.

Modular Cell Engineering Concept

Features	Conventional strain engineering	Modular cell engineering
Parent strain		
Modular cell	Absent	 Optimized common production phenotypes
Exchangeable modules	1	Multiple
Optimal production strains		
Design-build-test cycle	Repeated for every new product	One time for many products

Highly Compatible Designs Exhibit Minimal Metabolic Tradeoffs



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