Solving the Modular Cell Biocatalyst Design Problem with Multi-objective Evolutionary Algorithms

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Outline

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Modular design concepts

A *module* is an essential and self-contained functional unit relative to the product of which it is part. The module has, relative to a system definition, standardized interfaces and interactions that allow composition of products by combination.

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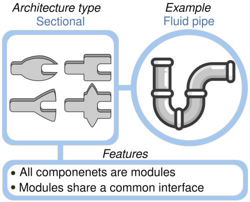

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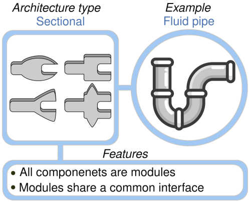

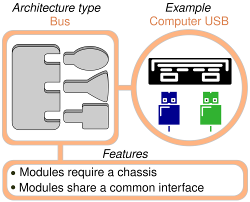

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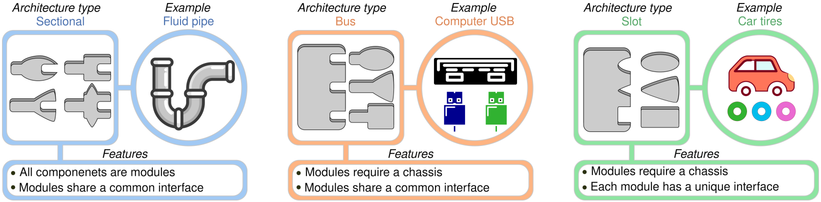
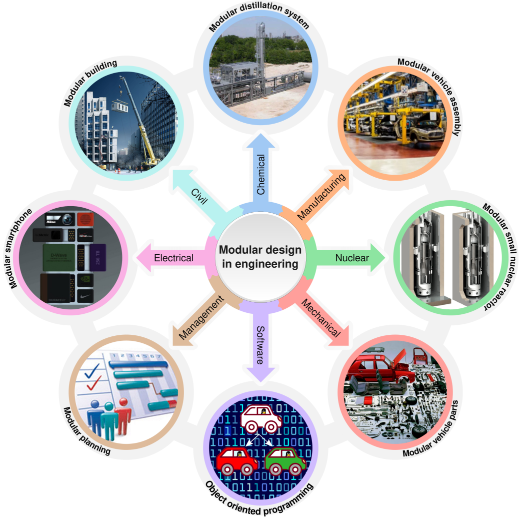


Driving forces and potential tradeoffs of modular design



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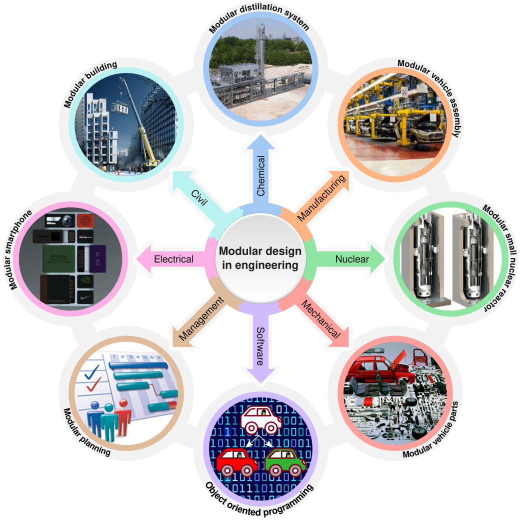

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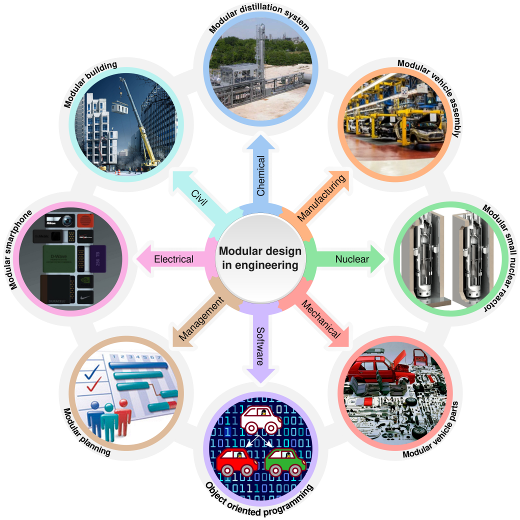

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Potential drawbacks:

- Novelty cost
- Need for specialization
- Transportation constraints

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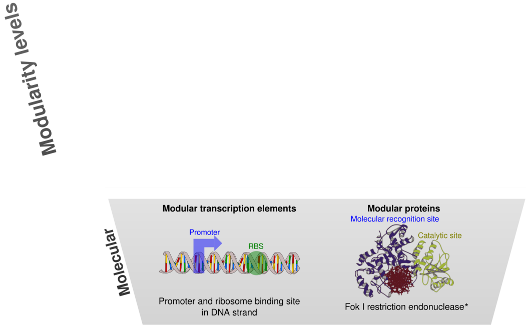

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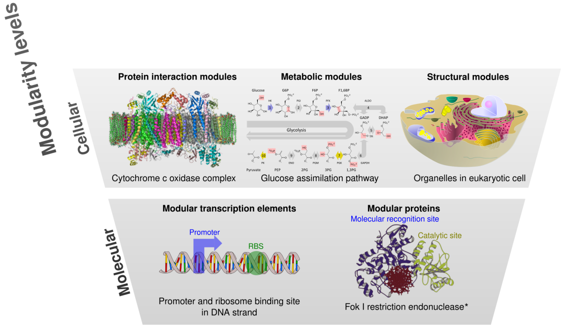

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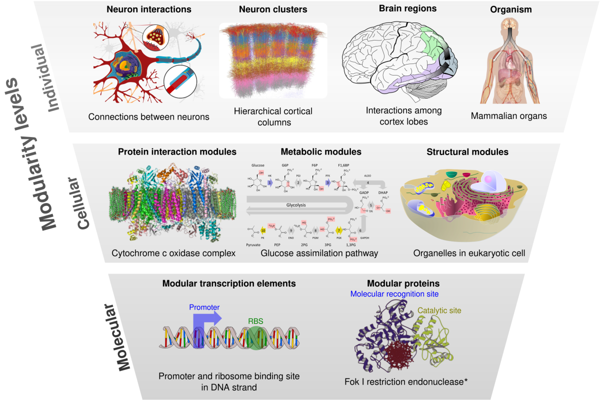

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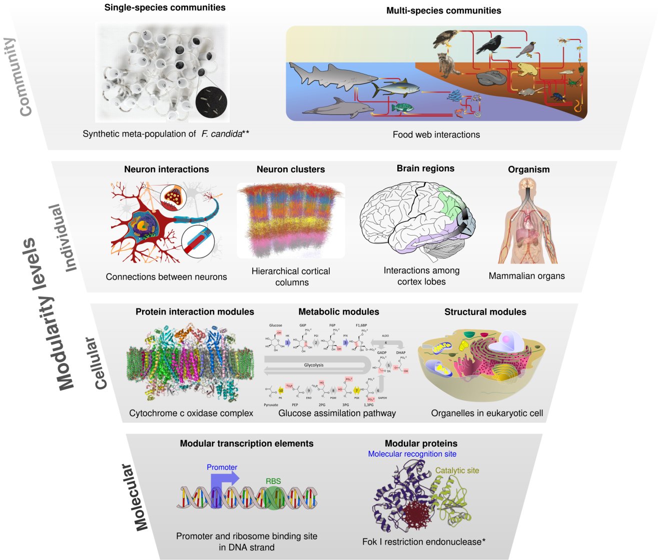

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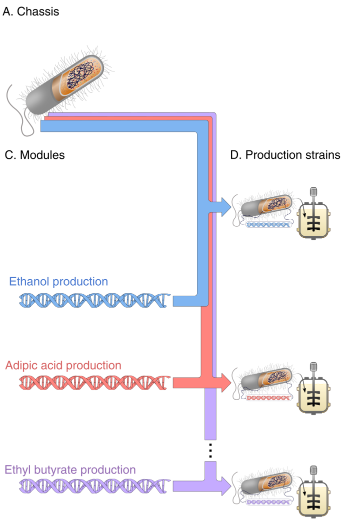
Principles of Modular Cell (ModCell) design



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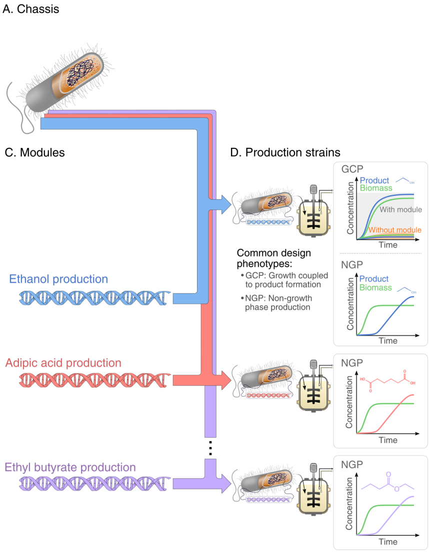

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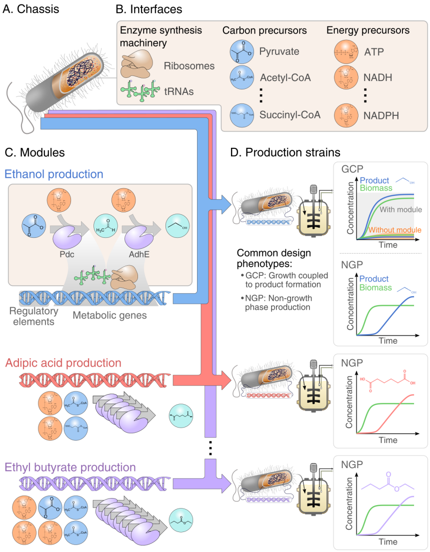

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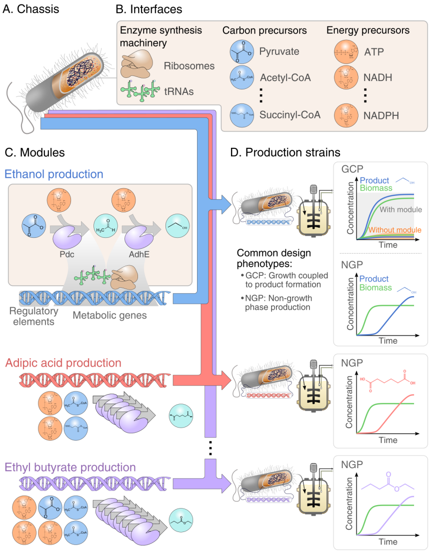

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- Each *production strain* displays a desirable phenotype
- Chassis, modules, and interfaces have to be designed in accordance to this desirable functions
- ModCell brings the same advantages of modularity in conventional engineering to metabolic engineering: efficiency and robustness

Mathematical formulation of ModCell

$$\max_{y_j, z_{jk}} \quad (f_{\mathbf{1}}, f_{\mathbf{2}}, \ldots, f_{|\mathcal{K}|})^T \quad \textbf{s.t.}$$

- Multi-objective optimization. Design objective f_k is the target phenotype of production strain k.

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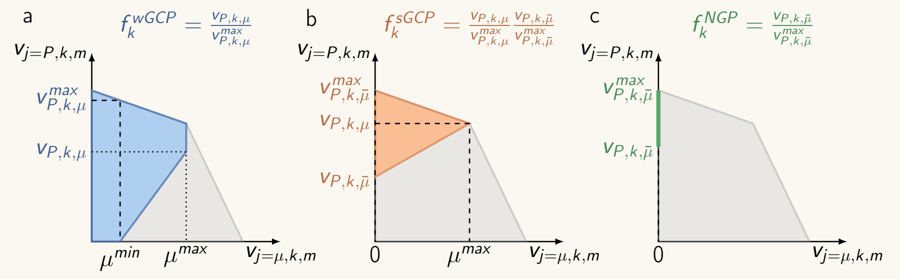

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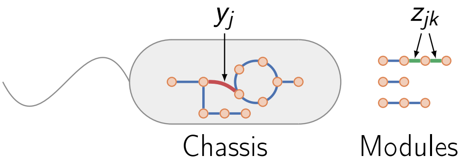

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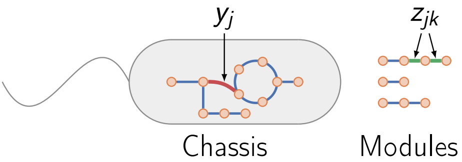
$$f_k \in \text{arg max} \left\{ \frac{1}{f_k^{max}} \sum_{j \in \mathcal{J}_k} c_{jk} v_{jk} \quad \text{s.t.} \right.$$

$$\sum_{j \in \mathcal{J}_k} S_{ijk} v_{jk} = 0 \qquad \text{for all } i \in \mathcal{I}_k$$

$$l_{jk} \leq v_{jk} \leq u_{jk} \qquad \text{for all } j \in \mathcal{J}_k$$

$$l_{jk} d_{jk} \leq v_{jk} \leq u_{jk} d_{jk} \qquad \text{for all } j \in \mathcal{C}$$

$$\left. \text{where } d_{jk} = y_j \vee z_{jk} \right\} \qquad \text{for all } k \in \mathcal{K}$$



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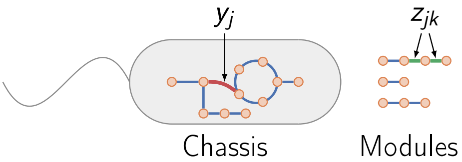


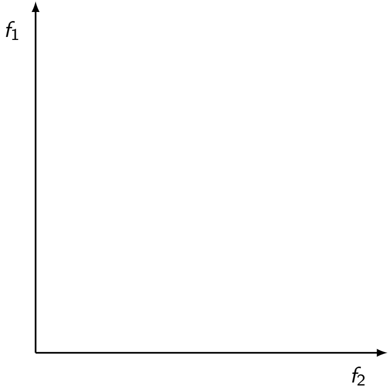
- Multi-objective optimization. Design objective f_k is the target phenotype of production strain k.
- Simultaneous design of chassis (y_j) and modules (z_{jk})
- Flux prediction based, but not limited, in constraint-based models
- New strain design approach to simultaneously consider an arbitrary number of target phenotypes, thus reducing redundant engineering efforts

Outline

What defines a solution?

Multi-objective optimization problem

$$\max_{x \in X} \quad F(x) = (f_1(x), f_2(x), \dots)^T$$



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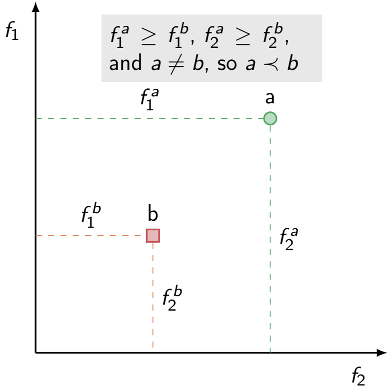

Definition of domination

A vector a dominates another vector b (denoted $a \prec b$) iff $a_i \geq b_i \; \forall i \in \{1, 2, \ldots, K\}$ and $a_i \neq b_i$ for at least one i.

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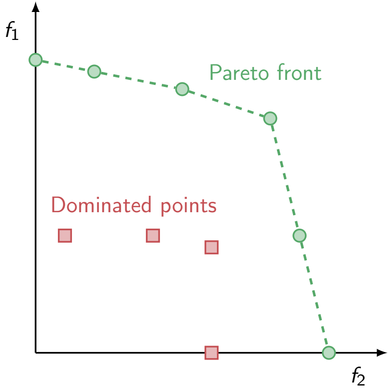

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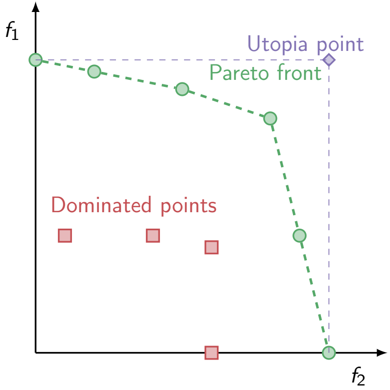

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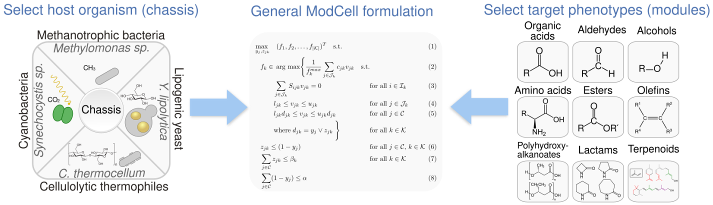
- Utopia point

Two complementary solvers: MOEA and MILP



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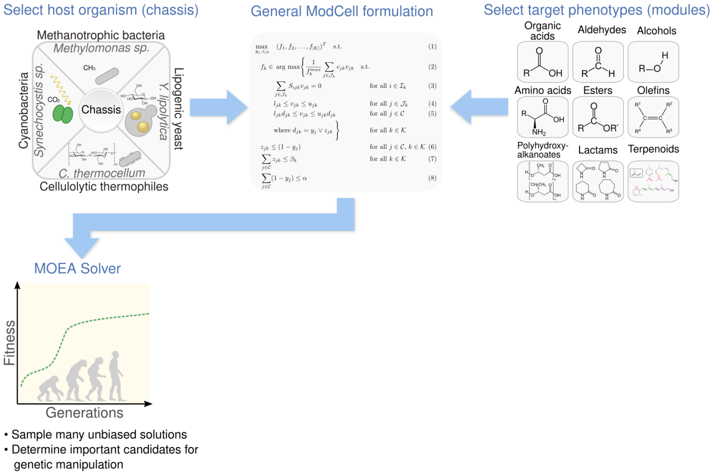

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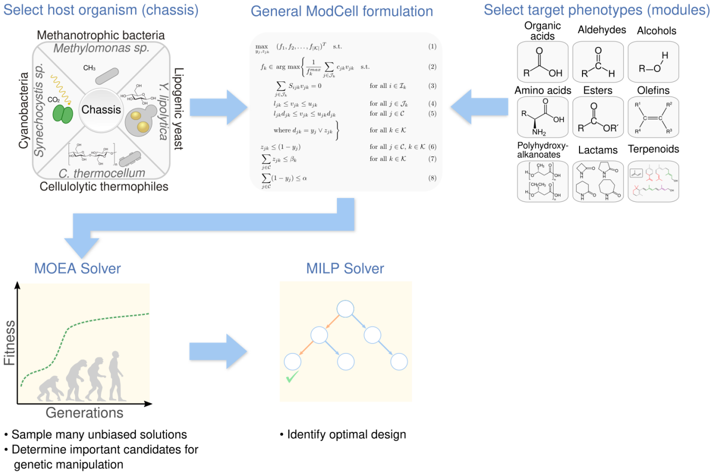

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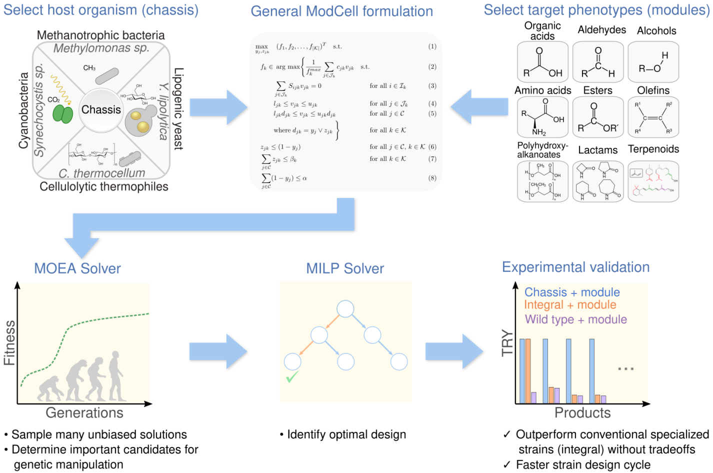

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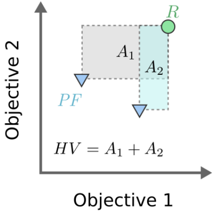

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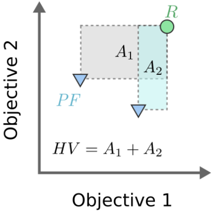

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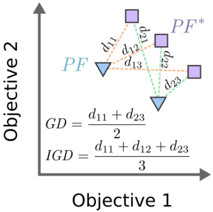

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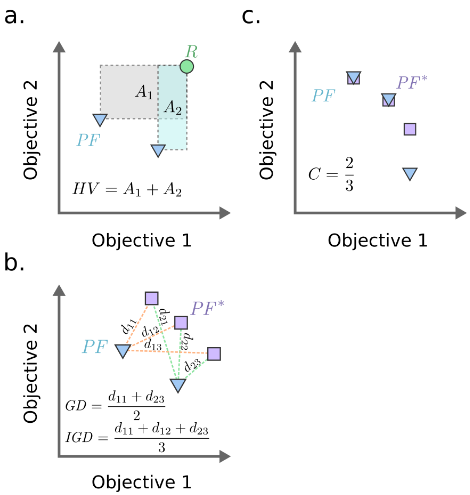

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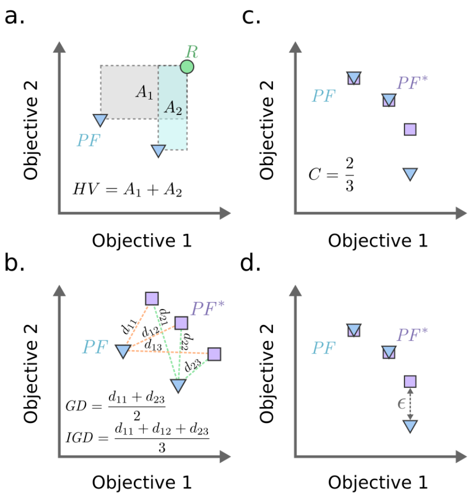

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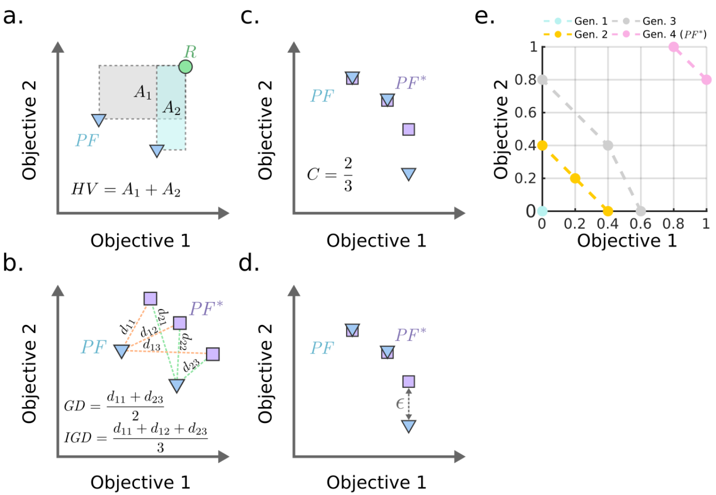

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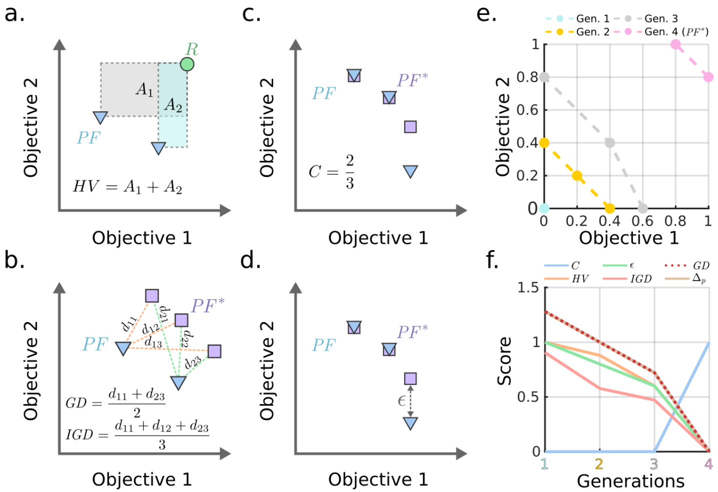
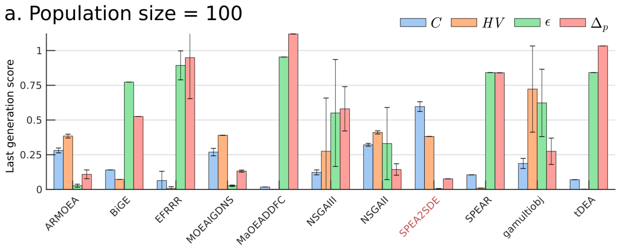


Population size is the most important factor in MOEA



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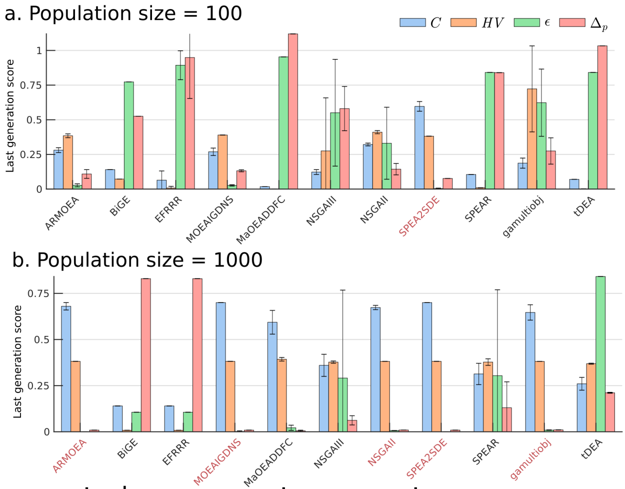

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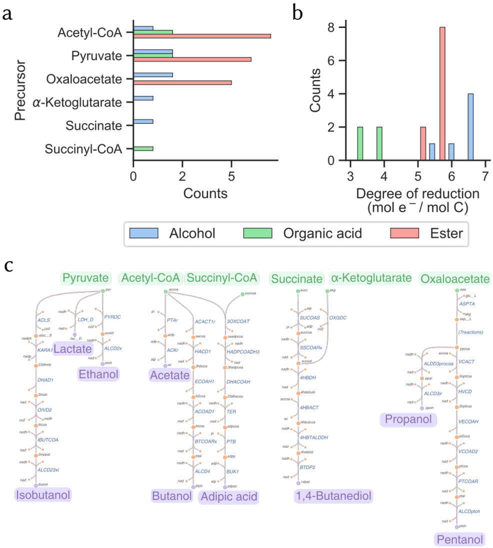
- For large population sizes several algorithms attain the best results.

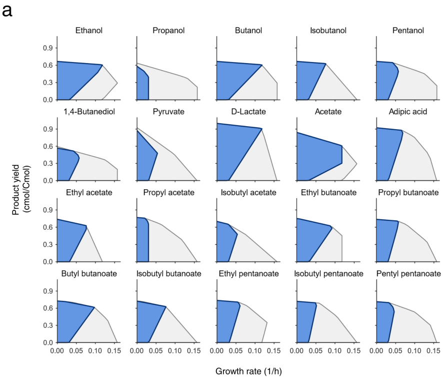
Outline

Input: 20 diverse products



- *E. coli* as a parent to build the chassis.
- 6 alcohols from C2 to C5.
- 4 carboxylic acids from C2 to C6.
- 10 derived esters from C4 to C10.
- Esters are synthesized from an acyl-CoA and alcohol by the AAT enzyme.

Results: Highly compatible chassis



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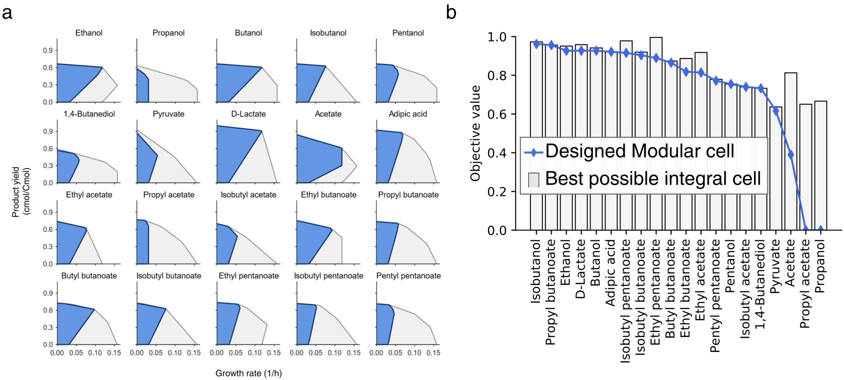

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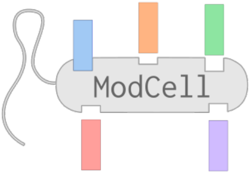
- No loss of performance with respect to conventional single-product (integral) strain design

Summary

- Inspired by conventional engineering modularity, develop modular cell design concept to accelerate biocatalyst R&D cycles.



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- Demonstrate MOEA and MILP approaches to solve the optimization problem.

Summary

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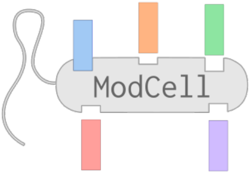
- Propose modular cell design as a multi-objective optimization problem, this framework allows to simultaneously design multiple target phenotypes minimizing redundant efforts.
- Demonstrate MOEA and MILP approaches to solve the optimization problem.
- Design a chassis cell compatible with growth-coupled synthesis of 17 out of 20 products without loss of performance with respect to integral (conventional) strain design.



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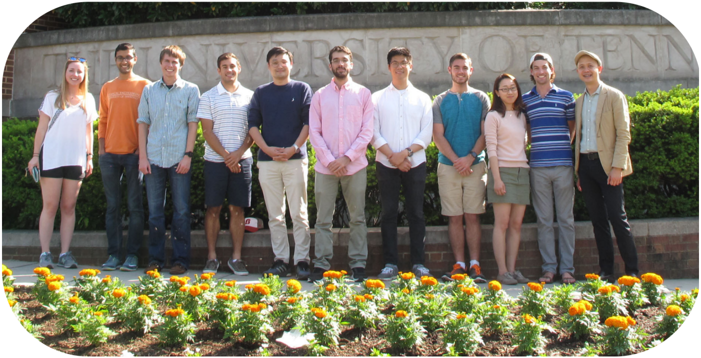
cbi THE CENTER FOR BIOENERGY INNOVATION

Trinh Lab



References

- Garcia, S. & Trinh, C. T. Multiobjective strain design: A framework for modular cell engineering. *Metabolic Engineering* **51** (2019).
- Garcia, S. & Trinh, C. T. Modular design: Implementing proven engineering principles in biotechnology. *Biotechnology Advances* (2019).
- Garcia, S. & Trinh, C. T. Comparison of Multi-Objective Evolutionary Algorithms to Solve the Modular Cell Design Problem for Novel Biocatalysis. *Processes* **7** (2019).

All programs and data analysis scripts are available on Github with detailed documentation to enable reproducibility and further use:
`https://github.com/trinhlab`