THE UNIVERSITY of TENNESSEE KNOXVILLE

Design of Modular Cells by Goal Attainment Optimization

Sergio Garcia and Cong T. Trinh

Department of Chemical and Biomolecular Engineering, The University of Tennessee, Knoxville, TN.

Presented at AIChE Annual Meeting 2019. Orlando, FL.

Outline

Modular design concepts

Definition:

> "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."

Modular design concepts

Definition:

> "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."

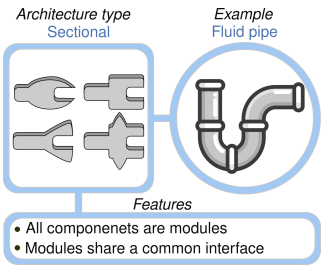
Types of modular architecture:

Modular design concepts

Definition:

> "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."

Types of modular architecture:

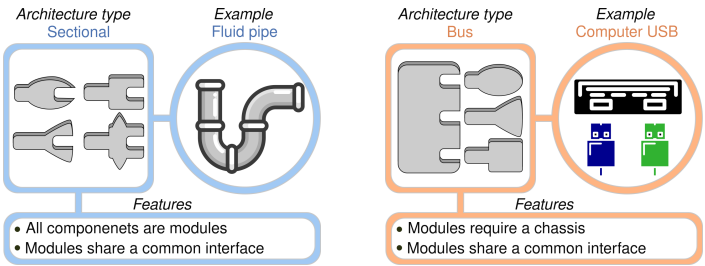


Modular design concepts

Definition:

"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."

Types of modular architecture:



Modular design concepts

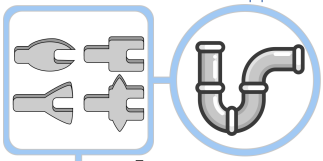
Definition:

"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."

Types of modular architecture:

Architecture type
Sectional

Example
Fluid pipe

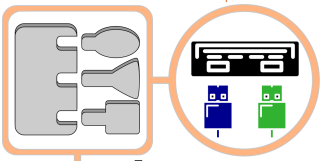


Features

- All componenets are modules
- Modules share a common interface

Architecture type
Bus

Example
Computer USB

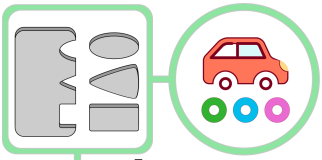


Features

- Modules require a chassis
- Modules share a common interface

Architecture type
Slot

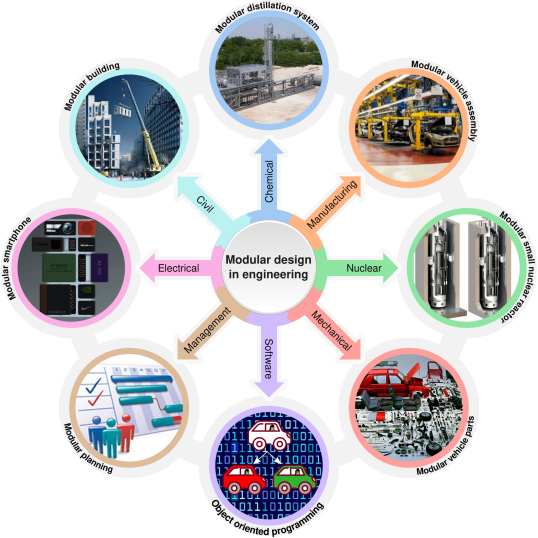
Example
Car tires



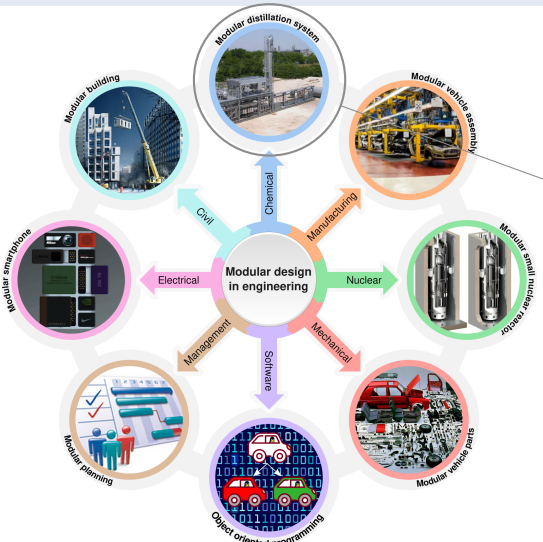
Features

- Modules require a chassis
- Each module has a unique interface

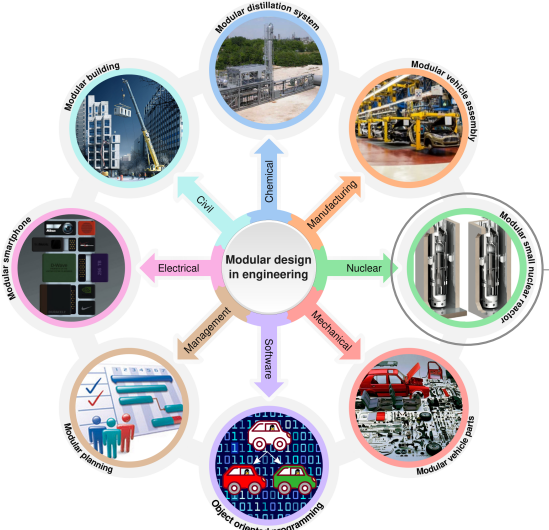
Driving forces and potential tradeoffs of modular design

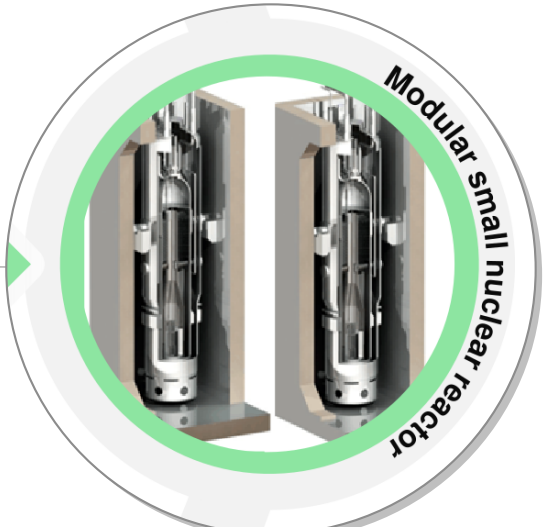


Driving forces and potential tradeoffs of modular design

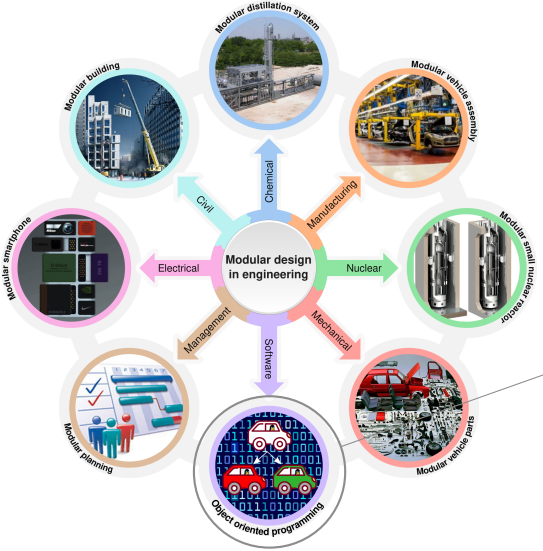


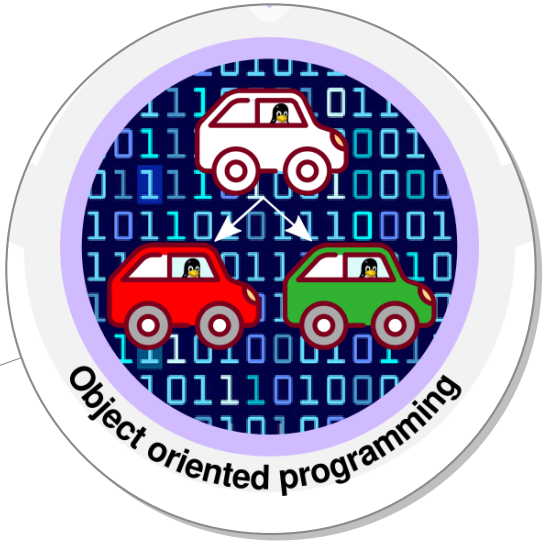
Driving forces and potential tradeoffs of modular design



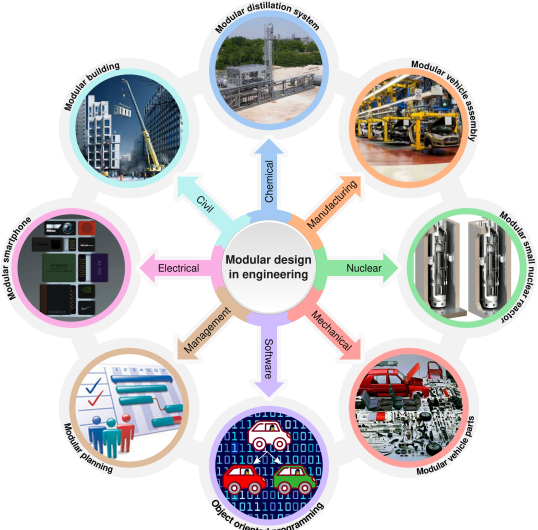


Driving forces and potential tradeoffs of modular design



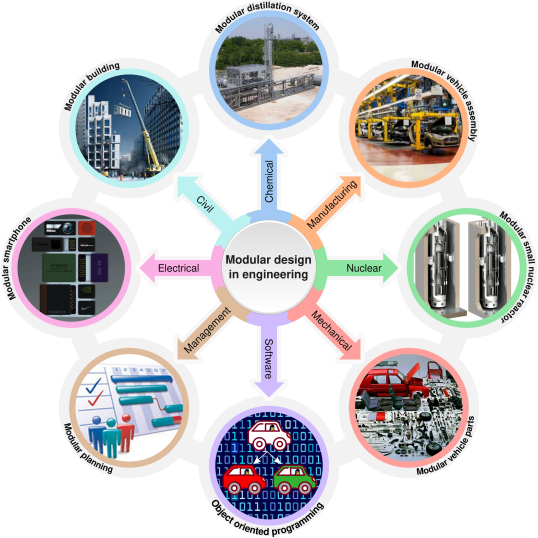


Driving forces and potential tradeoffs of modular design



Driving forces for modularization:

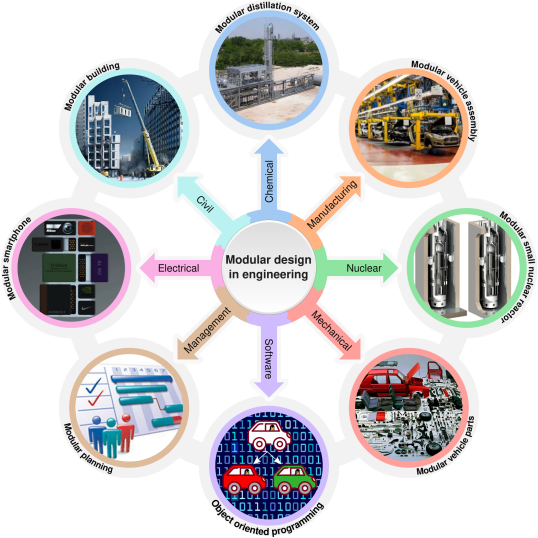
Driving forces and potential tradeoffs of modular design



Driving forces for modularization:

- Innovation: Novel solutions to existing problems

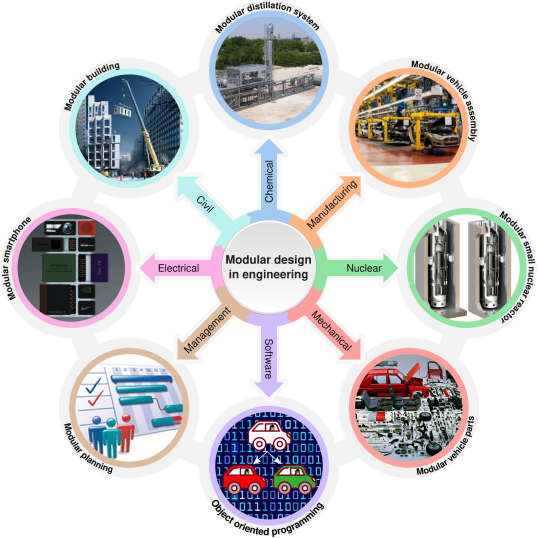
Driving forces and potential tradeoffs of modular design



Driving forces for modularization:

- Innovation: Novel solutions to existing problems
- Efficiency: Faster and cheaper product construction and maintenance

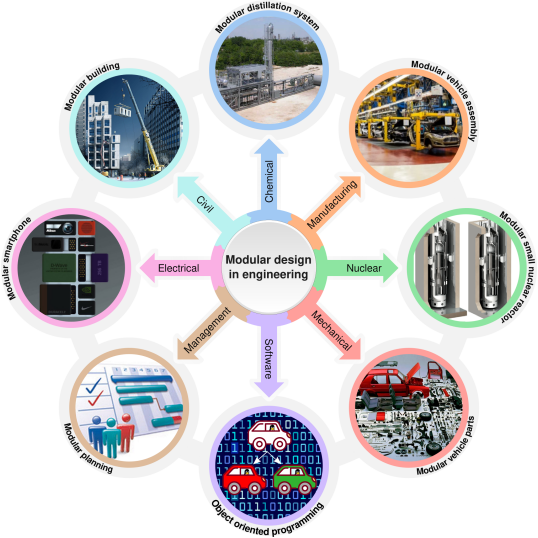
Driving forces and potential tradeoffs of modular design



Driving forces for modularization:

- Innovation: Novel solutions to existing problems
- Efficiency: Faster and cheaper product construction and maintenance
- Customizability: Better tailor a solution to specifics of the problem

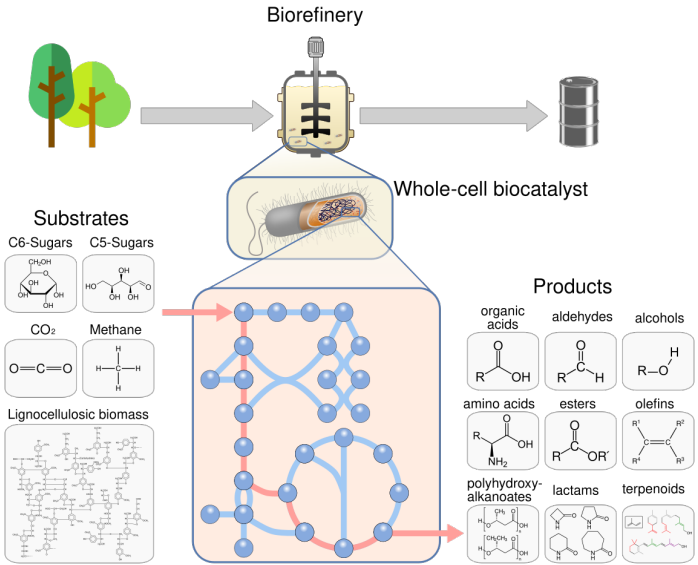
Driving forces and potential tradeoffs of modular design



Driving forces for modularization:

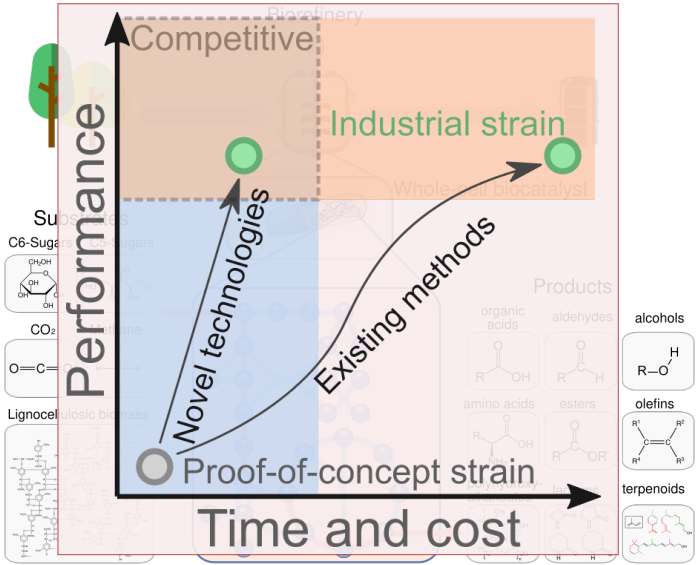
- Innovation: Novel solutions to existing problems
- Efficiency: Faster and cheaper product construction and maintenance
- Customizability: Better tailor a solution to specifics of the problem
- Predictability: Robust system behavior across diverse scenarios

Applications and challenges in microbial catalysis



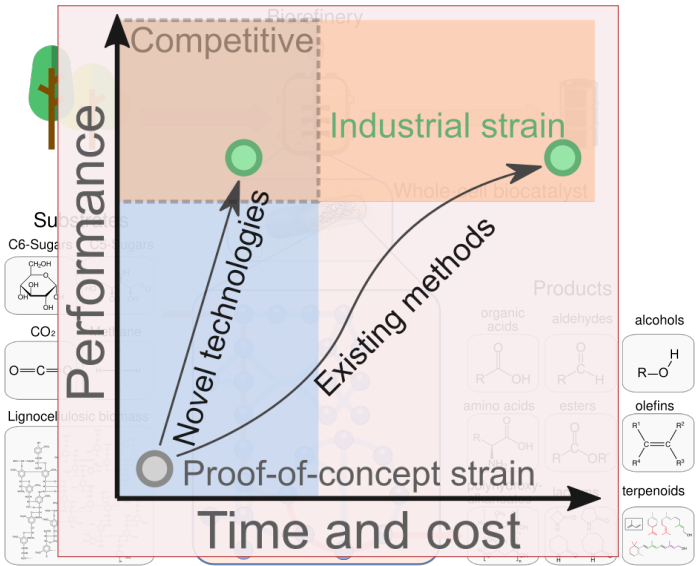
- Metabolic engineering entails many promising applications, including bioremediation, medical treatment, biocatalysis.

Applications and challenges in microbial catalysis



- Metabolic engineering entails many promising applications, including bioremediation, medical treatment, biocatalysis.
- However, current engineering design-build-test cycles are too slow to make these applications widely feasible, even when proof-of-concept designs exist.

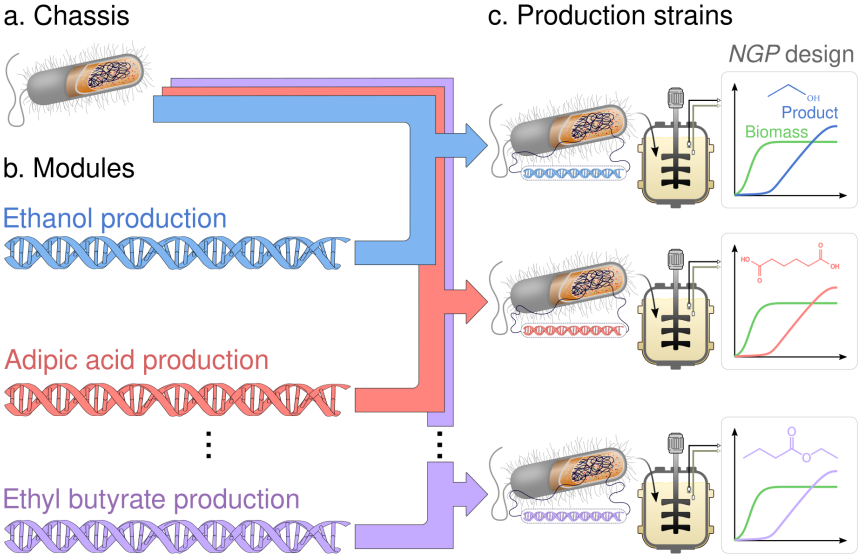
Applications and challenges in microbial catalysis



- Metabolic engineering entails many promising applications, including bioremediation, medical treatment, biocatalysis.
- However, current engineering design-build-test cycles are too slow to make these applications widely feasible, even when proof-of-concept designs exist.
- To address this challenge, we can apply proven modular design principles to biocatalyst engineering.

Outline

Principles of Modular Cell (ModCell) design



Mathematical formulation of ModCell

$$\max_{y_j, z_{jk}} \quad (f_1, f_2, \ldots, f_{|\mathcal{K}|})^T \quad \text{s.t.}$$

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

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

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

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

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

$$\sum_{j \in \mathcal{C}} (1 - y_j) \leq \alpha$$

$$\sum_{j \in \mathcal{C}} z_{jk} \leq \beta_k \qquad \text{for all } k \in \mathcal{K}$$

$$z_{jk} \leq (1 - y_j) \qquad \text{for all } j \in \mathcal{C},\ k \in \mathcal{K}$$

Mathematical formulation of ModCell

$$\max_{y_j, z_{jk}} \quad (f_1, f_2, \ldots, f_{|\mathcal{K}|})^T \quad \text{s.t.}$$

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

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

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

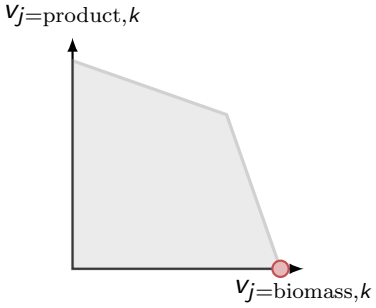
$$l_{jk} d_{jk} \leq v_{jk} \leq u_{jk} d_{jk} \qquad \text{for all } j \in \mathcal{C}$$

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

$$\sum_{j \in \mathcal{C}} (1 - y_j) \leq \alpha$$

$$\sum_{j \in \mathcal{C}} z_{jk} \leq \beta_k \qquad \text{for all } k \in \mathcal{K}$$

$$z_{jk} \leq (1 - y_j) \qquad \text{for all } j \in \mathcal{C},\ k \in \mathcal{K}$$



Mathematical formulation of ModCell

$$\max_{y_j, z_{jk}} \quad (f_1, f_2, \ldots, f_{|\mathcal{K}|})^T \quad \text{s.t.}$$

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

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

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

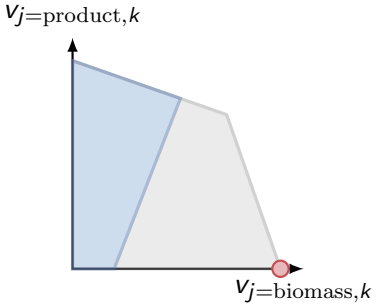
$$l_{jk} d_{jk} \leq v_{jk} \leq u_{jk} d_{jk} \qquad \text{for all } j \in \mathcal{C}$$

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

$$\sum_{j \in \mathcal{C}} (1 - y_j) \leq \alpha$$

$$\sum_{j \in \mathcal{C}} z_{jk} \leq \beta_k \qquad \text{for all } k \in \mathcal{K}$$

$$z_{jk} \leq (1 - y_j) \qquad \text{for all } j \in \mathcal{C},\ k \in \mathcal{K}$$



Mathematical formulation of ModCell

$$\max_{y_j, z_{jk}} \quad (f_1, f_2, \ldots, f_{|\mathcal{K}|})^T \quad \text{s.t.}$$

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

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

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

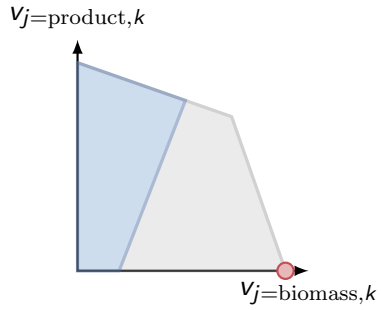
$$l_{jk} d_{jk} \leq v_{jk} \leq u_{jk} d_{jk} \qquad \text{for all } j \in \mathcal{C}$$

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

$$\sum_{j \in \mathcal{C}} (1 - y_j) \leq \alpha$$

$$\sum_{j \in \mathcal{C}} z_{jk} \leq \beta_k \qquad \text{for all } k \in \mathcal{K}$$

$$z_{jk} \leq (1 - y_j) \qquad \text{for all } j \in \mathcal{C},\ k \in \mathcal{K}$$



Mathematical formulation of ModCell

$$\max_{y_j, z_{jk}} \quad (f_1, f_2, \ldots, f_{|\mathcal{K}|})^T \quad \text{s.t.}$$

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

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

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

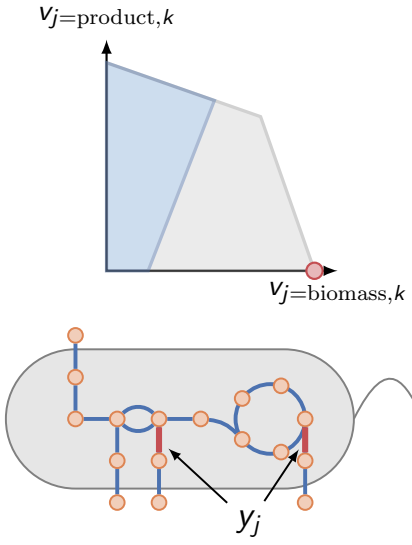
$$l_{jk} d_{jk} \leq v_{jk} \leq u_{jk} d_{jk} \qquad \text{for all } j \in \mathcal{C}$$

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

$$\sum_{j \in \mathcal{C}} (1 - y_j) \leq \alpha$$

$$\sum_{j \in \mathcal{C}} z_{jk} \leq \beta_k \qquad \text{for all } k \in \mathcal{K}$$

$$z_{jk} \leq (1 - y_j) \qquad \text{for all } j \in \mathcal{C},\ k \in \mathcal{K}$$



Mathematical formulation of ModCell

$$\max_{y_j, z_{jk}} \quad (f_1, f_2, \ldots, f_{|\mathcal{K}|})^T \quad \text{s.t.}$$

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

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

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

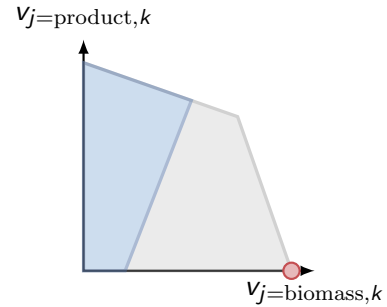
$$l_{jk} d_{jk} \leq v_{jk} \leq u_{jk} d_{jk} \qquad \text{for all } j \in \mathcal{C}$$

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

$$\sum_{j \in \mathcal{C}} (1 - y_j) \leq \alpha$$

$$\sum_{j \in \mathcal{C}} z_{jk} \leq \beta_k \qquad \text{for all } k \in \mathcal{K}$$

$$z_{jk} \leq (1 - y_j) \qquad \text{for all } j \in \mathcal{C},\ k \in \mathcal{K}$$



Mathematical formulation of ModCell

$$\max_{y_j, z_{jk}} \quad (f_1, f_2, \ldots, f_{|\mathcal{K}|})^T \quad \text{s.t.}$$

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

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

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

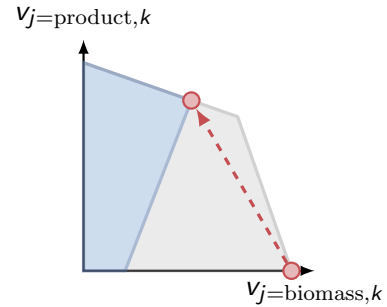
$$l_{jk} d_{jk} \leq v_{jk} \leq u_{jk} d_{jk} \qquad \text{for all } j \in \mathcal{C}$$

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

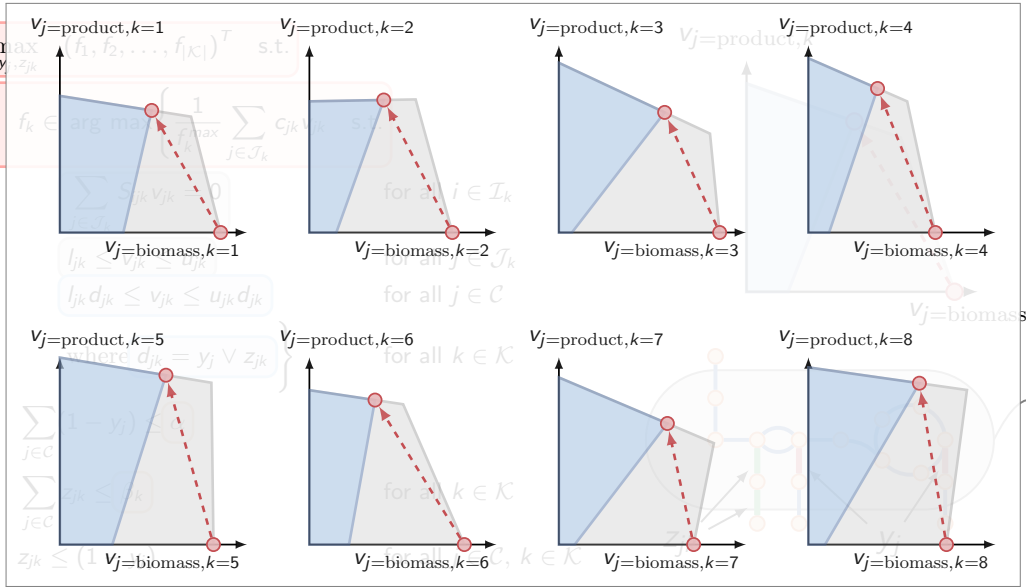
$$\sum_{j \in \mathcal{C}} (1 - y_j) \leq \alpha$$

$$\sum_{j \in \mathcal{C}} z_{jk} \leq \beta_k \qquad \text{for all } k \in \mathcal{K}$$

$$z_{jk} \leq (1 - y_j) \qquad \text{for all } j \in \mathcal{C},\ k \in \mathcal{K}$$



Mathematical formulation of ModCell



Design specification: Goal and blended formulations

Blended formulation:

$$\max \quad \sum_{k \in \mathcal{K}} a_k \, f'_k \quad \text{s.t. } f' \in \Omega \tag{1}$$

Design specification: Goal and blended formulations

Blended formulation:

$$\max \quad \sum_{k \in \mathcal{K}} a_k f'_k \quad \text{s.t. } f' \in \Omega \tag{1}$$

- Module priority, a_k, determined by criteria such as product market value or "pathway readiness level"

Design specification: Goal and blended formulations

Blended formulation:

$$\max \quad \sum_{k \in \mathcal{K}} a_k f'_k \quad \text{s.t. } f' \in \Omega \tag{1}$$

- Module priority, a_k, determined by criteria such as product market value or "pathway readiness level"

Goal attainment formulation:

$$\min \quad \sum_{k \in \mathcal{K}} (a_k^+ \delta_k^+ + a_k^- \delta_k^-) \tag{2}$$

s.t.

$$f'_k + \delta_k^+ - \delta_k^- = g_k \quad \forall k \in \mathcal{K} \tag{3}$$

$$\delta_k^+, \delta_k^- \geq 0 \quad \forall k \in \mathcal{K} \tag{4}$$

$$f' \in \Omega \tag{5}$$

Design specification: Goal and blended formulations

Blended formulation:

$$\max \quad \sum_{k \in \mathcal{K}} a_k f'_k \quad \text{s.t. } f' \in \Omega \tag{1}$$

- Module priority, a_k, determined by criteria such as product market value or "pathway readiness level"

Goal attainment formulation:

$$\min \quad \sum_{k \in \mathcal{K}} (a_k^+ \delta_k^+ + a_k^- \delta_k^-) \tag{2}$$

s.t.

$$f'_k + \delta_k^+ - \delta_k^- = g_k \quad \forall k \in \mathcal{K} \tag{3}$$

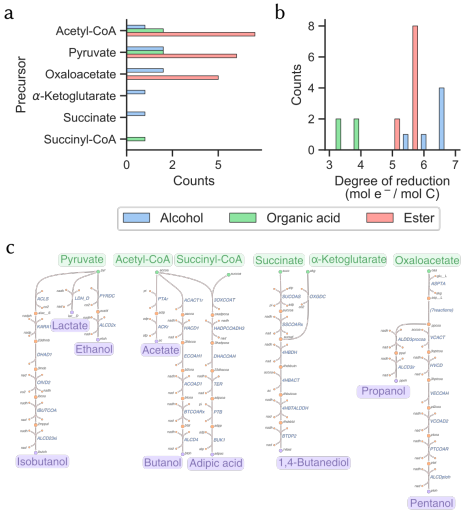
$$\delta_k^+, \delta_k^- \geq 0 \quad \forall k \in \mathcal{K} \tag{4}$$

$$f' \in \Omega \tag{5}$$

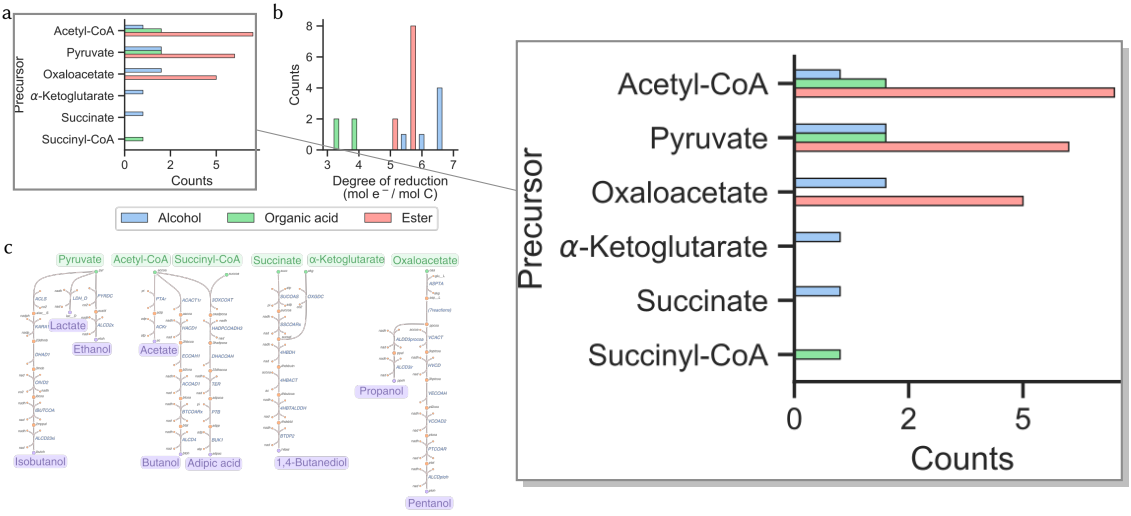
- Identification of the modular cell *compatible* (i.e., a module k is said to be compatible if $f'_k \geq g_k$) with the largest number of modules

Outline

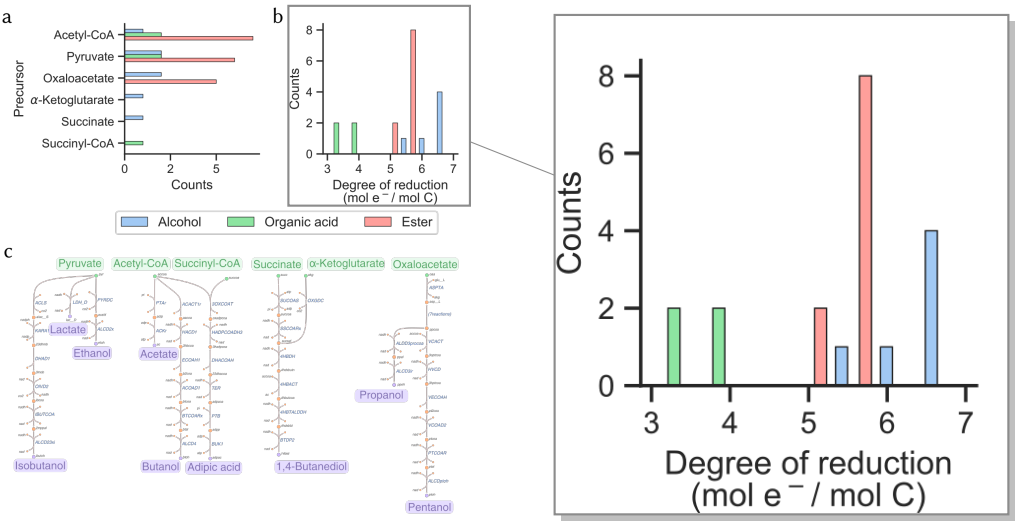
Input: 20 diverse products



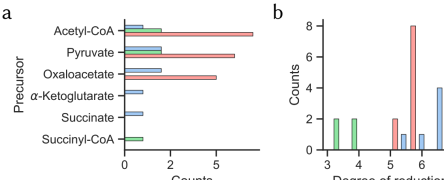
Input: 20 diverse products

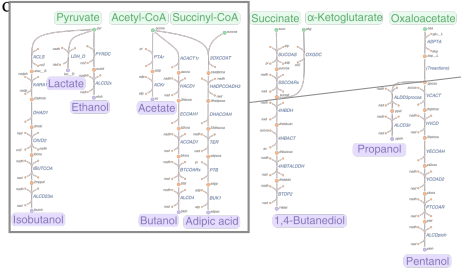


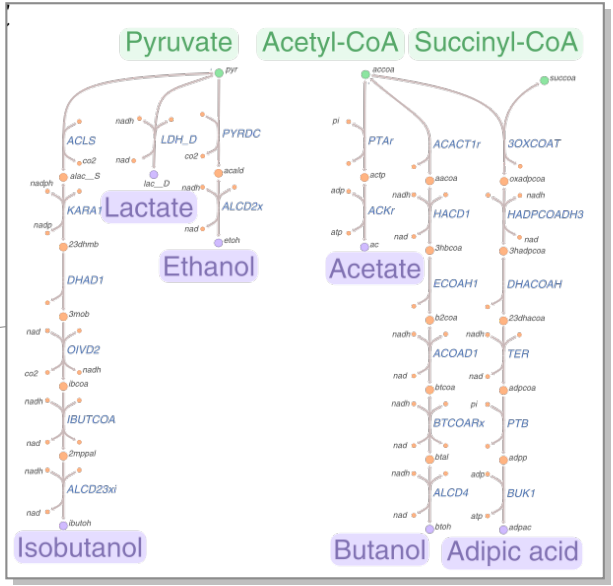
Input: 20 diverse products



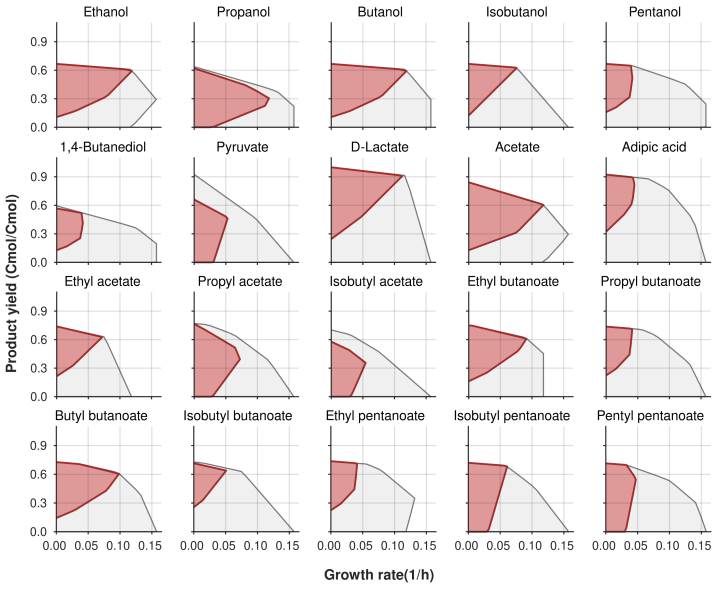
Input: 20 diverse products







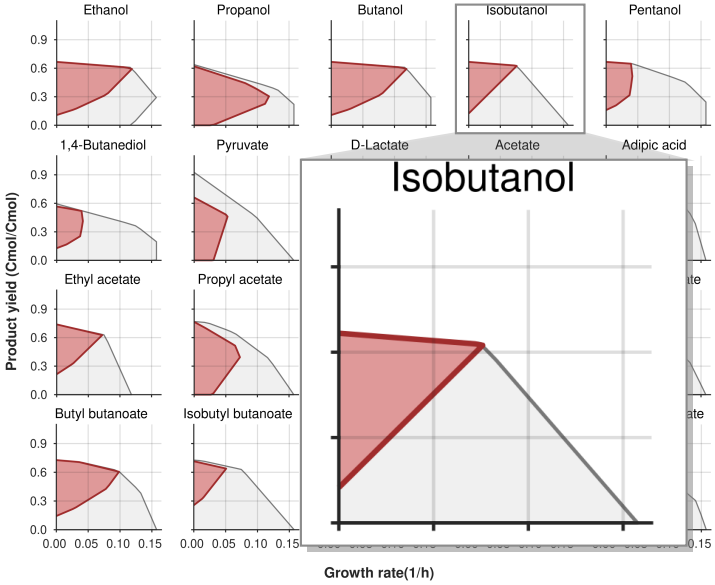
Results: Universal design



Phenotypic spaces:

- Represent feasible metabolic states according to stoichiometric constraints
- Gray region: Wild type + production module
- Red region: Designed chassis + production module

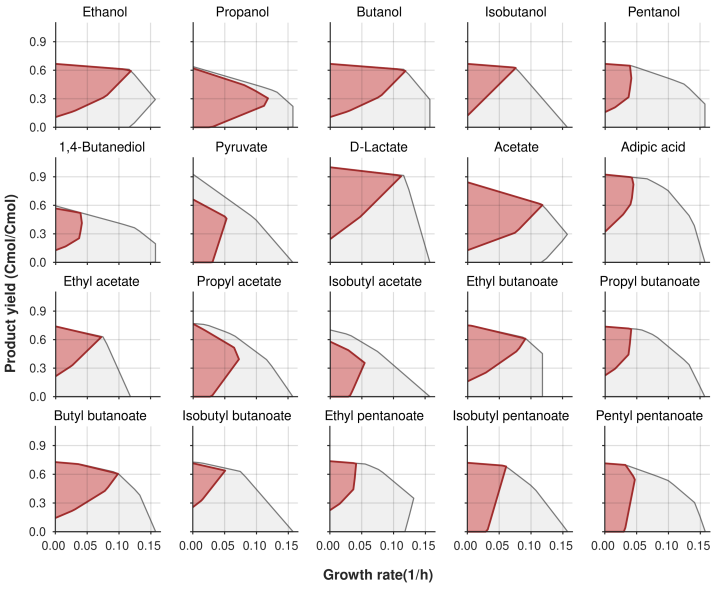
Results: Universal design



Phenotypic spaces:

- Represent feasible metabolic states according to stoichiometric constraints
- Gray region: Wild type + production module
- Red region: Designed chassis + production module

Results: Universal design

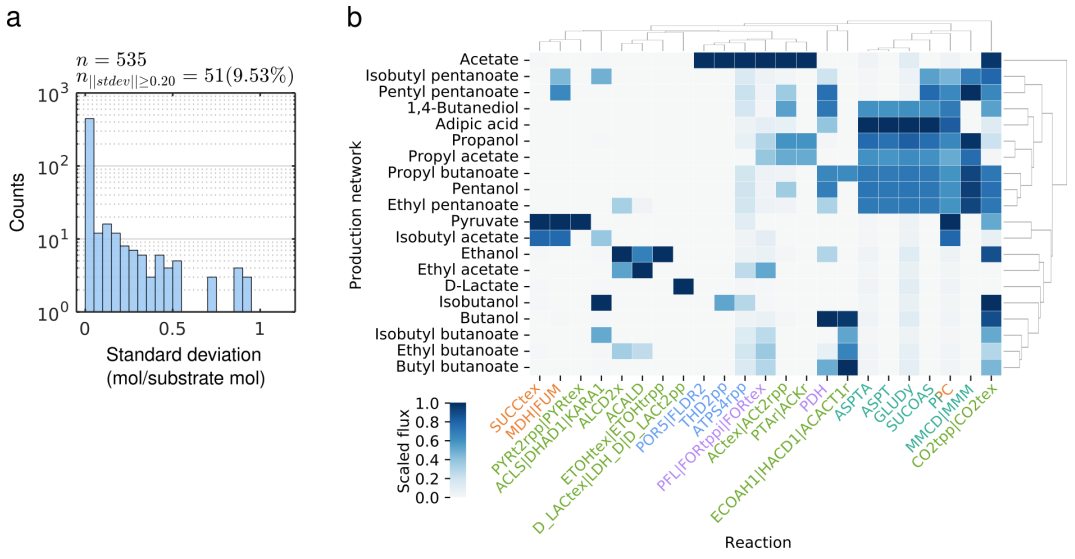


Phenotypic spaces:

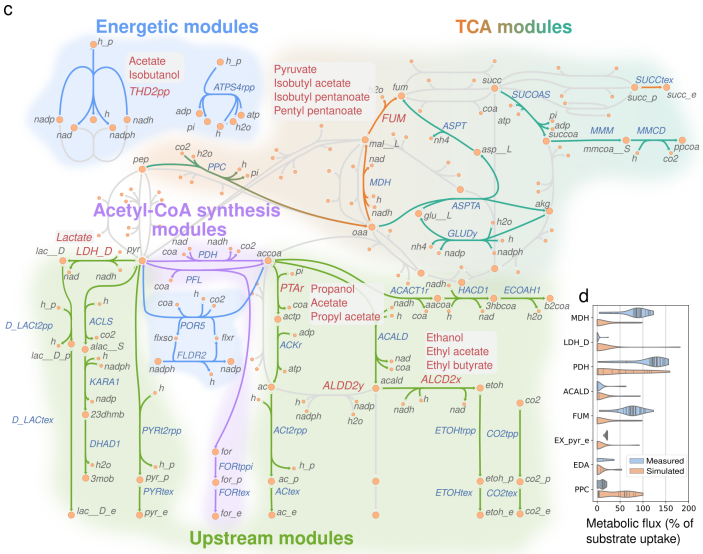
- Represent feasible metabolic states according to stoichiometric constraints
- Gray region: Wild type + production module
- Red region: Designed chassis + production module

The universal design leads to high product yields at the maximum growth rate for all combinations of chassis and production modules.

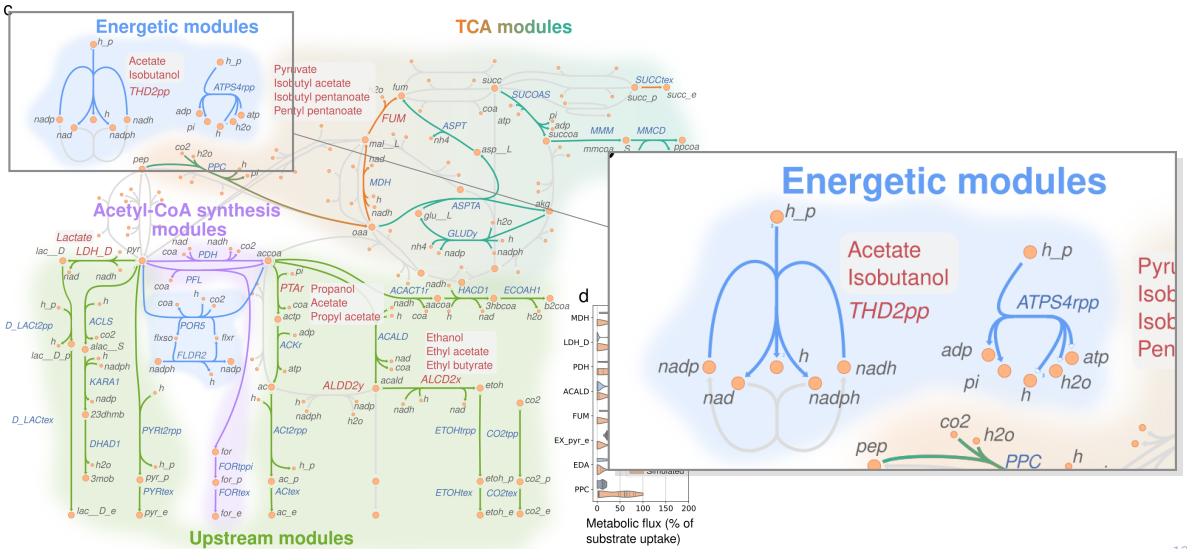
Identification of chassis metabolic interfaces



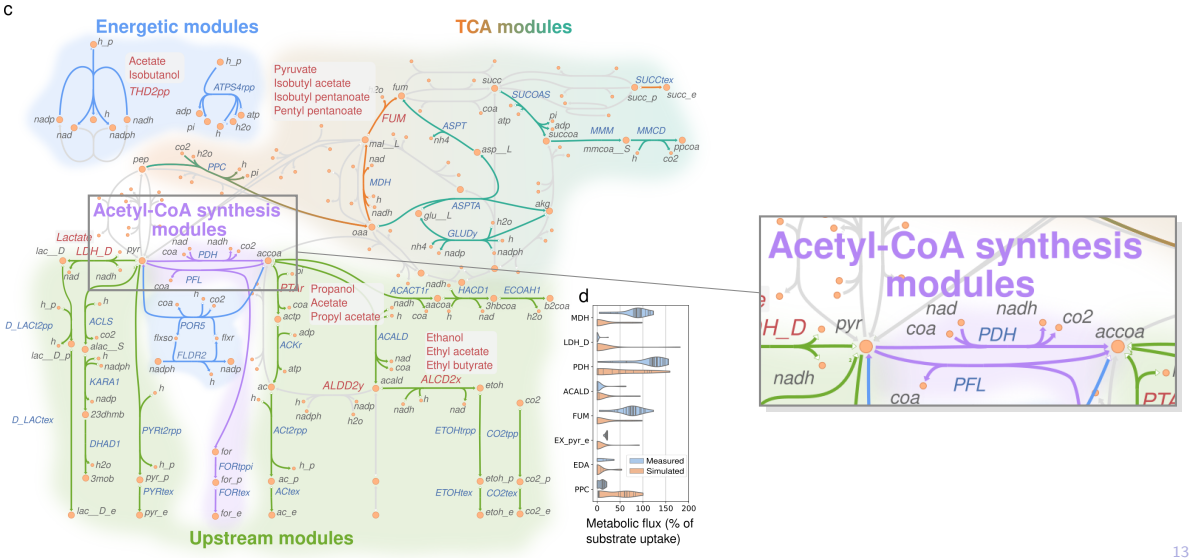
Natural modularity and flexibility of core metabolism enables universal design



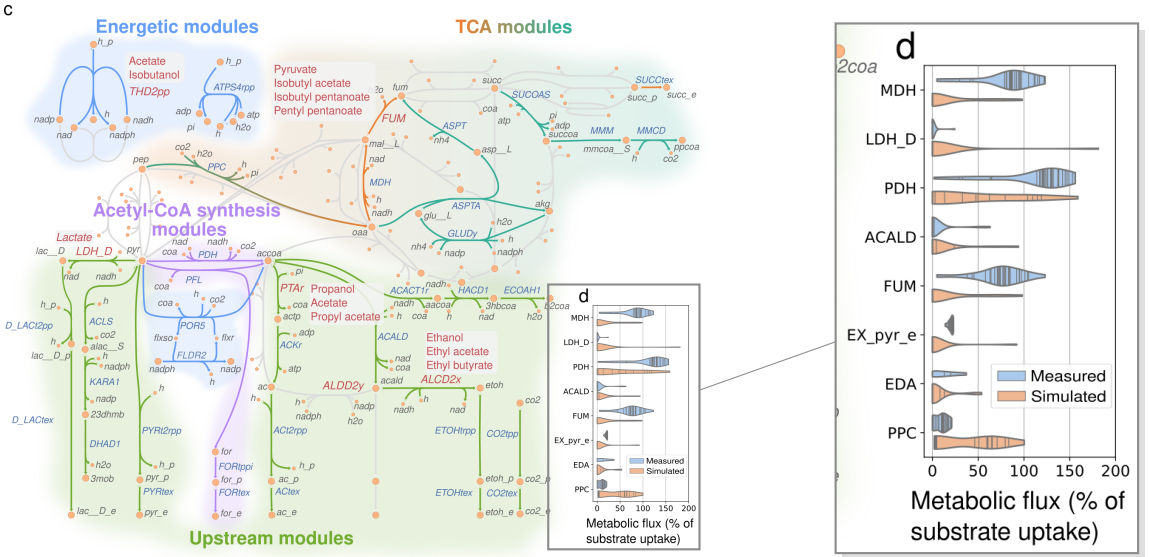
Natural modularity and flexibility of core metabolism enables universal design



Natural modularity and flexibility of core metabolism enables universal design



Natural modularity and flexibility of core metabolism enables universal design

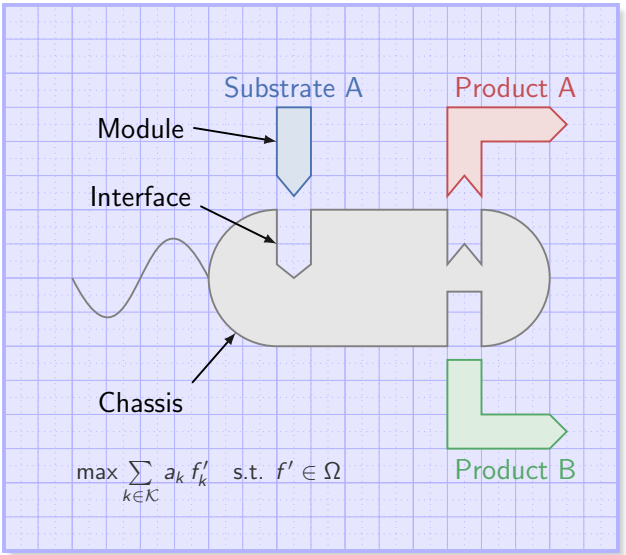


Outline

Summary

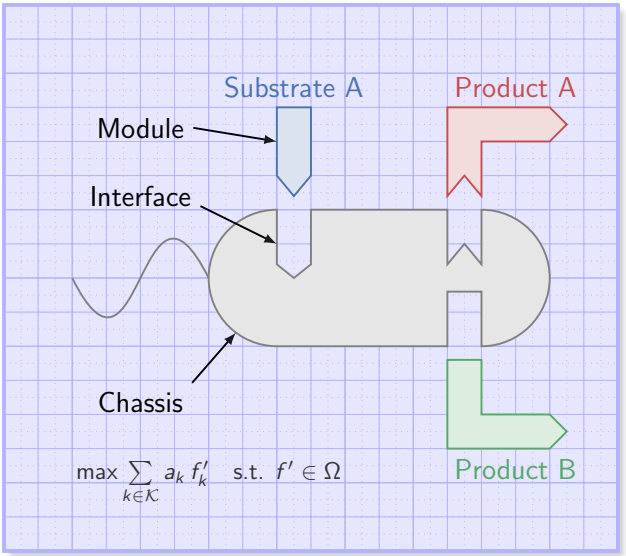
Summary

- Develop modular cell design principles to accelerate biocatalyst R&D cycles



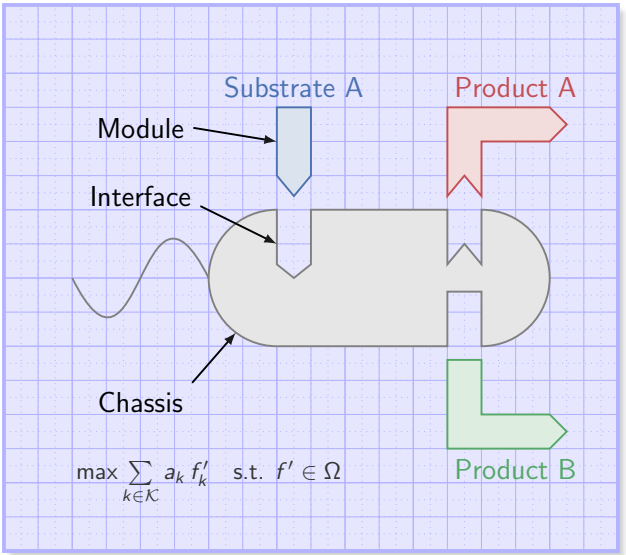
Summary

- Develop modular cell design principles to accelerate biocatalyst R&D cycles
- Propose modular cell design as a multi-objective optimization problem (MOP)



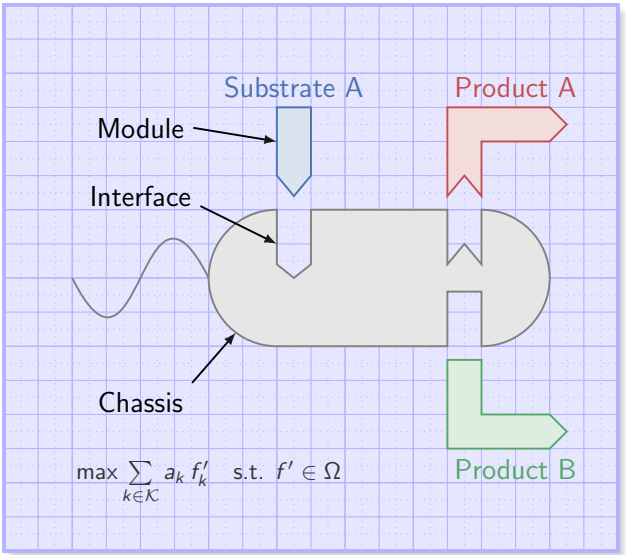
Summary

- Develop modular cell design principles to accelerate biocatalyst R&D cycles
- Propose modular cell design as a multi-objective optimization problem (MOP)
- Develop blended and goal attainment formulations to solve MOP



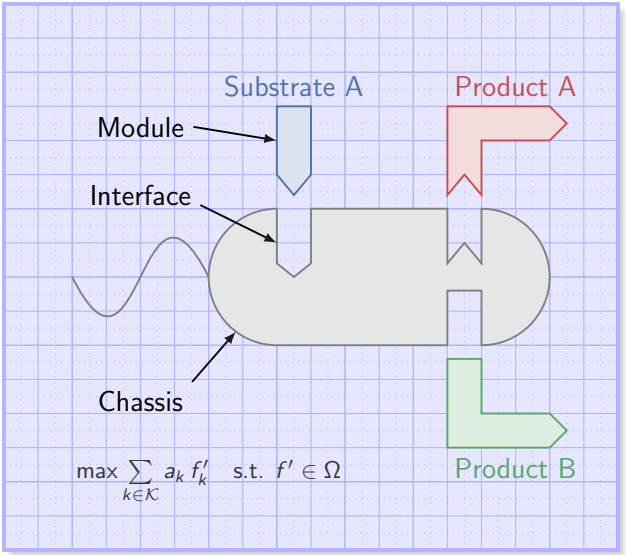
Summary

- Develop modular cell design principles to accelerate biocatalyst R&D cycles
- Propose modular cell design as a multi-objective optimization problem (MOP)
- Develop blended and goal attainment formulations to solve MOP
- Design a universal chassis compatible with a diverse group of products



Summary

- Develop modular cell design principles to accelerate biocatalyst R&D cycles
- Propose modular cell design as a multi-objective optimization problem (MOP)
- Develop blended and goal attainment formulations to solve MOP
- Design a universal chassis compatible with a diverse group of products
- Identify features of bacterial metabolism that enable universal modular design



Acknowledgements

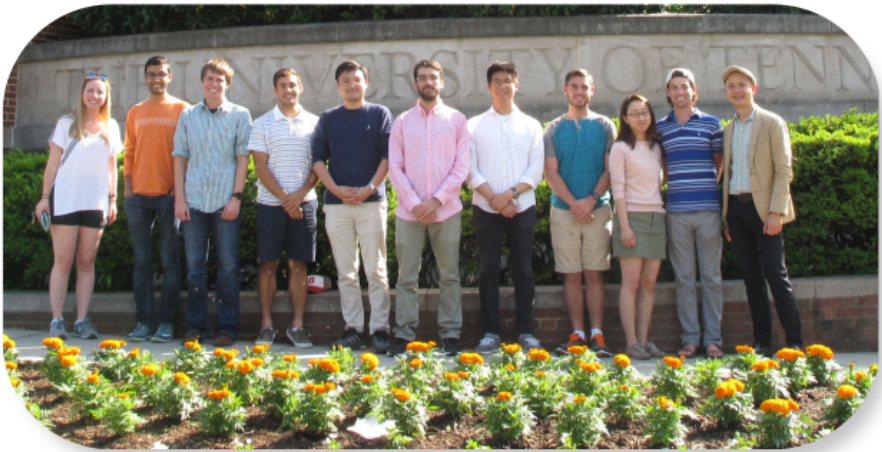
Funding Sources

NSF CAREER

THE CENTER FOR BIOENERGY INNOVATION

THE UNIVERSITY OF TENNESSEE KNOXVILLE

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* **37,** 107403 (2019).

Garcia, S. & Trinh, C. T. Harnessing natural modularity of cellular metabolism to design a modular chassis cell for a diverse class of products by using goal attainment optimization. *bioRxiv.* eprint: https://www.biorxiv.org/content/early/2019/08/28/748350.full.pdf (2019).

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