

# Multi-scale control of microbial systems: from single cells to metacommunities

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## OBJECTIVES

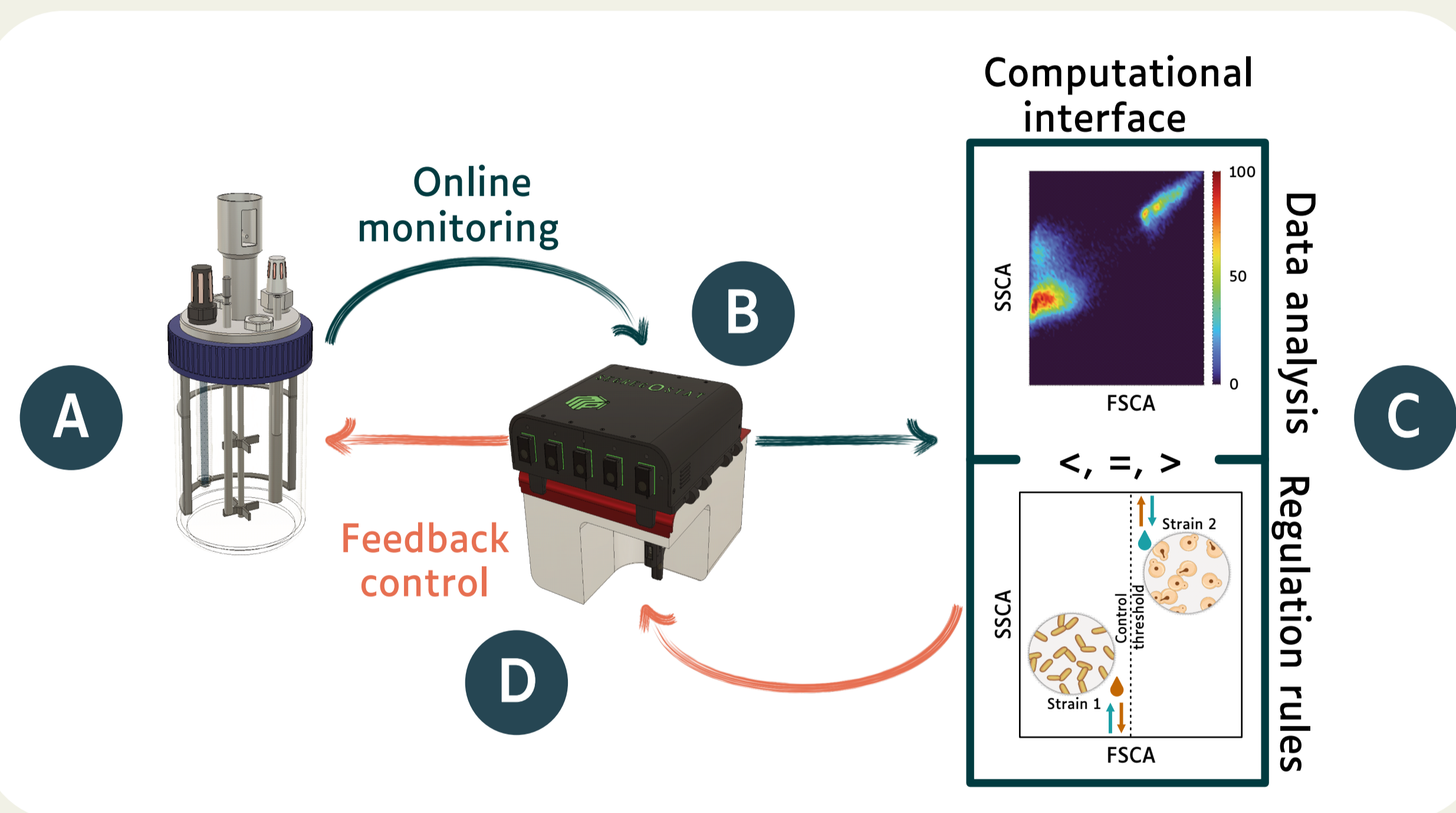
Multi-scale framework for microbial bioprocess engineering based on three complementary levels of control

## [B] TEMPORAL

Temporal control of synthetic co-cultures = **Automated Adjustment of Metabolic Niches (AAMN)**

Species-specific metabolic niches are regulated via nutrient pulses to control co-culture dynamics [3,4]

Real-time monitoring for continuous Segregostat-based control [2]



- A** Bioreactor with co-culture (2 species)
- B** Segregostat with online flow cytometry
- C** Co-culture strains percentage and applied regulation rules
- D** Carbon source pulsing to influence metabolic niches and regulate strains proportion

## PERSPECTIVE

Understand population and subpopulation dynamics & Implement our system in targeted production bioprocesses

[1] Nguyen, T. M. *et al.* Reducing phenotypic instabilities of a microbial population during continuous cultivation based on cell switching dynamics. *Biotechnol. Bioeng.* **118**, 3847–3859 (2021).

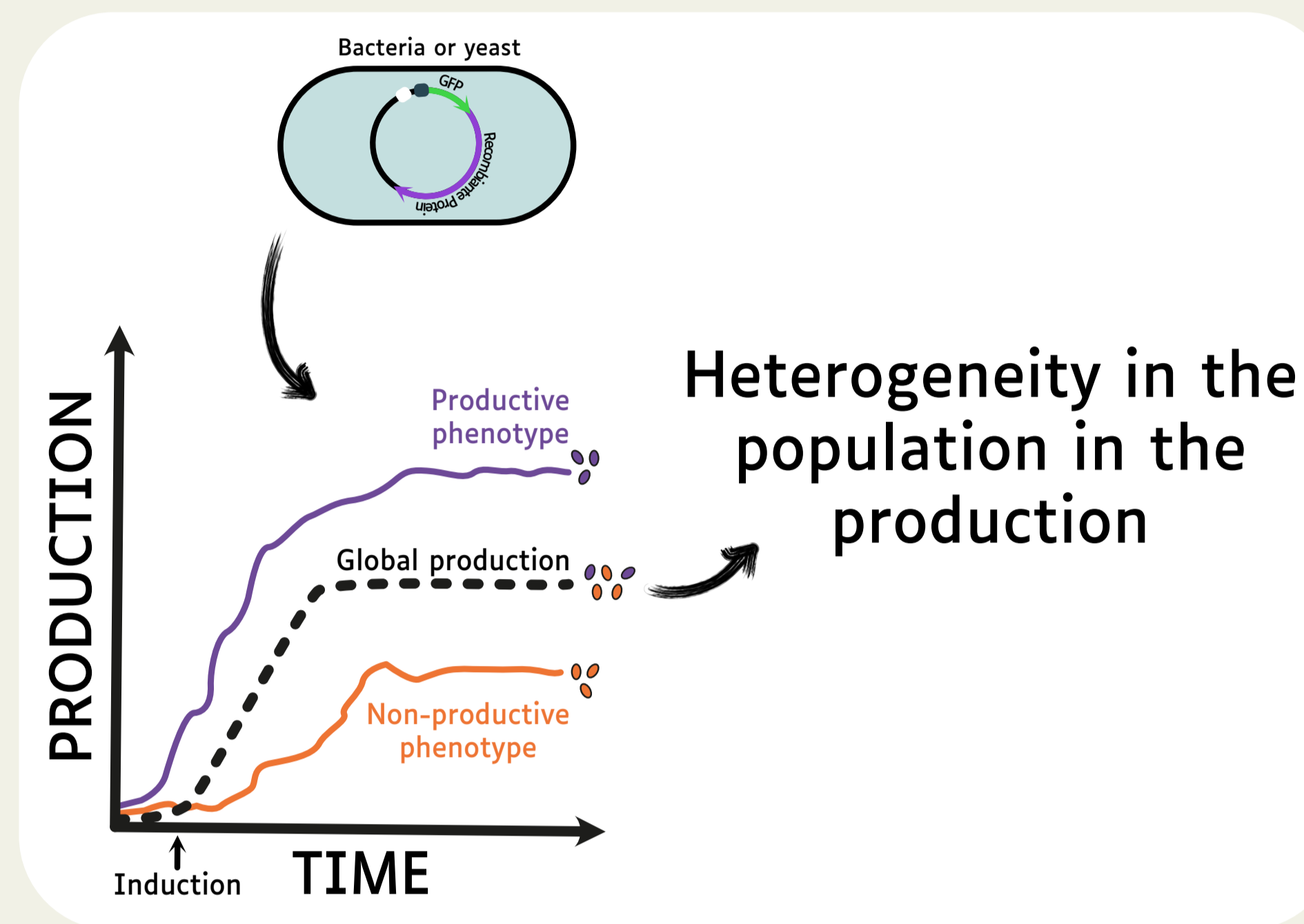
[2] Sassi, H. *et al.* Segregostat: a novel concept to control phenotypic diversification dynamics on the example of Gram-negative bacteria. *Microb. Biotechnol.* **12**, 1064–1075 (2019).

[3] Martínez, J. A. *et al.* Controlling microbial co-culture based on substrate pulsing can lead to stability through differential fitness advantages. *PLOS Comput. Biol.* **18**, e1010674 (2022).

[4] Martínez, J. A. *et al.* Automated adjustment of metabolic niches enables the control of natural and engineered microbial co-cultures. *Trends Biotechnol.* **43**, 1116–1139 (2025).

## [A] PHENOTYPIC DIVERSIFICATION

Control of intraspecies phenotypic diversification [1]



### DIVERSIFICATION CONTROL VIA INDUCTION STRATEGY

- \* Nutrient-based signals (e.g., glucose, xylose, arabinose)
- \* Synthetic inducers (non-consumable: IPTG, antibiotics)
- \* Metabolizable inducers (e.g., lactose)

## [C] SPATIAL

Spatial organization of microbial communities via interconnected bioreactors = **Continuous Culture of Meta-Communities (CCMN)**



## INTEGRATED MULTI-LEVEL CONTROL

