Reducing phenotypic instabilities of microbial population during continuous cultivation based on cell switching dynamics

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Abstract

Predicting the fate of a microbial population (i.e., growth, gene expression...) remains a challenge, especially when this population is exposed to very dynamic environmental conditions, such as those encountered during continuous cultivation. Indeed, the dynamic nature of continuous cultivation process implies the potential deviation of the microbial population involving genotypic and phenotypic diversification. This work has been focused on the induction of the arabinose operon in Escherichia coli as a model system. As a preliminary step, the GFP level triggered by an arabinose-inducible ParaBAD promoter has been tracked by flow cytometry in chemostat with glucose-arabinose co-feeding. For a large range of glucose-arabinose co-feeding, the simultaneous occurrence of GFP positive and negative subpopulation was observed. In a second set of experiments, continuous cultivation was performed by adding either glucose or arabinose, based on the ability of individual cells for switching from low GFP to high GFP states, according to a technology called segregostat. In segregostat mode of cultivation, on-line flow cytometry analysis was used for adjusting the arabinose/glucose transitions based on the phenotypic switching capabilities of the microbial population. This strategy allowed finding an appropriate arabinose pulsing frequency, leading to a prolonged maintenance of the induction level with limited impact on phenotypic diversity for more than 60 generations. This result suggests that constraining individual cells into a given phenotypic trajectory is maybe not the best strategy for directing cell population. Instead, allowing individual cells switching around a predefined threshold seems to be a robust strategy leading to oscillating, but predictable, cell population behavior.

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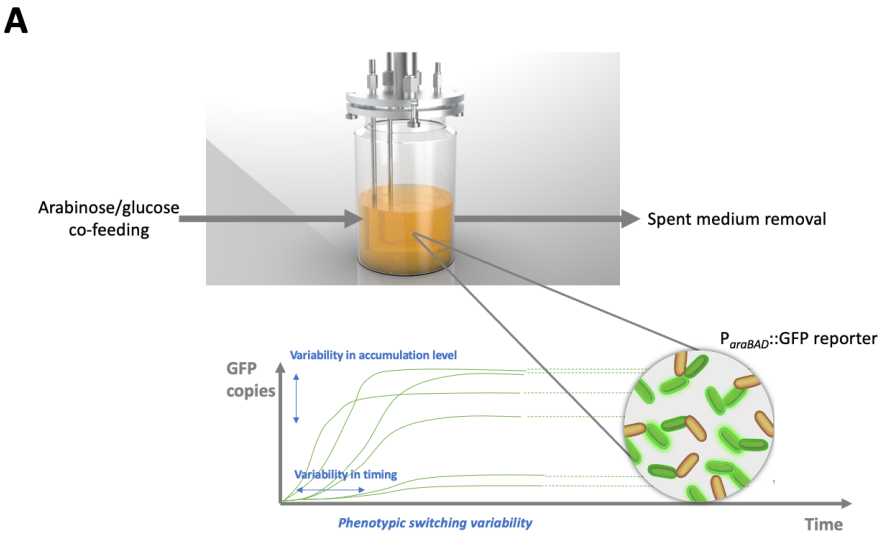

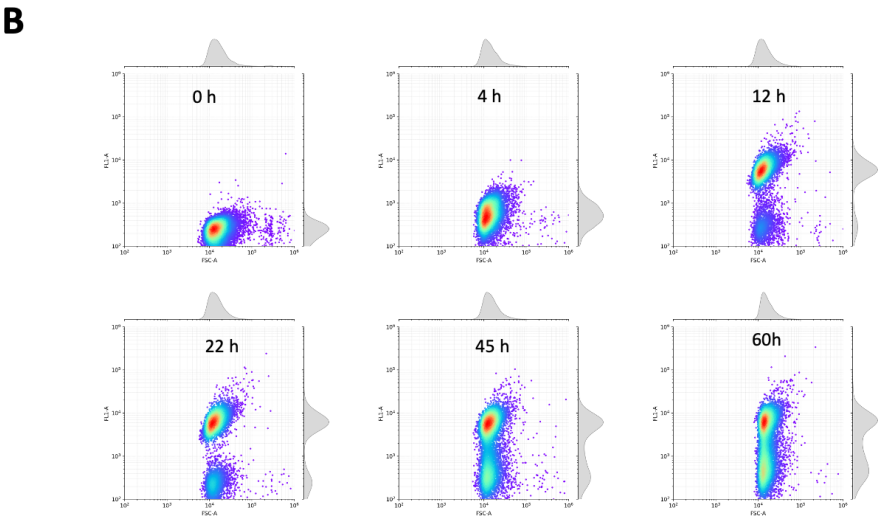

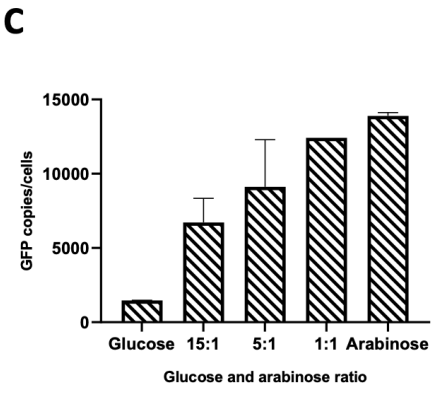

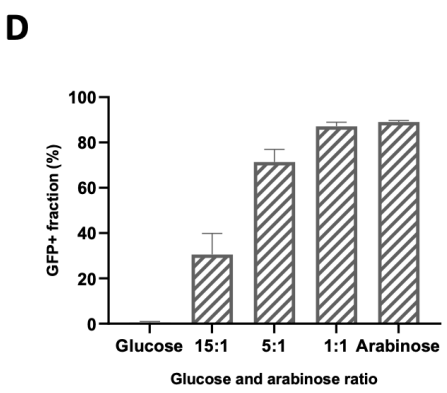

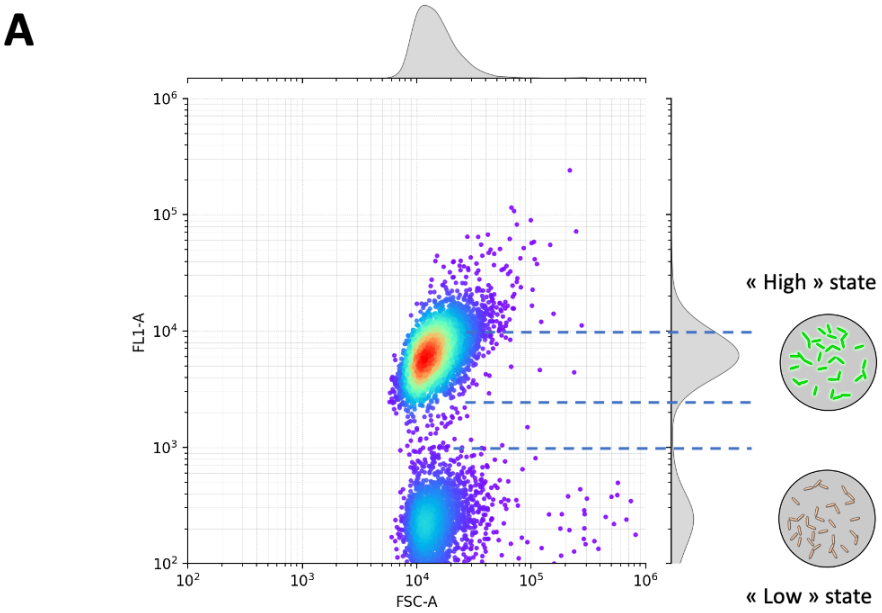

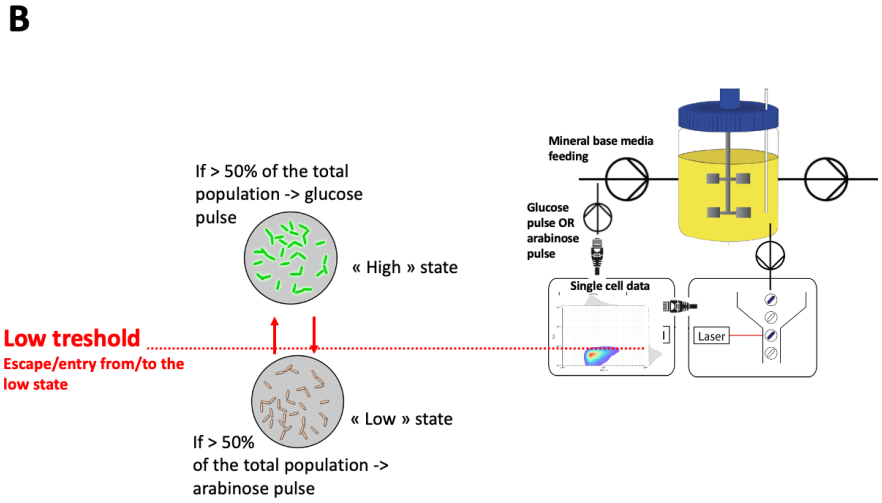

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