Switching cost as a main driver of phenotypic heterogeneity in continuous bio-process

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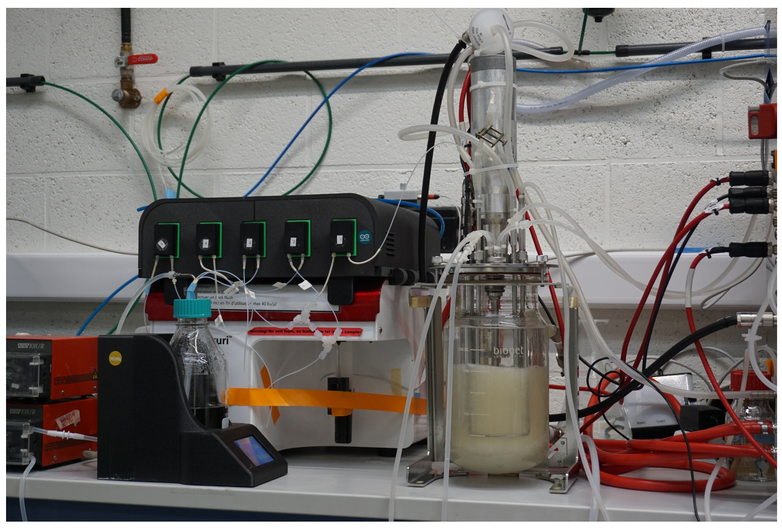
Introduction

Isogenic cell populations possess the ability to cope with unpredictable environmental changes by expressing a wide range of phenotypes. Although this adaptation is advantageous in natural settings, it is often undesirable in applications such as bioproduction, synthetic biology, and biomedicine, as it hinders control over the cellular population behavior. However, there is limited knowledge regarding the diversification profiles exhibited by cell populations.

Method

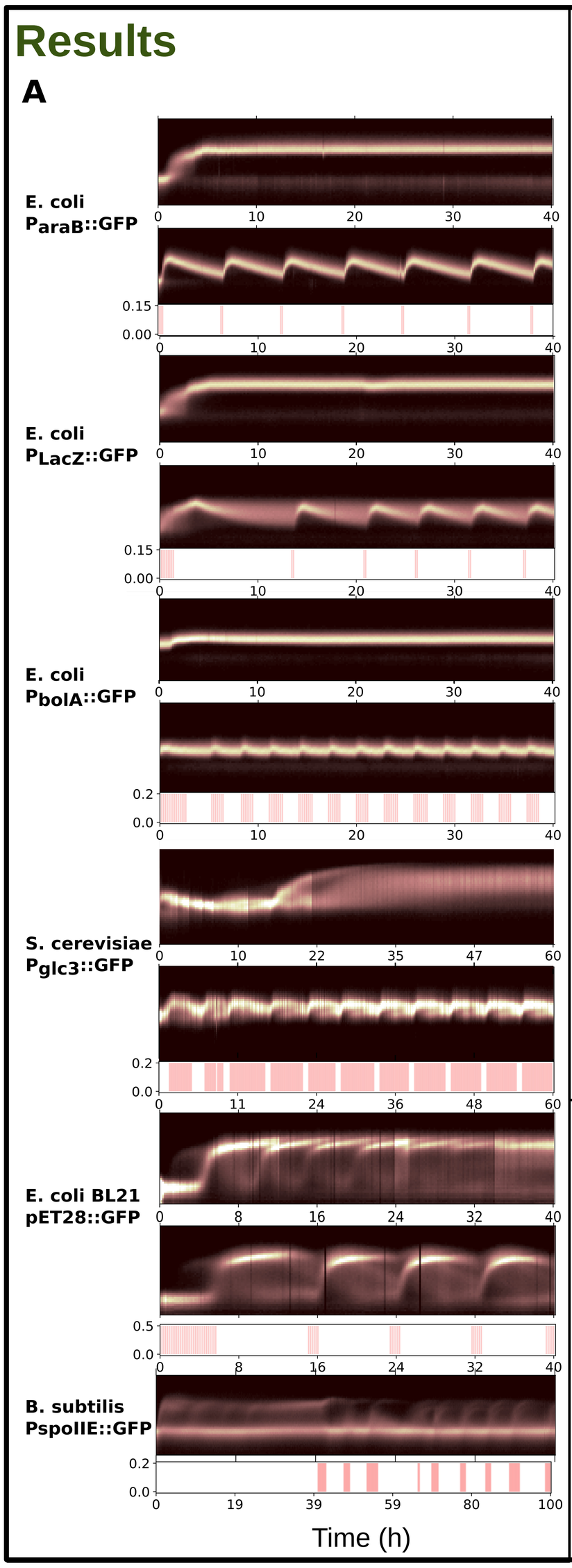
We have tracked the phenotype switching dynamics of multiple phenotypes across three biological systems with automated flow cytometry. With these data and a proxi derived from information theory, entropy, we have analysed the phenotypic heterogeneity with (Segregostat) and without (chemostat) external forcing.

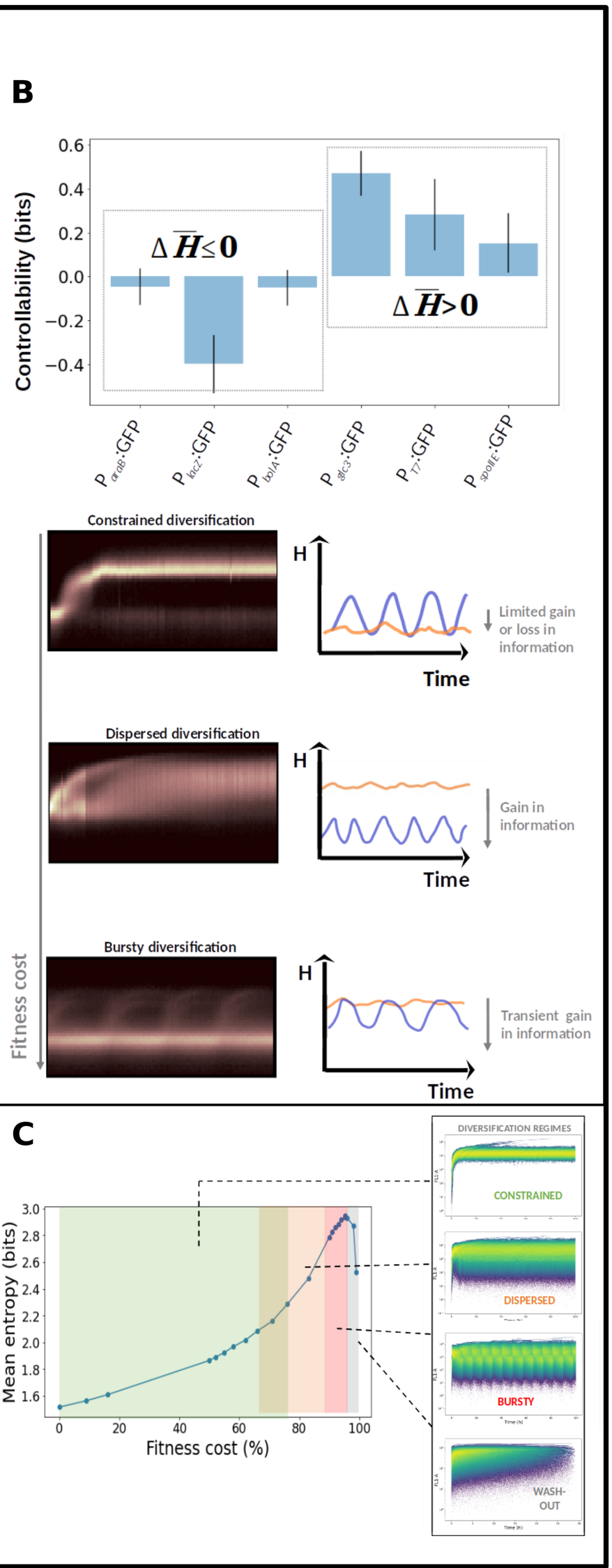


Findings

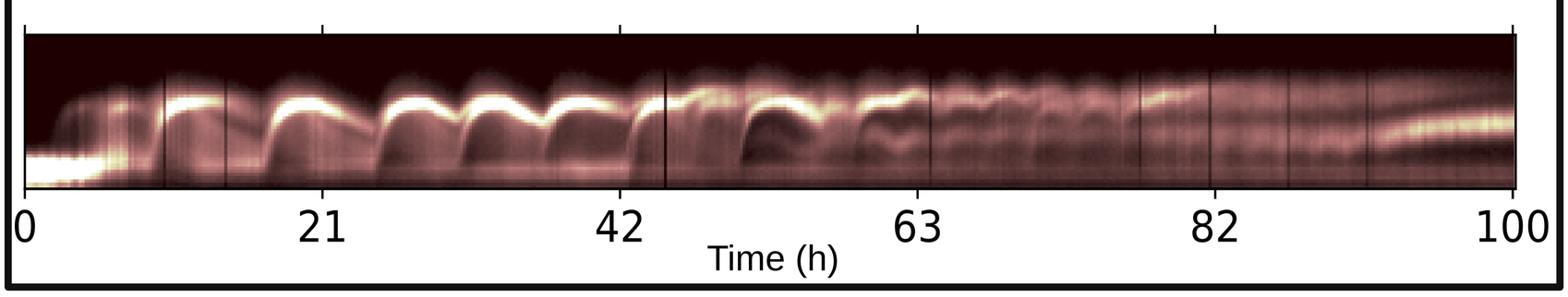
Our findings reveal a connection between the diversification and the associated fitness cost of cell switching. To isolate the influence of the switching cost on population dynamics, we developed a stochastic model that successfully replicated the experimentally observed dynamics. This modeling approach led us to identify three distinct diversification regimes: constrained (at a low switching cost), dispersed (at medium and high switching costs), and bursty (for very high switching costs). Cellular systems exhibiting the highest fitness cost are also the experiencing the greatest reduction of noise upon Segregostat cultivation. This is particularly relevant in industrial settings where production load, i.e., fitness cost, exists.

Results





Outlook: Tuning BL21 T7 expression level by changing the pulse frequency



Reference: Fitness cost associated with cell phenotypic switching drives population diversification dynamics and controllability https://www.biorxiv.org/content/10.1101/2023.04.06.535654v1

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