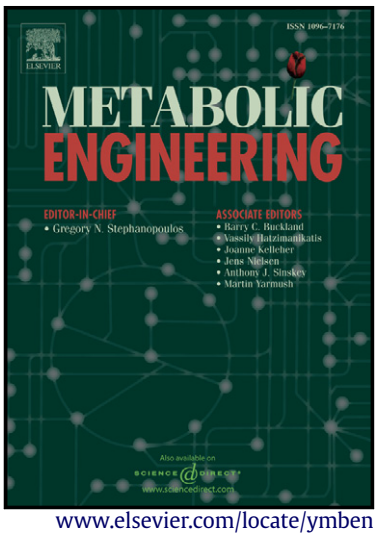

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Characterizing metabolic pathway diversification in the context of perturbation size

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Abstract

Cell metabolism is an important platform for sustainable biofuel, chemical and pharmaceutical production but its complexity presents a major challenge for scientists and engineers. Although *in silico* strains have been designed in the past with predicted performances near the theoretical maximum, real-world performance is often sub-optimal. Here, we simulate how strain performance is impacted when subjected to many randomly varying perturbations, including discrepancies between gene expression and in vivo flux, osmotic stress, and substrate uptake perturbations due to concentration gradients in bioreactors. This computational study asks whether robust performance can be achieved by adopting robustness-enhancing mechanisms from naturally evolved organisms– in particular, redundancy. Our study shows that redundancy, typically perceived as a ubiquitous robustness-enhancing strategy in nature, can either improve or undermine robustness depending on the magnitude of the perturbations. We also show that the optimal number of redundant pathways used can be predicted for a given perturbation size.

Keywords: strain design, optimization, robustness, succinate, amino acid, constraint-based modeling

1. Introduction

Naturally evolved systems exhibit robustness against a variety of perturbations, from intracellular noise in protein translation rates (Becskei and Serrano, 2000) to temporal variations in the weather (Tilman et al., 2006). By virtue of robust design principles, engineered systems can display comparable robustness (Csete and Doyle, 2002; Kitano, 2004). The finding that biological systems naturally acquire the same robustness-enhancing mechanisms as those utilized in

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