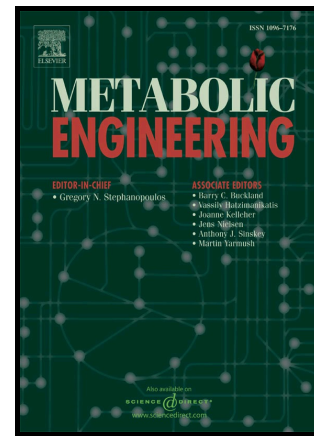


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A mathematical framework for yield (versus rate) optimization in constraint-based modeling and applications in metabolic engineering

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Abstract

Background: The optimization of metabolic rates (as linear objective functions) represents the methodical core of flux-balance analysis techniques which have become a standard tool for the study of genome-scale metabolic models. Besides (growth and synthesis) rates, metabolic yields are key parameters for the characterization of biochemical transformation processes, especially in the context of biotechnological applications. However, yields are ratios of rates, and hence the optimization of yields (as nonlinear objective functions) under arbitrary linear constraints is not possible with current flux-balance analysis techniques. Despite the fundamental importance of yields in constraint-based modeling, a comprehensive mathematical framework for yield optimization is still missing.

Results: We present a mathematical theory that allows to systematically compute and analyze yield-optimal solutions of metabolic models under arbitrary linear constraints. In particular, we formulate yield optimization as a linear-fractional program. For practical computations, we transform the linear-fractional yield optimization problem to a (higher-dimensional) linear problem. Its solutions determine the solutions of the original problem and can be used to predict yield-optimal flux distributions in genome-scale metabolic models. For the theoretical analysis, we consider the linear-fractional problem directly. Most importantly, we show that the yield-optimal solution set (like the rate-optimal solution set) is determined by (yield-optimal) elementary flux vectors of the underlying metabolic model. However, yield- and rate-optimal solutions may differ from each other, and hence optimal (biomass or product) yields are not necessarily obtained at solutions with optimal (growth or synthesis) rates. Moreover, we discuss phase planes/production envelopes and yield spaces, in particular, we prove that yield spaces are convex and provide algorithms for their computation. We illustrate our findings by a small example and demonstrate their relevance for metabolic engineering with realistic models of *E. coli*.

Conclusions: We develop a comprehensive mathematical framework for yield optimization in metabolic models. Our theory is particularly useful for the study and rational modification of cell factories designed under given yield and/or rate requirements.

Keywords: constraint-based modeling; elementary flux mode; elementary flux vector; flux-balance analysis; linear-fractional program; metabolic pathway analysis; production envelope; productivity; strain design; yield space.

1. Introduction

Productivity and yield are crucial characteristics of biotechnological production processes based on microbial cell factories [1, 2]. Yield is a relative measure of

the efficiency of (bio)chemical conversions. In particular, it is the amount of product or biomass formed per amount of substrate consumed. In contrast, productivity measures the speed of product formation, *i.e.*, the amount of product or biomass formed per unit of time. Thereby, one is mainly concerned with productivity quantified by *specific* production rate [*e.g.*, mmol product per gram dry weight and hour] or specific growth rate (with unit per hour).

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