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Efficient Estimation of Maximum Theoretical Productivity from Batch Cultures via Dynamic Optimization of Flux Balance Models

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Abstract : Production of chemicals from engineered organisms in a batch culture typically involves a trade-off between productivity, yield, and titer. However, strategies for strain design typically involve designing mutations to achieve the highest yield possible while maintaining growth viability. Such approaches tend to follow the principle of designing static networks with minimum metabolic functionality to achieve desired yields. While these methods are computationally tractable, optimum productivity is likely achieved by a dynamic strategy, in which intracellular fluxes change their distribution over time. One can use multi-stage fermentations to increase either productivity or yield. Such strategies would range from simple manipulations (aerobic growth phase, anaerobic production phase), to more complex genetic toggle switches. Additionally, some computational methods can also be developed to aid in optimizing two-stage fermentation systems. One can assume an initial control strategy (i.e., a single reaction target) in maximizing productivity - but it is unclear how close this productivity would come to a global optimum. The calculation of maximum theoretical yield in metabolic engineering can help guide strain and pathway selection for static strain design efforts. Here, we present a method for the calculation of a maximum theoretical productivity of a batch culture system. This method follows the traditional assumptions of dynamic flux balance analysis: that internal metabolite fluxes are governed by a pseudo-steady state and external metabolite fluxes are represented by dynamic system including Michealis-Menten or hill-type regulation. The productivity optimization is achieved via dynamic programming, and accounts explicitly for an arbitrary number of fermentation stages and flux variable changes. We have applied our method to succinate production in two common microbial hosts: E. coli and A. succinogenes. The method can be further extended to calculate the complete productivity versus yield Pareto surface. Our results demonstrate that nearly optimal yields and productivities can indeed be achieved with only two discrete flux stages.

Keywords : A. succinogenes, E. coli, metabolic engineering, metabolite fluxes, multi-stage fermentations, succinate
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