

# Inference of metabolic fluxes in nutrient-limited continuous cultures: A Maximum Entropy Approach with minimum information

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## Abstract

The study of cellular metabolism is often hindered by limitations in the amount of experimental data available. Therefore computational methods that exploit maximally the possible measurements, and are able to extract relevant predictions from a minimum of information are always welcome. Maximum Entropy (ME) inference has been successfully applied to genome-scale models of cellular metabolism in various cell culture contexts, yielding insights into biologically relevant properties which are not accessible to traditional optimization based methods. Recent data-driven studies have suggested that in chemostat cultures, the growth rate and uptake rates of limiting nutrients are the most informative parameters about the metabolism. In this work, we propose the thesis that chemostat dynamics typically drives the culture towards maximally restricted metabolic states. A practical consequence is that experimental values of limiting uptake rates can be replaced by more readily available measurements of metabolite concentrations in the feed media and the steady state cell concentration. We show how these results can be justified from a mechanistic perspective by studying simulations of a simplified model where we test the quality of the inference, and unveil the mechanisms defining the performance of our approach. We then apply our method to *E. coli* experimental data. We evaluate the effects of heterogeneity in chemostat cultures and its potential impact on flux inference quality of ME and optimization based strategies. Additionally, we evaluate the quality of the inference comparing ME to alternative formulations that rest on a Flux Balance Analysis (FBA).

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