Maximum entropy and population heterogeneity in continuous cell cultures, validation with experimental data

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1 Introduction

The study of cellular metabolism is a research area with direct potential impact in biological sciences, medicine and industry. An example is that cell culture-derived products are a major part of the multi-billion biotechnological industry portfolio. This products are obtained by exploding the capability of cellular metabolism to produce molecules with a wide range of chemical complexity. For this propose, cells are cultivated in three common modes: batch, fed-batch and continuous. In batch, cultivation starts with a medium rich in nutrients that will be consumed completely by the cells, often till starvation. Similarly, fed-batch cultures starts will a nutrient pool, but it is resupplied in discrete time intervals. On the other hand, in continuous mode, fresh medium constantly replaces culture fluid at a given rate.

The chemostat is an example of a continuous cultivation devise developed in the 50's (Monod, 1949; Novick & Szilard, 1950). Chemostat cultures are often run at constant working volume and in steady state condition, which is reach when the macroscopic variables of the culture stays constant with time (mainly cell and external metabolites concentrations). Although advantages of continuous cultivation have been commonly mentioned in the literature (*citeRequired*1), the preferred use of these technics over batch or fed-batch struggle with the complexity displayed by continuous systems, i.e., hysteresis, multi-stability or sharp transitions between metabolic states(*citeRequired*2). Mathematical modeling can guide our efforts to understand the cellular metabolism and then suggest strategies to improve production efficiency using continuous cultivation methods. This could lead to a decrease in the production costs and subsequently, to a reduction on medicine prices and a broader accessibility to treatments. Therefor, for the industry, it is fundamental the development of theoretical frameworks that allows, for example, predict how to reach an optimal stable cultivation state given a cell of interest and the medium to be used.

A major driver of biological discovery are currently found in increasingly accurate experimental techniques that generate unprecedented amount of thoughtful data. Information about cellular metabolism, at individual reaction (gene) level, had lead to the development of genome-scale metabolic networks ($GEMs$) ($citeRequire3$). These networks have been used to build mathematical models of the cellular metabolism ($citeRequired4$). Constraint-based technics as Flux balance Analysis (FBA) had have good results predicting, for example, cellular metabolism in growth phase of batch cultures (Palsson, 2006). Meanwhile, a methodology for applying (FBA) in the context of a chemostat continuous cultivation have It introduces a detailed characterization of the steady state of the chemostat, which is achieved by coupling cell metabolism with the dynamics of extra-cellular concentrations. Although this approach can explain different phenomena in the context of a detailed metabolic model, it have the drawback that it assume cell population to be homogeneous.

References

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