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POLY-PATHWAY MODEL APPROACH: SIMULATION OF MULTIPLE METABOLIC STATES

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Animal cell lines have a complex and flexible metabolism and can display varied metabolic behavior depending on the culture conditions. A model that simulate and predict these variations would be a precious tool in the development of media, feeds or processes. However, in order to function as a predictive tool such a model has to describe the multiple metabolic states that can occur for a variety of conditions. This leads to the challenge of identifying a flexible model structure of relevant metabolic pathways and kinetics. To address this challenge, we have introduced the poly-pathway model approach aiming at capturing multiple metabolic states in one single model. The approach assumes that the cells modulate their metabolism by using metabolic pathways in different combinations in response to external stimuli, e.g., to compensate for nutrient depletion or by-product accumulation. Each pathway is represented by a macro-reaction obtained via elementary flux mode (EFM) analysis of a metabolic network, and modeled by a kinetic equation e.g., Michaelis-Menten type kinetic equations. The model is identified using rich information*, e.g.,* experimental data obtained from parallel cultures of a CHO cell line subjected to depletion and abundance of amino acids. The measurements are limited to cell and extracellular metabolite concentrations obtained by analytical techniques achievable in most laboratories. For simplified networks, all possible EFMs can be found by enumeration. Such *a priori* simplifications may however exclude relevant macro-reactions from the set. Meanwhile, enumeration becomes prohibitive with increasing network complexity. To solve this issue, we have developed new mathematical algorithms that identify reduced sets of macro-reactions relevant to experimental data [1]. For the present work, we applied these algorithms to derive macro-reactions from complex metabolic networks for which complete enumeration is prohibitive. We also extended the kinetic equations to account for saturation and inhibition effects imposed by medium components and by-products. By using macro-reactions from a combination of complex networks together with the extended kinetics, the poly-pathway model achieved an excellent fit between simulated and experimental data and could accurately simulate the variations in growth and metabolic uptake/secretion rates for different metabolic states.

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