Combined mathematical and experimental platform for the design and optimization of metabolically balanced nutrient supplementation strategies in semi-continuous mammalian cell cultures

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Monoclonal antibodies (mAbs), particularly produced in fed-batch cultures of Chinese Hamster Ovary (CHO) cells, have become crucially important biopharmaceuticals, representing currently 30% of the newly approved drugs and generating annual sales of more than $140 billion (2014). Despite the commercial large scale demand, the design and optimization of industrial mammalian cell culture processes for therapeutic protein production remain fundamentally manual and based on historical records. Particularly for feeding strategies and media composition in cell culture design, the heavy focus on primary nutrients supplementation for net improvement of culture behavior leads cell metabolism towards energetically inefficient pathways.

Therefore, in order to address the limitations of current bioprocess engineering practice and understand metabolic bottlenecks during therapeutic protein production, our current research is focused on the design and optimization of bioprocesses based on a systems biotechnology approach. Our approach makes use of a combined wet lab experimentation and mathematical platform focused on the systematical development and analysis of predictive and robust mathematical models. It combines state of the art genome-scale metabolic reconstructions (GEM) and model analysis techniques such as Global Sensitivity Analysis, model based Design of Experiments and Multivariate Data Analysis, in order to represent quantitatively computable genotype-phenotype relationships underlying cellular functions in CHO cells under different bioprocessing conditions.

This systematic methodology will offer insights for the design, optimization and validation of metabolically balanced nutrient supplementation strategies for fed-batch mammalian cell cultures.