AN ENERGY-BASED MODELLING TOOL FOR CULTURE MEDIUM DESIGN AND BIOMANUFACTURING OPTIMIZATION

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Demand for high-value biologics, a rapidly growing pipeline, and pressure from competition, time-to-market and regulators, necessitate novel biomanufacturing approaches, including Quality by Design (QbD) principles and Process Analytical Technologies (PAT), to facilitate accelerated, efficient and effective process development platforms that ensure consistent product quality and reduced lot-to-lot variability. Herein, QbD and PAT principles were incorporated within an innovative *in vitro-in silico* integrated framework for upstream process development (UPD). The central component of the UPD framework is a mathematical model that predicts dynamic nutrient uptake and average intracellular ATP content, based on biochemical reaction networks, to quantify and characterize energy metabolism and its adaptive response, metabolic shifts, to maintain ATP homeostasis. The accuracy and flexibility of the model depends on critical cell type/product/clone-specific parameters, which are experimentally estimated. The integrated *in vitro-in silico* platform and the model's predictive capacity reduced burden, time and expense of experimentation resulting in optimal medium design compared to commercially available culture media (80% amino acid reduction) and a fed-batch feeding strategy that increased productivity by 129%. The framework represents a flexible and efficient tool that transforms, improves and accelerates conventional process development in biomanufacturing with wide applications, including stem cell-based therapies.