APPLICATION OF A GENOME-BASED PREDICTIVE CHO MODEL FOR INCREASED MAB PRODUCTION AND GLYCOSYLATION CONTROL

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Monoclonal antibody therapeutics continue to grow in both number and market share with recent forecasts of global sales reaching ~$125MM by 2020. Most mAb products currently on the market are produced using cultured mammalian cells, typically Chinese Hamster Ovary (CHO) cells, which provide the necessary post-translational modifications to make the antibody efficacious. Many post-translational modifications such as the oligosaccharide profile are considered critical quality attributes (CQAs) that must be tightly controlled throughout the manufacturing process to ensure product safety and effectiveness. Therefore, the ability to predict how cell culture media components, including potential contaminants like trace metals, will affect product formation and glycosylation is important from both a process development and process control viewpoint. A detailed genome-based, predictive CHO model from the Insilico Cells™ library was adapted by the reconstruction software Insilico Discovery™ for a representative fed-batch process through a collaborative effort leveraging the computational and experimental expertise of two companies. The final, compartmentalized network model contained 1900 reactions (including transport reactions), 1300 compounds and contains stoichiometric descriptions of anabolic pathways for amino acids, lipids and carbohydrate species. The genome-scale model was constrained using several assumptions on the cell physiology and then used to compute time-resolved flux distributions by the software module Insilico Inspector™. The Insilico Designer™ module was then used to subsequently reduce the large model to a computationally manageable reduced model able to describe all flux distributions using 5 flux modes, of which 4 combined several metabolic functions and one is independently responsible for product synthesis. Using Insilico Designer™, the kinetic parameters of the reduced model were estimated by fitting the model-predicted metabolite concentrations to the experimentally determined values. The calibrated model was able to properly describe the time-dependent trajectories of biomass, product and most metabolites. Simulations using the reduced model were run and a media composition predicted to improve mAb production was identified and experimentally verified. Furthermore, experiments probing the effects of trace metals on product glycosylation were used to extend the model's glycosylation predictability. The ability to identify both metabolic signatures, as well as media components, that correlate to specific glycan profiles will allow for fine-tuning of desired CQAs and enable more robust control strategies in upstream processes.