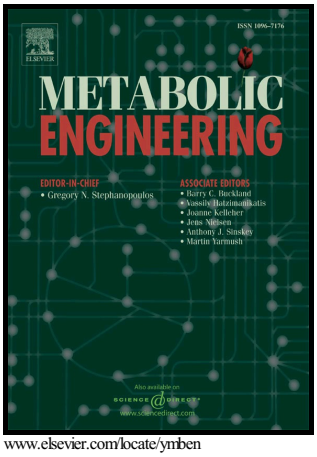

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Application of a curated genome-scale metabolic model of CHO DG44 to an industrial fed-batch process

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Abstract

CHO cells have become the favorite expression system for large scale production of complex biopharmaceuticals. However, industrial strategies for upstream process development are based on empirical results, due to a lack of fundamental understanding of intracellular activities. Genome scale models of CHO cells have been reconstructed to provide an economical way of analyzing and interpreting large-omics datasets, since they add cellular context to the data. Here the most recently available CHO-DG44 genome-scale specific model was manually curated and tailored to the metabolic profile of cell lines used for industrial protein production, by modifying 601 reactions. Generic changes were applied to simplify the model and cope with missing constraints related to regulatory effects as well as thermodynamic and osmotic forces. Cell line specific changes were related to the metabolism of high yielding production cell lines. The model was semi-constrained with 24 metabolites measured on a daily basis in *n*=4 independent industrial 2L fed batch cell culture processes for a therapeutic antibody production.

This study is the first adaptation of a genome scale model for CHO cells to an industrial process, that successfully predicted cell phenotype. The tailored model predicted accurately both the exometabolomics data ($r^2 \geq 0.8$ for 96% of the considered metabolites) and growth rate (r^2=0.91) of the industrial cell line. Flux distributions at different days of the process were analyzed for validation and suggestion of strategies for medium optimization. This study shows how to adapt a genome scale model to an industrial process and sheds light on the metabolic specificities of a high production process. The curated genome scale model is a great tool to gain insights into intracellular fluxes and to