Mathematical optimization of a CHO cell genome-scale metabolic model using linear programming techniques

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Abstract

Chinese hamster ovary cells (CHO) are the dominating expression platform for recombinant glycoproteins, due to their post-translational modifications, secretion and folding patterns – which makes the protein human friendly with fewer concerns for immunogenicity. However, the complex production framework in combination with the trade-off between growth and recombinant protein production makes the process expensive. In this work, we use model-based deterministic tools to analyse the metabolic behaviour of the CHO cells, as a means of optimization.

We used a Genome-Scale metabolic network (GeM) of the CHO cell [1], which contains 1,766 genes, 6,663 reactions and 4,456 metabolites; it describes most of the metabolism taking place inside the cell. First, we converted the GeM model to a model suitable for flux balance analysis (FBA), by removing the blocked reactions and limiting the cellular uptake and secretion rates, based on experimental data [2], both for the exponential and growth phase of the cell culture. Then, the permissible upper and lower bounds for all intracellular reactions are curated using a recently developed algorithm by the Kiparissides lab, named carbon constrained FBA (ccFBA), augmented with additional nitrogen based constraints. This algorithm resulted in stricter bounds for the reactions leading to a significant reduction of the solution space. Having reduced the size of the model and constrained the solution space, we then solved the FBA optimization problem and compared the intracellular fluxes to already published ^{13}C-MFA (Metabolic Flux Analysis) data [3-5].

After we validated the model, taking into account the different cell lines, medium and feeding strategies used from in each study, we are first planning to import thermodynamic date so to fix the directionality of the reactions. Then, to detect the genes using optimization algorithms, the regulation of which will result in a phenotype of higher mAb yield with a viable cell growth and ATP maintenance.

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