TRANSCRIPTOMICS GUIDED MECHANISTIC METABOLIC MODEL FOR PERFUSION CULTURE PROCESS

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Understanding mechanisms behind the effect of cell culture medium components on the metabolic phenotype of the cells would allow knowledge-based strategies for optimizing the feed medium with the final aim of maximizing the yield of monoclonal antibodies produced with Chinese Hamster Ovary (CHO) cells. Different *omics approaches, such as transcriptomics and metabolomics have been used to understand the intracellular changes connecting the cell culture environment to the metabolic phenotype. On the other hand, mechanistic stoichiometric reaction network-based modelling, such as elementary flux modes (EFM) based metabolic flux analysis (MFA) or flux balance analysis (FBA), has been used as an alternative computational approach. Here we combine these approaches into transcriptomics guided mechanistic modelling and compare the obtained guided model to an unguided mechanistic model.
Mediums with different amino acid compositions were used to obtain 25 different steady states in perfusion culture with CHO-K1 cells producing a monoclonal antibody (mAb). From each of the steady states, 25 cell culture components were measured and transcriptomics were carried out to obtain gene expression.
EFM model was constructed with an iterative enumeration (column generation) approach using only the measured metabolite fluxes and a reaction network of the central cell metabolism. The network consisted of 25 measured extracellular metabolites, 89 intracellular metabolites and 126 reactions. A total of 823 genes was mapped to these reactions. The gene-to-reaction mapping was used to identify additional EFMs using transcriptomics semi-quantitatively. This was followed by kinetics assignment with Bayesian estimation techniques. The model was constructed using 24 medium conditions (15 without and 9 with transcriptomics) and a cross-validation was performed with the remaining medium (without transcriptomics). We compared the modeling error of the transcriptomics guided model with unguided model and observed >60-fold error reduction on both training and prediction by utilizing the transcriptomics data.

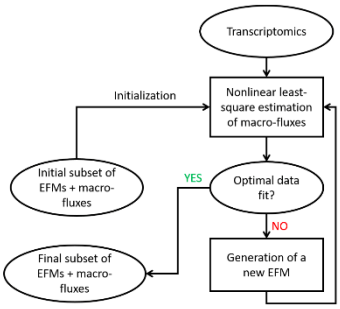

Figure 1 – Illustration of the approach

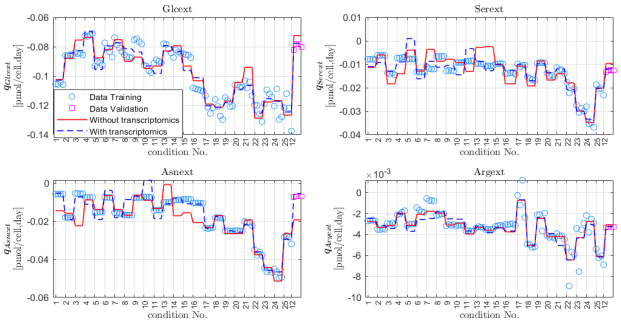

Figure 2 – Modelling performance of mechanistic metabolic model with and without transcriptomics