

PREDICTIVE MACROSCOPIC MODELS OF CELL GROWTH, METABOLISM AND MONOCLONAL ANTIBODY PRODUCTION OF FEDBATCH PROCESSES AT VARIOUS SCALES

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Recently, the pharmaceutical industry is increasingly focusing on early drug development which comes with increasing constraints to accelerate process development, reduce costs and demonstrate a deep understanding cell culture processes. However, cellular metabolism is very complex and by far not fully understood. Cells can be cultivated in various types of bioreactors applying sophisticated feeding strategies mostly based on experience and series of experiments. Modern systems biology promises modeling of such processes on the basis of a system-wide understanding of cellular processes but is still unable to deliver predictive models in due time at reasonable cost. Practically applicable, predictive models are highly demanded in industry for the purpose of process optimization and control. To this end, we developed a systematic methodology for metabolic and cell growth modeling that is directly applicable in an industrial environment. We demonstrate that the models developed are able to predict a wide range of new experimental cell culture conditions.

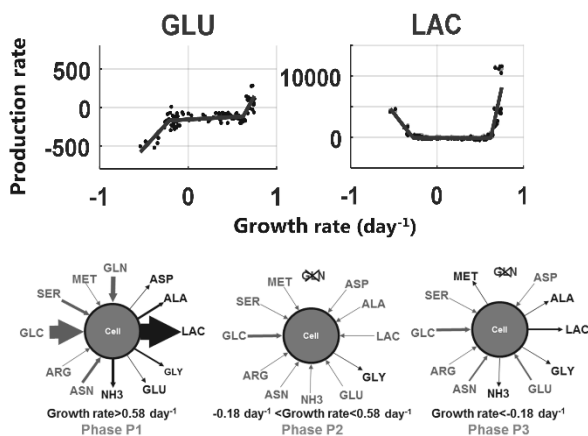


Figure 1 – Phase identification and metabolic fluxes in different phases

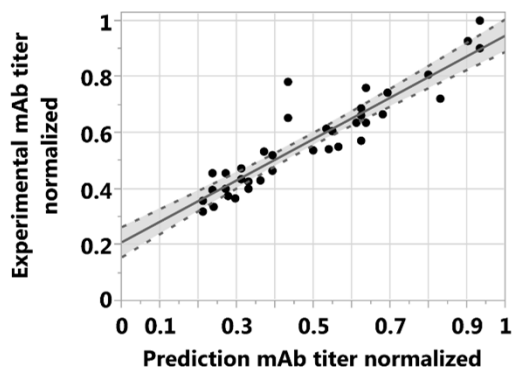


Figure 2 – Comparison of experimental with predicted mAb titers

We applied the metabolic steady state concept and used a segmented linear model to predict cell metabolism (Fig. 1). The external metabolite rates are expressed as a linear function of the specific growth rate with various breakpoints associated to each metabolic shifts [1]. To predict the cell growth, an extended Monod-type model with inhibitory characteristics and varying maximum specific growth rate was developed. The final mAb titer can be predicted even if the cells are starved in some essential metabolites (Fig. 2). The cell growth model prediction was compared to the experimental one were two distinct essential metabolites were varied. The prediction was accurate. It was further possible to test various feeding strategies and to identify optimal experimental conditions. The cell growth model combined with a linear piecewise regression model of cellular metabolism allows us to get an *in silico* prediction of the impact of untested feeding strategies on cell culture performance.

The models developed are believed to identify the essence of the biological processes and model parameters can be identified reliably. A complete metabolic network model is not required which makes the models more easily accessible. To the best of our knowledge, this is the first study that presents a simple linear model structure to describe mAb production but also amino acid, glucose, lactate and ammonium metabolism directly applicable for scale-up prediction.

References

[1] Ben Yahia, B., Gourevitch, B., Malphettes, L., Heinzle, E., 2016. Segmented linear modeling of CHO fed-batch culture and its application to large scale production. *Biotechnol Bioeng*. DOI: 10.1002/bit.26214.