BIOPROCESS INTENSIFICATION AND OPTIMIZATION USING MACROSCOPIC PREDECTIVE MODELS OF CELL CULTURE PROCESSES

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Chinese Ovary Hamster (CHO) are an indispensable tool for biotechnological production of biologics which is a multi-million business. Recently, the pharmaceutical industry is increasingly focusing in the use of perfusion mode. Nevertheless, the optimal perfusion rate during biopharmaceutical perfusion production is dependent on cell metabolism which can be characterized by mathematical models. This study provides insights into the predictive capacities of systematic and simple cell modeling approaches of metabolism, growth and production of monoclonal antibodies (mAb) [1] to optimized medium composition and perfusion rate during CHO perfusion culture.

We applied the metabolic steady state concept and used a segmented linear model to predict cell metabolism. The external metabolite rates are expressed as a linear function of the specific growth rate with various breakpoints associated to metabolic shift [1]. The composition of the perfusion medium was optimized based on this model and the perfusion rate was then daily determined as a function of the experimental specific growth rate. Two 2 L perfusion cultures using alternative tangential flow (ATF) were performed and analyzed.

Using the cell metabolism model structure and parameter values from Ben Yahia et al. [1], it was possible to predict metabolic rates of new perfusion cultures in 2 L scale. The perfusion rate and the optimum media composition was also determined. This relatively simple model structure, combined to a model calibration in a fed-batch mode, offer a simple way to optimized new perfusion cultures with no need of further optimization in order to maintain cell growth, cell viability and mAb productivity. This study proves the accuracy and predictability of the model developed in fed-batch mode by Ben Yahia et al. [1], to predict the cell metabolism of other mode of production.

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. 114(4): 785-797.