NOVEL MODELING METHODOLOGY TO PREDICT PRODUCT QUALITY AND CELL CULTURE PERFORMANCE IN FED-BATCH AND PERFUSION CULTURES

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The acceleration of biopharmaceutical process development is difficult when traditional experience-based sequential approaches are used. As a result, fully optimized and well understood cell culture processes prior to scale-up are rare. Here we show that an accurate, scalable and simple model able to predict cell growth, cell metabolism, titer and some product quality attributes will significantly accelerate process development, improve process development outcomes and reduce development and production costs.

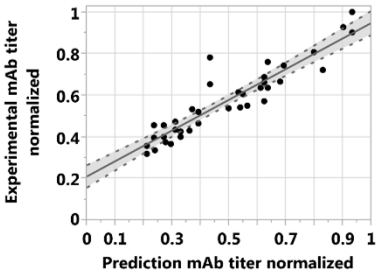

Figure 1 – Comparison of experimental with predicted mAb titers

In this paper we will present a simple systematic modeling methodology to study and predict fed-batch cell culture performance [**1**]. We will also show that this approach can be applied to the optimization of perfusion processes. Only a limited number of parameters need to be identified based on experimental results, which means that for each production process to be modeled, a minimal number of small scale bioreactor runs need to be performed before switching to *in silico* process development. We will show that this approach can accurately predict process performance both at small and large scale. Furthermore, various feeding strategies could be tested and optimized *in silico*. Moreover, the model was able to predict the impact of the depletion of essential metabolites on the specific productivity and also the impact of intracellular metabolite pools on cell growth.

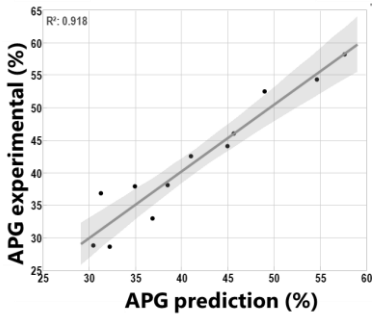

Figure 2 – Comparison of experimental with predicted acidic peak group (APG)

In a second step, the model was extended and applied to critical product quality attributes such as charge variants. This modeling approach shed further light on the impact of the feeding strategy on product quality. For instance, we will show that the total quantity of specific metabolites used throughout the bioreactor production process controls charge variants distribution, whereas within a given concentration range the daily concentration of these same metabolites is not predictive. To the best of our knowledge, this is the first study that shows that it is the total quantity of metabolites used that impacts mAb microheterogeneity.

Finally, the model was also applied to the development of continuous and hybrid/intensified production processes. The perfusion rate was controlled daily using the model calibrated with fed-batch production data. Moreover, a concentrated perfusion medium was developed and optimized *in silico*.

In summary, our modeling methodology provides a much better insight into the impact of process parameters on production yields and product quality, thus improving process understanding and control as well as accelerating process development.

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.