TOWARDS MODEL-BASED BIOPROCESS CHARACTERIZATION: A MATHEMATICAL MODEL OF CELL CYCLE, METABOLISM AND APOPTOSIS OF MAB-PRODUCING MAMMALIAN CELLS

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The biologics industry is changing and all players seek competitiveness through process optimization aiming at satisfying the market demand providing a compliant protein in as short time as possible. As blockbuster drugs experience patent expiry, several biosimilars are coming market and competition becomes fiercer. Unlike classical experiments-based optimization, bioprocess modeling is a rational, economically efficient and reliable alternative to deliver an optimized bioprocess. The biological aspects of a bioreactor are diverse and include cells growing and cycling, other cells dying, nutrients being consumed and by-products accumulating, energy production and usage and therapeutic proteins being produced. The understanding of the biology involved is crucial to ensure quality. Quality by Design (QbD) aspects that can be optimized from the design stages include clone selection, medium formulation, feeding strategies and culture conditions.

In this work, a mathematical model of mammalian cell cultures has been developed. It includes a detailed description of the viable cell population by segregating it according to the stage of the cell cycle (G0/G1, S and G2/M), transition from viable to early and late apoptotic stages. Apoptosis is monitored through gene expression profiles (caspases 3 and 8, bax and bcl-2) linked to the presence or absence of key nutrients. Indeed, the profiles of glucose and 19 amino acids are also captured by the model which allow for detailed information on energy production (ATP) which is essential to ensure viability and hence the delivery of a high-quality product.

The model was implemented in gProms and it comprises of 3 population balance equations (overall discretized in 1248 equations, 825 algebraic and 423 differential), 32 differential equations, 145 algebraic equations and requires 61 parameters. In spite of its complex structure, the model runs in 0.8 seconds in a personal computer with 16GB ram and a 3.4 GHz processor. Global sensitivity analysis was performed varying all 61 parameters ±50% from their nominal values and this allowed to identify the significant parameters (sensitivity index ≥ 0.1).

It will be shown that model predictions describe the experimental data of batch cultures of GS-NS0 cells producing an IgG4 monoclonal antibody in terms of cell populations (viable, apoptotic, dead, total) and the segregation of viable cells per cell cycle phase, metabolite profiles, ATP production and usage, monoclonal antibody production and gene expression. As an example, predictions for viable cells, mAb, G2/M phase, caspase 3, Aspartate and Alanine are shown in Figure 1.

This model provides a valuable tool to optimize bioreactor operating conditions, medium formulations and feeding strategies. Furthermore, a kinetic model that that can cope with the heterogeneity of a bioreactor can be integrated with computational fluid dynamics studies to understand how bioreactor design affects the process. In a time-horizon of hours, the optimal cell-culture conditions can be determined thereby significantly shortening the process development process and hence the time-to-market. This strategy can be applied at the whole-bioprocess level if this strategy is integrated with downstream processing as well.

Figure 1 – Model simulations and experimental data for GS-NS0 cultures (N=3, bars show 1 std. deviation)