MULTISCALE MODELING OF MONOCLONAL ANTIBODY (MAB) PRODUCTION AND GLYCOSYLATION IN A CHO CELL CULTURE PROCESS

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The production of recombinant therapeutic monoclonal antibodies (mAbs) using cultured mammalian cells accounts for approximately $80 billion in global sales annually. These antibodies are often produced using Chinese hamster ovary (CHO) cell lines that execute the necessary post-translational modifications (e.g., glycosylation) for the drug to be therapeutically efficacious. Glycosylation is an intracellular, enzymatic process by which glycans (i.e., sugar molecules) are attached to a specific location on the antibody. The structure of the glycans attached to the mAb affects the therapeutic function of the molecule, making glycan distribution a critical quality attribute. Consequently, the ability to predict how variations in process parameters and/or media components affect both product formation and glycosylation is important from both a process development and process control viewpoint. A multiscale, mathematical model describing CHO cell growth and antibody production was developed in MATLAB to provide a quantitative understanding of how to manipulate a cell culture process to improve antibody titer and control glycosylation effectively. At the macro (bioreactor) scale, the model uses Monod growth kinetics to describe cell growth, nutrient/metabolite concentrations, and mAb production; at the micro scale, the glycosylation process in the Golgi apparatus is modeled using a glycosylation reaction network governed by Michaelis-Menten enzyme kinetics. Although both macro and micro scale processes are dynamic, disparate time scales makes it possible to solve the (fast) glycosylation model as a static function of the (slowly changing) macro scale state variables. In this multidisciplinary study, we will present a design of experiments approach for (1) identifying significant factors affecting glycosylation—including concentrations of asparagine, glutamine, and copper in the media, and (2) using these factors as macro scale “inputs” to the micro scale model. Model predictions are validated against an independent data set from a representative industrial mammalian cell culture process. Ultimately, the models we discuss will be valuable for biopharmaceutical process development and model-based control system design.