# MODELING THE EFFECT OF GRADIENTS ON CELL CULTURE PERFORMANCE IN VARIOUS LARGE SCALE BIOREACTORS

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Monoclonal antibody (mAb) based treatments have been established as one of the most successful strategies to treat cancer, autoimmune diseases, and other conditions over the past 20 years. These are expensive therapeutic options due in part to the cost and complexity of their manufacturing processes and the increasing demand for such treatments. A major challenge in production scale manufacturing of mAbs is optimizing bioreactor operating conditions at a low cost. mAbs are typically produced in Chinese Hamster Ovary (CHO) cells which are sensitive to the chemical and physical environment in which they grow. Scale-up of bioreactors is necessary for industrialization of monoclonal antibody production but can lead to the formation of spatial gradients in important culture parameters, including dissolved gases, metabolites, and pH. Different concentrations or values of these culture parameters can have adverse effects on cell culture dynamics, resulting in lower cell density, productivity, and product quality (N-linked glycosylation) [1]. Cells experience fluctuations of environmental conditions as they move throughout large scale bioreactors, exposing them to not only transient suboptimal conditions, but also oscillating conditions over time, which has known negative effects [2,3].

To avoid excessive costly large-scale experiments, modeling of cellular metabolism and critical quality attributes can be performed and coupled with computational fluid dynamics (CFD) models to predict effects of scale-up on culture performance. Modeling of integrated fluid dynamics and bio-phase kinetics in large scale bioreactors can be achieved using large eddy simulation (LES) computational fluid dynamic (CFD) models with Euler-Lagrange tracking of micro-organisms [4]. Incorporation of free-surface hydrodynamics, multiphase mixing, mass transport and reaction kinetics based on local concentrations enables in-silico modeling of process performance in large scale bioreactors. This framework is henceforth referred to as a CFD-kinetic model.

The work presented is the CFD-kinetic model applied to the production of monoclonal antibodies in CHO cells grown in various designs and sizes of bioreactors operated in fed-batch mode. In fed-batch operation, spatial gradients are more prominent for dissolved gases supplied continuously in the form of sparged air, whereas gradients of metabolites are greatest temporally with spikes at each feed time over the 14-day process. Thus, to reduce computation time and avoid unnecessary complexity when modeling the full fed-batch process, metabolite concentrations are considered homogeneous and constant in the CFD-kinetic model for short periods of time. Pseudo-steady spatial gradients of dissolved gases are resolved with the CFD-kinetic model at each day, with metabolite concentrations and cell densities at each day defined by a metabolic model of CHO cell metabolism [5]. Predictions of viable cell density (VCD) and mAb production rates are compared to predictions based on spatially averaged tanks to predict the impact of gradients on process performance. Bioreactor designs and scales are compared for minimizing impact on product titer.

References

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