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Optimizing Cell Culture Performance in an Ambr15 Microbioreactor Using Dynamic Flux Balance and Computational Fluid Dynamic Modelling

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Abstract : The ambr15™ bioreactor is a single-use microbioreactor for cell line development and process optimization. The ambr system offers fully automatic liquid handling with the possibility of fed-batch operation and automatic control of pH and oxygen delivery. With operating conditions for large scale biopharmaceutical production properly scaled down, micro bioreactors such as the ambr15™ can potentially be used to predict the effect of process changes such as modified media or different cell lines. In this study, gassing rates and dilution rates were varied for a semi-continuous cell culture system in the ambr15™ bioreactor. The corresponding changes to metabolite production and consumption, as well as cell growth rate and therapeutic protein production were measured. Conditions were identified in the ambr15™ bioreactor that produced metabolic shifts and specific metabolic and protein production rates also seen in the corresponding larger (5 liter) scale perfusion process. A Dynamic Flux Balance model was employed to understand and predict the metabolic changes observed. The DFB model-predicted trends observed experimentally, including lower specific glucose consumption when CO_2 was maintained at higher levels (i.e. 100 mm Hg) in the broth. A Computational Fluid Dynamic (CFD) model of the ambr15™ was also developed, to understand transfer of O_2 and CO_2 to the liquid. This CFD model predicted gas-liquid flow in the bioreactor using the ANSYS software. The two-phase flow equations were solved via an Eulerian method, with population balance equations tracking the size of the gas bubbles resulting from breakage and coalescence. Reasonable results were obtained in that the Carbon Dioxide mass transfer coefficient (kLa) and the air hold up increased with higher gas flow rate. Volume-averaged kLa values at 500 RPM increased as the gas flow rate was doubled and matched experimentally determined values. These results form a solid basis for optimizing the ambr15™, using both CFD and FBA modelling approaches together, for use in microscale simulations of larger scale cell culture processes.

Keywords : cell culture, computational fluid dynamics, dynamic flux balance analysis, microbioreactor
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