OXYGEN TRANSFER RATE MODEL FOR CELL-FREE AND PREDICTIVE D.O. CONTROL IN INTENSIFIED BIOREACTOR PROCESSES

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Key Words: D.O. Control, Intensification, Predictive-Model, Cell-free

Upstream processes are depending upon developing intensified solutions within single-use bioreactors to realize greater facility flexibility and operational cost advantages. A key challenge when targeting the higher cell densities associated with intensified bioprocesses is meeting the increased oxygen demand with proper control to a specified dissolved oxygen (D.O.) set point. The aim of this work was to establish cell-free, physical, and mathematical models to mimic oxygen demand in the bioreactor, which could be leveraged to develop control strategies quickly and effectively for the cell-containing bioprocess. Mathematical model development included characterizing the volumetric oxygen transfer rate (k_La) of the bioreactor system(s) for a range of gas flow rates, sparger types, and impeller agitation rates. An oxygen concentration driving force was calculated using the % oxygen in the gas feed and the current oxygen concentration in solution, which was combined with the collected k_La values to mathematically derive oxygen transfer rate (OTR). A model is then created to predict OTR using the inputs of gas flow rate, power per unit volume, oxygen concentration in the feed gas, and the current oxygen concentration in solution. This model was validated by taking data from live cell cultures, calculating an oxygen uptake rate (OUR) from viable cell density (VCD) and cell specific oxygen consumption rate (q_{O2}), and using mass balance to compare an OTR calculated from live process conditions against the actual OUR. A predictive model for OUR was also created using nitrogen's oxygen stripping ability as a surrogate for bioprocess OUR. Both physical models were used along with the system's sensors and automation programs to rapidly test and adjust PID settings for the D.O. control loop without cells. This work results in a thorough understanding of bioreactor system capabilities, provides an approach to predict gassing needs throughout the bioprocess, and presents methodologies that can be applied to reduce the risk of process failure due to poor oxygen control.

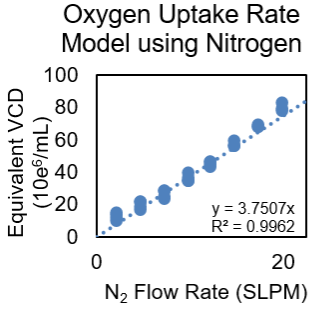
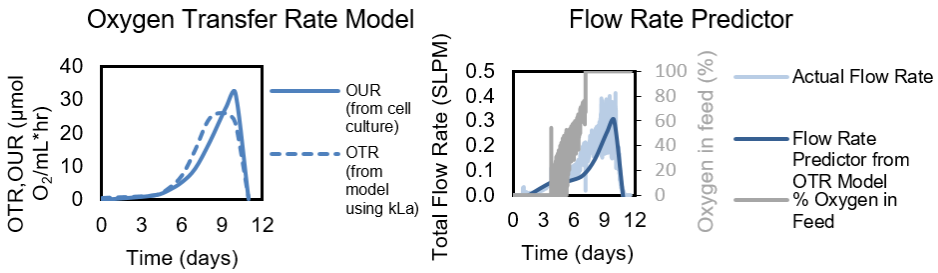


Figure 1 - Correlation of N_2 flow rate to equivalent VCD from oxygen uptake rate (OUR) model created in a 50 L bioreactor system at a q_{O2} of 5 pmol/cell/day to be used to dynamically mock cell culture and maintain D.O.



Figures 2,3 - OTR model is compared to cell culture run from calculated OUR. OTR model is solved for flow rate, creating a predictive tool with inputs of flow, power density, % oxygen in feed, VCD, q_{O2} to estimate flow based on sparger type to maintain a D.O. of 50%. Flow rate predictor is compared against run data.