ESTABLISHING A SMALL SCALE MODEL WITH MULTIVARIATE AND BAYESIAN STATISTICS

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One of the primary challenges during process characterization is establishing the suitability of the small scale models used to generate the data. Monte Carlo simulations of small scale data are able to account for increased variability in process parameters seen at large scale. However, this approach requires an accurate estimate of the large-scale variability, which is complicated by the small size of typical large-scale data sets. Bayesian statistics offer an alternate approach in which scale effects are accounted for by directly incorporating scaling offsets into predictive models. In this context, Bayesian methods are advantageous because they explicitly account for uncertainty in datasets, which is essential when attempting to estimate scaling offsets based on the small manufacturing-scale datasets. A CHO cell line known to demonstrate scale differences in lactate production was used as an experimental system, where lab-scale bioreactors typically underestimated the lactate levels observed in large-scale bioreactors. To address this issue, multifactor DOE experiments were run on process conditions known in influence lactate, including glucose, pH, cell generational age, base control and cell bank. Conditions were established for high and low lactate at small scale and a multivariate model of lactate production was established. To address the issue of scale predictability, Monte Carlo simulations were performed using both frequentist and hierarchal Bayesian methods. Both models more accurately described the large-scale lactate levels, and gave a more realistic picture of the robustness of the bioreactor process at scale. Overall the Bayesian model tended to predict a higher percentage of runs that would result in high-lactate and therefore a more accurate picture of large scale. Pilot studies were completed to verify the ability of each model to predict high and low-lactate production at large-scale.