Predictive Monitoring of Shake Flask Cultures with Online Estimated Growth Models

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Abstract:

Simplicity renders shake flasks ideal for strain selection and substrate optimization in biotechnology. Uncertainty during initial experiments may, however, cause adverse growth conditions and mislead conclusions. Using growth models for online predictions of future biomass (BM) and the arrival of critical events like low dissolved oxygen (DO) levels or when to harvest is hence important to optimize protocols. Established knowledge that unfavorable metabolites of growing microorganisms interfere with the substrate suggests that growth dynamics and, as a consequence, the growth model parameters may vary in the course of an experiment. Predictive monitoring of shake flask cultures will therefore benefit from estimating growth model parameters in an online and adaptive manner. This paper evaluates a newly developed particle filter (PF) which is specifically tailored to the requirements of biotechnological shake flask experiments. By combining stationary accuracy with fast adaptation to change the proposed PF estimates time-varying growth model parameters from iteratively measured BM and DO sensor signals in an optimal manner. Such proposition of inferring time varying parameters of Gompertz and Logistic growth models is to our best knowledge novel and here for the first time assessed for predictive monitoring of Escherichia coli (E. coli) shake flask experiments. Assessments that mimic real-time predictions of BM and DO levels under previously untested growth conditions demonstrate the efficacy of the approach. After allowing for an initialization phase where the PF learns appropriate model parameters, we obtain accurate predictions of future BM and DO levels and important temporal characteristics like when to harvest. Statically parameterized growth models that represent the dynamics of a specific setting will in general provide poor characterizations of the dynamics when we change strain or substrate. The proposed approach is thus an important innovation for scientists working on strain characterization and substrate optimization as providing accurate forecasts will improve reproducibility and efficiency in early-stage bioprocess development.

Keywords: particle filter, shake flask, Gompertz function, logistic function, time series forecasting, critical event prediction, harvest time estimation, Escherichia coli, strain and substrate optimization