Real-Time Monitoring of Early Cell Death in Mammalian Cell Culture using Capacitance Spectroscopy

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Abstract

Previous work developed a quantitative model using capacitance spectroscopy in an at-line setup to predict the dying cell percentage measured from a flow cytometer. This work aimed to transfer the at-line model to monitor lab-scale bioreactors in real-time, waiving the need for frequent sampling and enabling precise controls. Due to the difference between the at-line and in-line capacitance probes, direct application of the at-line model resulted in poor accuracy and high prediction bias. A new model with a variable range that had similar spectra shape across all probes was first constructed, which improved the prediction accuracy. Moreover, the global calibration method included the variance of different probes and scales into the model, reducing the prediction bias. External parameter orthogonalization also mitigated the interference from feeding, which further improved the model performance. The culture evolution trajectory predicted by the in-line model captured the cell death and alarmed cell death onset earlier than the trypan blue exclusion test. In addition, incorporation of at-line spectra following orthogonal design into the calibration set is more likely to generate robust calibration models than the calibration models constructed using the in-line spectra only. This is advantageous, as at-line spectra collection is easier, faster, and more material-sparing than in-line spectra collection. The root-mean-square error of prediction of the final model was 6.56% (8.42% of the prediction range) with an R2 of 92.4%.

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