Spiking based Raman Model Calibration for Perfusion Cell Culture using a Harvest Library

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Abstract

Raman spectroscopy has gained popularity to monitor multiple process indicators simultaneously in biopharmaceutical processes. However, robust and specific model calibration remains a challenge due to insufficient analyte variability to train the models and high cross-correlation of various media components and artefacts throughout the process. Therefore, a systematic Raman calibration workflow for perfusion processes enabling highly specific and fast model calibration was developed. A harvest library consisting of frozen harvest samples from multiple CHO cell culture bioreactors collected at different process times was established, capturing process variability as widely as possible. Model calibration was subsequently performed in an offline setup using a flow cell by spiking process harvest with various sugars known to modulate glycosylation patterns of monoclonal antibodies. In a screening phase, Raman spectroscopy was proven capable not only to distinguish glucose, raffinose, galactose, mannose, and fructose in perfusion harvest, but also to quantify them independently in process relevant concentrations. In a second phase, a robust and highly specific calibration model for simultaneous glucose (RMSEP = 0.32 g/L) and raffinose (RMSEP = 0.17 g/L) real-time monitoring was generated and verified in a third phase during a perfusion process. The proposed offline calibration workflow allowed proper Raman peak decoupling, reduced calibration time from months down to days and can potentially be applied to other analytes of interest including lactate, ammonia, amino acids, or product titer.

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