ENHANCING MULTIVARIATE CALIBRATION MODEL REPRODUCIBILITY FOR THE ONLINE MONITORING OF UPSTREAM PROCESSES IN CONTINUOUS BIOMANUFACTURING

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The complex mixtures present in biomanufacturing processes have traditionally required slow and expensive experimental assays, as well as time consuming and complicated analyses to be characterized properly. Multivariate Data Analysis (MVDA) can be integrated with spectroscopy to uniquely solve both of these problems simultaneously. Spectroscopic data has been generated in real-time, eliminating the need for offline assays; and MVDA has been used to rapidly analyze the data in a straightforward manner. Prior experiments have shown that this paradigm can be used offline to characterize the raw materials that are used to supplement cell culture media. However, online models that reliably quantify extracellular component concentrations in continuous bioprocesses require additional considerations. Even when the components' absorbance properties are well understood, cellular metabolism ensures that nutrient and product profiles vary collinearly with one another. This work explored supplementation strategies that break this collinearity to ensure that proper multivariate calibration models are constructed, instead of soft sensor models whose performance is inconsistent due to their reliance on component concentration collinearity for accurate predictions. This allows for more robust corrective action to be taken. Furthermore, the advantages of training multivariate calibration models from continuous bioprocesses' data, whose steady-state operation allows for more robust and complete design space coverage relative to batch processes, are explored as a way to guide ongoing and future research in this area. Disclaimer: This article reflects the views of the authors and should not be construed to represent official FDA's views or policies.