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TITLE: Production: Optimizing Cell Culture Processes with Digital Twins and Hybrid Modeling

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ABSTRACT: The manufacturing of biologic drugs relies heavily on sophisticated cell culture techniques. The optimization of these processes is often challenged by costly experiments, lengthy process cycles, and strict regulatory requirements for thorough process comprehension. Digital twins, dynamic virtual representations of unit operations such as bioreactors, enable the simulation of various scenarios to accelerate development and facilitate real-time process optimization for maintaining optimal conditions.

Traditional data-driven models (black-box approaches) efficiently detect statistical patterns but lack mechanistic understanding and reliable extrapolation, limiting their use in new or scaled-up situations. Fully mechanistic models rely on biological and physical principles for greater interpretability. However, they often struggle to represent the entire system because of gaps in knowledge and therefore cannot be directly applied. Hybrid models combine data-driven and mechanistic methods, making use of the strengths of both. These models enable the mechanistic components to be utilized where possible, while machine learning techniques address unknown aspects. As a result, hybrid models provide robust extrapolation capability and can capture complex phenomena like changes in cell growth rates and nutrient consumption influenced by environmental conditions. They also facilitate real-time optimization and should help better meet regulatory requirements by offering enhanced process characterization (FDA Stage 1) and setting real-time control limits for individual production batches (FDA Stage 3).

This work presents the application of digital twins for batch and perfusion bioreactor cell cultures, developed through hybrid modeling. The system integrates a Bayesian deep neural network, which processes input parameters such as temperature, agitation and nutrient feeding and predicts biological outcomes such as rates and yields values for biomass and product formation. These predictions feed into a system of ordinary differential equations (ODEs), the mechanistic part, to model the bioreactor's dynamic changes over time. Using probabilistic Bayesian deep neural networks enables uncertainty quantification in predictions, which is essential for drug development and manufacturing. Our case studies reveal that hybrid models can outperform conventional modeling strategies, especially when extrapolation is needed. We will also discuss how digital twins fit into contemporary manufacturing workflows.

BRIEF SPEAKER BIO: Thomas de Marchin is Associate Director of Statistics and Data Science at Cencora, where he applies advanced statistical methodologies and machine learning algorithms to optimize drug discovery and manufacturing efficiency. With deep expertise in regulatory compliance – particularly FDA and GMP standards – he bridges the gap between complex analytical approaches and practical pharmaceutical applications.