Application of Hybrid Neural Models to Bioprocesses: A Systematic Literature Review

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Abstract

Due to the complexity of biological processes, developing model-based strategies for monitoring, optimization and control is nontrivial. Hybrid neural models, combining mechanistic modeling with artificial neural networks, have been reported as powerful tools for bioprocess applications. In this paper, a systematic literature review is presented focused on the application of hybrid neural models to bioprocesses by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) over the last 30 years. This analysis showed that hybrid neural modeling has covered a wide range of microbial processes, animal cells, mixed microbial cultures, and enzyme biocatalysis. Hybrid neural models have been mainly applied for predictive modeling/process analysis, process monitoring/software sensors, open- and closed-loop control, batch-to-batch control, model predictive control, intensified design of experiments, process analytical technology, quality-by-design, and more recently, digital twins. Hybrid modeling experienced a decline in the number of publications after a peak in 2004 and is now surging again. A "model scale" research gap was identified, which will likely narrow by a better integration with deep learning and systems biology in the near future. The biopharma sector is currently a major driver but applications to biologics quality attributes (e.g. glycosylation), new modalities and downstream unit operations are significant research gaps.

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