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Peer Review

Review of: "Self-Driving Development of Perfusion Processes for Monoclonal Antibody Production"

Abdelaziz Abdelhamid[1]

1. Shaqra University, Saudi Arabia

I have reviewed the manuscript titled *"Self-Driving Development of Perfusion Processes for Monoclonal Antibody Production."* The study presents a novel integration of Bayesian experimental design, cognitive digital twins, and automated high-throughput bioreactor systems for developing perfusion processes. The work is highly relevant to advancing autonomous systems in biopharmaceutical manufacturing, with significant potential to impact efficiency and innovation. Below, I provide detailed feedback to further enhance the manuscript.

Content and Structure

The manuscript is well-organized, with a clear structure that guides the reader through the methodology, experiments, and conclusions. However, the following areas could benefit from refinement:

Introduction:

- Provide a stronger context for the role of self-driving laboratories in addressing industry bottlenecks, particularly for scaling up monoclonal antibody production.
- Highlight the novelty of integrating cognitive digital twins and Bayesian experimental design more explicitly compared to existing approaches.

Conclusion:

- Discuss the broader implications of deploying such systems, such as cost reduction, scalability, and workforce skill requirements in biopharmaceutical manufacturing.
- Include potential limitations, such as dependency on high-quality training data and challenges in real-time model adaptability.

Literature Review and Citations

The manuscript provides a strong review of relevant tools and methodologies. However, incorporating recent advancements in self-driving laboratories and hybrid modeling would strengthen the narrative. I recommend the following citations:

doi.org/10.32388/IEI1FP

- https://doi.org/10.1016/j.eswa.2023.122147
- https://doi.org/10.54216/JAIM.080103

These references discuss state-of-the-art optimization and machine learning techniques relevant to the study.

Technical Clarifications and Suggestions

The technical depth is impressive, but some areas require additional clarity:

Hybrid Modeling Framework:

- Expand on the theoretical foundation of the step-wise Gaussian process (SW-GP) and its advantages over conventional Gaussian process models.
- Include a comparative analysis of SW-GP with other hybrid modeling approaches in terms of computational efficiency and prediction accuracy.

Bayesian Optimization:

- Provide details on the acquisition function used in Bayesian optimization and its sensitivity to hyperparameter tuning.
- Discuss the computational overhead of retraining models during long-duration experiments.

Validation:

- Strengthen the validation by including a broader comparison with alternative modeling frameworks or commercially available solutions.

Visualization and Analysis

The figures and tables are well-constructed, but additional visualizations could enhance interpretability:

Process Dynamics:

- Include time-series plots comparing observed vs. predicted values for key variables like cell viability and glucose concentration.
- Add heatmaps to illustrate the impact of control variables on performance metrics such as viable cell volume (VCV).

Model Uncertainty:

- Visualize model uncertainty intervals alongside predictions to emphasize the confidence of retrained models.

Sensitivity Analysis:

- Highlight the sensitivity of model outputs to variations in input parameters, particularly for the Bayesian optimization process.

Practical Applications

The study offers exciting practical applications, but additional emphasis on implementation challenges and benefits is warranted:

Industry Integration:

- Discuss potential challenges in deploying such autonomous systems in large-scale manufacturing facilities.
- Address the regulatory implications of using AI-driven processes in GMP environments.

User Interface:

- Elaborate on the usability of the proposed system for non-expert operators and the training required for effective adoption.

Future Work

The outlined future directions are promising. Additional recommendations include:

Quality Attribute Modeling:

- Investigate the integration of critical quality attributes (CQAs) into the hybrid modeling framework for real-time quality control.

Multi-Objective Optimization:

- Explore extending the optimization framework to balance competing objectives like cost, yield, and quality.

Summary

This manuscript makes a significant contribution to the field of biopharmaceutical manufacturing by demonstrating the feasibility of autonomous process development systems. The integration of cognitive digital twins and Bayesian optimization is particularly noteworthy. With the recommended revisions, the manuscript will have a substantial impact on advancing self-driving laboratory technologies.

Declarations

Potential competing interests: No potential competing interests to declare.