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

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Potential competing interests: No potential competing interests to declare.

I have reviewed the manuscript titled *"Self-Driving Development of Perfusion Processes for Monoclonal Antibody Production."* The study proposes an integrated framework leveraging Bayesian experimental design, a cognitive digital twin, and advanced mini-bioreactor setups to autonomously optimize cultivation processes for monoclonal antibody (mAb) production. The experimental results demonstrating enhanced control and efficiency over 27 days are compelling and showcase the potential of autonomous systems in bioprocess development. Below, I offer feedback to refine the manuscript:

Content and Structure: The manuscript is well-written, with clear explanations of the problem, methodology, and experimental results. However, the introduction could benefit from further elaboration on the broader industrial implications of the proposed framework, such as cost reduction in biopharmaceutical manufacturing and its scalability to other bioproducts. Additionally, the discussion section should address the challenges of real-world implementation, particularly regarding regulatory compliance and data integrity in autonomous systems.

Literature Review and Citations: While the literature review is extensive, incorporating additional references on optimization techniques and advanced control in bioprocessing would enhance the discussion. I suggest including the following citations to provide a more comprehensive context:

- https://doi.org/10.1016/j.eswa.2023.122147
- https://doi.org/10.21608/jaiep.2024.386693
- https://doi.org/10.54216/JAIM.080103

Technical Clarifications and Suggestions: While the methodology is robust, additional clarifications in the following areas would enhance understanding:

- **Digital Twin Architecture:** Provide more details about the cognitive properties of the digital twin, including how it integrates prior knowledge and adapts to new experimental data.
- **Bayesian Optimization:** Elaborate on the parameter search space and the acquisition function used, as well as their impact on computational efficiency and experimental outcomes.
- **Dataset Diversity and Generalizability:** Discuss the extent to which the findings can be generalized to other cell lines or cultivation processes, and outline potential limitations.
- **Comparative Analysis:** Include a comparison of the proposed framework with other state-of-the-art approaches in

terms of scalability, cost, and performance.

I hope these suggestions assist in refining your manuscript. The integration of autonomous experimental systems with advanced computational tools presents a significant advancement for biopharma R&D, and with these revisions, the paper could make a substantial contribution to the field of process optimization and automation.