Development of Cybergenetic Twins for Enhanced Biomanufacturing Processes

Abstract

Biomanufacturing plays a critical role across modern healthcare and industry. Recently, the potential of the field to deliver solutions to unmet clinical needs was underscored by the rapid advancement and application of mRNA vaccine technology.

However, the robustness of conventional biomanufacturing processes is undermined by their reliance on macro-level variables (e.g., temperature, dissolved oxygen, pH) to monitor and control production. Macro-level variables can delay detection of the emergence of undesired cell physiological states until it is too late for effective intervention.

Here we aim to address this challenge and advance biomanufacturing by developing hybrid biological/digital twins, termed "cybergenetic twins". Using an innovative combination of Scientific Machine Learning (SciML), Constraint-Based Modelling, and Optimal Control principles, the candidate will develop a strategy for real-time, precise adjustments to bioprocesses, that promises to enhance their productivity and reliability.

Introduction

Biomanufacturing is pivotal in producing everything from pharmaceuticals to biofuels, playing an integral role in creating a sustainable future. Despite its importance, the field's reliance on traditional monitoring and control techniques that track macro-level variables like temperature and pH limits its efficiency and responsiveness. These variables, while useful, only serve as indirect proxies of the underlying cellular processes, often providing feedback when corrective measures are no longer effective.

The proposed research focuses on integrating cutting-edge AI algorithms (e.g. Neural Ordinary Differential Equations and Neural Optimal Controllers) with dynamic systems modelling to create a new paradigm in biomanufacturing. This project will develop "cybergenetic twins," which are sophisticated hybrid bio-digital models that simulate and predict the behaviour of biomanufacturing processes at the cellular level, allowing for pre-emptive adjustments and optimized outcomes.

Research Challenge

The primary challenge this research intends to address is the gap in real-time monitoring and responsive control of bioprocesses at the cellular level. Current biomanufacturing frameworks are not equipped to detect subtle but critical physiological changes in host cells, which can lead to significant deviations from desired production outcomes. This project will tackle the complexities of accurately modelling biological systems and integrating these models with real-time data analytics to create a robust digital twin that can predict and mitigate issues before they affect production.

Data & Methodology

The methodology will involve three core components:

1. **Scientific Machine Learning (SciML):** Leveraging the SciML.jl ecosystem in Julia, this project will develop machine learning models that are specifically tailored to understand and predict complex biological processes within biomanufacturing settings.
2. **Constraint-Based Modelling:** This approach will be used to accurately simulate cellular metabolism and other critical biological functions, thereby providing the foundation of the cybergenetic twins.
3. **Optimal Control Principles:** These principles will inspire the development of algorithms that dynamically adjust bioprocess parameters in real time, based on predictions and simulations provided by the cybergenetic twins.

The research will use historical data from existing biomanufacturing processes, supplemented by experimental data generated through controlled lab experiments designed to validate the models.

RRI/Ethical Considerations

Responsible Research and Innovation (RRI) principles will guide the entire project to ensure that technological advancements are developed in a manner that is ethical, inclusive, and sustainable. Key considerations will include the ethical implications of automation in biomanufacturing, potential impacts on employment and skills in the sector, and the environmental implications of new bioprocesses. Additionally, the project will address data privacy issues, particularly in the handling of proprietary and sensitive biomanufacturing data.

Expected outcome and impact

The development of cybergenetic twins is anticipated to have a transformative impact on the biomanufacturing sector. Indeed, the ability to enact real-time monitoring bioproduction at the cellular level will **further our understanding of bioprocesses**. In turn, this will allow manufacturers to both detect and predict undesired deviations of production processes before they manifest in end-product variability. As a result, **bioproduction reliability and consistency** will be **enhanced**, meeting the strict product quality requirements of pharmaceutical industries.

We anticipate the cybergenetic twins project will introduce a new level of **efficiency** in **bioprocess control**. Traditional methods that react to changes in macro-level variables often lead to delayed interventions. The availability of dynamic, predictive models for control supports instead proactive interventions, optimizing the trade-off between resources (material, energy) consumption and waste production. Beyond improving the economic performance of biomanufacturing facilities, this efficiency gain will contribute to **sustainability in biomanufacturing**, setting a new standard for future developments in the field.

References

Caringella, Gianpio, Lucia Bandiera, and Filippo Menolascina. "Recent advances, opportunities and challenges in cybergenetic identification and control of biomolecular networks." *Current opinion in biotechnology* 80 (2023): 102893.