Case Study

DATAHOW

Hybrid Modeling for Scalable Cardiomyocytes Expansion: A Use Case in Cell Therapy

Combining advanced therapies with advanced analytics

Introduction

Cell therapies are resource-intensive and complex, with high materials costs and outcomes that are highly sensitive to variables like oxygen levels and feed rates. Under these cost pressures and stringent quality standards, scientists are forced to explore the design space and **identify optimal conditions with limited experimental capacities**. Each experiment is crucial and must be maximized for its return on learning and insight.

AI-enabled hybrid modeling is optimal for such a challenge. Requiring minimal data to return actionable insight, it is designed to operate under data-scarce conditions. Additionally, its modeling structure offers the possibility to **simulate and learn beyond available experimental data**, offering a potentially valuable capability to explore the design space via simulation, and use insight to plan targeted experiments.

Hybrid Models vs. Statistical in Cell Therapy

A hybrid model was trained using data from six bioreactor runs. Bioprocess runs were conducted using **Eppendorf's** DASGIP® parallel bioreactors, managed via DASware® control, with all data consolidated in BioNsight Cloud for storage and analysis. The dataset included three distinct dissolved oxygen (DO) conditions: hypoxia at 5% O2, mild hypoxia at 10% O2, and normoxia at 21% O2. Dataset was generated at **iBET** under the scope of published work[1].

The performance of the hybrid model was **compared against a statistical linear model** for predicting VCD at the final day of the process. To further evaluate model capabilities, simulations were conducted using both the trained hybrid model and linear model to assess the impact of DO on final VCD.

[1] *Billion-Scale Expansion of Functional hiPSC-Derived Cardiomyocytes in Bioreactors Through Oxygen Control and Continuous Wnt Activation* Vicente et al., 2025, *Advanced Science*

Study Objectives

OBJ. 1: Assess the ability of hybrid to capture cell therapy process dynamics across oxygen conditions

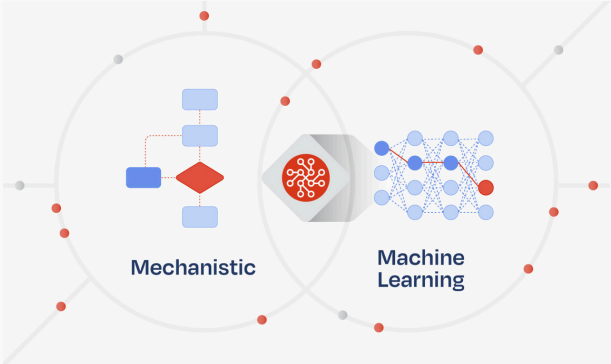
OBJ. 2: Comparing Hybrid and Statistical Models to validate process understanding and predictive performance.

OBJ. 3: Assess the impact of simulations using hybrid models to support learning and operational efficiency in cell therapy processes

These capabilities were assessed as part of this project.

Hybrid Models

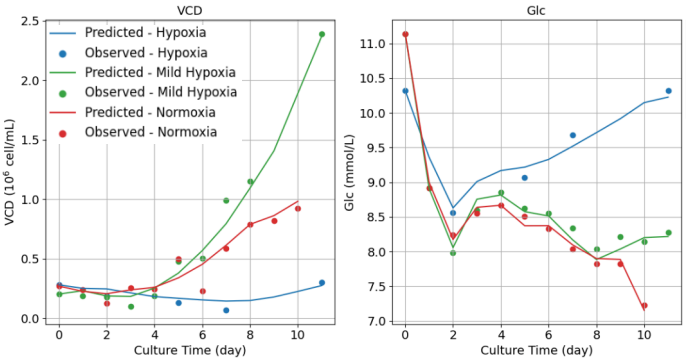
DataHow has pioneered the application of hybrid models to bioprocessing. They are a balance of **structured knowledge and flexible learning** that are perfectly adapted to the complex, yet data-scarce environment of bioprocessing.



The **mechanistic backbone** transports the domain's scientific knowledge to describe process dynamics, while the **machine learning** captures unknown, complex, and nonlinear behaviors.

Key Results and Insights

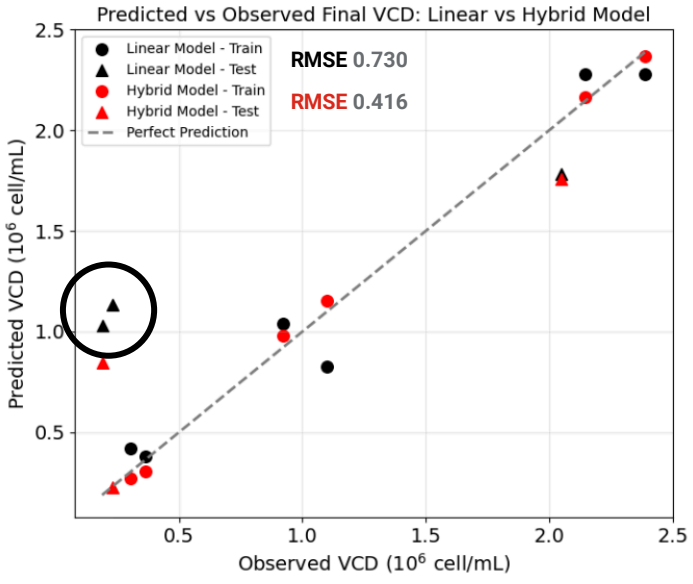
OBJ. 1: The hybrid model successfully predicted the complete profiles of critical process variables including viable cell density (VCD), glucose, lactate, and LDH.



The **model demonstrated strong predictive capability** in capturing and distinguishing the dynamic behaviors between these three operational conditions, indicating its ability to understand the underlying process differences driven by varying oxygen levels, with limited data.

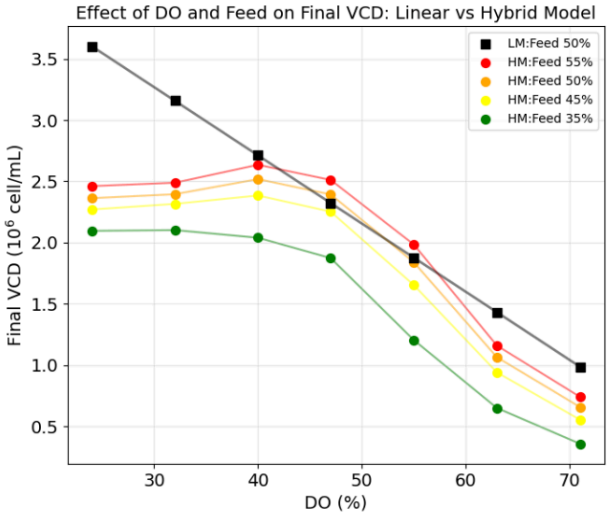
OBJ. 2: The hybrid model demonstrated superior predictive performance versus the linear model.

Simulations revealed that the hybrid model effectively captured the non-linear correlation between DO and final VCD, while the simple linear model failed to adequately capture this complex relationship.

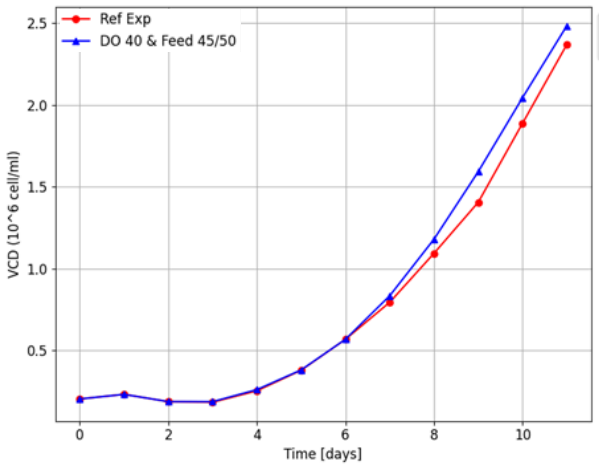


Compared to the linear model (black), the hybrid model (coloured) exhibited a unique advantage in detecting how feed changes affect the process, even when feed data remained constant in the training set. This results from the **model's incorporation of fundamental process dynamics**, such as material balances, which directly explain how feeding impacts cell growth and metabolite levels.

This mechanistic foundation makes the hybrid model a powerful tool for more dynamic process understanding, particularly when working with limited experimental data.



OBJ. 3: The hybrid model was used to simulate multiple scenarios, identifying an **optimal combination** of feed and DO that maximizes cell growth while minimizing media consumption. These insights support data-driven decision-making and experimental planning, and pave the way for cost-effective bioprocess optimization in cell therapy.



Insilico Simulation | **Less Data / More Insight** | **Targeted Experiments** | **Cost Reduction**