DATAHOW

Optimizing Microbial Processes across the Process Lifecycle with DataHowLab

Understanding microbial bioprocesses presents a unique set of challenges. Their speed, diversity, and dynamic behavior require modeling approaches tailored to their specific biological and operational characteristics.

Understanding the unique characteristics of microbial processes

Microbial bioprocesses present unique challenges that require specialized modeling approaches. Unlike mammalian systems, they operate on much faster time scales, often with exponential growth phases that demand high-resolution, dynamic models.

The diversity of microbial hosts—such as E. coli, Pichia pastoris, and Saccharomyces cerevisiae—means that models must adapt to organism-specific kinetics and metabolic behaviour. Additionally, many processes rely on inducers to trigger production, requiring models to capture time-dependent effects. Irregular sampling intervals and missing data are common, necessitating models that handle non-uniform time-series data robustly.

Assessing the impact of DataHowLab's hybrid models across a process lifecycle

DataHowLab's hybrid models—both structured and flexible—offer a robust solution to working effectively within challenging process conditions. DataHowLab's models and model-based applications:

- Enable deep and efficient understanding of complex microbial processes, even with their distinct characteristics
- Support the efficient design and optimisation of microbial processes during development
- Uncover the drivers of unexpected process behavior in microbial systems, despite low variability in controlled manufacturing conditions

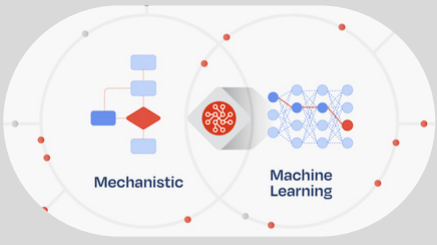
Case 1: Evaluate the effectiveness and efficiency of DataHowLab in modeing and understanding microbial processes.

Case 2: Evaluate the effectiveness and efficiency of DataHowLab in optimizing microbial processes.

Case 3: Evaluate DataHowLab's ability to identify root causes of variability in microbial manufacturing processes.

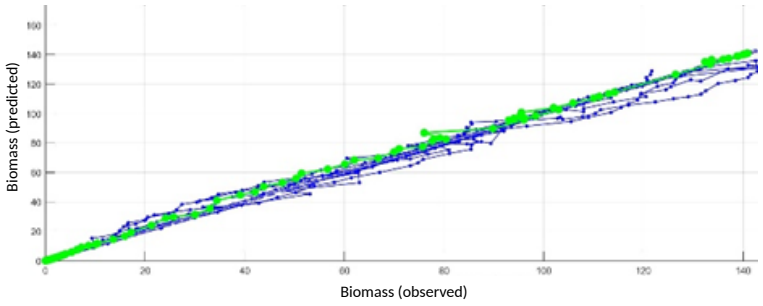
Why are Hybrid models so well suited to Microbial processes?

They are well-suited for microbial processes as they combine mechanistic insights (e.g., growth kinetics, inducer effects) with data-driven learning to capture process-specific, nonlinear behaviours and varying time scales that are difficult to model explicitly.



Their flexibility allows adaptation to various microbes and process setups, while capturing key factors like byproducts and inducer timing. They also enable multi-objective optimization of growth, yield, and quality.

Insight 1 - Rapid understanding of microbial processes with high prediction accuracy

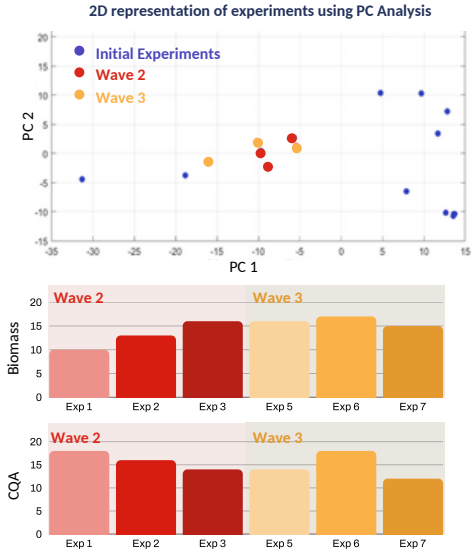


A yeast process with 12 experiments at 5.5L scale, was modeled with DataHowLab where **only 9 experiments** were used to train the model.

The resulting model accurately predicted the 3 test runs with an RMSE error of only 0.12.

- Hybrid models require minimal experimental data to accurately understand and predict microbial processes.
- DataHowLab's hybrid models are well adapted to microbial processes and demonstrate a strong ability to understand their full dynamic profiles.

Insight 2 - Efficient optimization via agile, iterative experimental design and insight generation



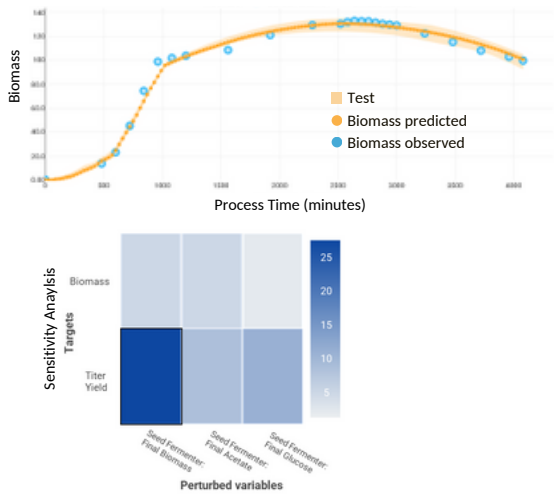
Optimisation objective: ↑Biomass ↑CQA (plasmid retention)

Insights from the initial 12 experiments were used to design 3 explorative experiments **(wave 2)** where knowledge was poor due to gaps in the initially investigated parameter space. The knowledge gained was then used to inform a second design cycle **(wave 3)** focused on exploiting the most promising areas identified to maximise both objectives simultaneously.

While trade-offs are seen between CQA and product in **wave 2**, the insights allowed scientists to efficiently maximise both objectives in **wave 3**.

- Hybrid-model-driven experimental design, in combination with enhanced learning capabilities, enables agile, iterative development cycles
- Shorter, faster learning cycles drive development efficiency while maximising process objectives

Insight 3 - Determine root cause of manufacturing variability within complex multiphase processes



A CDMO running a microbial (E.coli) manufacturing process across the seed and main fermenters experienced variations in final titer despite controlled conditions.

Combined run data from both the seed and main fermenters were used to train a model in DataHowLab, with high predictive accuracy across all phases of production (plot 1).

A sensitivity analysis (plot 2) revealed that, unexpectedly, the seed fermenter biomass was root-cause of poor titer in the main fermenter.

- DataHowLab models accurately capture and predict complex microbial processes across both seed and main fermenters
- The root cause sensitivity offered by DataHowLab supports proactive control strategies, even in low-variability manufacturing environments

Enhanced Insight into Microbial Processes

Short, Iterative Experimental Cycles

Development Efficiencies in R&D

Enhanced Root cause Diagnostics