

Digital AI-driven methodologies to support and accelerate mAbs development in the biopharmaceutical industry

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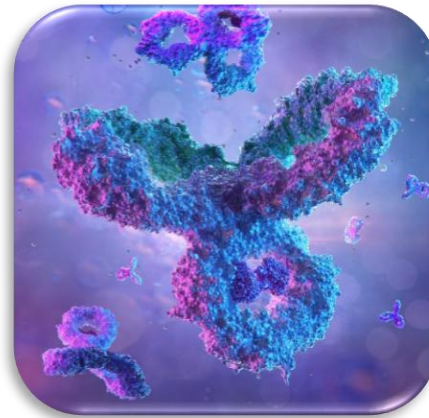


Monoclonal Antibodies

mAbs → Recombinant proteins → produced through mammalian cell cultures

217 billion \$

Global market value[†]



53.3 %

of biopharmaceutical approvals

Treatment of life-threatening conditions

**Autoimmune
disorders**

Infectious diseases

Cancers

mAbs development

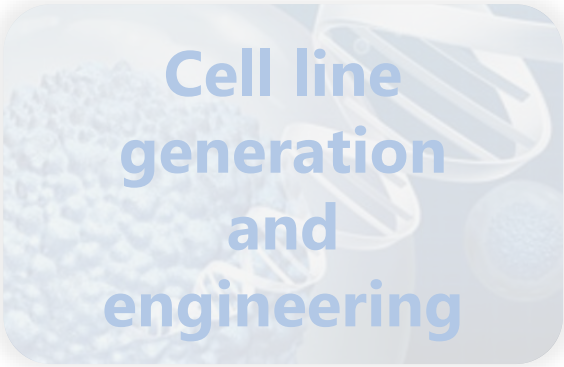
Long timelines[†]

10 years

Large costs

2 billion \$

Steps of process development



Cell line generation and engineering

- ▶ Produce a pool of transfected cell lines



Cell line selection

- ▶ Find best performing clone
- ▶ Multiscale procedure



Process characterization

- ▶ Identify relationship among CCP, CMA and CQA



Process optimization

- ▶ Identify best feeding schedule
- ▶ Maximize productivity & quality



Challenges in Biopharma



Long and expensive experiments

Large experimental variability due to biological difference among clones and batches



Labor-intensive experimental procedure

Requires expert skills for the analysis and execution of experiments



Development of AI-driven methodologies to support mAbs development



Challenges in Biopharma

Development of AI-driven methodologies to support mAbs development

Accelerate cell line selection

What standard culture behavior is?

Can biological information improve cell line selection?

Optimize feeding schedule

Are hybrid models and Design of Dynamic Experiments effective?

Can hybrid models and Reinforcement Learning reduce required experiments?

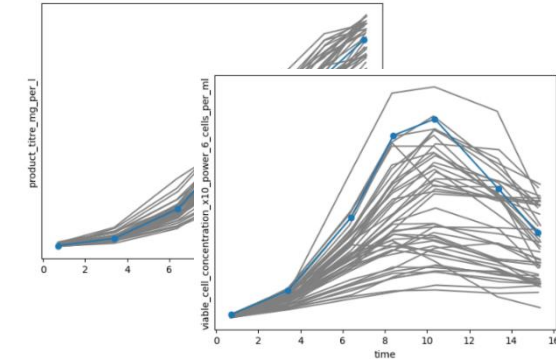
What standard culture behavior is?

AMBR15®



- ▶ High throughput bioreactor
- ▶ 48 parallel 15mL stirred tanks
- ▶ Automated sampling, feeding and control
- ▶ 10 variables (titer, VCC, pH, nutrients, ...)

Time trajectories



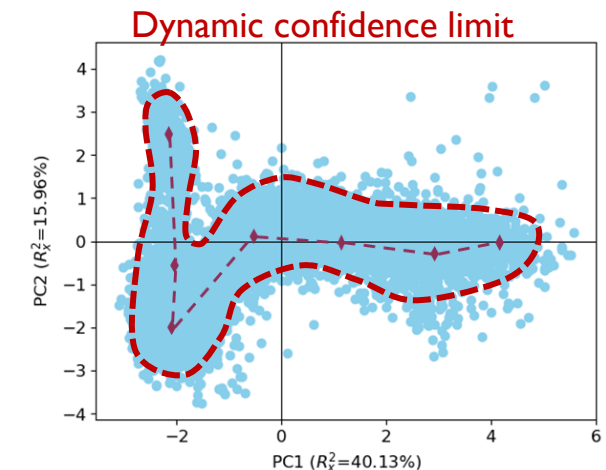
Understand the acceptable variability of batches and automate the analysis of AMBR15 time trajectories

1160 historical batches

- ▶ several therapeutic mAbs
- ▶ 15-days cultivation
- ▶ comparable feeding and conditions

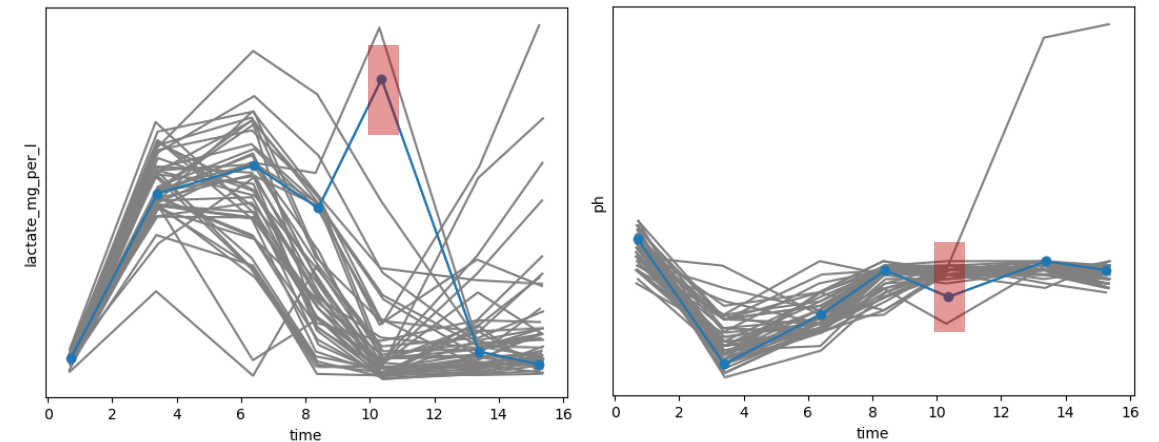
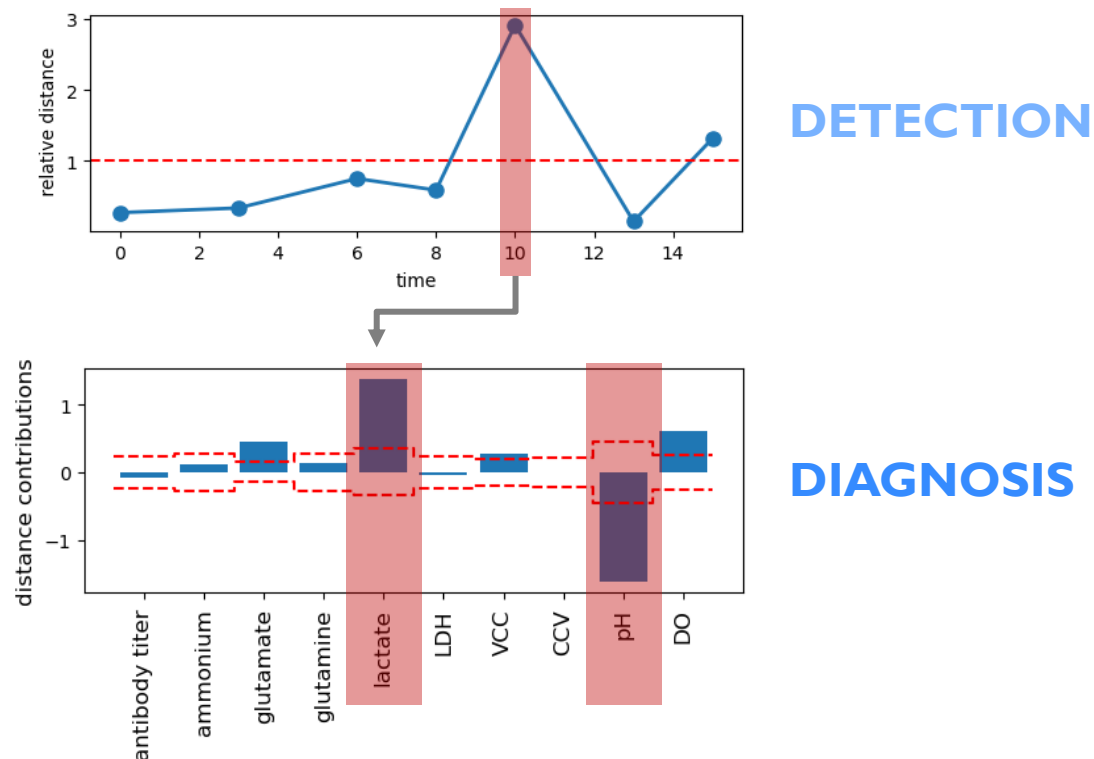
Multiway PCA[†] & assumption-free monitoring[‡]

- ▶ reduce data dimensionality
- ▶ understand correlations
- ▶ build dynamic confidence limits



Automate batch analysis

- ▶ **Understand standard behavior of cells**
 - ▶ Considering multivariate nature of data
- ▶ **Identify anomalies in culture behavior and diagnose the causes**

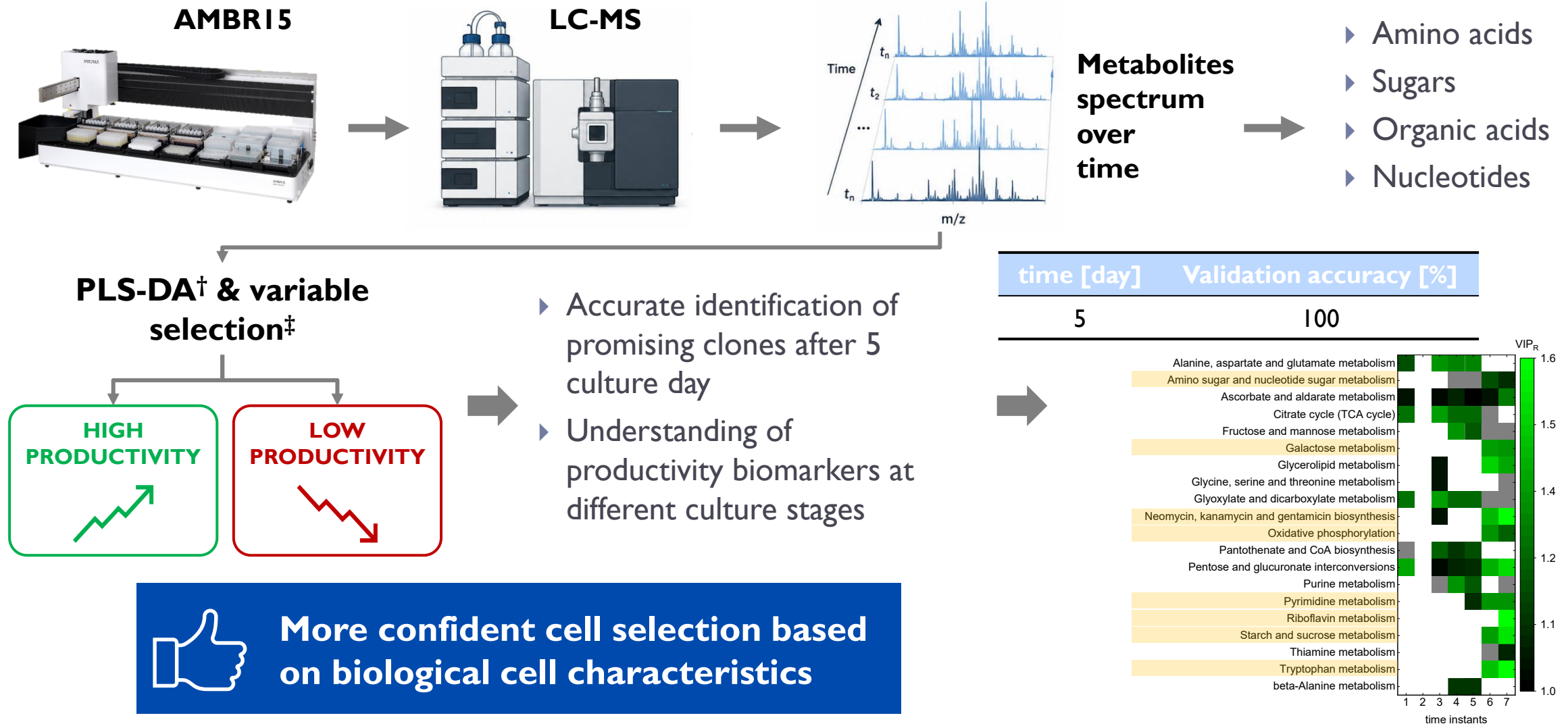


Comparison with expert inspection



Save expensive labor time & reduce effort of expert scientists

Can biological information improve cell selection?



Hybrid models of cell cultures

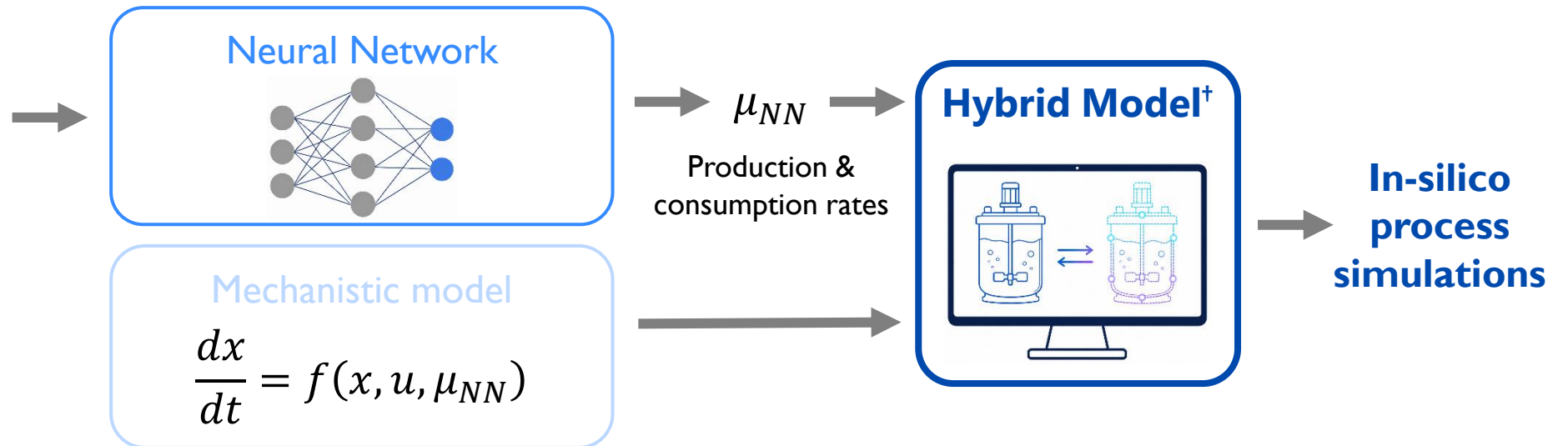
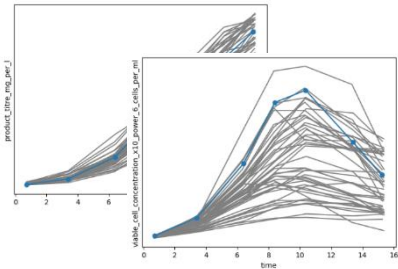
Mechanistic

- ▶ Process knowledge and physical constraints
- ▶ Biological interpretability
- ▶ Temporal consistency
- ▶ Better extrapolation

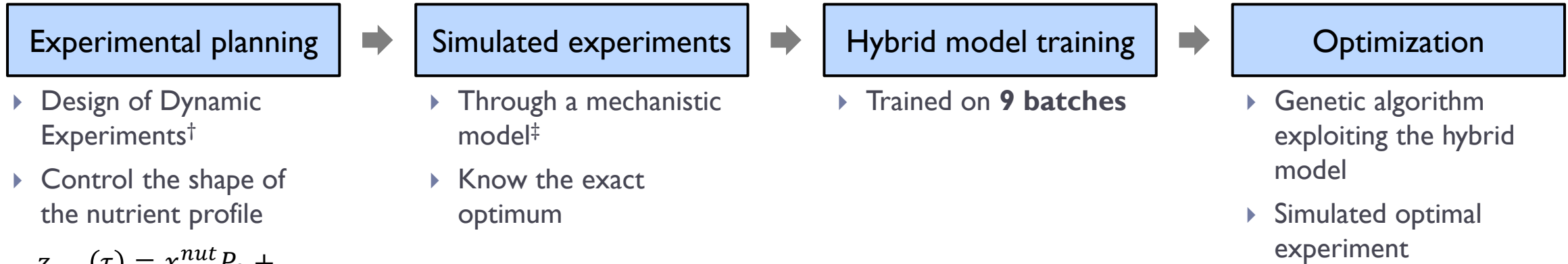
Data-driven

- ▶ Captures complex and unknown biological behaviors
- ▶ Learning from data
- ▶ Flexibility for different platforms
- ▶ Accurate predictions

Experimental data



Are hybrid models and DoDE effective?



$$z_{nut}(\tau) = x_1^{nut} P_0 + x_2^{nut} P_1 + x_3^{nut} P_2$$

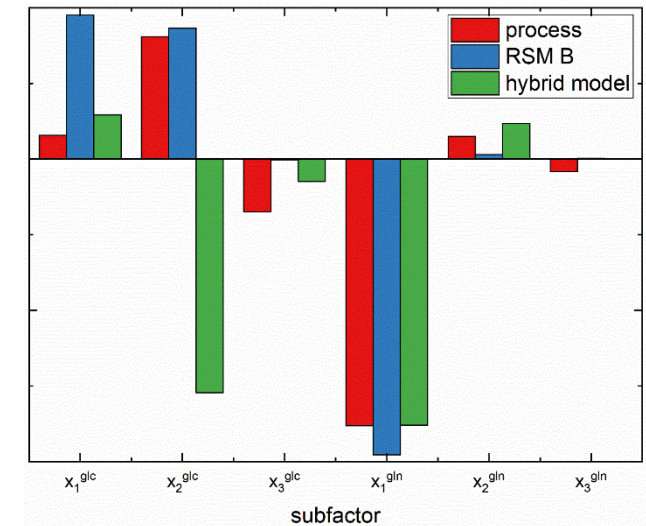
- Hybrid model achieves the highest optimal mAbs titer w.r.t. state-of-the-art techniques

Strategy	# train batches	Optimal titer [mg/L]
Real opt.	-	3228.8
Hybrid	9	3222.8
RSM	9	3136.3
RSM	31	3118.2

- The identified nutrient profile is very similar to the optimal one



Hybrid model is effectively used to optimize the feeding schedule



Can hybrid models reduce experiment requirements?

Simulated experiments

- ▶ Through a mechanistic model†
- ▶ Randomly generated manual feeding

Hybrid model training

- ▶ Trained on **10 batches**

Reinforcement Learning

Nutrient quantity

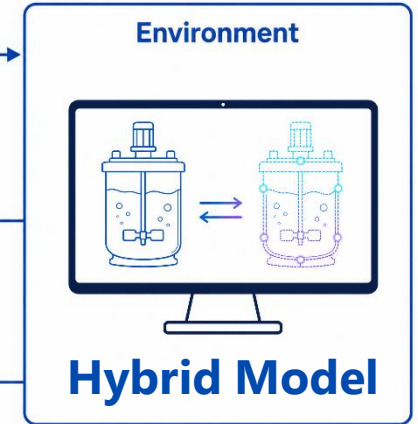
Action

Environment

Reward

State

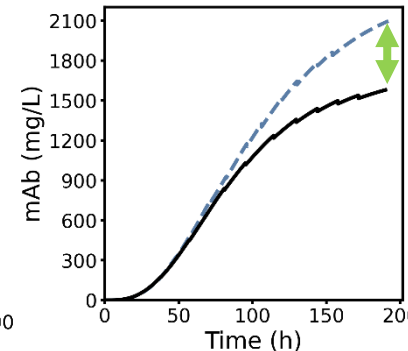
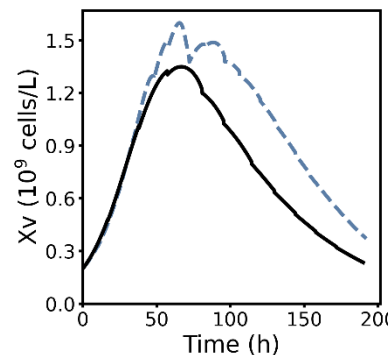
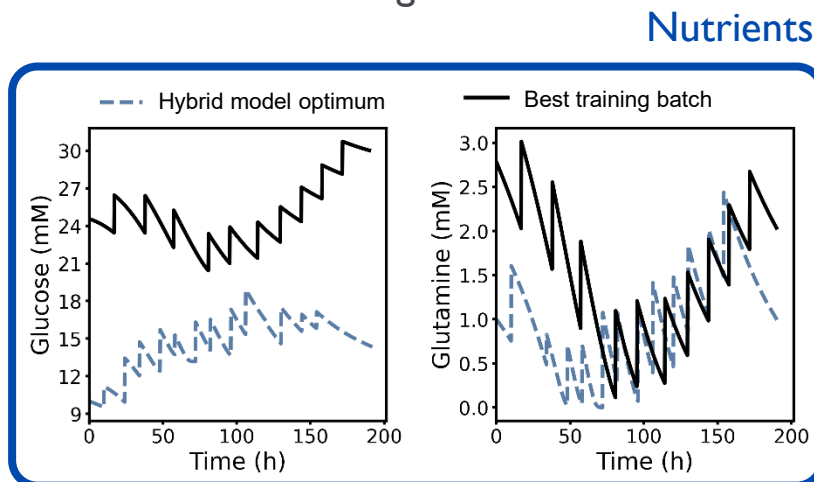
Culture variables



Hybrid Model

Reward

- ▶ High mAbs titer
- ▶ Low byproducts
- ▶ Physical consistency



- ▶ RL agent **improves mAbs titer** at harvest
- ▶ Identifies new optimal nutrient patterns



**Reduced experiment requirements
to optimize the process**

Conclusions



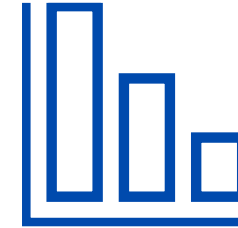
Lower the experimental effort for scientists

AI allows to **automate labor-intensive work** effectively accelerating development timelines



Improved selection of performing clones

AI and biological data support the a **more informed selection** of clones with desired behavior



Less experiments for process optimization

Hybrid models are effective tools to **optimize** the feeding schedule while **limiting required experiments**





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