

Improved metabolic understanding in biopharmaceutical product development through hybrid modelling

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Improve understanding of monoclonal antibody cultivation

Monoclonal antibodies (mAbs) are biopharmaceuticals cultured in CHO platforms¹

- ▶ **treat** different **diseases** → breast cancer, leukemia, arthritis, etc.

Process development is **costly** and **time consuming**
large biological variability and poorly understood phenomena



PROBLEM



**COMBINE
AVAILABLE
TOOLS**

Metabolomics data
*Dynamic insight into cell
metabolism*

Process data
*Macroscopic CHO
system behaviour
(VCC, glucose, etc.)*

CHO kinetics
*Mathematical system
representation*

**Machine-
learning**
Exploit data information

Hybrid modelling to improve the understanding of CHO cell cultures
accelerate biopharmaceutical development



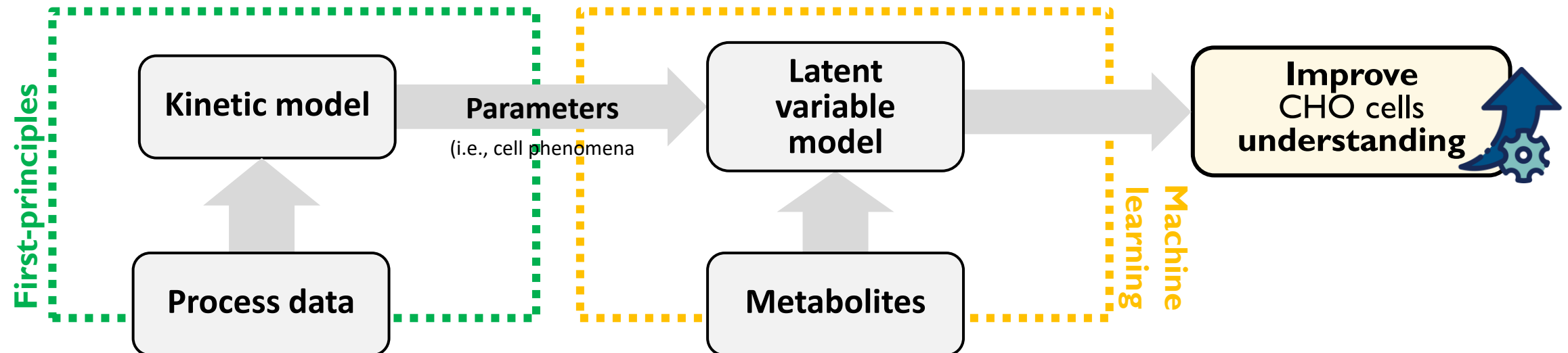
SOLUTION

Hybrid modelling in CHO cell cultures

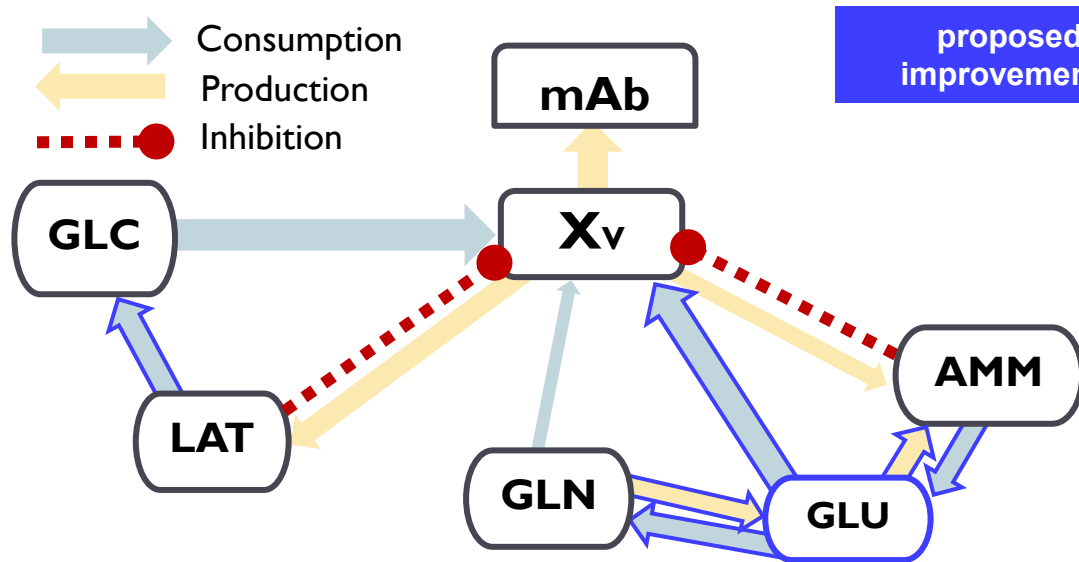
Hybrid modelling to improve the understanding of CHO cell cultures
accelerate biopharmaceutical development



- ▶ Hybridize **first-principles** models on **process data** and **machine learning** models on **cell metabolism** to link metabolic cell features with CHO cells main phenomena
 - ▶ **first-principles** → capture chemical-physical and biological phenomena through model parameters
 - ▶ **machine learning** → link metabolites with cell phenomena



Capture CHO cell phenomena with first-principles models

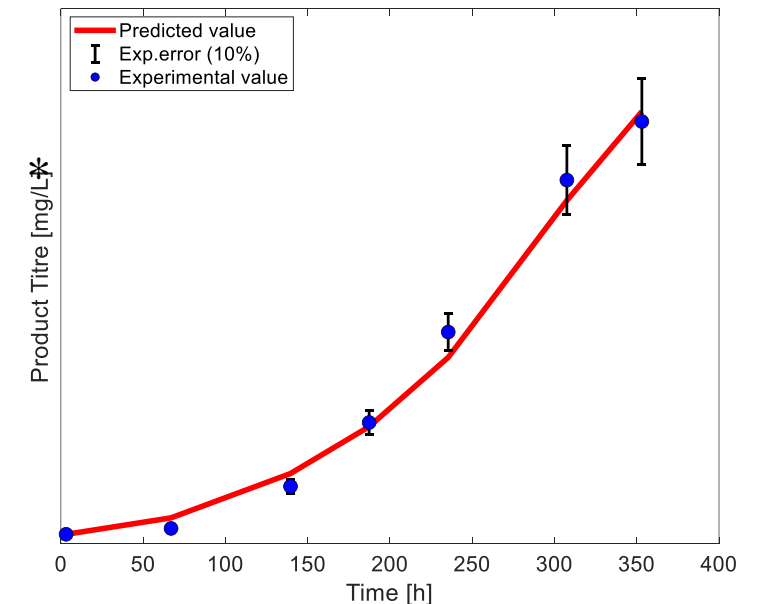


► A state-of-the art model³ is improved

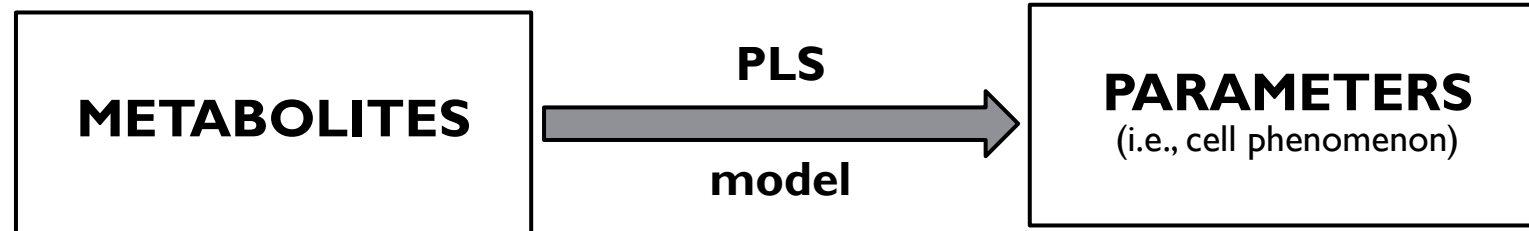
- account for Lactate consumption
- add Glutamate contribute

GLC	Glucose	GLN	Glutamine
LAT	Lactate	mAb	Monoclonal Antibody
GLU	Glutamate	Xv	Viable Cell Concentration
AMM	Ammonia		

- The most important model parameters are estimated on process data
 - sensitivity analysis⁴ identifies the most important parameters
 - **model parameters** are linked to **main cellular phenomenon**
 - $\mu_{\max}$ → cellular growth rate



Link metabolites with cell phenomena with PLS modelling



Preprocessing

- ▶ missing data treatment in the metabolites dataset⁶
- ▶ iterative selection of most informative metabolites⁷
 - ▶ based on highest VIP index⁸
- ▶ batch-wise unfolding⁵ of dynamic metabolite dataset

Validation results

- ▶ model's parameters are **highly correlated** to metabolomics dynamic data
- ▶ PLS allows investigating the correlations to unlock new valuable insight
 - ▶ investigates the regression coefficients that link the metabolites to the parameter

$$Q^2 = 1 - \frac{\sum_{v=1}^V \sum_{n=1}^N (x_{n,v} - \hat{x}_{n,v})^2}{\sum_{v=1}^V \sum_{n=1}^N (x_{n,v} - \bar{x}_v)^2}$$

Parameter	Q^2
$\mu_{\max}$	75.20%
Y_{Xglc}	50.00%
KI_{amm}	45.80%
Y_{Xglu}	90.40%
Y_{latglc}	76.40%
Y_{gluX}	80.90%
Y_{mAbglc}	82.20%

Metabolism relate to cellular growth

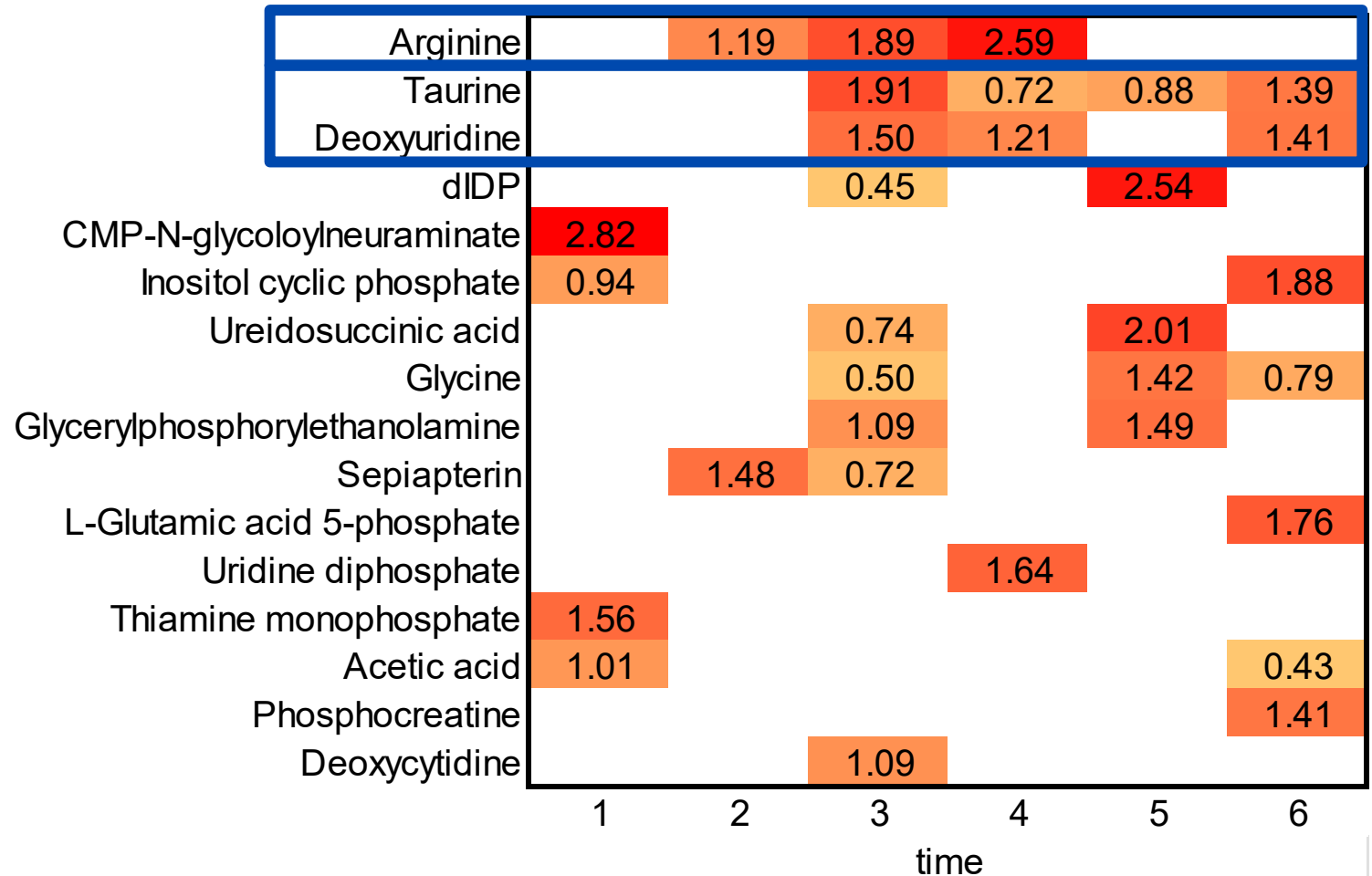
- ▶ Metabolites dynamics linked to $\mu_{\max}$
 - ▶ regulates cellular growth

▶ Arginine

- ▶ most important metabolite during the growing phase

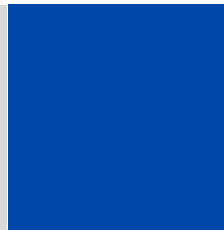
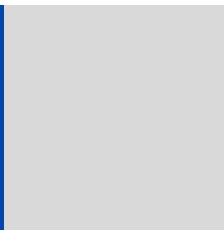
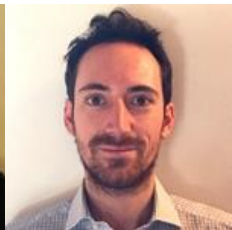
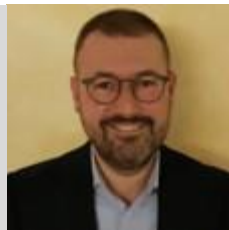
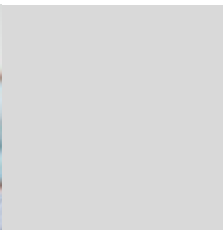
▶ Taurine and Deoxyuridine

- ▶ correlated to high final value of product titer and VCC



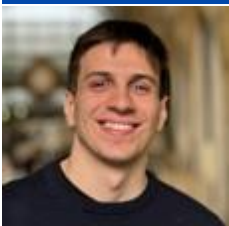
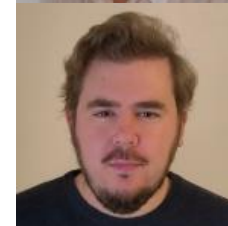
Conclusions

- ▶ **Hybrid modelling** to improve the understanding of CHO cell cultures
- 1. **CHO cell model** has been improved and used to identify main cell culture phenomena from process data
 - ▶ First-principle model parameters
- 2. **Data-driven models** link metabolites with cell phenomena
 - ▶ PLS modelling
- ▶ **Most important metabolites** coupled to cell physical, chemical and biological phenomena are investigated

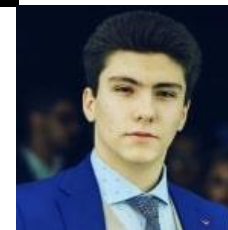
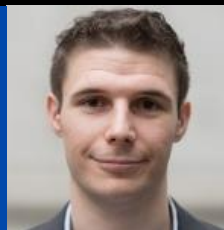
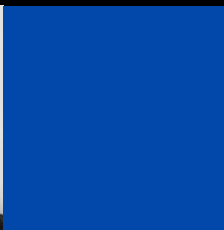
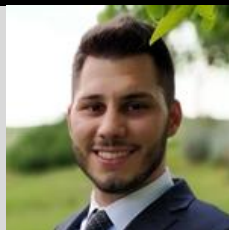
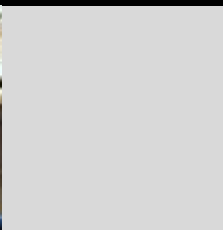
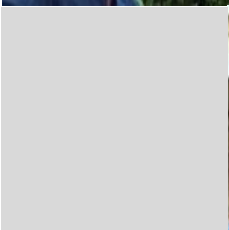


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