

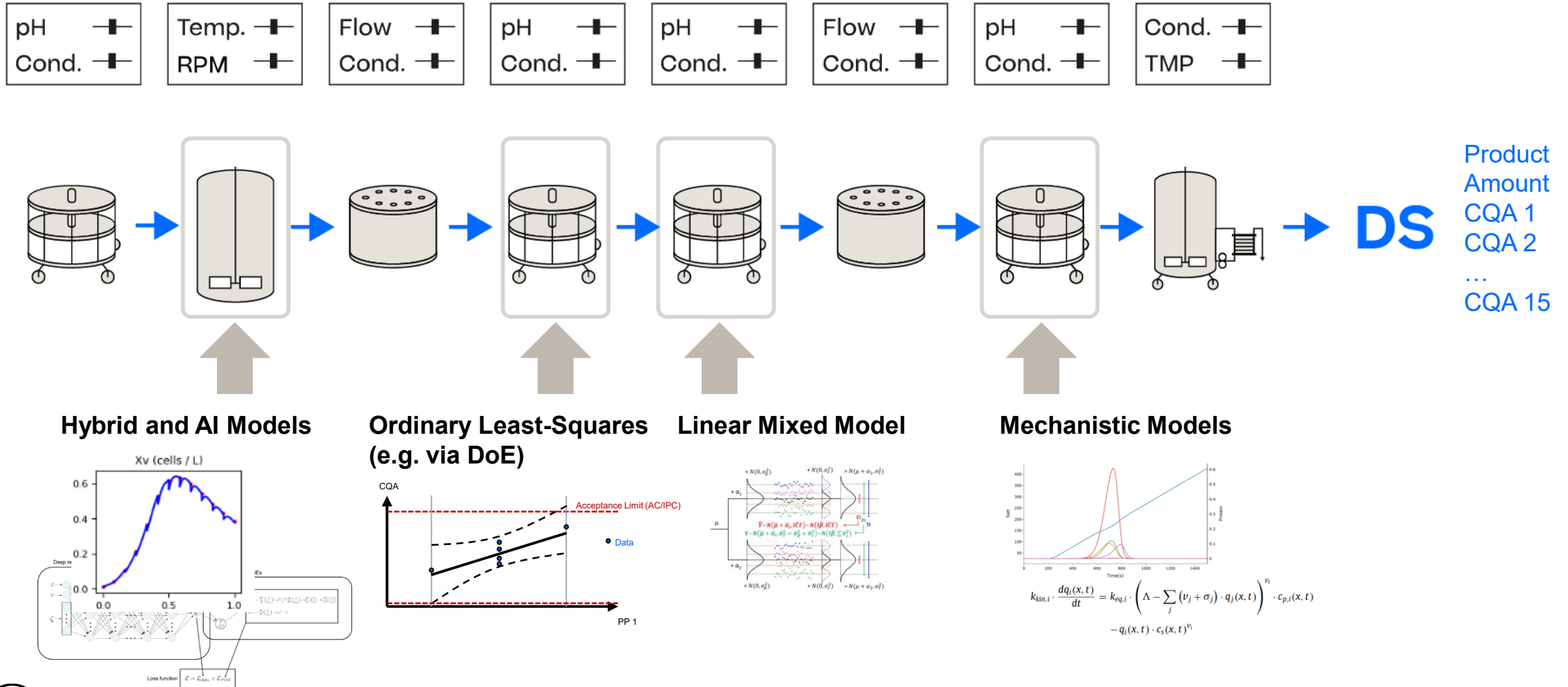
Physics Informed AI for CMC Applications

From Holistic Control Strategies towards Digital Twins in GMP

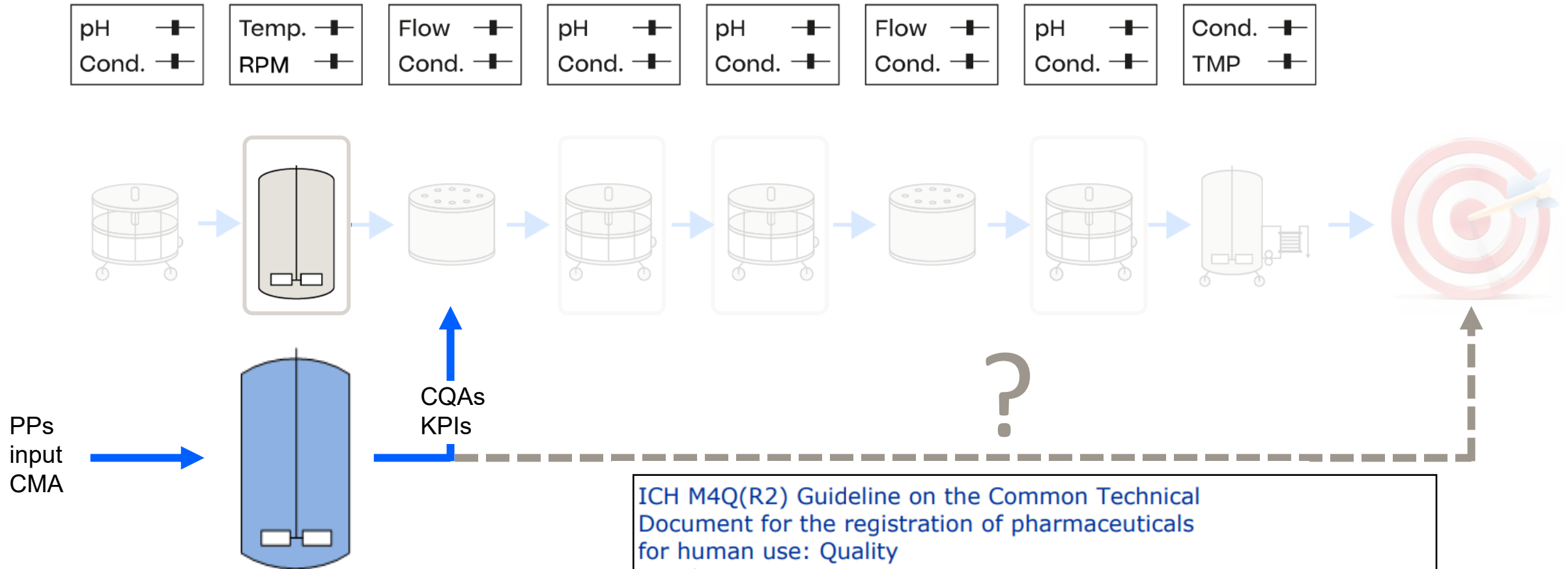
**Thomas Zahel,
Head of CMC Consulting and Innovation, Körber Pharma Austria**

23rd of September 2026, Padua, Italy

End-to-End Process Models



End-to-End Process Models



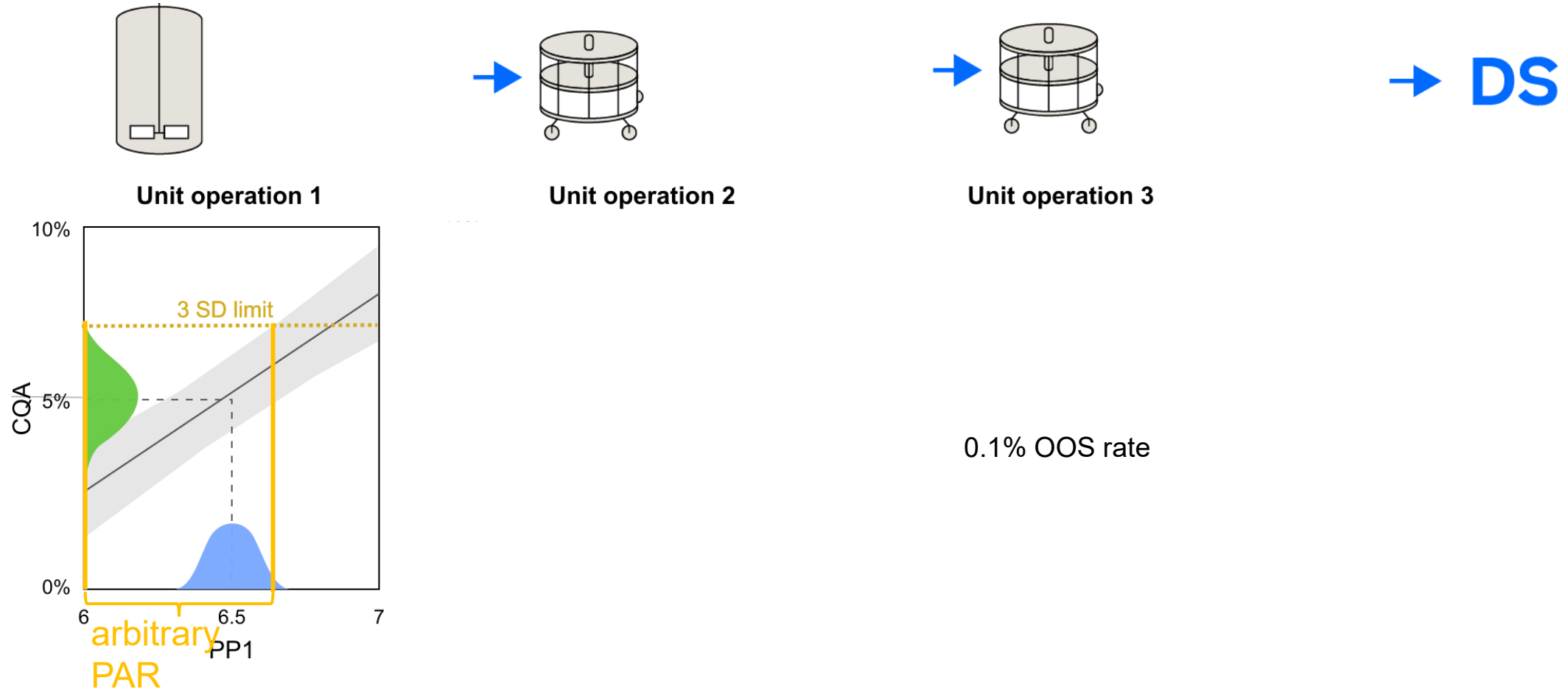
ICH M4Q(R2) Guideline on the Common Technical Document for the registration of pharmaceuticals for human use: Quality

Step 2b

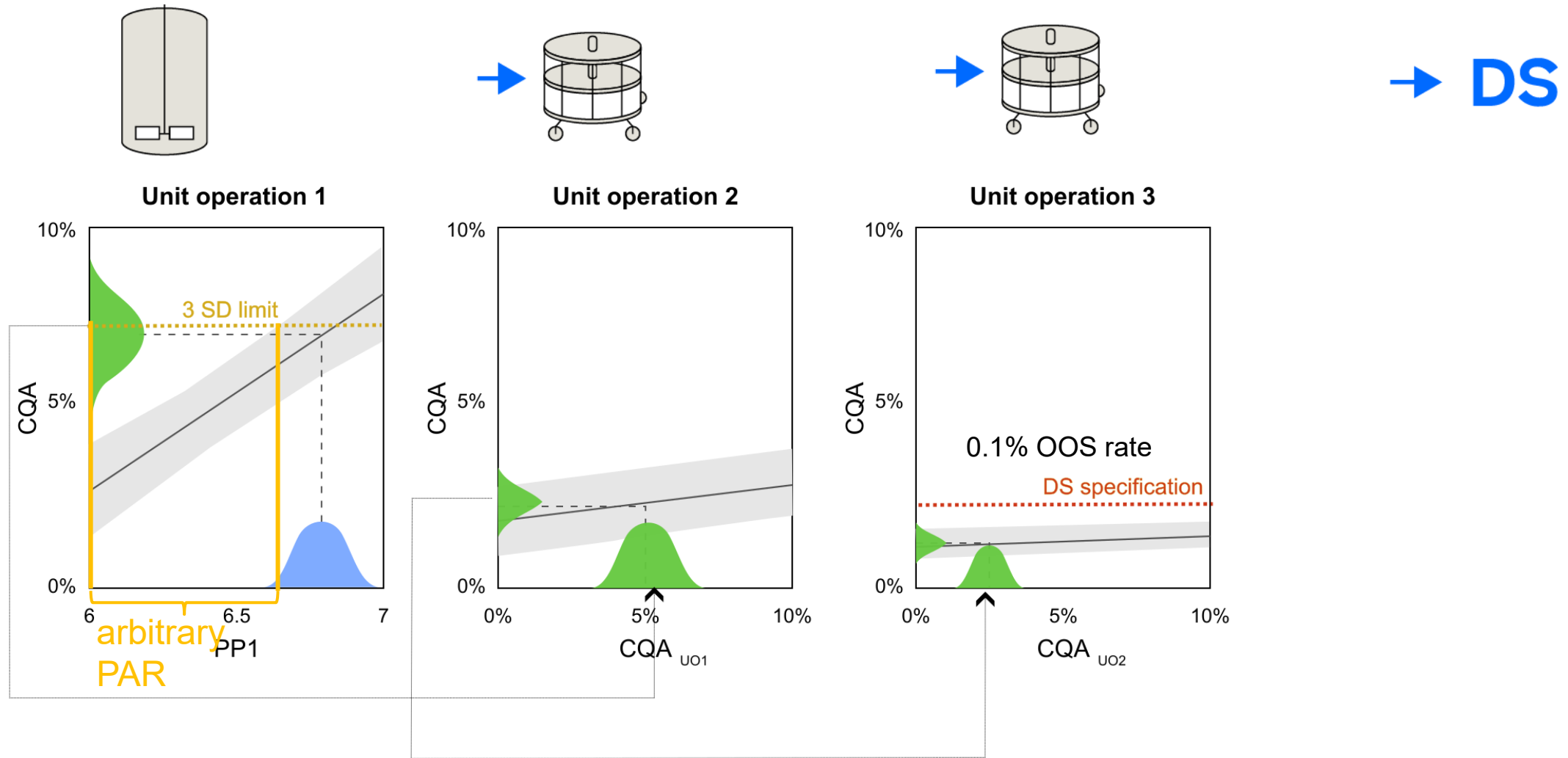
2.3.2.3 Overall Control Strategy Representation

The OCS is a holistic and integrated approach encompassing considerations from the CQAs to the end-to-end controls, describing how the individual control strategies interact to ensure product quality (ICH Q6A/Q6B, Q8, Q9, Q10, and Q11). A representation, such as a table, diagram, or flowchart of the proposed OCS should be included. This representation may cross-reference other sections of Module 2.3 (e.g., 2.3.3 CQI).

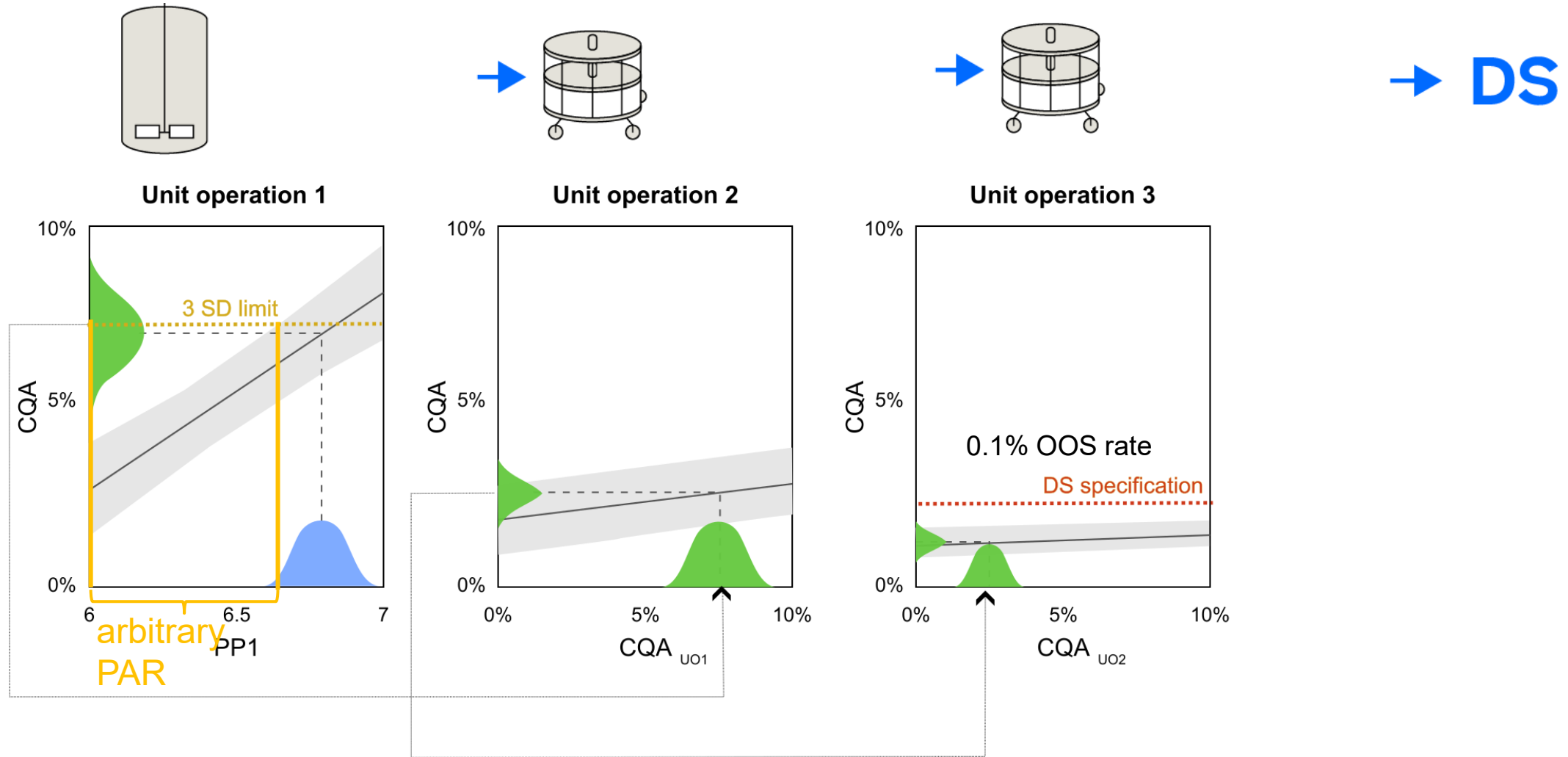
Local Control Strategies Do Not Ensure Final Product Quality



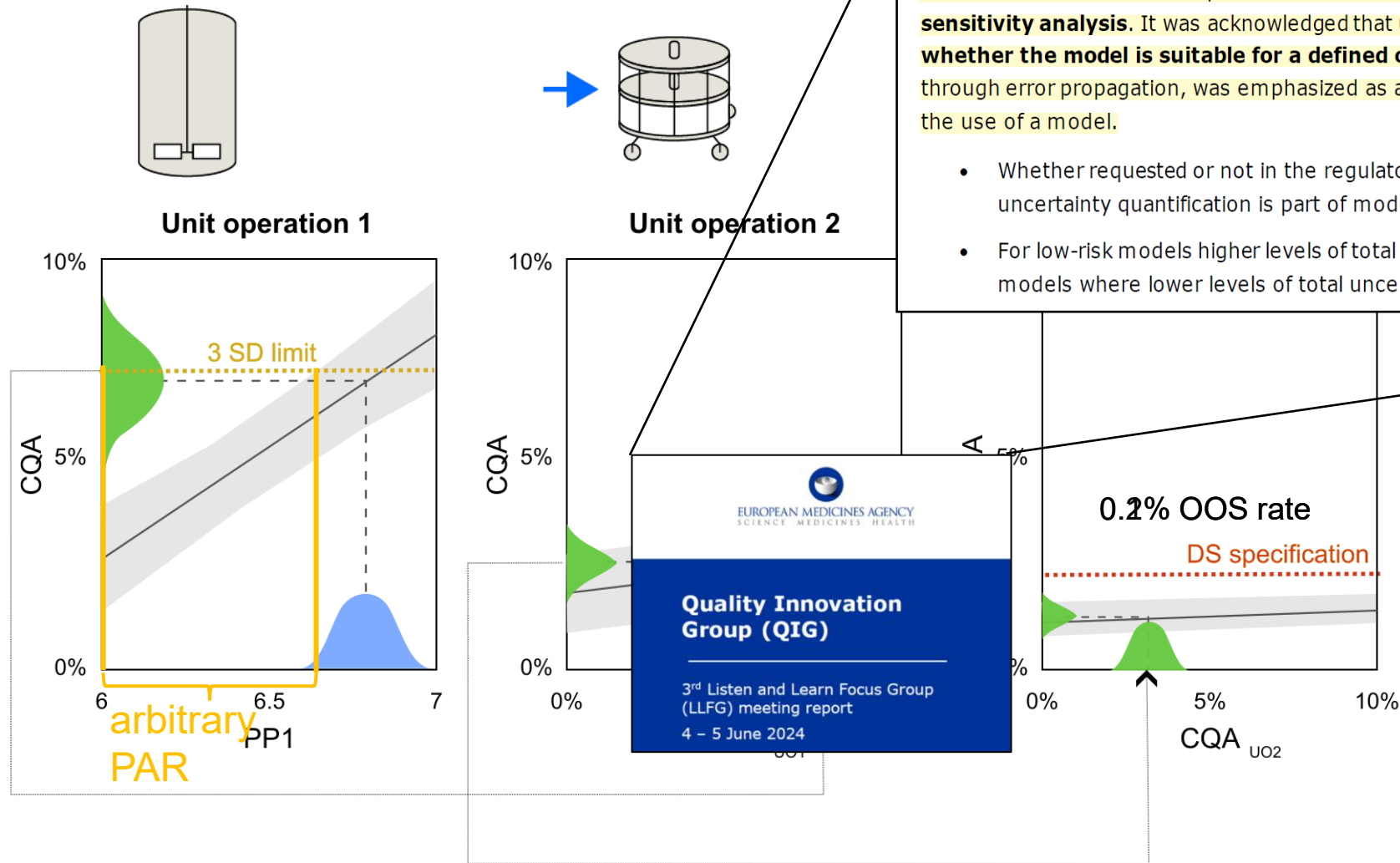
Local Control Strategies Do Not Ensure Final Product Quality



Local Control Strategies Do Not Ensure Final Product Quality



Local Control Strategies Do Not Ensure Final Product Quality



5. Summary of the discussions

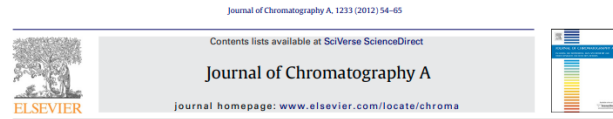
The discussions led to an important reflection around **model uncertainty quantification, or sensitivity analysis**. It was acknowledged that **uncertainty quantification is essential to validate whether the model is suitable for a defined context of use**. The concept of total uncertainty through error propagation, was emphasized as a powerful tool to determine the risk associated with the use of a model.

- Whether requested or not in the regulatory submission, depending on the use of the model, uncertainty quantification is part of model validation good practice.
- For low-risk models higher levels of total uncertainty could be accepted compared to high-risk models where lower levels of total uncertainty would be expected.

End-to-end process model identifies impact on final product quality → Holistic Control Strategy

Known Bottlenecks of Conventional Mechanistic and Hybrid Models

Osberghaus et al. example on CEX column with SMA isotherm



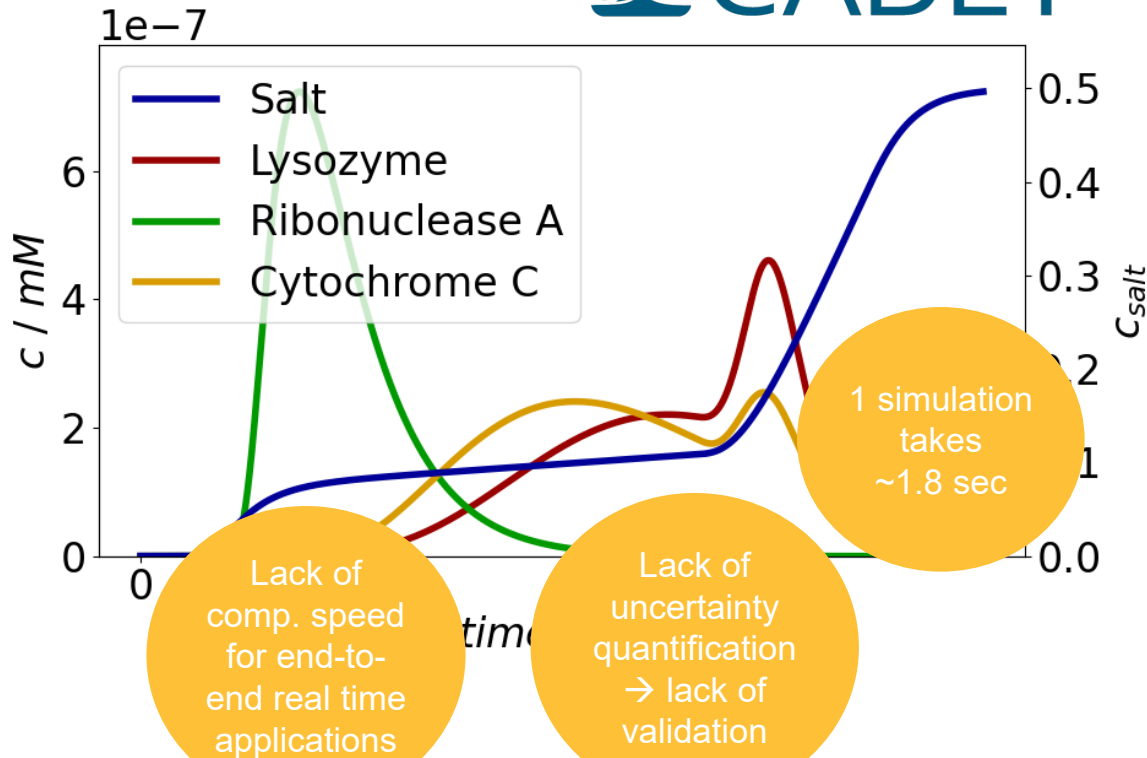
Determination of parameters for the steric mass action model—A comparison between two approaches

A. Osberghaus^a, S. Hepbildikler^b, S. Nath^b, M. Haindl^b, E. von Lieres^c, J. Hubbuch^{a,*}

^a Institute of Process Engineering in Life Sciences, Section IV: Biomolecular Separation Engineering, Karlsruhe Institute of Technology, Engler-Bunte-Ring 1, 76131 Karlsruhe, Germany
^b Pharmaceutical Biotech Production, Roche Diagnostics GmbH, Nonnenfeld 2, 82377 Penzberg, Germany
^c Institute of Bio- and Geosciences 1, Research Center Jülich, 52425 Jülich, Germany



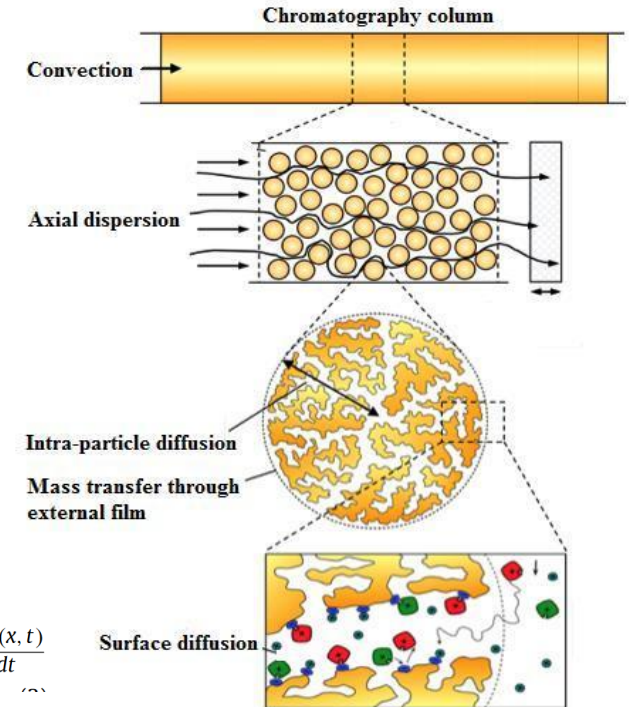
SOTA
PDE
Solver



$$\frac{\partial c_i(x, t)}{\partial t} = -\frac{u}{\varepsilon_{col}} \cdot \frac{\partial c_i(x, t)}{\partial x} + D_{ax} \cdot \frac{\partial^2 c_i(x, t)}{\partial x^2} - \frac{(1 - \varepsilon_{col})}{\varepsilon_{col}} \cdot \left(\frac{3}{r_p} \cdot k_{eff} (c_i(x, t) - c_{p,i}(x, t)) \right)$$

$$k_{kin,i} \cdot \frac{dq_i(x, t)}{dt} = k_{eq,i} \cdot \left(\Lambda - \sum_j (v_j + \sigma_j) \cdot q_j(x, t) \right)^{v_i} \cdot c_{p,i}(x, t) - q_i(x, t) \cdot c_s(x, t)^{v_i} \quad (3)$$

$$\frac{\partial c_{p,i}(x, t)}{\partial t} = \frac{3}{r_p} \cdot \frac{k_{eff,i}}{\varepsilon_p} \cdot (c_i(x, t) - c_{p,i}(x, t)) - \frac{1 - \varepsilon_p}{\varepsilon_p} \cdot \frac{dq_i(x, t)}{dt}$$



Can we overcome these limitation?

Boundary conditions:

$$\frac{\partial c_i}{\partial x}(0, t) = \frac{u}{D_{ax}} \cdot (c_i(0, t) - c_{in}(t))$$

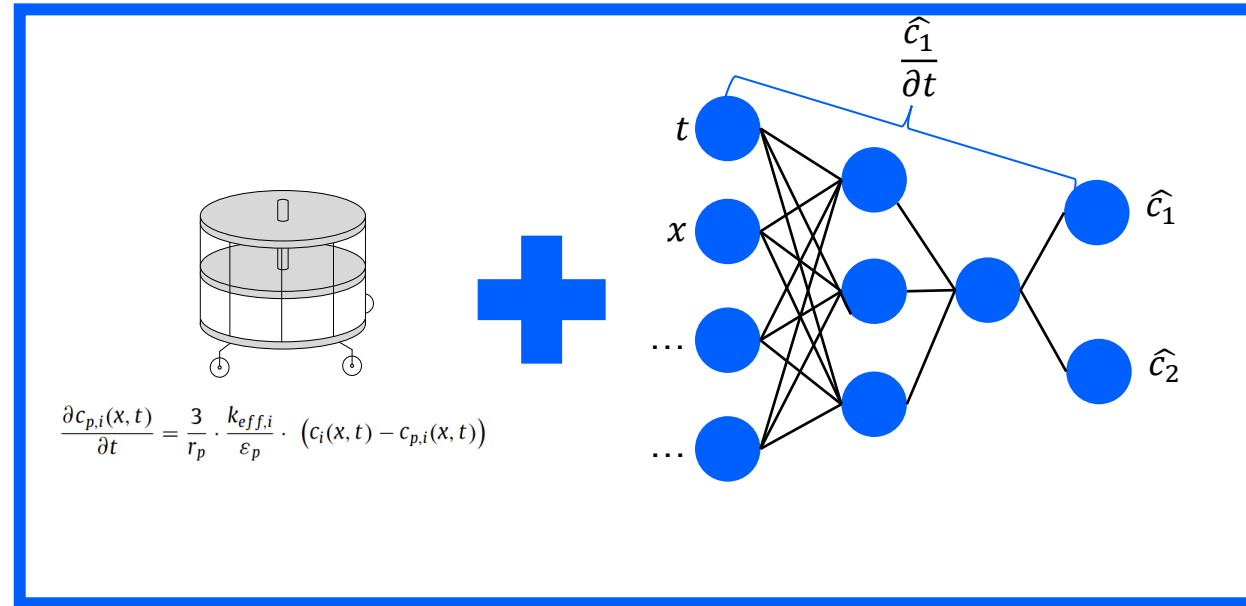
$$\frac{\partial c_i}{\partial x}(L_{col}, t) = 0$$

1 Million simulations ~ 1 Million seconds ~ **11.5 Days**

Physics-Informed Artificial Intelligence

Physics-Informed Artificial Intelligence: A Disruptive Breakthrough Technology

Teaching Neural Networks To Learn Physics



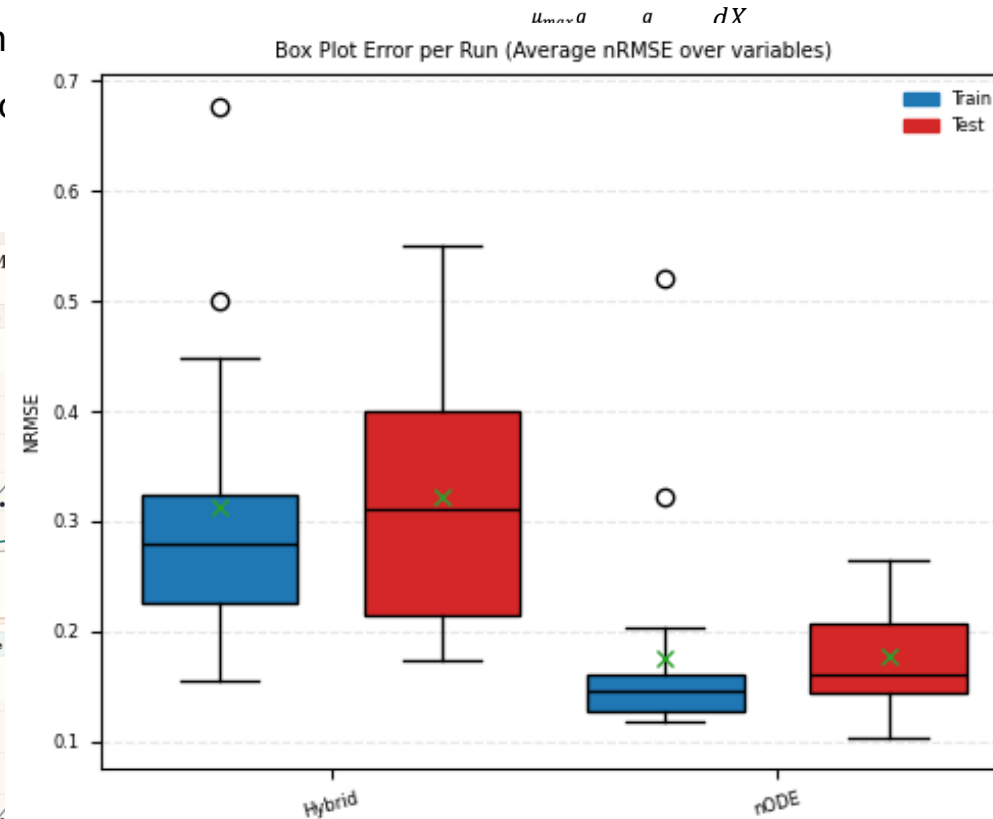
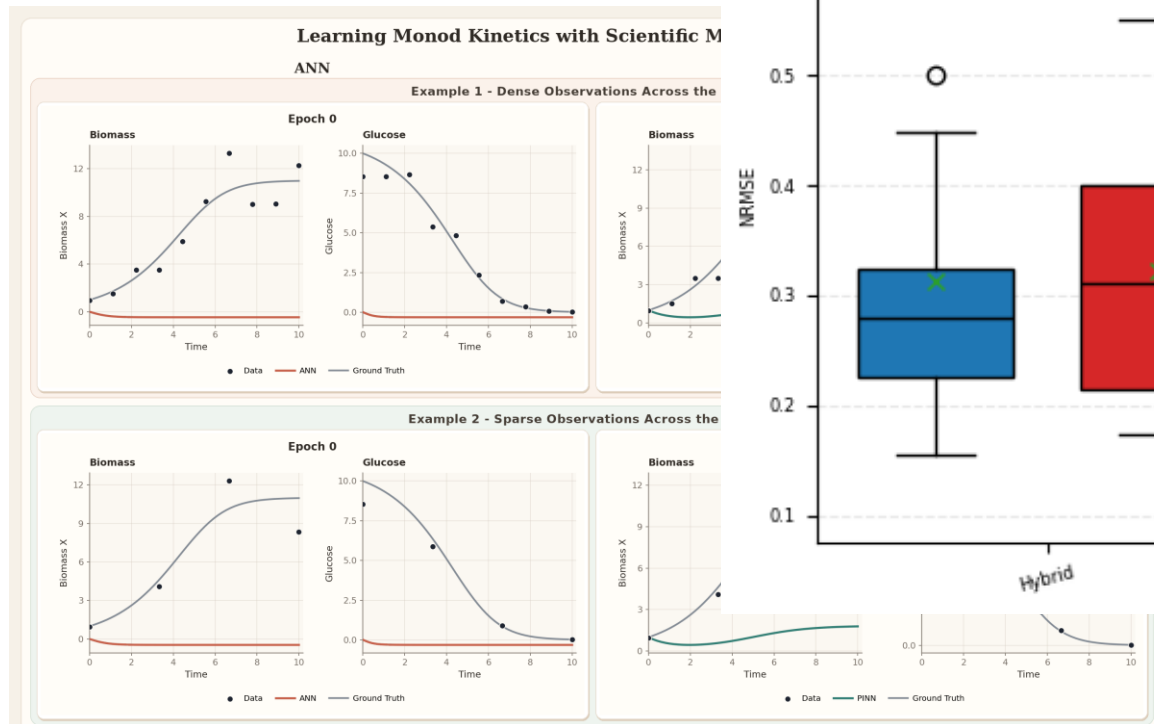
- Immensely speed up computation time comp. to ODE/PDE solvers
- Ensure extrapolation by physical knowledge

$$L = L_{data} + L_{physics} = (\hat{c}_1 - c_1)^2 + \left(\frac{\hat{c}_1}{\partial t} - RHS\right)^2$$

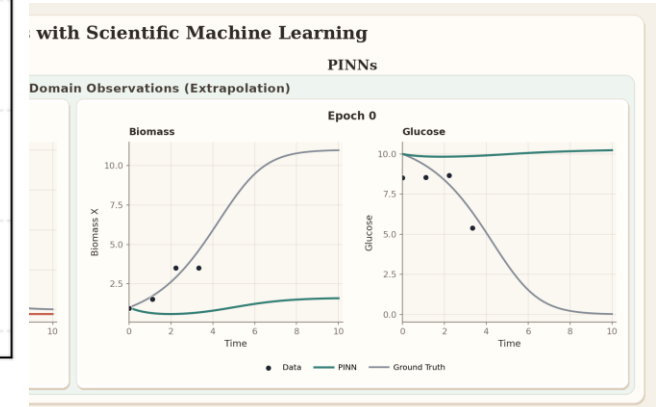
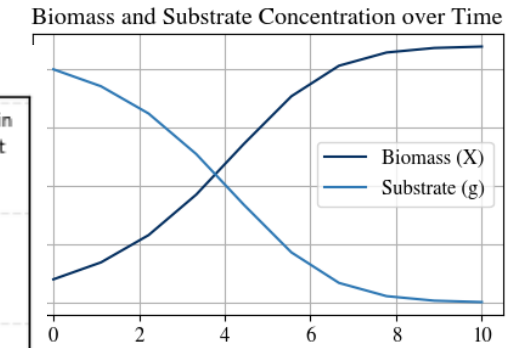
A Physics-Informed AI Toy Example in Bioprocess: Monod Kinetics

Naive ANN vs Physics-informed ANN (PINN)

- Assume cells grow according to Monod kinetics
- Once Glucose has been consumed, there is no further growth



Better Models/
Less Required Runs

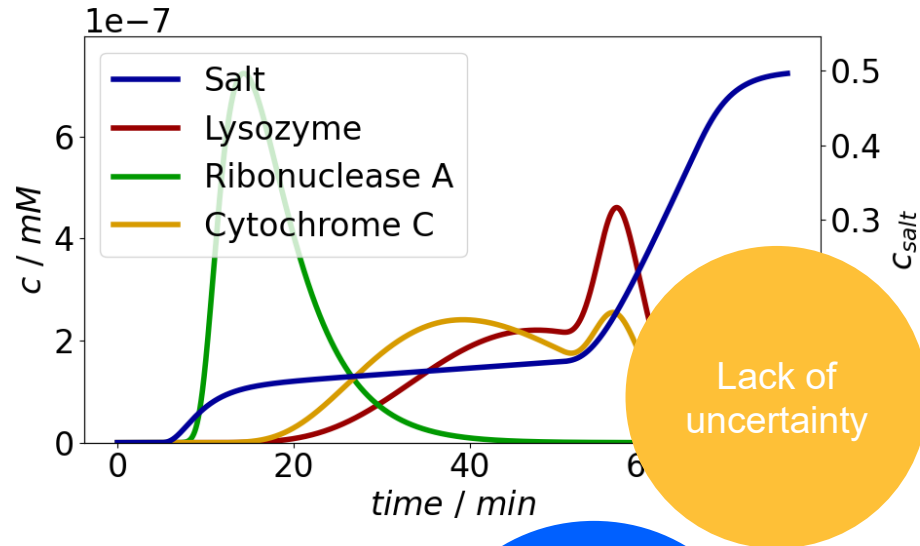


Physics-consistent
extrapolation



Proof of Concept: Speed Comparison of Conventional Solvers to Physics Informed AI

Gold Standard: CADET simulator

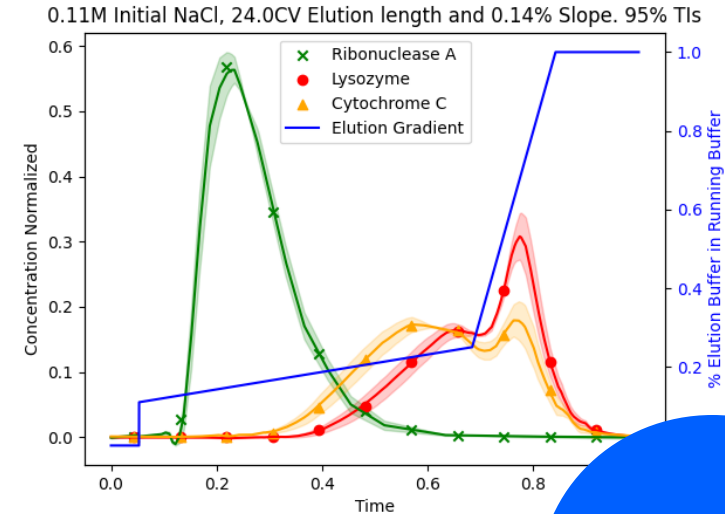


1 iteration:
~1.8 sec

**Risk-based Decision &
Regulatory-Compliant Model
Validation Allowed in Real Time**

intervals for
dynamic
models!

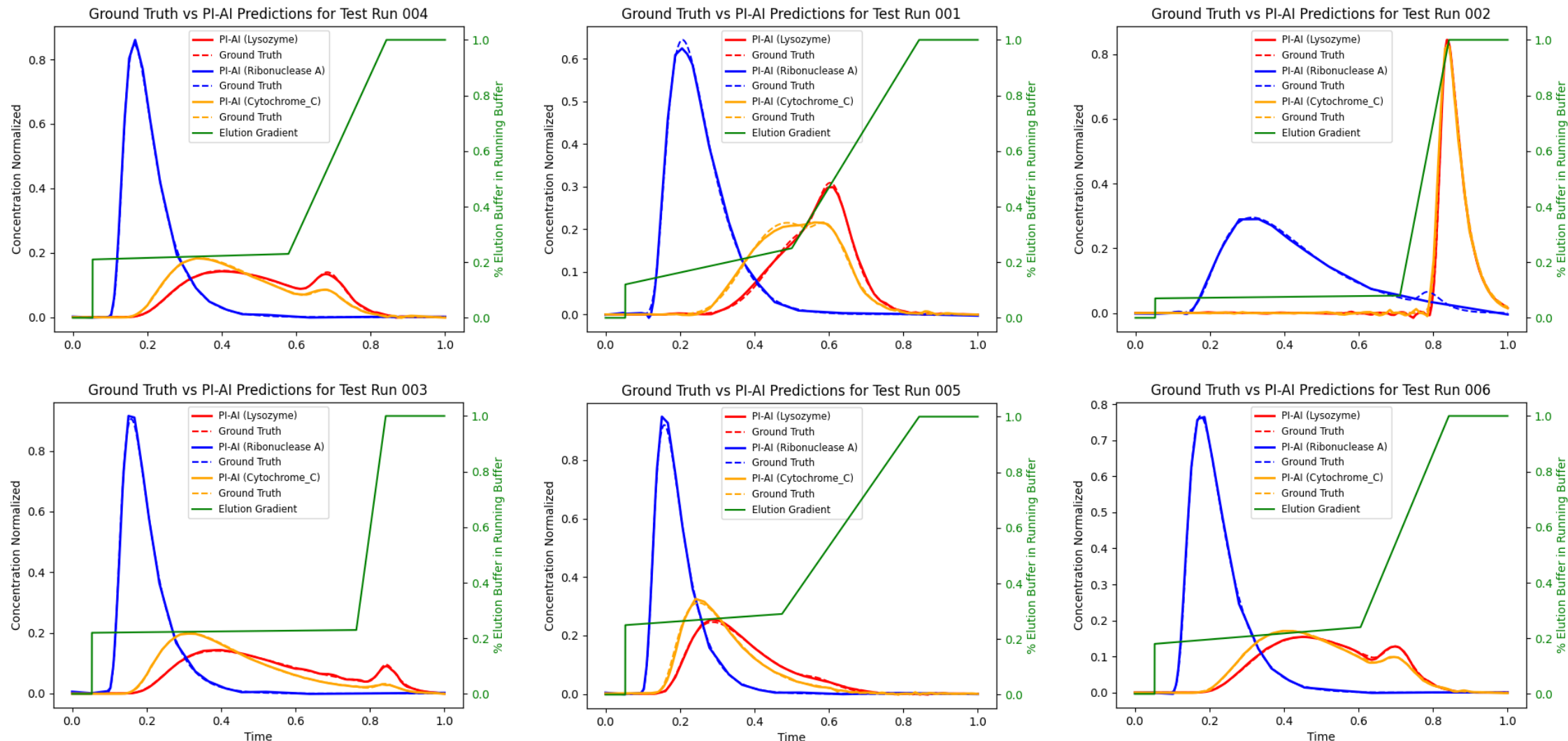
Novel Physics Informed AI



1000 times
faster on
CPU!!!

1000
iterations:
~1.8 sec

Test Run Predictions PI-AI Model vs Ground Truth CADET Model

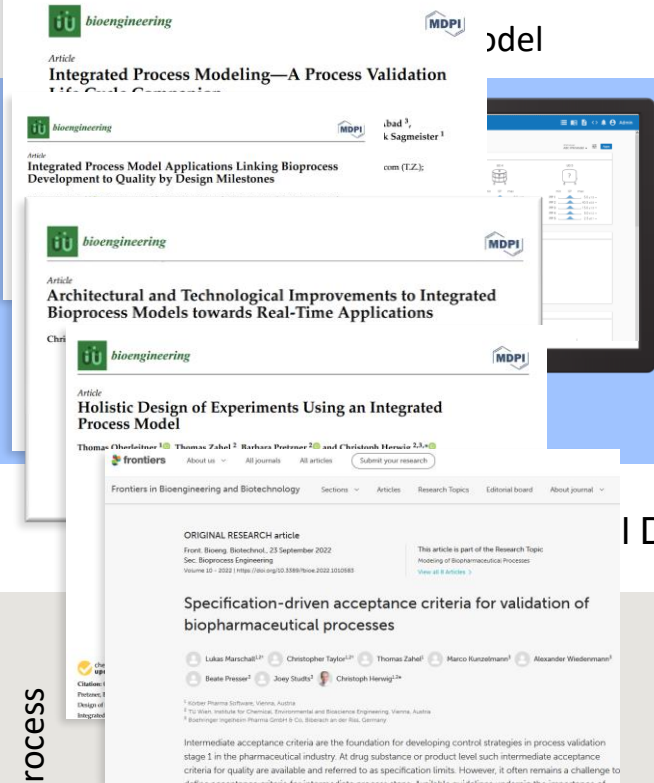


Data Connectivity Challenges – from Process Models to Digital Twins

Yield Optimization
Speed-up Process
Development

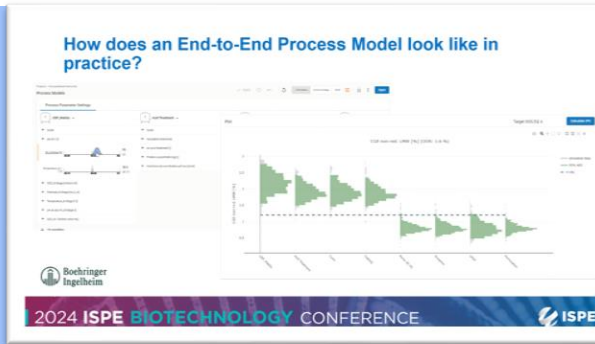
Real-time Prediction
Warnings/Monitoring

Real-time Optimization



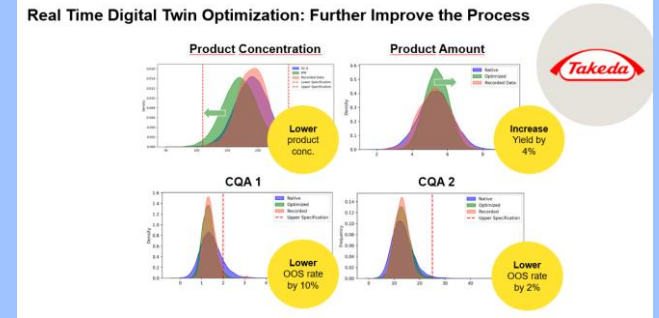
Model

Digital Shadow



<https://virtual.ispe.org/p/s/end-to-end-digital-twins-as-life-cycle-companions-11293>

Digital Twin



Data Flow

Automatic Data Flow

MES

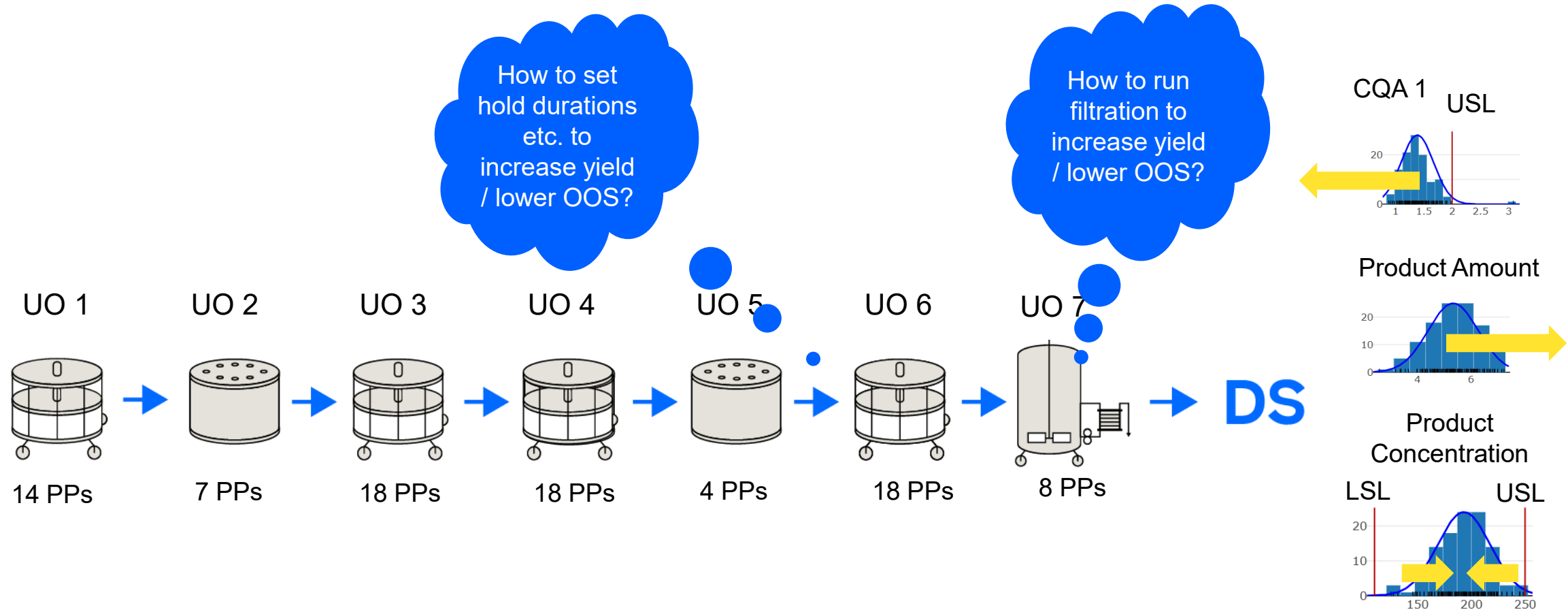
Business Value

Quality

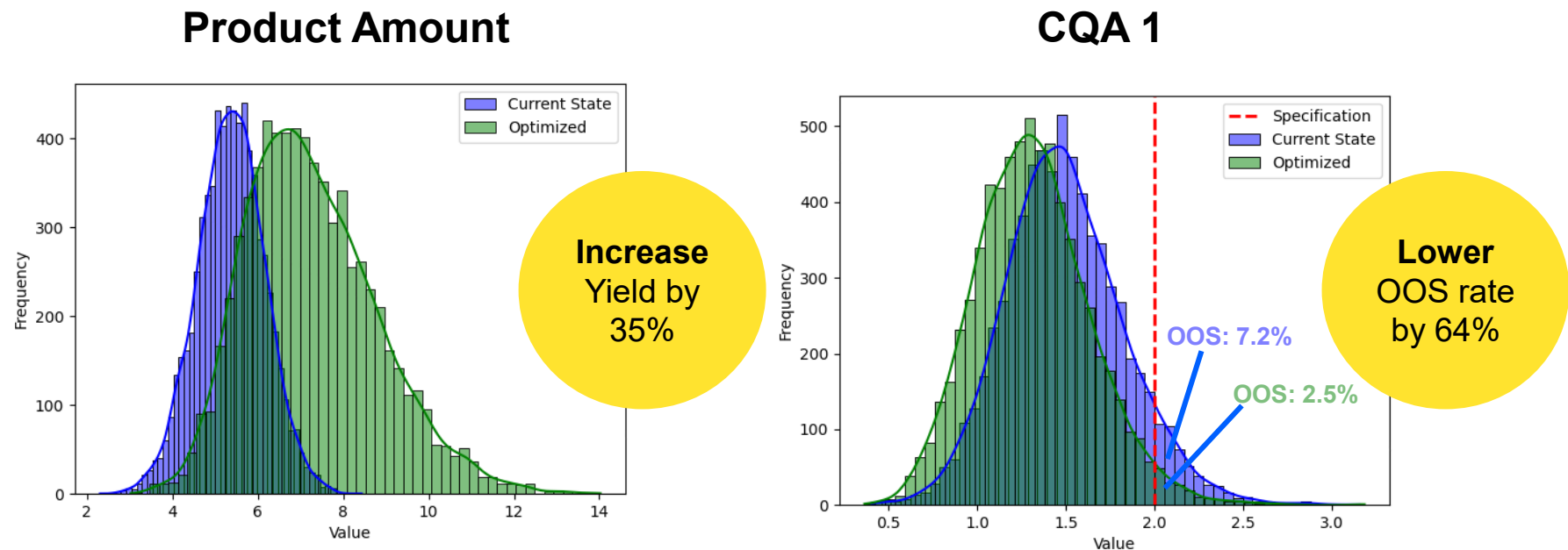
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PAS-X Savvy Digital Twin @ Takeda

Takeda Question of Interest: How to increase yield and meeting quality criteria at the same time?



Process Model Offline Optimization Potential

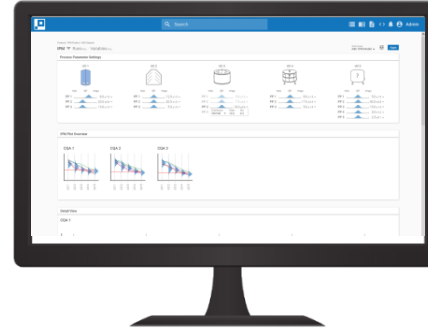


Tunable PPs*	Hold Duration	TMP	Flow rate end	Flow rate start	Hold Duration	Process Duration
Unit Operation	UO 3	UO 4	UO 4	UO 4	UO 7	UO 6
Current State	5.7	0.5	318.9	345.6	8.1	23.4
Optimized	9.0	0.7	215.6	411.7	3.1	20.6



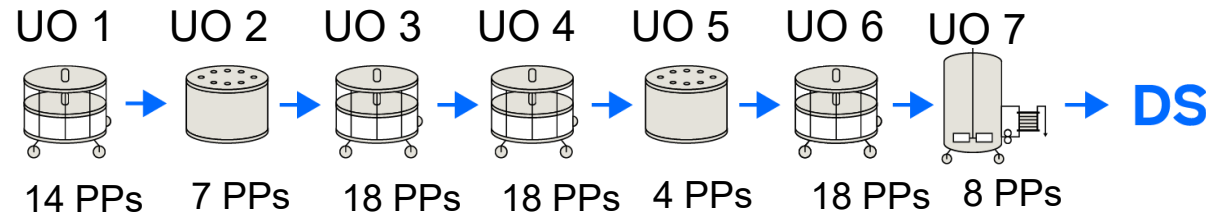
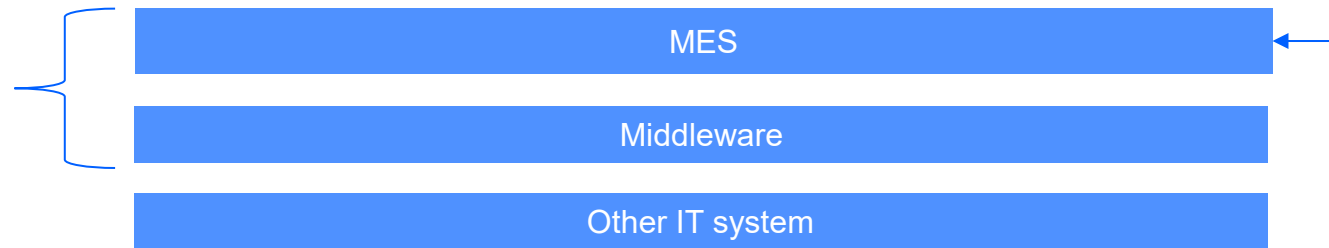
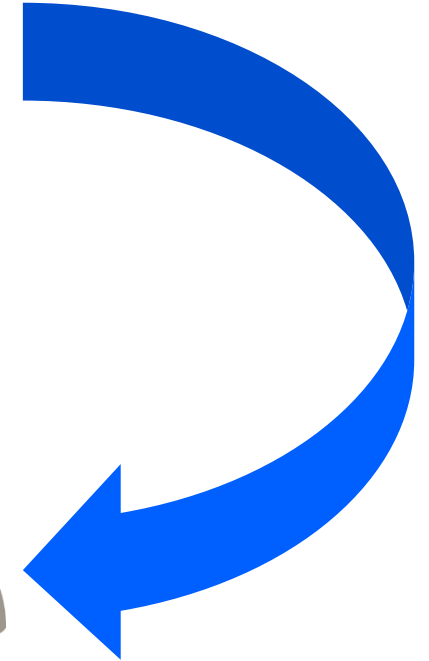
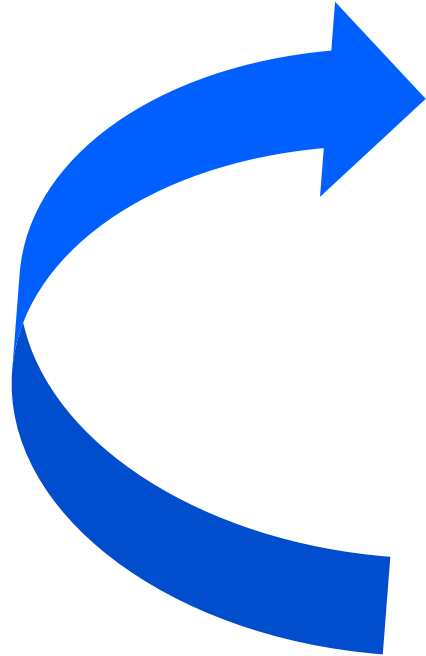
Takeda Use Case Description of the Digital Twin

Measurable process parameters are sent to the process model via established interfaces (mature and used also for other tools)

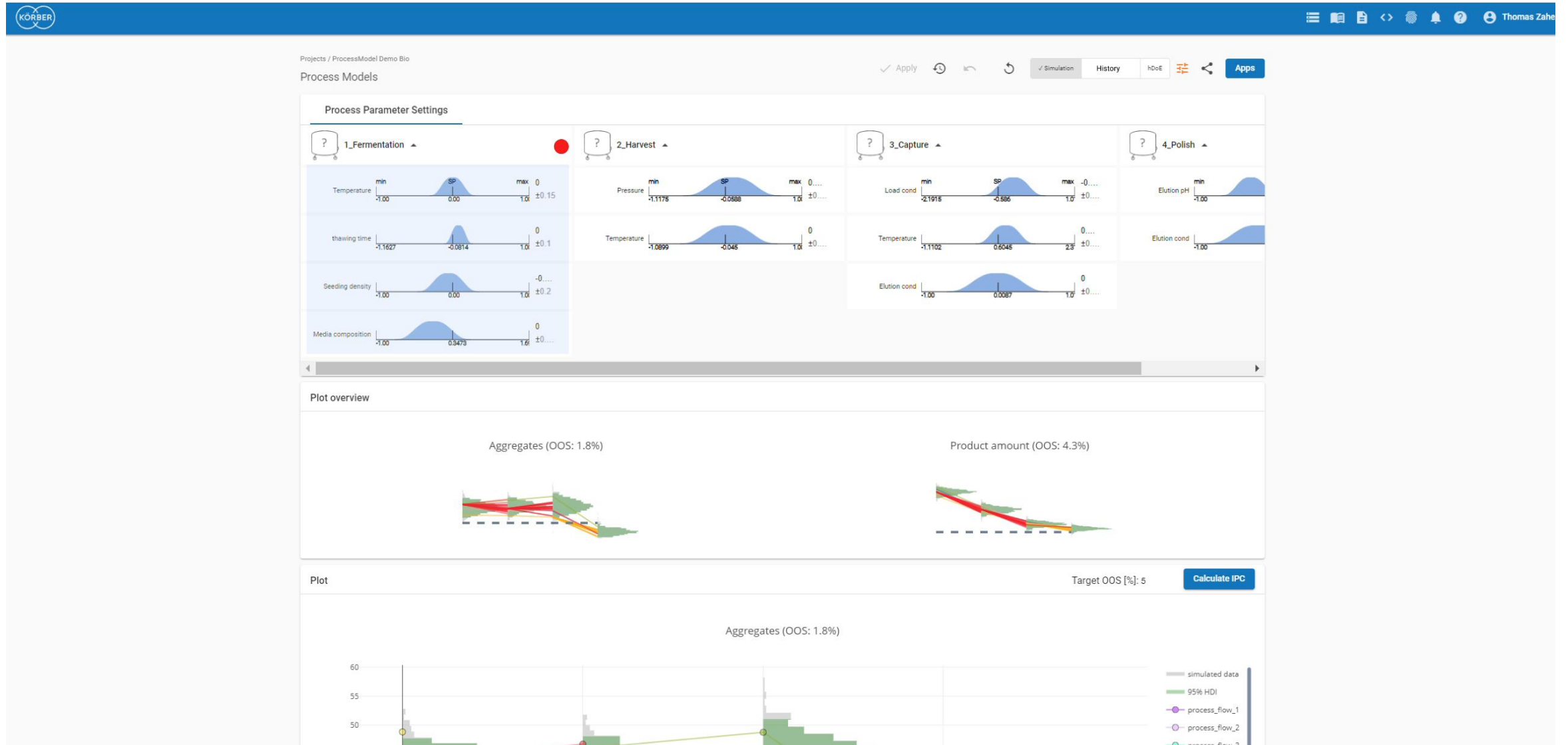


End-to-end process model predicting final CQA & product amount as a function of PP of all steps

Recommendations how to change the setpoint of **tunable process parameters** are sent to the MES system for human approval

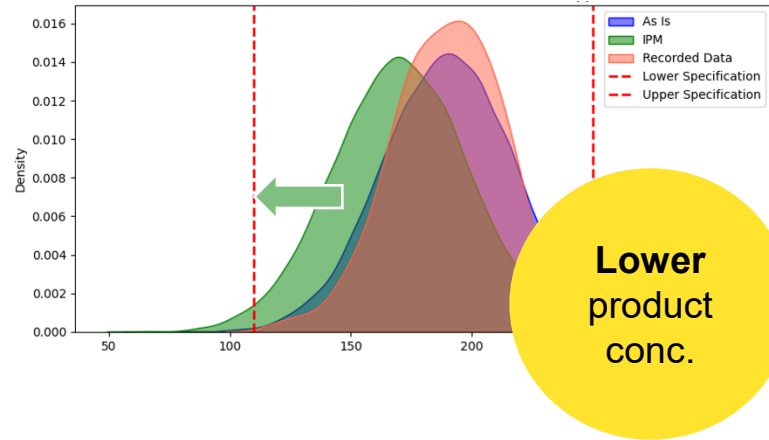


End-to-End Digital Twins as Recommender Systems in Manufacturing

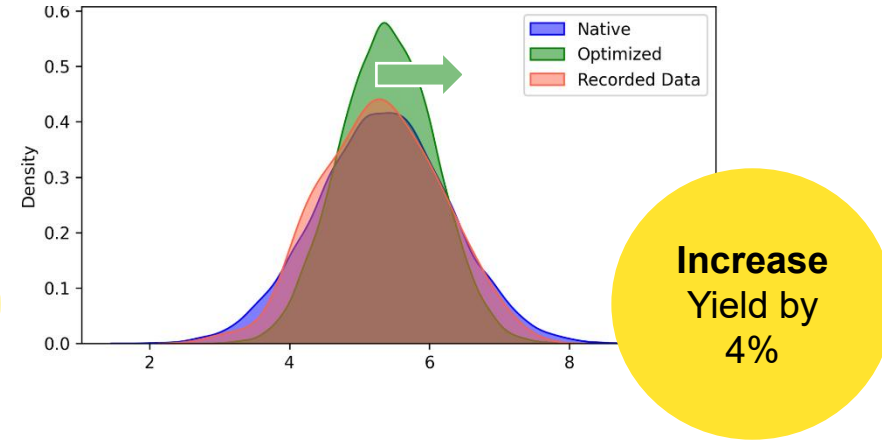


Real Time Digital Twin Optimization: Further Improve the Process

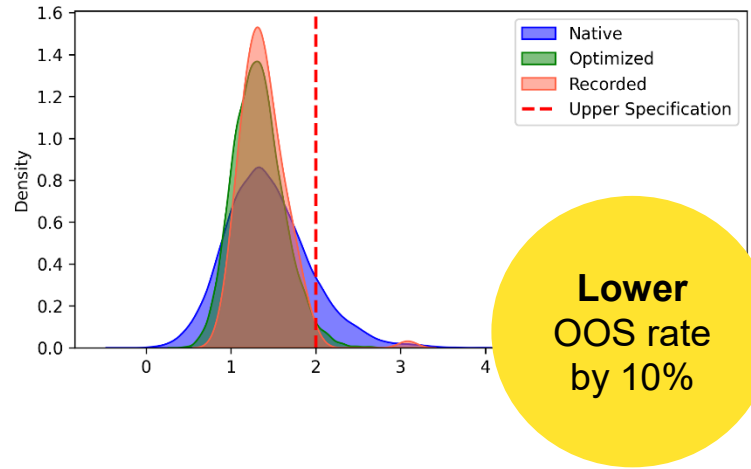
Product Concentration



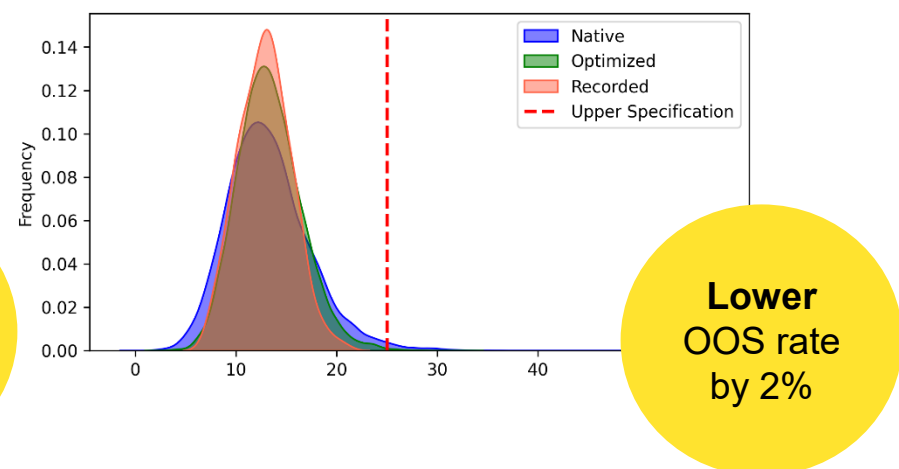
Product Amount



CQA 1



CQA 2



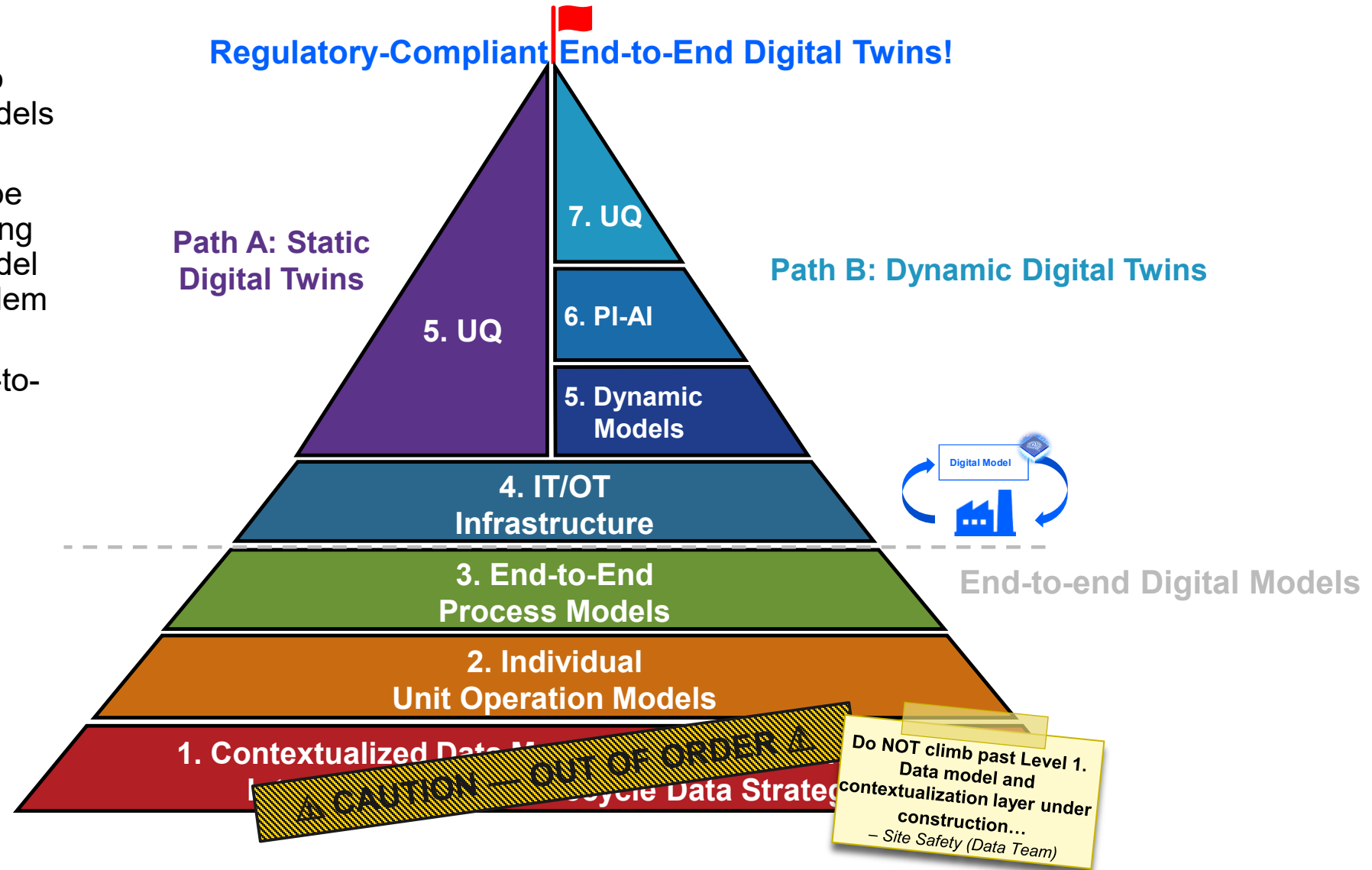
Conclusions – Physics Informed AI Enables UQ and End-to-End Digital Twins

Physics Informed AI overcomes two major limitations of mechanistic models due to massive speed up:

- Uncertainty Quantification: can be used for MCMC simulations during solving the inverse problem (model training) as well as forward problem (tolerance intervals)
- Real time application within end-to-end digital twins (Monte Carlo Simulation and Multi Objective Optimization)

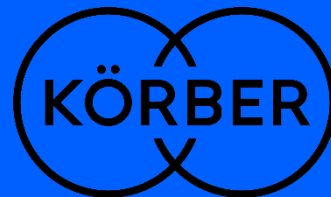
KEY TAKEAWAY

A Digital Twin is NOT ONLY a MODEL, it is a CONNECTED SYSTEM.



Thank You!

thomas.zahel@koerber.com



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