MODELING OF LYOPHILIZATION PROCESSES

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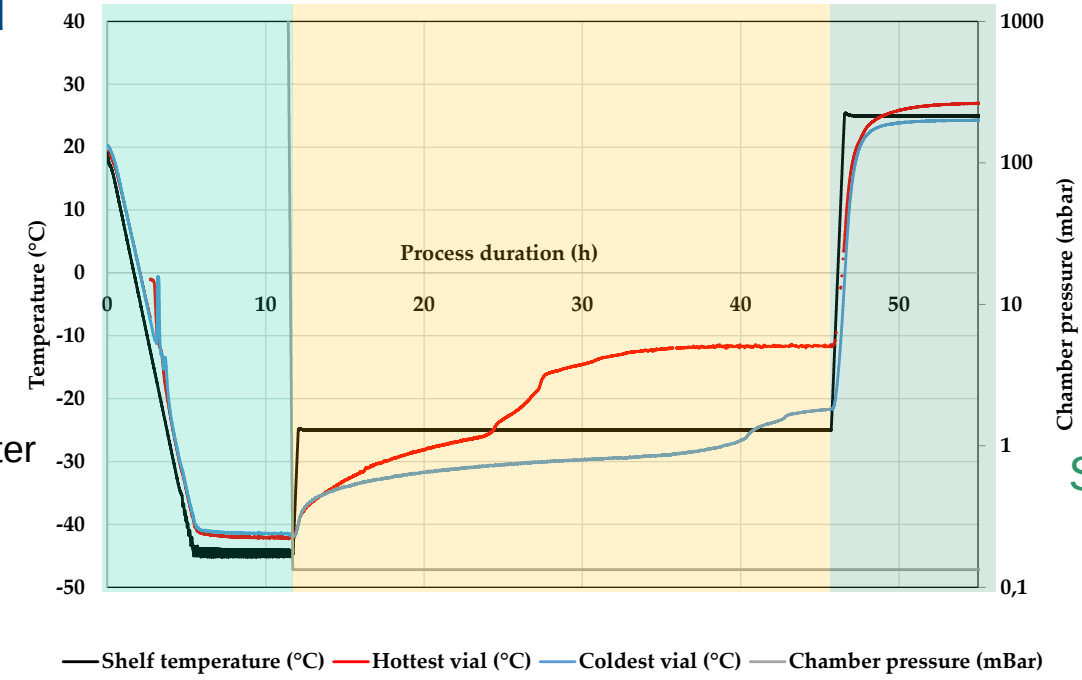
Agenda

- **Background**
- Modeling of lyophilization
- Model validation
- Summary

Background

- **Gold standard of drying processes**
- **60%** of biologics would not be available without lyophilization
- **Increasing number of biological products**
  - Rising demand
- Deep understanding of process interactions + control strategy necessary for improved product quality

Background



Freezing

- Conversion of water to ice
- Decrease of shelf temperature

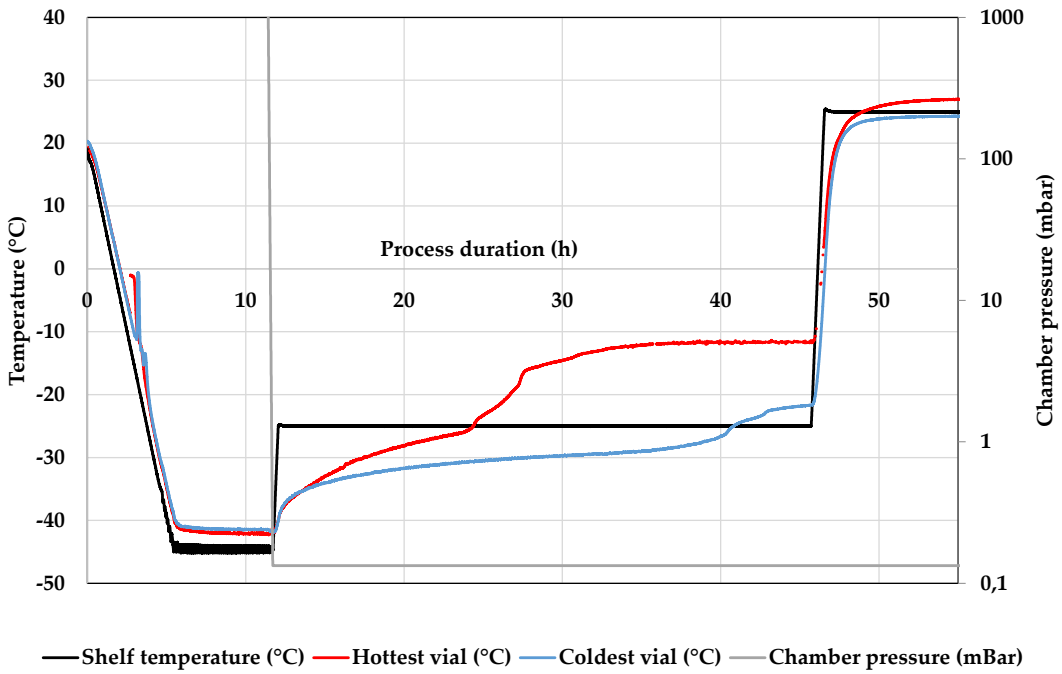
Primary drying

- Removal of frozen ice by sublimation
- Decrease of chamber pressure
- Increase of shelf temperature
- Usually longest process step

Secondary drying

- Removal of bound water by desorption
- Further increase of shelf temperature

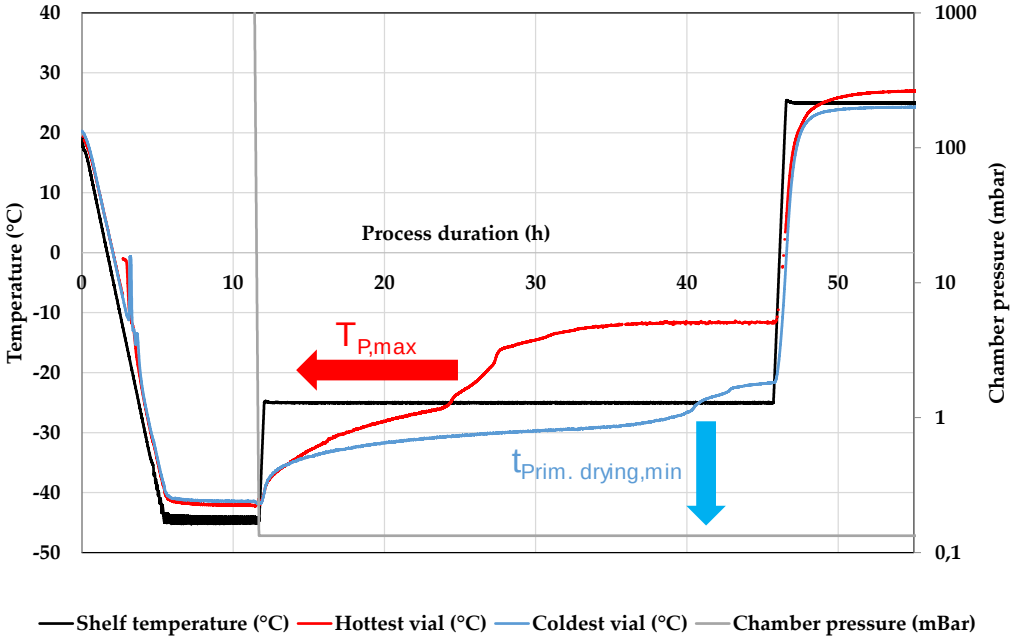
Background



Critical process parameters

Freezing	Primary drying	Secondary Drying
Shelf temperature	Shelf temperature	Shelf temperature
Cooling rate	Chamber pressure	Chamber pressure
Uncontrolled vs. controlled nucleation	Duration	Duration

Background



Product

Temperature constraint

$T_p < T_c$

Crystalline: $T_c = T_{eutect}$

Amorph: $T_c = T_{collapse}$

Determination

- Low temperature thermal analysis
- Freeze-dry microscope

Product temperature not directly controlled but established through process conditions

➢ Methods necessary to reliably predict the product temperature and primary drying endpoint that can be used in process development and process control

Background

- **What is Modeling?**
  - Creating a simplified image of reality
    - Examples:
      - ➢Art and literature
      - ➢Engineering
- **What is simulation?**

  „Simulation is the reproduction (...of the behaviour..) of a system with its dynamic processes in a model that can be experimented with in order to obtain knowledge that can be transferred to reality“ VDI 3633
- **Modeling and simulation shift a problem-solving process from reality to an abstracted copy**

Background

- **Why modeling and simulation?**
  - Knowledge can be gained about systems that cannot be experimented with in reality or only with considerably greater effort
- Simulations can be repeated at will
- Simulated models are fully observable
- The time and cost of projects can be significantly reduced

Advantages
Alternative to experiments
Improved system understanding
Capturing system complexity
Simplification of real world
Decision support
Strategy determination

Disadvantages
Unrealistic
Construction effort, limited resources
Credibility
Lack of transparency

Agenda

- Background
- **Modeling of lyophilization**
- Model validation
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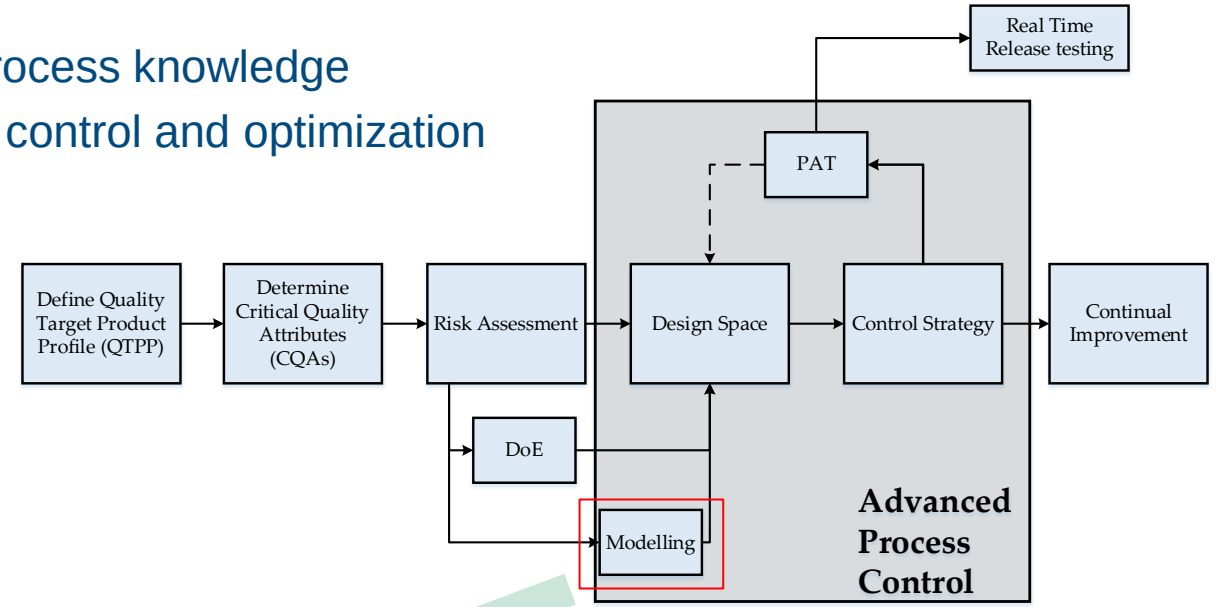
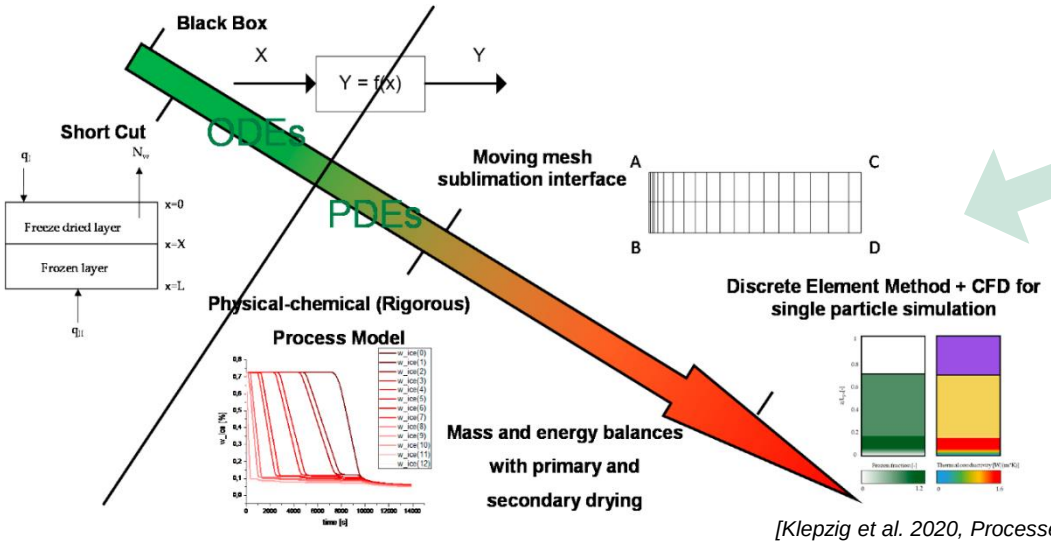
Modeling of lyophilization

- Process model deepen process knowledge
  - Process development, control and optimization
  - Technology transfer
  - Failure analysis



[Helgers et al. 2021, Processes 2021; 9(1),172]



*[Klepzig et al. 2020, Processes 2020; **8**(10),1325]*

Modeling of lyophilization

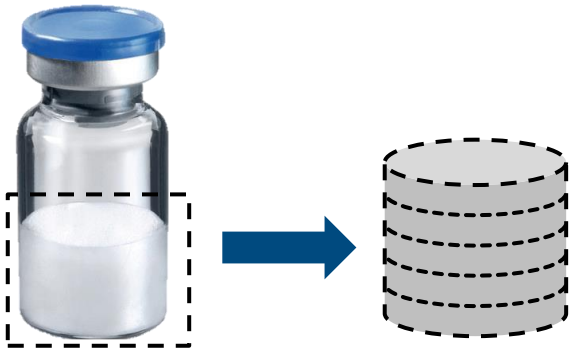
Energy balance: vial bottom

(1) $$m_{vial} \cdot c_{p,vial} \cdot \frac{\partial\ T_{vial}}{\partial t} = k_{vial} \cdot \frac{T_S - T_{vial}}{h_{vial}} \cdot A_{vial} - k_{product} \cdot \frac{T_{vial} - T_{product}}{h_{product}} \cdot A_{product}$$

Energy balance: product

(2) $$m_{product} \cdot c_{p,product} \cdot \frac{\partial\ T_{product}}{\partial t} + \frac{\partial m_{product}}{\partial t} \cdot c_{p,product} \cdot T_{product}$$

$$= k_{product} \cdot \frac{T_{vial} - T_{product}}{h_{product}} \cdot A_{product} + \dot{m}_{sublimation} \cdot h_{sublimation}$$

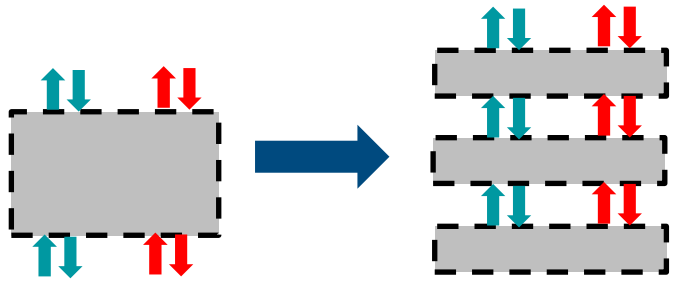


Mass balance: combined solid and vapor phase (prim. drying)

(5) $$\frac{\partial\ \rho_{solid}}{\partial t} \cdot V_{product} = \rho_{vapor} \cdot \frac{p_{sublimation} - p_C}{\eta_{vapor} \cdot K} \cdot A_{product}$$

Mass balance: bound water (sec. drying)

(6) $$\frac{\partial\ c_{bound\,water}}{\partial t} \cdot V_{product} = -k_{BW} \cdot \left(w_{BW} - w_{BW,Eq}\right)$$



Modeling of lyophilization

- Pseudo-steady state modeling

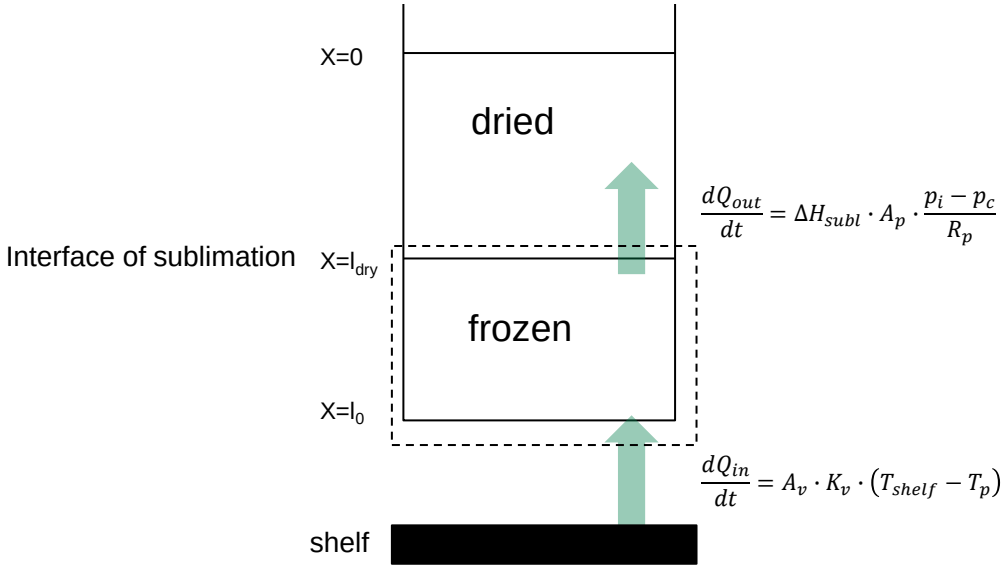
$$\frac{dQ}{dt} = A_v \cdot K_v \cdot (T_{shelf} - T_p)$$ Heat transfer

$$\left(\frac{1}{K_v} + \frac{L_{frozen}}{k_{frozen}}\right)^{-1} (T_{shelf} - T_i) = K_v \cdot (T_{shelf} - T_p)$$ Heat transfer to sublimation interface

$$\frac{dm}{dt} = A_p \cdot \frac{p_i - p_c}{R_p}$$ Mass transfer

Coupled heat and mass transfer

$$\frac{dQ}{dt} = \Delta H_{subl} \frac{dm}{dt}$$



Modeling task
- ➢ Determine primary drying product temperature
- ➢ Determine primary drying endpoint

Main application
- ❖ Process development, optimization and control

Modeling of lyophilization

- Pseudo-steady state modeling

$$\frac{dQ}{dt} = A_v \cdot \boldsymbol{K_v} \cdot (T_{shelf} - T_p)$$ Heat transfer

$$\left(\frac{1}{\boldsymbol{K_v}} + \frac{L_{frozen}}{k_{frozen}}\right)^{-1} (T_{shelf} - T_i) = \boldsymbol{K_v} \cdot (T_{shelf} - T_p)$$ Heat transfer to sublimation interface

$$\frac{dm}{dt} = A_p \cdot \frac{p_i - p_c}{\boldsymbol{R_p}}$$ Mass transfer

Coupled heat and mass transfer

$$\frac{dQ}{dt} = \Delta H_{subl} \frac{dm}{dt}$$

- Calculation of partial pressure of water with new sublimation-pressure equation
- K_v and R_p are model parameter

$$K_v = K_0 + \frac{K_1 \cdot p_c}{1 + K_2 \cdot p_c}$$

Dependence on:
- Vialtype + -position
- Freeze dryer
- Shelf temperature

$$R_p = R_0 + \frac{R_1 \cdot L_{dried}}{1 + R_2 \cdot L_{dried}}$$

Dependence on:
- Formulation
- Freezing protocoll
- Manufacturing environment
- Microcollapse

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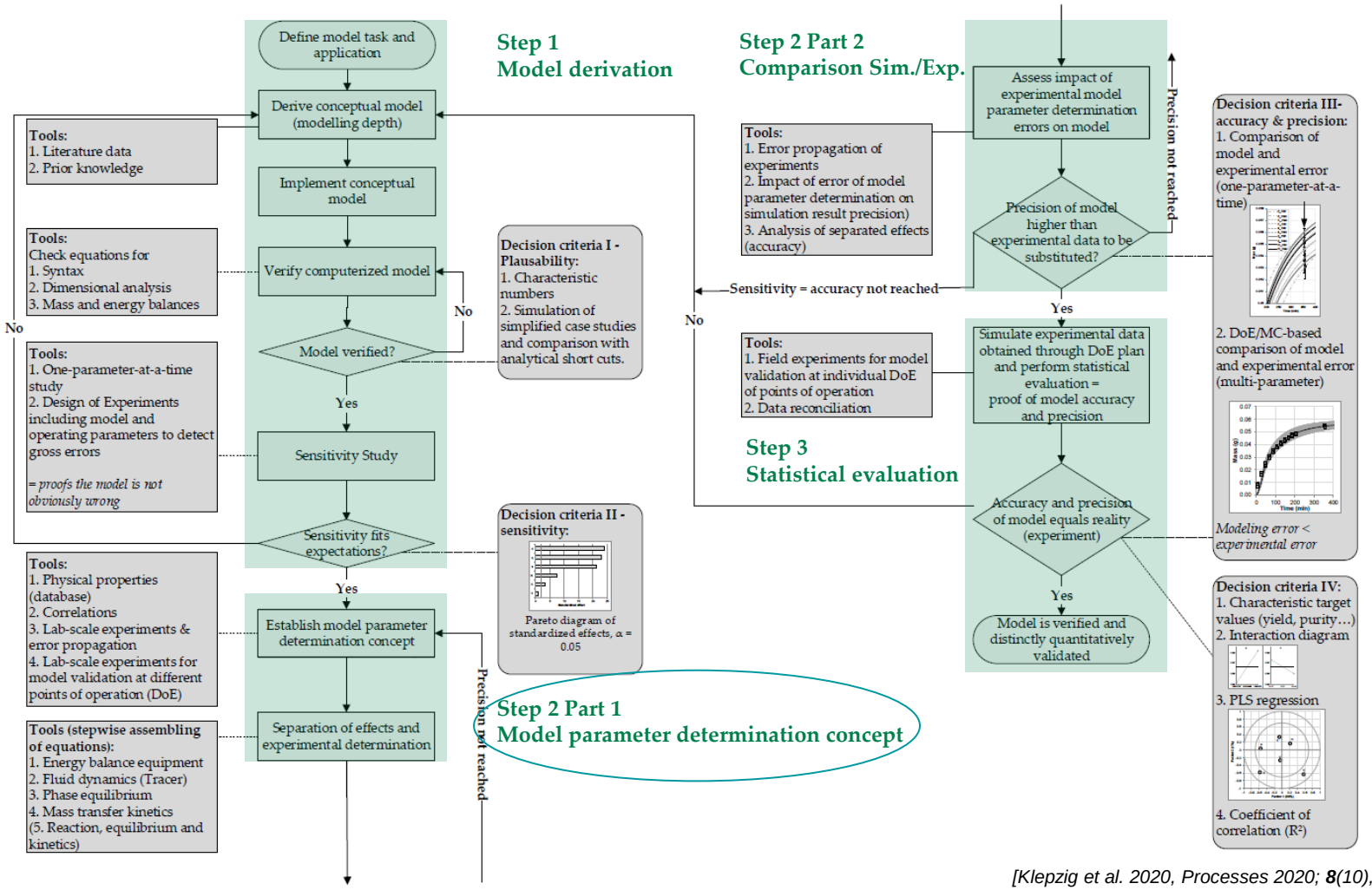
- Modeling of lyophilization
- **Model validation**
- Summary

Model validation



*[Klepzig et al. 2020, Processes 2020; **8**(10),1325]*

Model validation – Model parameter determination

Heat transfer $\frac{dQ}{dt} = A_v \cdot \boldsymbol{K_v} \cdot (T_{shelf} - T_p)$

Heat transfer to sublimation interface $\left(\frac{1}{\boldsymbol{K_v}} + \frac{L_{frozen}}{k_{frozen}}\right)^{-1} (T_{shelf} - T_i) = \boldsymbol{K_v} \cdot (T_{shelf} - T_p)$

Mass transfer $\frac{dm}{dt} = A_p \cdot \frac{p_i - p_c}{\boldsymbol{R_p}}$

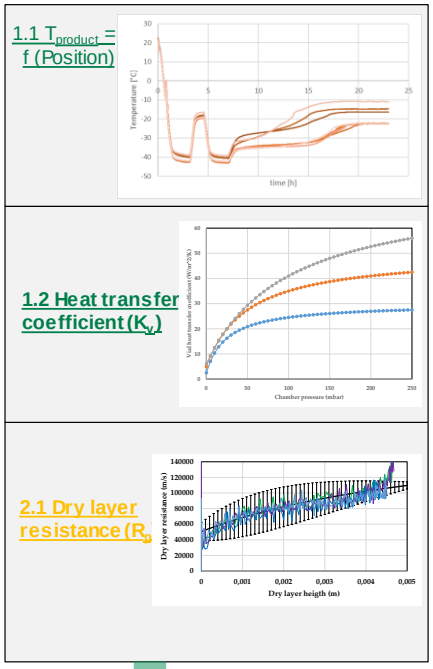
Coupled heat and mass transfer $\boldsymbol{\frac{dQ}{dt} = \Delta H_{subl} \frac{dm}{dt}}$

Product Temperature constraint

$T_{product} < \mathbf{T_{Collapse}}$

Equipment constraint

$J_{subl} < \mathbf{J_{Max}}$



Equipment characterization

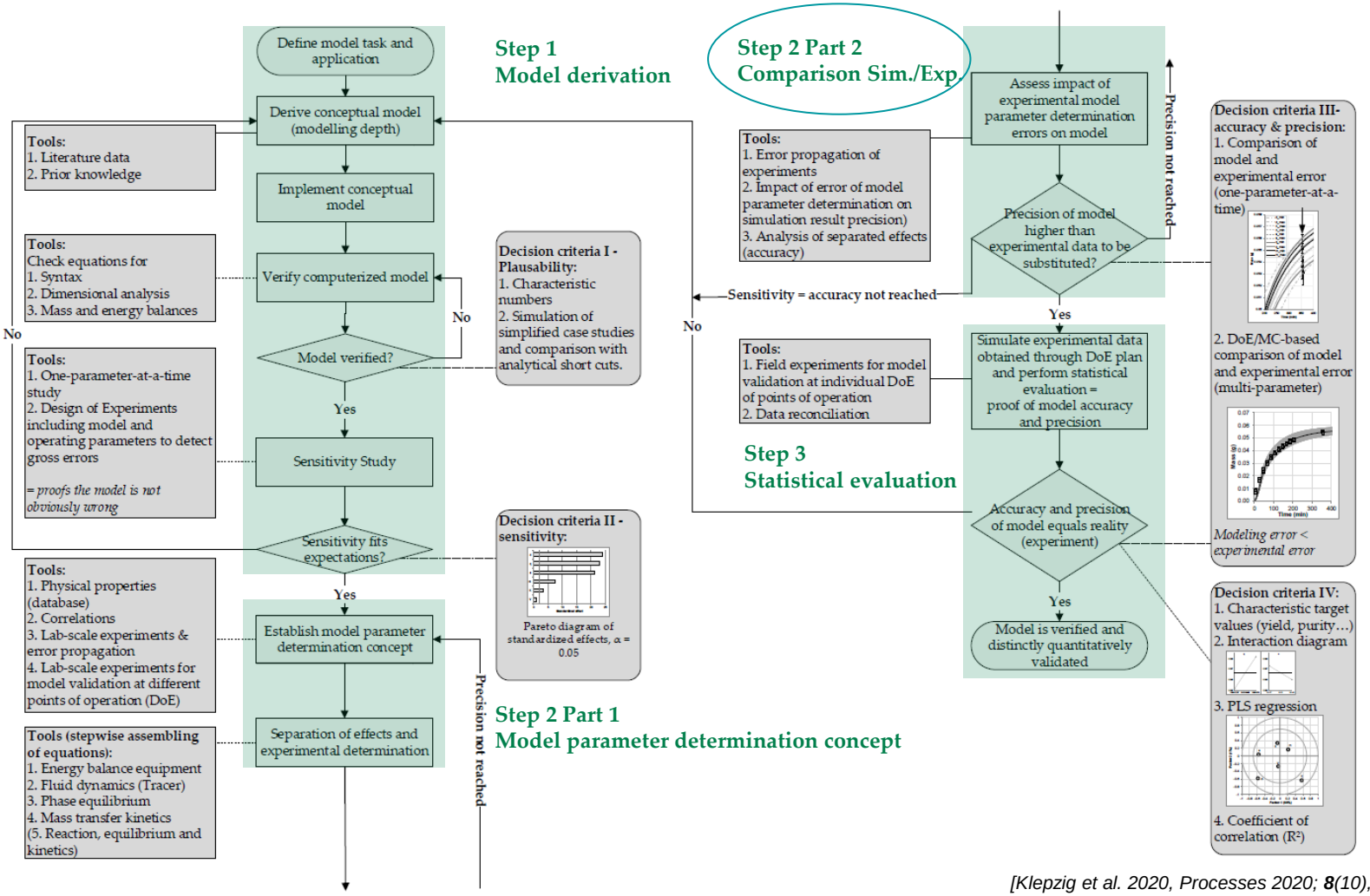
- 1.1 Shelf temperature distribution (T_{Shelf})
  - Determination of critical vials
- 1.2 Maximum allowed sublimation flux J_{Max}
  - Ice slab testing
- 1.3 Vial heat transfer coefficient K_v
  - $\boldsymbol{K_v} = \frac{\Delta m \cdot \Delta h_{subl}/\Delta t}{A_{vial} \cdot (T_{S,PD} - T_{product})}$
  - **Gravimetric determination**
  - $T_{product}$ **determination with WTM**

Formulation characterization

- 2.1 Collapse temperature $\mathbf{T_{Collapse}}$
  - DSC, LT-FDM, Literature
- **2.2 Dry layer resistance**
  - Experiment with product solution
  - $\boldsymbol{R_p} = \frac{A \cdot (p_{ice} - p_C)}{\dot{m}}$
  - Determination with **MTM** measurement and fitting to pressure rise data

[Juckers et al. 2021, Processes 2021; 9(9),1600]

Model validation



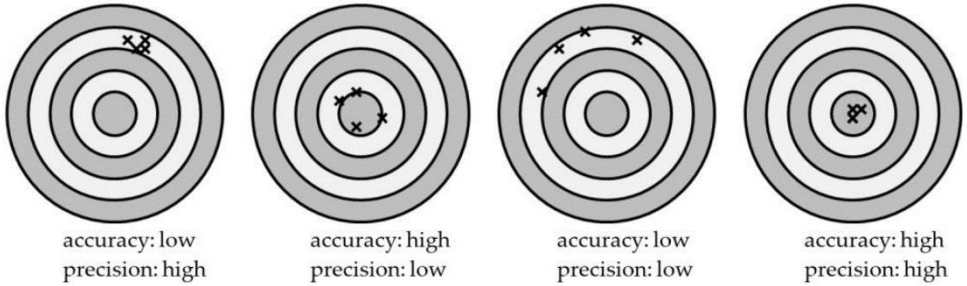
*[Klepzig et al. 2020, Processes 2020; **8**(10),1325]*

Model validation – Comparison Sim./Exp.

- **DoE/MC-based comparison** of model and experimental error (Multi-parameter study)

- **Case study**
  - Saccharose (amorph excipient)

- **Accuracy**
  - Correct prediction of experimental data within parameter set
- **Precision**
  - Effect of uncertainties of model parameter on simulated results



[Sixt et al. 2021, Processes 2018; 6(6),66]

Model validation – Comparison Sim./Exp.

- Design of Experiments
  - Fractional factorial design
  - Repition of centerpoint for statistic evaluation

	Primary Drying			
	Shelf Temperature (°C)	Chamber Pressure (mbar)	Fill Volume (mL)	Temperature Ramp (°C/min)
++++	0	0.15	2	1
+−+−	0	0.05	2	0.2
−+−+	−25	0.15	1	1
++−−	0	0.15	1	0.2
−−−−	−25	0.05	1	0.2
+−−+	0	0.05	1	1
−−++	−25	0.05	2	1
−++−	−25	0.15	2	0.2
CP	−12.5	0.1	1.5	0.6
CP	−12.5	0.1	1.5	0.6
CP	−12.5	0.1	1.5	0.6

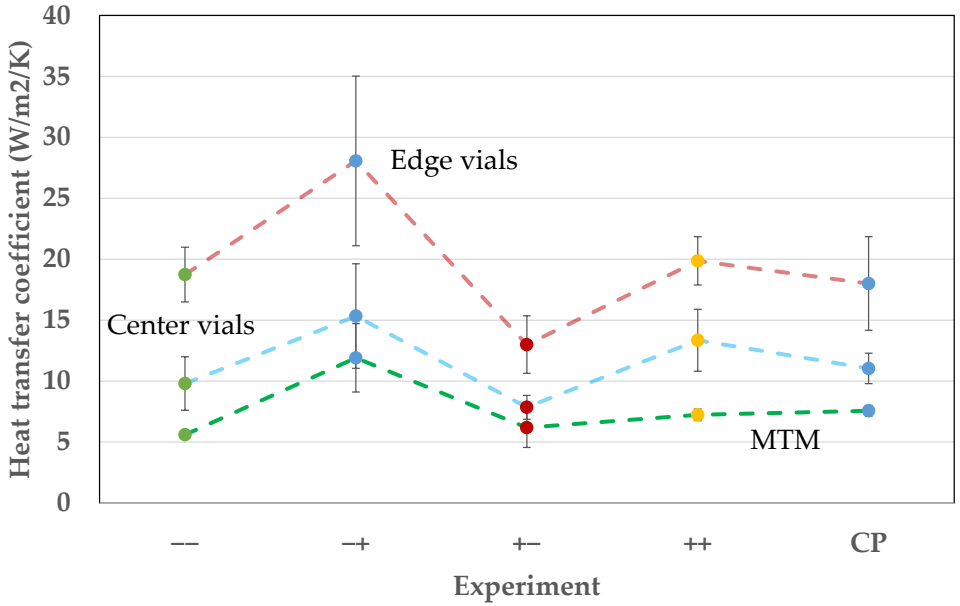
[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

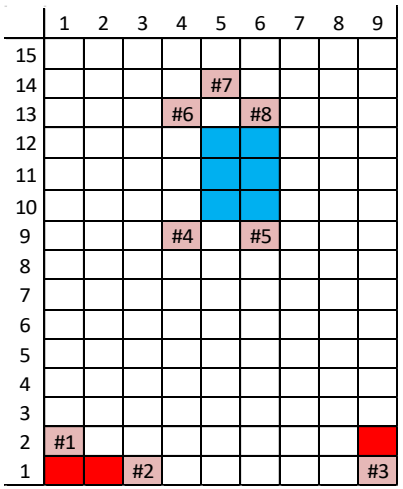
[Juckers et al. 2021, Processes 2021; 9(9),1600]

Model validation – Comparison Sim./Exp.

- **Vial heat transfer coefficient K_v**
  - Ice sublimation test, experiments dublets, 95% confidence

$$K_v = \frac{(\Delta m \cdot \Delta H_s)/\Delta t}{A_v \cdot (T_S - T_p)}$$





Pressure increase leads to higher heat transfer coefficients

Higher shelf temperature leads to smaller edge effect

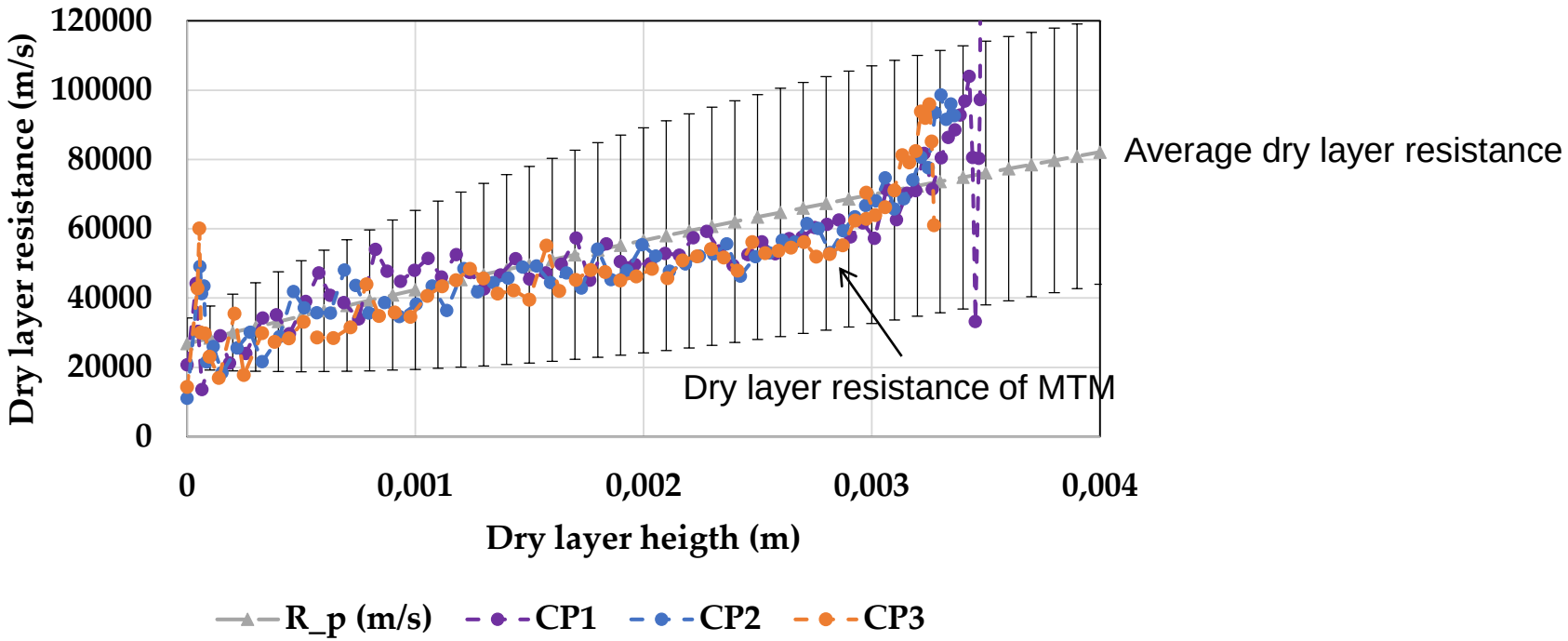
MTM yields lower coefficients than experiment

[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Model validation – Comparison Sim./Exp.

- **Dry layer resistance R_p**
  - Manometric temperature measurement, 95% confidence

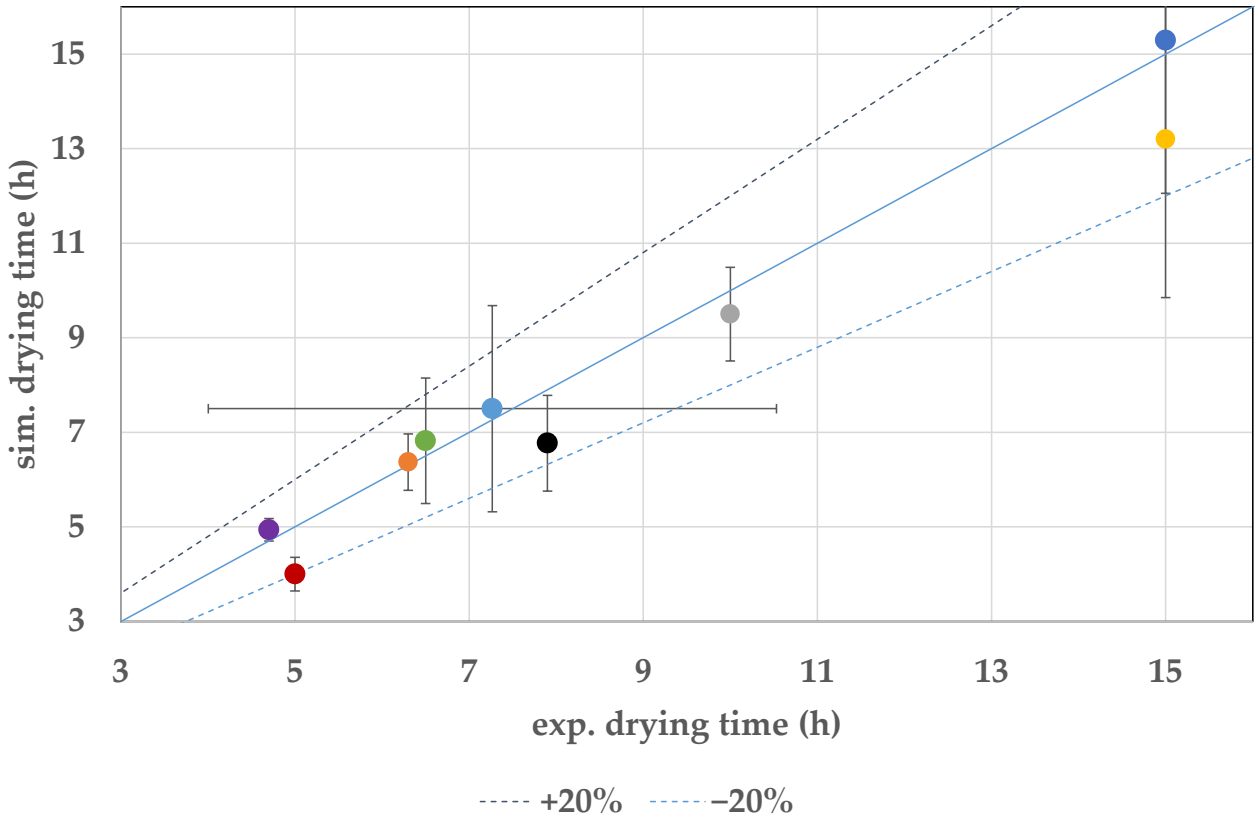
$$R_p = R_0 + \frac{R_1 \cdot L_{dried}}{1 + R_2 \cdot L_{dried}}$$

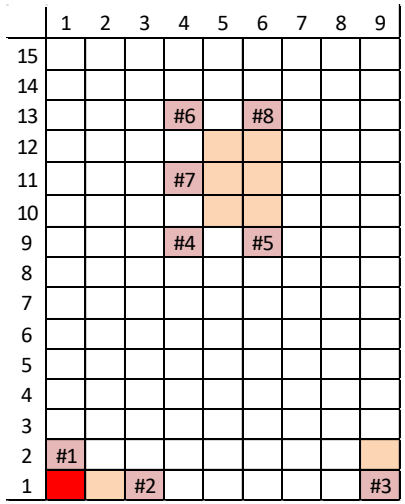


[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Model validation – Comparison Sim./Exp.

- Vial 1.1 vs. WTM#1



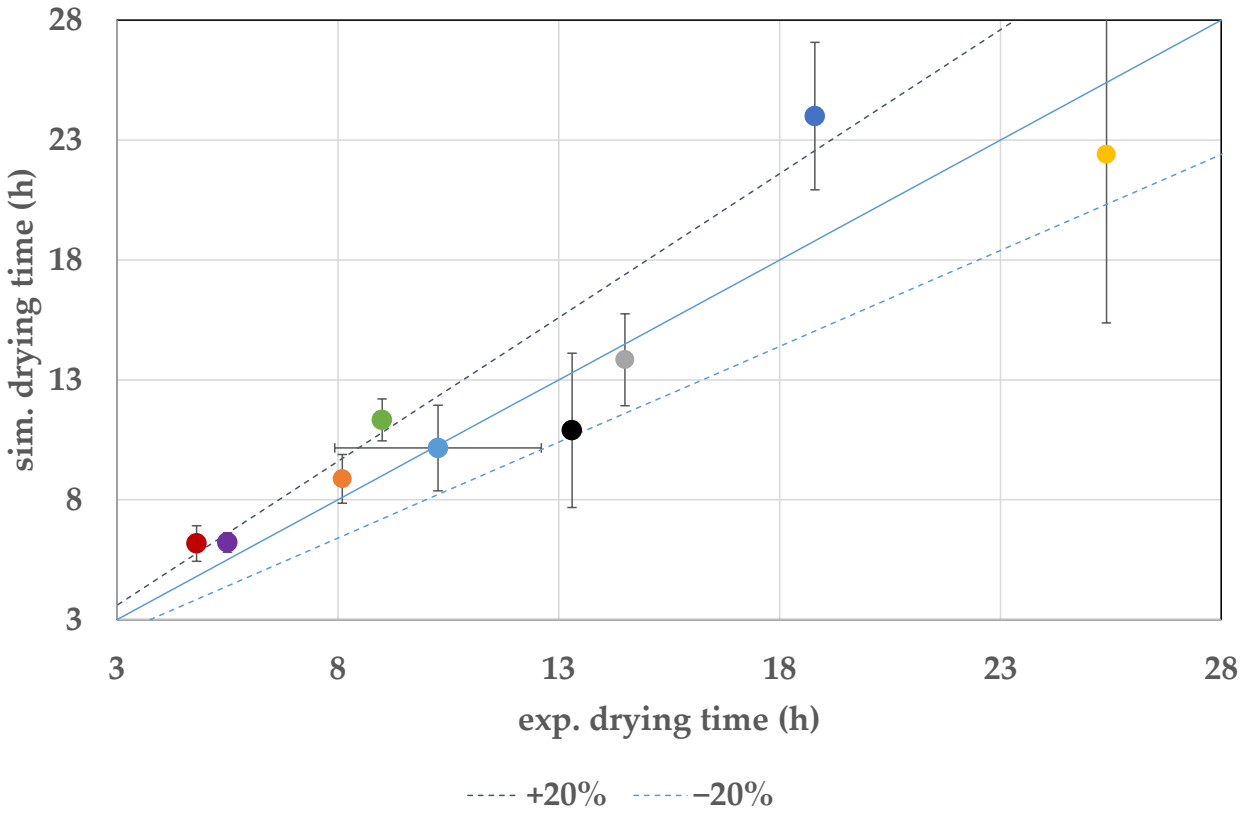


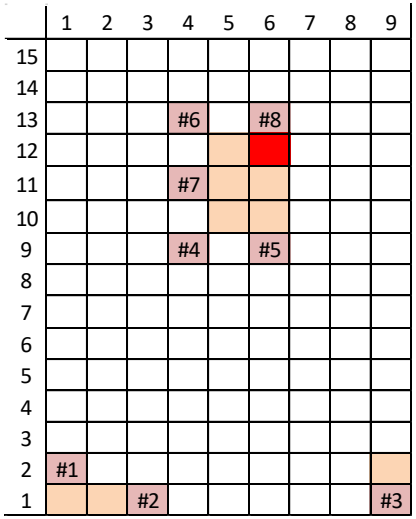
++−−
+−−+
++++
−+−+
CP
−−−
+−+−
−++−
−−++

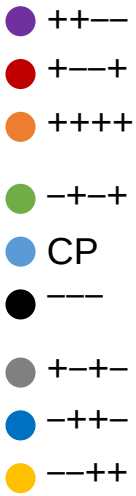
[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Model validation – Comparison Sim./Exp.

- Vial 12.6 vs. WTM#8



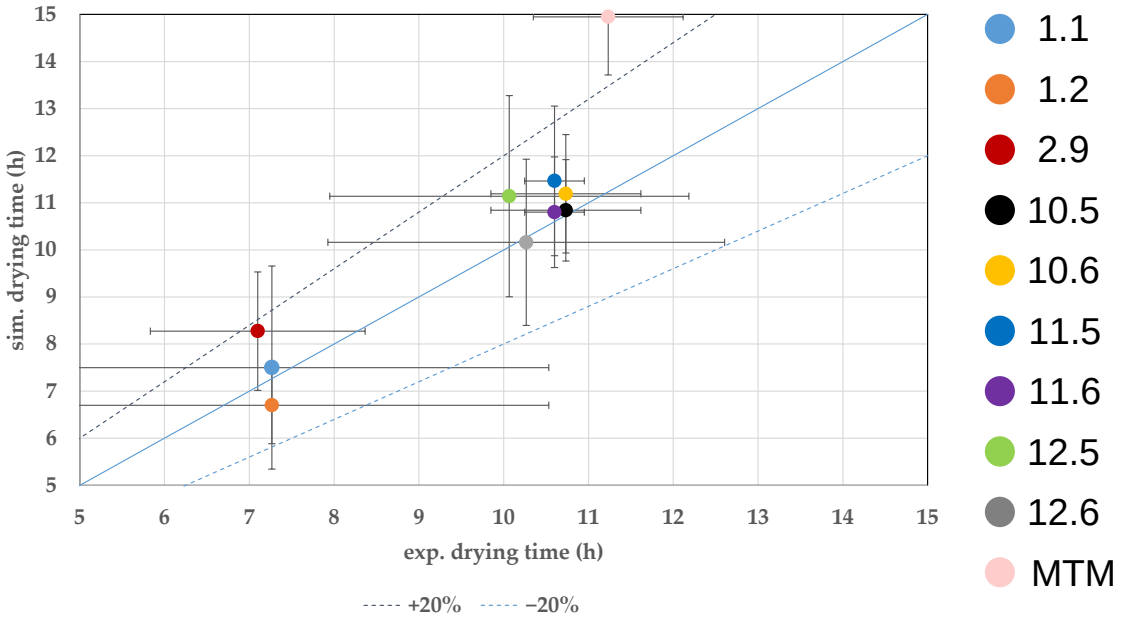


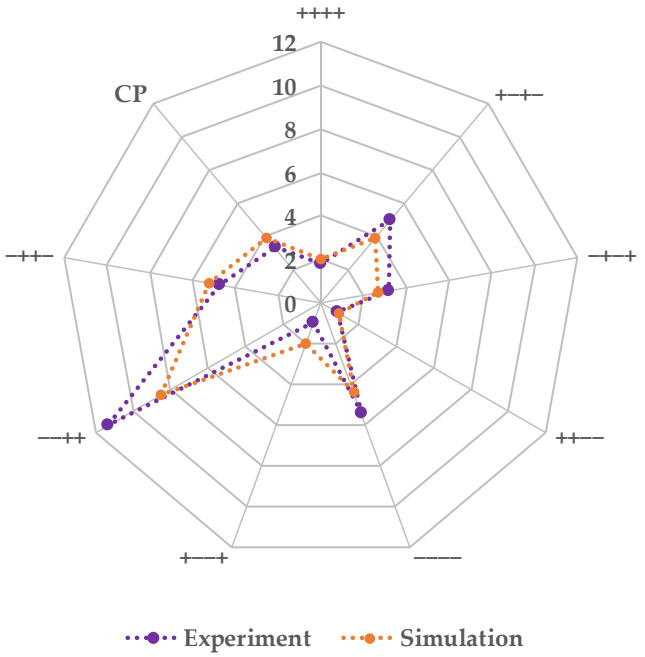


[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Model validation – Comparison Sim./Exp.

- Centerpoint (experiment repeated three times
  - Simulation error smaller than experimental
- Drying heterogenity detectable in accordance to experiments
- Optimized process parameters lead to decrease

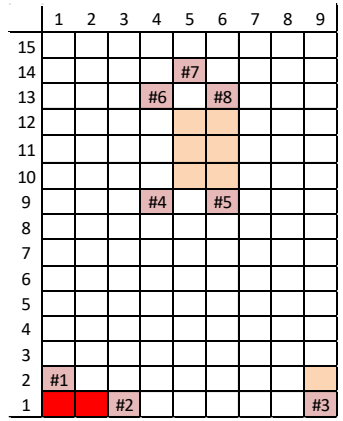


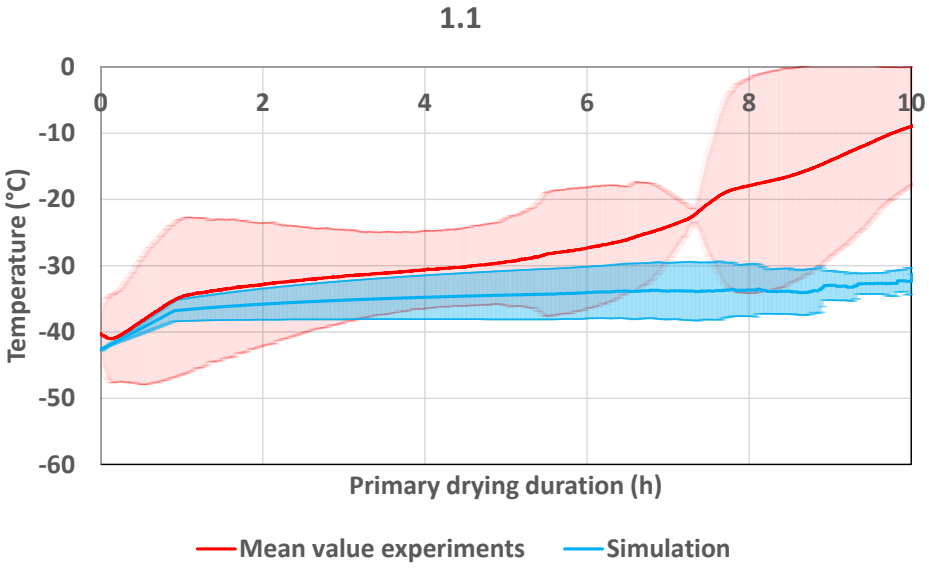


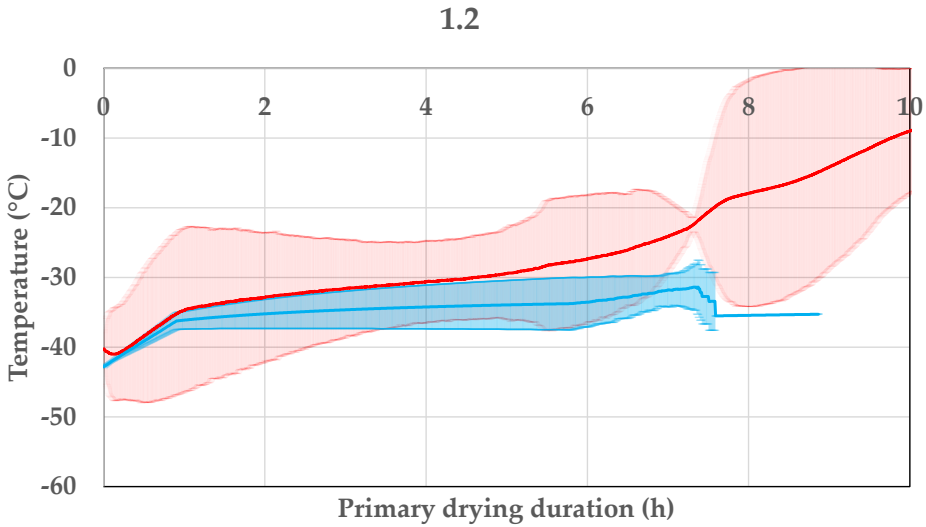
[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Model validation – Comparison Sim./Exp.

- **Product temperature determination edge vial, Centerpoint**





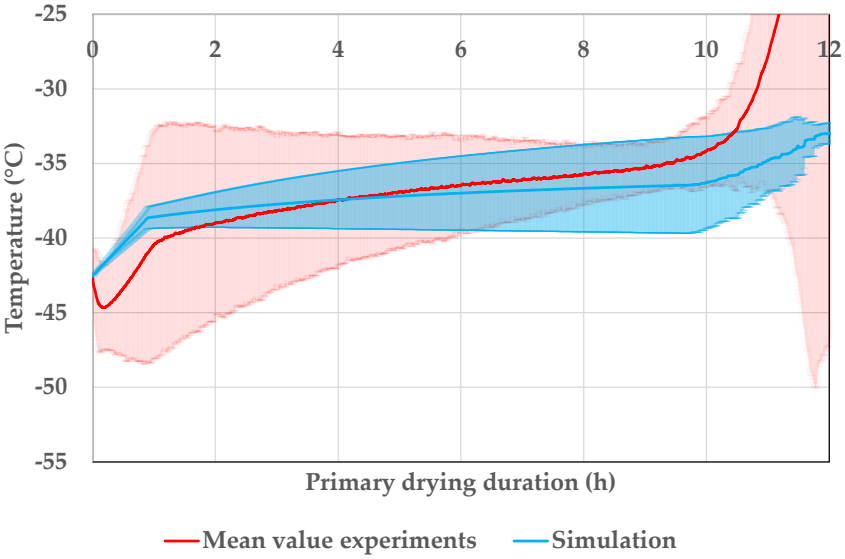


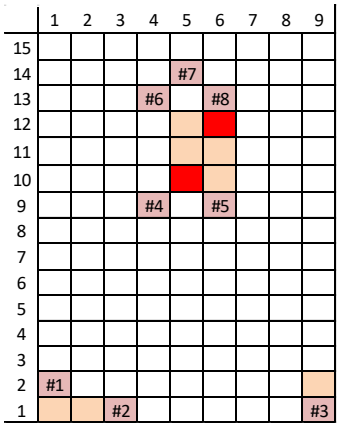
Good agreement of results in beginning but with increasing process duration temperatures drift apart

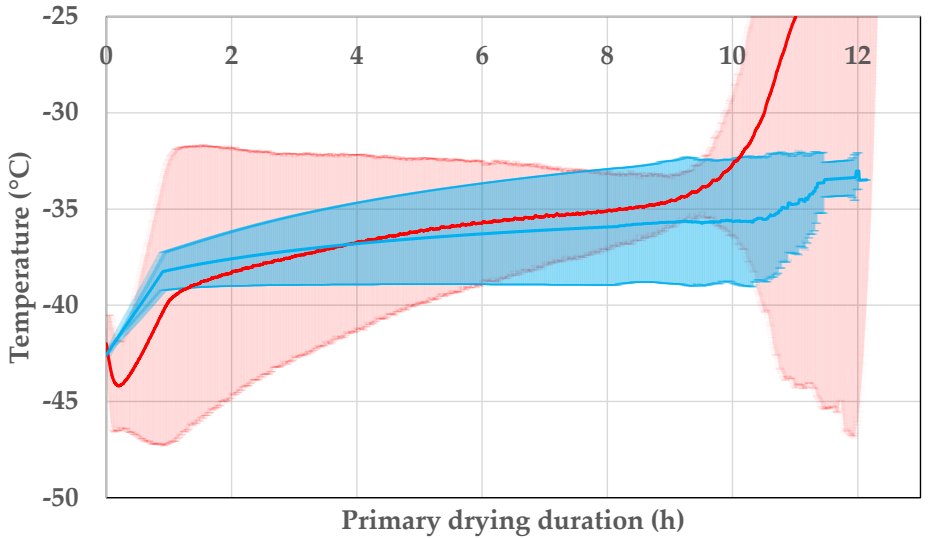
[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Model validation – Comparison Sim./Exp.

- **Product temperature determination center vial, Centerpoint**





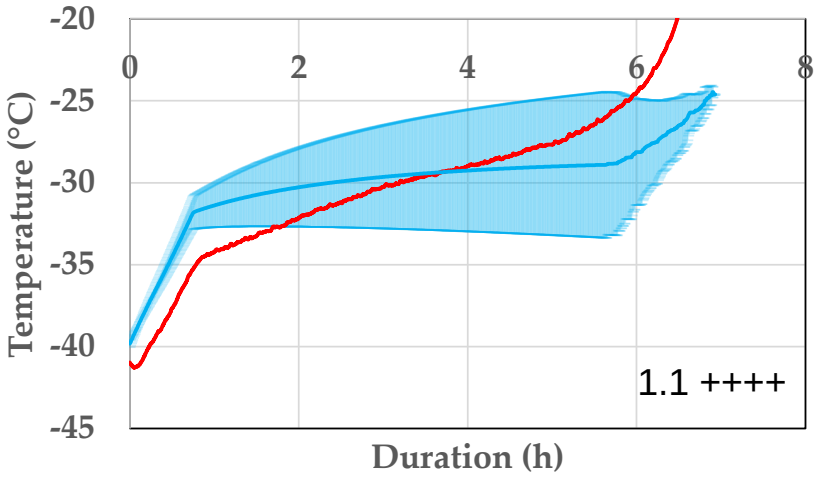


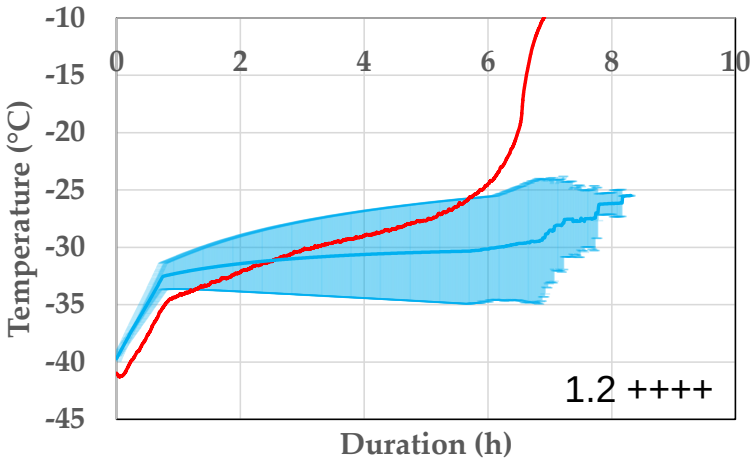
Simulation and experiments in good agreement

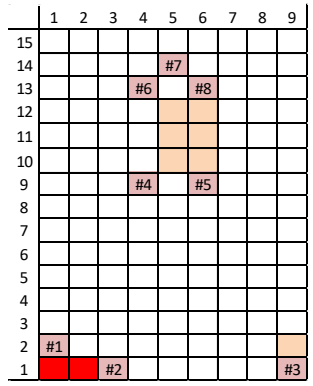
[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Model validation – Comparison Sim./Exp.

- **Product temperature determination edge vial**







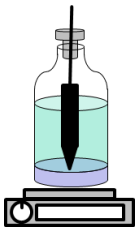
With more optimized process conditions predicition accuracy increases

[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Intermediate conclusion

Time effort needed

- Simulation
  - Ice sublimation test
  - Each experiment ~1day



- 4 pressure values, 2 shelf temp. (double determined)
- ~16 days

- Dry layer resistance MTM
- ~5 days

- Simulation
- ~5-20s
- 1200 simulations = 6,5h/Number PCs

- Experiment

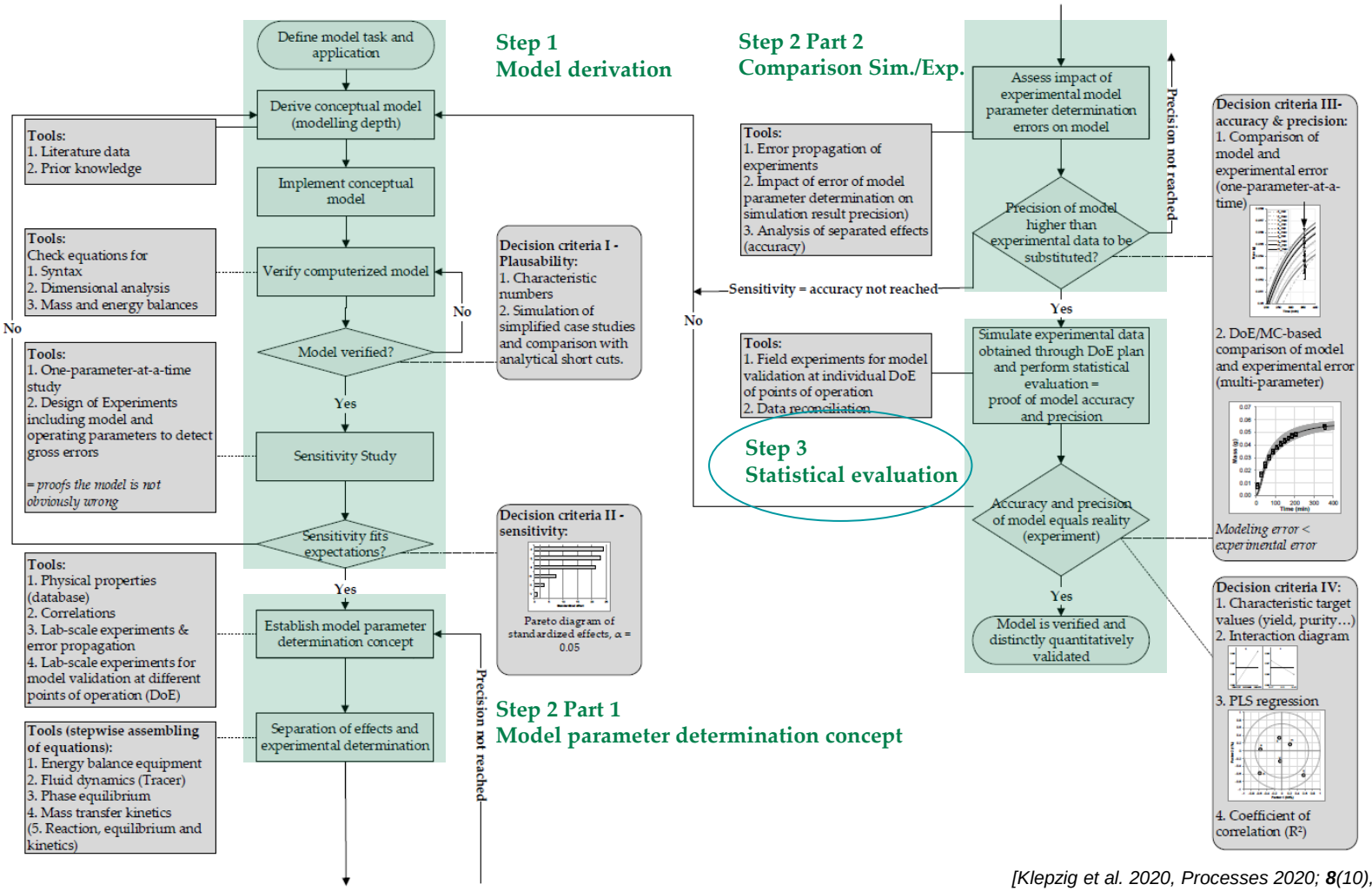
- Freezing ~ 3h
- Primary drying ~4-25h
- Defrosting ~2h

- 11 experiments
- ~15-20 days

For one study no significant time decrease but K_v equipment parameter

Used vial with freeze dryer does not need to be re-determined

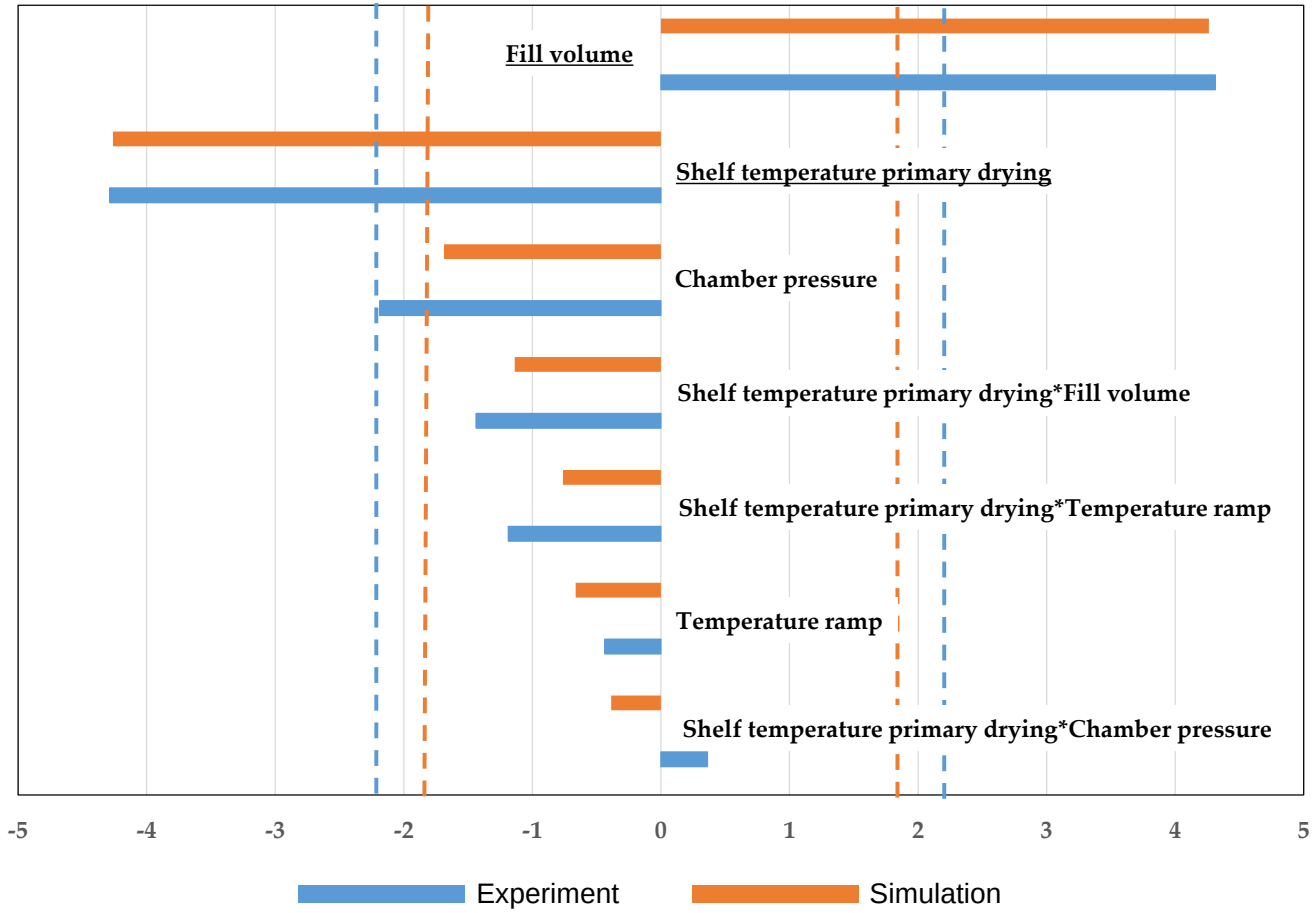
Model validation



*[Klepzig et al. 2020, Processes 2020; **8**(10),1325]*

Model validation – Statistical evaluation

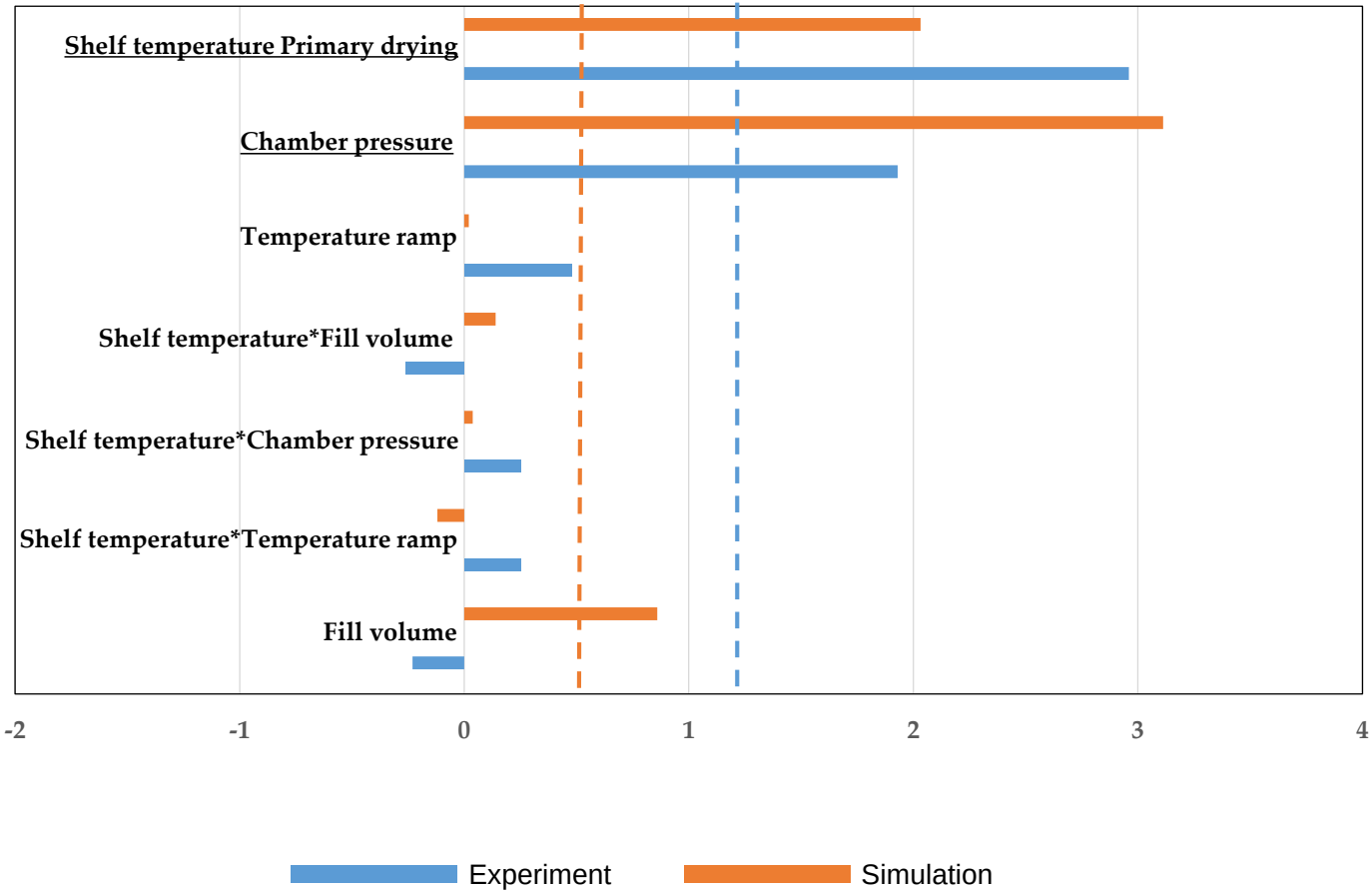
- Statistical evaluation endpoint



Parameter interaction and strength in good agreement

Model validation – Statistical evaluation

- Statistical evaluation product temperature



Parameter interaction and strength in good agreement but effect of fill volume overpredicted in simulation

Agenda

- Background
- Modeling of lyophilization
- Model validation
- **Summary**

Summary

- **Model validation** based on established validation workflow
  - **Example systems**: Saccharose (amorph)
- Model derivation and implementation
- Establishment of **model parameter determination concept**
  - Parameter show expected physical behaviour
- **Endpoint determination** through Design of Experiments
  - Results in good agreement
- **Temperature determination** through Design of Experiments
  - In good agreement for center vials, rising prediction for edge vials with optimized process parameters

Model is verified and distinctively, quantitatively validated
- Design space definition and control strategy development possible

Thank you for your attention!

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