Modeling of lyophilization processes

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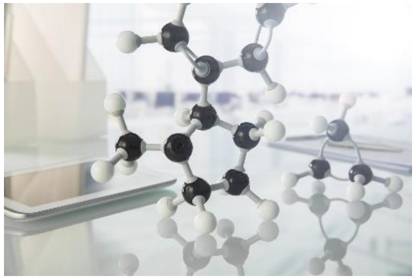
Agenda

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

Background

- **Gold standard of drying processes**
- **60%** of biologics would not be available without lyophilization
- **Process development still connected to high experimental workload**
- Mathematical modeling deepens process understanding and accelerates process development

Background

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

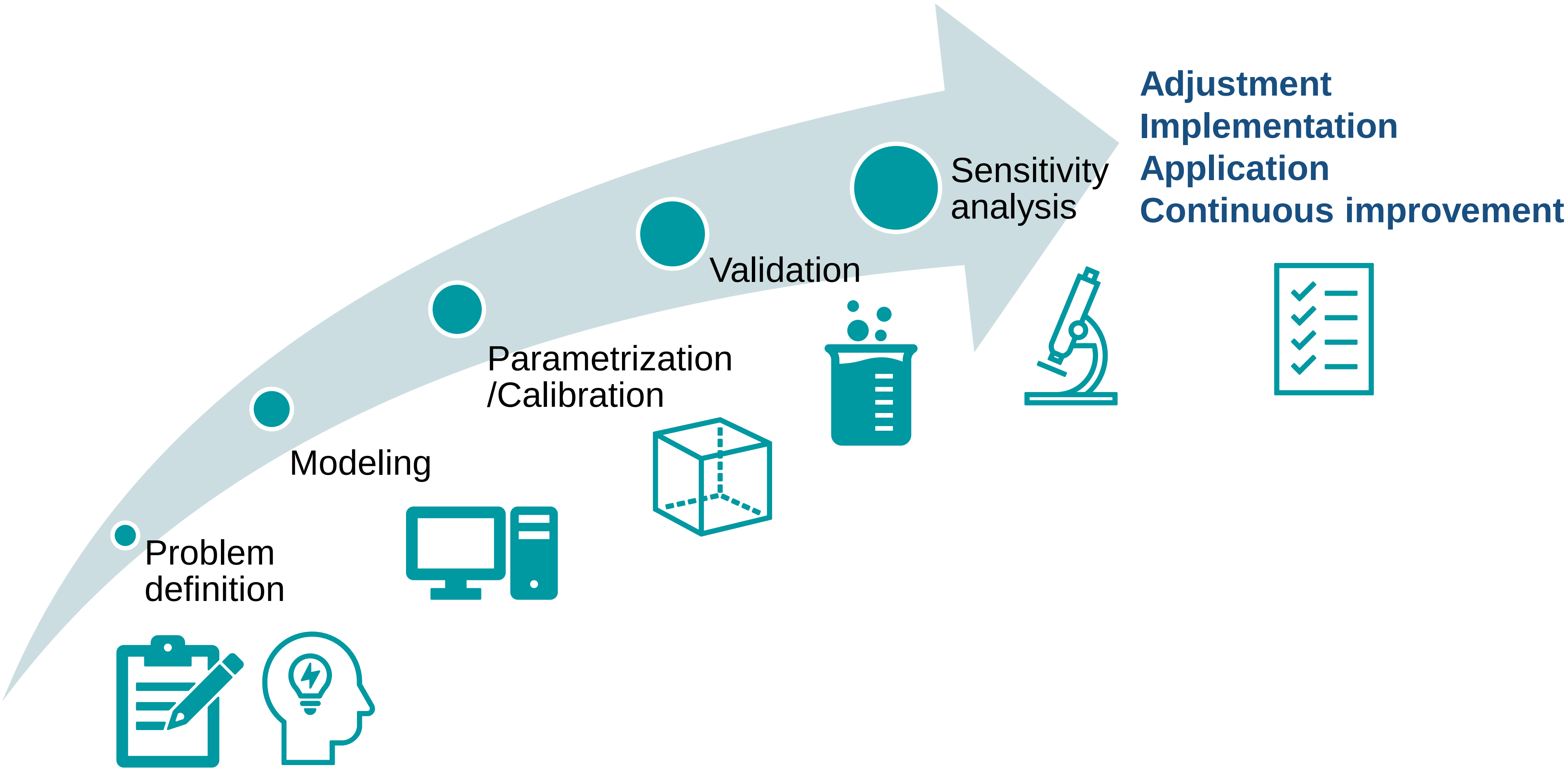
  „Simulation is the reproduction (...of the behaviour..) of a system with its dynamic processes in a model that can be experimented with in order to obtain knowledge that can be transferred to reality“ VDI 3633
- **Modeling and simulation shift a problem-solving process from reality to an abstracted copy**

Background

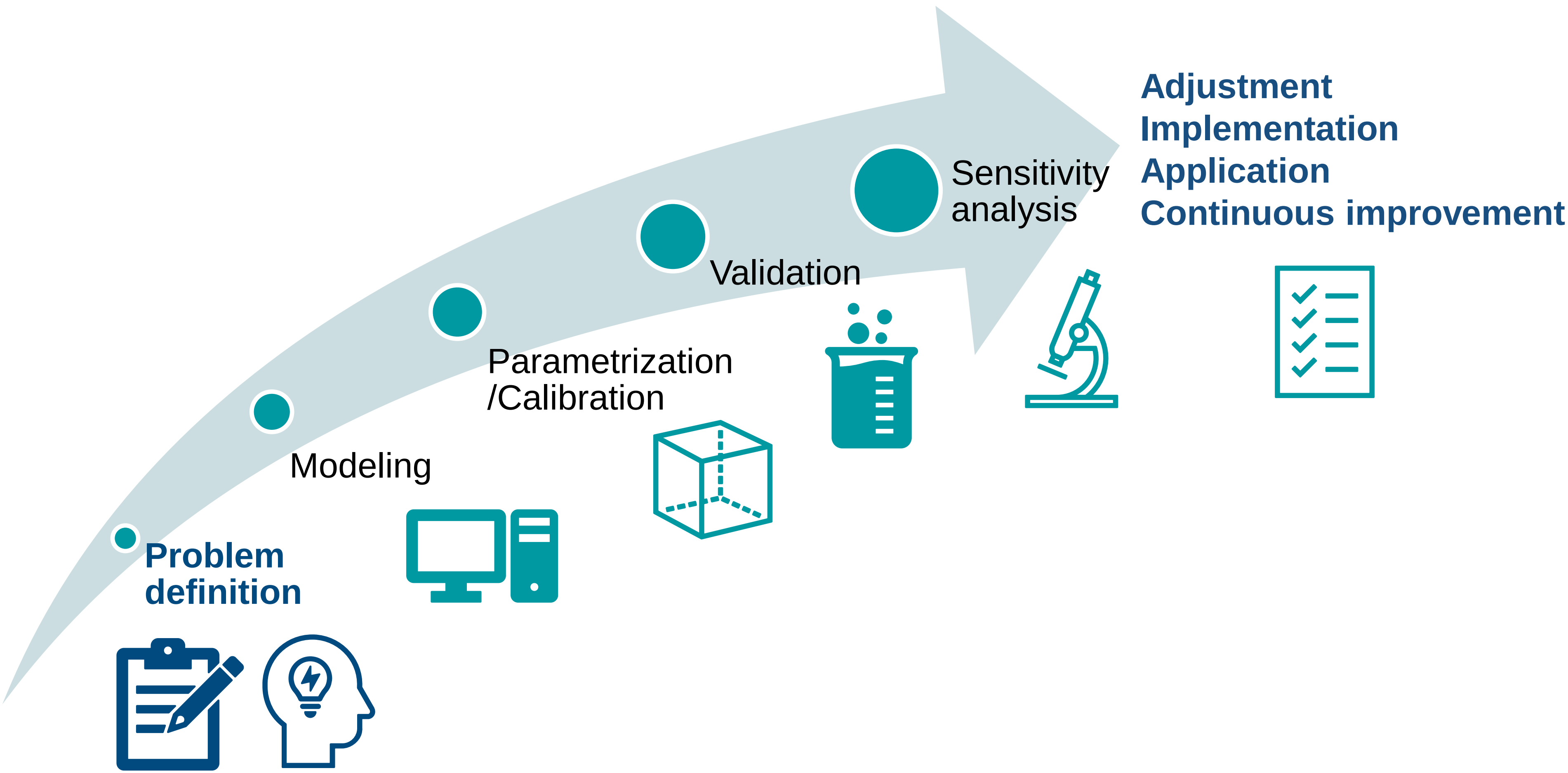
- **Why modeling and simulation?**
  - Knowledge can be gained about systems that cannot be experimented with in reality or only with considerably greater effort
- Simulations can be repeated at will
- Simulated models are fully observable
- The time and cost of projects can be significantly reduced

Advantages	Disadvantages
Alternative to experiments	Unrealistic
Improved system understanding	Construction effort, limited resources
Capturing system complexity	Credibility
Simplification of real world	Lack of transparency
Decision support	
Strategy determination	

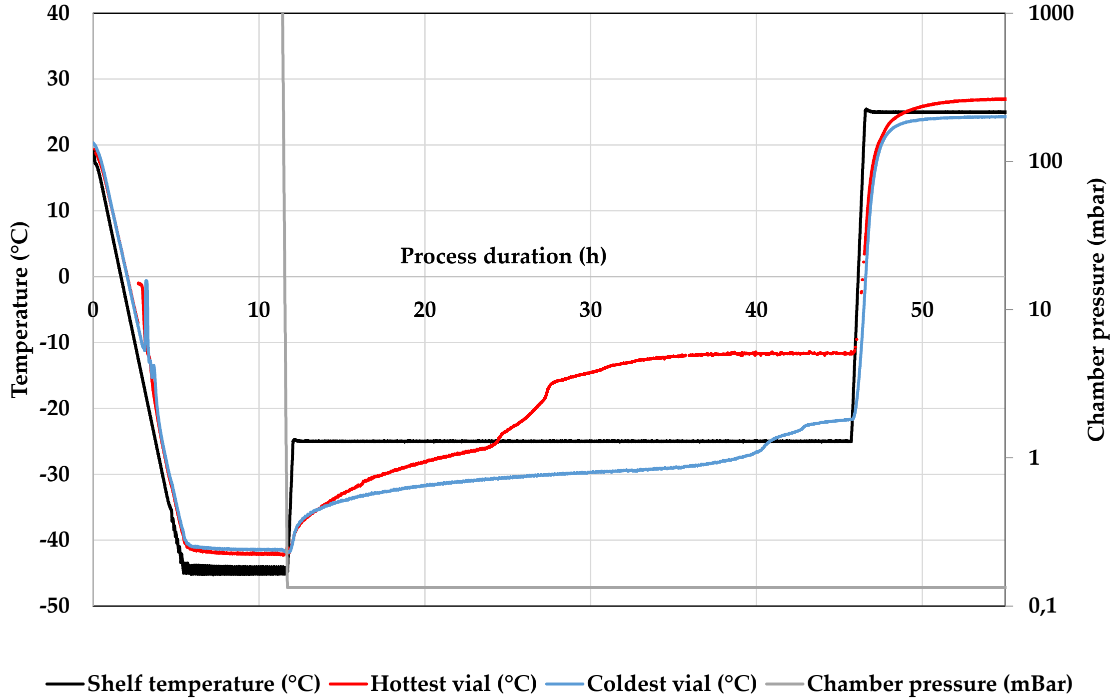
Modeling of lyophilization



Modeling of lyophilization



Modeling of lyophilization – Problem definition

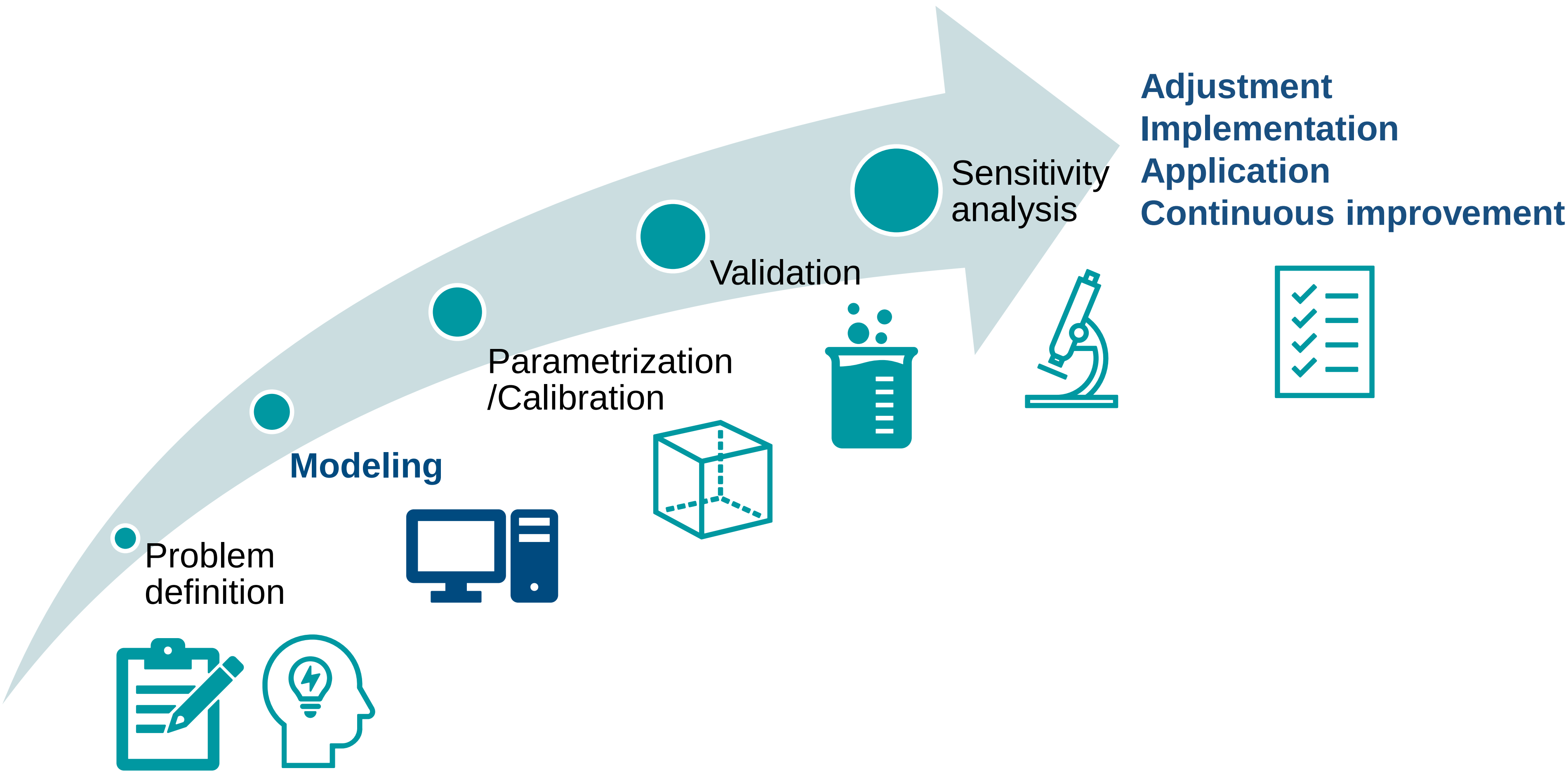


- Primary drying usually longest step
- High optimization potential

Modeling of primary drying phase to determine
- **product temperature**
- **primary drying endpoint**

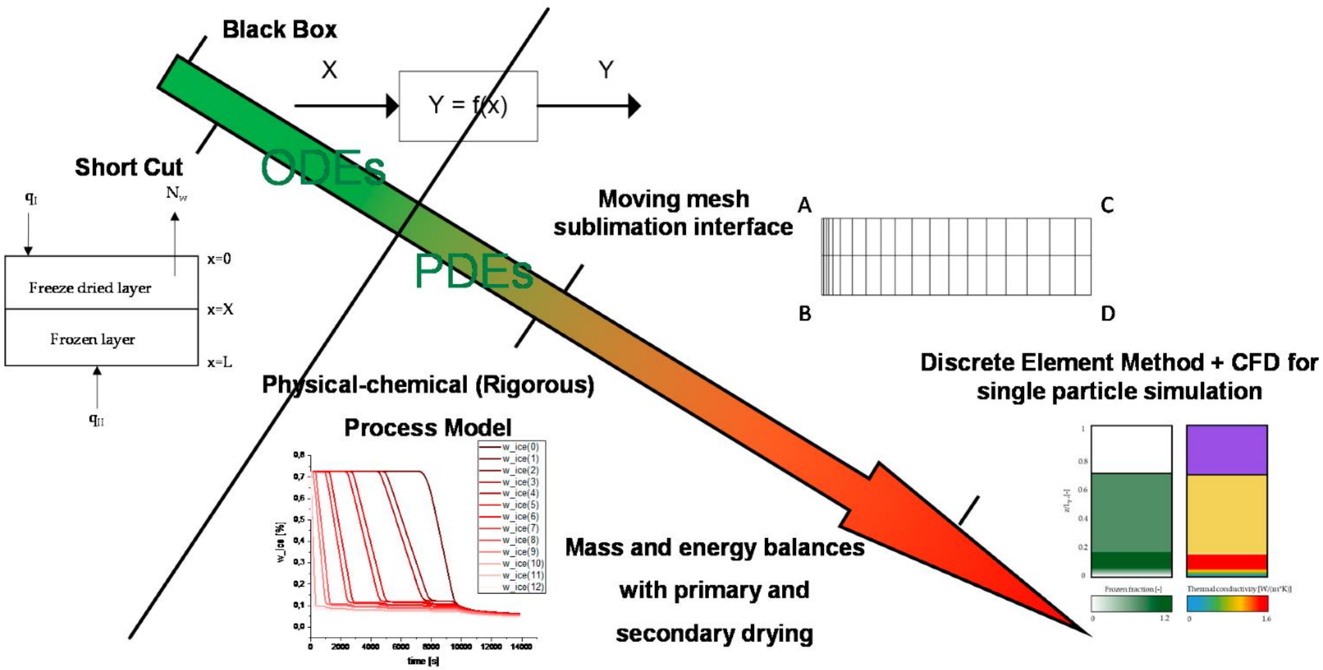
- **Description of process dynamics necessary**

Modeling of lyophilization



Modeling of lyophilization

- Different models available that describe the couple heat and mass transfer in varying degrees of detail



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

Modeling of lyophilization

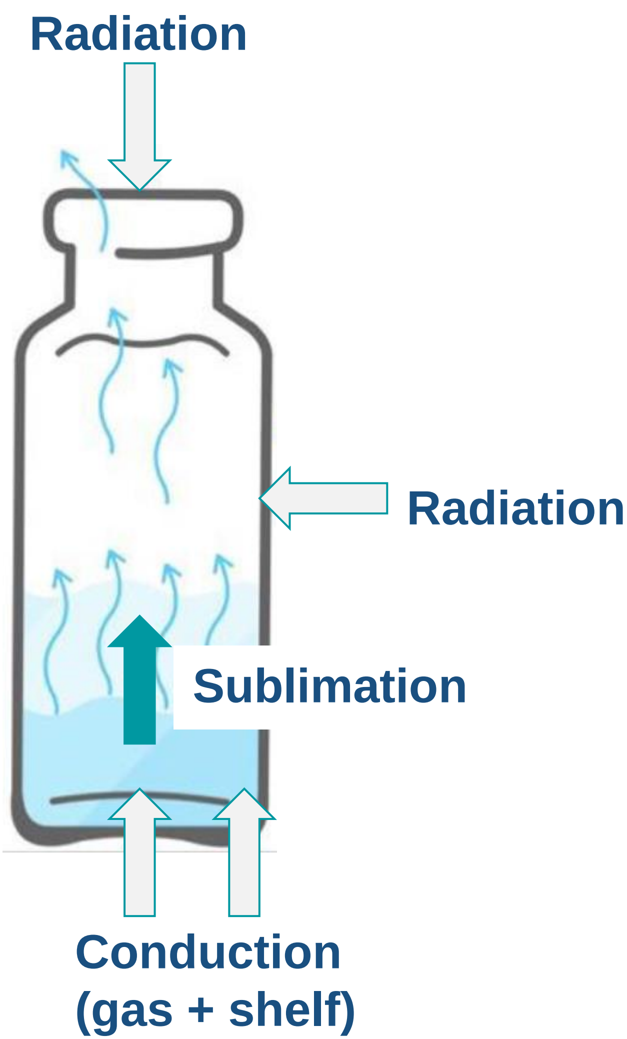
- **Heat transfer**
- Description of whole heat transfer mechanism through one overall vial heat transfer coefficient

$$K_v = K_c + K_r + K_g$$

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

- **Mass transfer**
- Description of all resistances against vapor flow in one coefficient

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



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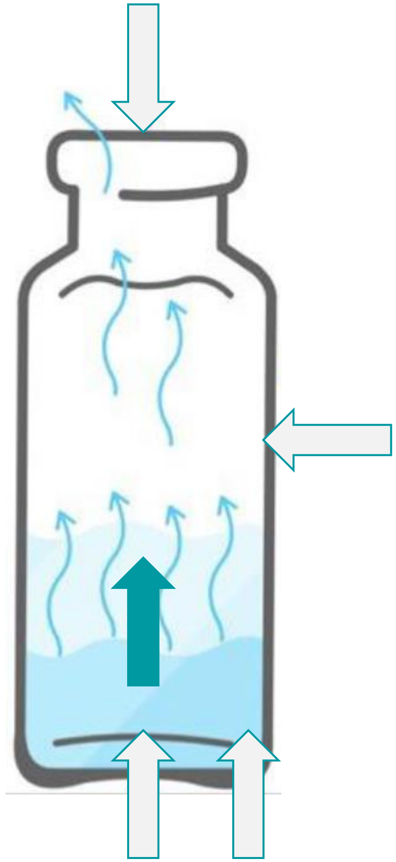
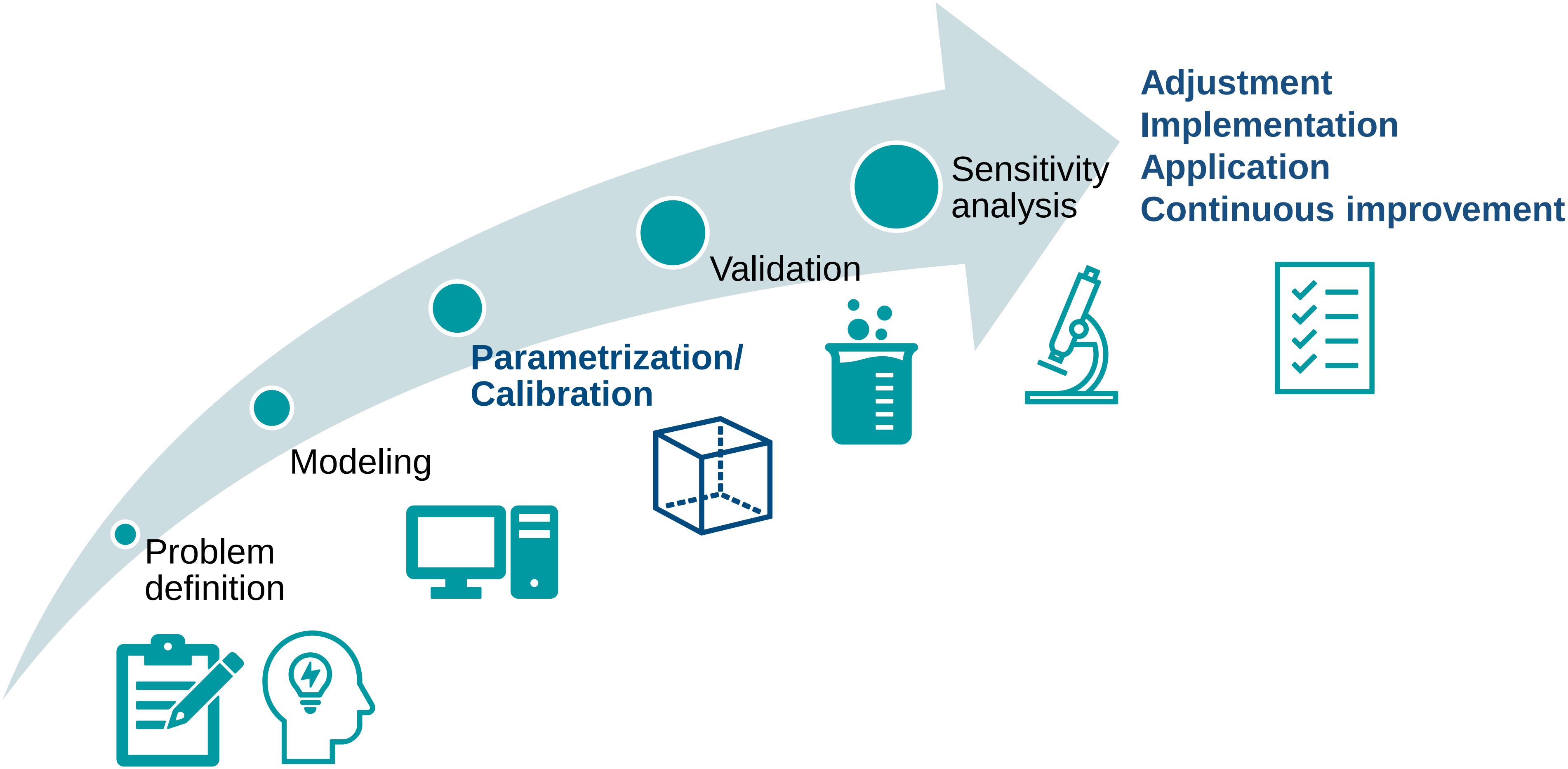


Coupled heat and mass transfer

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

Modeling of lyophilization



Modeling of lyophilization

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

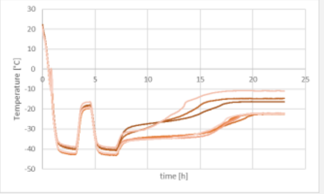
Product Temperature constraint

$T_{product} < T_{Collapse}$

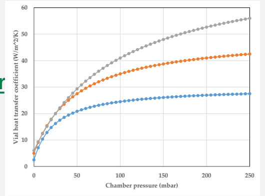
Equipment constraint

$J_{subl} < J_{Max}$

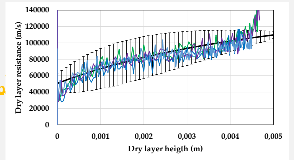
1.1 $T_{product}$ = f (Position)



1.2 Heat transfer coefficient (K_v)



2.1 Dry layer resistance (R_p)

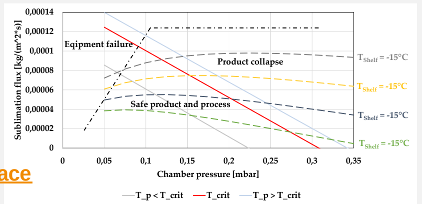


Equipment characterization

- 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
  - $K_v = \frac{\Delta m \cdot \Delta h_{subl} / \Delta t}{A_{vial} \cdot (T_{S,PD} - T_{product})}$
  - **Gravimetric determination**
  - $T_{product}$ **determination with WTM**

Formulation characterization

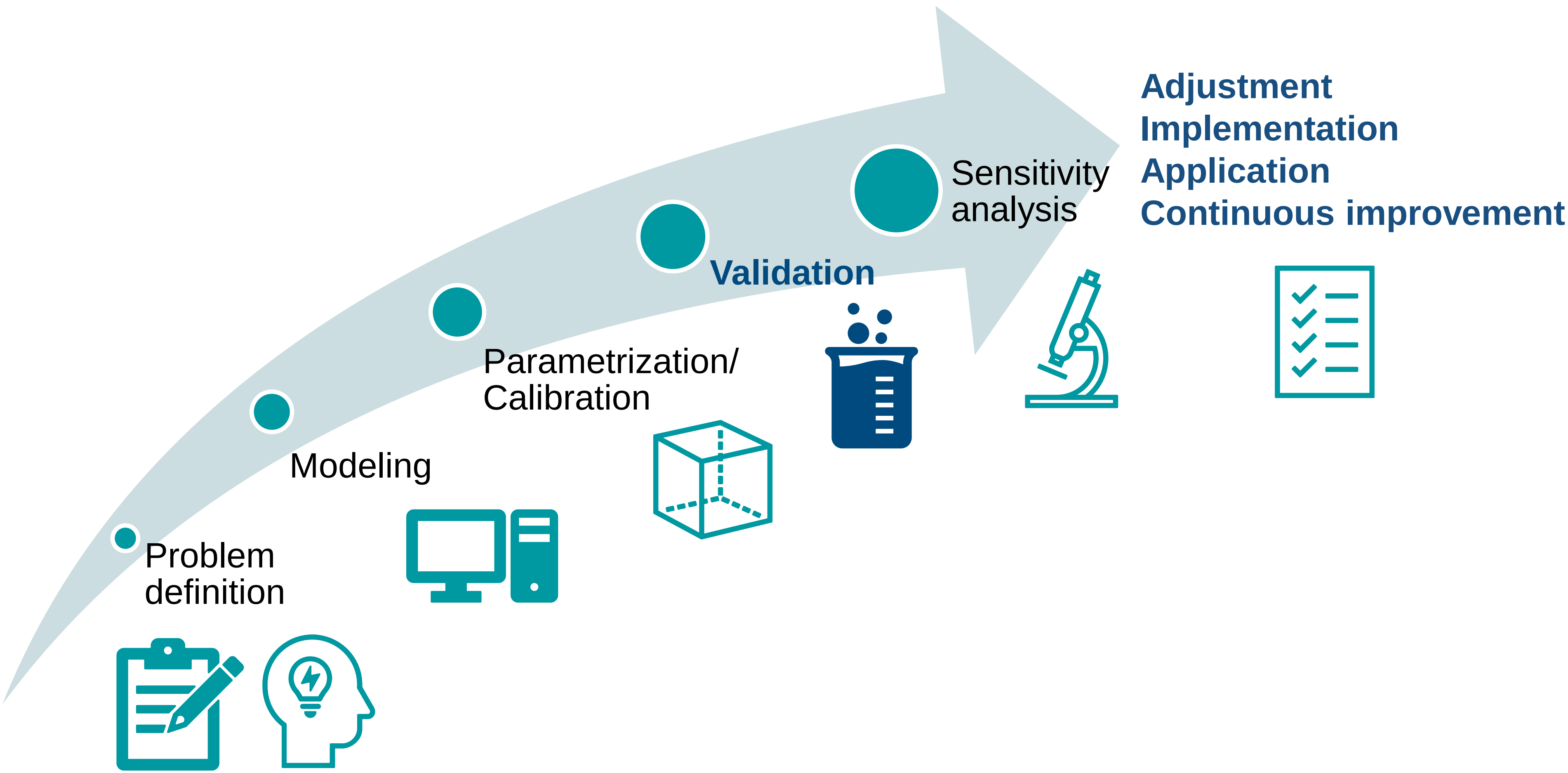
- 2.1 Collapse temperature $T_{Collapse}$
  - DSC, LT-FDM, Literature
- **2.2 Dry layer resistance**
  - Experiment with product solution
  - $R_p = \frac{A \cdot (p_{ice} - p_C)}{\dot{m}}$
  - Determination with **MTM** measurement and fitting to pressure rise data



Design Space

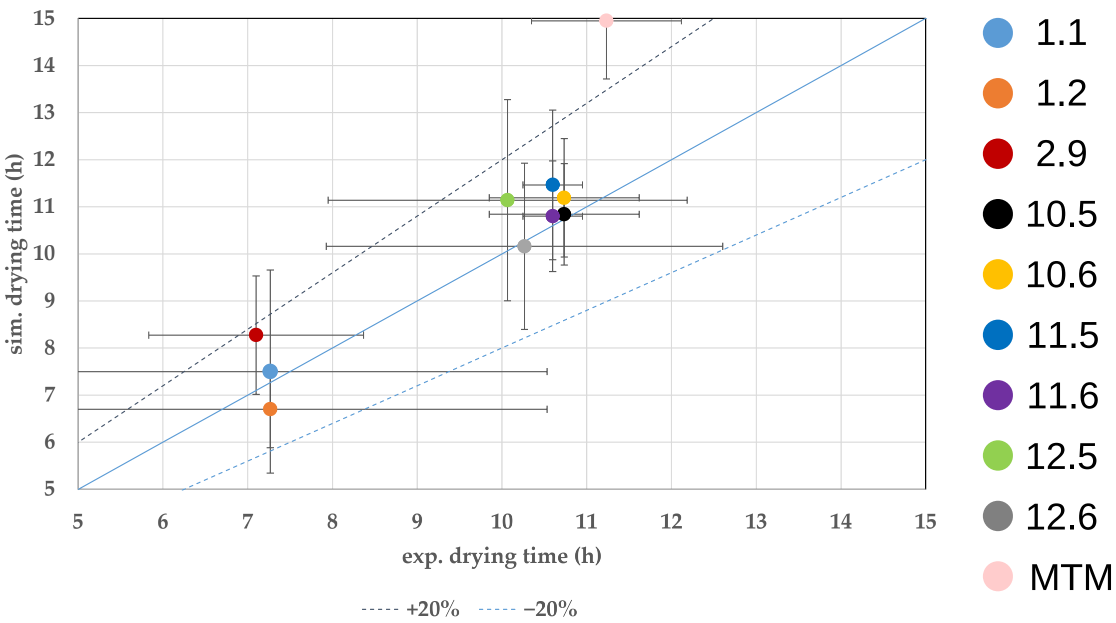
[Juckers et al. 2021, Processes 2021; 9(9),1600]

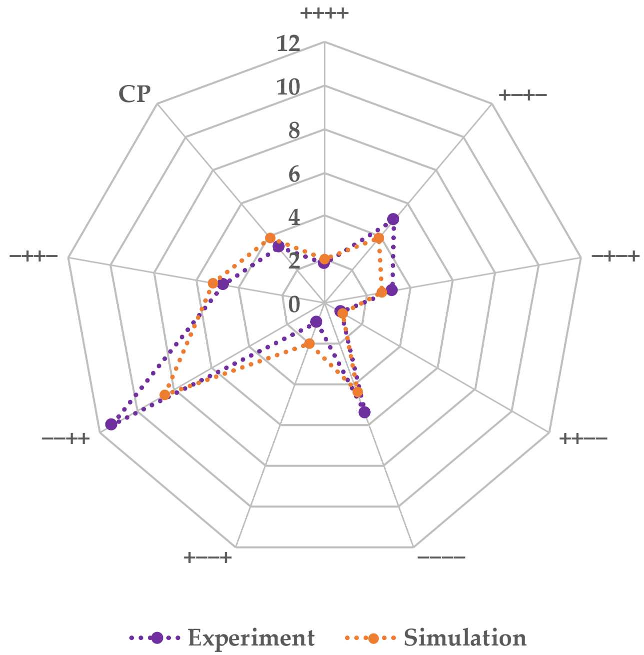
Modeling of lyophilization



Modeling of lyophilization – Validation

- Centerpoint (experiment repeated three times)
  - Simulation error smaller than experimental
- Drying heterogenity detectable in accordance to experiments



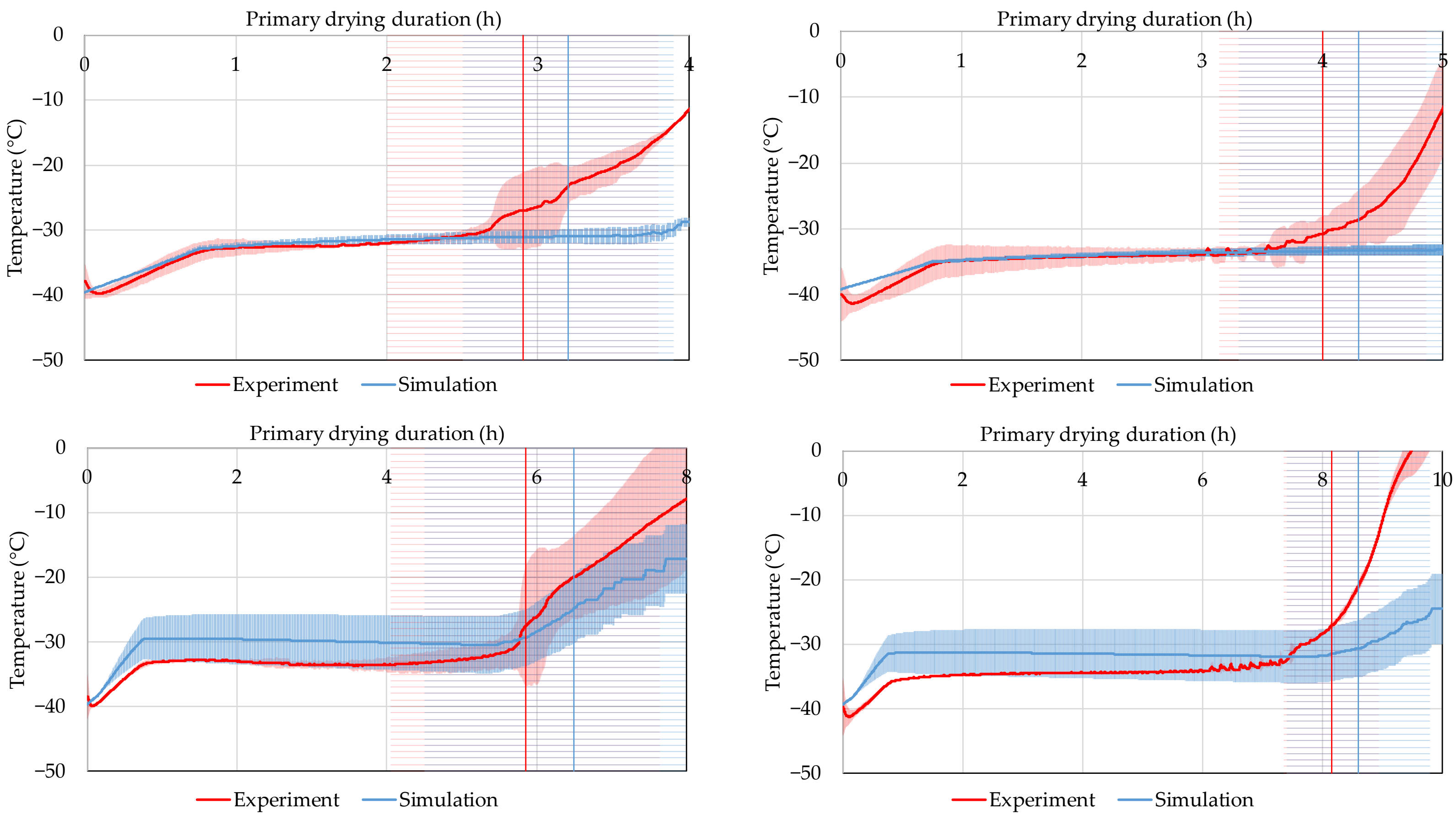


[Juckers et al. 2022, Pharmaceutics 2022; 14(4),809]

Modeling of lyophilization – Validation

T_n= -8 °C
T_{shelf}= 0 °C
p_c= 0.15 mbar
V_{fill}= 1 mL

T_n= -2 °C
T_{shelf}= 0 °C
p_c= 0.15 mbar
V_{fill}= 2 mL

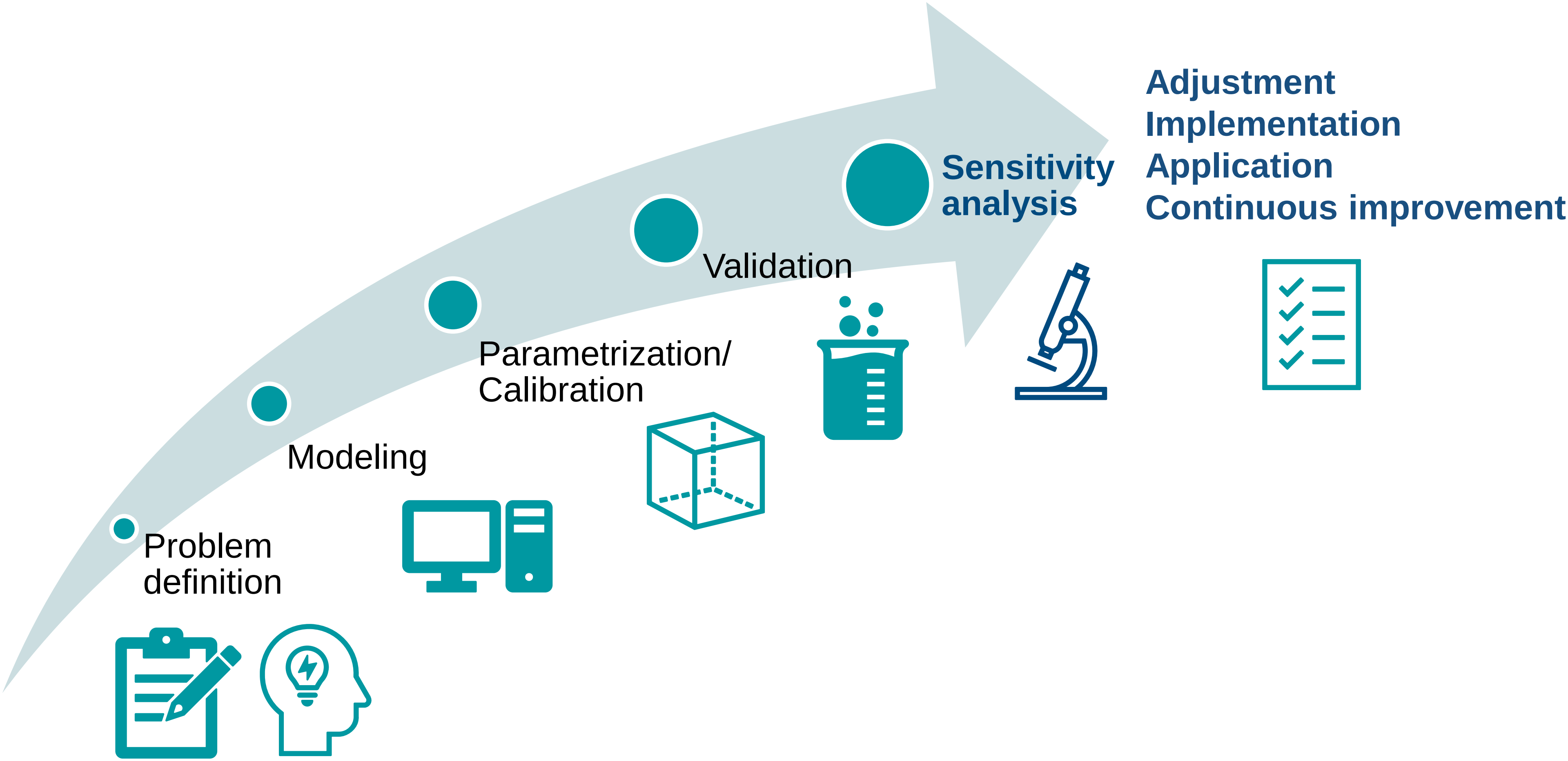


Edge

Center

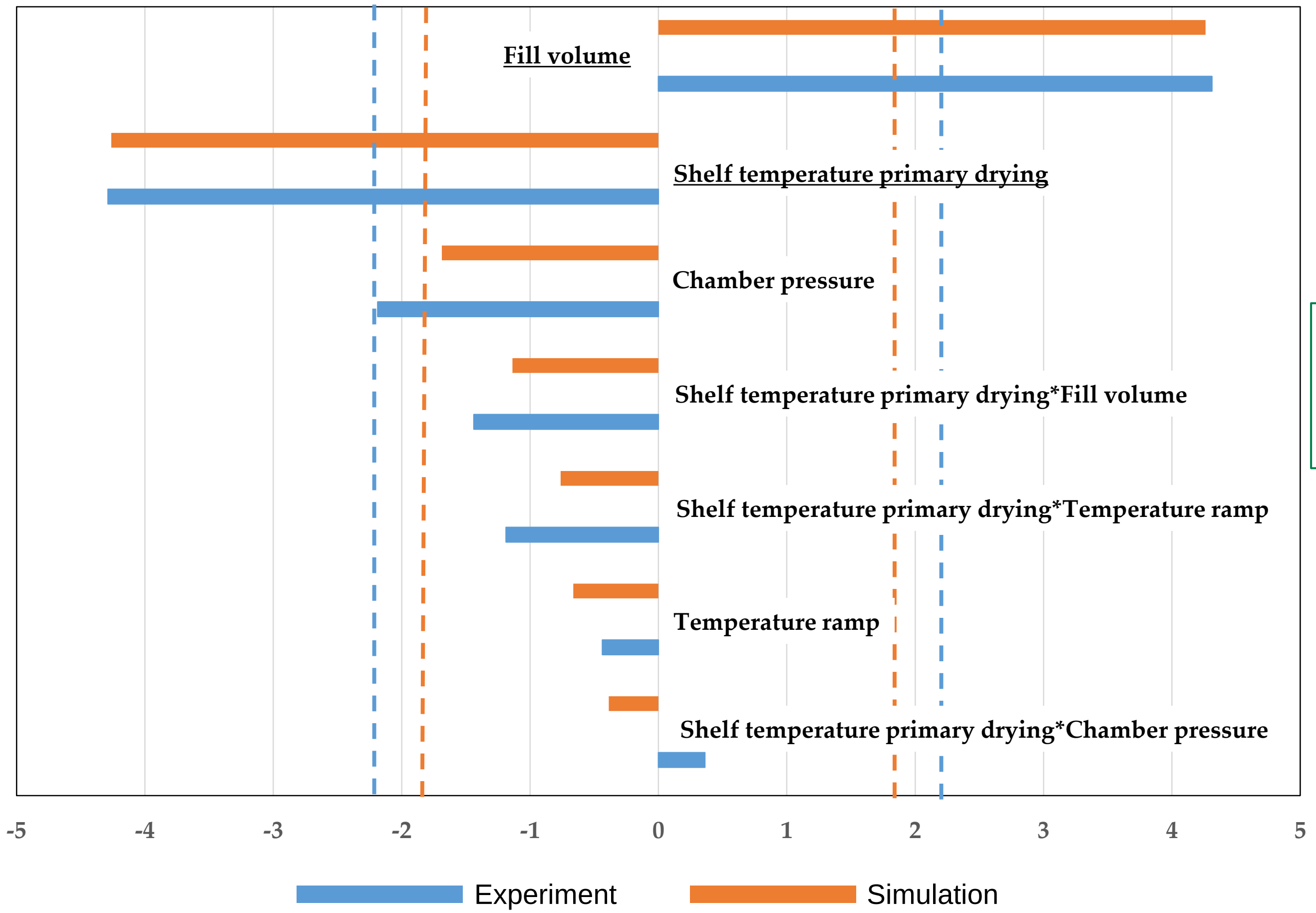
[Juckers et al. 2023, Processes 2023; 11(5):1404]

Modeling of lyophilization



Model validation – Statistical evaluation

- Statistical evaluation endpoint

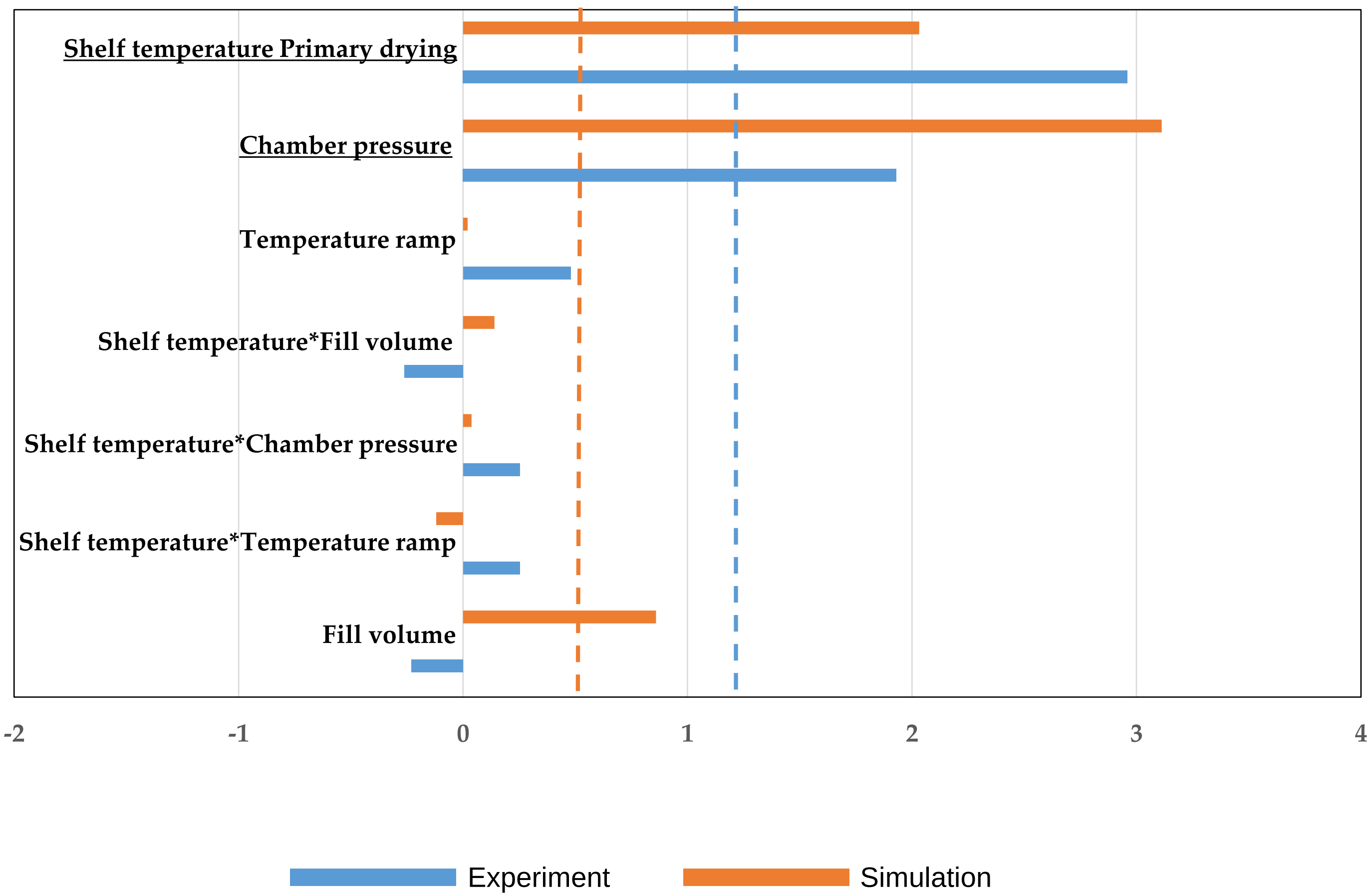


Parameter interaction and strength in good agreement

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

Model validation – Statistical evaluation

- Statistical evaluation product temperature



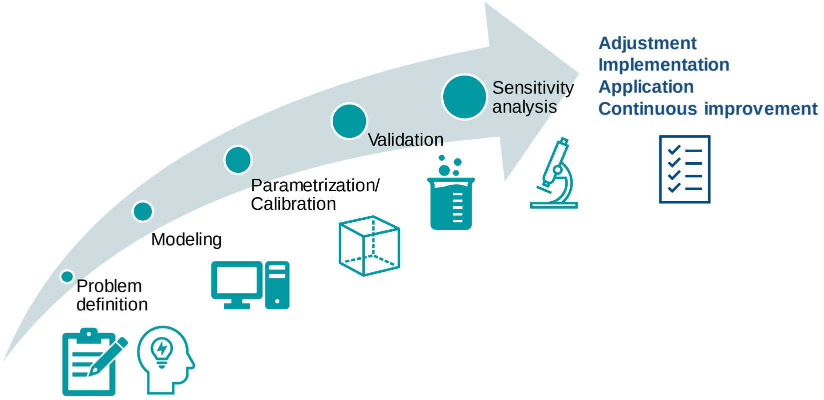
Parameter interaction and strength in good agreement but effect of fill volume overpredicted in simulation

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

Summary

- Development of process model for distinct problem definition
- Establishment of **model parameter determination concept**
  - Parameter show expected physical behaviour
- **Endpoint determination** in good agreement with experiments
- **Temperature determination** in good agreement with experiments
- Model shows **similar sensitivites** as experiment

- **Model validated**
  - **Process development possible**
  - **Process optimization possible**



Thank you for your attention!

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