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Modelling and monitoring of the freeze-drying process

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This work has been realised in the framework of:

Lyo-Pro

Competitive and Sustainable Growth European Project

The scientific objective of the proposal is to optimize the freeze-drying process of pharmaceutical proteins on a scientific basis in order to set up efficient and rational freeze-drying diagrams for industrial manufacturing of commercially-used drugs and diagnostic proteins.

Freeze-drying (or lyophilization)

Drying process whereby water or another solvent is removed from a frozen product by **sublimation**, generally under **vacuum.**

Freeze-drying is the best available technique to dry pharmaceutical proteins reducing the possibility of introduction of immunogenicity or other undesirable changes in the product properties.

Limitations

- **long process duration and high process costs**
- **optimisation by trial and error runs**
- **impossibility of direct measure of parameters of interest**

Theoretical modelling

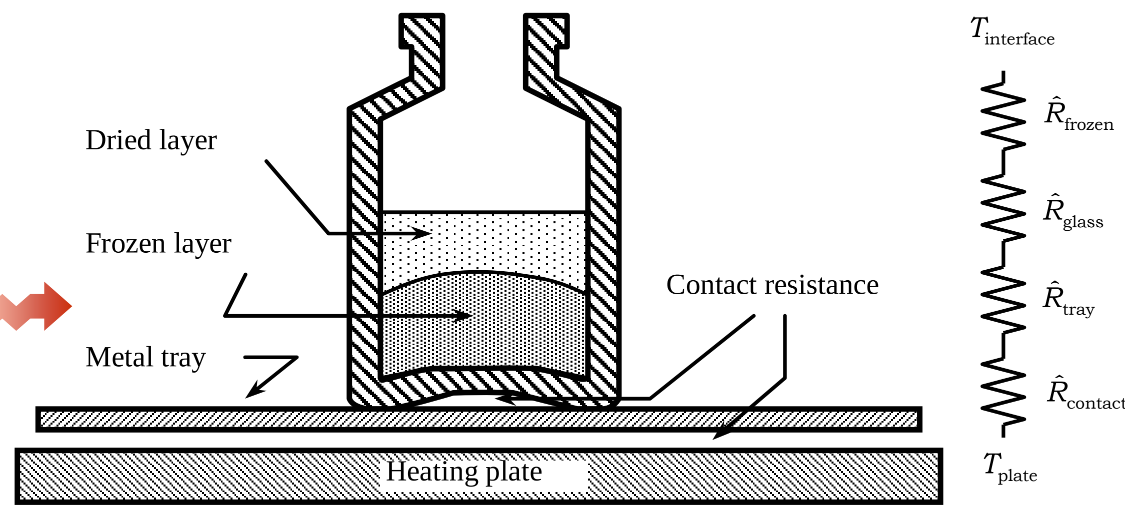
- **help in design, optimization, and control of the process**

Primary drying →

- **Sublimation** of frozen water
- **Condenser** to trap vapour
- Endothermic process, latent **heat must be provided**
- **Moving front** of sublimation
- **Critical parameter**: sublimating front temperature, $\mathbf{T_i}$
  - Collapse/melting
  - Sublimation speed depend directly on T_i
- **Coupled Heat and mass transfer**

Cooling (sublimation)

Heating (radiation, conduction)



Modelling

Bi-dimensional model for vial lyophilisation

Energy balance dried layer I

$$\varrho_{\mathrm{Ie}} c_{P,\mathrm{Ie}} \frac{\partial T_{\mathrm{I}}}{\partial t} = -c_{P,G} \mathbf{N}_{\mathrm{tot}} \cdot \nabla T_{\mathrm{I}} + \nabla \cdot \left(k_{\mathrm{Ie}} \nabla T_{\mathrm{I}} \right) + \Delta \hat{H}_{\mathrm{v}} \frac{\partial \varrho_{\mathrm{sw}}}{\partial t} = 0$$

Energy balance frozen layer II

$$\varrho_{\mathrm{II}} c_{P,\mathrm{II}} \frac{\partial T_{\mathrm{II}}}{\partial t} = \nabla \cdot \left(k_{\mathrm{II}} \nabla T_{\mathrm{I}} \right)$$

Material balance vapour

$$\varepsilon_{\mathrm{P}} \frac{\partial \varrho_{\mathrm{w}}}{\partial t} = -\nabla \cdot \mathbf{N}_{\mathrm{w}} - \frac{\partial \varrho_{\mathrm{sw}}}{\partial t}$$

Material balance inert

$$\varepsilon_{\mathrm{P}} \frac{\partial \varrho_{\mathrm{in}}}{\partial t} = -\nabla \cdot \mathbf{N}_{\mathrm{in}}$$

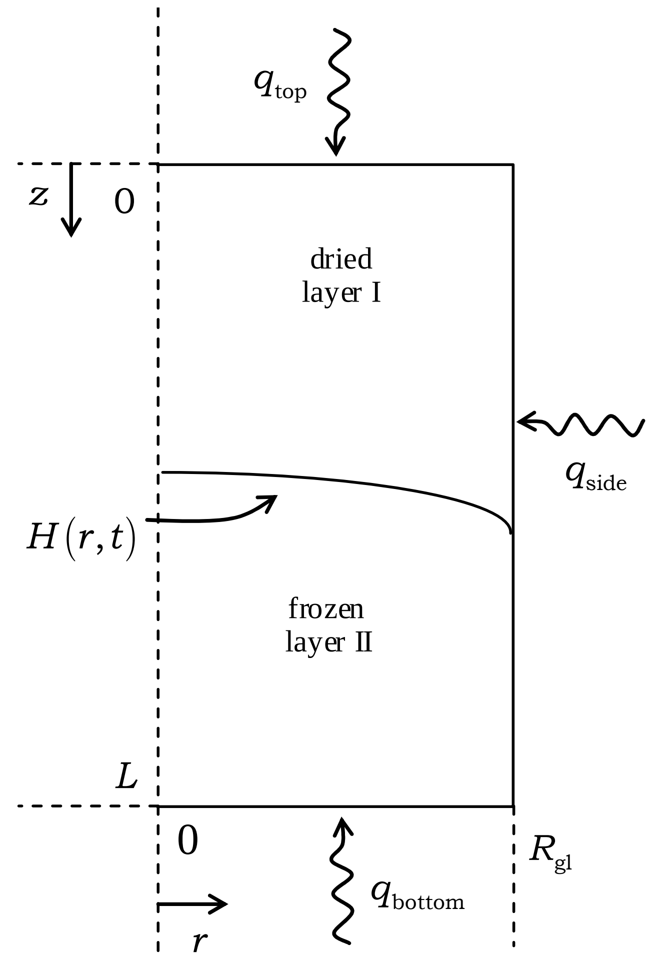
Material balance at the moving front

$$\mathbf{N}_{\mathrm{w}} \Big|_{z=H(r,t)} = -\mathbf{v} \left(\varrho_{\mathrm{II}} - \varrho_{\mathrm{Ie}} \right)$$

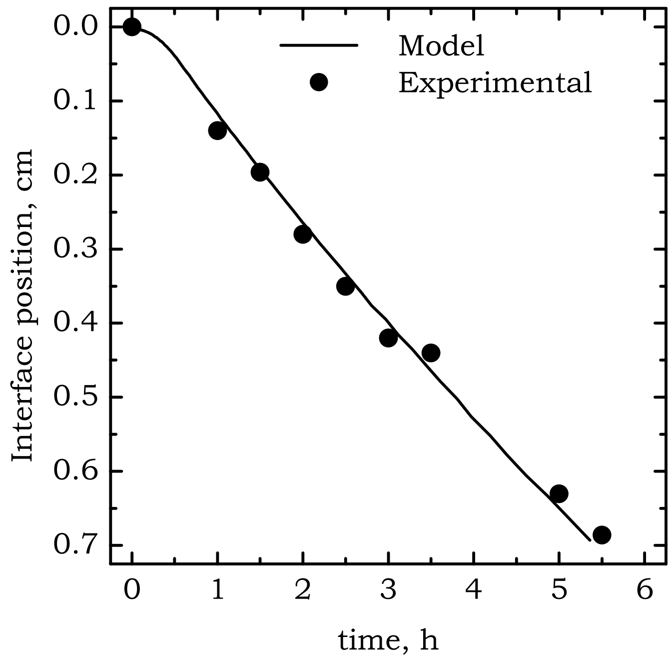
$$\frac{\partial H}{\partial t} = -\frac{1}{\varrho_{\mathrm{II}} - \varrho_{\mathrm{Ie}}} \left(N_{\mathrm{w},z} \Big|_{z=H(r,t)} - N_{\mathrm{w},r} \Big|_{z=H(r,t)} \frac{\partial H}{\partial r} \right)$$

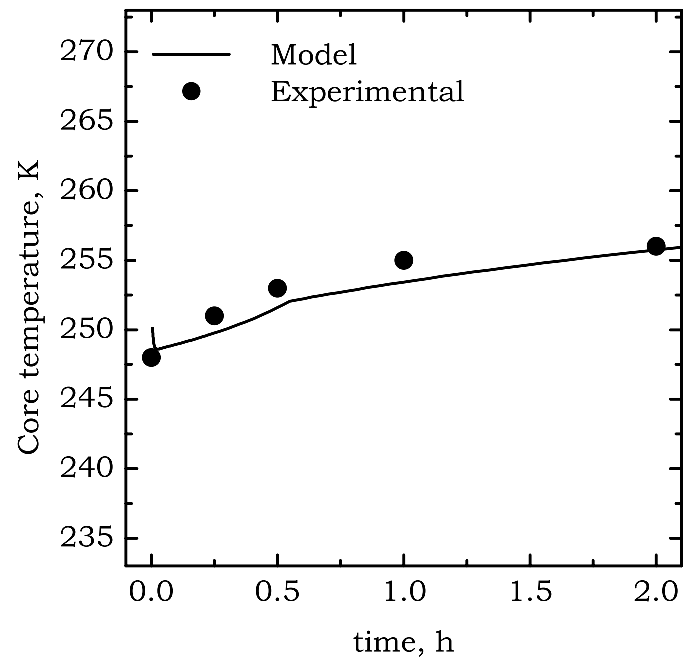
Energy balance at the moving front

$$-k_{\mathrm{II}} \nabla T_{\mathrm{II}} \Big|_{z=H(r,t)} + k_{\mathrm{Ie}} \nabla T_{\mathrm{I}} \Big|_{z=H(r,t)} - \mathbf{N}_{\mathrm{w}} \Big|_{z=H(r,t)} \left(c_{P,G} T_{\mathrm{i}} + \Delta H_{\mathrm{s}} \right) - \mathbf{v} \left(\varrho_{\mathrm{II}} c_{P,\mathrm{II}} T_{\mathrm{i}} - \varrho_{\mathrm{Ie}} c_{P,\mathrm{Ie}} T_{\mathrm{i}} \right) = 0$$



A literature case: freeze-drying of skim milk





Comparison between model simulations and experimental results by Wolff et al. (1989). Left hand side: interface position. Right hand side: frozen core temperature

Sample thickness, mm	Primary drying time, min		
	This work	*Millman et al. [30]*	*Mascarenhas et al. [37]*
3	13.96	13.77	13.47
6	54.65	54.07	55.26

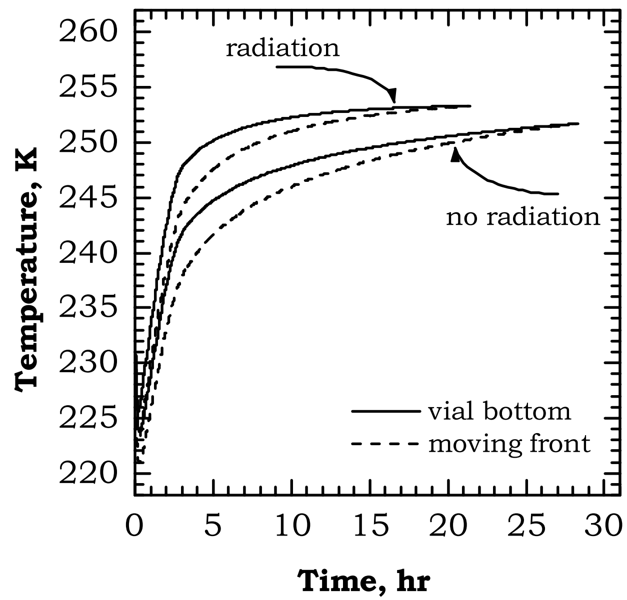
Effect of radiation

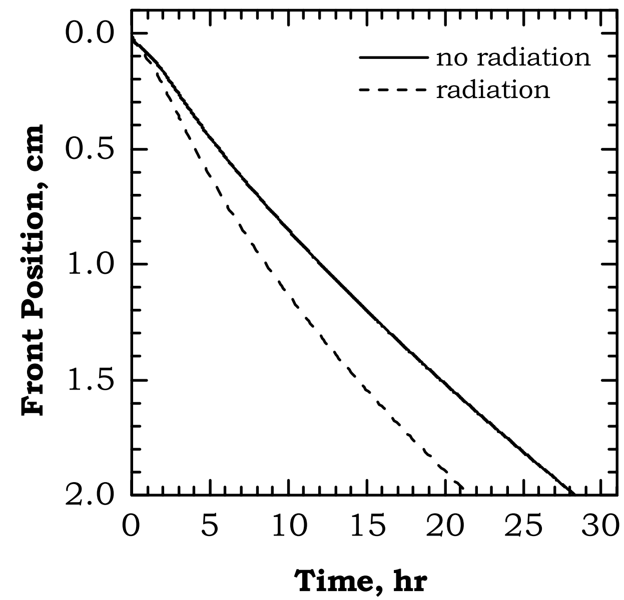
- Lower drying time
- Higher product temperature

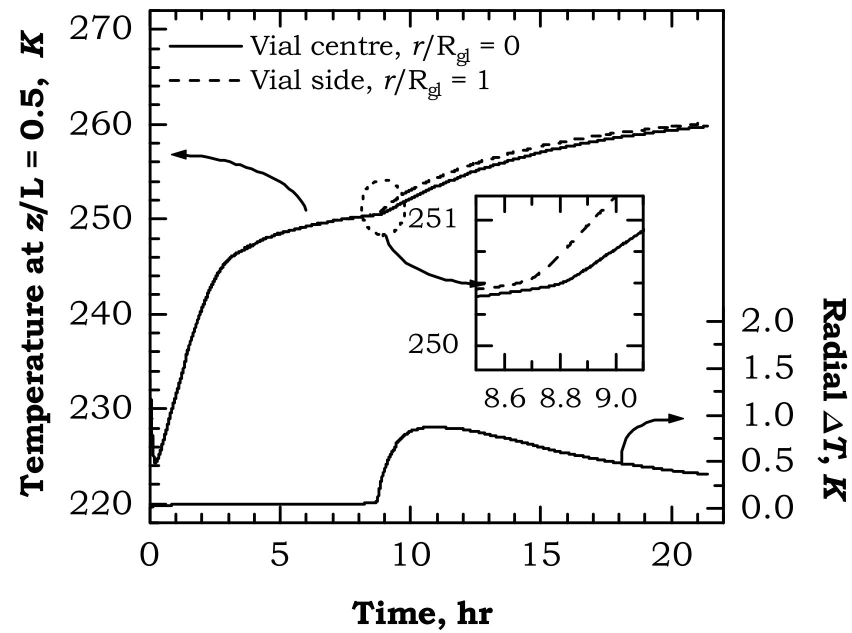
but

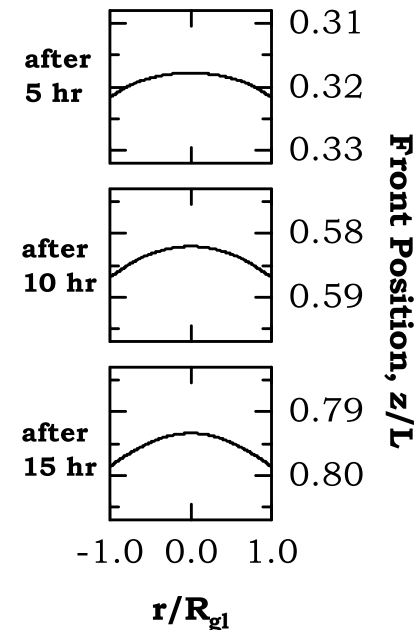
- Radial temperature difference is small
- Moving front curvature is small

Mono-dimensional approach feasible



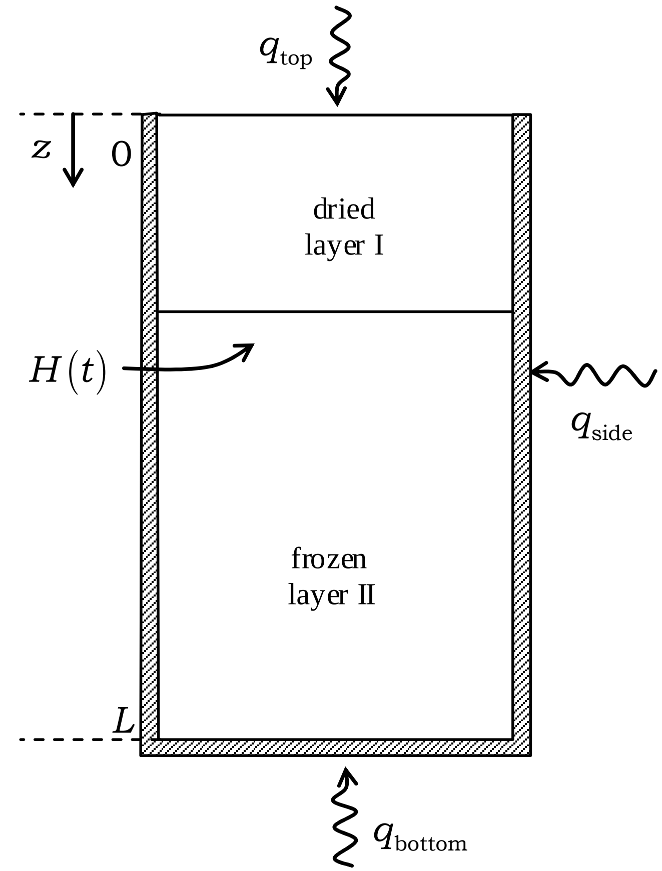






Mono-dimensional model for vial lyophilisation

- Mono-dimensional geometry forces the **moving front** to be **planar**
- **Vial sidewall heat transfer** is accounted



For the vial being in contact with the dried layer I:

$$\frac{\partial T_{\mathrm{I,gl}}}{\partial t} = +\left(\frac{\lambda_{\mathrm{gl}}}{\varrho_{\mathrm{gl}} c_{P,\mathrm{gl}}}\right)\frac{\partial^2 T_{\mathrm{I,gl}}}{\partial z^2} + \left(\frac{h_{\mathrm{I},i}}{\varrho_{\mathrm{gl}} c_{P,\mathrm{gl}}}\frac{2R_{\mathrm{gl},i}}{R_{\mathrm{gl},e}^2 - R_{\mathrm{gl},i}^2}\right)\left(T_{\mathrm{I}} - T_{\mathrm{I,gl}}\right) - + \left(\frac{1}{\varrho_{\mathrm{gl}} c_{P,\mathrm{gl}}}\frac{2R_{\mathrm{gl},e}}{R_{\mathrm{gl},e}^2 - R_{\mathrm{gl},i}^2}\right)\sigma F\left(T_{\mathrm{I,gl}}^4 - T_W^4\right)$$

For the vial being in contact with the frozen layer II:

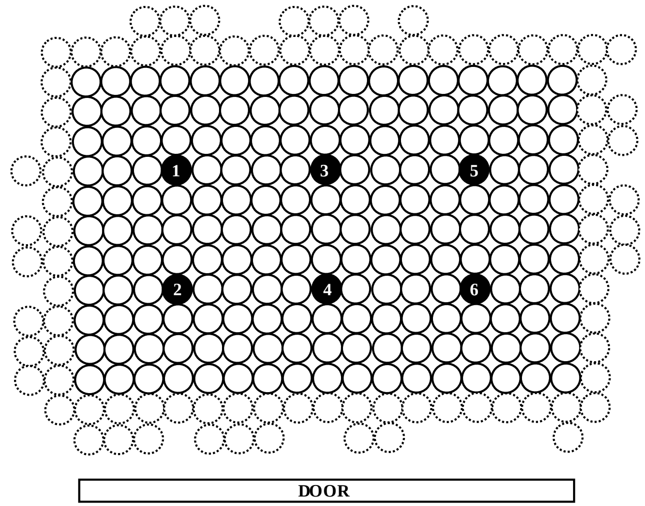
$$\frac{\partial T_{\mathrm{II,gl}}}{\partial t} = +\left(\frac{\lambda_{\mathrm{gl}}}{\varrho_{\mathrm{gl}} c_{P,\mathrm{gl}}}\right)\frac{\partial^2 T_{\mathrm{II,gl}}}{\partial z^2} + \left(\frac{h_{\mathrm{II},i}}{\varrho_{\mathrm{gl}} c_{P,\mathrm{gl}}}\frac{2R_{\mathrm{gl},i}}{R_{\mathrm{gl},e}^2 - R_{\mathrm{gl},i}^2}\right)\left(T_{\mathrm{II}} - T_{\mathrm{II,gl}}\right) - + \left(\frac{1}{\varrho_{\mathrm{gl}} c_{P,\mathrm{gl}}}\frac{2R_{\mathrm{gl},e}}{R_{\mathrm{gl},e}^2 - R_{\mathrm{gl},i}^2}\right)\sigma F\left(T_{\mathrm{II,gl}}^4 - T_W^4\right)$$

$$\xi^{\mathrm{I}} = \frac{z}{H(t)} \qquad \xi^{\mathrm{II}} = \frac{z - H(t)}{L - H(t)}$$

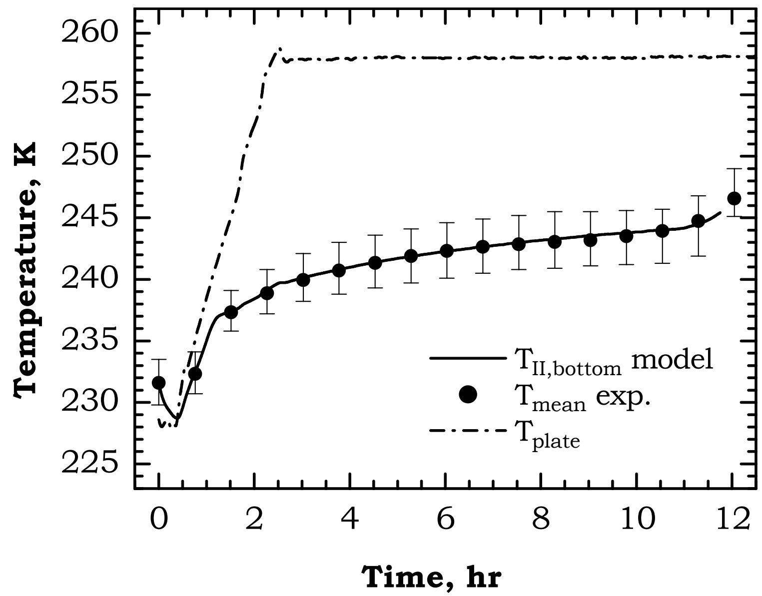
$$0 < z < H(t) \qquad H(t) < z < L$$

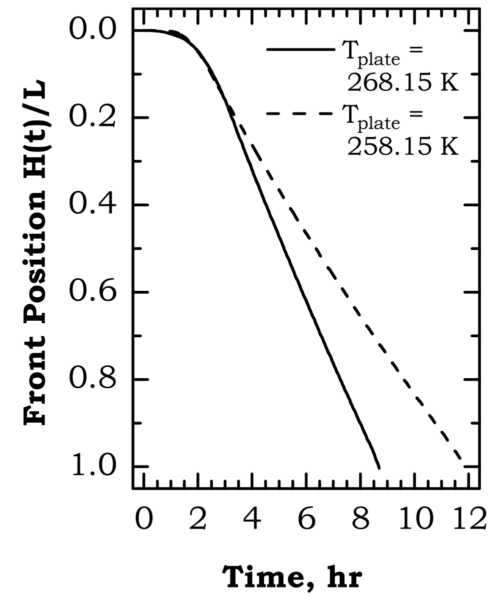
Freeze-drying of a 5 % bovine serum albumin solution (LAGEP, CPE Lyon)

- Pressure 26 Pa
- 200 vials
- 1 ml BSA solution
- 6 thermocouples measuring bottom product temperature



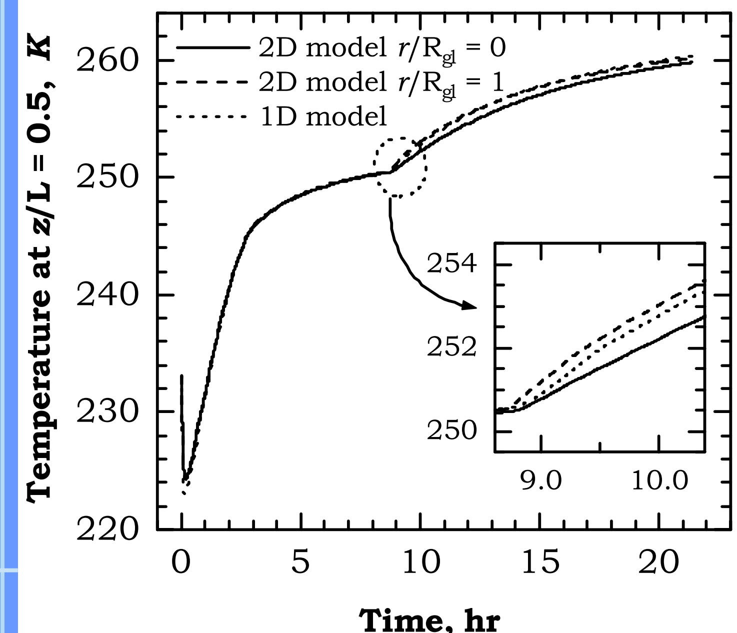
$$T_{plate} = \begin{cases} 228.15 & 0 < t < 0.5 \text{ hr} \\ 228.15 + 15(t - 0.5) & 0.5 < t < 2 \text{ hr} \\ 258.15 & t > 2 \text{ hr} \end{cases}$$

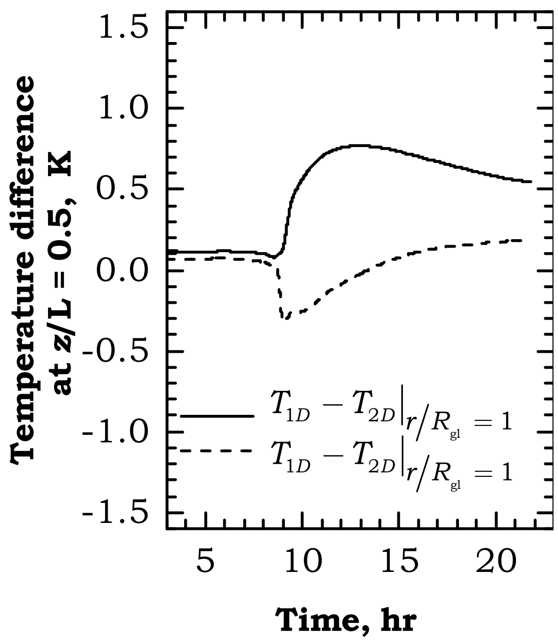


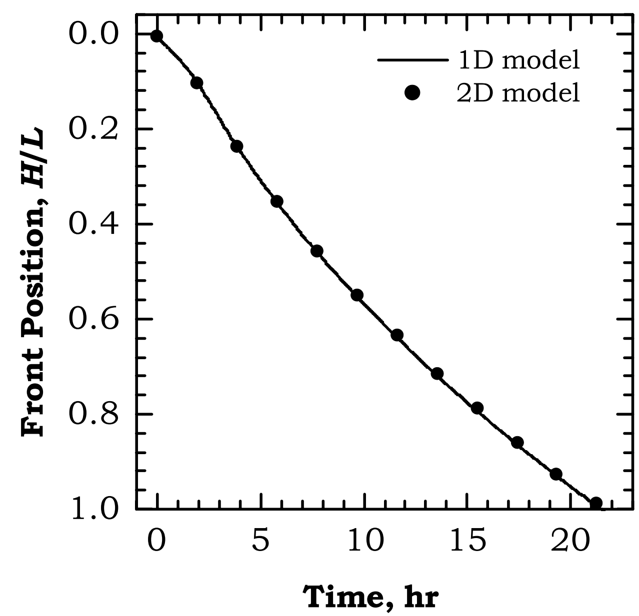


Comparison between 1D model and 2D model

- Temperature profiles of the frozen mass are practically coincident
- In the dried layer, predicted 1D temperature is comprised between the two values given by 2D model at extreme radial positions
- Maximum temperature difference between 1D and 2D model < 1°C
- Moving front evolution practically coincident







Optimal operating conditions

Optimal operating conditions (constant T_{plate})

At lower pressure

if pressure ↑
heat transfer ↑ ⇒ Drying time ↓

At higher pressure

if pressure ↑
mass transfer ↓ ⇒ Drying time ↑

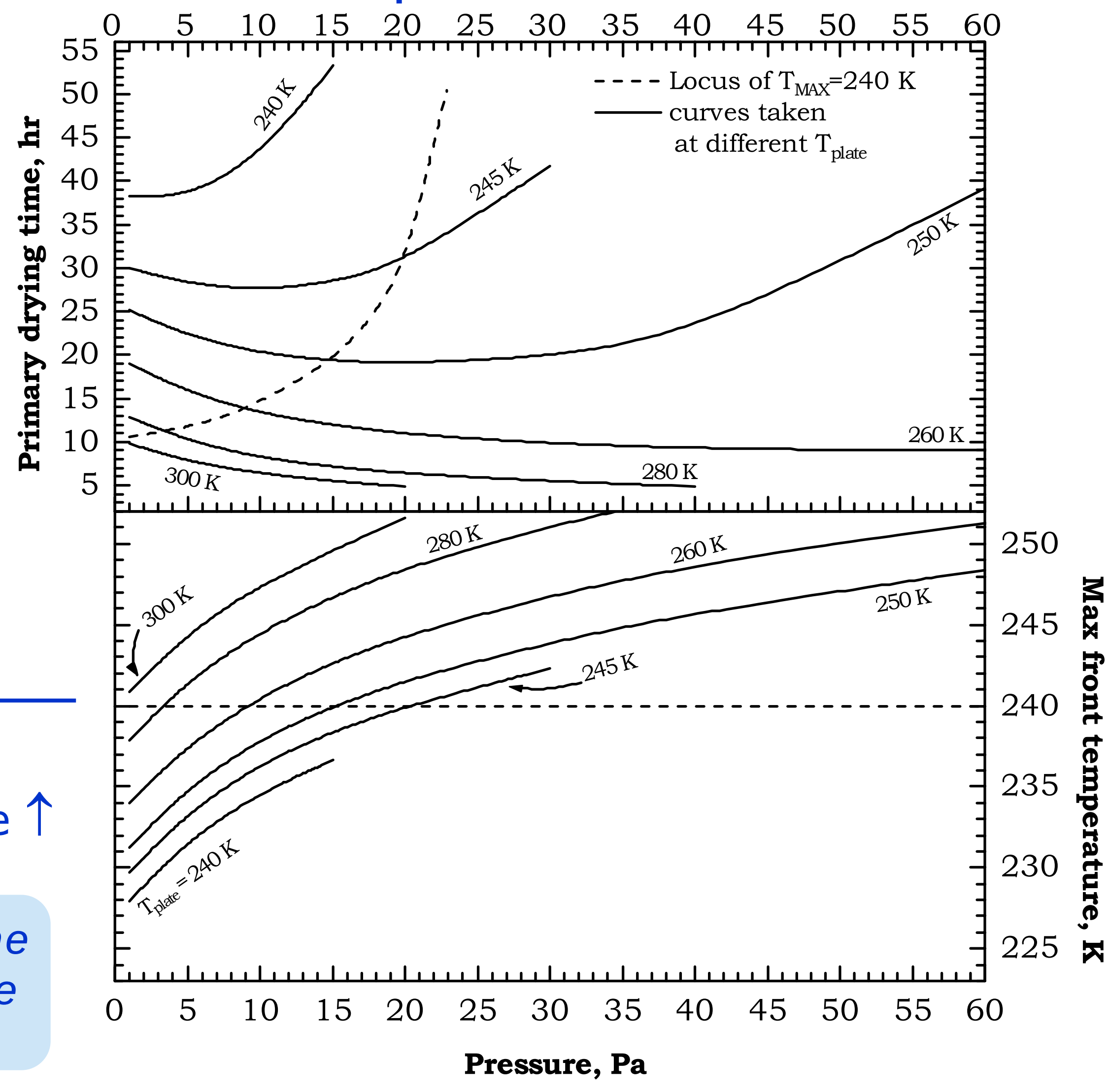
⬇

Minimum drying time

but…

if pressure ↑ ⇒ Max temperature ↑

The operative range is limited by the constraint of maximum temperature that allows safe operation



Optimal operating conditions (variable T_{plate})

When maximum allowable temperature is approached → **Plate temperature is regulated in such a way that $T_{i,max}$ is never overcome**

$$T_{\text{plate}}(t) = f\left(T_{\text{i,MAX}}, t, \ldots\right)$$

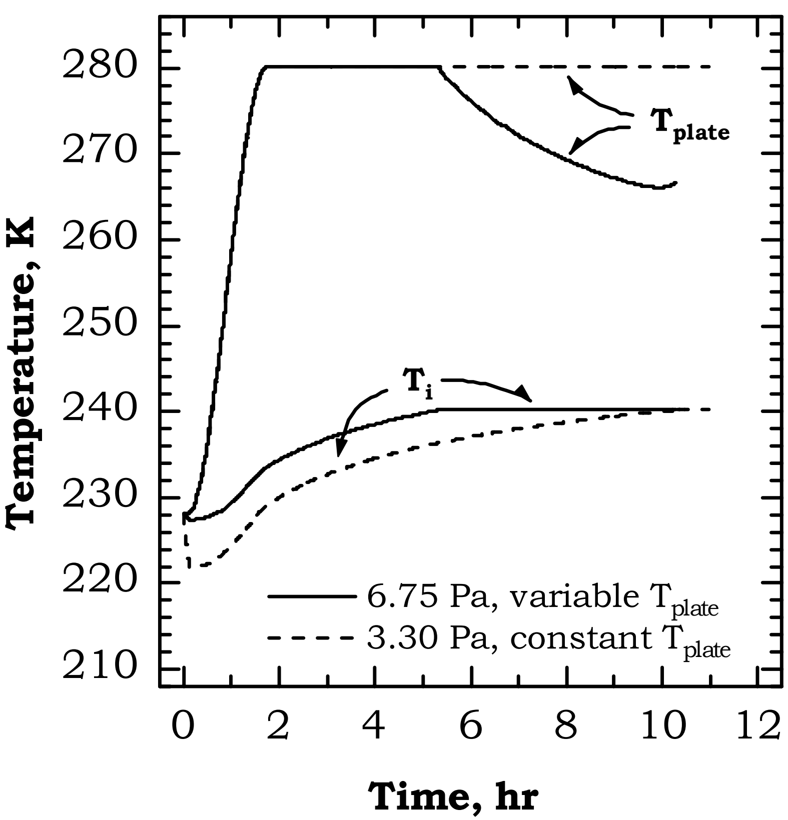
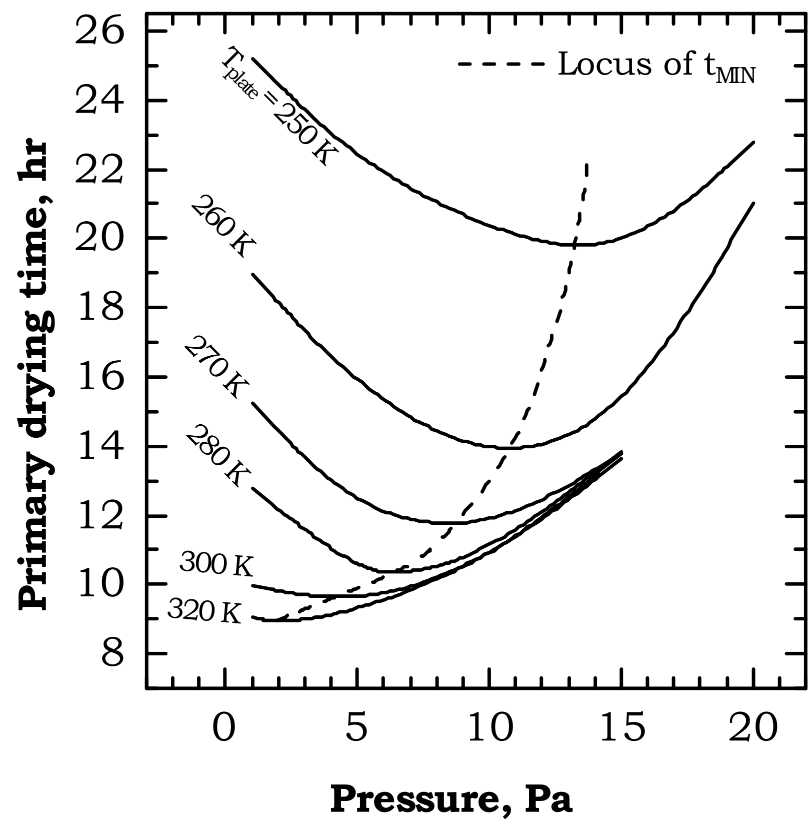


Chart of operating conditions, $T_{i,max}$ constraint is always satisfied



Monitoring and control

Technological innovation of freeze-drying in Lyo-Pro

A new analytical balance that permits to evaluate the mass of the product during the process

Use of the mass spectrometry to identify any anomaly in the process

Primary drying should be carried on at a **controlled sublimation temperature** in order **to avoid denaturation of the product**.

But front temperature can not be directly measured

Use of model-based estimators (soft sensors) and indirect non-invasive methods to monitor, control and optimize the process

example:

Manometric Temperature Measure

Manometric Temperature Method (or Pressure Rise Analysis)

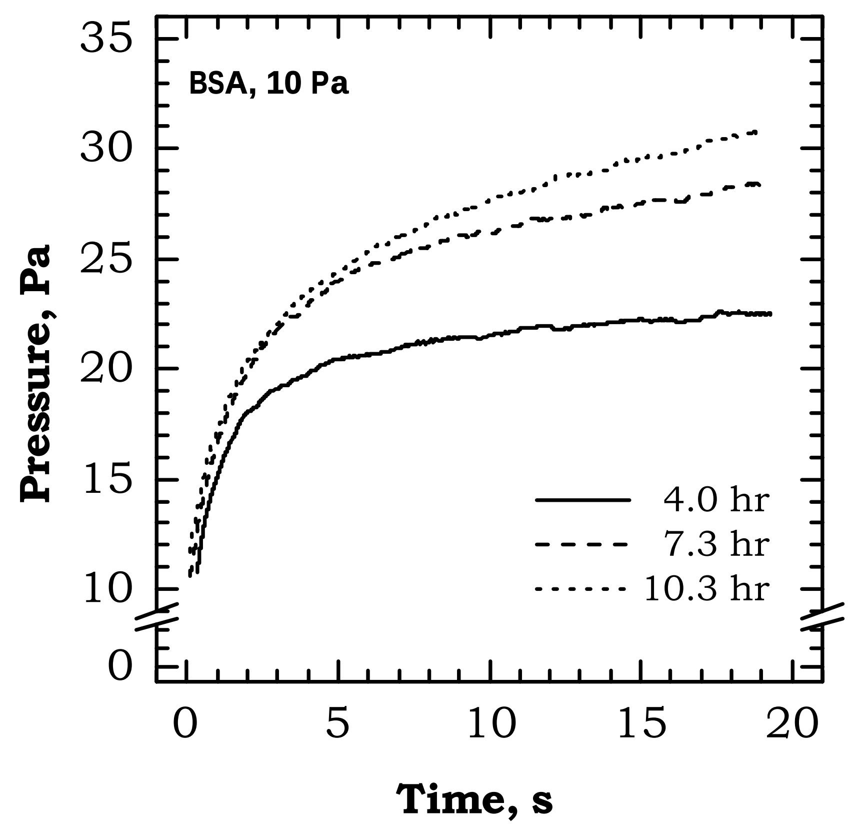
• Remote sensing procedure for **determining the temperature of the moving front** at different times during the primary drying stage

• The valve separating chamber and condenser is closed (≈20 seconds) and the chamber pressure increases

MTM is currently adopted in some units. Chamber pressure is assumed to reach equilibrium and sublimation T is calculated through thermodynamics

but

Effect of "drift" limits MTM test duration (otherwise product can be damaged)



Modified Manometric Temperature Method

A new approach to the description of the phenomena occurring during the MTM test

- The new model relates the measured pressure rise dynamics to the front temperature
- Time evolution of the product temperature is considered

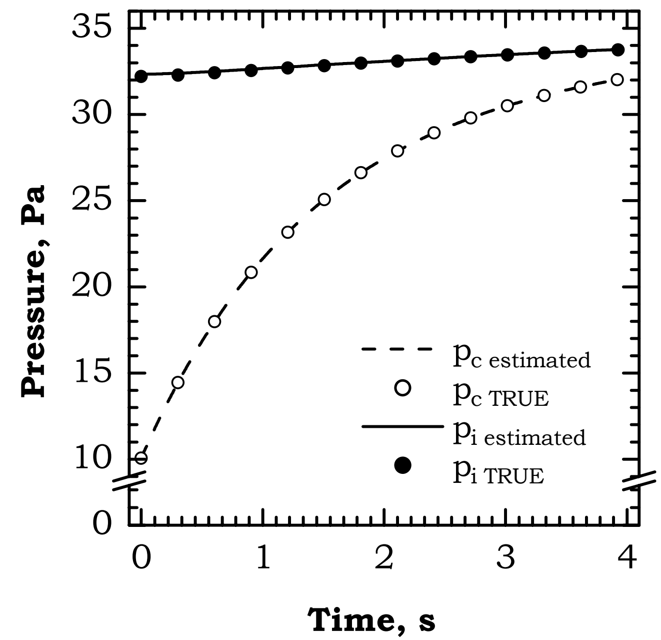
$$\begin{cases} \dfrac{dp_{\mathrm{w,c}}}{dt} = \dfrac{NA}{V}\dfrac{RT_c}{M_{\mathrm{w}}}\dfrac{1}{R_{\mathrm{P}}}\left(p_{\mathrm{i}}\left(T_{\mathrm{i}}\right) - p_{\mathrm{w,c}}\right) \\ \dfrac{\partial T}{\partial t} = \dfrac{k_{\mathrm{frozen}}}{\rho_{\mathrm{frozen}} c_{\mathrm{p,frozen}}}\dfrac{\partial^2 T}{\partial z^2} \end{cases}$$

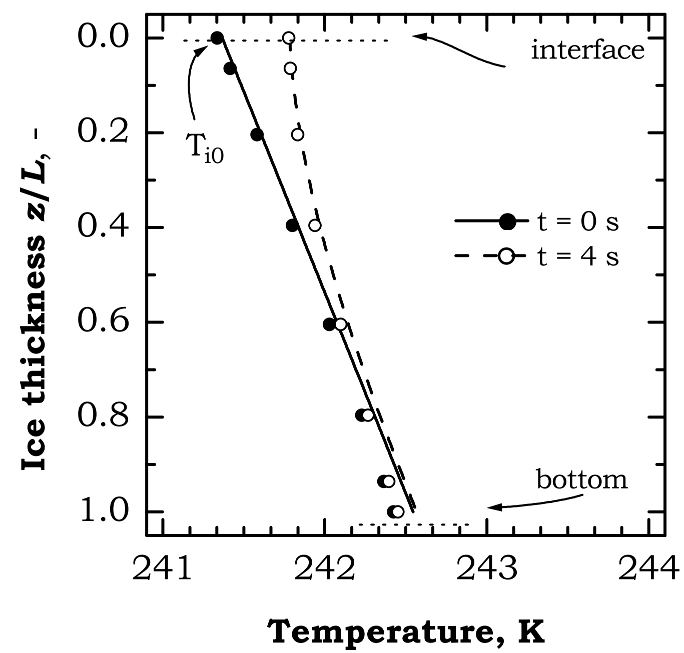
- Non-linear optimization problem is solved

$$\min_{T_{\mathrm{i0}}, R_{\mathrm{P}}} \tfrac{1}{2}\left\| p_{\mathrm{c}}\left(T_{\mathrm{i0}}, R_{\mathrm{P}}\right) - p_{\mathrm{c,measured}} \right\|_2^2$$

Front temperature $T_{\mathrm{i,0}} = T\big|_{\substack{z=0 \\ t=0}}$

Mass transfer resistance R_{P}





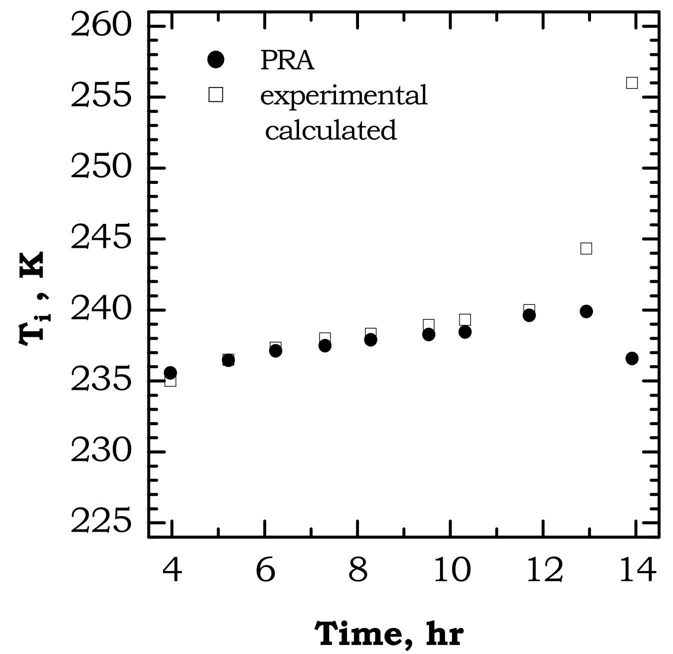
Modified Manometric Temperature Method

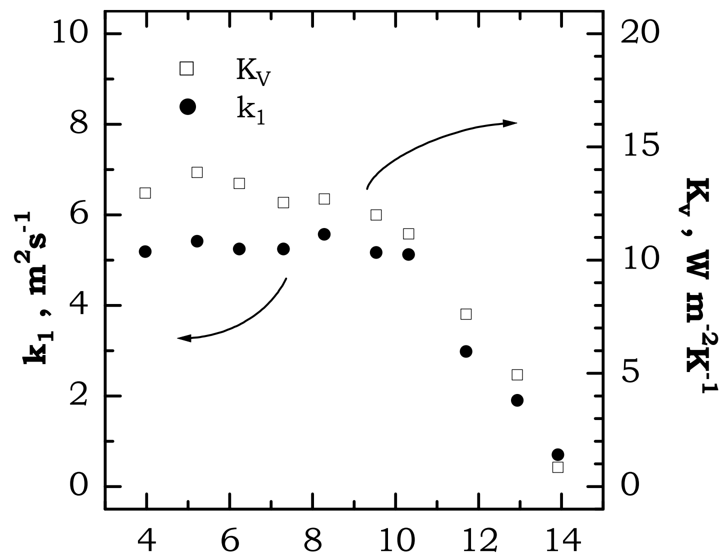
- MTM is repeated several times to provide an estimation of Ti through all primary drying
- From model equations we can also determine:

k_1	mass transfer coefficient
K_v	heat transfer coefficient at the vial bottom
L	ice thickness
$T(z)$	temperature profile along the frozen mass

- ***Limitation:***
  MTM is a global method, vials are considered as a whole

→ **if there are large heterogeneities between vials, MTM measure is inaccurate (end of primary drying)**





$$k_{1,\text{experimental}} = 5.3 \cdot 10^{-3}\ \text{m}^2 s^{-1}$$

Control

• Regulatory guidance do not allow closed loop in manufacturing processes (in a validated process all cycles must be the same)

→ Only monitoring is possible in manufacturing, used as a "process record" to know that cycles are reproducible

• During cycle development (pilot / lab scale freeze-driers) no regulatory limitations apply, closing loop is possible

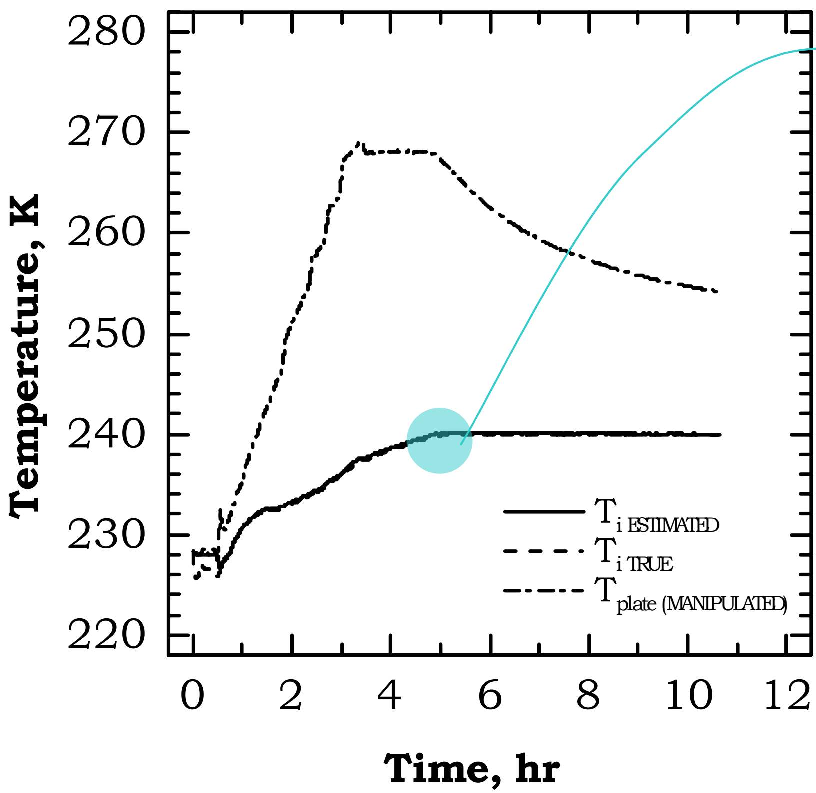
MTM or soft-sensor for estimation of T_i can be inserted in a feedback loop → control the product temperature in real time preventing product degradation, maximize heat input

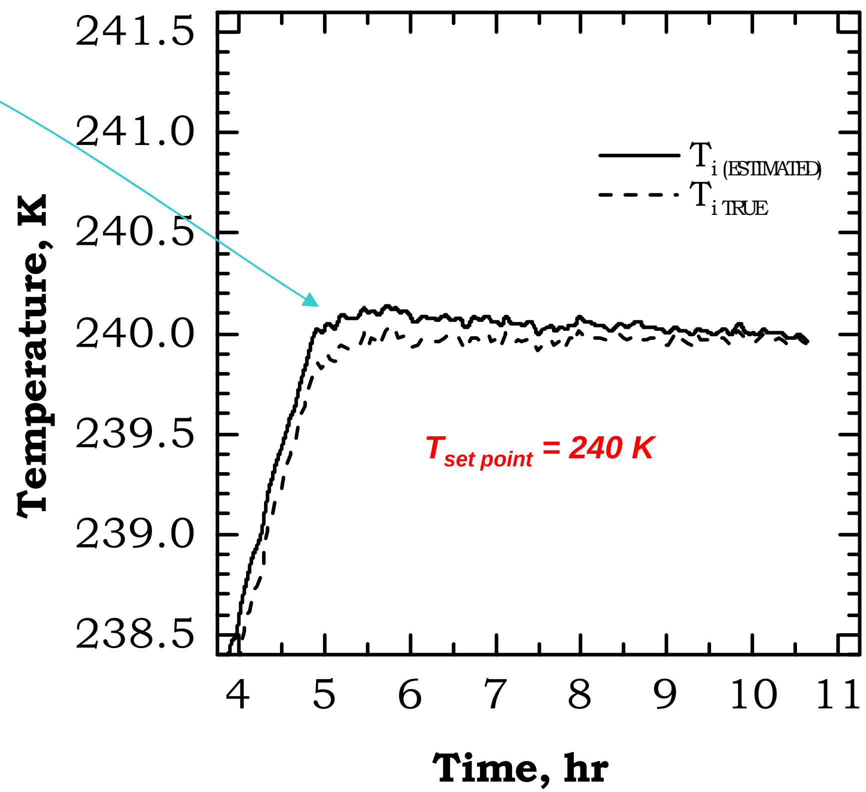
Output feedback control (5% BSA solution)

The temperature of the moving front is controlled by manipulating the temperature of the heating plate T_{plate}

A Proportional-Integral (PI) controller has been implemented

$$T_{\text{plate}}(t) = K\left(\hat{T}_{\text{i}}(t), T_{\text{i,MAX}}, \ldots\right) \Rightarrow T_{\text{plate}}(t) = -k_{\text{P}}\left(\hat{T}_{\text{i}}(t) - T_{\text{i,MAX}}\right) - \frac{1}{k_{\text{I}}}\int\left(\hat{T}_{\text{i}}(t) - T_{\text{i,MAX}}\right)dt + T_{\text{plate,0}}$$





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more slides...

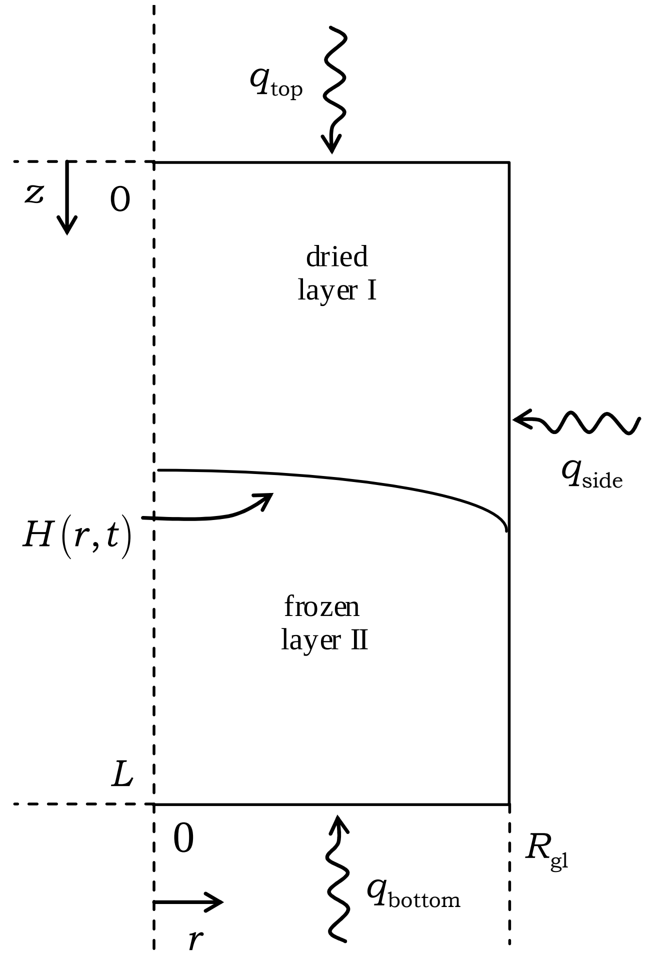
Bi-dimensional model for vial lyophilisation

- Transient material and energy balances
- Spatial and time evolution of:

  - ***Dried Layer I Temperature***
  - ***Frozen Layer II Temperature***
  - ***Water vapour pressure***
  - ***Inert pressure***
  - ***Bound water concentration***

and moving sublimating interface:

  - ***Position***
  - ***Velocity***
  - ***Temperature***



Bi-dimensional model for vial lyophilisation

- **Moving boundary or Stefan problem**

→ **Time changing spatial grid would be required**
Problems arise in time integration

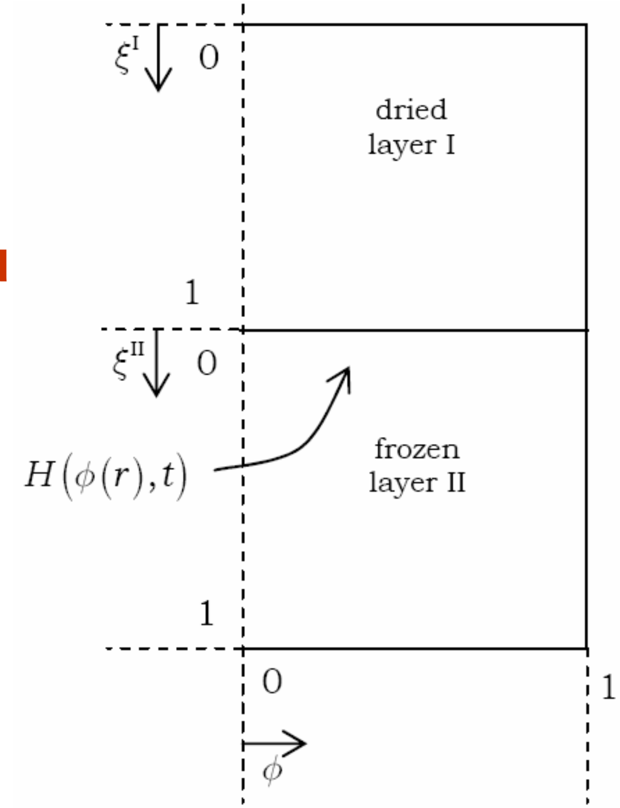
- ***Front-fixing* resolution method**

→ **Spatial grid fixed in time through a mathematical artifice**

→ **Complex mathematical formulation**

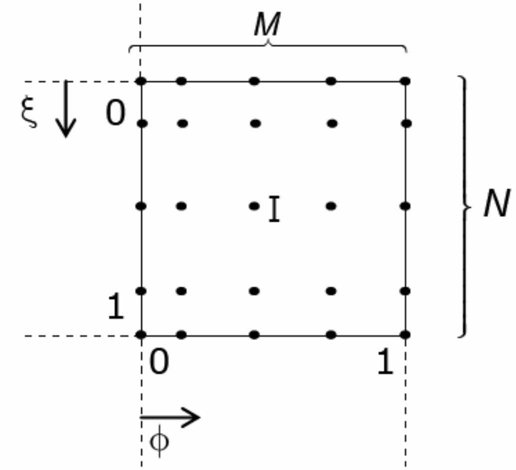
$$\xi^{\mathrm{I}} = \frac{z}{H(r,t)} \qquad \xi^{\mathrm{II}} = \frac{z - H(r,t)}{L - H(r,t)} \qquad \phi = \frac{r}{R_{\mathrm{gl}}}$$

$$0 < z < H(r,t) \qquad H(r,t) < z < L \qquad 0 < r < R_{\mathrm{gl}}$$



- **Orthogonal collocations**; spatial derivatives are determined via differentiation matrixes

- **Non-uniform N x M grid**

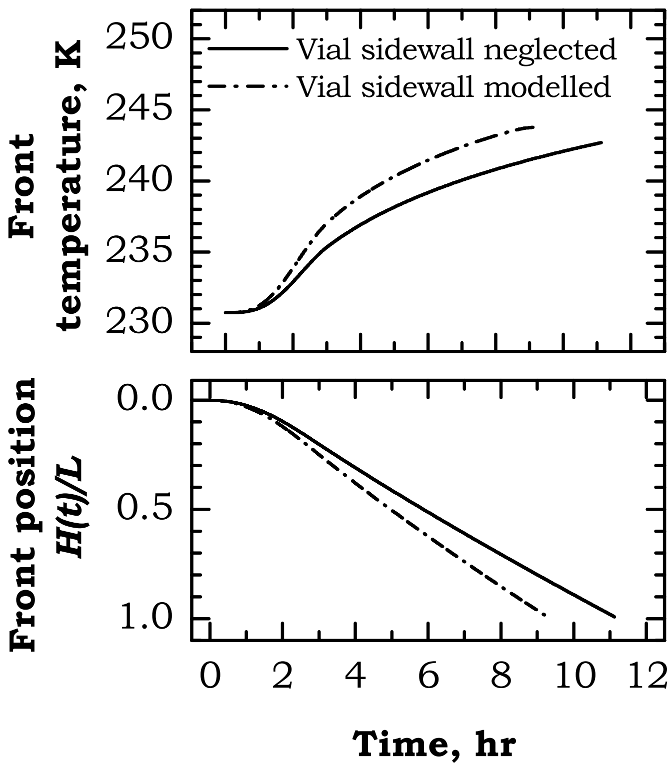


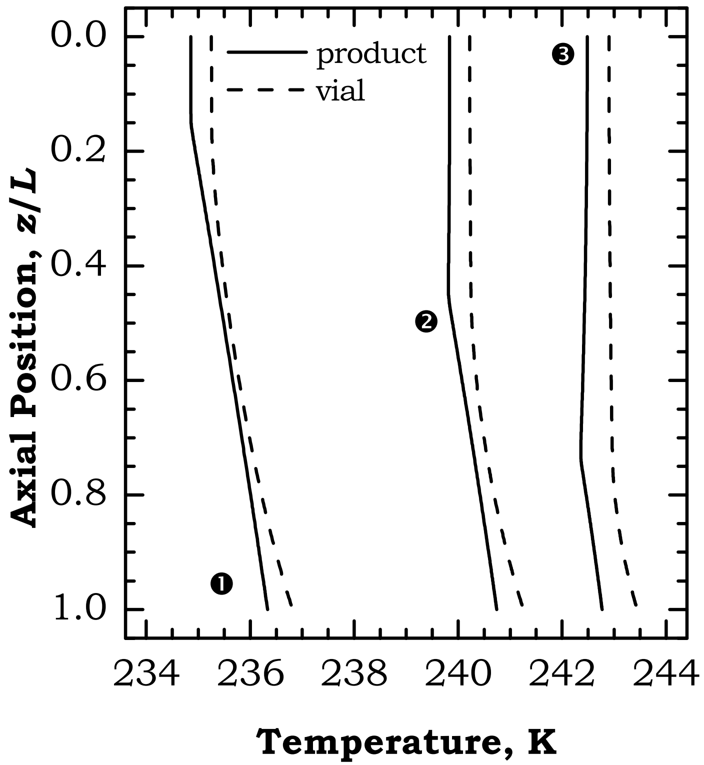
Heat transfer in the vial sidewall

- Energy provided by the heating plate is exchanged with the product mainly at the bottom and in part at the vial side

Lower drying time, Higher product temperature

Analogous effect of radiation on drying time and product temperature, but at a minor extent





Simplified models for real-time applications

Simplified models for real-time monitoring of primary drying

Detailed transient models of the process require:

→

Computational power

A large number of parameters, not always easily accessible

↓

Simplified models have been set up easier to implement for real time monitoring and control

Main hypothesis

- Pseudo-steady state conditions
- Radiation is neglected

→ Vials well shielded from edge effects

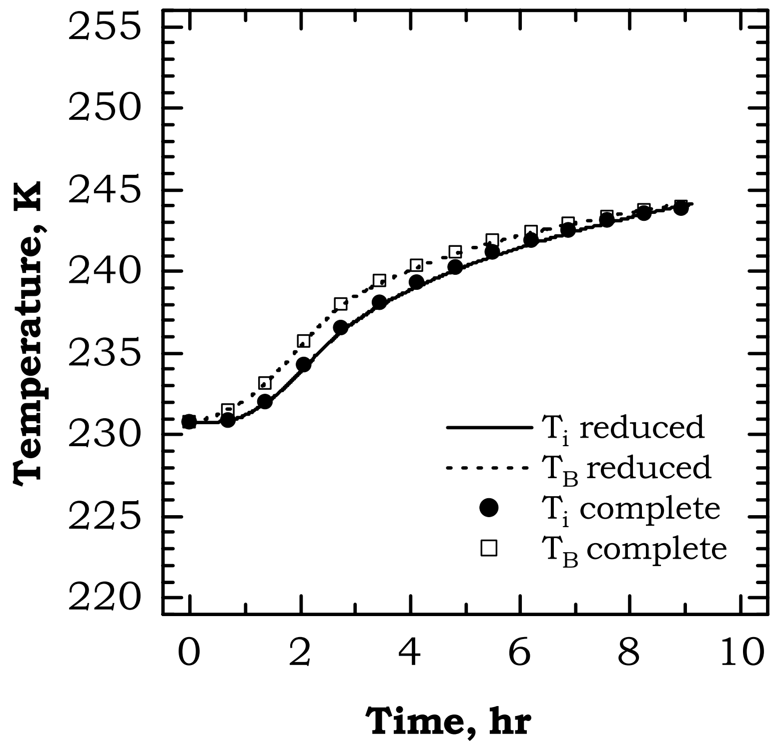
Simplified model I

- **Vial sidewall is not accounted for**
- Dynamic behaviour is retrieved by mass balance across the moving front
- Only 1 Ordinary differential equation
- Fast solution

$$\frac{dH}{dt} = \frac{1}{\varrho_{\mathrm{II}} - \varrho_{\mathrm{I}}} \frac{M}{RT_{\mathrm{i}}} \frac{k_1}{H} \left(p_{\mathrm{w,i}}\left(T_{\mathrm{i}}\right) - p_{\mathrm{w,c}} \right)$$

$$\left(\frac{1}{K_{\mathrm{v}}} + \frac{L-H}{k_{II}} \right)^{-1} \left(T_{\mathrm{plate}} - T_{\mathrm{i}} \right) = \frac{\Delta H_{\mathrm{s}} M}{RT_{\mathrm{i}}} \frac{k_1}{H} \left(p_{\mathrm{w,i}}\left(T_{\mathrm{i}}\right) - p_{\mathrm{w,c}} \right)$$

$$T_{\mathrm{II,b}} = T_{\mathrm{plate}} - \frac{1}{K_{\mathrm{v}}} \left(\frac{1}{K_{\mathrm{v}}} + \frac{L-H}{k_{II}} \right)^{-1} \left(T_{\mathrm{plate}} - T_{\mathrm{i}} \right)$$



Simplified model II

The simplified **balances can be integrated *analytically*** in order to get the equations for the temperature profiles along the product and along the vial sidewall

$$T_{\mathrm{I}} = -2(1-a_{\mathrm{I}})C_3\cosh(\alpha_{\mathrm{I}}H\xi) + a_{\mathrm{I}}C_6 \qquad T_{\mathrm{II}} = -(1-a_{\mathrm{II}})\left(C_1 e^{-\alpha_{\mathrm{II}}(L-H)\vartheta} + C_2 e^{\alpha_{\mathrm{II}}(L-H)\vartheta}\right) + a_{\mathrm{II}}(C_4\vartheta + C_5)$$

$$T_{\mathrm{I,gl}} = +2a_{\mathrm{I}}C_3\cosh(\alpha_{\mathrm{I}}H\xi) + a_{\mathrm{I}}C_6 \qquad T_{\mathrm{II,gl}} = +a_{\mathrm{II}}\left(C_1 e^{-\alpha_{\mathrm{II}}(L-H)\vartheta} + C_2 e^{\alpha_{\mathrm{II}}(L-H)\vartheta}\right) + a_{\mathrm{II}}(C_4\vartheta + C_5)$$

$$C_1 - C_2 + C_4\left(\frac{1}{\alpha_{\mathrm{II}}(L-H)}\frac{a_{\mathrm{II}}}{1-a_{\mathrm{II}}}\right) = \frac{b_2}{\alpha_{\mathrm{II}}(1-a_{\mathrm{II}})}$$

$$C_1 + C_2 - C_3\left[2\frac{a_{\mathrm{I}}}{a_{\mathrm{II}}}\cosh(\alpha_{\mathrm{I}}H)\right] + C_5 - C_6\left(\frac{a_{\mathrm{I}}}{a_{\mathrm{II}}}\right) = 0$$

$$C_1 - C_2 + C_3\left[2\frac{a_{\mathrm{I}}\alpha_{\mathrm{I}}}{a_{\mathrm{II}}\alpha_{\mathrm{II}}}\frac{L-H}{H}\sinh(\alpha_{\mathrm{I}}H)\right] - C_4\left(\frac{1}{a_{\mathrm{II}}}\right) = 0$$

$$C_1\left(-\frac{c_{\mathrm{II}}-\alpha_{\mathrm{II}}}{c_{\mathrm{II}}}e^{-\alpha_{\mathrm{II}}(L-H)}\right) + C_2\left(\frac{c_{\mathrm{II}}+\alpha_{\mathrm{II}}}{c_{\mathrm{II}}}e^{\alpha_{\mathrm{II}}(L-H)}\right) + C_4\left(1 + \frac{1}{c_{\mathrm{II}}(L-H)}\right) + C_5 = \frac{T_{\mathrm{plate}}}{a_{\mathrm{II}}}$$

$$C_1 + C_2 - C_3\left[2\frac{1-a_{\mathrm{I}}}{1-a_{\mathrm{II}}}\cosh(\alpha_{\mathrm{I}}H)\right] - C_5\left(\frac{a_{\mathrm{II}}}{1-a_{\mathrm{II}}}\right) + C_6\left(\frac{a_{\mathrm{I}}}{1-a_{\mathrm{II}}}\right) = 0$$

$$C_1\left(\frac{c_{\mathrm{II,gl}}-\alpha_{\mathrm{II}}}{c_{\mathrm{II,gl}}}e^{-\alpha_{\mathrm{II}}(L-H)}\right) + C_2\left(\frac{c_{\mathrm{II,gl}}+\alpha_{\mathrm{II}}}{c_{\mathrm{II,gl}}}e^{\alpha_{\mathrm{II}}(L-H)}\right) + C_4\left(\frac{L-H+c_{\mathrm{II,gl}}}{c_{\mathrm{II,gl}}}\right) + C_5 = \frac{T_{\mathrm{plate}}}{a_{\mathrm{II}}}$$

To complete the model the boundary conditions must be applied, given by the following set of ***linear* equations**. The ***analytical* solution** of the system gives the integration constants C_1…C_6.

The various parameters in the equations are function of H, T_i, K_v, k_1, geometry and thermal properties of the vial/product.

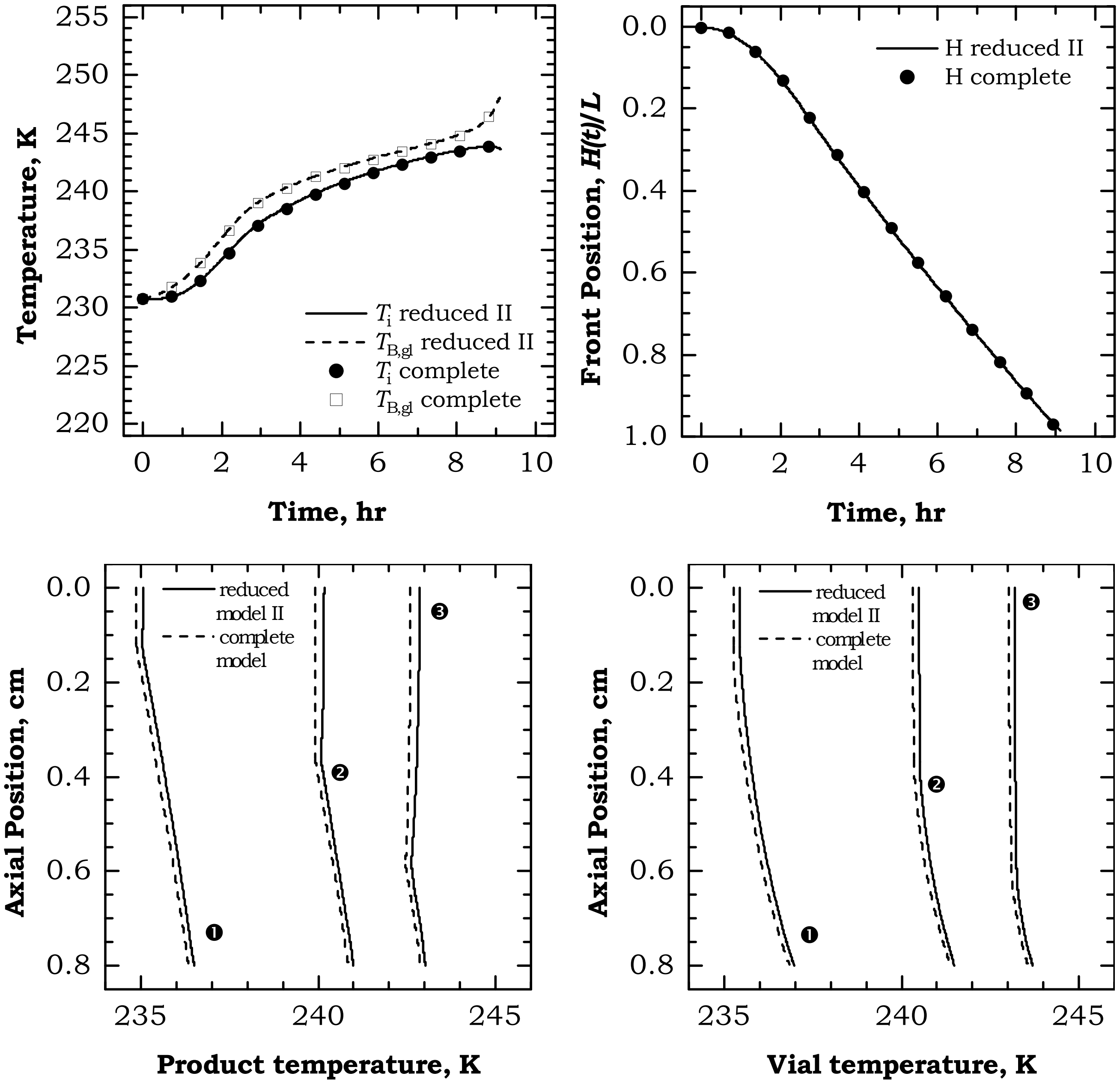
Simplified model II

- Vial sidewall is modelled

- Dynamics of:

  Front temperature
  Vial glass temperature
  Front position

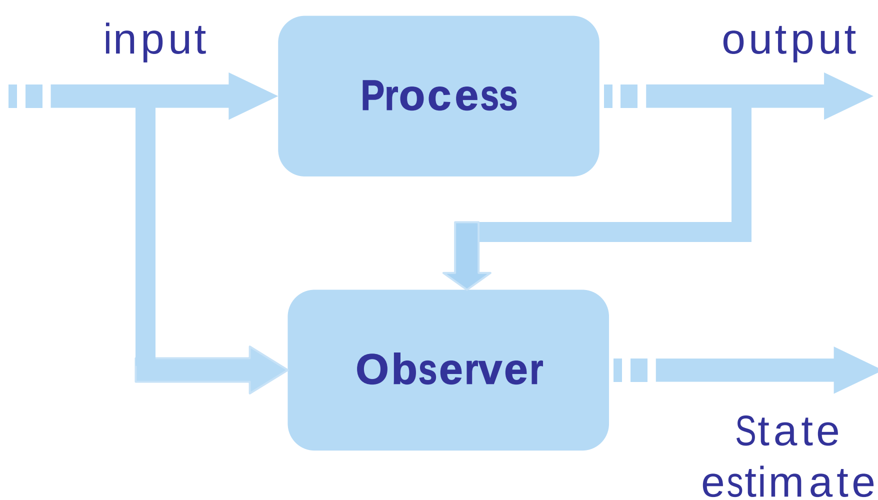
❶ t = 2.25 hr
❷ t = 4.5 hr
❸ t = 6.8 hr



Soft-sensors (observers)

In many engineering applications it is desirable to have **estimates of hard-to-measure or non-measurable quantities**.

An **observer** combines *a priori* knowledge about the physical system (**mathematical model**) with experimental data (**on-line measurements**) to provide an on-line estimation of the sought quantities.



Process

$$\dot{x} = f(x)$$
$$y = h(x)$$

Observer

$$\dot{\hat{x}} = f(\hat{x}) + K(\hat{y} - y)$$
$$\hat{y} = h(\hat{x})$$

correction

Soft-sensors (observers)

Primary drying should be carried on at a **controlled sublimation temperature** in order **to avoid denaturation of the product.**

Problem: ***front temperature can not be directly measured***

From simplified models →

- Non-linear observers (***Extended Kalman Filter***, ***High Gain Observer***) to estimate T_i on-line
- unknown heat and mass transfer parameters

Different typologies of observers (EKF, HG) → Different approaches to determination of the corrective term (gain)

Improvement of the control system

In order to improve both quality and reproducibility some objectives should be fulfilled:

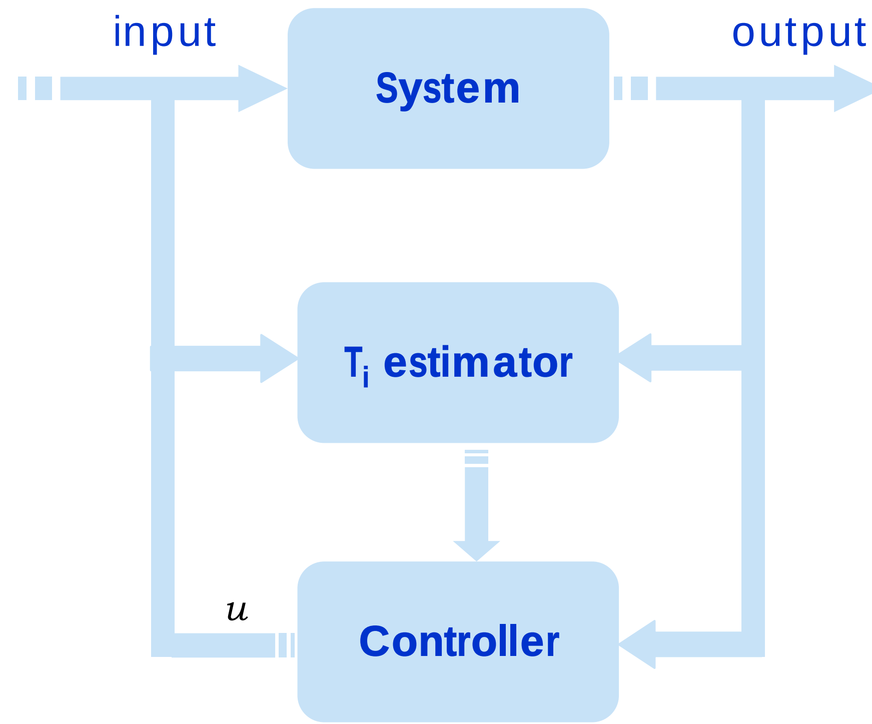
Objectives

- **Control the product end-use properties**
- **Develop a fault diagnosis software for controlling the process, detecting problems on-line and preventing large degradation**
- **Develop a software, based on remote sensing tools (soft-sensors, manometric temperature measurements) for the quality estimation of the end-use product**

Closed-loop control (for cycle development)

MTM or soft-sensor for estimation of Ti can be inserted in a feedback loop

It is possible to control the product temperature in real time preventing product degradation



Estimated T_i

$$u(t) = K\left(\hat{T}_i(t), p(t)\right)$$

Controller law (PI, MPC, …)

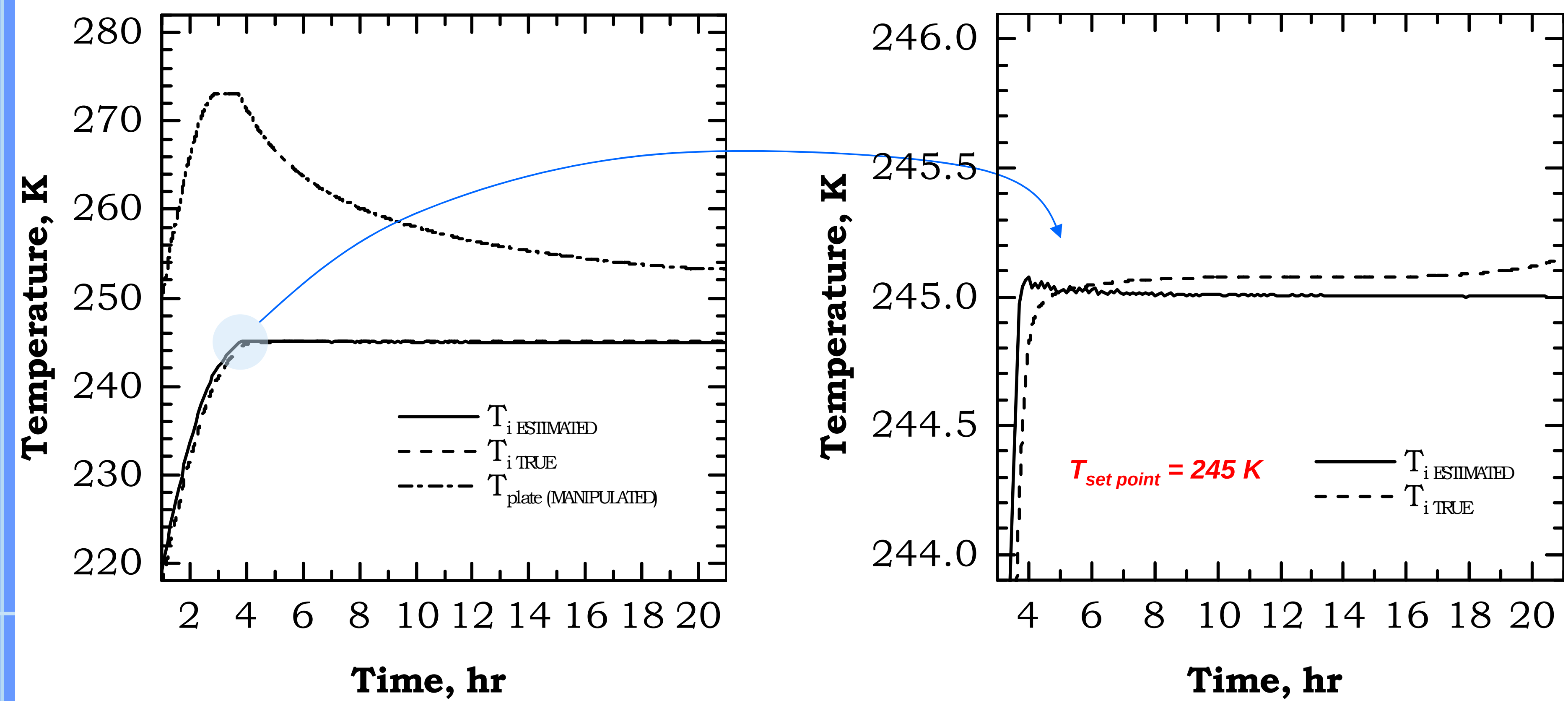
Constraints

Closed-loop control (skim milk)

The temperature of the moving front is controlled by manipulating the temperature of the heating plate T_{plate}

A conventional Proportional-Integral (PI) controller has been implemented

Controller tuning according to MIN of ISE: $\min_{K_P, K_I}(ISE) = \min_{K_P, K_I} \int_{t_0}^{t} \left(T_{i,\text{predicted}}(\tau) - T_{i,\text{MAX}}\right)^2 d\tau$



Lyo-Pro
Competitive and Sustainable Growth European Project

Innovative nucleation technology

The first prototype of freeze-dryer with the nucleation technology created by Asymptote and Telstar Industrial