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Model based process engineering: Recent advances in freeze-drying

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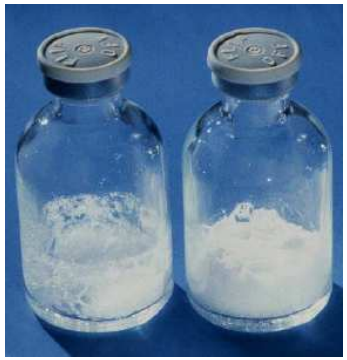
LYO LAB Research Team

Introduction

In a freeze-drying process it is mandatory to guarantee product quality.

To this purpose, product temperature has to be maintained below a maximum value, corresponding to the *eutectic point* in case of solutes that crystallize (in order to avoid the formation of a liquid phase), or to the *glass transition temperature* in case of solutes (e.g. proteins) that remain amorphous (in order to avoid the collapse of the cake structure).

Residual humidity and batch uniformity are very important

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Introduction – PAT Guideline US-FDS 2004

The scientific, risk-based framework outlined in this Guidance, is intended to **support innovation** and **efficiency** in pharmaceutical development, manufacturing, and quality assurance.

Manufacturers are encouraged to use the **latest scientific advances** in pharmaceutical manufacturing and technology.

PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.

Quality cannot be tested into products; it should be **built-in** or should be **by design**.

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Introduction

To get these results we need:

- an efficient **monitoring system** to measure product temperature and the residual water content (to establish the end of the primary drying);

- to **understand both process and equipment**, to be able to evaluate the effect of modifications in process conditions and equipment characteristics on final product properties;

- possibly an efficient **control system** that
    - optimizes the drying process,
    - takes into account the constraints on the product quality,
    - takes into account the characteristics of the equipment (heating/cooling rates),
    - manages the process if something goes wrong.

Both the monitoring and the control system have to take into account **batch heterogeneity**.

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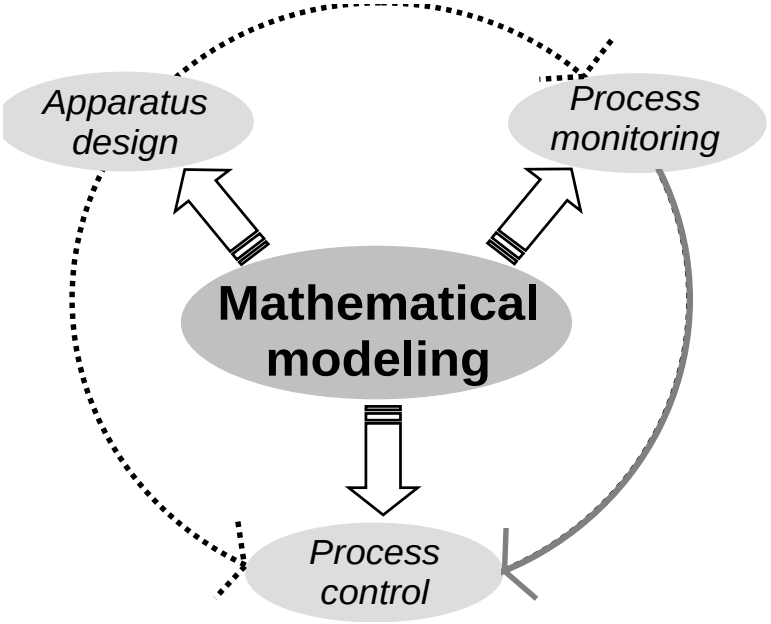
The model based approach

A model-based approach can be the solution!:



Model Based PAT tools based on measurement of:

- **product T (*soft-sensors*)**
- **chamber pressure (*Pressure Rise Tests*)**
- **sublimation flux (*TDLAS, valvless monitoring,*.)**

see Section 3

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The model based approach

Goals:

- Off-line optimization
- To control a production cycle
  - Minimization of the duration of the primary drying
  - Preservation of the product quality
  - Disturbance rejection: self-adaptive control system to compensate changes in the operating conditions
  - Batch unevenness evaluation
- Finding the optimal heating strategy in a single test (“cycle development”)
- Process transfer and scale up
- Optimized equipment design

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Outline

- **1. Mathematical modeling**
- **2. Quality by Design:**
  - Design space for primary drying and secondary drying;
  - effect of uncertainty; estimation of consequences of process failure
- **3. Process monitoring for primary and secondary drying**
  - Use of model based monitoring devices and soft-sensors (DPE+, PDT, valvless monitoring systems, SD monitoring)
- **4. Process control**
  - Model based control systems (LyoDriver, MPC, soft-sensor ideal control, hybrid control system)
- **5. Process design: cycle development and optimization**
- **6. Process understanding and process transfer**
- **7. Equipment design and optimization**

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1. Mathematical modeling

- A suitable model has to be selected, taking into account the complexity of the process, as well as the parameters that must be determined.
- The “quality” of the prediction can depend more on the uncertainty of the parameters, than on the complexity of the model.

The best material model of a cat is another, or preferably the same, cat (Wiener & Rosenblueth)

A theory has only the alternative of being right or wrong. A model has a third possibility: it may be right, but irrelevant (Egan)

- The level of detail must be chosen according to the final use.
- The time required for process simulation should be short, in particular when the model is used for an in-line optimization.

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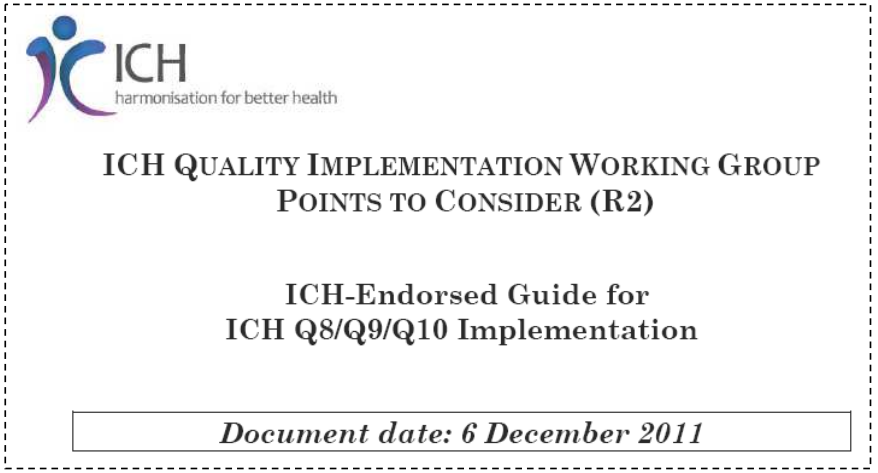
1. Mathematical modeling



- Low-Impact Models
- Medium-Impact Models
- High-Impact Models

They are typically used to support product and/or process development.

They can be useful in assuring quality of the product but are not the sole indicators of product quality.

Their prediction is a significant indicator of quality of the product.

1. Mathematical modeling

- **1D model generally reliable for primary drying (taking into account wall contribution)**

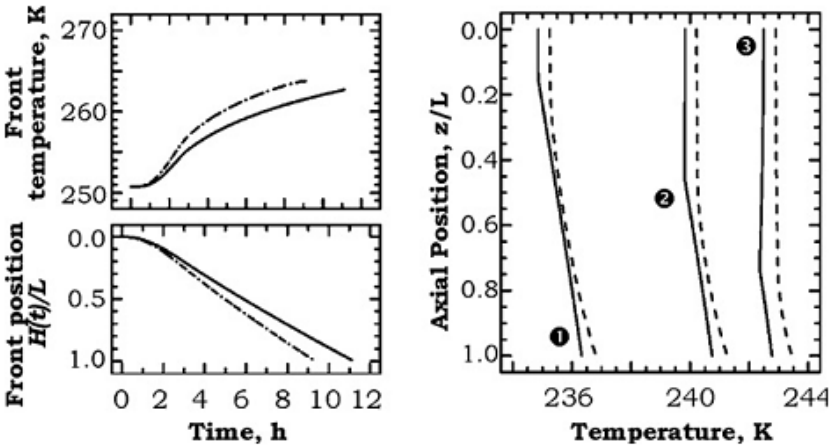


Fig. 5 – (Left hand side) Moving front temperature and position during the primary drying phase neglecting radiation. Solid line (—): case 1, wall influence neglected; dashed-dotted line (– · – · –): case 2, wall influence accounted for. (Right hand side) Temperature profiles along the product (—) and the vial glass (– – –), in case 2. Profiles are taken at three different times during primary drying: (1) 2.25 h, (2) 4.5 h, and (3) 6.8 h.

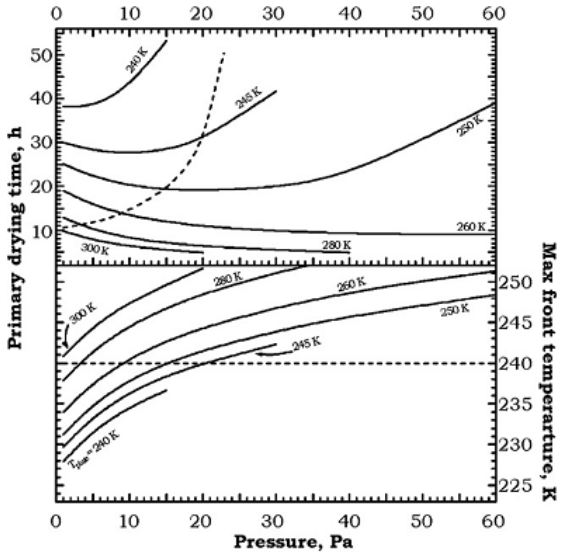


Fig. 6 – Effect of the chamber vapour pressure and of the heating plate temperature on the primary drying time (on the top) and on the maximum front temperature (bottom plot). Solid lines (—): curves taken at different T_{shelf}; dashed lines (– – –): locus of T_{MAX} = 240 K.

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1. Mathematical modeling

- **Semplified models required for monitoring and control purposes**

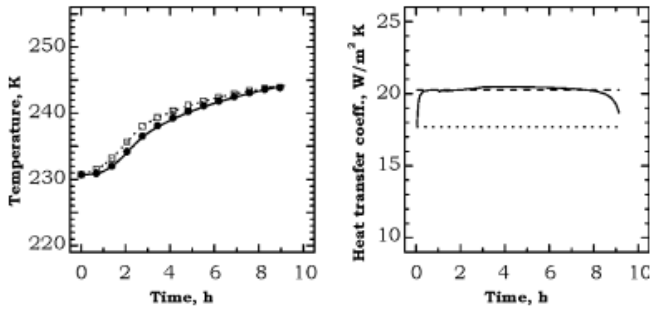

Fig. 7 – Comparison between simplified model I and detailed model for primary drying. (Left hand side) Temperature profiles; solid line (—): T_i from simplified model I; dotted line (···): T_B from simplified model I; solid circles (●): T_i from detailed model; open squares (□): T_B from detailed model. (Right hand side) Solid line (—): K_v effective; dashed line (– – –): K_v mean effective; dotted line (···): K_v used in detailed model simulations.

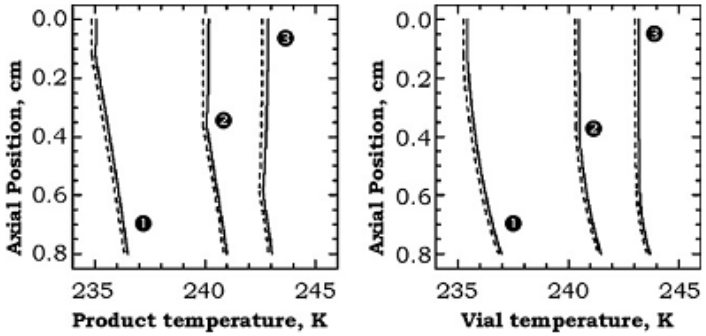

Fig. 9 – Comparison between simplified model II and detailed model for primary drying. (Left hand side) Temperature profiles along the product. (Right hand side) Temperature profiles along the vial glass. Solid line (—): simplified model II; dashed line (– – –): detailed model. Profiles are taken at three different times during primary drying: (1) 2.25 h, (2) 4.5 h, and (3) 6.8 h.

Velardi & Barresi, CERD **86** (2008)

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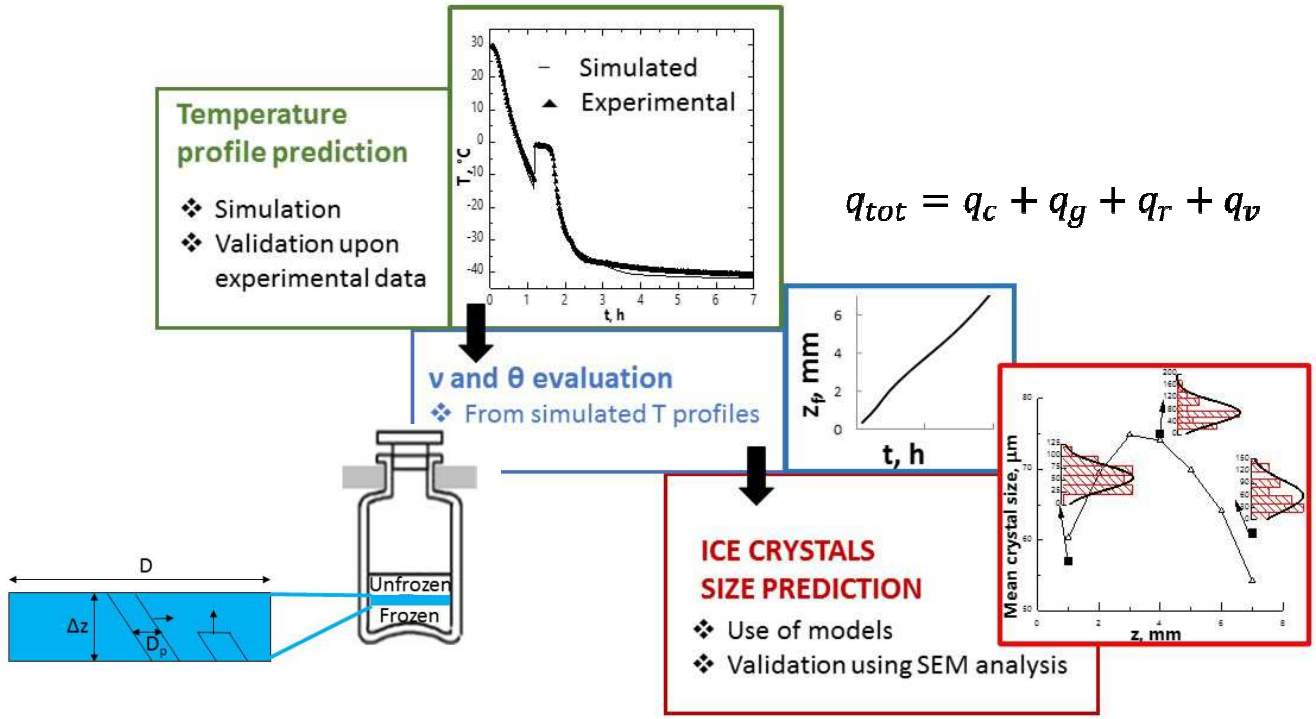
1. Mathematical modeling. Examples 1D

Modeling of freezing step: prediction of cake porosity



Arsiccio et al, EuroDrying 2017

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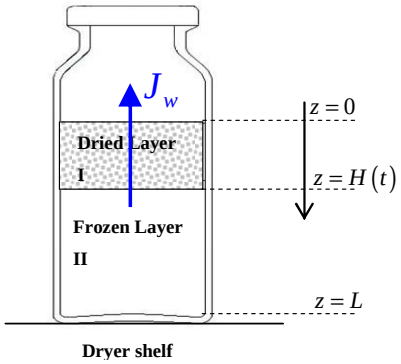
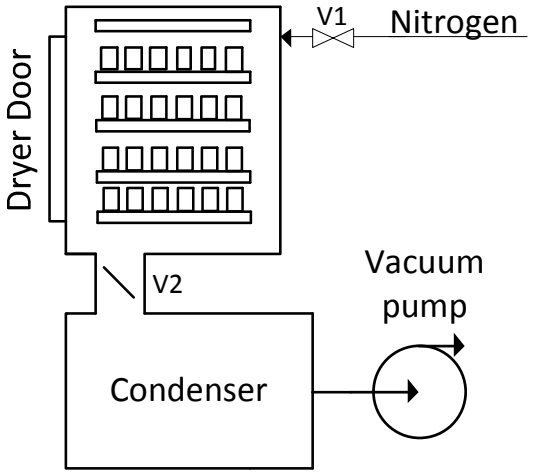
1. Mathematical modeling: 2D, 3D, multiscale

- **2 and 3 D modeling of vials (using COMSOL) to highligth role of radiation (and convection in the freezing step)**





- **Multiscale modeling of equipment**
- **Other modeling approaches (CFD, QMoM and Monte Carlo at very low pressure, ...)**

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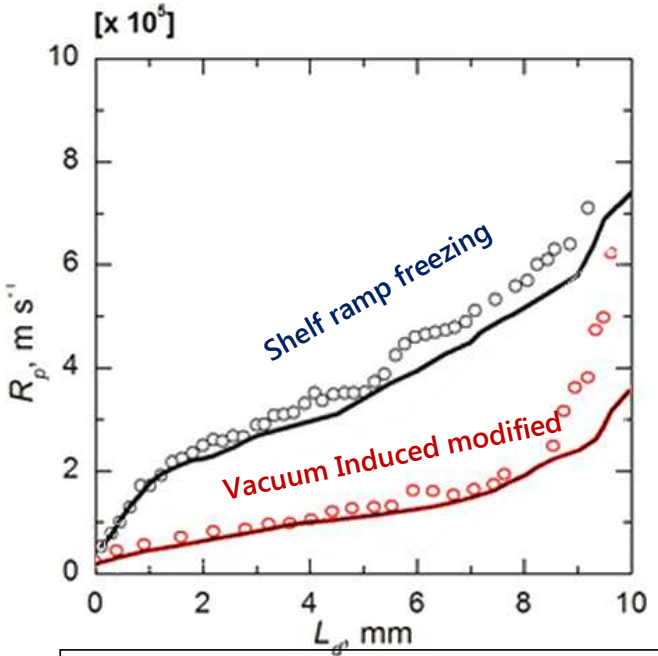
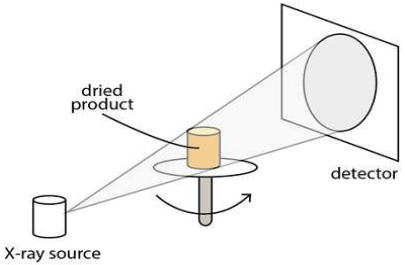
1. Mathematical modeling.
Example: estimation of influence of cake resistence

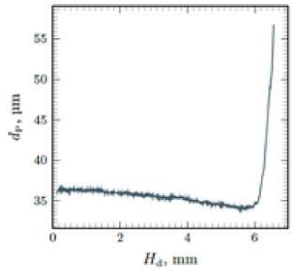
Multistep procedure used for the estimation of the resistance to vapour flow through the lyophilised product

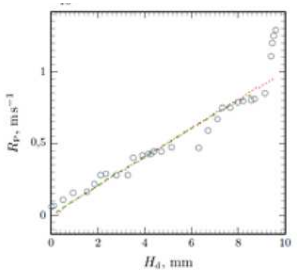




X-Ray computed tomography

product structure 3D-reconstruction





pore-size exstimation

mathematical modelling of heat and mass transfer for the freeze-drying process

Pisano *et al.*, *EuroDrying 2015; DT*, in press (online 2016)

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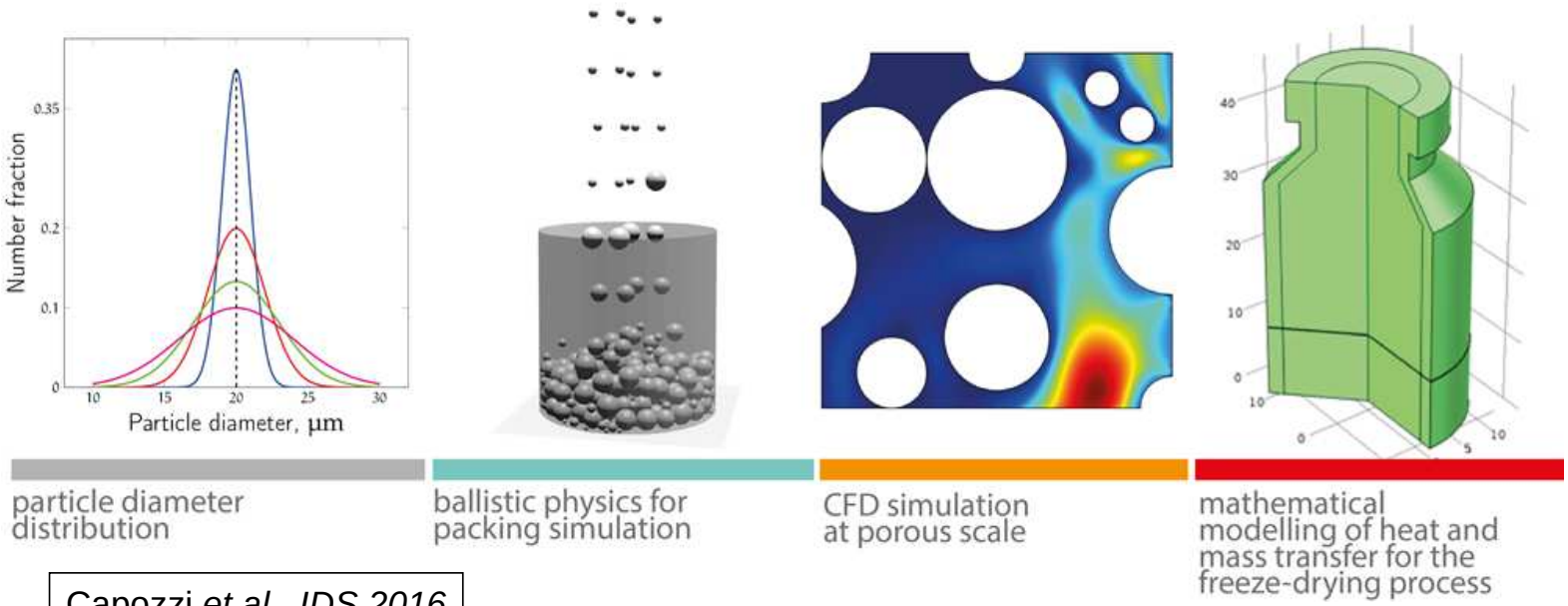
1. Mathematical modeling
Example: FD of granules

Workflow to estimate the properties and the freeze-drying behavior of packed-beds of uniform and non-uniform micro-particles within a vial



Capozzi *et al., IDS 2016*

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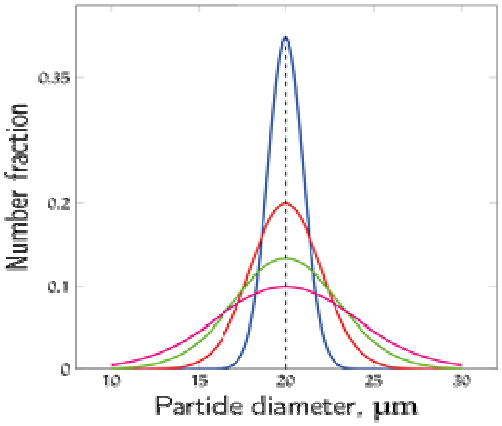
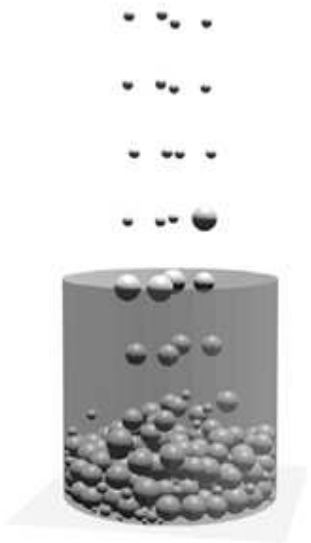
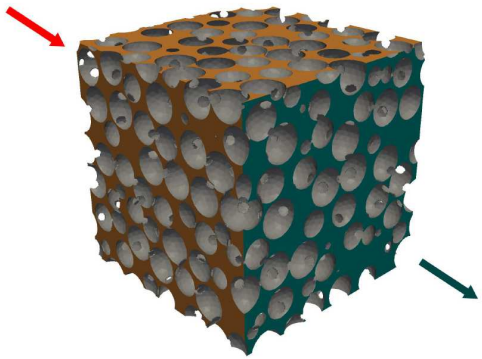
Ballistic physics and CFD at the pore-scale



Particle-size distribution is chosen



Ballistic Physics is used to simulate random packings of spheres



Computational Fluid Dynamics is used to calculate porosity, tortuosity, and permeability of the packed bed

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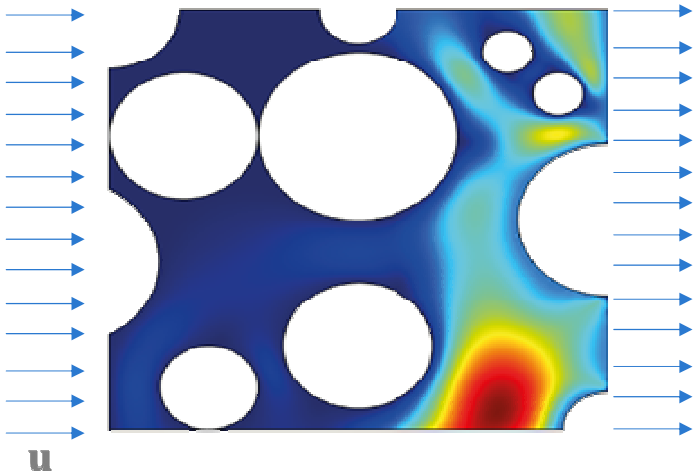
1. Mathematical modeling
Example: FD of granules

CFD for packed bed simulation



Navier-Stokes equation

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} - \nu \nabla^2 \mathbf{u} = -\frac{1}{\varrho}\nabla p + f$$

Stokes regime (Re < 0.1)
Steady-state conditions

$$\nabla p - \mu \nabla^2 \mathbf{u} = 0$$

- Simulations were carried out over a portion of the packed bed as extracted from the central part (porosity fluctuations at the edge of the container were neglected)
- Mesh refining close to particle surface
- A given pressure drop was imposed over the computational domain

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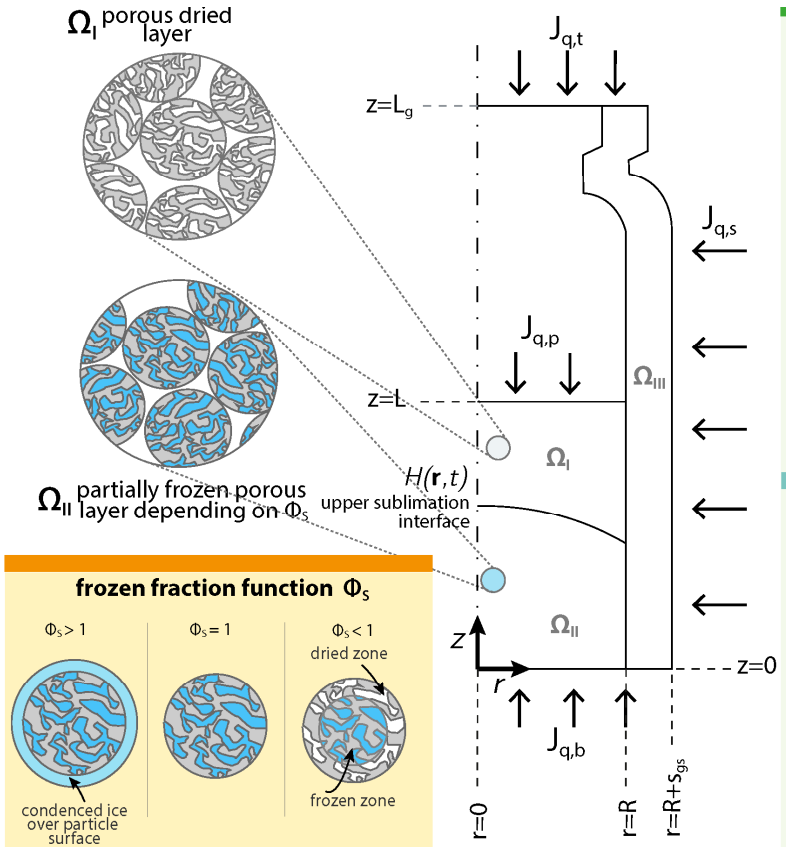
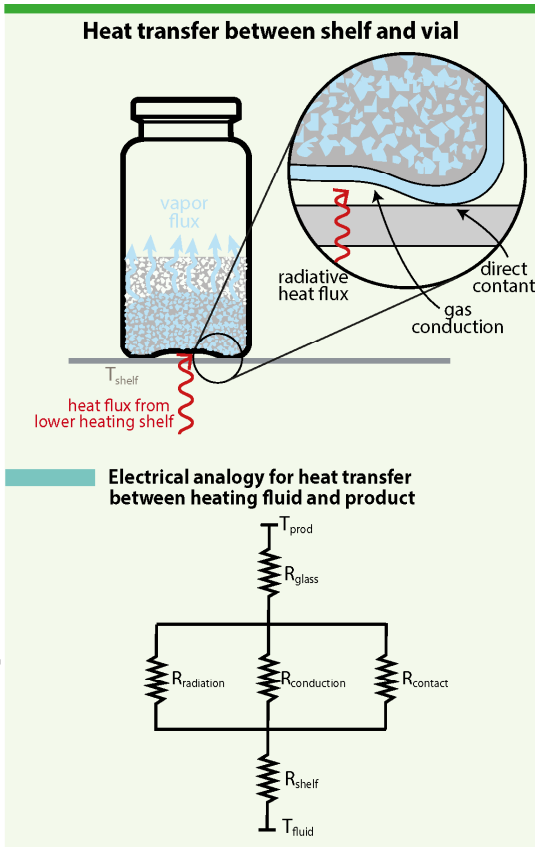
1. Mathematical modeling: freeze-drying process of granules





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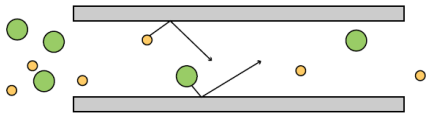
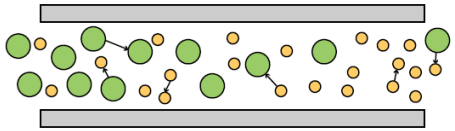
1. Mathematical modeling: mass transfer



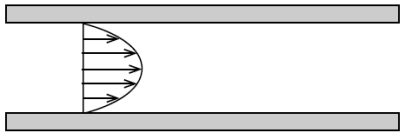
Knudsen diffusion

$$N_i^{Kn} = -\frac{\varepsilon}{\tau}\frac{d_p}{3}\sqrt{\frac{8RT}{\pi M_i}}\frac{y_i}{RT}\nabla p$$



Molecular diffusion

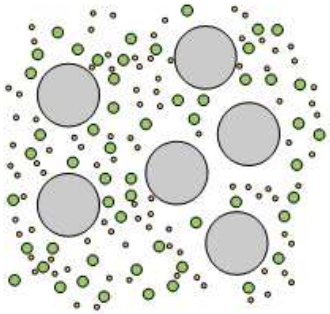
$$N_i^{D} = -\frac{\varepsilon}{\tau}\mathfrak{D}_{ij}\frac{y_i}{RT}\nabla p$$

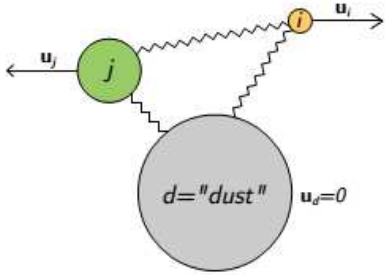


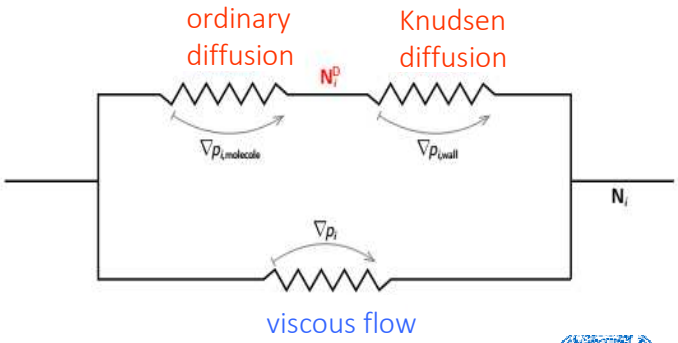
Viscous flow

$$N^{V} = -\frac{B_0}{\mu}\frac{p}{RT}\nabla p$$

- **Dusty Gas Model**: porous medium is a pseudo-component







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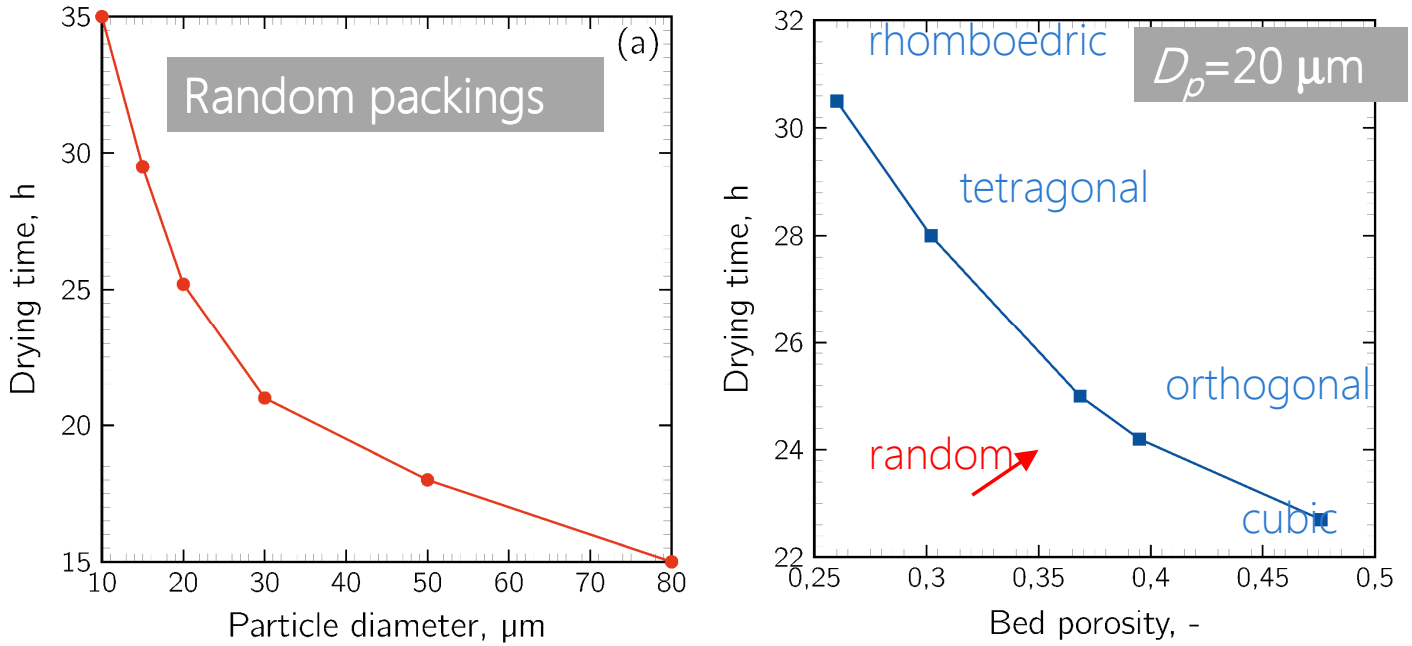
1. Mathematical modeling
Example: FD of granules

Effect of particle diameter and bed porosity



Effect of particle diameter (a) and bed porosity (b) on drying time in case of monodisperse particles.

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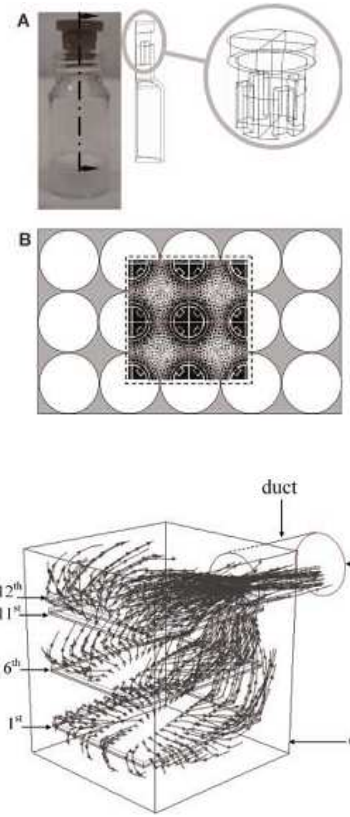
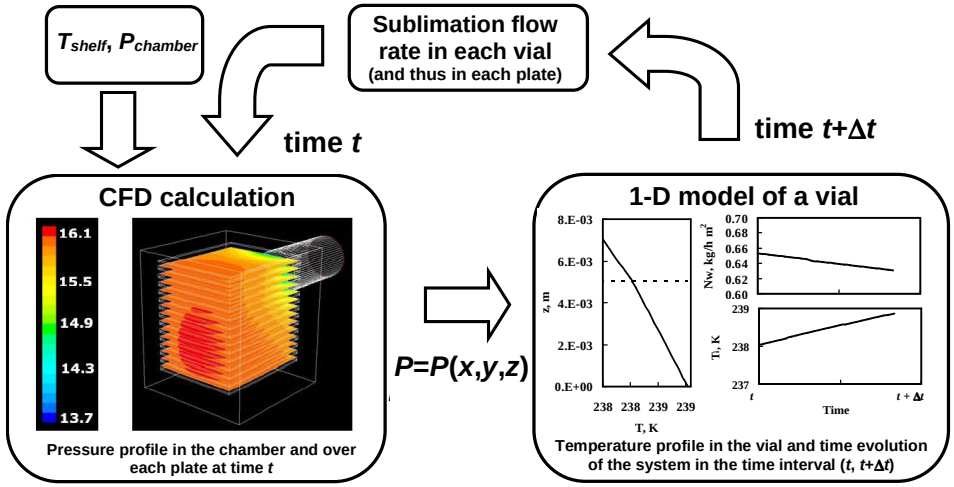
1. Mathematical modeling
Example: two-scale model



- **Two-scale model: on-line and off-line coupling. Different approaches to detailed prediction of the product behaviour or the equipment**



Rasetto *et al., Pharm. Technol.* 2010)

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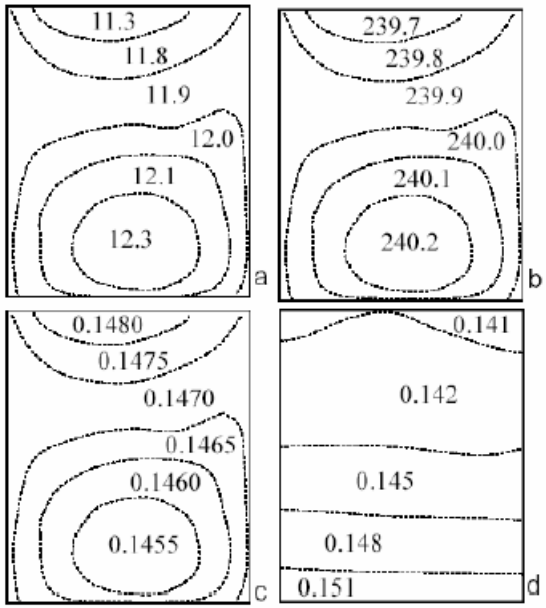
1. Mathematical modeling
Example: two-scale model

The use of a dual scale model can be very useful to understand the effect of different pieces of equipment on the product, addressing the scale up problems.



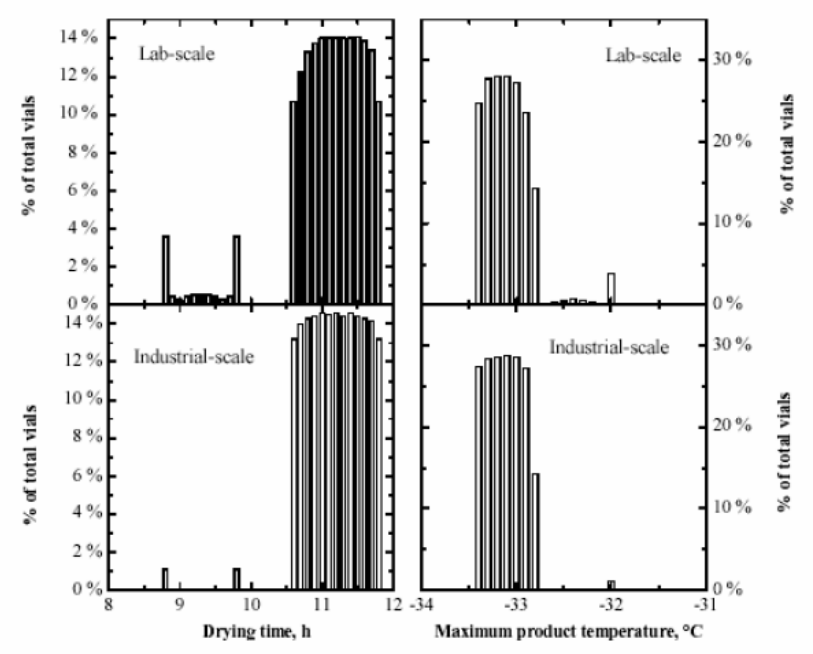
(a) absolute pressure, Pa,
(b) interface temperature, K
and sublimating flux in case of :
- constant shelf T (c)
- variable shelf T (d)

The local distribution of the properties is evaluated modelling the source [ice sublimation] in the CFD code; the approach can be used to evaluate and qualify "in silico" the equipment.

ref. Barresi A.A., Fissore D. and Marchisio D.L., 2010, Process Analytical Technology in industrial freeze-drying, in: "Freeze-Drying/Lyophilization of Pharmaceuticals and Biological Products, 3rd rev. Edition" (L. Rey and J. May, Eds.), Chap. 20. Informa Healthcare, New York, pp. 463-496.

1. Mathematical modeling
Example: two-scale model

The use of a dual scale model can be very useful to predict the batch characteristics in different pieces of equipments and estimate the variances.



Drying time and maximum product temperature distribution in pilot and industrial scale apparatus.

A different approach:
various classes of vials are modelled in detail, using correlations for hydrodynamics obtained by CFD simulations.

Ref. Rasetto V., Marchisio D.L., Fissore D. and Barresi A.A., 2010, On the use of a dual-scale model to improve understanding of a pharmaceutical freeze-drying process. *J. Pharm. Sci.* **99** (1), 4337-4350

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Recents developments and work in progress…

- **CFD modeling** of the whole apparatus: drying chamber, duct (valve included) and the condenser
- Development of a **variance optimization tool** in order to evaluate the expected batch unevenness for certain design conditions and calculate the required value of a design parameter for a maximum desired variance
- Dynamic Parameters Estimation in case of **co-solvents and with strong radiation heat flux**
- **Smart vials** (for parameter estimations, for non-uniform batch monitoring, ..): wireless or with sputtered thermocopules
- **Model Predictive Control** to manipulate both the shelf temperature and the chamber pressure
- **Valvless monitoring systems**

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2. Quality by Design

- **Design space for primary drying**
- **Effect of uncertainty**
- **Design space for secondary drying**
- **Estimation of consequences of process failure**

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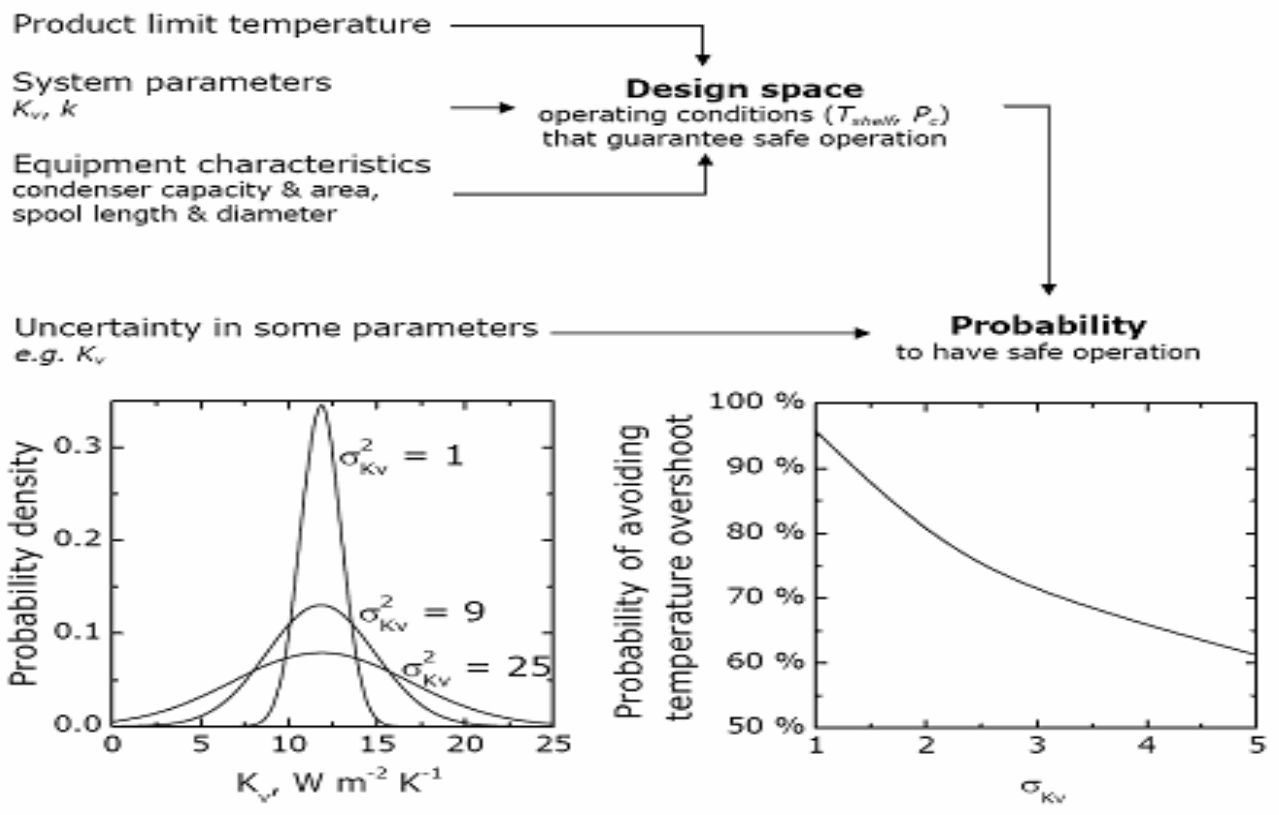
2. Quality by Design: Design Space for primary drying



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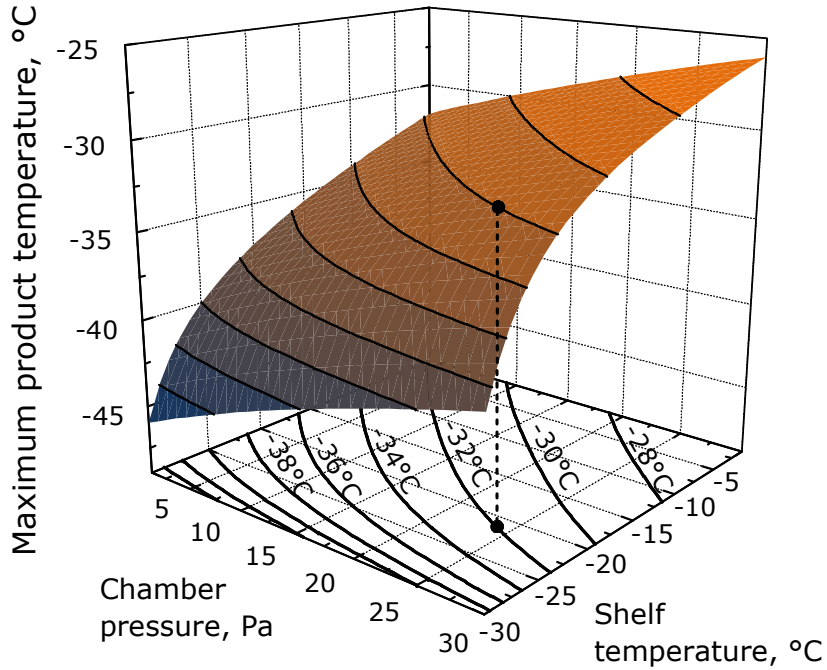
2. Quality by Design: Design Space for primary drying



- **A design space can be constructed with few experiments (to determine Rp and Kv)**
- **But modeling might be useful also to predict these parameters (or to transfer data from different pieces of equipment)**
- **Using a soft-sensor parameter can be estimated and DS built in-line (see part 5)**

Giordano *et al*, *JPS* **100** (2011)

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2. Quality by Design: Design Space for primary drying

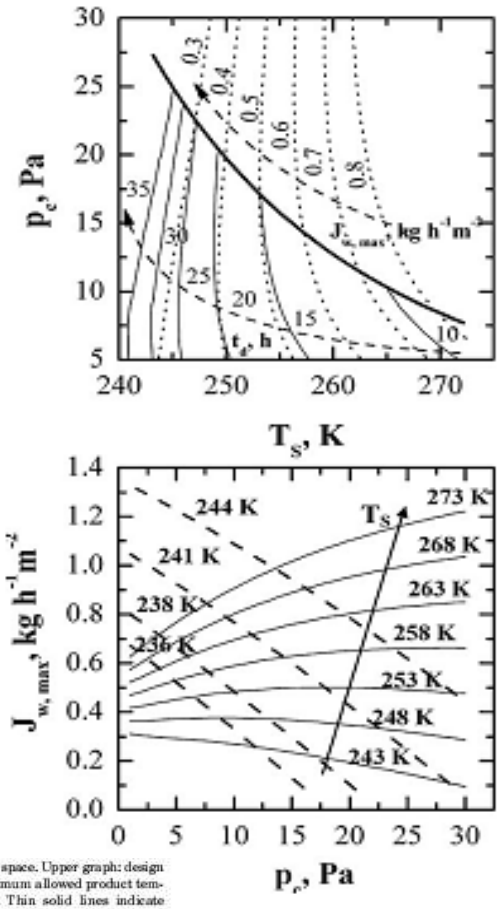

Figure 4. Examples of design space. Upper graph: design space obtained in case the maximum allowed product temperature is 241 K (thick line). Thin solid lines indicate operating conditions (T_S and p_c) resulting in the same drying time, while dotted lines refer to operating conditions giving the same maximum sublimation flux. Lower graph: maximum sublimation flux versus chamber pressure for various values of shelf temperature (solid lines). Dashed lines identify the maximum product temperature.

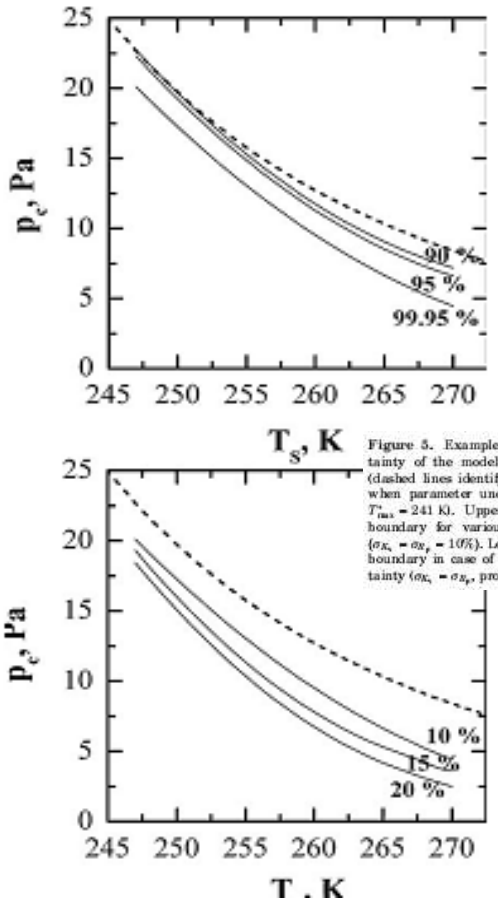

Figure 5. Examples of design space in case the uncertainty of the model parameters is taken into account (dashed lines identify the boundary of the design space when parameter uncertainty is not taken into account; T_{max} = 241 K). Upper graph: Solid lines: design space boundary for various values of probability of success ($\sigma_{K_v} = \sigma_{K_p}$ = 10%). Lower graph: Solid lines: design space boundary in case of various values of parameters uncertainty ($\sigma_{K_v} = \sigma_{K_p}$, probability of success = 99.95%).

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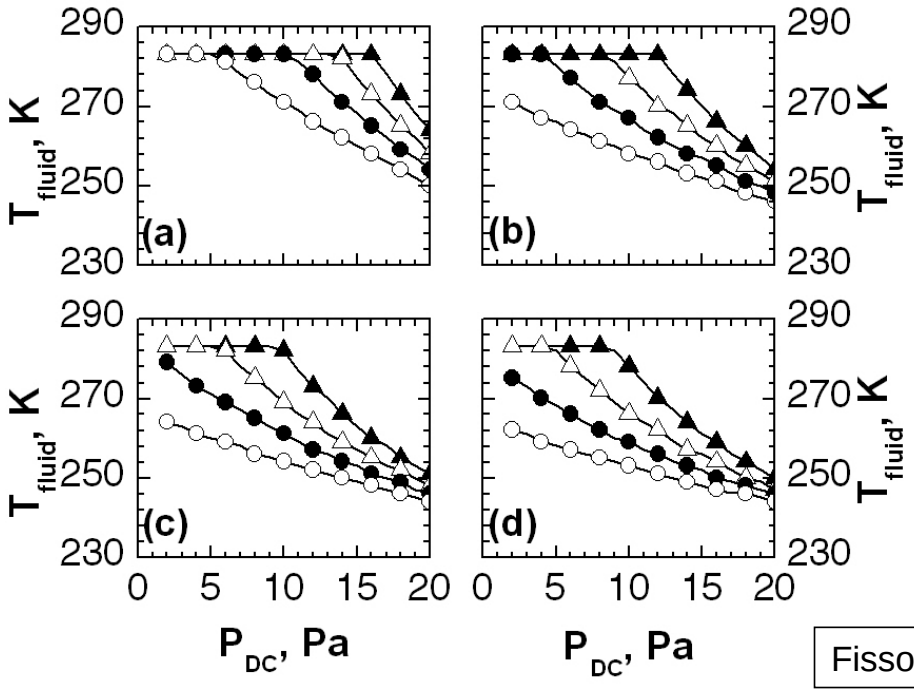
2. Quality by Design: Calculation of the design space (advanced)

Taking into account R_p variation with drying progress



Fissore *et al*, *JPS* **100** (2011)

Design space of the selected product calculated at various values of dried layer thickness: (**a**) L_{dried}/L =12%; (**b**) L_{dried}/L =34%; (**c**) L_{dried}/L =66% and (**d**) L_{dried}/L =99%. (○) B type; (●) C type; (△) D and (▲) E type.

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2. Quality by Design: Design Space for secondary drying

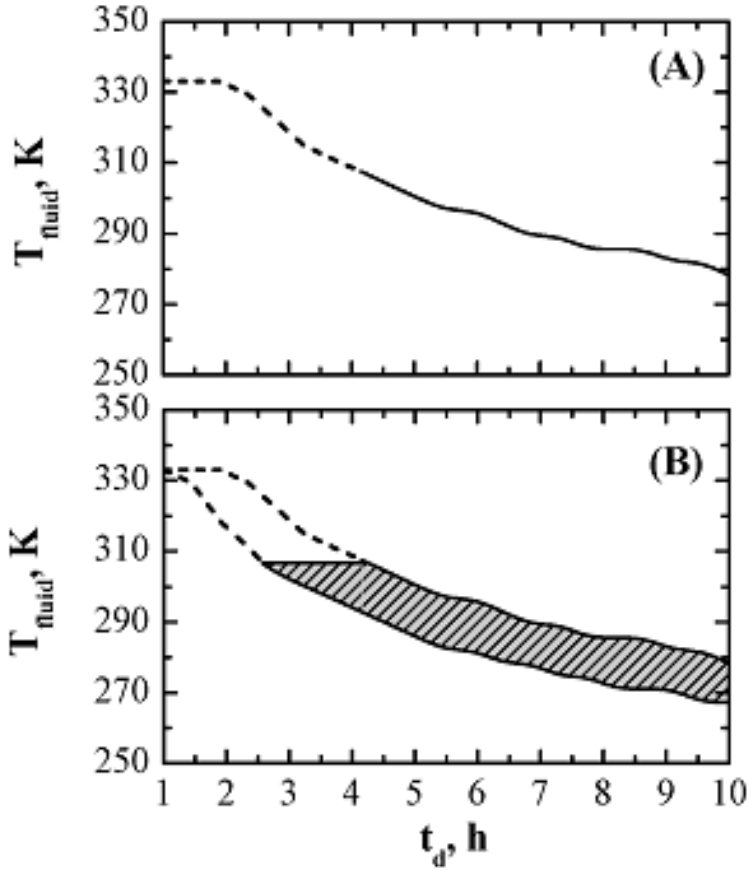

FIG. 5. Graph A: Design space calculated in case $C_{s,0} = 6\%$ and the target value of residual moisture is 2%. Graph B: Design space calculated in case $C_{s,0} = 6\%$ and the target value ranges from 1 to 2%. Dashed lines are the boundary of the portion of the design space where the constraint on the maximum value of product temperature is not satisfied.

Pisano *et al*, *Drying Technol.* **30** (2012)

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2. Quality by Design: Some tools to avoid drier failure

- Using the mathematical model of the process, it is possible to simulate the evolution of the batch when something goes wrong (pressure increase, anomalous shelf temperature,...), taking into account the control policy and, thus, pointing out if the batch can be “saved” or not;
- It is possible to monitor equipment performance and, up to a certain extent, to understand the reasons of anomalous behaviour (fault diagnosis);
- Data reconciliation from model-based monitoring system reduces the risk connected to wrong measurements
- Check of actual heating and cooling rates (process identification) to avoid failures due to actual thermal transients different from expected
- Autodiagnosis of the sensors to assure system efficiency.

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3. Process monitoring

Monitoring the whole batch

- **Use of model based monitoring devices for primary drying (***based on process identification by introducing disturbances whose response is interpreted***)**
  - DPE, DPE+, DPE++ (Dynamic Parameters Estimation)
  - PDT (Pressure Decrease Test)
  - VMS (Valvless Monitoring System)
- **Secondary drying monitoring**

Monitoring the single vials (batvh variability)

- **soft-sensors (observer): the “smart vial”**

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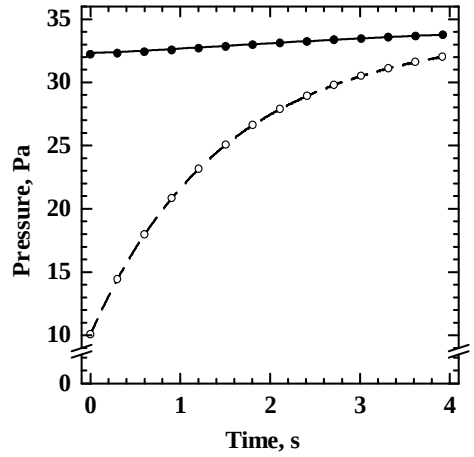
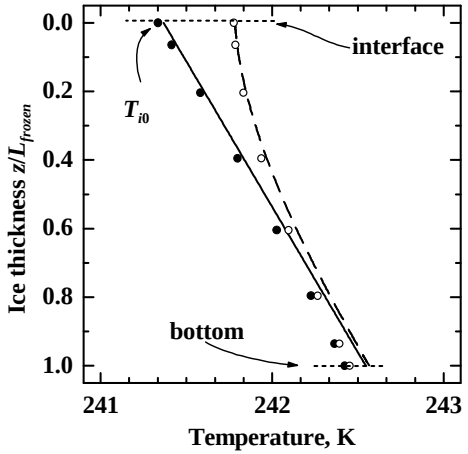
3. Process monitoring: Primary drying
the Dynamic Parameters Estimation (DPE) algorithm





DPE features:

1. Non-intrusive method useful for estimating the average state of the whole batch
2. Uses an unsteady mathematical model to interpret the pressure rise curve experimentally acquired
3. Supplies a full-state estimation of the system:
   - *Moving front temperature and position*
   - *Temperature profile over the frozen layer thickness*
   - *Mass and heat transfer coefficients*

Barresi *et al.*, *CEP* **48** (200); Velardi *et al.*, *IECR* **47** (2008)

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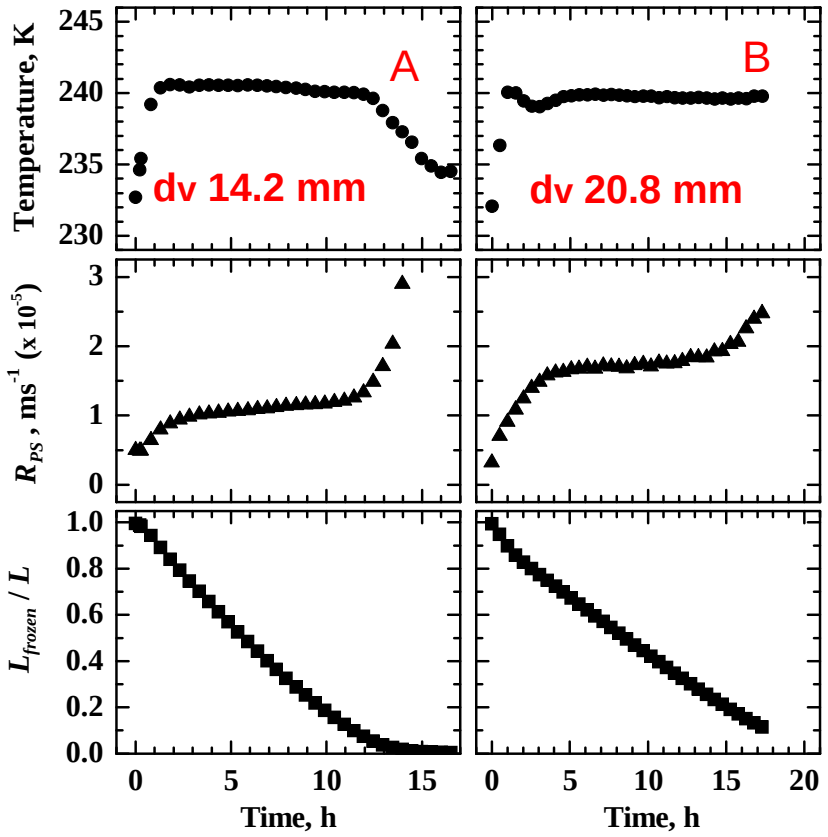
3. Process monitoring: DPE algorithm
estimation of the process parameters



Example of DPE estimations obtained in two cycles run with vials of different dimensions.

L.h.s.: type A vials, placed on a medium size rectangular tray and not shielded (P_C=10 Pa, T_{shelf}=263 K; total primary drying time 16h 35').

R.h.s.: type B vials, placed on a smaller circular tray and shielded by empty vials (P_C=10 Pa, T_{shelf}=253 K; total primary drying time 17h 17').

(●) moving front temperature
(▲) global mass transfer resistance
(■) ice thickness estimated by the DPE solver

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3. Process monitoring: DPE algorithm

DPE characteristics and advantages:

- based on the unsteady-state modeling of the process
- It computes consistent results almost up to the end of the primary drying
- It computes the product temperature profile (from the interface to the bottom) [instead of the lumped one] at the beginning and during the pressure rise test (dynamic)
- It can take into account the composition of the gas (water vapor, inert)
- Extendible to water-TBA mixtures solvent

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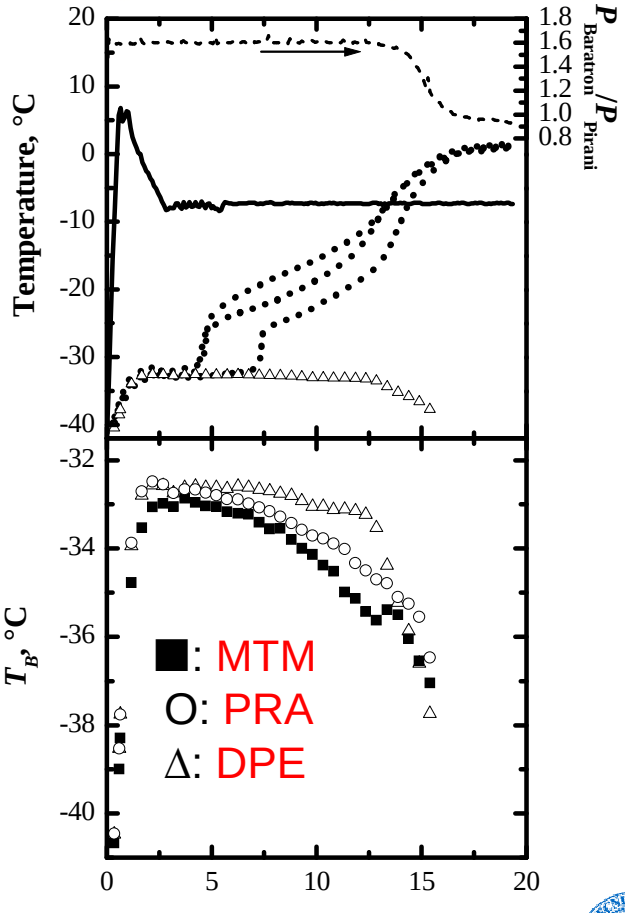
3. Process monitoring: DPE algorithm

DPE vs. other PRT methods

Monitoring of the freeze-drying cycle of a 10% by weight sucrose solution (N_{vials}=175, $d_{v,i}$=14.4x10^{-3} m, L_{froz}=7.2x10^{-3} m, P_C=10 Pa).

Upper graph: comparison of bottom product temperature estimated by DPE (Δ) with the values measured by thermocouples in close contact with the bottom of the vial (dotted line). The heating fluid temperature (solid line) and the Pirani to Baratron pressure ratio (dashed line) are also shown.

Lower graph: comparison between the predictions of the temperature at the bottom of the vial obtained using various algorithms (■: MTM, O: PRA, Δ: DPE).



Fissore *et al*, *Drying Technol.* **29** (2011)

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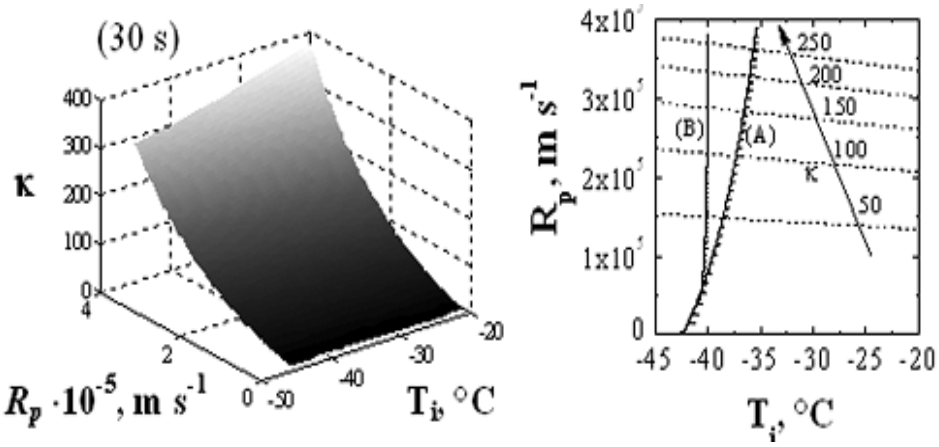
3. Process monitoring: DPE algorithm improvements

DPE+: improved robustness and estimation of the operating limits

- **Process identification by PRT: an ill-conditioned problem:**
  - reduction of the dimensionality of the problem and optimal selection of test time



Fissore *et al*, *Drying Technol.* **29** (2011)

DPE++: taking into account strong radiation heating (for food technology) and sensor dynamics

Pisano *et al*, *Drying Technol.* **29** (2011); I2MTC 2017

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3. Process monitoring: DPE+

- **DPE + comparison**

■ DPE+

□ DPE

◇ MTM

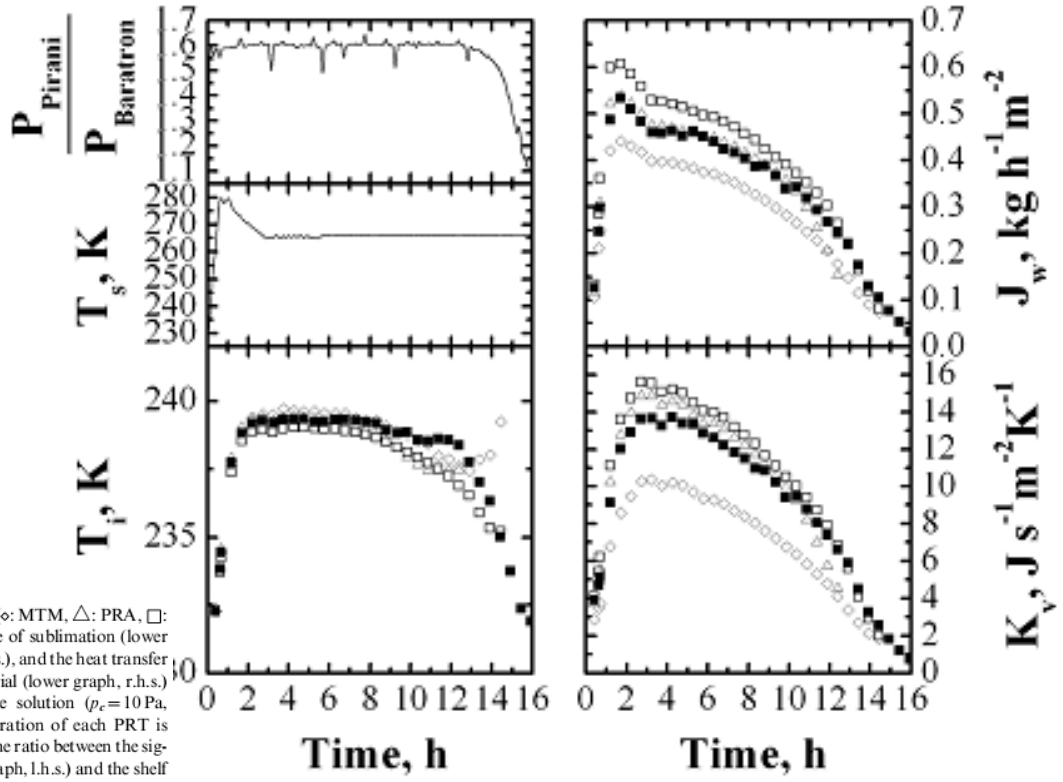

FIG. 8. Comparison between the estimated values (◇: MTM, △: PRA, □: DPE, ■: DPE$^+$) of the temperature at the interface of sublimation (lower graph, l.h.s.), the sublimation flow (upper graph, r.h.s.), and the heat transfer coefficient between the shelf and the bottom of the vial (lower graph, r.h.s.) during freeze drying of a 10% by weight sucrose solution ($p_c = 10$ Pa, $d_v = 14.25 \times 10^{-3}$ m, $N_v = 175$, $V_c = 0.2$ m^3). The duration of each PRT is 30 s; the time interval between two PRTs is 30 min. The ratio between the signals of the Pirani and the Baratron sensors (upper graph, l.h.s.) and the shelf temperature (middle graph, l.h.s.) are also shown. Experiments were carried out in *LyoBeta 25* freeze dryer by Telstar, with *LyoDriver* automatic control.

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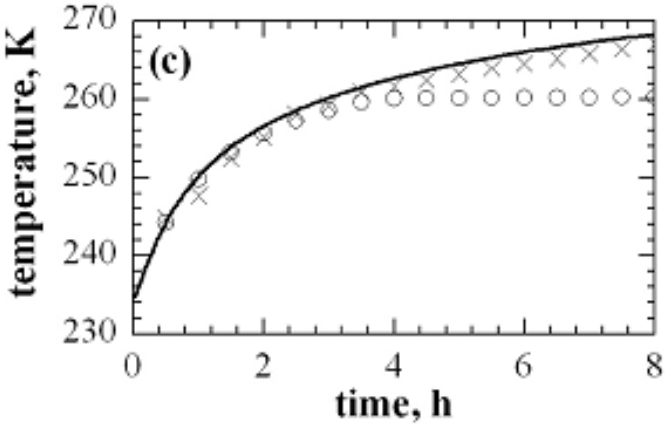
3. Process monitoring: DPE++

- **DPE ++**

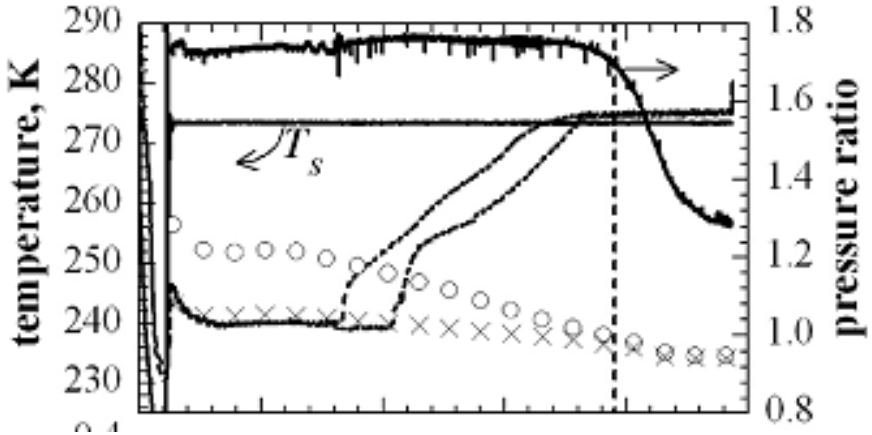
X DPE+

□ ○DPE

___ model



validation with model prediction: it is evident the deviation without correction at high radiation fluxes



Process monitoring

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3. Process monitoring: DPE with water-solvent

- **in this case an additional devices is required to acquire the water partial pressure (for example a laser) to obtain the solvent partial pressure from total pressure signal**

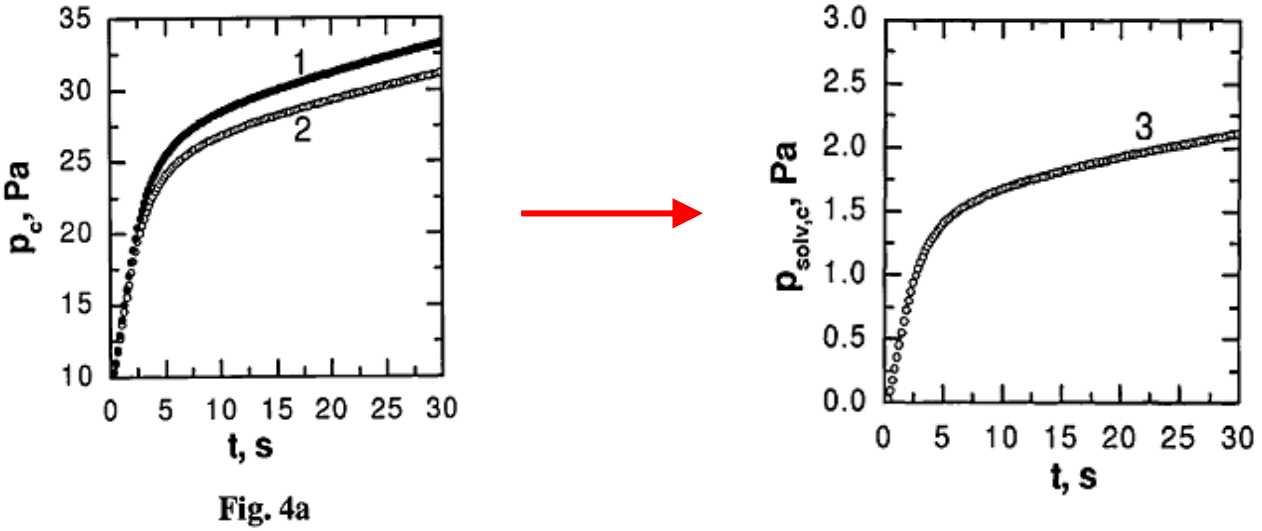

Fig. 4a

Fissore *et al*, US 9,170,049 B2 Patent (2015)

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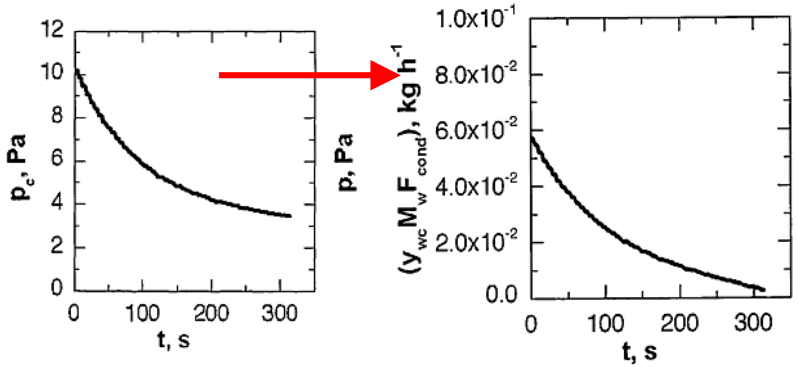
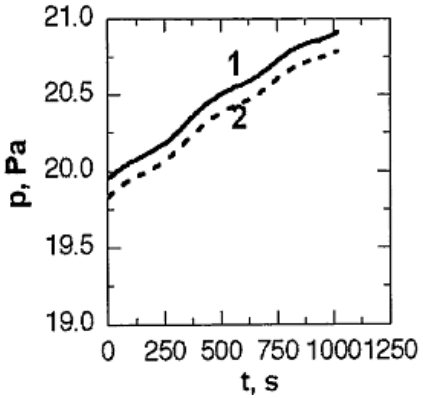
3. Process monitoring: other approaches

Different disturbances can be used to identify the process and to monitor product temperature (and eventually sublimation flux)

- Pressure decrease stopping the inert flow rate



- closing the connection to vacuum pump and monitoring the pressure in the condenser or in the chamber
- eventually monitoring the inert flow rate without any disturbance ("valvless monitoring")



Fissore *et al*, US 9,170,049 B2 Patent (2015)

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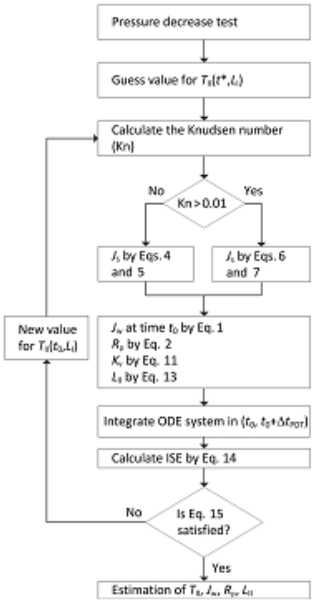
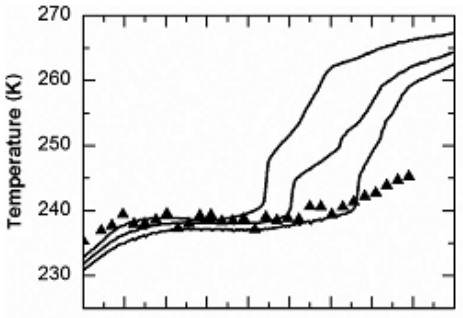
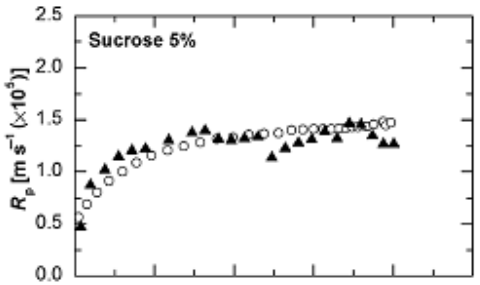
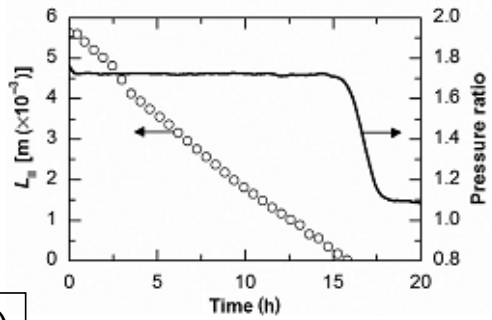
3. Process monitoring: PDT

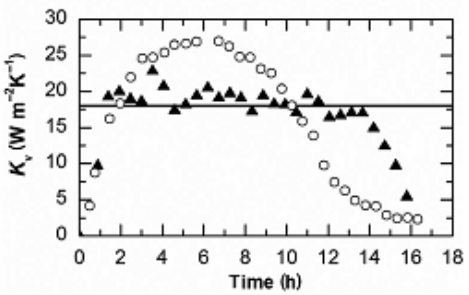
- **the Pressure Decrease Test method (suitable with Controlled Leackage P control) avoids T disturbances on thermolabile products and has been validated also with water –TBA mixtures**











Pisano *et al*, *JPS.* **103** (2014)

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3. Process monitoring: VMS

- **the Valvless Monitoring System has been validated for water and water-TBA mixtures. It allows monitoring the sublimation flux from P measurement in chamber and condenser and inlet inert flow measurement**

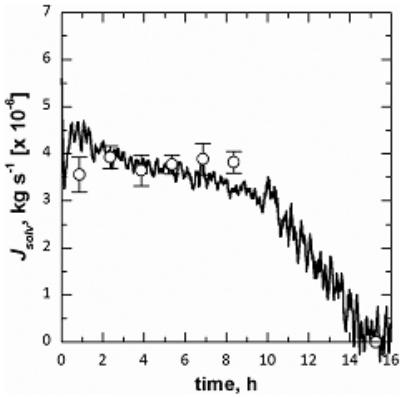


Figure 3. Evolution of the rate of sublimation as estimated by VMS (solid line) and as measured by the gravimetric procedure (○). Error bars represent standard deviation. Data refer to the freeze-drying of a 5% (w/w) sucrose solution (in 20% TBA–80% water system) processed at P_c = 10 Pa and T_{shelf} = 0 °C in vials ISO 80426 6R.

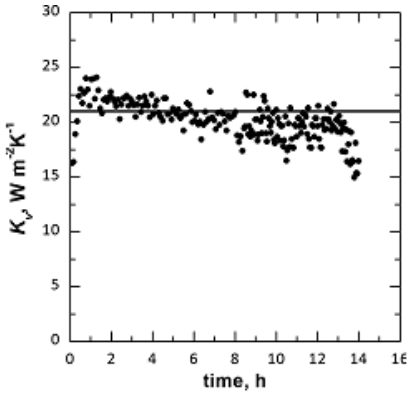
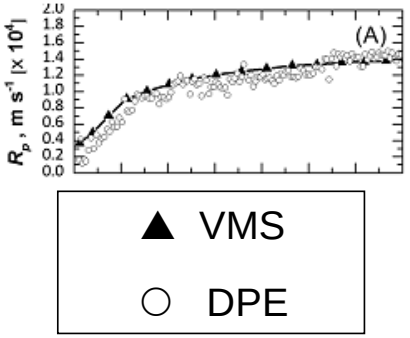


Figure 2. Comparison between the value of heat transfer coefficient for the vial used in this study as estimated by VMS and thermocouples (●) and that measured by gravimetric procedure (solid line). The comparison was carried out at P_c = 10 Pa and T_{shelf} = 0 °C using vials ISO 80426 6R.



T can be estimated if Kv is known; or Kv can nbe estimated if T is measured

Pisano *et al*, *IEC Res.* **55** (2016)

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3. Process monitoring: secondary drying

mathematical model of secondary drying [cfr. Liapis & Bruttini, 1995]

determination of desorption rate from PRT [cfr. Oetjen, 2001]

- estimation of the residual water content
- estimation of the ending point of the secondary drying according to the specified target (residual water content and/or desorption rate of water)

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3. Process monitoring: Secondary drying modeling

$$\rho V_{prod} c_{p,prod} \frac{dT_{prod}}{dt} = K_v A_v \left(T_{fluid} - T_{prod} \right) + V_{prod} \rho r_d \Delta H_d$$

$$\frac{dC_S}{dt} = r_d = -k_d C_S$$

Kinetic model

- **based on the measurement of r_d through the Pressure Rise Test (It is not required to extract any samples from the chamber).**

Fissore *et al*, *JPS* **100** (2011)

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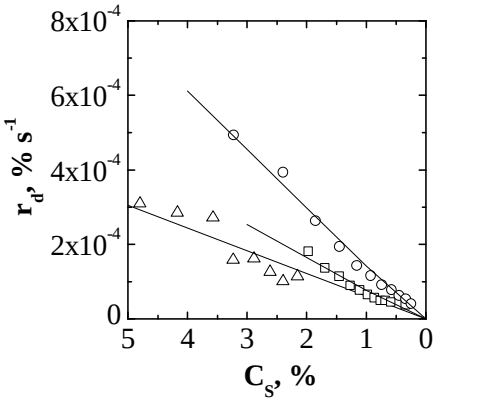
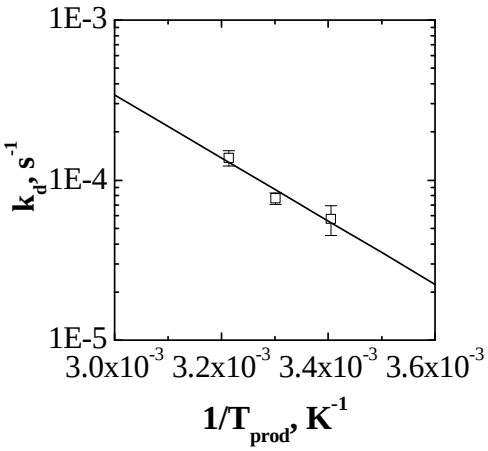
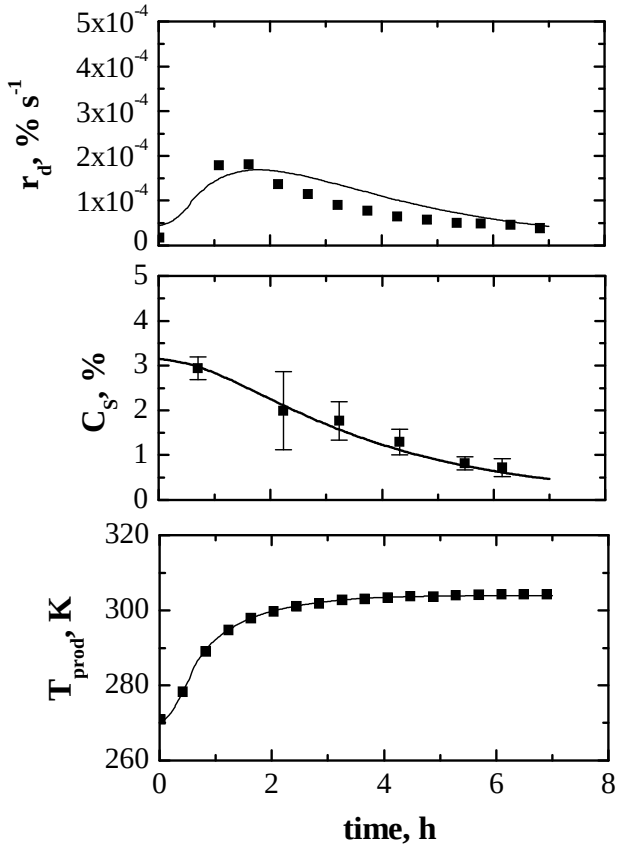
3. Process monitoring:
secondary drying parameters estimation







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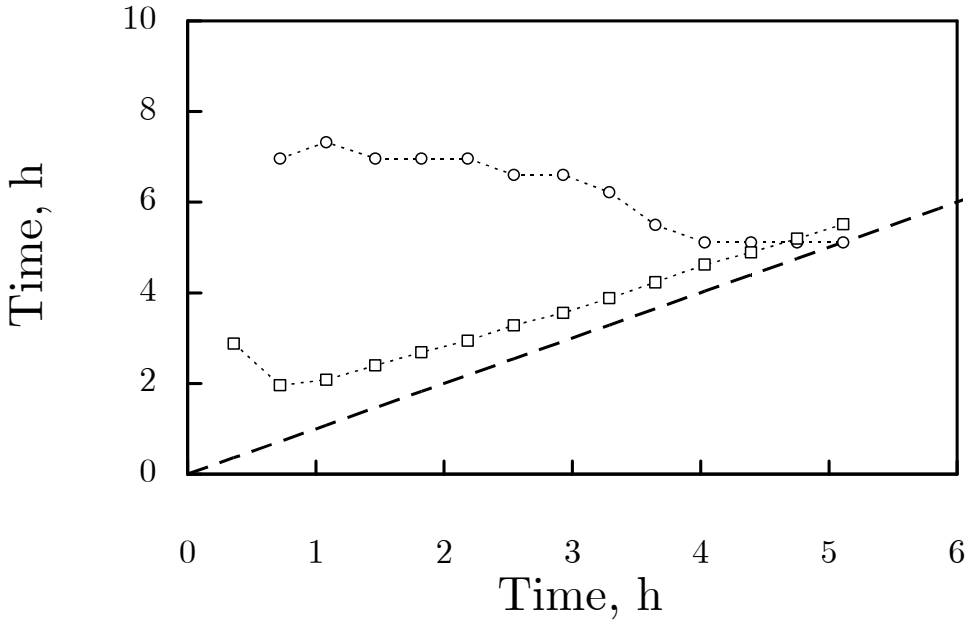
3. Process monitoring: secondary drying
comparison of POLITO's and Oetjen's method

Examples of the results: end-point prediction



- - - : Current time;
···o··· : End-point of secondary drying estimated by the proposed method;
···□···: End-point of secondary drying estimated using the method of Oetjen

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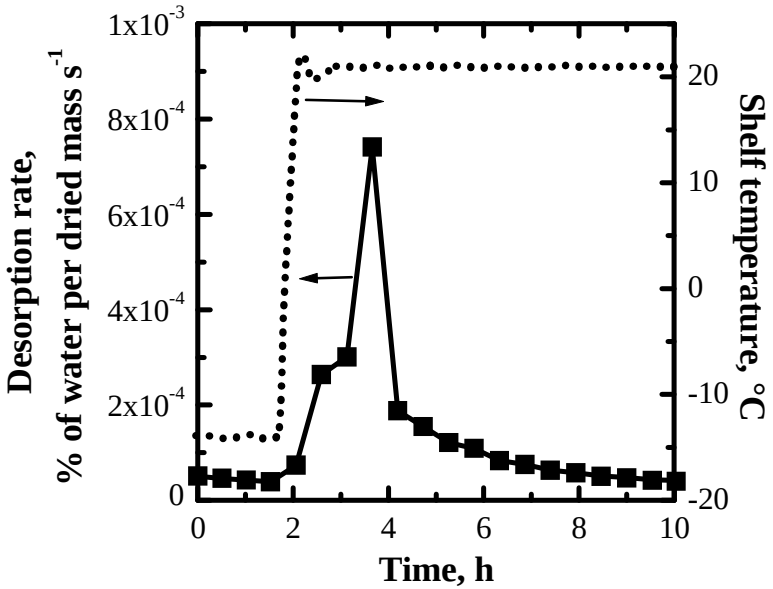
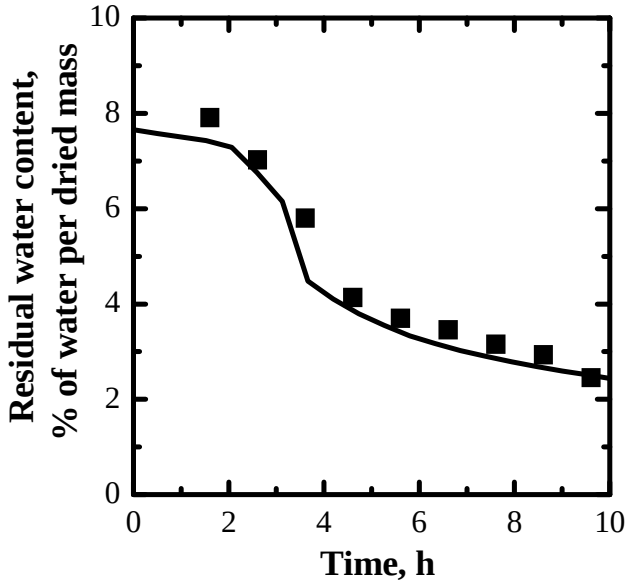
3. Process monitoring: secondary drying

Examples of the results: residual moisture estimation





Comparison between the experimental values (symbols) and those predicted by the proposed algorithm (solid line) of the desorption rate (left hand graph) and of the residual water content (right hand graph). The time evolution of the shelf temperature is also shown (dotted line). Time is set equal to zero at the beginning of the secondary drying.

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3. Monitoring of the secondary drying

Main advantages:

- it is not required to extract any samples from the drying chamber and to measure the residual water content at the beginning of the operation
- a reliable estimation of the ending point of the secondary drying is obtained
- model parameters (e.g. kinetic constants) are estimated in-line

Fissore *et al*, EP2148158 B1 Patent (2011)

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3. Process monitoring: Monitoring in pilot and production scale

Many devices can be employed in process development, but only a few are suitable for production plants:

- balances are suitable only in lab or pilot scale, for process development

- wired Smart Vial can be employed for equipment qualification and in pilot scale, but is incompatible with automatic loading

- NIR can eventually be used in the freeze drying chamber, but only for residual moisture, or end of primary drying

- Cold Plasma sensor and TDLAS can be employed in industrial scale but only for monitoring and have limitations (calibration, difficult retrofitting)

- MTM methods can be employed both in pilot scale and in production, but due to valve movement are limited to small/medium scale

- wireless soft sensors (active smart vial) can in principle be used also in industrial plants with automatic loading

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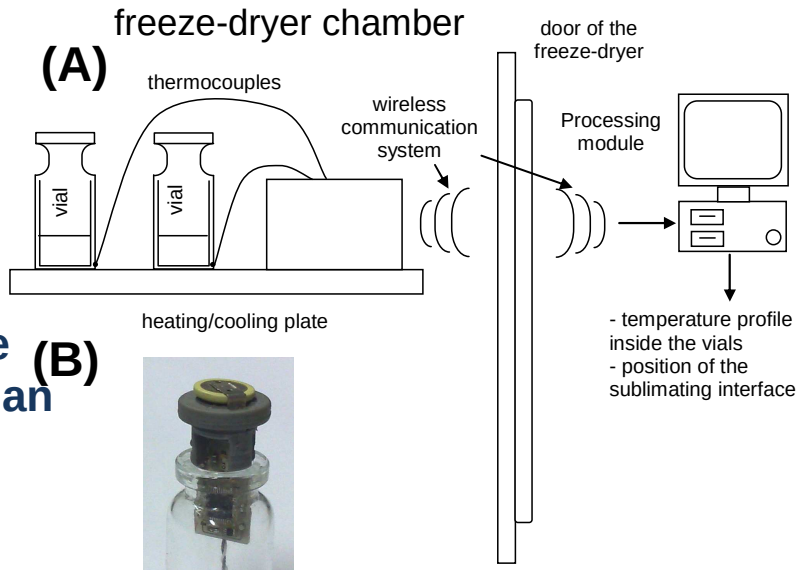
3. Process monitoring: The “smart vial”

- A vial equipped with a **thermocouple** (inserted, external, or even a TC array sputtered outside) and an **algorithm** becomes a **smart vial**
- able to estimate temperature profile, position of interface an sublimation rate
- Observer based on Kalman filter
- Posssibility to monitori a non-homogeneous batch (T_i and L_{frozen} vs. time)



Bosca & Fissore, *Chem. Eng. Sci.* **66** (2011); Bosca et al, *Int. J. pharm.* **451** (2013)

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3. Process monitoring: the S³ sensor

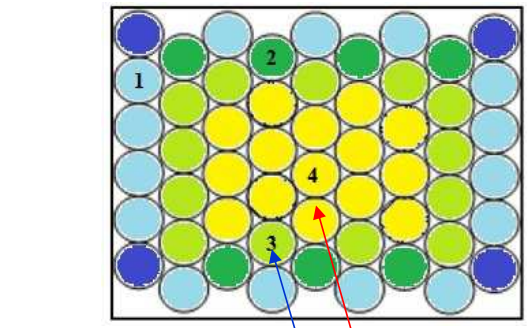
- Soft-sensor (observer)

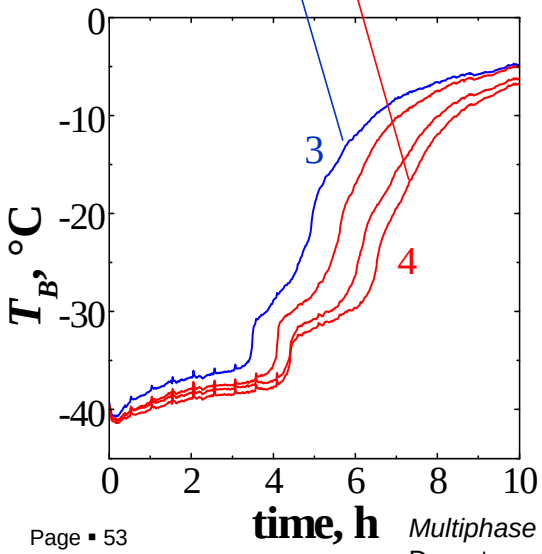
$$\dot{\hat{x}} = f(\hat{x}, u) + K(t)(\hat{y} - y) \qquad \mathbf{x} = \begin{pmatrix} T_i & R_p & K_v \end{pmatrix}$$

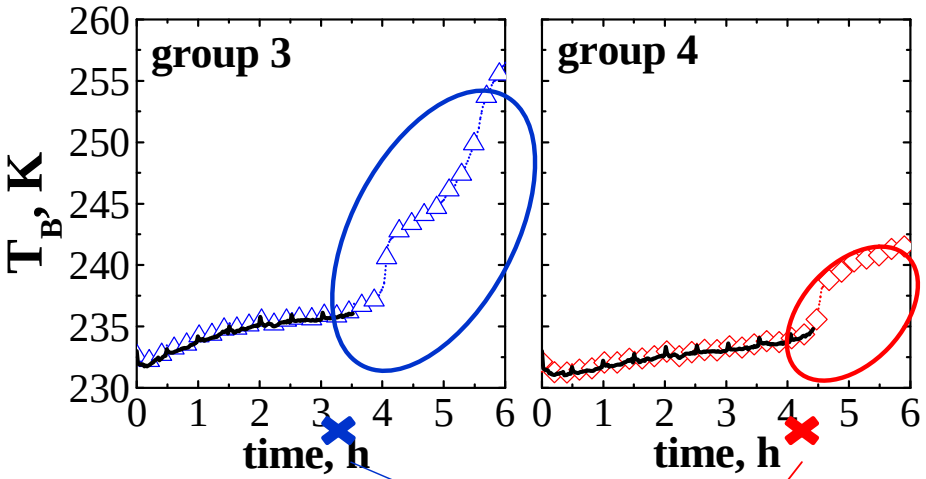
$$\hat{y} = h(\hat{x}, u)$$

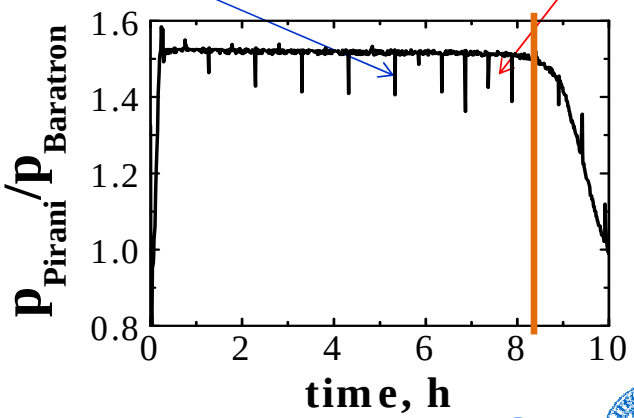
- It requires a thermocouple, to measure product temperature, and an algorithm (Kalman filter) to calculate the gain ***K***.
- It can be used:
  - to estimate the residual amount of ice
  - to evaluate K_v and R_p
  - to monitor product dynamics in the various vials of the batch

3. Process monitoring: The “smart vial”









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3. Process monitoring: The “smart vial”

- Observer + mathematical model to extend the range of application in the last part of primary drying

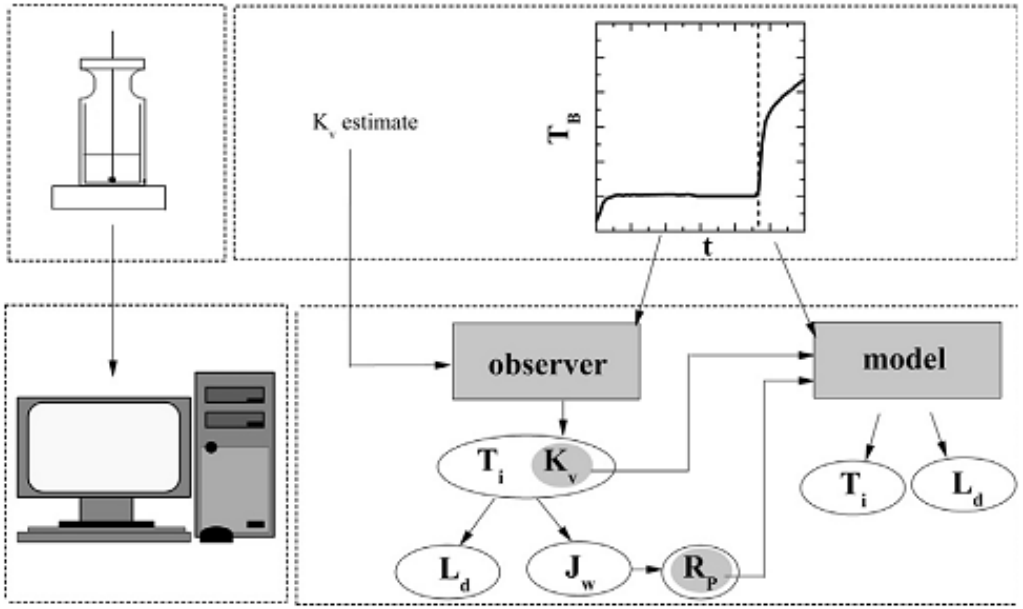

Fig. 1. Sketch of the working principle of the soft-sensor.

Bosca *et al*, *EJPB* **85** (2013)

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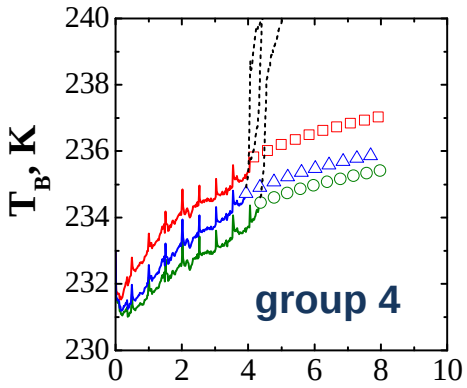
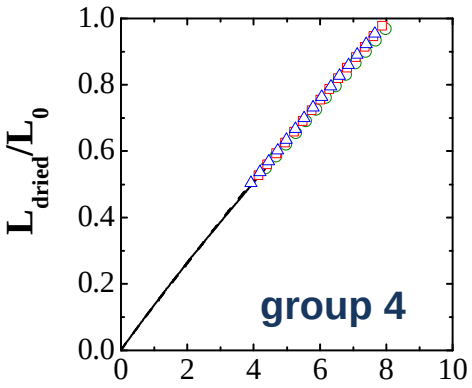
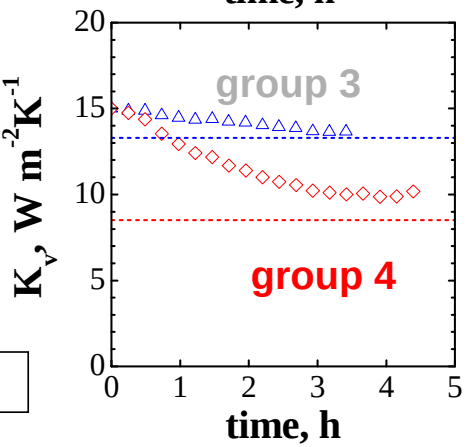
3. Process monitoring: The “smart vial”

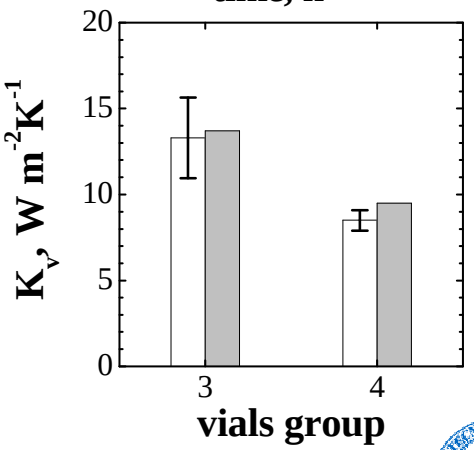
- Observer + mathematical

- K_v estimations









Bosca *et al*, *PDT* **19** (2014)

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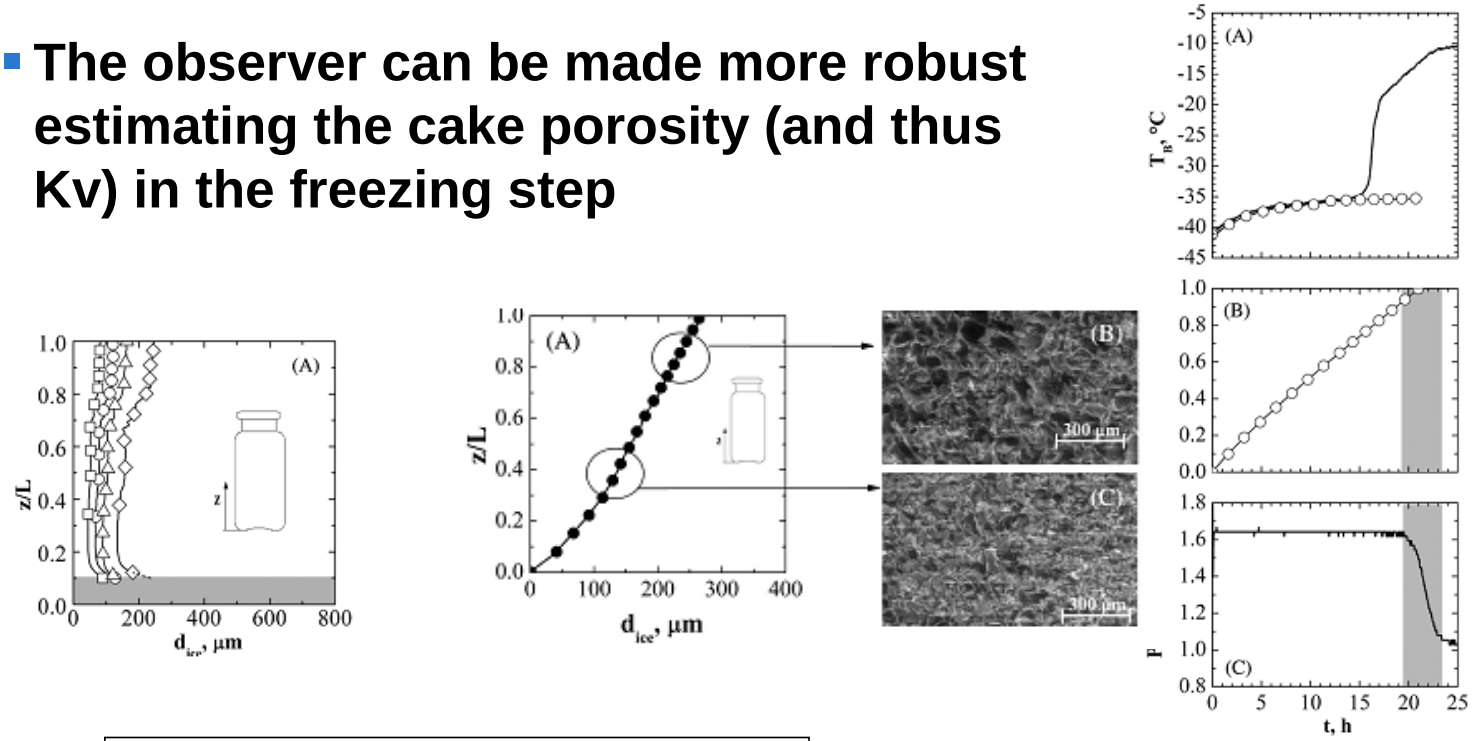
3. Process monitoring: The the robust soft sensor

- **The observer can be made more robust estimating the cake porosity (and thus Kv) in the freezing step**



Bosca *et al*, *Drying Technol* **33** (2015)

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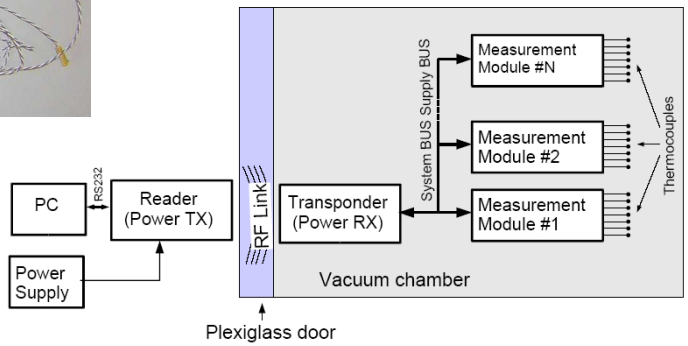
3. Process monitoring: The "smart vial"
T monitoring and determination of K_v

- **Wireless sensors can be used to measure product temperature in the vials, in particular in large-scale equipment.**

Hot plug&play architecture

system without batteries developed by POLITO, uses a radio-frequency link to supply energy and transfer the data



ref: Vallan A., Corbellini S. and Parvis M., 2005. A Plug&Play architecture for low-power measurement systems. *Proceedings of Instrumentation and Measurement Technology Conference - IMTC 2005,* Ottawa, Canada, Volume 1, 565–569.

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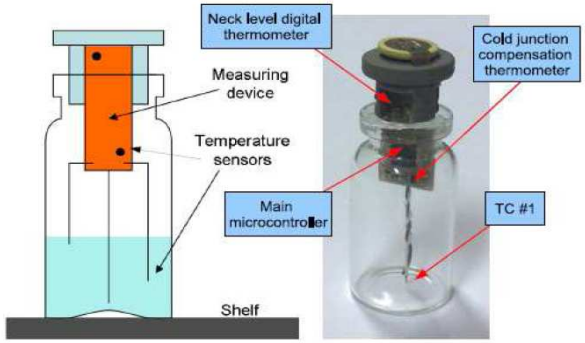
3. Process monitoring: The "smart vial"
T monitoring and determination of K_v

A system is composed by a transmitter that works inside the chamber, and a receiver placed outside the chamber and connected to a PC through a USB interface. The transmitter contains a battery and set of thermocouples (3 in this version) . Several transmitters can work simultaneously thus making the system suitable to map temperatures inside large freeze dryers.

- **A miniaturized version has been arranged to be contained inside the vials.**



ref: *Corbellini S., Parvis M. and Vallan A., 2009, A low-invasive system for local temperature mapping in large freeze dryers. Proceedings of International Instrumentation and Measurement Technology Conference - I2MTC, Singapore, Republic of Singapore.*

ref: *Corbellini S., Parvis M. and Vallan A., 2010, In-Process Temperature Mapping System for Industrial Freeze Dryers, IEEE Transactions on Instrumentation and Measurement **59**, 1134-1140.*

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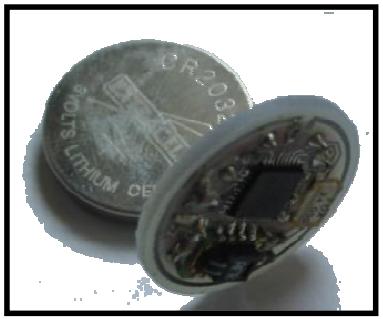
3. Process monitoring: The "smart vial"
T monitoring and determination of K_v

Miniaturized system with batteries

Microcontroller and 2.4 GHz Radio

CR2032 Lithium battery



Printed Antenna

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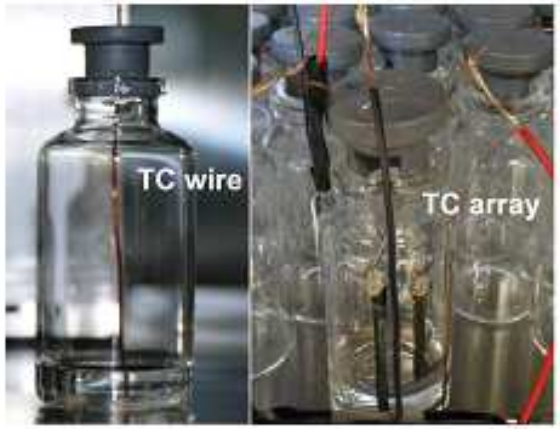
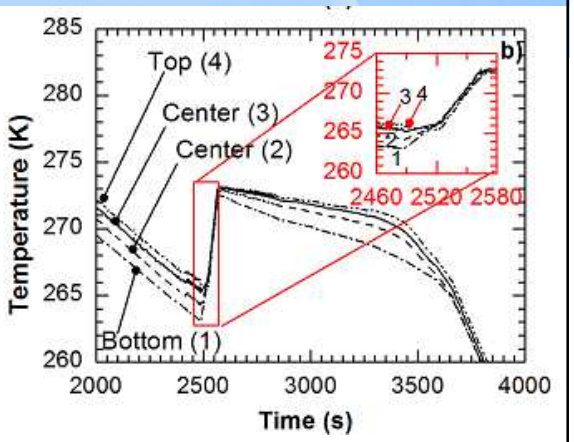
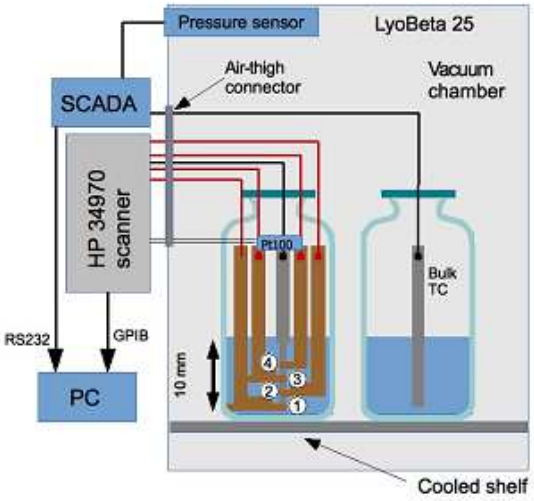
3. Process monitoring: sputtered thermocouples

- **it is possible to substitute the thermocuple wire with a thin sputtered thermocouple on the vial wall (internal or external) or even a thermocouple array**







Grassini *et al*., *IEEE Trans. Instrum. Measur.* **62** (2013); Parvis *et al*, *I2MTC 2014*; Oddone *et al*, *Drying Technol* **33** (2015)

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4. Process control

- **Model-based controllers** based on set-point tracking, manipulating only the shelf temperature (for primary and secondary drying)
- ***Multi-variables controller*** and ***Model Predictive Control*** manipulating both shelf temperature and chamber pressure
- **Model-based control using distributed soft sensors** to take into account batch nonuniformity

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Batch failure :
change of product loading or occurrence of disturbances

One typical case of occurrence of batch failure is when freeze drying is carried out with a loading different from usual, or in a “similar” equipment.

This happens because the “recipe” is just a sequence of set points in the freeze-drier operating parameters. The state of the product is not taken into account, and due to different heat fluxes, or for the effect of a different hydrodynamics and pressure distribution in the chamber, failure in some cases can occur.

The other frequent cause is some unexpected variation of the parameters set point (e.g. pressure), that can damage, or at least endanger, the quality of the product.

In both cases failure occurs if the recipe is not “robust enough”, that is if the design space is not wide enough that the system remain inside it.

The solution to the problem is a good control system that can compensate for disturbances and changes in the set up.

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4. Control of the primary drying

All the proposed model-based algorithms require that the model perfectly describes the dynamics of the process and that all the parameters and all the variables of the process are known.

The inadequacy of the model, a different value of some parameters, or an unexpected change in the general operating conditions will results in a more or less serious failure

Process measurements must be inserted in the control loop

Commercially available systems use the PRT approach:

- Thermodynamic Lyophilisation Control (uses BTM)
- SMART^{TM} Freeze-Dryer (uses MTM)
- *LyoDriver* (uses DPE)

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4. Control of the primary drying: *LyoDriver*

from process monitoring to process control

DPE outcomes
- Interface temperature
- Moving front position
- Mass and heat transfer coefficients

Process variables

LyoDriver controller:

1. LD estimates, using an unsteady-state mathematical model, the time varying product temperature
2. LD plans an initial heating at the maximum rate
3. LD computes a sequence of set-point fluid temperature

LyoDriver is able to control a production cycle and, of course, it can be used for cycle development

Velardi & Barresi, US 8,800,162 B2 Patent; Pisano *et al.*, *JPS* 99 (2010)

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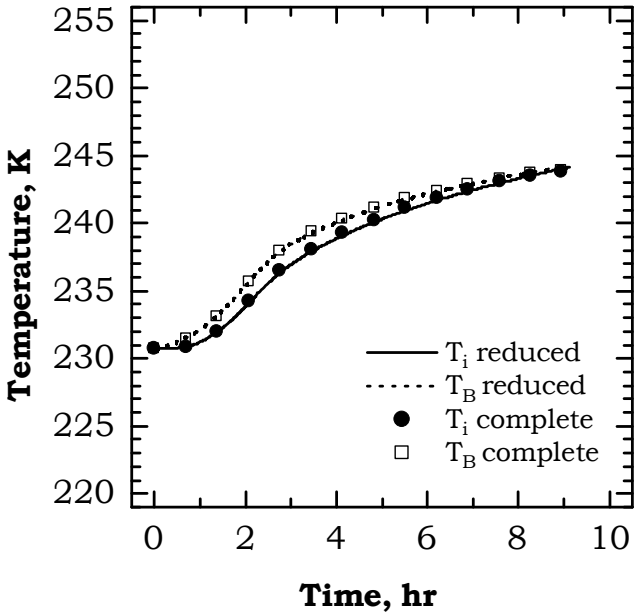
Development of mathematical models.....
.....*suited for the purposes*

- **A simplified model is required to design the controller**:
  - Pseudo-steady state conditions
  - Vial sidewall is not accounted for
  - Radiation is neglected
  - An effective heat transfer coefficient K_v must be adopted

similarly a reduced model is used for the soft-sensors



validation of the reduced model

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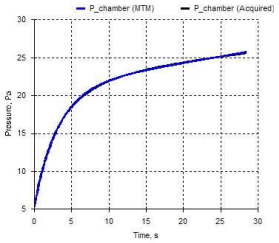
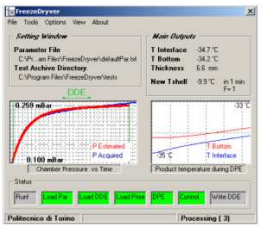
Control of the primary drying: *LyoDriver*

from process monitoring to process control





Process

PRT

DPE

Controller

$T_{fluid,\ sp}$

Batch parameters

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4. Control of the primary drying: *LyoDriver*
comparison of different control logics

Feedback controller:

- The optimal fluid temperature is calculated as a function of the difference between the simulated product temperature and its maximum value

$$\begin{cases} T_{f,sp1} = T_f(t_0) - K_P\,\varepsilon(t_1) - K_I\int_{t_0}^{t_1}\varepsilon(t) - K_D\frac{d\varepsilon}{dt} & t_0 \le t < t_1 \\ T_{f,sp2} = T_f(t_1) - K_P\,\varepsilon(t_2) - K_I\int_{t_1}^{t_2}\varepsilon(t) - K_D\frac{d\varepsilon}{dt} & t_1 \le t < t_2 \\ \vdots & \\ T_{f,spn} = T_f(t_{n-1}) - K_P\,\varepsilon(t_n) - K_I\int_{t_{n-1}}^{t_n}\varepsilon(t) - K_D\frac{d\varepsilon}{dt} & t_{n-1} \le t < t_n \end{cases}$$

- The tuning parameters of the controller have been selected according to the criterion of the minimization of two possible cost functions: ISE and ISE/time
- Experimental results show that a simple proportional controller is enough in order to optimize the cycle

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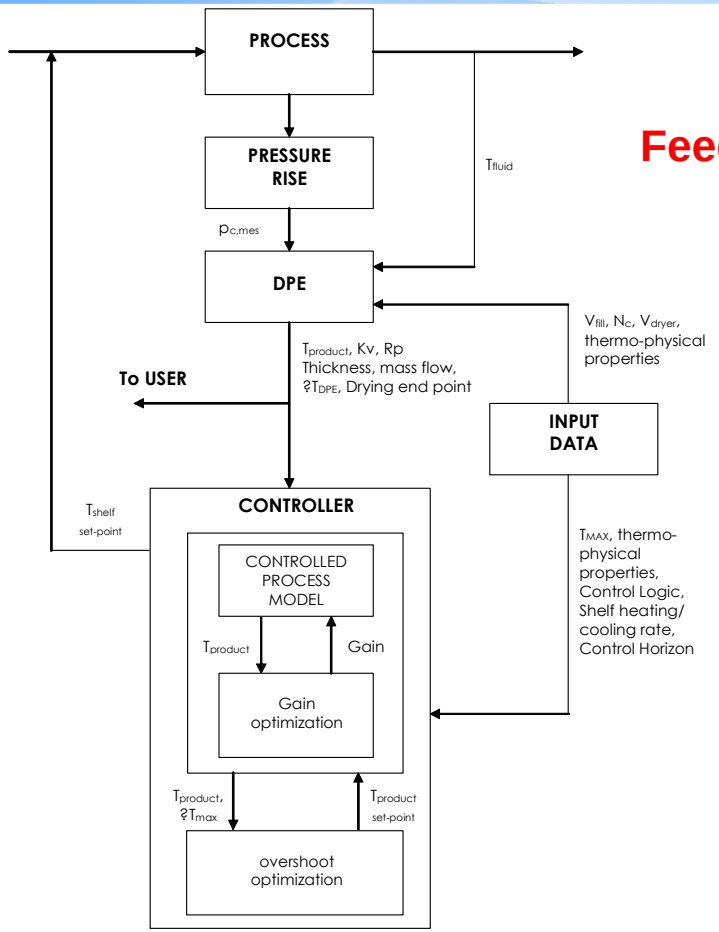
4. Control of the primary drying: *LyoDriver*



Feedback controller

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4. Control of the primary drying: *LyoDriver*

comparison of different control logics

Model-based controller:

- The optimal sequence of shelf temperature set-points throughout all the horizon time is calculated as a piecewise-linear function in such a way that the bottom product temperature is equal to the target value

$$\begin{cases} T_{f,sp1} = T_{B,sp} - \left[1 - k_v \left(\frac{1}{k_v} + \frac{L_f(t_0)}{k_f}\right)\left(T_{B,sp} - T_i(t_0)\right)\right]^{-1} & t_0 \le t < t_1 \\ T_{f,sp2} = T_{B,sp} - \left[1 - k_v \left(\frac{1}{k_v} + \frac{L_f(t_1)}{k_f}\right)\left(T_{B,sp} - T_i(t_1)\right)\right]^{-1} & t_1 \le t < t_2 \\ \vdots & \\ T_{f,spn} = T_{B,sp} - \left[1 - k_v \left(\frac{1}{k_v} + \frac{L_f(t_{n-1})}{k_f}\right)\left(T_{B,sp} - T_i(t_{n-1})\right)\right]^{-1} & t_{n-1} \le t < t_n \end{cases}$$

- **Pros**: simpler mathematical formulation, lower computational time, no need to solve additional optimization problems

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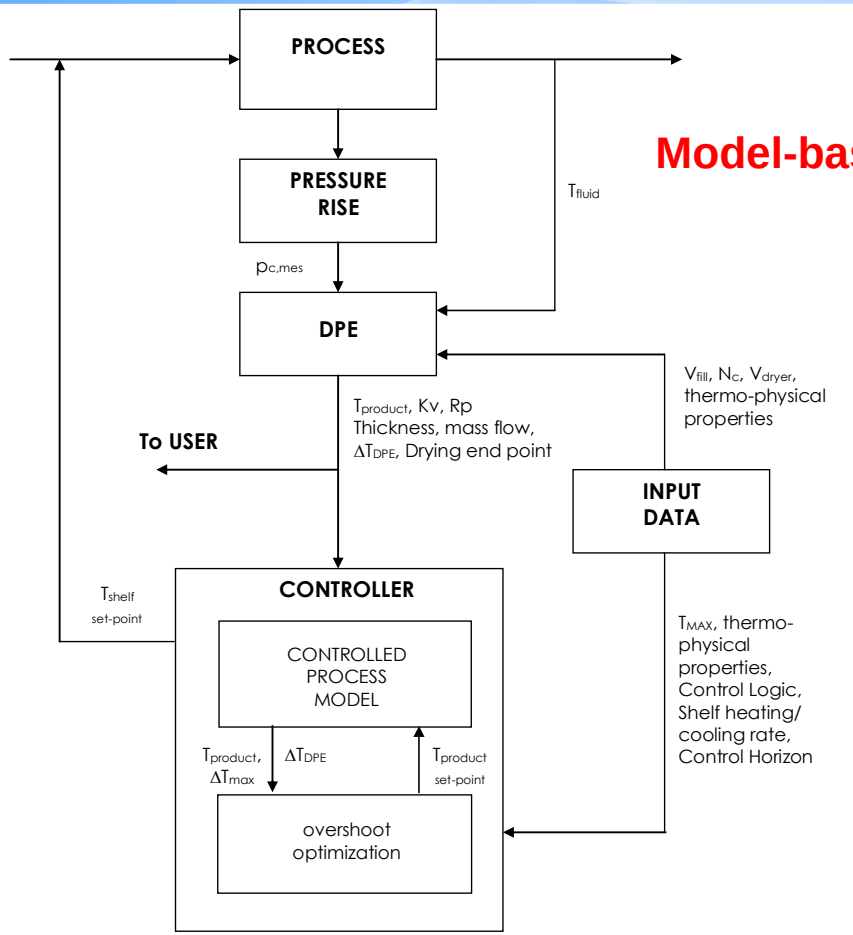
Control of the primary drying: *LyoDriver*



Model-based controller

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4. Control of the primary drying: *LyoDriver*

- In both approaches after each PRT the parameters of the model (e.g. the overall heat transfer coefficient between the shelf and the product, K_v, the water diffusivity in the dried layer,k_1, the product temperature) are updated
- **Pros**
  - unsteady-state modeling of the primary drying
  - based on an advanced predictive control algorithm
  - takes into account the real dynamic response of the heating system to change the fluid temperature set-point
  - predicts potentially damaging temperature overshoot and anticipates the control action accordingly
  - automatically select the best fluid temperature in such a way that the maximum allowable product temperature is never overcome, even during the PRT

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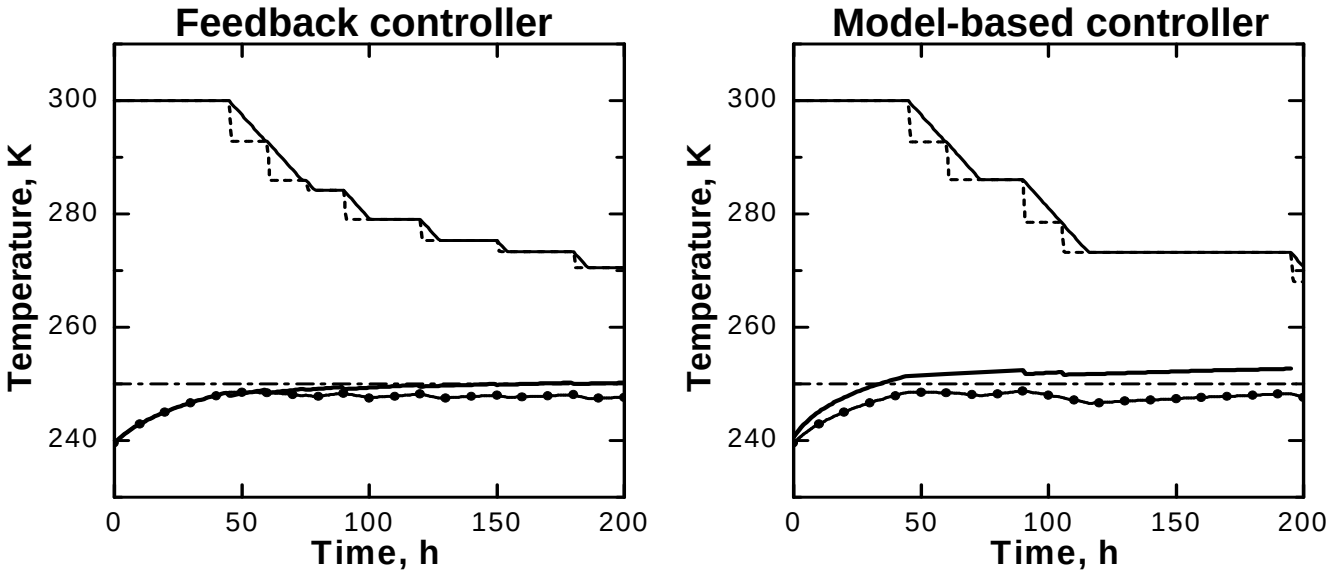
4. Control of the primary drying: *LyoDriver*

Robustness: influence of uncertainty in process variables estimation



Comparison between Feedback and Model-based controller in case of erroneous initial system state (a 25% error has been introduced on K_v).

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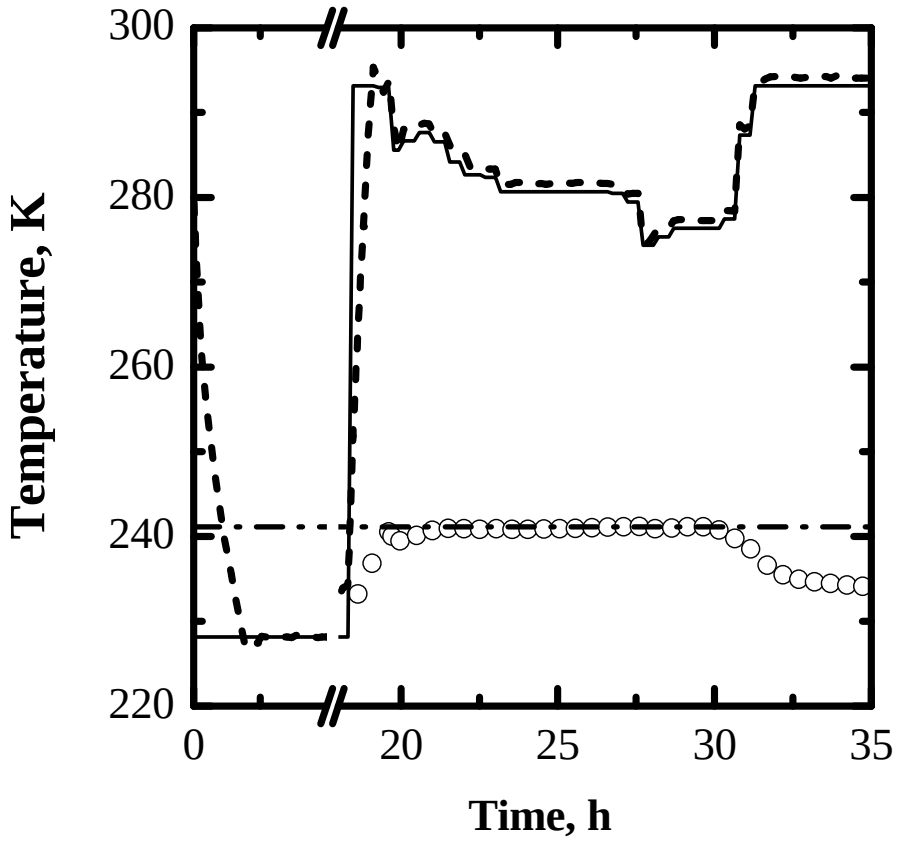
4. Control of the primary drying: *LyoDriver*

examples of process control in industrial prototype



Example of a freeze-drying cycle applied to 713 vials ($d_{v,i}$= 14.25 mm) filled with 1 mL of a 10% by weight sucrose solution (T_g=-32 °C).

The freezing phase has been run at 323 K for about 5 hours, while the sublimation step has been run at 10 Pa using *LyoDriver* controller to manipulate the heating fluid temperature.

special Lyobeta-25 prototype (Telstar, Terrassa).

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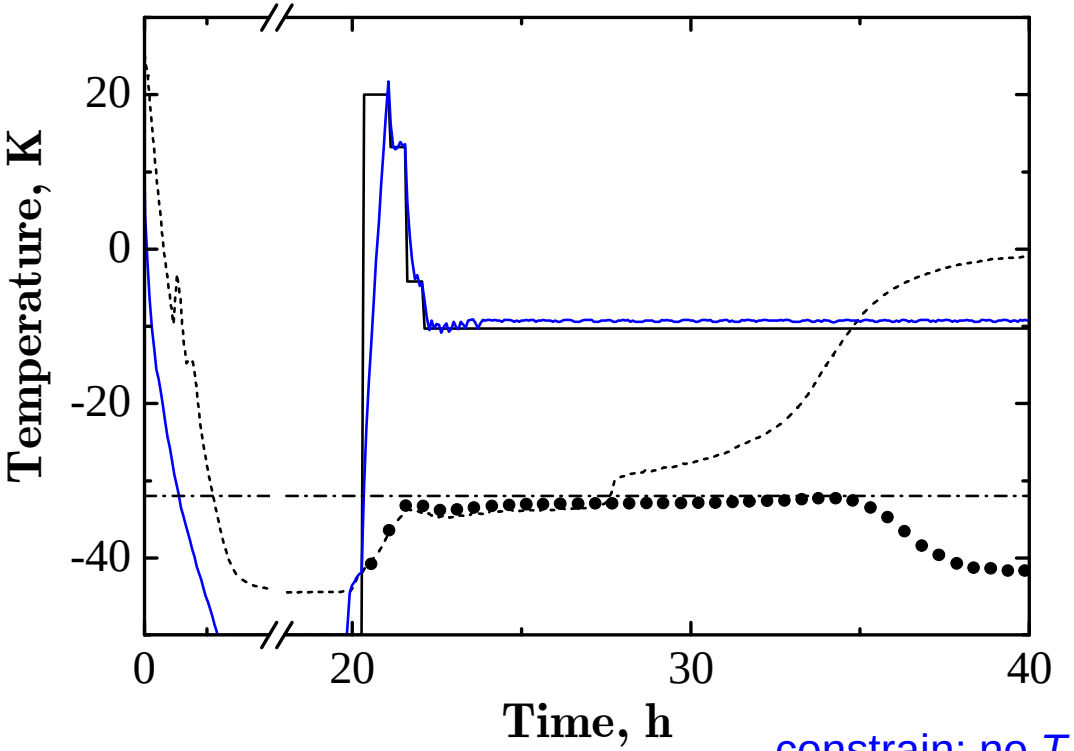
4. Control of the primary drying: *LyoDriver*

examples of process control in industrial prototype



Example of a freeze-drying cycle applied to 636 vials ($d_{v,i}$= 14.05 mm) filled with 1 mL of a 10% by weight sucrose solution (T_g=-32 °C).

The freezing phase has been run at 323 K for about 5 hours, while the sublimation step has been run at 10 Pa using *LyoDriver* controller to manipulate the heating fluid temperature.

constrain: no T increase after T_{shelf} started to be reduced

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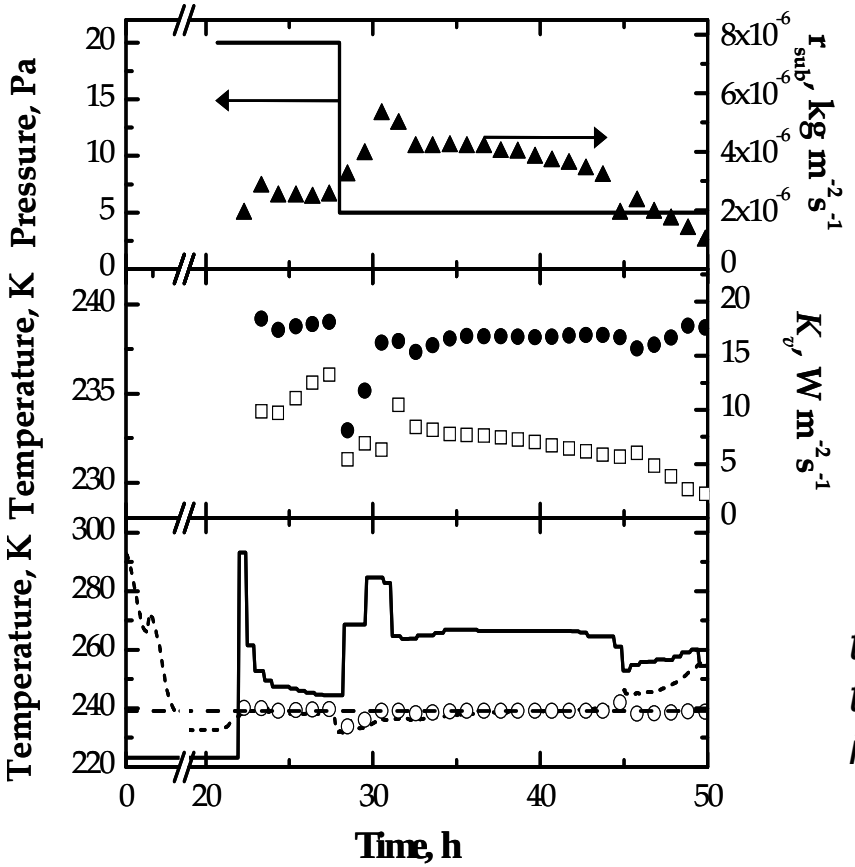
4. Control of the primary drying: *LyoDriver*

examples of process control in industrial prototype: ***pressure switch***



Example of results obtained during a FD cycle run using *LyoDriver* to monitor and control the main drying step.

The batch is composed of 155 medium-sized glass vials on tray ($D_{v,i}$= 20.85 mm) filled with 3 mL of a 10% by weight sucrose solution (T_g=241 K).

After freezing, the chamber pressure has been set at 20 Pa and lowered to 5 Pa after 5 hours.

the system can efficiently control the process following a change in pressure

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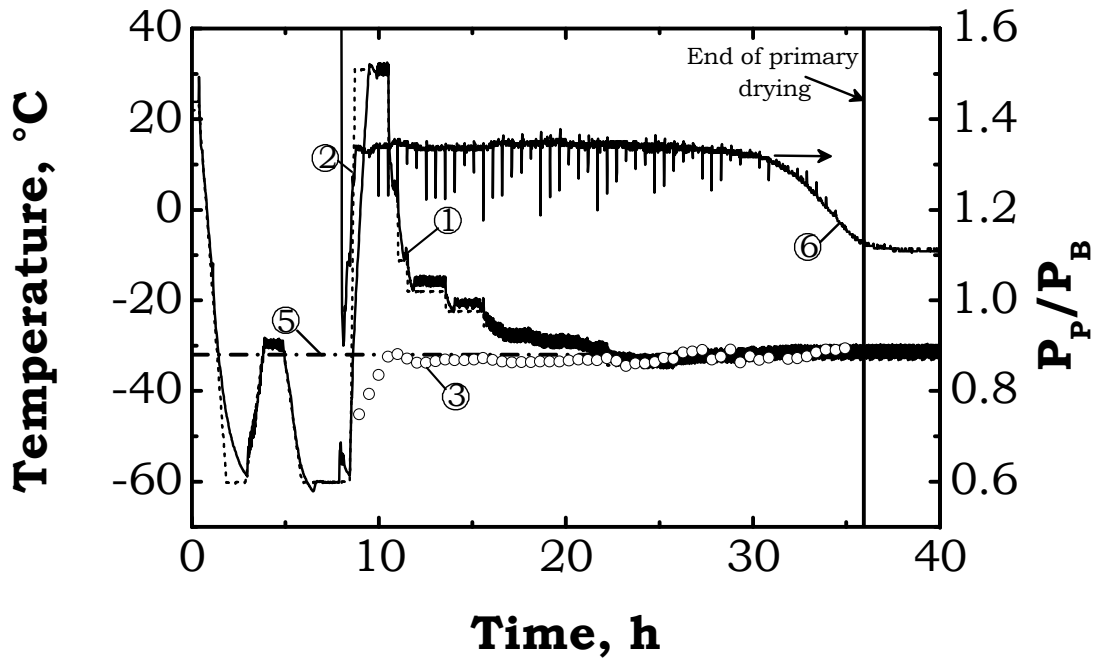
4. Control of the primary drying: *LyoDriver*

examples of process control: ***transition to mass transfer control***



(1) heating fluid temperature, °C
(2) set-point heating fluid temperature, °C
(3) bottom product temperature estimated through DPE, °C
(4) product temperature measured by a thermocouple in a vial, °C target temperature, K
(5) Pirani to Baratron pressure ratio

Example of optimal freeze-drying cycles obtained using LD controller to set the optimal fluid temperature for the primary drying stage of a complex formulation (4% mannitol, 1% sucrose, plus excipients). Data supplied by **Telstar**.

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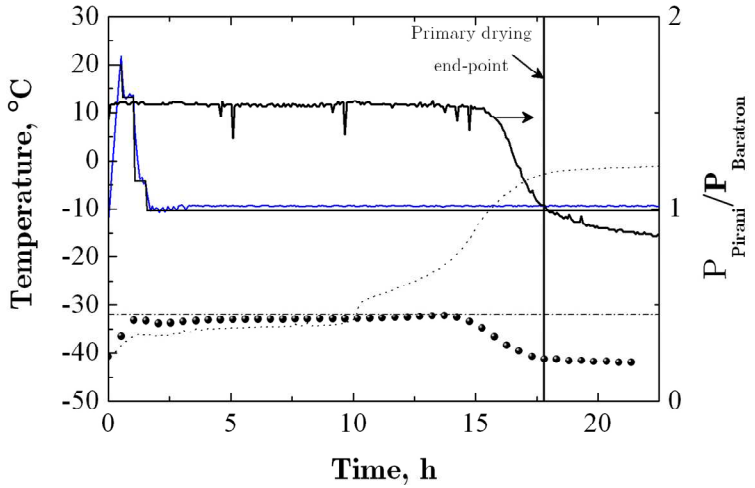
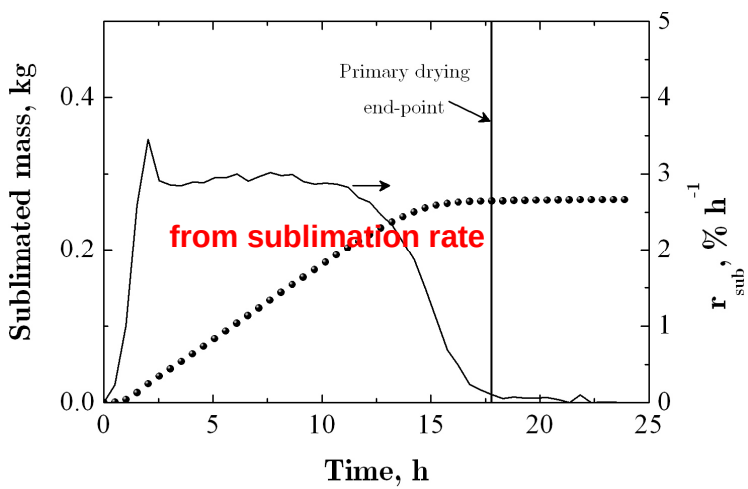
4. Process monitoring: detection of the primary drying end-poin: the *stop criterion in LyoDriver*





FD cycle applied to a 10% by weight sucrose solution.
(P_C=10 Pa, N_{vials}=235, $d_{v,i}$=20.85×10^{-3} m, L_{froz}=7.2×10^{-3} m, batch shielded).

A new criterion has been established and tested using:
- the estimation of the solvent flux evolution (from PRT) and its time evolution
- a reduced mathematical model of the vial that allows estimating the end-point time and distinguishes between the end and the start-up of the cycle, when the drying kinetics is very low

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4. Control of the primary drying: *pressure manipulation*

- The constant process pressure can be selected (and optimized)
- In case of mass transfer control, ***LyoDriver*** tries to minimize the drying time heating the product at its target, but in this case the shelf temperature approaches the product temperature, and the control action is not very effective (even if the product integrity is assured).
- A new value of pressure can be selected by an algorithm
- but a novel control tool that manipulates **both** the shelf temperature and the chamber pressure can be designed.

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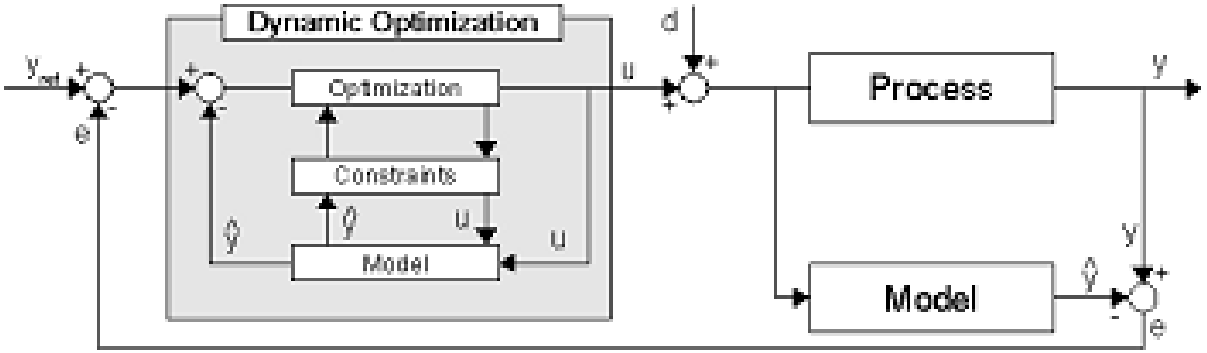
4. Control of the primary drying: MPC



Model Predictive Control is efficient tool to solve this problem; it utilizes a process model for two central tasks:

- Prediction of future plant behavior
- Computation of appropriate corrective control action required to drive the predicted output as close as possible to the desired target value

- An example of the MPC software developed by POLITO will be shown in section 5 for automatic cycle development

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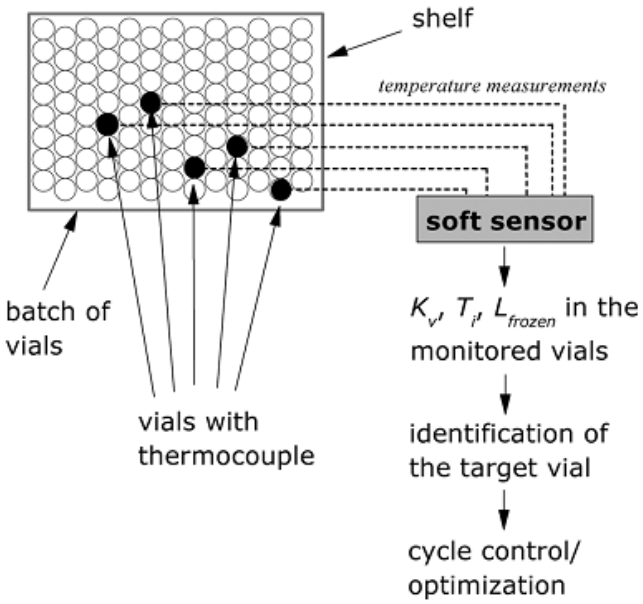
4. Control of the primary drying: use of soft sensors

- The same control logics previously described can be used coupled with other monitoring devices, e.g. the **soft-sensors**. This novel tools can also be exploited to evaluate the batch unevenness and, thus, calculate the best heating policy for the most critic vials.



An observer, or software sensor, allows to monitor immeasurable interesting process variables like product temperature and interface position, just measuring one or more temperatures.

Bosca *et al*, *Drying Technol* **31** (2013)

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4. Control of the primary drying: soft-sensors

Pros and Cons

- It can estimate the whole temperature profile
- It is a non-invasive method
- It gives just information concerning the monitored vial
- It can be used to evaluate batch heterogeneity

The soft-sensor can be particularly useful to control a process in case the batch is highly **heterogeneous**: various observers can track the dynamics in some vials placed in different position in the drying chamber and the higher product temperature can be used by the controller to manipulate the shelf temperature.

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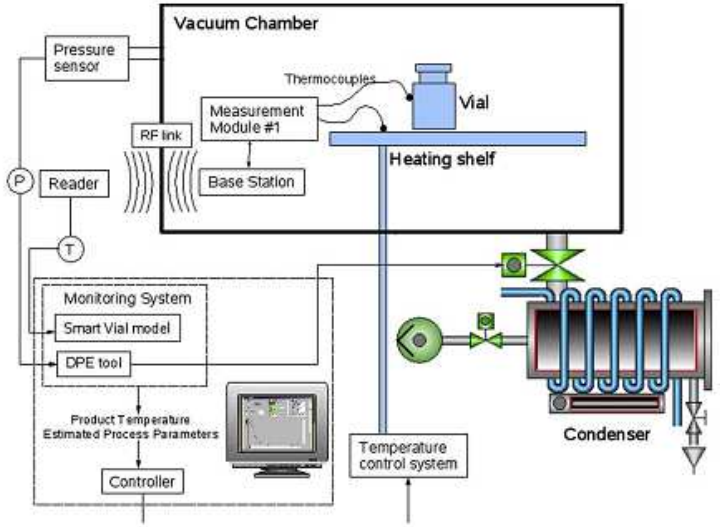
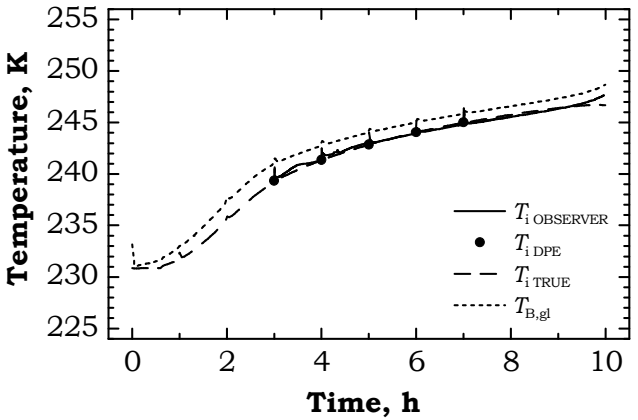
4. Control of the primary drying: soft-sensors

an hybrid control system





Barresi et al, *Int J Refrig.* **32** (2009)

Fig. 4 – Scheme of the monitoring and control system for the freeze-drier, including both the *smart vial* observer and the Dynamic Parameters Estimation (DPE) tool based on pressure rise tests. The architecture of the special thermometer with the wireless transmission system is also shown.

Synergic action of DPE and of the Kalman observer (*smart vial*) based on the measure of the external temperature of the vial (dotted line). Black symbols: temperatures identified by DPE method; continuous line: observer estimation; dashed line: true interface temperature.

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4. Control of the primary drying: new perspectives

- **Effective process control** (industrial production)
  - Eliminating the effect of disturbances
  - Reducing product variability
  - Estimating the batch unevenness and choosing a proper control action to meet the **6-sigma** goal

- **Scouting** (Lab scale)
  - **Development of the optimal recipe for a specific product in only one run** without resorting to empirical rules (*examples shown in section 5*)

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Cycle development and optimisation

- **off-line optimisation**
  - use of design space (*built by modelling*)
- **in-line optimisation**
  - by using a control system
  - by using the soft sensors to build and refine in-line the design space

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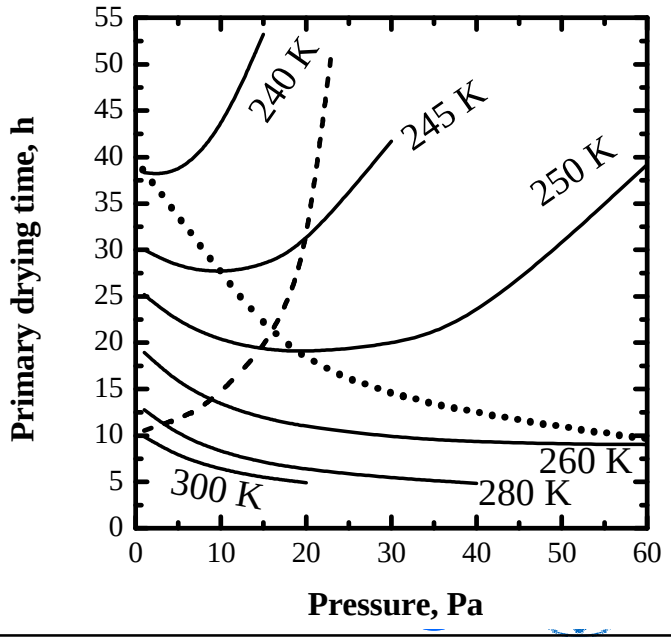
5. Process design: off line optimisation

The goal is the determination of an optimal heating shelf control strategy for the primary drying stage in order to minimize the drying time without impairing the integrity of the material.

A mathematical model of the process can be used to calculate off-line the optimal operating conditions (i.e. the shelf temperature and the chamber pressure) for the primary drying.

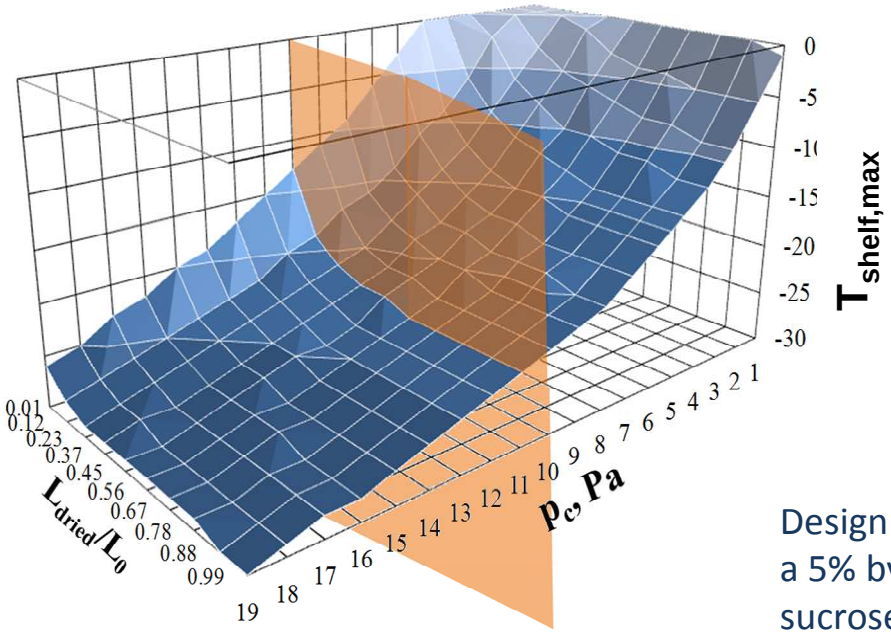
A very simple approach consists of carrying out the process using constant values for the chamber pressure and for the temperature of the heating shelf:



Effect of the chamber pressure and of the heating shelf temperature on the primary drying time in case of constant shelf temperature. The locus corresponding to the minimum of the primary drying time for the various shelf temperatures is also shown (dotted line). The dashed line corresponds to the values of chamber pressure and of shelf temperature that allow to satisfy the constraint on the maximum product temperature.

5. Process design: **design space**

At a given chamber pressure it is possible to determine the maximum temperature ($T_{shelf,max}$) of the heating shelf that maintain product temperature below the limit value.



Design space for the freeze-drying of a 5% by weight aqueous solution of sucrose.

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5. Process design: design space

- The design space of the process is defined by the set of operating conditions (*shelf temperature, chamber pressure, duration of the drying step*) that allow to fulfill product quality requirements, i.e. to maintain product temperature below the maximum allowed value
  - ✓ The design space can then be used to identify the "best" operating conditions, i.e. to minimize the duration of the primary drying.
  - ✓ **Mathematical modeling** (reduced or detailed) can be used to "build" the design space, starting from few experiments planned for characterizing the system, thus reducing the experimental effort.

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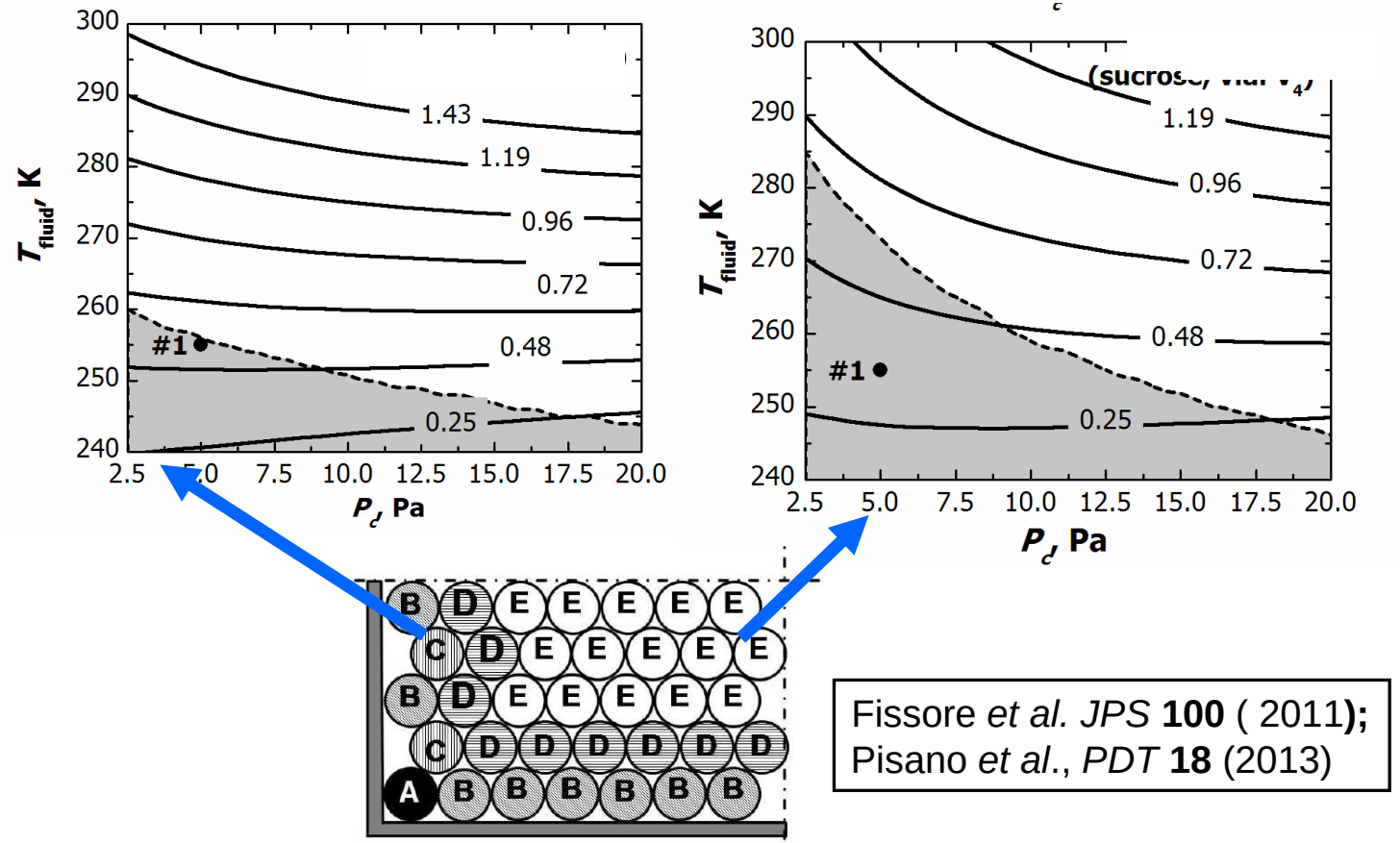
5. Process design: design space



Fissore *et al. JPS* **100** (2011**);**
Pisano *et al.*, *PDT* **18** (2013)

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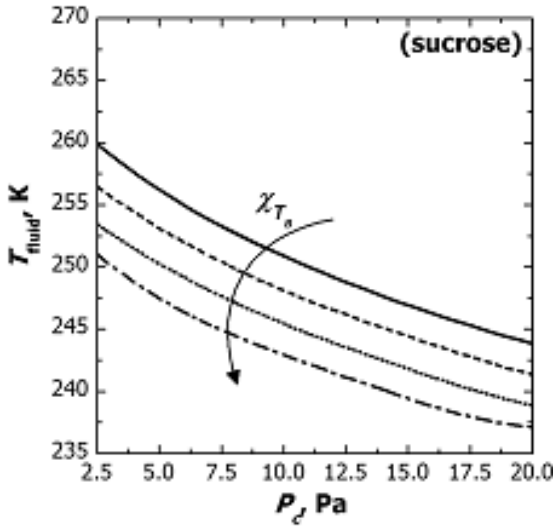
5. Process design: design space

- **Safety margin can be introduced also in the Design space**



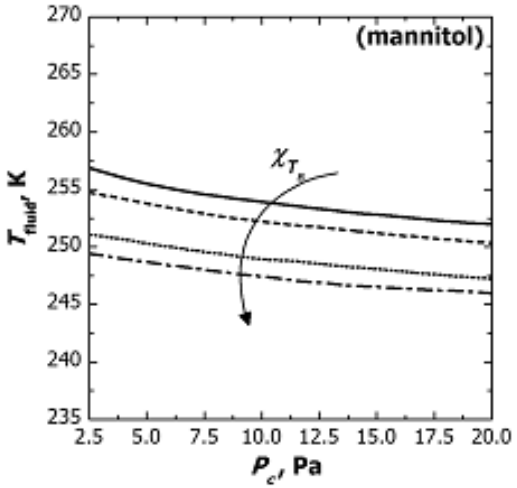


FIG. 5. Design space for 5% w/w sucrose ($T_{max}=240$ K) and 5% w/w mannitol ($T_{max}=248$ K) as calculated at $L_{dried}/L=99\%$ and considering a different value of target temperature ($T_{target}=T_{max}-\chi_{T_s}$): (solid line) $\chi_{T_s}=0$ K; (dashed line) $\chi_{T_s}=1$ K; (dotted line) $\chi_{T_s}=2$ K; and (dash-dotted line) $\chi_{T_s}=3$ K.

Fissore *et al.*, *Drying Technol.* **30** (2012)

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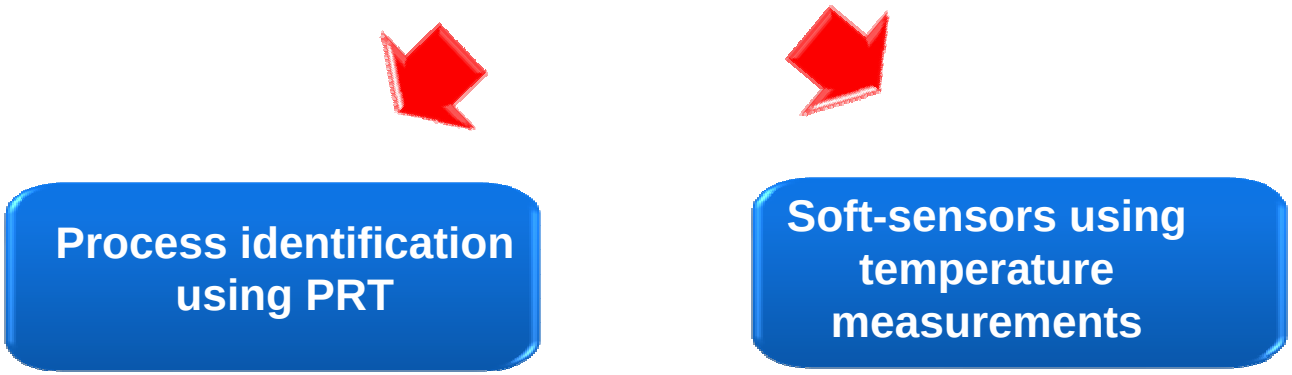
5. Process design: model based control

- **in-line optimization**, using available measurements of temperature or pressure (PRT: Pressure Rise Test) and a (reduced) mathematical model



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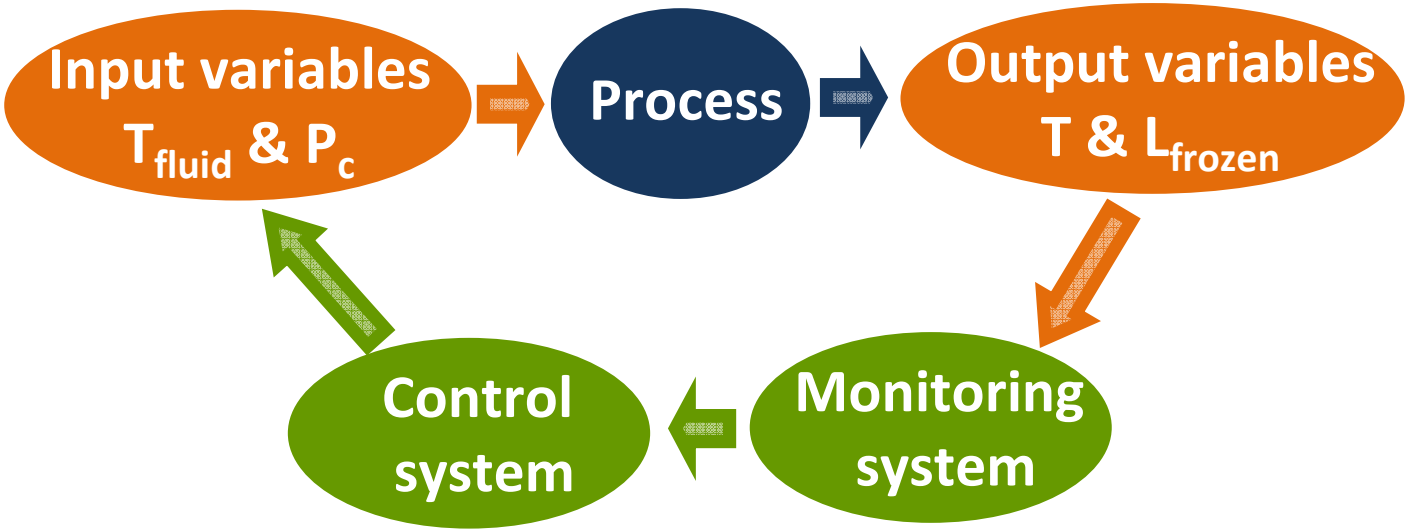
5. Process design: cycle development

- **Automatic control can allow recipe development in one step.**



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5. Process design: In-line recipe design

- **Traditionally, biotechnology processes are operated with fixed controls.**
- **A dynamic control strategy is used to operate the process:**
  - a PAT is used to monitor the state of the product
  - a mathematical model can be exploited to calculate the suitable control actions.
- **A Model Predictive Control (MPC) algorithm calculates a sequence of control actions, one for each sampling interval, solving an optimization problem:**

$$\min_{u(k)\ldots u(k+h_c-1)} \sum_{j=k+1}^{k+h_p} \left[y_{\text{ref}}(j) - \left(y(j) + \hat{e}(k) \right) \right]^2$$

Manipulated variables

Target value for the controlled variables

Controlled variables

Modeling error

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5. Process design: In-line recipe design by MPC

- **The manipulated variables in a freeze-drying process are T_{fluid} and P_c. Two different cases can be considered:**

✓ Both T_{fluid} and P_c are manipulated **MPC - 2**

The controller will minimize the difference between the sublimation flux and the target value

✓ Only T_{fluid} is manipulated **MPC - 1**

The controller will minimize the difference between maximum product temperature and the limit value

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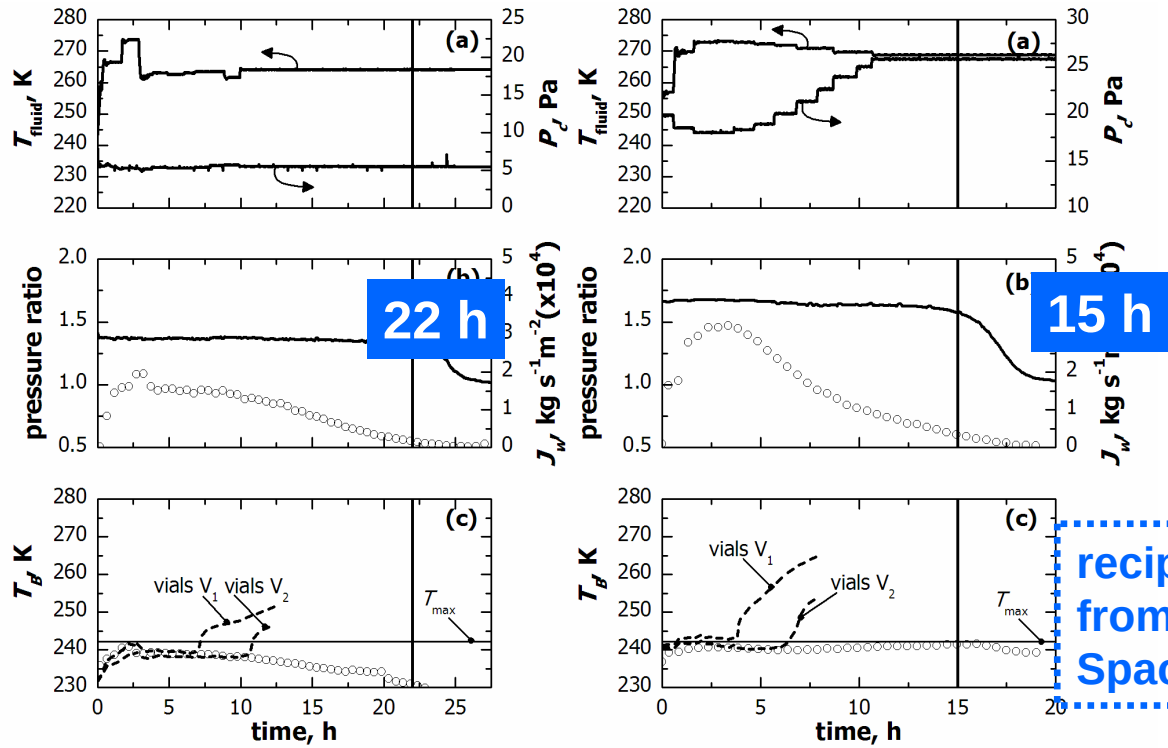
5. Process design: In-line recipe design by MPC

Freeze-drying cycles carried out using a **5% sucrose solution**, and the MPC algorithm to manipulate only T_{fluid} and both T_{fluid} and P_c.



recipe calculated from the Design Space: 27 h

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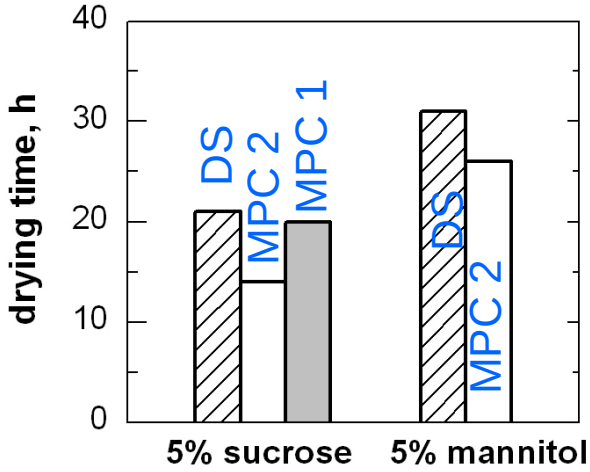
5. Process design: In-line recipe design: final remark

- The design space provides a lot of information about the effect of the operating conditions on the process (product temperature and process duration), but …
- recipe optimization can be **less effective** than that achieved using the model predictive control algorithm.



- The design space allows to easily manage the non-uniformity of the batch.

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5. Process design: In-line recipe design: final remark

- To provide an effective in-line optimization, the freeze-dryer has to be equipped by a proper monitoring device that, mainly in a manufacturing plant, is not always available, and...
- it can be difficult to take into account the non-uniformity of the batch.

Disturbance rejection

- When using the model predictive control system it is possible to get the optimal cycle in just one run, and potential disturbances affecting the dynamics of the process can be rejected.
- By contrast, a similar situation can be successfully managed by the off-line optimization only introducing a large “safety margin”, thus resulting in a longer drying time.

Recipe scale-up

- Both approaches can be used both in small-scale and in large-scale freeze-dryers for recipe design, thus avoiding to scale-up the cycle.

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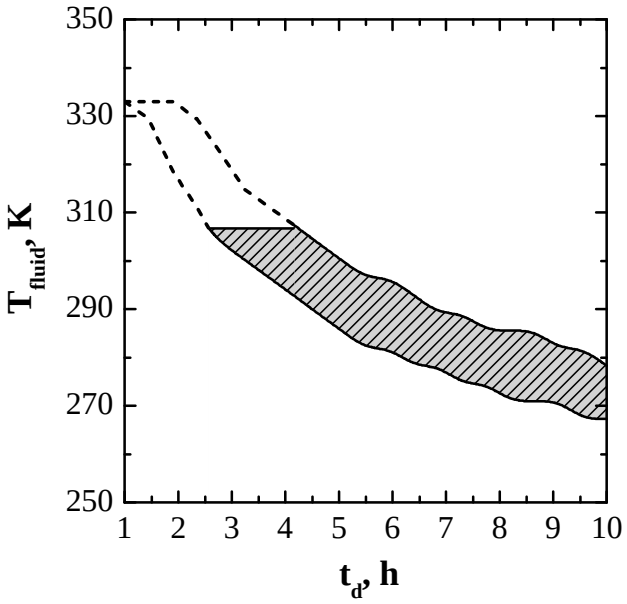
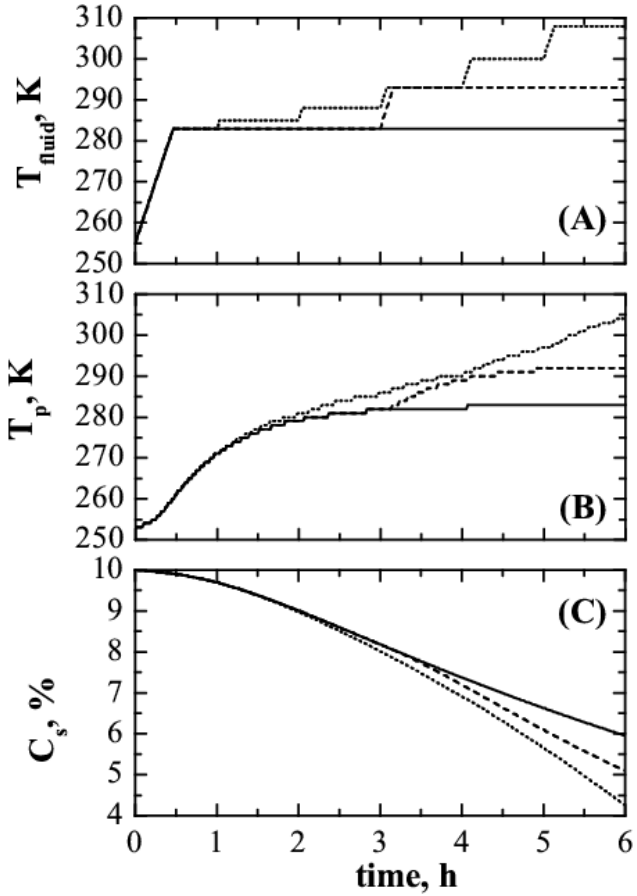
5. Process design: secondary drying step

Design space

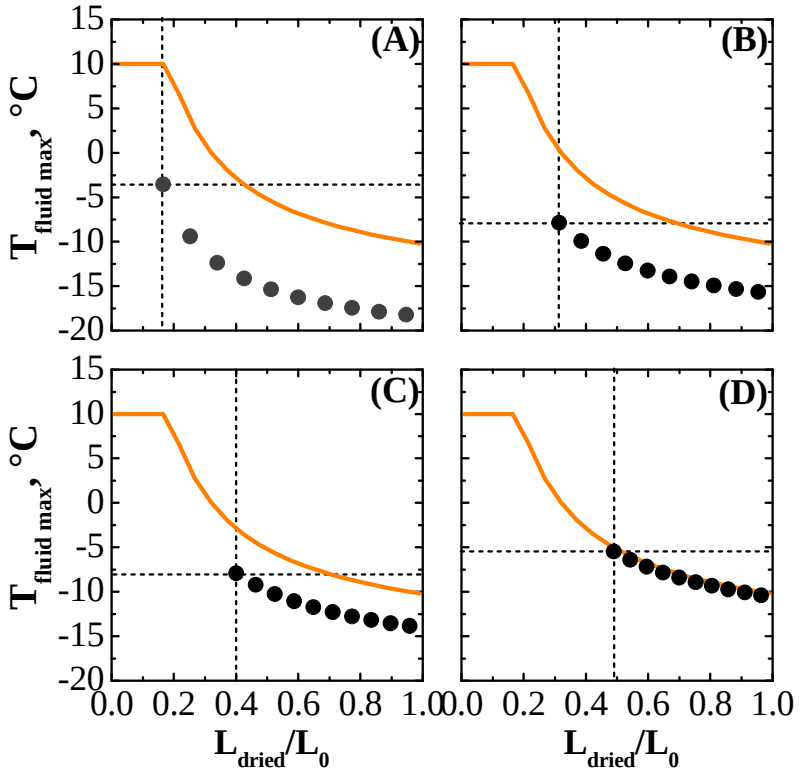


$C_{s,0}$ = 7%. $C_{s,t}$ = 2–4%.

Process Optimization



5. Process design:
In-line recipe design using soft sensors



$T_{shelf,max}$ vs. cake thickness can be determined using *ad hoc* experiments, or it can be determined in-line using the proposed soft-sensor.

Evolution of the design space estimated by the observer (●) as a function of the dried product thickness in comparison with the optimal one (—).

Bosca *et al. Drying Technol.* **34** (2016)

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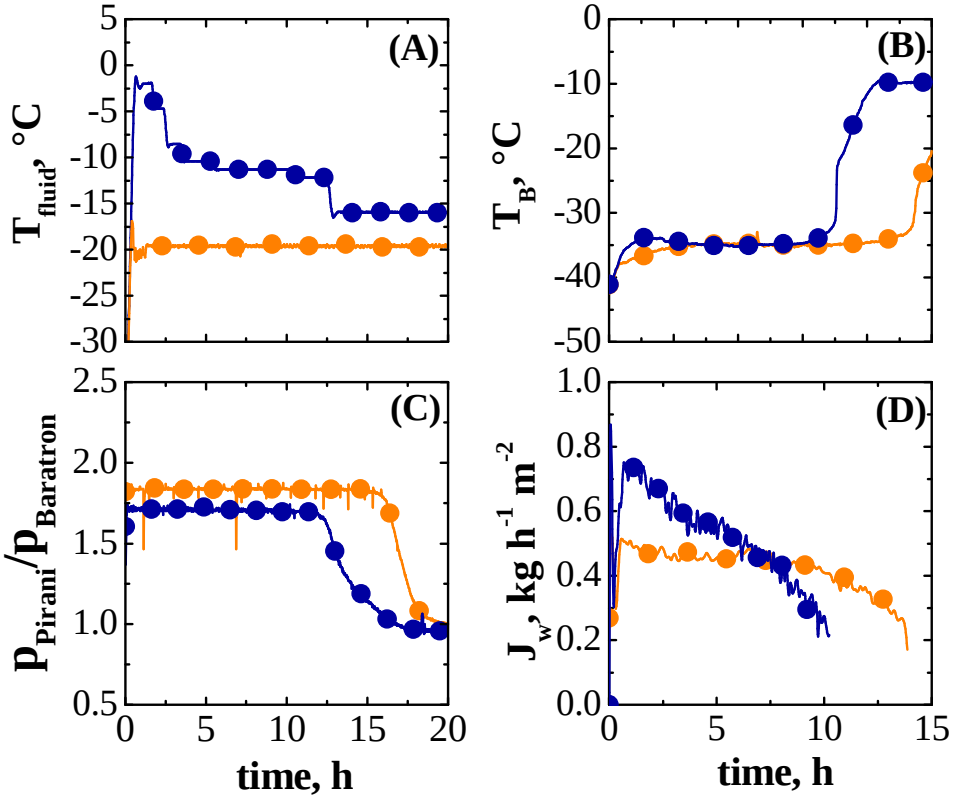
5. Process design:
In-line recipe design using soft sensors



Comparison between the results obtained in a freeze-drying process (5% by weight aqueous solution of sucrose, p_c = 10 Pa) carried out with a constant value of the shelf temperature (●) and with a cycle calculated using the observer (●).

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6. Process understanding and process transfer

Process transfer and scale up

- **Problem statement:**
  - the importance of an optimized and robust recipe
  - robustness and design space
  - process understanding at the base of a successful scale up
  - different approaches to scale-up
    - *use of automatic control systems*
    - *use of design space concept*
  - *equipment characterization and modeling*

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6. Batch failure: process transfer

One typical problem is the process transfer, from pilot to industrial scale, or from one plant to another. If failure occurs, an expensive procedure has to be undertaken to adapt the “recipe” to new conditions.

The monitoring of the process helps solving the problem: it is sufficient to think in terms of “recipe for the product” and not “recipe for the equipment”

Possible approaches:

- to develop “robust correlations” to transfer process from one equipment to another one. For scale up purposes it is possible to have a “magic couple” freeze drier, that is an industrial one, a pilot scale (and the know how for the process transfer, that has to be realized for that equipment)

- to ask the control system to do the job for you: just tell him which is the “product recipe” you want. If the large scale equipment is not equipped with the control system, this can be done virtually, using a simulation tool (after a proper equipment characterization)

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6. Process understanding and process transfer

- **The reasons at the basis of the scale-up/process transfer problem are numerous:**
  - **Environmental conditions in the processing area** can affect the nucleation of the ice crystals and, thus, the resistance of the dried layer to vapor flow in the primary drying step.
  - **Shelf surface temperature** can be different in different pieces of equipment even when the heat transfer fluid temperature set point is the same.
  - **Radiation from chamber walls** and from the shelf affects the heat transfer to the product.
  - **Local value of chamber pressure** and the composition of the gas are a function of the geometrical characteristics of the equipment and of the operating conditions.

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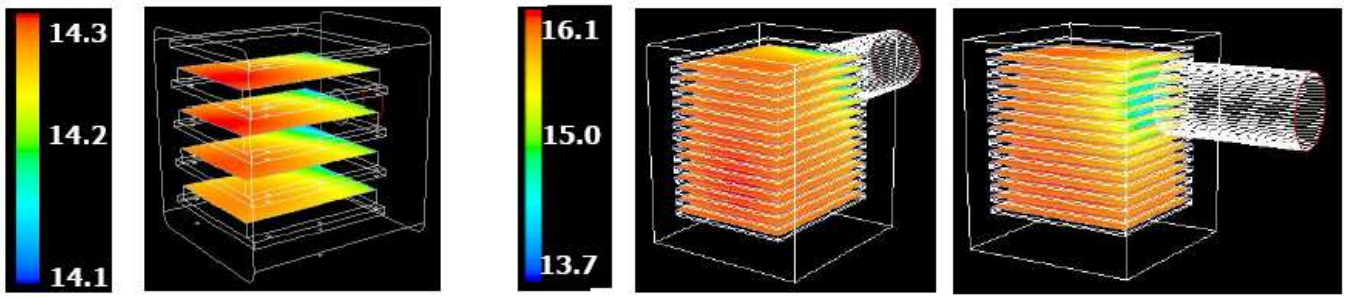
6. Process understanding

Scale up

Example of the difference in the pressure distribution in a small pilot and in an industrial scale apparatus



Results obtained by CFD calculations at Politecnico di Torino
[courtesy by Telstar Industrial, Terrassa, Spain]

ref. Barresi A.A., Pisano R., Rasetto V., Fissore D. and Marchisio D.L., 2010, Model-based monitoring and control of industrial freeze-drying processes: effect of batch nonuniformity. *Drying Technol*. **28** (5), 577-590

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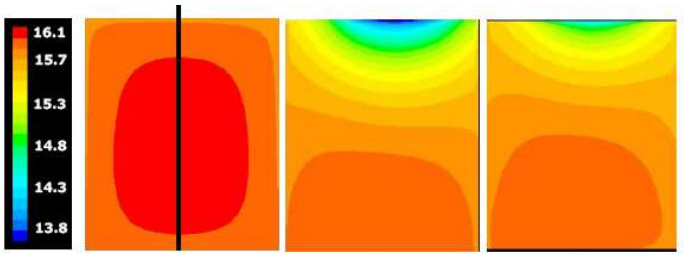
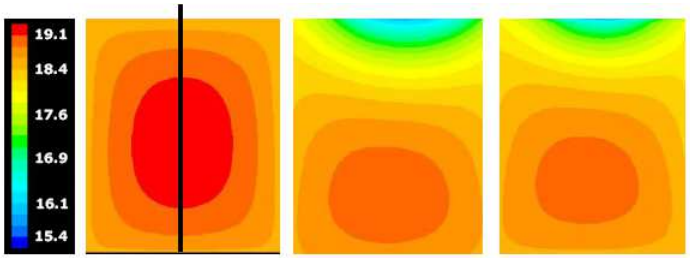
6. Process understanding

Process transfer

Example of differences in the pressure distribution over different shelves of the same equipment, for different shelf-to-shelf distances.



14 shelves, LyoMega 400



17 shelves, LyoMega 400

Results obtained by CFD calculations at Politecnico di Torino
[courtesy by Telstar Industrial, Terrassa, Spain]

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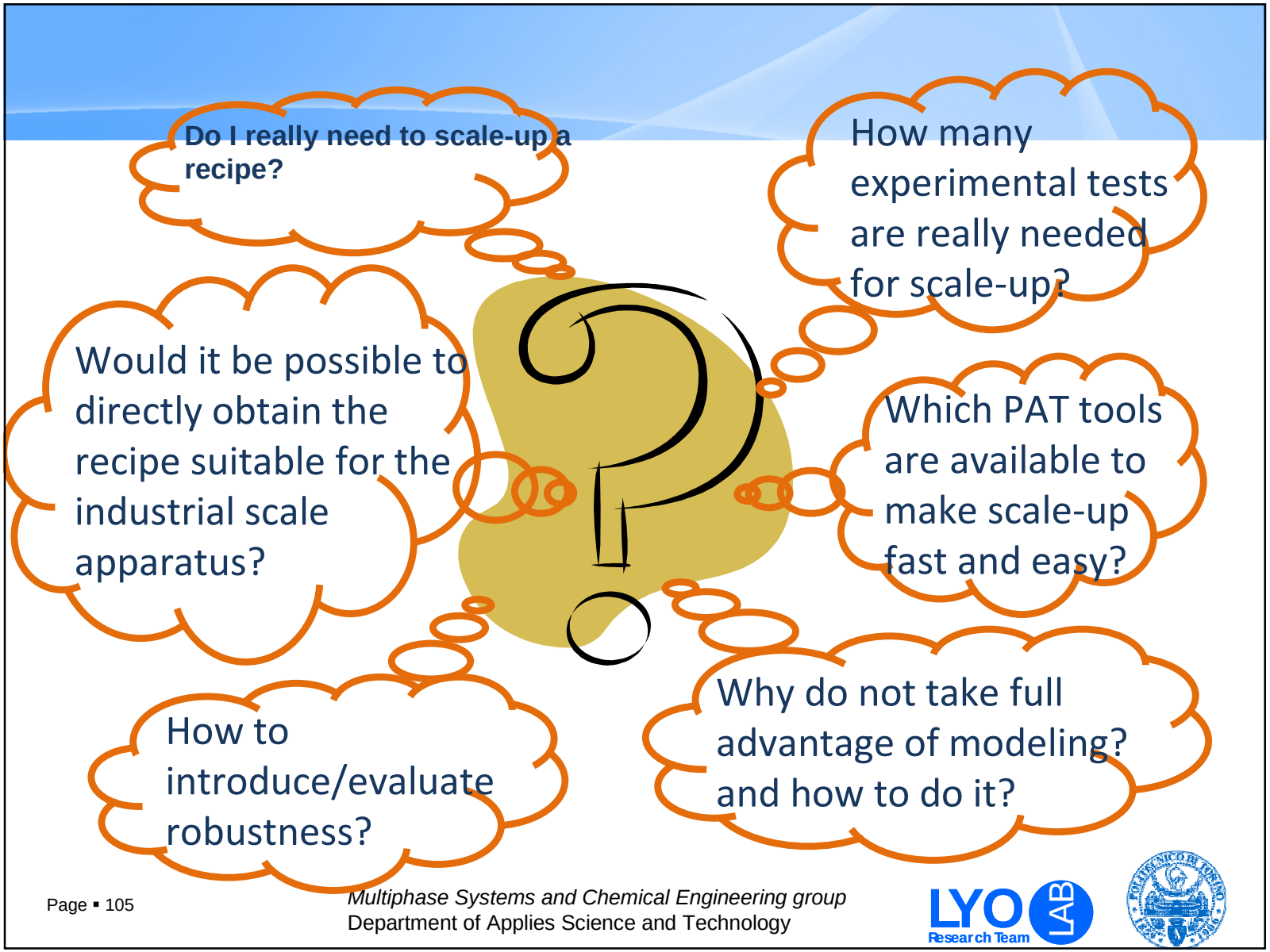

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6. Recipe scale-up: off line vs in line approach

The problem of recipe scale-up can be solved:

✓ **off-line**, calculating the new recipe in the large-scale freeze-dryer in such a way that the “history" of the product is equal to that obtained in the small-scale freeze-dryer

- ✓it may be necessary to limit the similarities to a selected fraction of the lot
- ✓in case the design space approach is used, it is sufficient to remain within the design space of the large scale equipment

✓ **in-line**, using an "advanced" control system (by this way we do not perform a true scale-up of the recipe, but we identify in-line the best oeprating conditions for the product)

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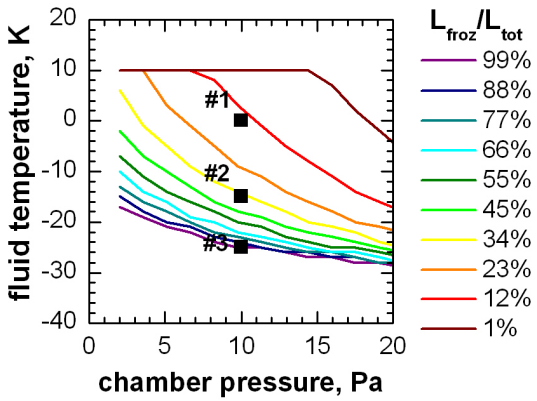
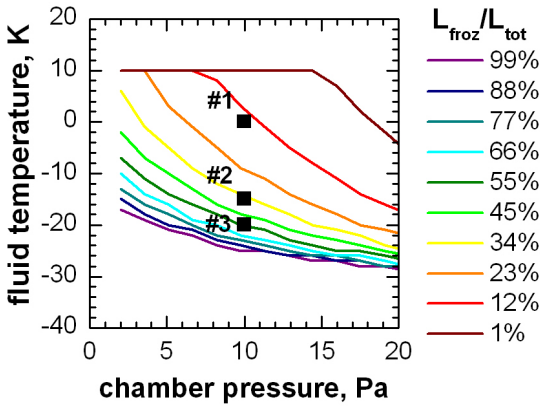
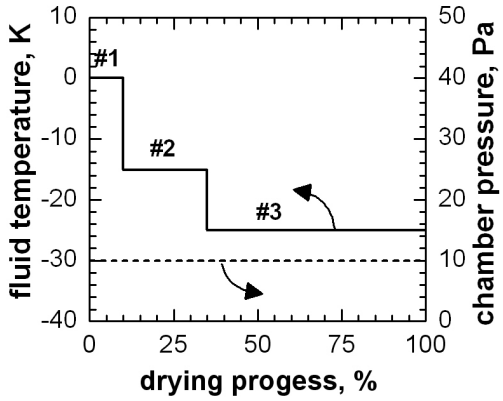
6. Process transfer: the design space

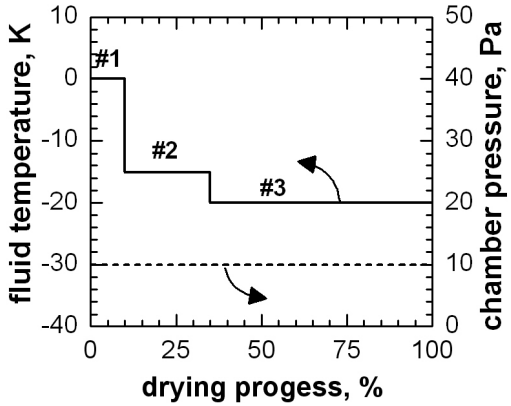
Mathematical modeling can be used to build the design space (in case model parameters are known) and, thus, it is possible to evaluate if the recipe can be used without modification or not.

process transfer required





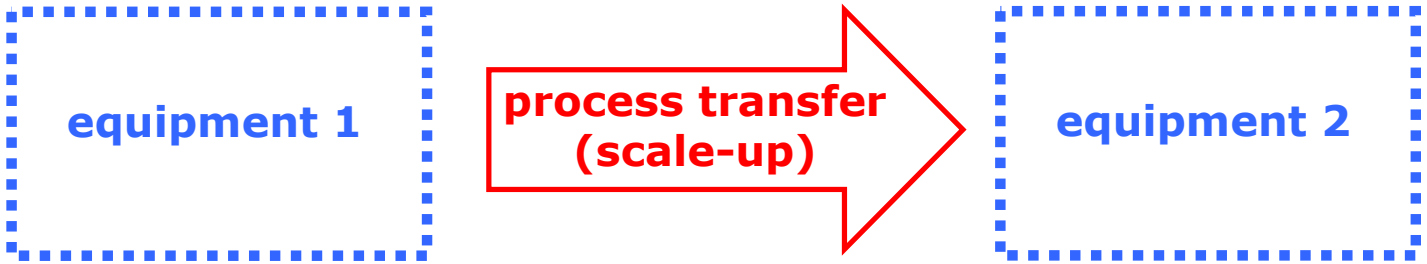




suitable recipe

6. Process transfer and scale up

The problem of the scale-up (or process transfer) of a freeze-drying recipe obtained in an equipment "1" to a different equipment "2" consists of determining the operating conditions in the equipment "2" so that the dynamics of the product (i.e. the values of temperature and residual amount of ice vs. time) is the same in the two pieces of equipment.



Barresi & Fissore, *Drying Technol.* **29** (2011)

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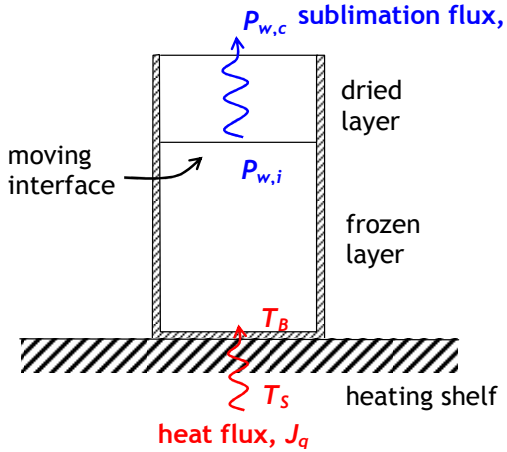
6. Process transfer and scale up: 1 D model

Radial gradients of temperature and composition are neglected.

Heat flux to the product $J_q = K_v\left(T_S - T_B\right)$

Sublimation flux of the solvent $J_w = \frac{1}{R_p}\left(P_{w,i} - P_{w,c}\right)$



A mono-dimensional model constituted by the energy balance for the frozen product and the mass balance for the water vapor in the dried product (both taken in pseudo-stationary conditions because of the slow dynamics of the process) can be used to simulate the primary drying.

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6. Process transfer and scale up: 1 D model

- **Heat transfer (from the shelf to the product in the vial)**

$$J_q = K_v \left(T_s - T_B \right)$$

$$K_v = A + \frac{B \cdot P_c}{1 + C \cdot P_c}$$

- **Mass transfer (from the interface of sublimation to the drying chamber)**

$$J_w = \frac{1}{R_p} \left(P_{w,i} - P_{w,c} \right)$$

$$R_p = R_{p,0} + \frac{P_1 \cdot L_d}{1 + P_2 \cdot L_d}$$

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6. Scale-up (process transfer) procedure

1. Gravimetric test in equipment “1” to determine the heat transfer coefficient K_v in each vial of the batch.
2. Identification of the groups of vials in equipment “1”.
3. At least other two gravimetric tests in equipment “1” at different pressures in order to the determine the coefficients A, B, & C.
4. One gravimetric test in equipment “2” to determine the heat transfer coefficient K_v in each vial of the batch.
5. Identification of the groups of vials in equipment “2”.
6. Determination of the parameter A for the various groups of vials in equipment “2”.
7. Determination of the curve R_p vs. L_{dried}, i.e. the parameters $R_{p,0}$, P_1 and P_2 in equipment “1”. It is possible to use the balance during the gravimetric tests, or to carry out a cycle and using the Pressure Rise Test or the TDLAS sensor.
8. Model validation in equipment “1” *(optional)*.
9. Determination of the curve R_p vs. L_{dried} in equipment “2”, or check if the curve determined in equipment “1” is suitable.

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6. Process transfer and scale up

Which is the target?

1. **The dynamics of the product (temperature and residual amount of ice *vs*. time) has to be the same in the two pieces of equipment**

   → It is possible only in case R_p is the same

2. **Only the evolution of the temperature of the product (or of the sublimation flux) has to be the same in the two pieces of equipment**

   → in case Rp is significantly different

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6. Process transfer and scale up

Let us consider the case where $R_{p,1} = R_{p,2}$, i.e. the resistance of the dried layer to vapor flow is not different in the two pieces of equipment (this hypothesis is not unrealistic in case the same cooling rate is used).

The following equation holds, that correlates the temperature of the heating shelf (T_S), the temperature of the product at the interface of sublimation (T_i), the temperature of the product at the bottom of the vial (T_B) and the thickness of the frozen layer (L_{frozen}):

$$T_B = T_{shelf} - \frac{1}{K_v}\left(\frac{1}{K_v} + \frac{L_{frozen}}{k_{frozen}}\right)^{-1}\left(T_{shelf} - T_i\right)$$

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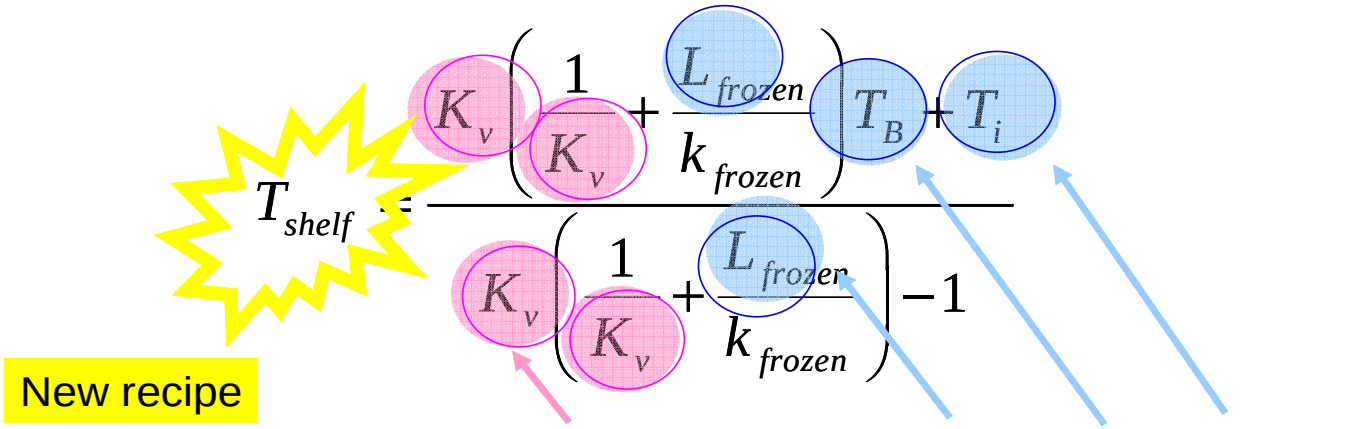
6. Process transfer and scale up

Previous equation can be written as:



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6. Scale-up (process transfer) procedure

[…]

10. Given the values of the operating conditions (T_S and P_c vs. time) and of model parameters (K_v and R_p) in the equipment "1" it is possible to calculate the evolution of the product during primary drying:

$$\frac{dL_{frozen}}{dt} = -\frac{1}{\rho_{frozen} - \rho_{dried}} \frac{1}{R_p} \left[P_{w,i}(T_i) - P_c \right]$$

$$\left(\frac{1}{K_v} + \frac{L_{frozen}}{k_{frozen}} \right)^{-1} (T_S - T_i) = \Delta H_s \frac{1}{R_p} \left[P_{w,i}(T_i) - P_c \right]$$

$$T_B = T_S - \frac{1}{K_v} \left(\frac{1}{K_v} + \frac{L_{frozen}}{k_{frozen}} \right)^{-1} (T_S - T_i)$$

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6. Scale-up (process transfer) procedure

11. **For each time instant *t*, given the values of T_i, T_B and L_{frozen} and the different value of the heat transfer coefficient in equipment "2" (K_v*) it is possible to calculate the value of the shelf temperature in equipment "2", at that time instant, in such a way that the state of the product (T_i, T_B and L_{frozen}) is the same:**

$$T_S^* = \frac{K_v^* \left(\frac{1}{K_v^*} + \frac{L_{frozen}}{k_{frozen}} \right) T_B + T_i}{K_v^* \left(\frac{1}{K_v^*} + \frac{L_{frozen}}{k_{frozen}} \right) - 1}$$

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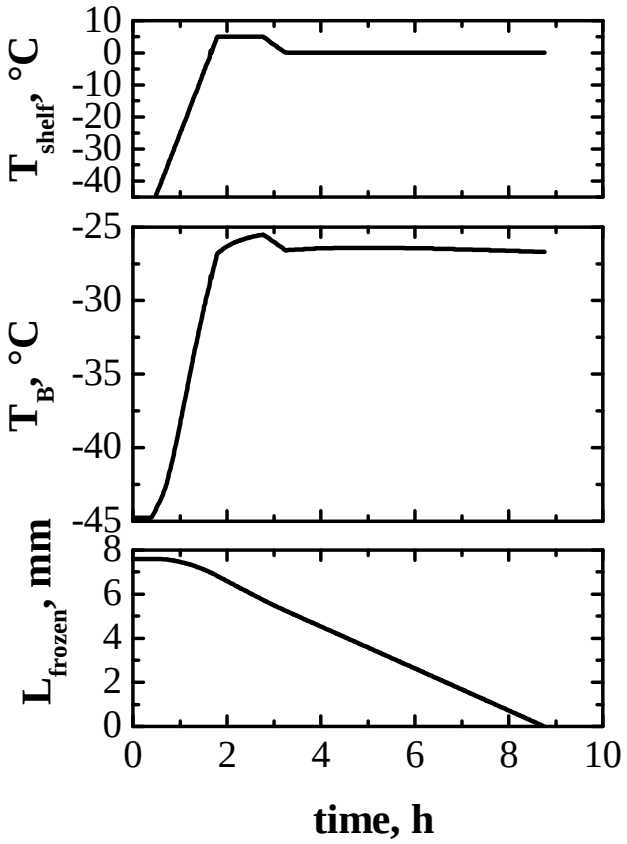
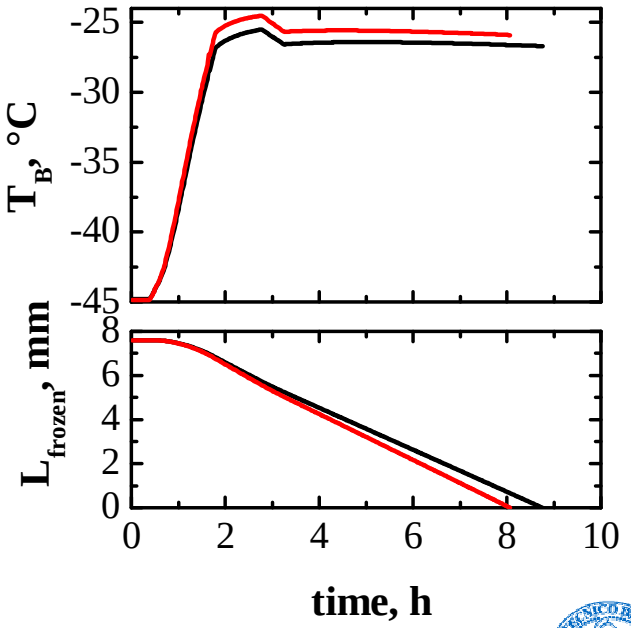
6. Process transfer and scale up

Equipment 1



Equipment 2

No scale-up



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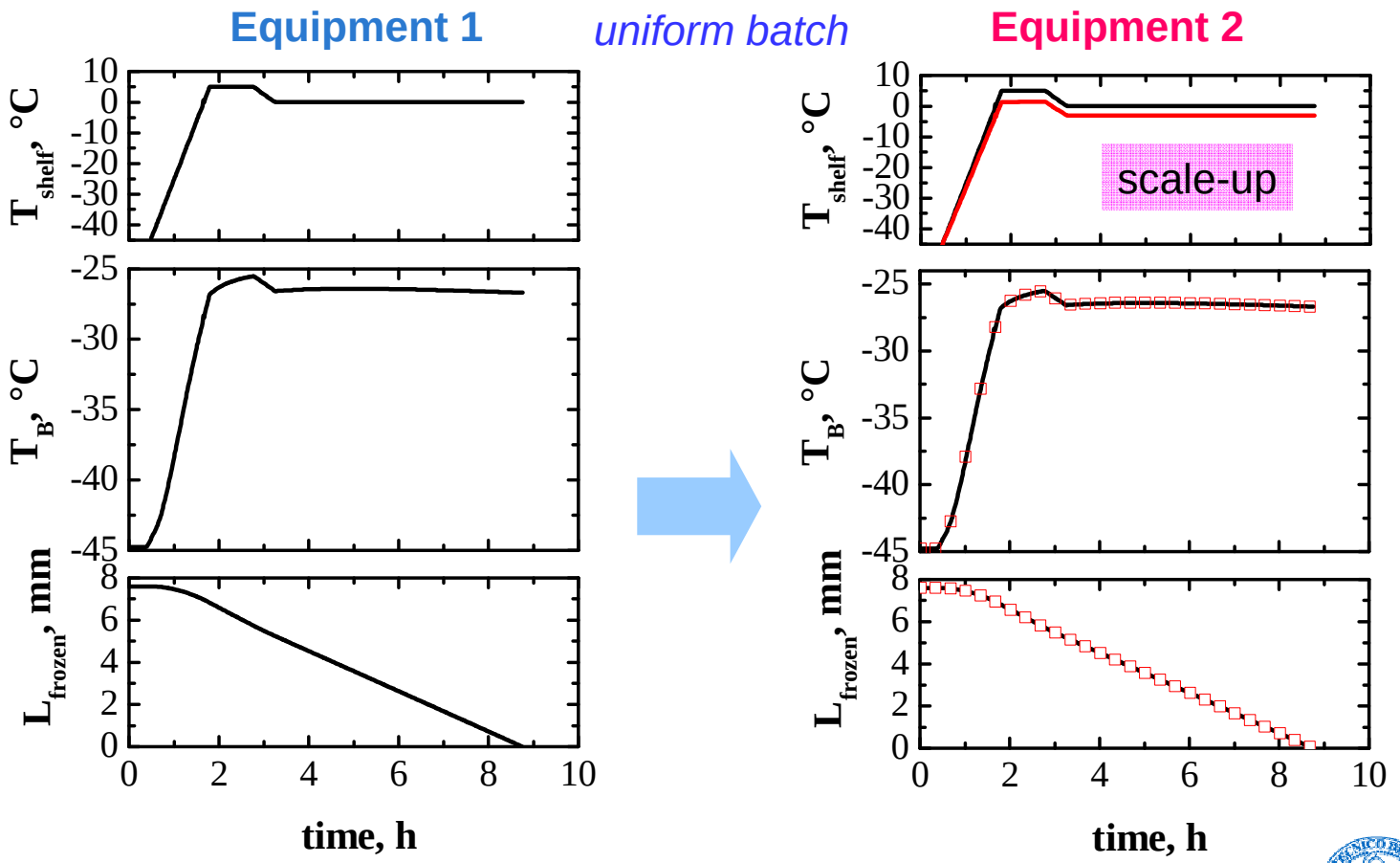
6. Process transfer and scale up



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6. Process transfer and scale up

In case of non-uniform batch we need:

1. **To identify the target dynamics that has to be scaled-up (i.e. the evolution of the vials in the central position of the shelf, or that of the vials at the edges of the shelf);**
2. **To identify which group of vials in equipment “2” has to follow the target dynamics previously selected;**
3. **To calculate the evolution of the vials of the various groups in equipment “2” using the scaled-up recipe in order to check if all the vials of the batch remains below the limit temperature, and to determine the drying time.**

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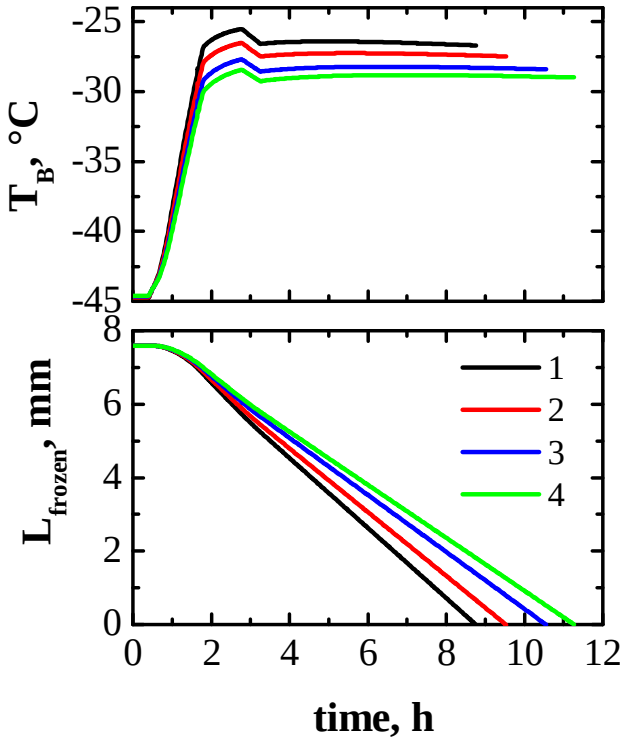
6. Process transfer and scale up

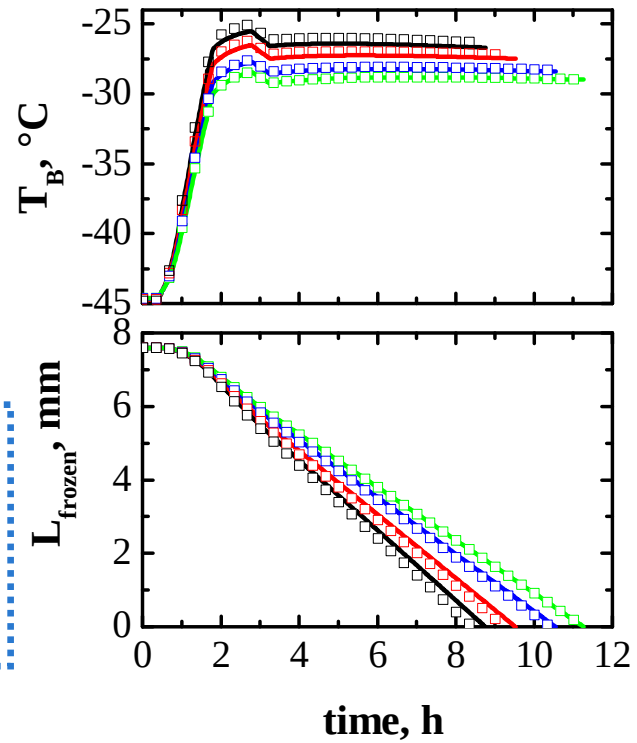
Equipment 1

non-uniform batch

Equipment 2



group 4 in eq. "1" = group 4 in eq. "2"



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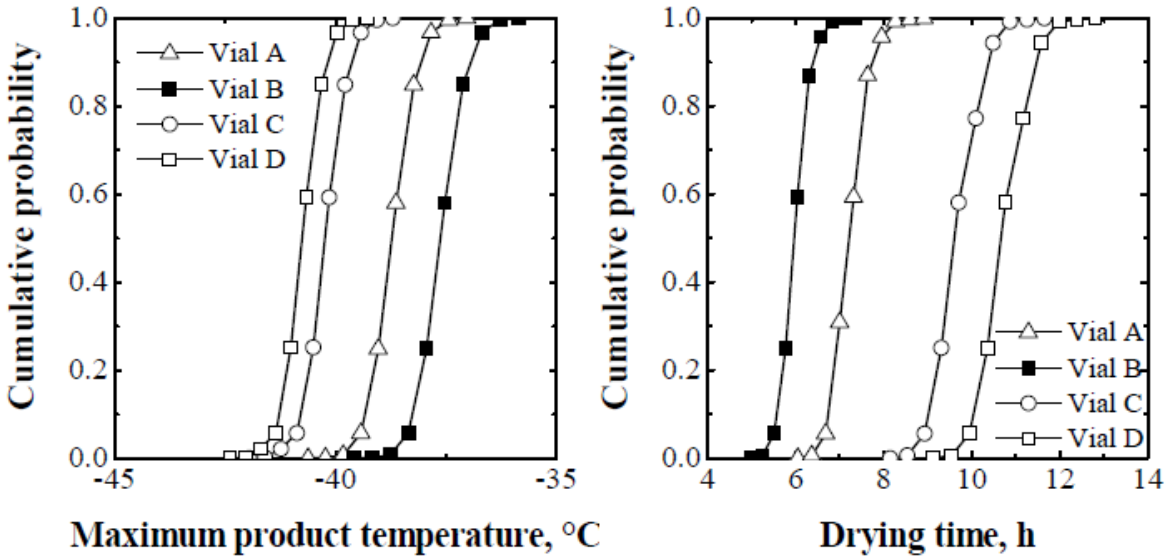
6. Process transfer and scale up: Evaluation of distributions

By this way, including variance and uncertainty, it is possible:

✓ To evaluate the distribution of product temperature, drying time, and residual water in your batch as a function of equipment design and operating conditions

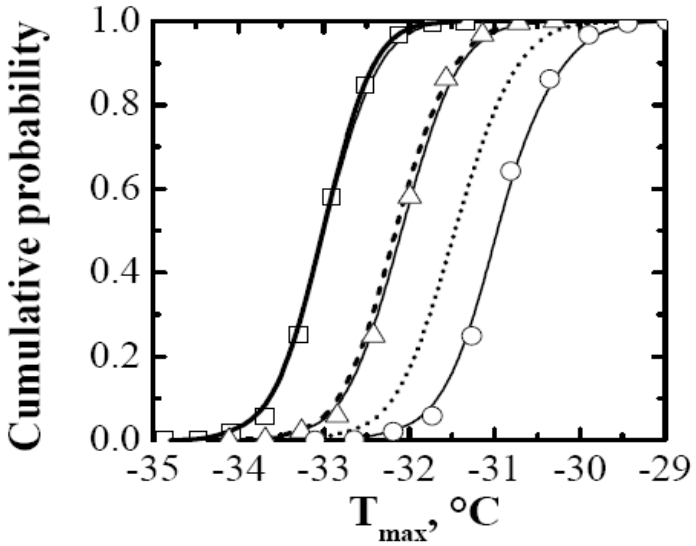
✓ To select the operating conditions that guarantee the **required percentage of success** for the product in hand

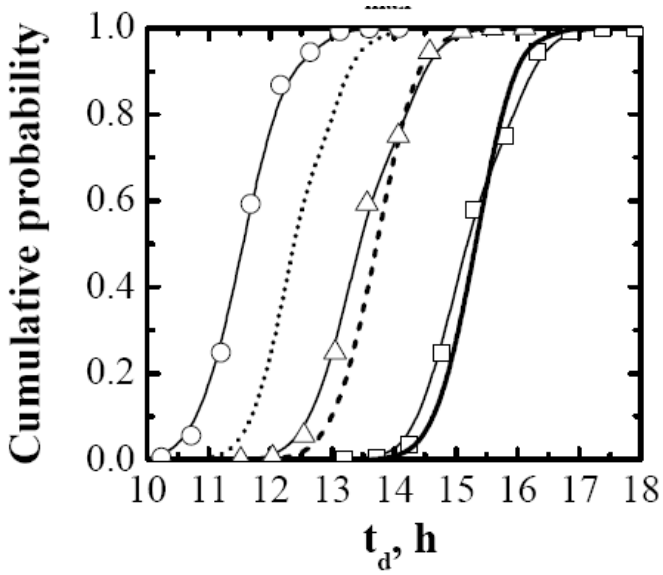


6. Process transfer and scale up: effect of parameters uncertainty

non-uniform batch

lines show the behaviour in the original apparatus, symbols in the scaled up one





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7. Equipment design and optimization

- A process is well understood if all critical sources of variability are identified and explained: accurate and reliable predictions reflect process understanding.
- Causes of heterogeneity:
  - Radiation
  - Fluid dynamics of water vapour in the chamber
  - Inert distribution
  - Non-uniform shelf temperature
  - **...**

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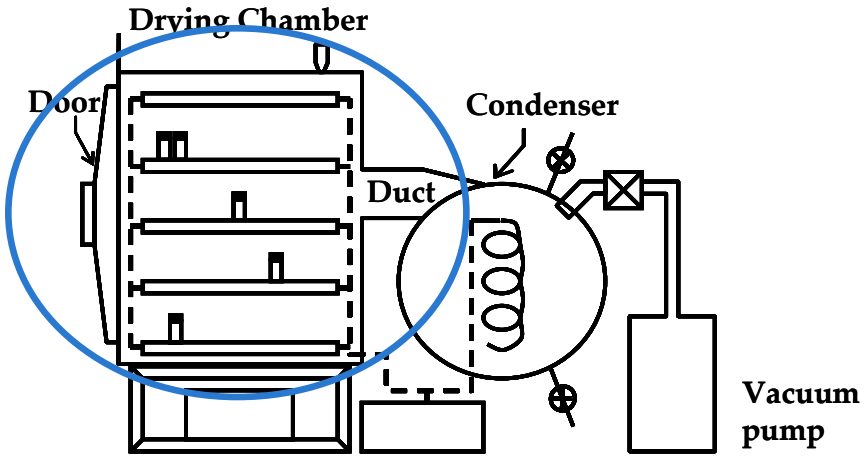
7. Study of the process using CFD

APPARATUS

Drying Chamber: where the product lays on shelves and where the process takes place typically under low pressure and low temperature conditions. ***Radiation and Fluid-dynamics can affect the homogeneity of the batch***.

Duct and valve: *Chocked flow can occur* (Mach number = 1)

Condenser: where the sublimated water vapor, flowing from the chamber, condenses. *Limited capacity of water vapor solidification can occur.*



7. Study of the process using CFD
The drying chamber

LyoBeta (labscale)

- Effect of the duct position

Flow field

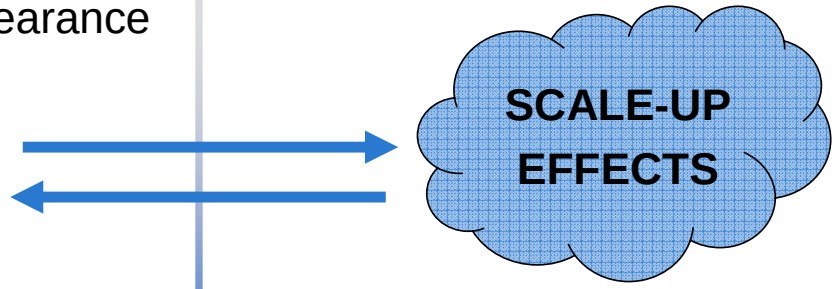
- Effect of the shelf-shelf clearance

Batch Heterogeneity
(Pressure Gradient)

LyoMega (production scale)

- Effect of the shelf-shelf clearance

Batch Heterogeneity



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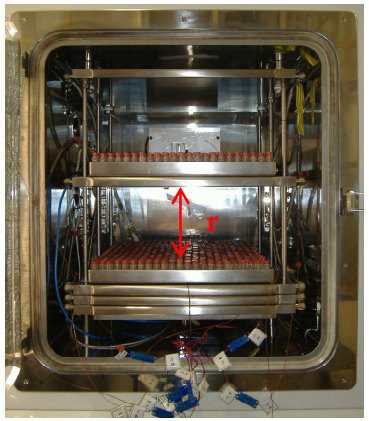
7. Study of the process using CFD

Drying chamber



Parameters of interest:

1. position of the duct
2. free space between the product and the upper shelf
3. Scale of the apparatus

→ 3 positions

2 scales

Small scale apparatus
(V_c= 0.2 m^3)

Large scale apparatus
(V_c= 10.3 m^3)

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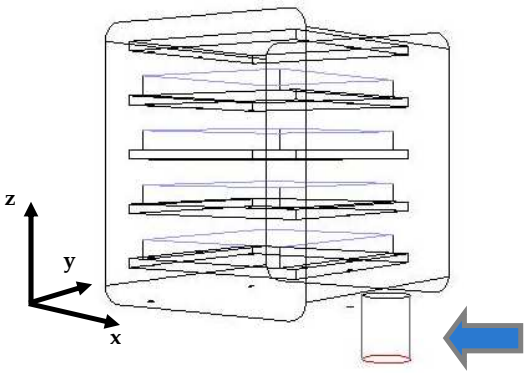
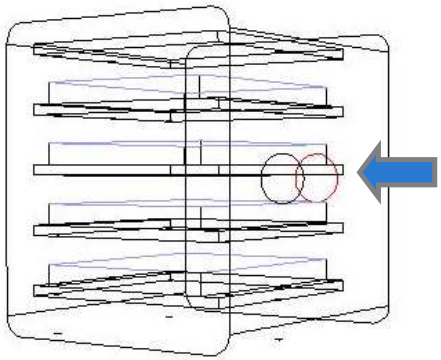
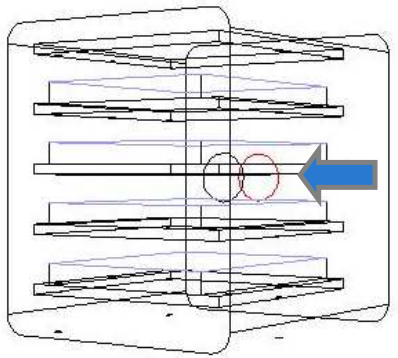
Flow field in the drying chamber – duct position



Bottom



Rear wall – centre



Rear wall – side

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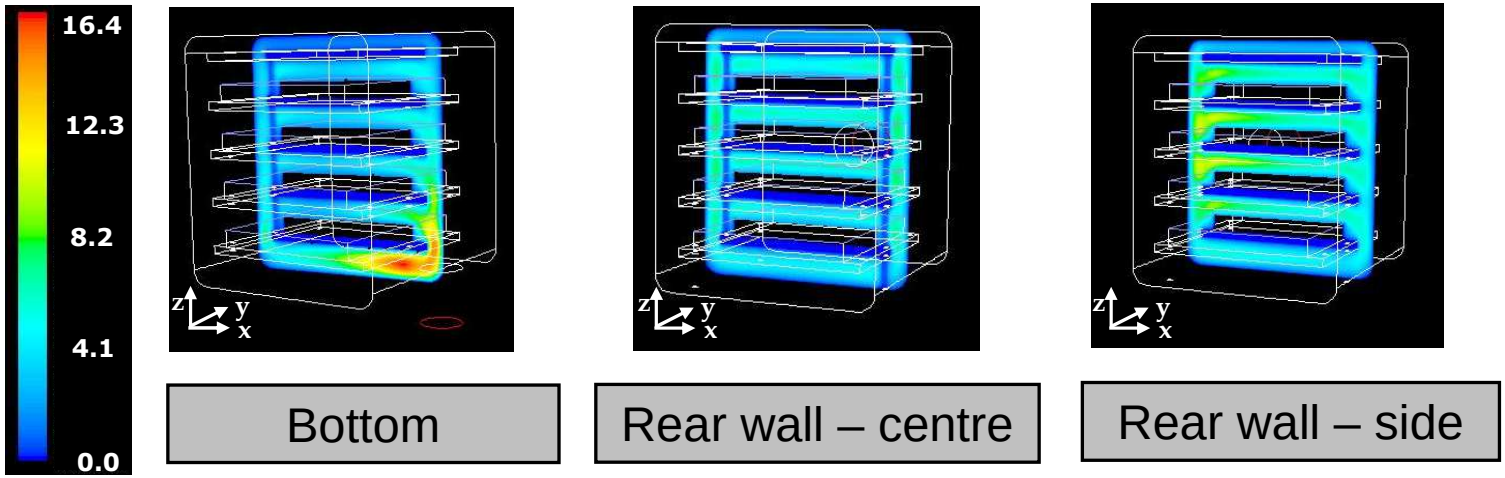
7. Study of the process using CFD

Flow field in the drying chamber – duct position



Operating conditions:

Pressure: 15 Pa; Shelves temperature: 258 K (-15.15°C)

Product temperature: 239 K (-34.15°C); Mass flow rate: 1kg/m^{2}h

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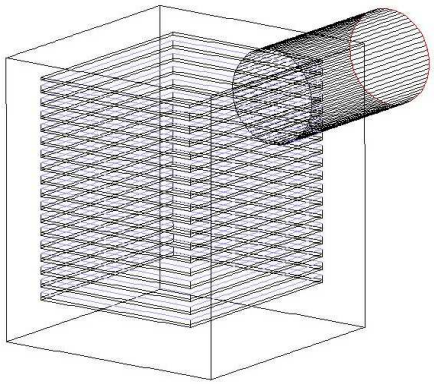
Pressure in the chamber – Clearance between shelves



large scale apparatus

	N° shelves	Clearance, cm
Configuration 1	**14+1**	**6.7**
Configuration 2	15+1	5.7
Configuration 3	16+1	5.0
Configuration 4	**17+1**	**4.37**

cases shown in the following

Operating conditions:

Pressure: 10 Pa; Shelves temperature: 258 K (-15.15°C)

Product temperature: 239 K (-34.15°C); Mass flow rate: 1kg/m^{2}h

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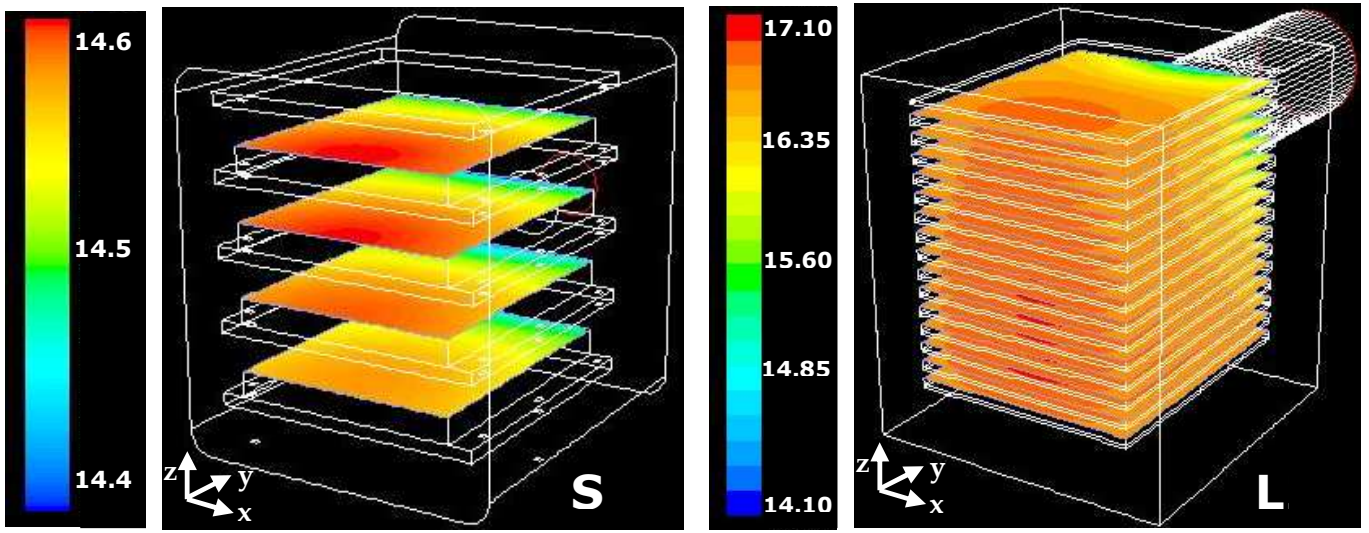
7. Study of the process using CFD

Pressure in the chamber – Small vs. Large apparatus



Global 3D representation of pressure contour plots computed for all the plates in the small scale apparatus (S) and in the large scale apparatus (L) when the clearance between the plates is 100 mm. The operating pressure set in the CFD code is 10 Pa and the mass flux is 1 kg m-2 h-1.

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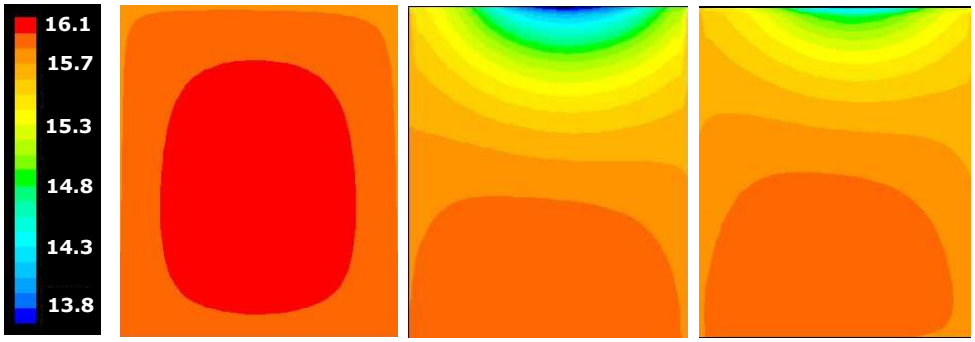
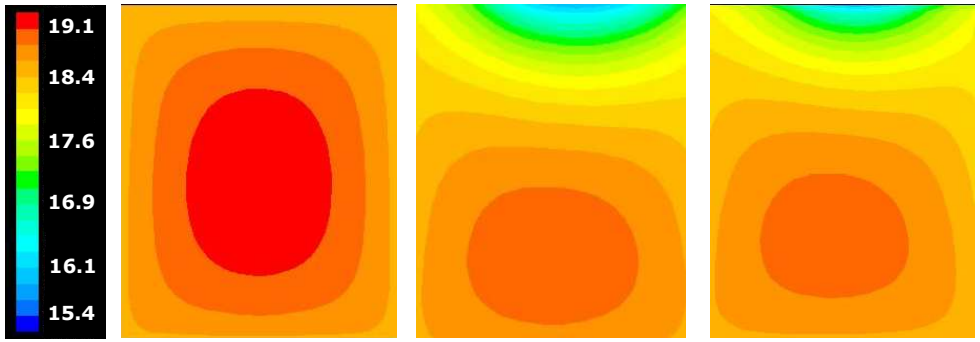
Effect of the clearance



Large scale apparatus, configuration 1 (14+1)

Absolute Pressure, Pa. Contour plot on 1st(a), 11th(b) and 14th (c) plate.



Large scale apparatus, configuration 4 (17+1)

Absolute Pressure, Pa. Contour plot on 1st(a), 13th(b) and 17th (c) plate.

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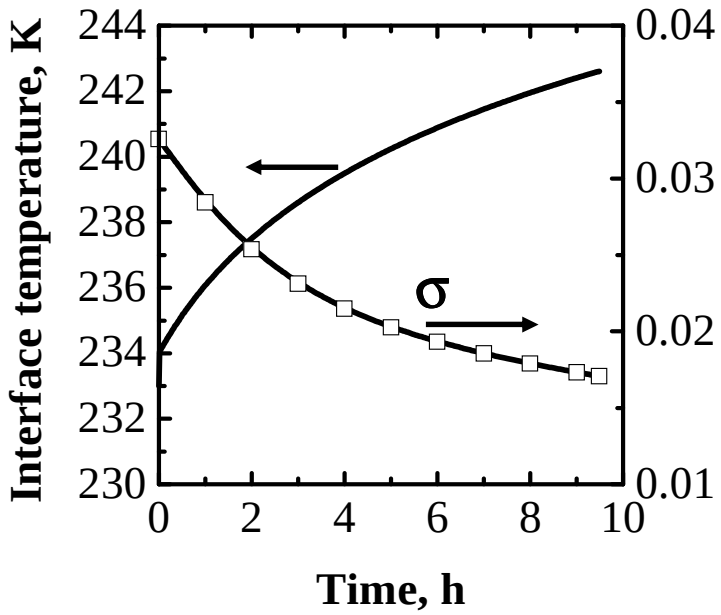
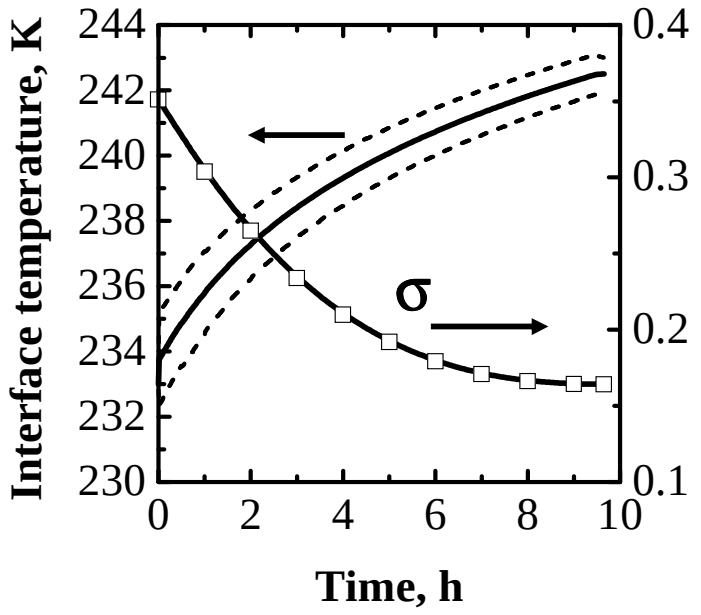
7. Study of the process: Multi-scale modelling

Shelf 1 – bottom of the chamber



Shelf 12 – close the duct



Time evolution of the mean value of the interface temperature (solid line) and of the standard deviation (s, symbols) for the vials on the 1st (LHS) and on the 12th (RHS) tray. Dashed lines identify the upper and lower bounds of the interface temperatures in the various vials.

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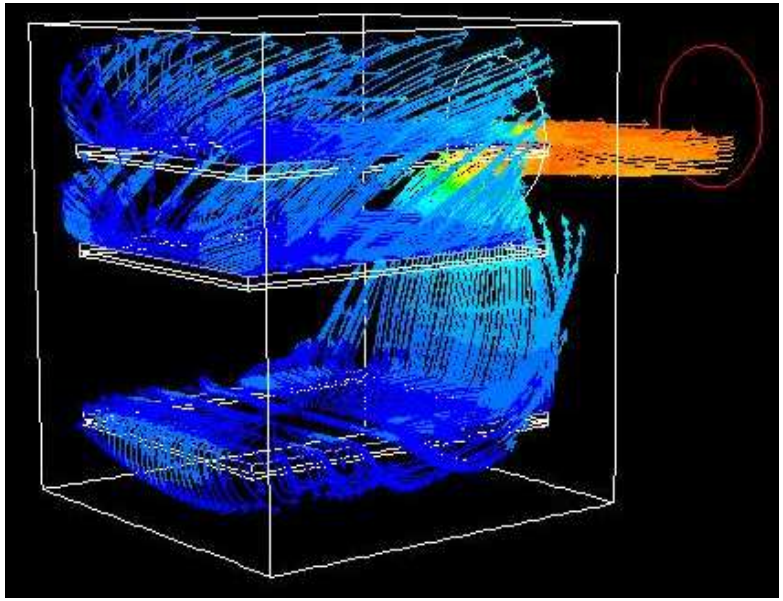
7. Design tool: the Variance Optimisation tool

- **A variance optimisation tool can be realised that:**
- **evaluates the expected variance in the batch for certain design conditions**
- **calculates the required value of a design parameter for a maximum desired variance**

Vapour flow field in the drying chamber – duct position



DATA

Case L3: 16 + 1 shelves

Operating pressure: 10 Pa

T shelf: 258 K

T source: 239 K

Vapour path way from shelves: 1^{th}, 8^{th}, 12^{th}

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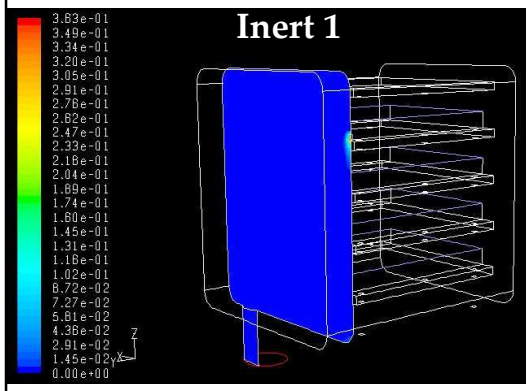
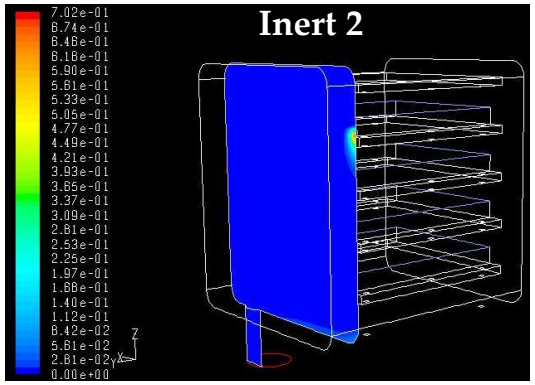
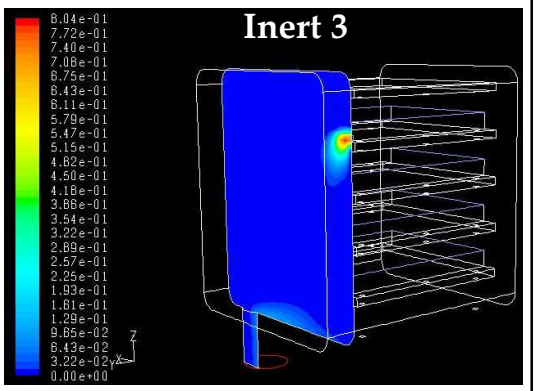
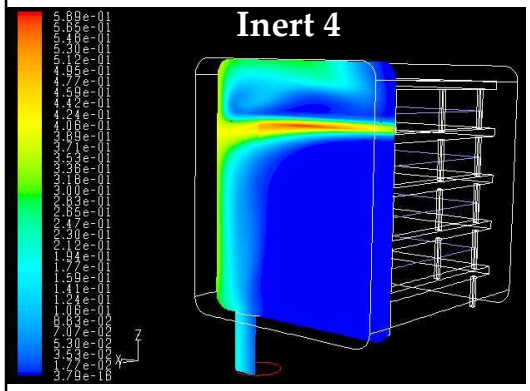
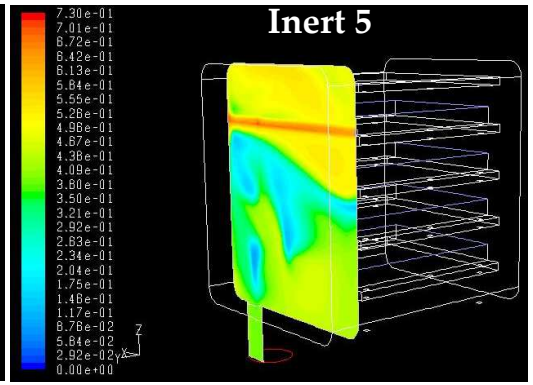
7. Study of the process using CFD
Inert distribution







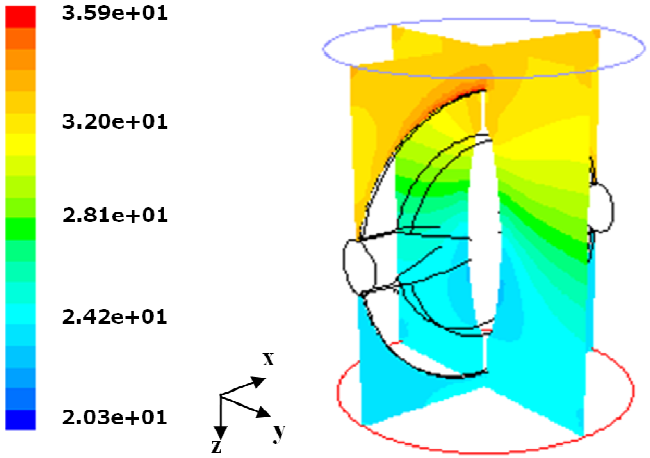




Case	Inert mass fraction in chamber, %
Inert1	0.015
Inert2	0.11
Inert3	0.49
Inert4	2.9
Inert5	34

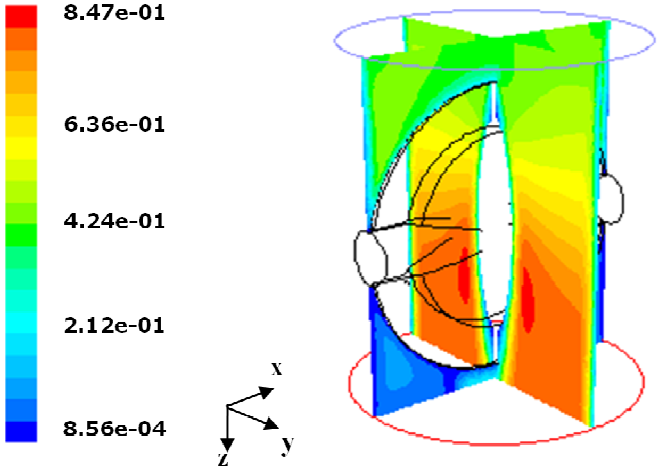
Inert mass fraction

7. Study of the process using CFD: **valves**



absolute pressure (Pa)

CFD to estimate chocked flow conditions in valves



Mach number

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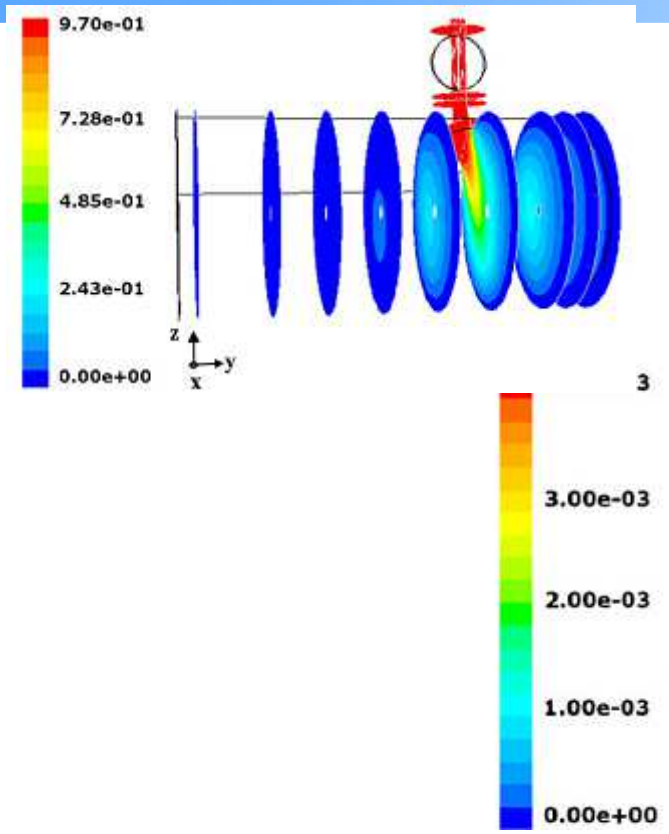
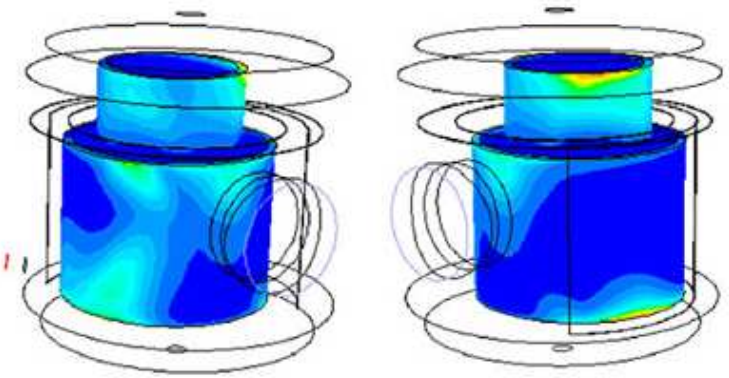
7. Study of the process using CFD: condensers



CFD to optimize condenser geometry:
difficulty in the ice deposition modeling



Petitti *et al*, *Sadhana* **38** (2013)

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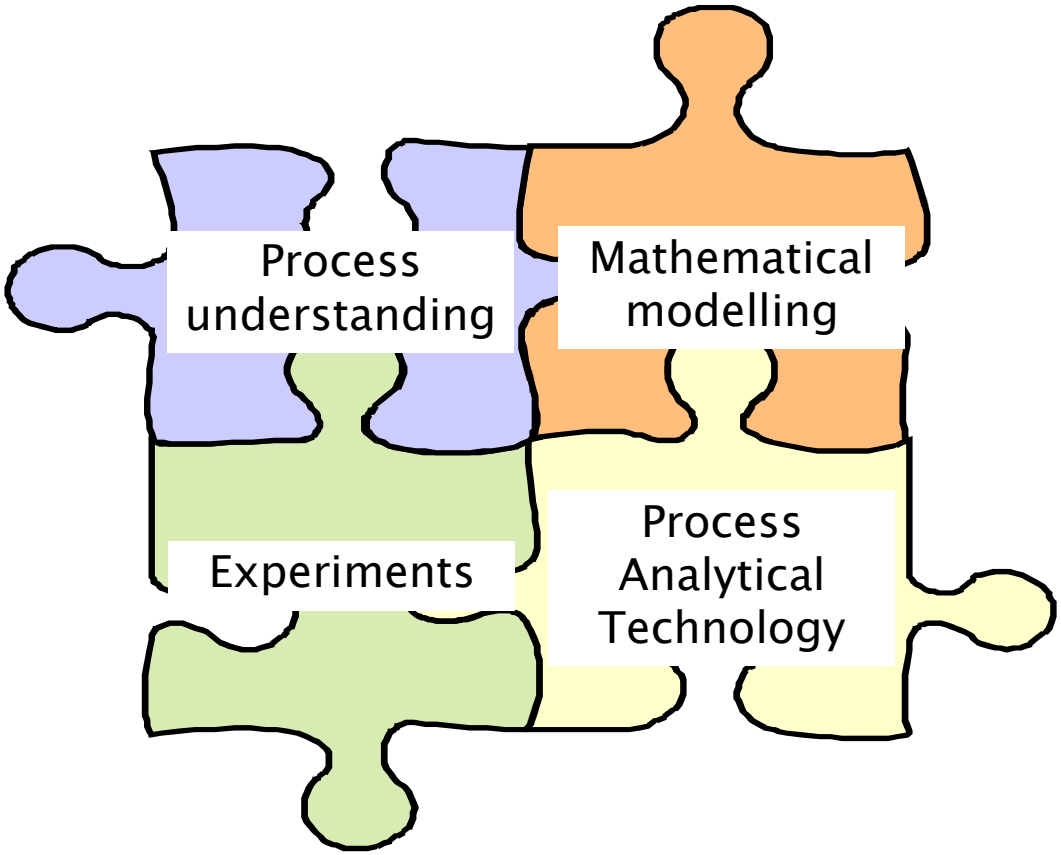
Conclusions



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Summary of the quoted references and some additional and related one

Process monitoring

- Velardi S.A., Rasetto V. and Barresi A.A., 2008, Dynamic Parameters Estimation method: advanced Manometric Temperature Measurement approach for freeze-drying monitoring of pharmaceuticals solutions. *Ind. Eng. Chem. Res*. 47(21); 8445-8457.
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Summary of the quoted references and some additional and related one

Process monitoring

- Pisano R., Fissore D. and Barresi A.A., 2014, A new method based on the regression of step response data for monitoring a freeze-drying cycle. *J. Pharm Sci.* 103(6), 1756-1765.
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Summary of the quoted references and some additional and related one

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