

Innovative software devices to monitor the primary drying phase of freeze-drying processes



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- In 1987, the US Food and Drug Administration issued its Guideline on General Principles of Process Validation. It defined validation as:

“establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes”



Validation without understanding

- The traditional approach presupposes that if nothing is changed from the validation batches, everything will remain the same.
- But this assumption is false, because neither ingredients nor processing conditions can remain fixed...
- It was never real that everything could be kept the same !



Lyophilisation: lack of understanding

How many times we have seen:

In the lyophilisation process, there are two independent variables, shelf temperature and chamber pressure, and once they are fixed, the dependent variable, product temperature, becomes also fixed...

But, it is not uncommon product collapse at the end of primary drying, with constant “independent variables” along the process...



PAT

“The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: **quality cannot be tested into products; it should be built-in or should be by design.**”



It is usually specified the recipe (Shelf temperatures and chamber pressures vs. time) but

This doesn't guarantee repeatable conditions for freezing

This doesn't guarantee that the sublimation parameters are repeated

- For Primary Drying, what it would be desirable is knowing (and controlling !!) the sublimation front temperature and the sublimation speed.
- Partial water pressure is good only to detect the end-point, but not to follow the process kinetics

Temperature, pressure and time are not scalable



Outline

- ❏ **The freeze-drying process**
 - relevance of monitoring and control
- ❏ **Innovative devices for monitoring**
 - "Smart vial"
 - Lyo-balance
 - DPE
- ❏ **Application to Control**
- ❏ **Conclusions**

The Lyo-Beta-special prototype by Telstar equipped with the new devices developed by POLITO





The freeze-drying process

The **Freeze-drying** consist of removing a solvent, usually water, from a frozen product by **sublimation**.

The main steps of the process are:

Freezing



Solidification

Primary Drying



Sublimation

Secondary Drying



Desorption



Introduction: the relevance of monitoring and control

Monitoring, control and optimising of the **Primary Drying** is required because of:

- **Long phase duration**
- **Expensive process**
- **Product damage can occur**



Primary Drying Heat / Mass Transfer

Lyophilizer Vapor Transport Resistance

Cooling
(sublimation)

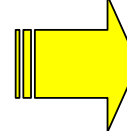
Dry Phase Vapor Flow Resistance

FROZEN PRODUCT

Heat Transfer Resistance

Heating
(cond+conv+rad)

Interface
Product
Temperature



Monitoring

Insertion of a thin **thermocouple** in a few vials is a widely used method to measure the product temperature during the process.

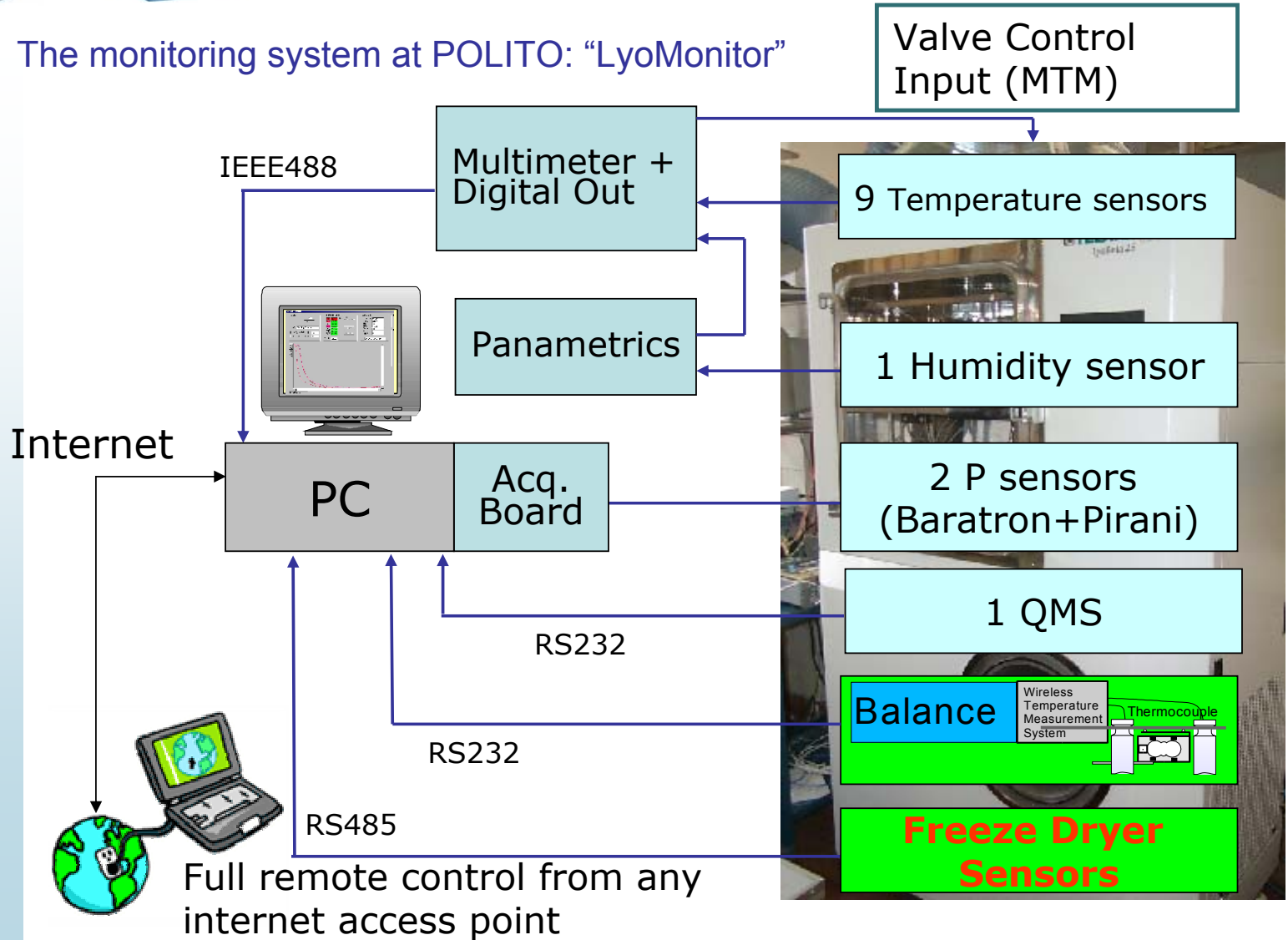


Disadvantages

- Intrusive for the product
- Influence ice nucleation and sublimation
- Problems concerning the sterility of the product

Using a thermocouple we can measure the temperature only in **one** point.

The monitoring system at POLITO: "LyoMonitor"



Valve Control Input (MTM)

IEEE488

Multimeter + Digital Out

9 Temperature sensors

Panametrics

1 Humidity sensor

Internet

PC

Acq. Board

2 P sensors (Baratron+Pirani)

RS232

1 QMS

Balance

Wireless Temperature Measurement System

Thermocouple

RS232

RS485

Freeze Dryer Sensors

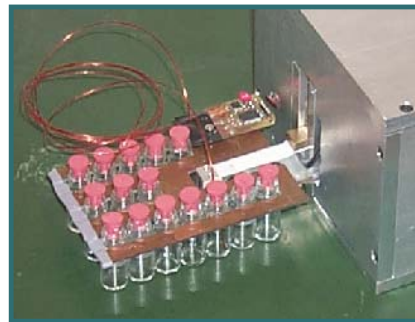
Full remote control from any internet access point



The “*Lyo-monitor*”

Three innovative methods have been investigated and implemented in the **Lyo-Monitor** developed by POLITO

- Smart Vial → **single** vial monitored
- Balance → **set** of vials monitored
- DPE → **whole** batch monitored





Monitoring – single vials

Soft – sensor (the “Smart vial” concept)

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

Advantages

- it can estimate the whole temperature profile (and thus the interface temperature) and the interface position
- it can be realised using a **non-invasive** measurement

Patent by POLITO (EU & USA)



Monitoring – single vials

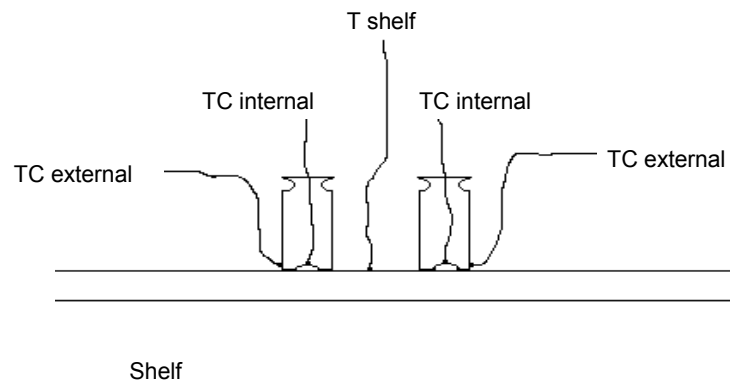
Soft – sensor (the “Smart vial” concept)

Various approaches: Kalman Filter & High Gain observer

Process dynamics: $\dot{x} = f(x)$

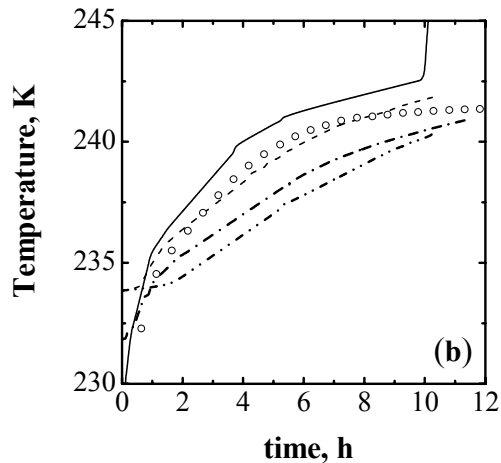
Observer dynamics: $\dot{\hat{x}} = f(\hat{x}) - K(\hat{y} - y)$

Various measures: temperature inside the vial (at the bottom) or outside the vial.

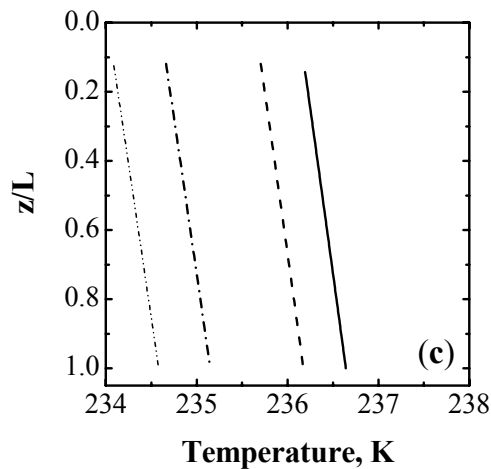


Monitoring – single vials

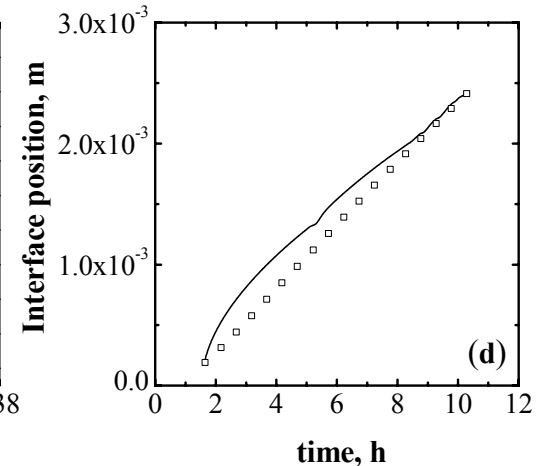
Example of the estimations of the temperatures of the product and of the moving front position obtained using a **Kalman filter in different vials**.



Estimated front temperature in vials placed in different positions on the shelf the average value estimated through DPE tests (o) is also shown for comparison.



Product temperature profiles of monitored vials at $t = 5000$ s after the beginning of the primary drying.



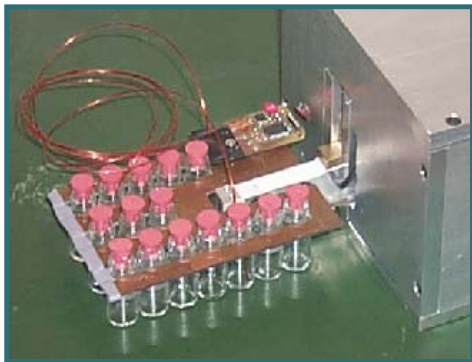
Interface position estimated by the Kalman filter (—) from the temperature measurement and through DPE tests (\square).

comparison with DPE average



Monitoring – group of vials

The POLITO Lyo-balance



Advantages

- **very limited effect** on the monitored system
- Contemporaneous monitoring of **several** vials
- Weighed vials are equal to the rest of the batch, no alteration of transfer coefficients

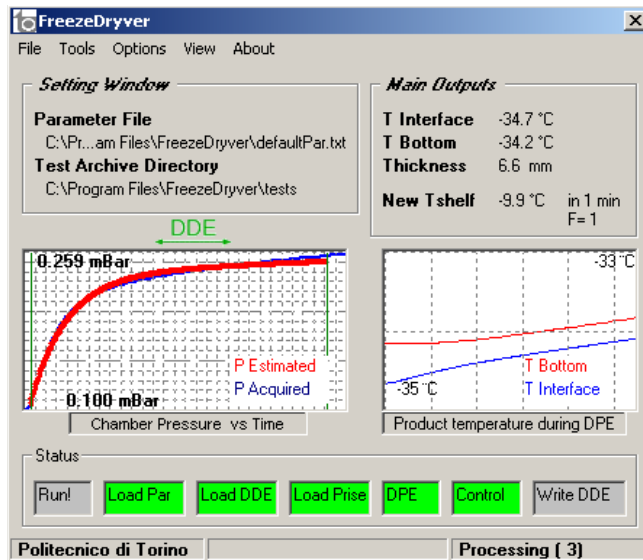
Italian Patent application by POLITO

POSTER



Monitoring – the whole batch/development of the MTM approach

DPE: Dynamic Parameters Estimation method







1. **Non intrusive** method to estimate the **average values over the whole batch**
2. **From measure and interpretation of the pressure rise curve**
3. **product temperature** (at interface and the whole profile), **frozen layer thickness, mass and heat transfer coefficients** are estimated

European Patent pending



Monitoring – the DPE method

Previously proposed methods based on pressure rise after BTM by Oetjen

- 1) MTM (1997), *Pikal*  Mathematical model based on the additivity of **four mechanisms**
- 2) MTM (1998), *Liapis*  More complex mathematical model based on the **dynamic pressure rise method**
- 3) MTM (2001), *Obert*  This mathematical model takes into account **two more** physical **phenomena**:
 - Desorption of bound water
 - Thermal inertia of the glass
- 4) PRA (2004), *Andrieu*  Model based on elementary **heat** and **mass balances**



Monitoring – the DPE method

DPE characteristics and advantages

- ✎ It is based on the **unsteady-state modeling** of the process
- ✎ computes consistent **results almost up to the end** of the primary drying
- ✎ computes the **product temperature** (from the **interface to the bottom**) during the pressure rise test (dynamic)
- ✎ can take into account the **composition of the gas** (water vapour, inert)



Monitoring – DPE vs MTM

DPE	MTM
DPE is based on the unsteady-state modeling of the process.	MTM is based on the arbitrary additivity of 4 elementary mechanisms.
DPE computes consistent results almost up to the end of the primary drying.	MTM provides good results up to 2/3 of the primary drying.
DPE computes the product temperature (from the interface to the bottom) during the pressure rise test (dynamic).	The interface temperature and the bottom temperature are provided only at the beginning of the test.
DPE can take into account the composition of the gas (water vapour, inert).	MTM has not this feature.



Monitoring – the DPE method

The model equations

Heat Transfer

$$t > t_0, \quad 0 < z < L_{\text{frozen}}$$

$$\frac{\partial T}{\partial t} = \frac{k_{\text{ice}}}{\rho_{\text{frozen}} c_{P,\text{frozen}}} \frac{\partial^2 T}{\partial z^2}$$

$$t = 0, \quad 0 < z < L_{\text{frozen}}$$

$$T|_{t=0} = T_{i0} + \frac{z}{k_{\text{frozen}}} \frac{\Delta H_s}{R_P} \left(p(T_{i0}) - p_{w0} \right)$$

$$t \geq 0, \quad z = 0$$

$$k_{\text{frozen}} \frac{\partial T}{\partial z} \Big|_{z=0} = \frac{\Delta H_s}{R_P} \left(p(T_i) - p_w \right)$$

$$t \geq 0, \quad z = L_{\text{frozen}}$$

$$k_{\text{frozen}} \frac{\partial T}{\partial z} \Big|_{z=L} = K_v \left(T_{\text{plate}} - T_B \right)$$



Monitoring – the DPE method

The model equations

Pressure dynamics

$$t > 0$$

$$\frac{dp_w}{dt} = \frac{N_v A}{V_c} \frac{RT_i}{M_w} \frac{1}{R_p} \left(p_i(T_i) - p_w \right)$$

$$t \geq 0$$

$$p_c = p_w + p_{in} = p_w + F_{leak} \cdot t + p_{in0}$$

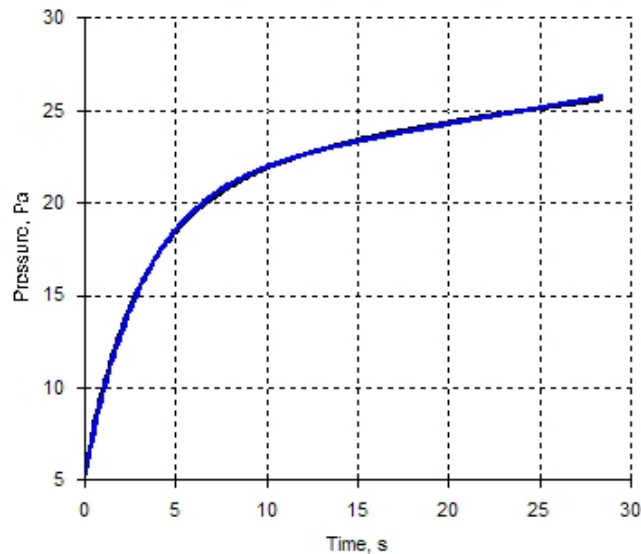
$$t = 0$$

$$p_w|_{t=0} = p_{c0} - p_{in0}$$

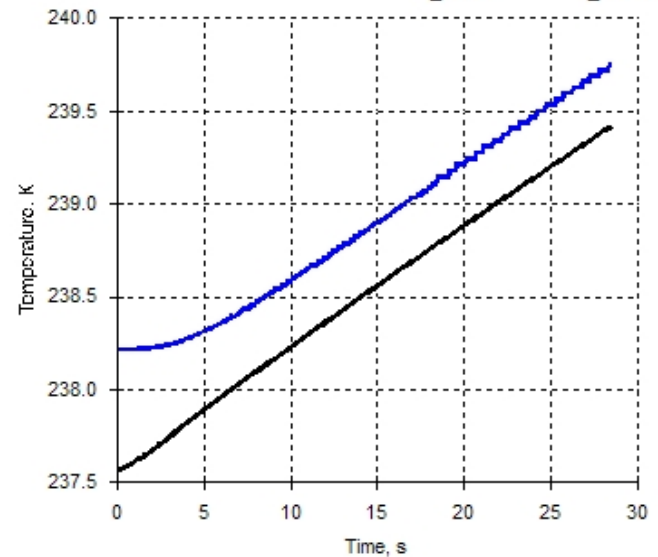


Monitoring – the DPE method

DPE performances



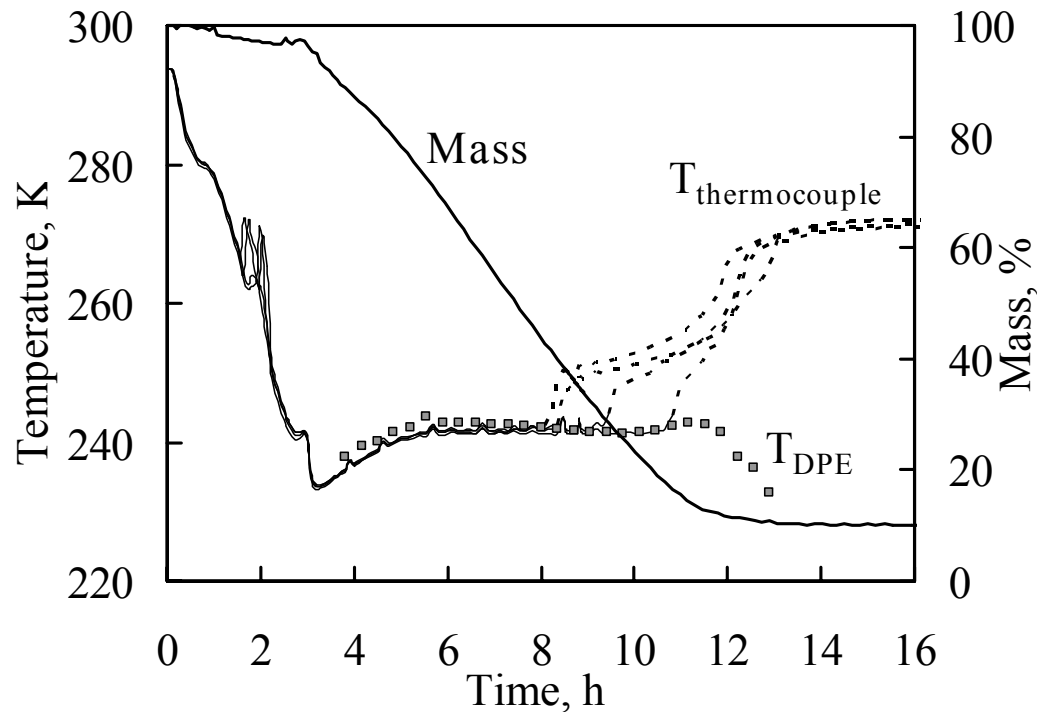
Measured and **estimated pressure** during a pressure rise test.



Estimated **interface** and **bottom temperature** during a pressure rise test.

Monitoring: comparison

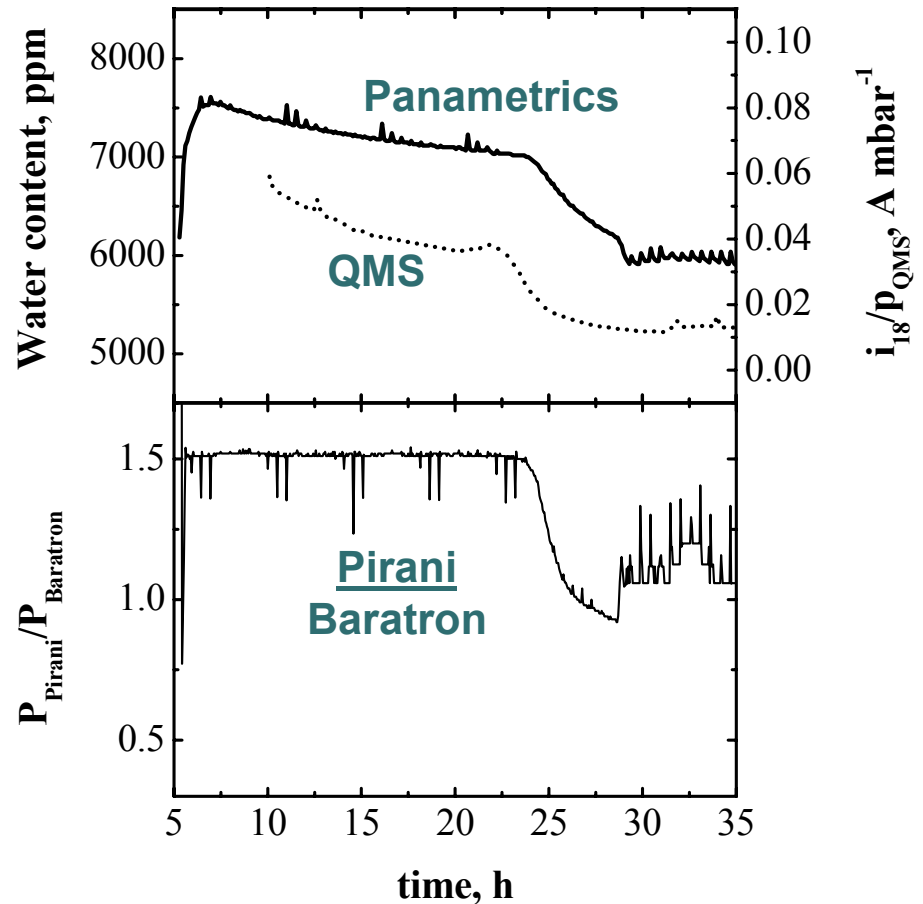
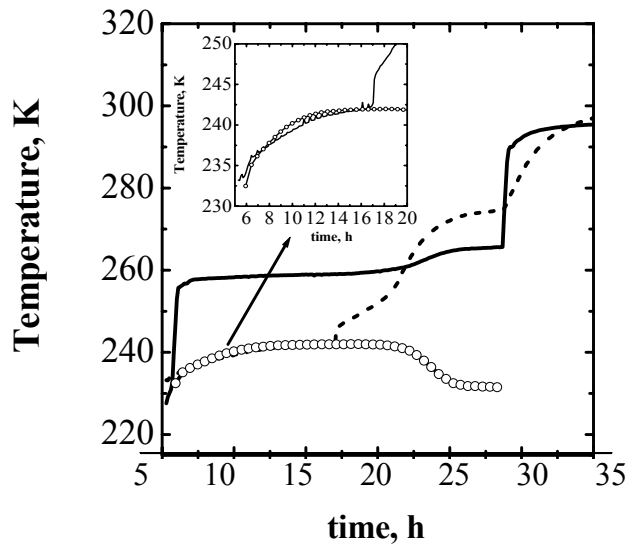
Experimental evidence of a good agreement between different monitoring systems, more reliable than conventional ones.



Temperature measured by thermocouples differs largely between vials

Monitoring: comparison

Good agreement is obtained also when the results are compared with those obtained using a Quadrupole Mass Spectrometer and the Pirani, Baratron and Panametrics measures





Monitoring and control

DPE output

- 1. Front temperature**
(and T profile vs. time)
- 2. Effective diffusivity**
- 3. Heat transfer coefficient**
- 4. Current frozen layer thickness**
5. Bottom temperature
6. Mass Flow of water vapour
7. Mass Flux of water vapour

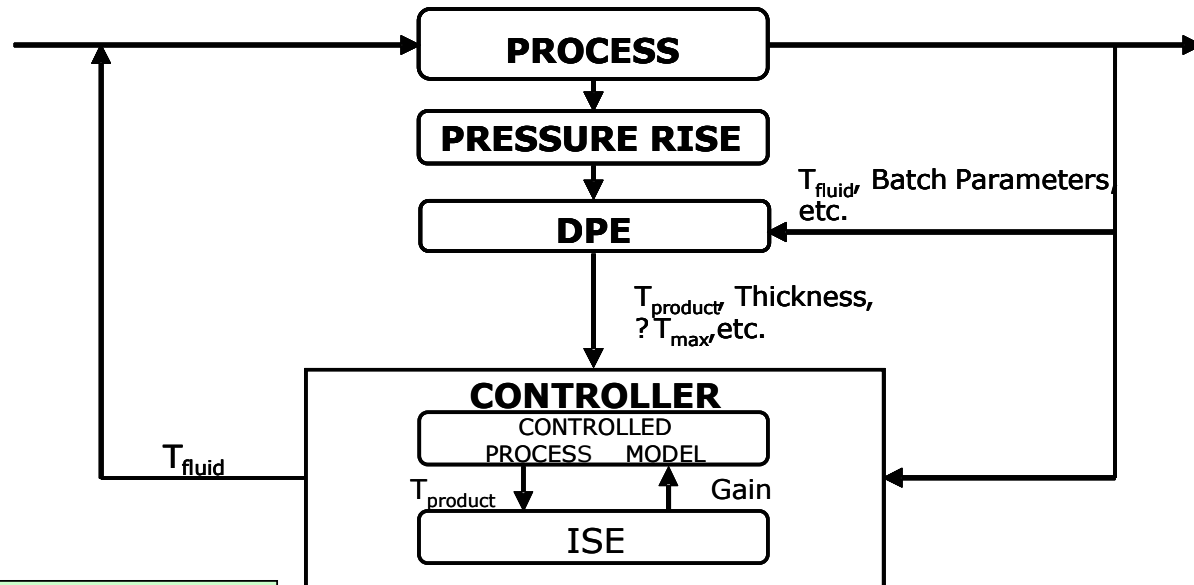


LyoDriver

Control: the innovation

Lyo-Driver (LD)

Goal: determination of an optimal heating shelf control strategy for primary drying in order to minimize the drying time avoiding to jeopardize the integrity of the material.



European Patent pending



Control: the innovation

Lyo-Driver Features

- **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



Control – LD software

How does LD work?

The operating principle of Lyo-Dryver can be summarize in four steps:

- a)** The *User* must provide the feature of the loaded batch
- b)** LD estimates the time varying product temperature
- c)** LD plans an initial heating at the maximum rate
- d)** LD computes a sequence of set-point fluid temperature

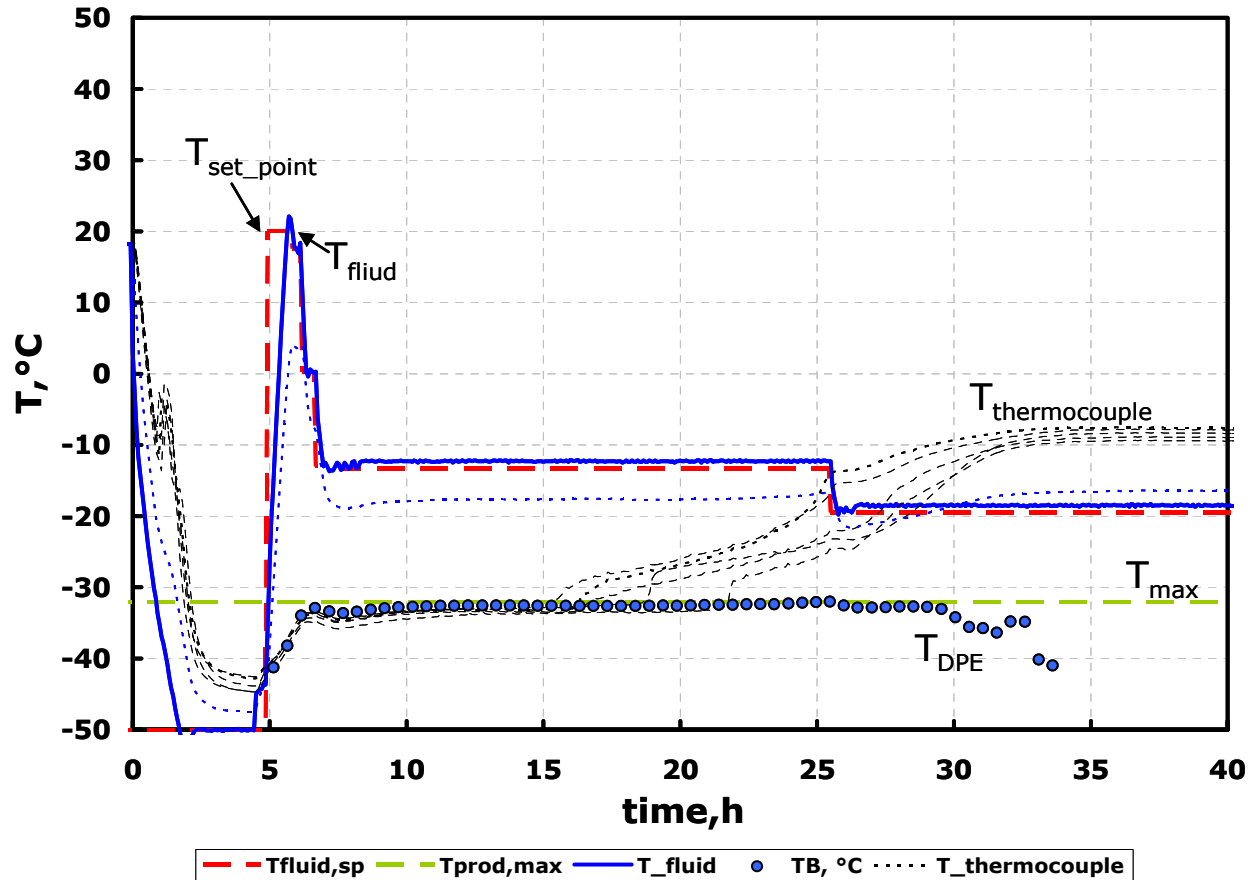


Control – LD vs Smart Freeze-drier

Lyo-Driver	Smart Freeze-drier
Unsteady-state modeling of the primary drying	Steady-state modeling
Based on an advanced predictive control algorithm	Is basically a feedforward controller combined with a number of empirical equation
Takes into account the real dynamic response of the heating system to change the fluid temperature set-point	MTM has not this features
Predicts potentially damaging temperature overshoot and anticipates the control action accordingly	It has not predictive capabilities
Automatically select the best fluid temperature in such a way that the maximum allowable product temperature is never overcome, even during the pressure rise test	This controller does not take into account the possibility that the maximum allowable temperature of the product is overcome during the pressure rise test

Control – the “Lyo-Driver” performances

Developing optimal heating rate in a single test





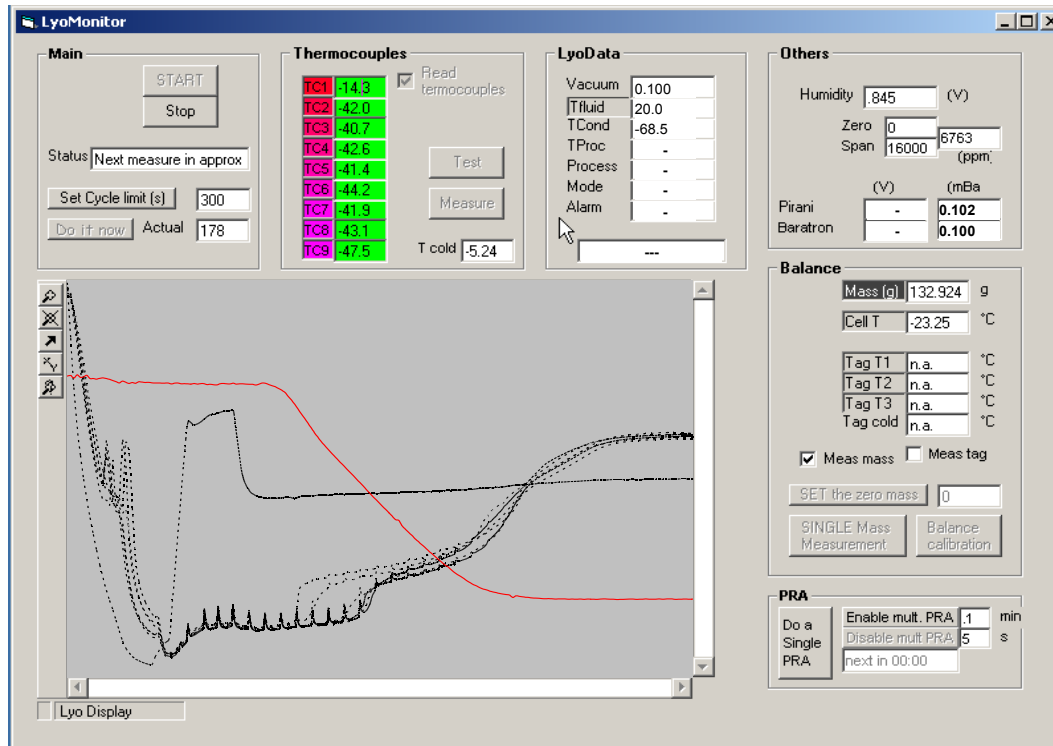
Conclusion - *control*

- ❖ DPE outputs can be successfully used in an **advanced control approach** in order to **optimise** the primary drying phase
- ❖ Experimental results evidence that using the LyoDryver during a lyophilisation cycle, the process is optimised because **the maximum allowable temperature is reached during the primary drying but the product never overcame its damage temperature**



Conclusion – *the LyoMonitor*

Reliable process monitoring is now possible



Thanks for your attention