Overcoming common lyophilization scale-up issues

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Some questions I will try to answer

- ✓ How many experimental tests are really needed for scale up?
- ✓ But first of all: ... Do I really need to scale up a recipe?
  Would be possible to directly obtain the recipe suitable for my industrial scale apparatus?
- ✓ Which PAT tools are available to make scale up easier?
- ✓ Why do not take full advantage of modeling? and how to do it?
  Which model must be used? which is its reliability?
- ✓ *Design space* vs. *recipe scale up* approach
- ✓ How to introduce/evaluate robustness?

Outline

- ✓ Characterizing your systems (apparatus, containers, product) with a limited number of experiments and a simple procedure
- ✓ Utilizing advanced monitoring tools to speed up the system characterization process
- ✓ Evaluating the distribution of product temperature, drying time, and residual water in your batch as a function of equipment design and operating conditions
- ✓ Choosing the operating conditions that guarantee the required level of success for the product in hand
- ✓ Predicting changes in the design space in different pieces of equipment by means of process model, taking into account model uncertainty and confidence limits
- ✓ Examining safe process transfer from one scale to another using either automatic control systems or a predictive modeling approach

Recipe development

An extended experimental campaign is generally carried out at lab-scale to identify the values of the heating shelf temperature (T_{shelf}) and of the drying chamber pressure (P_c) that allow obtaining a product with acceptable quality.

It is generally recognized that this result is achieved if product temperature is maintained below a limit value during primary drying, i.e. when the ice is removed from the frozen product by sublimation.

Automatic control can allow recipe development in one step!
Alternatively a design space can be constructed with a few experiments.

(http://apexlyo.com/page1.html)

Recipe scale-up and process transfer: difficulties

The same recipe obtained in the lab-scale equipment cannot generally be used without modifications to freeze-dry the product in a pilot-scale or industrial-scale freeze-dryer

The same dynamics of product temperature and of ice sublimation (i.e. the same primary drying length) is not generally obtained in the two different equipment with the same recipe.

The reasons at the basis of this are numerous and well known:

- ✓ Environmental conditions in the manufacturing area
- ✓ Shelf surface temperature
- ✓ Radiation effect
- ✓ Chamber pressure
- ✓ Heating and cooling rates

[see Fissore & Barresi, Drying Technology, 29(14), 1673-1684 (2011) for detailed discussion and review of current literature]

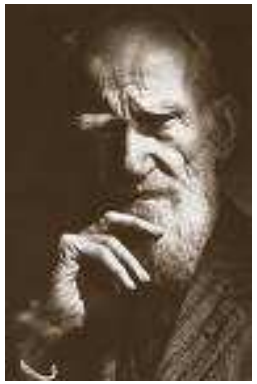
Recipe scale-up and process transfer: the approaches

The scale-up problem is well identified, but the solutions proposed in the literature are not always **simple** and **effective**:

Requirements: Similarity (or thermal similarity) of the two pieces of equipment
Aim: To reproduce the same thermal history of the product.
Problem: That is not always possible!.

Two approaches (in alternative to "trial and error") :

- ✓ Design of a (robust) recipe
- ✓ Construction of a (robust) design-space



The reasonable man adapts himself to the world; the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man.

George Bernard Shaw, 1856-1950

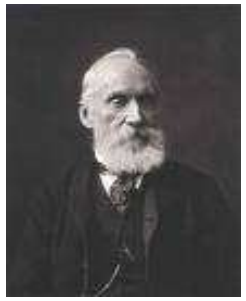
Recipe scale-up: combining experimental and modelling

A succesfull scale-up of a recipe requires a thorough understanding of the relationship between the critical quality attributes and the manufacturing process.

Such a result can be achieved using

✓ a **mathematical model** of the process, to simulate product evolution for a selected recipe,

✓ **few experiments** to determine model parameters and to characterize the different freeze-dryers.



If you can't measure it,
you can't improve it.

Lord Kelvin,1868

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)

Mathematical modeling

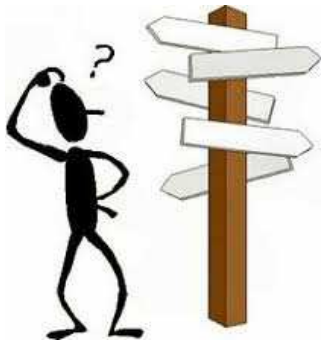
A suitable model has to be selected, taking into account the complexity of the process, as well as the parameters that must be determined.

The best material model of a cat is another, or preferably the same, cat

(Wiener & Rosenblueth)

It must be stressed that the “quality” of the prediction generally depends more on the uncertainty connected with the parameters used, than on the complexity (and the dimension) of the model.

The level of detail must be chosen according to the final use.



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

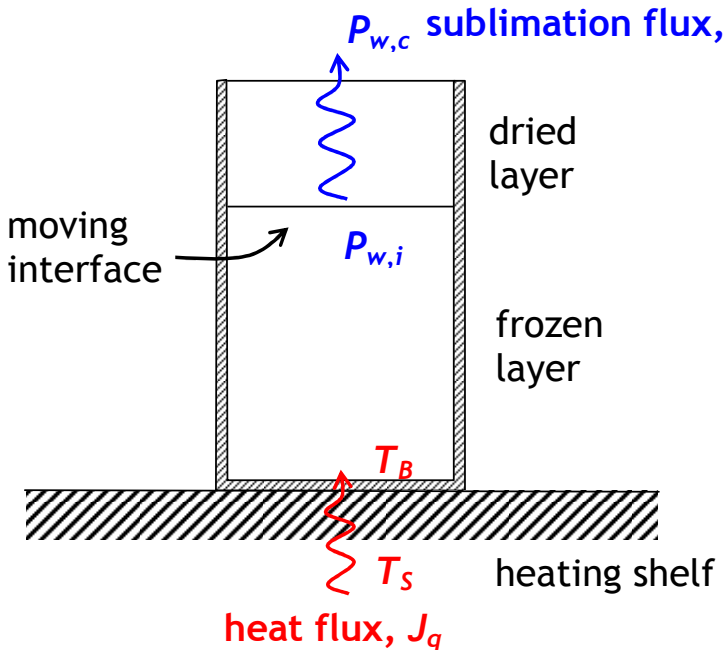
(Egan)

Mathematical modeling: *1D model sufficient*

Radial gradients of temperature and composition are neglected.

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

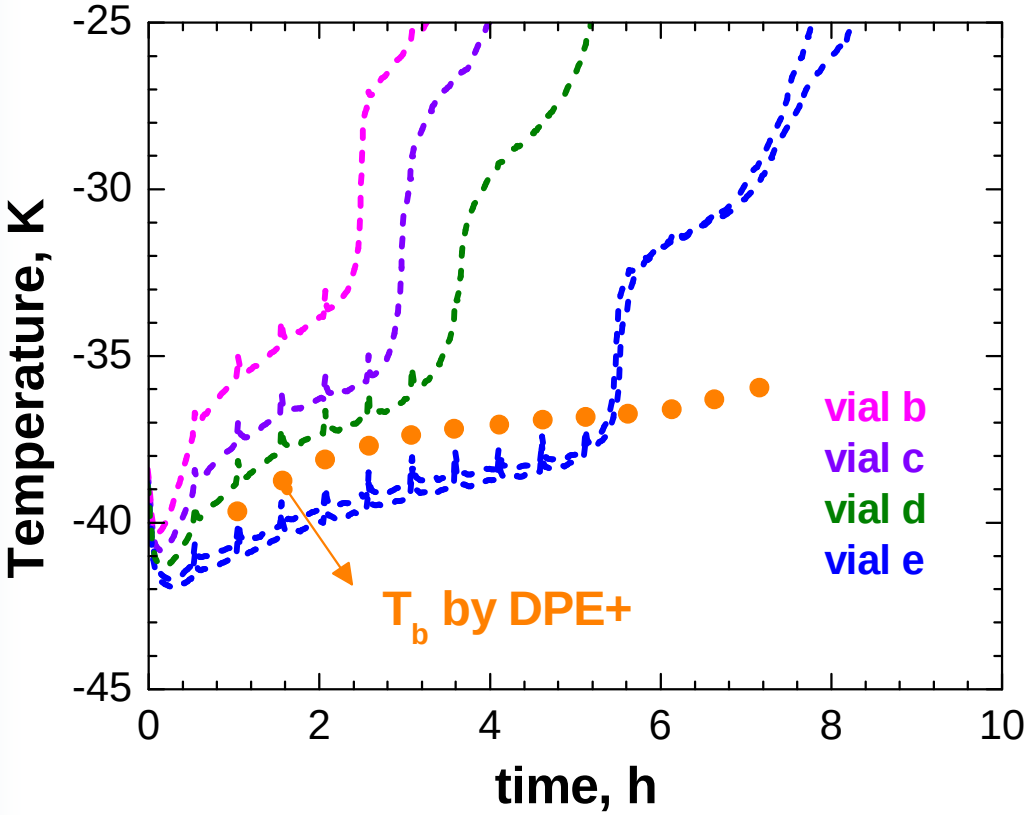
Sublimation flux of the solvent $J_w = \frac{1}{R_p}\left(P_{w,i} - P_{w,c}\right)$

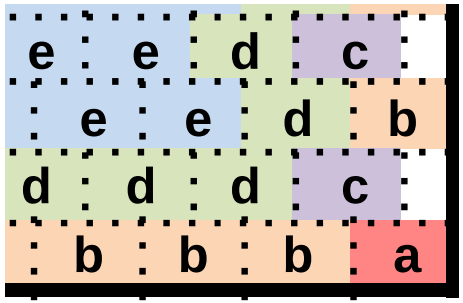


For mathematical modeling: determination of K_v

K_v is an effective coefficient that is used to take into account all the heat transfer mechanisms to the product.

Thus, the value of K_v is not the same for all the vials of the batch due to the various heat transfer mechanisms to the product. Different lots (or classes) of vials identified



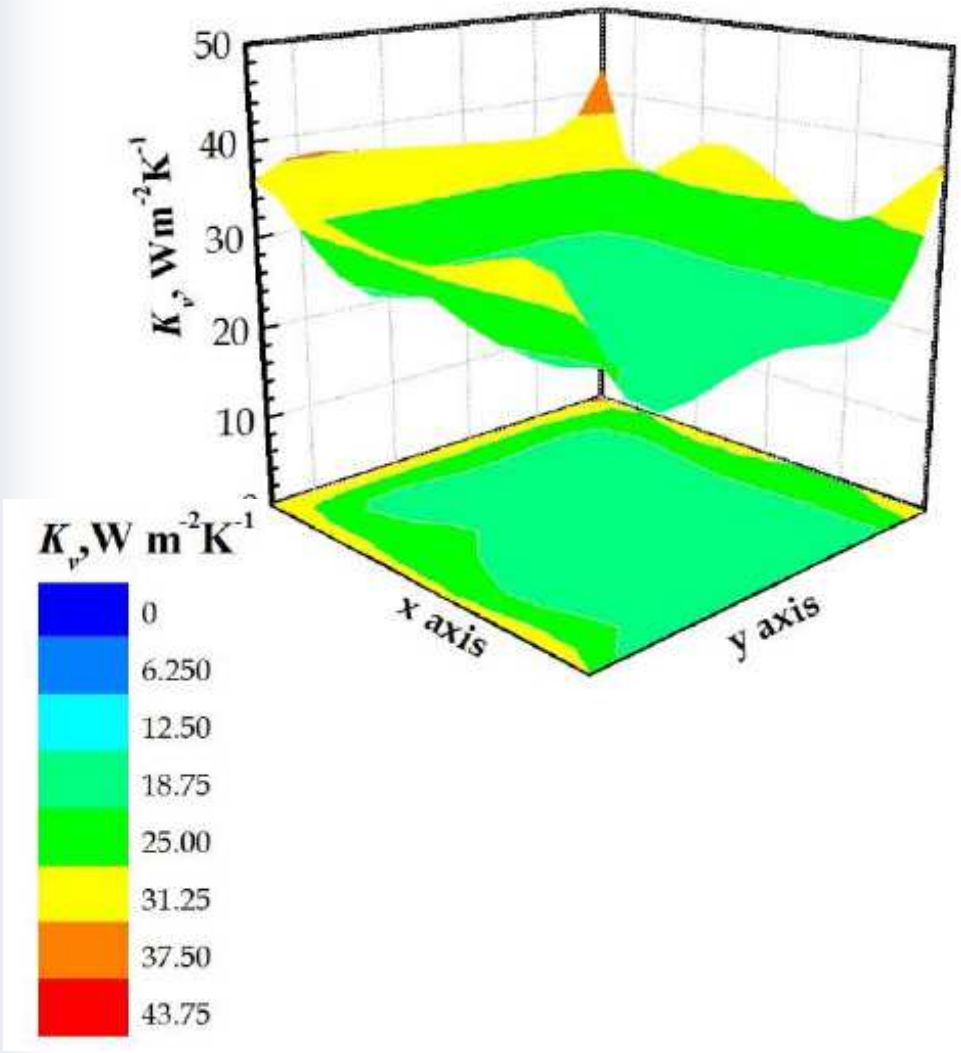


(a) vials in the corners
(b) edge-vials, in contact with the tray wall;
(c) edge-vials, not in contact with the tray wall;
(d) vials in the second raw;
(e) vials in the core of the batch

comparison of temperature measured in different vial classes by thermocouples and effective average estimated by DPE+, an improved method based on pressure rise test

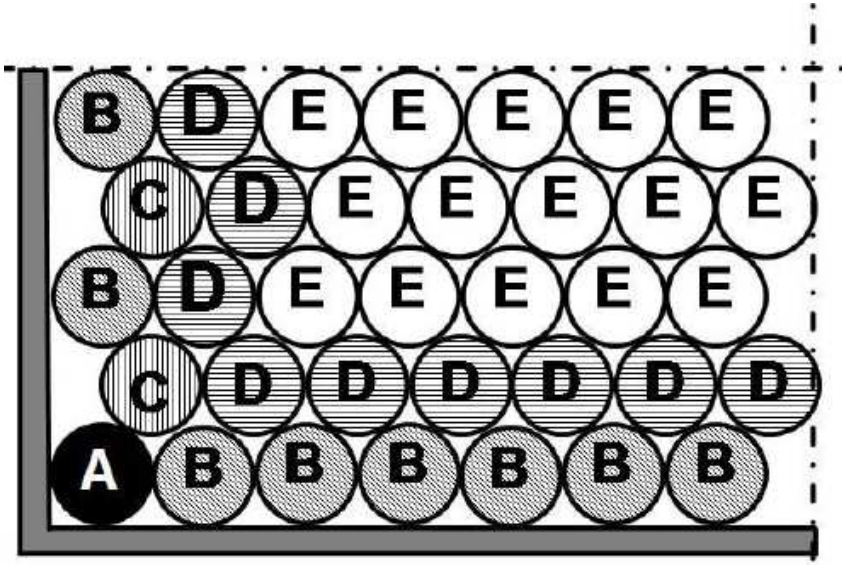
For mathematical modeling : determination of K_v

Determination of heat transfer coefficient K_v: gravimetric test

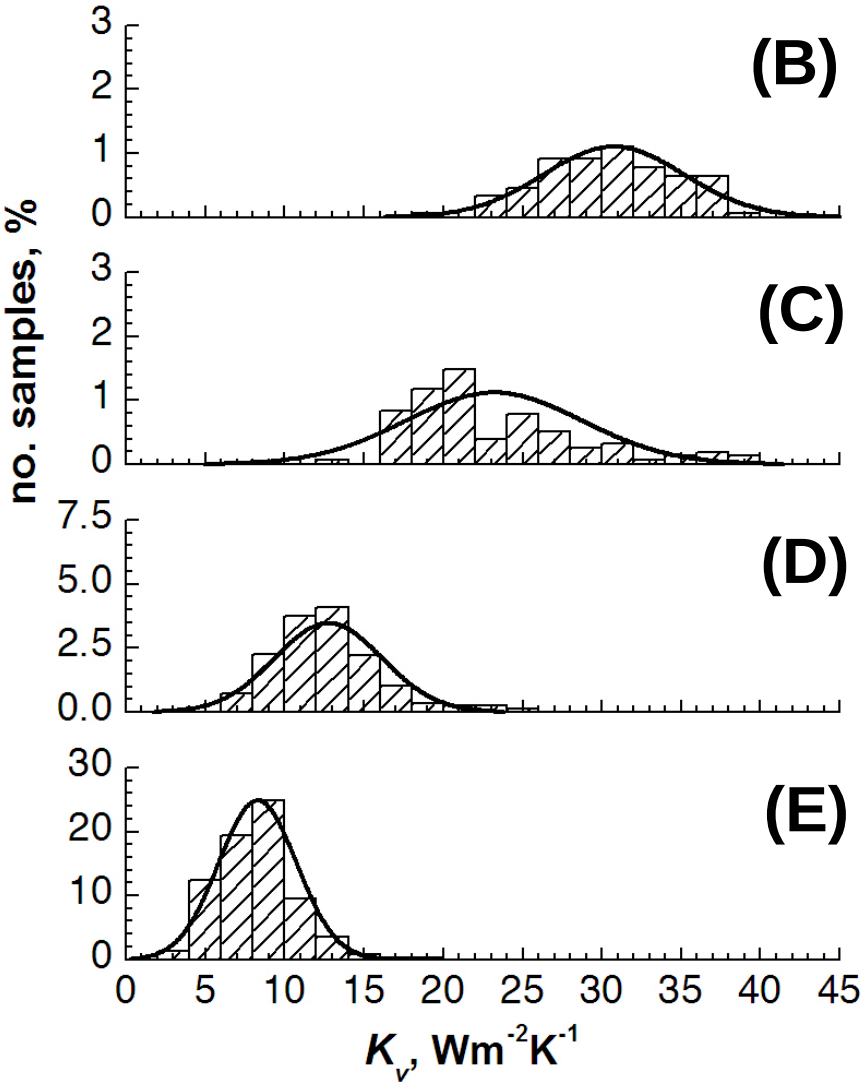


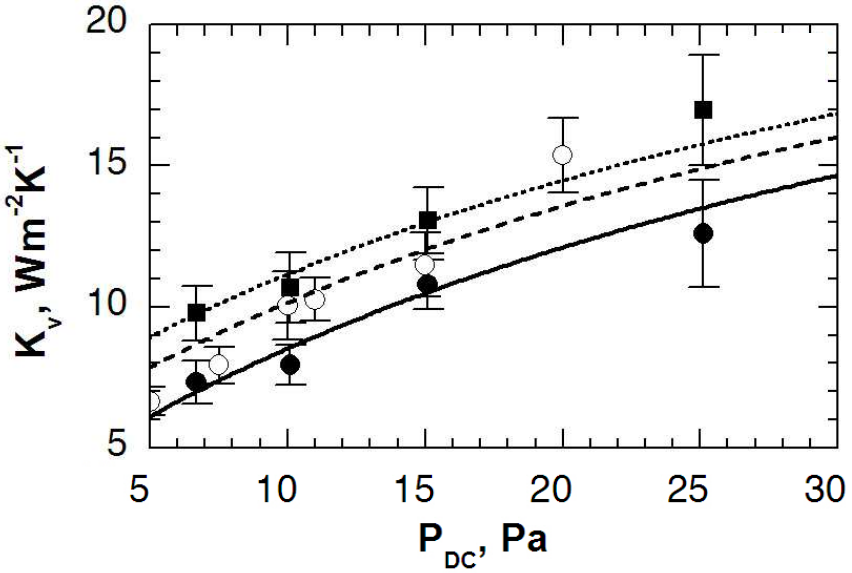
$$K_v = \frac{\Delta m \cdot \Delta H_s}{A_v \cdot \int_0^{\Delta t} (T_{\text{fluid}} - T_B)\,dt}$$

$$K_v = \frac{\Delta m \cdot \Delta H_s}{\Delta t \cdot (T_{\text{fluid}} - T_B) \cdot A_v}$$



For mathematical modeling : determination of K_v





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

Determination of K_v: *the importance of accurate T measurements*

K_v depends on vials and equipment

- Once determined for a vial type in one equipment (minimum 3 tests) it can be used for any product (in that vial type)
- At least one additional test in the large scale freeze-dryer must be carried out.

For accurate K_v determination, the temperature must be measured for each lot of vial considered; and for each class a number of vials sufficient for obtaining a K_v statistics must be measured

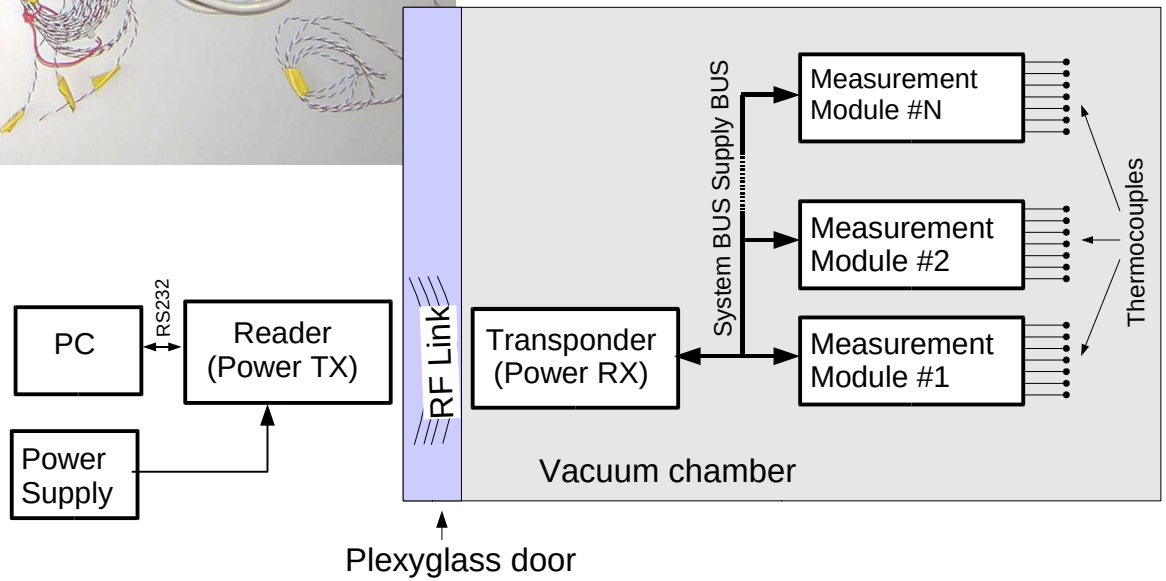
Miniature thermocouples allow a more accurate measurement.

In existing equipment the number of available temperature measuring device is generally limited.

Determination of K_v: wireless thermometers

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

different possible technical solutions: wireless power supply or use of batteries



Determination of K_v: *local* vs *batch average* values

The value of the sublimation flux (i.e. $\Delta m/\Delta t$) can be obtained also using the **Tunable Diode Laser Absorption Spectroscopy** (TDLAS) in case the velocity profile in the duct is known (also in this case the temperature at the bottom of the vial has to be measured).

✓ it can be installed in lab-scale as well as in production-scale equipment, even if it could be difficult to retrofit existing units as it should be located in the duct of the freeze-dryer.

✓ Calibration can be difficult: fluid flow modeling has to be used to provide acceptable density and velocity determinations.

✓ **The batch is assumed to be homogeneous!**

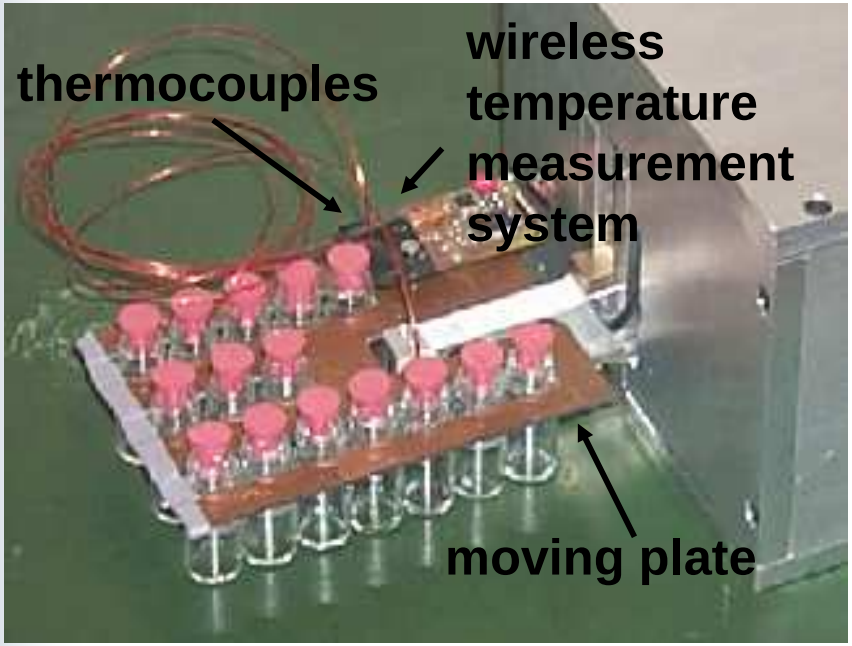
The use of Pressure Rise Tests (e.g. with the DPE algorithm) has less limitations, but similarly gives and average batch value.

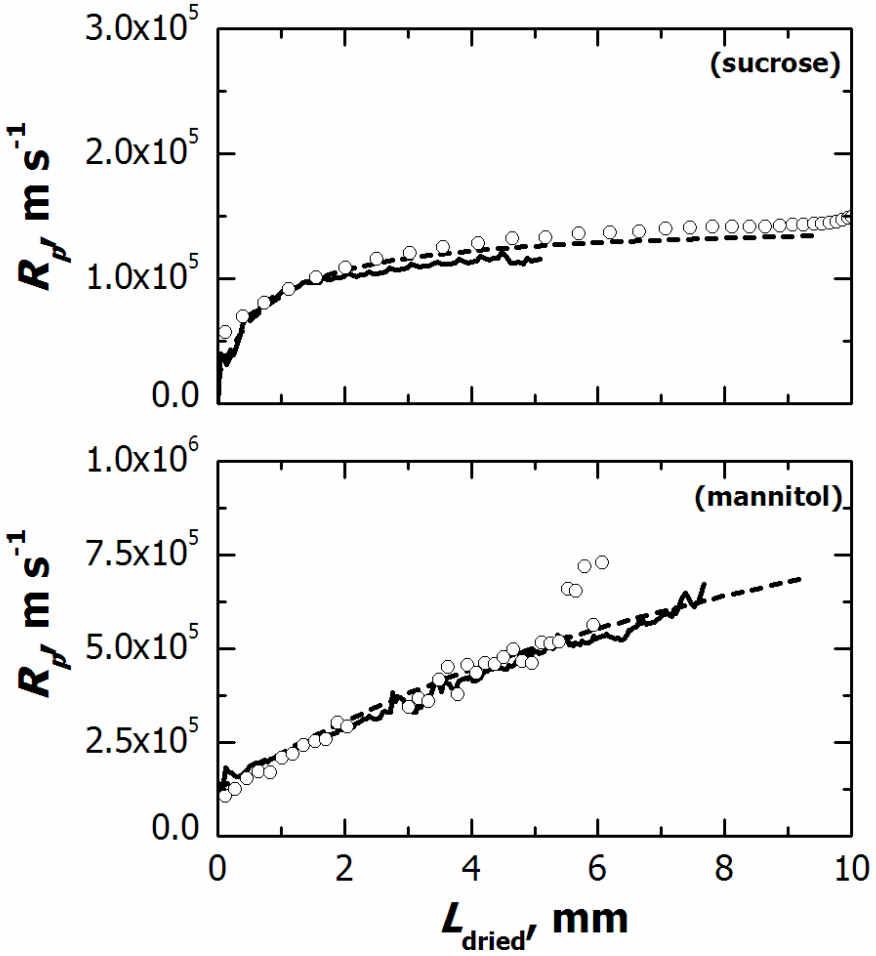
For mathematical modeling: determination of R_p

- ✓ Measurement of the sublimation flux

$$R_p = \frac{p_{w,i} - p_{w,c}}{J_w}$$

  - ✓ Pressure Rise Test
  - ✓ Use of Lyobalance





Comparison between the value of R_p vs. L_{dried} measured by Lyobalance (solid line) and estimated by the pressure rise test technique (symbol).

Determination of R_p

When using Lyobalance

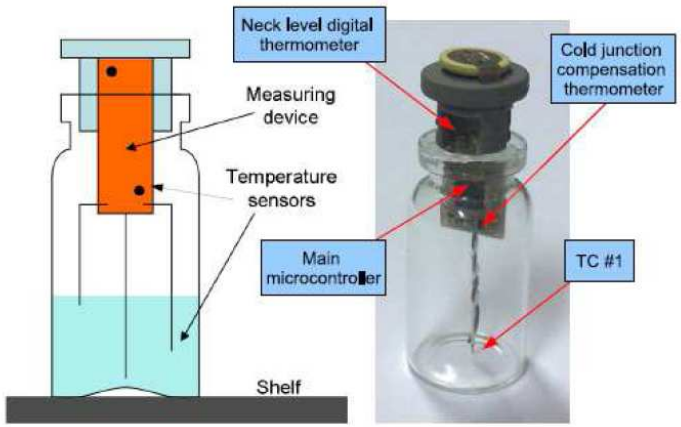
- ✓ The weighed vials are almost always in contact with the shelf and they are lifted just during the measurement.
- ✓ The sublimation flux is measured for vials placed in the drying chamber, that have been frozen with all the other vials of the batch.
- ✓ Even if the dynamics of the product in the weighed vials can be different from that of the other vials of the batch because of radiation from the balance case, **this does not affect the curve R_p vs. L_{dried}** as the temperature of the product in the weighed vials is measured.
- ✓ The device is simple and can be easily placed in every equipment, without requiring any modification.
- ✓ It is no longer required to carry out any PRT and, thus, the measurement of R_p does not affect the dynamics of the other vials of the batch.

Determination of K_v and R_p: use of a "smart vial"

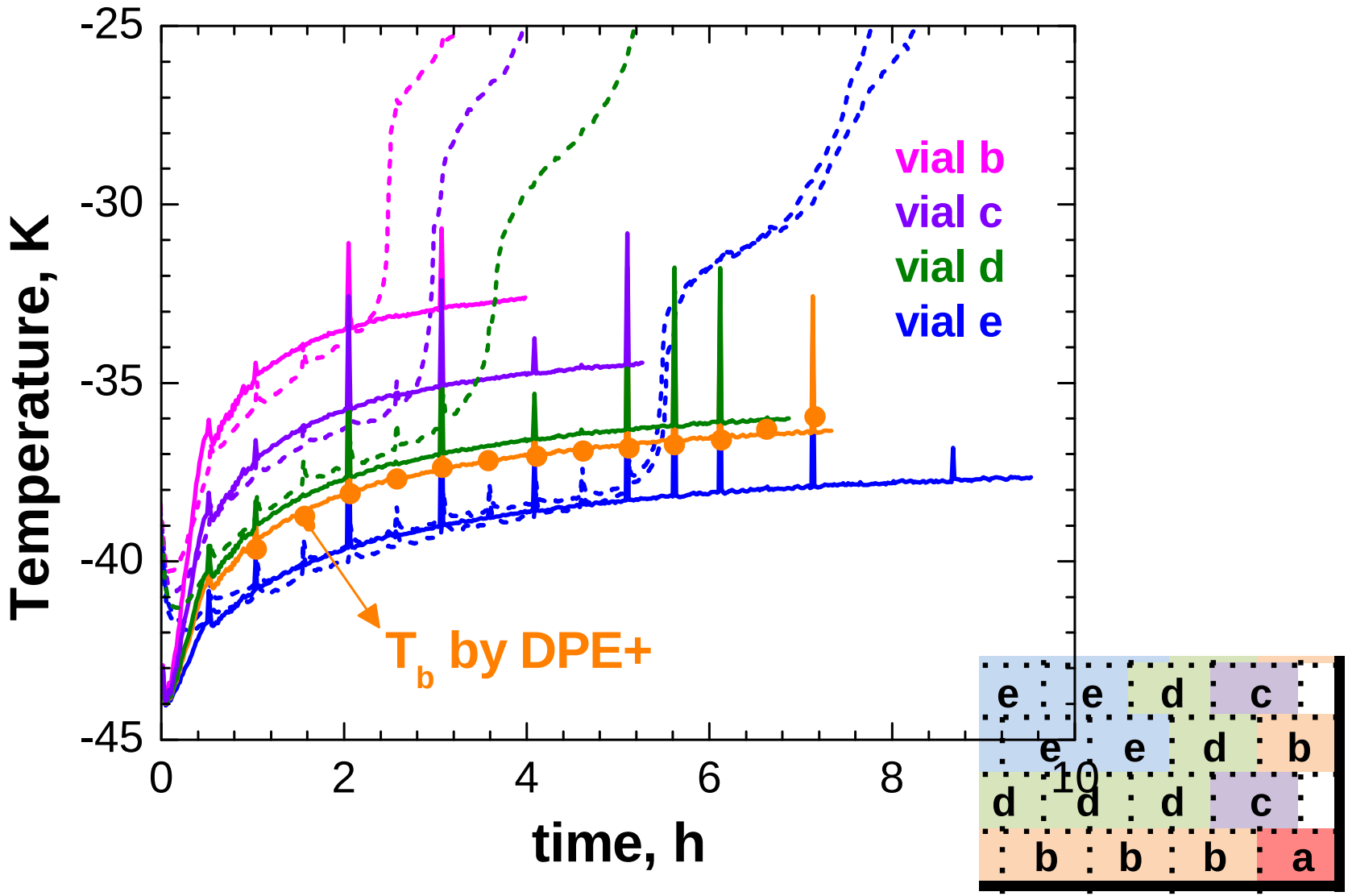
Coupling a wireless miniaturised thermocouple and a soft-sensor, a "smart vial" has been realised by POLITO, whichs allows:

- to measure the temperature of vial in different positions
  - compatible with automatic loading and unloading
  - usable for equipment qualification
  - suitable for process monitoring
  - suitable for advanced automatic control

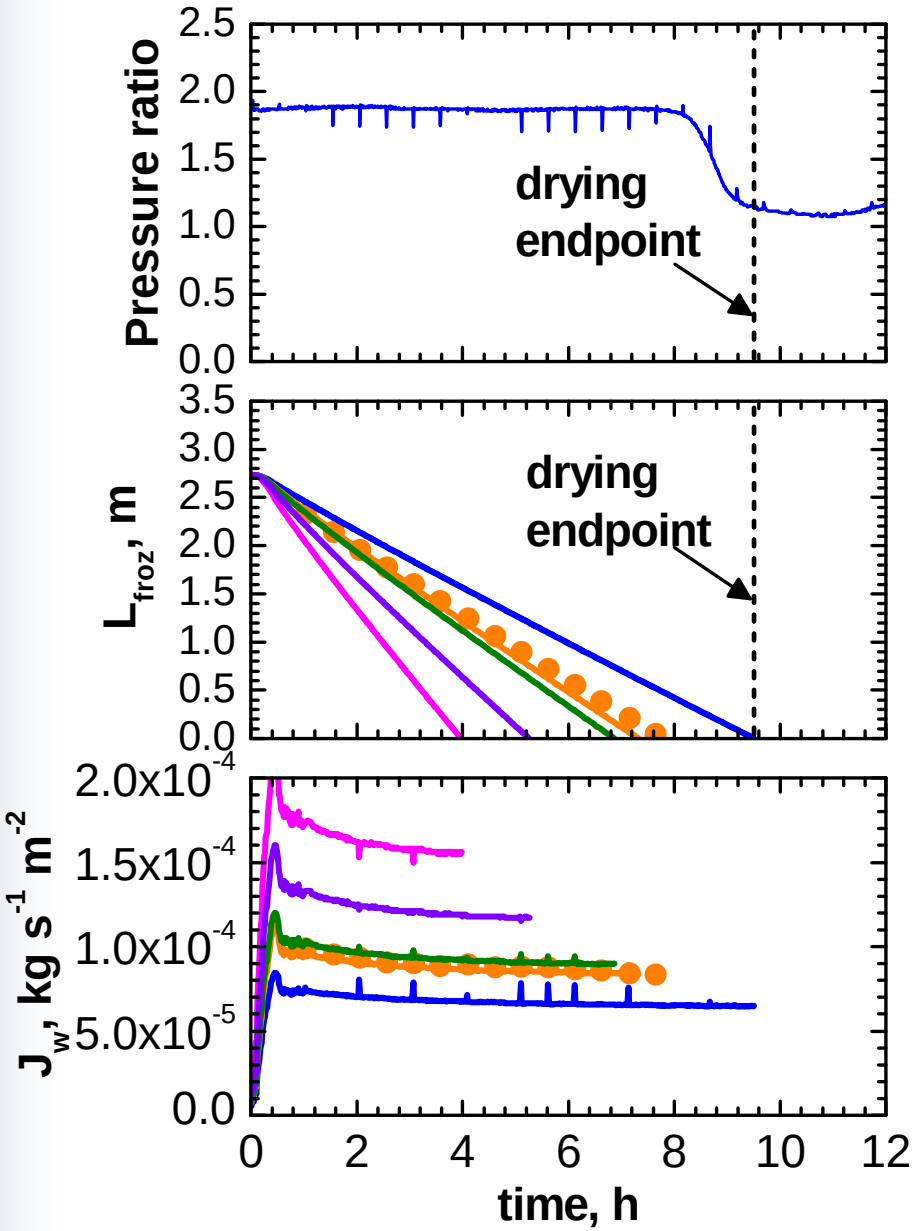
- to evaluate the K_v values easily in different equipment (included manifacture scale)
- to evaluate R_p easily also in the manifacture scale



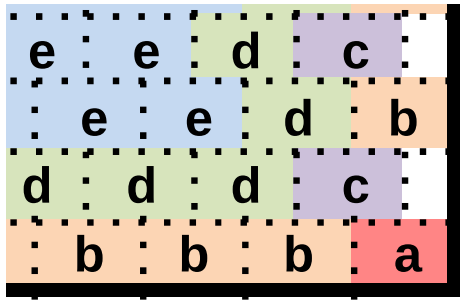
Mathematical modeling: model validation



Mathematical modeling: model validation



vial b
vial c
vial d
vial e



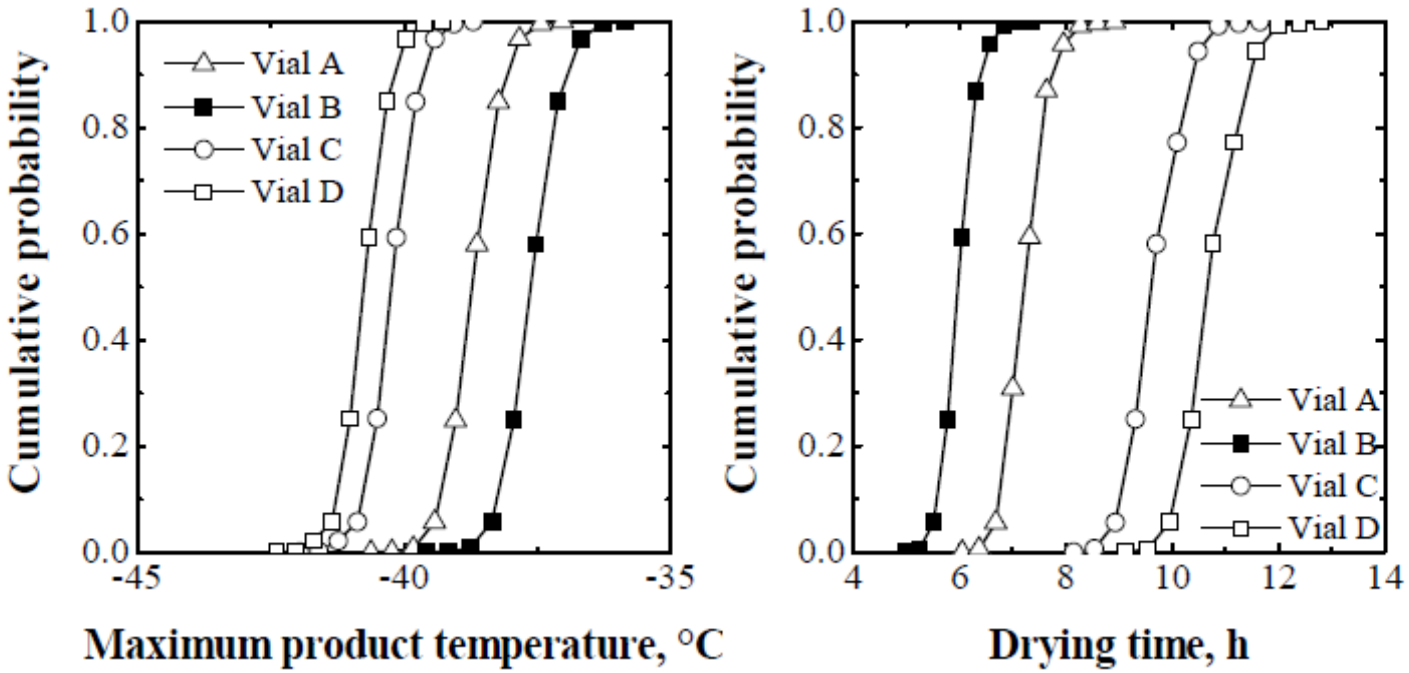
DPE+ (orange symbols) gives the batch average value

Mathematical modeling: *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



Recipe scale-up: the 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 three gravimetric tests in equipment "1" at different pressures in order to 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. One test to determine of the curve R_p vs. L_{dried} in equipment "1" (and, possibly, in equipment "2").

Recipe scale-up

Which is the target?

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

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 R_p is significantly different

Note: this is valid for a uniform batch,
or for the selected lot in the batch

Recipe 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 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}):

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

Recipe scale-up

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

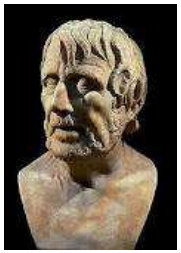
New recipe

K_v is used to characterize equipment "2"

L_{frozen}, T_i and T_B in equipment "1" have to be known

Experiments

Mathematical modeling



Per aspera sic itur ad astra

(Seneca, Hercules furens, act II, v. 437)

Recipe scale-up

8. Given the values of the operating conditions (T_{Shelf} 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 using the model of the process.
9. 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.

Conditions for the most critical lot must be considered if a 100% percentage of success is required

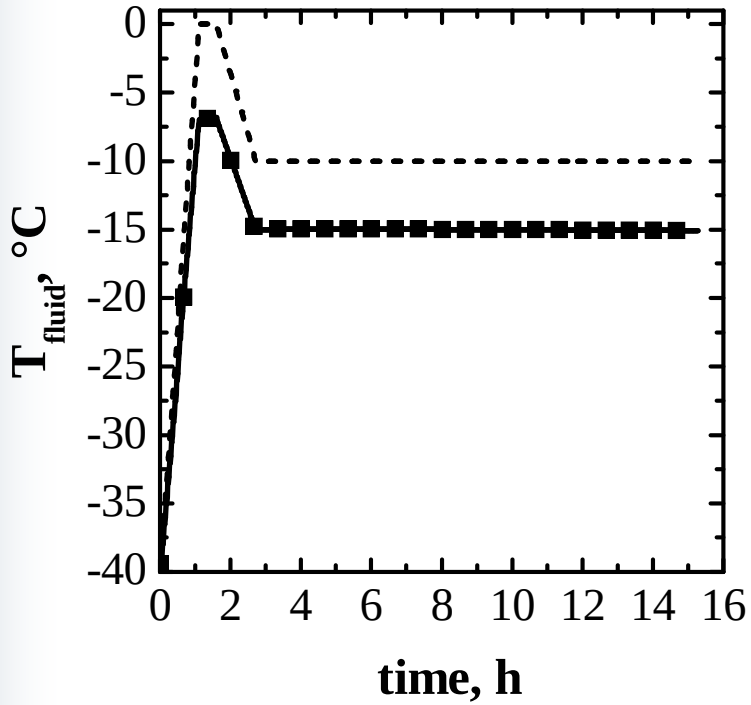
Recipe scale-up

Example of recipe scale-up

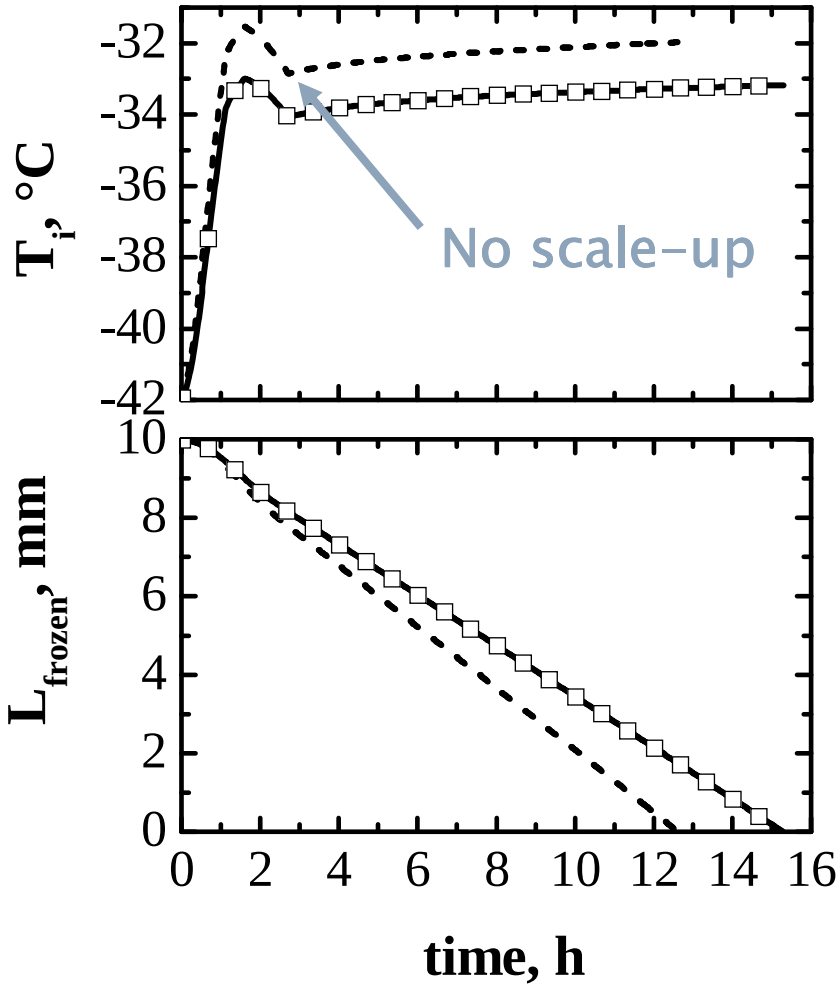
higher K_v for in equip. 2

Uniform batch

(or only core vials considered)



Comparison between the original recipe (dashed line) and the recipe calculate using the proposed scale-up algorithm (symbols).



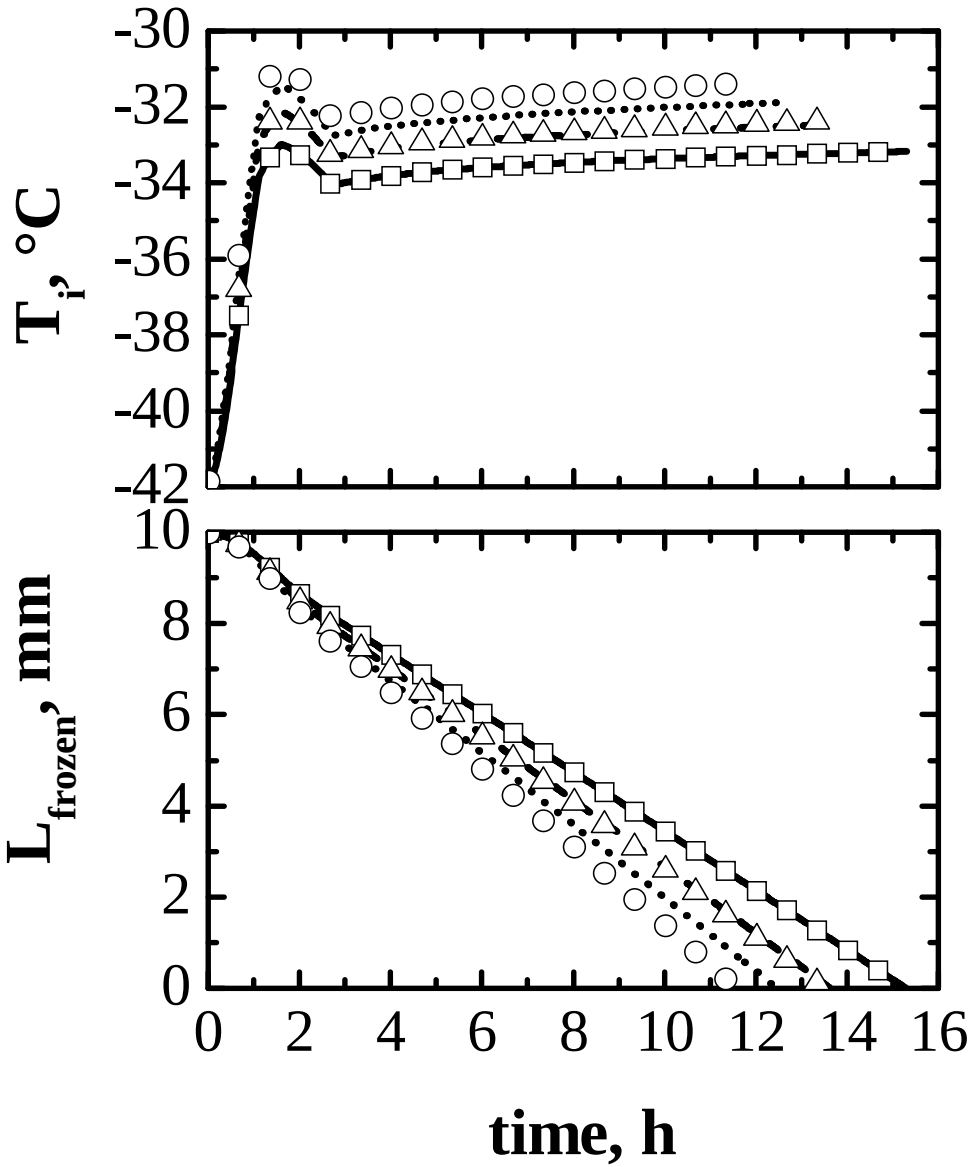
Evolution of the temperature at the interface of sublimation (upper graph) and of the thickness of the frozen layer (lower graph) in a vial in the first equipment (solid lines), and in the second equipment, when the original recipe is used (dashed lines) and when the scaled-up recipe is used (symbols).

Recipe scale-up

Example of recipe scale-up

considering non-uniformity of the batch: behaviour of the different lots

Evolution of the temperature at the interface of sublimation (upper graph) and of the thickness of the frozen layer (lower graph) in vials in the central part (solid line, □), and in the outer layer (group 2: dashed line, Δ; and 3: dotted line, ○) in the first equipment (lines), when the original recipe is used, and in the second equipment (symbols), when using the new recipe calculated in order to get the same dynamics in the central vials (group 1).



Recipe scale-up

In the previous case shown, the K_v was higher in the new equipment, thus the shelf temperature had to be lowered to avoid product overtemperature.

Often K_v is lower in large scale equipment: recipe transfer is safe in this case (lower product temperature) but not efficient:

- drying time is longer and the new required time must be taken into account to avoid failure in passing to secondary drying conditions.
- the recipe can be optimised rising the shelf temperature.

Robustness of the recipe is given by difference between product temperature e T_{max} fixed. The same ΔT can be maintained in the sacled up recipe.

But to properly evaluate “robustness” the possible deviations and their effect in the new equipment must be evaluated using modeling (failure analysis)

The Design Space

The Design space contains more information than a simple recipe.

Using modeling, it can be easily calculated

It is necessary to know K_v and R_p for the considered equipment

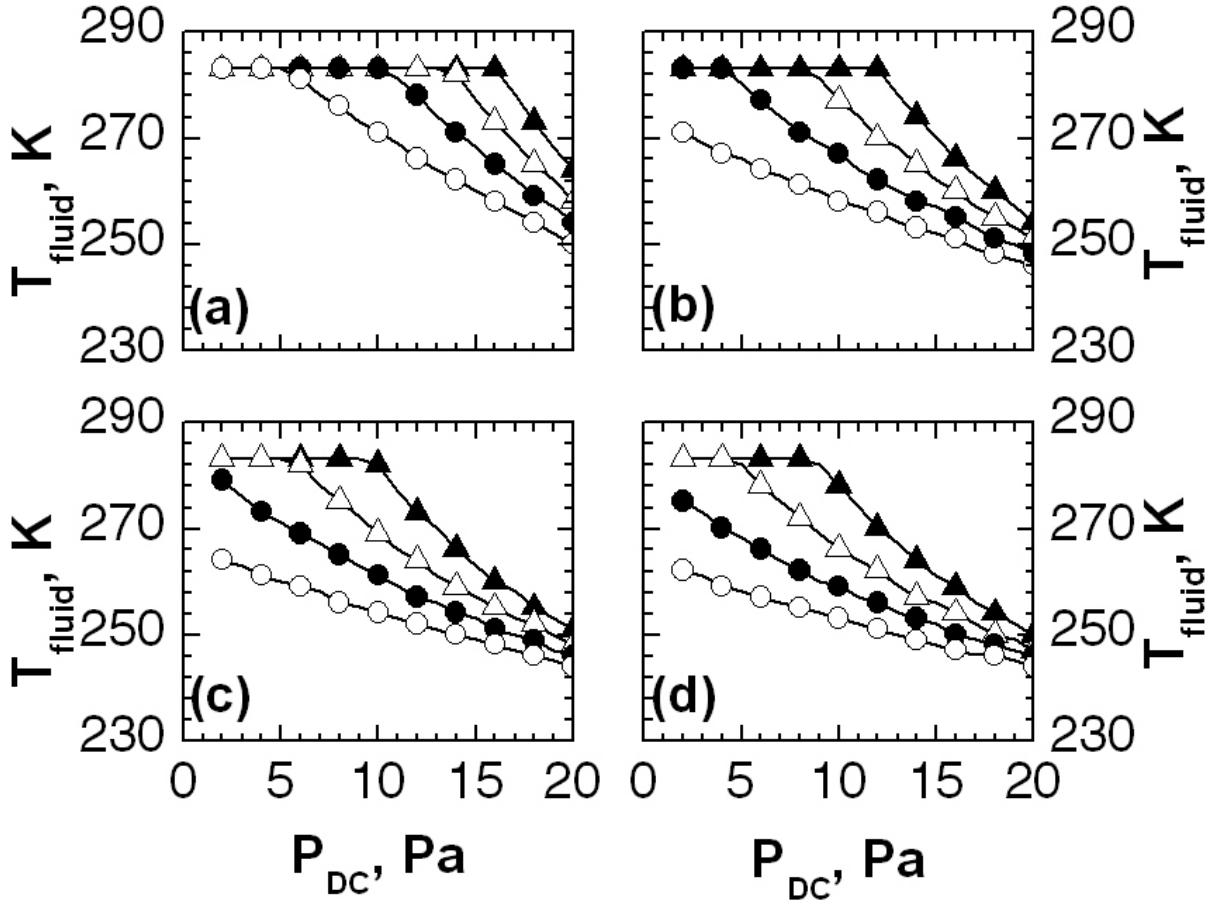
Thus having the data required for recipe scale up it is possible to build the whole design space

Robustness margin is immediately evident

Limits to the operating conditions, like choked flow conditions, can be easily included in the Design Space, and must be considered also in scaling up the recipe. This point is not treated in detail here, but literature supplies all necessary info.

Calculation of the design space

Taking into account R_p variation with drying progress

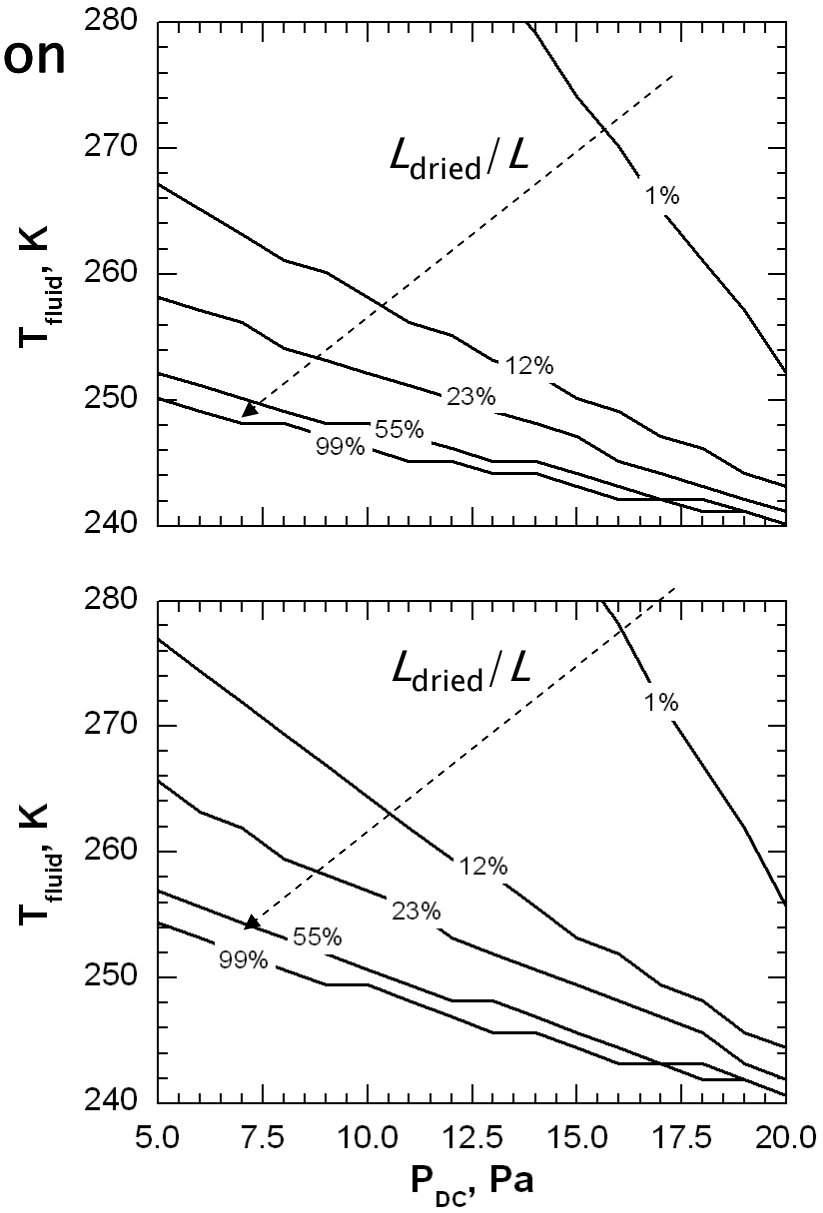


Design space of the selected product calculated at various values of dried layer thickness: (**a**) L_{dried}/L =12%; (**b**) L_{dried}/L =34%; (**c**) L_{dried}/L =66% and (**d**) L_{dried}/L =99%. (○) B type; (●) C type; (△) D and (▲) E type.

Process transfer using the Design Space approach

Example of design space construction

The design space can be directly calculated for the considered equipment (if K_v and R_p are known)



Example of design space for the selected product processed in freeze-dryer A (upper graph) and B (lower graph). Results refer to vials B.

Recipe scale-up and optimisation in one test: In-line approach

Traditionally, biotechnology processes are operated with fixed controls, thereby transferring variability in inputs and feed materials to variability in product quality.

In the **Quality-by-Design** paradigm, a dynamic control strategy is used to operate the process, managing the variability in inputs and feed materials to achieve consistent product quality.

By this way it is possible to preserve product quality during manufacturing, and to avoid testing final product quality, as recommended in the Guidance for Industry PAT (US-FDA, 2004).

The control system requires a device (**Process Analytical Technology**) to monitor the state of the product, and a mathematical model to calculate the suitable control actions.

A solution (already commercially available): *LyoDriver* automatic control using *DPE* monitoring tool.

In-line approach: MPC

A **Model Predictive Control** (MPC) algorithm calculates a sequence of control actions, one for each sampling interval, solving an optimization problem with a quadratic objective function, taking into account the cost of the control actions:

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

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

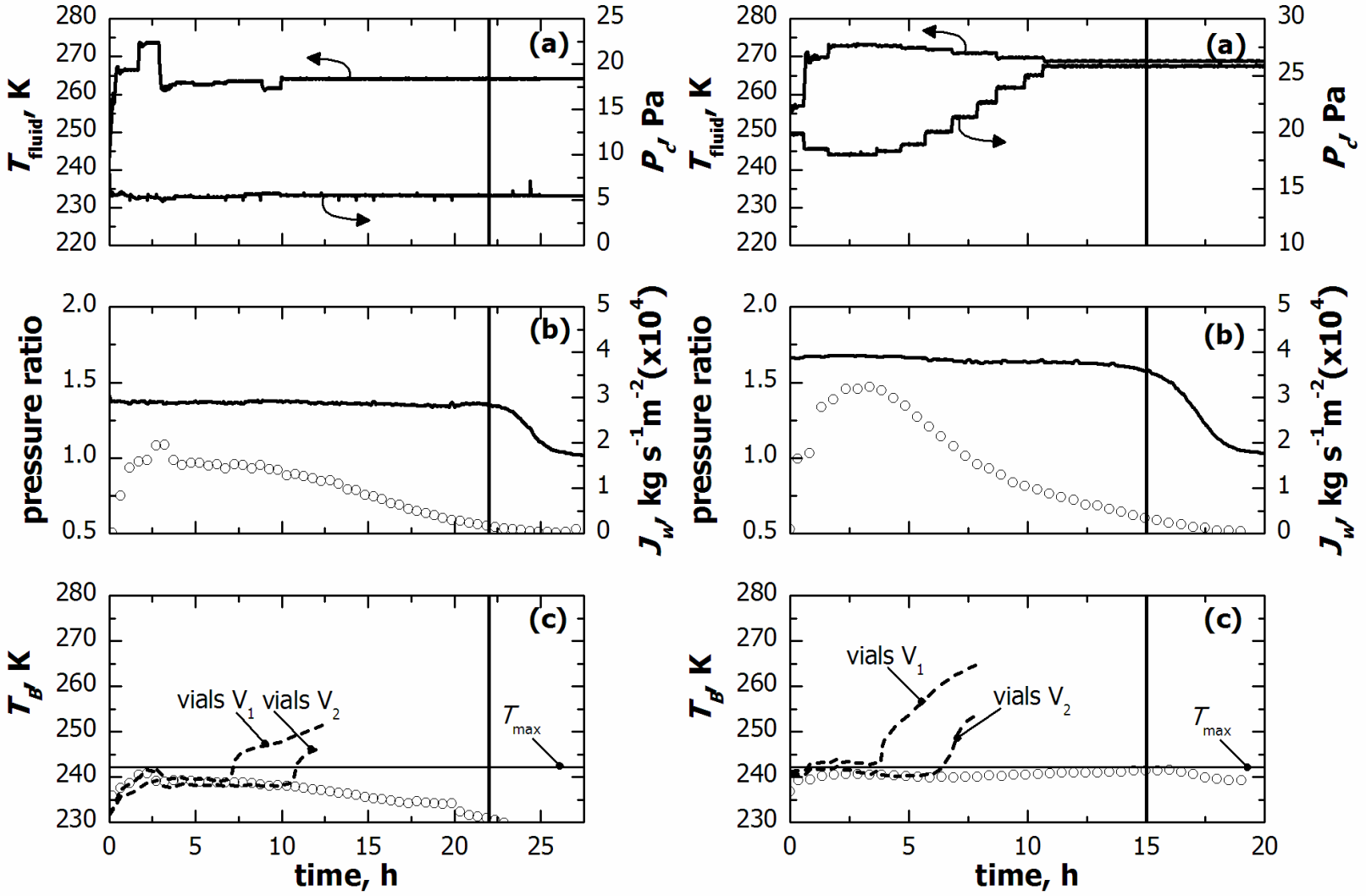
- ✓ Both T_{fluid} and P_c are manipulated

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

- ✓ Only T_{fluid} is manipulated

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

In-line approach: example of MPC results



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.

In-line approach: advantages and limitations

Advantages

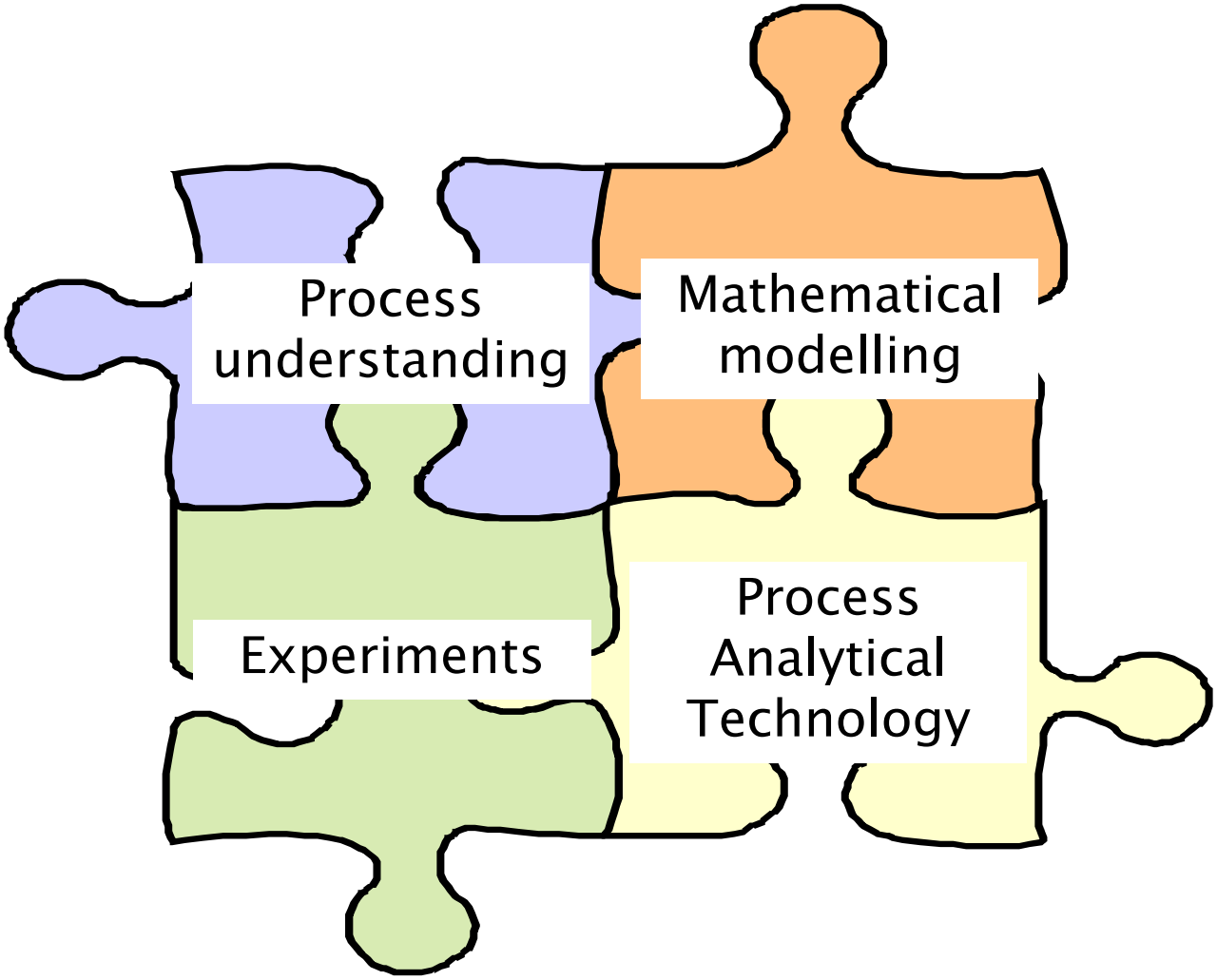
- the recipe is directly obtained, adapted for the considered equipment

- procedure suitable for any equipment (that has chamber and condenser separated by an isolation valve):
  - no retrofit problem, only software upgrade
  - no new expensive hardware required

Limitations

- using a batch averaged state estimation it does not take into account non-uniformity of the batch

Conclusions and final remarks



Ongoing developments at Politecnico di TORINO

- **Valvless batch state estimation**
- **wireless soft sensors** for evaluation of batch non-uniformity
- **smart vial** usable with automatic loading systems for Temperature measurement, K_v and R_p estimation
- **Advanced MPC controller** for non-unifrom batches
- Extension of **design space to secondary drying**

- **Improving of LyoDriver system**
  - extension to secondary drying monitoring
  - implementation of advanced monitoring tools for temperature and sublimation flux (DPE+)

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