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► **To cite this version:**

Nawal Daraoui, Pascal Dufour, Hassan Hammouri, Aurélie Hottot. Optimal operation of sublimation time of the freeze drying process by predictive control: Application of the MPC@CB Software. European Symposium on Computer Aided Process Engineering (ESCAPE), Jun 2008, Lyon, France. pp.453-458. hal-00352454v1

**HAL Id: hal-00352454**

**<https://hal.science/hal-00352454v1>**

Submitted on 13 Jan 2009 (v1), last revised 22 Jan 2009 (v2)

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# Optimal operation of sublimation time of the freeze drying process by predictive control: Application of the MPC@CB Software

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## Abstract

This paper presents the application of a model based predictive control strategy for the primary stage of the freeze drying process, which has not been tackled until now. A model predictive control framework is provided to minimize the sublimation time. The problem is directly addressed for the non linear distributed parameters system that describes the dynamic of the process. The mathematical model takes in account the main phenomena, including the heat and mass transfer in both the dried and frozen layers, and the moving sublimation front. The obtained results show the efficiency of the control software developed (MPC@CB) under Matlab. The MPC@CB based on a modified levenberg-marquardt algorithm allows to control a continuous process in the open or closed loop and to find the optimal constrained control.

**Keywords:** Freeze drying, moving boundary, non linear distributed parameter systems, model based predictive control, internal model control.

## 1. Introduction

Freeze drying is a separation process in biotechnology, food and pharmaceutical industries, frequently used to stabilize and preserve the products [1-2]. Compared with conventional drying techniques, freeze drying is generally considered to produce highest quality dried products. In freeze drying, major costs being apportioned are: the energy for sublimation of frozen solvent during the primary drying stage, the energy for the removal (desorption) of bound (unfrozen) solvent during the primary and secondary drying stages, the energy to support vacuum and labor, and overhead costs which are all a function of the drying time. Moreover, one very important parameter in the study of freeze drying is the temperature of the product which must carefully be controlled during the primary and the secondary stages of freeze drying.

A number of freeze-drying models have been published in the literature to describe the freeze-drying process. The model of Liapis and Litchfield [3] was seen to be more accurate than the model of King [4]. The sublimation model was then improved upon [5] by including the removal of bound water in equations. This model is commonly known as the "sorption-sublimation model". Various numerical methods can be used to solve the governing equations. Liapis and co-workers used a one-dimensional method which the method of orthogonal collocation [6] was applied to solve the equations. Ferguson et al. [7] used the finite element method to solve the governing equations.

Very few papers deal with the on-line optimal control of freeze drying. The optimal control of the primary and secondary drying stages of bulk solution freeze drying in trays was formulated and solved by [8]. The contribution of this paper is therefore to provide a model predictive control (MPC) framework, as applied in [9], to minimize under constraints the drying time during the primary stage of the freeze drying process of Bovin Serum Albumin (BSA) solution, a formulation whose physical data are available and freeze drying were already carried out. To satisfy this purpose, a control software (MPC@CB) is used, allowing solving any other constrained optimal control problems for any processes. The dynamics of the moving sublimation ice front and the temperature profiles of the product are presented here.

## 2. Freeze drying process

Freeze-Drying is a drying process where the solution is first frozen, thereby converting most of the water to ice, and the ice is removed by sublimation at low temperature and low pressure during the primary drying stage of the process. Since freeze drying is the most complex and expensive technique of drying, its use is usually restricted to delicate heat sensitive products. In the pharmaceutical industry, the solution is normally filled into glass vials, the vials are placed on temperature controlled shelves in a large vacuum chamber, and the shelf temperature is lowered to freeze the product. After complete solidification, the pressure in the chamber is lowered to initiate rapid sublimation.

To carry out the objective of this paper, we consider a one-dimensional freeze drying model based on the work of Liapis and Sadikoglu [8]. During the primary drying, the vial contains two regions: a dry layer, in which the majority of water was sublimated and a frozen layer. These two areas are separated by a moving interface called the sublimation front. In this work, it is assumed that [5]:

- One dimensional heat and mass transfer.
- The sublimation front is planar and parallel to the horizontal section of the vial.
- The gas phase inside the pores of the dry layer is composed only of pure water vapor, i.e. the effect of inert gas is negligible because the amount of inert gas in the drying chamber is much smaller than that of water vapor.
- The value of the partial pressure of water vapor at the top of the dry layer is equal to the total pressure in the sublimation chamber.
- The frozen region is considered to be homogeneous with uniform thermal conductivity, density and specific heat.

The mathematical model consists of the unsteady state energy balance in the dried and frozen regions:

$$\left\{ \begin{array}{l} \frac{\partial T_1}{\partial t} = \frac{k_{1e}}{\rho_{1e}c_{p1}} \frac{\partial^2 T_1}{\partial z^2} - \frac{c_{pg}}{\rho_{1e}c_{p1}} \frac{\partial(N_w T_1)}{\partial z} - \frac{\Delta H_v \rho_1}{\rho_{1e}c_{p1}} k_d C_{sw} \quad , t > 0, 0 < z < H(t) \\ \frac{\partial T_2}{\partial t} = \alpha_2 \frac{\partial^2 T_2}{\partial z^2} \quad , t > 0, H(t) < z < L \\ \frac{dH}{dt} = -\frac{1}{\rho_2 - \rho_1} N_w \quad , t > 0, z = H(t) \\ \frac{\partial C_{sw}}{\partial t} = -k_d C_{sw} \quad t > 0, 0 < z < H(t) \end{array} \right. \quad (1)$$

Where  $T_1$  is the dried layer temperature,  $T_2$  is the frozen layer temperature,  $N_w$  is the mass transfer flux of the water vapour,  $C_{sw}$  is the bound water and  $H$  is the sublimation interface. The different parameters of the model are presented in [12]. In this work, we use a simplified equation to describe the dynamic of the mass flux based on the diffusion equations of Evans. The equation is given by the following expression:

$$N_w = \frac{-M_w k_1}{R_g T_1 H} (p_H - p_0), t > 0 \quad (2)$$

Where  $p_0$  and  $p_H$  is the partial pressures of water vapor at  $z=0$  and  $z=H(t)$  respectively. The pressure boundary condition at the top surface of the material being dried is defined as a constant pressure inside the drying chamber, and the vapor pressure at the sublimation interface is defined as an equilibrium vapor pressure according to the temperature of the interface.

The initial conditions for the equation (1) are given by:

$$\begin{cases} T_1(z, t) = T_2(z, t) = T^o & \text{for } 0 \leq z \leq L, t = 0 \\ H(t) = 0^+ & \text{for } t = 0 \\ C_{sw}(z, t) = C_{sw}^0 & \text{for } 0 \leq z \leq L, t = 0 \end{cases} \quad (3)$$

The boundary conditions for the equations (1) are as follows:

$$\begin{cases} -k_{1e} \frac{\partial T_1}{\partial z} = q_1, & t > 0, z = 0 \\ -k_{1e} \frac{\partial T_1}{\partial z} = -k_2 \frac{\partial T_2}{\partial z} + \left( -\Delta H_s + \frac{\rho_2 c_{p2} T_2 - \rho_1 c_{p1} T_1}{\rho_2 - \rho_1} \right) N_w, & t > 0, z = H(t) \\ -k_2 \frac{\partial T_2}{\partial z} = q_2, & t > 0, z = L \end{cases} \quad (4)$$

Where  $T_{lp}(t)$ ,  $T_{up}(t)$  are respectively the temperatures of the lower and upper heating plates. For general freeze dryers, the temperature of the upper and lower heating plates are the same, i.e.  $T_{lp}(t) = T_{up}(t)$ .

The important objective of the on-line control is to decrease the drying time under constraints, while maintaining the quality of the product. Furthermore, an important constraint for primary drying is that one must never allow the product temperature to exceed its glass transition temperature. This constraint can be expressed by:

$$T_2(z, t) \leq T_g, \quad H(t) < z < L, \forall t > 0 \quad (5)$$

The output variable of the process considered in our control problem corresponds to the measured temperature at the bottom of the vial. In the sequel, it is assumed that only the process output is constrained to satisfy the inequality (5). The second constraints during the primary drying stage of the freeze drying process dealing with the heat flux at the top and bottom surfaces and respectively. Their magnitudes depend respectively on the value of the temperature of the heating plate at the upper surface of the vials, and the temperature of the heating plate at the bottom surface of the vials. These temperatures are assumed to be the same and the manipulated variable  $u(t)$  is subjected to the constraints in the following form:

$$T_{\min} \leq u(t) = T_{lp}(t) = T_{up}(t) \leq T_{\max}, \forall t > 0 \quad (6)$$

### 3. Simulation results

In this study, we are interested to find the optimal on-line tuning of the manipulated variable for the constrained optimization of the sublimation time. To realize the MPC under constraints of the freeze drying process, we used the MPC@CB software<sup>1</sup> developed with Matlab.

#### Control Software: main features of [MPC@CB](#)

The codes of the MPC@CB software have been written to run with Matlab. It allows realizing the MPC under constraints of the specified continuous process. The originality of these codes is first the easy use for any continuous SISO process (Single Input Single Output), through the user files (where model equations have to be specified), synchronized by few main standards files (where the user has to make few (or no) changes. The original feature of the software is the straightforward resolution of various model based control problems through different choices:

1. Open or closed loop control.
2. MPC for a trajectory tracking problem, with or without the output constraint.
3. MPC to solve an operating time minimization problem, with or without the output constraint.

The other originality is the method used to develop the codes : it is very easy to introduce new parts in the code, such as :

1. MPC with an user defined control problem.
2. Handle SIMO, MISO or MIMO model .
3. Introduce a software sensor (observer).
4. Apply the software for a real time application [11].

For more the details about the MPC@CB software and the operations conditions, the reader can refer to [12]. The optimal minimization of the drying time under constraints may be equivalent to define the performance index as the maximization of the velocity of the sublimation interface. Since MPC@CB solves a minimization problem, the objective function is:

$$\min_u J(u) = \sum_j \frac{1}{\|\vartheta + V(j)\|^2} \quad \forall j \in J_1^{N_p} \quad (7)$$

accounting for the magnitude constraints for the manipulated variable and the output process. The velocity  $V$  is given by  $V=dH/dt$  and  $\vartheta >0$  is a small positive parameter, introduced to avoid the division by zero in (7).

In Figure 1, the dynamics of the moving sublimation ice front  $H(t)$  and its velocity are presented. The optimization procedure based on the MPC@CB software is iterated until the position  $H(t)$  reaches the length  $L$ , which means the end of the primary drying stage.

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<sup>1</sup> © University Claude Bernard Lyon 1 - EZUS. In order to use MPC@CB, please contact the author : dufour@lagep.univ-lyon1.fr

The profile of the bottom surface temperature of the material being dried, the heating plate temperature, as well as the glass transition temperature are presented in Figure 2. In order to satisfy the output constraint, the temperature is then kept near this constraint value for the rest of the time of the primary drying stage by reducing iteratively the heat flux input. The efficiency of the IMC-MPC strategy over open loop control can be seen: The drying time obtained for the primary drying stage using the MPC@CB software is equal 18 hours, while the required time for the sublimation step is about 24.11 hours in open loop.

#### **4. Conclusion**

This study tackled the model based predictive control of the primary stage of the freeze drying process. Using the mathematical model of Liapis et al., in which the dynamic of the mass flux was simplified, the model based predictive control of the freeze drying is studied. Taking into account of the non linear partial differential equation model of the process, the idea was to combine the IMC structure and the MPC framework. The resulting IMC-MPC chart corrected the modelling errors introduced in the model based on line optimizer. Constraints on the manipulated variable and controlled variables are handled. This framework was used to optimize the drying time during the primary drying stage of the freeze drying process. The simulations results of the minimization problem were established using the MPC@CB code developed in Matlab. The difficulty related to this problem was the choice of the trajectory given by  $u_0$ . Since the measured temperature is at the bottom surface of the vial, one may design an observer that estimates the temperatures at different  $z$ .

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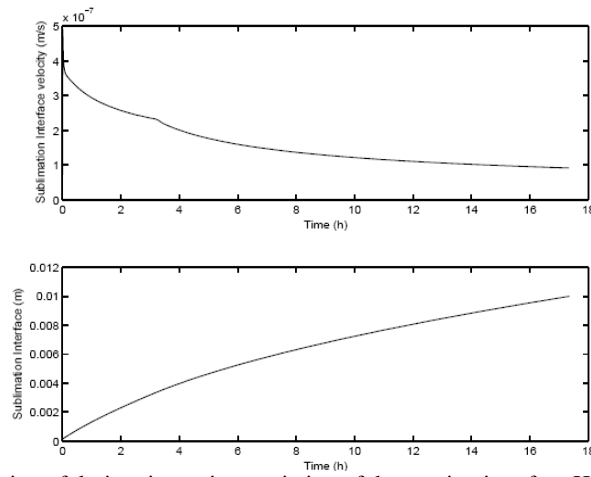


FIG. 1: Optimization of drying time : time variation of the moving interface  $H(t)$ (bottom) and its velocity (top) during the primary drying stage

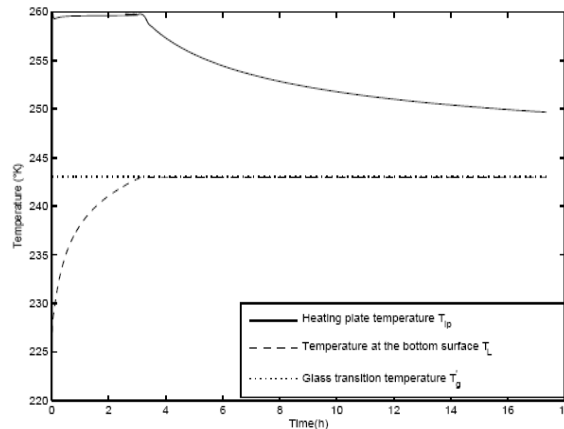


FIG. 2: Optimization of drying time : time variation of the bottom surface and heating plate temperatures during the primary drying stage