NCO-tracking Based Control of Semi-batch Antisolvent Crystallization Processes in the Presence of Uncertainties

V.K. Kamaraju, B. Srinivasan and M.S. Chiu

Abstract—Control of crystallization processes in order to obtain desired product specifications is very critical in pharmaceutical industries, as it influences not only the efficiency of the other downstream processes but also the bioavailability of the drug. Hence, motivated to counter the pragmatic limitations of implementing the optimal control policies in the presence of plant-model mismatch, measurement-based optimization (MBO) schemes for real-time optimal operation of (semi-)batch pharmaceutical antisolvent crystallization processes has been presented in this paper. MBO schemes are based on tracking the Necessary Conditions of Optimality (NCO), usually a sequence of boundary and (or) interior arcs, using measurement feedback. The current study explores this approach by designing neighboring extremal (NE) controller to follow the optimal trajectory in the interior arcs during the real-time optimal control. Furthermore, performance assessment of the NE controller is done by comparing to different control strategies for various scenarios of plant model mismatch.

I. INTRODUCTION

Control of crystallization processes in order to obtain desired product specifications is very critical in pharmaceutical industries, as it influences not only the efficiency of the other downstream processes but also the bioavailability of the drug [1], [2]. Usually, for non-polymorphic systems, product crystal size distribution is the most important variable to be controlled either through the addition of antisolvent or temperature cooling or, in certain situations, combining both these modes. Conventional operation of these processes involve the implementation of an optimal trajectory obtained from an offline model. However, this open loop approach has shown significant loss in optimality i.e., by deviating far from the desired product quality, in the presence of process variations and disturbances [3]. Hence, direct design approaches like supersaturation or concentration control (C-control) have been studied in the literature, that have displayed lesser sensitivity to process variations. Towards this end, owing to the advancements in sensor technology for in situ process measurements and application of Process Analytical Technology (PAT) tools, closed loop control strategies for batch crystallization processes that are robust to process disturbances have gained much attention [4], [5], [6], [7].

According to optimal control theory, in the presence of any slight variations in the process, the optimal control policy obtained through the nominal process model has to be modified completely in order to satisfy the necessary conditions of optimality (NCO) for the perturbed optimal control problem. One of the techniques to overcome such issues in real-time control is the use of Model Predictive Control (MPC). Using the current state information and a nominal model, the MPC formulation requires repetitive optimization of the nonlinear dynamic formulation in order to find the future optimal input moves [8]. Even though, MPC is a proven technology in process industries, the necessity of the solution of the online re-optimization formulation for its implementation, may sometimes, make it formidable to unattractive for control of (semi-)batch processes. Alternatively, instead of either tracking an optimal trajectory or using repetitive optimization based on an offline model, measurement based schemes that track the NCO have been developed. However, these approaches require the characterization of the nominal solution using boundary and interior arcs, that are necessarily invariant even in the presence of uncertainty and disturbances [9], [10].

In this current study, a NCO tracking based control strategy has been employed for optimal operation of semi-batch antisolvent crystallization processes in the presence of plant-model mismatch. In order to track the interior arcs, a Neighboring Extremal (NE) controller has been designed. The rest of the paper has been organized as follows: Section II gives the relevant overview of NCO and design of NE controller. Section III-A provides details of the process model used for crystallization of paracetamol in acetone-water mixture. Characterization of the nominal solution is shown in Section III-B, while the design and performance of the NE controller are discussed in III-C. A comparative study using several case studies is carried out in order to show the advantages of using NE controller over not only implementing nominal profile, but also the direct design C-control.

II. BACKGROUND

A. Optimal Control Problem Formulation

Consider the formulation of the optimal control problem as follows:

\[
\min_{u(t)} J = \Phi(x(t_f)) + \int_0^{t_f} L(x(t), u(t), \theta) \, dt \quad (1)
\]

s.t \quad \dot{x}(t) = F(x(t), u(t), \theta), \quad x(0) = x_0 \quad (2)

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where \( t_f \) is the batch time, \( \Phi(x(t_f)) \) is the terminal cost function and \( L \) is the integral cost function. \( x \) is the state vector function with the initial conditions as \( x_0 \) and \( \theta \) is the vector of uncertain time-invariant parameters. \( F \) describes the system dynamics, while \( J \) is the cost function to be minimized. Furthermore, assuming that if all the functions in Eqs. (1)-(3) are continuously differentiable with respect to their arguments, then there exists optimal control \( u^*(t) \in [u^L, u^U] \forall t, 0 \leq t \leq t_f \) for the nominal parameter values. Note that this solution profile consists of both boundary (constraint-seeking) and interior (sensitivity-seeking) arcs.

B. Necessary Conditions of Optimality

Based on Pontryagin’s Minimum Principle (PMP), the problem of optimizing the scalar cost functional \( J \) in Eqs. (1) to (3) can be reformulated by defining the Hamiltonian function \( H(t) \) as [11]:

\[
H(x, u, \theta, \mu^L, \mu^U) = L(x, u, \theta) + F(x, u, \theta)^T \lambda + \mu^L (u^L - u) + \mu^U (u - u^U), \quad (4)
\]

and the necessary conditions of optimality give

\[
H_u = L_u + F_u^T \lambda - u^L + u^U = 0; \quad H_{uu} > 0, \quad (5)
\]

where \( \lambda \) represents the adjoint vector function given as

\[
\dot{\lambda} = -H_x = -L_x - F_x^T \lambda; \quad \lambda(t_f) = \Phi_x(x(t_f)) \quad (6)
\]

and \( \mu^L, \mu^U \) denote the Lagrange multiplier functions satisfying

\[
\mu^L (u^L - u) = 0; \quad \mu^L \geq 0 \quad (7)
\]

\[
\mu^U (u - u^U) = 0; \quad \mu^U \geq 0 \quad (8)
\]

Notice that, \( \mu^L(t) = \mu^U(t) = 0 \) only along the interior arcs, while \( \mu^L(t) \neq 0 \) and \( \mu^U(t) \neq 0 \) along the boundary arcs. During real-time control of the process, boundary arcs can be easily tracked. However, in order to push the path sensitivities to zero, approximate methods such as neighboring extremal control can be employed [12].

C. Design of Neighboring Extremal Controller for Non-singular Problems

As the optimal control profile \( u^*(t), 0 \leq t \leq t_f \) is designed based on the initial condition \( x_0 \) and nominal parameters values \( \theta \), any slight variation \( \delta x_0 \) in the initial states requires the modification of the entire profile. For the case of unconstrained problems or when the constraints remain inactive, the first-order approximation of the optimal trajectory for the perturbed control is considered as

\[
u(t; \eta) = u^*(t) + \eta \delta u(t) + o(\eta) \quad (9)
\]

and the correction \( \delta u \) is computed as the solution of the so-called accessory minimum problem, i.e., the minimization of the second-order variation of the cost functional subject to the linearized dynamics [13],

\[
\min_{\delta u(t)} \frac{\delta^2 J}{\delta u(t)} = \frac{1}{2} \delta x(t_f)^T \Phi_{xx}(x(t_f)) \delta x(t_f) + \frac{1}{2} \int_0^{t_f} \left( \begin{array}{c} \delta x(t) \\ \delta \theta \end{array} \right)^T \left( \begin{array}{cc} H_x^T & H_{ux}^T \\ H_{ux} & H_{uu}^{-1} H_{ux} \\ H_{ux}^T & H_{uu}^{-1} H_{ux} \end{array} \right) \left( \begin{array}{c} \delta x(t) \\ \delta \theta \end{array} \right) \, dt \quad (10)
\]

s.t. \( \delta x(t) = F_x \delta x + F_u \delta u + F_\theta \delta \theta, \quad \delta x(0) = \delta x_0 \quad (11) \)

Thus, when the problem of Eq. (10) to (11) has a solution, it can be shown that there exists an optimal control trajectory \( u(t; \eta) \), in the neighborhood of \( \eta = 0 \). Therefore, the correction \( \delta u \) satisfying the strengthened Legendre-Clebsch condition \( H_{uu}^T > 0 \) condition along the nominal solution \( u^*(t), x^*(t), \lambda^*(t) \), is then given by

\[
\delta u(t) = -(H_{uu}^T)^{-1} (H_{ux}^T \delta x + F_u^T \delta \lambda + H_{u\theta}^T \delta \theta) \quad (12)
\]

Furthermore, a NE state feedback law that enforces the necessary conditions of optimality can be designed via backward sweep method that assumes linear relation between the states and adjoint variables and parameters as \( \delta \lambda(t) = S_x(t) \delta x(t) + S_\theta(t) \delta \theta \). For a detailed derivation, please refer [12].

\[
\begin{align*}
\delta u(t) &= -K_x \delta x(t) - K_\theta \delta \theta \\
K_x(t) &= (H_{uu}^T)^{-1} (H_{ux}^T + F_u^T S_x(t)) \\
K_\theta(t) &= (H_{uu}^T)^{-1} (H_{u\theta}^T + F_{u\theta}^T S_\theta(t)) \\
S_x(t) &= -H_{ux}^T S_x(t) - S_x(t) F_x^T + F_{ux}^T S_x(t) + (H_{ux} + S_x(t) F_u) K_x(t); S_x(t_f) = \Phi_{xx}^* \\
S_\theta(t) &= -H_{u\theta}^T S_\theta(t) - S_\theta(t) F_{u\theta}^T + F_{u\theta}^T S_\theta(t) + (H_{u\theta} + S_\theta(t) F_u) K_\theta(t); S_\theta(t_f) = 0
\end{align*}
\]

The neighboring extremal is obtained by solving the Riccati equation within the unconstrained arcs.

III. OPTIMAL CONTROL OF ANTISOLVENT CRYSTALLIZATION PROCESSES

A. Process Model

The population balance equation along with the mass balance equations and kinetic expressions are solved in order to simulate the process. For the purpose of simplification, crystal agglomeration, growth dispersion and breakage phenomena are neglected by most of the literature on batch crystallization [14]. Further simplification is done by avoiding both the length dependency of the growth kinetics and also the formation of new nuclei by secondary nucleation mechanisms. In the seeded operations, with the consideration that the nucleation takes place at negligible crystal size, the mathematical model represented using the most celebrated 1-D population balance equation is given as

\[
\frac{\partial n(L, t)}{\partial t} + G(t) \frac{\partial n(L, t)}{\partial L} = B \delta(L) \quad (18)
\]
with a parabolic distribution for the initial seed loading given by
\[ n(L)|t=0 = \begin{cases} a_p L_s^2 + b_p L_s + c_p, & L_s,i \leq L_s \leq L_s,f \\ 0, & \text{otherwise} \end{cases} \] (19)
where \( n \) represents the number density of the crystals, \( L \) is the characteristic size of the solute crystal, \( G \) is the length independent growth kinetics, \( B \) is the nucleation kinetics and \( \delta \) is the Dirac delta function.

\[ L_{s,i} = L_{s,mean}(1 - L_{s,s,d}) \] (20a)
\[ L_{s,f} = L_{s,mean}(1 + L_{s,s,d}) \] (20b)
where \( L_{s,mean} \) is the mean size of the seeds, \( L_{s,s,d} \) is the standard deviation in the seed distribution and the coefficients \( a_p, b_p \) and \( c_p \) are determined based on the seed mass, \( m_{seed} \). The method of moments transforms the hyperbolic partial differential equation represented by the population balance equation in Eq. (18) into a set of ordinary differential equations called the moment equations. Considering \( L_0 \) to be the crystal size at nucleation (critical size, assumed to be close to \( 0 \, \mu m \)), the moment equations defined on a per mass of solvent basis are obtained as follows [15]

\[ \mu_0 = B \]
\[ \mu_i = iG\mu_{i-1} \quad \text{where} \quad i = 1, 2, 3, 4 \]
\[ C = -3\rho_c k_v G(t)\mu_2(t) \] (21)
where \( \rho_c \) is the solute density and \( k_v \) is the shape factor.

During this study, the moment equations corresponding to \( \mu_0 \) to \( \mu_4 \) are solved along with the mass balance equations using the ode45 solver in MATLAB. Thus, the process states are \( x = [\mu_0, \mu_1, \mu_2, \mu_3, \mu_4, C]^T \). The generic representation of the definition of the moments of the CSD is as follows

\[ \mu_i = \int_0^\infty L^i n(L, t) dL \quad \text{where} \quad i = 0, 1, 2, \ldots \] (22)

In this study, a laboratory-scale, semi-batch, isothermal, seeded antisolvent crystallization process model for paracetamol in acetone-water mixture is considered [16], [17], [5]. The corresponding expressions for the crystal kinetics and solubility are summarized as follows

\[ B = k_b \Delta C^b \] (23)
\[ G = k_g \Delta C^g \] (24)
where \( k_b \) and \( b \) represent the nucleation kinetic parameters, \( k_g \) and \( g \) represent the growth kinetic parameters and \( \Delta C(= C - C_{sat}) \) represents the absolute supersaturation\(^1\). Table I lists the different parameters used in the mathematical model. The optimal control problem is formulated to maximize the volume-weighted mean size of the product crystals. Therefore, the cost function reads as

\[ \min_{u(t)} J = \phi(x(t_f)) = - \left( \frac{\mu_4}{\mu_3} \right)_{t_f} \] (25)

\(^1\)The units of \( C, C_{sat} \) and \( \Delta C \) are \( \text{gm/solute/gm/antisolvent} \). \( k_b \) and \( k_g \) have the same units as \( B \) (no. of particles/ \( m^3 \) s) and \( G \) (m/s) respectively, while \( b \) and \( g \) are dimensionless.

### TABLE I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape factor</td>
<td>( k_v )</td>
<td>0.7465</td>
<td>-</td>
</tr>
<tr>
<td>Solute density</td>
<td>( \rho_c )</td>
<td>1293</td>
<td>\text{kg/m}^3</td>
</tr>
<tr>
<td>Seed mass</td>
<td>( m_{seed} )</td>
<td>0.4986</td>
<td>\text{gm}</td>
</tr>
<tr>
<td>Mean seed size</td>
<td>( L_{s,mean} )</td>
<td>187.3</td>
<td>\text{( \mu m )}</td>
</tr>
<tr>
<td>Standard deviation in seed distribution</td>
<td>( L_{s,s,d} )</td>
<td>0.27368</td>
<td>-</td>
</tr>
<tr>
<td>Initial mass of solvent (acetone)</td>
<td>( M_{\text{solvent}} )</td>
<td>120</td>
<td>\text{gm}</td>
</tr>
<tr>
<td>Initial antisolvent mass percent</td>
<td>( m_{w,\text{initial}} )</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>Maximum antisolvent mass percent</td>
<td>( m_{w,\text{max}} )</td>
<td>76</td>
<td>-</td>
</tr>
<tr>
<td>Initial solute concentration</td>
<td>( C_0 )</td>
<td>0.1871</td>
<td>\text{gm/gm}</td>
</tr>
<tr>
<td>Maximum product concentration</td>
<td>( C_{\text{final,max}} )</td>
<td>0.11226</td>
<td>\text{gm/gm}</td>
</tr>
<tr>
<td>Minimum antisolvent flowrate</td>
<td>( FR_{\text{min}} )</td>
<td>0</td>
<td>\text{ml/min}</td>
</tr>
<tr>
<td>Maximum antisolvent flowrate</td>
<td>( FR_{\text{max}} )</td>
<td>6</td>
<td>\text{ml/min}</td>
</tr>
<tr>
<td>Batch time</td>
<td>( t_f )</td>
<td>120</td>
<td>\text{min}</td>
</tr>
<tr>
<td>Reactor volume</td>
<td>( V_{\text{max}} )</td>
<td>500</td>
<td>\text{ml}</td>
</tr>
</tbody>
</table>

where \( \mu_3 \) and \( \mu_4 \) are the third and fourth moments of the product crystal size distribution, respectively.

### B. Characterization of the Nominal Solution

By optimizing the cost function in Eq. (25), while satisfying the equality and inequality constraints given in Eq. (21) and Table I, the solution of the optimal control formulation is determined. The entire antisolvent flowrate profile of the batch is parameterized using three switching times and four flowrate values. Thus, the entire flowrate trajectory can be dissected into four intervals. During the first interval, \( \text{i.e.,} \) until the first switching instant \( (t_{s,1}) \), the flowrate is kept constant at \( FR_{\text{max}} \). The maximum volume constraint on the amount of antisolvent that can be added into the system dictates the third switching instant, \( (t_{s,3}) \) and thus, consequently the flowrate between \( t_{s,3} \) and \( t_f \) is set equal to \( FR_{\text{min}} \). Furthermore, the flowrate is kept constant at \( FR_{\text{max}} \) during the third interval, \( \text{i.e.,} \) between \( t_{s,2} \) and \( t_{s,3} \). Within the interior arc, the flowrate profile between the two switching times \( t_{s,1} \) and \( t_{s,2} \) is described using a first order spline that connects the flowrate values at these two time instants. Thus, the two time instants, \( t_{s,1} \) and \( t_{s,2} \) and the values of the antisolvent flowrate at these two instants are determined through optimization using nominal parameter values. Thus, the resulting optimal antisolvent masspercent and flowrate trajectories in Figures 1(a) and 1(b), respectively are used to design the NE controller.

### C. Neighboring Extremal Feedback Control

1) NE controller design: During this study, antisolvent masspercent (inside the crystallizer) \( m_w \) is considered as the input \( u \) for the design of the NE controller. When the antisolvent flowrate \( FR \) is considered as the input, the formulation results in a input-affine system, which usually
with \( \theta \leq \mu - K_\theta \mu_0 \leq \) is considered during this study, \( \delta x \) corresponds to nominal implementation of the C-control strategy a value of \( \delta \theta \) based on optimizing the product quality for the nominal model.

The range of values for the perturbation of each of the parameters are defined alongside. Thus, if \( \Delta \theta \) represents the vector of model parameters, then \( \Delta \theta_i = 0, i = 1, 2, \ldots, 5 \), represent the nominal parameters, i.e., \( \theta = \bar{\theta} \).

During this study, two versions of the NE controller are considered depending on the availability of the information about the uncertainty in the parameters – (i) only \( K_x \) with \( \delta x \) feedback (NE-\( K_x \)) and (ii) both both \( K_x \) and \( K_\theta \) with \( \delta x \) and known \( \delta \theta \) feedback (NE-\( K_x-K_\theta \)). When the perturbations in the parameters are precisely known, the controller gain corresponding to sensitivity of the parameters, \( K_\theta \) is kept active along with \( K_x \). However, as \( \delta \theta \) values can only be approximated in the case of batch processes, the NE controller with both \( K_x \) and \( K_\theta \) is considered during this study in order to account for the optimality loss that can be recovered with the inclusion of \( K_\theta \). Also, this can provide the motivation for the development of adaptation strategies based on integrating the run-to-run control to counter the uncertainty in the parameters.

Direct design concentration control (C-control) approaches for the control of batch crystallization processes have received increasing interest during the recent past due to their robustness to process variations and disturbances. Earlier studies by [5], [6] on semi-batch antisolvent crystallization processes have shown to provide optimal product quality in terms of the volume-weighted mean size with the use of constant relative supersaturation (SS) setpoint. However, these approaches tend to have variable batch times due to the constraints on the minimum product yield, which usually poses as a bottleneck for the smooth operation of the plant in industrial practice. Moreover, these approaches were shown to exhibit poor performance in the presence of shifts in the solubility curve.

Table II provides the details of the perturbations introduced into the process for different cases considered to compare the performance of the NE controller against the nominal open-loop, direct design C-control and the true optimal values for each specific case. During this study, in order to make a fair comparison between all these approaches, the flexibility offered by the C-control strategy to operate the process with variable batch time is avoided. Thus, if the volume of antisolvent at any instant during the batch, \( V(t) \leq V_{max} - FR_{max}(t_f - t) \), then the antisolvent is added into the crystallizer at the rate of \( FR_{max} \), so that the volume constraint at the end of the batch is always satisfied.

Figure 1(a) shows the antisolvent masspercent profiles when different strategies are implemented on nominal process. The profiles resulting from the NCO based tracking overlaps with the nominal and true optimal profiles as the values of \( \delta x(t) \) and \( \delta \theta \) corresponding to nominal implementation are always zero. Thus, the NE controller law updates the correction as \( \delta u(t) = 0, \forall t \), within the interior arc. For the implementation of the C-control strategy a value of 0.101 is chosen as the constant relative SS setpoint, which is tuned based on optimizing the product quality for the nominal model.

![Antisolvent masspercent and flowrate profiles for the nominal case](image)

**Fig. 1.** Optimal antisolvent masspercent and flowrate profiles for the nominal case

exhibits singularity and thus, poses difficulty while obtaining the solution of the interior arc.

For designing the NE controller, all the states \( x = [\mu_0, \mu_1, \mu_2, \mu_3, \mu_4, C]^T \) are assumed to be measurable and hence a full state feedback law Eqs. (13) to (17) is integrated backward from time \( t_f \) to 0, along the nominal solution \( u^*(t), x^*(t), \lambda^*(t), 0 \leq t \leq t_f \). Thus, the obtained gain vectors, \( K_x(t) \) and \( K_\theta(t) \) are used to realize the real-time NCO tracking based control of the perturbed process.

2) Performance of the NE controller: In order to compare the performance of the NE controller, various scenarios of plant-model mismatch are considered by introducing uncertainties in the kinetic parameters of growth and nucleation rates and disturbance in the initial conditions as

\[
g'(t) = g(1 + \Delta \theta_1),
\]

\[
k'_g = k_g(1 + \Delta \theta_2),
\]

\[
b' = b(1 + \Delta \theta_3),
\]

\[
k'_b = k_b(1 + \Delta \theta_4),
\]

\[
C'_{sat} = C_{sat}(1 + \Delta \theta_5),
\]

\[
x'_0 = x_0(1 + \Delta x_0),
\]

where \( \Delta \theta_1 \) and \( \Delta \theta_2 \) are the uncertainties in the growth kinetics; \( \Delta \theta_3 \) and \( \Delta \theta_4 \) are the uncertainties in the nucleation kinetics; \( \Delta \theta_5 \) is the uncertainty in the solubility curve of paracetamol in acetone-water system, while \( \Delta x_0 \) is the disturbance in the initial conditions of the states, \( x_0 \).
For most of the cases discussed below, it can be seen from Table III that the optimality loss resulting from the implementation of both the versions of the NE controller is either lesser or sometimes comparably equal to the loss through the open loop nominal profile. Therefore, NE controller provides robustness to certain disturbances in the process through feedback. In case 1, where deviation in the initial conditions is given by setting the parameters to nominal values, the recovery in the optimality loss by the NE controller is very high. Also, it can clearly seen from Figure IV that the input profiles implemented by the NE controller follow very close to the true optimal profile.

However, in case 2 and 3 the recovery in the optimality loss is low. This can be explained based on the fact that case 2 corresponds to the worst case perturbations in the process, where the implementation of a NE controller based on linear approximations of the model may not remain valid. On the other hand, the C-control approach that uses a nonlinear mapping between the measured concentration and the corresponding input setpoint performs better. While in case 3, the active constraint set towards the end of the batch are changed in order to meet the minimum yield constraint. Thus, the NE controller designed based on the active constraint set of the nominal profile may not perform well. Therefore, these two issues form the inherent shortcomings of the traditional NE controller design. This can also be interpreted from the input profiles shown in Figures IV and IV.

Furthermore, for case 4 and 5, the optimality loss due to the implementation of NE controller with only $K_x$ is much higher than the other version that uses the $K_\theta$ gain along with known uncertainties. This can be attributed to the fact that the NE controller cannot cope with the changes in the solubility curve, similar to the limitation exhibited by the C-control approach. On the other hand, when the direction and magnitude of the perturbations are precisely known, higher recovery in the optimality loss is achieved. The same can be observed from the input profiles shown in Figures IV and IV, where the NE controller with known perturbations and $K_\theta$ gain is shown to track the true optimal profiles very closely.

**IV. CONCLUSIONS**

Real-time optimal control based on tracking the necessary conditions of optimality is presented in this paper. Based on the given nominal solution, the input profile is dissected into boundary and interior arcs. In order to track the interior arcs in the presence of uncertainties and process disturbances, the neighboring extremal controller is designed. Performance assessment based on the loss of optimality with respect to the true optimal and open loop nominal profiles is carried out. Furthermore, a comparative study with the direct design C-control strategy with constant relative supersaturation setpoint is also reported. It has been observed that the NE controller with only state feedback fails to adapt to the shifts in solubility curves, similar to the inherent limitation of the C-control approach. However, with design of NE controller that accounts for the sensitivities of the parameters and known uncertainties, the loss in optimality is minimized to a much greater extent and thus providing an attractive solution to the real time optimal control of batch crystallization processes.

**REFERENCES**


Fig. 2. NE controller for case 1

Fig. 3. NE controller for case 2

Fig. 4. NE controller for case 3

Fig. 5. NE controller for case 4

Fig. 6. NE controller for case 5