

NONLINEAR PREDICTIVE CONTROL USING LOCAL MODELS – APPLIED TO A BATCH FERMENTATION PROCESS

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Abstract. The problem of controlling processes that operate within a wide range of operating conditions is addressed. The operation of the process is decomposed into a set of operating regimes, and simple local state-space model structures are developed for each regime. These are combined into a global model structure using an interpolation method. Unknown local model parameters are identified using empirical data. The control problem is solved using a model predictive controller based on this model representation. As an example, a simulated batch fermentation reactor is studied. The model-based controller's performance is compared to the performance with an exact process model, and a linear model. It is experienced that a non-linear model with good prediction capabilities can be constructed using elementary and qualitative process knowledge combined with a sufficiently large amount of process data.

Key Words. Nonlinear systems; Process Models; Identification; Predictive control; Fermentation processes.

1. INTRODUCTION

Dynamic optimization has for decades been a basis for control. During the 60's and 70's, closed-form solutions to the optimization problem was the driving force for much research activity. The linear-quadratic controller seemed to provide a solution to many multi-variable control problems. Experience has shown that this approach has serious shortcomings: First, the solution assumes no constraints on the states and control inputs. Second, the linear-quadratic controller need not be robust when estimator dynamics are included for state estimation, as shown by Doyle (1978).

Within the domain of optimization-based process control research, the interest and successful industrial applications have the last decade focused on model-based predictive control (MPC); see (Garcia *et al.*, 1989) and (Rawlings *et al.*, 1994) for comprehensive surveys of this field. The idea is to solve the optimization problem at a given time instant by utilizing the most recent process measurements. The optimization problem is defined on some horizon, and a control trajectory is computed on this horizon. Only the first part of the control trajectory is applied to the process, and the entire optimization is repeated at the next sampling instant, again utilizing process measurements up until this new time instant. This methodology was first presented by

Cutler and Ramaker (1979), and they minimize a quadratic criterion weighting the control errors and changes in the control inputs. They use a linear moving-average model for prediction. More important, this optimization-based controller can handle constraints in both the control inputs and the controlled variables.

The large majority of MPC is based on linear models. An important reason for this is that linear MPC, like other linear controllers, can handle processes with weak non-linearities. Although the use of MPC within the process industries has been extensive, it has been mainly limited to continuous processes. Such processes are often characterized by small variations in operating conditions. This is not the case for batch and fed-batch processes which are also widely used in industry. The difference between batch and fed-batch processes is that no feed is added and no product is removed in a batch process, while this is done in a fed-batch process. Batch processes will typically exhibit large variations in the operating conditions during a batch. Moreover, the product specifications may differ among batches, thereby changing the operating conditions significantly between batches. Johnson (1987) compares control of continuous processes and batch-type processes by stating that the optimization problem of batch processes is a dynamic problem involving highly

nonlinear process models. As a contrast, continuous processes can often be optimized by a static formulation. Control of a batch reactor is usually carried out by a two step procedure. Time-varying trajectories for the important variables are first derived. This is either done in a heuristic manner based on process insight and experience from earlier operation, or by open-loop optimization based on a model of the batch reactor. Second, the tracking of the variables is accomplished by set-point controllers. Reviewing the batch reactor control literature, emphasizing fermentation reactors, shows that four questions are focused; the generation of optimal trajectories, controller design for setpoint control, computing on-line estimates of reactor states, and the issue of reactor modeling, (Rippin, 1989), (Johnson, 1987) and (Jørgensen and Jensen, 1989).

The work on optimal trajectories is usually based on some non-linear mechanistic model of the process in question. The cost criterion typically include productivity and input costs, and the optimization problem is solved off-line. Examples of this can be found in (Impe *et al.*, 1994) and (Sargantanis *et al.*, 1993). There are, however, also examples on the use of on-line optimization, i.e. use of MPC, (Lim and Lee, 1991).

There is a quite extensive literature on setpoint control of batch-type reactors, in particular the use of adaptive control and feedback linearization. Bastin and Dochain (1988) and Pomerleau *et al.* (1989) base their controller design on mechanistic models, while recent work by Proll and Karim (1994) and Keulers (1993) use empirical models for nonlinear control.

A major problem when implementing advanced control in biotechnical processes is the lack of good measurements. Hence, research has also focused on-line estimation of reactor states, particularly substrate and product concentrations. Examples of this is found in (Hengjie *et al.*, 1989; Hilaly *et al.*, 1994; Keulers, 1993).

Reactor modeling for the purpose of control, span from linear and nonlinear mechanistic models to linear and nonlinear empirical models. Of particular interest to our work is (Zhang *et al.*, 1994). They utilize the fact that different phenomena dominate during different parts of a batch cycle, and construct a set of local models that that are valid during different parts of a batch cycle. In addition, they specify a method to select the appropriate model at a given time. The advantage of this concept is that the individual local models are simpler than a global model that can represent the whole batch cycle. A similar approach is proposed by Konstantinov and Yoshida (1989).

This work investigates the use of MPC on batch processes using a non-linear model in the controller. There are some reports on this in the literature. Lim and Lee (1991) describe the use of MPC using on-line parameter estimation. The control trajectory is computed by simultaneous parameter estimation and re-optimization. Garcia (1984) extends the method introduced by Cutler and Ramaker (1979) by using a nonlinear model for output prediction. This controller is tested on a polymerization reactor model. A similar approach is presented by Peterson *et al.* (1989).

The present work rests on two assumptions. The first assumption is that the performance of MPC depends critically on the predictive capabilities of the underlying process model. The wide operating range of a batch makes the use of a non-linear prediction model particularly interesting. The second assumption is that nonlinear model building is a cumbersome task. Hence, empirical modeling techniques are interesting. This is also motivated by the observation that practically all predictive control loops implemented in industry are based on empirical models. A modeling framework denoted operating regime based modeling is applied. This framework allows a decomposition of the modeling work, and has interesting capabilities for blending different types of process knowledge and empirical data during modeling.

The continuation of this paper is structured as follows: First, the operating regime based modeling framework is briefly presented. This includes a discussion on the use of different types of knowledge. Second, the predictive control problem is defined. This is, essentially, nonlinear MPC utilizing the operating regime based modeling framework. The claims are supported by application of the method on a simulated batch fermentation process. Model development is emphasized. MPC based on local modeling is compared to the use of a conventional nonlinear state-space model and a linear model. Some conclusions finalize the paper.

2. OPERATING REGIME BASED MODELING

This section reviews a technique for developing non-linear models based on operating regime based modeling. Further details can be found in (Takagi and Sugeno, 1985; Johansen and Foss, 1993*a*; Johansen, 1994; Zhang *et al.*, 1994). Consider the problem of developing a state-space model of the form

$$\begin{aligned}\dot{x} &= f(x, u, v) \\ y &= g(x, w)\end{aligned}$$

where $x \in R^n$ is state vector, $u \in R^k$ is control input vector, $v \in R^n$ is disturbance vector, $y \in R^m$ is measurement vector, and $w \in R^m$ is measurement noise. When the system operates within a small operating regime, a simple (possibly linear) *local model* structure

$$\dot{x} = f_i(x, u, v, \theta_i) \quad (1)$$

$$y = g_i(x, w, \theta_i) \quad (2)$$

parameterized with the vector $\theta_i \in R^{p_i}$ will always describe the the system sufficiently well, provided the system is smooth. The local model structure will be valid within this particular operating regime, and more or less invalid outside this regime. The *operating point* is denoted ϕ , and the full range of operation is the set of operating points Φ . An *operating regime* is defined as a subset $\Phi_i \subset \Phi$ where the local model structure (1)-(2) is an adequate description of the system. The choice of which variables, ϕ , to use to characterize the operating regimes will be highly problem dependent. Typically, ϕ will contain a subset of the states, inputs, and disturbances, i.e. given by a function $\phi = H(x, u, v)$, but can also contain other model variables. Next, assume that for the local model structure (1)-(2) there exists a smooth *model validity function* $\rho_i : \Phi \rightarrow [0, 1]$ that is designed such that its value is close to one for operating points where the local model structure (1)-(2) is a good description of the system, and close to zero otherwise. If the system's operating range Φ is decomposed into N operating regimes, $\Phi_1, \dots, \Phi_N \subset \Phi$, and local model structures and local model validity functions for each operating regime are developed, then the following interpolation gives a global model structure:

$$\dot{x} = \sum_{i=1}^N f_i(x, u, v, \theta_i) w_i(\phi) \quad (3)$$

$$y = \sum_{i=1}^N g_i(x, w, \theta_i) w_i(\phi) \quad (4)$$

$$w_i(\phi) = \frac{\rho_i(\phi)}{\sum_{j=1}^N \rho_j(\phi)} \quad (5)$$

The *interpolation function* $w_i : \Phi \rightarrow [0, 1]$ is a normalization of the model validity function ρ_i , and has the property $\sum_{i=1}^N w_i(\phi) = 1$ for all $\phi \in \Phi$. To guarantee a complete global model, it must be assumed that at any operating point $\phi \in \Phi$, not all local model validity functions vanish. With this framework, the modeling problem consists of the following major subtasks:

First, decompose the system's operating range into a number of operating regimes that completely cover the interesting range of operation. Such a decomposition can often be found by using

an elementary understanding of the mechanisms in the system, as will be seen in the example. Alternatively, there exist computer algorithms that can make such a decomposition on the basis of an informative data sequence, e.g. (Sugeno and Kang, 1988; Johansen and Foss, 1994; Jordan and Jacobs, 1993; Murray-Smith and Gollee, 1994).

Second, for each operating regime, a local model structure must be developed. One may choose between mechanistic or empirical local model structures. In addition, local model validity functions must be designed. However, this is usually a quite straightforward task when the decomposition into regimes has been accomplished.

Third, the unknown parameters $\theta_1, \dots, \theta_N$ must be identified. If the local model structures are linearly parameterized, the global model structure will also be linearly parameterized, since the local model validity functions do not contain unknown parameters. Standard system identification tools can be applied. Since the model is non-linear it is particularly important with informative data that covers all operating regimes with local models that contain unknown parameters.

Much of the power of this modeling framework comes from the flexibility to incorporate different kinds and amounts of process knowledge, and the transparency of the procedure and resulting model. In particular, the decomposition into regimes can be based on either mechanistic process knowledge or empirical data. Also, some of the local model structures can be empirical, while others may be mechanistic. Another important property of the framework is that it is quite close to engineering thinking. It has been justified by various examples (Johansen, 1994) that quite elementary and qualitative process knowledge combined with process data is often sufficient to develop an accurate and transparent model. Hence, the framework may be well suited for industrial applications.

3. MODEL PREDICTIVE CONTROL

In the previous section, we focused on operating regime based state-space modeling. This leads to a nonlinear state-space MPC problem, cf. (Balchen *et al.*, 1992). For batch and semi-batch processes, this nonlinear state-space MPC problem can be formulated as

$$\max_{u \in U} \left(m(x(T_s)) + \int_t^{T_s} l(x(\tau), y(\tau), u(\tau)) d\tau \right)$$

subject to

$$\dot{x} = f(x, u, v), \quad x(t) \text{ given}$$

$$y = g(x, w)$$

$$h(x, y, u) \leq 0$$

where typically $T_s = \min(t + T, T_f)$. The optimization is defined on some horizon T , starting at the present time t . Time $t = 0$ defines the start of a batch and $t = T_f$ defines the end of a batch. The end time T_f need not be fixed, and this variable is often optimized, too.

Both equality and inequality constraints can be defined. Soft constraints may be defined as an integrated part of the optimization criterion. Measurements are explicitly mentioned in the formulation to emphasize the fact that it is sometimes natural to optimize with respect to these variables.

To reduce the complexity of the optimization problem, the set of possible control input trajectories U is restricted to a finite-dimensional space. The control input is here parameterized as a piecewise constant function:

$$u(\tau) = \begin{cases} \mu_1, & \tau \in [t, t + \Delta T) \\ \mu_2, & \tau \in [t + \Delta T, t + 2\Delta T) \\ \vdots & \end{cases}$$

where ΔT is the sampling interval. The optimization problem is solved by the use of a nonlinear programming algorithm at time instants $t \in \{0, \Delta T, 2\Delta T, \dots, T_f - \Delta T\}$ using the most recent process measurements. Only, the first part of the optimal trajectory, μ_1 , is applied as the control input.

A major problem with the above formulation is its dependence on the initial states $x(t)$. In practice, these are not readily available. Hence, some estimate of the states must be computed. This may be accomplished by state estimation or an observer.

Since most batch-type processes are highly nonlinear, there are two potential advantages in applying nonlinear MPC for batch processes, compared to linear MPC. First, the predictive capability on the optimization horizon may improve by utilizing a nonlinear as opposed to a linear model. Second, the states $x(t)$ may be estimated with improved accuracy by the use of a nonlinear model.

4. SIMULATION EXAMPLE

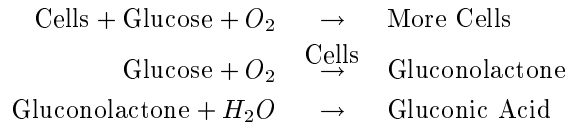
A semi-realistic simulation study of a batch fermentation process illustrates the ideas presented in this paper. In this study, five controllers are formulated, based on the above formulation. All controllers utilize the same performance criterion and constraints, equal control input parameterization, and identical optimization algorithms. The

controllers differ in the following way:

1. The 1st MPC uses an ideal process model, i.e. the model and the “true system” are identical. Provided the initial values $x(0)$ are correct, this controller gives an upper limit to the performance of MPC.
2. The 2nd MPC uses a nonlinear operating regime based state-space model for both prediction and state estimation.
3. The 3rd MPC uses a global linear state-space model for both prediction and state estimation.
4. The 4th controller is an open-loop optimal controller (OLOC) using the same non-linear model as the 2nd MPC.
5. The 5th controller is also an open-loop optimal controller (OLOC), using the global linear model for prediction.

4.1. System Description

The simulated “true system” model is adapted from (Ghose and Ghosh, 1976) and (Rai and Constantindes, 1973), and describes the fermentation of glucose to gluconic acid by the micro-organism *Pseudomonas ovalis* in a well-stirred batch reactor. The main overall reaction mechanism can be described by



The first reaction is the reproduction of cells, using the substrate glucose and oxygen. The second reaction is the production of gluconolactone, again using glucose and oxygen. This reaction is enzyme-catalyzed by the cells, while the final product, gluconic acid, is formed by the last reaction. The following state-space model is used to simulate the “true system”:

$$\begin{aligned} \dot{x}_1 &= \mu_m \frac{x_1 x_4 x_5}{K_s x_5 + K_0 x_4 + x_4 x_5} \\ \dot{x}_2 &= v_L \frac{x_1 x_4}{K_L + x_4} - 0.9082 K_p x_2 \\ \dot{x}_3 &= K_p x_2 \\ \dot{x}_4 &= -\frac{1}{Y_s} \mu_m \frac{x_1 x_4 x_5}{K_s x_5 + K_0 x_4 + x_4 x_5} \\ &\quad - 1.011 v_L \frac{x_1 x_4}{K_L + x_4} \\ \dot{x}_5 &= k_I a (x_5^* - x_5) - 0.09 v_L \frac{x_1 x_4}{K_L + x_4} \\ &\quad - \frac{1}{Y_0} \mu_m \frac{x_1 x_4 x_5}{K_s x_5 + K_0 x_4 + x_4 x_5} \end{aligned}$$

where x_1 is the cell concentration, x_2 is gluconolactone concentration, x_3 is gluconic acid concentration, x_4 is glucose concentration and x_5 is dissolved oxygen concentration. The parameters

μ_m , K_L , v_L , and K_p and pH. This dependency is given by an interpolated lookup table based on the experimental data in (Rai and Constantindes, 1973). The remaining parameters can be found in (Rai and Constantindes, 1973) and (Ghose and Ghosh, 1976). Initial values for the batch are $x_1(0) = x_{10}$, $x_2(0) = 0$, $x_3(0) = 0$, $x_4(0) = x_{40}$, and $x_5(0) = x_5^*$.

The setpoints to the temperature and pH basis-control loops are used as control inputs by the predictive controller. The basis-control loops are assumed to be perfect, which is realistic, since the system dynamics are slow compared to the typical bandwidth of these loops.

Three perfect on-line measurements are available at 0.5 h intervals during the batch: Dissolved oxygen concentration, biomass concentration and gluconic acid concentration. There are no noise or disturbances in the simulations.

4.2. Modeling and Identification

All the local models are chosen to have the same linear structure

$$x(t+1) = a_i + A_i x(t) + B_i u(t) + v(t) \quad (6)$$

where $x = (x_1, \dots, x_5)$, $u = (\text{pH}, \text{temp})$, a_i is a vector of unknown parameters, B_i is a 5×2 -matrix of unknown parameters, and A_i has the structure

$$A_i = \begin{pmatrix} A_{11}^i & 0 & 0 & A_{14}^i & A_{15}^i \\ A_{21}^i & A_{22}^i & 0 & A_{24}^i & 0 \\ 0 & A_{32}^i & 1 & 0 & 0 \\ A_{41}^i & 0 & 0 & A_{44}^i & A_{45}^i \\ A_{51}^i & 0 & 0 & A_{54}^i & A_{55}^i \end{pmatrix}$$

The structural zeros follow from a simple mass-balance based on the reaction mechanism and the assumption that the reaction rates only depends on x_4 and x_5 , in addition to u , which is a quite natural assumption to make, since these are the rate-limiting components.

By examining the main reaction mechanisms, four operating regimes can be identified, see also (Johansen and Foss, 1993b). At the beginning of the batch, the production of gluconolactone is small due to the small concentration of cells. Hence, the production of gluconic acid is small due to the low concentration of gluconolactone. This regime is characterized by a relatively high concentration of both dissolved oxygen and glucose. In the intermediate stages of the batch, the production of cells and gluconolactone proceeds at a high rate, and some gluconic acid is produced. There is a relatively low concentration of dissolved oxygen, and the concentration of glucose is decreasing. Depending on whether the dissolved oxygen concen-

tration is so low that the transfer of oxygen to the cells is rate-limiting or not, the dynamic behavior of the process is different. This gives two regimes that are characterized by a medium concentration of glucose, and either low or medium concentration of oxygen. During the final stages of the batch, the production of cells and gluconolactone is reduced due to shortage of glucose. The only significant reaction is the production of gluconic acid from gluconolactone. This regime is characterized by low substrate concentration, and high dissolved oxygen concentration.

These four regimes can all be characterized by the concentration of dissolved oxygen and glucose, and these two variables are chosen to be the variables that defines the operating point ϕ . The four regimes were chosen on the basis of the discussion above, and their interpolation functions are shown in Fig. 1. Since the dependencies on pH and temperature are highly nonlinear, the local model within each of these four regimes should therefore depend non-linearly on temperature and pH. The chosen local model structure (6) does not, so each of these four regimes is therefore further decomposed into four new regimes along the temperature and pH axes, as shown in Fig. 2. Hence, the model is based on a total of 16 local models. The model validity functions ρ_i were chosen to be Gaussian functions, with some suitable overlap.

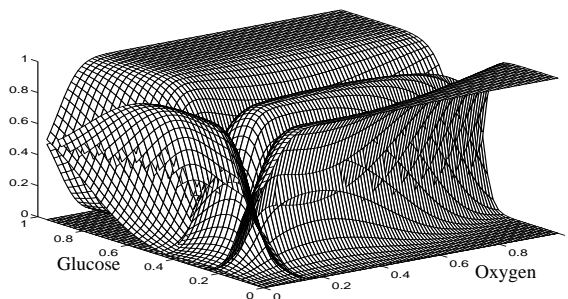


Fig. 1. Interpolation functions for the four regimes in the plane spanned by oxygen concentration and glucose concentration. Notice that the axes are scaled.

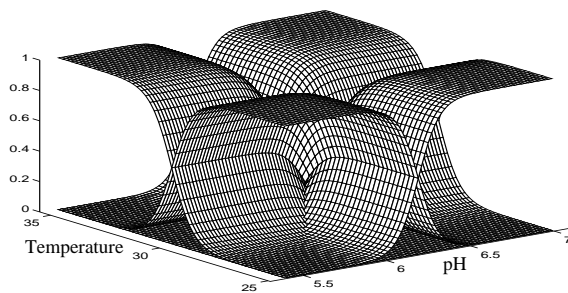


Fig. 2. Interpolation functions for the four regimes in the plane spanned by temperature and pH.

The 448 unknown model parameters are estimated using the least-squares method, and simulated data from 600 batches, each run for 10 h , and all states “measured” every 0.5 h . For every batch, the initial states x_{10} and x_{40} were randomly chosen from the intervals $[0.4, 0.5]$ and $[40, 50]$, respectively. The control input trajectories were designed by randomly selecting between 0 and 2 step changes, within the allowable ranges of both temperature and pH, during the batch. A global linear model was also found using the same estimation method and identification data.

Both models were visually “validated” on a number of independent batches not used for identification. In these batches, the pH and temperature were randomly changed every 0.5 h . A typical ballistic prediction is shown in Fig. 3, and indicates that the prediction accuracy of the non-linear model is satisfactory, while the linear model has poorer prediction capabilities on the full batch length.

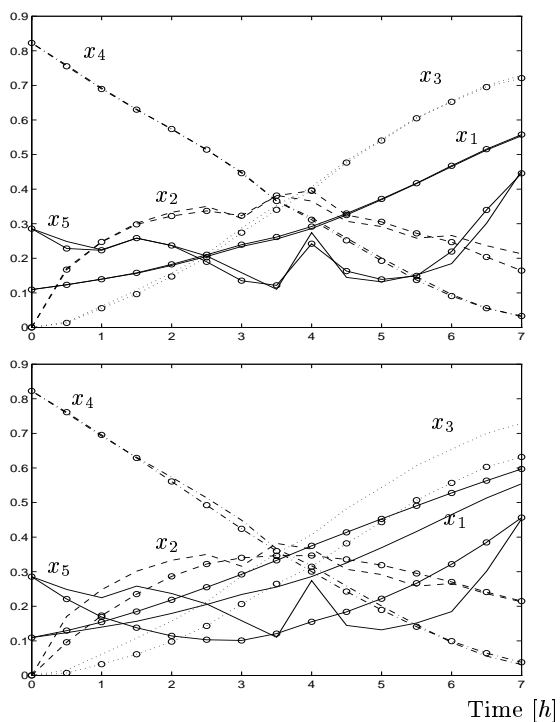


Fig. 3. Simulation (ballistic prediction) from correct initial values for a typical batch, marked with circles (\circ), and “true system” trajectories. The upper part is with the non-linear model based on 16 local models, while the lower part is with the linear model. Notice that the variables are scaled.

Due to the inaccuracy in the models used for MPC, and because not all states are measured, state estimators are implemented, using a time-varying extended Kalman filter for the non-linear model, and a time-varying Kalman filter for the linear model. The initial state-estimates of the fil-

ters equals the initial states of the “true system”. The covariance matrices were tuned to make the estimator loop fast compared to the system dynamics.

4.3. Model Predictive Control

The objective of the MPC is to maximize the average production rate of gluconic acid, neglecting the costs of substrate, cells, and separation. The time T_c from finishing one batch to starting the next, due to emptying, cleaning and initializing the reactor, is $T_c = 1 h$.

This optimization problem is formulated as

$$\max_{(u, T_f) \in (U, \mathcal{T})} \frac{x_3(T_f)}{T_f + T_c} \quad (7)$$

subject to the model equations, and the restrictions $5.4 \leq u_1 \leq 7.0$, $25.0 \leq u_2 \leq 35.4$, and $x_1, \dots, x_5 \geq 0$ at all time. The trajectories are optimized from time t to the batch end time T_f . The batch end time is restricted to $\mathcal{T} = \{t, t + \Delta T, t + 2\Delta T, \dots\}$, and the sampling interval is $\Delta T = 0.5 h$. In the optimization, the current state is estimated using the extended Kalman filter, and the model is used to compute ballistic predictions from this initial value. The criterion (7) is maximized using a sequential quadratic programming algorithm with line search (MATLAB function `constr`, (Grace, 1990)). The initial values to the search algorithm are constant input trajectories corresponding to pH = 5.6 and temp = 28.3.

4.4. Results

The results of simulations using the five controllers described at the beginning of this section are summarized in Table 1. The results are averages computed over seven representative initial states. The temperature and pH trajectories for one typical initial state for these five cases are shown in Fig. 4. The corresponding state trajectories for the three MPC simulations are shown in Fig. 5.

Table 1 Summary of results.

	Average Prod. Rate \dot{p} [g/lh]	Average End time T_f [h]
MPC, Ideal model	6.03	5.5
MPC, Local modeling	5.90	5.5
MPC, Linear model	5.47	6.9
OLOC, Local modeling	5.88	5.1
OLOC, Linear model	5.51	6.4

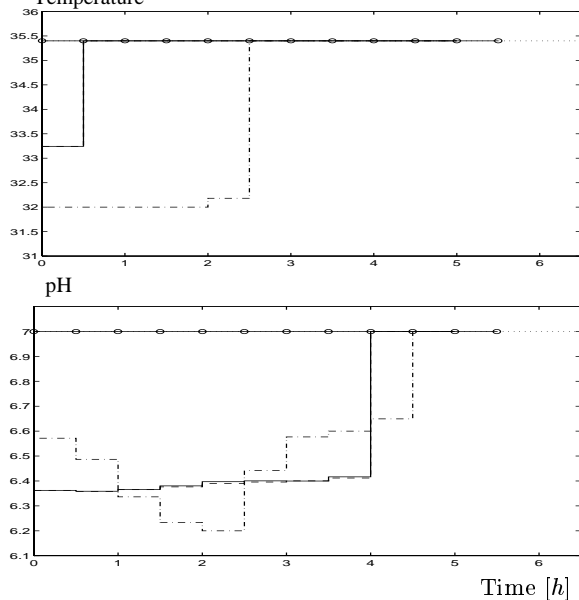


Fig. 4. Optimal temperature (upper part) and pH trajectories (lower part) computed by the five controllers, for a typical initial state. MPC, ideal model - dashed-dotted line, MPC, local modeling - solid line, MPC, linear model - dotted line, OLOC, local modeling - dashed line, and OLOC, linear model - solid line with circles. Notice that the different trajectories have different end times, see Table 1.

4.5. Discussion

The results show, as might be expected, significantly improved performance by moving from a linear to a non-linear model as the basis for MPC for this type of process. The improvement is somewhat limited by the fact that the control inputs for all five controllers are limited by hard upper constraints during significant parts of the batch. Furthermore, the results show that re-optimization during a batch by MPC may be advantageous compared to open-loop optimization. However, this is not true for the linear model, since the poor prediction capabilities make the optimization unreliable.

The experience from the modeling and identification suggests that with the local modeling method, it is both sufficient and necessary to have some rather elementary process knowledge to develop the model structure, and a set of informative empirical data for parameter estimation. In particular the decomposition into operating regimes is a critical part of the modeling, where it is important to use process knowledge to get a sound model structure. However, the applied process knowledge is significantly less than what would be needed for developing a mechanistic model based on mass balances. On the other hand, the amount of data is significantly larger than what would

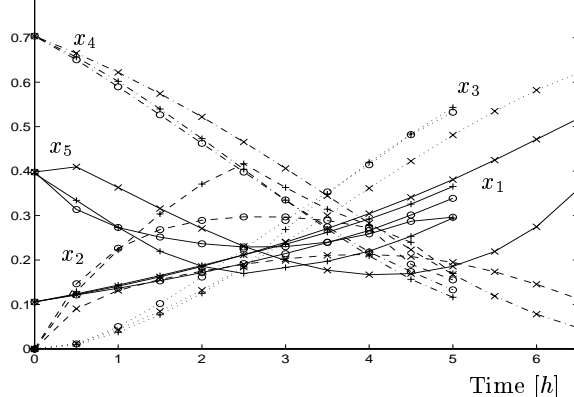


Fig. 5. System trajectories for the three MPC simulations and a typical initial state. Notice that the variables are scaled. Lines marked + are with the ideal model, lines marked o are with operating regime based modeling, and lines marked x are with the linear model.

be needed for the identification of a mechanistic model. It should be mentioned that less empirical data may be sufficient to identify an accurate model. While this aspect is obviously important from a practical point of view, we have not investigated it here.

5. CONCLUSIONS

This investigation has shown that the operating regime based modeling framework can be used as a means for modeling processes that operate over a wide range of operating conditions. The method is flexible with respect to the available process knowledge. A potential application of the modeling method by using the derived model in MPC on a batch fermentation reactor has been demonstrated, with encouraging results.

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6. REFERENCES

- Balchen, J. G., D. Ljungquist and S. Strand (1992). State-space predictive control. *Chemical Engineering Science* **47**, 787–807.
- Bastin, G. and D. Dochain (1988). Non linear adaptive control algorithms for fermentation processes. In: *Proc. American Control Conference, Atlanta*. pp. 1124–1128.
- Cutler, C. R. and B. L. Ramaker (1979). Dynamic matrix control - a computer control algorithm. In: *AICHE 86th National Meeting, Houston*.

- Doyle, J.C. (1978). Guaranteed margins for LQG regulators. *IEEE Trans. Automatic Control*.
- Garcia, C. (1984). Quadratic/dynamic matrix control of nonlinear processes. In: *AIChE Annual Meeting, San Francisco*.
- Garcia, C. E., D. M. Prett and M. Morari (1989). Model predictive control: Theory and practice - A survey. *Automatica* **25**, 335–348.
- Ghose, T. K. and P. Ghosh (1976). Kinetic analysis of gluconic acid production by *Pseudomonas ovalis*. *J. Applied Chemical Biotechnology* **26**, 768–777.
- Grace, A. (1990). *Optimization Toolbox User's Guide (MATLAB)*. The MathWorks, Inc.
- Hengjie, Z., L. Jianzhong, W. Shuqing and W. Jicheng (1989). Nonlinear feedback control of a fed-batch spiramycin fermentation process. In: *Proc. DYCORDER '89, Maastricht*. pp. 155–160.
- Hilaly, A., M. Karim and J. Linden (1994). Use of an extended Kalman filter and development of an automated system for xylose fermentation by recombinant *Escherichia coli*. *J. Industrial Microbiology* **13**, 83–89.
- Impe, J. Van, B. Nicola, P. Vanrolleghem, J. Spriet, B. De Moor and J. Vandewalle (1994). Optimal control of the Penicillin G fed-batch fermentation. *Optimal control appl. and meth.* **15**, 13–34.
- Johansen, T. A. (1994). Operating regime based process modeling and identification. Technical Report 94-109-W. Dr. Ing. thesis. Department of Engineering Cybernetics, Norwegian Institute of Technology, Trondheim, Norway.
- Johansen, T. A. and B. A. Foss (1993a). Constructing NARMAX models using ARMAX models. *Int. J. Control* **58**, 1125–1153.
- Johansen, T. A. and B. A. Foss (1993b). State-space modeling using operating regime decomposition and local models. In: *Preprints 12th IFAC World Congress, Sydney, Australia*. Vol. 1. pp. 431–434.
- Johansen, T. A. and B. A. Foss (1994). Identification of non-linear system structure and parameters using regime decomposition. In: *Preprints IFAC Symposium on System Identification, Copenhagen (also accepted for Automatica)*. Vol. 1. pp. 131–136.
- Johnson, A. (1987). The control of fed-batch fermentation processes - A survey. *Automatica* **23**, 691–705.
- Jordan, M. I. and R. A. Jacobs (1993). Hierarchical mixtures of experts and the EM algorithm. Technical Report 9301. MIT Computational Cognitive Science.
- Jørgensen, S. B. and N. Jensen (1989). Dynamics and control of chemical reactors - selectively surveyed. In: *Preprints DYCORDER '89, Maastricht*. pp. 359–371.
- Keulers, M. (1993). *Identification and Control of a Fed-Batch Process*. Dr. thesis, Technical University, Eindhoven.
- Konstantinov, K. and T. Yoshida (1989). Physiological state control of fermentation processes. *Biotechnology and Bioengineering* **33**, 1145–1156.
- Lim, H.C. and K. Lee (1991). Control of bioreactor systems. In: *Biotechnology: Measuring, Modeling, and Control* (H.-J. Rehm and G. Reed, Eds.). Vol. 4. VCH, Weinheim.
- Murray-Smith, R. and H. Gollee (1994). A constructive learning algorithm for local model networks. In: *Proceedings of the IEEE Workshop on Computer-Intensive Methods in Control and Signal Processing, Prague, Czech Republic*. pp. 21–29.
- Peterson, T., E. Hernandez, Y. Arkun and F. Schork (1989). Nonlinear predictive control of a semi batch polymerization reactor by extended DMC. In: *Proc. American Control Conference, Pittsburg*. pp. 1534–1539.
- Pomerleau, Y., M. Perrier and D. Dochain (1989). Adaptive nonlinear control of the bakers' yeast fed-batch fermentation. In: *Proc. American Control Conference, Pittsburgh*. pp. 2424–2429.
- Proll, T. and M. Karim (1994). Real-time design of an adaptive nonlinear predictive controller. *Int. J. Control* **59**, 863–889.
- Rai, V. R. and A. Constantides (1973). Mathematical modeling and optimization of the gluconic acid fermentation. *AIChE Symposium Series* **69**, 114–122.
- Rawlings, J. B., E. S. Meadows and K. R. Muske (1994). Nonlinear model predictive control: A tutorial and survey. In: *Preprints IFAC Symposium ADCHEM, Kyoto, Japan*. pp. 203–214.
- Rippin, D. W. T. (1989). Control of batch processes. In: *Proceedings DYCORDER '89, August, Maastricht, The Netherlands*. pp. 115–125.
- Sargantanis, J., V. Murphy M. Karim and D. Ryoo (1993). Effect of operating conditions on solid substrate fermentation. *Biotech. and Bioengr.* **42**, 149–158.
- Sugeno, M. and G. T. Kang (1988). Structure identification of fuzzy model. *Fuzzy Sets and Systems* **26**, 15–33.
- Takagi, T. and M. Sugeno (1985). Fuzzy identification of systems and its application to modeling and control. *IEEE Trans. Systems, Man, and Cybernetics* **15**, 116–132.
- Zhang, X.-C., A. Visala, A. Halme and P. Linko (1994). Functional state modelling approach for bioprocesses: Local models for aerobic yeast growth processes. *J. Process Control* **4**, 127–134.