Product Optimization of a Fed-batch Fermentation Process
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Product Optimization of a Fed-batch Fermentation Process

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Abstract

This paper discusses the development of constrained optimization strategies for a fed-batch penicillin fermentation process. To facilitate the study, a mathematical model of the system is developed based on published materials, and simulated using MATLAB software. Good agreement is obtained when the results are validated against published work. To provide on-line estimates of the difficult to measure penicillin concentration, Partial Least Squares model is employed. Using these estimates, good control of product concentration is established thus enabling it to be implemented as part of product concentration control loop. Further improvements are introduced using dynamic optimization aiming at increasing the achievable product concentration while satisfying all process constraints. Two strategies are considered. These are optimal control policy using direct-shooting algorithm and unconstrained Dynamic Matrix Control (DMC). From this two optimization approaches, it is possible to estimate the optimal operating conditions as substrate feed rate so that the systems presents high performance within threshold value limit. The result also revealed that the use of DMC approach is superior the direct shooting method in term of the penicillin concentration as well as penicillin purity. Results obtained in this study have exposed the potentials of dynamic optimization schemes in improving the product purity in a fed-batch fermentation process.

Keywords: penicillin, partial least squares, direct shooting method, dynamic matrix control

1. Introduction

In biological-based sector, the trend is shifting towards manufacturing in multi-product batch fermentation plants from the conventional continuous manufacturing plants. There is also an increasing interest in fed-batch operation because of its ability for operational edibility. Fed-batch operation is one where the substrate is added at,

or over, particular intervals of time during the course of the batch, and, as in batch reactors, the product is withdrawn only at the end of the batch (Parulekar and Lim, 1995.

Process optimization is crucial for fermentation processes due to sensitive nature of microorganisms involved, high operating costs and long process cycle. However, optimization efforts are typically carried out off-line. The reactor is fed with the determined optimal feed profile. Once the batch proceeds there is no provision to account for disturbances occurring during the batch. This problem of implementing the optimal policy on-line and ensuring that the system follows the optimal trajectory in the presence of disturbances has received limited prior consideration (Balsa-Canto et al., 2000).

Lack of on-line measurement is another issue. Efficient fermentation process is often hampered by the difficulty in measuring some of the key component because of the lack of robust on-line sensors. The inability to provide on-line measurement of fermentation variables such as biomass concentration has proved to be a significant obstacle for the implementation of advanced control and optimizations solutions (Zhang and Lennox, 2004). The availability of such measurements is important for establishing optimum operation and minimising product quality variability. Although off-line measurement via laboratory analyses can be used to provide delayed measurements but sometimes a little bit too late to be useful especially for process control. This is perhaps the main motivation behind the use of various forms of soft-sensor technology.

Soft-sensor is founded on the assumption that data and theoretical information can be use to formulate a model that can represent the measurement of difficult to measure variables. Synonymous to model-based on-line estimation, soft sensors are useful in fermentation since several key variables such as product, biomass and substrate concentration in fact difficult to measure. A particularly promising approach is the application of multivariate analysis techniques such as Principal Component Analysis (PCA) and Partial Least Squares (PLS). Successful implementation has been presented by the work on fed-batch fermentation systems by (Zhang and Lennox, 2004). An overview of the basic PLS algorithm is provided in the following section along with a description of how this linear modeling approach can be extended to identify characteristics within a highly nonlinear fed-batch fermentation process.

Disturbances that occur due to the fluctuations during the fed-batch process can cause the open-loop feed policy to be suboptimal. Thus it is necessary to incorporate feedback either in the form of estimating the key model parameters or resetting the initial conditions of the model and regenerating the optimal policy using on-line optimization once a new measurement is available. Unavailability of measurements due to lack of sensors have led to the use of various observers for the estimation of both the unmeasured states and the uncertain parameters. This has been the subject of various studies by Bastin and Dochain (1986) and Tatiraju et al. (1999). Impe and Bastin (1995) have coupled the estimation with optimal control and proposed adaptive control method for fed-batch bioreactors for tracking the optimal profiles.

Rodrigues and Filho (1999) presented an approach for product optimization of a fed-batch penicillin production process with a dynamic matrix control (DMC) predictive controller. Thus there have been several approaches for the optimization of fed-batch processes and these are detailed in the next section.

This work intends to provide some answers to the above mentioned concerns. In this work, we concentrate on product optimization of a Penicillin G fermentation process. The unstructured model of Ahmad et al. (2003) was utilized as the basis of our modeling efforts. An inferential model constructed using partial least squares (PLS) regressions is employed for estimating the product concentration in to facilitate process control. Then optimal control strategies for fed-batch penicillin fermentation system are examined using two different optimization approaches. Firstly, dynamic optimization using direct shooting method and secondly is the implementation of single step ahead Dynamic Matrix Control (DMC).

2. Simulation Model of Penicillin Process

The penicillin fermentation model was solved simultaneously using Matlab software. The ordinary differential equations were solved using Fourth-Order Runge-Kutta algorithm with adaptive step size mechanism. Sampling time was fixed at 0.02 hour. The mathematical modeling and kinetic parameters as well as the initial values can be found in Ahmad et al. (2003). Feedback control strategy with Proportional-Integral-Derivative (PID) controller was adopted for all control loops in the fed-batch bioreactor. Since temperature and pH play important roles in the fermentation process, both were fixed at some optimum values. pH was kept constant at 5.1 and temperature of the culture medium was kept constant at 298 K. Figure 1 shows the dynamic simulations for penicillin fermentation process.

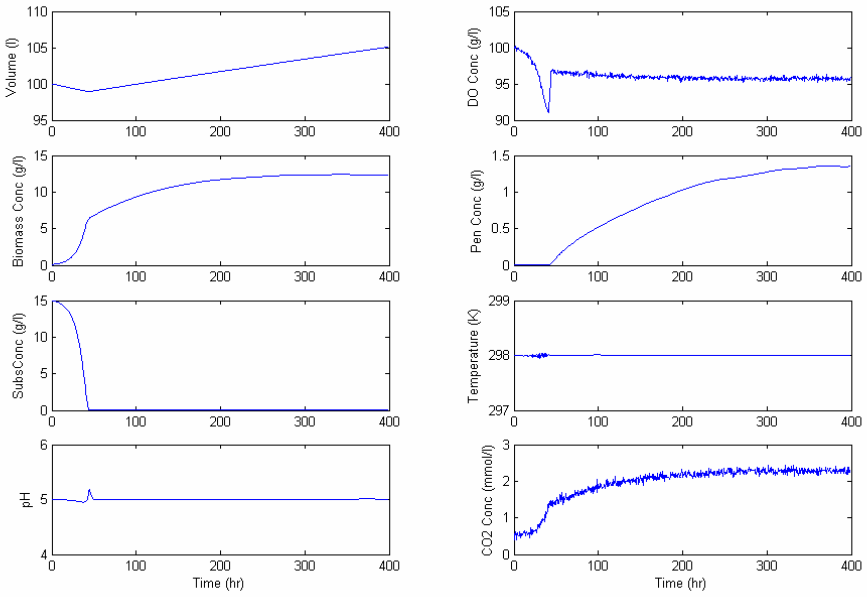

Figure 1 Dynamic simulation for penicillin fermentation process

In order to validate this simulation data can represent the penicillin fermentation process, the data comparison between simulation and Birol et al. (2002) work result was carried out. Table 1 shows the comparison between simulation and Birol et al. (2002) work data.

Output	Nominal Condition	Birol et al. [9]
Volume (l)	104.71	104.72
Biomass Concentration (g/l)	15.717	15.659
Substrate Concentration (g/l)	0.010087	0.01086
Penicillin Concentration (g/l)	1.4127	1.4108
Dissolved Oxygen Concentration (g/l)	1.1127	1.1105
Heat Generation (kcal/h)	94.105	94.004
Carbon Dioxide Concentration (mmol/l)	2.7831	2.7888
Substrate Feed Rate (l/h)	0.0426	0.0426
Temperature (K)	298	298
pH	5.1	5.1
Product Purity (%)	53.14	53.14

Table 1 Comparison between simulation and Birol et al. (2002) work data

The results obtained suggested that the model adequately represent the fed-batch penicillin fermentation process. From Table 1 there are only slight differences between simulation and Birol et al. (2002) work data. This minor discrepancy detected in the simulation results were due to different convergence simulator within programming environment between this simulation and Birol et al. (2002) work simulation process. However, these errors were not significant and we can therefore conclude that simulation of fed-batch penicillin fermentation model constructed here was a reasonably accurate match of penicillin fermentation process from Birol et al. (2002) work.

2. Partial Least Squares Regression (PLS)

Partial least squares regression is one of the multivariate analysis methods. According to Wold (1985), it is a linear system identification method that projects the input-output data down into a latent space, extracts a number of principal factors with an orthogonal structure, while capturing most of the variance in the original data. Referring to this definition, it is also named as Projection to Latent Structures. PLS model is built using the Non-linear Iterative Partial Least Squares (NIPALS)

algorithm introduced by Wold (1985). Details description of the PLS algorithm can be found in Geladi and Kowalski (1986).

The selection input variables play pivotal role in ensuring high accuracy of the model estimation. One important criterion is to have variables that give direct impact on the intended product quality. The inputs must also be available at high frequency and as such, input variables such as substrate concentration or biomass concentration were excluded because these variables cannot be rapidly measured on-line. Based on research by Zhang and Lennox (2004), the following measurements were selected as input variables: substrate feed rate, aeration rate, agitator power, substrate feed temperature, culture volume, pH, fermenter temperature and heat generation.

So the first stage in the development of the estimation system is to generate data necessary from dynamic simulation of fed-batch penicillin fermentation discussed earlier in previous chapter. To generate the data necessary for the development of this model, data from 10 batches was collected. 5 of these batches were used to train the PLS model (training batches) and the remainder were used to validate the model (validation batches). The sampling interval used in this work was 0.02 hour.

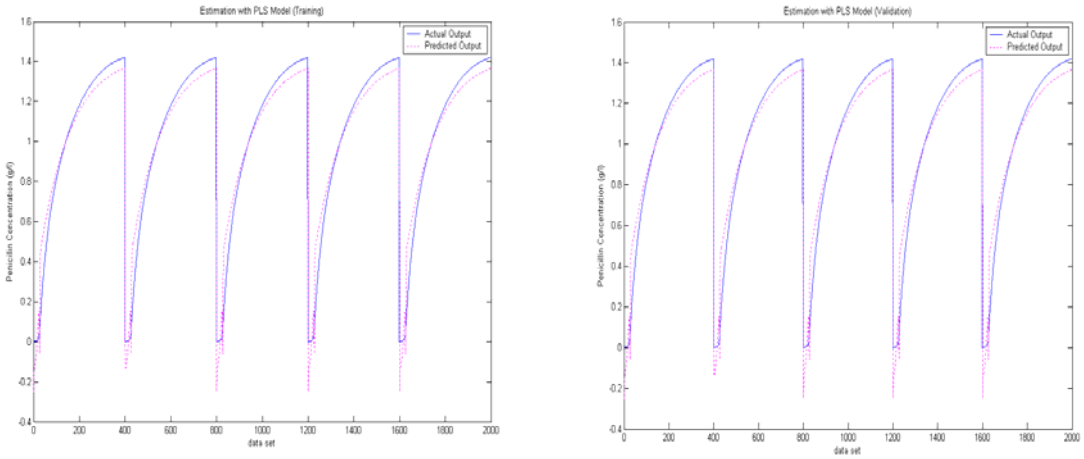

Figure 2 Training and Validation using PLS model

The accuracy of PLS model prediction is illustrated in Figure 3 which compares the actual penicillin concentration with that predicted by the PLS model for one of the batches. This figure shows that the model provided good estimates of penicillin concentration within the fermenter.

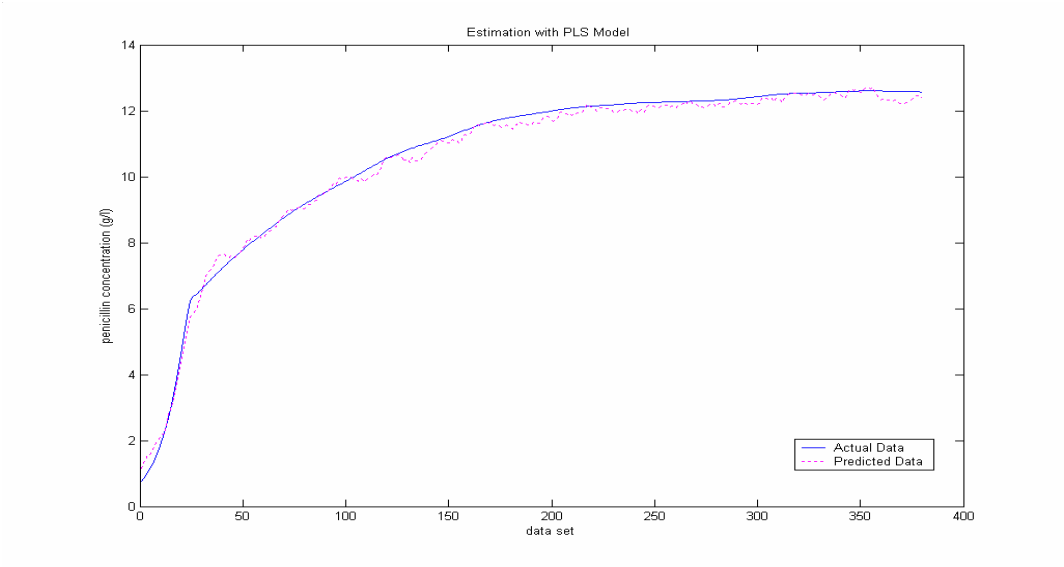

Figure 3 PLS model prediction

3.1 Model Testing

In order to evaluate the performance of the PLS estimator, the model was tested on three sets of data. These three sets of data were made up of different operating conditions.

Data A - Failure of substrate feed rate at 100 hour operation
Data B - Aeration rate failure at 150 hours for 20 hour

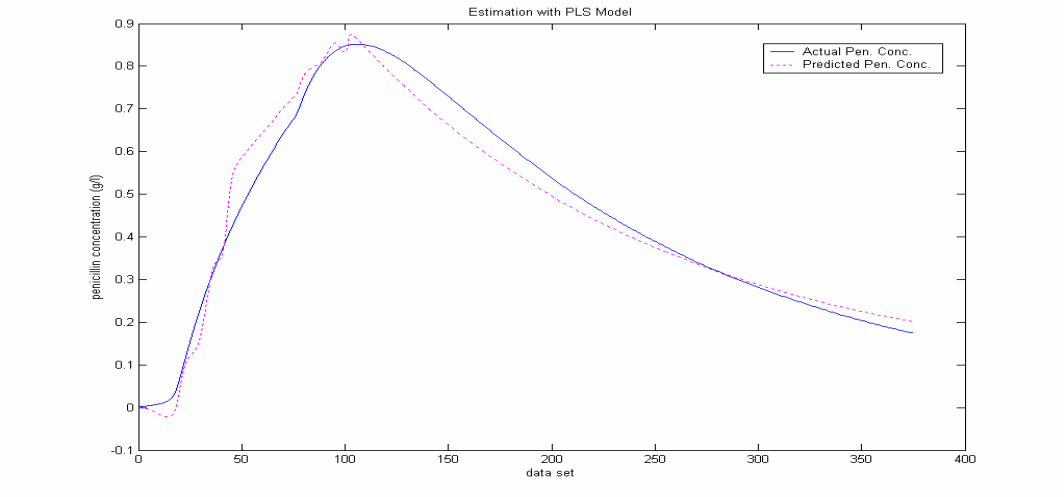

Figure 4 Estimation results of Data A by using PLS

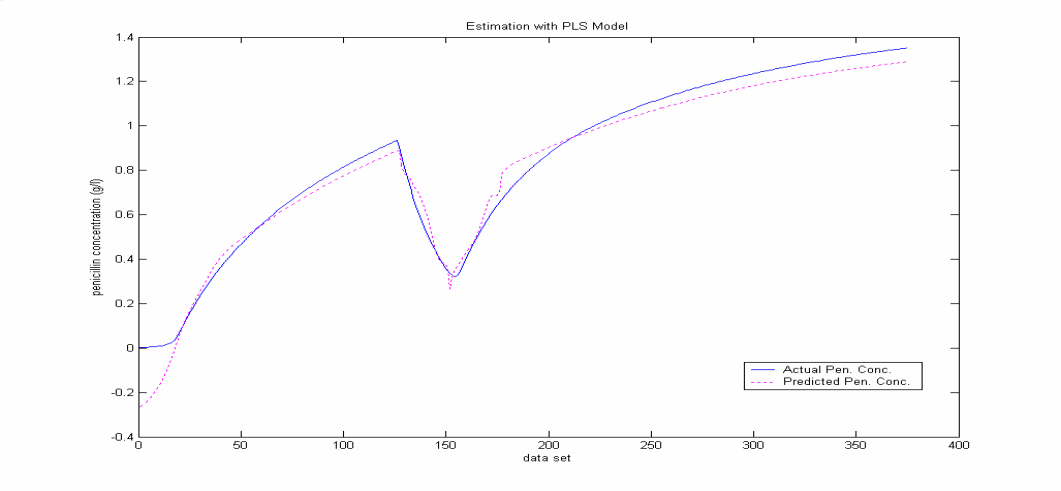

Figure 5 Estimation results of Data B by using PLS

The model obtained good estimations of penicillin concentration in nominal condition. When the PLS model was tested on data with different operating conditions, the prediction results were still good and acceptable. Referring to Figure 4 and 5, the predicted penicillin concentration is close to the actual value for Data A and B. All the prediction values follow the trend of the actual values. These conclude that the PLS model are able to provide good estimations of penicillin concentrations, thus can be adopted as the process estimator.

4. Direct Shooting Method

Direct Shooting Method combines the features of both the sequential approach and the simultaneous approach. The batch time is divided into several smaller intervals and the differential equations are integrated over these intervals. The control variables are parameterized throughout the batch time in this approach and the state variables are parameterized only at the beginning of the intervals. State continuity constraints are enforced as equality constraints. The state inequality constraints at the intervals are incorporated into the optimization problem. The general formulation of the optimal control problem is now presented (Bryson and Ho, 1975). Consider that the system dynamics are described by,

$$\dot{x} = f\left[x(t), u(t), t\right] \text{ for } t_0 \le t \le t_f \text{ and } x(t_0) \text{ is given} \qquad (1)$$

In this equation, *x (t)* and *u (t)* is vector valued state and input respectively, t_0 is the initial time and t_f is the final time. Associated with the process operation is an objective function that needs to be maximized and the general formulation for the objective function is given as,

$$J = \phi\left[x(t_f), t_f\right] + \int_{t_0}^{t_f} L(x(t), u(t), t)\ dt \qquad (2)$$

The optimization problem is to determine optimal feed rate policy serves as objective function for *u (t)*. So it is necessary condition for *u (t)* to be optimal is that it should maximize the Hamiltonian as described by Equation (3). Hence, the dynamic optimization can be formulated mathematically as follows:

$$\max_{t_f,u(t)} H(t) = \lambda^T f(x,u) + \mu^T L(x,u), \tag{3}$$

$$\text{Subject to: } \dot{x} = f(x,u), \qquad x(0) = x_0, \tag{4}$$

$$\dot{\lambda}^T = -\frac{\partial H}{\partial x}, \qquad \lambda^T(t_f) = \left.\frac{\partial \phi}{\partial x}\right|_{t_f} + v^T \left.\left(\frac{\partial T}{\partial x}\right)\right|_{t_f}, \tag{5}$$

$$\mu^T L = 0, \qquad v^T T = 0, \tag{6}$$

Where;

$H(t)$ is the scalar performance index to be minimized;

x is the n-dimensional vector of states with initial conditions x_0;
u is the m-dimensional vector of inputs;
L is the path dependence in the objective function;
T is the τ-dimensional vector of terminal constraints;
F is a smooth vector function;
ϕ is a smooth scalar function representing the integral cost;
t_f is a final time

In order to get the most efficient parameterization in terms of the number of parameters, it is possible to obtain analytical expressions for the optimal inputs for each interval. Thus, the state and adjoint equations (4) and (5) read:

$$\dot{x} = F(x,u(x,\lambda)) = \Re(x,\lambda), \qquad x(0) = x_0, \tag{7}$$

$$\dot{\lambda}^T = -\frac{\partial H}{\partial x}(x,\lambda), \qquad \lambda^T(t_f) = \left.\frac{\partial \phi}{\partial x}\right|_{t_f} + v^T \left.\left(\frac{\partial T}{\partial x}\right)\right|_{t_f} \tag{8}$$

For a free terminal time, an additional condition, referred to as the transversality condition, has to be satisfied:

$$H(t_f) = (\lambda^T f + \mu^T L)\,|_{t_f} = 0 \tag{9}$$

In the shooting approach, the optimization problem is cast into that of solving a system of differential-algebraic equations. The optimal inputs are expressed analytically in terms of the states and the adjoints, $u(x,\lambda)$. The decision variables include the initial conditions $\lambda(0)$ that are chosen in order to satisfy $\lambda(t_f)$. The basic procedure is as follows:

1. Parameterize μ using a finite number of variables. The vector of decision variables also includes $\lambda(0)$, v and t_f.
2. Choose an initial guess for the decision variables.
3. Integrate equations (7) and (8) forward in time using $x(0)$, $\lambda(0)$ and compute $\lambda(t_f)$.
4. Check whether equations (8), (6) and (9) are verified; for the terminal conditions $\lambda(t_f)$, the values obtained by integration in Step 4 should match those specified in equation (5).
5. Update the decision variables using Quasi-Newton methods.
6. Repeat Steps 4-5 until convergence.

5. Single Step Ahead Dynamic Matrix Control

Over the past decade, Model Predictive Control (MPC) has established itself in industry as an important form of advanced control due to its advantages over traditional controllers. The rise of MPC is attributed to several practitioners who outlined the algorithms and demonstrated their capability for industrial applications. Since then, MPC has gained acceptance in academia and has become the focus of academic research (Qin and Badgwell, (2003). In general, MPC refers to a class of computer control algorithms that utilizes explicit process models to predict future responses of a plant. At each control interval an MPC algorithm attempts to optimize future plant behavior by computing a sequence of future manipulated variable adjustments. The first input in the optimal sequence is then sent into the plant and the entire calculation is repeated at subsequent control intervals (Qin and Badgwell, (2003).

Originally developed to meet the specialized control needs of power plants and petroleum refineries, MPC technology can now be found in a wide variety of application areas including chemicals, food processing and automotive. One of the MPC technologies is a Dynamic Matrix Control (DMC). Dynamic Matrix Control (DMC) algorithm can be separated into two parts, a predictor and an optimizer. In the original DMC formulation a step response model of the plant is used to predict the future behavior of the control variables (Lundstrom et al., (1994). For the step response of a system with n_u inputs and n_y outputs:

$$S_i = \begin{bmatrix} S_{1,1,i} & S_{1.2.i} & \cdots & S_{1,n_u,i} \\ S_{2,1,i} & S_{2,2,i} & \cdots & S_{2,n_u,i} \\ \vdots & \vdots & \ddots & \vdots \\ S_{n_y,1,i} & S_{n_y,2,i} & \cdots & S_{n_y,n_u,i} \end{bmatrix} \quad i = 1,....,n. \tag{10}$$

The step response model can be represented in the following state space form:

$$Y(k+1) = GY(k) + S\Delta u(k) \tag{11}$$

$$y(k) = HY(k) \tag{12}$$

Where:

$$\Delta u(k) = u(k) - u(k-1) \tag{13}$$

$$Y(k) = \left[y(k)^T \; y(k+1)^T \ldots y(k+n-1)^T \right]^T \tag{14}$$

$$G = \begin{bmatrix} 0 & I_{n_y} & 0 & \cdots & 0 & 0 \\ 0 & 0 & I_{n_y} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & I_{n_y} & 0 \\ 0 & 0 & 0 & \cdots & 0 & I_{n_y} \\ 0 & 0 & 0 & \cdots & 0 & I_{n_y} \end{bmatrix} \quad n \times n_y ;$$

$$S = \begin{bmatrix} S_1 \\ S_2 \\ \vdots \\ S_{n-2} \\ S_{n-1} \\ S_n \end{bmatrix} \tag{15}$$

And

$$H = \left[\overbrace{I_{n_y} \quad 0 \quad 0 \quad \cdots \quad 0 \quad 0}^{n \times n_y} \right] \tag{16}$$

$\Delta u(k)$ is a vector of changes in the manipulated inputs at time *k*. $y(k)$ is the output vector at time *k*. The vector $Y(k+1)$ represents the dynamic states of the system.

Each state $y(k+1)$ is the future output vector at time $(k+1)$ assuming constant inputs. The new state vector $Y(k+1)$ is the old vector $Y(k)$ shifted up n_y elements plus the contribution made by the latest input change $\Delta u(k)$.

5.1 DMC Predictor

The objective of the predictor is to generate a vector, $y(k+1|k)$ of predicted open loop outputs over a horizon of P future time steps, the prediction horizon. This prediction vector is then used as an input to the optimizer. The DMC optimizer is described by the following equations:

$$\bar{Y}(k) = G\bar{Y}(k-1) + S\Delta u(k-1) \tag{17}$$

$$\bar{y}(k) = H\bar{Y}(k) \tag{18}$$

$$y(k+1|k) = G_p\bar{Y}(k) + \ell\left[\hat{y}(k) - \bar{y}(k)\right] \tag{19}$$

Where G_p is the first $p \times n_y$ rows of G and:

$$\ell = \left[\overbrace{I_{n_y} \quad I_{n_y} \quad \cdots \quad I_{n_y} \quad I_{n_y}}^{p \times n_y}\right]^T \tag{20}$$

$\hat{y}(k)$ is a vector of measured outputs at time k. $\hat{y}(k)$ and $\bar{y}(k)$ are discontinuous at k- while $u(k)$ at k. This is because $\hat{y}$ is measured slightly before time k and u is adjusted slightly after time k.

5.2 DMC Optimizer

A general form of the optimization problem at time step k is:

$$\min_{\Delta U(k|k)} \left\{ \left\| \Gamma \left[\hat{y}(k+1|k) - R(k+1|k) \right] \right\|^2 + \left\| \Lambda \Delta U(k|k) \right\|^2 \right\} \tag{21}$$

Where

$$\Delta U(k|k) = \left[\Delta u(k|k)^T \, \Delta u(k+1|k)^T \ldots \Delta u(k+M-1|k)^T \right]^T \tag{22}$$

$$\hat{y}(k+1|k) = \left[y_M(k+1|k)^T \, y_M(k+2|k)^T \ldots y_M(k+P|k)^T \right]^T \tag{23}$$

$$R(k+1|k) = \left[r(k+1|k)^T \, r(k+2|k)^T \ldots r(k+P|k)^T \right]^T \tag{24}$$

$\Delta U(k|k)$ is the optimal control sequence computed at time *k* for *M* future input moves, where *M* is the input horizon. $R(k+1|k)$ is a vector describing the desired output trajectory (set points) over *p* future time steps. Γ and Λ are weighting matrices and are usually chosen to be diagonal. $\hat{y}(k+1|k)$ is a vector of outputs predicted at time *k*, over a horizon of *P* future time steps including the effect of the *M* optimal input moves:

$$\hat{y}(k+1|k) = Y(k+1|k) + \ell_P^M \Delta U(k|k) \tag{25}$$

Where

$$\ell_P^M = \begin{bmatrix} S_1 & 0 & \cdots & 0 \\ S_2 & S_1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ S_M & S_{M-1} & \cdots & S_1 \\ \vdots & \vdots & \ddots & \vdots \\ S_P & S_{P-1} & \cdots & S_{P-M-1} \end{bmatrix} \tag{26}$$

In case where M = 1, Equation (22) must be reconstruct. In order to obtain optimal solution for the model, a least squares solution must be implemented. Then, Equation (22) becomes:

$$\Delta U(k|k) = \left[S_1^T \Gamma^T \Gamma S_1 + \Lambda^T \Lambda \right]^{-1} S_1^T \Gamma^T \Gamma \times \left[R(k+1|k) - \hat{y}(k+1|k) \right] \tag{27}$$

Equation (27) is then become a single step ahead DMC. Only the first input move is implemented in this single step ahead DMC algorithm and the resulting optimizer is a constant gain matrix, K_{MPC} :

$$\begin{aligned} \Delta u(k) &= \begin{bmatrix} I & 0 & \ldots & 0 \end{bmatrix} \Delta U(k|k) \\ &= K_{MPC} \left[R(k+1|k) - Y(k+1|k) \right] \end{aligned} \tag{28}$$

$$K_{MPC} = \begin{bmatrix} I & 0 & \ldots & 0 \end{bmatrix} (S_1^T \Gamma^T \Gamma S_1 + \Lambda)^{-1} \times S_1^T \Gamma^T \Gamma \tag{29}$$

6. Results and Discussion

For the numerical integration of the state equations, the ode45 routine in MATLAB was used and the optimization based on direct shooting method was carried out using

the MATLAB routine *fmincon* while single step ahead DMC algorithm was solved by its algorithm available in MATLAB. Figure 6 and 7 shows the performance comparison between this two optimization approach and nominal operation for substrate feed rate and penicillin concentration.

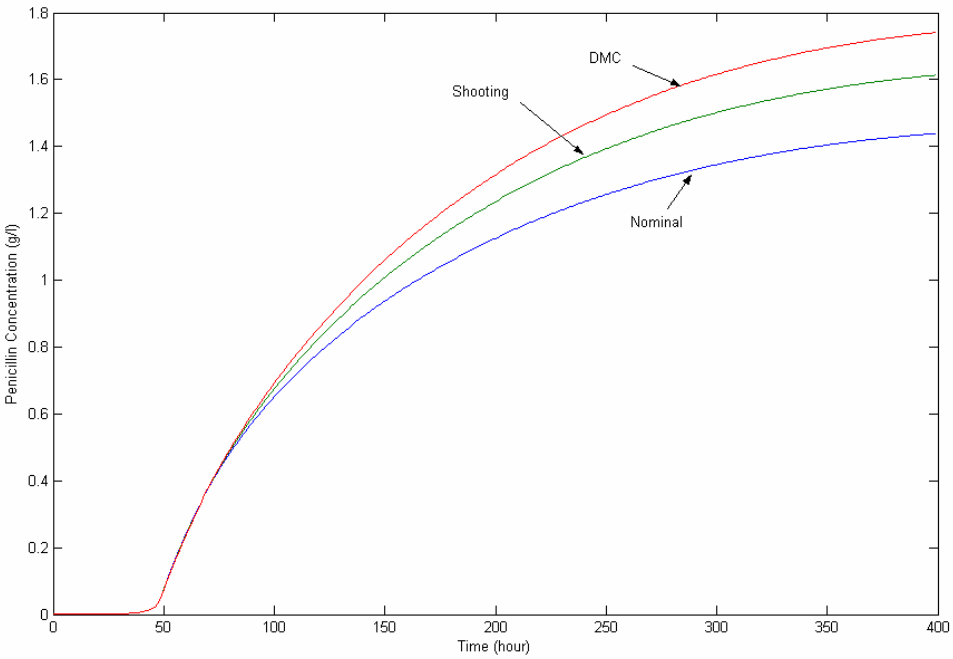

Figure 6 Penicillin concentration profile for direct shooting method, single model DMC and nominal operation

Initial substrate feed rate all cases, i.e., for both optimization schemes and nominal operation, when the system switched to the fed batch operation was 0.0426 l/h. A constant substrate feed rate was used during the fed-batch operation under nominal operating condition. But substrate feed rate was increased when both optimization approaches were implemented in the system. The final substrate feed rate for direct shooting method was 0.050169 l/h and single step ahead DMC was 0.055213 l/h. In the end of the batch, the process obtained 1.7413 g/l penicillin concentration when single step ahead DMC was implemented compared to only 1.6136 g/l when the direct shooting method was implemented. The results obtained show that single step ahead DMC optimization which is based on quadratic programming performed better than direct shooting method. The single step ahead DMC not only increased penicillin concentration but also improved the purity of penicillin up to 57.99 %. Table 2 shows comparison performance of dynamic optimization of the fed-batch fermentation. Both optimization approaches proposed in this work were able to elevate the penicillin production to greater heights. Direct shooting method is known to suffer from TPBVP problem and in this case, it was the probable cause for the inferior performance compared to the DMC optimizer. Of all, the use of single step ahead DMC is proved to be most efficient. Thus DMC approach will be used as a benchmark to further works.

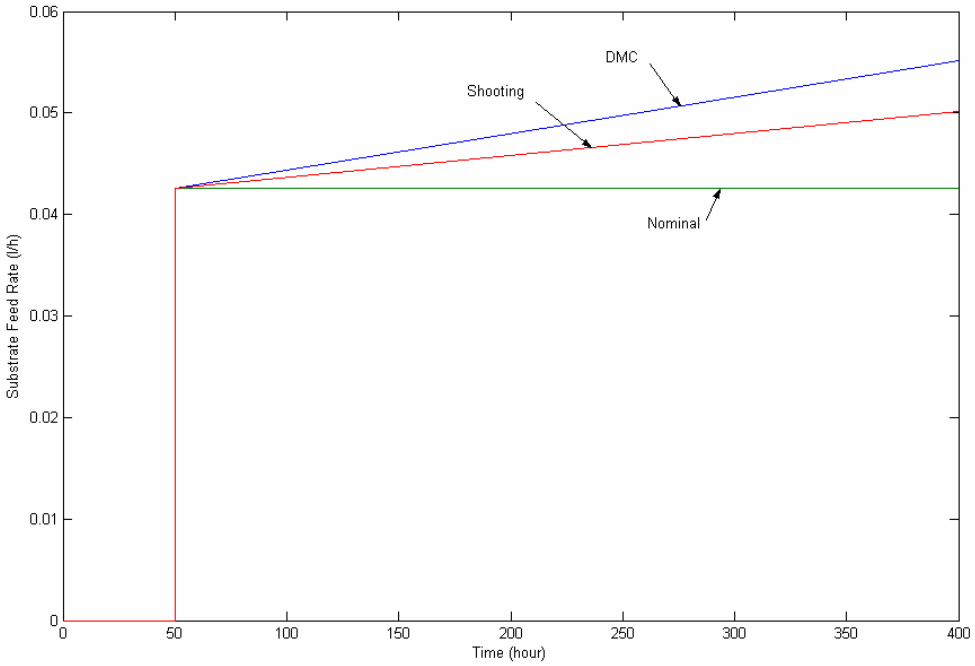

Figure 7 Substrate feed rate profile for direct shooting method, single model DMC and nominal operation

Optimization Algorithm	Initial Substrate Feed Rate (l/h)	Final Substrate Feed Rate (l/h)	Penicillin Concentration (g/l)	Penicillin Purity (%)
Nominal Operation	0.0426	0.0426	1.4127	53.14
Direct Shooting Method	0.0426	0.050169	1.6136	56.03
DMC	0.0426	0.055213	1.7413	57.99

Table 2 Comparison performance fed-batch fermentation with different optimization algorithm

6.1 Performance for Disturbance Rejection

From previous section, the use single step ahead DMC is proved to be most efficient. In order to test the optimization performance when dealing with disturbance rejection, a ±10% change in the substrate feed concentration was made. The results are shown in Figure 8 and 9:

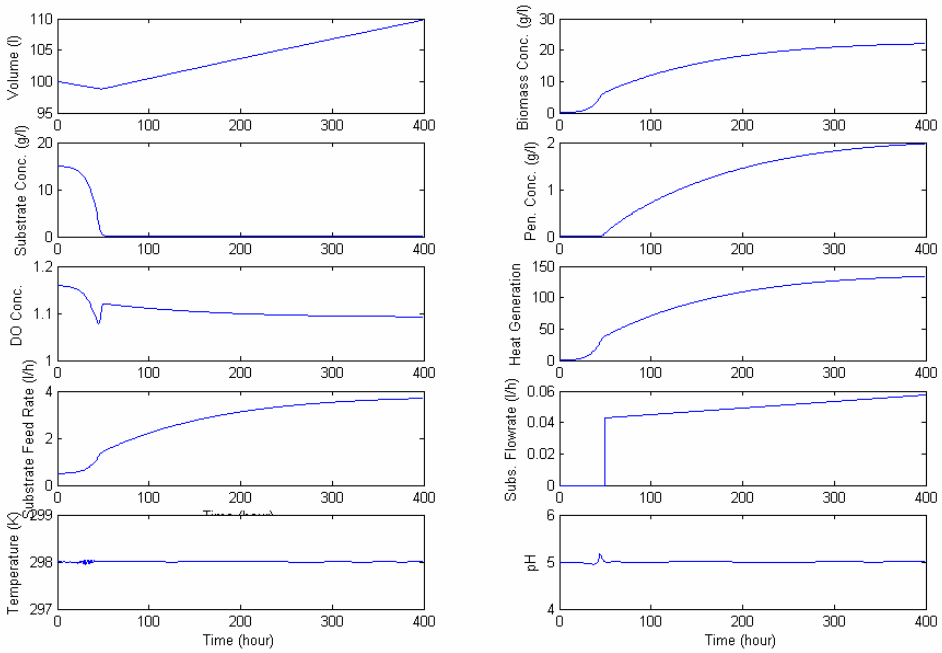

Figure 8 Plot of penicillin fermentation using single step ahead DMC for a -10 % change in substrate feed concentration

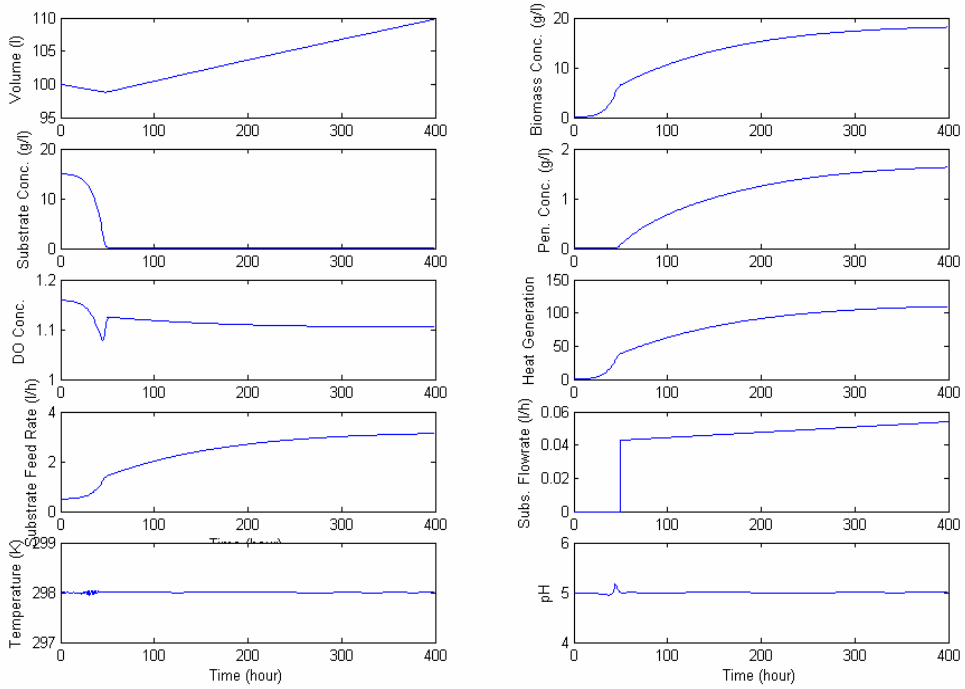

Figure 9 Plot of penicillin fermentation using single step ahead DMC for a +10 % change in substrate feed concentration

From Figure 8 and 9, it can be observed that the final penicillin concentration attained were 1.8543 g/l and 1.6291 g/l respectively. When the substrate feed concentration was decreased, the controller initially increased the volume of feed into the reactor. This led to an increase in the input profile substrate feed rate in order to satisfy the volume constraint. As a result of the increase on the input rate, the concentration of penicillin was significantly increased. Similar trend occurred when an increase in substrate feed concentration was imposed. As the batch approached completion, the controller increased the amount of feed more rapidly in order to avoid violation final volume constraint. Finally the penicillin concentration reduced due to the dilution effect of the added volume. Due to the feed disturbance, the original reference trajectory is no longer optimal and this results in the decreased penicillin concentration at the end of the batch. In order to correct this disturbance, reoptimization can be carried out to generate a new reference trajectory thereby taking into account the increased amount of substrate within the feed.

7. Conclusion

A detailed unstructured model was proposed for penicillin production in a fed-batch mode. Compared to other published works, the proposed mathematical model contains additional input variables such as pH, temperature, aeration rate, agitation power, substrate feed flow rate as well as output variables like carbon dioxide evolution and heat generation terms. With the introduction of pH and temperature terms to the model equations, it is possible to investigate the influences of such environmental variables on system dynamics. PID controllers were used to control pH and temperature. It was shown that both controllers worked well and good controls of pH and temperature were obtained. Furthermore analyses of disturbances were also carried out in order to gain further insight on the process. The simulation results were also in good agreement with the simulation work from Birol et al., (2002).

The inferential estimator for the penicillin concentration of a fed-batch bioreactor was built using a PLS model. The measured process variables such as substrate feed rate, aeration rate, agitator power, substrate feed temperature, culture volume, pH, fermentor temperature and heat generation were used to construct the estimator. This estimator had been performing well in the nominal condition. The robustness and accuracy of the PLS estimator were also tested in three different operating condition. In all cases, reasonably accurate estimations were obtained. Therefore, the PLS proposed model is considered adequate to be used as process estimators for the penicillin fermentation process.

The optimal control policy using direct shooting method and single step ahead DMC has been developed, aiming at optimizing the end of the batch penicillin concentration. From this two optimization approaches, it is possible to estimate the optimal operating conditions as substrate feed rate so that the systems presents high performance within threshold value limit. The result also showed that the single step ahead DMC approach is superior the direct shooting method in term of the penicillin concentration as well as penicillin purity. However in the present of feed

concentration disturbance, reoptimization of the reference trajectory was needed to attain the fed-batch target while satisfying the final volume constraint.

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