Optimal Operation of Baker's Yeast Fermentation in the Presence of Uncertainty

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In this paper, we consider the problem of determining the optimal feeding policy for a fed-batch fermentation for the production of Baker's yeast in the presence of uncertainty. Two algorithms are discussed for the computing the optimal solution in the presence of uncertainty. The first method is a measurement-based closed-loop approach where process measurements are utilized to make on-line adjustments to the optimization routine. The second method is simulator-based open-loop approach where simulations are run assuming various operating policies utilizing the simulator as if it were the real process. These two methods are implemented on a Baker's yeast fermentation with uncertain parameters and it is shown that both approaches lead to improved performance over the conventional open-loop operation.

Introduction

Batch and semi-batch processes are of considerable importance to the fine chemicals and pharmaceutical industry. Since the production volumes are low, batch plants are typically *multi-product* facilities in which several different products share the same piece of equipment. With the recent trend in building small flexible plants that are close to the markets of consumption, there has been a renewed interest in batch processes [Biegler *et al.*, 1999]. In particular, the optimization of batch and fed-batch fermentations has attracted the attention of several researchers in the past two decades. In the mid to late 1980s several studies were conducted in the optimization of microbial fermentations by manipulating the feed rate of substrate to the reactor [see for instance, Lim *et al.*, 1986; Menawat *et al.*, 1987]. While these papers were responsible for introducing formal optimization methods to the biochemical engineering community, one major unresolved issue is the fact that the optimization methods depend strongly on the accuracy of the process model. Given the fact that accurate models are not available for most industrially relevant fermentations, open-loop implementation of the solution obtained by optimizing the process model does not guarantee that the fermenter is being run optimally and can lead to substantial losses in product yield and quality over the course of several batch runs [Palanki *et al.*, 1993].

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for a fed-batch fermentation for the production of Baker's yeast in the presence of uncertainty. In section 2, the end-point optimization problem is formulated mathematically. The solution strategies available in the literature to solve this class of problems are briefly reviewed. In section 3, the effect of parametric uncertainty is presented. Two algorithms are discussed for the computing the optimal solution in the presence of uncertainty and simulation studies are conducted to determine the efficacy of these algorithms. Finally, in section 4, the major conclusions of this study are summarized.

Problem Formulation

The production of baker's yeast in a fed-batch reactor is considered. The dynamic model for fed-batch reactor consists of the material balance on the biomass X, substrate S, and the overall volume V of the system [Menawat *et al.*, 1987]:

$$\begin{aligned}\frac{d(XV)}{dt} &= \mu XV \\ \frac{d(SV)}{dt} &= -\frac{\mu XV}{Y_{X/S}} + C_{SF}F \\ \frac{d(V)}{dt} &= F\end{aligned} \qquad \ldots(1)$$

where F is the volumetric feed rate of substrate with concentration C_{SF}, $Y_{X/S}$ is the yield coefficient and μ is the specific growth rate given by the following function:

$$\mu = \frac{\mu_m S}{k_1 + S}\frac{S}{k_2 + S} \qquad \ldots(2)$$

The objective is to find the optimal volumetric feed rate F that maximizes the amount of biomass at a end of a fixed final time. This can be stated mathematically as:

$$min\ J = -XV \qquad \ldots(3)$$

The volumetric feed rate is constrained to be between F_{min} and F_{max} and the volume of the reactor is constrained to not more than V_{max}.

Note that the problem of maximizing the biomass is posed as a minimization problem in eq. (3). In the optimization literature, optimization problems are generally posed as *minimization* problems and so the problem of maximizing an objective function is converted to a minimization problem by changing the sign of the objective function [Bryson and Ho, 1975].

The model *structure* of the Baker's yeast fermentation is well defined by the lumped parameter model described by eq. (1) and eq. (2). This model predicts the general *trend* of the overall cell mass growth kinetics as well as the substrate consumption rate when the fermentation is conducted in batch or fed-batch mode. However, in an industrial setting, due to minor changes in fermentation media and sterilization conditions in every batch, the cell mass profile and the substrate consumption profile differ from batch to batch [Terwiesch *et al.*, 1994]. For this reason, if one fits the general model structure described by eq. (1) and eq. (2) to several batch run data, each run will show slightly different model parameters [Palanki *et al.*, 1993]. For this reason, optimal operation of this process involves the development of a strategy that takes into account the fact that while the model *structure* for the fermentation process does not change, the *parameters* could change from batch to batch.

The problem of computing the optimal operating strategy in a real-time framework for *continuous* processes in the presence of process disturbances and modeling uncertainty is a well studied problem [see, for instance, Marcos *et al.*, 2004; Yip and Marlin, 2002]. However, these results are not directly applicable to the batch problem considered here where the model structure is known but the parameters could change from batch to batch.

Defining the variables:

$$\begin{aligned} x_1 &= SV \\ x_2 &= V \end{aligned} \qquad \ldots(4)$$

the reduced model for this system is given as follows

$$\begin{aligned} \frac{dx_1}{dt} &= -\mu x_2 + C_{SF}F \\ \frac{dx_2}{dt} &= F \end{aligned} \qquad \ldots(5)$$

The substrate concentration S is given by

$$S = \frac{x_1}{x_2} \qquad \ldots(6)$$

Furthermore, the biomass X can be computed from the following algebraic expression:

$$X = Y_{X/S}\left[\frac{V_0}{x_2}S_0 - \frac{x_1}{x_2} + C_{SF} - \frac{V_0}{x_2}C_{SF} + \frac{V_0}{x_2}.\frac{X_0}{Y_{X/S}}\right] \qquad \ldots(7)$$

where V_0, X_0 and S_0 are the initial fermentor volume, initial cell mass concentration and , initial substrate concentration. The input constraint ($F_{min} \leq F \leq F_{max}$) can be written as:

$$\begin{aligned} &F_{min} - F \leq 0 \\ &F - F_{max} \leq 0 \end{aligned} \qquad \ldots(8)$$

and the volume constraint can be written as:

$$x_2 - V_{max} \leq 0 \qquad \ldots(9)$$

It will be shown in the next section that this *reduced* model is useful in generating an analytical expression for the optimal operating strategy which is straightforward to implement on-line.

The end-point optimization problem described above is of the general form:
Minimize the objective function

$$J = \phi(x(t_f)) \qquad \ldots(10)$$

subject to

$$\begin{aligned} \dot{x} &= f(x,u) \\ x(0) &= x_0 \\ Pu - b &\leq 0 \qquad (input\ constraints) \\ Qx - c &\leq 0 \qquad (state\ constraints) \end{aligned} \qquad \ldots(11)$$

where x is the state vector of dimension n, u is the input vector of dimension m, f is a smooth vector function of dimension n, $Pu - b \leq 0$ represent p input constraints and $Qx - c \leq 0$ represent q state constraints.

Solution Strategies

General methods for solving optimization problems of the form of eq. (10) and eq. (11) were first developed for aerospace applications in the 1950s and 1960s [Bryson and Ho, 1975]. Since then, there have been a plethora of papers in the application of these methods to specific case studies of end-point optimization problems in batch processes.

Using calculus of variations, the problem of minimizing a scalar cost function eq. (10) subject to the dynamic constraints eq. (11) can be reformulated as minimizing the Hamiltonian H which leads to a class of indirect optimization methods [Bryson and Ho, 1975]. This reformulation leads to the following Euler-Lagrange equations:
Minimize the Hamiltonian

$$H(x, \lambda, u) = \lambda^T f(x, u) + \mu_1^T (Pu - b) + \mu_2^T (Qx - c) \qquad \ldots(12)$$

subject to:

$$\begin{aligned} \dot{x} &= f(x, u); & x(0) &= x_0 \\ \dot{\lambda}^T &= -\lambda^T \frac{\partial F}{\partial x} - \mu_2^T Q; & \lambda(t_f) &= \frac{\partial \phi}{\partial x}\Big|_{t=t_f} \end{aligned} \qquad \ldots(13)$$

where $\lambda(t) \neq 0$ is the n-vector of adjoint states and the vectors μ_1 and μ_2 are the Kuhn-Tucker parameters of dimension p and q respectively. When any constraint is active, the corresponding Lagrange multiplier is positive and when a constraint is not active, the corresponding Lagrange multiplier is equal to zero [Maurer, 1977]. Thus, $\mu_1^T (Pu - b)$ and $\mu_2^T (Qx - c)$ are always equal to zero. The necessary condition for optimality of H is given by the following m relations:

$$H_u = \lambda^T \frac{\partial f}{\partial u} + \mu_1^T P = 0 \qquad \ldots(14)$$

which implies that $x,\ u,\ \lambda,\ \mu_1$, and μ_2 exist such that the following expressions hold:

$$\begin{aligned} \dot{x} &= f(x, u) \\ x(0) &= x_0 \\ \dot{\lambda}^T &= -\lambda^T \frac{\partial f}{\partial x} - \mu_2^T Q \\ \lambda(t_f) &= \frac{\partial \phi}{\partial x}\Big|_{t=tf} \\ \lambda^T \frac{\partial f}{\partial u} + \mu_1^T P &= 0 \\ \mu_1^T (Pu - b) &= 0 \\ \mu_2^T (Qx - c) &= 0 \\ \mu_1 &\geq 0 \\ \mu_2 &\geq 0 \end{aligned} \qquad \ldots(15)$$

The formulation represented by eq. (15) provides an indirect method for solving for the optimal inputs. One can see that to solve eq. (15) for the optimal inputs u_i, one needs to integrate the state equations ($\dot{x} = f(x, u)$) forward in time and the adjoint

***Table 1**. Reaction Conditions for Baker's Yeast Fermentation*

Parameter	Value	Units
Simulation time t	10	h
Specific growth rate (μ_m)	0.5	(h^-1)
Haldane-Monod parameter k_1	0.5	(kg/m^3)
Haldane-Monod parameter k_2	500	(kg/m^3)
Yield coefficient (Y_{XS})	0.5	$(kgcell/kgsubstrate)$
Concentration of substrate in feed (C_{SF})	300	(kg/m^3)
Initial reactor volume V_0	1	m^3
Initial concentration of substrate (C_{S0})	100	(kg/m^3)
Initial concentration of cell mass (C_{X0})	10	(kg/m^3)
Maximum reactor volume (V_{Max})	10	m^3

equations ($\dot{\lambda}^T = -\lambda^T \frac{\partial f}{\partial x} - \mu_2^T Q$) backwards in time. Thus, a *two-point* boundary value problem needs to be solved numerically for the inputs u_i. A variety of numerical methods have been utilized for solving this two point boundary value problem. For instance, the shooting method was utilized for the optimization of batch polymerization [Hicks *et al.*, 1969; Chen and Jeng, 1978], and for determining the optimal operating policy in batch antibiotic fermentation [Lim *et al.*, 1986; Parulekar, 1992].

By applying of the Euler-Lagrange equations to the system represented by eq. (5), it can be shown that the optimal input is either to keep the system on an input constraint ($F = F_{min}$ or $F = F_{max}$) or is such a flow rate that keeps the system represented by eq. (5) on the surface described by [Palanki *et al.*, 1993]:

$$S = \sqrt{k_1 k_2} \qquad \ldots(16)$$

Simulations are conducted using the parameters and reaction conditions given in Table 1. It can be seen that the condition given by eq. (16) corresponds to a substrate concentration of 15.81 kg/m^3. Since the initial substrate concentration inside the reactor is 100 kg/m^3, no substrate is fed until the substrate concentration inside the reactor drops to 15.81 kg/m^3 after 3.8 h. At this point, the substrate feed rate is adjusted to maintain the substrate concentration at 15.81 kg/m^3. It can be seen from Figure 1 that the substrate concentration remains constant at 15.81 kg/m^3 after 3.8 h while the cell mass concentration continues to increase. The input profile used to maintain the substrate concentration and the corresponding increase in the reactor volume are shown in Figure 2. The final amount of cell mass obtained at the end of the 10 h batch corresponding to the optimal substrate feed rate shown in Figure 2 is 972.8 kg.

Optimization Under Uncertainty

Most optimization methods, including those discussed above, involve one underlying assumption: the mathematical model used in the method and the parameters associated with the model are accurate and truly represent the original batch process. However, such accurate models are seldom available in reality, especially for batch processes. Parameters involved with the modeling, kinetics and thermodynamics of a reaction for

Figure 1. *Substrate and Biomass Concentrations*

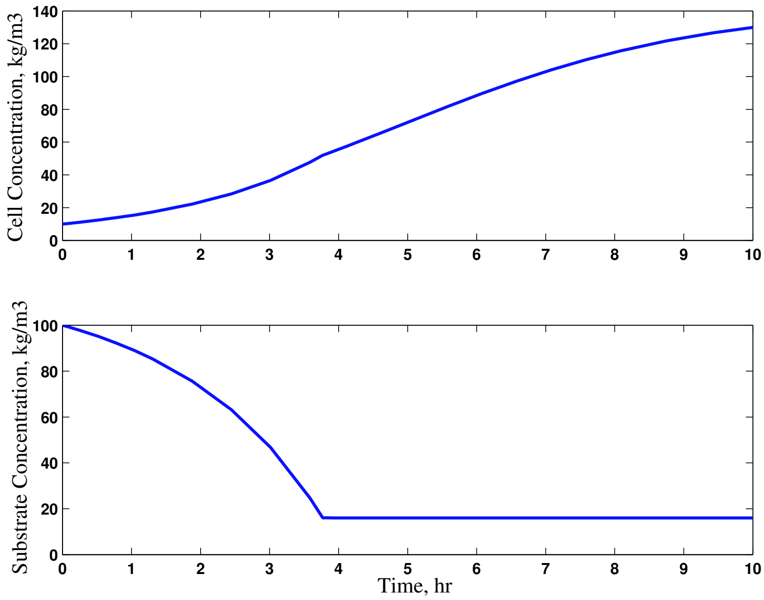
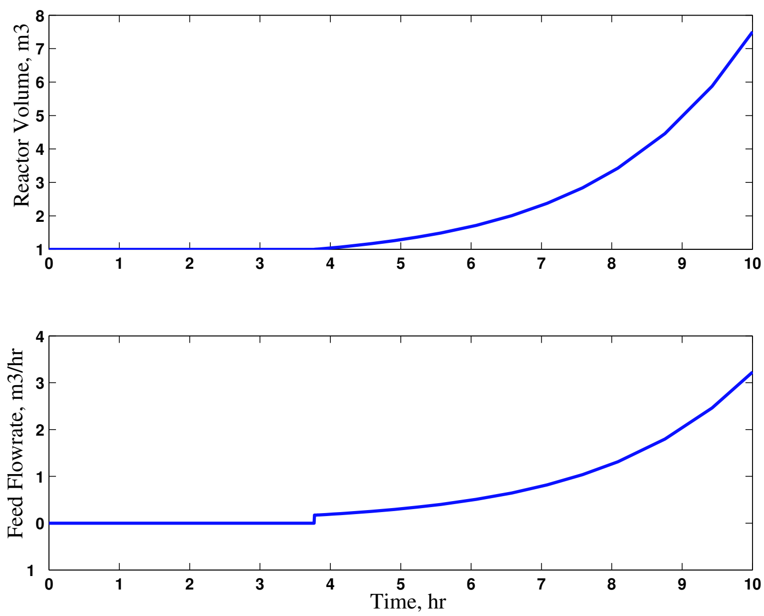


Figure 2. *Optimal Flowrate and Volume*



instance, are not completely established for most batch processes and their dynamic nature is often not very well understood. For this reason, the optimal solutions obtained by using the mathematical models may not remain optimal.

In addition to inaccurate model parameters, there may also be variations in operating conditions contributing to the uncertainty. For instance, scale-up of a process from laboratory scale to the actual plant may also contribute to uncertainty. In addition, there could be uncertainty in loading conditions, especially when reactants are added as solids and mixed with solvent after charging. This can lead to batch-to-batch variations in product quality and poor reproducibility.

Effect of Uncertainty on Nominal Solution

Most batch industries currently use input profiles that are determined heuristically. These input profiles typically result in sub-optimal process operation in presence of uncertainty. Using sub-optimal input profiles on the actual process may risk the violation of safety constraints, production off-spec products, and more importantly the loss of invaluable time, energy and money. Despite the awareness in the batch chemical industry regarding the influence of parametric uncertainty, few measures are taken to rectify the current situation [Terwiesch, 1994; Bonvin, 1998].

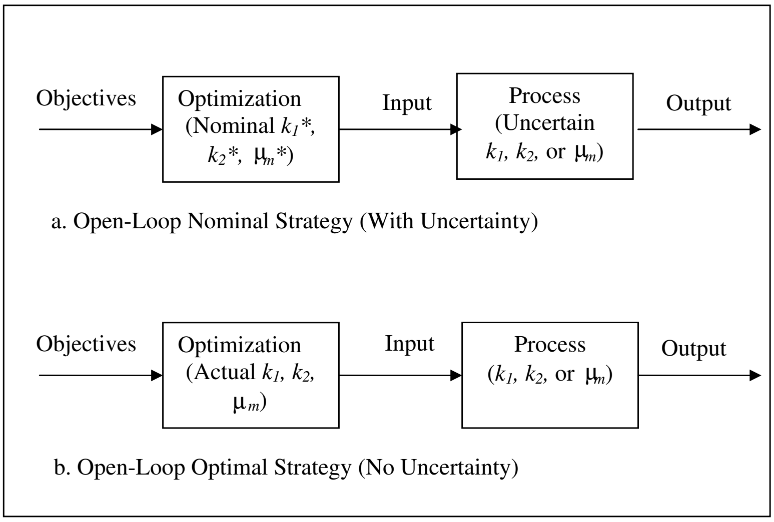
Batch reactors are very sensitive to uncertainty in model parameters such as kinetic rate constants and heat capacity coefficients. From a computations perspective, the solution obtained from nominal model does not remain optimal in the presence of uncertainty to such sensitive parameters. However, for certain parameters, it is possible that the nominal solution remains optimal for a range of parameters values, as the model may be insensitive to uncertainty in those parameters. The effect of parametric uncertainty on the Baker's yeast fermentation operation is considered.

The three parameters involved in the fermenter model are the parameters k_1, and k_2, and the specific growth rate, μ_m. The nominal values of these parameters are $0.5\ kg/m^3$, $500\ kg/m^3$ and $0.5\ hr^{-1}$ respectively. Other parameters and reaction conditions associated with this reaction may be found in Table 1. When there is no uncertainty in the model parameters, the open loop solution corresponds to the optimal solution. The open-loop solution, as shown in Figure 1, refers to the case when no periodic adjustments are made to the optimal solution based on the output from the process.

The extent of uncertainty in each of the three parameters is assumed to vary between -50% and +50% of their corresponding nominal values. Two different simulations are performed for each case of uncertainty: open-loop simulation and simulation with optimal operation as shown in Figure 3. The solution for optimization problem is found offline using the nominal parameters, k_1^*, k_2^*, μ_m^*, and this achieved solution is implemented even in the presence of parametric uncertainty. Clearly, the two open-loop strategies shown in Figure 3 correspond to identical outputs only when k_1^*, k_2^*, and μ_m^* are exactly equal to k_1, k_2, and μ_m.

We first computed the optimal substrate feed rate and the optimal switching time based on a fixed model. This achieved solution was implemented in open-loop on the process (simulator) for different values of the parameters. The biomass achieved from this open-loop implementation is compared with the biomass that would have been

***Figure 3**. Open-loop Strategies*



achieved if the parameter values had been exactly known. The effect of uncertainty in k_1 is summarized in Table 2. The target substrate concentration is indicated for both open-loop as well as optimal simulations. The time taken for the substrate to reach this target concentration, t_{switch}, is also indicated for both the cases. Finally, the objective function, the amount of biomass produced at the end of batch time is also tabulated. The simulations set in which the parameter k_1 is at its nominal value (no uncertainty) is shown in bold font. It can be seen from the last column of Table 2 that the percentage deviation of the output in open-loop simulation from that in optimal simulation is negligible. All the simulations resulted in deviations under 2% and most simulations resulted in identical objective values for open-loop and optimal operation. This indicates that the uncertainty in the parameter k_1 has a very minor effect on the accuracy of the optimal solution. Thus, open-loop implementation suffices even in the presence of uncertainty in k_1.

The effect of uncertainty in k_2 is summarized in Table 3. The organization of this table is similar to that of Table 2. The simulations set in which the parameter k_2 is at its nominal value (no uncertainty) is indicated in bold font. It can be seen that the percentage deviation in results from open-loop simulation and optimal operation is more significant in this case compared to the case when the uncertain parameter was k_1. The maximum deviation is a significant 40% versus the negligible 2% in case of k_1. This indicates that the uncertainty in the parameter k_2 has a significant effect on the accuracy of the optimal solution. Thus, open-loop implementation in the presence of uncertainty in k_2 could lead to significant loss in product (and hence profit).

The effect of uncertainty in μ_m is summarized in Table 4. The case when there is no uncertainty in μ_m is in bold font. The deviation of the open-loop solution from the

Table 2: Effect of Uncertainty in k_I on Nominal Solution

Uncertainty		$S \quad \sqrt{k_1 k_2}$ (kg/m^3)		t_switch (hr)		Objective J (kg of Biomass)		% Deviation
%	k_I	Open-Loop	Optimal	Open-Loop	Optimal	Open-Loop	Optimal	
+50	0.75	15.81	19.36	3.77	3.72	919.9	928.9	1
+40	0.70	15.81	18.71	3.77	3.73	929.4	938.6	1
+30	0.65	15.81	18.03	3.77	3.74	939.4	949.3	1
+20	0.60	15.81	17.32	3.77	3.75	950.4	954.3	0
+10	0.55	15.81	16.58	3.77	3.76	961.4	967.5	1
0	**0.50**	**15.81**	**15.81**	**3.77**	**3.77**	**973.4**	**973.4**	**0**
-10	0.45	15.81	15.00	3.77	3.79	981.3	984.6	0
-20	0.40	15.81	14.14	3.77	3.80	991.9	995.4	0
-30	0.35	15.81	13.23	3.77	3.82	1002.6	1006.6	0
-40	0.30	15.81	12.25	3.77	3.83	1011.4	1023.2	1
-50	0.25	15.81	11.18	3.77	3.85	1018.5	1037.3	2

optimal solution is indicated in the last column. It can be clearly seen from Table 4 that there is a significant loss in using open-loop strategy and that the results deviate drastically from the optimal solution. The maximum deviation of 90% corresponding to 50% uncertainty in μ_m is the highest deviation in Tables 2, 3 and 4. This indicates that the uncertainty in parameter μ_m may strongly influence the optimum operation of the process and the open-loop strategy may result in a poor operation of the semi-batch reactor.

It can be seen from the analysis of the effect of uncertainty in three model parameters, k_1, k_2,and μ_m, that the open-loop strategy may not always prove to be the optimal strategy in presence of uncertainty. The extent of deviation from optimal solution in presence of uncertainty varies from parameter to parameter. Some parameters do not influence the optimal solution under uncertainty while other parameters may significantly affect the optimal solution. To effectively handle uncertainty in the parameters that significantly influence the optimal solution, two methods are proposed: measurement-based optimization and simulator-based optimization.

Measurement-Based Optimization

On-line and off-line measurements taken during the fermentation process can be effectively used to adjust the operating strategy under the presence of uncertainty. In measurement-based optimization method, several state variables of the process (e.g. substrate concentration, cell mass, and liquid volume) are measured on-line. The measurements are utilized in estimating the actual values of uncertain parameters. The

Table 3. Effect of Uncertainty in k_2 on Nominal Solution

Uncertainty		$S \quad \sqrt{k_1 k_2}$ (kg/m^3)		t_switch (hr)		Objective J (kg of Biomass)		% Deviation
%	k_2	Open-Loop	Optimal	Open-Loop	Optimal	Open-Loop	Optimal	
+50	750	15.81	19.36	3.77	3.55	1001.5	1082.5	7
+40	700	15.81	18.71	3.77	3.58	1000.8	1065.8	6
+30	650	15.81	18.03	3.77	3.62	1000.0	1048.7	5
+20	600	15.81	17.32	3.77	3.67	996.8	1025.4	3
+10	550	15.81	16.58	3.77	3.72	989.9	1002.9	1
0	**500**	**15.81**	**15.81**	**3.77**	**3.77**	**973.4**	**973.4**	**0**
-10	450	15.81	15.00	3.77	3.84	923.6	945.1	2
-20	400	15.81	14.14	3.77	3.92	836.6	907.1	8
-30	350	15.81	13.23	3.77	4.02	717.2	858.3	16
-40	300	15.81	12.25	3.77	4.15	575.6	802.5	28
-50	250	15.81	11.18	3.77	4.33	430.5	735.8	41

estimates are then incorporated into the process dynamic model and the optimization problem is solved for the modified dynamic model. The updated input profiles obtained from the optimization algorithm are then sent to the actual process in closed-loop. The flow diagram for measurement-based optimization strategy proposed in this work is shown in Figure 4. The basic procedure for this strategy is given below:

1. Find the solution to the optimization problem using the process model with nominal parameters, P^*.

2. Implement the nominal solution on the process (with actual parameters, P).

3. Measure the output from the real process on-line and estimate the parameters using the measurements.

4. Update the process model with the estimated parameters, P_e.

5. Solve the optimization problem with the updated model.

6. Modify the input to the process, on-line, and in closed-loop, based on the solution from optimization problem.

7. Go to step 3 and repeat the process until the output from the model is the same as that from the real process.

In the above algorithm, the parameter estimation described in step 3 can be avoided when the measured variable itself is a combination of the uncertain parameters. When

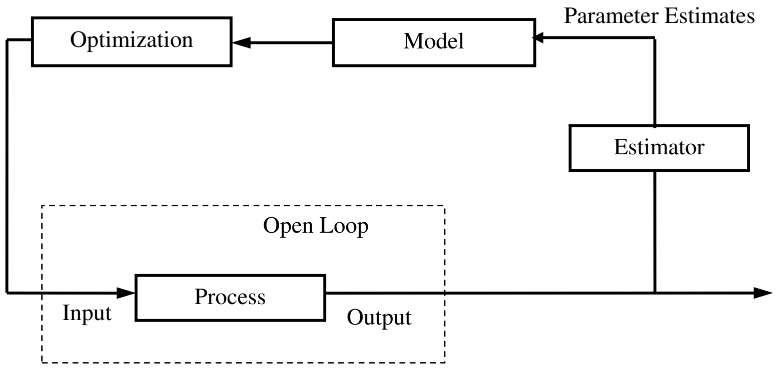
Table 4. Effect of Uncertainty in μm on Nominal Solution

Uncertainty	m	t_switch Nominal (hr)	J_Nominal (kg of Biomass)	t_switch Optimal (hr)	J_Optimal (kg of Biomass)	% Deviation
+50 %	0.75	3.77	1032.8	2.5	10202.0	90
+40%	0.70	3.77	1032.6	2.7	6388.8	84
+30%	0.65	3.77	1031.4	2.9	3976.6	74
+20%	0.60	3.77	1029.5	3.2	2478.7	58
+10%	0.55	3.77	1024.8	3.4	1562.5	34
0%(Nominal)	**0.50**	**3.77**	**973.4**	**3.8**	**973.4**	**0**
-10%	0.45	3.77	476.0	4.2	608.1	22
-20%	0.40	3.77	271.6	4.7	380.6	29
-30%	0.35	3.77	167.4	5.4	237.7	30
-40%	0.30	3.77	107.4	6.3	148.4	28
-50%	0.25	3.77	70.6	7.6	92.7	24

the output is not expressed explicitly in terms of the uncertain parameters, it is necessary to estimate these parameters online based on real-time data of the states. This real-time data must be sufficiently excited for estimating the uncertain parameters [Wittenmark, 1995]. The issue of estimating parameters from process data is a well studied problem in the literature, both in a stochastic framework [Ljung, 1987; Sage and White, 1977] as well as in a deterministic framework [Robertson *et al.*, 196; Rupen *et al.* 1998] and is not reviewed here.

The measurement-based optimization strategy is applied to the Baker's yeast fermentation problem. In this simulation study, the measured variable is the concentration of substrate. Note that the substrate concentration is an explicit function of the parameters k_1, and k_2. Hence the parametric estimation step in the general algorithm is not necessary. This algorithm is implemented for the fermentation for various extents of uncertainty in the two parameters k_2 and μ_m. The optimal substrate concentration is maintained via a PID controller. The results obtained for uncertainty in k_2 are summarized in Table 5. The second column of the table indicates the substrate concentration in the reactor at the switching time, t_{switch}. It should be noted that the switching time for all the runs is the same. However, the input policy obtained from the controller to maintain constant substrate concentration in the reactor is different for various extents of uncertainty. The percentage deviation of the amount obtained in closed-loop from the optimal solution is zero for all extents of uncertainty, indicating that the measurement-based optimization handles the uncertainty in the parameter k_2 effectively. The results obtained for uncertainty in μ_m are summarized in Table 6. It can be seen from the table that the amount of biomass obtained from closed-loop is equal to the optimal

***Figure 4**. Measurement-based Optimization Strategy*



value for a negative uncertainty in μ_m. However, the deviation is as large as 61% for positive uncertainty in μ_m, indicating that closed-loop method may not work very well for positive uncertainties in μ_m. This may be due to the high sensitivity of the process to uncertainty in μ_m. However, an adjustment could be made to the measurement-based strategy to minimize this deviation. It can be seen that the switching times vary between 2.5 and 7.6 hours corresponding to uncertainties ranging from +50% to -50%. Since the amount of biomass corresponding to positive uncertainties is deviating more, intuitively the nominal profile corresponding to the highest possible value of μ_m should give the best results. This has been verified by making the profile corresponding to $\mu_m = 0.75$ (+50% uncertainty) nominal. It can be seen from the results shown in Table 7 that the deviation of the amount of biomass obtained in closed-loop from the optimal value is negligible.

Simulator-Based Optimization Under Uncertainty

Process simulators (either developed in-house or by commercial vendors) offer a tightly integrated suite of simulation technologies for the process engineer. This integration between a steady state process model, a dynamic model, equipment sizing and equipment costing allows an engineer to seamlessly and realistically perform new design and troubleshooting quickly and accurately. The quality of chemical processes learning can be enhanced significantly by simulation of complex systems with user-friendly software. In addition to being user-friendly, simulators are especially useful when their real world analogs are expensive and/or dangerous. Simulations can introduce realistic problem situations and can be used to manipulate and analyze the process information without having to run the real experiments in the industry. Most chemical process industries such as oil and gas, petrochemicals, pharmaceuticals, and fine chemicals are turning towards process simulators to enhance the product yield and decrease capital expenditure. AspenTech, company that designed the simulator ASPEN, recently claimed that their process industry clients achieve measurable return on investment by reducing operating costs by up to 3%, decreasing the capital expenditures by up to 10% and improving engineering productivity by up to 30% [Chemical Engineering Progress,

Table 5. Effect of Uncertainty in k_2 on Closed-Loop Optimization

Uncertainty		$S \quad \sqrt{k_1 k_2}$ (kg/m^3)		t_switch (hr)		Objective J (kg of Biomass)		% Deviation
%	K_2	Closed loop	Optimal	Closed loop	Optimal	Closed loop	Optimal	
+50	750	15.81	19.36	3.77	3.55	1080.1	1082.5	0
+40	700	15.81	18.71	3.77	3.58	1064.2	1065.8	0
+30	650	15.81	18.03	3.77	3.62	1044.1	1048.7	0
+20	600	15.81	17.32	3.77	3.67	1026.1	1027.4	0
+10	550	15.81	16.58	3.77	3.72	998.1	1002.9	0
0	**500**	**15.81**	**15.81**	**3.77**	**3.77**	**973.4**	**973.4**	**0**
-10	450	15.81	15.00	3.77	3.84	940.4	945.1	0
-20	400	15.81	14.14	3.77	3.92	902.8	907.1	0
-30	350	15.81	13.23	3.77	4.02	858.1	858.3	0
-40	300	15.81	12.25	3.77	4.15	800.7	802.5	0
-50	250	15.81	11.18	3.77	4.33	731.2	735.8	0

2004].

However, the simulators today are generally used more for design and safety considerations of the process and less for process optimization. Most simulators have well-developed physical property data bank, phase equilibrium and kinetic data that can be used to simulate any chemical process with little effort. In this subsection, a simulator-based optimization is analyzed.

Most simulators offer the flexibility to perform several trials off-line, with excellent speed and accuracy. This feature of simulators makes them extremely useful in developing optimal operating policies in presence of uncertainty. The simplest version of simulator-based optimization is by trial and error. Simulations are first performed using nominal operating policy. This operating policy is repeatedly changed by trial and error till the optimum value is obtained. In this approach, optimization is carried out off-line, similar to the optimization step in measurement-based optimization. On the contrary, unlike measurement-based optimization, implementation of operation policy in this method is performed open-loop. The following basic procedure is followed:

1. Within a given minimum and maximum extents of uncertainty, optimal solutions are computed for a finite number of the fixed parameter values.

2. All the operating policies are implemented in the simulator and the outputs are measured for each run.

3. Among the set of outputs obtained from step 2, the best operating policy corresponding to parameter P^* is chosen and its performance is compared to that of the achieved solution.

Table 6. Effect of Uncertainty in μm on Closed-Loop Optimization

Uncertainty	m	t_switch Closed-Loop (hr)	J_Closed-Loop (kg of Biomass)	t_switch Optimal (hr)	J_Optimal (kg of Biomass)	% Deviation
+50 %	0.75	3.8	3971.0	2.5	10363.0	61
+40%	0.70	3.8	3573.9	2.7	6396.2	44
+30%	0.65	3.8	2663.5	2.9	3976.6	33
+20%	0.60	3.8	1990.6	3.2	2478.7	20
+10%	0.55	3.8	1485.8	3.4	1562.5	5
0%(Nominal)	**0.50**	**3.8**	**973.4**	**3.8**	**973.4**	**0**
-10%	0.45	3.8	607.4	4.2	608.1	0
-20%	0.40	3.8	379.5	4.7	380.6	0
-30%	0.35	3.8	236.7	5.4	237.7	0
-40%	0.30	3.8	148.1	6.3	148.4	0
-50%	0.25	3.8	92.4	7.6	92.7	0

4. If the difference between the two outputs in step 3 is negligible, the nominal operating policy corresponding to P^* is the optimum.

The above algorithm is tested via simulations for uncertainty in k_2. The results of the simulation are summarized in Table 8. For the purpose of illustration of this method, a black box process was created in MATLAB with a k_2 value of 450. Values from 250 through 750 are chosen for k_2 and the corresponding solutions are implemented in the simulator (containing the actual k_2) individually. It can be seen from these results that the maximum output was obtained between runs 6 and 8. Since the difference between achieved output and optimal output is less than 5%, the value 450 is chosen as the actual parameter value and the operating policy corresponding to this value is implemented in open-loop process. This value of 450 was exactly the value the simulator used for the process and hence it can be said that the trial and error method works for most practical purposes.

A variation of simulator-based optimization approach called switch-based approach is shown in Figure 5. The difference between this method and trial and error method lies in the iteration method of the optimization step. The basic procedure for this method is given below:

1. An approximate solution involving sequence of arcs and switching times is determined for the nominal model.

2. The approximate solution obtained from step 1 is sent to the simulator, which contains the accurate process model (black box).

Table 7. Effect of Uncertainty in μm on Closed-Loop Optimization: Modifying the Nominal Solution

Uncertainty	m	t_switch Closed-Loop (hr)	J_Closed-Loop (kg of Biomass)	t_switch Optimal (hr)	J_Optimal (kg of Biomass)	% Deviation
+50%(Nominal)	**0.75**	**2.5**	**10363.0**	**2.5**	**10363.0**	**0**
+40%	0.70	2.5	6395.1	2.7	6396.2	0
+30%	0.65	2.5	3982.4	2.9	3982.4	0
+20%	0.60	2.5	2487.6	3.2	2486.8	0
+10%	0.55	2.5	1557.7	3.4	1562.5	0
0%	0.50	2.5	973.4	3.8	973.4	0
-10%	0.45	2.5	607.4	4.2	608.1	0
-20%	0.40	2.5	379.5	4.7	380.6	0
-30%	0.35	2.5	236.7	5.4	237.7	0
-40%	0.30	2.5	148.1	6.3	148.4	0
-50%	0.25	2.5	92.3	7.6	92.7	0

3. If the output from the simulator is optimum, proceed to step 5.

4. If the output from the simulator is not optimum, the switching times in the operating policy are modified and steps 2 through 4 are performed until optimum.

5. The optimal operating policy is sent to the process and implemented in open-loop.

The value of the switching times is varied over a grid of values and the one that provides the best value of the objective function is chosen. This method was tested via simulations. As described above, a black-box process was first created in MATLAB where the values of k_2 and μ_m are fixed at 350 and 0.35 respectively for case 1 and at 650 and 0.65 respectively for case 2. Simulations are run to verify if switch-based method converges to these values. The results corresponding to uncertainty in μ_m are summarized in Table 9. The results indicate that the maximum amount for case 1 corresponds to run 3 and that for case 2 corresponds to run 9. It can be seen from the table that run 3 corresponds to a value of 0.35 and run 9 corresponds to 0.65 for μ_m, which clearly are the values the actual process used. Similar results were obtained for uncertainty in k_2 as shown in Table 10. In the table, run 2 and run 9 indicate that the optimum operating policy corresponds to the values 300 and 650 for k2 in case 1 and case 2 respectively. Although the optimum value for k_2 would have been 350 for case 1, the negligible difference between amounts obtained using both the values indicates that a value of 300 makes a negligible difference to the optimum amount of biomass.

Table 8. Results of Simulator-Based Trial and Error Method for Uncertainty in k_2

Run #	Guessed k_2* (kg/m^3)	Optimum t_switch for Guessed k_2*	Optimum Amount of Biomass (kg) for k_2*	Nominal Amount of Biomass (kg)
1	750	3.55	1082.5	909.9
2	700	3.58	1065.8	912.4
3	650	3.62	1048.7	918.7
4	600	3.67	1027.4	926.8
5	550	3.72	1002.9	933.5
6	500	3.**77**	973.4	**945.1**
7	450	3.84	945.1	941.0
8	400	3.92	907.1	935.3
9	350	4.02	858.3	875.6
10	300	4.15	802.5	163.7
11	250	4.33	735.8	60.0

Conclusions

In this paper, the effect of parametric uncertainty on a fed-batch fermentation for the production of Baker's yeast on the performance of nominal optimization strategies is investigated. It is shown that the solution obtained from the nominal optimization strategy does not remain optimal in presence of uncertainty. Two different strategies are proposed to efficiently handle parametric uncertainty in batch reactors. The first method is a measurement-based approach where process measurements are utilized to make on-line adjustments to the optimization routine. It is shown that this method offers considerable improvement over the conventional open-loop optimization under the influence of uncertainty and in the presence of batch-to-batch variation. However, the this method does not always guarantee an optimum under uncertainty and the accuracy of this method strongly depends on the estimation of parameters.

The second method proposed in this paper to handle uncertainty is simulator-based. This method utilizes a simulator as a black box process with accurate model and parameters. Simulations are run assuming various operating policies utilizing the simulator as if it were the real process. The operation policy that gives the best objective function is chosen as the optimum policy. Unlike the measurement-based approach, this method is an open-loop approach, since the optimal operating policy obtained from the black box simulations is implemented on the real process in open-loop.

The results obtained when these two methods are implemented on a Baker's yeast fermentation with uncertain parameters indicated that both approaches lead to improved performance over the conventional open-loop operation.

Figure 5. *Switch-Based Optimization Strategy*

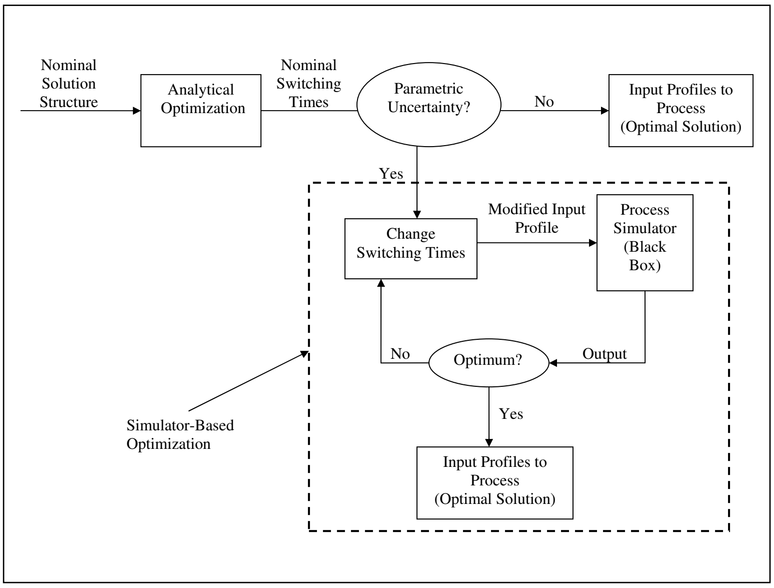


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Table 9. Results of Switch-Based Optimization Approach for uncertainty in μm

Run #	Guessed t_switch (t^*)	$_m$ for which t^* is Optimum	Amount obtained for Case1[14] (kg)	Amount obtained for Case2[15] (kg)
1	2.5	0.25	3593.5	201.3
2	2.7	0.30	3835.9	203.1
3	2.9	0.35	**3997.9**	205.0
4	3.2	0.40	60.1	207.7
5	3.4	0.45	60.0	210.5
6	3.8	0.50	60.0	216.1
7	4.2	0.55	60.0	222.2
8	4.7	0.60	60.0	229.7
9	5.4	0.65	60.0	**238.2**
10	6.3	0.70	60.0	60.0
11	7.6	0.75	60.0	60.0

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Table 10. Results of Switch-Based Optimization Approach for uncertainty in k_2

Run #	Guessed t_switch (t^*)	k_2 for which t^* is optimum	Amount obtained for Case1[16] (kg)	Amount obtained for Case2[17] (kg)
1	3.55	250	1045.4	779.6
2	3.58	300	**1054.8**	786.9
3	3.62	350	1046.5	793.1
4	3.67	400	1044.2	804.5
5	3.72	450	1037.5	815.1
6	3. **77**	500	1029.8	825.5
7	3.84	550	979.4	837.7
8	3.92	600	797.4	851.3
9	4.02	650	63.8	**859.8**
10	4.15	700	60.0	826.9
11	4.33	750	60.0	61.9