The Optimal Design of Dynamic Experiments

A robust and efficient algorithm is developed to calculate dynamic inputs for optimal experimental designs. Different objective functions are presented to allow designs for both model discrimination and the improvement of parameter precision. Time-varying inputs are calculated by reformulating the optimal design problem as an optimal control problem. This approach can provide large improvements in the ability to discriminate among a series of models, and then increase the accuracy of the resulting parameters.

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Introduction

The aim of experimental design is to select the values of experimental conditions (e.g., temperature, pressure, feed compositions) that optimize some objective, such as the discrimination among several models. Traditionally, experimental design has dealt with steady-state, constant-input experiments (Froment and Hosten, 1981). The use of transient experiments has meant the extension of these designs to models containing ordinary differential equations (Hosten and Emig, 1975, Kalogerakis and Luus, 1984). These techniques for the design of dynamic experiments are still based upon a coarse grid search over the range of the experimental conditions with time-constant values of the inputs. It has been shown, however, that properly selected time-varying inputs can offer considerable improvements. The form of these inputs is usually limited to step or square wave inputs and the reported results have considered only a single variable at a time. Hawkins (1978) and Kalogerakis (1984) considered dynamic experiments for model discrimination. Hawkins used an optimal control approach but presented only one simple example. Kalogerakis showed the advantages of time-varying inputs, but was restricted to periodic inputs.

Murray and Reif (1984) used periodic inputs to improve the parameter estimates for a packed-bed reactor. Step and square pulses were compared to square waves of varying frequency. The authors also demonstrated the advantages of using periodic inputs. There is, however, in general no reason why the optimal inputs should be periodic. Therefore, there is a need for a rigorous and efficient method for designing dynamic experiments with multiple time-varying inputs, and that is the subject of this paper.

We will consider in particular kinetic models for dynamic chemical reactors, consisting of sets of mixed differential and algebraic equations (DAE's):

$$\underline{f}(\underline{y}, \dot{\underline{y}}, \underline{\theta}, \underline{x}, t) = 0 \qquad \underline{y}\,(t = 0) = \underline{y}_0 \tag{1}$$

where $\underline{y}$ is an n-dimensional vector of state variables, $\dot{\underline{y}}$ is the derivative with respect to t (usually time), $\underline{x}$ is the set of experimental conditions, including both time-varying and constant conditions, and $\underline{\theta}$ is a set of constant parameters in the model.

This paper presents a systematic approach to the design of dynamic experiments that can combine a number of different experimental objectives and aims. The optimal experimental design problem is reformulated as an optimal control problem which is then solved using a robust and efficient algorithm. By using this approach a large number of variables, such as the levels of time-varying inputs, any constant experimental variables, initial conditions, and even the final time of the experiment can be optimized simultaneously.

In the next section we briefly review the criteria used for experimental design and their application to dynamic experiments. Then the optimal control problem is outlined and the traditional criteria are simplified for use in our algorithm. Finally, we present an example of the use of this design method for the sequential design of experiments for both model discrimination and precise parameter estimation.

Experimental Design Criteria

The two commonest experimental designs that have been considered in chemical engineering applications are for discrimination among a series of models and for the improvement of the precision of the parameters in a given model.

Model discrimination

Experiments to discriminate among a series of models are performed so that the differences between the responses of the models are maximized. Hunter and Reiner (1965) proposed that the design criterion should be

$$D(x) = \sum_{k=1}^{n_t} \sum_{i=1}^{m} \sum_{j=i+1}^{m} \Delta \underline{y}_{ijk}^T Q \Delta \underline{y}_{ijk} \tag{2}$$

where i and j are indices representing m different models; n_t is

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the number of data points; $\Delta \underline{y}_{ijk} = \underline{y}_i(t_k, \underline{x}) - \underline{y}_j(t_k, \underline{x})$ is the difference in response between model i and model j, at time t_k; Q is a diagonal scaling matrix that accounts for magnitude differences in the variables; and the state vector $\underline{y}^T = (\underline{y}_1^T \underline{y}_2^T, \ldots, \underline{y}_m^T)$.

Box and Hill (1967) used the concept of entropy as a measure of the uncertainty of distinguishing between models because Eq. 2 did not take into account the variance of the estimated response. A number of problems have, however, been associated with the Box-Hill criterion, mostly due to difficulties or inconsistencies in calculating posterior model probabilities required for the model discrimination. Other criteria have been defined (Buzzi-Ferraris et al., 1984) but we will not consider them in this paper.

Precise parameter estimation

Parameter precision is measured in terms of the variances of the parameter estimates, and a good design is one that minimizes the elements of the covariance matrix. In order to compare experiments, various real-valued functionals of the covariance matrix have been used as design criteria. For example, D optimality minimizes the determinant, A optimality minimizes the trace, and E optimality minimizes the maximum eigenvalue.

In order to calculate the optimal time-varying inputs for either precise parameter estimation or model discrimination, it is necessary to consider a systematic procedure that can optimize a large number of variables efficiently.

Formulation of the Optimal Control Problem

We can split the vector of experimental input conditions, $\underline{x}$, into two parts. One of these, $\underline{u}(t)$, includes the time-varying inputs, and the other, $\underline{v}$, includes the experimental conditions which are constant. These must all be calculated for an experimental design to optimize some design criterion. The optimal control problem in its basic unconstrained form is to fund $\underline{u}(t)$, which minimizes an objective J:

$$J = Jo[t_f, \underline{y}(t_f), \dot{\underline{y}}(t_f), \underline{u}(t_f), \underline{v}, \underline{\theta}, \underline{y}_0] + \int_{t_0}^{t_f} F[\underline{y}(t), \dot{\underline{y}}(t), \underline{u}(t), \underline{v}, \underline{\theta}, t]\, dt \quad (3)$$

where $\underline{y}(t)$ and $\dot{\underline{y}}(t)$ are defined by the system of DAE's, Eq. 1, and t_0 and t_f are the initial and final times.

This system can then be subject to various constraints:

Bounds on the initial conditions and the controls

$$\underline{a}^0 < \underline{y}_0 < \underline{b}^0 \quad (4)$$

$$\underline{a}^u < \underline{u}(t) < \underline{b}^u \quad (5)$$

Terminal constrants

$$\underline{a}^g < G[t_f, \underline{y}(t_f), \underline{u}(t_f), \underline{v}, \underline{\theta}, \underline{y}_0] < \underline{b}^g \quad (6)$$

The problem is then to find an admissible set of initial states, and controls to minimize Eq. 3 subject to Eqs. 1, 4, 5, and 6.

To solve this optimal control problem, the package VOPCON (Morison, 1984) is used. Morison uses a control vector parameterization method in which the controls $\underline{u}(t)$ are approximated by a finite dimensional representation. The time interval $[t_0, t_f]$ is divided into a number of subintervals each with a set of piecewise constant functions:

$$\underline{u}(t) = \Phi^j(t_j, z_j) \quad (7)$$

as in Figure 1.

The controls are defined by the constants z_j and the switching times t_j. In the simplest case, used in the present version of VOPCON, $\Phi^j = z_j$, that is, piecewise constant controls. These control levels $\underline{z}$ and the switching times $\underline{t}$ along with any initial states and any constant experimental variables that we can manipulate become decision variables for the nonlinear optimization algorithm VFO2AD (Powell, 1977). The algorithm used by VOPCON is briefly summarized below; for a more detailed discussion the reader is referred to the original reference.

Algorithm

1. Set up the problem by defining the system of model equations, the initial conditions, the objective function, the terminal constraints, the set of decision variables, and the initial guesses of these variables.
2. Integrate the system of equations to obtain $\underline{y}(t)$, up to t_f, and calculate the objective function and constraint values.
3. Calculate the gradients of the objective function and of each constraint, using a variational method. A system of adjoint equations is defined at the end point t_f, and these are then integrated backward in time from t_f to t_0. The gradients are defined by a quadrature rule.
4. Use the objective function, the constraint values, and their gradients to make a step in the nonlinear programming routine. If the nonlinear program converges, stop; otherwise repeat from 2.

Other authors have reformulated experimental design as an optimal control problem (Kalaba and Springarn, 1977) but have had severe numerical problems solving the optimal control problem. The use of VOPCON now allows the efficient calculations of these experimental inputs.

Simplification of the Design Criteria

In order to use the optimal control algorithm given above the objective function, Eq. 3, must be continuously differentiable. It

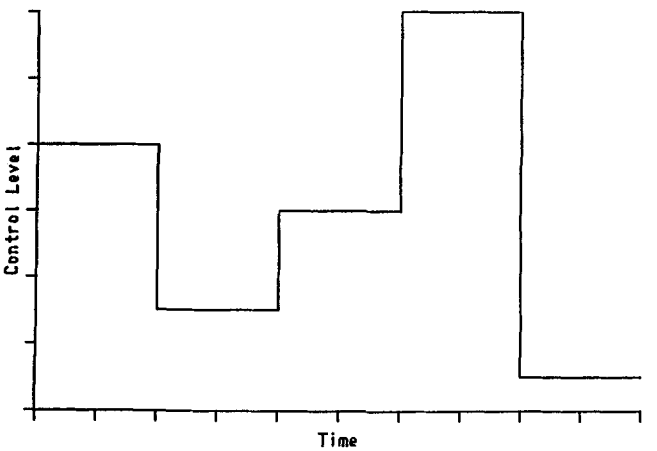

Figure 1. Piecewise controls implemented in VOPCON.

must also be relatively inexpensive to compute, because the computational load spent in evaluating the objective function and its gradients can be very high. The traditional criteria for steady-state experiments do not meet these requirements, and therefore need to be slightly modified.

Model discrimination

Following Hawkins (1978) and Kalogerakis (1984), it was considered adequate to use the simple Hunter-Reiner criterion in order to save computational effort. The summation over the data points is replaced by an integral over the interval $[t_0, t_f]$. The objective function for model discrimination is then defined as:

$$J_{md} = -\int_{t_0}^{t_f} \sum_{i=1}^{m} \sum_{j=u+1}^{m} [\Delta \underline{y}_{ij}^T(t)\, Q\, \Delta \underline{y}_{ij}(t)]\, dt \tag{8}$$

where $\Delta \underline{y}_{ij}(t) = \underline{y}_i(t) - \underline{y}_j(t)$.

In going from a discrete, Eq. 2, to a continuous function Eq. 8, we are strictly solving a slightly different problem. However, Hertzberg and Asbjørnsen (1977) used a similar approach in solving least-square problems for precise parameter estimation and the errors they observed as a consequence of the above approximation were much smaller than other errors—for example, those likely to be introduced by linearizations in the solution of experimental design problems (Emig and Hosten, 1974).

Precise parameter estimation

Calculation of the determinant or eigenvalues of the covariance matrix for each objective function evaluation could be done but would be prohibitively expensive. Also it would not be possible to supply analytical expressions for the derivatives except for small examples.

In practice, rather than calculating the covariance matrix directly, the inverse covariance matrix H is calculated and it is some functionals of H that are maximized. For dynamic models the covariance matrix is calculated using the method of Rosenbrook and Storey (1966):

$$V(\underline{\theta}) = H^{-1} \tag{9}$$

where

$$H = \sum_{r=1}^{n_t} G_r^T(t_r) D_r^T(t_r) M_r^{-1} D_r(t_r) G_r(t_r) \tag{10}$$

G_r is the sensitivity of the observations to the model variables (which is defined by the variables that are measured), M_r is the covariance matrix associated with the errors in the experimental measurements, and D_r is the sensitivity matrix of the responses to the parameters $[\partial \underline{y}/\partial\theta]$. For the case where G_r is the identity matrix and M_r is a constant diagonal matrix—that is, direct measurement of the variables and constant measurement noise—then

$$H = C \sum_{r=1}^{n_t} D_r^T(t_r) D_r(t_r) \tag{11}$$

where C is a scalar.

Since the elements of the inverse covariance matrix consist of the products of the sensitivities summed over all the data points, an optimal design maximizes some measure of the magnitudes of the elements of the sensitivity matrix. It is therefore proposed that the sensitivities should be optimized directly.

A criterion that maximizes all the sensitivities can be defined as:

$$J_{pp}^D = -\int_{t_0}^{t_f} \sum_{i=1}^{p} \sum_{j=1}^{n} W_{ij} \left[\frac{\partial \underline{y}_i}{\partial \theta_i}\right]^2 dt \tag{12}$$

where W_{ij} is a weighting factor.

The weighting factors determine which of the sensitivites should be given the most importance. In practice, the use of equal weighting ($W_{ij} = 1$, all i, j) has proved very successful, while remaining computationally inexpensive (Espie, 1986). It may, however, be possible to improve the performance further by defining W_{ij} as the ith element of the jth eigenvector of the covariance matrix. This would be very expensive, however, because W_{ij} would then be a nonanalytical function of $\underline{u}$ and require finite-difference calculation of the objective function gradients.

When there is no interaction between the parameters, that is, cov $(\theta_i, \theta_j) = 0$, the eigenvalues are the diagonal elements, and maximizing the sensitivities with respect to a parameter will minimize the variance of that parameter. Equation 12 is then equivalent to D optimality. In the more usual case with interaction between the parameters, there will be some off-diagonal terms in the covariance matrix, and there is no simple equivalence between the proposed criterion and D optimality. The new measure J_{pp}^D is, however, a norm of the inverse covariance matrix and does include all the interactions (off-diagonal elements). The main advantages associated with Eq. 12 are that J_{pp}^D is continuous with respect to $\underline{u}$, and can be optimized using optimal control techniques without the need for additional integrations or complex analytical differentiation.

All the sensitivities $[\partial \underline{y}/\partial\theta]$ are calculated by integrating the sensitivity equations (Bard, 1970) and this requires the integration of a further $n \times p$ equations in addition to the model equations. For the special class of problems that are ill conditioned but have only low interaction between the parameters, it is possible to reduce the computational load still further by only maximizing the sensitivities with respect to the parameter θ_e associated with the smallest eigenvalue of H. Our objective function is then:

$$J_{pp}^E = -\int_{t_0}^{t_f} \sum_{i=1}^{n} W_i \left[\frac{\partial \underline{y}_i}{\partial \theta_e}\right]^2 dt \tag{13}$$

where W_i is again a weighting factor.

This only increases the number of equations to be integrated to n equations. If there is moderate interaction, the sensitivities with respect to more than one parameter can be included in Eq. 13. This can be determined by investigating the eigenvector associated with the smallest eigenvalue. It is recommended that if more than two parameters must be included, then Eq. 12 should be used.

The following case study will show the improvements in the standard design criteria that can be achieved using the optimal design methods that have been described.

Example

In this section a complete case study is presented for the continuous yeast fermenter example first presented by Kalogerakis (1984), in which a stream containing an organic substrate (e.g., glucose) is fed to a well-stirred tank, and a model is sought to describe the substrate and biomass consumption. Optimal dynamic experiments are initially designed to select the best model from a set of candidate models, then to produce improved parameter estimates for the remaining model.

Model discrimination

Initially there were four competing models to describe the biomass and substrate consumption:

1. Monod kinetics with constant specific death rate

$$\dot{y}_1 = (r_m - k_4 - u_1)y_1$$

$$\dot{y}_2 = \frac{r_m}{k_3} y_1 + u_1(u_2 - y_2)$$

$$r_m = \frac{k_1 y_2}{k_2 + y_2} \tag{14}$$

with $\underline{k}^{(1)} = [0.30, 0.25, 0.56, 0.02]$.

2. Contois kinetics with constant specific death rate

$$\dot{y}_1 = (r_c - k_3 - u_1)y_1$$

$$\dot{y}_2 = \frac{r_c}{k_3} y_1 + u_1(u_2 - y_2)$$

$$r_c = \frac{k_1 y_2}{(k_2 y_1 + y_2)} \tag{15}$$

with $\underline{k}^{(2)} = [0.30, 0.03, 0.55, 0.03]$.

3. Linear specific growth rate

$$\dot{y}_1 = (r_l - k_3 - u_1)y_1$$

$$\dot{y}_2 = \frac{-r_l}{k_2} y_1 + u_1(u_2 - y_2)$$

$$r_l = k_1 y_2 \tag{16}$$

with $\underline{k}^{(3)} = [0.12, 0.56, 0.03]$.

4. Monod kinetics with constant maintenance energy

$$\dot{y}_1 = (r_m - u_1)y_1$$

$$\dot{y}_2 = -\left(\frac{r_m}{k_3} + k_4\right) y_1 + u_1(u_2 - y_2)$$

$$r_m = \frac{k_1 y_2}{k_2 + y_2} \tag{17}$$

with $\underline{k}^{(4)} = [0.30, 0.30, 0.55, 0.05]$.

In these four models y_1 and y_2 are the measured biomass and substrate concentrations in the bioreactor. The two controls u_1 and u_2 are the space velocity (h^{-1}) and the substrate concentration in the feed (g/L). For simplicity the initial conditions are fixed at $y_1(0) = 1.0$ g/L and $y_2(0) = 0.01$ g/L.

The true model is model 1 with the parameter values $\underline{k} = [0.31, 0.18, 0.55, 0.03]$. Artificial measurements were generated by adding normally distributed noise with zero mean and a standard deviation of 0.2 g/L. Initially, a fixed final time of 72 h was used for all the experimental designs, with a sampling time of 0.75 h. By using only one control interval over the period t_0 to t_f, the special case of optimal constant inputs was also calculated using VOPCON. The values of the constant inputs giving the maximum divergence were $u_1 = 0.2\ h^{-1}$ and $u_2 = 35$ g/L and this gave an overall divergence, $D(\underline{x})$, of 71,759. Figures 2 and 3 show the biomass and substrate responses of the fermenter, compared to the predictions from the four models. Kalogerakis (1984) considered the case where u_2 had a square wave input, and the best square wave produced a value of $D(\underline{x})$ of 84,040.

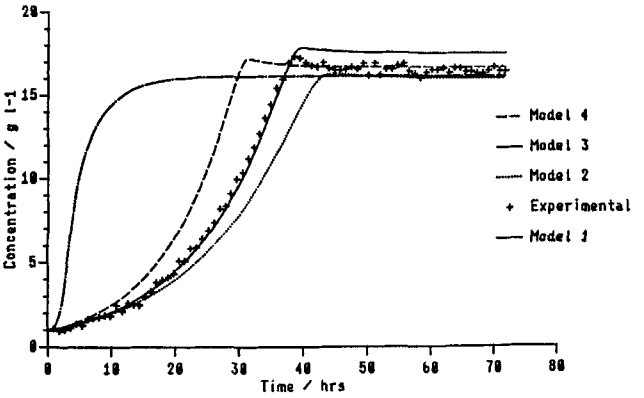

Figure 2. Biomass concentration with a constant feed.

In order to calculate the optimal time-varying inputs, all the models were integrated simultaneously and Eq. 8 was used as the objective function. Both controls and the switching times were optimized over three control intervals, with the initial guess of u_1 being constant at 0.2 h^{-1} and u_2 being a square wave input between 5 and 35 g/L.The optimal solution, Figures 4 and 5, was found in 10 iterations and 10 function evaluations. The optimal value of $D(\underline{x})$ was 91,006, an increase of 26.8% over the constant inputs and 8.2% over the best square wave input.

After updating the parameters, model adequacy tests can be performed to determine if any of the models can be discarded. A full review of model adequacy tests is given by Froment and Hosten (1981), but for this example it was assumed that the standard deviation of the measurement noise was known so that a χ^2 test could be performed on the experimental data. The procedure of experimental design, parameter estimation, and model

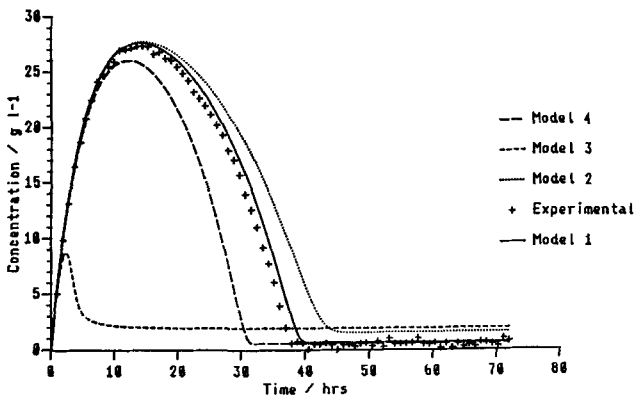

Figure 3. Substrate concentration with a constant input.

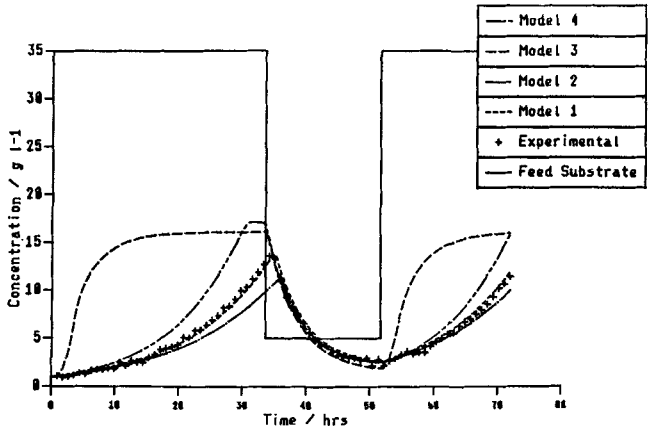

Figure 4. Optimal input for model discrimination: biomass concentration.

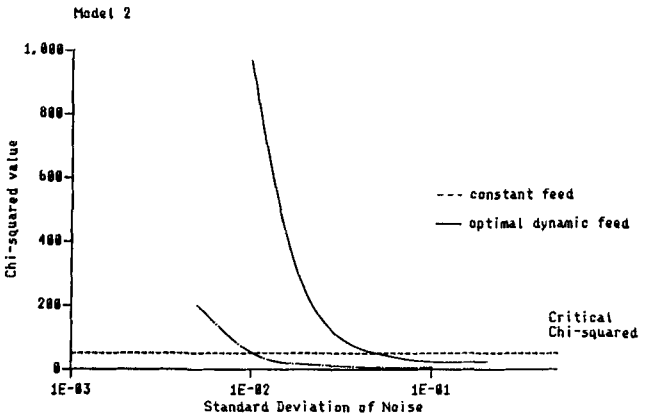

Figure 6. Discrimination criterion as a function of measurement noise.

adequacy testing could then be repeated until a satisfactory model had been found.

The discrimination achievable between a series of models is dependent upon the measurement noise. In our case we could arbitrarily choose the variance of the measurement noise. Figure 6 compares the discrimination achieved with constant input and optimally designed experiments over a range of noise levels for model 2. For this example the noise levels can be up to eight times higher if experiments with optimal dynamic inputs are used.

This example has assumed that a fixed final time is used. It is also possible to use the optimal control approach to optimize the final time along with control inputs. If pure discrimination is of interest and there is no cost associated with the experiment, then the optimum is to extend the experiment for as long as possible. The optimum solution has a form very similar to Figures 2 and 3, with u_2 being repeatedly switched from 35 g/L for approximately 33 h to 5 g/L for 18 h, then back to 35 g/L. If the cost of the experiment is a concern, the objective function could, for example, be divided by t_f, which corresponds to optimizing the discrimination per unit time. In this case it was found that it is more efficient to run a series of short experiments with steps of 33h length.

Once a model has been shown to be adequate by the discrimination tests then a series of experiments can be performed to improve the precision of the parameters. With an experimental noise of 0.2 g/L, either model 1 or model 4 would be adequate after the first experiment. For this study, model 1 is used in the following section.

Precise parameter estimation

The designs for precise estimation were calculated using the parameter values estimated after the model discrimination experiment. Figure 7 shows the first designed experiment based upon Eq. 12. After each experiment the parameters are reestimated and a new experiment designed. Figure 8 shows a comparison of the determinant of the inverse covariance matrix between constant inputs and a sequence of optimally designed experiments, and this shows that there is an increase in the determinant of H ($\underline{\theta}$) of up to an order of magnitude when using optimal dynamic experiments.

When the eigenvalues of the inverse covariance matrix were calculated, it was found that the eigenvalues of k_2 and k_3 were of similar magnitude, much smaller than the other two eigenvalues and highly correlated. In order to maximize the smallest eigenvalue of H, it was necessary to include both the sensitivities with respect to k_2 and k_3 in Eq. 13. Unless both sets of sensitivities were maximized the smallest eigenvalue was transferred between the two parameters. Providing that both sensitivites were maximized, then the minimum eigenvalue could be increased.

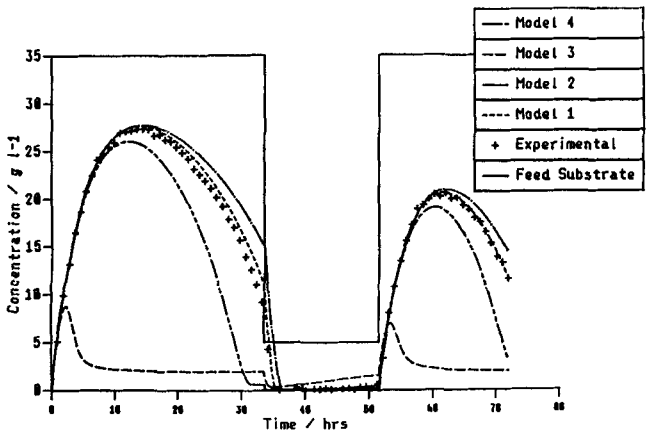

Figure 5. Optimal input for model discrimination: substrate concentration.

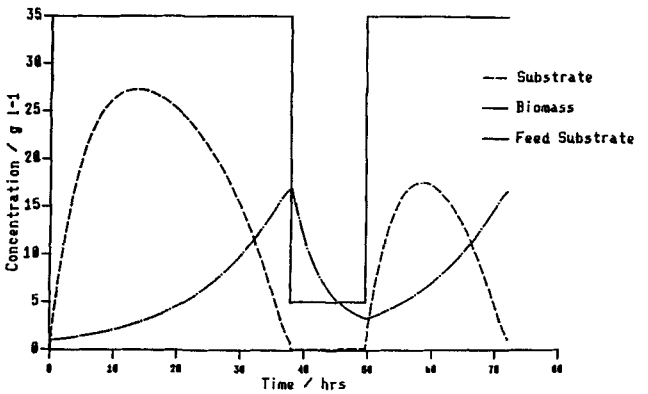

Figure 7. Optimal experiment for improving parameter precision with determinant criterion.

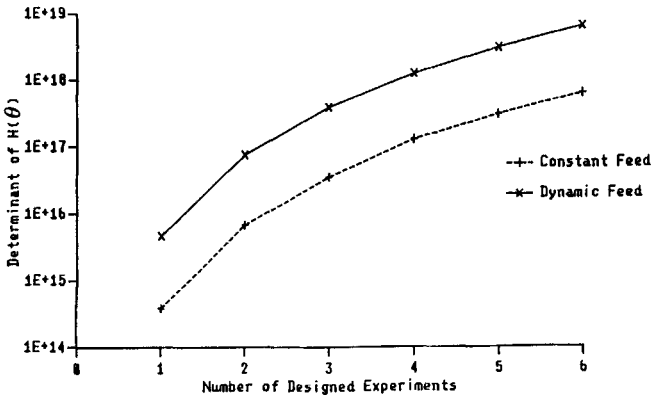

Figure 8. Determinant of inverse covariance matrix.

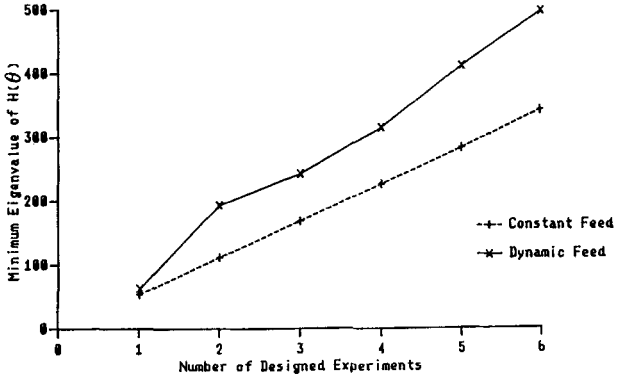

Figure 10. Minimum eigenvalue of inverse covariance matrix.

Figure 9 shows the first experiment using Eq. 13 and Figure 10 shows the minimum eigenvalue of H for a series of sequential experiments. In this case the optimal experiments increased the minimum eigenvalue of H ($\underline{\theta}$) by almost 100% over six experiments.

Conclusions

The design of dynamic experiments has been posed as an optimal control problem, and solved using an efficient, easy to use algorithm. The advantage of this approach is that optimal dynamic inputs can be generated for experiments for both model discrimination and precise parameter estimation using the same algorithm. It is also possible to test a variety of experimental conditions, and to optimize the most important of these simultaneously. The resulting experimental designs often can improve the accuracy of the parameters by an order of magnitude and provide large increases in the ability to discriminate between rival dynamic models.

Some computational difficulties may arise when the number of variables that need to be optimized is large, and VOPCON may then become limited by the performance of the optimization algorithm. Scaling of the variables is important since the gradients tend to vary widely in magnitude. Since local optima may exist, the initial guesses of the controls can be important and several different initial guesses should be used to test the result.

On the other hand, the optimization does not have to be converged very tightly to produce much improved experiments. An advantage of the method presented is that it is not restricted to the particular choice of objective functions used in this work and other forms may be equally suited. Similarly, dynamic inputs are not restricted to piecewise constant controls, and other functions containing adjustable parameters may be used. An example using piecewise linear controls was presented by Espie and Macchietto (1986).

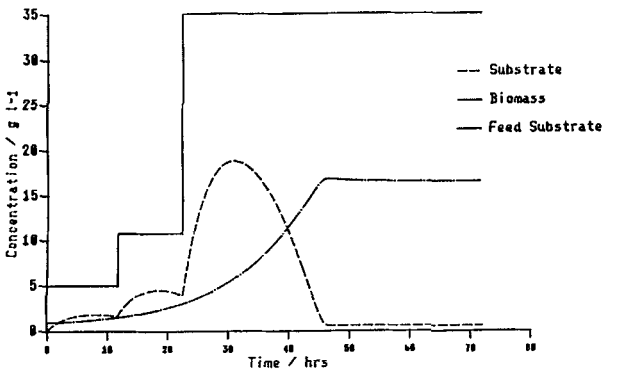

Figure 9. Optimal experiment for improving parameter precision with minimum eigenvalue criterion.

Notation

$\underline{a}^0, \underline{a}^u, \underline{a}^g$ = lower bounds on initial conditions, controls, and point constraints
$\underline{b}^0, \underline{b}^u, \underline{b}^g$ = upper bounds on initial conditions, controls, and end point constraints
f = dynamic model
$D(\underline{x})$ = model discrimination criterion
$\underline{D}_r$ = sensitivity matrix
F = objective function
G_r = sensitivity of observations to state variables
G = end point constraints
$H(\underline{\theta})$ = inverse covariance matrix
J, J_0 = objective functions
J_{MD} = criterion for model discrimination
J^D_{pp}, J^E_{pp} = criteria for precise parameter estimation
m = number of models
n = number of state variables
n_t = number of measurements
p = number of constant parameters
Q = diagonal scaling matrix
t = time
t_0, t_f = initial and final times
$\underline{u}(t)$ = time-varying controls
$\underline{v}$ = constant experimental conditions
$V(\underline{\theta})$ = covariance matrix
W_{ij}, W_i = weighting factors
$\underline{x}$ = vector of experimental conditions
$\underline{y}, \underline{\dot{y}}$ = state variables and their derivatives with respect to t
$\underline{y}_j$ = state variable vector for model j
$\underline{y}_0$ = initial conditons of state variables
z_j = piecewise control levels
$\underline{\theta}$ = time-invariant parameters
χ^2 = chi-squared statistic

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