On Adaptive Optimal Input Design: A Bioreactor Case Study

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The problem of optimal input design (OID) for a fed-batch bioreactor case study is solved recursively. Here an adaptive receding horizon optimal control problem, involving the so-called E-criterion, is solved "on-line," using the current estimate of the parameter vector θ at each sample instant $\{t_k, k = 0, \ldots, N - h\}$, where N marks the end of the experiment and h is the control horizon for which the input design problem is solved. The optimal feed rate $F_{in}^{*}(t_k)$ thus obtained is applied and the observation $y(t_{k+1})$ that becomes available is subsequently used in a recursive prediction error algorithm to find an improved estimate of the actual parameter estimate $\hat{\theta}(t_k)$. The case study involves an identification experiment with a Rapid Oxygen Demand TOXicity device (RODTOX) for estimation of the biokinetic parameters μ_{max} and K_S in a Monod type of growth model. It is assumed that the dissolved oxygen probe is the only instrument available, which is an important limitation. Satisfactory results are presented and compared to a "naïve" input design in which the system is driven by an independent binary random sequence. This comparison shows that the OID approach yields improved confidence intervals on the parameter estimates. © 2006 American Institute of Chemical Engineers *AIChE J,* 52: 3290–3296, 2006
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Introduction

The problem of optimal input design (OID) has received ample attention in the identification literature. Indeed, it is one of the classical identification problems that seeks to address an essential question for the model developer, that is, whether it is possible to design a certain experiment in such a way that the parameters in the model structure can be uniquely identified and, moreover, how to design an input signal that minimizes (respectively, maximizes) an a priori chosen norm of the Fisher information matrix (FIM) associated with the specific experimental setup and corresponding input signal. We shall not elaborate too extensively on the historical developments in this interesting field of study, but will only summarize some recent developments that have been reported on the subject. For some historical work we refer to, for example, Mehra,[1] Goodwin and Payne,[2] and Walter and Pronzato,[3] who give a more general account of the developments in optimal input design. Our main goal in the current study is to focus on the OID problem for a specific case study that seems to be relevant in the field of bioprocess control and, in addition, to introduce a new *adaptive* approach that solves the input design problem for a specific case study "on-line," meaning that the best (current) estimate of the set of parameters θ, that is, $\hat{\theta}(t_k)$ is used to design an optimal input signal with respect to a cost criterion (including the FIM), after which the current estimate is "optimally" updated to $\hat{\theta}(t_{k+1})$ using a so-called recursive parameter estimation algorithm.

Recently, we have found analytical solutions for OID signals with respect to one specific parameter θ_i in the model structure.[4-7] In this case the FIM reduces to a scalar value that may be optimized using a singular control law that can be applied on

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a singular arc in state space that may be reached by a bang-bang control. The singular control law is derived by solving a set of algebraic equations, generated through repeated differentiation of the Pontryagin optimality condition $d\mathbf{H}/du \equiv 0$ on the compact interval $[t_1, t_2]$, where $\mathbf{H}$ is the familiar Hamiltonian associated with the process model and a goal function that, essentially, depends on the parametric output sensitivities $dy(t)/d\theta$. The solution of this set of algebraic equations yields an *explicit* expression for the input function $u(t)$. In addition, if the cost criterion involves the trace of the inverse of the FIM, that is, the A-criterion, the input design problem may also be solved analytically and involves a maximization of the output sensitivities of *a number of parameters* for which an optimal input signal needs to be found.[7]

Recent work of Versyck[8] and co-workers includes the solution of the OID problem, with respect to the modified E-criterion, for several case studies using an approach in which the dynamic evolution of the sensitivity equations is analyzed in detail. This analysis is subsequently used to arrive at an optimal control problem that may be solved numerically, yielding an optimal switching time, initial substrate concentration, and substrate set-point concentration for a fed-batch reactor case study. An optimal modified-E criterion is achieved for this experimental setup.

Although the reported analytical and numerical results are promising, their application in a practical case study involving a real experimental setup is still limited. This is especially the case in biochemical case studies where (1) the number of sensors is usually limited, meaning that not all the states can be measured directly; (2) the sensors themselves may be very costly; and (3) may also involve high measurement uncertainties that deteriorate the parameter estimate $\hat{\theta}$ drawn from an experimental setup and corresponding input design. The search for more advanced algorithms that allow inclusion of these limitations is therefore a challenging problem that has an important practical significance. In addition, to our knowledge the literature does not show an example in which the OID problem is solved *in tandem* with a recursive parameter update scheme, although this seems to be a natural choice. This is even clearer after realizing that both the OID problem and the parameter estimation problem include the output parametric sensitivities to (1) arrive at the FIM for the experiment and (2) to arrive at a gradient $dy/d\theta$ pointing to a direction where a minimum of the innovations residuals (with respect to some norm) can be found. However, let us first introduce some formal definitions to be able to be more specific in our discussion.

Definitions

Let the general, possibly nonlinear, model structure $\mathcal{M}(\theta)$ for a specific system be given by

$$\frac{dx(t)}{dt} = f[x(t),\, u(t),\, \theta] \tag{1}$$

$$y(t_k) = h[x(t_k),\, u(t_k),\, \theta] + \eta(t_k) \tag{2}$$

where f: $\mathbb{R}^n \times \mathbb{R}^r \times \mathbb{R}^p \to \mathbb{R}^n$ is a real valued vector function, that is, the dynamical model, h: $\mathbb{R}^n \times \mathbb{R}^r \times \mathbb{R}^p \to \mathbb{R}^m$ is the observation (or read-out) equation, θ is a p-dimensional vector of time-invariant parameters, $x(t)$ is the n-dimensional state vector, $u(t)$ is the r-dimensional input vector, and $y(t)$ is the m-dimensional output vector. We further assume that the observations $Y(t_N) = \{y(t_k), 0 \le k < N\}$, where N marks the end of the experiment, is contaminated with a Gaussian white measurement noise process $\{\eta(t_k), 0 \le k < N\}$ with covariance matrix R. Note that the above model definition is in continuous-discrete format, which is a natural notation for physically based models, often used in biochemical and mechanical engineering.

The Optimal Control Problem

Because we seek to optimally identify the parameter set θ our control problem may be defined as follows:

$$\max_{u \in \mathbb{U}_{\text{adm}}} \phi(t_k) = \|F(\theta, t_k)\|_E \tag{3}$$

under the dynamical constraints (Eq. 1), including the dynamical evolution of the local parametric output sensitivities $y_\theta(t) \triangleq dy(t)/d\theta$, which can be derived straightforwardly from the model and observation equations (Eqs. 1 and 2, respectively). Here, $\mathbb{U}_{\text{adm}}$ is the set of admissible controls. In the above we have chosen, with some foresight into what follows, to use the so-called E-criterion of the Fisher information matrix (F), that is, maximization of its minimal eigenvalue at the final time t_f. Other criteria such as D-, modified E-, or A-criterion, may be applied—each with its own advantages/disadvantages.[9]

Note that the cost function $\phi(t_f)$ in the above depends on the parameters θ whose values are not known a priori and its value therefore needs to be estimated. Let $u^*(t_k \mid t_k)$ denote the optimal input calculated on the basis of the estimate $\hat{\theta}(t_k)$, having processed the data record $Y(t_k)$. Then, a natural choice for a solution of the input design problem at time instant t_k is to

(1) Use the current estimate $\hat{\theta}(t_k)$ and solve the optimal input design problem (Eq. 3) over a time horizon $[t_k, t_{k+h}]$.

(2) Apply the "optimal" input $u^*(t_k \mid t_k)$ thus obtained on the interval $[t_k, t_{k+1}]$, assuming for simplicity a zero-order-hold mechanism for the input signal $u^*(t_k \mid t_k)$.

(3) Sample the system at time instant t_{k+1}, thereby obtaining a new measurement $y(t_{k+1})$.

(4) Process the new measurement to find an improved value of the current estimate $\hat{\theta}(t_k)$, yielding $\hat{\theta}(t_{k+1})$, and repeat the procedure using $\hat{\theta}(t_{k+1})$.

In summary, our approach is to solve the above identification problem as an adaptive receding horizon optimal control problem that processes the parameter estimates recursively each time an observation $y(t_{k+1})$ becomes available.

Our choice for the recursive parameter reconstruction algorithm to update the estimate $\hat{\theta}(t_k)$, in step (4) above, is a so-called recursive prediction error algorithm in continuous-discrete format.[10,11] The advantage of this specific algorithm is that it includes the parametric sensitivities of the states, that is, $W \triangleq dx(t, \hat{\theta})/d\theta$, in a natural way as to arrive at an estimate of the gradient $dx(t, \hat{\theta})/d\theta$, which is used to minimize the prediction error of the prediction $\hat{y}(t_{k+1}, \theta)$. The algorithm achieves this minimization through calculation and subsequent interpretation of the innovation

$$\varepsilon(t_k) = y(t_k) - \hat{y}[t_k, \hat{\theta}(t_k)] \tag{4}$$

which is, loosely speaking, the mismatch of the last model prediction $\hat{y}[t_k, \hat{\theta}(t_k)]$ with respect to the current sample $y(t_k)$. The interpretation of the innovation is performed through calculation of a gain matrix, which is assumed at steady state for the state vector and is calculated explicitly on the basis of a variance-covariance matrix $P_{\theta\theta}(t_k)$ for the estimated parameters in the model structure. Because the parametric sensitivities $W(t)$, an $n \times p$ matrix, become available once the receding horizon optimal control problem is solved at time instant t_k [step (1) in the above procedure], these sensitivities can be used immediately for an update of the parameter vector $\hat{\theta}(t_k)$. Thus, the recursive prediction error framework, as applied here, provides a unifying perspective on the problem of optimal input design in tandem with recursive parameter estimation, given that both algorithms use the same sensitivity functions—each, however, for its own distinctive goal.

The Case Study

The case study we seek to address here has been defined in the work by Vanrolleghem and Daele.[12] To determine the biokinetic parameters $\mu_{\max}$ and K_S, an identification experiment with a so-called Rapid Oxygen Demand TOXicity (RODTOX) device can be conducted and respirometic data can be obtained. Generally speaking, the respirogram characterizes the healthy state of a biomass concentration [$C_X(t)$] and may be used, for instance, to identify a toxic alarm, that is, the respirometric signature obtained with a RODTOX device may be "nonstandard," meaning that the biomass does not perform healthily because of the presence of a toxic substance in the feeding substrate [$C_S(t)$].

The biokinetic model for the RODTOX device may be presented in a more general context, that is, as a fed-batch reactor in which substrate (including dissolved oxygen) is fed into the reactor with a feed rate $F_{in}(t)$, instead of "only " one initial impulse substrate concentration at the very beginning of the experiment. We assume that the dissolved oxygen concentration in the feeding substrate is at saturation level, that is, it is not affected by the solute or the presence of bacteria, which are assumed not to be present in the feeding substrate. The consumption of substrate by the bacteria in the reactor is aerobic and directly affects the dissolved oxygen concentration in the vessel. A dynamic model of the process reads:

$$\frac{dC_{DO}(t)}{dt} = k_{La}[C_{sat}^{en} - C_{DO}(t)] - OUR(t) + \frac{F_{in}(t)}{V(t)}[C_{sat} - C_{DO}(t)] \quad (5)$$

$$\frac{dC_X(t)}{dt} = \mu[C_S(t)]C_X(t) - \frac{F_{in}(t)}{V(t)}C_X(t) \quad (6)$$

$$\frac{dC_S(t)}{dt} = -\frac{\mu[C_S(t)]}{Y}C_X(t) - \frac{F_{in}(t)}{V(t)}[C_{S_{in}}(t) - C_S(t)] \quad (7)$$

$$\frac{dV(t)}{dt} = F_{in}(t) \quad (8)$$

Table 1. Biokinetic Parameter Values, Together with Initial Estimates of the Parameters in the Two Optimal Adaptive Input Designs Experiments with the RODTOX Device*

	$\bar{\theta}$	$\hat{\theta}(0)$
$\mu_{\max}$	$2.62 \cdot 10^{-4}$	$5.0 \cdot 10^{-4}$
K_S	1.0	0.5
Y	0.64	N/A

*From Vanrolleghem and Daele.[12]

$$OUR(t) = (1 - Y)\frac{\mu[C_S(t)]}{Y}C_X(t) \quad (9)$$

$$\mu[C_S(t)] = \frac{\mu_{\max}C_S(t)}{K_S + C_S(t)} \quad (10)$$

$$y(t_k) = (1 \quad 0 \quad 0)\begin{bmatrix} C_{DO}(t) \\ C_X(t) \\ C_S(t) \end{bmatrix} + \eta(t_k) \quad (11)$$

where k_{La} is the reaeration constant (1/min); $V(t)$ is the volume of the solvent (L), including biomass and substrate; C_{sat}^{en} is the saturation concentration of dissolved oxygen (DO), including a small (constant) correction for the endogenous respiration of the biomass (mg/L); C_{sat} is the (normal) saturation concentration of dissolved oxygen (mg/L); $\mu_{\max}$ is the maximum specific growth rate (mg/min), K_S is the saturation constant (mg/L), Y is the yield coefficient of biomass on substrate [mg(C_X)/mg(C_S)]; $OUR(t)$ is the oxygen uptake rate of the biomass in the reactor [mg/(L·min)]; and $\eta(t_k)$ is a discrete-time white noise process reflecting measurement uncertainty.

It is important to note that in the above model it is assumed that there are *DO data only* and no biomass concentration data, nor substrate data, nor oxygen uptake rate data [OUR data would require differentiation of the dissolved oxygen data with respect to time and would therefore be sensitive to high frequencies in the measurement noise process $\eta(t_k)$]. This limitation in available observations (both qualitative and quantitative) imposes a challenging optimization problem. Indeed, the limited sensor availability causes the problem of reconstructing $\mu_{\max}$ and K_S to be badly defined. Moreover, the reconstruction of these parameters from noise-corrupted data is hampered because of the same measurement noise process and, although the two parameters are theoretically identifiable, practical identification from these data is indeed very difficult.[13] At the root of this persistent problem lies a *correlation* between the parametric sensitivities

$$y_{\mu_{\max}}(t) \triangleq \frac{dy(t)}{d\mu_{\max}} \quad \text{and} \quad y_{K_S}(t) \triangleq \frac{dy(t)}{dK_S}$$

Results and Discussion

In a numerical experiment the true values for the parameters and initial conditions were set to the values summarized in Tables 1 and 2. The goal function to be minimized was chosen to be the E-criterion, meaning that maximization of the minimum eigenvalue of $F(t_f)$ was desired. Other criteria, such as the modified E-criterion and the D-criterion, were considered too but it appeared that the modified E-criterion was extremely difficult to achieve. Between the E-criterion and D-criterion,

Table 2. Initial Values for Dissolved Oxygen, Substrate, and Biomass Concentrations (mg/L)

$C_S(0)$	0.0
$C_{DO}(0)$	7.0
$C_X(0)$	4000

the best results were obtained using the E-criterion and these results will therefore be presented here. An important variable in the numerical experiment is the control horizon h, whose value influences the "smoothness " of the optimal solution $u^*(t_k \mid t_k)$ on the prediction-horizon interval $[t_k, t_{k+h}]$. A workable value appeared to be $h = 4$ min. Because the discretization variable $\Delta t = t_{k+1} - t_k$ was set to 10 s, the optimal control algorithm optimized 24 constant input values $u^i(t_k \mid t_k)$, $i = 1 \cdots 24$, on the interval $[t_k, t_{k+h}]$. As stated earlier, this optimization was performed each time after the next dissolved oxygen observation $y(t_{k+1})$ was processed by the recursive prediction error algorithm to improve the actual estimate $\hat{\theta}(t_k)$. Clearly, the computational burden can become intense if a finer discretization grid or larger control horizon is chosen a priori. The presented values for h and Δt, however, turned out to give "manageable " CPU times on a personal computer platform. The observations $y(t_k)$ were generated "*on-line* " through simulation of the true system, after which a measurement noise with a variance $R = 0.05$ was added to the simulated values.

Initial conditions for the specific setup

To make a good comparison of the adaptive optimal input design solution this case was compared with an identical case, but now with a random binary input sequence with a switching probability $P = 0.5$. Implementation of this sequence causes the substrate feed-rate pump to switch from $F_{in}(t) = 0$ to $F_{in}(t) = F_{\max} = 0.2$ L/min at random on the switching times t_k, $k = 0, \ldots, N$ (see Figure 1, bottom). Figure 1 shows the adaptive optimal receding horizon inputs for both cases. It is interesting to see that the optimal result is to inject a pulse of substrate into the reactor at about 3 min, *after* the recursive estimator has already learned from the initial "modest " feeding phase where the feed rate is only small. This pulse causes the uncertainty in the estimate of $\mu_{\max}$ to decrease substantially, as desired (Figure 2, top left). Note also that the tail of the optimal input signal $u^*(t_k)$ exhibits slight "ringing " behavior, causing the feed pump to add small pulses of substrate that, on average, represent an almost constant, small feed rate. These small pulses are added after the biomass has settled in a short zero feeding phase, just after the large pulse of substrate. It is also interesting to see that the confidence intervals for the parameter K_S are much smaller in the adaptive optimal receding horizon case than in the case of a random binary input sequence (Figure 2, right two panels). Apparently, the random binary sequence is not sufficiently exciting the dynamics in the bioreactor to deduce a reliable estimate of the half-saturation constant. This confirms the well-known fact that estimation of the parameter K_S from oxygen (uptake) data is difficult in practice and requires a careful design.

Figure 3 shows both the unobserved and observed state estimates generated by the recursive prediction error algorithm. Clearly, the algorithm is capable of tracking the dissolved oxygen dynamics in the bioreactor sufficiently well. The unobserved states were also found to be reliable reconstructions. The optimal input sequence $u^*(t_k \mid t_k)$ causes the dissolved oxygen state to settle down in an almost steady state after the increased oxygen demand because the substrate pulse at 3 min

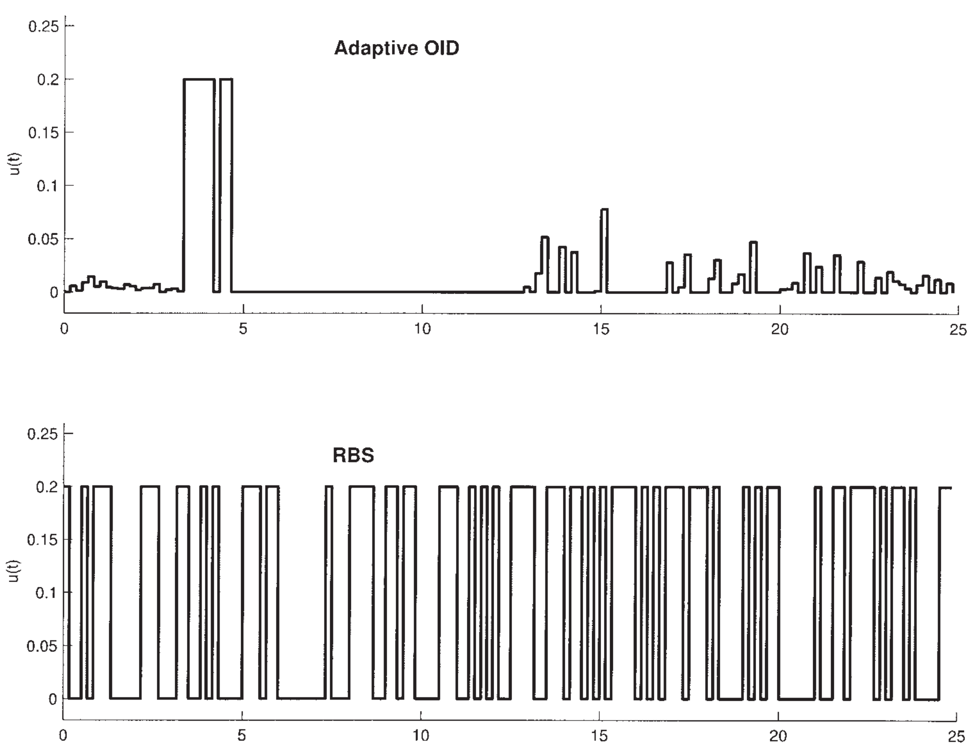

Figure 1. Optimal adaptive receding horizon input (top) and random binary sequence input.

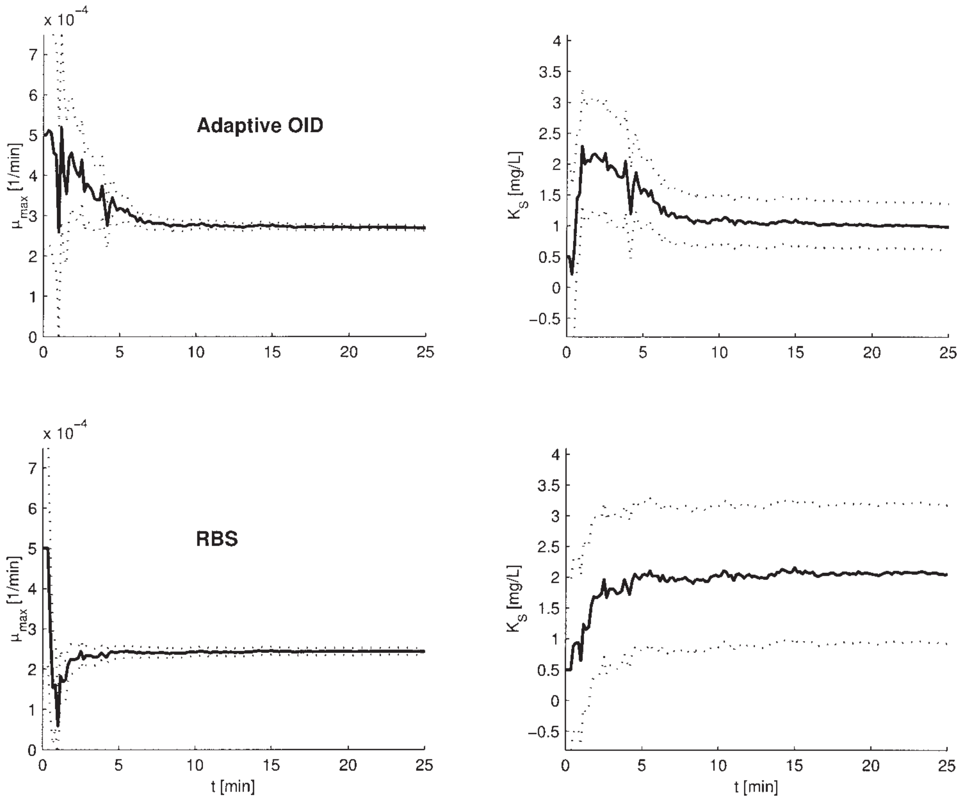

Figure 2. Optimal adaptive receding horizon estimates including parametric uncertainties.

The top two figures are generated by a recursive prediction error algorithm with OID input signal; the bottom two figures are generated by the same recursive prediction error algorithm, but now for the case of a random binary input sequence.

has decayed away. In this steady state the recursive estimator is learning at only a small rate because the confidence intervals on the parameter estimates do not decrease substantially after nearly 8 min (Figure 2). Finally, a good indicator for the information content of the conducted experiment is to inspect the trajectories of the FIM elements $\{f_{ij}(t), i, j = 1, 2\}$. Figure 4 presents these trajectories, including the evolution (in time) of the goal function (E-criterion) for the two cases of adaptive optimal receding horizon control and random binary sequence control. Clearly, the information content for the parameter K_S, corresponding to $f_{22}(t)$ in Figure 4, substantially increases if the input is carefully designed using an E-criterion. This is confirmed after calculating the corresponding ellipsoids for estimates of the parameters $\hat{\mu}_{max}$ and $\hat{K}_S$ at two time instances, that is, $t_0 = 5$ min when the experiment has just started and $t_f = 25$ min when the experiment is finished (see Figure 5). The major and minor axes of the ellipsoids reflect the information content of the parameters in the experiment, which clearly increases when applying adaptive optimal input design. Maximization of the E-criterion causes the minor axis of the ellipsoids to increase substantially in comparison to a "naïve" random binary sequence input design and the adaptive optimal input design is therefore to be preferred.

Conclusions

An adaptive receding horizon optimal control problem was solved using a (direct) optimal control algorithm in tandem with a recursive prediction error algorithm. For more details on the algorithms used we refer to Bryson[14] (optimal control and dynamic optimization) and the work of Stigter[11,15] (recursive estimation and its application in environmental case studies). The specific fed-batch case study shows that the combination of these two algorithms yields satisfactory results that can be implemented "on-line." The specific solution obtained here includes a small feeding phase, followed by a substrate pulse, after which the feed rate is switch off for a short time interval and continues at a small constant feed rate. It was argued that if the experiments are costly and involve a limited number of sensors, then the approach may prove very useful.

Generally speaking, first-principle models, based on a sound physical foundation, are vehicles of our hypotheses and, as such, are rewarding because they provide insight into the process under study. It is well known that it is increasingly difficult to derive these types of models if the process is complex and exhibits a myriad of interactions between numerous states and their associated parameters. In fact, the growth model considered in our case study may be regarded as "black-box" and it is considered an archetypical model that has shown its value in many instances. It is important to focus on optimal input design studies as presented in the current study because the search for better confidence intervals on the parameters in the model structure, obtained by the input/output data record, increases the validity, or otherwise, of the model structure as a whole for both physically based and "black-box" type of models.[15] Optimal input design tools may therefore become very useful in the search for a satisfactory model for a complex biochemical system such as presented here or, for example, in the classical "biochemical oxygen demand–dissolved

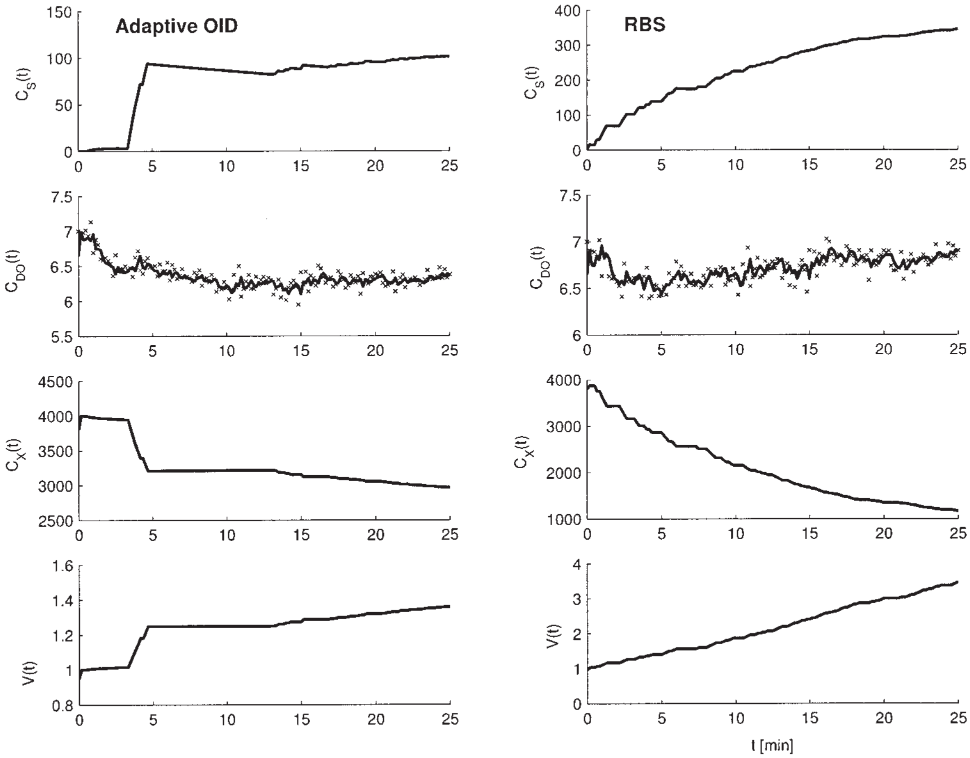

Figure 3. State estimates, that is, *unmeasured* signals $C_X(t)$, $C_S(t)$, and $V(t)$, and *measured* signal $C_{DO}(t)$, generated by a recursive prediction error algorithm.

True and estimated states were both plotted and can hardly be discerned in these figures.

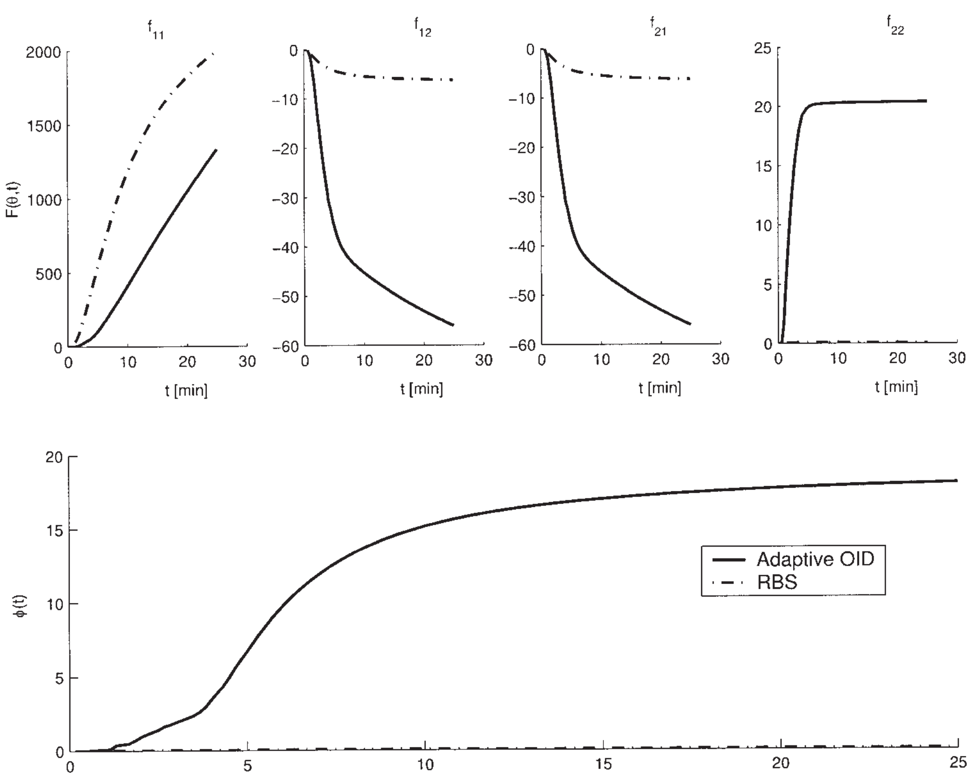

Figure 4. Fisher information matrix (FIM) elements trajectories $\{f_{11}(t), f_{12}(t), f_{21}(t), f_{22}(t)\}$ and the evolution of the E-criterion for both cases.

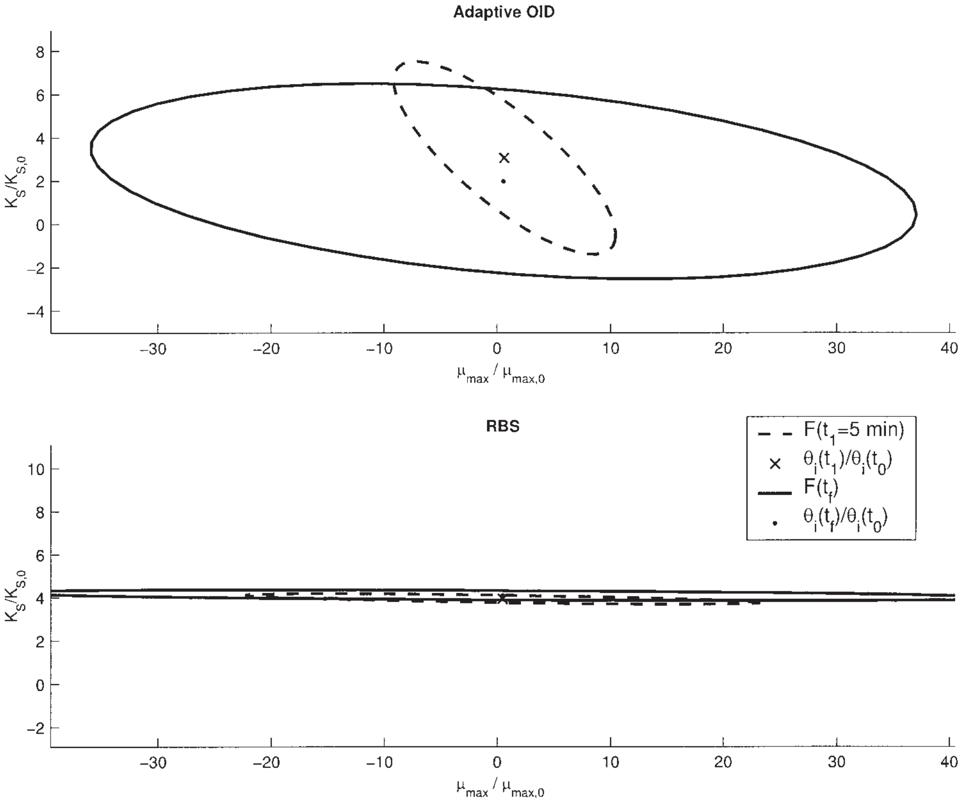

Figure 5. Ellipsoids of the FIM at time $t = 5$ min and $t = 25$ min for the adaptive receding horizon case (top) and the random binary sequence case (bottom).

Clearly, the adaptive receding horizon approach yields a more informative experiment in comparison to the random binary sequence approach.

oxygen ” interaction model, often used in water quality modeling.[16] Although not all these systems may be controlled freely at will, meaning essentially that the set $\mathbb{U}_{adm}$ can indeed be very small, one could progress similar to the avenue taken by Vanrolleghem and Daele,[12] where a small pilot plant was constructed that allows a broader range of admissible input signals and subsequent excitations. In these cases an adaptive optimal input design algorithm may be applied, not only to estimate the values of the parameters in the model structure, but to assess the validity of the model as a whole.

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