Adaptive Multirate State and Parameter Estimation Strategies with Application to a Bioreactor

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The design and development of a multirate software sensor for use in the chemical process industry are presented. The measurements of process outputs that arrive at different sampling rates are formally accommodated into the estimation strategy by using the multirate formulation of the iterated extended Kalman filter. Measurement delays associated with some of the process outputs are included in the system description by addition of delayed states. Observability issues associated with state and parameter estimation in a multirate framework are discussed and modified measurement equations are proposed for systems with delayed measurements to ensure relatively "strong" system observability. The evaluation of the proposed multirate state and parameter estimator through simulations and an experimental application on a fed batch fermentation system gave satisfactory performance and illustrated the practicality of this approach.

Introduction

This article addresses issues related to continued monitoring of process outputs when they are measured at infrequent and/or irregular times with or without a delay. Such problems are frequently encountered in typical chemical and biochemical processes when it is often difficult to measure the key process variables on-line on a regular basis due to lack of adequate sensors. In addition, even if such measurements are possible, there may be delays between the time the samples are taken and when the actual measurements are obtained due to elaborate assay procedures. Typical examples of traditional chemical processes where such problems arise are fermentation reactors, distillation columns, and polymerization processes. In particular, this study examines the issues of software sensors or inferential estimators in the context of classic control concepts of system observability and Kalman filters based on state-space system descriptions.

Inferential estimation strategies have been and continue to be used to address the above problems just mentioned. An inferential estimation strategy uses frequently available measurements of secondary process outputs whose behavior is correlated with that of primary output (process variables or outputs that need to be carefully monitored and/or controlled) via a process model that describes the correlation, to generate frequent regular estimates of the primary output. If the process is time-varying, the process model can be estimated and updated in an adaptive framework. Early work in the area of inferential estimation for chemical processes for the time-invariant case was done by Brosilow and co-workers (Brosilow, 1978; Joseph and Brosilow, 1978). Morari and Stephanopoulos (1980) have discussed strategies for optimal selection of secondary measurements to perform state estimation in the face of persistent unknown disturbances. Applications in the area of inferential estimation for bioprocesses include the work by Mou and Cooney (1983), Stephanopoulos and San (1984), and Bastin and Dochain (1990). In the study by Mou and Cooney (1983), elemental cell balances based on an empirically derived molecular formula for the biomass formed the inferential model that related secondary outputs such as the carbon dioxide evolution rate (CER) to the biomass (primary output) growth. In the antibiotic fermentation considered by them, a different correlation was used in the production phase to account for the time-varying process behavior resulting from the changing maintenance activity of the culture. To account for noise in real time measurements and also simultaneously estimate critical parameters of the culture such as specific growth rate and the culture states, Stephanopoulos and San (1984) proposed the extended Kalman filter (EKF) approach. They recommended compensation of the secondary measurements for the maintenance activity if the latter was significant. The EKF is, however, known to be very sensitive to modeling errors and can generate biased estimates of the states in the pres-

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ence of model plant mismatch. In a different approach to simultaneous state and parameter identification, Ramirez (1987) and Chattaway and Stephanopoulos (1989) used the Kalman filter coupled with the sequential parameter updating strategy of Ljung and Soderstrom (1983) to perform the state and parameter estimation. Park and Ramirez (1990) have also successfully applied the preceding strategy to regulate nutrient levels in a bioreactor. They assumed, however, that the primary state variables such as the biomass and substrate concentrations were measurable on an on-line basis.

The performance of inferential estimation strategies proposed earlier can be made more robust by formally incorporating the infrequently available primary measurement. With the advent and possible application of on-line flow injection sampling and analysis systems (Reda and Omstead, 1990) or by including infrequent "off-line" monitoring of the bioprocess, such measurements can be made available only at slow sampling rates. It thus appears logical to incorporate these infrequently available measurements formally as feedback information to the estimator, that is, use this information to correct the frequent estimates of the primary states that are generated inferentially from the frequently available secondary measurements. To achieve this objective when the process is time varying, adaptive multirate system identification strategies need to be used to formally accommodate the two or more sampling rates that exist in such a scenario. Guilandoust et al. (1987, 1988) proposed an adaptive multirate inferential estimation algorithm in state space and transfer function form. Lu and Fisher (1990) have formulated the multirate estimation problem such that the working equations explain the inferential relationships in a more fundamental way and thus have formally proved the convergence properties of such an inferential control algorithm. Tham et al. (1991) have used an adaptive inferential estimation algorithm in a multirate framework to estimate process variables in various processes such as polymerization reactors, distillation columns, and continuous fermentors. All of the preceding approaches to the problem of multirate identification carry out the adaptation of a transfer function model of the process. While such a black box approach has inherent advantages with respect to global applicability, it is also useful to study the parameter adaptation of a state-space model that results from a qualitative or structural description of the process. The merits of the latter lie in the use of *a priori* information such as mass and energy balances, albeit in a qualitative form, for performing estimation. The model parameters in such a state-space description also have a physical significance in relation to the process. Such *a priori* process information is not directly usable in the transfer-function-based approaches. It is also often difficult to relate transfer-function parameters to the physical parameters of the actual process.

The main contribution of this article is the introduction of a novel approach to address the problem of adaptive multirate filtering and estimation. To generate optimally filtered estimates of the primary states when the measurements arrive at different sampling rates, the model-based multirate Kalman filtering strategy of Glasson (1980, 1983) is used. The model that is used is the type that would result from direct linearization and discretization of the mass and energy balance equations based on a qualitative description of the process. To adapt the model used for the inferential estimation to the time-varying characteristics of the process, a Bayesian formulation of the multirate Kalman filter is used so as to include estimation of the time-varying parameters. The deterioration in estimator performance caused by nonlinearities in the measurement equation is addressed by using the iterative version of the extended Kalman filter (Jazwinski, 1970) expressed in a multirate framework. Delays, that result due to relatively long analysis times in elaborate off-line assay procedures, are accounted for in the proposed formulation by incorporating delayed state variables in the state-space model. The incorporation of delayed states increases the order of the model and thus reduces the relative observability of the overall system. Therefore, to enhance system observability, we propose retaining past measurements in the output equations. Thus, a simple yet robust method to ensure relatively strong system observability at all sampling instants has been incorporated. The resulting multirate, iterative, extended-Kalman-filter-based sensor is evaluated by simulated and experimental applications on antibiotic fermentations involving the microorganism *Streptomyces clavuligerus*.

Problem Formulation

Consider the following state description of the process:

$$\dot{\boldsymbol{x}} = f(\boldsymbol{x}, \boldsymbol{u}, \boldsymbol{\theta}, t) + \boldsymbol{\xi}(t) \tag{1}$$

$$\boldsymbol{z} = \boldsymbol{g}(\boldsymbol{x}, \boldsymbol{u}, \boldsymbol{\theta}, t) + \boldsymbol{\eta}(t) \tag{2}$$

where $\boldsymbol{\xi}$ and $\boldsymbol{\eta}$ are both zero mean, independent noise processes with unspecified distributions. The state vector $\boldsymbol{x}$ could consist of states such as reactant/product concentrations in a semibatch exothermic reactor or biomass/substrate concentrations in a fed-batch bioreactor. In a chemical or a biochemical process, these are the states of primary interest but are, however, sampled slowly, sometimes off-line, due to lack of adequate on-line sensors. We term these state variables as primary variables. A suitable requirement for control is that these measurements be available more frequently. Let the size of the state vector $\boldsymbol{x}$ be n. θ is the vector of time-varying system parameters. These parameters are modeled as zero mean white noise processes with unspecified distributions. Thus,

$$\dot{\boldsymbol{\theta}} = \boldsymbol{w}(t). \tag{3}$$

Let the dimension of θ be $n\theta$. Commonly, the time-varying parameters θ are appended to the system state $\boldsymbol{x}$ to constitute an augmented state vector $\boldsymbol{X} = [\boldsymbol{x};\theta]$. The augmented system description can be written as,

$$\dot{\boldsymbol{X}} = \boldsymbol{F}(\boldsymbol{X},\boldsymbol{u},t) + \boldsymbol{\xi}_1(t) \tag{4}$$

$$\boldsymbol{z} = \boldsymbol{G}(\boldsymbol{X},\boldsymbol{u},t) + \boldsymbol{\eta}(t) \tag{5}$$

where $\boldsymbol{\xi}_1 = [\boldsymbol{\xi};\boldsymbol{w}]$. The preceding augmented description is clearly nonlinear either due to inherent nonlinearities in the system description Eqs. 1 and 2 and/or due to bilinear product terms consisting of the states in $\boldsymbol{x}$ and the parameters in θ. $\boldsymbol{z}$ is the measurement vector that, at some instants, could

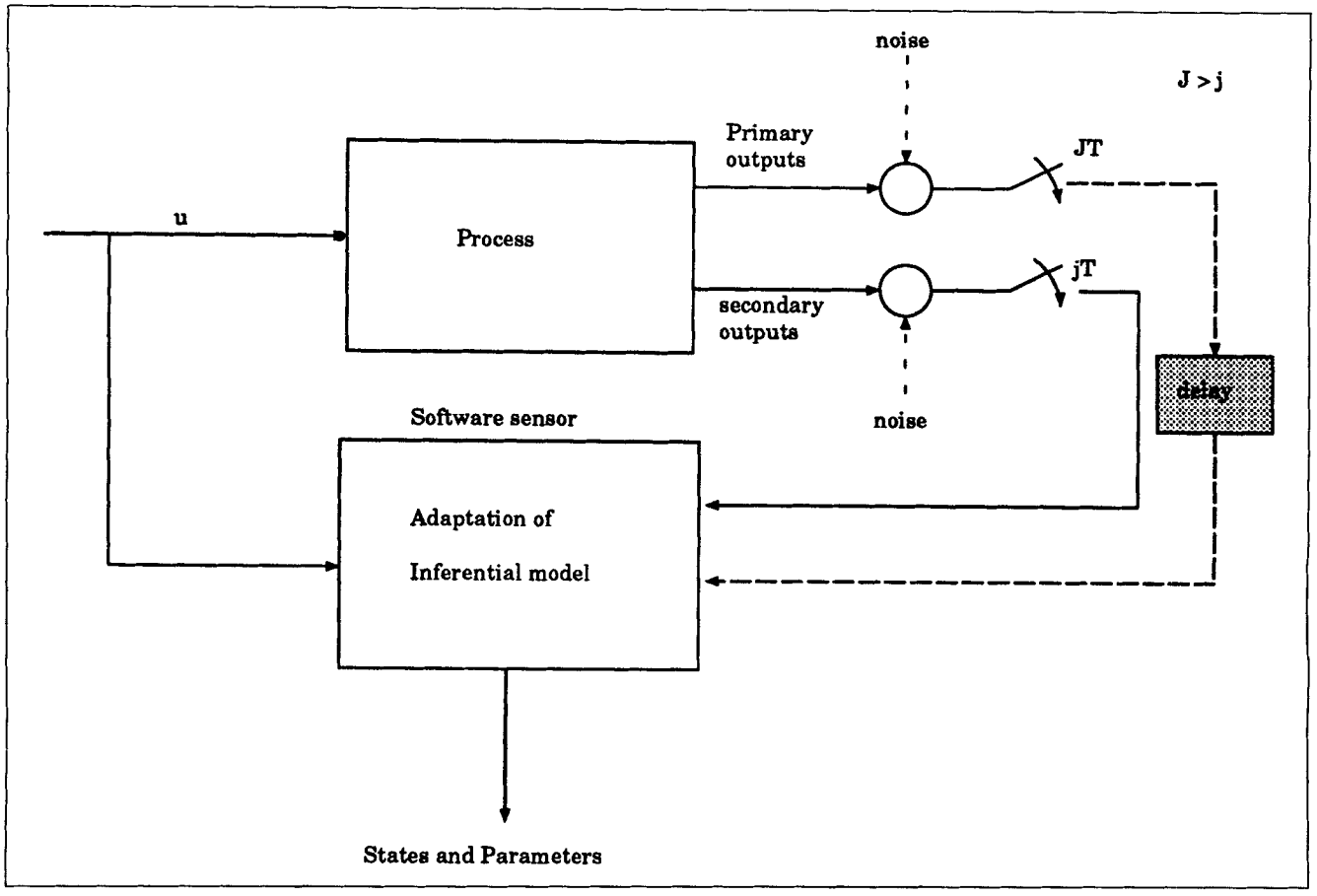

Figure 1. Multirate sampling for chemical processes.

consist of both primary as well as other inferential, secondary measurements. At some other sampling instants, only the secondary measurements could be available. If *ns* secondary outputs exist, the dimension of z would be $n + ns$ or ns, depending on the measurement set available at any sampling instant. The secondary measurements relate to those process outputs whose behavior is correlated with that of the primary states and that can be used with the process model in an inferential estimation scheme to generate estimates of the primary states, that is, they are process outputs from which the primary states are observable. The secondary measurements are available more rapidly than the primary ones due to availability of robust on-line sensors. Therefore there exists a multirate sampling scenario where the measurements of the primary states are available only slowly and the secondary measurements are available more rapidly. Such a scenario can be depicted as seen in Figure 1. We term the sampling instant at which both the primary and secondary measurements arrive as the major sampling instant and the sampling instant at which only secondary measurements are taken as the minor sampling instant. We also term the time elapsed between two minor sampling instants as the basic sampling time τ.

Many strategies to estimate the primary states from only the secondary measurements have been proposed. These range from the model-based Bayesian filtering strategies such as the Kalman filter for linear time-invariant systems to the extended Kalman filter (EKF) for nonlinear, time-varying systems. In a recursive implementation, the EKF is prone to divergence problems due to repeated linearization of the process model around the filter's latest states estimate. The latter problem causes any initial error/model mismatch to propagate, which eventually leads to divergence. When the states in the state vector represent physically measurable variables in the system such as would result from a linearization and discretization of the mass and energy balance equations of a system, it is logical to use these slowly sampled primary measurements as feedback information to the estimator and thus make the estimation more robust. In earlier studies, Gudi and Shah (1993) and Gudi et al. (1993) used a Kalman filter coupled with a sequential parameter updating strategy in a multirate framework to perform the state and parameter identification. However, it was not possible to tailor this strategy for the case of measurement delay. Furthermore, tuning guidelines for robust performance of the overall algorithm could not be easily expressed. In this article, we address the preceding problems by using a Bayesian approach in a multirate extended Kalman filter framework.

Multirate Software Sensor

Multirate iterated extended Kalman filter

We first present the equations for the extended form of the linear multirate Kalman filter. Linearizing Eq. 4 around

the latest state prediction $\bar{X}(i)$ and discretizing using a sampling time τ yields,

$$\delta X(i+1) = \phi \delta X(i) + \Gamma \delta u(i) + \xi_1(i) \tag{6}$$

where ϕ and Γ are the linearized and discretized system matrices and $\delta(.)$ denotes the perturbation or the deviation operator. At the major sampling instant when the measurements of both primary as well as the secondary variables are available, the measurement vector $z = z_{\text{major}}$ is of a larger dimension $(n + ns \times 1)$. The linearized, discrete measurement equation can be written by linearizing Eq. 5 at the major sampling instant as,

$$\delta z(i)_{\text{major}} = H_{\text{major}} \delta X(i) + \eta_{\text{major}} \tag{7}$$

where

$$H_{\text{major}} = \frac{\delta G_{\text{major}}}{\delta X} | X = \bar{X}(i) \tag{8}$$

is the linearized measurement matrix at the major sampling instant and has dimensions $n + ns \times n + n\theta$. The measurement noise covariance matrix corresponding to the major sampling instant $R_{z,\text{major}} = E(\eta_{\text{major}}, \eta^T_{\text{major}})$ would also be a larger diagonal matrix of measurement noise covariances. The Kalman gains can then be evaluated at the major sampling instant as,

$$K_{\text{major}} = MH^T_{\text{major}} \left(H_{\text{major}} MH^T_{\text{major}} + R_{z,\text{major}} \right)^{-1} \tag{9}$$

where M is the *a priori* estimate of the covariance matrix. Note that the Kalman gain matrix (size $n + n\theta \times ns + n$) is a larger matrix with as many columns as the number of measurements. At the minor sampling instants, only the inferential secondary measurements are available and the measurement vector $z = z_{\text{minor}}$ is of a smaller dimension (size $ns \times 1$). The linearized measurement matrix H_{minor} is also a smaller matrix (size $ns \times n + n\theta$) with as many rows as the number of measurements. The linearized measurement equation can be written as,

$$\delta z(i)_{\text{minor}} = H_{\text{minor}} \delta X(i) + \eta_{\text{minor}} \tag{10}$$

where

$$H_{\text{minor}} = \frac{\delta G_{\text{minor}}}{\delta X} | X = \bar{X}(i). \tag{11}$$

The measurement noise covariance matrix $R_{z,\text{minor}}$ corresponding to the minor sampling instants would then be a diagonal matrix of measurement noise covariances with an appropriately smaller dimension. The Kalman gains for the minor sampling instant can then be written as

$$K_{\text{minor}} = MH^T_{\text{minor}} (H_{\text{minor}} MH^T_{\text{minor}} + R_{z,\text{minor}})^{-1}. \tag{12}$$

Note that for the minor sampling instant, the Kalman gain matrix is a smaller matrix (size $n \times ns$) with as many columns as the number of measurements. The overall extended Kalman filter equations in multirate form are therefore the same as those of the classical extended Kalman filter, but with periodicity in Kalman gains, measurement and process covariance matrices. The two-step formulation of the time-varying Kalman filter (Franklin et al., 1990) can then be used to express the extended Kalman filter in its multirate form as:

(a) Major sampling instant:

(i) Measurement update:

$$\hat{X}(i) = \bar{X}(i) + K_{\text{major}} \epsilon(i) \tag{13}$$

$$\epsilon(i) = z_{\text{major}} - G_{\text{major}} \tag{14}$$

$$P(i) = M(i) - K_{\text{major}} H_{\text{major}} M(i). \tag{15}$$

(b) Minor sampling instant:

(i) Measurement update:

$$\hat{X}(i) = \bar{X}(i) + K_{\text{minor}} \epsilon(i) \tag{16}$$

$$\epsilon(i) = z_{\text{minor}} - G_{\text{minor}} \tag{17}$$

$$P(i) = M(i) - K_{\text{minor}} H_{\text{minor}} M(i). \tag{18}$$

To perform the measurement update at every sampling instant, predictions of the state X and the covariance M are required. These are obtained using the time update equations by performing an actual integration of the nonlinear augmented system description. Thus,

$$\dot{X} = F(\hat{X}, u, t) \tag{19}$$

$$\dot{M} = F_X P + P F_X^T + Q \tag{20}$$

where F_X is the Jacobian of the augmented system description and is given as,

$$A_{(n,n)} = \frac{df}{dx} \tag{21}$$

$$F_X = \begin{bmatrix} A & \mathbf{0} \\ \mathbf{0} & I_{n\theta, n\theta} \end{bmatrix}. \tag{22}$$

The measurement update step at any instant could be interpreted as a step toward minimization of the objective function of the estimation/measurement error suitably weighed by the covariance matrices. For linear time-invariant systems, the Kalman gain represents the necessary information for this minimization quite accurately and therefore the measurement update step, when performed once, minimizes the relevant objective function. For a nonlinear system, however, the extent to which the Kalman gain represents the minimization information is dependent on the reference trajectory around which the system linearization is done. If an *a priori* nominal trajectory is chosen, the information accuracy depends on how close the nominal trajectory is to the true one. If the linearization is done around the latest state estimates, the information accuracy depends on filter performance itself, and the objective function may not be necessarily

minimized in one step of the measurement update equation. This motivates the use of an iterated version of the extended Kalman filter equations (Denham and Pines, 1966; Jazwinski, 1970). The iterated extended Kalman filter (IEKF) has been recommended for strong nonlinearities in the output equation and has been successfully used for fermentation processes by Bellgardt et al. (1986) and Sargantanis and Karim (1994). The iterated version of the extended Kalman filter equations can be expressed as shown below: Assume that the state prediction $\bar{X}(i)$ is available at instant i, then the local recursive scheme can be invoked by initializing $\gamma(1)$ to be equal to $\bar{X}(i)$ and then recursing over the equation,

$$\bar{\gamma}(k+1) = \bar{X}(i) + K[\bar{\gamma}(k)]\{z_i - G[\bar{\gamma}(k), u(i)] - H[\bar{\gamma}(k)](\bar{X}(i) - \bar{\gamma}(k))\}, \quad k = 1, \ldots, l. \tag{23}$$

The Kalman gains K and the linearized output matrix H are based on the latest estimate $\gamma(k)$. As has been shown by Denham and Pines (1966), significant improvements in the estimates occur in the first few local iterations. Nevertheless, the previous equation is iterated until there is no significant improvement in any successive estimates of γ. The preceding locally iterated EKF-based strategy has been used in a multirate framework in this work, for robust estimation. The iterative extended multirate Kalman filter formulation can thus be used to formally incorporate the slowly sampled primary measurement into the overall filtering and estimation scheme. It is important to note that the previous multirate formulation does not require a fixed integer ratio of the minor and major sampling instants. In earlier approaches to multirate identification (Lu and Fisher, 1990; Guilandoust et al., 1987) using transfer function models, it was required that the major sampling time arrives every fixed integer, say J, sampling intervals of the minor sampling instants. This is too restrictive a requirement for the resulting strategy to be generally applicable at an implementation level. The preceding multirate Kalman filter formulation is more flexible as it simply uses a different set of equations at the major sampling instants whenever the primary measurements arrive, and otherwise switches back to the inferential equation set at the minor sampling instants.

Measurement delays

Typically, measurement of the primary state could involve sampling followed by elaborate off-line assays in the laboratory, thus leading to a delay in the availability of the results of sampling. Such delays can easily be incorporated into the system model equations by addition of delayed states. Consider, for simplicity, the following discrete state-space model:

$$\delta x(i+1) = \phi \delta x(i) + \Gamma \delta u(i) + w(i) \tag{24}$$

$$\delta z(i) = H \delta x(i) + v(i). \tag{25}$$

Assume for simplicity that there is only one sampled state x_1 in the state vector x. The measurement relationship H is then equal to 1. If the state x_1 is sampled with a measurement delay of t_d time units, the equations to obtain the delayed state x_m in continuous time can be written as

$$x_m(t) = x_1(t - t_d). \tag{26}$$

Assuming for simplicity that the delay time is an integral multiple of the basic sampling time, τ, we can write the delay equations for the case of $t_d = 2\tau$, in terms of perturbation variables in the discrete domain as

$$\delta x_2(i+1) = \delta x_1(i) \tag{27}$$

$$\delta x_3(i+1) = \delta x_2(i) \tag{28}$$

where x_2 and x_3 are the delayed states. The corresponding measurement equation should also then be modified to indicate that the measurement of the primary state arriving at any instant i relates to the delayed state x_3 and not to x_1. Thus, the overall augmented system description can be written as

$$\delta X(i+1) = \phi_1 X(i) + \Gamma \delta u(i) + w(i) \tag{29}$$

$$\delta z(i) = H_1 \delta X(i) + v(i) \tag{30}$$

where

$$\phi_1 = \begin{bmatrix} \phi & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix} \tag{31}$$

$$H_1 = [0 \quad 0 \quad H]. \tag{32}$$

The augmented system consisting of the basic system states and the delayed states can now be considered as representative of the system behavior. In general, measurement delays reduce system observability and deteriorate estimator performance. However, as will be shown in the modified observer formulation, it is possible to enhance system observability by using past inferential measurements in the measurement equation. Thus, the preceding equations, along with the modified observer formulation, can be used to effectively address the problems posed by measurement delays in the primary variables.

Comments on system observability

Implicit in the foregoing development is the basic assumption that the augmented system consisting of the original system states, time-varying parameters, and delayed states is completely observable from the process outputs. This needs to be verified before the strategy can be used. For nonlinear systems, observability properties are relatively difficult to verify (Ray, 1981). It is often recommended that the tools developed for observability analysis of linear systems be used for nonlinear systems by considering a linearized approximation of the latter about some nominal, *a priori* assumed trajectory. Thus, the observability matrix can be constructed for the linear approximation of the nonlinear system and conditions on the positive definiteness of the information matrix (Jazwinski, 1970) or the rank of the observability matrix can be applied to ensure system observability. It must be noted that linear filters constructed for nonlinear systems can still diverge even though the preceding tests on observability are met. In gen-

eral, system observability is a "yes" or "no" measure. *Ad hoc* measures of observability, such as "weakly" or "strongly" observable systems, can be obtained by examining the singular values of the observability matrix (Lin, 1979; Shah et al., 1981).

In a multirate framework, tests for observability must be carefully carried out because the dimensions of the process output vector varies between the major and minor sampling instant. Ideally, one would like the system to be completely observable from the secondary process outputs alone. However, the availability of the slowly sampled primary measurement at the major sampling instant can serve to make the estimator performance more robust in the face of uncertain initial conditions and parameters by providing additional feedback information to the estimator rather than relying on feedback from estimates generated from the secondary outputs alone. The availability of the primary measurement also serves to update a larger set of system parameters, if necessary, and may thus help to make the system strongly observable.

Case Study

Analysis of the proposed software sensor has been carried out on simulation and experimental data from fermentation systems. Such systems exhibit significant time-varying behavior due to changing conditions in the growth medium throughout the fermentation. For example, the specific growth rate and maintenance coefficient vary with time. In fermentations of recombinant organisms, the growth rate could change due to induction of the plasmids. Fermentations exhibiting diauxic growth phenomena can also exhibit time-varying specific growth rates due to a change in the type of nutrients being assimilated. The system considered in this case study is a fed batch antibiotic producing fermentation known to exhibit significant maintenance activity and endogenous metabolism during the secondary product (antibiotic) expression phase.

For numerical simulation, the system was modeled using dynamic balances along with empirical growth models for cell growth and product formation (Bajpai and Reuss, 1980; Tsobanakis et al., 1990) and dynamic balances for the gas phase (Cardello and San, 1988). The detailed equations are presented in the Appendix. The system was simulated using a stiff equation solver LSODES (Lawrence Livermore Labs). The profiles of various states thus generated by simulation were then sampled according to a multirate sampling scheme chosen for the study. Validation on an experimental basis was carried out with data obtained from a fed-batch fermentation of *Streptomyces clavuligerus* NRRL 3885 grown in a complex medium. The experimental conditions are described elsewhere (Gudi et al., 1994).

Estimator equations

Inferential estimation of the biomass, net specific growth rate μ, and the maintenance coefficient m_c were proposed to be carried out from (i) frequent and regular measurements of the carbon dioxide evolution rate (CER) available at the basic sampling rate, and (ii) infrequent, delayed measurements of the biomass available at a slower sampling rate, which is assumed to be some integral multiple of the basic sampling rate.

The balance equation for cumulative amount of biomass $x_1 (= xV)$ can be written by performing a simple transformation of the dynamic balance equation for the biomass (Eq. A1) as

$$\frac{dx_1}{dt} = \mu x_1. \tag{33}$$

Commonly, structural models, such as the Monod model, that relate the growth rate to biomass and substrate concentrations are used to explain the variation in μ. In the previous equation, however, μ is assumed to be a time-varying parameter, and no growth model is assumed to describe it. A measurement delay $t_d = 2$ basic sampling instants was assumed for the biomass. In continuous time, the following equation simulates the delay.

$$x_m(t) = x_1(t - t_d). \tag{34}$$

However, two delayed states need to be introduced as discussed in the third section, to simulate the delays in the discrete domain. The discrete, output equation can be expressed in terms of the CER (mmol/h) by assuming the gas phase dynamics to be significantly faster than the rates of growth or substrate consumption. Thus from Eq. A7,

$$\mathrm{CER}(i) = [k_1 \mu(i) + m_c(i)]x_1(i) \tag{35}$$

where k_1 is the yield coefficient.

The measurement equation at the major sampling instant, when we have measurements of the cumulative biomass and CER, can be written as,

$$z_{\text{major}} = \begin{bmatrix} x_3(i) \\ \mathrm{CER}(i) \end{bmatrix} + \boldsymbol{\nu}_{\text{major}} = \begin{bmatrix} x_3(i) \\ [k_1 \mu(i) + m_c(i)]x_1(i) \end{bmatrix} + \boldsymbol{\nu}_{\text{major}}. \tag{36}$$

At the minor sampling instant, measurement of only CER is available and the measurement equation can be written as

$$z_{\text{minor}} = \mathrm{CER}(i) + \boldsymbol{\nu}_{\text{minor}} = [k_1 \mu(i) + m_c(i)]x_1(i) + \boldsymbol{\nu}_{\text{minor}}. \tag{37}$$

The specific growth rate μ and the maintenance coefficient m_c are time varying and need to be estimated along with the states. They are modeled as discussed earlier as

$$\dot{\mu} = w_2 \tag{38}$$

$$\dot{m}_c = w_3 \tag{39}$$

where w_2 and w_3 are zero-mean noise processes with unspecified probability densities.

Observability analysis

For time-varying, nonlinear systems observability conditions can be checked by considering linearized approxima-

tions. Structural unobservabilities, if any, would render the system unobservable at all sampling instants. These can be easily detected if the relevant observability matrices are constructed symbolically and then checked for rank deficiencies. The results of such a symbolic observability analysis are independent of the values that the parameters can take and are thus generic. For the preceding nonlinear system of equations, we perform a structural observability analysis using Maple (1981). We consider the observability of the system in a locally linearized sense under the following scenarios:

System with No Measurement Delays. The system equations that need to be considered here are Eqs. 33, 38 and 39. The state transition matrix after linearization and discretization of the preceding system equation can be written as,

$$\phi = \begin{bmatrix} 1+\tau\mu(i) & \tau x_1(i) & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}. \tag{40}$$

At the major sampling instants, measurements of biomass and CER are available and the linearized measurement equation is

$$h_{\text{major}} = \begin{bmatrix} 1 & 0 & 0 \\ k_1\mu(i)+m_c(i) & k_1x_1(i) & x_1(i) \end{bmatrix}. \tag{41}$$

The corresponding structural observability matrix, $O_{\text{major}} = [h_{\text{major}};\ h_{\text{major}}\phi;\ h_{\text{major}}\phi^2]^T$ can be written as

$$O_{\text{major}} = \begin{bmatrix} 1 & 0 & 0 \\ k_1\mu(i)+m_c(i) & k_1x_1(i) & x_1(i) \\ [1+\tau\mu(i)] & \tau x_1(i) & 0 \\ [k_1\mu(i)+m_c(i)][1+\tau\mu(i)] & [k_1\mu(i)+m_c(i)]\tau x_1(i)+k_1x_1(i) & x_1(i) \\ [1+\tau\mu(i)]^2 & \tau x_1(i)[2+\tau\mu(i)] & 0 \\ [k_1\mu(i)+m_c(i)][1+\tau\mu(i)]^2 & [k_1\mu(i)+m_c(i)][2+\tau\mu(i)]\tau x_1(i)+k_1x_1(i) & x_1(i) \end{bmatrix}. \tag{42}$$

Using Maple, this matrix can be shown to be of full rank and therefore the augmented system of the states and the parameters is completely observable from the process outputs at the major sampling instant.

At the minor sampling instants, since only measurements of the CER are available, the linearized measurement equation can be written as

$$h_{\text{minor}} = [(k_1\mu(i)+m_c(i))\ k_1x_1(i)\ x_1(i)]. \tag{43}$$

The observability matrix for this case can be verified to be,

$$O_{\text{minor}} = \begin{bmatrix} k_1\mu(i)+m_c(i) & k_1x_1(i) & x_1(i) \\ [k_1\mu(i)+m_c(i)][1+\tau\mu(i)] & [k_1\mu(i)+m_c(i)]\tau x_1(i)+k_1x_1(i) & x_1(i) \\ [k_1\mu(i)+m_c(i)][1+\tau\mu(i)]^2 & [k_1\mu(i)+m_c(i)][2+\tau\mu(i)]\tau x_1(i)+k_1x_1(i) & x_1(i) \end{bmatrix}. \tag{44}$$

The preceding matrix can be shown to be rank deficient. It has a rank of 2, that is, a rank defect of 1. The system is thus structurally unobservable, so that the overall system of states and parameters is only partially observable from the secondary measurements. From intuition and from systems theory (such as the directed mode expansion of the output), it is easy to verify that at minor sampling instants, only the state x_1 and the specific growth rate μ are observable from the CER. Thus if the maintenance coefficient m_c is constant, state estimation can still be done.

System with Measurement Delay. The system equations that need to be considered for this case are 33, 34, 38, and 39. The state transition matrix after linearization and discretization can be written as,

$$\phi = \begin{bmatrix} 1+\tau\mu(i) & 0 & 0 & \tau x_1(i) & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}. \tag{45}$$

Major Sampling Instant. The measurement of the biomass that is available at this sampling instant corresponds to the delayed state x_3. Thus the measurement equation can be written as

$$z_{\text{major,delay}} = \begin{bmatrix} x_3(i) \\ [k_1\mu(i)+m_c(i)]x_1(i) \end{bmatrix} + \nu_{\text{major,delay}}. \tag{46}$$

The linearized measurement equation thus is

$$h_{\text{major,delay}} = \begin{bmatrix} 0 & 0 & 1 & 0 & 0 \\ k_1\mu(i)+m_c(i) & 0 & 0 & k_1x_1(i) & x_1(i) \end{bmatrix}. \tag{47}$$

Using Maple, the observability matrix (omitted here for brevity) can be constructed and verified to be of full rank. Thus even for the case of measurement delay, the system is fully observable at the major sampling instant.

Minor Sampling Instant. The measurement equation remains the same as the case of no measurement delay, since the delayed biomass measurements are not available at this sampling instant at all. The state vector, however, does include the delayed states and the linearized measurement equation can be written as

$$h_{\text{minor,delay}} = [k_1\,\mu(i) + m_c(i) \quad 0 \quad 0 \quad k_1 x_1(i) \quad x_1(i)]. \quad (48)$$

Using Maple, the observability matrix for this case can be found to be rank deficient with a rank of 2. Compared to the case of minor sampling instant with no measurement delay, we see that there is an increase in the rank defect. From intuition and from systems theory, it is easy to see that this increase in rank defect of 2 is due to the addition of the delayed states at the minor sampling instant. These delayed states are not correlated with the system output (CER) and are thus not observable at the minor sampling instants. Thus at the minor sampling instants, when there is delay, the maintenance coefficient and the delayed states are not observable.

Modified observer

From the preceding observability analysis, it is then possible to conclude that

(i) The system with measurement delay is fully observable at the major sampling instants

(ii) At the minor sampling instants, the system is unobservable.

One obvious implementation of the estimator for the case of undelayed measurement is to update the maintenance coefficient at the major sampling instant and to assume that the major sampling instants arrive frequently enough to track the changing maintenance coefficient. For the case with measurement delay, however, one can then extend the same ideas, provided of course that it is possible to make the delayed states observable in some way. This motivates the use of a modified observer presented below.

The basis for the modified observer formulation lies in the fact that past inferential measurements must be correlated with the delayed states. Since we know that the rank defect at the minor sampling instant increases by the number of added delayed states, by including past measurements in the observation equation, we can attempt to decrease the rank defect by the same number. The motivation for doing so can also be drawn in analogy with the philosophy of adding delayed states. The latter are only hypothetical states added to simulate delay in the state space description, that is, for mathematical tractability. Thus, to observe them we can add as many delayed measurements, that is, past measurements in the measurement equation. For the preceding minor sampling instants, the measurement equation can then be written as

$$z_{\text{minor,modified}} = \begin{bmatrix} \text{CER}(i) \\ \text{CER}(i-1) \\ \text{CER}(i-2) \end{bmatrix} + \nu_{\text{minor,modified}}. \quad (49)$$

If we now make the additional assumption that μ and m_c remain constant during the delay time (a valid assumption, considering the dynamics of the bioprocess), we can write

$$z_{\text{minor,modified}} = \begin{bmatrix} [k_1\,\mu(i) + m_c(i)]x_1(i) \\ [k_1\,\mu(i) + m_c(i)]x_2(i) \\ [k_1\,\mu(i) + m_c(i)]x_3(i) \end{bmatrix} + \nu_{\text{minor,modified}}. \quad (50)$$

The linearized measurement matrix can be written as

$$h_{\text{minor,modified}} = \begin{bmatrix} k_1\,\mu(i) + m_c(i) & 0 & 0 & k_1 x_1(x) & x_1(i) \\ 0 & k_1\,\mu(i) + m_c(i) & 0 & k_1 x_2(i) & x_2(i) \\ 0 & 0 & k_1\,\mu(i) + m_c(i) & k_1 x_3(i) & x_3(i) \end{bmatrix}. \quad (51)$$

Using Maple, the observability matrix for the linearized system with the modified measurement equation can be verified to be of full rank. Comparing the results obtained at the minor sampling instants in this section with the modified measurement equation with those obtained in the previous section, it is possible to conclude that by inclusion of the past measurements and by exploiting the system structure it has been possible to decrease the rank defect to zero and make the system completely observable.

As mentioned earlier, *ad hoc* measures of observability such as "weakly" or "strongly" observable systems can be obtained by examining the singular values of the observability matrix. Thus, a system could be termed as "strongly" observable if it had a well-conditioned observability matrix. In the foregoing analysis, although the observability matrix was of full rank at the major sampling instants, indicating that the system was fully observable at these instants, past measurements were still used in a modified measurement equation to improve the condition number of the resulting observability matrix and thus make the system more strongly observable at the major sampling instants.

Thus at the major sampling instants, the measurement equation is written as

$$z_{\text{major,modified}} = \begin{bmatrix} x_3(i) \\ [k_1\,\mu(i) + m_c(i)]x_1(i) \\ [k_1\,\mu(i) + m_c(i)]x_2(i) \\ [k_1\,\mu(i) + m_c(i)]x_3(i) \end{bmatrix} + \nu_{\text{major,modified}}. \quad (52)$$

The linearized measurement equation can be written as

$$h_{\text{major,modified}} = \begin{bmatrix} 0 & 0 & 1 & 0 & 0 \\ k_1\mu(i)+m_c i & 0 & 0 & k_1x_1(i) & x_1(i) \\ 0 & k_1\mu(i)+m_c(i) & 0 & k_1x_2(i) & x_2(i) \\ 0 & 0 & k_1\mu(i)+m_c(i) & k_1x_3(i) & x_3(i) \end{bmatrix} \quad (53)$$

It was verified using symbolic computation that the observability matrix, when the modified observer equations were used at the major sampling instants, was also of full rank.

Thus the system that initially had structural unobservabilities at the minor sampling instants has been made fully observable at all sampling instants by including past measurements in the system description.

Remark 1. The results of the preceding structural observability analysis can be said to be *generic*, and applicable to all systems having a similar structure. However, their *validity* as applied to nonlinear systems is restricted to the locally linearized system description.

Remark 2. Such delayed and/or infrequent sampling of the primary process variables, in a multirate scenario as presented earlier, is present in many chemical processes that involve sampling and elaborate off-line analysis or assay procedures. The structural unobservabilities just seen are also typical of many chemical process systems. For example, in an exothermic batch reactor, the temperature of the reactor contents is influenced by the reaction as well as the heat-transfer rates. Commonly, reactor temperature measurements are used to infer typical reactor states (reactant compositions) and parameters (reaction rates) (Bonvin et al., 1989; de Valliere and Bonvin, 1989). If the heat-transfer rates change due to a change in the overall heat-transfer coefficient, the state and parameter estimates, generated from temperature measurements alone, could be biased. It would then be necessary to update the heat-transfer coefficient in exactly the same way as the maintenance coefficient discussed earlier, to enhance the quality of the state and parameter estimates.

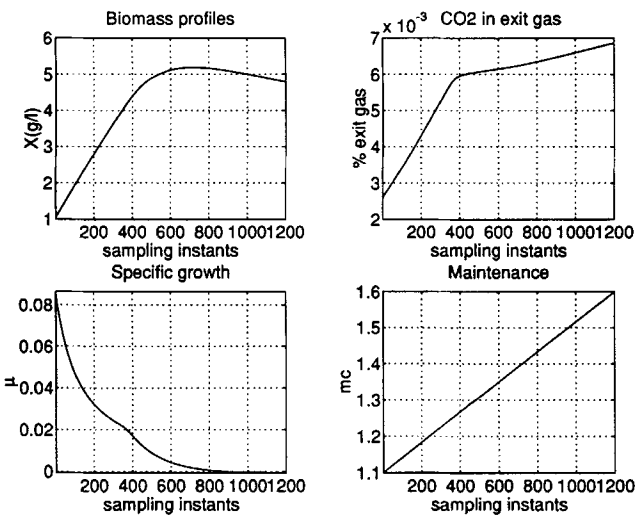

Figure 2. Profiles of process variables and parameters from simulation of a fed batch fermentation.

Estimation Results

Simulation study

The system of equations presented in the Appendix was solved for a time interval of 120 h for a linearly changing value of the maintenance coefficient m_c between 1.1 and 1.6 mmol CO_2/h-L. A constant nutrient feed rate of 5.6 mL/h was assumed. The initial conditions used in the simulation are presented in the Notation section of the article along with their appropriate units. The profiles for biomass concentration, CO_2 content in the exit gas, the specific growth rate, and the maintenance coefficient thus generated are shown in Figure 2.

A multirate sampling scenario was chosen as follows. Measurement of the biomass was assumed to arrive every 3 h from the simulations. Measurements of the CO_2 content in the exit gas and the broth volume were assumed to arrive every 6 min. In terms of the sampling instants, the major sampling instant varied every 3 h or after every 30 minor sampling instants. A delay of two minor sampling instants was assumed for the primary measurement. White Gaussian noise with zero mean was added to the measurements to simulate noisy measurements with a relatively smaller signal-to-noise ratio. The objective of the estimator was thus to estimate, from the measurements arriving at multiple rates of sampling described earlier, the cumulative biomass, the specific growth rate, and the maintenance coefficient.

Base Case Estimation. Figure 3 shows the behavior of the estimator for the base case estimation. It can be seen that

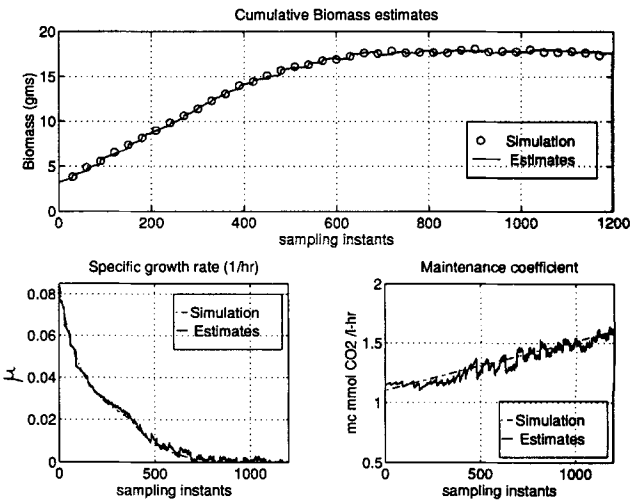

Figure 3. Performance of estimation strategy on simulated data (base case).

The process noise covariance matrix was assumed to be 1,000 times diagonal (1,1,1, 50, 50). The measurement noise covariance matrix was assumed to be 0.1 times appropriately sized identity matrix.

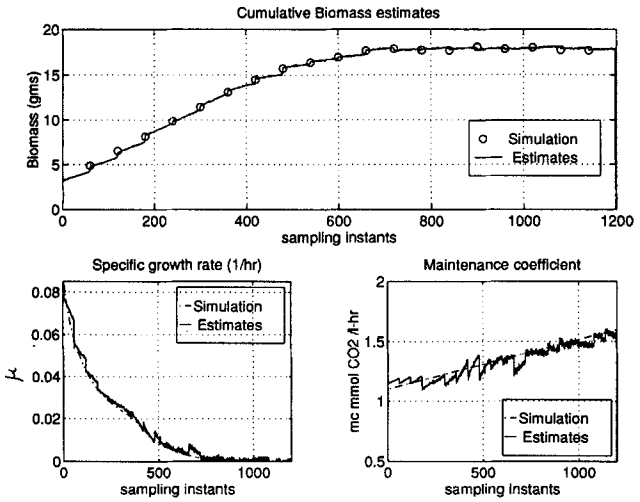

Figure 4. Effect of an increase in the major sampling internal on the estimator performance (major sampling instant occurs once every 60 minor sampling instants).

The process noise covariance matrix was assumed to be 1,000 times diagonal (1,1,1,...,50, 50). The measurement noise covariance matrix was assumed to be 0.1 times the appropriately sized identity matrix.

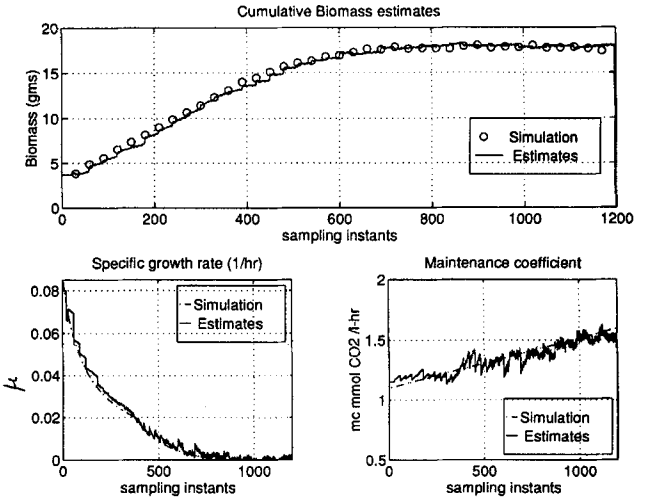

Figure 5. Effect of a measurement delay of 30 sampling instants on estimation performance using simulated data.

The process noise covariance matrix was assumed to be 1,000 times diagonal (1,1,1, 50, 50). The measurement noise covariance matrix was assumed to be 0.1 times the appropriately sized identity matrix.

state and parameter estimation is excellent. The parameters are tracked quite well, but the estimates are noisy due to the high sensitivity of the filter to the measurement noise added. For the preceding run, the process noise covariance matrix Q was assumed to be a diagonal matrix with entries corresponding to the "process noise" levels of each of the states. The measurement noise covariance matrix was also assumed to be a diagonal matrix with entries corresponding to the covariance of measurement noise. The actual values of these matrices that were used in the estimation run are mentioned in the appropriate figure captions.

The cumulative biomass profiles show corrections on arrival of a biomass measurement at the major sampling instants. This is through the appropriate specification of the process and measurement noise covariances such that greater confidence is placed on the estimates of the biomass generated from primary measurements that are available at any sampling instant as opposed to the estimates generated inferentially from the CER.

Effect of Major Sampling Frequency. Figure 4 shows the performance of the estimator when the major sampling instant arrives every 60 minor sampling instants. It can be seen that, due to slower availability of the primary measurement, the tracking of the true parameters is sluggish. This can also be judged from the drastic corrections made by the estimator at the major sampling instant to generate the biomass estimates. These drastic corrections indicate that, due to slower tracking of the parameters, the estimates of the biomass generated inferentially from the CER at the minor sampling instants do not track the true values correctly.

Effect of Measurement Delay. Figure 5 depicts the performance of the estimator when there is a measurement delay of 30 sampling instants. Comparing with the base case (Figure 3), it is easy to conclude that the estimator can robustly accommodate measurement delays. The estimator run in Figure 5 corresponds to a sampling regime where a primary sampling is made when the results of the previous measurement is obtained. Due to large delays in measurement availability, the tracking of the parameters is quite sluggish.

Effect of Parameter Covariance. Figure 6 depicts the estimator performance when the parameter covariance matrix assumes values 10,000 times the appropriate identity matrix. For the extended Kalman filter formulation used in this work, this parameter covariance matrix is a subset of the overall process noise covariance matrix. The measurement noise co-

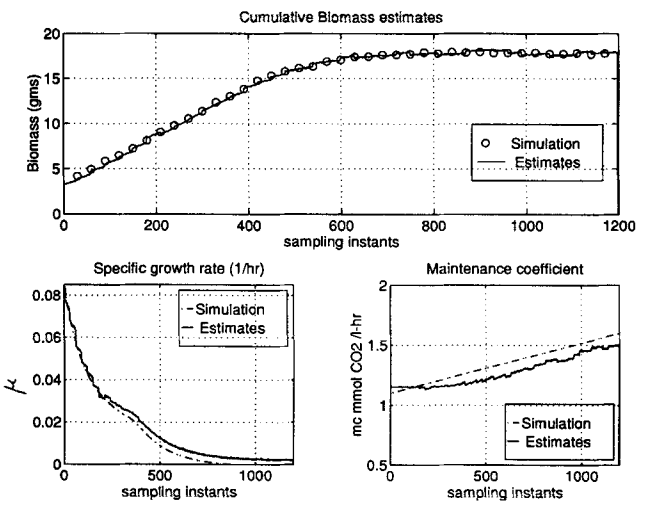

Figure 6. Estimator performance on simulated data with modified parameter covariance.

The process noise covariance matrix was assumed to be 1,000 times diagonal (1,1,1, 10, 10). The measurement noise covariance matrix was assumed to be 0.1 times the appropriately sized identity matrix.

variance matrix was assumed to be 0.1 times the appropriate identity matrix for both the major and minor sampling instants.

Figure 6 shows that biased parameters are obtained for a small value of the parameter covariance. However, the tracking of the primary state is quite good. Furthermore, because the tracking of the parameters is sluggish, these trajectories are quite smooth and are not sensitive to the measurement noise at all. As the parameter covariance is increased, the parameter estimates become less biased and converge to the true values. However, when the parameter covariance is increased, the filter becomes more and more sensitive to the measurement noise and the parameter estimates are noisy. This can be seen by comparing parameter trajectories in Figure 3 and Figure 6.

Validation with experimental data

The performance of the multirate inferential estimator was also analyzed using experimental data obtained from fed-batch fermentation of *Streptomyces clavuligerus* NRRL 3885. The detailed experimental conditions are discussed elsewhere (Gudi et al., 1994). The cumulative biomass measurements were made every 3 h, whereas the CER measurements were made every 20 min. A measurement delay of two minor sampling instants (40 min) was assumed for the biomass measurements. It was decided to generate, as before, estimates for the maintenance coefficient, the specific growth rate, and the cumulative biomass level from the multirate measurements available as just described. For comparison, reference trajectories for the parameters were first generated by assuming that the biomass and CER measurements were available at every sampling instant. The biomass measurements were generated by linear interpolation of the experimental values. The reference trajectories for the parameters so generated were used as a basis to compare the estimator performance in a multirate sampling scenario. A value of 1.1 mmol CO_2/h-g biomass was assumed for the yield coefficient k_1 (Pirt and Righelato, 1967; Stone et al., 1992). The estimator was initialized with values of $\mu(0) = 2.0\ h^{-1}$ for the specific growth rate and $m_c(0) = 1.1$ mmol CC_2/h·g biomass for the maintenance coefficient. Due to lack of *a priori* knowledge about the time evolution of the parameters, a trial-and-error-based tuning procedure was used to tune the process noise covariance matrix relative to the measurement noise covariance matrix. The estimator performance was found to depend only on the relative magnitudes of the process noise and the measurement noise covariance matrices. Specification of a high process noise covariance relative to the measurement noise covariance gave good but relatively noisy parameter tracking. This corresponds to the case when measurements are given higher weighting relative to model predictions. The lower value of the assumed measurement noise covariance was thus limited by the noise levels in the measurements. Accordingly, the measurement noise covariance matrix was chosen to be 0.001 times an appropriately sized identity matrix. The process noise covariance matrix was also a diagonal matrix with entries equal to 10 for the states and 50 for the parameters.

Figure 7 shows the performance of the estimator for the multirate sampling scenario just stated, using only the current CER measurement. As discussed in the fourth section, if only the current CER measurements are used, the system is fully observable only at the major sampling instants. Thus no parameter updating takes place at the minor sampling instants. Expectedly the parameter tracking becomes more sluggish as the measurement delay increases.

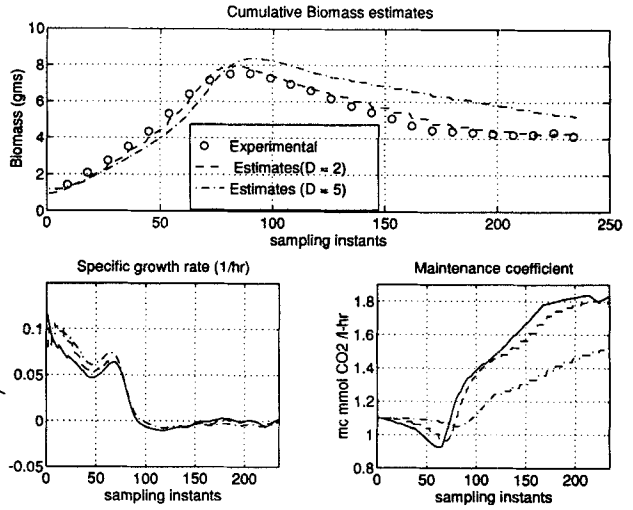

Figure 7. Estimator performance with experimental data using instantaneous CER measurements.

Biased estimates are seen because parameter updating is not done at the minor sampling instants. The bias is seen to increase with an increase in measurement delay from 2 to 5 sampling instants.

Figure 8 shows the performance of the estimator using the modified observer. It can be seen that good estimation of the cumulative biomass and the parameters is obtained during the linear region of the feed rate. The feed rate was dropped to a low constant value of 0.0035 L/h after about 24 h of

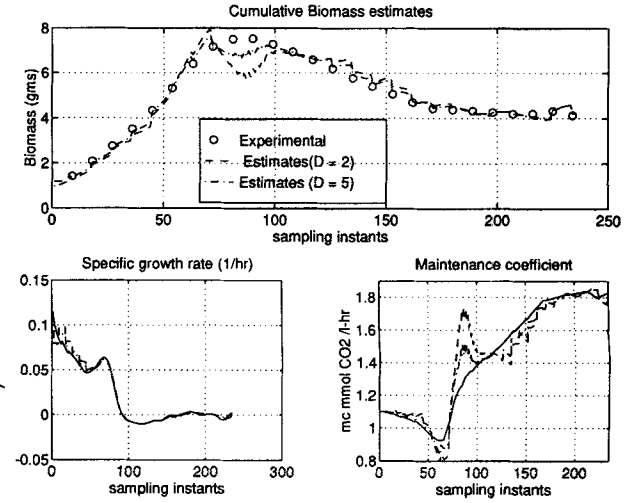

Figure 8. Validation of multirate state and parameter estimation method with experimental data when past CER measurements are used in the measurement vector.

The estimator is also seen to be fairly robust to measurement delays of five sampling instants.

growth to prevent inhibition of the secondary product formation due to high levels of substrate. This action seems to trigger a phase of significant maintenance activity and endogenous metabolism, due to which the maintenance coefficient starts to change. It can be seen that there are quite drastic corrections to the estimated biomass in this phase. During this phase, the biomass levels off and starts to fall. The CER profile also starts to drop, although this drop is not as fast as expected. This slow dropping of the CER can be attributed to an increase in the maintenance activity of the culture. The estimation of the maintenance coefficient exhibits some transients before this increasing trend is tracked. Also shown in Figure 8 are the estimate profiles when the measurement delay is assumed to be 5 sampling instants (1.5 h). It can be seen that the estimator is fairly robust to measurement delays.

The terminal value of the maintenance coefficient is in agreement with the expected value obtained by setting the growth rate to zero in the measurement equation that relates the CER to its growth and maintenance-associated terms. At the terminal conditions, the growth rate is close to zero and all the CO_2 that is evolved can be attributed to maintenance activity. The expected terminal value of the maintenance coefficient is about 1.8–2.0 mmol CO_2/h-g biomass, in agreement with the value predicted by the estimator.

Conclusions

- An algorithm to formally accommodate the multiple rates of sampling that typically exist in chemical processes has been proposed. It has been shown to have a sound theoretical basis by formulating it as an extended version of the multirate Kalman filter.
- Measurement delays associated with the primary measurement are formally incorporated into the system description. The subsequent decrease in system observability due to incorporation of the delays, if any, is addressed by using past measurements in the measurement vector to annul the rank deficiency of the observability matrix.
- The algorithm has also been shown to not have restrictive assumptions on the frequency of primary and secondary measurements as in the transfer-function-based approaches proposed in the literature. These features allow the estimator to be easily implementable in a typical real time sampling scenario involving measurement delays and irregularities in measurement availability.
- The algorithm has been validated on a case study involving fermentation systems. Validation using both simulation and experimental data from an antibiotic fermentation has been successfully carried out. The practicality of the proposed algorithm has thus been confirmed by the latter experimental application.

Notation

$a_i' = k_L a$ correlation exponent (0.9)
A = Jacobian of the unaugmented system
$b_i' = k_L a$ correlation exponent (0.667)
$c_i' = k_L a$ correlation exponent (-0.86)
C_G = gaseous CO_2 concentration (0.0 mol fraction)
C_{in} = CO_2 inlet concentration (0.0 mol fraction)
C_L = dissolved CO_2 concentration (33d-05 mmol/L)
F = substrate feedrate (1/h)
G = measurement matrix at any sampling instant
h = nonlinear measurement equation
H_c = Henry's law coefficient for CO_2 at 30°C (0.035 atm-L/mmol)
H_o = Henry's law coefficient for O_2 at 30°C (0.96 atm-L/mmol)
k_d = degradation constant for P (0.01 h^{-1})
kdl = lysis constant for biomass $= 1 - \exp(-0.06*t)$
$k_L a$ = mass-transfer coefficient (h^{-1})
K_I = inhibition constant for S on P (0.1 g/L)
K_{op} = Contois constant for O_2 limitation of P (3.0e-05 mM/g)
K_{ox} = Contois constant for O_2 limitation of X (1.11e-03 mM/g)
K_P = Monod constant for S limitation of P (1.0e-04 g/L)
K_X = Contois constant for S limitation of X (6.0e-03 g/g)
m_o = maintenance coefficient for O_2 (0.467 mmol/g·h)
m_s = maintenance coefficient for S (0.029 g/g)
N_i = number of impellers
O_G = gaseous O_2 concentration (0.21 mol fraction)
O_i = observability matrix at instant i
O_{in} = O_2 inlet concentration (0.21 mol fraction)
O_L = dissolved O_2 concentration (1d-03 mmol/L)
p = operating pressure
P = product (penicillin) concentration (0 g/L)
$P(i)$ = *a posteriori* estimate of the estimation errors at the ith instant
P_g = gassed power (23.1 HP/10001)
Q_{in} = gas inlet flow rate (1/h)
Q_{out} = gas outlet flow rate (1/h)
r_P = penicillin production (g/h)
r_X = cell mass growth rate (g/h)
R = gas constant (0.082 atm·L/mol·K)
S = substrate concentration (1d-06 g/L)
S_f = substrate feed concentration (g/L)
t = time of fermentation (h)
T = operating temperature (K)
u = vector of process inputs
v_i = measurement noise at instant i
v_s = superficial gas velocity (cm/s)
V_L = broth volume (3.0 l)
w = white noise process
X = biomass concentration (1.05 g/L)
$Y_{p/c}$ = yield of P on C (g/g)
$Y_{p/o}$ = yield of P on O (g/g)
$Y_{p/s}$ = yield of P on S (g/g)
$Y_{x/c}$ = yield of X on C (g/g)
$Y_{x/o}$ = yield of X on O (g/g)
$Y_{x/s}$ = yield of X on S (g/g)

Greek letters

γ = dummy iteration variable for the iterative EKF
Θ = parameter vector for estimation
μ_P = production rate for P (h^{-1})
μ_X = growth rate for X (h^{-1})
ν_{app} = apparent viscosity (pseudo-*cp*)
ν_0 = apparent viscosity bias (21.29 pseudo-*cp*)
ν = measurement noise vector
ρ = exponent of O_L in P equation
ϕ = state transition matrix for the discrete system
ϵ = voidage in the reactor (0.1)
ϵ_i = innovation vector at the ith instant

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Appendix

Dynamic balances to simulate a fed-batch fermentation

Biomass

$$\frac{dX}{dt} = r_X - \frac{X}{V_L}F. \tag{A1}$$

Substrate

$$\frac{dS}{dt} = -\frac{r_X}{Y_{x/s}} - \frac{r_P}{Y_{p/s}} + \frac{S_F}{V_L}F - m_s\frac{S}{K_m + S}X - \frac{S}{V_L}F. \tag{A2}$$

Secondary Product

$$\frac{dP}{dt} = r_P - k_d P - \frac{P}{V_L}F. \tag{A3}$$

Dissolved Oxygen

$$\frac{dO_L}{dt} = k_L a(O_L - O_L^*) - m_o X - \frac{r_X}{Y_{X/O}} - \frac{r_P}{Y_{P/O}} - \frac{O_L}{V_L}F. \tag{A4}$$

Dissolved Carbon Dioxide

$$\frac{dC_L}{dt} = k_L a(C_L^* - C_L) + m_C X + \frac{r_X}{Y_{X/C}} + \frac{r_P}{Y_{P/C}} - \frac{C_L}{V_L}F. \tag{A5}$$

Oxygen in Gas Phase

$$\frac{dO_g}{dt} = \frac{RT}{\epsilon p}\left[-K_{la}(O_l^* - O_l) + \frac{pq_{in}[O_{in} - O_g]}{RTV}\right]. \tag{A6}$$

Carbon Dioxide in Gas Phase

$$\frac{dC_g}{dt} = \frac{RT}{\epsilon p}\left[-K_{la}(C_l^* - C_l) + \frac{pq_{in}[C_{in} - C_g]}{RTV}\right]. \tag{A7}$$

Fermentor Volume

$$\frac{dV_L}{dt} = F. \tag{A8}$$

Growth Model

$$r_X = \mu_X \frac{S}{K_X X + S} \frac{O_L}{K_{OX} O_L^* X + O_L} X - kdl\,\mu_X X. \tag{A9}$$

Product Formation Model

$$r_P = \mu_P \frac{S}{K_P + S\left(1 + \frac{S}{K_I}\right)} \frac{O_L^p}{K_{OP} X + O_L^p}. \tag{A10}$$

Rheological Properties

$$k_L a = (1.0 + 2.8 N_i)\left(\frac{1{,}000 P_g}{V_L^3}\right)^{\acute{a}} (\nu_s)^{\acute{b}} (\nu_{app})^{\acute{c}} \tag{A11}$$

$$\nu_{app} = \nu_0 + \alpha X^{2.5}. \tag{A12}$$

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