Reparameterization of Inestimable Systems with Applications to Chemical and Biochemical Reactor Systems

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Mathematical models of physical systems often have parameters that must be estimated from measured data. Inestimable models have more parameters than can be estimated from available data. In this work, a method for identifying inestimable parameters or parameter combinations is proposed. The method is based on partitioning the parameter space into estimable and inestimable subspaces. Parameter combinations in the inestimable subspace have little effect on measured values and can therefore be fixed at a nominal value. The number of effective parameters is thereby reduced to the dimension of the estimable subspace. The proposed method is applicable over a range of experimental conditions. Detailed examples, including a batch bioreactor and a three-phase reactor system, are included for illustration. © 2008 American Institute of Chemical Engineers *AIChE J,* 54: 1270–1281, 2008
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Introduction

Mathematical models of physical systems are used in almost every branch of science and engineering. Such models are, generally, functions of unknown parameters that must be estimated from available data. Often, models contain more parameters than can be estimated from a given data set. In this case the model parameters are said to be inestimable. Inestimability implies that there are several possible parameter values that yield statistically indistinguishable predictions.

Estimability in models is a very useful property. If a model is estimable (from a given data set) then the value of each parameter in the model can be accurately determined. As a result, the model, or parameters, can be used for design, analysis, and scale-up. Furthermore, accurate parameter estimates allow system behavior to be extrapolated beyond the region where data is collected. This is especially useful for systems whose behavior cannot be studied under all conditions. For example, accurate parameter estimation may allow a clinician to choose an appropriate drug dosage for a human patient.

The problem of inestimability has been well documented in the literature.[1–4] For every model that is inestimable there exists a simpler, estimable, model (i.e., one with fewer parameters) that provides near identical predictions over the region for which data is available. Usually, a sensitivity-based approach[1,3,4] is used to identify model parameters that have little or no effect on model predictions and can therefore be either lumped, discarded, or held at a fixed value for the purpose of estimation.

The sensitivity-based framework for model simplification holds that a simpler identifiable model can be obtained by effectively removing some of the model parameters. However, the sensitivities of the model predictions to parameter values are functions of estimated parameter values and the experimental conditions. As a result, sensitivity analysis can suggest reparameterizations that only hold locally (i.e., near a nominal parameter value).

In this work, a method is proposed for reparameterizing inestimable models. The proposed approach allows *a priori*

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knowledge of the model structure to be used to reduce the number of model parameters. This reparameterization is achieved using a nonlinear transformation in the parameter space. The proposed transformation is insensitive to experimental conditions and parameter estimates. Furthermore, the proposed approach can be readily integrated with sensitivity-based approaches for parameter estimation.

Background

Models (or Systems) that have parameters that cannot be estimated, even under ideal conditions, are unidentifiable. Tests for unidentifiability have been proposed in the literature for a wide variety of linear and nonlinear systems.[5,6] Typically, a system can be tested for unidentifiability *a priori* because unidentifiability is a structural fault in the model formulation.

Systems that are identifiable (i.e., have parameters that can be estimated under idealized conditions) are often inestimable. That is, they may contain parameters that cannot be accurately estimated based on a specific data set or given specific experimental conditions.[1,7]

As an example, consider a plug-flow reactor (PFR) system in which the following generic gas phase reaction occurs

$$A + B \rightarrow C$$

whose kinetic rate law is

$$-r_A = k(T)C_A C_B \tag{1}$$

where C_A and C_B are the concentrations of A and B, respectively. The function $k(T)$ is the (temperature-dependent) specific reaction rate given by the Arrhenius relation:

$$k(T) = Ae^{-E/RT}$$

With the given measurements of C_A and C_B at several points in the reactor, one can estimate the value of $k(T)$. If experiments are done at two or more (different) temperatures then the parameters E and A can, in theory, be computed from measured data. However, the estimation of the parameters in the Arrhenius equation from experimental data is often difficult.[8] In the general case, an iterative approach may be required to obtain good estimates for the system parameter.[9] One reason for the difficulty in parameter estimation is that the effect of A on k may be very small as compared to the effect of E or vice versa. More specifically,

$$\frac{\partial k}{\partial A} = e^{-E/RT}$$
$$\frac{\partial k}{\partial E} = -\frac{A}{RT}e^{-E/RT}$$

The ratio comparing the effects is given by

$$\frac{\frac{\partial k}{\partial A}}{\frac{\partial k}{\partial E}} = -\frac{A}{RT} \tag{2}$$

which may be very large (or small) depending on the value A even for a range of T values. For example, estimates of A and E for an isomerization reaction over a Zn-triflate/K60 catalyst are available in the literature.[10] The estimated parameter values are $A = 3.40 \times 10^{-3}$ and $E = 9.84 \times 10^3$ J/mol, and the temperature range over which the data was gathered is 298 to 358 K. Under these conditions, the ratio in Eq. 2 is between 1.37×10^{-6} (at 298 K) and 1.14×10^{-6} (at 358 K). As a result, it is very likely that the uncertainty associated with the estimate of A is quite large in this case. Note that the lack of estimability does not imply that temperature has an insignificant effect on the reaction rate. Rather, it implies that the temperature dependence of $k(T)$ may be locally parameterized using fewer than two parameters. Note as the value of T varies, so will the relative importance of E and A. As a result, using a sensitivity-based framework, one may make only local conclusions regarding the relative importance of each parameter.

Parameter estimates for inestimable systems are likely to be inaccurate and therefore cannot be used for scale-up, design, or control. Generally, the problem of inestimability can be treated in one of two ways: more data can be obtained or the model can be modified. Obtaining additional data via experimentation will improve parameter estimates but may be expensive or otherwise impractical. As a result, it is common to attempt and reduce the number of parameters (to be estimated) to ensure that the parameter estimation problem is computationally feasible.

Model reduction via the removal of inestimable parameters is an active area of research. The general idea is to simplify the proposed model (via removal of parameters) until each parameter has a detectable effect on the model predictions. For example, the parameters believed *a priori* to have an insignificant effect on model predictions can be fixed at a nominal value.[11] Alternatively, correlation information can be used to sequentially fix parameters at nominal values.[12] Other methods for parameter reduction include the following. A sensitivity-based approach has been used to estimate a proper subset of the parameters in a gas-phase copolymerization reaction.[1] This approach has also been used to construct joint confidence regions for parameters in ecological models.[3] A Bayes theorem-based scheme has been proposed whereby different subsets of the parameters are identified at different times.[13] A similar, Monte-Carlo-based approach has been proposed to obtain a measure of estimability.[4] An algorithm where the parameter estimates are iteratively (manually) adjusted until a satisfactory fit is obtained has also been proposed.[14] Each of the listed approaches relies, in practice, on identifying a subset of parameters which are not estimable. However, as is shown in this work, although individual parameters may be inestimable, it is often parameter combinations which are inestimable. Furthermore, the combinations of parameters which are inestimable may be a strong function of experimental conditions.

This work presents a novel transformation-based approach for reparameterizing unidentifiable or inestimable systems. Transformations that partition nonlinear systems have been well studied in the literature.[15,16] Typically, nonlinear transformations are used to partition nonlinear systems into observable/unobservable or controllable/uncontrollable subsystems. However, the application of such a transformation, in the parameter space, to parameter estimation problems has received less attention. More specifically, there has been little

attention paid, in the literature, to the application of differential geometry to parameter estimation problems. The reparameterization approach presented in this work is based on developing a transformation which partitions the parameter space into an estimable part and an inestimable part.

Proposed Approach

Overview

The proposed approach allows *a priori* knowledge of the model structure to aid parameter estimation. Specifically, a methodology is proposed for reparameterizing nonlinear ODE systems by identifying process quantities (possibly nonlinear combinations of parameters or states), such as reaction rates, which are believed *a priori*, or after some preliminary analysis, to have a strong impact on model predictions. The main idea is that these process quantities, labeled pseudo-outputs, will be accurately estimated even if specific model parameters are not.

Once the pseudo-outputs are chosen, they are used to partition the parameter space into an estimable and an inestimable subspace. The parameters that lie in the estimable subspace are likely to be estimable from measured data, while parameters in the inestimable subspace are not. The proposed approach can be used as a preconditioner for a sensitivity-based approach for selecting subsets of estimable parameters. Alternatively, sensitivity analysis can be used to provide insight into which quantities should be chosen as pseudo-outputs. The proposed approach, however, does not require sensitivity information and is, furthermore, insensitive to the choice of experimental conditions or initial guesses for parameter values. Finally, the proposed approach does not require the cause or mechanism of inestimability to be identified.

The approach proposed in this work is to obtain a (possibly nonlinear) coordinate transformation that partitions the parameter space into estimable and inestimable portions. Consider a system with d parameters given by $p = [p_1, \ldots, p_d]$. First, parameter-dependent quantities that are known *a priori* to affect the model predictions are identified and treated as pseudo outputs. For example, pseudo outputs may be chosen as the reaction rates in a reaction network or the steady state gain of a dynamical system. The issue of how to select pseudo outputs is discussed later in this work. Let there be d_1 such combinations $\phi^+(p) = [\phi_1^+(p),\ldots,\phi_{d_1}^+(p)]$. Note that in the general case, the pseudo outputs $\phi^+(p)$ will be functions of both the parameters and state variables (e.g., temperature). As a result, $\phi^+(p)$ may need to be evaluated at some nominal value of the states. This issue is discussed in detail in the next section.

Once $\phi^+(p)$ is defined, a set of parameter combinations $\phi^-(p) = [\phi_1^-(p),\ldots,\phi_{d-d_1}^-(p)]$ are defined so that the mapping $\Phi = [\phi^+,\phi^-]$ is a local diffeomorphism (on an open and dense subset of the parameter space) and furthermore,

$$\langle d\phi_i^+, d\phi_j^- \rangle = 0 \tag{3}$$

for all $i \in \{1,2,\ldots,d_1\}$ and $j \in \{1,2,\ldots,d-d_1\}$, where $d\phi^+ = \frac{\partial \phi^+}{\partial p}$ and $d\phi^- = \frac{\partial \phi^-}{\partial p}$. The fact that Φ is a diffeomorphism and that $\phi^+(p)$ are inestimable implies that, if $p^+ = \phi^+(p)$ and $p^- = \phi^-(p)$, then optimizing over the d parameters $p_1, p_2, \ldots, p_d$ is approximately equivalent to optimizing over the d_1 variables $p_1^+, \ldots, p_{d_1}^+$ while holding the $d - d_1$ variables $p_1^-, \ldots, p_{d-d_1}^-$ at a fixed value. However, optimizing in the p^+ coordinates has the following key advantages:

- The parameters p^+ are estimable.
- The parameters p^- are inestimable.
- The parameters p^- and p^+ are independent (because of Eq. 3).

As a result, the optimization problem in the p^+ coordinates is well posed, computationally efficient, and the estimates obtained for p^+ are independent of the fixed values used for p^-. This last point is critical because if p^+ are not independent of the p^-, then values obtained for the estimated parameters are, at least in part, implicit functions of the values chosen for the p^-. Note that the coordinate transformation Φ is independent of experimental observations.

Systems with state-dependent transformations

For most reaction systems, the combination of parameters that most strongly and directly affect the measured data are the reaction rates. However, these rates are often functions of the state variables. As a result, the mapping Φ must be evaluated at a nominal value of the state variables. For example, consider Eq. 1, and suppose that $p = [A, E]$ and that the pseudo output is the function $k(p)$. The relationship $k(p) = p_1 e^{-p_2/(RT)}$ is a function of both p and T. As a result, one must choose a reference temperature T_{nom} at which to define:

$$\phi^+ = p_1 e^{\frac{-p_2}{RT_{nom}}}$$

To compute ϕ^-, we must find a vector field $d\phi^-$ that is orthogonal to $d\phi^+$. The vector field $d\phi^+$ is given by

$$d\phi^+ = \left[\frac{\partial \phi^+}{\partial p_1}, \frac{\partial \phi^+}{\partial p_2}\right] = \left[e^{-p_2/RT_{nom}}, -\frac{p_1}{RT_{nom}} e^{-p_2/RT_{nom}}\right]$$

which can be written as

$$d\phi^+ = \left[1, \frac{-p_1}{RT_{nom}}\right] e^{-p_2/RT_{nom}}$$

which implies that a vector field is orthogonal to $d\phi^+$ if and only if it is orthogonal to $\left[1, \frac{-p_1}{RT_{nom}}\right]$. One such vector field is $d\phi^- = [p_1, RT_{nom}]$. Integrating the partial differential equations

$$\frac{\partial \phi^-}{\partial p_1} = p_1, \quad \frac{\partial \phi^-}{\partial p_2} = RT_{nom}$$

defined by $d\phi^-$ one can obtain the function

$$\phi^- = \frac{1}{2} p_1^2 + RT_{nom} p_2 \tag{4}$$

which gives the (local) diffeomorphism

$$\begin{bmatrix} p^+ \\ p^- \end{bmatrix} = \Phi(p) = \begin{bmatrix} p_1 e^{\frac{-p_2}{RT_{nom}}} \\ \frac{1}{2} p_1^2 + RT_{nom} P_2 \end{bmatrix} \tag{5}$$

In practice, if a reaction system is found to be inestimable (but still parameter dependent), one could use the parameter transformation in Eq. 5 and estimate only p^+ while holding p^- constant.

The parameter combinations p^- play a critical role in the proposed approach despite not being directly used in the estimation procedure. These combinations are the quantities which are deemed to be inestimable, and are therefore held at a fixed value during estimation. As a result, it is important to ensure that all parameters in p^- are orthogonal to all parameters in p^+ in the sense that the vector fields associated with their differentials ($d\phi^-$ and $d\phi^+$, respectively) are orthogonal. This is mathematically expressed in Eq. 3. For example, consider what would happen if one were to naively choose a coordinate $p^- = \phi^-(p) = p_2$ for Eq. 4. In this case,

$$\langle d\phi^-, d\phi^+ \rangle = -\frac{p_1}{\mathrm{RT_{nom}}} e^{-p_2/\mathrm{RT_{nom}}} \neq 0$$

which implies that $d\phi^-$ and $d\phi^+$ are not orthogonal. As the definition of ϕ^- implies, keeping p^- constant would be equivalent to keeping p_2 (the activation energy E) constant and estimating only A. However, if, as discussed in the background section, the pre-exponential factor is inestimable, this choice of p^- will have the unintended effect of attempting to estimate an inestimable quantity. Choosing coordinates p^- that are normal to the coordinates which are estimable has the beneficial effect, therefore, of ensuring that no estimable quantities are implicitly held at a fixed value by their relation to p^-.

Summary of the proposed approach

The proposed procedure can be summarized using five steps as follows.

1. Identify d_1 key process variables to be treated as pseudo outputs.
2. Compute $d - d_1$ coordinates in the parameter space so that Eq. 3 is satisfied, thereby defining the mapping Φ.
3. If necessary, choose a nominal operating condition, at which Φ will be evaluated.
4. Choose nominal (fixed) values for p^- (the inestimable parameters).
5. Use Φ to estimate only p^+ while keeping p^- at their nominal values.

Of the steps listed in this section, Step 1 is the most critical. Psuedo outputs should be chosen as (possibly nonlinear) combinations of system states and parameters that are critical to understanding or predicting the behavior of a system. Examples include reaction rates, conversion, heat removal rate, and adsorption rates. The general idea is that while, for example, one is willing to entertain the idea of having several parameter values that predict the same adsorption rate, the estimate of the adsorption rate itself must be accurate for engineering design and control. Choosing pseudo outputs is, therefore, a way to formally integrate engineering knowledge into the parameter estimation problem.

Integration of the proposed approach with a sensitivity-based approach

The proposed method can be seen as a preconditioner for a sensitivity-based test for parameter estimability. Under this view, the proposed procedure allows the use of *a priori* information to remove parameter combinations that are unlikely to affect the model predictions. By removing inestimable parameter combinations, the number of model parameters is reduced to the parameters given by $p^+ = \phi^+(p)$. A sensitivity based-approach is applied to the parameters in the (p^+, p^-) coordinates. Specifically, the sensitivity of the model predictions, y, to a change in p^+ is given by

$$\frac{\partial y}{\partial p^+} = \frac{\partial y}{\partial p}\Big|_{p^-} \frac{\partial p}{\partial p^+}\Big|_{p^-}$$

where $\frac{\partial y}{\partial p}$ is the sensitivity of y to a change in p and

$$\frac{\partial p}{\partial p^+} = \frac{\partial [\Phi^{-1}]}{\partial p^+}$$

where $\frac{\partial [\Phi^{-1}]}{\partial p^+}$ is the Jacobian of the inverse mapping Φ^{-1}: (p^+, p^-) $\mapsto p$ with respect to the pseudo outputs. The sensitivity of y with respect to p^+ can be computed by integrating the sensitivity equations with respect to p and multiplying by the constant Jacobian matrix $\frac{\partial [\Phi^{-1}]}{\partial p^+}$.

The ability to obtain sensitivity information for p^+ is important because sensitivity information can be used to rank parameters according to their effect on model predictions. Estimability analysis can therefore be done in two steps. First, key parameters p^+ are identified. Second, sensitivity estimates are obtained for p^+ for a given experimental design and nominal parameter values. The sensitivity information can then be used to modify the experimental design so that the most critical parameters (from an engineering or a design perspective) are also the most estimable. Finally, note that the availability of sensitivity information implies that confidence regions can be computed for the p^+ coordinates.

Connection with differential geometry

The coordinates $p^- = \phi^-(p)$ may be difficult to compute for systems with more than a handful of parameters. Even for a simple system, it may not be obvious how to solve for ϕ^-. For example, consider Eq. 1 with $d\phi^+ = \left[e^{-p_2/\mathrm{RT_{nom}}}, -\frac{p_1}{\mathrm{RT_{nom}}} e^{-p_2/\mathrm{RT_{nom}}}\right]$. The vector field

$$d\phi^* = \left[1, \frac{RT_{\mathrm{nom}}}{p_1}\right] \tag{6}$$

is also normal to $d\phi^+$. However, there does not exist a function ϕ^* corresponding to $d\phi^*$ because Eq. 6 implies that $\frac{\partial^2 \phi^*}{\partial p_1 \partial p_2} \neq \frac{\partial^2 \phi^*}{\partial p_2 \partial p_1}$.

The general problem of finding a set of coordinates $p^- = \phi^-(p)$ that are orthogonal to a known set of coordinates $p^+ = \phi^+(p)$ can be solved using the method of characteristics.[17] Under this approach, the problem of finding an inestimable coordinate amounts to finding functions, ϕ_1^-, ϕ_2^-, ..., $\phi_{\mathrm{d-d_1}}^-$ such that for each function ϕ_j^- with $j \in \{1, 2, \ldots, d - d_1\}$, and any $i \in \{1, 2, \ldots, d_1\}$, which Eq. 3 holds.

Let $f_l^i(p) = \frac{\partial \phi_i^+}{\partial p_l}(p)$. Equation 3 evaluated over $i = 1, 2, \ldots, d_1$ implies that the following conditions hold for each $j \in \{1, 2, \ldots, d - d_1\}$:

$$\begin{aligned} \sum_{l=1}^{d} f_l^1(p) \frac{\partial \phi_j^-}{\partial p_\ell} &= 0 \\ \sum_{l=1}^{d} f_l^2(p) \frac{\partial \phi_j^-}{\partial p_\ell} &= 0 \\ &\vdots \\ \sum_{l=1}^{d} f_l^{d_1}(p) \frac{\partial \phi_j^-}{\partial p_\ell} &= 0 \end{aligned} \tag{7}$$

Equation 7 forms a system of linear partial differential equations. These equations can be integrated to give $d - d_1$ independent solutions $\phi_1^-, \ldots, \phi_{d-d_1}^-$. However, this integration may require the solution to a set of nonlinear ordinary differential equation systems that do not, in general, have an analytical solution.[15,17]

Limitations of the proposed approach

The proposed approach has several limitations. Firstly, it relies on some *a priori* knowledge to obtain suitable pseudo inputs. Secondly, it provides no way of "ranking" parameters or parameter groups in terms of their effect on the model predictions. This limitation can be overcome by using a sensitivity-based ranking as discussed previously in this section. Finally, while the tools of differential geometry can be used to treat systems with several regressors and parameters, the computation involving large-scale systems may be intractable. In future work, this size limitation might be treated by using an approximation of the mapping ϕ^+ to compute ϕ^-.

Case Study: A Batch Bioreactor System

The system model

Parameter estimation in biological systems is often difficult because of lack of identifiability[18] and high variability in data collection.[19] Consider a bioreactor modeled by the following system[20]:

$$\begin{aligned} \dot{x}_1 &= \tilde{r} x_1 \\ \dot{x}_2 &= -\tilde{r} x_1 Y^{-1} \end{aligned} \tag{8}$$

where $Y = 2$ is the yield coefficient and the reaction rate is described by Monod kinetics:

$$\tilde{r} = \frac{\mu x_2}{k + x_2}$$

If the concentration of x_2 is measured, then one may, without loss of generality, choose

$$r = \tilde{r}/x_2 = \frac{\mu}{k + x_2}$$

as a pseudo output for this system.

The parameters $p = [k, \mu]$ in System 8 can become inestimable under several scenarios including:

1. If the substrate concentration x_2 is very low then $r \sim \frac{\mu}{k}$.
2. If the substrate concentration x_2 is very high then $r \sim \frac{\mu}{x_2}$.
3. If the concentrations are only measured at the end of batch. That is, only $x_1(t_f)$ and $x_2(t_f)$ are known, for some fixed t_f (not necessarily steady state).
4. If experimental data is only available for a narrow range of initial conditions.

Inestimability implies that knowledge of the rate law cannot be used to reconstruct the value of each parameter in $p = [k, \mu]$. For example, at very low substrate concentration, only the ratio of the parameters k and μ can be computed. Knowledge of the rate without knowledge of the parameters k and μ is equivalent to being able to identify which constant rate curve (in the $k - \mu$ space) describes the system, but being unsure of where on the constant rate curve lie the true parameter values.

Reparameterization of the bioreactor system

Using the proposed procedure, the new coordinates in the parameter space can be computed as

$$\begin{aligned} p^+ &= \phi^+(p) = r(k, \mu)|_{x_2} = x_{2\text{nom}} \\ p^- &= \phi^-(p) = \frac{1}{2}\mu^2 + \frac{1}{2}(k + x_2)^2|_{x_2} = x_{2\text{nom}} \end{aligned}$$

where $x_{2\text{nom}}$ is the nominal value of the state x_2. By assumption, x_2 is measured, and so some nominal value of $x_{2\text{nom}}$ can be chosen as the reference point at which to apply the parameter transformation. Note that the coordinate p^- is chosen so that Eq. 3 is satisfied. Geometrically, this reparameterization is shown in Figure 1. As will be shown, $\phi^-(p)$ quantifies the information that would be difficult or impossible to measure given an unidentifiable or inestimable system. The mapping

$$\Phi = \begin{bmatrix} \phi^+(p) \\ \phi^-(p) \end{bmatrix} = \begin{bmatrix} \frac{\mu}{k + x_{2\text{nom}}} \\ \frac{1}{2}\mu^2 + \frac{1}{2}(k + x_{2\text{nom}})^2 \end{bmatrix}$$

is a local diffeomorphism that allows the parameter estimation to be done, interchangeably, in the (p^+, p^-) or the (k, μ) coordinates. The advantage of using the (p^+, p^-) coordinates is that p^+ and p^- are orthogonal. Furthermore, for a system that is inestimable, it is precisely the parameter p^+ that can be estimated while p^- cannot.

For each of the inestimable Scenario 1 to 4, only p^+ need be estimated. For Scenario 1, the coordinate p^+, aligned with the vector field $d\phi^+$ in Figure 1, is perpendicular to (almost) straight lines whose equation is given by $\mu = mk$ for a constant value m. This is because, for low values of $x_{2\text{nom}}$ the near linear relation $r \approx \frac{\mu}{k}$ holds. Alternatively, in Scenario 2, at high values of $x_{2\text{nom}}$, the coordinate p^+ (aligned with $d\phi^+$) is almost perpendicular to the line described by $\mu = b$ for a constant value b. This situation is illustrated in Figure 2. In the former case, estimating r amounts to determining which value of $m = \frac{\mu}{k}$ best describes the observed behavior, while in the latter case, estimating r amounts to estimating μ. Note that the parameter transformation Φ, for this system, was computed without having to determine the cause

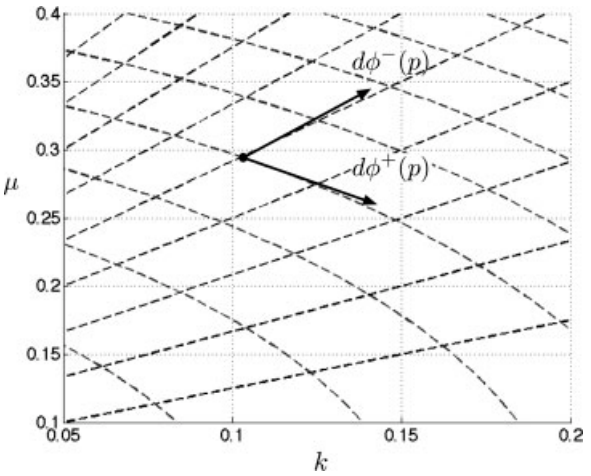


Figure 1. Geometric representation of the reparameterization of two-parameter bioreactor system with $x_{2nom} = 0.05$.

of inestimability, without having to do analysis to determine the best way to lump or drop parameters and without having to do any sensitivity analysis. While the reparameterizations (e.g., $r \approx \frac{\mu}{k}$ for Scenario 1) can be obtained by examination of the model equations, this is not always the case. For example, simple analysis of the model equations cannot be used to obtain a reparameterization for Scenarios 3 and 4. This is because it is not clear how the parameters μ and k interact in Scenarios 3 and 4 to affect the model predictions.

Simulation result

In this section, the kinetic parameters (μ and k) of a bioreactor system will be estimated using the proposed reparameterization approach. Four different case studies will be presented corresponding to Scenarios 1 to 4. The results obtained using the proposed approach will be compared to

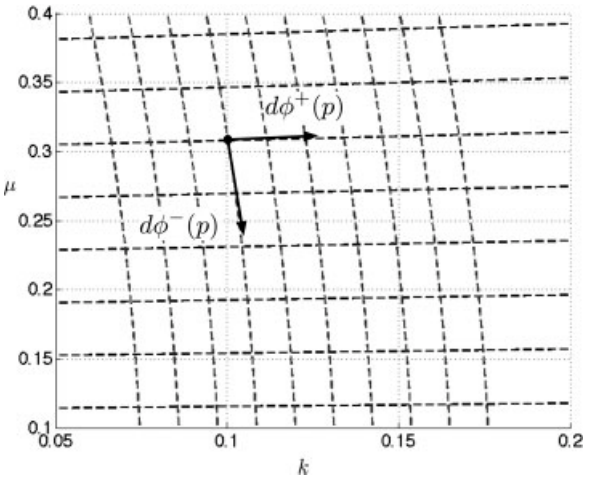


Figure 2. Geometric representation of the reparameterization of two-parameter bioreactor system with $x_{2nom} = 3.0$.

Table 1. True Values and Initial Guesses for Parameters in Bioreactor System

Parameter	True Value	Initial Guess	Units
k	0.12	0.15	kg/m^3
μ	0.23	0.40	s^{-1}

the results obtained by (a) attempting to estimate both parameters individually and (b) estimating only the appropriate subset or combination of parameters. The true (for the purpose of illustration) values, as well as the initial guesses for each of the parameters are listed in Table 1. Other experimental conditions (such as initial concentrations) are presented in Table 2. The parameter transformation Φ was evaluated at a nominal concentration of x_2, which was computed as the mean of the high and low numbers in the ranges shown in Table 2. Note that these values would typically be available to the experimenter.

The parameter estimation was done in Matlab version 7.4 running on a workstation computer with an AMD Opteron 280 processor running at 2.6 GHz and 4 Gb of RAM. Each estimation problem was solved using data from 10 equally spaced (with respect to the initial condition of x_2) runs. Other than reparameterization no attempt was made to optimize code. The parameter estimation problem was treated as an optimization problem, which was solved with Matlab's built-in "fminsearch" routine. The same measurement noise was added to each data set. This noise is Gaussian with zero mean, and a standard deviation of 0.05 was used for Scenarios 2, 3, and 4. For Scenario 1, a Gaussian noise with zero mean and a standard deviation 0.005 was used. The variance of the noise was lower for Scenario 1 because the absolute magnitude of the change in biomass concentration was much smaller. Table 3 lists the parameters estimated for each approach.

The number of data points used for parameter estimation is 20 for Scenario 3 and 1000 for Scenarios 1, 2, and 4. In Scenario 3, only the final concentrations (for both x_1 and x_2) for 10 runs was known, and in Scenarios 1, 2, and 4, concentration for each of the three runs was sampled at 50 equally spaced points in time. This number of measurements is likely to be higher than one would expect to obtain via sampling a physical system. However, the fact that the inaccurate parameter estimates were obtained even for a large data set implies that the lack of parameter estimability is quite severe.

Table 2. Initial Substrate Concentration (mol/m^3) for Different Scenarios.

Scenario	Initial Conditions		Description
1	$x_1(0) = 1$,	$x_2(0) \in [0.005,0.01]$	Low substrate concentration
2	$x_1(0) = 1$,	$x_2(0) \in [3,3.5]$	High substrate concentration
3	$x_1(0) = 1$,	$x_2(0) \in [1.5,2]$	Only final concentrations known
4	$x_1(0) = 1$,	$x_2(0) \in [1,1.05]$	Limited operating range

Table 3. Parameters Estimated for Each Scenario and Estimation Approach

Scenario	Estimate All Parameters	Reparameterize Using μ and k	Reparameterize Using Φ
1	$\{\mu,k\}$	$\{\tilde{\mu}=\frac{\mu}{k}\}$	$\{p^+\}$
2	$\{\mu,k\}$	$\{\mu\}$	$\{p^+\}$
3	$\{\mu,k\}$	N/A	$\{p^+\}$
4	$\{\mu,k\}$	N/A	$\{p^+\}$

Discussion of Results for the Bioreactor System

Parameter estimates, computation time, and SSE for each scenario are shown in Table 4. In each case, attempting to estimate both μ and k results in parameter estimates that are significantly different than the true values. To further support the conclusion of inestimability, note that in each case, choosing to estimate only one parameter did not significantly improve the quality of the fit. As shown in Figure 3, the biomass concentration predictions for the three parameter sets are similar. Indeed, estimating only a single parameter (as opposed to two) causes a relatively small increase in the SSE. In Scenarios 1, 2, and 4, the increases were 0.17%, 0.25%, and 1.3%, respectively. For Scenario 3, the change in SSE is significant. It is important to note, however, that in Scenario 3, the accuracy of the parameter estimates did not improve by estimating two parameters. As a result, the lower SSE observed for the two-parameter system is due to overfitting of the data and the system is inestimable.

To highlight the benefit of the proposed approach over the traditional approach of estimating a subset of parameters while holding the remaining parameters at a fixed value, consider the approximate 95% confidence regions for the parameters μ and k as shown in Figures 4a and 4b for Scenarios 3 and 4, respectively. Note that these confidence regions are based on local (in the parameter space) values of the sensitivity of the model predictions with respect to the parameter values.

The ellipsoids in Figures 4a and 4b correspond to the subset of the parameter space that is statistically indistinguishable from the estimated values (shown in Table 4). As can be seen from Figure 4, there is a wide variety of values for μ and k that would provide near-identical model predictions. This conclusion holds even if the set of possible parameters were constrained to lie in $\mathbf{R}^{2+}$. Note that both ellipses in Figure 4 have one axis, which is much longer than the other. A similar trend was noted in other studies of biological systems.[3] The elongated shape of the ellipses in Figure 4 implies that the choice of μ and k is not independent. Indeed, by fixing the value of one parameter, the other is implicitly fixed as well. Under the proposed approach, the values of both μ and k are allowed to vary, jointly, along a subspace of the parameter space.

The estimation problem in this section serves to highlight the utility of the proposed reparameterization approach. The proposed approach is compared to two other parameter estimation approaches for four different scenarios. In each scenario, the system is made inestimable by constraining the type of data that is available for parameter estimation. It is shown that estimating all system parameters yields parameter estimates that are both inaccurate and have very large confidence regions. Existing techniques can be used to lump or remove parameters from the system, under certain conditions, to reduce the number of parameters. However, this parameter reduction approach depends on a good physical understanding of the mathematical model and is otherwise correct only locally and for a specific set of experimental conditions. In contrast, the proposed reparameterization approach is effective at reparameterizing the system without the need for a priori understanding of the mechanism that causes lack of estimability. In addition, with the proposed approach, it is not necessary to compute sensitivities or plot joint confidence regions in the parameter space to choose an appropriate reparameterization. Indeed, one need only use a single transformation that is appropriate for a variety of conditions.

Case Study: A Five-Parameter Three-Phase Industrial Batch Reactor

To illustrate the application of the proposed technique for a system with more than one identifiable and one unidentifi-

Table 4. Simulation Results for Each scenario and Estimation Approach

Method	Estimate All Parameters	Reparameterize using μ and k	Reparameterize using Φ
Scenario 1: Low substrate concentration			
CPU Time (s)	8.84	3.95	3.88
Estimates for μ and k	(0.117, 0.057)	(0.275, 0.150)	(0.379, 0.196)
SSE	2.394×10^{-2}	2.400×10^{-2}	2.398×10^{-2}
Scenario 2: High substrate concentration			
CPU Time (s)	13.39	5.42	5.33
Estimates for μ and k	(0.227, 0.085)	(0.232, 0.150)	(0.233, 0.165)
SSE	2.392	2.397	2.398
Scenario 3: Only final concentrations known			
CPU Time (s)	10.81	N/A	5.11
Estimates for μ and k	(0.222, 0.0685)	N/A	(0.240, 0.177)
SSE	0.0500	N/A	0.0575
Scenario 4: Limited operating range			
CPU Time (s)	11.01	N/A	5.40
Estimates for μ and k	(0.234, 0.132)	N/A	(0.250, 0.191)
SSE	2.393	N/A	2.424

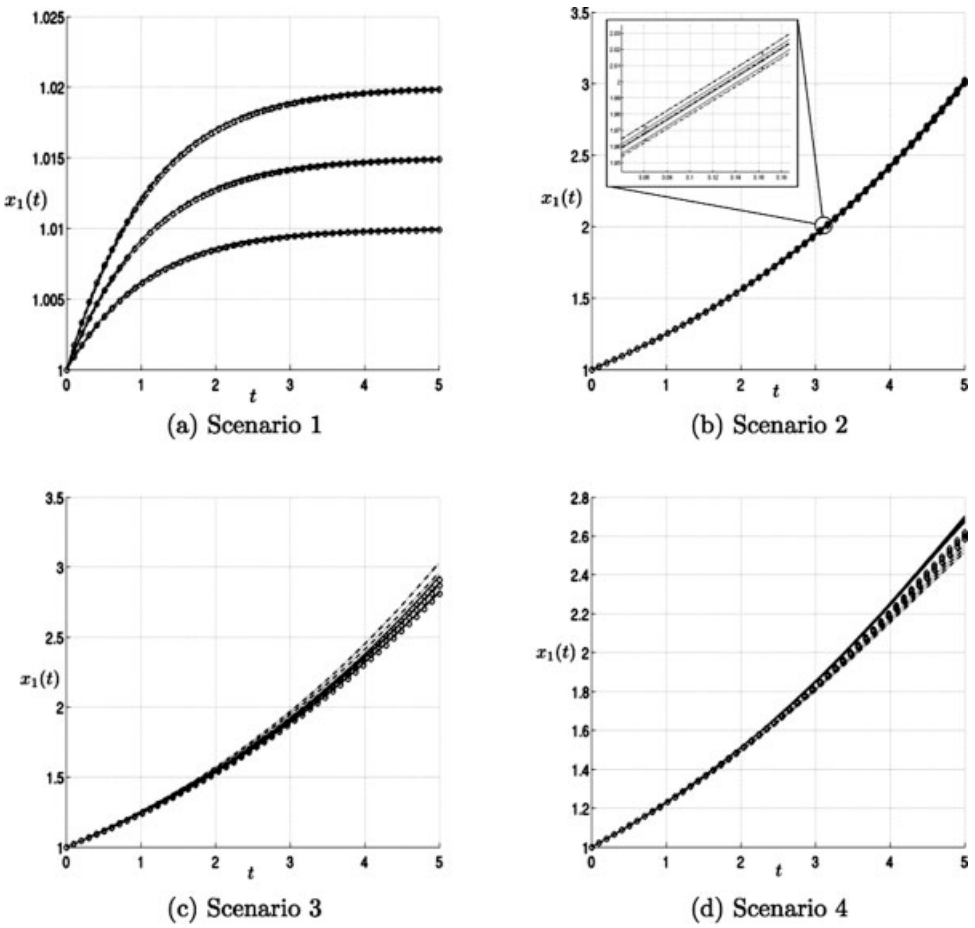


Figure 3. Predicted biomass concentrations (mol/m^3) for each scenario at the low, nominal, and high initial condition for x_1.

The model obtained by estimating both μ and k (—), reparameterizing using μ and k (- -), estimating only p^+ (– · –), and the true parameters (○).

able parameter, consider the following reaction scheme which describes the reaction in a three-phase batch reactor system.[21]

$$A_s \leftrightarrows A_l \tag{9}$$

$$A_l + B \leftrightarrows C + D \tag{10}$$

$$B + C \leftrightarrows E + D \tag{11}$$

$$B + E \leftrightarrows F + D \tag{12}$$

$$B + F \leftrightarrows P + D \tag{13}$$

Under this reaction scheme, a solid feed A is dissolved in a liquid (Eq. 9) and then undergoes a series of reactions, given by Eqs. 10 to 13. The final product is the species P. The system is typically operated so that the reaction mixture is boiling and species D is favorably removed from the liquid phase (i.e., it is the lightest component).

Under laboratory (i.e., small-scale) conditions, the removal rate of species D from the system is fast and the reverse reactions in Eqs. 9 to 13 is negligible. Under these conditions, the system of equations which describe the dynamics of the three-phase batch reactor system are[21]:

$$\frac{dn_{\mathrm{A_s}}}{dt} = -3(n_{\mathrm{A_s}}(0)\mathrm{MW_A})^{\frac{1}{3}}(n_{\mathrm{A_s}}\mathrm{MW_A})^{\frac{2}{3}}\frac{k_{\mathrm{MT}}}{\rho_{\mathrm{A}}R_{P0}V}\left(n_{\mathrm{A}_l}^{\mathrm{eq}} - n_{\mathrm{A}_l}\right)$$

$$\frac{dn_{\mathrm{B}}}{dt} = (-r_1 - r_2 - r_3 - r_4)V$$

$$\frac{dn_{\mathrm{C}}}{dt} = (r_1 - r_2)V$$

$$\frac{dn_{\mathrm{E}}}{dt} = (r_2 - r_3)V$$

$$\frac{dn_{\mathrm{F}}}{dt} = (r_3 - r_4)V$$

$$\frac{dn_{\mathrm{P}}}{dt} = r_4 V$$

where $n_{\mathrm{A_s}}(0)$ is the initial mole number of the solid component A. The system states that $n_{\mathrm{A_s}}$, n_{A_l}, n_{B}, n_{C}, n_{E}, n_{F}, and n_{P} are the mole numbers of the various species in the reactor. The parameters MW_{A}, ρ_{A}, R_{Po}, $n_{\mathrm{A}_l}^{\mathrm{eq}}$, and V are assumed known.

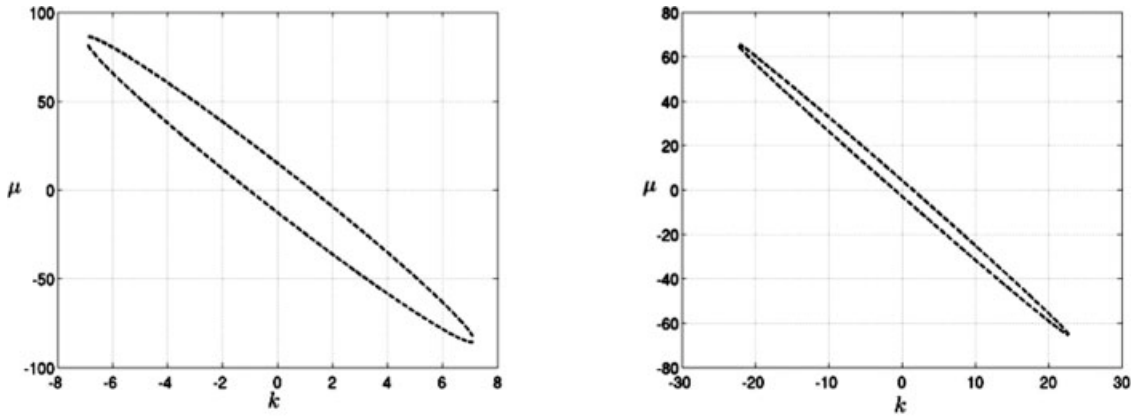


Figure 4. Approximate 95% confidence intervals obtained for parameter estimates when simultaneously estimating both μ and k.

At a constant temperature, the rates r_1 to r_4 are given by

$$r_i = k_i \frac{n_B n_x}{V^2}$$

where n_x is n_{A_l}, n_C, n_E, and n_F for $i = 1, 2, 3$, and 4, respectively. The unknown parameters in the model are k_1, k_2, k_3, k_4 and k_{MT}. A description of all the parameters is available in Table 5. Due to confidentiality reasons, the values of all system parameters are not available.[21] The values listed in Table 5 are therefore chosen for illustration purposes only.

Under the proposed experimental conditions only n_B and n_P are measured. As a result, the pseudo outputs, p_1^+ and p_2^+, chosen for this system correspond to the net consumption of n_B and production of n_P, respectively.

$$\begin{aligned} p_1^+ &= (r_1 + r_2 + r_3 + r_4)V \\ p_2^+ &= r_4 V \end{aligned} \tag{14}$$

Note that p_1^+ is a function of k_1, k_2, k_3, and k_4. This function describes the dynamics of the measured state n_B. The second pseudo output p_2^+ is a function of k_4 and describes the dynamics of the measured state n_P.

Table 5. Values of System Parameters for the Three-Phase Reactor Model

Parameter	Description	Value	Units
MW_A	Molecular weight of A	1.0	kg/mol
ρ_A	Density of A_s	500	kg/m^3
R_{Po}	Initial A_s	0.10	m
$n_{A_l}^{eq}$	Equilibrium solubility for component A	0.10	mol
V	Reactor volume	1.0	m^3
k_{MT}	Solid-liquid mass transfer coefficient	0.10	m/s
k_1	Rate constant for Eq. 10	1.0	m^3/mol s
k_2	Rate constant for Eq. 11	1.5	m^3/mol s
k_3	Rate constant for Eq. 12	0.50	m^3/mol s
k_4	Rate constant for Eq. 13	1.2	m^3/mol s

The inestimable parameter combinations (i.e., ϕ^-) can be computed using the method of characteristics.[15–17] First, the differentials of the pseudo outputs at the nominal operating conditions are computed:

$$d\phi_1^+|_{nom} = \left[0, \frac{n_{B,nom} n_{A_l,nom}}{V}, \frac{n_{B,nom} n_{C,nom}}{V}, \frac{n_{B,nom} n_{E,nom}}{V}, \frac{n_{B,nom} n_{F,nom}}{V}\right]$$

$$d\phi_2^+|_{nom} = \left[0, 0, 0, 0, \frac{n_{B,nom} n_{F,nom}}{V}\right]$$

Next the solution of the differential equations given by $\dot{\xi} = d\phi_1^+|_{nom}$ and $\dot{\xi} = d\phi_2^+|_{nom}$ are computed as a function of a time-like variable τ_1 and τ_2, respectively:

$$\xi(\tau_1) = \begin{bmatrix} \xi_1(0) \\ \xi_2(0) + n_{B,nom} n_{A_l,nom} \tau_1 \\ \xi_3(0) + n_{B,nom} n_{C,nom} \tau_1 \\ \xi_4(0) + n_{B,nom} n_{E,nom} \tau_1 \\ \xi_5(0) + n_{B,nom} n_{F,nom} \tau_1 \end{bmatrix}$$

$$\xi(\tau_2) = \begin{bmatrix} \xi_1(0) \\ \xi_2(0) \\ \xi_3(0) \\ \xi_4(0) \\ \xi_5(0) + n_{B,nom} n_{F,nom} \tau_2 \end{bmatrix}$$

where the numerical value of the volume $V = 1$, from Table 5, has been substituted to simplify the notation. Three additional independent vectors

$$\begin{aligned} v_1 &= [1, 0, 0, 0, 0] \\ v_2 &= [0, 1, 0, 0, 0] \\ v_3 &= [0, 0, 1, 0, 0] \end{aligned}$$

are chosen so that $\text{span}\{v1, v2, v3, d\phi_1^+|_{nom}, d\phi_2^+|_{nom}\} = \mathbf{R}^5$. The solutions to the differential equations given by $\dot{\xi} = v1$,

$\dot{\xi} = v2$, and $\dot{\xi} = v3$ are computed as a function of a time variable τ_3, τ_4, and τ_5, respectively:

$$\xi(\tau_3) = \begin{bmatrix} \xi_1(0) + \tau_3 \\ \xi_2(0) \\ \xi_3(0) \\ \xi_4(0) \\ \xi_5(0) \end{bmatrix} \xi(\tau_4) = \begin{bmatrix} \xi_1(0) \\ \xi_2(0) + \tau_4 \\ \xi_3(0) \\ \xi_4(0) \\ \xi_5(0) \end{bmatrix}$$

$$\xi(\tau_5) = \begin{bmatrix} \xi_1(0) \\ \xi_2(0) \\ \xi_3(0) + \tau_5 \\ \xi_4(0) \\ \xi_5(0) \end{bmatrix}$$

Next, a mapping F, made of the composition of the solutions $\xi(\tau_1)$ to $\xi(\tau_5)$ is computed:

$$F = \begin{bmatrix} \xi_1(\tau_1, \tau_2, \tau_3, \tau_4, \tau_5) \\ \xi_2(\tau_1, \tau_2, \tau_3, \tau_4, \tau_5) \\ \vdots \\ \xi_5(\tau_1, \tau_2, \tau_3, \tau_4, \tau_5) \end{bmatrix} = \xi(\tau_1) \circ \cdots \circ \xi(\tau_5)$$

$$= \begin{bmatrix} \xi_1(0) + \tau_3 \\ \xi_2(0) + \tau_4 + n_{\mathrm{B,nom}} n_{\mathrm{A_1,nom}} \tau_1 \\ \xi_3(0) + \tau_5 + n_{\mathrm{B,nom}} n_{\mathrm{C,nom}} \tau_1 \\ \xi_4(0) + n_{\mathrm{B,nom}} n_{\mathrm{E,nom}} \tau_1 \\ \xi_5(0) + n_{\mathrm{B,nom}} n_{\mathrm{F,nom}} (\tau_1 + \tau_2) \end{bmatrix}$$

At $\xi_1(0) = \xi_2(0) = \xi_5(0) = 0$, the mapping F is given by $F = M\tau$ with

$$M = \begin{bmatrix} 0 & 0 & 1\ 0\ 0 \\ n_{\mathrm{B,nom}} n_{\mathrm{A_1,nom}} & 0 & 0\ 1\ 0 \\ n_{\mathrm{B,nom}} n_{\mathrm{C,nom}} & 0 & 0\ 0\ 1 \\ n_{\mathrm{B,nom}} n_{\mathrm{E,nom}} & 0 & 0\ 0\ 0 \\ n_{\mathrm{B,nom}} n_{\mathrm{F,nom}} & n_{\mathrm{B,nom}} n_{\mathrm{F,nom}} & 0\ 0\ 0 \end{bmatrix}$$

and $\tau = [\tau_1,\tau_2,\tau_3,\tau_4,\tau_5]^T$. Note that the matrix M is invertible if the number of moles for each species is nonzero. As a result, the variables τ are given by $\tau = M^{-1}F$. In terms of the coordinates ξ, the solution is

$$\tau_1 = (n_{\mathrm{B,nom}} n_{\mathrm{E,nom}})^{-1} \xi_4$$
$$\tau_2 = (n_{\mathrm{B,nom}} n_{\mathrm{F,nom}})^{-1} \xi_5 - (n_{\mathrm{B,nom}} n_{\mathrm{E,nom}})^{-1} \xi_4$$
$$\tau_3 = \xi_1$$
$$\tau_4 = \xi_2 - \frac{n_{A_l,\mathrm{nom}}}{n_{\mathrm{E,nom}}} \xi_4$$
$$\tau_5 = \xi_3 - \frac{n_{C,\mathrm{nom}}}{n_{\mathrm{E,nom}}} \xi_4$$

The coordinates ξ were defined with respect to partial derivatives in the basis $\left[\frac{\partial}{\partial k_{\mathrm{MT}}}, \frac{\partial}{\partial k_1}, \frac{\partial}{\partial k_2}, \frac{\partial}{\partial k_3}, \frac{\partial}{\partial k_4}\right]$. As a result, the following substitutions are defined as $\xi_1 \mapsto k_{\mathrm{MT}}$, $\xi_2 \mapsto k_1$, $\xi_3 \mapsto k_2$, $\xi_4 \mapsto k_3$, $\xi_5 \mapsto k_4$. Under these substitutions, the expressions for τ are given by

$$\tau_1 = (n_{\mathrm{B,nom}} n_{\mathrm{E,nom}})^{-1} k_3$$
$$\tau_2 = (n_{\mathrm{B,nom}} n_{\mathrm{F,nom}})^{-1} k_5 - (n_{\mathrm{B,nom}} n_{\mathrm{E,nom}})^{-1} k_3$$
$$\tau_3 = k_{MT}$$
$$\tau_4 = k_1 - \frac{n_{\mathrm{A_1,nom}}}{n_{\mathrm{E,nom}}} k_3$$
$$\tau_5 = k_2 - \frac{n_{\mathrm{C,nom}}}{n_{\mathrm{E,nom}}} k_3$$

Note that $\langle d\tau_i, d\phi_j^+ \rangle = 0$ for each $i \in \{3,4,5\}$ and $j \in \{1,2\}$. The parameter combinations τ_3, τ_4, and τ_5 therefore satisfy Eq. 3, and the inestimable parameter combinations are therefore given by

$$p_1^- = k_{MT}$$
$$p_2^1 = k_1 - \frac{n_{A_l,\mathrm{nom}}}{n_{\mathrm{E,nom}}} k_3$$
$$p_3^- = k_2 - \frac{n_{C,\mathrm{nom}}}{n_{\mathrm{E,nom}}} k_3$$

The transformation Φ is therefore given by

$$\Phi = \begin{bmatrix} \frac{n_{\mathrm{B}}}{V} (k_1 n_{\mathrm{A}_l} + k_2 n_{\mathrm{C}} + k_3 n_{\mathrm{E}} + k_4 n_{\mathrm{F}}) \\ k_4 \\ k_{\mathrm{MT}} \\ k_1 - \frac{n_{\mathrm{A}_l,\mathrm{nom}}}{n_{\mathrm{E,nom}}} k_3 \\ k_2 - \frac{n_{\mathrm{C,nom}}}{n_{\mathrm{E,nom}}} k_3 \end{bmatrix}$$

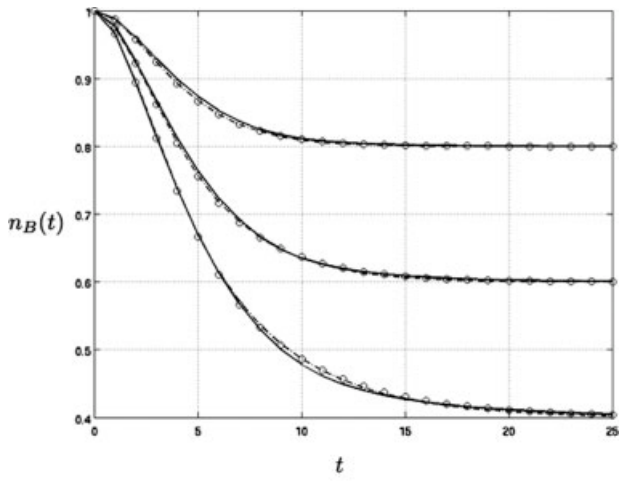
In this simulation example, the system parameters will be estimated under the following conditions. Experimental data will be obtained from three experiments corresponding to an initial A_s values of 0.05, 0.10, and 0.15 mols, respectively. The measured variables are n_{B} and n_{P}. Samples are taken every second for 25 seconds. The initial values of all states is zero with the exception of n_{B} whose initial value is 1 mol and n_{A_s} whose initial condition is the manipulated variable. The measurement noise for n_{B} and n_{P} is zero mean with a standard deviation of 0.05 and 0.0167, respectively.

This transformation was evaluated at nominal values of 0.25 for all states with the exception of n_{B} whose nominal value was 0.50. The nominal value of n_{B} was chosen as half the initial concentration. The nominal values of the other states were picked arbitrarily at half the value for n_{B}. The effect of changing the nominal values of the unmeasured variables on the parameter estimates was negligible. The sum-of-squared difference between the values of the parameters estimated using a nominal value of 0.25, 0.10, or 0.50 for n_{B} is less than 1×10^{-13}.

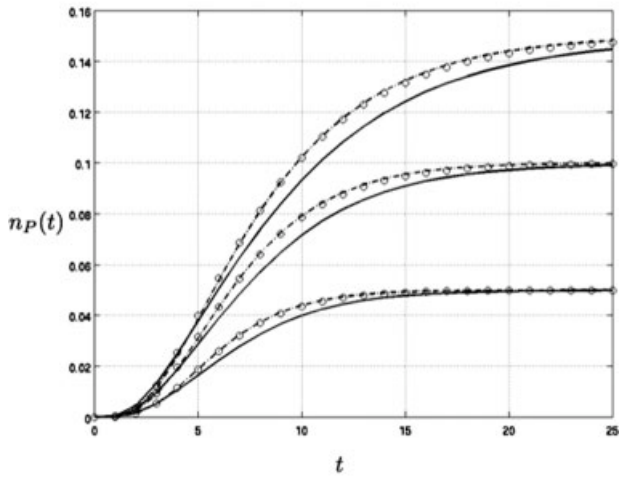
Under the experimental conditions chosen for this example, the original, five-parameter, reactor system is inestimable. Estimation of all five parameters is difficult in the sense that the predicted response and parameter estimates are inaccurate. Using the reduced parameter set $\{p_1^+, p_2^+\}$ it is possible to obtain a more accurate match of the predicted response and a lower SSE value using less CPU time. A comparison between system trajectories generated by the true parameters

and the model prediction for both the full (five-parameter) and the reduced (two-parameter) model are shown in Figure 5. As shown in Figure 5, the model fit obtained for the reduced model is better than the fit for the full model. The parameter estimates obtained for the full and reduced model are listed in Table 6. The SSE for the full and reduced model is 1.02 and 0.346, respectively. The computation time required to estimate the parameters (using the same workstation as for the bioreactor example) is 16.8 and 71.4 s for the reduced and full model, respectively. Note that even if a better parameter estimation algorithm was used to estimate the parameters in the full model, the fit obtained is not likely to be qualitatively better than the fit of the reduced model (as shown in Figure 5 for the selected data set.

If a temperature-dependant expression for r_1, r_2, r_3, and r_4 is used (e.g., an Arrhenius relation) then the mapping Φ may be difficult to compute. Letting



(a) Value of n_B



(b) Value of n_P

Figure 5. A plot of the predictions of the full model (—), the reduced model (– · –) and the using the true parameter values (○).

Table 6. Values of Estimated System Parameters for the Three-Phase Reactor Model

			Estimated Values	
Parameter	Value	Initial Guess	Full Model	Reduced Model
k_{MT}	0.10	0.15	0.0531	0.15
k_1	1.0	1.0	0.167	0.859
k_2	1.5	1.0	0.137	0.859
k_3	0.50	1.0	4.02	0.859
k_4	1.2	1.0	0.391	0.162

$$k_i = A_i e^{\frac{-E_i}{RT}}$$

for $i \in \{1,2,3,4\}$, and defining a new parameter vector

$$p = [k_{MT}, A_1, A_2, A_3, A_4, E_1, E_2, E_3, E_4]$$

the mapping ϕ^+ is given by

$$\phi^+ = \begin{bmatrix} \phi_1^+ \\ \phi_2^+ \end{bmatrix} = \begin{bmatrix} \frac{n_B}{V}\left(A_1 e^{\frac{-E_1}{RT}} n_{A_l} + A_2 e^{\frac{-E_2}{RT}} n_C + A_3 e^{\frac{-E_3}{RT}} n_E + A_4 e^{\frac{-E_4}{RT}} n_F\right) \\ A_4 e^{\frac{-E_4}{RT}} \frac{n_E}{V} \end{bmatrix}$$

It is very difficult to solve for the mapping ϕ^- using the differential geometric approach used in this section because the solution requires obtaining an analytical solution to the differential equation given by $\dot{\xi} = d\phi_1^+|_{nom}$. This integration is difficult to do analytically in the nonisothermal case because of the exponential terms for the activation energy parameters in ϕ_1^+. Future work should focus on developing numerical tools to obtain ϕ^-.

An alternative approach for reparameterizing the three-phase reactor system is to choose a new set of pseudo outputs. Let the rate constants r_1, r_2, r_3, and r_4 be chosen as pseudo outputs in addition to those listed in Eq. 14. In this case, the transformation, described in the background section, which reparameterizes the Arrhenius relation in terms of a single variable can be used. This allows the temperature-dependent case to be treated in the same manner as the constant temperature case under a redefinition of variables (e.g., letting the pseudo output $A_1 e^{\frac{-E_1}{RT_{nom}}}$ take the place of k_1).

Conclusions and Future Work

In this work, a novel approach for the reparameterization of inestimable models is proposed. The approach relies on computing a transformation which partitions the parameter space into an orthogonal estimable and inestimable subspaces. The proposed approach allows *a priori* information about the system to aid in parameter estimation. Furthermore, the transformation obtained does not require sensitivity calculations and is applicable over a wide variety of experimental conditions. The proposed approach can be integrated with sensitivity-based analysis. A systematic approach for obtaining the partitioning transformation is provided using a differential-geometric framework.

The proposed approach is illustrated using a bioreactor and a three-phase reactor system. For the bioreactor system, four different inestimability scenarios are considered and three different parameter estimation approaches are compared. The proposed approach provides a common reparameterization for all four scenarios. Furthermore, it is shown to be computationally efficient and to produce reasonable parameter estimates for all four scenarios. The three-phase reactor system is used to illustrate the utility of differential geometry and the method of characteristics in partitioning the parameter space. For the isothermal case, an analytic expression for the inestimable parameter combinations can be found. However, for the nonisothermal case an analytical solution may be impossible to find.

The utility of the proposed approach has only been demonstrated for small-scale systems. For large-scale systems, however, the computations required to obtain the partitioning transformation may be intractable. Future work should focus on applying (or modifying, if necessary) this approach for systems with many regressors and parameters.

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