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Chapter 19

IDENTIFIABILITY

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I. INTRODUCTION

In 1956, Mones Berman and Robert Schoenfeld published a paper that was concerned with the information content of measurements on some

compartments of a multicompartment system. They pointed out that in general an n-compartment linear system with constant coefficients has n^2 rate constants in the coefficient matrix; the entries in the coefficient matrix are invariants, i.e., fixed, but unknown. Assuming the eigenvalues are distinct and there are no unusual circumstances, measurement of the time course of one compartment gives only $2n - 1$ parameters that are functions of the invariants. For each additional compartment one obtains only $n - 1$ more such parameters. In theory we need measurements on all compartments to obtain enough information to determine all n^2 invariants.

From the connectivities of our models, some of the rate coefficients are zero so there may not actually be n^2 invariants. Even so the same issue is present; if we measure only a subset of the compartments how do we know there is enough information in the measurements to uniquely define all of the rate coefficients?

Suppose there are Z transfer coefficients that are zero and that we can estimate P compound parameters (parameters that are functions of the basic rate parameters); then there are $n^2 - Z - P$ degrees of freedom in the data. If $P = n^2 - Z$, one has P equations, generally nonlinear, in P unknowns and it may be possible to solve for the values of the basic parameters. However, there is no guarantee that P nonlinear equations in P unknowns has a unique solution. If $n^2 - Z - P > 0$ the basic rate parameters are determinable as functions of $n^2 - Z - P$ free variables. Note that some of the invariants (the basic rate parameters) may be determinable; in that case, if d are determinable, the remaining $n^2 - Z - d$ are functions of $n^2 - Z - P - d$ free variables. Using similarity transformations and imposing constraints such as positivity of the nonzero invariants Berman and Schoenfeld showed that the values of the free variables are constrained to fall in subspaces of the space of the free variables.

In their paper, Berman and Schoenfeld (1956) presented an example of a three-compartment model and an experiment in which only compartment 1 and the excretion from compartment 1 could be measured. With the measurements available there were two degrees of freedom left in the measurements. Figure 2 in their paper shows the subspaces in the two free variables in which all permissable models must fall.

That work comes very close to what is now called the identifiability problem; however, they did not separate out the effects of measurement error. They summarized their work in a subsequent paper (1958) on the information content of data in which they did distinguish between the two sources of uncertainty. "The uncertainty in these values arises from the fact that the collected data may not be sufficient to define the system completely and that the collected data have associated fluctuations."

In the meanwhile, work on this problem was being done in statistics (Koopmans and Reiersol, 1950), econometrics (Fisher, 1959), and systems engineering (Astrom and Eykhoff, 1971) where identifiability was defined as a distinct problem. It was not until 1970 that a paper on identifiability of a compartmental system appeared. That was the paper of Bellman and Astrom (1970) which is now cited as the first paper to address the identifiability problem for compartmental systems. Since that time, a growing body of literature on identifiability for compartmental models and other types of models of biological systems has come to dominate the literature on identifiability. For compartmental systems, although the problem has not been solved in full generality, a large amount of theory is available and we have a clear picture of its extent and difficulties. For an introduction, see the review of Cobelli and DiStefano (1980) and Chap. 14 of my book (Jacquez, 1985). For a simplified introduction see Jacquez (1987). More advanced papers by Cobelli, DiStefano, Godfrey, and others can be found in the collection edited by Eric Walter (1987). A catalog of identifiability properties of three-compartment models is given by Norton (1982).

In conclusion, a crucial step in the development of our ideas was the recognition that the two problems: Are the observations obtained sufficient to specify the invariants of the model?, and, What are the effects of the errors of measurement?, are separable and should be treated in that order. The first problem is that of the identifiability of the parameters, the second concerns the propagation of errors through the calculations and their effects on the estimates, the estimation problem.

II. EXAMPLES

To introduce the idea of identifiability, we start with two very simple problems, one from enzyme kinetics and one from compartmental modeling. In the next section, we classify the parameters; section IV then gives a general statement of the identifiability problem.

A. INITIAL VELOCITY IN MICHAELIS–MENTEN KINETICS

Consider a one-substrate, one-product enzyme reaction, as shown in Fig. 1. Suppose one can do the experiment of measuring the initial velocity of

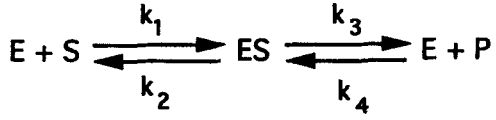

FIG. 1.

the formation of product, P, at a series of substrate concentrations, S. If the rate of formation of the intermediate complex, ES, is rapid in relation to the rate of formation of product, P, it is well known that the initial velocity shows saturation kinetics in the substrate concentration, as given by Eq. (1) for the initial forward velocity, v_f.

$$v_f = \frac{V_{Mf}[S]}{K_{mf} + [S]}. \tag{1}$$

Here, $[S]$ is standard chemical notation for concentration of S. V_{Mf} and K_{mf} are parameters that are functions of the basic kinetic parameters, k_1, k_2, k_3, and of the total enzyme concentration, E_0, as given by

$$V_{Mf} = k_3 E_0 \tag{2}$$

$$K_{mf} = \frac{(k_2 + k_3)}{k_1}. \tag{3}$$

Both V_{Mf} and K_{mf} can be estimated from the initial velocity experiment, but notice that the basic kinetic parameters may not be determinable. If we know E_0, k_3 is determined by Eq. (2); it is identifiable. However, unique solutions for k_1 and k_2 cannot be obtained and k_4 does not even appear in Eq. (2) and (3).

Now suppose that one can do the same experiment for the backwards initial velocity of formation of substrate at different concentrations of product. Under the same assumptions, the backwards initial velocity is given by

$$v_b = \frac{V_{Mb}[P]}{K_{mb} + [P]}. \tag{4}$$

The analogs of Eqs. (2) and (3) are now

$$V_{Mb} = k_2 E_0 \tag{5}$$

$$K_{mb} = \frac{(k_2 + k_3)}{k_4}. \tag{6}$$

For this experiment, if we know E_0, k_2 is identifiable, but although k_3 and k_4 influence K_{mb}, they are not identifiable. Not only is k_1 not identifiable, it does not even appear in Eqs. (5) and (6).

It is clear that only if one knows E_0 and can do both of the above experiments, can one obtain estimates of all four basic kinetic parameters.

B. A TWO-COMPARTMENT MODEL

Consider the simple two compartment system shown in Fig. 2. We suppose the inflow to compartment 1 is constant and the system is at a steady state. The experiment consists of injecting an impulse of D units of tracer into compartment 1 and measuring the tracer concentration in compartment 1. The solution for total tracer in compartment 1 is given by

$$q_1 = De^{-(k_{01}+k_{21})t}. \tag{7}$$

The observation function or response function (the function that describes what is observed without the errors of observation) is

$$y = \frac{D}{V_1}e^{-(k_{01}+k_{21})t}, \tag{8}$$

where V_1 is the volume of distribution in compartment 1.

Notice that the actual observations are samples at different times of the observation function with some experimental error added. To check identifiability, we only need to examine the observation function.

From y, one can determine the two compound parameters

$$\phi_1 = \frac{D}{V_1} \tag{9}$$

$$\phi_2 = k_{01} + k_{21}. \tag{10}$$

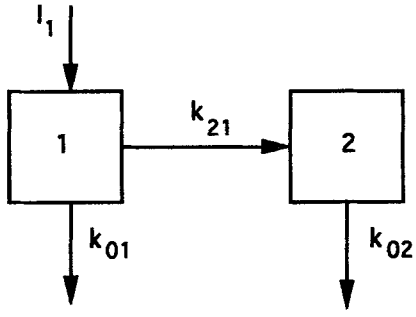

FIG. 2.

Thus, knowing D, V_1 is uniquely determined (identifiable). However, k_{01} and k_{21} are not uniquely determined, only the sum $k_{01} + k_{21}$ is determined, and k_{02} has no effect on the observations.

III. CLASSIFICATION OF PARAMETERS

Both of the above examples illustrate a number of important points about the basic parameters of the system (Berman's invariants) and the parameters that are determinable by a particular experiment.

1. The first point is that one has to clearly distinguish between the basic parameters and the parameters that are determinable by an experiment. I have called the latter observational parameters and denote them by the symbol ϕ_i, $i = 1, \ldots$. Notice that in each of the above experiments, the observational parameters are functions of the basic kinetic parameters.
2. A basic kinetic parameter may or may not influence the observations in a particular experiment. If the observational parameters are not functions of a particular basic parameter, the basic parameter can be changed without affecting the observations. Such a parameter is insensible in the experiment and is called an insensible parameter. If a basic parameter does influence the observations in an experiment, it is sensible by that experiment. However, a sensible parameter may or may not be uniquely determined (identifiable) by the experiment. In each of the above examples, there were sensible parameters that were identifiable and others that were not identifiable.
3. Basic parameters may also be introduced by an experiment. We have talked so far as though the basic parameter set consisted of the invariants of the system and that the observational parameters are functions of the those invariants. That is very often the case and it is easy to think of the problem in those terms. However, it is not quite that simple. The design of an experiment may also introduce basic parameters. A good example is the impulsive input (dose) D in example 2 above. If that is not known and is to be estimated, it appears as a basic parameter in Eq. (8).

We conclude this section with a summary of the classification of the parameters.

A. OBSERVATIONAL PARAMETERS

The observational parameters are determined by the experimental design and are functions of a basic parameter set.

B. BASIC PARAMETERS

The basic parameters are the system invariants (kinetic parameters of the system) plus possibly some parameters introduced by the experimental design. For a given experiment, they may be: (i) insensible, i.e., do not influence the observations, or (ii) sensible, i.e., influence the observations in the experiment. In that case, they may be: (a) identifiable or (b) nonidentifiable.

IV. PARAMETER IDENTIFIABILITY AND ESTIMATION

With that background, let us proceed to a more formal statement of the identifiability problem and distinguish between the identifiability problem and the estimation problem.

We do experiments on systems in the real world but analyze the results on models of experiments done on models of the systems. We have in mind a model of the system which incorporates current hypotheses of its structure, rate laws, and values of some of the parameters. An experiment involves adding inputs and making measurements (outputs). So we are concerned with models of the experiments. Let $\mathbf{x}$ be the vector of state variables of the model. The inputs in the experiment are often described as the product of a matrix $\mathbf{B}$ and a vector of possible inputs, $\mathbf{u}$. The inputs are combinations of the components of the vector $\mathbf{u}$, i.e., $\mathbf{Bu}$. For given initial conditions and input to the model, the time course of change in the vector of state variables is usually given by a set of differential equations.

$$\dot{\mathbf{x}} = \mathbf{F}(\mathbf{x}, \theta, \mathbf{Bu}, t) \quad \mathbf{x}(0) = \mathbf{x}_0, \tag{11}$$

where θ is a vector of basic parameters and $\mathbf{x}_0$ gives the initial conditions.

To fully specify an experiment, we also have to give the observations. The observations are usually specified by giving the vector function of the state variables that describes what is measured.

$$\mathbf{y} = \mathbf{G}(\mathbf{x}, \mathbf{x}_0, \mathbf{Bu}, t) = \mathbf{G}(t, \phi). \tag{12}$$

We call $\mathbf{y}$ the observation function; $\mathbf{y} = \mathbf{G}(t, \phi)$ is also called the response function. In engineering it is common to refer to input–output experiments, the response function being the output, in the information sense. With compartmental systems that could be confused with the material outputs or outflows from the system so I will try to use only the terms response

function or observation function. Remember that the experiment could also introduce some basic variables, which are not explicitly shown in Eq. (12).

The actual observations, $\mathbf{z}_i$, are samples of the observation function at different times with added experimental errors of measurement.

$$\mathbf{z}_i = \mathbf{y}(t_i, \phi) + \varepsilon_i \quad i = 1, \ldots, n, \tag{13}$$

where ε_i is the vector of measurement errors at sample time t_i.

If the model is a compartment model with constant fractional transfer coefficients, the equation corresponding to (11) is

$$\dot{\mathbf{q}} = \mathbf{Kx} + \mathbf{Bu} \quad \mathbf{q}(0) = \mathbf{q}_0. \tag{14}$$

In Eq. (14), **K** is the matrix of transfer coefficients. The components of **K** are basic or structural parameters of the model. If the observations are linear combinations of the compartments, the observation function is given by Eq. (15), in which **C** is the observation matrix.

$$\mathbf{y} = \mathbf{Cq}. \tag{15}$$

Basic parameters could be introduced by the experimental design by way of the initial conditions, $\mathbf{q}_0$, the inputs **Bu,** and the observational matrix **C.**

Now we can restate the identifiability problem. Equation (12) determines the observational parameters (ϕ_i); the ϕ_i are by definition the compound parameters that are uniquely determined by the observation functions. For the given model and experiment, are the basic parameters, the θ_j, uniquely determined by the ϕ_i? That is the identifiability problem. Notice that data collection is not needed to solve that problem. We only have to know the model of the experiment. Then we calculate the observation functions and check to see if the θ_j are uniquely determined.

Given that the parameters of interest are identifiable, one can then proceed to collect data and estimate the θ_j. However, there is no point to doing the experiment if the parameters of interest are not identifiable!

One final point; the term identification is sometimes used to mean the estimation of parameters from the data and in some papers one may find both terms, identifiability and identification. Do not be confused. Identifiability has the meaning we have just given. Identification refers to the actual estimation of the parameter values.

V. IDENTIFIABILITY: DEFINITIONS

Now that it is clear that identifiability is concerned with the question of uniqueness of solutions for the basic parameters from the observation function of a given experiment, we have to introduce the various types of identifiability that have been defined in the literature.

A. LOCAL IDENTIFIABILITY

If the observation function for an experiment determines a finite number of values for a parameter, the parameter is locally identifiable. Auxiliary information may be needed to decide which one of the values is the appropriate one for the physiological system you are working on. This includes cases of symmetry in models in which two or more parameters play equivalent roles, so their values can be interchanged.

B. GLOBAL IDENTIFIABILITY

If a parameter is locally identifiable but the observation function determines exactly one solution in the entire parameter space, that parameter is globally identifiable for that experiment. Thus, global identifiability is a subcategory of local identifiability. The term unique identifiability is equivalent to global identifiability.

C. STRUCTURAL IDENTIFIABILITY

A property of a parameter is structural if it holds for almost all values of the parameter, i.e., almost everywhere in parameter space. The qualification, "almost everywhere" means that the property may not hold on a special subset of measure zero. Thus a parameter could be globally identifiable almost everywhere but only locally identifiable for a few special values. Structural global or local identifiability are generic properties that are not dependent on the values of the parameters, in the almost everywhere sense (Walter, 1982).

D. MODEL IDENTIFIABILITY

If all of the parameters of a model are globally identifiable, the model is globally identifiable for that experiment. If all of the parameters are identifiable but at least one is not globally identifiable, the model is only locally identifiable.

E. CONDITIONAL IDENTIFIABILITY

If for a model and experiment a parameter is not identifiable but setting the values of one or more other parameters makes it identifiable, the parameter is identifiable conditioned on the parameters that are preset. Note that by "setting a parameter" we mean we assign a value to it and then treat it as known, i.e. remove it from the parameter set.

F. INTERVAL IDENTIFIABILITY AND QUASI-IDENTIFIABILITY

Following up on the work of Berman and Schoenfeld (1956, 1958), DiStefano (1983) has used the term interval identifiability to describe the restriction of a parameter to a subspace by the constraints of a problem. It is possible for such an interval to be small enough for a parameter to be "identifiable for practical purposes" and DiStefano calls that quasi-identifiability.

VI. METHODS OF CHECKING IDENTIFIABILITY

For very simple problems, such as the two examples in section II, one can often determine identifiability by inspection of the observation function. However, as soon as the models get more complex, that is no longer possible. A number of methods are available for checking identifiability. Here, I want to give brief descriptions of them. For more details see the books by Carson *et al.* (1983), Godfrey (1983), Jacquez (1985), and Walter (1982).

The methods differ for linear and nonlinear systems; I present them in that order. First, let us make clear the distinction between linear and nonlinear systems and linear and nonlinear parameters. For a linear system, the rates of change of the state variables are given by linear differential equations. Such systems have the superposition or input linearity property. By that I mean, the response to a sum of two inputs equals the sum of the responses to the individual inputs. In contrast, the rates of change of the state variables of nonlinear systems are given by nonlinear differential equations, and superposition does not hold.

When applied to the parameters of a system, the terms linear and nonlinear have entirely different definitions; they then refer to the way the parameters appear in the solutions for the state variables or the observation functions. Suppose x is a state variable and the solution of the differential equation is of the form

$$x = c + \theta f(t). \tag{16}$$

The parameter θ is a linear parameter because it appears linearly in the solution. For the solution of a one compartment system with two parameters, the initial value and the excretion coefficient, the solution is

$$q = q_0 e^{-\lambda t}. \tag{17}$$

The initial value q_0 is a linear parameter and λ is a nonlinear parameter. Even for linear systems, many of the parameters appear nonlinearly in the solutions.

A. METHODS FOR LINEAR SYSTEMS WITH CONSTANT COEFFICIENTS

Some simple topological properties of the connection diagram should be checked first. They provide necessary but not sufficient conditions for identifiability.

(i) *Input and output connectability.* There must be a path from some input to each of the compartments of the model and there must be a path from each compartment to some observation site.
(ii) *Condition on number of parameters.* The number of unknown parameters must not exceed a number which depends on the topology of the system; see Carson *et al.* (1983) for the method of calculation.

For checking parameter identifiability, three methods have received most attention.

1. The Similarity Transformation Method

Consider a system for which $\mathbf{K}$ has been subjected to a similarity transformation to give a system with a coefficient matrix $\mathbf{P}^{-1}\mathbf{K}\mathbf{P}$, where $\mathbf{P}$ is nonsingular. Recall that under a similarity transformation, the eigenvalues do not change. Impose on $\mathbf{P}^{-1}\mathbf{K}\mathbf{P}$ all the structural constraints on $\mathbf{K}$ and require that the response function of the system with matrix $\mathbf{P}^{-1}\mathbf{K}\mathbf{P}$ be the same as that of the system with matrix $\mathbf{K}$. If the only $\mathbf{P}$ that satisfies those requirements is the identity matrix, all parameters are globally identifiable. If a $\mathbf{P} \neq \mathbf{I}$ satisfies the requirements, one can work out which parameters are not identifiable and which are.

2. The Modal Matrix Method

The matrix whose columns are the eigenvectors is the modal matrix. In this approach, one looks at the response function to see if the eigenvalues

and the components of the modal matrix are identifiable; both are of course functions of the basic parameters. This method has not been developed as fully as a formal method as the next one and seems to offer no advantages.

3. *The Laplace Transform or Transfer Function Method*

This method is simple in theory and is the most widely used, although it becomes quite cumbersome with large models. First we note that if a linear model is identifiable with some input in an experiment, it is identifiable from impulsive inputs into the same compartments. That allows one to use impulsive inputs in checking identifiability even if the actual input in the experiment is not an impulse. Take Laplace transforms of the system differential equations and solve the resulting algebraic equations for the transforms of the state variables. Then write the Laplace transform for the observation function (response function). That will be of the form

$$Y_i = \frac{\phi_{i,m+1}s^{m-1} + \cdots + \phi_{i,2m}}{s^m + \phi_{i,1}s^{m-1} + \cdots + \phi_{i,m-1}s + \phi_{i,m}}. \tag{18}$$

The coefficients, $\phi_{i,r}$ are the observational parameters and are functions of the basic parameters. That gives a set of nonlinear algebraic equations in the basic parameters. The hard part is to determine which of the basic parameters are uniquely determined by this set of nonlinear equations.

To illustrate its use, let us apply this method to example B of section II. The equations for tracer flow are

$$\begin{aligned} \dot{q}_1 &= -(k_{01} + k_{21})q_1 \\ \dot{q}_2 &= k_{21}q_1 - k_{02}q_2 \\ q_1(0) &= D \\ q_2(0) &= 0. \end{aligned} \tag{19}$$

The Laplace transforms are

$$\begin{aligned} sQ_1 - D &= -(k_{01} + k_{21})Q_1 \\ sQ_2 &= k_{21}Q_1 - k_{02}Q_2. \end{aligned} \tag{20}$$

Thus,

$$\begin{aligned} Q_1 &= \frac{D}{s + (k_{01} + k_{21})} \\ Q_2 &= \frac{k_{21}D}{s^2 + (k_{01} + k_{21} + k_{02})s + k_{02}(k_{01} + k_{21})}. \end{aligned} \tag{21}$$

We do not really need Q_2 for this problem. The transform of the observation function is

$$Y = \frac{D/V_1}{s + (k_{01} + k_{21})}. \tag{22}$$

That gives us

$$\phi_1 = D/V_1 \tag{9}$$

$$\phi_2 = k_{01} + k_{21}. \tag{10}$$

B. METHODS FOR NONLINEAR SYSTEMS

Although there is a large literature on identifiability for linear systems with constant coefficients, less has been done on nonlinear systems. Two general properties should be remembered. Whereas for linear systems one can substitute impulsive inputs for the experimental inputs for the analysis of identifiability, one cannot do that for nonlinear systems. One must analyze the input–output experiment for the actual inputs used. That is a drawback. On the other hand, experience shows that frequently the introduction of nonlinearities makes a formerly nonidentifiable model identifiable for a given input–output experiment. Two methods are available.

1. Taylor Series

A method used widely depends on expanding the observation function (response function) in a Taylor's series around $t = 0^+$ (Pohjanpalo, 1978). The coefficients of the expansion are functions of the basic parameters and are the observational parameters. Although there are an infinite number of coefficients, only a finite number are independent. As one adds coefficients from terms of higher and higher order, eventually one reaches coefficients that are no longer independent of the preceeding ones. One problem is that it is not always obvious when that point is reached.

2. Similarity Transformation

The method of similarity transformations has been extended to nonlinear systems (Vajda *et al.*, 1989). I have had no experience with this method but point out that the similarity transformation method for linear systems is often much more work than the Laplace transform method.

VII. LOCAL IDENTIFIABILITY AT A POINT

A large part of the literature on identifiability is concerned with checking global and/or local identifiability of models. That is a problem of great interest from the viewpoint of basic theory but can also be very difficult because basically it is the problem of solving simultaneous nonlinear algebraic equations. A less difficult problem but one that gives considerable useful information is that of testing local identifiability at a given point in parameter space. In physiology we are concerned with testing hypotheses and focus on those parameters that have to be estimated to test a hypothesis. Furthermore we often have auxilliary information and results from other experiments that provide initial estimates of the parameter values. Even if our estimates are rough, tests of local identifiability at a number of points provide sufficient information for practical applications. In fact, for compartmental models with constant fractional transfer coefficients, we are assured that if a parameter is locally identifiable at one value it is locally identifiable for almost all values of the parameter (Eisenfeld, 1986; Walter, 1982), so we obtain structural local identifiability.

It is natural to develop the theory in terms of the two levels of parameters, the basic parameters, θ_j, and the observational parameters, ϕ_i, which are identifiable functions of the basic parameters. For problems of low dimensionality it is easy to generate the ϕ_i explicitly as functions of the θ_j and check identifiability on the functional relations, $\phi_i = f_i(\theta_1, \ldots, \theta_p)$. For problems of even moderate magnitude the algebraic work involved in finding the ϕ_i and solving the equations may become limiting.

An important finding is that if one has initial estimates of the basic parameters one can determine local identifiability numerically at the initial estimates directly without having to generate the observational parameters as explicit functions of the basic parameters. That is the approach used in the IDENT programs which use the method of least squares (Jacquez and Perry, 1990; Perry, 1991). It is important to realize that the method works for linear and nonlinear systems, compartmental or noncompartmental. Furthermore, for linear systems it gives structural local identifiability.

A. LEAST SQUARES

Let there be p basic parameters and assume we have estimates, $\theta_1^o, \ldots, \theta_p^o$. For the θ_j set at these estimates, calculate a set of values of the observation function at n points in time for $n > p$. Then linearize the observation function in the parameters θ_k around the estimates which now play the

role of known values. What follows can be repeated for a number of values for the parameters or it can be done sequentially as one obtains more estimates of the values of the parameters

$$y_j = G_j^o + \sum_{k=1}^{p} \frac{\partial G_j^o}{\partial \theta_k} \Delta\theta_k + e_j. \tag{23}$$

The superscript ^{o} means the term is to be evaluated at the known values (the estimates) of the parameters. Notice that the e_j are not measurement errors, they are truncation errors in the expansion.

Form the squared deviations around the initial estimates and sum over the set of calculated values of the response function, as in

$$S = \sum_{j=1}^{n} \left[y_j - G_j^o - \sum_k \frac{\partial G_j^o}{\partial \theta_k} \Delta\theta_k \right]^2. \tag{24}$$

Notice that $y_j - G_j^o = 0$. Next, find the least squares estimate of $\Delta\theta_k$. Let $\Delta\hat{\theta} = (\Delta\hat{\theta}_1, \ldots, \Delta\hat{\theta}_p)$ be the least squares estimates of $\Delta\theta$ and $\mathbf{g}$ be the sensitivity matrix

$$\mathbf{g} = \begin{vmatrix} \frac{\partial G_1^o}{\partial \theta_1} & \cdots & \frac{\partial G_1^o}{\partial \theta_p} \\ \vdots & \ddots & \vdots \\ \frac{\partial G_n^o}{\partial \theta_1} & \cdots & \frac{\partial G_n^o}{\partial \theta_p} \end{vmatrix}. \tag{25}$$

The normal equations for the estimates $\Delta\hat{\theta}_k$ are given by

$$\mathbf{g}^{\mathbf{T}}\mathbf{g}\Delta\hat{\theta} = \mathbf{g}^{\mathbf{T}}(\mathbf{y} - \boldsymbol{G}^{\mathbf{o}}) = 0. \tag{26}$$

If the determinant of $\mathbf{g}^{\mathbf{T}}\mathbf{g}$ is nonzero, except possibly on a subspace of the parameter space of lower dimensions, the model is locally identifiable; if the system is a linear system, it is structurally locally identifiable.

B. LOCAL IDENTIFIABILITY

1. Insensible Parameters

Examine the columns of **g**. For the insensible parameters the corresponding columns have only zero entries.

2. *Sensible Parameters*

Suppose we delete the columns of $\mathbf{g}$ corresponding to the insensible parameters to form the matrix $\mathbf{g}_s$ and also delete the insensible parameters from the parameter vector. Then the normal equations corresponding to the sensible parameters are given by

$$\mathbf{g}_s^T\mathbf{g}_s\Delta\hat{\theta}_s = 0. \tag{27}$$

For the identifiable parameters, θ_k, we should obtain for solutions, $\Delta\hat{\theta}_k = 0$. For the nonidentifiable parameters there should not be such unique solutions. To check that, use row reduction to row echelon form, with pivoting on maximum elements. When completed, the equations should have the following form.

(i) Rows with one nonzero entry on the diagonal. The column indexes of the diagonal elements of these rows give the identifiable parameters.

(ii) Rows with nonzero entries on the diagonal and elsewhere. The column indexes of the nonzero elements of these rows give the nonidentifiable parameters.

(iii) Rows with all zero entries. These are evidence of redundancy in the equations.

C. CORRELATIONS BETWEEN IDENTIFIABLE PARAMETERS

The final step is to find the pairwise correlations for the identifiable parameters. Even if identifiable it may be difficult to estimate two parameters separately in the presence of measurement error if they are highly correlated. To check that, we reduce the matrix $\mathbf{g}_s^T\mathbf{g}_s$ by eliminating rows and columns corresponding to the nonidentifiable parameters to obtain $\mathbf{g}_I^T\mathbf{g}_I$. Since $\mathbf{g}_I^T\mathbf{g}_I$ is the matrix corresponding to the identifiable parameters, it is nonsingular so we can invert it to obtain $(\mathbf{g}_I^T\mathbf{g}_I)^{-1}$. The correlation matrix is obtained by dividing the i,j element of $(\mathbf{g}_I^T\mathbf{g}_I)^{-1}$ by the square root of the product of the ith and jth diagonal elements.

VIII. CONCLUSION

In experiments in the biological sciences one generally cannot sample all state variables (compartments). In that case, some parameters of the system may not be uniquely determined (identifiable) by the observations of the experiment. In order to check identifiability, one need only examine

the model of the experiment; there is no need to do the experiment. Check identifiability before committing resources to doing the experiment.

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