Chapter 9

Identifiability and Accuracy: Two critical problems associated with the application of models in nutrition and the health sciences

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This presentation will review two fairly recent contributions to the area of the application of mathematical models in the nutrition and health sciences: identifiability and accuracy. Identifiability in model advancement helps us with the question 'will a proposed experiment on a system enable us to determine values for the parameters of a model of that system?' The model is assumed to be known and to reflect the response of the system to the experiment. Identifiability is not concerned with the precision with which the parameters can be estimated. The adequacy of an approach to characterize an aspect of a system is the relative agreement between the results based on the approach compared with the results based on a "gold" standard method; accuracy and precision are key components of the adequacy of a model. Or, we could say that two approaches to characterizing an aspect of a system agree if the results from the two approaches concord. In fact, concordance is a much more profound issue than merely correlation or regression. For example concordance needs to embrace the observation range over which the two series of measurements exist, it needs to penalize a quantification of agreement for not predicting the origin as a critical point, and also for not engaging a line of perfect agreement (slope unity) into its consideration. Recently an index of concordance correlation coefficient (CCC) with all the properties needed to effectively quantify agreement was developed. Unfortunately though, this index did not account for tail weighting in deriving the measure. This index has been shown to be biased under certain important observation settings. We reviewed several recent works regarding the computation of CCC and demonstrate its application with cardiac output measurements.

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Introduction

This chapter deals with two disparate issues that surface in mathematical modeling: identifiability and accuracy. Each has emerged of importance within the last 20 or so years as a result of, on the one hand, the philosophical principles underpinning modeling having been found wanting in each of these domains and, on the other hand, tools and techniques for investigating these issues having been refined.

Identifiability is the body of science and mathematics that enables us to ask, 'if we perform a proposed experiment on a (known) system will we obtain enough information to enable us to determine all the (unknown) parameters of the system'. Identifiability is concerned neither with data nor the error of data, and it is not concerned with uncertainties linked to the model used to portray the system … error per se in data simply adds to the complexity of model estimation but, as we shall see, not in a way that directly impacts identifiability … the model of the system is presumed known, and 'correct', so issues of either the model's topological basis or its underlining mechanisms do not arise in the investigation of identifiability.

It was discovered as far back as 1956 or so (Berman and Schoenfeld (3)) that while kinetic data such as from radio iodine turnover in thyroid studies provides a perfect basis for fitting exponential models there was actually a limit to the extent and structure of kinetic models that could be derived, or mapped, from those exponentials. Indeed, it seemed that if two exponentials existed in the response it was not possible to derive kinetic models with more than three parameters. Thus while the observation of two exponentials implies an iodine system with two exchanging pools only one of the pools could have irreversible loss. This is a serious problem because we naturally imagine two paths by which iodine is irreversibly lost, one coinciding with binding, and the other coinciding with elimination. In answer to the question above then, what can go wrong from here is that failure to acknowledge the limitations of our 'experiment' on a system to expose enough information to determine **all** the parameters of a model of the system will lead to a failure to resolve any of the parameters of the system … at worst we may mischaracterize the system state, healthy versus un-healthy and at best we could draw no inferences at all about the system state.

Whereas identifiability analysis, or identifiability, may tell us in quite precise terms that a proposed experiment on a system will not yield enough information about a system to permit the determination of all the model parameters it can also help us, as we shall see, design an experiment on the system that will indeed yield the level of information that we seek to determine all the parameters.

Naturally then we need to inquire 'if identifiability is so powerful why is it only occasionally used, and only for models of modest size and complexity?' To answer this question fully here would disserve our account of the details of identifiability

below but, suffice it to say, identifiability analysis is very complex and this situation has not been improved by the array of definitions and demonstrations that appear in the literature. For example Godfrey (4) whose account of identifiability is by far the clearest, and uncompromising has the following to say … 'a number of definitions of terms associated with identifiability have appeared over the years, but these have led to some criticism. … Cobelli and DiStefano (5) have proposed some rather formal definitions but several aspects of their definitions have been criticized (LeCourtier and Walter (6)). There seems to be a need to keep terms and definitions as simple as possible and Godfrey (4) certainly does an excellent job in this regard. Jacquez (7) who in chapter 15 of his book takes several 'passes' to convey the meaning of identifiability says 'If one can check global identifiability, that is the way to go. But at times that process can be very difficult to carry out'. He then goes on to say that 'in many applications in the biological sciences there are prior estimates of parameters or information to constrain the parameters … In such cases much can be learned by checking the ... identifiability … by numerical methods'. In our section on identifiability we will draw heavily on Godfrey's work as we demonstrate how this type of analysis is advanced and how the results can be used.

Adequacy is the ability of a mathematical model to correctly predict (real) values. Determination of model adequacy is extremely important in building confidence and acceptance of the predictions of a model with broad applicability. For instance, it is essential to reliably predict possible outcomes without having to conduct field experimentation and data collection of novel chemicals or products that are hard to measure (e.g. medication) or have hazardous outcome (e.g. environmental pollution).

Precision and accuracy are two key components in assessing the adequacy of mathematical models (11). Precision is related to the ability of a mathematical model to predict similar values consistently whereas accuracy is the ability to predict the real values. Several techniques have been devised to assess the correctness of predictions of models (11-13). In our section on accuracy we will discuss the application and usefulness of a subset of evaluation techniques referred as concordance correlation coefficients (CCC) to assess model accuracy.

Identifiability

Preliminary Definitions. Figure 9.1 portrays an experiment on a system, in the terms of identifiability analysis. The system is 'represented' as a two-compartment model with exchange between the two compartments and irreversible loss from the first compartment (number 1). The experiment comprises a pulse input to the first compartment and subsequent sampling of that compartment, capturing the response of the system to the pulse.

The equations to the response, presuming linear kinetics (we shall presume

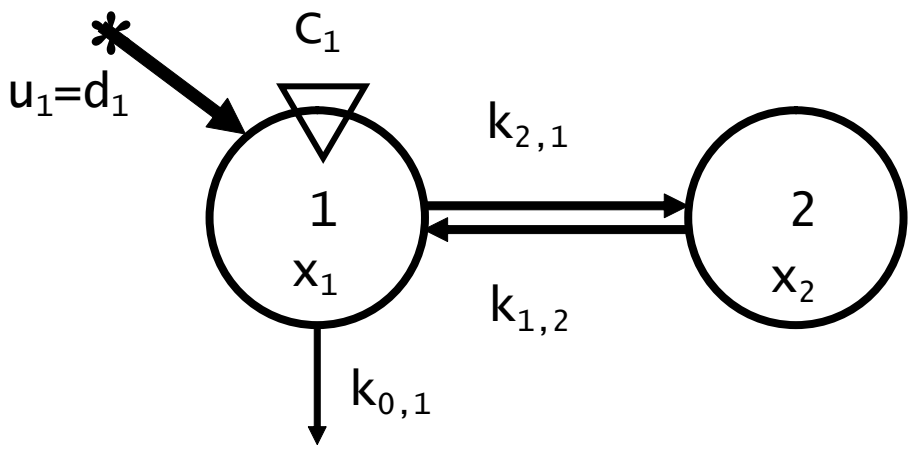

Figure 9.1. Experiment on a two compartmental system. A bolus injection ($u_1=d_1$) into compartment 1 and sampling C_1 also from compartment 1. Note the three linear exchanges with basic parameters k_{21}, k_{12}, and k_{01}. The responses of compartments 1 and 2 are respectively x_1 and x_2.

linear kinetics throughout our discussion) are as follows:

$$\dot{\underline{x}} = A\underline{x} + B\underline{u} \tag{1}$$

and the observations are given by:

$$\underline{y} = C\underline{x} \tag{2}$$

Where u = system challenges (δ or k_i, for example), B = input (or application) matrix, C = observation (or output) matrix, x = predicted response, and y = observed response, and A = condensed, or well-formed matrix representation of k_{ij}, viz:

$$A = \begin{bmatrix} -a_{11} & a_{12} \\ a_{21} & -a_{22} \end{bmatrix}$$

$$a_{11} = k_{01} + k_{21}$$

$$a_{12} = k_{12}$$

$$a_{21} = k_{21}$$

$$a_{22} = k_{02} + k_{12} \qquad (\text{if } k_{02} > 0)$$

Taking Laplace transform of (1) and (2), we obtain:

$$Y = C.X = C.(sI - A)^{-1} B.U$$

or, solving for Y we have

$$Y = g_n(s, \underline{\phi}_n) / g_d(s, \underline{\phi}_d)$$

Where k_{ij} = basic or model parameters, ϕ_i = observational parameters, V_j = volume of distribution (compartment j), basic parameter, and $g_{n/d}$ = numerator or denominator polynomial in s.

Using the Laplace transform approach (and there are several other approaches available, see below) identifiability ensues when the number of basic parameters is less than or equal to the number of observational parameters.

Example 1. Figure 9.2 below shows a two-compartment model, portraying a system which is perturbed, or pulsed, in the first compartment, and also sampled in the first compartment, thus exposing the pattern of damping of the pulse, and propagation of the residue of the pulse throughout the system. We then have:

$$U = \left[t = 0^+, \delta, 0 \right]$$

$$C = \left[1, 0 \right]$$

which represent the input (compartment 1 pulse, δ) and output (compartment 1 sampled) situations we proposed. The condensed form of the model parameters is again:

$$A = \begin{bmatrix} -a_{11} & a_{12} \\ a_{21} & -a_{22} \end{bmatrix}$$

and we now have with the added basic parameter (k_{02})

$$a_{11} = k_{01} + k_{21} \quad a_{12} = k_{12}$$

$$a_{22} = k_{02} + k_{12} \quad a_{21} = k_{21}$$

The state equations for this system are:

$$\dot{x}_1 = -a_{11}.x_1 + a_{12}.x_2 + u_1 \ (=\delta)$$

$$\dot{x}_2 = a_{21}.x_1 - a_{22}.x_2 + u_2 \ (=0)$$

Taking the Laplace transform of the state equations (we remind the reader that an uppercase X or Y represents the Laplace transform of the lowercase response functions x or y) we have:

$$X_1 (s + a_{11}) - X_2 a_{12} = U_1$$

$$-X_1 a_{21} + X_2 (s + a_{22}) = 0$$

Solving this for X_1 yields:

$$X_1 = \frac{\begin{vmatrix} U_1 & -a_{12} \\ 0 & (s+a_{22}) \end{vmatrix}}{\begin{vmatrix} (s+a_{11}) & -a_{12} \\ -a_{21} & (s+a_{22}) \end{vmatrix}}$$

or

$$X_1 = \frac{U_1(s+a_{22})}{(s+a_{11})(s+a_{22}) - a_{12}a_{21}}$$

Thus, if u_1=δ=1

$$X_1 = \frac{s+a_{22}}{s^2 + s(a_{22}+a_{11}) + a_{11}a_{22} - a_{12}a_{21}} = \frac{s+\phi_1}{s^2+\phi_2 s+\phi_3}$$

We observe three parameters, ϕ_1, ϕ_2, and ϕ_3 but we need four parameters so this system is unidentifiable based on the current, 'proposed', experiment.

Inputs and Outputs. Inputs are the assaults, or challenges to the system which expose its pattern of distribution of challenge 'composition' as the challenge subsides. Linear systems respond linearly to the challenge regardless of its magnitude. Sites or compartments must be accessible to accept inputs of an experimental nature. Most experiments only involve a single input though, when such experiments fail to identify systems, multiple inputs, of possibly different forms, may be necessary.

Outputs, in the experimental sense, are the observations of the response of a system to a specific input, or series of inputs. Just as inputs need to be accessible to expose the input points, outputs need to be accessible to expose the observation sites. Usually single input, single output (SISO) type experiments are presumed to be comprehensive enough to determine all we need about the system but this is not always so.

Global Identifiability. Jacquez (7) writes that '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 the experiment'.

Example 2. Consider the model of a system as captured in Figure 9.1, and let's inject a pulse into compartment 1 and sample compartment 1, only, with a view to determining the basic parameters.
The state equations are as shown:

$$\dot{x}_1 = -a_{11}.x_1 + a_{12}.x_2 + u_1 \ (=\delta)$$
$$\dot{x}_2 = \ a_{21}.x_1 - a_{22}.x_2 + u_2 \ (=0)$$

The output, y, is

$$y = \frac{x_1}{C}$$

And, also as above, the Laplace transform of the system is:

$$X_1(s + a_{11}) - X_2 a_{12} = U_1$$
$$-X_1 a_{21} + X_2(s + a_{22}) = 0$$

Thus,

$$X_1 = \frac{\begin{vmatrix} U_1 & -a_{12} \\ 0 & (s+a_{22}) \end{vmatrix}}{\begin{vmatrix} (s+a_{11}) & -a_{12} \\ -a_{21} & (s+a_{22}) \end{vmatrix}}$$

and, since $C=V_1$

$$X_1 = \frac{U_1(s+a_{22})/V_1}{(s+a_{11})(s+a_{22}) - a_{12}a_{21}} = \frac{\phi_1 s + \phi_2}{s^2 + \phi_3 s + \phi_4}$$

hence the system is globally identifiable … the number of observational parameters is just equal to the number of basic parameters.

In the above analysis we have admitted the apparent volume of distribution as a (basic) parameter to be resolved. This was done for two reasons: 1) to show how V_1 enters into the identifiability considerations, and 2) to show that, based on the proposed experiment it is indeed identifiable.

It seems that the idea of treating V_1 as a 'common' basic parameter needing to be identified from our experiment is original with Cobelli and DiStefano (5). Godfrey (4) suggests that we advance cautiously here saying that there are so few situations where the volumes of distribution are identified that we may miss more than we gain in trying to extend our experiments to resolve these features. Indeed, Godfrey (4) shows that a relatively easily derived measure of drug distribution is the steady state volume of distribution $V_2(\infty)$. For an exchanging two-compartment system:

$$V_2(\infty) = -\frac{a_{21}}{a_{22}} V_1 = \frac{k_{21}}{k_{02} + k_{12}} V_1$$

It is instructive to show the differences between the effect of the roots of the transfer function and the coefficients of the transfer function on the observational form of the response. We found for our two-compartment, identified system above, that:

$$Y = \frac{\phi_1 s + \phi_2}{s^2 + \phi_3 s + \phi_4} = \frac{\phi_1 s + \phi_2}{(s+\theta_1)(s+\theta_2)}$$

Using partial fractions we obtain:

$$Y = \alpha . e^{-\theta_1 t} + \beta . e^{-\theta_2 t}$$

Thus,

$$Y = \frac{\alpha}{s+\theta_1} + \frac{\beta}{s+\theta_2}$$

Where

$$\alpha = \frac{\varphi_1 \theta_1 - \varphi_2}{\theta_1 - \theta_2} \quad , \beta = \frac{\varphi_2 - \varphi_1 \theta_2}{\theta_1 - \theta_2}$$

Thus the factor in the observational function that scales the results appears as a scale factor in the analytic observational form. Only the roots of the observational function denominator appear in the analytic form of the observational function as exponents.

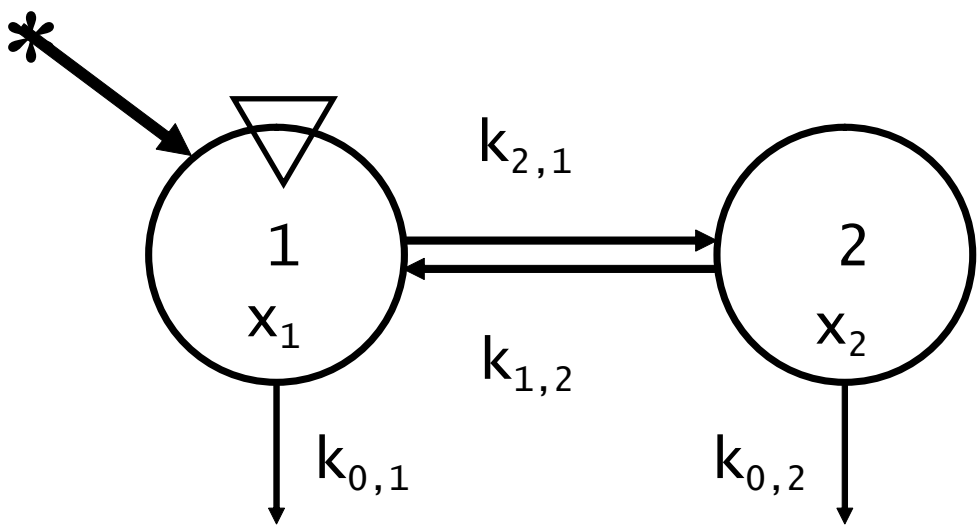

Figure 9.2. As for Figure 9.1 except that here we have four linear exchanges with basic parameters k_{21}, k_{12}, k_{01}, and k_{02}.

The steps of Identifiability Analysis. The approach employed in each identifiability analysis conducted above is routinely advanced as follows:

1. Make a note of basic parameters (e.g. k_{ij}) to be determined
2. Write down the state equations (x`) including inputs
3. Write down observable equations ($y=f(x,q)$)
4. Transform the state equations
5. Solve the transformed equations for $X = L(x)$
6. Solve for the observable transforms $Y=f(X)$
7. Express the solution to Y as: $Y=g_n(s,\phi_n)/g_d(s,\phi_d)$
8. Check that the number of ϕ_j (observational parameters) is at least equal to the number of k_{ij} (basic parameters) to be determined

Ranges (or Interval Identifiability). Although experiments on systems may result in unidentifiable parameters this may not be the end of the story. Three options exists at the point where we conclude the parameter determination phase, and we stress that, as a matter of course, identifiability takes place ordinarily before we conduct the experiment, and they are: 1) to constrain our model so that the number of observational and basic parameters now match, 2) to alter our experiment in such a fashion that it yields more information about our system, enabling all parameters of the system to be determined, and 3) to locate value ranges as opposed to single values for our parameters. We address the third option here.

Berman and Schoenfeld (3) showed that by invoking the principle of physical realizability (positive valued-ness) of parameters it is possible to determine ranges of parameter values consistent with our observational parameters in situations where one or more of the basic parameters are unidentifiable. If it turns out that the ranges are narrow we may not be overly compromised. In our standardized notation physical realizability implies:

$$a_{ij} = k_{ij} \geq 0 \tag{3}$$

$$a_{ii} = -k_{0i} - \sum_{\substack{j=1 \\ j\neq i}}^{p} k_{ji} \leq 0 \tag{4}$$

Consider an unidentifiable two-compartment model, then as above:

$$\dot{x}_1 = -k_{11}\, x_1 + k_{12}\, x_2$$

$$\dot{x}_2 = \; k_{21}\, x_1 - k_{22}\, x_2$$

It is not too hard to show that, quite generally:

$$k = E.e.E^{-1}, \quad E = \begin{bmatrix} A & B \\ C & D \end{bmatrix}, \quad e = \begin{bmatrix} \alpha & \\ & \beta \end{bmatrix}$$

and

$$C = -D$$

Here E is the problem boundary condition matrix, or eigenvector matrix, and e is the eigenvalue matrix.

Godfrey (4) has shown using Equations (3) and (4) in conjunction with the eigenvectors and eigenvalues that the physical bounds for the basic parameters are as follows:

$$\frac{A.B(\alpha-\beta)^2}{(A+B)(A\beta+B\alpha)} \le k_{21} \le \frac{A\alpha+B\beta}{A+B}$$

$$\frac{A.B(\alpha-\beta)^2}{(A+B)(A\alpha+B\beta)} \le k_{21} \le \frac{A\beta+B\alpha}{A+B}$$

$$0 \le k_{01} \le \frac{(A+B)\alpha\beta}{A\beta+B\alpha}$$

$$0 \le k_{02} \le \frac{(A+B)\alpha\beta}{A\alpha+B\beta}$$

Note that if one of the parameters is determined to be at one of its bounds then others will also be at their bounds. In Table 9.1 we demonstrate how various combinations of A, B, α, and β affect the range of the basic parameters of the unidentifiable model. In Figure 9.3 we present plots of the basic parameter ranges against A for combinations of a and b.

Changing the Design of an Experiment to make a Model Identifiable. When an experiment on a system can be shown to render a model unidentifiable, and when the boundaries of parameter values afforded from such an experiment are excessively wide then we can modify our experiment in such a way that will expose enough information about the system as to allow all the model parameters to be identifiable. Godfrey (4) demonstrates this point with clarity and simplicity in Example 1 above. Here we found that the experiment, as designed, provided three unique pieces of information about the model but, for identifiability purposes, the model called for four pieces of information.

Example 3. A suggested extension to the experiment is to admit a step infusion into compartment two thus we examine the output from compartment one using a DISO (Double Input; bolus to compartment one, infusion to compartment two, Single Output; sample only compartment one) design. Figure 9.4 captures unique features of

Table 9.1. For the experiment foreshadowed in Figure 2 we present intervals for the basic parameters (k_{12}, k_{21}, k_{01}, and k_{02}) which satisfy the requirement of physiological realizability for various combinations of the observational parameters (A, B, a, and b).

A	B	a	b	k21_l	k21_h	k12_l	k12_h	k01_h	k02_h	dk21	dk12
0.9	0.1	1	0.1	0.38	0.91	0.08	0.19	0.53	0.11	0.53	0.11
0.8	0.2	1	0.1	0.46	0.82	0.16	0.28	0.36	0.12	0.36	0.12
0.7	0.3	1	0.1	0.46	0.73	0.23	0.37	0.27	0.14	0.27	0.14
0.6	0.4	1	0.1	0.42	0.64	0.3	0.46	0.22	0.16	0.22	0.16
0.5	0.5	1	0.1	0.37	0.55	0.37	0.55	0.18	0.18	0.18	0.18
0.4	0.6	1	0.1	0.3	0.46	0.42	0.64	0.16	0.22	0.16	0.22
0.3	0.7	1	0.1	0.23	0.37	0.46	0.73	0.14	0.27	0.14	0.27
0.9	0.1	3	0.3	1.15	2.73	0.24	0.57	1.58	0.33	1.58	0.33
0.2	0.8	1	0.1	0.16	0.28	0.446	0.82	0.12	0.36	0.12	0.36
0.8	0.2	3	0.3	1.39	2.46	0.47	0.84	1.07	0.37	1.07	0.37
0.7	0.3	3	0.3	1.38	2.19	0.7	1.11	0.81	0.41	0.81	0.41
0.6	0.4	3	0.3	1.27	1.92	0.91	1.38	0.65	0.47	0.65	0.47
0.1	0.9	1	0.1	0.08	0.19	0.38	0.91	0.11	0.53	0.11	0.53
0.5	0.5	3	0.3	1.1	1.65	1.1	1.65	0.55	0.55	0.55	0.55
0.9	0.1	5	0.5	1.92	4.55	0.4	0.95	2.63	0.55	2.63	0.55
0.8	0.2	5	0.5	2.31	4.1	0.79	1.4	1.79	0.61	1.79	0.61
0.4	0.6	3	0.3	0.91	1.38	1.27	1.92	0.47	0.65	0.47	0.65
0.7	0.3	5	0.5	2.3	3.65	1.17	1.85	1.35	0.68	1.35	0.68
0.9	0.1	7	0.7	2.69	6.37	0.56	1.33	3.68	0.77	3.68	0.77
0.6	0.4	5	0.5	2.11	3.2	1.52	2.3	1.09	0.78	1.09	0.78
0.3	0.7	3	0.3	0.7	1.11	1.38	2.19	0.41	0.81	0.41	0.81
0.8	0.2	7	0.7	3.24	5.74	1.11	1.96	2.5	0.85	2.5	0.85
0.5	0.5	5	0.5	1.84	2.75	1.84	2.75	0.91	0.91	0.91	0.91
0.7	0.3	7	0.7	3.22	5.11	1.63	2.59	1.89	0.96	1.89	0.96
0.2	0.8	3	0.3	0.47	0.84	1.39	2.46	0.37	1.07	0.37	1.07
0.4	0.6	5	0.5	1.52	2.3	2.11	3.2	0.78	1.09	0.78	1.09
0.6	0.4	7	0.7	2.96	4.48	2.13	3.22	1.52	1.09	1.52	1.09
0.5	0.5	7	0.7	2.58	3.85	2.58	3.85	1.27	1.27	1.27	1.27
0.3	0.7	5	0.5	1.17	1.85	2.3	3.65	0.68	1.35	0.68	1.35
0.4	0.6	7	0.7	2.13	3.22	2.96	4.48	1.09	1.52	1.09	1.52
0.1	0.9	3	0.3	0.24	0.57	1.15	2.73	0.33	1.58	0.33	1.58
0.2	0.8	5	0.5	0.79	1.4	2.31	4.1	0.61	1.79	0.61	1.79
0.3	0.7	7	0.7	1.63	2.59	3.22	5.11	0.96	1.89	0.96	1.89
0.2	0.8	7	0.7	1.11	1.96	3.24	5.74	0.85	2.5	0.85	2.5
0.1	0.9	5	0.5	0.4	0.95	1.92	4.55	0.55	2.63	0.55	2.63
0.1	0.9	7	0.7	0.56	1.33	2.69	6.37	0.77	3.68	0.77	3.68

this situation. Using our standard notation the state equations giving the anticipated response of the system are as follows:

$$\dot{x}_1 = -a_{11}x_1 + a_{12}x_2 + \delta\left(t = 0^+, d\right)$$

$$\dot{x}_2 = a_{21}x_1 - a_{22}x_2 + k_i$$

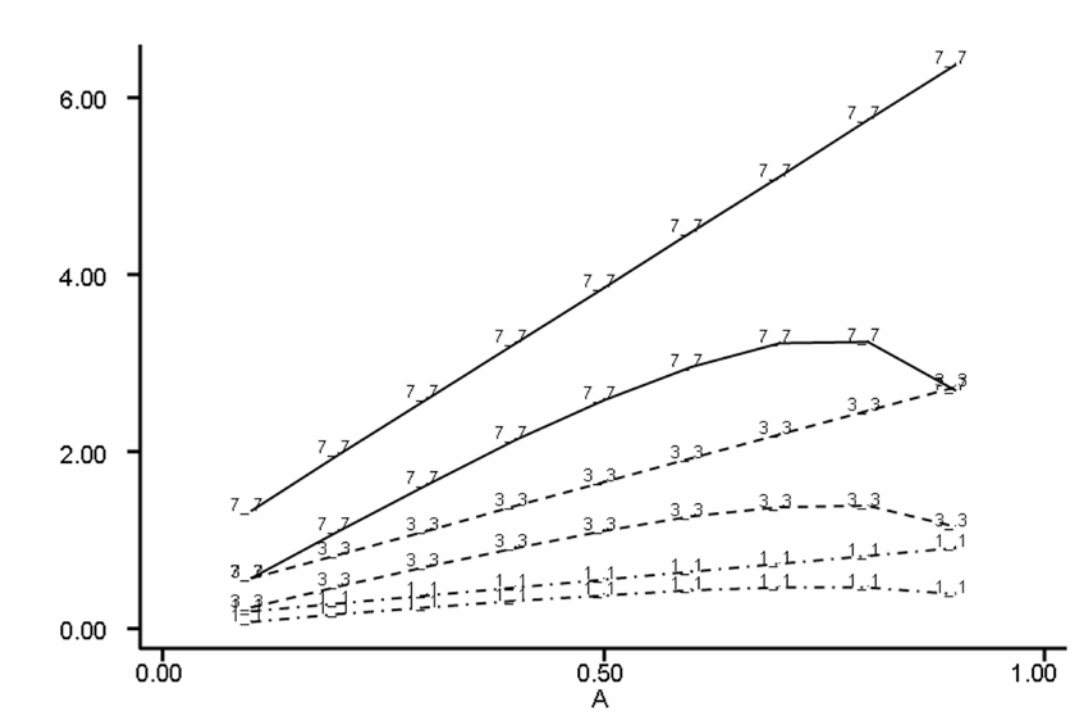

Figure 9.3. Plots of the range of physiologically realizable ranges for the basic parameter k_{21} for the experiment on the system portrayed in Figure 9.2. The response is A×exp(-a×t) + B×exp(-b×t), where 0.1 < A < 0.9, a=1,3, and 7, B=1-A, and b=a/10.

Taking Laplace transforms we obtain:

$$X_1(s+a_{11}) - X_2 a_{12} = \delta$$

$$-X_1 a_{21} + X_2(s+a_{22}) = k_i / s$$

and our output, *y*, is given by:

$$y = \frac{x_1}{C}$$

Solving we obtain:

$$X_1 = \frac{(d.s^2 + d.a_{22}.s + k_i.a_{12})}{s(s^2 + \beta_1 s + \beta_2)}$$

We now see that we have gone from three to four, or five, observational parameters whereas before we reported just three observational parameters yielded from the experiment. Whether we need four or five parameters depends on our observation units. If we measure concentrations then, as Godfrey points out, the determination of the volume of distribution (C, above) when the same site is 'pulsed' and 'observed' is trivial but nevertheless consumes 'one of our observational parameters'. Thus whereas in Example 1 we ignored the distribution volume we can here say that the residual four observational parameters provide enough information to determine the four basic parameters.

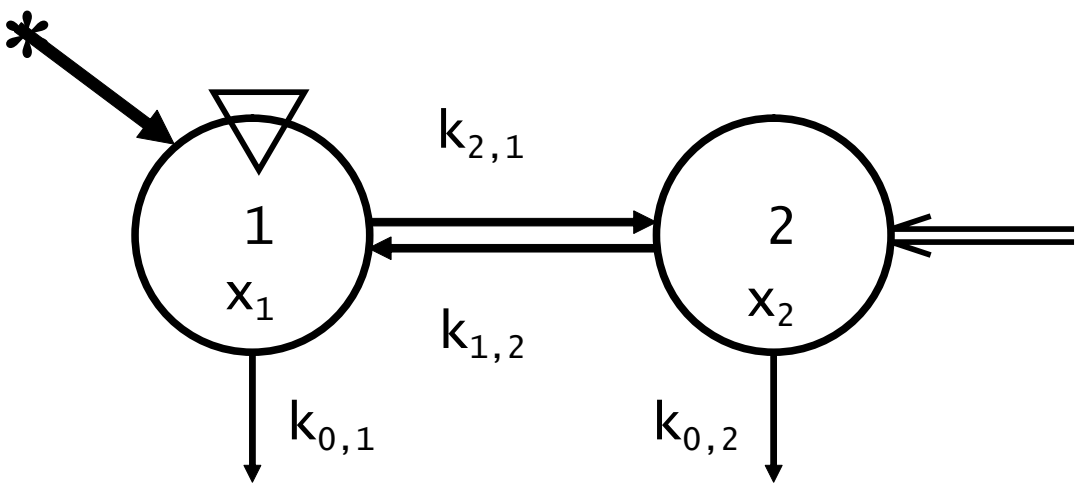

Figure 9.4. A modification to the experiment on the two compartment system of Figure 9.2 reflecting an infusion into compartment 2. The new experiment can be shown using identifiability analysis to yield enough additional information to render the system identifiable.

Because of the way matrix manipulation is managed in WinSAAM (14), it is one of few computer packages that allows the accurate demonstration of the principle of identifiability. For the model of example one we use the input specification shown in Figure 9.5 where the 'qo(1)' construct allows us to define the observed response, or, in identifiability terms, the output from the experiment. We then iteratively adjust the basic parameters and finally obtain the parameter estimates and their uncertainties as shown. That the errors of the parameters are so large, almost to five thousand percent tells us that we can have no confidence in our capacity to exclude other values for the parameters, and the model itself is thus not identifiable.

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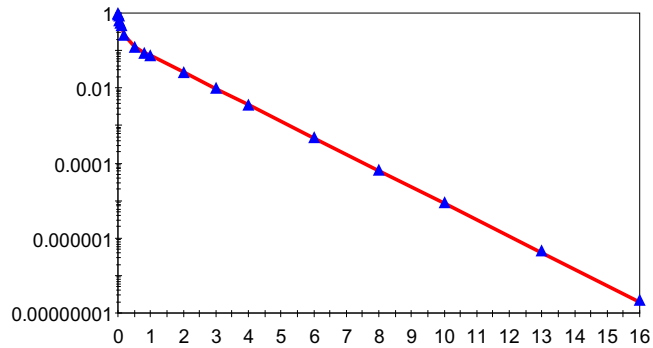
A SAAM31
H PAR
C
C Demonstration of the capacity of a SISO experiment to
C not expose the parameters of a 4 basic parameter model
C
   L(2,1)    8.000000E+00  0.000000E+00   1.000000E+02
   L(1,2)    1.000000E+00  0.000000E+00   1.000000E+02
   L(0,1)    2.000000E+00  0.000000E+00   1.000000E+02
   L(0,2)    1.000000E-01  0.000000E+00   1.000000E+02
ic(1)=1
H DAT
x qo(1)=0.78*exp(-10*t)+.2*exp(-t)
101 qo(1)                    fsd=.1
            0
            .01
            .02
            .05
            .08
            .1
            .2
            .5
            .8
            1
            2
            3
            4
            6
            8
            10
            13
            16
```




```
      > fsd(i)
      * VALUES MAY NOT RELATE TO CURRENT PARAMETERS
      * L ( 2, 1)    6.615E+00     FSD( 1)   1.105E+01
      * L ( 1, 2)    2.009E+00     FSD( 2)   1.115E+01
      * L ( 0, 1)    1.540E+00     FSD( 3)   4.748E+01
      * L ( 0, 2)    8.622E-01     FSD( 4)   2.574E+01
```

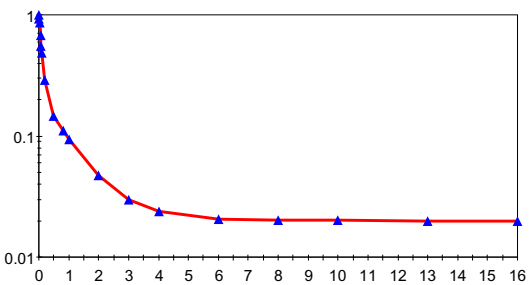
Figure 9.5. A WinSAAM model reflecting the consequences of an attempt to estimate the basic parameters of the model of Figure 9.2 based on the experiment on the system shown in Figure 9.2.

Next we change a) the observations ‘qo(1)’, and b) the experiment (we added the infusion into compartment two `uf(2)’, in addition to the pulse, or bolus, into compartment one), see Figure 9.6.

We again iteratively adjust the parameters and see that they converge a) to the correct values, and b) to well-resolved estimates, thus supporting that the new experiment leads to identifiability of all model parameters, and thus the model is itself identifiable based on this new experiment.

We caution readers from applying this assessment procedure with kinetic modeling software other than WinSAAM (14). If a model is not identifiable from a proposed experiment then proceeding to explore this from a numerical perspective is fraught with problems. Three outcomes are possible here: 1) the program may simply fail ingloriously (because the covariance matrix has lower rank than required for inversion), or 2) the program may not fail but provide 'identifiable results' whose values actually depend on 'precautionary code' (see Jacquez's (15) cautionary note here), or 3) the program may be equipped with the computational machinery to appropriately handle this situation (potentially inversion of a singular matrix) and provide information for you such as the above enabling appropriate decisions to be made. WinSAAM is in the latter class.

```
A SAAM31
H PAR
C
C Demonstration of the capacity of a DISO experiment to
C expose the parameters of a 4 basic parameter model
C
   L(2,1)    8.000000E+00  0.000000E+00   1.000000E+02
   L(1,2)    1.000000E+00  0.000000E+00   1.000000E+02
   L(0,1)    2.000000E+00  0.000000E+00   1.000000E+02
   L(0,2)    1.000000E-01  0.000000E+00   1.000000E+02
 ic(1)=1
   uf(2)    .1
H DAT
x qo(1)=0.78*exp(-10*t)+.2*exp(-t)+0.02
101 qo(1)                          fsd=.1
            0
            .01
            .02
            .05
            .08
            .1
            .2
            .5
            .8
            1
            2
            3
            4
            6
            8
            10
            13
            16
```




```
> fsd(i)
* VALUES MAY NOT RELATE TO CURRENT PARAMETERS
* L ( 2, 1)    7.005E+00     FSD( 1)   1.437E-04
* L ( 1, 2)    1.999E+00     FSD( 2)   1.865E-04
* L ( 0, 1)    9.949E-01     FSD( 3)   1.020E-03
* L ( 0, 2)    1.000E+00     FSD( 4)   2.220E-04
```

Figure 9.6. A WinSAAM model reflecting the consequences of an attempt to estimate the basic parameters of the model of Figure 9.2 based on the experiment on the system shown in Figure 9.4.

Statistical Constraints. In Example 2 above we found that by eliminating one basic (model) parameter from the model of example one we moved from a situation where the model was unidentifiable to a situation with the model was globally identifiable. This is actually a case of conditional identifiability. That is, the model of experiment one has been rendered identifiable conditional on removing one of the irreversible eliminations (basic parameters).

Of course sacrificing reality in the interest of generating an identifiable model is quite unreasonable, and we have already highlighted circumstances justifying a two-compartment model with bi-directional exchange and irreversible losses from each compartment. On the other hand, there are virtually no situations now where investigations are advanced against the background where nothing is known. Either similar studies have already been undertaken, perhaps with different constraints or on different subjects, or in vitro investigations (versus in vivo) have yielded allied information to the study at hand. The point is that we don't exist, or study, in a vacuum and the scope for introducing established, allied, statistical information into our modeling venture lurks at every corner. In the identifiability sense, admitting information, 'statistically speaking', is akin to widening our experiment base, and admitting that any experiment we foreshadow for a system exposes only additional features to those already available.

This type of modeling or statistical analysis is referred to as Bayesian Analysis and we advance our modeling objective by admitting key pertinent statistical knowledge available from prior related research. In the biological sciences allometric information is a rich source of Bayesian statistics.

Example 5. In Example 5 (Figure 9.7) we demonstrate, using WinSAAM (14), how a statistical constraint on one of our losses of our two-compartment model (Example 1) is introduced and facilitates the identifiability of the model.

Local Identifiability

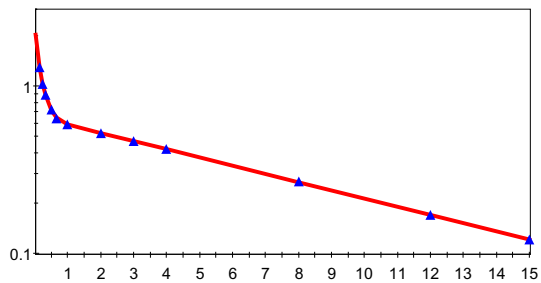
Example 6. In Example 6 we propose an experiment on the model captured in Figure 9.1 in which compartment one is pulsed (input) and compartment two is sampled (output). The state equations are as usual:

$$\dot{x}_1 = -a_{11}x_1 + a_{12}x_2 + \delta\left(t = 0^+, 1\right)$$

$$\dot{x}_2 = a_{21}x_1 - a_{22}x_2$$

and our output is:

```
A SAAM31
2       10
H PAR
C
c Kinetics of Amrinone
c Each subject received 75 mg as an IV bolus
c IV drug levels with time are shown
   L(2,1)    3.833943E+00  0              10
   L(1,2)    1.614766E+00  0              10
   L(0,2)   .05                           1
   L(0,1)    1.732317E-01  0              1
   ic(1)    75
   K(1)      3.015881E-02  0              1
H DAT
110
   L(0,1)                  .04            .01
101                                       fsd=.4
C           [hr]           [mg/l]
            0
            .16            1.30
            .25            1.03
            .33            0.89
            .5             0.72
            .67            0.64
            1              0.59
            2              0.52
            3              0.47
            4              0.42
            8              0.27
            12             0.17
            15             0.12
```




```
PARAMETER     VALUE       ERROR       FSD
L ( 2, 1)  3.971E+00  1.243E-01  3.129E-02
L ( 1, 2)  1.560E+00  1.960E-02  1.257E-02
L ( 0, 2)  1.408E-01  1.039E-03  7.382E-03
L ( 0, 1)  3.999E-02  1.825E-04  4.564E-03
K ( 1, 0)  3.018E-02  6.500E-04  2.154E-02
CORRELATION MATRIX
 COLUMN   1     2     3     4     5
ROW 1  1.00  0.48 -0.45  0.00  0.96
ROW 2  0.48  1.00  0.37  0.00  0.26
ROW 3 -0.45  0.37  1.00 -0.07 -0.55
ROW 4  0.00  0.00 -0.07  1.00  0.00
ROW 5  0.96  0.26 -0.55  0.00  1.00
```

Figure 9.7. A WinSAAM model reflecting the consequences of an attempt to estimate the basic parameters of the model of Figure 9.2 based on a) the experiment on the system shown in Figure 9.2, and b) additional information available regarding one of the basic parameters, k_{01}, of the system. Note that in the syntax of WinSAAM k_{ij} =L(I,J).

$$X_1(s+a_{11}) - X_2 a_{12} = 1$$
$$-X_1 a_{21} + X_2(s+a_{22}) = 0$$

Applying the Laplace transform in customary fashion leads to:

$$y = \frac{x_2}{V_2}$$

Solving for X_2 yields:

$$X_2 = \frac{\begin{vmatrix} s+a_{11} & 1 \\ -a_{21} & 0 \end{vmatrix}}{\begin{vmatrix} (s+a_{11}) & -a_{12} \\ -a_{21} & (s+a_{22}) \end{vmatrix}}$$

or

$$X_2 = \frac{a_{21}}{(s+a_{11})(s+a_{22}) - a_{12}a_{21}}$$

Here we have:

$$a_{11} = k_{21} + k_{01}$$
$$a_{22} = k_{12}$$
$$a_{21} = k_{21}$$

Replacing X_2 with our observation variable Y as defined above we have:

$$Y = \frac{\phi_1}{s^2 + s\phi_2 + \phi_3}$$

where

$$\phi_1 = \frac{k_{21}}{V_2}$$
$$\phi_2 = k_{01} + k_{12} + k_{21}$$
$$\phi_3 = k_{01}.k_{12}$$

Now, if V_2 is unknown (which according to Godfrey (4) may often be the case) the model is unidentifiable. If V_2 is known then we have three observational parameters and three basic parameters needing to be determined and hence the model is globally identified. But in solving for k_{01} and k_{12} we encounter a quadratic equation possibly yielding two feasible solutions for the parameters … feasible in the sense that both solutions produce positive (i.e. physically realizable) values for k_{12} and k_{01} ($k_{21} = \phi_1 V_2$). Under such circumstances we say that the model is locally identifiable.

Accuracy

Concordance Correlation Coefficient. Evaluation between two or more identities (i.e. raters, graders, observers, methods, or observed versus model-predicted values) to quantify agreement of responses is important in research. When measurements are categorical variables, Cohen's (16, 17) kappa statistic is a well-known approach to appropriately assess their agreement. However, this technique is not adequate for continuous variables.

Krippendorff (18) has initially introduced the idea of agreement of continuous variables obtained by two methods and had proposed an equation similar to that one shown in Equation 7. Later, Lin (4) expanded Krippendorff's (18) accomplishment and developed an index that assesses the correlation between two variables assuming that their linear relationship would have a slope of unity (45° line) and would pass through the origin (concordance line). This index is commonly known as the concordance correlation coefficient (CCC) and it is based on precision and accuracy measurements. Similarly, the classical Pearson's correlation coefficient measures the correlation between two variables, but fails to detect any departure from the 45° line.

Equation 5 shows the overall format to compute the estimate of the CCC (ρ_c). The numerator is the expected squared perpendicular deviation from the concordance line whereas the denominator is the expected squared perpendicular deviation from the concordance line when Y and X are uncorrelated, which means the correlation between Y and X is zero (4).

$$\rho_c = 1 - \frac{\mathrm{E}\left[(Y-X)^2\right]}{\sigma_Y^2 + \sigma_X^2 + (\mu_Y - \mu_X)^2} \tag{5}$$

The expected squared perpendicular deviation from the concordance line is shown in Equation 6. Therefore, if $\sigma_{YX} = 0$ (no correlation between Y and X), the second term of Equation 5 becomes 1, hence the $\rho_c = 0$ (no concordance).

$$\mathrm{E}\left[(Y-X)^2\right] = (\mu_Y - \mu_X)^2 + \left(\sigma_Y^2 + \sigma_X^2 - 2\sigma_{YX}\right) \tag{6}$$

Substituting Equation 6 into Equation 5 yields Equation 7.

$$\rho_c = \frac{2\sigma_{YX}}{\sigma_Y^2 + \sigma_X^2 + (\mu_Y - \mu_X)^2} \tag{7}$$

Furthermore, the ρ_c can be easily computed using the moment statistics (standard deviation and means) of Y and X (4) as shown in Equation 8. The C_b estimate ($0 < C_b \leq 1$) is a bias correction factor that measures how far the best-fit line deviates from the concordance line (accuracy). Therefore, if $C_b = 1$, "perfect" accuracy, no deviation from the concordance line occurs; however, variation around the line is still possible and the Person's correlation coefficient will be lower than 1.

$$\rho_c = \rho \times C_b$$
$$C_b = \frac{2}{v + v^{-1} + u^2}$$
$$v = \frac{\sigma_Y}{\sigma_X} \qquad (8)$$
$$u = \frac{\mu_Y - \mu_X}{\sqrt{\sigma_Y \sigma_X}}$$

Where ρ_c is the concordance correlation coefficient estimate, ρ is the Person's correlation coefficient (precision estimate), C_b is the accuracy estimate, σ_Y and σ_X are the standard deviation of Y and X variables, and μ_Y and μ_X are the means of Y and X variables.

The "perfect" accuracy is only possible when some assumptions are met and the characteristics of the CCC as described by Lin (4) are observed.

i. $-1 \leq -|\rho| \leq \rho_c \leq |\rho| \leq 1$
ii. $\rho_c = 0$ if and only if $\rho = 0$
iii. $\rho_c = \rho$ if and only if $\sigma_Y = \sigma_X$ and $\mu_Y = \mu_X$
iv. $\rho_c = \pm 1$ if and only if
   a. $(\mu_Y - \mu_X)^2 + (\sigma_Y - \sigma_X)^2 + 2\sigma_Y\sigma_X(1 \pm \rho) = 0$, or
   b. $\rho = \pm 1$, $\sigma_Y = \sigma_X$, and $\mu_Y = \mu_X$, or
   c. each pair of data is in perfect or reversed agreement.

Lin (4, 19) suggested the inverse hyperbolic tangent transformation would improve the normal approximation of the distribution of the CCC. The author was able to show that transformed CCC is robust for uniform (short-tailed symmetric) and Poisson (long-tail, asymmetric to the right) distributions even when sample size was 10.

Limitations of the Concordance Correlation Coefficient. Several critical limitations to the CCC technique have been discussed (20). Deyo et al. (21) have shown than if the variance of the difference between X and Y is zero or a large number of samples are used, the CCC is similar to an intraclass correlation coefficient (ICC), suggesting that for large sample size no difference would be detected between ICC and CCC. Müller and Buttner (22) and Atkinson and Nevill (23) indicated that CCC and ICC behave quite similarly, but CCC does not fulfill the definition of ICC. These authors discouraged the use of CCC because it has the same problems as previous correlation methods, which are highly sensitive to sample heterogeneity. Nickerson (24) stated that Lin's (4) CCC might have no clear advantages over the existing ICC as a way to assess

the reproducibility of measurements, suggesting that CCC is a special case of the ICC defined as a two-way analysis of variance.

Further analysis of Carrasco and Jover (25) demonstrated that at the parameter level, the CCC is equal to the ICC when observers (i.e. Y and X) are considered fixed effects (Equation 9). However, at the estimator level, σ_ε^2/n should be added to the σ_β^2 calculation (25). As sample size increases and/or the magnitude of the error variance (σ_ε^2) decreases, this adjustment is negligible. These authors recommended that mixed models using variance components can be used successfully to compute CCC. Additionally, they suggested that more than two observers can be added to the model in contrast to using Lin's (4) moment-statistics approach.

Liao and Lewis (20) expanded the discussions about the limitations of the Lin's (4) CCC calculation. Based on the characteristics of the CCC (4), when $E(x) = E(y)$ and $Var(x) = Var(y)$, C_b will always be one. Therefore, because Lin's (4) CCC calculation does not include the coefficient of correlation in the calculation of accuracy, the accuracy will always be the same no matter how the two measurements are correlated, so long as they have the same mean and variance.

$$\rho_{ICC} = \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\beta^2 + \sigma_\varepsilon^2}$$

where

$$\sigma_\alpha^2 = \frac{2}{k \times (k-1)} \sum_{i=1}^{k-1} \sum_{j=i+1}^{k} \sigma_{ij}$$

$$\sigma_\beta^2 = \frac{1}{k \times (k-1)} \sum_{i=1}^{k-1} \sum_{j=i+1}^{k} \left(\mu_i - \mu_j\right)^2 \qquad (9)$$

$$\sigma_\varepsilon^2 = \frac{1}{k} \sum_{i=1}^{k} \sigma_i^2 - \sigma_\alpha^2$$

$\alpha_i : i = 1 \ldots n$ subjects

$\beta_j : j = 1 \ldots k$ observers or graders (if Y vs X, $k = 2$)

Based on this limitation, Liao (26) proposed a modification to the original CCC calculation in which instead of using the squared perpendicular distance between any paired observations, the expected square value for an area formed by two paired observations is used. Thus, two points (i.e. two paired observations) are used to determine both the regression line and the distance to the line of identity (26). Liao's (26) CCC is more conservative than Lin's (4) CCC. This disagreement is more likely when variances are not similar.

A Generalized Concordance Correlation Coefficient. Similar to Liao's (26) discussions, King and Chinchilli (27) identified situations in which the CCC is not adequate. These authors indicated that when the data contains outliers or it is a heavy-tailed distribution, the Lin's (4) CCC may not give accurate assessment of agreement that may exist in the majority of the data. Therefore, a generalized concordance correlation coefficient (GCCC) was proposed to offset this limitation. King and Chinchilli (27) proposed alternative distance functions to the original squared distance in order to construct robust versions of the CCC.

King and Chinchilli (27) assumed a $g(\cdot)$ distance function defined on the real line which would satisfy the following properties: (i) $g(0) = 0$, (ii) $g(z)$ is an even function, i.e. $g(-z) = g(z)$ for all z, and (iii) $g(z)$ is a non-decreasing function of z for all $z \geq 0$. Four distance functions were proposed (27): (i) squared difference, (ii) absolute difference, (iii) winsorized squared difference, and (iv) Huber's difference (Equation 10).

$$
\begin{aligned}
&i.\ g(z) = z^2 \\
&ii.\ g(z) = |z| \\
&iii.\ g(z) = \begin{cases} z^2 \text{ if } |z| \leq z_0 \\ z_0^2 \text{ if } |z| > z_0 \end{cases} \\
&iv.\ g(z) = \begin{cases} \frac{1}{2} z^2 \text{ if } |z| \leq z_0 \\ z_0 |z| - \frac{1}{2} z_0^2 \text{ if } |z| > z_0 \end{cases}
\end{aligned}
\tag{10}
$$

Comparison of Coefficients of Agreement. Several simulations were conducted using the Monte Carlo technique to compare important correlation coefficients.

First Evaluation. In the first evaluation, 1,000 simulations were conducted assuming normal distribution for Y and X, three theoretical correlations (r = 0.50, 0.70, and 0.90) between Y and X, two sample sizes (n = 50 and 100), and means and variances of X and Y varied as shown in Table 9.2.

In general, the absolute difference (Equation 10.ii) (27) was smaller than any other agreement coefficient (Table 9.2) regardless the Pearson's correlation coefficient and sample size. The Lin's (4), Liao's (26), and squared difference of King and Chinchilli's (27) CCC were nearly identical regardless the Pearson's correlation coefficient and sample size; however, they increased as Pearson's correlation coefficient increased.

As discussed by King and Chinchilli (27), as sample size increases there is a tendency to increase the mean of the CCC estimates and to decrease the standard

Table 9.2. Empirical simulations of 1,000 runs to compare several coefficients of agreement (mean ± SD) between Y and X assuming linearity, normal distribution, three levels of correlation (0.50, 0.70, and 0.90), and two sample sizes (50, 100, and 200), varying the mean (100 and 105) and variance (100 and 130) of the Y data.

Ref.[1]	r = 0.50			r = 0.70			r = 0.90		
	n = 50	n = 100	n = 200	n = 50	n = 100	n = 200	n = 50	n = 100	n = 200
Case 1. mean of X=100, mean of Y=100, variance of X=100, variance of Y=100									
1	0.49	0.49	0.49	0.68	0.69	0.70	0.89	0.90	0.90
2	0.49	0.49	0.49	0.68	0.69	0.70	0.89	0.90	0.90
3	0.49	0.49	0.49	0.68	0.69	0.70	0.89	0.90	0.90
4	0.49	0.29	0.29	0.44	0.45	0.45	0.67	0.68	0.68
5	0.49	0.49	0.50	0.69	0.70	0.70	0.90	0.90	0.90
6	0.33	0.33	0.33	0.48	0.49	0.49	0.71	0.71	0.71
7	0.49	0.49	0.50	0.68	0.70	0.70	0.89	0.90	0.90
Case 2. mean of X=100, mean of Y=100, variance of X=100, variance of Y=130									
1	0.47	0.49	0.49	0.68	0.68	0.69	0.88	0.89	0.89
2	0.47	0.48	0.49	0.67	0.68	0.69	0.88	0.88	0.88
3	0.47	0.49	0.49	0.68	0.68	0.69	0.88	0.89	0.89
4	0.27	0.28	0.29	0.43	0.44	0.44	0.66	0.67	0.67
5	0.49	0.49	0.50	0.69	0.69	0.70	0.90	0.90	0.90
6	0.33	0.33	0.33	0.49	0.49	0.49	0.71	0.71	0.71
7	0.48	0.49	0.50	0.68	0.69	0.70	0.89	0.89	0.89
Case 3. mean of X=100, mean of Y=105, variance of X=100, variance of Y=100									
1	0.43	0.44	0.44	0.61	0.61	0.62	0.79	0.80	0.80
2	0.44	0.46	0.46	0.62	0.63	0.64	0.80	0.80	0.81
3	0.43	0.44	0.44	0.61	0.61	0.62	0.79	0.79	0.80
4	0.24	0.25	0.25	0.37	0.37	0.38	0.52	0.53	0.53
5	0.49	0.50	0.50	0.69	0.69	0.70	0.89	0.90	0.90
6	0.33	0.33	0.33	0.49	0.49	0.49	0.71	0.71	0.71
7	0.43	0.45	0.44	0.61	0.62	0.62	0.79	0.80	0.80
Case 4. mean of X=100, mean of Y=100, variance of X=100, variance of Y=130									
1	0.43	0.44	0.44	0.62	0.62	0.62	0.79	0.80	0.80
2	0.44	0.46	0.46	0.62	0.63	0.63	0.80	0.80	0.80
3	0.43	0.44	0.44	0.61	0.62	0.62	0.79	0.80	0.80
4	0.24	0.25	0.25	0.38	0.38	0.38	0.53	0.54	0.54
5	0.49	0.50	0.50	0.69	0.70	0.70	0.90	0.90	0.90
6	0.33	0.33	0.33	0.49	0.49	0.49	0.71	0.71	0.71
7	0.44	0.45	0.45	0.62	0.63	0.63	0.80	0.81	0.81

[1] 1 = Lin (4), 2 = Liao (26), 3 = King and Chinchilli (27) squared difference, 4 = King and Chinchilli (27) absolute difference, 5 = Pearson's correlation coefficient, 6 = Kendal's τ (36), 7 = King and Chinchilli (27) Huber's function.

deviation. Most of the coefficients of agreement decreased as the variance of Y increased (Case 1 x Case 2, Table 9.2).

Second Evaluation. In the second evaluation we tested the effect of non-constant patterns for the variances of the Y data. The variances were exponentially or quadratically related to the X variable as shown in Equation 11. Additionally, three scenarios were evaluated: 1,000 YX points and 10 simulations, 500 XY points and 20 simulations, and 100 XY points and 100 simulations.

$$X = (1+\alpha) + 0.1 \times \varepsilon_1$$
$$Y = (1+\alpha) + 0.1 \times \varepsilon_2$$

where

α = random number between 0 and 1

$\varepsilon_1 \sim N(0,1)$

$\varepsilon_2 \sim N(0,\sigma^2)$

$$\sigma^2 \begin{cases} \exp(1.2 \times X); \text{ for distribution 1} \\ 12 - 15 \times X + 5 \times X^2; \text{ for distribution 2} \end{cases} \quad (11)$$

Table 9.3. Empirical simulations (1,000, 500, and 100) assuming different sample sizes (Trials: 10, 20, and 100, respectively) to compare several coefficients of agreement (mean ± 100×SE) between Y and X assuming two relationships between Y and X (exponential and quadratic).

Ref.[1]	Number simulations, trials and relationships[2]					
	S=100, T=100		S=500, T=20		S=1000, T=10	
	Exp	Quad	Exp	Quad	Exp	Quad
1	0.257	0.364	0.256	0.378	0.262	0.369
2	0.229	0.336	0.231	0.349	0.236	0.344
3	0.257	0.364	0.256	0.378	0.262	0.369
4	0.164	0.223	0.166	0.234	0.164	0.225
5	0.370	0.449	0.366	0.470	0.373	0.453
6	0.262	0.319	0.264	0.336	0.259	0.322
7	0.271	0.377	0.269	0.391	0.276	0.383
8	0.103	0.192	0.10	0.197	0.103	0.196
9	0.371	0.434	0.374	0.459	0.369	0.442

[1] 1 = Lin (4), 2 = Liao (26), 3 = King and Chinchilli (27) squared difference, 4 = King and Chinchilli (27) absolute difference, 5 = Pearson's correlation coefficient, 6 = Kendal's τ (36), 7 = King and Chinchilli (27) Huber's function, 8 = King and Chinchilli (27) winsorized, and 9 = Spearman's correlation coefficient.

[2] S = simulations, T = trials, Exp = exponential, and Quad = quadratic.

Table 9.3 has the results of the simulations. The concordance values were different depending on the technique used. In general, the King and Chinchilli's (5) winsorized and absolute methods had the lowest values regardless the relationship between Y and X (exponential or quadratic). In general, the simulations with the relationship between Y and X had greater concordance values than the exponential one. The CCC values for exponential and quadratic relationships between Y and X were 0.257 and 0.364 (Table 9.3), respectively. Assuming $\varepsilon_2 \sim N(0, 1)$, the Lin's (4) CCC value would be around 0.90.

These simulations indicated that changing the relationship between Y and X affected all these methods to compute concordance among two raters (Y and X). The King and Chinchilli's (5) winsorized values were almost three times lower than the Lin's (4) CCC.

Third Evaluation. In the third evaluation we generated 1,000 XY points using Equation 11 and assuming $\varepsilon_2 \sim N(0, 1)$. Then, we step-wisely removed XY points surrounding the mean of X using regressions perpendicular to the Y and X linear regression. We used the following intervals ±5, ±10, ±15, ±20, ±25, ±30, and ±35% around the mean of X for the evaluation. Results of some correlation coefficients are shown in Figure 9.8.

Our simulations indicated that as the depletion of XY points increased, Spearman's and Kendall's τ coefficients decreased. However, all other CCC indicators increased likely because the Person's correlation coefficient increased consistently, suggesting that clusters of points may not yield the correct concordance if data is missing. Conversely, the accuracy as measured by the C_b estimates (4) was similar, corroborating with the change in CCC due to the changes in the Peason's correlation coefficient.

In summary, the agreement coefficients evaluated performed well under the normal distribution assumption. Departures from the normal distribution will likely decrease the estimates of the concordance between Y and X. In contrary, missing of data is likely to increase the concordance between Y and X and it is dependent upon the extension of the depletion of points. This is likely because high leverage points or clouds of points increase in the Pearson correlation coefficient; therefore, increasing the CCC so long the accuracy (C_b) does not change. When using the CCC technique for evaluation, it is necessary to ensure the data does not departure from the normal distribution or the data fit in one of the special cases as discussed by Lin (4) and others.

Example of Application. The data from Wilkins et al. (28) was used to compare the

coefficients of agreement discussed above. Figure 9.9 depicts the relationship between carotid versus pulmonary artery impedance-based (Figure 9.9A) and temperature-based (Figure 9.9B) cardiac output; the distribution of the carotid and the pulmonary output is log-logistic.

The concordance analysis of Wilkins et al. (28) database (Table 9.4) indicated a greater concordance between carotid and pulmonary artery using the same method (either impedance or temperature) to assess cardiac output. However, the relationship between the same site (either carotid or pulmonary) using different methods (impedance versus temperature) resulted in a lower concordance coefficient, suggesting different methods are not likely to measure the same quantity. These findings were confirmed by the accuracy measurement proposed by Lin (4), which measures the perfect agreement (ranges from 0 to 1).

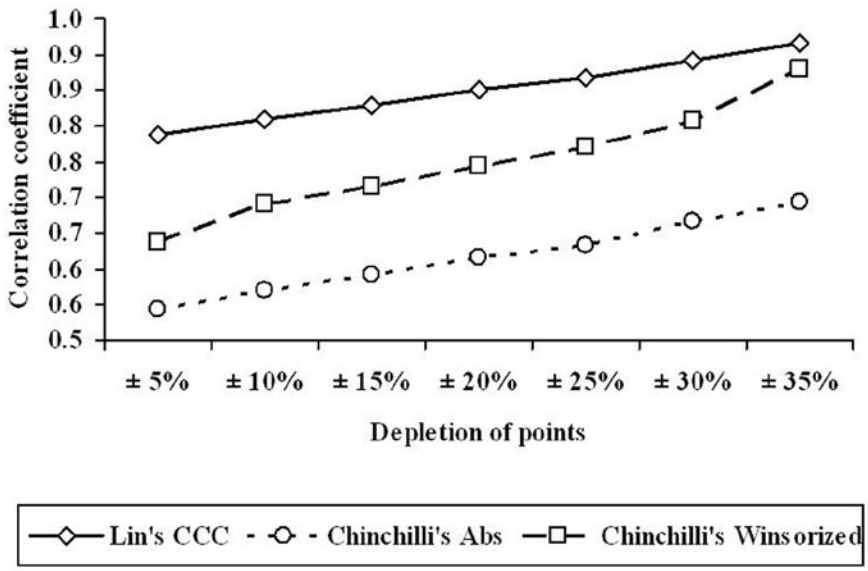


Figure 9.8. Relationship between correlation coefficients and percentage of depletion of point from the mean of X, using a synthetic database with 1,000 XY data points.

Carrasco and Jover (25) suggested that CCC can be estimated by variance components through a mixed effects model assuming a fixed effects for observers (i.e. Y and X). Interestingly, more than two observers (variables) can be analyzed simultaneously.

The CCC values using variance components and a mixed model were 0.85 ±

0.0259 (CAI x PAI), 0.846 ± 0.0266 (CAT x PAT), 0.824 ± 0.0304 (PAI x PAT), and 0.679 ± 0.05 (CAI x CAT). In general, these values were greater than those shown in Table 9.4, but tended to assess the correlation similarly. That means, CAI x PAI and CAT x PAT had higher concordance than PAI x PAT and CAI x CAT. The CCC technique may not be suitable for repeated measures of different subjects because it does not consider variation amongst subjects.

The overall CCC value for all variables (CAI, PAI, CAT, and PAT) using Carrasco and Jover (25) technique indicated a relatively good concordance amongst these variables to measure cardiac output (0.779 ± 0.0286).

Table 9.4. Concordance correlation coefficients of four methods of measurement of cardiac output: carotid artery impedance-based (CAI), pulmonary artery impedance-based (PAI), carotid artery temperature-based (CAT), and pulmonary artery temperature-based (PAT)

Ref.[1]	CAI x PAT	CAT x PAT	PAI x PAT	CAI x CAT
N	95	99	91	102
1	0.85 ± 0.028	0.78 ± 0.035	0.70 ± 0.040	0.47 ± 0.050
2	0.85 ± 0.123	0.77 ± 0.081	0.69 ± 0.055	0.48 ± 0.051
3	0.85 ± 0.029	0.78 ± 0.029	0.71 ± 0.028	0.47 ± 0.036
4	0.78 ± 0.049	0.62 ± 0.050	0.64 ± 0.048	0.40 ± 0.043
5	0.87 ± 0.029	0.80 ± 0.029	0.74 ± 0.028	0.51 ± 0.036
6	0.99	0.90	0.81	0.64

[1] 1 = Lin (1), 2 = Liao (26), 3 = King and Chinchilli (27) squared difference, 4 = King and Chinchilli (27) winsorized square difference, 5 = King and Chinchilli (27) Huber's function, and 6 = Lin's (1) accuracy measurement (C_b).

Conclusion

In the identifiability section of our chapter we have introduced some of the key terms and methodologies surrounding the application of the Laplace Transform method for identifiability analysis. By applying this method to an array of modest size problems we hope the reader has gained a feeling for the concepts of identifiability and unidentifiable models per se. We have presented examples specifically illustrating aspects of global identifiability, the impact of the experiment on system identifiability, interval identifiability (or parameter range identifiability), local identifiability, and how statistical constraints and, say, allometric information can help with identifiability.

The Laplace Transform method for identifiability analysis is not the only approach available, though, it is, by all accounts the most straight-forward. Two other methods are the Taylor Series (29) approach and the method of Normal Modes (30). Neither of these is more direct than the Laplace Transform method but the former

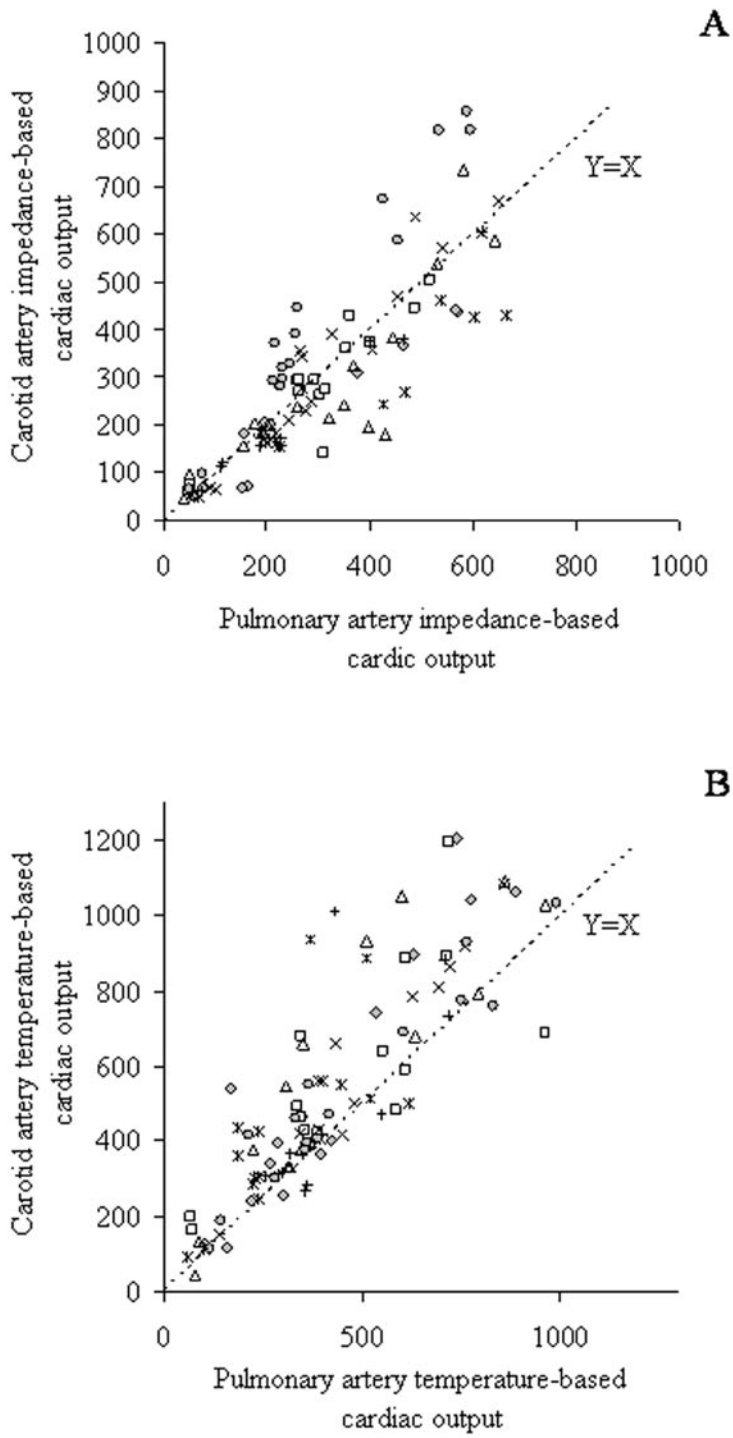


Figure 9.9. Relationship between carotid versus pulmonary artery impedance-based (A) and temperature-based (B) cardiac output. Symbols are subjects in the study. Data from Wilkins et al. (28).

does indeed offer an approach to establishing identifiability of nonlinear systems (31). Unfortunately space limitations preclude expansion of this material into nonlinear systems.

It is interesting to note that the strongest proponents of identifiability are engineers, or mathematicians … indeed, there seem to be neither statisticians, nor biologists amongst the foundation group who developed and promoted identifiability analysis. When we reflect on the terms and tools of identifiability analysis this situation makes sense. It is somewhat predictable too, because whereas biological modeling from the scientific perspective is steeped in the notions of scientific hypotheses and statistical uncertainty, from the engineering and physical perspectives systems theory, and the concepts of controllability and reachability (32) are pervasive. Indeed engineering-orientated investigators will more than likely follow the paths of Kalman (32) and Bellman (33), than those of Zilversmit et al. (34). We insist that the reader, regardless of his/her background be aware of all styles of contributions to biological modeling … each offers help in regard to a pursuit in the undeniable background of traps and turns.

So with all its complexity (15) does identifiability analysis fall within the province of the 'routine investigator. Does it offer tools and techniques to facilitate the modeling process and protect us from the difficulties and false inferences a wrong turn can lead us. On balance, there is a lot to be learned from this area, not the least of which is to allow the fabrication of a dialog medium between classes of investigators (biologists, biomathematicians, bioengineers, biophysicists, biostatisticians, and biochemists). It is clear that Cobelli (35) himself must have grappled with these issues as he dedicated so much time and effort towards the refinement of highly complex, though user-friendly computer software for the automated identifiability of systems.

The last point is that to simply summarize the connection between the experimental model and the biological model with its basic parameters in a fashion where a kinetic study yielding n experimental 'slopes' describes a model with n exchanging pools or compartments and 2×n-1 rate parameters does the subtlety of kinetic investigation a disservice. What you get depends on what you do and how hard you look.

In the accuracy section of our chapter we presented several techniques currently being used to assess concordance between two or more variables or instruments using continuous data. The accuracy of an approach to characterize an aspect of a system is the relative agreement between the results based on the approach compared with the results based on a "gold" standard method. Concordance is a much more profound issue than merely correlation or regression because it needs to embrace the observation range over which the two series of measurements exist, it needs to penalize a quantification of agreement for not predicting the origin as a critical point, and also for not engaging

a line of perfect agreement (slope unity) into its consideration. We compared several methods used to compute the concordance correlation coefficient. Unfortunately, these coefficients had different behaviors under different structures of error variance (non-normal distribution), depletion of data points, and sample size. The use of CCC has to be performed after meticulous analysis of the assumptions underlying the technique, including normality, relationship between means and variances of Y and X variates, and range of the data. The generalized CCC technique using different methods to assess the distance between Y and X might be less prone to non-normality departures. We suggest the use of at least three techniques to calculate CCC when comparing different models or assessing calibration of equipments.

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