March 23, 1988

STATISTICAL VARIABILITY OF PARAMETER BOUNDS FOR n-POOL UNIDENTIFIABLE MAMMILLARY AND CATENARY COMPARTMENTAL MODELS

Robert Lindell*,

Joseph J. DiStefano III**,

and

Elliot M. Landaw***

Biocybernetics Laboratory*

Departments of Computer Science and Medicine**

and

Department of Biomathematics***

University of California, Los Angeles

Short Title: Variability of Parameter Bounds

ABSTRACT

Analytic (asymptotic) expressions are derived for estimating the variances of the parameter bounds for unidentifiable n-pool mammillary and catenary compartmental models with input and output probes in pool 1 (central, or first pool) only. These equations provide information about how output data errors propagate into the estimation of parameter bounds determined from interval identifiability analysis of the deterministic model. A key feature of the variance algorithm involves use of the Laplace transform to compute output sensitivity functions with respect to the structural invariants of the model, required for estimating covariances in an intermediate step. The resulting variance algorithm is compared with Monte Carlo simulations for several test cases, using constant coefficient of variation (CV) data error models. The asymptotic variances compare favorably with simulated results, tending to slightly underestimate the true variances of the parameter bounds with greatest variability. Overall, the results suggest that the variances of parameter bounds for these two classes of models may be uniformly well-behaved, at least for constant CV data errors. This last result appears to hold for quasiidentifiable models in the presence of noisy data, as well as interval identifiable models that are far from being quasiidentifiable.

Mammillary and catenary compartmental models are used quite often as paradigms in many areas of science, especially biology and chemistry. For this reason, a fair amount of attention has been devoted to understanding their mathematical properties and determining methods for estimating specific unknown parameters, which may be structurally identifiable or not, depending on the input/output probes available and the total number of unknown parameters. This paper is an extension of the work of DiStefano, Chen, and Landaw on parameter interval analysis of unidentifiable, deterministic mammillary and catenary models [1-3], extending their results to include the effects of noisy experimental data.

The important issue is how these output data errors propagate into the estimation of parameter bounds. This problem is explored here using two different techniques for estimating the variability in parameter bound estimates, based on known variabilities in experimental data: an analytical and a Monte Carlo simulation approach.

Mammillary and Catenary Models: The *n-pool mammillary compartmental model consists of one central pool* exchanging reversibly with n-1 peripheral pools (Fig. 1). All pools can leak to the environment and no exchange occurs between peripheral pools. The *n-pool catenary compartmental model consists of a series concatenation of* n pools with exchange only between nearest neighboring pools (Fig. 2). Leaks to the environment are possible from all pools. We consider only open single pool input/single pool output (SPISPO) models, with input and output in pool 1, strongly connected so that all eigenvalues are real and negative.

The equations that describe the mass $q_i(t) \equiv q_i$ in pool i at time t for either model are:

$$\dot{\mathbf{q}}(t) = K\mathbf{q}(t) + \mathbf{b}u(t) \tag{1}$$

where $\mathbf{b} = [1\ 0 \cdots 0]^T$, $\mathbf{q} = [q_1\ q_2 \cdots q_n]^T$, $\mathbf{q}(0) \equiv \mathbf{q}_0$. For simplicity, we choose u(t) as the unit impulse (dirac delta) function and $\mathbf{q}_0 = 0$, the most common case in applications. For nonunit impulse inputs, results generally differ only by scale factors. For other inputs, the approach is similar, but the algebra can become quite complicated. The system matrix K for the mammillary model is:

$$K = \begin{bmatrix} k_{11} & k_{12} & k_{13} & . & . & k_{1n} \\ k_{21} & k_{22} & 0 & . & . & 0 \\ k_{31} & 0 & k_{33} & 0 & . & 0 \\ . & . & 0 & . & . & 0 \\ . & . & . & . & . & 0 \\ k_{n1} & 0 & 0 & 0 & 0 & k_{nn} \end{bmatrix} \tag{2}$$

and for the catenary model:

$$K = \begin{bmatrix} k_{11} & k_{12} & 0 & . & . & 0 \\ k_{21} & k_{22} & k_{23} & 0 & . & 0 \\ 0 & k_{32} & k_{33} & . & . & 0 \\ . & 0 & . & . & . & 0 \\ . & . & . & . & . & k_{n-1,n} \\ 0 & 0 & 0 & 0 & k_{n,n-1} & k_{nn} \end{bmatrix} \tag{3}$$

where the fractional transport rates $k_{ij} \geq 0$, $i \neq j$, have $time^{-1}$ units, and k_{ii} is the negative of the sum of all k_{ij} directed from (leaving) pool i (see Eq. (6) and (8) below).

We first assume the output $y(t) = q_1(t)$, which for either model with a unit impulse input can be written:

$$y(t) \equiv \mathbf{c}^T\mathbf{q} = [1\ 0 \cdots 0]\mathbf{q} = \sum_{i=1}^{n} A_i e^{\lambda_i t} \tag{4}$$

where $A_i > 0$ and $\lambda_i < 0$. The λ_i are distinct for the mammillary model if the peripheral pools can be indexed so that $k_{22} < k_{33} \cdots < k_{nn}$, and they are distinct for the catenary model if $k_{i,i+1}k_{i+1,i} > 0$ [2,3]. We treat the concentration measurement case, $y(t) = \dfrac{q_1(t)}{V_1}$, where V_1 is the volume of pool 1, in a later section. For both cases, the output y(t) is assumed to be measured with additive zero-mean, white noise e(t) (not necessarily gaussian), so the measurement data model is given by $z(t) = y(t) + e(t)$, or its discrete-time equivalent $z(t_k) = y(t_k) + e(t_k)$, $k = 1, 2, \cdots, N$. The noise variance at time t is $\sigma^2(t)$.

Identifiability Analysis of Mammillary and Catenary Models: In general, mammillary and catenary models are unidentifiable from the impulse response function $y(t) \equiv h_{11}(t)$, or its Laplace transform $H_{11}(s) = \mathbf{c}^T[sI-K]^{-1}\mathbf{b}$, with **b** and **c** given in Eq. (1) and (4) , based on input and measurement in pool 1 only [4]. However, it has been shown that the following 2n-1 *parameter combinations* (structural invariants [10]) are uniquely identifiable for the *mammillary* model [1,2]:

$$\gamma_i = k_{1i}k_{i1} \quad \text{for} \quad i = 2,3, \cdots ,n \tag{5}$$

$$k_{ii} = \begin{cases} - k_{01} - k_{21} - k_{31} \cdots - k_{n1} & \text{for} \quad i = 1 \\ - k_{0i} - k_{1i} & \text{for} \quad i = 2,3, \cdots ,n \end{cases} \tag{6}$$

and the following 2n-1 parameter combinations (structural invariants) are uniquely identifiable for the *catenary* model [3]:

$$\gamma_i = k_{i,i-1}k_{i-1,i} \quad \text{for} \quad i = 2,3, \cdots ,n \tag{7}$$

$$k_{ii} = \begin{cases} - k_{01} - k_{21} & \text{for} \quad i = 1 \\ - k_{0i} - k_{i+1,i} - k_{i-1,i} & \text{for} \quad i = 2,3, \cdots ,n-1 \\ - k_{0n} - k_{n-1,n} & \text{for} \quad i = n \end{cases} \tag{8}$$

DiStefano and coworkers developed expressions in terms of these identifiable parameter combinations that bound the values of all of the k_{ij} [1,3]. All k_{ij} of mammillary and catenary models are thus *interval identifiable* [1]. With the lower bound on all leaks being zero ($k_{0i}^{min} \equiv 0$, $i \geq 1$), the generalized parameter bounds for n-pool *mammillary* models were given in [1] as:

$$k_{i1}^{min} \equiv -\frac{\gamma_i}{k_{ii}} \leq k_{i1} \leq \sum_{\substack{j=2 \\ j \neq i}}^{n} \frac{\gamma_j}{k_{jj}} - k_{11} \equiv k_{i1}^{max} \quad , \quad i > 1 \tag{9}$$

$$k_{1i}^{min} \equiv \frac{\gamma_i}{k_{i1}^{max}} \leq k_{1i} \leq -k_{ii} \equiv k_{1i}^{max} \quad , \quad i > 1 \tag{10}$$

$$k_{0i}^{min} \equiv 0 \leq k_{0i} \leq \left\{ \begin{array}{lll} \sum_{j=2}^{n} \frac{\gamma_j}{k_{jj}} - k_{11} & \text{for} & i = 1 \\ -\frac{\gamma_i}{k_{i1}^{max}} - k_{ii} & \text{for} & 1 < i \leq n \end{array} \right\} \equiv k_{0i}^{max} \tag{11}$$

The parameter bounds for n-pool *catenary* models were given in [3] as:

$$k_{i+1,i}^{min} \equiv \frac{\gamma_{i+1}}{k_{i,i+1}^{max}} \leq k_{i+1,i} \leq \left\{ \begin{array}{lll} -k_{11} & \text{for} & i = 1 \\ -k_{ii} - \frac{\gamma_i}{k_{i,i-1}^{max}} & \text{for} & 1 < i < n \end{array} \right\} \equiv k_{i+1,i}^{max} \tag{12}$$

$$k_{i-1,i}^{min} \equiv \frac{\gamma_i}{k_{i,i-1}^{max}} \leq k_{i-1,i} \leq \left\{ \begin{array}{lll} -k_{nn} & \text{for} & i = n \\ -k_{ii} - \frac{\gamma_{i+1}}{k_{i,i+1}^{max}} & \text{for} & 1 < i < n \end{array} \right\} \equiv k_{i-1,i}^{max} \tag{13}$$

$$k_{0i}^{min} \equiv 0 \leq k_{0i} \leq \left\{ \begin{array}{lll} -k_{11} - k_{21}^{min} & \text{for} & i = 1 \\ -k_{ii} - k_{i-1,i}^{min} - k_{i+1,i}^{min} & \text{for} & 1 < i < n \\ -k_{nn} - k_{n-1,n}^{min} & \text{for} & i = n \end{array} \right\} \equiv k_{0i}^{max} \tag{14}$$

In references [1-3], the interval identifiability algorithm, i.e. the procedure for computing the k_{ij}^{min} and k_{ij}^{max} from the above relationships, was established in three transformation steps:

$$\{A_i,\lambda_i\} \rightarrow \{\alpha_i,\beta_i\} \rightarrow \{k_{ii},\gamma_i\} \rightarrow \{k_{ij}^{min},k_{ij}^{max}\} \tag{15}$$

where α_i and β_i are the coefficients of the transfer function:

$$H_{11}(s) = \frac{\beta_n s^{n-1} + \cdots + \beta_2 s + \beta_1}{s^n + \alpha_n s^{n-1} + \cdots + \alpha_2 s + \alpha_1} \quad (16)$$

The same approach is used here for the variance algorithm.

AN ANALYTIC APPROXIMATION OF THE PARAMETER BOUND COVARIANCE MATRIX

The Asymptotic Variance for the Parameter Bounds: As shown in Eqs. (9) - (14) , the parameter bounds k_{ij}^{min} and k_{ij}^{max} ($i \neq j$) of the general n-pool mammillary and catenary models are functions of the 2n-1 identifiable parameter combinations, expressed by vector $\mathbf{p}^c$:

$$\mathbf{p}^c \equiv \left[\, k_{11}\ k_{22}\ k_{33}\ \cdots\ k_{nn}\ \gamma_2\ \gamma_3\ \cdots\ \gamma_n \right]^T \quad (17)$$

For real data, in the presence of measurement error, weighted least squares or any other suitable statistical procedure can be used to generate a consistent estimate $\hat{\mathbf{p}}^c$ of the unknown identifiable parameter combinations. However, bounds computed from $\hat{\mathbf{p}}^c$ will themselves be estimates and subject to estimation error. We derive here an approximation for the variance of the bounds (VAR) using the covariance of $\hat{\mathbf{p}}^c$ and derivatives of the parameter bounds with respect to $\mathbf{p}^c$.

The variance of a scalar analytic function f of a random column vector $\mathbf{x} = \left[x_1\ x_2\ \cdots\ x_n\right]^T$ can be approximated by the following formula, based on a first-order Taylor series approximation of $f(\mathbf{x})$ about a fixed point $\mathbf{x}_0$ (e.g., the expected value of $\mathbf{x}$ or a consistent estimate of this value):

$$\mathrm{VAR}[f(\mathbf{x})] \approx \frac{\partial f(\mathbf{x})}{\partial \mathbf{x}} \mathrm{COV}(\mathbf{x}) \frac{\partial f(\mathbf{x})}{\partial \mathbf{x}}^T \equiv \mathrm{VAR_a}[f(\mathbf{x})] \quad (18)$$

where $\frac{\partial f(\mathbf{x})}{\partial \mathbf{x}} = \left[\frac{\partial f(\mathbf{x})}{\partial x_1}\ \frac{\partial f(\mathbf{x})}{\partial x_2}\ \cdots\ \frac{\partial f(\mathbf{x})}{\partial x_n}\right]$ is a row vector evaluated at $\mathbf{x}_0$. If $\mathbf{x}$ in Eq. (18) is the identifiable parameter combination vector $\hat{\mathbf{p}}^c$ estimated from noisy data, and $f \equiv k_{ij}^m$ is a specific estimated parameter bound denoted $k_{ij}^m = k_{ij}^{min}$ or k_{ij}^{max}, $i \neq j$, $i = 0,1, \cdots ,n$ and $j = 1,2, \cdots ,n$, then the approximation is:

$$\mathrm{VAR}_a[\hat{k_{ij}^m}] = \frac{\partial k_{ij}^m}{\partial \mathbf{p}^c} \mathrm{COV}(\hat{\mathbf{p}}^c) \frac{\partial k_{ij}^m}{\partial \mathbf{p}^c}^T \tag{19a}$$

Remark: An *asymptotic covariance matrix* of the vector **f** defined by:

$$\mathbf{f} = \left[k_{01}^{min} \ \cdots \ k_{ij}^{min} \ \cdots \ k_{n,n-1}^{min} \ k_{01}^{max} \ \cdots \ k_{n,n-1}^{max} \right]^T$$

may be similarly derived. In this case:

$$\mathrm{COV}(\mathbf{f}) \approx \frac{\partial \mathbf{f}}{\partial \mathbf{p}^c} \mathrm{COV}(\hat{\mathbf{p}}^c) \frac{\partial \mathbf{f}}{\partial \mathbf{p}^c}^T \equiv \mathrm{COV}_a(\mathbf{f}) \tag{19b}$$

where the ij^{th} element of $\frac{\partial \mathbf{f}}{\partial \mathbf{p}^c}$ is $\frac{\partial \mathbf{f}_i}{\partial \mathbf{p}_j^c}$. We show next how to obtain an approximation for $\mathrm{COV}(\hat{\mathbf{p}}^c)$. Analytic expressions for $\frac{\partial k_{ij}^m}{\partial \mathbf{p}^c}$ are then derived for the mammillary and catenary models.

Asymptotic Covariance Matrix for the Identifiable Parameter Combinations: For N discrete-time, noisy output measurements $z(t_1), \cdots ,z(t_N)$, we choose:

$$\mathrm{COV}_a(\hat{\mathbf{p}}^c) \equiv M^{-1} = \left[\sum_{i=1}^{N} M_i \right]^{-1} \tag{20}$$

where

$$M_i = \frac{1}{\sigma^2(t_i)} \left[\frac{\partial y(t_i,\mathbf{p}^c)}{\partial \mathbf{p}^c} \right]^T \left[\frac{\partial y(t_i,\mathbf{p}^c)}{\partial \mathbf{p}^c} \right] \tag{21}$$

and $\frac{\partial y}{\partial \mathbf{p}^c}$ is a row vector. When $\frac{\partial y}{\partial \mathbf{p}^c}$ is evaluated at the true value of $\mathbf{p}^c$, or its consistent weighted least squares estimate $\hat{\mathbf{p}}^c$, this M^{-1} is generally an asymptotically correct expression for $\mathrm{COV}(\hat{\mathbf{p}}^c)$ for sufficiently large N or vanishingly small $\sigma^2(t_i)$, for any functional form of the data error distribution. Specifically, this asymptotic theory is for weighted least squares estimation, where the weights are proportional to $\frac{1}{\sigma^2(t_i)}$ [7,8]. Furthermore, by the chain rule for differentiation, the right hand side of Eqs. (19a) with $COV_a(\hat{\mathbf{p}}^c)$ replacing $COV(\hat{\mathbf{p}}^c)$ can be developed directly from asymptotic theory applied to the parameter bounds and therefore is an asymptotically correct expression for $VAR[\hat{k}_{ij}^m]$ under weighted least squares estimation.

It is of interest to note that this approximation of a covariance matrix is also well-founded in information theory, for gaussian distributed error models. By the *Cramer-Rao* theorem [11], $COV(\hat{\mathbf{p}}^c) \geq M^{-1}$, where $COV(\hat{\mathbf{p}}^c)$ is the covariance of an unbiased estimate of $\mathbf{p}^c$, M is the *Fisher Information matrix* and $A \geq B$ denotes that A - B is positive semidefinite. The inverse of M is the *Cramer-Rao Lower Bound* (CRB). The CRB may be used here as an approximation of the true covariance of $\hat{\mathbf{p}}^c$. Under suitable conditions, the CRB is achieved asymptotically for maximum likelihood estimators [7,8]. M is commonly represented in terms of the likelihood function L:

$$M = E\left[\frac{\partial \ln L}{\partial \mathbf{p}^c}^T \frac{\partial \ln L}{\partial \mathbf{p}^c}\right] \tag{22}$$

where $\frac{\partial \ln L}{\partial \mathbf{p}^c}$ is a row vector and

$$L = \prod_{i=1}^{N} \frac{1}{\sqrt{2\pi\sigma^2(t_i)}} e^{-\frac{(z(t_i) - y(t_i))^2}{2\sigma^2(t_i)}} \tag{23}$$

when the data errors are gaussian and white, with zero mean and known variance $\sigma^2(t_i)$. Under these conditions, one obtains Eqs. (20) and (21) .

To calculate $COV(\hat{\mathbf{p}}^c)$, an expression for $\frac{\partial y(t,\mathbf{p}^c)}{\partial \mathbf{p}^c}$ is needed, which is different for each model structure under consideration.

Sensitivity Function Derivations Using a Transfer Function Approach: Instead of evaluating the derivatives $\frac{\partial y(t,\mathbf{p}^c)}{\partial \mathbf{p}^c}$ directly in the time domain, it is easier to take advantage of the following, assuming $y(t,\mathbf{p}^c)$ and $\frac{\partial y}{\partial \mathbf{p}}$ are continuous and appropriate convergence of integrals, so that the operations of differentiation and integration can be interchanged. If $Y(s,\mathbf{p}^c)$ is the Laplace transform of $y(t,\mathbf{p}^c)$, i.e. $Y(s,\mathbf{p}^c) = \int_0^\infty y(t,\mathbf{p}^c)e^{-st}dt$, then

$$\frac{\partial Y(s,\mathbf{p}^c)}{\partial \mathbf{p}^c} = \frac{\partial}{\partial \mathbf{p}^c}\left[\int_0^\infty y(t,\mathbf{p}^c)e^{-st}dt\right] = \int_0^\infty \frac{\partial}{\partial \mathbf{p}^c}\left[y(t,\mathbf{p}^c)e^{-st}\right]dt \tag{24}$$

or

$$\frac{\partial Y(s,\mathbf{p}^c)}{\partial \mathbf{p}^c} = \int_0^\infty \frac{\partial y(t,\mathbf{p}^c)}{\partial \mathbf{p}^c}e^{-st}dt \tag{25}$$

Thus, if $y(t,\mathbf{p}^c)$ is an impulse response, the sensitivity functions $\frac{\partial y(t,\mathbf{p}^c)}{\partial \mathbf{p}^c}$ can be calculated by taking the derivative $\frac{\partial Y(s,\mathbf{p}^c)}{\partial \mathbf{p}^c}$ of the Laplace transform of the impulse response of the model and then converting this expression back into the time domain by inverse Laplace transformation.

The Asymptotic Variance Algorithm: For any compartmental model, we have the following algorithm. Calculate:

1. The derivative $\frac{\partial y(t,\mathbf{p}^c)}{\partial \mathbf{p}^c}$ using the inverse Laplace transform of Eq. (25) .

2. $COV_a(\hat{k}_{ii},\hat{\gamma}_i)$ from Eqs. (20) and (21) and the results of step (1).

3. The derivatives of the parameter bounds $\frac{\partial k_{ij}^{min}}{\partial \mathbf{p}^c}$ and $\frac{\partial k_{ij}^{max}}{\partial \mathbf{p}^c}$.

4. The approximate variance for the parameter bounds from Eq. (19a) .

We develop this algorithm for the mammillary and catenary models in the Appendix.

EXTENSIONS TO CONCENTRATION MEASUREMENTS

For the concentration model, consider

$$H(s) = \frac{H_{11}(s)}{V_1} \tag{26}$$

where $H_{11}(s)$ is the previous mass model transfer function, and unknown parameter V_1 is the volume in pool 1. For the concentration model, we consider the 2n parameter space where

$$\{A_i,\lambda_i\} \rightarrow \{k_{ii},\gamma_i,V_1\} \tag{27}$$

and $\mathbf{p}^c$ is now defined as the 2n vector

$$\mathbf{p}^c \equiv \left[\; k_{11}\; k_{22}\; k_{33} \;\; \cdots \;\; k_{nn};\; \gamma_2\; \gamma_3 \;\; \cdots \;\; \gamma_n;\; \frac{1}{V_1} \right]^T \tag{28}$$

The derivatives needed for COV($\mathbf{p}^c$) are

$$\frac{\partial H(s)}{\partial V_1^{-1}} = H_{11}(s) \tag{29}$$

$$\frac{\partial H(s)}{\partial k_{ii}} = \frac{1}{V_1}\frac{\partial H_{11}(s)}{\partial k_{ii}} \tag{30}$$

$$\frac{\partial H(s)}{\partial \gamma_i} = \frac{1}{V_1}\frac{\partial H_{11}(s)}{\partial \gamma_i} \tag{31}$$

Therefore, in the time domain, the derivatives used in (21) are simple functions of the impulse response and derivatives already developed for the mass model. The derivatives of the parameter bounds with respect to the first 2n-1 components of $\mathbf{p}^c$ are identical to those developed for the mass model. For the derivative with respect to the last component of $\mathbf{p}^c$,

$$\frac{\partial k_{ij}^{m}}{\partial V_1^{-1}} = 0 \tag{32}$$

ANALYTIC VS. SIMULATED RESULTS

A Monte Carlo simulator (MCEXP) was developed to generate "experimental" results for computing sample variances of parameter bounds in mammillary and catenary models. It is a modification of one presented in [9].

Several test cases are described below. Each is based on a specific mammillary or catenary model with fixed nominal $\{A_i, \lambda_i\}$ values, a mass or a concentration output, and a given measurement error variance and sampling schedule. Both analytic (asymptotic) and Monte Carlo simulated variances for the parameter bounds were computed for each test case. For the analytic variances, the M_i matrices in (20) and the derivatives in (19a) were evaluated at the nominal (true) parameter values. Each simulation consisted of generating uncorrelated Gaussian errors from the given statistics, and adding these to the nominal sum of exponentials solution for the specific test case. A sum of exponentials was fitted to this "random" data set, yielding new estimates $\{\hat{A}_i, \hat{\lambda}_i\}$, data and parameter bounds were computed from these $\{\hat{A}_i, \hat{\lambda}_i\}$ using (15) . As the measurement error variance in all test cases was constant coefficient of variation (CV), $\frac{1}{z(t)^2}$ was used as the approximate weight for each datum in the weighted least squares fit. For the mass outputs, weighted least squares fits were constrained by $\sum \hat{A}_i = 1$.

Each test case was simulated 600 times, resulting in 600 realizations of each parameter bound estimate. A 95% confidence interval for the "true" standard deviation (SD) of a parameter bound estimate was obtained by jackknifing [12] the SD of the set of 600 estimates, to obtain a bias-corrected point estimate of the SD and a standard error (SE) of this estimate. The limits of the 95% confidence interval (CI) were then computed as: (point estimate) ±

1.964 SE, where 1.964 is the 97.5^{th} percentile of a t-distribution with 599 degrees of freedom. All asymptotic SD's and confidence limits of the SD's are expressed as %CV = 100 SD / (parameter bound). There were no important estimation biases of the parameter bound estimates, the mean of the 600 estimated bounds being at most a few percent different from the true parameter bound. Two-pool models, which are both mammillary and catenary, were used in three of the five test cases illustrated here (Table 1), and the mammillary and catenary algorithms for the analytic (asymptotic) variances produced exactly the same results.

Results: Table 1 summarizes results for a specific 2-pool model under different output and data error conditions. For (constant) 5% and 30% data error CV's, the parameter bound estimate variabilities in this example are the same order of magnitude as data error variability. For 5% data error CV's, the concentration model parameter bound estimate %CV's are somewhat larger than for the mass model, as expected, because the concentration model has one additional unknown parameter. Also, the asymptotic %CV's agree very well with the 95% CI's for the true %CV's. In contrast, for 30% data error CV's, the asymptotic %CV's tend to slightly underestimate the true %CV's.

Tables 2 and 3 summarize the results for 2 different 3-pool mammillary models with concentration output originally fitted to real data from the rat [1]. Data error CV's and the number of sample times are the same in each case. The two models differ, however, in that one (Table 2) is quasiidentifiable [1], i.e., $\Delta k_{ij} \equiv k_{ij}^{max} - k_{ij}^{min}$ values range over 1.3 - 6.5% of k_{ij}^{min} (worst case), excluding leaks for which this concept is undefined because $k_{0j}^{min} \equiv 0$. The other model (Table 3) is not quasiidentifiable, because $100\frac{\Delta k_{ij}}{k_{ij}^{min}}$ (% range) values are 185% or 477%, $i \neq 0$. We note that the asymptotic %CV's in Table 2 are somewhat larger than those in Table 3. Also, the smallest asymptotic %CV's (those under about 10%) tend to fall within the midrange of the 95% CI for the true %CV's, whereas the larger asymptotic %CV's tend to slightly underestimate the true %CV's.

We also computed variability measures for the Δk_{ij}'s (ranges), using Eq. (19b) to obtain asymptotic covariance relations between k_{ij}^{max} and k_{ij}^{min} (not shown in the Tables). We have previously shown [1] that $\Delta k_{21} \equiv \Delta k_{31} \equiv k_{01}^{max}$, $\Delta k_{12} \equiv k_{02}^{max}$ and $\Delta k_{13} \equiv k_{03}^{max}$. Therefore, the magnitude of the variability of the Δk_{ij}'s is the same as that of the corresponding k_{0j}^{max}. For example, the largest Δk_{ij} in Table 2 is $\Delta k_{31} = 0.0348$, with an asymptotic %CV of only 11.5% and a 95% CI for the true %CV of 11.4 - 12.7%. Furthermore, the % range for Δk_{31}, which is also the largest, at 6.5, has an asymptotic SD of only 1.4. Therefore, this model remains quasiidentifiable in the presence of real noisy data.

Conclusions

Analytic estimates for the variances of the parameter bounds for the general mammillary and catenary models are useful for understanding how experimental errors propagate into the estimation of parameter bounds. In this paper, asymptotically correct estimates for the variance of the parameters bounds were derived. Numerical results were presented for 5 test cases, and these were compared with the results of Monte Carlo simulations. Asymptotic variances compared favorably with simulated results, tending to slightly underestimate the largest parameter bound estimate %CV's. Overall, the numerical results suggest that the variances of the parameter bounds for mammillary and catenary models may be uniformly well-behaved, at least for constant CV data errors. Furthermore, this result appears to hold even for quasiidentifiable models in the presence of noisy data.

Clearly these examples alone cannot be interpreted as a validation of the general agreement between asymptotic and true variances. As noted earlier, the analytic variances may be asymptotically correct only for sufficiently large data sets or vanishingly small data errors. Likewise, since the analytic solution is a first order approximation, the analytic estimates may be expected to diverge from the true value of the variance for larger data errors.

The numerical algorithms have been implemented in our mammillary and catenary model analyzers, MAMPOOL [1,2] and CATPOOL [3,5], and are being used in our laboratory for routinely exploring these model classes in real data situations. Example computer output for the 5% CV data error concentration model is illustrated in Fig. 3.

ACKNOWLEDGEMENTS

This research was supported by grants from the National Science Foundation (NSF/DCB 84-11823), NATO (Collaborative Research Grant No. RG 85/0207), and National Institutes of Health (AM34839 and AM25744).

APPENDIX: ALGORITHMS FOR THE MAMMILLARY AND CATENARY MODELS

Mammillary Model

Sensitivity Functions for Mammillary Model Impulse Response: From Eq. (2) and (5) - (8) , the transfer function $H_{11}(s)$ is:

$$H_{11}(s) = \frac{1{,}1^{\text{th}} \text{ minor of } [sI-K]}{\text{determinant of } [sI-K]} = \frac{(s - k_{22})(s - k_{33}) \cdots (s - k_{nn})}{\prod_{i=1}^{n}(s - k_{ii}) - \sum_{i=2}^{n}\gamma_i \left[\prod_{\substack{j=1 \\ j\neq i}}^{n}(s - k_{jj})\right]} \tag{A1}$$

$$= \frac{\prod_{i=2}^{n}(s - k_{ii})}{\prod_{i=2}^{n}(s - k_{ii})\left[(s - k_{11}) - \sum_{i=2}^{n}\frac{\gamma_i}{(s - k_{ii})}\right]} = \left[(s - k_{11}) - \sum_{i=2}^{n}\frac{\gamma_i}{(s - k_{ii})}\right]^{-1} \tag{A2}$$

Using this simplified form, the derivatives of $H_{11}(s)$ with respect to $\mathbf{p}^c$ are derived as follows:

$$\frac{\partial H_{11}(s)}{\partial k_{11}} = \left[(s - k_{11}) - \sum_{i=2}^{n}\frac{\gamma_i}{(s - k_{ii})}\right]^{-2} = \left[H_{11}(s)\right]^2 \tag{A3}$$

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \frac{\gamma_i}{(s - k_{ii})^2}\left[(s - k_{11}) - \sum_{i=2}^{n}\frac{\gamma_i}{(s - k_{ii})}\right]^{-2} = \frac{\gamma_i}{(s - k_{ii})^2}\left[H_{11}(s)\right]^2 \tag{A4}$$

$$\frac{\partial H_{11}(s)}{\partial \gamma_i} = \frac{1}{(s - k_{ii})}\left[(s - k_{11}) - \sum_{i=2}^{n}\frac{\gamma_i}{(s - k_{ii})}\right]^{-2} = \frac{1}{(s - k_{ii})}\left[H_{11}(s)\right]^2 \tag{A5}$$

The transfer function $H_{11}(s)$ can be alternatively expressed in terms of the multiexponential impulse response: $H_{11}(s) = \sum_{i=1}^{n}\frac{A_i}{(s - \lambda_i)}$. Thus,

$$\left[H_{11}(s)\right]^2 = \sum_{i=1}^{n}\sum_{j=1}^{n}\frac{A_iA_j}{(s - \lambda_i)(s - \lambda_j)} = \sum_{i=1}^{n}\left[\frac{A_i^2}{(s - \lambda_i)^2} + 2\sum_{\substack{j=1 \\ j>i}}^{n}\frac{A_iA_j}{(s - \lambda_i)(s - \lambda_j)}\right] \tag{A6}$$

the latter being computationally simpler. Finally, the required derivatives for $COV_a(\hat{k}_{ii},\hat{\gamma}_i)$ are expressed in the time domain by first substituting $\left[H_{11}(s)\right]^2$ in Eq. (A6) into the previous expressions for the derivatives and then taking the inverse Laplace transformations as follows:

$$\frac{\partial H_{11}(s)}{\partial k_{11}} = \left[H_{11}(s)\right]^2 = \sum_{i=1}^{n}\left[\frac{A_i^2}{(s - \lambda_i)^2} + 2\sum_{\substack{j=1\\ j>i}}^{n}\frac{A_iA_j}{(s - \lambda_i)(s - \lambda_j)}\right] \qquad (A7)$$

$$\frac{\partial h_{11}(t)}{\partial k_{11}} = \sum_{i=1}^{n}\left[A_i^2te^{\lambda_i t} + 2\sum_{\substack{j=1\\ j>i}}^{n}\frac{A_iA_j}{(\lambda_i - \lambda_j)}\left[e^{\lambda_i t} - e^{\lambda_j t}\right]\right] \qquad (A8)$$

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \frac{\gamma_i}{(s - k_{ii})^2}\left[H_{11}(s)\right]^2$$

$$= \gamma_i\sum_{j=1}^{n}\left[\frac{A_j^2}{(s - \lambda_j)^2(s - k_{ii})^2} + 2\sum_{\substack{k=1\\ k>j}}^{n}\frac{A_jA_k}{(s - \lambda_j)(s - \lambda_k)(s - k_{ii})^2}\right]$$

$$= \gamma_i\sum_{j=1}^{n}\left[\frac{A_j^2}{(\lambda_j - k_{ii})^2}\left[\frac{1}{(s - \lambda_j)^2} + \frac{1}{(s - k_{ii})^2} + \frac{2}{(\lambda_j - k_{ii})}\left[\frac{1}{(s - k_{ii})} - \frac{1}{(s - \lambda_j)}\right]\right]\right.$$

$$+ 2\sum_{\substack{k=1\\ k>j}}^{n}A_jA_k\left[\frac{1}{(\lambda_j - \lambda_k)}\left[\frac{1}{(\lambda_j - k_{ii})^2(s - \lambda_j)} - \frac{1}{(\lambda_k - k_{ii})^2(s - \lambda_k)}\right]\right. \qquad (A9)$$

$$\left.\left. + \frac{1}{(\lambda_j - k_{ii})(\lambda_k - k_{ii})}\left[\frac{1}{(s - k_{ii})^2} + \frac{\lambda_j + \lambda_k - 2k_{ii}}{(\lambda_k - k_{ii})(\lambda_j - k_{ii})(s - k_{ii})}\right]\right]\right]$$

$$\frac{\partial h_{11}(t)}{\partial k_{ii}} = \gamma_i\sum_{j=1}^{n}\left[\frac{A_j^2}{(\lambda_j - k_{ii})^2}\left[te^{\lambda_j t} + te^{k_{ii}t} + \frac{2}{(\lambda_j - k_{ii})}\left[e^{k_{ii}t} - e^{\lambda_j t}\right]\right]\right.$$

$$+ 2\sum_{\substack{k=1\\k>j}}^{n} A_j A_k \left[\frac{1}{(\lambda_j - \lambda_k)} \left[\frac{e^{\lambda_j t}}{(\lambda_j - k_{ii})^2} - \frac{e^{\lambda_k t}}{(\lambda_k - k_{ii})^2} \right. \right. \tag{A10}$$

$$\left. \left. \left. + \frac{e^{k_{ii} t}}{(\lambda_j - k_{ii})(\lambda_k - k_{ii})} \left[t + \frac{\lambda_j + \lambda_k - 2k_{ii}}{(\lambda_k - k_{ii})(\lambda_j - k_{ii})} \right] \right] \right] \right]$$

$$\frac{\partial H_{11}(s)}{\partial \gamma_i} = \frac{1}{(s - k_{ii})} \left[H_{11}(s) \right]^2 \tag{A11}$$

$$\frac{\partial H_{11}(s)}{\partial \gamma_i} = \sum_{j=1}^{n} \left[\frac{A_j^2}{(s - \lambda_j)^2 (s - k_{ii})} + 2\sum_{\substack{k=1\\k>j}}^{n} \frac{A_j A_k}{(s - \lambda_j)(s - \lambda_k)(s - k_{ii})} \right]$$

$$= \sum_{j=1}^{n} \left[\frac{A_j^2}{(\lambda_j - k_{ii})} \left[\frac{1}{(s - \lambda_j)^2} + \frac{1}{(\lambda_j - k_{ii})} \left[\frac{1}{(s - k_{ii})} - \frac{1}{(s - \lambda_j)} \right] \right] \right.$$

$$+ 2\sum_{\substack{k=1\\k>j}}^{n} A_j A_k \left[\frac{1}{(\lambda_j - \lambda_k)} \left[\frac{1}{(\lambda_j - k_{ii})(s - \lambda_j)} - \frac{1}{(\lambda_k - k_{ii})(s - \lambda_k)} \right] \right. \tag{A12}$$

$$\left. \left. + \frac{1}{(\lambda_j - k_{ii})(\lambda_k - k_{ii})(s - k_{ii})} \right] \right]$$

$$\frac{\partial h_{11}(t)}{\partial \gamma_i} = \sum_{j=1}^{n} \left[\frac{A_j^2}{(\lambda_j - k_{ii})} \left[t e^{\lambda_j t} + \frac{1}{(\lambda_j - k_{ii})} \left[e^{k_{ii} t} - e^{\lambda_j t} \right] \right] \right]$$

$$+ 2\sum_{\substack{k=1\\k>j}}^{n} A_j A_k \left[\frac{1}{(\lambda_j - \lambda_k)} \left[\frac{e^{\lambda_j t}}{(\lambda_j - k_{ii})} - \frac{e^{\lambda_k t}}{(\lambda_k - k_{ii})} \right] \right. \tag{A13}$$

$$+ \frac{e^{k_{ii}t}}{(\lambda_j - k_{ii})(\lambda_k - k_{ii})}\Bigg]\Bigg]$$

Sensitivity Functions for Mammillary Model Parameter Bounds: From the parameter bounds in Eqs. (9) - (11) , the derivatives of the parameter bounds with respect to $\mathbf{p}^c$ are as follows, for i > 1:

$$\frac{\partial k_{i1}^{min}}{\partial k_{jj}} = \begin{cases} \dfrac{\gamma_j}{k_{jj}^2} & \text{for} \quad j = i \\ 0 & \text{otherwise} \end{cases} \qquad \frac{\partial k_{i1}^{min}}{\partial \gamma_j} = \begin{cases} \dfrac{-1}{k_{jj}} & \text{for} \quad j = i \\ 0 & \text{otherwise} \end{cases} \tag{A14}$$

$$\frac{\partial k_{i1}^{max}}{\partial k_{jj}} = \begin{cases} -1 & \text{for} \quad j = 1 \\ 0 & \text{for} \quad j = i \\ -\dfrac{\gamma_j}{k_{jj}^2} & \text{otherwise} \end{cases} \qquad \frac{\partial k_{i1}^{max}}{\partial \gamma_j} = \begin{cases} 0 & \text{for} \quad j = i \\ \dfrac{1}{k_{jj}} & \text{otherwise} \end{cases} \tag{A15}$$

$$\frac{\partial k_{1i}^{min}}{\partial k_{jj}} = \begin{cases} \dfrac{\gamma_i}{\left[k_{i1}^{max}\right]^2} & \text{for} \quad j = 1 \\ 0 & \text{for} \quad j = i \\ \dfrac{\gamma_i \gamma_j}{k_{jj}^2\left[k_{i1}^{max}\right]^2} & \text{otherwise} \end{cases} \qquad \frac{\partial k_{1i}^{min}}{\partial \gamma_j} = \begin{cases} \dfrac{1}{k_{i1}^{max}} & \text{for} \quad j = i \\ -\dfrac{\gamma_i}{k_{jj}\left[k_{i1}^{max}\right]^2} & \text{otherwise} \end{cases} \tag{A16}$$

$$\frac{\partial k_{1i}^{max}}{\partial k_{jj}} = \begin{cases} -1 & \text{for} \quad j = i \\ 0 & \text{otherwise} \end{cases} \qquad \frac{\partial k_{1i}^{max}}{\partial \gamma_j} = 0 \tag{A17}$$

$$\frac{\partial k_{01}^{max}}{\partial k_{jj}} = \begin{cases} -1 & \text{for} \quad j = 1 \\ -\dfrac{\gamma_j}{k_{jj}^2} & \text{otherwise} \end{cases} \qquad \frac{\partial k_{01}^{max}}{\partial \gamma_j} = \frac{1}{k_{jj}} \tag{A18}$$

$$\frac{\partial k_{0i}^{max}}{\partial k_{jj}} = \begin{cases} -\dfrac{\gamma_i}{\left[k_{i1}^{max}\right]^2} & \text{for} \quad j = 1 \\ -1 & \text{for} \quad j = i \\ \dfrac{-\gamma_i\gamma_j}{k_{jj}^2\left[k_{i1}^{max}\right]^2} & \text{otherwise} \end{cases} \qquad \frac{\partial k_{0i}^{max}}{\partial \gamma_j} = \begin{cases} \dfrac{-1}{k_{i1}^{max}} & \text{for} \quad j = i \\ \dfrac{\gamma_i}{k_{jj}\left[k_{i1}^{max}\right]^2} & \text{otherwise} \end{cases} \tag{A19}$$

Catenary Model

Sensitivity Functions for Catenary Model Impulse Response: The determinant of [sI–K] may be expressed recursively as [3]:

$$D_i = (s - k_{ii})D_{i+1} - \gamma_{i+1}D_{i+2}, \qquad D_i = \begin{cases} (s - k_{nn}) & \text{for} \quad i = n \\ 1 & \text{for} \quad i = n + 1 \\ 0 & \text{for} \quad i > n + 1 \end{cases} \tag{A20}$$

where D_i is the determinant of the lower right (n-i+1)-by-(n-i+1) block of [sI–K], and K is given by Eq. (3) . The transfer function $H_{11}(s)$ is then:

$$H_{11}(s) = \frac{1,1^{th} \text{ minor of } [sI-K]}{\text{determinant of } [sI-K]} = \frac{D_2}{D_1}$$

and the derivatives of $H_{11}(s)$ with respect to k_{ii} are:

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \frac{1}{D_1^2}\left[D_1 \frac{\partial}{\partial k_{ii}}\left[D_2\right] - D_2 \frac{\partial}{\partial k_{ii}}\left[D_1\right]\right]$$

Then, using Eq. (A20) :

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \frac{1}{D_1^2}\left[D_1 \frac{\partial}{\partial k_{ii}}\left[D_2\right] - D_2 \frac{\partial}{\partial k_{ii}}\left[(s - k_{11})D_2 - \gamma_2 D_3\right]\right]$$

and since $\frac{\partial D_j}{\partial k_{ii}} = 0$ for $j > i$,

$$\frac{\partial H_{11}(s)}{\partial k_{11}} = \left[\frac{D_2}{D_1}\right]^2 \tag{A21}$$

Otherwise, for i > 1:

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \frac{1}{D_1^2}\left[\left[D_1 - (s - k_{11})D_2\right]\frac{\partial}{\partial k_{ii}}\left[D_2\right] + \gamma_2 D_2 \frac{\partial}{\partial k_{ii}}\left[D_3\right]\right]$$

Since $D_1 - (s - k_{11})D_2 = -\gamma_2 D_3$, then for i > 1:

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \frac{1}{D_1^2}\left[\gamma_2 D_2 \frac{\partial}{\partial k_{ii}}\left[D_3\right] - \gamma_2 D_3 \frac{\partial}{\partial k_{ii}}\left[D_2\right]\right]$$

$$= \frac{\gamma_2}{D_1^2}\left[D_2 \frac{\partial}{\partial k_{ii}}\left[D_3\right] - D_3 \frac{\partial}{\partial k_{ii}}\left[D_2\right]\right]$$

Continuing the substitution of Eq. (A20) a total of i-1 times yields:

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \frac{\gamma_2\gamma_3 \cdots \gamma_i}{D_1^2}\left[D_i \frac{\partial}{\partial k_{ii}}\left[D_{i+1}\right] - D_{i+1} \frac{\partial}{\partial k_{ii}}\left[D_i\right]\right]$$

Then

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \frac{\gamma_2\gamma_3 \cdots \gamma_i}{D_1^2}\left[0 - D_{i+1} \frac{\partial}{\partial k_{ii}}\left[(s - k_{ii})D_{i+1} - \gamma_{i+1}D_{i+2}\right]\right]$$

or

$$\frac{\partial H_{11}(s)}{\partial k_{ii}} = \gamma_2\gamma_3 \cdots \gamma_i \left[\frac{D_{i+1}}{D_1}\right]^2, \qquad i > 1 \tag{A22}$$

For the derivative with respect to γ_i:

$$\frac{\partial H_{11}(s)}{\partial \gamma_i} = \frac{1}{D_1^2}\left[D_1 \frac{\partial}{\partial \gamma_i}\left[D_2\right] - D_2 \frac{\partial}{\partial \gamma_i}\left[D_1\right]\right]$$

$$= \frac{1}{D_1^2}\left[D_1 \frac{\partial}{\partial \gamma_i}\left[D_2\right] - D_2 \frac{\partial}{\partial \gamma_i}\left[(s - k_{11})D_2 - \gamma_2 D_3\right]\right]$$

Since $\frac{\partial D_j}{\partial \gamma_i} = 0$ for j≥i, then:

$$\frac{\partial H_{11}(s)}{\partial \gamma_2} = \frac{D_2 D_3}{D_1^2} \qquad \text{(A23)}$$

Otherwise, for i > 2:

$$\frac{\partial H_{11}(s)}{\partial \gamma_i} = \frac{1}{D_1^2}\left[\left[D_1 - (s - k_{11})D_2\right]\frac{\partial}{\partial \gamma_i}\left[D_2\right] + \gamma_2 D_2 \frac{\partial}{\partial \gamma_i}\left[D_3\right]\right]$$

$$= \frac{1}{D_1^2}\left[\gamma_2 D_2 \frac{\partial}{\partial \gamma_i}\left[D_3\right] - \gamma_2 D_3 \frac{\partial}{\partial \gamma_i}\left[D_2\right]\right]$$

$$= \frac{\gamma_2}{D_1^2}\left[D_2 \frac{\partial}{\partial \gamma_i}\left[D_3\right] - D_3 \frac{\partial}{\partial \gamma_i}\left[D_2\right]\right]$$

Continuing the substitution a total of i-2 times yields:

$$\frac{\partial H_{11}(s)}{\partial \gamma_i} = \frac{\gamma_2 \gamma_3 \cdots \gamma_{i-1}}{D_1^2}\left[D_{i-1} \frac{\partial}{\partial \gamma_i}\left[D_i\right] - D_i \frac{\partial}{\partial \gamma_i}\left[D_{i-1}\right]\right]$$

Then

$$\frac{\partial H_{11}(s)}{\partial \gamma_i} = \frac{\gamma_2 \gamma_3 \cdots \gamma_{i-1}}{D_1^2}\left[0 - D_i \frac{\partial}{\partial \gamma_i}\left[(s - k_{i-1,i-1})D_i - \gamma_i D_{i+1}\right]\right]$$

or

$$\frac{\partial H_{11}(s)}{\partial \gamma_i} = \gamma_2 \gamma_3 \cdots \gamma_{i-1} \frac{D_i D_{i+1}}{D_1^2} \qquad , i > 2 \qquad \text{(A24)}$$

Transforming these derivatives into the time domain by inverse Laplace transformation involves a recursive algorithm. From the characteristic polynomial $D_1(s) = \prod_{i=1}^{n}(s - \lambda_i)$ and knowledge that the λ_i are distinct, we have for i > 1

$$\frac{D_i(s)}{D_1(s)} = \frac{D_i(s)}{\prod_{j=1}^{n}(s - \lambda_j)} = \sum_{j=1}^{n} \frac{D_i(\lambda_j)}{(s - \lambda_j)\prod_{\substack{k=1 \\ k\neq j}}^{n}(\lambda_j - \lambda_k)}$$

Define: $d_{ij} = \frac{D_i(\lambda_j)}{\prod_{\substack{k=1 \\ k\neq j}}^{n}(\lambda_j - \lambda_k)}$. Then: $\frac{D_i(s)}{D_1(s)} = \sum_{j=1}^{n} \frac{d_{ij}}{(s - \lambda_j)}$ for $i > 1$. Since the λ_j are the roots of $D_1(s)$, then:

$$d_{1j} \equiv 0 \tag{A25}$$

Also, from the transfer function $\frac{D_2(s)}{D_1(s)} = \sum_{i=1}^{n} \frac{A_i}{(s - \lambda_i)}$ we obtain:

$$d_{2j} = A_j \qquad j = 1,2, \cdots ,n \tag{A26}$$

Thus, from Eq. (A20) and the definitions of d_{ij} above, we have:

$$d_{ij} = \frac{(\lambda_j - k_{i-2,i-2})d_{i-1,j} - d_{i-2,j}}{\gamma_{i-1}} \tag{A27}$$

and Eq. (A27) can be used recursively with Eqs. (A25) and (A26) as initial conditions to generate all d_{ij}. Finally:

$$\frac{D_iD_j}{D_1^2} = \sum_{k=1}^{n} \frac{d_{ik}}{(s - \lambda_k)} \sum_{r=1}^{n} \frac{d_{jr}}{(s - \lambda_r)} = \sum_{k=1}^{n} \left[\frac{d_{ik}d_{jk}}{(s - \lambda_k)^2} + \sum_{\substack{r=1 \\ r>k}}^{n} \frac{d_{jr}d_{ik} + d_{ir}d_{jk}}{(s - \lambda_k)(s - \lambda_r)} \right]$$

$$= \sum_{k=1}^{n} \left[\frac{d_{ik}d_{jk}}{(s - \lambda_k)^2} + \sum_{\substack{r=1 \\ r>k}}^{n} \frac{d_{jr}d_{ik} + d_{ir}d_{jk}}{(\lambda_k - \lambda_r)} \left[\frac{1}{(s - \lambda_k)} - \frac{1}{(s - \lambda_r)} \right] \right] \tag{A28}$$

In the time domain (Lap ≡ Laplace transform):

$$\mathrm{Lap}^{-1}\left\{\frac{D_i D_j}{D_1^2}\right\} = \sum_{k=1}^{n}\left[d_{ik}d_{jk}te^{\lambda_k t} + \sum_{\substack{r=1\\ r>k}}^{n}\frac{d_{jr}d_{ik} + d_{ir}d_{jk}}{(\lambda_k - \lambda_r)}\left[e^{\lambda_k t} - e^{\lambda_r t}\right]\right] \tag{A29}$$

Sensitivity Functions for Catenary Model Parameter Bounds: The derivatives of the parameter bounds are determined by inspection of Eqs. (12) - (14) . These are:

$$\frac{\partial k_{i+1,i}^{max}}{\partial k_{jj}} = \begin{cases} -1 & \text{for } j = i \\ \dfrac{\gamma_i}{\left[k_{i,i-1}^{max}\right]^2}\dfrac{\partial k_{i,i-1}^{max}}{\partial k_{jj}} = -\displaystyle\prod_{r=j+1}^{i}\frac{\gamma_r}{\left[k_{r,r-1}^{max}\right]^2} & \text{for } j < i \\ 0 & \text{for } j > i \end{cases} \tag{A30}$$

$$\frac{\partial k_{i+1,i}^{max}}{\partial \gamma_j} = \begin{cases} \dfrac{-1}{k_{i,i-1}^{max}} & \text{for } j = i \\ \dfrac{\gamma_i}{\left[k_{i,i-1}^{max}\right]^2}\dfrac{\partial k_{i,i-1}^{max}}{\partial \gamma_j} = \dfrac{-1}{k_{j,j-1}^{max}}\displaystyle\prod_{r=j+1}^{i}\frac{\gamma_r}{\left[k_{r,r-1}^{max}\right]^2} & \text{for } j < i \\ 0 & \text{for } j > i \end{cases} \tag{A31}$$

$$\frac{\partial k_{i,i+1}^{min}}{\partial k_{jj}} = \begin{cases} -\dfrac{\gamma_{i+1}}{\left[k_{i+1,i}^{max}\right]^2}\dfrac{\partial k_{i+1,i}^{max}}{\partial k_{jj}} & \text{for } j \le i \\ 0 & \text{for } j > i \end{cases} \tag{A32}$$

$$\frac{\partial k_{i,i+1}^{min}}{\partial \gamma_j} = \begin{cases} 0 & \text{for } j > i+1 \\ \dfrac{1}{k_{i+1,i}^{max}} & \text{for } j = i+1 \\ -\dfrac{\gamma_{i+1}}{\left[k_{i+1,i}^{max}\right]^2}\dfrac{\partial k_{i+1,i}^{max}}{\partial \gamma_j} & \text{for } j < i+1 \end{cases} \tag{A33}$$

$$\frac{\partial k_{i-1,i}^{max}}{\partial k_{jj}} = \begin{cases} -1 & \text{for} \quad j = i \\ \dfrac{\gamma_{i+1}}{\left[k_{i,i+1}^{max}\right]^2} \dfrac{\partial k_{i,i+1}^{max}}{\partial k_{jj}} = -\prod_{r=i}^{j-1} \dfrac{\gamma_{r+1}}{\left[k_{r,r+1}^{max}\right]^2} & \text{for} \quad j > i \\ 0 & \text{for} \quad j < i \end{cases} \tag{A34}$$

$$\frac{\partial k_{i-1,i}^{max}}{\partial \gamma_j} = \begin{cases} \dfrac{-1}{k_{i,i+1}^{max}} & \text{for} \quad j = i+1 \\ \dfrac{\gamma_{i+1}}{\left[k_{i,i+1}^{max}\right]^2} \dfrac{\partial k_{i,i+1}^{max}}{\partial \gamma_j} = \dfrac{-1}{k_{j-1,j}^{max}} \prod_{r=i}^{j-1} \dfrac{\gamma_{r+1}}{\left[k_{r,r+1}^{max}\right]^2} & \text{for} \quad j > i+1 \\ 0 & \text{for} \quad j < i+1 \end{cases} \tag{A35}$$

$$\frac{\partial k_{i,i-1}^{min}}{\partial k_{jj}} = -\frac{\gamma_i}{\left[k_{i-1,i}^{max}\right]^2} \frac{\partial k_{i-1,i}^{max}}{\partial k_{jj}} \quad \text{for} \quad j \geq i \tag{A36}$$

$$\frac{\partial k_{i,i-1}^{min}}{\partial \gamma_j} = \begin{cases} \dfrac{1}{k_{i-1,i}^{max}} & \text{for} \quad j = i \\ -\dfrac{\gamma_i}{\left[k_{i-1,i}^{max}\right]^2} \dfrac{\partial k_{i-1,i}^{max}}{\partial \gamma_j} & \text{for} \quad j > i \end{cases} \tag{A37}$$

$$\frac{\partial k_{0i}^{max}}{\partial k_{jj}} = \begin{cases} -\dfrac{\partial k_{11}}{\partial k_{jj}} - \dfrac{\partial k_{21}^{min}}{\partial k_{jj}} & \text{for} \quad i = 1 \\ -\dfrac{\partial k_{ii}}{\partial k_{jj}} - \dfrac{\partial k_{i-1,i}^{min}}{\partial k_{jj}} - \dfrac{\partial k_{i+1,i}^{min}}{\partial k_{jj}} & \text{for} \quad 1 < i < n \\ -\dfrac{\partial k_{nn}}{\partial k_{jj}} - \dfrac{\partial k_{n-1,n}^{min}}{\partial k_{jj}} & \text{for} \quad i = n \end{cases} \tag{A38}$$

where

$$\frac{\partial k_{ii}}{\partial k_{jj}} = \begin{cases} 1 & i = j \\ 0 & i \neq j \end{cases} \tag{A39}$$

$$\frac{\partial k_{0i}^{max}}{\partial \gamma_j} = \begin{cases} - \dfrac{\partial k_{21}^{min}}{\partial \gamma_j} & \text{for} \quad i = 1 \\ - \dfrac{\partial k_{i-1,i}^{min}}{\partial \gamma_j} - \dfrac{\partial k_{i+1,i}^{min}}{\partial \gamma_j} & \text{for} \quad 1 < i < n \\ - \dfrac{\partial k_{n-1,n}^{min}}{\partial \gamma_j} & \text{for} \quad i = n \end{cases} \tag{A40}$$

References

[1] DiStefano, J.J., III, Complete parameter bounds and quasiidentifiability conditions for a class of unidentifiable linear systems, *Math Biosc.* 65:51-68(1983).

[2] Landaw, E.M., Chen, B.C., and DiStefano, J.J., III. An algorithm for the identifiable parameter combinations of the general mammillary compartmental model. *Math Biosc.* 72:199-212(1984).

[3] Chen, B.C., Landaw, E.M., and DiStefano, J.J., III. Algorithms for the identifiable parameter combinations and parameter bounds of unidentifiable catenary compartmental models. *Math Biosc.* 76:59-68(1985).

[4] K.R. Godfrey, *Compartmental Models and Their Applications*, Academic Press, New York and London, 1983

[5] DiStefano, J.J., III, and Landaw, E.M. Multiexponential, multicompartmental, and noncompartmental modeling. I. Methodological limitations and physiological interpretations. *Am. J. Physiol. 246 (Regulatory Integrative Comp. Physiol. 15):* R651-R664, 1984

[6] Landaw, E.M., and DiStefano, J.J., III. Multiexponential, multicompartmental, and noncompartmental modeling. II. Data Analysis and statistical considerations. *Am. J. Physiol. 246 (Regulatory Integrative Comp. Physiol. 15):* R665-R677, 1984

[7] Jennrich, R.I. Asymptotic properties of nonlinear least squares estimators. *Ann. Math. Statist.* 40:633-643. 1969

[8] Jennrich, R.I. and Ralston, M.L. Fitting nonlinear models to data. *Annual Reviews of Biophysics and Bioengineering,* 8:195-238, 1979

[9] McIntosh, J, McIntosh, R. *Mathematical Modelling and Computers in Endocrinology.* Springer-Verlag, New York. 1980.

[10] Vajda, S. Analysis of Unique Structural Identifiability via Submodels. *Math Biosciences* 71:125-146, 1984.

[11] Rao, C. Radhakrishna. *Linear Statistical Inference and its Applications.* John Wiley and Sons, New York, 1973

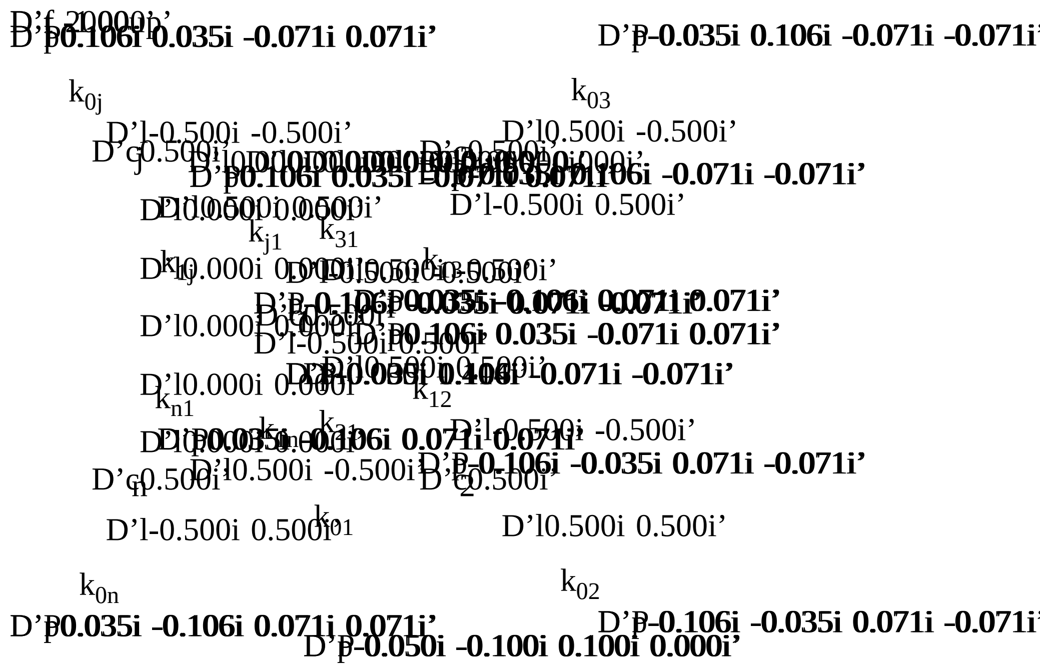
[12] Mosteller, F. and Tukey, J.W. *Data Analysis and Regression.* Addison-Wesley: Reading. 1977, pp. 133-163.

FIGURE LEGENDS

Figure 1. The Mammillary Compartmental Model

Figure 2. The Catenary Compartmental Model

Figure 3. Example computer output from MAMPOOL, for the 5% data error CV concentration model of Table 1, abbreviated to illustrate only the variance and covariance matrix computations.


D’p0.106i 0.035i -0.071i 0.071i’
D’p-0.035i 0.106i -0.071i -0.071i’
k0j
k03
D’l-0.500i -0.500i’
D’l0.500i -0.500i’
D’l-0.500i 0.500i’
k12
D’p-0.106i -0.035i 0.071i -0.071i’
D’l-0.500i 0.500i’
D’l0.500i 0.500i’
k0n
k02
D’p0.035i -0.106i 0.071i 0.071i’
D’p-0.106i -0.035i 0.071i -0.071i’
D’p-0.050i -0.100i 0.100i 0.000i’

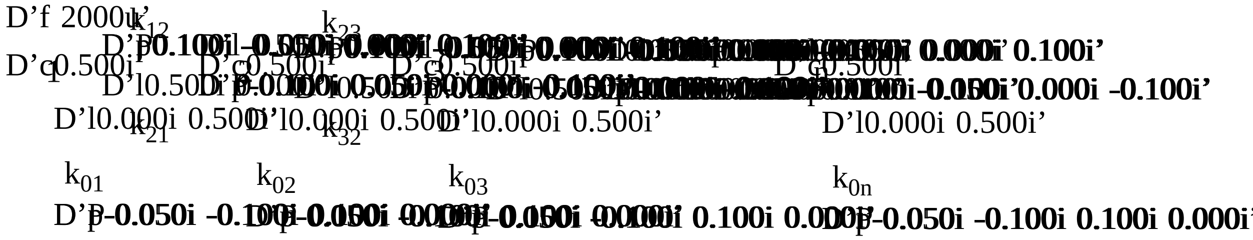

D’f 2000i’
k12
k23
D’c 0.500i
k21
k32
D’l 0.000i 0.500i’
k01
k02
k03
k0n

Table 1 - Iodine Kinetics in the Rat: A Quasiidentifiable Model

VARIANCE OF THE PARAMETER BOUNDS EXPRESSED IN %CV $y(t) = 5.54e^{-3.75t} + 0.44e^{-0.151t} + 0.47e^{-0.0026t}$, Data Error CV = 16% at t=0, 5% otherwise 12 Point Sampling Schedule = 2 x (0, 1.0, 2.0, 10.2, 56.6, 1440)			
Parameter Bound	Analytic %CV (Asymptotic)	600 Simulations	
		$\%\hat{CV}$	95% CI For True %CV
k_{12}^{min}	17.512	24.702	19.726 - 29.678
k_{12}^{max}	17.368	24.461	19.548 - 29.374
k_{13}^{min}	18.593	20.745	17.978 - 23.511
k_{13}^{max}	17.348	19.380	16.784 - 21.976
k_{21}^{min}	12.427	22.451	17.181 - 27.721
k_{21}^{max}	12.317	22.214	17.015 - 27.413
k_{31}^{min}	23.476	25.560	23.563 - 27.557
k_{31}^{max}	22.360	24.360	22.503 - 26.217
k_{01}^{max}	11.531	12.062	11.395 - 12.729
k_{02}^{max}	10.315	11.205	10.066 - 12.344
k_{03}^{max}	5.751	5.916	5.483 - 6.350

Table 2 - Reverse-Triiodothyronine (rT_3) Kinetics in the Rat: An Interval Identifiable Model

VARIANCE OF THE PARAMETER BOUNDS EXPRESSED IN %CV			
$y(t) = 5.25e^{-1.25t} + 1.21e^{-0.27t} + 0.41e^{-0.02t}$, Data Error CV = 16% at t=0, 5% otherwise			
12 Point Sampling Schedule = 2 x (0, 1.61, 4.89, 13.4, 30.13, 90)			
Parameter Bound	Analytic %CV (Asymptotic)	600 Simulations	
		$\%\hat{CV}$	95% CI For True %CV
k_{12}^{min}	13.868	15.263	14.354 - 16.172
k_{12}^{max}	7.869	8.433	7.963 - 8.903
k_{13}^{min}	7.190	6.941	6.517 - 7.364
k_{13}^{max}	4.680	4.621	4.347 - 4.895
k_{21}^{min}	15.938	18.041	16.930 - 19.151
k_{21}^{max}	10.541	11.834	11.135 - 12.532
k_{31}^{min}	6.909	7.681	7.257 - 8.104
k_{31}^{max}	8.112	8.853	8.358 - 9.348
k_{01}^{max}	8.571	9.280	8.762 - 9.799
k_{02}^{max}	5.567	5.780	5.460 - 6.099
k_{03}^{max}	4.417	4.409	4.152 - 4.665

Table 3 - Widely Spaced Eigenvalues

VARIANCE OF THE PARAMETER BOUNDS EXPRESSED IN %CV $y(t) = 5e^{-t} + e^{-0.05t}$, Data Error CV = 5% 12 Point Sampling Schedule = 3 x (0, 1.33, 7, 50)			
Parameter Bound	Analytic %CV (Asymptotic)	600 Simulations	
		$\%\hat{CV}$	95% CI For True %CV
k_{12}^{min}	6.431	6.441	6.078 - 6.804
k_{12}^{max}	5.103	5.102	4.817 - 5.387
k_{21}^{min}	5.109	5.111	4.826 - 5.395
k_{21}^{max}	3.757	3.754	3.547 - 3.961
k_{01}^{max}	1.611	1.583	1.497 - 1.669
k_{02}^{max}	2.483	2.409	2.271 - 2.547

Table 4 - Large Measurement Errors

VARIANCE OF THE PARAMETER BOUNDS EXPRESSED IN %CV $y(t) = 5e^{-t} + e^{-0.05t}$, Data Error CV = 30% 12 Point Sampling Schedule = 3 x (0, 1.33, 7, 50)			
Parameter Bound	Analytic %CV (Asymptotic)	600 Simulations	
		$\%\hat{C}V$	90% CI For True %CV
k_{12}^{min}	38.586	49.026	43.352 - 54.700
k_{12}^{max}	30.617	39.512	35.329 - 43.695
k_{21}^{min}	30.655	43.041	38.818 - 47.263
k_{21}^{max}	22.544	33.994	30.901 - 37.087
k_{01}^{max}	9.663	20.173	17.137 - 23.209
k_{02}^{max}	14.896	22.230	16.291 - 28.168

```
1 TO n POOL MAMMILLARY MODEL ANALYZER: MULTIEXP INPUT
*****************************************************

                  k01
     TEST INPUT       A       OUTPUT y(t)
              \   |   /
               \  |  /
  .....         \ .|.. /          .....
 /     \    k31    /     \    k21    /     \
:       :<--------:       :-------->:       :
:   3   :         :   1   :         :   2   :
:       :-------->:       :<--------:       :
 \...../    k13    \...../    k12    \...../
    |              A   |              |
    |  .           |   |         .    |
    |   .     kn1  |   | k1n      .   |
    V    .         |   V          .   V
   k03    .        .....         .   k02
                  /     \
                 :       :
                 :   n   :
                 :       :
                  \...../
                     |
                     |
                     V
                    k0n

         (c) Copyright 1987  VAX version 3.1
           UCLA Biocybernetics Laboratory
           ******************************
```

ENTER RUN IDENTIFIER & DATE :

2 pool concentration model with 5% CV data error

Model specifications:

```
ENTER NUMBER OF POOLS ( 1, ... , n):
  n =   2

Exponential Model Input :

        y(t) = A1 exp(L1 t) + A2 exp(L2 t) + ......
                 Units: Ai are %dose/vol, Li are 1/time
                 Be sure A(i) > 0 and L(i) < L(i+1) < 0.


PLEASE ENTER A 1 L 1  (any format, separated by a blank)
   5.00000   -1.00000

PLEASE ENTER A 2 L 2  (any format, separated by a blank)
   1.00000   -0.05000
```

The following option provides variability estimates for the parameter bounds based on y(t) data, sampling times t(i), and error variances VAR(i).

ENTER THE NUMBER OF SAMPLE TIMES (DATA POINTS):

12   sample times

ENTER t(1) ... t(12) :

```
t( 1) =      0.0000  t( 2) =      0.0000  t( 3) =      0.0000
t( 4) =      1.3300  t( 5) =      1.3300  t( 6) =      1.3300
t( 7) =      7.0000  t( 8) =      7.0000  t( 9) =      7.0000
t(10) =     50.0000  t(11) =     50.0000  t(12) =     50.0000
```

ENTER THE # CORRESPONDING TO THE TYPE OF
MEASUREMENT ERROR VARIANCE (VAR)
#1) CONSTANT COEFFICIENT OF VARIATION
    (CV = 100 SD / mean %)
#2) CONSTANT STANDARD DEVIATION (SD)
#3) CONSTANT VAR
#4) VAR = B + C*(Z**D)
#5) VARIABLE CV

1

ENTER THE CONSTANT CV (in %):

5.00000000000000

RESULTS :

****

IDENTIFIABLE PARAMETER COMBINATIONS :

-k 1 1 = k 0 1 + k 2 1 = 0.841667

-k 2 2 = k 0 2 + k 1 2 = 0.208333

(k 1 2)(k 2 1) = 0.125347

INDIVIDUAL PARAMETER BOUNDS ((1/TIME))
AND % RANGES :
%CV BELOW PARAMETER BOUNDS

0.601667 < k 2 1 < 0.841667 (39.9% RANGE)
6.10% 4.90%

0.148927 < k 1 2 < 0.208333 (39.9% RANGE)
6.43% 5.10%

0.000000 < k 0 1 < 0.240000
0.00% 3.12%

0.000000 < k 0 2 < 0.059406
0.00% 2.52%

CORRELATION MATRIX FOR THE PARAMETER BOUNDS

	K01 MAX	K02 MAX	K12 MAX	K12 MIN	K21 MAX	K21 MIN
K01 MAX	1.00	-0.33	-0.14	-0.10	0.66	0.54
K02 MAX	-0.33	1.00	0.74	0.66	0.04	0.11
K12 MAX	-0.14	0.74	1.00	0.99	0.57	0.67
K12 MIN	-0.10	0.66	0.99	1.00	0.63	0.73
K21 MAX	0.66	0.04	0.57	0.63	1.00	0.99
K21 MIN	0.54	0.11	0.67	0.73	0.99	1.00