NUMERICAL METHODS FOR POINT AND INTERVAL PARAMETER ESTIMATION IN COMPARTMENTAL MODELS USED IN SMALL SAMPLE PHARMACOKINETIC AND EPIDEMIOLOGICAL STUDIES

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We present three parameter estimation methods for compartmental models used in epidemiology and pharmacokinetics. Two of these methods are based on transforming both sides of the model using either the log transform or the Laplace transform, while the other method is based on using the structure of the compartmental matrix to solve a sequence of smaller dimensional problems. We find that the Laplace transform method yields numerically superior results on two criterion based on the mean-square error and the performance of the bootstrap on both real and simulated data sets.

Key Words: Nonparametric bootstrap; Mastitis; Two-Compartment Oral Absorption(TCOA) model; SIR model; Laplace transform; Transform-Both-Sides; Heteroscedasticity.

1 INTRODUCTION

The need to fit multi-compartment models given a limited number of observations arises often in pharmacokinetics and epidemiology. In the former, the interest may be to predict concentration levels of a drug in unobserved regions of the body from a small amount of data collected typically in the plasma, and in the

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latter, the interest may be in understanding the long term behavior or stability of the system in the presence of a small amount of observed cases of an infectious disease. Anderson and May (1991), Walter and Contreras (1999), and Brauer and Castillo-Chavez (2001) give detailed explanation of their use in the biological sciences as well as provide recent literature references. However, these models are difficult to fit since these problems are ill-posed, that is, error in the data can cause a significant bias in the estimates. Sources for this date back to the work of Bellman and Åström (1971), Westlake (1971), and more recently Davidian and Giltinan (1995) and Wakefield (1996), for example.

In this paper, we use two models, the *Susceptible-Infected-Recovered* (SIR) dynamic models used in epidemiology (see, e.g., Brauer and Castillo-Chavez 2001) and the *Two-Compartment Oral Absorption* (TCOA) model used in pharmacokinetics (see, e.g., Holdford and Sheiner 1981), to conduct a numerical comparison of three estimation methods when there are data size limitations and the error in the data is heteroscedastic or depends on the mean. These methods include *transforming -both-sides* (TBS) based on log-of-the-data and log-of-the-model (Carroll and Ruppert 1988) ; the *Split* method based on using the structure of the compartmental matrix to separately solve a sequence of smaller problems; and the *Laplace transform* method based on TBS ideas using a descretization of the Laplace model together with eigenvalue information.

Our analysis will primarily be based on simulated data sets from the pharmacokinetic and epidemiologic literature. We will compare the reduction in the relative-square root-Mean-Square Error(rsMSE) of these methods when estimating the flow rates in the TCOA model. We consider two particular models involving the kinetics of Theophylline and Lithium and those of the transmission rates in a SIR model recently used to model the infectious disease *Streptococcus uberis* (Strep. uberis) (Contreras, Zadoks, Allore, and Schukken 2000), a causative agent

of mastitis in cattle.

However, for those estimates arising from a real data set, we will see if the bootstrap can be successfully applied, that is, if the resulting estimates lie within a plausible range of values for the parameters in these problems. In particular, a nonparametric bootstrap is used to construct *Bias Corrected and accelerated* (BCa) confidence intervals for the analysis of the Strep. uberis data. Our numerical results show that the Laplace transform method is superior based on our criterion to the alternatives, next to the Split method. However, because the SIR and the TCOA problems are inherently different, our development will primarily focus on the TCOA model while our numerics will deal with both models.

This paper is organized as follows. In Section 2 we provide two motivating examples from epidemiology and pharmacokinetics. In Section 3 we describe our three methods of estimation and give a criterion for optimality of the estimates. In Section 4 we discuss the bootstrap and our numerical results. In Section 5 we give some concluding remarks summarizing our numerical findings, and in the Appendix we provide some of the technical details of these estimation methods and discuss some of their theoretical properties.

2 PRELIMINARIES

Compartmental models are commonly used in pharmacokinetics and epidemiology. Recently, Contreras, Zadoks, et al. (2000) discuss the following model for the dynamics of Strep. uberis in a dairy herd

$$\begin{pmatrix} \frac{dI_U}{dt}(t) \\ \frac{dI_R}{dt}(t) \end{pmatrix} = \begin{pmatrix} (1-q)\beta_U - \xi & (1-q)\beta_U \\ q\beta_R & q\beta_R - \xi \end{pmatrix} \begin{pmatrix} I_U(t) \\ I_R(t) \end{pmatrix} + \begin{pmatrix} \delta(t) \\ 0 \end{pmatrix}$$

$$:= A\boldsymbol{I}(t) + \delta(t)\boldsymbol{e}_1, \tag{2.1}$$

where $\delta(t)$ is the Dirac delta function, and $\boldsymbol{e}_1$ is the natural basis element of the Eucledian space R^2, which indicates that at the beginning of the observed outbreak there was one infected unit in the I_U compartment and none in the I_R compartment. Then, A is the *compartmental matrix* whose entries q, ξ, β_U and β_R are the system parameters characterizing the *transmission rates* from the various compartments of the system at steady state, and $\boldsymbol{I}$ is the 2×1 vector indicating size of the respective compartments through time. For furthered details see Contreras, Zadoks, et al. (2000).

A related problem comes from an extension of the *one-compartmental oral absorption* (OCOA) model for modeling the kinetics of a drug ingested orally, or the TCOA model, that is schematically represented as

$$\rightarrow \boxed{\text{gut}} \xrightarrow{a_{12}} \boxed{\text{plasma}} \underset{a_{32}}{\overset{a_{23}}{\rightleftarrows}} \boxed{\text{targeted}}, \qquad (2.2)$$

where a_{12}, a_{20}, a_{32}, and a_{23} are the parameters of the system or the *flow rates* from one compartment to the other or to the outside of the system (see, e.g., Holford or Sheiner 1981; Davidian and Giltinan 1995).

Diagram 2.2 leads to the *mass balance equations*

$$\begin{pmatrix} \frac{dC_1}{dt}(t) \\ \frac{dC_2}{dt}(t) \\ \frac{dC_3}{dt}(t) \end{pmatrix} = \begin{pmatrix} -a_{12} & 0 & 0 \\ a_{12} & -(a_{23}+a_{20}) & a_{32} \\ 0 & a_{23} & -a_{32} \end{pmatrix} \begin{pmatrix} C_1 \\ C_2 \\ C_3 \end{pmatrix} + \begin{pmatrix} \text{dose } \delta(t) \\ 0 \\ 0 \end{pmatrix}$$

$$:= AC + dose\ \boldsymbol{e}_1, \qquad (2.3)$$

where A is now a 3×3 compartmental matrix, C is the concentration vector in all compartments, and $\boldsymbol{e}_1 \in R^3$.

Since sampling typically occurs only in the plasma compartment (see diagram

2.2), the solution to (2.3) can be seen to be (see Walter and Contreras (1999))

$$C_2(t) = (0,1,0)e^{At}\begin{pmatrix} dose \\ 0 \\ 0 \end{pmatrix}. \tag{2.4}$$

Similarly, in the SIR model in (2.1), the solution is

$$\boldsymbol{I}(t) = e^{At}\begin{pmatrix} 1 \\ 0 \end{pmatrix} \tag{2.5}$$

where

$$e^{At} = I + At + \frac{(At)^2}{2!} + \frac{(At)^3}{3!} + ...$$

or the *matrix exponential.*

With either (2.4) or (2.5) as the model, of interest is the estimation of the entries of A when the error in the data is assumed to be heteroscedastic or to depend on the mean (see, e.g., Wakefield 1996). This leads to the following estimation problem. Find an estimate of $\boldsymbol{\theta} \geq \mathbf{0}$ when data $\mathbf{y}_i$ satisfies

$$\mathbf{y}_i = \mathbf{m}(t_i, \boldsymbol{\theta})(1 + \epsilon_i), \tag{2.6}$$

where $i = 1, ...k$, ϵ_i is distributed $N(0, \sigma^2)$, $\boldsymbol{\theta}$ are the transmission or flow rates in matrix A, and $\boldsymbol{m}$ is either as in (2.4) or (2.5).

3 ESTIMATION METHODS

In this section we give three estimation methods for problem (2.6) and discuss some optimality criterion.

3.1 TRANSFORM-BOTH-SIDES

The first method is based on transforming both sides by taking the log-of-the-data and log-of-the-model; that is,

$$\min_{\boldsymbol{\theta}\geq 0} \sum_{i=1}^{k} [\log(\mathbf{y}_i + \alpha) - \log(\boldsymbol{m}(t_i, \boldsymbol{\theta}) + \alpha)]^2, \tag{3.1}$$

where α is some nonnegative value chosen so that it preserves key properties of the data structure. Typically, this value is chosen to be 1 since then the log transform maps zero to zero.

This method changes the error structure from heteroscedastic to homoscedastic and thus enjoys similar large sample properties as does *nonlinear least squares* (NLS) on additive *independent and identically distributed* (i.i.d.) data (see, e.g., Carroll and Ruppert 1988). However, as our numerics will show, it appears the least successful when dealing with small sample data with the TCOA model but not so with the SIR model under the conditions considered here.

3.2 SPLIT METHOD FOR TCOA MODEL

The Split method uses the structure of the compartmental matrix to solve a sequence of smaller dimensional problems. We called it the "Split" method because it solves the problem in two separately identifiable parts. That is, it regards problem (2.3) as two sub-problems by first fitting the standard model for orally administered drugs, or the OCOA model, and then fitting the *two-compartment open* (TCO) model for intravenously administered drugs (see, e.g, Gibaldi and Perrier 1982; Katz, Schumitzky, and Azen 1982). That is, step one of this method consists of fitting all the data to the forcing function into the plasma compartment by considering

$$\log(y_i + \alpha) = \log(\mathbf{e}_2' e^{A_1 t_i} (\text{dose}) \mathbf{e}_1 + \alpha), \tag{3.2}$$

where $\mathbf{e}_1, \mathbf{e}_2 \in R^2$ are the canonical two-dimensional basis elements and

$$A_1 = \begin{pmatrix} -a_{12} & 0 \\ a_{12} & -(a_{20} + a_{23}) \end{pmatrix}.$$

Fitting (3.2), yields estimates of the rate of absorption from the gut to the plasma, or a_{12}, and of the exit rate from the plasma, or $(a_{20} + a_{23})$. However, we are interested only in a_{12} since the absorption by the plasma is much more rapid than the excretion from this compartment. Thus, for the next step of the Split method, we only hold the a_{12} entry fixed at $\hat{a}_{12}$. Hence, Step two consists of using all the data to now estimating the lower entries of $\hat{A}$ in

$$log(\boldsymbol{y}_i + \alpha) = log(\mathbf{e}_2' e^{\hat{A}t_i}(\text{dose})\mathbf{e}_1 + \alpha), \tag{3.3}$$

where $\mathbf{e}_1, \mathbf{e}_2 \in R^3$ are the three-dimensional canonical basis elements and

$$\hat{A} = \begin{pmatrix} -\hat{a}_{12} & 0 & 0 \\ \hat{a}_{12} & -(a_{23} + a_{20}) & a_{32} \\ 0 & a_{23} & -a_{32} \end{pmatrix}.$$

With this choice of $\hat{A}$, we obtain the TCO model with known continuous infusion forcing function into the plasma compartment, see diagram 2.2.

The method outline in (3.2) and (3.3) would work when A_1 or $\hat{a}_{12}$ is known exactly; however, that it should work when there is error in this estimate, or it is slightly misspecified is not clear. From the numerical perspective, this depends on the condition number of the matrix exponential (see, e.g., Golub and Van Loan 1996). From the statistical perspective, the idea of separately estimating some entries in either model (2.5) or (2.4) and then holding them fixed in the general estimation problem, may be viewed as based on pseudo-likelihood ideas (see Liang and Self 1996). However, trial and error lead us to conclude that holding a_{12} fixed at its estimate, $\hat{a}_{12}$, was numerically superior than holding any other of the entries fixed. This choice is in contrast to the SIR model considered in (2.1) where q and

ξ were held fixed, because they could be separately estimated from the data while β_U and β_R could not (Contreras, Zadoks, et al. 2000).

3.3 Laplace Transform Method

Our last method is the Laplace transform method, which is described in detail by Contreras, Liu, Casella, Ryan, and Van Loan (1997), but we briefly discuss it here. In the Appendix, we give some conditions under which it relates to NLS for the TCOA problem.

For an a priori chosen sequence $\{s_q\}_{q=1}^{p} \geq 0$ fit (2.6) in the NLS sense by taking the Laplace-of-the-data and then the Laplace-of-the-model to obtain

$$\int_{\Omega} \sum_{i=1}^{k-1} e^{-s_q t} y_i \delta(t - t_i) \Delta(y_i, t_i) dt = \int_{\Omega} e^{-s_q t} m(t, \boldsymbol{\theta}) dt [1 + \epsilon_i], \tag{3.4}$$

where $\Omega = (0, t_{last})$, t_{last} is the time of last observation, $\Delta(y_i, t_i)$ is as in Simpson's quadrature rule (for example), s_q is some uniformly spaced sequence between $[0, \hat{a}_{12}]$, and $\delta(t)$ is the Dirac delta function.

For the TCOA problem or (2.4), this choice of variables of the transformation, s_q, picks all eigenvalues when they are negative since we assume $-a_{12}$ is the dominant eigenvalue of the compartmental matrix (Walter and Contreras 1999) while $s_q = 0$ equates the average of the data to the mean of the model. Contreras, Liu, et al. 1997 provide justification for this choice of the variable of the transformation, but we discuss this in the Appendix. Likewise, an analogues theory could be developed for the SIR model with (2.5) whose compartmental matrix, A, does not satisfy the properties of the TCOA model matrix; however, for the numerical analysis conducted in this paper, we picked the dominant eigenvalue of the matrix A in (2.5) since this worked in practice.

3.4 SUFFICIENT ESTIMATOR

To differentiate between these methods we first make the following definition of what we consider a sufficient estimator.

We say that an estimator is *sufficient* if the following two criteria are met:

1. upon repeated sampling that estimator is within the 95% or the 65% range based on the rsMSE, that is, if the estimated value lies in the interval ($true \pm \alpha\sqrt{mse}$) where $\alpha = 1.96$ or 1.64 for the 95% or the 65% percentile range, respectively, and where 'true' is the true value of the parameter and 'mse' is the mean-square error.

2. per sample, the bootstrap can be applied successfully (that is, the true value is contained in the BCa confidence interval and the length of the bootstrap interval, max(bootstrap estimate)-min(bootstrap estimate), gives a plausible range of values for the estimated parameters).

We then compare the three methods by counting the number of times the estimator is sufficient under various simulations.

4 SIMULATIONS AND RESULTS

To address the numerical performance of the methods proposed in Section 3, we consider two means of generating replicate data sets. One is through repeated sampling with a set of fixed matrices and the other by generating replicate data sets from the nonparametric bootstrap per matrix (see, e.g, Shao and Tu 1996). We report on the former first.

4.1 TCOA Model Simulations

The following tables are summary results of the analysis involving several matrices most of which exhibited the behavior of those curves resulting from the data analysis of Theophylline or Lithium. That is, simulations were done for matrices in the range of values for the flow rates

$$a_{12} \in [.38, 3.38], \quad a_{20} \in [.01, 3.17], \quad a_{23} \in [.15, 1.54], \quad \text{and} \quad a_{32} \in [.0003, .83].$$

This range includes the values obtained from the analysis of the Theophylline data set fitted using *nonlinear mixed effects* (NLME) in Splus and those values for Lithium reported by Westlake (1971). This range of values reflects a rapid plasma peak right before the drug peaks at the plasma level, while the decay from the plasma may be slow or fast as reflected by a_{20} and a_{23}, and while the return to the plasma may also be slow or fast as reflected by the values of a_{32}.

In Table 1, we report the results of repeated sampling with a fixed set of matrices where the number of sampling times was chosen to be consistent with those from the pharmacokinetic literature for healthy volunteer data, particularly those corresponding to the 11 observations. The small amount times were chosen to be the first 5 observations of a standard data set, while the large sample or the 82 observations were chosen equally space on the nonzero range of the data. The purpose of picking these times was to inform on the small and large sample performance of these methods on these problems.

In particular, simulations were done as follows. Per fixed compartmental matrix in the TCOA model or (2.4), an observation was simulated with heteroscedastic error. For the small sample, the 5 observations were made at times=(0,.25,.5,1,2). The medium size sample consisted of 11 observations made at times=(0,.28,.56,1,2, 3.5,5,7,9,12,24), while the large sample was collected at .1 increments from 0 to 5 and then at point 1 increments from 5 to 35, which for most of our matrices,

this range corresponded to the nonzero range of the data. To reflect the fact that some occasional observation might be an outlier, any particular simulated data set came from a mixture of normals; i.e. 90% of the data came from a normal distribution with .15 standard error while the remaining of the data came from a normal with a .20 standard error. This process was repeated a 100 times per fixed matrix.

In Table 1, we define *success* in terms of whether a estimator meets Criterion 1 of Section 3 or whether $R := \frac{\sqrt{mse}}{true} \leq 1$. Table 1 includes the results of the small, medium and large data sets with the three estimation methods presented in Section 3. Some of the entries on the table are left blank for presentation purposes only and since they did not provide different information than that already presented.

Table 1: **Success in meeting Criterion 1** (out of **21** mtxs)

	5 obs.			**11 obs.**			**82 obs.**		
	TBS	Split	Lap.	TBS	Split	Lap.	TBS	Split	Lap.
95% (all rates)	0	0	6	3	10	18	13	9	19
65% (all rates)	0	1	13	4	15	18	19	19	21
95% (a_{12}, a_{20}, a_{23})	0	1	15	5	17	19	15	13	20
65% (a_{12}, a_{20}, a_{23})	0	10	21	7	20	20			
95% (a_{12}, a_{20})	0	5	16	16	17	19	20	17	21
65% (a_{12}, a_{20})	8	12	21						
95% (a_{12}, a_{23})	0	5	18	4	19	19			
65% (a_{12}, a_{23})	0	11	21						
95% (a_{12})	9	21	21	15	21	21			
65% (a_{12})	10	21	21						

In terms of meetings Criterion 1 of a sufficient estimator, Table 1 shows that

the Split method is better than the TBS method except for the large sample size or the 82 obs. column, but neither method is as good as the Laplace transform method on any sample size. However, if we impose Criterion 2, as our next tables show, it appears that the bootstrap favors only the Laplace method.

4.2 The Bootstrap

Since the error structure in (2.6) is assumed to be heteroscedastic, on those matrices resulting from the real data analysis with the TCOA model and the real data analysis from the SIR model, we bootstrapped the weighted residuals

$$\epsilon_i^* = \frac{\boldsymbol{y}_i - \boldsymbol{m}(t_i, \hat{\boldsymbol{\theta}})}{\boldsymbol{m}(t_i, \hat{\boldsymbol{\theta}})}, \tag{4.1}$$

which are *i.i.d.* $N(0, \sigma^2)$ and where $\hat{\boldsymbol{\theta}}$ is from TBS, Split or Laplace transform methods. Then, from (4.1) we see that bootstrapped data comes from

$$\boldsymbol{y}_i^* = \boldsymbol{m}(t_i, \hat{\boldsymbol{\theta}})(1 + \epsilon_i^*), \tag{4.2}$$

to obtain the bootstrapped estimates $\hat{\boldsymbol{\theta}}_b^*$ via TBS, Split, or Laplace transform methods, respectively.

In tables 2 and 3, we report the individual results of the simulations and the bootstrap with the matrices resulting from the NLME analysis of the Theophylline data (see first 4 rows of tables 2 and 3) and the NLS analysis (see the last 4 rows of tables 2 and 3). These simulations were done using the compartmental matrix obtained from the data via the Split method as the true matrix. Likewise, in tables 4 and 5, we report those results from using the Lithium matrix reported by Westlake (1971) as the true matrix (see first 4 rows of tables 4 and 5), and those results from using the compartmental matrix obtained via the Split method as the true matrix in Westlake's simulated data set (see the last 4 rows of tables 4 and 5).

The labels are defined as follows. Per method, we computed the following quantities. 'R' corresponds to the rsMSE as discussed in Section 3. 'Av' corresponds to the average length of the bootstrap intervals or Av=mean(max(bootstrap estimate)-min(bootstrap estimate)) and this mean is computed per parameter and the sum is over all replications. 'Sd' corresponds to the standard deviations for the bootstrap interval lengths, 'Cv' is the proportion of times that the BCa intervals contained the true value. Lastly, 'f' denotes an unacceptable value of any of the table entries, that is, the interval length was larger than 10 times the maximum value of the flow rates per matrix.

Table 2: **Theophylline: 11 sampling times**

	TBS				Split				Lap.			
Rate	R	Av	Sd	Cv	R	Av	Sd	Cv	R	Av	Sd	Cv
$a_{12} = .70$	.18	.5	.2	.73	.14	.1	f	.72	.13	.49	.9	.78
$a_{20} = .10$	.28	.09	.1	.62	.31	.1	f	.54	.11	.06	.02	.69
$a_{23} = .14$	3.89	2.43	3.6	.73	.36	f	f	.58	.51	.28	.10	.75
$a_{32} = .23$	4.16	2.43	f	.72	.58	f	f	.64	.41	.28	38	.69
$a_{12} = 1.21$	.22	1.21	.54	.70	.27	.63	f	.57	.17	1	.36	.88
$a_{20} = .12$	.08	.07	.04	.77	.09	.10	.1	.77	.09	.05	.02	.68
$a_{23} = .42$	1.27	3.69	2.29	.77	.49	1.23	10	.34	.18	.57	.19	.79
$a_{32} = .82$	1.18	3.69	f	.80	.55	1.23	f	.80	.15	.57	f	.78

Table 3: **Theophylline: 5 observations**

	TBS				Split				Lap.			
Rate	R	Av	Sd	Cv	R	Av	Sd	Cv	R	Av	Sd	Cv
$a_{12} = .70$	.33	1.04	3.3	.55	.14	f	f	.64	.14	.28	.15	.68
$a_{20} = .10$	.57	.66	.3	.49	.20	f	f	.45	.20	.32	.18	.62
$a_{23} = .14$	f	6.40	3.6	.53	.42	f	f	.38	.42	.18	.11	.63
$a_{32} = .23$	8.54	6.4	f	.27	f	f	f	.33	.82	.18	3.44	.66
$a_{12} = 1.21$	.25	1.28	.1	.56	.16	.5	.1	.61	.14	.50	.28	.66
$a_{20} = .12$	.68	.29	.1	.45	.62	.4	.1	.50	.33	.12	.07	.59
$a_{23} = .42$	f	f	f	.47	.53	f	f	.31	.26	.55	.37	.50
$a_{32} = .82$	f	f	f	.34	f	f	f	.50	.62	.55	329	.50

Table 4: **Lithium: 11 Observations**

	TBS				Split				Lap.			
Rate	R	Av	Sd	Cv	R	Av	S	Cv	R	Av	Sd	Cv
$a_{12} = 2.38$	.52	f	f	.82	.23	1.75	.56	.74	.18	1.71	.51	.80
$a_{20} = .10$	.16	.1	f	.71	.17	.16	.05	.69	.11	.09	.03	.68
$a_{23} = .14$	1.34	9	f	.83	.22	.50	.19	.74	.21	.57	.26	.80
$a_{32} = .23$	1.86	9	f	.81	.30	.50	14	.78	.19	.57	.11	.81
$a_{12} = 1.74$	.21	f	f	.83	.25	1.17	.30	.57	.13	1.24	.39	.83
$a_{20} = .24$	.15	.2	f	.69	.17	.24	.05	.72	.08	.12	.04	.70
$a_{23} = .85$	.52	12	f	.84	.21	.67	.24	.67	.12	.63	.29	.80
$a_{32} = .30$	1.41	12	f	.83	.34	.67	.57	.49	.13	.63	.07	.82

Table 5: **Lithium: 5 observations**

	TBS				Split				Lap.			
Rate	R	Av	Sd	Cv	R	Av	Sd	Cv	R	Av	Sd	Cv
$a_{12} = 2.38$	.86	4.74	7.89	.61	.19	1.14	.69	.62	.15	1.06	.56	.62
$a_{20} = .16$	.37	.30	.16	.45	.74	.37	.16	.40	.38	.22	.14	.60
$a_{23} = .54$	3.15	4.53	7.21	.45	.47	.68	.38	.35	.30	.40	.20	.85
$a_{32} = .25$	7.49	4.53	7.97	.40	1.34	.68	f	.42	1.49	.40	43.92	.58
$a_{12} = 1.74$	1.14	2.74	5.28	.49	.13	.69	.1	.58	.12	.66	.35	.60
$a_{20} = .24$	.36	.37	.23	.42	.36	.70	.1	.45	.35	.31	.25	.55
$a_{23} = .85$	3.35	3.73	4.52	.49	.30	1.1	.1	.15	.37	.62	.33	.85
$a_{32} = .30$	6.40	3.73	3.58	.36	8.6	1.1	f	.56	1.31	.62	1.31	.53

Tables 2-5, indicate that while the value of R or the rsMSE can be acceptable based on Criterion 1 for either the TBS or the Split methods, their values are not acceptable based on Criterion 2 of Section 3.4 of an optimal estimator. In considering Table 4 for the Split method, we see that this is one of the few times that the bootstrap results are satisfactory on all measures. However, these tables also show that the Laplace transform approach appears to be consistently satisfactory on any of the criterion for 11 observations and less so for 5 observations.

4.3 SIR Model and Strep.uberis Data

In this section we report on the bootstrapped and simulated results resulting from the analysis of the Strep. uberis mastitis data using the SIR model given in (2.5). We simulated 7 observations at times=[0,1,...,6] with heteroscedastic error from a normal distribution with .18 standard error for both the I_R and I_U compartments. Also, observations made on both compartments were assumed independent. See Contreras, Zadoks, et al. (2000) for further details.

For the simulations, our analysis indicates that either a TBS approach to estimation based on the log transform or one based on the Laplace transform gives little difference in terms of the BCa interval coverage. In particular, see the values of Cv in Table 6 and those of the confidence intervals in Table 7. However, in terms of the analysis of the Strep. uberis data, we see from Figure 1 that the histogram resulting from the Laplace transform bootstrap estimates of β_R, is more symmetric than that for the TBS method although the BCa interval gives about the same coverage with either method.

Table 6: **SIR simulated data: 7 observations**

	TBS				Lap.			
Rate	R	Av	Sd	Cv	R	Av	Sd	Cv
$\beta_U = .69$	.029	.10	.03	.76	.029	.10	.03	.84
$\beta_R = 6.15$	.11	3.31	1.04	.71	.095	3.03	.97	.74
$\beta_U = .68$	.03	.10	.03	.77	.03	.10	.03	.82
$\beta_R = 6.54$	.10	3.48	1.10	.71	.094	3.19	1.02	.74

Table 7: **Model fitting for Strep. uberis data**

	Estimates		**BCa Confidence Intervals**	
	Btstrp(mean)	TBS	LB	UB
β_U	.68	.68	.61	.72
β_R	3.51	6.54	5.85	8.80
	Btstrp(mean)	Lap.	LB	UB
β_U	.69	.69	.64	.74
β_R	4.10	6.15	5.38	8.60

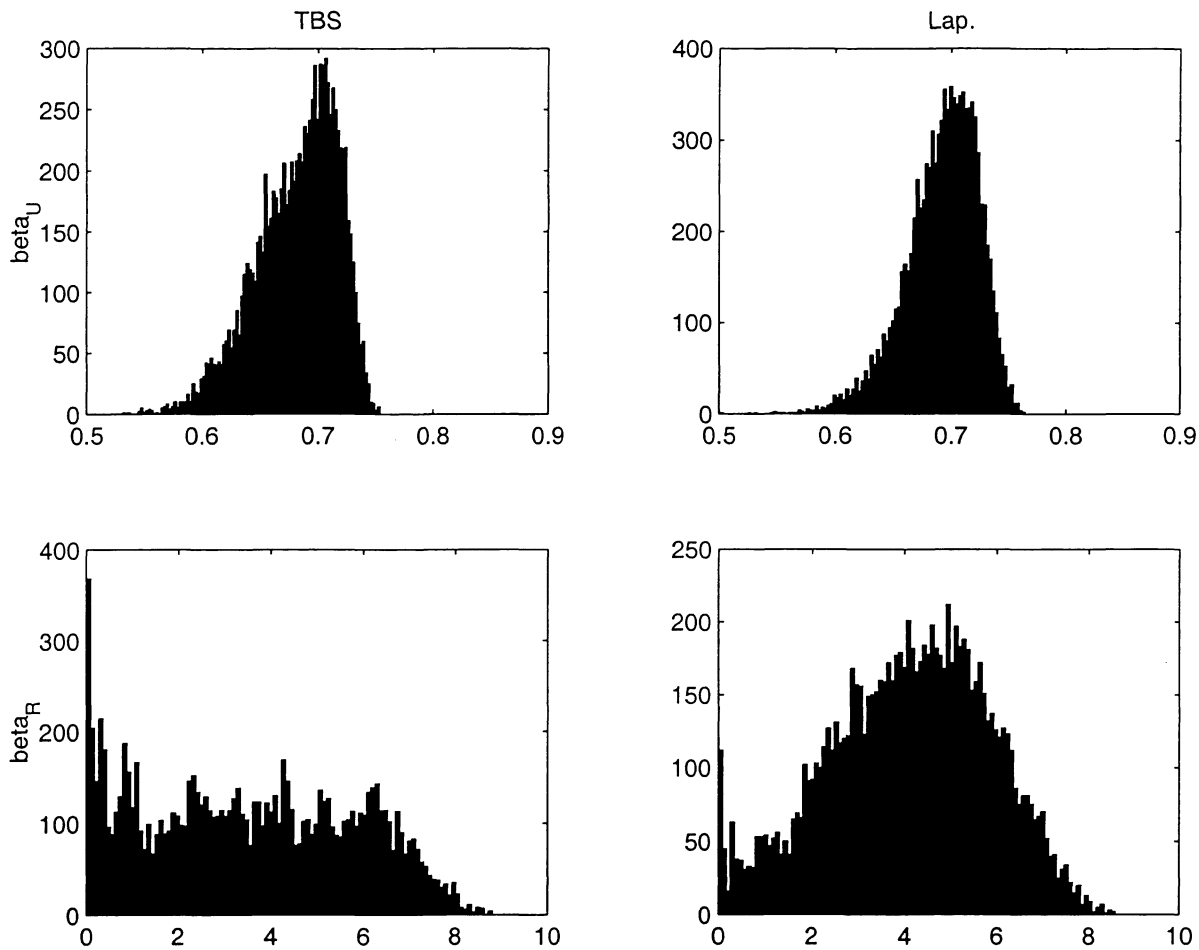

Figure 1: Top histograms correspond to the Strep. uberis data bootstrap estimates for β_U in the SIR model with the TBS and Laplace estimation methods, respectively, while the bottom histograms correspond to those of the β_R estimates.

5 CONCLUSION

We have presented three methods for the estimation of the transmission parameters in the SIR model and the flow rates in the TCOA model. Our analysis indicates that the TBS estimation method is not satisfactory for the TCOA model, and, based on the bootstrap analysis of the Strep. uberis data, it appears to also not be satisfactory for the SIR model. The former conclusion is made due to the lack of symmetry in the bootstrap histogram for one of the transmission parameters. In fact, based on the observed normality of the histograms for the Laplace transform method (see Figure 1, second column of figures), one suggestion could be to take the mean of the bootstrap estimates as an estimate of the parameter, while the standard error of the bootstrap estimates, may serve as reasonable indicators for the construction of confidence intervals based on normality. However, further work is needed to reach a general decision on this. Moreover, we comment that we obtained similar results, to those reported here with the TBS and Split methods, as if we had not transformed the data or the model but rather had done standard NLS on the original data structure, but we do not report those results here.

As for the reported results based on the Split method, we note that the first estimation step corresponds to the standard method of estimation involving the OCOA model which is typically the model fitted to this type of kinetic data (see, e.g., Pinheiro and Bates 1995; Davidian and Giltinan 1995; Wakefield 1996). The difference is that they fit a different form for the solution to the OCOA model; that is, a sum of two exponentials with unknown initial conditions of the system. Nonetheless, the Split method gives satisfactory results based on Criterion 1 of Section 3, and this may be due to its digraph not being strongly connected. In particular, this means that it is possible to separately estimate a_{12} which also corresponds to the dominant eigenvalue of the system (Walter and Contreras

1999). However, the coefficients of the system are still dependent on all the entries of the model, so that possibly error in the estimation of this entry could adversely influence the estimates of the coefficients. We do not comment on this further since this may be due to the condition number of the matrix exponential(see, e.g, Golub and Van Loan 1996).

As for the observed success of the Laplace transform method, we provide some justification as to when this method is similar to NLS in the Appendix. Here, we note that there are other estimation methods based on the Laplace transform. Recently, Chen, Lawson, Reiman, Cooper, Feng, Huang, Bandy, Ho, Yun, and Palant (1998) have suggested a method based on the deconvolution of the Laplace transform that works well for large data sets and is more computationally amenable to these larger data set problems. However, we found their estimation method to perform non satisfactorily for the type of small data sets that we considered here.

Lastly, although we are primarily concern with the small sample performance of these methods, the large sample properties are of theoretical interest for the Split or Laplace transform methods. We note that the idea of fixing some of the parameters may be viewed as pseudo-likelihood ideas (see, e.g., Liang and Self 1996). Based on this, it is not surprising that the performance for the large sample simulations are not as good as those for the TBS method (see third column block of Table 1). However, of theoretical and practical interest is that the Laplace transform methods seems to perform well for small, medium, and large data sets on the original data structure (see third column of any block in Table 1). We comment that we could have taken the log of both sides of the Laplace transform model (3.4) and then turned the error structure into an additive i.i.d. error structure, so that standard large sample theory could be applied, however, we found that for the small sample sizes we considered, this tended to over smooth the data thus

yielding unsatisfactory results.

APPENDIX: SOME TECHNICAL ISSUES

Here we address some technical issues associated with the fitting of the TCOA model with any of the methods discussed in Section 3. For further details see corresponding references.

We first define what we mean by *a priori identifiability.* In particular, we consider the well-posedness of the estimation problem involving the TCOA model under the assumption of no error in the data with a sub-problem of the TCOA model, namely. the TCO model. From diagram 2.2, we see that the compartmental matrix of the TCO model is

$$A = \begin{pmatrix} -(a_{20} + a_{23}) & a_{32} \\ a_{23} & -a_{32} \end{pmatrix}.$$

Then, if this A has distinct eigenvalues, i.e. $\lambda_1 \neq \lambda_2$, then

$$\boldsymbol{e}_1' e^{At} \boldsymbol{e}_1 := c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t}, \tag{0.1}$$

where c_1, c_2, λ_1, and λ_2 are functions of the entries of A. Upon taking the Laplace transform of both sides of (0.1), we have

$$\begin{aligned} \int_0^\infty e^{-st}(\boldsymbol{e}_1' e^{At} \boldsymbol{e}_1)dt : &= \int_0^\infty e^{-st}(c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t})dt \\ \mathbf{e}_1'(sI - A)^{-1}\mathbf{e}_1 &= \frac{s + a_{23} + a_{20}}{s^2 + (a_{23} + a_{32} + a_{20})s + a_{32}a_{12}}. \end{aligned} \tag{0.2}$$

Then, by equating coefficients in (0.2), we have the following system

$$\begin{aligned} a_{23} + a_{20} &= c_1\lambda_2 + c_2\lambda_1 \\ a_{23} + a_{32} + a_{20} &= \lambda_2 + \lambda_1 \\ a_{32}a_{20} &= \lambda_2\lambda_1. \end{aligned} \tag{0.3}$$

From (0.3), we see that the problem meets the necessary conditions for a priori identifiability (Bellman and Åström 1970), that is, we have three equations in

terms of the three unknown parameters of the TCO model. Likewise, it is possible to show that the OCOA model is a priori identifiable. Since the OCOA model can be regarded as the forcing function into the plasma compartment of the TCOA model (see diagram 2.2) , it then follows that the TCOA model is a priori identifiable.

However, from (0.3), we see that we can conclude more than a priori identifiability. Upon analyzing the right-hand-side of the Jacobian of (0.3), the product rule for differentiation yields that the coefficients c_1 and c_2 need to depend continuously on the entries of A as well.

That is, suppose that λ_1 and λ_2 are fixed then, in considering fitting two error free observations, y_1 and y_2, to the right hand-side of (0.1), we have the following system in terms of the coefficients c_1 and c_2

$$\begin{aligned} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} &= \begin{pmatrix} e^{\lambda_1 t_1} & e^{\lambda_2 t_1} \\ e^{\lambda_1 t_2} & e^{\lambda_2 t_2} \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \end{pmatrix} \\ &=: \boldsymbol{X} \begin{pmatrix} c_1 \\ c_2 \end{pmatrix}. \end{aligned} \tag{0.4}$$

Thus, we see that $\lambda_1 \neq \lambda_2$ is needed for $\boldsymbol{X}$ in (0.4) to be invertible. Thus, if the eigenvalues of the compartmental matrix are distinct, then the coefficients of the system will depend continuously on the entries of A. In particular, this implies that for the Split method, that if $\hat{a}_{12}$ is not too far from the true value, and if the eigenvalues of the system are distinct, then the Split method should yield estimates close to those of the true value. In fact, one of the eigenvalues of the TCOA model, a_{12}, is not even a function of the other entries of the compartmental matrix since its digraph is not strongly connected (Walter and Contreras, (1999)).

In terms as to when the Laplace transform method relates to the standard NLS method, we have the following claim.

Claim 1 *Suppose the l_2-inner product of*

$$(e^{-s_q t}, \quad e_2' e^{At}(\text{dose})e_1 - \sum_{i=1}^{m-1} y_i \delta(t-t_i) w(y_i, t_i))_{l_2(\Omega)} = \epsilon, \tag{0.5}$$

where ϵ is small and $\{-s_q\} \leq 0$ are chosen to include the eigenvalues of A. Then, $||f-g||_{l_2}$ is also small.

The proof is by contradiction. That is, suppose that $f-g \neq 0$ a.e. and $w_q \neq 0$ while their inner product is $((f-g), w_q)_{l_2} = 0$. This, then implies that $(f-g)$ and w_q are orthogonal. However, in considering the TCOA model and letting $f := e_2' e^{At}(\text{dose})e_1 = c_1 e^{-\lambda_1 t} + c_2 e^{-\lambda_2 t} + c_3 e^{-\lambda_3 t}$, $g = \sum_{i=1}^{k-1} y_i \delta(t-t_i)\Delta(y_i, t_i)$, and $\{w_q\} = \{e^{-s_q t}\}$, where $s_q \in [0, a_{12}]$ for all q and in particular $-s_q$ is chosen to equal the eigenvalues of the compartmental matrix for some q. This then implies that either $(f-g) = 0$ a.e. or $w_q = 0$ for all q; however, w_q is chosen nonzero. Therefore, by the Implicit Function Theorem, $||f-g||_{l_2}$ is small in the l_2-norm.

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