FITTING LARGER COMPARTMENTAL MODELS TO PHARMACOKINETIC DATA

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Fitting larger compartmental models to pharmacokinetic data

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Abstract

In this paper, we argue that to directly account for the *lag-time* and the duration of an effect in *dose-response* models, that the kinetic model must include an *effects* or *targeted* compartment. Through simulations and the analysis of the Theophylline data, we show that it is possible to successfully fit larger models provided the structure of the compartmental model is used or that the dimension of the problem is reduced. We illustrate this estimation approach with the two-compartment oral absorption model allowing for random effects in the model parameters. Our analysis shows that this model is more appropriate for this data set than the more common one-compartment oral absorption model. Moreover, our simulated analysis shows that our estimates have smaller standard error and mean-square error than those of the ordinary least squares approach or when the structure of the model is not employed.

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1 Introduction

A central problem in pharmacology is the relationship between the dose and subsequent effect of a drug; in particular, the relationship between a drug's concentration at the *targeted* or *effects* compartment and its observed response, see [14, 10] for instance. There are various technical and practical reasons as to why this is a challenging problem. Among them is the common situation involving human subjects; that is, it is not possible to administer a drug or sample at the targeted compartment, and hence it is not possible to directly relate the concentration in this compartment to its observed effect. Consequently, researchers often relate the effect of a drug to the concentration in the sampling compartment, typically the plasma compartment, with some empirical account for the lag time. See [10] or [8], for instance.

Moreover, methodology based on *physiological compartmental models* to directly account for the lag time suffers from practical and technical problems. That is, these models typically require more data to fit since they can involve a large number of unknown parameters, and they may not have a uniquely *a priori* locally or globally identifiable solution (see [3, 1, 16, 15, 2], and the sources found there in, for instance). However, even when sufficient data is available and a local unique solution could exist, these problem could be numerically unstable or ill-conditioned; for instance, minor error in the data can lead to bias in its prediction of the concentration of a drug in the unobserved compartments from data gathered in some intermediate compartment, see [17]. Methodology that does not properly accommodate any of the above issues can result in the miscalculation of the concentration in any compartment even more so in the unobserved compartments, see [6] for a particular illustration.

In this paper, we will see that despite these technical issues, using a "simpler" model to predict concentration levels of a drug can both fail to

describe the data and, even when it does, it fails to predict the duration of the effects of a drug, so that a model which includes an effects compartment must be considered. We will also see that by employing the structure of the model, it is possible to fit a sequence of *smaller* problems and thereby fit a more numerically stable problem and reduce the data demands in terms of the number of unknown parameters. Using the *one-compartment oral absorption model*(1COA model), we will compare the fit of the Theophylline data to that of the *two-compartment oral absorption model*(2COA model). Our data analysis and simulations indicate that it is possible to fit these models reliably; that is, our estimates have smaller mean-square error and standard deviations than the ordinary least squares method or when the structure of the model is disregarded, Moreover, this approach allows for randomness in the model parameters. Possible extensions of this method include the three-compartment mammillary or catenary model with sampling and input by necessity limited to the central compartment.

This paper is organized as follows. In sections 2, 3, and 4, we give a brief introduction to compartmental models and their use in pharmacology. In sections 5, 6, and 7, we discuss estimation with these models and present the analysis of our approach. Lastly, we conclude with a summary of our findings, and in section 9 we established some identifiability results for the models considered in this paper.

2 Preliminaries

Because it is important for the reading of this paper, in the following three sections, we provide a brief introduction to compartmental models, discuss some of the common models within pharmacology, the role of the initial conditions to the system, the solutions to these problems and the relationship these solutions have to the duration of an effect from an administered dose.

Not all compartmental models are physiologically based but rather are simplified versions of such models. For instance, one of the common experiments in the pharmacokinetic literature consists of a single or a series of bolus injections into the plasma or into the gut, the later being referred to as *first order absorption* or oral administration of a drug, with sampling typically occurring in the plasma compartment, see [10, 9]. That is, a drug's flow through the body is assumed to follow linear kinetics from its administration site, say compartment 1 with concentration ϕ_1 (arrows indicate direction of flow), to the sampling compartment p, and then to the targeted compartment n. It then returns to the plasma compartment from which it leaves the system. In the case of the oral absorption of a drug, this is indicated by the following diagram

$$\rightarrow \boxed{\phi_1} \overset{a_{12}}{\rightarrow} \boxed{\phi_2} \overset{a_{23}}{\rightarrow} \ldots \overset{a_{p-1,p}}{\longrightarrow} \boxed{\phi_p} \overset{\uparrow a_{po}}{} \ldots \underset{\leftarrow}{\overset{\rightarrow}{a_{n,n-1}}} \overset{a_{n-1,n}}{} \boxed{\phi_n}, \tag{2.1}$$

where ϕ_i denotes the concentration in compartment i, a_{ij} the flow rate of the drug from compartment i to compartment j, and a_{po} refers to the flow rate to the outside of the system from the p^{th} compartment(corresponding to the arrow pointing out of ϕ_p), where the a_{ij} are nonnegative by necessity, see [1, 16].

Although our proposed estimation approach could be generalized to include other models in particular the first-order absorption experiment, we will concentrate on the following simplified version of diagram (2.1). That is, data limitations typically mean that one can only consider the case when $n = 2$ and $p = 1$ which gives the diagram corresponding to the *one-compartment oral absorption model* (from here on referred to as the *1COA model*) or the choice of $n = 3$ and $p = 2$ which gives the diagram corresponding to the *two-compartment oral absorption model* (from here on referred to as the *2COA* model) to be considered in the next sections(note that in the compartmental analysis literature, these models correspond to two and three compartment models, respectively).

Then, under the above assumptions, models based on diagram (2.1) can have closed form solutions. [4] obtained closed form solutions for various common pharmacokinetic experiments via the use of partial fractions and the Laplace transform. The reader is referred to [4] for details or to [9] or [10] for a summary of some of these solutions. However, as we will see in sections 5 and 6, if one is interested in estimation, then a closed-form solution to a system is not needed. Nonetheless, we point out that these solutions are special cases of a more general problem in compartmental analysis (see [1], [11], or [16] and the reference found there in).

3 Compartmental models and pharmacologic example

A general compartmental system is described in vector notation as follows,

$$\begin{aligned} \frac{d\boldsymbol{\phi}}{dt}(t) &= A\boldsymbol{\phi}(t) + B\mathbf{u}(t), \quad t \geq 0 \\ \boldsymbol{\phi}(0) &= 0 \\ \boldsymbol{\xi}(t) &= C\boldsymbol{\phi}(t), \end{aligned} \tag{3.1}$$

where $\boldsymbol{\phi}$ is the concentration vector, $\mathbf{u}$ is the input vector, and $\boldsymbol{\xi}$ the observation vector. In scalar notation this is a system of n equations where the i^{th} equation is given by

$$\frac{d\phi_i}{dt}(t) = \sum_{j=1}^{n} a_{ij}\phi_j + \sum_{k=1}^{r} b_{ik}u_k(t), \quad i = 1, ..., n. \tag{3.2}$$

In (3.1), $A := [a_{ij}]$ is the $n \times n$ *compartmental matrix* representing interaction between compartments. Its entries are the unknown flow rates that are to be determined from a set of observations.

To estimate these flow rates or parameters, an experiment is designed in which r inputs enter the compartments causing them to interact with one another. The r inputs are regarded as the (transposed) vector, $\mathbf{u}(t) =$

$(u_1(t), u_2(t), ..., u_r(t))$, where $\mathbf{u}(t)$ is the *input* or *forcing* function. The paths by which the r inputs enter the n compartments is represented by a $n \times r$ matrix $B = [b_{ik}]$, called the *input matrix* where entry b_{ik} is positive if input $u_k(t)$ enters compartment i, and zero otherwise. Since it is usually not possible to sample each individual compartment, a $q \times n$ matrix C is introduced and called the *sampling matrix.* This matrix represents the paths from compartments to sampling devices where entry c_{ij} is positive if compartment j influences output function component $\xi_i(t)$; otherwise $c_{ij} = 0$. Then the *response function* is $\boldsymbol{\xi}(t) = (\xi_1(t), \xi_2(t), ..., \xi_q(t))$.

Typically, in experiments involving human subjects, both B and C consists of multiples of the natural basis elements, $\mathbf{e}_j$, where compartment j is the only compartment receiving input or the only compartment being sampled.

Some of the commonly used pharmacokinetic models are especial cases of a *compartmental system.* To see this, we consider a generalization of the models discussed in [10]. (In the Appendix, we establish that they are also *identifiable*).

The system of differential equations resulting from diagram (2.1), assuming that ϕ_1 receives $\frac{D_i}{V}$ units of bolus inputs administered at times t_i, can be verified to consist of a *bi-diagonal* compartmental matrix A up to the sampling compartment, ϕ_p, after which the matrix is *tri-diagonal.* That is, from (3.2) we have that

$$\begin{aligned}
\frac{d\phi_1}{dt}(t) &= -a_{12}\phi_1 + \sum_i \frac{D_i}{V}\delta(t - t_i) \\
\frac{d\phi_2}{dt}(t) &= a_{12}\phi_1 - a_{23}\phi_2 \\
&\vdots \\
\frac{d\phi_p}{dt}(t) &= a_{p-1,p}\phi_{p-1} - (a_{p0} + a_{p,p+1})\phi_p \\
&+ a_{p+1,p}\phi_{p+1} \\
\frac{d\phi_{p+1}}{dt}(t) &= a_{p,p+1}\phi_p - (a_{p+1,p} + a_{p+1,p+2})\phi_{p+1}
\end{aligned} \tag{3.3}$$

$$
\begin{aligned}
&+ \quad a_{p+2,p+1}\phi_{p+2} \\
&\vdots \\
\frac{d\phi_n}{dt}(t) &= a_{n-1,n}\phi_{n-1} - a_{n,n-1}\phi_n
\end{aligned}
$$

which can be rewritten as a system as in (3.1)

$$\frac{d\boldsymbol{\phi}(t)}{dt} = A\boldsymbol{\phi}(t) + B\mathbf{u}(t), \tag{3.4}$$

where $\delta(\cdot)$ is the *Dirac delta function*, A is a tridiagonal $n \times n$ compartmental matrix, and $B\mathbf{u}(t) = \mathbf{e}_1 \sum_i \frac{D_i}{V}\delta(t - t_i)$ is the input or forcing function into compartment one or $\phi_1(t)$. Note that D_i is the dose given at times t_i while V is the *volume of the distribution.*

The volume of the distribution is a function of the *clearance* parameter, Cl, and the rate at which the drugs clears the plasma or the sampling compartment, see [9] for instance. Jointly they form the initial conditions to the system of differential equations (3.3) and (3.4); that is, for the 2COA model,

$$V = \frac{Cl}{a_{20} + a_{23}}. \tag{3.5}$$

Because it is important for the reading of this paper, with consider as examples of system (3.3) the 1COA and the 2COA models. From (3.4), we see that these models correspond to the following tridiagonal compartmental matrices with $p = 1$, $n = 2$ and with $p = 2$, $n = 3$, respectively.

$$A_{1-cmpt} = \begin{pmatrix} -a_{12} & 0 \\ a_{12} & -(a_{23} + a_{20}) \end{pmatrix} \tag{3.6}$$

and

$$A_{2-cmpt} = \begin{pmatrix} -a_{12} & 0 & 0 \\ a_{12} & -(a_{23} + a_{20}) & a_{32} \\ 0 & a_{23} & -a_{32} \end{pmatrix}. \tag{3.7}$$

Moreover, considering the initial conditions to the system as the one time dose $\frac{D}{V}$, (see, for instance, [17] and [6]) then the input function $B\mathbf{u}(t) =$

$\mathbf{e}_1 \frac{D}{V}\delta(t)$ forms the initial conditions to the system, where D is the administered one-time dose, V is the volume of the distribution, and with sampling matrix $C = \mathbf{e}_2^T$. This then can only have the following solutions.

Through the *method of variation of parameters* [7], the formal solution to (3.1) and (3.4) can be found to be

$$\xi(t) = C \int_0^t e^{(t-\tau)A} B\mathbf{u}(\tau) d\tau, \tag{3.8}$$

for which with A as given in (3.6) or (3.7) and C and B as previously discussed, (3.8) gives

$$\xi(t) = \mathbf{e}_2^T e^{At} \frac{D}{V} \mathbf{e}_1, \tag{3.9}$$

where e^{At} is the *matrix exponential* ([7, 16]).

4 Closed-form solutions and effective threshold

As we will see, for estimation purposes, it is not necessary to have a closed-form solution to (3.8); however, the solutions do provide useful information if one is interested in analyzing the relative asymptotic behavior of the system. It is straightforward to see that the closed-form solution to the 2COA model is as follows.

From (3.9), we find that the concentration in compartment one in either the 1COA or the 2COA model is

$$\phi_1(t) = \frac{D}{V} e^{-a_{12}t},$$

where $\frac{D}{V}$ are the initial conditions to the system. We next focus only on that for the 2COA model.

To obtain the solution to the 2COA model, we solve for $\phi_2(t)$ and $\phi_3(t)$ in (3.2) by treating the solution to compartment one as the forcing function in compartment two; that is, we then redefine the system by letting

$(B\mathbf{u}(t))^T = (\frac{D}{V}e^{-a_{12}t}, 0)^T$ in (3.1) and consider the lower 2×2 block of A_{2-cmpt} in (3.7), denoted by A_l, as the new compartmental matrix, that is,

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

Then, the new system is

$$\begin{pmatrix} \frac{d\phi_2}{dt}(t) \\ \frac{d\phi_3}{dt}(t) \end{pmatrix} = \begin{pmatrix} -(a_{20} + a_{23}) & a_{32} \\ a_{23} & -a_{32} \end{pmatrix} \begin{pmatrix} \phi_2(t) \\ \phi_3(t) \end{pmatrix} + \frac{D}{V}e^{-a_{12}t} \begin{pmatrix} 1 \\ 0 \end{pmatrix}, \tag{4.1}$$

which, assuming that $-\alpha$ and $-\beta$ are the distinct eigenvalues of A_l and not equal to $-a_{12}$ with $0 < \beta < \alpha < a_{12}$, yields the solutions to the 2COA model found in several places including [17]. These solutions then are

$$\begin{aligned} \phi_2(t) &= a_{12}\frac{D}{V}[\frac{(\alpha - a_{32})e^{-\alpha t}}{(\alpha - \beta)(a_{12} - \alpha)} + \frac{(a_{32} - \beta)e^{-\beta t}}{(\alpha - \beta)(a_{12} - \beta)} - \frac{(a_{12} - a_{32})e^{-a_{12}t}}{(a_{12} - \alpha)(a_{12} - \beta)}] \\ \phi_3(t) &= a_{12}a_{23}\frac{D}{V}[\frac{e^{-a_{12}t}}{(a_{12} - \alpha)(a_{12} - \beta)} - \frac{e^{-\alpha t}}{(\alpha - \beta)(a_{12} - \alpha)} + \frac{e^{-\beta t}}{(\alpha - \beta)(a_{12} - \beta)}]. \end{aligned} \tag{4.2}$$

As we will see from (4.2), we can know infer about the asymptotic levels of the concentration in the unobserved compartment relative to that in the sampling compartment. To do this we first make the following definition.

The *effective threshold* of a drug corresponds to the level of the drug in the targeted compartment. That is, a pre-specified value, say τ, for which the concentration in the targeted compartment stays near τ. In practice this level is difficult to estimate. As a result the level in the plasma compartment is used instead. However, this can suffer from drawbacks, in particular, it may not give correct indication as to the level in the unobserved compartment of interest relative to that in the sampling compartment. To see this, we consider the behavior of $\phi_2(t)$ and $\phi_3(t)$ for time t large enough in the two-compartment model.

Since t is large enough, we can ignore the term involving $e^{-\alpha t}$ and e^{-a12t} in (4.2) since they converge to zero more rapidly than $e^{-\beta t}$. This gives the

following asymptotic forms

$$\begin{aligned} \phi_2(t) &\approx a_{12}\frac{D}{V}\frac{(a_{32}-\beta)e^{-\beta t}}{(\alpha-\beta)(a_{12}-\beta)} \\ \phi_3(t) &\approx a_{12}a_{23}\frac{D}{V}\frac{e^{-\beta t}}{(\alpha-\beta)(a_{12}-\beta)}. \end{aligned} \tag{4.3}$$

Hence, the ratio

$$\frac{\phi_2(t)}{\phi_3(t)} = \frac{a_{32}-\beta}{a_{23}} \tag{4.4}$$

can provide some indication as to the asymptotic level of drug in the unsampled third compartment. That is, say the plasma level curve decreased before the effects compartment does (as is the case of Westlake's model in Table 1), then (4.4) indicates that this will be the case whenever the ratio is less than 1; or if

$$a_{23} \geq a_{32} - \beta.$$

However, this will follow whenever

$$a_{23} \geq a_{32}. \tag{4.5}$$

To see this, note that since $a_{12}\frac{D}{V} > 0$ and $0 < \beta < \alpha < a_{12}$, it follows that $(\alpha - \beta) > 0$ and $(a_{12} - \beta) > 0$ and the desired conclusion is reached.

In practice one could check (4.5), or that the flow rate from compartment two to compartment three is greater than the flow rate from compartment three to compartment two. However, establishing an inequality for the case when the plasma clears slower than the targeted compartment is less obvious in terms of a sufficient conditions that the flow rates must meet; it is however feasible to check (4.4) since the eigenvalue β can be computed from knowledge of the estimated flow rates which we do in the next section.

5 Estimation

In the following three sections, we discuss our estimation approach, present the results of our simulation studies, and those of our data analysis.

Even for a well-posed experiment, or an experiment where apriori identifiability of the flow rates has been established as discussed in the Appendix, numerical or statistical estimation, regardless of noise in the data, is non-trivial even if the problem is identifiable. In this section we will consider the following *hierarchical* nonlinear modeling problem.

Suppose one makes observations

$$y_{ij} = \psi(t_{ij})(1 + \epsilon_{ij}), \quad i = 1, ..., m, \quad j = 1, ..., m_i, \tag{5.1}$$

where i represents the number of subjects and j the number of observations per subject, and ϵ_{ij} is the error term associated with observation ij. Since the error structure, in biological experiments, is argued to be multiplicative or to depend on the mean (see [8], for instance), the error then is assumed to distributed $N(0, \sigma^2\psi)$.

Although other models are possible, for our analysis, we will only be considering the case when the model in (5.1) is as given in (3.9) or that is

$$\psi(t_{ij}) := \phi_2(t_{ij}) = \mathbf{e}_2^T e^{A_i t_{ij}} \frac{D}{V} \mathbf{e}_1, \tag{5.2}$$

where A_i corresponds to the matrix for the 2COA model given in (3.7) for the i^{th} individual. The *random effects* are then assumed to follow

$$A_i = A + E_i, \tag{5.3}$$

where, due to the nonnegativity of the entries of A, the error term entries of E_i are distributed *log-normal* with mean 0 and with covariance matrix R.

Solving problem (5.1) with the model given in (5.2) and assuming (5.3) may not only require more data than the ordinary least squares approach to fit successfully (since for the 2COA model, it has 16 unknowns if we assume that R is unstructured and the initial conditions of the system are unknown as well) but it can only be solve approximately since the random effects and the nonlinearity of the model make it so that no closed form expression for

the marginal distribution can be found, so that approximation methods must be employed (See for instance [8] and [13] for details).

We found no software that could directly handle problem (5.1) given (5.2) and (5.3); however, it is possible to handle this problem in the following manner.

6 Dimension reduction estimation

Although this approach could be generalized to include other models, in this we work we propose that the way to handle the nonlinear hierarchical problem discussed in this section is to regard the 2COA model as a combination of two simpler problems: the 1COA model and then handle the the remaining of the system as the *two-compartment open model* ([9]). This implies that one is dealing with simpler hierarchical modeling problems both of which have been previously considered (see [13, 8, 12]).

This approach can also be viewed as motivated by the manner in which the closed-form solution to the 2COA model is found in sections 3 and 4 or the way in which the identifiability results are established in the Appendix. That is, we propose that the data be used to estimate the parameters in the 1COA model and that once these quantities are estimated that they be held fixed in the remaining of the compartmental matrix A in (3.7), and that then the remaining entries of the lower block matrix, A_l, be estimated.

That is, we first solve for a_{12}, $a_{20} + a_{23}$ in A_{1-cmpt}, and $\frac{D}{V}$ as given in (3.6) with the following model

Step One

$$y_{ij} = \mathbf{e}_2^T e^{A_{1-cmpt}t} \frac{D}{V} \mathbf{e}_1, \tag{6.1}$$

where $\mathbf{e}_1$ and $\mathbf{e}_2$ are the two-dimensional canonical basis elements. Then holding a_{12}, $a_{20}+a_{23}$, and $\frac{D}{V}$ fixed, solve for the remaining entries of A_{2-cmpt} with

Step Two

$$y_{ij} = \mathbf{e}_2^T e^{A_{2-cmpt}t} \frac{D}{V} \mathbf{e}_1, \tag{6.2}$$

where $\mathbf{e}_1$ and $\mathbf{e}_2$ are now the three-dimensional canonical basis elements.

In practice, for these problems typically an estimate of the initial conditions, $\frac{D}{V}$, is available so this should be used in Step One. Moreover, when data is generated from a three compartment model, the estimate of the diagonal element of A_{1-cmpt} may not be good since, as we will see in the next section(see Figure 2), this may fail to capture the decay of the concentration curve. Hence, we proposed that Step Two be modified to also estimate the diagonal of A_{2-cmpt} so that the only entries of A_{2-cmpt} to be held as fixed and known are a_{12}, or the absorption rate into the plasma or the sampling compartment, and the initial conditions to the system, $\frac{D}{V}$.

As our simulations and data analysis will show, n the estimation approach outlined in (6.1) and (6.2) can prove successful.

7 Application and simulation

In this section we report the results of our simulation and data analysis.

Although we witnessed similar results for a larger class of matrices, in Table 1 and Table 2, we report the outcome for the matrix described in [17] and its computed ordinary least squares solution, and in Table 2, we simulate with the computed matrices of Table 5 and Table 3 as the true matrices.

The simulations were done in Matlab using *lsqnonlin* for the least squares problem and the built-in matrix exponential function *expm*. The random effects data analysis was done in Splus using *nlme* and computing the *spectral decomposition* for the matrix exponential. Table 1 consisted of 14 fixed time observations per data set and Table 2 of 11 observations out of 100 data sets each generated with multiplicative $\sigma = .15$ normal error 90% of

the time and $\sigma = .2$ normal error the remaining 10% of the time.

The data for both tables was simulated according to *Method 1* which corresponds to the ordinary least squares fit of problem (5.1) and not according to *Method 2* corresponds to 'splitting' the estimation problem as outlined in Step One and Step Two. To inform on the numerical behavior of these problems, we report the mean condition number of the Jacobian at the computed solution for both methods and the quantity *d.e.r.* which corresponds to the mean estimate of the *duration of effect ratio* as reported in (4.4). Westlake's matrix corresponds to the simulated matrix reported in [17] and so do the chosen time points and initial conditions. Lastly, the Theophylline matrices corresponded to the *nlme* and the ordinary least squares fit of the Theophylline data reported in Table 5 and Table 3, respectively. In Table 3, the initial conditions and time points correspond to the average values of the data set reported in Pinheiro and Bates (1995); that is, the initial conditions were computed by calculating the average over all 11 subjects of the value of *weight/dose* which were available per subject.

Note that in both Table 1 and Table 2, Method 2 produces estimates that which have consistently smaller standard error and mean-square error than Method 2. This is significantly so for the parameters a_{23} and a_{32}. Moreover, note that in Table 1 and in the second half of Table 2, despite the error in the simulated data, the mean condition number of the Jacobian(cond. # Jac.) is small so that the problem is numerically well-behaved for these matrices. However, if we consider the first half of Table 2, we see that while the estimates of Method 1 do tend to have smaller standard error and mean-square error than those of Method 1, Method 2 yields an estimate of the mean duration of the effects ratio(d.e.r.) which gives an erroneous indication as to which compartment is emptying out first relative to the third unsampled compartment, yet Method 1 does not.

Table 1: **Westlake mtx simulated data:(OLS):I.C.=.441**

		Method 1			Method 2		
	True Value	Mean	SD	MSE	Mean	SD	MSE
a_{12}	2.388	2.546	.4877	.5101	2.2792	.4319	.4435
a_{20}	.1689	.1663	.0166	.0167	.1623	.0162	.0174
a_{23}	.5413	.5832	.1856	.1894	.5335	.0906	.0905
a_{32}	.2503	.3016	.2256	.2302	.2311	.0754	.0774
d.e.r.	.3770	.4312			.3538		
cond. # Jac.		7.1492			6.9198		
a_{12}	1.7459	1.8300	.4891	.4938	1.5285	.2347	.3190
a_{20}	.2489	.2483	.0188	.0187	.2399	.0181	.0202
a_{23}	.8582	.9622	.8245	.8270	.7702	.1062	.1375
a_{32}	.3022	.3934	.5900	.5941	.2358	.0640	.0920
d.e.r.	.2874	.3429			.2449		
cond. # Jac.		9.7456			7.0217		

Table 2: **Theophylline mtx simulated data:OLS fit:**

Ave(I.C)=15.7757

		Method 1			Method 2		
	True value	Mean	SD	MSE	Mean	SD	MSE
a_{12}	.7040	.7487	.1303	.1372	.6252	.1097	.1346
a_{20}	.1086	.0928	.0361	.0392	.0819	.0389	.0470
a_{23}	.1442	.2512	.1952	.2217	.1416	.0414	.0413
a_{32}	.2326	.4263	.4834	.5185	.1483	.1054	.1345
d.e.r.	1.2018	1.4768			.7919		
cond. # Jac.		1.168e+03			2.636e+03		
a_{12}	1.2177	1.3393	.2388	.2669	.9323	.1741	.3339
a_{20}	.1278	.1225	.0149	.0157	.1203	.0116	.0138
a_{23}	.4220	.6890	.5879	.6430	.2170	.0742	.2179
a_{32}	.8290	1.2973	1.1576	1.2434	.3769	.1559	.4780
d.e.r.	1.7709	1.7694			1.4122		
cond. # Jac.		31.1828			10.4211		

In this table we report the ordinary least squares fit of the Theophylline data when the initial conditions of the system are assumed to be unknown; that is, the estimate of initial dose from the data is used but V as given in (3.5) is assumed to be unknown. To be consistent with this notation, we report this quantity as Cl^{-1} in the table. The heading of *2COA(Method 1)* corresponds to the fit of (5.1) when the matrix is as given in (3.7)(or when Step One and Step Two are not followed), and that of 1COA to that when the matrix is as given in (3.6).

Table 3: **Theophylline data:OLS fit: I.C. unknown**

	2COA(Method 1)		1COA	
	Mean	SD	Mean	SD
Cl^{-1}	7.3495	2.6237	25.4189	8.9747
a_{12}	1.2177	.8708	1.9468	2.4357
a_{20}	.1278	.0251	.3022	.4598
a_{23}	.4220	.3760		
a_{32}	.8290	.6229		
d.e.r.	1.7709			
cond. # Jac.	3.5145e+04		1.84e+03	

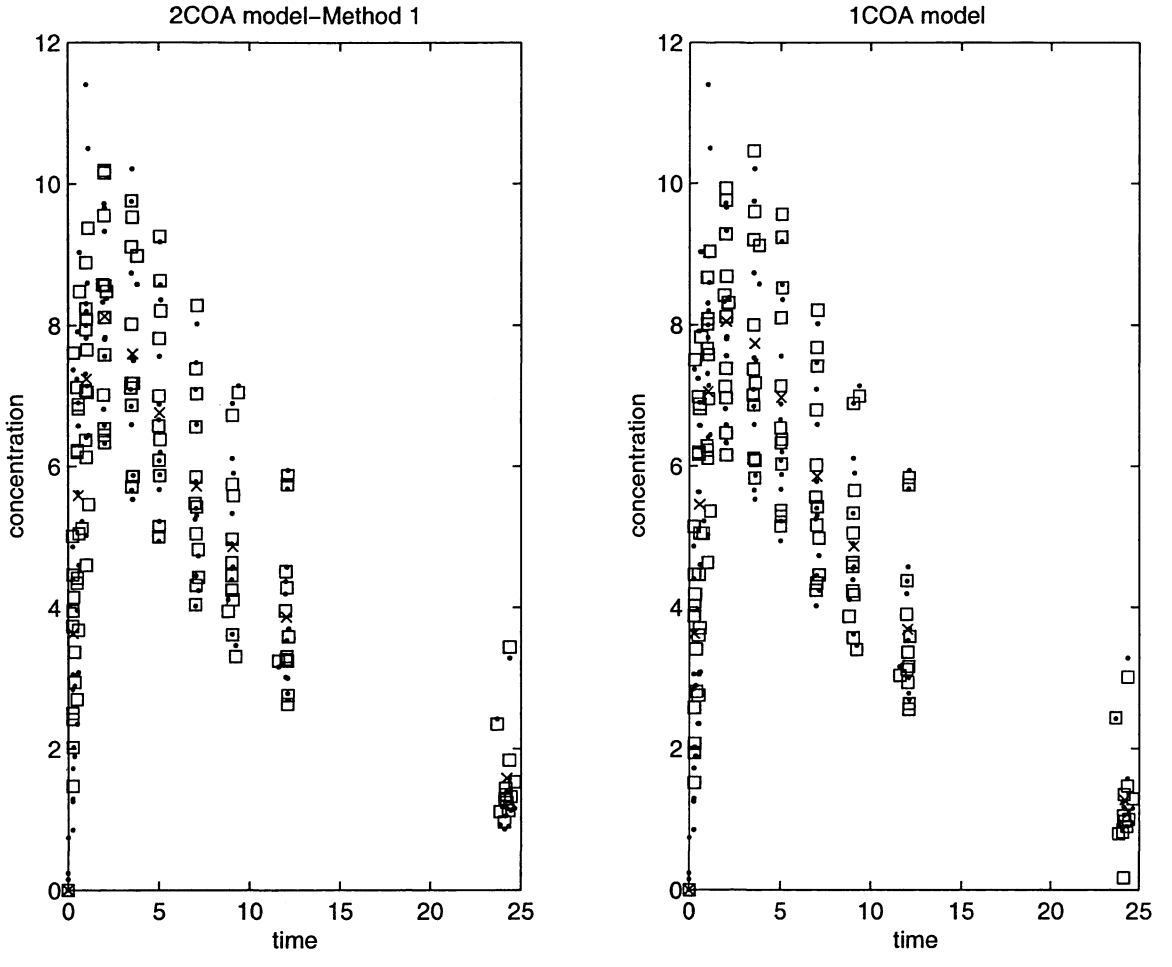

Figure 1: Results of Table 3. The '.' corresponds to the data, 'square' to the estimated fit, and the 'x' to the mean estimate.

In the following table we see that it is not possible to fit the one-compartment oral absorption model to the Theophylline data since the estimates fail to capture the decay of the curve(see Figure 2); however, the numerical sensitivity of these problems is such that the 2COA model when the initial conditions are known could not be used to described subjects $5, 10, 12$ either. The estimates of the initial conditions used was that of *weight/dose* which were available per subject. In Table 4 we report these findings.

Table 4: **Theophylline data: OLS fit(I.C. known)**

	2COA(Method 1)		1COA	
	Mean	SD	Mean	SD
a_{12}	1.1081	.6218	.8340	.5092
a_{20}	.1580	.0541	.2071	.1393
a_{23}	.7738	.9166		
a_{32}	.7225	.4682		
d.e.r.	.8404			
cond. # Jac.	12.8226		1.3355	

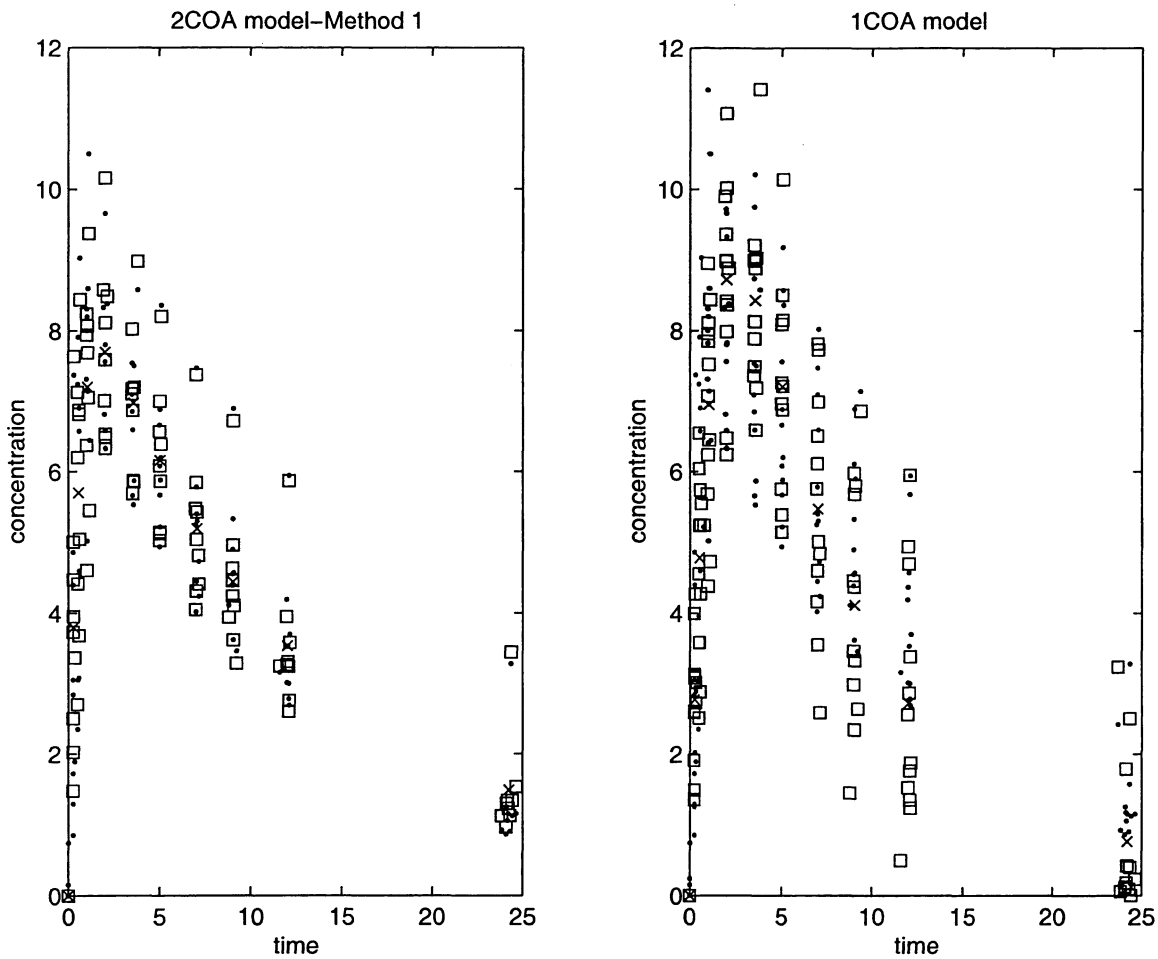

Figure 2: Results of Table 4. The '.' corresponds to the data, 'square' to the estimated fit, and the 'x' to the mean estimate.

In Table 5 and Figure 3, we see that it is possible to fit random effects and describe all the data with the 2COA model if we follow the procedure outlined in Step One and Step Two or Method 2. We also use the fact that the initial conditions are known. The results are reported on a *log* scale, *SD(fe)* corresponds to the standard deviations of estimates for the fixed effects, and *SD(re)* corresponds to that of the random effects. Lastly, *likrat* corresponds to the reported likelihood ratio.

Table 5: **Theophylline data:*nlme*:I.C.=weight/dose**

	2COA(Method 2)			1COA		
	Mean	SD(fe)	SD(re)	Mean	SD(fe)	SD(re)
$\log(a_{12})$	-.3510	.1431	.4518	-.3510	.1431	.4518
$\log(a_{20})$	-2.2197	.1714	.4359	-1.7705	.1922	.6429
$\log(a_{23})$	-1.9366	.5198	1.6399			
$\log(a_{32})$	-1.4585	.2963	.4732			
likrat	-239.4758			-259.3699		
d.e.r.	1.2018					

In Table 6, *fix* and *rand* correspond to the fixed correlation population coefficients and to those of the random effects, respectively. Entries are reported on a *log* scale. The *1COA(P&B)* column corresponds to the correlation coefficient estimates obtained by [13] when they considered a_{12} and the clearance parameter *cl* as random in their analysis(Note that *cl* is considered part of the initial conditions as discussed in sections 3 and 4.).

Table 6 **Correlation coefficients(*nlme* fit)**

	2COA			1COA			1COA(P&B)	
	fix	rand		fix	rand		fix	rand
$(\log(a_{20}, a_{23})$	.562	.976	$(\log(a_{12}, k))$	-.77	-.861	$(\log(a_{12}, cl))$	-.540	0
$(\log(a_{20}, a_{32}))$	.685	.999						
$(\log(a_{23}, a_{32}))$	.513	.969						

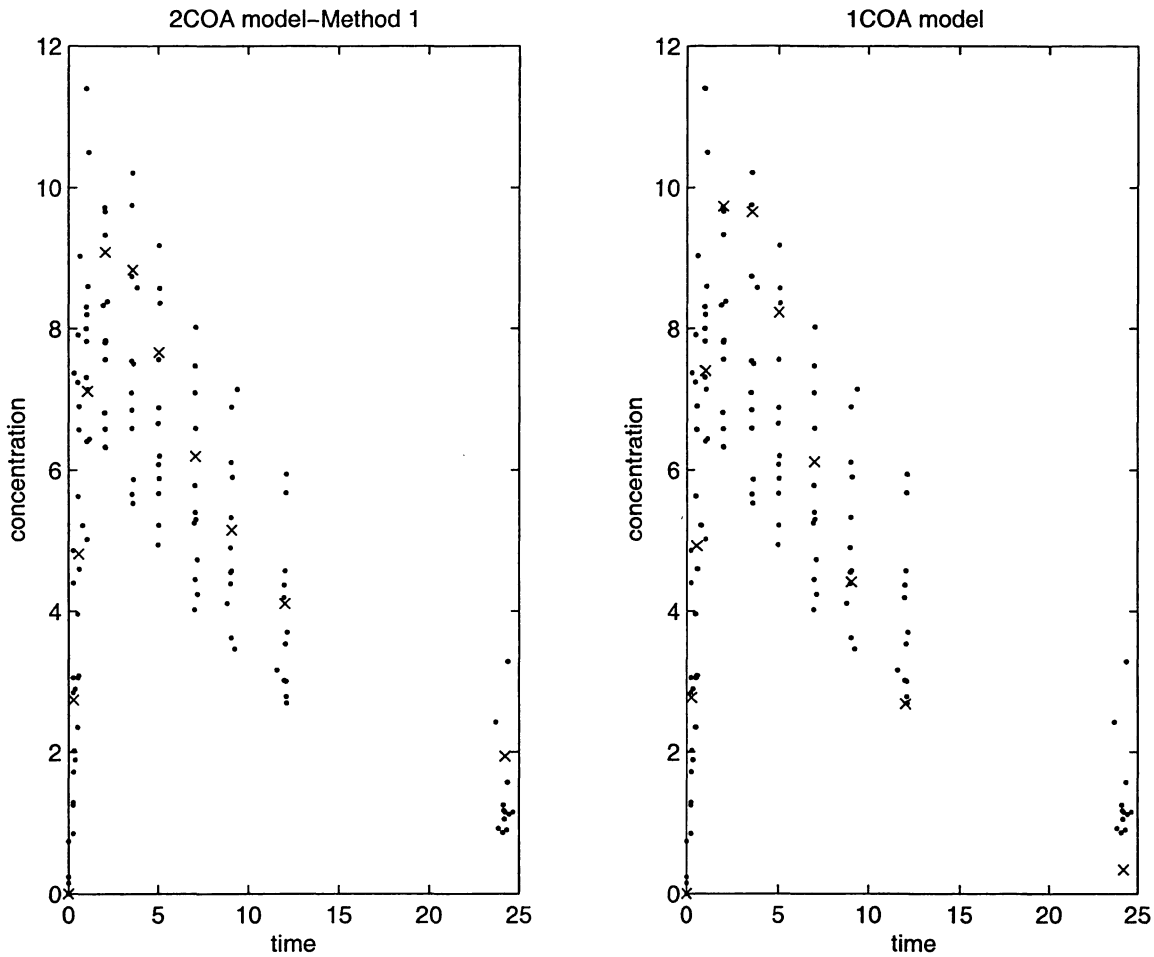

Figure 3: Results of Table 5. The '.' corresponds to the data and the 'x' to the mean estimate.

8 Summary

In this paper we discussed the need for models which include an *effects* or *targeted* compartment to directly account for the lag-time and the duration of the effect of a drug. We also presented some of the technical difficulties associated with fitting these models, and for completeness and ease of reading we provided a brief introduction to compartmental models, and showed that some of the common models within the pharmacology literature form an identifiable subset of these models (see sections 2, 3, 4, and the Appendix).

We have also seen that it is possible to fit the 2COA model successfully to both true and simulated data provided in part that the structure of the model is used or that the dimension of the problem is reduced as outlined in Step One and Step Two of section 6. However, we caution about generalizing these results to arbitrary compartmental matrices since in our simulations we found that the relative size of the magnitude of the flow rates plays a critical, yet not well-quantified, role in the estimation of these problems. In fact for the matrix of Table 5 or that in the first half of Table 2, we found that as we increased the value of the a_{12} flow rate that the quantity d.e.r. approached one while the condition number of the Jacobian gradually decreased but still remained in the 1000's. Nonetheless, generally we found that the estimates given by Method 2 tended to have smaller standard error and mean-squared error than those of Method 1 or when the structure of the model was disregarded(see Table 1 and Table 2) and, perhaps less surprising, that Method 2 tended to be well-conditioned whenever Method 1 was.

We have also seen that by employing the structure of the model, it is possible to allow for random effects in the estimates and thereby account for the variability within the data and the correlation structure. As Table 5 and Table 6 indicate, our data analysis results are comparable to those

obtained by [13], except we make use of the fact that the initial conditions of the system are known since *dose* and the covariate of *weight* are available per subject in the Theophylline data set. This, then give an estimate of the initial conditions of the system as discussed in sections 2, 3, and 4. Since the initial conditions are known, we have also argued that the correct model to fit is the 2COA model rather than the 1COA as typically done, see [8] and [13]. In fact, Table 3 and Figure 2 and Table 5 and Figure 3 indicate that the 1COA fails to capture the decay of the data so that a model which includes a third compartment must be included when the initial conditions to the system are known.

More immediate future work includes extending the estimation approach outlined in Step One and Step two to include other common experiments within pharmacology such as those employing the three-compartment mammillary or catenary model with sampling and input limited to the central or second-compartment.

9 Appendix

In this section we show that the pharmacologic models discuss in sections 2, 3, and 4 form part of a larger class of identifiable models. However, we first define what its meant by identifiable.

We say a system is *identifiable* if for a hypothetically error free experiment (error free both in the data and in the model structure), a sampling and input matrix is given and the structure of A is correspondingly well-specified so that the necessary conditions for a unique global or local solution to the model parameters are met, see [1].

Claim 1 It is possible to identify all the entries of A in system (3.3) for a general known input function $u(t)$ with input matrix $B = \mathbf{e}_1$ and sampling matrix $C = \mathbf{e}_p^T$.

Note that in Claim 1 the choice of $p = 1$ or $p = 2$ and $n = 4$ and $B\mathbf{u}(t) = \mathbf{e}_1(dose)\delta(t)$ includes the class of models considered by [10].

Corollary 1 Claim 1 holds for a compartmental matrix A where A_l has a *mammillary* structure or one where A_l only has nonzero entries on its first row, first column, and diagonal.

Proof of Claim 1:

The method of proof that we will follow consists of breaking up the problem into two pieces. Similar to the example previously considered, we will first analyze the compartmental matrix only up to the sampling compartment p, showing that this portion is identifiable; that is, labeling the upper block of A, A_u, where A_u is the $p \times p$ upper bi-diagonal block of A. The solution to this part of the problem will then form the forcing function into compartment p.

We first establish the claim for the case $p = 2$. Then the sampling matrix is $C = e_2'$ and the unit bolus input function $Bu(t) = e_1 u(t)$. Then this gives the *impulse-response* function

$$\xi(t) = C \int_0^t e^{(t-\tau)A_u} e_1 \delta(\tau) d\tau$$

whose Laplace transform is

$$C(sI - A_u)^{-1} e_1 = \frac{-a_{12}}{s^2 + (a_{20} + a_{12})s + a_{12}a_{20}}.$$

Thus, we see that knowledge of this function determines a_{20} and a_{12} uniquely and hence this system is identifiable.

To see if this same choice of C and B allows for the identification of all the rates for a general p, the reader can verify that the $(p,1)^{th}$-entry of the matrix $(sI - A_u)^{-1}$ is

$$\frac{(-a_{12})(-a_{23})...(-a_{p-2,p-1})(-a_{p-1,p})}{(s + a_{12})(s + a_{23})...(s + a_{p-2,p-1})(s + a_{p-1,p})(s + a_{p0})}.$$

From the above, we see that the numerator is a scalar while the denominator is a polynomial in s of degree p, this then results in $p + 1$ equations

in terms of the unknown flow rates; hence, it is possible to identify $p+1$ unknowns from the chosen experiment. Thus, the experiment is identifiable up to this point.

To see that the entire system is identifiable, we proceed by considering the solution $a_{p-1,p}\phi_{p-1}(t)$ of the $p-1^{th}$ compartment as the forcing function into the p^{th} compartment. That is, we take $C = e_p^{'}$ and let $Bu(t) = e_1\phi_p(t)$. Then to see that the remaining portion is identifiable, we recognize the remaining lower block of the compartmental matrix, A_l, as *catenary* or tri-diagonal, for which, [3] established that with this new choice of input matrix B and sampling matrix C, that it is possible to identify all of the entries of A_l. This together with the previous result gives us the result that all of A is identifiable. Hence the claim is established.

Proof of Corollary 1:

The result follows in a similar fashion to Claim 1 and from considering [3] work pertaining to mammillary matrices or matrices which have nonzero entries only on their first row, first column, and diagonal.

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