BU-1434-M

Models in Pharmacokinetics: Identifiability, Estimation, and Effectiveness of a Drug

MARTHA CONTRERAS [1] AND GILBERT G. WALTER [2]

Contribution from the Biometrics Department, Cornell University, Ithaca, NY 14853.

[1]Corresponding author. Telephone: (607) 255-1640. Fax: (607) 255-4698. E-mail: mpc14@cornell.edu
[2]Department of Mathematical Sciences, University of Wisconsin-Milwaukee, Milwaukee, WI 53201.

Abstract □ In this paper we will see that PBPK models form part of a larger class of identifiable models within compartmental analysis. We will also review a method for estimating the flow rates in PBPK models based on the Laplace transform, and then via simulations we will discuss the performance of this method under the presence of noise and a small set of observations, and the role of this method in predicting the duration of effectiveness of a drug.

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* compartment and its observed response, see Wagner[1], or Holford and Sheiner[2], 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. Furthermore, methodology, based on the class of models known as *physiologically based compartmental (PBPK) models*, sometimes is biased in its prediction of the concentration of a drug in the targeted compartment from data gathered in some intermediate compartment. This then subsequently results in a miscalculation of the concentration in the unobserved targeted compartment[3]. Consequently, researchers often relate the effect of a drug to the concentration in the sampling compartment, typically the plasma, see Davidian and Giltinan[4], for example.

In this paper, we will compare these two approaches. We first observe that PBPK models form part of a larger class of identifiable models within *compartmental analysis*. Then, we will discuss a current method to estimate the *flow rates* in PBPK models and its drawbacks in predicting the concentration of a drug in the unobserved compartments. We begin with a brief review of compartmental analysis and present new results pertaining to the identifiability of PBPK models. We conclude with some numerical simulations which confirm the failure of both approaches to accurately predict the effect of a drug from the concentration in the plasma or the concentration in the targeted compartment. However, using the estimate of the concentration in the targeted compartment is clearly better if one is interested in the duration of the effectiveness of the drug.

Models

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[2,4]. More precisely, 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. This is indicated by the following diagram.

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

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 (corresponding to the arrow pointing out of ϕ_p). Then, under the above assumptions, models based on diagram 1 have convenient closed form solutions. Benet[5] obtained closed form solutions for various common pharmacokinetic experiments via the use of partial fractions and the Laplace transform. The reader is referred to Benet[5] for details or to Gibaldi and Perrier[6] or Holford and Sheiner[2] for a summary of some of these solutions. However, we will see that these solutions are special cases of a more general problem in compartmental analysis.

Compartmental models

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

$$\begin{aligned} \frac{d\phi}{dt}(t) &= A\phi + Bu(t), \quad t \geq 0 \\ \phi(0) &= 0 \\ \xi(t) &= C\phi(t), \end{aligned} \tag{2}$$

where ϕ is the concentration vector, u is the input vector, and ξ the observation vector. In scalar notation this is a system of n equations where the i^{th} equation is given by

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

In eq 2, $A := [a_{ij}]$ 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 vector, $u(t) = (u_1(t), u_2(t), ..., u_r(t))'$, where $u(t)$ 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 $\xi(t) = (\xi_1(t), \xi_2(t), ..., \xi_p(t))$. Typically, in experiments involving human subjects, both B and C consists of multiples of the natural basis elements, e_j, where compartment j is the only compartment receiving input or the only compartment being sampled. Through the *method of variation of parameters*[7], the formal solution to eq 2 can be found to be

$$\xi(t) = C \int_0^t e^{(t-\tau)A} B u(\tau) d\tau. \tag{3}$$

Pharmacokinetic models

To see that some of the current pharmacokinetic models are especial cases of a compartmental system, we consider a generalization of the models discussed in Holford and Sheiner[2].

The system of differential equations resulting from diagram 1, assuming that ϕ_1 receives D_i 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 eq 2 we have that

$$\begin{aligned}
\frac{d\phi_1}{dt}(t) &= -a_{12}\phi_1 + \sum_i D_i\delta(t-t_i) \\
\frac{d\phi_2}{dt}(t) &= a_{12}\phi_1 - a_{23}\phi_2 \\
&\vdots \\
\frac{d\phi_p}{dt}(t) &= a_{p-1,p}\phi_{p-1} - (a_{p0} + a_{p,p+1})\phi_p \\
&+ a_{p+1,p}\phi_{p+1} \\
\frac{d\phi_{p+1}}{dt}(t) &= a_{p,p+1}\phi_p - (a_{p+1,p} + a_{p+1,p+2})\phi_{p+1} \\
&+ a_{p+2,p+1}\phi_{p+2} \\
&\vdots \\
\frac{d\phi_n}{dt}(t) &= a_{n-1,n}\phi_{n-1} - a_{n,n-1}\phi_n
\end{aligned} \tag{4}$$

which can be rewritten as a system

$$\frac{d\phi(t)}{dt} = A\phi(t) + Bu(t),$$

where $\delta(\cdot)$ is the Dirac delta function, A is a tri-diagonal $n \times n$ compartmental matrix, and $Bu(t) = \sum_i D_i\delta(t-t_i)$ is the input or forcing function into compartment one or $\phi_1(t)$.

As an example of eq 4, consider the *two-compartment* model with a one time initial oral dosage of $\frac{D}{V}$ units used by Westlake[3]. These assumptions lead to the following tri-diagonal compartmental matrix

$$A = \begin{pmatrix} -a_{12} & 0 & 0 \\ a_{12} & -(a_{23}+a_{20}) & a_{32} \\ 0 & a_{23} & -a_{32} \end{pmatrix}, \tag{5}$$

with $p = 2$, $n = 3$, input function $Bu(t) = e_1\frac{D}{V}\delta(t)$, and sampling matrix $C = e_2'$. Then the solution for any of the compartments is as follows.

By using the *method of integrating factors* we obtain the concentration in compartment one to be

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

There are several approaches to solve for $\phi_2(t)$ and $\phi_3(t)$, however to be consistent with traditional approaches, we prefer to treat the solution to compartment one as the forcing function in compartment two; that is, we re-define the system by letting $(Bu(t))' = (\frac{D}{V}e^{-a_{12}t}, 0)'$ in eq 2 and consider the lower 2×2 block of A, 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

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

which, assuming that α and β are the distinct eigenvalues of A and not equal to a_{12}, yields the solutions to the *two-compartment model with oral administration* found in Westlake[3], namely

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

These are the solutions corresponding to the so called *"bolus two-compartment* and the *first-order (absorption) one-compartment"* models found in Holford and Sheiner[2].

Claim 1 It is possible to identify all the entries of A in system eq 4 for a general input function $u(t)$ with input matrix $B = e_1$ and sampling matrix $C = e_p'$.

Note that in Claim 1 the choice of $p = 1$ or $p = 2$ and $n = 4$ and $Bu(t) = e_1(dose)\delta(t)$ includes the class of models consider by Holford and Sheiner[2].

Corollary 1 Claim 1 holds for a compartmental matrix A where A_l has a *mammillary* structure.

Estimation

In general, it is possible to identify up to $n + rq(n-1)$ parameters or entries of A where this number comes from knowledge of the sampling matrix, $C_{q\times n}$, and input matrix, $B_{n\times r}$. See Anderson[8] for further details. While identifiability of the flow rates from a chosen experiment is a necessary condition (i.e. for a particular experiment, a sampling and input matrix is given and the structure of A is correspondingly well-specified), estimation under the presence of noise remains non-trivial even if the problem is identifiable.

In this section we discuss a known approach to estimating the flow rates based on the *Laplace transform*, see Gibaldi and Perrier[6] for a brief discussion or Anderson[8] for further details. This method need not involve solving the system of differential equations a priori, but rather first fitting the data to a sum exponentials (or the solution to the system if available) where the number of exponentials corresponds to the size of the compartmental matrix A. That is, if A is 3×3, then one fits the data to

$$g(t) := \hat{c}_1 e^{\hat{\lambda}_1 t} + \hat{c}_2 e^{\hat{\lambda}_2 t} + \hat{c}_3 e^{\hat{\lambda}_3 t}.$$

To estimate the entries of A, the Laplace transform of $g(t)$ is formed

$$L(g(t))(s) := \frac{\hat{c}_1}{s - \hat{\lambda}_1} + \frac{\hat{c}_2}{s - \hat{\lambda}_2} + \frac{\hat{c}_3}{s - \hat{\lambda}_3}. \tag{6}$$

Then, upon obtaining a common denominator in eq 6, the numerator will be a polynomial of degree two while the denominator will be a polynomial of degree three. One then equates these coefficients to those found by calculating the *transfer function* or the Laplace transform of eq 3

$$C(sI - A)^{-1}B \cdot L(u(t))(s). \tag{7}$$

So in particular, in eq 7, if we let $Bu(t) = \frac{D}{V}e_1\delta(t)$ then its corresponding Laplace transform is $L(u(t))(s) = \frac{D}{V}e_1$ and letting $C = e_2'$ with A as given by eq 5, we have that this method gives the following nonlinear system of equations to solve for the unknown rates and initial dosage $\frac{D}{V}$.

$$\begin{pmatrix} a_{12}\frac{D}{V} \\ a_{12}\frac{D}{V}(a_{12} + a_{23} + a_{20} + \hat{\lambda}_1 + \hat{\lambda}_2 + \hat{\lambda}_3) \\ a_{12} + a_{23} + a_{20} + a_{32} \\ a_{32}a_{20} + a_{12}(a_{23} + a_{20} + a_{32}) \\ a_{12}a_{32}a_{20} \end{pmatrix} = \tag{8}$$

$$\begin{pmatrix} -(\hat{c}_1(\hat{\lambda}_2 + \hat{\lambda}_3) + \hat{c}_2(\hat{\lambda}_1 + \hat{\lambda}_3) + \hat{c}_3(\hat{\lambda}_1 + \hat{\lambda}_2)) \\ -(\hat{c}_1\hat{\lambda}_2\hat{\lambda}_3 + \hat{c}_2\hat{\lambda}_1\hat{\lambda}_3 + \hat{c}_3\hat{\lambda}_1\hat{\lambda}_2) \\ -(\hat{\lambda}_1 + \hat{\lambda}_2 + \hat{\lambda}_3) \\ \hat{\lambda}_1\hat{\lambda}_2 + \hat{\lambda}_3\hat{\lambda}_1 + \hat{\lambda}_3\hat{\lambda}_2 \\ -\hat{\lambda}_1\hat{\lambda}_2\hat{\lambda}_3 \end{pmatrix}.$$

Once the estimated rates are known, and thereby the entries of $\hat{A}$, then with this choice of A, B, and C from eq 3 we find that the solution to the compartmental system is

$$\phi(t) := \begin{pmatrix} \phi_1(t) \\ \phi_2(t) \\ \phi_3(t) \end{pmatrix} = e^{\hat{A}t}\frac{\hat{D}}{\hat{V}}e_1, \tag{9}$$

from which we get the solution in particular at the tissue compartment, $\phi_3(t)$.

Numerical Estimation and Duration of Effectiveness

While this approach has the property that it a priori fits an identifiable model to the data, it can yield biased estimates under the presence of noise in the data. Nonetheless, as our example will illustrate, when constraints are placed on the flow rates, this estimation method yields a better estimate of the duration of effectiveness of a drug. To illustrate this, we revisited the oral administration two-compartmental model considered by Westlake[3]. For this example the true compartmental matrix is

$$A := \begin{pmatrix} -2.3888 & 0 & 0 \\ 2.3888 & -.7102 & .2503 \\ 0 & .5413 & -.2503 \end{pmatrix}$$

with initial dosage $\frac{D}{V} = .441$. We then at fixed times generated 14 observations with normally distributed random error and standard deviation .01. Then, using *Matlab*'s subroutines *leastsq* and *fsolve* (employing the Levenberg-Marquardt option in both) to fit $\phi_2(t)$ to the data and to solve the system of rates given by eq 8, we have that the estimated matrix of flow rates yields

$$\hat{A} := \begin{pmatrix} -1.7459 & 0 & 0 \\ 1.7459 & -1.1071 & .3022 \\ 0 & .8582 & -.3022 \end{pmatrix}$$

and estimated initial dosage $\frac{\hat{D}}{\hat{V}} = .5789$. The corresponding estimates of the parameters of $\phi_2(t)$ and $\phi_3(t)$ are

$$(\hat{a}_{12}, \hat{\alpha}, \hat{\beta}, \hat{a}_{32}, \frac{\hat{D}}{\hat{V}}, \hat{a}_{23}) = (1.7458, 1.3537, .0556, .3022, .5789, .8582).$$

To compute the 95% confidence intervals for the parameters of $\phi_2(t)$ and $\phi_3(t)$, we used *Matlab*'s subroutine *nlparci* and obtained the following range of values for $\hat{a}_{12}$, $\hat{\beta}$, $\hat{\beta}$, $\hat{a}_{32}$, $\frac{\hat{D}}{\hat{V}}$, and $\hat{a}_{23}$ correspondingly

$$[(1.6282, 1.8635), (1.2541, 14534), (.0546, .0565), (.2958, .3085), (.5424, .6154), (.7813, .9351)].$$

Figure 1 shows the true data both in the sampling and unobserved compartment together with their estimated curves and corresponding confidence bands. We see that we have over-estimated the true curve in the unobserved compartment, $\phi_3(t)$; while estimated the curve in the observed compartment $\phi_2(t)$ well, as Westlake[3] reported.

However, from Figure 1 we also see that if the effective threshold of a drug (or some pre-determined level above which the drug has the desired effect) is attained in the tissue compartment, then using the plasma level as an approximation to the effective threshold will not yield as good of an estimate of the duration of the effectiveness of a drug. This is the case since the plasma level time interval is much shorter than that of the tissue level. In fact, although we do not report this here, our numerical findings showed this pattern to persist as long as the flow rate from compartment two to compartment three is greater than the flow rate from compartment two to the outside of the system and if this is also greater than the flow rate from compartment three to compartment two. That is, as long as the following holds

$$a_{23} \geq a_{20} \text{ and } a_{23} \geq a_{32}.$$

Summary

In this paper, we have seen that PBPK models can be regarded as part of a larger class of models within compartmental analysis and that PBPK models are well-defined in the sense that they come from a family of identifiable compartment models. Moreover, these models can be used to predict the concentration in unobserved compartments. However, care must be taken, since estimation methodology, such as that primarily based on least squares, can lead to bias estimates of the concentration in these unobserved compartments. Further investigation is needed to properly account for this bias. Nevertheless, even with these inaccurate predictions, this method gives better estimates of the duration of the effectiveness of the drug than does the estimate obtained from the plasma compartment. This can be

seen from the example but is true for similar examples under plausible constraints on the flow rates.

Appendix

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 stage.

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, Bellman and Åström[9] established that with this 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 Bellman and Åström[9]'s work pertaining to mammillary matrices or matrices which have nonzero entries only on their first row, column, and diagonal.

References

1. Wagner, J.G. Relations between drug concentrations and response. *J. Mond. Pharm.* **1971**, *4-14.*

2. Holford, N.; Sheiner, L. Understanding the dose-effect relationship: Clinical applications of pharmacokinetics-pharmacodynamics models. *Clin. Pharm.* **1981**, *6, 429-453.*

3. Westlake, W.J. Problems associated with analysis of pharmacokinetic models. *J. Pharm. Sci.,* **1971** *60, 6, 882-885.*

4. Davidian, M.; Giltinan, D. Nonlinear models for repeated measurement data; Chapman and Hall: New York, NY, 1995.

5. Benet, L.Z. General treatment of linear mammillary models with elimination from any compartment as used in pharmacokinetics. *J. Pharma. Sci.,* **1972**, *61, 536-541.*

6. Gibaldi, M.; Perrier, D. Pharmacokinetics; Marcel Dekker, Inc.: New York, NY, 1982.

7. Borrelli, R.L.; Coleman, C.S. Differential Equations: A modeling approach; Prentice-Hall, Inc.: Englewood Cliffs, NJ, 1987.

8. Anderson, D.H. Compartmental Modeling and Tracer Kinetics; Springer-Verlag: New York, NY, 1983.

9. Bellman, R.; Åström, K.J. On structural identifiability. *Math. Biosci.,* **1970**, *7, 329-339.*

Acknowledgments

Research funded by NSF grant DMS-9710081 and Hatch Project NYC-151413.

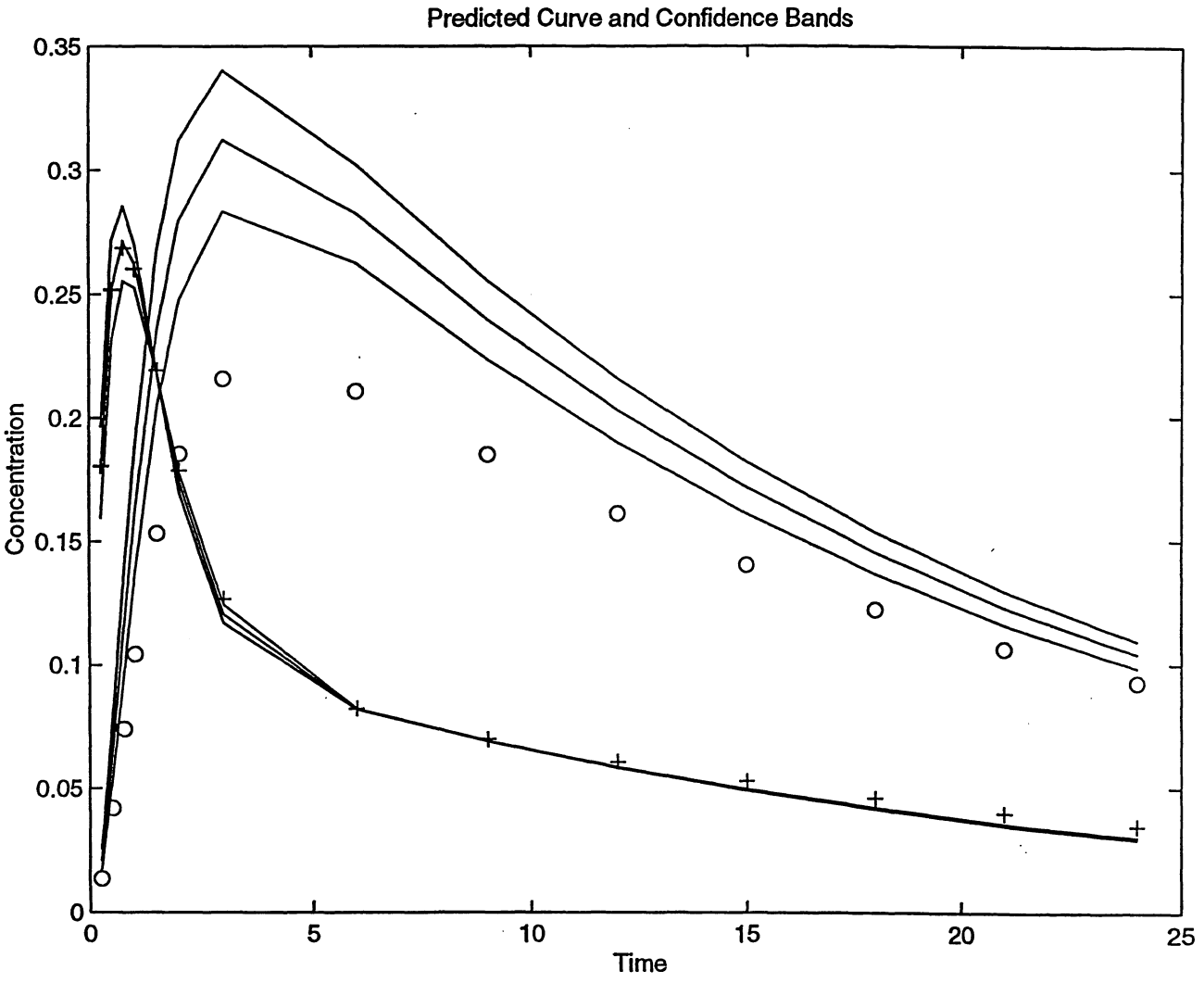

Figure 1: Estimated concentration $\phi_2(t)$ and confidence band corresponds to the faster descending curves and the '+' and 'o' to the true data.