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Properties and application of a two-compartment model with absorption of order zero and first order elimination

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ABSTRACT

In this paper a simple two-compartment model with absorption of order zero and elimination of order one is introduced in order to describe the penetration of a drug from a central to a peripheral tissue after a bolus administration of the drug in the central tissue. The mathematical properties of the model are studied and mathematical expressions for relevant pharmacokinetic quantities describing the penetration of the drug are derived. These quantities include AUC, t_{max}, C_{max}, and $t_{1/2}$. Estimation of the unknown constants associated with the model based on observations of the drug concentration in the peripheral tissue at different time points is addressed. The model is applied to a real life data set and estimates and confidence intervals for all relevant pharmacokinetic parameters are given. Focus is on enabling researchers with a non-mathematical background to apply the model in practice, and R and Stata code to achieve this is provided.

Keywords: Compartment model; Pharmacokinetics; Identifiability; Time over MIC.

1 Introduction

The distribution of drugs in the human body is very important when you want to ensure that enough of the drug is present in a certain tissue for example undergoing surgery and therefore at risk of sustaining an infection[1]. Typically, the distribution of a drug is studied by taking samples from different peripheral tissues after administration of the drug in a central tissue (most often the stomach after an oral ingestion or the blood stream after an intravenous administration). Based on these samples different measures of the penetration of the drug are then calculated. Such measures include the area under the drug concentration curve (AUC) and the time that the drug concentration is above a certain value that is deemed important to combat an infection (minimum inhibitory concentration - MIC).

Most often, all measures of the penetration of the drug are calculated directly from the drug concentration measurements. For example, time to peak concentration is the measurement time point with the maximal observed associated drug concentration and time above MIC is the observed duration of drug concentrations above MIC maybe after some interpolation between observed drug concentrations. The biggest problem with this approach is that it depends heavily on the sampling scheme, and if the sampling is coarse, such calculations could be very imprecise. Another problem is that any measurement error associated with the drug concentration measurements is ignored. Finally, only measurements around the time points of interest contribute to the calculation of the penetration measures, whereas time points far away are ignored to a large extent.

A way to overcome these problems is to model the observed drug concentration curve using an appropriate non-linear mathematical function of time since administration and with a few associated kinetic constants typically in the shape of rate constants and volumes. If a good fit of the observed drug concentrations is achieved, the advantages are numerous[2]. Most often the rate constants and volumes have direct interpretations and give insight into the understanding of the physical system under study. Furthermore, all measures of drug penetration can be calculated from the constants associated with the non-linear function, and they do not depend on the chosen sampling scheme (though the precision of the estimates of the constants do depend on the distribution of the sampling time points). Finally, the measurement error is taken into account through the usual distributional assumptions associated with non-linear regression. This allows for the calculation of confidence intervals for all relevant quantities.

Usually, in the pharmacokinetic models, first order kinetics is assumed, that is the elimination from a single compartment is a constant proportion of the drug in that compartment per unit time. Occasionally, though, zero order kinetics is assumed, that is a constant amount of drug is eliminated per time unit. The appropriate order of the processes depends on the nature of the physiological system under study[3].

Numerous journals and books deal with such mathematical models typically termed pharmacodynamic or pharmacokinetic models, see for example[4]. Often, though, such models are very elaborate in an attempt to take into account many aspects of the human body. As measurements are normally restricted to very few sites, it is hard to determine if any insight is gained into the processes involved in the dynamical system under study. A better approach is to start out with a very simple model and then only extend it if clear deviations are observed between measurements and the fitted values based on the model[5]. In this paper such a simple pharmacokinetic model in the shape of a two-compartment model is proposed. The focus of the paper is on the mathematical properties of the model, calculating appropriate penetration measures based on the model, and how to apply the model in practice. Different expressions for the drug concentration in the peripheral tissue in terms of various summary measures are presented, and this allows the user to calculate confidence intervals directly for all relevant drug penetration parameters.

The aim of the paper is to present a simple compartment model that is useful in medical research, allows for easy calculations of relevant quantities associated with the penetration of the administered drug, and which is straight forward to apply in real life data analysis for medical researcher without special mathematical skills, using standard statistical software.

2 The proposed compartment model

Consider a simple model for the concentration of a drug in a peripheral tissue after a bolus administration of the drug in a central tissue. In the model we describe the absorption or distribution from the central tissue to the peripheral tissue by a kinetic model of order zero and the elimination from the peripheral tissue by first order kinetics. The model is illustrated in the Figure 2.1.

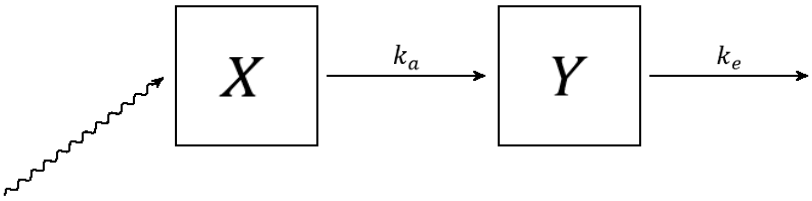

Figure 2.1: *Illustration of a simple two-compartment model with distribution of order zero and first order elimination. The drug is given as a bolus administration (wiggly line), and the rate constants corresponding to absorption and elimination are denoted* k_a *and* k_e *respectively. The concentration of the drug in the central tissue is denoted by* X *and in the peripheral tissue by* Y*.*

The concentration of the drug in the central tissue is denoted by X and the concentration in the peripheral tissue by Y. Typically, measurements of the drug concentration at different time points after the bolus administration will be available for the peripheral tissue only. Note also that we assume that there is no flow of the drug from the peripheral tissue back to the central tissue, and that elimination of the drug is only from the peripheral tissue.

We assume that the absorption of the drug from the central tissue to the peripheral tissue can be described by kinetics of order zero with absorption rate constant k_a, that is we assume the following differential equation for the drug concentration in the central tissue at time t after the bolus administration (X_t),

$$\frac{\mathrm{d}X_t}{\mathrm{d}t} = -k_a, \quad X_0 = x_0, \qquad (2.1)$$

where x_0 is the initial concentration of the drug in the central tissue immediately after the bolus administration of the drug (the amount of drug in the bolus dose divided by the volume of the central tissue). As the volume of the central tissue is typically unknown, x_0 usually has to be estimated from the data.

The elimination of the drug from the peripheral tissue is assumed to be described by first order kinetics with elimination rate constant k_e, so we have the following differential equation for the drug concentration in the peripheral tissue (Y_t) at time t after the bolus administration,

$$\frac{\mathrm{d}Y_t}{\mathrm{d}t} = k_a - k_e \cdot Y_t, \quad Y_0 = y_0 \qquad (2.2)$$

where y_0 is the initial concentration of the drug in the peripheral tissue. Often y_0 will be assumed to be 0 as there is typically no natural presence of the drug in the peripheral tissue at time 0. The rate constants and the initial concentration in the central tissue are all assumed to be positive: $k_a > 0$, $k_e > 0$, and $x_0 > 0$.

The differential equation for the drug concentration in the central tissue (2.1) is readily solved to yield

$$X_t = x_0 - k_a \cdot t, \quad t \geq 0, \qquad (2.3)$$

with the additional restriction that $X_t = 0$ for $t \geq \frac{x_0}{k_a}$, that is the concentration of the drug in the central tissue is 0 when all of it has been absorbed into the peripheral tissue.

Solving the differential equation corresponding to the drug concentration in the peripheral tissue (2.2), we get

$$Y_t = \begin{cases} \frac{k_a}{k_e} + (y_0 - \frac{k_a}{k_e})e^{-k_e t}, & t \leq \frac{x_0}{k_a} \\ \left[\frac{k_a}{k_e} e^{\frac{k_e}{k_a}x_0} + (y_0 - \frac{k_a}{k_e})\right] e^{-k_e t}, & t > \frac{x_0}{k_a} \end{cases} \qquad (2.4)$$

In the special situation where there is no drug in the peripheral tissue at time 0 ($y_0 = 0$), the drug concentration in the peripheral tissue is given by

$$Y_t = \begin{cases} \frac{k_a}{k_e}\left(1 - e^{-k_e t}\right), & t \leq \frac{x_0}{k_a} \\ \frac{k_a}{k_e}\left(e^{\frac{k_e}{k_a}x_0} - 1\right) e^{-k_e t}, & t > \frac{x_0}{k_a} \end{cases} \qquad (2.5)$$

The two lines in (2.5) represent the absorption phase and the post-absorption phase respectively. The simple two-compartment model given by (2.5) is the one that we will focus on in the remaining part of the paper.

As the rate constants and the initial concentration in the central tissue are all assumed to be positive, we have that $e^{\frac{k_e}{k_a}x_0} > 1$ so that the drug concentration in the peripheral tissue, given by (2.5), is strictly positive except at time 0 where it is 0, $Y_0 = 0$ and $Y_t > 0$ for $t > 0$.

In Figure 2.2 the drug concentration in the peripheral tissue is plotted against time based on the simple two-compartment model given by (2.5).

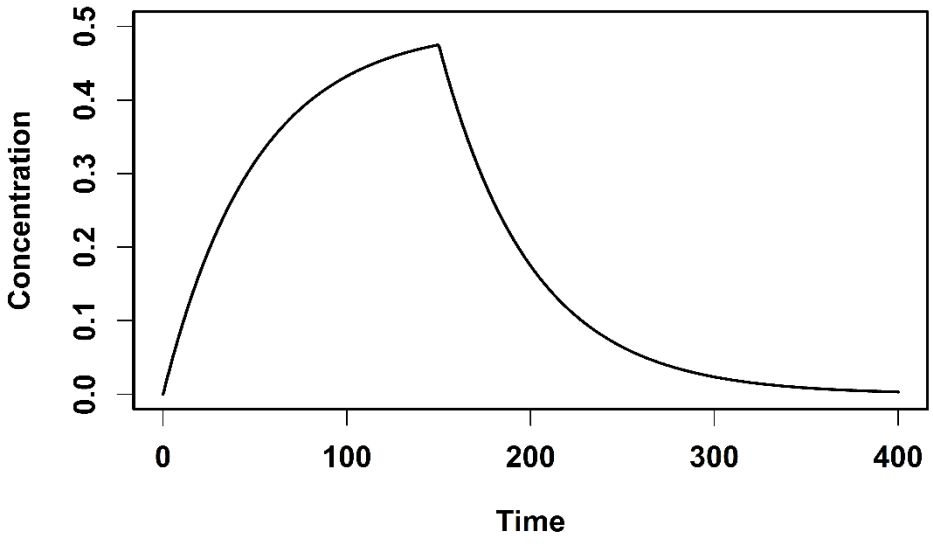

Figure 2.2: *The drug concentration in the peripheral tissue as a function of time. The unknown constants in (2.5) are* $k_a = 0.01$, $k_e = 0.02$ *and* $x_0 = 1.5$.

From the expression in (2.5) it follows that the drug concentration in the peripheral tissue increases as long as the drug is still present in the central tissue (the absorption phase) after which it decreases until all of the drug has left the peripheral tissue (the post-absorption phase).

At the time point corresponding to the maximal drug concentration in the peripheral tissue, there is a sharp turn in the drug concentration curve as illustrated in Figure 2.2. In mathematical terms this means that the drug concentration curve for the peripheral tissue is not smooth (continuous but not differentiable) in the time point $t = x_0/k_a$. Both before and after this time point the drug concentration curve corresponding to the peripheral tissue is smooth. Before the time point corresponding to the maximal drug concentration in the peripheral tissue, the curve

has an upward pointing arch whereas after that time point the arch points downwards. It is easily shown mathematically that the drug concentration curve is concave before the time point $t = x_0/k_a$ and convex after that time point.

3 Summary measures

In pharmacokinetics it is common to look at a number of summary measures for the drug concentration curve for the peripheral tissue. These are measures of the drug penetration from the central to the peripheral tissue. The time point corresponding to the maximal drug concentration in the peripheral tissue is denoted by t_{max} and in the simple two-compartment model it is given by

$$t_{max} = \frac{x_0}{k_a} \qquad (3.1)$$

The maximal drug concentration in the peripheral tissue is denoted by C_{max} and is given by the expression

$$C_{max} = \frac{k_a}{k_e} \cdot \left(1 - e^{-\frac{k_e}{k_a} x_0}\right) \qquad (3.2)$$

The area under the drug concentration curve (AUC) is obtained by integrating the expression in (2.5) over the time interval from zero to infinity. For this two-compartmental model the expression for the AUC is especially simple,

$$AUC = \frac{x_0}{k_e} \qquad (3.3)$$

Finally, the half-time $t_{1/2}$ that is the time it takes from a given time point after t_{max} until the drug concentration is halved, is given by this simple expression,

$$t_{1/2} = \frac{\log(2)}{k_e} \qquad (3.4)$$

It may be more convenient to use the summary measures t_{max}, AUC and $t_{1/2}$ directly in the expression for the drug concentration in the peripheral tissue given by (2.5), yielding

$$Y_t = \begin{cases} \frac{AUC}{t_{max}}\left(1 - e^{-\frac{\log(2)}{t_{1/2}} t}\right), & t \le t_{max} \\ \frac{AUC}{t_{max}}\left(e^{\frac{\log(2)}{t_{1/2}} t_{max}} - 1\right) e^{-\frac{\log(2)}{t_{1/2}} t}, & t > t_{max} \end{cases} \qquad (3.5)$$

Another option is to use the summary measures k_e, C_{max} and t_{max} in the expression given by (2.5), giving

$$Y_t = \begin{cases} \frac{C_{max}}{1 - e^{-k_e t_{max}}}\left(1 - e^{-k_e t}\right), & t \le t_{max} \\ C_{max} e^{-k_e (t - t_{max})}, & t > t_{max} \end{cases} \qquad (3.6)$$

The different ways of expressing the drug concentration in the peripheral tissue are useful when estimating specific summary measures, as it allows the user to achieve estimates and confidence intervals directly from a nonlinear regression procedure, see Section 5.

Time above MIC can also be calculated from (2.5). If MIC is equal to or above C_{max} then time above MIC (T>MIC) equals 0, so it is assumed that $0 < MIC < C_{max}$. The time points where the peripheral drug concentration is above MIC is an interval [a , b] where $0 < a \le t_{max}$ and $t_{max} \le b$ see Figure 3.1.

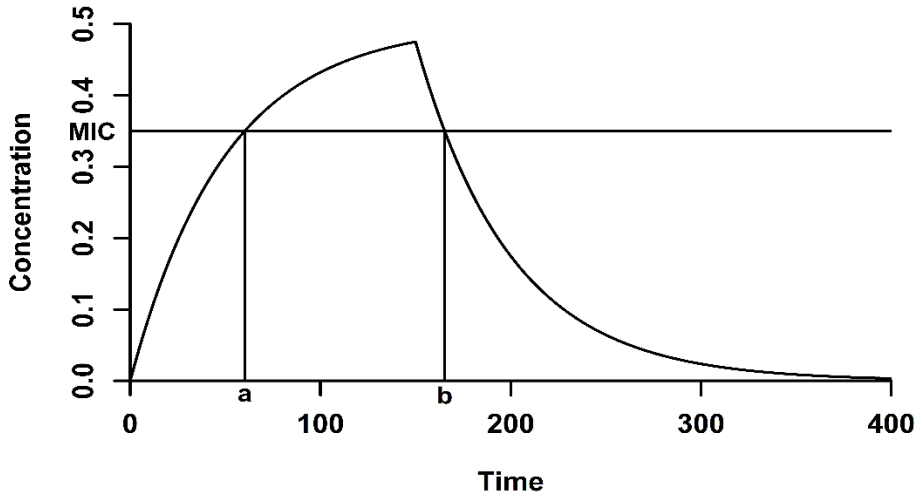

***Figure 3.1**: The drug concentration in the peripheral tissue as a function of time. The unknown constants in (2.5) are $k_a = 0.01$, $k_e = 0.02$ and $x_0 = 1.5$. The MIC-value of 0.35 is illustrated and T > MIC is b−a.*

The following expression for T>MIC is obtained:

$$\mathrm{T} > \mathrm{MIC} = b - a = \frac{1}{k_e}\log\left(\left(\frac{k_a}{k_e \cdot \mathrm{MIC}} - 1\right)\left(e^{\frac{k_e}{k_a}x_0} - 1\right)\right) \qquad (3.7)$$

The different summary measures are collected in Table 3.1.

***Table 3.1**: Fact box with the most important quantities and properties associated with the model.*

Concentration	$\begin{cases} \frac{k_a}{k_e}(1 - e^{-k_e t}), & t \le \frac{x_0}{k_a} \\ \frac{k_a}{k_e}\left(e^{\frac{k_e}{k_a}x_0} - 1\right)e^{-k_e t}, & t > \frac{x_0}{k_a} \end{cases}$
t_{max}	$\frac{x_0}{k_a}$
C_{max}	$\frac{k_a}{k_e} \cdot \left(1 - e^{-\frac{k_e}{k_a}x_0}\right)$
AUC	$\frac{x_0}{k_e}$
$t_{1/2}$	$\frac{\log(2)}{k_e}$
T > MIC	$\frac{1}{k_e}\log\left(\left(\frac{k_a}{k_e \cdot \mathrm{MIC}} - 1\right)\left(e^{\frac{k_e}{k_a}x_0} - 1\right)\right)$
Properties	1. Positive everywhere except at time 0. 2. Smooth everywhere except at t_{max} 3. Concave for $t \le t_{max}$. 4. Convex for $t > t_{max}$.

4 Estimation

The parameters k_a, k_e and x_0 in (2.5) or alternatively AUC, t_{max} and $t_{1/2}$ in (3.5), or k_e, t_{max} and C_{max} in (3.6) are typically estimated from drug concentration measurements in the peripheral tissue at different time points. At the $n+1$ time points t_0, t_1, ..., t_n we assume that we have $n+1$ observations of the drug concentration in the peripheral tissue denoted by

$$y_{t_0}, y_{t_1}, \dots, y_{t_n}, \text{ or in shorter notation } y_0, y_1, \dots, y_n \quad (4.1)$$

Any non-linear regression procedure can then be used to estimate the parameters from the concentration measurements. In Stata the function nl can be used, and in R a relevant function is nls. See Section 7 for example code.

Good starting values for the non-linear regression procedure are often essential. One possibility is to obtain rough estimates for AUC, t_{max} and k_e directly from the data and then calculate starting values for other parameters from these. A rough estimate of AUC can be obtained from the trapezoidal rule,

$$\text{AUC} = \sum_{i=1}^{n} \frac{y_i + y_{i-1}}{2}(t_i - t_{i-1}) \qquad (4.2)$$

A good starting value for t_{max} could simply be the time point where the observed drug concentration is largest,

$$t_{max} = t_j, \quad \text{where } j = \text{argmax}_i y_i \qquad (4.3)$$

An initial estimate of the rate constant k_e and thereby of the half-time $t_{1/2}$ according to (3.4) is the slope in a simple linear regression of the log-concentration in the peripheral tissue on time for time points larger than or equal to t_{max}, see (2.5),

$$k_e = \frac{\sum_{i=j}^{n}(\log(y_i) - \overline{\log(y)})(t_i - \bar{t})}{\sum_{i=j}^{n}(t_i - \bar{t})^2}, \text{ for } y_i > 0 \quad (4.4)$$

Here j is the index corresponding to the peak drug concentration value and $\overline{\log(y)}$ is the mean of the log-concentration measurements from t_{max} and onwards. Similarly, $\bar{t}$ is the mean of the time points larger than or equal to t_{max}.

See Section 7 for R-code that utilizes these starting values to build a self-starting nonlinear regression model.

When you have observations from several compartments and several individuals you need to take that into account in the estimation. Typically this is done by introducing random patient and compartment effects for the three parameters describing the non-linear drug concentration curve. In Stata this can be done using the function menl whereas in R the function nlme can be used. See Section 7 for example code.

5 An example

In[6] we studied the distribution of cisplatin in various abdominal tissues during and after intraperitoneal chemotherapy in a porcine model with varying temperature of the active drug (high and normal). For the first pig undergoing treatment at high temperature (HIPEC), the cisplatin concentrations in the liver at various time points are given in Table 5.1.

***Table 5.1**: Concentration measurements (µg/ml) in the liver at 12 time points (minutes) after intraperitoneal chemotherapy using cisplatin at high temperature administered at time 0.*

Time	Concentration
15	0.1492
45	0.7865
75	0.9683
105	1.0103
135	0.5502
165	0.2611
195	0.1585
225	0.0528
270	0.0171
330	0.0000
390	0.0000
450	0.0000

In Table 5.2 estimates of the parameters are given along with the starting values calculated from the expressions shown in the previous section. The parameter estimates are obtained using nls in R with the code for the self-starting nonlinear regression model presented in Section 7.

Table 5.2: Starting values and parameter estimates with profile likelihood 95% confidence intervals.

Parameter	AUC	t_{max}.	C_{max}.	k_a	k_e	x_0	$t_{1/2}$
			Starting values				
Start	117.2	105.0	1.010	0.0278	0.0249	2.918	27.83
			Estimates and 95%-CI				
Estimates	123.7	102.2	1.063	0.0249	0.0206	2.548	33.65
Lower	112.9	94.1	0.973	0.0219	0.0169	2.175	25.44
Upper	134.8	115.6	1.155	0.0293	0.0272	3.320	41.02

From Table 5.2 we observe that the parameter estimates are fairly close to the initial values. A clear advantage of estimating the parameters using the nonlinear regression model based on the proposed compartment model is that we also get confidence intervals. In this case the R function profileCI is used to obtain the confidence intervals, see[7]. Here we have used all the three ways of writing up the expression for the drug concentration in the peripheral tissue given in Section 2 and 3, that is equations (2.5), (3.5) and (3.6), in order to get confidence intervals for all parameters.

In Figure 5.1 the observed cisplatin concentration measurements are plotted against time with the fitted curve given by (2.5) superimposed as the full curve. The dashed curve corresponds to a two-compartment model with first order absorption and first order elimination.

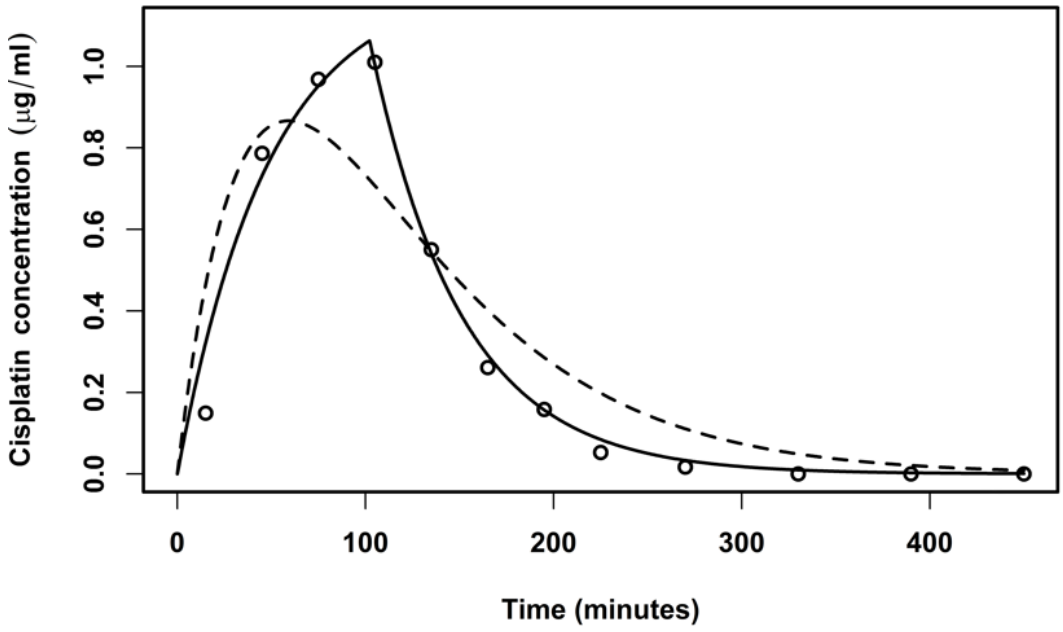

***Figure 5.1**: Observed and fitted cisplatin concentration in the liver as a function of time. The full curve corresponds to the model given by (2.5) and the dashed curve to a two-compartment model with first order absorption and elimination. Estimates for the unknown constants in (2.5) are $k_a = 0.0249$, $k_e = 0.0206$ and $x_0 = 2.548$.*

We see a much better description of the liver cisplatin concentration data using the model proposed in this paper compared to a purely first order kinetic model.

In[6] as well as in[8] and[9] we used the proposed compartment model in studies involving different cisplatin treatments (high and normal temperature of intraperitoneal chemotherapy and intravenous infusion) with several animals and tissues within animals. This was done using a non-linear mixed effects model with fixed effects of treatment and tissue and random effect of tissue within animal for each of the three constants in (2.5) using menl in Stata.

6 Discussion

The purpose of this paper is to present a simple model with appropriate properties for a lot of real life data, and which enables the researcher to easily fit the model to the data and present relevant quantities calculated from the model fit to the data. So when should you use the compartment model proposed in this paper? The proposed model should be used if your understanding of the physiological processes under study points in the direction of absorption of order zero and first order elimination. Also, if a plot of the drug concentration curves exhibits an increase with an upward pointing arch followed by a decrease with a downward pointing arch, then the model proposed in this paper may be appropriate.

Other authors have considered similar compartmental models. In chapter 1 in[10] a one-compartment model, with constant infusion over a pre-specified time interval [0,T], is briefly mentioned, and such a model is also considered in[11]. Although this model shares a lot of properties with the one presented in this paper, then the length of the absorption phase after a bolus administration is not known so this has to be estimated and the model proposed in this paper presents one way to do this.

Many possible extensions of the model proposed in this paper exist. In[12] the authors consider a similar two-compartment model with an additional rate constant associated with transfer of the drug from the peripheral tissue to the central tissue. No properties of this model were studied though. In[13] plasma amino acid data after the oral administration of protein supplements were analysed using the model proposed in this paper without assuming that the initial concentration in the peripheral tissue (y_0) was set to zero.

Many software packages exist that will enable the user to fit very complicated compartmental models to the data at hand. Two such software programs are NONMEM[14], and Monolix[15]. Even though you can readily determine whether the model fits the data well enough, it can be very hard to calculate relevant quantities such as time over MIC for very complicated models. Another problem is the issue of lack of identifiability, that is the situation where different combinations of parameters give exactly the same non-linear curve, see for example section 14.3 in[16]. This along with the black-box nature of many of the software packages have resulted in that compartment models are not used as much as they should by applied researchers (of course provided that the data are described adequately by a model), who would rather rely on crude methods that they understand.

7 Code

The following R-code sets up a self-starting non-linear regression model corresponding to the proposed compartment model, see[17]. The self-starting model is then used in a call to the function nls.

```
comp01.fun <- function(ka, ke, x0, X){
   ifelse(ka*X<x0,ka/ke,ka*exp(ke*x0/ka-ke*X)/ke)  -(ka/ke)*exp(-ke*X)

 }


 comp01.init <- function(mCall, LHS, data, ...)  {
     xy <- sortedXyData(mCall[["X"]], LHS, data)

     x <- xy[, "x"]

     y <- xy[, "y"]

     n <- length(y)

     auc <- 0.5*sum((y[-1]+y[-n])*(x[-1]-x[-n]))
     tmax <- x[which.max(y)]

     ke <- unname(abs(coef(lm(log(y[x>=tmax & y>0]) ~ x[x>=tmax & y>0]))[2]))

     x0 <- auc*ke

     ka <- x0/tmax


     start <- c(ka, ke, x0)

     names(start) <- mCall[c("ka", "ke", "x0")]
     start

 }
SScomp01 <- selfStart(comp01.fun, comp01.init, parameters=c("ka", "ke", "x0"))

nls(formula = conc ~ SScomp01(ka,ke,x0,time))
```

Code-box 7.1: *R selfStart function with ka, ke, and x0 as parameters.*

In Stata the function nl can be used to fit the non-linear regression model corresponding to the compartment model proposed in this paper.

```
nl (conc = ({ka=0.028}*time <= {x0=2.9})*({ka}/{ke=0.025})*(1 - exp({ke}*time)) + ///

({ka}*time > {x0})*({ka}/{ke})*(exp({ke}*{x0}/{ka}) - 1)*exp(-{ke}*time))
```

Code-box 7.2: *The non-linear regression in Stata with ka, ke, and x0 as parameters.*

When there are numerous subjects and several compartments measured within each subject, this can be taken into account by introducing random effects corresponding to each of the parameters describing the nonlinear drug concentration curve.

In Stata this could be achieved using the function menl, for example in the following way.

```
menl conc = ({ka:}*time <= {x0:})*({ka:}/{ke:})*(1 - exp(-{ke:}*time)) + ///

({ka:}*time > {x0:})*({ka:}/{ke:})*(exp({ke:}*{x0:}/{ka:}) - 1)* exp(-{ke:}*time), ///

define(ka: i.comp U4[id>comp]) ///

define(ke: i.comp U5[id>comp]) ///

define(x0: i.comp U6[id>comp]) ///

initial({ka:} 0.028 {ke:} 0.025 {x0:} 2.9)
```

Code-box 7.3: *Non-linear mixed effects regression in Stata using the proposed compartment model. Subjects are identified by the factor id and compartment by comp. Here there is a systematic effect of compartment and a random effect of compartment within subject for each parameter.*

In R the same analyses can be done using the function nlme in package nlme.

```
nlme(conc ~ SScomp01(ka, ke, x0, time),
       fixed = list(ka ~ comp, ke ~ comp, x0 ~ comp),
       random = list(idcomp = pdDiag(ka+ke+x0 ~ 1)),
       start = rep(c(0.028,0.025,2.9),rep(numcomp,3)), data = data)
```

Code-box 7.4: *Non-linear mixed effects regression in R using the proposed compartment model. Compartments are identified by the factor comp and compartments within subjects by the factor idcomp. Here there is a systematic effect of compartment and a random effect of compartment within subject for each parameter. The number of compartments is denoted numcomp and the data are in the data set called data.*

Conclusion

In this paper a two-compartment model with absorption of order zero and first order elimination is introduced to describe the drug concentration in a peripheral tissue after a bolus administration of the drug in a central tissue. Mathematical properties of the proposed model are explained so that a non-mathematical reader may relate to them. Relevant pharmacokinetic measures of drug penetration are derived and estimation of these are discussed. The model is applied to a real data set and Stata- and R-code to do the data analysis is presented.

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