

APPROACHES TO THE MULTIVARIATE RANDOM VARIABLES
ASSOCIATED WITH STOCHASTIC PROCESSES

A Dissertation

by

JIHNHEE YU

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

August 2003

Major Subject: Statistics

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ABSTRACT

Approaches to the Multivariate Random Variables Associated with Stochastic Processes. (August 2003)

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Stochastic compartment models are widely used in modeling processes for biological populations. The residence time has been especially useful in describing the system dynamics in the models. The direct calculation of the distribution for the residence time of stochastic multi-compartment models is very complicated even with a relatively simple model and often impossible to calculate directly. This dissertation presents an analytical method to obtain the moment generating function for stochastic multi-compartment models and describe the distribution of the residence times, especially systems with nonexponential lifetime distributions.

A common method for obtaining moments of the residence time is using the coefficient matrix, however it has a limitation in obtaining high order moments and moments for combined compartments in a system. In this dissertation, we first derive the bivariate moment generating function of the residence time distribution for stochastic two-compartment models with general lifetimes. It provides any order of moments and also enables us to approximate the density of the residence time using the saddlepoint approximation. The approximation method is applied to various situations including the approximation of the bivariate distribution of residence times in two-compartment models or approximations based on the truncated moment gen-

erating function.

Special attention is given to the distribution of the residence time for multi-compartment semi-Markov models. The cofactor rule and the analytic approach to the two-compartment model facilitate the derivation of the moment generating function. The properties from the embedded Markov chain are also used to extend the application of the approach.

This approach provides a complete specification of the residence time distribution based on the moment generating function and thus provides an easier calculation of high-order moments than the approach using the coefficient matrix. Applications to drug kinetics demonstrate the simplicity and usefulness of this approach.

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CHAPTER I

INTRODUCTION

1.1 Overview

Stochastic compartment models are widely used in fields such as ecology or pharmacokinetics to describe the change of a population and explain the basic kinetic structure of a process. Matis and Kiffe (2000) stated in their book, *Stochastic Population Models*, that stochastic compartment models are a useful tool “to analyze population data, to make statistical inference relating to population size, and ultimately to predict, or even help manage, population size”. Variables such as the residence time or the number of particles that describe the particle transfer between compartments have been of special interest. Generally, stochastic compartment models are based on the concept of homogeneous, well-stirred compartments (Matis and Wehrly, 1990) that result in Markov processes. The retention time for a single visit of a particle, therefore, has an exponential distribution. The mean residence time and other moments for stochastic compartment models have been developed and applied to pharmacokinetic problems. Matis, Wehrly and Metzler (1983) provide the theoretical framework to obtain the mean and variance of a residence time using the transfer coefficient matrix in the compartment model as a Markov process. However, a number of researchers in certain applications have questioned the use of homogeneous compartment models, thus stochastic semi-Markov models have also been developed. The semi-Markov model is based on an arbitrary retention time density function and does

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not necessarily have an exponential distribution (Matis and Wehrly, 1998). Certain non-exponential distributions of the retention time can be described by a collection of sub-compartments called pseudo-compartments (Matis and Wehrly, 1998). Matis and Wehrly (1985) dealt with a compartment model where the residence time has the gamma distribution using exponential pseudo-compartments in a semi-Markovian model.

The objective of the research outlined in this dissertation is to develop the distributional approach to the variables of interest that depend on the stochastic compartment models. We are interested in the structure of the bivariate distribution of the residence times for the two-compartment model that is often used to describe the relatively simple kinetics of a drug. We also expand the same distributional approach to more complicated models than the two-compartment model. Rather than the direct calculation of the exact density or distribution that is extremely complicated in such models, we adapt the flowgraph theory (Butler and Huzurbazar, 1997) that allows for the computation of the moment generating function of the waiting time in the model, which can be used to approximate the distribution or density.

We investigate the saddlepoint approximation as an important tool to obtain the distribution of the variables. The introduction of the saddlepoint approximation by Daniels (1954) has led to the saddlepoint approximation, various techniques of approximation. Given the moment generating function (MGF) or cumulant generating function (CGF) of a variable of interest, the saddlepoint approximation is used to approximate the density or tail probability of the variable. It is known that its error rate is smaller than that of the Edgeworth expansion. In the light of the better approximation we investigate an alternative saddlepoint approximation that can be applied to various situations. We also present the method that uses an approximated CGF with only a limited number of cumulants instead of the exact CGF.

1.2 Nature of the Problem

Residence times in stochastic compartment models have distributions that are mostly skewed to the right. When we use the ordinary saddlepoint approximation formula that is derived by using the normal distribution, the approximation to a right-skewed distribution is not as good as that to a symmetric distribution with a small sample. When the distributions are skewed to the right like the exponential or gamma distribution, the peak in the approximating density is more likely to shift to the middle than the true density, thus causing a considerable discrepancy near the origin of the distribution. However, other distributions or density functions than the normal can be used to form the formula in the Edgeworth expansion. It is known that the approximation of a right-skewed distribution is improved by using the gamma distribution (Jensen, 1995).

Approximating the density or distribution using the MGF or CGF has some advantages. In some cases, even if the explicit form of the density or distribution does not exist, we can obtain the specific form of the MGF. As an example, a distribution such as the noncentral χ^2 has a single termed MGF but the distribution is represented as an infinite sum (Coutis and Casella, 1999). In such a case the saddlepoint approximation can provide a relatively simple density expression with excellent precision. However, it is not always true that we can obtain the exact moment or cumulant generating function, and in such a case, we need to approximate the MGF itself using only part of the moments.

This research looks at the distribution of variables of two-compartment models that subsequently have a bivariate distribution. Using the method of the exponential tilting that provides the multivariate form of the saddlepoint approximation, we are interested in seeing the fairly precise approximation of the density or distribution in

such cases. Obtaining the saddlepoints for each bivariate point can be troublesome since there can be multiple solutions in some cases. If we cannot obtain the explicit form of the saddlepoint, it should be handled numerically.

How to calculate the distribution of the variables or at least the MGF for the approximation in multi-compartment model is another problem. The retention time of a particle at a single visit has the exponential distribution in Markov processes. However, the marginal distribution for an accumulated retention time, or simply the residence time of a particle before escaping a system, was not known when the model consists of multiple compartments. In order to obtain the distribution of the residence time in such a case, we have to take into account the relationship between compartments. It is not usually feasible to find out the exact distribution of the residence time for a multi-compartment model by considering every possible movement of a particle when there are more than two compartments. Interpreting a continuous Markov or semi-Markov process as a Markov chain is very helpful for this purpose because the theory for the particle movement in the Markov chain is well documented (e.g., Çinlar 1975).

1.3 Outline of the Dissertation

The dissertation is divided into five chapters. Chapter I provides an overview of the dissertation, and briefly suggests the nature of the problems. Chapter II explains general facts about stochastic compartment models, and presents a modification of a previous drug-kinetics model which demonstrates the general application of the stochastic compartment model to the population data. Chapter III discusses the topics related to the saddlepoint approximations. It provides an introductory discussion about its derivation, and deals with various situations in the application of that. Specifically, the modification of the saddlepoint approximation using the gamma dis-

tribution is discussed. We first see that the modified approximation is better for a gamma-like distribution. We also investigate how the saddlepoint approximation is affected when we use the approximated CGF based on the first few cumulants. In Chapter IV, we investigate the approximation of the distribution of residence times for the two-compartment model with non-exponential lifetime distributions. For that, we derive the moment generating function of the bivariate residence time distribution for the two-compartment model with general lifetimes. An analytically calculated MGF is used to approximate the density by the saddlepoint approximation. Using the MGF of the residence time for each compartment, the marginal distribution of the residence time for each compartment is also approximated. The exact form of the distribution is compared with the approximation. In Chapter V, we extend the distributional approach to the residence time for multi-compartment semi-Markov models combining the cofactor rule for a single destination and the analytic approach to the two-compartment model. Applications to drug kinetics are presented. We conclude the dissertation with suggestions for future research in Chapter VI. The problems and limitations of the approach in previous chapters are discussed. We project the possible application of the approach to the survival analysis by introducing several papers in this subject.

CHAPTER II

A NON-MARKOVIAN COMPARTMENT MODEL APPROACH FOR
DESCRIBING CALCIUM KINETICS**2.1 Introduction**

Stochastic compartment models have been used in drug kinetics to study the time course of drugs including the absorption, distribution, metabolism, and excretion of drugs. A common assumption underlying compartment models is homogeneous and well-stirred compartments, resulting in a Markov process model with an exponentially distributed retention time for a single compartment. However, this assumption can be inappropriate in cases such as describing the body using a few compartments or representing a poorly stirred compartment. The semi-Markov process is a useful tool to describe these nonhomogeneous compartments. It is a generic term to describe a continuous time process where the retention time, the time between transitions for a single visit, does not necessarily have an exponential distribution.

Matis and Wehrly (1998) provide a theoretical frame work representing a semi-Markov (or non-Markov) model as an expanded Markov model using the concept of a phase-type (PH) distribution. A PH distribution is defined as the distribution of the time until absorption in a finite-state Markov process with n transient states and one absorbing state, and any nondegenerate distribution of retention time may be expressed as a PH distribution (Matis and Wehrly, 1998). Therefore, a non-exponential distribution of the retention time for a compartment can be described by a collection of sub-compartments called pseudo-compartments. For certain incompletely specified models, a linearly connected compartment system can generate observed time lags (Jacquez and Simon, 2002). However, in using PH distributions, a compartment

system described by the pseudo-compartments does not necessarily have a physiological interpretation but is rather a mathematical device to generate the desired retention time distribution.

The residence time variable, a quantity that describes the dynamics of a particle transfer between compartments, is defined as the accumulated waiting time (retention time) for the particle during its several visits to a compartment before exiting to the system exterior. The residence time provides a useful insight into the kinetics of a drug because it is easier to interpret than the transfer rate. Thus, often the residence time distribution based on the estimated transfer rates is useful to describe the kinetics of a drug or provide a comparison between different drugs or subjects.

Matis and Wehrly (1985) provide stochastic formulations to obtain moments of the residence times in compartment models in a couple of ways. First, the moments of the retention time for a particle during a single visit could be calculated using its approximated PH distribution that is usually expressed as a sum of exponentials. Moments for the residence time of a compartment are obtained by using the PH distribution and the distribution of the number of visits of a particle to the compartment. A PH distribution might not have a unique expression, and Johnson and Taaffe (1990) found approximating PH distributions that match the first three moments of a distribution. However, Jacquez (1985) shows that the general form of pdfs generated by linear compartmental systems is expressed as the sum-of-exponentials with coefficients that consist of polynomials of the time variable, and this implies that the summation of a few exponential terms may not be appropriate to express the distribution of the retention time for some non-homogeneous compartments.

The other way to obtain moments of the residence time is by using the coefficient matrix that is composed of transfer rates, or specifically, the probability intensity coefficients (Matis and Wehrly, 1985). This method is relatively easy to implement

compared with the approach of using the approximated distributions directly. The method will be explained in Chapter V in detail.

In this chapter, we explain general facts about compartment models, and illustrate PH distribution to describe the calcium kinetics models. First, we show the existing models to explain calcium kinetics. Then, we investigate an updated model by adding an additional compartment to an existing model. It shows how the PH distribution can be formulated and demonstrates the effect of pseudo-compartments on the change of the distribution of the residence time.

2.2 Definitions and Methodologies

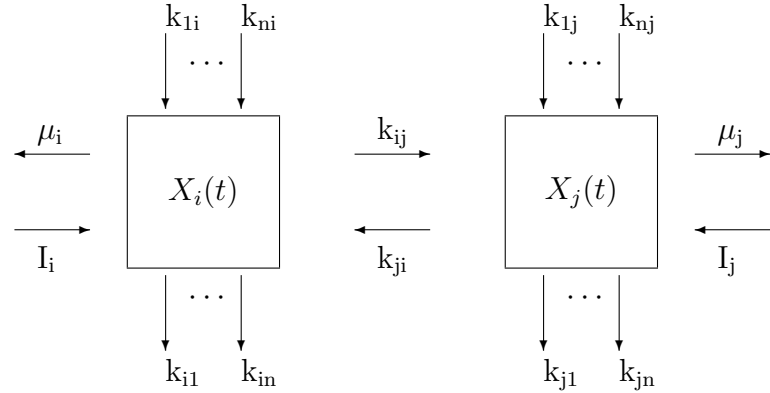


Figure 1: The general structure of a multi-compartment model.

Figure 1 shows the general structure of an n -dimensional death-migration process. $X_i(t)$ denotes the population size of particles, k_{ij} is the transfer rate from compartment i to j , I_i the immigration rate to compartment i , and μ_i the death rate of compartment i . The model satisfies following.

1. $k_{ij} \geq 0$ for every i and j .
2. No state is absorbing.

3. All states are reachable.
4. The system is open, which means that $\mu_i > 0$ for some i .

In the linear death-migration model (Matis and Kiffe, 2000, page 119), the conditional probabilities of possible unit changes from t to $t + \Delta t$ are

$$\begin{aligned}
 \text{Prob}\{X_i \text{ will increase by 1 due to immigration}\} &= I_i \Delta t, \\
 \text{Prob}\{X_i \text{ will decrease by 1 due to death}\} &= \mu_i X_i \Delta t, \\
 \text{Prob}\{X_j \text{ will increased by 1 and } X_i \text{ will decrease by 1 due to migration}\} \\
 &= k_{ij} X_i \Delta t, \text{ for } i \neq j.
 \end{aligned} \tag{2.1}$$

In the linear death-migration model, it is known that the retention time has an exponential distribution, and consequently the process is Markov. The deterministic differential equation to describe the model is

$$\begin{aligned}
 \dot{X}_1(t) &= k_{11}X_1(t) + k_{21}X_2(t) + \dots + k_{n1}X_n(t) + I_1 \\
 &\vdots \\
 \dot{X}_n(t) &= k_{1n}X_1(t) + \dots + k_{n-1,n}X_{n-1}(t) + k_{nn}X_n(t) + I_n,
 \end{aligned} \tag{2.2}$$

where $k_{ii} = -(\mu_i + \sum_{j=1, j \neq i}^n k_{ij})$. A standard approach to find the stochastic solution for the probability is using the Kolmogorov differential equations. As a simple example, let us look at a two-compartment model that consists of two population variable $X(t)$ and $Y(t)$. Let $P_{xy}(t)$ be $P\{X(t) = x, Y(t) = y\}$. The joint probability distribution in the increment of time, Δt can be expresses as

$$\text{Prob}\{\Delta X(t) = i, \Delta Y(t) = j | X(t), Y(t)\} = f_{ij}(X, Y) \Delta t,$$

where i and j are not both 0. The Kolmogorov differential equation (Matis and Kiffe,

2000, page 115) is then

$$\frac{dP_{xy}}{dt} = -P_{xy} \sum_{i,j} f_{ij}(x,y) + \sum_{i,j} P_{x-i,y-j} f_{i,j}(x-i,y-j). \quad (2.3)$$

The summation does not include the case of $i = j = 0$. Under an assumption that the population is changed only by a unit at a time, the possible changes are

$$f_{1,0} = I_1, \quad f_{-1,1} = k_{21}X_1, \quad f_{0,-1} = \mu_2X_2.$$

Then, using (2.3)

$$\begin{aligned} \dot{P}_{xy}(t) &= -(I_1 + k_{21}x + \mu_2y)P_{x,y}(t) + I_1P_{x-1,y}(t) \\ &\quad + k_{21}(x+1)P_{x+1,y-1}(t) + \mu_2(y+1)P_{x,y+1}(t). \end{aligned}$$

Matis and Kiffe (2000) or Bailey (1964) give a more detailed illustration about the derivation of the differential equation. The corresponding partial differential equation (pde) for the moment generating function of (2.3) is

$$\frac{\partial M(\theta_1, \theta_2, t)}{\partial t} = \sum_{i,j} (e^{i\theta_1 + j\theta_2} - 1) f_{ij} \left(\frac{\partial}{\partial \theta_1}, \frac{\partial}{\partial \theta_2} \right) M(\theta_1, \theta_2, t), \quad (2.4)$$

where j and k are not both 0 (Bailey, 1964). In the linear death-migration model with immigrations, one can show that $(X(t), Y(t))$ has a bivariate Poisson distribution (Matis and Kiffe, 2000, page 117). The solution for a pde for the MGF may be intractable in many cases. In such cases, we can replace the Taylor expansion of the moment generating function into (2.4), and solve the differential equation for the moments.

The parameter estimation is based on the solutions from (2.2) or (2.4). Parameters, transfer rates, are implicitly defined by the other parameters in the model. The parameters are estimated using the method of non-linear least squares or the Gauss-Newton algorithm (Allen, 1998). The Gauss-Newton algorithm provides the

asymptotic standard errors of the estimates, too. The least squares method is to minimize the residual sum of squares. It does not provide the standard error for the parameters, however it is known that the asymptotic standard error can be calculated using an analogous way to the linear models based on the assumption that the parameters are consistent and asymptotically normally distributed. Many specialized software programs have been developed for least squares parameter estimation (Matis et al., 1996a). KINETICA (Allen and Matis, 1990) is used for the parameter estimation in this research. The program also provides confidence interval for the coefficients, and the mean residence time, the estimated function of time for the population, and the approximated residence time distribution.

2.3 Model Illustration of the Calcium Kinetics

The scientific effort to explain better the calcium clearance data in plasma has continued, and it was found that stochastic non-Markovian models describe such data well (e.g., Matis and Wehrly 1998, Weiss et al. 1994). Weiss et al. (1994) assumed that the retention time in the bone compartment could be modeled as a mixture of exponential distributions, and this assumption gives a well-fitting overall model as shown in Section 2.3.1. However their model showed a lack of fit in the tail of data; the lack of fit can be shown more strikingly with the log-scaled data. A model based on non-Markovian ideas given by Matis and Wehrly (1998) produced improved fitting of tail values, while keeping a good fitting for the initial part of the data. They also suggested that further research implementing the underlying non-Markovian methodology might find still better fitting models. We expand this non-Markovian approach to provide a better description of the tail part of the data. We also discuss some results and implications of the changed model.

2.3.1 The previous models

The model by Weiss et al. (1994) illustrated in Figure 2 utilizes two linear bone “binding sites” so that the phase type (PH) distribution of bone is assumed to be a mixture of exponential distributions.

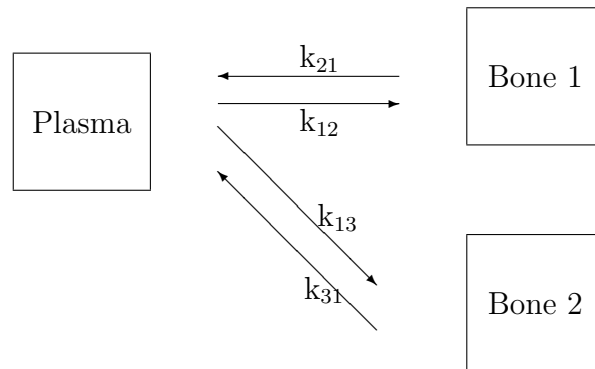


Figure 2: The model of Weiss et al. that uses two compartments for the bone structure.

The resulting equation of the fitted curve of calcium data in plasma from KINETICA is

$$C(t) = 351.39e^{-5.835t} + 197.20e^{-0.375t} + 145.31e^{-0.0144t}.$$

Another model by Matis and Wehrly (1998), say the M&W model, is illustrated in Figure 3. To obtain a non-exponential phase-type (PH) distribution in a compartment, the authors developed an equivalent model using pseudo-compartments based on Markov processes. This model also uses two binding sites of bone, but assumes that one site is nonlinear, and can be modeled using four compartments. Compartments 1 and 2 represent plasma and tissue or “shallow” bone site, respectively. The other compartments compose the third compartment, the deep peripheral compartment

which mainly represents bone with slow exchange. Those multiple sub-compartments in the deep compartment, also called pseudo-compartments, have no physiological implication but are only used to describe a long residence time in the deep compartment. The sequence of compartments generates a nonexponential retention time distribution in the deep compartment and thus describes a nonhomogeneous, poorly stirred compartment.

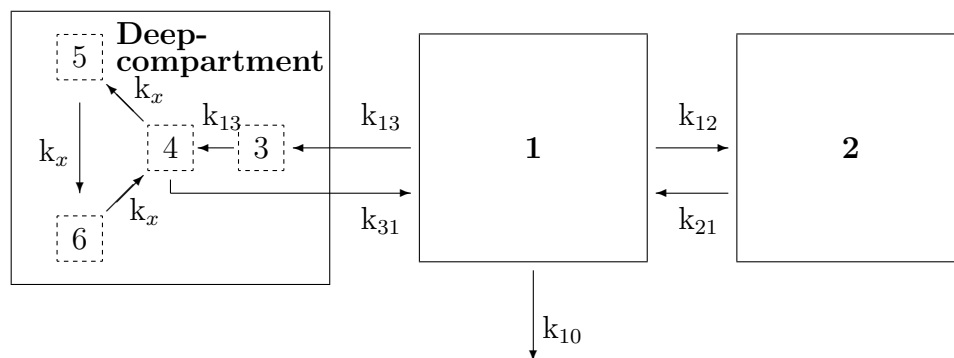


Figure 3: The model illustration of Matis and Wehrly.

The equation of the fitted curve for the M&W model is

$$\begin{aligned}
 C(t) = & 356.16e^{-7.105t} + 68.50e^{-0.0078t} \\
 & + e^{-0.5659t} \{44.98 \sin(0.2852t) + 187.85 \cos(0.2852t)\} \\
 & + e^{-0.0380t} \{32.85 \sin(0.0162t) + 110.26 \cos(0.0162t)\}.
 \end{aligned}$$

Figure 4 shows the data and the fitted curve. Its mean square error is 4.9364. The log-transformed data can be used to focus more on the “tail” of the fitted line. Comparing with the model of Weiss et al., Figure 5 shows, on a log scale, a better fit in the tail part.

Using a mixture of Erlang distributions is one approach to get a longer tail. To compare the retention time distribution for two models, let the retention time distribution of bone 1 and bone 2 be $f_1(t)$, and $f_2(t)$ respectively. Then the distribution

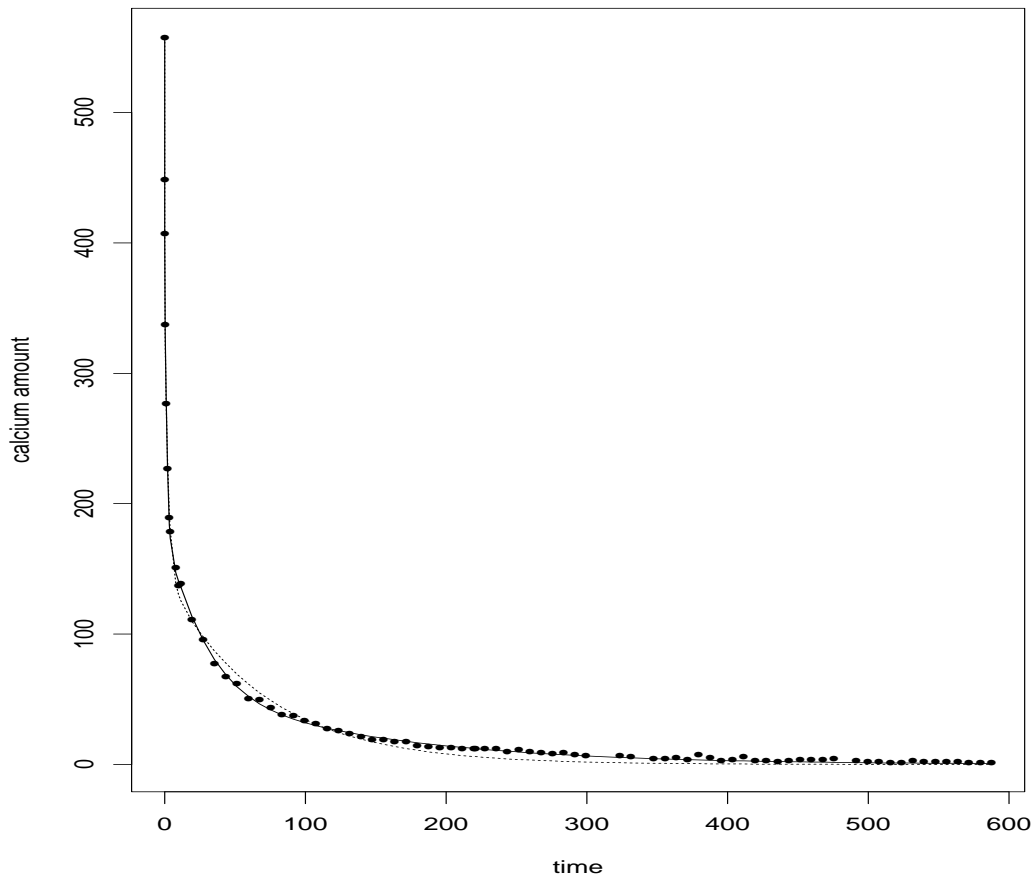


Figure 4: Plasma clearance data and the fitted lines of Weiss et al. (the dotted line) and the M&W model (the solid line).

of the retention time for the total bone site, $\psi(t)$ can be expressed as

$$\psi(t) = \theta f_1(t) + (1 - \theta) f_2(t), \quad (2.5)$$

where θ is the probability of a particle to go to bone 1. In Figure 2, the retention time for each bone has an exponential distribution. Using the estimated parameters, we can find that the pdf of the retention time for the bone site is

$$\psi(t) = 2.61e^{-3.00t} + 0.021e^{-0.16t}.$$

The approximated retention time distribution from KINETICA for M&W model,

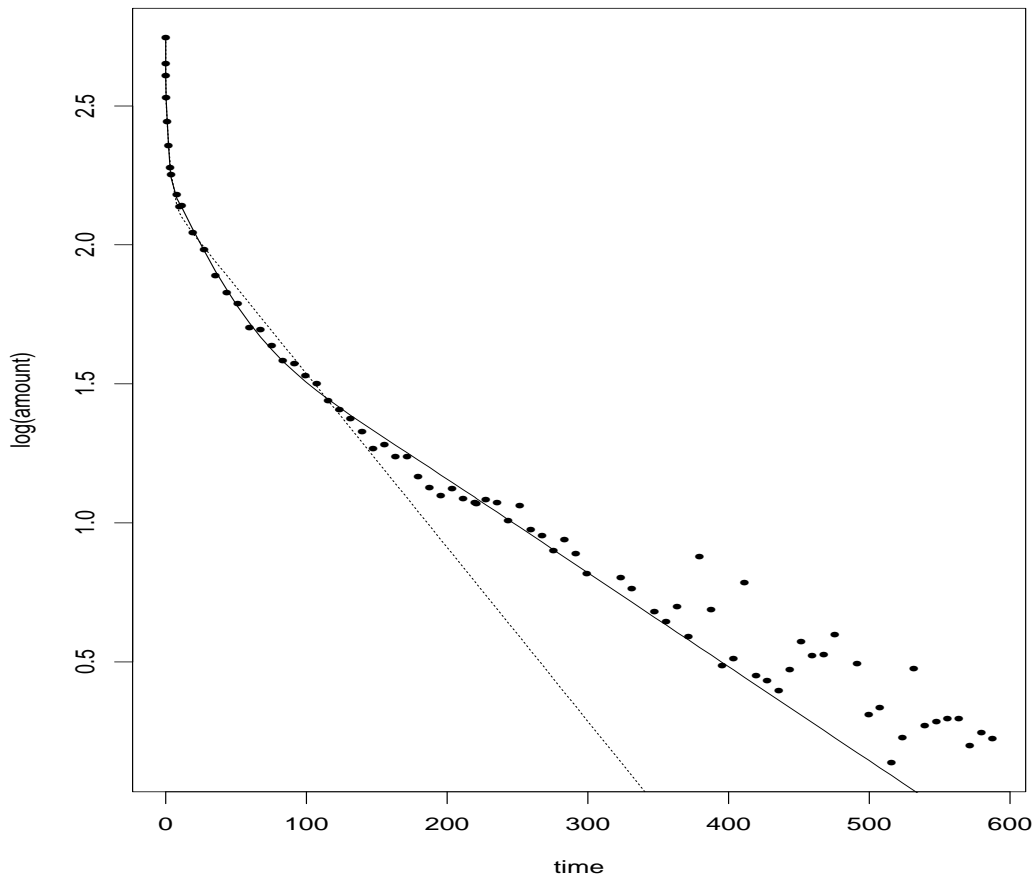


Figure 5: Log scaled plasma clearance data and the fitted lines of Weiss et al. (the dotted line) and the M&W model (the solid line).

however, is

$$\psi(t) = 3.27e^{-3.74t} + 0.124f_2(t),$$

where $f_2(t)$ is

$$f_2(t) = 1151.3e^{-0.44t} - 1151.3e^{-0.44t} + 0.00412e^{-0.02t} - 0.005e^{-0.04t}.$$

Figure 6 compares the densities of retention times of the two models in the log scale. The peak of the PH distribution of the retention time in the bone in M&W model is shifted to the right, whereas the model of two-compartment bone structure is

monotonically decreasing with rapid initial decay. Hence there exists a large initial qualitative difference between the two distributions. This clearly shows that the M&W model has a longer retention time than Weiss'. The mean and variance of the

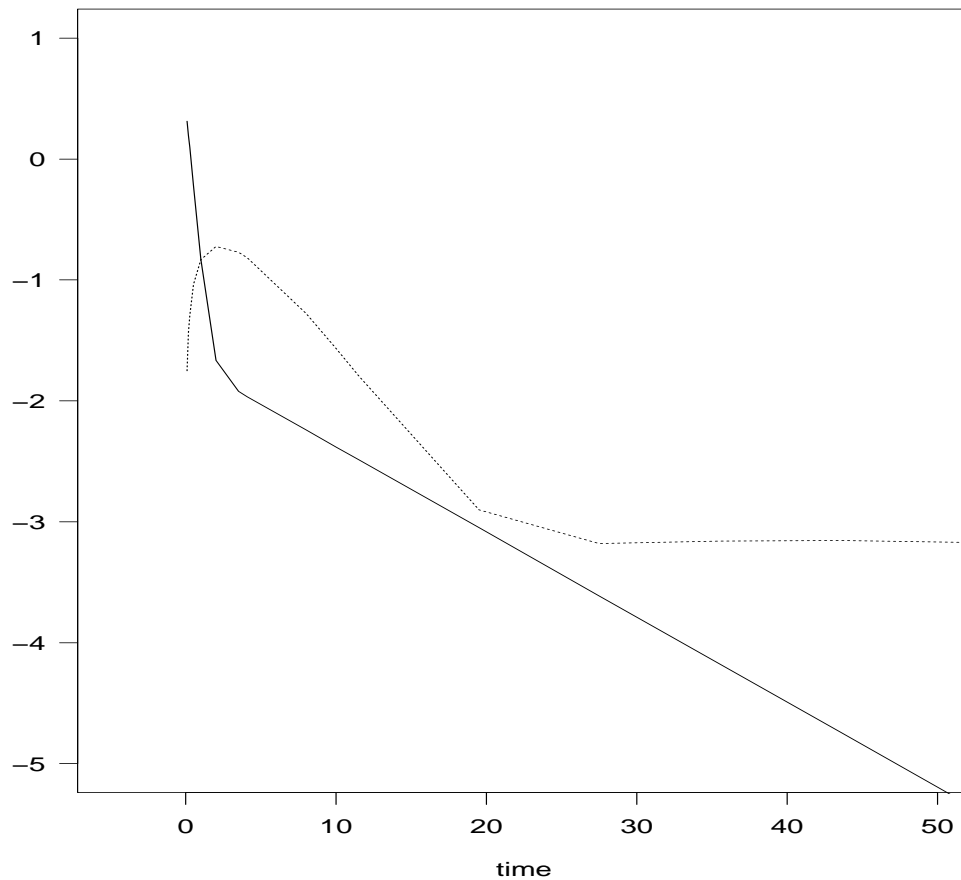


Figure 6: Logarithms of retention time densities (Y-axis) for the fitted plasma clearance data. The dotted line is the M&W model, and the solid line Weiss et al. model.

retention time can be calculated based on the estimated retention time density. The resulting mean retention times in the M&W model are 16.469 in plasma, and 83.276 in bone, which are longer than the ones given by the Weiss et al. model, which are 15.344 and only 50.230 respectively.

2.4 An Updated Model

We still observe a lack of fit in the tail part with the log-scaled data in the M&W model. This suggests that adding more compartments may improve the fit in the tail part of the distribution. Figure 7 shows a possible new model, say an updated model, in which a fifth pseudo-compartment is added to the “deep” bone site of the previous model. This implements the idea that calcium particles may stay even longer in deep bone site. The same flow rate k_x is used for this new compartment to avoid

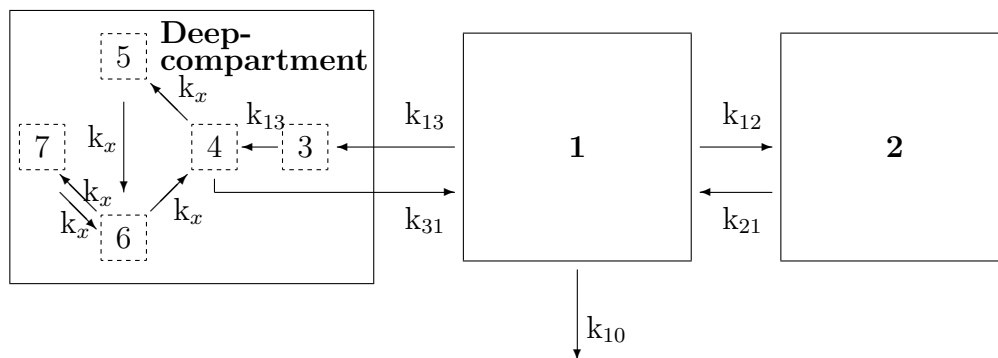


Figure 7: The illustration of the updated model.

possible multicollinearity (Matis et al., 1996a) caused by adding new parameters. The rate parameter estimates for this new model are $k_{01} = 0.0581$, $k_{21} = 3.7774$, $k_{12} = 3.1638$, $k_x = 0.03353$, and $k_{31} = 0.4212$, with $k_{13} = k_x + k_{31} = 0.4547$. The fitted curve of the calcium data using KINETICA is

$$\begin{aligned}
 C(t) = & 357.214e^{-7.183t} \\
 & + \{45.5643 \sin(0.291t) + 187.650 \cos(0.291t)\}e^{-0.5781t} \\
 & + 144.9453e^{-0.033t} + 43.509e^{-0.006t} - 8.322e^{-0.0861t}.
 \end{aligned}$$

This line gives an excellent fit as shown in Figure 8, with the mean square error 4.9326, that indicates a bit better fit than that of M&W model. The mean retention

times of a calcium particle in plasma and bone site for this model are 17.212 and 105.950, respectively. The distribution of time for a single visit of a calcium particle

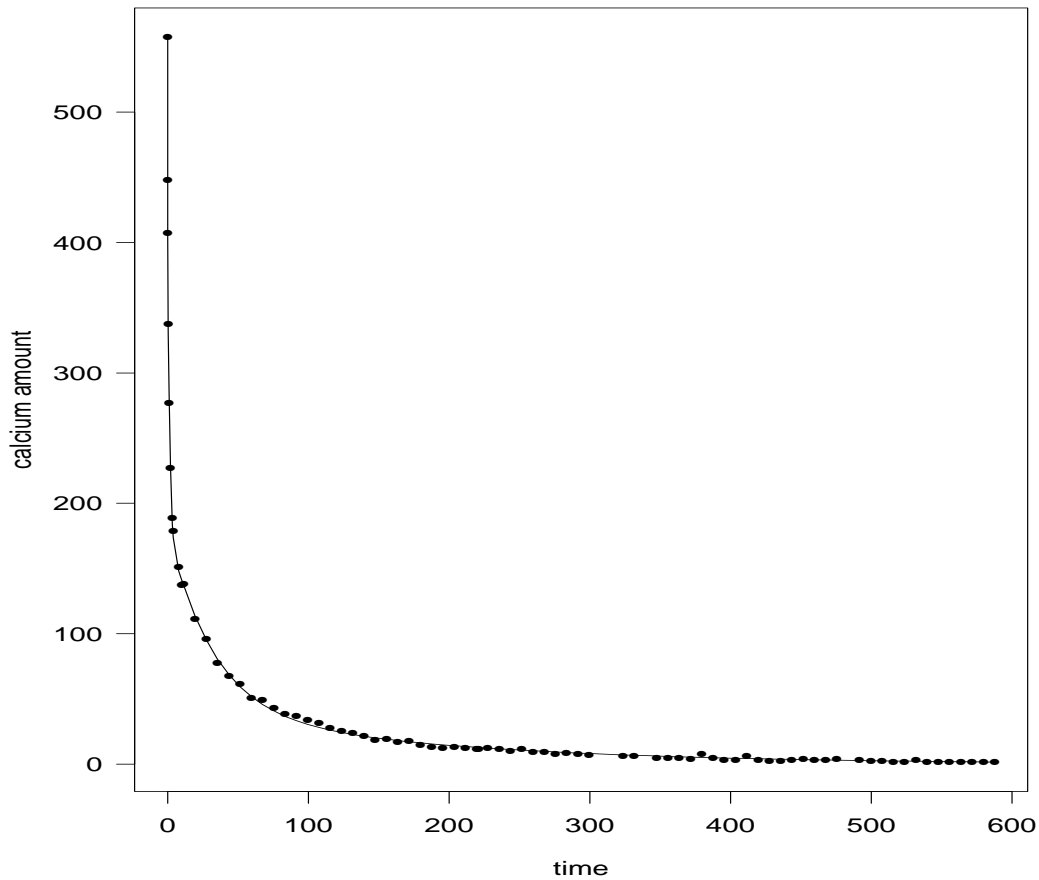


Figure 8: Plasma clearance data and fitted curve with the updated model.

to the long tailed binding site is found to be,

$$f_2(t) = -948.08e^{-0.4547t} + 2086.00e^{-0.4545t} \\ - 0.00191e^{-0.0891t} + 0.00107e^{-0.01169t}.$$

The estimated retention time distribution of the total exchangeable bone is hence

$$\psi(t) = 0.87434 \cdot 3.1638e^{-3.1638t} + 0.12566f_2(t).$$

Figure 9 shows the log-scaled distributions for the retention time for the deep compartment in the bone site for the updated model along with that of the model by Matis and Wehrly. Clearly the qualitative features are very similar, that is, both start from zero initially and reach peaks afterwards at about the same elapsed time. The mean and variance of this distribution are 1.71471 and 163.79548, respectively,

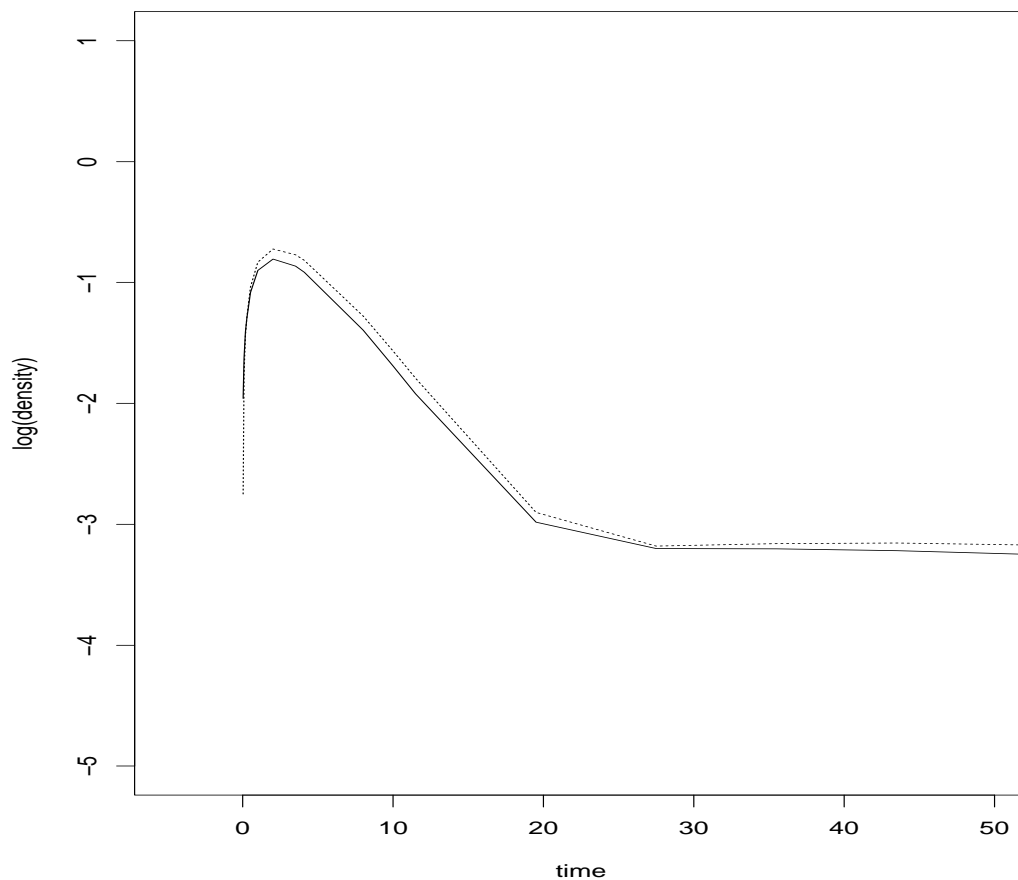


Figure 9: Comparison of retention time densities for the fitted plasma clearance data of the M&W model (the dotted line) and the updated model (the solid line).

whereas those of the M&W model are 1.413 and 76.04, so the mean of the updated model is a little larger than the one of the alternative model. Even though the similar retention time distributions, the smaller k_{10} and the bigger k_{13} in the updated model

leads to the longer mean retention time than that of the M&W model.

2.5 Discussion

The previous non-Markovian model by Matis and Wehrly, and the updated model both give good fittings to the data, but the latter gives a smaller mean square error (MSE) and a longer mean residence time. However, the difference of MSE between two models is very small. In fact MSE=4.9326 of the updated model shows only 0.08% decrease comparing with MSE=4.9364 of M&W model. It seems not a noticeable improvement of the curve in the tail part of the data, but this is because the initial values are much larger than the tail values. The residuals for the initial values are larger than the latter ones, hence the latter residuals contribute only small part of the MSE. Though the MSE's are close, the mean retention times of the updated model are much larger than those from the M&W model.

To explain these longer retention times, consider the fitted values on a log scale, as shown in Figure 10. The differences in the residuals on a log scale are very distinct, and demonstrate the large improvement of the fitted curve. The M&W model shows the lack of fit in the tail after $t=300$, whereas the updated model describes log scaled data well, yielding the longer mean retention time. The MSE of this log scaled line of M&W model is 0.02479, whereas the updated model shows very small $MSE = 0.00651$, which is only 26.3% of the other, indicating that the improvement after adding one more compartment is remarkable with log scaled data.

One way to compare models visually is using residual plots of the log-scaled fitted line, which is shown in Figure 11. It shows that the updated model is more likely to give smaller residuals than any other models, so we can verify that the fitted line absorbs more information from data. Especially the residuals of the updated model are still centered around 0 even after $t=400$, while the residuals of M&W model are

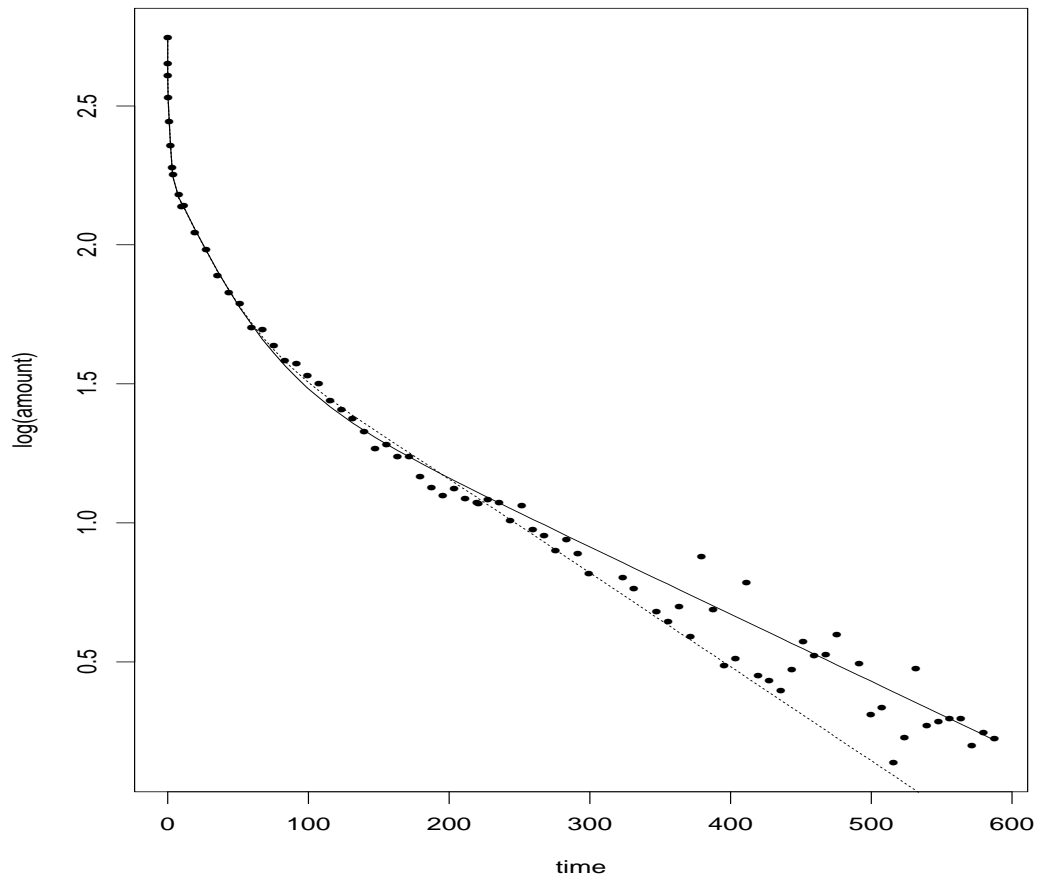


Figure 10: Log scaled plasma clearance data and fitted curve with the M&W model (the dotted line) and the updated model (the solid line).

slowly increasing.

It is expected that the variability would be a function of the amount of calcium amount. The residual plot in Figure 12 shows that variability increases with increasing amount of calcium. It seems reasonable to assume that the variance would be a function of the calcium amount. One method of incorporating this heteroscedasticity of the variance in the data is fitting with the weighted data. The variance might be proportional to the magnitude of the response. Specifically, if the observations are radioactive counts, then the dependent variable is approximately Poisson

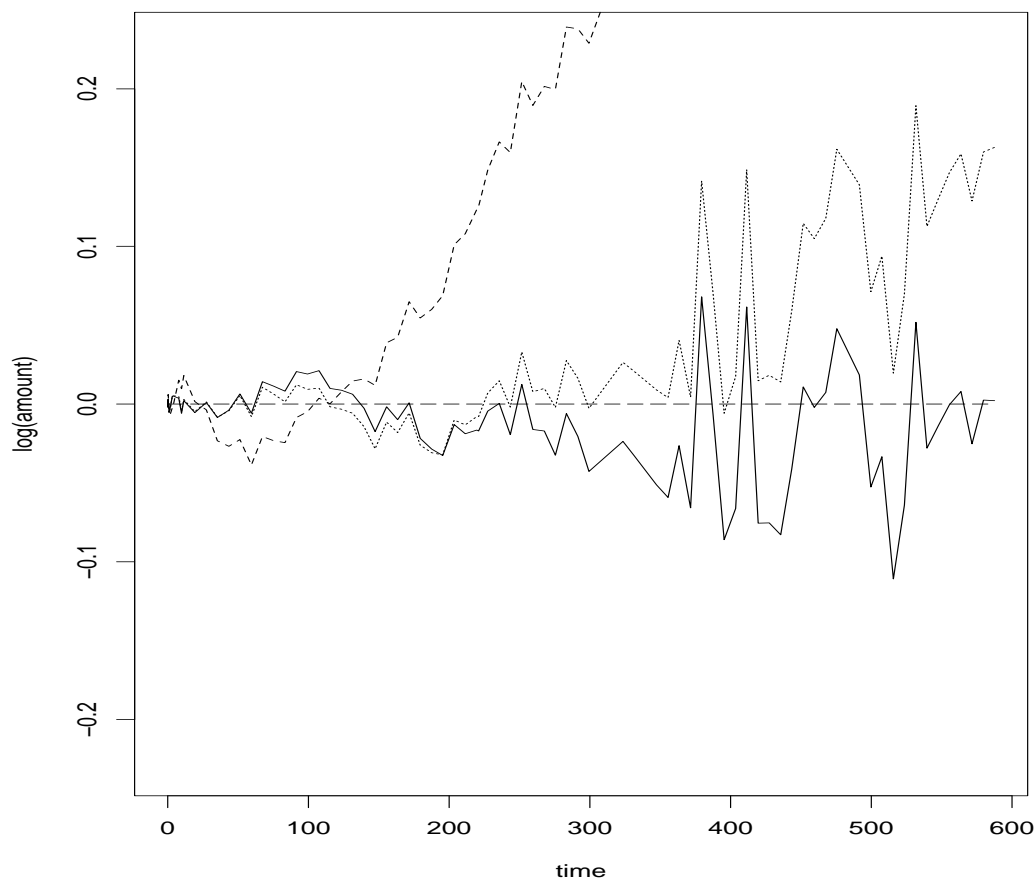


Figure 11: Natural log scaled residual plots with the models. The solid line is the updated model, the dotted line, the M&W model, and the dashed line, Weiss et al. model.

distributed (Thakur, 1988). As a result, the weight should be proportional to the inverse of the magnitude of the original response. KINETICA also provides the way to obtain the weighted nonlinear least square equations. Log-scaled fitted lines are shown in Figure 13. Both fitted lines for M&W model and the updated model show some improvements comparing with log-scaled fitted lines with the original data.

The resulting mean retention times are 18.126 in plasma, 91.829 in bone under M&W model, and 16.020 in plasma, 99.889 in bone under the updated model. The

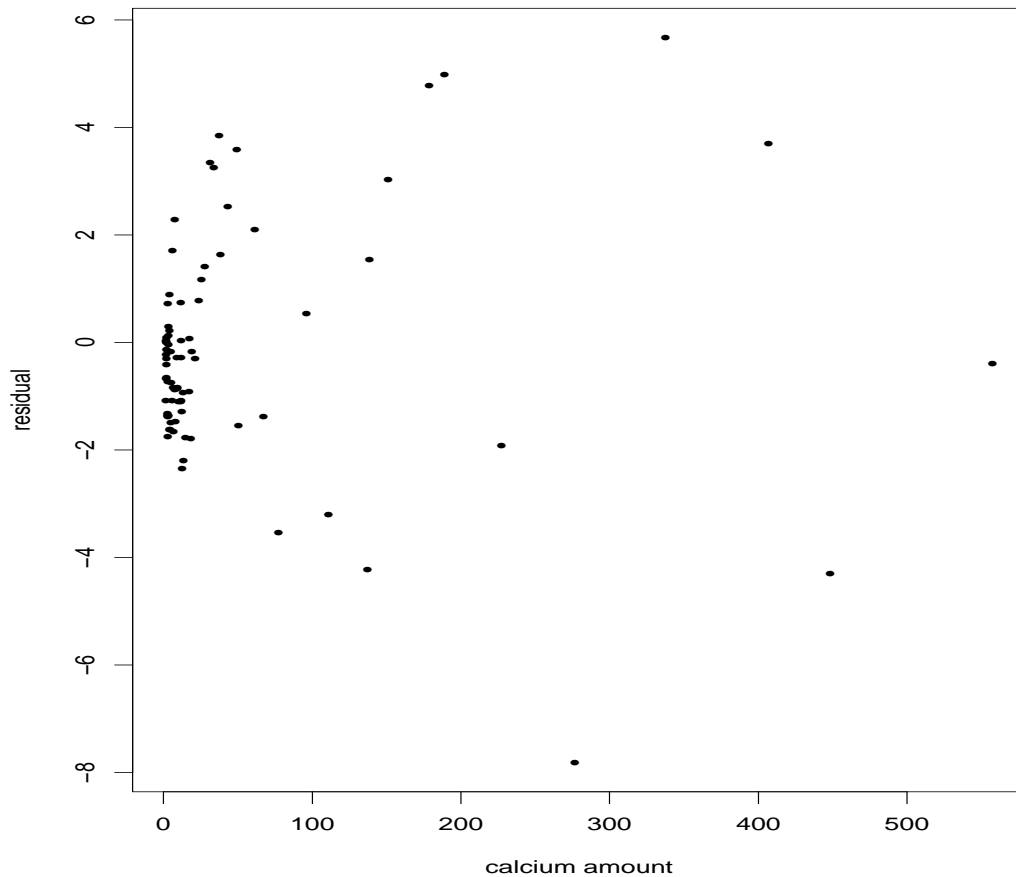


Figure 12: Residual plot of the updated model.

mean retention time of plasma for the updated model is a little smaller than that for the model by Matis and Wehrly, whereas that of bone for the updated model is still longer than for the M&W model. Figure 14 shows the residual plot of the updated model and M&W model with the weighted data. The residuals from both models show very similar patterns and magnitudes. The MSE of the M&W model is 0.1606, that of the updated model 0.1595. A 0.69% decrease of MSE was made by the updated model, and which is the larger improvement than the 0.08% reduction in the MSE between the models with the original data.

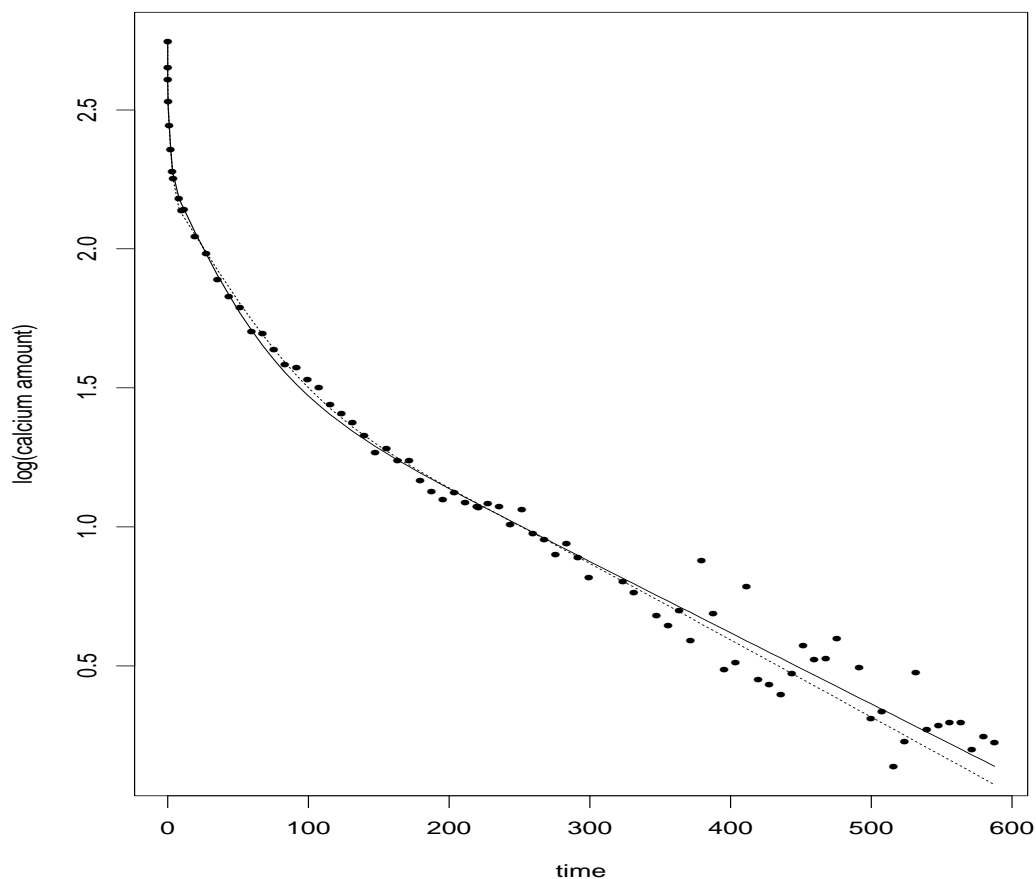


Figure 13: Log-scaled plasma clearance data and weighted fitted curve with M&W model (the dotted line) and the updated model (the solid line).

We investigated the calcium clearance using the models with nonexponential retention times. The results of the updated model are very encouraging. We could see that a non-Markovian model is a powerful theoretical tool to provide a better model for pharmacokinetics. The concept of the non-Markovian model overcomes the drawbacks of the ordinary multi-compartment Markov model, and this suggests that it can be a very useful concept in general.

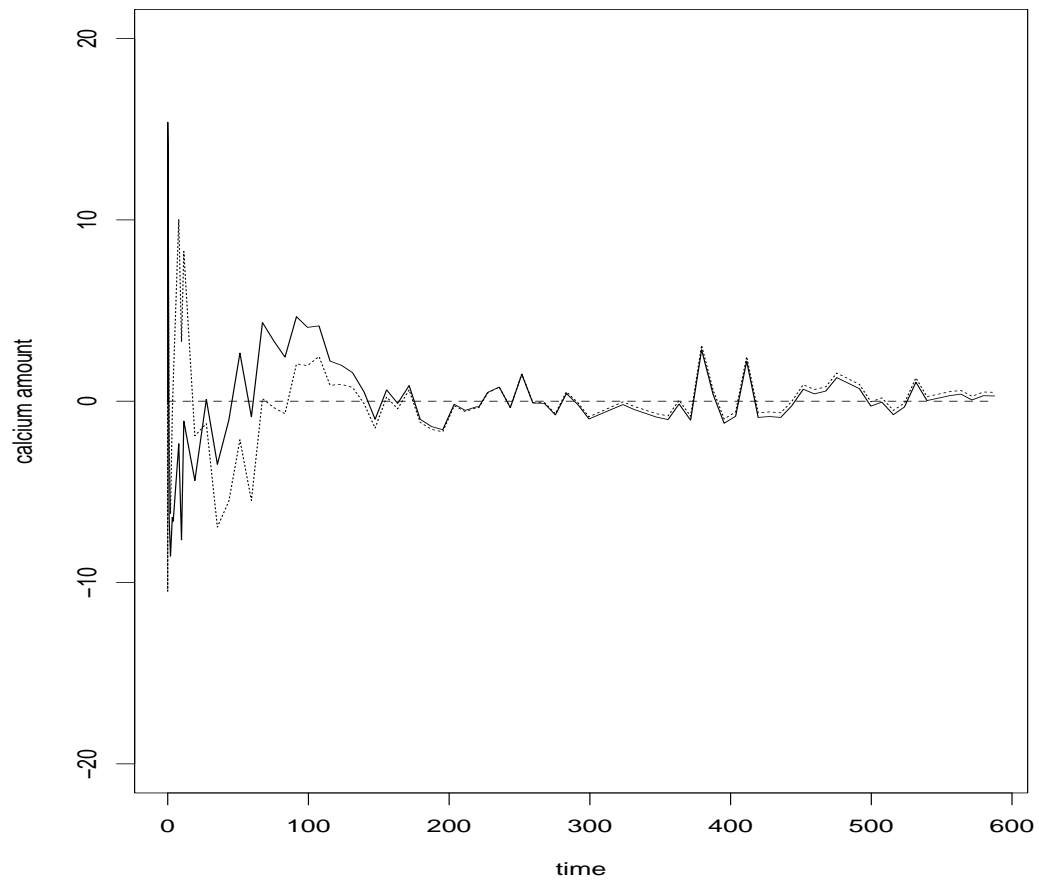


Figure 14: Residual plot of weighted data with updated model (the solid line) and M&W model (the dotted line).

CHAPTER III

THE SADDLEPOINT APPROXIMATIONS, STOCHASTIC PROCESSES
PERSPECTIVE**3.1 Introduction**

Saddlepoint approximations or saddlepoint expansions are powerful tools for approximating the density or tail probability using the cumulant generating function (CGF). The accuracy of these approximations is well-addressed in various papers and books (e.g., Barndorff-Nielsen and Cox 1989, Coutis and Casella 1999, Jensen 1995, Renshaw 1998). The approximation is well-known for providing good approximations to very small tail probabilities or densities because the error rate for the approximation is directly proportional to the magnitude of the density or distribution function.

The saddlepoint approximation is based on the concept that the moment generation function can be converted to the density or distribution function using the Fourier inversion formula. The inversion formula is integrated through a saddlepoint using the method of steepest descents (Daniels, 1954), and that method names the approximation. Unlike the Edgeworth approximation, the saddlepoint approximation always provides positive densities and has an error that depends on the magnitude of the approximation, so-called relative error that assures a more accurate approximation, especially in the tail part of densities or probabilities.

Because of the fact that the density or the distribution can be approximated once we have the moment generating function, the saddlepoint approximation has been applied in various areas including stochastic processes. As an example, Daniels obtains the approximation of the distribution for the population size in non-linear birth processes using the saddlepoint approximation. In the non-linear birth process,

when the population size is large, an explicit formula for the required probabilities is not available (Daniels, 1982). The probability is obtained using the Laplace transformation for the population size at a certain time and the saddlepoint approximation. It shows that the saddlepoint approximation is remarkably accurate for calculating probabilities for the birth process when it is compared with some tractable true probabilities.

Butler and Huzurbazar (1997) show that the moment generating function of the waiting time of stochastic network models can be easily calculated by Mason's rule, which is equivalent to the cofactor rule that Butler discussed in the later paper (2000). They calculate the Bayesian predictive distribution of the waiting time for the stochastic network model, where many times the exact densities are very complicated with even a simple model. Using the moment generating function, the density of the waiting time corresponding to the generated posterior parameter based on the data can be easily calculated by the saddlepoint approximation. This methodology was applied to the survival analysis for the pathology of various disease such as AIDS, dementia and cancer.

Even though the full moment generating functions are not available, the saddlepoint approximation can be applied with only the part of cumulants that are tractable. Matis et al. (2003) suggest approximating the distribution of the population using the saddlepoint approximation based on the so-called truncated CGF in the logistic growth model with birth and death in ecology. It is not known how to solve the partial differential equation to obtain the exact solution for the moment generating function or the cumulant generating function for the stochastic approach to such models. The exact probability of the equilibrium distribution of the population could be obtained using a recurrence relationship, but because the calculation of the equilibrium distribution is done iteratively, it is computationally intensive. They

suggest approximating the CGF using the first three cumulants, since the formula of the saddlepoint approximation can be expressed in a simple analytical form. The first three cumulants can be obtained by solving the partial differential equation of the cumulants using the moment closure approach (see Matis and Kiffe 2000, or Renshaw 2000). Because most population data and other ecological measurements have markedly skewed distributions (Matis et al., 2003), the saddlepoint approximation is clearly more accurate than the normal approximation that uses only the mean and variance. Renshaw (2000) also showed a similar approach to a bivariate stochastic compartment model that includes migrations. With all third and lower order cumulants known in a two-compartment birth-death-immigration-migration process, the cumulant generating function is approximated by optimizing fourth-order cumulants iteratively in order that the volume under the approximated density is one. The probabilities based on the method show markedly better accuracy compared to the normal based approximation (Renshaw, 2000).

First in this chapter, we explain the general approach to the saddlepoint approximation for the density. Then we investigate the saddlepoint approximation using the truncated CGFs, and assess the relative errors in that approach. Alternative approximation using other than a normal distribution in the univariate case is also discussed. And finally, we develop an experimental saddlepoint approximation in the bivariate distribution case, which is based on the exponential distribution. We also investigate the conditions for obtaining saddlepoints in each case.

3.2 Derivation of the Saddlepoint Approximation

Daniels obtained the saddlepoint approximation formula of the sample mean, say T , in the univariate case using the method of steepest descents. It starts from

Fourier inversion formula,

$$f(t) = \frac{n}{2\pi i} \int_{\tau-\infty}^{\tau+\infty} \exp[n(K(\theta) - \theta t)] d\theta. \quad (3.1)$$

By letting $\hat{\theta}$ be the real root of $K'(\theta) - t = 0$, which is also called the saddlepoint, we can express (3.1) as

$$f(t) = \frac{n}{2\pi} \exp \left[n \{ K(\hat{\theta}) - \hat{\theta} t \} \right] \int_{\mathcal{P}} \exp \{ -n \gamma(t) \} d\theta,$$

where $\gamma(t) = K(\hat{\theta}) - \hat{\theta} t - [K(\theta) - \theta t]$, and \mathcal{P} denotes the deformed path that passes through the saddlepoint, which satisfies $\text{Im}(K(\theta) - \theta t)$ as constant (Field, 1990). This new path assures that $\gamma(t)$ is a real number since the imaginary part is constant. The integrand becomes negligible outside the immediate neighborhood of the saddlepoints. The saddlepoint approximation is obtained by the asymptotic expansion of integrand (Field, 1990).

A tilting approach (Jensen, 1995) provides an alternative method to obtain the saddlepoint approximation. A detailed explanation is provided by Jensen (1995). The argument below is an excerpt of it. For a random vector $X \in R^d$, the Laplace transform $\varphi(\theta)$ for $\theta \in R^d$ is defined as

$$\varphi(\theta) = E [\exp(\theta \cdot X)] = \int \exp(\theta \cdot X(\omega)) P(dw),$$

where \cdot denotes the inner product of vector in R^d . The domain of the transformation is $\Theta = \{\theta \in R^d : \varphi(\theta) < \infty\}$. Derivatives of all orders of $\varphi(\theta)$ are

$$\frac{\partial^k \varphi(\theta)}{\partial \theta_1^{k_1} \dots \partial \theta_d^{k_d}} = E \{ X_1^{k_1} \dots X_d^{k_d} \exp(\theta \cdot X) \} \quad (3.2)$$

where $k_i \geq 0$ and $k_1 + \dots + k_d = k$.

If we are interested in the density of a statistic T with respect to a measure m , we can write the distribution by the tilting known as the Esscher tilting as

$$\frac{dP_T}{dm}(t) = \frac{dP_T}{dQ_T}(t) \frac{dQ_T}{dm}(t) = \left\{ \frac{dQ_T}{dP_T}(t) \right\}^{-1} \frac{dQ_T}{dm}(t), \quad (3.3)$$

where Q should be taken such that t is a central point of the distribution. Q is called a tilted measure. The exponential family generated by X and P consists of the probability measure P_θ , $\theta \in \Theta$, given by

$$\frac{dP_\theta}{dP}(\omega) = \varphi(\theta)^{-1} \exp(\theta \cdot X(\omega)). \quad (3.4)$$

Let the first d_1 coordinates $X_i^{(1)}$ of X_i be continuous variables and the remaining $d_2 = d - d_1$ coordinates $X_i^{(2)}$ be discrete variables. Let f_n be the density of $\bar{X} = (X_1 + \dots + X_n)/n$. The direct application of (3.3) and (3.4) gives

$$f_n(x) = \varphi(\theta)^n \exp(-n\theta \cdot x) n^{(d_1-d_2)/2} f_{n,\theta}(0) \quad (3.5)$$

for any $\theta \in \Theta$, where $f_{n,\theta}$ is $n^{d_2/2}$ times the density of $\{\sqrt{n}(\bar{X}^{(1)} - x^{(1)}, \bar{X}^{(2)} - x^{(2)})\}$ under the measure P_θ (Jensen, 1995).

In (3.5), the term $f_{n,\theta}(0)$ is approximated by the Edgeworth expansion. The Edgeworth expansion is

$$f_n(x) = g(x) \left\{ 1 + \frac{1}{\sqrt{n}} \frac{\lambda_3}{6} H_3^d(x; \{\kappa\}) \right\} + O(n^{-1}), \quad (3.6)$$

where $g(x)$ is the density of $N(0, \Sigma(\theta))$, H 's are the Hermite polynomials,

$$H_m^d(x; \{\kappa\}) = \sum_{i_1, \dots, i_m=1}^d \kappa_{m, (i_1, \dots, i_m)} H_{m, (i_1, \dots, i_m)}(x; \kappa_2),$$

and

$$H_{m, (i_1, \dots, i_m)}^d(x; \kappa_2) = (-1)^m \phi(x; \kappa_2)^{-1} \frac{\partial^m}{\partial y_{i_1} \dots \partial y_{i_m}} \phi(x; \kappa_2),$$

where $\phi(x)$ is the density of the normal distribution in R^d with mean 0 and covariance matrix k_2 that can be obtained by letting θ equal to 0 in (3.2). Using (3.6) and (3.5), we obtain

$$f_n(x) = \varphi(\theta)^n \exp(-n\theta \cdot x) n^{(d_1-d_2)/2} g(0; \Sigma(\theta)) \left\{ 1 + \frac{1}{6\sqrt{n}} H_3^d(x; \kappa) + O(n^{-1}) \right\}. \quad (3.7)$$

For $x = 0$, all coefficients corresponding to odd powers disappear because $H_r(0) = 0$ when r is odd so that the equation has the order of $O(n^{-1})$. The leading term is the saddlepoint approximation. θ is chosen to satisfy

$$K'(\hat{\theta}) = x, \quad (3.8)$$

and this is sensible because $\hat{\theta}$ becomes the maximum likelihood estimate of (3.5). This has the same formula as Daniels' for the univariate distribution and also easily provides the approximation formula for the multivariate distribution without additional difficulties.

In the univariate case, Daniels proves that under general conditions (3.8) has a single real root $\hat{\theta}$ in the legitimate support $(-c_1, c_2)$ for every value of x such that $0 < F(x) < 1$, and that $K'' > 0$, where c_1 and c_2 are positive real numbers and $F(x)$ is the CDF of X . Suppose that a variable X has a support (a, b) , that is not infinite, then it can be shown that for every $\xi \in (a, b)$ there is a unique simple root $\hat{\theta}$ of $K'(\theta) = \xi$, and $K'(\theta)$ increases continuously from $\xi = a$ to $\xi = b$ (Daniels, 1954). This implies that the saddlepoint given by (3.8) must fall in the set of θ where $K'(\theta)$ strictly increases, and this is an important fact to find the appropriate boundary for θ . A difficulty exists when the support of X is infinite but $c_2 < \infty$. It may be possible that $K'(\theta) \not\rightarrow \infty$ when $\theta \rightarrow \infty$. In such a case, (3.8) may have no real root though the distribution may extend to ∞ . We will discuss the boundary of θ for different situations in later sections.

Let us consider the noncentral chi-squared density as an example of the saddlepoint approximation (Coutis and Casella, 1999). The density has no closed form and is expressed as

$$f(x) = \sum_{k=0}^{\infty} \frac{x^{p/2+k-1} e^{-x/2}}{\Gamma(p/2 + k) 2^{p/2+k}} \frac{\lambda^k e^{-\lambda}}{k!},$$

where p is the degrees of freedom and λ is the noncentrality parameter. The density is an infinite mixture of central chi-squared densities with the Poisson probability weights. Figure 15 compares the approximation of the density with the true density, and shows the excellent approximation of the density. The relative errors are slightly over 2% close to origin, and consistently less than 2 % in the tail part.

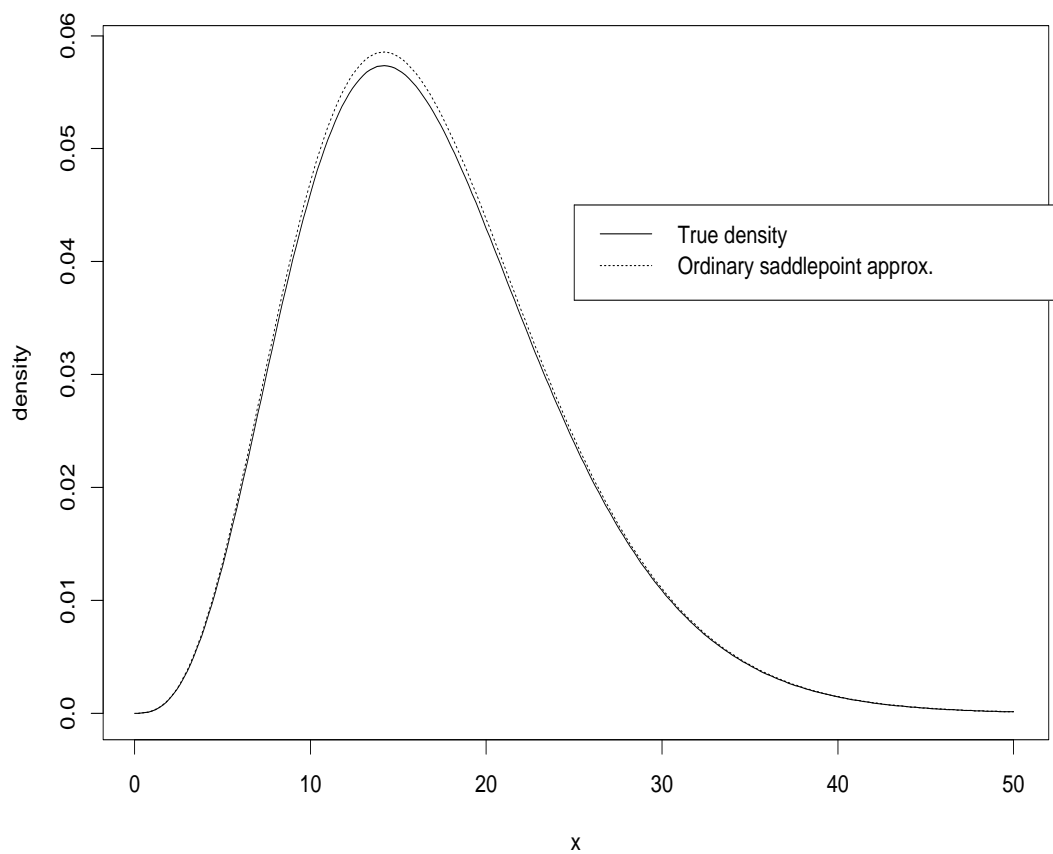


Figure 15: The comparison of the true density and saddlepoint approximation of the noncentral Chi-Square density (df=7, noncentral parameter=5).

3.3 Saddlepoint Approximation Using the Gamma Distribution

Suppose that $F(x)$ and $G(x)$ are two univariate distribution functions with characteristic functions $\chi(\theta)$ and $\xi(\theta)$ and their r th cumulants are β_r and γ_r , respectively. Using the Taylor expansion of $\log \frac{\chi(\theta)}{\xi(\theta)}$ (Field, 1990), we can express $\chi(\theta)$ as

$$\chi(\theta) = \exp \left\{ \sum_{r=1}^{\infty} (\beta_r - \gamma_r) \frac{(i\theta)^r}{r!} \right\} \xi(\theta). \quad (3.9)$$

Using the Taylor expansion of the exponential function and Fourier inversion of (3.9) together, we can show that

$$F(x) = \exp \left\{ \sum_{r=1}^{\infty} (\beta_r - \gamma_r) \frac{(-D)^r}{r!} \right\} G(x), \quad (3.10)$$

where D denotes the differential operator. Letting $G(x)$ be a normal distribution function and differentiating both sides of (3.10), we can obtain the well-known Edgeworth expansion. In the previous section, the saddlepoint approximation based on the normal distribution is derived by replacing $f_{n,\theta}$ in (3.5) by the Edgeworth expansion. However, the relationship between two distribution functions in (3.10) illustrates the fact that the normal distribution in the Edgeworth expansion can be replaced by the other distributions. In fact, it is known that an asymptotically equivalent saddlepoint approximation can be obtained using the centered gamma distribution (Jensen, 1995).

Let $X \sim \text{Gamma}(\alpha, \beta)$, Then X has the density

$$g(x) = \frac{1}{\Gamma(\alpha)\beta^\alpha} x^{\alpha-1} e^{-x/\beta},$$

and MGF

$$\left[\frac{1}{1 - \beta t} \right]^\alpha.$$

Then, the density of standardized variable $Y = \sqrt{n}(\bar{x} - \alpha\beta)$ is

$$g_Y(y) = \frac{1}{\Gamma(n\alpha)(\beta/n)^{n\alpha}} \left(\frac{y}{\sqrt{n}} + \alpha\beta\right)^{n\alpha-1} \exp\left\{\frac{-y/\sqrt{n} - \alpha\beta}{\beta/n}\right\} \frac{1}{\sqrt{n}}.$$

Therefore,

$$g_Y(0) = \frac{1}{\Gamma(n\alpha)(\beta/n)^{n\alpha}} (\alpha\beta)^{n\alpha-1} \exp\{-n\alpha\} \frac{1}{\sqrt{n}}$$

By plugging this into $f_{n,\theta}(0)$ in (3.5), we obtain the approximation of the distribution of the sample mean,

$$f_n(x) = (\varphi(\hat{\theta}))^n \exp(-n\hat{\theta}x) \sqrt{n} \frac{\nu_n^{\nu_n-1/2} \exp(-\nu_n)}{\sigma_n(\hat{\theta})\Gamma(\nu_n)}, \quad (3.11)$$

where $\hat{\theta}$ satisfies (3.8), ν_n corresponds to the shape parameter of a sum of variables, and $\sigma_n(\theta)$ is the standard deviation in the approximation,

$$\sigma_n(\hat{\theta}) = K''(\theta), \text{ and } \nu_n = \frac{4nK''(\theta)^{3/2}}{K^{(3)}(\theta)^2}.$$

When the value of X increases, $\hat{\theta}$ also moves toward its upper bound. We can show that the gamma-like distribution, (3.11) converges to the gamma density when $\hat{\theta}$ increases to its upper bound (Jensen, 1995). The argument below is a sketch of Jensen's proof in (1995) of this fact. Let us assume a density $q(\cdot)$ and there exist constants $\alpha > 0, \tau > 0$ and A such that

$$q(x) = Ax^{\alpha-1}l(x) \exp(-\tau x),$$

where X has a positive support and $l(x)$ is slowly varying at zero. This is termed a gamma-like distribution. Similarly to (3.4), the exponential family generated by $q(x)$ is

$$q_\theta(x) = \varphi(\theta)^{-1} \exp(\theta x) q(x). \quad (3.12)$$

Then, τ becomes the upper bound of θ in (3.12). The standardized tilted density, $Y = \frac{X - \mu(\theta)}{\sigma(\theta)}$ is then

$$q_\theta(y) = \sigma(\theta)\varphi(\theta)^{-1} \exp\{\theta(\sigma(\theta)y + \mu(\theta))q(\sigma(\theta)y + \mu(\theta))\},$$

where $\mu(\theta) = E(X)$ and $\sigma(\theta) = \text{Var}(X)$.

Now, let $Z = \frac{X - \mu_\theta}{\sigma_\theta}$ where $\mu_\theta = \sigma_\theta = (\tau - \theta)^{-1}$. We then obtain the tilted density,

$$g_\theta(z) = \frac{A\sigma_\theta^\alpha l(\mu_\theta)}{\varphi(\theta)} (z + 1)^{\alpha-1} \frac{l\{(z + 1)/(\tau - \theta)\}}{l\{1/\tau - \theta\}} \exp\{-(z + 1)\}.$$

For $\theta \rightarrow \tau$, $\frac{l\{(z+1)/(\tau-\theta)\}}{l\{1/\tau-\theta\}}$ converges to 1, and $\frac{A\sigma_\theta^\alpha l(\mu_\theta)}{\varphi(\theta)} \rightarrow \Gamma(\alpha)^{-1}$ using the fact that $g_\theta(z)$ is a density and the dominated convergence theorem. Therefore

$$g_\theta \rightarrow \Gamma(\alpha)^{-1}(z + 1)^{\alpha-1} \exp\{-(z + 1)\}, \text{ when } \theta \rightarrow \tau \text{ for } z > -1. \quad (3.13)$$

Letting $X = \sigma_\theta Z + \mu_\theta$ and using (3.13), we can show that the distribution of X has converged to the gamma(α, σ_θ) distribution, which means that $q_\theta(y)$ is the density of the standardized gamma distribution. Since the exponentially tilted gamma-like densities converge to the gamma density when $\theta \rightarrow \tau$, a gamma approximation to (3.5) seems natural.

The noncentral χ^2 distribution is presented in Figure 16. The relative differences for the gamma-based saddlepoint approximation are less than 1 % through the support as shown in Figure 17. This provides an example where the gamma-based approximation shows better accuracy to a right-skewed distribution than the normal-based approximation.

Figure 18 shows quite accurate approximations for both of the normal-based and gamma-based saddlepoint approximations to the Poisson distribution. Figure 19 shows the relative differences from both approximations. Both approximations start with considerably big relative errors near the origin, but relative error decreases

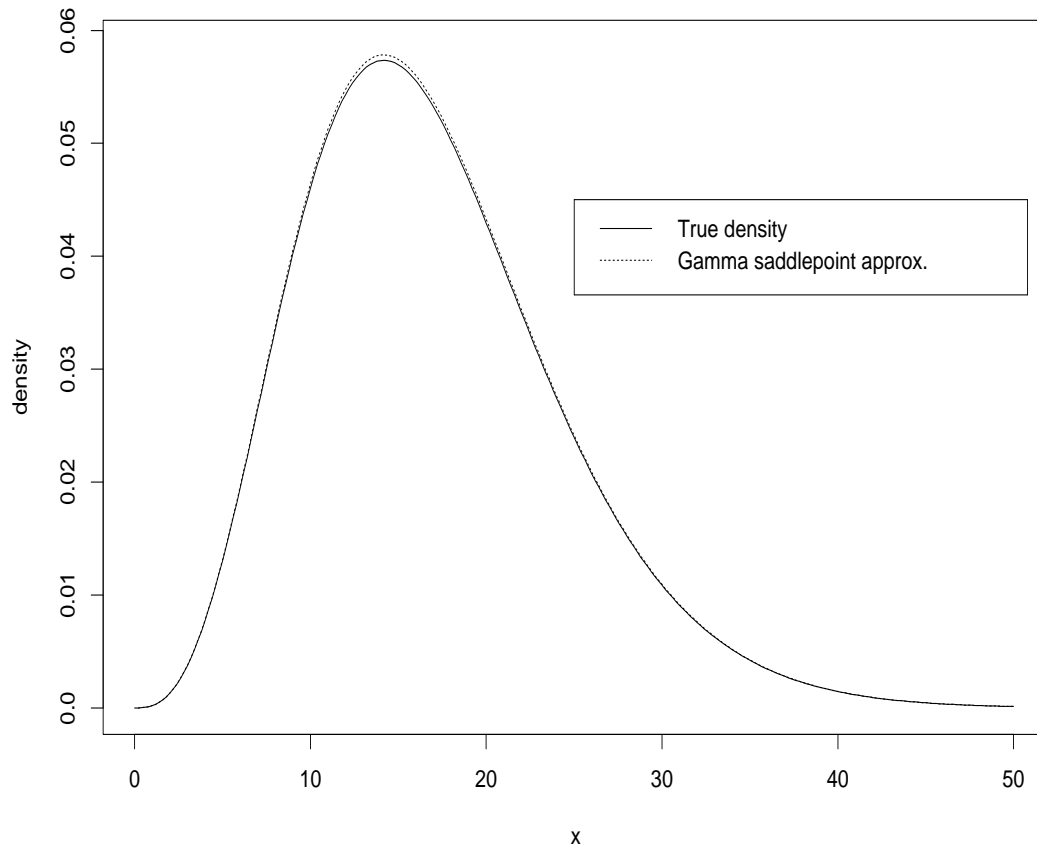


Figure 16: The comparison of the true density and the gamma saddlepoint approximation of noncentral chi-square density ($df=7$, noncentral parameter=5).

rapidly so that it becomes less than 0.5 % in the tail part of the density. The gamma saddlepoint approximation shows a little better approximation throughout the support.

3.4 The Approximation with the Truncated CGF

Easton and Ronchetti approached the saddlepoint approximation of general statistics using the truncated CGF that is the first four terms of the Taylor series of the cumulant generating function (Easton and Ronchetti, 1986). Renshaw (1998) also

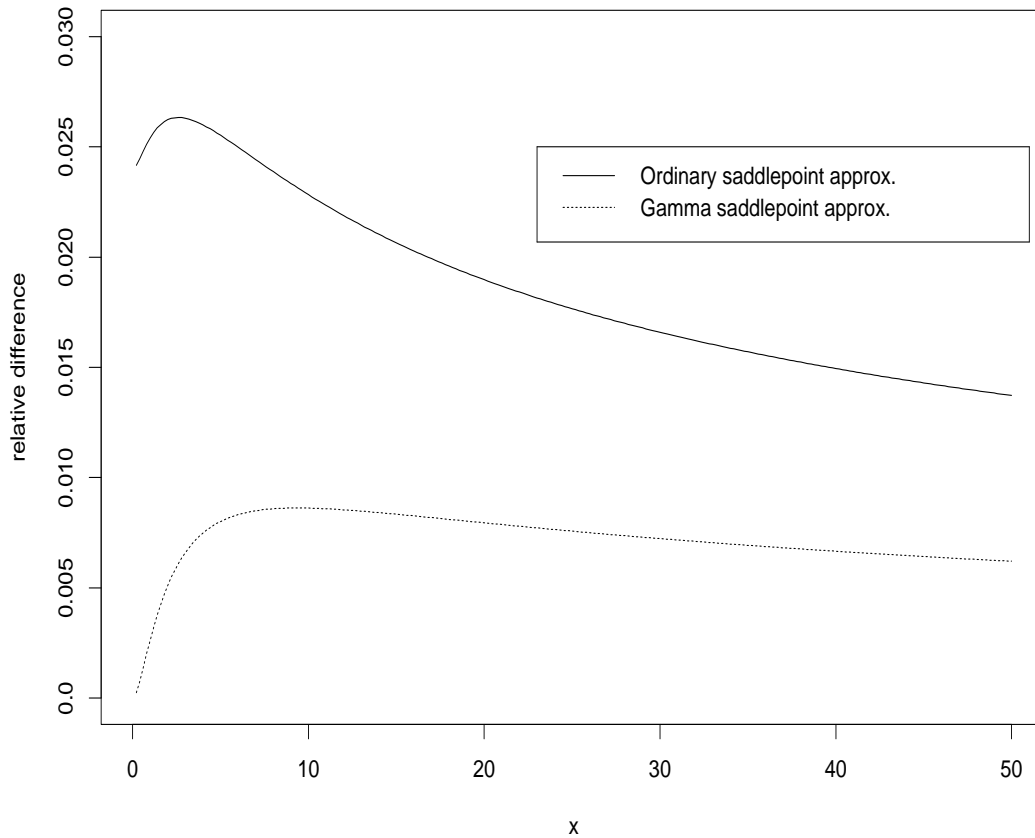


Figure 17: The comparison of the relative differences of the ordinary saddlepoint approximation and the gamma saddlepoint approximation of the noncentral Chi-Square density (df=7, noncentral parameter=5).

used a similar approach to assess the error induced into the underlying probability structure by truncating higher-order cumulants in the cumulant generating function. The problem is suggested in order to see the effect of the truncation method that Matis et al. (1996b) suggested to solve a specific partial differential equation with the cumulant generating function in the nonlinear birth-death models. In the approximation using the truncated CGF, we do not need to assume any underlying parametric model and specific assumptions on statistics (Easton and Ronchetti, 1986). Renshaw

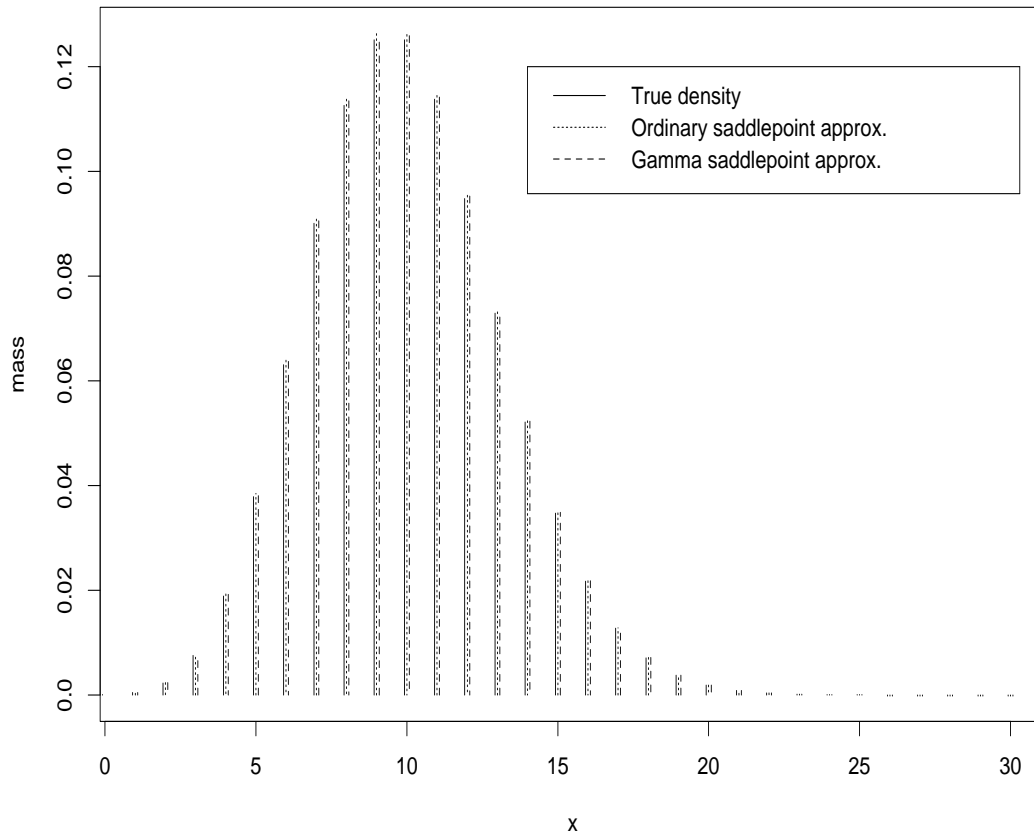


Figure 18: The comparison of the ordinary saddlepoint approximation and the gamma saddlepoint approximation of Poisson(10) with its true density. The point at 0 is the true density.

asserts that “we obtain an algebraic form for the associated p.d.f. irrespective of whether or not we have complete knowledge of the cumulants” (Renshaw, 2000) using this method. Since $\kappa_i/i!$, an element of the CGF becomes zero rapidly for bounded κ_i when i , the order of the cumulant becomes higher, the value of the higher order cumulant has the less effect on the CGF (Renshaw, 1998).

Suppose that we are interested in the distribution of a statistic $V_n(X_1, \dots, X_n)$ that is based on n i.i.d. observations. Let $K_n(\theta)$ be the CGF of the statistic and κ_{in}

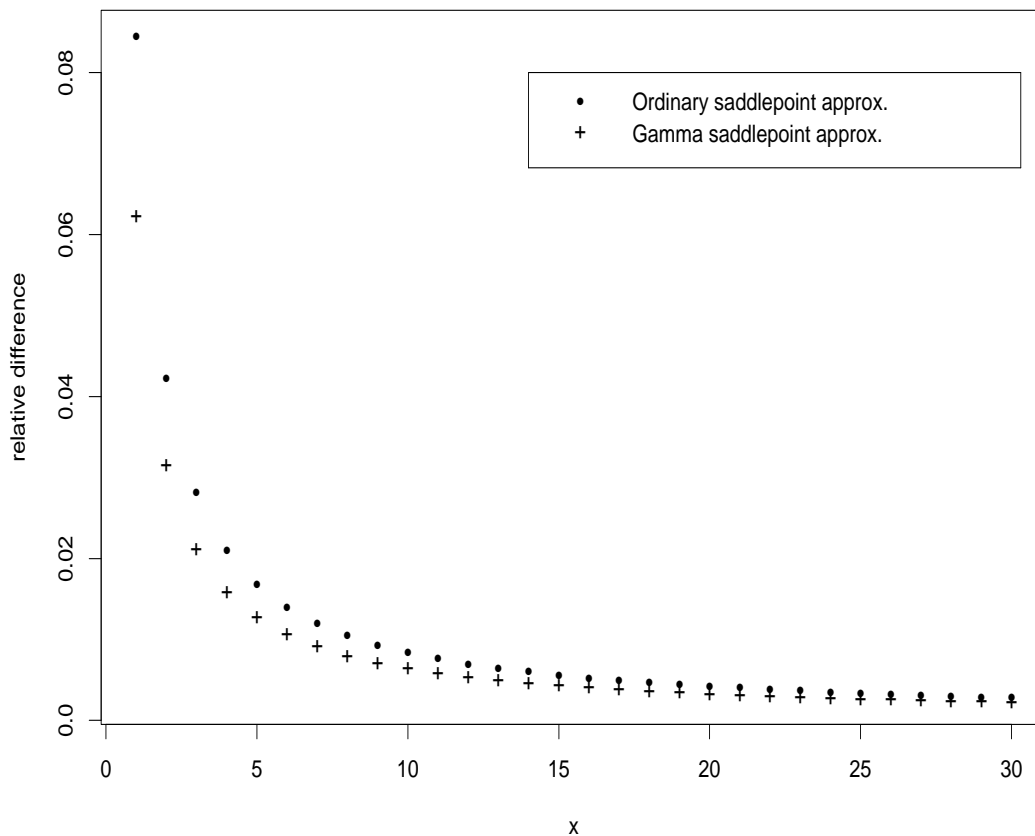


Figure 19: The relative differences of the ordinary saddlepoint approximation and the gamma saddlepoint approximation of Poisson(10).

be the i th order cumulant of the V_n . Then the CGF that is truncated after the 4th term is

$$\tilde{K}_n(\theta) = \kappa_{1n}\theta + \frac{\kappa_{2n}}{2!}\theta^2 + \frac{\kappa_{3n}}{3!}\theta^3 + \frac{\kappa_{4n}}{4!}\theta^4.$$

Let $\tilde{R}_n(\theta) = \tilde{K}_n(n\theta)/n$, then the saddlepoint approximation of the density for V_n (Wang, 1992) is

$$\tilde{f}_n(x) = \left[\frac{n}{2\pi\tilde{R}_n''(\hat{\theta})} \right]^{1/2} \exp \left[n \left\{ \tilde{R}_n(\hat{\theta}) - \hat{\theta}x \right\} \right], \quad (3.14)$$

where $\hat{\theta}$ satisfies

$$\tilde{R}'_n(\hat{\theta}) = x. \quad (3.15)$$

If V_n is the sample mean, then $R_n(\theta) = K(\theta)$ where $K(\theta)$ is the CGF of a variable X_i (Easton and Ronchetti, 1986).

Using (3.9) and (3.10), we can show that the Edgeworth expansion up to the term of order n^{-1} corresponds to the CGF that has the first four cumulants. This together with (3.5) implies that the saddlepoint approximation using the truncated CGF has the same relative error of $O(n^{-1})$ for all x such that $|x - \mu| \leq d/n^{1/2}$ for any fixed constant d (Easton and Ronchetti, 1986), which is the same error rate as the approximation using the full CGF. In fact, the difference between the univariate forms of (3.7) by the full CGF and the truncated CGF is caused only by $\varphi(\theta)$, the MGF of the variable. If differences are uniform, we can expect that the renormalization of the approximation using the truncated CGF will be improved significantly. With a single sample, we can show that the truncated CGF reproduces the exact normal distribution density, and the density of gamma distribution that differs only from the exact result in that $\Gamma(\alpha)$ is replaced by Stirling's approximation (Renshaw, 1998).

An important issue in the approximation is to obtain saddlepoints. The formula like (3.15) can have multiple roots since $\tilde{K}'(\theta)$ is not always strictly increasing. The density approximation exists only on $\hat{\theta}$ that satisfies the condition $\tilde{K}''(\hat{\theta}) > 0$. In the gamma distribution, we can show that $\tilde{K}'(\theta)$ is always strictly increasing with the support of θ that corresponds to $x \in (0, \infty)$, which assures a unique root of (3.15), and always gives an approximated density by (3.14). The mode in the approximation is likely to be shifted to the right of that of the true density because of the truncation of higher order term of the CGF.

The closed form of the CGF of the beta distribution does not exist, however

we can approximate the CGF with the first few cumulants. Unlike the gamma distribution, the beta distribution does not always have the corresponding saddlepoint through the support $(0, 1)$ in (3.15), that is, for $\theta \in (c_1, c_2)$ that satisfies $\tilde{K}''(\theta) > 0$, $\lim_{\theta \rightarrow c_1} \tilde{K}'(\theta) \not\rightarrow 0$ and $\lim_{\theta \rightarrow c_2} \tilde{K}'(\theta) \not\rightarrow 1$. Wang (1992) addresses this problem. He suggests a modification by multiplying the third and fourth term of the CGF by an exponential term, $\exp\{-\kappa_{2n}b^2t^2/2n\}$. It controls the effect of third and fourth cumulants to make $\tilde{K}'_n(t)$ strictly increasing. He shows that this method approximates the beta distribution of the sample mean of the sample size, 5 excellently. Figure 20 shows its approximation with the sample size, 1. It shows that the saddlepoint approximation using the truncated CGF does not have the approximation in the full range of its support, but the modified approximation overcomes the problem.

If the cumulants are increasing quickly for the higher orders, the effect of truncation is more likely to be severe as shown in Table 1 with the gamma distribution. It shows that the relative errors for the mean and the values one standard deviation away toward each tail become bigger when the scale parameters are increasing. The approximation is likely to underestimate near the origin and overestimate near the tail. All relative errors of the gamma distribution tend to become bigger when the values are closer to the tail. For the Poisson distribution in Table 2, the relative errors for those values also tend to be bigger when the location parameter increases. However, the effect of changing the parameter is not as severe as that for the gamma distribution. Also, unlike the gamma distribution, the relative error is decreasing when the values are closer to tail. The approximation overestimates near the origin, and under estimate near the tail in the poisson distribution.

Table 1: The relative errors for the saddlepoint approximation of the gamma distribution using the truncated CGF. “To the tail” and “To the origin” indicate the value of 1 standard deviation away to each direction.

Distribution	Relative error in %		
	To the origin	Mean	To the tail
Gamma(2,0.5)	64.3	12.4	18.9
Gamma(2,1)	49.5	22.4	67.9
Gamma(2,2.1)	26.8	79.6	143.3
Gamma(2,4)	1.0	200.6	235.7
Gamma(2,6)	23.7	365.9	311.2

Table 2: The relative errors for the saddlepoint approximation of the Poisson distribution using the truncated CGF. “To the tail” and “To the origin” indicate the value of 1 standard deviation away to each direction.

Distribution	Relative error in %		
	To the origin	Mean	To the tail
Poisson(2)	6.0	23.9	35.5
Poisson(4)	21.5	44.4	52.1
Poisson(6)	43.9	58.7	64.6
Poisson(8)	51.2	69.9	79.4
Poisson(10)	57.7	79.3	87.5

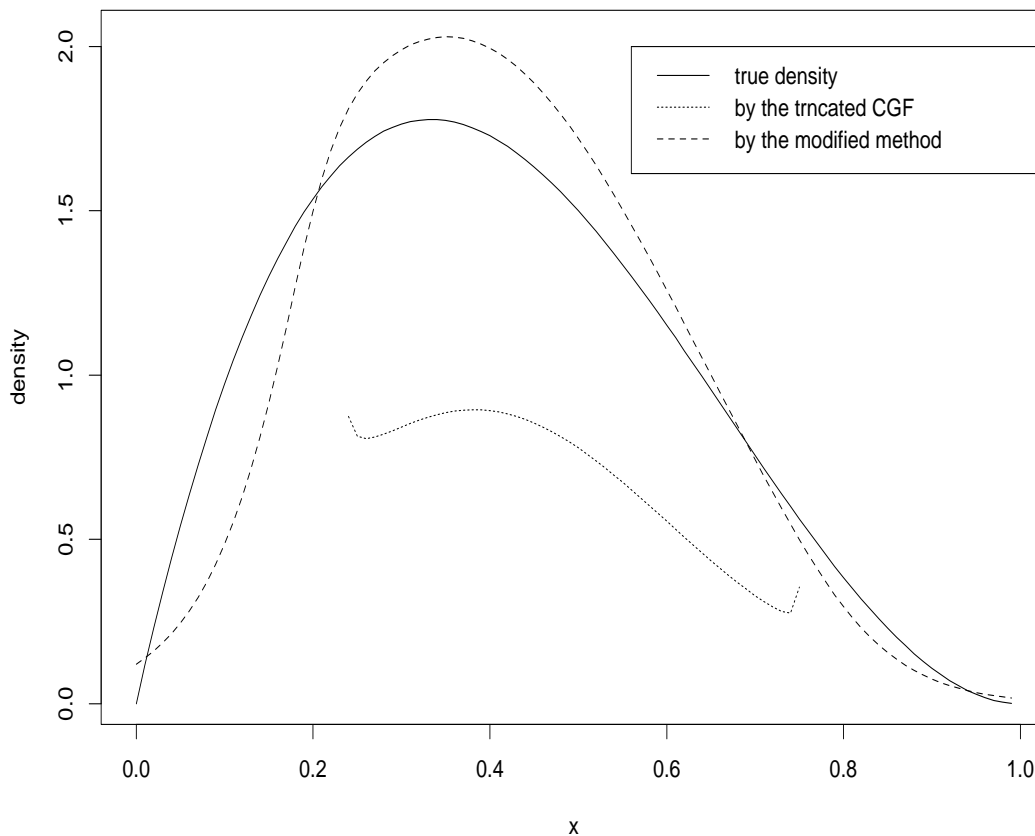


Figure 20: The true density of $\text{Beta}(2,3)$, the solid line is compared with its saddlepoint approximation using the truncated CGF and Wang's modified saddlepoint approximation that are the dotted line and the dashed line, respectively.

3.5 Application to Bivariate Distributions

The leading term of (3.7) conveniently provides the density of multivariate distributions. In this section, we are specifically interested in the saddlepoint approximation for densities of bivariate variables that do not have closed forms for the densities, but have tractable moment generating functions. Let $(Y_1, Y_2) = (X_1 + X_2, X_2 + X_3)$ where $X_1 \sim \text{Gamma}(\alpha_1, \beta_1)$, $X_2 \sim \text{Gamma}(\alpha_2, \beta_2)$, and $X_3 \sim \text{Gamma}(\alpha_3, \beta_3)$. Then

the true density is

$$f(y_1, y_2) = c \int_0^{\min(y_1, y_2)} (y_1 - x_2)^{\alpha_1 - 1} e^{-\frac{y_1 - x_2}{\beta_1}} (y_2 - x_2)^{\alpha_3 - 1} e^{-\frac{y_2 - x_2}{\beta_3}} x_2^{\alpha_2 - 1} e^{-\frac{x_2}{\beta_2}} dx_2,$$

where the c is $(\Gamma(\alpha_1)\beta_1^{\alpha_1}\Gamma(\alpha_2)\beta_2^{\alpha_2}\Gamma(\alpha_3)\beta_3^{\alpha_3})^{-1}$. The closed form of the bivariate density does not exist. However, the MGF is

$$M_{Y_1, Y_2}(\theta_1, \theta_2) = \left(\frac{1}{1 - \beta_1 \theta_1} \right)^{\alpha_1} \left(\frac{1}{1 - \beta_2(\theta_1 + \theta_2)} \right)^{\alpha_2} \left(\frac{1}{1 - \beta_3 \theta_2} \right)^{\alpha_3}. \quad (3.16)$$

The CGF is the logarithm of (3.16). To obtain appropriate saddlepoints, we expand the condition for the univariate variable to that for the bivariate variable. As an analogy of Daniels' proof with the univariate variables (Daniels, 1954), we can show that the saddlepoint $(\hat{\theta}_1, \hat{\theta}_2)$ satisfies $\frac{\partial^2 K(\theta)}{(\partial \theta_1)^2} \Big|_{\theta = \hat{\theta}} > 0$, and $\frac{\partial^2 K(\theta)}{(\partial \theta_2)^2} \Big|_{\theta = \hat{\theta}} > 0$ in bivariate variables. In the bivariate gamma distribution, (Y_1, Y_2) , under the fixed value of θ_2 , say θ_2^* , we can show that $\frac{\partial K(\theta)}{\partial \theta_1} \Big|_{\theta_1, \theta_2^*}$ is strictly increasing in the support of θ_1 , (c_1, c_2) . Also, $\lim_{\theta_1 \rightarrow c_1} \frac{\partial K'(\theta)}{\partial \theta_1} \Big|_{\theta_1, \theta_2^*} = 0$, and $\lim_{\theta_1 \rightarrow c_2} \frac{\partial K'(\theta)}{\partial \theta_1} \Big|_{\theta_1, \theta_2^*} = \infty$. We can show the same thing by fixing the value of θ_1 . The saddlepoints and the density approximations are easily obtained using mathematical software like Maple.

Figure 21 and Figure 22 show the true density and the saddlepoint approximation of the bivariate gamma distribution. The approximation expresses the trend of the original distribution well, however the approximation tends to underestimate the density. The relative errors are around 10% near the origin and peak, and around 15% near the tail.

To approximate the bivariate density, the gamma distribution can replace the normal distribution in the saddlepoint approximation formula as shown in (3.11), but the closed form of the bivariate gamma distribution is not obvious. There is no known bivariate gamma distribution that has a closed form and has a positive support on the variables without any restriction. Instead, we use the centered density

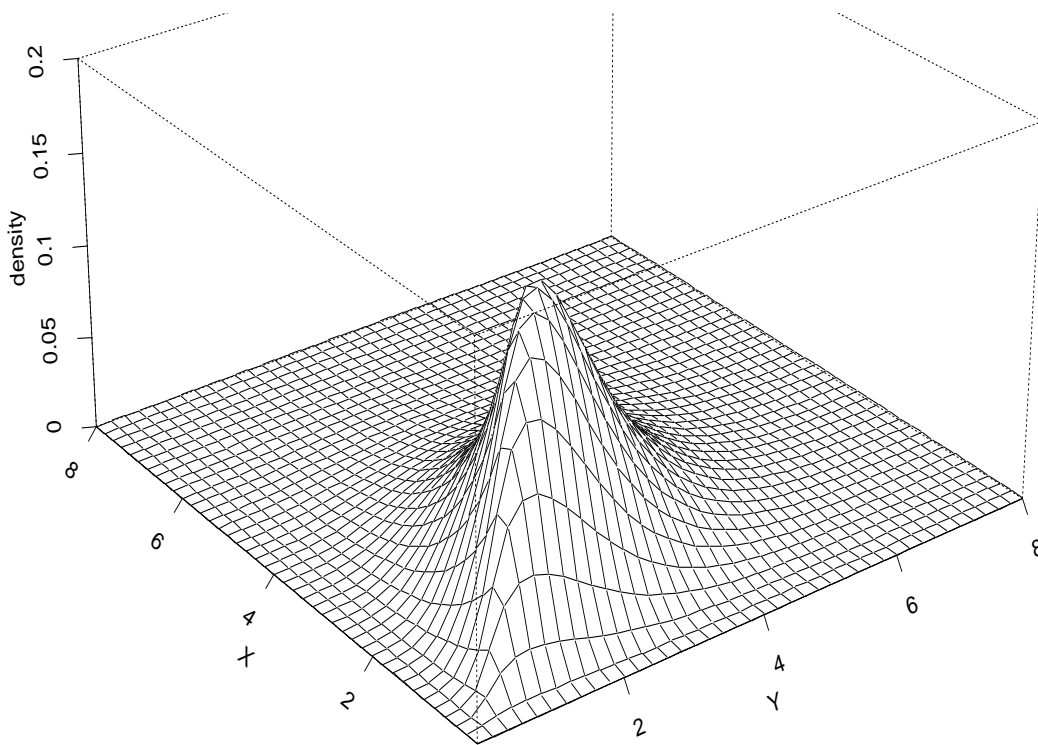


Figure 21: The true density of $(Y_1, Y_2) = (X_1 + X_2, X_2 + X_3)$ where $X_1 \sim \text{Gamma}(1, 1)$, $X_2 \sim \text{Gamma}(3, 0.5)$, and $X_3 \sim \text{Gamma}(2, 0.7)$. X-axis indicates Y_1 and Y-axis Y_2 .

of (X_1, X_2) where X_1 and X_2 are independent univariate gamma distributions as a simple approach. The saddlepoint approximation of (Y_1, Y_2) based on this is

$$\hat{f}(y_1, y_2) = \frac{\varphi(\hat{\theta}) \exp(-\hat{\theta}_1 y_1 - \hat{\theta}_2 y_2)}{\Gamma(\nu_1) \Gamma(\nu_2) \sigma_1 \sigma_2} \nu_1^{\nu_1 - 1/2} \nu_2^{\nu_2 - 1/2} e^{-\nu_1} e^{-\nu_2}, \quad (3.17)$$

where $\nu_1 = \frac{4}{(\kappa_{30}(\hat{\theta})/\kappa_{20}(\hat{\theta})^{3/2})^2}$, $\nu_2 = \frac{4}{(\kappa_{03}(\hat{\theta})/\kappa_{02}(\hat{\theta})^{3/2})^2}$, $\sigma_1 = \sqrt{\kappa_{20}(\hat{\theta})}$, and $\sigma_2 = \sqrt{\kappa_{02}(\hat{\theta})}$. $\hat{\theta}$ is obtained by (3.8) and κ_{ij} is $\left. \frac{\partial^{i+j} K(\theta)}{\partial \theta_1^i \partial \theta_2^j} \right|_{\theta=0}$. (Y_1, Y_2) here is a single bivariate variable, not a statistic such as the sample mean. Figure 23 shows the approximation using (3.17). The approximated density closely follows the trend of the true density

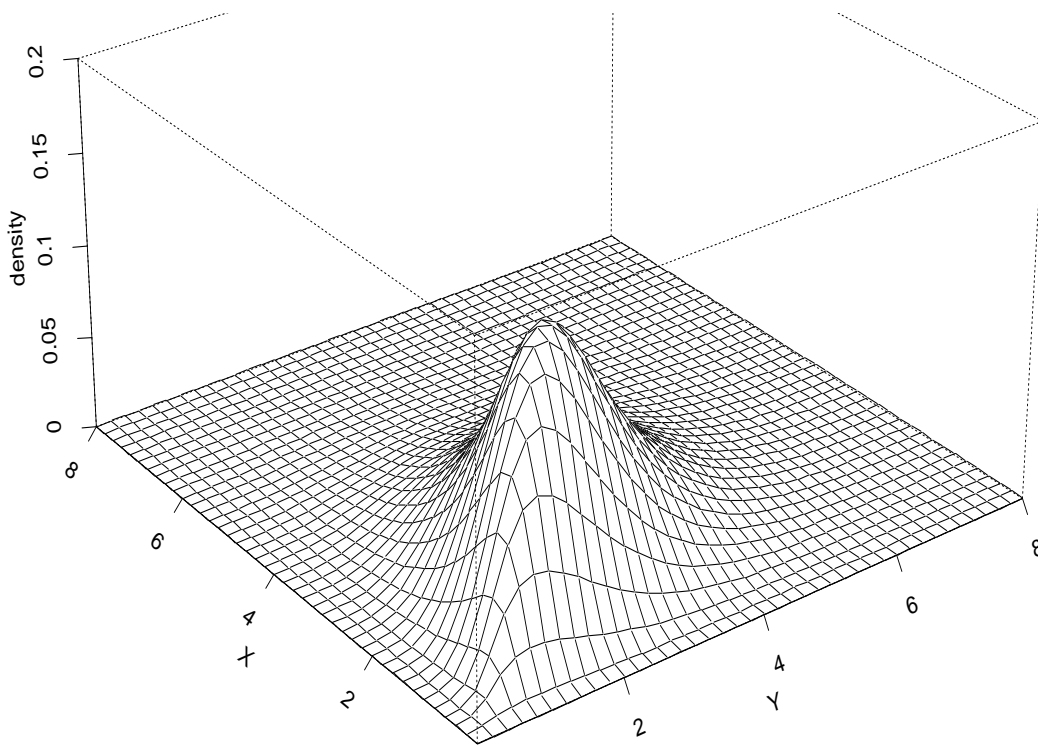


Figure 22: The saddlepoint approximation of $(Y_1, Y_2) = (X_1 + X_2, X_2 + X_3)$ where $X_1 \sim \text{Gamma}(1, 1)$, $X_2 \sim \text{Gamma}(3, 0.5)$, and $X_3 \sim \text{Gamma}(2, 0.7)$. X-axis indicates Y_1 , Y-axis Y_2 .

in Figure 21. The error rate near the origin and peak are similar to the saddlepoint approximation based on the normal distribution, however those near the tail part are around 35%, which are bigger than those of the normal-based saddlepoint approximation. A possible reason of the poor approximation is the fact that we use the centered bivariate gamma where the correlation is ignored.

Let us consider another example that can take into account the correlation between variables in the centered bivariate distribution. We can derive a bivariate

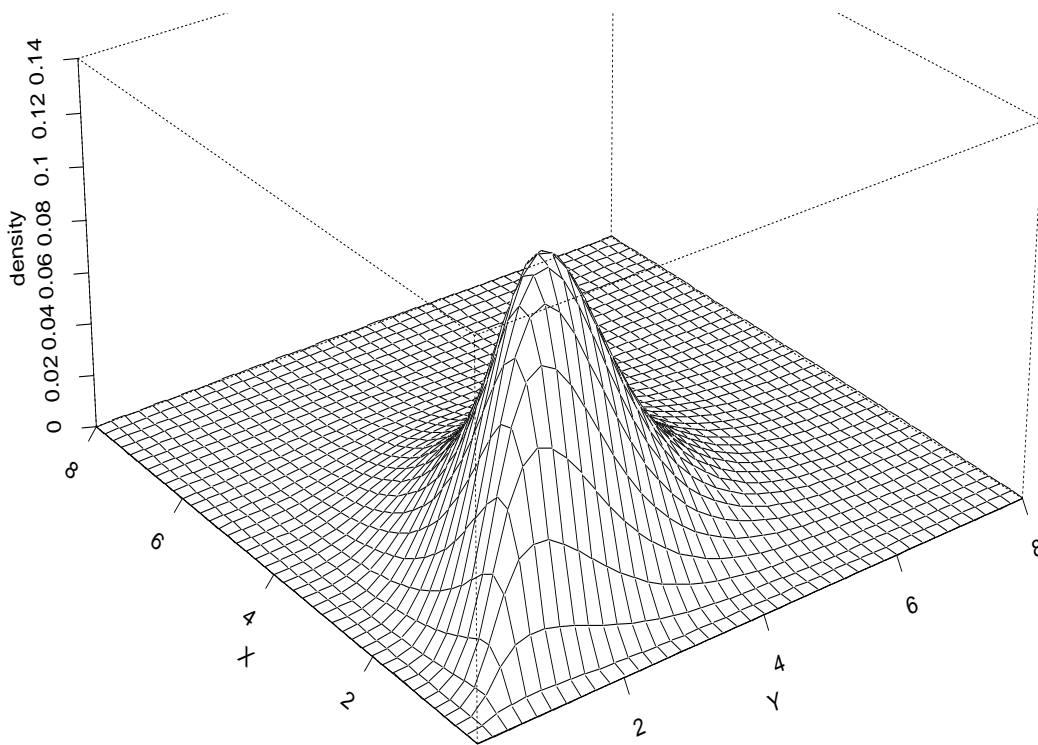


Figure 23: The saddlepoint approximation using the formula in (3.17) of $(Y_1, Y_2) = (X_1 + X_2, X_2 + X_3)$ where $X_1 \sim \text{Gamma}(1, 1)$, $X_2 \sim \text{Gamma}(3, 0.5)$, and $X_3 \sim \text{Gamma}(2, 0.7)$.

saddlepoint approximation based on the bivariate exponential distribution, that is, (X_1, X_2) where $X_1 = Z_1 + Z_2$, and $X_2 = Z_2 + Z_3$, also $Z_1 \sim \text{Exp}(\beta_1)$, $Z_2 \sim \text{Exp}(\beta_2)$ and $Z_3 \sim \text{Exp}(\beta_3)$ are independent. This provides a closed form of a centered bivariate distribution, and the saddlepoint approximation of a single bivariate variable based on this is

$$\hat{f}(y_1, y_2) = \frac{\varphi(\hat{\theta}) \exp(-\hat{\theta}_1 y_1 - \hat{\theta}_2 y_2)}{\beta_2 \beta_3 + \beta_1 \beta_2 - \beta_1 \beta_3} e^{-\frac{\beta_1 + \beta_2}{\beta_1} - \frac{\beta_2 + \beta_3}{\beta_3}} \left[e^{(\frac{1}{\beta_1} + \frac{1}{\beta_3} - \frac{1}{\beta_2})(\beta_2 + \alpha)} - 1 \right], \quad (3.18)$$

where $\alpha = \beta_1$, if $y_1 < y_2$, and $\alpha = \beta_2$, if $y_1 > y_2$, also $\beta_1 = \kappa_{10}(\hat{\theta}) - \sqrt{\kappa_{11}(\hat{\theta})}$,

$\beta_2 = \sqrt{\kappa_{11}(\hat{\theta})}$, and $\beta_3 = \kappa_{01}(\hat{\theta}) - \sqrt{\kappa_{11}(\hat{\theta})}$. We can see how well this bivariate ap-

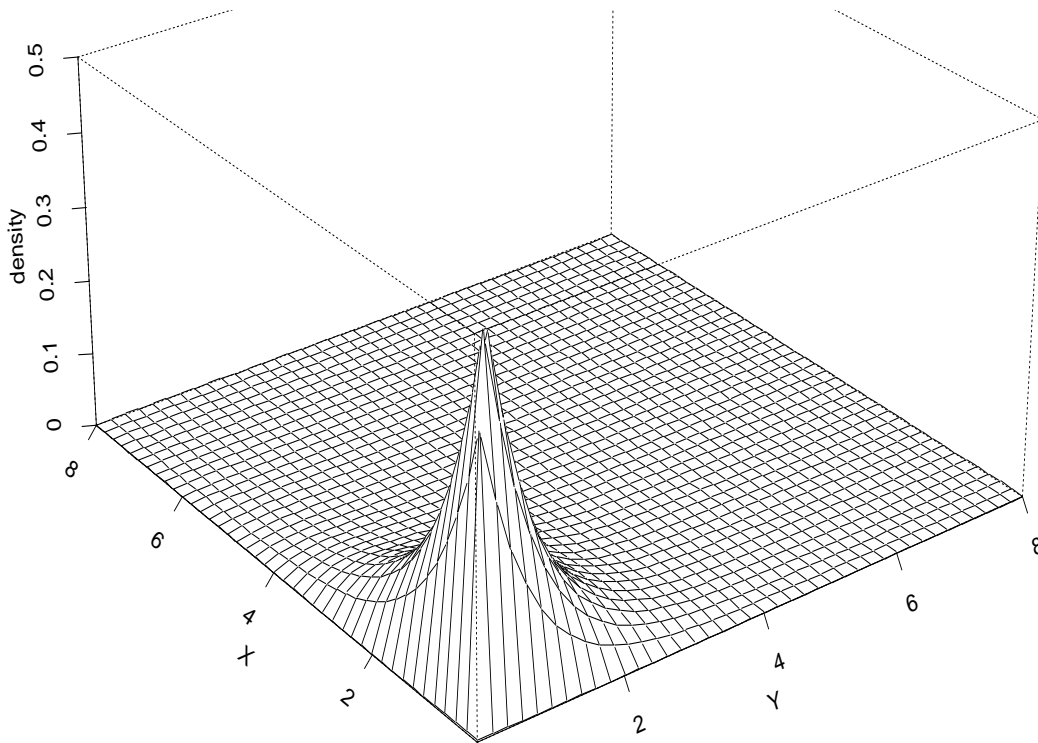


Figure 24: The saddlepoint approximation using the formula in (3.18) of $(Y_1, Y_2) = (X_1 + X_2, X_2 + X_3)$ where $X_1 \sim Exp(1)$, $X_2 \sim Exp(0.5)$, and $X_3 \sim Exp(0.7)$.

proximation works when the correlation between two variables is taken into account with a bivariate exponential distribution. Figure 24 is the saddlepoint approximation of a bivariate exponential distribution using (3.18) and Figure 25 the true density. Except the area just near the axis (around 90 % relative error), the approximation shows practically no difference with the true density. This indicates that the approximation to the bivariate gamma distribution by (3.17) can be improved if we can replace the centered gamma density based on two independent gamma distribution

that considers the correlation between Y_1 and Y_2 .

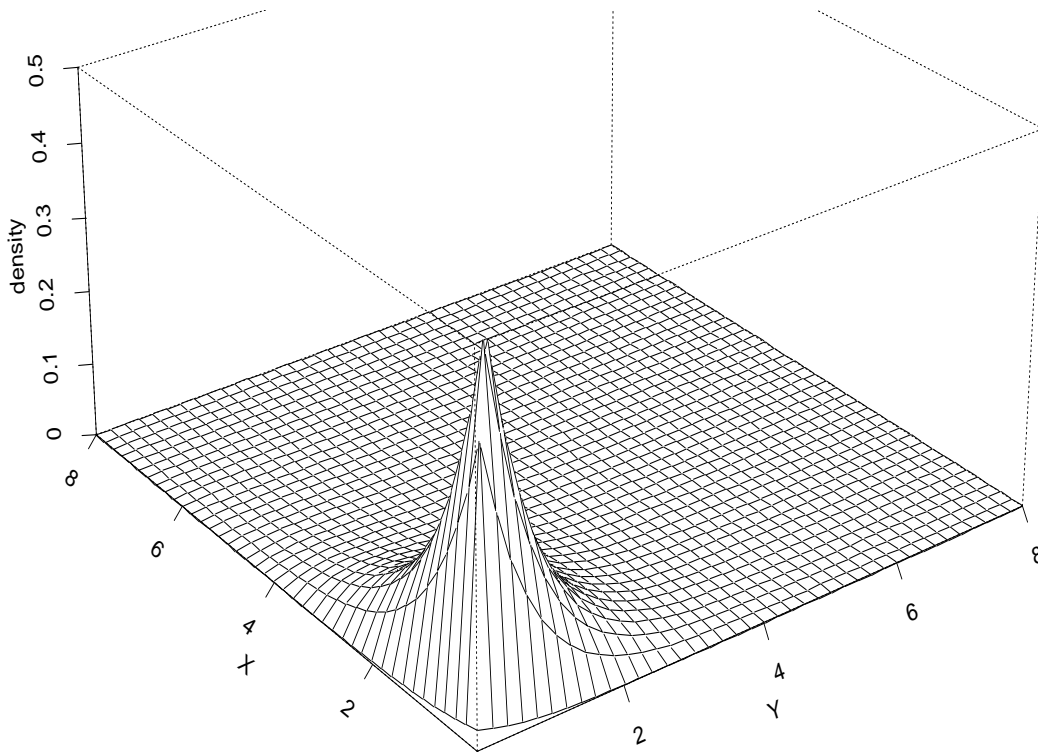


Figure 25: The true density of $(Y_1, Y_2) = (X_1 + X_2, X_2 + X_3)$ where $X_1 \sim \text{Exp}(1)$, $X_2 \sim \text{Exp}(0.5)$, and $X_3 \sim \text{Exp}(0.7)$.

The approximation of the bivariate gamma by (3.18) shows approximately 100% error near the axis that is similar to the approximation to the bivariate exponential distribution, 20-30% relative errors on the area near $Y_1 = Y_2$, and approximately 5-10% error for the other area, thus the error rates are not consistently good or bad compared to the approximation based on the normal distribution.

The approximation using a truncated CGF also can be used in the bivariate distribution theoretically, but in practice, the differences are quite huge because of

the effect of truncated cumulants, thus it seems hardly to have a practical meaning.

3.6 Discussion

The saddlepoint approximation easily provides the density as shown in previous sections when the closed form of the MGF or CGF exists. It shows overall excellent approximations in univariate cases with the full CGF. When the distribution is skewed to the right, the saddlepoint approximation based on the centered gamma distribution shows better approximation than that based on the normal distribution. Much larger differences in the approximation are shown if the truncated CGF is used. The effect of the truncated cumulants is more serious if the cumulants increase with the order such as for the gamma distribution. With bivariate gamma distributions, the approximation with the full CGF describes the distribution well, however it tends to underestimate the distribution. The selection of saddlepoints is not trivial. Appropriate saddlepoints do not exist in some cases. Daniels provides well-defined conditions for the uniqueness and existence of saddlepoints in the univariate case. We adapted this condition in the bivariate distribution case in a similar fashion. The bivariate saddlepoint approximation using a truncated CGF shows a poor approximation, thus seems inadequate for the practical use. An approach by Renshaw to approximate densities iteratively implemented by renormalization may improve this problem as shown on his paper (2000).

The saddlepoint approximation for the density provides a good description of the variable of interest. It can be used for the maximum likelihood estimation, and also approximates the density of the log-likelihood ratio and the score statistics (Reid, 1988). For statistical inference in general, the saddlepoint approximation for the tail probability is more appropriate. Many formulas such as Skovgaard's formula and Lugannani and Rice saddlepoint approximation can be used for this purpose (e.g.,

Jensen 1995, Butler and Huzurbazar 1993).

CHAPTER IV

THE DISTRIBUTION OF THE RESIDENCE TIME FOR SEMI-MARKOV TWO-COMPARTMENT MODELS

4.1 Introduction

In pharmacokinetics, the kinetic behavior of many drugs is described using multi-compartment models. One-compartment models are based on the assumption that the concentration of a drug in various system reaches an equilibrium almost instantaneously (Wartak, 1983). However, because the distribution of most drugs involves various fluids and tissues, the kinetics are often depicted using multi-compartment models.

Our objective in this chapter is to investigate the distribution of residence times for the two-compartment model as a simple case of multivariate compartment models. We specify the distribution of the number of visits first and obtain a bivariate moment generating function (MGF) of the residence times based on that. We use the saddlepoint approximation to approximate densities for the residence times from the MGF.

4.2 Two-Compartment Models

Two-compartment models are composed of a central compartment and a peripheral compartment and are often preferred to more complicated models in terms of fewer parameters (Laurent et al., 2001). The central compartment represents the circulatory system, called simply “plasma”, where the drug is exchanged rapidly with other parts of the body (Metzler, 1971). The peripheral compartment, also called “tissue”, exchanges a significant amount of drug with the central compartment at a

slower rate (Metzler, 1971). Figure 26 describes a generalized schematic of a two-compartment model that has two linear eliminations to the system exterior, each of them working in a different compartment. In deterministic models, k_{ij} with $i = 1, 2$, $j = 0, 1, 2$, $i \neq j$ denotes a constant transfer rate from compartment i to j , where 0 denotes the system exterior. However, under the Markov process assumption, we define a probability intensity coefficient for transfer rate k_{ij} in units of time^{-1} ,

$$\text{Prob}\{\text{a given particle in } i \text{ transfer to } j \text{ in } (t, t + \Delta t) | X(t)\} = k_{ij}\Delta t + o(\Delta t) \quad (4.1)$$

for $i = 1, 2$, $j = 0, 1, 2$, $i \neq j$, and it yields the transfer probability when multiplied by a small time increment (Matis and Wehrly, 1985). The retention time during a single visit to the compartment has an exponential distribution with the mean equal to the reciprocal of the sum of all outflow coefficients from the compartment (Matis and Wehrly, 1985). In a non-Markovian process setting, the probability intensity coefficient is replaced by the probability intensity rate function to express the transfer probability (Matis and Wehrly, 1985). An example of the rate function is the hazard rate that depends on the “age” of particle and produces the gamma distribution for the retention time (Matis and Wehrly, 1985). These statistical concepts of transfer rates provide distributional approaches to the quantities of interest such as residence times of compartments.

4.2.1 *The Distribution of the Number of Visits*

In Figure 26, a particle starts from compartment 1 and moves between compartments until escaping to the system exterior. We assume that the retention time of a particle during a single visit prior to its next transfer to another compartment has an arbitrary distribution, and thus, this is a semi-Markov process with state space consisting of one absorbing and two transient states. A semi-Markov process allows

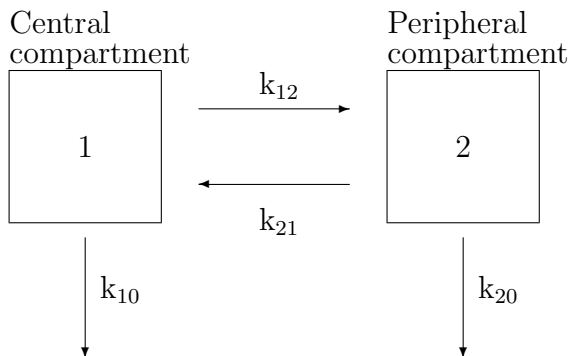


Figure 26: A generalized schematic of two-compartment model.

non-instant mixing and heterogeneous compartments (Matis and Wehrly, 1985). In semi-Markov processes, the successive states visited by a particle form a Markov chain (Çınlar, 1975), where the probability for a particle to move from one state to another depends only on the present state.

In Figure 26, let the probability of escaping to the system exterior from compartment 1 be π_1 and from compartment 2, π_2 . Since the transition probability depends on the parameters of the present state, $\pi_1 = \frac{k_{10}}{k_{10}+k_{12}}$ and $\pi_2 = \frac{k_{20}}{k_{20}+k_{21}}$. Let N_i denote the random number of visits for a particle starting at compartment 1 to compartment i before escaping to the system exterior. Since a particle starts from compartment 1 in Figure 26, using mathematical induction, we can show that the probability mass function (pmf) of (N_1, N_2) is

$$P_{N_1, N_2}(n_1, n_2) = (1 - \pi_1)^{n_2} \pi_1^{n_1 - n_2} (1 - \pi_2)^{n_1 - 1} \pi_2^{n_2 - n_1 + 1}, \quad (4.2)$$

where $n_1 = 1, 2, 3, \dots$ and $n_2 = n_1, n_1 - 1$. Subsequently, the marginal pmfs for N_1 and N_2 are

$$P_{N_1}(n_1) = p(1 - p)^{n_1 - 1}, \quad n_1 = 1, 2, 3, \dots, \quad (4.3)$$

and

$$P_{N_2}(n_2) = \pi_1 I_{[0]}(n_2) + (1 - \pi_1)p(1 - p)^{n_2} I_{[1, 2, \dots]}(n_2), \quad (4.4)$$

where $p = \pi_1 + \pi_2 - \pi_1\pi_2$ and $I(\cdot)$ is the indicator function. Thus, N_1 has the geometric distribution with the success rate p . However, the distribution of N_2 depends on the probability of not visiting compartment 2. This causes the total residence time during all visits to have a distribution that is not strictly continuous.

4.2.2 The MGF of the Residence Time

Let R_{ij} be the j th retention time of the particle in compartment i during a single visit prior to its next transfer out of i and S_i be the total residence time (or simply residence time) in i during all of its N_i visits. If the process is a Markov process, then R_{ij} has an exponential distribution, and we can directly calculate the distribution for S_i using (4.3) and (4.4). However, if R_{ij} does not have an exponential distribution, the approach using the MGF is relatively easy and provides an interpretation for the distribution. Using the fact that conditioned on N_i , R_{i1}, \dots, R_{iN_i} are independent and identically distributed, the MGF of the residence time in compartment 1 is

$$\begin{aligned} M_{S_1}(t) &= E \left[e^{t \sum_{j=1}^{N_1} R_{1j}} \right] \\ &= \sum_{n=1}^{\infty} E \left[e^{t \sum_{j=1}^{N_1} R_{1j}} | N_1 = n \right] P_{N_1}(n) = \sum_{n=1}^{\infty} [M_{R_1}(t)]^n P_{N_1}(n) \\ &= \frac{pM_{R_1}(t)}{1 - (1-p)M_{R_1}(t)}. \end{aligned} \quad (4.5)$$

where $M_{R_i}(t)$ is the MGF of each R_{ij} . Similarly,

$$M_{S_2}(t) = \pi_1 + (1 - \pi_1) \left[\frac{pM_{R_2}(t)}{1 - (1-p)M_{R_2}(t)} \right]. \quad (4.6)$$

A difference between the distributions of S_1 and S_2 is that S_2 has a chance of equaling 0. Also, the distributions of retention time can be different for the two compartments. If the distributions of retention times are similar, we expect that the magnitude of the density of S_2 is proportionally smaller than that of S_1 on its positive support.

Suppose that the two-compartment model is the Markov process with transfer rates given in Figure 26. Using (4.5) and (4.6),

$$M_{S_1}(t) = \frac{1}{1 - \frac{t}{(k_{12}+k_{10})p}},$$

and

$$M_{S_2}(t) = \pi_1 + (1 - \pi_1) \frac{1}{1 - \frac{t}{(k_{21}+k_{20})p}}.$$

This shows that the distribution of the residence time for compartment 1 is an exponential distribution, and for compartment 2 is a mixture of an exponential distribution and a mass on 0.

Using (4.2), the MGF of the bivariate distribution of (S_1, S_2) can be calculated as

$$M_{S_1, S_2}(t_1, t_2) = \frac{\pi_1 M_{R_1}(t_1) + (1 - \pi_1) \pi_2 M_{R_1}(t_1) M_{R_2}(t_2)}{1 - (1 - \pi_1)(1 - \pi_2) M_{R_1}(t_1) M_{R_2}(t_2)}. \quad (4.7)$$

The MGF expression directly provides a complete set of moments. Also it is equivalent to knowing the exact distribution if the MGF exists. In fact, when the MGF is known, we can approximate the density or distribution by the saddlepoint approximation even though the distribution or density function may not have a closed form.

4.3 The Approximation of the Density Using the Saddlepoint Approximation

The basic formula for the saddlepoint approximation of a multivariate distribution is as follows. Suppose that a continuous multivariate variable $\mathbf{X} = (x_1, x_2, \dots, x_d)$ has the MGF, $M_{\mathbf{X}}(\mathbf{t})$, and the cumulant generating function (CGF) $K_{\mathbf{X}}(\mathbf{t}) = \log M_{\mathbf{X}}(\mathbf{t})$. The saddlepoint approximation for the density using (3.7) is

$$f(\mathbf{x}; \hat{\mathbf{t}}) = \frac{1}{(2\pi)^{d/2}} \exp\{K_{\mathbf{X}}(\hat{\mathbf{t}}) - \hat{\mathbf{t}} \cdot \mathbf{x}\} |\Sigma(\hat{\mathbf{t}})|^{-1/2}, \quad (4.8)$$

where $\hat{\mathbf{t}}$ is the solution of the equation

$$\frac{\partial K_{\mathbf{x}}(\hat{\mathbf{t}})}{\partial t_i} = x_i, i = 1, 2, \dots, d, \quad (4.9)$$

and $|\Sigma(\mathbf{t})|$ is the determinant of the covariance matrix composed of the second derivatives of $K_{\mathbf{x}}(\mathbf{t})$. As an example, for a bivariate variable, $|\Sigma(\mathbf{t})| = \frac{\partial^2 K_{\mathbf{x}}(\mathbf{t})}{\partial t_1^2} \frac{\partial^2 K_{\mathbf{x}}(\mathbf{t})}{\partial t_2^2} - \left(\frac{\partial^2 K_{\mathbf{x}}(\mathbf{t})}{\partial t_1 \partial t_2}\right)^2$ (Renshaw, 2000). The point $\hat{\mathbf{t}}$ satisfying the equation (4.9) is the maximum likelihood estimate of \mathbf{t} in $f(\mathbf{x}; \mathbf{t})$ after exponential tilting (Barndorff-Nielsen and Cox, 1989, page 181). The solution of (4.9) in the univariate case is also known as the saddlepoint for the integrand of the Fourier inversion of the density function (Daniels, 1954). The solution of the equation (4.9) is not unique when $K_{\mathbf{x}}(\mathbf{t})$ is not strictly increasing.

It is common practice that retention times are assumed to have exponential or gamma distributions. In such a case, an MGF like (4.7) has multiple poles which cause multiple solutions for (4.9). With a single variable, Daniels (1954) shows that (4.9) has a unique real root \hat{t} on the support of x with conditions such that the distribution function is between 0 and 1, and the CGF is a convex function of t . Using these conditions, the range of saddlepoints may be limited at either or both ends. In (4.9) with the exponential or gamma distribution, the range for each element of \mathbf{t} is upper-bounded by the biggest scale parameter that is the reciprocal of the mean in exponential distribution case, and has $-\infty$ as the lower bound. Within that range, the CGF is convex and the first derivative of the CGF is continuously increasing.

In practice, equation (4.8) may not integrate to one over the support of the variable. In such cases, we can renormalize (4.8) by multiplying by an appropriate constant. It can be shown that renormalization gives even smaller error rate and often improves the approximation (Barndorff-Nielsen and Cox, 1989, page 182). We use this renormalization to approximate densities in this paper.

Approximating the density of residence times for a compartment model like Figure 26 using the saddlepoint approximation has some advantages. First, we always obtain the density of the distribution once we have the MGF of the variable of interest even though the exact density is not in a closed form. Second, it results in an accurate approximation even when we handle multi-dimensional variables. In the case like Figure 26, the distribution of two residence times is not a typical bivariate continuous distribution. The probability of $(\Delta S_1, S_2 = 0)$ is not 0 because of the chance that $N_2 = 0$, and thus the bivariate distribution conditioned on $S_2 = 0$ has a mass on the set $\{(S_1, 0) : S_1 > 0\}$. Also, a closed form of the density or distribution does not exist when $S_2 > 0$. The conditional bivariate density given $S_2 > 0$ is a mixture of infinitely many densities that depend on the retention time distribution for each compartment and the number of visits. If the compartment model is based on Markov processes, the bivariate density is a mixture of Erlang variables with smaller weights when the shape parameter increases. Refer to Section 4.5 to see the calculation and the exact form of the bivariate density for the continuous part. We decompose the MGF (4.7) into the cases where $S_2 = 0$ and $S_2 > 0$ separately to approximate the density rather than the simply applying the saddlepoint approximation using the whole MGF. Then the MGF (4.7) could be expressed as

$$M_{S_1, S_2}(t_1, t_2) = \pi_1 M_{R_1}(t_1) + (1 - \pi_1) \frac{\pi_2 M_{R_1}(t_1) M_{R_2}(t_2) + \pi_1 (1 - \pi_2) M_{R_1}^2(t_1) M_{R_1}(t_1)}{1 - (1 - \pi_1)(1 - \pi_2) M_{R_1}(t_1) M_{R_1}(t_1)}. \quad (4.10)$$

This is the MGF of a mixture of two bivariate distributions, one bivariate continuous and the other with a point mass at zero for S_2 and the retention time distribution in a single compartment for S_1 .

To demonstrate the saddlepoint approximation, let the two-compartment model be a Markov process with transfer rates 1.0, 0.5, 0.4, and 0.6 for k_{10}, k_{12}, k_{21} , and

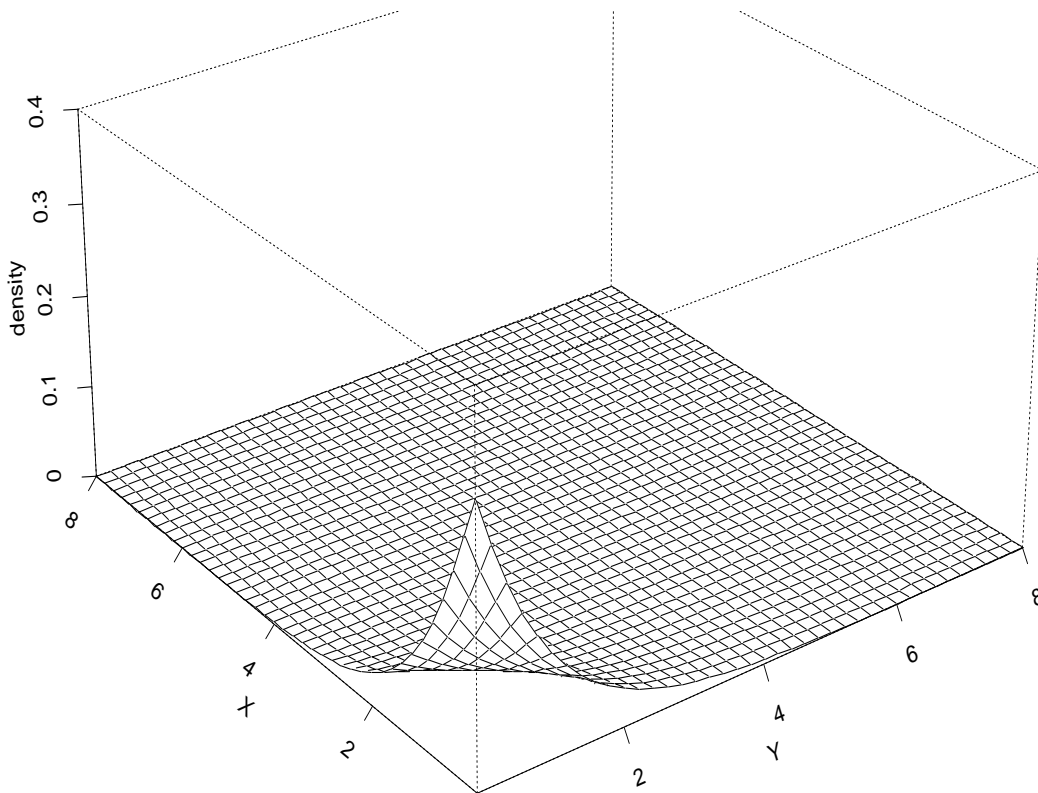


Figure 27: The renormalized saddlepoint approximation of bivariate density of $(S_1 > 0, S_2 > 0)$. X-axis is S_1 , and Y-axis S_2 .

k_{20} , respectively. Then, each retention time has an exponential distribution with a mean that is the reciprocal of the sum of all outflowing transfer rates from the compartment. When $S_2 = 0$, the density is simply the exponential density with mean 0.667 times π_1 , the probability of exiting the system from compartment 1 at the first visit by the univariate part of (4.10). When $S_2 > 0$, Figure 27 shows the renormalized bivariate approximation using the saddlepoint approximation. Figure 28 shows the true density where the infinite sum is approximated with $n_1 = 100$ terms. Among solutions satisfying (4.9), the smallest pair was chosen as the saddlepoint for each

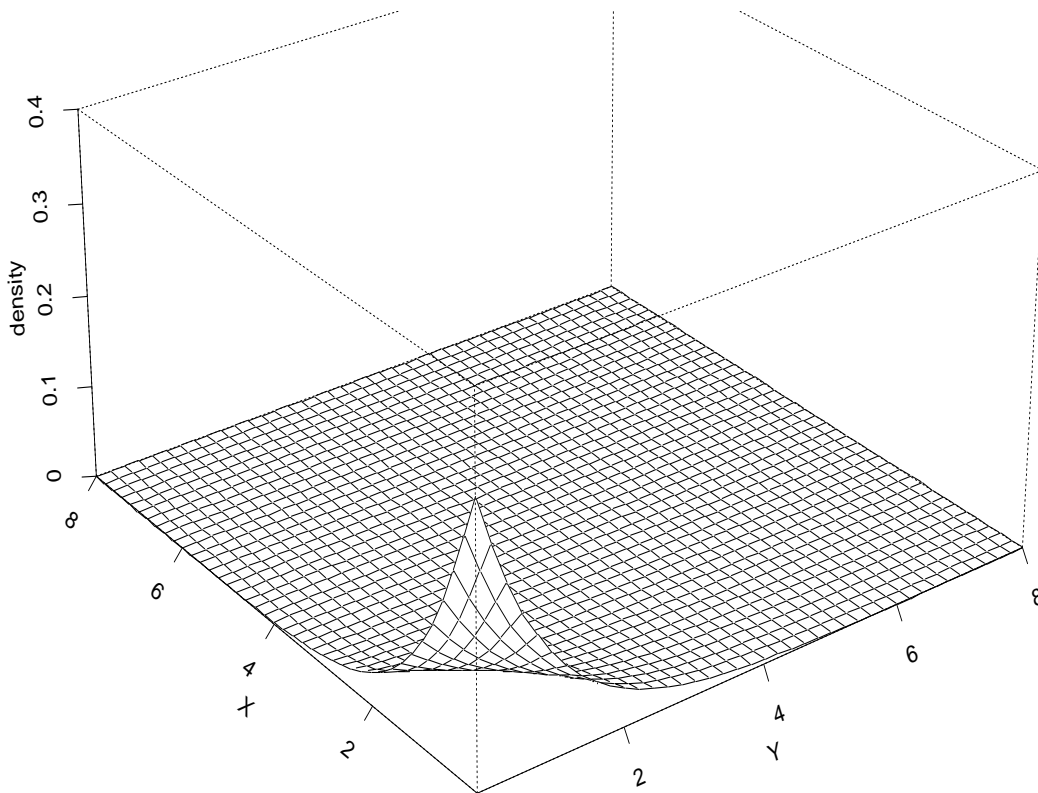


Figure 28: The true bivariate density of (S_1, S_2) . X-axis is S_1 , and Y-axis S_2 .

\mathbf{x} because that satisfies conditions for a unique root for the saddlepoint. We can see that the approximation follows the trend of the true density very closely. After renormalization, the approximation shows less than 1% relative error close to origin, and less than 5% relative error near the tail part.

The MGF of the residence time for the entire system, which is the residence time for a particle coming into the system until exiting the system, is easily obtained by replacing t_1 and t_2 by the same dummy variable t in (4.7). Figure 29 compares the saddlepoint approximation and the renormalized saddlepoint approximation of the

residence time with the numerical approximation of true univariate density of the residence time of the two-compartment model. As the picture is shown, the saddlepoint approximation closely follows the true density, although it slightly overestimates the density. The relative errors for saddlepoint approximation are mostly 10 to 11 % in the tail part, around 13 % in the middle and around 8 % close to origin. Renormalization of the approximation results in a relative error for the tail part less than 1 %, and the error for middle and origin part is less than 4 %. True differences in the tail part are so small due to the small magnitude of the approximation that the actual difference between true density and the saddlepoint approximation without renormalization is at most 10^{-4} .

The benefit of using the saddlepoint approximation is more distinctive in this case, because we do not have to derive the distribution for the convolution of variables from the multivariate density through a variable transformation.

4.4 Discussion

The direct calculation of the MGF using the distribution of the number of visits allowed us to express the exact distribution of the residence time for the two-compartment model. It was also shown that the residence time of the central compartment has an exponential distribution regardless of multiple visits in Markov processes. The MGF of the bivariate residence time for the two-compartment model is expressed as a closed form unlike the density of that. The MGF shows that the residence time does not have a simple bivariate continuous form due to the probability of a particle exiting the system without visiting compartment 2. The saddlepoint approximation was performed only on the continuous part of the bivariate distribution. The approximated density shows that the density of bivariate residence time has the peak at origin, and monotonically decreases to the tail. The saddlepoint approxi-

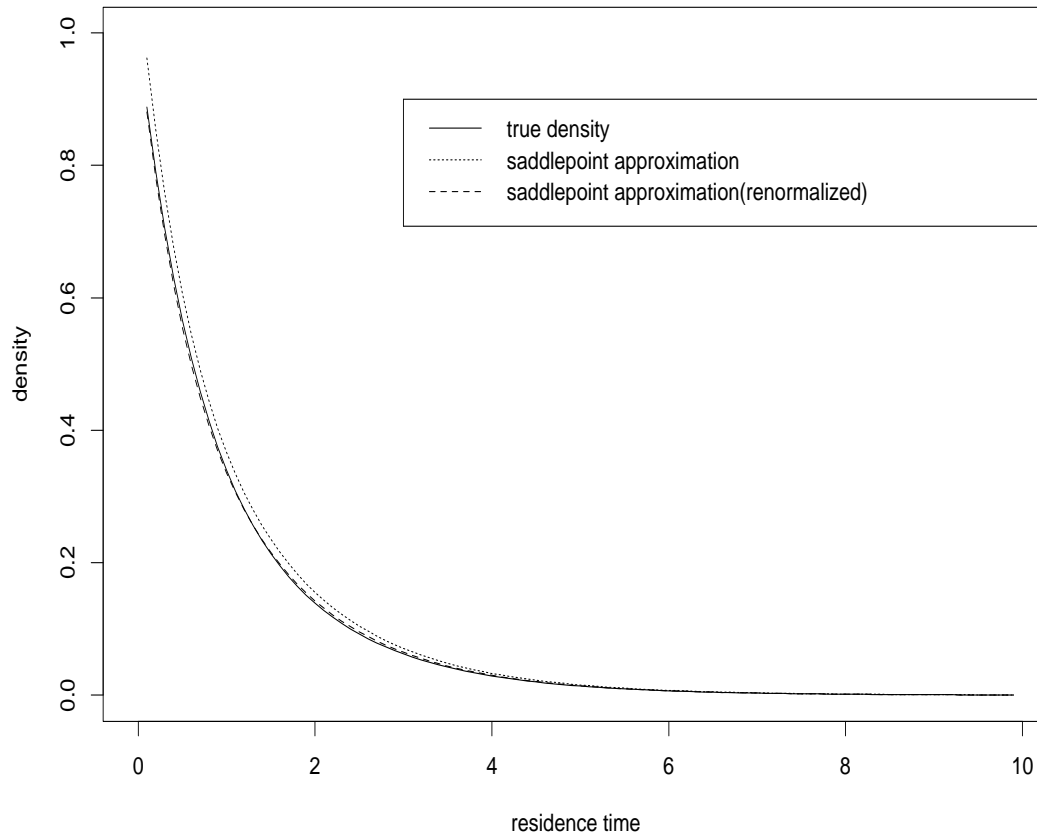


Figure 29: The comparison of the saddlepoint approximation and the renormalized saddlepoint approximation with numerically approximated true density for the two compartment model in Figure 27.

mation approximates the density accurately once we have the MGF of a variable of interest whether or not a closed form of the density exists. However, one needs to be cautious in the choice of the saddlepoint if there are multiple solutions for (4.9) as discussed previously. It was demonstrated that there always exists a single root on the range that satisfies certain conditions. The benefits of having an exact bivariate MGF are clear in this case. We can not only obtain a higher order moments by differentiating it, but also it can be converted to the density using the saddlepoint

approximation.

4.5 The Calculation of the Bivariate Distribution of the Residence Time

Let S_1 and S_2 be the residence time for compartments 1 and 2 respectively in Figure 26, and N_1 and N_2 the number of visits for the particle starting in compartment 1 to compartment 1 and 2, respectively. Using (4.2), the bivariate density for $(S_1, S_2 > 0)$ is

$$\begin{aligned}
f(s_1, s_2) &= \sum_{n_1=1}^{\infty} \sum_{n_2=1}^{\infty} f(s_1, s_2 | n_1, n_2) P(n_1, n_2) \\
&= f(s_1, s_2 | n_1 = 1, n_2 = 1) (1 - \pi_1) \pi_2 + \sum_{n_1=2}^{\infty} \sum_{n_2=n_1-1}^{n_1} f(s_1, s_2 | n_1, n_2) P(n_1, n_2) \\
&= (1 - \pi_1) c g(s_1 | n_1 = 1) g(s_2 | n_2 = 1) \\
&\quad + \sum_{n_1=2}^{\infty} [g(s_1 | n_1) g(s_2 | n_1 - 1) (1 - \pi_1)^{n_1-1} \pi_1 (1 - \pi_2)^{n_1-1}] \\
&\quad\quad + \sum_{n_1=2}^{\infty} [g(s_1 | n_1) g(s_2 | n_1) (1 - \pi_1)^{n_1} (1 - \pi_2)^{n_1-1} \pi_2] \\
&= \pi_2 \sum_{n_1=1}^{\infty} g(s_1 | n_1) g(s_2 | n_1) (1 - \pi_1)^{n_1} (1 - \pi_2)^{n_1-1} \\
&\quad + \pi_1 \sum_{n_1=2}^{\infty} g(s_1 | n_1) g(s_2 | n_1 - 1) (1 - \pi_1)^{n_1-1} (1 - \pi_2)^{n_1-1}, \tag{4.11}
\end{aligned}$$

where $g(s_i | n_i = 1)$ is the density of the retention time for a compartment i , and $g(s_i | n_i)$ is the density of the sum of n_i independent retention times.

CHAPTER V

AN APPROACH TO THE RESIDENCE TIME DISTRIBUTION FOR
STOCHASTIC MULTI-COMPARTMENT MODELS**5.1 Introduction**

Compartments in models usually have physiological implications, and thus simple compartment models are often too naive to describe the kinetics of a drug through the whole body, although many researchers prefer simple models like the two-compartment model. We expand our interest to multi-compartment models in an effort to generalize the results about the two-compartment model in previous chapter.

When a more complicated model than a two-compartment model is required to describe the kinetics of drugs, one interest is the residence time for the entire system or a part of the system that consists of several compartments. Another interest is simplifying the system by combining compartments that result in a non-exponential retention time distribution. In pharmacokinetics, a structural transformation of a complex pharmacokinetics model to obtain a simpler model with identical kinetic behavior is called lumping, and that is a common approach to reduce whole-body physiologically based pharmacokinetic model dimensionality and complexity (Nestorov et al., 1998).

We implement the two-compartment approach using the cofactor rule for a single destination (Butler, 2000) that provides the MGF for the retention time for combined compartments or the entire system. The cofactor rule and the results from the two-compartment model together lead us to specify the MGF for the residence time in the combined compartments. Using a semi-Markov process model that describes the kinetics of calcium in the human body in Chapter II, we compare the accuracy of this

new method with the method using the probability intensity coefficient matrix. In an application, we compare the residence times for two different kinetics of a drug called pravastin that result from different administration methods, oral administration and intravenous injection.

5.2 Cofactor Rule for a Single Destination

In this section, we introduce the cofactor rule and use the results from the two-compartment model in the previous section to obtain the MGF of residence times for combined compartments in more complicated compartment models.

Cofactor rules were first derived and proved by Butler in 1997, and later he showed that they can be derived using methods of matrix algebra (Butler, 2000). It is equivalent to a flowgraph technique called Mason's rule that is based on flowgraph analyses to solve stochastic problems (Whitehouse, 1983). Butler and Huzurbazar (1997) applied Mason's rule to obtain the empirical likelihood for the distribution of survival time based on the stochastic flow graph model. However, cofactor rules are more simple in formula and easier to compute using mathematical computer packages such as Maple or Mathematica.

In semi-Markov processes, the successive states visited form a Markov chain, and a waiting time has a distribution that depends on the state being visited (Çinlar, 1975). Therefore, we can characterize the behavior of a semi-Markov system in terms of the matrix of one-step branch transmittances that combine transition probabilities and MGFs for each state change (Butler and Huzurbazar, 1997). Let $W(t)$ be the matrix of one-step branch transmittances for the n -state semi-Markov process, and w_{ij} , an element of $W(t)$. Each w_{ij} is a product of the MGF of the retention time of a current compartment with the outflow transfer rate as a parameter and the conditional probability that a particle moves to compartment j given that it starts

in i .

Suppose that S is the first passage time from state 1 to state n or equivalently the residence time for the entire system. State 1 is the entering state, and state n is the destination state. Define $f_{1n} = Pr(S < \infty)$ and $M_S(t)$ is the conditional MGF of S given $S < \infty$. Then the cofactor rule for the first passage transmittance from state 1 to state $n \neq 1$ is

$$f_{1n}M_S(t) = \frac{(n, 1) \text{ cofactor of } I_n - W(t)}{(n, n) \text{ cofactor of } I_n - W(t)} := \frac{(-1)^{n+1}|\Phi_{n1}(t)|}{|\Phi_{nn}(t)|}, \quad (5.1)$$

where $\Phi_{ij}(t)$ is the (i, j) th minor of $I_n - W(t)$ (Butler, 2000). If the MGF for the retention time at each state is well defined on an open neighborhood of 0, and passage $1 \rightarrow n$ is possible, then $f_{1n}M_S(t)$ is well defined over $(-\infty, c)$ for $c > 0$ (Butler, 2000). If the passage from state 1 to state n is certain to occur, f_{1n} becomes 1 so that the cofactor rule provides the MGF for the first passage through the system directly.

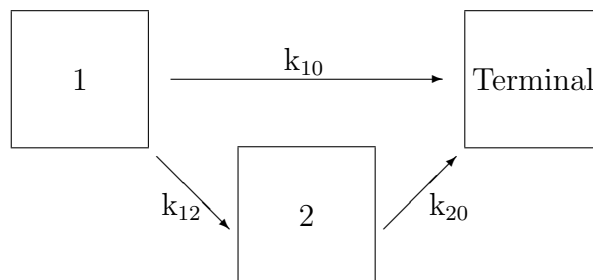


Figure 30: An example of a Markov process.

To demonstrate the cofactor rule, consider a simple two-compartment model based on the Markov process in Figure 30. The compartment “terminal” is added to express the exterior of the system. Physiologically this model could describe the absorption in compartment 1 and elimination process in compartment 1 and 2 in a drug administration. Each k_{ij} indicates the transfer rate from compartment i to j .

As an example, suppose $k_{12} = 2$, $k_{20} = 2$ and $k_{10} = 1$, where subscript 0 indicates the terminal compartment. Then, retention times for compartment 1 and 2 have the exponential distribution with means $1/3$ and $1/2$, respectively. Let $M_{R_1}(t)$ and $M_{R_2}(t)$ be the MGFs of the retention times for compartments 1 and 2. Then the matrix of one-step branch transmittances is

$$W(t) = \begin{bmatrix} 0 & \frac{k_{12}}{k_{12}+k_{10}}M_{R_1}(t) & \frac{k_{10}}{k_{12}+k_{10}}M_{R_1}(t) \\ 0 & 0 & M_{R_2}(t) \\ 0 & 0 & 0 \end{bmatrix}.$$

Therefore the MGF of the residence time S for the whole system using (5.1) is

$$M_S(t) = \frac{1}{3}M_{R_1}(t) + \frac{2}{3}M_{R_1}(t)M_{R_2}(t).$$

The cofactor rule is easily applicable to the much more complicated model which has some feedback loops like the system in Figure 31. Since a particle starting from compartment 1 will go to the absorbing compartment 6 in finite time, the MGF of the residence time for the system is

$$M_S(t) = \frac{w_{12}w_{26}(1 - w_{34}w_{43})}{1 - w_{23}w_{32} - w_{34}w_{43} - w_{25}w_{52} + w_{25}w_{52}w_{34}w_{43}}$$

where the one-step transmittance w_{ij} depends on the probability of going to state j from i and the MGF of the retention time that does not necessarily have an exponential distribution.

We can apply the cofactor rule to the two-compartment model in Section 4.2. The matrix of one-step transmittance of the two compartment model in Figure 26 is

$$W(t) = \begin{bmatrix} 0 & \frac{k_{12}}{k_{12}+k_{10}}M_{R_1}(t) & \frac{k_{10}}{k_{12}+k_{10}}M_{R_1}(t) \\ \frac{k_{20}}{k_{12}+k_{10}}M_{R_1}(t) & 0 & \frac{k_{20}}{k_{12}+k_{10}}M_{R_1}(t) \\ 0 & 0 & 0 \end{bmatrix}.$$

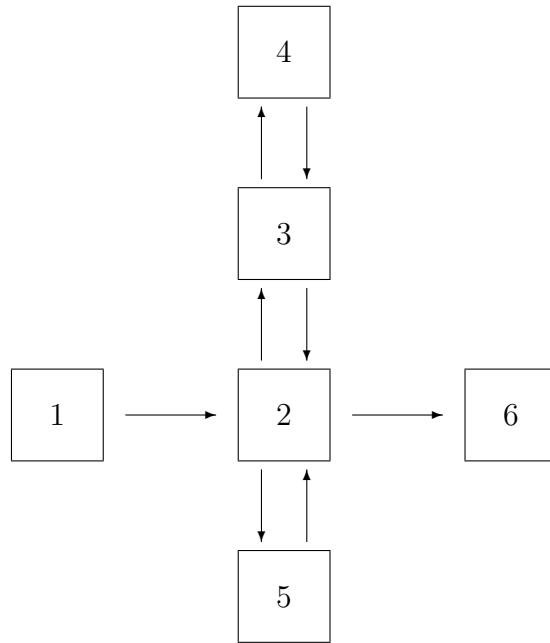


Figure 31: An example of semi-Markov process model with feedbacks.

By letting $\frac{k_{10}}{k_{12}+k_{10}} = \pi_1$ and $\frac{k_{20}}{k_{21}+k_{20}} = \pi_2$, and using (5.1), we obtain

$$M_S(t) = \frac{\pi_1 M_{R_1}(t) + (1 - \pi_1)\pi_2 M_{R_1}(t)M_{R_2}(t)}{1 - (1 - \pi_1)(1 - \pi_2)M_{R_1}(t)M_{R_2}(t)}.$$

which is the same MGF as (4.7) by replacing t_1 and t_2 by t .

5.3 Two-Compartment Model to Multi-Compartment Model

Many times, the residence time of a part of system is of interest, and in such a case the cofactor rule can be used to obtain the MGF of the retention time during a single visit for that part of the system. This MGF can be incorporated into two-compartment models to calculate the MGF of the total residence time in the system. We illustrate this with the previously shown calcium kinetics model, M&W model in Figure 3.

The method in (Matis and Wehrly, 1990) to obtain the mean and variance of a

residence time for a compartment or compartments of interest is using a coefficient matrix, say K . The component of K , k_{ij} is defined in (2.1). Under some regularity conditions, the expectation of residence times θ and the variances are

$$\theta = -K^{-1} \quad (5.2)$$

and

$$V(S) = 2\theta\theta_D - \theta_{(2)} \quad (5.3)$$

where θ_D is the diagonal matrix, $\text{diag}(\theta_{11}, \dots, \theta_{nn})$ and $\theta_{(2)}$ is the matrix of squared elements of θ (Matis et al., 1983).

Using the estimated parameters provided in (Matis and Wehrly, 1990) as $\hat{k}_{12} = 3.253$, $\hat{k}_{21} = 6.469$, $\hat{k}_{13} = 0.188$, $\hat{k}_{31} = 1.047$, $\hat{k}_{10} = 0.0504$, and $\hat{k}_x = 1.235$ in hours⁻¹, the coefficient matrix is

$$K = \begin{bmatrix} -3.636 & 3.131 & 0.444 & 0 & 0 & 0 \\ 3.735 & -3.735 & 0 & 0 & 0 & 0 \\ 0 & 0 & -0.444 & 0.444 & 0 & 0 \\ 0.414 & 0 & 0 & -0.444 & 0.030 & 0 \\ 0 & 0 & 0 & 0 & -0.030 & 0.030 \\ 0 & 0 & 0 & 0.030 & 0 & -0.030 \end{bmatrix}.$$

Using this matrix, the equation in (5.2), and combining results using appropriate transformation, the mean residence times of compartment 1, 2, and 3 are calculated as 19.86, 9.99, and 90.13 respectively. Each ij element in the matrix resulting from the equation (5.3) is the variance of the residence time at compartment j for a particle starting i . Some limitations are shown for this method. First, the manipulation of the matrix is not easy if we try to obtain higher order moments than the mean and variance. Second, methods for combining several compartments to obtain the second

or higher order moments for the residence time are still not clearly developed. Third, this approach does not provide exactly, or even approximately, the distributions of the retention times or the residence times.

Using M&W model, we will calculate the MGF of the retention time directly using the cofactor rule and compare the resulting moments with the results based on the coefficient matrix above. First, we apply the cofactor rule to get the retention time for the deep compartment. Compartment 3 is the entering compartment, and compartment 1 can be considered as the exterior of the deep compartment. Then the one-step transmittance matrix for the deep compartment is

$$W(t) = \begin{bmatrix} 0 & M(t|k_{13}) & 0 & 0 & 0 \\ 0 & 0 & \frac{k_x}{k_x+k_{31}}M(t|k_x+k_{31}) & 0 & \frac{k_{31}}{k_x+k_{31}}M(t|k_x+k_{31}) \\ 0 & 0 & 0 & M(t|k_x) & 0 \\ 0 & M(t|k_x) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad (5.4)$$

where $M(t|\beta)$ is the MGF of the exponential(β) distribution. Therefore, by (5.1), the MGF for the time to stay in the deep compartment for a single visit, say $M_{R_{deep}}(t)$, using the cofactor rule and the MGF of the exponential distribution is

$$M_{R_{deep}}(t) = \frac{\frac{k_{31}}{k_x+k_{31}} \left\{ \frac{1}{1-t/k_{13}} \right\} \left\{ \frac{1}{1-t/(k_x+k_{31})} \right\}}{1 - \frac{k_x}{k_x+k_{31}} \left\{ \frac{1}{1-t/(k_x+k_{31})} \right\} \left\{ \frac{1}{1-t/k_x} \right\}^2}. \quad (5.5)$$

The mean and variance of retention time R_{deep} using the parameters given above are 3.68 and 39.34. The next step is calculating the MGF of the residence time for a particle during all of its visits at the deep compartment before exiting to the exterior of the system using (5.5). Figure 32 shows the schematic of the two-compartment model derived from Figure 3. Let S_{deep} be the total residence time for the deep

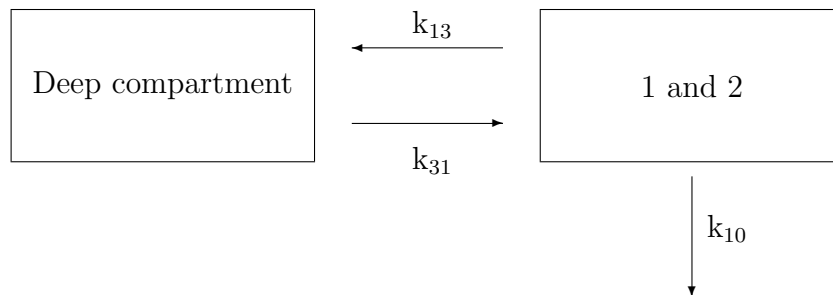


Figure 32: Two-compartment schematic of the 3-compartment model to calculate the residence time for the deep compartment.

compartment and π the probability of a particle to escape the system from the combined compartment (1 and 2). Using the distribution of the number of visits we can calculate that

$$M_{S_{deep}}(t) = \frac{\pi}{1 - (1 - \pi)M_{R_{deep}}(t)}, \quad (5.6)$$

where $\pi = \frac{k_{10}}{k_{13} + k_{10}}$. The mean residence time of S_3 using (5.6) is 90.05. The mean residence time using the coefficient matrix (5.4) is 90.13. Rounding causes the small difference. The MGF of residence time for entire system S_{total} is also easily found by the cofactor rule as

$$M_{S_{total}}(t) = \frac{w_{10}}{1 - w_{12}w_{21} - w_{13}M_{R_{deep}}(t)}, \quad (5.7)$$

where $w_{10} = \frac{k_{10}}{k_{13} + k_{12} + k_{10}} \frac{1}{1 - t/\{k_{13} + k_{12} + k_{10}\}}$, $w_{12} = \frac{k_{12}}{k_{13} + k_{12} + k_{10}} \frac{1}{1 - t/\{k_{13} + k_{12} + k_{10}\}}$, $w_{21} = \frac{1}{1 - t/k_{21}}$, and $w_{13} = \frac{k_{13}}{k_{13} + k_{12} + k_{10}} \frac{1}{1 - t/\{k_{13} + k_{12} + k_{10}\}}$. We can obtain the same results as above directly from the one-step transmittance matrix for the entire system. The mean of S_{total} is 119.87, and again this agrees with the mean 119.98 using the coefficient matrix. We can obtain higher moments than the mean by repeatedly differentiating the MGFs. For the example, variances of S_{deep} and S_{total} using (5.6) and (5.7) are 9403.26 and 15665.75, respectively.

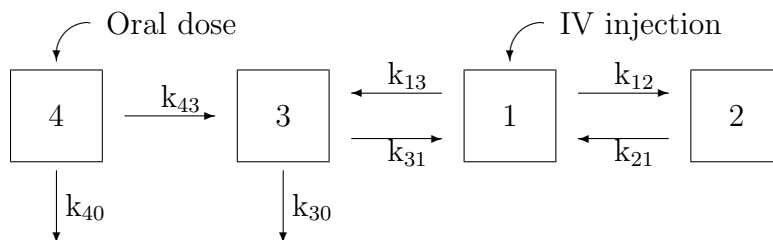


Figure 33: The pharmacokinetic model for pravastatin. The compartment 1, 2, 3, and 4 represent the central, deep, shallow and absorption compartment.

5.4 Comparison of Oral Administration and IV Bolus Injection

Drugs are administered through many different routes for reasons such as convenience, availability, or economic reasons. Different routes obviously result in different pharmacokinetics inside the body. As an example, oral administration usually requires an absorption compartment to describe the kinetics of drugs, but intravenous injection (iv injection) does not. Also, the residence time after absorption may be different depending on the different scheme of the drug distribution.

The compartment model in Figure 33 by Hatanaka et al. (1998) describes the pharmacokinetics of pravastatin after single intravenous and oral administrations in rats. Pravastatin is a tissue-selective inhibitor of cholesterol synthesis for the treatment of hypercholesterolemia. It is more permeable across the plasma membrane of hepatic cells than that of nonhepatic cells. Compartments 1, 2, and 3 represent the central, deep, and shallow compartments, respectively, for iv bolus injection. Compartment 4 represents an absorption compartment, mainly the gastrointestinal tract after oral administration. The deep compartment reflects mainly muscle, and the shallow compartment reflects the liver, the target compartment. The model implies that the drug accesses the shallow compartment after absorption when the drug is administered orally. For iv injection it goes through the central compartment to ac-

cess the shallow compartment. Once the drug is absorbed or administered through iv injection, it is eliminated only through the shallow compartment. Hatanaka et al. show that plasma concentration is dose-dependent, and that may be caused by nonlinear kinetics in the hepatic uptake rate k_{13} . However, in this paper we assume that the transfer rates are fixed for the purpose of illustration, and thus the retention times have the exponential distribution. We are interested in comparing the residence times inside the body for the central, deep and shallow compartments after absorption for oral administration and iv injection. We calculate the MGFs of the residence time for the oral administration and the iv injection and compare the moments and distributions for both cases. Figure 34 illustrates the kinetics of the drug after iv injection. Using (5.1), the MGF of the residence time of the model is

$$M_{S_{iv}}(t) = \frac{w_{13}w_{30}}{1 - w_{12}w_{21} - w_{13}w_{31}} \quad (5.8)$$

where w_{ij} represents the one-step transmittance from compartment i to j using the MGF as defined in Section 5.2. We use the transfer rates: $k_{12} = 0.324$, $k_{21} = 0.121$, $k_{31} = 0.910$, and $k_{30} = 0.480$ in the unit of min^{-1} provided in Hatanaka et al. (1998). The transfer rate from compartment 1 to 3 is not constant but depends on the amount of the drug in the central compartment, however we fix $k_{13} = 1.10$, that is the transfer rate for the drug amount 10mg/kg in the central compartment which is also given in Hatanaka et al. (1998). Using (5.8) and the given transfer rates, the mean and variance of the residence time are 11.765 and 241.003.

The kinetics of the drug after absorption for oral administration are shown in Figure 35. The MGF of the residence time of the model using cofactor rule is then

$$M_{S_{oral}}(t) = \frac{w_{30}(1 - w_{12}w_{21})}{1 - w_{12}w_{21} - w_{13}w_{31}} \quad (5.9)$$

The mean and variance using (5.9) are 8.421 and 189.590. We can see that the mean residence time of the drug inside the body for an oral dose is smaller than that for an

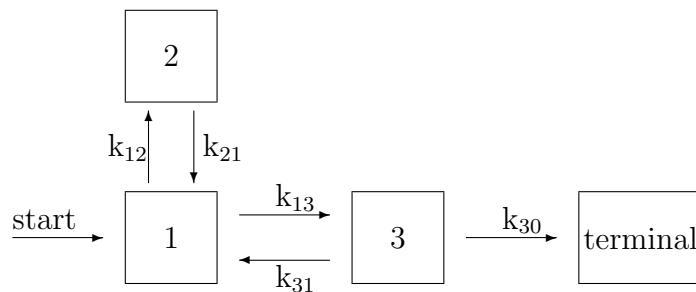


Figure 34: The illustration of the kinetics for pravastin by iv bolus injection.

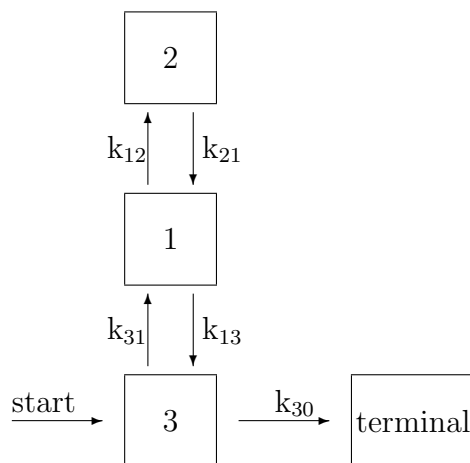


Figure 35: The illustration for the kinetics of pravastin after absorption by oral administration.

iv injection. Figure 36 compares the approximated densities of the residence times for the two administrations using the renormalized saddlepoint approximation. Figure 36 illustrates the large initial qualitative differences between the two distributions. The density for the oral dose is monotonically decreasing with rapid initial decay, whereas the density for the iv injection starts at 0 and reaches a peak afterwards resulting in a longer residence time.

Now, let us focus on the residence times for specific compartments rather than the entire system. For illustration, suppose that in the kinetics of pravastin we are

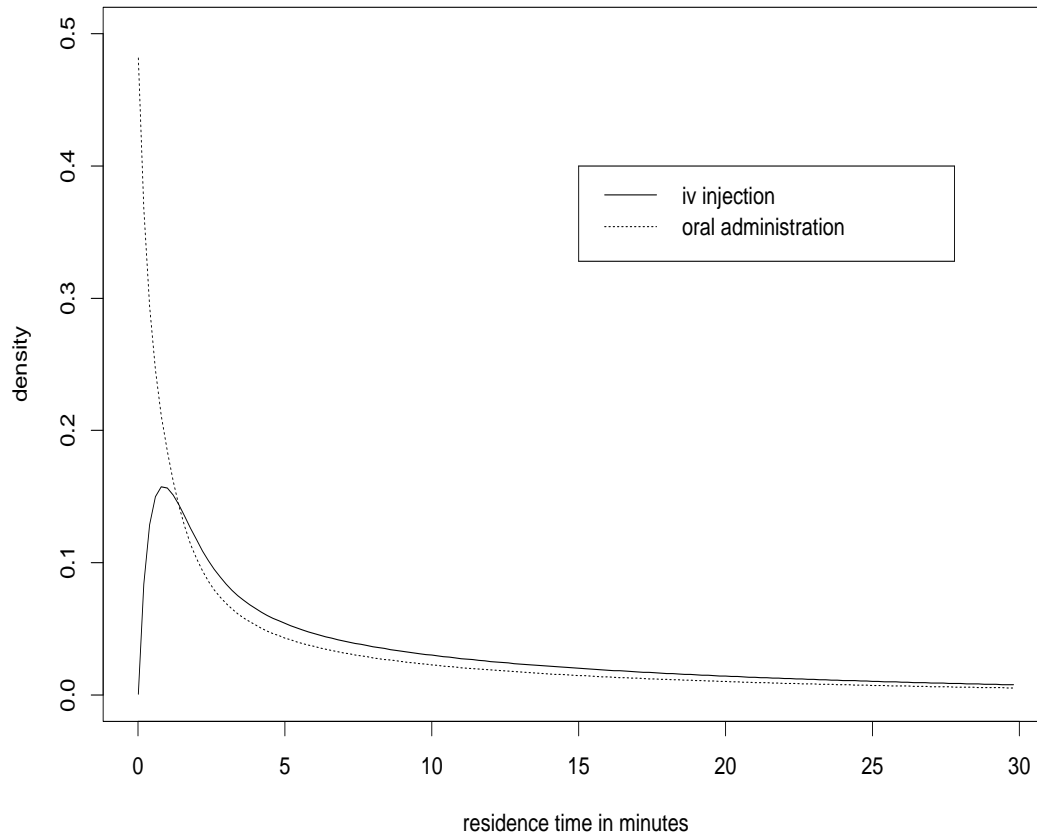


Figure 36: The renormalized saddlepoint approximation of densities of the residence time for the central, deep and shallow compartment by oral and iv injection administration. The solid line is for iv injection and the dashed line oral dose.

initially interested in the residence time only for the central and deep compartments which are plasma and muscle combined. We first obtain the MGF of the retention time for the combined deep and central compartments. In the both the iv injection and oral administration models, the only route to the outside (the shallow compartment) from the combined compartment is through the central compartment. Therefore the

one-step transmittance matrix for the combined compartments is

$$W(t) = \begin{bmatrix} 0 & w_{12} & w_{13} \\ w_{21} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Then the MGF of the retention time for the new compartment using (5.1) is

$$M_{R_{new}} = \frac{w_{13}}{1 - w_{12}w_{21}}. \quad (5.10)$$

Since Figures 34 and 35 have a schematic of a two compartment model by considering the central and the deep compartment together as the new compartment, we can apply the results for two-compartment model in Section 4.2. Let N_1 and N_2 be the number of visits of a particle at the shallow compartment and the combined compartment. Using (4.3), N_2 for iv injection has the pmf

$$P_{N_2}(n_2) = \pi(1 - \pi)^{n_2-1}, n_2 = 1, 2, 3, \dots,$$

where $\pi = \frac{k_{30}}{k_{31} + k_{30}}$. Then the MGF of the residence time for the new compartment $M_{S_{new_{iv}}}(t)$ using (4.5) is

$$M_{S_{new_{iv}}}(t) = \frac{\pi M_{R_{new}}(t)}{1 - (1 - \pi)M_{R_{new}}(t)} \quad (5.11)$$

The mean and variance using (5.10) are 9.682 and 210.253. The pmf of N_2 for oral injection using (4.3) is

$$P_{N_2}(n_2) = \pi(1 - \pi)^{n_2}, n_2 = 0, 1, 2, \dots,$$

which shows that the probability of $N_2 = 0$ is not 0. Therefore the MGF using (4.6) is

$$M_{S_{new_{oral}}}(t) = \pi + (1 - \pi) \left(\frac{\pi M_{R_{new}}(t)}{1 - (1 - \pi)M_{R_{new}}(t)} \right), \quad (5.12)$$

and this gives the mean residence time 6.34 and variance 158.839. Figure 37 compares the approximated densities using the renormalized saddlepoint approximation between iv injection and oral administration. Since the distribution for oral administration has a probability mass π on 0, it has a lighter tail causing a smaller mean residence time and variance than those of iv administration.

We may be also interested in the residence time for the shallow compartment, which is in fact the target compartment of the drug. The number of visits N_1 for iv and oral administration both have the same distribution with pmf, using (4.3),

$$P_{N_1}(n_1) = \pi(1 - \pi)^{n_1-1}, n_1 = 1, 2, 3, \dots$$

The renormalized saddlepoint approximation of the density for the shallow compartment residence time is shown in Figure 38. The mean and variance are 2.083 and 4.340, respectively. Note that adding this mean residence time of the shallow compartment to the mean residence time of the central and shallow system for both administration cases respectively gives back the mean residence times for entire system, 11.765 and 8.421. Even though nonlinearity of hepatic absorption was not considered, these results demonstrate the difference in the distributions of residence times between oral administration and iv injection.

5.5 An Application Using the Markov Chain

We can approach the distribution of the univariate residence time using the general facts from the Markov chain. The concept based on this approach in this section is that any successive state visited in a semi-Markov process forms a Markov chain. Let Y be a semi-Markov process. Suppose that we are interested only in the time at which state Y is changed, say T_1, T_2, T_3, \dots , and let T_0 be 0. This defines a

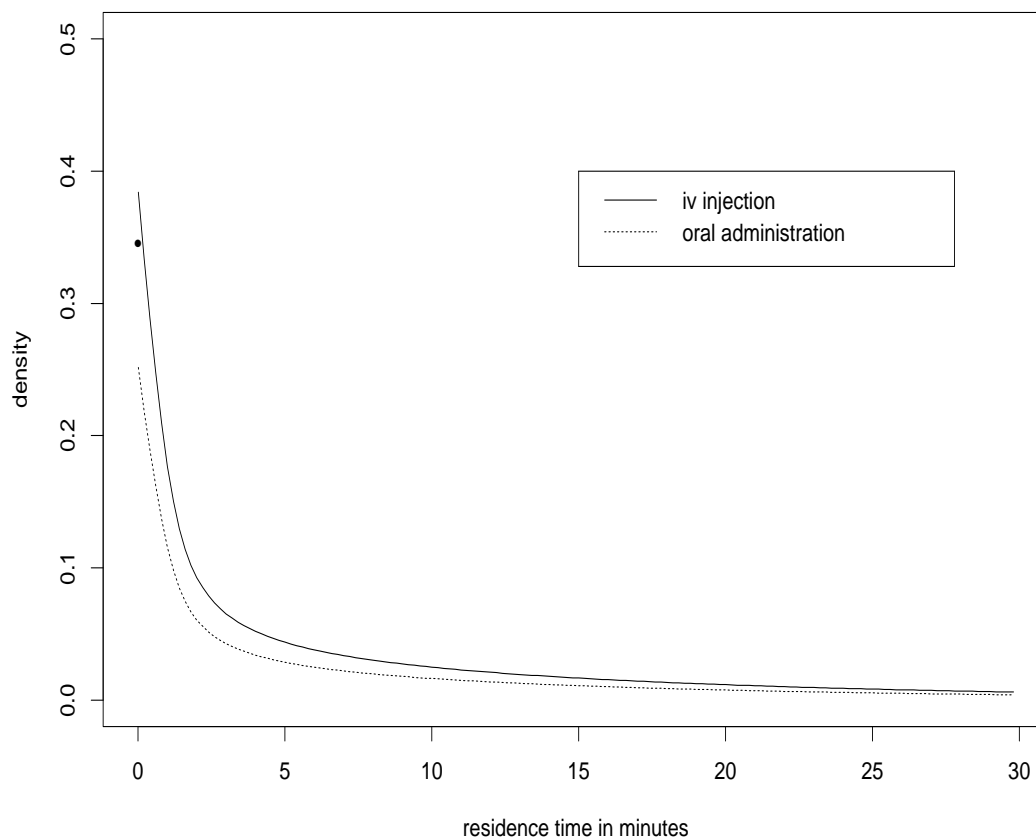


Figure 37: The renormalized saddlepoint approximation of densities of the residence time for the combined central and deep compartments. The solid line is for iv injection and the dotted line oral dose. The point indicates the probability for the drug particle to escape the body without visiting the central and deep compartments when the drug is orally administered.

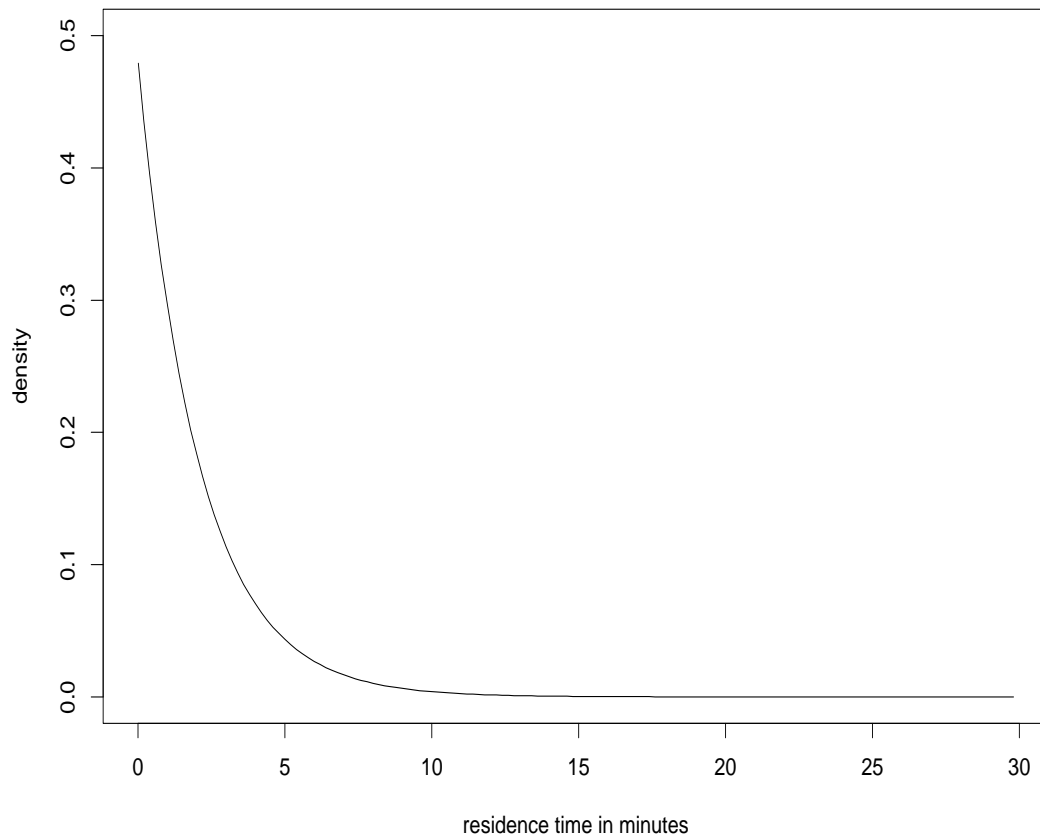


Figure 38: The renormalized saddlepoint approximation of the density of the residence time of the shallow compartment.

new process which is

$$X_n = Y(T_n),$$

where n is a natural number. If $X_n = i$, the interval $[T_n, T_{n+1})$ is said to be a sojourn interval in i . It was known that X_n is a Markov chain, and in Markov processes, $T_{n+1} - T_n$ has an exponential distribution with the parameter depending on X_n (Çınlar, 1975, page 247). The transition probability $P(i, j)$, is defined as

$$P(i, j) = P\{X_{n+1} = j | X_n = i\}, \quad i, j \in E, \quad (5.13)$$

where E is the state space. It is obvious that $P(i, i)$ is equal to 0. Let $F(i, j)$ be the probability of ever reaching j starting from i . Then it is known that

$$F(i, i) = 1 - \frac{1}{M(i, i)}, \quad F(i, j) = \frac{M(i, j)}{M(j, j)} \quad (5.14)$$

for transient states (Çınlar, 1975, page 148), where $M(i, j)$ is an element of the matrix

$$M = I + P + P^2 + \dots,$$

where P consists of $P(i, j)$ in (5.13). Let Q be the matrix of transient states obtained from P (Çınlar, 1975, page 145), then

$$M^* = I + Q + Q^2 + \dots = (I - Q)^{-1}. \quad (5.15)$$

Let N_{ij} be the total number of visits starting in i will make to j before its departure from the system, then we can observe the relationship that

$$P\{N_{jj} = m\} = F(j, j)^{m-1}(1 - F(j, j)), \quad m = 1, 2, \dots, \quad (5.16)$$

and for $i \neq j$,

$$P\{N_{ij} = m\} = \begin{cases} 1 - F(i, j), & m = 0, \\ F(i, j)F(j, j)^{m-1}(1 - F(j, j)), & m = 1, 2, \dots \end{cases} \quad (5.17)$$

Let S_{ij} denote the total residence time that the particle starting in i will accumulate in j during all its N_{ij} visits and ν_i denotes the sum of all transfer rates from compartment i . Also let $r = F(i, j)$, the probability of a particle from i to ever reach to j where $i \neq j$, and $p = 1 - F(j, j)$. Using (5.14) and (5.16), for $i = j$,

$$\begin{aligned} E[e^{tS_{ij}}] &= \sum_{n=1}^{\infty} E[e^{t\sum_{i=1}^N R_i} | N = n] P_N(n), \\ &= \sum_{n=1}^{\infty} M_{R_i}(t)^n p(1-p)^{n-1}, \\ &= \frac{pM_{R_i}(t)}{1 - (1-p)M_{R_i}(t)}. \end{aligned} \quad (5.18)$$

Similarly, using (5.14), and (5.17), for $i \neq j$,

$$E[e^{t\sum_{i=0}^n R_i}] = 1 - r + r \frac{pM_{R_i}(t)}{1 - (1-p)M_{R_i}(t)}.$$

If the process is the Markov process case, the results above show $S_{ii} \sim \text{Exp}(\frac{1}{\nu_i p})$, and $S_{ij} \sim 1\{S_{ij} = 0\}(1-r) + 1\{S_{ij} > 0\}r \cdot \text{Exp}(\frac{1}{\nu_j p})$ where β is the mean residence time of the compartment j , and $1\{\cdot\}$ is 1 if the condition in the brace meets, otherwise 0.

This approach lets us know the univariate distribution of the residence time at any compartment or directly connected compartments in the system. To illustrate the approach above, let see the two compartment model in Figure 26. Let $\pi_1 = \frac{k_{10}}{k_{12} + k_{10}}$ and $\pi_2 = \frac{k_{20}}{k_{21} + k_{20}}$ represent the probabilities of escaping the system from compartment 1 and compartment 2, respectively. Then the transition matrix with only transient part, Q is

$$Q = \begin{bmatrix} 0 & 1 - \pi_1 \\ 1 - \pi_2 & 0 \end{bmatrix}. \quad (5.19)$$

Therefore,

$$(I - Q)^{-1} = \begin{bmatrix} \frac{1}{\pi_1 + \pi_2 - \pi_1 \pi_2} & \frac{1 - \pi_1}{\pi_1 + \pi_2 - \pi_1 \pi_2} \\ \frac{1 - \pi_2}{\pi_1 + \pi_2 - \pi_1 \pi_2} & \frac{1}{\pi_1 + \pi_2 - \pi_1 \pi_2} \end{bmatrix}. \quad (5.20)$$

Then, $F(1, 1) = 1 - \pi_1 - \pi_2 + \pi_1\pi_2$, $F(1, 2) = 1 - \pi_1$, and $F(2, 2) = 1 - \pi_1 + \pi_2 + \pi_1\pi_2$ using (5.14). The probability of the number of visits are then

$$P_{N_1}(n_1) = \{\pi_1 + \pi_2 - \pi_1\pi_2\}\{1 - (\pi_1 + \pi_2 - \pi_1\pi_2)\}^{n_1-1}, \quad n_1 = 1, 2, \dots, \quad (5.21)$$

and

$$P_{N_2}(n_2) = \begin{cases} \pi_1, & n_2 = 0, \\ \{1 - \pi_1\}\{\pi_1 + \pi_2 - \pi_1\pi_2\}\{1 - (\pi_1 + \pi_2 - \pi_1\pi_2)\}^{n_2-1}, & n_2 = 1, 2, \dots. \end{cases}$$

These are the same results as (4.3) and (4.4).

For an example in which we can not find the distribution of the residence time using the two-compartment model approach, let us consider again the calcium clearance model in Figure 3. Compartment 1, plasma, is connected with more than one compartment, thus it can not be interpreted as a similar structure to the two-compartment model as demonstrated in Section 5.3. The transition matrix for the transient parts for the entire system is

$$Q = \begin{bmatrix} 0 & \frac{k_{12}}{k_{12}+k_{13}+k_{10}} & \frac{k_{13}}{k_{12}+k_{13}+k_{10}} \\ 1 & 0 & 0 \\ 1 & 0 & 0 \end{bmatrix},$$

where each (i, j) element represents the transition probability from compartment i to j . Note that the third row and third column indicate the entire deep compartment.

Then,

$$(I - Q)^{-1} = \begin{bmatrix} \frac{k_{12}+k_{13}+k_{10}}{k_{10}} & \frac{k_{12}}{k_{10}} & \frac{k_{13}}{k_{10}} \\ \frac{k_{12}+k_{13}+k_{10}}{k_{10}} & \frac{k_{12}+k_{10}}{k_{10}} & \frac{k_{13}}{k_{10}} \\ \frac{k_{12}+k_{13}+k_{10}}{k_{10}} & \frac{k_{12}}{k_{10}} & \frac{k_{13}+k_{10}}{k_{10}} \end{bmatrix}.$$

The probability that a particle starting at compartment 1 ever visits compartment 1 is $F(1, 1) = \frac{k_{12}+k_{13}}{k_{12}+k_{13}+k_{10}}$ by (5.14). Equation (5.16) and (5.18) give the distribution of the

residence time and the MGF. The mean residence time with the transition coefficient used in previous section is 19.841. The mean residence time by the coefficient matrix manipulation is 19.865. The small difference is caused by rounding. The calculated variance is 787.352.

5.6 Discussion

The approach for the two-compartment model was used in combination with the single destination cofactor rule in order to obtain the distribution of the residence time for complicated compartment models. This makes it possible to provide not only the residence time for the entire system but also for the part of system in which we are specifically interested.

This methodology has some distinct advantages compared to the coefficient matrix manipulation (Matis and Wehrly, 1985) or approximation using the PH distribution (Johnson and Taaffe, 1990). First, this approach provides a complete set of moments for the residence time using direct calculation from the MGF. Obtaining the moments by matrix manipulation is not simple if we try to get higher order moments than means and variances. Also, in matrix manipulation, obtaining the variance for combined compartments introduces additional complexity due to the covariances between residence times for different compartments. Second, the new approach allows any possible distribution for each compartment or pseudo-compartment in contrast to the matrix approach based on Markov processes that limits the residence time to only an exponential distribution. Finally, obtaining the MGF is equivalent to knowing the distribution if the MGF exists in a neighborhood of zero. The density function corresponding to the MGF can be derived by the Fourier inversion formula for a continuous random variable. In addition, the saddlepoint approximation can be derived from the inversion formula (Daniels, 1954), and we observed that the saddlepoint

approximation using the MGF tracked the trend of the true density very closely .

The approach presented in this paper may have limitations in some cases. The approach to obtaining the bivariate distribution of the residence time distribution is based on the two-compartment model structure. The application using the Markov chain only provides a univariate residence time distribution. It is not known how the multivariate distribution can be defined if the structure of the system involves more than two compartments. This approach is also limited to connected compartments in a model, so that the direct application of the approach may be difficult if unconnected compartments in a model are interest. More investigation in these matters is needed. By demonstrating a method that transforms one model to the simpler model and an application of two-compartment model or Markov chain structure, the approach in this chapter suggests a useful frame work for the distributional approach.

CHAPTER VI

CONCLUSIONS

6.1 Summary

We investigated methods to approach the residence time distribution analytically throughout the research presented in this dissertation. In the semi-Markov processes, the distribution of the residence time with general life times in the two-compartment model was specified by the inductive approach using the discrete distribution for the number of visits and the distribution of the retention time. Especially under the Markov process assumption, regardless of multiple visits of a particle in the system, that is the summation of exponential variables, the resulting moment generation function proves the residence time of each compartment has an exponential distribution or is a mixture of the exponential distribution and a point mass on 0. The bivariate moment generating function of residence times can be converted to the density using the saddlepoint approximation. After renormalization, the approximation very closely follows the trend of the density.

In more complicated structures like multi-compartment models, the approach used in two-compartment models helps to find out the distribution of a compartment or a series of connected compartments in the system. Using the cofactor rule for a single destination, the approach to the multi-compartment system specifies the residence time distribution of a complicated structure for the system. Furthermore, adapting the properties from the Markov chain makes the application more resilient to the univariate residence time for a more complicated structure so that we can find the residence time distribution of the structure where we can not apply the two-compartment approach.

Throughout the dissertation, the saddlepoint approximation had an important role in approximating the density. We observed that various distributions could be used to obtain the formula for the saddlepoint approximation in theory. We also observed that the saddlepoint approximation based on the normal distribution provides relatively a reasonable approximation especially for multivariate distributions.

As asserted in the discussion part of Chapter V, the approach presented in this dissertation shows some advantages compared to the method using the coefficient matrix. First, it had no difficulty in finding the higher order moments of a compartment or combined compartments. Second, the approach is based on the complete specification of the MGF, and we can find/approximate the distribution of the residence time using it.

6.2 Future Research

Through the dissertation, we mainly assume that the retention time has the exponential distribution that implies the hazard rate is constant. Under the condition of independent particles, this results in a linear transfer rate, that is proportional to the population size (Matis and Kiffe, 2000). In many important applications, the hazard rate is not constant. In the dissertation, we mentioned a case that the hazard rate is age-varying, which is explained by semi-Markov models. Matis and Kiffe (2000) state that these “extensions are very useful in practice and yet are not readily conceptualized for the corresponding deterministic models” for the population. In fact, in drug kinetics, it is very common that the transfer rates are not linear depending on the population size, or concentration. In a drug elimination process that involves enzyme systems, drug metabolism and active transport are limited by reaching a capacity that the enzymes can handle (Wartak, 1983). When the enzyme systems are saturated, metabolism rate is fixed regardless of the drug concentration. In such a

case, the drug elimination rate is expressed by Michaelis-Menten equation (Wartak, 1983), that is the zero-order function of the concentration when the concentration is high. It seems that the elimination process follows an immigration process until the concentration approaches the capacity, then becomes a migration process by which the concentration lowers. We can expect that there is no such hazard function to describe the process as a simple time-dependent function, therefore deriving the distribution of the retention time does not seem feasible. We do not know if there is an analytically available deterministic solution for such a model.

As an application of the analytical approach by the MGF and the saddlepoint approximation, one may consider the development of a method to estimate the transfer rates. The parameter estimation is usually done using the non-linear least squares to fit the mean model or deterministic differential equation of the population (Matis et al., 1996a). Using the method in this dissertation, we are able to obtain or approximate the density of the residence time, which is also interpreted as the likelihood function of transfer rates. It may be possible that we can obtain parameters by maximizing the likelihood. In a similar fashion, Kay (1986) obtains the transfer rate using the likelihood in survival studies. An instant problem with this idea is the fact that most data in stochastic compartment research is the population data, which means that we need an appropriate method to transform the population size to the residence time.

In fact, the studies presented on this dissertation focus on the residence time in the system, which can also use for the survival analysis. We can find some examples in survival studies that utilize the stochastic model based on the Markov processes.

Kay shows an application of Markov processes to survival studies among cancer patients. Commonly, the data are available in the form of time points together with some general health measure such as a cancer marker. The purpose of the study

is to find cancer markers that can be used as a measure of relative survival rates. Defining different states of cancer by a potential cancer marker concentration in the body, a Markov model is constructed, which has a few different states of the disease and an absorbing state (death). Each transition probability can be expressed by the transition rates by solving the Kolmogorov equation numerically (if high dimension) or analytically (if low dimension). The likelihood with respect to transition rates for each individual is specified as a product of the transition probabilities. The maximum likelihood estimates of the parameters are obtained using an iterative procedure. The difference of the death rates from each state is tested using the asymptotic property of the Wald's test using the difference between estimated death rates and covariance of the difference.

A direct application of non-homogeneous Markov processes to the survival analysis is found in Anderson et al. (1991). The different states of the disease by an index of a substance form a multi-compartment Markov process similarly to Kay's, where the transition intensities are not necessarily independent of time. The cumulative hazard functions of transitions (to other state) are calculated by the Nelson-Aalen estimator. They form the transition matrix at the time point of each transition. Then, the probability for the occurrence of the event, transition to other state, can be expressed as a multiplication of the transition matrices in a similar manner to the calculation of the absolute probabilities (Bailey, 1964) in the Markov chain. The difference of this approach from the product limit (Kaplan-Meier) method is the fact that it takes into account in-between stages in the course of the final stage. The probability for each subject is expressed by not only the life time but also covariate measurements at the time of the patients' multiple visits. Both methods of the probability estimation show similar trends, however the approach using the Markov processes shows smaller standard deviations by considering that more information is contributed to the model.

Anderson et al. applied this approach to the Cox type regression model to estimate the hazard rate that takes the time independent-covariates.

This methodology is restricted by the Markov assumption. In fact, authors emphasize that the Markov assumption should be checked in applications of these method. However, these applications are enough to suggest the versatility of the stochastic compartment models in applications in different aspects.

In future research, we are interested in exploring the two-compartment model even more, since it is still very popular and useful model in cases that the model only needs relatively simple structure. First, we can develop the method to estimate the parameters using the analytic approach presented in this paper if the lifetime data are available. Second, we also can apply the analytic method shown here to a procedure that can provide the survival probability or waiting time distribution. Third, we may study how the distribution of retention time or the residence time for the two-compartment structure can be approximately or analytically described when non-linear transfer rates are present in the model.

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