STOCHASTIC MODELING OF RANDOM DRUG TAKING PROCESSES AND THE USE OF SINGULAR PERTURBATION METHODS IN PHARMACOKINETICS

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Failure to stick to a well-planned drug taking protocol may lead to drug inefficiency during medical treatments. In this dissertation, a stochastic model of the drug delivery process is studied, where the elimination of the drug between each dosage interval is modeled by a single or a set of ordinary differential equations (ODEs), and whether a new dosage of drug is taken or not is modeled by a stochastic impulsive condition.

We first derive several important algebraic equations that can be used to determine steady state probability distribution of the drug concentration, as well as some other statistics and relations to help understand this probability distribution. We then show numerical results of this distribution using two different methods for different sets of parameter values. Both linear and nonlinear drug elimination rates are studied and discussed.

We next examine the dynamics of this random drug taking process by considering the first exit time problems associated with this random iteration. Specifically, we study the mean of the first exit time the drug concentration passes an effective level. We show that this mean exit time is finite and we give bounds for these estimations.

We then discuss the issue of whether the patient should take a single or double dose if a dose is missed on the previous day. We show, by constructing a stochastic model that incorporates both an effective level and a toxicity level, that for a fixed toxicity level, when the effective level is high, then taking a double dose is the better strategy than if only one dose is taken and vice versa.

Finally, assuming drugs are injected into the body through extravascular routes on time at each scheduled time, i.e, assuming no randomness in the timing of drug intake, we apply singular perturbation techniques to obtain critical conditions under which there is a stable periodic solution of the model equations, assuming nonlinear elimination kinetics. We also construct composite expansions with this asymptotic solution and calculate typical important biomarkers that cannot be obtained otherwise.

For my parents.

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CHAPTER 1

INTRODUCTION

The time evolution of the concentration of the drug after one time or periodic injections through either intravascular or extravascular routes can be mathematically modeled with a set of ordinary differential equations (ODEs) that describes transportation and elimination of these drugs in and out of the human body or across different compartments in the body. By drugs, we mean any type of substance that includes pharmaceutical agents, hormones, nutrients, and toxins [5].

With these systems of ODEs, the design and development of new drugs, and the re-assessment of old drugs, become possible, since it is typical and common that important biological and medical information can be directly or indirectly inferred from the solutions of these system of ODEs. Examples include the time the plasma concentration of the drug reaches its peak and its magnitude and the average plasma concentration over a dosage interval.

Among all these ODE models, the one-compartment model is the most studied model in the field, where we regard the human body as a single, kinetically homogeneous unit [5]. Under the one-compartment framework, the drug is taken into the body through either extravascular or intravascular routes and is eliminated from the body through enzymatic reactions. For this dissertation, we make the assumption that drugs are to be taken periodically under the one-compartment framework, i.e., drugs are assumed to be taken at some certain fixed times nT for $n = 1, 2, ...$, where T denotes the length of the dosage time interval. Below, we introduce the concepts of first-order and nonlinear elimination kinetics, as well as intravenous and extravascular pathways through which drugs may be administered. We also introduce the concept and the issue of poor drug compliance, which is one of the major topics we model and tackle in this dissertation.

1.1 First-Order Elimination Kinetics

1.1.1 Intravenous Administration Regime

As the quickest way drugs can be delivered throughout the body, under the intravenous administration regime, we regard the human body as a single compartment (called the central compartment) and we assume that the plasma concentration everywhere in the body is the same. At the same time, urinary and biliary excretion, excretion in expired air, and biotransformation in the liver or other fluids or tissues are major pathways for drug elimination from the body. For example, glomerular filtration in the kidney can be regarded as a diffusion process, the rate of which can be characterized by first-order kinetics. By first-order kinetics, we mean that the elimination rate is proportional to the drug concentration in the plasma.

Suppose that the elimination kinetics is of first order. Let C be the drug concentration in the plasma. Then, we have the following differential equation that describes the elimination

$$\frac{dC}{dt} = -KC, \tag{1.1}$$

where K is the elimination rate constant. The solution to this equation can be obtained by separation of variables

$$C(t) = C(0)e^{-Kt}, \tag{1.2}$$

where $C(0)$ denotes the initial concentration of the drug in the body. However, since we are assuming that drugs should be taken on a periodic basis, we need to include that information through an additional impulse condition at discrete times when drugs are assumed to be taken. With this being said, the entire system of equations now reads

$$\begin{cases} \dfrac{dC}{dt} = -KC, & (1.3) \\ C(nT^{+}) = C(nT) + J, & (1.4) \end{cases}$$

for $n = 0, 1, 2..$, where J denotes the concentration of the drug of a single dosage and the superscript '$+$' denotes the right-hand limit. This type of system of differential equations is called a system of impulsive differential equations, since at some fixed times, an impulse

J is added to the some of the variables in the ODE model. To solve this system, notice that we have

$$C(nT) = C\left((n-1)T^+\right)e^{-kT}, \tag{1.5}$$

so that the sequence $x_n := C(nT^+)$ satisfies the difference equation

$$x_n = x_{n-1}e^{-kT} + J. \tag{1.6}$$

The solution to this iteration can be found as

$$x_n = \frac{J}{1-e^{-kT}}\left[1 - \left(e^{-kT}\right)^{n+1}\right]. \tag{1.7}$$

The only positive stable fixed point is

$$x^* = \frac{J}{1-e^{-KT}} > 0. \tag{1.8}$$

A typical plot can be seen from Figure 1.1. Notice that in this situation, we have discontinuities (jumps) at discrete times nT, for nonnegative integers n.

1.1.2 Extravascular Administration Regime

If instead, drugs are taken through extravascular routes, for example through oral administrations, then we modify the previous model by adding an additional compartment, called the absorption compartment (or absorption site) preceding the central compartment, so that any extravascular administration will be administered into the absorption compartment first, and then it will enter the central compartment immediately afterwards. If we assume that the loss of the drug from the absorption site obeys first-order kinetics, and the elimination of the drug in the central compartment obeys first-order kinetics as well, then we end up having the following system, for one time injection

$$\begin{cases} \dfrac{dC_a}{dt} = -K_aC_a, & (1.9) \\ \dfrac{dC}{dt} = K_aC_a - KC, & (1.10) \end{cases}$$

where we have used K_a and C_a to denote the the first-order elimination rate and concentration of the drug in the absorption compartment, respectively. The solution to this system can be found analytically to give

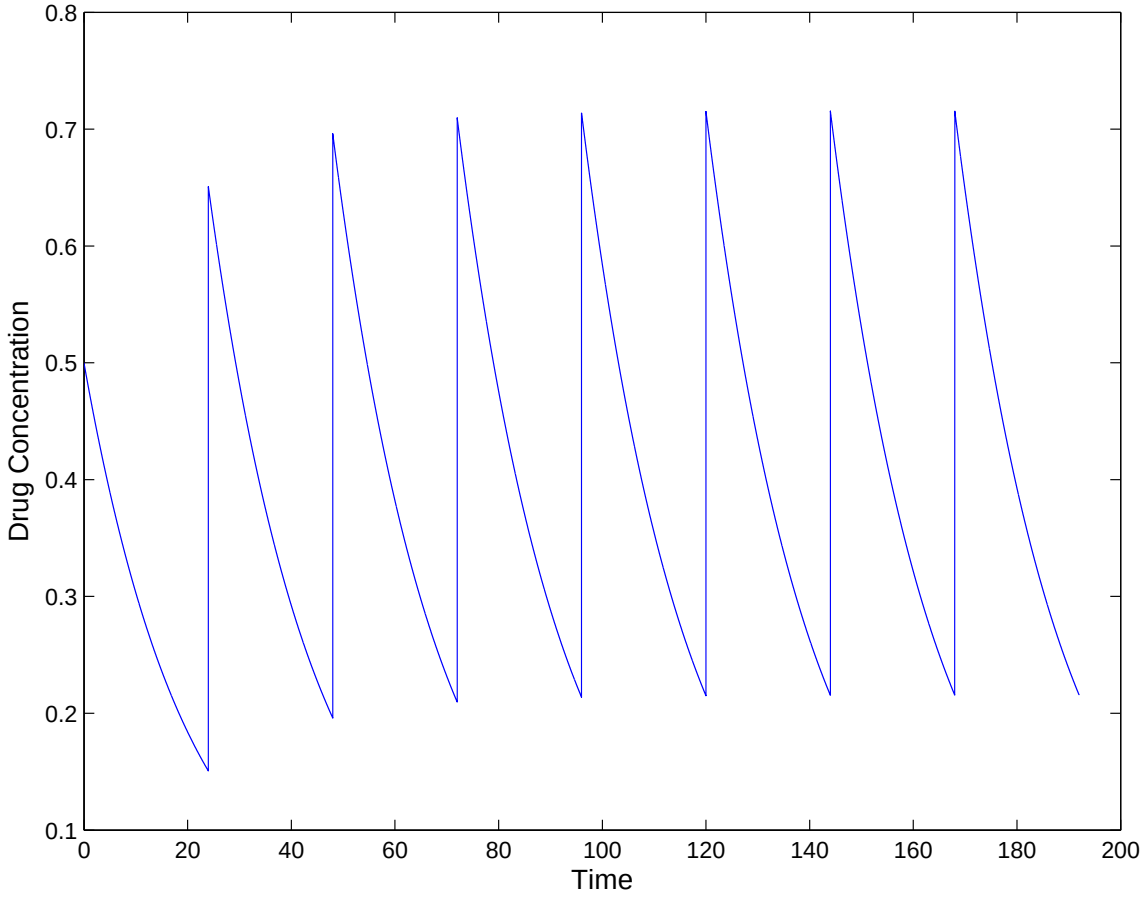


Figure 1.1. In this figure, we plot the time evolution of the system (1.3) $\sim$ (1.4). Parameter values are: $K = 0.05$, $T = 24$, and $J = 0.5$.

$$\begin{cases} C_a(t) = Je^{-K_a t}, & (1.11) \\ C(t) = \dfrac{K_a J}{K - K_a}\left(e^{-K_a t} - e^{-Kt}\right), & (1.12) \end{cases}$$

if the initial conditions are taken to be $C_a(0) = J$ for the absorption compartment and $C(0) = 0$ for the central compartment. If the drug is taken periodically, then the system of equations becomes

$$\begin{cases} \dfrac{dC_a}{dt} = -K_a C_a, & (1.13) \\ C_a(nT^+) = C_a(nT) + J, & (1.14) \\ \dfrac{dC}{dt} = K_a C_a - KC. & (1.15) \end{cases}$$

This system of equations can be solved to give

$$C_a(nT^+) = J \cdot \left[\frac{1 - \left(e^{-K_a T}\right)^{n+1}}{1 - e^{-K_a T}}\right], \tag{1.16}$$

for nonnegative n so that on each half open half closed interval $(nT, (n+1)T]$, we find that the solution reads

$$\begin{cases} C_a(t) = J \cdot \left[\dfrac{1 - \left(e^{-K_a T}\right)^{n+1}}{1 - e^{-K_a T}}\right] \cdot e^{-K_a(t-nT)}, & (1.17) \\ C(t) = \dfrac{(1 - e^{-K_a T})^{n+1}}{1 - e^{-K_a T}} \dfrac{K_a J}{K - K_a} e^{-K_a(t-nT)} + C_{0,n} e^{-Kt}, & (1.18) \end{cases}$$

where $C_{0,n}$ forms a sequence that satisfies the following iteration

$$C_{0,n-1} e^{-K(n-1)T} - C_{0,n} e^{-nKT} = \frac{K_a J}{K - K_a} \frac{\left(2e^{-K_a T} - 1\right)\left(1 - e^{-K_a T}\right)^n}{1 - e^{-K_a T}}, \tag{1.19}$$

for positive integers n. We show numerical results for system (1.13) $\sim$ (1.15) in Figure 1.2 . Notice that there is a jump in C_a at discrete times, but $C(t)$ is continuous at those times.

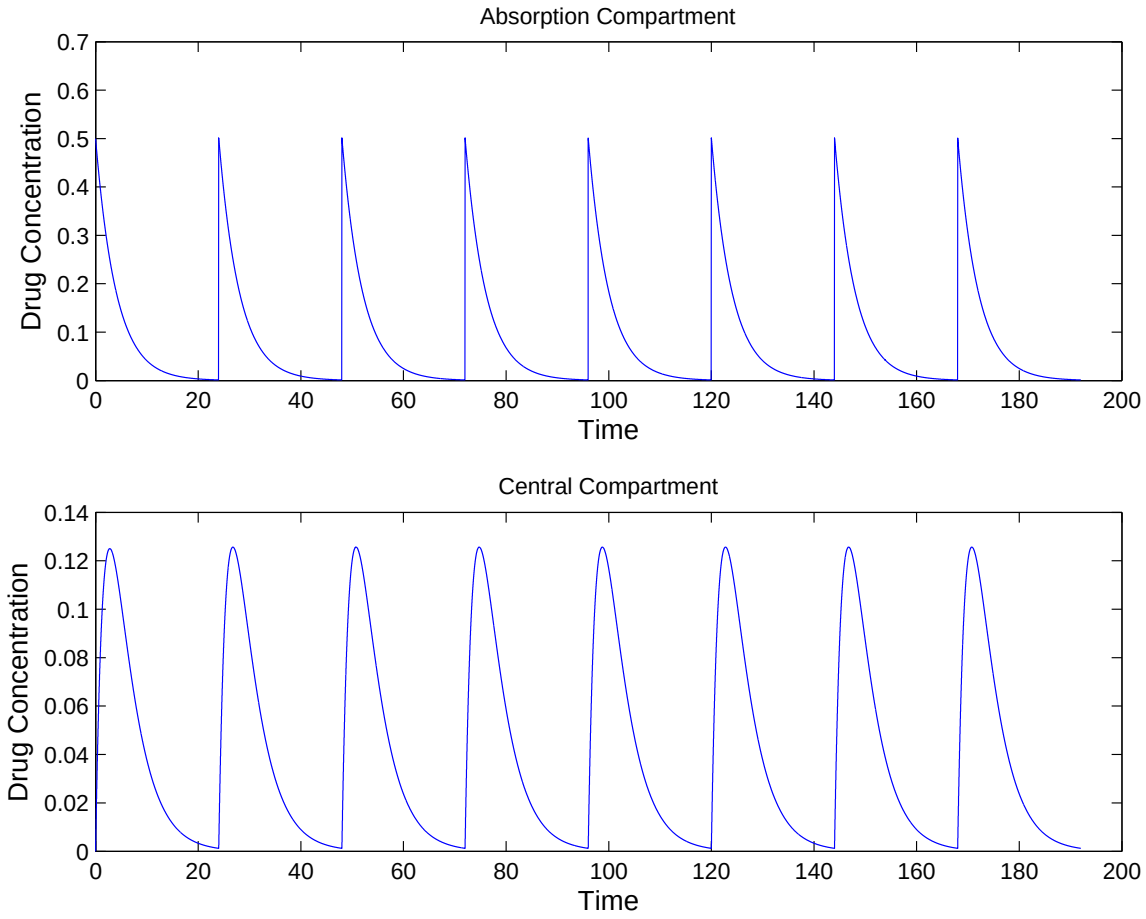


Figure 1.2. Extravasuclar injection model with first-order elimination kinetics under periodic injection condition. The top panel shows the dynamics of the absorption site, whereas the lower panel shows the dynamics of the central compartment. Parameter values are: $K_a = 0.25$, $K = 0.5$, $J = 0.5$, and $T = 24$.

1.2 Nonlinear Elimination Kinetics

Many of the processes of drug absorption, distribution, biotransformation, and excretion involve enzymes or carrier-mediated systems. It has been observed for many drugs that at high concentration, the elimination rate tends to be of zeroth order rate, whereas the elimination rate can be well approximated by first-order rate at low plasma drug concentration. This type of situation occurs when limited amounts of enzyme are present in the plasma, causing the effect of saturation at high drug level in the body. If we assume that elimination is time independent, i.e., the differential equation that describes the elimination rate is autonomous, then the differential equation can be modeled by

$$\frac{dC}{dt} = -h(c), \tag{1.20}$$

where $h(c)$ is a nonnegative increasing function of the drug concentration c. One well-studied nonlinear elimination is the Michaelis-Menten (M-M) elimination dynamic

$$\frac{dC}{dt} = -\frac{V_{max}C}{K_m + C}, \tag{1.21}$$

where V_{max} denotes the maximum rate at which the drug is eliminated from the body, with units of $concentration/time$, and where K_m stands for half saturation constant, with units of $concentration$. Its more general form, which is called the Hill function, has the representation

$$\frac{dC}{dt} = -\frac{V_{max}C^m}{K_m + C^m}, \tag{1.22}$$

where V_{max} and K_m have the same verbal meaning as in the M-M equation case, with K_m having units of $(concentration)^m$; the number m in the equation stands for Hill coefficient, representing the cooperativity level of enzymes. In this dissertation, many numerical simulations within the nonlinear elimination framework are examined with Hill function elimination rates, with Hill coefficient $m = 2$.

1.2.1 Intravenous Administration Regime

If doses are given periodically through intravenous injections, assuming the elimination dynamic to be that of Hill function type, then we obtain a system of equations

$$\begin{cases} \dfrac{dC}{dt} = -\dfrac{V_{max}C^m}{K_m + C^m}, & (1.23) \\ C(nT^+) = C(nT) + J. & (1.24) \end{cases}$$

In 2007, Tang and Xiao [19] studied the case for $m = 1$, i.e., when the elimination kinetics is of M-M type. They showed that a stable periodic solution exists if and only if

$$J < V_{max}T, \tag{1.25}$$

using LambertW function, which is the function $y(x)$ implicitly defined by

$$y(x)e^{y(x)} = x. \tag{1.26}$$

1.2.2 Extravascular Administration Regime

If drugs need to be taken through extravascular pathways, then as before, we include an absorption compartment preceding the central compartment in the model and the entire system of equations is constructed as

$$\begin{cases} \dfrac{dC_a}{dt} = -K_a C_a, & (1.27) \\ \dfrac{dC}{dt} = BK_a C_a - f(C), & (1.28) \end{cases}$$

subject to the impulse condition

$$C_a(nT^+) - C_a(nT) = J, \tag{1.29}$$

where $f(C)$ denotes the nonlinear elimination from the central compartment, C_a and C denote the concentration of the absorption and central compartment, respectively, and B is a dimensionless parameter denoting the fraction of the volume of the absorption compartment to that of the central compartment. In the case when the elimination is of Hill function, the system of equations reads

$$\begin{cases} \dfrac{dC_a}{dt} = -K_a C_a, & (1.30) \\ \dfrac{dC}{dt} = BK_a C_a - \dfrac{V_{max}C^m}{K_m + C^m}, & (1.31) \end{cases}$$

subject to the impulse condition

$$C_a(nT^+) - C_a(nT) = J. \tag{1.32}$$

For the system (1.30) $\sim$ (1.32), an analytical solution cannot be obtained, since equation (1.31) becomes nonautonomous once we substitute (1.30) into this equation and this nonautonomous equation does not have an analytical solution. Hence, in order to quantitatively study this system, other mathematical tools and techniques need to be applied. By

noting the fact that K_a is usually large, which is documented in ([5]), in Chapter 5, we treat $\epsilon = 1/(K_a T)$ as a small parameter and then perform singular perturbation analysis on this system to get the leading order solution to approximate the true solution of this system. This leading order solution, in turn, enables the calculation of important biomarkers, as well as the establishment of the critical condition under which this system of equations admits a stable periodic solution. Details of the application of the singular perturbation method can be found in Chapter 5.

1.3 Mathematical Modeling of Poor Drug Compliance

Poor compliance to well-designed drug intake protocols is a worldwide problem [3, 14, 18, 20] , especially for chronic diseases [18]. The time evolution of drug concentration can be heavily influenced by the random drug intake due to poor adherence to a doctor's prescription, which usually results in drug inefficiency for the patient, which might even be lethal to the patient.

So far, several mathematical models have been proposed to account for randomness in times when drugs are taken and randomness in the drug amount the patient might take each time [3, 14, 20]. In this dissertation, we concentrate on modeling the effects of poor compliance to times at which drugs should be taken, i.e., we assume that the patient has a certain probability of forgetting to take drugs at some times when drugs are supposed to be taken. As can be seen from this assumption, we treat the entire drug taking process as a discrete time random process, even though we treat the concentration of the drug as a continuous variable, which is discussed further in Chapter 2. Thus, we treat the concentration variable as a continuous space discrete time random variable, which we will focus on from Chapter 2 to Chapter 4.

Most of the studies (see for example, [3, 14, 20]) so far are based on the assumption that the rate at which the drug is eliminated is of first order. However, with just a bit more work, many results can also be extended to cases where drug elimination is nonlinear. Since one of the most widely used nonlinear elimination dynamics is of Michalis-Menten type, or its more general form, the Hill function type, for many theoretical and numerical results in this dissertation where we assume the elimination is nonlinear, we take the elimination to be of Hill function type with a Hill coefficient of 2. The reason that we take the Hill

coefficient to be $m = 2$ is that this makes numerical simulation much faster than if a Hill coefficient $m = 1$ is used, for which the so-called *LambertW* function [2] has to be solved implicitly at each time step.

As has just been mentioned, mathematical modeling of poor drug compliance and its results are discussed in detail in Chapter 2, 3 and 4. In Chapter 2, we study the steady state probability distribution of the drug concentration assuming that the patient has a fixed probability of forgetting to take drugs at some random times; both linear and nonlinear elimination dynamics are considered and we make the assumption that drugs are taken through intravenous pathways, even though similar results hold if oral administrations are assumed. Specifically, we derive some meaningful equations, as well as some useful statistics to help us understand this steady state probability distribution and at the same time, 2 numerical schemes are introduced to visualize these probability densities.

In Chapter 3, we discuss the first exit time problems associated with the random dynamic that is introduced previously in Chapter 2. This random process can be essentially treated as a random map or a random function iteration. We show that for a broad class of random functions that include the random dynamic introduced in Chapter 2, the mean first passage time to pass a threshold level l from either below or above a threshold level in the support of the random map is finite once some certain assumptions of the structure of the random map are satisfied.

In Chapter 4, we discuss the situation where patients are allowed to take a multiple of dosage amounts at one time if they previously forgot to take the drug for several consecutive times. The advantage of this strategy is that the drug will be effective for a longer period of time on average, but the drawback is that the patient faces the risk of drug overdose. We show that if the patient will take either a single or double dose the second day to compensate for the loss of a previously missed dose, then taking a double dose is the better strategy than taking a single dose when the effective level is high and vice versa. By effective level, we mean the level above which the drug is effective.

CHAPTER 2

PROBABILITY DISTRIBUTION OF THE DRUG DELIVERY PROTOCOLS IN STEADY STATE

In this chapter, we construct a stochastic model to study the probability distribution of the drug concentration in steady state, assuming that the patient has a certain probability of forgetting to take drugs on time.

2.1 First-Order Elimination

In the current section, we study the case when the elimination is assumed to be of first order. Assume that the probability of forgetting to take drug is r. Then the probability of taking it on time is $1-r$. Then, letting the concentration of the drug at time step n be x_n, where by time step, we mean the n-th time the drug is assumed to be taken, the random dynamic reads

$$x_n = \begin{cases} a(x_n+1), \text{with probability } r, & (2.1) \\ ax_n, \text{with probability } 1-r, & (2.2) \end{cases}$$

where we assume that the concentration of the drug injected into the body each time is 1 and where a is defined by $a := e^{-KT} < 1$, through the first-order elimination dynamic

$$\frac{dx}{dt} = -Kx, \tag{2.3}$$

where K is the first-order elimination rate constant and T is the length of the dosage time interval. (2.1) and (2.2) can be viewed as a random map such that at each discrete time n, x_n might be mapped into x_{n+1} by a function f with a probability of r, or by another function g with a probability of $1-r$

$$x_{n+1} = \begin{cases} f(x_n), \text{with probability } r, & (2.4) \\ g(x_n), \text{with probability } 1-r. & (2.5) \end{cases}$$

For (2.1) and (2.2), we have that $f = a(x+1)$ and $g = ax$, respectively. Since $f = a(x+1)$ and $g = ax$, the lower bound x_g of this random map can be solved from the equation

$$x_g = a x_g, \tag{2.6}$$

which gives $x_g = 0$ and the upper bound x_f can be solved from

$$x_f = a(x_f + 1), \tag{2.7}$$

which gives $x_f = \frac{a}{1-a}$. Hence, the support of this random map is $[x_g, x_f] = [0, \frac{a}{1-a}]$. We plot several sample paths in Figure 2.1.

2.1.1 Discrete Time Analysis

Let i_j for $j = 1, 2, ...$ denote the probability indictor

$$i_j = \begin{cases} 1, \text{with probability } r & (2.8) \\ 0, \text{with probability } 1 - r. & (2.9) \end{cases}$$

Let $h_{i_1 i_2 ... i_m}$ denote the value of the sequence x_m at the m-th step. Then it can be verified directly that

$$h_{i_1 i_2 ... i_m} = \sum_{j=1}^{m} i_{m+1-j} a^j, \tag{2.10}$$

is with the following probability distribution

$$P_{i_1 i_2 ... i_m} = r^{\sum_{j=1}^{m} i_j} (1-r)^{(m - \sum_{j=1}^{m} i_j)}. \tag{2.11}$$

Letting $m \to +\infty$, it can be concluded directly that in steady state, we have

$$h_{i_1 i_2 ... i_m} \leq \sum_{k=1}^{+\infty} a^k < +\infty, \tag{2.12}$$

which shows the validity of the definition of the following concise form of the concentration in steady state

$$X = \sum_{j=1}^{+\infty} i_j a^j, \tag{2.13}$$

where i_j's are indicator functions defined by (2.8) and (2.9). Since the probability density function (pdf) of the sum of any 2 random variables X_1 and X_2 is the convolution of the pdf of each, i.e,

$$p_{X_1 + X_2}(Y) = \int_{-\infty}^{+\infty} p_1(Y - x) p_2(x) dx, \tag{2.14}$$

where p_1, p_2, and $p_{X_1+X_2}$ denote the pdf of X_1, X_2, and $X_1 + X_2$, respectively, it follows that the pdf of X should be the infinite convolution of the pdf of $i_k a^k$ for $k = 1, 2, ...$, i.e.,

$$p(X) = p(i_1 a) * p(i_2 a^2) * p(i_3 a^3) ..., \tag{2.15}$$

where $*$ denotes convolution.

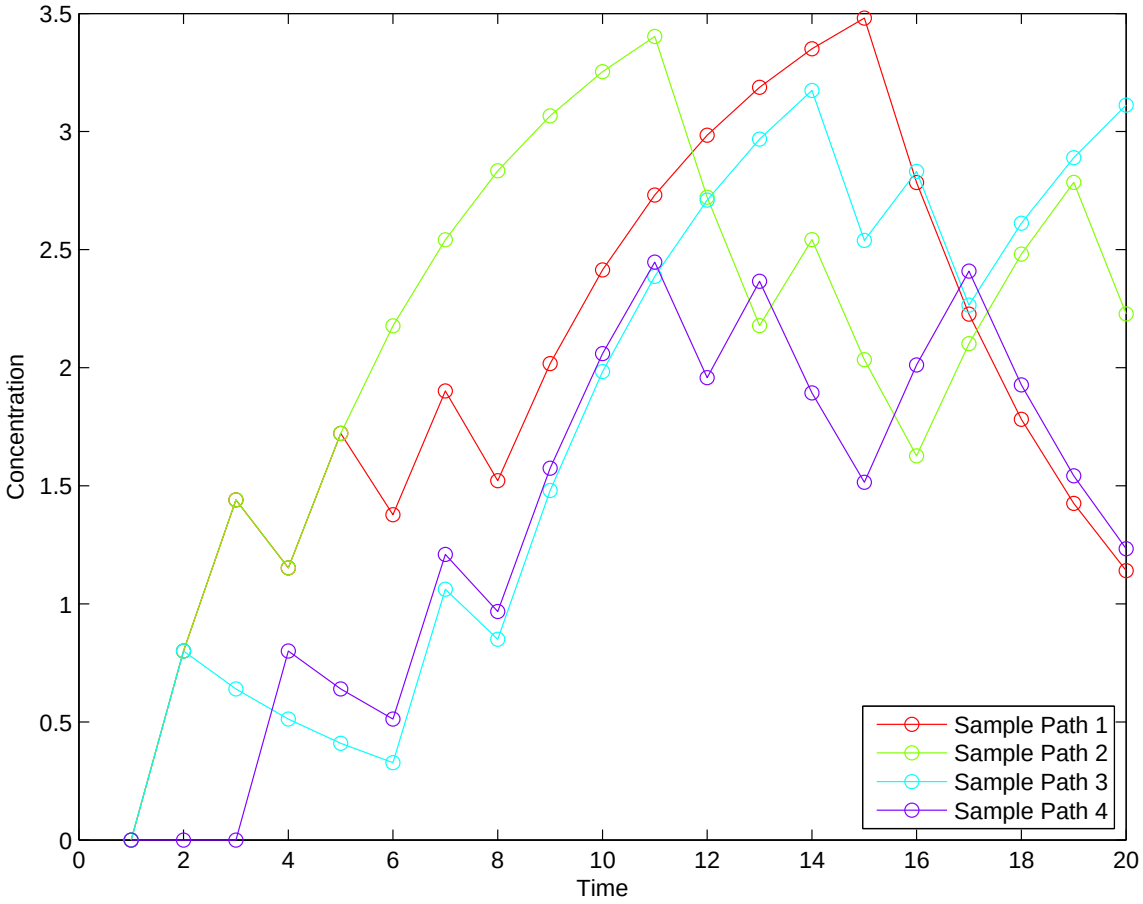


Figure 2.1. In this figure, we plot 4 sample paths. Parameters values are: $r = 0.65$ and $a = 0.8$. For each path, we stop at time $n = 20$.

For any j, the probability density function for $i_j a^j$ can be derived easily, which gives

$$P(Y=)\begin{cases} a^j, \text{with probability } r & (2.16) \\ 0, \text{with probability } 1-r. & (2.17) \end{cases}$$

Since the Fourier transform of the convolution of an infinite sequence is the algebraic product of the Fourier transform of each, i.e.,

$$FT(Y_1 * Y_2 * ...) = \prod_{j=1}^{+\infty} FT(Y_j), \tag{2.18}$$

where FT denotes the Fourier transform operation and $*$ denotes convolution, it follows that

$$FT(p(X)) = FT(p(\sum_{i=1}^{+\infty} i_j a^j)) = FT(p(i_1 a) * p(i_2 a^2)...) = \prod_{j=1}^{+\infty} FT\Big(p(i_j a^j)\Big). \tag{2.19}$$

Since the Fourier transform of the pdf of $i_j a^j$ is

$$e^{-iua^j} r + e^0(1-r) = e^{-iua^j} r + (1-r), \tag{2.20}$$

it follows that the Fourier transform of X as a function of the variable u is

$$L(u) = FT(p(X)) = \prod_{j=1}^{+\infty} \Big(re^{-iua^j} + (1-r)\Big). \tag{2.21}$$

Although this expression of $L(u)$ is hard to simplify further for general a and r, for the special case when $a = r = 1/2$, this infinite product can be simplified by observing that

$$\begin{aligned} L(u) &= \prod_{j=1}^{+\infty} \Big(\frac{1}{2} e^{-iua^j} + \frac{1}{2}\Big) && (2.22) \\ &= \prod_{j=1}^{+\infty} \Big(\frac{1}{2}\Big)\Big(e^{-iu\frac{a^j}{2}}\Big(e^{-iu\frac{a^j}{2}} + e^{iu\frac{a^j}{2}}\Big)\Big) && (2.23) \\ &= \prod_{j=1}^{+\infty} e^{\frac{-iua^j}{2}} \cos\Big(\frac{ua^j}{2}\Big) && (2.24) \\ &= e^{-\frac{iu}{2}(\sum_{j=1}^{+\infty} a^j)} \prod_{j=1}^{+\infty} \cos\Big(\frac{ua^j}{2}\Big) && (2.25) \\ &= e^{-\frac{iua}{2(1-a)}} \prod_{j=1}^{+\infty} \cos\Big(\frac{ua^j}{2}\Big). && (2.26) \end{aligned}$$

Since by double angle formula

$$\frac{\sin x}{x} = \prod_{j=1}^{+\infty} \cos\Big(\frac{x}{2^j}\Big), \tag{2.27}$$

it follows directly that when $a = 1/2$, (2.26) becomes

$$L(u) = e^{-\frac{iu}{2}} \frac{\sin \frac{1}{2}u}{\frac{1}{2}u}. \tag{2.28}$$

By applying the inverse Fourier transform, we obtain

$$p(x) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} e^{-iu/2} \frac{\sin \frac{1}{2}u}{\frac{1}{2}u} e^{iux} du = H(t) - H(t-1), \tag{2.29}$$

where $H(x)$ is the Heaviside function, defined by

$$H(x) = \begin{cases} 1, \text{for } x \geq 0, & (2.30) \\ 0, \text{for } x < 0. & (2.31) \end{cases}$$

A plot of (2.29) can be seen from Figure 2.2.

Based on above analysis, we know that we can get an analytical solution for the probability density function when $a = r = 1/2$. However, for general a and r, such an analytical solution is usually hard to obtain and it is hard to visualize this density function based on analytical solution. So we need other tools to study the property of the pdf.

2.1.2 Continuous Variable Analysis

The discussions so far in this chapter are based on a discrete time version analysis, that is, we look at certain statistics as functions of time and then let time go to infinity. Instead, We may also perform the continuous variable version analysis, where we directly look at the concentration variable in steady state by letting $t \to +\infty$ and assume that the concentration variable is a continuous variable in the support $[x_g, x_f] = [0, \frac{a}{1-a}]$. Many more analytical results can actually be derived and obtained in this manner and the probability density function can also be obtained numerically by 2 different methods introduced later in this chapter.

We begin by considering the random map defined by (2.4) and (2.5). Let P denote the probability measure in the support $[x_g, x_f]$. Then by the relationship between the definition of probability and its associated density function, we obtain

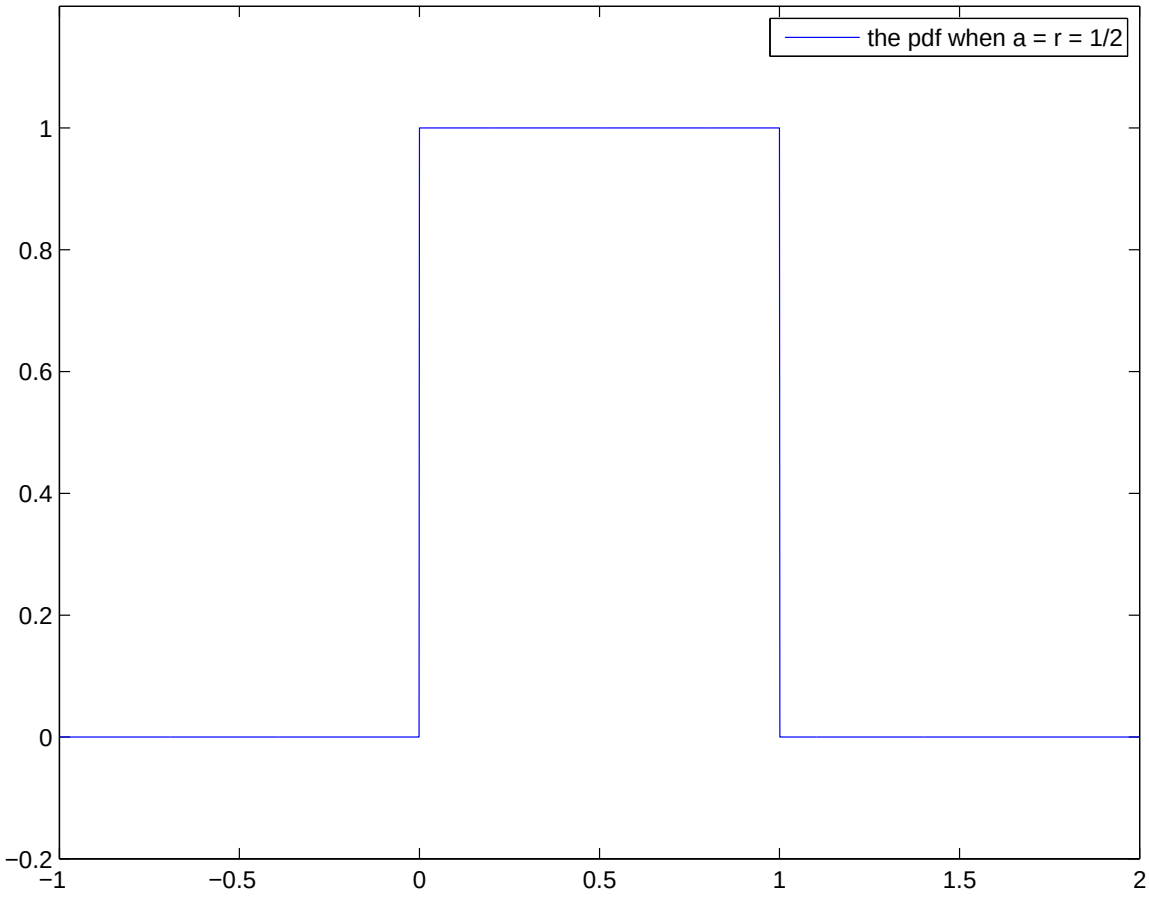


Figure 2.2. In this figure, $a = r = 1/2$. The probability density function in (2.29) is a rectangular function when $a = r = 1/2$.

$$P\left(y < X < y + \delta y\right) = (1-r)P\left(g^{-1}(y) < X < g^{-1}(y+\delta y) + hot\right) + rP\left(f^{-1}(y) < X < f^{-1}(y+\delta y) + hot\right), \tag{2.32}$$

where δy is a small perturbation around y and hot stands for higher order term in δy. Dividing both sides by δy and letting $\delta y \to 0$, then applying Taylor expansion and using the definition of probability density function yields

$$p(y) = [(1-r)(g^{-1})'(y)]p\left(g^{-1}(y)\right) + [r(f^{-1})'(y)]p\left(f^{-1}(y)\right). \tag{2.33}$$

By letting

$$\begin{cases} r^{+}(y) = (1-r)\cdot\dfrac{d\left(g^{-1}\right)}{dy}, & (2.34) \\ r^{-}(y) = r\cdot\dfrac{d\left(f^{-1}\right)}{dy}, & (2.35) \end{cases}$$

equation (2.33) reduces to

$$p(y) = r^{+}(y)p\left(g^{-1}(y)\right) + r^{-}(y)p\left(f^{-1}(y)\right). \tag{2.36}$$

Hence, if the elimination dynamic is assumed to be of first order, i.e., if $f = a(x+1)$ and $g = ax$, then the steady state equation for its pdf is

$$p(y) = \frac{1-r}{a}p\left(\frac{y}{a}\right) + \frac{r}{a}p\left(\frac{y}{a} - 1\right). \tag{2.37}$$

For the special case when $r = 1$, that is when a patient takes drugs on time each time, equation (2.37) reduces to

$$p(y) = \frac{1}{a}p\Big(\frac{y}{a} - 1\Big). \tag{2.38}$$

It is not hard to see that $p(y) = \delta(y - \frac{a}{1-a})$ is the unique solution to this equation, since

$$\begin{aligned} \frac{1}{a}p\left(\frac{y}{a} - 1\right) &= \frac{1}{a}\delta\left(\frac{y}{a} - 1 - \frac{a}{1-a}\right) && (2.39) \\ &= \frac{1}{a}\delta\left(\frac{y}{a} - \frac{1}{1-a}\right) && (2.40) \\ &= \frac{1}{a}\delta\left(\frac{1}{a}(y - \frac{a}{1-a})\right) && (2.41) \\ &= a\cdot\frac{1}{a}\delta\left(y - \frac{a}{1-a}\right) && (2.42) \\ &= \delta\left(y - \frac{a}{1-a}\right) && (2.43) \\ &= p(y). && (2.44) \end{aligned}$$

Since outside the support $[0, \frac{a}{1-a}]$, by iterating equation (2.38), we find that $p(y) = 0$ for all $y \in [0, \frac{a}{1-a})$. However, as we require that

$$\int_0^{\frac{a}{1-a}} p(s)ds = 1, \tag{2.45}$$

the only possibility is that $p(y) = \delta(y - \frac{a}{1-a})$. On the other hand, in the case when $r = 0$, that is when the patient never takes the drug, the solution to (2.37) is

$$p(y) = \delta(y), \tag{2.46}$$

which can be examined similarly to the case when $r = 1$.

With the expression (2.37), we may calculate moments and central moments up to any order. This is a special advantage of first-order elimination dynamics. Let

$$M_m := \mathbb{E}(y^m) = \int_0^A y^m p(y)dy, \tag{2.47}$$

be the m-*th* order moment for the distribution $p(y)$, where $A = \frac{a}{1-a}$ is the fixed point of the map f. Then by using (2.37), we may proceed to compute the quantity M_k in the following manner

$$\int_0^A y^m p(y)dy = \frac{1-r}{a} \int_0^A y^m p\left(\frac{y}{a}\right) dy + \frac{r}{a} \int_0^A y^m p\left(\frac{y}{a} - 1\right) dy. \tag{2.48}$$

Since $a < 1$, $A/a > A$, and $p(y)$ has been shown to have no measure outside the interval $[0, A]$, upon using change of variables in the integrals whenever needed, the last equation reduces to

$$\int_0^A y^m p(y)dy = (1-r)a^m \int_0^A y^m p(y)dy + ra^m \int_0^A (y+1)^m p(y)dy, \tag{2.49}$$

from which we conclude that

$$\mathbb{E}(y^m) = M_m = \frac{ra^m}{1-a^m} \int_0^A \left[(x+1)^m - x^m\right] p(x)dx \tag{2.50}$$

$$= \frac{ra^m}{1-a^m} \int_0^A \left(\sum_{k=0}^{m-1} C_m^k x^k\right) p(x)dx \tag{2.51}$$

$$= \frac{ra^m}{1-a^m} \sum_{k=0}^{m-1} C_m^k M_k, \tag{2.52}$$

which indicates that $M_m := \mathbb{E}(y^m)$ is a linear combination of M_1, M_2 ,..., M_{m-1}. Since the m-th central moments C_m is defined as $C_m := \mathbb{E}(y - M_1)^m$, we expand this expression to find that

$$C_m = \mathbb{E}(y - M_1)^m \tag{2.53}$$

$$= \mathbb{E}\left(\sum_{j=0}^{m} C_m^j y^j (-1)^{m-j} (M_1^{m-j})\right) \tag{2.54}$$

$$= \sum_{j=0}^{m} C_m^j (-1)^{m-j} (M_1)^{m-j} M_j \tag{2.55}$$

$$= \sum_{j=0}^{m} \frac{(1-r)a^j}{1-a^j} C_m^j (-1)^{m-j} (M_1)^{m-j} \left(\sum_{i=0}^{j-1} C_j^i M_i\right), \tag{2.56}$$

which implies that the m-th central moment C_m is also a linear combination of the moments M_k up to order $m-1$. Thus, as long as M_1 can be computed, M_m for $m \geq 2$ can be computed inductively. For example, the leading 3 central moments, i.e., mean, variance, and skewness, can be computed

$$\begin{cases} C_1 = \dfrac{ar}{1-a}, & (2.57) \\ C_2 = \dfrac{a^2 r(1-r)}{1-a^2}, & (2.58) \\ C_3 = \dfrac{a^3 r(1-r)(2r-1)}{a^3-1}. & (2.59) \end{cases}$$

The plot of these central moments as functions of r can be seen in Figure 2.3. These central moments have physiological meanings. For example, suppose $a = 0.8$. If we learn that a certain patient manages to take pills on time for 17 days out of the first 20 days during the entire medical treatment, and this frequency is believed to be a long-term statistic, then C_1 can be computed by $C_1 = \frac{0.8 \times 0.85}{1-0.8} = 3.4$. If the long-term drug effective level is less than 3.4, then we may assert that on average, the treatment is effective; However, if the the effective level is greater than 3.4, then either forcing the patient to take pills on time or taking more pills once a dose is missed might be needed in order for the drug to be effective in the long run. This will be discussed further in Chapter 4.

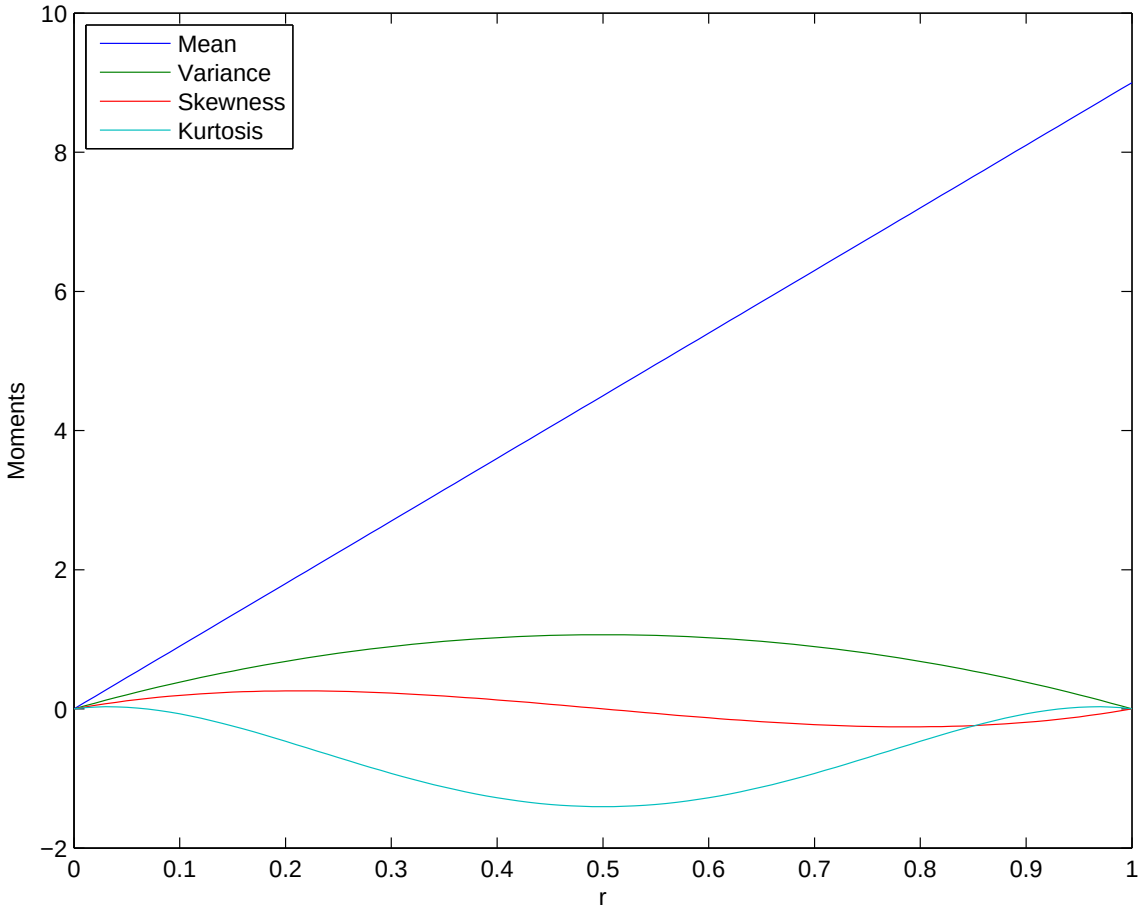


Figure 2.3. In this figure, we plot the leading three central moments as functions of r, based on formula (2.57)∼(2.59). The parameter value of a is $a = 0.9$.

2.1.3 Methods to Visualize the Probability Density Function

In order to plot the pdf of X in steady state, two different methods are used and compared that shall be discussed below.

- **Method 1 (Iteration Method):** We put subscript index n to the left-hand side term in equation (2.36) and put $n-1$ to the right-hand side p terms and then iterate according to this scheme which reads

$$p_n(y) = r^+(y)p_{n-1}\left(g^{-1}(y)\right) + r^-(y)p_{n-1}\left(f^{-1}(y)\right), \tag{2.60}$$

for $n = 1, 2, 3..$, where the initial function $p_0(x)$ is chosen to satisfy the constraint

$$\int_0^{\frac{a}{1-a}} p_0(x)dx = 1. \tag{2.61}$$

We also require that $p_0(x) = 0$ outside the interval $[0, \frac{a}{1-a}]$. For example,

$$p_0(x) = \frac{6(1-a)^3}{a^3}\left(x^2 - \frac{a}{1-a}x\right)H(x)H\left(\frac{a}{1-a} - x\right), \tag{2.62}$$

can be such an initial function, which can be see in Figure 2.4.

- **Method 2 (Finite Difference Method):** Since the random process $x_n \mapsto x_{n+1}$ is clearly a Markov process, we know from the ergodic property of a stationary Markov process [4] that the distribution function can be practically approximated by the frequency diagram of the iterations provided that the total number of trials (iterations) N is large, to ensure first, the process is in stationary phase and second, the law of large number effectively works. The cdf (cumulative density function) can be obtained through the "sort" command in Matlab. Then we discretize the cdf in space to obtain the pdf of X, since the pdf is by definition the derivative of its cdf.

2.1.4 Numerical Results

We show numerical results by employing methods we discuss in the previous subsection. We first show numerical simulations obtained with **Method 1** in Figure 2.5. As can be seen, as we increase the probability of forgetting to take drugs from top left to bottom right, the pdf becomes more and more dense on the left. And it can also be seen that when r is close to 1 or 0, the density has an obvious staircase behavior on the right or left, whereas when r is close $1/2$, the density is very smooth. If we fix r at $r = 0.8$, then probability densities for 4 different a are shown in Figure 2.6.

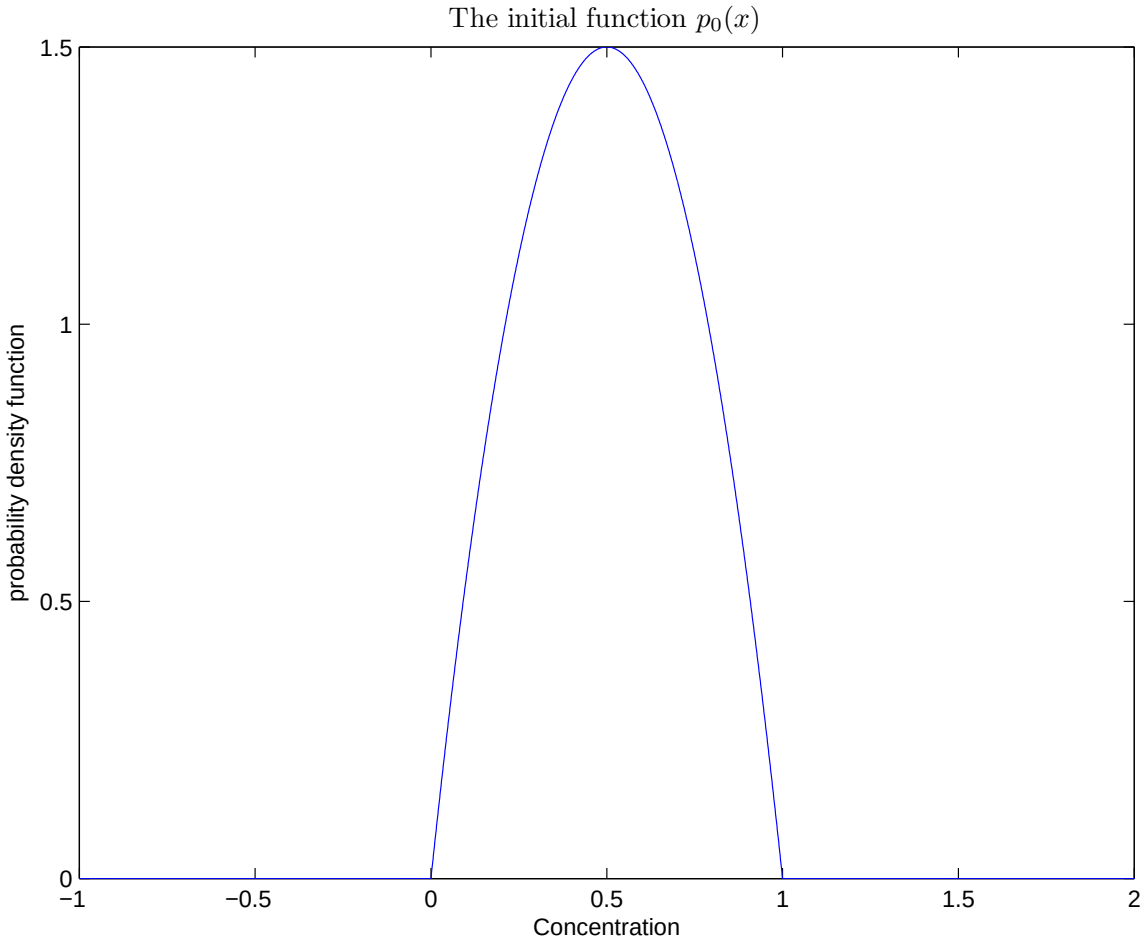


Figure 2.4. We plot the initial function $p_0(x) = \frac{6(1-a)^3}{a^3}\left(x^2 - \frac{a}{1-a}x\right) H(x)H\left(\frac{a}{1-a} - x\right)$, which is quadratic in the support $[0, \frac{a}{1-a}]$ and is 0 outside the support. In this figure, $a = 0.5$.

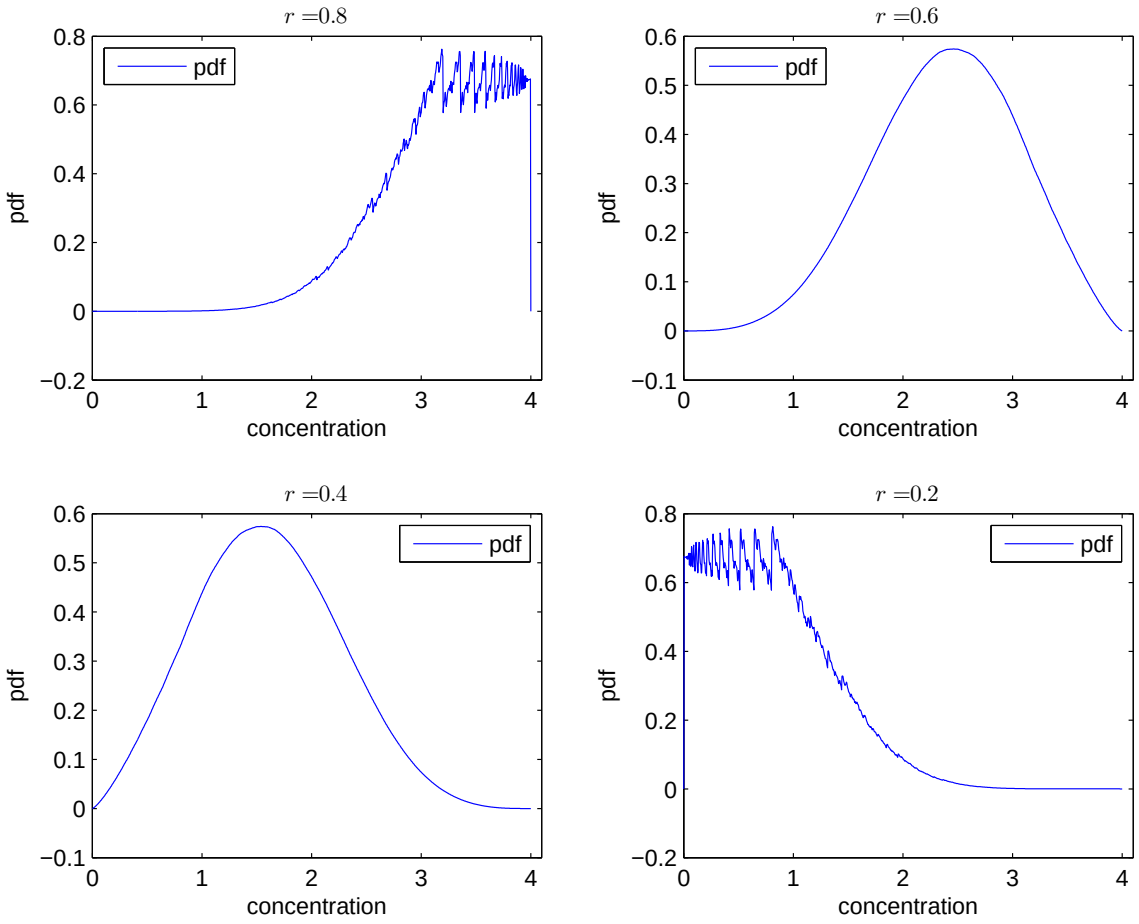


Figure 2.5. In this figure, $a = 0.8$. 4 different pdfs are plotted for different values of r.

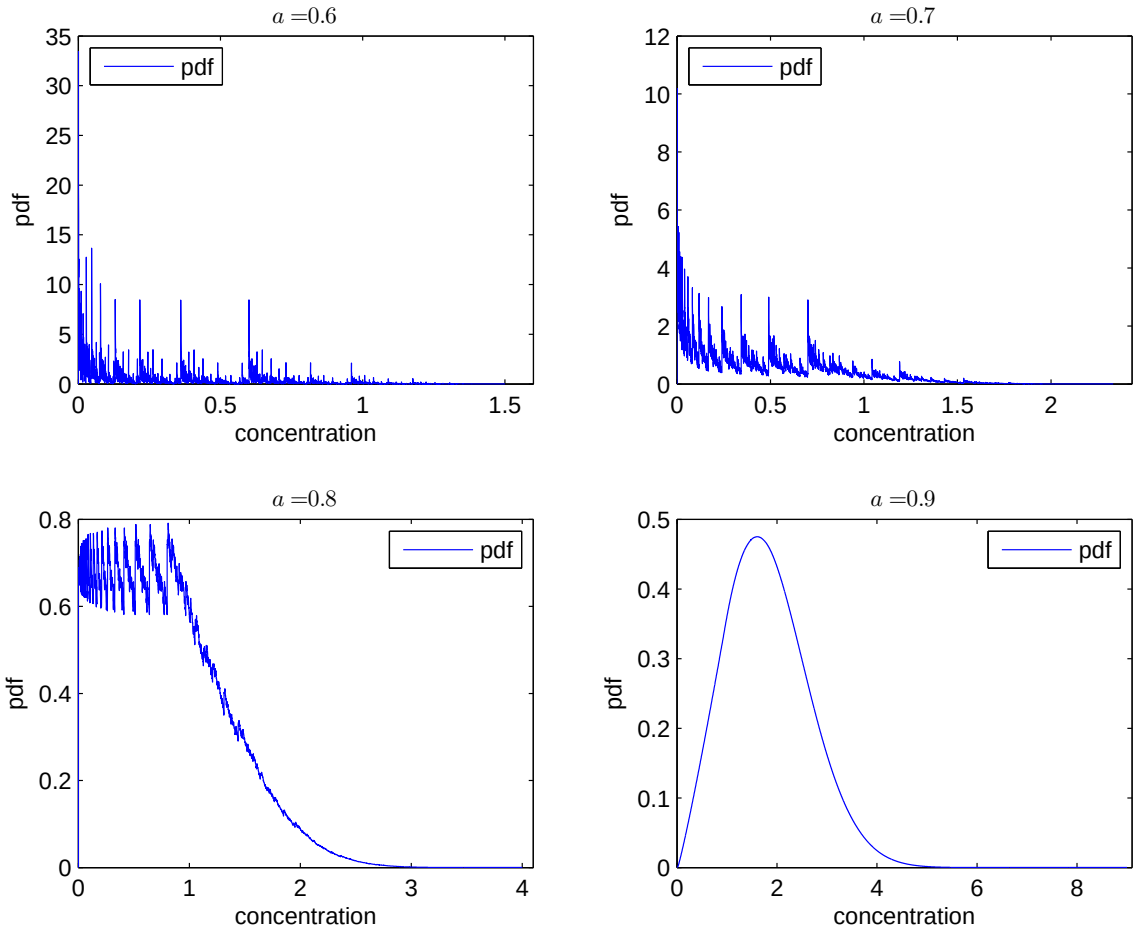


Figure 2.6. In this figure, $r = 0.8$. As can be seen in this figure, as we increase a, the pdf becomes more smooth.

We see from Figure 2.6 that the pdf becomes more smooth as we increase a from top left to bottom right. In Figure 2.7, we create surface plots for pdfs for 4 different values of a, where we treat concentration and r as independent variables. As is shown in this figure, as we increase the value of a from the top left to bottom right, the two peaks at two corners $[0,0]$ and $[x_f,1]$ gradually disappear and the density becomes more and more smooth as we increase a.

2.2 Nonlinear Elimination

For many drugs, its elimination from the body goes through complex biological processes and hence its elimination rate differs significantly from a first-order elimination. In this section, we assume that the elimination rate is a nonnegative increasing nonlinear function $h(C)$ such that $h(0) = 0$. The differential equation that describes this elimination over each dosage interval is

$$\frac{dx}{dt} = -h(x), \tag{2.63}$$

which is subject to the random drug taking impulse condition

$$x_n^+ = \begin{cases} x_n + 1, \text{with probability } r, & (2.64) \\ x_n, \text{with probability } 1-r. & (2.65) \end{cases}$$

By letting $H(x) := \int \frac{1}{h(s)} ds$, upon integrating over one dosage time interval of length T, we obtain

$$H(x_{n+1}) = -T + H(x_n^+), \tag{2.66}$$

from which we deduce that

$$x_{n+1}^+ = \begin{cases} H^{-1}\left(-T + H(x_n+1)\right), \text{with probability } r, & (2.67) \\ H^{-1}\left(-T + H(x_n)\right), \text{with probability } 1-r. & (2.68) \end{cases}$$

The invertibility of $H(x)$ is seen from $h(x)$ being positive. Thus, the f function (defined in 2.4) and the g function (defined in 2.5) associated with this random map are

$$f(x) = H^{-1}\left(-T + H(x+1)\right), \tag{2.69}$$

and

$$g(x) = H^{-1}\left(-T + H(x)\right), \tag{2.70}$$

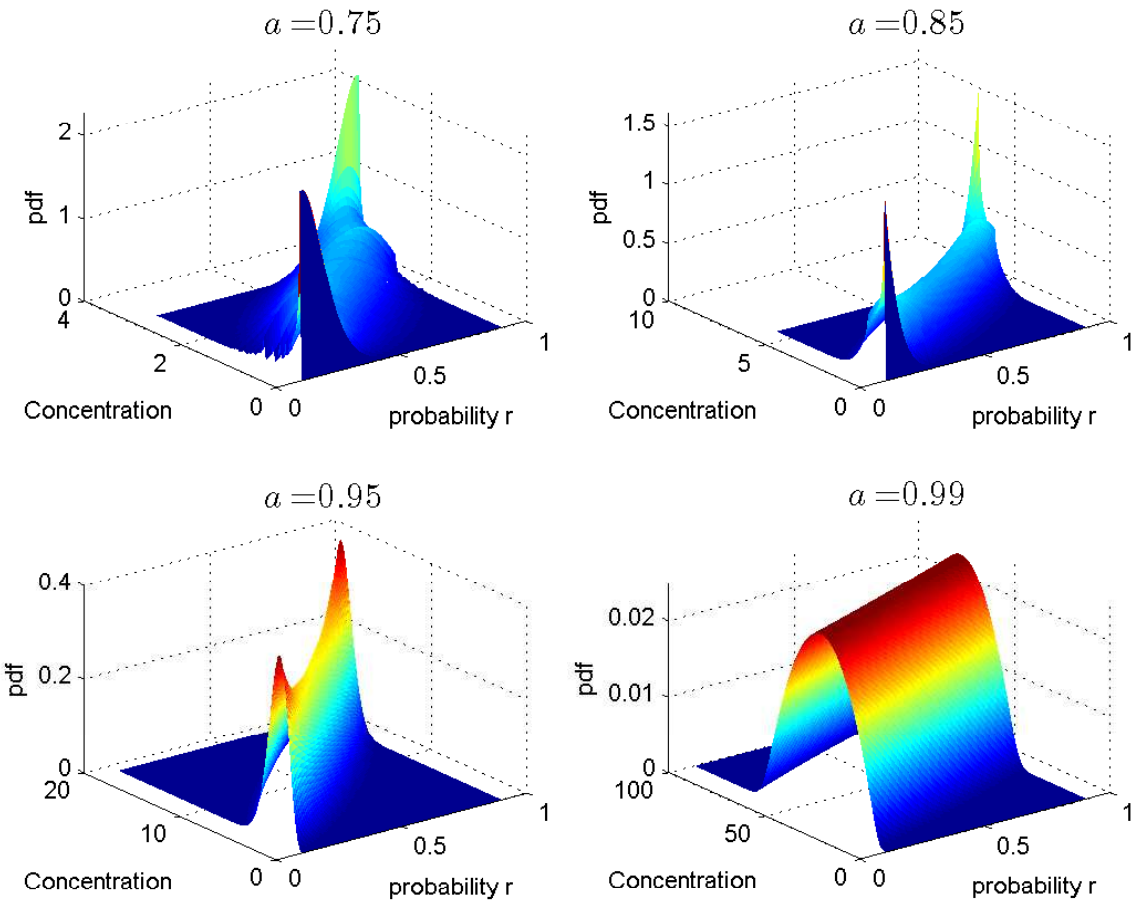


Figure 2.7. In this figure, the values of a are 0.75, 0.85, 0.95, and 0.99 for each subplot, respectively. For each subplot, r ranges in $[0, 1]$.

respectively. The only possible fixed point of the map g is $x = 0$, since $1/h(x)$ has singularity at $x_g = 0$; The map f admits a unique positive fixed point x_f if and only if

$$\lim_{x\to+\infty} \int_x^{x+1} \frac{1}{h(s)} ds < T, \tag{2.71}$$

and

$$\int_0^1 \frac{1}{h(s)} ds \geq T, \tag{2.72}$$

This is true, since (2.69) indicates that x_f satisfies the equation

$$H(x_f + 1) - H(x_f) = T. \tag{2.73}$$

Now that the function $H(x)$ is defined, we find that the mean of $H(x)$ and $H(x+1)$ satisfy a certain relationship, regardless of what the actual nonlinear elimination dynamic is. We let $p(x)$ denote the probability distribution of the drug concentration x in steady state. We begin by considering the expectation of the random variable $H(x)$. By using equation (2.33), we obtain that

$$\begin{aligned}\int_0^{x_f} H(x)p(x)dx = (1-r)\int_0^{x_f} H(x)\frac{dg^{-1}}{dx} p\left(g^{-1}(x)\right) dx \\ + r\int_0^{x_f} H(x)\frac{dg^{-1}}{dx} p\left(g^{-1}(x) - 1\right) dx,\end{aligned} \tag{2.74}$$

where we have used the identity (2.36) and the fact that $g^{-1}(x) = f^{-1}(x) + 1$ for $x \in [x_g, x_f]$. The first term , by letting $f^{-1}(x) = y$, becomes

$$(1-r)\int_0^{x_f} H(z+1)p(z)dz - T(1-r), \tag{2.75}$$

where we have used the identity (2.69) and the fact that $p(z)$ has no measure outside the support $[x_g, x_f] = [0, x_f]$. Similarly, the second term reduces to, by the same principle,

$$r\int_0^{x_f} H(z)p(z)dz - rT. \tag{2.76}$$

Therefore, by substituting (2.75) and (2.76) into (2.74), we obtain the following identity

$$\mathbb{E}\left[H(x+1) - H(x)\right] = \frac{T}{r}. \tag{2.77}$$

However, we do not have the knowledge of how $\mathbb{E}(H(x+1))$ and $\mathbb{E}(H(x))$ can be evaluated separately. Similarly to the above analysis, by considering the expectation of the random variable $g^{-1}(y)$, we can establish the following result

$$\mathbb{E}\left[g^{-1}(y) - y\right] = r, \tag{2.78}$$

or

$$\mathbb{E}\left[y - f^{-1}(y)\right] = (1 - r). \tag{2.79}$$

This measures the expected value of the concentration drop over one time interval in steady state as a function of the probability r. It can be seen from this expression that this expected value of concentration drop depends only on the global parameter r, which does not depend on any model specific parameters in the model, which means that this relationship holds true for any linear or nonlinear elimination dynamics and it is independent of T. Like the mean of $H(x)$ and $H(x+1)$, however, we do not know how to separate $\mathbb{E}(g^{-1}(y))$ or $\mathbb{E}(y)$ from (2.78) and we conjecture that these 2 listed quantities might depend on a model-specific parameter other than r.

A numerical simulation of $\mathbb{E}(g^{-1}(y))$, $\mathbb{E}(y)$ and their difference (2.78) can be seen in Figure 2.8. In this figure, we assume the elimination rate is of Hill function type with Hill coefficient $m = 2$ i.e., we take $h(x)$ in (2.63) to be

$$h(x) = \frac{v_m x^2}{K + x^2}, \tag{2.80}$$

where v_m stands for the maximum rate at which drug is eliminated and K with units of $concentration^2$ stands for the saturation constant. The simulated results in this figure suggest the correctness of (2.78). In Figure 2.9, we show numerically computed $\mathbb{E}(H(x))$, $\mathbb{E}(H(x+1))$ and their difference, assuming the same elimination dynamic and parameter values as in Figure 2.8. This figure numerically verifies the correctness of (2.77).

In the mean time, we may numerically simulate the mean, variance, and skewness for the concentration variable y (see Figure 2.10) as functions of r, assuming that the elimination is described by (2.8). It can be seen that the mean is increasing as we increase the probability of taking drugs on time, and the pdf skews positively when r is small and is negatively skewed when r is greater than a threshold level r_0 close to 0.2; when r becomes even larger, it has the tendency to go back to 0, which is theoretically true since when $r = 1$, the process is deterministic.

Lastly, the pdf for the nonlinear elimination case can be obtained by employing the same techniques that we used to generate pdfs for linear elimination cases, i.e., we can iterate a well-chosen initial pdf through equation (2.60) or we can choose to use the Monte Carlo method to obtain data first and then create the pdf based off these data. In Figure

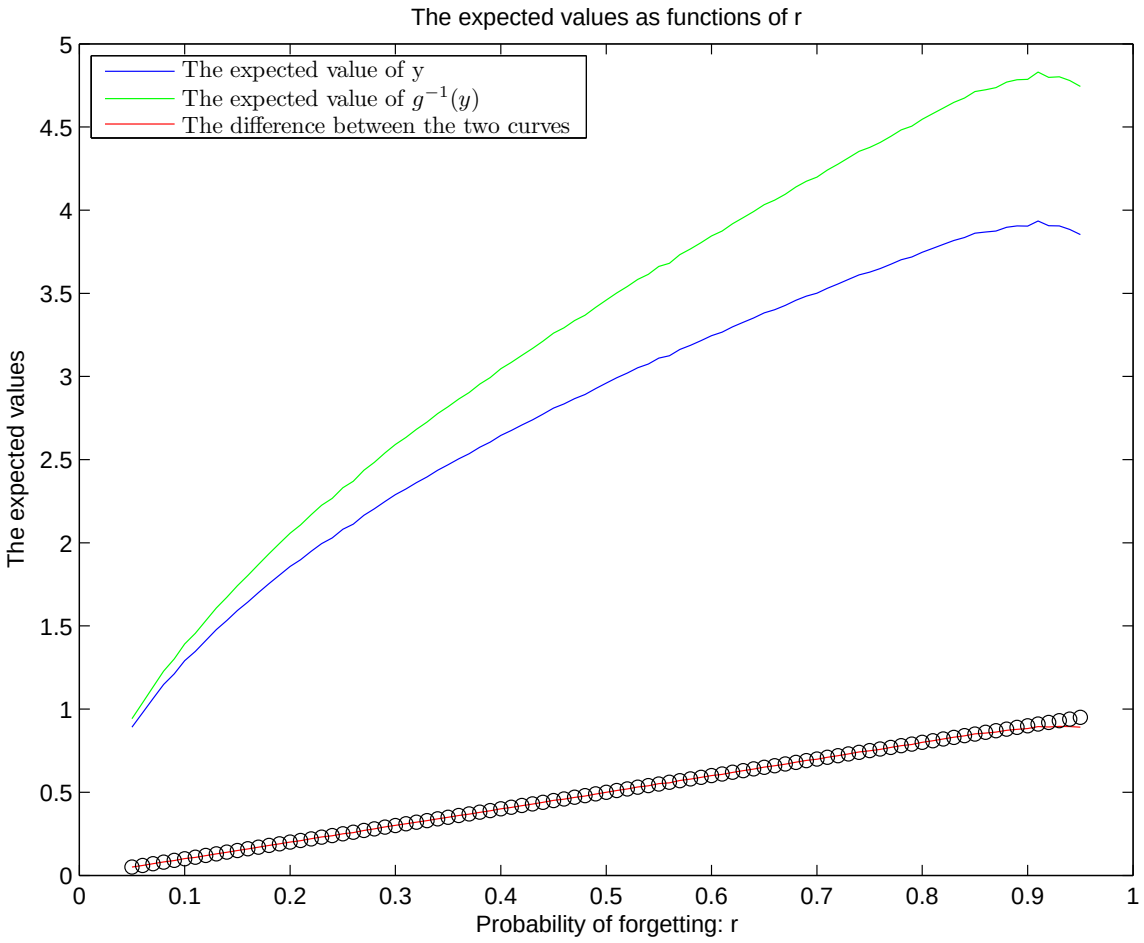


Figure 2.8. In this plot, the blue and green curves are numerically simulated $\mathbb{E}(y)$ and $\mathbb{E}(g^{-1}(y))$ as functions of r, respectively; the red curve is the difference between the blue and green curves, and the circles form the $y(r) = r$ line, where y denotes y coordinates of this $x - y$ plane. The range of r in this figure is $[0.05, 0.95]$. Parameter values in this figure are: $K = 500$, $T = 24$ and $v_m = 1$.

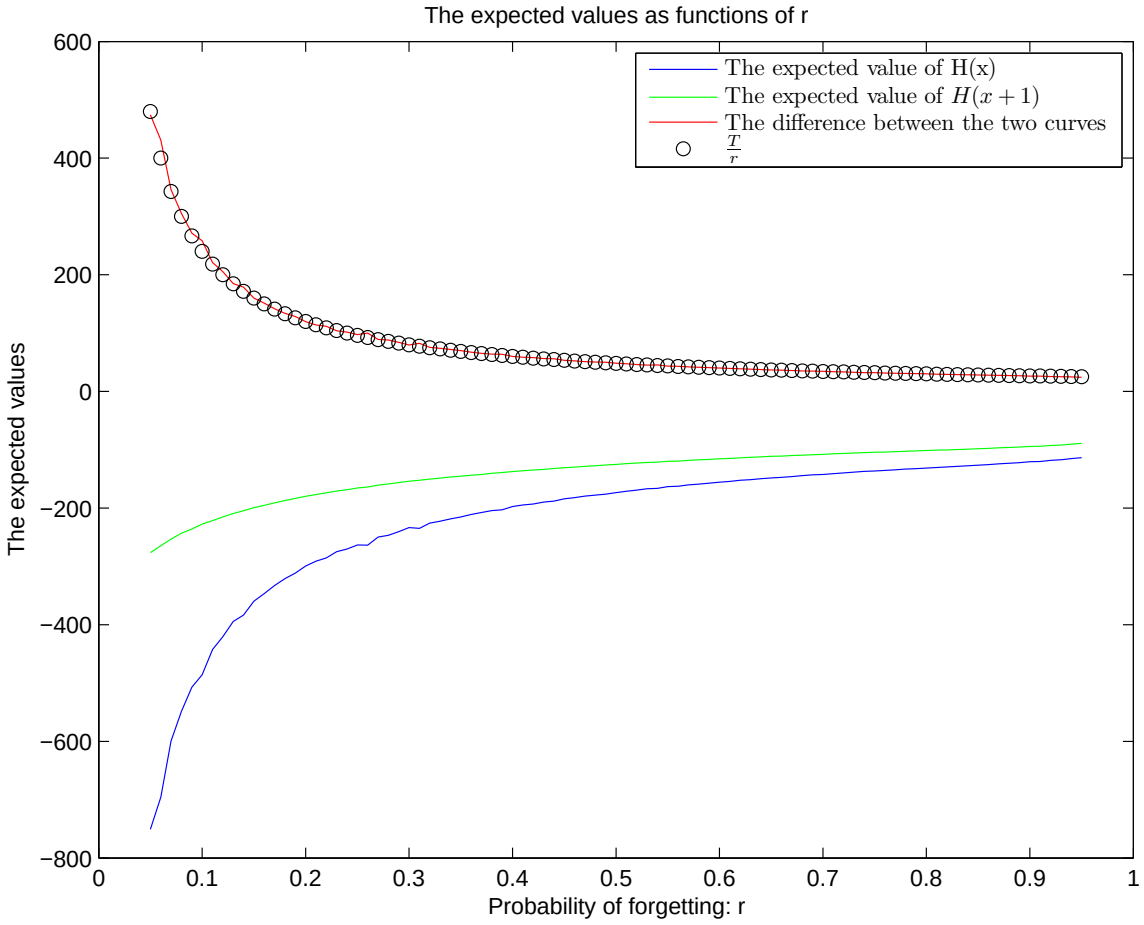


Figure 2.9. In this plot, parameter values are the same as in Figure 2.8. Colored curves in this plot are numerically simulated using Monte Carlo methods and dots are plotted according to equation (2.77). Parameter values for K, v_m, and T are the same as in Figure 2.8.

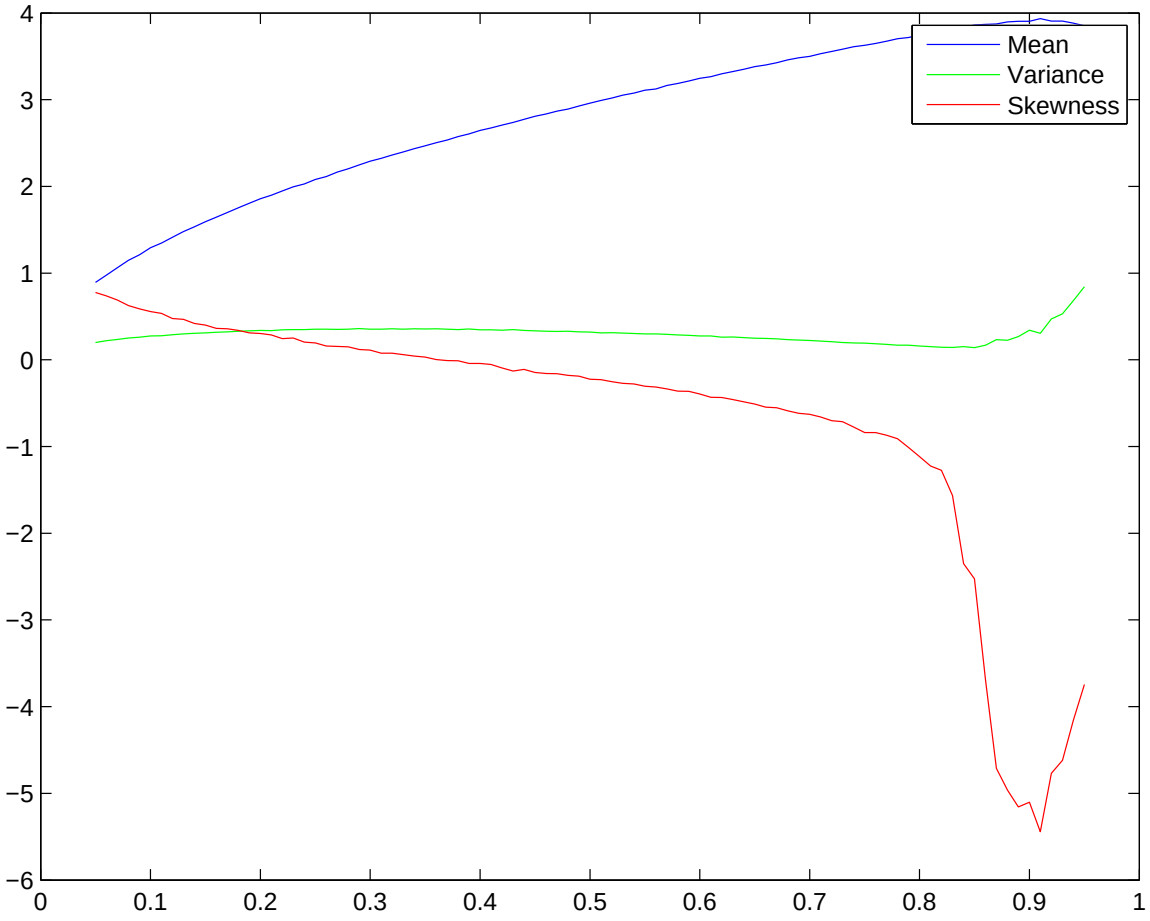


Figure 2.10. In this plot, we show the first three central moments as functions of r, which are simulated numerically. The parameter values for K, v_m, and T used in this plot are the same as those in Figure 2.8 and 2.9.

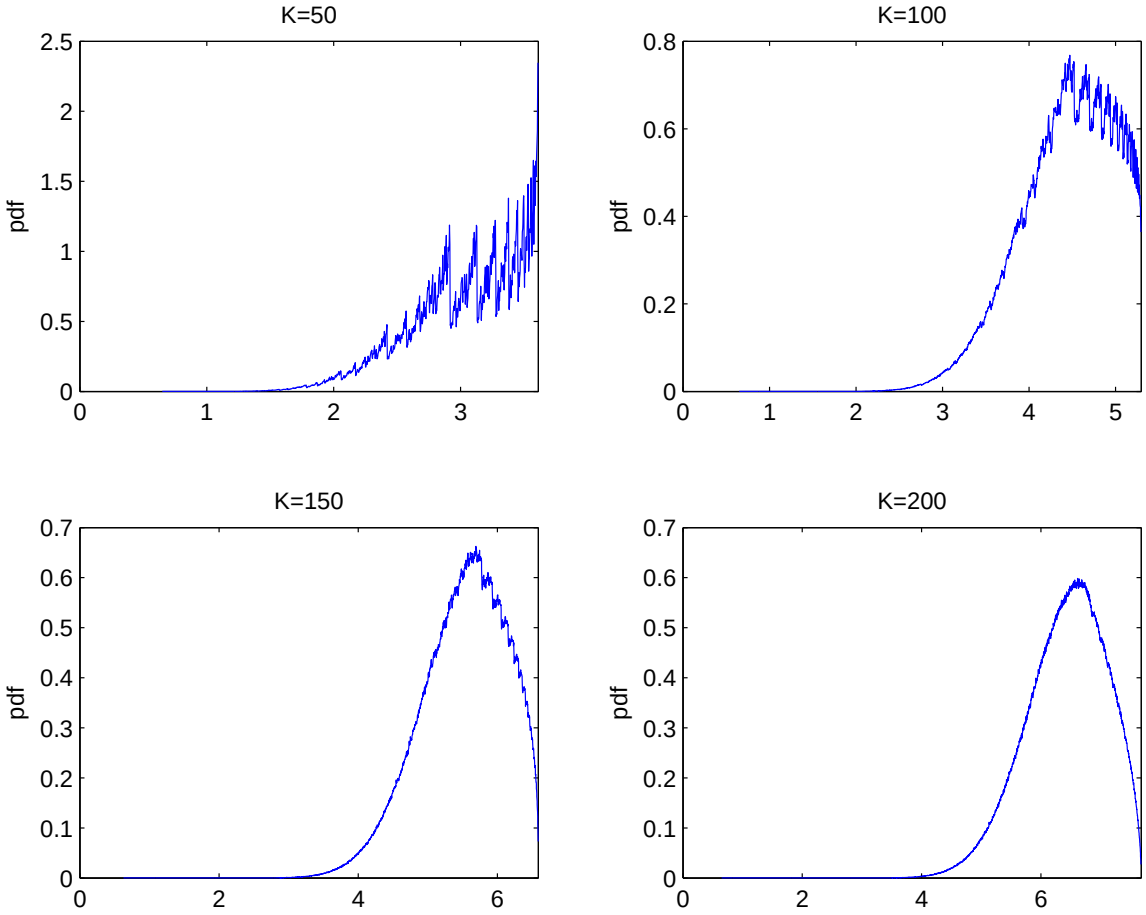


Figure 2.11. In this figure, $v_m = T = 2$ and $r = 0.75$. 4 pdfs are plotted for 4 different values of K. As we can see, as we increase K, the pdf becomes more smooth from top left to bottom right.

2.11, we show numerical results for the Hill function type elimination dynamics with Hill coefficient $m = 2$. We treat the saturation K as the varying parameter in this plot. It can be seen that the pdf becomes more and more smooth as we increase the value of the saturation constant K.

2.3 Discussion

Our purpose in this chapter is to study the steady state probability distribution and related problems for the drug delivery protocol, where the patient is assumed to have a fixed probability of forgetting to take drugs on time at some random times.

We first mathematically formalize the random dynamic of this drug taking process and then start analyzing this random process by discrete time analysis directly. We are able to get the exact pdf for the special case for $a = r = 1/2$ by considering the Fourier transformation of the pdf, even though much remains unknown for general a and r.

Hence, we turn our attention to treating the concentration variable as a continuous variable, by which an algebraic equation is obtained in steady state and if we iterate this equation, we may be able to get the plot of the density function. Meanwhile, several moments that have physiological meanings can be calculated and in the case of linear elimination, any order moments and central moments can always be computed, even though for many nonlinear elimination cases, many moments need to be computed numerically.

Even though the steady state probability distribution of the concentration might provide useful information regarding the long-term effectiveness of the entire drug taking process if the patient is assumed to take the drug for a relative long time, it does not discuss at all the dynamic of this drug taking process as a function of time. In the next chapter, we study the first passage time problems associated with this random dynamics, where we show that the mean first passage time that concentration of the drug passes a certain level is finite as long as the probability of taking the drug is nonzero.

CHAPTER 3

FIRST PASSAGE TIME PROBLEMS

3.1 Main Results on First Passage Times

In the current chapter, we focus our attention on the dynamic of the random process we discuss in Chapter 2 and we specifically study the first passage time problems associated with this random mapping.

3.1.1 Motivation

To account for a broader class of random mappings, we consider the more general discrete random maps of the form

$$x_{n+1} = \begin{cases} f(x_n), \text{with probability } r, & (3.1) \\ g(x_n), \text{with probability } 1-r, & (3.2) \end{cases}$$

for $n = 0, 1, 2 \ldots$, where f and g are continuous functions (maps) and $r \in (0, 1]$ denotes a probability. As we can see, when $f = a(x+1)$ and $g = ax$ with $0 < a < 1$, the random dynamic reads

$$x_{n+1} = \begin{cases} a(x_n + 1), \text{with probability } r, & (3.3) \\ ax_n, \text{with probability } 1-r, & (3.4) \end{cases}$$

which is the process with linear elimination rate we discuss in Chapter 2.

If the patient never forgets to take the drug, then the time series of the drug concentration goes up monotonically to a fixed point, denoted by U, which can be solved from the equation

$$U = f(U), \text{ or } U = a(U+1), \tag{3.5}$$

to give

$$U = \frac{a}{1-a}. \tag{3.6}$$

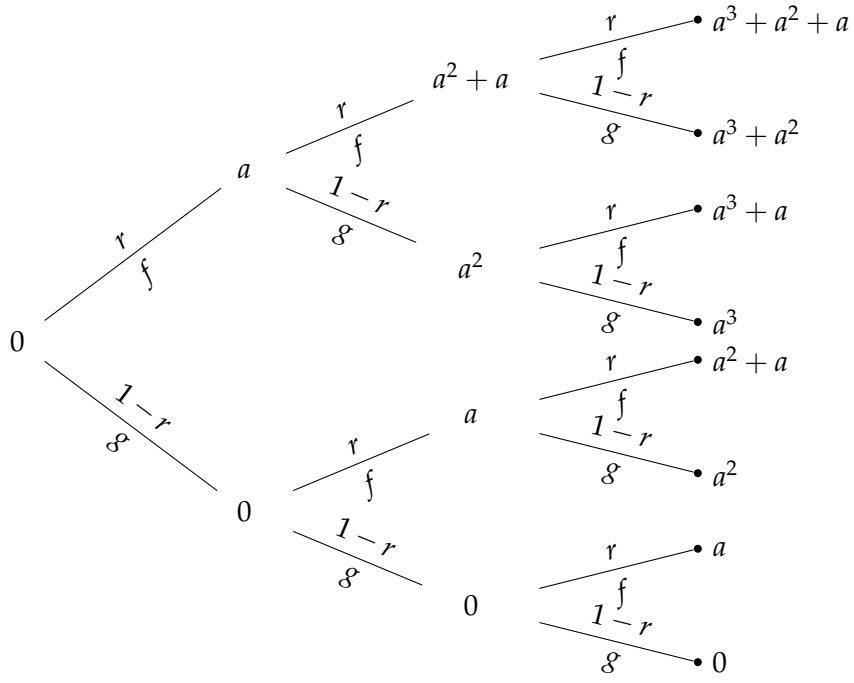
If the patient never takes the drug, on the other hand, then we solve $L = g(L)$ or $L = aL$ to obtain a lower fixed point $L = 0$. Thus, the support of this random map is $[L, U] = [0, \frac{a}{1-a}]$.

Under the scenario that the patient has a certain probability of forgetting to take drugs at some times, the first natural question one might ask is what the average amount of time is for the drug concentration in the body of the patient to pass a certain level l, above which the drug turns effective. In mathematical language, our goal is to compute

$$\mathbb{E}\Big(\min\left(m : x_m \geq l\right)\Big), \tag{3.7}$$

for any threshold level $l \in [0, \frac{a}{1-a}]$, given $x_0 = 0$.

The tree structure of this random map is shown below



As can be seen from this tree, the top path is the sequence $\{\sum_{s=1}^{j} a^s | j = 0, 1, 2 \dots\}$, which depicts the situation in which the patient takes pills every day on time, whereas the bottom path is a sequence of 0's, depicting the situation in which the patient never takes the drug. All the nodes and trajectories in the middle are when the patient may forget to take the drug at some random times.

We show some sample paths and trajectories in Figure 3.1 to help visualize the random map. We also show the simulated distribution of first exit times in Figure 3.2. The top panel in the figure shows the distribution of first exit times through $l = 1$. This panel suggests an exponential distribution for the first passage times. The bottom panel shows the *log* of exit times, which is well fitted by a straight line (red). This gives further credence to the possibility that the tail of this distribution is exponential.

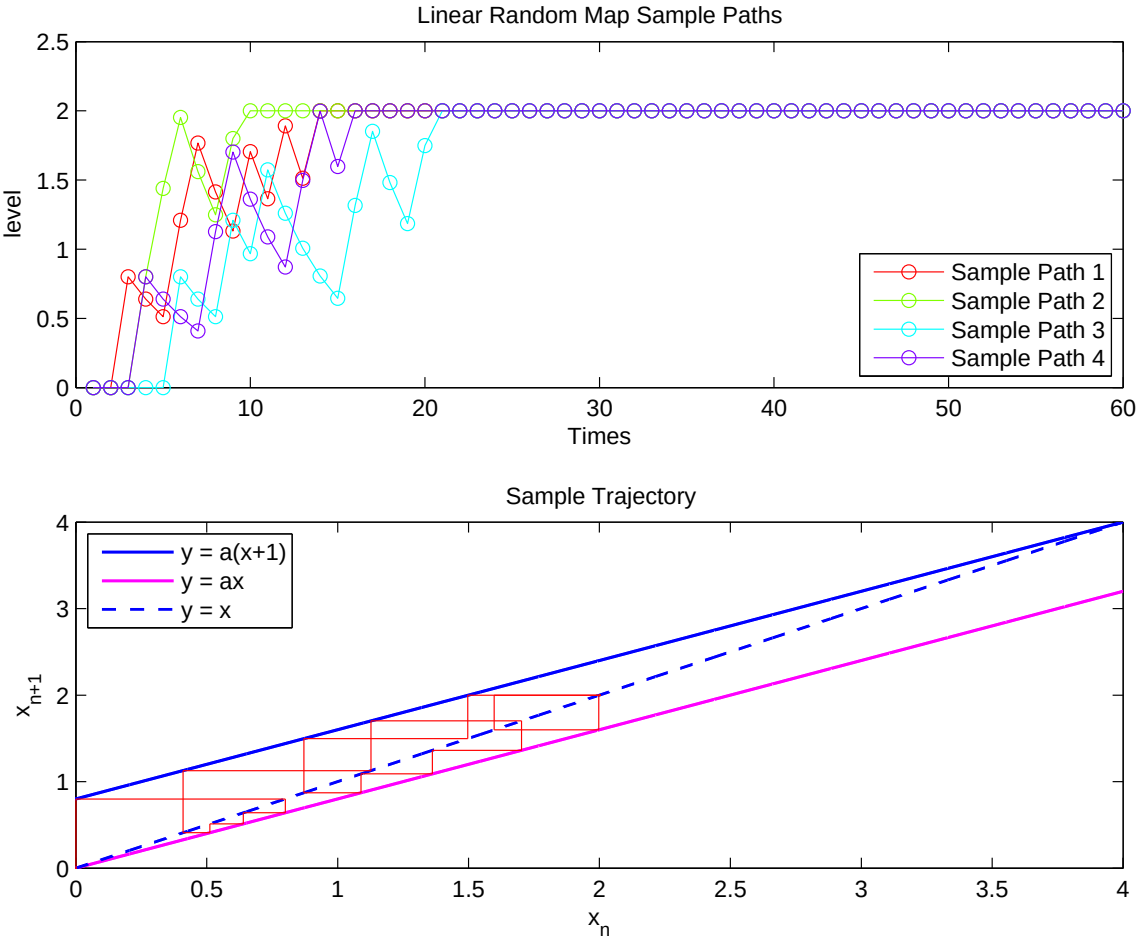


Figure 3.1. In this figure, $a = 0.8$, $r = 0.4$. The fixed point $U = 0.8/(1-0.8) = 4$. The threshold level $l = 2$. 4 sample paths are plotted in the top panel, and the trajectory of the sample path 4 (purple curve) is plotted in the $x_n - x_{n+1}$ plane in the bottom panel. $l = 2$ is treated as absorbing for both the top and bottom panels.

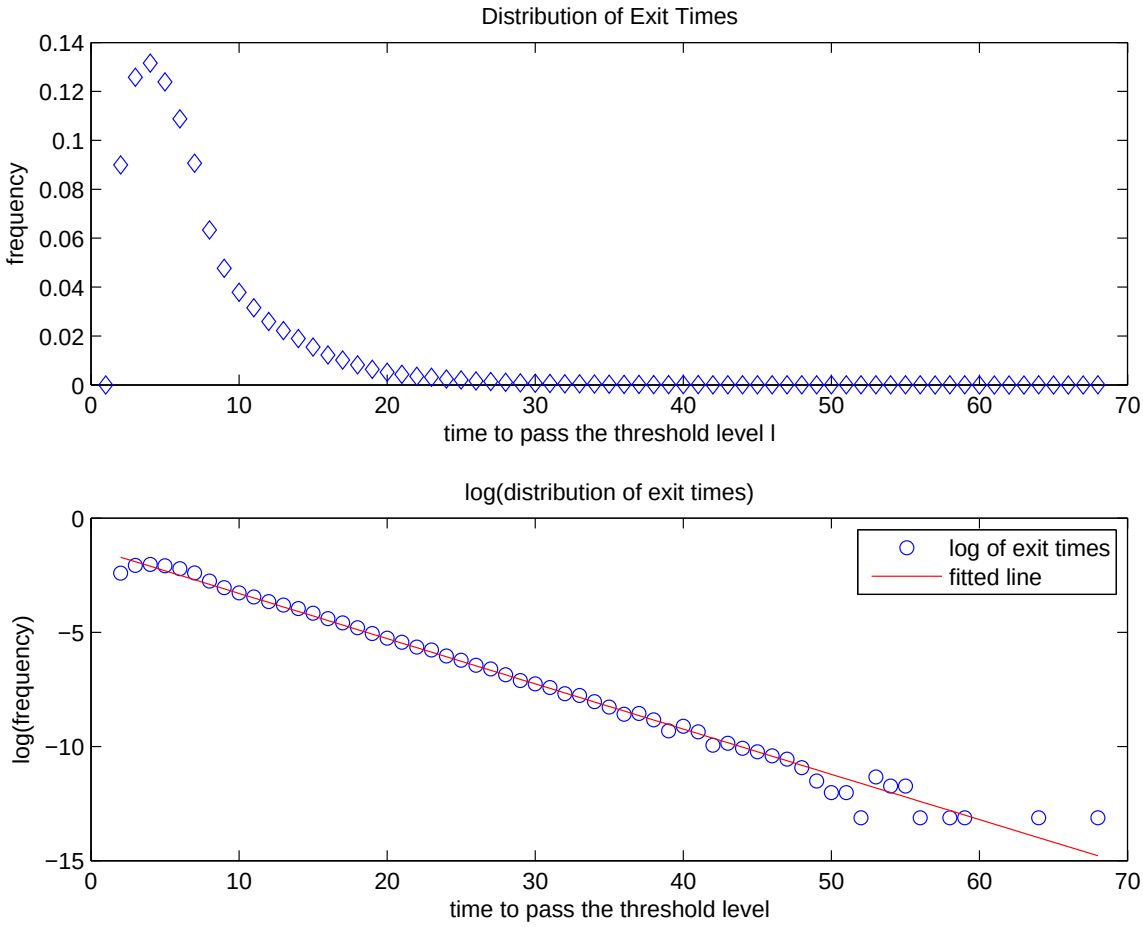


Figure 3.2. In this figure, $a = 0.8$, $r = 0.3$, and $l = 1.0$. The total number of trials is $N = 500000$.

An analytical expression of the mean is hard to obtain due to the complexity of the tree at higher time steps. Instead, we show the numerically computed mean as a function of l in Figure 3.3. Most importantly, this figure suggests that the mean is finite for $l < U$ and tends to ∞ as $l \to U$. We shall, in fact, prove in the section of main results that for a broad class of random functions that satisfy 3 simple assumptions, this is true.

We consider another example with nonlinear elimination rate before we prove our main results. Recall from Chapter 2 that if we assume the elimination is nonlinear, then the differential equation that describes this elimination process is

$$\frac{dx}{dt} = -h(x), \tag{3.8}$$

and the random impulse condition is assumed to be of the form

$$x_n^+ = \begin{cases} x_n + 1, \text{with probability } r, & (3.9) \\ x_n, \text{with probability } 1 - r. & (3.10) \end{cases}$$

Then by letting $H(x) := \int \frac{1}{h(s)} ds$, upon integrating over one dosage time interval of length T, we obtain

$$H(x_{n+1}) = -T + H(x_n^+), \tag{3.11}$$

from which we deduce that

$$x_{n+1}^+ = \begin{cases} H^{-1}\left(-T + H(x_n + 1)\right), \text{with probability } r, & (3.12) \\ H^{-1}\left(-T + H(x_n)\right), \text{with probability } 1 - r. & (3.13) \end{cases}$$

We now discuss the case when the elimination rate is of Hill function type with Hill coefficient $k = 2$. Specifically, the differential equation describing elimination of drug is

$$\frac{dx}{dt} = -\frac{vx^2}{k_m + x^2}, \tag{3.14}$$

where v denotes the maximum removal rate and k_m denotes the saturation constant. It can be checked easily that $H(x)$ is

$$H(x) = \frac{1}{v}\Big(-\frac{k_m}{x} + x \Big), \tag{3.15}$$

and its algebraic inverse is

$$H^{-1}(x) = \frac{vx + \sqrt{v^2x^2 + 4k_m}}{2}. \tag{3.16}$$

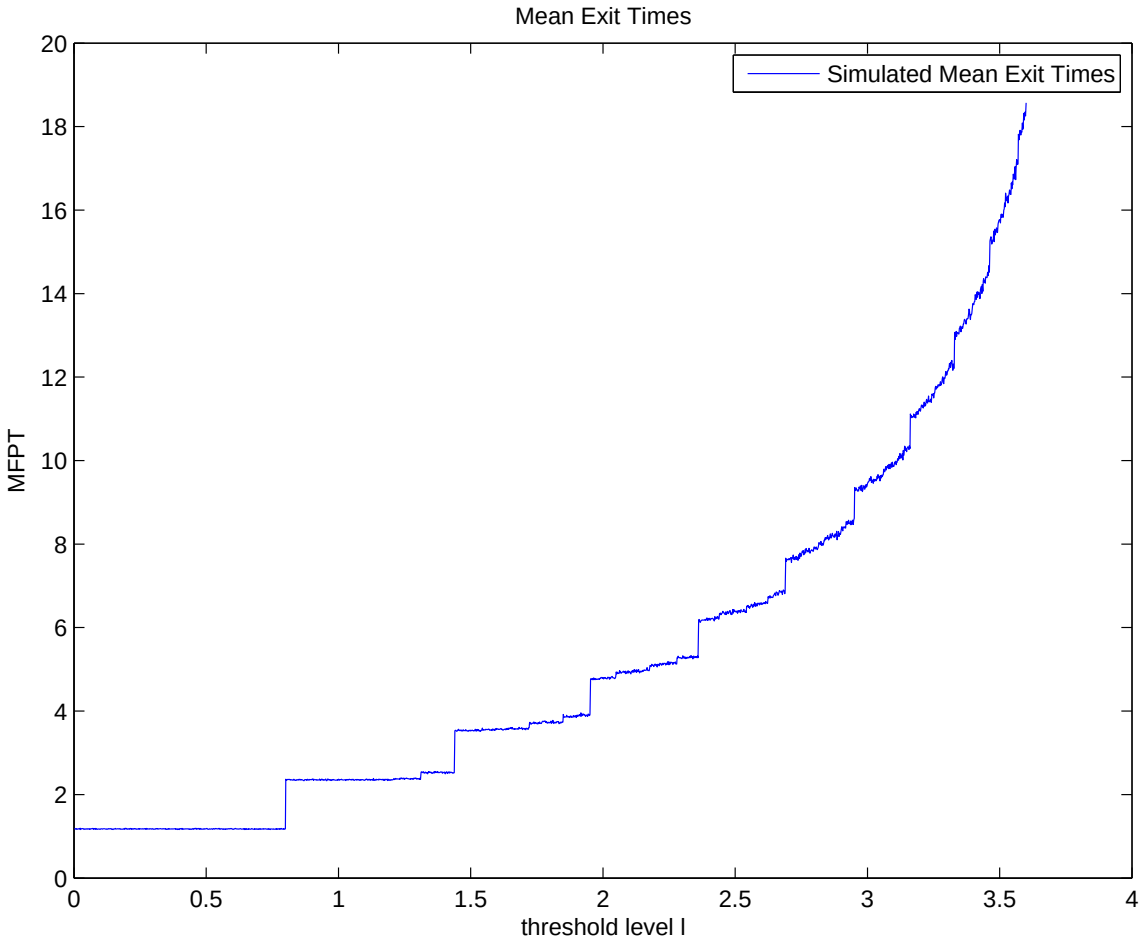


Figure 3.3. In this figure. $a = 0.8, r = 0.85$. The range of l in this simulation is $[0, 0.9 \times \frac{a}{1-a}]$ and 2000 equally distributed l from this interval were used as threshold levels. For each level, 5000 first exit times were simulated and their mean was calculated to approximate the true mean.

For the upper fixed point x_u to exist, we solve

$$H(x_u) = H(x_u + 1) - T, \tag{3.17}$$

to find that

$$\frac{1}{x_u} - \frac{1}{x_u + 1} = \frac{vT - 1}{k_m}. \tag{3.18}$$

It is easy to show that this equation has a positive solution if and only if $vT - 1 > 0$ and this fixed point is globally stable. This says that either the maximum rate at which drug is eliminated is big enough or that the time interval between each dosage is long enough so that the drug does not build up without bound.

We provide a sample path for the first exit time variable and its trajectory for this process in the $x_n - x_{n+1}$ plane in Figure 3.4. The distribution of first exit times is shown in Figure 3.5. Again, the top panel suggests that the mean first exit time is finite and the bottom panel suggests that the tail of the mean follows an exponential distribution.

3.1.2 Main Results

In this section, we prove our main results, which show that for a certain type of random maps that satisfy 3 conditions, the mean first passage time is bounded above and below by piecewise constant functions of l.

Theorem 3.1. Let $r \in (0, 1]$ denote a probability. Consider the random sequence

$$x_{n+1} = \begin{cases} f(x_n), \text{ with probability } r, \\ g(x_n), \text{ with probability } 1 - r, \end{cases}$$

for $n = 0, 1, 2...$, where f and g are continuous functions defined on the interval $[L, U]$. Without loss of generality, we shift L to the origin, i.e., we take $L = 0$. The following 3 conditions on f and g are imposed:

(1) both f and g are increasing on $[0, U]$;

(2) $y = f(x)$ and $y = x$ intersect at (U, U) and $f(x) > x$ for $x < U$, i.e., $f(U) = U$;

(3) $y = g(x)$ and $y = x$ intersect at $(0, 0)$ and $g(x) < x$ for $x > 0$, i.e., $g(0) = 0$.

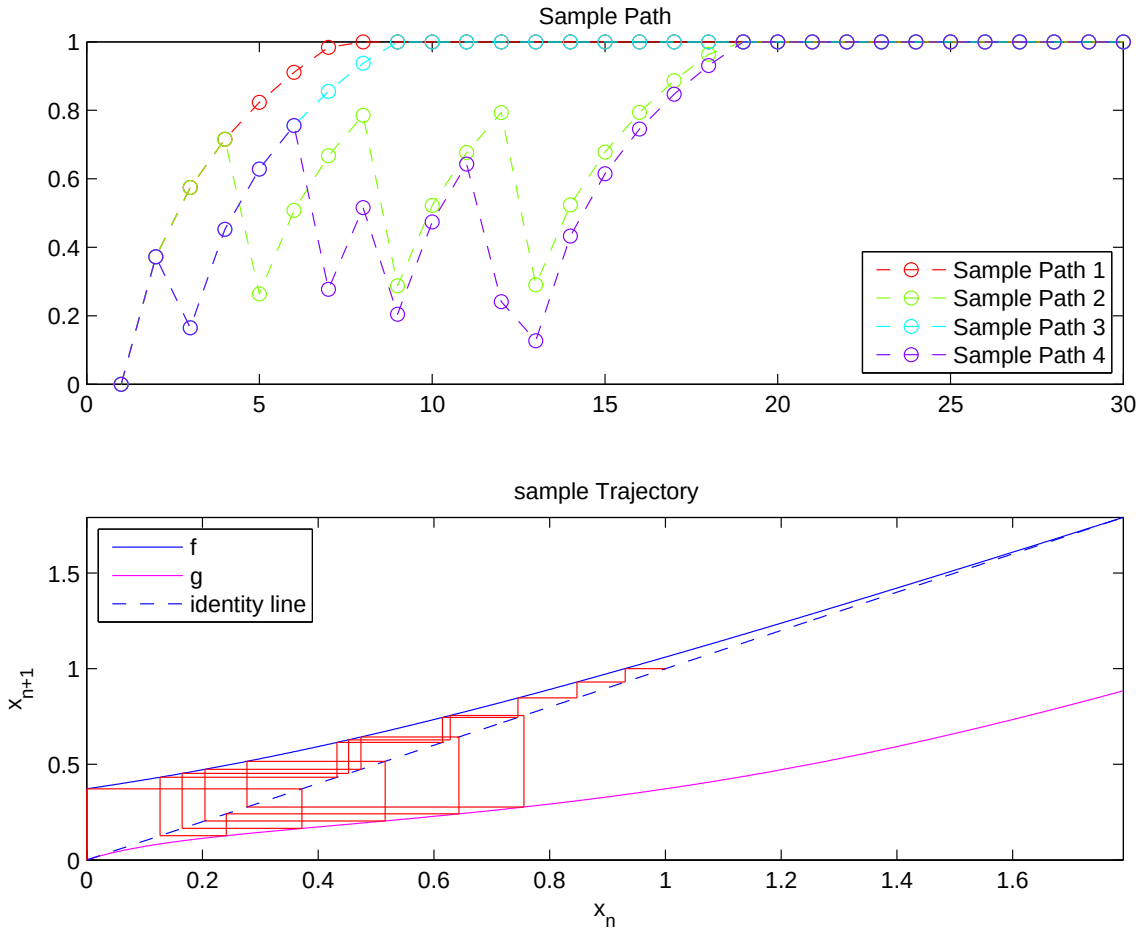


Figure 3.4. In this figure, $vT = 1.05$, $k_m = 0.25$, $r = 0.8$, $l = 1$. The upper fixed point is approximately 1.7912. We treat $l = 1$ as an absorbing state.

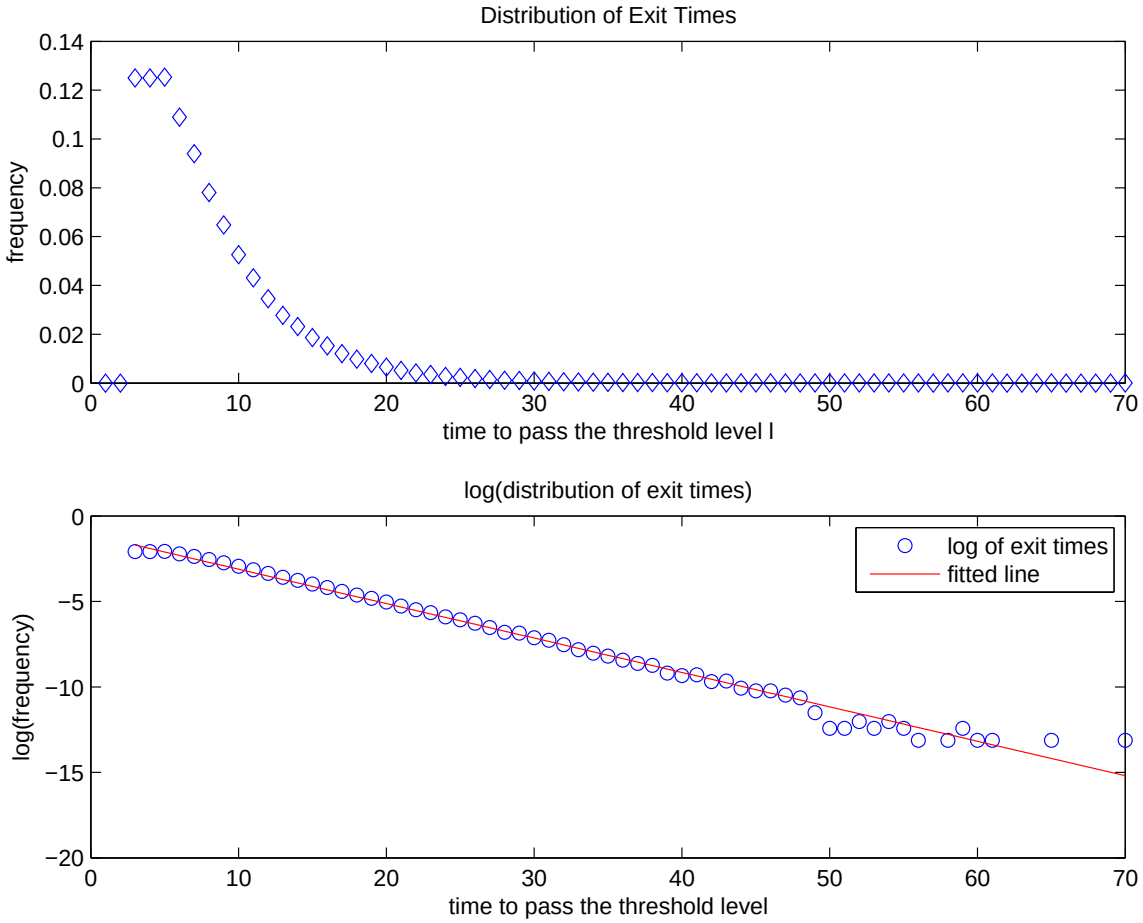


Figure 3.5. In this figure, $vT = 1.05$, $k_m = 1$, $r = 0.8$, $l = 1$. Frequency data are collected based on 500000 trials.

We study the behavior of the first passage time variable τ^x, defined by

$$\tau^x := \min\left(\{m : x_m \geq l, |x_0 = 0\}\right)$$

for any $0 < l < U$. If conditions (1)$\sim$(3) are satisfied, then we have the following conclusions:

(A) There exists a pair of finite positive integers $k = k(l)$ and $j = j(l)$ such that

$$\frac{j}{r} + E_{k-j} \leq \mathbb{E}(\tau^x) \leq E_k,$$

where the function E_n is defined as

$$E_n := \frac{\left(\frac{1}{r}\right)^n - 1}{1 - r},$$

for any nonnegative integer n. Specifically, $k = k(l)$ is defined as the unique integer such that $f^{k-1}(0) < l \leq f^k(0)$ and $j = j(l)$ is defined as the unique integer such that $f^{j-1}(0) < g(l) \leq f^j(0)$.

(B)

$$\lim_{l \to U} \mathbb{E}(\tau^x) \to +\infty.$$

Examples: It is easy to see that the 2 examples in the Introduction satisfy all 3 of these conditions.

Proof of (A). We first provide the proof for the upper bound for τ^x. By monotonicity of f, it follows immediately that $0 < f(0) < f^2(0) < ... < f^k(0) < U$ and

$$\lim_{k \to +\infty} f^k(0) = U.$$

As a direct result, we conclude that for any $0 < l < U$, there exists a unique finite positive integer k, such that

$$f^{k-1}(x_0) < l,$$

and

$$f^k(x_0) \geq l.$$

Consider the following comparison random sequence

$$y_{n+1} = \begin{cases} f(y_n), \text{ if } x_{n+1} = f(x_n), & (3.19) \\ 0, \text{ if } x_{n+1} = g(x_n), & (3.20) \end{cases}$$

with initial condition $y_0 = 0$. It is immediately apparent that since $x_0 = y_0 = 0$, we have

$$\mathbb{E}(\tau^x) \leq \mathbb{E}(\min(\{t : y_t \geq l\})).$$

For the sequence $\{y_n\}$, define a corresponding sequence $\{u_n\}$ such that $u_n = 1$ if $y_n = f(y_{n-1})$ and $u_n = 0$ if $y_n = 0$. We identify the event $u_n = 1$ as a success.

Let $p_k(t)$ denote the probability that it takes exactly t times to get a sequence of k successes in a row for the first time, i.e., the sequence u_n has a string of k ones in a row for the first time. Equivalently, this is the event that $y_t \geq l$ for the first time. We calculate

$$\mathbb{E}(\tau_k^y) := \mathbb{E}(\min(t : y_t \geq l)) = \sum_{n=1}^{\infty} n p_k(n). \tag{3.21}$$

Let T_k denote the waiting time until a sequence of consecutive successes of length k appears. It follows that

$$p_k(n) = P(T_k > n-1) - P(T_k > n). \tag{3.22}$$

Inspired by [13], we construct a sequence of probability vectors $\{P_j\}_{j=0,1,2..}$ such that the length of each vector P_j is $k-1$; Each element of P_j, denoted by $P_{j,s}$ for $s = 1, 2, ..., k-1$, is the probability that after j trials, the last run of successes is s long. We accumulate states $k, k+1, ...$ into an absorbing state. For example, suppose $k = 3$. If the last three elements of the sequence u_k are 110, 101, 011, or 010, then the last success run lengths are 0, 1, 2, and 0, respectively. Furthermore, when $k = 3$, we have that the probability of success run length being 0, 1, or 2 at time $j+1$ given that the success run length is 0 at time j is $1-r$, r, 0, respectively. Based on the same principle, it is not hard to write down the entire transition matrix for $P_n \to P_{n+1}$, for $k = 3$

$$A_3 = \begin{pmatrix} 1-r & 1-r & 1-r \\ r & 0 & 0 \\ 0 & r & 0 \end{pmatrix}, \tag{3.23}$$

so that

$$P_{n+1} = A_3 P_n, \tag{3.24}$$

for any $n \geq 0$. In fact, for any k, the transition matrix has the feature that the first row of the matrix is filled with $1-r$ and the sub-diagonal elements are filled with r so that A_k has the form

$$A_k = \begin{pmatrix} 1-r & 1-r & \dots & 1-r & 1-r \\ r & 0 & \dots & 0 & 0 \\ \vdots & \vdots & \dots & \vdots & \vdots \\ 0 & 0 & \dots & r & 0 \end{pmatrix}_{k\times k}, \tag{3.25}$$

and

$$P_{n+1} = A_k P_n, \tag{3.26}$$

for any k and $n \geq 0$. Hence, by iteration, we have $P_n = A_k^n P_0$, where the initial condition P_0, given $y_0 = 0$, is

$$P_0 = \begin{pmatrix} 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix}_k. \tag{3.27}$$

Let the superscript T denote matrix transpose. The probability $P(T_k > n)$, based on the above observations, has the representation

$$P(T_k > n) = \mathbf{1}^T P_n = \mathbf{1}^T A_k^n P_0. \tag{3.28}$$

Hence,

$$p_k(n) = 1^T \Big(A_k^{n-1} - A_k^n \Big) P_0,$$

so that

$$\begin{aligned} \mathbb{E}(\tau_k^y) &= \sum_{n=1}^{\infty} n \times 1^T \Big(A_k^{n-1} - A_k^n \Big) P_0 \\ &= \sum_{n=1}^{\infty} 1^T n A_k^{n-1} \Big(I - A_k \Big) P_0 \\ &= 1^T \left(\sum_{n=1}^{\infty} n A_k^{n-1} \right) \Big[\Big(I - A_k \Big) P_0 \Big] \\ &= 1^T (I - A_k)^{-2} (I - A_k) P_0 \\ &= 1^T (I - A_k)^{-1} P_0, \end{aligned} \tag{3.29}$$

provided

$$||A_k|| < 1.$$

We now show that the spectral radius of A_k, denoted by ρ, is less than 1. By applying induction on k, it can be shown that A_k^k (k-th power of A_k) is positive and since A_k is non-negative, A_k is primitive. Thus, by the Perron-Frobenius Theorem [11, 12], the largest eigenvalue of A_k, denoted by λ_{max}, is simple and positive. Furthermore, applying the Gerschgorin Theorem [1] on A_k^T, we know that

$$\rho = \lambda_{max} \leq \max_j \sum_i a_{ij} = (1-r) + r = 1.$$

We now show that $\rho \neq 1$. If $\rho = 1$, let $w = (w_1, w_2, \ldots, w_k)^T$ be the corresponding eigenvector of $\rho = 1$, that is, $Aw = w$. By expanding this equation, we learn that

$$\begin{cases} (1-r)(w_1 + w_2 + \cdots + w_k) = w_1 \\ rw_1 = w_2, \\ rw_2 = w_3, \\ \quad \vdots \\ rw_{k-1} = w_k. \end{cases}$$

By substituting the last $k-1$ equations in the above system into the first equation, we have

$$(1-r)\left(1 + r + r^2 + \cdots + r^{k-1}\right) = 1, \tag{3.30}$$

which does not have a solution, since the left-hand side of equation (3.30) is strictly less than 1. Hence, the spectral radius $\rho < 1$. Thus, invoking (3.29) we solve the following linear system for X

$$(I - A_k)X = P_0, \tag{3.31}$$

to obtain

$$X = \begin{pmatrix} r^{-k} \\ r^{-k+1} \\ \vdots \\ r^{-1} \end{pmatrix}_k, \tag{3.32}$$

so that

$$\mathbb{E}(\tau_k^y) = 1^T X = \frac{\left[\left(\frac{1}{r}\right)^k - 1\right]}{1-r} = E_k. \tag{3.33}$$

As a direct result, $\mathbb{E}(\tau^x) \leq \mathbb{E}(\tau_k^y) < +\infty$. We now provide the proof for the lower bound estimate for τ^x, that is, we prove

$$\frac{j}{r} + E_{k-j} \leq \mathbb{E}(\tau^x). \tag{3.34}$$

We construct a comparison sequence z_n, defined by

$$z_{n+1} = \begin{cases} f(z_n), \text{if } x_{n+1} = f(x_n), & (3.35) \\ h(z_n), \text{if } x_{n+1} = g(x_n), & (3.36) \end{cases}$$

where the function $h(x)$ is a piecewise linear function, defined as

$$h(x) = \begin{cases} x, \text{if } x \leq f^j(0), & (3.37) \\ f^j(0), \text{if } x > f^j(0). & (3.38) \end{cases}$$

Basically, the sequence z_n can be viewed as composed of two distinct phases:

(1) Phase 1: before z_n hits $f^j(0)$ for the first time;

(2) Phase 2: after z_n hits $f^j(0)$.

In phase 1, z either increases to $f^s(0)$ from $f^{s-1}(0)$ or it stays at the current level $f^{s-1}(0)$ for $s = 1, 2, ...j$. Based on this, the range of z is finite

$$\text{Range}(z) = \{f^s(0) | s = 0, 1, ...j\}, \tag{3.39}$$

and the mean time τ_s^z for z to exit to the next level $f^s(0)$ from the current level $f^{s-1}(0)$ for any $s = 1, 2, ...j$ is given by the geometric series

$$\begin{aligned} \mathbb{E}\left(\tau_s^z\right) &= r \sum_{j=1}^{+\infty} j(1-r)^{j-1} \\ &= \frac{1}{r}, \end{aligned}$$

so that the mean of the total amount of time z_n stays in phase one is $\sum_{k=1}^{j} \frac{1}{r} = \frac{j}{r}$. In phase 2, since z_n is defined similar to the sequence y_n defined in the proof for the upper bound, with only one exception that the starting point is $f^j(0)$ instead of $f^0(0) = 0$, we conclude that the mean exit time in phase 2 is E_{k-j}. Hence, the mean exit time of $\tau^z := \min\{n : z_n \geq l | z_n = 0\}$ is

$$\mathbb{E}(\tau^z) = \frac{j}{r} + E_{k-j}. \tag{3.40}$$

Note that since in both phase 1 and 2, $x_n \leq z_n$, we conclude that

$$\frac{j}{r} + E_{k-j} = \mathbb{E}(\tau^z) \leq \mathbb{E}(\tau^x), \tag{3.41}$$

and the lower bound proof is finished. Thus, the proof of (A) is completed. From the above analysis and results, we make the following remarks (1) $\sim$(3):

(1) The upper bound U is allowed to be infinite: $U = +\infty$, as long as the lower bound L and the threshold l are both finite. This is true, since the number of times to pass l by consecutive successes for y_n is $k(l) < +\infty$ so the above analysis still holds. For example, we state that in order for (3.18) to have a finite positive solution, it must be that $vT > 1$ or the upper fixed point U would be infinite. However, since for any $l \in [0, +\infty)$, there exists a finite k such that $f^k(0) > l$, the finiteness of the mean still holds for $vT < 1$.

However, if both L and U are unbounded, say $L = -\infty$ and $U = +\infty$, then the result might not hold. A classic example is the standard symmetric random walk, for which $f = x + 1$ and $g = x - 1$ so the random dynamic is

$$x_n = \begin{cases} x_{n-1} + 1, \text{with probability } 1/2 \\ x_{n-1} - 1, \text{with probability } 1/2 \end{cases}$$

given $x_0 = 0$. The mean of the exit time to 1 from 0 for this process is known to be infinite [17].

(2) We establish an inequality for the mean exit time to go beyond l from below; Similar results on the mean exit time to drop below l from above can be established as well given any initial condition $x_0 > l$, as long as the upper bound U is finite.

(3) The integer $k(l)$ is a piecewise constant monotonically increasing function of l for any function f. Hence, the upper bound E_k increases monotonically as l increases, since E_k is an increasing function of k. At the same time, $j(l)$ is also an increasing function of l; However, $k(l) - j(l)$ might not be an increasing function of l so the lower bound might not increase monotonically as l increases for some range of l. Since the mean first exit time is clearly a nondecreasing function of l, the non-monotonicity of the lower bound is an artifact of our method of proof. This is illustrated further with concrete examples in the section of numerical results.

Proof of (B): To see this, we construct another random sequence v_n as follows

$$v_{n+1} = \begin{cases} f(v_n), \text{ with probability 1,} \\ g(v_n), \text{ with probability 0,} \end{cases}$$

and we take initial condition to be $v_0 = x_0 = 0$. In fact, this random process is actually a deterministic process, and what directly follows from this definition is an inequality relating sequences x_n and v_n

$$\mathbb{E}(\tau^x) \geq \mathbb{E}(\tau^v), \tag{3.42}$$

where $\mathbb{E}(\tau^v) := \mathbb{E}(\{m : v_m \geq l\})$. Since we know that the sequence $x_0, f(x_0), f^2(x_0) \ldots$ approaches U but $f^n(x_0) < U$ for all finite n, we may construct a sequence of l that approaches U from below, defined by

$$l_n = f^n(x_0), \tag{3.43}$$

and it is not hard to see that $\mathbb{E}(\{m : v_m \geq l_n\}) = n \to +\infty$ as $n \to +\infty$. Hence,

$$\lim_{l \to U} \mathbb{E}(\tau^x) = +\infty.$$

Thus, the entire proof is completed.

3.1.3 Numerical Results

In this section, we re-examine the 2 examples discussed in the Introduction, by providing more related numerical and graphical results to test the theory. We first reconsider the random sequence

$$x_{n+1} = \begin{cases} a(x_n + 1), \text{with probability } r, & (3.44) \\ ax_n, \text{with probability } 1 - r, & (3.45) \end{cases}$$

with $0 < a < 1$ and $0 < r \leq 1$. To determine $k(l)$, we solve

$$l < a^k + \cdots + a^2 + a, \tag{3.46}$$

to obtain

$$k = \left\lceil \log_a^{\left(1 - \frac{l(1-a)}{a}\right)} \right\rceil, \tag{3.47}$$

where $\lceil \rceil$ denotes the ceiling function. At the same time, we solve

$$al < a + a^2 + \cdots + a^j, \tag{3.48}$$

to obtain

$$j = \left\lceil \log_a^{(1-(1-a)l)} \right\rceil. \tag{3.49}$$

We summarize the numerical results in Figure 3.6. We plot both the upper and lower bounds, as well as the mean exit time against the threshold level l in this figure. Upper

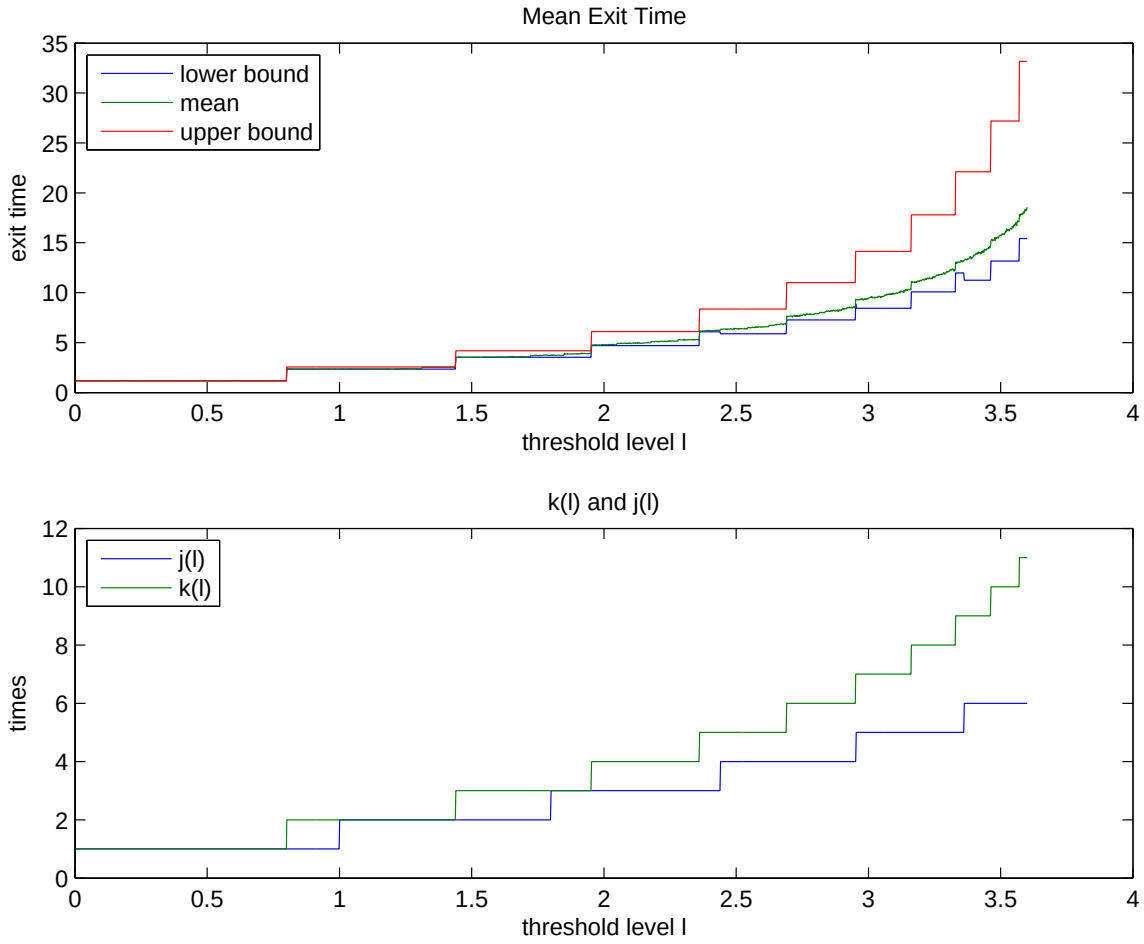


Figure 3.6. In this figure, $a = 0.8$ and $r = 0.85$. Initial conditions for all three curves in the figure are $x_0 = 0$.

and lower bounds are computed using part (A) of the main theorem, and the mean exit time for each different threshold l is simulated with Monte Carlo Method. We take the mean of 1000 first exit times for each l to approximate the true mean. It can be easily seen from the top panel in this figure that the computed mean exit time is well bounded between the upper and lower bounds, and we see that both $k(l)$ and $j(l)$ are increasing functions of l. However, around $l = 2.4$ and $l = 3.4$, the lower bound is not monotone, as can be seen from the top panel. This is because the monotonicity of k and j as functions of l, as shown in (3.47) and (3.49), respectively, is not preserved for their difference $k(l) - j(l)$ at some points.

For the second example with Hill function type elimination kinetics, unlike the first example, $k(l)$ and $j(l)$ can only be computed numerically as analytic expressions for k and j are unavailable. A plot of the computed mean and its bounds is shown in Figure 3.7.

As we have mentioned in the remark of Theorem 1, the mean of the drug concentration to drop below a threshold level l is also expected to be finite. We plot the numerically computed mean for the linear elimination case. For illustration purposes, we assume that the initial condition for this scenario is $x_0 = U = \frac{a}{1-a}$. See Figure 3.8 for results. This figure suggests that the mean exit time as a function of l is decreasing monotonically, and as $l \to 0$, the mean exit time is approaching infinity.

3.2 Conclusion

In this chapter, we discuss the mean first exit times for a broad class of random functions and prove that the mean is bounded above and below by piecewise constant functions of the threshold level l. One key point we make based on our results is the difference between the birth-death process defined by (3.3) and (3.4) and a standard random walk: the mean exit time for the first process is finite for any threshold level in the support of the random map, while the mean of the latter is always infinite for any exit level. This conclusion is interesting and meaningful and is verbally reassuring: Unlike a coin tossing gambling, which is usually modeled by a symmetric random walk, the drug taking process is not a "fair game": as long as the probability of taking it is nonzero, then on average, the drug will be effective some day. This should be good news to even forgetful patients.

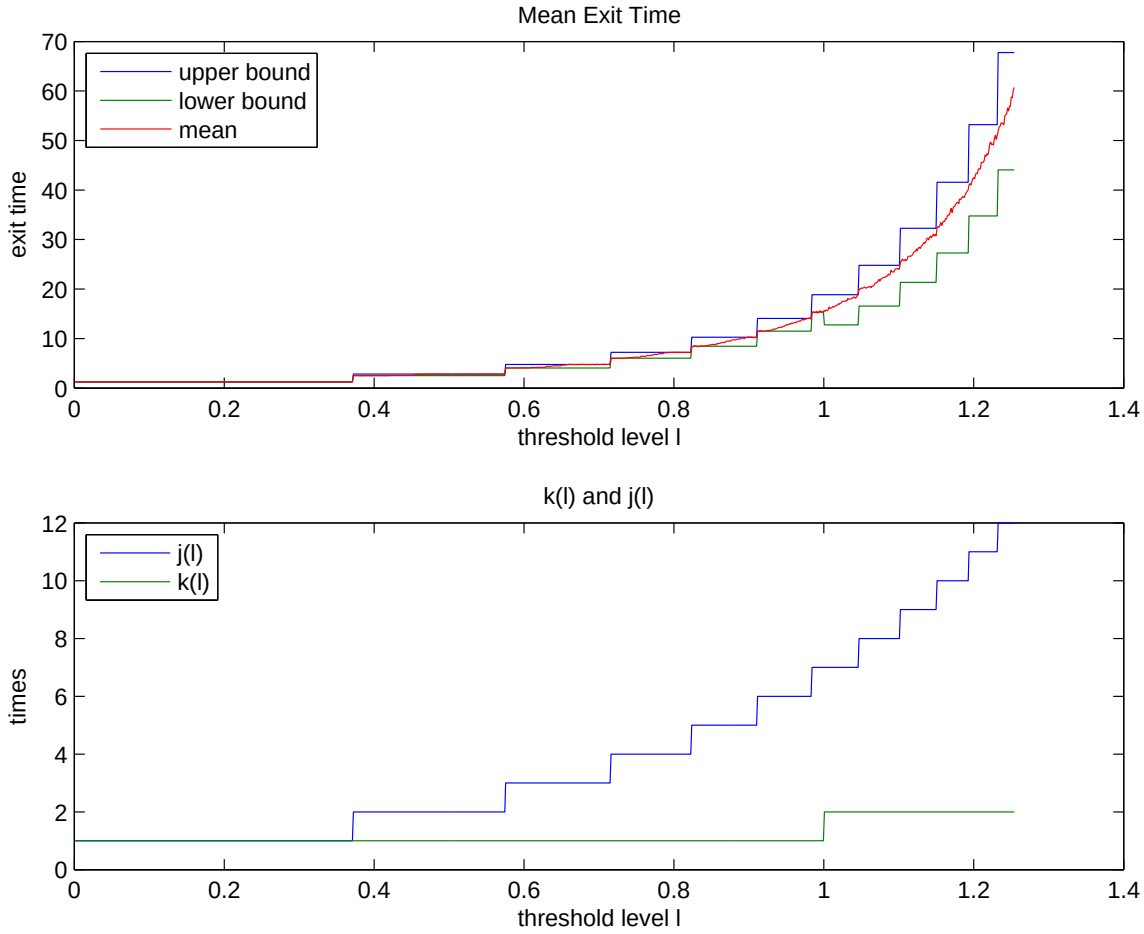


Figure 3.7. In this figure, $k_m = 0.25$, $vT = 1.05$, $r = 0.8$. The range of l is $l \in [0, 0.7 \times U]$. For each threshold level l, 10000 first exit times were simulated to approximate the true mean.

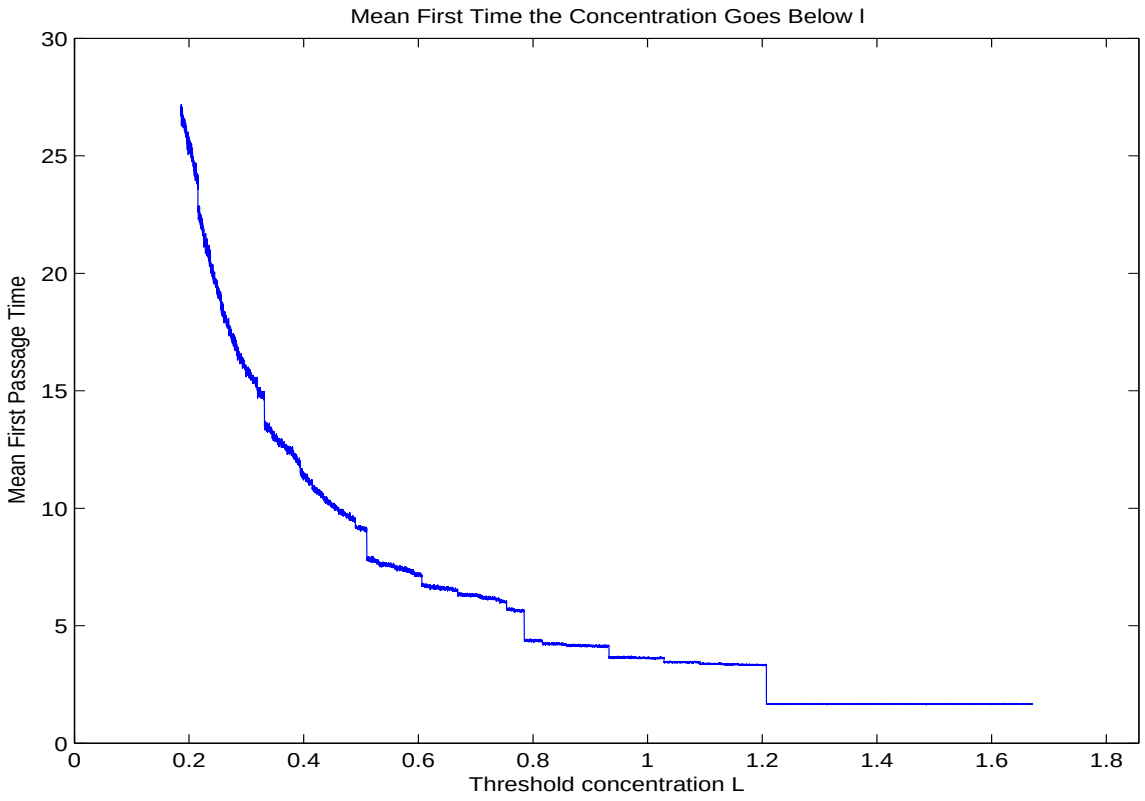


Figure 3.8. In this figure, the mean first time the concentration drops below the threshold level l is plotted as a function of l. Parameter values are: $a = 0.65$, $r = 0.4$. The range of l in the figure is $[0.1U, 0.9U]$.

CHAPTER 4

MULTIPLE DOSAGE TAKING STRATEGIES

It has been reported [6] that at least 80% of patients might miss a dose of their medication at some point during their medical treatment but less than 50% of patients [16] in the U.S. received the information on what to do after such an event occurs, while in a study of more than 200 people [9], 90% rated having such information as critical. It appears that for many drugs, if one dose is missed, then taking only the regular amount of drug at the scheduled time on the following day does not have much impact on the patient since a single missed dose is of little consequence. However, if a relatively high drug concentration needs to be maintained [6] in the body, then more drugs might be needed (for example, a double dose should be taken) or some other actions should be performed to compensate for the loss of the previously missed dose.

Up until now, not many studies have focused on the impact of a missed dose [6], even though for some certain drugs, such studies have been performed experimentally. For example, from [6] we learn that if an active oral contraceptive pill is missed during the first week of treatment, then it is recommended that the patient take it as soon as it is remembered even though sometimes this means taking two tablets at the same time, since there is a higher probability that the patient becomes pregnant if this pill is not compensated for.

However, since in general, much still remains unknown for many other drugs, our goal in the current chapter is to quantitatively study under what circumstances the patient should take only the regular amount of drug as prescribed and under what circumstances he should take a double dose instead, after a previous dose is missed. One of our basic assumptions is that the drug could be lethal in two different ways:

(1) Since the patient might forget to take drugs, the concentration level cannot be maintained above an effective level persistently, which results in drug inefficiency in a lethal

way;

(2) If the patient decides to take a double dose to compensate for the loss of a previously missed dose, then the drug could bring side effects to him in a lethal way.

To achieve our goal in this chapter, we incorporate the concept of a therapeutic window into our mathematical model, by which we define what we mean by the better strategy. This window is constructed in terms of an effective level as well as a toxic level. By effective level, we mean the concentration above which the drug is effective and by toxic level, we mean the level above which the drug is unsafe.

4.1 Model Derivations

To construct our mathematical model, we assume that once a single dose is missed, the patient either forces himself or is forced by other people to take a single or double dose. Namely, we assume that the probability of forgetting to take the drug for more than 2 consecutive days is 0. Thus, a discrete time random process can be constructed as

$$x_{n+1} = \begin{cases} f(x_n), \text{if drug is taken both yesterday and today,} & (4.1) \\ g(x_n), \text{if drug is taken yesterday but not today,} & (4.2) \\ g(g(x_n) + A), \text{if drug is not taken yesterday,} & (4.3) \end{cases}$$

where functions f and g are defined in Chapter 2 and A is the amount to be taken, either 1 or 2 for the two different situations. Notice that if the patient forgets to take the drug on day n, then a 2 period chain is formed, which reads

$$x_n \mapsto g(x_n) \mapsto g(g(x_n) + A). \tag{4.4}$$

We denote x_f as the fixed point of the map $x \mapsto f(x)$. Similarly, we denote x_{g1} and x_{g2} as fixed points for the 2 period chain for map (4.4) for $A = 1$ and $A = 2$, respectively. Then it is easy to show the following proposition.

Proposition 4.1. $x_{g2} \geq x_f \geq x_{g1}$.

Proof. We first note that $f(x) = g(x + 1)$. We also note that x_{g_1} satisfies

$$x_{g1} = g(g(x_{g1}) + 1), \tag{4.5}$$

and x_f satisfies

$$x_f = g(x_f + 1) = g(g(x_f + 1) + 1). \tag{4.6}$$

Since the function $g_1(y) := g(g(y+1)+1)$ is always greater than the function $g_2(y) := g(g(y)+1)$ for any positive y provided g is monotonically increasing, it follows directly that $g_1(y)$ intersects $y = x$ at a higher value than $g_2(y)$ intersects $y = x$, which implies that $x_{g1} < x_f$. On the other hand, x_{g_2} satisfies

$$x_{g2} = g(g(x_{g2}) + 2). \tag{4.7}$$

Since $g(x) = H^{-1}(-T + H(x))$, where $H(x) := \int_c^x \frac{1}{h(s)} ds$, it follows that $H(g(x)) = (-T + H(x))$ and by differentiating this equation with respect to x, we obtain

$$\frac{dH}{dg}\frac{dg}{dx} = \frac{dH}{dx}, \tag{4.8}$$

$$\implies \frac{dg(x)}{dx} = \frac{dH/dx}{dH/dg} = \frac{\frac{1}{h(x)}}{\frac{1}{h(g(x))}} \tag{4.9}$$

$$= \frac{h(g(x))}{h(x)} < 1, \tag{4.10}$$

since $g(x) < x$. It follows immediately that $g(y) + 1 > g(y+1)$ and hence, $x_{g2} > x_f$ by (4.6) and (4.7). If we assume that the doctor's prescribed amount of a single dose is safe, i.e, if the toxicity level, denoted by l_{tox}, satisfies $x_f < l_{tox}$, then taking only a single dose after a previous dose is missed cannot put the patient into danger in any way; However, taking two pills may do so since $l_{tox} < x_{g2}$.

Denote the effective level by l_{eff}. The therapeutic window, or just window, is denoted as $[l_{eff}, l_{tox}]$, where we make the assumption that $l_{eff} \leq x_f \leq l_{tox}$ so that the doctor's prescription is assumed to be both effective and safe when taken on a daily taking basis.

Let x_n denote the time series for the case when no compensation action is performed and let y_n and z_n denote the time series defined by $(1) \sim (3)$ for $A = 1, 2$, respectively. We call the 3 strategies associated with x_n, y_n, and z_n the no, 1 pill, and 2 pills strategy, respectively. We further make the following assumptions for our model:

(A) $l_{eff} < x_f < l_{tox} < x_{g2}$;

(B) In our numerical simulation, we take $l_{eff} = l_1(x_f, u_1)$ and $l_{tox} = l_2(x_f, u_2)$, where u_1 and u_2 are two control parameters that satisfy:

   (a) $u_1, u_2 \in [0, 1]$;

   (b) $l_1(x_f, 1) = 0$, $l_1(x_f, 0) = x_f$ and $l_2(x_f, 1) = x_{g_2}$, $l_2(x_f, 0) = x_f$;

(c) $\frac{\partial l_1}{\partial u_1} < 0$ and $\frac{\partial l_2}{\partial u_2} > 0$.

(C) For numerical simulations in this chapter, we assume that the drug elimination is of first order or by Hill function type with Hill coefficient $m = 2$, i.e., $h(x) = Kx$ or $h(x) = \frac{Vx^2}{K_m + x^2}$.

Explanation of assumptions: Assumption (A) says that taking a double dose after a single dose is missed could potentially bring side effects to the patient since $l_{tox} < x_{g_2}$; Assumption (B) says that we define 2 control parameters u_1 and u_2, by varying which l_{eff} and l_{tox} satisfy assumption (B). One such choice is $l_{tox} = (1 + (\frac{x_{g_2}}{x_f} - 1)u_2)x_f$ and $l_{eff} = (1 - u_1)x_f$ for $u_1, u_2 \in [0, 1]$, for which both l_{eff} and l_{tox} depend linearly on u_1, u_2 as well as x_f. A simulation for $\{x_n\}$, $\{y_n\}$ and $\{z_n\}$ can be seen in Figure 4.1, where in this figure, the 2 red lines represent x_{g_1} and x_{g_2}, respectively, and the top and bottom black lines represent the toxic and effective levels, respectively. It can be seen that the sequence $\{y_n\}$ (1 pill strategy) never goes above the toxicity level but the sequence $\{z_n\}$ (2 pills strategy) sometimes does. Furthermore, for both sequences, drug levels might drop below the effective level after a dose is missed.

We now first look at the relationship between the three mean first passage times: $\mathbb{E}(m_1 : x_{m_1} \geq l)$, $\mathbb{E}(m_2 : y_{m_2} \geq l)$, and $\mathbb{E}(m_3 : z_{m_3} \geq l)$. We show that

Theorem 4.1. The three mean first passage times for the three sequences x_n, y_n, and z_n satisfy

$$\mathbb{E}\Big(m_3 : z_{m_3} \geq l\Big) \leq \mathbb{E}\Big(m_2 : y_{m_2} \geq l\Big) \leq \mathbb{E}\Big(m_1 : x_{m_1} \geq l\Big). \tag{4.11}$$

Proof: Let 1 and 0 denote the event that the patient does or does not take the drug, respectively. To show that $\mathbb{E}(m_2 : y_{m_2} \geq l) \leq \mathbb{E}(m_1 : x_{m_1} \geq l)$, we note that for the same sequence of unconstrained events $i_1, i_2, ..., i_n...$, where $i_j = 0$ or 1 for $j = 1, 2, 3...$, if m_1 is the first time such that $i_{m_1} = 0$, then to find y_{m_1}, y_{m_1-1} is first mapped to $y^*_{m_1}$ by $y^*_{m_1} = g(y_{m_1-1})$ and then $y^*_{m_1}$ is mapped into $y_{m_1} = g(y^*_{m_1} + 1) = g(g(y_{m_1-1}) + 1)$, since a drug is forced to be taken. Since $x_i = y_i$ for all $i < m_1$, it follows that $x_{m_1} = g(x_{m_1-1}) = g(y_{m_1-1})$. Since $g(y) + 1 > g(y + 1) = f(y) > y$ for all positive y, it follows that

$$g(g(y_{m_1-1}) + 1) = y_{m_1} > x_{m_1} = g(x_{m_1-1}) = g(y_{m_1-1}). \tag{4.12}$$

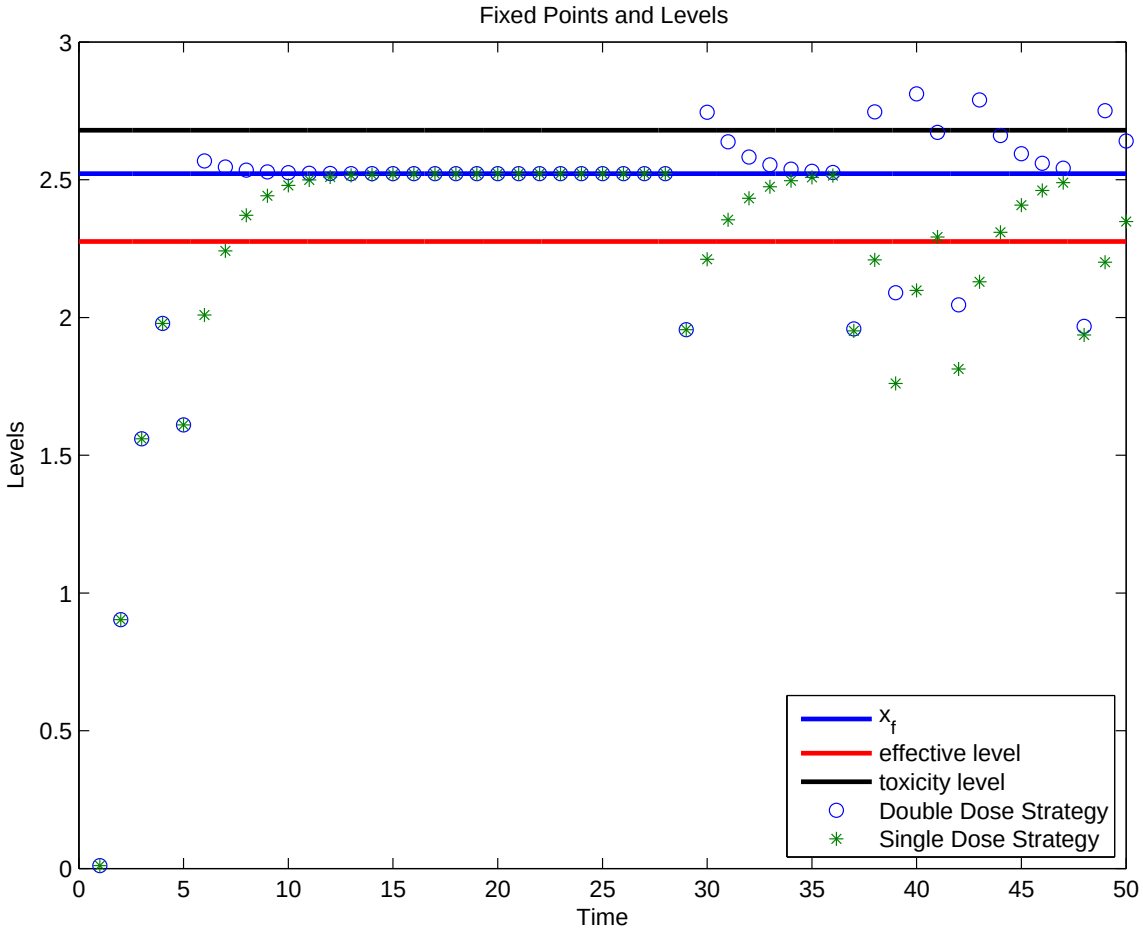


Figure 4.1. In this figure, $K_m = 200$, $r = 0.8$, $V = 1$, $T = 24$. The top red curve is the horizontal level $y = x_{g_2}$, whereas the bottom red curve is the level $y = x_{g_1}$; The 2 black curves in the middle represent l_{tox} and l_{eff}, respectively. The yellow line represents the level $y = x_f$. $\{z_n\}$ (blue dots) and $\{y_n\}$ (green asteroids) are also simulated in this figure.

Since $y_{m_1} > x_{m_1}$, by induction, we can show that for all m where $i_m = 0$, we have that $y_m > x_m$. Hence, $y_i \geq x_i$ for all i. Therefore, $\mathbb{E}\Big(m_2 : y_{m_2} \geq l\Big) \leq \mathbb{E}\Big(m_1 : x_{m_1} \geq l\Big)$. The proof of the first half of the inequality (4.11) is trivial by the fact that $1 < 2$. Hence, the proof is completed.

Inequality (4.11) shows that by taking extra pills after a previous dose is missed, the mean first passage time to pass the effective threshold level l_{eff} is reduced and the more pills taken, the larger the reduction. However, the threshold level can also be the toxic level l_{tox}. By proposition 1 and assumption (B), as well as our main results in Chapter 3, we conclude that the mean first passage time satisfies

$$\mathbb{E}\Big(m_3 : z_{m_3} \geq l_{tox}\Big) < +\infty, \tag{4.13}$$

for $x_{g_2} > l_{tox} > x_f$ for $r < 1$, but $\mathbb{E}(m_2 : y_{m_2} \geq l_{tox}) = \mathbb{E}(m_1 : x_{m_1} \geq l_{tox}) = +\infty$. This shows that while taking 2 extra doses reduces time to pass l_{eff}, it also reduces the time to pass l_{tox}. If mean first passage time is used to determine the best strategy, then the 1 pill strategy outperforms the 2 pills strategy, since it reaches l_{eff} faster than the no pill strategy but at the same time, it is safer than the 2 pills strategy. A plot of the mean first passage time as a function of time for all 3 sequences can be seen in Figure 4.2.

However, it is clear that only looking at first passage times ignores a substantial amount of useful information, since the entire drug taking process is assumed to be a long-term process. Another way of assessing these strategies is to count the frequency that each sequence x_n, y_n, and z_n falls within the window $[l_{eff}, l_{tox}]$. Specifically, let $p_x(s)$, $p_y(s)$, and $p_z(s)$ denote steady state probability distribution for x_n, y_n, and z_n, respectively. We first show that support for p_x is $[0, x_f]$ and for p_y, and p_z, supports are subsets of $[g(x_{g_1}), x_f]$ and $[g(x_f), x_{g_2}]$, respectively, in the following theorem.

Theorem 4.2. The support for x_n, y_n, and z_n satisfies

$$supp(p_x(s)) = [0, x_f] \ , supp(p_y(s)) \subset [g(x_{g_1}), x_f], \tag{4.14}$$

and

$$supp(p_z(s)) \subset [g(x_f), x_{g_2}], \tag{4.15}$$

in steady state.

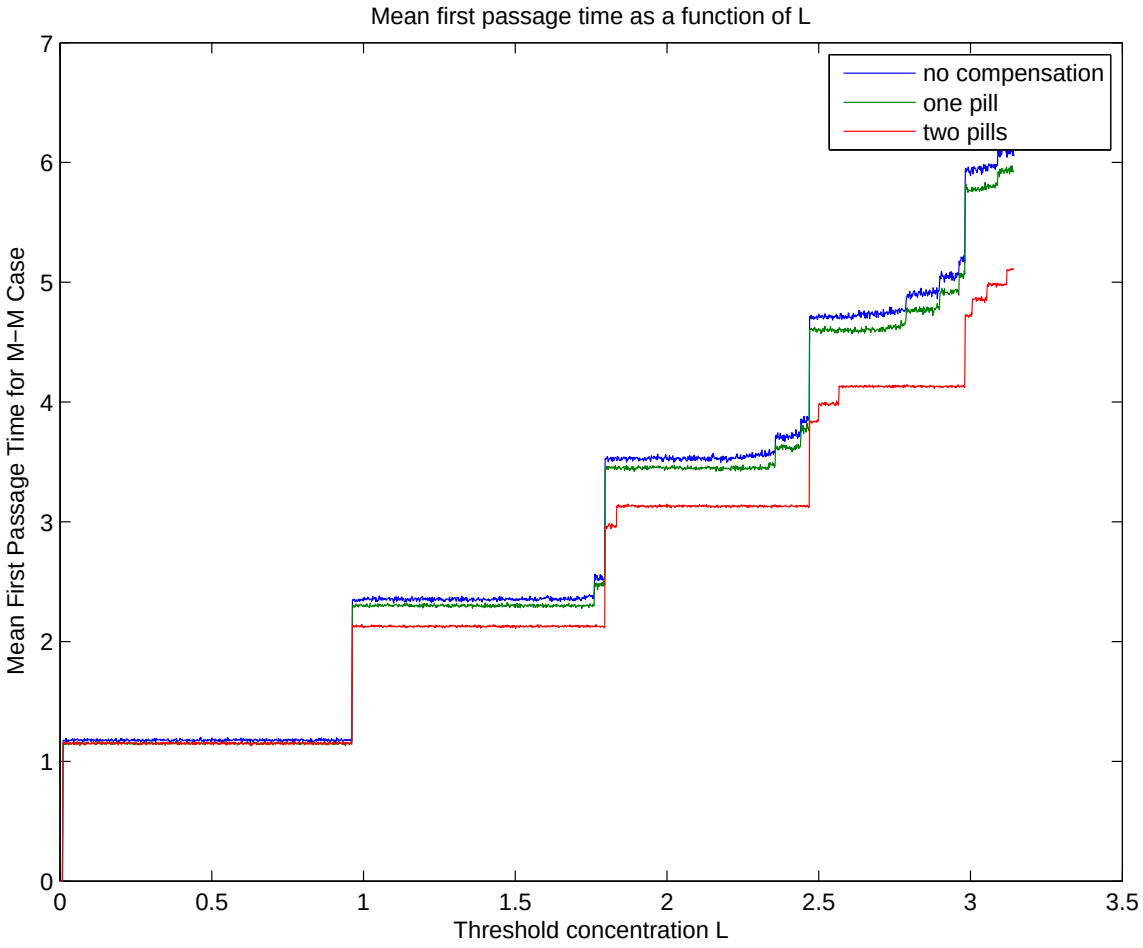


Figure 4.2. In this figure, $r = 0.85$, $K_m = 500$, $V = 1$, $T = 24$. The range for L is $[0, 0.75 * x_f]$.

Proof: That the support for x_n in steady state is $[0, x_f]$ is trivial, which has been shown in Chapter 2. For the sequence y_n in steady state, suppose the initial condition satisfies $y_0 < g(x_{g_1})$. Then if we assume that the first m pills are all missed, we have that $x_{2m} \to x_{g_1}$ and $x_{2m+1} \to g(x_{g_1})$ monotonically from below as m gets large. Since $g(x_{g1}) < x_{g_1}$, it follows that there exists a positive integer i such that $x_{2i} > g(x_{g_1})$. Since $r \neq 0$, then at some time if the drug is taken at step $2j$ for some positive $j > i$, it follows that $f(x_{2j}) \geq f(x_{2i}) > f(g(x_{g_1})) = g(g(x_{g_1}) + 1) = x_{g_1}$. Since $g([x_{g_1}, x_f]) = [g(x_{g_1}), g(x_f)]$, we conclude that the sequence up until the time $2j$ has successfully escaped from the region $[0, g(x_{g_1})]$. Hence, the probability measure for $[0, g(x_{g_1})]$ is identically zero. That x_f is an upper bound of the support follows directly from the fact that $x_n \leq x_f$ for every positive n. Similar arguments can be made to conclude that the support for the pdf of z_n in steady state is a subset of $[g(x_f), x_{g_2}]$. Plots for steady state pdfs of x_n, y_n, and z_n are shown in Figure 4.3 using the finite difference method introduced in Chapter 2, which justify this theorem numerically.

In fact, the exact support for y_n is $[g(x_{g1}), g(x_f)] \cup [x_{g_1}, x_f]$ if $g(x_f) < x_{g_1}$ and is exactly $[g(x_{g_1}), x_f]$ if $g(x_f) \geq x_{g_1}$. Which one between $g(x_f)$ and x_{g_1} is greater might depend on parameter values in the model. For example, if linear elimination dynamic is assumed, then it is easy to show that when $a < \frac{\sqrt{5}-1}{2}$, $g(x_f) < x_{g_1}$ and vice versa. However, since for either case, the exact support is a subset of $[g(x_{g_1}), x_f]$, we denote $[g(x_{g_1}), x_f]$ as the support for notational simplicity. The same story holds for the sequence z_n in steady state.

Having established support for pdfs of x_n, y_n, and z_n, we now begin calculating what we mean by the frequency that falls in the window. By frequency, we mean

$$\mathbb{E}(u \in [l_{eff}, l_{tox}]) := \int_{s=l_{eff}}^{s=l_{tox}} p_u(s)ds, \tag{4.16}$$

for $u = x, y, z$. By elementary calculus, we know that $\mathbb{E}(u \in [l_{eff}, l_{tox}])$ is increasing in the variable l_{tox} and is decreasing in l_{eff}. By assumption (C), equation (4.16) becomes

$$\mathbb{E}(u \in [l_{eff}, l_{tox}]) = \int_{l_1}^{l_2} p_u(s)ds = \int_{l_1(x_f,u_2)}^{l_2(x_f,u_1)} p_u(s)ds, \tag{4.17}$$

for $u = x, y, z$. We now first compute the difference

$$\mathbb{E}(z \in [l_{eff}, l_{tox}]) - \mathbb{E}(y \in [l_{eff}, l_{tox}]) = \int_{l_1(x_f,u_1)}^{l_2(x_f,u_2)} \Big(p_z(s) - p_y(s)\Big)ds. \tag{4.18}$$

If $u_1 = 0$ in (4.18), we obtain that

$$\int_{x_f}^{l_2(x_f,u_2)} \Big(p_z(s) - p_y(s)\Big)ds = \int_{x_f}^{l_2(x_f,u_2)} p_z(s)ds > 0, \tag{4.19}$$

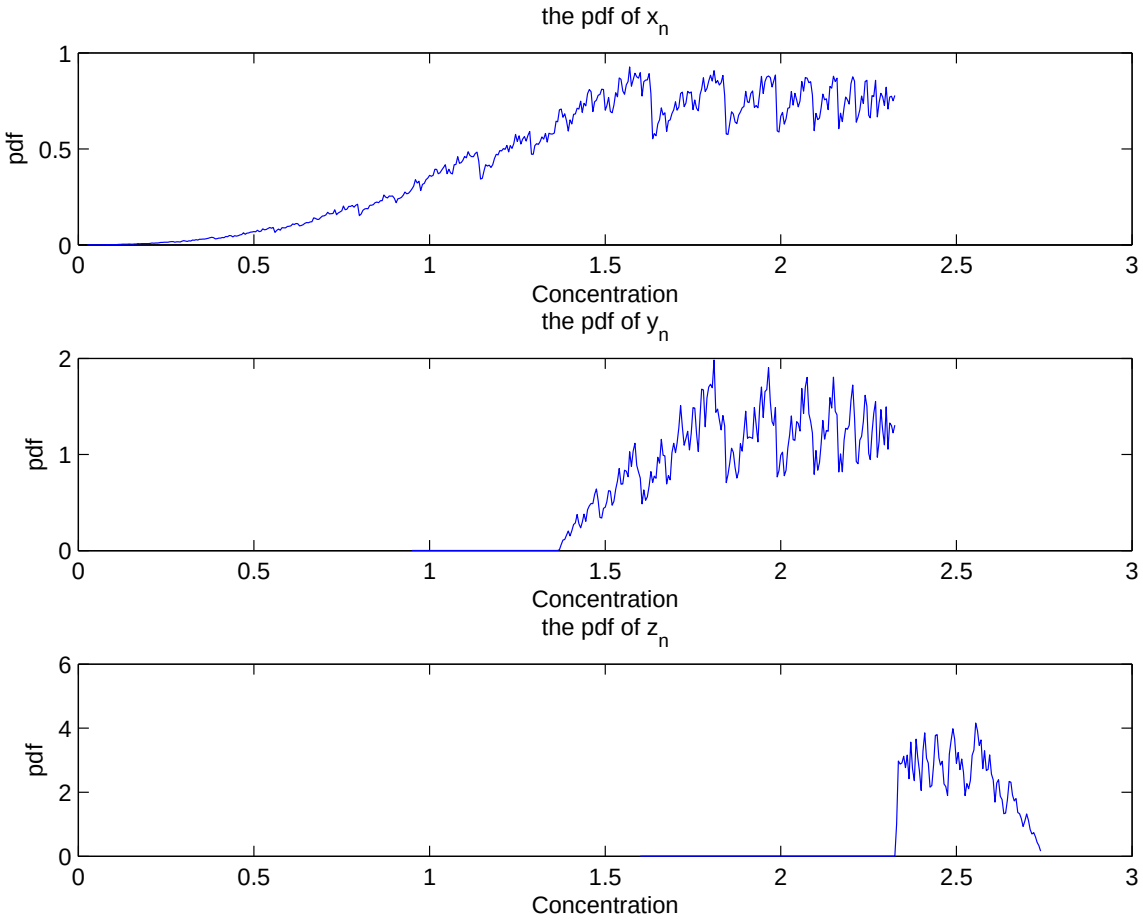


Figure 4.3. In this figure, $a = 0.8$ and $r = 0.75$ and it can be concluded that $x_f = a/(1-a) \approx 2.33$, $x_{g_2} = 2a/(1-a^2) \approx 2.74$ and $x_{g_1} = a/(1-a^2) \approx 1.37$, so that $g(x_{g_1}) \approx 0.96$ and $g(x_f) \approx 1.63$. Hence, $[g(x_{g_1}), x_f] = [0.96, 2.33]$ and $[g(x_f), x_{g_2}] = [1.63, 2.74]$ and our conclusions in Theorem 2 are justified numerically.

since $p_y(s) = 0$ for $y \in [x_f, l_2]$ because the support of y_n is $[g(x_{g_1}), x_f]$. On the other hand, if $u_1 = 1$, then from (4.18), we obtain that

$$\int_0^{l_2(x_f,u_2)} \Big(p_z(s) - p_y(s)\Big)ds = \int_0^{l_2(x_f,u_2)} p_z(s)ds - 1 < 0, \tag{4.20}$$

since by assumption (C), $l_2 = l_2(x_f, u_2) < x_{g_2}$ for $u_2 < 1$ and the fact that $p_z(s) \neq 0$ for $s \in [l_2, x_{g_2}]$. Hence, for any fixed $u_2 < 1$, that is, for any threshold toxicity level $l_{tox} < x_{g_2}$, there must exist at least one $u_1 = u_1(u_2)$ such that $(4.18) = 0$ if we assume that the integral in (4.18) depends on u_1 continuously. However, such a point at which $(4.18) = 0$ might not be unique. We show numerical results in Figure 4.4. We plot equation (4.18) as a function of u_1 for 2 different K_m in this figure and results are simulated by counting the actual frequencies that fall within the window. In this figure, we take the elimination to be of Hill function type. We use $l_{eff} = (1 - u_1)x_f$ and $l_{tox} = (1 + u_2)x_f$ for this numerical experiment, where we fix $u_2 = 0.05$. As we can see from the bottom subplot, when $K_m = 500$, equation (4.18) admits 3 distinct zeros so we conclude that the uniqueness of zeros of equation (4.18) is not guaranteed in general. However, if we denote by u_1^* the smallest u_1 such that equation $(4.18) = 0$ and by u_1^{**} the largest u_1 such that equation $(4.18) = 0$, then the conclusion that when $u_1 < u_1^*$, equation $(4.18) > 0$ and when $u_1 > u_1^{**}$, equation $(4.18) < 0$ holds true in general.

Physiologically speaking, this means that if the toxicity level is fixed, then when the effective level is high ($u_1 < u_1^*$), we conclude that the 2 pills strategy outperforms the 1 pill strategy whereas if the effective level is low ($u_1 > u_1^{**}$), then the 1 pill strategy outperforms the 2 pills strategy. The reason for this is that if the effective level is low, then taking just 1 pill is, on average, enough for the drug to be effective during the entire period of the treatment and taking 2 pills simply brings side effects to the patient's body. On the other hand, if the effective level is high, i.e., a high concentration is needed to persist during the course of the treatment, then taking 2 pills is the better choice since the drug concentration that is below the effective level is viewed as being lethal to the patient in this case.

We also note that the patient should try to force himself or be forced by other people to take at least the regular amount of drug the second day when a previous dose is missed, in that we find

$$\int_{l_1}^{l_2} \Big(p_y(s) - p_x(s)\Big)ds = \int_{l_1}^{x_f} \Big(p_y(s) - p_x(s)\Big)ds \geq 0, \tag{4.21}$$

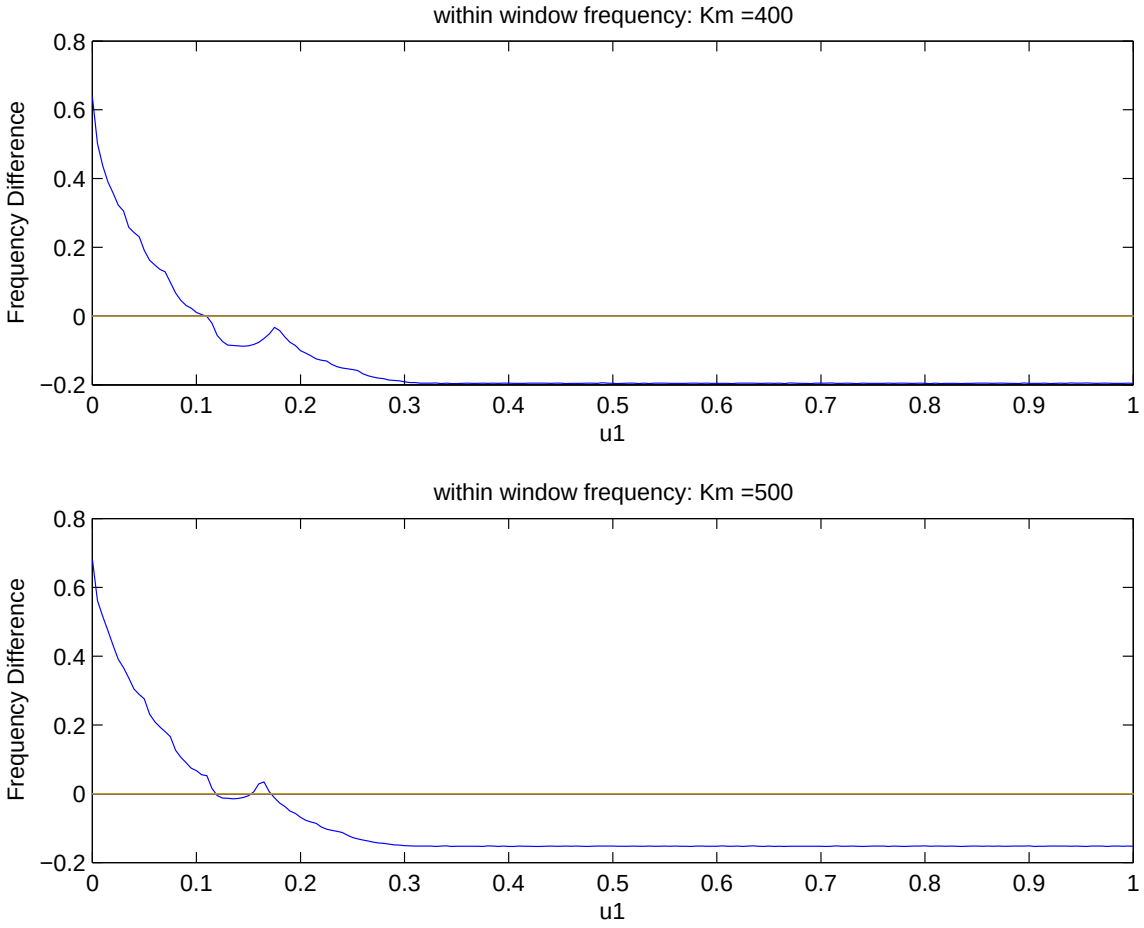


Figure 4.4. In this figure, we plot (4.18) as a function of u_1, for $K_m = 400$, (upper subplot) and $K_m = 500$ (lower subplot). Parameter values are: $r = 0.8$, $V = 0.98$, $T = 24$. It can be seen from the lower subplot that there are 3 zeros over the range of $[0, 1]$ for u_1.

and

$$\int_0^{l_1} \Big(p_y(s) - p_x(s)\Big)ds = 0 - \int_{l_1}^{x_f} \Big(p_y(s) - p_x(s)\Big)ds \leq 0, \tag{4.22}$$

and finally,

$$\int_{l_2}^{U} p_y(s)ds = \int_{l_2}^{U} p_x(s)ds = 0, \tag{4.23}$$

for all $l_1 \leq x_f$ and any $U > l_2$. (4.21) and (4.22) can be derived from the fact that for any sequence of random numbers $\{i_j\}_{j=0,1,2\ldots}$, $y_j \geq x_j$ (see the proof of theorem 1). This shows that by forcing the patient to take the regular amount of drug the next day after a dose is missed, in the long term, the drug is both safe as indicated by equation (4.23) and is more effective, as indicated by (4.21) and (4.22), than if the patient is not forced to do so, in that there is a nonzero probability that the patient may forget to take drugs for several consecutive days.

Lastly, very similar to the proof of the existence of u_1^* and u_1^{**}, if we simply replace p_y by p_x and y by x in equation (4.18), (4.19), and (4.20), we can show that there exists a pair of quantities u_1' and u_1'' such that

$$\mathbb{E}(z \in [l_{eff}, l_{tox}]) - \mathbb{E}(x \in [l_{eff}, l_{tox}]) = \int_{l_1(x_f,v)}^{l_2(x_f,u_2)} \Big(p_z(s) - p_x(s)\Big)ds = 0, \tag{4.24}$$

where $v = u_1', u_1''$ are defined as the smallest and biggest u_1 such that equation $(4.24) = 0$. (In many situations, $u_1' = u_1''$.) Then, it follows directly that when $u_1 < u_1'$, $(4.24) > 0$ and for $u_1 > u_1''$, $(4.24) < 0$. We now prove that

Theorem 4.3. u_1^* and u_1' satisfy

$$u_1^* \leq u_1'.$$

Proof. By the definition of u_1', we have that

$$\int_{l_1(u_1')}^{l_2} (p_z - p_x)ds = \int_{l_1(u_1')}^{l_2} (p_z - p_y)ds + \int_{l_1(u_1')}^{l_2} (p_y - p_x)ds \tag{4.25}$$

$$= \int_{l_1(u_1')}^{l_2} (p_z - p_y)ds + \int_{l_1(u_1')}^{x_f} (p_y - p_x)ds \tag{4.26}$$

$$= 0, \tag{4.27}$$

and by the definition of u_1^*,

$$\int_{l_1(u_1^*)}^{l_2} (p_z - p_y)ds = 0. \tag{4.28}$$

Since the second term in (4.26) is greater than or equal to 0, we deduce that

$$\int_{l_1(u_1')}^{l_2} (p_z - p_y) ds \leq 0. \tag{4.29}$$

Hence, by comparing (4.28) to (4.29), we conclude that $l_1(u_1^*) \geq l_1(u_1')$, since $u_1 = u_1^*$ is defined as the first time at which $(4.28) = 0$ and when $u_1 = 0$, equation $(4.19) > 0$. This shows, by the monotonicity of $l_{eff} = l_1$ as a function of u_1, that $u_1^* \leq u_1'$. Hence, the proof is completed. If we assume the uniqueness of both u_1^* and u_1', then this theorem shows that we should choose to switch to the no pill strategy from the 2 pills strategy at a lower effective threshold level than if we switch from the 2 pills strategy to the 1 pill strategy.

4.2 Conclusion

In this chapter, we have shown that if the mean first passage time to pass the effective level is used as the criteria, then taking 1 extra pill is the best strategy in that it does not bring any side effects and it has a smaller mean time to pass the effective level; If the frequency counting measure is used, then for fixed toxicity level, if the effective level is high, then taking 2 pills is the better strategy since a high concentration of the drug needs to be maintained, whereas if the effective level is low, then simply taking a single dose as prescribed is better since not much time shall be spent above the toxic level, but the frequency the concentration is above the effective level is also well maintained at the same time.

CHAPTER 5

THE USE OF SINGULAR PERTURBATION METHODS IN PHARMACOKINETICS

5.1 Introduction

In this chapter, we focus on obtaining analytical solutions for one-compartment models with nonlinear elimination rates, with periodic extravascular injections. The elimination is assumed to be nonlinear in the current chapter. Previously, in 1958, Lundquist and Wolthers [15] obtained the integrated form of the solution for one-compartment model with M-M elimination rate with zero and first-order intravenous administrations; Later in 1972, Wagner [21] obtained some useful properties of the Michaelis-Menten equation by investigating its integrated form; In 1978, Wagner [22] studied the one-compartment model with M-M elimination with multiple intravenous or first-order oral administrations, but only numerically; In 2007, Tang and Xiao [19] derived the analytical solution of the one-compartment model with M-M elimination kinetics with repetitive intravenous dose regime using the LambertW function [2]. In that paper, the authors were able to obtain conditions under which the steady state periodic solution of the system is stable. Later in 2011, Goličnik [7] provided alternative analytical expressions to approximate true solutions of the same systems. These expressions may be used when the Lambert $W(x)$ function is unavailable in the software being used.

However, as has been mentioned in [19], if the drug is taken extravascularly, then because of the inclusion of a preceding compartment (absorption compartment) to the central compartment, a closed form analytical solution of the system cannot be obtained. Therefore, in this present work, we seek asymptotic solutions to the system of interest. Using these solutions, we are able to construct composite expansions that agree well with the numerical solutions of the system, as well as to obtain some meaningful biomarkers that cannot be investigated otherwise. These enable us to rigorously establish conditions under which stable positive periodic solutions for this system exist.

5.2 Motivations

Here we are concerned with two compartment models with nonlinear elimination kinetics with an absorption compartment and a central compartment included. When a new dose of drug is administered, it enters the absorption compartment and then it is released from there, entering the central compartment immediately afterwards.

Like notations used in previous chapters, throughout this chapter, like we let C_a and C denote the concentration of the drug in the absorption and central compartment, respectively.

For now, suppose the rate of loss of drug from the absorption compartment is of first-order kinetics so that

$$\frac{dC_a}{dt} = -K_a C_a, \tag{5.1}$$

where K_a denotes the first-order absorption rate constant. To model that a fixed amount of drug with concentration J is administered periodically with a fixed period T, impulse (jump) conditions are applied at times $t = nT$ for nonnegative integers n

$$C_a(nT^+) - C_a(nT) = J, \tag{5.2}$$

To describe the evolution of the drug concentration in the central compartment, we assume that the drug is eliminated with elimination rate f so the differential equation

$$\frac{dC}{dt} = BK_a C_a - f. \tag{5.3}$$

applies. Since the drug does not directly enter the central compartment, C changes continuously when drug is supplied

$$C(nT^+) = C(nT), \tag{5.4}$$

where the superscript '$+$' denotes the right limit at any point. We assume that initially, both compartments are empty of drugs

$$C_a(0) = C(0) = 0. \tag{5.5}$$

From (1) and (2), it follows that on each half open interval $((n-1)T, nT]$

$$C_a(t) = C_a\left((n-1)T^+\right) e^{K_a(-t+(n-1)T)}, \tag{5.6}$$

When an impulse is applied at $t = nT$, we have

$$C_a(nT^+) = C_a\left((n-1)T^+\right)e^{-K_aT} + J. \tag{5.7}$$

By letting $x_n = C_a(nT^+)$, we obtain the difference equation

$$x_n = x_{n-1}e^{-K_aT} + J. \tag{5.8}$$

This difference equation has a fixed point, denoted by x^*, which satisfies the equation

$$x^* = x^*e^{-K_aT} + J := q(x^*), \tag{5.9}$$

from which we readily find that

$$x^* = \frac{J}{1 - e^{-K_aT}}. \tag{5.10}$$

Let $y_n = x_n - \frac{J}{(1 - e^{K_aT})}$ for $n = 0, 1, 2, \cdots$. By equation (5.8), we find that $y_n's$ form a geometric sequence

$$y_{n+1} = e^{-K_aT}y_n, \tag{5.11}$$

from which by substitution, we find that x_n can be solved to give

$$x_n = J\sum_{j=0}^{n}\left(e^{-K_aT}\right)^j. \tag{5.12}$$

Let

$$C_n = C(nT), \tag{5.13}$$

for all nonnegative n. Notice that although $C_a(t)$ has jumps at discrete times, $C(t)$ is continuous everywhere, with jumps in its first-order derivative. Upon substituting (5.12) into (5.3), we obtain a map $C_n \mapsto C_{n+1}$

$$\begin{cases} \dfrac{dC}{dt} := G(t, C) = Bx_nK_ae^{-K_at} - f, & (5.14) \\ C(0) = C_n, & (5.15) \\ C(T) = C_{n+1} = C_n + \displaystyle\int_0^T G\left(s, C(s)\right)ds, & (5.16) \end{cases}$$

where we have transformed the interval $[nT, (n+1)T]$ to the interval $[0, T]$ for simplicity, for every nonnegative integer n. A plot for C_a and C as functions of time is plotted in Figure 5.1.

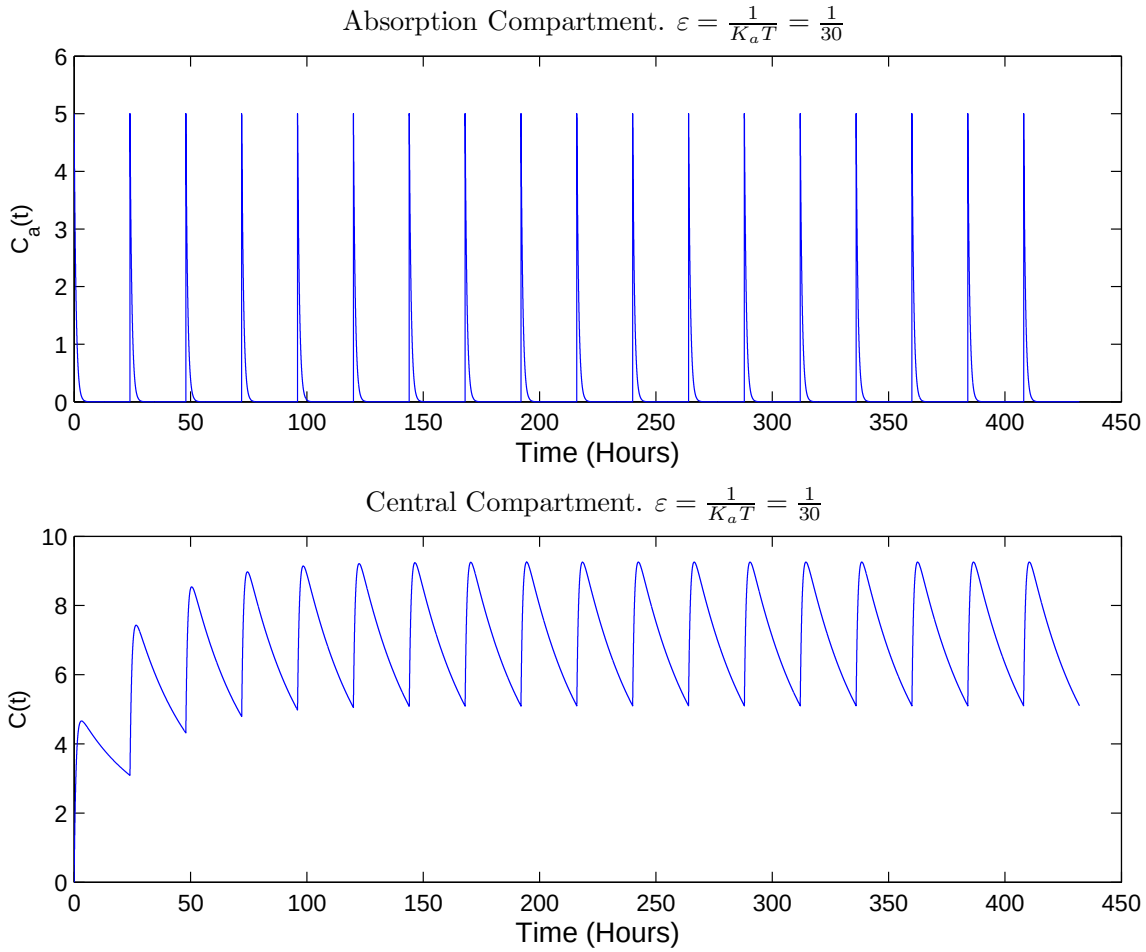


Figure 5.1. The numerical solution of the system (5.1) $\sim$ (5.5). The top panel shows the time course of the concentration of the absorption compartment, whereas the bottom figure shows the time course of the concentration of the central compartment. Upon the injection of a new dose, $C(t)$ has a rapid increase in its value, suggesting an initial (boundary) layer when $K_a T \gg 1$. In this plot, constants are: $B = 1$, $K_a = 1.25$, $T = 24$.

In general, an analytical solution of (5.14) cannot be found. The use of perturbation methods is motivated by the evidence mentioned in the literature [5] that the absorption rate constant K_a, more often than not, is significantly greater than the elimination rate, and by the fact that when K_a is large enough, the term $K_a e^{-K_a t}$ in (5.14) in fact suggests that there is an initial (boundary) layer at the left end-point [8] (Figure 5.1). Inspired by these observations, we let

$$H_n = Bx_n, \tag{5.17}$$

and the differential equation (5.3) can be written in nondimensional units as

$$\frac{dC}{dt'} = \frac{H_n}{\epsilon} e^{-\frac{1}{\epsilon}t'} - Tf, \;\; t' \in [0,1], \tag{5.18}$$

where the time variable t is nondimensionalized to $t' = t/T$ and $\epsilon = 1/(K_a T)$. Further suppressing the 'primed' for the variable t, we obtain the governing differential equation

$$\frac{dC}{dt} = \frac{H_n}{\epsilon} e^{-\frac{1}{\epsilon}t} - Tf \;, \; t \in [0,1]. \tag{5.19}$$

Let the outer solution of (5.19) be $Y(t)$, and the inner solution of (5.19) be $X(t/\epsilon)$ in the boundary layer time variable $\tau := t/\epsilon$. We now seek a power series expansion in the dimensionless variable $\epsilon = \frac{1}{K_a T}$ for the following quantities using Singular perturbation techniques

$$\begin{cases} \text{Outer Solution} : Y(t) = \sum_{j=0}^{+\infty} \epsilon^j Y_j(t) = Y_0(t) + \epsilon Y_1(t) + ..., & (5.20) \\ \text{Inner Solution} : X(t/\epsilon) = \sum_{k=0}^{+\infty} \epsilon^k X_k(t/\epsilon) = X_0(t/\epsilon) + \epsilon X_1(t/\epsilon) + ..., & (5.21) \\ \text{Left Boundary Value} : C(0) = C_n = X(0), & (5.22) \\ \text{Right Boundary Value} : C(1) = C_{n+1} = Y(1). & \\ & (5.23) \end{cases}$$

And then by matching the inner solution $X(t/\epsilon)$ to the outer solution $Y(t)$, we obtain the map $C_n \mapsto C_{n+1}$. Thus, the initial condition for each dosage interval can be determined analytically and asymptotically and therefore, the composite expansion can be constructed along the full time course of the treatment.

5.3 More General Settings

In the above discussion, we have assumed that the transfer rate from the absorption compartment to the central compartment is of first order. However, the analysis can be extended to cases where transfer rates are of nonlinear kinetics as well, to include a broader class of functions. We now make assumptions about the transfer rate g.

(A) The transfer rate g depends only on the local concentration of the absorption compartment, that is, $g = g(C_a)$;

(B) The function $g = g(C_a)$ is at least C^1 smooth, and has the property that $g(0) = 0$ and $g'(0) > 0$. The condition $g(0) = 0$ implies that there is no transfer from the absorption compartment to the central compartment if there is no drug in the absorption compartment.

(C) The transfer rate $g(C_a)$ increases monotonically as C_a increases.

Under these assumptions, the system of equations we study is

$$\begin{cases} \dfrac{dC_a}{dt} = -g(C_a), & (5.24) \\ \dfrac{dC}{dt} = Bg(C_a) - f, & (5.25) \end{cases}$$

under the jump condition

$$C_a(nT^+) - C_a(nT) = J. \tag{5.26}$$

The initial conditions are taken to be $C_a(0) = C(0) = 0$. By rescaling the time variable t through $t := t/T$, letting $h(C_a) = g(C_a)/g'(0)$ and $\epsilon = 1/(g'(0)T)$, the system of equations can be rewritten in nondimensional units as

$$\begin{cases} dC_a/dt = -g(C_a) := -\dfrac{1}{\epsilon}h(C_a), & (5.27) \\ dC/dt = Bg(C_a) - f := B\left(\dfrac{1}{\epsilon}h(C_a)\right) - f, & (5.28) \end{cases}$$

subject to the impulse condition:

$$C_a(nT^+) - C_a(nT) = J, \tag{5.29}$$

where the elimination rate f is redefined by $f := Tf$. Let x_n denote the sequence $x_n := C_a(nT^+)$. Solving equation (5.27) over the time interval $[0, 1]$, we have

$$\int_{x_n}^{C_a((n+1)T)} \frac{ds}{h(s)} = \int_0^1 -\frac{1}{\epsilon}dt. \tag{5.30}$$

Since $x_{n+1} = J + C_a((n+1)T)$, we end up with a map $x_n \mapsto x_{n+1}$ that is defined implicitly through an integral

$$\int_{x_{n+1}-J}^{x_n} \frac{ds}{h(s)} = \frac{1}{\epsilon}. \tag{5.31}$$

We define a function $\tilde{H}(x)$

$$\tilde{H}(x) = \int_{x-J}^{x} \frac{ds}{h(s)}. \tag{5.32}$$

Since the function $h(x) = g(x)/g'(0)$ is C^1 and $h(0) = 0$, it follows that

$$\tilde{H}(J) = \int_0^J \frac{ds}{h(s)} = +\infty. \tag{5.33}$$

At the same time, by the monotonicity of $h(x)$, it follows that

$$\tilde{H}'(x) = \frac{1}{h(x)} - \frac{1}{h(x-J)} < 0. \tag{5.34}$$

Furthermore, since $h(x) > 0$ over $[J, +\infty)$, it follows immediately that (5.31) has a unique fixed point $x^* > J$ if and only if $H_\infty < \frac{1}{\epsilon}$, where

$$H_\infty = \lim_{x \to +\infty} \tilde{H}(x). \tag{5.35}$$

To show that this fixed point is stable, we consider both the map (5.31) and the equation the fixed point x^* satisfies

$$\int_{x^*-J}^{x^*} \frac{ds}{h(s)} = \frac{1}{\epsilon}. \tag{5.36}$$

Suppose $x_n < x^*$. We now show that $x_{n+1} < x^*$ as well. From (5.31) and (5.36), we conclude that

$$\int_{x_{n+1}-J}^{x_n} \frac{ds}{h(s)} - \int_{x^*-J}^{x^*} \frac{ds}{h(s)} = 0, \tag{5.37}$$

so that

$$\int_{x_{n+1}-J}^{x^*-J} \frac{ds}{h(s)} + \int_{x^*}^{x_n} \frac{ds}{h(s)} = 0. \tag{5.38}$$

Since $h(s) > 0$, it is immediate that the integral $\int_{x_{n+1}-J}^{x^*-J} \frac{ds}{h(s)}$ and $\int_{x^*}^{x_n} \frac{ds}{h(s)}$ are of opposite sign, so that $x_{n+1} - x^*$ and $x^* - x_n$ are of opposite sign, i.e., $x_{n+1} - x^*$ and $x_n - x^*$ have the same sign. We thus conclude that if $x_n < x^*$, then $x_{n+1} < x^*$ for all nonnegative n, which implies that the sequence x_n is bounded above, if the initial value of the sequence is chosen

to be to the left of the fixed point x^*. Furthermore, since the function $\tilde{H}(x)$ decreases, it follows that

$$\tilde{H}(x) = \int_{x_n - J}^{x_n} \frac{ds}{h(s)} > \tilde{H}(x^*) = \frac{1}{\epsilon} = \int_{x_{n+1} - J}^{x_n} \frac{1}{h(s)} ds, \tag{5.39}$$

it follows from this inequality that $x_n - J < x_{n+1} - J$ since the function $1/h(s)$ is positive for $s > 0$. Therefore, we conclude that $x_{n+1} > x_n$, if $x_n < x^*$. Thus, we learn that the sequence defined iteratively by (5.31) $x_n \mapsto x_{n+1} \mapsto x_{n+2} \cdots$ increases monotonically and is bounded above. Hence, this sequence converges and it actually converges to x^* by its uniqueness. Similarly, if x_n is chosen such that $x_n > x^*$, then we end up having a monotonically decreasing sequence that tends toward x^* as well. Hence, the sequence $\{x_n\}_{n \in \mathbb{N}}$ converges. We conclude our results in **Theorem 5.1**.

Theorem 5.1. Consider the differential equation

$$\frac{dC_a}{dt} = -g(C_a), \tag{5.40}$$

under the repetitive impulse condition

$$C_a(nT^+) = C_a(nT) + J, \tag{5.41}$$

where $g(C_a)$ is a positive function that increases monotonically in C_a that satisfies $g(0) = 0$ and $g'(0) > 0$. Let $h(s) = g(s)/g'(0)$. Then the sequence $\{x_n\}_{n \in \mathbb{N}}$ defined by

$$x_n := C_a(nT^+), \tag{5.42}$$

converges to a positive and stable fixed point x^* if and only if

$$H_0 = \lim_{x \to +\infty} \tilde{H}(x) < \frac{1}{\epsilon}, \tag{5.43}$$

where $\tilde{H}(x) = \int_{x-J}^{x} \frac{ds}{h(s)}$ and $\epsilon = 1/g'(0)T$.

For instance, in the case when the elimination rate from the absorption compartment to the central compartment is taken to be of first order, that is, when $h(x) = x$,

$$\lim_{x \to +\infty} \tilde{H}(x) = \lim_{x \to +\infty} \ln\left(\frac{x}{x - J}\right) = 0 < \frac{1}{\epsilon}, \tag{5.44}$$

which is automatically satisfied. However, if the elimination rate is taken to be of M-M type, that is, if

$$\frac{dC_a}{dt} = -\frac{V_a C_a}{K_a + C_a}, \tag{5.45}$$

where V_a denotes the maximum rate at which drugs can be transported and K_a denotes the saturation constant, it is an easy matter to check that the condition $\lim_{x\to+\infty} \tilde{H}(x) < \frac{1}{\epsilon}$ is equivalent to the condition $J < V_a T$. The interpretation of this result is straightforward: for fixed V_a, one should avoid injecting drugs too frequently or keep the dose amount lower than a certain threshold, since the capability of removing drugs from the absorption compartment is not unlimited.

We now study the dynamics of the central compartment. Denote the antiderivative of $\frac{1}{h(t)}$ by $H(t) := \int_a^t \frac{1}{h(s)} ds$, where $a > 0$ is a constant. Solving equation (5.27) for any time $t \in [0, 1]$ yields

$$H(C_a(t)) = H(x_n) - \frac{1}{\epsilon} t. \tag{5.46}$$

Substituting (5.46) into (5.28), we obtain the governing equation for C,

$$\frac{dC}{dt} = \frac{B}{\epsilon} h\left(H^{-1}\left(H(x_n) - \frac{1}{\epsilon} t\right)\right) - f. \tag{5.47}$$

The first term in this equation may exhibit boundary layer behavior for ϵ small. For example, when $h(x) = x$, that is when the absorption rate is of first order, this equation reduces to

$$\frac{dC}{dt} = \frac{B x_n}{\epsilon} e^{-\frac{1}{\epsilon} t} - f, \tag{5.48}$$

where we see a term of the form $\frac{1}{\epsilon} e^{-\frac{1}{\epsilon} t}$, which is a reminder of a boundary layer. Equation (5.47) may be rewritten in the form

$$\frac{dC}{dt} = \frac{1}{\epsilon} S(x_n, \frac{1}{\epsilon} t) - f(C), \tag{5.49}$$

where

$$S(x_n, \frac{1}{\epsilon} t) := Bh\left(H^{-1}\left(H(x_n) - \frac{1}{\epsilon} t\right)\right). \tag{5.50}$$

In this equation, we assume that the elimination rate f from the central compartment is a function of only C, i.e., $f = f(C)$. To find the inner solution of this equation, rescale the time variable $\tau = t/\epsilon$, equation (5.49) becomes

$$\frac{dC}{d\tau} = S(x_n, \tau) - \epsilon f(C), \tag{5.51}$$

with initial condition $C(0) = C(nT) := C_n$. Suppose $C(\tau)$ has power series representation in powers of ϵ:

$$C(\tau) = \sum_{n=0}^{+\infty} \epsilon^n X_n(\tau) = X_0(\tau) + \epsilon X_1(\tau) + \cdots. \tag{5.52}$$

Following this assumption, we find the hierarchy of equations

$$\begin{cases} \dfrac{dX_0(\tau)}{d\tau} = S(x_n, \tau), & (5.53) \\ \dfrac{dX_1(\tau)}{d\tau} = -f\left(X_0(\tau)\right), & (5.54) \\ \dfrac{dX_2(\tau))}{d\tau} = X_1(\tau) f'\left(X_0(\tau)\right), & (5.55) \end{cases}$$

and so on, subject to the initial conditions

$$\begin{cases} X_0(0) = C_n, & (5.56) \\ X_j(0) = 0, & (5.57) \end{cases}$$

for all $j \geq 1$. The solutions are

$$X_0(\tau) = C_n + \int_0^\tau S(x_n, u) du, \tag{5.58}$$

and

$$X_1(\tau) = -\int_0^\tau f\left(C_n + \int_0^\eta S\left(x_n, u\right) du\right) d\eta, \tag{5.59}$$

and so on. Now suppose we also have an expansion for the outer solution of the form

$$Y(t) = Y_0(t) + \epsilon Y_1(t) + \cdots. \tag{5.60}$$

The Kaplun Matching principle ([8,11]) requires

$$0 = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \left(Y_0(\epsilon^{1/2}\eta) + \epsilon Y_1(\epsilon^{1/2}\eta) - X_0(\frac{\eta}{\epsilon^{1/2}}) - \epsilon X_1(\frac{\eta}{\epsilon^{1/2}}) \right). \tag{5.61}$$

Hence, for zeroth order matching, we set

$$Y_0(0) = X_0(+\infty), \tag{5.62}$$

that is,

$$Y_0(0) = C_n + S_0(n), \tag{5.63}$$

where $S_0(n)$ is defined by

$$S_0(n) = \int_0^{+\infty} S(x_n, u) du, \tag{5.64}$$

which we assume to be finite. This assumption is true for the case when the transfer rate is of first order or $M - M$ type. Since the outer solution is $Y(t, \epsilon)$, the quantity we seek is $Y(1)$. If the zeroth order approximation of the outer solution $Y = Y_0$ is used, we obtain

$$F(Y(1)) - F(Y(0)) = -1, \tag{5.65}$$

where

$$F(Y) := \int \frac{dY}{f(Y)}. \tag{5.66}$$

Since $Y(1) = C_{n+1} = C((n+1)T)$ and $Y(0) = C_n + S_0(n)$, as a result, we obtain a map $m : C_{n+1} = m(C_n)$ that is defined through an integral

$$\int_{C_{n+1}}^{C_n+S_0(n)} \frac{1}{f(y)} dy = 1, \tag{5.67}$$

which defines C_{n+1} implicitly as a function of C_n: $C_{n+1} = m(C_n)$. We establish our next theorem, which can be proved in the same manner as has been done for Theorem 5.1.

Theorem 5.2. Let a sequence $\{C_n\}$ be defined implicitly through

$$\int_{C_{n+1}}^{S_0(n)+C_n} \frac{dx}{f(x)} = 1. \tag{5.68}$$

Suppose the function $f(x)$ defined on $[0, +\infty)$ satisfies the following conditions:

(a) $f(0) = 0$,

(b) $f'(x) > 0$ for all $x > 0$,

(c) $\int_0^{S_0} \frac{1}{f(y)} dy > 1$, where $S_0 = \lim_{n\to+\infty} S_0(n)$ and $S_0(n)$ is defined by (5.64).

Then there is a unique positive stable fix point of the map m if and only if

$$S_0 < M, \tag{5.69}$$

where

$$M = \lim_{x\to+\infty} f(x) \leq +\infty. \tag{5.70}$$

Assumptions (a) $\sim$ (c) can be interpreted as follows. Condition (a) makes the equation physiologically realistic, since the elimination should be zero when there is no substrate around. Condition (b) says that the elimination rate is an increasing function of the concentration of the existing substrate. Condition (c) states that the amount of time for the drug concentration to drop from S_0 to 0 cannot be too small. Note that condition (a) does not necessarily indicate that the integral in condition (c) is not integrable. For example, $f(x) = x^{1/2}$ satisfies condition (a) but is integrable over $[0, S_0]$. Then, the theorem says that there exists a unique positive stable fixed point of the map if and only if the saturation

level M is above the fixed constant S_0. Notice that $S_0 < M$ is automatically satisfied if $M = +\infty$, which is satisfied, for example, by the function $f(x) = x$.

Proof of Theorem 5.2. Very similar to the proof of Theorem 1, we can show first that a unique positive fixed point $C^*$of the map m exists if and only if $S_0/M < 1$, which satisfies, by its definition, the equation

$$\int_{C^*}^{S_0+C^*} \frac{dx}{f(x)} = 1. \tag{5.71}$$

The stability of this fixed point can be proved by letting $\epsilon = 1$ on the right-hand side of (5.36) and then replacing $h(s)$ with $f(s)$ in the denominator of the integrand. The final step is to replace the previous fixed point x^* with the current fixed point C^* and J with S_0, and then shift the interval over which the integrand is integrated to the right by S_0 and the proof is done.

5.4 Composite Expansion

The leading order inner solution is (5.58). The leading order outer solution Y_0 satisfies

$$\frac{dY_0}{dt} = -f(Y_0), \tag{5.72}$$

subject to the boundary condition (5.63). The solution is

$$Y_0(t) = F^{-1}(F(C_n + S_0(n)) - t). \tag{5.73}$$

Once both inner and outer solutions are found, the composite expansion is the sum of these two solutions, less what they have in common, which in this case is C_n. Specifically, the composite expansion on the interval $[nT, (n+1)T]$ takes the following form

$$\begin{aligned} C(t) &\sim \left(C_n + \int_0^{\tau} S(x_n, u)du\right) + F^{-1}\left(F\left(C_n + S_0(n)\right) - t\right) - \left(S_0(n) + C_n\right) \\ &= -\int_{t/\epsilon}^{+\infty} S(x_n, u)du + F^{-1}\left(F\left(C_n + S_0(n)\right) - t\right), \end{aligned} \tag{5.74}$$

where $F = \int \frac{dy}{f(y)}$. Note that in this expression, the sequence x_n ,$S_0(n)$, and C_n are known as long as the elimination rates g and f are known. These sequences are defined through (5.31), (5.64), and (5.67), respectively. Thus, the leading order composite expansion can be fully constructed for any time interval once elimination rates are known.

5.5 Calculation of Biomarkers Using Composite Expansion

Biomarkers are quantities that serve as important indicators of how drug concentration behaves in the human body. With the composite expansion (5.74), we calculate three typical biomarkers, denoted by TB1,TB2, and TB3, which are defined as:

(1) TB1: $t_{max}(n)$, the time at which plasma concentration reaches its peak on the time interval $[nT, (n+1)T]$.

(2) TB2: $C_{max}(n)$, the peak plasma concentration on the time interval $[nT, (n+1)T]$;

(3) TB3: $C_{ave}(n)$, the average plasma concentration over one dosage time interval $[nT, (n+1)T]$.

We begin by calculating TB1 and TB2. By differentiating (5.74) with respect to the time variable t, we obtain

$$C'(t) = \frac{1}{\epsilon} S(x_n, \frac{t}{\epsilon}) - f\left(F^{-1}\left(F(C_n + S_0(n))\right) - t\right). \tag{5.75}$$

This is true, since the second term in equation (5.74) comes from the outer solution, which satisfies the ordinary differential equation

$$\frac{dC}{dt} = -f(C), \tag{5.76}$$

and $C = F^{-1}\left(F\left(C_n + S_0(n)\right) - t\right)$ on $[0, 1]$. To compute the time at which peak plasma concentration occurs, note that since we expect this peak to occur quickly after a new dose is administered, that is, we expect that t_{max} to be small, to the leading order approximation, we perform Taylor series expansion on the second term in (5.75) and then only take the leading order term from that expansion and finally set $C'(t) = 0$ to find

$$t_{max}(n) = \epsilon S^{-1}\Big(x_n, \epsilon f\left(C_n + S_0(n)\right)\Big), \tag{5.77}$$

where S^{-1} denotes the inverse function with respect to the second variable in $S = S(x_n, \frac{t}{\epsilon})$ as defined in (5.49). Substituting (5.77) into (5.74), we find that

$$\begin{aligned} C_{max}(n) = &- \int_{S^{-1}\left(x_n, \epsilon f(C_n + S_0(n))\right)}^{+\infty} S(x_n, u)du + \\ &F^{-1}\left(F\Big(C_n + S_0(n)\Big) - \epsilon S^{-1}\Big(x_n, \epsilon f\big(C_n + S_0(n)\big)\Big)\right). \end{aligned} \tag{5.78}$$

It is apparent that since $S = S(x_n, t/\epsilon)$ is a decreasing function of its second variable, S^{-1} increases as ϵ tends to 0 so that the first term in (5.78) increases monotonically as $\epsilon \to 0$. Upon assuming that

$$\epsilon S^{-1}\Big(x_n, \epsilon f\big(C_n + S_0(n)\big)\big)\Big), \tag{5.79}$$

decreases monotonically to 0 for small ϵ as $\epsilon \to 0$, we learn that for small ϵ uniformly, an upper bound for C_{max} would be

$$\begin{aligned} C^b_{max}(n) &= -\int_{S^{-1}(x_n,0)}^{+\infty} S(x_n, u)du + \big(C_n + S_0(n)\big) \\ &= \int_0^{S^{-1}(x_n,0)} S(x_n, u)du + C_n. \end{aligned} \tag{5.80}$$

The assumption that (5.79) decreases to 0 as $\epsilon \to 0$ is valid at least for the most frequently assumed scenario where the transfer rate from the absorption rate to the central compartment is of first order, in which case, we find that (see equation(5.48))

$$S(x_n, t/\epsilon) = Bx_n e^{-\frac{t}{\epsilon}}, \tag{5.81}$$

which indicates that

$$\epsilon S^{-1}\Big(x_n, \epsilon f\big(C_n + S_0(n)\big)\big)\Big) = -\epsilon \ln\Big(\frac{\epsilon f}{Bx_n}\Big). \tag{5.82}$$

It is an easy matter to check that in this case, the function $-\epsilon \ln(\frac{\epsilon f}{Bx_n})$ has a local maximum at $\epsilon_s = \frac{e^{-1}}{f/Bx_n}$, where f is short for $f = f(c_n + S_0(n))$. This implies that below e_s,

$$\epsilon S^{-1}\Big(x_n, \epsilon f\big(C_n + S_0(n)\big)\big)\Big) \to 0, \tag{5.83}$$

as $\epsilon \to 0$. We hence conclude that once assumption (5.79) is satisfied, then (5.80) provides an exact upper limit for $C_{max}(n)$ for uniformly small ϵ, for each integer n. Furthermore, a uniform upper limit for all time step n can be derived by letting $n \to +\infty$ in (5.80). In other words, We find that $C^b_{max}(n)$ goes monotonically to C^b_{max}, defined by

$$C^b_{max} = \int_0^{S^{-1}(x^*,0)} S(x^*, u)du + C^*, \tag{5.84}$$

since $x_n \to x^*$ and $C_n \to C^*$ monotonically at the same time if initial condition is taken to be $x_0 = C_0 = 0$, where x^* and C^* are steady state drug concentration in the absorption and central compartment, respectively, that satisfy equation (5.36) and (5.71), respectively.

The quantity C^b_{max} is the exact upper limit of the drug concentration over the whole course of treatment. Thus, this value provides significant insights on how the dosage amount J should be controlled to prevent the individual from being overdosed. By this, we mean that if C^b_{max} is less than the minimum concentration above which the drug becomes toxic, then during the entire time of treatment, the individual is free of being overdosed. Notice the J dependence is included in the term x_n or x^*, namely, C^b_{max} depends on J through x_n or x^*.

We next calculate TB3, the average drug concentration over one dosage interval, which is defined mathematically as

$$C_{ave}(n) = \frac{\int_0^T C dt}{T}, \tag{5.85}$$

in terms of original variables. Thus, we have, by substituting (5.74) into (5.85)

$$\begin{aligned} C_{ave}(n) &= -\int_0^1 \left(\int_\tau^{+\infty} S(x_n, u)du + F^{-1}\left(F\left(C_n + S_0(n)\right) - t\right) \right) dt \\ &= -\int_0^1 \int_{t/\epsilon}^{+\infty} S(x_n, u)dudt + \int_0^1 F^{-1}\Big(F(C_n + S_0(n)) - t\Big)dt. \end{aligned} \tag{5.86}$$

By letting $u = F^{-1}\Big(F(C_n + S_0(n)) - t\Big)$, we have (5.86) to become

$$\begin{aligned} C_{ave}(n) &= \left(\int_0^{+\infty} \Big[\int_0^1 S(x_n, u)dt \Big] du - \int_0^{1/\epsilon} \Big[\int_{\epsilon u}^1 S(x_n, u)dt \Big] du \right) - \int_{A(n)}^{B(n)} u dF(u) \\ &= \left(\int_{1/\epsilon}^{+\infty} S(x_n, u)du + \epsilon \int_0^{1/\epsilon} S(x_n, u)udu \right) - \left(uF(u)\Big|_{A(n)}^{B(n)} - \int_{A_n}^{B_n} F(u)du \right), \end{aligned} \tag{5.87}$$

where $A(n) = C_n + S_0(n)$ and $B(n) = F^{-1}(F(A(n)) - 1) = C_{n+1}$ to leading order approximation. Thus, as long as we know the elimination rates g and f, $C_{ave}(n)$ can be fully determined, since the function S depends on g and F depends on f through (5.50) and (5.66), respectively.

5.6 Examples

5.6.1 Case I

As a practical example, we first study the case where the transfer rate g between compartments is of first order, whereas the rate at which drug is removed from the central

compartment is of Hill function type ([10]), which is a generalized $M-M$ type elimination, with cooperativity between enzymes being included. The Hill coefficient is denoted by m, where it could be any positive integer. The system of equations to consider thus has the representation

$$\begin{cases} \dfrac{dC_a}{dt} = -K_a C_a, & (5.88) \\ \dfrac{dC}{dt} = BK_a C_a - \dfrac{V_{max} C^m}{K_m + C^m}, & (5.89) \end{cases}$$

subject to the impulse condition

$$C_a(nT^+) - C_a(nT) = J, \tag{5.90}$$

at nT for $n = 0, 1, 2 \cdots$, where K_a denotes the absorption rate constant, B denotes the ratio of volumes of the absorption compartment to the central compartment, V_{max} denotes the maximum rate at which drug is removed from the central compartment, and K denotes the saturation constant. It can be readily seen from the nonlinearity of the Hill function that a closed form analytic solution is unobtainable, which lets us seek an asymptotic result as an alternative. We take the dimensionless variable $\epsilon := 1/(K_a T)$ as the small parameter in this case. By applying the same techniques we have performed in the previous text, we find that

$$x_n := C_a(nT^+) = J \sum_{j=0}^{n} \left(e^{-K_a T} \right)^j = J \sum_{j=0}^{n} \left(e^{-\frac{1}{\epsilon}} \right)^j, \tag{5.91}$$

and to the leading order approximation we have

$$C_{n+1} = W_m^{-1} \left(-V_m + W_m(S_0(n) + C_n) \right), \tag{5.92}$$

where $C_n := C(nT)$, $V_m := V_{max} T$, $S_0(n) = \displaystyle\int_0^{+\infty} S(x_n, u) du = Bx_n$, and $W_m(x)$ is defined as the antiderivative of the reciprocal of the Hill function

$$W_m(u) := \int \left(\frac{K_m + u^m}{u^m} \right) du. \tag{5.93}$$

The function W_m^{-1} in (5.92), defined as the algebraic inverse of W_m, can be solved symbolically and analytically for $m = 1$ and $m = 2$, respectively, and they are

$$W_m^{-1}(x) = \begin{cases} K_m \cdot \text{LambertW}\left(\dfrac{1}{K_m} e^{x/K_m} \right), & m = 1 \quad (5.94) \\ \dfrac{x + \sqrt{x^2 + 4K_m}}{2}, & m = 2 \quad (5.95) \end{cases}$$

where the 'LambertW' function is defined implicitly as the solution $y = y(x)$ through the relationship

$$y(x)\exp(y(x)) = x, \tag{5.96}$$

for $x \geq 0$. The LambertW function is a well-defined function on $[0, +\infty)$, whose applications, asymptotic behaviors, and other important features are summarized in [2].

Condition (5.69) for the model (5.88)∼(5.90), in terms of original variables, reads

$$BJ < \frac{V_{max}T}{1 - e^{-\frac{1}{\epsilon}}}. \tag{5.97}$$

The leading order composite expansion can be constructed as

$$C(t) \sim -Bx_n e^{-\frac{t}{\epsilon}} + W_m^{-1}\left(-V_m t + W_m(Bx_n + C_n)\right), \tag{5.98}$$

for $t \in [0, 1]$. We show numerical results for the drug concentration in the central compartment in Figure 5.2. The blue curves in each figure are numerical solutions of the system implemented by the standard Runge-Kutta method; Red and green curves are leading and second-order composite expansions, respectively. The initial fast increase in concentration (boundary layer) on each interval can be clearly seen from the picture, which is well approximated by composite expansions formed by the combination of outer and inner solutions.

We now compute biomarkers for Case I. We use formula (5.77) and (5.78) to calculate $t_{max}(n)$ and $c_{max}(n)$, respectively. The function S^{-1} in this case is found to be

$$S^{-1}(x_n, \frac{1}{\epsilon}t) = \ln\Big(\frac{Bx_n}{\frac{1}{\epsilon}t}\Big). \tag{5.99}$$

Thus, $t_{max}(n)$ can be found to give

$$t_{max}(n) = \epsilon \ln\Big(\frac{Bx_n}{\epsilon f(C_n + Bx_n)}\Big), \tag{5.100}$$

where $f(y) = \frac{V_{max}Ty^m}{K_m + y^m}$. Substituting (5.100) into (5.98), we find $C_{max}(n)$ to equal

$$C_{max}(n) = -\epsilon f(C_n + Bx_n) + W_m^{-1}\Big(V_m \epsilon \ln\Big(\frac{\epsilon f(C_n + Bx_n)}{Bx_n}\Big) + W_m(Bx_n + C_n)\Big). \tag{5.101}$$

We show in Appendix A an error estimate of C_{max} calculated using (5.101) relative to C_{max} found by solving the system (5.88)∼(5.90) numerically with the Runge-Kutta method.

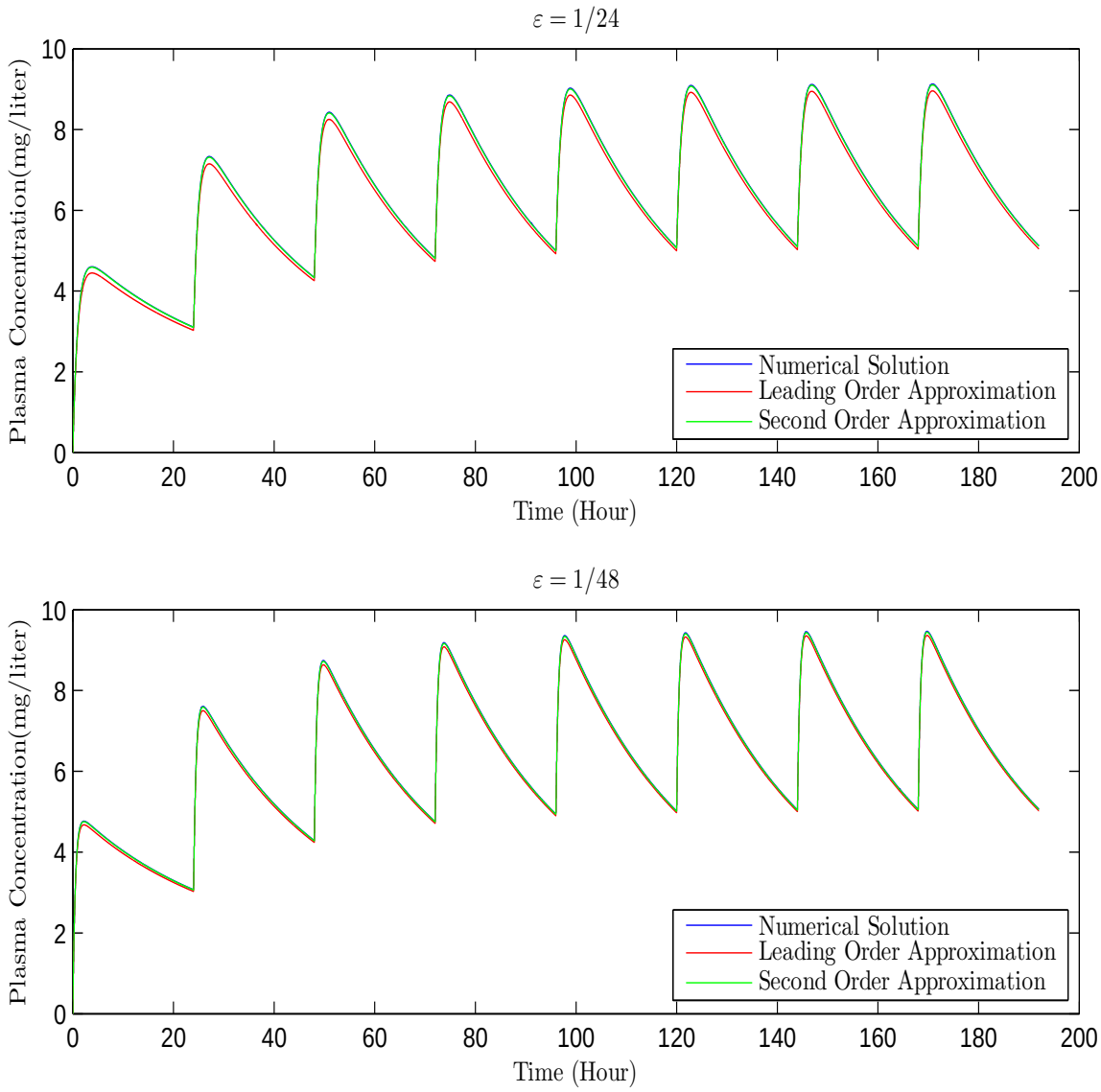


Figure 5.2. Composite expansions are plotted in this figure. We take the Hill coefficient $m = 2$ for both panels. For the absorption rate K_a, we take $K_a = 1$ for the top panel and $K_a = 2$ for the bottom panel. The numerical values for other parameters are: $V_{max} = 0.625$, $K_m = 100$, $B = 1$, $T = 24$, $J = \frac{D}{V} = 5$.

For $C_{ave}(n)$, formula (5.87) is used to produce the result, which yields

$$C_{ave}(n) = \epsilon B x_n \left(e^{-1/\epsilon} - 1\right) - \frac{1}{V_m} \int_{C_n + Bx_n}^{C_{n+1}} u dW_m(u). \tag{5.102}$$

The integral term $\int_{C_n+Bx_n}^{C_{n+1}} u dW_m(u)$ can be evaluated exactly once m is known. For example, when the Hill coefficient m is 1 or 2, this integral term is found to be

$$\int_{C_n+Bx_n}^{C_{n+1}} u dW_m(u) = \begin{cases} \left(\frac{1}{2}u^2 + K_m u\right)\Big|_{C_{n+1}}^{C_n+Bx_n}, & m = 1 \quad (5.103) \\ \left(\frac{1}{2}u^2 + K_m\left(\ln u - 1\right)\right)\Big|_{C_n+Bx_n}^{C_{n+1}}, & m = 2 \quad (5.104) \end{cases}$$

where evaluation is with respect to the variable u.

5.6.2 Case II

Consider a scenario where the transfer rate between compartments has an M-M type dynamic. Specifically, the system of equations is the following

$$\begin{cases} \frac{dC_a}{dt} = -\frac{V_1 C_a}{K_1 + C_a}, & (5.105) \\ \frac{dC}{dt} = B\frac{V_1 C_a}{K_1 + C_a} - \frac{V_2 C}{K_2 + C}, & (5.106) \end{cases}$$

subject to the impulse condition

$$C_a(nT^+) - C_a(nT) = J. \tag{5.107}$$

We use previous notation to let $x_n = C_a(nT^+)$. The variable we regard as the small variable in this case is the dimensionless quantity $\epsilon = \frac{K_1}{V_1 T}$. By rescaling the time variable $t := t/T$, we obtain the following set of equations for $t \in [0, 1]$

$$\begin{cases} \frac{dC_a}{dt} = -\frac{1}{\epsilon}\frac{C_a}{1 + \left(\frac{C_a}{K_1}\right)}, & (5.108) \\ \frac{dC}{dt} = \frac{B}{\epsilon}\frac{C_a}{1 + \left(\frac{C_a}{K_1}\right)} - \frac{V_2 T C}{K_2 + C}. & (5.109) \end{cases}$$

The differential equation (5.108) subject to the impulse condition (5.107) can be solved to give

$$C_a = K_1 \mathrm{LW}\left(\frac{Z_n^+}{K_1} e^{\frac{Z_n^+}{K_1}} e^{-\frac{1}{\epsilon}t}\right), \tag{5.110}$$

where $Z_n^+ := C_a(nT^+)$ satisfies the equation

$$Z_{n+1}^+ = K_1 \mathrm{LW}\left(e^{-\frac{1}{\epsilon}} \frac{Z_n^+}{K_1} e^{\frac{Z_n^+}{K_1}}\right) + J, \tag{5.111}$$

where LambertW abbreviates to LW. The map (5.111) admits a unique fixed point $Z^* = \frac{Je^{-\frac{J}{K_1}}}{e^{-\frac{J}{K_1}}-e^{-\frac{1}{\epsilon}}}$, which is positive if and only if $J < V_1T$. Substituting (5.110) back into equation (5.109), we obtain

$$\frac{dC}{dt} = \frac{BK_1}{\epsilon}\frac{LW\left(\frac{Z_n^+}{K_1}e^{\frac{Z_n^+}{K_1}}e^{-\frac{1}{\epsilon}t}\right)}{1+LW\left(\frac{Z_n^+}{K_1}e^{\frac{Z_n^+}{K_1}}e^{-\frac{1}{\epsilon}t}\right)} - \frac{V_2TC}{K_2+C}. \tag{5.112}$$

Let $b_n := \frac{Z_n^+}{K_1}e^{\frac{Z_n^+}{K_1}}$. To search for the inner layer solution, we need to solve

$$\frac{dX_0}{d\tau} = BK_1\frac{LW\left(b_ne^{-\tau}\right)}{1+LW\left(b_ne^{-\tau}\right)}, \tag{5.113}$$

subject to the initial condition

$$X_0(0) = C_n, \tag{5.114}$$

where $\tau := t/\epsilon$. Upon integrating equation (5.113), we obtain the following relationship

$$X_0(\tau) = C_n - BK_1\left(LW\left(b_ne^{-\tau}\right) - \frac{Z_n^+}{K_1}\right), \tag{5.115}$$

which is true since

$$\frac{dLW(x)}{dx} = \frac{LW(x)}{x\left(1+LW(x)\right)}. \tag{5.116}$$

The leading order outer solution Y_0 is the solution of

$$\frac{dY_0}{dt} = -\frac{V_2TY_0}{K_2+Y_0}, \tag{5.117}$$

subject to the initial condition

$$Y_0(0) = X_0(+\infty) = C_n + BZ_n^+. \tag{5.118}$$

Thus, to the leading order approximation, we obtain

$$C_{n+1} = K_2LW\left(\frac{C_n+BZ_n^+}{K_2}e^{\frac{C_n+BZ_n^+}{K_2}}e^{-\frac{V_2T}{K_2}}\right), \tag{5.119}$$

where Z_n^+ satisfies the map (5.111). The map (5.119) admits a unique fixed point C^*:

$$C^* = \frac{BZ^*e^{\frac{BZ^*-V_2T}{K_2}}}{1-e^{\frac{BZ^*-V_2T}{K_2}}}, \tag{5.120}$$

where Z^* is the fixed point of the map (5.111). For this fixed point C^* to be positive, we need that

$$B\left(\frac{Je^{-\frac{J}{K_1}}}{e^{-\frac{J}{K_1}}-e^{-\frac{1}{\epsilon}}}\right) - V_2T \approx BJ - V_2T < 0, \tag{5.121}$$

where we have used the fact that $e^{-\frac{1}{\epsilon}}$ is transcendentally small. Figure 5.3 shows the composite expansion.

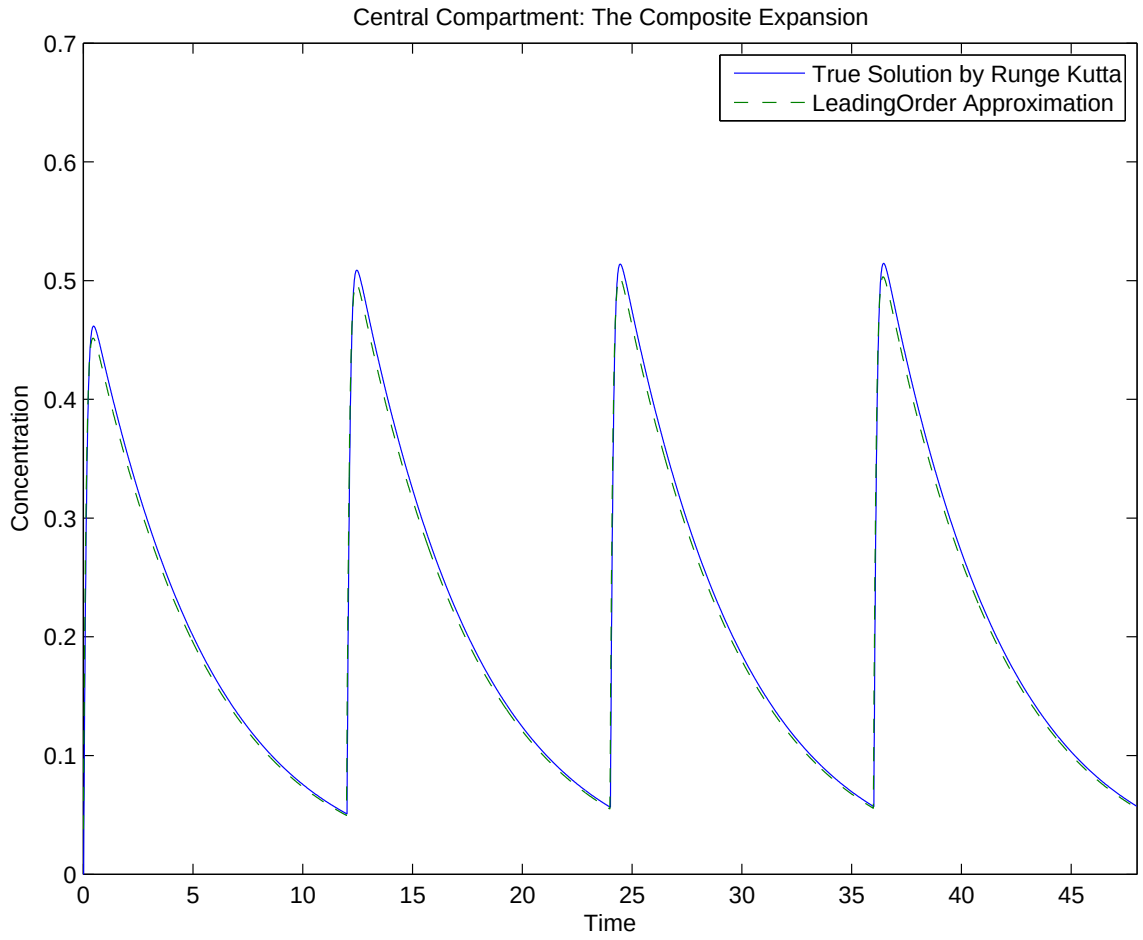


Figure 5.3. In this figure, parameter values are: $k_1 = 1$, $T = 12$, $v_1 = 10$, $J = 0.5$, $B = 1$, $v_2 = 1$, $k_2 = 5$. Therefore, $\epsilon = k_1/(v_1 T) = 1/120$.

5.7 Discussion and Conclusions

In this paper, we have used singular perturbation arguments to study the dynamics of a one-compartment model with periodic extravascular drug administrations. The use of these methods allows us to consider nonlinear elimination dynamics, such as Michaelis Menten or Hill type kinetics, to construct analytical solutions with which biomarkers can be estimated, and to determine parameter ranges for which stable periodic solutions exist. These composite solutions agree fairly well with the numerically computed solutions, indirectly verifying the validity of these analytical solutions.

We point out that the definition of ϵ might not be unique for many such models. For instance, for model (87)$\sim$ (89), one could instead choose the small quantity ϵ to be

$$\epsilon = \frac{V_{max}}{K_a K^{1/m}}, \tag{5.122}$$

which is a well-defined dimensionless variable that directly measures the ratio of the rate of elimination from the central compartment to that of the absorption compartment and is assumed to be small. However, we made our choice of ϵ in favor of $\epsilon = 1/(K_a T)$ since the combination $K_a T$ frequently appears and the nondimensionalization of the system is easier to obtain than if $\epsilon = V_{max}/(K_a K^{1/m})$ were used. Nevertheless, we emphasize that there might be multiple ways of nondimensionalizing the system of equations when related problems are considered, and it might be worthwhile to perform an overall evaluation of which dimensionless variable should be used in the analysis and computation, since the computational complexity might be reduced with alternate choices.

We plot in Figure 5.4 the relative error against the variable K_a, where relative error (RE) is defined by the following formula

$$RE = \frac{C_N^{asym} - C_N^{num}}{C_N^{num}}, \tag{5.123}$$

where C_N^{asym} and C_N^{num} denote the value of $C_{max}(n)$ found by formula (5.101) and solved by Runge-Kutta method at time step $n = N$. We take $N = 20$, for which we believe that the system has reached steady state based on numerical results. The time step size h within each interval $[nT, (n+1)T]$ is taken to be $h = T/200000$, where T ix fixed at $T = 24$.

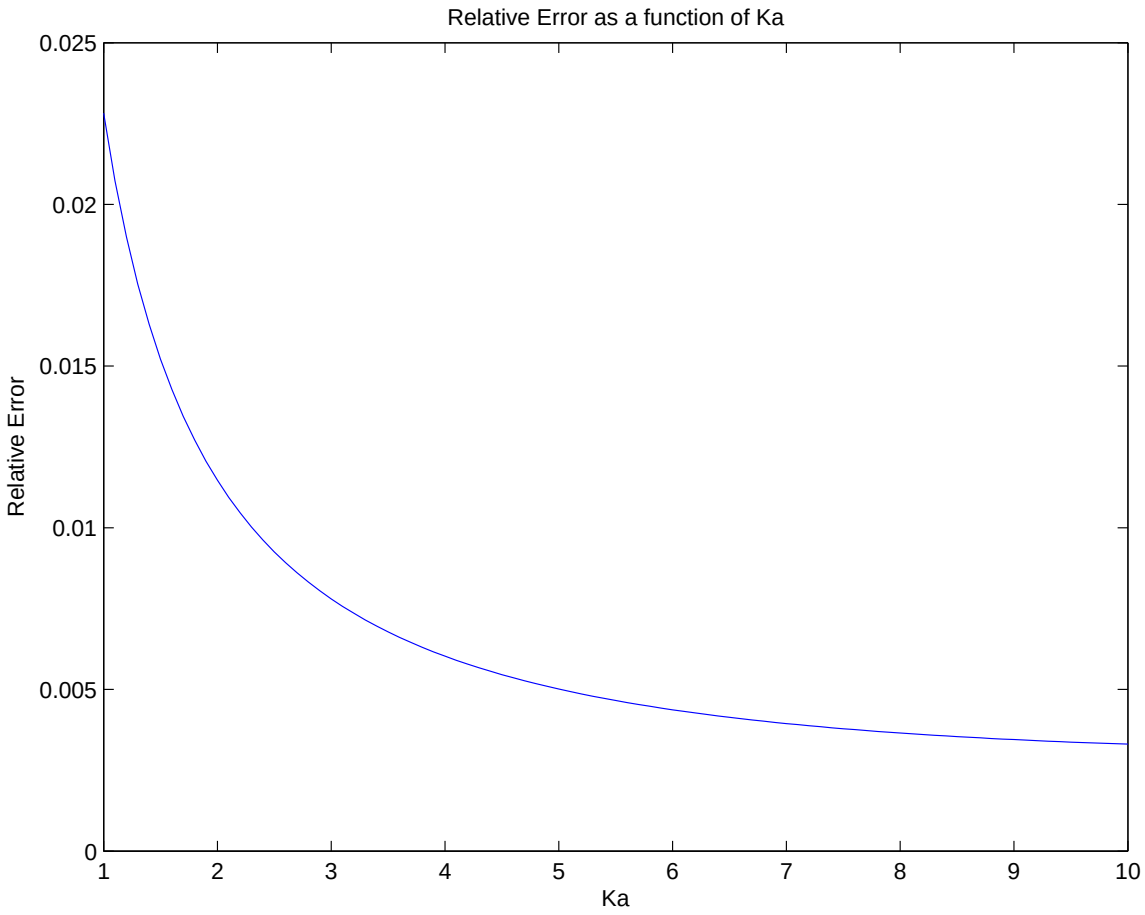


Figure 5.4. In this figure, $T = 24$, $B = 1$, $V_{max} = 0.5$, $J = 5$, $m = 2$ and $K_m = 100$. K_a ranges in the interval $[1, 10]$. Therefore, since $\epsilon = 1/(K_a T)$, ϵ decreases from $1/24$ to $1/240$ correspondingly, as K_a increases from 1 to 10. Relative Error is calculated using formula (5.123).

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