TWO COMPARTMENT MODEL FITTING FROM DIALYSIS DATA

By

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CHAPTER I

Introduction

I.1 Background

Acute kidney injury (AKI) is a serious condition that his been reported to affect about 2%, or about 560,000, hospitalizations in the United States annually[7]. Several studies have shown that the severity of AKI correlates with increase mortality rates and healthcare costs incurred from prolonged length of stay and post-hospitalization care[3; 7; 10]. While there are varying degrees for categorizing the severity of AKI[5], the disease is most commonly characterized by a sudden decrease in kidney function; in effect, the patient's kidneys lose their ability to effectively filter out excess waste and fluid from the patient, thus requiring some cases to use a dialysis machine to help "clean" the patient's blood.

Furthermore, sepsis has been shown as a common development related with patients diagnosed with AKI, and its presence correlates with increased mortality among AKI patients[11]. Fortunately, the prevention and treatment of sepsis is commonly achieved by the administration of antibiotics, but the dosing of such antibiotics becomes problematic in the presence of the dialysis procedure; on one hand, drug is being administered to combat the bacteria involved with the infection; on the other hand, the same drug is being removed indiscriminately along with the excess waste and fluid by the dialysis machine. Additionally, correct antibiotic dosing is important – too low of a concentration may fail to provide any benefits, while too high of a concentration may be toxic to the patient. Some antibiotics address this delicate balancing act with certain recommendations that account for patient variability and dialysis removal, but studies involving patients receiving continuous renal replacement therapy (CRRT) found that such a broad approach might not produce the most optimal results. For example, the clinical guidelines for prescribing piperacillin and tazobactam were still found to be insufficient to account for the wide variability between

patients, and most of the patients studied were unable to reach the correct antibiotic levels needed for effective therapy[2]. Similarly, the guidelines for other related antibiotics were also found to produce insufficient antibiotic concentrations in CRRT patients[12].

To address such difficulties, we first make an observation on how pharmacokinetic models are usually formed. An experiment is performed where a known amount of drug is administered to the patient and the resulting drug concentration in the patient's blood is then monitored over time. These observations of the drug concentration are then fit to a curve that serves as a model describing the underlying pharmacokinetics of the patient. By having such a model, a physician can then tailor the dosing levels so that the drug concentration in the patient will be in the therapeutic range.

On the other hand, the presence of dialysis will most likely cause such dosing levels to be incorrect as both the dosing and the dialysis machine will act on the patient to affect his drug levels. Note that in this formulation of the problem, the dialysis machine plays the same role as a drug infusion; both act as external inputs on the patient to affect his drug levels. Essentially, we are treating the underlying pharmacokinetic structure of the patient as a constant; only the input to the model changes. Therefore, the "input signal" given by the dialysis machine, though negative in nature, should have effects on the "output signal" of the patient's drug levels in keeping with the underlying pharmacokinetic model of the patient.

When recast in the terms of an "input signal" acting on a "model" to create an "output signal", the dialysis procedure offers a novel opportunity to use the concepts of mathematical systems modeling to asses patient pharmacokinetics. The goal of this thesis is to explore the use of such concepts by specifically re-framing the dialysis procedure in the context of linear systems theory; such an analysis will allow for the utilization of some of the well studied properties offered in that domain. Additionally, the analysis will be able to inform a procedure that address the problems of wide patient variability and antibiotic dosing under renal replacement therapy; if the physician is able to quickly and easily create

a personalized pharmacokinetic estimate of a particular patient, then the doctor can tailor the antibiotic dosing specifically for that patient.

I.2 Related Work

Linear systems representations of pharmacokinetic models have been studied in the past, although not in the context of the dialysis procedure. The work of Cutler [4] gives some basic results in reframing pharmacokinetics in the language of linear systems theory, while the work of Anderson [1] and McWilliams and Anderson [9] explore the mathematical properties of general compartmental pharmacokinetic models in a linear systems context. In terms of experimental verification, Madden et al. [8] shows good results of applying linear systems to simulated sets, while the work of [13] shows the applicability on real data. The method of this thesis bears the most similarity to the CODE algorithm [6] which also uses a constrained optimization using by using biologically plausible search values. These aforementioned approaches have shown good results in a traditional pharmacokinetic setting by using data that is collected over a period of four hours. With such results, we hope to further leverage the utility offered by linear systems theory in the context of dialysis; due its fast and very noticeable effect of patient drug levels, dialysis offers a novel opportunity for establishing individualized pharmacokinetics without the need for a dedicated experiment.

I.3 Overview

This thesis is organized as follows: Chapter 2 serves as a background into basic pharmacokinetics with the two-compartment model. Chapter 3 re-examines those basic ideas from a linear systems perspective and focuses on a linear systems representation of the two-compartment model. Chapter 4 describes a method for utilizing the linear systems representation of the two compartment model to create pharmacokinetic models from dialysis data. Chapters 5 gives some results on real clinical data while the conclusion is stated in Chapter 6.

CHAPTER II

Basic pharmacokinetics and the two-compartment model

One of the most basic mathematical constructs for modeling the pharmacokinetic behavior of a particular drug is the two-compartment model. While other, more sophisticated models exist, the two-compartment model is a commonly used, well known model that provides good insight into the underlying behavior of most drugs. An overview of the model is shown in Figure II.1.

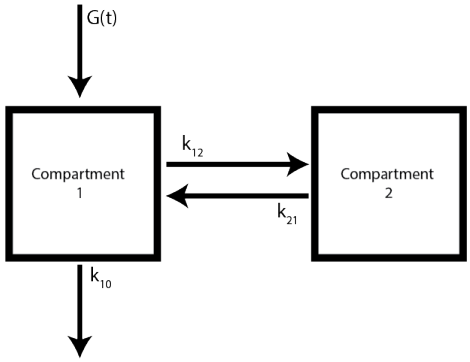


Figure II.1: Structure of the two-compartment model

The model begins by assuming that the body is essentially two compartments: a central compartment and a peripheral compartment. For our purposes, we consider that the central compartment represents the patient's bloodstream while the peripheral compartment represents the tissues and other body components not directly related with the patient's blood. Let $N_1(t)$ and $N_2(t)$ represent the amount of drug at time t in the central and peripheral compartments respectively. If we assume that each compartment is well mixed and that the volume of each compartment is constant and denoted by V_1 and V_2, then $C_1(t) = \frac{N_1(t)}{V_1}$ and $C_2(t) = \frac{N_2(t)}{V_2}$ are the respective drug concentrations of the central and peripheral compartments at time t.

In addition, assume that drug transport between compartments and with the outside world is controlled by particular rate constants k_{12}, k_{21}, k_{10} respectively, and let $G(t)$ repre-

sent the amount of drug given to the patient at time t. As an added simplification, assume that the rate of transport between both compartments is equal in both directions, that is, $k_{12} = k_{21}$. From basic diffusion laws involving semi-permeable membranes, we end up with the following set of coupled differential equations.

$$N_1^{'}(t) = -k_{10}c_1(t) - k_{12}c_1(t) + k_{12}c_2(t) + G(t) \tag{II.1}$$

$$N_2^{'}(t) = k_{12}c_1(t) - k_{12}c_2(t) \tag{II.2}$$

As a final simplification to the model, assume that $N_1(0) = N_2(0) = 0$, $G(t)$ is administered as an impulse of magnitude D at time $t = 0$, and we observe the behavior of the system only after the infusion ends. Furthermore, since we are more concerned with the concentration of drug in the patient rather than the absolute amount of drug, we divide both equations by their respective volumes. Equations II.1 and II.2 then simplify to:

$$\frac{\mathrm{d}c_1(t)}{\mathrm{d}t} = -\frac{k_{10}+k_{12}}{V_1}c_1(t) + \frac{k_{12}}{V_1}c_2(t) \tag{II.3}$$

$$\frac{dc_2(t)}{dt} = \frac{k_{12}}{V_2}c_1(t) - \frac{k_{12}}{V_2}c_2(t) \tag{II.4}$$

Since the bolus drug infusion of magnitude D must either have been eliminated or still in the tissues, we can write the following equation based on mass balance

$$D = c_1(t)V_1 + c_2(t)V_2 + \int_0^t k_{10}c_1(t)\mathrm{d}t$$

Or, rearranging:

$$c_2(t) = \frac{D - c_1(t)V_1 - \int_0^t k_{10}c_1(t)\mathrm{d}t}{V_2} \tag{II.5}$$

We then substitute equation II.5 into equation II.3 to get an expression for the rate of

change of drug concentration in the patient's blood

$$\frac{\mathrm{d}c_1(t)}{\mathrm{d}t} = -\frac{k_{10}+k_{12}}{V_1}c_1(t) + \frac{k_{12}}{V_1}\left(\frac{D - c_1(t)V_1 - \int_0^t k_{10}c_1(t)\mathrm{d}t}{V_2}\right)$$

Removing the integral from the above expression involves taking the derivative with respect to t:

$$\frac{\mathrm{d}^2c_1(t)}{\mathrm{d}t^2} = -\frac{k_{10}+k_{12}}{V_1}\frac{\mathrm{d}c_1(t)}{\mathrm{d}t} + \frac{k_{12}}{V_1}\left(\frac{-\frac{\mathrm{d}c_1(t)}{\mathrm{d}t}V_1 - k_{10}c_1(t)}{V_2}\right) \tag{II.6}$$

The above now represents a second order differential equation for $c_1(t)$. The solution to that equation is of the form:

$$c_1(t) = A\mathrm{e}^{-\alpha t} + B\mathrm{e}^{-\beta t} \tag{II.7}$$

Where A, B, α, and β are constants. Furthermore, equation II.7 represents the concentration of drug in the patient's bloodstream at time t. Therefore, the traditional approach to creating a pharmacokinetic model is to inject a bolus into a patient and then collect many samples of the drug concentration in the patient's blood. The collected data can then be used to fit a sum of exponentials curve of the form given in equation II.7. Finally, the resulting constants A, B, α, and β are then used to estimate the original parameters as follows:

$$k_{10} = \frac{D\alpha\beta}{A\beta + B\alpha}$$

$$k_{12} = \frac{D(A\alpha + B\beta)}{(A+B)^2} - \frac{D\alpha\beta}{A\beta + B\alpha}$$

$$V_1 = \frac{D}{A+B}$$

$$V_2 = \frac{(A\alpha + B\beta)}{(A+B)(A\beta + B\alpha)} - \frac{\alpha\beta(A+B)}{(A\beta + B\alpha)^2}$$

While the above analysis has been shown to be effective in producing pharmacokinetic models for patients, there are two aspects of the model that we would like to revisit:

1. Curve fitting an exponential model to the collected data

2. Assuming an idealized bolus infusion as the input

In effect, the above discussion relies on using least squares curve fitting approaches on collected data; such techniques may require many samples in order to overcome such methods' sensitivity to noise and outliers. The obvious flaw in this requirement is the fact that, in order to minimize patient risk, only a limited amount of blood can be sampled in a given time frame. Furthermore, the need to fit an exponential curve to the data was motivated by the assumption that there was an idealized bolus infusion as the input to the two-compartment model. Therefore, to perform the preceding analysis in a clinical setting, one has to set up a dedicated experiment in which a bolus is injected and the patient is monitored for a long period of time so that enough data can be collected to perform a least squares fit of a pharmacokinetic model.

The dialysis procedure, on the other hand, offers a potential solution to both of the above drawbacks. First, for the patients that we wish to create pharmacokinetic models for, dialysis is a necessary procedure that must be performed anyway; there is no need to create a separate lengthy experiment for assessing the patient's pharmacokinetics. Furthermore, since the machine can be precisely controlled and the removed drug concentration in the dialysate can be monitored, we needn't constrain ourselves to assuming bolus drug infusions; rather, we can observe the dialysis procedure as administering a "negative" drug dose whose exact value over time can be precisely measured. That "negative input signal" along with the "output signal" measured from the patient's blood suggests that we can take a linear systems approach in creating an individualized pharmacokinetic model for a particular patient.

CHAPTER III

A linear systems approach to pharmacokinetics

III.1 A general linear model

We base our initial analysis of the dialysis procedure on the traditional difference equation for linear systems. Let $y[0], y[1], \ldots, y[n-1]$ be the n equally spaced samples of the drug concentration in the patient's blood. In addition, let $x[0], x[1], \ldots, x[n-1]$ be the corresponding drug concentration samples in the dialysate. If we assume that the i^{th} blood sample has a concentration $y[i]$ that is a linear combination of the current dialysate sample $x[i]$, the previous q dialysate samples $x[i-1], x[i-2], \ldots, x[i-q]$, and the previous p blood samples $y[i-1], y[i-2], \ldots, y[i-p]$, then the difference equation can be written as:

$$y[i] = -a_1 y[i-1] - a_2 y[i-2] - \ldots - a_p y[i-p] + b_0 x[i] + b_1 x[i-1] + \ldots + b_q x[i-q] \quad \text{(III.1)}$$

Where $a_1, \ldots, a_p, b_0, \ldots, b_q$ are unknown filter coefficients. Taking the Z-transform of both sides yields:

$$Y(z) = -Y(z)(a_1 z^{-1} + a_2 z^{-2} + \ldots + a_p z^{-p}) + X(z)(b_0 + b_1 z^{-1} + b_2 z^{-2} + \ldots + b_q z^{-q})$$

Rearranging terms gives an expression for the transfer function of the linear system $H(z)$

$$H(z) = \frac{Y(z)}{X(z)} = \frac{b_0 + b_1 z^{-1} + b_2 z^{-2} + \ldots + b_q z^{-q}}{1 + a_1 z^{-1} + a_2 z^{-2} + \ldots + a_p z^{-p}} \quad \text{(III.2)}$$

Such an expression means that, once the values of the unknown coefficients, $a_1, \ldots, a_p$, $b_0, \ldots, b_q$, are determined, an output response can be predicted from any arbitrary input signal. Note that the form in equation III.2 can be tailored by a user's choice for the values of p and q; one can make higher or lower order models as needed, given enough data exist

to support the chosen model.

In order to determine the values for the unknown coefficients of equation (III.2), we return to the original difference equation given by equation (III.1). We start by writing a difference equation for each of the $n-M$ output samples, where $M = max(p,q)$. Let $\vec{y} = \begin{bmatrix} y[M] & y[M+1] & \dots & y[n-1] \end{bmatrix}^\top$. Furthermore, let $\vec{a} = \begin{bmatrix} a_1 & a_2 & \dots & a_p \end{bmatrix}^\top$ and $\vec{b} = \begin{bmatrix} b_0 & b_1 & \dots & b_q \end{bmatrix}^\top$ be the vectors of unknown coefficients for the model from equation III.1. The resulting matrix equation can then be set up:

$$\vec{y} = \begin{bmatrix} \mathbf{Y} & \mathbf{X} \end{bmatrix} \begin{bmatrix} \vec{a} \\ \vec{b} \end{bmatrix} \tag{III.3}$$

Where $\mathbf{Y}$ and $\mathbf{X}$ are the Toeplitz matricies consisting of the respective output and input samples as follows:

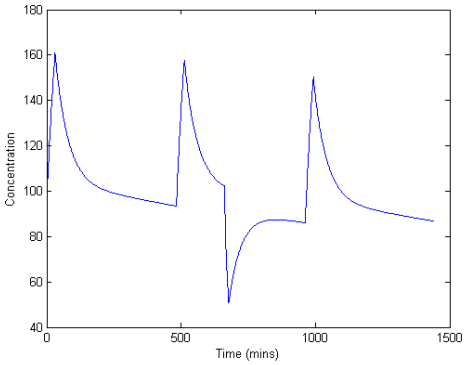
$$\mathbf{Y} = \begin{bmatrix} y[M-1] & y[M-2] & \dots & y[M-p] \\ y[M] & y[M-1] & \dots & y[M+1-p] \\ y[M+1] & y[M] & \dots & y[M+2-p] \\ \vdots & \vdots & \vdots & \vdots \\ y[n-2] & y[n-3] & \dots & y[n-p-1] \end{bmatrix}$$

$$\mathbf{X} = \begin{bmatrix} x[M] & x[M-1] & \dots & x[M-q] \\ x[M+1] & x[M] & \dots & x[M+1-q] \\ x[M+2] & x[M+1] & \dots & x[M+2-q] \\ \vdots & \vdots & \vdots & \vdots \\ x[n-1] & x[n-2] & \dots & x[n-q-1] \end{bmatrix}$$

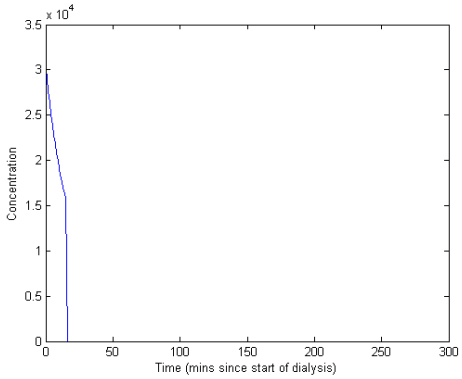
Equation (III.3) can then be solved by any variety of techniques, usually involving least-squares. Again, we stress the generality of the aforementioned approach; the output response of a patient can be predicted from **any** arbitrary input signal without any particular assumption of the underlying pharmacokinetic model of the patient.

Figure III.1 shows the validity of such an approach. A patient was simulated in MATLAB by using the original coupled differential equations of the two-compartment model. Simulated doses were given as square pulses until the patient reached steady state. A simulated dialysis session was then applied to the patient for fifteen minutes. We took a sample of the drug concentration of the blood and the dialysate at each minute during the 15 minute dialysis session and in the 285 minute period immediately after the dialysis session had completed(For a total of 300 samples). Using $p = q = 10$ the values for the filter coefficients were found with the least-squares approach stated above. We then used the resulting estimated model to filter the original sequence of simulated doses to get the results in Figures III.1d and III.1e. Note that we were able to create a close approximation of the original model's steady state behavior without any knowledge of the underlying system; the choice of $p = q = 10$ was completely arbitrary and could be changed to any value that would be supported by having 300 sample pairs.

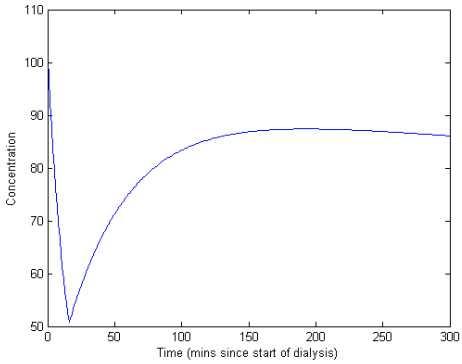
While such a simulation shows that one has the potential to create arbitrarily good approximations without any particular concern for the underlying pharmacokinetics, the utility of the general least squares approach is still hindered by the need of many samples in order to create higher order models and to overcome sensitivities to outliers and noise. Such limitations necessarily arise from the very general nature of this approach to system modeling, as we are essentially searching for the best model (in a least-squares sense) among **all** possible models. This large of a search space is unnecessary; since we are modelling patients instead of arbitrary black boxes, we can constrain the search space by searching only for models that are plausible in a biological sense. In doing so, we can minimize the number of samples required to still create models that can predict the output response for any arbitrary input.



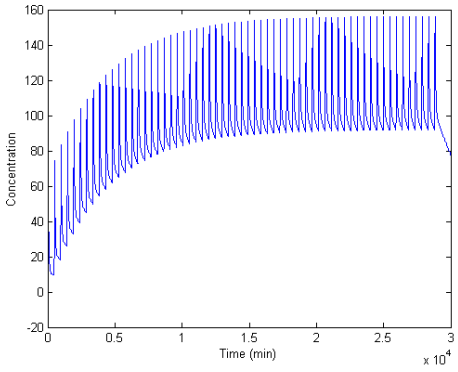
(a) Simulated Data



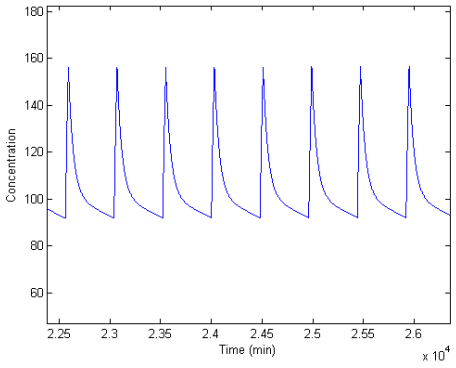
(b) Drug concentration in dialysate



(c) Drug concentration in blood



(d) Output of predicted model



(e) Steady state behavior of the predicted model

Figure III.1: Simulated example illustrating the least-squares approach

III.2 A linear systems analysis of the two-compartment model

To understand what transfer functions are acceptable in a biological sense, we return to the two-compartment model and observe how the biological parameters V_1, V_2, k_{10}, k_{12} behave in a linear systems context.

Recall that the core of the two compartment model was the following set of coupled differential equations.

$$c_1'(t) = -\frac{k_{10}+k_{12}}{V_1}c_1(t) + \frac{k_{12}}{V_1}c_2(t) + \frac{1}{V_1}G(t)$$

$$c_2'(t) = \frac{k_{12}}{V_2}c_1(t) - \frac{k_{12}}{V_2}c_2(t)$$

Taking the Laplace transform of both equations yields:

$$C_1(s)\cdot s = -\frac{k_{10}+k_{12}}{V_1}C_1(s) + \frac{k_{12}}{V_1}C_2(s) + \frac{1}{V_1}G(s)$$

$$C_2(s)\cdot s = \frac{k_{12}}{V_2}C_1(s) - \frac{k_{12}}{V_1}C_2(s)$$

Or, in matrix form:

$$\begin{bmatrix} C_1(s) \\ C_2(s) \end{bmatrix} s = \begin{bmatrix} \frac{-k_{10}+k_{12}}{V_1} & \frac{k_{12}}{V_1} \\ \frac{k_{12}}{V_2} & -\frac{k_{12}}{V_1} \end{bmatrix} \begin{bmatrix} C_1(s) \\ C_2(s) \end{bmatrix} + \begin{bmatrix} \frac{1}{V_1} \\ 0 \end{bmatrix} G(s)$$

Rearranging, we get:

$$(s\mathbf{I} - \begin{bmatrix} \frac{-k_{10}+k_{12}}{V_1} & \frac{k_{12}}{V_1} \\ \frac{k_{12}}{V_2} & -\frac{k_{12}}{V_1} \end{bmatrix}) \begin{bmatrix} C_1(s) \\ C_2(s) \end{bmatrix} = \begin{bmatrix} \frac{1}{V_1} \\ 0 \end{bmatrix} G(s)$$

Where $\mathbf{I}$ is the identity matrix. The solution to this system is therefore:

$$\begin{bmatrix} C_1(s) \\ C_2(s) \end{bmatrix} = (s\mathbf{I} - \begin{bmatrix} \frac{-k_{10}+k_{12}}{V_1} & \frac{k_{12}}{V_1} \\ \frac{k_{12}}{V_2} & -\frac{k_{12}}{V_1} \end{bmatrix})^{-1} \begin{bmatrix} \frac{1}{V_1} \\ 0 \end{bmatrix} G(s)$$

Since the blood samples taken from the patient reflect our observations of C_1, we are most interested in the transfer function $H(s) = \frac{C_1(s)}{G(s)}$ as that succinctly characterizes the relationship between a drug dose and the drug concentration in the blood. Multiplying both sides by $\begin{bmatrix} 1 & 0 \end{bmatrix}$ and rearranging terms creates a transfer function of the form:

$$H(s) = \frac{C_1(s)}{G(s)} = \frac{\frac{1}{V_1}s + \frac{1}{k_{10}}B_H}{s^2 + A_H s + B_H} \tag{III.4}$$

Where:

$$A_H = \frac{k_{12}}{V_2} + \frac{k_{10}+k_{12}}{V_1}$$

$$B_H = \frac{k_{10}k_{12}}{V_1 V_2}$$

Note that the form in equation (III.4) is the continuous s-domain transfer function relationship between the blood's drug concentration and dosing input. In reality, since we are observing the blood concentrations through discrete samples, the transfer function must be converted to its discrete time z-domain representation. If the time between samples is T, we perform the conversion with the bilinear transform by evaluating $H(s)$ at $s = \frac{2}{T} \cdot \frac{1-z^{-1}}{1+z^{-1}}$. The resulting expression gives a discrete time transfer function of the form:

$$H(z) = H(s)\Big|_{\frac{2}{T}\cdot\frac{1-z^{-1}}{1+z^{-1}}} = \frac{b_0 + b_1 z^{-1} + b_2 z^{-2}}{1 - a_1 z^{-1} - a_2 z^{-2}} \tag{III.5}$$

Where the coefficients of the transfer function are:

$$b_0 = \frac{\frac{2T}{V_1} + \frac{1}{k_{10}}T^2 B_H}{4 + 2TA_H + T^2 B_H}$$

$$b_1 = \frac{\frac{2}{k_{10}}T^2B_H}{4+2TA_H+T^2B_H}$$

$$b_2 = \frac{\frac{1}{k_{10}}T^2B_H - \frac{2T}{V_1}}{4+2TA_H+T^2B_H}$$

$$a_1 = \frac{2T^2B_H-8}{4+2TA_H+T^2B_H}$$

$$a_2 = \frac{4-2TA_H+T^2B_H}{4+2TA_H+T^2B_H}$$

III.3 Properties of the two-compartment model with biological parameters

Notice that the preceding discussion shows that the original coupled differential equations that describe the traditional two-compartment model can be transformed into transfer functions in either the continuous or discrete domain. Furthermore, we notice that the coefficients of the filters are constants that are dependent on the constants of the original two compartment parameters. Here we describe some interesting properties of the two-compartment model when using biologically plausible values for V_1, V_2, k_{10}, k_{12}

Property 1. *$V_2 \geq V_1$ is a sufficient condition for the poles of $H(z)$ to be real*

Proof. For this fact, we simply need to observe the value of the determinant of the denominator of $H(z)$. Simplifying that expression (in Mathematica) yields:

$$a_1^2 + 4a_2 = 16\frac{T^2(k_{10}^2V_2^2 + 2k_{10}k_{12}V_2(V_2-V_1) + k_{12}^2(V_1+V_2)^2)}{(k_{12}T(k_{10}T+2V_1)+2((k_{10}+k_{12})T+2V_1)V_2)^2} \tag{III.6}$$

Because the values for V_1, V_2, k_{10}, k_{12} are greater than zero, a only the middle term in the numerator $(V_2 - V_1)$ could lead to a negative value. Therefore, a sufficient condition for real poles is that $V_2 \geq V_1$. This condition $V_2 \geq V_1$ is reasonable to expect, as V_1 represents the volume of the blood while V_2 represents everything else. □

Property 2. *The two compartment model is stable when using biological values*

Proof. This is most easily seen by using the continuous representation of the transfer function $H(s)$, restated here for convenience:

$$H(s) = \frac{\frac{1}{V_1}s + \frac{k_{12}}{V_1V_2}}{s^2 + (\frac{k_{12}}{V_2} + \frac{k_{10}+k_{12}}{V_1})s + \frac{k_{10}k_{12}}{V_1V_2}}$$

Since the denominator of $H(s)$ is second order, we can use a special case of the Routh-Hurwitz stability criterion which simply requires the coefficients of the denominator to have the same sign. Indeed, this is the case as biologically plausible values of V_1, V_2, k_{10}, k_{12} must necessarily be greater than zero and will thus cause the coefficients of the denominator to all be positive. □

Property 3. *One of the zeros of $H(z)$ is equal to -1*

Proof. In the interest of clarity, we exclude the denominators of b_0,b_1, and b_2 as they are equivalent and will not affect our analysis in finding the zeros of the numerator of $H(z)$.

First observe the value of the discriminant $b_1^2 - 4b_0b_2$

$$\begin{aligned} b_1^2 - 4b_0b_2 &= (\frac{2}{k_{10}}T^2B_H)^2 - 4(\frac{1}{k_{10}}T^2B_H + \frac{2T}{V_1})(\frac{1}{k_{10}}T^2B_H - \frac{2T}{V_1}) \\ &= \frac{4}{k_{10}^2}T^4B_H^2 - \frac{4}{k_{10}^2}T^4B_H^2 + 16\frac{T^2}{V_1^2} \\ &= 16\frac{T^2}{V_1^2} \end{aligned}$$

Since this result must necessarily be positive, an interesting side note is that the zeros of $H(z)$ will in fact be real. Now observe one of the roots of the numerator of $H(z)$

$$\begin{aligned} \frac{-b_1 - \sqrt{b_1^2 - 4b_0b_2}}{2b_0} &= \frac{-\frac{2}{k_{10}}T^2B_H - \sqrt{16\frac{T^2}{V_1^2}}}{2(\frac{1}{k_{10}}T^2B_H + \frac{2T}{V_1})} \\ &= \frac{-1(\frac{2}{k_{10}}T^2B_H + \frac{4T}{V_1})}{\frac{2}{k_{10}}T^2B_H + \frac{4T}{V_1}} \\ &= -1 \end{aligned}$$

□

Property 4. *The numerator of $H(z)$ can be rewritten as $b_0 + (b_0 + b_2)z^{-1} + b_2 z^{-2}$*

Proof. Again, we ignore the denominators of b_0,b_1, and b_2 as they are equivalent

$$\begin{aligned} b_0 + b_2 &= (\frac{1}{k_{10}} T^2 B_H + \frac{2T}{V_1}) + (\frac{1}{k_{10}} T^2 B_H - \frac{2T}{V_1}) \\ &= \frac{2}{k_{10}} T^2 B_H \\ &= b_1 \end{aligned}$$

□

The above properties allow for some interesting observations on the behavior of the two compartment model we will be searching for. From properties 1 and 2 we know that the impulse response from an idealized bolus infusion will be expected to be stable and behave as a sum of decaying exponentials. Furthermore, property 3 implies that the model has an inherent low-pass characteristic. These behaviors are expected, as these properties are identical to the behaviors observed from our original analysis of the two-compartment model. However, with this analysis in creating transfer functions $H(s)$ and $H(z)$, we can describe the response of the model to **any** input signal, rather than limiting ourselves to considering just idealized bolus infusions.

Property 4 is particularly interesting as we can now rewrite the form of $H(z)$ from equation III.5 as follows:

$$H(z) = \frac{b_0 + (b_0 + b_2)z^{-1} + b_2 z^{-2}}{1 - a_1 z^{-1} - a_2 z^{-2}} \tag{III.7}$$

This form of a model from equation III.7 means that a vector of biologically feasible values for V_1, V_2, k_{10}, k_{12} will map to a vector of model coefficients a_1, a_2, b_0, b_2, thus implying a search for 4 coefficients instead of the original 5. Along with the other properties stated, we see that such a search using biologically reasonable parameters for a two-compartment

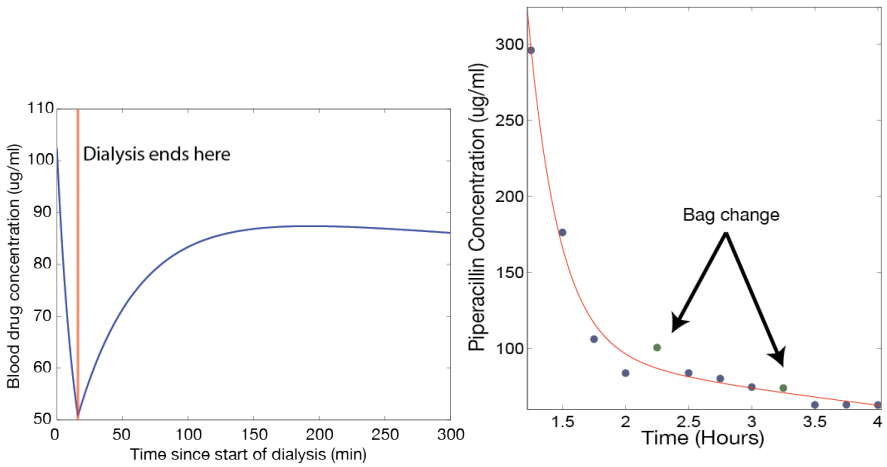
model further constrains the search space of all possible linear models to a space of stable linear models that have two real poles and two real zeros with one zero fixed at -1.

CHAPTER IV

Methods

IV.1 Data Collection

In order to use the information found in the preceeding section about biologically plausible two-compartment models, we first note the typical response of a two-compartment model when dialysis is applied. Figure IV.1 shows the output response of a two-compartment model in both simulations and in a preliminary pilot study. Figure IV.1a is the same graph from the simulated two-compartment model used in the preceeding section. Meanwhile, Figure IV.1b shows the drug level of a pharmacokinetic experiment involving a patient under continuous renal replacement therapy (CRRT). For the simulated example, we see



(a) Simulated two-comparment patient (b) Real CRRT Patient

Figure IV.1: Response of patient drug levels from turning off the dialysis machine

the drug levels in the blood increase slightly when dialysis ends; this movement is representative of the transfer of drug from the peripheral compartment back into the central compartment. A similar effect can be seen in the real CRRT case as the green circles indicate when the dialysis machine was turned off in order to perform a bag change. Note both examples illustrate the presence of characteristic changes in drug concentration not only

when the dialysis machine is on, but also when it is turned off. As these transient responses are highly informative of the behavior of the underlying pharmacokinetic system, we will use the following collection strategy:

1. Turn the dialysis machine on
2. Collect $\frac{N}{2}$ pairs of blood and dialysate by sampling every T minutes
3. Turn the dialysis machine off and place the patient under ultrafiltration.
4. Immediately begin the collection of the other $\frac{N}{2}$ samples of blood and dialysate pairs by sampling every T minutes

This strategy will then give us N evenly spaced samples of the input $x[0], x[1], \ldots, x[\frac{N}{2}-1], x[\frac{N}{2}], x[\frac{N}{2}+1], \ldots, x[N-1]$ and output $y[0], y[1], \ldots, y[\frac{N}{2}-1], y[\frac{N}{2}], y[\frac{N}{2}+1], \ldots, y[N-1]$ signals of the dialysate and blood respectively.

IV.2 Model Estimation

We then set up the same matrix equation as equation III.3. Since we will be looking for a two-compartment model with two poles and two zeros, we form equation III.3 with $p = q = 2$. Let $\vec{y} = \begin{bmatrix} y[2] & y[3] & \ldots & y[N-1] \end{bmatrix}^\top$ and $\vec{\theta} = \begin{bmatrix} a_1 & a_2 & b_0 & b_1 & b_2 \end{bmatrix}^\top$. Equation III.3 now becomes:

$$\vec{y} = \mathbf{A}\vec{\theta} \tag{IV.1}$$

Where $\mathbf{A}$ is the matrix:

$$\mathbf{A} = \begin{bmatrix} y[1] & y[0] & x[2] & x[1] & x[0] \\ y[2] & y[1] & x[3] & x[2] & x[1] \\ y[3] & y[2] & x[4] & x[3] & x[2] \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ y[N-2] & y[N-3] & x[N-1] & x[N-2] & x[N-3] \end{bmatrix}$$

This time, however, we will not be solving for the unknown coefficients in the vector $\vec{\theta}$ directly. Since the number of samples N will most likely be too small for an accurate estimation by a direct application of least-squares, we will use our knowledge of biological parameters to set up a search space involving V_1, V_2, k_{10}, k_{12} with the following constraints:

1. V_1, V_2, k_{10}, k_{12} are all greater than $V_{1_{Min}}, V_{2_{Min}}, k_{10_{Min}}, k_{12_{Min}}$ respectively.

2. V_1, V_2, k_{10}, k_{12} are all less than $V_{1_{Max}}, V_{2_{Max}}, k_{10_{Max}}, k_{12_{Max}}$ respectively.

These max and min values can be chosen by the physician and needn't be strict; these are simply to limit the search space to models that have a plausible interpretation. Furthermore, since we know that any choice of V_1, V_2, k_{10}, k_{12} in this search space can be mapped to a point in the space of filter coefficients a_1, a_2, b_0, b_2, a search in our constrained search space corresponds to a search in the coefficient space. Therefore, we try to optimize the parameters V_1, V_2, k_{10}, k_{12} by minimizing the squared error in equation IV.1. More formally:

$$\begin{aligned} &\underset{\vec{x}}{\text{minimize}} \quad (\vec{y} - Af(\vec{x}))^2 \\ &\text{subject to} \quad \left[V_{1_{Min}}\ V_{2_{Min}}\ k_{10_{Min}}\ k_{12_{Min}}\right]^\top \leq \vec{x} \leq \left[V_{1Max}\ V_{2Max}\ k_{10Max}\ k_{12Max}\right]^\top \end{aligned} \tag{IV.2}$$

Where $\vec{x} = \left[V_1\ V_2\ k_{10}\ k_{12}\right]$ and $f(\vec{x})$ is the function that maps $\vec{x}$ to the vector of filter coefficients $\vec{\theta}$, using the formulas from the previous section. As the minimization objective in equation IV.2 is difficult to evaluate in closed form, we adopt a random search procedure to identify potential candidate models. A set of K candidate vectors of biological parameters $\vec{x}_i$ within our constrained search space are randomly generated. The minimization of equation IV.2 for each of the K candidates is then performed using the Nelder-Mead optimization algorithm. We note that in performing this optimization, the input and output values $x[n]$ and $y[n]$ should be scaled so that the range of the input values should be roughly on par with the range of the output values; we noticed that if the $x[n]$ values are too large with respect to the $y[n]$ values, the Nelder-Mead optimization would tend to push candidate models to the fringe of the biological search space rather than pushing each of the models

toward a local minima. Furthermore, as Nelder-Mead is an iterative approximation method, there is the potential that certain candidates may have gotten stuck in local minima that are not very meaningful. Therefore, we choose the B best candidate models based on their final squared error values.

However, recall that the behavior of a transfer function $H(z)$ is dictated by the value of its poles and zeros rather than the actual value of its coefficients; two transfer functions may behave similarly from having similar poles and zeros but have completely different values in terms of filter coefficients. To account for this fact, we take each of the transfer functions represented by each of the B best candidate models and re-parametrize them by their poles and zeros. Our final estimated model is simply the average of the B best models in pole-zero space. If the i^{th} model is represented by the vector $\vec{m}_i = [p_{1i}, p_{2i}, z_{1i}, -1]^\top$ where p_{1i} and p_{2i} are the poles of the i^{th} model and z_{1i} is the zero that does not equal -1, then our model estimate $\hat{\vec{M}}$ is therefore:

$$\hat{\vec{M}} = \frac{1}{B}\sum_{i=1}^{B} \vec{m}_i \tag{IV.3}$$

The poles and zeros represented by $\hat{\vec{M}}$ can be used to estimate a filter $\hat{H}(z)$. However, a filter constructed only from the poles and zeros will produce a filter with only unity gain. Therefore, as a final step, we still need to find a gain value $\hat{G}$ to fully estimate the behavior of our filter. To accomplish this goal, we use the patient's medical history leading up to dialysis as follows:

1. Simulate an input signal $X(t)$ of the patient's dosing history as a sequence of square pulses

2. Filter $X(t)$ with $\hat{H}(z)$ to produce $\hat{Y}(t)$

3. If the first blood sample at the start of dialysis was taken at $t_{firstsample}$, $\hat{G}$ should be calculated as the value that scales $\hat{Y}(t_{firstsample})$ to the actual value measured at the

start of dialysis.

In other words, we treat the first blood sample taken at the start of dialysis as the "correct" drug concentration that resulted from the previous doses and calculate the gain of the estimated filter to reflect that fact. Now that an estimate of $\hat{G}$ and $\hat{H}(z)$ have been found, a physician can easily predict the patient's drug levels in response to any arbitrary dosing scheme.

CHAPTER V

Results and Discussion

V.1 Experimental Setup

Four data sets were collected on three patients receiving dialysis. More specific information on the patients and data is described in the next subsection. Each dataset was broken into two parts, dialysis day data and non-dialysis day data. The dialysis day data was collected in the same manner described in the previous section; we collected six samples at 5 minute intervals during the start of dialysis, and then collected six more samples at 5 minute intervals as soon as the dialysis machine was turned off. This data was then used to search for a filter based on the two compartment model; $V_{1_{Max}}$ and $V_{2_{Max}}$ were set to the patient's weight, while $k_{10_{Max}}$, and $k_{12_{Max}}$ were set to 1000. Also,$V_{1_{Min}}$ and $V_{2_{Min}}$ were set at 1000, while $k_{10_{Min}}$, and $k_{12_{Min}}$ were set to 1. The number of candidate models we used in our search was 1000. We then simulate the patient's dosing history leading up to the times of the samples collected on his non-dialysis day. This simulated signal is then fed through our estimated filter to get predictions for the patient's drug concentration during his off-dialysis day. These predictions are compared to the actual measured values to assess method accuracy.

V.2 Individual Patient Results

Patient 1

This was a 97kg patient dosed with two antibiotics: piperacillin and tazobactam. This combination allowed us to get two datasets, one each for the piperacillin concentrations and the tazobactam concentrations. Both drugs were administered to the patient every 12 hours with infusions of 3.375g spread out over four hours. The non-dialysis data was collected 3 days after the start of infusions and the dialysis day data was collected later on the same day. Dialysis flow rate was 800ml/min while the ultrafiltration rate was set to

14.5ml/min. From the final squared errors of the candidate models, we chose to average the smallest 700 models.

Predicted	25.49	24.50	23.51	21.71	18.56
Measured	23.10	22.88	21.55	20.87	19.18
% Error	10.33	7.08	9.08	4.02	3.21

Table V.1: Comparison of predicted and measured values for non-dialysis day in the tazobactam dataset for patient 1

Predicted	188.59	181.75	174.93	162.46	140.46
Measured	194.31	191.55	181.04	173.43	152.30
% Error	2.93	5.12	3.38	6.32	7.77

Table V.2: Comparison of predicted and measured values for non-dialysis day in the piperacillin dataset for patient 1

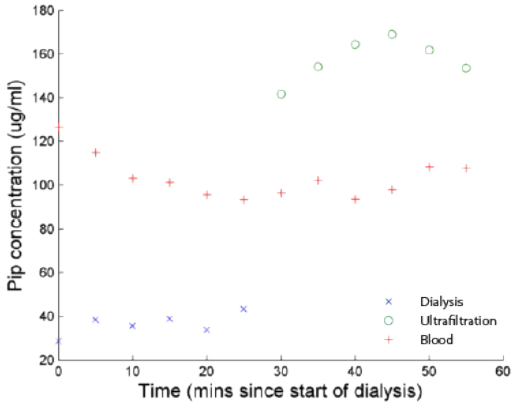
Patient 2

This was a 100kg patient injected with meropenem. Drug was administered every 8 hours with infusions of 1 gram spread out over three hours. The non-dialysis day data was collected 5 days after the start of infusions while the dialysis day data was collected the following day. Dialysis flow rate was set to 800ml/min while ultrafiltration was set to 4.16ml/min. From the final squared errors of the candidate models, we chose to average the smallest 800 models.

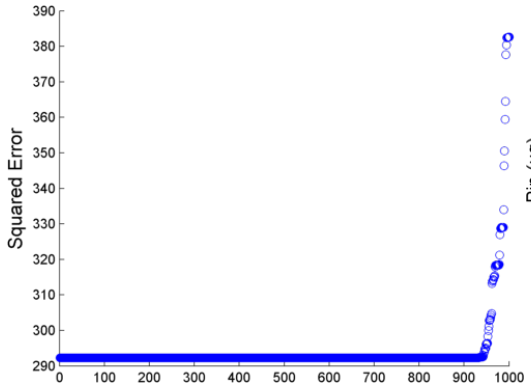
In looking at the collected dialysis day data, the circled point in Figure V.3a appears to be an erroneous measurement and its inclusion does lead to a poor model estimation.(Figure V.3) However, when that data point is excluded, (along with the next two points since they depend on the excluded point) the estimation method appears to produce reasonable results.(Figure V.4)

Patient 3

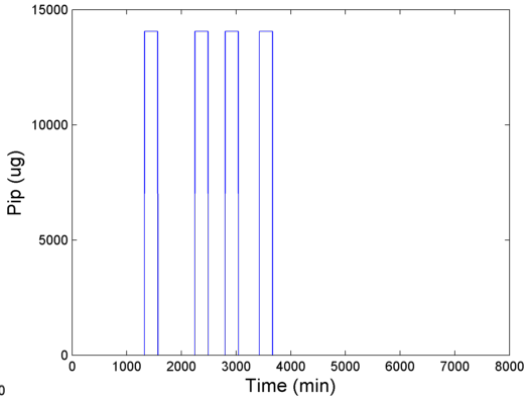
This was a 102kg patient dosed with piperacillin. Drug was administered every 12 hours with infusions of 3.375g spread out over four hours. Dialysis day data was collected the



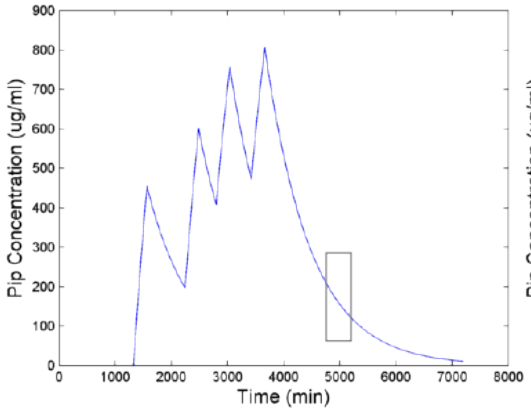
(a) Observed data from dialysis



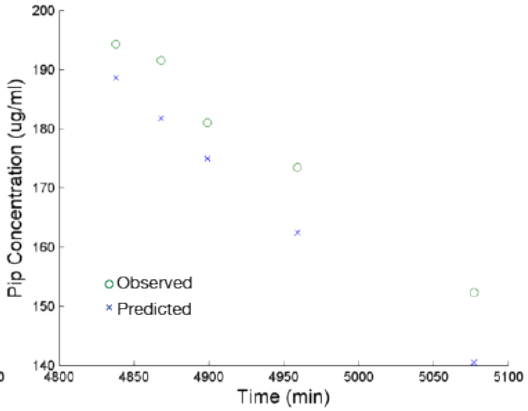
(b) Final errors of candidate models



(c) Simulated dosing history of patient

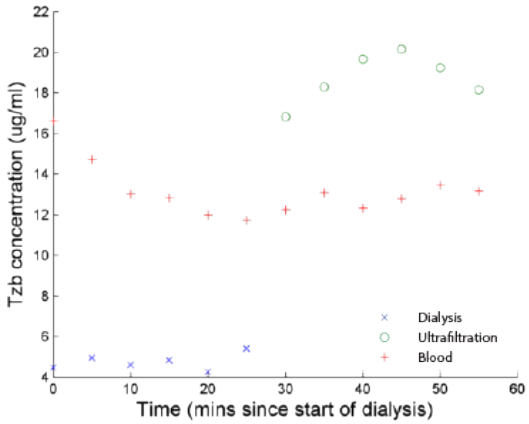


(d) Predicted drug levels

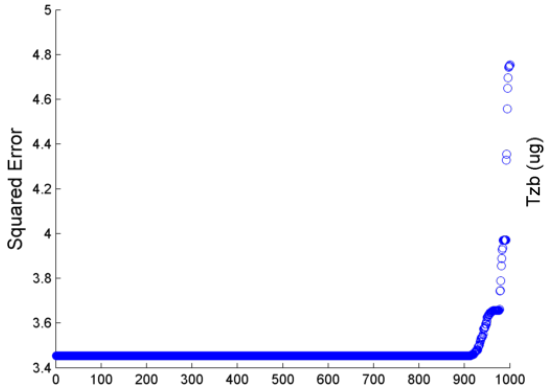


(e) Comparison with ground truth

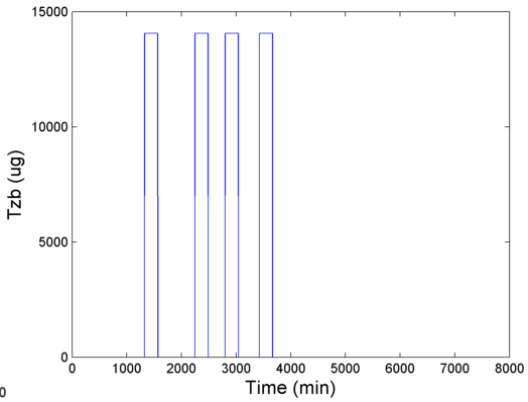
Figure V.1: Results on piperacillin dataset for patient 1



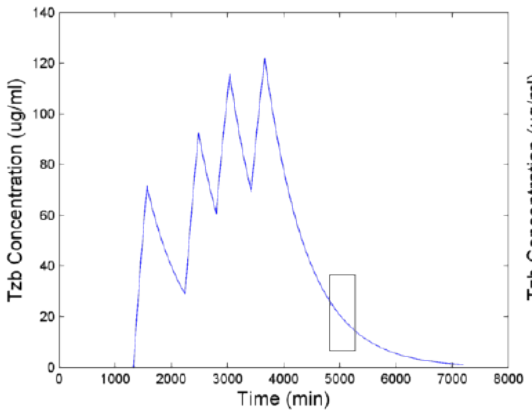
(a) Observed data from dialysis



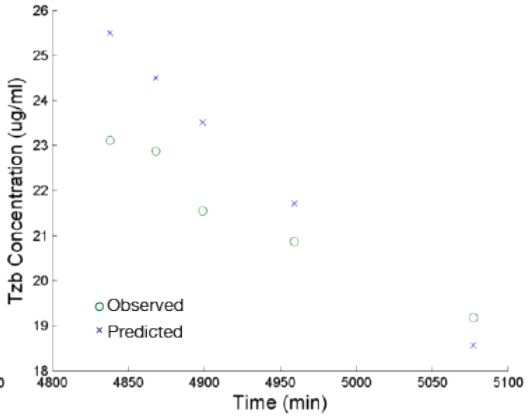
(b) Final errors of candidate models



(c) Simulated dosing history of patient

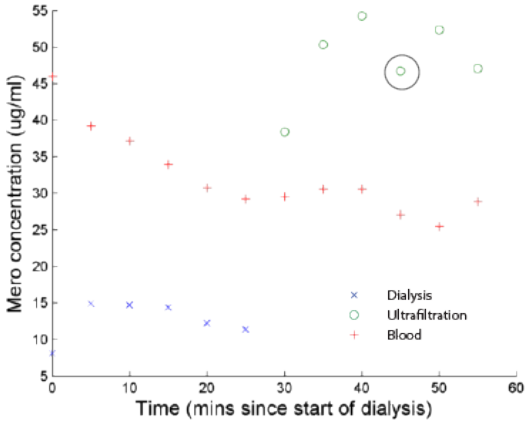


(d) Predicted drug levels

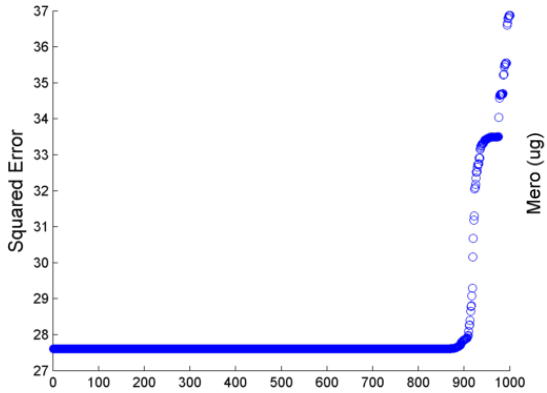


(e) Comparison with ground truth

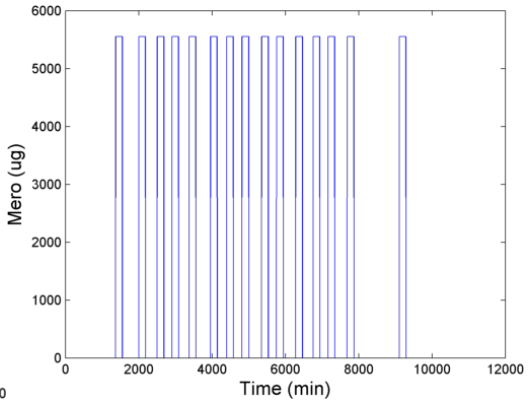
Figure V.2: Results on tazobactam dataset for patient 1



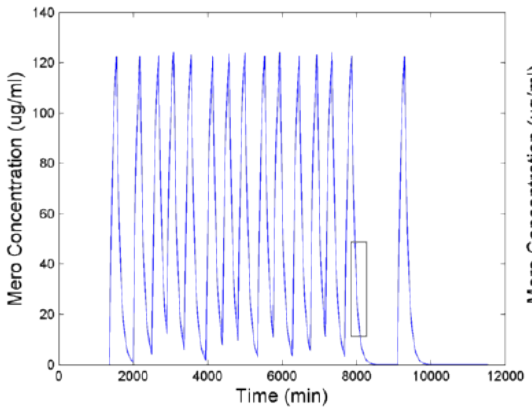
(a) Observed data from dialysis



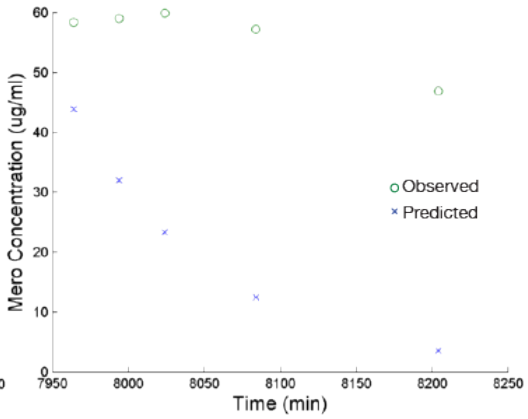
(b) Final errors of candidate models



(c) Simulated dosing history of patient

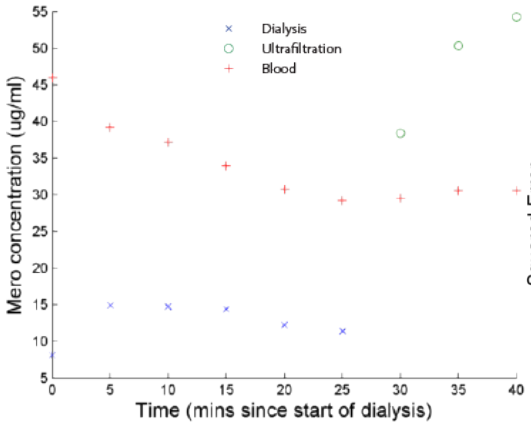


(d) Predicted drug levels

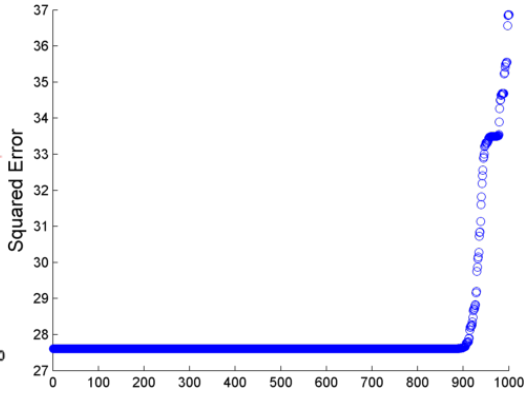


(e) Comparison with ground truth

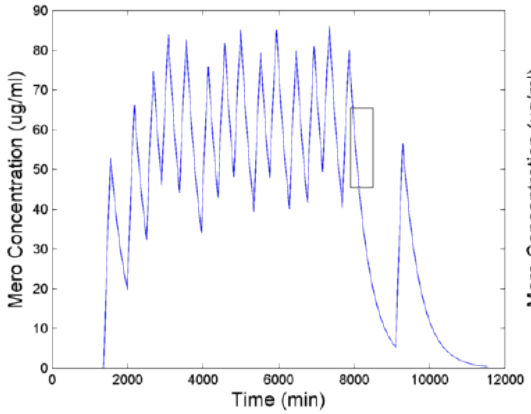
Figure V.3: Results on meropenem dataset for patient 2



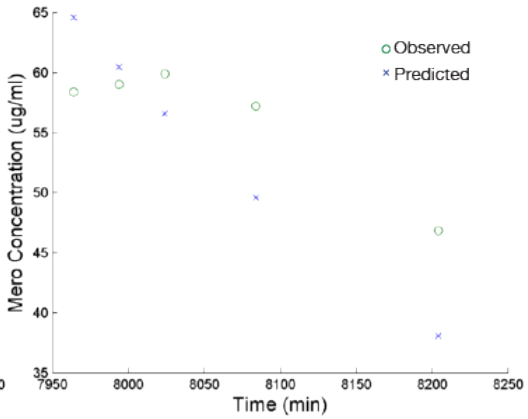
(a) Observed data from dialysis excluding the outlier



(b) Final errors of candidate models



(c) Predicted drug levels



(d) Comparison with ground truth

Figure V.4: Results on meropenem dataset for patient 2 when excluding the outlier

Predicted	43.82	31.98	23.33	12.42	3.52
Measured	58.39	59.03	59.90	57.21	46.86
% Error	25.94	45.82	61.04	78.28	92.48

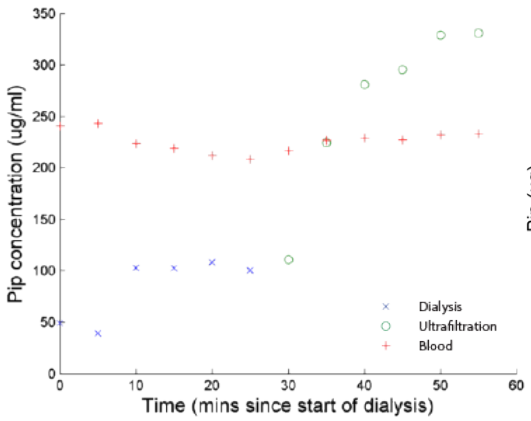
Table V.3: Comparison of predicted and measured values for non-dialysis day in the meropenem dataset for patient 2 using all of the data

Predicted	64.58	60.45	56.58	49.57	38.05
Measured	58.39	59.03	59.90	57.21	46.86
% Error	10.60	2.39	5.54	13.35	18.80

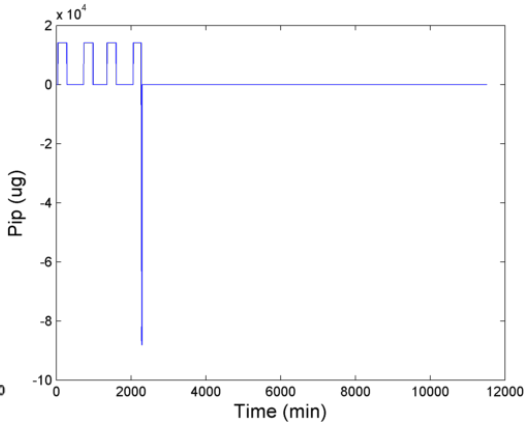
Table V.4: Comparison of predicted and measured values for non-dialysis day in the piperacillin dataset for patient 2 excluding the suspected outlier

day following the start of infusions. We note here that there was some ambiguity in the medical record as to the nature of the last dose given to the patient before the dialysis data was taken. According to the chart, the dose should have ended **during** the collection of the dialysis data. However, according to the nurse, there was no observable amount of drug left in the I.V. bag. This leads to an ambiguity as to exactly the rate and the amount of drug was given to the patient during the last dose, and if the infusion of drug was interfering with the drug removal from the dialysis machine. Nonetheless, we model the final dose as if the infusion ended when it was scheduled (during dialysis) and then calculating the overlapping values by subtracting the amount of drug present in the measured dialysate samples. The dialysis flow rate was set to 800ml/min while the ultrafiltration rate was set to 4.1667ml/min. From the final squared errors of the candidate models, we chose to average the lowest 900 models.

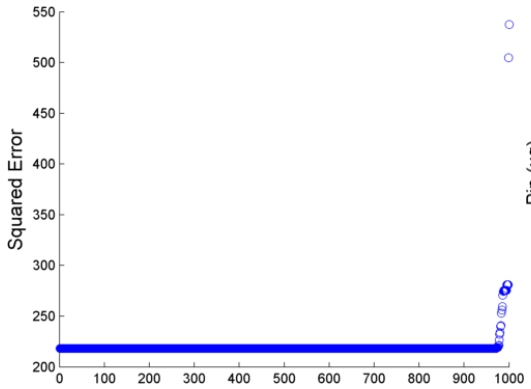
After the data was collected for the dialysis day samples, the patient received a 4 hour dialysis session. The patient then did not receive another dose for another 24 hours later. From these two facts, we assume that the patient had reached a drug concentration of zero. Therefore, we model the next set of doses leading up to the collection of the non-dialysis day data to reflect this assumption. These doses were also modeled as 12 hour infusions of 3.375g spread out over four hours. The non dialysis day data was collected the day following the start of this new set of infusions.



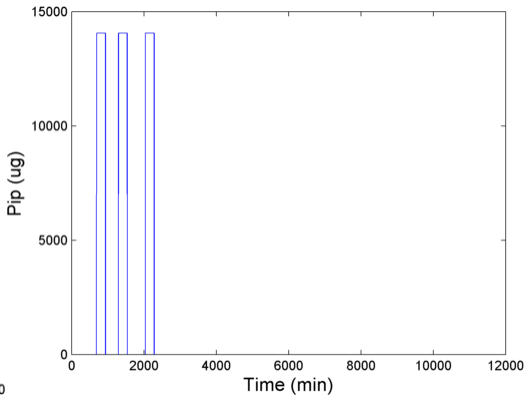
(a) Observed data from dialysis



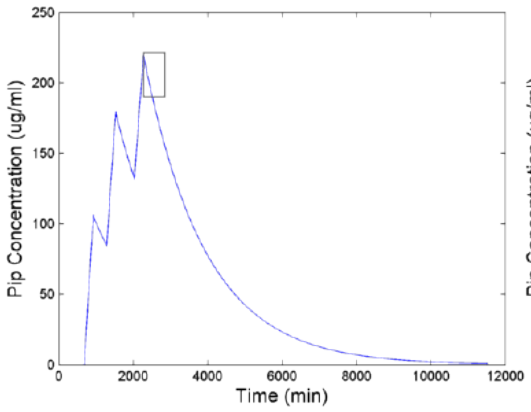
(b) Simulated dosing history leading to dialysis day



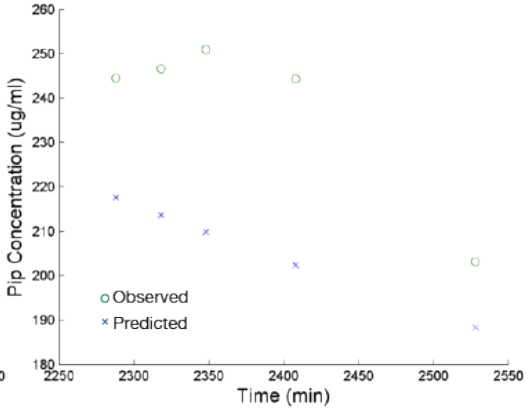
(c) Final errors of candidate models



(d) Simulated dosing history leading to off-day data



(e) Predicted drug levels



(f) Comparison with ground truth

Figure V.5: Results on piperacillin dataset for patient 3

Predicted	217.55	213.66	209.83	202.39	188.28
Measured	244.53	246.62	251.00	244.38	203.22
% Error	11.03	13.36	16.40	17.18	7.35

Table V.5: Comparison of predicted and measured values for non-dialysis day in the piperacillin dataset for patient 3

V.3 Discussion

Our results on the real clinical data suggest that our method of pharmacokinetic modeling has some potential. For patient 1, our method had its best performance by successfully predicting both drugs to less than 10% average error. Our method had less success for the other two patients, but still produced reasonable predictions of less than 20% average error. We further note that our models created predictions for drug levels that occurred **days** after the start of a dosing regimen; the predictions for patient 1 were three days in the future while the future predictions of patients 2 and 3 were five days and two days respectively.

Additionally, we note an interesting observation of final squared errors of our candidate models; for all of the datasets, a significant portion of the randomly generated models, when optimized using Nelder-Mead, converged to the exact same set of biological parameters. Such a result suggests that the error surface of biological parameters is not very "hilly". Furthermore, since so many of the points ended up in the same place, one could achieve faster performance by reducing the number of candidates to optimize. Nonetheless, our method was still reasonable in terms of computing resources; when searching with 1000 possible models, a MacBook Pro laptop was able to perform the computation in under five minutes.

In terms of the limitations of our approach, we have already noted some of the problems with the datasets of patients 2 and 3; patient 2 had a questionable data point while patient 3 had some ambiguity in the reporting of his dosing schedule. Thus, in the presence of truly "strange" data, we cannot expect very good predictions on the order of patient 1. However, it should also be noted that the off-day dialysis data for any of the datasets do

not follow a smooth trend in keeping with the expected behavior of a two-compartment model; measurement noise could be an obvious factor in this observation, but there also exists the possibility that there are unmodeled factors in the biology of the patient that cause deviations from a two-compartment pharmacokinetic behavior. Nevertheless, the quality of our predictions suggest the robustness of our approach and the strength of the two compartment model as an underlying assumption.

In moving forward, more datasets need to first be collected in order to better identify and describe this method's strengths and weaknesses. In particular, the question of the method's robustness across the wide variation in patients and drugs still need to be addressed. Furthermore, when answering that question, traditional pharmacokinetic experiments should be performed; due to the limited scope of our study, we were only able to collect samples for validation during a small 4 hour window corresponding to the non-dialysis day; it is difficult to know exactly what the patient's actual drug levels looked like outside of that window. Additionally, looking at drug and patient variability can lead to more informed choices in setting up the constraints for the model search space. Finally, a more rigorous understanding of the mapping between biological parameters and filter coefficients should take place; while our estimates of $\hat{H}(z)$ and $\hat{G}$ can be mapped back to **a** set of biological parameters, we are unsure if those are **the** correct set of biological parameters; the correct model that may be "close by" our estimate in the space of filter coefficients does not necessarily imply that it is "close by" our biological parameter estimate and vice versa.

CHAPTER VI

Conclusion

Correct antibiotic dosing is important in the prevention and treatment of sepsis for patients with AKI. While dialysis is also necessary in the treatment of AKI, its presence complicates effective dosing using strategies derived from lengthy "one-size-fits-all" phamacokinetic experiments. However, by interpreting the dialysis procedure as a "negative input signal" to a linear system, the methods of linear systems theory can provide insight into an individual's pharmacokinetics. While collecting lots of data can provide arbitrarily good approximations to this underlying model, we have shown that a few samples collected during the first **hour** of dialysis can be used with a linear systems representation of the two compartment model to potentially produce reasonable predictions of drug levels **days** in the future. The presence of such a procedure can enable physicians to no longer view dialysis as a hinderance to antibiotic dosing; rather, the data collected during dialysis can be seen as a helpful tool in tailoring antibiotic dosing schemes that are specific to individual patients.

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