Numerical Analysis of Drug Administration

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***Abstract*—Prescription dosages require the utmost precision, as a small difference could dramatically alter a body's response to the drug. Ventricular arrhythmia is a condition originating in the ventricles that causes a person to experience irregular heartbeats. A common medication for people who endure ventricular arrhythmia consists of lidocaine. This drug that can become toxic if overdosed, which could result in the patient suffering from a number of potentially lethal disorders. This toxicity is regulated by measuring how it has cleared through the body tissue and bloodstream. Using Ordinary Differential Equations (or $ODEs$), we model a function in which such variables are inputted, along with renal clearance rate, rate of drug exchange from tissue to the bloodstream, and rate of drug exchange from bloodstream to the tissue. We further conduct a test of the model by implementing data collected by Cushing [1] and analyze the results.**

I. Introduction

The relation between drug dosage and the concentration of drug already present in a human body is a subject of extreme importance. The dosage, dosage frequency, and drug concentration in a human body can produce both beneficial and harmful effects.

Spruill [2] defines pharmacokinetics as the study of how a drug behaves in the human body, specifically, how the human body processes the drug over a period of some time. The basic principles of pharmacokinetics are the rates of absorption, distribution, metabolism, and excretion.

Understanding the relationship between the rates of the basic principles is crucial for medical professionals, because they use that information to prescribe the drug dosage and dosage frequency to individual patients to obtain a desired therapeutic response.

Stanford Healthcare [3] describes ventricular arrhythmia as abnormal heartbeats that originate in the lower heart chambers, called ventricles. This type of arrhythmia causes the heart to beat too fast, which prevents oxygen-rich blood from circulating to the brain and body and may result in cardiac arrest.

According to Gianelly [4], the drug lidocaine (Xylocaine) has been one of the most used drugs in the treatment of ventricular arrhythmias since the 1960s. However, it is not without complications. There have been numerous case reports over the decades of intravenous lidocaine administration to patients, resulting in lidocaine toxicity due to incorrect concentration of drug, drug dosage, or drug frequency.

Brown [5] states that patients with lidocaine toxicity due to accidental overdose may experience respiratory depression, seizures, coma, and cardiac arrest. Close attention needs to be given to the individual patient before administering lidocaine to deter accidental lidocaine overdose.

Using mathematical models and numerical analysis as predictive tools for drug administration to individual patients can decrease incidents of lidocaine toxicity due to accidental overdose. Mathematical models, such as compartment models, are widely used in pharmacokinetics as a mathematical representation of a biological system or its parts. Therefore, they play a critical role in pharmaceutical research and development.

II. Modeling

The problem at hand is of great importance in Pharmacokinetics experiments and studies. A popular method of modeling drug administration that is used by many researchers is employment of *compartment models*.

A compartment method of modeling is used to represent a flow of well mixed materials from one component to another. Blomhøj et al. [6] denote applications and strengths of this method in practice. For instance, a compartment model can be used to model an ecological system or to model the flow of mixtures in and out of a tank.

In this paper, we are interested in using a compartment model to generate a representation of the drug administration process. Cushing [1] describes the process of deriving a two-compartment model that can be used for drug administration purposes.

We shall start by establishing an overall sketch of the model of drug kinetics in a body. A drug is usually injected into the bloodstream to transmit the drug to and out of body tissues. This process can be represented as a function that maps the time elapsed from injection and dosage of the drug to the amount of drug in each component, body tissue and bloodstream.

The variables of such a model are:

- $x =$ amount of drug in bloodstream,
- $y =$ amount of drug in body tissue,
- $r_1 =$ rate of renal clearance,
- $r_2 =$ rate of drug exchange from a tissue to bloodstream,
- $r_3 =$ rate of drug exchange from bloodstream to tissue.

Figure 1 gives an outlook of the proposed method.

Given this representation of the model, we can establish the following equations:

1) Let x represent the amount of drug in the bloodstream at time t. Thus, x' is equal to the amount of drug transmitted

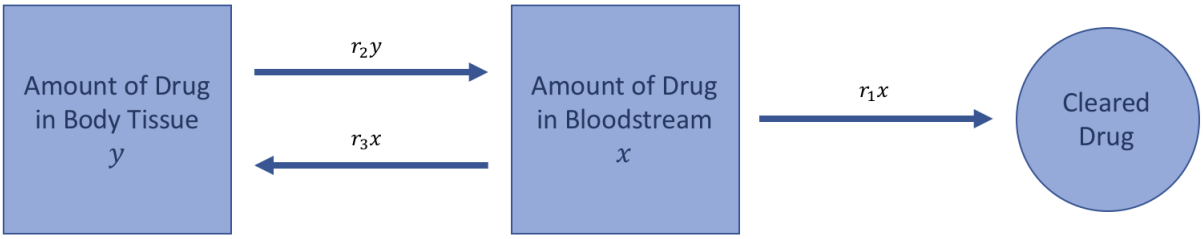

Fig. 1. Overall representation of the two-comportment model used to model drug administration.

into the bloodstream subtracted from the amount of drug transmitted out of the bloodstream. If we assume that no additional drug enters the body at time t, then the only source of drug transmission into the bloodstream is the body tissue. Additionally, the drug is transmitted out in two forms: renal clearance, and transmission from bloodstream to body tissue. Therefore,

$$x' = r_2y - (r_1 + r_3)x.$$

2) Similarly, let y represent the amount of drug in the body tissue at time t. Hence, y' is equal to the amount of drug flowing into the body tissue subtracted from the amount flowing out of the tissue. Therefore,

$$y' = r_3x - r_2y.$$

Differential equations (1) and (2) form a system of *ODEs*. We can solve this system using the initial conditions $x(0) = 0$ and $y(0) = y_0$. These conditions are true, considering that the amount of drug in the bloodstream is initially zero, and the amount of drug in the body tissue is equivalent to that of the dose administered.

III. Solutions of the System of Equations

In the previous section, a two-compartment model was developed to simulate the drug administration process using a system of differential equations. In this section, we want to develop a method of solving this system numerically. Solving the proposed system of $ODEs$ for the exact solution is relatively difficult and is beyond the scope of this paper. There are different methods of solving systems of differential equations numerically, such as Forward Euler for Systems. However, the nature of the problem demands maximal accuracy in a minimal time window. Thus, not every approximation method is suitable for this problem. One of the methods of numerically approximating solutions of a system of differential equations is *Runge-Kutta Method of Order 4 for systems*. This method has a global error of $\mathcal{O}(h^4)$. Therefore, it is suitable for real-time approximation of drug dosage requirements within a reasonable range of accuracy. Next, we provide the pseudocode of this method.

IV. Runge-Kutta Method of Order 4 for systems

Runge-Kutta Method (Order Four) Pseudocode
Input: Endpoints a, b; integer N; initial condition α.
Output: Approximation w to y at the $N+1$ values of t.

1) Set $h = (b-a)/N$;
$t_1 = a$;
$w_{\cdot,1} = \alpha$;
2) For $i = 2, 3, \ldots, N+1$ *do STEPS 3-4.*
3) Set $K_1 = hf(t_{i-1}, w_{\cdot,i-1})$;
$K_2 = hf(t_{i-1} + \frac{h}{2}, w_{\cdot,i-1} + \frac{K_1}{2})$;
$K_3 = hf(t_{i-1} + \frac{h}{2}, w_{\cdot,i-1} + \frac{K_2}{2})$;
$K_4 = hf(t_{i-1} + h, w_{\cdot,i-1} + K_3)$;
4) Set $w_{\cdot,i} = w_{\cdot,i-1} + (K_1 + 2K_2 + 2K_3 + K_4)/6$;
$t_i = a + (i-1)h$;
5) OUTPUT $(t,\ w)$; *STOP.*

V. Practical Analysis of the Model

In this section, we shall analyze the proposed system using real world values for variables and determine the performance of the system. First, we need to determine the values of the constants used in the model. These values are based on Cushing's [1] work.

- Rate of renal clearance is determined by analyzing timed urine samples. The analysis of renal clearance demands derivation of a new model which is beyond the scope of this paper. Therefore, we assume that the rate of renal clearance is constant and is known to be:

$$r_1 = 2.40 \times 10^{-2}\ (per\ minute).$$

- Rate of drug exchange from a tissue to bloodstream and vice versa is a function of multiple variables such as vascular permeability, regional blood flow, cardiac output and perfusion rate. Again, we assume that these values are relatively constant through the process of the lidocaine adminstration. In this example,

$$r_2 = 3.80 \times 10^{-2}\ (per\ minute),$$

$$r_3 = 6.60 \times 10^{-2}\ (per\ minute).$$

Now if we substitute these constants into the two-compartment model developed in Section II, we will get the following initial value problem:

$$x' = -0.09x + 0.038y,$$
$$y' = 0.066x - 0.038y,$$
$$x(0) = 0,\ y(0) = y_0,$$

where y_0 is the dosage of the injected drug at a given time.

This can be transformed into the matrix vector system

$$Y'(t) = f(t, Y(t)),$$

where

$$Y(t) = \begin{bmatrix} x(t) \\ y(t) \end{bmatrix}, \qquad f(t, Y(t)) = \begin{bmatrix} -0.09x + 0.038y \\ 0.066x - 0.038y \end{bmatrix},$$

with initial conditions vector

$$Y_0 = \begin{bmatrix} 0 \\ y_0 \end{bmatrix}.$$

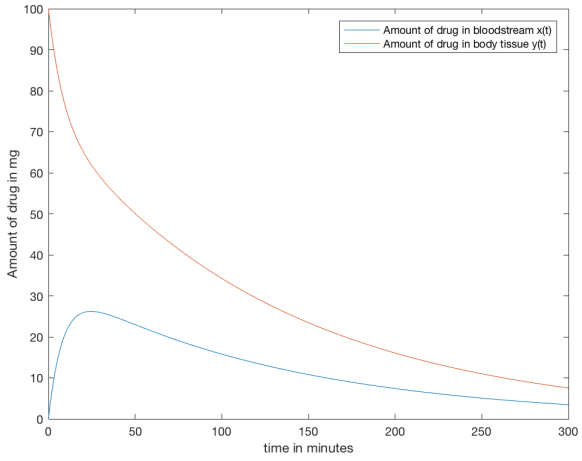

Fig. 2. Change in the amount of lidocaine from t = 0 to 300 min when a dose of 100 mg is administered.

We developed a function in *MATLAB* using *Runge-Kutta Method of Order 4 for systems* that was mentioned in Section IV. The function inputs values r_1, r_2, r_3, the amount of drug injected, y_0, the time interval of interest, (t_0, t_k), and the number of sub-intervals, N. Then it outputs two vectors. One vector represents the value t_i which is the time elapsed up to that point. The other vector is a two dimensional vector that represents the amount of drug in the bloodstream, x, and the amount of drug in the body tissue, y, for each time step. This data can be used by drug administrators to simulate the administration process and determine the effective amount of the drug.

For lidocaine, Cushing's [1] denotes that a dose is considered effective if the concentration of the drug in the bloodstream is above 1.5 $mg/liter$. However, any concentration above 6.0 $mg/liter$ can cause severe side effects and, in some cases, can be lethal. A human being with a body mass of 70 kg, on average, has 5 $liters$ of blood. Thus, the effective dose for such a person is between 7.5 mg and 30 mg. Figure 2 shows the concentration of the drug in the bloodstream and body tissues from $t = 0$ to 300 minutes. In this case we assumed that the injected dose is 100 mg. We can see that the concentration of the drug in the bloodstream never exceeds the lethal level.

VI. Conclusions

Determining the correct amount of dosage is essential in every prescription, but those that include potentially lethal doses require absolute detail. In the case of ventricular arrhythmia, the condition's most commonly-administered treatment lidocaine, can pose dangerous consequences to those who are prescribed over their capacity. Therefore, pharmacists require an accurate representation of the amount of lidocaine in the bloodstream at time t, as well the amount of the drug in the body tissue at time t. We obtained these by using other variables: drug amount in the bloodstream, drug amount in the body tissue, renal clearance rate, rate of drug clearance from the tissue to the bloodstream, and rate of drug clearance from the bloodstream to the tissue. Differential equations (1) and (2) provide a depiction of how this drug is processed throughout the body.

We implemented a model of the $ODEs$ into $MATLAB$, utilizing the *Runge-Kutta Method of Order 4 for systems*. This provided high accuracy for the estimation, as it possessed a global error of $\mathcal{O}(h^4)$. To test such accuracy, we measured the model by implementing the known values obtained from Cushing's [1] work. Using a starting dosage of 100 mg, we determined that the average individual would require a dosage between 7.5 and 30 mg. Throughout the time in which t was between 0 and 300 minutes, the drug concentration in both the body tissue and bloodstream dramatically decreased, as depicted in Figure 2. Since the results are below that of lethal dosage, our model effectively determines the correct estimate of how much lidocaine to administer to a patient.

Future developments of lidocaine dosage models might want to look into some areas that potentially hindered our analysis. For instance, we assumed that the rate of renal clearance and rates of drug exchange remained constant throughout the entirety of drug administration. This does not account for possible factors that could influence these rates, such as dialysis or blood transfusions. Rather than analyzing constants, future researchers might want to study how a range of values for r_1, r_2, and r_3 could impact x' and y'. Another potential area that could be further explored is human body mass and amount of blood. We analyzed using the average amount, with 70 kg and 5 $liters$. Individuals who are less or more than these amounts might have a different range of how long the drug is in their bloodstream and body tissue, in turn affecting their amount of dosage. Hence, further research ought to analyze the impact on individuals who diverge from the average.

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