Lab - 2

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In this lab, we numerically and analytically analyze the drug dosage problem through different compartment models. We will try to determine the effective and correct dosages for various drugs. It is dependent on factors, such as drug absorption, distribution, metabolism, and elimination. Therefore we need to study different compartment models, such as one-compartment and multiple-compartment models to ensure safe drug consumption (neither an overdose nor an underdose).

I. INTRODUCTION

Every drug has both **minimum effective concentration (MEC)**, which is the least amount of drug that is helpful and **minimum toxic concentration (MTC)**, which is the largest amount that is helpful without having dangerous or intolerable side effects. Therefore, drug concentration range lies between MEC and MTC, which is also called **Therapeutic Range**.
In order to ensure safe intake of drug, so that drug concentration lies in the Therapeutic range, we will study different models. Absorption depends on the absorption factor of the drug, while elimination depends on the amount of drug present in the system.

II. MODEL

Here, we will briefly discuss the following models:

- one-compartment model of single dosage
- one-compartment model of multiple doses
- multiple-compartment model of single dosage
- multiple-compartment model of multiple doses

A. One Compartment Model

In this model, the whole body is reffered to as a single system (assumed as a homogenous compartment). This avoids complexity of the problem and is easy to evaluate. We know that, the concentration of the drug is proportional to the drug dosage and the rate of elimination depends on the amount of drug in the system at that instant.
Let the amount of drug in plasma be Q(in μ g). The elimination of the drug is proportional to the drug present, therefore, we can write:

$$\frac{dQ}{dt} = -KQ$$

where:

- $\frac{dQ}{dt}$ denotes elimination rate.
- The negative sign signifies elimination.
- K is the proportional constant.

By solving the above equation, we get:

$$Q = Q_0.e^{-Kt} - (1)$$

where Q_0 denote initial concentration of drug in plasma. To evaluate K (elimination constant), we use the concept of half-life.
In the above equation, by taking $Q = Q_0/2$ and $t = t_{\frac{1}{2}}$, we get:

$$\frac{Q_0}{2} = Q_0 \cdot e^{-kt_{\frac{1}{2}}}$$

$$\ln(\frac{1}{2}) = -Kt_{\frac{1}{2}}$$

$$K = \frac{\ln(2)}{t_{\frac{1}{2}}} = -\frac{0.5}{t_{\frac{1}{2}}} - (2)$$

B. Two Compartment Model

As the model is extended, it is moved to the two compartment model, where the drug is not immediately absorbed. The first compartment is assumed to be the digestive track, and the second compartment is the blood stream. Drug is absorbed from the second compartment, and eliminated from the first compartment, at a rate proportional to the drug concentration in compartment 1. The total drug concentration in the system equals the concentration in compartment 2. The rate of drug elimination from compartment 2 is the rate at which the drug is eliminated from the body.
Hence,

$$\frac{dQ_1}{dt} = -k_1Q_1$$

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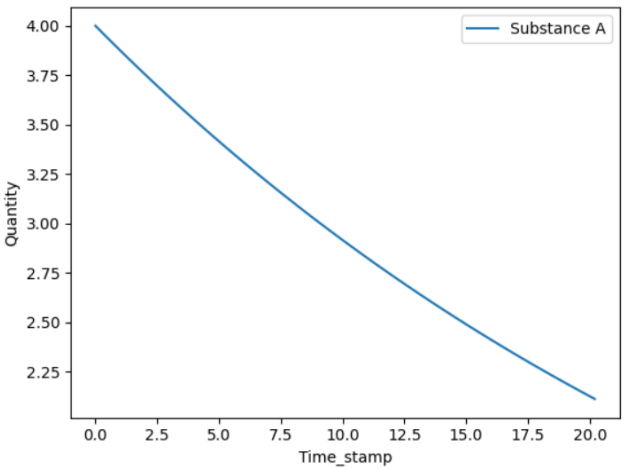

FIG. 1: Elimination Constants with the help of half lives

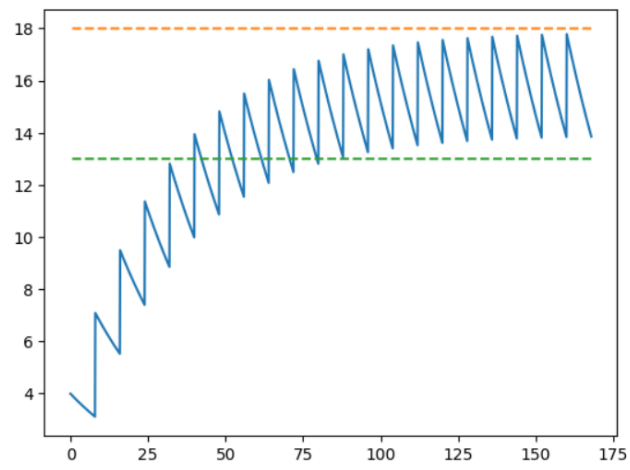

FIG. 2: Dilantin Concentration in the body as time progresses

$$\frac{dQ_2}{dt} = k_1 Q_1 - k_2 Q_2$$

where k_1 and k_2 are elimination constants of Compartment1 and Compartment2 respectively and Q_1 and Q_2 are the drug concentration in Compartment1 and Compartment2.

III. RESULTS

A. One-Compartment Model of single dosage

Think about a case where a patient uses the one-compartment model and takes a single dose of Dilantin. It is understood that Eq 2 can be used to find the constant linked to elimination. Figure 1 presents a graphic representation of these constants.

The image shows a clear pattern: as the drug's half-life lengthens, the elimination constant consistently shortens. As a result, when medicine has a longer half-life, its effects last for a longer period of time in the body.

In cases where the administered dosage is substantial, the drug concentration can surpass the Minimum Toxic Concentration (MTC). However, given the single-dose administration, the drug's effects are confined to a specific time frame, extending only until a designated point in time after which the concentration descends below the Minimum Effective Concentration (MEC)

B. One compartment Model of Multiple Doses

Dilantin is a drug that requires multiple doses to be administered at regular intervals. The one compartment model will be used to conceptualize the situation. Similar to the previous one compartment model, we will hypothesize that the drug will be absorbed immediately. The Dilantin example shows that a 100mg dose of the drug should be taken every 8 hours, with the postulated absorption fraction being 12% (0.12).

In order to illustrate the cycle of drug supply, the influx is represented as a repeating sequence of pulses. At any point in time, the amount of efflux from a drug reservoir in the system (known as Q_0) is proportional to the amount of drug present at that point in time.

We notice that the outflow of the drug is mentioned via Eq. 1, which will be indirectly used to calculate the amount of drug in the system. In the context of Dilantin, empirical observations indicate that its half-life ranges from 7 to 42 hours. We have adopted a half-life assumption of 22 hours. Furthermore, the average volume of blood serum is approximated as 3000mL. Armed with these particulars, the outcomes of the model are depicted in Figure 2.

A scenario is considered where deviations arise in terms of both prescribed dosage and frequency, leading to an analysis of the resultant drug concentration within the system. Our focus centers on the behavior of Dilantin within the human body, contrasting two distinct scenarios: one which sees the daily administration of 300mg dosage and the other entailing a dosage of 100mg every 8 hours. Essential thresholds within this context include the Minimum Effective Concentration (MEC), set at 10μg/mL, and the Minimum Toxic Concentration (MTC), established at 20μg/mL.

Fig 2 illustrates that the drug concentration in the system fluctuates frequently and exceeds the maximum systemic concentration (MTC) for the 300mg daily dosage pattern. This dosage pattern can be highly detrimental to the patient and is therefore not recommended.

As you can see above, the concentration of the drug in the system converges to a steady state after a

certain time interval. Let's look at the mathematical equation to find the drug's concentration in the system following the n$^{\text{th}}$ dose, assuming the absorption fraction is 0.09 and the dose is 300mg.
The effective dosage is:

$$Q_1 = (0.09)(300)mg = 27mg$$

The elimination constant, for the given half-life of 22 hrs:

$$K = \frac{\ln 2}{22} = 0.0315hr^{-1}$$

After an interval of 8 hours, drug conc. in the system will be:

$$Q = Q_1 \cdot e^{-0.0315\times 8} = (27)(0.7772) \approx 9.326mg$$

At the end of 8 hrs interval, 77.72% of the drug stays in the system. After the administering of the second dose, the total Dilantin amount will be:

$$Q_2 = pQ_1 + Q_1$$

Here, $p_0 = 0.7772$ (% of the drug remained in the system) pQ_0 is the drug left from the first dose and Q_0 is the drug injected during second dose. Similarly, we sind concentration of Dilantin after the third dose as:

$$Q_3 = pQ_2 + Q_1$$

From the above two equations, we get:

$$Q_3 = (p^2 + p + 1)Q_1$$

To generalize, the amount of Dilantin, immediately after n^{th} dose can be represented by:

$$Q_n = Q_1(1 + p + ... + p^{n-2} + p^{n-1})$$

It can be further simplified as:

$$Q_n = Q_1\frac{1-p^n}{1-p}$$

Substituting the values, we get:

$$Q_4 = (0.09)(300)\frac{1-(0.7772)^4}{1-0.7772} = 76.97mg$$

Since, the long-term value of the quantity of Dilantin in the system immediately before the nth dose $Q_{n1} \times p$
Quantity of Delantin immediately before the 5^{th} dose

$$= Q_4 \times p = 59.82mg$$

C. Two Compartment Model for Multiple Doses

On occasions, medical practitioners may opt to administer a patient a loading dose—a preliminary dosage that markedly exceeds the subsequent maintenance dose, which helps in promptly elevating the concentration of Dilantin within the system. Specifically, for Dilantin, a loading dose comprises usually of three administrations: 400 mg, 300 mg, and 300 mg, all spaced 2 hours apart. Following the loading dose regimen, the routine dosage schedule commences, which involves administering 100mg every 8 hours. It is assumed that other pertinent variables, such as absorption rate, blood volume, and Dilantin half-life, remain consistent with the factors previously discussed.

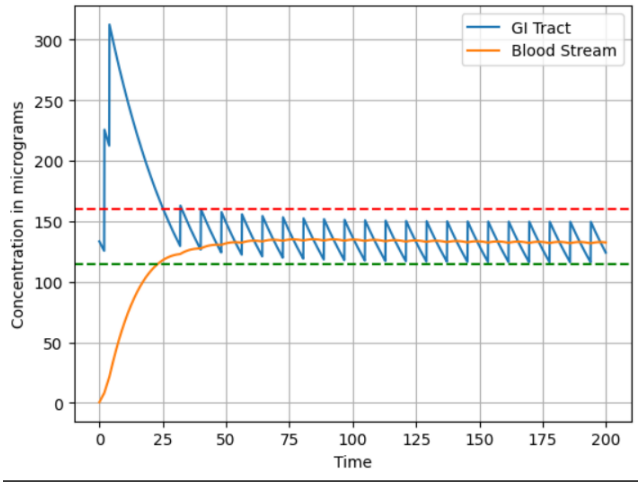

FIG. 3: Initial spike due to the Dilantin and how the concentration varies in time after the spike

Illustrated in Figure 3 is a graphical representation of the initial loading prescription. Notably, upon analysis, it becomes apparent that the concentration of Dilantin initially surpasses the Minimum Toxic Concentration (MTC) threshold. However, following the first six doses, the concentration levels gradually settle within the therapeutic range. This observation underscores the effectiveness of the loading dose in swiftly achieving medicinal levels of Dilantin within the system.

Therefore, when comparing the single dose Dilantin to multiple dose Dilantin, the results indicate that multiple doses are more effective as this distinction is evident from the graph, that Dilantin remains in the suitable range throughout the multiple-dose process, whereas single dosage Dilantin drops below the MEC (Minimum Effective Concentration) level after a specific point and thus becomes ineffective.

The instance involves a male patient weighing 90kg. Given that around 65-70% of body weight is liquid, this equates to approximately 60.75 kg of liquid weight or 60.75L of liquid volume. With the Minimum Effective Concentration (MEC) for aspirin established at 150μg/mL, the necessary aspirin quantity is calculated to be 9,112.5mg.

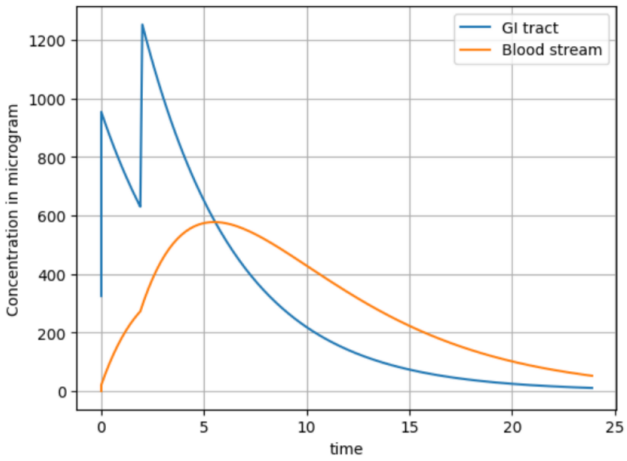

FIG. 4: Two Compartment Model (Aspirin): 3 tables initially and 2 tablets after 2 hrs

The above graph shows a two-compartment model for Aspirin when someone with a headache takes three aspirin tablets and 2hr later takes two more aspirin tablets. An increase in compartment 1 first occurs, which then causes compartment 2's blood drug concentration to rise. As a result, the blood's aspirin content peaks in the first two hours. The drug concentration in compartment 2 begins to rise once more with the appearance of the second peak in compartment 1, and the curve achieves even higher maxima. We notice a sudden change in the bloodstream which is because that is when the 2^{nd} dosage momentarily increases the concentration of the drug.

This also demonstrates that the two-compartment model provides a far better assessment of the drug absorption phenomena since it simulates drug concentration variations as continuous variations rather than the sharp pulses found in the one-compartment model.

D. Two compartment Model of Single Dosage

Let's understand the model by Aspirin. Its half-life is 3.2 hours. The drug is absorbed by the second compartment and eliminated by the first compartment at a rate equal to 0.216 and eliminated by the second compartment at a rate of 0.216. The total amount of Aspirin in the system is equal to the concentration of Aspirin in compartment 2.

Initially we have no drugs being absorbed into the bloodstream, hence we notice that the concentration is 0 for the bloodstream and maximum for the GI Tract. Predictably, as time passes the drugs get absorbed into the bloodstream hence we see an exponential decrease in the graph of the GI Tract. During this phase, the drug concentration in the bloodstream rises as absorption takes place. The graph shows an increasing curve during this phase. As the drug is absorbed into the bloodstream, it starts to distribute throughout the body, At this point, the drug concentration in the central compartment (bloodstream) is higher than in the peripheral compartment (GI tract). Once the drug is distributed throughout the body, the elimination or decay processes start to take effect. The drug is metabolized and/or excreted from the body, leading to a decrease in its concentration over time. Therefore, the graph shows a decreasing curve during this phase.

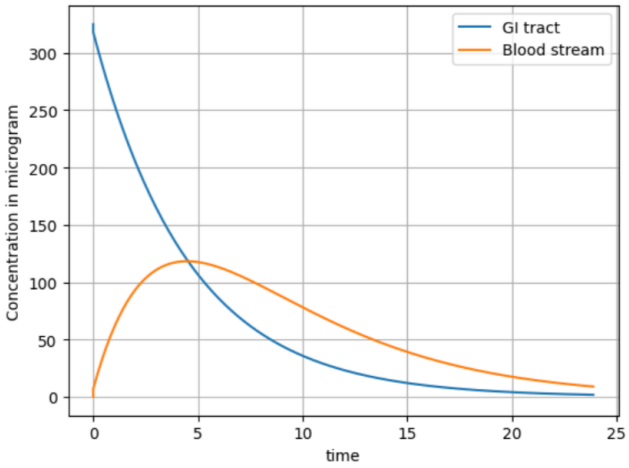

FIG. 5: Changes in concentration using single Dosage of Aspirin

IV. CONCLUSIONS

We discussed the mathematical model of drug dosage in living systems, in much detail. First, we studied that concentration in our body follows an exponential decay curve and that the rate of elimination is proportional to the half-life of the drug. Then, we discussed the frequency at which the drug is administered. Then, we discussed the two-compartment model for a more in-depth understanding of drug absorption in the system. We dealt with a concerning issue and created models in order to prevent life-threatening errors in medication.