Lab - 2: Compartment Models

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MC312, Modeling and Simulation

In this lab, we will attempt to model the problem of drug dosage in the human body. We will model and analyze the one-compartment and two-compartment models of the drug Dilantin and Aspirin.

I. INTRODUCTION

In the previous lab, we tried to model and analyze the radioactive decay problem using a single-compartment model. Here we will introduce the dynamic problem of drug dosage and try to analyze the one-compartment and two-compartment models of the problem. We will make some simplifying assumptions regarding the drugs and the body as we attempt to model the problem.

II. MODEL

We might have observed that the doctors prescribed us medicines to be taken at certain intervals for several days. Under this report, we will generate the One-Compartment Model of Repeated Doses for the drug Dilantin, which is used for the treatment of epilepsy. Further, we will extend our knowledge to the two-compartment model, where we will analyse different cases of Drug Dosage and try to make useful conclusions from it. We will assume that the internal interactions within any compartment are largely absent. Further, we will make certain assumptions to model our problem which are stated in their respective sections.

A. One-Compartment Model

In this model, we consider the body to be one homogeneous compartment in which the distribution of the drugs is instantaneous. We define the concentration of the drug in the system as the amount of drug divided by the volume of the blood or plasma, instead of using the amount of drug injected into the body as a quantity as a certain amount might be appropriate for a small child could be ineffective for a large adult. The concentration of the drug is proportional to the drug dosage and the elimination constant is proportional to the amount of drug in the body.
Let Q be the concentration of the drug in the blood, as per the above-mentioned assumptions we have the rate of change of drug leaving the system proportional to the quantity of drug present in the system.

$$\frac{dQ}{dt} \propto Q$$

$$\frac{dQ}{dt} = -kQ \tag{1}$$

Applying Laplace's transforming equation 1 we get,

$$sQ(s) - Q(0) = -kQ(s)$$

where Q(0) is the initial concentration of and s is the frequency parameter, solving for $Q(s)$:

$$Q(s) = \frac{Q(0)}{s+k}$$

Next, let's perform the inverse Laplace transform to get back to the time domain:

$$q(t) = \mathcal{L}^{-1}\{Q(s)\} = \mathcal{L}^{-1}\left\{\frac{Q(0)}{s+k}\right\}$$

We already know the inverse Laplace transform of the above equation. So, the solution in the time domain is:

$$Q(t) = Q(0)\, e^{-kt} \tag{2}$$

Let us now solve for k. Half-life $t_{\frac{1}{2}}$ of Delatin is given to us. When $t = t_{1/2}$, the quantity $Q(t_{1/2})$ is halved compared to $Q(0)$:

$$Q(t_{1/2}) = \frac{1}{2} \cdot Q(0) = Q(0) \cdot \frac{1}{2}$$

Substitute into the equation:

$$Q(0) \cdot \frac{1}{2} = Q(0) \cdot e^{-kt_{1/2}}$$

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

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Taking the natural logarithm of both sides:

$$\ln\left(\frac{1}{2}\right) = -kt_{1/2}$$

$$-\ln(2) = -kt_{1/2}$$

$$k = -\frac{\ln(2)}{t_{1/2}}$$

Since, $\ln(0.5) = -\ln(2)$:

$$k = -\frac{\ln(0.5)}{t_{1/2}} \tag{3}$$

Therefore, the elimination constant given by k can be obtained as above.

B. Two-Compartment Model

The first compartment indicates the digestive system (GI tract) and the second compartment is the blood serum/plasma. Since the rate of change of absorption from the GI tract to plasma is proportional to the amount of drug in the GI tract, we can write the mathematical model as,

$$\frac{dX}{dt} = I(t) - kX \tag{4}$$

where X is the amount of drug in GI tract and $I(t)$ is the dosage of the drug as a function of time. Similarly, for the second compartment, the absorption amount of plasma is proportional to the amount of drug in GI tract and the desorption amount of drug in plasma is proportional to the amount of drug in plasma, hence we can say

$$\frac{dY}{dt} = k_1 X - k_2 Y \tag{5}$$

For the sake of simplicity in implementing the model numerically, we assume $k_1 = k_2$ and plot the concentration of the drug in both compartments against time.

III. RESULTS

A. One-Compartment Model For Dilantin

Considering dilantine half-life = 22 h, Dosage = $100 * 1000\mu g$, if the patient takes each dosage of (100 mg) every 8 hours, and assumes that the human body only absorbs 12% of the dosage the concentration of the drug in plasma can be given as figure below. (Here the **MEC (Minimum Effective Concentration** is the smallest amount of drug that is effective and **MTC (Minimum Toxic Concentration)** is the largest amount of drug that is effective without having any dangerous side effect).

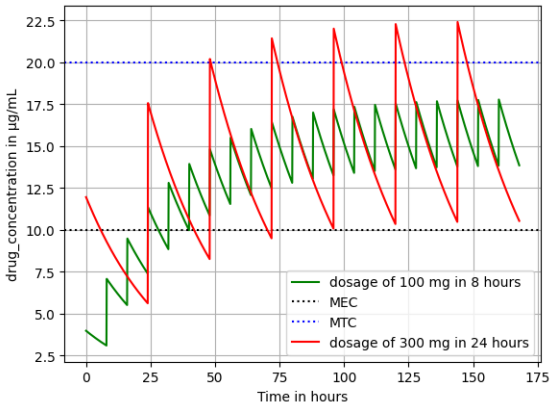

FIG. 1. Change in Dilantin concentration in the human body with repeated doses

For Delantin the $MEC = 10\mu g/mL$ and $MTC = 20\mu g/mL$. The following figure gives us the Delantin concentration in the body given the above-mentioned dosage and half-life. Clearly, from Fig. 1 we can infer that a dosage of 300mg of Delatin every 24 hours will make the concentration of Delatin in the blood above the **MTC**. Therefore, this dosage will not be beneficial.

We can infer from Fig. 1 that given the **MEC** and **MTC** for the body, we can adjust the drug dosage and the time interval of the drug so that the drug concentration remains within the **MEC** and **MTC** as in Fig. 1

We will now find out the concentration of the drug in the system, exactly after administering the n^{th} dose. From Eq. 3, and substituting the half-life for Delatin. we get $k = -0.0315hr^{-1}$. Assuming the absorption fraction as 0.12 and dosage of $100mg$. The effective dosage can be calculated as $Q_1 = 0.12\,100mg = 12mg$. From Eq. 2, we can calculate the amount after the first dose, i.e. after an interval of $8hrs$ as

$$Q = Q_1\, e^{-0.0315\cdot 8} = 12\,0.7772 = 9.3264mg$$

. From this, we can infer that approximately a 0.7772 fraction of Delatin remains in the system after a single dose. Let us denote this fraction as p. Now, after administering the second dose the total amount of delatin in the system becomes

$$Q_2 = p\,Q_1 + Q_1 \tag{6}$$

Similarly, immediately after the third dose it becomes

$$Q_3 = p\,Q_2 + Q_1$$

, Using Eq. 6 recursively we get, the following geometric series

$$Q_n = Q_1\,(1 + p + ... + p^{n-2} + p^{n-1}) \tag{7}$$

Using the summation of geometric series, the above Eq. 7 can be easily written as

$$Q_n = Q_1 \frac{1-p^n}{1-p} \tag{8}$$

Substituting the values of $p = 0.7772$ and $Q_1 = 12mg$ in Eq. 8, we get

$$Q_4 = 12 \cdot \frac{1-(0.7772)^4}{1-0.7772} = 2.85mg$$

. Therefore after the 4^{th} dose the concentration of the drug in the system will be $2.85mg$

B. Two-Compartment Model For Aspirin

In the example of Aspirin with a single dosage for the two-compartment model. Considering aspirin half-life = 3.2 hour, dosage = 325 mg. Assuming that the elimination constant for both compartments is the same as k. MEC occurs for Aspirin at 150-300 $\mu g/mL$ whereas MTC occurs at 350 $\mu g/mL$.
Fig. 2 shows the representation of a two-compartment model for aspirin.

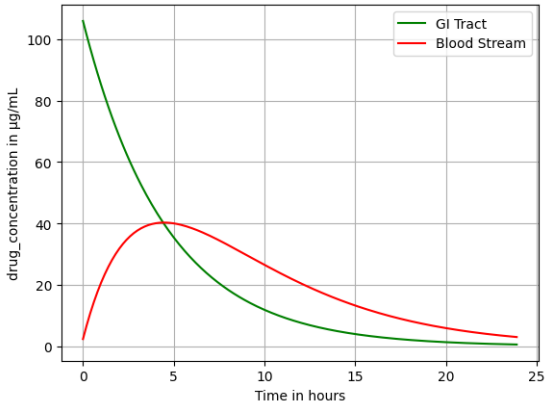

FIG. 2. Single dosage of Aspirin(325 mg) with two-compartment model

In this model after the single dosage, drug concentration decreases exponentially in compartment1, whereas compartment2 attains a maximum and then decreases.

Now consider the case of Two-compartment model with repeated dosage.

a) Someone took 3 aspirin tablets and after 2 hours takes two more tablets, Therefore the concentration spikes up after 2 hours. As the concentration of the drug increases in the GI Tract, the concentration in Bloodstream attains a maximum value and then decreases.

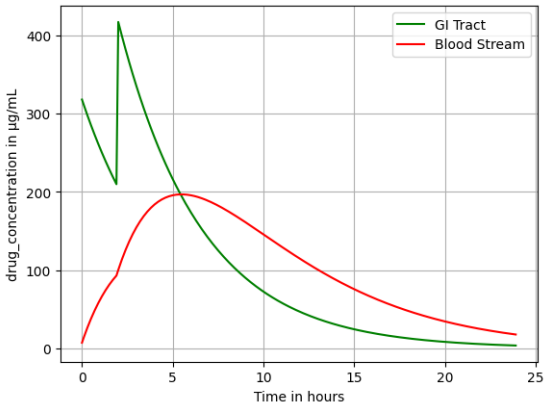

FIG. 3. Person took 3 Aspirin tablets and after 2 hours took two tablets

b) Two-compartment model with the loading dose of Dilantin. Dosages of 400 mg, 300 mg and 200 mg were given at every 2 hours, after the loading dose, 100 mg of normal dose with 8 hours interval begins. Assuming all other variables same as above and absorption rate = 1, Fig 4 shows the model for the given scenario.

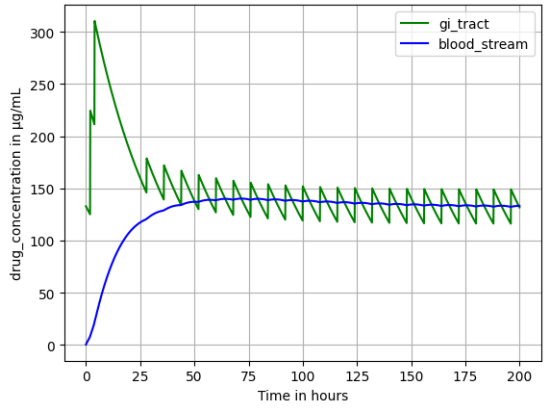

FIG. 4. Loading dose 400 mg, 300 mg, 200 mg every 2 hours, and after 24 hours 100 mg with 8 hours

Loading dose helps to increase the drug concentration in the system immediately, then during the next 24 hours, it decreases significantly, and then after a few normal doses it falls in the therapeutic range.

IV. CONCLUSIONS

In conclusion, we have studied the modeling of the drug dosage problem in a biological system. We can conclude from our analytical results and empirical observations that the drug concentration decays at an exponential rate and that the rate of elimination is proportional to the half-life of the drug. We also analyzed different scenarios where changing the amount of dosage and the frequency of each dose can help in

keeping the drug concentration within toxicity levels.

Lab 2 - Google Colab link :

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[1] A. Shiflet and G. Shiflet, *Introduction to Computational Science: Modeling an Simulation for the Sciences*, Princeton University Press.3, 276 (2006).