Lab - 2

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CS-302, Modeling and Simulation

In this lab we numerically and analytically analyze metabolism of drug in human body. We will use one compartment and two compartment models for our purpose. We will consider case of single dosage and multiple dosage of drug.

INTRODUCTION

Metabolism of a drug in the human body is a complex system to represent in a model. One-compartment model is a simplified representation of how a body processes a drug.In one compartment model, we assume whole body acts like a single compartment. One compartment model is appropriate for an injection of a drug into the system. In the two compartment model, the first compartment represents the digestive system, stomach or intestine. Whereas the second compartment represents blood, plasma, serum or a particular organ. This model is more appropriate for pills as they first enter the body through the digestive system, stomach or intestine and then get distributed in blood, plasma, serum or a particular organ.

One Compartment Model

MODEL

In this model, we consider the body to be one homogeneous compartment, where distribution is instantaneous, the concentration of the drug in the system is proportional to the drug dosage, and the rate of elimination is proportional to the amount of drug in the system. So the equation assuming one compartment model with the aspirin immediately available in the plasma be,

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

Here, k is elimination constant, which is related to Half-life of a drug (t_h) with equation $k = \frac{ln(2)}{t_h}$.

SINGLE DOSE

In this case, only a initial dosage of drug is given. Only a fraction of the drug given gets absorbed by the system (absorption fraction) and dividing that fraction with volume of system, we get Q_0 which is increase in concentration of drug in the system.

$$Q(t) = Q_0 e^{-kt} \tag{2}$$

A typical model of plasma concentration is as follows, half life of aspirin is 3.2 hours, plasma volume is taken as 3000 mL and at time t = 0 aspirin concentration in plasma is taken as 650 g the plasma concentration is taken as the ratio of aspirin in plasma to plasma volume. Figure (1) shows this situation.

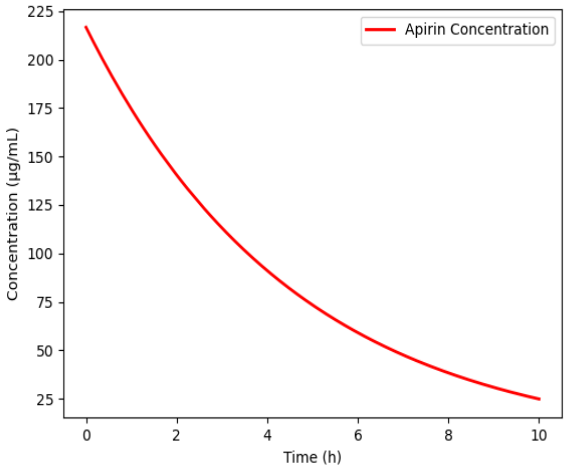

FIG. 1: Concentration of Aspirin v/s Time for $Q_0 = 216.67$ µg/mL.

The least amount of drug that is helpful is called minimum effective concentration (MEC) and the maximum amount of drug that is helpful without having adverse side-effects is called minimum toxic concentration (MTC). The therapeutic range for a drug consists of concentrations between the MEC and MTC. Dosage of drug should be such that initially the concentration doesn't go above MTC. Also, after time $t = \frac{1}{k} ln\left(\frac{Q_0}{MEC}\right)$, drug will become ineffective as its concentration will drop below MEC.

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MULTIPLE DOSE

We model the concentration in the body of the drug dilantin, a treatment for epilepsy that the patient takes on a regular basis. For simplicity, we assume a one-compartment model with instantaneous absorption. We employ a pulse function with a number of variables such as start time of the initial dose, dosage amount, intervals between the dosages(t_k) presuming that only a fraction of actually enters into the system. Lets suppose after time t_k, we give dosage such that concentration increases by amount of Q_0, then we can formulate following recurrence relation,

$$Q_{i+1} = Q_i(1 + e^{-kt_k}) \tag{3}$$

From recurrence relation in equation (3), we can formulate following equation for Q_i,

$$Q_i = Q_0 \left(\frac{1 - e^{-nkt_k}}{1 - e^{-kt_k}} \right) \tag{4}$$

For a very large n we can write,

$$Q_n = \frac{Q_0}{1 - e^{-kt_k}} \tag{5}$$

Note that Q_n is maximum of concentration of drug over all time. By using equation (5), we found that in order to keep amount of drug below MTC all the time, t_k and Q_0 must be related by following formula,

$$t_k > \frac{1}{k} ln \left(\frac{MTC}{MTC - Q0} \right) \tag{6}$$

Figure (2) represent situation where a patient takes dosage of 100 mg repeatedly after time interval of 8 hours. Here, MEC = 10 µg/mL and MTC = 20 µg/mL. Also, $k = 0.0315\ h^{-1}$, $Q_0 = 4$ µg/mL. Note that equation (6) is getting satisfied in this case. So, concentration of drug will always be lesser than MTC. Whereas for the second case it is not true.

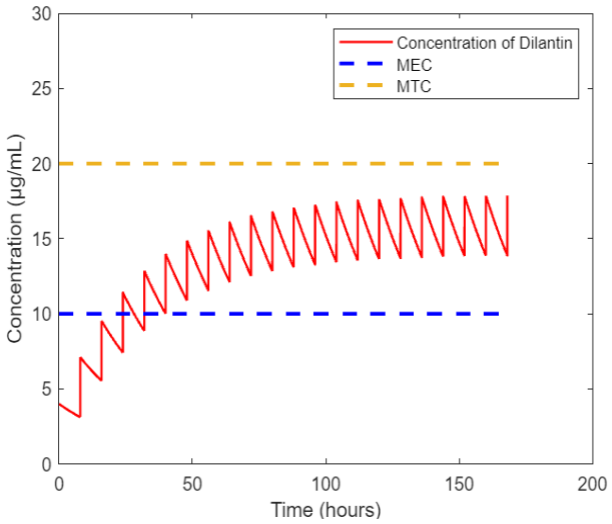

FIG. 2: Concentration v/s Time for Repeated dilantin dosage of 100mg every 8 hours.

Figure (3) represents a situation where a patient takes dosage of 300 mg every 24 hours. Here, $Q_0 = 12$ µg/mL. This case doesn't satisfy the equation (6), so concentration of drug will not always be lesser than MTC.

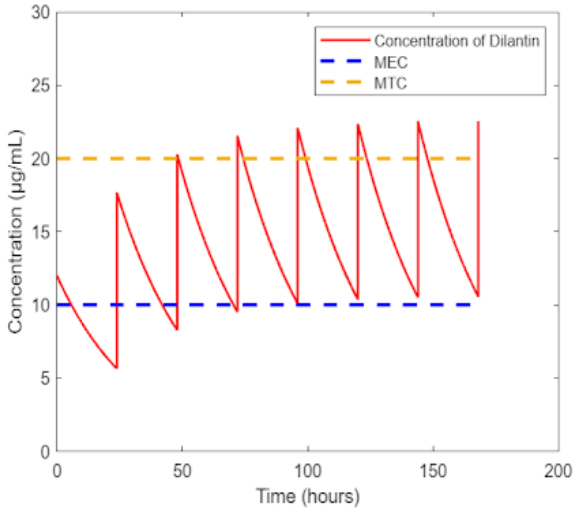

FIG. 3: Concentration v/s Time for Repeated dilantin dosage of 300mg every 24 hours.

Two Compartment Model

MODEL

In the two compartment model, we can assume that rate of change of mass of drug in the first compartment is proportional to the concentration of the drug in

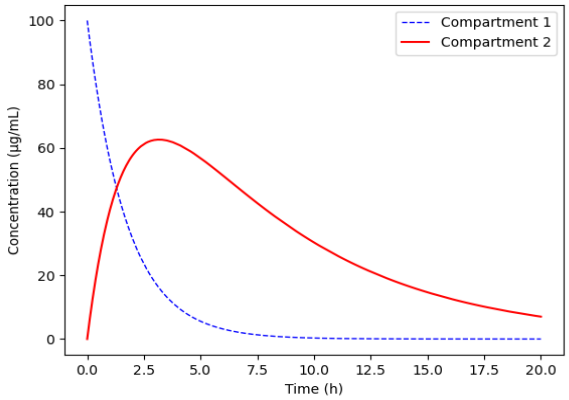

FIG. 4: Concentration v/s Time for Aspirin Single Dose.Q_0 = 100 µg/mL, Absorption Half-life = 1.2 h and Elimination Half-life = 4.7 h.

the first compartment. For the second compartment, outflow is proportional to the concentration of the drug in the second compartment and inflow is proportional to the concentration of the drug in the first compartment. Thus, we get the equations (7) and (8).

$$\frac{dQ(t)}{dt} = -aQ(t) \tag{7}$$

$$\frac{dP(t)}{dt} = aQ(t) - bP(t) \tag{8}$$

Here,
Q(t) = Concentration of the drug in compartment one at time t.
P(t) = Concentration of the drug in compartment two at time t.

SINGLE DOSE

In this case a certain amount of drug enters the first compartment and thereafter no dosage of drug is given. Thus, we have Q(0) = Q_0 and P(0) = 0. Solving equations (7) and (8) analytically with given initial values we get,

$$Q(t) = Q_0 e^{-at} \tag{9}$$

$$P(t) = \frac{aQ_0}{b-a}(e^{-at} - e^{-bt}) + P(0)e^{-bt} \tag{10}$$

Figure (4) shows concentration of aspirin time in both compartments v/s time.

Here, from equations (9) and (10), we can find time at which amount of drug in second compartment reaches maximum is,

$$t_m = \frac{1}{b-a} ln(\frac{b}{a})$$

And the maximum value of drug in second compartment is,

$$P_{max} = Q_0 \left(\frac{a}{b}\right)^{\frac{b}{b-a}}$$

Here, Q_0 should be set such that P_{max} should not become above the MTC for the organ representing compartment two. Also, Q_0 should be less than MTC of compartment one.

MULTIPLE DOSE

In this case, a certain amount of drug dosage is given after some fixed intervals of time. Let A be the increase in concentration of the drug due to a dose. A dose is given at time $t = 0$ and consecutively after a time interval of t_k.

Let Q_i be concentration of drug in compartment one and P_i be concentration of drug in compartment two after $i * t_k$ amount of time (just after a dosage is given).

We have, $Q_0 = A$ and $P_0 = 0$, using equations (9) and (10) we get following relations,

$$Q_{i+1} = Q_i e^{-at_k} + A \tag{11}$$

$$P_{i+1} = \frac{Q_i a}{b-a}(e^{-at_k} - e^{-bt_k}) + Pe^{-bt_k} \tag{12}$$

Using equations (11) and (12) we plotted figure (5) which shows concentration of aspirin v/s time for repeated dosages.

By solving recurrence in equation (11) and (12), we get,

$$Q_i = A\left(\frac{1 - e^{(i+1)at_k}}{1 - e^{-at_k}}\right) \tag{13}$$

$$P_i = \frac{aA}{b-a}\left[e^{-at_k}\left(\frac{1 - e^{-iat_k}}{1 - e^{-at_k}}\right) - e^{-bt_k}\left(\frac{1 - e^{-ibt_k}}{1 - e^{-bt_k}}\right)\right] \tag{14}$$

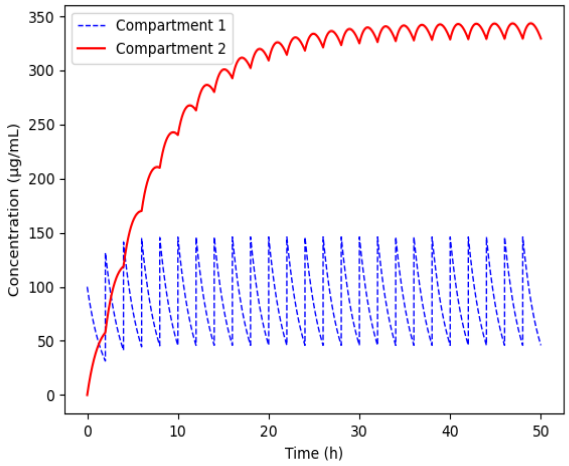

FIG. 5: Concentration v/s Time for Multi Dose Aspirin. Here, $A = 100$ µg/mL and $t_k = 2$ h.

We observed that if t_k is smaller then concentration of the drug in compartment one and compartment two is going to saturate at a higher value. Also, if amount of drug given in each dose is higher than saturation value is going to be higher.

LOADING

Sometimes doctors give patients a loading dose, which is an initial dosage that is much higher than the maintenance dosage. We can model this type of drug dosage by tweaking the value of t_k and A in equation (11) and (12) for some initial doses. Figure (6) shows example of Dilantin loading dose, a loading dose for Dilantin is three doses 400 mg, 300 mg, and 300 mg 2 h apart. Twenty-four hours after the loading dose, normal dosage of 100 mg every 8 h begins. We will assume that volume of compartment one (plasma in this case) is 3000 mL.

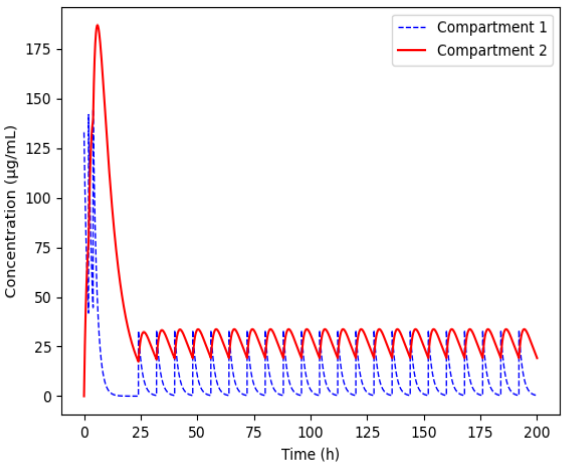

FIG. 6: Concentration of dilantin v/s Time for the case of Loading.

CONCLUSION

In this lab, we modeled change of concentration of drug in human body. We used one compartment and two compartment model for the same. Case of single dose of drug and repeated dose after certain interval of time were considered by us. We observed various dependency between different parameters. We also established some formulas for this parameters so that concentration of drug in body never goes above minimum toxicity concentration (MTC).