Lab -2

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MC312, Modeling and Simulation

In this lab we numerically and analytically analyzed the drug dosage problem. In this, we tried to analyze how the concentration of the ingested amount of drug changes in the body as a function of time. This is quite an important thing to analyze because how the body responds to the drug depends on the concentration of the drug in the blood plasma.We considered two different drugs :- Aspirin and Dilantin.
We modelled the problem using one-compartment and two compartment model. We have done simulations by changing the amount of drug that is taken in one impulse dose and also by varying the time interval after which the dose is taken periodically. We observed that in the case of repeated doses the concentration of the drug converges to a constant value. Also we compared the two models(one compartment and two compartment), and found that one compartment model gives apparently higher concentrations than the actual concentrations in the blood plasma, so we should prefer two compartment model. As using one compartment model, it might give us false impression that the concentration of drug in the plasma is in the effective range, but in reality it might be much lower than the effective concentration range.

I. INTRODUCTION

There are many systems in the physical world where the rate of change of a substance is directly proportional to the amount of substance. Here, the scenario is of the amount of drug concentration in the body, the rate of elimination of a drug from the blood plasma is directly proportional to the amount of drug in the blood plasma . Also the amount of drug in the body also depends on the impulsive amount of dose taken each time and the time duration between such intervals. The dynamics depend on the amount of impulsive dose taken and also on the time interval after which dose is taken.

II. MODEL

A. One Compartment

We can analyze the given problem first by using a one-compartment model. Here we assume the body to be a homogeneous system and consider it as a single entity. This leads us to make a crucial assumption that the distribution of any drug(or substance) in the body is instantaneous. That is when we ingest some amount of substance in the body , it is immediately and completely available in the blood plasma at that instant itself.We can say that x is the amount of drug present in the blood plasma at any instant of time .We can write the equation for the model as:-

$$\frac{dx}{dt} = -k.x \tag{1}$$

As the rate of elimination of the drug from the body is directly proportional to the amount of drug. Also we can consider the volume of the body to be constant and can divide by volume on both sides of the equation to get the concentration on both the sides. On solving (6), we get that :-

$$x = x_0 e^{-kt} \tag{2}$$

Time taken for half of the substance to get out of the body is known as half life of the drug, by putting $x = x_0/2$ in the (7) ,we get that:-

$$t_{1/2} = \frac{\ln 2}{k} \tag{3}$$

Usually half-life of the drug is given to us and we use that to find the elimination constant k of the drug .So, I observed that longer half life of a drug correspond to smaller elimination constant for the drug.

B. Two Compartment

In this model, we tried to somewhat correct our assumption from the one-compartment model where we were assuming instantaneous distribution of the drug in the body. In two-compartment model, we assume the body to be made of 2 sections i.e. one compartment of the digestive tract and the other of the blood plasma. The drug ingested at any instant first goes into the digestive tract and then into to the blood plasma. Drug which gets eliminated from the digestive tract is the one which gets absorbed into the blood plasma, and here the rate of change of the drug in the digestive tract will depend on the inflow and outflow of the drug . Inflow will be governed by the impulse function (which might

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be some periodic function as drugs are taken periodically after equal intervals of time). And the outflow by the amount of the drug in the digestive tract .In this model also, we assume that the blood plasma is homogeneous and the drug will get uniformly distributed. We can write the following equations:-

$$\frac{dx}{dt} = I(t) - k_1.x \tag{4}$$

$$\frac{dy}{dt} = k_1.x - k_2.y \tag{5}$$

Here x denotes the amount of drug in the digestive tract and y is the amount of drug in the blood plasma.

The corresponding difference equations for the (4) and (5), that I had used for generating plots are as follows:-

$$x_{t+\Delta t} = x_t + I(t) - (k_1.x_t).\Delta t \tag{6}$$

$$y_{t+\Delta t} = y_t + (k_1.x_t - k_2.y_t).\Delta t \tag{7}$$

III. RESULTS

A. One-compartment

In general, regular dose Dilantin for adults is 100 mg every 8 h. Also the MEC(Minimum effective concentration) of Dilantin is 10 ug/ml and MTC(Maximum effective concentration is 20 ug/ml.) Dosage is measured in units of ug/ml. Also absorption fraction of the Delantin is assumed to be equal to 0.12. The simulation for this regular dose is shown in the figure:-

We should not change the amount and frequency of the drug by ourselves, as we can see from that it will not be medically advisable to take 300 mg Dilantin once a day(absorption constant and half life are same as in the above case) as we observe in the **??** that the concentration of Dilantin goes beyond the MTC , which can be toxic. Also, there will not be any problem if we change the absorption constant to 0.09 in the above case where we were taking 100mg Dilantin every 24 hours , because reduction in absorption constant will reduce the effective dose.

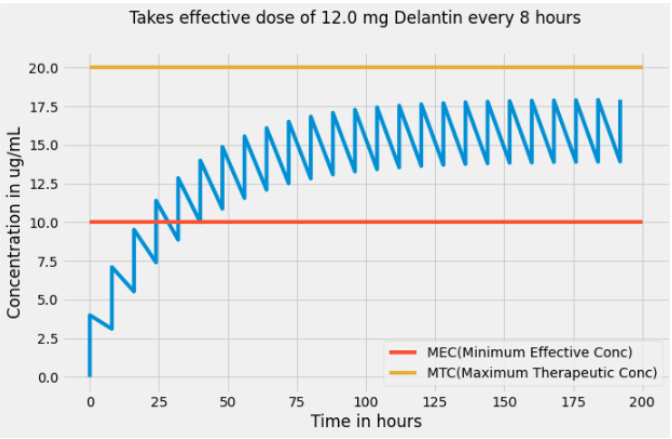

FIG. 1: Conc of Delantin vs Time in one compartment model, time step taken for simulation =0.1 hour

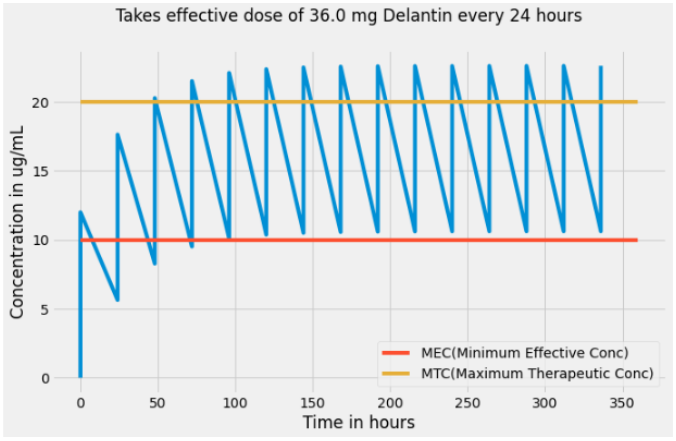

FIG. 2: Concentration of Delantin vs Time in one compartment model with changed amount and frequency, time step taken for simulation =0.1 hour

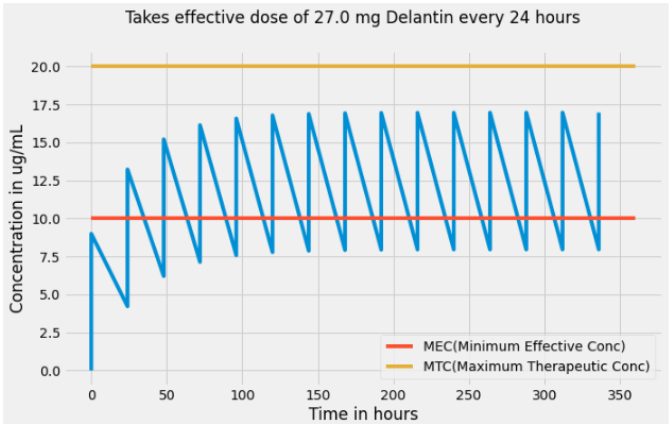

FIG. 3: Concentration of Delantin vs Time in one compartment model with reduced effective dose and frequency=24 hours, time step taken for simulation =0.1 hour

For writing the formula of the drug just after any nth dose, we need to add the amount of drug present already in the system due to the previous n-1 doses and the impulse amount of dose added in this nth dose. So let Q_0 be the effective dose(after multiplying the original dose with absorption constant), and Q_n be the amount of drug just after nth dose , so we get that:-

$$Q_n = Q_0(1 + e^{-k.t_0} + e^{-k.2t_0} + ... + e^{-k.nt_0}) \tag{8}$$

We also know that the amount of drug that might be effective for a baby would not be for an adult male, because the effect of a drug depends on the concentration of it in the blood plasma. For example, in figure:- **??** , an adult male whose 60 to 70 % body is liquid, would require to take about 18900 mg of a single dose aspirin so that the concentration of drug remains in the effective range for about 4 hours.

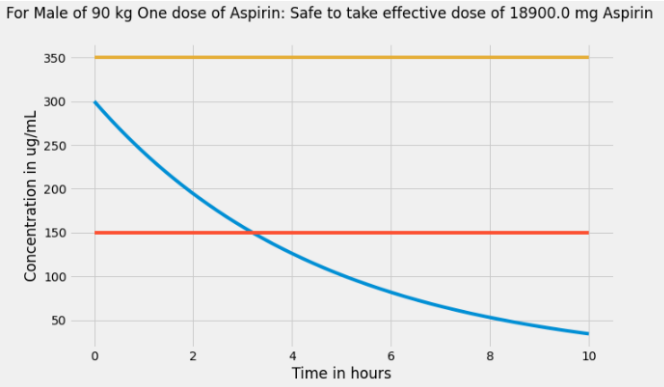

FIG. 4: Concentration of Aspirin wrt Time in one compartment model with single dose for a male of about 90kg, time step taken for simulation =0.1 hour

B. Two compartment

The below figure shows the concentration of aspirin when we assume a two compartment model for the aspirin where we are taking a single effective dose of 325 mg. One of the key observations in 5 that we can make

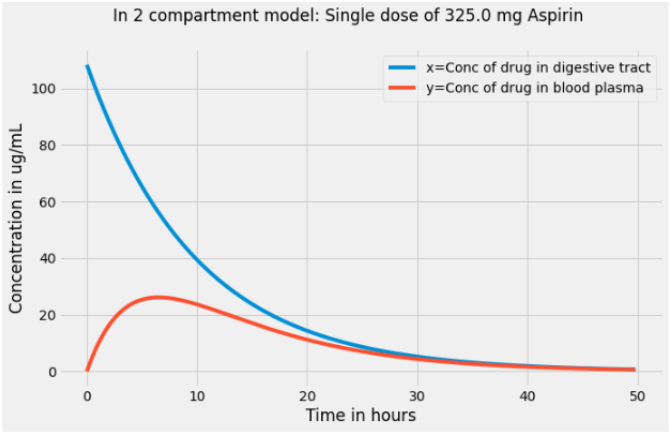

FIG. 5: Concentration of Aspirin wrt Time in two compartment model with effective single dose of 325 mg , time step taken for simulation =0.2 hour

is that the concentration of the drug in the blood plasma is much lower when compared to the concentration which was coming in the case of one compartment model. So if we take an effective dose of 325 mg , according to the 2 compartment model , it will never be in the effective range of concentration at any point in time(150 to 350 ug/ml for Aspirin).

In another case that we looked at involved taking initial dose of 3 aspirin tablets i.e. 3x325 mg and after 2 hours take another 2 aspirin tablets 2x325 mg. The below figure represents the plot of concentration of Aspirin wrt time.

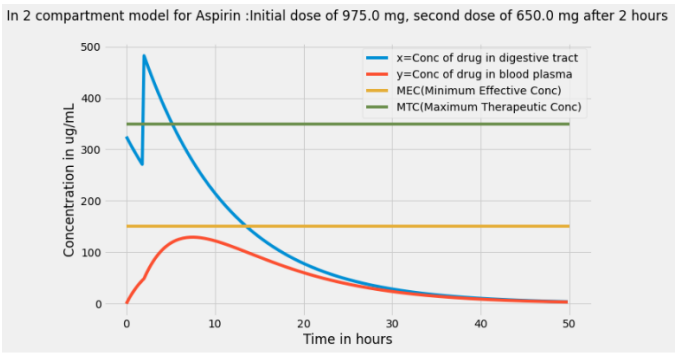

FIG. 6: Concentration of Aspirin wrt Time in two compartment model , takes 3 aspirin tablets initially and 2 more after 2 hours , time step taken for simulation =0.2 hour

Observation that we can make from 6 is that the conc in blood plasma never reaches the effective range , it just becomes closer to the minimum value of effective range at t=8 hours.

The last case that we had analyzed involved taking loading doses followed by regular doses of the drug Dilantin in 7 . At t=0, initial dose of 400 mg was given and then at t=2 hours and t=4 hours, 300 mg was given.Then at t=28 hours and after every 8 hours from t=28 hours, regular dose of 100 mg was given.

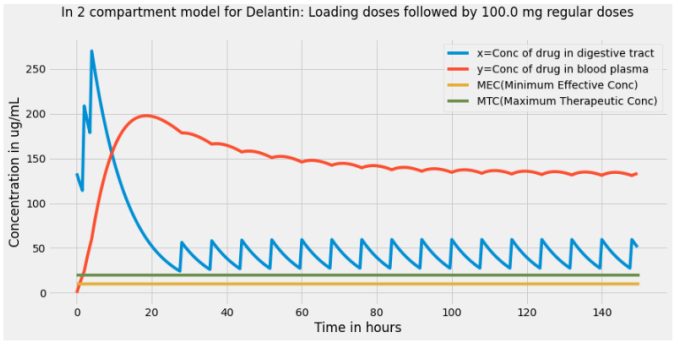

FIG. 7: Concentration of Delantin wrt Time in two compartment model ,400 mg at t=0 , 300 mg at t=2 and t=4 hours , 100 mg at t=28 hours and 100 mg after every 8 hours thereafter , time step taken for simulation =0.2 hour

We observe in 7 that conc of Delantin converges to about 140 ug/ml, which is much higher than safe range which is 10 to 20 ug/ml for Delantin.

IV. CONCLUSIONS

We can conclude that the 2-compartment model can give us accurate conc. of drug in the blood plasma compared to 1-compartment model. Also our calculations didn't become too complicated while in 2-compartment model. As we understand that the substance ingested in the body doesn't get dissolved in the blood at that instant only and takes time to dissolve. This is taken care by 2 compartment model. The 1 compartment model can be a good starting point for starting the modelling process.