Lab - 2

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CS-302, Modeling and Simulation

In this lab, we numerically and analytically analyze the drug dosage problem which is a very important and practical problem. We discuss one compartment and two compartment models for two drugs namely Aspirin and Dilatin. We explore the effect of taking different amount of dosages with the help of one and two compartment models. We also explore the effect of different half lives on the elimination constant k. We also work out the mathematics of repeated doses.

I. INTRODUCTION

Drug dosage problem is an important problem and falls under the quantitative science of *pharmacokinetics*[1]. Errors in dispensing and administering of drugs can be fatal and to correctly model the drug dosage problem is a crucial task. In this lab, we try to model the drug dosage problem using one compartment model and two compartment model for two drugs, Aspirin and Dilatin. A one-compartment model is a simplified representation of how a body processes a drug. To model the drug dosage problem as a one compartment model we take into account few assumptions [1]:

- Body is considered as a single homogeneous compartment
- The distribution of drug is instantaneous in the body
- The concentration of the drug in the system (amount of drug/volume of blood) is proportional to the drug dosage
- The rate of elimination is proportional to the amount of drug in the system.

For modeling as two compartment model we take below assumptions into account [1]:

- Drug is absorbed first in the first compartment and then passed on to the second compartment.
- The first compartment represents the digestive system or the gastrointestinal tract and the second compartment represents the blood stream.
- The elimination constants of both the compartments are assumed to be different.

One compartment model is useful for modeling drug dosage via injection into the blood stream directly. Two compartment model is more appropriate to model drug dosage via oral pill ingestion. A drug's half life is useful for modeling the system. We begin with modeling the Aspirin drug dosage. Aspirin has analgesic effectiveness only if the concentration of drug in plasma is above $150\mu g/mL$ while it may get toxic if the concentration in plasma is above $350\mu g/mL$ [1]. These concentrations are called Minimum Effective Concentration (MEC) and Minimum Toxic Concentration (MTC) respectively [1]. The half life of Aspirin for a 300 - 650 mg dosage is known to be about 3.2 hours [1].

II. MODEL

Keeping into account the assumptions, we model the system using following equations:
For one compartment model:

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

On solving this differential equation,

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

Here, $Q(t)$ is the concentration of drug (in $\mu g/mL$) in the compartment and k is the elimination constant (in per hour).

For two compartment model:

$$\frac{dx(t)}{dt} = -k_1 x(t) \tag{3}$$

$$\frac{dy(t)}{dt} = -k_2 y(t) + k_1 x(t) \tag{4}$$

Here $x(t)$ is the concentration of drug in the first compartment and $y(t)$ is the concentration of drug in the second compartment. k_1 and k_2 are elimination constants for first and second compartments respectively. Elimination constant $k = \frac{ln(2)}{t_{1/2}}$ from Eq. (2).

III. RESULTS

We can observe that for larger value of $t_{1/2}$ the value of elimination constant k is small.

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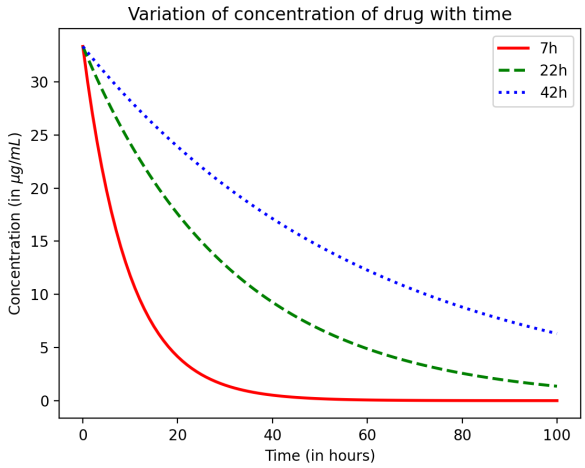

FIG. 1: Variation of drug concentration with time for different values of $t_{1/2}$

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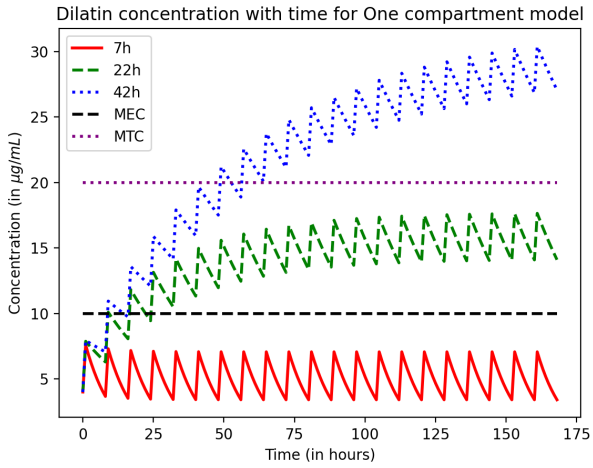

FIG. 2: Variation of concentration of Dilatin with time for multiple doses at time interval of 8 hours. The plot is for different values of $t_{1/2}$.

It is very well evident that the variation is exponential decay from Fig. (1) and also larger values of k will result in rapid decrease.

Dilantin is used as treatment for epilepsy patients. Adult dosage is often one 100 mg capsule three times daily. The effective serum blood level is 10 $\mu g/mL$ (MEC) where as serious side effects can appear at a level above 20 $\mu g/mL$ (MTC). The half life of Dilantin varies from 7h to 42h but on average it is 22h [1]. We assume that a fraction ingested dosage is absorbed and the ingestion is instantaneous. We plot the concentration vs time graph for different values of half life.

Some inferences that can be drawn from Fig. (2) are:

- For $t_{1/2} = 7$ hours, the drug concentration never reaches MEC.
- For $t_{1/2} = 42$ hours, drug concentration reaches MEC but for some time interval also reaches MTC and hence can be considered toxic.
- After some point in time, the concentration reaches some constant value.

We have also tried to explore what if we change the interval at which doses are given. Fig.(3) shows the plot of Dilatin concentration for different intervals.

Suppose some patient takes a 300 mg tablet at interval

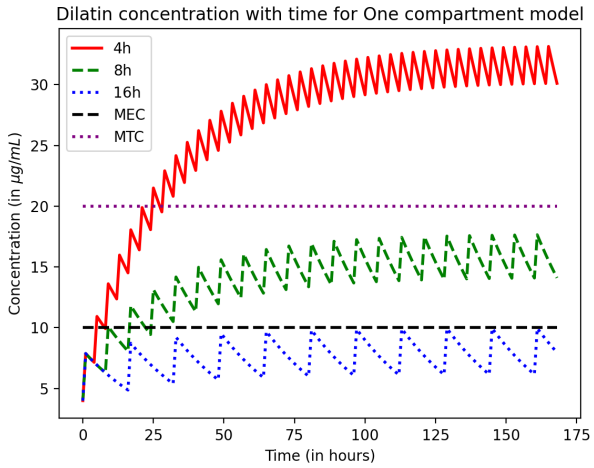

FIG. 3: Concentration vs Time plot for repeated doses at different interval values.

of 24 hours instead of 100 mg every 8 hours. Fig. (4) shows the concentration plot for such dosage and how such type of a decision is not advisable. From the figure it is evident that the peaks of 300 mg at 24h interval plot is higher that MTC for some time interval which could be toxic and also the drug concentrations in the blood vary at a larger scale which could again be harmful for the patient.

Let us now move our discussion towards understanding the mathematics behind the repeated doses. Let a be the fraction of concentration remaining in the system after some fixed interval and concentration of drug at time t be $Q(t)$. On taking the 1st tablet, concentration in the system will be Q_0. Before the second tablet, the concentration in the system will be $a \times Q_0$. After taking the second tablet, the concentration will be $Q_0 + a \times Q_0$. Taking forward this idea,

$Q_1 = Q_0$

$Q_2 = Q_0 + a \times Q_0$

$Q_3 = Q_0 + a \times Q_0 + a^2 \times Q_0$

$Q_n = Q_0 + a \times Q_0 + a^2 \times Q_0 + a^3 \times Q_0 + ...$

Thus, after n^{th} tablet, concentration of drug in the system will be,

$$Q_n = Q_0(1 + a + a^2 + a^3 + ...) \tag{5}$$

Using sum of geometric series we can find out the concentration after nth tablet,

$$Q_n = Q_0 \frac{1 - a^n}{1 - a} \tag{6}$$

At some large time (∞), value of Q_n tends to $\frac{Q_0}{1-a}$ which is a constant. Hence we find the curve to be saturating.

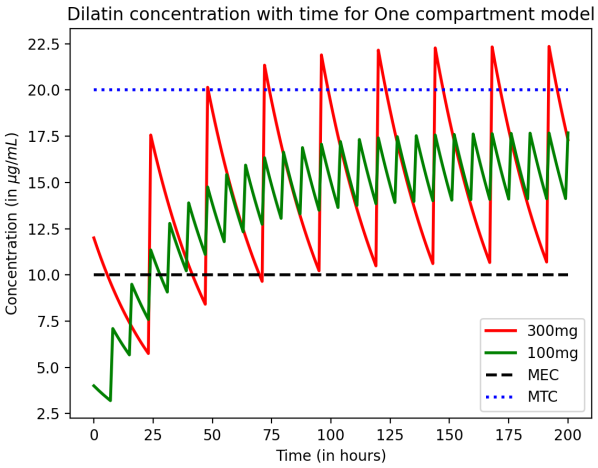

FIG. 4: Variation of concentration of Dilatin with Time for different dosages i.e 300 mg at 24h interval and 100mg at 8h interval.

Fig.(5) shows the plot for concentration in two compartment model of Aspirin dosage. Two tablets of 325 mg are taken at t = 0, which is considered a standard dosage. Here on experimenting with the values of elimination constants we find that $k_1 = 2k_2$ works the best to model the system correctly. Here $t_{1/2} = 3.2h$ and $k_2 = \frac{ln(2)}{t_{1/2}}$.

Suppose some patient takes 3 tablets of Aspirin at $t = 0$, and takes 2 more tablets after 2 hours. Plot in Fig. (6) demonstrates the concentration in such a case.

Considering another case, in an attempt to raise the concentration of a drug in the system to the minimum effective concentration quickly, sometimes doctors give a patient a *loading dose*, which is an initial dosage that is much higher than the maintenance dosage. 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 [1]. Fig. (7) demonstrates the plot of such a dosage. This kind of dosage could be toxic as evident from the plot and hence should not be taken without doctor's prescription. One can observe although concentration of drug in Gastrointestinal tract exceeds MTC, concentration in the blood stream never exceeds MTC.

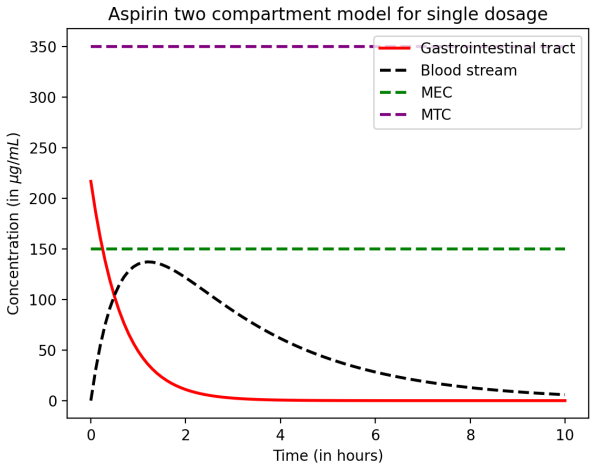

FIG. 5: Variation of concentration of Aspirin in two compartment model with time. Here MEC = 150 $\mu g/mL$ and MTC = 350 $\mu g/mL$

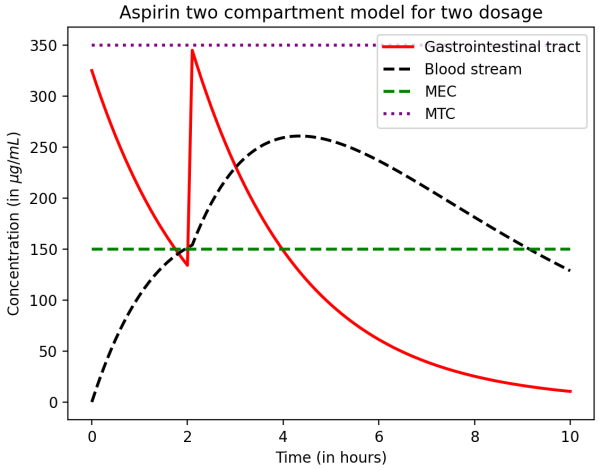

FIG. 6: Concentration vs Time in two compartment model for Aspirin with 2 doses at interval of 2 hours.

IV. CONCLUSIONS

In conclusion, we have studied one and two compartment models to model the drug dosage problem. Some important conclusions to draw are modeling drug dosage is a very difficult and challenging problem but is very important to model it correctly. Making errors can result in fatal circumstances. Using multiple compartments result in better approximation and modeling since body is a complex system. We observed how drug concentration decreases exponentially with time for a single dosage. We also observed how different intervals can affect the concentration of drug for repeated doses. We worked out the mathematics behind repeated doses and concluded that the concentration of drug in the body after n^{th} dose will

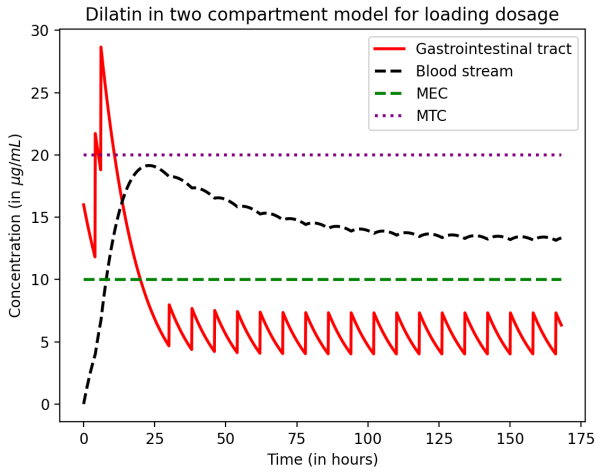

FIG. 7: Plot of loading dosage of Dilatin for two compartment model. In this, k_1 is assumed to be 2.4 times the value of k obtained for one compartment model. k_2 is assumed to be $k = \frac{ln(2)}{t_{1/2}}$

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be $Q_n = Q_0 \frac{1-a^n}{1-a}$ using concept of sum of geometric series where a is the fraction of drug left before next dose. Finally, we observed different cases of drug dosage and concluded that the concentration in the body should be more than MEC for it to be effective and be less than MTC for it to be safe.

[1] A. Shiflet and G. Shiflet, *Introduction to Computational Science: Modeling an Simulation for the Sciences*, Princeton University Press.3, 234 (2006).