Lab - 2: Modelling Drug Dosage

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CS-302, Modeling and Simulation

An error in drug doses are quit frequent challenge faced in medical fields. One of the most important quantity that can measure the degree of error is concentration of drug. Therefore, In this paper, we have analyzed how body process the drug. We have developed three different model that give information about concentration of drug in human body. Each successive model drops a few assumptions from previous model and tries to get closer to real life processes. This paper also includes some applied examples with simulated graphical results for the purpose of understanding.

I. INTRODUCTION

Drugs are prescribed to cure the disease of a patient, but errors in the dosage of these drugs can sometimes worsen the health of the patient. We have enough instances where the error in drug dosage has done damage to the human body. From the medical perspective, the concentration of a drug in the blood is a crucial quantity. The therapeutic range for a drug lies between Minimum Effective Concentration(**MEC**) and Minimum Toxic Concentration(**MTC**). Now, the question is, how can one prescribe a correct drug dosage? To answer this question, one must take a few factors such as drug absorption, distribution, metabolism, and elimination into account. To address the problem of errors in drug dosage, We make an effort to build models that provide information about the concentration of drugs in the human body considering the factors mentioned above.

II. ONE COMPARTMENT MODEL FOR SINGLE DOSE

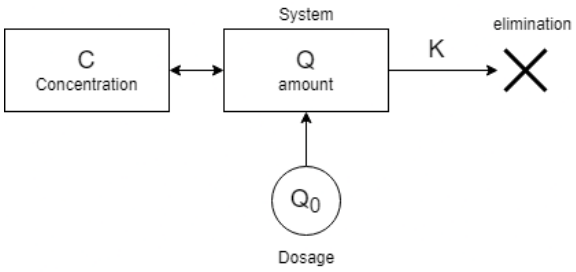

FIG. 1: Schematic of one compartment model for single dose

Although the metabolism of drugs in the human body is a complex process, we can simplify the model by making a few assumptions, which are as follows,

1. Only one dose is given to the system.
2. The concentration of drug in system (for eg. blood, plasma, serum etc.) is proportional to drug dosage.
3. The rate of the elimination (rate at which drug is leaving of the system) of the drug is proportional to amount of the drug present in the system.
4. Drug immediately becomes available into system i.e metabolism is very fast.
5. The absorption of drug in the system 100%

From our second assumption, We can write,

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

Here, Q is amount of drug present in the system and K is the proportionality constant.

Eq. 1 represents the case of unconstrained decay whose solution is given as,

$$Q = Q_0 e^{-Kt} \tag{2}$$

where Q_0 is initial (and the only) amount of drug given to the system.

At $t = t_{1/2}$, the amount of drug present in the system would half of the initial value. Using it we get,

$$Q_0/2 = Q_0 e^{-Kt_{1/2}}$$

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

The unit of K is h^{-1}, however it depends on the units in which time is measured for the system. The concentration C of the drug in the system is given by,

$$C = \frac{Q}{V} \implies C = \frac{Q_0}{V} e^{-Kt} \implies C = C_0 e^{-kt} \tag{4}$$

where V is total volume of the system and $C_0 = Q_0/V$ is concentration of drug at the $t = 0$. Concentration is often represented in $\mu g/mL$ whereas dosage is measured in mg. So, while applying this model in practice, dosage is multiplied by 1000 in order to convert it into μg.

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In practice, volume is calculated using the weight of a person. It is assumed that a male body consists fluid volume equal to 65-70% of the total weight. In addition to that, 1 kilogram of body has $1L$ of fluid and hence the fluid volume in a male of weight W kilogram can be approximated in the range of $0.6W$ - $0.7W$ L. We can use this approximation to incorporate weight in Eq. **??**

III. ONE COMPARTMENT MODEL FOR REPEATED DOSES

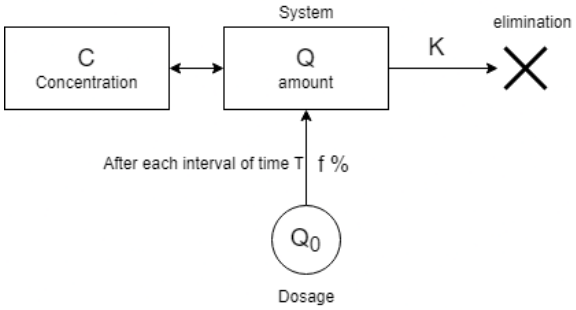

FIG. 2: Schematic of one compartment model for repeated dose

The previous model considers only one dosage of the drug. However, in most cases the therapeutic concentration of the drug is not achieved by a single dose but by a series of repeated doses. With the understanding that we developed in model 1, let's model the process of repeated doses starting with a few assumptions.

1. The drug dose is repeated after each specific interval.
2. Each drug dose is partially absorbed.
3. Assumption 2 and 3 of previous model.

By partial absorption, we mean that system only absorbs some fraction of total dosage. This fraction is given by *absorption constant* of drug. One thing that is evident here is we can apply the *One Compartment Model for Single Dose* in between the time of consecutive doses. Before, We understand this process step-by-step, we have to define certain variables. Q represents the current amount of drug present in the system, Q_0 is the drug dosage, f is the absorption constant, T is the time between two successive doses and K represents elimination rate.

At time t=0, drug of amount Q_0 enters the system. System absorbs fQ_0 amount of drug and eliminates the remaining drug immediately. So, just after 1^{st} dose

$$Q_1 = fQ_0$$

Applying the *One Compartment Model for Single Dose* until $t = T$ we get,

$$Q = fQ_0e^{-Kt} \text{ for } t \in [0, T)$$

At time $t = T$, the next dose of amount Q_0 enters the system.The system absorbs fQ_0 amount of drug and hence just after 2^{nd} dose, we get

$$Q_2 = fQ_0(1 + e^{-KT})$$

At time $t = 2T$, the 3rd dose of amount Q_0 enters the system. The system absorbs fQ_0 amount of drug and hence just after 3^{rd} dose, we get

$$Q_3 = fQ_0(1 + e^{-KT} + e^{-2KT})$$

Similarly, after the n^{th} dose we have,

$$Q_n = fQ_0(1 + e^{-KT} + e^{-2KT} + ... + e^{-(n-1)KT}) \quad (5)$$

Eq. 5 represents the general formula for the amount of drug in the system after the n^{th} dose. The terms of Eq. 5 represent a geometric series with the first term $a = fQ_0$ and the common ratio $r = e^{-KT}$.

The general form of a geometric series is as follows,

$$S = a + ar + ar^2 + ar^3 + ... + ar^{n-1} \quad (6)$$

Multiplying both sides of Eq. 6 with r, we get

$$Sr = ar + ar^2 + ar^3 + ... + ar^n \quad (7)$$

Subtracting Eq. 6 from Eq. 7, we get the sum of a geometric series as,

$$S = \frac{a(1 - r^n)}{1 - r} \quad (8)$$

Using Eq. 8 we get,

$$Q_n = \frac{fQ_0(1 - e^{-nKT})}{1 - e^{-KT}} \quad (9)$$

$$Q = Q_ne^{-Kt}, C = C_ne^{-Kt} \quad (10)$$

where $C_n = Q_n/V$, V is volume and $n = 1, 2, 3, 4, ...$

Graphical Analysis

1. For the first case(Fig. 3) we considered 100mg dosage of Dilantin administered every 8 hrs and having an absorption factor of 0.12. We assumed the total volume to be 3000ml.
2. For the second case (Fig. 4) we considered 300mg dosage of Dilantin (as compared to 100mg in case 1) administered every 24 hrs (as compared to 8 hrs in case 1) and having an absorption factor of 0.12. We assumed the total volume to be 3000ml.

   From Fig. 4 we can see that the concentration goes above MTC which is not advisable and hence 100mg every 8hrs is advisable as compared to 300mg every 24hrs.

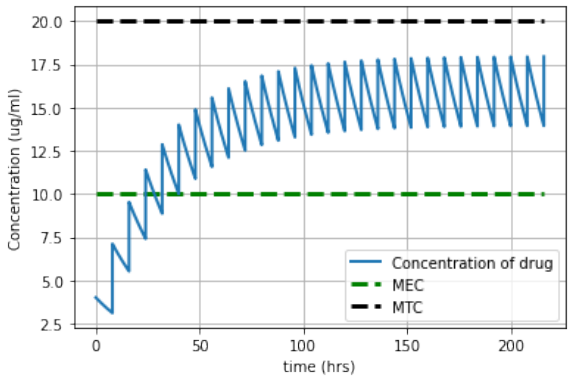

FIG. 3: Graph of concentrations MEC = $10\mu g/ml$, MTC = $20\mu g/ml$, and concentration ($\mu g/ml$) vs time (h)

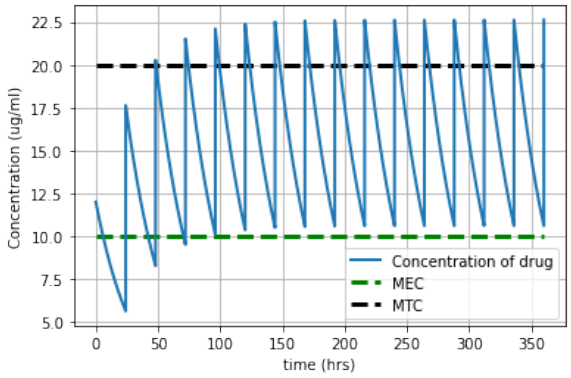

FIG. 4: Graph of concentrations MEC = $10\mu g/ml$, MTC = $20\mu g/ml$, and concentration ($\mu g/ml$) vs time (h)

3. For the third case (Fig. 5) we consider loading dosage administration for Dilantin. The loading dose is used initially to increase the concentration in order to achieve **MEC** quickly. 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.

IV. TWO COMPARTMENT MODEL

Two compartment model, as the name suggests would have two compartments where the first compartment represents the digestive system (stomach/intestine) and the second compartment is the one where the drug targets (for eg. blood, serum, plasma etc.). Several assumptions associated with this model are list below.

1. The rate of elimination of drug in a compartment is proportional to the amount of drug present in the compartment.

2. A part of the drug gets completely eliminated while remaining gets back to the digestive system.

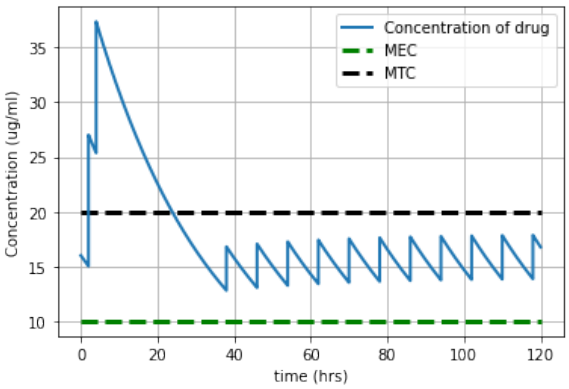

FIG. 5: Graph of concentrations MEC = $10\mu g/ml$, MTC = $20\mu g/ml$, and concentration ($\mu g/ml$) vs time (h) for loading dosage

The following figure 6 shows a simplified form of a two compartment model. For compartment 1, the amount of drug at time t depends on three factors, the rate of elimination from compartment 1, the rate at which the drug is transferred to compartment 2 and the rate at which it gets transferred back to compartment 1 from compartment 2. Similarly for the second compartment, the amount of drug at time t depends on the amount incoming from compartment 1 and the amount dissipated from compartment 2. The mathematical model for the

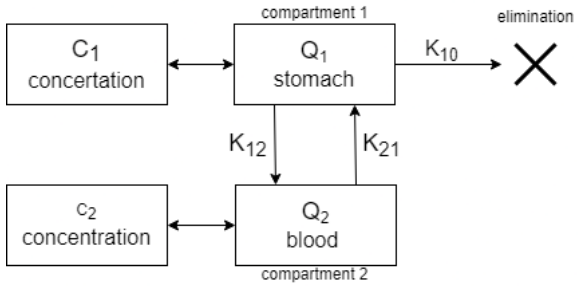

FIG. 6: Schematic of two compartment model

above figure would be,

$$\frac{dQ_1}{dt} = k_{21}Q_2 - (k_{10} - k_{12})Q_1 \tag{11}$$

$$\frac{dQ_2}{dt} = k_{12}Q_1 - k_{21}Q_2 \tag{12}$$

Here, Q1 and Q2 represents the amount of drug present in compartment 1 and compartment 2 respectively.k_{12}, k_{21} and k_{10} represents the rate constant for elimination from compartment 1 to compartment 2, from compartment 2 to compartment 1, and from compartment 1 to out of the system respectively.

Graphical Analysis

1. For the first case (Fig. 7) we consider a single 100mg dose of Aspirin with an absorption factor of 0.12 and the volume of the system being 2500ml. The values of the constant k_{10}, k_{12} and k_{21} are $1/da$, $1.5/da$ and $2.5/da$ respectively.

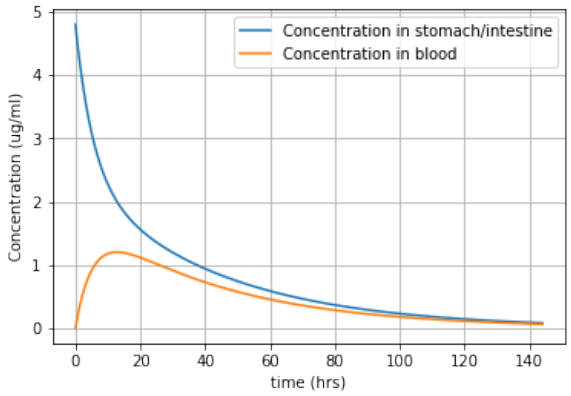

FIG. 7: Graph of concentration($\mu g/ml$) vs time (h) for two compartment model of single dose Aspirin

2. For the second case (Fig. 8) we consider taking 3 Aspirin tablets (100mg each) at the start and another 2 tablets (100mg each) after 2 hours. Considering the same values for the constants as the above case we get the graph as follows,

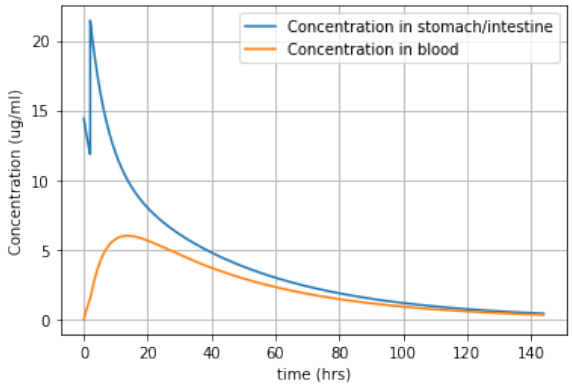

FIG. 8: Graph of concentration($\mu g/ml$) vs time (h)

3. For the third case (Fig. 9) we considered administration of 100mg Dilatin every 6hrs with the absorption factor being 0.12 and considering the volume to be 3000ml. The values of the constant k_{10}, k_{12} and k_{21} are $1/da$, $1.5/da$ and $2.2/da$ respectively.

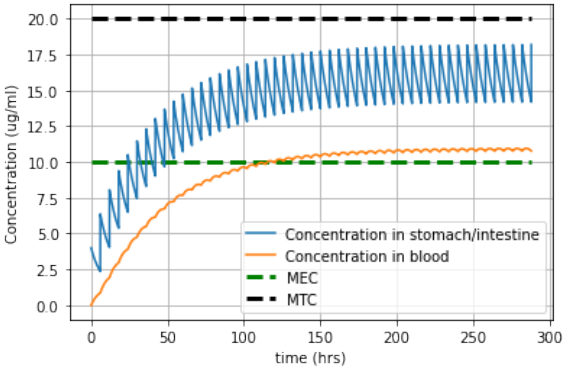

FIG. 9: Graph of concentration($\mu g/ml$) vs time (h) for repeated doses of Dilantin using two compartment model.

V. CONCLUSIONS

In this paper, we have analyzed the process of drug administration in and its flow in blood. The models allows us to predict drug concentration in the blood. In addition to that, It provide information about frequency of dose that maintains drug concentration in therapeutic range. We have also learnt that it might be possible that single drug is not sufficient to achieve therapeutic concentration. In such cases, model of repetitive dose helps use to to decide the dosage and its frequency. We have learnt though an example that change in frequency of drug dose has serious consequences in the body. We have studies the process of loading doses, which becomes very effective when a patient requires quick increase in concentration. At last, we made an effort to model drug flow process that resembles with real life situations in best possible manner. In conclusion, we can say that, drug dosage and it frequency are key parameters to maintains drug concentration in therapeutic range.