MMPS Project 4: Drug Delivery

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1 Problem Statement

Infections can often be alleviated by injecting drugs into the bloodstream. However, once in the bloodstream, the drug is quickly cleared by the kidneys, so the quantity of drug in the bloodstream available to fight infection will reduce swiftly unless replenished. Whilst sufficient drug is required to effectively fight infection, too much drug can be toxic to the system. You are asked to advise doctors on appropriate dosing regimes which will maintain drug levels within the therapeutic range.

You are given the following experimental data for an injection of 300mg of a drug:

Time since injection (hours)	1	3	5	7	9	11	13	15	17	19
Measured concentration in blood (mg/l)	10.0	7.0	5.0	3.5	2.5	2.0	1.5	1.0	0.7	0.5

This drug is ineffective if the concentration in the blood is below 5 mg/l, whilst it is toxic at levels above 20 mg/l.

2 Introduction

This problem is an insight into how drugs react in the bloodstream and how maths is used in the medical world to determine how to administer drugs safely and effectively.

3 Methods and Analysis

3.1 Assumptions

We begin this section by defining the assumptions and variables we will be using in our model.

- We can predict what happens in the gaps of the experimental data
- We can predict what happens in the first hour of the injection entering the bloodstream

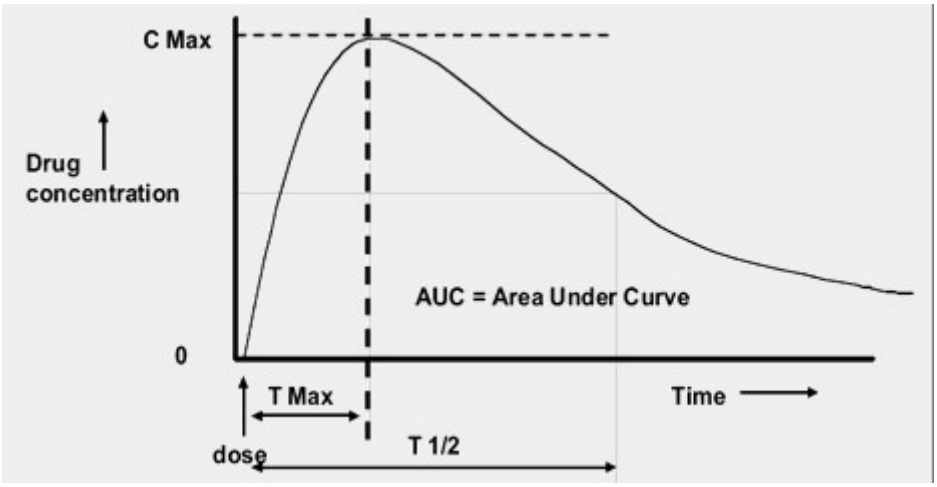

Figure 1: Concentration of drug against time

3.2 Drug Absorption

Drug absorption into the blood depends on how you take the drug, either by way of a pill or by injection. A pill takes up to an hour or even two hours to reach highest concentration in the blood due to the fact it has to be swallowed and then absorbed into the blood through the stomach walls. However, an injection that is injected directly into the blood work much faster, sometimes in seconds or minutes. When a drug is taken it will reach a peak level and then these levels will go down as the body breaks down the active ingredients, usually as the circulating blood is filtered by the liver and kidneys. Drugs are always absorbed more quickly than the body can break them down, so the highest concentration is reached quickly and then the body removes them from the body slower. [1] This can be shown via the drug absorption curve (Figure 1):

- The highest concentration is called the C_{max}.
- The total exposure to drug over the dosing period is the area under the curve.
- The time taken to get to the highest concentration is called the T_{max}.
- The time taken to reduce the highest concentration by half is called the half life ($\mathrm{T}\frac{1}{2}$).

3.3 Half-life Equations

We see that the experimental data reflects exponential decay (Figure 2) and we can model this using equations of half-life of radioactive substances. The standard equation of exponential decay is given by

$$y = Ae^{-Bt}$$

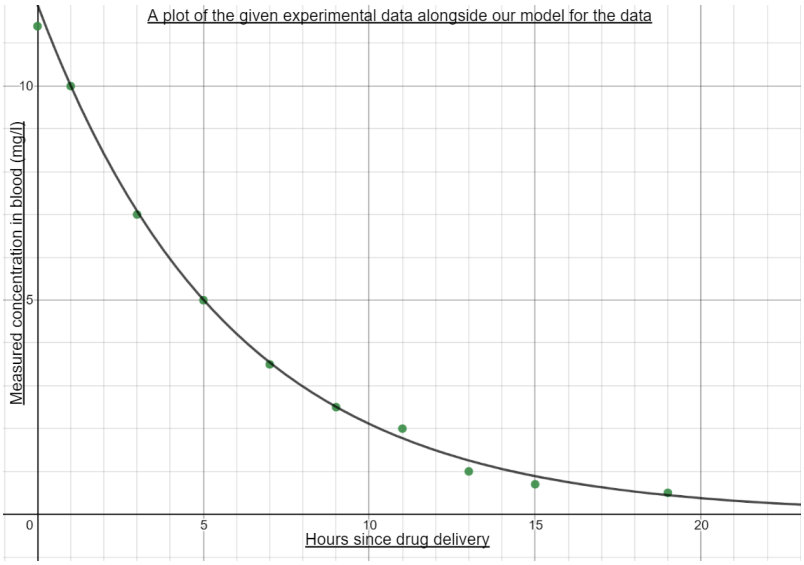

Figure 2: Concentration of drug against time

where y is the amount of active substance after t hours, A is the initial amount of substance, B is the decay constant and t is time taken in hours [2].
We need to calculate the value of A and B. For value B, we express the equation as:
$B = \frac{\log 2}{t} = \frac{\log 2}{4} = 0.173$, then $y = A * e^{-0.173t}$
Next, for the value of A, we choose one point t=1 and y=10 and substitute these values into the equation:$A * e^{-0.173*1} = 10$, giving the value of $A = 11.9$.
Finally, we get the decay equation $y = 11.9 * e^{-0,173t}$.

3.4 Line Of Best Fit

When we plot the data given and the exponential line of best fit through the data, we notice that our calculated decay constant is different from the line of best fit. The calculated value is 7.2 percent away from the line of best fit decay constant. The concentration at 0 would also be different giving two separate exponential decay curves. In figure 3, we can see a plot of both our model and the line of best fit.

The difference is subtle, however, combined over multiple dosages, it changes the results of our model. We can decide to keep our decay curve and ignore the difference in the decay constants and initial values due to the obvious half life values we saw in the data. For all but three values in the given data (11th through to the 15th hour), the half life graph fits exactly through the data points, where as the line of best fit didn't go through a single point in the given data.

3.5 Time between injections

Obviously, the problem statement requires that we administer multiple injections so that the patient doesn't drop out of the therapeutic range of the drug.

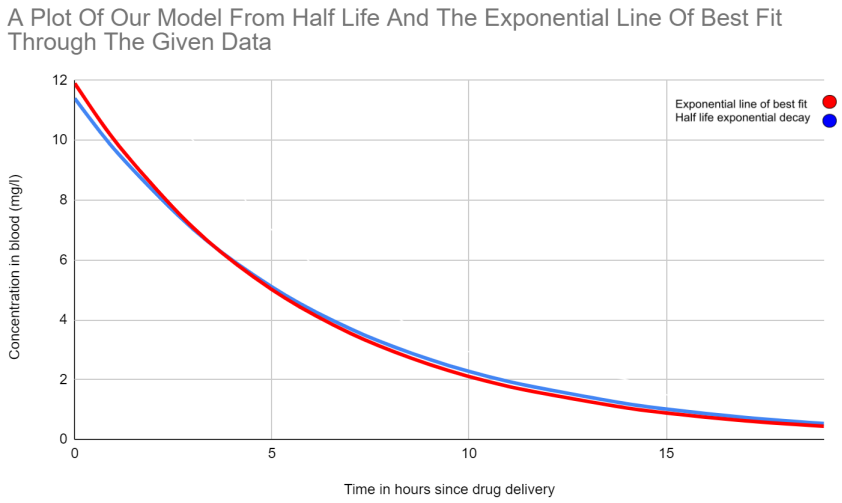

Figure 3: Concentration of drug against time of the two curves

We decide to divide one day (24hours) into several time periods for the injection. We decide to use 8 hours per period as 24 is divisible by 8 so we can arrange one day into three periods. Also, we need to make sure the patients get enough time to rest so we should not wake them up for the drug injection at midnight. Hence we will make a schedule for the injections. We start at 7am in the morning then another injection will happen at 3pm and the last injection at 11pm just before the patients fall asleep.

3.6 Multiple Injections

To scale our model for one injection into a schedule of injections to maintain concentration, we have to consider multiple injections. This is due to the decaying nature of concentration in our model. After a 300mg dosage of the drug within 5.05 hours the concentration in the blood is below the effective amount, therefore this is when another dosage is needed. From the subsection 3.2, drugs administered via injection circulate the blood stream in an almost negligible time. This means we can maximise the usefulness of each injection by waiting until the point of none-effectiveness of the drug where the concentration reaches 5mg/l in the blood before another dosage is needed. So as soon as the concentration reaches 5mg/l, we schedule another injection. From 3.5, 8 hours is the time between injections, this also comes from the fact 8 hours is almost the maximum time starting at the cut off point of poisonous concentration of 20mg/l dropping down to ineffectiveness of 5mg/l. The actual value of time between these two point from our model is 8.03 hours. When we inject the patient again, the initial drug continues to exist in the blood stream along side the second dosage. To account for this we sum a second decaying exponential function starting at 0 hours to the original exponential function that continues with the time from the in initial dosage. This resultant model means less drug is needed in following injections as there already exists drug in the blood stream.

If the same amount of drug was added each time, the total value would increase by 5mg/l with every injection as this is the amount in the blood already at the time of subsequent injections.

3.6.1 Dosage

As mentioned above, the first dosage would need to be larger than following dosages to stop the total concentration increasing indefinitely. We assume that the concentration of the drug scales linearly with the dosage. This allows us to predict a concentration within the blood from a given dosage. We want the drug to start at 20mg/l concentration in the blood and fall to 5mg/l before each injection. This maximises the time between doses and reduces the inconvenience of more injections throughout the day. To achieve this, an initial dosage of 526 mg ($3.s.f$) is needed to give a starting concentration of 20mg/l. This value is calculated by

$$(20/11.9) * 300mg$$

Following the initial injection, a reduced dosage of 395mg ($3.s.f$) calculated by

$$(15/11.9) * 300mg$$

is needed. This is because we inject again when the total concentration of previous injection falls to 5mg/l. The dose 395mg ($3.s.f$) gives a concentration increase of 15mg/l which would boost total concentration back to the 20mg/l poisonous - effective limit.

4 Results and Graph

To bring together all of the requirements for our model, we plot the initial decay equation which starts at the 20mg/l poisonous - effective limit and allow the concentration to fall to 5mg/l which occurs at 8.05 ($3.s.f$) hours in. Then we provide the second dose to raise the concentration back to 20mg/l and allow it to fall back again to 5mg/l. The final dose is at 16.08 ($3.s.f$) hours after the initial injection which again raises the concentration to 20mg/l before allowing it to fall back to 5.09mg/ ($3.s.f$) after 24 hours of the initial injection. Figure 4 shows our model over the one day cycle.

The figure 5 shows the residual effect of previous dosage across our 1 day cycle. Due to the exponential shape of each injection, technically the concentration would never reach 0mg/l; the previous injections would always need to be considered. In reality, the concentration of each injection reaches 1mg/l after around 17hours and we consider it negligible (sub 0.1mg/l) after 31 hours.

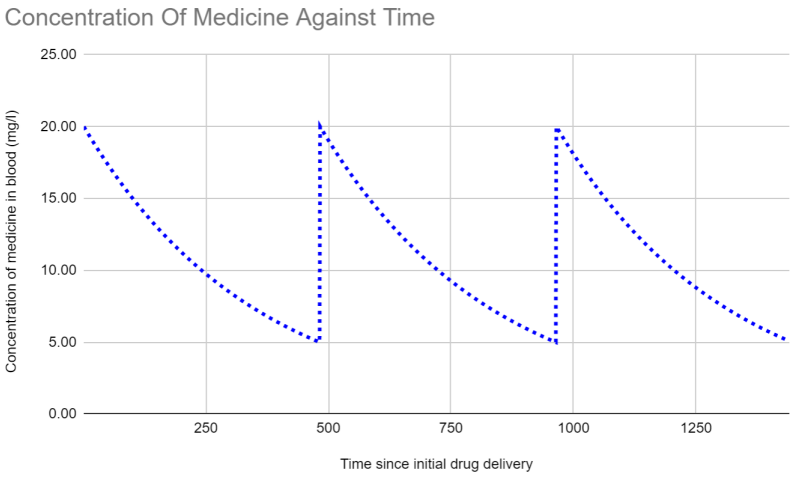

Figure 4: Concentration of drug against time

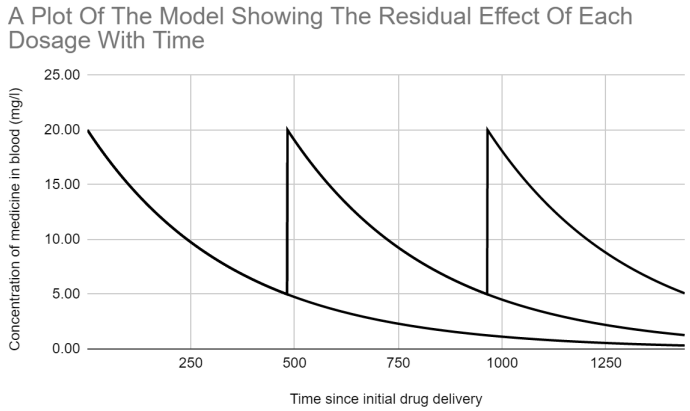

Figure 5: Concentration of drug against time with the residual effect of each injection plotted after the following injection is summed

5 Discussion

To extend our model, we could consider modeling the data as a differential equation to solve.

Different drugs in the body have different dissolution ability. We can consider the dissolution rate by Noyes-Whiteney:

$$\frac{dC}{dt} = \frac{DS}{h} * (C' - C)$$

$\frac{dC}{dt}$ represents the dissolution rate.
D is the diffusion co-efficient of dissolved drug.
S is the area of contact between the drug and the medium.
H is the diffusion depth.
C' is the solubility of a drug in gastric juice or medium.
$C' - C$ is the difference of solubility.

6 Conclusions

In conclusion the model we created would allow a patient a 24hour cycle of injection over the course of recover which we predict would remain stable over the course of a few weeks. Due to 0.09mg/l unaccounted extra concentration which would increase each day the model would not be suitable over a longer time than a few weeks, this wasted concentration at end of the 24hour could be accounted for with a smaller dosage for-example a increase of 14 mg/l after 11 days to increase the effectiveness of our model over longer periods.

References

[1] i-Base. *What happens when you take a drug? (2009).* URL: `http://i-base.info/ttfa/learning-resources/what-happens-when-you-take-a-drug/`. (accessed: 12.12.2019).

[2] Frank Rösch. *Nuclear- and Radiochemistry: Introduction. 1.* Walter de Gruyter, 2014.