XSEDE 2016 FSU

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1 Pharmacokinetics of Medicinal Drugs

Pharmacokinetics describes how drugs pass through the body and interact with our physiology. As stated in the introductory document, "the amount of medicine in the bloodstream needs to reach a medicinal level in order to be effective ... but above a certain level, the medicine will become toxic" (Pharmacokinetic Model of Drug Dosage and Concentrations). These medicinal and toxic levels vary for each medicine and each person. The code that we were given and expanded on is capable of determining a healthy, but effective dosage regimen for an individual given that individual's weight (which is a proxy for blood volume).

2 Model Design

2.1 Description of Main Code

The main code uses the Forward Euler method to solve the differential equation that describes the concentration of the drug in the blood plasma. At each time step, the intake loop determines whether medicine should be added to the bloodstream based on the time of day and the number of doses scheduled per day. If medicine needs to be added at the current time step, then the dosage amount is added to the drug intake variable.

After running the intake loop, the program executes a loop that calculates the blood plasma concentration of the drug. In order to make this calculation, the loop updates the intermediate variables: drug absorption, drug excretion, intestinal medicine/drug level, and plasma drug level. Excretion of the drug is the drug excretion rate times the plasma drug level; intestinal medicine/drug level is the prior intestinal drug level minus the drug absorption, plus the drug intake; and plasma level is the prior plasma level minus the drug excretion, plus the drug absorption. Given these values, the blood plasma concentration of the drug is determined as `plasma_level/blood_volume`.

these would be better illustrated explained with a set of equations

~~Importantly,~~ the main code is parameterized such that it can give the blood plasma concentration for different drugs and different people. Different drugs will have different absorption and excretion rates, and different medicinal and toxic levels. These parameters can all be updated in the code. Similarly, different people will have different blood volumes, and therefore different blood plasma concentrations of the drug. As such, the main code allows the blood volume to be adjusted to accurately reflect the blood plasma concentrations of the drug for a particular person.

2.2 Baseline Model Parameter Derivation

By manually adjusting the model parameters for number of doses per day and the total daily dosage level, we discovered two distinct relationships. The dosage level controls the steady-state blood plasma drug concentration. The number of doses controls the frequency and amplitude of

oscillations in the blood plasma drug concentration. The higher the dosage, the higher the steady state blood plasma drug concentration. The higher the doses taken per day, the smaller and more frequent the oscillations around the steady-state blood plasma drug concentration. Shown below are a series of four different plots which show different values for the parameters. As the plots show, the optimal dose is 4 doses of 12000 mg per day. To be safe, a lower dose of 11800 mg will also remain in the toxic-medicinal bounds.

What was your criteria for optimality? Safety?

Figure 1

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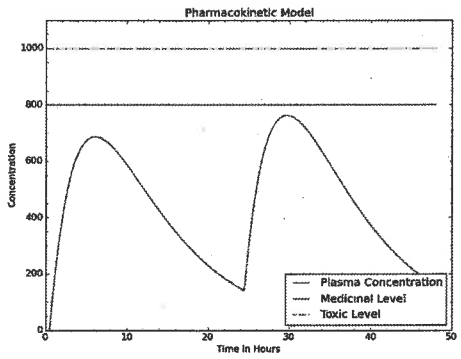
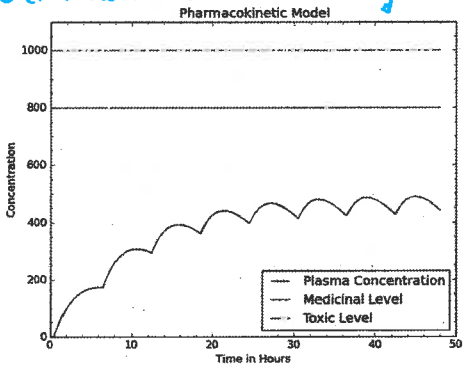
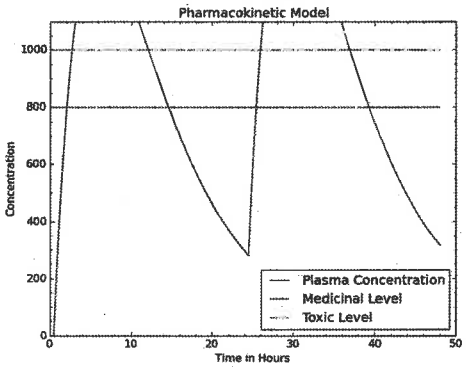
it would be helpful to use different linestyles if someone prints B/W



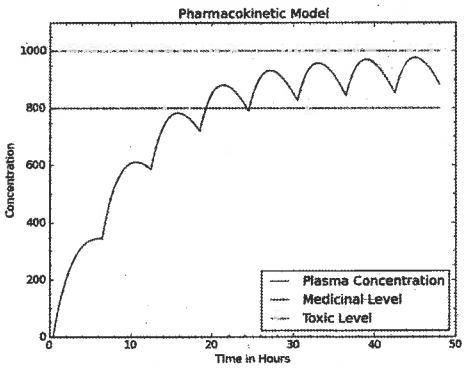
(a) 1 Dose totaling 6000 mg Per Day



(b) 4 Doses totaling 6000 mg Per Day



(c) 1 Doses of 12000 mg Per Day



(d) 4 Doses totaling 12000 mg Per Day

2.3 Baseline Model Assumptions and Improvements

Both the model of plasma drug concentration and the code to implement the model rely upon simplifying assumptions. Below, we discuss several of these assumptions, and make changes when possible.

initial implementation

First, the code assumed that the number of doses per day was a divisor of 24, which was done to make the calculation of the dose-timing simpler. In our codes, we removed this assumption in order to allow for doses per day that weren't divisors of 24.

implementation

Next, we accounted for the fact that a person on average is only awake for 16 hours a day. While the original code allowed people to take doses in the middle of the night, we assumed that people can only take their doses during a 16-hour window. Below you can see a graph of how this affects the concentration of the drug in ~~someone's~~ blood.

√√ good point

a patient's/person's

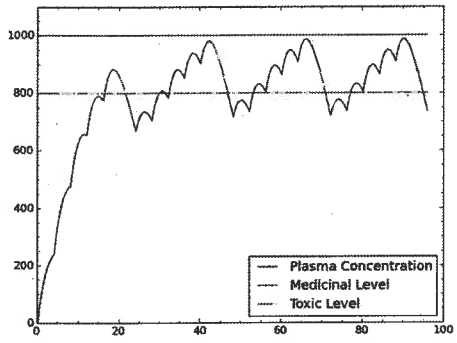


Figure 2: 4 Doses totaling 8800 mg per day, all doses taken during 16 hours of awake time

We were not able to keep the concentration within the medicinal-toxic level window during the 8 hours of sleep where no drugs are taken. Even increasing the dosages per day to an inconvenient number (such as 128) did not solve the problem, and we believe this is due to the `half_life` of the drug being too fast. We doubled the half-life to 12 hours and were able to keep the fluctuations of the concentration within the window.

what about varying the dosage ~~amount~~ amount and delivery time?
ex. 1x 8am "
1x 12 noon "
2x 8pm 10pm

A theoretical assumption made by the model was that we are dealing with one compartment. I.e., the model assumed that the body is one compartment that absorbs and eliminates the drug at specific rates, but in reality the body has multiple compartments, each with a different rate of absorption and elimination based on biological features (such as tissue density).

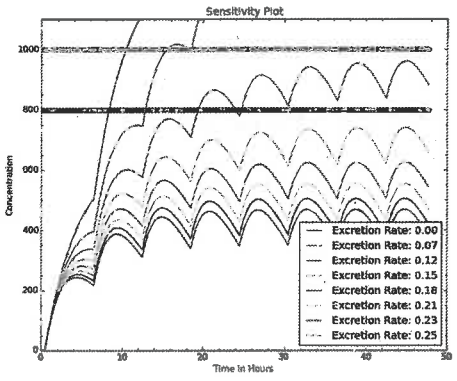
Lastly, with drugs taken orally, it is not guaranteed that 100% of the drug will be absorbed into the body. The model assumes that this is the case.

Also assumed that the same amount would be taken @ regular intervals rather than more right before bed or an irregular schedule ex: 2hr 2hr 8hr 4hr 2hr 2hr

3 Model Solution

3.1 Sensitivity Analysis of Excretion Rate

A sensitivity analysis was conducted on the `excretion_rate` parameter which is defined as $\frac{log(n)}{t_{1/2}}$ where $t_{1/2}$ is half life. We ran the model with n varying from 1 to 5 in increments of 0.5. This sensitivity analysis showed that `excretion_rate` has the effect of depressing the steady-state blood plasma concentration of the drug. The result of varying `excretion_rate` is shown in the plots below.



why only 50 hrs?

Figure 3: Plot of Sensitivity Analysis. Note that the thick red line is the toxic level and the thick green line is the medicinal level

These models were all run with a dosage of 11800 mg and 4 doses per day. As the model shows, for the given dosage and number of doses per day, the excretion rates can very easily determine whether or not the plasma concentration reaches the medicinal level or overshoots the toxic level. Thus it is very important to correctly tune the dosage and number of doses per day to the excretion rate of the drug. Otherwise, there is risk of the drug not being effective or possibly exceeding the toxic level.

3.2 Results and Conclusions

It would have been nice if you could quantify this relationship with an equation.

Our two main findings were: 1) the dosage level controls the steady-state blood plasma drug concentration; and 2) the number of doses controls the frequency and amplitude of oscillations in the blood plasma drug concentration. Specifically, the higher the dosage, the higher the steady state blood plasma drug concentration. Also, the higher the doses taken per day, the smaller and more frequent the oscillations around the steady-state blood plasma drug concentration. As Figure 1 showed, the optimal dose is 4 doses of 12000 mg per day. To be safe, a lower dose of 11800 mg will also remain in the toxic-medicinal bounds.

4 Bonus Questions

4.1 Time Release

For a time released drug, we have assumed the intake at each time step will be the same. We calculated the intake to be the dosage per day times the time step divided by the hours in a day (24). This causes the concentration of the drug in a person's blood to change continuously, as is visible in the figure below. The figure also shows the minimum dosage per day (10272 mg) required to reach the medicinal level, and the maximum dosage per day (12827 mg) without reaching the toxic level. These amounts correspond to hourly dosages of 428mg and 534mg, respectively.

what is the new equation you used to model this?

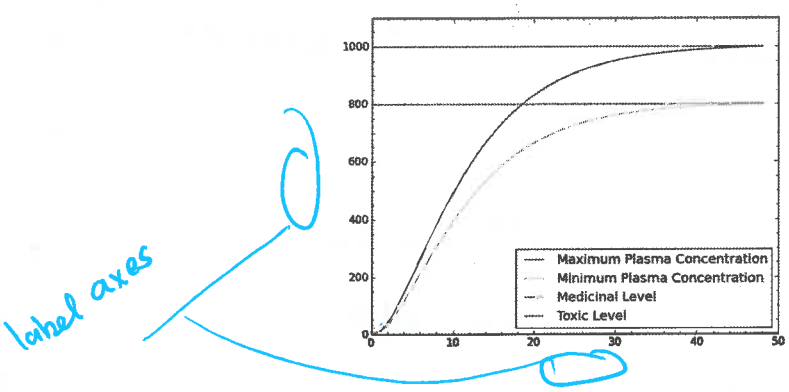
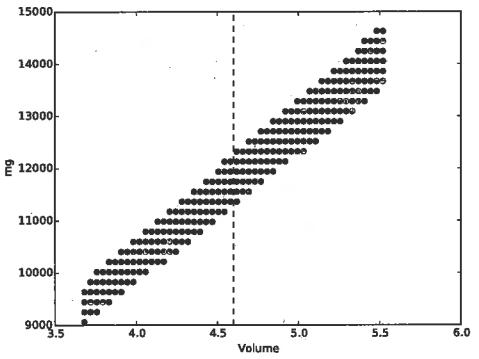


Figure 4: Plot of minimum dosage per day to reach the medicinal level and maximum dosage per day without reaching the toxic level

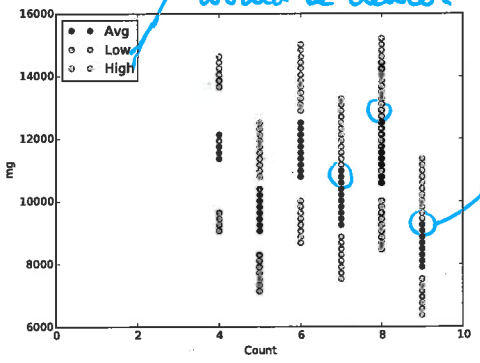
4.2 Plasma Volume Variability

There is a large variability in weight distribution and thus in plasma volume. Smaller people have to take smaller doses to avoid entering the toxicity region, whereas larger people might need larger doses to reach the medicinal region. We wrote code to come up with ideal dosages given a person's size.

First a function was written to check whether a simulation was in the safe region after the 48 hour window. We looked at the plasma concentration of the drug since the last dose and verified it was in the medicinal-toxic bounds. This function enabled us to run many simulations for the different combinations of doses, and plot the safe combinations. In Figure 5a, we plot the region of safe total daily dosage levels for people with ± 20% average blood volume. Here we assumed that the does per day was kept at a level of 4. The region slightly broadens as the weight is increased, meaning that a wider range of doses is acceptable for larger people.



(a) Region of safety for 4 doses per day



(b) Safe regions for a +/- 20 % average blood volume

Figure 5: Studies on Plasma Volume Variability

Figure 5b shows that the window of safe dosages shifts up for larger blood volumes and down for smaller blood volumes as expected. An interesting phenomenon is the oscillation in the safety

region between even and odd number of doses per day. This was not fully explored but could be a result of the way the original program handled the dose schedule. ← Explain more fully why you think that is.

4.3 Interactive Model

The methods developed in section 4.2 were done in a functional form so that making the simulations interactive was quite easy. Using the `input()` function in python, the program asked for the users weight in kilograms. The equation used to convert weight to blood volume was `BloodVol = Weight * AvgBloodVolperKg`, which was found on Medscape. The same functions were used from section 4.2 except that blood volume was held constant. The average of the range was returned as the suggested total daily dosage level.

doesn't change based on the user?

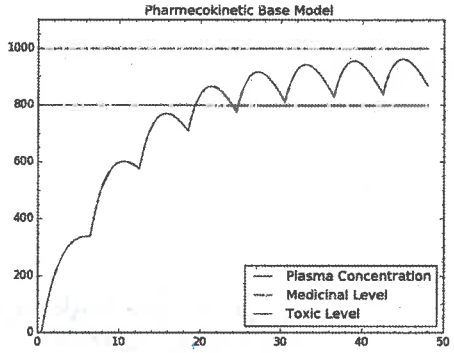
Citation needed

what about a version that takes arguments from the commandline and saves to file?

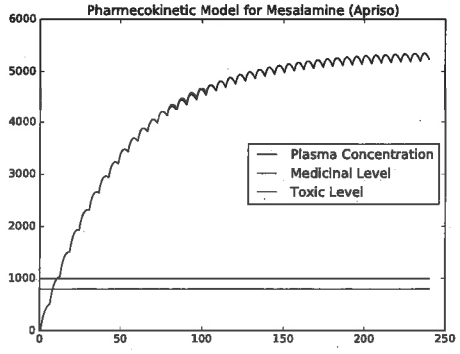
4.4 Case Study

We went through Webmd.com and found the prescribing information of Mesalamine (Apriso). Mesalamine has a 32% absorption rate and 2% excretion rate. To get the steady state concentration of the drug, we had to alter the end time to 240, which is equal to 10 days or 5 * 48 hours (the original end time).

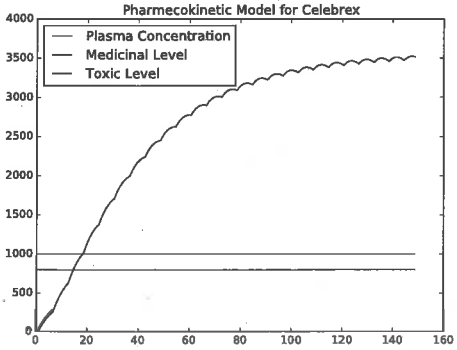
How do you quantitatively assert that this is steady state beyond a graphical check? What about checking the derivative of the mean? w/o oscillations



(a) 25.0% Absorption, 11.2% Excretion Rate



(b) 32.0% Absorption, 2.0% Excretion Rate



(c) 10.0% Absorption, 3.0% Excretion Rate

The original drug had a 25% absorption rate and 11.5% excretion rate (Figure (a)). According to the prescribing information, Mesalamine increased the excretion level by $\frac{11.2\%}{2.0\%} \simeq 6$, and we see that this causes the steady state to rise to 5000 (Figure(b)). Approximately, we can say that there's a linear relation between the rate of excretion and the steady-state concentration of the drug (as well as the time taken to reach the steady state).

As shown in Figure(c), we tested this observation with Celebrex, which has a 10% absorption rate and 3% excretion rate. We expected the time taken to reach the steady state to increase by the ratio of excretion rates $\frac{10.\%}{3.0\%} \simeq 3$, and this is what Figure(c) shows (144 hours = 3 * 48 hours). Similarly, the new steady-state concentration also tripled.

Lastly, it's important to note that lowering the excretion rate leads to higher steady state concentrations, which could be more toxic depending on the drug.

5 References

Apriso. http://www.aprisorx.com/Portals/192/assets/pdf/apriso-pi.pdf
Celebrex.http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020998s027lbl.pdf
Pharmecokinetic Model of Drug Dosage and Concentrations (Part of the Instructions Package)