

NCAAPMT Calculus Challenge 2011-2012

Challenge #1

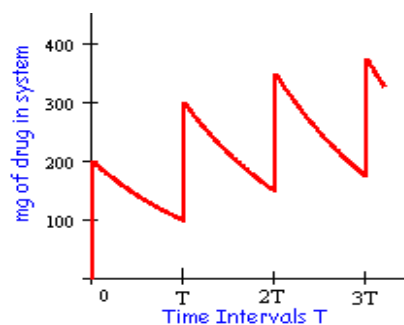
Due: September, 28, 2011

Determining the Proper Drug Dosage

After working too long in the yard over Labor Day weekend, I had several options for my strained back: acetaminophen (take 500 mg every 4-6 hours), naproxen sodium (take 220 mg every 8-12 hours), aspirin (take 325 mg every 4 hours), and ibuprofen (take 200 mg every 4-6 hours). Why the different dosages and intervals between doses? When taking repeated doses of a drug, how are the size of the pill and the time between pills determined so that there is a safe and effective concentration of the drug in the blood?

In practice, it is the concentration of a drug (mg/ml blood) that is of most interest. To keep things simple, in this problem we consider a “standard person” with a fixed blood volume (on average, people have about 60 milliliters of blood per kilogram body weight), so we can use the amount of a drug (size of the pill in milligrams) rather than the concentration of the drug as our basic unit.

A patient is given a fixed dosage Q mg of a drug at regular intervals of time T hours. Assume that the drug enters the system immediately upon ingestion and that the decrease in the concentration in the blood over time is proportional to the concentration itself. This means that in between dosages the amount, A , of the drug in your system decreases so that $A = A_0 e^{-kt}$. The value of k for each medication is often given in terms of its half-life. By repeated administrations of the drug every T hours, the



amount of medication in the body has the shape at right since not all of the drug from the previous dose has been metabolized before the next one is taken. The dosage shown is 200 mg every T hours.

If the first dose is administered at $t = 0$, the amount of medication remaining in the blood at time T , and before the next dose is taken, can easily be determined and expressed in terms of the parameters in the model: the initial dose and the decay parameter k . This amount is known as the first residual and is denoted R_1 . The residual, R_1 , of the first time period plus a new dose is the initial amount for the second time period.

- a) Find $R_1 \dots R_5$, and generalize for the n th residual R_n .

Interval n	Amount A_n	Residual R_n
1	Q	Qe^{-kT}
2		
3		
4		
5		
n		

You should notice that both the amounts $-A_n$, at the beginning of each time period and residuals, R_n , at the ends of each time period – involve a series you should recognize. The sums of those series give the accumulated amounts at each end of the time interval.

b) The value of R_n approaches its limiting value R asymptotically. This is denoted $R = \lim_{n \rightarrow \infty} R_n$.

By considering the infinite series found above, determine the limiting value of the residual amount for dose of size Q mg repeated forever at intervals of T hours.

The goal of repeated dosing is to maintain levels of medication in the system that are large enough to be effective, but small enough to be safe. Every medication has both a minimum level for effectiveness (L), and a maximum level at which it becomes toxic (H). For example, salicylate (aspirin) concentrations of at least 100 $\mu\text{g/ml}$ are required for analgesia, and concentrations of roughly 150-300 $\mu\text{g/ml}$ are necessary for anti-inflammatory effects. Tinnitus can occur when salicylate concentrations reach 300 $\mu\text{g/ml}$, and this can be used as a monitoring parameter in patients with normal hearing. Severe toxic side effects can occur at concentrations greater than 400 $\mu\text{g/ml}$.

c) If an accumulated level above H mg is unsafe and a level below L mg is ineffective, find a time schedule T for a dose Q in terms of H and L for a safe and effective amount of the drug in the system. (Your answer will also depend on the parameter k .)

d) Ibuprofen follows this model well. Suppose I take 200 mg every 6 hours. In the 6 hour time period, the “standard human” will have metabolized 50% of the drug in the body. Suppose I’ve been taking the medication repeatedly for several weeks, so the amount of ibuprofen in my body has “reached” its asymptotic levels. Now, suppose I forget to take a pill. At the next time to take a pill, I can either take just one or double up to make up for the one I missed. What would be the difference in maximum and minimum amounts in my system if I take one or two after missing a pill for 6 hours?

e) In many medications, several different medicines are combined. Often the optimal amount of each medicine and the time until the next pill differ, so the timing is optimized only the most important ingredient. This is why, if you take a cold tablet that has a cough suppressant and a decongestant, you will likely begin coughing before your nose gets congested again.

A few years ago, I began taking two Aggrenox each day, one in the morning and one 12 hours later in the evening. Aggrenox is a combination of two drugs, 20 mg of Aspirin and 200 mg of Dipyridamole. These two drugs do not interact, so the pharmacokinetics in combination are the same as when each is administered in isolation. Describe the concentrations in $\mu\text{g/ml}$ of these two drugs in my body for a 48 hour period beginning 6 days after I initially began taking the Aggrenox. I weigh 90 kilograms.

Pharmacokinetics

Aspirin: At low doses, the elimination is first-order and the half-life remains constant at 2-3 hours. **Source:** <http://www.migraines.org/>

Dipyridamole: Dipyridamole is metabolized in the liver and has a prolonged elimination phase, with a half-life of about 13.6 hours. **Source:** <http://www.aggrenox.com/bipi/PageIndex>