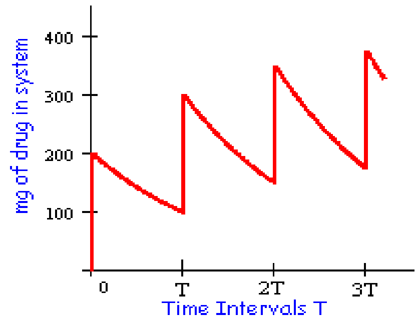
NCAAPMT Calculus Challenge 2011-2012

Challenge #1 SOLUTION

In this challenge and in all future challenges, it is not necessary to use the same techniques as shown in the sample solution. The sample solutions just show one way to answer the questions.

Determining the Proper Drug Dosage

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 $R_1 \ldots R_5$, and generalize for the nth residual R_n.

The residual is always $(A_n)\cdot e^{-kT}$, and the new value of A_n is $R_n + Q$.

Interval n	Amount A_n	Residual R_n
1	Q	Qe^{-kT}
2	$Qe^{-kT} + Q$	$(Qe^{-kT} + Q)e^{-kT}$
3	$(Qe^{-kT} + Q)e^{-kT} + Q$	$[(Qe^{-kT} + Q)e^{-kT} + Q]e^{-kT}$
4	$[(Qe^{-kT} + Q)e^{-kT} + Q]e^{-kT} + Q$	$\{[(Qe^{-kT} + Q)e^{-kT} + Q]e^{-kT} + Q\}e^{-KT}$
5	$\{[(Qe^{-kT} + Q)e^{-kT} + Q]e^{-kT} + Q\}e^{-KT} + Q$	$(\{[(Qe^{-kT} + Q)e^{-kT} + Q]e^{-kT} + Q\}e^{-KT} + Q)e^{-kT}$
n		

In this form, it is difficult to see the form for the n^{th} interval. If we multiply through, we see that both terms are geometric series with a common ratio of e^{-kT} .

Interval n	Amount A_n	Residual R_n
1	Q	Qe^{-kT}
2	$Q+Qe^{-kT}$	$Qe^{-kT}+Qe^{-2kT}$
3	$Q+Qe^{-kT}+Qe^{-2kT}$	$Qe^{-kT}+Qe^{-2kT}+Qe^{-3kT}$
4	$Q+Qe^{-kT}+Qe^{-2kT}+Qe^{-3kT}$	$Qe^{-kT}+Qe^{-2kT}+Qe^{-3kT}+Qe^{-4kT}$
5	$Q+Qe^{-kT}+Qe^{-2kT}+Qe^{-3kT}+Qe^{-4kT}$	$Qe^{-kT}+Qe^{-2kT}+Qe^{-3kT}+Qe^{-4kT}+Qe^{-5kT}$
n	$Q+Qe^{-kT}+Qe^{-2kT}+\cdots+Qe^{-(n-1)kT}$	$Qe^{-kT}+Qe^{-2kT}+\cdots+Qe^{-nkT}$

So, using the formula for finite geometric series, $A_n=\dfrac{Q+Qe^{-(n)kT}}{1-e^{-kT}}$ and $A_n=\dfrac{Qe^{-kT}+Qe^{-(n+1)kT}}{1-e^{-kT}}$.

b) The value of R_n approaches its limiting value R asymptotically. This is denoted $R=\lim\limits_{n\to\infty}R_n$. 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 series for both the Amount, A_n, and the Residual, R_n, are geometric, we can use the formula for an infinite geometric series to find the asymptotic values.

Since, $A_n=\dfrac{Q+Qe^{-(n)kT}}{1-e^{-kT}}$ and $A_n=\dfrac{Qe^{-kT}+Qe^{-(n+1)kT}}{1-e^{-kT}}$, in the limit, we have $A=\lim\limits_{n\to\infty}A_n=\dfrac{Q}{1-e^{-kT}}$ and $R=\lim\limits_{n\to\infty}R_n=\dfrac{Qe^{-kT}}{1-e^{-kT}}$.

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 μg/ml are required for analgesia, and concentrations of roughly 150-300 μg/ml are necessary for anti-inflammatory effects. Tinnitus can occur when salicylate concentrations reach 300 μg/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 μg/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*.)

If a residual level above *H* is unsafe and below *L* is ineffective, we must find a dose schedule *T* for dose size *A* that maintains a safe and effective concentration of the drug in the blood.

This will happen if we let $H = \frac{Q}{1-e^{-kT}}$ and $L = R = \frac{Qe^{-kT}}{1-e^{-kT}}$, then $H - L = Q$, so the dose size could be the difference in the maximum safe dosage and the minimum effective dosage. The appropriate time interval can be found by realizing that you need to move from the high point H to the low point L exponentially in time T, so $L = He^{-kT}$ and solving for *T*. We have $e^{-kT} = \frac{L}{H}$ so $T = \frac{1}{k}\ln\left(\frac{H}{L}\right)$.

There are lots of other ways to answer this part of the question. All reasonable solutions will be accepted. For example, a more sophisticated solution would be to note that, in practice, we would like to have some fairly wide margin of error. As a consequence our interval might reasonably fall in the middle of the interval between *H* and *L*. So, we might consider the interval between $L^* = L + \frac{H-L}{4} = \frac{3L+H}{4}$ and $H^* = H - \frac{H-L}{4} = \frac{3H+L}{4}$. If we repeat the calculation above, we have $H^* - L^* = Q = \frac{H-L}{2}$ and $T = \frac{1}{k}\ln\left(\frac{H^*}{L^*}\right) = \frac{1}{k}\ln\left(\frac{3H+L}{3L+H}\right)$.

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?

If we take one 200 mg tablet every 60 hours, with a decay rate of 0.5, then the steady state levels will be $A = \frac{Q}{1-e^{-kT}} = \frac{200}{1-e^{-0.5(6)}} = 210.5$ mg and $R = \frac{Qe^{-kT}}{1-e^{-kT}} = \frac{200e^{-3}}{1-e^{-3}} = 10.5$ mg.

If we miss a pill, the lower level continues to decrease from 10.5 mg for another 6 hours, leaving 0.52 mg (essentially, it's all gone). So, you would be starting over. The next level will go back to 200.52 then decrease to about 10 mg and you are back to normal immediately.

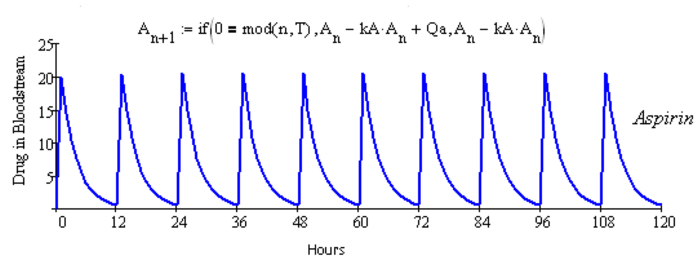
If you take a double-dose, you move from 0.52 up to 400.42 mg. After 6 hours you are back down to 20 mg and after another 6 hour period you are back to normal.

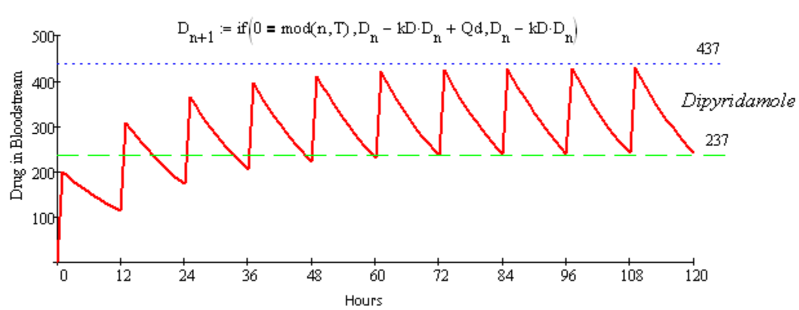
Since most of the medication is utilized in the 6 hour period, it is better to simply take a single dose rather than "make up" for the lost dose.

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 µg/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.

Here, we need to change the units from mg to µg/ml. I'll wait to do that at the end. We also need to approximate the decay rate from the half-life. For Aspirin, we will use a half-life of 2.5 hours, so $k = \frac{\ln(2)}{2.5} = 0.277$. For dipyridamole, we will use $k = \frac{\ln(2)}{13.6} = 0.051$. Like the ibuprofen, almost all of the aspirin will be metabolized in the 12 hours, while only a portion of the dipyridamole will b metabolized. For aspirin, we have steady state values of a maximum of $Aspirin = \frac{20}{1-e^{-0.277(12)}} = 20.7$ mg and minimum of $Aspirin = \frac{20e^{-0.277(12)}}{1-e^{-0.277(12)}} = 0.75$ mg. For dipyridamole, steady state values of a maximum of $\frac{200}{1-e^{-0.051(12)}} = 436.9$ mg and minimum of $\frac{200e^{-0.051(12)}}{1-e^{-0.051(12)}} = 236.9$ mg. Graphs describing each are shown below.





Since there are approximately 60 ml of blood for every kg of weight, I have about 5400 ml of blood in my body. Also, there are 1,000 µg/mg So, 20.7 mgs and 0.75 mgs of aspirin are equivalent to 20,700 µg and 750 µg. So, the minimum concentration is 0.14 µg/ml and the maximum concentration is 3.83 µg/ml in my system. For dipyridamole, the steady state values of a maximum of 80.97 µg/ml and minimum of 43.87 µg/mg.