Suppose a drug is metabolized and excreted in the body in a manner so that it decays with a half-life of 3 hours. The effective dosage range for this drug has been found to be fairly broad - from 4 mg per kg of body weight to 11 mg per kg of body weight. You have prescribed this drug for a 100 kg patient and specified that a dose is to be given every 4 hours.

a. What fraction of the drug in the patient's body will decay between each dose?

b. What periodic dose of the drug must be given in order to ensure that the amount of drug in the patient remains within the effective dosage range and the amount drops just to the lower end of this range at the time of each dose?

c. What is the loading (bolus) dose to be given to this patient?

If you haven't already, read through the solutions for problems 27 and 28 from the Section 48 homework first.

This problem must be broken up into (at least) two parts. First, we need to handle the decay of the drug in the body, which is a continuous time process. Then, we can combine it with the drug dosage, which is a discrete time process.

Experimental evidence tells us that for most drugs, the amount of the drug in the body decays exponentially over time. (See example 48.5 on pages 537-538 of the textbook.)

We are given the half-life of the drug, and we can use this to find what fraction of the drug decays in 4 fours (that is, between each dose). From the half-life, we can find the decay rate using the formula:

$$r = \frac{\ln 2}{t_h} = \frac{\ln 2}{3} \approx 0.231$$

Next we can calculate what fraction of the drug is still in the body after 4 hours using the exponential decay equation:

$$N(t) = N_0 e^{-rt}$$

Since we don't know the initial amount of the drug in the body, we will have to just use N_0, but since this will cancel out later, it won't matter that we don't know its actual value yet.

After 4 hours, the amount of the drug left in the body is:

$$N(4) = N_0 e^{-0.231 \cdot 4} \approx .4 \cdot N_0$$

or about 40% of the original amount.

So for part (a), this means that 60% (or $\frac{3}{5}$) of the drug will decay between each dose.

Now, if we include the drug dosage, the change in the amount of the drug in the body (every 4 hours) is -60% times the amount present and then <u>plus</u> the dosage of the drug, which can be written as

$$\Delta x = -60\% \cdot x_n + b$$

$$x_{n+1} - x_n = -0.6 \cdot x_n + b$$

$$x_{n+1} = x_n - 0.6 \cdot x_n + b$$

$$x_{n+1} = 0.4 \cdot x_n + b$$

which is a linear first order difference equation where $a = 0.4$ and b is the amount of the dosage. So the equilibrium for this equation is $A = \frac{b}{1-a} = \frac{b}{1-0.4} = \frac{5}{3}b$. Since $a = 0.4$ is between -1 and 1, this equilibrium is stable.

At the equilibrium, the dosage of the drug exactly makes up for the amount of the drug that has decayed in the body. So before the dosage is given, the amount of the drug in the body is

$$A - b = \tfrac{5}{3}b - b = \tfrac{2}{3}b.$$

For part (b), we want this value to equal the lower end of the effective dosage range. For a 100 kg patient, that would be 4 mg per kg of body weight times 100 kg, for a total of 400 mg. So we want

$$A - b = \tfrac{2}{3}b = 400 \Rightarrow b = 600.$$

So the periodic dose of the drug should be 600 mg.

This will take the amount of the drug in the patient's body back up to 1000 mg. Then over the next 4 hours, the amount of the drug will decay to 400 mg, and the next dosage of the drug will take the amount back up to 1000 mg. Continuing this process will keep the amount of the drug in the patient's body between 400 mg and 1000 mg, which is within the effective dosage range.

For part (c), we want the loading (bolus) dose to equal the equilibrium value, so that the periodic dose will keep the amount of the drug in the patient's body within the effective dosage range (as just mentioned). The equilibrium value is

$$A = \tfrac{5}{3}b = \tfrac{5}{3}\cdot 600 = 1000.$$

So the loading (bolus) dose should be 1000 mg.