Math 312 Lecture Notes Periodic Drug Doses

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11 March 2005*

Periodic Drug Doses

In this lecture, we consider the concentration of a drug in the bloodstream of an individual when the drug is administered periodically. We'll look at a simple model that involves both a differential equation and a discrete map. We'll also see another example of using dimensional analysis.

Clearing of a Drug from the Bloodstream

There is a variety of mechanisms for a drug to be cleared from the bloodstream. Organs in the body may actively absorb the drug, the drug may react with other chemicals in the bloodstream, or the drug may naturally breakdown into simpler components. The simplest model of how a drug is cleared from the bloodstream results from assuming that the rate of loss of the drug is proportional to the concentration of the drug. If c(t) is the concentration of the drug at time t, the differential equation for this simple model is

$$\frac{dc}{dt} = -rc,\tag{1}$$

where r > 0 is the proportionality constant that determines the rate of clearance¹. We know that the solution to this equation is $c(t) = c_0 e^{-rt}$, where c_0 is the concentration at time t = 0.

Equation (1) is the same as the equation for the decay of radioactive materials, so we can define the *half-life* of the drug. This is the time required for the amount of the drug to be reduced to half the original amount. For example, according to an article on **Slate** by Sam Schechner² about the poisoning of Viktor Yushchenko, some isomers of dioxin have a half-life of more than seven years. If a drug has a half-life of seven years, then

$$c(7) = c_0 e^{-7r} = \frac{c_0}{2},\tag{2}$$

which implies

$$r = \frac{\ln 2}{7} \approx 0.0990,\tag{3}$$

^{*}This version: 18 March 2005

¹Note: r is not "the rate at which the drug is cleared". The rate at which the drug is cleared is $\frac{dc}{dt}$, which is changing over time. Sometimes r is called the rate constant.

²http://slate.msn.com/id/2110979/, Dec. 13, 2004



Figure 1: A plot of the concentration c(t) for a drug administered periodically. In this example, r = 0.3, h = 2 and b = 1. At t = 0, h, 2h, ..., c(t) increases by b; otherwise the concentration decays according to (1).

where we assumed t was measured in years, and therefore r has the units of years⁻¹.

Question 1 Suppose a drug has a half-life of seven years. (a) How long will it take for the amount of the drug to be reduced to one-quarter of the original amount? (b) How long will it take to be reduced to one percent of the original amount?

Answers: (a) 14 years, (b) 46.5 years.

Administering a Drug with Periodic Doses

We now suppose that a drug is administered periodically. That is, every h time units, a dose is administered that increases the concentration by b. (If the *amount* administered is a, and the volume of the blood in bloodstream is V, then b = a/V. We will work with b from here on.) We assume that the dose causes an instantaneous increase in the concentration. This is probably a good assumption for a drug administered by an injection. Whether this is a good assumption for a drug taken orally depends on the properties of the drug. Alcohol, for example, enters the bloodstream fairly rapidly, so the instantaneous increase in concentration is probably a reasonable approximation for alcohol.

We assume that the first dose is administered at time t = 0, and the concentration of the drug in the bloodstream before then is zero. At t = 0 the concentration jumps to b, and then for 0 < t < h, the concentration decays according to (1). At t = h, another dose is administered, and the concentration increases by b. The concentration then decays for h < t < 2h, and the process continues. We expect the plot of the concentration to look like the graph shown in Figure 1.

Parameter	Meaning	Dimension
r	proportionality constant for the clearance of the drug	\mathcal{T}^{-1}
h	time period	\mathcal{T}
b	instantaneous change in concentration due to each dose	\mathcal{C}
x_{∞}	asymptotic concentration just before the next dose	\mathcal{C}

Table 1: The list of variables and parameters along with their dimensions. \mathcal{T} means time and \mathcal{C} means a concentration. (In a problem with a wider variety of parameters, we might want to express concentration as an amount \mathcal{A} divided by a volume \mathcal{V} or even divided by the cube of a length \mathcal{L} , but this is not necessary in this case.)

We need some additional notation to describe the graph shown in the figure. Let

$$c(h^{-}) = \lim_{t \to h^{-}} c(t) \qquad \text{(the limit from below)},$$

$$c(h^{+}) = \lim_{t \to h^{+}} c(t) \qquad \text{(the limit from above)}.$$
(4)

and define

$$x_n = c((nh)^-). \tag{5}$$

Thus, x_n is the concentration at the moment before a new dose is administered. It is clear the graph of c(t) will consists of periods of decay, separated by jumps. What we would like to know is what happens to x_n as n increases? Does x_n increase without bound? Or does x_n approach some value asymptotically? If so, what value does is approach?

Dimensional Analysis of x_{∞}

We'll find the exact formula for x_n in the next section. In this section, we assume that x_n approaches a finite value x_{∞} asymptotically as $n \to \infty$. We use dimensional analysis to determine (as far as possible) how x_{∞} depends on the other parameters.

We use the procedure that we saw for the period of the pendulum in an earlier lecture. Our first task is to find all the *independent* nondimensional parameters. We list all the relevant parameters along with their dimensions in Table 1. We see that $\pi_1 = rh$ and $\pi_2 = x_{\infty}/b$ are nondimensional combinations of the parameters. With a little thought, we could probably convince ourselves that these are the *only* nontrivial (or independent) combinations. (For example, rhb^2/x_{∞}^2 is nondimensional, but it is equivalent to π_1/π_2^2 , so it is not really a "new" parameter.) However, for the sake of pedagogy, we will follow the formal procedure, and pretend we didn't see the "obvious" choices.

We must choose exponents α , β , γ and δ such that

$$\pi = r^{\alpha} b^{\beta} h^{\gamma} x_{\infty}^{\delta} \tag{6}$$

is dimensionless. Substituting in the dimensions from Table 1, we require

$$\left(\mathcal{T}^{-1}\right)^{\alpha}\mathcal{C}^{\beta}\mathcal{T}^{\gamma}\mathcal{C}^{\delta} = \mathcal{T}^{0}\mathcal{C}^{0} = 1 \quad \Longrightarrow \quad \mathcal{T}^{-\alpha+\gamma}\mathcal{C}^{\beta+\delta} = \mathcal{T}^{0}\mathcal{C}^{0}.$$
(7)

This results in the linear system of equations

$$-\alpha + \gamma = 0,$$

$$\beta + \delta = 0.$$
(8)

This is easy enough to solve: $\alpha = \gamma$ and $\beta = -\delta$, where γ and δ are arbitrary. Equivalently, we can express this as

$$\alpha = p, \quad \beta = -q, \quad \gamma = p, \quad \delta = q, \tag{9}$$

where p and q are arbitrary parameters. In vector form,

$$\begin{bmatrix} \alpha \\ \beta \\ \gamma \\ \delta \end{bmatrix} = \begin{bmatrix} p \\ -q \\ p \\ q \end{bmatrix} = p \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \end{bmatrix} + q \begin{bmatrix} 0 \\ -1 \\ 0 \\ 1 \end{bmatrix}.$$
 (10)

A basis for the solution set of (8) is given by the vectors $\{[1, 0, 1, 0], [0, -1, 0, 1]\}$ (written as row vectors for convenience). Each basis vector gives us exponents that we can plug into (6) to form a nondimensional parameter. Thus we have found (as expected) that there are only two independent nondimensional parameters:

$$\pi_1 = r^1 b^0 h^1 x_\infty^0 = rh, \text{ and } \pi_2 = r^0 b^{-1} h^0 x_\infty^1 = \frac{x_\infty}{b}.$$
 (11)

Now we assume that there is some functional relationship among r, h, b and x_{∞} . Since we don't know what it is, we'll assume the general form

$$f(r,h,b,x_{\infty}) = 0. \tag{12}$$

We expect f to be dimensionally homogeneous; then the Buckingham Pi Theorem implies that there is an equivalent relationship of the form

$$F(\pi_1, \pi_2) = 0. \tag{13}$$

Moreover, we expect that for most values of π_1 and π_2 , this equation can be solved for π_2 in terms of π_1 . That is, there is some function G such that (13) is equivalent to

$$\pi_2 = G(\pi_1). \tag{14}$$

Substituting in the definitions of π_1 and π_2 gives

$$\frac{x_{\infty}}{b} = G(rh),\tag{15}$$

or

$$x_{\infty} = bG(rh). \tag{16}$$

This gives us the form of the equation that will result if we can solve for x_{∞} in terms of r, h and b. That is, x_{∞} must be a product of b and some function of rh only.

Derivation of the Formula for x_{∞}

In this section, we derive the actual formula for x_n . From that we obtain the formula for x_{∞} . You may find it helpful to label the plot in Figure 1 using the notation from the following discussion.

The instant after the first dose, we have

$$c(0^+) = b. (17)$$

Then, for 0 < t < h, we have $c(t) = be^{-rt}$, so

$$c(h^-) = be^{-rh}. (18)$$

At t = h, the concentration increases by b, so

$$c(h^{+}) = c(h^{-}) + b = be^{-rh} + b = b\left(e^{-rh} + 1\right)$$
(19)

Then in the next interval, the solution again decays, and we have

$$c((2h)^{-}) = c(h^{+})e^{-rh} = b\left(e^{-rh} + 1\right)e^{-rh} = b\left(e^{-2rh} + e^{-rh}\right)$$
(20)

and after the jump at t = 2h we have

$$c((2h)^{+}) = c((2h)^{-}) + b = b\left(e^{-2rh} + e^{-rh}\right) + b = b\left(e^{-2rh} + e^{-rh} + 1\right)$$
(21)

Once again, in the next time interval, the solution decays and we have

$$c((3h)^{-}) = c((2h)^{+})e^{-rh} = b\left(e^{-2rh} + e^{-rh} + 1\right)e^{-rh} = b\left(e^{-3rh} + e^{-2rh} + e^{-rh}\right)$$
(22)

Recall that we defined $x_n = c((nh)^-)$. The process that we are describing defines a one dimensional mapping

$$x_{n+1} = (x_n + b)e^{-rh}$$
, with $x_0 = 0$. (23)

Equations (18), (20) and (22) give the formulas for the first three iterations of this map. In general, we have

$$x_n = c((nh)^-) = b\left(e^{-nrh} + e^{-(n-1)rh} + \dots + e^{-rh}\right) = b\sum_{k=1}^n e^{-krh} = b\sum_{k=1}^n \rho^k,$$
 (24)

where $\rho = e^{-rh}$. (Note that, since r > 0 and h > 0, we have $0 < \rho < 1$.) The formula in Equation (24) is a geometric sum. By using Equation (30) from the appendix, we obtain

$$x_n = b\rho\left(\frac{1-\rho^n}{1-\rho}\right) = be^{-rh}\left(\frac{1-e^{nrh}}{1-e^{-rh}}\right)$$
(25)

Finally, since $\lim_{n \to \infty} \rho^n = 0$, we have

$$x_{\infty} = \frac{b\rho}{1-\rho} = \frac{be^{-rh}}{1-e^{-rh}}.$$
(26)

(This agrees with the result of the dimensional analysis of the previous section.)

The example shown earlier was for r = 0.3, h = 2 and b = 1. With these values we find $x_{\infty} \approx 1.2164$. Figure 2 shows the result of ten periods for these parameters. The dashed line in this plot indicates x_{∞} .



Figure 2: The graph of c(t) for r = 0.3, h = 2, and b = 1. The dashed line shows $x_{\infty} \approx 1.2164$.

Appendix: The Geometric Sum

In this appendix, we derive the formula for the geometic sum $\sum_{k=0}^{n} \rho^{k}$.

Let

$$S = \sum_{k=0}^{n} \rho^k \tag{27}$$

We multiply both sides by ρ , and then manipulate the right side so that it is expressed in terms of S:

$$\rho S = \rho \sum_{k=0}^{n} \rho^{k}$$

$$= \sum_{k=0}^{n} \rho^{k+1}$$

$$= \sum_{k=1}^{n+1} \rho^{k}$$

$$= \rho^{n+1} - 1 + \sum_{k=0}^{n} \rho^{k}$$

$$= \rho^{n+1} - 1 + S$$
(28)

Now solve for S to obtain

$$S = \frac{1 - \rho^{n+1}}{1 - \rho}.$$
 (29)

In the analysis of the periodic drug doses, we actually needed the formula for $\sum_{k=1}^{n} \rho^{k}$. Note that the starting index is 1, not 0. We can derive a formula for this case by using the previous result:

$$\sum_{k=1}^{n} \rho^{k} = \sum_{k=0}^{n-1} \rho^{k+1}$$

= $\rho \sum_{k=0}^{n-1} \rho^{k}$
= $\rho \left(\frac{1-\rho^{n}}{1-\rho}\right).$ (30)

Question 2 Derive this result by using the same method as in Equation (28).