Mathematical modelling: Drug dosing

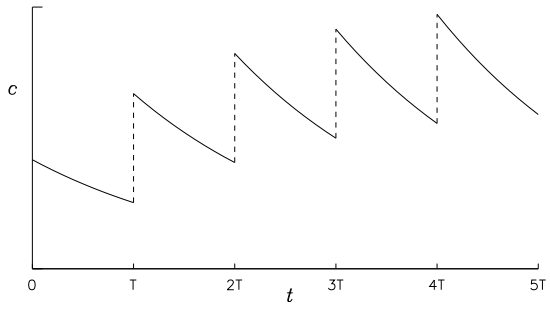
We examine the concentration c of the drug (mass of drug per unit volume of blood) in the bloodstream. In the second assignment, we have modelled the effects of periodic drug dosing using a discrete model. Here, we first model the effects of the periodic drug dosing using both discrete and continuous models.

Cleaning of drugs in the blood: There are a variety of mechanisms for this. Organs in the body may actively absorb the drug, the drug may react with other chemicals in the blood, or the drug may break down into simpler compounds. The simplest model is the assumption that the rate of loss of the drug is proportional to the concentration of the drug, i.e.,

$$\frac{dc}{dt} = -rc, \quad c > 0. \tag{1}$$

If c_0 is the initial concentration of the drug at time $t = t_0$, then $c(t) = c_0 \mathrm{e}^{-r(t-t_0)}$. As with radioactive decay, we can assign a half-life to a drug.

Periodic doses: Suppose at every time interval T, a dose is administered that increases the drug concentration by b (if the amount of drug is a and the volume of the blood is V, then $b = a/V$). We assume that the doses cause an instantaneous increase in concentration (e.g., intravenous drugs). Suppose the first dose is administered at $t = 0$ and the concentration of the drug before that in the blood is zero. The concentration in the blood increases to b at $t = 0$ and decays according to (1) for $0 < t < T$. Another dose is administered at $t = T$, and the concentration increases by b. The concentration then decays for $T < t < 2T$, and this process continues. We expect a figure like the one shown below, in which the lengths of the dashed vertical lines represent the value of b.



Mathematical formulation: Let

$$x_n = \lim_{t \to (nT)^-} c(t) \quad \text{and} \quad y_n = \lim_{t \to (nT)^+} c(t)$$

Thus, x_n is the residual concentration just before the n-th dose (the first dose at $t = 0$ is the zeroth dose). Similarly, y_n is the concentration just after the n-th dose. Clearly, $x_0 = 0$ and $y_0 = b$. We also have

$$c(t) = y_0 \mathrm{e}^{-rt} = b\mathrm{e}^{-rt}, \quad 0 < t < T, \quad \text{and} \quad x_1 = y_0 \mathrm{e}^{-rT} = b\mathrm{e}^{-rT}, \;\; y_1 = x_1 + b = b\left(1 + \mathrm{e}^{-rT}\right)$$

Similarly,

$$c(t) = y_1 \mathrm{e}^{-r(t-T)} = b\left(1 + \mathrm{e}^{-rT}\right)\mathrm{e}^{-r(t-T)}, \quad T < t < 2T,$$
$$x_2 = y_1 \mathrm{e}^{-rT} = b\left(\mathrm{e}^{-rT} + \mathrm{e}^{-2rT}\right),\ y_2 = x_2 + b = b\left(1 + \mathrm{e}^{-rT} + \mathrm{e}^{-2rT}\right)$$

Hence,

$$x_{n+1} = y_n e^{-rT} = (x_n + b)\mathrm{e}^{-rT} \quad \text{with } x_0 = 0.$$

Iterating we find

$$\begin{aligned}
x_n &= (x_{n-1} + b)\mathrm{e}^{-rT} = \left((x_{n-2} + b)\mathrm{e}^{-rT} + b\right)\mathrm{e}^{-rT} = \left(b\mathrm{e}^{-rT} + b\mathrm{e}^{-2rT} + x_{n-2}\mathrm{e}^{-2rT}\right) \\
&= \left(b\mathrm{e}^{-rT} + b\mathrm{e}^{-2rT} + \cdots + x_1\mathrm{e}^{-(n-1)rT}\right) \\
&= \left(b\mathrm{e}^{-rT} + b\mathrm{e}^{-2rT} + \cdots + b\mathrm{e}^{-nrT}\right) \\
&= b\rho\left(1 + \rho + \rho^2 + \cdots + \rho^{n-1}\right) \qquad \text{where } 0 < \rho = e^{-rT} < 1 \\
&= b\rho\frac{1-\rho^n}{1-\rho} \to x_\infty = \frac{b\rho}{1-\rho} \quad \text{as } n \to \infty.
\end{aligned}$$

Consequently

$$y_n = b + x_n = b\frac{1-\rho^{n+1}}{1-\rho} \to y_\infty = \frac{b}{1-\rho} \quad \text{as } n \to \infty.$$

If the drug has a safe level H, then we want y_n to approach H. Further, if there is a threshold level L (below which the drug is not effective), then we want b to be $H - L$.

Note that

$$0 < y_n = b\frac{1-\rho^{n+1}}{1-\rho} < \frac{b}{1-\rho} = y_\infty, \quad \forall n.$$

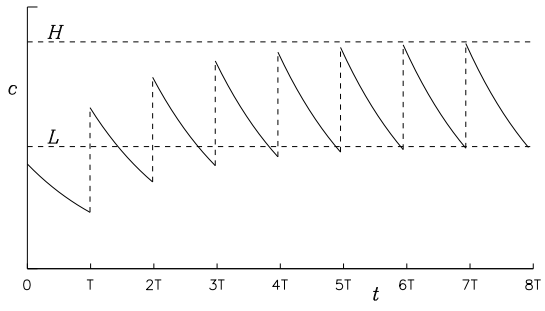
Similarly,

$$0 < x_n = b\rho\frac{1-\rho^{n}}{1-\rho} < \frac{b\rho}{1-\rho} = x_\infty, \quad \forall n.$$

Also, x_n and y_n are monotone increasing since $0 < \rho < 1$. We would like $x_\infty = L$ and $y_\infty = H$. From $y_\infty = H$, we find

$$\frac{b}{1-\rho} = H \implies 1 - \rho = \frac{b}{H} \implies \rho = \frac{H-b}{H} \implies e^{-rT} = \frac{L}{H} \implies T = \frac{1}{r}\ln\frac{H}{L}$$

This gives the time interval between successive doses. Here, the threshold level may not be attained immediately, as shown in the figure below.



To attain the threshold level immediately, we may proceed as follows: we give the initial dose $b_0 = H$, then repeat the doses $b = H - L$ at intervals of $T = \frac{1}{r} \ln \frac{H}{L}$. Note that in this case, $x_0 = 0$ and $y_0 = b_0 = H$. Now

$$x_1 = y_0 \mathrm{e}^{-rT} = H \frac{L}{H} = L, \quad y_1 = x_1 + b = L + (H - L) = H$$

Clearly, the drug concentration at the beginning of each interval is H and L at the end of the interval, as shown in the figure below. This is a better strategy if the drug has a threshold level and a safe level.