CASE STUDY 1b Kill Curves and Antibiotic Effectiveness

We are studying the relationship between the magnitude of antibiotic treatment and the effectiveness of the treatment. Recall that the extent of bacterial killing by an antibiotic is determined by both the *antibiotic concentration profile* and the *dose response relationship*. Figure 1 shows the antibiotic concentration profile for ciprofloxacin.[1] Our first goal here is to choose an appropriate mathematical description of this profile.

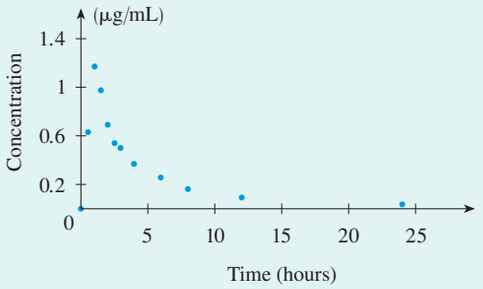

FIGURE 1
Antibiotic concentration profile in plasma of a healthy human volunteer after receiving 500 mg of ciprofloxacin

In Case Study 1a we modeled the initial increase in concentration as occurring instantly. We then need to determine how to model the decay in concentration. From Figure 1 it looks as though the rate of decay (that is, the slope of the relationship between concentration and time) is smaller for lower concentrations. We also know that the rate of decay must be zero when the concentration is zero. Therefore, as a simple model, let's suppose that the rate of decay of concentration is proportional to the current concentration; that is,

(1) $$\frac{dc}{dt} = -kc$$

for some positive constant k. Here c is measured in $\mu g/mL$ and t is measured in hours.

1. If the concentration at $t = 0$ is c_0, verify that the concentration function $c(t) = c_0 e^{-kt}$ satisfies Equation 1. Suppose that the antibiotic ciprofloxacin has a half-life of 4 hours. What is the value of k?

Next we wish to model the bacteria population dynamics. When a bacteria population is small, it grows at a rate that is proportional to its size because each bacterium produces a constant number of offspring per unit time. A simple model for the growth of the bacteria population size P when small is therefore

(2) $$\frac{dP}{dt} = rP$$

where r is a constant called the *per capita growth rate* (it is the rate of offspring production by each individual bacterium). As a result, if the bacteria population starts at size P_0, its predicted size at time t is $P(t) = P_0 e^{rt}$.

1. Adapted from Imre, S. et al., "Validation of an HPLC Method for the Determination of Ciprofloxacin in Human Plasma," *Journal of Pharmaceutical and Biomedical Analysis* 33 (2003): 125–30.

As the population grows, resources become depleted. Eventually the bacteria population reaches a size at which it no longer changes. For the data in Figure 2[2] it looks as though the maximum population size is around 12 CFU/mL. A simple model is therefore that the population grows according to Equation 2 if $P < 12$ and it remains constant at $P = 12$ if the value of P predicted from the model in Equation 2 is ever greater than or equal to 12.

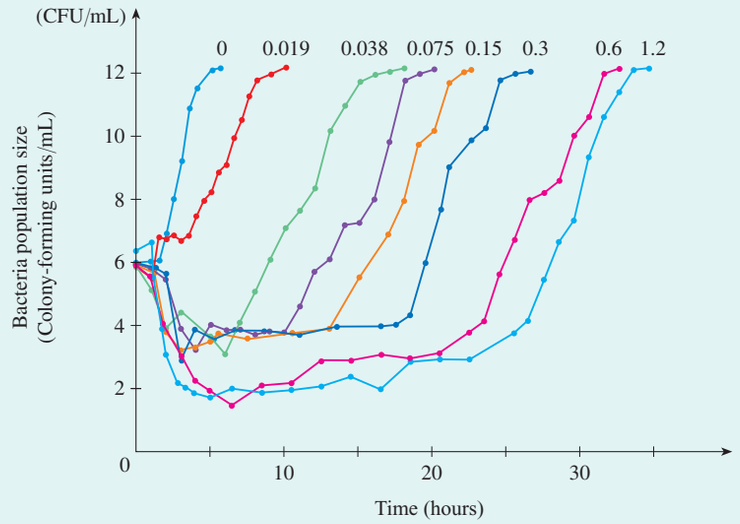

FIGURE 2
The kill curves of ciprofloxacin for *E. coli* when measured in a growth chamber. The concentration of ciprofloxacin at $t = 0$ is indicated above each curve (in μg/mL).

Our final step is to connect the model for bacteria population growth to the model for the antibiotic concentration profile. The connection between the two is given by the dose response relationship. Recall that in Case Study 1a we modeled the dose response relationship with the piecewise defined function

$$r(c) = \begin{cases} r_2 & \text{if } c < MIC \\ r_1 & \text{if } c \geq MIC \end{cases}$$

where $r(c)$ is the per capita growth rate of the bacteria population and MIC is a constant referred to as the *minimum inhibitory concentration* ($MIC = 0.013$ μg/mL in this case). The constants r_1 and r_2 give the per capita growth rate under high and low antibiotic concentrations, respectively, with $r_1 < 0$ and $r_2 > 0$ (Figure 3).

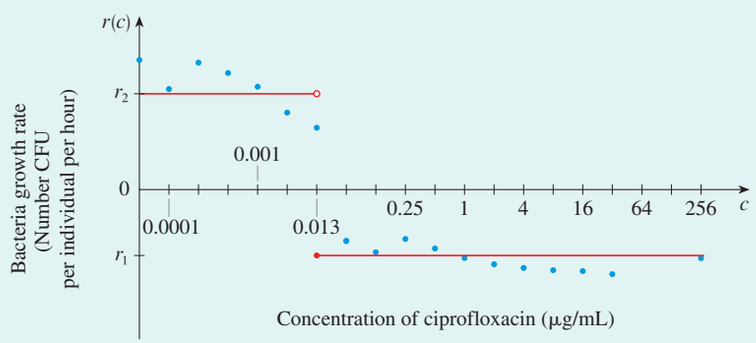

FIGURE 3
Dose response relationship modeled by the piecewise defined function $r(c)$

Source: Adapted from W. Bär et al., "Rapid Method for Detection of Minimal Bactericidal Concentration of Antibiotics," *Journal of Microbiological Methods* 77 (2009): 85–89, Figure 1.

2. Adapted from A. Firsov et al., "Parameters of Bacterial Killing and Regrowth Kinetics and Antimicrobial Effect Examined in Terms of Area Under the Concentration–Time Curve Relationships: Action of Ciprofloxacin against *Escherichia coli* in an In Vitro Dynamic Model," *Antimicrobial Agents and Chemotherapy* 41 (1997): 1281–87.

Suppose the bacteria population starts at $t = 0$ at a size of 6 CFU/mL. Suppose also that $MIC = 0.013$, $k = 0.175$, $r_1 = -\frac{1}{20}$, and $r_2 = \frac{1}{3}$.

2. Using the form of the solution to Equation 2, show that the bacteria population size at time t is given by the function

(3a)
$$P(t) = \begin{cases} 6e^{t/3} & \text{if } t < 2.08 \\ 12 & \text{if } t \geqslant 2.08 \end{cases}$$

if $c_0 < MIC$, where $MIC = 0.013$. On the other hand, if $c_0 > MIC$, show that

(3b)
$$P(t) = \begin{cases} 6e^{-t/20} & \text{if } t < a \\ 6Ae^{t/3} & \text{if } a \leqslant t < b \\ 12 & \text{if } t \geqslant b \end{cases}$$

where the constants a, b, and A are defined by $a = 5.7 \ln(77c_0)$, $b = 6.6 \ln(77c_0) + 2.08$, and $A = (77c_0)^{-2.2}$.

Equations 3 are the predicted kill curves explored in Case Study 1a.

3. Using the form of the solution to Equation 2, show that for arbitrary MIC, k, r_1, and r_2 the bacteria population size at time t is given by

(4a)
$$P(t) = \begin{cases} 6e^{r_2 t} & \text{if } t < t_2 \\ 12 & \text{if } t \geqslant t_2 \end{cases}$$

if $c_0 < MIC$, and

(4b)
$$P(t) = \begin{cases} 6e^{r_1 t} & \text{if } t < t_1 \\ 6e^{r_1 t_1} e^{r_2 (t - t_1)} & \text{if } t_1 \leqslant t < \left(1 - \dfrac{r_1}{r_2}\right) t_1 + t_2 \\ 12 & \text{if } \left(1 - \dfrac{r_1}{r_2}\right) t_1 + t_2 \leqslant t \end{cases}$$

if $c_0 \geqslant MIC$, where $t_1 = \dfrac{1}{k} \ln\left(\dfrac{c_0}{MIC}\right)$ and $t_2 = \dfrac{\ln 2}{r_2}$.