CASE STUDY 1d Kill Curves and Antibiotic Effectiveness

In this case study we have explored the relationship between the magnitude of antibiotic treatment and the effectiveness of the treatment. To do so, in Case Study 1b we showed that a suitable model for the size of the bacteria population $P(t)$ (in CFU/mL) as a function of time t (in hours) is given by the piecewise defined function

(1a)
$$P(t) = \begin{cases} 6e^{t/3} & \text{if } t < 2.08 \\ 12 & \text{if } t \geqslant 2.08 \end{cases}$$

Recall that *MIC* is a constant referred to as the minimum inhibitory concentration of the antibiotic and c_0 is the concentration at time $t = 0$.

if $c_0 < MIC$, where $MIC = 0.013\ \mu\text{g/mL}$. On the other hand, if $c_0 > MIC$

(1b)
$$P(t) = \begin{cases} 6e^{-t/20} & \text{if } t < a \\ 6Ae^{t/3} & \text{if } a \leqslant t < b \\ 12 & \text{if } t \geqslant b \end{cases}$$

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 $A = (77c_0)^{-2.2}$.

In Case Study 1a we used these so-called kill curves to plot the relationship between α (a measure of the magnitude of antibiotic treatment) and two different measures of the killing effectiveness, denoted by Δ and T. The quantity Δ is the drop in population size before the population rebound occurs, and T is the time taken to reduce the bacteria population size to 90% of its initial size. (Refer to Figure 1.)

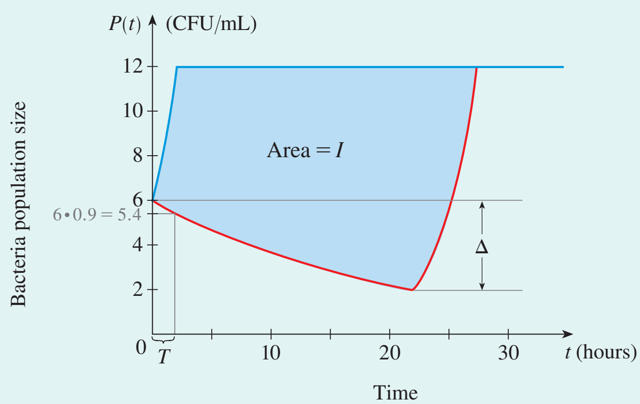

FIGURE 1
Three measures of killing effectiveness. The blue curve is bacteria population size in the absence of antibiotic. The red curve is bacteria population size in the presence of antibiotic.

Now that we have a model that works reasonably well, we can use it to make predictions about other patterns, and then compare these with available data. As an example, another measure of the killing effectiveness of an antibiotic is the area I between the population size curve in the absence of antibiotic, and the kill curve in the presence of the antibiotic as shown in Figure 1. In many cases this measure might be preferable because it incorporates both the drop in bacteria population size, and the length of time for which this reduced population size is maintained. Let's see what our model predicts about the relationship between I and the magnitude of antibiotic treatment α.

1. Suppose that $a > 2.08$ [that is, $5.7 \ln(77c_0) > 2.08$]. Find an expression for I in the modeled populations in terms of c_0. You should assume that $c_0 > MIC$.

2. The result from Problem 1 should give you a function of the form $I = g(c_0)$ for some function g. Substitute the values $k = 0.175$ and $MIC = 0.013$ into the expression for α obtained in Case Study 1c. This will give $\alpha = h(c_0)$ for some function h.

3. Using the concept of a function's inverse, explain how to obtain an expression giving I as a function of α in terms of g and h^{-1}. Find an explicit expression for this function.

4. Plot the function obtained in Problem 3.

The experimental kill curves shown in Figure 2 have also been used to quantify the relationship between I and α.[1] In other words, the values of I and α have been calculated for each experimental kill curve in Figure 2. If we overlay these data points on the plot from Problem 4, we obtain Figure 3. You can see that, again, our model predicts the observed data reasonably well.

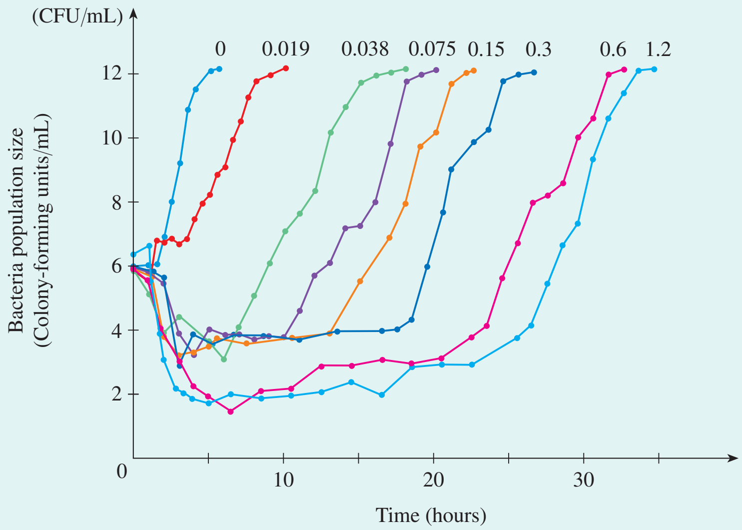

FIGURE 2
The kill curves of ciprofloxacin for *E. coli* when measured in a growth chamber. The concentration of ciprofloxacin at $t = 0$ is indicated above each curve (in $\mu g/mL$).

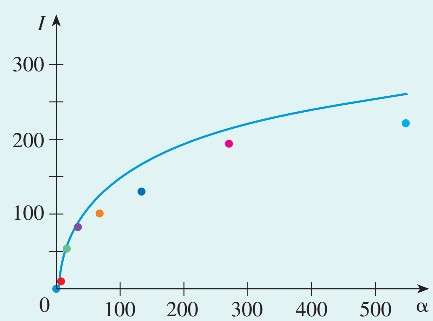

FIGURE 3
Predicted relationship between I and α, along with experimental observations obtained using the kill curve data in Figure 2.

1. Adapted from A. Firsov et al., "Parameters of Bacterial Killing and Regrowth Kinetics and Antimicrobial Effect 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.