CASE STUDY 1c Kill Curves and Antibiotic Effectiveness

Recall that in this case study we are exploring the relationship between the magnitude of antibiotic treatment and the effectiveness of the treatment. One of the most important components of our analysis is the antibiotic concentration profile, which is a plot of the antibiotic concentration as a function of time.

In the simple model of Case Studies 1a and 1b we modeled a single dose of antibiotic using the equation

$$\frac{dc}{dt} = -kc \tag{1}$$

for some positive constant k. From this we saw that the concentration as a function of time is

$$c(t) = c_0 e^{-kt} \tag{2}$$

where c_0 is the concentration at $t = 0$. (See Figure 1.)

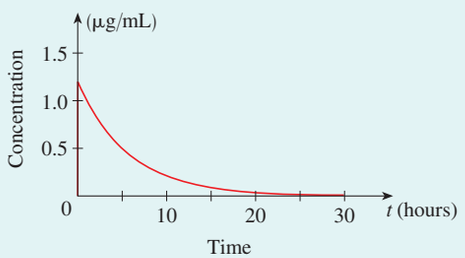

FIGURE 1
Antibiotic concentration profile modeled by the function $c(t) = c_0 e^{-kt}$ with $c_0 = 1.2$ μg/mL and $k = 0.175$

Three of the most common measures of the magnitude of antibiotic treatment are (1) the peak antibiotic concentration divided by *MIC*, denoted by ρ; (2) the duration of time for which the antibiotic concentration remains above *MIC*, denoted by τ; and (3) the area under the antibiotic concentration profile divided by *MIC*, denoted by α. These are shown in Figure 2. In Case Study 1a you derived expressions for the first two.

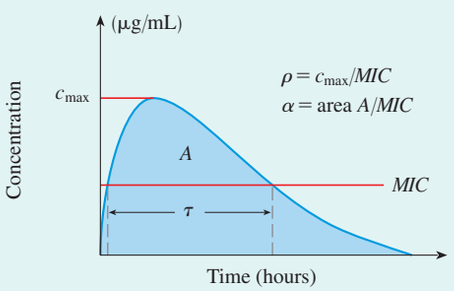

FIGURE 2
Three measures of the magnitude of antibiotic treatment

1. Find an expression for α in terms of k, c_0, and *MIC*, using Equation 2. The area under the concentration profile should be calculated from $t = 0$ to ∞.

We saw in Case Study 1a that, for a given antibiotic and bacteria species (in other words, for a given value of k and *MIC*), all three quantities ρ, τ, and α increase with one another. In other words, it is not possible to have a high value of α without also having high values of ρ and τ. Here you will show that we can break this dependency if we

divide the total amount of antibiotic given c_0 into multiple smaller doses. This is referred to as *dose fractionation*.

In the simplest case, suppose that instead of giving a total amount of c_0 μg/mL of antibiotic at $t = 0$, we instead give $c_0/2$ at $t = 0$ and another dose of $c_0/2$ at time $t = \hat{t}$. The time $\hat{t}$ is called the interdose interval. Furthermore, suppose that at each dose the concentration instantly increases by $c_0/2$, and otherwise it decays according to Equation 1.

2. Find an equation for the concentration as a function of time. Figure 3 plots this function for a specific choice of constants, along with the concentration profile when a single dose of c_0 μg/mL is given at $t = 0$.

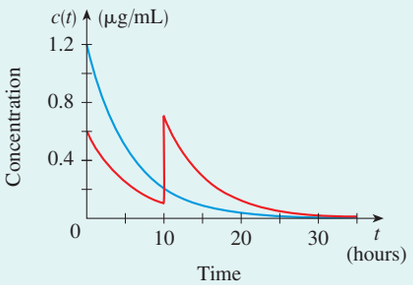

FIGURE 3
Red curve is the concentration profile modeled by the function from Problem 2 with $c_0 = 1.2$ μg/mL, $\hat{t} = 10$, and $k = 0.175$. Blue curve is the concentration profile when all the antibiotic is given at $t = 0$.

3. Use your answer to Problem 2 to find an expression for ρ, the peak concentration divided by *MIC*.

4. Use your answer to Problem 2 to show that α is the same under dose fractionation as it is for the single dose case in Problem 1.

5. Using your answers from Problems 3 and 4, explain how it is possible to use dose fractionation to increase ρ without also increasing α.

One of the reasons different drug doses and interdose intervals are used for different infections is to achieve different values of α, ρ, and τ.