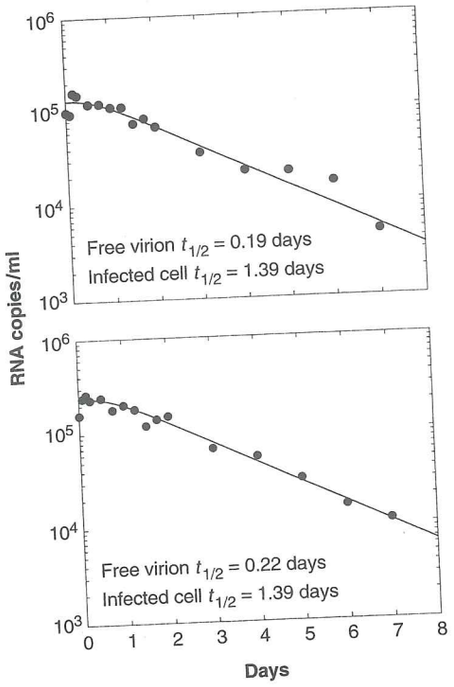

Figure 4.5. Log of plasma concentrations (copies per mL) of HIV-1 RNA (circles) for two representative patients (upper panel, patient 104; lower panel, patient 107) after *ritonavir* treatment was begun on day 0. The solid line is a nonlinear least square fit to the data. HIV-1 RNA level is an easier measure of HIV virions since each HIV virion contains two RNA molecules. (See exercise 5 for more details.) (From Perelson et al. [1996], used by permission of Alan S. Perelson.)

Thus c is determined to be 2.06 to 3.81 per day. $V(t_0)$ was also measured as the viral concentration before the drugs took effect:

$$V(t_0) \sim 3 \times 10^5 \text{ virions per mL of plasma.}$$

To find P, the authors assumed that before the administration of drugs, there was a quasi-steady state when viral production was balanced by viral clearance. (In fact, only patients not yet experiencing the onset of full-blown AIDS, when viral production overwhelms the body's ability to clear it, were chosen for the study.) For this quasi-steady state, $\frac{d}{dt}V$ was set to zero in Eq. (4.5), leading to

$$P - cV = 0, \text{ for } t \le t_0. \tag{4.8}$$

From this, they found

$$P(t_0) \cong cV(t_0) \sim 2 \times 3 \times 10^5$$

virions per mL of plasma per day.

That amounts to almost a billion new viral particles a day produced in each liter of blood during what, at the time, was thought of as the "dormant" phase of AIDS! It turns out that even in the early stages of HIV infection, the virus was being produced at an incredible rate ("the raging fire of active HIV replication"). The body was able to clear the virus out at a rapid rate also, until it could not keep up any longer. Based on this work, the authors suggested that "early and aggressive therapeutic intervention is necessary if a marked clinical impact is to be achieved."

A review article for applied mathematicians can be found in Perelson and Nelson (1999).

4.7 Exercises

1. *Christ and the Disciples at Emmaus*

In the 1930s, the painting *Christ and the Disciples at Emmaus* (Figure 4.6) was certified as a genuine 17th century Vermeer by a noted art historian, A. Bredius, and bought by the Rembrandt Society. In 1945, an art forger, Han van Meegeren, announced in a Belgian prison that he was the painter of *Disciples at Emmaus*, an admission made presumably to avoid prosecution on the charge that he had sold actual Vermeer paintings to Nazis during the war.

A pigment of major importance in paintings is white lead, which contains a radioactive isotope, ^{210}Pb. It is manufactured from ores that contain uranium and elements to which uranium decays. One of these elements is radium-226 (^{226}Ra), which has a half-life of 1,600 years, and decays to ^{210}Pb, which has a half-life of 22 years. While still part of the ore, the amount of ^{226}Ra decaying to ^{210}Pb is equal to the amount of ^{210}Pb disintegrating into some other element. That is, ^{226}Ra and ^{210}Pb are in a "radioactive equilibrium."

In the manufacture of the pigment, the radium and most of its descendants are removed. The ^{210}Pb begins to decay without replenishment.

Let $y(t)$ be the number of ^{210}Pb atoms per gram of ordinary lead at time t. Let t_0 be the time the pigment was manufactured and r the number of disintegrations of ^{226}Ra per gram of ordinary lead per unit time.

Figure 4.6. *Christ and the Disciples at Emmaus.*

a. Explain why the following equations should govern the change in the amount of ^{210}Pb:

$$\frac{dy}{dt} = -\lambda y + r \quad \text{while in the ore,} \tag{4.9}$$

$$\frac{dy}{dt} = -\lambda y \quad \text{after manufacture.} \tag{4.10}$$

λ is the decay constant for ^{210}Pb.

b. Measurements from a variety of ores over the earth's surface gave a range of values for the rate of disintegration of ^{226}Ra per gram of ordinary lead as

$$r = 0 - 200 \text{ per minute.}$$

Show that it is reasonable to assume that

$$\lambda y(t_0) = r = 0 - 200 \text{ per minute.}$$

c. Solve (4.10) subject to the initial condition

$$y(t_0) = r/\lambda.$$

d. For the *Disciples at Emmaus* painting, it was measured that

$$-\frac{dy}{dt}(t) \cong 8.5 \text{ per minute.}$$

Estimate $t - t_0$ to decide if the painting can be 300 years old.

2. *Lascaux Cave paintings*

Charcoal from the dwelling level of the Lascaux Cave in France gives an average count of 0.97 disintegrations of ^{14}C per minute per gram of sample. Living wood gives 6.68 disintegrations per minute per gram. Estimate the date of occupation and hence the probable date of the wall painting in the Lascaux Cave.

3. *Age of uranium*

The currently measured value of $\log_{10}(U/Th)$ in star CS31082-001 is -0.74 ± 0.15. U denotes the concentration of the ^{238}U isotope, and Th that of ^{232}Th, which has a half-life of 14 Gyr. Because of the proximity of the two elements in their atomic mass numbers, their initial ratio, $(U/Th)_0$, at the time of their nuclearsynthesis is less affected by theoretical uncertainties. The theory gives $\log_{10}(U/Th)_0 = -0.10$. Derive the age of uranium in that ancient star, and hence the minimum age of the universe.

4. *A slightly more involved HIV model*

Cells that are susceptible to HIV infection are called T (target) cells. Let $T(t)$ be the population of uninfected T-cells, $T^*(t)$ that of the infected T-cells, and $V(t)$ the population of the HIV virus. A model for the rate of change of the infected T-cells is

$$\frac{dT^*}{dt} = kVT - \delta T^*, \tag{4.11}$$

where δ is the rate of clearance of infected cells by the body, and k is the rate constant for the infection of the T-cells by the virus. The equation for the virus is the same as Eq. (4.5):

$$\frac{dV}{dt} = P - cV, \tag{4.12}$$

but now the production of the virus can be modeled by

$$P(t) = N\delta T^*(t).$$

Here N is the total number of virions produced by an infected T-cell during its lifetime. Since $1/\delta$ is the length of its lifetime, $N\delta T^*(t)$ is the total rate of production of $V(t)$.

At least during the initial stages of infection, T can be treated as an approximate constant. Equations (4.11) and (4.12) are the two coupled equations for the two variables $T^*(t)$ and $V(t)$.

A drug therapy using RT (reverse transcriptase) inhibitors blocks infection, leading to $k \cong 0$. Setting $k = 0$ in (4.11), solve for $T^*(t)$. Substitute it into (4.12) and solve for $V(t)$. Show that the solution is

$$V(t) = \frac{V(0)}{c-\delta}[ce^{-\delta t} - \delta e^{-ct}].$$

5. Protease inhibitors

A drug therapy using protease inhibitors causes infected cells to produce noninfectious virions. It becomes necessary in our model to separate the infectious virion population $V_I(t)$ from the noninfectious virion population $V_{NI}(t)$, with $V(t) = V_I(t) + V_{NI}(t)$. Equations (4.11) and (4.12) remain valid except with V replaced by $V_{NI}(t)$:

$$\frac{d}{dt}T^* = kV_I T - \delta T^*, \tag{4.13}$$

$$\frac{d}{dt}V_{NI} = N\delta T^* - cV_{NI}. \tag{4.14}$$

The equation for $V_I(t)$ is given by

$$\frac{d}{dt}V_I = -cV_I \tag{4.15}$$

because infectious virions are no longer produced with an effective protease inhibitor treatment but are only being cleared by the body at the rate c.

a. Solve Eq. (4.15), substituting it into Eq. (4.13) to show that the solution for $T^*(t)$ is, assuming $T = T_0$ is a constant,

$$T^*(t) = T^*(0)e^{-\delta t} + \frac{kT_0V_0(e^{-ct} - e^{-\delta t})}{\delta - c}$$

$$= kV_0T_0[ce^{-\delta t} - \delta e^{-ct}]/[\delta(c-\delta)].$$

The last step is obtained by assuming that T^* is in a quasi-steady state before the therapy (set $\frac{d}{dt}T^* = 0$ at $t = 0$ in (4.13), with $T = T_0$ and $V_I = V_0$).

b. Substitute $T^*(t)$ found in (a) into (4.14) to show:

$$V_{NI}(t) = \frac{cV_0}{c-\delta}\left[\frac{c}{c-\delta}(e^{-\delta t} - e^{-ct}) - \delta te^{-ct}\right].$$

c. Adding $V_{NI}(t)$ and $V_I(t)$, show that the total virion concentration is given by

$$V(t) = V_0e^{-ct} + \frac{cV_0}{c-\delta}\left[\frac{c}{c-\delta}(e^{-\delta t} - e^{-ct}) - \delta te^{-ct}\right].$$

Since measurements cannot distinguish between infectious and noninfectious virions, it is the total virions that are measured in Figure 4.5. There are two decay rates, c and δ. These are obtained by best fitting the observed decay of $V(t)$ with the above solution, using δ and c as the two parameters.