4

Differential Equation Models: Carbon Dating, Age of the Universe, HIV Modeling

Mathematics required:

solution of first-order linear ordinary differential equations as reviewed in Appendix A

4.1 Introduction

Towards the end of the last chapter, we showed that in the limit of Δt approaching 0, difference equations become differential equations. Differential equations are good approximations to situations where there are a large number of events happening on average and when the time scale over which we are examining these averages is much longer than the interval between events.

Decay of radioactive elements is often modeled using differential equations. In the 1940s an American chemist, W. F. Libby, developed the technique for carbon dating; for this work he received the Nobel Prize in Chemistry in 1960. In a recent letter to *Nature*, Cayrel et al. (2001) reported the most accurate determination of the age of our universe so far, using uranium line emission from a very old, metal-poor star—known as CS31082-001—near the edge of our Milky Way.

During the early days of AIDS research, it was not understood that in HIV-infected individuals the virus was being produced at a prolific rate even before the onset of symptoms and full-blown AIDS. The modeling effort of Perelson et al. (1996) reported in *Science* quantified this viral production rate and did much to advance the treatment strategies of David Ho (1996 *Time* Person of the Year) and others.

4.2 Radiometric Dating

Radiometric dating methods are based on the phenomenon of radioactivity, discovered and developed at the beginning of the 20th century

TABLE 4.1
Some radioactive isotopes and their half-lives

Substance	τ, *half-life*
Xenon-133	5 days
Barium-140	13 days
Lead-210	22 years
Strontium-90	25 years
Carbon-14	5,568 years
Plutonium	23,103 years
Uranium-235	0.707×10^9 years
Uranium-238	4.5×10^9 years

by the British physicist Lord Ernest Rutherford (1871–1937) and others. Certain atoms are inherently unstable, so that after some time and without any outside influence they will undergo transition to an atom of a different element, emitting in the process radiation (in the form of alpha particles or beta particles, which are detected by a Geiger counter). From experimental evidence, Rutherford found that the rate of decay is proportional to the number of radioactive atoms present in the sample,

$$\frac{d}{dt}N = -\lambda N, \tag{4.1}$$

where N is the number of atoms in a radioactive sample at time t and λ is a positive constant, known as the *decay constant*. This constant has different values for different substances.

Experimentally measured values for the *half-life*, τ, are used to find λ. τ is defined as the time taken for half of a given quantity of atoms to decay (Table 4.1). So if $N = N_0$ at $t = 0$, then $N(\tau) = N_0/2$.

Since the solution to Eq. (4.1) is

$$N(t) = N_0 e^{-\lambda t}, \tag{4.2}$$

$$N(\tau)/N_0 = e^{-\lambda\tau} = \frac{1}{2},$$

then

$$\lambda = \frac{\ln 2}{\tau}. \tag{4.3}$$

(So for carbon-14, an isotope of carbon, $\lambda = 1.245 \times 10^{-4}$ per year.)

4.3 The Age of Uranium in Our Solar System

The heavy elements we find on earth were not produced here. Some (up to iron) were produced in the nuclear furnace of the sun. Elements heavier than iron were produced elsewhere, most likely in a supernova, whose explosion spewed elements such as uranium into the "stardust." The solar system then formed out of these elements. So the uranium we now find on earth probably originated in a recent supernova explosion nearby. Nuclearsynthesis theory, which we will not go into here, tells us that the heavy elements close to each other in atomic number should have been produced in nearly equal concentrations.

The two isotopes of uranium closest to each other found on earth are ^{238}U and ^{235}U. The superscripts indicate the atomic number: the sum of the number of protons and the number of neutrons in the element. Both elements are radioactive. ^{235}U decays faster, with a half-life of 0.707Gyr, while ^{238}U's half-life is 4.468Gyr (1Gyr $\equiv 10^9$ years). The *isotopic ratio* $^{238}\mathrm{U}/^{235}\mathrm{U}$ is measured at present to be 137.8. We do not know each isotope's original abundance.

If we find the age of the uranium (and hence the time of the nearby supernova explosion), we will obtain an upper bound on the age of our solar system.

The concentration of each element, $U_1(t) \equiv {}^{238}\mathrm{U}(t)$ and $U_2(t) \equiv {}^{235}\mathrm{U}(t)$, decays according to Eq. (4.1),

$$\frac{d}{dt}U_1 = -\lambda_1 U_1,$$
$$\frac{d}{dt}U_2 = -\lambda_2 U_2,$$

where $\lambda_1 = \ln 2/4.47\mathrm{Gyr}$, $\lambda_2 = \ln 2/0.707\,\mathrm{Gyr}$.

Solving, we find

$$U_1(t) = U_1(0)e^{-\lambda_1 t}, \quad U_2(t) = U_2(0)e^{-\lambda_2 t}.$$

Unfortunately we do not know the initial isotopic concentrations: $U_1(0)$ and $U_2(0)$. However, we have some theoretical idea about their isotopic ratio. Therefore, we form the ratio

$$U_1(t)/U_2(t) = (U_1(0)/U_2(0))e^{-(\lambda_1-\lambda_2)t}. \tag{4.4}$$

From nuclearsynthesis theory, we have

$$U_1(0)/U_2(0) \cong 1.$$

From measurement at the present time t, we have

$$U_1(t)/U_2(t) = 137.8.$$

Substituting these numbers into (3.4), we get

$$137.8 = 1 \cdot e^{(\lambda_2 - \lambda_1)t}.$$

Thus

$$t = \frac{\ln(137.8)}{\lambda_2 - \lambda_1} \cong 5.97\text{Gyr}.$$

Our solar system is at most six billion years old.

4.4 The Age of the Universe

In a recent letter to *Nature*, Cayrel et al. (2001) reported the most accurate determination of the minimum age of the universe so far. A headline in the *PhysicsWeb* of February 7, 2001, reads:

> **Uranium Reveals the Age of the Universe**
> Astronomers have spotted for the first time the fingerprint of uranium-238 in an ancient star—and have used it to make the most reliable guess yet of the age of the universe. Roger Cayrel of the Observatoire de Paris-Meudon, France, and colleagues have used a kind of "stellar carbon dating" to estimate the age of the star—and therefore the minimum age of the universe. The new estimate makes the universe 12.5 billion years old—give or take 3 billion years. (R. Cayrel et al., 2001, *Nature*, **409**, 691)

An excerpt from the Cayrel et al. paper describes the rationale and the method:

> The ages of the oldest stars in the Galaxy indicate when star formation began, and provide a minimum age for the universe. Radioactive dating of meteoritic material and stars relies on comparing the present abundance ratios of radioactive and stable nuclear species to the theoretically predicted ratio of their production. The radio isotope ^{232}Th (half-life 14.05Gyr) has been used to date Galactic stars, but it decays by only a factor of two over the lifetime of the universe. ^{238}U (half-life 4.468Gyr) is in principle a more precise age indicator, but even its strongest spectral line, from singly ionized uranium at a wavelength of 385.957 nm, has previously not been detected in stars.

Figure 4.1. The ancient star CS31082-001 surrounded by the Milky Way star field. (Courtesy of ESO.)

This is because other metals, such as iron, have spectral lines in nearby wavelengths and often obscure the emission line of uranium. Fortunately, one very old star—CS31082-001—near the edge of our Milky Way was found by the authors to be very metal-poor. (See Figure 4.1.) Metals were scarce in very old stars because very few supernovae, which create metals, had yet exploded. The traces of uranium-238 in the star's atmosphere could have come from just one supernova in the early history of the universe.

Ideally, one should use the abundance ratio of the two closest isotopes of uranium, $^{238}\mathrm{U}/^{235}\mathrm{U}$, to determine the age of uranium in that old star. No $^{235}\mathrm{U}$ emission was found. This is understandable: because of its rather short half-life (the time for it to decay to half its original number of atoms is 0.707Gyr), there is probably not much $^{235}\mathrm{U}$ left by now. The next choice is to use the stable elements osmium (Os) and iridium (Ir), whose emission lines have also been detected from this old star.

Since absolute abundances cannot be measured, abundance ratios are often used. The ratios $^{238}\mathrm{U}/\mathrm{Os}$ and $^{238}\mathrm{U}/\mathrm{Ir}$ are measured. Os and Ir are stable. The presently measured (at time t) ratios are

$$\log_{10}(^{238}\mathrm{U}/\mathrm{Os}) = -2.19 \pm 0.18,$$
$$\log_{10}(^{238}\mathrm{U}/\mathrm{Ir}) = -2.10 \pm 0.17.$$

The ratios, when produced (at time 0), are not 1 because the elements are not close to each other in atomic number. Nuclearsynthesis models

predict the following theoretical values at $t = 0$:

$$\log_{10}(^{238}\text{U}/\text{Os})_0 = -1.27,$$
$$\log_{10}(^{238}\text{U}/\text{Ir})_0 = -1.30.$$

Let $U(t)$ denote the concentration of ^{238}U at the present time, and $t = 0$ is the time since it was created. It decays according to

$$U(t) = U(0)e^{-\lambda_1 t}, \quad \text{where } \lambda_1 = \frac{\ln 2}{4.47\text{Gyr}}.$$

For stable elements,

$$Os(t) = Os(0),$$
$$Ir(t) = Ir(0).$$

So,

$$(U(t)/Os(t)) = (U(0)/Os(0))e^{-\lambda_1 t},$$
$$\ln(U(t)/Os(t)) = \ln(U(0)/Os(0)) - \lambda_1 t.$$

Similarly

$$\ln(U(t)/Ir(t)) = \ln(U(0)/Ir(0)) - \lambda_1 t.$$

Therefore

$$\begin{aligned} t &= 6.45\text{Gyr}[\ln(U/Os)_0 - \ln(U(t)/Os(t))] \\ &= 14.8\text{Gyr}[\log_{10}(U/Os)_0 - \log_{10}(U(t)/Os(t))] \\ &= 14.8\text{Gyr}[-1.27 + 2.19] \\ &= 13.6\text{Gyr}. \end{aligned}$$

Similarly, we have

$$\begin{aligned} t &= 14.8\text{Gyr}[\log_{10}(U/Ir)_0 - \log_{10}(U(t)/Ir(t))] \\ &= 14.8\text{Gyr}[-1.30 + 2.10] \\ &= 11.8\text{Gyr}. \end{aligned}$$

Taking the error bars into account, the authors deduced an age for ^{238}U of 12.5 billion years, give or take 3 billion years. This is the age of the heavy element and is therefore the time since what was probably the earliest supernova explosion. When increased by 0.1–0.3 billion years to account for the time between the creation of the universe and the earliest supernova to form as the end stage of a star's life cycle,

Figure 4.2. Professor Willard F. Libby (1908–1980). (©The Nobel Foundation.)

these estimates give the minimum age of the universe to be around 13 billion years old.

4.5 Carbon Dating

Another, more common, method for dating objects on earth is called carbon dating, which was developed in the late 1940s by an American chemist, W. F. Libby, at the University of California at Los Angeles (Figure 4.2). For this work he received the Nobel Prize in Chemistry in 1960.

Let us introduce the application of this method to the problem of authenticating King Arthur's Round Table, as discussed in the book *Applying Mathematics*, by D. N. Burghes, I. Huntley, and J. McDonald (1982).

In the great hall in Winchester Castle there is a big round table made of oak that is 18 feet in diameter and divided into 25 sections, one for the king and the other sections for the 24 knights whose names are inscribed (Figure 4.3). It fits the legend of King Arthur's Round Table from the 5th century. The table was known to be at least several hundred years old, as the medieval historian John Harding reported in his *Chronicle* (1484) that the round table "began at Winchester and ended at Winchester, and there it hangs still."

To put an end to the speculation about the Winchester round table, in 1976 it was taken down from the wall on which it was hung, and

Figure 4.3. The Winchester round table. Winchester was the presumed site of Camelot. (Used by permission of Hampshire County Council.)

a series of tests were done to determine the age of the table. Carbon dating was one of the methods used.

Earth's atmosphere is continuously bombarded by cosmic rays. This produces neutrons in the atmosphere, and these neutrons combine with nitrogen, forming carbon-14 (^{14}C). (See Figure 4.4.) Living plants "breathe in" CO_2, along with $^{14}CO_2$; the rate of absorption of ^{14}C is balanced by the natural decay, and an equilibrium is reached. When the sample is formed (in this case, when the table was made) the wood is isolated from its original environment and the ^{14}C atoms decay without any further absorption. This behavior of (dead) wood, i.e., wood whose ^{14}C atoms decay without being replenished, is governed by Eq. (4.1) or (4.2). The rate of decay at present (1977) was measured with the sample taken from the table. It was found that $R(t) \equiv -dN/dt = 6.08$ per minute per gram of sample.

Using Eqs. (4.1) and (4.2), we know that the rate of decay $R(t)$ is, theoretically,

$$R(t) \equiv -dN/dt = \lambda e^{-\lambda t} N_0 = e^{-\lambda t} R(0),$$

where $R(0) = \lambda N_0$ would be known if we knew the original concentration of ^{14}C in the wood, which we don't!

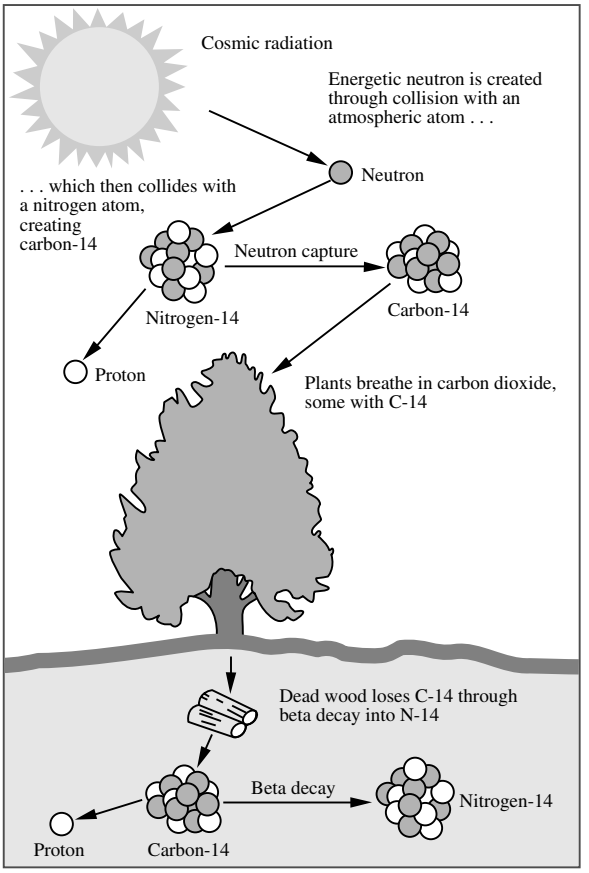

Figure 4.4. The natural cycle of carbon-14.

Here is the crucial *assumption* in carbon dating: we can measure $R(0)$ at present from living plants. That is, the rate of cosmic production of ^{14}C and its decay in living plants in the 5th century is assumed to be approximately the same as the rate in living plants today. By measuring living wood, we find, by this argument, $R(0) = 6.68$ per minute per gram of sample. Thus

$$t = \frac{1}{1.245 \times 10^{-4}} \ln \frac{6.68}{6.08} = 756 \text{ years.}$$

This gives a date for the table of about AD 1220, which clearly indicates that the table was not King Arthur's (he lived in the 5th century).

4.6 HIV Modeling

During the early days of AIDS (acquired immunodeficiency syndrome) research, it was not understood that, in individuals infected with HIV (human immunodeficiency virus), the virus was being produced at a prolific rate even before the onset of symptoms and full-blown AIDS. The modeling effort of Perelson et al. (1996) quantified this viral production rate and did much to advance the treatment strategies for AIDS by David Ho and others.

Perelson et al.'s model was incredibly simple. The rate of change of $V(t)$, the concentration of viral particles (called virions) in blood plasma, is given by

$$\frac{dV}{dt} = P - cV, \tag{4.5}$$

where P is the rate of production of new HIV virions and c is the "clearance" rate for the virions in the plasma. The virus is eliminated continually by the body's own immune cells or by natural body clearance functions, even in the absence of any drug therapy. Both $P(t)$ and c are, however, unknown.

A protease inhibitor, *ritonavir*, was administered orally to five infected patients. After treatment, the HIV virus concentrations in plasma were measured at very high frequency (every two hours until the sixth hour, every six hours until day 2, and every day until day 7).

It was found that each patient responded with a similar pattern of viral decay (see Figure 4.5). Assuming that the drug killed the production of new virus completely, P was set to zero. Equation (4.5) becomes

$$\frac{dV}{dt} = -cV, \tag{4.6}$$

which was solved to yield

$$V(t) = V(t_0)e^{-c(t-t_0)} \quad \text{for } t > t_0, \tag{4.7}$$

where t_0 is the time when the effect of the drug took hold, a day or so after treatment started.

By plotting $\ln(V(t)/V(t_0))$ against $t - t_0$ and using linear regression to determine the slope, the authors found a mean half-life of the virus in the plasma of

$$\tau = \ln 2/c \cong 0.18 \text{ to } 0.34 \text{ days}.$$

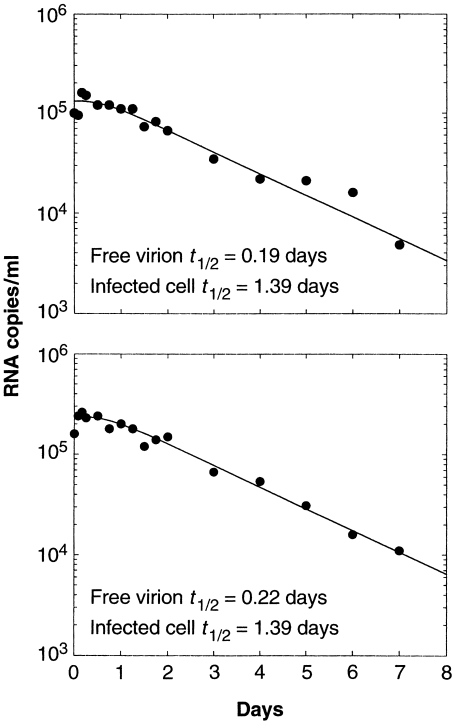

Figure 4.5. Log of plasma concentrations (copies per mL) of HIV-1 RNA (circles) for two representative patients (upper panel, patient 104; lower panel, patient 107) after *ritonavir* treatment was begun on day 0. The solid line is a nonlinear least square fit to the data. HIV-1 RNA level is an easier 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

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

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

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

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 $V(t)$.

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:

$$V_{NI}(t) = \frac{kNT_0V_0}{c-\delta}\left[\frac{c}{c-\delta}(e^{-\delta t} - e^{-ct}) - \delta te^{-ct}\right].$$

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

$$V(t) = V_0e^{-ct} + \frac{kNT_0V_0}{c-\delta}\left[\frac{c}{c-\delta}(e^{-\delta t} - e^{-ct}) - \delta te^{-ct}\right].$$

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.