CHAPTER 1

The HIV Pandemic

1.1. Introduction

When our immune system is compromised, it is only a matter of time before the numerous pathogens that surround us wreak their deadly damage. One of the most effective adversaries that the immune system may have to face is the HIV class of viruses, which targets some of its principal components. We will not go into great detail as to the precise fashion in which it does so, in part because this knowledge remains quite incomplete. We will focus instead on more general characteristics of the time development of the interacting virus and cell populations as an example of the thought processes that are useful in putting such biological events into a quantitative framework. In this chapter, we will also introduce a number of incompletely defined biological terms, reserving details for the thoroughly descriptive Chapter 2.

A virus is composed of a relative short string of genes (or perhaps two strings in parallel), normally protected by protein, and in the case of HIV surrounded by a lipid membrane. It infects a cell by binding to it via receptor molecules on the cell surface, and then injects its genes into the cell; they infiltrate the cell's manufacturing facility and cause it to produce more copies of the virus's genome (its string of genes) and proteins, which assemble and bud out of the cell as new viruses. A DNA virus simply inserts its DNA genome into the cell's DNA, while an RNA virus requires reverse transcriptase from the virus to construct its usable DNA. HIV, aside from its target, which is primarily a helper T-cell, a mainstay of the immune system, goes about its business pretty much like any other RNA virus, as cartooned in Figure 1.1. It binds to a cell via the cell's CD4 receptor, among others, injects its RNA through the cell membrane into the cell cytoplasm, the RNA produces a DNA copy which passes through the nuclear membrane, is integrated into the host DNA, and waits. When the T-cell is activated, which is bound to happen if it responds to an infection, all elements of the virus are manufactured, together with much of the cell's own needs; many of the viral proteins are made as one big string. This is then cleaved by proteases to produce the functional proteins of the virus, and the self-assembled virus (or "virion," used interchangeably to denote a single viral particle) leaves the cell by punching its way out.

Under drug-free conditions, HIV infection, once developed, is nonetheless held almost completely in check by the host immune system. This marvel of evolution, which we will later examine in great detail, both kills infected cells and digests viral particles. During the long (5- to 15-year) period of control, which gradually

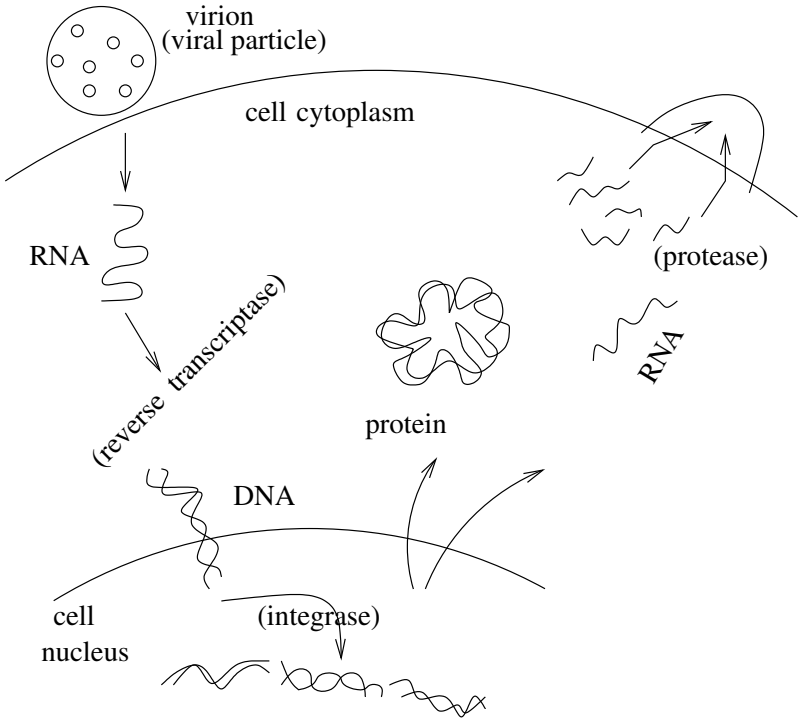

FIGURE 1.1. Major events in initial HIV infection.

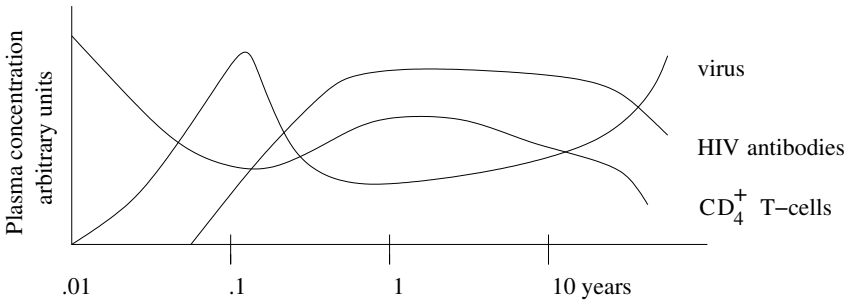

FIGURE 1.2. Typical time development of HIV infection.

weakens, the host is in an almost steady asymptomatic state, and it is during this period that one stands a better chance of understanding the population dynamics of the joint virus-immune system, hoping in this way to rationalize pharmaceutical treatment.

1.2. Prototype Dynamics

There are very rapid changes in viral and immune cell populations during the first few months of infection. We will attend mainly to the long, seemingly steady-state asymptomatic period that follows (Figure 1.2), the sustained levels normally referred to as the *set point*. A big hint as to what is going on in steady state stems

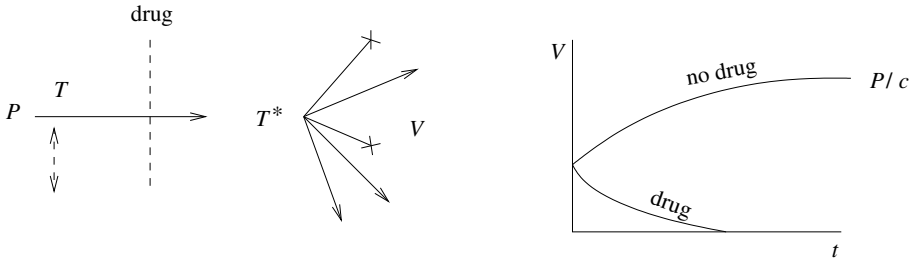

FIGURE 1.3. Effect of ideal drug treatment.

from the clinical observation that treatment with a powerful antiretroviral drug, thereby removing the source of new virus, results in rapid exponential decrease of virus. This strongly suggests that the virus population $V(t)$ is being controlled by a combination of constant source P (every T-cell gets zapped by virus, producing an infected T-cell T*, which spews forth virus), an effective clearance rate for virus:

$$\frac{dV}{dt} = P - cV.$$

A completely efficient drug (Figure 1.3) would make $P = 0$ so that $V(t) = V(0)e^{-ct}$, and clinical data results in $1/c = 1$ hour. Given this, then in steady state without the drug, $0 = P - cV$, and estimates of $V(0)$ allow us to estimate $P \sim 10^{10}$ virions/day. Since drug efficiency is less than 100%, we have an overestimate for $1/c$ (c really has to be higher than observed, to take care of the remnant of P).

The above argument leaves unexplained both the contributions to the viral growth rate and the size of the T-cell population that unwittingly serves as the source of virus. For these, we need a more detailed model. Let us refer all populations to some unit volume (generally taken in the business as 1 $\mu\ell = 1$ mm^3). Then, to start, we distinguish between the susceptible but uninfected T-cell population $T(t)$, and the population $T^*(t)$ that has been successfully ("productively") infected. The uninfected T's will be modeled via a source s, a natural death rate d, and a rate at which they become infected, taken (as in the chemical kinetics law of mass action) as proportional both to the viral concentration and T-cell concentration:

$$\frac{dT}{dt} = s - dT - kVT. \tag{1.1a}$$

The infected T's are of course produced at the same rate kVT, and have their own natural death rate δ after infection:

$$\frac{dT^*}{d\tau} = kVT - \delta T^*. \tag{1.1b}$$

The infected cells are indeed the source of new virions, but each T* can churn out a large number, say $N \sim 10^2 - 10^4$, of virions before dying, so now

$$\frac{dV}{dt} = N\delta T^* - cV. \tag{1.1c}$$

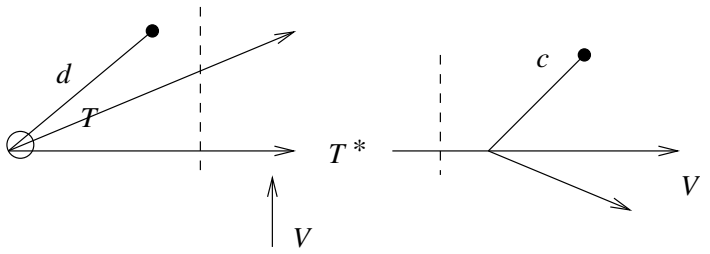

FIGURE 1.4. Schematic representation of interacting populations.

Schematically, one can represent the situation as in Figure 1.4 with drug interference locations shown dotted, and more succinctly in the notation of chemical reactions:

$$O \xrightarrow{s} T, \quad T \xrightarrow{d} \bullet,$$

$$T + V \xrightarrow{k} T^*$$

$$T^* \xrightarrow{\delta} NV, \quad V \xrightarrow{c} \bullet.$$

This basic model of three coupled ODEs is fairly simple but not analytically trivial, and it is worth looking at some extreme cases to get a feeling for its properties. To do so, we must decide what "extreme" means; after all, there are six parameters to play with. Since there are three concentration variables and one time variable, we can choose units so that two of the rate contributions in each equation have the same coefficient, and one of the time derivatives as well. Scaling as $T = \alpha\tau$, $T^* = \alpha^*\tau^*$, $V = \beta v$, and $t = \gamma t'$, we have

$$\frac{\alpha}{\gamma}\frac{d\tau}{dt'} = s - d\alpha\tau - k\beta\alpha v\tau,$$

$$\frac{\alpha^*}{\gamma}\frac{d\tau^*}{dt'} = h\beta\alpha v\tau - \alpha^*\delta\tau^*,$$

$$\frac{\beta}{\gamma}\frac{dv}{dt'} = n\delta\alpha^*\tau^* - c\beta v,$$

and so choosing $d\alpha = k\beta\alpha$, $k\beta\alpha = \alpha^*\delta$, and $\beta/\gamma = N\delta\alpha^* = c\beta$, or

$$\beta = \frac{d}{k}, \quad \gamma = \frac{1}{c}, \quad \alpha^* = \frac{cd}{N\delta k}, \quad \alpha = \frac{c}{Nk},$$

there results the canonical form

$$\frac{c}{d}\frac{d\tau}{dt'} = a - \tau - v\tau, \tag{1.2a}$$

$$\frac{c}{\delta}\frac{d\tau^*}{dt'} = v\tau - \tau^*, \tag{1.2b}$$

$$\frac{dv}{dt'} = \tau^* - v, \tag{1.2c}$$

where $a = \frac{Nk}{cd}s$. Note that time has now been scaled by that of the viral dynamics.

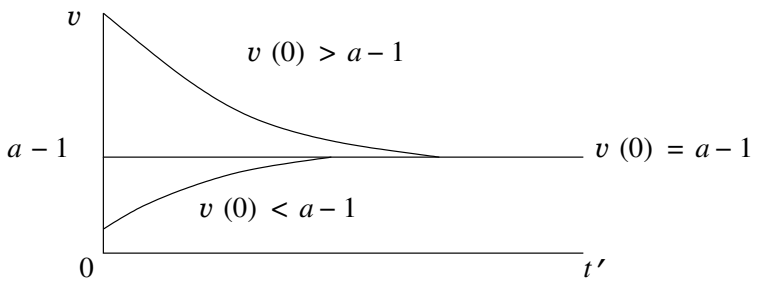

FIGURE 1.5. Time course for condition (1) when $a > 1$.

Actually, clinical estimates give

$$c \sim 23/\text{day}, \quad d \sim .01/\text{day}, \quad \delta \sim 1/\text{day}$$

but let us ignore these "details" in our enumeration of extremes. A first extreme might be the assumption that $c/\delta \to \infty$; then (1.2b) implies $\tau^* = \text{const}$, reducing (1.2c) to the primitive case we previously examined.

The opposite and more questionable extreme is $c/\delta \to 0$. This says that reaction (1.2b) remains in "equilibrium," being fed by (1.2a) and feeding (1.2c); as the Michaelis-Menten condition for intermediates, it is often used and often valid. There are now two "subextremes":

(1) $c/d \to 0$ as well, in which case both τ and τ^* can be solved for in (1.2a) and (1.2b), and substituted into (1.2c),

$$\frac{dv}{dt'} = v\,\frac{a-(1+v)}{1+v}, \tag{1.3}$$

stationary at the values $v_0 = 0$ or $v_0 = a - 1$. Solution of this single ODE is routine (do it). If $a > 1$, it is best written as

$$|v-(a-1)| = Kv^{1/a}e^{-t'(a-1)/a},$$

and if a is really large (Figure 1.5), as

$$|v-(a-1)| \sim Ke^{-t'}.$$

Thus, high initial v settles exponentially to $a - 1$, typical perhaps of the approval to steady state that we have seen. On the other hand, if $a < 1$, we write instead

$$v = K'(v+1-a)^a e^{-(1-a)t'},$$

so that for really small a (remember: $a = Nks/cd$ is an overall production rate divided by an overall destruction rate)

$$v \sim K'e^{-t'},$$

the infection being quenched.

(2) The second subextreme is $c/d \to \infty$, in which case $\tau = \text{const}$, and one has instead

$$\frac{dv}{dt'} = (\tau - 1)v,$$

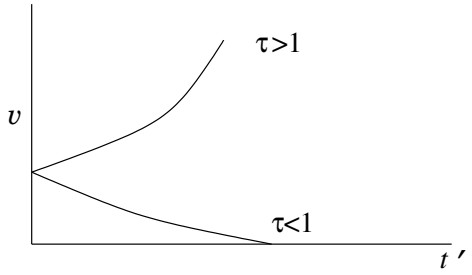

FIGURE 1.6. Time course for condition (2).

showing (Figure 1.6) for $\tau > 1$ an unstable divergence in v whenever the source τ is large enough and decay when $\tau < 1$. Here, viral production is controlled by the number of cells available to be infected.

Perhaps we should instead say nothing about $p = c/d$, in which case (1.2a) and (1.2b) become

$$\begin{aligned} p\,\frac{d\tau}{dt'} &= a - \tau - v\tau, \\ \frac{dv}{dt'} &= (\tau - 1)v. \end{aligned} \tag{1.4}$$

Now, there is a nontrivial repertoire, and we have the opportunity of trotting out a little more standard mathematical machinery. The interesting case is that of $a > 1$, and we would like to know, for example, what the system settles down to at long time. Stationary solutions, i.e., $0 = a - \tau - v\tau$, $0 = (\tau - 1)v$, certainly exist:

$$\begin{cases} \tau_0 = 1 \\ v_0 = a - 1 \end{cases} \quad \text{or} \quad \begin{cases} \tau_0 = a \\ v_0 = 0 \end{cases}$$

but is either one stable? To find out, we perturb the stationary state, $\tau = \tau_0 + \Delta\tau$, $v = v_0 + \Delta v$, and write out the dynamics to first order in the perturbation:

$$\begin{aligned} p\,\frac{d\Delta\tau}{dt'} &= -(1 + v_0)\Delta\tau - \tau_0\Delta v, \\ \frac{d\Delta v}{dt'} &= v_0\Delta\tau + (\tau_0 - 1)\Delta v. \end{aligned}$$

As a pair of homogeneous linear equations, the elementary solutions have the form

$$\begin{pmatrix} \Delta\tau(t') \\ \Delta v(t') \end{pmatrix} = \begin{pmatrix} c_\tau \\ c_v \end{pmatrix} e^{\lambda t'}$$

for suitable constants c_τ, c_v, and λ, and we can write

$$\begin{pmatrix} p\lambda + 1 + v_0 & -\tau_0 \\ v_0 & \lambda + 1 - \tau_0 \end{pmatrix} \begin{pmatrix} c_\tau \\ c_v \end{pmatrix} = 0,$$

solvable if the coefficient determinant vanishes:

$$p\lambda^2 + \lambda(1 + v_0 - p(\tau_0 - 1)) + 1 + v_0 - \tau_0 = 0.$$

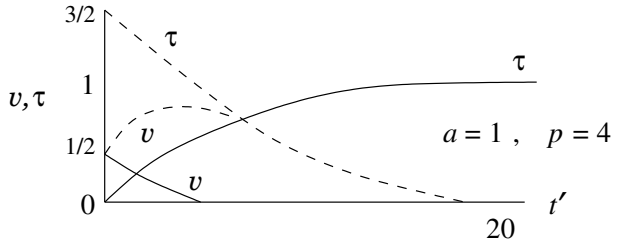

FIGURE 1.7. Time course when $c = 4d$, $a = 1$.

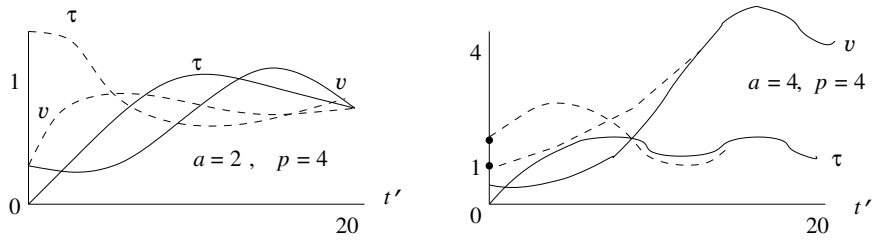

FIGURE 1.8. Cases $a = 2$ and $a = 4$.

The available values of λ for the above two stationary points are then

$$\lambda = \frac{1}{2p}\Big(-a \pm \sqrt{a^2 - 4(a-1)p}\Big), \quad \lambda = \left\{-\frac{1}{p}, a-1\right\}.$$

Let us first polish off the weak source, $a < 1$, case. Since $v(t')$, satisfying $d \ln v(t')/dt' = \tau(t') - 1$ from (1.4), can never get negative (the integral over t' of $d \ln v(t')/dt'$ cannot get to $-\infty$), the first stationary point, with $v_0 = a - 1 < 0$, is not accessible. The second one is, and the two possible exponents λ in $e^{\lambda t'}$ are both negative. Thus, the virus is eliminated, $v_0 = 0$, at long time, and any perturbation dies out. The $a = 1$ case is marginal, and which stationary solution is achieved depends upon initial conditions. For example, for $v(0) = \frac{1}{2}$ and $\tau(0) = 0$ or $\tau(0) = \frac{3}{2}(\cdots)$ at $p = 4$, we have the results pictured in Figure 1.7. But for $a > 1$, the second stationary point yields a perturbation solution with one positive exponent, so that unless the perturbation is tuned impossibly carefully, it will necessarily diverge at first and set the dynamics on the path to the fully stable solution at the elevated virus concentration $a - 1$. Note that at $p > a/4$ (Figure 1.8), the path to the stable high virus state is expected to oscillate, since each λ is complex.

1.3. Effect of Drug Treatment

A leading problem is how to interfere with, or reverse, the progression of HIV infection to a high-V, low-T state. Of course, this is a matter of increasing the death rate of viable virus, decreasing its birth rate, or both. We will look first at external interference, and then at interference by other components of the immune system.

Let us now drop the Michaelis-Menten intermediate equilibrium approximation in favor of the tacit assumption that the T-cell population is invariant in time, which would indeed be the case for $c/d \to \infty$ in our model. In fact, one knows that this population is under tight homeostatic control, which is another way of saying that the source strength s depends upon the population level (as well, of course, as on the depletion rate—see later). Although there is certainly a time lag in the resetting of s, it is not unreasonable to imagine that the concentration $T(t)$ is fixed at some T_0 and later on drop this strict assumption. And this substantially simplifies the ensuing analysis: In unscaled form, our system is now represented by

$$\begin{aligned} \frac{dT^*}{dt} &= -\delta T^* + kT_0V, \\ \frac{dV}{dt} &= N\delta T^* - cV, \end{aligned} \tag{1.5}$$

a strictly linear pair of homogeneous ODEs with $T_0^* = 0$, $V_0 = 0$, as the only stationary state except for the very special setting $NkT_0 = c$. The question is whether this state is stable or unstable.

We'll scale a bit differently from our previous treatment: now take $\alpha = \alpha^* = 1$, $\beta = N\delta/c$, $\gamma = 1/c$, leading to

$$\dot{\tau}^* = -\tau^* + bv, \quad \dot{v} = \tau^* - v, \tag{1.6}$$

$$\text{where } q = \frac{c}{\delta},\ b = \frac{NkT_0}{c},\ a = \left(\frac{s}{dT_0}\right)b,$$

and d/dt' is denoted by an upper dot. Note that in the absence of virus, our previous T-dynamics would have given the stationary state $T_0 = s/d$, so that if this value were retained, b would reduce to the source strength a of the previous notation. At any rate, the dynamics of the above pair will be a linear combination of two exponentials whose exponents now satisfy (show this)

$$q\lambda^2 + (q+1)\lambda + 1 - b = 0. \tag{1.7}$$

Without even solving, it is clear that there will be two negative λ's if $b < 1$, and the system will sink to $\tau^* = v = 0$; but one λ will be positive if $b > 1$. If the system is initially in a high viral load steady state, held there by control of the source s, then clearly the exact $\lambda = 0$ requires precisely that $b = 1$, the special setting alluded to above. With this as a starting point, all of the parameters T_0, c, N, and k can then be altered, and it is to this alteration that we now turn our attention.

The effect of a viral source elimination such as RTI (reverse transcriptase inhibitor) is to decrease k, the parameter measuring T-cell infection rate by virus. A perfect inhibitor makes $k = 0$, or $b = 0$, and so, from (1.6), τ^* decreases exponentially as $\exp -t'/q$; v has the additional $\exp -t'$ contribution (see Figure 1.9). An imperfect inhibitor of efficiency η_{RTI}, converting k to $k' = (1 - \eta_{\text{RTI}})k$, will still send the system to its uninfected virus-free origin if $b' = (1 - \eta_{\text{RTI}})b < 1$ or

$$(1 - \eta_{\text{RTI}})k < \frac{c}{NT_0}.$$

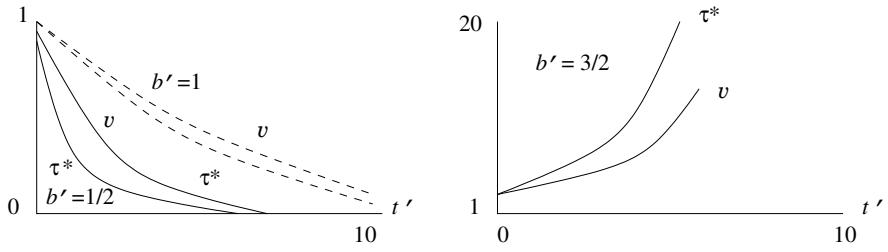

FIGURE 1.9. Time course at homeostatically stabilized T_0.

In particular, $\eta_{\text{RTI}} > 0$ suffices for T_0 determined by the initial drug-free steady state, for which we know that $b = 1$. The drug fails as soon as the virus has mutated to the point that the RT inhibitor can no longer maintain this value of k' in the face of concomitant changes in c, N, and T_0.

A second category of drugs, protease inhibitors (PI), has a very different biological effect: of the N virions produced, a fraction, say $\eta_{\text{PI}}N$, will be noninfectious, V_{NI}, leaving only $(1-\eta_{\text{PI}})N$ to produce the infectious V. Thus, at efficiency η_{PI}, the virus production splits into

$$\frac{dV}{dt} = (1-\eta_{\text{PI}})N\delta T^* - cV,$$
$$\frac{dV_{\text{NI}}}{dt} = \eta_{\text{PI}}N\delta T^* - cV_{\text{NI}}.$$

But the effect on infectious virus production $V(t)$ is unchanged in form: now

$$b' = (1-\eta_{\text{PI}})\frac{NkT_0}{c},$$

and so the $b' < 1$ condition reads

$$1-\eta_{\text{PI}} < \frac{c}{NkT_0}.$$

In combination therapy, in which both RTI and PI are used, k changes as well. Thus, viral extinction requires

$$(1-\eta_{\text{PI}})(1-\eta_{\text{RTI}}) < \frac{c}{Nk\tau_0}.$$

Source Control. The parameters not yet modified are T_0 and c. Since T_0 is not really a fixed parameter but is systemically controlled by a homeostatic mechanism, we should examine how this is done. In effect, the source itself is concentration dependent, and the most reliable model for accomplishing this is a species of "logistic equation"

$$\frac{dT}{dt} = s + \xi T\left(1-\frac{T}{T_M}\right) - dT,$$

in which T-cells are produced both by an external source—e.g., the thymus—and by replication at rate ξ, modified by repression as T approaches a control value of

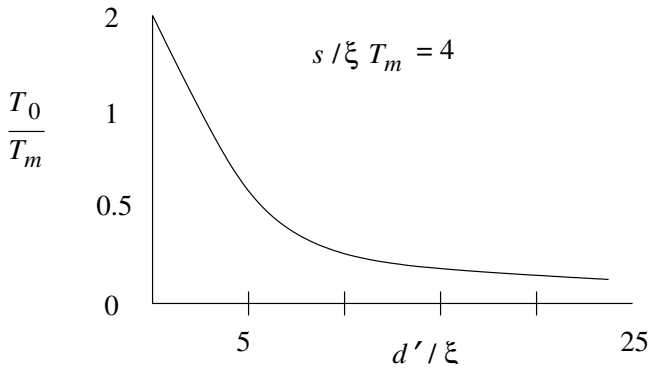

FIGURE 1.10. Viral depletion ratio.

T_M. Indeed, the population now becomes stationary, $dT/dt = 0$, at a value T_0 given by

$$\frac{T_0}{T_M} = \pm\left[\frac{\xi - d}{\xi} + \left(\left(\frac{\xi - d}{\xi}\right)^2 + 4\,\frac{s}{\xi T_M}\right)^{1/2}\right]. \tag{1.8}$$

(Show that $T_0 > T_M$ or $T_0 < T_M$ as $\xi/b > T_M$ or $\xi/b < T_M$).

In the presence of virus at level V_0, the death rate d must be replaced by

$$d' = d + kV_0,$$

and we have the operating curve shown in Figure 1.10, which illustrates the basic T-cell depletion due to viral infection.

Recovery of T-cells After Initiation of Therapy. One consequence of the autonomous control is part of the recovery of T_0 seen after RTI quenches virus production. That is, suppose $T(0) = T_V$ in initial steady state, where d is replaced by the full death rate d' in the presence of virus V_0:

$$s + (\xi - d - kV_0)T_V - \left(\frac{\xi}{T_M}\right)T_V^2 = 0. \tag{1.9}$$

Then, if V is taken as dropping to 0 at once on the scale of process considered, we have immediately after the drug treatment starts

$$\begin{aligned}\left.\frac{dT}{dt}\right|_0 &= s + (\xi - d)T_V - \left(\frac{\xi}{T_M}\right)T_V^2 \\ &= kV_0T_V.\end{aligned}$$

Thus, after the start of therapy, T-cell levels should rise at a rate equal to the rate at which they were being infected (and killed) before therapy was initiated. It follows that the effective T_0 to be inserted into the T^* production equation is given at short time by

$$T_0(t) = (1 + kV_0t)T_V.$$

1.4. Other Players in the Immune System

There remains the possibility of controlling the viral death rate c, and here internal interference comes into play—the normal drug-free control.

CTL Effect. We have thus far acted as if the only T-cell species of interest is the CD4 + T-cell, i.e., a T-cell with CD4 receptor, because this is the helper cell that orchestrates so much of the immune response. But there are many other cellular species that can affect the viral elimination process. We first focus on the cytotoxic T-lymphocytes (CTL)—which harbor the CD8 receptor rather than CD4—and remain available to kill antigenically marked virally infected cells, in effect increasing the viral death rate: Referring to the concentration of fully competent CTLs or effector cells as $E(t)$, and once more assuming the usual mass action chemical kinetics, the T^* and viral dynamics would now be modified to

$$\frac{dT^*}{dt} = -(\delta + \mu E)T^* + kVT, \quad \frac{dV}{dt} = N\delta T^* - cV. \tag{1.10}$$

Suppose that we can imagine $T = T_0$ and $E = E_0$ as held constant; then the exponents for the coupled pair of ODEs are determined as usual by

$$\det \begin{pmatrix} -\delta - \mu E_0 - \lambda & kT_0 \\ N\delta & -c - \lambda \end{pmatrix} = 0,$$

or $\lambda^2 + (\delta + c + \mu E_0)\lambda + c(\delta + \mu E_0) - N\delta k T_0 = 0$, so that the system converges to extinction at the origin if both values of $\lambda < 0$, or

$$c\left(1 + \frac{\mu}{\delta} E_0\right) > NkT_0,$$

as if we have increased the viral death rate c.

What controls the dynamics of E? Its precursors are quiescent or naive CD8 + T-cells, held homeostatically, say at L_0. These are then activated if they are simultaneously coupled to an antigen-presenting cell (APC) and a "helper" CD4 cell. Since the former should mirror the viral population, and the latter the assumedly steady population T_0, we expect that activation should occur at a rate $\zeta V T_0 L_0$ for suitable ζ. The activated CD8 + T-cells have two options, depending upon the concentration of antigenically marked cells to be targeted for destruction: they either differentiate to the lethal "effector" cells E, or they propagate and then differentiate. Any portion of the population not called upon will gradually decay. The net effect is that we can assume

$$\frac{dL}{dt} = \zeta T_0 L_0 V - \nu T^* L - \kappa L$$

for suitable decay constant κ. Finally, the net concentration of effector cells will be some multiple of the L-population entering the proliferative level but will die out at its own natural rate:

$$\frac{dE}{dt} = M\nu T^* L - d^* E.$$

At the moment, we will will simply draw the conclusion from these two equations that at steady state we will have the nontrivial relation

$$E_0 = \left(\frac{M}{d^*}\right)\zeta T_0 L_0\left(\frac{\nu T^*}{\kappa + \nu T^*}\right)V \tag{1.11}$$

if T^* and V can be regarded as slowly varying in time, in which case $T^*(t)$ and $V(t)$ determine an $E_0(t)$.

B-Cell Interactions. CTLs prevent the birth of virus, and so decrease the excess of births over deaths, leading to an effective increase in the natural death rate c. But virus can also be neutralized and hence effectively killed on its way to infect T-cells by B-cells, the purveyors of humoral (bathing fluid) immunity. Without giving any details at this juncture, we suppose that the escape mode of the viral population, due to the virus mutating so that it is no longer recognized by the B-cells, results in a steady weakening of the B-cell lethality, and hence of the clearance rate c. Confining our attention to the consequences of this mechanism, we can ask about the slowly changing steady state in response to a slowly changing $c(t)$. Sticking to our minimal model, this means that

$$\begin{aligned} \dot{T} &= 0 = s - dT - kVT, \\ \dot{T}^* &= 0 = kVT - \delta T^*, \\ \dot{V} &= 0 = N\delta T^* - cV, \end{aligned} \tag{1.12}$$

from which we infer that, on the high virus branch,

$$V(t) = \frac{Ns}{c(t)} - \frac{d}{k}, \quad T(t) = \frac{c(t)}{Nk}. \tag{1.12$'$}$$

Then indeed, a steady drop in $c(t)$ would yield a steady drop in $T(t)$, culminating in a spectacular rise in $V(t)$. Vaccine might have the opposite effect: increasing antibody, increasing c, and decreasing $V(t)$.

HIV Sanctuaries. Other cells of the immune system are CD4+ and become infected by HIV but are not destroyed as rapidly by the trauma of HIV production. For example, CD4 + macrophages are thought to emit HIV less copiously, but over a long period of time before dying, and subclasses of T-cells may do the same. Denoting the new population by M and its infected version by M^*, we would now

have, in the absence of drugs,

$$\begin{aligned}
\frac{dT}{dt} &= s - dT - kVT,\\
\frac{dM}{dt} &= s' - d'M - k'VM,\\
\frac{dT^*}{dt} &= kVT - \delta T^*,\\
\frac{dM^*}{dt} &= k'VM - \delta' M^*,\\
\frac{dV}{dt} &= N\delta T^* + N'\delta' M^* - cV.
\end{aligned}$$

Assuming that T and M are feedback stabilized at T_0 and M_0 by augmenting the dT/dt and dM/dt equations, only the remaining three equations are relevant. In particular, steady state requires

$$T_0^* = \frac{kV_0T_0}{\delta}, \quad M_0^* = \frac{k'V_0M_0}{\delta'}, \quad \text{where } N\delta T_0^* + N'\delta' M_0^* = cV_0.$$

Note that T_0 and M_0 would therefore have to be adjusted so that

$$NkT_0 + N'k'M_0 = c.$$

But no assumptions are needed if RT and protease inhibitor therapy has started. The only new virus would then be noninfective, and we would have instead

$$\begin{aligned}
\frac{dT^*}{dt} &= -\delta T^*, \quad \frac{dM^*}{dt} = -\delta' M^*,\\
\frac{dV}{dt} &= -cV, \qquad \frac{dV_{\mathrm{NI}}}{dt} = N\delta T^* + N'\delta' M^* - cV_{\mathrm{NI}},
\end{aligned}$$

a very solvable system for which

$$T^*(t) = T^*e^{-\delta t}, \quad M^*(t) = M_0^*e^{-\delta' t}, \quad V(t) = V_0e^{-ct}.$$

Consequently, $V_{\mathrm{NI}}(t) = (d/dt + c)-'(N\delta T^* + N'\delta' M^*) + Ke^{-ct}$, the sum of a particular and general solution. Since $(d/dt + c)^{-1}e^{at} = (1/a + c)e^{at}$ as a special solution, we have

$$V_{\mathrm{NI}}(t) = \frac{N\delta}{c-\delta}\,T_0^*e^{-\delta t} + \frac{N'\delta'}{c-\delta'}\,M_0^*e^{-\delta' t} + Ke^{-ct};$$

the unknown K is fixed by imposing $V_{\mathrm{NI}}(0) = 0$. Of course, the observable virus is given by $V_{\mathrm{tot}}(t) = V(t) + V_{\mathrm{NI}}(t)$:

$$\begin{aligned}
V_{\mathrm{tot}}(t) = &\left(V_0 - \frac{N\delta T_0^*}{c-\delta} - \frac{N'\delta' M_0^*}{c-\delta'}\right)e^{-ct}\\
&+ \frac{N\delta}{c-\delta}\,T_0^*e^{-\delta t} + \frac{N'\delta'}{c-\delta'}\,M_0^*e^{-\delta' t}.
\end{aligned}$$

The last term (δ' is by far the smallest exponent) constitutes a long-time tail, which, once the drugs are no longer effective, is released in infective form. A typical time dependence is shown in Figure 1.11.

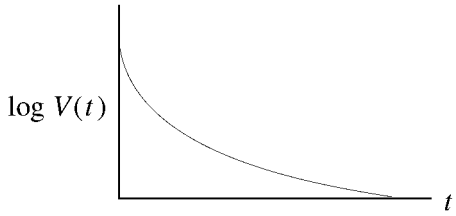

FIGURE 1.11. Generic time dependence.

1.5. Time Delay

We have more than once mentioned the possibility of time-delayed response and then ignored it. Now our ODE description by necessity chooses a few cellular and molecular types to focus on. The effect of neglected reactants is typically to buffer and delay the reaction taking place. As a trivial example, take the sequence

$$\rightarrow A \xrightarrow{k} B \xrightarrow{\ell} C$$

and imagine that B is ignored by ignorance or design. Since $\dot{C} = \ell B$, but $\dot{B} = kA - \ell B$ has the solution $B(t) = Ke^{-\ell t} + k\int_0^t A(t-t')e^{\ell t'}dt'$ (just substitute and see), then

$$\dot{C}(t) = K\ell e^{-\ell t} + k\ell \int_0^t A(t-t')e^{-\ell t'}\,dt'.$$

At time long compared to $1/\ell$, the K-term can be neglected and the upper limit taken to ∞, so we have

$$\begin{aligned} \dot{C}(t) &= k\ell \int_0^\infty A(t-t')e^{-\ell t'}dt' \\ &\equiv k\bar{\mathrm{A}}(t) \end{aligned} \tag{1.13}$$

with the interpretation that intermediate B does not change the rate $A \xrightarrow{k} C$, but all $A(t')$ for $t' < t$ contribute to $\bar{\mathrm{A}}(t)$, albeit in decreasing weight as one goes back in time.

A much-used approximation is to replace the average memory by a single delayed amplitude. Clearly, since $A(t-t') = A(t-\tau) + (\tau - t')A'(t-\tau) + \cdots$, the first-order correction to

$$\bar{\mathrm{A}}(t) = \ell \int_0^\infty A(t-t')e^{-\ell t'}dt' = A(t-\tau) + \left(\tau - \frac{1}{\ell}\right)A'(t-\tau) + \cdots$$

will vanish if $\tau = 1/\ell$, precisely the mean time delay:

$$\tau = \frac{\int_0^\infty t'e^{-\ell t'}\,dt'}{\int_0^\infty -e^{-\ell t'}\,dt'} = \frac{1}{\ell}.$$

We would then have

$$\dot{C}(t) = kA(t-\tau),$$

a discrete delay equation. Of course, the reverse can be carried out when a discrete time delay is realistic: it can be mimicked by a single artificial intermediary.

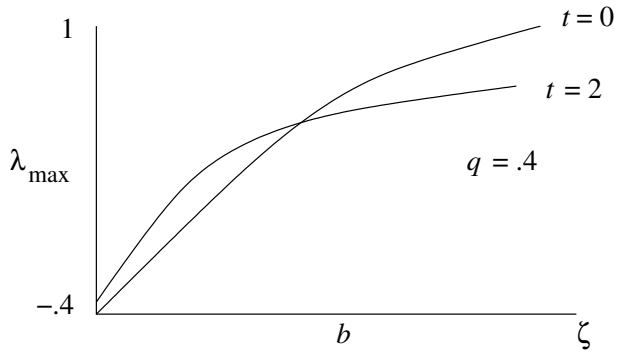

FIGURE 1.12. Decay exponent under time delay.

Delay equations introduce many novel effects, including oscillations and chaos. Let us now look only at a simple example that is devoid of such pathologies. Suppose we take into account the fact that there is certainly a time delay between the entrance of a virus into a T-cell and the exit of newly produced virions from the stricken cell. Then our basic equations (1.5) at homeostatically controlled T_0 become

$$\begin{aligned} \frac{dT^*(t)}{dt} &= -\delta T^*(t) + kT_0V(t), \\ \frac{dV(t)}{dt} &= N\delta T^*(t-\tau) - cV(t). \end{aligned} \tag{1.14}$$

These are still linear homogeneous, and so we still have elementary solutions of the form $\binom{C_{T^*}}{C_V}e^{\lambda t}$. But these now imply

$$\begin{aligned} \lambda C_{T^*} &= -\delta C_{T^*} + kT_0C_V, \\ \lambda C_V &= N\delta e^{-\lambda\tau}C_{T^*} - cC_V, \end{aligned}$$

effectively replacing N by $Ne^{-\lambda\tau}$, or in our previously scaled notation, b by $be^{-\lambda\tau}$. Without bothering to solve the consistency equation for λ, which is changed to

$$q\lambda^2 + (q+1)\lambda + 1 - be^{-\tau\lambda} = 0, \tag{1.15}$$

it is clear that precisely when $\lambda < 0$, the effect of drug therapy, which is to decrease b, is, unsurprisingly, countered by the delay (see Figure 1.12). The effect of delay will not always be unsurprising.

1.6. Conclusion

The population dynamics level of analysis we have been concerned with is highly empirical, with multiple interrelated phenomena being cartooned by a few effective parameters. It is certainly the first thing one should do in the face of wildly fluctuating incomplete data. But of course, it is knowledge of the details that enter into these model population dynamics parameters that allows nature, and ultimately allows us, to beneficially interfere with the pathological aberrations we

are faced with. We now turn to these details, first in a qualitative overview, and then at a quantitative level at the many junctures in immunological response at which this is possible.

Homework Assignment 1

(1) Obtain the quoted solutions of (1.3).
(2) Derive (1.7) and its properties.
(3) Show that (1.8) has the properties cited.
(4) How does (1.12′) change if $c(t) = c - \alpha t$ where α is not small?

References for Chapter 1

Levine, A. *Viruses*. Scientic American Library, New York, 1992.

Perelson, A. S., and Nelson, P. W. Mathematical analysis of HIV-1 dynamics in vivo. *SIAM Rev*. 41(1): 3–44, 1999 (electronic).