10

A Biomathematical Approach to HIV and AIDS

Introduction

Acquired immunodeficiency syndrome (AIDS) is medically devastating to its victims, and wreaks financial and emotional havoc on everyone, infected or not. The purpose of this chapter is to model and understand the behavior of the causative agent of AIDS—the human immunodeficiency virus (HIV). This will necessitate discussions of viral replication and immunology. By the end of this chapter, the student should have a firm understanding of the way that HIV functions and be able to apply that understanding to a mathematical treatment of HIV infection and epidemiology.

Viruses are very small biological structures whose reproduction requires a host cell. In the course of viral infection the host cell is changed or even killed. The host cells of HIV are specific and very unique: They are cells of our immune system. This is of monumental importance to the biological and medical aspects of HIV infection and its aftermath. HIV infects several kinds of cells, but perhaps its most devastating cellular effect is that it kills helper T-lymphocytes. Helper T-lymphocytes play a key role in the process of gaining immunity to specific pathogens; in fact, if one's helper T-lymphocytes are destroyed, the entire specific immune response fails. Note the irony: HIV kills the very cells that are required by our bodies to defend us from pathogens, including HIV itself! The infected person then contracts a variety of (often rare) diseases to which uninfected persons are resistant, and that person is said to have AIDS.

10.1 Viruses

Viruses are small reproductive forms with powerful effects. A virus may have only four to six genes, but those genes enable it to take over the synthetic machinery of a normally functioning cell, turning it into a small biological factory producing thousands of new viruses. Some viruses add another ability: They can insert their nucleic acid into that of the host cell, thus remaining hidden for many host cell generations prior to viral reproduction.

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HIV is an especially versatile virus. It not only inserts its genetic information into its host's chromosomes, but it then causes the host to produce new HIV. Thus the host cells, which are immune system components, produce a steady stream of HIV particles. Eventually, this process kills the host cells and the patient becomes incapable of generating critical immune responses.

A virus is a kind of parasite.

Each kind of virus has its own special anabolic ("building up") needs, which, because of its genetic simplicity, the virus may be unable to satisfy. The host cell then must provide whatever the virus itself cannot. This requires a kind of biological matching between virus and host cell analogous to that between, say, an animal parasite and its host. Host specificity is well developed in viruses: As examples, the rabies virus infects cells of our central nervous system, cold viruses affect cells of our respiratory tract, and the feline leukemia virus affects certain blood cells of cats (see [1]).

The basic structure of a virus is a protein coat around a nucleic acid core.

Simple viruses may have only four to six genes, but most viruses have many more than that. In the most general case the viral nucleic acid, either DNA or RNA, is surrounded by a protein coat, called a *capsid* (see Figure 10.1.1). In addition, many viruses have outer layers, or *envelopes*, which may contain carbohydrates, lipids, and proteins. Finally, inside the virus there may be several kinds of enzymes along with the nucleic acid.

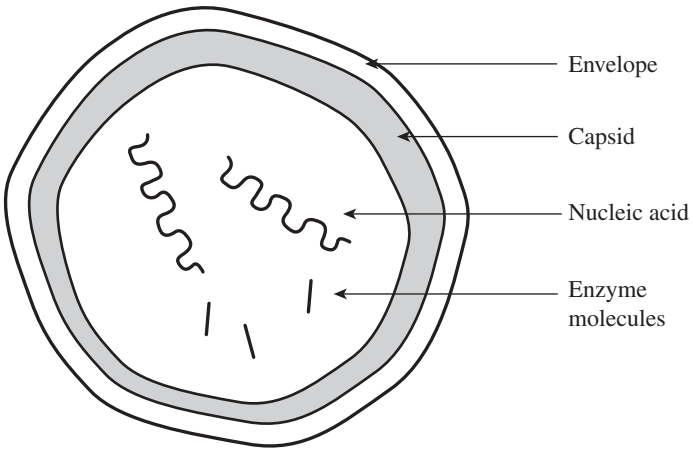


Fig. 10.1.1. A generalized drawing of a virus. In a given real case the envelope and/or enzyme molecules may be absent and the nucleic acid may be DNA or RNA.

A virus cannot reproduce outside a host cell, which must provide viral building materials and energy. All the virus provides is instructions via its nucleic acids and, occasionally, some enzymes. As a result, viruses are not regarded as living things.

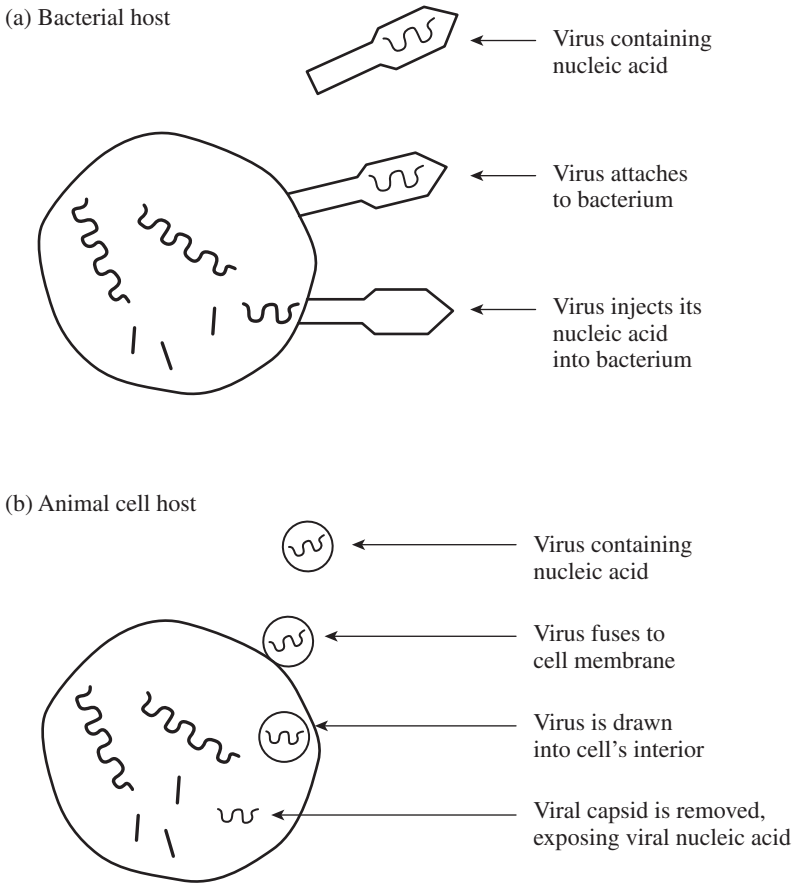


Fig. 10.1.2. Some models of viral infection. (a) A virus whose host is a bacterium recognizes some molecular feature of the correct host, attaches to it, and injects its nucleic acid into it. (A virus whose host is a bacterium is called a *bacteriophage*.) (b) A virus whose host is an animal cell recognizes some molecular feature of the correct host cell and is then drawn into the host cell, where the capsid is removed.

Viral nucleic acid enters the host cell and redirects the host cell's metabolic apparatus to make new viruses.

A virus attaches to its specific host's outer covering, host–virus specificity being ensured by host-to-viral molecular recognition. The molecules involved are proteins or *glycoproteins*, a sugar–protein combination. At this point the viral nucleic acid enters the host cell, the precise means of entry depending on the nature of the virus (see Figure 10.1.2). For instance, viruses called *bacteriophages* infect bacteria. Bacteriophages have no envelope and seem to inject their nucleic acid into the bacterium, leaving the viral protein capsid outside. Alternatively, nucleic acids from viruses that

infect animals can enter the host cell by *fusion*, in which a virus joins its envelope to the cell membrane of the host cell and the entire viral capsid is drawn into the host cell. Fusion is facilitated by the fact that the viral envelope is chemically similar to the cell membrane. The capsid is then enzymatically removed, thus exposing its contents—the viral nucleic acid and possibly certain viral-specific enzymes.

What happens next depends on the identity of the virus, but it will ultimately lead to viral multiplication. Viral replication requires the production of viral-specific enzymes, capsid proteins, and, of course, viral nucleic acid. The synthesis of these components is carried out using the host cell's anabolic machinery and biochemical molecules. To do this, the host cell's nucleic acid must be shut down at an early stage in the infection, after which the viral nucleic acid takes control of the cellular machinery. It is said that the host cell's metabolic apparatus is changed from "host directed'' to "viral directed.'' An analogue can be found in imagining a computer-controlled sofa-manufacturing plant. We disconnect the original (host) computer and install a new (viral) computer that redirects the existing construction equipment to use existing materials to manufacture chairs instead of sofas.

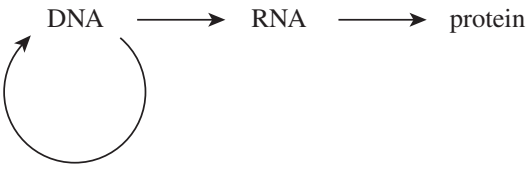
Typically a virus uses the enzymes of the host cell whenever possible, but there are important situations in which the host cell may lack a critical enzyme needed by the virus. For example, some viruses carry single-stranded nucleic acids, which must become double stranded shortly after being inserted into the host. The process of forming the second strand is catalyzed by a particular polymerase enzyme, one that the host lacks. The viral nucleic acid can code for the enzyme, but the relevant gene is on the nucleic acid strand that is complementary to the one strand the virus carries. Thus the gene is unavailable until the viral nucleic acid becomes double stranded—but of course the nucleic acid cannot become double stranded until the enzyme is available! The virus gets around this problem by carrying one or more copies of the actual enzyme molecule in its capsid and injecting them into the host at the time it injects the nucleic acid.[1]

As the virus's various component parts are constructed, they are assembled into new, intact viruses. The nucleic acid is encapsulated inside the protein capsid, perhaps accompanied by some critical viral enzymes. The assembly of the capsid is spontaneous, like the growth of a crystal. The newly assembled viruses then escape from the host cell and can start the infection process anew.

Many RNA viruses do not use DNA in any part of their life cycle.

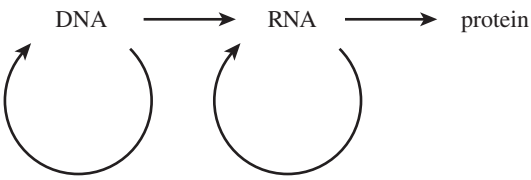
The central dogma was presented in Chapter 8 to show the path of genetic information flow:

[1] Recall from Chapter 8 that in a given segment of DNA, only one of the two DNA strands actually codes for RNA. That strand is called the *coding strand*. In the example given above, the coding strand would be the strand formed after infection. Thus its genes would not be available until after the nucleic acid became double stranded.



Note that because RNA is complementary to DNA, it should be possible to skip the DNA part of the scheme. All that is necessary to justify this assertion is to demonstrate that RNA can code for its own self-replication. While this does not seem to happen in cellular systems, it is well known in viruses: Viral RNA replicates just as DNA does, using complementary base-pairing. After replication, the RNA is packaged into new viruses.[2]

Our revised statement of the central dogma, accounting for RNA self-replication, now looks like this:



There are several variations in the host-cell-escape mechanism for viruses.

Some viruses merely replicate their nucleic acid, translate out the necessary proteins, encapsulate, and then burst out of the host cell an hour or two after infection. This bursting process kills the host cell and is called *lysis*; the virus is said to be *lytic*.

Other viruses, said to be *lysogenic*, delay the lytic part of their reproductive process. For example, the DNA of some DNA viruses is inserted into the host cell body and then into the host's DNA. Thus when the host's DNA is replicated at cell division, so is the viral DNA. The inserted viral DNA is called a *provirus*, and it can remain inserted in the host DNA for many cell generations. Sooner or later, depending on the lysogenic virus, host, and culture conditions, the provirus begins to replicate its nucleic acid and produces RNA, which then produces viral proteins. New viruses are then assembled and lyse the host to get out.

There is an alternative to lysis in the escape process: When the viruses exit the host cell, they may instead *bud off* from the host cell, in a process that is the reverse of fusion. In the process, they take a piece of the cell membrane for an envelope, but do not kill the host cell. Cells that release viruses by budding can therefore act as virtually unending sources of new viruses. This, in fact, is the behavior of certain blood cells infected with HIV.

[2] There are single-stranded and double-stranded RNA viruses, just as there are single- and double-stranded DNA viruses. HIV is a single-stranded RNA virus—its conversion to double-stranded form will be described in Section 10.3.

10.2 The Immune System

Our bodies fight off pathogens by two means. One is a general defense system that removes pathogens without much regard to their biological nature; stomach acid is such a system.

Of more concern to us in our considerations of HIV is a second, specific response to pathogens (and other foreign substances); this response is tailored to each infective agent. Specialized blood cells called lymphocytes have the ability to recognize specific molecular parts of pathogens and to mount a chemical response to those fragments. Initially, we have at most only a few lymphocytes that can recognize each such fragment, but upon contact with the fragment, the lymphocyte will start to divide extensively to provide a clone of cells. Thus there results a large clone of identical lymphocytes, all of which are chemically "tuned" to destroy the pathogen.

In this section, we describe the means by which lymphocytes respond to foreign substances to keep us from getting diseases and from being poisoned by toxins. This subject is of great importance to our understanding of HIV because certain lymphocytes are hosts for HIV. Thus HIV infection destroys an infected person's ability to resist pathogens.

Some responses to pathogens are innate, or general.

We possess several general mechanisms by which we can combat pathogens. These mechanisms have a common property: They are essentially nondiscriminatory. Each one works against a whole class of pathogens and does not need to be adapted for specific members of that class. For example, tears and egg white contain an enzyme that lyses the cell walls of certain kinds of bacteria. Stomach acid kills many pathogens that we eat. Damaged tissue attracts blood- clotting agents and dilates capillaries to allow more blood to approach the wound. Finally, there are blood cells that can simply engulf pathogens; these cells are *granulocytes* and *macrophages*.

The problem with the innate response is that it cannot adapt to new circumstances, whereas many pathogens are capable of rapid genetic change. Thus many pathogens have evolved ways to circumvent the innate response. For such pathogens, we need an immune response that can change in parallel with the pathogen (see [1] and [2]).

Blood cells originate in bone marrow and are later modified for different functions.

Humans have bony skeletons, as do dogs, robins, snakes, and trout, but sharks and eels have cartilaginous skeletons. In the core, or *marrow*, of our bones is the blood-forming tissue, where all of our blood cells start out as *stem cells*. Repeated division of stem cells results in several paths of cellular specialization, or *cell lines*, as shown in Figure 10.2.1. Each cell line leads to one of the various kinds of mature blood cells described in Section 9.6. One cell line becomes red blood cells. Another line generates cells involved in blood clotting. Still other lines have the ability to engulf and digest pathogens. Finally, there is a cell line that generates cells capable of specifically adapted defenses to pathogenic agents. They are called *lymphocytes*.

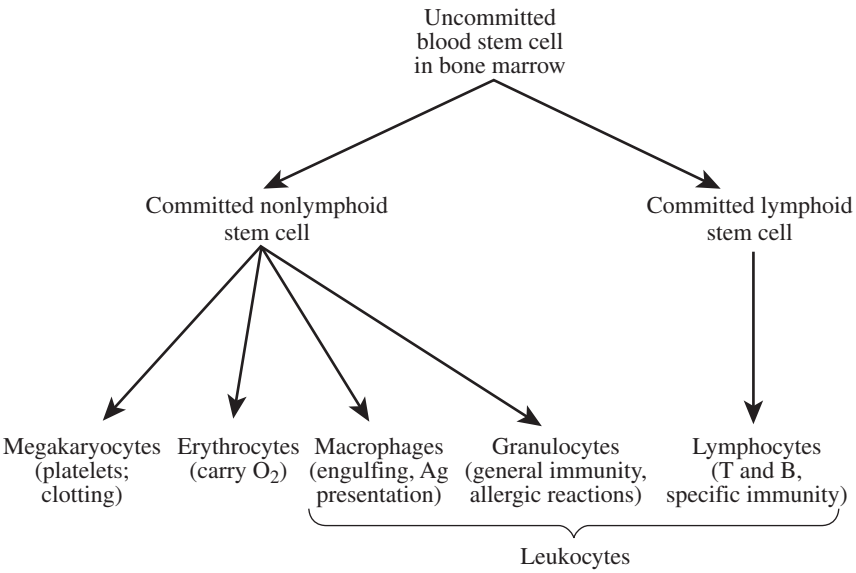


Fig. 10.2.1. A flow chart showing the development of mammalian blood cells from their generalized state to their final, differentiated state.

Some immune responses are adaptive, or specific, to the pathogen.

Our immune system is capable of reactions specifically tailored to each foreign substance, or *antigen*; in other words, each and every antigen elicits a unique response. At first glance, we might think that the finite amount of information that a cell can contain would place a ceiling on the number of specific responses possible. We will see that the restriction is not important because the specific immune system works against as many as 10^{12} distinct antigens![3]

Certain cell lines, derived from bone marrow stem cells, mature in our lymphatic system to become *lymphocytes*. For example, T-lymphocytes, or *T-cells*, mature in the thymus gland, which is found prominently under the breastbone of fetuses, infants, and children. B-lymphocytes, or *B-cells*, mature in bone marrow. These two kinds of lymphocytes are responsible for the adaptive immune responses, but they play different and complementary roles.

T-cells are responsible for the cell-mediated immune response.

We will be especially interested in two groups of T-cells: *helper T-cells* and *cytotoxic T-cells* (see Figure 10.2.2). After they mature in the thymus of neonatal and prenatal animals, these T-cells are *inactive*. On their outer surfaces, inactive T-cells have recognition proteins that can bind to antigens (via hydrogen bonds and other interac-

[3] The size of this number, even its order of magnitude, is subject to some debate. In any case, it is *very* big.

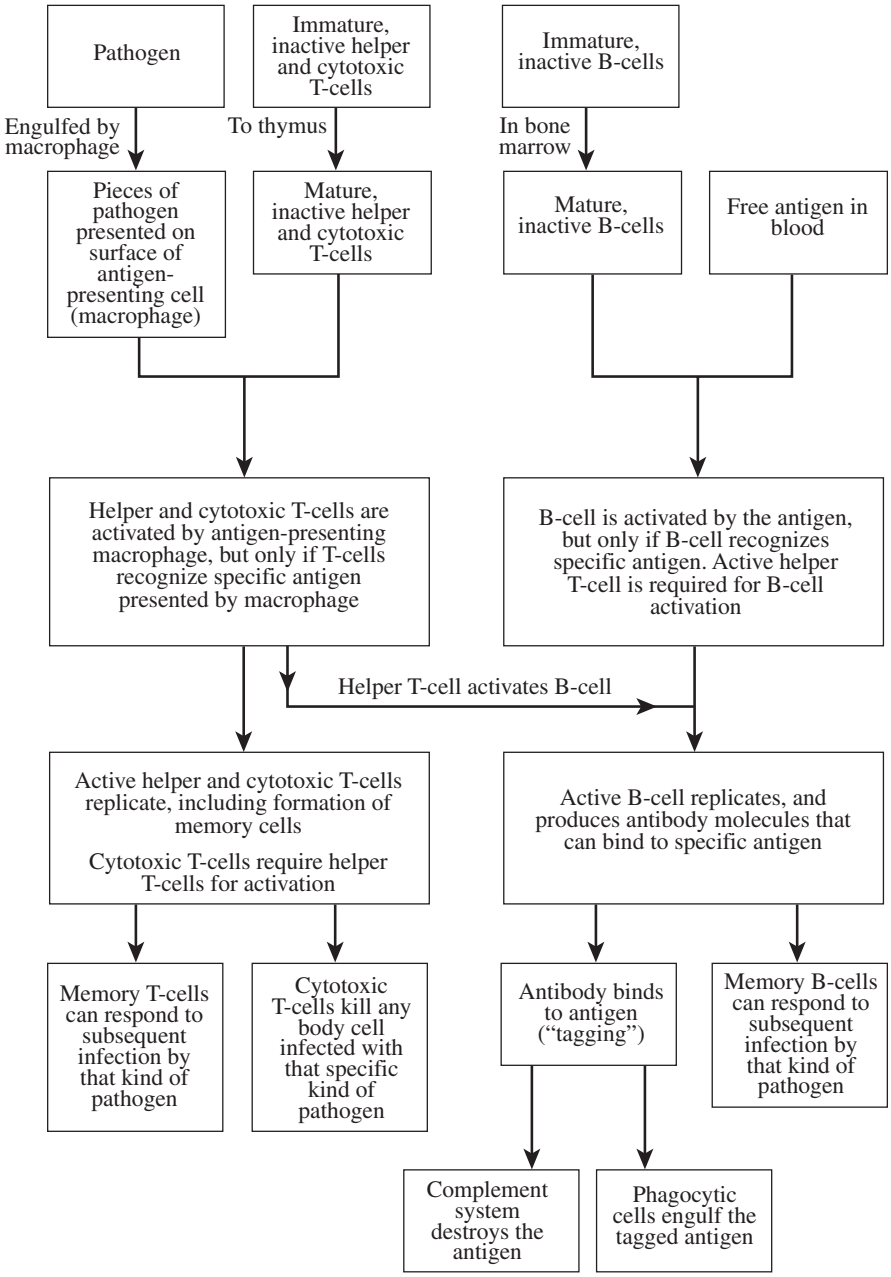


Fig. 10.2.2. A flow chart showing the events and interactions surrounding the specific immune response. The cell-mediated response begins at the top left and the humoral response begins at the top center. The two responses interact at the center of the page. The details are described in the text.

tions). This binding cannot take place, however, unless some preliminary steps have already occurred: First, one or more *antigen-presenting cells*, or *macrophages*, must ingest the pathogen. Second, the antigen-presenting macrophages must then break off various molecular pieces of the pathogen and move them to their own surface, i.e., *present* the various antigenic fragments (called *epitopes*) to inactive T-cells. This presentation activates the T-cells and causes them to divide repeatedly into clones, each of which consists of identical, active helper T-cell or cytotoxic T-cells. In fact, there should result a clone of active helper and cytotoxic T-cells for each of the various epitopes that the antigen-presenting cells display, one clone originating from each activated T-cell.[4] An important point: The active helper T-cells are required in the activation of the cytotoxic T-cells. The active cytotoxic T-cells then approach and kill cells infected with the pathogen, thus killing the pathogen at the same time. The cytotoxic T-cell recognizes the infected cells because the infected cells, like macrophages, present epitopes on their surfaces. The T-cell response is often called *cell-mediated* immunity because the effect requires the direct and continued involvement of intact T-cells.

The concept of an adaptive response, or *immunological specificity*, is associated with the recognition of an infected antigen-presenting cell by a helper T-cell or cytotoxic T-cell. An inactive T-cell will be activated only if its specific receptors recognize the specific antigenic fragment being presented to it. Evidence suggests that the surface receptors of each individual inactive T-cell are unique, numerous, and of a single kind. Because there are upward of a trillion or so different inactive T-cells in our bodies, the presented parts of virtually every pathogen should be recognized by at least a few of the T-cells.

B-cells are responsible for the humoral immune response.

Like T-cells, B-cells are inactive at the time they mature and have recognition proteins on their surfaces. As with helper T-cells, these surface receptors vary from cell to cell and can recognize antigens. However, while helper T-cells require that the antigen appear on an antigen-presenting cell, B-cells can recognize an antigen that is free in the liquid fraction of the blood. When an inactive B-cell recognizes and binds to the antigen to which its surface proteins are complementary, the B-cell is then activated, and it subsequently divides many times to form a clone of identical active B-cells, sometimes called *plasma cells*. Active B-cells then secrete large quantities of a single kind of protein molecule, called an *antibody*, into the blood. These antibodies are able to bind to the antigen, an act that "labels'' the antigen for destruction by either of two mechanisms: A set of chemical reactions, collectively called *complement*, can kill certain antibody-tagged bacteria, or tagged antigens can attract macrophages, which devour the antigen. The B-cell response is often called the *humoral* immune response, meaning "liquid-based.''

[4] When antigen-presenting cells cut up a pathogen, many different antigenically active epitopes may result. Potentially, each epitope can activate a different T-cell upon presentation. Thus a single infecting bacterium could activate many different T-cell clones.

The concept of specificity for B-cell activation arises in a way similar to that for T-cells, namely in the recognition of the antigen by B-cell surface receptors. Evidently, all or most of our approximately one trillion inactive B-cells have different surface receptors. The recognition by a B-cell of the exact antigen for which that particular B-cell's surface is "primed" is an absolute requirement for the activation of that B-cell. Fortunately, most pathogens, bacteria, and viruses, for example, have many separate and distinct antigenic regions; thus they can trigger the activation of many different B-cells.

Intercellular interactions play key roles in adaptive immune responses.

The specificity of both T- and B-cell interactions with pathogens cannot be overemphasized; no adaptive immune response can be generated until receptors on these lymphocytes recognize the one specific antigen to which they can bind.

Note how T- and B-cells provide interlocking coverage: The cytotoxic T-cells detect the presence of intracellular pathogens (by the epitopes that infected cells present), and B-cells can detect extracellular pathogens. We would therefore expect T-cells to be effective against already-infected cells and B-cells to be effective against toxins, such as snake venom, and free pathogens, such as bacteria, in the blood.

Our discussion so far has emphasized the individual roles of T- and B-cells. In fact, correct functioning of the adaptive immune system requires that these two kinds of cells interact with each other. It was pointed out earlier that the activation of cytotoxic T-cells requires that they interact with active helper T-cells. In fact, helper T-cells are also needed to activate B-cells, as shown in Figure 10.2.2. Note the pivotal role of active helper T-cells: They exercise control over cell-mediated immunity *and* humoral immunity as well, which covers the entire adaptive immune system.

Lymphocytes diversify their receptor proteins as the cell matures.

At first glance, the central dogma of genetics would seem to suggest that the information for the unique surface protein receptor of each inactive lymphocyte should originate in a different gene. In other words, every inactive lymphocyte would merely express a different surface receptor gene. In each person, there seem to be about 10^{12} unique inactive lymphocytes, and therefore there would have to be the same number of unique genes! Actually, independent estimates of the *total* number of genes in a human cell indicate that there are only about 30,000; see Section 14.3.

The many variant forms of lymphocyte surface receptor proteins originate as the cell matures, and are the result of the random scrambling of genetic material—which leads to a wide variety of amino acid sequences without requiring the participation of a lot of genetic material. As an example, Figure 10.2.3 shows a length of hypothetical DNA that we will use to demonstrate the protein diversification process. We imagine the DNA to consist of two contiguous polynucleotide strings, or classes, labeled A and B. Each class has sections 1 through 4. The protein to be coded by the DNA will contain two contiguous polypeptide strings, one coded by a single section of A and one coded by a single section of B. Thus there are 16 different proteins that could result. To generate a particular protein, the unneeded sections of genetic material

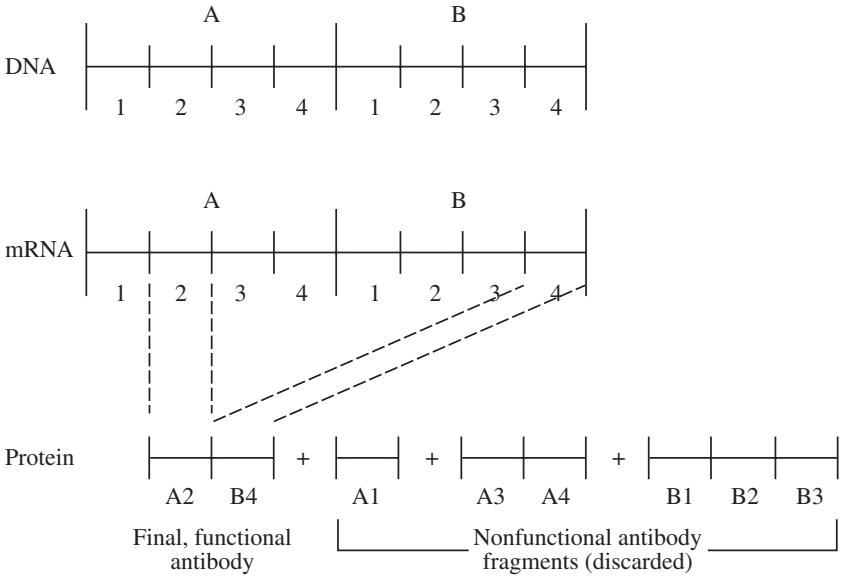


Fig. 10.2.3. A simplified picture of the creation of a specific antibody by a single lymphocyte. The final antibody molecule is coded from one section each of DNA regions A and B. Because the two sections are picked at random there are 16 possible outcomes. This figure shows how many possible antibodies could be coded from a limited amount of DNA. In a real situation, there would be many sections in many DNA regions, and the final, functional antibody would contain contributions coded by several regions.

will be enzymatically snipped out, either at the DNA stage or the mRNA stage. The protein that ultimately results in the figure is derived from DNA sections A2 and B4. The selection of A2 and B4 was random; any of the other 15 combinations was equally likely.

In a real situation, namely, the DNA coding for one of the proteins in B-cell antibodies, there are about 240 sections distributed among four classes. Of these, perhaps seven sections are actually expressed in a given cell, meaning that there are thousands of combinations of seven sections that were not expressed in that cell. These other combinations will be expressed in other B-cells, thereby generating a large number of lymphocytes with different surface proteins.

There are still other ways that lymphocytes generate diverse recognition proteins. For example, B-cells form antibodies by combining two completely separate polypeptides, each of which uses the random "pick and choose" method described in the previous two paragraphs. Further, when maturing, the nucleic acid segments that code for lymphocyte surface recognition proteins mutate very rapidly, more so than do other genes. All of this leads to the great variability in recognition proteins that is so crucial to the functioning of the adaptive immune system, and it does so while requiring a minimum amount of DNA for its coding.

The adaptive immune system recognizes and tolerates "self" (*clonal deletion*).

The whole idea behind the immune system is to recognize foreign material and rid the body of it. On the other hand, it would be intolerable for a person's adaptive immune system to treat the body's own tissues as foreign. In order to prevent such rejection of self-products, or *autoimmune reactions*, the adaptive system must have some way to distinguish "self'' from "nonself.'' This distinction is created during fetal development and continues throughout postnatal development.

The organ systems of a human fetus, including the blood-forming organs, are formed during the *organogenetic* period of fetal development, as discussed in Chapter 9. Most organogenesis is completed at least a month or two before birth, the remaining fetal period being devoted to enlargement and maturation of the fetus. Embryonic (immature) lymphocytes, which are precursors to inactive T- and B-cells, are present during the time of organogenesis. Each one will have a unique kind of recognition protein across its surface, inasmuch as such proteins are essentially generated at random from cell to cell. We could thus expect that among these embryonic lymphocytes there would be not only those that can bind to foreign substances, but also many that can bind to the embryo's own cells. The *clonal deletion* model explains how these self-reactive lymphocytes can be neutralized: Because there are no pathogens in a fetus, the only cells capable of binding to lymphocytes would be the fetus's own cells. Therefore, embryonic B- or T-cells that bind to *any* cell in the fetus are killed or inactivated. Only self-reacting embryonic lymphocytes should be deleted by this mechanism. This reduces the possibility of maturation of a lymphocyte that could subsequently generate an autoimmune response.

There is good evidence for clonal deletion: Mouse embryos can be injected early *in utero* with a virus or other material that would normally be antigenic in a postnatal mouse. After birth, the treated mouse is unable to respond immunologically to subsequent injections of the virus. The mouse has developed an *acquired immunological tolerance* to the antigen. What has happened at the cellular level is that any embryonic mouse lymphocytes that reacted with the prenatally injected virus were killed or inactivated by clonal deletion—the virus was treated as "self.'' Thus there can be no mature progeny of these lymphocytes after birth to react to the second exposure to the virus.

There is another mechanism for killing self-reacting lymphocytes.

Clonal deletion reduces the possibility of an autoimmune response, but does not eliminate it. Recall that clonal deletion requires that self-products meet up with embryonic lymphocytes; mature lymphocytes will not do. The fact is that some embryonic lymphocytes slip through the clonal deletion net by not meeting the self-products that would have inactivated them. In addition, lymphocytes seem to mutate frequently, a process that postnatally may give them receptors that can react with self-products. Finally, the thymus gland, while much reduced in adults, continues to produce a limited number of new T-cells throughout life. These new cells, with receptors generated at random, may be capable of reacting with self-products.

There is a mechanism for getting rid of mature T-cells that can react with their own body's cells: Recall that a T-cell is activated when an infected antigen-presenting cell presents it with a piece of antigen. In fact, this activation has another requirement: The antigen-presenting cell must also display a *second* receptor, one that is found only on *infected* antigen presenters. If a mature T-cell should bind to an uninfected antigen presenter, one lacking the second receptor, the T-cell itself is inactivated (because that binding is a sign that the T-cell receptors are complementary to uninfected self-products). On the other hand, if a mature T-cell binds to an infected antigen presenter, the infection being signaled by the second receptor, that binding is acceptable, and the normal activation of the T-cell ensues.

Inactive lymphocytes are selected for activation by contact with an antigen (*clonal selection*).

The clonal deletion system described above results in the inactivation or killing of immature T- and B-cells if they react with any antigen. This process provides the individual with a set of lymphocytes that can react only with nonself products. These surviving T- and B-cells then remain in our blood and lymphatic circulatory systems in an inactive state until they come into contact with the antigens to which their surface receptors are complementary. This will be either as free, extracellular antigens for B-cells or on an antigen-presenting cell in the case of T-cells.

Once the proper contact is made, the lymphocyte is activated and begins to divide rapidly to form a clone of identical cells. But what if the correct antigen never appears? The answer is an odd one—namely, the lymphocyte is never activated and remains in the blood and lymphatic systems all of our life. What this means is that only a tiny fraction of our lymphocytes ever become activated in our lifetimes; the rest just go around and around our circulation or remain fixed in lymph nodes. This process of activating only those few lymphocytes whose activity is needed, via contact with their appropriate antigens, is called *clonal selection*.

The notion of clonal selection suggests an immense amount of wasted effort on the part of the immune system. For example, each of us has one or more lymphocytes capable of initiating the rejection of a skin transplant from the seventieth president of the United States (in about a century), and others that would react against a cold virus that people contracted in Borneo in 1370 AD. None of us will ever need those capabilities, but we have them nevertheless. It might seem that a simpler mechanism would have been the generation of a single generic kind of lymphocyte and then its adaptation to each individual kind of antigen. This process is called the *instructive mechanism*, but it is not what happens.

The immune system has a memory.

Most people get mumps or measles only one time. If there are no secondary complications these diseases last about a week, which is the time it takes for the activation of T- and B-cells by a pathogen and the subsequent destruction of the pathogen. Surely these people are exposed to mumps and measles many times in their lives, but they

seem to be unaffected by the subsequent exposures. The reason for this is well understood: First, they have antibodies from the initial exposure, and second, among the results of T- and B-cell activation are "memory" cells, whose surface recognition proteins are complementary to the antigenic parts of the activating pathogen (refer back to Figure 10.2.2). These memory cells remain in our blood and lymphatic systems for the rest of our lives, and if we are infected by the same pathogen again, they mount a response just like the original one, but much more intensely and in a much shorter time. The combination of preexisting antibodies from the initial exposure and the intense, rapid secondary response by memory cells usually results in our being unaware of the second exposure.

Why, then, do we get so many colds if the first cold we get as babies generates memory cells? The answer lies in two facts: The adaptive immune response is very specific, and the cold virus mutates rapidly. The memory cells are as specific for antigen as were their original inactive lymphocyte precursors. They will recognize only the proteins of the virus that caused the original cold; once having gotten a cold from that particular strain of cold virus, we won't be successfully infected by it again. The problem is that cold viruses mutate rapidly, and one effect of mutation is that viral-coat proteins (the antigens) change their amino acid sequences. Once that happens, the memory cells and antibodies from a previous infection don't recognize the new, mutated strain of the virus and therefore can't respond to it. The immune response must start all over, and we get a cold that requires a week of recovery (again). If it is possible to say anything nice about mumps, chicken pox, and such diseases, it is that their causative agents do not mutate rapidly and we therefore get the diseases only once, if at all. We shall see in the next section that rapid mutation characterizes HIV, allowing the virus to stay one step ahead of the specific immune system's defenses.

Vaccinations protect us by fooling the adaptive immune system.

The idea behind immunization is to generate the immune response without generating the disease. Thus the trick is to inactivate or kill the pathogen without damaging its antigenic properties. Exposure to this inactive pathogen then triggers the immune responses described earlier, including the generation of memory cells. During a subsequent exposure, the live, active pathogen binds to any preexisting antibody *and* activates memory cells; thus the pathogen is inactivated before disease symptoms can develop. As an example, vaccination against polio consists in swallowing live-but-inactivated polio virus. We then generate memory cells that will recognize active polio viruses if we should be exposed to them at a later date.

Exposure to some pathogenic substances and organisms is so rare that vaccination of the general population against them would be a waste of time and money. Poisonous snake venom is a case in point: The active agent in snake venom is a destructive enzyme distinctive to each kind of snake genus or species, but fortunately almost no one ever gets bitten by a snake. Snake venom is strongly antigenic, as we would expect a protein to be, but the symptoms of snake bite appear so rapidly that the victim could die long before the appropriate lymphocytes could be activated. Unless the snakebite victim already has preexisting antibodies or memory T-cells against the venom, say,

from a previous survivable exposure to the venom, he or she could be in a lot of trouble. The way around this problem is to get another animal, like a horse, to generate the antibodies by giving it a mild dose of the venom. The antivenom antibodies are then extracted from the horse's blood and stored in a hospital refrigerator until a snakebite victim arrives. The antibodies are then injected directly into the bitten area, to tag the antigenic venom, leading to its removal.

A snakebite victim probably won't take the time to identify the species of the offending reptile, and each snake genus or species can have an immunologically distinctive venom. To allow for this, hospitals routinely store mixtures of antibodies against the venoms of all the area's poisonous snakes. The mixture is injected at the bite site, where only the correct antibody will react with the venom—the other antibodies do nothing and eventually disappear without effect.[5] This kind of immunization is said to be passive, and it has a very important function in prenatal and neonatal babies, who get passive immunity via interplacental transfer of antibodies and from the antibodies in their mother's milk. This protects the babies until their own immune systems can take over.

10.3 HIV and AIDS

The human immunodeficiency virus defeats the immune system by infecting, and eventually killing, helper T-cells. As a result, neither the humoral nor the cell-mediated specific immune responses can function, leaving the patient open to opportunistic diseases.

As is true of all viruses, HIV is very fussy about the host cell it chooses. The problem is that its chosen hosts are immune system cells, the very same cells that are required to fend it off in the first place. Initially, the victim's immune system responds to HIV infection by producing the expected antibodies, but the virus stays ahead of the immune system by mutating rapidly. By a variety of mechanisms, some poorly understood, the virus eventually wears down the immune system by killing helper T-cells, which are required for the activation of killer T-cells and B-cells. As symptoms of a low T-cell count become manifested, the patient is said to have AIDS.

In this section, we will describe the reproduction of HIV as a prelude to a mathematical treatment of the behavior of HIV and the epidemiology of AIDS.

The human immunodeficiency virus (HIV) infects T-cells and macrophages, among others.

The outer coat of HIV is a two-layer lipid membrane, very similar to the outer membrane of a cell (see Figure 10.3.1). Projecting from the membrane are sugar–protein projections, called gp120. These gp120 projections recognize and attach to a protein called CD4, which is found on the surfaces of helper T-cells, macrophages, and monocytes (the latter are macrophage precursors). The binding of gp120 and CD4

[5] Note that the unneeded antibodies do not provide a "memory" because there is no activation of lymphocytes—hence no memory cells.

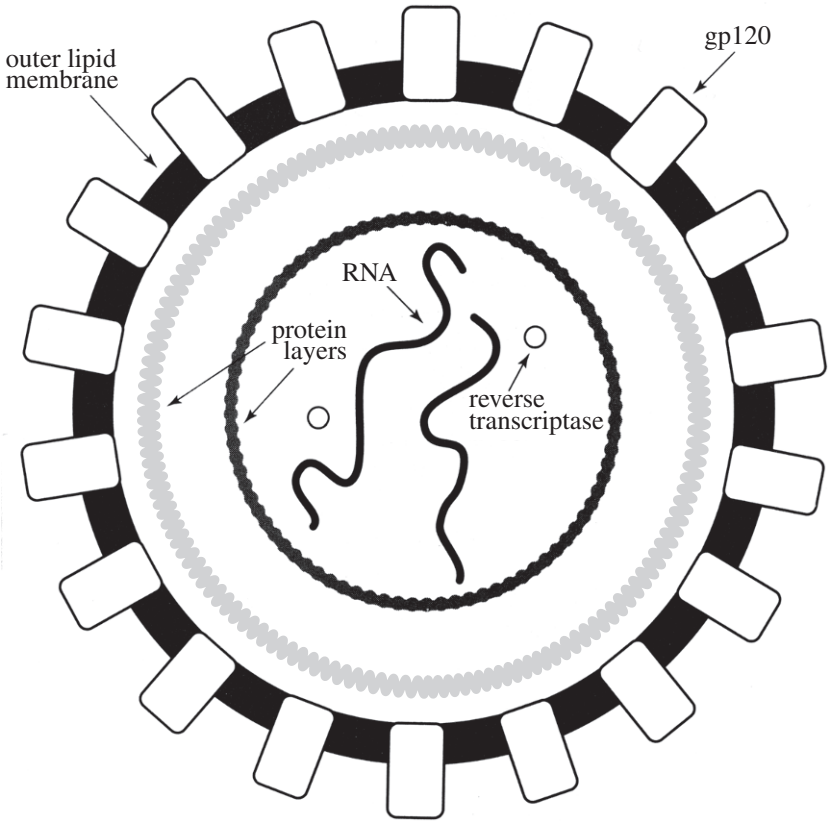


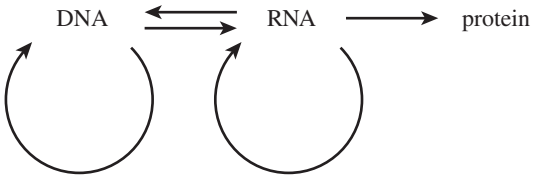
Fig. 10.3.1. A model of the human immunodeficiency virus (HIV). The outer membrane of the HIV is derived from the outer membrane of the host cell. Thus an antibody against that part of the HIV would also act against the host cell. Note that the HIV carries copies of the reverse transcriptase enzyme.

leads to the fusion of the viral membrane and the cell membrane. Then the viral capsid is brought into the blood cell (see [3] and [4]).

HIV is a retrovirus.

The HIV capsid contains two identical single strands of RNA (no DNA). The capsid is brought into the host cell by fusion between the viral envelope and the cell membrane, as described in Section 10.1. The capsid is then enzymatically removed. The HIV RNA information is then converted into DNA information, a step that is indicated by the straight left-pointing arrow in the following central dogma flow diagram:[6]

[6] This is our final alteration to "dogma."



The conversion of RNA information into DNA information involves several steps and is called *reverse transcription*: First, the single-stranded HIV RNA acts as a template for the creation of a strand of DNA. This process entails complementary H-bonding between RNA nucleotides and DNA nucleotides, and it yields a hybrid RNA-DNA molecule. The RNA is then removed and the single-strand of DNA acts as a template for the creation of a second, complementary, strand of DNA. Thus a double helix of DNA is manufactured, and it carries the HIV genetic information.

The chemical process of covalently polymerizing DNA nucleotides and depolymerizing RNA nucleotides, like most cellular reactions involving covalent bonds, requires enzymatic catalysis to be effective. The enzyme that catalyzes reverse transcription is called *reverse transcriptase*. Reverse transcriptase is found inside HIV, in close association with the viral RNA, and it enters the host cell right along with the RNA, ready for use. Once HIV DNA is formed it is then spliced into the host cell's own DNA; in other words, it is a provirus.

In a general sense, a provirus becomes an integral part of the host cell's genetic material; for instance, proviruses are replicated right along with the host cell's genome at cell division. It should therefore not be surprising that the physiology and morphology of the host cell changes as a result of the incorporated provirus. For example, one important consequence of HIV infection is that gp120 projections appear on the lymphocyte's surface.

Once in the form of a provirus, HIV starts to direct the host cell's anabolic machinery to form new HIV. As the assembled viruses exit the host cell by budding, they pick up a part of the cell's outer lipid bilayer membrane, along with some of the gp120 placed there by the provirus. The newly formed virus is now ready to infect a new cell.

The budding process does not necessarily kill the host cell. In fact, infected macrophages seem to generate unending quantities of HIV. T-cells do eventually die in an infected person, but as explained below, it is not clear that they die from direct infection by the virus.

The flow of information from RNA to DNA was omitted when the central dogma was first proposed because at the time, no one believed that information flow in that direction was possible. As a consequence, subsequent evidence that it existed was ignored for some years—until it became overwhelming. The process of RNA-to-DNA informational flow is still called "reverse transcription," the key enzyme is called "reverse transcriptase," and viruses in which reverse transcription is important are still called "retroviruses," as though something were running backward. Of course, there is nothing actually "backward" about such processes; they are perfectly normal in their natural context.

HIV destroys the immune system instead of the other way around.

As Figure 10.3.2 shows, the number of helper T-cells in the blood drops from a normal concentration of about 800 per ml to zero over a period of several years following HIV infection. The reason for the death of these cells is not well understood, because budding usually spares the host cell, and besides, only a small fraction of the T-cells in the body ever actually become infected by the HIV in the first place. Nevertheless, all the body's helper T-cells eventually die. Several mechanisms have been suggested for this apparent contradiction: Among them, the initial contact between HIV and a lymphocyte is through the gp120 of the HIV and CD4 of the T-cell. After a T-cell is infected, gp120 projections appear on its own surface, and they could cause that infected cell to attach to the CD4 receptors of other, *uninfected* T-cells. In this way, one infected lymphocyte could attach to many uninfected ones and disable them all. In fact, it has been observed that if cells are artificially given CD4 and gp120 groups, they clump together into large multinuclear cells (called *syncitia*).

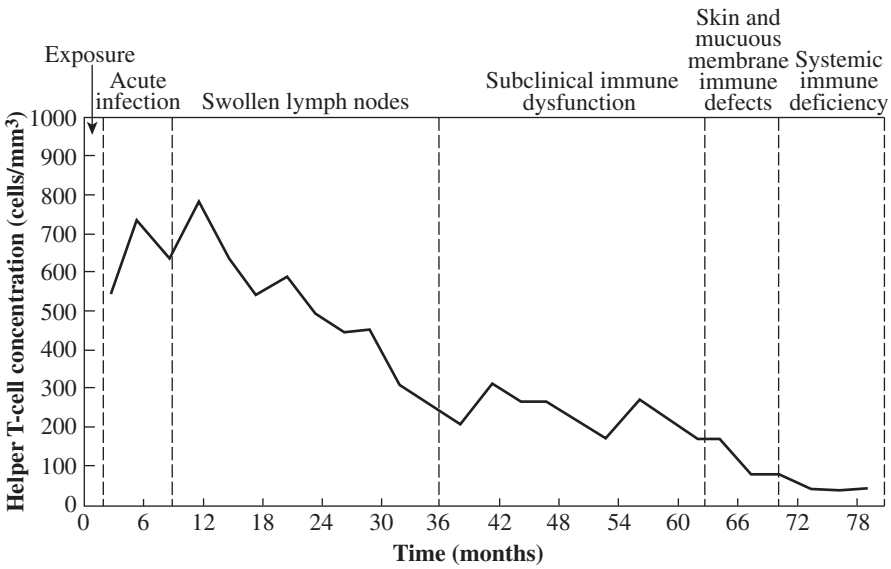


Fig. 10.3.2. A graph of the helper T lymphocyte count of an HIV-infected person. Clinical symptoms are indicated along the top of the figure. Note the correlation between the decrease in T-cell count and the appearance of the clinical symptoms. (Redrawn from R. Redfield and D. Burke, HIV infection: The classical picture," *Sci. Amer.*, **259**-4 (1988), 90–98; copyright ©1988 by Scientific American, Inc. All rights reserved.)

A second possible way that helper T-cells might be killed is suggested by the observation that the infected person's lymph nodes atrophy. The loss of those parts of the lymphatic system may lead to the death of the T-cells.

Third, a normal function of helper T-cells is to stimulate killer T-cells to kill viral-infected cells. It may be that healthy helper T-cells instruct killer T-cells to kill infected helper T-cells. Eventually, this normal process could destroy many of the body's T-cells as they become infected, although, as noted earlier, only a small fraction of helper T-cells ever actually become infected.

Fourth, it has been demonstrated that if an inactive HIV-infected lymphocyte is activated by antigen, it yields greatly reduced numbers of memory cells. In fact, it seems that the activation process itself facilitates the reproduction of HIV by providing some needed stimulus for the proper functioning of reverse transcriptase.

HIV infection generates a strong initial immune response.

It is shown in Figure 10.3.3 that the immune system initially reacts vigorously to HIV infection, producing antibodies as it should.[7]

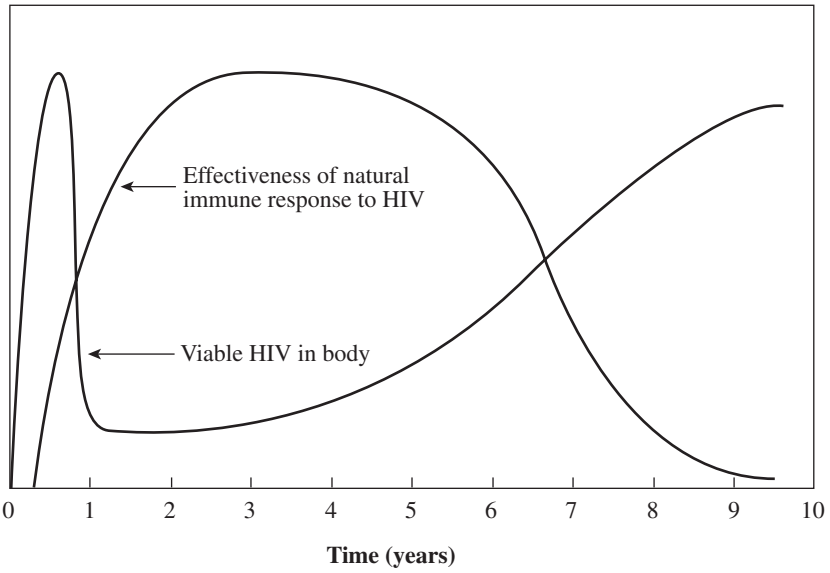


Fig. 10.3.3. A graph of immune response and viral appearance vs. time for an HIV-infected person. The initial infection generates a powerful immune response. That response, however, is later overwhelmed by the virus, which kills the helper T-lymphocytes that are required by the humoral and cell-mediated immune responses. (Redrawn from R. Redfield and D. Burke, HIV infection: The classical picture, *Sci. Amer.*, **259**-4 (1988), 90–98; copyright ©1988 by Scientific American, Inc. All rights reserved.)

[7] The presence of antibodies against HIV is the basis for the diagnosis of HIV infection. Note that it takes several months to get a measurable response.

Nonetheless, the circulating helper T-cell count soon begins an irreversible decrease toward zero, as discussed above. As helper T-cells die off, the ability of the adaptive immune system to combat any pathogen, HIV or other, also vanishes.

In Section 10.4, we will describe a mathematical model for the interaction between helper T-cells and HIV.

The high mutability of HIV demands continued response from the adaptive immune system.

Mutations occur commonly in HIV RNA, and the reason is reasonably well understood: Reverse transcriptase lacks a "*proofreading*" capacity. This proofreading ability is found in enzymes that catalyze the polymerization of DNA from a DNA template in the "forward" direction of the central dogma. Thus the occasional mismatching of H-bonds between nucleotides, say the pairing of A opposite G, gets corrected. On the other hand, reverse transcriptase, which catalyzes DNA formation from an RNA template, seems not to be able to correct base-pairing errors, and this leads to high error rates in base placement—as much as one mismatched base out of every 2000 polymerized. The two RNA polynucleotides of HIV have between 9000 and 10000 bases distributed among about nine genes, so this error rate might yield up to five changed bases, and perhaps three or four altered genes, per infection.

We are concerned here especially with the effects of mutated viral surface antigens, e.g., proteins and glycoproteins, on immune system recognition. Every new antigenic version of these particular viral products will require a new round of helper T-cell activation to defeat the virus. The problem there is that, as pointed out earlier, activation of an HIV-infected helper T-cell seems to help the HIV inside it to replicate and, further, leads to the formation of stunted memory T-cell clones. Thus each new antigenic form of HIV causes the immune system to stimulate HIV replication, while simultaneously hindering the immune system's ability to combat the virus. The HIV stays just ahead of the immune system, like a carrot on a stick, affecting helper T-cells before the T-cells can respond properly, and then moving on to a new round of infections. One could say, "The worse it gets, the worse it gets!"

The mutability of HIV has another unfortunate effect for its victims. Current therapy emphasizes drugs that interfere with the correct functioning of reverse transcriptase; AZT is an example. The high mutation rate of HIV can generate new versions of reverse transcriptase, and sooner or later, a version will appear that the drug cannot affect.

In Section 10.5, we will model the mutability of HIV and its eventual overwhelming of the immune system.

HIV infection leads to acquired immunodeficiency syndrome (*AIDS*).

A person infected with HIV is said to be "HIV positive." Such people may be asymptomatic for a considerable time following infection, or the symptoms may be mild and transient; the patient is, however, infectious. Eventually, the loss of helper T-cells will leave the person open to infections, often of a rare kind (see Figure 10.3.2). As examples, pneumonia caused by a protozoan called *Pneumocystis carinii* and a cancer

of blood vessels, called Kaposi's sarcoma, are extremely rare in the general population, yet they frequently are found in HIV-positive people. Everyone is exposed to the pathogens that cause these diseases, but people do not get the disease if their immune systems are working properly. When HIV-positive persons exhibit unusual diseases as a result of low helper T-cell counts, they are said to have AIDS.

10.4 An HIV Infection Model

A model for HIV infection involves four components: normal T-cells, latently infected T-cells, infected T-cells actively replicating new virus, and the virus itself. Any proposed model should incorporate the salient behavior of these components and respect biological constraints. In this section, we present such a model and show that it has a stationary solution. This model was developed and explored by Perelson, Kirschner, and coworkers.

T-cell production attempts to maintain a constant T-cell serum concentration.

In this section, we will be presenting a model for T-cell infection by HIV, as described in Section 10.2 (see [5, 6, 7, 8]). This model tracks four components, three types of T-cells and the virus itself, and therefore requires a four-equation system for its description. As a preliminary step toward understanding the full system of equations, we present first a simplified version, namely, the equation for T-cells in the absence of infection. In forming a mathematical model of T-cell population dynamics based on the discussion of Section 10.2, we must incorporate the following assumptions:

- Some immunocompetent T-cells are produced by the lymphatic system; over relatively short periods of time, their production rate is constant and independent of the number of T-cells present. Over longer periods of time their production rate adjusts to help maintain a constant T-cell concentration, even in adulthood. Denote this *supply rate* by s.
- T-cells are produced through clonal selection if an appropriate antigen is present, but the total number of T-cells does not increase unboundedly. Model this using a logistic term, $rT(1 - \frac{T}{T_{\max}})$, with per capita growth rate r (cf. Section 4.3).
- T-cells have a finite natural lifetime after which they are removed from circulation. Model this using a death rate term, μT, with a fixed per capita death rate μ.

Altogether, the differential equation model is

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T}{T_{\max}}\right) - \mu T. \tag{10.4.1}$$

In this, T is the T-cell population in cells per cubic millimeter.

We want the model to have the property that solutions, $T(t)$, that start in the interval $[0, T_{\max}]$ stay there. This will happen if the derivative $\frac{dT}{dt}$ is positive when $T = 0$ and negative when $T = T_{\max}$. From (10.4.1),

$$\left.\frac{dT}{dt}\right|_{T=0} = s,$$

and since s is positive, the first requirement is fulfilled. Next, substituting $T = T_{\max}$ into (10.4.1), we get the condition that must be satisfied for the second requirement,

$$\left.\frac{dT}{dt}\right|_{T=T_{\max}} = s - \mu T_{\max} < 0,$$

or, rearranged,

$$\mu T_{\max} > s. \tag{10.4.2}$$

The biological implication of this statement is that when the number of T-cells has reached the maximum value $T_{\max}$, then there are more cells dying than are being produced by the lymphatic system.

Turning to the stationary solutions of system (10.4.1), we find them in the usual way, by setting the right-hand side to zero and solving for T:

$$-\frac{r}{T_{\max}}T^2 + (r-\mu)T + s = 0.$$

The roots of this quadratic equation are

$$T = \frac{T_{\max}}{2r}\left((r-\mu) \pm \sqrt{(r-\mu)^2 + 4s\frac{r}{T_{\max}}}\right). \tag{10.4.3}$$

Since the product $\frac{4sr}{T_{\max}}$ is positive, the square root term exceeds $|r-\mu|$,

$$\sqrt{(r-\mu)^2 + \frac{4sr}{T_{\max}}} > |r-\mu|,$$

and therefore one of the roots of the quadratic equation is positive, while the other is negative. Only the positive root is biologically important, and we denote it by T_0, as the "zero virus" stationary point (see below). We now show that T_0 must lie between 0 and $T_{\max}$. As already noted, the right-hand side of (10.4.1) is positive when $T = 0$ and negative when $T = T_{\max}$. Therefore, it must have a root between 0 and $T_{\max}$, and this is our positive root T_0 calculated from (10.4.3) by choosing the + sign. We will refer to the difference $p = r - \mu$ as the T-cell *proliferation rate*; in terms of it, the globally attracting stationary solution is given by

$$T_0 = \frac{T_{\max}}{2r}\left(p + \sqrt{p^2 + 4s\frac{r}{T_{\max}}}\right). \tag{10.4.4}$$

This root T_0 is the only (biologically consistent) stationary solution of (10.4.1).

Now consider two biological situations.

Table 10.4.1. Parameters for Situation 1.

Parameter	Description	Value
s	T-cell from precursor supply rate	$10/\text{mm}^3/\text{day}$
r	normal T-cell growth rate	0.03/day
$T_{\max}$	maximum T-cell population	$1500/\text{mm}^3$
μ	T-cell death rate	0.02/day

Situation 1: Supply rate solution. In the absence of an infection, or at least an environmental antigen, the clonal production rate r can be small, smaller than the natural death rate μ, resulting in a negative proliferation rate p. In this case, the supply rate s must be high in order to maintain a fixed T-cell concentration of about 1000 per cubic millimeter. The data in [6] confirm this.

With these data, calculate the stationary value of T_0 using (10.4.3) as follows:

MAPLE
```
> f:=T–>s+r*T*(1-T/Tmax)- mu *T;
> s:= 10; r:=.03; mu:=.02; Tmax:=1500;
> fzero:=solve(f(T) = 0,T);
> T0:=max(fzero[1],fzero[2]);
```

MATLAB
```
> s=10; r=.03; mu=.02; Tmax=1500;
> p=[-r/Tmax (r-mu) s];
> T0=max(roots(p))
```

Next calculate and display trajectories from various starting points:

MAPLE
```
> deq:={diff(T(t),t)=f(T(t))};
> with(DEtools):
> inits:={[0,0],[0,T0/4],[0,T0/2],[0,(T0+Tmax)/2],[0,Tmax]};
> phaseportrait(deq,T(t),0..25,inits,stepsize=1,arrows=NONE);
```

MATLAB
```
  % make up an m-file, hiv1.m, with
  % function Tprime=hiv1(t,T); s=10; r=.03; mu=.02, Tmax=1500;
  %   Tprime=s+r*T*(1-T/Tmax)-mu*T;
> [t,T]=ode23('hiv1',[0 50],0);
> plot(t,T); hold on
> [t,T]=ode23('hiv1',[0 50],T0/4); plot(t,T)
> [t,T]=ode23('hiv1',[0 50],T0/2); plot(t,T)
> [t,T]=ode23('hiv1',[0 50],(T0+Tmax)/2); plot(t,T)
> [t,T]=ode23('hiv1',[0 50],Tmax); plot(t,T)
```

Situation 2: Clonal production solution. An alternative scenario is that adult thymic atrophy has occurred, or a thymectomy has been performed. As a hypothetical and limiting situation, take s to equal zero and ask how r must change to maintain a comparable T_0. Use the parameters in Table 10.4.2.

MAPLE
```
> s:= 0; r:=.06; mu:=.02; Tmax:=1500;
> fzero:=solve(f(T)=0,T);
> T0:=max(fzero[1],fzero[2]);
> deq:={diff(T(t),t)=f(T(t))};
> inits:={[0,0],[0,T0/4],[0,T0/2],[0,(T0+Tmax)/2],[0,Tmax]};
> phaseportrait(deq,T(t),t=0..25,inits,stepsize=1,arrows=NONE);
```

MATLAB
```
> s=0; r=.06; mu=.02; Tmax=1500;
```

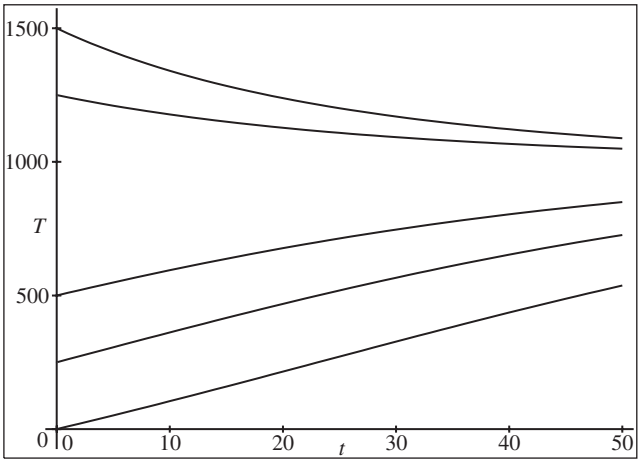


Fig. 10.4.1. Time vs. number of T-cells per cubic millimeter.

Table 10.4.2. Parameters for Situation 2.

Parameter	Description	Value
s	T-cell from precursor supply rate	$0/\text{mm}^3/\text{day}$
r	normal T-cell growth rate	0.06/day
$T_{\max}$	maximum T-cell population	$1500/\text{mm}^3$
μ	T-cell death rate	0.02/day

```
> p=[-r/Tmax (r-mu) s];
> T0=max(roots(p))
  % make an m-file, hiv2.m, same as before execpt s=0; r=.06; mu=.02; Tmax=1500;
> hold off
> [t,T]=ode23('hiv2',[0 50],0);
> plot(t,T); hold on
> [t,T]=ode23('hiv2',[0 50],T0/4); plot(t,T)
> [t,T]=ode23('hiv2',[0 50],T0/2); plot(t,T)
> [t,T]=ode23('hiv2',[0 50],(T0+Tmax)/2); plot(t,T)
> [t,T]=ode23('hiv2',[0 50],Tmax); plot(t,T)
```

As above, T_0 is again about 1000 T-cells per cubic millimeter. Trajectories in this second situation are plotted in Figure 10.4.2; contrast the convergence rate to the stationary solution under this clonal T-cell production situation with the supply rate convergence of Situation 1.

Remark. Contrasting these situations shows that upon adult thymic atrophy or thymectomy, the response of the T-cell population is much slower. This suggests that one would find differences in the dynamics of T-cell depletion due to an HIV infection in people of different ages. Clearly, there is a need for r, the T-cell growth rate, to be large in compensation when the supply rate, s, is small. How can one influence one's value of r? The answer should be an inspiration for continuing biological and medical research.

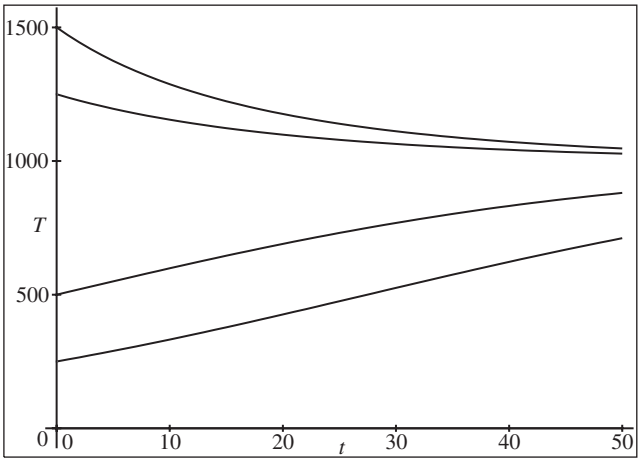


Fig. 10.4.2. Time vs. T-cell count with a reduced thymus function.

A four-equation system is used to model T-cell–HIV interaction.

To incorporate an HIV infection into the above model, we follow the approach taken by Perelson, Kirschner, and DeBoer [6] and differentiate three kinds of T-cells: Besides the normal variety, whose number is denoted by T as before, there are T-cells infected with provirus, but not producing free virus. Designate the number of these *latently* infected T-cells by T_L. In addition, there are T-cells that are infected with virus and are *actively* producing new virus. Designate the number of these by T_A. The interaction between virus, denoted by V, and T-cells is reminiscent of a predator–prey relationship; a mass action term is used to quantify the interaction (see Section 4.4). However, only the active type T-cells produce virus, while only the normal T-cells can be infected.

We now present the model and follow with a discussion of its four equations separately:

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T + T_L + T_A}{T_{\max}}\right) - \mu T - k_1 V T, \tag{10.4.5a}$$

$$\frac{dT_L}{dt} = k_1 V T - \mu T_L - k_2 T_L, \tag{10.4.5b}$$

$$\frac{dT_A}{dt} = k_2 T_L - \beta T_A, \tag{10.4.5c}$$

$$\frac{dV}{dt} = N\beta T_A - k_1 V T - \alpha V. \tag{10.4.5d}$$

The first equation is a modification of (10.4.1) with the inclusion of an infection term having mass action parameter k_1. When normal T-cells become infected, they immediately become reclassified as the latent type. In addition, note that the sum of all three types of T-cells counts toward the T-cell limit, $T_{\max}$.

The first term in the second equation corresponds to the reclassification of newly infected normal T-cells. These cells disappear from (10.4.5a) but then reappear in (10.4.5b). In addition, (10.4.5b) includes a per capita death rate term and a term to account for the transition of these latent-type cells to active type with rate parameter k_2.

The first term of (10.4.5c) balances the disappearance of latent T-cells upon becoming active, with their appearance as active-type T-cells. It also includes a per capita death rate term with parameter β corresponding to the lysis of these cells after releasing vast numbers of replicated virus. It is clear that T-cells active in this sense perish much sooner than do normal T-cells, therefore β is much larger than μ:

$$\beta \gg \mu. \tag{10.4.6}$$

Finally, the fourth equation accounts for the population dynamics of the virus. The first term, $N\beta T_A$, comes from the manufacture of virus by the "active"-type T-cells, but the number produced will be huge for each T-cell. The parameter N, a large value, adjusts for this many-from-one difference. The second term reflects the fact that as a virus invades a T-cell, it drops out of the pool of free virus particles. The last term, with per capita rate parameter α, corresponds to loss of virus through the body's defense mechanisms.

Remark. Note that in the absence of virus, i.e., $V = 0$, then both T_L and T_A are 0 as well, and setting these values into system (10.4.4), we see that this new model agrees with the old one, (10.4.1).

The T-cell–HIV model respects biological constraints.

We want to see that the model is constructed well enough that no population goes negative or goes unbounded. To do this, we first establish that the derivatives $\frac{dT}{dt}$, $\frac{dT_L}{dt}$, $\frac{dT_A}{dt}$, and $\frac{dV}{dt}$ are positive whenever T, T_L, T_A, or $V = 0$, respectively. This means that each population will increase, not decrease, at low population sizes.

But from (10.4.5a), if $T = 0$, then

$$\frac{dT}{dt} = s > 0,$$

and if $T_L = 0$, then (10.4.5b) gives

$$\frac{dT_L}{dt} = k_1 VT > 0;$$

likewise, if $T_A = 0$, then from (10.4.5c),

$$\frac{dT_A}{dt} = k_2 T_L > 0,$$

and finally (10.4.5d) becomes, when $V = 0$,

$$\frac{dV}{dt} = N\beta T_A > 0.$$

We have assumed that all the parameters are positive, and so these derivatives are also positive as shown.

Following Perelson, Kirschner, and DeBoer [6], we next show that the total T-cell population as described by this model remains bounded. This total, T_Σ is defined to be the sum $T_\Sigma = T + T_L + T_A$, and it satisfies the differential equation obtained by summing the right-hand side of the first three equations in system (10.4.5),

$$\frac{dT_\Sigma}{dt} = s + rT\left(1 - \frac{T_\Sigma}{T_{\max}}\right) - \mu T - \mu T_L - \beta T_A. \tag{10.4.7}$$

Now suppose $T_\Sigma = T_{\max}$; then from (10.4.7),

$$\frac{dT_\Sigma}{dt} = s - \mu T - \mu T_L - \beta T_A + \mu T_A - \mu T_A,$$

and combining the second, third, and last terms as $-\mu T_{\max}$ gives

$$\frac{dT_\Sigma}{dt} = s - \mu T_{\max} - (\beta - \mu)T_A < s - \mu T_{\max},$$

where (10.4.6) has been used to obtain the inequality. Recalling condition (10.4.2), we find that

$$\frac{dT_\Sigma}{dt} < 0 \quad \text{if } T_\Sigma = T_{\max},$$

proving that T_Σ cannot increase beyond $T_{\max}$.

In summary, system (10.4.5) has been shown to be consistent with the biological constraints that solutions remain positive and bounded.

The T-cell infected stationary solution is stable.

To find the stationary points of the T-cell–HIV model, that is, (10.4.5), we must set the derivatives to zero and solve the resulting (nonlinear) algebraic system, four unknowns and four equations. Solving the third equation, namely, $0 = k_2 T_L - \beta T_A$, for T_A gives $T_A = (\frac{k_2}{\beta})T_L$, which may in turn be substituted for in all its other occurrences. This reduces the problem to three unknowns and three equations. Continuing in this way, we arrive at a polynomial in, say, T whose roots contain the stationary points. We will not carry out this approach here. Instead, we will solve this system numerically, below, using derived parameter values. However, in [6] it is shown symbolically that at the uninfected stationary point T_0, (10.4.4) is stable (see Section 2.4) if and only if the parameter N satisfies

$$N < \frac{(k_2 + \mu)(\alpha + k_1 T_0)}{k_2 k_1 T_0}.$$

By defining the combination of parameters on the right-hand side as N_{crit}, we may write this as

$$N < N_{\text{crit}}, \quad \text{where } N_{\text{crit}} = \frac{(k_2 + \mu)(\alpha + k_1 T_0)}{k_2 k_1 T_0}. \tag{10.4.8}$$

In Table 10.4.3, we give values of the parameters of system (10.4.5) as determined in [6].

This model reflects the clinical picture as presented in Greene [9].

Table 10.4.3. Parameters of the HIV infection model.

Parameter	Description	Value
s	T-cell from precursor supply rate	$10/\text{mm}^3/\text{day}$
r	normal T-cell growth rate	0.03/day
$T_{\max}$	maximum T-cell population	$1500/\text{mm}^3$
μ	normal/latently infected T-cell death rate	0.02/day
β	actively infected T-cell death rate	0.24/day
α	free virus death rate	2.4/day
k_1	T-cell infection rate by free virus	2.4×10^{-5} mm^3/day
k_2	latent-to-active T-cell conversion rate	$3 \times 10^{-3}/\text{day}$
N	virus produced by an active T-cell	taken as 1400 here

Exercises/Experiments

1. In the uninfected situations, for both $s = 0$ and $s = 10$, derive the numerical solution T for $f(T) = 0$. Which of the roots for this equation is in the interval $[0, T_{\max}]$?

2. In the virus-free situation, give a biological interpretation for r. Suppose that r is increased to r_n so that

$$\frac{r_n - r}{r} = 0.10.$$

That is, r is increased by 10%. What is the percentage of increase of the steady state of T cells corresponding to a 10% increase in r?

3. With the parameters as stated for the infected situation, what is the numerical value for each of these: $T_{\max}$, the uninfected steady state of T cells, the infected steady state of T cells, and N_{crit}. Is N_{crit} more or less than the N used in these parameters? What are the implications of this last answer?

4. Sketch a graph of how T, T_L, T_A, and V evolve during the first year and move toward equilibrium. Continue the graph for two more years. Here is syntax that will accomplish this integration of the equations:

MAPLE

```
> deq:=diff(T(t),t)=-mu*T(t)+r*T(t)*(1-(T(t)+TL(t)+TA(t))/Tmax)-k1*V(t)*T(t),
    diff(TL(t),t)=k1*V(t)*T(t)-mu*TL(t)-k2*TL(t),
    diff(TA(t),t)= k2*TL(t)-b*TA(t),
    diff(V(t),t)=N*b*TA(t)-k1*V(t)*T(t)-a*V(t);
> s:=10; r:=0.03; Tmax:=1500; mu:=0.02; N:=1400;
> b:=.24; a:=2.4; k1:=0.000024; k2:=0.003; N:=1400;
> init:=T(0)=1000,TL(0)=0, TA(0)=0,V(0)=0.001;
> Digits:=16;
> sol:=dsolve({deq,init},{T(t),TL(t),TA(t),V(t)},numeric,output=listprocedure);
> Tsol:=subs(sol,T(t));
> TAsol:=subs(sol,TA(t));
> TLsol:=subs(sol,TL(t));
> Vsol:=subs(sol,V(t));
> plot('Tsol(t)','t'=0..900);
> plot('TLsol(t)','t'=0..600);
> plot('TAsol(t)','t'=0..365);
> plot('Vsol(t)','t'=0..365);
```

MATLAB

```
% contents of m-file exer104.m:
```

```
  %   function Yprime=exer104(t,Y)
  %   % Y(1)=T, Y(2)=TL, Y(3)=TA, Y(4)=V
  %   s=10; r=0.03; Tmax=1700; mu=0.02; b=.24;
  %   a=2.4; k1=0.000024; k2=0.003; N=1400;
  %   Yprime=[s-mu*Y(1)+r*Y(1).*(1-(Y(1)+Y(2)+Y(3))/Tmax)-k1*Y(4).*Y(1);...
  %              k1*Y(4).*Y(1)-mu*Y(2)-k2*Y(2); k2*Y(2)-b*Y(3); N*b*Y(3)-k1*Y(4).*Y(1)-a*Y(4)];
  %
> [t,Y] = ode23('exer104',[0 365],[1000; 0; 0; 0.001]);
> plot(t,Y)
  % try out to about 3 1/2 years
> [t,Y] = ode23('exer104',[0 1200], [1000; 0; 0; 0.001]);
> plot(t,Y)
```

10.5 A Model for a Mutating Virus

The model of the previous section illustrated the interaction of HIV with T-cells. It did not account for mutations of HIV. The following is a model for evolving mutations of an HIV infection and an immune system response. This model is based on one introduced into the literature by Nowak, May, and Anderson.

Any model of an HIV infection should reflect the high mutability of the virus.

In Section 10.3, we discussed the high degree of mutability characteristic of the HIV virus, which results in a large number of viral quasi-species. However, the human immune system seems able to mount an effective response against only a limited number of these mutations. Furthermore, the activation of a latently infected helper T-cell appears to stimulate viral reproduction, with the result that every time a new mutant activates a T-cell, vigorous viral population growth ensues. The immune system's T-cell population evidently can endure this cycle only a limited number of times. The objective of this section is to modify the T-cell–HIV model to reflect these facts in the model. In this, we follow Nowak, May, and Anderson [10]; see also Nowak and McMichael [4].

Key assumptions:

1. The immune response to a viral infection is to create subpopulations of immune cells that are specific to a particular viral strain and that direct immunological attack against that strain alone. The response is directed against the highly variable parts of the virus.
2. The immunological response to the virus is also characterized by a response that is specific to the virus but that acts against all strains. In other words, it acts against parts of the virus conserved under mutations.
3. Each mutant of the initial viral infection can cause the death of all immune system cells whether those cells are directed at variable or conserved regions.

In this modified model, we keep track of three sets of populations. Let $\{v_1, v_2, \ldots, v_n\}$ designate the various subpopulations of viral mutants of the initial HIV infection. Let $\{x_1, x_2, \ldots, x_n\}$ designate the populations of specific lymphocytes created in response to these viral mutations. And let z designate the immune response that

can destroy all variations of the infective agent. The variable n, for the number of viral mutations that arise, is a parameter of the model. We also include a parameter, the *diversity threshold* N_{div}, representing the number of mutations that can be accommodated before the immune system collapses.

The equation for each HIV variant, v_i, consists of a term, with parameter a, for its natural population growth rate; a term, with parameter b, for the general immune response; and a term, with parameter c, for the specific immune response to that variant,

$$\frac{dv_i}{dt} = v_i(a - bz - cx_i), \quad i = 1, \ldots, n. \tag{10.5.1}$$

The equation for each specific immune response population x_i consists of a term, with parameter g, that increases the population in proportion to the amount of its target virus present, and a term, with parameter k, corresponding to the destruction of these lymphocytes by any and all viral strains,

$$\frac{dx_i}{dt} = gv_i - kx_i(v_1 + v_2 + \cdots + v_n), \quad i = 1, \ldots, n. \tag{10.5.2}$$

Finally, the equation for the general immune response population z embodies a term, with parameter h, for its increase in proportion to the sum total of virus present but also a mass action term for its annihilation upon encounter with any and all virus,

$$\frac{dz}{dt} = (h - kz)(v_1 + v_2 + \cdots + v_n). \tag{10.5.3}$$

In order to compute with the model later on, we enter these differential equations into the computer system now. Take the value of n to be 6, as will be explained shortly. Although the code is lengthy, it is all familiar and very repetitious:

MAPLE

```
> mutatingSystem:=diff(v1(t),t)=(a-b*z(t)-c*x1(t))*v1(t),
                 diff(v2(t),t)=(a-b*z(t)-c*x2(t))*v2(t),diff(v3(t),t)=(a-b*z(t)-c*x3(t))*v3(t),
                 diff(v4(t),t)=(a-b*z(t)-c*x4(t))*v4(t),diff(v5(t),t)=(a-b*z(t)-c*x5(t))*v5(t),
                 diff(v6(t),t)=(a-b*z(t)-c*x6(t))*v6(t),
                 diff(x1(t),t)=g*v1(t)-k*x1(t)*(v1(t)+v2(t)+v3(t)+v4(t)+v5(t)+v6(t)),
                 diff(x2(t),t)=g*v2(t)-k*x2(t)*(v1(t)+v2(t)+v3(t)+v4(t)+v5(t)+v6(t)),
                 diff(x3(t),t)=g*v3(t)-k*x3(t)*(v1(t)+v2(t)+v3(t)+v4(t)+v5(t)+v6(t)),
                 diff(x4(t),t)=g*v4(t)-k*x4(t)*(v1(t)+v2(t)+v3(t)+v4(t)+v5(t)+v6(t)),
                 diff(x5(t),t)=g*v5(t)-k*x5(t)*(v1(t)+v2(t)+v3(t)+v4(t)+v5(t)+v6(t)),
                 diff(x6(t),t)=g*v6(t)-k*x6(t)*(v1(t)+v2(t)+v3(t)+v4(t)+v5(t)+v6(t)),
                 diff(z(t),t)=(h-k*z(t))*(v1(t)+v2(t)+v3(t)+v4(t)+v5(t)+v6(t));
```

MATLAB

```
% make up an m-file, hivMVRate.m, with
%   function Yprime=hivMVRate(t,Y);
%   % Y(1)=v1,..., Y(6)=v6, Y(7)=x1,...,Y(12)=x6, Y(13)=z
%   a=5; b=4; c=5; g=1; h=1; k=1;
%   Yprime=[(a - b*Y(13) - c*Y(7))*Y(1); (a - b*Y(13) - c*Y(8))*Y(2);
%               (a - b*Y(13) - c*Y(9))*Y(3); (a - b*Y(13) - c*Y(10))*Y(4);
%               (a - b*Y(13) - c*Y(11))*Y(5); (a - b*Y(13) - c*Y(12))*Y(6);
%               g*Y(1) - k*(Y(1)+Y(2)+Y(3)+Y(4)+Y(5)+Y(6))*Y(7);
%               g*Y(2) - k*(Y(1)+Y(2)+Y(3)+Y(4)+Y(5)+Y(6))*Y(8);
%               g*Y(3) - k*(Y(1)+Y(2)+Y(3)+Y(4)+Y(5)+Y(6))*Y(9);
%               g*Y(4) - k*(Y(1)+Y(2)+Y(3)+Y(4)+Y(5)+Y(6))*Y(10);
%               g*Y(5) - k*(Y(1)+Y(2)+Y(3)+Y(4)+Y(5)+Y(6))*Y(11);
%               g*Y(6) - k*(Y(1)+Y(2)+Y(3)+Y(4)+Y(5)+Y(6))*Y(12);
%               (h-k*Y(13))*(Y(1)+Y(2)+Y(3)+Y(4)+Y(5)+Y(6))];
%
```

The fate of the immune response depends on a critical combination of parameters.

Again drawing on [10], we list several results that can be derived from this modified model. The model adopts one of two asymptotic behaviors depending on a combination of parameters, denoted by N_{div}, defined by

$$N_{\text{div}} = \frac{cg}{ak - bh}, \quad \text{where } \frac{a}{b} > \frac{h}{k}. \tag{10.5.4}$$

If the number n of viral variants remains below or equal to N_{div}, then the virus population eventually decreases and becomes subclinical. On the other hand, if $n > N_{\text{div}}$, then the virus population eventually grows unchecked.

Note that N_{div} depends on the immune response to the variable and conserved regions of the virus in different ways. If specific lymphocytes rapidly respond (a large g) and are very effective (a large c), then N_{div} will be large in proportion to each, meaning a large number of mutations will have to occur before the virus gains the upper hand. By contrast, the general immune response parameters, h and b, appear as a combination in the denominator. Their effect is in direct opposition to the comparable viral parameters a and k.

Naturally, the size of N_{div} is of considerable interest. Assuming that the denominator of (10.5.4) is positive, $ak > bh$, we make three observations; their proofs may be found in [10].

Observation 1. *The immune responses, the x_is and z, in total have only a limited response to the HIV infection. That is, letting $X = x_1 + x_2 + \cdots + x_n$ be the sum of the specific immunological responses, then*

$$\begin{aligned} \lim_{t\to\infty} X(t) &= \frac{g}{k}, \\ \lim_{t\to\infty} z(t) &= \frac{h}{k}, \end{aligned} \tag{10.5.5}$$

where the parameters g, h, and k are as defined as in (10.5.2)–(10.5.4)*. The implication is that even though the virus continues to mutate, the immune system cannot mount an increasingly larger response.*

The next observation addresses the possibility that after some time, all the immune subspecies populations are decreasing.

Observation 2. *If all mutant subspecies populations v_i are decreasing after some time τ, then the number of mutants will remain less than N_{div} and the infection will be controlled. That is, if there is a time τ such that all derivatives $v_i'(t) < 0$ are negative for $t > \tau$, $i = 1, \ldots, n$, then the number of mutations n will not exceed N_{div}.*

In the next observation, we see that if the number of variations increases to some level determined by the parameters, then the viral population grows without bound.

Observation 3. *If the number of mutations exceeds N_{div}, then at least one subspecies increases without bound. In fact, in this case, the sum $V(t) \equiv v_1 + v_2 + \cdots + v_n$ increases faster than a constant times e^{at} for some positive number a.*

Observation 4. *If $ak < bh$, the immune system will eventually control the infection.*

Numerical studies illustrate the observations graphically.

In what follows, we give parameters with which computations may be made to visualize the results discussed here. These parameters do not represent biological reality; likely the real parameters are not known. The ones used illustrate the features of the model. In [10], the authors choose $a = c = 5$, $b = 4.5$, and $g = h = k = 1$. This choice yields the diversity threshold as 10 ($N_{\text{div}} = 10$). To keep our computation manageable, we choose the same values except $b = 4$:

MAPLE
```
> a:=5: b:=4: c:=5: g:=1: h:=1: k:=1: Ndiv:= c*g/(a*k-b*h);
```

MATLAB
```
> a=5; b=4; c=5; g=1; h=1; k=1; Ndiv=c*g/(a*k-b*h)
```

Hence for this set of parameters $N_{\text{div}} = 5$.

Suppose that first there is an initial infection and the virus runs its course without mutation. We can achieve this in our model, and see the outcome, by taking some initial infection, $v_1(0) = \frac{5}{100}$, for the original virus but zero level of infection initially for all the mutants.

MAPLE
```
> initialVals:=v1(0)=5/100,v2(0)=0,v3(0)=0,v4(0)=0,v5(0)=0,v6(0)=0,
              x1(0)=0,x2(0)=0,x3(0)=0, x4(0)=0,x5(0)=0,x6(0)=0,z(0)=0;
> sol1:=dsolve({mutatingSystem, initialVals},{v1(t),v2(t),v3(t),v4(t),v5(t),v6(t),
                x1(t),x2(t),x3(t),x4(t),x5(t),x6(t),z(t)},numeric,output=listprocedure);
> v1sol1:=subs(sol1,v1(t)); x1sol1:=subs(sol1,x1(t)); zsol1:=subs(sol1,z(t));
> plot(['t','v1sol1(t)','t'=0..10]);
```

MATLAB
```
> hold on
> init1=[0.05;0;0;0;0;0;0;0;0;0;0;0;0];
> [t1,Y]=ode23('hivMVRate',[0 .5],init1);
> X=Y(:,7:12); % sum the x's
> S1=X(:,1)+X(:,2)+X(:,3)+X(:,4)+X(:,5)+X(:,6);
> z1=Y(:,13); % retain the z's
> V=Y(:,1:6); plot(t1,V)
```

The result, shown in Figure 10.5.1, is a plot of the number of (unmutated) viral particles against time. One sees that the infection flares up but is quickly controlled by the immune system.

Now we explore what happens when there is one mutation of the original virus, effectively $n = 2$ in this case, where n counts the number of genetically distinct viruses. Following our technique above, only the original virus and one mutant will be given a nonzero initial value. Further, to incorporate a delay in the onset of mutation, we take $v_2(t) = 0$ for $0 \le t < T_2$ and $v_2(T_2) = \frac{1}{100}$, where $T_2 = \frac{1}{2}$ is the time of the first mutation. From the run above, we know the size of the population of original virus at this time, $v_1(T_2)$.

MAPLE
```
> initialVals:=v1(1/2)=v1sol1(1/2), v2(1/2)=1/100, v3(1/2)=0, v4(1/2)=0, v5(1/2)=0, v6(1/2)=0,
              x1(1/2)=x1sol1(1/2), x2(1/2)=0, x3(1/2)=0, x4(1/2)=0, x5(1/2)=0, x6(1/2)=0, z(1/2)=zsol1(1/2);
> sol2:=dsolve({mutatingSystem, initialVals}, {v1(t),v2(t),v3(t),v4(t),v5(t),v6(t),
                x1(t),x2(t),x3(t),x4(t),x5(t),x6(t),z(t)}, numeric,output=listprocedure);
> v1sol2:=subs(sol2,v1(t)); v2sol2:=subs(sol2,v2(t));
> x1sol2:=subs(sol2,x1(t)); x2sol2:=subs(sol2,x2(t)); zsol2:=subs(sol2,z(t));
> ###
> initiaVals:=v1(1)=v1sol2(1),v2(1)=v2sol2(1), v3(1)=1/100, v4(1)=0,v5(1)=0,v6(1)=0,
```

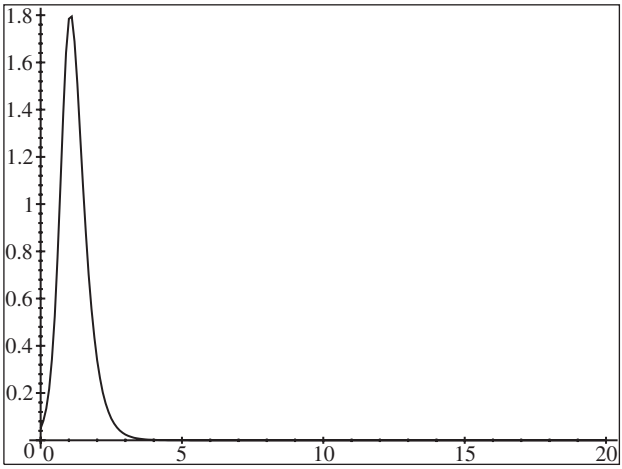


Fig. 10.5.1. A viral infection with no mutation.

```
                x1(1)=x1sol2(1),x2(1)=x2sol2(1),x3(1)=0, x4(1)=0,x5(1)=0, x6(1)=0, z(1)=zsol2(1);
> sol3:=dsolve({mutatingSystem, initialVals}, {v1(t), v2(t),v3(t),v4(t),v5(t),v6(t),
                    x1(t),x2(t),x3(t),x4(t),x5(t),x6(t),z(t)}, numeric,output=listprocedure);
> v1sol3:=subs(sol3,v1(t)); v2sol3:=subs(sol3,v2(t)); v3sol3:=subs(sol3,v3(t));
> x1sol3:=subs(sol3,x1(t)); x2sol2:=subs(sol3,x2(t));
> x3sol3:=subs(sol3,x3(t)); zsol3:=subs(sol3.z(t));
> plot({['t','v1sol1(t)','t'=0..1/2], ['t','v1sol2(t)', 't'=1/2..1], ['t','v1sol3(t)','t'=1..10],
        ['t','v2sol2(t)','t'=1/2..1], ['t','v2sol3(t)', 't'=1..10], ['t','v3sol3(t)','t'=1..10]}, color=black);

  MATLAB
> s=size(t1);
  % the ending values = last row = Y(s(1),:), add 1/100 to its 2nd component,
  % that becomes start values for next period
> init2=Y(s(1),:); init2(2)= init2(2)+0.01;
> [t2,Y]=ode23('hivMVRate',[.5 1],init2);
> X=Y(:,7:12); S2=X(:,1)+X(:,2)+X(:,3)+X(:,4)+X(:,5)+X(:,6);
> z2=Y(:,13); V=Y(:,1:6); plot(t2,V)
> s=size(t2); % add 2nd mutant
> init3=Y(s(1),:); init3(3)= init3(3)+0.01;
> [t3,Y]=ode23('hivMVRate',[1 1.5],init3);
> X=Y(:,7:12); S3=X(:,1)+X(:,2)+X(:,3)+X(:,4)+X(:,5)+X(:,6);
> z3=Y(:,13); V=Y(:,1:6); plot(t3,V)
```

We see the result in Figure 10.5.2. Each new mutant strain engenders its own flare-up, but soon the immune system gains control.

So far, the number of mutations has been less than N_{div}, but we now jump ahead and allow six mutations to occur:

```
  MAPLE
> restart; with(plots):
> a:=5: b:=4: c:=5: g:=1: h:=1: k:=1:
> Ndiv:=c*g/(a*k-b*h);
> eq:=seq(diff(v[n](t),t)=(a-b*z(t)-c*x[n](t))*v[n](t), n=1..7),
       seq(diff(x[n](t),t)=g*v[n](t)-k*x[n](t)*(sum(v[p](t), p=1..7)),n=1..7),
            diff(z(t),t)=(h-k*z(t))*sum(v[q](t),q=1..7):
> NG:=6; #number of mutations to generate initial conditions for the infections
> init[1]:=v[1](0)=5/100,seq(v[n](0)=0,n=2..7),seq(x[n](0)=0,n=1..7),z(0)=0:
> for p from 1 to NG do
> sol[p]:=dsolve({eq,init[p]},numeric,output=listprocedure):
```

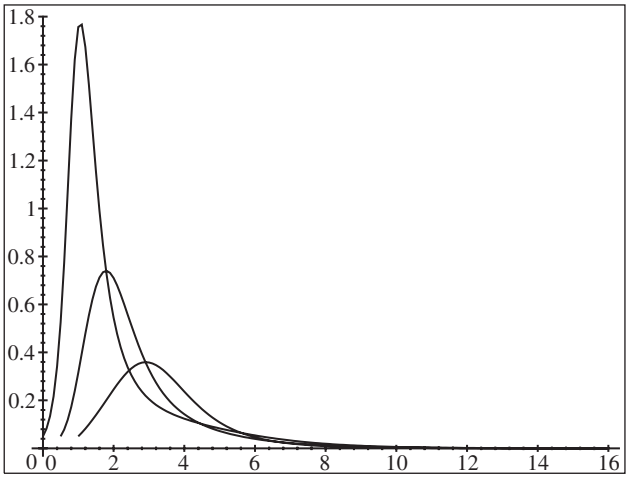


Fig. 10.5.2. Infection with two mutations.

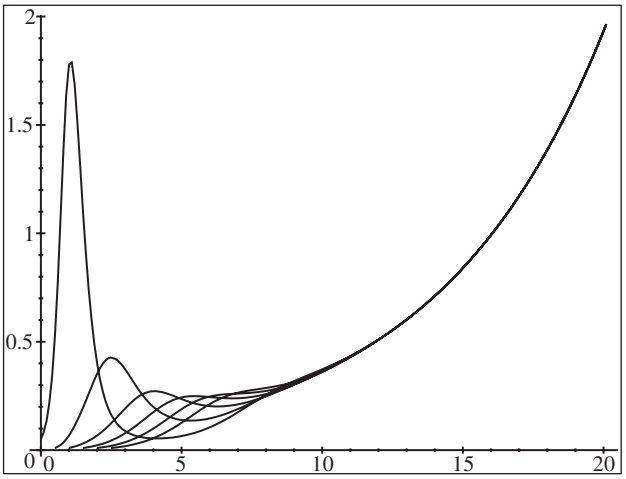


Fig. 10.5.3. Six mutations, with $N_{\text{div}} = 5$.

```
> for n from 1 to 7 do
      vs[p,n]:=subs(sol[p],v[n](t)):
      xs[p,n]:=subs(sol[p],x[n](t)):
   od:
> zs[p]:=subs(sol[p],z(t)):
> vs[p,p+1](p/2):=1/100;
> init[p+1]:=seq(v[m](p/2)=vs[p,m](p/2),m=1..7),seq(x[m](p/2)=xs[p,m](p/2),m=1..7),z(p/2)=zs[p](p/2):
> od:
> for m from 1 to NG do
   J[m]:=plot([seq([t,vs[n,m](t),t=(n-1)/2..n/2],n=1..NG),[t,vs[NG,m](t),t=NG/2..15]],color=BLACK):
   od:
> display([seq(J[i],i=1..NG)]);
```

```
MATLAB
> s=size(t3);init4=Y(s(1),:);
> init4(4)= init4(4)+0.01;
> [t4,Y]=ode23('hivMVRate',[1.5 2.0],init4);
> X=Y(:,7:12);
> S4=X(:,1)+X(:,2)+X(:,3)+X(:,4)+X(:,5)+X(:,6);
> z4=Y(:,13); V=Y(:,1:6); plot(t4,V)
  %%% end 4th step
> s=size(t4); init5=Y(s(1),:);
> init5(5)= init5(5)+0.01;
> [t5,Y]=ode23('hivMVRate',[2.0 2.5],init5);
> X=Y(:,7:12);
> S5=X(:,1)+X(:,2)+X(:,3)+X(:,4)+X(:,5)+X(:,6);
> z5=Y(:,13); V=Y(:,1:6); plot(t5,V)
  %%% end 5th step
> s=size(t5);init6=Y(s(1),:);
> init6(6)= init6(6)+0.01;
> [t6,Y]=ode23('hivMVRate',[2.5 20],init6);
> X=Y(:,7:12);
> S6=X(:,1)+X(:,2)+X(:,3)+X(:,4)+X(:,5)+X(:,6);
> z6=Y(:,13); V=Y(:,1:6); plot(t6,V)
  %%% end 6th step
> hold off
> t=[t1;t2;t3;t4;t5;t6]; S=[S1;S2;S3;S4;S5;S6];
> z=[z1;z2;z3;z4;z5;z6]; plot(t,S); plot(t,z)
```

One sees that the result is unexpected. At first things go as before: After an initial flare-up, the immune system begins to gain control and viral population tends downward. But then something happens: The immune system is overwhelmed.

Observation 2 predicts that since more mutations have occurred than N_{div}, the population will grow without bound. The graphs show this.

We now verify Observation 3 for these parameters. First, note that from (10.5.2), the sum of the x_is satisfies the differential equation

$$X' = V * (g - kX),$$

where $X = x_1 + x_2 + \cdots + x_6$ and $V = v_1 + v_2 + \cdots + v_6$. We could compute the solution of this equation and expect that

$$\lim_{t\to\infty} (x_1(t) + x_2(t) + \cdots + x_6(t)) = \frac{g}{k}.$$

Or, using the computations already done, add the x_is. The level of the x_is are kept in this syntax in the eighth through thirteenth positions. The "time'' variable is kept in the first position of the output. We add these x_is in each output.

```
MAPLE
> plot({['t','x1sol1(t)','t'=0..1/2], ['t','x1sol2(t)+x2sol2(t)','t'=1/2..1],
        ['t','x1sol3(t)+x2sol3(t)+x3sol3(t)','t'=1..3/2],['t','x1sol4(t)+x2sol4(t)+x3sol4(t)+x4sol4(t)','t'=3/2..2],
        ['t','x1sol5(t)+x2sol5(t)+x3sol5(t)+x4sol5(t)+x5sol5(t)','t'=2..5/2],
        ['t','x1sol6(t)+x2sol6(t)+x3sol6(t)+x4sol6(t)+x5sol6(t)+x6sol6(t)','t'=5/2..10]},color=BLACK);

MATLAB
% These plots done via code above.
```

The plot of the response z, no matter where you start, should have asymptotic limit $\frac{h}{k}$ and looks essentially the same as that for $(x_1 + x_2 + \cdots + x_6)$. Here is one way to plot the values of z. What you should see is that the z reaches a maximum:

```
MAPLE
> plot(['t','zsol1(t)','t'=0..1/2],['t','zsol2(t)','t'=1/2..1],['t','zsol3(t)','t'=1..3/2],['t','zsol4(t)','t'=3/2..2],
>      ['t','zsol5(t)','t'=2..5/2],['t','zsol6(t)','t'=5/2..10],color=BLACK);
```

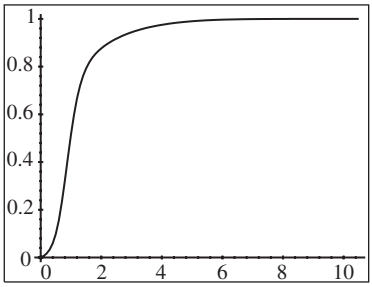


Fig. 10.5.4. Graph of $x_1 + x_2 + \cdots + x_n$.

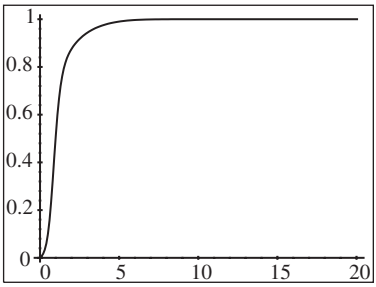


Fig. 10.5.5. Graph of $z(t)$ from (10.5.3).

Viral suppression is possible with some parameters.

It was stated in Observations 1 and 4 that there are two ways to achieve viral suppression. These are experiments that should be run. One could choose parameters such that $ak < bh$; then the immune system will eventually control the infection. No change need be made in the syntax, only $a = 4$ and $b = 5$. Other parameters could remain the same.

The simple models as presented in these two sections give a good first understanding of the progress from infection to remission to AIDS. Such an understanding provokes further study.

10.6 Predicting the Onset of AIDS

Most diseases have a latency or incubation period between the time of infection and the onset of symptoms; AIDS is no exception. The latency period for AIDS varies greatly from individual to individual, and so far, its profile has not been accurately determined. However, assuming a given form of the incubation profile, we show that the onset of symptoms occurs, statistically, as the time of infection convolved with this profile.

AIDS cases can be statistically predicted by a convolution integral.

In this chapter, we have discussed the epidemiology of the HIV infection and subsequent appearance of AIDS. For most diseases, there is a period of time between infection by the causative agent and the onset of symptoms. This is referred to as the *incubation period*; an affliction is asymptomatic during this time. Research is showing that the nature of this transition for HIV is a complicated matter. Along with trying to learn the mechanism of this process, considerable work is being devoted in an attempt to prolong the period between HIV infection and the appearance of AIDS. This period varies greatly among different individuals and appears to involve, besides general health, particular characteristics of the individual's immune system. See [5, 6, 7, 8] for further details.

The incubation period can be modeled as a probability density function $p(t)$ (see Section 2.8), meaning that the probability that AIDS onset occurs in a Δt time interval containing t is

$$p(t) \cdot \Delta t.$$

To discover the incubation density, records are made, when possible, of the time between contraction of HIV and the appearance of AIDS. See Bacchetti [12] for several comments by other researchers, and for a comprehensive bibliography. At the present this probability density is not known, but some candidates are shown in Figure 10.6.1(a)–(d).

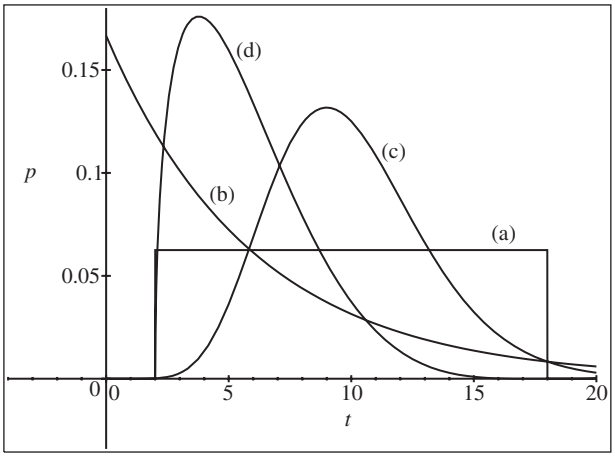


Fig. 10.6.1. Some HIV incubation probability densities. Graphs of (a) uniform distribution, (b) $\frac{e^{-t/6}}{6}$, (c) $t^9 e^{-t}$ normalized, (d) $\sqrt{\frac{t-2}{16}}(1-\frac{t-2}{16})^4$ normalized.

Figure 10.6.1(a) is a uniform distribution over the period of 2 to 18 years. This distribution has no preferred single incubation moment, but incubation is guaranteed to occur no sooner than two years after infection and no later than 18 (18.0) years

afterward. It is unlikely that this is the operating distribution, but we include it for comparison purposes.

Figure 10.6.1(b) is an exponential distribution. This distribution pertains to many "arrival time" processes in biology such as times for cell division (which occurs upon the "arrival" of cell maturation). As can be seen, incubation is likely to occur right away and diminishes with time. The incubation period can be infinitely long. (A fraction of those infected with HIV have, so far, remained asymptomatic "indefinitely.")

Figure 10.6.1(c) is a gamma distribution incorporating both a preferred incubation "window" and the possibility of an indefinitely long incubation period.

Figure 10.6.1(d) is a beta distribution. It allows for a preferred window, but as with the uniform distribution, incubation must occur between given times. Their graphs are illustrated in Figure 10.6.1.

The functions we have used to draw Figure 10.6.1 are p_1, p_2, p_3, and p_4 as defined in the following:

```
  MAPLE
> c1:=int(t^9*exp(-t),t=0..infinity);
> c2:=evalf(Int(sqrt((t-2)/16)*(1-(t-2)/16)^4,t=2..20));
> p1:=t->1/16*(Heaviside(t-2)-Heaviside(t-18));
> p2:=t->exp(-t/6)/6;
> p3:=t->t^9*exp(-t)/c1;
> p4:=t->sqrt((t-2)/16)*(1-(t-2)/16)^4/c2;
> plot({p1(t),p2(t),p3(t),p4(t),t=0..20});

  MATLAB
  % make an m-file, incubationProfile.m:
  % function y=incubationProfile(t);
  % if t<2
  %   y=0;
  % elseif t<18
  %   y=1/16;
  % else
  %   y=0;
  % end
> t=linspace(0,20,100)
> for k=1:100
>    p1(k)=incubationProfile(t(k)); % uniform
> end
> plot(t,p1); hold on
> p2=exp(-t/6)/6; plot(t,p2) % exponential
> p3=t.^9.*exp(-t);
> c1=trapz(t,p3); % for normalization
> p3=p3/c1; plot(t,p3) % gamma distribution
> for k=1:100
>    if t(k)<2
>       p4(k)=0;
>    elseif t(k)<20
>       p4(k)=sqrt((t(k)-2)/16)*(1-(t(k)-2)/16)^4;
>    else
>       p4(k)=0;
>    end
> end
> c2=trapz(t,p4);
> p4=p4/c2; plot(t,p4) % the beta distribution
```

To derive a mathematical relationship for the appearance of AIDS cases, we will assume that the probability distribution for the incubation period can be treated as a deterministic rate. Let $h(t)$ denote the HIV infection density, that is,

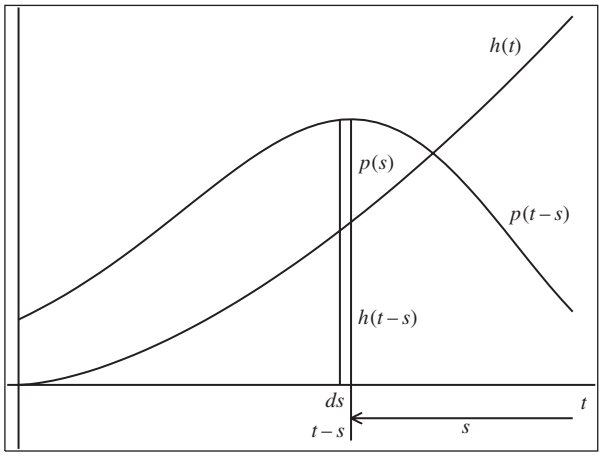


Fig. 10.6.2. $a(t) \approx \sum_s h(t-s) \cdot ds \cdot p(s)$.

$$\text{the number of new HIV infections during } [t, t+\Delta t) = h(t) \cdot \Delta t,$$

and let $a(t)$ denote the AIDS density; thus

$$\text{the number of new AIDS cases during } [t, t+\Delta t) = a(t) \cdot \Delta t.$$

We wish to determine $a(t)$ from $h(t)$. How many AIDS cases occur now, on day t due to infections s days ago? See Figure 10.6.2. The number of newly infected persons during the interval from $t-(s+ds)$ to $t-s$ is $h(t-s) \cdot ds$ and the fraction of them to become symptomatic s days later is $p(s)$. Hence the contribution to $a(t)$ here is

$$h(t-s) \cdot ds \cdot p(s).$$

Since $a(t)$ is the sum of such contributions over all previous times, we get

$$a(t) = \int_0^\infty h(t-s)p(s)ds. \tag{10.6.1}$$

This sort of integral is known as a *convolution*; such integrals occur widely in science and engineering.

Convolution integrals have an alternative form under change of variable. Let $u = t-s$; then $s = t-u$ and $ds = -du$. Since $u = t$ when $s = 0$ and $u = -\infty$ when $s = \infty$, the integral of (10.6.1) becomes

$$a(t) = -\int_t^{-\infty} h(u)p(t-u)du.$$

Absorbing the minus sign into a reversal of the limits of integration and replacing the dummy variable of integration u by s gives

$$a(t) = \int_{-\infty}^{t} h(s)p(t-s)ds. \tag{10.6.2}$$

This equation exhibits a striking symmetry between the roles of h and p. Equation (10.6.2) is sometimes easier to work with than (10.6.1).

The occurrence of symptoms is strongly affected by the incubation distribution.

In order to determine whether a proposed incubation distribution is the correct one, we must use it in conjunction with our newly derived formula, either (10.6.1) or (10.6.2), to predict the pattern of cases. To this end, we track an HIV infected *cohort*, that is, a group of people infected about the same time, through the calculation.

Consider those infected over a two-year period, which we take to be $t = 0$ to $t = 2$. We will assume that there are 1000 cases in each of the two years; thus the HIV density we are interested in is

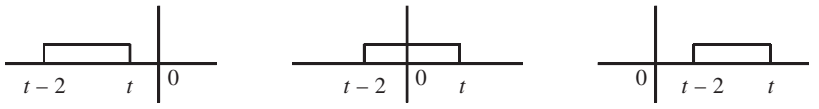
$$h(t) = \begin{cases} 1000 & \text{if } 0 \le t \le 2, \\ 0 & \text{otherwise.} \end{cases} \tag{10.6.3}$$

The total number of cases is $\int_0^2 h(s)ds = 2000$. With this choice for h, we can simplify the factor $h(t-s)$ in (10.6.1). By subtracting t from the inequalities $0 \le t - s \le 2$ and multiplying by -1, we get the equivalent form $t - 2 \le s \le t$. In other words,

$$\text{if } t-2 \le s \le t, \quad \text{then } h(t-s) = 1000; \quad \text{otherwise, } h \text{ is } 0. \tag{10.6.4}$$

Therefore, the only contribution to the integral in (10.6.1) comes from the part of the s-axis between $t-2$ and t.

There are three cases depending on the position of the interval $[t-2, t]$ relative to 0; see Figure 10.6.3. In (a), $t < 0$ and the interval is to the left of 0; in (b), $t - 2 < 0 < t$, the interval contains 0; and in (c), $0 < t - 2$, the interval is to the right of 0.



(a) interval to left of 0 (b) interval includes 0 (c) interval to right of 0

Fig. 10.6.3. Contributory subinterval of the s-axis.

Consider each case. If (a), $t \le 0$, then $a(t) = 0$ from (10.6.2) and (10.6.3). If (c), $t \ge 2$, then $t - 2 \ge 0$ and (10.6.1) becomes, taking into account (10.6.4),

$$a(t) = 1000 \int_{t-2}^{t} p(s)ds, \quad t \ge 2.$$

Finally, for (b), $0 < t < 2$, the part of the interval to the left of $s = 0$ makes no contribution, and in this case (10.6.1) becomes

$$a(t) = 1000 \int_0^t p(s)ds, \quad 0 < t < 2.$$

Putting these three together, we have

$$a(t) = \begin{cases} 0, & t \le 0, \\ 1000 \int_0^t p(s)ds, & 0 < t < 2, \\ 1000 \int_{t-2}^t p(s)ds, & t \ge 2. \end{cases} \tag{10.6.5}$$

Because it is inconvenient to deal with a function defined by cases, such as $a(t)$ is defined by (10.6.5), a standard set of "cases"-type functions have been devised. One of these is the *Heaviside* function $H(t)$, and another is the *signum* function $S(t)$. The first is defined as

$$H(t) = \begin{cases} 0, & t < 0, \\ 1, & t \ge 0. \end{cases} \tag{10.6.6}$$

The signum function is just the *sign* of its argument, that is,

$$S(t) = \begin{cases} -1, & t < 0, \\ 0, & t = 0, \\ 1, & t > 0. \end{cases} \tag{10.6.7}$$

Actually, there is a relationship between the two, except for $t = 0$:

$$H(t) = \frac{1}{2}(S(t) + 1), \quad S(t) = 2H(t) - 1, \quad t \neq 0. \tag{10.6.8}$$

The Heaviside function $H(2 - t)$ cuts out at $t = 2$, while $H(t - 2)$ cuts in at $t = 2$, so in terms of Heaviside functions, (10.6.5) can be written as

$$a(t) = 1000H(2 - t) \int_0^t p(s)ds + 1000H(t - 2) \int_{t-2}^t p(s)ds. \tag{10.6.9}$$

For the simplest example, assume that the incubation density is the uniform distribution, P_1 above (Figure 10.6.1(a)):

$$P_1(t) = \begin{cases} \frac{1}{16} & \text{if } 2 \le t \le 18, \\ 0 & \text{otherwise.} \end{cases}$$

Substituting into (10.6.9) and integrating gives the onset distribution $a(t)$.

MAPLE

```
> restart:
> h:=t->1000*(Heaviside(2-t)-Heaviside(-t));
> plot(h(t),t=-3..3);
> int(h(t-s),s=2..18)/16;
```

```
> a:=unapply(int(h(t-s),s=2..18)/16,t);
> plot(a(t),t=0..20);
```

MATLAB

```
% make an m-file, casesOnset.m:
% function a=casesOnset(t);
%  if t<0   %     a=0;
%  elseif t<2
%     r=linspace(0,t,20);
%     for i=1:20
%        y(i)=incubationProfile(r(i));
%     end
%     a=1000*trapz(r,y);
%  else
%     r=linspace(t-2,t,20);
%  for i=1:20
%        y(i)=incubationProfile(r(i));
%  end
%     a=1000*trapz(r,y);
%  end % end of casesOnset.m
% recall t=linspace(0,20,100)
> for k=1:100
    a(k)=casesOnset(t(k)) % vector same size as t
> end
> plot(t,a)
> trapz(t,a) % integral 0 to 20
```

The output of this calculation is (in MAPLE syntax)

$$a(t) = \left(\frac{125}{4}t - \frac{1125}{2}\right)\text{signum}(18-t) + \left(\frac{125}{4}t - 125\right)\text{signum}(t-4) + \left(-\frac{125}{4}t + \frac{125}{2}\right)\text{signum}(2-t) + \left(-\frac{125}{4}t + 625\right)\text{signum}(20-t). \tag{10.6.10}$$

This provides an alternative realization for a formula for $a(t)$. Its form is different from that of (10.6.5). We can recover the previous one, however, by evaluating the signum function with various choices of t. To do this, suppose that $2 < t < 4$ or $4 < t < 18$ or $18 < t < 20$, respectively, and evaluate (10.6.10).

Eventually, all those infected will contract AIDS; therefore,

$$\int_0^\infty a(s)ds = \int_0^2 h(s)ds.$$

But the first integral reduces to the interval [0, 20]. That is, the total number of people who develop AIDS during the 20-year period is the same as the total number of people in the initial two-year cohort. This computation is done as

MAPLE

```
> int(a(s), s=0..20);
```

This gives 2000.

Several observations should be made with the graph for each of the other distributions. There should be a gradual increase of the number of cases as the cohorts begin to develop symptoms of AIDS. Also, there should be a gradual decrease that may last past 20 years: those in the cohorts who were infected near the end of the second

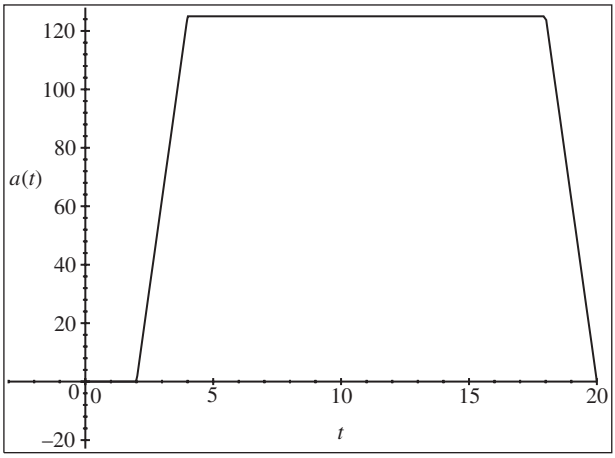


Fig. 10.6.4. Graph of $a(t)$ from (10.6.10).

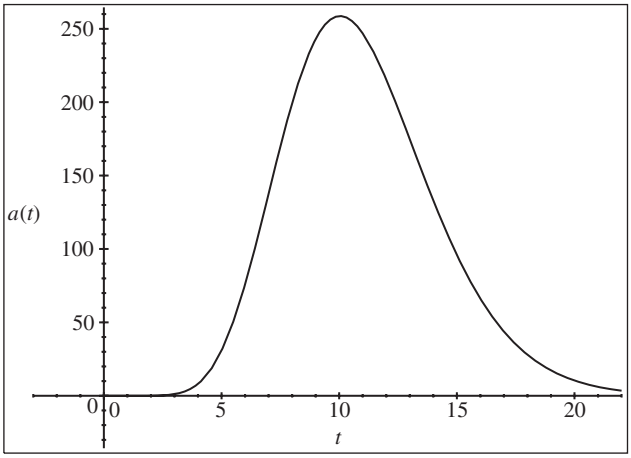


Fig. 10.6.5. Onset of AIDS cases for a two-year HIV cohort assuming gamma incubation.

year may not begin to show symptoms until the twenty-second year, depending on whether P_2, P_3, or P_4 is used.

We leave the computations for the other distributions to the exercises. However, Figure 10.6.5 shows the graph for the onset of AIDS cases for a two-year cohort assuming incubation as with the gamma distribution $P_3(t)$. The function $a(t)$ defined, evaluated, and plotted by

$$a(t) = \int_0^\infty h(t-s)P_3(s)ds$$

is evaluated with the following code:

```
MAPLE
#repeating P3 and c1 from before
> t:='t';
> c1:=int(t^9*exp(-t),t=0..infinity);
> P3:=t->t^9*exp(-t)/c1;
> int(1000*P3(s),s=0..t)*Heaviside(2-t)+int(1000*P3(s),s=t-2..t)*Heaviside(t-2):
> a:=unapply(%,t);
> plot(a(t),t=0..22);

MATLAB
% for onset of cases with the gamma incubation period, make up an m-file, onsetGam.m, containing
% function a=onsetGam(t);
% c1=3.6107e+05; % from text calculation
% if t<0
%   a=0;
% elseif t<2
%   r=linspace(0,t,20);
%   for i=1:20
%     y(i)=r(i)^9*exp(-r(i))/c1; %values of t.^9.*exp(-t) at r(i)
%   end
%   a=1000*trapz(r,y);
% else
%   r=linspace(t-2,t,20); % integral of y from 0 to t
%   for i=1:20
%     y(i)=r(i)^9*exp(-r(i))/c1; %values of t.^9.*exp(-t) at r(i)
%   end
%   a=1000*trapz(r,y);
% end
> t=linspace(0,20,100);
> for k=1:100
    a(k)=onsetGam(t(k)); % creates a vector same size as t
> end
> plot(t,a)
> trapz(t,a) % integral of a over 0 to 20
```

We verify (symbolically) that

$$\int_0^\infty a(s)ds = 2000.$$

```
MAPLE
> evalf(Int(a(s),s=0..infinity));
```

Comparing these figures, we can gauge the effect of the incubation period. Note that for research purposes, it would require more than comparing figures like these with AIDS epidemiologic data to determine the incubation distribution because one could not separate the AIDS cases into those stemming from a particular cohort; all cohort onsets are mixed together.

Exercises/Experiments

1. Choose each of the two remaining hypothetical incubation densities of Figure 10.6.1 in turn. (The uniform and gamma have been done in the text.) Draw the graph of the number of AIDS cases expected to develop, $a(t)$, for the cohort of (10.6.2) with the assumption that the one you have chosen is correct.
2. We pose a *what if* experiment. Suppose that around 2010, a vaccine for HIV is developed, and while current cases cannot be cured, HIV is no longer transmitted. The number of reported new cases of HIV, $h(t)$, drops dramatically to zero by 2020. Model the reported cases of HIV with a hypothetical scenario such as

$$h(t) = \frac{t - 1980}{40}\left[1 - \frac{(t - 1980)^6}{40^6}\right].$$

(a) Draw a graph of $h(t)$. Observe that $h(1980) = 0$ and $h(2020) = 0$.

MAPLE

```
> restart;
> h:=t->((t-1980)/40)*(1-(t-1980)^6/40^6);
> plot(h(t),t=1980..2020,xtickmarks=0,ytickmarks=2);
> h(1980); h(2020);
```

MATLAB

```
% contents of m-file infectDensity.m:
% function h=infectDensity(t) % won't vectorize due to the conditionals
% if t<1980
%   h=0;
% elseif t<2020
%   h=((t-1980)/40)*(1-((t-1980)/40)^6);
% else
%   h=0;
% end
> t=linspace(1980,2020); % 100 values
> for k=1:100
    h(k)=infectDensity(t(k));
  end
> plot(t,h)
```

(b) Determine where the maximum value of h occurs. This represents the time when the reported new cases of HIV-infected individuals peaks if this "optimistic scenario" were to happen.

MAPLE

```
> sol:=solve(diff(h(s),s)=0,s);
> evalf(sol[1]);
```

MATLAB

```
> hmax=max(h)
> m=0;
> for i=1:100
    if h(i)==hmax
      m=i;
    end
  end
> maxYear=t(m)
```

(c) Define a "later rather than sooner" hypothetical incubation density and draw its graph:

MAPLE

```
> c5:=int(1/16*(t-2)*(1-(1/16*(t-2))^2),t=2..18);
> P5:=t->1/16*(t-2)*(1-(1/16*(t-2))^2)/c5;
> plot([t,P5(t),t=2..18],t=0..20);
```

MATLAB

```
> s=linspace(2,18);
> incDen=((s-2)/16).*(1-((s-2)/16).^2);
> c5=trapz(s,incDen)
> incDen=incDen/c5;
> plot(s,incDen)
```

(d) Find $a(t)$ as in (10.6.1) associated with this distribution.

MAPLE

```
> a15:=t->int(h(t-r)*P5(r),r=2..t-1980);
> a25:=t->int(h(t-r)*P5(r),r=2..18);
> a:=t->a15(t)*Heaviside(2000-t)+a25(t)*Heaviside(t-2000);
> plot(a(t),t=1982..2020);
```

MATLAB

```
% the integral a(t)=int(h(t-s)*p(s)*ds)
% from 0 to infinity has 5 cases:
%     t<1982, a(t)=0,
% 1982<t<1998, a(t)= int(h(t-s)*p(s)ds from 2 to t-1998
% 1998<t<2022, a(t)= int(h(t-s)*p(s)ds from 2 to 18
% 2022<t, a(t)= int(h(t-s)*p(s)ds from t-2020 to 18
% Here's why. First case: suppose t=1981; since p(s)=0 unless s>2,
% t-s<1979 so h(t-s)=0.
% Second case: suppose t=1994;
% again p(s)=0 unless s>2, so the lower limit must be at least 2.
% For t=1994, t-1980=14, so s runs from 2 to 14 and t-s runs from 1992 down to 1980;
% after that h(t-s)=0.
% We leave the remaining cases for you.
%
% But all cases will be done automatically
% since we have defined infectDensity(t)=0 for t<1980 or t>2020
> t=linspace(1980,2050); % get the graph for 1980 to 2050
> for k=1:100 % k= time index
    T=t(k);
    for j=1:100 % j= s index
      S=s(j);
      y(j)=infectDensity(T-S)*incDen(j);
    end
    a(k)=trapz(s,y);
  end
> plot(t,a)
```

(e) Sketch the graphs for the hypothetical $h(t)$ and associated $a(t)$.

MAPLE

```
> plot({[t,h(t),t=1980..2020],[t,a(t),t=1982..2029.432]});
> int(h(t),t=1980..2020);
> int(a(t),t=1982..2029.432);
```

Questions for Thought and Discussion

1. What are four suspected ways that HIV kills cells?
2. Why do viral mutations lead to the development of new antibodies by the immune system?
3. Describe the life cycle of HIV.
4. Why do we continue to get colds, year after year, but seldom get mumps more than once?
5. Describe clonal selection and clonal deletion.
6. How does the clonal deletion model explain the fact that a mouse injected prenatally with a virus never will raise antibodies against the virus after the mouse is born?
7. Describe three general immunologic mechanisms.
8. How does HIV infection result in the inactivation of both the humoral and cell-mediated immune responses?
9. Most DNA replication includes a proofreading function that corrects mismatched DNA nucleotides during DNA replication. The reverse transcriptase of HIV seems to lack this ability, which results in high mutation rates (as much as one or more per generation). Discuss this problem in terms of antibody production by a host's immune system.

References and Suggested Further Reading

[1] BLOOD CELLS, IMMUNITY:
W. T. Keeton and J. L. Gould, *Biological Science*, 5th ed., Norton, New York, 1993.

[2] Immunity: Special issue on the immune system, *Sci. Amer.*, **269**-3 (1993).

[3] HIV AND AIDS:
What science knows about AIDS [full issue], *Sci. Amer.*, **259**-4 (1988).

[4] HIV AND AIDS:
M. A. Nowak and A. J. McMichael, How HIV defeats the immune system, *Sci. Amer.*, **273**-2 (1995), 58.

[5] HIV AND T CELLS:
A. S. Perelson, Modeling the interaction of the immune system with HIV, in C. Castillo-Chavez, ed., *Mathematical and Statistical Approaches to AIDS Epidemiology*, Lecture Notes in Biomathematics, Vol. 83, Springer-Verlag, New York, 1989, 350–370.

[6] HIV AND T CELLS:
A. S. Perelson, D. E. Kirschner, and R. J. De Boer, The dynamics of HIV infection of $CD4^+$ T cells, *Math. Biosci.*, **114** (1993), 81–125.

[7] HIV AND T CELLS:
K. E. Kirschner and A. S. Perelson, A model for the immune system response to HIV:AZT treatment studies, in O. Arino, D. E. Axelrod, M. Kimmel, and M. Langlais, eds., *Mathematical Population Dynamics: Analysis of Heterogeneity and the Theory of Epidemics*, Wuerz Publishing, Winnipeg, ON, Canada, 1995, 295–310.

[8] HIV AND T CELLS:
A. S. Perelson, Two theoretical problems in immunology: AIDS and epitopes, in G. Cowan, D. Pines, and D. Meltzer, eds., *Complexity: Metaphors, Models and Reality*, Addison–Wesley, Reading, MA, 185–197.

[9] THE IMMUNE RESPONSE:
W. C. Greene, AIDS and the immune system, *Sci. Amer.*, **269**-3 (special issue) (1993).

[10] MUTATIONS OF HIV:
M. A. Nowak, R. M. May, and R. M. Anderson, The evolutionary dynamics of HIV-1 quasi species and the development of immunodeficiency disease, *AIDS*, **4** (1990), 1095–1103.

[11] MUTATIONS OF HIV:
M. A. Nowak and R. M. May, Mathematical biology of HIV infections: Antigenic variation and diversity threshold, *Math. Biosci.*, **106** (1991), 1–21.

[12] CALCULATIONS OF THE TIME FROM HIV INFECTION TO AIDS SYMPTOMS:
P. Bacchetti, M. R. Segal, and N. P. Jewell, Backcalculation of HIV infection rates, *Statist. Sci.*, **8**-2 (1993), 82–119.