

M1 BBS - EM8BBSEM

Simulation de Systèmes Biologiques

(#10)

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Triggers (déclencheurs) génétiques

All cells of a biological organism contain the same genetic information. It is only natural, as they are all formed by divisions of the same initial cell of fertilized egg.

On the other hand, cells of various organs differ both in features and functions. Hence we conclude that functioning of different cells of an adult organism is based on different fragments of the genetic code.

A fertilized cell divides into $10^3 \div 10^4$ new equivalent cells. Then the first **differentiation** takes place: cells form groups working in different regimes. At the same time the embryo changes its shape. Further differentiation occurs, leading to a formation of a fully developed organism.

The mechanism, regulating this important process is not yet known. However, we suspect **cellular self-organization** to be responsible for this effect. We may find out more by analyzing an appropriate mathematical model.

It seems that an adult cell, working in a specified regime, may occasionally ***switch*** to another regime. Think of cancerous tissues: cells grow rapidly, in a way characteristic of early development.

So far, we have been unable to find ways to control switching cellular regimes. We can, however, artificially affect these processes by introducing certain external factors.

Similar problems arise in the analysis of the ***evolution of biosphere***. Elementary act of evolution consists in creating two different individuals coming from the same ancestor. Analogous to the cellular differentiation, this process should be described by a similar mechanism.

Let's construct and analyze a model, which may give us some insight into the mechanism of differentiation. It is easy to see that our model should allow the existence of at least two stationary points, which would correspond to two different regimes of work under the same external conditions. In other words, the system's phase portrait should contain a certain number of singular points, located at the intersections of isoclines. Such systems are well known in electronics; they are called ***triggering (switching) systems***.

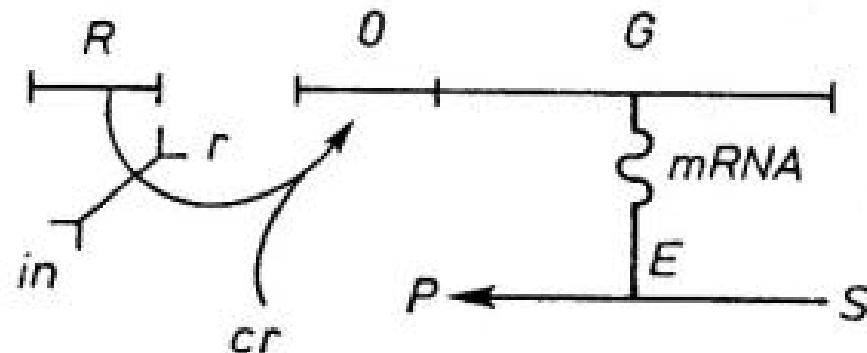
A perfect example of a ***trigger*** is ***protein biosynthesis***. We will base the analysis of this mechanism on the model of its biochemical control given by Jacob and Monod (1961).

Properties of a protein depend on the sequence of amino acids, forming its ***primary structure***. This sequence is determined by the sequence of nucleotides in that part of DNA, which controls the biosynthesis of that particular protein (***structural gene, G***).

Before the structural gene in the DNA sequence, there is the ***operator DNA (O)***. The biosynthesis is initiated when RNA polymerase binds to the operator and starts the ***transcription*** by moving along the nucleotide chain and catalyzing the creation of complementary messenger RNA (***mRNA***) molecules.

Next, the ***translation*** takes place, i.e. the synthesis of the protein's amino acid sequence, coded in mRNA, on appropriate ribosomal units. In this process, catalyzed by enzyme ***E***, substrates ***S*** are processed into products ***P***.

The process thus far described can be visualized in the rhs of the figure below.



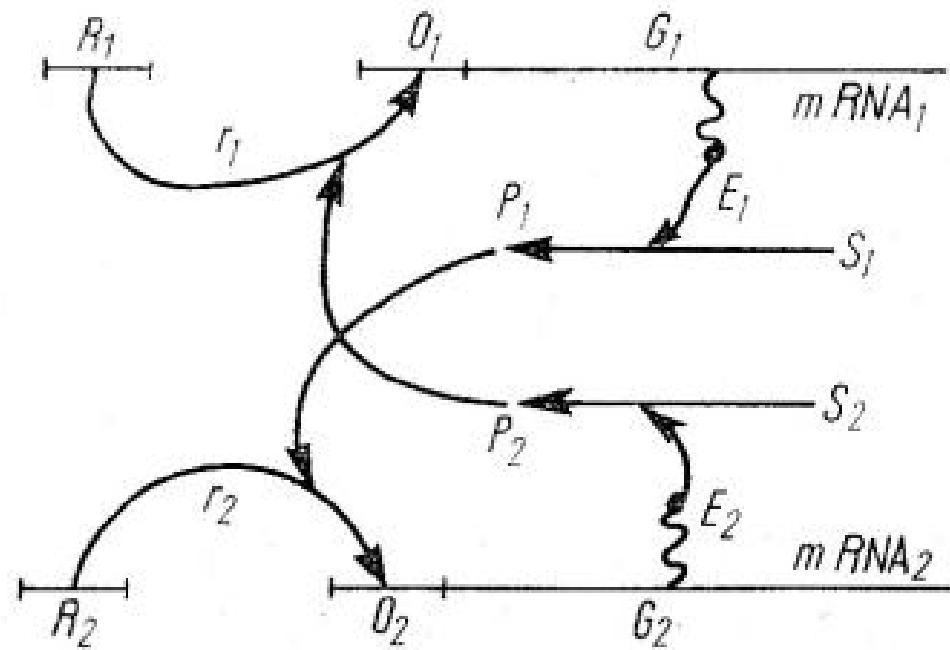
The biosynthesis of a protein proceeds only if the RNA polymerase binds to the operator DNA (**O**). If **O** is occupied by another molecule, the biosynthesis is effectively blocked. Enzymes that bind to **O** and thus control the biosynthesis are called **repressors** (**r**). They are synthesized by another part of DNA, the **regulator DNA** (**R**).

Binding of repressors to operator DNA is controlled by two types of other molecules (usually small and not necessarily proteins). The molecules of the first type (**inductors**, *in*) induce biosynthesis by binding to repressors and thereby preventing them from binding to **O**. The molecules of the second type (**co-repressors**, *cr*) inhibit biosynthesis by binding to repressors and thus increasing their affinity for binding to the operator DNA **O**.

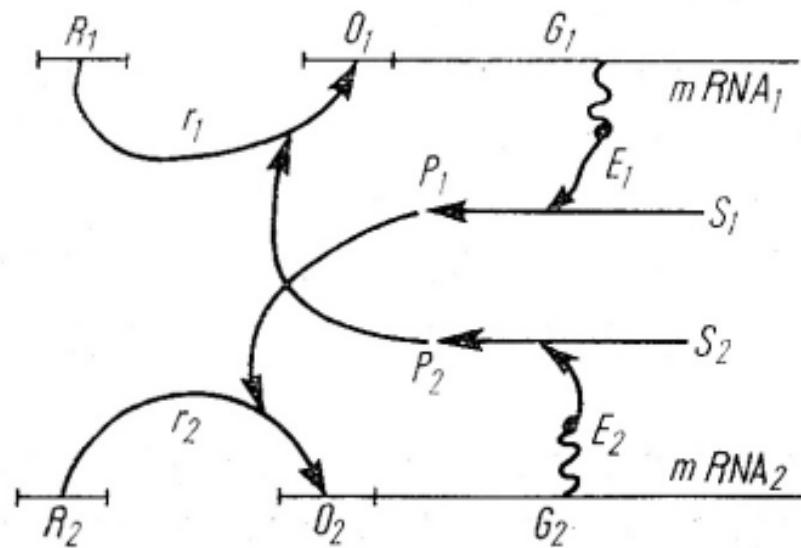
Inductors and co-repressors regulate the process of biosynthesis by providing it with appropriate **feedback** mechanisms. In both cases, the actual interaction between these molecules and that of a repressor results in a modification of the structure and/or function of the latter.

In many cases it is the product **P**, resulting from the activity of enzyme **E**, which plays the role of a co-repressor. In such a case the synthesis of enzyme **E** is interrupted when the concentration of its product **P** is high and the enzyme is no longer needed by the cell.

In other cases, a co-repressor may be a product of activity of another enzyme. Jacob and Monod suggested a schema of a system, which plays the role of a **switch**. It is shown below:



Arrows linking P_1 and r_1 as well as P_2 and r_2 indicate that products of activities of enzymes E_1 and E_2 are each a co-repressor for the synthesis of the 'opposite' enzyme. This system may work in two mutually exclusive regimes.



Suppose that the concentration of the product P_1 is high. The synthesis of the enzyme E_2 is then inhibited, and the product P_2 is no longer created. The system may work arbitrarily long in this state.

If for some reason (e.g. a transient fluctuation) the concentration of the product P_2 increases, the synthesis of the enzyme E_1 and its product P_1 will be repressed. Hence, the system will switch to another regime of work, in which the syntheses of E_2 and P_2 are prevalent.

In order to construct a mathematical model of a trigger, we will follow the changes in concentrations of the products of enzymatic reactions. Their decrease is due to the utilization of the products by the cell, while the increase of their concentrations comes from the synthesis, described by a constant rate of the enzymatic activity:

$$\frac{dP_1}{dt} = C_1 - \kappa_1 P_1$$

$$\frac{dP_2}{dt} = C_2 - \kappa_2 P_2$$

The enzymatic activity may be inhibited by the presence of molecules of the 'other' type of co-repressor. Therefore we will use the following formula for the growth rate of the products:

$$C_1 = \frac{A_1}{B_1 + P_2^m}$$

$$C_2 = \frac{A_2}{B_2 + P_1^n}$$

These relations reflect the ***cross co-repression***, i.e. the inhibiting effect of one of the products on the growth rate of the other one. In this case, parameters ***B*** correspond to the inhibition constants. Coefficients ***A*** are complex functions of many kinetic processes; they depend on the activity of the RNA polymerase, on the rate of ribosomal processes and on concentrations of substrates ***S***. The substrates reflect the level of nutrients in a cell and constitute the only way of exerting an external influence on a cell. Hence, parameters ***A*** reflect generally the rate of cellular metabolism.

The exponents ***m*** and ***n*** define the order of repression, i.e. the number of molecules of each product ***P*** necessary for the efficient repression to occur. If one molecule is sufficient, ***m=n=1***, etc.

First, let's consider a symmetric system, in which $A_1 = A_2 = A$, $B_1 = B_2 = B$, $\kappa_1 = \kappa_2 = \kappa$ and $m = n$:

$$\frac{dP_1}{dt} = \frac{A}{B + P_2^n} - \kappa P_1$$

$$\frac{dP_2}{dt} = \frac{A}{B + P_1^n} - \kappa P_2$$

Let's introduce dimensionless variables:

$$x = \frac{P_1}{B^{\frac{1}{n}}}, \quad y = \frac{P_2}{B^{\frac{1}{n}}}, \quad \tau = \kappa t, \quad \text{and} \quad \bar{A} = \frac{A}{\kappa B^{\frac{1+1}{n}}}$$

The original system of equations is transformed to the following form:

$$\frac{dx}{d\tau} = \frac{\bar{A}}{1 + y^n} - x$$

$$\frac{dy}{d\tau} = \frac{\bar{A}}{1 + x^n} - y$$

The stationary states can be found in the usual way:

$$\left. \begin{aligned} 0 &= \frac{\bar{A}}{1 + \bar{y}^n} - \bar{x} \\ 0 &= \frac{\bar{A}}{1 + \bar{x}^n} - \bar{y} \end{aligned} \right\} \Rightarrow \frac{\bar{A}(1 + \bar{x}^n)^n}{\bar{A}^n + (1 + \bar{x}^n)^n} - \bar{x} = 0$$

For $n = 1$:

$$\frac{\bar{A}(1 + \bar{x})}{\bar{A} + (1 + \bar{x})} - \bar{x} = 0 \Rightarrow$$

$$x^2 + \bar{x} - \bar{A} = 0 \Rightarrow$$

$$\bar{x}_1 = \frac{1}{2} \left(-1 - \sqrt{4\bar{A} + 1} \right) \quad \bar{x}_2 = \frac{1}{2} \left(-1 + \sqrt{4\bar{A} + 1} \right)$$

Note the following:

$$\bar{A} > 0, \quad \sqrt{4\bar{A} + 1} > 1$$



$$\bar{x}_1 < 0, \quad \bar{x}_2 > 0$$

The root corresponding to the negative value of the product's concentration has no physical sense. Consequently, there is only one stationary state in this system. Clearly, such a system cannot be a trigger, because switching requires at least two stationary states.

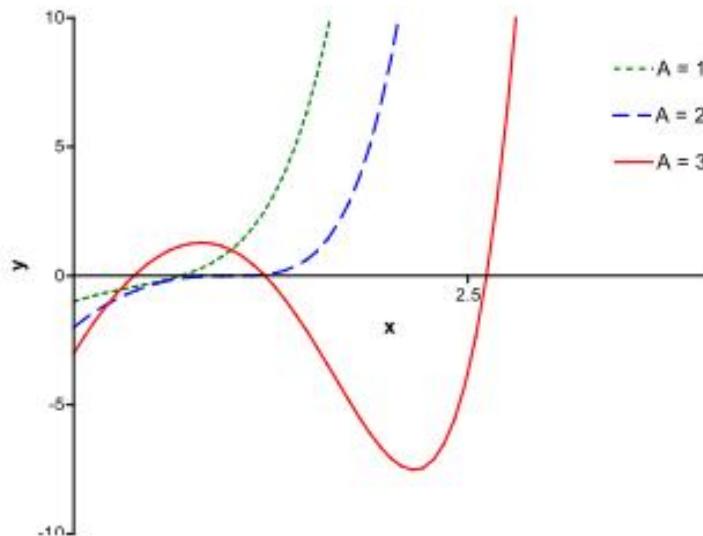
It follows that the Jacob-Monod schema can become a trigger only when at least two molecules participate in the process of repression (or co-repression).

For $n = 2$:

$$\frac{\bar{A}(1+\bar{x}^2)^2}{\bar{A}^2 + (1+\bar{x}^2)^2} - \bar{x} = 0 \quad \Rightarrow$$

$$\bar{x}^5 - \bar{A}\bar{x}^4 + 2\bar{x}^3 - 2\bar{A}\bar{x}^2 + (\bar{A}^2 + 1)\bar{x} - \bar{A} = 0$$

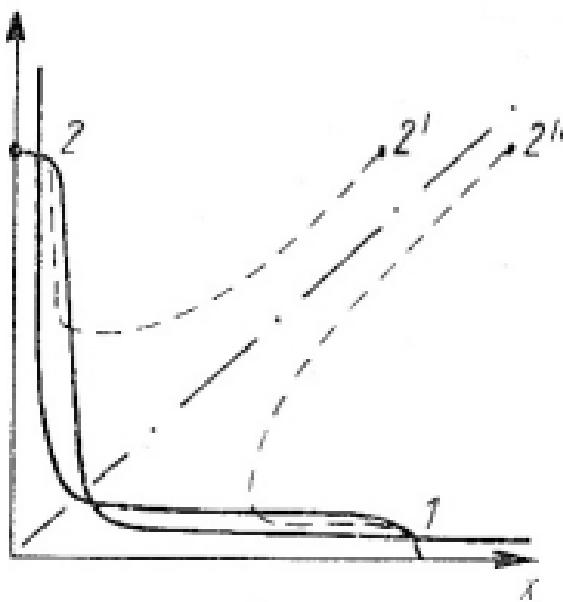
The number of stationary states depends on the parameter A :



If $A < A_{cr} = 2$, there is only one stationary state, hence no triggering is possible.

The value of $A_{cr} = 2$ corresponds to a **bifurcation**. There appear no asymptotic cycles, only multiple unstable states.

For $A > A_{cr}$, there appear three stationary states. Two of them are stable nodes and the third one is a saddle. The phase portrait is presented in the figure below. ***This system may work as a trigger.*** The separator passing through the saddle shows the border between the two regions corresponding to the two regimes of the trigger's work.

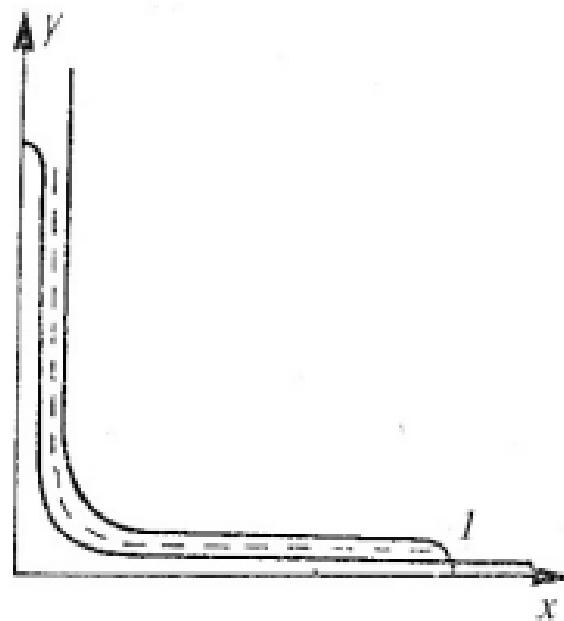


How to force a transition from one regime to the other?

Basically, in two ways. First, we may increase the concentration of one of the products directly inside the cell. It corresponds to moving the system to another state, e.g. from 2 to $2'$. If the dose is insufficient, the system will revert to its original state. If the separator will be crossed, as in $2''$, it will follow a trajectory leading to the new state. From the point of view of biology, we may call this method ***specific***, because it requires adding specific enzymes to the cells.

Another way of affecting the system is to change the system's parameters, e.g. by reducing the supply of one of the substrates. This method is called ***non-specific***; it is easier to control the concentration of substrates than the content of specific substances within a cell. The system's phase portrait is thus deformed. Let's look at the details.

Affecting a substrate's concentration is equivalent to introducing asymmetry in the system. So far, we have dealt with symmetric systems ($\mathbf{A}_1 = \mathbf{A}_2 = \mathbf{A}$, etc). But the general case is more interesting. An example of an asymmetric phase portrait is shown below.



The saddle point merges with one of the stable nodes and they both disappear (e.g. when \mathbf{A}_1 remains constant while \mathbf{A}_2 decreases).

When the concentration of one of the substrates is modified, the phase portrait may look as in the figure above and the system will tend to the only stationary point left. When the system's state is close to the point **1**, the substrate's original concentration (and thus A_2) can be restored. The phase portrait will change back to normal, but the system will remain in the new state. Hence, a switching has occurred.

A trajectory corresponding to such a case is shown in the figure (dashed line). As can be seen, it passes close to the isoclines. It means that initially the concentrations of the metabolites corresponding to the old state decrease, and only then those of the new state increase. Between the two regimes there is a ***lag period***, during which a cell is in neither of the regimes.

To go back to the original problem – ***the differentiation of cells*** – we may make analogies between evolution of a fertilized egg and the parameters of a trigger system.

The initial, rapid division of the original cell corresponds to the state, described by a single stationary point. It is equivalent to the phase portrait obtained for $A < A_{cr}$. As the metabolism of the ensemble of cells accelerates, the value of A gradually increases. At some point it will reach the critical value A_{cr} and thus it will find itself in the unstable state of bifurcation, in which any factor may induce the actual differentiation.

The process presented above may be perceived as an ***elementary act of differentiation***. A whole organism would require many of these processes. In principle, we may assume that an ensemble of cells which has successfully completed an act of differentiation, becomes a starting point for another process of this kind on a higher level.

The analysis of the trigger model indicates a possibility of ***self-organization of cellular development***. The basic mechanism of self-organization consists in a marked increase of existing stationary states. The final result of self-organization depends mainly on the parameters of the model, i.e. on the factors, determined by properties of enzymes, coded by DNA. Moreover, each of these parameters is a function of properties of various enzymes. Therefore, ***information about each act of differentiation is coded in many different structural genes***.

This kind of information, dispersed among many different structural elements, may be regarded as ***distributed coding***.

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.

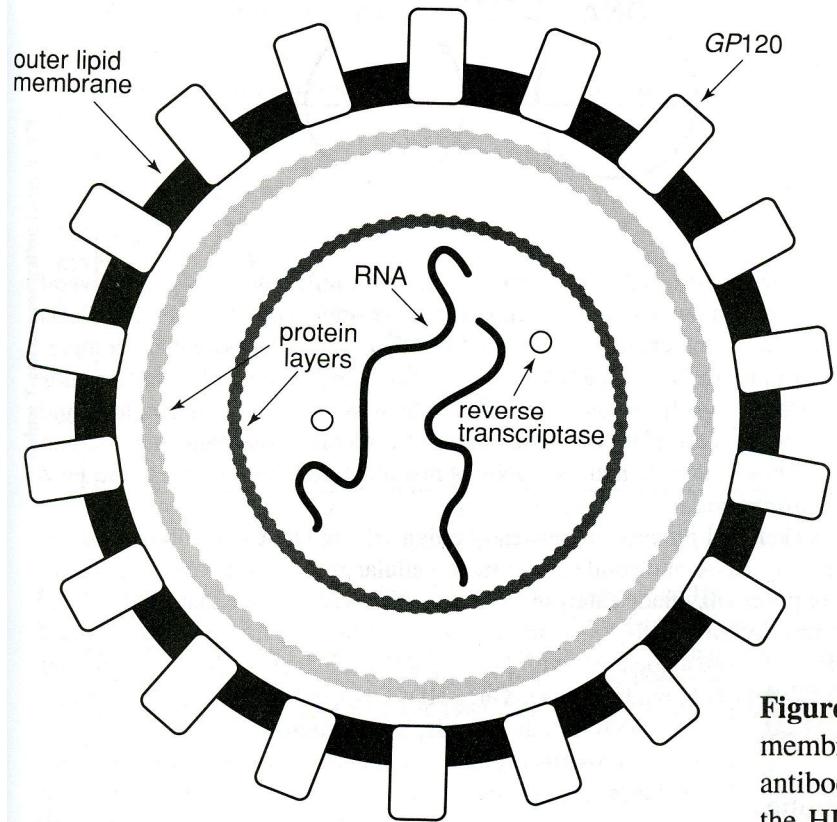


Figure 10.3.1 A model of the Human Immunodeficiency Virus (HIV). The outer membrane of the HIV is derived from the outer membrane of the host cell. Thus, an antibody against that part of the HIV would also act against the host cell. Note that the HIV carries copies of the reverse transcriptase enzyme.

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

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.

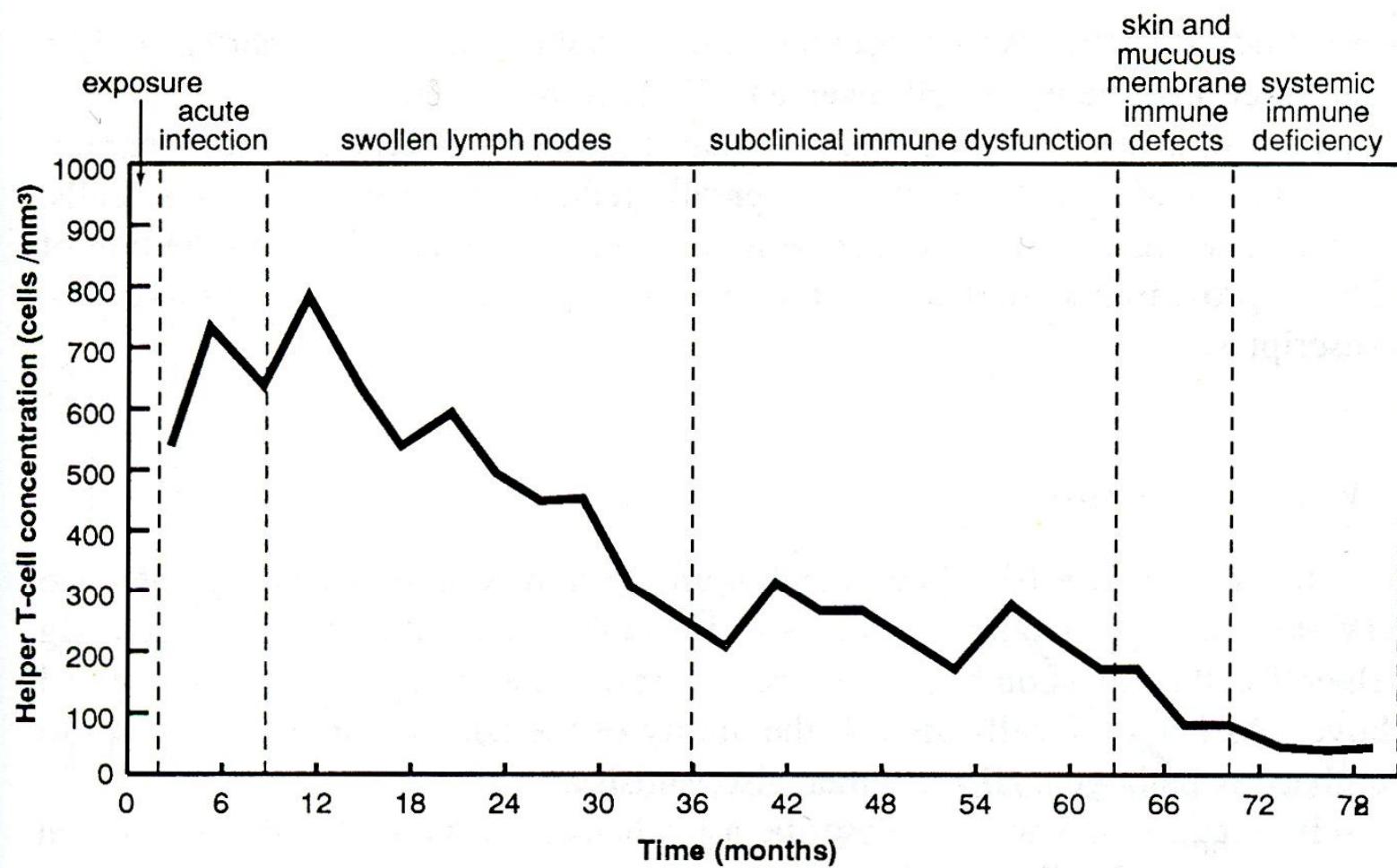


Figure 10.3.2 A graph of the helper T lymphocyte count of an HIV-infected person. Clinical symptoms are indicated along the top of the figure. Note the correlation between the decrease in T cell count and the appearance of the clinical symptoms. (Redrawn from "HIV Infection: The Classical Picture," by Robert Redfield and Donald Burke, *Scientific American*, October 1988, Vol. 259, no. 4; copyright © 1988 by Scientific American, Inc. All rights reserved.)

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*).

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.

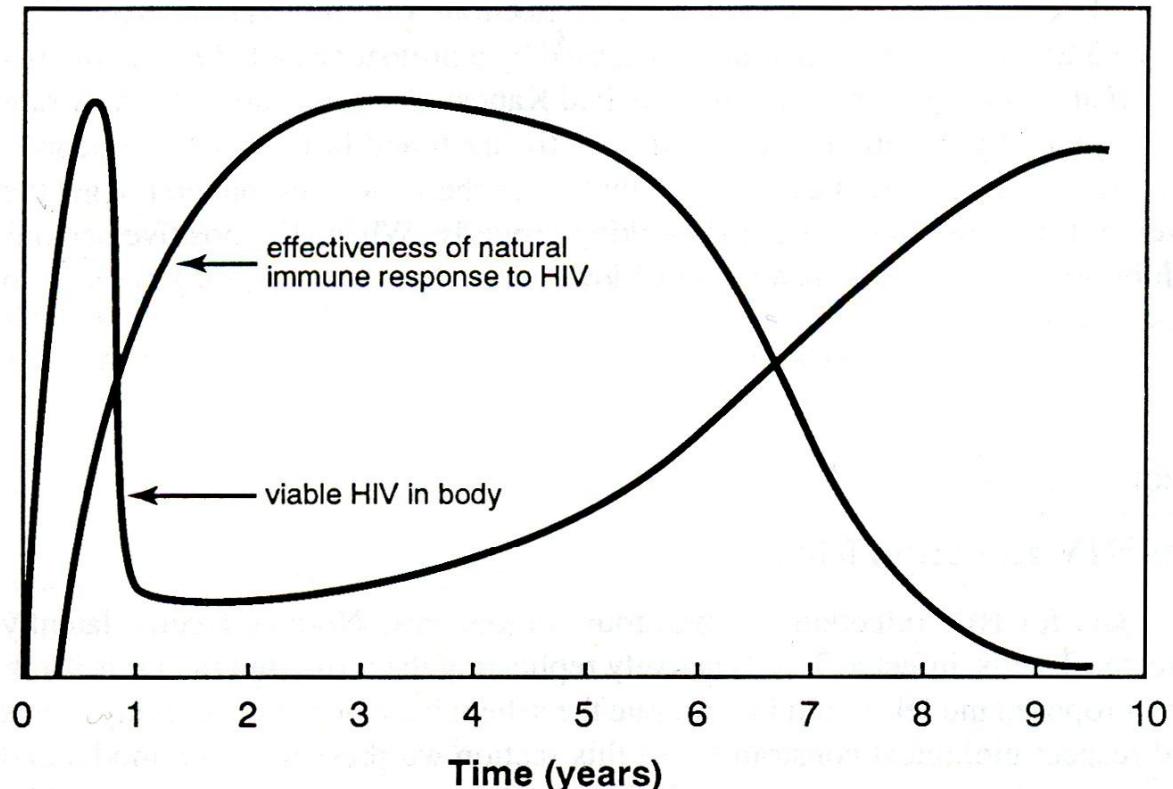


Figure 10.3.3 A graph of immune response and viral appearance versus time for an HIV-infected person. The initial infection generates a powerful immune response. That response, however, is later overwhelmed by the virus, which kills the helper T lymphocytes that are required by the humoral and cell-mediated immune responses. (Redrawn from “HIV Infection: The Clinical Picture,” by Robert Redfield and Donald Burke, *Scientific American*, October 1988, Vol. 259, no. 4; copyright © 1988 by Scientific American, Inc. All rights reserved.)

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

An HIV Infection Model

A model for HIV infection involves four components: Normal T cells, latently infected T cells, infected T cells actively replicating the 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 co-workers.

In this section we will be presenting a model for T cell infection by HIV, as described in Section 10.2 (see References [5–8]). 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 cannot increase unboundedly. Model this using a logistic term, $rT(1 - T/T_{\max})$, with per capita growth rate r (cf., Section 3.4).
- 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

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

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

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

$$\mu T_{\max} > s. \quad (10.4.2)$$

The biological implication of this statement is that when the number of T cells have 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

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

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

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

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 equation (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} ; this is our positive root T_0 calculated from equation (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

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

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

Now consider two biological situations.

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 deathrate 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. Data in Reference [6] confirm this.

Table 10.4.1 Parameters for Situation 1

Parameter	Description	Value
s	T cell from precursor supply rate	10/mm ³ /day
r	normal T cell growth rate	.03/day
T_{\max}	maximum T cell population	1500/mm ³
μ	T cell death rate	.02/day

With these data, calculate the stationary value of T_0 using equation (10.4.3)

Next calculate and display trajectories from various starting points.

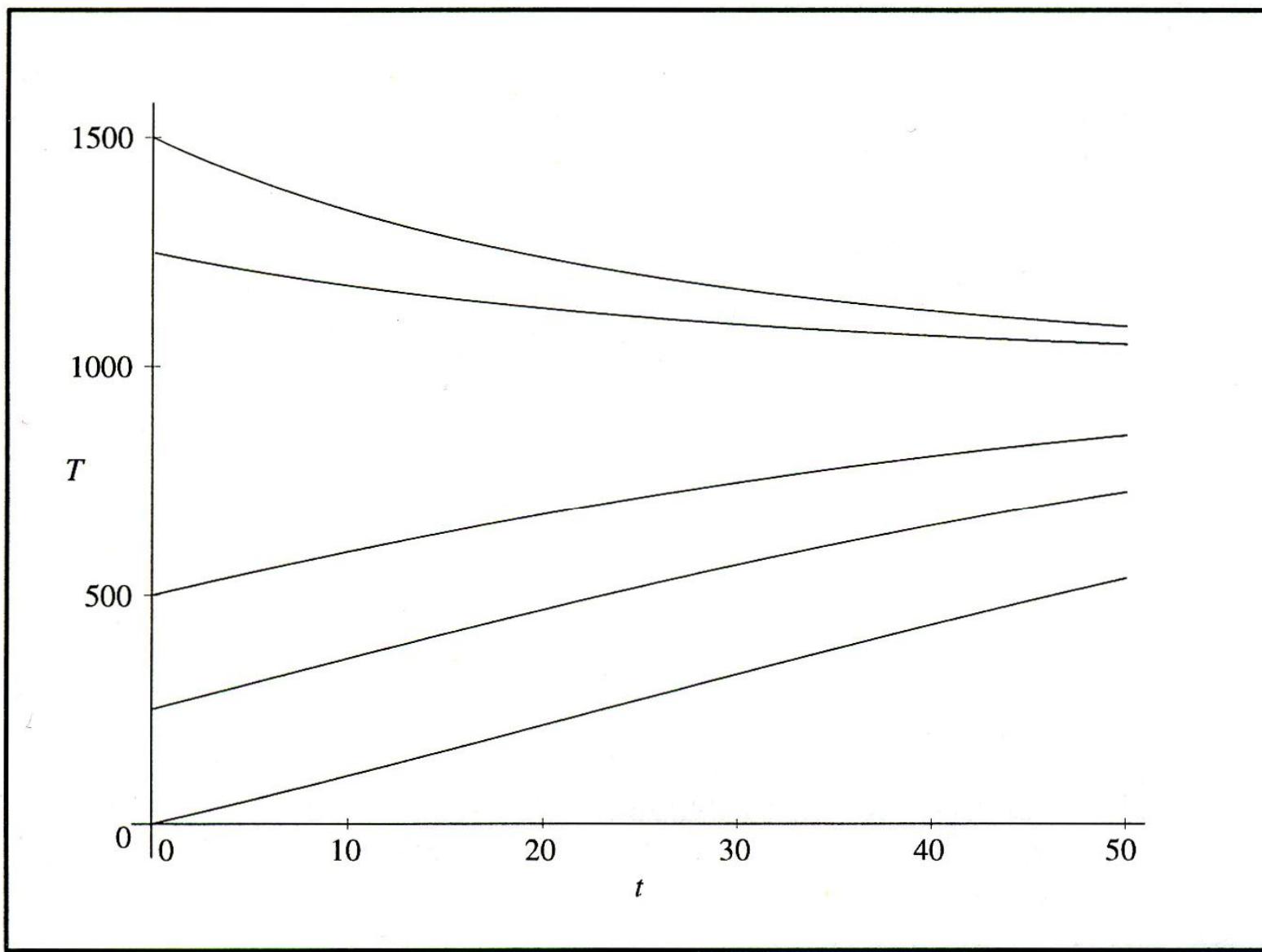


Figure 10.4.1 Time vs. number of T cells per cubic millimeter

Situation 2: Clonal Production Solution. An alternate 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 these parameters:

Table 10.4.2 Parameters for Situation 2

Parameter	Description	Value
s	T cell from precursor supply rate	0/mm ³ /day
r	normal T cell growth rate	.06/day
T_{\max}	maximum T cell population	1500/mm ³
μ	T cell death rate	.02/day

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.

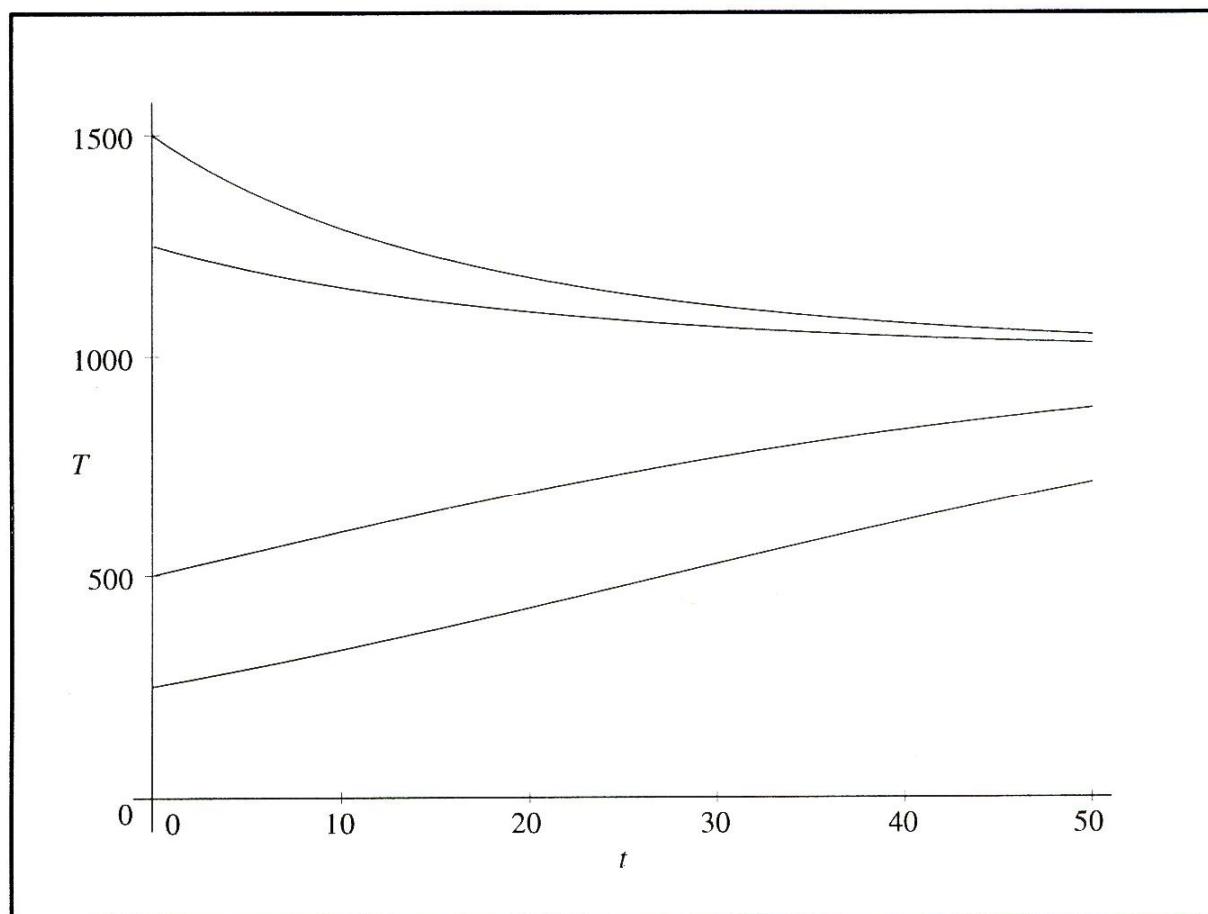


Figure 10.4.2 Time vs. T cell count with a reduced thymus function

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 De Boer [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:

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

$$\frac{dT_L}{dt} = k_1 V T - \mu T_L - k_2 T_L, \quad (b)$$

$$\frac{dT_A}{dt} = k_2 T_L - \beta T_A, \quad (c)$$

$$\frac{dV}{dt} = N\beta T_A - k_1 V T - \alpha V. \quad (d)$$

(10.4.5)

The first equation is a modification of equation (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 count 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 equation (a) but then reappear in equation (b). In addition, equation (b) 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 equation (c) 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 ,

$$\beta \gg \mu. \quad (10.4.6)$$

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 $T_L = T_A = 0$ as well and, setting these values into system (10.4.5), we see that this new model agrees with the old one, equation (10.4.1).

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 would mean that each population will increase, not decrease, at low population sizes.

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

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

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

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

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

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

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

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

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

Following Perelson, Kirschner, and De Boer [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 satisfies the differential equation obtained by summing the right-hand side of the first three equations in system (10.4.5)

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

Now suppose $T_\Sigma = T_{\max}$. Then from equation (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 $-\mu T_{\max}$, this gives

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

where equation (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, the 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, equation (10.4.5), we must set the derivatives to zero and solve the resulting (non-linear) algebraic system in four equations and four unknowns. Solving the third equation, namely $0 = k_2 T_L - \beta T_A$, for T_A gives $T_A = (k_2/\beta)T_L$, which may in turn be substituted for all its other occurrences. This reduces the problem to three equations and three unknowns. 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 Reference [6] it is shown symbolically that 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

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

In Table 10.4.1 we give values of the parameters of the system (10.4.5) as determined by Reference [6].

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	.03/day
T_{\max}	maximum T cell population	$1500/\text{mm}^3$
μ	normal/latently infected T cell death rate	.02/day
β	actively infected T cell death rate	.24/day
α	free virus death rate	2.4/day
k_1	T cells infection rate by free virus	$2.4 \times 10^{-5} \text{ mm}^3/\text{day}$
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

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