Published in final edited form as:

J Pharmacokinet Pharmacodyn. 2014 October ; 41(5): 415–429. doi:10.1007/s10928-014-9387-8.

Modeling T cell responses to antigenic challenge

Dominik Wodarz

Department of Ecology and Evolutionary Biology, 321 Steinhaus Hall, University of California, Irvine, CA 92617, dwodarz@uci.edu, Phone: 949-824-2531, Fax: 949-824-2181

Abstract

T cell responses are a crucial part of the adaptive immune system in the fight against infections. This article discusses the use of mathematical models for understanding the dynamics of cytotoxic T lymphocyte (CTL) responses against viral infections. Complementing experimental research, mathematical models have been very useful for exploring new hypotheses, interpreting experimental data, and for defining what needs to be measured to improve understanding. This review will start with minimally parameterized models of CTL responses, which have generated some valuable insights into basic dynamics and correlates of control. Subsequently, more biological complexity is incorporated into this modeling framework, examining different mechanisms of CTL expansion, different effector activities, and the influence of T cell help. Models and results are discussed in the context of data from specific infections.

Introduction

T cell responses are a crucial component of the immune system in the fight against infectious diseases [1, 2]. T cells can be broadly divided into CD4 positive helper T cells and into CD8 positive killer T cells, also known as cytotoxic T lymphocytes or CTL. CTL are immune cells that are particularly important to combat viral infections. They act by either killing infected cells or by inhibiting viral replication inside infected cells by non-lytic mechanisms. CD4 helper T cells have important regulatory roles and provide stimuli that are required for successful CTL responses and also B cell responses (immune cells that produce and secrete antibodies). The interactions between T cells and infectious agents are complex and multi-factorial, and it is difficult to predict the outcome of such dynamics and to properly understand the correlates of successful T cell mediated control of infections. In this respect, mathematical models have been very useful in complementing experimental data [3–7]. They capture a set of biological assumptions and follow them to their logical conclusions. They help to gain novel insights into the dynamics, to understand unexplained observations, and to estimate important kinetic parameters.

Mathematical models of T cell responses are the topic of this review. Emphasis will be placed on the dynamical interactions between viruses and CTL and the biological messages that the models give rise to. The article will not cover in detail the dynamics of CD4 T helper cell responses, except in their role as helpers for the development of successful CTL responses. CTL responses can be modeled at various levels of biological complexity. Simple, or minimally parameterized, models have been very useful for understanding basic principles underlying the dynamics of CTL responses, which would have been impossible to

achieve with experimentation alone. Such models, however, have important limitations because of their lack of biological detail. In contrast, more complex models have been explored that take into account more of the biology that underlies CTL responses, although rising biological complexity leads to a reduced ability to completely understand the properties of the model, analytically or otherwise. There are advantages and disadvantages to simpler and more complex models, and the exact structure of the mathematical model will depend on the particular question under investigation.

This review will start with a summary of basic virus dynamics models upon which models for CTL responses are subsequently built. First, the simplest types of CTL models will be investigated, and important biological implications that arise from them will be explored. Subsequently, additional biological details will be incorporated into this model, based on kinetic data that have become available over the years. The models and topics explored here are certainly only a subset of the large literature that exists on modeling CTL responses, and the review serves more as an introduction to the topic rather than as a comprehensive summary of all work that has been performed in this context.

Virus dynamics

In order to study the dynamics of CTL responses with mathematical models, we first need a modeling framework to describe the basic dynamics between viruses and their target cells. Virus dynamics can be described with a variety of models, depending on the questions that are being asked and on the degree of complexity that one seeks to capture [4, 5, 7, 8]. Most models of virus infection, however, are based upon the following framework [4, 5, 7, 8]. Consider three populations: uninfected, susceptible target cells, S , infected cells, I , and free virus, V . Susceptible target cells are produced with a rate λ , die with a rate d , and upon contact with virus are infected with a rate β . Infected cells produce free virus with a rate k , and free virus decays with a rate u . The dynamics can be formulated by a set of ordinary differential equations that describe the average time-evolution of these populations. They are given as follows.

$$\begin{aligned}\frac{dS}{dt} &= \lambda - dS - \beta SV \\ \frac{dI}{dt} &= \beta SV - aI \\ \frac{dV}{dt} &= kI - uV\end{aligned}\quad (1)$$

In the equation for the virus population, the term $-\beta SV$ has been omitted because it is thought to be negligible compared to the other terms. In many cases, it is realistic to assume that the free virus population turns over significantly faster than the infected cell population. In this case, the model can be simplified by assuming the free virus population to be in a quasi-steady state, giving rise to the following formulation.

$$\begin{aligned}\frac{dS}{dt} &= \lambda - dS - \beta' SI \\ \frac{dI}{dt} &= \beta' SI - aI,\end{aligned}\quad (2)$$

where β' is given by $\beta' = \beta k/u$. This system is characterized by two basic outcomes. (i) The virus population goes extinct, and the system converges towards an equilibrium where the

number of susceptible target cells are at the infection-free level. That is, $S^{(0)}=\lambda/d$; $I^{(0)}=0$. (ii) The virus successfully established a persistent infection, and the system converges to the following equilibrium. $S^{(1)}=a/\beta'$; $I^{(1)}=\lambda/a-d/\beta'$. Which outcome is observed depends on a quantity called the basic reproductive ratio of the virus [4, 9]. It describes the average number of newly infected cells generated by a single infected cell when placed in a pool of susceptible target cells. In this model, it is given by $R_0=\lambda\beta'/da$. If $R_0>1$, a persistent infection is established. In contrast of $R_0<1$, the virus population declines to extinction. The concept of the basic reproductive ratio of the virus is further explained in Figure 1.

It is important to point out that this is only one out of many different formulations that can be used to describe virus dynamics. Even on the simplest level, without incorporating further biological complexity, the model can be formulated differently. For example, the infection term $\beta'SI$ can be altered such that it saturates in the number of uninfected and/or the number of infected cells [10, 11]. While the basic outcomes tend to remain the same across such model variations, the dynamics and the approach to equilibria can be different. In the current context, we will use model (2) as a basis for exploring T cell dynamics. The reason is that it is analytically the simplest model and suffices for demonstration of general principles.

Because model (2) will be used as a basis, the notation will be changed for simplicity. Instead of β' , this parameter will just be referred to as β from now on.

The simplest models of CTL dynamics

The process of CTL activation and expansion is very complex, and no model so far has captured all aspects of this process. For model formulation, the biological complexity is reduced to a set of assumptions that are geared towards examining specific questions. This section introduces the simplest way to model CTL responses, and this type of model has been successfully used to interpret biological data. Subsequent sections will introduce more complicated models that introduce further biological realism.

The model introduced here captures the CTL response in a single variable, which is denoted here by Z . The model assumes that upon antigenic stimulation, the CTL proliferate with a rate c . In the absence of antigenic stimulation, the CTL die with a rate b . CTL are assumed to kill infected cells upon contact with a rate p . The model is thus given by the following set of ordinary differential equations, analyzed eg. in [12].

$$\begin{aligned}\frac{dS}{dt} &= \lambda - dS - \beta SI \\ \frac{dI}{dt} &= \beta SI - aI - pIZ \\ \frac{dZ}{dt} &= cIZ - bZ\end{aligned}\quad (3)$$

The parameter c has also been referred to as the CTL responsiveness [12]. It can be thought of capturing the many regulatory processes that drive the process of CTL expansion. Note that naïve CTL are produced by the thymus with a certain rate. This production term has been ignored in this model. Instead, it is assumed that a certain number of naïve CTL exist before the host becomes infected, ready for expansion upon infection. This renders the model analytically more tractable.

Model (3) is similar to Lotka-Volterra type predator-prey models, where CTL correspond to predators and infected cells correspond to prey [4]. How realistic this is can be subject of debate and will be addressed further below. However, on a basic level, this model has been useful to shed light onto the dynamics of CTL responses to viral infections.

Assume that the basic reproductive ratio of the virus $R_0 > 1$, such that the virus can successfully establish an infection. Now we observe two possible outcomes. If $c(\lambda/a - d/\beta) < b$, then the CTL response fails to become established. This is because the CTL responsiveness, c is too low to ensure sustained CTL expansion. This outcome is thus described by the following equilibrium expressions:

$$S^* = \frac{a}{\beta}, I^* = \frac{\lambda}{a} - \frac{d}{\beta}, Z^* = 0.$$

On the other hand, if $c(\lambda/a - d/\beta) > b$, then a sustained CTL response develops, and the system converges to the following equilibrium.

$$S^* = \frac{\lambda c}{dc + \beta b}; I^* = \frac{b}{c}; Z^* = \frac{c(\beta\lambda - ad) - ab\beta}{p(dc + b\beta)}$$

In a typical simulation of this system (Figure 2), virus first grows and stimulates the CTL. The CTL population expands and fights the virus population. Damped oscillations occur and the system approaches its steady state. Virus load at the steady state is determined by two parameters. The rate of CTL proliferation or CTL responsiveness, c , and the death rate of CTL in the absence of antigenic stimulation, b . The higher the CTL responsiveness (higher value of c), and the longer the life-span of CTL in the absence of antigen (lower death rate of CTL, i.e. lower value of b), the lower virus load. These are thought to be properties of a CTL memory response, and this concept is developed further in [13]. Because the model is deterministic, virus load can never be reduced to zero. Instead, however, it can be reduced to infinitely low values which correspond to virus extinction in practical terms (average virus load is reduced to less than one virus particle).

The approach to equilibrium in model (3) can involve pronounced oscillations, especially for larger values of c . This kind of unstable dynamics is not typically observed in data that track CTL responses and virus load over time. As with the basic virus infection model (2), however, the dynamics can depend on the exact formulation of the model. Thus, variations of this basic model have been explored. An example is saturated CTL expansion. This is expressed by the following differential equation [14].

$$\frac{dZ}{dt} = \frac{cIZ}{Z+1} - bZ.$$

The level at which CTL expansion saturates is expressed in the variable ε . The condition for the establishment of the CTL response is the same as in model (3). If a sustained CTL response becomes established, the system converges to the following equilibrium.

$$S^* = \frac{\beta b(\epsilon a - p) - pcd + \sqrt{[\beta b(\epsilon a - p) - pcd]^2 + 4\beta^2 b \epsilon \lambda c p}}{2\beta^2 b \epsilon}$$

$$I^* = \frac{\lambda - dS^*}{\beta S^*}$$

$$Z^* = \frac{\beta S^* - a}{p}$$

This model has similar properties compared to model (3). A higher CTL responsiveness, c , and a longer life-span of the CTL in the absence of antigen (lower value of b), correlate with lower virus load. In addition, however, virus load is also a function of viral parameters, most importantly the replication rate of the virus, β . An increase in the parameter β leads to an increase in viral load up to an asymptote. Also, if the CTL-mediated anti-viral activity converges to zero ($p \rightarrow 0$), then the number of CTL does not increase to infinity, but only up to a defined value. Thus, inclusion of the saturation term eliminates some biologically unrealistic features of model (3). However, this comes at the cost of having more complicated equilibrium expressions which make the model less tractable by analytical means.

If saturation already occurs at lower numbers of CTL (high value of ϵ), it is possible to use a simpler version of this model which is given by [15]

$$\frac{dZ}{dt} = cI - bZ$$

In this model the rate of CTL expansion is simply proportional to the amount of antigen, but not to the number of CTL. The rate of CTL expansion is therefore weakened. In this model, the CTL response can never go extinct. Instead, if the CTL responsiveness, c , is low, the CTL persist at low levels. Therefore, if $R_0 > 1$, there is only one stable equilibrium, and this is given by the following expressions.

$$S^* = \frac{\beta b a - pcd + \sqrt{[\beta b a - pcd]^2 + 4\beta^2 b \lambda c p}}{2\beta^2 b}$$

$$I^* = \frac{\lambda - dS^*}{\beta S^*}$$

$$Z^* = \frac{\beta S^* - a}{p}$$

These equilibrium expressions have qualitatively the same properties as those of the saturation model discussed above. There are several other variations to describe CTL dynamics, and they all lead to more realistic features compared to model (3). Since they will not be used in this article, however, they will not be discussed here, see e.g. [16]. A note of caution: while these models do exhibit more realistic behaviors, the saturation terms are arbitrary and are not based on any specific biological detail. This has to be kept in mind when interpreting modeling results.

Different CTL subpopulations

The models discussed so far capture the CTL in a single population, Z . In reality, however, the population of CTL can be divided into at least two subpopulations: CTL precursors or

CTLp and CTL effectors or CTLe [17]. CTLp do not have any antiviral activity, while CTLe do have antiviral activity. Naïve CTL (which have never seen antigen before), exist as precursors. When they become stimulated by antigen, the population of CTLp expands. This culminates in the differentiation into CTL effectors which fight the virus. Memory CTL are again precursor CTL without antiviral activity. In order to attain antiviral activity, the memory CTL need to be stimulated again.

Various attempts have been made to model effector and memory cells explicitly. Initial work assumed that naïve CTL become an expanding population of memory precursor cells, which in turn differentiate into effector CTL [13, 18–21]. This work was subsequently criticized because researchers interpreted experimental data to paint a different picture [22]. According to this revised scenario, naïve cells activate and undergo clonal expansion to give rise to effector cells first. Subsequently, they can either die or differentiate into effector memory and central memory cells [23, 24]. Such a model has different properties and is characterized by different dynamics. In contrast to this notion, however, a recent study re-examined this issue using *in vivo* fate mapping and mathematical analysis to distinguish between all possible CTL differentiation pathways. This study concluded that naïve CTL give rise to relatively slowly expanding central memory precursors, which in turn give rise to faster expanding effector memory cells and effector cells [25]. This result is much closer to the assumptions made in the initial mathematical models that distinguished between precursor and effector CTL [13, 18–21]. Importantly, this history highlights the difficulties associated with rejecting models based on experimental data. Different experimental studies can come to different conclusions, and it is important to keep in mind the complexity and consequent uncertainty of the biological system. Furthermore, insights and interpretation of experiments typically evolve over time, and this has to be kept in mind for model interpretation.

With this in mind, the mathematical model will be summarized that assumes a linear differentiation pathway from native to memory precursor to effector cells. For simplicity, the model includes two populations: the memory precursors (W), and the effector CTL (Z). Naïve cells are not taken into account explicitly. Instead, the model assumes that an initial number of CTL is present that have just been activated from a naïve state. The model is thus given by the following set of ordinary differential equations.

$$\begin{aligned}\frac{dW}{dt} &= cIW(1 - q) - bW \\ \frac{dZ}{dt} &= cqIW - hZ.\end{aligned}\quad (4)$$

Upon contact with antigen, CTLp proliferate, and this is described by the term cIW . Differentiation into effectors is described by $cqIW$. The parameter c describes the rate of CTL expansion, as before. The parameter q is the probability that the precursor CTL will differentiate into an effector CTL. CTL precursors die at a rate b , and effectors die at a rate h . In this model, CTL memory lies in the population of precursors, W . If the life-span of the CTLp is long in the absence of antigen (low value of b), then the CTLp population persists at elevated levels for prolonged periods of time after acute infection, as observed *in vivo*. On

the other hand, the life-span of the effector CTL is assumed to be short (relatively high value of h), as prolonged effector activity can have damaging consequences for the host.

Assume that the basic reproductive ratio of the virus is greater than one. A sustained immune response can become established if $c(1-q)(\lambda/a-d/\beta) > b$. In this case, the system converges to the following equilibrium.

$$\begin{aligned} S^* &= \frac{\lambda c(1-q)}{dc(1-q)+b\beta} \\ I^* &= \frac{b}{c(1-q)} \\ W^* &= \frac{Z^* h(1-q)}{bq} \\ Z^* &= \frac{\beta S^* - a}{p}. \end{aligned}$$

According to these expressions, virus load is reduced by a high responsiveness and a long life-span of the memory CTLp. Therefore, this model indicates that the memory phenotype of the CTL is crucial for virus control. The level of virus load is independent from the parameters of the effector CTL. These notions are further developed in [13].

Note that the approach to the equilibrium can be more complex compared to the simpler models discussed earlier in this chapter. For low values of b (long life-span of CTL in the absence of antigen), the system takes a long time to equilibrate. After an initial transient phase, the dynamics lead to a quasi-equilibrium $\hat{y}$ at which virus load decays only at a very small rate. Virus load at the quasi-equilibrium is higher than at the true equilibrium, but has similar properties. Hence, virus load at the quasi-equilibrium can be approximated by $\hat{y} = \alpha y^*$, where $\alpha > 1$. After a time period of $1/b$, the system approaches the true equilibrium, y^* . This can have implications for the control of persistent infections at low levels [13].

Memory CTL and protection against re-infection

Model (4), distinguishing between memory and effector CTL, can also be used to study correlates of protection against re-infection [21], i.e. to identify which properties of the response do or do not contribute to protection. Immunological memory is generated when a relatively large population of memory cells remains after the infection has been resolved. This phenomenon is also observed with CTL, and the ability of memory cells to protect against re-infection has been discussed [26–28]. In model (4), we can ask to what degree an elevated number of memory CTL (high levels of W) protects against initial virus growth upon infection. The number of effector cells is not assumed to be elevated because long-term memory is thought to persist in the precursor population. Since effector cells are required to combat the infection, the virus will be able to grow without inhibition at the beginning of the secondary challenge. Thus, protection against secondary challenge depends mainly on the amount of time required for the CTL to migrate to the focus of infection and to differentiate into effector cells. In our model, this is captured in the parameter cq , the rate of differentiation into effector cells. Figure 3 shows the effect of increased memory CTL abundance on the size of the peak virus load upon secondary challenge, assuming different rates of effector cell production (cq). Increased memory CTL levels are only protective if effector function is produced sufficiently fast (large cq) once the pathogen has entered the

host. Strikingly, if there is a longer time delay in the production of effector function (small cq), increasing the abundance of memory CTL even by four orders of magnitude does not lead to a significant reduction of the peak virus load and thus of clinical symptoms (Figure 3). This might contribute to the finding that CTL-based vaccines have not been very effective in a variety of different viral infections, a prominent example being HIV [29].

Programmed CTL proliferation

The models discussed so far assumed that CTL require continuous antigenic stimulation for cell division and proliferation. That is, if antigenic stimulation was withdrawn, the CTL would stop to proliferate. However, this notion might not be true. Instead, a single encounter with antigen might trigger a program of CTL expansion and differentiation which is independent from further antigenic stimulation events [30–33] (Figure 4). This is referred to as programmed proliferation. Even if antigen is withdrawn at any time during the expansion process, the CTL proliferation and differentiation program can still be completed. If this process does not result in the clearance of the pathogen, the memory CTL are reactivated and further expansion occurs. It has been argued that the existence of the program significantly alters the properties of CTL dynamics, and that conclusions reached by earlier models might have to be revised. Hence, it is important to construct a model of programmed CTL proliferation and to compare its properties to those of the continuous stimulation models discussed above. This is done as follows.

The mathematical model which describes programmed CTL proliferation [34, 35] contains the following variables: resting and memory CTL, M ; newly activated CTL, M_0 ; activated CTL which have undergone i ($i=1..n$) cell divisions, M_i ; and effector CTL, Z . It is given by the following set of differential equations.

$$\begin{aligned} \frac{dZ}{dt} &= 2rM_{n-1} - \gamma Z - \delta Z, \\ \frac{dM_{n-1}}{dt} &= 2rM_{n-2} - rM_{n-1}, \\ &\dots \\ \frac{dM_1}{dt} &= 2rM_0 - rM_1, \\ \frac{dM_{n-1}}{dt} &= 2rM_{n-2} - rM_{n-1}, \\ \frac{dM_1}{dt} &= 2rM_0 - rM_1, \\ \frac{dM_0}{dt} &= \alpha IM - rM_0, \\ \frac{dM}{dt} &= \gamma Z - \alpha IM - \epsilon M. \end{aligned} \quad (5)$$

We start with a population of resting CTL, denoted by M . Upon antigenic encounter, these cells become activated at a rate αIM . These activated cells are denoted by M_0 . Following activation, the CTL undergo n rounds of proliferation, and this is independent from antigenic stimulation. Proliferation occurs with a rate $2rM_i$, where M_i denotes CTL which have undergone i divisions ($i=1..n-1$). The factor 2 is included to describe division. The n th division gives rise to effector cells, denoted by Z . They can kill infected cells. Effectors die at a rate δZ and differentiate back into memory cells at a rate γZ . Memory cells are again denoted by M , since they are resting. Thus, in contrast to model (4), this model (5) assumes that memory cells can be generated from effectors, and we will compare the resulting model properties with those of the previously explored models. If the virus is not cleared after this

first round of programmed proliferation, the memory cells are re-activated according to the same principles as described above and undergo another round of programmed proliferation. The only difference is that memory cells are characterized by an elevated activation and proliferation rate compared to naive cells (higher values of α and r , respectively).

The acute infection dynamics are obviously different in the program model compared to those observed in models which assume continuous antigenic stimulation. This is because during this phase, the response is on autopilot, and is not influenced by antigen. The acute phase of infection can be defined by the first round of programmed CTL proliferation which ends with the generation of memory cells (that is, memory cells are not restimulated). Here we concentrate on the long-term dynamics. In this case, there is persistent infection and restimulation of memory cells. That is, the virus is not cleared after the first round of programmed proliferation. The properties of the program model will be compared to those of the models which assume continuous antigenic stimulation in this context.

Recurring rounds of CTL proliferation will be induced, and the system will eventually converge towards a steady state. Virus load at this steady state determines the degree of virus control.

The equilibrium expressions are given as follows.

$$\begin{aligned} S^* &= \frac{a + g I^* M^*}{\beta}, \\ I^* &= \frac{\epsilon}{(\frac{2^n \gamma}{\gamma + \delta} - 1) \alpha}, \\ M^* &= \frac{1}{g I^*} \left(\frac{\lambda}{d/\beta + I^*} - a \right), \\ Z^* &= g I^* M^*, \\ M_0^* &= \frac{\alpha P}{r} M^*, \\ M_i^* &= 2^i M_0^*, 1 < i < n - 1, \end{aligned}$$

where $g = (2^n p \alpha) / (\gamma + \delta)$.

Virus load is determined by a number of immunological factors. A high activation rate of memory CTL (high value of α) and a long life span of memory CTL in the absence of antigen (low value of ϵ) contribute to low virus loads. Also, the higher the number of CTL proliferations (higher value of n), the lower virus load. The number of CTL at the steady state is mainly determined by the rate of anti-viral activity, p . The lower the rate of CTL-mediated anti-viral activity, the higher the number of CTL. Interestingly, these properties are almost identical to the properties derived from mathematical models which assume that CTL proliferation requires continuous antigenic stimulation. In fact, the continuous stimulation models are a special case of the programmed proliferation model in which the program is executed with a very fast rate. This is shown mathematically as follows.

Assume that upon antigenic stimulation, the program is executed at a very fast rate (high values of r), and that the turnover of activated and effector CTL is significantly faster than the turnover of memory cells. In this case, the programmed proliferation model can be reduced to a single equation for the memory CTL. It is given by

$$\frac{dM}{dt} = \left(\frac{\gamma 2^n}{\gamma + \delta} - 1 \right) \alpha I M - \epsilon M.$$

This is basically the same equation as the simplest continuous stimulation model (3), where the CTL responsiveness is given by

$$c = \left(\frac{\gamma 2^n}{\gamma + \delta} - 1 \right) \alpha.$$

Therefore, the single CTL population in the continuous stimulation model should be considered as the population of memory CTL. The effector CTL population can be assumed to be in quasi steady state and is given by $Z = 2^n \alpha I M / (\gamma + \delta)$. Consequently, the rate of killing is described by $p I^2 M$, where $p = 2^n \alpha / (\gamma + \delta)$. The killing term is proportional to the square of virus load (I) because the generation of effector cells from memory cells is proportional to virus load. In the simple continuous stimulation model (3), the killing term is only linearly proportional to virus load because the model does not distinguish between memory and effector CTL. The more complicated continuous stimulation model (4), which distinguishes between memory and effector CTL, has the killing term essentially proportional to the square of virus load.

Given the similarities in the steady state properties of the programmed proliferation and the continuous stimulation models, we ask the question why programmed proliferation exists. The answer is that the equilibrium outcome of the model does not tell the whole story (Figure 5). Instead, the dynamical approach to the equilibrium provides interesting insights. We compare the properties of programmed proliferation, model (5), to those of continuous antigenic stimulation model (3). We distinguish between two scenarios. First we assume a strong CTL memory response which gives rise to a very low virus load at equilibrium (practically clearance). Then we assume a weaker CTL response which correlates with the persistence of higher virus load at equilibrium.

Assume that the CTL response is strong (Figure 5i). Consider the continuous stimulation model first. Initially, the CTL response can be very efficient at stopping viral growth and reducing virus load. This is because higher virus load increases the rate of CTL proliferation. As virus load declines, however, the effectiveness of the response becomes greatly diminished. This is because generation of effectors requires constant antigenic stimulation, and the amount of antigen is low. Consequently, the dynamics enter a phase where virus load settles at a level which is significantly higher than the predicted equilibrium and where virus load declines at a very slow rate (Figure 5i, quasi-equilibrium discussed above). Now, consider the programmed proliferation model. In this case, CTL divisions are independent from antigenic stimulation. This provides an initial disadvantage: as virus load grows, the increased level of antigenic stimulation does not result in faster CTL expansion and the virus can more easily grow to high levels and cause acute pathology. As virus load is reduced to low levels by the CTL, however, the CTL can keep dividing despite the small amounts of antigenic stimulation. Thus, in contrast to the continuous stimulation

model, production of effectors does not slow down abruptly as virus load drops. Consequently, CTL-mediated pressure is maintained at low virus loads and this results in efficient reduction of the virus population to very low levels or extinction. Thus, clearance can occur before the system converges to an equilibrium (Figure 5i). According to these arguments, we observe a tradeoff between the ability of the CTL to clear an infection and the ability of CTL to reduce acute phase symptoms. If the CTL are more efficient at virus clearance, they are less efficient at containing acute virus load, and vice versa. Thus, to optimize the fitness of the host, there should be enough programmed divisions to ensure clearance, but no more such that acute pathology is limited. We hypothesize that the 7–10 antigen-independent CTL divisions observed in experimental data represent this optimum.

Now assume a weaker CTL memory response (Figure 5ii). In this case, equilibrium virus load is higher which can correspond to persistent infection. The same equilibrium is reached, both in the continuous stimulation and the programmed proliferation model. The outcome of the dynamics does not depend significantly on these model differences. Thus, if the CTL fail to resolve the infection, the continuous stimulation and the programmed proliferation models give rise to similar predictions.

In summary, the process of programmed CTL proliferation can enhance the ability of the response to clear viral infections because it allows elevated CTL effector activity to persist at low virus loads. In the context of persistent infections, however, the properties of programmed proliferation and continuous stimulation are very similar. Therefore, it is likely that results obtained from continuous stimulation models regarding CTL responses against persistent infections remain robust in the context of programmed proliferation. Many of the results which are based on continuous stimulation models are therefore valid.

Lytic versus non-lytic effector activity

The model explored so far assumed that CTL act by killing infected cells. It is clear, however, that CTL also secrete soluble factors that can prevent infection or inhibit viral replication inside cells [36–39]. In the context of some infections, such non-lytic CTL activity has been thought to be more important than the lytic component [40–42]. In fact, non-lytic CTL activity can be vital if CTL-induced pathology should be prevented in the context of viral infections such as in Hepatitis B and C virus infections [43, 44].

The following describes a modification of model (3) to include both lytic and non-lytic CTL activity [15]. As before, CTL-mediated killing is described by the term pIZ . In addition, it is now assumed that CTL reduce the rate of viral replication, and this is described by the expression $\beta SI/(qZ+1)$. Hence, the parameter p expresses the strength of the lytic component, while the parameter q expresses the strength of the non-lytic component of the CTL response. The model is thus described by the following set of differential equations.

$$\begin{aligned}\frac{ds}{dt} &= \lambda - dS - \frac{\beta SI}{qZ+1} \\ \frac{dI}{dt} &= \frac{\beta SI}{qZ+1} - aI - pIZ \\ \frac{dZ}{dt} &= cI - bZ\end{aligned}\quad (6)$$

The model has similar properties as model (3), so a full analysis will not be provided here. Instead, some biological insights that arise from the model will be discussed. When discussing virus control so far, the focus was on virus load, and to what degree CTL responses can reduce the amount of virus. Another aspect, however, can be equally important, and this is the number of tissue cells that remain during the infection and during the activity of the CTL response. If CTL-induced killing significantly reduces the number of tissue cells, pathology can be observed, brought about directly by CTL activity. This is called CTL-induced pathology or immunopathology [45, 46]. Hence, in the current context, the number of tissue cells that remain during a CTL response at equilibrium (as a measure of pathology) will be considered in addition to virus load. The distinction will be made between non-cytopathic viruses (those that do not reduce the death rate of target cells) and cytopathic viruses (those that cause significant cell death as a consequence of replication).

First consider non-cytopathic viruses. The most famous example is Lymphocytic Choriomeningitis Virus (LCMV), which does not kill their target cells at all [47–50]. Similar considerations apply to viruses that cause only limited amounts of cell death as a consequence of replication. The outcomes for this case are shown in Figure 6. According to this picture, both lytic and non-lytic responses can successfully reduce virus load. However, the effect on the total number of target cells depends on the replication rate of the virus. If the viral replication rate is relatively low, no significant tissue pathology occurs whether non-lytic responses accompany the lytic activity or not (Figure 6i). The situation is different for faster replicating viruses (Figure 6ii). Now, pronounced tissue pathology can be observed if CTL-mediated lysis is the only activity exerted by CTL. Faster replication leads to the infection of more cells, and ongoing CTL-mediated killing leads to CTL-induced pathology. This effect is alleviated if CTL also act by non-lytic mechanisms. The non-lytic activity serves to slow down the rate of viral replication, and hence to avoid CTL-induced pathology. Therefore, for faster replicating non-cytopathic or weakly cytopathic viruses, a combination of lytic and non-lytic activity is required to successfully control the virus. Note, that while non-lytic activity can come from CTL, a similar effect could in principle also come about by a combination of lytic CTL and antibodies. For LCMV, the soluble cytokine IFN- γ has been shown to reduce the rate of viral replication. With the slowly replicating Armstrong strain, analysis revealed that although IFN- γ -deficient mice infected with this strain did not show symptoms of disease, the infection was not controlled completely and significant levels of virus could be demonstrated in spleen and lungs months after infection [51, 52]. In these mice, an equilibrium was established describing persistent LCMV replication controlled by an ongoing CTL response. Because virus load was kept at relatively low levels, pathology was virtually absent [51–53]. This observation is in agreement with the theory presented here. Because the virus replicates at a slow rate, the model predicts that lack of non-lytic effector mechanisms will only result in a small loss of virus control and lack of severe immunopathology. The situation is different with faster replicating LCMV strains. IFN- γ -deficient mice infected with LCMV Traub quickly lose control of the infection despite the presence of efficient lytic effector mechanisms. In contrast to wild-type mice, a relatively large fraction of infected IFN- γ $-/-$ mice succumbed to immunopathology caused by a lytic CTL response [53]. This is, again, in agreement with theoretical predictions. Because the virus replicates at a fast rate, soluble factors are required

to significantly slow down the replication kinetics of the virus to avoid immunopathology. The absence of soluble mediators augments CTL-induced tissue damage and death of the host.

Next, consider viruses that are more strongly cytopathic (Figure 7). Now, either a lytic response alone, or a non-lytic response alone can successfully fight the infection without causing significant levels of tissue pathology. A cytopathic virus kills the target cells at a relatively fast rate and thus causes pathology by itself in the absence of CTL. In such a scenario, an increase in the death rate of infected cells by CTL likely lowers the degree of pathology, because the death rate of infected cells increases sufficiently such that the overall spread of the virus becomes slow. For an in depth analysis of the relationship between the virus-induced death rate of infected cells, the CTL-induced death rate of infected cells, and pathology, see [54]. An example of a cytopathic virus is influenza infection in mice [55]. Recovery from murine influenza virus infection has been shown to require intact T-cell responses [55–57]. More specifically, experiments have revealed that both CD4+ and CD8+ T cells can promote recovery through independent mechanisms [55–57]. In the absence of CD8+ T cells, the infection can be resolved by a CD4+ T-cell-dependent antibody response [58]. Absence of CD4+ T cells or B cells also does not result in loss of virus control [59, 60]. Experiments have shown that CD8+ T cells can resolve the infection through a lytic mechanism, mediated either by perforin or Fas [61]. The result that both lytic and non-lytic effector mechanisms can independently clear influenza infection in mice is in agreement with the theoretical considerations presented here. Because the virus is cytopathic, both a sufficient increase in the death rate of infected cells and a decrease in the rate of viral replication are expected to have a beneficial effect on the host and lead to resolution of the disease. With cytopathic viruses, a collaboration between both types of effector is less likely to be required to ensure resolution of the disease, especially if the virus challenge is not overwhelming.

CD4 T cell help and CTL responses

In the model explored so far, the rate of CTL expansion was determined by the CTL responsiveness parameter c . This parameter can be thought to phenomenologically include all the factors that contribute to the regulation of CTL responses. A particularly important regulatory component are CD4 T helper cell responses [62–65]. T helper cells interact with antigen presenting cells (APC) to activate them, and the activated APCs interact and activate CTL. This process results in the activation of the CTL and in the consequent response. The importance of helper T cells is evident in diseases in which this help is compromised. Most prominently, this occurs in human immunodeficiency virus (HIV) infection, where the virus infects and kills helper T cells. The interactions between helper T cells, APCs, and CTL have been formulated in terms of kinetic models, and ODE formulations have been derived [66]. According to this, the CTL dynamics explicitly taking into account T cell help can be formulated by the following equation.

$$\frac{dZ}{dt} = \frac{c \in XIZ}{1 + \in X} - bZ, \quad (7)$$

Where the variable X denotes the number of helper T cells. The rate of CTL activation and proliferation is thus a saturating function of the number of helper cells with $1/\varepsilon$ as the half saturation constant. In the presence of large amounts of help, the rate of CTL proliferation approximates cI . The level of help is given by the number of helper cells, X , as well as the efficacy of those helper cells, ε . The higher the efficacy of help, ε , the lower the number of helper cells, X , required to induce maximal stimulation of the CTL response.

In this model, the CTL response becomes established if $\varepsilon X > \frac{b}{(c\tilde{I} - b)}$, where $\tilde{I}$ denotes virus load in the absence of a CTL response. In other words, the CTL response only becomes established if the amount of CD4 cell help lies above a critical threshold. This result makes sense in that an immune response is wasted when triggered by too low concentrations of antigen. Equilibrium virus load in the presence of CTL is given by

$\hat{I} = \frac{b(1+\varepsilon\hat{X})}{c\varepsilon\hat{X}}$. As shown in Figure 8, an increase in the amount of help reduces virus load down to an asymptote, at which the helper-induced stimulation of the CTL response has reached its maximum. At the asymptote, $\hat{I} = b/c$.

Conclusion

The article has reviewed mathematical models of CTL responses, starting with the simplest possible model and introducing further biological realism into this framework. While this provides a flavor of the mathematical approaches to studying T cell dynamics, this is by no means exhaustive. More complex models have been analyzed in a variety of settings. Examples are given as follows. Some modeling approaches included an explicit description of the process of antigen-driven T helper cell expansion [67, 68]. Other models took into account multiple CTL clones directed against multiple viral epitopes, with implications for explaining the phenomenon of immunodominance [69, 70]. CTL models are often analyzed in the context of virus evolution, in particular, virus evolution of antigenic escape from CTL responses [71–74]. Similarly, the impairment of T cell responses in viral infections, especially HIV, has been investigated with a variety of mathematical models [20, 67, 75, 76]. The latter studies have also been used to explore implications for using drug therapies to strengthen immunity against viruses, which could improve the overall ability to control infections. These different modeling approaches have also highlighted complex and important evolutionary dynamics that might be crucial in explaining the development of disease caused by human pathogens. In addition, work has been performed to quantify various aspects of CTL dynamics, e.g. [77–88]. In general, the work developed in this context has shown that mathematical analysis can be a very important tool for gaining insights into the basic principles of T cell dynamics, for interpreting experimental data, and for defining what needs to be measured to improve understanding. At the same time, many aspects underlying these models remain uncertain, and this limits their power. The biology of T cell responses is complex, and several processes that drive T cell activation and expansion are not well understood. Obviously, model predictions depend on underlying assumptions, and this has to be kept in mind when interpreting results from mathematical studies. As progress is made in the field, the knowledge of the biological processes that

drive T cell dynamics can change and shift, as highlighted in this review. Thus, both modeling and experimental results should be viewed as a work in progress that can potentially change as more data become available.

References

1. Knipe, DM.; Howley, P. Fields Virology. 6. Lippincott Williams & Wilkins; 2013.
2. Owen, J.; Punt, J.; Stranford, S. Kuby Immunology. 7. W.H. Freeman; 2013.
3. Wodarz, D. Killer cell dynamics: mathematical and computational approaches to immunology. Springer; New York: 2006.
4. Nowak, MA.; May, RM. Virus dynamics Mathematical principles of immunology and virology. Oxford University Press; 2000.
5. Perelson AS. Modelling viral and immune system dynamics. Nature Rev Immunol. 2002; 2(1):28–36. [PubMed: 11905835]
6. De Boer RJ, Homann D, Perelson AS. Different dynamics of CD4+ and CD8+ T cell responses during and after acute lymphocytic choriomeningitis virus infection. Journal of immunology. 2003; 171(8):3928–3935.
7. De Boer RJ, Perelson AS. Towards a general function describing T cell proliferation. Journal of theoretical biology. 1995; 175(4):567–576. [PubMed: 7475092]
8. Perelson AS, Ribeiro RM. Modeling the within-host dynamics of HIV infection (Translated from Eng). BMC Biol. 2013; 11(1):96. (in Eng). [PubMed: 24020860]
9. Anderson RM, May RM. Population biology of infectious diseases: Part I. Nature. 1979; 280(5721):361–367. [PubMed: 460412]
10. Komarova NL, Wodarz D. ODE models for oncolytic virus dynamics (Translated from eng). Journal of theoretical biology. 2010; 263(4):530–543. (in eng). [PubMed: 20085772]
11. Wodarz D, Komarova N. Towards predictive computational models of oncolytic virus therapy: basis for experimental validation and model selection (Translated from eng). PLoS ONE. 2009; 4(1):e4271. (in eng). [PubMed: 19180240]
12. Nowak MA, Bangham CR. Population dynamics of immune responses to persistent viruses. Science. 1996; 272(5258):74–79. [PubMed: 8600540]
13. Wodarz D, May RM, Nowak MA. The role of antigen-independent persistence of memory CTL. International Immunology. 2000; 12:467–477. [PubMed: 10744648]
14. Wodarz D, Nowak MA. Immune responses and viral phenotype: do replication rate and cytopathogenicity influence virus load? Journal of Theoretical Medicine. 2000; 2:113–127.
15. Wodarz D, Christensen JP, Thomsen AR. The importance of lytic and nonlytic immune responses in viral infections. Trends Immunol. 2002; 23(4):194–200. [PubMed: 11923114]
16. De Boer RJ, Perelson AS. Target cell limited and immune control models of HIV infection: a comparison. Journal of theoretical biology. 1998; 190(3):201–214. [PubMed: 9514649]
17. Williams MA, Bevan MJ. Effector and memory CTL differentiation. Annual review of immunology. 2007; 25:171–192.
18. Wodarz D, Arnaout RA, Nowak MA, Lifson JD. Transient antiretroviral treatment during acute simian immunodeficiency virus infection facilitates long-term control of the virus (Translated from eng). Philos Trans R Soc Lond B Biol Sci. 2000; 355(1400):1021–1029. (in eng). [PubMed: 11186303]
19. Wodarz D, Klennerman P, Nowak MA. Dynamics of cytotoxic T-lymphocyte exhaustion. Proc R Soc Lond B Biol Sci. 1998; 265(1392):191–203.
20. Wodarz D, Nowak MA. Specific therapy regimes could lead to long-term control of HIV. Proc Natl Acad Sci USA. 1999; 96:14464–14469. [PubMed: 10588728]
21. Wodarz D, et al. A new theory of cytotoxic T-lymphocyte memory: implications for HIV treatment [In Process Citation]. Philos Trans R Soc Lond B Biol Sci. 2000; 355(1395):329–343. [PubMed: 10794051]

22. Antia R, Ganusov VV, Ahmed R. The role of models in understanding CD8+ T-cell memory. *Nature reviews Immunology*. 2005; 5(2):101–111.
23. Wherry EJ, Ahmed R. Memory CD8 T-cell differentiation during viral infection. *Journal of virology*. 2004; 78(11):5535–5545. [PubMed: 15140950]
24. Wherry EJ, et al. Lineage relationship and protective immunity of memory CD8 T cell subsets. *Nat Immunol*. 2003; 4(3):225–234. [PubMed: 12563257]
25. Buchholz VR, et al. Disparate individual fates compose robust CD8+ T cell immunity. *Science*. 2013; 340(6132):630–635. [PubMed: 23493420]
26. Zinkernagel RM. On immunological memory. *Philos Trans R Soc Lond B Biol Sci*. 2000; 355(1395):369–371. [PubMed: 10794057]
27. Lau LL, Jamieson BD, Somasundaram T, Ahmed R. Cytotoxic T-cell memory without antigen [see comments]. *Nature*. 1994; 369(6482):648–652. [PubMed: 7516038]
28. Wherry EJ, Barber DL, Kaech SM, Blattman JN, Ahmed R. Antigen-independent memory CD8 T cells do not develop during chronic viral infection. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101(45):16004–16009. [PubMed: 15505208]
29. Schiffner T, Sattentau QJ, Dorrell L. Development of prophylactic vaccines against HIV-1. *Retrovirology*. 2013; 10:72. [PubMed: 23866844]
30. Mercado R, et al. Early programming of T cell populations responding to bacterial infection. *Journal of immunology*. 2000; 165(12):6833–6839.
31. Kaech SM, Ahmed R. Memory CD8+ T cell differentiation: initial antigen encounter triggers a developmental program in naive cells. *Nat Immunol*. 2001; 2(5):415–422. [PubMed: 11323695]
32. van Stipdonk MJ, Lemmens EE, Schoenberger SP. Naive CTLs require a single brief period of antigenic stimulation for clonal expansion and differentiation. *Nat Immunol*. 2001; 2(5):423–429. [PubMed: 11323696]
33. van Stipdonk MJ, et al. Dynamic programming of CD8+ T lymphocyte responses. *Nat Immunol*. 2003; 4(4):361–365. [PubMed: 12640451]
34. Wodarz D, Thomsen AR. Does programmed CTL proliferation optimize virus control? *Trends Immunol*. 2005; 26(6):305–310. [PubMed: 15922946]
35. Wodarz D, Thomsen AR. Effect of the CTL proliferation program on virus dynamics. *Int Immunol*. 2005; 17(9):1269–1276. [PubMed: 16103027]
36. Guidotti LG, et al. Noncytopathic clearance of lymphocytic choriomeningitis virus from the hepatocyte. *The Journal of experimental medicine*. 1999; 189(10):1555–1564. [PubMed: 10330434]
37. Guidotti LG, et al. Viral Cross-Talk – Intracellular Inactivation of the Hepatitis-B Virus During an Unrelated Viral-Infection of the Liver. *Proceedings of the National Academy of Sciences of the United States of America*. 1996; 93(10):4589–4594. [PubMed: 8643448]
38. Guidotti LG, et al. Intracellular Inactivation of the Hepatitis-B Virus By Cytotoxic T-Lymphocytes. *Immunity*. 1996; 4(1):25–36. [PubMed: 8574849]
39. Guidotti LG, et al. Viral clearance without destruction of infected cells during acute HBV infection. *Science*. 1999; 284(5415):825–829. [PubMed: 10221919]
40. Elemans M, et al. Why Don't CD8+T Cells Reduce the Lifespan of SIV-Infected Cells In Vivo? (Translated from English). *Plos Comput Biol*. 2011; 7(9) (in English).
41. Levy JA. The search for the CD8+ cell anti-HIV factor (CAF). *Trends Immunol*. 2003; 24(12): 628–632. [PubMed: 14644135]
42. Levy JA, Mackewicz CE, Barker E. Controlling HIV pathogenesis: the role of the noncytotoxic anti-HIV response of CD8+ T cells. *Immunol Today*. 1996; 17(5):217–224. [PubMed: 8991383]
43. Chang KM, Rehmann B, Chisari FV. Immunopathology of hepatitis C. *Springer Semin Immunopathol*. 1997; 19(1):57–68. [PubMed: 9266631]
44. Chisari FV, Ferrari C. Hepatitis B virus immunopathology. *Springer Semin Immunopathol*. 1995; 17(2–3):261–281. [PubMed: 8571172]
45. Zinkernagel RM, Hengartner H. T-cell-mediated immunopathology versus direct cytolysis by virus: implications for HIV and AIDS. *Immunol Today*. 1994; 15(6):262–268. [PubMed: 7915115]

46. Zinkernagel RM. Immune protection vs. immunopathology vs. autoimmunity: a question of balance and of knowledge. *Brain Pathol.* 1993; 3(2):115–121. [PubMed: 8293172]
47. Klenerman P, Zinkernagel RM. What can we learn about human immunodeficiency virus infection from a study of lymphocytic choriomeningitis virus? *Immunol Rev.* 1997; 159:5–16. [PubMed: 9416499]
48. Lehmann-Grube F. Lymphocytic choriomeningitis virus. *Viol Monogr.* 1971; 10:1–173.
49. Zinkernagel RM, Althage A, Jensen FC. Cell-mediated immune response to lymphocytic choriomeningitis and vaccinia virus in rats. *Journal of immunology.* 1977; 119(4):1242–1247.
50. Buchmeier MJ, Welsh RM, Dutko FJ, Oldstone MB. The virology and immunobiology of lymphocytic choriomeningitis virus infection. *Advances in immunology.* 1980; 30:275–331. [PubMed: 6160740]
51. Bartholdy C, Christensen JP, Wodarz D, Thomsen AR. Persistent virus infection despite chronic cytotoxic T-lymphocyte activation in gamma interferon-deficient mice infected with lymphocytic choriomeningitis virus (Translated from eng). *Journal of virology.* 2000; 74(22):10304–10311. (in eng). [PubMed: 11044074]
52. Thomsen AR, Nansen A, Andreassen SO, Wodarz D, Christensen JP. Host factors influencing viral persistence. *Phil Trans Roy Soc Lond B.* 2000; 355:1031–1041. [PubMed: 11186304]
53. Nansen A, et al. Compromised virus control and augmented perforin-mediated immunopathology in IFN-gamma-deficient mice infected with lymphocytic choriomeningitis virus. *Journal of immunology.* 1999; 163(11):6114–6122.
54. Wodarz D, Krakauer DC. Defining CTL-induced pathology: implications for HIV. *Virology.* 2000; 274(1):94–104. [PubMed: 10936092]
55. Doherty PC. Cell mediated immunity in virus infections. *Biosci Rep.* 1997; 17(4):367–387. [PubMed: 9367053]
56. Gerhard W, Mozdzanowska K, Furchner M, Washko G, Maiese K. Role of the B-cell response in recovery of mice from primary influenza virus infection. *Immunol Rev.* 1997; 159:95–103. [PubMed: 9416505]
57. Moskopidhis D, Kioussis D. Contribution of virus-specific CD8+ cytotoxic T cells to virus clearance or pathologic manifestations of influenza virus infection in a T cell receptor transgenic mouse model. *The Journal of experimental medicine.* 1998; 188(2):223–232. [PubMed: 9670035]
58. Eichelberger M, Allan W, Zijlstra M, Jaenisch R, Doherty PC. Clearance of influenza virus respiratory infection in mice lacking class I major histocompatibility complex-restricted CD8+ T cells. *The Journal of experimental medicine.* 1991; 174(4):875–880. [PubMed: 1919440]
59. Topham DJ, Tripp RA, Hamilton-Easton AM, Sarawar SR, Doherty PC. Quantitative analysis of the influenza virus-specific CD4+ T cell memory in the absence of B cells and Ig. *Journal of immunology.* 1996; 157(7):2947–2952.
60. Tripp RA, Sarawar SR, Doherty PC. Characteristics of the influenza virus-specific CD8+ T cell response in mice homozygous for disruption of the H-2IAb gene. *Journal of immunology.* 1995; 155(6):2955–2959.
61. Topham DJ, Tripp RA, Doherty PC. CD8+ T cells clear influenza virus by perforin or Fas-dependent processes. *Journal of immunology.* 1997; 159(11):5197–5200.
62. Aubert RD, et al. Antigen-specific CD4 T-cell help rescues exhausted CD8 T cells during chronic viral infection. *Proceedings of the National Academy of Sciences of the United States of America.* 2011; 108(52):21182–21187. [PubMed: 22160724]
63. Kumamoto Y, Mattei LM, Sellers S, Payne GW, Iwasaki A. CD4+ T cells support cytotoxic T lymphocyte priming by controlling lymph node input. *Proceedings of the National Academy of Sciences of the United States of America.* 2011; 108(21):8749–8754. [PubMed: 21555577]
64. Kurts C, Robinson BW, Knolle PA. Cross-priming in health and disease. *Nature reviews Immunology.* 2010; 10(6):403–414.
65. Swain SL, McKinstry KK, Strutt TM. Expanding roles for CD4(+) T cells in immunity to viruses. *Nature reviews Immunology.* 2012; 12(2):136–148.
66. Wodarz D, Jansen VAA, Nowak MA, Thomsen AR. CTL dynamics in CD4 cell deficient hosts. 1999 submitted.

67. Korthals Altes H, Ribeiro RM, de Boer RJ. The race between initial T-helper expansion and virus growth upon HIV infection influences polyclonality of the response and viral set-point. *Proceedings Biological sciences/The Royal Society*. 2003; 270(1522):1349–1358. [PubMed: 12965025]
68. Roy SM, Wodarz D. Infection of HIV-specific CD4 T helper cells and the clonal composition of the response. *Journal of theoretical biology*. 2012; 304:143–151. [PubMed: 22480435]
69. Nowak MA. Immune-Responses Against Multiple Epitopes – a Theory For Immunodominance and Antigenic Variation. *Seminars in Virology*. 1996; 7(1):83–92.
70. Nowak MA, et al. Antigenic Oscillations and Shifting Immunodominance in Hiv-1 Infections. *Nature*. 1995; 375(6532):606–611. [PubMed: 7791879]
71. Nowak MA, et al. Antigenic Diversity Thresholds and the Development of Aids. *Science*. 1991; 254(5034):963–969. [PubMed: 1683006]
72. Ganusov VV, et al. Fitness costs and diversity of the cytotoxic T lymphocyte (CTL) response determine the rate of CTL escape during acute and chronic phases of HIV infection (Translated from eng). *Journal of virology*. 2011; 85(20):10518–10528. (in eng). [PubMed: 21835793]
73. Ganusov VV, Neher RA, Perelson AS. Mathematical modeling of escape of HIV from cytotoxic T lymphocyte responses. *Journal of Statistical Mechanics: Theory and Experiment*. 2013; 2013(01):P01010. [PubMed: 24660019]
74. Seich AI, Basatena NK, et al. Can non-lytic CD8+ T cells drive HIV-1 escape? *PLoS pathogens*. 2013; 9(11):e1003656. [PubMed: 24244151]
75. Wodarz D, Arnaout RA, Nowak MA, Lifson JD. Transient antiretroviral treatment during acute SIV infection facilitates long-term control of the virus. *Phil Trans Roy Soc Lond B*. 2000; 355:1021–1029. [PubMed: 11186303]
76. Ribeiro RM, Mohri H, Ho DD, Perelson AS. In vivo dynamics of T cell activation, proliferation, and death in HIV-1 infection: why are CD4+ but not CD8+ T cells depleted? *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99(24):15572–15577. [PubMed: 12434018]
77. Asquith B, et al. Quantifying lymphocyte kinetics in vivo using carboxyfluorescein diacetate succinimidyl ester (CFSE). *Proceedings Biological sciences/The Royal Society*. 2006; 273(1590):1165–1171. [PubMed: 16600897]
78. Asquith B, Debacq C, Macallan DC, Willems L, Bangham CR. Lymphocyte kinetics: the interpretation of labelling data. *Trends Immunol*. 2002; 23(12):596–601. [PubMed: 12464572]
79. Asquith B, Edwards CT, Lipsitch M, McLean AR. Inefficient cytotoxic T lymphocyte-mediated killing of HIV-1-infected cells in vivo. *PLoS Biol*. 2006; 4(4):e90. [PubMed: 16515366]
80. De Boer RJ, Mohri H, Ho DD, Perelson AS. Estimating average cellular turnover from 5-bromo-2'-deoxyuridine (BrdU) measurements. *Proceedings Biological sciences/The Royal Society*. 2003; 270(1517):849–858. [PubMed: 12737664]
81. De Boer RJ, Mohri H, Ho DD, Perelson AS. Turnover rates of B cells, T cells, and NK cells in simian immunodeficiency virus-infected and uninfected rhesus macaques. *Journal of immunology*. 2003; 170(5):2479–2487.
82. Ganusov VV, et al. Quantifying cell turnover using CFSE data. *Journal of immunological methods*. 2005; 298(1–2):183–200. [PubMed: 15847808]
83. Mandl JN, Regoes RR, Garber DA, Feinberg MB. Estimating the effectiveness of simian immunodeficiency virus-specific CD8+ T cells from the dynamics of viral immune escape. *Journal of virology*. 2007; 81(21):11982–11991. [PubMed: 17699572]
84. Regoes RR, Barber DL, Ahmed R, Antia R. Estimation of the rate of killing by cytotoxic T lymphocytes in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104(5):1599–1603. [PubMed: 17242364]
85. Wick WD, Yang OO, Corey L, Self SG. How many human immunodeficiency virus type 1-infected target cells can a cytotoxic T-lymphocyte kill? (Translated from eng). *Journal of virology*. 2005; 79(21):13579–13586. (in eng). [PubMed: 16227278]
86. Beltman JB, Maree AF, de Boer RJ. Spatial modelling of brief and long interactions between T cells and dendritic cells. *Immunology and cell biology*. 2007; 85(4):306–314. [PubMed: 17420768]

87. Beltman JB, Maree AF, de Boer RJ. Analysing immune cell migration. (Translated from eng). *Nature reviews Immunology*. 2009; 9(11):789–798. (in eng).
88. Beltman JB, Maree AF, Lynch JN, Miller MJ, de Boer RJ. Lymph node topology dictates T cell migration behavior. *The Journal of experimental medicine*. 2007; 204(4):771–780. [PubMed: 17389236]

Figure 1.

(a) Schematic of the basic model of virus dynamics, model (1). See text for details. (b) The basic reproductive ratio of the virus, R_0 . This measure expresses the average number of newly infected cells produced by a single infected cell at the beginning of the infection. If $R_0 > 1$, the infection becomes established. If $R_0 < 1$, the infection goes extinct. If $R_0 = 1$, then one infected cells on average gives rise to one newly infected cell. This case is a border case, and irrelevant for practical purposes.

Figure 2.

Simulation of the simplest model which describes CTL dynamics, i.e. model (3). Virus growth is followed by CTL expansion, and CTL-mediated activity reduces virus load. Subsequent damped oscillations bring the system towards an equilibrium. The level of virus load at this equilibrium shows how well the infection is controlled. If virus load lies below a threshold, this indicates virus clearance in practical terms. After expansion, the population of CTL remains at an elevated memory level. Parameters were chosen as follows. $\lambda=1$, $d=0.1$, $\beta=0.1$, $a=0.2$, $p=0.5$, $c=0.2$, $b=0.1$.

Figure 3.

Protection against secondary challenge after virus clearance. Plots are derived from model (4). Peak virus load upon secondary challenge decreases with an increase in the initial number of memory CTLp. However, this decrease in peak virus load is only significant if the rate of effector cell production is fast and the delay between virus entry and effector cell production is minimal (expressed in the value of q). Baseline parameters were chosen as follows. $\lambda=10$, $d=0.1$, $\beta=0.001$, $a=0.5$, $p=1$, $c=0.1$, $b=0.001$, $h=0.1$.

Figure 4.
Schematic representations of (i) the programmed proliferation and (ii) the continuous stimulation concepts.

Figure 5.

Comparison between the programmed proliferation model (5) and the continuous stimulation model (3). We distinguish between virus dynamics in the presence of a strong CTL response (which can lead to low virus loads and clearance), and a weak CTL response which results in persistent infection. (i) If the response is strong, programmed proliferation leads to higher peak virus loads during acute infection, but leads to more efficient clearance compared to the continuous stimulation scenario. In the continuous stimulation model, virus load converges only very slowly to its equilibrium value, and this hinders clearance. The

reason is that effector production relies on continuous encounter with antigen which is limiting at low loads. (ii) If the CTL are weak and persistent infection is established, both the programmed proliferation model and the continuous stimulation model have similar properties: they converge to the same equilibrium. The program model takes slightly longer to converge to the equilibrium because there is delay between induction of the response and the generation of effectors. Parameters were chosen as follows. (i) $\lambda=10$; $d=0.1$; $\beta=0.05$; $a=0.1$; $r=5$; $\gamma=1$; $\alpha=0.01$; $\delta=0.5$; $p=0.2$; $\varepsilon=0.001$; (ii) $\lambda=10$; $d=0.1$; $\beta=0.05$; $a=0.1$; $r=5$; $\gamma=0.1$; $\alpha=0.005$; $\delta=1$; $p=0.1$; $\varepsilon=1$.

(i) Non-cytopathic, slowly replicating virus

(ii) Non-cytopathic, fast replicating virus

Figure 6.

Control of non-cytopathic viruses by lytic and non-lytic effector mechanisms. (i) Slowly replicating virus. Lytic effectors alone can achieve a similar level of virus control as a combination of lytic and non-lytic effectors. (ii) Fast replicating virus. Lytic effectors alone cannot control the infection, because it results in immunopathology. Cooperation of lytic and non-lytic effector mechanisms can control the infection, because non-lytic mechanisms slow down the overall replication kinetics of the virus. Note that the effect of a non-lytic response alone has not been plotted. This is because we consider non-cytopathic viruses which do not kill their target cells. Since the life span of infected cells is not reduced, absence of lysis is unlikely to result in virus control in a short period of time. Plots are based

on model (6). Parameters were chosen as follows: $\lambda=10$; $d=0.1$; $a=0.1$; $q=10$; $p=1$; $c=0.1$; $b=0.1$. For (i) $\beta=0.01$; For (ii) $\beta=0.1$;

Figure 7.

Control of a virus characterized by a high degree of cytopathicity relative to its replication rate. Both lytic and non-lytic effector mechanisms can in principle independently control the infection. Plots are based on model (6). Parameter values were chosen as follows. $\lambda=10$; $d=0.1$; $a=0.4$; $\beta=0.01$; $q=10$; $p=1$; $c=0.1$; $b=0.1$.

Figure 8.

Effect of CD4 cell help on virus load, according to model (7). Virus load decreases asymptotically with increasing degrees of help. Virus load approaches a value of b/c for high degrees of help. Parameters were chosen as follows. $c=1$, $b=0.1$, $\varepsilon=0.01$.