Mathematically modeling dynamics of T cell responses: Predictions concerning the generation of memory cells

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Received 10 May 2006; received in revised form 19 October 2006; accepted 19 October 2006

Available online 28 October 2006

Abstract

Mathematical models of T cell population dynamics after infection typically assume that T cells differentiate according to a linear process in which they first become effector cells, and then after some time, differentiate further into memory cells. In this paper, we offer a different mathematical model which can equally well capture T cell dynamics, using data from lymphocytic choriomeningitis (LCMV) infection. Our model assumes that memory cells are intermediates that further differentiate into effector cells only from additional or stronger antigenic stimulation. Our assumption naturally leads to a testable prediction about the generation of T cell memory—that the memory phenotype of T cells should be present in detectable numbers during the expansion phase of the response. We use our model to estimate a rate of differentiation from memory type cells to effectors. We argue that this differentiation assumption, where memory cells are intermediates, captures recent experimental work on T cell differentiation, and hence this new mathematical model could be helpful in doing further studies of T cell population dynamics. We also propose a method of distinguishing the models by examining the ratio of memory T cells detectable long after an infection to the peak numbers of T cells at the end of the expansion phase.

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Keywords: T cell dynamics; T cell differentiation; T cell memory; Mathematical models

1. Introduction

Lymphocytic choriomeningitis virus (LCMV) is an arenavirus that is widely used for studies of T cell mediated immune responses (Wong and Palmer, 2003). In mice LCMV infects several types of immune system cells and glial cells to stimulate strong and robust cytotoxic T lymphocyte responses, yet LCMV causes little host damage since it is noncytopathic. Viral growth induces an LCMV-specific T cell response that normally leads to viral elimination within 8–10 days. The precise epitopes of LCMV that trigger CD4+ T cells and CD8+ T cells are known for some mouse strains. Through various experimental methods the dynamics of these specific lineages have been tracked and recorded. It is well known that the rapid viral growth of LCMV is followed by the expansion of specific lineages of CD4+ and CD8+ T cells. After the expansion phase, the specific T cell populations die out to some degree, referred to as the retraction phase. Subsequently, a memory population consisting of about 5% of the peak response remains over a much longer time frame: the memory phase.

For over a decade, researchers have described competing models for T cell differentiation (Ahmed and Gray, 1996; Kaech et al., 2002b). One model, which may be called traditional linear differentiation, assumes that activated T cells become effector cells that can later convert to memory type cells. The second, sometimes referred to as the decreasing potential hypothesis, asserts that intermediate activated cells survive as memory cells unless they further differentiate into effector cells. Hence, in one model memory type cells are created last, and in the other, memory cells are generated first. Early on in this debate, Lanzavecchia and Sallusto advocate the latter differentiation scheme, and further identify two classes of memory cells: central memory and effector memory types of T cells (Lanzavecchia and Sallusto, 2000a). The central memory type has more potential for expansion and lymph node homing markers, while the effector memory type has less...
potential for further expansion yet is more readily available for exhibiting effector function. Many recent studies have aimed at improving our understanding of these categories of memory T cells (Fearon et al., 2001; Rivino et al., 2004; Sallusto et al., 2004; Sabbagh et al., 2004; Lanzavecchia and Sallusto, 2005).

Researchers continue to have differing views about how and when the memory subset of T cells becomes differentiated from the effector class (Wherry et al., 2003) and some debate exists as to whether or not the path is a unidirectional linear development, or whether conversions can occur between cell types. Furthermore, there are potentially significant differences in CD4+ and CD8+ T cell differentiation pathways. Some evidence suggests that CD4+ cells do not follow an effector to memory population transition (Wu et al., 2002). Added complexity to the system is indicated by evidence that CD8+ memory may depend on appropriate activation of CD4+ cells (Kaech and Ahmed, 2003; Williams and Bevan, 2004). A related development in the past six years is that T cells undergo some kind of programmed expansion and can continue to proliferate even when antigen is removed (Mercado et al., 2000; van Stipdonk et al., 2001; Kaech and Ahmed, 2001). Precisely how antigen is involved in the activation and differentiation process is still an active area of research.

Mathematical models have been used along the way to improve our understanding of the dynamics of T cell responses. A detailed study modeling the programmed proliferation was done by de Boer et al. (2001) in which simple models were used and fit to data in order to calculate proliferation and death rates of cells. In 2003, models were again used to report notably different dynamics of the retraction phase for CD4+ T cells and CD8+ T cells (de Boer et al., 2003). Both of these studies make use of a mathematical model in which memory cells are derived from effector cells after a programmed expansion period. A summary of the role and importance of using mathematical models for understanding T cell dynamics can be found in Antia (2005).

The mathematical model presented here is fit to the same data as de Boer et al. (2003) and much of the modeling techniques are analogous. The proposed alternate model, however, has a fundamentally different differentiation assumption and can therefore be compared and contrasted in terms of its parameter predictions and potential for interpreting data.

2. The models

We begin with a summary of the model in which memory cells are derived from effectors by de Boer et al. because we wish to compare and contrast this model to an alternative. De Boer et al. formulate the following simple mathematical model of T cell dynamics, dividing T cell clones into activated (A) cells and memory (M) cells (de Boer et al., 2003). The T cell response is divided into two pre-set phases: a proliferation phase in which activated cells grow exponentially, and a retraction phase in which they die off or are converted into memory cells. In their most general formulation, the authors further prescribe a pre-set stage of the retraction phase in which activated cells are additionally susceptible to rapid apoptosis. Fig. 1 shows the assumed differentiation order.

For \( t \leq T \) the dynamics are given by

\[
\frac{dA}{dt} = \rho A \tag{1}
\]

and for \( t > T \), the dynamics are

\[
\frac{dA}{dt} = -(r + \delta_A + z)A, \tag{2}
\]

\[
\frac{dM}{dt} = rA - \delta_M M. \tag{3}
\]

Without the additional apoptosis term \((z)\), the model has six parameters. They are: \( A_0 \) or \((A(0)\) interpreted as a generalized recruitment parameter, \( \rho \) denoting the proliferation rate of activated cells, \( T \) the time the proliferation phase ends, \( r \) the rate activated cells convert to memory cells, and \( \delta_A \) and \( \delta_M \) which are activated cell and memory cell death rates, respectively. The authors find that this six parameter version of the model captures the CD8+ T cell data quite well. In fact, one can assume the death rate of memory cells is zero and with only five parameters the CD8+ data is captured. A significant improvement in fit was achieved, however, for the CD4+ T cell data when the apoptosis phase was added. In this case, the authors used the constant \( z \) for the rate of apoptosis of activated cells, until time \( T + \Delta \), after which \( z \) was set to zero. Hence, two additional parameters were added to capture the CD4+ T cell data.

The solution of these ordinary differential equations is easily found to be

\[
A(t) = A_0 \exp(\rho t), \quad M(t) = 0 \quad \text{for } t \leq T. \tag{4}
\]

For \( T < t \leq T + \Delta \), the solution is

\[
A(t) = A(T) \exp(-\delta(t - T)), \tag{5}
\]

\[
M(t) = \frac{rA(T)}{\delta - \delta_M} (\exp(-\delta_M(t - T)) - \exp(-\delta(t - T))), \tag{6}
\]

where \( \delta = r + \delta_A + z \). When \( t > T + \Delta \), the solution is

\[
A(t) = A(T + \Delta) \exp(-\delta(t - T - \Delta)), \tag{7}
\]

Fig. 1. Differentiation order of the de Boer model. Naive T cells (N) become activated cells (A). Then after the proliferation phase is complete activated cells differentiate to memory cells (M).
\[ M(t) = M(T + \Delta) \exp(-\delta_M(t - T - \Delta)) \]
\[ + \frac{rA(T + \Delta)}{\delta - \delta_M} \exp(-\delta_M(t - T - \Delta)) \]
\[ - \exp(-\delta(t - T - \Delta)), \]

where \( \delta = r + \delta_A \). We state this solution explicitly for comparison and since the appendix of the original paper contained some minor typographical errors.

### 2.1. An alternative model—memory cells precede effectors

Lanzavecchia’s linear differentiation theory of T cell development (Lanzavecchia and Sallusto, 2000b), proposes an alternative scenario in which memory cells form at the outset of antigen stimulation of naive T cells. Rather than assuming memory cells emerge as a class after the peak response, suppose that the partially differentiated activated cells are those which linger as memory cells after the clearance of the virus. We propose an equally simple model, yet based on this fundamentally different order of T cell differentiation. This order is shown in Fig. 2.

We similarly consider two types of cells: cells that have encountered some antigen and become memory cells (M), and cells that have made substantially more antigen contacts and are fully differentiated into effector cells (E). We assume that during the expansion phase, M and E cells proliferate at a rate \( \rho \), M cells encounter sufficient antigen to become E cells at a rate \( r \), and the death rates are \( \delta_M \) and \( \delta_E \) for M cells and E cells, respectively. We also add the possibility of additional death of effector cells due to apoptosis at a rate \( \alpha \), as in the original model. This apoptosis could be what is sometimes called activation induced cell death (AIDC).

Hence, a simple alternate model has the equations

\[ \frac{dM}{dt} = \rho M - rM - \delta_M M, \]
\[ \frac{dE}{dt} = \rho E + rM - \delta_E E - \alpha E \]

for \( t \leq T \) and for \( t \geq T \), \( \rho \) and \( r \) are set to zero, and finally for \( t \geq T + \Delta \), \( \alpha \) is set to zero.

Again we have six parameters without the additional apoptosis period, or eight parameters for the full model. This time we assume \( E(0) = 0 \). Our parameters are \( M(0) = M_0 \) to represent a general recruitment parameter of antigen primed intermediate cells. The rate \( r \) is the transition rate that these precursor memory cells become fully differentiated effector cells and may be a function of antigen presented with appropriate second signals. The proliferation rate \( \rho \) is the same for \( M \) and \( E \) cells. We can interpret \( T \) as a time during which antigen is available above a certain threshold and capable of stimulating proliferation and differentiation. Or we can simply assume it is a pre-set parameter of the proliferation time and differentiation time. Effectors can die by AIDC at the rate \( \alpha \) up until time \( T + \Delta \). Moreover, we can interpret \( \Delta \) as a period during which enough antigen is still available to interact with effectors. Finally, \( \delta_M \) and \( \delta_E \) are death rates.

The primary significant difference between this model and that of de Boer et al. is that memory cells are generated from the outset of the immune response and not only during the retraction phase. Memory cells in the alternate model further differentiate to a shorter-lived class, rather than having short-lived cells require differentiation to become long-lived cells after the population expansion is complete. This model also does not require \( T \) and \( \Delta \) to be predetermined times after activation, but they may be interpreted as functions of available antigen. We leave open the possibility that antigen availability may be a driving factor in proliferation of cells and differentiation into effectors.

Again the model is easy to solve. The solution is

\[ M(t) = M_0 e^{\rho(t-(r+\delta_M)t)/r}, \]
\[ E(t) = \frac{rM_0}{r + \delta_M - \delta_E - \alpha} (e^{\rho(t-(\delta_E + \delta_M)t)/r} - e^{(\rho(r+\delta_M)t)/r}) \]

for \( t \leq T \), and for \( T < t \leq T + \Delta \)

\[ M(t) = M(T) e^{-\delta_M(t-T)}, \]
\[ E(t) = E(T) e^{-\delta_E(t-T-T)}, \]

where \( M(T) \) and \( E(T) \) are given by Eqs. (11) and (12). For \( t > T + \Delta \) the solution is

\[ M(t) = M(T + \Delta) e^{-\delta_M(t-T-D)}, \]
\[ E(t) = E(T + \Delta) e^{-\delta_E(t-(T+\Delta)} \]

where \( M(T + \Delta) \) and \( E(T + \Delta) \) are given by Eqs. (13) and (14).

Both models capture the CD8+ T cell data with six parameters and the CD4+ T cell data with the additional period in which rapid apoptosis occurs requiring all eight parameters. In fact, by allowing no death of memory cells (as in the model by de Boer et al.) the CD8+ T cell data can be captured just as effectively with only five parameters.

### 2.2. Variation of the de Boer model with ongoing differentiation from effectors to the memory class

While the original de Boer model allows differentiation to occur only after the peak response, the alternative we just described restricts differentiation to the expansion phase. Combining ideas from both models we have another variant of the de Boer model in which once again, effector

![Fig. 2. Differentiation order of the alternative model. Naive T cells (N) become intermediate cells which ultimately survive as central memory cells (M). Additional TCR stimulation drives cells to further differentiate to effector cells (E).](image-url)
cells precede memory cells. In this variant, effector cells continuously differentiate to memory cells from the outset of the infection. The differentiation order is the same as the de Boer model, but memory cells are predicted to be present even in the expansion phase of the response with this modification.

Consider the equations
\[
\frac{dE}{dt} = \rho E - rE - \delta_E E - zE, \quad (17)
\]
\[
\frac{dM}{dt} = \rho M + rE - \delta_M M \quad (18)
\]
and for \( t \geq T \), \( \rho \) is set to zero, and for \( t \geq T + \Delta \), \( z \) is set to zero.

The solution to these equations is
\[
E(t) = E_0 e^{(\rho-(r+\delta_E+\delta_M))t}, \quad (19)
\]
\[
M(t) = \frac{r E_0}{r + \delta_E - \delta_M + z} (e^{(\rho-(r+\delta_E+\delta_M))t} - e^{(\rho-\delta_M)t}) \quad (20)
\]
for \( t \leq T \), and for \( T < t \leq T + \Delta \)
\[
E(t) = E(T) e^{-(r+\delta_E+\delta_M)(t-T)}, \quad (21)
\]
\[
M(t) = M(T) e^{(-\delta_M)(t-T)} + \frac{r E(T)}{r + \delta_E - \delta_M + z} \times (e^{(\rho-\delta_M)(t-T)} - e^{(\rho+\delta_M)(t-T)}), \quad (22)
\]
where \( M(T) \) and \( E(T) \) are given by Eqs. (20) and (19). For \( t > T + \Delta \) the solution is
\[
E(t) = E(T + \Delta) e^{-(r+\delta_E)(t-(T+\Delta))}, \quad (23)
\]
\[
M(t) = M(T + \Delta) e^{(-\delta_M)(t-(T+\Delta))} + \frac{r E(T + \Delta)}{r + \delta_E - \delta_M} \times (e^{(-\delta_M)(t-(T+\Delta))} - e^{(r+\delta_E)(t-(T+\Delta))}), \quad (24)
\]
where \( M(T + \Delta) \) and \( E(T + \Delta) \) are given by Eqs. (22) and (21). And once again an eighth parameter version of the model captures CD4+ T cell dynamics, and a six parameter version (or merely five parameters when the death rate of memory cells in neglected) captures the CD8+ T cell dynamics.

In the following section we detail the method we used to fit our parameters and interpret the different predictions of each model.

2.3. Comparing the fits

We fit the parameters of the models by minimizing the squared difference of the logarithm of the solution and the logarithm of the data. If \( D(t) \) represents the value from mouse data for time \( t \) and \( Y(t) \) is the model prediction at time \( t \), we minimize the generalized sum of squared residuals:
\[
\text{GSS} = \sum [\log(Y(t)) - \log(D(t))]^2.
\]
The reason we first take the logarithm is due to an assumed heteroscedasticity of the data, meaning that the spread in the data increases as larger numbers of T cells are counted. (Note: we did not have the raw data to work with, only points that were averages of 2–4 mice.) To find the minimum sum of squared residuals over the multidimensional system, we used MATLAB’s built in multidimensional unconstrained nonlinear minimization function, fminsearch, which uses a Nelder–Mead (1965) scheme.

The models with the same numbers of parameters fit the data equally well, yet they assume a different T cell maturation order. In the de Boer model, the differentiation begins after the proliferation, where in our version, the T cells differentiate at the same time as the proliferation.

The five parameters required to fit the CD8+ data are listed in Table 1. Fig. 3 illustrates the fit of the models to that data. In this case the death rate of memory cells was assumed to be 0. We do not show plots of the data and fit for the variation of the de Boer model with continual differentiation, but it is essentially indistinguishable as far as how it fits the data points.

The parameters that best fit the data for CD4+ T cells are shown in Table 2. (Note that the values published here do not exactly match the results published in de Boer et al. (2003).) We obtained the matching published values only when \( T + \Delta \) were held fixed. The values here represent the minimum sum of squared residuals when all eight parameters are free.) Displayed in this same table are the results of fitting the variation of the de Boer model to the data when differentiation from effectors to memory cells is assumed to occur in all phases of the response. Fig. 4 shows the data for CD4+ cells along with the model predictions of the de Boer model and the alternate model with memory cells first.

Analogous parameters with the same names actually have slightly different meanings in the different models, yet are nonetheless quite similar in value. The proliferation rates \( \rho \) of roughly 1.7 divisions per day are consistent with prior observations and estimations. To fit the CD4+ T cell data, both models are significantly improved with their respective eight parameter versions. The values of analogous parameters are all very much the same with the exception of \( r \), which describes the rate of differentiation.

### Table 1

Parameter values for the alternative model (left), the de Boer model (center), and the variation of the de Boer model (right) with five parameters fit to the NP205 peptide data for CD8+ T cells

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( M_0 )</td>
<td>27.37 cells</td>
<td>48.57 cells</td>
<td>50.85 cells</td>
</tr>
<tr>
<td>( \rho )</td>
<td>1.80/day</td>
<td>1.42/day</td>
<td>1.84/day</td>
</tr>
<tr>
<td>( r )</td>
<td>0.655/day</td>
<td>0.026/day</td>
<td>0.0009/day</td>
</tr>
<tr>
<td>( \delta_E )</td>
<td>0.43/day</td>
<td>0.40/day</td>
<td>0.4252/day</td>
</tr>
<tr>
<td>( T )</td>
<td>8.02 days</td>
<td>8.01 days</td>
<td>8.01 days</td>
</tr>
<tr>
<td>min GSS</td>
<td>1.6602</td>
<td>1.6531</td>
<td>1.6504</td>
</tr>
</tbody>
</table>

We assume \( \delta_M = 0 \) since adding that parameter did not improve the fits.
Beyond simply fitting the data, this parameter is a prediction of the models.

The models, and not the data, provide a way to distinguish memory cell subsets from shorter-lived T cell subsets. In the de Boer model, \( r \) means the rate active T cells differentiate into memory cells. According to its value of approximately 0.001 per day for CD4\(^+\) T cells, the expected time for an activated cell to differentiate to a memory type is about 1000 days. Since the life-span of a mouse is on that same order of magnitude, memory cells are generated only by the extremely high numbers of activated cells at the peak response and an assumed high variability of this conversion process. Other estimates of

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**Table 2**

Parameter values for the memory first model (left), the original de Boer model (center), and the variation on the de Boer model (right) with eight parameters fit to the GP61 peptide data for CD4\(^+\) T cells

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>( M_0 )</td>
<td>8.02 cells</td>
<td>8.26 cells</td>
<td>8.29 cells</td>
</tr>
<tr>
<td>( A_0 )</td>
<td>1.708/day</td>
<td>1.688/day</td>
<td>1.896/day</td>
</tr>
<tr>
<td>( r )</td>
<td>0.53/day</td>
<td>0.0017/day</td>
<td>0.000086/day</td>
</tr>
<tr>
<td>( \delta_M )</td>
<td>0.0012/day</td>
<td>0.0012/day</td>
<td>0.0012/day</td>
</tr>
<tr>
<td>( \delta_E )</td>
<td>0.0213/day</td>
<td>0.020/day</td>
<td>0.020/day</td>
</tr>
<tr>
<td>( T )</td>
<td>7.55 days</td>
<td>7.54 days</td>
<td>7.54 days</td>
</tr>
<tr>
<td>( A )</td>
<td>9.23 days</td>
<td>9.16 days</td>
<td>9.21 days</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>0.19/day</td>
<td>0.18/day</td>
<td>0.19/day</td>
</tr>
<tr>
<td>min GSS</td>
<td>0.5277</td>
<td>0.5264</td>
<td>0.5280</td>
</tr>
</tbody>
</table>
this parameter yield a value as high as 0.1 per day corresponding to a differentiation process that would take roughly 100 days. The variation of the de Boer model in which memory cells continually differentiate from effectors predicts an even slower conversion rate: \( r \) is approximately 0.0007 per day corresponding to an expected 3.9 years for conversion from an effector to a memory cell. Such a small predicted parameter value which nonetheless is a sensitive parameter in terms of its effect on predicted memory cell dynamics is certainly noteworthy.

In the alternative model, \( r \) is the rate at which partially differentiated cells (perhaps central memory cells) completely differentiate into effector cells in the presence of antigen. The value of approximately 0.5 means that it takes about 2 days for these cells to become effectors. This conversion rate applies in the expansion phase of the immune response, presumably while antigen is presented with appropriate second signals. We believe that this time scale of 2 days is reasonable when considering the short life span of a mouse, and also has useful implications about how many days it may take to generate effectors from memory cells upon secondary antigenic stimulation.

Why are these estimates of \( r \) so different? In the de Boer model and the variant with continual differentiation, the conversion from effectors to memory cells takes place over a very long period of time. In the alternate model with memory cells first, all memory cells must be generated during the expansion phase—an eight-day period. Otherwise
the models behave the same—meaning that once effector cells are gone or negligible the dynamics of memory cells must be the same. Since the period when memory cells can be generated from effectors is over 200 days in the case of CD4+ T cells, and about 25 days for the CD8+ T cells, it is no surprise that conversion rates work out to be so much slower when memory cells come from effectors. The alternate model proposed here requires an urgency to generate large numbers of memory cells over the very short expansion phase and hence predicts a fast conversion rate.

3. Discussion

The model of de Boer et al. and the alternate model presented here fit the data equally well, and both fit with proliferation and death rates that seem consistent with experimental observation. We reiterate that although the models are essentially the same and equally capture the data, the most significant difference is in the prediction of the parameter $r$. This parameter indicates conversion from intermediate memory T cells to effectors in the alternate model, and conversion of activated cells that have completed a pre-set course of proliferation cycles to memory cells in the de Boer version. We compare the models to point out that it is theoretically unclear whether long-lived cells are intermediates, or whether long-lived memory cells are the final differentiation stage of T cells. One point in favor of the alternate model is its consistency with recent findings on the existence of memory cells early in the infection and at the peak response (Kaecch et al., 2002a; Wong et al., 2004). However, the variation of the de Boer model that has continuous differentiation to the memory class throughout the infection eliminates this problem and also is consistent with the recent data.

What other models fit the data? Suppose that only the memory cells (or memory precursor cells) proliferate. Another model that fits the data is given by

$$\frac{dM}{dt} = \rho M - rM - \delta_M M,$$

$$\frac{dE}{dt} = rM - \delta_E E$$

with $\rho$ and $r$ set to zero for $t > T$. The parameter values that make this model fit the CD4+ T cell data for the peptide GP61 are listed in Table 3. The cell proliferation rate in this case comes out to be absurdly high—30 cell divisions per day. For this reason, we reject that only $M$ cells proliferate, and prefer the other models. This version is similar to another model that followed a progression from memory cells to effector cells for cytotoxic T lymphocyte responses (discussed in Wodarz et al., 2000) that also includes viral dynamics. This mathematical analysis for eliminating a model in which proliferating memory cells are precursors to non-proliferating effector cells was described before in Antia (2005).

A way to distinguish the models is to compare the predicted ratio of memory cells to the total cells at the peak of the T cell response. In LCMV infection the ratio of long lived (CD8+) memory cells to the total activated cells at the peak of the response is about 5%. All models here capture that value, but because of the difference in the way that memory cells are generated, the models make different predictions about this ratio as a function of the duration of the expansion phase. In the alternate model, the memory cells are generated only in the expansion phase, and the longer the expansion phase lasts, the smaller the fraction of memory cells at the peak. Hence, the memory to peak ratio is a decreasing function of the duration of the expansion phase. Mathematically, this ratio for the CD8+ T cell model where $\delta_M$ and $\alpha$ are zero is found to be

$$\frac{1 - \exp(-(r - \delta_E)T))}{(1 + r/(r - \delta_E)\exp((r - \delta_E)T)).}$$

The original de Boer model assumes a constant memory to peak ratio of

$$\frac{r}{(r + \delta_E)}.$$

Finally, the variation on the de Boer model in which T cells continually differentiate from effectors to memory cells yields a memory to peak ratio which increases with the duration of the expansion phase:

$$\frac{r}{(r + \delta_E)} + \frac{(r - r \exp(-(r + \delta_E)T))}{(r + \delta_E)(r + \delta_E \exp(-(r + \delta_E)T)).}$$

The above ratios for the different models are plotted in Fig. 5. One might investigate the memory to peak ratio for infections which have different periods of the expansion phase to decide on a preferred model.

We also propose using these models to investigate the dynamics of secondary infections. The difficulty is we need a greater understanding of the virus dynamics based on the effector cells. It is known that the CD8+ T cells are essential for viral clearance, and the CD4+ T cell help is required for activating the CD8+ memory cells and hence necessary for clearance of a secondary infection. Our goal, however, is to model or predict these secondary dynamics without adding much complexity to the existing models.

A simple way to simulate secondary infections with the proposed alternate model is to assume virus is again present so $\rho$ and $r$ are again nonzero, for some additional

<table>
<thead>
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<th>Value</th>
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<tr>
<td>$M_0$</td>
<td>1.8 cells</td>
</tr>
<tr>
<td>$\rho$</td>
<td>30.13/day</td>
</tr>
<tr>
<td>$r$</td>
<td>28.73/day</td>
</tr>
<tr>
<td>$\delta_M$</td>
<td>0.0025/day</td>
</tr>
<tr>
<td>$\delta_E$</td>
<td>0.1876/day</td>
</tr>
<tr>
<td>$T$</td>
<td>8 days</td>
</tr>
</tbody>
</table>

Table 3
Fitting a model without proliferating effector cells to the CD4+ T cell data for the GP61 peptide, we obtain the parameter values listed here.
period of time. We use the solution of the model for the primary infection to determine our starting $M_0$ and $E_0$ values for the second infection. If we assume that $T$ (and $A$) are fixed values independent of the virus titer, then we predict that the subsequent antigen challenge would produce a large increase in effectors and memory cells. If, however, we assume that $T$ (and possibly $A$) is much smaller upon secondary infection since it is in part determined by how quickly the virus gets cleared, then we predict a simple boosting of the memory population. We may also try this experiment with the de Boer model by crudely assuming that the $M$ cells after a primary response instantaneously convert to effectors and so provides the analogous $A_0$ for further infections.

The most elusive parameters in the general models of this presentation are the generalized recruitment parameters $M_0$, $E_0$, or $A_0$, which have something to do with the initial activation of cells. This initial priming most likely takes place as T cells interact with mature dendritic cells in the lymph nodes. Future work details how T cell receptor triggering in the lymph nodes can generate a distribution of differently differentiated activated cells.

References


