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DEVELOPMENT OF THE T-CELL REPERTOIRE: CLONE SIZE DISTRIBUTION

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Dedicated to Paul Waltman on the occasion of his 60th birthday

ABSTRACT. The development and maintenance of the T lymphocyte repertoire, which determines which antigens will elicit an immune response, involve a complicated learning process involving internal interactions and external (environmental) factors. The dynamics are not unlike that of thousands of nearly identical competing species. This paper examines the distribution of clone (species) populations, how it is created and how it is maintained.

1. Introduction. Diversity of the immune system repertoire is necessary to insure both that antigens are recognized and that specific challenges are met with precise (and proportional) responses. It is also necessary to insure that autoantigens do not elicit a strong response and that the system maintaining this diversity be adaptable to environmental conditions while holding a memory of the antigens encountered. And, this must be accomplished in both the B and T lymphocyte populations.

The establishment and maintenance of the T cell repertoire is studied here through the mechanisms which must be present in order that the system satisfy the demands of its required role. This study results in a novel picture of the dynamics of clonal selection [**1**].

T cells are produced in the bone marrow and mature and expand their population in the thymus before entering the circulation. While in the thymus, there is a "negative selection" which removes potentially autoreactive T cells and a "positive selection" for the ability of the T cell receptor (TCR) to bind one of the classes of the major histocompatibility complex (MHC). This positive selection provides the maturation signals for both the $CD4^+$ and $CD8^+$ populations depending on the class of MHC binding. The first selection process involves cellular proliferation and the second does not [**10**]. As a result, the output from

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the thymus can be seen as a diverse collection of allowable specificities. Further shaping of the population must come from interactions with antigen within the peripheral tissue. This is also seen in the need, in humans and in many other mammals, for the periphery to renew the T cell population as the thymus regresses beginning at puberty [**16**]. In adults, removal of the thymus leads to a slight decrease in the number of peripheral T cells, but no noticeable loss in the ability to mount an immune response [**4**]. In mice, induction of significant T cell deficiency requires removal of the thymus before the second day after birth [**9**]. Thus, after initial seeding from the thymus, the periphery must both shape the adult repertoire and maintain that shape.

The periphery provides several forces which may be used in this effort. One is, of course, reaction with exogenous antigen. But this is not the only source of stimulation as a workable repertoire with the appropriate population sizes is found in mice not subject to intentional antigen stimulation [**12**]. Other aspects which could be supplying stimulatory signals to the T cells could be self reactivity and network interactions. As the mechanism necessary for this stimulation is not elucidated, we will emphasize the dynamic requirements of the regulatory process.

The mechanisms for self-renewal poses a problem that was first recognized in the context of ecological models, competitive exclusion. Populations competing for sufficiently similar resources have been shown to be unable to coexist, and exclusion of the "least efficient" is accomplished over time (cf. [**8**]). If T cells are dividing, they have to compete for space, nutrients, growth factors and other cytokines in the lymphoid tissues with other T cells. Since T cells of the same class are seen as different from one another primarily through differences in the TCR, and that receptor is a primary source for the stimulation signals that each responds to, their competition for space, growth factors, etc., suggests that certain clones will be excluded while others will be able to grow based on differences in stimulatory signals received through the TCR [**11**]. The problem with competitive exclusion in this setting is that clones corresponding to the highest levels of stimulation (e.g., ubiquitous antigens) would eventually eliminate all others. Recently a class of "superantigens" has been discovered that react with a third or so of all T cells, and which can in fact cause fatal disease [**7**]. Our approach to the problem of competitive exclusion of specificities will be to study the properties of models in which different T cell clones are

randomly activated by different (unspecified) stimuli.

It is unclear what to expect for coexistence in a model of the T cell repertoire where the individual clone's self-renewal is based on a "lottery system" delivering stimulatory signals. The equilibrium theory developed by May predicts that the greater the (environmental) variability the less likely it is that species coexist in the long run. Conversely, variability has been shown to promote coexistence in lottery based competitive systems [2]. To explore the issue in this context, we develop a model, based on having dynamic equations to describe each clone's population, in which only the distribution of clone sizes is described. By examining different versions of the model, necessary features of the regulatory process which give rise to coexistence are described. The more general question of the role of environmental variability, as opposed to the random (but stationary) environment presented here, will not be explored, as the features which characterize the regulation are of primary interest. These features, termed "local" and "global" control, are shown to shape the repertoire in different but complementary ways.

2. Motivation. The basic equation governing the growth of a particular clone numbered i is

$$\frac{dT_i}{dt} = \gamma_i R f(T_{TOT}) g(T_i) T_i - (1 - \gamma_i)\, dT_i \tag{1}$$

where

$$T_{TOT} = \sum_i T_i.$$

In this expression, R is the maximum growth rate and γ_i is the fraction of the cells in the clone receiving antigenic stimulation sufficient for growth (a parameter varying in time). Those cells in the clone not receiving sufficient stimulation slowly die ("starve"). $f(T_{TOT})$ is a function representing "global control," the realization of the limit to growth of all clones based on the size of the entire population of T lymphocytes. $g(T_i)$ is a function termed "local control" that depends on the size of the clone and embodies the usual density dependent limits to population growth in a given niche. Note that the model contains no source of new T cells. Thus, the model applies to the growth of

established clones of T cells in the periphery. The effect of adding a source is examined in Section 5.

Coutinho (personal communication) has suggested that the immune system can count, since the total number of lymphocytes in an animal is finely controlled [**13**]. To achieve this control, individual clones must stop growing when the total population size gets too large. The function $f(T_{TOT})$ is the realization of the Coutinho counting hypothesis. Exactly how such global control is maintained is not at all clear, and it may in fact be an emergent property of system of clones growing without a pre-specified global control function. A recent model for the development of an idiotypic network in which the growth of B cell clones was determined by their interaction with serum antibody maintained global population control without an explicit maximum population level being preset [**3**]. In fact, in this model the attained maximum population level was an emergent property of the system and its local interaction rules. Here we will study the consequences of both having and not having global control.

To maintain a general model, we only assume the following for the function f:

$$(2) \qquad 0 \leq f(x) \leq 1, \quad f(0) = 1, \quad f'(x) < 0 \quad \text{and} \quad \lim_{x \to \infty} f(x) = 0.$$

Even when the total population of lymphocytes is not near the carrying capacity of the organism, there are limits to the growth of a single clone. The precise maximal size of a clone is unknown, but one can imagine that physical space within the microenvironment of a lymph node or spleen as well limits to the number of divisions of a cell (the Hayflick limit) will prevent a clone from growing too large. The "local control" function g, which also stays between 0 and 1, depends only on the size of the i^{th} clone. Specifically, we assume

$$(3) \qquad 0 \leq g(x) \leq 1, \quad g(0) \leq 1, \quad g'(x) < 0 \quad \text{and} \quad \lim_{x \to \infty} g(x) = 0.$$

The use of both local and global control functions in immune system models is not novel and has been introduced previously by Segel and Perelson [**14**]. A particular choice of functions f and g was made in the models explored by Segel and Perelson [**14, 15**]. Here we explore the entire class of functions compatible with Equations (2) and (3).

Because the growth rate of any clone is assumed to depend on both the size of the clone and T_{TOT}, the evolution of a population of clones is coupled. To directly study the overall clone size distribution, this simple model can be further abstracted. The direction of this abstraction is best illustrated by noting that

$$(4) \qquad (\ln T_i(t))' = \gamma_i(Rf(T_{TOT})g(T_i) + d) - d$$

which implies

$$(5) \quad \ln T_i(t+\Delta t) - \ln T_i(t) = (\gamma_i(Rf(T_{TOT})g(T_i) + d) - d)\Delta t + o(\Delta t).$$

3. Derivation of the bin model. The form of equation (5) suggests that a type of birth-and-death structure would be appropriate, especially if only order of magnitude changes (significant changes in the logarithm) are recorded. To accomplish that, we will "bin-up" or collect those clones with population sizes that are of the same order of magnitude, that is, have the same characteristic of the logarithm of clone size. Here we use $\log_{10}$ for convenience, but any base is equally fine and all results are stated for the general case. If the base of the logarithm is b, we assume clones in bin j contain on the order of b^j cells, and thus local control will be a function of b^j. With that in mind, and letting C_i be the characteristic of the logarithm of the population of the i^{th} clone, define the probability of registering the growth to the next largest order of magnitude over a time Δt as

$$(6) \quad \Pr[C_i(t+\Delta t) - C_i(t) = 1 | C_i(t) = j \text{ and } T_{TOT} = T] = \rho f(T)g(b^j)\Delta t + o(\Delta t),$$

where ρ is a constant. We assume that a clone registers a loss of an order of magnitude in its population in time Δt with probability

$$(7) \quad \Pr[C_i(t+\Delta t) - C_i(t) = -1 \mid C_i(t) = j \text{ and } T_{TOT} = T] = \delta\Delta t + o(\Delta t),$$

δ is a constant death rate. It will also be assumed that

$$\Pr[C_i(t+\Delta t) - C_i(t) = 0 \mid C_i(t) = j \text{ and } T_{TOT} = T] = 1 - (\rho f(T)g(b^j) + \delta)\Delta t + o(\Delta t)$$

so that the probability of changes of two or more orders of magnitude in unit time Δt is $o(\Delta t)$.

With these definitions, the expected change in C_i over time Δt has the same form as the right hand side of (5), preserving the link between (1) and the abstract model. Note that the choice of the base of the logarithm affects the constants ρ and δ.

The death part of the process seen in (7) is modeled by assuming that cell death occurs at a constant rate, and hence is not antigen driven nor density dependent. It is assumed in (7) that the rate at which a clone loses an order of magnitude in its populations is linear. To understand this, assume that many clones are spread uniformly (in the log) over population sizes of the same order of magnitude. If we would now have one of those populations decline exponentially (the log declining linearly), the probability that it would cross an order of magnitude boundary, increases linearly in Δt.

The model that results can be put in the form of Kolmogorov forward equations for a birth-and-death process. The process is not birth-and-death as defined, however, due to the "global control" term. Let $B_j(t)$ be the contents of bin j (the fraction of the clones with size having order of magnitude j) at time t. Then for $j \geq 1$, using (6)–(8)

$$B_j'(t) = \rho f(T_{TOT}) g_{j-1} B_{j-1} + \delta B_{j+1} - \rho f(T_{TOT}) g_j B_j - \delta B_j. \tag{9}$$

For $j = 0$,

$$B_0'(t) = \delta B_1 - \rho f(T_{TOT}) g_0 B_0, \tag{10}$$

and

$$T_{TOT} = \sum_j b^j B_j. \tag{11}$$

In this expression, $g_j = g(b^j)$, and the initial condition is specified at time 0, $B_j(0) = B_{j,0}$, with $\sum_j B_{j,0} = 1$. Note that there is no source or loss of clones. Clones only get larger or smaller and hence move from bin to bin.

The actual stochastic structure of the model is the following. Suppose the process starts with i identical particles (corresponding to single

cell clones) at time 0. Each one grows as a continuous-time branching process, except that the offspring probabilities depend on some function of the current total population (here T_{TOT}). As such, it is most like a multi-type density-dependent continuous-time branching process. The structure gains its density-dependence from the "local control" term. It, in addition, has the coupling due to the "global control." Also, we are interested in a somewhat unusual quantity,

$$P_j^i = \Pr(\text{a particle from an initial population of } i \text{ particles at time 0 has } j \text{ descendents by time } t). \tag{12}$$

Here the "number of descendents" is the bin number. This is a hard quantity to deal with directly through branching process methods as at time t, T_{TOT} is also a random variable, and thus knowledge of all the other bins is required. Here we use a version of the Chapman-Kolmogorov equation for counting the number of descendents. We also use (6)–(8) and an averaged value for T_{TOT}.

$$\begin{aligned} P_j^i(t+\Delta t) = {} & P_{j-1}^i(t)P_{j-1,j}^T(\Delta t) + P_{j+1}^i(t)P_{j+1,j}^T(\Delta t) \\ & + P_j^i(t)P_{j,j}^T(\Delta t) + o(\Delta t) \end{aligned} \tag{13}$$

where

$$P_{k,j}^T(\Delta t) = \int \Pr(\text{a transition from } k \text{ to } j \text{ descendents in time } \Delta t \text{ when } T_{TOT} = T \text{ at time 0})\, dP(T).$$

The integration here is over all potential T_{TOT} sizes. If we assume, however, that the entire state of the process is known at time t, T_{TOT} can actually be computed, and as a result,

$$\begin{aligned} P_{j-1,j}^T(\Delta t) &= \rho f(T_{TOT})g(b^{j-1})\Delta t + o(\Delta t) \\ P_{j+1,j}^T(\Delta t) &= \delta \Delta t + o(\Delta t) \end{aligned} \tag{14}$$

and

$$P_{j,j}^T(\Delta t) = [1 - \rho f(T_{TOT})g(b^j) + \delta]\Delta t + o(\Delta t).$$

Using these in (13), we again have the bin model, (9)–(11). The recognition of the variable ways in which the same model can be seen also suggests ways in which the model can be analyzed.

4. Analysis.

4.1. Existence of a unique equilibrium. Any distribution where the net flows between the states is zero is clearly a stationary distribution. The converse is also true and is well known for birth-and-death processes.

Proposition 1. *Every equilibrium (stationary distribution) of* (9)–(11) *satisfies*

$$\delta B_{j+1} = \rho f(T_{TOT}) g_j B_j \qquad \text{for all } j = 0, 1, \ldots .$$

Proof. An equilibrium distribution has zero net flow between the states, that is, $B_j' = 0$ for all j. Let $0 \leq k$, and suppose that B^0 is an equilibrium vector. At this equilibrium,

$$\sum_{j=0}^{k} B_j'(t) = \delta B_{k+1} - \rho f(T_{TOT}) g_k B_k = 0.$$

This holds for all k. □

From Proposition 1, the bin contents at equilibrium must satisfy

$$\begin{aligned} B_1 &= \left(\frac{\rho}{\delta} f(T_{TOT})\right) g_0 B_0 \\ B_2 &= \left(\frac{\rho}{d} f(T_{TOT})\right)^2 g_0 g_1 B_0 \\ &\vdots \\ B_k &= \left(\frac{\rho}{\delta} f(T_{TOT})\right)^k \prod_{i=0}^{k-1} g_i B_0 \\ &\vdots \end{aligned} \tag{15}$$

Because B_j is defined to be the fraction of clones with size in bin j, $\sum_j B_j = 1$. This implies

$$B_0 = \left(1 + \sum_k \left[\left(\frac{\rho}{\delta} f(T_{TOT})\right)^k \prod_{i=0}^{k-1} g_i\right]\right)^{-1}. \tag{16}$$

Further, T_{TOT} satisfies

$$T_{TOT} = \sum_j b^j B_j = B_0\left(1 + \sum_k \left(b\frac{\rho}{\delta} f(T_{TOT})\right)^k \prod_{i=0}^{k-1} g_i\right). \tag{17}$$

Note that, given a T_{TOT}, the distribution (15) is specified. To establish that a unique equilibrium exists, we will show that for a given set of parameters there is a unique T_{TOT} satisfying (17). The dynamics of T_{TOT} itself will also be explored below.

Let

$$E_k = \prod_{i=0}^{k-1} g_i, \tag{18}$$

and let $F(x)$ be defined by

$$F(x) = \frac{1 + \sum_{j=1}^{\infty} b^j (\rho/\delta)^j E_j (f(x))^j}{1 + \sum_{j=1}^{\infty} (\rho/\delta)^j E_j (f(x))^j}. \tag{19}$$

The T_{TOT} value at the equilibrium is a fixed point of F, that is, it satisfies

$$F(x) = x. \tag{20}$$

First note that $F(0) > 1$. The main idea is to show that $F'(x) < 0$ and hence that there is a unique intersection of the line $y = F(x)$ with the line $y = x$. To show $F'(x) < 0$ we need two lemmas.

Lemma 1. *Let $b > 1$ and k and j be positive integers with $k > j$; then*

$$(kb^k + jb^j) - (jb^k + kb^j) > 0. \tag{21}$$

Proof. As

$$b^j(k - j) > k - j, \quad b^k[(k - j)b^{k-j} + j - k] > 0. \tag{22}$$

The result follows. □

Lemma 2. *Let* $h(y) = 1 + \sum_{n=1}^{\infty} a_n y^n$, *where the series converges in some interval about* 0. *Then, if* $b > 1$,

$$\left(\frac{h(by)}{h(y)}\right)' > 0 \qquad \text{for } y > 0. \tag{23}$$

Proof.

$$\begin{aligned}\left(\frac{h(by)}{h(y)}\right)' &= \frac{h(y)bh'(by) - h(by)h'(y)}{(h(y))^2} \\ &= \frac{y[h(y)bh'(by) - h(by)h'(y)]}{y(h(y))^2}\end{aligned} \tag{24}$$

The sign of the derivative is the sign of the numerator of (24),

(25)

$$\begin{aligned}&\left(1+\sum_{j=1}^{\infty} a_j y^j\right) by\left(\sum_{j=1}^{\infty} j a_j (by)^{j-1}\right) - \left(1+\sum_{j=1}^{\infty} a_j (by)^j\right) y\left(\sum_{j=1}^{\infty} j a_j y^{j-1}\right) \\ &= \left(1+\sum_{j=1}^{\infty} a_j y^j\right)\left(\sum_{j=1}^{\infty} j a_j (by)^j\right) - \left(1+\sum_{j=1}^{\infty} a_j (by)^j\right)\left(\sum_{j=1}^{\infty} j a_j y^j\right) \\ &= \left(\sum_{j=1}^{\infty} j a_j (by)^j - \sum_{j=1}^{\infty} j a_j y^j\right) \\ &\quad + \left(\sum_{j=1}^{\infty} a_j y^j \sum_{j=1}^{\infty} j a_j (by)^j - \sum_{j=1}^{\infty} a_j (by)^j \sum_{j=1}^{\infty} j a_j y^j\right).\end{aligned}$$

The first term is clearly positive as $y > 0$ while in the second, by identifying terms with the same powers of y, one finds that corresponding to y^n is a sum of terms involving $a_k a_j$ where $k + j = n$. The coefficient of all terms involving $a_k a_k$ for any k is zero. For any other choice, say $a_k a_j$ with $k > j$ the coefficient is

$$(kb^k + jb^j) - (kb^j + jb^k). \tag{26}$$

From Lemma 1, the coefficients are all positive. As a result, the numerator of (24) is positive. □

Theorem 1. *With $F(x)$ defined as in* (19), *and $f(x)$ strictly monotone decreasing,* (20) *has a unique solution.*

Proof. Let $a_n = E_n$ and $y = bf(x)$. Then, using the notation of Lemma 2, $F(y(x)) = h(by))/h(y)$. By the chain rule, $dF/dx = (dF/dy)f'(x)$. By Lemma 2, $dF/dy > 0$. Thus, $dF(x)/dx < 0$, since $f'(x) < 0$. As $F(0)$ is finite, there must be a unique crossing of $F(x) = x$. □

4.1.1. Dynamics of T_{TOT}. As $T_{TOT} = \sum_{j=1}^{\infty} b^j B_j + B_0$, differentiating and using (9)–(10) we find that

(27)
$$T'_{TOT} = \sum_{j=1}^{\infty} b^j [\rho f(T_{TOT}) g_{j-1} B_{j-1} + \delta B_{j+1} - \rho f(T_{TOT}) g_j B_j - \delta B_j] + [-\rho f(T_{TOT}) g_0 B_0 + \delta B_1].$$

Collecting the terms having the same B'_js,

(28)
$$\begin{aligned} T'_{TOT} &= \sum_{j=1}^{\infty} B_j [-b^j (\rho f(T_{TOT}) g_j + \delta) + b^{j-1}\delta + b^{j+1}(\rho f(T_{TOT}) g_j)] \\ &\quad + B_0[-\rho f(T_{TOT}) g_0 + b^1 \rho f(T_{TOT}) g_0] \\ &= \sum_{j=0}^{\infty} B_j [b^j \rho f(T_{TOT}) g_j (b-1)] + \sum_{j=1}^{\infty} B_j [b^{j-1}\delta(1-b)] \\ &= (b-1) \sum_{j=0}^{\infty} b^j (\rho f g_j B_j - \delta B_{j+1}). \end{aligned}$$

This can also be written as a "dot product" in the following way

$$T'_{TOT} = (b-1) \begin{pmatrix} b^0 \\ b^1 \\ \vdots \end{pmatrix} \begin{pmatrix} \rho f(T_{TOT} g_0 B_0 - \delta B_1 \\ \rho f(T_{TOT} g_1 B_1 - \delta B_2 \\ \vdots \end{pmatrix}. \tag{29}$$

The second vector in (29) is looking at the net flows between each of the states in turn. This structure causes T_{TOT} to increase (or decrease) rapidly when the current state is far from the equilibrium.

4.2. No global control case. The model (9)–(11), being an infinite set of nonlinear differential equations has potential difficulties with existence, uniqueness, and continuability of solutions (especially in preserving $\sum_j B_j(t) = 1$ for all $t \geq 0$). To address this, we first examine a submodel consisting of only "local control." In this model, f will be set to be identically one. The system is

$$\begin{aligned} L_j'(t) &= \rho g_{j-1} L_{j-1} + \delta L_{j+1} - \rho g_j L_j - \delta L_j, \qquad \text{for } j \geq 1 \\ L_0'(t) &= \delta L_1 - \rho g_0 L_0. \end{aligned} \tag{30}$$

These are the Kolmogorov forward equations of a birth-and-death process, and, as such, the theorems of Karlin and McGregor [**5**] apply. First define

$$b_0 = 1 \quad \text{and } b_j = \left(\frac{\rho}{\delta}\right)^j \prod_{i=0}^{j-1} g_i \qquad \text{for } j = 1, 2, \ldots . \tag{31}$$

Theorem 2. *There is a unique solution of system* (31). *Moreover, this solution satisfies*

$$\sum_j L_j(t) = 1 \qquad \textit{for all } t \geq 0. \tag{32}$$

Proof. The conditions of Karlin and McGregor require that

$$\sum_j b_j < \infty \quad \text{and} \quad \sum_j [\rho g_j b_j]^{-1} = \infty. \tag{33}$$

To check these conditions, note that since $\lim_{i \to \infty} g_i = 0$, there is an index i_0 such that

$$\frac{\rho}{\delta} g_{i_0} = \beta < 1. \tag{34}$$

Each $b_j = b_{j-1}(\rho/\delta)g_{j-1})$; thus, for $j \geq i_0 + 1$, and using (3),

$$b_j \leq b_{j-1}\beta \tag{35}$$

and as a result the tail of the series $\sum_j b_j$ is dominated by a convergent geometric series. Thus, the first condition in (34) is satisfied. The verification of the second condition depends on noting that as

$$\frac{\rho}{\delta} g_j < 1 \qquad \text{for } j \text{ large}, \tag{36}$$

its reciprocal is greater than one, and thus the sum must diverge as the n^{th} term of the sum does not go to zero. □

This establishes that the reduced model is well defined. As the purpose of these models was to describe the clonal size distribution, the following results describing both the existence and the shape of the limiting distribution are important. Recall that the existence of a unique stationary (equilibrium) distribution was established in Theorem 1, for the general case, and depended on $f'(x) < 0$ which does not hold here.

4.2.1: Existence and characterization of the limiting distribution. In this special case, because of the structure of the equations in (31), other theorems of Karlin and McGregor [6] guarantee that the limiting distribution exists and is proper. By again recalling that the net flux between states must be zero at the equilibrium, the relationship between the contents of the states at equilibrium is

$$\begin{aligned} L_1 &= \frac{\rho}{\delta} g_0 L_0 \\ L_2 &= \left(\frac{\rho}{\delta}\right)^2 g_0 g_1 = L_1 \left(\frac{\rho}{\delta} g_1\right) \\ &\vdots \\ L_k &= \left(\frac{\rho}{\delta}\right)^k \prod_{i=0}^{k-1} g_i L_0 \\ &\vdots \end{aligned} \tag{37}$$

and $\sum_{i=0}^{\infty} L_i = 1$ is the defining relationship for L_0. The information concerning the limiting distribution, a globally stable equilibrium point, is collected in the following

Theorem 3. *System* (31) *has a proper limiting distribution satisfying* (37). *Moreover, the mode of this distribution is at* $i-1$ *for* $i \geq 1$ *if* i *is the smallest index with* $(\rho/\delta)g_i < 1$, *and the mode is at* L_0 *if* $(\rho/\delta)g_0 < 1$.

Proof. The conditions in Karlin and McGregor [6] are the same as those in Theorem 2 (33), which have been shown to be satisfied for all choices of the parameters. For the second part, note from (37), that

$$\frac{L_{k+1}}{L_k} = \left(\frac{\rho}{\delta} g_k\right). \tag{38}$$

As a result, the L_k's increase to the first index that the ratio is less than one, then they decrease monotonically to zero. □

4.3. Existence in the general case. The result presented above in Theorem 2 indicates the way in which existence of solutions for the differential equations (9)–(11) on $[0, \infty)$ can be established. As in Theorem 2, the primary concern is that the process may "explode," that is, have infinitely many transitions in finite time. As the states are bounded below by 0, if there are infinitely many transitions, there must be infinitely many transitions up. The approach will be to use (2) so that we can write

$$\rho f(T_{TOT}) g_j \leq \rho g_j, \qquad \text{for all } j \text{ and } T_{TOT}.$$

Thus,

$$1 + \sum_{j=1}^{\infty} \left(\frac{\rho}{\delta} f(T_{TOT}) \prod_{i=1}^{j-1} g_i\right) \leq 1 + \sum_{j=1}^{\infty} \left(\frac{\rho}{\delta} \prod_{i=1}^{j-1} g_i\right)$$
$$= \sum_{j=0}^{\infty} b_j < \infty.$$

As $\rho f(T_{TOT}) g_j$ is bounded, then it is also the case that

$$\sum [\rho f(T_{TOT}) g_j b_j]^{-1} \geq \sum [\rho g_j b_j]^{-1} = \infty.$$

In this set of inequalities, we have discovered a birth-and-death process, whose forward Kolmogorov equation is (31), that has mean time to upward transition always smaller at each state (rate is larger) than that corresponding to system (9)–(11). As solutions of (31) satisfy Theorem 2, the probability that a sample path of that process explodes is zero. As the upward transition rates of the birth-and-death are larger than those of (9)–(11), it also has probability of exploding zero. As a result, we have

Theorem 4. *Solutions of* (9)–(11) *exist for all* $t \geq 0$ *and satisfy*

$$\sum_{j=0}^{\infty} B_j(t) = 1 \qquad \textit{for all time } t \geq 0.$$

4.4. No local control. We now examine the case when local control is absent ($g_i \equiv 1$). In this model, a form of competitive exclusion is seen, in that a few large clones dominate the population. It is this result, stated in Theorem 4, that best presents the case for a "local control" in the dynamics which govern clone growth, as in (1).

The bin model (9)–(11) with $g_j \equiv 1$ is

(39)
$$G_j'(t) = \rho f(G_{TOT})G_{j-1} + \delta G_{j+1} - \rho f(G_{TOT})G_j - \delta G_j \qquad \text{for } j \geq 1$$
$$G_0'(t) = \delta G_1 - \rho f(G_{TOT})G_0$$

where

$$G_{TOT} = \sum_{j=0}^{\infty} b^j G_j.$$

In this case the equation for G_{TOT}' as seen from (28) can be put in the form

(40)
$$G_{TOT}' = (b-1)\mathbf{G}(\rho f(G_{TOT})\mathbf{v}_1 - \delta \mathbf{v}_2)$$

where

$$\mathbf{v}_1 = \begin{pmatrix} b^0 \\ b^1 \\ \vdots \\ b^j \\ \vdots \end{pmatrix} \quad \text{and} \quad \mathbf{v}_2 = \begin{pmatrix} 0 \\ 1 \\ \vdots \\ b^{j-1} \\ \vdots \end{pmatrix}.$$

If $f(G_{TOT}) \geq \delta/(b\rho)$, then, using the above,

$$G'_{TOT} > 0$$

as each component of $\mathbf{G}$ is nonnegative. As $G_{TOT}(t)$ is increasing in that region, $f(G_{TOT})$ is decreasing. As a result, $f(G_{TOT})$ eventually reaches values less than $\delta/(b\rho)$ and stays less than $\delta/(b\rho)$.

4.4.1. Equilibrium vector and its characterization. In this section the equilibrium vector for the no local control case will be explored.

First note that the proof of Theorem 1 still holds for this case, so we know that a unique equilibrium vector exists for each choice of parameter values. Moreover, in this case, the components satisfy

$$G_j = \left(\frac{\rho}{\delta} f(G_{TOT})\right)^j G_0. \tag{41}$$

Theorem 5. *With $b = 10$, for the unique equilibrium vector in (41), the contents of bin 0, G_0, have the property that $G_0 > .9$ and the distribution is always monotone decreasing.*

Proof. As G_0 must satisfy

$$1 = G_0 + \left(\frac{\rho}{\delta} f(G_{TOT})\right)^1 G_0 + \cdots + \left(\frac{\rho}{\delta} f(G_{TOT})\right)^n G_0 + \cdots,$$

$G_0 = 1 - (\rho/\delta) f(G_{TOT})$ (by summing the geometric series). As we have established for $b = 10$ that

$$f(G_{TOT}) < \frac{\delta}{10\rho},$$

at any equilibrium, it must be the case that

$$G_0 < 1 - \frac{1}{10} = .9.$$

The monotonicity comes from the geometric form with common ratio less than .1. □

In this case, then, although G_{TOT} is large, most clones are of size order of magnitude 0 and, as a result, very few clones are large. This is a form of "competitive exclusion."

5. Extensions of the theory.

5.1. Loss of clones and source of new clones. In the previous discussion, especially as seen in (10), we have assumed that there is no source of new clones of loss of existing clones. An equivalent assumption is that the two, loss and source, always balance. In this section we examine that assumption by allowing a loss of clones from B_0 and a constant source of new clones.

Assuming that the death rates are independent of local control (clone size) and global control (total T cell count), the rate of loss of clones from bin 0 should be proportional to the number of clones in bin 0. Unfortunately, B_0 is the fraction of clones that are in bin 0, and thus to examine the loss of clones, we need to define a new quantity, $N_c(t)$, the number of clones at time t. As presently defined, the system (9)–(11) is closed, and hence the number of clones remains a constant. If we allow a source and sink, the equation governing N_c is

$$N_c'(t) = -\delta B_0 N_c + s. \tag{42}$$

In the above, the number of clones in bin 0 at time t is $B_0 N_c$ and δ is the rate at which they become extinct. Note that

$$N_c' > 0 \quad \text{if } N_c < \frac{s}{\delta B_0(t)}$$

and

$$N_c' < 0 \quad \text{if } N_c > \frac{s}{\delta B_0(t)}.$$

Thus, $N_c(t)$ tries to "track" the value $s/(\delta B_0(t))$. If B_0 approaches a limit, so must N_c.

In the B_0 equation, the loss/source term is somewhat different. As the source term s is in the units of clones per time, and B_0 is a relative frequency, we first examine the quantity $D_j(t)$, defined by

$$D_j(t) = B_j(t) N_c(t) \quad \text{or} \quad B_j(t) = D_j / N_c,$$

which counts the number of clones in bin j. To discover how the bin j equation changes, we first compute the differential equation governing D_0,

$$D_0'(t) = \delta D_1 + s - \delta D_0 - \rho f(T_{TOT}) g_0 D_0.$$

Then, using the quotient rule, one finds that

$$\begin{aligned} B_0'(t) &= \frac{N_c D_0' - D_0 N_c'}{N_c^2} \\ &= \delta B_1 - \rho f(T_{TOT}) g_0 B_0 + \left(\frac{s}{N_c} - \delta B_0 \right)(1 - B_0). \end{aligned}$$

The equations for all the other bins also have an additional term:

$$-B_j(t)\left(\frac{N_c'(t)}{N_c(t)}\right).$$

From this, it can be seen that the assumption of no source is equivalent to (3) being at quasi-steady state ($N_(t)' \approx 0$) or that $N_c(t) \gg N_c'(t)$.

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