A STOCHASTIC MODEL FOR CD8$^+$ T CELL DYNAMICS IN HUMAN IMMUNOSENESCENCE: IMPLICATIONS FOR SURVIVAL AND LONGEVITY

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ABSTRACT

We propose here a stochastic model for the CD8$^+$ T lymphocyte dynamics on the long time scale of the human life span. Our purpose has been to test the hypothesis, recently proposed on the basis of our experimental data (Fagnoni et al., 2000), that the depletion of virgin CD8$^+$ T lymphocytes can be considered a reliable biomarker related to the risk of death. This hypothesis is embedded in a more general theory of immunosenescence according to which the accumulation of antigen experienced (AE) T cells and the concomitant exhaustion of antigen non experienced (ANE) T cells with age, mostly due to the chronic lifelong exposure to antigens, is a major characteristic of the remodeling of the human immune system with age. We considered in our model a deterministic balance of ANE and AE T cell concentrations plus a stochastic forcing, which describes the chronic antigenic stress fluctuations, assuming a mean genetically determined capability of individuals to respond to antigens. The major results of our model is the validation of the above mentioned hypothesis, since the model is capable of fitting the experimental data concerning the changes of ANE T cell concentration over age, and at the same time to reproduce survival curves similar to the demographic ones. Furthermore, the stochastic process results to be responsible for the peculiar shape of the survival curves.

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1 - INTRODUCTION

The immune system (IS) as a whole can be envisaged as a very complex and sophisticated machinery devoted to the recognition and neutralization of a particular type of damaging agents, i.e. pathogenic viruses, bacteria, parasites and other foreign agents, collectively called antigens. Survival is largely dependent on a well functioning IS, and old people are more prone to a variety of life-threatening diseases, including viral and bacterial infections, as a consequence of the changes occurring with age in the IS. This phenomenon, we will refer to as immunosenescence, is a long time scale dynamics occurring over decades, and its study is particularly important for the comprehension and the conceptualization of the physiology of the IS in humans. Before describing our model on the internal dynamics of the IS T cell pool and the changes it undergoes with age, we remind here that peripheral blood T lymphocytes are commonly subdivided in a large number of subsets, on the basis of the expression of cell surface molecules, or markers, indicated as CD (cluster designation). The presence of CDs identifies functionally distinct T cell populations. The most important subsets are CD4\(^+\) (T helper) cells, which have a support function for other IS cells, and CD8\(^+\) (T cytotoxic) cells with the function of destroying those cells that are recognized as potentially dangerous for the organism, such as virally infected or cancer cells. Furthermore, three major functional subsets of CD8\(^+\) T cells are identified: virgin (antigen not experienced, ANE cells) and memory and effector (antigen experienced, AE cells) as depicted in Fig. 1. A profound reshaping of all the above mentioned T cell subsets, and consequently of the adaptive clonotypic immunity, is the major characteristic of immunosenescence in humans (Franceschi et al., 1995; Wack et al., 1998; Nociari et al., 1999; Franceschi et al., 1999; Franceschi et al., 2000a). A recent investigation (Fagnoni et al., 2000) describes in quantitative terms the age-related dynamics of AE and ANE T cells in a large number of healthy subjects, covering the entire life-span from young people (18 years old) to centenarians (108 years old). In that investigation the CD95\(^-\) T lymphocytes were identified as ANE cells and the CD95\(^+\) T lymphocytes as AE cells. The most striking finding, which inspired the mathematical model presented here, was the unexpected exhaustion of the ANE CD8\(^+\) T-cell reservoir in the oldest old, suggesting that such change may be related to human mortality and life span.

2 - THE EXHAUSTION OF ANE T CELLS AS A CONSEQUENCE OF THE AGE-RELATED EFFECTS OF THE ANTIGENIC LOAD

During an immune response a crucial phenomenon occurring in the IS after stimulation with antigens is the activation and the clonal expansion of antigen specific T lymphocytes. Concomitantly, ANE T cells become AE cells, either memory or effector. The IS undergoes two different types of antigenic load that, presumably, differently affect the activation and the clonal expansion of T lymphocytes. The first refers to acute antigenic challenges (acute infections), which are able to cause
spectacular expansions of T cells on the time scale of days and weeks (Maini et al., 1999), whereas the second refers to chronic sub-clinical infections, whose effect on the clonal expansion of T lymphocytes, both CD4$^+$ and CD8$^+$, is less known. Both acute and chronic antigenic load impinge upon the IS over time, and are responsible for immunosenescence. An age-related increase of AE T cells in percentage and absolute number, predominantly among CD8$^+$ T cells, was found (Fagnoni et al., 1996; Cossarizza et al., 1996). Moreover, the number of T cell clones (T cell repertoire) shrinks markedly with age, owing to the expansion of relatively few T cells, which are progressively selected and stimulated by antigens over years. Indeed, expanded CD8$^+$ AE T cell clones are predominant in 70-75 years old subjects and centenarians (Wack et al., 1998, Schwab et al., 1997). Concomitant with the increased number of AE cells and clones, an exhaustion of ANE T cells (CD95$^-$), particularly within the CD8$^+$ T cell subset, occurs with age. We surmise that this last phenomenon may represent a crucial constraint for the immune responses to occur. The extreme reduction of ANE cells, capable of defending the body against new antigens, can substantially contribute to the high susceptibility of old people to infections and other immune related diseases (Fagnoni et al., 2000). According to this scenario a stress theory of immunosenescence has been proposed, which anticipates that the IS ages because of the variety of the acute and mostly chronic antigenic stress impinging upon the system lifelong (Ottaviani & Franceschi, 1997; Franceschi et al., 1999; Franceschi et al., 2000a; Franceschi et al., 2000b).

3 - THE STOCHASTIC MODEL

The mathematical model presented here is a simplified stochastic model by which we wanted to test the hypothesis that the chronic antigenic load affects the dynamics of CD8$^+$ T cells over the long time scale of the human life span, and that the consequent exhaustion of CD8$^+$ ANE T cells, accompanied by a accumulation of CD8$^+$ AE T cell clones, is related to an increased risk of death (mortality). Our model has been eventually applied to our experimental data on CD8$^+$CD95$^-$ ANE and of CD8$^+$CD95$^+$ AE T cells. We assumed that there is a threshold of ANE T cell concentration under which the probability of dying is remarkably high, and we used this assumption to eventually compare the results obtained by the mathematical model with the shape of demographic mortality curves in humans. We applied the following general equation which is currently used to represent a linear dynamical system being subject to stochastic fluctuations

$$\frac{dx}{dt} = A(t)x + s(t) + \gamma \xi(t)$$  

where $x = (V, M_E)$ is the vector of virgin $V$ (i.e. ANE CD8$^+$), and memory plus effector $M_E$ (i.e. AE CD8$^+$) T cells. The first term $A(t)x$ globally describes the conversion of ANE to AE CD8$^+$ T cells, due to the acute and average chronic antigenic stress, the amplification of AE CD8$^+$ T cell clones due to further stimulation
by means of the same or highly cross reactive antigens and the death of cells by apoptosis. The second term \( s(t) \) represents the input from the thymus, and the third term \( \gamma \xi(t) \) describes the rate of change of cells due to the fluctuations of the chronic antigenic load with respect to its averaged value. Such a term is responsible for the fluctuations of cell number within both ANE and AE CD8\(^+\) T cells pools. The matrix \( A(t) \) has been assumed as the average of the genetically controlled capabilities of the IS of each individual in the population to respond to antigenic stimuli.

Due to the long time scale considered in our model, we are allowed to neglect the input of new cells from poietic organs such as the thymus and the output of cells because of apoptosis. Moreover, despite recent evidence that the thymic activity is still present even in the elderly (Poulin et al., 1999; Douek et al., 1999), the major benefit of thymic emigrants to the peripheral IS is likely not the maintenance of overall cellularity but in ensuring the ongoing replenishment of the T cell repertoire (Berzins et al., 1999) a function which dramatically declines over age. The balance between generation and death of cells is crucial only when a short time scale dynamics is taken into account, as in the case of an acute antigenic stimulation (Maini et al., 1999). The natural time step of our model is one year and thus, on the considered time scale, the system evolves through a sequence of quasi-equilibrium states, characterized by transfers of cells between the ANE and AE T cell compartments, maintaining almost constant the overall number of cells (homeostasis). In fact, this number varies on the very short time scale corresponding to the time typical of the fluctuations of the chronic antigenic stress (assumed to be days) but the corresponding fluctuations of the cell numbers are hidden when considering the long time scale dynamics characterized by a time step of about one year. Consequently, we assumed in our model that the immunological space, given by the sum of AE and ANE T cells (Franceschi et al., 2000a; Franceschi et al., 2000b), does not change with age, even though, according to available experimental evidence a continuous modest shrinkage occurs (Sansoni et al., 1993). Our last assumption has been that the matrix \( A(t) \) is independent of time. The further constraint that the overall number of CD8\(^+\) T cells is constant is implemented by choosing the matrix as \( A = \begin{pmatrix} -\alpha & -\beta \\ \alpha & \beta \end{pmatrix} \). This choice allows us to move from a system based on the absolute number of cells to a system based on the concentrations of cells preserving the linearity and the structure itself of the equations. Indicating the concentration of ANE and AE T cells with, respectively:

\[
 v = \frac{V}{V + M_E} \quad m_E = \frac{M_E}{V + M_E} \quad (2)
\]

to which \( m_E = 1 - v \) obviously follows, the deterministic part of the equation (1) becomes:

\[
 \frac{dv}{dt} = -\alpha v - \beta m_E, \quad \frac{dm_E}{dt} = \alpha v + \beta m_E \quad (3)
\]

\[
 v = \frac{V}{V + M_E} \quad m_E = \frac{M_E}{V + M_E} \quad (2)
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\]

\[
 4
\]
The terms in the right hand side of equations (3) mean that the CD8$^+$ T cell number variations are determined by the following mechanisms: 1. ANE T cells (V) become AE T cells ($M_E$) after activation, due to antigen recognition and stimulation. Consequently, the number of V cells decreases by a constant rate $\alpha$ and ($M_E$) cells increase by the same amount. 2. the number of AE T cells increases independently with a constant rate $\beta$ as a consequence of the secondary antigenic stimulation, which contributes to their clonal expansion; the corresponding decrease of ANE T cells is a consequence of our assumption that $ANE + AE = const$. Finally adding the stochastic fluctuation term and using $m_E = 1 - v$ the resulting equation is:

$$ \frac{dv}{dt} = -\beta - (\alpha - \beta)v + \gamma \xi(t) $$

(4)

where $\gamma \xi(t)$ is assumed to be white noise:

$$ \langle \xi(t) \rangle = 0 \quad \langle \xi(t)\xi(t') \rangle = \delta(t - t') $$

(5)

The mean solution of the stochastic equation (4) is also the solution of the deterministic part of the same equation that, by introducing the following variables

$$ T = \frac{1}{\alpha - \beta} \quad v_\infty = \frac{-\beta}{\alpha - \beta} \equiv -\beta T $$

reads

$$ \langle v \rangle = v_\infty + (1 - v_\infty)e^{-t/T} $$

(7)

From a biological viewpoint this solution is representative of the evolution of the ANE CD8$^+$ T cell concentration within the IS of an ideal individual who did not experience any fluctuations of the antigenic load. The presence of antigenic load fluctuations gives to each individual a particular temporal evolution of the T cell concentrations, notwithstanding the same initial condition. Each individual trajectory, which differs from the deterministic (mean) curve, is the solution of the evolution equation (4) corresponding to a particular realization of the stochastic process. At any time the concentration of ANE CD8$^+$ T cells has a spectrum of values around the mean given by (7). The probability to find their concentration in a given interval at time $t$ is given by a Gaussian integral (Van Kampen, 1992). The probability density $\rho$ is the solution of the Fokker-Planck equation of the Ornstein-Ulembeck stochastic process, whose Langevin equation is given by (4) (Risken, 1989). The density explicitly reads

$$ \rho(v, t) = \frac{1}{\sqrt{2\pi \sigma^2(t)}} \exp \left( -\frac{(v - \langle v \rangle(t))^2}{2\sigma^2(t)} \right) $$

(8)

where the mean square deviation

$$ \sigma^2(t) = \gamma^2 \frac{T}{2} (1 - e^{-2t/T}) $$

(9)
reaches asymptotically a constant value. As a consequence, the probability that at time $t$ the ANE CD8$^+$ T cell concentration of an individual has a value in the interval $[\langle v \rangle(t) + a\sigma(t), \langle v \rangle(t) + b\sigma(t)]$ does not depend on $t$ and reads

$$\text{Prob}(\langle v \rangle(t) + a\sigma(t) < v < \langle v \rangle(t) + b\sigma(t)) = \frac{1}{\sqrt{2\pi}} \int_{a}^{b} \exp\left(-\frac{u^2}{2}\right) du$$

(10)

Under our hypothesis that the death of individuals occurs when the ANE CD8$^+$ T cells are almost exhausted, the probability of having a concentration above a small positive threshold $v_*$ at time $t$ corresponds to the survival probability. Neglecting the fluctuations, the death age $t_*$ would be the same for all individuals and given by $\langle v \rangle(t_*) = v_*$

$$t_* = T \log \left(\frac{1 - v_\infty}{v_* - v_\infty}\right)$$

(11)

provided that the asymptotic concentration is below the threshold $v_\infty < v_*$. If on the contrary $v_\infty > v_*$, a death age $t_*$ does not exist. This result is the consequence of the assumption that an average genetically controlled capability to respond to antigenic stress has been assumed. If we choose $v_* = 0$ the survival probability $S(t)$ at age $t$ is given by the probability that the ANE CD8$^+$ T cell concentration remains positive up to that age $S(t) = \text{Prob}(v(t') > 0, 0 \leq t' \leq t)$. We can easily evaluate the probability to have a positive concentration of ANE CD8$^+$ T cells at age $t$: this is indeed an overestimate of $S(t)$, since the trajectories that reach a positive value at age $t$, after having assumed negative values, are non discarded (see Fig. 2). The survival probability is given by

$$S(t) \leq \text{Prob}(v_* \leq v \leq 1) = \frac{1}{\sqrt{2\pi}} \int_{a(t)}^{b(t)} \exp\left(-\frac{u^2}{2}\right) du,$$

(12)

The integration range is determined by imposing that

$$\langle v \rangle(t) + a\sigma(t) = v_*, \quad \langle v \rangle(t) + b\sigma(t) = 1$$

which gives for $a(t)$

$$a(t) = \frac{v_* - \langle v \rangle(t)}{\sigma(t)}$$

(13)

By replacing the upper limit of the integral with $+\infty$ we further overestimate $S(t)$, but the difference is negligible. The asymptotic value of $a(t)$ is given by

$$a(\infty) = \frac{\sqrt{2}}{\gamma \sqrt{T}} (v_* - v_\infty)$$

(14)

The estimate of $S(+\infty)$ is positive but very close to zero provided that $a(+\infty) \gg 1$. To be more explicit we distinguish the following two cases:
\[ a(t) = \frac{\sqrt{2}}{\gamma \sqrt{T}} \frac{(1 - v_{\infty}) e^{-t/T} - e^{-t/T}}{\sqrt{1 - e^{-2t/T}}} \]  

(15)

and \( v_{\infty} > v_{\ast} \) where we have

\[ a(t) = \frac{\sqrt{2}}{\gamma \sqrt{T}} \frac{v_{\ast} - v_{\infty} - (1 - v_{\infty}) e^{-t/T}}{\sqrt{1 - e^{-2t/T}}} \]  

(16)

In the second case the asymptotic value \( a_{\infty} \) is negative and leads to a large probability of indefinite survival. From the search of parameter values giving a reasonable fit of experimental data we obtained: \( T = 74, v_{\infty} = -0.4 \). With these values we have \( t_{\ast} = 93 \), and assuming the threshold \( v_{\ast} \) to be exactly zero, the asymptotic survival probability is vanishingly small. Indeed, for the fluctuation intensities \( \gamma = 0.018 \) and \( \gamma = 0.025 \), whose survival curves are shown in Fig. 3, we found \( a(+\infty) = 2.7 \) and \( a(+\infty) = 3.6 \), so that the asymptotic upper bounds to the survival probability are \( 10^{-2} \) and \( 10^{-4} \) respectively. In Fig. 3 we show the experimental data concerning CD8\(^{+}\)CD95\(^{-}\) T cells and their fit obtained with the stochastic spread \( \langle v \rangle(t) \pm 2\sigma(t) \) with respect to the average solution \( \langle v \rangle(t) \). The survival plots shown in Fig. 3 exhibit a qualitative behavior very similar to the curves obtained from demographical studies (Vaupel & Jeune, 1996; Yashin et al., 1999). In Fig. 4 we show that demographic data can be fitted by our model with a very similar set of parameters. The model predicts that different mean life-span can be obtained if other values for average genetic capability to respond to antigens are taken into account. The age of death \( t_{\ast} \), averaged on the genetics, is the age at which the survival probability is \( 1/2 \), taking into account the antigenic fluctuations. The time \( T \) basically governs the slope of the survival curve.

### 4 - DISCUSSION

The model here presented has been inspired by our experimental data obtained on a large number of people of different ages, from young subjects to centenarians (Fagnoni et al., 2000). These data suggested that the depletion of ANE CD8\(^{+}\) T cells, due to the lifelong chronic antigenic stress, could be a crucial phenomenon of immunosenescence (Franceschi et al., 1999; Franceschi et al., 2000a; Franceschi et al., 2000b).

The main issues of the present paper are the followings:

1. two main immunological assumptions, derived from the above quoted experimental data, underlie our mathematical model: i) the relevance of the chronic antigenic stress (impinging upon the IS lifelong) in determining the internal dynamics of the
IS during immunosenescence; ii) the relevance of the depletion of ANE CD8+ T cells for the individual risk of death. We modeled the effect of the chronic antigenic load by adding a stochastic term to a deterministic linear dynamical system which represents a basic simplified model of the immunological relationship between ANE and AE T cells. We used the model to ascertain the appropriateness of the hypothesis that the exhaustion of AE CD8+ T cells is related to human mortality. To this purpose, the theoretical survival curves generated by the model were compared to those obtained from real demographic data;

2. the model is capable of fitting experimental data on CD8+CD95− T cells over the entire life span of a population of individuals, and the survival plot obtained by the model is superimposable to demographic survival data (Vaupel & Jeune, 1996) (Fig. 4). Since the CD95 marker reliably discriminates ANE from AE CD8+ T cells, we can conclude that the chronic antigenic load lifelong is relevant for the internal IS dynamics, and that the hypothesis we put forward that the number of circulating ANE CD8+ T cells is a candidate biomarker of mortality in humans, is validated.

Testing this last hypothesis on the experimental data regarding the age dynamics of CD45RO+ and CD45RA+ CD8+ T cells, an appropriate fit was obtained (see Fig. 5), but the generated survival curves were meaningless as far as real demographic survival curves were concerned. This outcome confirms that both ANE and AE cells contribute to the CD45RA+CD8+ T cell pool, and thus that the CD45 marker does not allow to appropriately distinguish between AE and ANE CD8+ T cells, as suggested by experimental findings (Hamann et al., 1997);

3. the model was not able to appropriately fit the experimental data regarding CD4+CD95− T cells (data not shown), suggesting that CD4+ T cells are less affected than CD8+ T cells by the continuous antigen exposure, as pointed out by a variety of experimental observations (Wack et al., 1998; Maini et al., 1999; Posnett et al., 1999);

4. the fit of experimental data on CD8+ ANE T cells obtained by the CD95 marker is not completely satisfactory before 30 years of age. This period is complex from an immunological point of view, because on one side it envisages the strong, peculiar effects of the initial antigenic load, and on the other side it envisages a great activity of the thymus in refurbishing the periphery of newly generated ANE T cells. This last phenomenon declines sharply after puberty, even if the thymus seems to remain active up to advanced age (Poulin et al., 1999; Douek et al., 1999). However, it is noteworthy to remind that this period is the least relevant for the outcome taken into account, i.e. the mortality of the population. Thus, being interested in the IS long time scale dynamics, we deliberately did not take into account the above mentioned situations;

5. an innovative aspect of our model relies on the fact that the stochastic process theory is applied to the dynamics of T cell populations over a long time scale. The advantage of this approach is that it accounts for the variability found in experi-
mental cross-sectional studies. Indeed, for sake of simplicity, the model assumed a mean genetically determined capability of responding to antigens but, despite this simplification, the stochasticity inherent in the model allowed us to re-create the heterogeneity of the values of CD8+CD95− T cells in different individuals, and consequently to generate survival curves similar to those observed in human populations. The shape of survival curves is strikingly similar from lower invertebrates to humans, and in outbred and inbred populations. In particular, experimental data in animal model systems, such as genetically homogeneous C. elegans, a nematode frequently investigated in important studies on aging and longevity, indicate that the mean life span is genetically determined, and that the shorter and longer individual life span only represent stochastic fluctuations (Cypser & Johnson, 1999; Vanfleteren et al., 1998). In fact, genetic mutations in genes coordinating stress response can prolong or shorten the mean life span but they do not alter the shape of the survival curves. Thus, the universal shape of such curves likely depends on stochastic fluctuations of environmental stressors, acting lifelong on a population of genetically identical individuals. The same considerations apply to humans, whose survival curves depend on the genetics, the average environmental stress and its stochastic fluctuations. These considerations help in understanding the factors that are involved in the dramatic change of survival, which has occurred in humans in the last 50-100 years. Indeed, since the genetic pool of humans remained almost constant in the last century, the recent spectacular improvement in survival can be largely, if not exclusively, attributed to an improvement in the life conditions and hygiene. Therefore, in accordance with a major prediction of our model, we surmise that the decrease of the antigenic load which occurred in the last decades in developed countries played a major role in prolonging the mean life span of humans (Franceschi et al., 2000b). Consequently, it can be predicted that living in poor countries, characterized by poor hygiene, involves a strong average antigenic stress, which could contribute to the short mean life span observed in such environmental conditions;

6. this stochastic model allowed us to introduce a short time scale phenomenon, such as the chronic fluctuations of antigenic stress, in the description of the evolution of T cell population over a typical time scale of the whole human life span;

7. this model has been particularly successful in capturing a macroscopic phenomenon, the mortality demographic distribution, starting from a mathematical description of a microscopic phenomenon, the CD8+ T cell dynamics. This result, obtained in spite of the oversimplified assumptions of the model, strongly supports the underlying biological hypothesis that the exhaustion of AE CD8+ T cells with age is an important phenomenon crucial for survival. The model also reinforces the concept that immunosenescence is the ultimate outcome of the continuous lifelong chronic antigenic stress (Franceschi et al., 1999; Franceschi et al., 2000a);

8. finally, the re-exposure of AE CD8+ T cells to antigens, which gives a negative contribution to the ANE T cell compartment (term −βmE in eq. (3) ), deserves a specific discussion. Indeed, in our model this term is the consequence of the
assumption that the overall number of CD8$^+$ T cells is constant over time. We think that this characteristic of the model is compatible with recent immunological data indicating that cells with suppressor activity are present within the pool of AE T cells (Ciubutariu et al., 1998). New experiments can be envisaged under this perspective.

Acknowledgments

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Figure 1 Schematic representation of CD8$^+$ T lymphocyte dynamics caused by antigenic load. On the left side we show the "traditional" nomenclature for T cells subsets (virgin, V, and memory plus effector T cells, $M_E$), used in the equations, while on the right side we propose the new definition for virgin (Antigen Non Experienced, ANE) and memory plus effector (Antigen Experienced, AE) T cells. By Ag$^n$ we denote the effect of the $n$-th contact with the same antigen. According to recent data of literature (Cossarizza et al., 1996; Fagnoni et al., 1996; Bell et al., 1998; Globerson & Effros, 2000; Pawelec et al., 1999; Fagnoni et al., 2000) ANE CD8$^+$ T cells are characterized by the lack of expression of CD95 and CD45RO molecules, and the presence on their surface of CD45RA and CD28 molecules. Indeed, CD45RA and CD45RO expression is mutually exclusive (Cossarizza et al., 1996). ANE cells become AE T cells, which express CD95 molecules, as a consequence of antigenic stimulation. AE cells can be further distinguished into effector and memory cells, according to the presence or absence of CD28 molecule and CD45RA or CD45RO molecules.

Figure 2 Trajectories $v(t)$ of ANE T cells concentration $v(t)$ (zig-zag curves). In both pictures we show the average trajectory $\langle v \rangle(t)$ (middle curve) and the curves $v_{\pm}(t) = \langle v \rangle(t) \pm a\sigma(t)$ separated by $a$ times the mean square deviation. In the pictures we also show two vertical segments whose endpoints are on the curves $v_{\pm}(t)$. The probability that a trajectory hits any of these segments (ANE cells concentration interval at a given time) is the same, and depends only on the amount of spread $a$. The dashed regions correspond to positive concentrations, in the left picture the average concentration has a positive asymptote $\beta < 0$, in the right picture a negative asymptote $\beta > 0$. As a consequence, for large times the probability of having a positive concentration on the left picture is finite, whereas it vanishes on the right picture.

Figure 3 Top frame. Experimental data concerning ANE T cells concentration $v(t)$ obtained with the CD95 marker (raw data: open circles; averages: full circles). Fit of the average data with the model $\langle v \rangle(t)$ (central curve) and spread $\langle v \rangle(t) \pm 2\sigma(t)$ obtained with $\gamma = 0.018$ (left), $\gamma = 0.025$ (right). Bottom frame. Corresponding survival curves $S(t)$; in both frames, the time $t$ unit is one year.

Figure 4 Comparison of demographic data (Vaupel & Jeune, 1996) (small circles) with a fit obtained from the survival function $S(t)$ with the parameters $T = 65$, $v_\infty = -0.45$. We remark that these values are comparable with those obtained from the fit of the data concerning the decrease of CD95$^-$ T cells with age. The time unit $t$ is one year.

Figure 5 Experimental data concerning AE T cells concentration obtained with
the CD45 marker. Fit of the average data with the model $\langle v \rangle(t)$ (central curve) and spread $\langle v \rangle(t) \pm 2\sigma(t)$ obtained with $\gamma = 0.03$.

**Table 1** Achronim used

**Table 2** Biological meaning of the used mathematical symbols
CD8+ T Lymphocytes

surface markers

V [ VIRGIN CD8+
CD45RA+RO-CD95-CD28+ ] ANE

Ag1

EFFECTOR CD8+
CD45RA+RO-CD95+CD28-

AgT

MEMORY CD8+
CD45RA-RO+CD95+CD28+

Agn

ME [ ] AE

16
### TABLE 1

<table>
<thead>
<tr>
<th>ANE</th>
<th>Antigen Non Experienced: cells which have not encountered the antigen</th>
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<tbody>
<tr>
<td>AE</td>
<td>Antigen Experienced: cells which have encountered the antigen</td>
</tr>
<tr>
<td>CD4⁺</td>
<td>Marker for helper T cells</td>
</tr>
<tr>
<td>CD8⁺</td>
<td>Marker for cytotoxic T cells</td>
</tr>
<tr>
<td>CD45RA⁺</td>
<td>Marker shared by virgin and effector T cells</td>
</tr>
<tr>
<td>CD45RO⁺</td>
<td>Marker for memory T cells</td>
</tr>
<tr>
<td>CD95⁻</td>
<td>Marker for virgin T cells</td>
</tr>
<tr>
<td>CD95⁺</td>
<td>Marker shared by memory and effector T cells</td>
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</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
<th>$V$</th>
<th>Absolute number of ANE $T$ cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_E$</td>
<td>Absolute number of AE $T$ cells</td>
</tr>
<tr>
<td>$v$</td>
<td>Concentration of ANE $T$ cells ($v = \frac{V}{V + M_E}$)</td>
</tr>
<tr>
<td>$m_E$</td>
<td>Concentration of AE $T$ cells ($m_E = \frac{V}{V + M_E}$)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Conversion rate from ANE to AE $T$ cells</td>
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<tr>
<td>$\beta$</td>
<td>Proliferation factor of AE $T$ cells due to secondary antigenic stimuli</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Amplitude of the chronic antigenic stress</td>
</tr>
<tr>
<td>$t_*$</td>
<td>Age of death in the absence of chronic antigenic stress. Age at which the survival probability is 50%</td>
</tr>
<tr>
<td>$T$</td>
<td>Decay rate of ANE $T$ cells without chronic antigenic stress</td>
</tr>
<tr>
<td>$\sigma^2_\infty = \frac{1}{2} \gamma^2 T$</td>
<td>Asymptotic variance of the ANE $T$ cells concentration</td>
</tr>
</tbody>
</table>