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A continuum analysis of cellular growth for a model of immune response relevant to HIV infection

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Abstract. — A continuum approach is proposed to study the population dynamics of an immune response model relevant to HIV infections. Effects of dysfunction of the helper/inducer T cells are taken into account by a failure probability \( p \) of interleukins. Using the numerical analysis of the inhomogeneous coupled differential equations, it is shown that the incubation time for the viral growth can be increased by reducing the failure probability \( p \). Despite the differences, both the continuum and discrete methods lead to a common result.

1. Introduction.

Understanding the immune response \( \text{via} \) theoretical models has been a subject of considerable interest in recent years [1, 2]. Most of the theoretical attempts can be classified into two main approaches, the discrete and the continuum methods. In the continuum description [3-6], the growth of the cellular elements is described by a set of differential equations in which a probabilistic approach is commonly used to implement the growth and decay rates; some linear approximations are invoked very often in order to avoid the mathematical complexities and to derive closed form expressions for the population of cellular elements. On the other hand, in the discrete method [2, 3, 7-9], one starts with simplified interactions in which the cellular population is evolved by a set of discrete logical interactions in an iterative process; such a method is not necessarily restricted to a linear regime. The use of arbitrary parameters is almost unavoidable in both methods. However, comparing the results of analyzing the same problem by both discrete as well as continuum methods would be interesting.

In this paper, we introduce a continuum model to capture some of the details of a discrete model [10] for the immune response relevant to HIV infection. While our approach of analysing the growth equations is similar to recent theoretical attempts [16, 17] towards modelling the cellular growth in HIV infections, it is different in two respects: (i) it involves indeterministic coupled equations, and (ii) the growth parameters are chosen to make this model compatible with a discrete model. In the following section 2, we briefly describe the discrete model [10] with its main findings. The continuum model and its analysis is provided in section 3 with a summary and conclusion in section 4.
2. Discrete model.

Using a probabilistic cellular automata a simplified model has been studied by Pandey and Stauffer [10] with a discrete approach where an attempt has been made to understand the long incubation time in HIV infections. Five cellular elements are considered in which the concentration of the macrophages (the main antigen presenting cells (APC)) is kept constant at their high concentration, whereas the concentration of the other cellular elements such as the virus (V), the helper/inducer T cells (T_h), the cytotoxic T cells (T_c) and the interleukin molecules (I) evolve from their interaction. Binary variables «1» and «0» are used to describe «high» and «low» concentrations respectively of these cellular elements. The growth and decay of these binary cells are governed by the logical interactions in the following boolean expressions [15]:

\[
\begin{align*}
V(t+1) &= T_h(t) \text{ or } \neg T_c(t) \\
T_h(t+1) &= I(t) \text{ or } \neg V(t) \\
T_c(t+1) &= I(t) \\
I(t+1) &= T_h(t) 
\end{align*}
\]

(1)

where \( t \) represents the time. The interleukins at the next time step are produced by \( T_h \) cells at the current time step, and, similarly, the \( T_c \) cells at the next time step are induced from the interleukins at the current time step. Virus will grow only when the \( T_h \) cell is present and the \( T_c \) cell is absent, whereas the \( T_h \) cell will grow only if the interleukins are present and the viruses are absent. This simplified interaction is also presented in figure 1 where continuous and broken lines represent the stimulatory and inhibitory signals. Thus, after an HIV infection, the dynamics becomes simple if we fix the APC concentration as high [10].

This set of interaction does capture some of the main features of the cell mediated immune response [13]. The helper/inducer \( T_h \)-cells play a crucial role in coordinating the functions of all cell types by releasing a variety of mediators/effectors such as lymphokines (which include interleukin 2). \( T_h \)-cells cannot recognize the free antigens on their own; antigens must be presented in a specific form by APC along with MHC II markers (« major histocompatibility

![Fig. 1. — Schematic representation of the interactions between virus (V), \( T_h \) cell, \( T_c \) cell and Interleukin molecules. The concentration of APC is kept high. The full lines with arrow represent the stimulatory function and broken lines, the inhibitory function of the cells (Ref. [10])]

complex ») for T_h-cells to interact and recognize the antigens. The conformational complementarity of the surface markers such as CD4 on T_h-cells and that of gp120 of HIV [14, 15] (a protein section which is part of the virus) leads the virus to be more reactive with T_h-cells. The HIV behaves like a retrovirus. The path of their sporadic growth makes these HIVs unique and complex [14, 15]: (i) On the one hand, the HIVs seem to manipulate the genetic transformations (with the help of reverse transcriptase and host enzymes) to remain latent in the T_h-cell nucleus as a provirus. (ii) On the other hand, with the aid of integrase, other effectors, and messenger RNA within the cell, HIVs multiply, rupturing the T_h-cell leading to a burst of virus. This sporadic growth of virus may lead to an irregular stimulation in the growth of T_h-cells and therefore, in the production of interleukins. With the help of the above set of interactions these facts are taken into account in the following.

With the four binary variables, V, T_h, T_c and I, there are 16 possible initial configuration. If we start with any of these configuration randomly we end up with two fixed points and one limit cycle [10]. The fixed point (V, T_h, T_c, I) = (1000), corresponds to the complete destruction of the immune system while the other fixed point (1111) corresponds to a weak (an infected but fully present) immune system. The limit cycle is an oscillation between the two states (1110) and (1001) with partially destroyed immune system. We should point it out that the configuration (1111) describes the state in which a healthy body is just infected and it will remain infected as this is a fixed point in the meanfield discrete model. With nearest neighbor interaction [10] on a lattice, the immune system always run into the stable state (1111) regardless of initial configuration. Further more these stable states are reached within a very short time. In the mean field approach (with only one cell variable, without lattice) if we introduce a probabilistic cellular automata with a small probability p of interleukin failure, then all the sixteen configurations lead to the same fixed point (1000). However, the time required to reach this fixed point is sufficiently large and depends on the interleukin failure probability p. This long relaxation time (to reach the stable state) is interpreted [10] as the long incubation time in HIV infections; the small failure probability p of the interleukin is assigned to the effects of dysfunction of infected T_h cells or due to some rare events peculiar to HIV infection [10]. We now focus on this model with the continuum approach.

3. Continuum model.

Let us consider the growth rate of these cellular elements, introduced in preceding section, by the following equations:

\[
\begin{align*}
\frac{d[V(t)]}{dt} &= a + P_1(t) \times T_h(t) - P_2(t) \times T_c(t) \\
\frac{d[T_h(t)]}{dt} &= a + P_3(t) \times I(t) - P_4(t) \times V(t) \\
\frac{d[I(t)]}{dt} &= P_5(t) \times T_h(t) \\
\frac{d[T_c(t)]}{dt} &= P_6(t) \times I(t)
\end{align*}
\]  

with,

\[
\begin{align*}
P_1(t) &= V(t) / [V(t) + T_h(t)] \\
P_2(t) &= V(t) / [V(t) + T_c(t)] \\
P_3(t) &= T_h(t) / [T_h(t) + I(t)] \\
P_4(t) &= T_h(t) / [T_h(t) + V(t)] \\
P_5(t) &= I(t) / [I(t) + T_h(t)] \\
P_6(t) &= T_c(t) / [T_c(t) + I(t)]
\end{align*}
\]
where \( a \) is the product of the concentration of antigen presenting cells and the associated probability of growth. The growth rate probabilities \( P_i(t) \)'s are assumed to be directly proportional to the population of the growing cellular elements normalized by the total population of interacting cells.

Irrespective of the results, let us see the solution of these equations (2) in their steady state where the time derivatives of each cellular population i.e. the left hand side of equations (2) will vanish. From equations (2c) and (2d) we get,

\[ I(t) = I_0 \quad \text{and} \quad T_c(t) = T_c^0 \]  
\[ \text{(4)} \]

where \( I_0 \) and \( T_c^0 \) are constants (\( I_0 = 0 \) is one possible solution). Equations (2a) and (2b), on the other hand, lead to coupled equations,

\[ V = [ - a(T_c^0 + T_h) + (C_1)^{1/2} ] [ 2(a + T_h - T_c^0) ] \]  
\[ \text{(5)} \]

\[ T_h = [ - a(I_0 + V) + (C_2)^{1/2} ] [ 2(a + I_0 - V) ] \]  
\[ \text{(6)} \]

where,

\[ C_1 = a(a - 4T_c^0)T_h^2 + 2aT_c^0(2T_c^0 - a)T_h + a^2T_c^0 \]  
\[ \text{(7)} \]

\[ C_2 = a(a + 4I_0).V^2 - 2aI_0(a + 2I_0).V + a^2I_0^2. \]  
\[ \text{(8)} \]

As we see that for a meaningful solution of the steady state values of viral and \( T_h \) cell populations both \( C_1 \) and \( C_2 \) must be positive. In addition, from equation (5), for a nonzero positive viral populations, we must have, (i) \( a + T_h > T_c^0 \) and \( (C_1)^{1/2} > a(T_c^0 + T_h) \), or (ii) \( a + T_h < T_c^0 \) and \( (C_1)^{1/2} < a(T_c^0 + T_h) \). To obtain a zero value of \( V \) we must have \( T_h = 0 \) and \( a > T_c^0 \). On the other hand, from equation (6), for a nonzero positive \( T_h \) cell population following conditions must be satisfied: (iii) \( a + I_0 = V \) and \( C_2^{1/2} > a(I_0 + V) \), or (iv) \( a + I_0 < V \) and \( (C_2)^{1/2} < a(I_0 + V) \). The population of the activated \( T_h \) cells in the steady state vanishes if \( V = 0 \) and \( I_0 > V \); as it should be at the end of immune response in normal state. Instead of going through the numerical analysis of these steady state coupled equations, for arbitrary values of cellular constants such as \( a \), as is usually done in such studies [1], we will concentrate here on the analysis of the growth equations for the interleukin failure case. We should, however, point it out that a numerical study of equation (2) shows that both \( T_h \) cells as well as viral populations continues to increase within the limit of our time steps \( (10^5) \) for all values of initial cellular concentrations we have studied; however, the population of \( T_h \) cells (and that of the interleukins and \( T_c \) cells) remain dominant over the viral populations.

As we mentioned in section 2, in the discrete model with the probabilistic cellular automata, the long incubation time in HIV infection appears due to small interleukin failure. The failure probability \( p \) of the interleukin is justified [10] in the proceeding section as an effect of infected \( T_4 \) cells or due to some peculiar events characteristics of HIV infections. Implementing the interleukin failure with a probability \( p \) and finding a closed form solution of the coupled equation (2) is not possible here and therefore, we resort to numerical studies of these equations. To avoid the technical problems (specially the divergence) we add unity in the denominators of growth probabilities \( P_i \)'s (Eq. (3)) ; the constant \( a \) is taken to be unity throughout. We start with a very small value of the initial concentrations \( c_i \) of these cell types, and look into the time development of the cellular populations. The interleukin concentration and its growth rate \( P_5 \) are then set to zero with probability \( p \) with the help of a pseudo random number generator on our main frame (DPS-90, Honeywell machine), as we analyse equation (2) by finite difference method. A random number, between zero and one is selected randomly at each time step; if the random number is less than or equal to the
interleukin failure probability $p$, then the interleukin concentration and its growth rate $P_5$ is set to zero. Up to $10^5$ time steps are used to study the time evolution of equation (2). Further more, « NRUN » independent runs are used to get a reliable estimate of the average population growth of these cells.

We have carried out a detailed numerical study of the evolution of cellular populations at several interleukin failure probabilities as a function of the initial concentrations of the cellular elements for various time scales, each with a number of independent samples (NRUN). At the high values of the interleukin failure probability ($p > 0.2$), with NRUN = 500, for all values of the initial concentrations of the cellular elements, we observe that the population of the virus ($N_v$) increases and that of the $T_h$ cells ($N_{bh}$) decays very fast to a very low value; the interleukin counts ($N_i$) goes down to zero while the population of the cytotoxic $T$ cells ($N_{tc}$) reaches a constant value which is comparable to the maximum value of $N_{th}$. The viral population dominates over that of the $T_h$ cells leading to an immunodeficient state in which the immune system continuously weakens as $N_v$ grows and $N_{th}$ decays with time. On decreasing the interleukin failure probability $p$ (0.11-0.15), with the initial concentrations $c_i$ (0.001-0.01) of all cell types, the population of the $T_h$ cells, rises very fast to a maximum value ($N_{tm}$) and then it decays very slowly with time. The magnitude of $N_{tm}$ varies with $c_i$ and with runs, in fact we observe a large fluctuation in the magnitude of $N_{tm}$ within independent samples. The viral population, on the other hand, continues to increase with time. In most of the runs, the viral population is greater than that of the $T_h$ cells while in some runs, the population of the $T_h$ cells outnumbers the viral population (for time steps up to $4 \times 10^6$). The population of the cytotoxic $T_c$ cells increases to a saturation value comparable to $N_{tm}$ while the interleukin counts goes down to zero. A typical variation of the $T_h$ cells and viral populations are shown in figure 2. Although the viral population always increases continuously in the full range of our time scale, its population $N_v$ is greater than that of the $T_h$ cells in most of the runs beyond a certain time step which depends on the magnitude of $N_{tm}$; however, the constant decay of $N_{th}$ and continuous growth in $N_v$ leads us to believe that in the long time regime $N_v > N_{th}$ even if it is other way around in the beginning. Therefore, we ascribe this state as an immunodeficient state similar to state (1000) observed in the discrete approach.

On decreasing the probability $p$ of interleukin failure, the maximum population of $T_h$ cells, $N_{tm}$ increases. Then the decay in its magnitude with time is so slow that $N_{th}$ remains much larger than $N_v$ during the time interval of our observation ($10^5$ time steps) specially at extremely low values of $p$ (0.001-0.08). Let us define the relaxation time $t_r$ in which the population of $T_h$ cells remain dominant over the viral population. This relaxation time $t_r$ is very large at extremely low values of interleukin failure probability $p$; on increasing the value of $p$, $t_r$ decreases. Thus the relaxation time $t_r$ or the incubation time of the viral detection can be made sufficiently large by reducing $p$ and in this regards this model captures one of the main findings of the discrete approach recently proposed by Pandey and Stauffer [10]. Although it is not feasible to compare these results quantitatively with experimental findings, it appears that our model may be further developed to understand some of the experimental observations (i.e. by Layne et al. [15] on the effects of soluble CD4 density).

4. Summary and conclusion.

We have introduced a continuum approach to study a simple model of immune response relevant to HIV infections in which the growth and decay of viruses, $T_h$ cells, $T_c$ cells and interleukins are considered. Attempts have been made to consider the inhomogeneous cellular interactions recently studied by a discrete method [10] using probabilistic cellular
automata. Unlike the two stable configurations and a limit cycle in immunodeficient states in discrete model, here we observe a constantly growing cellular population with $N_{th}$ (the number of helper $T$ cells) much larger than that of the viral populations for parameters such as the concentration of APC, and the initial concentration of cells $c_i$. We have also obtained a variety of stable solutions describing the immunological states, some of which have been discussed in a closed form steady state solution. An interleukin failure probability $p$ is introduced to take into account the effects of the dysfunction of $T_{th}$ cells and other defects due

Fig. 2. — Variation of $T_{th}$ cells and viral population with time steps at the initial concentration of the cellular elements $c_i = 0.003$ and interleukin failure probability $p = 0.11$ in (a); $c_i = 0.003$ and $p = 0.12$ in (b). 500 independent runs were used in both sets to find out the average values of cellular populations.
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Fig. 2 (continued).

to HIVs. The resulting inhomogeneous coupled equations are numerically studied in detail. At high values of $p (> 0.2)$, the viral population $N_v$ dominates over that of the $T_h$ cells beyond the incubation time $t_r$; $N_v$ continues to increase while $N_{th}$ rises sharply to a maximum value $N_{tm}$ and then it continues to decay slowly. Both $N_{th}$ and $t_r$ depend upon the initial concentration of cells and on the interleukin failure probability. On decreasing the failure probability $p$, the relaxation (i.e. the incubation) time $t_r$ tends to increase considerably. The result of reducing the interleukin failure probability $p$ to a very small value and obtaining a very long incubation time leading to metastability is similar to that observed in the discrete approach with binary cellular elements [10]; in this regard, both discrete and continuum models give the same result here.
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