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1990 J. Phys. A: Math. Gen. 23 4321

(http://iopscience.iop.org/0305-4470/23/19/017)

J. Phys. A: Math. Gen. **23** (1990) 4321-4331. Printed in the UK

Growth and decay of a cellular population in a multicell immune network

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Received 24 July 1989, in final form 5 January 1990

Abstract. An interacting network of eight binary cellular elements is used to model some of the general features of immune response in an immune weakness disease. Both humoral as well as cell mediated responses are considered. Two logical intercell interactions are examined. With infinite-range interactions both models lead to 24 fixed points (stable configurations) with various degrees of immunocompetence and immunodeficiency. A simple cubic lattice is used with a cellular automata to take into account a nearest-neighbour intracell interaction. The evolution of cellular populations is studied for a random binary mixture of these two interactions with probability f and a crossover is observed from an immunodeficient state for f below a characteristic value $f_c(\simeq 0.8)$ to an immunocompetent state above it.

1. Introduction

Studying the problems in immune response by theoretical methods has attracted a lot of interest in recent years (Perelson 1988, Kaufman *et al* 1985, Kaufman 1988, 1989, Weisbuch and Atlan 1988, Weisbuch 1989, Atlan 1989, Cohen and Atlan 1989, Dayan *et al* 1988, Pandey and Stauffer 1989, Pandey 1989a, b, Neumann 1989, Chowdhury 1989, Cooper 1986, Parisi 1988, Kurten 1988, Behn and van Hemmen 1989). Immune systems consist of a huge number of cells ($\simeq 10^9$) and molecules ($\pm 10^{12}$) which are subject to continuous decay and renewal (Jerne 1973, Lawrence 1985, *Sci. Am.* 1988). Most of the cellular participants possess different specificity and perform specific functions in a random but coordinated fashion (Roitt 1988). There is a growing list of varieties of immune responses and reaction mechanisms. A complete understanding, from triggering the reaction to shutting down the response, is one of the most difficult issues.

Numerous attempts have been recently made to model a variety of immune responses and some progress has been made in describing some of diversity observed in immune systems (Perelson 1988). A simplified discrete method has been frequently used in recent years to model some of the immune responses such as autoimmunity (Weisbuch and Atlan 1988, Cohen and Atlan 1989), acquired immune defficiency syndrom (AIDS) (Pandey 1989a, b). We develop it further to explore some general features of the immune response in an infection caused by human immunodeficiency virus (HIV). In this approach, a cellular state is described by a binary variable, 0 and 1 representing the low and the high concentrations of the cells which interact with each other with logical interactions. We have already studied some of the general

0305-4470/90/194321+11$03.50

features of the immune response using an interacting network of three cells (Pandey and Stauffer 1989, Pandey 1989a). A system of four cells (Pandey 1989b) where only a part of the cell mediated the response, was examined without considering the effects of shutting down the reactions. For the first time, we use here an eight-cell interacting-network model to study the response from the beginning to the end with both cell-mediated as well as humoral responses.

In section 2 we briefly describe the main cellular elements involved and their pathways in immune response along with the unique feature of HIV in AIDS. Models and results for the infinite range and nearest-neighbour interacting networks will be presented in sections 3 and 4, respectively. Results are summarised in section 5.

2. Cellular participants, reaction pathways and HIV growth

Introduction of a foreign element, say a virus, triggers the immune system to a response in which a variety of cellular elements begin to multiply and decay. T_4 cells, T_8 cells, B cells and macrophages are some of the primary cellular elements (Jerne 1973, Lawrence 1985, *Sci. Am.* 1988) that participate in a coordinated fashion with the help of a variety of mediators such as lymphokines (IL_1, IL_2 interleukines for example), cell growth factors and effectors; these cells possess different specificities which enable them to perform their specific functions. In general, the antigen presenting cells (such as macrophages) engulf the virus and present its antigenic component in a specific form to the T_4 cells receptors as they cannot recognise antigens otherwise. Once the T_4 cells recognise such expressed antigens along with MHC II they begin to multiply and produce chemical signals such as lymphokines (Roitt 1988, *Sci. Am.* 1988) which regulate the populations of B cells and T_8 cells. On receiving the chemical signals both B cells and T_8 cells start proliferating and differentiating in order to perform different types of cytotoxic functions leading to what is known as 'humoral' and 'cell mediated' response, respectively. T_8 cells differentiate into cytotoxic (killer) and suppressor cells while B cells proliferate into plasma cells and memory cells; the mature cells are then released into the blood stream. On encounter with antigens expressed in a specific form (by the antigen presenting cells) along with MHC I markers, the cytotoxic T_8 cells kill them in a cell-mediated response, while suppressor T_8 cells, in order to shut down the response, prevent T_4 cells from releasing lymphokines. On the other hand, in a humoral response, the antibodies secreted by the plasma cells bind to free antigen and neutralise them; the memory cells guard against the same invader (i.e. virus) in a future encounter. Figure 1 illustrates the main features of this general mechanism. We should point out that in our simplified model all specific functions of these and other cell types and cell mediators are not considered explicitly.

The human immunodeficiency viruses in AIDS have high tropism for T_4 cells which play the key role in delegating the immune response. Thus, by depleting the population of T_4 cells that regulate the populations of T_8 cells and B cells, the HIVs weaken both the cell-mediated as well as humoral defence mechanism. T_4 cells carry CD_4 protein molecules, which are good receptors for the virions (*Sci. Am.* 1988) as they carry gp120 protein molecules on their surface; the conformational complementarity of the CD4 and gp120 molecules enhances their interactions and fusion. In fact the HIV can interact and bind together with all cells carrying CD_4 molecules on their surface in which T_4 cells are badly damaged; thus they share a large part of the infection. Some of

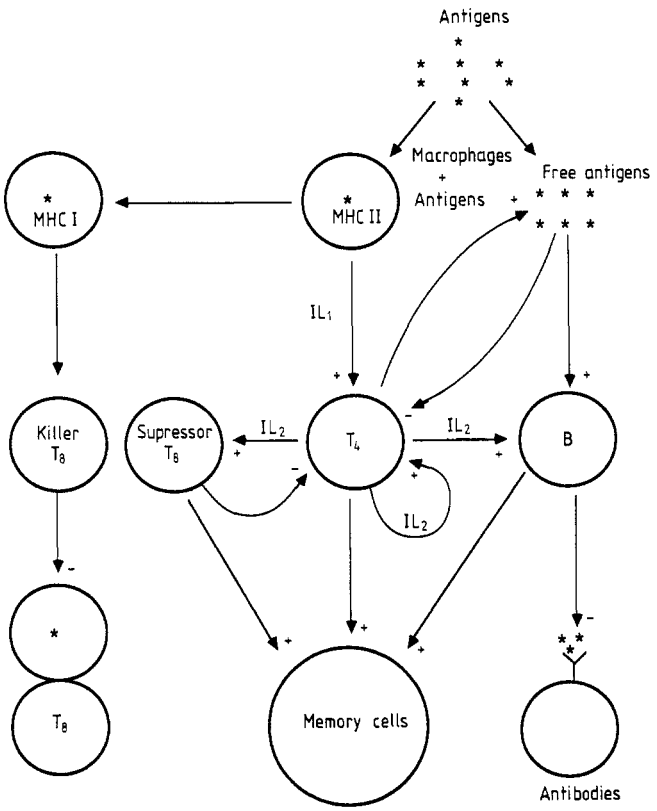

Figure 1. A sketch of immune response. Arrows indicate the pathways and + and − signs shows the stimulatory and inhibitory functions; details are described in the text.

macrophages also carry CD_4, and an HIV can bind without destroying them; the macrophages thus serve as a reservoir for HIV transport. We attempt to take into account these general features of cellular interactions including tropism of HIV for T_4 cells to study the population growth in section 3.

HIV behave like retroviruses which seem to reverse the normal flow of genetic information. The genes of a retrovirus are encoded in RNA which must be converted into DNA, after which the viral genes, as in usual sequence, are transcribed into messenger RNA and translated into proteins. When an HIV particle binds to a cell, it injects its core, which consists of two strands of RNA as well as proteins and enzymes that carry out later steps in the life cycle. One enzyme helps to convert the viral genetic information into DNA polymerase which makes a single-strand DNA copy of the viral RNA; the original RNA is destroyed by ribonuclease, and polymerase makes a second DNA copy using the first one as a template. This double-strand DNA migrates to the cell nucleus where, with the help of integrase, it is integrated into the cell's own DNA. Such viral DNA, known as the provirus, remains latent, giving no sign of its presence and is duplicated together with the cell's own genes every time when the cell divides.

In an alternate mechanism of the viral growth, the production of new virus particles takes place sporadically and only in some infected cells. The nucleotide sequences in the long terminal repeats (LTR) direct enzymes of the host cells to copy the DNA of the integrated virus into RNA. Some RNA provide the genetic material for a new

generation of virus while other RNA strands serve as mRNA to guide the cellular mechanism in producing structural (viral) proteins on ribosomes. The proteins and additional RNA then aggregate to form new virions that bud from the cell. This process may take place slowly, sparing the host cell or so rapidly that the cell is lysed, leading to a burst of virions. In section 4, attempts will be made to incorporate this dubious nature of HIVs and their erratic growth along with the general features described above.

3. Infinite-range interacting network

In the framework of the simplified picture outlined above for an immune response, it appears that, to describe the response from beginning to end, we need to consider eight cellular elements: free antigen (C_1), antigen expressed in a specific form (C_2), antigen presenting cells like macrophages (C_3), T_4 cells (C_4), cell mediators like lymphokines (C_5), cytotoxic T_8 cells (C_6), suppressor T_8 cells (C_7) and antibodies secreted by B cells (C_8); memory cells are ignored at present. This is the first time we have considered such a large number of cellular elements for studying the complete response, in our previous studies fewer cells were considered where modelling was restricted to the initial stage of only the cell-mediated response. As we mentioned before, in our simplified analysis we resort to the discrete methods in which the cellular states will be represented by binary variables and the interactions by logical expressions (Kaufman *et al* 1985).

In immune response, cells interact with each other by several mechanism such as direct contact among the cellular elements, by secreting the soluble molecules and releasing the chemical signals and via specific pattern recognitions (epitop-paratop network) etc. It is rather difficult to take into account all the complex mechanisms that lead to interactions among the huge arrays of cellular elements with diverse specificities. However, some of the overall effects can be incorporated in simplified forms and in the following we consider a set of Boolean expressions to describe interaction (1):

$$\begin{aligned}
C_1(t+1) &= (C_1(t) \text{ or } C_4(t)) \text{ and } (\text{not } C_8(t)) \\
C_2(t+1) &= (C_1(t) \text{ and } C_3(t)) \text{ and } (\text{not } C_6(t)) \\
C_3(t+1) &= C_3(t) \text{ or } C_1(t) \\
C_4(t+1) &= (C_4(t) \text{ or } C_2(t)) \text{ and } (\text{not } C_1(t)) \\
C_5(t+1) &= (C_5(t) \text{ or } C_4(t)) \text{ and } (\text{not } C_7(t)) \\
C_6(t+1) &= C_6(t) \text{ or } C_5(t) \\
C_7(t+1) &= C_7(t) \text{ or } C_5(t) \\
C_8(t+1) &= C_8(t) \text{ or } C_5(t)
\end{aligned} \tag{1}$$

where $C_k(t+1)$ is a binary state of cell type $k(=1, 2, \ldots, 8)$ at time step $t+1$ emerging from interactions among cells at the previous time step t. We assume that the viruses lead to two types of antigens (free C_1 and expressed C_2 antigens). The first equation represents the growth of free antigens for which antibodies secreted by B cells must be absent and either a free antigen (for self-interaction) or a T_4 cell (receptor for the virus) be present. We consider only macrophages as antigen presenting cells here.

Thus for antigens to be presented in a specific form, the cytotoxic T_8 cell must be absent and both the free antigen as well as the macrophage be simultaneously present, these macrophages then engulf the virus to display its antigenic material on their surface; this process is described by the second equation. In the third equation, the presence of a macrophage (self-interaction) or a free antigen (to trigger the reaction) leads to the activation of macrophages. In the absence of free antigens, T_4 cells proliferate if either a T_4 cell or an antigen (displayed by macrophages) or both are present at the previous time step; this is described by the fourth equation. The lymphokines grow with the help of T_4 cells and by self-interacting, but at a previous time step the suppressor T_8 cells must be absent otherwise they will prevent lymphokine production, as expressed by the fifth equation. The remaining three equations represent the growth of cytotoxic and suppressor T_8 cells and antibodies (from B cells) with the help of lymphokine signals in addition to their self-interactions at the previous time step.

This pool of eight cells give rise to 256 configurations; if we start with one of these configurations randomly at $t=0$, we obtain a flow of configurations emerging from the above interaction in successive time steps $(t+1)$. Such flows end up in a fixed point which describes a stable configuration. The set of interaction (1) gives rise to 24 fixed points which are presented in table 1 with corresponding weights, i.e. with the fraction of the total configurations leading to that fixed point. Caution must be exercised in interpreting the weight factors in table 1, as not all the 256 possible configurations are relevant in immune response; these weights are presented in the

Table 1. Representation of cellular state $(C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8)$.

Interaction (1)		Interaction (2)	
Fixed point	Probability	Fixed point	Probability
0 = (00000000)	$\frac{1}{256}$	0 = (00000000)	$\frac{1}{256}$
1 = (00000001)	$\frac{1}{256}$	1 = (00000001)	$\frac{1}{256}$
2 = (00000010)	$\frac{1}{256}$	2 = (00000010)	$\frac{1}{256}$
3 = (00000011)	$\frac{1}{256}$	3 = (00000011)	$\frac{1}{256}$
4 = (00000100)	$\frac{1}{256}$	4 = (00000100)	$\frac{1}{256}$
5 = (00000101)	$\frac{1}{256}$	5 = (00000101)	$\frac{1}{256}$
6 = (00000110)	$\frac{1}{256}$	6 = (00000110)	$\frac{1}{256}$
7 = (00000111)	$\frac{9}{256}$	7 = (00000111)	$\frac{9}{256}$
19 = (00001011)	$\frac{2}{256}$	32 = (00100000)	$\frac{1}{256}$
23 = (00010111)	$\frac{25}{256}$	33 = (00100001)	$\frac{1}{256}$
32 = (00100000)	$\frac{1}{256}$	34 = (00100010)	$\frac{1}{256}$
33 = (00100001)	$\frac{3}{256}$	35 = (00100011)	$\frac{1}{256}$
34 = (00100010)	$\frac{1}{256}$	36 = (00100100)	$\frac{1}{256}$
35 = (00100011)	$\frac{5}{256}$	37 = (00100101)	$\frac{1}{256}$
36 = (00100100)	$\frac{1}{256}$	38 = (00100110)	$\frac{1}{256}$
37 = (00100101)	$\frac{5}{256}$	39 = (00100111)	$\frac{90}{256}$
38 = (00100110)	$\frac{1}{256}$	224 = (11100000)	$\frac{4}{256}$
39 = (00100111)	$\frac{115}{256}$	225 = (11100001)	$\frac{4}{256}$
51 = (00110011)	$\frac{7}{256}$	226 = (11100010)	$\frac{14}{256}$
55 = (00110111)	$\frac{37}{256}$	227 = (11100011)	$\frac{14}{256}$
164 = (10100100)	$\frac{4}{256}$	228 = (11100100)	$\frac{4}{256}$
166 = (10100110)	$\frac{14}{256}$	229 = (11100101)	$\frac{4}{256}$
224 = (11100000)	$\frac{4}{256}$	230 = (11100110)	$\frac{14}{256}$
226 = (11100010)	$\frac{14}{256}$	231 = (11100111)	$\frac{85}{256}$

table in case the reader want to check the result. Configuration $39 = (00100111) = (C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8)$ represents a state in which only macrophages are present along with cytotoxic and suppressor T_8 cells. We define the 'immunodeficient' and the 'immunocompetent' states by the presence and absence, respectively, of the antigens. Note that the production of T_4 cells and lymphokines is suppressed and therefore this fixed point describes the completion of response in an immunocompetent state. Configuration $55 = (00110111)$ also represents an immunocompetent state in which macrophages, T_4 cells, T_8 cells and B cells (the antibodies) are present, all other cells are absent. The last four fixed points $164 = (10100100)$, $166 = (10100110)$, $224 = (1110000)$ and $226 = (11100010)$ lead to immunodeficient states in which free antigens, expressed antigens, and macrophages (a shelter for the virus) are present.

In order to enhance the viral proliferation, we consider the following set of interactions:

$$\begin{aligned} C_1(t+1) &= (C_1(t) \text{ or } C_4(t)) \text{ and } [\text{not } (C_8(t) \text{ and } C_5(t))] \\ C_2(t+1) &= (C_1(t) \text{ and } C_3(t)) \text{ and } [\text{not } (C_6(t) \text{ and } C_5(t))] \end{aligned} \tag{2}$$

for free and expressed antigens, keeping all other interactions the same as those in the set of interactions (1) for the remaining cell types. Note that now, unless there is a sufficient amount of lymphokine signals, T_8 cells and B cells (via antibodies) are unable to perform their cytotoxic (viral killing) functions (Roitt 1988); as a result, both free antigens and those displayed in specific form may grow with larger probability. This second set of interactions also leads to 24 fixed points. However, some of these fixed points are different than those with interaction (1) (see table 1). Fixed points $19 = (00010011)$, $23 = (00010111)$, $51 = (00110011)$ and $55 = (00110111)$ which help to achieve immunocompetence and $164 = (10100100)$ and $166 = (10100110)$ that lead to immunodeficiency with interaction (1) (see table 1) are absent here. Instead, six new fixed points, $225 = (11100001)$, $227 = (11100011)$, $228 = (11100100)$, $229 = (11100101)$, $230 = (11100110)$ and $231 = (11100111)$ appear, all of which drive the whole immune system towards the immunodeficient state.

4. Nearest-neighbour interacting network

Cellular elements participating in immune response are inside the body where immune reactions take place in local regions such as thymus gland, bone marrow, blood vessels etc. The spatial host medium in which various mediators, growth factors, effectors etc are in stochastic motion and where these cells are interacting, dividing, decaying and growing should have some bearing in the analysis of immune response. In our previous analysis (section 3), the spatial distribution of cell types is completely ignored, i.e. no matter how far and in what fashion different cellular elements are distributed, each cell type at all positions behaves in the same way. This is an oversimplification. The fact is that these cellular elements possess finite size and that steric hindrances (due to host space and due to the presence of other cells) may influence their interactions (including conformal fitting) and growth. Furthermore, in a limited space cells may interact more effectively with their neighbouring cells in comparison to cells far away from them. Ideally, one should consider a host space similar to the participating medium and take into account all interactions (short- to long-range). However, to avoid the complexities we restrict ourselves in our exploratory study here to a simple

cubic lattice as a host medium and to the nearest-neighbour interactions as the extreme opposite case to the mean-field description presented in previous section.

To study the effect of nearest-neighbour intracell interactions, we consider a simple cubic lattice of size $L \times L \times L$ and use a multispin code (Herrmann 1986) to store each site per bit in a 64-bit word as we did in our previous studies (Pandey 1989b) on a Cray YMP machine. We place each cell of eight different types at each lattice site. Initially, a fraction $p(k)$ of lattice sites is occupied by k cell types in their binary state of high concentration (state 1), while the rest, a fraction $1\text{-}p(k)$, are empty (in other words they are occupied by these cell types in their binary state of low concentration (state 0)). Now we use cellular automata rules for the NN intracell interaction (Pandey and Stauffer 1989). A cell type k with a current binary state, say $C_k(t)$, is selected at a site i. Then the binary states of cell type k at the neighbouring sites are added to $C_k(t)$ at site i. If this sum of seven binary states of cell type k is positive then a temporary binary state $C_k(t)'$ of high concentration (state 1) is assigned to this cell type k at site i. Otherwise its binary state remains at 0. Similar temporary binary states are assigned to all other cell types at site i and to each cell type at all lattice sites using a logical 'or' operation for the intersite intracell interactions. With their temporary binary states, all eight cells at a site i then interact with each other according to intercell interaction (1) or (2) to get a final binary state $C_k(t+1)$ at the next time step $t+1$. This process is repeated again and again for all cell types at each lattice site with several independent runs for the time step in which the populations of all cell types reach their steady-state value. An attempt to update the binary state of a cell type at each lattice site is defined as one time step.

It is worth pointing out that the lattice itself is not realistic in modelling the host space of the immune system. We know that various cell mediators, growth factors and effectors help in activating and stimulating the cellular elements. The level of reactivity is therefore enhanced during the course of immune response. We capture some of these effects by a NN intracell interaction mechanism followed by intercell interaction. Moreover, the introduction of a lattice provides us a way of looking at the change in population (see below) rather than describing just the overall state, as in section 3.

The next step in developing our model is to consider the unique features of HIV pointed out briefly in section 2. It is now well established that HIV belong to retrovirus systems in which its reverse transcriptase function, inaccurate replication and genetic drift make it difficult to understand its growth pattern. However, there is no unique pathway in which viral growth takes place. As we mentioned before, in one pathway the genetic material of HIV is integrated into cell nuclei where the provirus (the double-standard DNA) remains latent and multiplies only when such infected cells divide. On the other hand, in an alternate pathway, using the cell's genetic materials and manipulating their biochemical functions, these proviruses assemble virion particles, resulting in a burst of viral particles. To take into account this erratic nature of HIV, i.e. their latent and sporadic growth, we consider a random binary mixture of interactions (1) and (2) with a mixing probability f (Pandey 1989b). In other words, we assume that these dormant viruses leads to intercell interaction (1) with probability f and to intercell interaction (2) with probability $1-f$. Now we address the question of how the cell population depends upon f, how do these cellular elements evolve with time and how does the initial concentration host cells affect the population growth? The computer simulation is performed on a Cray YMP machine and a multispin code (Herrmann 1986) is used to produce data with a sample of size $64 \times 64 \times 64$; another sample of size $192 \times 192 \times 192$ is also used to see if there is any change in the qualitative

behaviour due to finite-size effects. The maximum speed is found to be about 100 sites, i.e. 800 cells per microsecond per YMP processor. At the lowest initial concentration of all cell types, $p(k) = 0.000\,005$ where only one cell of each cell type is present at a site in its high-concentration state, we study the evolution of cellular elements. With interaction (1) (i.e. at $f = 1.0$) figure 2(a) shows the growth and decay of 'free antigens', 'expressed antigens' and 'T_4 cells'. The population of both types of antigens (free and expressed) grows first at the initial stage and then decays down to a very small steady-state value. On the other hand, T_4 cells multiply sharply to reach their steady-state population; before reaching a steady state the population growth does not show non-monotonic behaviour as in case of antigens. In the steady state, populations of these cellular elements oscillate with different amplitudes (see figure 2). This oscillation does not mean that there is no stable state, in fact the population of T_4 cells (even in its lower limit) dominates over that of viruses in their steady state and therefore it may be described as an immunocompetent state. To maintain clarity the growth of the remaining cells is not included in the figure. Populations of macrophages, cytotoxic and suppressor T_8 cells and B cells grow smoothly to high values (comparable to the sample size and T_4 cell population) in the steady state. The lymphokine population fluctuates during the initial stage of response before it finally decays down to zero; this feature is compatible within the framework of our model in which the action of suppressor cells is very effective in switching off the response by stopping the release of lymphokines. The population of T_4 cells (along with other host cells (T_8 cells, B cells and macrophages)) is much larger than that of antigens in the steady state at this extreme value of $f(=1.0)$. Since T_4 cells play a key role in delegating the immune response, this steady-state behaviour describes an 'immunocompetent' state.

On lowering the value of f by a small about to 0.9, the evolution of growth pattern remains the same (see figure 1(b)). However, the steady-state population of T_4 cells

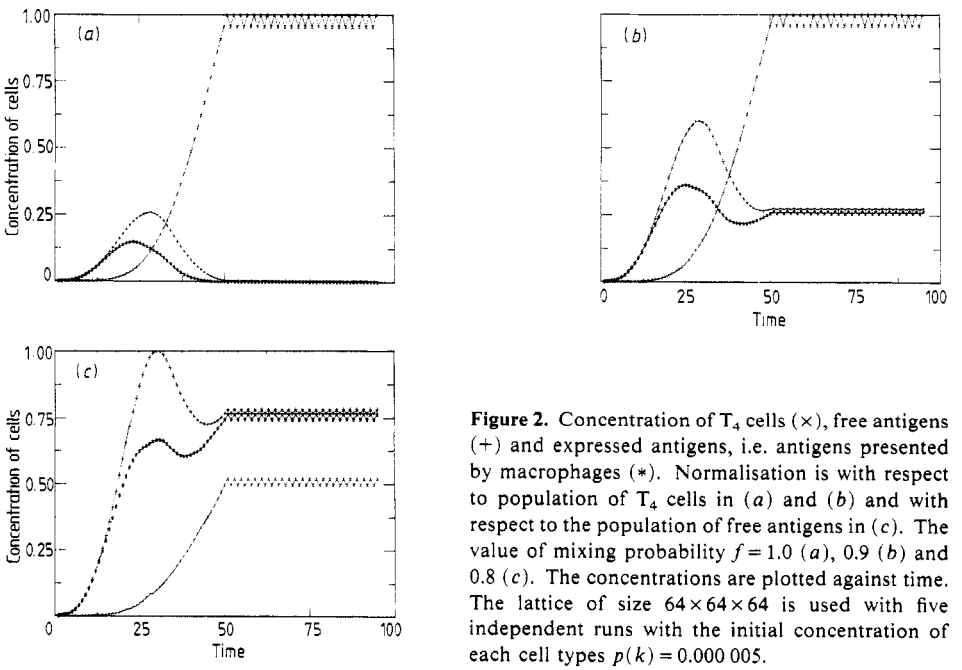

Figure 2. Concentration of T_4 cells (×), free antigens (+) and expressed antigens, i.e. antigens presented by macrophages (*). Normalisation is with respect to population of T_4 cells in (a) and (b) and with respect to the population of free antigens in (c). The value of mixing probability $f = 1.0$ (a), 0.9 (b) and 0.8 (c). The concentrations are plotted against time. The lattice of size $64 \times 64 \times 64$ is used with five independent runs with the initial concentration of each cell types $p(k) = 0.000\,005$.

is reduced down to about half of its value at the extreme $f(=1.0)$. On the other hand, the population of free antigens and that of the antigens presented by macrophages is increased by a very large amount in comparison to their corresponding $f = 1.0$ populations (figure 2(b)). On decreasing the value of f further down to 0.8, the steady-state populations of both types of antigens far exceed the population of T_4 cells (see figure 2(c)) leading to an 'immunodeficient' state. A similar qualitative behaviour is also observed with a larger sample of size $192 \times 192 \times 192$ (see figure 3). The steady-state population pattern remains unchanged for all cell types. However, the time to approach the steady-state population for each cell type increases on increasing the sample size. Note the different normalisations at different values of f; they are the maximum value of the population of T_4 cells in parts (a) and (b) at $f = 1.0$ and 0.9, respectively and that of the free antigens in part (c) as the T_4 are the most numerous among the cell types shown. We should point out that the qualitative behaviour such as the non-monotonic growth of antigens and the monotonic growth of T_4 cells remain the same (see figures 2 and 3).

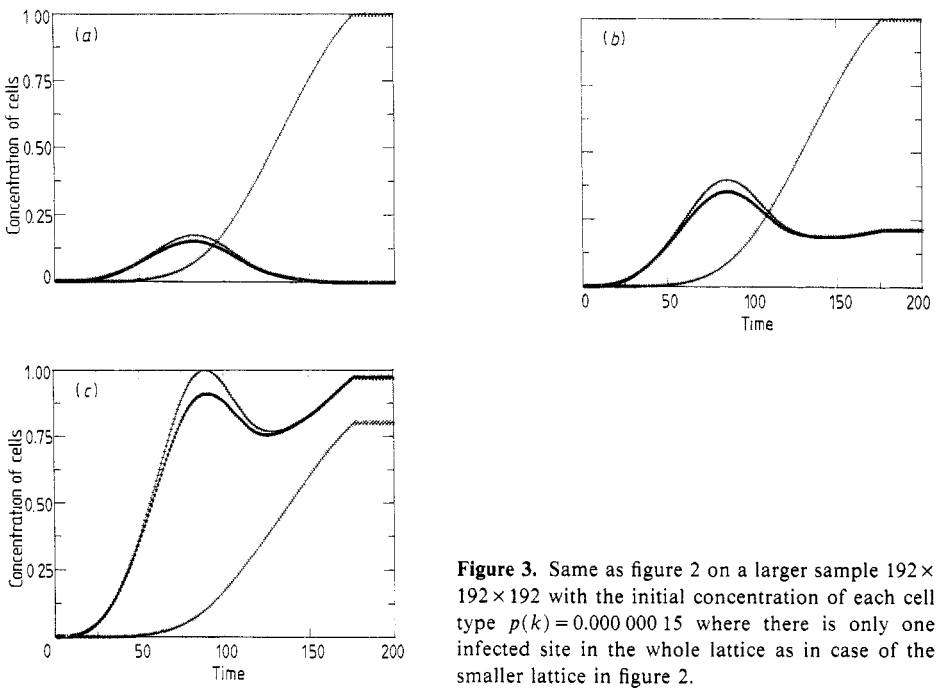

Figure 3. Same as figure 2 on a larger sample $192 \times 192 \times 192$ with the initial concentration of each cell type $p(k) = 0.000\,000\,15$ where there is only one infected site in the whole lattice as in case of the smaller lattice in figure 2.

So far we are limited to the lowest initial concentration of the host cells in studying the population growth of cellular elements involved in immune response. A similar growth pattern also prevails for higher initial concentrations of the host cells (macrophages, T_4 cells, T_8 cells, B cells and lymphokines) keeping the initial viral (i.e. both antigens) concentration to its lowest level. The response time in which the populations of each cell type reach their steady-state value decreases on increasing the initial concentrations of the host cells. On decreasing the value of f from its extreme value (1.0), we observe a crossover from an immunocompetent state (at high values of f) to an immunodeficient state (at lower values of f). To characterise the

crossover here we define a 'survival probability' as (T_4 cells − free antigens) population/(maximum population of T_4 cells, i.e. the steady-state population at $f = 1.0$) in the steady-state configuration as a function of f; the resulting plot is presented in figure 4. The survival probability is a measure of immunocompetence, which increases above a certain characteristic value $f_c(-0.8)$ below which the viral population dominates over the host cell populations, leading to an immunodeficient state. The crossover behaviour remains unchanged for the larger sample.

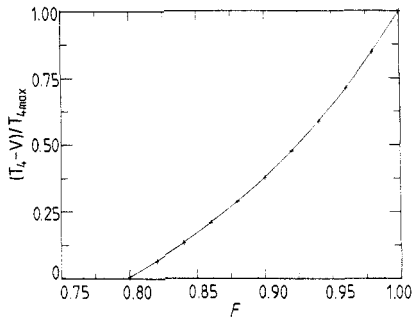

Figure 4. Survival probability defined as (T_4 cells population (T_4)-population of free antigen (V)/(maximum value of T_4 cells population (T_{4MAX})) as a function of f for the initial concentration of host cells 0.005 with the initial concentration of virus (i.e. both free as well as expressed antigens) $p(i) = 0.000\,005$. The lattice of size $64 \times 64 \times 64$ is used with 50 independent runs.

5. Summary

In summary, we have presented an eight-cell interacting network model in order to study the population growth of cellular elements involved in an immune response where an attempt has been made to incorporate some of the general features of HIV infections. To our knowledge, for the first time we have explicitly taken into account some immune mediators like lymphokines, and both humoral as well as cell-mediated responses are considered. Two intercell interactions are examined. With the infinite-range interacting network, both interactions give rise to 24 fixed points (stable configurations), however, all fixed points with interaction (1) are not the same as those with interaction (2). Furthermore, different weights are associated with these stable configurations such that an immunocompetent state is more favourable with one interaction (1) and an immunodeficient state, with the other (interaction (2)).

A simple cubic lattice is used to take into account the nearest-neighbour intracell interactions with the help of a cellular automata rule (of logical 'or' for the cellular state involved in the interaction). Evolution of cells is studied for a random binary mixture of interactions (1) and (2) with probability f. At the extreme high value of $f(=1.0)$ where cells are interacting with intercell interaction (1), we observe a viral growth followed by a viral decay (for both free as well as expressed antigens) while T_4 cells multiply steadily to a saturation value; in the steady state, the T_4 cell population is much larger than that of antigens, leading to an immunocompetent state. On lowering the value of f, the steady-state population of T_4 cells decays while that of antigens grows. Below a characteristic value of f, ($f_c \simeq 0.8$) the viral population dominates over that of the T_4 cells leading to an immunodeficient state; in a narrow regime for f above f_c we observe an immunocompetent state. The crossover from immunocompetent to immunodeficient state is described by a survival probability. Production of lymphokines goes down to zero as a result of suppressor T_8 cells while all other cell types

grow in a normal fashion as a function of time for all initial concentrations of host cells. Many details, such as variety of other cell types (natural killer cells, white blood cells other than macrophages, etc), diverse specificities of the cellular elements, mobility of cells and a realistic host space are not considered explicitly. However, in our continued efforts towards understanding the immune response, the simplified model presented here does capture some of its main features.

Acknowledgments

The author would like to thank Dietrich Stauffer for helpful discussions and HLRZ for the financial support and computer time.

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