A Mesoscopic Approach to Modeling Immunological Memory

Yongle Liu and Heather J. Ruskin

School of Computer Applications
Dublin City University, Dublin 9, Ireland

Abstract. In recent years, the study of immune response behaviour through mathematical and computational models has been the focus of considerable efforts. We propose a mesoscopic model to combine the most useful features of the microscopic and macroscopic approaches, which have been the alternatives to date. Cellular automata and Monte Carlo simulation are used to describe the humoral and T-cell mediated immune response, where the nature of the response induced depends on the polarization of T_H1 and T_H2 cells. Memory immunity is introduced to our model, so that we can simulate primary and secondary immune response. The high affinity between memory B-cells and antibodies contributes to a quick and intense response to repeated infection. The experiments on $P_{affB-AB}$ and $P_{affMB-AB}$, which control antibody production, explore the different roles of B-cell and memory B-cell in immune response stages. The duration of immunological memory is also studied.

Keywords: Cellular automata; Monte Carlo; Humoral; T-cell mediated; Immune response; Immunisation; Mesoscopic.

1 Introduction

A number of mathematical and computational models have been developed over recent years to describe the human immune system and its response to threat. These efforts can be grouped principally in terms of their focus on microscopic or macroscopic features respectively. Microscopic models thus provide detailed information on the immune system, such as T-cell polarisation, (where naive CD4 T-cells differentiate into T_H1 and T_H2 cells) [1-2], vaccine complexity [1], repertoire descriptors, (where receptors of T and B-cells, epitope and peptide of antigen and antibody are described by bit-strings [3]), and antigen-specific clonal expansion, (where only one kind of T-cell is likely to be specific to a particular antigen) [4, 5]. The microscopic model IMMSIM is a well-known and much studied example [4, 5]. It includes seven entities or cell types, with bit-strings used to simulate the key-lock interactions between the elements of the immune system. In comparison to the detailed microscopic approach, other cellular automata-based or similar models have until now used less cell types or simpler inter-cell interactions [9-16], whereas ordinary differential equations (ODE)-based [6-8] or continuous models are essentially macroscopic in outlook. The aim has been to study the overall disease evolution, such as global aspects of the viral infection,

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overall symptoms, and related statistics. Thus, use of reduced and simplified interactions and system parameters permits an overview of the entire population of cells and molecules. Mannion et al. [9, 10], proposed models of cellular automata (Monte Carlo) type for the T-cell mediated response to HIV. Four cell types, two sets of interactions, and two global parameters, P_{mut} and P_{mob}, which built on earlier models with few cell types [12, 13], are involved in this MC model.

In contrast, we propose a mesoscopic model here, which seeks to bridge microscopic and macroscopic features. The cell types and global parameters in the original model [9,10] are retained, and an increasing number of cells of different types are used to more densely populate the host space. This approach thus increases the detail on the immune space, with all cell populations interacting on an individual cell-by-cell basis, rather than as a well-mixed cell population described by ODEs [6-8]. Furthermore, Instead of using the combination of scalars for immune cells and antigen and allowing several of them on a single lattice site (like IMMSIM [4, 5]), we choose Booleans for all cell states. We simplify the cell populations, permitting a maximum of one cell of each type per site, which allows us to simulate on a larger-scale (computationally expensive for a detailed microscopic model), but compromises on highly local detail (at a given site). However, population dynamics of immune cells and overall disease evolution is obtained from the whole lattice, which is large scale. Hence, we describe an intermediate approach between microscopic and macroscopic.

In particular, we include *both* humoral and T-cell mediated immune response in what follows. Thus, the mesoscopic model attempts to describe T-cell polarizations, and to characterise primary and secondary humoral response.

2 Model

2.1 The entities

The immune system is extremely complex with many different cell types, proteins and molecules involved in its efficient operation. It is impossible to take into account all factors in a computational model, so we limit the cell types to eight key ones in the humoral and T-cell mediated immune response. These cells are not precisely those of a former 8-cell model proposed by Pandey [17], since some different entities are included and some omitted. Included here are Macrophage (M), T_H1 cell (T1), T_H2 cell (T2), Cytotoxic T-cell (CT), Memory T-cell (MT), B-cell (B), Memory B-cell (MB), Antibody (AB) and Antigen (AG). As well as the key entities described, receptors, molecules and other signals are also involved in immune response operation, which control e.g. the proliferation and elimination of the eight on which we focus. In our model, we do not consider these factors in terms of separate units, but present their function through parameters, which control cell-cell interactions.

2.2 Updating cells on the host systemic spatial lattice

The human immune system is represented by a simple cubic lattice, where each site has six neighbouring sites, with square cross-section. The lattice has linear dimension L, with L^3 sites, and periodic boundary conditions, so that edges of the lattice are wrapped. Any site can be occupied by any one of the eight cell types, but there is *at most one* cell of each cell type at a site. The cellular state is described by a Boolean variable, where "true" is used to indicate the high concentration of a given cell type at one site and "false" the low concentration.

A Monte Carlo method is used, which stochastically updates cellular states, following interactions, with one update of the whole lattice equal to one Monte Carlo step (MCS): (asynchronous updating). A site is randomly selected to be updated and this selection is repeated L^3 times for one MCS. Around 1000 MCS are used to monitor the disease evolution.

In updating cell types at any one site, a number of features, such as growth, inter-cell interactions and death must be considered in order to mimic real biological processes. States of all cells *at a given site* are simultaneously updated. At the beginning of an update, the information is saved in temporary states. All states evolve from these temporary ones, so that results of updating all cell types are independent of the sequence used.

2.3 The growth

Every cell type at a site at time $t+1$ depends on the states of its six neighbouring sites at time t. In Equation (1), if any cell type at a given site has a neighbouring site, occupied by the same cell type with state = "true" at time t, then the state of the given cell type will evolve to "true" at time $t+1$.

$$\begin{aligned} S'_{ic}(x, y, z, t+1) = & S_{ic}(x, y, z, t) .or. S_{ic}(x+1, y, z, t) \\ .or. & S_{ic}(x-1, y, z, t) .or. S_{ic}(x, y+1, z, t) .or. S_{ic}(x, y-1, z, t) \\ .or. & S_{ic}(x, y, z+1, t) .or. S_{ic}(x, y, z-1, t) \end{aligned} \tag{1}$$

where S' is the intermediate state of a given cell; ic is the cell type and x, y and z are the coordinates of the site. Equation (1) is the same as that of our original model [9, 10], but cells may not always proliferate successfully. In every inter-site interaction of any one cell type, a probability ($P_{prolrate}(ic)$) is assigned to successful growth. Different values of $P_{prolrate}(ic)$ reflect the fact that every cell type has different growth rate to proliferate in real immune system. After growth, the cellular states are temporary as before, and are used as a basis for updating the cellular states in inter-cell interactions. These involve different cell types at any one site, i.e. account for affinities and triggers between cell types.

2.4 Interactions

The following set of intra-site inter-cell interactions are used to describe the immune-response to antigens. All cellular states at time $t+1$ are evolved from

the temporary states (S'_{ic}) after growth.

$$
\begin{aligned}
M(t+1) &= M'.or.AG'.and.[not[M'.and.AG']] && (2.1)\\
T1(t+1) &= [T1'.or.[AG'.and.M']].and.[not[T1'.and.AG']] && (2.2)\\
T2(t+1) &= [T2'.or.[AG'.and.M']].and.[not[T2'.and.AG']] && (2.3)\\
CT(t+1) &= CT'.or.[AG'.and.M'.and.T1'] && (2.4)\\
B(t+1) &= B'.or.[T2'.and.AG'] && (2.5)\\
AB(t+1) &= AB'.or.[[B'.or.MB'].and.AG'] && (2.6)\\
AG(t+1) &= AG'.and.[not[CT'.or.AB']] && (2.7)
\end{aligned}
\qquad (2)
$$

Our model thus attempts to describe in more detail the immune system behaviour through simple interaction equations, limited though these still are in terms of the biological reality. All the interactions above are taken to be stochastic, and the success or failure of every interaction is controlled by independent probabilities. Values of all parameters are set between "0" and "1", with a probability close to "1" implying that the specific inter-cell interaction is highly likely. The mechanism for cooperative interactions is described below.

In Equation (2.1), the presence of antigen, but no macrophage at one site, implies that the antigen can induce the growth of a macrophage with a probability $P_{\mathrm{a}ff_{AG-M}}$. If both antigen and macrophage are present at the same site, the antigen can kill the macrophage with a probability $P_{\mathrm{i}nfect_M}$. In Equation (2.2) and (2.3), the presence of an antigen and a macrophage together can activate growth and differentiation of T-cells with a probability $P_{\mathrm{a}ff_{TH}}$. A proportion ($P_{\mathrm{r}op_{T1}}$) of the newly generated T-cells differentiate into T_H1 T-cells, and the others (1-$P_{\mathrm{r}op_{T1}}$) into T_H2 T-cells. If no macrophage presents to the antigen, it becomes free and can kill T_H1 and T_H2 cells with a probability $P_{\mathrm{i}nfect_{TH}}$. Equation (2.4) shows that with probability $P_{\mathrm{a}ff_{T1-CT}}$, a cytotoxic T-cell grows when an antigen, a macrophage and a T_H1 T-cell are all present at that site. Further, the presence of a T_H2 T-cell and an antigen can induce the growth of a B-cell with a probability $P_{\mathrm{a}ff_{T2-B}}$ (Equation (2.5)). Antibody secretion is described in Equation (2.6). When the antigen presents at the same site, a B-cell secretes antibody with a probability $P_{\mathrm{a}ff_{B-AB}}$; a memory B-cell can secrete antibody with a higher probability $P_{\mathrm{a}ff_{MB-AB}}$ than that for the B-cell, and the antibodies spread to all six neighbouring sites. Equation (2.7) describes the elimination of antigen. A cytotoxic T-cell (with a probability $P_{\mathrm{k}ill_{CT-AG}}$)or an antibody cell (with a probability $P_{\mathrm{k}ill_{AB-AG}}$) will kill an antigen which is present at the same site.

2.5 Death of all cell types

One MCS simulates activity in a unit period of time equivalent to a time period in the immune-response, which is equivalent to the smallest half-life of the eight entities. Consequently some cells may die naturally in this period. All the cells in the lattice are allowed to experience a natural death process with probability $P_{\mathrm{d}eath}$. This death process is assumed (somewhat naively) to occur after cellular growth and the inter-cell interactions have taken place, ensuring that a new

generation of cells are produced. Newborn cells and original cells are taken to have the same probability of natural death, (again a simplification) with no account taken of degradation of cell function in our model. This treatment of newborn cells and original cells as effectively memory-less is assumed to have little effect on the evolution of the total populations, which are the major focus for study, but this is clearly a limitation on the model as a whole. We have based the probability of cell death in a unit of time on the biological half-life data, where *half-life* is defined to be the time required for half the number of a given cell type to be eliminated. Then

$$P_{death} = e^{-\frac{(ln2)\times\sigma}{\tau}} \tag{3}$$

where P_{death} is the death rate of the cell type, τ is half-life, σ is the period that one MCS represents in the real immune system.

2.6 The cellular mobility

In the immune system, realistically, all cell types are mobile. For example, T-cells and B-cells circulate continuously from the bloodstream to the lymphoid tissues and back to blood, and macrophages bring antigens from blood to lymphoid organs. The mobility of these cells increases the opportunity to interact with other cells. At the end of each MCS, all cells are permitted to move to their neighbouring sites with probability P_{mob}, which is omni-directional i.e., one cell can move to any one of its six neighbouring sites with equal probability. Directional mobility, in which one cell can move in only selected axial directions e.g. positive only may have some relevance, for example in chemotaxis. The mobility algorithm remains as described in the original model [9, 10] with the motivation for movement of a given cell based on the attraction for it to interact with other cell types. For example, a cytotoxic T-cell, an antibody or memory B-cell randomly move to a neighbouring site occupied by an antigen to kill it, whereas, an antigen randomly moves to a neighbouring site occupied by a macrophages, T_H1 or T_H2 cell to infect them. The T_H1 cell, T_H2 cell or B-cell randomly move to anyone of their six neighbouring sites, and do not require further special conditions.

3 Results

In order to investigate the immunological memory, we have included memory B-cells in our model, which have higher affinity to antibodies than B-cells. When B-cells die in the death process, some of them become memory B-cells. The parameter $P_{transRateMB}$ is the rate that decides what proportion of those dying B-cells can differentiate into memory B-cells. $P_{transRateMB}$ is set to 0.1 in the simulations.

We show a typical simulation of immunisation in Fig. 1 for selected entities only. At the start of the simulation, the system has no immune cells, and only low density of antigen (1%) uniformly distributed on a S.C. lattice of size $50 \times$

50×50. The antigen induces a quick and intense immune response, in which both humoral and T-cell mediated entities are involved. Antigen levels peak then decrease, because the immune response suppresses further growth. Finally, the antigen is eliminated, and the primary immune-response is complete. After the primary immune-response, all immune cells except memory B-cells gradually decrease then disappear, but memory B-cells remain due to their long half-life. The immune system is thus returned to the healthy state, but retains memory of the antigen. If the same dose of antigen is again distributed randomly into the lattice, the secondary immune-response is activated. This is characterised by faster and more effective response to antigen [18]. A large amount of antibodies are produced very quickly, so the density of antigens is limited to a low level, which is far below that of primary immune response. The density of B-cells is also lower than in the primary response. This suggest secondary immune response is far more intense and effective than the primary, and that the antigen causes less damage to the immune system. This behaviour is similar to the behaviour of a real immune system.

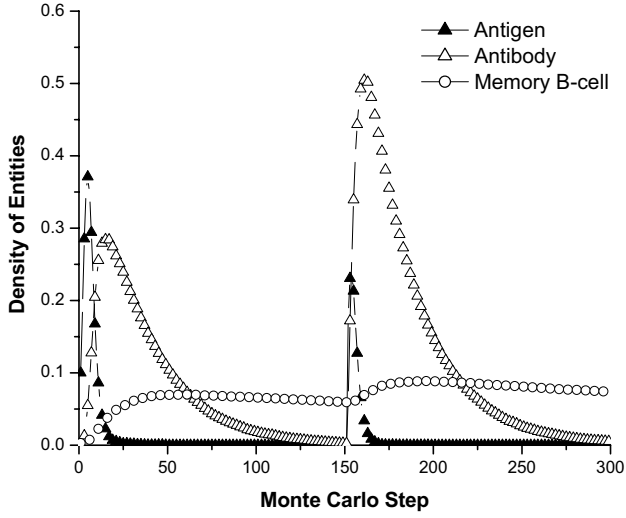

Fig. 1. Immunological memory to repeated infection

In our model, the ability of B-cells and memory B-cells to secrete antibody are controlled by parameters $P_{\mathrm{a}ffB-AB}$ and $P_{\mathrm{a}ffMB-AB}$, and the humoral immune response is predominantly driven by these two parameters. In Fig. 2, we look at the effect of $P_{\mathrm{a}ffB-AB}$ and $P_{\mathrm{a}ffMB-AB}$ on the antigen population in primary and secondary immune response. We fix the value of $P_{\mathrm{a}ffMB-AB}$, and

increase the value of $P_{affB-AB}$ from 0.3 to 1.0 in Fig. 2a. The selection of other parameters involved in this humoral immune response are shown in Table 1. We vary the parameters individually to investigate how sensitive results are to parameter values chosen. $P_{affA\,G-M}$, P_{affTH} and $P_{killAB-AG}$, which control the growth of immune cells, just affect the growth speed of these cells, and have little influence on values of peak densities. The period of an immune cell's half-life and $P_{prolRate-AG}$ decide the peak densities of these immune cells and antigen respectively. With low density of macrophage, T_H2 cell or B-cell, there are not enough antibodies produced, so antigens can not to be eliminated from the immune system. If $P_{prolRate-AG}$ is high, antigens have a high growth rate, and survive the immune response.

Parameter	Value	Parameter	Value
$P_{transRateMB}$	0.13	$P_{prolRate-AG}$	0.2
$P_{affA\,G-M}$	1.0	Half-life of M	10(days)
P_{affTH}	1.0	Half-life of T2	10(days)
P_{T2-B}	1.0	Half-life of AB	20(days)
$P_{killAB-AG}$	1.0	Half-life of MB	400(days)

Table 1. Parameter selections in Fig. 2.

With the increase of $P_{affB-AB}$, the peak antigen population increases in primary response, but remains at the same level in the secondary, which suggests that the parameter principally influences the former, and is negligible for the latter. In Fig. 2b, the value of $P_{affB-AB}$ is fixed, and the value of $P_{affMB-AB}$ is changed from 0.3 to 1.0. Little difference in primary immune response is observed, but peak antigen density increases, when $P_{affMB-AB}$ is increased for the secondary stage. This phenomenon suggests that $P_{affMB-AB}$ drives the secondary immune response, but has little effect on the primary.

Immunological memory is sustained by long-lived memory B-cells, induced by the original exposure[18], so that memory B-cells provide long-term protection after the primary immune-response is over. In Fig. 3, we investigate results from our model for the maximum antigen density in secondary immunity (D_{maxAG}) vs. the time interval between antigen injections (Δt), where an expression of the form

$$D_{maxAG} \propto \Delta t^{\beta} \tag{4}$$

clearly applies. If the antigen injection interval is short, a more intense secondary response is induced, and the antigen population is limited to a low level. If the interval is very long, the secondary immune response is not as effective as before, and maximum antigen density achieves the same level as that in primary immune response (dotted line Fig. 3). Results thus support the fact that immunological

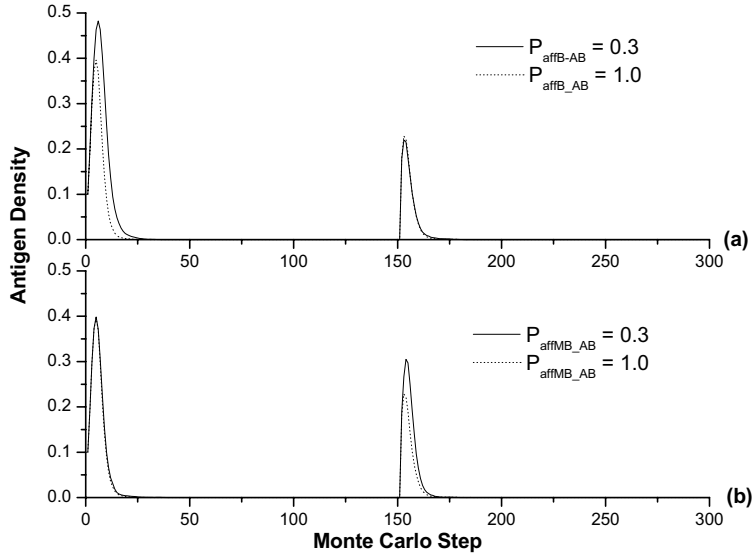

Fig. 2. $P_{\mathrm{a}ffMB-AB}$ is fixed to 1.0 (a) and $P_{\mathrm{a}ffB-AB}$ is fixed to 1.0 (b); Lattice size is $30 \times 30 \times 30$; Ten samples are generated for each value of $P_{\mathrm{a}ffB-AB}$ and $P_{\mathrm{a}ffB-AB}$, and the average results are displayed.

memory gradually fades after exposure to initial antigen attack. The immunological memory is related to half-life of memory B-cells and the transfer rate of B to memory B-cells. The larger the percentage of memory B-cells, the longer the duration of relative immunity.

4 Conclusion

In conclusion, we studied immunological memory in this paper through a mesoscopic model incorporating key cell types and stochastic interactions with T_H1 T_H2 differentiation. Main features of the immunological memory were captured, but details of cell population dynamics are not presented. In repeated infection, we obtained a more rapid and intense secondary response compared to that of the original exposure, so that antigen population is suppressed to a low level. A preliminary analysis of the influence of probabilities assigned to antibody secretion of B and memory B-cells demonstrated that first infection immune response is driven predominantly by B-cells while memory B-cells drive repeated infection. Immunological memory (based on memory B-cells) diminishes with time, so that after a very long period, the antigen invasion is treated as a first infection because of the loss of memory to the antigen. This is reflected in our model (Fig.3) with $D_{\mathrm{m}axAG} \propto \Delta t^{\beta}$. The long half-life of memory B-cells and large transfer rate from B to memory B-cells sustain long immunological memory.

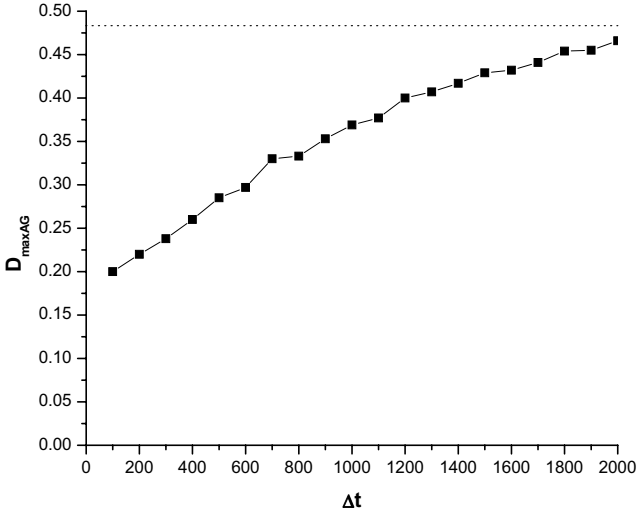

Fig. 3. Decline in immunological memory. Maximum antigen density in primary immune response (dotted line).

Our model attempted an intermediate approach between microscopic and macroscopic, and results of this paper show that some features of immune response could be reproduced, notably immunological memory. Currently, we are also studying T-cell mediated immune response specific to HIV, and cooperation of the humoral and the T-cell mediated reactions, as well as chemotaxis (directional mobility) from a mesoscopic viewpoint.

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