Mathematical models of clonal expansion

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Abstract:- We present a simple microscopic model for the clonal expansion of the immune system. We consider the virgin T lymphocytes moving in a network (the lymphatic system) through which they may reach some preferred areas (lymphoidal tissues or organs). The relevant process we describe is the recognition of an antigen and the transition of a virgin T lymphocyte into a memory or effector T cell, belonging to the clonal species related to the antigen. The growth of the clone is counterbalanced by other mechanisms such as apoptosis and attrition so that a quasi equilibrium state (homeostasis) is reached. We propose a microscopic version of a previously developed phenomenological model based on populations of lymphocytes and antigens. The antigens and the memory T cells lymphocytes belong to repertoires whose interaction strength is known as cross-reactivity. The lymphocytes are modeled as a gas of automata moving randomly in a network. The results of the simulations are compared with the mean field computation based on population dynamics.

*Key words:-*Immune system, Microscopic models, Lotka Volterra equations, Mean field equations

1 Introduction

We propose a preliminary version of a microscopic model for the clonal expansion of T lymphocytes in the immune system (IS). The goal is to introduce the basic ideas underlying the behaviour of the clonotipic IS such as pattern recognition, degeneracy and cross reactivity, learning and memory [1] jointly with a description of the environment from the topological and dynamical viewpoint, taking into account its random fluctuations.

To this end we introduce two populations of Von Neumann automata [2] moving and interacting in a network, that we may identify with the lymphatic system with the addition of some organs like the thymus, spleen etc. The automata correspond to the antigens and the T lymphocytes, which are split into subgroups belonging to a repertoire. At the beginning the T lymphocytes are identical and called virgin; the change occurs when they meet an antigen (their receptors interact with a peptidic chain belonging to an antigen, exposed by a APC cell) and after this imprinting they become memory cells and form a clone. This is a sort of learning process since the memory cell is capable, at later times, of recognizing antigens with the same or a very similar molecular structure and to activate defense strategies.

Agent based models have been developed in information science to describe complex systems of biological (ant nests, swarms) or artificial (airports) origin. Our agent-like elementary unit is a Von Neumann automaton (VNA), endowed with sensors, actuators, a central processing unit, a software with evolutionary properties and possibly self replicating capabilities. The implementation of a VNA is a nontrivial task, but presently we are interested only in a few properties which allow to mimic the interaction of virgin T lymphocytes with antigens and the transition to the memory state.

We simplify the problem assuming a 2D geometry and choosing a square lattice with periodic boundary conditions. No specific organ, except for the thymus, which produces the virgin T lymphocytes, is inserted, but we may consider a superimposed super-lattice whose nodes play the role of lymph nodes. The rules of the game are simple and we describe first the case of a single species of antigens A and the corresponding memory clone M which grows due to the imprinting of virgin T lymphocytes V. The antigens enter the system at a well defined location and propagate by a random walk throughout the system which is topologically a $\mathbb{T}^2$ torus. As a consequence, in the absence of interactions, they diffuse, reaching a uniform distribution after the input (acute antigenic stimulus) is over. If we take into account their self reproducing capability, then the uniform density will grow exponentially to reach a given asymptotic limit. For instance we may assume that each node of the elementary lattice can host one antigen and one lymphocyte at most at any time: this rule limits the moves in our lattice. If the antigen is represented by a VNA then the move at each step will not be decided simply by assigning a probability to reach the nearest unoccupied lattice points, but on the basis of the inspection of the half plane whose normal is given by the last move. The second population we introduce are the virgin T lymphocytes, which are produced continuously at a specific site where the thymus is located and move randomly on the network being eventually attracted by the lymph nodes. The interaction between an antigen and a virgin T lymphocyte is based on a pattern recognition process effected by the T cell receptors which are sterically complementary to the molecular structures of the antigen, separated by the proteasoma and exhibited by the APC (antigen presenting cells). We drastically simplify this process assuming that when the antigen A and the virgin T lymphocyte V have a contact there is an imprinting which changes the T lymphocyte into a memory cell M. The number of different antigens and of the corresponding memory clones is very high, moreover the correspondence is not 1 to 1. A memory T cell specific for a given antigen is capable of recognizing other antigens with a lower efficiency (cross reactivity). As a consequence if we order

the antigens on a string so that the distance is related to the structural difference, the affinity between a memory cell i and an antigen j will decrease with the distance $|i-j|_N$ [1,9] (where N is the length of the string defining the repertoire and the distance is taken modulo N). An important issue for the T-A dynamics is homeostasis: this term refers to the quasi equilibrium states through which the system constantly moves. Indeed a living system though working permanently out of the thermodynamical equilibrium, which is unavoidable to develop ordered structures, tends nevertheless to avoid strong deviations. When some perturbation occurs like a massive input of antigens, the system actively reacts but, after a transient during which some rearrangements occur, it tends to reach a new equilibrium, either monotonically or performing oscillations of decreasing amplitude. In a phenomenological model previously developed we have considered the response of the IS to a single species of antigens occurring in two distinct ways: the acute antigenic load, acting with high intensity for a short period of time, and the chronic antigenic stress acting with low average intensity and rapid fluctuations on long time intervals. The chronic antigenic stress, provided by the environment (viruses, bacteria, alien molecules) and by the self (mutated cells), plays an important role of permanent stimulus. We have considered two models: the first one describing the virgin into memory conversion in presence of antigenic noise, which showed a decrease of the V cell compartment with a time increasing spread [3,4,5,6]. A second model was proposed to describe the expansion of a memory clone in presence of acute and chronic antigenic stimuli [7]. The antigens stimulate not only the V to M conversion and consequent clone expansion, but also the clone contraction by apoptosis of the M cells, a phenomenon recently discovered and known as heterologous immunity. Since the clone size appears to be quantized the model was based on a system of two first order equations for the logarithm of the clone size $x = \log c$ and its time derivative $v = dx/dt$. The model included a periodic landscape potential, a counteracting action to variation of the clone size (attrition), and both acute and chronic antigenic load. This model, whose mechanical analogue is a damped pendulum subject to a strong impulsive force and to a weak fluctuating one, successfully describes the recovery of the homeostatic equilibrium after an acute antigenic load, with damped oscillations as observed in experiments with mice [8]. This type of recovery has not an obvious microscopic counterpart, unlikely the usual exponential recovery we shall consider here, and to which the standard mathematical models refer.

2 The microscopic prey-predator model

In order to build a microscopic model for the evolution of a cytotoxic memory T cell clone under an antigenic stimulus, we consider the following simple prey-predator model. In this system we introduce an "environment" with a constant number of omnivore predators. These predators have a defined lifetime, but we for simplicity assume that when a predator dies, a new one enters the system. At the starting time a given number of preys enters the environment. When a predator meets a prey, the prey is eaten, and the predator retains the memory of this event through the rest of its life and becomes more efficient in predation. We denote with A the preys, V the unexperienced predators and M the experienced predators whose overall number we assume to remain constant. In this model we don't have any kind of reproduction mechanism, and there's no way to pass information to the "new generations" of predators: the memory is lost when the predator dies.

The purpose of this simple model is to understand how the proliferation of memory T cells can arise from the mechanism of casual meetings with antigens. For this reason we refer to the predators as "T cells" and to the preys as "antigens"; the unexperienced predators are the virgin T cells, the experienced predators are the antigen experienced (memory plus effector) T cells. At the present stage we don't claim to provide an accurate description of the immune system. At every time step t_i each object moves one step on the lattice in a random direction, obeying an exclusion principle: at every lattice site we cannot have more than one element of the population A, and no more than one element of the populations V or M. Every object has a mean lifetime τ, which means that at each time step it has a probability $p = \frac{1}{\tau}$ to be removed from our lattice (to "die"). We impose a conservation rule

$$V(t) + M(t) = T \tag{1}$$

When a prey A and an unexperienced or experienced predator V or M meet at given time t_i on a lattice site, the prey A is removed. If the predator is unexperienced V, it changes its state and becomes experienced M. Since this is a prey-predator system, the mean field equations for the populations are given by Lotka-Volterra type of equations provided that these populations are sufficiently large and the space-time steps sufficiently small. The mean field equations read

$$\dot{A} = c_1\, A - c_2\, A(V + q\, M) \qquad \dot{M} = -c_3 M + c_4 A V$$

$$V + M = T \tag{2}$$

where $q \geq 1$ takes into account the increased ability in predation due to the first experience.

In order to simplify the analytic solution we choose $q = 1$ so that $V + q\, M$ is replaced by the constant value T and we obtain a skew system which is immediately integrated

$$A(t) = A_0 e^{-\alpha t} \qquad \alpha = c_2 T - c_1 > 0 \tag{3}$$

with $A_0 = A(0)$. Substituting $V = T - M$ into the second equation we obtain

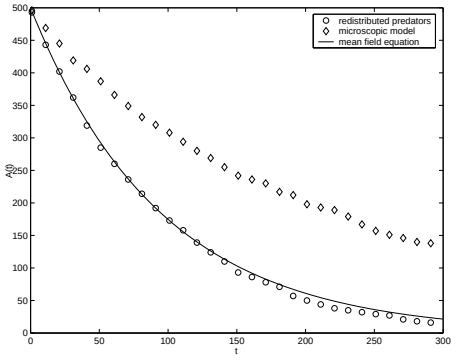

Figure 1 Comparison of the microscopic prey-predator model (rhombi and circles) with the mean field theory (continuous line). The rhombi correspond to the population of preys obtained from the original microscopic model, the circles to the same population obtained after a random redistribution of predators at every time step. The initial values are $A_0 = 500,\ M_0 = 200,\ p_A = p_M = 10^{-4},\ N = 160 \times 120$

$$\dot{M} = -c_3 M + c_4 A_0 e^{-\alpha t}(T - M) \qquad)4)$$

whose solution reads

$$M(t) = M_0 + \exp\left(-c_3 t + \frac{c_4 A_0}{k} e^{-\alpha t}\right) \times$$

$$\times \int_0^t dt'\ c_4 A_0 T e^{-\alpha t'} \exp\left(c_3 t' - \frac{c_4 A_0}{k} e^{-\alpha t'}\right)$$

where $M_0 = M(0)$.
In the first realization of our microscopic model we don't consider any reproduction mechanism. Coefficient c_1 is negative and together with c_3 describes the removal probabilities p_A and p_M of preys and predators (a negative value of c_1 doesn't change the nature of the system, since we need $c_2 T - c_1 > 0$). As expected, studying the evolution of a population of antigens in absence of T cells, we see that the result of the microscopic model is in excellent agreement with the mean field solution (3). The chosen parameters are $T = 0$ and $c_1 = -p_A$. The statistical fluctuations are small since the initial population is large $A(0) = 1.92 \times 10^4$ and the removal probability is very small $P_A = 10^{-3}$ so that the solution of the discrete time map $A(i+1) = A(i) - p_A A(i)$ is very close to the solution (3) of the differential equation.
Assuming random and uniform distribution of the populations of preys and predators, the number of events in which a prey meets a predator is $\frac{AT}{N}$ (where N is the total number of sites), and the number of events in which an antigen meets an unexperienced predator is $\frac{AV}{N}$ so that $c_2 = c_4 = \frac{1}{N}$. Using these values the microscopic model produces results in agreement with the mean field theory only for short times (we have a perfect agreement with the discrete time map on the first time step).

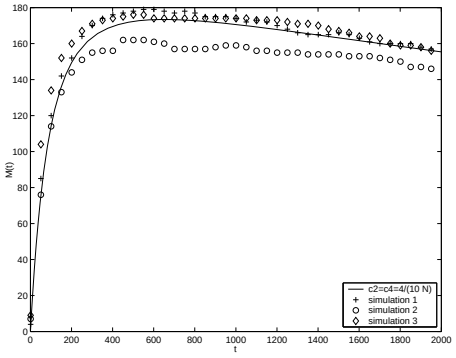

Figure 2 Comparison of the results of the microscopic model for the population M (circles, rhombi and crosses) with the mean field theory (continuous line), where $c_2 = \frac{0.4}{N}$ is taken from the best-fit.

For greater times we see that the evolution of the model is slower than expected, which means that the events in which preys and predators interact are fewer than expected (see figure 1). This follows from the hypothesis that the populations of preys and predators are uniformly distributed over the lattice. Even though the initial distribution is uniform, after few time steps the predators, eating nearby preys, tend to be surrounded by a region poor of preys. The chance to interact is therefore reduced. (As we'll see later, this behaviour is dominant in this model as we assumed that predators, regardless of their state, are "perfect killers": they remove with probability 1 a prey at every encounter.) To test this interpretation we have modified the microscopic model by randomly redistributing the predators at every time step: with this change the results of the simulation are in a excellent agreement with the solutions of the mean field equations, see figure 1.

In the original model we have computed an effective interaction coefficient $c_{2\ \mathrm{eff}}$ which takes into account the local rarefaction of preys after predation, by a bestfit $A(0) - c_{2\ \mathrm{eff}}\, t$ to the linear decay of $\log A(t)$. Replacing c_2 and c_4 in equation (2) with $c_{2\ \mathrm{eff}}$ a good agreement of the microscopic model with the mean field equations is recovered for the population of experienced predators, see figure 2.

3 The Immune system microscopic model

In the present version of the microscopic model we consider three populations: the antigens A, the virgin and memory T lymphocytes $V,\ M$. Every cell ($V,\ M,\ A$) moves randomly on a lattice with N sites with limit of occupancy of one antigen plus one lymphocyte per site. Microscopically we give a probability of conversion of V into M when the encounter with an antigen occurs on a lattice site. In a previous work [3,5] the virgin T cells decrease mainly due conversion, the proliferation and apoptosis being comparable; the antigen experienced T cells increase

by the same amount so that the total number $V + M$ remains constant. The equations read

$$\dot{V} = -\alpha\, V - \beta\, M \qquad \dot{M} = \alpha\, V + \beta\, M \tag{5}$$

where the first term describes the conversion from V to M due to primary antigenic stimulus, the second term takes into account the contribution due to antigenic restimulation. The second coefficient, being much smaller than the first one, will be neglected here. Moreover the decrease of the population of antigens is due to the interaction with the antigen experienced population M. The coefficients α, β depend on the antigen load and in the previous model, which referred to a long time period, an average value was considered. Referring to a shorter time period following an acute stimulus the dependence of α on the antigenic load cannot be neglected. The mean field equations that we propose read

$$\dot{A} = c_1 A - c_2 A\, M \qquad \dot{V} = -\alpha(A) V \qquad V + M = T \tag{6}$$

We choose

$$\alpha = c_4\, A - c_3 \tag{7}$$

so that it is positive as soon as the antigens are above a threshold $A_c = c_3/c_4$. In the absence of antigens it is reasonable that $-\alpha = c_3 > 0$. Since c_3 is a small term this means that the virgin cells slowly expand because the production (by thymus) overcomes the apoptosis, whereas the antigen experienced cells decrease at the same rate. The coefficient c_3 being small on the considered time interval $T \ll 1/c_3$ the growth is approximately linear. Inserting into equations (6) we obtain

$$\dot{A} = c_1 A - c_2 A\,(T - V) \qquad \dot{V} = c_3\, V - c_4 A V \tag{8}$$

The previous equations can be recast in the canonical Lotka-Volterra form

$$\dot{A} = -c_1' A + c_2 A\, V \qquad \dot{V} = c_3\, V - c_4 A V \tag{9}$$

where $c_1' = c_2\, T - c_1$ is assumed to be positive. In this case we observe that there is an equilibrium state

$$A_c = \frac{c_3}{c_4} \qquad V_c = \frac{c_1'}{c_2} \tag{10}$$

Linearizing the equations around the equilibrium we verify that there is a center so that the equilibrium is stable.

$$\frac{dV}{dt} = -\frac{c_4 c_1'}{c_2}\,(A - A_c) \qquad \frac{dA}{dt} = \frac{c_2 c_3}{c_4}\,(V - V_c) \tag{11}$$

Both $V,\ A$ oscillate periodically around the equilibrium with a period $\tau_c = 2\pi/\omega$ with $\omega^2 = c_1' c_3$. The mean field equations describing the response of the immune system to an acute antigenic stimulus according to this model can be summarized as

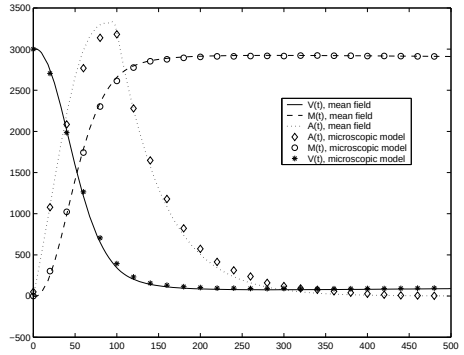

Figure 3 Comparison of the results of the microscopic model for the immune system (V stars, M circles and A rhombi) with the mean field theory (dotted line for A, dash line for M, and continuous line for V). The initial values and parameters of the model are $V_0 = 3000$, $M_0 = 0$, $A_0 = 0$, $F(t) = 50$ for $t < 100$, $c_3 = 10^{-3}$, $c_1 = 10^{-2}$, $p_2 = p_4 = 0.1$,

$$\dot{V} = c_3 V - c_4 V A \qquad \dot{M} = -c_3 V + c_4 V A$$

$$\dot{A} = c_1 A - c_2 A M + f(t) \tag{12}$$

where we choose $f(t) = A_*/\epsilon$ for $0 \le t \le \epsilon$ and $f(t) = 0$ for $t > \epsilon$.

In the microscopic model we have described the proliferation mechanism in the following nonlocal way: at each time step the virgin lymphocytes and antigens have a given probability to duplicate (c_3 and c_1): the new object is created in a random position of the lattice. While in the previous prey-predator model predators become experienced and preys are eliminated every time they meet a predator at the same lattice site, we now introduce a given probability for these events to happen (we will call these probabilities p_4 and p_2 referring to their obvious connection with coefficients c_4 and c_2). The results of this microscopic model have been compared with the numerical solution of the mean field equations (11) (we used coefficients $c_4 = \frac{p_4}{N}$, $c_2 = \frac{p_2}{N}$) see figure 3. For an overall population of T lymphocytes $T = 3000$ the equilibrium values are $A_c = 100,\ V_c = 2000$ and the period of small oscillation around the equilibrium is $\tau_c \sim 1250$. As a consequence they cannot be appreciated because of the discrete nature of the simulation which leads to extinction of the antigens since A_c is very close to zero.

The good agreement with the mean field theory indicates that for the values of the parameters and the time scale used in these simulations the assumption of random distribution of the populations is a good one. This is due to the presence of the "antigen elimination probability" p_2. The lower is the value of this probability, the better is the hypothesis of random distribution of populations. (This approximation is also a good one when we have an high value of c_1 and c_3, since in this model the reproduction mechanism, not present in the prey-predator model, mixes the populations).

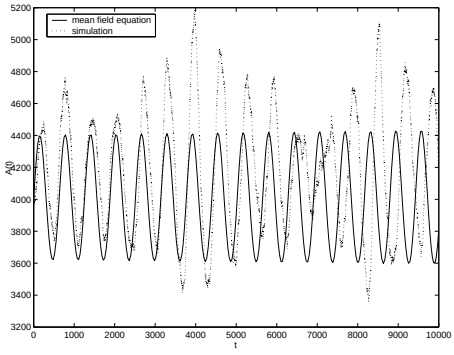

Figure 4 Comparison of the results of immune system microscopic model (dots) with the mean field theory (continuous line) for the population A. The parameters of the model are $c_1 = c_3 = 10^{-2},\ p_2 = p_4 = 0.1$, and the initial values are close to the equilibrium $A_c = V_c = 4 \times 10^3$ so that periodic oscillations of the populations are observed.

Furthermore, the distribution of antigens has to be considered absolutely random at least while the source $f(t)$ is switched on, since in our microscopic model this term creates antigens in random positions. We have considered a different set of parameters ($c_1 = 0.01,\ p_2 = 0.1,\ c_3 = 0.01,\ p_4 = 0.1,\ T = 8000$) so that $A_c = V_c = 4000$ on a lattice of size 200×200. In this case the period is $\tau_c \sim 630$ but the amplitude of the oscillations is large as shown by figure 4. The agreement of the simulation with mean field theory is good concerning the period of the oscillations, whereas the amplitude varies in rather regular way and decreases by increasing the number of lattice points while keeping the average population density constant. As a consequence we claim that this behaviour is due to the discrete and probabilistic nature of the simulation.

4 Conclusions

We have presented a preliminary version of a microscopic model of the clonotipic immune system to describe the interaction of the virgin T lymphocytes with the antigens and their conversion into memory and effector T cells. The model refers to a rather short time scale, a few times the period of an acute stimulus, to describe the evolution of these populations on the basis of local interaction rules. This model inherits some features of two mesoscopic models [3,5] previously developed to describe the memory conversion and the clonal expansion, but neglects the chronic antigenic stress relevant on long time scales. The motion on the network is random with a local rule: when a T lymphocyte and antigen A meet, the antigen is removed with a given probaility and, if T is virgin lymphocyte , it is converted into a memory lymphocyte M. The mean field theory leads to Lotka-Volterra like equations, where the coefficients are specified by the local probabilities. A renormalization is needed when the local density fluctuations become important, unless a random redistribution is imposed. The comparison between the microscopic model and the mean field theory is excellent within the statistical errors. The decrease of the antigens after the impulse and the increase of the memory clone is exponential as expected, however oscillations around an equilibrium of center type are possible. Damped oscillations of the clonal size, which are suggested by some experiments [8], require additional damping mechanisms such as attrition [7], which might be included. The model will be developed along two distinct lines. First a repertoire will be introduced with a cross reactivity matrix for the A-M interactions; the topology of the network will be modified to resemble the lymphatic system and a subnetwork of main nodes (lymphatic nodes and organs), where most of the interactions take place, will be included. The experience gained with the simulator of mobility MOBILIS [10] will be exploited, by establishing correspondences between the lymphatic and urban networks, lymph nodes and chronotopoi, social and immunonological repertoires. The second objective is to replace the random walkers having simple interaction and proliferation-extinction rules with true Von-Neumann automata endowed with sensors and cognitive capabilities: the latter allow environment oriented displacements, pattern recognition and to simulate the memory mechanisms on which the clonotipic immune response is based. The automata describing the lymphocytes and the antigens will be first developed and tested on regular lattices to compare the average properties with some mean field approximations. On the other side the simple random walkers described in the present note will be moved on a complex network (self similar or scale free) in order to compare the results of the simulation with the mesoscopic equations which allow to describe anomalous diffusion phenomena. The last step, further in the future, will be to move the automata on a complex network. The difficulty of the last step is not only to develop a simulator but also to find the theoretical tools to interpret the virtual experiments. A population of Von Neumann automata moving on a complex network is a prototype of complex system, suitable to describe the immune system or the urban mobility, but its theoretical understanding is still in its early infancy.

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