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Response to Invasion by Antigens and Effects of Threshold in an Immune Network Dynamical System Model with a Small Number of Degrees of Freedom

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We study a dynamical system model of an idiotypic immune network with a small number of degrees of freedom, focusing mainly on the effect of a threshold above which antibodies can recognise antibodies. The response of the system to invasions by antigens is investigated in models both with and without such a threshold, and we find that the system changes in a desirable way for a moderate magnitude of the perturbation; that is, the system changes to a state in which the antigen is neutralized more quickly than in the unperturbed state. Also, the propagation of a disturbance caused by an antigen is investigated in a system of one-dimensionally connected basic units, taking the closed 3-clone system as a unit, and it is found that the threshold of the system has the effect of enhancing the stability of the network and to localise the immune response.

Introduction It is well known through experimental studies that an immune system is activated by interacting with itself to prepare for unknown antigens.[1),2)] With this fact in mind, Jerne introduced an immune network model.[3)] Later, a dynamical system model of the immune network was introduced by Varela et al.[4)] In the latter model, the basic elements are antibodies and B-cells, which produce antibodies. The effects of helper and suppressor T-cells are taken into account by introducing functions that represent interactions between antibodies and between B-cells and antibodies. In this model, some important mechanisms, such as recognition, memory, and tolerance, have been studied.[5)-8)]

In a previous paper,[9)] we investigated a model with a threshold above which antibodies can recognise antibodies and reported that the system possesses chaotic states, and also a peculiar type of limit cycle, which we call a "differentiating state". Further, regarding the response to the invasion by antigens, we have found that when the system is in a differentiating state, it responds sensitively to a specific type of antigen.

An important issue that has not yet been addressed is the question of how important the use of thresholds is to the results found. We study this issue in the present paper. We also study the localisation of immune responses. It has been pointed out by De Boer et al. that a fault of the network view of immune systems is that when only one clone interacts with one antigen, immune responses spread over the entire system. Indeed, the activation caused by the invasion of antigens is not localised in the model by Varela et al. This behaviour seems inappropriate, because it suggests that large networks, such as those that might be found in real immune systems, can be unstable, because small local perturbations can generate global effects by spreading over the entire system. Thus, it would be very interesting to find a mechanism that can localise immune responses and thereby construct a model that does not suffer from this fault. One solution for this problem has been obtained by taking multi-cross-linking into account.[10] In this paper, we show that it is also possible to solve this problem by introducing a simple element, thresholds, in Varela's model in order to localise immune responses. We study the effect of thresholds on the response to the invasion of antigens by investigating the propagation of disturbances in one-dimensionally connected basic units.

Model The evolution in time of the concentrations of an antibody, f_i, and of a B-cell, b_i, of the ith idiotype ($i = 1, 2, \cdots, N$) are given by the following equations:[9]

$$df_i/dt = -K_1\sigma_i f_i - K_2 f_i + K_3 Mat\,(\sigma_i)\, b_i, \tag{1}$$

$$db_i/dt = -K_4 b_i + K_5 Prol\,(\sigma_i)\, b_i + K_6. \tag{2}$$

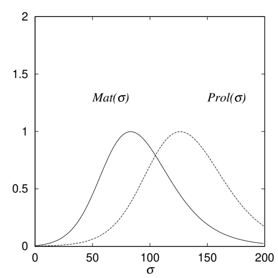

Fig. 1. Profiles of $Mat(\sigma)$ and $Prol(\sigma)$ adopted in this paper.

Here, σ_i is the sensitivity of the network to the ith idiotype, defined as

$$\sigma_i = \sum_{j=1}^{N} m_{ij}^0 f_j. \tag{3}$$

The interaction between two different idiotypes i and j is represented by the connectivity m_{ij}^0. We choose $m_{ij}^0 > 0$ if there is an affinity between i and j and $m_{ij}^0 = 0$ if there is not. For simplicity, we assume $m_{ij}^0 = 1 - \delta_{i,j}$, where $\delta_{i,j}$ is the Kronecker delta. The quantities $Mat\,(\sigma_i)$ and $Prol\,(\sigma_i)$ are the interaction functions between antibodies and between antibodies and B-cells, respectively. The functions we adopt here are the following (see Fig. 1):

$$Mat\,(\sigma_i) = U_1 \left[\tanh\left\{U_2\left(\sigma_i - T_{lm}\right)\right\} - \tanh\left\{U_3\left(\sigma_i - T_{um}\right)\right\}\right], \tag{4}$$

$$Prol\,(\sigma_i) = U_4 \left[\tanh\left\{U_5\left(\sigma_i - T_{lp}\right)\right\} - \tanh\left\{U_6\left(\sigma_i - T_{up}\right)\right\}\right]. \tag{5}$$

Model with threshold First, we study a 3-clone closed chain system with a threshold κ_0 above which the ith antibody can recognise other antibodies. Each element of the connectivity matrix $M = \{m_{ij}\}$ is defined as

$$m_{ij}(t) = m_{ij}^0 \Theta(f_j(t) - \kappa_0), \tag{6}$$

where $\Theta(x)$ is the Heaviside function ($\Theta(x) = 1$ for $x \geq 0$ and 0 for $x < 0$). In this system, there exist differentiating states.[9] A differentiating state is an asymmetric limit cycle in which the amplitudes of oscillation in the concentrations of antibodies are not equal. We consider the response of the system in differentiating states to invasion by antigens. In these states there exist clones with a long activation period and clones with a short activation period. We denote the former by L and the latter by S. In the following, we treat two cases of antigen invasion by controlling the rate K_7 of antigen invasion in the system.

Case 1

In this case, an antigen A that is similar to the antibody f_1 invades the system. We assume in this case that antibodies f_2 and f_3 recognise both the antigen and the antibody f_1. Further, thresholds related to the antigen are also set to κ_0. The differential equation for the antigen A is given by

$$\frac{dA}{dt} = -K_1\sigma_A(t)A + K_7, \quad \sigma_A(t) = m_{12}(t)f_2(t) + m_{13}(t)f_3(t). \tag{7}$$

Case 2

In this case, an antigen A interacts only with the antibody f_1. Let us define $\kappa_{i,j}$ as the threshold above which f_j recognises f_i. Here i and j take integer values from 1 to 4, where $i = 4$ denotes the antigen. Then, the equation for the antigen A is

$$\frac{dA}{dt} = -K_1\sigma_A(t)A + K_7, \quad \sigma_A(t) = \Theta(f_1 - \kappa_{4,1})f_1. \tag{8}$$

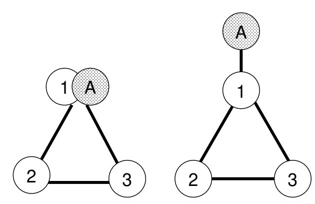

Fig. 2. Invasion of an antigen.

The sensitivity σ_i of the ith clone is modified as

$$\sigma_i = \sum_{j=1}^{3} m_{ij}^0 \Theta(f_j - \kappa_{i,j})f_j + l_i\Theta(A - \kappa_{i,4})A, \tag{9}$$

where l_i is the strength of the interaction between f_i and A and is set to $l_i = s_A\delta_{i,1}$, with $s_A = 0.3$. We assume that $\kappa_{i,j} = \kappa_{j,i} = \kappa_0 = 50$ for any $i, j = 1, 2, 3$ and $\kappa_{i,4} = \kappa_{4,i} = \kappa_1 = 10$ for $i = 1, 2, 3$.

As shown in Ref. 9), there is a differentiating state with two L clones and one S clone, and the neutralization of the antigens becomes faster as the activation period of clones that interact with antigens becomes longer. In both Cases 1 and 2, if the input rate K_7 of the antigen takes a value in some finite interval, the system modifies itself and comes to exist in the state that has the shortest relaxation time of the antigen. However, in both cases, if K_7 is sufficiently large, the network is destroyed.

The network is destroyed by the antigen more easily in Case 2 than in Case 1.

Model without threshold Next, we study the response of the system without the threshold to invasion by an antigen in Cases 1 and 2. We introduce a strength parameter s of the connectivity and set the elements of the connectivity matrix as

$$m_{ij} = sm_{ij}^0 = s(1 - \delta_{i,j}). \tag{10}$$

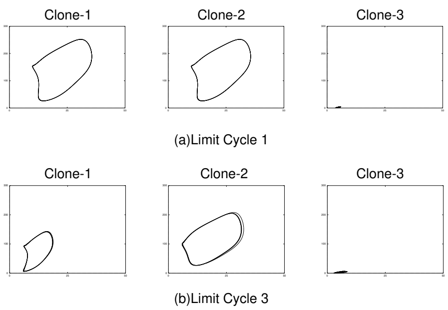

Fig. 3. Limit cycle 1 and limit cycle 3.

As s increases from 0, the system changes as follows: fixed point $\rightarrow$ limit cycle 1 (Fig. 3(a)) $\rightarrow$ chaos $\rightarrow$ limit cycle 2 $\rightarrow$ fixed point. If the state is either a limit cycle 2 or chaotic, the entire network is activated. Contrastingly, in limit cycle 1 state, only a part of the network is activated, in the sense that one clone takes negligibly small values. By fixing the initial value of the antigen and changing K_7, we study the responses of these three states. In both Cases 1 and 2, for a small value of K_7, the state of the system does not change very much, but for large K_7, the network is destroyed. In Case 1, as K_7 increases from 0, one of two clones that can recognise the antigen takes a negligibly small value. The other clone and the clone that cannot interact with the antigen oscillate with opposite phase. Thus, the system is nearly in limit cycle 1 state [Fig. 3(a)]. When K_7 becomes larger, the activation period of the clone interacting with the antigen becomes longer [Fig. 3(b)]. This limit cycle 3 state has a longer activation period than limit cycle 1 state. To see this, let us define the period τ_r as the total period during which the concentration of the clone 2 interacting with the antigen is greater than that of the non-interacting clone 1. We have investigated the dependence of τ_r on K_7 and have found that τ_r of limit cycle 3 is larger than that of limit cycle 1 (see Fig. 4). In Case 2, when K_7 takes intermediate values, the attractor changes to a chaotic state in which the clone 1 oscillates in a state with activation periods longer than those of other clones. These types of behaviour occur for all initial states, except for the state of limit cycle 1 in which the clone 1 takes small values. Thus, in both Cases 1 and 2 the system tends to assume configurations that are better able to deal with the antigen during its invasion.

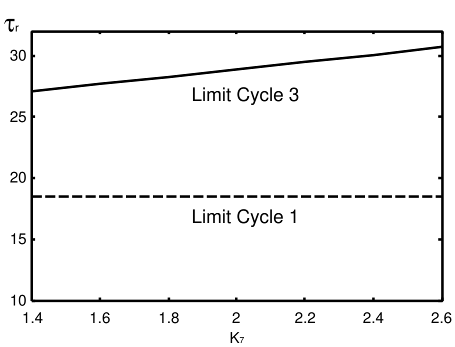

Fig. 4. K_7 dependence of τ_r.

From the above results, we can conclude that whether there is the threshold or not, in both Cases 1 and 2, the system changes in a desirable way with regard to the neutralisation of the antigen for moderate magnitudes of the perturbation. Further, we find that the network is destroyed by the antigen more easily in Case 2 than in Case 1. The reason for this seems to be that the effect of the antigen on the network is more direct in Case 2 than in Case 1.

Loosely connected 3-clone units Here, to study the effect of thresholds on the spreading of the response to the invasion by antigens, we investigate one-dimensionally connected basic units, where each basic unit is composed of a 3-clone closed system.

A. Basic units with a threshold

As the initial state of a basic unit, we take a limit cycle in which the configuration of clones is (L, L, S). When two basic units are connected, for each unit the network architecture is similar to that in Case 2 of the invasion by an antigen [see Fig. 5(a)]. Thus, from the result above for Case 2, if the interaction between units is large, the combined system is destroyed when the amplitude in either unit becomes large. For this reason, hereafter, we consider loosely connected systems.

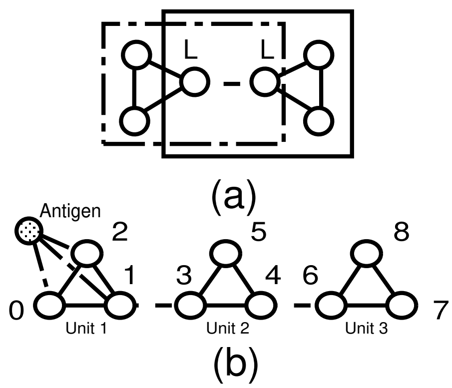

Fig. 5. Connection of 3-clone units.

In the case of two units, the clone that is connected to the other unit tends to stay in a state with a long activation period, and the basin of attraction of this type of solution becomes large. We have found that this is a characteristic feature of loosely connected systems. Now, let us study an open chain of three basic units, unit 1, unit 2 and unit 3 [see Fig. 5(b)]. Let s_U and κ_U be the strength of the connection between units and the strength of the threshold between units, respectively. To see the response behaviour quantitatively, we have calculated in limit cycle states the differences between the phases of oscillations in the presence and in the absence of antigens. We have also studied the effect of changing κ_0 (the threshold between clones) and κ_U. From this investigation, we have observed that the disturbance is reduced more in unit 3 than in unit 2. However, we have not found a significant difference between the cases $\kappa_U = 0$ and $\kappa_U > 0$. Further, we have found that the disturbance is not always reduced as κ_0 is increased, and that the threshold between clones causes complicated dynamical behaviour. To see the effect of the threshold more clearly, we also investigated a system composed of the basic units without thresholds.

B. Basic units without a threshold

Here, we set $\kappa_0 = 0$. In this case, for $s = 2.5$ and $s_U = 0.05$, there exist limit cycle states in both the cases $\kappa_U = 0$ and 50. As in the case with a threshold considered above, setting $A_0 = 80, \kappa_1 = 10$ and $s_A = 0.3$, we investigated the response behaviour of these limit cycles quantitatively. We have observed that the disturbance again does not spread significantly to unit 3. Further, we have found that the disturbance in unit 2 is reduced considerably for $\kappa_U = 50$, while it is still large for $\kappa_U = 0$ (see Fig. 6).

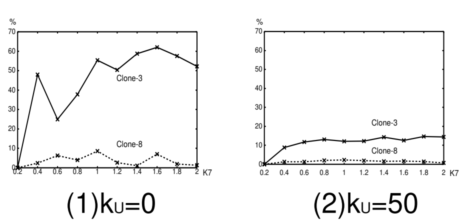

Fig. 6. K_7 dependence of the magnitude of fluctuations in clones 3 and 8 relative to that in clone 0.

These results show that the thresholds have the effects of substantially reducing the magnitudes of interactions between units and of enhancing the independence of each unit.

Discussion In this paper, we have analysed a model constructed from the point of view of Jerne, that antibodies perceive other antibodies as imaginary antigens. It has been pointed out as a major fault of his network theory that the network is not necessarily stable. There have been several studies on this subject.[6),8),11)] However, it seems that this problem has not yet been entirely solved. The result regarding immune responses obtained in the first part of this paper implies that the system studied here does not always change randomly, but can change in an ordered way in some cases. Whether the immune network is composed of many small subnetworks or is completely connected is an open question. If the former is true, the study of small networks is very important, and the above result is very significant, since it may refute the criticism of Jerne's network theory. Studies of large systems and such evolutionary systems as that studied in Ref. 12) are currently being conducted.

Now, we discuss the effects of thresholds of concentrations. The result obtained in the second part of this paper shows that the structural stability of the network is increased by the existence of thresholds. It has been pointed out that a cross-linking structure composed of antibody molecules is very important for the purpose of allowing phagocytes to recognize and seize antigens in real immune systems.[13)] It is natural to assume that the formation of a three-dimensional cross-linking structure by antibodies depends on the concentrations of antibodies and antigens. Thus, the introduction of the threshold of the concentrations not only gives a desirable effect that makes the network more stable but also can be interpreted as accounting theoretically for one of the mechanisms of real immune responses.

We believe that the study of such small networks is very important to establish the relation between the behaviour of large networks and that of small networks.

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