Response to Invasion by Antigen 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, mainly focusing on the effect of a threshold above which antibodies can recognise antibodies. The response of the system to invasions by antigens is investigated in the both models with and without the threshold and it turns out that the system changes in a desirable direction for moderate magnitude of perturbation. Also, the propagation of disturbance by an antigen is investigated in the system of one-dimensionally connected basic units taking the closed 3-clone system as a unit, and it is clarified that the threshold of the system has effects to enhance the stability of the network and to localise the immune response.

Introduction

It is experimentally well-known that an immune system is activated by interacting with itself to prepare for unknown antigens. Taking this fact into account, an immune network model was introduced by N. K. Jerne. Later, a dynamical system model of the immune network was introduced by F. J. Varela et al. In this 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 which represent interactions between antibodies, and between B-cells and antibodies. This has been called the “second generation immune network model”.

In this model, some important mechanisms such as recognition, memory, and tolerance have been studied.

In the previous paper, we studied the original Varela model and also the modified model. Mainly, we have investigated the model with a threshold above which antibodies can recognise antibodies and have reported that the system has chaotic states, and also a peculiar type of limit cycle, which we called differentiating state. Further, as for the response to the invasion by antigens, we have found that when the system is in a differentiating state, its response to a specific type of antigen is sensitive. That is, differentiating states are considered to represent a kind of short term memory of the invasion by antigens. Further, we have found that the response time in a chaotic state takes an intermediate value compared to differentiating states.

An important issue which has not yet been addressed is the question of how central the use of thresholds is to the results found. This is investigated in the first part of the present paper. In the second part of the paper we go on to 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 whole system and the activation by the invasion by antigens is not localised in the model by Varela et al. This behaviour seems inappropriate because it suggests that large networks, such as might be found in the real immune system, can be unstable since small local perturbations can generate global effects by spreading over the whole system. Thus, it is very interesting to find a mechanism to remove this fault and to localise the immune responses. Thresholds may be one of such candidate. Therefore, we study the effect of thresholds on the response to the invasion by antigens, by investigating the propagation of disturbances in one-dimensionally-connected basic units.

**Model**

The evolution in time for the concentrations of an antibody, $f_i$, and of a B-cell, $b_i$, with the idiotype $i (i = 1, 2, \ldots, N)$ are given by the following equations.

\[
\frac{df_i}{dt} = -K_1 \sigma_i f_i - K_2 f_i + K_3 \text{Mat}(\sigma_i) b_i, \quad (0.1)
\]

\[
\frac{db_i}{dt} = -K_4 b_i + K_5 \text{Prol}(\sigma_i) b_i + K_6. \quad (0.2)
\]

See Ref. 9) for detailed definitions and explanations. Here, $\sigma_i$ is the sensitivity of the network to the $i$th idiotype, defined as

\[
\sigma_i = \sum_{j=1}^{N} m_{ij}^0 f_j. \quad (0.3)
\]

The interaction between two different idiotypes $i$ and $j$ are represented by the connectivity $m_{ij}^0$. We set $m_{ij}^0 > 0$ 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’s delta. $\text{Mat}(\sigma_i)$ and $\text{Prol}(\sigma_i)$ are the interaction functions between antibodies, and antibodies and B-cells, respectively. In general, $\text{Mat}(\sigma_i)$ and $\text{Prol}(\sigma_i)$ are assumed to be unimodal functions and $\text{Prol}(\sigma_i)$ to be shifted to the right with respect to $\text{Mat}(\sigma_i)$ in order to take the roles of T-cells into account. The functions we adopt here are the followings. See Fig.1.

\[
\text{Mat}(\sigma_i) = U_1 \left[ \tanh \left\{ U_2 (\sigma_i - T_{lm}) \right\} - \tanh \left\{ U_3 (\sigma_i - T_{um}) \right\} \right], \quad (0.4)
\]

\[
\text{Prol}(\sigma_i) = U_4 \left[ \tanh \left\{ U_5 (\sigma_i - T_{lp}) \right\} - \tanh \left\{ U_6 (\sigma_i - T_{up}) \right\} \right]. \quad (0.5)
\]

**Model with Threshold**

First, let us study a 3-clone closed chain system with a threshold $\kappa_0$ above which the $i$th antibody can recognise other antibodies. Each element of the connectivity matrix $M = \{m_{ij}\}$ is defined as

\[
m_{ij}(t) = m_{ij}^0 \Theta(f_j(t) - \kappa_0), \quad (0.6)
\]

where $\Theta(x)$ is the Heaviside function (i.e., $\Theta(x) = 1$ for $x \geq 0$ and $0$ for $x < 0$). In this system, there exist differentiating states. We consider the response of the
system in differentiating states to invasion by antigens. In these states there exist a clone with a long period and a clone with a short period. We denote the former by L, and the latter by S, respectively. We treat two cases of invasion by antigens in the followings.

**Case 1**

An antigen $A$ similar to the antibody $f_1$ invades the system. We assume in this case that antibodies $f_2$ and $f_3$ recognise the antigen as the antibody $f_1$. Thus, in the sensitivities $\sigma_2$ and $\sigma_3$, $f_1$ is replaced by $f'_1 = f_1 + A$. Further, thresholds related to the antigen are also set to $\kappa_0$. On the other hand, in general, the antibody $f_1$ cannot recognise the antigen. Then, by assuming that the antigens enter the system at a rate $K_7$ per unit time, the differential equation for the antigen $A$ is given by

$$\frac{dA}{dt} = -K_1 \sigma_A(t) A + K_7, \quad (0.7)$$

$$\sigma_A(t) = m_{12}(t)f_2(t) + m_{13}(t)f_3(t).$$

**Case 2**

An antigen $A$ interacts only with the antibody $f_1$. Then, the antibodies $f_1$ recognise the antigen, but antibodies $f_2$ and $f_3$ cannot recognise the antigen, in general. Let us define $\kappa_{i,j}$ as the threshold above which $f_j$ recognises $f_i$. Here $i$ and $j$ take integer values between 1 and 4 where $i = 4$ denotes the antigen. Then the equation for the antigen $A$ is

$$\frac{dA}{dt} = -K_1 \sigma_A(t) A + K_7, \quad (0.8)$$

$$\sigma_A(t) = \Theta(f_1 - \kappa_{4,1})f_1.$$ 

The sensitivity $\sigma_i$ of the $i$th clone is modified as

$$\sigma_i = \sum_{j=1}^{3} m_{ij}^0 \Theta(f_j - \kappa_{i,j})f_j + l_i \Theta(A - \kappa_{i,4})A, \quad (0.9)$$

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 $\kappa_{i,j} = \kappa_{j,i} = \kappa_0 = 50$ for any $i, j = 1, 2, 3$ and $\kappa_{i,4} = \kappa_{4,i} = \kappa_1 = 10$ for $i = 1, 2, 3$.

We have performed numerical calculations in these two cases and have found the following results about the response of the system. As is shown in Ref. 9), there is a differentiating state with two L clones and one S, which responds to the antigen much better than the other states. In both cases 1 and 2, if the input rate $K_7$ of the antigen is neither very small nor very large, the system modifies itself by evolving to that differentiating state in which the relaxation time of the antigen is shortest among differentiating states. This phenomenon is regarded as a kind of short term memory of the invasion by the antigen. However, in both cases, if $K_7$ is sufficiently large, the concentration of antibody which can interact with the antigen converges.
to a fixed point, while the antigen concentration grows exponentially with the result that the system is destroyed by the antigens. The dependence on the initial condition of this behaviour is less sensitive than that on $K_7$. Further, we have found that the network is destroyed by the antigen more easily in the case 2 than in the case 1.

**Model without Threshold**

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

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

(0.10)

As $s$ increases from 0, the system changes as a fixed point $\rightarrow$ limit cycle 1 $\rightarrow$ chaos $\rightarrow$ limit cycle 2 $\rightarrow$ a fixed point. If the state is either limit cycle 2 or chaotic, the whole network is activated. On the other hand, in the limit cycle 1 state, a part of the network is activated, in the sense that one clone takes negligibly small values and does not affect the other clones. By fixing the initial value of the antigen and changing $K_7$, we study the responses of these three states. In both Case 1 and Case 2, for a small value of $K_7$, the state of the system does not change very much, but for large $K_7$, each clone converges to a fixed point and the network is destroyed. The magnitude of the value of $K_7$ that causes the breakdown of the system is of order 1 in Case 1, and is $10^{-1}$ in Case 2. In Case 1, for intermediate values of $K_7$, regardless of initial states, the attractor changes to a new periodic state (limit cycle 3) (Fig.3). This state is considered to be a better state against the invasion by the antigen because one of two clones which can interact with the antigen is in the long-period state, L.

In Case 2, when $K_7$ takes intermediate values, the attractor changes to the chaotic state in which the clone 1 oscillates in relatively longer pulse states. These behaviours occur for all initial states except for the state of the limit cycle 1 in which the clone 1 takes small values. Thus, as well as in Case 1, in Case 2 the system tends to take better configurations to deal with the antigen.

Therefore, whether there is the threshold or not, it turns out that in both cases 1 and 2, the system changes to a desirable direction for moderate magnitudes of perturbation. Further, it turns out that the network is destroyed by the antigen more easily in Case 2 than in Case 1. The reason 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 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 threshold
As an 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 Case 2 of the invasion by the antigen. See Fig. 4(a). Thus, from the above result in Case 2, if the interaction between units is large, the combined system is destroyed when the amplitude in either unit becomes large. Hence, hereafter, we consider loosely connected systems. In the case of two units, the clone which is connected to the other unit tends to stay in the long pulse state, and the basin of attraction of this type of solution becomes large. It turns out that this is a characteristic feature for the loosely connected systems. Now, let us study an open chain of three basic units: unit 1, unit 2 and unit 3. See Fig. 4(b). Let $s_U$ and $\kappa_U$ be the strength of the connection between units and that 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 the absence of the antigens. We have also changed $\kappa_0$ (the threshold between clones) and $\kappa_U$. As a result, we have observed that the disturbance is reduced more in unit 3 than in unit 2. However, significant difference between in the cases of $\kappa_U = 0$ and $\kappa_U > 0$ has not been observed. See Fig. 5. Further, we have found that the disturbance is not always reduced as $\kappa_0$ is increased, and that the threshold between clones provokes complicated dynamical behaviours. Therefore, to see the effect of the threshold more clearly, we investigate the system composed of the basic units without thresholds.

**B. Basic units without threshold**

We set $\kappa_0 = 0$. In this case, for $s = 2.5$ and $s_U = 0.05$, there exist limit cycle states in both cases of $\kappa_U = 0$ and 50. As in case A, setting $A_0 = 80, \kappa_1 = 10$ and $s_A = 0.3$, we have investigated the response behaviour of these limit cycles quantitatively. We have observed that the disturbance again hardly spreads 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.

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

In this letter, we have analysed the model constructed from the point of view of N. K. Jerne that antibodies look upon other antibodies as internal images of antigens. It has been pointed out as a big fault in his network theory that the stability of the network is not guaranteed. There have been several studies on this subject. However, it seems that this problem has not yet been fully investigated. The result on immune responses obtained in the first part of this paper implies that the system does not always change randomly but can change in an ordered way in some cases. This may be a refutation of the above criticism of the network theory. Since this result has been obtained in systems with few degrees of freedom, it is necessary to study larger systems. This is now under investigation.

Now, let us discuss the effects of thresholds of concentrations. The result 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 made by antibody molecules is very important in order that phagocytes can catch antigens in real immune systems. It is natural to assume that the formation of the 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 which makes the network more stable, but also can be interpreted as taking one of the mechanisms of real immune responses into account theoretically. It would be very interesting to know whether the threshold provokes the localisation of the immune response in larger systems. This is a future problem.

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(a) $g_u=0$

(b) $g_u=50$
