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Analysis of an Immune Network Dynamical System Model with a Small Number of Degrees of Freedom

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We numerically study a dynamical system model of an idiotypic immune network with a small number of degrees of freedom. The model was originally introduced by Varela et al., and it describes antibodies interacting in an organism in order to prepare for the invasion of external antigens.

The main purpose of this paper is to investigate the direction of change in the network system when antigens invade it. We investigate three models, the original model, a modified model, and a modified model with a threshold of concentration, above which each antibody can recognize other antibodies.

First, we study possible attractors of the networks. In all these models, both chaotic and periodic states exist. In particular, we find peculiar periodic states organized in the network, the differentiating states. In these states, one clone plays the role of switching the clones to be excited. That is, it causes an excited clone to become suppressed and a suppressed clone to become excited.

Next, we investigate the response of the system to invasions by antigens. We find that in some cases the system changes in a positive direction when it is invaded by antigens, and the differentiating state can be interpreted as short term memory of such invasion. We also find tolerant behavior. Further, from the investigation of the relaxation times for invasions by antigens, it is found that in a chaotic state, the average response time takes an intermediate value among those in asymmetric periodic states. This suggests a positive aspect of chaos in immune networks.

§1. Introduction

In this paper, we consider an immune network dynamical system model with a small number of degrees of freedom. First, we explain the present understanding of immune systems briefly. [1)-3)]

The main constituents of an immune system are B-lymphocytes (B-cells) produced in the bone marrow, T-lymphocytes (T-Cells) produced in the thymus and free antibodies produced by B-cells. B-cells and T-cells have protein molecules called receptors on their surfaces. The receptors of B-cells are antibodies (immunoglobulin, abbreviated Ig), and antibodies recognize and connect to antigens to neutralize them. On the other hand, T-cell receptors (TcR) cannot recognize antigens, but they recognize pieces of antigens which appear on the surfaces of antigen presenting cells. When this happens, as a result, helper T-cell expedites the immune response, and the suppressor T-cells suppress it. Killer T-cells attack and kill cells which are infected by viruses, and other foreigh bodies. The receptors of B- and T-cells have the corresponding 3-dimensional structures, and these are called 'idiotyes'. A family of B-cells that are generated from a B-cell is called a 'clone'. Therefore, a clone and antibodies produced by the clone have the same idiotype. In a human body, the total number of clones which are generated from a single B-cell is about 10 to 10^4, the total number of clones amounts to 10^8, and the total number of antibodies is about 10^{20}. Thus, the total number and variety of antibodies are sufficient to bind to any antigen. This diversity is due to the recombination and the mutation of genes.

The response to an invasion by antigens is understood as follows. When antigens enter an organism, clones which can recognize the antigen bind to it, and mature with the help of the helper T-cells, and some of them proliferate. Others become antibody-forming cells. In the antibody-forming cells, many antibodies are produced and secreted. As a result, many antibodies appear and neutralize antigens. When the neutralization is completed, through the action of the suppressor T-cells, the proliferation of B-cells is suppressed, and the immune response ends.

In the hypothetical process of the immune response described above, a clone of the B-cells that can recognize an antigen is selected. Thus, this theory is called a 'clonal selection theory'. It has been confirmed experimentally.

B-cells, T-cells and antibodies die if they are not stimulated. As is mentioned above, in a human body there are a huge number of these cells. To explain this, in 1974 Jerne proposed the so-called network view of immune systems.[1] In his theory, these cells interact with and activate each other, organizing a network. However, after Jerne's theory appeared, within 10 years, it was considered as failing to live up to its initial promise. This is because this theory cannot explain the correct direction of change of the system when antigens invade a body. Another reason is that during this time, T-cells and their actions were discovered, and to include these elements in the original theory it would lose the simplicity which attracted many researchers.

However, there are several experimental results that support the network theory.[4),5)] For example, it was found that in newborn mice, activated lymphocytes are retained even though mices are isolated from any antigen. That is, it seems that the immune system activates itself to prepare for the invasion of external antigens.

In recent years, several dynamical system models of immune networks have been proposed and studied.[6)-18)] Let us summarize these models briefly. Farmer et al. introduced a 'bit-string model'. In this model, concentrations of antigens and antibodies obey coupled oridinary differential equations. Antibodies and antigens are represented by binary strings. Then, defining the distance between two strings, they introduced complementarity by which the interactions are determined. Based on this model, Bagley et al.[7)] proposed an adaptive network model of immune systems using principles of meta-dynamics. Then, they investigated the topology of idiotypic networks, that is, the structure of the connectivity of antibodies induced by injection of an antigen into the system.

In these models, only antibodies and antigens are considered. There exist other models in which B-cells interact with antigens, and this interaction determines the kinetics of the cell response. This is called a "B-model".[8),9)] In B-models, B-cells proliferate according to a phenomenological log bell-shaped function. The function depends on a single field h, given by $h = \sum_j m_{ij} b_j$, where m_{ij} is affinity between the ith and jth B-cells and b_j is the concentration of the jth B-cell. In Ref. 10), De Boer et al. modified this interaction function by considering multiple ligands and taking into account both the binding affinity and cross-linking affinity. The resultant function depends on two fields, a binding field and a cross-linking field. They discussed the differences in behavior, such as percolation, when a one-field or two-field interaction function is adopted.

In 1988, Varela et al. proposed a dynamical system model in which both B-cell and antibodies are taken into account.[11] They call this the "second generation immune network model".[12] This model has been studied extensively, changing the interaction function, number of clones, network connectivities, and so on.[12)-18] In this model, several biologically significant functions, such as recognition, memory and tolerance, have been studied.

In this paper, we study the dynamical system model of Varela et al., because it takes into account the essential characteristics of the real immune systems. That is, not only antibodies, but also B-lymphocytes which produce antibodies, and the roles of T-lymphocytes, i.e., the activation and the suppression of B-lymphocytes, are included.

We would like to investigate the effects of the interaction among lymphocytes and antigens, to analyze the kinds of states and structures the network can have, and to see in what directions the network moves when antigens invade the system. Further, we consider a kind of short term memory and tolerance. Also, we are interested in the mathematical structures of network systems from the viewpoint of dynamical systems.

In reality, an immune system has a huge number of degrees of freedom. However, in this paper we focus on the Varela model with a small number of degrees of freedom. Our objective is to investigate the possible states in the network and the change experienced by these states when antigens invade a small system, as a necessary step toward obtaining an understanding of the states of the immune network and the immune response in large systems.

Now, let us explain the model we treat in this paper. The constituents of the network, free antibodies and B-lymphocytes (B-cells), interact with each other through idiotypes. Between two different idiotypes i and j, there may occur an affinity, which is represented by the connectivity m_{ij}. We set $m_{ij} = 1$ if there is an affinity between i and j and $m_{ij} = 0$ if there is none. In some cases, m_{ij} is experimentally measurable.[4),5] Let us denote the concentration of B-lymphocytes of the ith idiotype by b_i and that of free antibodies produced by the B-lymphocytes by f_i. These antibodies have the same idiotype as the B-lymphocytes. The sensitivity of the network for the ith idiotype is defined as

$$\sigma_i = \sum_{j=1}^{N} m_{ij} f_j, \tag{1·1}$$

where N is the number of idiotypes. This represents the strength of the influence of other antibodies on the ith antibody. The numbers of B-lymphocytes and antibodies change in time through the following causes. Free antibodies are removed from the constituents of the network because they have a natural lifetime and also because they interact with other idiotypes and are thereby neutralized. On the other hand, they are produced by B-cells as a result of the maturation of B-cells. The probability of this maturation is assumed to depend on their sensitivity σ. This is expressed by the function $Mat(\sigma)$. In the beginning of an immune response, antibodies which interact with antigens maturate with the help of T-cells. Then, it is natural to assume that $Mat(\sigma)$ is an increasing function of σ when σ is small. If the number of antibodies becomes large, and the immune response ceases, the creation of antibodies will be suppressed. Thus, for large values of σ, $Mat(\sigma)$ should be a decreasing function of σ. Thus, $Mat(\sigma)$ is assumed to have the convex form illustrated in Fig. 1.

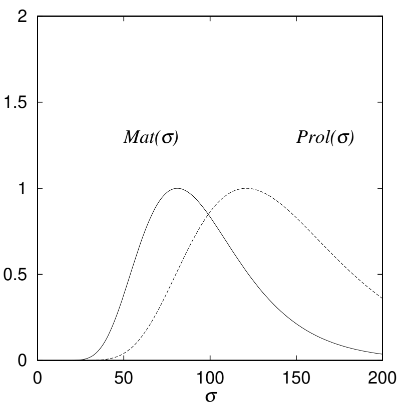


Fig. 1. $Mat(\sigma)$ and $Prol(\sigma)$ used in the original model.

Then, a differential equation describing the change in time of the concentration f_i of the ith antibody can be written

$$\frac{df_i}{dt} = -K_1\sigma_i f_i - K_2 f_i + K_3 Mat\,(\sigma_i)\, b_i, \tag{1·2}$$

where K_1 is the rate of the neutralization by other antibodies, K_2 is the rate of the death of the ith antibody, and K_3 is the rate of the creation of the antibodies by B-cells. Correspondingly, B-cells carrying the ith idiotype on their surfaces decay at a given rate and proliferate when they mature. The probability of the proliferation of B-cells is represented by the function $Prol(\sigma)$. When B-cells mature, they begin to proliferate. Again, $Prol(\sigma)$ is assumed to be an increasing function of σ when σ is small. When the neutralization of antigens is completed, the proliferation of B-cells is suppressed by T-cells. Therefore, we assume that $Prol(\sigma)$ is a decreasing function of σ when σ is large. Thus, $Prol(\sigma)$ also has a convex shape. Further, it seems that the proliferation of B-cells ends after their maturation ends. Thus, it is a reasonable assumption that $Prol(\sigma)$ is shifted to the right with respect to $Mat(\sigma)$(Fig. 1). Then, the evolution equation for the concentration b_i of the B-cells of the ith idiotype can be written as

$$\frac{db_i}{dt} = -K_4 b_i + K_5 Prol\,(\sigma_i)\, b_i + K_6, \tag{1·3}$$

where K_4 is the death rate of the B-cells and K_5 is their rate of production. Further, the term K_6 is added to take into account the cells that are added to the active network from the bone marrow.

Next, we describe the version of the Varela model introduced by H. Bersini and B. Calenbuhr, which we investigate and modify in this paper.

Bersini and Calenbuhr [15)] have investigated a dynamical system model of immune networks in the above described framework using the following functions of the maturation and the proliferation with a small number of degrees of freedom (Fig. 1). In their model, B-cells and antibodies of the same idiotype are considered to form a unit. Though the interaction between two units, this 2-unit system oscillates, and the phase of one unit is opposite to that of the other:

$$Mat\,(\sigma_i) = \exp\left[-\left\{\frac{\ln(\sigma_i/\mu_m)}{S_m}\right\}^2\right], \tag{1·4}$$

$$Prol\,(\sigma_i) = \exp\left[-\left\{\frac{\ln(\sigma_i/\mu_p)}{S_p}\right\}^2\right]. \tag{1·5}$$

For a 3-unit network, to begin with, they considered the connection between two units in an open chain fashion (Fig. 2(a)). Then, three units can be constrained with opposite phases. Next, they considered the closed network by connecting three units as shown in Fig. 2(b). The connectivity matrix they used is

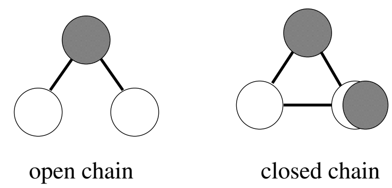


Fig. 2. Type of connection. Open and black circles have opposite phase. (a) A 3-unit open chain. (b) A 3-unit closed chain.

$$M = \begin{bmatrix} 0 & 1 & 1 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \end{bmatrix}. \tag{1·6}$$

Although each pair of units must independently comply with the imposed constraint that they oscillate with opposite phases, it is not possible for all units to satisfy this constraint. This phenomenon has been designated by the term "frustration", and it occurs in a network with a closed loop composed of an odd number of units. In general, frustration induces instability. As a result of this instability, although the time evolution of each unit resembles that in an open chain network, this motion does not continue more than several oscillations, and the network behaves in random way after this.

In the following section, first we summarize the characteristics of the behavior displayed by the original model of Bersini and Calenbuhr in more detail, and then we modify this model by adopting simpler functions of $Mat(\sigma)$ and $Prol(\sigma)$ to see the effects of the choice of these functions. In the modified model, we consider a threshold above which each antibody can recognize others. This is introduced in §3. In §4, we consider networks with more than 3 units and investigate the effect of additional degrees of freedom. The invasion of antigens is investigated in §5. Finally, §6 is devoted to summary and discussion.

§2. The basic model

In the original model of Bersini et al., there always exists the fixed point

$$(f_i, b_i) = (0, K_6/K_4) \quad \text{with } i = 1, \cdots, N, \tag{2·1}$$

and this point is stable. However, this solution has no meaning as a network, because there is no interaction between units.

First, to investigate the instability of the system, we calculated the Lyapunov characteristic exponents in a closed chain with $N = 3$ for the original model and obtained the following result for the Lyapunov spectrum:

$$(\lambda_1, \cdots, \lambda_6) = (+, 0, -, -, -, -).$$

In the calculation, we used the following parameter values: $K_1 = 0.0016$ [conc^{-1}day^{-1}]; $K_2 = 0.02$ [day^{-1}]; $K_3 = 2.0$ [day^{-1}]; $K_4 = 0.1$ [day^{-1}]; $K_5 = 0.2$ [day^{-1}]; $K_6 = 0.1$ [day^{-1}]; $\mu_m = 80$ [conc]; $S_m = 0.5$; $\mu_p = 120$ [conc]; $S_p = 0.5$.

Next, to see how chaos appears in this system, we changed the strength of connectivity, retaining the permutational symmetry. To be specific, we set the connectivity matrix as

$$M = S \times \begin{bmatrix} 0 & 1 & 1 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \end{bmatrix}. \tag{2·2}$$

Then, considering a range of values of S, we obtained the following results (see Fig. 3). When S is less than S_1 (~ 0.4), the trajectory converges to a fixed point. For $S_1 < S < S_2$ (~ 1.7) the system exhibits chaos, which is symmetric with respect to permutation of the units. For $S_2 < S < S_3$ (~ 4.7), a limit cycle appears, and this breaks this permutational symmetry. We call this limit cycle "type A". For $S_3 < S < S_4$ (~ 6.0) a limit cycle of completely broken symmetry appears. We call this limit cycle "type B". For $S > S_4$, another fixed point appears. The route to chaos at $S \sim S_2$ is considered to be characterized by intermittency through heteroclinic intersections.*) The sudden disappearance of chaos near $S \sim S_1$ seems to be crisis; that is, the basin of chaos intersects that of the stable fixed point.

In this model, the functions $Mat(\sigma)$ and $Prol(\sigma)$ are rather complicated. Thus, it is interesting to investigate whether the existence of these types of limit cycles and chaos is due to the special choice of these functions. In order to understand the effect of these functions, we modify the above model by choosing simpler functions $Mat(\sigma)$ and $Prol(\sigma)$. We next proceed with this study.

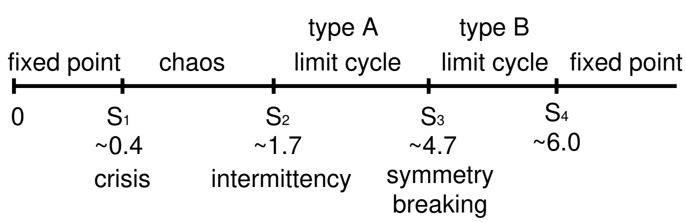


Fig. 3. Bifurcation diagram in the original model.

*) It has been reported that when some parameter is changed, this system exhibits intermittency.[17]

We change the functions of the maturation and the proliferation as follows:

$$Mat\,(\sigma_i) = U_1 \times [\tanh\{U_2 \times (\sigma_i - T_{lm})\} - \tanh\{U_3 \times (\sigma_i - T_{um})\}]\,, \tag{2·3}$$

$$Prol\,(\sigma_i) = U_4 \times [\tanh\{U_5 \times (\sigma_i - T_{lp})\} - \tanh\{U_6 \times (\sigma_i - T_{up})\}]\,. \tag{2·4}$$

Here, $U_1 \sim U_6$, T_{lm}, T_{um}, T_{lp} and T_{up} are constants. We set $U_1 = 0.975$, $U_2 = 0.035$, $U_3 = 0.022$, $U_4 = 0.878$, $U_5 = 0.030$, $U_6 = 0.022$, $T_{lm} = 60$, $T_{um} = 100$, $T_{lp} = 100$, $T_{up} = 150$. In Fig. 4 we plot the graphs of these functions. They are quite similar to those of the previous functions. As a connectivity matrix, we assume the same form as Eq. (2·2). When the above functions are adopted as $Mat(\sigma)$ and $Prol(\sigma)$ and S is set to 1, in the case of two units, the system converges to a fixed point, and in the case of a 3-unit closed chain, a strange attractor appears. This strange attractor possesses permutational symmetry. The Lyapunov spectrum for chaos is the same as that of original model. Thus, the chaos in this system has the same topological dimension as that in the original system.

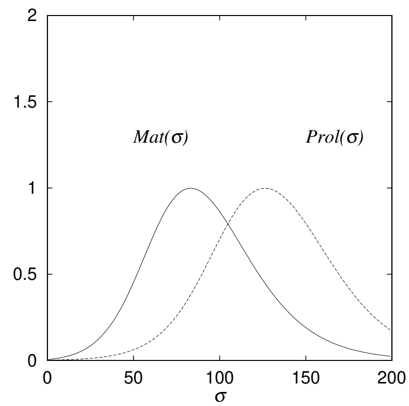


Fig. 4. $Mat(\sigma)$ and $Prol(\sigma)$ for the modified model.

To investigate the mechanism of the onset of chaos, we constructed the bifurcation diagram corresponding to the magnitude S of the connectivity matrix in the same manner as for the original model (see Fig. 5). For $0 < S < S_1$ (~ 0.25), only the fixed point is stable. For $S_1 < S < S_2$ (~ 0.25), a limit cycle appears and is stable. For the limit cycle state, two of the three units oscillate with opposite phase, and the other unit takes negligibly small values. We call this limit cycle "type C". For $S_2 < S < S_3$ (~ 1.5), chaos appears. For $S_3 < S < S_4$ (~ 4.0), there exists a type A limit cycle (see Fig. 6). At $S = S_4$, the symmetry is recovered, and a completely symmetric limit cycle appears. We call this limit cycle "type S". At

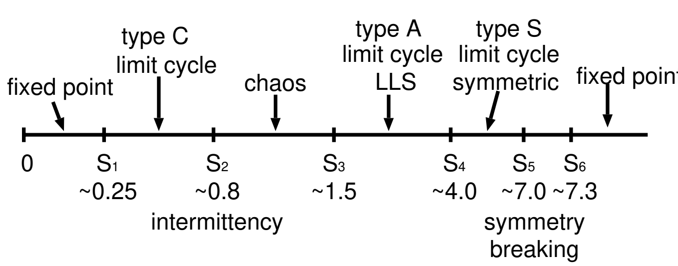
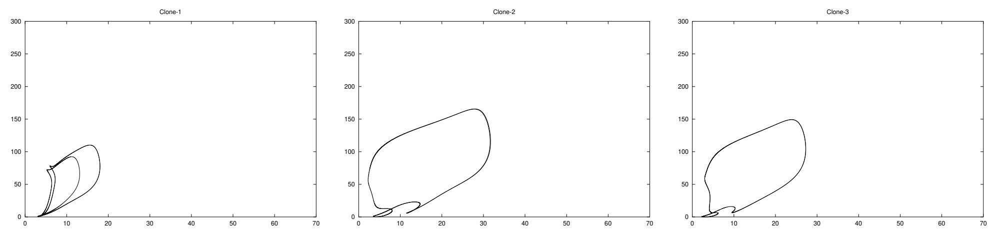
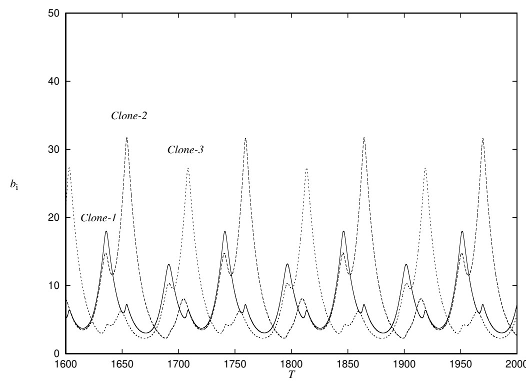


Fig. 5. Bifurcation diagram of the modified model.



(a)



(b)

Fig. 6. Periodic solution at $S = 1.57$. (a) Phase portraits. (b) Time series of b_i.

$S = S_5$ (~ 7.0), the symmetry is broken again, and another type of limit cycle appears. At $S = S_6$ (~ 7.3), through a Hopf bifurcation, another fixed point appears. Thus, in this model, we also obtain the type A limit cycle. To see the bifurcation phenomena in detail, we calculated the first Lyapunov characteristic exponent. We confirmed that in both transitions to chaos taking place at $S = S_2$ and $S = S_3$, the routes to chaos are intermittency through heteroclinic intersections, as in the original model.

Now, let us consider the characterisitics of the oscillation of the attractors in the original and modified models. As for the type A limit cycle, as is shown in Fig. 6(a), the phase portraits of two of the units are the same, but they oscillate in opposite phases. We call these units "long-pulse units". One unit has a smaller amplitude than the other two units. We call it the "short-pulse unit". Let us take note of the time series of antibodies (Fig. 6(b)). At almost all times, one of the long-pulse units has a large concentration, while the others have small concentrations. When the largest concentration of a long-pulse unit, say f_1, becomes small, the other two, f_2 and f_3, increase, taking similar values initially. Then, at some value of the concentrations, the concentration of the other long-pulse unit, say f_2, becomes large, and that of the short-pulse unit, f_3, becomes small. Next, when f_2 becomes small, f_1 and f_3 increase, taking similar values, and then f_1 becomes large and f_3 becomes small. Thus, it seems that the short-pulse unit, the unit 1, plays the role of 'switching' the activation of the long-pulse units. Therefore, there is a division of roles among clones. Further, as is shown in §5, the response to an antigen differs in each asymmetric type A limit cycle. Because of these results, we call this state a "differentiating state".

Another characteristic feature of this model is the "winner-take-all" mechanism. That is, only one clone dominates, not only in limit cycle states but also in chaotic states.

We checked that the systems are robust with respect to permutational symmetry breaking perturbations in two models.

From the results in this section, we conclude that almost all features of the modified model are similar to those in the original model.

§3. The modified model with threshold

In this section, we introduce a threshold above which antibodies can recognize antibodies and antigens. There are several reasons to take such a threshold into account. One is that it seems that there exists some threshold for the concentration of antibodies to recognize antigens. Another reason is that we would like to consider the situation in which the concentration of an antigen can become large without being recognized by antibodies for some reason. As such a situation, we can consider the case that the ability of detecting antigens in the immune system becomes weak. Further, as a technical reason, introducing thresholds makes it possible to define states clearly.

When a threshold is introduced, the system exhibits various types of interesting behavior.

Threshold

In a 3-unit closed chain system, we introduce a threshold above which the ith antibody can recognize other antibodies. For simplicity we use a common value f_0 as the thresholds for all antibodies as follows:

$$\begin{cases} m_{ij}(t) = 1 \text{ for any } j(\neq i) & \text{when } f_j(t) \geq f_0, \\ m_{ij}(t) = 0 \text{ for any } j(\neq i) & \text{when } f_j(t) < f_0. \end{cases}$$

That is,

$$m_{ij}(t) = m_{ij}\Theta(f_j(t) - f_0), \tag{3·1}$$

where $\Theta(x)$ is the Heaviside function (i.e., $\Theta(x) = 1$ for $x \geq 0$ and 0 for $x < 0$). Hereafter, m_{ij} on the right-hand side of Eq. (3·1) is fixed to the value in Eq. (1·6). We considered the values 0, 5, 10, $\cdots$ of the threshold f_0 and found the following behavior of the system (see Fig. 7).

$0 < f_0 < 5$	Chaos.
$f_0 \cong 5 \sim 15$	Type B limit cycle.
$f_0 \cong 20$	Type A limit cycle (with period two).
$f_0 = 25 \sim 40$	Chaos.
$f_0 = 45 \sim 50$	Type A limit cycle.
$f_0 > 50$	Fixed point.

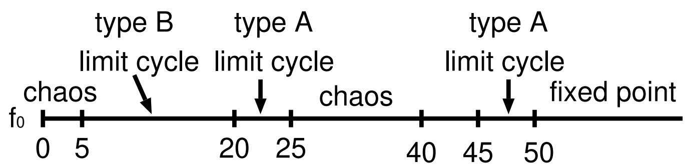


Fig. 7. Bifurcation diagram of the modified model with respect to the threshold f_0.

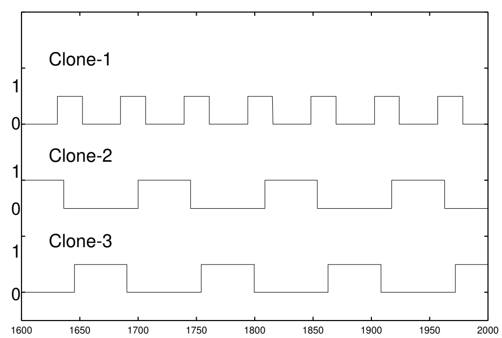


Fig. 8. On-off time series in a differentiating state.

For $f_0 = 5 - 20$ and $45 - 50$, the system is in a differentiating state. Here, two long-pulse units have longer durations above the threshold, and the short-pulse unit has a shorter duration.

For the time series analysis, we define the on-off time series as follows. Let us associate 0 or 1 with each unit, according to the value of f_i; that is, 0 for $f_i < f_0$ and 1 for $f_i \geq f_0$. We call the former the "off state" and the latter the "on state", and the sequence of values 0 and 1 as a function of time the "on-off time series". As shown in Fig. 8, at almost all times, there exists only one on state; that is, there is a "winner-take-all" mechanism. Further, the short-pulse unit plays the role of switching. These are the same phenomena as those observed in §2. Thus, these phenomena take place in all models we studied. These phenomena are believed to be due to the nature of the interaction. We discuss this in the final section.

In the limit cycle regions, if we use an initial state in which that all units are less than the threshold, the system converges to the fixed point. On the other hand, if at least one unit exceeds the threshold initially, then the system goes to the differentiating state.

We investigated the bifurcation structure in the case that the system is in the differentiating state for $f_0 = 50$. To see the bifurcation structure clearly, we introduce the strength of effective interaction, $\langle I_{ij} \rangle$. The quantity $\langle I_{ij} \rangle$ is defined by the following relation:

$$\langle I_{ij} \rangle = \lim_{T \to \infty} \frac{1}{T} \int_0^\infty dt I_{ij}(t), \tag{3·2}$$

$$I_{ij}(t) = m_{ij}(t) + m_{ji}(t). \tag{3·3}$$

For example, if $f_1(t) \geq f_0, f_2(t) \geq f_0$ and $f_3(t) < f_0$, then $m_{21}(t) = m_{31}(t) = 1, m_{12}(t) = m_{32}(t) = 1$ and $m_{13}(t) = m_{23}(t) = 0$. Thus, $I_{12}(t) = I_{21}(t) = 2, I_{13}(t) =$

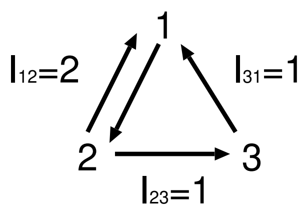


Fig. 9. Effective interactions.

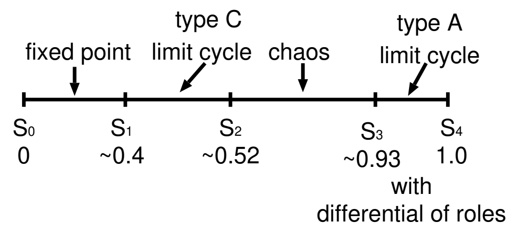


Fig. 10. Bifurcation diagram of the modified model with respect to the threshold.

$I_{31}(t) = 1$ and $I_{23}(t) = I_{32}(t) = 1$ (see Fig. 9). Here, we summarize the bifurcation structure for $0 < S < 1$ (see Fig. 10). We display the S dependence of $\langle I_{ij} \rangle$ in Fig. 11.

1. $0 < S \leq S_1$ (~ 0.4). Fixed point.
2. $S_1 \leq S \leq S_2$ (~ 0.52). Type C limit cycle.
   In this regime, for the usual time series, one unit takes negligibly small values, and the other two units oscillate with opposite phase. Then, the symmetry of this state is broken, and two units always exceed the threshold, while the other never exceeds the threshold. Reflecting this behavior, the values of $\langle I_{ij} \rangle$ are divided into two groups. In one group $\langle I_{ij} \rangle$ tends to 2, and in the other it tends to 1 as $S \to S_1$. Since here one unit does not affect other units, it is not appropriate to call this a differentiating state.

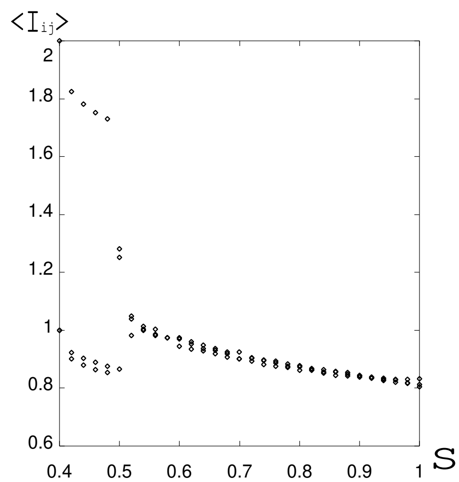


Fig. 11. S dependence of $\langle I_{ij} \rangle$.

3. $S_2 \leq S \leq S_3$ (~ 0.93). Chaos.
   Here, the permutational symmetry is recovered. All $\langle I_{ij} \rangle$ take almost the same values. The typical value is

$$I_{LL} \sim I_{LS} \sim 0.85.$$

4. $S_3 \leq S \leq 1$. Type A limit cycle (differentiating state).
   Here, there occurs differentiation, and there are two groups of $\langle I_{ij} \rangle$, the interaction between two long-pulse units, say I_{LL}, and the interaction between the long-pulse unit and the short-pulse unit, say I_{LS}. Typical values are

$$I_{LL} \sim 0.83, \; I_{LS} \sim 0.8.$$

From these observations, we note that $\langle I_{ij} \rangle$ can be used to distinguish solutions. In particular, in the chaotic state, all the $\langle I_{ij} \rangle$ have almost the same value.

The Lyapunov spectrum for chaos is the same as in the original and the modified models, and the routes to chaos at $S \sim 0.52$ and $S \sim 0.93$ are again characterized by intermittency through heteroclinic intersections.

§4. The effect of increasing the number of degrees of freedom

Here we investigate the behavior of the network when the number of units is increased for the modified model with threshold. We assume that there exist interactions between any two units and that the connectivity matrix is symmetric, i.e., $m_{ij} = m_{ji} = 1$ for all i and j $(i \neq j)$.

We investigated the cases $N = 3, 4, \cdots, 10$. In all cases there exists an asymmetric limit cycle in which all units oscillate, taking values both below and above the threshold. We call this limit cycle type A, as in the $N = 3$ case. It seems that the type A limit cycle appears more frequently in the case of an odd number of units, and chaos appears more frequently in the case of an even number of units in the parameter ranges which we investigated. Indeed, for $N = 3, 5, 7$ and 9 and when the threshold is the same for all units, differentiation takes place, and for $N = 4, 6, 8$ and 10, it does not, and chaos appears. In Figs. 12(a) and (b), we describe the effective interactions schematically. In these figures, a thick line denotes a large strength, a thin line represents a medium strength, and a dotted line represents a small strength. In the differentiating state, the number of the long-pulse units is larger by 1 than the number of short-pulse units. There are three values of the strength of the effective interaction in the system (see Fig. 12(b)). The strength of the effective interaction takes the largest value, I_{LL}, between two long-pulse units, the smallest value, I_{SS}, between two short-pulse units, and an intermediate value between the long-pulse unit and the short-pulse unit. When chaos occurs in the system, the strengths of the effective interactions are almost the same (see Fig. 12(a)).

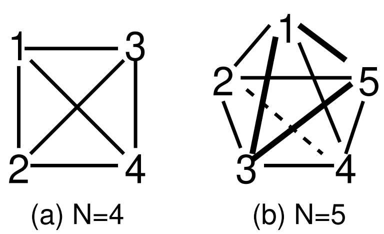


Fig. 12. Strength of effective interactions.

We show the on-off time series for $N = 3$ in Fig. 8 and for $N = 6$ in Fig. 13. For odd N, there are only two types of units, long-pulse units and short-pulse units. On the other hand, for even N, for any unit, the duration of the on state varies in time. To clarify this, we construct the histogram for the duration (see Figs. 14 and 15). In the case of an odd number of units, we note that the duration T_L for the long pulse unit is nearly twice that T_S, for the short-pulse unit. On the other hand, in the case of an even member of units, although there are various durations, we can find two peaks of the long duration and the short duration. That is, in the chaotic state, the role of each unit changes dynamically.

In conclusion, both the chaotic states and differentiating states appear when N becomes large.

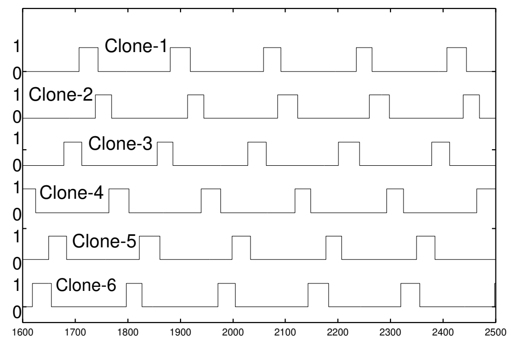


Fig. 13. On-off time series ($N = 6$).

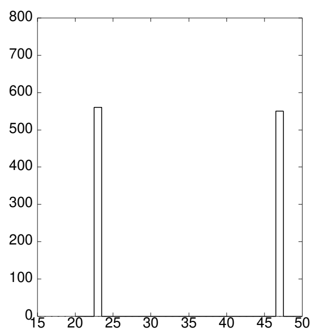


Fig. 14. Histogram of duration ($N = 5$).

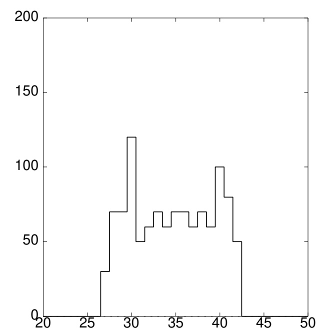


Fig. 15. Histogram of duration ($N = 6$).

§5. The invasion of an antigen

In this section, we consider the response of the system to the invasion of antigens in the modified model with threshold.

<u>Case 1</u>

Here, we consider the differentiating state in the 3-unit closed network. Suppose that external antigens similar to antibodies f_1 invade the system. Let us denote the concentration of the antigen by a_1 and that of the corresponding antibodies by f_1. Then, antibodies f_2 and f_3 recognize the antigens, because a_1 resembles f_1. However, in general the antibodies f_1 cannot recognize the antigens. Further, we assume that the antigen does not proliferate by itself.*) Thus, the differential equation for the antigen is given by

$$\frac{da_1}{dt} = -K_1 \sigma_a(t) a_1 + K_7, \qquad (5\cdot1)$$

where $\sigma_a(t) = m_{12}(t) f_2(t) + m_{13}(t) f_3(t)$. Here, we assume that the antigens enter

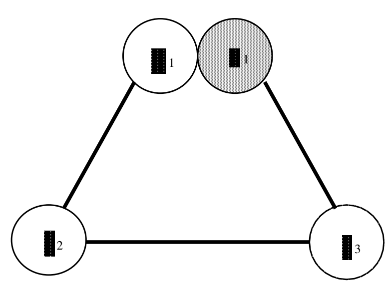


Fig. 16. Schematic figure of the interaction between antibodies and an antigen in case 1.

*) This restricts the type of antigens. For example, pollen is one candidate.

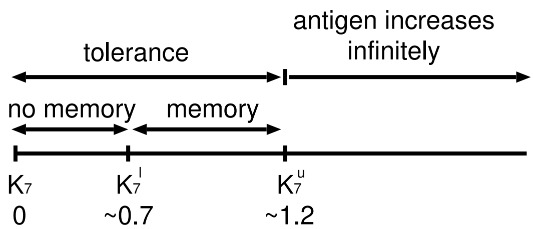


Fig. 17. Summary of the behavior of the system.

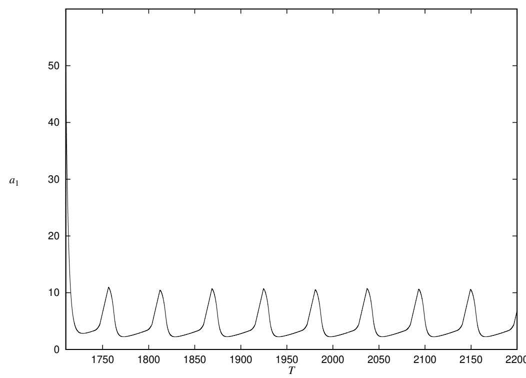


Fig. 18. Time series of antigen a_1.

the system at a rate K_7 per unit time. On the other hand, since antibodies f_2 and f_3 interact with the antigens, σ_2 and σ_3 become $\sigma_2 = m_{21}(f_1 + a_1)\Theta(f_1 + a_1 - f_0) + m_{23}(t)f_3$ and $\sigma_3 = m_{31}(f_1 + a_1)\Theta(f_1 + a_1 - f_0) + m_{32}(t)f_2$. Then, using these σ_i, the equations for antibodies and B-cells become the same as the previous ones. In the following, we set $f_0 = 50$.

Now, let us see what happens in this system. The behavior of the system depends on the rate of increase of the antigen K_7. Here, we summarize the behavior of the system (see Fig. 17). If K_7 is sufficiently large, say $K_7 > K_7^u$ (~ 1.2), the concentration of the antigen a_1 increases infinitely, and the system is completely invaded and destroyed by the antigen.*) If K_7 is less than some value, say $K_7 < K_7^l$ (~ 0.7), the system copes with the antigens completely. The number of antigens finally becomes small, and the system comes to exist near one of the differentiating states. Which such state the system chooses is determined by the initial conditions. Thus, in this case there is no memory of the invasion by antigens.

If we set K_7 between K_7^l and K_7^u (e.g., $K_7 = 0.7$), a_1 does not increase infinitely, but oscillates in some range of concentration when the initial value of a_1 is less than 288.**) The time series of a_1 is given in Fig. 18. In this case, in the resultant state the duration of the on state for f_2 and f_3 are longer, i.e., the units 2 and 3 are long-pulse units, no matter what state the system is in before the invasion by antigens.

*) In this case the system tends to a fixed point.

**) When the initial value of a_1 is greater than 288, the system tends to a fixed point, and the network collapses.

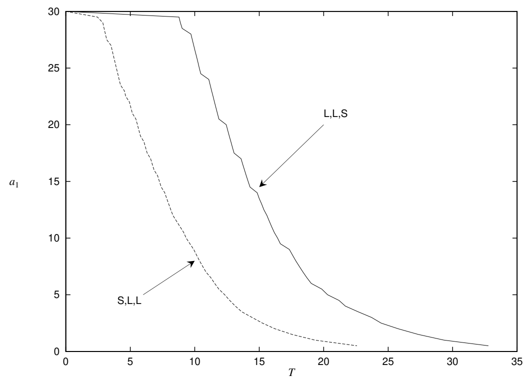


Fig. 19. Relaxation times in differentiating states.

Now, let us study the response times of the differentiating state when $K_7 = 0$. To do this, starting from $a_1 = 30$ in each state, we calculated the relaxation time in which the concentration of the antigen becomes negligibly small (see Fig. 19). Here, we use the abbreviations LLS and SLL. (For example, LLS means that the first and the second units are the long-pulse units and the third unit is the short-pulse unit.) The LLS and SLL states remain even when the antigens almost disappear. From Fig. 19, we note that the response time is shorter in the state in which the units 2 and 3 are the long-pulse units. Since in the resultant attractor, the units 2 and 3 are the long-pulse units, this result on the relaxation time implies that when $K_7^l < K_7 < K_7^u$, the system modifies itself so as to neutralize the antigen as effectively as possible. Thus, it seems that the resultant state can respond much better than other states. Therefore, we obtain the characteristic feature that the resultant attractor represents a kind of short term memory of the invasion by the antigen.*)

Another characteristic feature is seen for $K_7 < K_7^u$. Although the system is modified by the invasion by the antigen, the overall nature of the network is maintained. This phenomenon represents a type of tolerance.

Case 2

Next, we consider the case that an antigen A_1 interacts only with the antibody f_1 in the 3-unit closed network (Fig. 20). In this case, to obtain differentiating states, we must set the thresholds and affinity between the antigen and the antibody to values different from those between antibodies. Here, we introduce new thresholds, $g_{1,0}$ and $g_{A,0}$. $g_{1,0}$ is the threshold above which the antibody f_1 recognizes the antigen, and $g_{A,0}$ is the threshold above which the antigen A_1 recognizes the antibody f_1. Then the equation for the antigen A_1 is

$$\frac{dA_1}{dt} = -K_1\sigma_A(t)A_1 + K_7,$$
$$\sigma_A(t) = \Theta(f_1 - g_{1,0})f_1. \tag{5·2}$$

The first term in this equation expresses the decrease of the antigen due to

*) We use the term 'memory' to express the change in the positive direction of the system under an invasion by antigens. It should not be confused with the creation of memory B-cells.

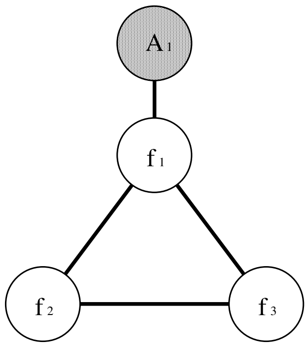


Fig. 20. Schematic figure of the interaction between the antibodies and antigen in case 2.

neutralization by the antibody 1, and the second term represents the continuous invasion of the antigen.

The sensitivity σ_i of the ith unit is modified as

$$\sigma_i = \sum_{j=1}^{n} m_{ij}\Theta(f_j - f_0)f_j + l_i A_1 \Theta(A_1 - g_{A,0}), \qquad (5\cdot3)$$

where l_i is the strength of the interaction between f_i and A_1. We set $l_i = s_A\delta_{i,1}$, where $\delta_{i,1}$ is the Kronecker delta. The behavior of this network depends strongly on the thresholds, the value of connectivity s_A, the initial value of the antigen A_1, and the rate of invasion of the antigen K_7. If these values are taken appropriately, the concentration of the antigen oscillates in some range. When we set $f_0 = 50$, $g_{A,0} = g_{1,0} = 10$ and $s_A = 0.3$, for $K_7 = 0.1 - 0.2$, the system comes to exist near one of differentiating states (see Fig. 21).

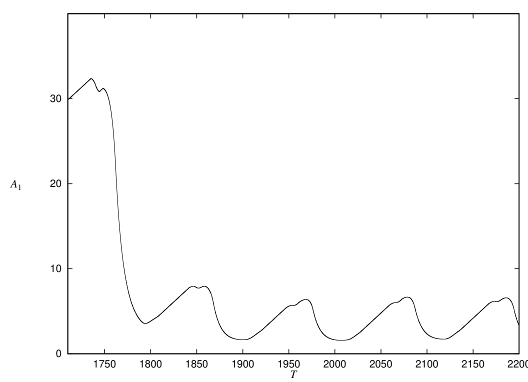


Fig. 21. Time series of antigen A_1.

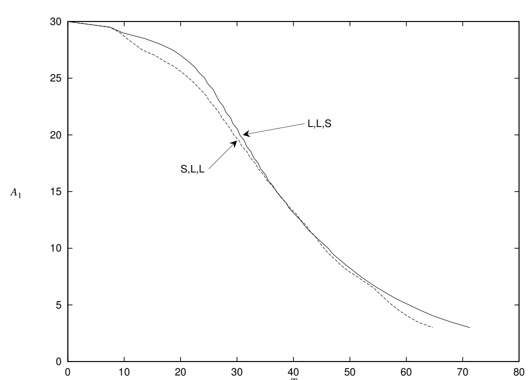


Fig. 22. Relaxation times in differentiating states.

As in case 1, the unit 1 which can interact with the antigen is activated and finally comes to exist near to the long-pulse state, no matter which states the system exists in before the invasion by antigens. It is expected that in the LLS state the relaxation time is shorter than that in the SLL state. However, it turns out that the two states have comparable relaxation times, as shown in Fig. 22. We believe that the reason for this is as follows. In contrast to case 1, in this case the SLL state does not always persist, but rather it may change to the LLS state, depending on the timing of the invasion. The transition to the LLS state takes place very quickly. Then, the relaxation progresses, while the system remains in the LLS state for almost all times. Since the average over the injection timing is taken in the calculation of the relaxation time, as a result, the relaxation times in the two states become comparable. We note that the absolute values of relaxation times in case 2 are longer than those in case 1. From this result, it hypothesized that the relaxation time decreases as the number of units that can interact with antigens increases.

Case 3

Now, let us consider a network with 4 units. We assume that the antigen (a_1) has a three-dimensional structure that is similar to that of the antibody 1, and thus that it can interact with the units 2, 3 and 4, but not with the unit 1 (see Fig. 23).

The differential equation for the antigen is

$$\frac{da_1}{dt} = -K_1\sigma_a(t)a_1 + K_7, \quad (5\cdot4)$$

$$\sigma_a(t) = (m_{12}(t)f_2 + m_{13}(t)f_3 + m_{14}(t)f_4). \quad (5\cdot5)$$

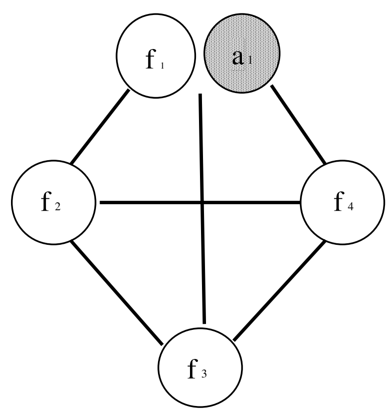


Fig. 23. Schematic figure of interaction between antibodies and the antigen in case 3.

For the unit i, the differential equations are

$$\frac{df_i}{dt} = -K_1\sigma_i(t)f_i - K_2 f_i + K_3 Mat(\sigma_i(t))b_i, \quad (5\cdot6)$$

$$\frac{db_i}{dt} = -K_4 b_i + K_5 Prol(\sigma_i(t))b_i + K_6, \quad (5\cdot7)$$

$$\sigma_1(t) = \sum_{j\neq 1} m_{1j}(t)f_j, \quad (5\cdot8)$$

$$\sigma_i(t) = m_{i1}(f_1 + a_1)\Theta(f_1 + a_1 - f_{i,0}) + \sum_{j\neq 1} m_{1j}(t)f_j, \quad i \neq 1. \quad (5\cdot9)$$

Here, $f_{i,0}$ ($i = 1 - 4$) represents a new threshold. That is, $f_{i,0}$ is the threshold above which the ith antibody recognizes other antibodies. When the system possesses permutational symmetry, a chaotic state appears. If we break the symmetry of the system by lowering the threshold of one of the four units, there appears a type A

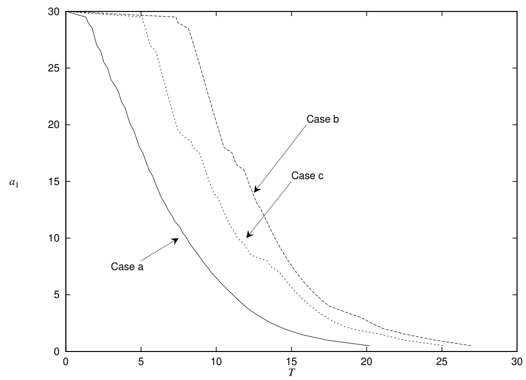


Fig. 24. Relaxation times in differentiating states and in chaos.

limit cycle in which the unit with the lower threshold value stays in the short-pulse state and the other units stay in the long-pulse states.

From the result of case 1, it is expected that the relaxation time of the system is short when the unit that resembles the antigen is in the short-pulse state. Further, from the result of case 2, it is expected that the relaxation time decreases as the number of units that interact with the antigens increases. Thus, here we investigate the relaxation time for the following three cases:

Case a. Unit 1 is in the short-pulse state. ($f_{1,0} = 35$, $f_{i,0} = 50$ for $i \neq 1$)

Case b. Unit 1 is in the long-pulse state. ($f_{2,0} = 35$, $f_{i,0} = 50$ for $i \neq 2$)

Case c. The system is chaotic. ($f_{i,0} = 50$ for any i)

We give the result in Fig. 24. The relaxation time τ_a for case a is shortest, and that τ_b for case b is longest. τ_c for case c is between τ_a and τ_b. This result suggests that a chaotic state is more effective than the differentiating states to prepare for various types of antigens.

§6. Summary and discussion

In this paper, we have studied three models of the immune network for a small number of degrees of freedom N, up to 10, the original model introduced by Bersini et al., the modified model with functions of the maturation and the proliferation of B-cells that differ from those of the original model, and the modified model, with a threshold above which antibodies can recognize other antibodies and antigens. First, we summarize characteristics common to these models.

In these models there exist fixed points, limit cycle states and chaotic states. We checked that the system is stable with respect to symmetry breaking perturbations. We investigated bifurcation structures by changing several parameters and found that the transitions to chaos are characterized by intermittency through heteroclinic intersections.

There is a peculiar type of limit cycle. In this limit cycle, the permutational symmetry of the system is broken, and the concentrations of antibodies and B-cells oscillate in a characteristic manner. There is a "winner-take-all" mechanism. Here, one unit plays the role of "switching" the other units. Because of this division of roles, we call this state a "differentiating state". On the other hand, in the chaotic state, no such explicit division of roles exists. Instead, the role of each unit changes dynamically. That is, in a chaotic state, a dynamical change of roles takes place.

Next, we summarize the results obtained in the modified model with threshold.

We investigated the cases $N = 3, 4, \cdots, 10$ and the effect of changing the number of degrees of freedom. We found that limit cycles tend to appear in the case of odd N, and chaos appears in the case of even N.

We studied invasion by antigens when the differentiation takes place in the following three cases: case 1, in which $N = 3$ and two units interact with antigens, case 2, in which $N = 3$ and only one unit interacts with antigens, and case 3, in which $N = 4$ and three units interact with antigens. We found that in each case, when the number of antigens is not too large and antigens and antibodies interact for a sufficiently long period, before the concentration of antigens is reduced to a small value, the unit which can interact with antigens comes to exist near the long-pulse unit for some range of parameter values. By investigating the relaxation time, we found that it depends on which differentiating or chaotic state the system exists in. In case 1, the relaxation time is short or long when the unit which interacts with antigens is the long-pulse unit or short-pulse unit, respectively. On the other hand, in case 2, the relaxation time takes similar values when the unit which interacts with antigens is the long-pulse unit and the short-pulse unit. From these results, we conclude that if multiple units can interact with antigens, as a result of the invasion of antigens the system will move to the state in which the response to antigens is most efficient. Then, the differentiating state is considered to be a kind of short term memory of the invasion by antigens.

In a system of 4 units, we observed an interesting feature in response to the invasion by antigens, the positive aspect of chaos. In the response to the antigen invasion, we found that the relaxation time in a chaotic state takes an intermediate value between the large and the small relaxation times in the two different differentiating states. This suggests a positive aspect of chaos in immune networks. That is, there is the possibility that chaotic dynamics may allow the system to cope with the invasion by any kind of antigens equally well. Since a chaotic state is symmetric and differentiating states are asymmetric, this feature may be attributable to the symmetry of the chaotic state.

Now, let us discuss the cause of the appearance of the differentiating state. This is related to the mechanism of the switching of long-pulse units, or the dynamical role change. Let us consider the 3-unit closed chain (see Fig. 6(b)). In the present interaction, any two units tend to oscillate in opposite phases. If the concentration of the antibody in one unit, say f_1, increases, then the sensitivities of the other two units become large. As a result, the second terms of the differential equations for f_2 and f_3 become large, and f_2 and f_3 decrease. This is a kind of 'winner-take-all' mechanism. Then, the sensitivity σ_1 becomes small. Thus, when f_1 becomes large, the third term in the differential equation for f_1 becomes small compared to the other two terms. Then, f_1 begins decreasing. This causes a decrease of σ_2 and σ_3 and an increase of f_2 and f_3. Since f_2 and f_3 begin to increase from small values, they take similar values. However, when these become rather large, the corresponding units are forced to stay in states with opposite phases. Thus, one increases further and the other decreases. At this stage, for the differentiating state, the increasing unit is the long-pulse unit, but in a chaotic state, it is not so fixed, and a dynamical switching of roles takes place. Therefore, the behavior of the switching is due to the 'winner-take-all' mechanism and the 'anti-ferromagnetic'-type interaction between any two units.

The phenomenon of differentiation has been studied by Kaneko et al. using meta dynamics in systems of a large number of degrees of freedom.[19] However, in this paper we consider only a small number of degrees of freedom without meta-dynamics, but nonetheless, differentiating states are obtained. These states are peculiar asymmetric limit cycles and related to short term memory. Not only there is a division of roles of clones in each differentiating state, but also responses to antigens differ in different differentiating states. Thus, these phenomena represent differentiation in its simplest form.

As for the dynamical change of roles, since chaos occurs through the heteroclinic intersection between stable and unstable manifolds of differentiating states, this phenomenon has some similarities with chaotic itineracy. Chaotic itineracy has been observed experimentally in the brain[20] and theoretically in large systems, with regard to which biological implications have been discussed.[21] In our case, the significance of chaos is that since the system wanders among several differentiating states in the chaotic state, it can cope with the invasion by any kind of antigens. Determining whether this phenomenon is observed in a system with a large number of degrees of freedom and its relation to chaotic itineracy are very interesting problems. These are important future problems.

Now, let us discuss the behavior in the case that the number of units N is increased. First, we note that in all models studied here, both limit cycles and chaos appear for the same value $N = 3$. Thus, although there is a tendency for limit cycles to appear for odd N and chaos to appear for even N, we cannot come to a definite conclusion from these results. Bersini et al. also studied the effect of changing the number of degrees of freedom in the original model. The network topology they studied is a closed chain composed of N clones. They treated a system with N up to 19 and found chaos for odd N and limit cycles for even N. Similar to ours, their result is not definite, but they found both limit cycles and chaos for $N = 19$. Therefore, in both models, the limit cycles and chaos coexist in some parameter ranges. These two models have different network topologies and different thresholds (finite or 0) for detection of antigens. Thus, further study of the effect of the number of degrees of freedom should be carried out for each model separately. This study is beyond the scope of this paper and is left as a future problem.

De Boer et al. studied the effect of interaction in Ref. 10). They analyzed the model for the cross-linking of bivalent receptors due to a bivalent antigen, and derived a log bell-shaped function that depends on a binding field and a cross-linking field. They found localized immune responses in the two-field models. This behavior is in contrast to the percolation observed in single-field models, which is the phenomenon that immune responses spread over the whole system. Thus, the dynamical behavior of networks seems to depend on the choice of the interaction functions. In this paper, our main purpose is to investigate the possible states organized in the network and the direction of the change in the network system when antigens invade it. Thus, to begin with, it is better to adopt the simplest interaction functions, rather than to adopt complicated ones, such as the two-field functions derived by De Boer et al. In the model introduced by Varela, interaction functions Mat and $Prol$ are introduced phenomenologically by taking into account the roles of T-cells. Their model is a single-field one, and Mat and $Prol$ are required only to have convex profiles. Therefore, the choice of these functions is rather arbitrary. Thus, this model is appropriate for our purpose, and we simplified these functions.

Now, let us discuss short term memory and tolerance. In Ref. 13), Stewart and Varela investigated the model of Varela with Mat and $Prol$ that differ from the functions used here. In their model, $N = 26$, and the matrix of affinities was determined with experimental data. They studied the effect of coupling with an antigen in the situation that the antigen interacts with only one clone. They found 'dynamical memory', which is the phenomenon that the sensitivity to the antigen persists for some time after the antigen is removed. In our model, we observed a type of memory that differs from the dynamical memory. This is a kind of short term memory. That is, the system changes to the state in which the immune response is most efficient. In Ref. 13) Stewart and Varela found another significant feature of immune systems, tolerance, in which the activity of the clone that can interact with the antigen is suppressed. In Refs. 17) and 18), Calenbuhr et al. investigated a natural torelance in the original model by Varela. In these papers, tolerance is defined as the phenomenon that the system does not explode in the presence of a constant concentration of an antigen. In the latter paper, they investigated tolerance by changing the number of clones N and the range of interaction C. Although in a closed chain of $N = 3$, chaos changes to a limit cycle, and the system exhibits tolerance, for general N and general C the system does not always exhibit tolerance.

In these models, one kind of antigen interacts with only one clone, and the concentration of the antigen is kept constant. The assumption that the concentration of antigens is constant is rather artificial, because in immune network models, antibodies are considered to be internal images of antigens in the network, and thus the dynamics of both of antibodies and antigens should be taken into account. In our model, we considered the dynamics of an antigen, and we investigated three different cases of interactions in which the number of clones that interact with an antigen is 1, 2 and 3. In some range of parameter values, the system neither explodes nor tends to a fixed point, and the concentration of the antigens oscillates in some range. We call this state "tolerant". Although the definitions of tolerance in the above mentioned studies differ slightly, it is clear that there exists tolerant behavior in dynamical system models of immune networks.

Our calculations in this paper are restricted to systems with a small number of degrees of freedom. In order to see whether the results obtained here are generic, it is necessary to investigate larger systems. Further, from the perspective of real immune networks, the existence of memory states and tolerance, and the response to the invasion by antigens, and in particular the positive aspect of chaos, in a system with a large number of degrees of freedom are very interesting problems. These will be studied in the future.

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