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Evolution of Specificity in an Immune Network

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A dynamic antigen response of the immune network is discussed, based on shape-space modelling. The present model extends the shape-space modelling by introducing the evolution of specificity of idiotypes. When the amount of external antigen increases, a measure of stability of the immune network is lost and thus the network can respond to the antigen. It is shown that specific and non-specific responses emerge as a function of antigen amounts. A specific response is observed with a fixed-point attractor, and a non-specific response is observed with a chaotic attractor for the lymphocyte population dynamics. The network topology also changes between fixed-point and chaotic attractors. For some antigen amounts, chaotic attractors will vanish or become long-lived super-transient states. A dynamic bell-shaped response function will thus emerge. The relevance of long-lived chaotic transient states embedded in fixed-point attractors is discussed with respect to immune functions.

1. Introduction

Complementarity between molecular shapes is a basic and commonly used mechanism of communication in many biochemical systems. In the case of immune systems, it is used for self-/non-self-discrimination. Non-self-antigens are first detected by complementary shape matching (binding affinity) between the antibody surface ligands and lymphocyte receptors. The degree of complementarity or "specificity" is not fixed in time and/or in specific types of lymphocyte clones. It should be dynamically determined. For example, Wedemayer *et al.* (1997) showed that the structure of the antigen-binding site of germline antibodies can change slightly, according to the reaction opponent. The mechanism of flexible specificity relates to how some kinds of chemical bonds are formed within the antigen-binding site.

In immune systems, no single antibody type determines self-/non-self-discrimination. It is, rather, a manifestation of the immune system as a whole (Varela *et al.*, 1988). Therefore, it is reasonable to assume that immune responses are controlled globally by a network. To sustain such global control, specific components of the immune network, namely different lymphocytes, must be functionally coupled in certain ways. One possibility for such a coupling was first proposed by Jerne (1974), who suggested that lymphocytes form a so-called "idiotype network" (see also Bona & Kohler 1983). Each lymphocyte has its own molecular shape, called its idiotype, which is recognized by idiotypes of other lymphocytes by complementarity between their respective shapes.

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Many theoretical models based on the idiotype network hypothesis have been proposed to explain immune functions such as immune memory, self-/non-self-discrimination, and adaptability to the antigen environment (Hoffman, 1975; Ikegami, 1989; Rössler & Lutz, 1979; DeBoer *et al*., 1993; Farmer *et al*., 1986). Consequently, some conceptual advances have been made in theoretical immune modelling. The first and most basic concept is termed "shape-space modelling" (Segel & Perelson, 1988; Perelson & Oster, 1979; DeBoer & Perelson, 1991). In this method, the shape space simulates a particular aspect of the population dynamics of clones. Thus, each point on the space refers to a different idiotype of the clones. The degree of complementarity between two idiotypes is modelled either by bit pattern matching (Farmer *et al*., 1986), or by function overlapping over a continuous/discrete shape space (Perelson & Oster, 1979).

The next conceptual advance in modelling involves embedding plasticity in an immune network (Bagley *et al*., 1989). This process governs both the removal of certain idiotypes from the active population and the recruitment of new idiotypes into the network (Varela *et al*., 1988; DeBoer & Perelson, 1991). This process enables the immune system to decide which new idiotypic variables should be included in the network, and which should be removed from the network without referring to an explicit fitness function. Consequently, the network is flexible and is able to change its structure. Researchers generally agree that this structural flexibility of a network is sufficient to establish natural tolerance and immune memory. However, studies of the meta-dynamics of shape space prove that this type of flexibility is not enough to sustain immune functions. As a remedy, we introduce a new type of flexibility: the flexible recognition ability of the antibody. Our model is based on shape-space modelling, and employs meta-dynamics with respect to the degree of recognition of the shape pattern.

Previous studies of theoretical models have concentrated mainly on (i) the localization of the external stimulus; (ii) the structural changes of the idiotype network, and (iii) the relevant dynamical attractors. We also focus on these issues. Our basic assumption is that idiotypes do not recognize other idiotypes with equal precision. We here include the ambiguity of affinity binding as a new degree of freedom, in addition to those of shape space. Kearney *et al*. (1987) have confirmed experimentally the existence of ambiguity of recognition in the antibody-binding site of early B cells. The basic concepts of ambiguity of the affinity bindings originated in the Weinand & Conrad "generalists-specialists model" (1991). It is generally believed that the progression of lymphocyte cells from being generalists to specialists against antigens is caused by somatic hyper-mutation (Wedemayer *et al*., 1997). However, how such a hyper-mutation functions is still unclear, both experimentally and theoretically. Without considering idiotypic interactions, some theoretical models have argued that a certain amount of hyper-mutation is necessary to produce sufficient antigen-specific antibodies. Kepler and Perelson have shown that the optimum mutation schedule to produce antigen-specific antibody is one characterized by brief bursts of high mutation rates, interspersed between periods of mutation-free growth (Kepler & Perelson, 1993). Celada & Seiden (1996) have shown that, if the repertoire of B cell specificities is large, hyper-mutation in itself is not necessary for antibody specificity to increase, though it is essential when B cell diversity is limited.

On the other hand, several characteristics of idiotypic network models have been examined in idiotype sets based on a fixed specificity level with no mutation among specificity levels. For example, in the bit-matching model, an affinity threshold around 6-bits in length is selected for the 32-bit shape space, in accordance with experimental data (DeBoer *et al*., 1993). In a function overlapping model with a Gaussian falling-off function, the standard deviation is selected to be $\sigma = 10\%$ (DeBoer *et al*., 1992). In either case, the expected clone size and the connectivity of the network become a function of this matching threshold (DeBoer & Perelson, 1991; De Boer *et al*., 1992, 1993).

Practical idiotypes have a three-dimensional complicated folding pattern. Even a slight difference in molecular pattern can affect its recognition ability (Kobayashi *et al*., 1997). This instability in recognition, however, is important in adaptability (Tada, 1993). The degree of

specificity can be dynamically determined and can evolve, as in the case of reinforcing synaptic activity in central nervous systems (Frauenfelder & Wolynes, 1994). We therefore introduce meta-dynamics to control the degree of specificity in the shape space.

By adding dynamics to the standard idiotypic network model we show that specific response to the antigen is governed dynamically by the transients and attractors of an immune network. A specific response is observed with a fixed-point attractor and a non-specific response is observed with a chaotic state for the lymphocyte population dynamics. Network topology also changes between fixed-point and chaotic states. The chaotic state was found to be a long-lived super-transient state. The relevance of such states is discussed with respect to immune functions.

2. Modelling with a Shape Space

Antibodies are characterized by pairing between idiotope and paratope patterns. Those patterns are often called "shapes", and their space is called a "shape space". In standard idiotypic network modelling, the interactions between idiotypes can be either symmetric or asymmetric. If an antibody is only recognized by the idiotype of the other antibody, we call the model asymmetric. On the other hand, if both idiotope and paratope patterns can be recognized by the other antibodies, we call the model symmetric. No physiological data can select between the two assumptions of symmetry or asymmetry. For example, Fons *et al.* (1986) showed experimentally that inter-strain "recurrent idiotopes" on the first antibody (Ab1) induce second antibodies (Ab2) in the immune response to rabies virus. At the same time, they found that, in the case of polio virus infection, Ab2 has the internal image of the polio virus antigen. Thus, Ab2 is induced not by the idiotope, but by the paratope of the Ab1. Of course, this single experiment is insufficient to validate an symmetric model, but it is also true that we have no strict criterion on which to base this. However, from a theoretical point of view, the asymmetric model provides a wider class of behaviour, which includes the symmetric situation as a special case. In the following, we thus assume an asymmetric model for the idiotype network.

In an asymmetric idiotypic network model, a pair of surface sites characterizes each idiotype. One is called the idiotope and the other is the paratope. If the idiotope site of a lymph cell is bounded by the paratope of the other lymph cells, the recognized lymph cells become inactivated. By contrast, the recognizing cells become activated to increase their respective clone size. Thus, the growth dynamics of the clone size of an idiotype of paratope k and idiotope j is given as

$$x_{k,j}^{n+1} = x_{k,j}^{n} + x_{k,j}^{n} \sum_{p} \sum_{q} (b_{k,q} - \alpha b_{p,j}) x_{p,q}^{n} - d x_{k,j}^{n} + s, \tag{1}$$

where $x_{k,j}^{n}$ represents the clone size of the idiotype (k, j) at the n-th generation. The second term describes the fact that the clone proliferation of idiotype (k, j) occurs by recognizing the other idiotypes (p, q). The third term describes the notion that the clone removal of idiotype (k, j) occurs following recognition by idiotypes (p, q). The fourth and the fifth terms correspond to the death and birth processes, respectively. The idiotope–paratope interaction is assumed to have the following form:

$$b_{i,j} = \frac{1}{\sigma} \mathrm{e}^{-|i-j|/\sigma}. \tag{2}$$

Thus, the interaction becomes more specific if the value of the mean deviation σ is small. In addition to the above equation, we further consider the meta-dynamics of specificity. The equation describes the evolution of specificity. We first quantize σ by the power of 2 as the simplest case.

$$\sigma_m = 2^{M-m}, \tag{3}$$

where the values m correspond to positive integers less than M. Each idiotype recognizes other idiotypes more precisely if it has a larger value of m, while if it has a smaller value of m, the idiotype recognition is less precise. The evolution of specificity of the antibody is also demonstrated experimentally. It is caused by a high level of somatic mutations that occur when antibodies

are secreted from B cells (French *et al.*, 1989; Wedemayer *et al.*, 1997).

Due to the multiple M levels of specificity, each idiotype is now characterized by three variables: paratope k, idiotope j, and the specificity m,

$$x^{n+1}_{k,j,m} = (1-\mu')x^n_{k,j,m} + \mu'/2 \sum_{m'=m-1,m+1} x^n_{k,j,m'} + s_m\delta_{0,m}, \quad (4)$$

where μ' is a mutation rate for the specificity.

The source term s_m depends on the specificity level m. Because it is also believed experimentally that the immature B cell has a lower specific antigen-binding site, and only clones with the lowest specificity level can arise spontaneously.

By combining these equations, we establish the complete clone growth dynamics with mutations among idiotypes, and the evolution of specificity thus:

$$x^{n+1}_{k,j,m} = (1-\mu')x^n_{k,j,m} + \mu'/2 \sum_{m'=m-1,+1} x^n_{k,j,m'} + x^{n+1}_{k,j,m} \sum_{p,q,r} (b_{k,q,r} - \alpha b_{p,j,r})x^n_{p,q,r} - dx^n_{k,j,m} + s_m\delta_{0,m}. \quad (5)$$

The shape space assumed here has a periodic boundary. There are five different types of idiotopes and paratopes, so that there are 25 different combinations of idiotope and paratope (i.e. idiotypes) with $M = 5$ different levels of specificity.

The rest of the system parameters (i.e. $\mu' = 0.3$, $s = 1.0$, $d = 0.1$, and $\alpha = 2.0$) are selected so that the size of each clone never diverges. Differences in the dynamic behaviour of this system due to these parameter values has been reported elsewhere. We report on the typical features of our model and compare it with immunological functions.

3. Dynamic Bell-shaped Function

We mainly pay attention to how the idiotype network responds to a persistent antigenic stimulation. This situation simulates immune responses against various antigenic molecules in a body; e.g. self-antigens.

The static antigen with binding site i is introduced as the constant term in the above dynamics.

By adding the antigen source term $+ A_i b_{k,i,m} x_{k,j,m}$ to eqn (5), we study the effect on network dynamics. We define the average network specificity by averaging the specificity of all idiotypes bearing paratope type i,

$$Sp^n_i = \frac{\sum_j \sum_m m x^n_{i,j,m}}{\sum_j \sum_m x^n_{i,j,m}}. \quad (6)$$

The network specificity Sp^n_i is a function of the amount of the antigens. We have used an antigen of type 4 as an example, namely, idiotypes with paratope type 4 can react directly against the antigen. Because we adopt the periodic boundary condition for the shape space, each idiotype is equivalent within a network. Therefore, the following result does not depend on the selected antigen type.

First, we show a plot of the time-averaged specificity (Sp_4) against the antigen invasion over 10^4 generations after initial transient (see Fig. 1).

As expected, the network specificity increases when we increase the amount of antigen. However, at a certain amount of antigen (about 9.5 units in Fig. 1), it unexpectedly diverges to a value with high specificity. We say that a *specific response* has occurred at this antigen amount. Beyond this antigen amount, however,

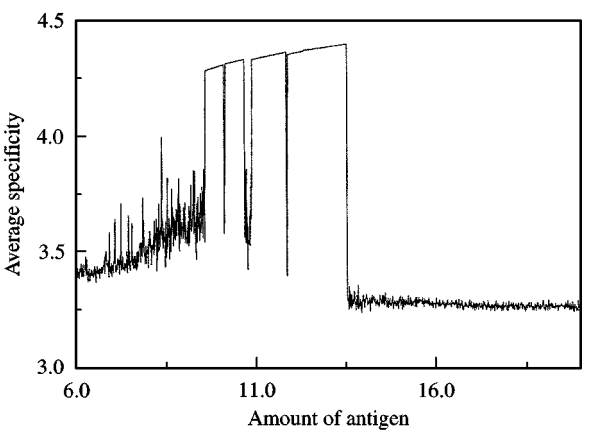

FIG. 1. The average network specificity is computed against the antigen amount ranging from six to 20 units. The initial 10 000 generations are neglected as a transient state.

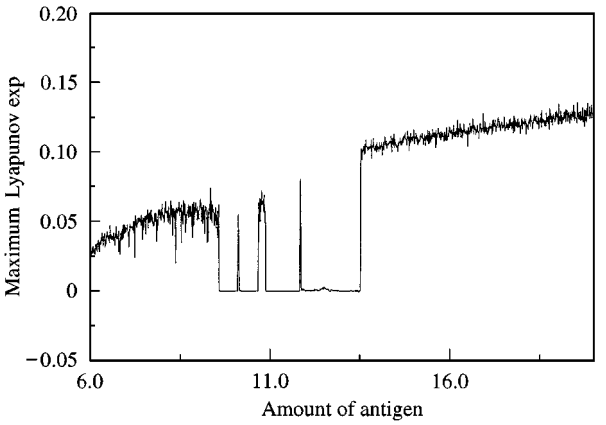

FIG. 2. The maximum Lyapunov exponent computed against the antigen amount corresponds to data for Fig. 1.

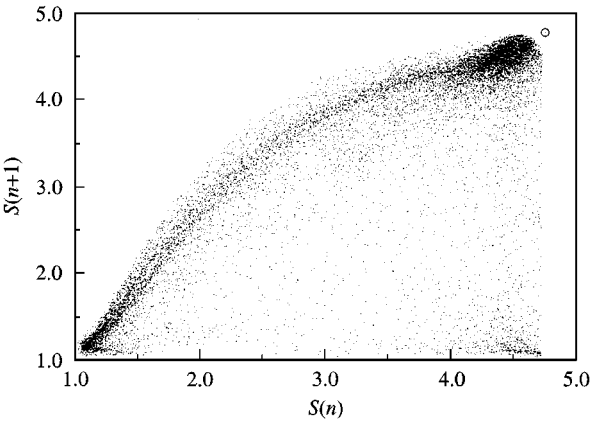

FIG. 3. A return map for the averaged specificity Sp_4^n for a fixed-point attractor with higher specificity, and chaotic attractors with lower specificity. It is obtained by computing over 10 000 generations for an antigen amount of 12 units. Here, the fixed-point attractor and the chaotic state are represented by a circle and a dot, respectively.

the response curve is not a smooth function of antigens. The specific response exhibits a dependence that is highly sensitive to the amount of antigen. This specific response is observed until the antigen amount reaches 13.5 units (Fig. 1). After this critical point, the specific response is no longer observed. It is sustained at lower values until the amount of antigen reaches 25 units, and is not dependent on the amount of antigen thereafter. This lower sustained response can be compared to *natural tolerance* to the antigen.

Why does the specificity Sp_4 rise steeply and in bursts depending on the antigen amount? We propose an explanation from a dynamical systems point of view. First, we have calculated the maximum Lyapunov exponent as a function of antigen amount. As predicted from Fig. 1, when the amount of the antigen is between 9.5 and 13.5 units, there seems to be two different attractors corresponding to different values of specificity: one high and one low.

Comparing Fig. 1 with Fig. 2, it is evident that the attractor with the higher specificity is a fixed-point attractor, and the attractor with the lower specificity shows chaotic instability. As clearly seen from Fig. 1, the system naturally possesses a bell shaped (specific) response function caused by the two attractor types. To examine the correspondence between dynamical instability and the response specificity in detail, we have plotted the return map of specificity Sp_4^n against Sp_4^{n+1} for those attractors (Fig. 3). Here, the fixed-point attractor with the higher specificity, and the chaotic attractors with lower specificity, are represented by circles and dots, respectively. The observations that the fixed-point attractor is found in the middle range and that the chaotic attractors are found at both ends of the antigen concentration are rather insensitive to different network sizes (Fig. 4).

4. Chaotic Transients and Immune Cognition

Chaotic attractors are also found among the fixed-point attractors in the middle region. For example, a network with five different idiotopes and paratopes shows the coexistence of two attractors (Fig. 1). However, the chaotic attractor is not a true attractor in this region. It is found to be a super-transient chaotic state. As discussed in models of coupled map lattices, super-transient phenomena are rather common in high-dimensional systems (Crutchfield & Kaneko, 1988; Kaneko, 1990). It is hypothesized that the length of a super-transient state shows a stretched exponential form as a function of system size. The mechanism that causes the long transient state is still unclear except in several trivial cases.

When these super-transient phenomena occur, discrimination between super-transient states and the attractor is often quite difficult. We have thus estimated the ratio of transition to the

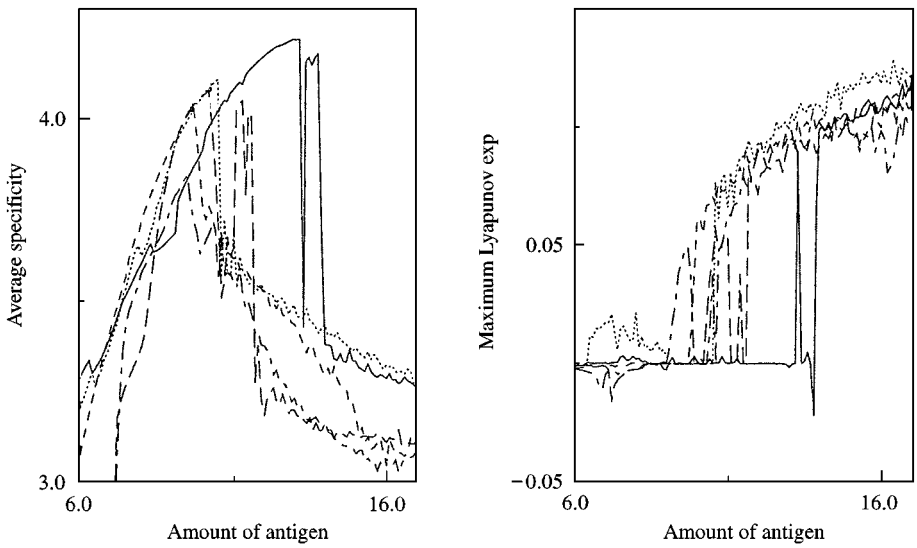

FIG. 4. The network size dependence of the average network specificity and the maximum Lyapunov exponents against the amount of antigen. The number of different shapes of idiotope and paratope assumed for the simulations are (——) 6, (·····) 7, (- - - -) 8, (– – –) 9, and (– – – –) 10 shapes.

fixed-point state from the chaotic state as a function of the transient time length, by averaging 100 random initial distributions, and have computed it as a function of antigen amount (Fig. 5).

From this analysis, we find that when the observation period is extended, the transition probability increases in a system depending on the amount of antigen [9.5, 13.75], and that there is no inverse transition from the fixed-point attractor to the chaotic state. We thus hypothesize that the chaotic state is a super-transient chaotic state, although it is not an attractor. These super-transient states are highly dependent on the antigen amount. For example, when the antigen amount is given at 11.5 units in Fig. 5, the transition probability from a chaotic transient state to a fixed-point state is still less than 12%. In such cases, it behaves as an attractor in a practical sense.

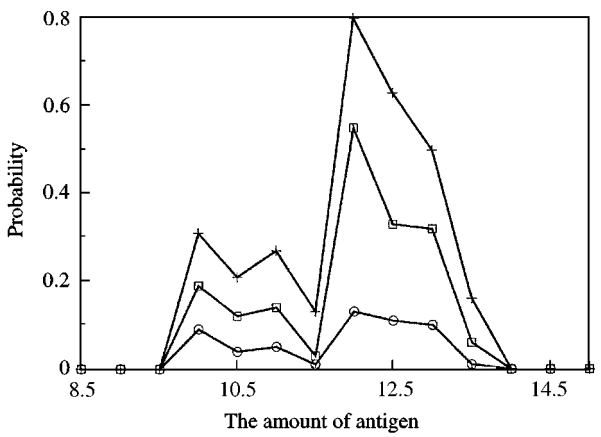

FIG. 5. The stability of the chaotic state is computed against the antigen amount. The ratio of initial distribution of idiotypes that show a transition from a chaotic state to a fixed-point state before a given time step, is computed. The given time steps are (○——○) 10 000, (□——□) 50 000 and (+——+) 100 000.

The chaotic transient state with the lower specificity changes into a fixed-point state with higher specificity. A specific final response against antigens is thus assured. From an immunological point of view, this assurance is very important. As Celada & Seiden (1996) pointed out, what is important in an immune response is not its eventual specificity, but the rate at which it occurs (in other words, what time period is necessary to reach a specific response). When the specific response is very slow, the effect approximates that of no specific response. If we assume that the relevant time-scale for the immune response should be less than 10,000 generations, in a practical sense there will be no specific response even against higher amounts of antigen (see Fig. 5). Indeed, Kauffman *et al.* (1991), using fitness landscape modelling, have estimated how many time steps are necessary to produce an antibody of

higher specificity from one of lower specificity. Kauffman's model is composed of the set of antigen binding sites represented as a bit sequence, and each binding site is given a fitness value. Here a high fitness value means a high specific binding site for the given antigen. Using a one bit mutation among idiotypes, Kauffman estimated that the number of steps necessary to reach specificity against the antigen is relatively few if there is no correlation among idiotype bits. If, however, there exists some correlation between each idiotype bit and some other idiotype bit, then the number of steps required to reach specificity increases. The situation becomes more complex when there are idiotypic interactions. Our results suggest that a certain amount of antigen causes the super-transient state to suppress fast immune responses under the idiotype network. We further speculate that a natural tolerance to an amount of antigen can be a result of super-transient phenomena, in which case the long super-transient state means that the system has recognized the antigen as a self-component.

5. Structural Change of the Network and Some Immunological Meanings

Some theoretical immunologists have focused on how the change of the network topology produces meaningful immunological phenomena (Stewart *et al*., 1989; Stewart & Varela, 1989, 1991; Detoures *et al*., 1994). For example, a dynamics of the immune network that is sensitive to the network topology has been discussed (Bersini & Calenbuher, 1997; Calenbuhr *et al*., 1995).

Here we argue that the transition from a lower specificity state to a higher specificity state causes a simultaneous change of network topology in the middle range of amounts of antigen. An analysis of the network topology of the higher, and lower specific states is shown in Figs 6 and 7, respectively. Of course, a lower specific state in the range of high amount of antigen has the same structure as that in Fig. 7.

As we see from the figure, a chaotic super-transient state with lower specificity has a more complex network than does a fixed-point state with higher specificity. The maintenance of idiotypic diversity can be attributed to chaotic dynamics.

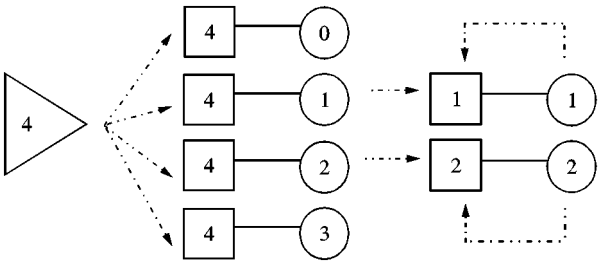

FIG. 6. Topology of an idiotype network of a fixed-point attractor with higher specificity against an antigen amount of 12 units. Only idiotypes that have a population of 1.0 in an average of over 10 000 time steps are depicted. Each idiotype in this figure is denoted by a pair of square and circle symbols. The square with the numeral inside denotes the paratope, whereas the circle with the numeral inside denotes the idiotope. The triangle with the number inside represents the injected antigen type. A stimulation wave from idiotype to paratope is shown by a dotted arrow. As seen in the figure, the network size corresponding to the fixed-point attractor is small, and is maintained by a simple coupling structure.

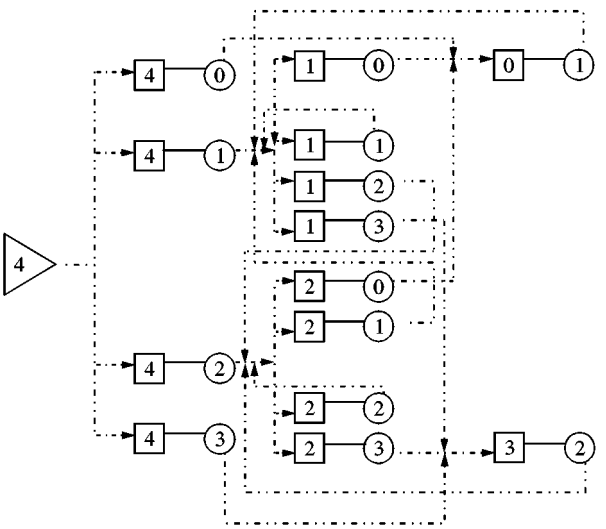

FIG. 7. As seen in this figure, the network size corresponding to the chaotic state with lower specificity becomes larger than that of the fixed-point state with higher specificity. It is maintained by a coupling structure more complex than that of the higher specificity state. (For meanings of symbols and arrows, refer to the captions for Fig. 6.)

This view is discussed in a more generic host–parasite system, where such chaos is called "homeochaos" (Kaneko & Ikegami, 1992), which is defined as a high-dimensional weak chaos that sustains species diversity. Homeochaos is studied by use of a model with evolvable mutation rates. Here, we have introduced the evolution of

specificity instead. Lower specificity as a result of the chaotic instability in our model, corresponds to the higher mutation rate in homeochaotic dynamics.

The transition from a lower specificity state to a higher specificity state can also be taken as a reversed percolation from a distributed to a localized state. The transition here is controlled by the antigen amount, and by an initial distribution of idiotypes. It differs from the usual percolation phenomenon in the sense that a re-entry transition to a localized state does not occur. It has been verified that distributed and localized states form a fractal structure for the initial distribution of idiotypes.

From the perspective of whole network specificity, the practically percolated state and the localized state can be immunologically relevant. When one draws the landscape with respect to the amount of time-averaged specificity in Figs 8 and 9, and compares those data with those in a distributed state and those in a localized state, it appears that in general each idiotype has a low specificity in the distributed state. Thus, each idiotype interacts weakly with many idiotypes to attain high connectivity. As a result, the stimulation to the network by dosed antigen is distributed over the network, and is not concentrated only on idiotypes bearing a binding site (paratope with type 4) for the antigen. The immune response to the antigen therefore has a tendency to be suppressed. This result would support Stewart's (1989) extrapolation that "The higher the connectivity among idiotypes, the greater the degree of tolerance" based on an *Autopoetic view*.

Recently, theoretical immunologists have tried to establish natural tolerance following an autopoetic view, though their simulation results show difficulty in establishing this (see, for example, Detoures *et al*., 1994; DeBoer & Perelson, 1994). These immunologists have used meta-dynamics (the process governing the removal of certain idiotypes from the active population and recruitment of new idiotypes into the network) to introduce the flexibility to retain natural tolerance in the network. Unfortunately, this type of flexibility, without a special assumption, failed to prevent aggression for the self-antigen. We have overcome this difficulty by adding an additional flexibility, i.e. meta-mutation dynamics with

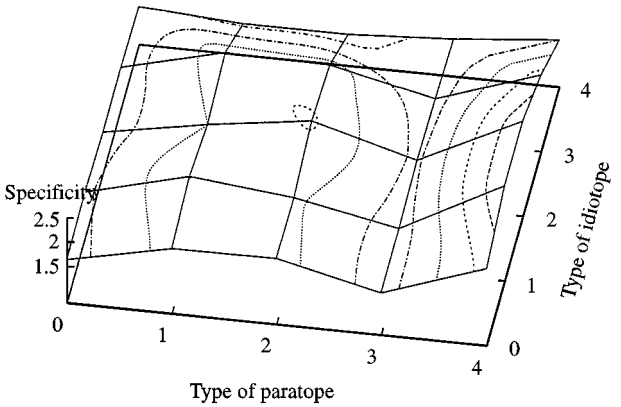

FIG. 8. A landscape with respect to the averaged specificity of each idiotype forming the lower specific state is computed. The amount of the antigen used is 12 units on an arbitrary scale. The idiotypes tend to connect with each other more densely than the idiotypes in the high-specific state: (– – – –) 2.5, (- - - -) 2.25, (· · · · ·) 2, (– · – · –) 1.75, (- · - · -) 1.5.

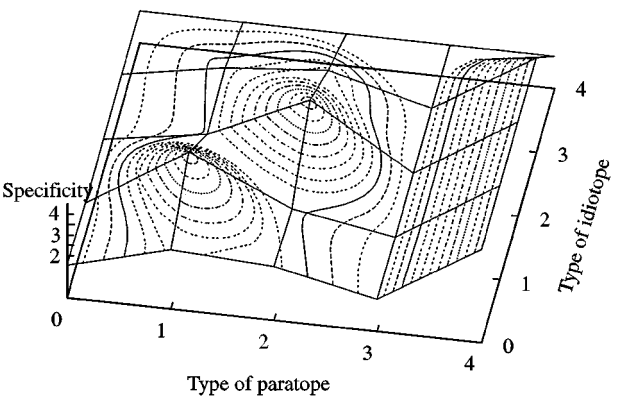

FIG. 9. A landscape with respect to the averaged specificity of each idiotype forming the higher specificity state is computed. The amount of the antigen used is 12 units on an arbitrary scale. As seen in the figure, the areas with higher specificity consist of the idiotypes, each with its paratope type 4. That is, the higher specific idiotypes are selected and sustained by the dosed antigen rather than by the idiotypic interactions: (- - - - -) 4.25, (· · · · · ·) 4, (·····) 3.75, (– · – · –) 3.5, (- · - · -) 3.25, (· · · · · ·) 3, (· · · · · ·) 2.75, (· · · · · ·) 2.5, (——) 2.25, (- - - - -) 2, (· · · · · ·) 1.75.

specificity of idiotype to the standard idiotypic network.

6. Immunological Relevance on Idiotypic Affinity Maturation

We here discuss the immunological relevance for the dynamics of specificity evolution through idiotypic interaction and hyper-mutation. The present study implies that the specificities of antibodies are dynamically controlled via the

idiotypic network. An initial antigenic impact will change the specificity of the first-excited antibody (Ab1) by mutating the V_H genes that encode the paratope sites. However, the antigenic impact will penetrate through the idiotypic network to cause changes in Ab2, Ab3, and all the way down. The propagation of mutations thus changes the specificity of antibodies.

The same situation has been observed experimentally by Roger *et al.* (1990). By immunizing a man with rabies vaccine, they observed the occurrence of mutations in a small V region gene (V_HV family), that encodes the paratope patterns of "anti-idiotypic Ab" (Ab2 from $CD5^+$ B cells) against "anti-rabies virus Ab". Compared with the other germ-line V_HV gene from the same individual, they found that the V region contained 19 replacements in a nucleotide. This is not the usual situation. With no antigenic stimulation, the diversity of natural antibodies derived from $CD5^+$ B cells is maintained by the small V_H families of germ-line genes. Thus, a propagation of mutations that occurred in the V region of Ab2, could only be caused by idiotypic interactions, initially triggered by the antigen response. Moreover, Roger *et al.* claim that the specificity-modified Ab2s can be involved in the regulation of the immune response. Therefore, the specificity evolution dynamics that we have proposed here, have an experimental counterpart. It is thus immunologically plausible.

7. Discussion

We have shown a possible dynamics of specificity evolution, based on idiotype interactions. Chaotic super-transient and fixed-point attractors are detected in our system. Lower average specificity with higher diversity of idiotype is characteristic of the chaotic transient. Conversely, the fixed-point attractor has higher average specificity with lower diversity of idiotype. In other words, the chaotic transient corresponds to a suppressed state of immune responses, and the fixed-point one corresponds to an active state with responding attractors. This picture would remain valid also for a supertransient region if a relevant biological time-scale were introduced, because the chaotic supertransient will eventually change to the fixed-point state in the region.

The transition from chaotic transients to a fixed-point state implies a change in active network size and whole network specificity. A spontaneous transition from a distributed to a localized network state is sensitive to the initial distribution of idiotypes.

Based on a landscape of each idiotype specificity, the lower average specificity state has been confirmed to be consistent with the explanation of natural tolerance conforming to the Autopoetic view suggested by Stewart *et al.* (1989). On the other hand, in a state of high specificity with a simple network, only idiotypes bearing the paratope to the type of antigen respond, and these idiotypes appear to have been selected by the antigen. This state appears to be consistent with the *clonal selection theory*, *antigen-driven view*, presented by Burnett (1957).

By introducing meta-mutation dynamics on specificity, we have introduced new flexibility into the idiotypic network, enabling it to become more adaptive dynamically to the antigen environment, and to demonstrate natural tolerance.

It is generally believed that there is no chemical difference between self- and non-self-antigens. Some mechanisms that control self- and non-self are known. First, when antigens present before an immune network matures, the antigen becomes "self". Otherwise, antigens become "non-self". Second, the duration of exposure to an immune system determines the "self-non-self" state. However, these mechanisms do not always work. There is experimental evidence from Varela *et al.* (1991) that differences in such dynamic states are related to self and non-self. They showed that the concentration of auto-antibodies in a normal body fluctuates chaotically in the experiment on men and mice. On the contrary, in autoimmune diseases of men and mice, auto-antibody concentration fluctuates either periodically or completely randomly. This experimental result is consistent with our hypothesis that the chaotic state of an immune system can be related to the normal or natural tolerant state. Without assuming a lack of idiotypic interaction, the tolerance in the higher amount antigen is known as a cross-linking process. However, from our results the higher amount of antigen is likely to induce natural tolerance.

We argue that tolerance occurs under the higher amount of antigens, with the chaotic dynamics caused by idiotypic networks. The bell-shaped function is also a natural result from idiotypic networks.

We believe that the immune response should have a more dynamic nature. The specific antigen response and the dynamical percolation related to natural tolerance to an antigen are caused by the meta-dynamics controlling the degree of specificity we have introduced here.

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