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Dynamical Behaviors of the Immune Network

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The immune system is a network of antibodies, exhibiting an autonomous behavior even in the absence of foreign antigens. Taking into account the death and birth processes of antibodies, we propose here the model of immune network which consists of antibodies and their generated complexes. Possible dynamical states and their mutual transitions are investigated by computer simulations, and are related to some biological natures. The number of different types of antibodies which constitute the network is estimated.

§ 1. Introduction

An immune system is a complex adaptive network which can perform various cognitive functions such as perception, pattern recognition, memory, learning, etc.

A neural system is known as another well-known adaptive network, but underlying dynamics and interactive means are considered to be different. Elements of the immune network are cells and melecules which are not located on a spatial rigid site and destroyed or created by their mutual interactions. A mathematical description of the immune network has started since Jerne[1),2)] has proposed a network theory of the immune system.

The main point of his theory is that an immune function is caused by an internal network of antibodies where each antibody also works as an antigen to other antibodies. Many experiments[3)] and theoretical models[4)~10)] have been proposed to verify his theory and to clarify a role of the network. Most of early theoretical models aimed to explain several immune functions based on the network theory. Few of the explanations, however, have been verified by physiological experiments. Dynamical behaviors of those models, even of the simplest one, are presumed to be quite complex and difficult to predict. One of recent approaches[9),10)] is, thus, to characterize its dynamical behavior first.

We developed a model for the immune network to investigate the following characters: 1) Relations between dynamical states and the immune functions. 2) Effects of a size of the network on the observed dynamical states. 3) Possibility of a dynamical memory in the immune system. A dynamical memory is expected to be completely different from those stored in some proteins or cells. In the next section, we briefly review the real immune system and Jerne's network theory.

§ 2. Brief review of the immune system[11),12)] and Jerne's theory

Based on Jerne's idea, each antibody element (Ab) is known to be connected with other Ab's as well as with a foreign body called antigen (Ag). For this, one can connect Ab_1 with Ab_2 provided that an 'idiotope' (acceptor) of Ab_1 contact with a

'paratope' (donor) of Ab_2. The idiotope and paratope form a complementary junction with each other.

When the immune system is invaded by Ag which has an idiotope, Ab having a matching paratope against Ag is generated. The Ag is linked with Ab and only the resultant Ag-Ab complex is removed from the system as a foreign element.[13] A large variety of Ab's are made in the absence of foreign Ag. By such diversity of paratopes and idiotopes, the immune system can respond to any kind of Ag.

Not only a specific idiotope but also sufficient quantity of the Ag is necessary to induce a response.[14] A system has positive and negative memory of once invaded Ag. If a system is invaded by too many or too small numbers of Ag, the system can no more respond to that Ag. It is called a negative memory or tolerance. If its secondary response is faster and greater in amplitude than the primary one, the system has a positive memory of that Ag. Those mechanisms of memory are still unknown. A positive memory is said to be brought by memory B-cells. A part of B-cells which have a capacity to generate the Ab's against the encountered Ag may live for some months or even years and prepare for the next encounter. These are called memory B-cells. Judging from the fact that we can develop lifelong immunity, some mechanism is needed to excite the system to generate and conserve the constant amount of memory B-cells.

Ab's are not only generated when a system is invaded by the foreign Ag. Any open idiotope of Ab will induce another matching Ab and a cascade reaction takes place among Ab's. Dynamical behavior of the immune system is considered to originate from such an immune response among Ab elements in the internal network. Our simulation is to uncover such an autonomous behavior in the absence of foreign Ag.

§ 3. Description of the model

Labelings are made for the idiotope-paratope pair*) (X_i, Y_i) of $Ab_i (i=1, 2, \cdots, P)$, where X_i and Y_i are integers. We assume a cyclic network of size P, that is,

$$X_i = i\,,$$

$$Y_i = X_i + 1 \qquad (3\cdot1)$$

with a cyclic boundary condition,

$$X_P = P\,,$$

$$Y_P = 1\,. \qquad (3\cdot2)$$

There can be many Ab_k's as a system element of k-type. We assume that Ab_k can interact with Ab_{k-1} or Ab_{k+1}, generating linked complexes as follows:

$$(k, k+1)+(k+1, k+2)\rightarrow(k, k+2). \qquad (3\cdot3)$$

*) Farmer et al.[10] have first proposed this representation. They expressed each component by a binary string and took into account an incomplete matching among elements.

or

$$(k, k+1)+(k-1, k)\rightarrow(k-1, k+1)\,. \tag{3·4}$$

Thus generated complex has a combined idiotope-paratope pair, and can further react with other elements. The reaction rate between the complexes are assumed to be limited below a certain value, that is, if a generated random number becomes less than a parameter c, the reaction ceases even if either idiotope matches the other paratope. Such a parameter c is fixed at 0.001 through our simulation.

In order to simulate the immune function, we will here consider further processes of sink and source for system elements. If the number ratio of a certain idiotype Y_k to the total elements exceeds a given birth threshold α_B, we assume that there be injected an amount Δ_B of elementary Ab's having a complementary paratope, that is, X_{k+1}. In addition to this, one element will be injected for every Ab_k at each step. As to the removal of the resultant complexes, a similar assumption will be made. If the number ratio of a certain idiotype to the total elements exceeds a given death threshold α_D, those complexes will be removed by an amount up to Δ_D.

The above processes will be treated by a Monte-Carlo method. Because we do not have to set up the variables of complexes in advance, MC method is powerful when a network size becomes large. MC process for this model is as follows. We have a pool of elements which satisfy (3·1) and (3·2). The above matching rules are applied to randomly selected pairs of elements. A total amount of system element N decreases by generating new elements and increases by the birth. Each MC step consists of $\alpha_L * N$ times of this matching rule and the birth/death rules are applied at each end of the steps. The parameter $\alpha_L(=3.0)$ is fixed through the simulation.

The threshold values α_B and α_D which satisfy the condition $\alpha_B > \alpha_D$ and the birth/death number Δ_B and Δ_D are adjustable parameters, which are related to functions of slow reacting cells (e.g., B cells, complement systems, etc.). On the contrary, the parameters (α_L and c) are related to the rate of generating complexes which is a fast reaction. The fast reaction rate is of the order of seconds to minutes and the slow reaction rate is usually of the orders of hours.[15]

Here we will fix the latter two parameters of fast reactions and deal with the former slow reacting processes. For the simplicity of analysis, a birth threshold is fixed at $\alpha_B = .5$ which means an idiotope is detected as an antigen when its number ratio to the total elements is more than 50 %. When it is detected, there be injected elementary Ab's, $\Delta_B = 200$. Parameters, α_D and Δ_D, are major adjustable parameters through the following simulation.

§ 4. Phenomenology of metastable states

Strength of interactions (Int.) among Ab's is assumed to take the following form,

$$\text{Int.} \propto [Ab_1][Ab_2][\text{goodness of matching}]\,, \tag{4·1}$$

where $[Ab_i]$ is the concentration of antibody Ab_i. Goodness of matching is a degree of matching between idiotopes and paratopes of Ab_1 and Ab_2. The idiotope-paratope

pair is denoted by integers, and the goodness of matching takes 0 (non-matching) or 1 (perfect matching) in the present model.

Memory of invaded antigens is established by elevating the concentration of corresponding antibodies (Ab_1). According to Eq. (4·1), the antibody Ab_1's which are not removed with antigens enhance the interaction between Ab_1 and the anti-Ab_1 antibodies (Ab_2). After the antigens are removed, Ab_1's are thus removed by Ab_2's. The purpose of the present simulation, however, is to seek for the dynamical states where a large amount of Ab_1 still survive without being removed by Ab_2.

By adjusting parameters, a network preserves the initial inhomogeneity of a certain antibody distribution. For example, one idiotype is rich in numbers and others are suppressed. After several time steps, the rich idiotype is switched to another idiotype (Fig. 1).

A long lasting state with one rich idiotype is called S state and the other transient

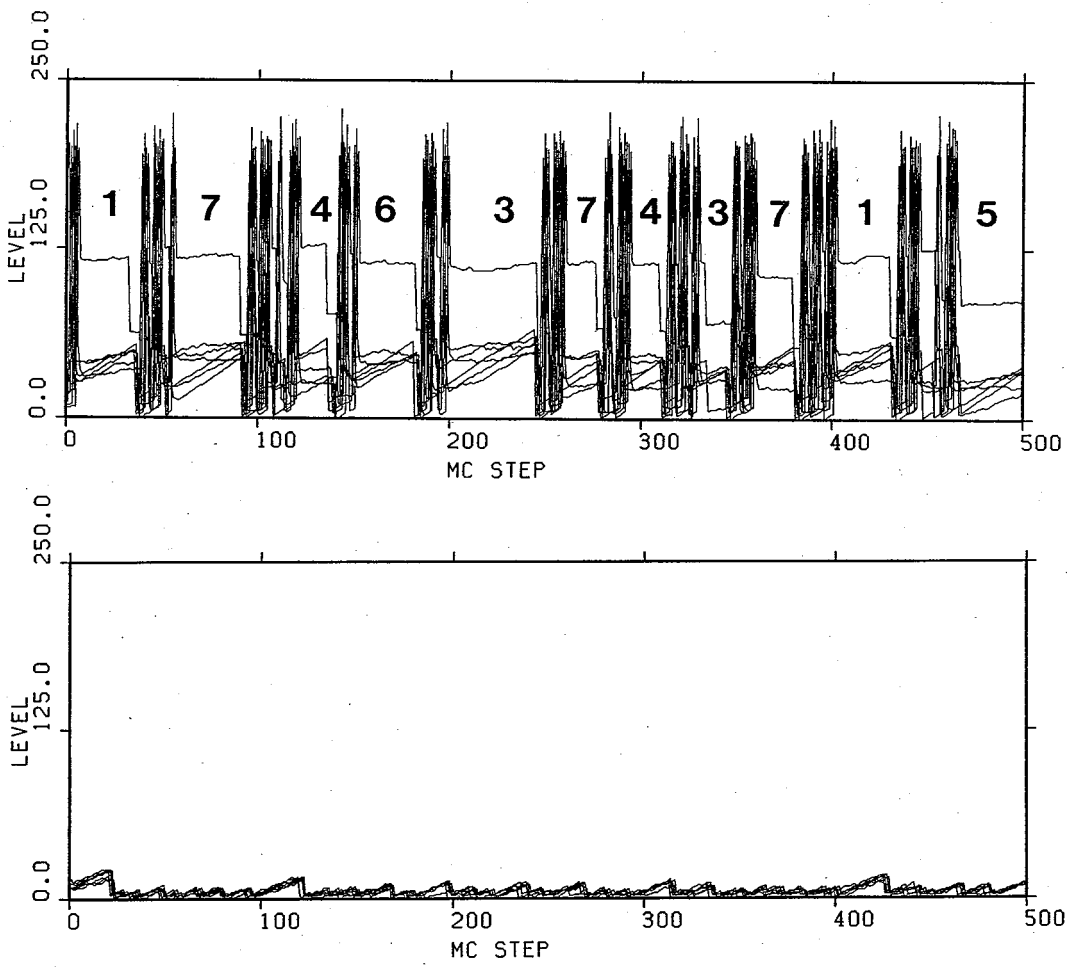


Fig. 1. Time evolution of number levels for each of the seven idiotopes($p=7$) is simultaneously recorded, where the numbers denote the idiotype of a maximum level in each S state (upper figure) which is almost periodically switched to the B state associated with a bunch of spikes, for the case $\alpha_B=0.5$, $\Delta_B=200$, $\alpha_b=0.14$ and $\Delta_b=80$. The lower figure corresponds to an evolution of the N state which has an equal distribution of every idiotope.

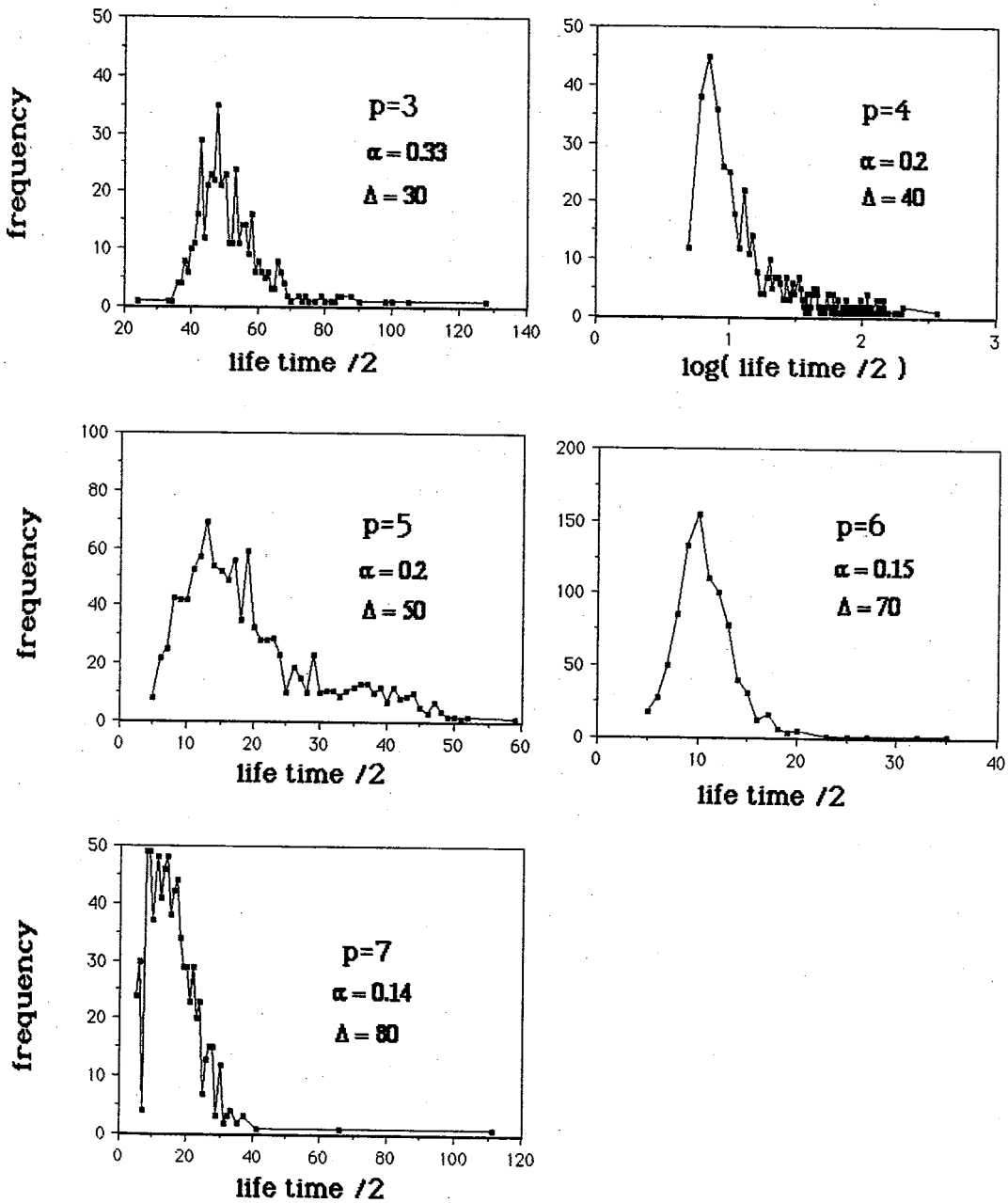
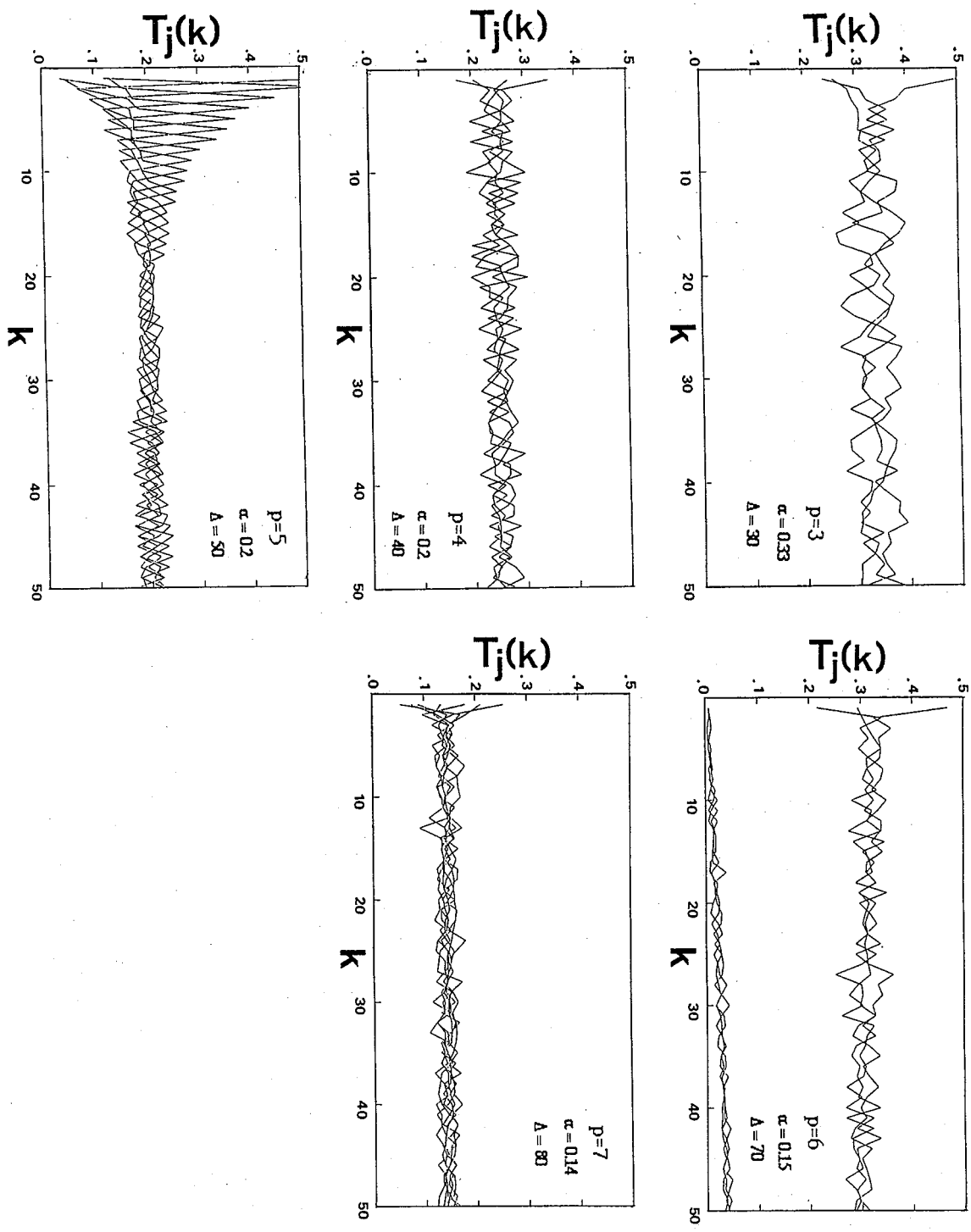


Fig. 2. Distribution of lifetime of the S state is computed from 50000 time steps after 10000 transients, for our network with α_B=0.5. Tuning parameters (α_b and Δ_b) are depicted on each figure.

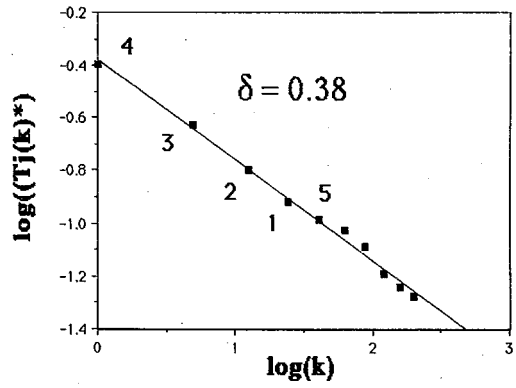
state, which is characterized by many successive bursts of idiotopes, is called B state. These two states are distinguished from their characteristic lifetime.(See Fig.2.) Since the lifetime distributes over a wide range, if the characteristic lifetime is more than 10 time steps, we regard it in the S state, and if shorter, it is in the B state.

It is crucial point of the present simulation that the best immune function will be achieved in the S state, since it has the following characteristics.



(a)

Fig. 3. (continued)



(b)

Fig. 3. (a) $T_j(k)$ vs k is plotted for each network size. $T_j(k)$ is also computed as in Fig. 2.
(b) The logarithm of the maximum numbers of $T_j(k)$ with respect to j at each step k is plotted against the logarithm of k for $P=5(T_j^*(k)\propto k^{-\delta})$, where the numbers denote the values of j which give the maximum $T_j(k)$.

1) The network is rich in one idiotype (Ab_k) and other Ab's are suppressed. Elementary Ab_{k+1} and Ab_{k-1} cannot increase their numbers because they are combined to complexes by connecting to the Ab_k. 2) Rich idiotypes conserve their number, because the supply of elementary Ab_k's to the rich idiotype is just compensated by generating complexes. 3) The network has a long term memory, although it is only observed when its size is equal to $5(=P)$.

By computing transition probabilities between the S states, we find that memory of an initial abundant idiotope decays as a power law (Fig. 3). The transition probabilities are computed as follows.

Each S state is coded by the dominant idiotype of the S state. By numbering each separated state in order, $P_a(b)$ is defined as the probability of observing the b-th S state with a dominant idiotype a. A k-th order transition probability $T_j(k)$ from the n-th S state to the $(n+k)$-th S state is defined as

$$T_j(k)=\lim_{T\to\infty}1/T\sum_{n=1}^{T}\sum_{r=1}^{P}P_r(n)P_q(n+k)\,, \tag{4·2}$$

where j equals a difference between numbering of idiotype of the n-th and that of the $(n+k)$-th S state (e.g., $j=(q-r)\mathrm{mod}\ P$).

The j value that gives the maximum $T_j(k)$ with a given k is marked in Fig. 3(b), which equals $(5-k)$ mod 5. Namely, the numbering of idiotype of the n-th S state is the same as that of paratope in the $(n+1)$-th S state. In the case $P=6$, $T_j(k)$ takes two branches. The high value branch corresponds to the even j's, and the low value branch to the odd j's. This will be due to an even parity of P.

Usually an S state switches to other S state via B state. In addition to these S and B states, we have an N state (see Fig. 1) which has an equal size distribution of every idiotope for even P and two different size distributions for odd P. For a small network size P(e.g., a few kinds of idiotypes), the network has only two states of S and B. By increasing P, the irrelevant N state appears more frequently, which is taken as an irrelevant state for the immune function as it cannot have any memory

of idiotopes. A long-term memory between the successive S states is truncated by the appearance of N states.

§ 5. Stability vs network size

The S, B and N states are again quantitatively distinguished by the following averaged entropy:

$$I_f=\langle -\sum P_i \log_P P_i \rangle , \tag{5·1}$$

where $P_i=n_i/N_f$ is the number ratio of elementary idiotopes of type (i) to the overall elementary idiotypes, N_f and $\langle\cdot\rangle$ denotes time averaging.

Entropies I_f for the S state are expected to be much smaller than those of the N state, since the S state has one dominant idiotype. The defined entropy I_f takes a different value in each S state, but there is a sharp peak in the distribution of I_f (see Fig. 4), and we can use a threshold to separate the S state from N state. A different threshold value is used with respect to a parity of the network size. The entropy I_f distributes around 1 for odd P's and takes about $1-\log_P 2$ for even P in the N states.

In the S state, elementary idiotopes are grouped into three classes by their numbers $(F_1>F_2>F_3)$. (See Fig. 5.) There are F_1 Ab's of the same idiotype in Class 1. The number of Ab elements and the number of different idiotopes in Class 2(3) are denoted by $F_2(F_3)$ and $m(n)$, respectively. The relation $[1+m+n=P]$ holds by definition. It should be remarked here that Ab_k is a prey for Ab_{k+1} and a predator for Ab_{k-1}. As the result, if Ab_{2k} belong to Class 2 (or 1), Ab_{2k+1} must belong to Class 3, where k is an integer. Through this process, we may conclude that the possible range of m is restricted in $\{0, 1, \cdots, [(P-2)/2]\}$, where $[x]$ denotes the maximum integer less than x. By using these symbols, I_f can be written as

$$I_f=-F_1/F\log_P(F_1/F)-mF_2/F\log_P(F_2/F)-nF_3/F\log_P(F_3/F) , \tag{5·2}$$

where $F=F_1+mF_2+nF_3$ and values of F_1, F_2 and F_3 are observed to be almost size-independent.

Such a system can switch to another S state by inducing the B state. The condition to generate B state from S state can be given by

$$\frac{F_1+\omega}{F_1+mF_2+(P-1-m)F_3+P\omega}>\alpha_B , \tag{5·3}$$

where ω is the number of such complexes that remain after the elimination and satisfies the following condition,

$$\omega<\alpha_D(F+P\omega) . \tag{5·4}$$

The death threshold α_D is set at a value not larger than $1/P$, which is the most probable value for having the S state. It is predicted from Eqs. (5·3) and (5·4), that the critical size (P_c) must be

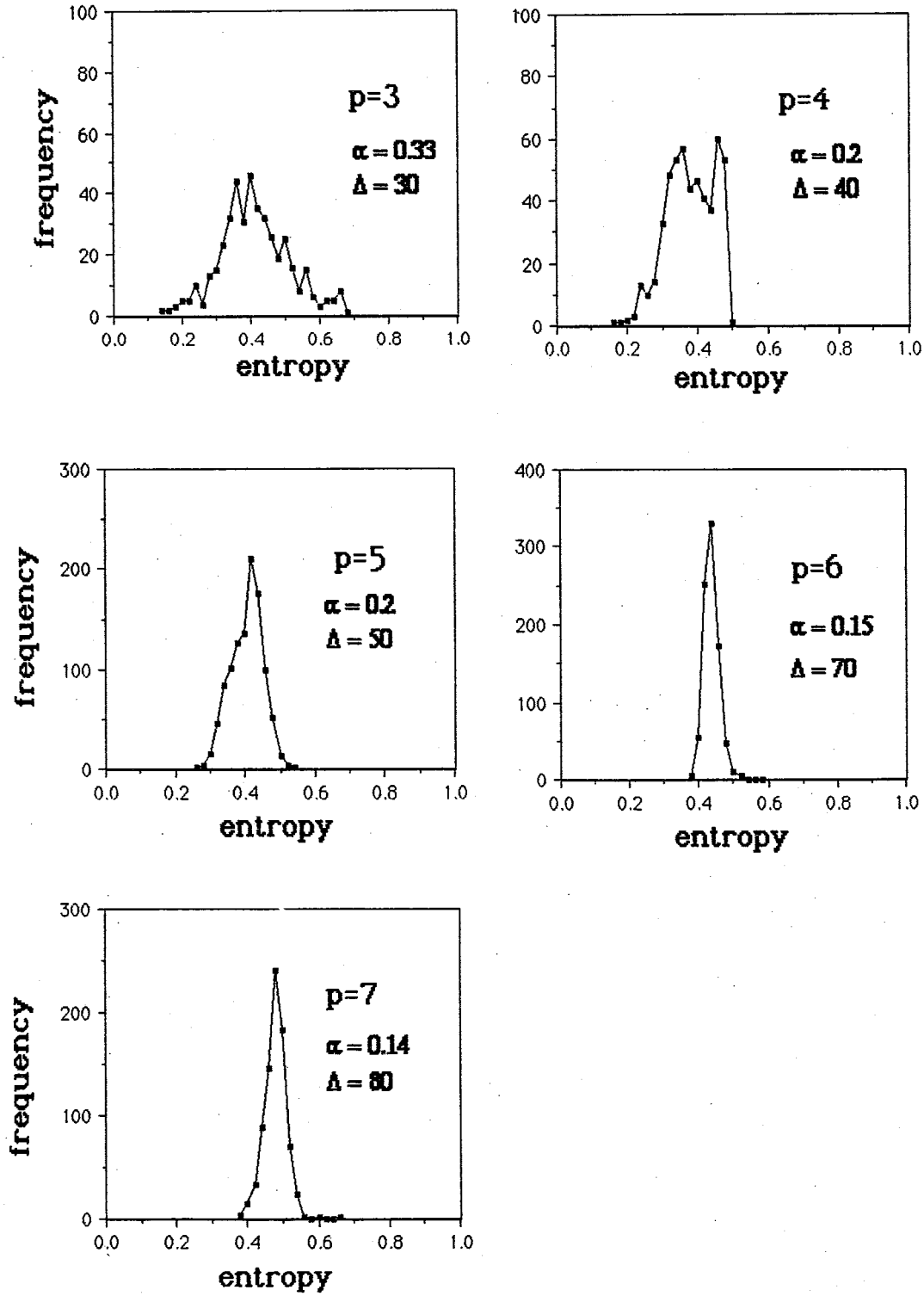


Fig. 4. Distribution of the averaged entropy (I_r) for the S states. It is also computed as in Fig. 2.

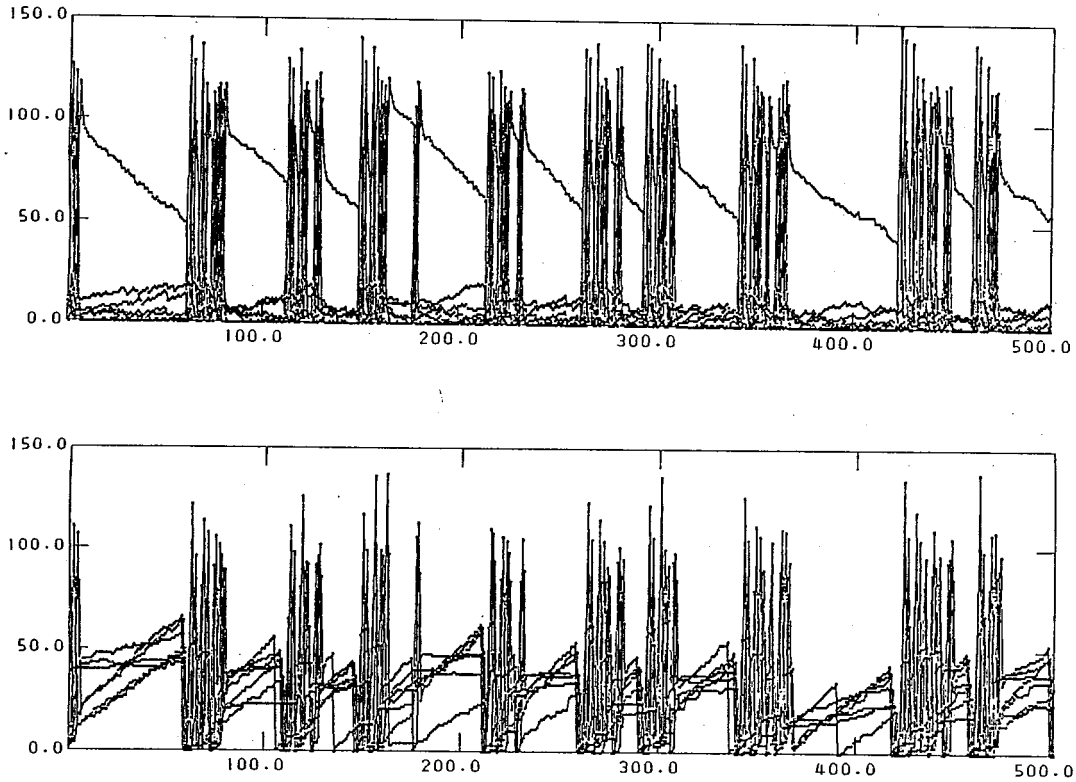


Fig. 5. The upper and lower figure show time evolution of levels for complex and elementary Ab's, respectively. Levels are computed for each idiotype by summing up its paratope. These are the S states with one element in Class 1 and few in Class 2 ($m \simeq 2, 3$) for the case $P=7$, $\alpha_b=0.14$ and $\Delta_b=80$.

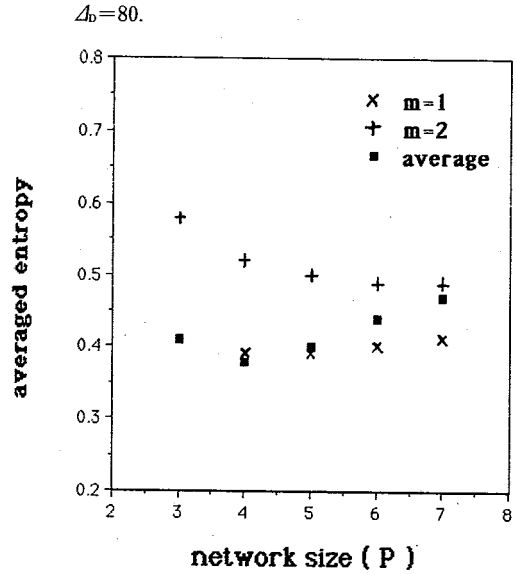


Fig. 6. Plotting of the averaged value of the entropy vs a network size. The cross marks denote the expected value which are computed from Eq. (6·1) by using $F_1=80$, $F_2=10$ and $F_3=2$.

$$P_c=\frac{F_1}{F_3+\omega}+O\left(\frac{F_2}{F_1},\frac{F_3}{F_1}\right) \quad (5\cdot5)$$

with the approximation $F_1 \gg F_2, F_3$ and ω, which is confirmed always to hold in the simulation experiment. The experimental value of I_f can be deduced in case of the parameters, $F_1=80$, $F_2=10$ and $F_3=2$ as shown in Fig. 6, and the critical value for P_c is obtained to be approximately 10.

The number of different idiotypes (m) in Class 2 is effected by the network size P. If P is an even number, each class tends to develop into a group of equal quantity and there results in F_1, F_2 and F_3, that is, Class 1 disappears eventually. The number m can take as large as $P/2$ at maximum without frustration when P is an even number. As the l.h.s

of Eq. (5·3) is proportional to m^{-1} for large m, the inequality breaks when m exceeds a certain value. This brings out either S state or N state. In case of an odd P, it can anticipated that m stays at a small value as also observed in the simulation experiment, and the inequality Eq. (5·3) will be always held.

Even parity of P is reflected in the following characteristics: Transition probability $T_j(k)$ for even j's is larger than that for odd j's as shown in Fig. 3. N state consists of two-different-size-distribution of idiotypes, where each size corresponds to even and odd idiotopes Y_k. In other words, we have $P/2$ different idiotopes in both Class 2 and in Class 3 for even P.

§ 6. Discussion and future problems

The autonomous oscillatory behavior in our model is related to the experimental observations. An oscillatory phenomenon in the physiological experiments is examined by injecting the antigen only initially and then measuring the kinetics of idiotypes that appear. After the primary response, the corresponding idiotope cyclically appears. A length of cycle is synchronized to the period of about 5~10 days.[16),17)]

A self-sustained oscillation in a neural network is often said to bear a short-term memory. Before the short-term memory decays, a part of short-term memory is transformed into a long-term memory. Some protein or a plasticity of synapses is said to be responsible for the long-term memory. A plasticity of synapses is the mechanism that tunes the efficiency of transmitting signals in the neural network. As we have stated, memory B-cells are responsible for the long-term memory in the immune system, but their generation and conservation are not well understood. We impose these mechanisms on the S state of the network. One suggestion is that a switching between S states plays a role of a short-term memory in the immune network and memory transfer to memory B-cells is performed during each S state.

It is considered crucial in our model that a removal of Ag's is always in a form of a complex containing Ag and retaining the complexes until they reach a given threshold. As a result, we have such S states and an autonomous behavior. Experimentally, it is said that Ag-Ab complexes enhance the activity of other cells[18)] and engage in generating memory B cells.[19),20)]

In our model, every idiotope participates in a cyclic behavior in order to keep memory of one idiotype. A memory in the immune network is thus to excite one loop including the corresponding paratope rather to excite the single idiotype. Simultaneous appearance of other idiotopes by injecting one type of Ag is reported in the physiological experiments.[21)] Theoretical and experimental interests are thus to know the number of idiotopes engaged in one immune response. This is, in other words, to know the size of Jerne's network, which we have estimated for this cyclic network.

A network thus should be modeled in order to contain many loops. It means that there are antibodies which have a common paratope but a different idiotope and vice versa. Introducing these antibodies would violate the present picture in several aspects. We should further insist that the interaction between idiotopes need not be

perfect. Some incomplete matching in paratopes and idiotopes is allowed, as it is too difficult to select one completely matched paratope from the tremendous variety of idiotopes. Such confusion will be relaxed by the incomplete matching, though the risk of attacking the self-body is also elevated.

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