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REALIZATION OF IMMUNE RESPONSE FEATURES BY DYNAMICAL SYSTEM MODELS

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Abstract. Among the features of real immune responses that occur when antigens invade a body are two remarkable features. One is that the number of antibodies produced in the secondary invasion by identical antigens is more than 10 times larger than in the primary invasion. The other is that more effective antibodies, which are produced by somatic hypermutation during the immune response, can neutralize the antigens more quickly. This phenomenon is called "affinity maturation".

In this paper, we try to reproduce these features by dynamical system models and present possible factors to realize them. Further, we present a model in which the memory of the antigen invasion is realized without immune memory cells.

1. **Introduction.** The immune system has evolved specific mechanisms to defend against numerous invading pathogens and any toxic molecules they produce. The acquired immune system effectively eliminates foreign molecules (i.e., antigens) from its body. This specific immune system can distinguish the body's own tissues (self) from tissues and particles not normally found in its own body (nonself) and efficiently remove nonself antigens to protect itself from harmful environments. In this paper, we propose dynamical system models that can reproduce the most characteristic phenomena in immune responses.

First, we briefly summarize specific immune responses [1, 2, 3]. In specific immune responses, many cells and physiologically active molecules interact in complicated ways. Among them, the main constituents are T-lymphocytes (T-cells) produced in the thymus, B-lymphocytes (B-cells) produced in the bone marrow, and antibodies (immunoglobulins). T-cells have two main functions. One kills cells infected by viruses and cancer cells, etc., so-called cell-mediated immunity. Such

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T-cells are called killer (cytotoxic) T-cells. We will not consider this immune response. On the other hand, the second provides control of the immune response. Such T-cells, so-called helper T-cells, play several roles in regulating immune responses mediated by B-cells through antigen-antibody interactions. This response is called humoral immunity, and we construct models for it. Helper T-cells promote the maturation and proliferation of B-cells responding to specific antigens and terminate immune responses by suppressing the maturation and proliferation of B-cells after the neutralization of antigens. B-cells generate and secrete antibodies. On the surface of each B-cell, B-cell receptors (BCR) exist that are antibodies with transmembrane structures. Some antibodies attach to a specific antigen and form an immune complex that is easier for phagocytes to eliminate from the body than the antigen. An antibody is a protein that possesses an immunoglobulin structure consisting of a constant region (C region) and a variable region (V region). The variety of the C region is mainly related to the method of antigen elimination. Based on the differences in C regions, antibodies are classified as IgM, IgG, IgE, etc. On the other hand, the V region allows a variety of specific associations with corresponding antigens.

Let us explain the V region in more detail. The V region of a BCR and an antibody has a proper three-dimensional structure that consists of several small structures called idiotopes. A set of idiotopes can bind to the antigenic determinant of a specific antigen. Such a set of idiotopes is called a paratope, and the antigenic determinant is called an epitope. An idiotope can also be recognized by other antibodies (anti-idiotypic antibodies). The total set of idiotopes is called an "idiotype". A family of B-cells that has the same idiotype is called a "clone". Therefore, antibodies produced by the clone have the same idiotype. For each of the various antigens, clones with specific idiotypes selectively correspond and respond to the antigen. This scenario is called clonal selection theory.

Now we list the features observed in real immune systems that we consider in this paper:

1. Clonal selection [2]
2. Reduction of apoptosis rate [4]
3. Class switching and somatic hypermutation [5, 6]
4. Reservation of memory cells [2]
5. Affinity maturation [3, 6]
6. Mass secretion of antibodies in the secondary response [2]
7. Existence of anti-idiotypic antibodies [2]

Next we briefly explain these features.

1. Clonal selection

In a body, a huge number of immune cells can respond to any kind of antigen. When an antigen invades the system, at least one clone exists whose affinity to the antigen is high; that clone is stimulated and responds to the antigen. This is clonal selection theory and has been confirmed experimentally.

2. Reduction of apoptosis rate

Usually, in their genes, cells are programmed to die naturally. This spontaneous death of cells is called apoptosis. However, it has been reported that for maturated B-cells, apoptosis is suppressed during a proliferation period. Experiments that prove this phenomenon are as follows. First, an appropriate amount of stimulus is given. As a result, the number of B-cells increases. After that, if the amount of the stimulus is either increased or decreased, the number of B-cells always decreases.

That is, in the beginning of the immune response when B-cells proliferate, apoptosis of B-cells is suppressed.

3-1. Class switching

Before invasion by one kind of antigen, B-cells exist that can produce antibodies of class IgM. The antibodies of class IgM have a lower ability to neutralize antigens. After the invasion of antigens, depending on the number of antigens and their kind, B-cells switch the class of antibodies they produce to either IgG or others. The antibodies of class IgG have a higher ability to neutralize antigens.

3-2. Somatic hypermutation

In recent studies, an enzyme has been found that simultaneously induces class switching and the mutation of the V regions of B-cells. This process is called somatic hypermutation.

4. Reservation of memory cells

The B-cells created by somatic hypermutation finally disappear after the immune response due to apoptosis. However, a fraction of them become immune memory cells by differentiation whose lifetimes are as long as the living body. In secondary response, these memory cells are activated, they become activated memory cells, and they secrete antibodies of the IgG class. As a result, antigens are neutralized efficiently from the beginning of the secondary response.

5. Affinity maturation

Through class switching and somatic hypermutation, B-cells with new idiotypes are created. Some of those B-cells, which have higher affinity than the B-cells before class switching, play a main role in the secondary response. In fact, it is commonly known that antibodies produced in the secondary response have higher affinity to antigens than those produced in the primary response [2]. This phenomenon, called affinity maturation, is considered to take place in two processes [2].

(a) At the later stage of the primary immune response, clones with higher affinities are produced.
(b) In the secondary immune response, clones with higher affinities proliferate selectively by stimulus of the antigen.

6. Mass secretion of antibodies in secondary response

In real systems, the number of antibodies produced in the secondary response ranges from 10 to 1000 times as many as in the primary response.

7. Existence of anti-idiotypic antibodies

In real systems, anti-idiotypic antibodies exist that can interact with specific clonal antibodies [2].

Before explaining our models, we briefly cite previous theoretical and experimental works related to these features.

Among many theoretical studies [7] on affinity maturation is a model introduced by Kepler and Perelson [8, 9], who considered somatic hypermutation and studied the optimal mutation schedule. They treated a dynamical system model taking into account the change of the affinity of B-cells. However, they did not explicitly consider antibodies. Since the mass secretion of antibodies in the secondary response (feature 6) concerns the number of antibodies, we need a model in which not only B-cells but also antibodies are included, taking into account somatic hypermutation. As for the existence of anti-idiotypic antibodies (feature 7), since Jerne introduced the idiotypic network [10], many network models have been proposed. Among others, we concentrate on the so-called "second-generation immune network model"

proposed by Varela et al [11]. In this model, B-cells and antibodies are explicitly considered, and the roles of T-cells are taken into account. This model is so general that situations in which immune cells do not interact with one another and do not constitute a network can also be considered. Further, since responses to antigens can be treated by this model, we adopt it as our basic model for the present study.

As for experimental studies, a huge number of experiments have been performed on the features listed above. For a compact review, we refer to paper [7]. As for papers related to apoptosis and somatic hypermutation, we refer to papers [4], [5], and [6].

Now let us explain our models. We have two purposes in this paper. One is to construct a model that realizes the features of affinity maturation (feature 5) and the mass secretion of antibodies in the secondary response (feature 6). That is our main goal. In this paper, as a criterion for the realization of the mass secretion of antibodies in the secondary response, the number of antibodies in the secondary response is set to 10 times the number of antibodies in the primary response. This number 10 is rather arbitrary, and it can be replaced by a larger multiple of 10, such as 100. The second purpose is to construct a model that remembers the antigen invasion without immune memory cells. To achieve these purposes, we study the second generation immune network model. Although this model is based on idiotypic immune network theory, we do not consider interaction between immune cells for the model to attain the first purpose. That is, we do not adopt a network point of view. On the other hand, to realize immune memory without memory cells, we consider interaction between immune cells.

First, we explain the models for the realization of affinity maturation (feature 5) and the mass secretion of antibodies in the secondary response (feature 6). We consider the four features listed above to construct a realistic immune model: clonal selection (feature 1), reduction of the apoptosis rate (feature 2), class switching and somatic hypermutation (feature 3), and the reservation of memory cells (feature 4). Below, we explain how these features are treated.

1. Clonal selection

We assume that one clone of the B-cells with high affinity against antigens is selected in the primary response.

2. Reduction of apoptosis rate

In our models, a stimulus by one kind of antigen is expressed by sensitivity σ, which is the product of the affinity to antigens and the concentration of antigens. When antigens invade the system, σ decreases monotonically because we assume that after some number of antigens invade the system, they do not proliferate but are just neutralized. Therefore, to include the reduction of the apoptosis rate, we assume that if σ is large and the maturation and proliferation rates are high, the apoptosis rate of the B-cells is low, and it is high otherwise.

3. Class switching and somatic hypermutation

We assume that the B-cells, which are chosen by clonal selection in the primary response, switch their class and undergo somatic hypermutation and that several B-cells appear with lower and higher affinities than the B-cells before somatic hypermutation. That is, the first of the two processes of affinity maturation, (5-(a)), is assumed, although it is not guaranteed that B-cells with higher affinities dominate the primary response. Therefore, our main purpose is to realize the second process, (5-(b)). We investigate whether the concentrations of B-cells that have higher affinity become dominant in the primary and secondary responses.

4. Reservation of memory cells

Since the mass secretion of antibodies of the IgG class is observed in the secondary response, we assume that part of the concentrations of each clonal B-cell, which secretes antibodies of the IgG class, is preserved as immune memory cells every time concentrations increase by some constant number. Further, we assume that the apoptosis rate of the immune memory cells is 0 when they are produced and are not activated in the primary response. In the secondary response, we assume that immune memory cells are activated when the number of antigens exceeds a threshold value and the activated memory cells have a finite apoptosis rate but different response properties to antigens from normal B-cells. The differences are expressed by maturation and proliferation functions.

We study a model with features 1, 2, 3, and 4 that is described by an ordinary differential equation system. We call it model 1. With this model, we can realize affinity maturation (feature 5) when the number of antigens is in a certain range. However, the sum of the concentrations of antibodies produced in the secondary response is only several times as many as that produced in the primary response. That is, the mass secretion of antibodies in the secondary response (feature 6) is not realized.

Real systems require time for B-cells to recognize antigens when they invade the system. A time delay exists for the B-cells to recognize the antigens. Taking this time delay into account, we study a modified model, that is now described by a delay-differential equation system and call it model 2. Now we can realize both the features of affinity maturation and mass secretion of antibodies in the secondary response. Therefore, we have clarified that time delay is one of the most important factors to realize feature 6.

Next we explain a model for the realization of immune memory without memory cells. In model 2, the existence of immune memory cells (feature 4) is taken into account. It is very interesting to study whether the concentrations of antibodies that can respond to antigens are retained spontaneously without immune memory cells, even after the primary response is finished. In other words, we are interested in another mechanism for memorizing the invasion by antigens without assuming immune memory cells. For this purpose, we include the existence of anti-idiotypic antibodies in the model and consider the interaction between antibodies and anti-idiotypic antibodies (feature 7).

We also take into account clonal selection (feature 1) and somatic hypermutation (feature 3-2) in a model called model 3. As a result, in model 3 we find that several pairs of antibodies and anti-idiotypic antibodies are excited whose concentrations continue to oscillate even after the primary response is finished, although affinity maturation does not necessarily take place.

Now we summarize the relation between models 1, 2, and 3. In this paper, we have two purposes: one is to construct a model that realizes affinity maturation (feature 5) and the mass secretion of antibodies in the secondary response (feature 6) and the second is to construct a model which realizes immune memory without memory cells. To realize the first purpose, we construct model 1 with features 1 to 4, which realizes only feature 5. To realize feature 6, we add time delays in model 1 and we call it model 2. On the other hand, to realize the second purpose, we adopt a network point of view and construct model 3 with features 1, 3-2 (somatic hypermutation), and 7.

The construction of this paper is as follows. In the next section, we explain the basic model. Models 1, 2, and 3 are studied in Sections 3, 4, and 5, respectively. We give summary and discussions in Section 6.

2. **Basic model.** As a basic model, we use the second generation immune network model introduced by Varela et al. [11] The main constituents of the Varela model are B-cells, T-cells, and free antibodies produced by the B-cells. The role of the T-cells is taken into account through interaction between the B-cells and antibodies.

Let us distinguish idiotypes by index i. Let us call B-cells with ith idiotype clone i and denote their concentration as b_i and the concentration of free antibodies produced by B-cells as f_i. The sensitivity of the network for the ith idiotype is defined as

$$\sigma_i = \sum_{j=1}^{N} m_{ij} f_j, \ (m_{ii} = 0), \tag{1}$$

where N is the number of idiotypes. The term m_{ij} is called the affinity, which represents the strength of the B-cells (and T-cells) with the ith idiotype to detect antibodies with the jth idiotype. This is a general setting for the immune network model. In this paper, we do not adopt a network point of view. Thus, instead of (1), we define σ_i as

$$\sigma_i = m_{iA} A. \tag{2}$$

Here, A is the concentration of the antigen that invades the system, and m_{iA} is the strength of clone i that detects the antigen.

The numbers of B-cells and antibodies change in time for the following reasons. The free antibodies are removed from the system because they have a natural lifetime and interact with the antigens and neutralize them. On the other hand, they are produced by the B-cells as a result of the maturation of the B-cells. The probability of maturation is assumed to depend on their sensitivity σ. This effect is expressed by maturation function $M(\sigma)$.

In a real immune system, if the number of molecules is huge, the system regards the molecules as a part of itself and ignores them. To reflect this fact, we assume that when σ representing the amount of stimulus is large enough, maturation does not take place, and we set $M(\sigma) = 0$. Around the boundary value of the stimulus that the system can respond to, we assume that $M(\sigma)$ decreases as σ increases. When antigens are almost removed from the system and the immune response ends, the creation of antibodies is suppressed. It is considered that maturation does not take place when the amount of the stimulus becomes small. Thus, $M(\sigma)$ should decrease toward 0 as σ decreases toward 0. Based on these features, $M(\sigma)$ is assumed to have a trapezoid profile:

$$M(\sigma) = \begin{cases} a\sigma & (0 < \sigma < \frac{1}{a}) \\ 1 & (\frac{1}{a} < \sigma < \frac{1}{a} + d) \\ a(r - \sigma) & (\frac{1}{a} + d < \sigma < r) \\ 0 & (\sigma < 0, r < \sigma), \end{cases} \tag{3}$$

where the slope of the trapezoid is a, the length of the smaller size is d, and the longer size is r. This is illustrated in Figure 1. We assume $M(\sigma)$ is a symmetric trapezoid and set $a = 0.01, d = 500$, $r = 700$. Correspondingly B-cells decay at a given rate due to apoptosis, and they proliferate when they maturate. The probability of the proliferation of B-cells is represented by proliferation function

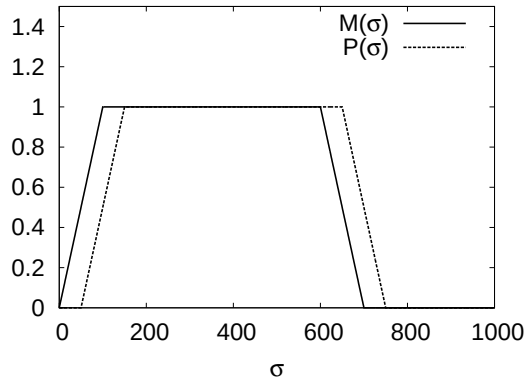

FIGURE 1. Maturation and proliferation functions for normal cells, $M(\sigma)$ and $P(\sigma)$.

$P(\sigma)$. B-cells do not proliferate by stimulus of the self as in maturation. When the stimulus weakens and the immune response ends, the proliferation of B-cells is suppressed by T-cells. Therefore, we assume that $P(\sigma)$ decreases as σ decreases for small σ. We also assume that $P(\sigma)$ has a trapezoid shape. Further, the suppression of proliferation begins before maturation does. Thus, it is reasonable to assume that $P(\sigma)$ is shifted to the right from $M(\sigma)$ (Figure 1):

$$P(\sigma) = \begin{cases} a\sigma & (h < \sigma < h + \frac{1}{a}) \\ 1 & (h + \frac{1}{a} < \sigma < h + \frac{1}{a} + d) \\ a(r - \sigma) & (h + \frac{1}{a} + d < \sigma < h + r) \\ 0 & (\sigma < h, h + r < \sigma), \end{cases} \tag{4}$$

where the length of the shift between $P(\sigma)$ and $M(\sigma)$ is h and we set $h = 50$. In the present model, we assume that $M(\sigma)$ and $P(\sigma)$ have the same symmetric trapezoid shape.

Next the time evolutions of f_i and b_i are given by the following ordinary differential equation system:

$$\frac{df_i}{dt} = -K_1\sigma_i f_i - K_2 f_i + K_3 M(\sigma_i) b_i, \tag{5}$$

$$\frac{db_i}{dt} = -K_4 b_i + K_5 P(\sigma_i) b_i + K_6, \tag{6}$$

where K_1 is the rate of antigen neutralization, K_2 is the rate of annihilation of the antibodies, K_3 is the rate of the creation of antibodies by B-cells, K_4 is the apoptosis rate of the B-cells, and K_5 is the rate of the production of the B-cells. Further, term K_6 is added to incorporate the cells recruited into the active system from the bone marrow. As these parameters, we adopt the following values, which are estimated from real data. Here, we set 1 unit_b as the number of B-cells with an idiotype supplied by the bone marrow in 10 days, and 1 unit_f is the number of antibodies produced by B-cells with an idiotype per day. Therefore, we set $K_6 = 0.1$ [unit_b day^{-1}] and $K_3 = 1.0$ [unit_f $\text{unit}_\text{b}^{-1}$ day^{-1}]. The rate of elimination of the immune complex from the body is about 10^{-3} [day^{-1} $\text{unit}_\text{f}^{-1}$], and then we set $K_1 = 0.001$ [day^{-1} $\text{unit}_\text{f}^{-1}$]. The lifetime of the antibodies and the B-cells is estimated as one week and two days, respectively, and then we set $K_2 = 0.15$ [day^{-1}] and $K_4 = 0.5$

[day^{-1}]. Cell fission takes place once about every 18 hours. Thus, K_5 is the order of 1 [day^{-1}]. In this paper, we set $K_5 = 1.5$ [day^{-1}].

This is our basic model. Based on it, we consider several models using the features listed in Section 1.

In the next section, we study model 1 and the features of clonal selection (feature 1), the change of the apoptosis rate (feature 2), the class switching and somatic hypermutation of clones (feature 3), and immune memory cells (feature 4).

3. **Introduction of clonal selection, change of apoptosis rate, somatic hypermutation and immune memory cells: Model 1.** Here we explain model 1. See Figure 2. We assume the following. Let us consider the situation where one

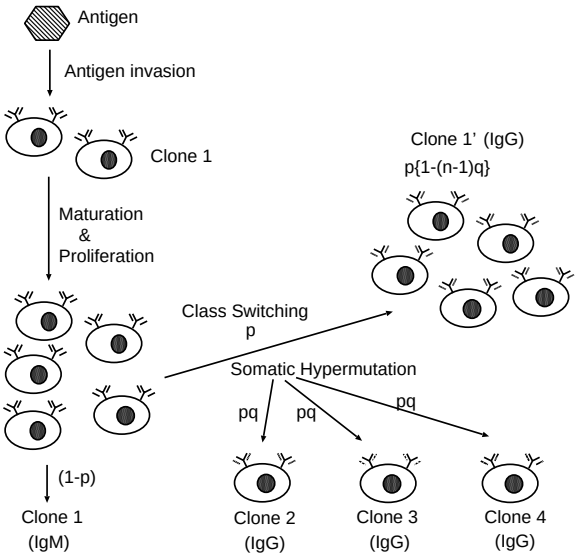

FIGURE 2. Explanation of model 1, in which somatic hypermutation takes place. Symbols in parentheses denote classes of secreting types of immunoglobulins.

kind of antigen invades the system. Let A be the concentration of antigens. By clonal selection, among several B-cells that can detect antigens, the clone that detects antigens most effectively is selected. Let this clone be clone 1, and let m_{1A} be the strength of the affinity for clone 1 to detect antigens. Clone 1 secretes antibodies of the IgM class. We set $m_{A1} = m_{1A} = m_1$ for simplicity, where m_{A1} is the strength of the affinity for antigens to clone 1. Parameters K_1 to K_6 for clone 1 are equal to those in the basic model.

Initially, clone 1 is in the rest state, that is, $b_1 = \dfrac{K_6}{K_4}$ and $f_1 = 0$, the stationary state of equations (5) and (6). During the primary invasion by antigens, when b_1 exceeds 30 [unit$_\mathrm{b}$], we assume that class switching and somatic hypermutation simultaneously take place, which for simplicity, we assume only takes place once. Further, we assume that clone $1'$ is produced by class switching, and clone 2 to clone n is produced by somatic hypermutation. These clones secrete antibodies of the IgG class. Here we consider the case of $n = 4$. The concentrations of clones 1,

$1'$, and 2 to 4 after class switching and somatic hypermutation are assumed as

$$b_1 = (1-p)b_1^0,\ b_{1'} = p\{1-(n-1)q\}b_1^0,\ b_2 = b_3 = b_4 = pqb_1^0,$$

where b_1^0 is the concentration of clone 1 just before class switching. We set $p = 0.7, q = 0.1/3$. That is, class-switched clone $1'$ is 70% of clone 1, and 10% of class-switched clone $1'$ undergoes somatic hypermutation. We assume that clone $i (i = 1', 2, 3, 4)$ has strength of interaction with antigens $m_{iA} = m_{Ai} = m_i$. We put $m_1 = 2, m_{1'} = 2, m_2 = 3, m_3 = 8, m_4 = 1$. For simplicity, we ignore the difference of ability to neutralize antigens between clone 1 (IgM) and clone $1'$ (IgG). Parameters Ks for clones $1'$ and 2 to 4 are identical as those for clone 1, except for K_6, which is set to 0 for clones $1'$ and 2 to 4. In the basic model, K_4 is fixed to 0.5 [day^{-1}]. To include the reduction of the apoptosis rate (feature 2), we assume that for clones 1, $1'$, and 2 to 4, K_4 changes depending on sensitivity σ as

$$\begin{aligned} K_4 &= K_{4l} \text{ for } \sigma_i \geq 50[\text{unit}_\text{f}], \\ &= K_{4s} \text{ for } \sigma_i < 50[\text{unit}_\text{f}], \end{aligned} \tag{7}$$

where $K_{4l} = 0.001$ [day^{-1}] and $K_{4s} = 0.5$ [day^{-1}]. We take $K_{4l} = 0.001$ [day^{-1}] because the apoptosis rate for B-cells is enough to survive during the immune response.

f_i and b_i obey equations (5) and (6) in which σ_i are given as

$$\sigma_i = m_{iA}A = m_iA. \tag{8}$$

Before somatic hypermutation, only $i = 1$ is considered. On the other hand, the equation of A is given by

$$\begin{aligned} \frac{dA}{dt} &= -K_1\sigma_A A, \qquad (9) \\ &\sigma_A = m_{A1}f_1 = m_1 f_1 \text{ (before somatic hypermutation)}, \\ &\sigma_A = \sum_{j=1}^{5} m_{Aj}f_j = \sum_{j=1}^{5} m_j f_j \text{ (after somatic hypermutation)}. \end{aligned}$$

Further, we assume that for clones $1'$ and 2 to 4, every time the concentration of these B-cells increases by 25 [unit$_\text{b}$], a 0.1 [unit$_\text{b}$] number of B-cells is transformed into immune memory cells. We assume that immune memory cells have an infinite lifetime without being activated in the primary response.

When the same type of antigens invade the system again, we assume the following. When the number of antigens exceeds 50 [unit$_\text{f}$], immune memory cells with idiotype i are activated, and they will have the same properties as clone i of the normal B-cells except for maturation and proliferation functions. Here, $i = 1', 2, 3, 4$. In particular, these cells preserve immune memory cells and the value of K_4 changes, as shown in equation (7).

Since the response by the activated memory cells is quicker than the normal B-cells, we assume that maturation and proliferation functions $M(\sigma)$ and $P(\sigma)$ for activated memory cells change more rapidly as functions of σ than those for normal cells. See Figure 3. In this paper, we assume that $M(\sigma)$ and $P(\sigma)$ have the same rectangular shapes:

$$M(\sigma) = \begin{cases} 1 & (0 < \sigma < r) \\ 0 & (\sigma < 0, r < \sigma) \end{cases} \tag{10}$$

$$P(\sigma) = \begin{cases} 1 & (h < \sigma < h + r) \\ 0 & (\sigma < h, h + r < \sigma) \end{cases}, \tag{11}$$

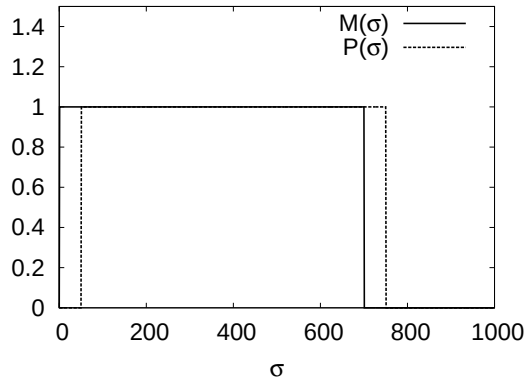

FIGURE 3. Maturation and proliferation functions for activated memory cells, $M(\sigma)$ and $P(\sigma)$.

where width r is 700. $P(\sigma)$ is shifted to the right from $M(\sigma)$ by 50, that is, $h = 50$. Under these assumptions, we perform numerical simulations.

3.1. **Numerical results of model 1.** Before the invasion by antigens, no clones are activated; that is, $f_i = 0$ and $b_i = \dfrac{K_6}{K_4}$. We assume that at time $t = 0$, antigens with concentration A_0 invade the system and when b_1 reaches 30 [unit$_\mathrm{b}$] for the first time, somatic hypermutation takes place. When the immune response ends, clones $1'$ and 2 to 4 disappear since $K_6 = 0$. We assume that the second invasion by the same antigens with concentration A_0' takes place at about 100 [day].

We display an example of the simulations with $A_0 = 50$ [unit$_\mathrm{f}$] and $A_0' = 50$ [unit$_\mathrm{f}$] in Figure 4. Note that in the first and the second invasions by the antigens

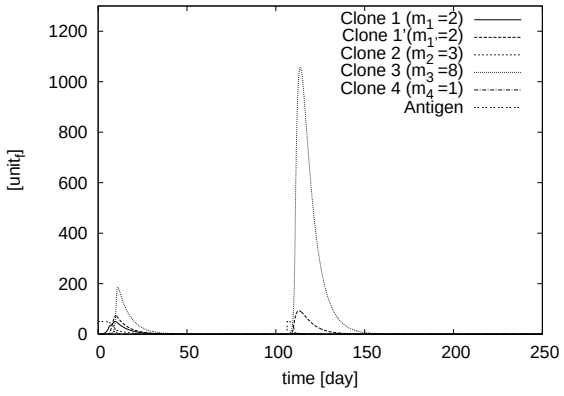

FIGURE 4. Time series of concentrations of antibodies f_i for model 1. $A_0 = 50$ [unit$_\mathrm{f}$], $A_0' = 50$ [unit$_\mathrm{f}$].

clone 3, which has the strongest interaction with the antigens among the clones, responds to the antigens secreting the most antibodies. That is, affinity maturation is realized. The number of immune memory cells after the primary response is 0.2 [unit$_\mathrm{b}$] for clone $1'$, 0 [unit$_\mathrm{b}$] for clone 2, 0.8 [unit$_\mathrm{b}$] for clone 3, and 0 [unit$_\mathrm{b}$] for

clone 4. The immune memory cells for clone 3 are the most. The half-life of the antigens (i.e., the period in which the number of initial antigens is reduced by half), is 9.2 days in the primary response and 3.8 days in the secondary response. Thus, the system responds to antigens more quickly in the secondary response than in the primary response.

However, the sum of concentrations of all antibodies in the secondary response is at most three times as many as in the primary response. The mass secretion of antibodies in the secondary response is not realized in the present model.

Next, we display another example of simulations with $A_0 = 120$ [unit$_\mathrm{f}$] and $A_0' = 50$ [unit$_\mathrm{f}$] in Figure 5. In this case, clone $1'$, which appears by class switching,

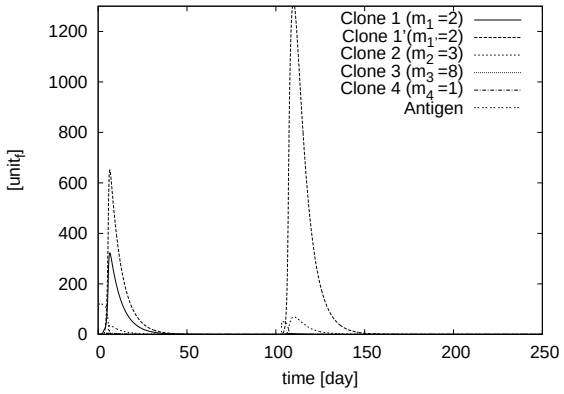

FIGURE 5. Time series of concentrations of antibodies f_i for model 1. $A_0 = 120$ [unit$_\mathrm{f}$], $A_0' = 50$ [unit$_\mathrm{f}$].

responds to the antigen secreting the most antibodies in the first and the second invasions, and affinity maturation does not take place. The following reason is considered. For any clone i with large affinity m_i to antigens, if A_0 is large, $\sigma_i (= m_i A_0)$ becomes very large and then the values of $M(\sigma_i)$ and $P(\sigma_i)$ become nearly 0. Thus, clone i responds very slowly to the antigens or does not respond to them any more. In real immune responses, if the number of antigens is low, B-cells with high affinity respond to the antigens, and if high, any B-cell responds to the antigens regardless of affinity [2]. Therefore, the present result in which affinity maturation takes place for the concentration of antigens, which are neither too small nor excessive, is consistent with this fact. In this simulation, the number of immune memory cells after the primary response is 3.1 [unit$_\mathrm{b}$] for clone $1'$, 0.1 [unit$_\mathrm{b}$] for clone 2, 0 [unit$_\mathrm{b}$] for clone 3, and 0 [unit$_\mathrm{b}$] for clone 4. Clone $1'$ has the most immune memory cells. The half-life of the antigens is 5.5 and 3.7 days in the primary and the secondary responses, respectively. Comparing the half-life for $A_0 = 120$ and $A_0' = 50$ with that for $A_0 = 50$ and $A_0' = 50$, note that half-life in the primary response is reduced by about four days when affinity maturation takes place. The results of the number of memory cells and half-life also indicate that when the number of antigens is large and affinity maturation does not take place, neutralization of antigens by the antibodies secreted by any kind of B-cell is preferential to affinity maturation.

We performed simulations in which apoptosis rate K_4 is not changed throughout immune responses to confirm the necessity of the reduction of the apoptosis rate

(feature 2). The results for $A_0 = 50$ [unit$_\mathrm{f}$] and $A_0' = 50$ [unit$_\mathrm{f}$] are shown in Figure 6. As is clearly seen from Figure 6, insufficient antibodies are produced to

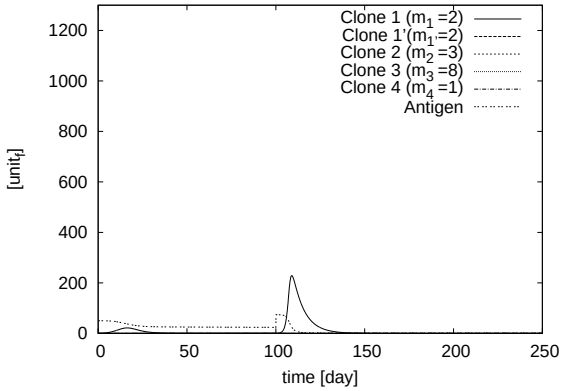

FIGURE 6. Time series of concentrations of antibodies f_i for model 1 in which apoptosis rate K_4 is not reduced but constant. $K_4 = 0.5$, $A_0 = 50$ [unit$_\mathrm{f}$], $A_0' = 50$ [unit$_\mathrm{f}$].

completely neutralize the antigens, so antigens remain after the primary response is finished. In Figure 7, we show the results of $A_0 = 60$ [unit$_\mathrm{f}$] and $A_0' = 50$ [unit$_\mathrm{f}$] without reduction of the apoptosis rate. In this case, antibodies neutralize

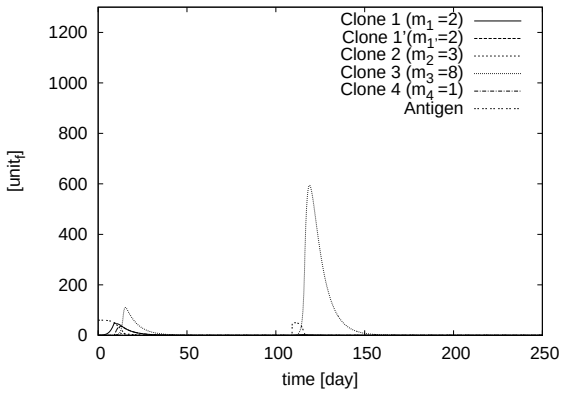

FIGURE 7. Time series of concentrations of antibodies f_i for model 1 in which apoptosis rate K_4 is not reduced but constant. $K_4 = 0.5$, $A_0 = 60$ [unit$_\mathrm{f}$], $A_0' = 50$ [unit$_\mathrm{f}$].

the antigens in the primary response, and affinity maturation is realized. However, compared with the case of $A_0 = 60$ [unit$_\mathrm{f}$] and $A_0' = 50$ [unit$_\mathrm{f}$] with the reduction of the apoptosis rate (feature 2), the total number of antibodies is smaller, and it takes more time to neutralize the antigens without feature 2 than with feature 2. The half-life of the antigens without feature 2 is 12.1 days in the primary response and 5.9 days in the secondary response. On the other hand, the half-life of the antigens with feature 2 is 7.2 days in the primary response and 3.7 days in the secondary response. Further, in Figure 8, we show the results of $A_0 = 120$ [unit$_\mathrm{f}$]

and $A_0' = 50$ [unit$_{\rm f}$] without reduction of the apoptosis rate. In this case, antibodies

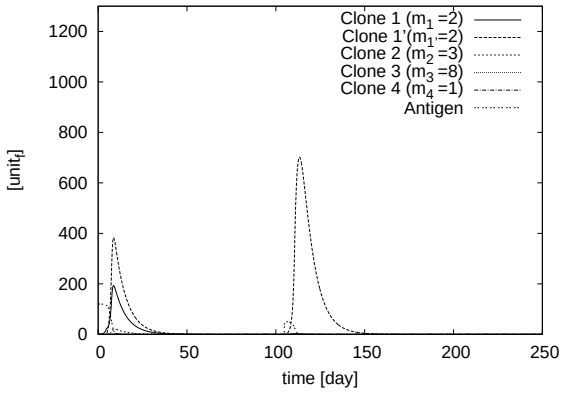

FIGURE 8. Time series of concentrations of antibodies f_i for model 1 in which apoptosis rate K_4 is not reduced but constant. $K_4 = 0.5$, $A_0 = 120$ [unit$_{\rm f}$], $A_0' = 50$ [unit$_{\rm f}$].

neutralize the antigens but affinity maturation does not take place. However the total number of antibodies in Figure 8 is smaller than in Figure 5. The half-life of the antigens without reduction of the apoptosis rate is 7.4 days in the primary response and 5.8 days in the secondary response. On the other hand, the half-life of the antigens with reduction of the apoptosis rate (Figure 5) is 5.5 days in the primary response and 3.7 days in the secondary response. Therefore, it takes longer time to neutralize the antigens without feature 2 than with it.

Now we summarize the results of the reduction of the apoptosis rate (feature 2). Both with and without feature 2, affinity maturation is realized when the number of invading antigens is not so small and not so large, and antigen neutralization by any kind of antibody is preferential to affinity maturation when a large number of antigens invades. However the half-life of antigens is shorter and the concentration of the secreting antibodies is larger with feature 2 than without feature 2. Further, without feature 2, sometimes the system cannot completely neutralize the antigens.

To confirm the necessity of the changes of maturation and proliferation functions for memory cells, we also performed simulations in which maturation and proliferation functions for memory cells were identical as those for normal B-cells. In this case, since the primary responses are the same as in model 1, we focus on secondary responses. The result for $A_0 = 50$ [unit$_{\rm f}$] and $A_0' = 50$ [unit$_{\rm f}$] is shown in Figure 9. In this case, affinity maturation is realized.

In the secondary response, the half-life of antigens is 3.8 days, which is similar to that (3.7 days) obtained in model 1.

However, the total concentration of the secreting antibodies in the secondary response is smaller than in model 1. In Figure 10, we show the results of $A_0 = 120$ [unit$_{\rm f}$] and $A_0' = 50$ [unit$_{\rm f}$] without the changes of $M(\sigma)$ and $P(\sigma)$ for memory cells. In this case, affinity maturation is not realized because a large number of antigens invades in the primary response and antigen neutralization by any kind of antibody is preferential to affinity maturation. This is the same tendency as in model 1. However, a big difference exists between Figures 5 and 10; in Figure 10, the number of antibodies in the secondary response is smaller than in the primary

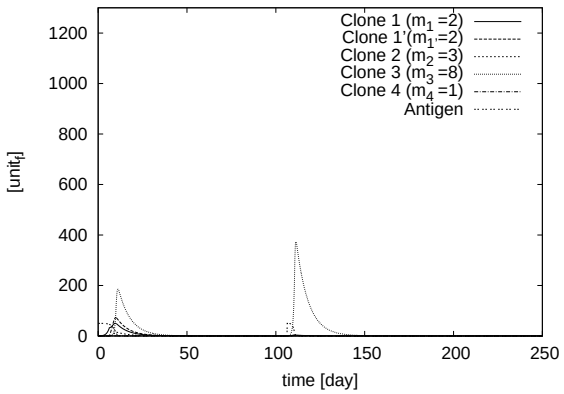

FIGURE 9. Time series of concentrations of antibodies f_i for model 1 in which $M(\sigma)$ and $P(\sigma)$ for memory cells are not changed from those for normal B-cells. $A_0 = 50$ [unit$_\mathrm{f}$], $A_0' = 50$ [unit$_\mathrm{f}$].

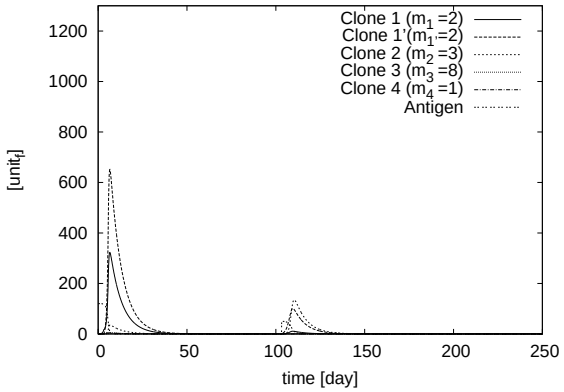

FIGURE 10. Time series of concentrations of antibodies f_i for model 1 in which $M(\sigma)$ and $P(\sigma)$ for memory cells are not changed from those for normal B-cells. $A_0 = 120$ [unit$_\mathrm{f}$], $A_0' = 50$ [unit$_\mathrm{f}$].

response and much smaller than in the secondary response in model 1. Further, half-life in the secondary response is 5.5 days in this case, which is longer than 3.7 days in model 1.

From these results, we find that the change of $M(\sigma)$ and $P(\sigma)$ for memory cells generates a big difference between primary and secondary responses.

In model 1, mass secretion of antibodies in the secondary response (feature 6) was not realized. Next we study model 2 and treat the time delay of response in the next section.

4. **Introduction of time delay: Model 2.** We introduce time delay to reflect the fact that in real immune responses, B-cells require time to recognize antigens. This effect is realized by substituting $\sigma_i^m \equiv m_i A(t-\tau_m)$ for σ_i in $M(\sigma_i)$ of equation (5) and by substituting $\sigma_i^p \equiv m_i A(t-\tau_p)$ for σ_i in $P(\sigma_i)$ of equation (6). The other σ_is and σ_A in equations (5), (6), and (9) are not changed. It is considered that

delay periods are about a few days and we set $\tau_m = 1.3$ [day] and $\tau_p = 2$ [day]. The existence of immune memory cells is taken into account in model 2 as well as in model 1. We display an example of the simulations with $A_0 = 50$ and $A_0' = 50$ in Figure 11. In Figure 12, we display the semi-log plot of the concentrations of antigens, IgM (clone 1), and IgG (clones $1'$ and 2 to 4). As clearly seen from

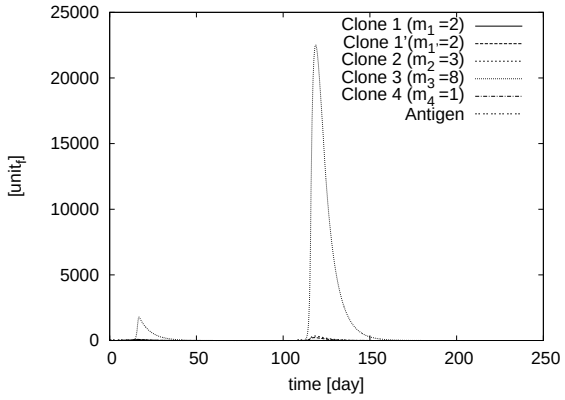

FIGURE 11. Time series of concentrations of antibodies f_i for model 2. $A_0 = 50$ [unit$_{\mathrm{f}}$], $A_0' = 50$ [unit$_{\mathrm{f}}$].

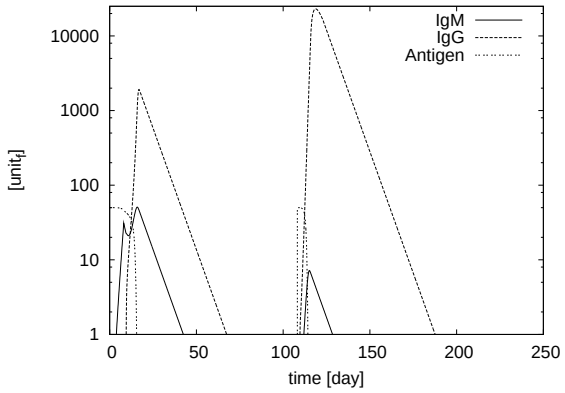

FIGURE 12. Time series of concentrations of antibodies f_i for model 2. $A_0 = 50$ [unit$_{\mathrm{f}}$], $A_0' = 50$ [unit$_{\mathrm{f}}$]. Semi-log plot.

Figure 12, the sum of the concentrations of all antibodies in the secondary response is more than 10 times higher than in the primary response. And in this simulation, the number of immune memory cells after the primary response is 0.2 [unit$_{\mathrm{b}}$] for clone $1'$, 0.2 [unit$_{\mathrm{b}}$] for clone 2, 7.2 [unit$_{\mathrm{b}}$] for clone 3, and 0 [unit$_{\mathrm{b}}$] for clone 4. The introduction of time delay results in the creation of a huge number of antibodies in the secondary response. Thus, mass secretion of antibodies in the secondary response (feature 6) is realized in model 2. Affinity maturation is also realized.

Let us examine the details of the time sequences. In the primary response, somatic hypermutation takes place on the 9.5th day after the first invasion by antigens, and the sum of IgG concentrations reaches its maximum value 1,900 [unit$_{\mathrm{f}}$]

on the 17th day. On the other hand, in the secondary response, IgM concentration becomes maximum on the 7th day after the second invasion by antigens and the sum of IgG concentrations reaches its maximum value 23,000 [unit_f] on the 10.5th day. In real systems, the number of antibodies becomes maximum in about 10 to 14 days in the primary response, and it becomes maximum faster in the secondary response. Thus, the present results about dates, when the number of antibodies becomes maximum, resemble those in real systems. The half-life of antigens is 13.7 days in the primary response and 5 days in the secondary response. Both are longer than in model 1, because it takes time in the present model for the antibodies to increase due to the existence of a time delay for the response.

We also studied model 2 by changing the values of time delays τ^m and τ^p. We found that for $\tau^p \geq \tau^m$, the number of antibodies in the secondary response can be extremely high compared to the primary response. On the other hand, for $\tau^p < \tau^m$, the number of antibodies is similar both in the primary and secondary responses. We investigated antibody concentrations by changing τ^p under condition $\tau^m \geq \tau^p$. Then we found that at $\tau^p \geq 2.6$, the concentration of an antibody goes to infinity in the secondary response. This implies that in the present model antibodies in the secondary response can be any amount if τ^p and τ^m are chosen appropriately, and the criterion on the number of antigens for the mass secretion of antibodies in the secondary response (feature 6) we set is irrelevant to the conclusion. Therefore, we could construct a model in which affinity maturation and the mass secretion of antibodies in the secondary response are satisfied by considering clonal selection, the change of the apoptosis rate, class switching and somatic hypermutation, immune memory cells, and time delays.

5. **Introduction of anti-idiotypic antibody: Model 3.** In the previous sections, we assumed the existence of immune memory cells. In real systems, when one kind of antigen invades the system, not only the antibodies that interact with antigens are produced but also anti-idiotypic antibodies that interact with antibodies are produced. Therefore, theoretically, it is possible that the invasion by antigens provokes the creation of antibodies and anti-idiotypic antibodies, and the antibodies and the anti-idiotypic antibodies stimulate each other and retain their concentrations spontaneously, even after the elimination of the antigens.

To investigate whether this scenario is possible, we introduce an anti-idiotypic clone C_1 that can respond to clone 1 and also clone C_i that can respond to clone i that appears by somatic hypermutation ($i = 2 \sim n$). For simplicity, we do not consider class switching. Since we are mainly interested in the possibility of retaining the concentrations of immune cells produced after the first invasion by an antigen, we assume neither immune memory cells, nor the change of the apoptosis rate, nor introduce time delay. Model 3 is the basic model in Section 2 with clonal selection (feature 1), somatic hypermutation (one part of feature 3), and anti-idiotypic antibodies (feature 7).

Now, we explain model 3 in detail. See Figure 13.

We assume that clones 2 to 5 appear by somatic hypermutation. Clones 1 and C_1 to C_5 have the same parameters, K_1 to K_6, as in the basic model. On the other hand, for clones 2 to 5, parameters K_1 to K_5 are the same as in the basic model, but $K_6 = 0$. Initially, clone 1 and clones C_1 to C_5 are in a rest state. We assume that the strength of interaction $m_{iC_i} = m_{C_i i}$ between clone i and clone C_i is 10 for $i = 1 - 5$. As for the strength of affinity $m_{iA} = m_{Ai} = m_i$,

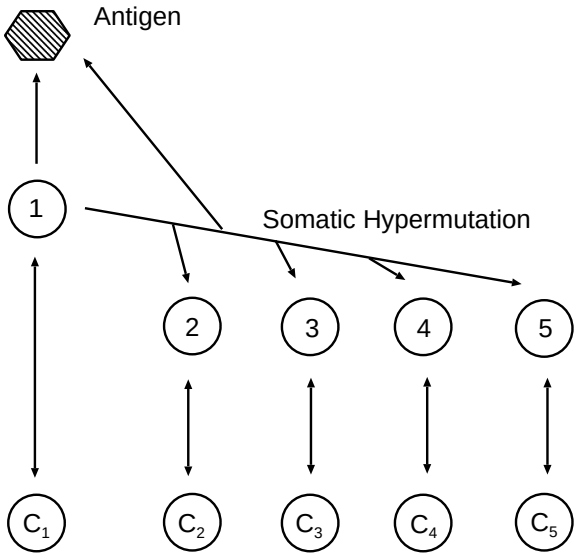

FIGURE 13. Explanation of model 3 in which antibodies and anti-idiotypic antibodies are taken into account.

we set $m_1 = 2, m_2 = 2.5, m_3 = 1, m_4 = 8$, and $m_5 = 10$. Further, we adopt a natural assumption that somatic hypermutations take place at different times successively, because all phases of the oscillations would be identical if they took place simultaneously, as in models 1 and 2. We assume that at the first invasion by antigens, when b_i exceeds 30 [unit$_b$] for the first time, clone 1 undergoes somatic hypermutation and clone 2 appears. We also assume that somatic hypermutation takes place three times, once a day after the first somatic hypermutation. At each somatic hypermutation, 20% of the concentration of clone 1 is transformed into a new clone. That is, we put $b_1 = 0.8b_1^0$ and $b_i = 0.2b_1^0 (i = 2 - 5)$, where b_i^0 is the concentration of clone 1 just before somatic hypermutation. Under these assumptions, we performed numerical simulations.

We display two examples of simulations with $A_0 = 55$ and $A_0' = 55$ in Figures 14 and 15. In these examples, the timing of the secondary invasion by antigens differs. As is seen in Figure 14, after the first invasion, four pairs of clones remain showing oscillatory behavior, but clone 3 with the smallest m disappears. Similar results where clones with smaller m disappear are obtained for other choices of ms, if the values of ms are not too large. That is, the first process of affinity maturation 5-(a) is realized. On the other hand, if the value of A_0 is large, clones with smaller m remain and the others disappear. In the secondary invasion, the remaining clones do not necessarily have larger affinity m. In fact, whether a clone remains depends on the phase of the oscillation of antibody concentration f_i at the moment of the secondary invasion by the antigens. If f_i is small when the antigen invades again, f_{C_i} is large and then $\sigma_i (= m_i A + m_{iC_i} f_{C_i})$ is large, because f_i and f_{C_i} oscillates in the anti-phase. Thus, f_i and b_i tend to 0. For $i \geq 2$, once b_i tends to 0, clone i disappears due to $K_6 = 0$, i.e., no B-cells are supplied from the bone marrow. However, since the oscillation phase of each clone differs, not all clones disappear. Thus, memory reservation is realized. On the other hand, in this model the mass secretion of antibodies in the secondary response was not realized.

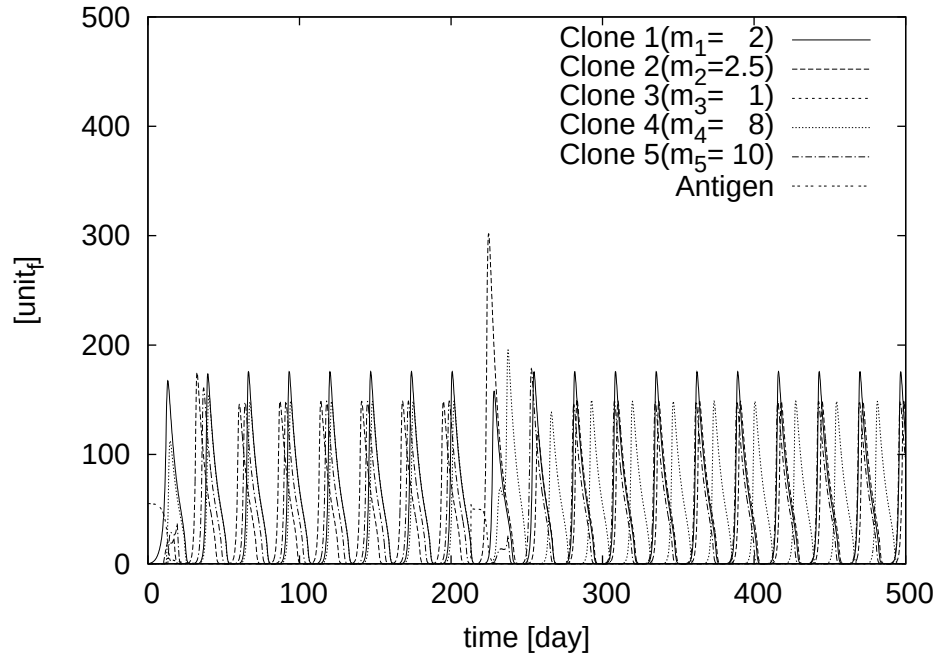

FIGURE 14. Time series of concentrations of antibodies f_i for model 3. $A_0 = 55$ [unit$_\mathrm{f}$], $A_0' = 55$ [unit$_\mathrm{f}$].

6. **Summary and discussions.** We studied the second generation immune network model introduced by Varela et al., taking into account the features of immune response. In models 1 and 2, we tried to realize the following two observed features:

- Affinity maturation. Among the B-cells produced by somatic hypermutation, those with higher affinity to antigens remain and secrete a huge number of antibodies (feature 5).
- The mass secretion of antibodies in the secondary response. The number of antibodies produced by the secondary response is more than 10 times larger than that produced by the primary response (feature 6).

In the first model (i.e., model 1), we took into account clonal selection (feature 1), the change of the apoptosis rate (feature 2), class switching and somatic hypermutation of the clones (feature 3), and the immune memory cells (feature 4). We found that affinity maturation is realized for some range of the concentration of invading antigens. This result is consistent with the fact that if the number of antigens is low, B-cells with high affinity respond to the antigens, and if high, any B-cell responds to the antigens regardless of their affinity. On the other hand, we could not realize the mass secretion of antibodies in the secondary response (feature 6) in model 1 for the following reason. In model 1, when antigens invade the system a second time, the immune memory cells become the activated B-cells and their maturation takes place instantaneously. Thus, the system neutralizes the antigens before the proliferation of B-cells sufficiently takes place. The concentrations of antibodies do not increase very much. In reality, when antigens invade the system, immune cells need time to recognize them. Thus, it is natural to introduce a time delay for the system to detect antigens.

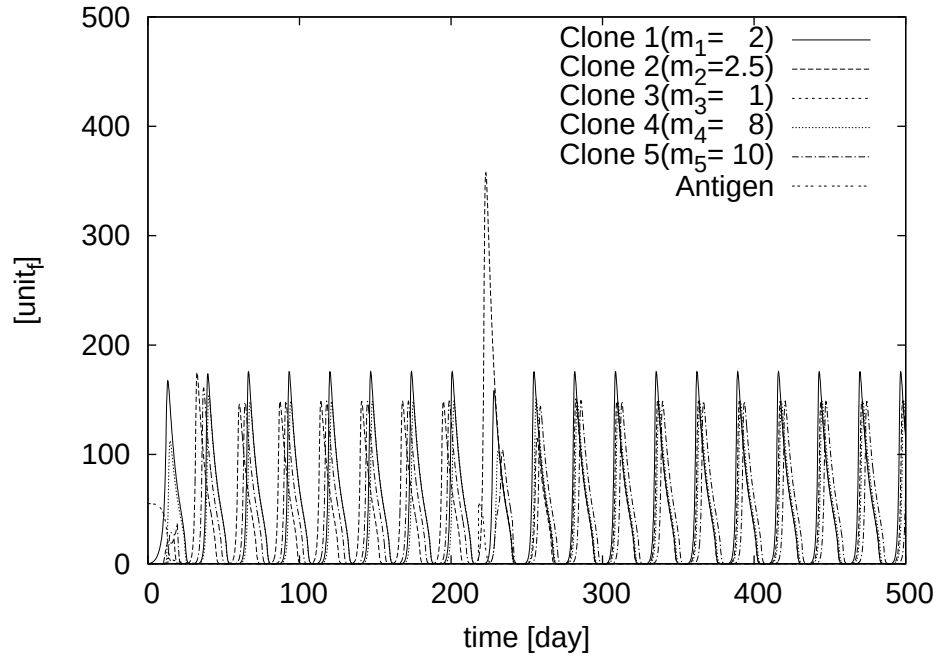

FIGURE 15. Time series of concentrations of antibodies f_i for model 3. $A_0 = 55$ [unit$_\mathrm{f}$], $A_0' = 55$ [unit$_\mathrm{f}$]. Timing of second invasion is different from that in Figure 10.

Therefore, as a more realistic model, we considered model 2 in which delay time τ of the response to the invasion by the antigens is taken into account. We assumed somatic hypermutation of the B-cells, immune memory cells, and the change of the apoptosis rate as well as in model 1. As a result, the response of the system at time t is caused by the number of antigens at time $t - \tau$, and immune memory cells need time to maturate, and then the B-cells have enough time to proliferate. So, the mass secretion of antibodies in the secondary response is realized. Thus, we found that time delay is one of the most important factors to realize the mass secretion of antibodies in the secondary response in the present model. We found another important factor: different maturation and proliferation functions for activated memory cells from normal B-cells. We confirmed that if we adopt the same maturation and proliferation functions for activated memory cells as for normal B-cells, the number of antibodies do not differ between the primary and secondary responses, even if the time delay is included. The assumption that considers different maturation and proliferation functions in normal and activated memory cells is reasonable, because in reality, activated memory cells respond to antigens more quickly than normal cells.

In models 1 and 2, as a mechanism for memorizing the primary invasion by antigens, we assumed the existence of immune memory cells whose maturation and proliferation functions increase rapidly for a small value of sensitivity σ. It is interesting to see if another mechanism can memorize the invasion by antigens without assuming immune memory cells. One such candidate is the interaction between

antibodies and their anti-idiotypic antibodies. The interaction was originally proposed by Jerne to activate an immune system spontaneously without stimulation by antigens. To determine whether the idea works, in model 3 we introduced anti-idiotypic antibodies that respond to antibodies (feature 7). We assumed clonal selection and somatic hypermutation and assumed neither change of the apoptosis rate, nor class switching, nor immune memory cells, and nor a time delay in the immune response. As a result, we found that several pairs of antibodies and anti-idiotypic antibodies with higher affinities stimulate and inhibit each other and that their concentrations oscillate in time and are retained after the primary response is finished. In section 1, we described two processes of affinity maturation: 5-(a) and 5-(b). 5-(a) is at the later stage of the primary immune response where clones with higher affinities are produced, and 5-(b) is in the secondary immune response where clones with higher affinities proliferate selectively by stimulus of antigens. We found that the first process (5-(a)) is realized in model 3. However, we found that although several clones always survive after the secondary invasion by antigens, clones that can survive depend on the timing of the invasion due to the oscillatory nature of the concentration of each clone. Clones with higher affinity do not always survive. Therefore, process 5-(b) is not realized. Further, we found that mass secretion of antibodies in the secondary response is not realized. We surmise that this is because immune memory cells, time delay, and the change of the apoptosis rate are not included in this model. Although model 3 does not satisfy desired features 5 and 6, the mechanism to retain the concentration of immune cells in this model is interesting as the possibility of the memory of the invasion by antigens other than immune memory cells.

Here we make several comments on the values of parameters adopted in this paper.

As for K_1 to K_6, realistic values were chosen. As for other parameters, we tried many choices. In the following, we explain the significance of the following system parameters in the models: reduced apoptosis rate K_{4l}, the threshold of the activation for memory cells, the maturation and proliferation functions, the concentration of invading antigens A_0, A_0', and the affinities ms, and delay times τ^m and τ^p.

As for the apoptosis, if we do not assume the reduction of the apoptosis rate, that is, if we fix K_4, antibodies cannot increase sufficiently and/or antigens are not completely neutralized, as shown in this paper. Therefore, reduction of the apoptosis rate is also an important factor to realize affinity maturation and the mass secretion of antibodies in the secondary response. We assumed that immune memory cells are activated when antigen concentration exceeds a threshold in the secondary response. We did not set the threshold for sensitivity but for antigen concentration to determine its effect by simultaneously activating all memory cells. If we gave the threshold of the activation of the memory cells for σ, affinity maturation would be realized more easily.

Now, let us discuss the relation between the parameters of maturation function $M(\sigma)$ and proliferation function $P(\sigma)$ of normal B-cells and antigen concentration A and affinities ms. For maturation function $M(\sigma)$ and proliferation function $P(\sigma)$, we adopted a symmetric trapezoid shape to study the effect of sensitivity σ because the σ dependences of these functions are simple and easy for identifying such areas as the fully maturated region, the region corresponding to self recognition, and so on. The parameters in $M(\sigma)$ and $P(\sigma)$ are slope a of the trapezoid, length d of its

smaller size, and length h, which is the length of the shift between $P(\sigma)$ and $M(\sigma)$. Roughly speaking, the typical values of antigen concentration A^* and affinity m^* to the antigen are determined by the relation

$$\frac{1}{a} + \frac{d}{2} = m^* A^*. \tag{12}$$

The left-hand side of equation (12) is simply the central point of the interval of sensitivity σ in which $M(\sigma)$ is maximum. This relation is interpreted in terms of affinity maturation. That is, the degree of affinity maturation depends on the number of antigens. The affinity with which B-cells can respond to the antigen is large for a small number of antigens and small for a large number of them. Although we do not know the precise values of each affinity, when parameters a, d, and ms are set to certain values, then the concentration of antigens for which the immune system responds most effectively is determined by the relation (12). For the parameters we chose in this paper, affinity maturation is realized when the number of invading antigens in the primary response A_0 is about 50 [unit$_{\mathrm{f}}$], and antigen neutralization by any kind of antibody is preferential to affinity maturation when the number of invading antigens in the primary response A_0 is about 120 [unit$_{\mathrm{f}}$]. As for a and d, we found that d is a robust parameter, but a must be tuned because when a becomes very small, it takes a long time to neutralize the antigens. For example, if we set $a = 0.005$ instead of $a = 0.01$ with the other parameters fixed in model 2, then it takes more than 1 month to neutralize the antigens. As for h, we assumed that $P(\sigma)$ is shifted to the right from $M(\sigma)$ by h. This seems reasonable, because it is considered that suppression of proliferation begins before maturation does. Value h is set to 50 in the paper. If shift h becomes large (e.g., $h > 75$ in model 2), proliferation ends soon, and it takes time to neutralize the antigen.

In this paper $M(\sigma)$ is assumed to be proportional to σ in the interval $[0, \frac{1}{a}]$. That is, the system responds to antigens even if their concentration is very small. However, this assumption is not necessary. We tried other $M(\sigma)$ such that $M(\sigma) = 0$ in the interval $[0, \sigma_0]$ for some $\sigma_0 > 0$. If σ_0 is not too large (for example, about 50 in model 2), it does not take much time to neutralize antigens.

As for time delays τ^m and τ^p, we found that the condition to realize feature 6 is $\tau^p \geq \tau^m$ for an appropriate value of τ^p (~ 2).

We also investigated the models by changing the parameters of maturation and proliferation functions in the activated memory cells in model 2. As a result, we found that activated memory cells can produce a lot of antibodies by making slope a of the left edge of the trapezoid steeper. We also found that mass secretion of antibodies in the secondary response (feature 6) is realized when we adopt similar maturation and proliferation functions in both normal and activated memory cells and increase the height of those functions in the activated memory cells more than in the normal cells.

From these investigations, we discovered that to realize desired features such parameters as K_{4l} and a have to be set to appropriate values. Once such values are set, there is robustness in the values of parameters; slight changes of the values of parameters do not change the qualitative behavior of the system.

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