Artificial Immune Memory Formed by Dynamics of Antibody Networks

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***Abstract*—Immune memory can be regarded as an equilibrium state of immune network system with nonlinear dynamical behavior. The rapid response of immune systems to the secondary antigen is owing to the stable structure of memory state forming by a closed idiotypic immune network. Internal image of an antigen is defined while memory state is formed via such network. Antibody chain based on tree structure is proposed which explains how the memory state is formed in the immune network. We also propose a network dynamics model of idiotypic immune network based on cross-reactive correlation matrix to explain the artificial immune memory.**

Keywords-immune network; immune memory; antibody chain; internal image

I. INTRODUCTION

It is well known that the injection of a given amount of some antigen into a mammal's body will stimulate the production of antibodies directed against that antigen, if the antibody is with a high affinity for that antigen [1]. The immune system of the animal has thus learned to produce high quantities of the antibody directed against that very antigen, which is called vaccinated. Therefore, the biological immune system can learn itself and memorize the characteristics of invading antigens.

Memory in a physical system refers to the ability of the system to preserve information of its environment at some previous time. Memory mechanism of biological immune systems is still a mystery. From computational biology viewpoints, memory mechanisms in immune systems can be regarded some physical systems. There are basically two theories to explain the immune memory [1]. The first one is the theory of memory cells, which are generated after the B-cell proliferations. These cells will remain for an immune memory in the human body until the death of the individual. On the other hand, immune memory mechanisms can be explained through Jerne's immune network theory [2] by investigation them as complex adaptive systems. Immune memory belongs to a class of sparse and distributed associative memory [3]. The concept of artificial immune memory is the following. Complex Adaptive Systems (CASs) have to deal with constant change of environment. Based on memory mechanisms, CASs can respond immediately to the same or similar environment. Here, we are adopting immune memory mechanisms in CASs. According to Fernandez et al. [4], it is an ongoing research topic to exploit relationship between immune memory and internal image. The internal image can be regarded as a portion of immune memory of antigen [5].

Immune memory mechanisms can also be modeled from immune network theory [2][6]. Jerne also proposed that once the foreign antigen is removed, the immune system would restore some information of such antigen by some memory mechanism. Debates of whether memory cell theory or associative property is true have been discussed. The immune memory can be explained by the following network viewpoint. Assuming that an antibody Ab_1 is produced by the stimulating antigen. Then the production of Ab_1 is increased in the presence of another type of antibody Ab_2. The population of T-helper cell TH_1 specified by Ab_1 is also increased. In this way, Ab_2 can be considered as some "internal image" of this antigen. This image will be remained after the antigen is removed. The interactions can be a long chain with length greater than 2.

Many idiotypic network models focus on the interactions between antibodies and antigens. The network interactions provide dynamical memory mechanism, by keeping the concentrations of antibodies, in particular those internal images [7]. However, how immune systems recalls similar antigen is still unknown. From computations viewpoints, it is worthwhile considering state transition, which represents the network dynamics of such unfamiliar pathogen. If this antigenic state converges, then immune systems gain some control and activate some (associative) recall process.

The major goal of this paper is to study the associative memory based on statistical immunodynamics inspired by [8]. This network structure will proved to be major contributions to the immune memory mechanism. The related research can be referred to Abbattista et al. [9]. The arrangement of this paper is as follows. In Section II, some preliminary knowledge of immune memory is introduced. In Section III, dynamical behavior of idiotypic immune network is described. Simulation analysis of immune network memory is also given.

II. BACKGROUND KNOWLEDGE

A. Immune Responses

While a specific antigen invades human body, the immune system will respond by producing some antibodies, which can eliminate this invaded antigen. It has three phases, namely, first immune response, second immune response and

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cross-reactive response. For the first invaded antigen, the immune systems will massively produce the antibody, which binds to Ag. Therefore the amount of antigen will be reduced tremendously after the peaking and tended to some constant value. We can say that immune systems are turned to the memory state. For the second phase, the same antigen invades and the antibody will take much less time than that of first immune response to reach the population peak. Therefore this antigen cannot proliferate tremendously. This is the reason why we don't get sick at this stage. On the other hand, if a similar antigen invades, then the same antibody will also proliferate soon and eliminate population. We will analyze the network transitions between each phase. Once the first immune response has activated, we are particularly interested in the third stage, namely the associate memory mechanism for the immune response to similar antigens.

B. *Idiotypic Immune Network*

Idiotypic network theory implies that immune systems will mimic the presence of the antigen even after it is destroyed [3]. This way, the antibody and receptor of the lymphocytes can recognize each other. The epitope of antibody molecule is called an "idiotope". An epitope of antigen Ag is recognized by the antibody molecule Ab_1 and by the receptor molecule on the lymphocyte of LU_1. The antibody Ab_1 and the receptor of LU_1 have the idiotope, which is recognized by antibody Ab_2 and the receptor on the lymphocyte of LU_2. Continuously, we reach an antibody Ab_N, while the antibody Ab_1 and the receptor on the lymphocyte of LU_1 also recognize idiotopes on antibody Ab_N. Ab_N constitutes an internal image of the antigen Ag (see Figure 1). The idiotypic network theory has been proposed as a central aspect of the associative properties of immune memory [3][10]. However, computational aspect of this paradigm needs to be further explored.

For simplicity, it is reasonable that we consider antibodies rather than LUs of IINs from both network dynamics and population dynamics perspectives. Some immune network models can be contributed to this antibody dynamics such as [11]. Such antigen-antibody interactions can be a long sequence structure, namely, an antibody chain, which is formerly defined as follows.

Definition 1. For an idiotypic immune network $\left\langle \{LU_i\}_{i=1}^{N}, M \right\rangle$, an antibody chain $AC = \{Ab_1, Ab_2, ...Ab_N\}$ is defined as follows.

- $Ab_i \in LU_i$, for all $i = 1,2,\ldots N$.
- Ab_i can recognize Ab_{i+1}, namely, $Ab_i \rightarrow Ab_{i+1}$, for all $i = 1,2,\ldots N-1$.
- $Ab_N \rightarrow Ab_1$.

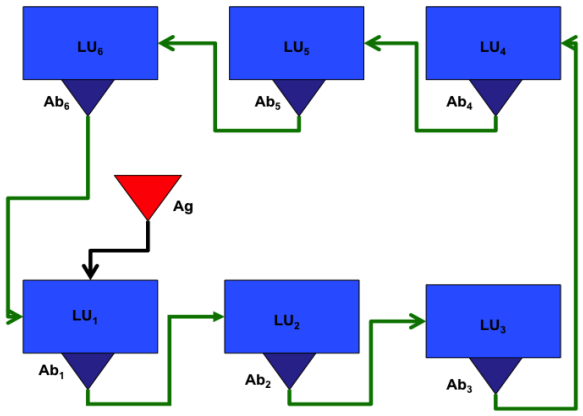

Figure 1. Schematic diagram of a closed idiotypic immune network.

The final element of the antibody chain Ab_N interests us. It can stimulate the antibody Ab_1 even Ag is eliminated. In this way, population of Ab_1 will be stable in small amount. In particular, its role in immune memory can be analyzed by network dynamics.

C. *Immune Memory*

An immune system will react rapidly to the same or similar antigens which had invaded the same human body before. This phenomenon implies that immune system can "memorize" associatively the formations of previously invaded antigens. An evidence for immune memory is that it is strongly affected by the populations of soluble antibodies in the blood. Therefore, some variable quantified the immune memory can be correlated to the amount of antibodies. In fact, this is a major inspiration for this research, but different angle from computational biology.

The immune memory mechanism is not fully understood so far; according to Smith et al. [3], at the end of an immune response, when the antigen is cleared, the B cell population decreases, leaving a persistent sub-population of memory cells. The newer view of memory cells is that they are not intrinsically longer-lived than virgin cells, but that memory depends instead on the persistence of antigen [12]. However, some researches, especially those related to immune network theory, imply the immune memory is formed by a cyclic idiotypic network rather than specific memory cell [11]. Immunologists have discovered the vaccination mechanism for human immune systems for a long time. This takes advantages of so-called the associative memory of immune systems. The associative memory mechanism can be explained as follows [13]. If the secondary antigen is "similar" to the primary one, the set of antibodies activated by this antigen will overlap with the one activated by the primary antigen. The similarity between antigens can be defined by affinity of molecules. This memory is able to be store and recall patterns when immune systems need. Associative recall is a general phenomenon of immune memory [3].

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III. MAIN RESULTS

A. Tree Structure of Idiotypic Immune Network

Perelson [14] suggested a tree structure with varied levels for idiotypic immune networks. Ag is the root note. Level 1 is the collection of all antibodies which are complementarily matching with Ag. Level 2 is the collection of all antibodies which are complementarily with those at level 1. This way, we may construct a tree structure for antibody chain (see Figure 2). We also define the directed edge $\rightarrow$ from antibody at higher level to the one at lower level. Based on this structure $T = \{A_g, AC, \rightarrow\}$, all possible internal images for a given antigen can be searched within some antibody populations. We also observe the existence of internal image can be guaranteed if and only if second level is inward and outward according to some affinity relation $\rightarrow$. The following algorithm is the detailed description for the tree constructions for antibody chains.

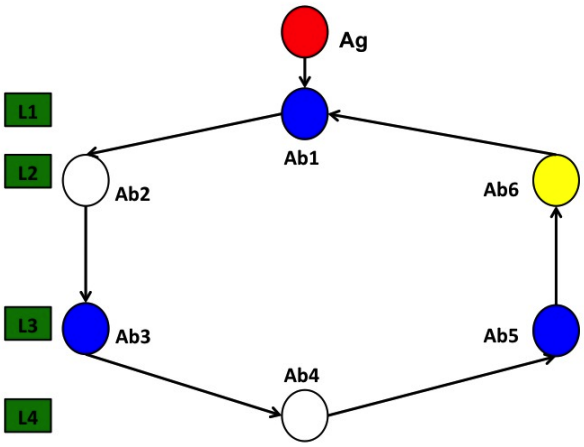

Figure 2. Tree Structure for an Antibody Chain (N=6).

Proposition 1. The tree structure of idiotypic immune network $T = \{A_g, AC, \rightarrow_\varepsilon\}$ satisfies the following properties: (1) Each antibody in AC can be located at most one level; (2) The edge can only exist between adjacent level; (3) If AC is closed, then its length is even; (4) If AC is closed, then number of level of T is equal to $N/2+1$. (5) Internal image must locate at the level 2. (6) The internal image exists if and only if $Level(AC) = N/2 + 1$.

This is obvious by definition of tree structure. If $Ab_i \in AC$ is located to Level i of T and $Ab_1 \rightarrow Ab_i$. Then Ab_i has to be located to Level 2. If $Ab_i \rightarrow Ab_j$, then Ab_j must be located at level $i+1$. If the length of the left AC is equal to m, then the number of level is also m by the closeness of AC. The right AC is $N-m$, which is also even. However, m and $N-m$ must have difference equal to 2 by the closeness of AC and the fact that Ab_N must be located at level 2. Therefore the length of AC is equal to m+(m-2)=2m-2 , which must be even. According to (3), N must be even. Ab_N and Ab_2 are at the level 2; Ab_{N-1} and Ab_3 are at the level 3; continuing in this way, $Ab_{N/2+1}$ is the unique antibody located the level $N/2+1$. If $Level(AC) < N/2+1$ then $length(AC_j) < N/2+1$. Therefore, $length(AC) \le N/2 + N/2 - 1 = N-1$, which is a contradiction. Therefore $Level(AC) = N/2$.

If an internal image is highly complementary match with Ab_1, then it can be regarded as an reasonable stimulus for Ab_1 even Ag is eliminated. Ab_1 plays a pivotal role for internal image. If the ε of the ε-complementary match between Ab_1 and Ag is higher, then the internal image and Ag are more similar. From mathematical viewpoint, it is still a question that Ag and its internal image may be of low similarity.

The network-layered structure for CIINs provide some evidences that the population dynamics cannot provide, such as recall process of immune memory. Every closed antibody chain $T(AC)$ can be represented as a k-level tree structure, where $k = N/2+1$. Furthermore, internal image Ab_N must locate at level 2.

Theorem 1. For idiotypic immune network $\rightarrow$ as the relation of "being recognized", the internal image of an antigen exists if and only if

- The tree structure of AC one antibody path P_1 with length $N/2+1$ and the other one $N/2-1$, for some even integer N.
- $P_1(end) \rightarrow P_2(1)$.
- $P_2(end)$ is an internal image.

B. Network Dynamics based on Autocorrelation Matrix

From immunology viewpoints, a better antibody chain has the following two aspects: the first is that it will respond fast to the second-time antigenic invasion; the second one is that it will act adaptively to the similar antigenic invasion. The question is how to build some mathematical model to connect the concepts of tree structure with the dynamics of immune responses such as immune memory and recall. Most importantly, response to a similar antigen rather than second. This is related to the associative memory mechanism [15] [16].

The attractor networks proposed by Morita [17] and defined by tree structures can generate a dynamics. It is a transition of states represented by nodes of antigens. A network dynamics F can be defined on states of network S as follows. An antigen will induce an antibody chain, which will generate a network dynamics for interpreting immune

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memory formation and recall process. Moreover, this attractor network dynamics can interpret the associative property of immune memory while population dynamics cannot. Let F be a function defined on state space S. For a given state $S(t)$ at time t, the network dynamics can be defined as a transition of state S from time t to time $t+1$, namely, S(t+1)=F(S(t)). According to the basic concept of dynamical systems, we may define an attractor μ of the network dynamics F, if there exists a state S such that $F^n \to u$, as $n \to \infty$, where t is a temporal variable and S is the state variable. Now we define the associative memory based on stability analysis of equilibrium points (states) of such network dynamics.

Definition 2 (Associative Memory) For an immune network $\{AC, F\}$, if there exists a set of p antigenic patterns, $\{\mu^1, \mu^2, \cdots, \mu^p\}$ which are attractors of the network dynamics F, then we say the immune network can memorize p patterns of antigens associatively.

The stable states of immune networks can guarantee that if an antigenic format fallen into the basin of attraction of μ_k, then by memory recalling process, this antigen can invoke the same antibody proliferation immediately. The following question arises: what is the mathematical model of network dynamics F, if an antigen-antibody chain (Ag, AC) is given. We will first concentrate on some binary-valued function F to illustrate the dynamics of immune memory, rather than on discussing some complex and high-dimensional dynamical systems.

This mechanism is named autocorrelation matrix memory (ACMM) inspired by [17]. For an antigen Ag, there exists an antibody chain AC such that it is a CIIN. This AC will induce a autocorrelation matrix W as

$$W = \frac{1}{N-1}\sum_{i=1}^{N-1} Ab_i^T * Ab_{i+1} \qquad (1)$$

Given a pattern S such as an antigen as an initial state $X(0)$, the network dynamics of W is given by $X(t+1) = sgn(W \cdot X(t))$, where $sgn(x_i(t)) = 1$, if $x_i(t) > 0$; $sgn(x_i(t)) = -1$, if $x_i(t) < 0$. If $X(t) \to S$, as $t \to \infty$, then we call S a memory format (MF). Therefore, an antigen activates an antibody chain whose network dynamics can generate antigenic memory format.

C. Associative Memory formed by the Immune Systems

How immune memory pertains associativity is still a mystery for scientists even for the advances and success of vaccinations for more than 300 years. However, we propose a network dynamics model to describe this mechanism from computational immunology viewpoints. An immune network $\langle \{LU_i\}_{i=1}^N, M \rangle$ is equipped with with associative memory, if for any $\varepsilon > 0$, there exists $\alpha > 0$, such that whenever a new antigen Ag' with $d(Ag, Ag') < \alpha$ implies that $Ag' \to_\varepsilon Ab_1$.

If a new antigen Ag', which is very similar to the previous invaded antigen Ag, invades human body, then the antibody Ab_1 which binds Ag can also bind Ag' and invokes another immune response.

For an antigen Ag activating the antibody chain AC, the network dynamics defined on pattern space for memory formation and recall with $s(t+1) = W \cdot s(t)$ must induce attractors, where W is some state transition matrix. This means, starting from an initial configuration s which is sufficiently closed to (or overlapped with) one Ab_i, the system will flow to a fixed point of the dynamics, which is either the pattern itself or the configuration with high overlap with that pattern.

Memory Recall Process based on Network Dynamics

Once the same or "similar" antigen to Ag invades immune systems again, the memory recall process of the immune systems will be activated by comparing the memory format generated and stored in the previous antigenic invasion of Ag. From system dynamics, we can define such similar antigens by basin of attraction. Suppose the same antigen Ag invades the immune systems again, then network dynamics F, namely, $F^n(Ag)$ will immediately converges to memory format of Ag, say $M(Ag)$. On the other hand, if some similar antigen Ag' invades, the network dynamics $F^k(Ag')$ converges to the same $M(Ag)$ if $Ag' \in BA(Ag)$. Therefore, basin of attraction of Ag is the major criterion that Ag' will activate the Ab_1 and the same antibody chain.

The third question we are interested here is the following. For a similar antigen Ag', whether the original antibody chain AC activated by Ag can also produce immune response effectively to this mutated Ag' ? In this way, the immune network reflects a decent associative memory. If the internal image Ab_N is similar to Ag, then it is also similar to Ag'. If for initial condition $X(0)$, we have the following network dynamics of recall process inspired by [16] and [18].

$$X(i) = sgn\left(\frac{1}{N-1}\sum_{i=1}^{N-1}(Ab_i^T X(i-1))Ab_{i+1}\right) \qquad (2)$$

Therefore, if $X(0) = Ag$ and $\{Ab_k\}_k$ is a set of antibodies with sufficiently high dimension , then Ab_1 is recall at $t = 1$, as $X(1) = Ab_1$. In the same way, $X(2) = Ab_2$, $X(3) = Ab_3$, or the stored antibody sequence of Ag is recalled. Once the same antigen Ag invades, $Ab_1, Ab_2, \cdots, Ab_N$ are activated successively. On the other hand, If a similar antigen Ag' invades, then the recall process can be computed as follows.

$$X(1) = sgn\left(\frac{1}{N}\sum_{i=0}^{N-1}(Ab_i^T Ag')Ab_{i+1}\right) \approx (Ag \cdot Ag')Ab_1$$

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$$= \alpha_1 \cdot Ab_1 \quad (3)$$

where $\alpha < 1$ is a small positive number. In the similar fashion, $X(k) = \alpha_k \cdot Ab_k$. Therefore this similar antigen Ag' will activate antibodies $\alpha_1 Ab_1, \alpha_2 Ab_2, \cdots, \alpha_N Ab_N$.

Based on (3), there exists $\lambda > 0$ such that $d(Ag, Ag') < \lambda$ implies that $d(F^k(Ag'), Ab_k) < \lambda_k$. If $\lambda_K \approx 1/k$, then this network dynamics can guarantee that $F^k(Ag')$ is approximately equal to internal image Ab_N. Therefore, CIINs, from computation viewpoints, is stable for memory recall. However, we are interested in the critical value for λ such that network dynamics will deviate the antibody chain.

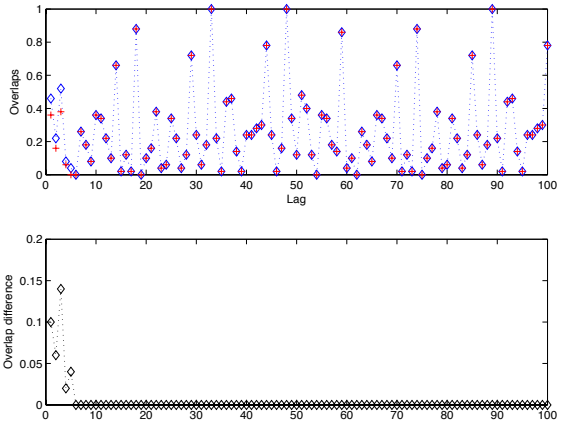

Figure 3. Stable Network Dynamics for Immune Memory Recall.

Figure 3 is a simulation that a particular network dynamics activated by a specific antibody chain could recall a mutated antigen completely. The parameters are set as follows. N=100, the antibody population is 20,000. The length of (randomly generated) antibody chain is N=4.

IV. DISCUSSIONS

Overlapping difference function shown in Figure 3 is stable. However, it is very often that such function is unstable for varied parameter values, for example, $\varepsilon < 0.6$. In fact, simulations have shown different unstable behaviors, from simple to complex ones. Anyway, Figure 3 shows that the mutated antigen Ag' can invoke the exact memory for the original antigen Ag; and antibody Ab_1 can eliminate this Ag'. Another issue is the existence of CIINs for invaded antigen Ag. If the affinity threshold $\varepsilon \geq 0.6$, the simulations have also shown that it is generally difficult to form CIINs.

V. CONCLUSION AND FUTURE WORK

We proposed an immune memory mechanism, based on the closed idiotypic immune network. The latter is analyzed by some tree structure. The formation of immune memory can be deduced by close loop of the cell's interactions, in particular, by antibody dynamics such as internal image recognition. Network dynamics which describes the immune memory formation and recall process is modeled based on cross-reactive correlation matrix of antibody chains. This mechanism is associative by analyzing the state transitions of mutated antigens.

There are some issues for future research. As mentioned in Section VI, observation leads to the research of adopting weak connection principle to CIINs forming. This is inspired by the small-world network structure; it is reasonable that antibody-antigen biding should be based on high affinity threshold while lower affinity threshold for the antibody-antibody biding.

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