Associative Memory based on Network Dynamics

Chung-Ming Ou
Department of Information Management
Kainan University
Luchu,33857
Email: cou077@mail.knu.edu.tw

***Abstract*—Immune memory of antigens are formed as limit behavior of cyclic idiotypic immune networks equipped with antibody dynamics. Immune memory mechanism is studied by combining network structure and dynamical systems. Moreover, associative memory can be explored by network dynamics determined by affinity index of antibody chain. Antibody chains with larger affinity indexes generate associative immune memory.**

***Keywords*—idiotypic immune network; antibody dynamics; antibody chain; associative memory; Lyapunov exponent**

I. Introduction

Dynamical systems for studying the immune response have been extensively treated by Nowak and May [15]. One theory for immune memory is on the basis of immune network theory proposed by Jerne [12]. The memory of each previously invaded antigen is distributed through the immune network. Short-living memory cells, which form some immune networks, is a reasonable model for immune memory. Immune memory mechanism can be explained through Jerne's immune network theory by regarding immune systems as complex adaptive systems [12]. On the other hand, rather than a centralized architecture, immune memory mechanism have been extensively analyzed in terms of sparse and distributed associative memory [18][5][2].

Based on the above considerations, we are looking forward to building a mathematical model of immune memory mechanism, which can describe the paradigm of short-lived memory cells with network dynamics. We will follow the immune network theory to discuss the mechanism of immune memory.

Many researches have been proceeded according to the immune network theory proposed by Jerne [11]. Perelson has proposed the shape space analysis for the immune network theory [17]. Carneiro et al. have discussed immune networks based on cooperations of B- and T-cells [7]. The process of antibody concentration variations can describe dynamics of idiotypic immune network. It is an ongoing research topic to exploit relationship between immune memory and internal image that can be regarded as a portion of memory format of antigen [10][6]. In particular, some closed loop network structure, namely cyclic idiotypic immune network (CIIN), can emulate the existence of such antigen even its clones are completely eliminated.

We simplify immune networks to some network structure, namely, antibody chains. We then analyze the network structure of antibody chains. This structure leads us to implement the algorithm of antibody chain forming. One advantage of antibody chains is its simplicity to define the network dynamics.

978-1-5090-5795-5/17/$31.00 © 2017 IEEE

The major goal of this research is to explore the immune memory mechanism based on antibody dynamics. There are two aspects for the latter: (1) simplified architecture of idiotypic immune network proposed by [19]; (2) associative memory based on statistical immunodynamics inspired by [14][3][1]. This network structure of (1) and (2) is adapted to the immune memory mechanism; one contribution of such approach is to establish the associativity of immune memory inspired by an attractor-like dynamics.

Our idea is the following. First the traditional idiotypic immune networks are too complicated to define network dynamics. Therefore we simplify such IINs to some network structure, namely, antibody chains. We then analyze the network structure of antibody chains. Such structure leads us to implement the algorithm of antibody chain forming. One advantage of antibody chains is its simplicity to define the network dynamics rather than population dynamics. Namely, the state transitions generated by network dynamics is more suitable for population dynamics from immune memory viewpoints.

Another challenge for network dynamics of antibody chain is as follows. What is the reasonable dynamics represented by those antibody which leads to the formations of antigenic memory? One aspect is the dynamics of cross-reactive immune response, namely, the mechanism of associative memory. Morita has proposed non-monotonic dynamics for associative memory [14]. It introduced the autocorrelation matrix for such dynamics. We are inspired by such statistical dynamics for antibody chain, namely, discrete chaotic dynamical system defined by logistic function. In details, the memory format of the corresponding antigen can be defined as limiting behavior of such network dynamics.

II. Research Background

A. Immune Memory

Immune system will react rapidly to the same or similar, even mutated antigens which had invaded the same human body before. This phenomenon implies that immune system can "memorize" associatively the formations of previously invaded antigens. One major evidence for such immune memory mechanism is that it is strongly affected by the concentration of soluble antibodies in the blood. Therefore some variables related to the immune memory might be correlated to the antibody concentration from the aspect of computational biology.

Immune memory mechanism is not fully understood so far. The newer viewpoint of memory cells is that they are not lived longer than virgin cells; their life cycles depend on the persistence of antigens [13]. Besides memory cell mechanism, researches related to immune network theory imply the immune memory mechanism is formed by cyclic idiotypic immune networks (CIINs) than specific memory cells [19]. It is important to explain how memory recalls are activated for similar antigenic invasions. Therefore, for such associative memory mechanism of immune systems, it is worth of considering the immune network theory.

In particular, its role in immune memory can be analyzed by network dynamics. We can mathematically describe the formation of a immune memory, and the recall process of such memory. The idiotypic network theory has been proposed as a central aspect of the associative properties of immune memory [18][9].

B. Antibody Chain Generated by Idiotypic Immune Network

Idiotypic network theory implies that immune systems will emulate the presence of antigens even after they are eliminated [18].

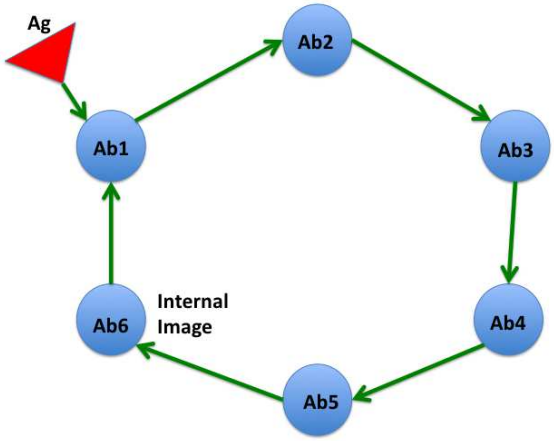

Fig. 1. Antibody Chain

IINs can be represented by antibody Ab_i (Figure 1). The advantage of this simplified network, namely, *antibody chain*, is the following. The immune response, in particular, immune memory, can be exploited by state transitions determined by such simplified networks. There are two stable states for idiotypic immune network; for the first state, the antibody Ab_1 is not produced. For the second stable state, Ab_1 is produced and antigen may or may not be completely eliminated [16]. The memory of such antigen is thus established. Network models of immune responses described by ordinary differential equations can be referred to [21][8][20].

Certain immune network models can be contributed to this antibody dynamics such as the one proposed in [19]. Such antigen-antibody interactions can be a long sequence, namely, an antibody chain, which is defined as follows. For an idiotypic immune network $\langle \{LU_i\}_{i=1}^{N}, M \rangle$, an antibody chain $AC = \{Ab_1, Ab_2, \cdots Ab_N\}$ is defined as follows. (1) $Ab_i \in LU_i$, for all $i = 1, 2, \cdots N$; (2) The idiotype of Ab_i can be recognized by the partatope of Ab_{i+1}, namely, $Ab_i \rightarrow Ab_{i+1}$, for all $i = 1, 2, \cdots N-1$; (3) $Ab_N \rightarrow Ab_1$.

C. One-dimensional Chaotic Dynamical System

One-dimensional chaotic dynamical systems have shown many applications in highly nonlinear systems which are sensitively dependent on initial conditions. One of the well-known one-dimensional chaotic systems is the iteration generated by the logistic function which is defined as follows.

$$F(x;\alpha) = \alpha \cdot x(1-x) \tag{1}$$

where $n = 1, 2, \cdots$. $x_0 \in [0, 1]$ is called the initial condition of (1). $\alpha \in [0, 4]$ is the bifurcation parameter of (1). Such parameter is the major character for dramastic change of system behavior. (1) also generates a one-dimensional discrete dynamical system defined as follows.

$$x_{n+1} = F(x_n) = \alpha \cdot x_n(1-x_n) \tag{2}$$

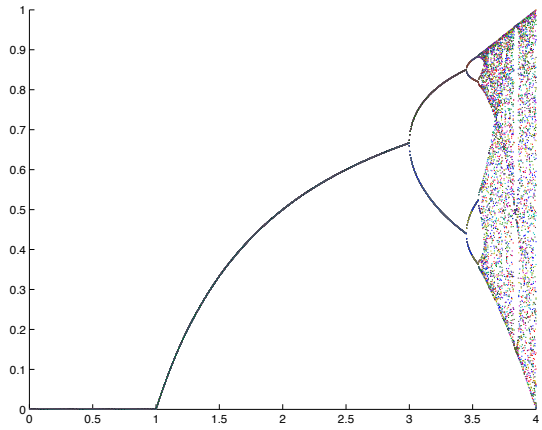

Fig. 2. Bifurcation Diagram of (2)

$n = 0, 1, \cdots$. x_0 is called an initial condition of (2). Fig. 2 is the bifurcation diagram of (2). It shows that the values of fixed points for (2) for varied $\alpha \in [0, 4]$. While $1 < \alpha < 3$, the dynamics has two fixed points, one is 0, the other is $x = \frac{\alpha-1}{\alpha}$. As $\alpha \approx 3.5$, periodic orbit with periodicity 2 appears. As α increases, periodic orbits with higher periodicities appear. As $\alpha > 3.65$, (2) shows chaotic behavior (Fig. 2).

The method of Lyapunov exponents, which is defined as follows, is one important way to determine whether an initial condition x_0 of (2) with parameter α_0 will show chaotic behavior or not.

Definition 1. *Let $f : D \subset R^1 \rightarrow R^1$ be a real-valued continuous function. Consider the discrete dynamical system $x_{n+1} = f(x_n)$. The Lyapunov exponent of this system at x_0 is defined by $\lambda(x_0) = \lim_{n\to\infty} \frac{1}{n} \sum_{i=0}^{n-1} \ln |f'(x_i)|$, if the limit exists.*

The Lyapunov exponents of the logistic map (1) can be referred to Fig LEfig. We also note that for $\alpha < 3.65$, the Lyapunov exponent for any $x_0 \in (0,1)$ is negative. As for $\alpha > 0$, the Lyapunov exponents is greater than zero in general. However, some values are negative.

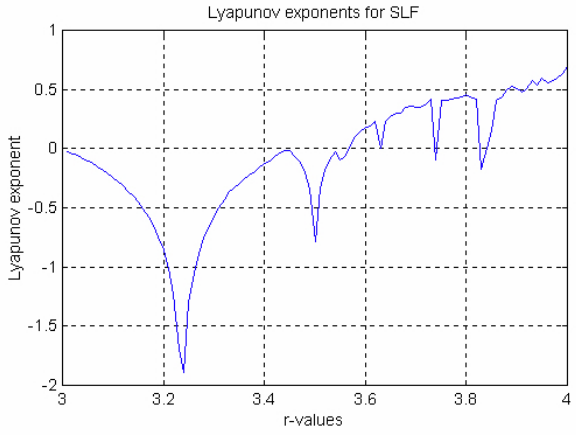

Fig. 3. Lyapunov Exponents of (2)

III. Results

First we propose a model of immune memory mechanism inspired by one-dimensional chaotic system (2). This dynamical system can be regarded as the biologically-reasonable computation to transform antigenic format to memory format. Every antibody chain can induce some network dynamics which generate memory formats of antigens. This immune memory mechanism can explain the associativity property based on the bifurcation parameter of (2). We also verify this model based on the associative memory of immune systems and the affinity index define in this section.

A. Network Dynamics of Antibody Chains

We propose a network dynamics F of antibody chains inspired by the logistic function (1). This dynamics is a type of state transition function which can generate immune memory of any given antigen. The idea of this model is as follows. Some character of the antibody chain AC can influence the forming of immune memory. If an AC has strong affinity for each pair of its adjacent antibodies $(Ab_i, Ab_{i+1}$, then it will incur strong associative memory for antigens "similar" to previously invaded ones. Therefore, we will define the affinity index of an antibody chain by the sum of affinities between all adjacent antibodies.

Definition 2. *Let n be the length of molecules X and Y. The the affinity between X and Y, denoted by $\gamma(X,Y)$, is defined by $1 - \frac{d(X,Y)}{n}$, where d is the Hamming distance.*

Definition 3. *The affinity index L_{AC} induced by an antibody chain AC is defined by*

$$L_{AC} = 4 \cdot (1 - \frac{1}{N-1}(\sum_{i=1}^{N-1} \gamma(Ab_{i+1}, Ab_i)) \qquad (3)$$

L_{AC} is a real number in $[0,4]$ which represents the average of affinities among pairs of adjacent antibodies (Ab_{i+1}, Ab_i). Given an antigen Ag^T (column vector), we transform Ag^T to a real number $x_0 = \sum_{i=1}^{n} Ag_i 2^{-i}$ between 0 and 1, where Ag_i is the i-th component of Ag. For example, if $Ag =$ "11001", then $x_0 = 2^{-1} + 2^{-2} + 2^{-5} = 0.78125$.

The basic concept of the immune memory mechanism is that the degree of the associativity is proportional to some inner structure of immune systems. Affinity index can be regarded as such inner strength of the corresponding antibody chain. The smaller the index, the more associative the immune memory mechanism exhibits. This index computes ratio of the same attributes between adjacent antibodies. Now the network dynamics F derived by the affinity index, L_{AC}, is the following.

$$x_{n+1} = F(x_n; L_{AC}) = L_{AC} \cdot x_n(1 - x_n) \qquad (4)$$

$n = 0, 1, 2, \cdots$.

B. Memory formed by Antibody Chains

We establish a mathematical model of the immune memory mechanism. First we define the immune memory function based on the antibody dynamics as follows.

Definition 4. *The immune memory function $f : \mathbb{R} \to \mathbb{R}$ is a real-valued continuous function defined on $\mathbb{R}$ with the following condition. There exists some nonempty set $E \subset \mathbb{R}$ such that $\lim_{k\to\infty} f^k(x)$ exists for all $x \in E$.*

E is called a memory set of f. E is called a maximal memory set of f if for any memory set $\hat{E}$ of f, then $\hat{E} \subset E$.

Remark 1. *If F is the logistic function (1), then $f(\cdot) := F(\cdot, \alpha)$ is a immune memory function, for any $\alpha \in (0,1)$.*

Definition 5. *Let $\gamma(\cdot,\cdot)$ represent the affinity between two binary molecule formats. An immune network $AC = \{Ab_i\}_{i=1}^N$ activated by an antigen Ag is equipped with associative memory mechanism, if for $\epsilon \in (0,1)$, there exists some $\delta \in (0,1)$ and k_0 a positive integer, such that whenever a new antigen Ag' with $\gamma(Ag, Ag') > \delta$ implies that $\gamma(f^k(Ag), f^k(Ag')) > \epsilon$.*

For antibody dynamics, the limit behavior of $f^k(Ag)$ depends on the affinity index of AC.For higher affinity threshold, the higher the possibility that the memory format of Ag i simply a stable equilibrium point. Moreover, we have the following theorem for our immune memory mechanism. Let $L^- \subset [0,1]$ be the region of negative Lyaponov exponents.

Proposition 1. *Let F be logistic function. Then the immune memory of any antigen exists for all $(\lambda, x_A g) \in L_-$.*

Once the same or a similar" antigen to Ag, say Ag', invades the immune system again, the memory recall process of the immune systems will be activated by comparing the $F^k(Ag')$ with S^1, the memory format of Ag. According to system dynamics, such similar antigens are elements of domain of attraction of the dynamics F, namely $A_g \in \mathcal{A}(S^1)$. Suppose the same antigen Ag invades the immune systems again, then $F^k(Ag)$ will immediately converges to S^1. On the other hand, if some similar antigen Ag' invades, the network dynamics $F^k(Ag')$ converges to S^1, if $Ag' \in \mathcal{A}(S^1)$. Therefore, the domain of attraction of antigen memory format is the major

criterion whether similar or mutated antigens will activate the original antibody Ab_1 and the same antibody chain AC. In this way, the dynamics of antibody chains is the key for cross-reactive immune responses which show the associative memory mechanism for the immune systems.

C. Simulations

We simulate memory forming process via network dynamics (3)-(4). In this way, we can analyze memory formats of mutated antigens Ag' which are similar to the previously invaded and memorized antigens Ag with only a few different attributes (m is the number of mutated attributes). We give a complete list of parameters as (Table I) with $iterno = 100$, $n = 30$ and $m = 5$ for every simulation. Memory formats can be represented as real number between 0 and 1 which have described in previous section.

TABLE I. PARAMETERS FOR IMMUNE NETWORKS

Para.	Description
L_{AC}	Affinity Index of Antibody Body AC
λ	Affinity Threshold
m	Number of mutated attributes from Ag
$iterno$	Numbers of Iterations
α	bifurcation parameter for logistic function
n	Length of Ag, Ab
N	Length of antibody chain AC

Algorithm 1 Forming Antibody Chain

Input: Ag: Antigen $\mathcal{P}$: a pool of antibody population $MaxAC$: The maximal size of antibody chain λ: affinity threshold

Output: $AC = \{Ab_i\}_{i=1}^{N}$: an activated set of antibody chain

Find an antibody denoted by Ab_1 from $\mathcal{P}$ such that $Ab_1 \rightarrow_\lambda Ab_1$.
Find an antibody denoted by Ab_2 such that $Ab_2 \rightarrow_\lambda Ab_1$.
if Ab_2 does not exist **then**
  return "Such antibody chain does not exist"
else if $Ab_2 \rightarrow_\lambda Ag$ **then**
  $N = 2$
  $AC = \{Ab_1, Ab_2\}$
  Close
end if
$i = 3$
Find $Ab_k \in \mathcal{P}$ such that $Ab_k \rightarrow_\lambda Ag$;
while $i \leq MAXAC$ **do**
  Find an antibody in $\mathcal{P}$, denoted by Ab_i such that $Ab_i \rightarrow_\lambda Ab_{i-1}$;
  if Ab_i does not exist **then**
    There is no antibody chain
    Close
  else if $Ab_i \rightarrow_\lambda Ag$ **then**
    $N = i$
    $AC \leftarrow AC \cup \{Ab_i\}$
    Close
  end if
  $i = i + 1$
  $\mathcal{P} \leftarrow \mathcal{P} \setminus \{Ab_i\}$
end while
output: AC

The following algorithm describes the process of memory forming inspired by antibody dynamics.

Algorithm 2 Cross-reactive immune memory

Input:
$Size\_of\_Pool$: size of antibody pool
Ag: antigen
Ag': mutated antigen of Ag
k: $k-$level immune memory

Output: d_k: Overlapping difference between memory formats of Ag and Ag'

Randomly generating a pool of antibodies with fixed length n.
(Antibody Chain Forming) Applying Algorithm 1 to find an antibody Chain of Ag
Calculating affinity index of AC, L_{AC}
Forming memory format of Ag by calculating $F^k(Ag, L_{AC}$
Memory Recall of mutated antigen Ag' by calculating $F^k(Ag', L_{AC}$.
for $i = 1 \cdots k$ **do**
  $d_i \leftarrow F^i(Ag, L_{AC}) - F^i(Ag', L_{AC})$
end for

However, we realize, even with simple dynamics as, it is very difficult to classify completely memory formats of varied antigens. One better way in this research is the following. Rather than seeking different format of immune memories, we focus on classify the different types of "difference" between antigens and their mutations.

1) Simulation One: $1 < L_{AC} < 2$.*:* Fig. 4 shows the memory formats of (randomly generated) Ag and its mutated antigen Ag' ($m = 5$, $\lambda = 0.7$). Two memory formats are identical and equal to 0.025. $L_{AC} = 1.0211$

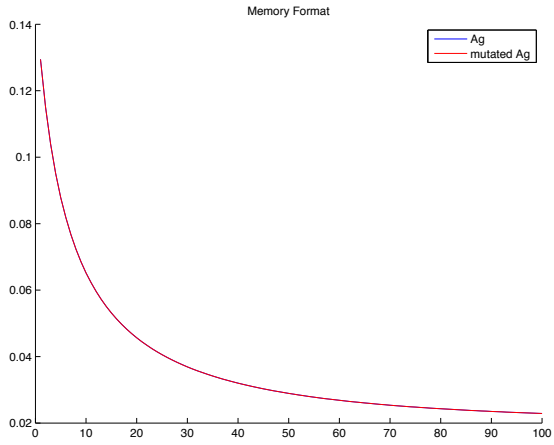

Fig. 4. Memory Format for Some Antigen ($1 < L_{AC} < 2$)

2) Simulation Two: $2 < L_{AC} < 3$.*:* Fig. 5 shows that memory format for Ag is equal to 0.55. Its mutated antigen Ag' induces a cross-reactive immune response activated by original antibody chain, as its memory format is also convergent to that of Ag. $L_{AC} = 2.20$

3) Simulation Three: $3 < L_{AC} < 3.6$.*:* According to varied simulations, we observe that AC is difficult to form if affinity

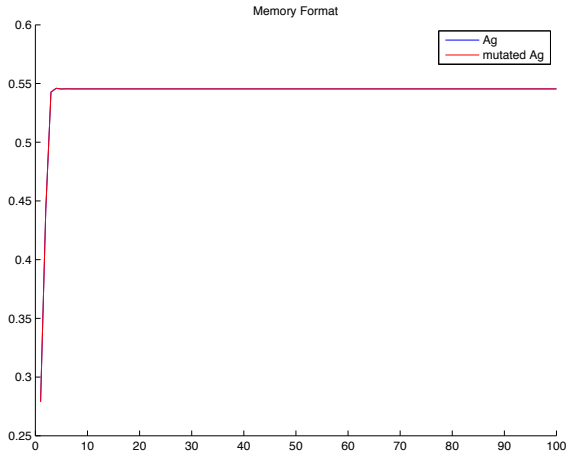

Fig. 5. Memory Format for some Antigen ($2 < L_{AC} < 3$)

threshold $\lambda \geq 0.7$. Therefore we will simulate the memory format for $\lambda \geq 0.7$ by assigning L_{AC} values directly to (4) without generating antibody chains.

$L_{AC} = 3.1026$. As for the memory format of mutated antigen Ag', Fig. 6 illustrates a better view that two memory formats are identical (after 30 iterations). The mutated antigen Ag' induces a cross-reactive immune response activated by original antibody chain, as its memory format is also convergent to that of Ag.

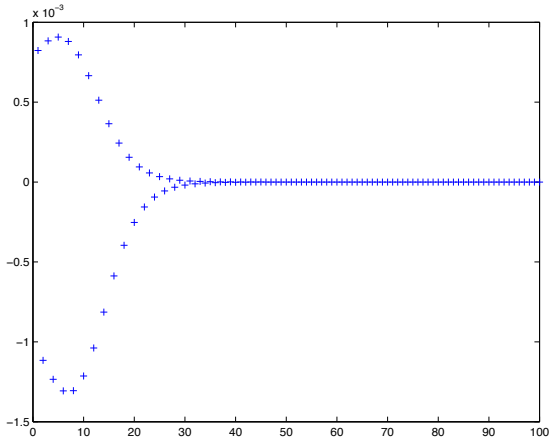

Fig. 6. Difference of Memory Formats between Ag and Ag'

4) Simulation Four: $3.6 \leq L_{AC} < 4$*:* Now $L_{AC} = 3.6$. As for the memory format of mutated antigen Ag', Fig. 7 illustrates a better view that two memory formats are completely different. In this case, the corresponding AC cannot activate a cross-reactive immune response to Ag'; Ab_1 cannot effectively eliminate Ag' clones.

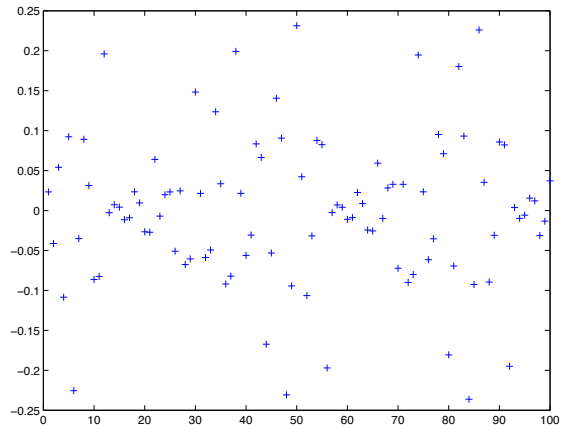

Fig. 7. Difference of Memory Formats between Ag and Ag' ($L = 3.6$).

IV. Conclusions

We propose an antibody dynamics model based on one-dimensional chaotic dynamical system. This model can describe the associativity of immune memory mechanism. The affinity index of antibody chain controls the bifurcation parameter of logistic function. Moreover, for higher affinity index, the immune network show associative memory for mutated antigens.

Our model focuses on the memory forming process which is unique while comparing to other researches. For example, Anderson et al. studied intensively about the immune network model with antibody dynamics based on Cayley tree [4]. For further research direction, we are interested in adopting such network structure of antibody dynamics to our model of memory forming. There are two folds for such model; one is the memory format of an given antigen related to the limit behavior of the dynamical systems F^k as $k \to \infty$. The other is the cross-reactive behavior of mutated antigen, namely $F^k(Ag')$, for $\gamma(Ag, Ag')$ is large.

Acknowledgment

The author would like to thank support from the Ministry of Science and Technology of Taiwan under the grant number MOST-105-2221-E-424-002.

References

[1] F. Abbattista, G. D. Gioia, G. D. Santo, and A. Fanelli, "An asspciative memory based on the immune networks," in *Proceedings of the IEEE Internatinal Conference on Neural Networks, 1996*, 1996, pp. 519–523.

[2] E. Agliari, A. Barra, G. Ferraro, F. Guerra, and D. Tantari, "Anergy in self-directed b lymphocytes: A statistical mechanic perspective," *J. Theoretical Biology*, vol. 375, pp. 21–31, 2015.

[3] S.-I. Amari and K. Maginu, "Statistical neurodynamics of associative memory," *Neural Networks*, vol. 1, pp. 63–73, 1988.

[4] R. Anderson, A. Neumann, and A. Perelson, "A cayley tree immune network model with antibody dynamics," *Bulletin of Mathematical Biology*, vol. 55, pp. 1091–1131, 1993.

[5] A. Barra and E. Agliari, "Stochastic dynamics for idiotypic immune networks," *Physica A*, vol. 389, pp. 5903–5911, 2010.

[6] C. Bona, "Internal image concept revisited," *Proceeding of the Society for Experimental Biology and Medicine*, vol. 213, pp. 32–42, 1996.

[7] J. Carneiro, A. Coutinho, J. Faro, and J. Stewart, "A model of the immune networks with bt cell co-operation. i-prototypical structures and dynamics," *J. Theoretical Biology*, vol. 182(4), pp. 513–529, 1996.

[8] A. Coutinho, "A walk with francisco varela from first- to second generation networks: In search of the structure, dynamics and metadynamics," *Biol. Res.*, vol. 36, pp. 17–26, 1993.

[9] J. Farmer, N. Packard, and A. Perelson, "The immune system, adaptation, and machine learning," *Physica*, vol. 22D, pp. 187–204, 1986.

[10] J. Fernandez, G. Acostra, and M. Mayosky, "From network-to-antibody robustness in a bio-inspured immune system," *BioSystems*, vol. 104, pp. 109–117, 2011.

[11] G. Hoffman, "A theory of regulation and self-nonself discrimination in an immune network," *Eor. J. Immunol.*, vol. 5, pp. 638–647, 1975.

[12] N. Jerne, "Towards a network theory of the immune system," *Ann. Immunol. (Inst. Pasteur)*, vol. 125C, p. 373, 1974.

[13] P. Matzinger, "Memories are made of this ?" *Nature*, vol. 369 (23 June), pp. 605–606, 1994.

[14] M. Morita, "Associative memory with nonmonotone dynamics," *Neural Networks*, vol. 6, pp. 115–126, 1993.

[15] M. Novak and R. May, *Virus Dynamics: Mathematical Principles of Immunology and Virology*. Oxford University Press, 2001.

[16] G. Parisi, "An introduction to the immune network," *arXiv*, vol. http://arxiv.org/abs/cond-mat/9501046v1, 1995.

[17] A. S. Perelson, "Immune network theory," *Immunological Reviews*, vol. 10, pp. 5–36, 1989.

[18] D. Smith, S. Forrest, and A. Perelson, "Immunological memory is associative," *Artificial Immune Systems and Their Applications,The international Conference on the Multi-Agent Systems Workshop Notes, Kyoto, 1996*, pp. 62–70, 1999.

[19] T. Sonoda, "Formation and stability of a memory state in the immune network," *J. Physical Society of Japan*, vol. 81(4), pp. 1408–1424, 1992.

[20] P. Varela and A. Coutinho, "Second generation immune networks," *Immunol. Today*, vol. 12, pp. 159–166, 1991.

[21] G. Weisbuch, R. DeBoer, and A. Perelson, "Localized memories in idiotypic networks," *J. Theor. Biol.*, vol. 146, p. 483, 1990.