# Evolution of Multispecificity in an Immune Network

Kouji Harada and Takashi Ikegami

Institute of Physics, The Graduate School of Arts and Sciences,
University of Tokyo,
3-8-1, Komaba, Meguro-ku, Tokyo 153, Japan
harada@sacral.c.u-tokyo.ac.jp
ikeg@sacral.c.u-tokyo.ac.jp

June 21, 2017

#### Abstract

Divergence in antigen response of the immune network is discussed, based on shape-space modelling. The present model extends the shape-space model by introducing the evolution of specificity of idiotypes. When the amount of external antigen increases, stability of the immune network changes and the network responds to the antigen. It is shown that specific and non-specific responses emerge as a function of antigen levels. A specific response is observed with a fixed point attractor, and a non-specific response is observed with a long-lived chaotic transient state of the lymphocyte population dynamics. The network topology also changes between these two states. The relevance of such a long-lived transient state is discussed with respect to immune function.

#### 1 Introduction

The 'lock and key' concept has been central to understanding the specificity of biochemical molecular interactions, from enzyme-substrate relationships to antigen-antibody matchings. However, it has gradually been realized that such a 'lock and key' concept is not strictly valid, particularly in immune systems [1]. Antigen-antibody interactions are found to be plastic or 'multispecific' rather than fixed or single-specific. Namely, antibodies inherently have a flexible recognition capacity. Kearney et al.[2] have confirmed experimentally the existence of such ambiguity of recognition in the antibody binding site of immature B cells. It is generally believed that development from ambiguous to specific recognition is caused by somatic hypermutations [3]. We here propose a new dynamics of specificity evolutions based on Jerne's network hypothesis [4]. Our model is characterized by a meta-dynamics of idiotype specificity on shape-space [5]. We

show here that specific and non-specific responses to an antigen are governed dynamically by a fixed point attractor and a chaotic long-lived transient state of an immune network, respectively. The relevance of such a long-lived transient state is discussed with respect to immune function.

### 2 Modeling with a Meta-dynamics of Specificity

We first introduce the standard idiotypic network model. Each idiotype is characterized by a pair of surface sites, called the idiotope and the paratope. If the idiotope site of a lymph cell is bounded by paratopes of other lymph cells, the recognized lymph cells become inactivated, whereas the recognizing cells become activated. Thus the growth dynamics of clone size  $x_{k,j}^n$  of an idiotype of paratope k and idiotope j is given as,

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

The idiotope-paratope interaction  $b_{i,j}$  is assumed to have an exponential form:  $\frac{1}{\sigma}e^{\frac{-|i-j|}{\sigma}}$ . We characterize the ambiguity of the antigen-antibody by the deviation parameter  $\sigma$ . The proposed meta-dynamics controls this parameter. First, as a simple example, we quantize  $\sigma$  by the power of 2:  $\sigma_m = 2^{M-m}$ . The maximum specificity is given by m = M.

Now each idiotype is characterized by three variables: idiotope k, paratope j, and the specificity m. We thus describe the evolution of specificity as follows:

$$x_{k,j,m}^{n+1} = (1 - \mu')x_{k,j,m}^n + \mu'/2 \sum_{m'=m-1,m+1} x_{k,j,m'}^n + s_{m=1},$$
 (2)

where  $\mu'$  is the mutation rate of specificity. Here the source term  $s_{m=1}$  is added for the least specific antibody. This dependency reflects the fact that the premature B-cells are believed to have lower specificities.

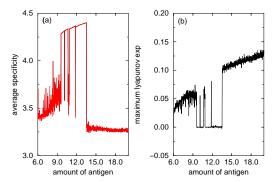
By combining these equations, we establish the complete clone growth dynamics with mutations among idiotypes and the evolution of the specificities.

In our model, there are five different types of idiotopes and of paratopes, so that there are 25 different idiotypes, with M=5 different levels of specificity. The rest of the system parameters (i.e.  $\mu'=0.3,\,s=1.0$ , d=0.1, and  $\alpha=2.0$ ) are selected so that the size of each clone never diverges.

The following results (especially, the natural tolerance at high amount of antigen) are confirmed not to depend on the values of the mutation rate  $\mu'$  and the source s. The dependency of system size is still unclear.

# 3 Dynamical Natures of the Network

We pay most attention to how the idiotype network responds to persistent antigenic stimulations. A static antigen with a binding site k is introduced by



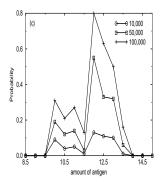


Figure 1: The average network specificity and the maximum Lyapunov exponents are plotted against the antigen level in Fig. 1(a) and (b) respectively, and in Fig. 1(c), the stability of the type I attractor is plotted against the antigen level. Stability is measured by the proportion of idiotypes in the initial distribution that show a transition from a type I to a type II state before a given time step. The time intervals used are 10,000, 50,000, and 100,000 steps. The number of initial distribution sets is 100.

adding the constant term  $+A_k b_{k,j} x_{i,j,m}$  to the above equation. Estimating the mean network specificity  $Sp_k$  by averaging the specificity of all idiotypes bearing paratope type k, we study the antigenic effect on the network dynamics.

An antigen of type 4 is used as an example, but the following result does not depend on the selected antigen type. Because we adopt the periodic boundary condition for the shape-space, each idiotype is equivalent within a network.

We show a plot of the averaged specificity  $(S\bar{p}_4)$  and the maximum Lyapunov exponent under the antigen stimulations over  $10^4$  steps (see Fig. 1(a), (b)).

In Fig.1(a), as expected, the network specificity increases when we increase the amount of antigen. At about 9.5 units of antigen, however, the specificity abruptly diverges to a high value. We say that a specific response has occurred at this antigen level. This specific response is observed until the antigen level reaches 13.5 units. Beyond this critical value, the specific response is no longer observed. Inversely, the specificity is sustained at the lower values. This lower sustained response can be compared to natural tolerance to the antigen.

On the other hand, by comparing Fig.1(a) with (b), when the amount of the antigen is set between 9.5 and 13.5 units, we notice that the lower specificity emerges with chaotic dynamics, and the higher specificity emerges with a fixed point dynamics. We shall call the former dynamics a type I attractor and the latter a type II attractor.

However, the type I attractor is not a true attractor. It was found to be a long-lived transient state referred to as a *super-transient state*, which is a common phenomenon in high-dimensional dynamical systems [6]. In Fig.1(c),

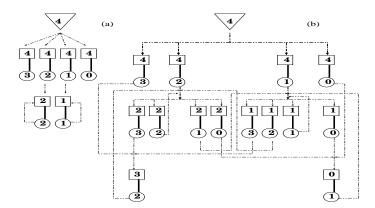


Figure 2: Topology of an idiotype network of type II and I attractors is shown in Fig.2 (a) and (b), respectively, for an antigen level of 12 units. Only idiotypes that have a population of 1.25 on average of over 10,000 time steps are depicted. Each idiotype in this figure is represented by a pair of symbols, square and circle. The square with the numeral inside denotes the paratope, whereas the circle with the numeral inside denotes the idiotope. The triangle with the number inside represents the injected antigen type. A stimulation wave from idiotope to paratope is shown by a dotted line.

when the observation period is extended, we observe a transition from type I to type II attractor. There is no inverse-transition from the type II to the type I attractor. The super-transient states are highly dependent on the antigen level. For example, when the antigen level is 11.5 units in Fig.1(c), the transition probability from type I to type II is still less than 12 percent. In such cases, it behaves as an attractor in a practical sense.

From a practical viewpoint, response time is also worth noticing. If we say that the relevant time scale for the immune response should be less than 10,000 time steps, in a practical sense there is no specific response even at higher levels of antigen (see Fig.1(c)). Our results suggest that a certain level of antigen causes the super-transient state to suppress fast immune responses under the idiotype network.

Besides the response time, much attention has been paid in the field of theoretical immunology to topological changes of the network [7, 8, 9]. Here we argue that the transition from type I (unspecific) to type II (specific) causes a simultaneous change of network topology. The network topology of each of these two states is shown in Fig.2.

As we see from the figure, a chaotic super-transient state of type I has a more complex network than does type II. Inversely, higher specificity to the dosed antigen is maintained by a simpler network structure. The maintenance of idiotypic diversity can be attributed to chaotic dynamics.

By estimating the amount of specificity of all idiotypes in the type I's dis-

tributed state and the type II's localized state respectively, it is found that each idiotype in type I's distributed state has a low specificity on the whole. Namely, each idiotype interacts weakly with many idiotypes in order to have high connectivity. As a result, the stimulation of the network by dosed antigen is distributed over the network, not concentrated only on idiotypes bearing a binding site (paratope with type 4) for the antigen. Thus, the immune response to the antigen has a tendency to be suppressed. This result would support Stewart's extrapolation that 'The higher connectivity among idiotypes, the greater the degree of tolerance' [10].

Recently, a chaotic oscillation was found experimentally in a natural tolerant state. Subsequently, theoretical immunologists have tried to establish 'natural tolerance under chaotic dynamics' against a static antigen [7, 8], though their simulation results show difficulty establishing such a tolerance without assuming a special network topology of an 'odd-loop structure' and so-called 'bell-shaped function' as an activation function. We have shown how such a tolerance can arise naturally under a chaotic dynamics, without these assumptions, by adding an additional flexibility; i.e., meta-mutation dynamics with specificity of idiotype. We have used a simple idiotypic network model, and have not ventured to use the more complex' bell-shaped function model' because of focusing on capabilities of the meta-dynamics we introduced. Applying the meta-dynamics we introduced here with the bell-shaped function model is left as a future problem.

## 4 Concluding Remarks

In this paper, we have expanded the possibilities of theoretical immunology by introducing new meta-dynamics. We believe that the immune response should be seen as having a more dynamic nature than allowed by most current models [11], and that the specific antigen-response and the dynamical percolation related to natural tolerance are caused by the meta-dynamics controlling the degree of specificity, as introduced here.

#### References

- [1] Ghosh, S., Campbell, A.M.; Immunology today. 7 (1986) 217–222
- [2] Kearney, J.M., Vakil, M., Nicholson, N.; Evolution and Vertebrate Immunity.
   G.Kelose and D.Schulze Eds. Texas University Press, Austin. (1987) 175–190
- [3] Wedemayer, G.J., et al.; Science. **276** (1997) 1665–1669
- [4] Jerne, N.K.; Ann. Immunol. **125C** (1974) 373–389
- [5] Segel, L.A., Perelson, A.S.; Theoretical Immunology edited by Perelson, A.S. Addison-Wesley Pub. Company (1987) 321-344

- [6] Kaneko, K. Phys.Lett. **149** A (1990) 105–112
- [7] Bersini, H., Calender, N.; J.theor.Biol. 188 (1997) 187–200
- [8] Calenbuhr, V., Bersini,<br/>H., Stewart, J., Valera, F.J.; J.<br/>theor.biol.  $\bf 177$  (1995) 199-213
- [9] Detoures, V., Bersini, H., Stewart, J., Varela, F.J.; J.theol.Biol. 170 (1994) 401--414
- [10] Stewart, J. et al.; J. Autoimmune. 2 (1989) 15–23
- [11] Harada, K., Ikegami, T.; submitted to J. theol. Biol (1998)