A large scale dynamical system immune network model with finite connectivity

Tatsuya UEZU†, Chihiro KADONO†, Jon HATCHETT‡ and Anthony C.C. COOLEN‡

† *Graduate School of Humanities and Sciences, Nara Women's University, Nara 630-8506, Japan*
‡ *Department of Mathematics, King's College, University of London, London WCR 2LS, United Kingdom*

We study a model of an idiotypic immune network which was introduced by N. K. Jerne. It is known that in immune systems there generally exist several kinds of immune cells which can recognize any particular antigen. Taking this fact into account and assuming that each cell interacts with only a finite number of other cells, we analyze a large scale immune network via both numerical simulations and statistical mechanical methods, and show that the distribution of the concentrations of antibodies becomes non-trivial for a range of values of the strength of the interaction and the connectivity.

§1. Introduction

There are many numerical and theoretical studies of biological networks in which there is a global coupling between the constituent elements, e.g. Hopfield-type neural networks and networks of Kuramoto-type phase oscillators.[1),2)] In contrast, relatively few studies have been carried out of networks where each component interacts with only a small number of randomly selected other components. One such system is the immune network, introduced by Jerne[3)] to explain the activation of immune cells in the absence of external stimulation.

Let us briefly summarize the main mechanism of cell-interaction in the immune system. Its main constituents are B-lymphocytes (B-cells), T-lymphocytes (T-Cells) and antibodies produced by B-cells. B-cells and T-cells have receptors on their surfaces. The receptors of B-cells are antibodies, which recognize and connect to antigens in order to neutralize them; they have specific 3-dimensional structures which are called 'idiotypes'. A family of B-cells which are generated from a given B-cell is called a 'clone'. Hence, all members of a clone as well as the antibodies produced by this clone have the same idiotype. In general, each antibody could present several 3-dimensional structures which can be recognized by other B-cells. This then generates, indirectly, an effective interaction between antibodies.

This paper is organized as follows. In section 2 we formulate the model, followed by a summary of previous studies in section 3. In section 4, we present the results of our present study. Section 5 is devoted to a summary and a discussion.

§2. Formulation of the model

Taking the roles of T-cells into account, Varela et al. introduced a dynamical system model for B-cells and antibodies.[4)] The specific equations for the dynamics of the concentrations f_i of antibodies and b_i of B-cells in this model are

$$\frac{d}{dt}f_i = -K_1\sigma_i(\boldsymbol{f})f_i - K_2 f_i + K_3 M[\sigma_i(\boldsymbol{f})]b_i, \qquad (2{\cdot}1)$$

$$\frac{d}{dt}b_i = -K_4 b_i + K_5 P[\sigma_i(\boldsymbol{f})]b_i + K_6, \qquad (2{\cdot}2)$$

where $i = 1, \ldots, N$ labels the various clones, of which there are N in total. We abbreviate $\boldsymbol{f} = (f_1, \ldots, f_N)$. The function $\sigma_i(\boldsymbol{f}) = \sum_{j=1}^{N} m_{ij} f_j$ represents the sensitivity of the system to the i-th idiotype, and the so-called maturation and proliferation functions $M[\sigma]$ and $P[\sigma]$ are defined as $M[\sigma] = e^{-[S_m^{-1}\log(\sigma/\mu_m)]^2}$ and $P[\sigma] = e^{-[S_p^{-1}\log(\sigma/\mu_p)]^2}$, respectively. These latter functions embody the role of T-cells in the system. The control parameters $\{K_1, \ldots, K_6\}$ have been determined empirically. The matrix $\{m_{ij}\}$, with non-negative entries and with $m_{ii} = 0$ for all i, defines the network connectivity.

§3. Previous results

In this section we summarize our previous results on the above model.[5),6)] First we turn to numerical simulations. We first studied the (simplest) case of global coupling, by taking uniform interactions of the form $m_{ij} = \frac{\kappa}{N}$. Here, the average antibody and B-cell concentrations $\bar{f} \equiv \frac{1}{N}\sum_i f_i$ and $\bar{b} \equiv \frac{1}{N}\sum_i b_i$ obey relatively simple differential equations. For the parameter values that we adopted, stable solutions were found to be the trivial fixed point $(\bar{f}, \bar{b}) = (0, \frac{K_6}{K_4})$ and a non-trivial fixed point $(\bar{f}, \bar{b}) = (\bar{f}^*, \bar{b}^*)$. In either case one has $f_i = \bar{f}$ and $b_i = \bar{b}$ for all i, i.e. all clones have the same concentration and the system is uniform. This is undesirable and unnatural for the immune system. Next we studied the case where the average number c of interactions per clone is proportional to the number of clones N. We also took the strength of those interactions present to be uniform, i.e. $m_{ij} \in \{0, \frac{\kappa}{c}\}$. Numerical simulations showed that the distribution $p(f)$ of the concentrations $\{f_i\}$ always converges to the trivial distribution $\delta(f)$ as $N \to \infty$. Therefore, we were again led to an unnatural result for the immune system. Finally, we turned to the case of finite connectivity (i.e. finite c, independent of N) as found in real immune systems. Defining $m_{ij} \in \{0, \kappa\}$, we performed numerical simulations and found that as $N \to \infty$, the distribution $p(f)$ of antibody concentrations converges once more to $\delta(f)$ for $\kappa = 0.2$, but for $\kappa = 2$ or 20 it converges to a non-trivial distribution. The latter result is biologically meaningful for immune systems.

Next, we summarize the theoretical results obtained so far. To analyze the above model mathematically we used the Dynamical Replica Theory (DRT),[7)] which results in a nonlinear partial differential equation (PDE) for the joint distribution $p(f, b, \sigma)$ of single-clone variables (f_i, b_i, σ_i) (i.e. antibody and B-cell concentrations, and clone sensitivities). It is, however, quite difficult to solve this diffusion equation (or that of the marginal distributions) numerically, even when using approximations, due to the required resolution in the 3-dimensional space of the arguments (f, b, σ). Hence, here we turn to a simplified model in which the concentrations of B-cells, rather than evolving according to equation (2·2), are kept constant at the value $b_0 = \frac{K_6}{K_4}$.

§4. Results of the present study

Upon replacing (2·2) by $b = b_0 = \frac{K_6}{K_4}$, the remaining equation (2·1) for f_i becomes

$$\frac{d}{dt} f_i = -K_1 \sigma_i f_i - K_2 f_i + K_3 M(\sigma_i) b_0. \tag{4·1}$$

As might have been expected, if c is of the order of N and the strength of interactions present is uniform, the antibody distribution $p(f)$ once more converges to $\delta(f)$. The biologically relevant regime is therefore again that of *finite* connectivity: $m_{ij} \in \{0, \kappa\}$, with c finite (independent of N). We performed numerical simulations of the network defined by (4·1), for several values of N, c and κ. Typical results are shown in Fig.1; they suggest that $p(f)$ converges to a non-trivial function as $N \to \infty$.

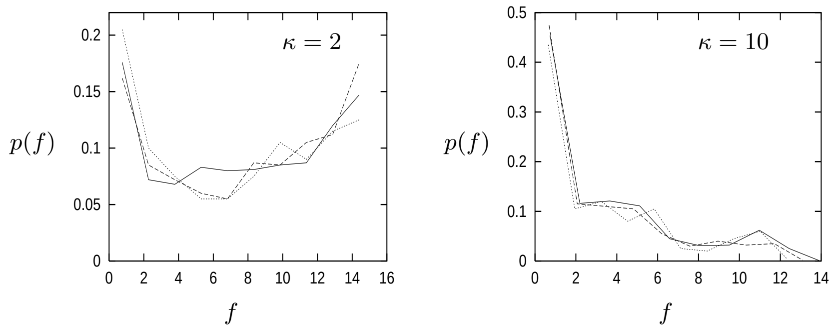

Fig. 1. The distribution $p(f)$ of antibody concentrations, for the finitely connected network with $c = 5$. Solid line: $N = 800$, dashed line: $N = 400$, dotted line: $N = 200$. Left: $\kappa = 2$. Right: $\kappa = 10$.

Next we turn to theoretical approaches. In DRT one finds the following nonlinear partial differential equation for the joint distribution $p(f, \sigma)$ of single-clone antibody concentrations f and clone sensitivities σ (see[6]):

$$\frac{\partial}{\partial t} p(f,\sigma) = -\frac{\partial}{\partial f}\Big[F(f,\sigma)p(f,\sigma)\Big] - \kappa c \frac{\partial}{\partial \sigma}\Big[\langle B(f,\sigma;f',\sigma')F(f',\sigma')\rangle p(f,\sigma)\Big], \tag{4·2}$$

where $F(f,\sigma) = K_3 M[\sigma] b_0 - K_1 \sigma f - K_2 f$ and $\langle G(f',\sigma')\rangle = \int df' d\sigma' p(f',\sigma') G(f',\sigma')$. The quantity $B(\ldots)$ is a complicated object, which makes the numerical solution of (4·2) prohibitively difficult. Rational approximations are e.g. (see[6] for details)

1. NSC – neglecting site correlations: $B(f,\sigma;f',\sigma') = 1$.
2. ANN – annealed approximation: $B(f,\sigma;f',\sigma') = \frac{p(f,\sigma-\kappa f')p(f',\sigma'-\kappa f)}{p(f,\sigma)p(f',\sigma')}$.

We explored direct numerical calculations using both NSC and ANN approximations, but we have not yet obtained convergent solutions. Instead, we exploit the fact that (4·2) is of the Liouville form, allowing us to write the solution $p(f,\sigma)$ formally as

$$p(f,\sigma) = \int \mathrm{d}f_0 \mathrm{d}\sigma_0 \; p_0(f_0,\sigma_0)\delta[f - f^*(t; f_0,\sigma_0)]\delta[\sigma - \sigma^*(t; f_0,\sigma_0)], \tag{4·3}$$

where $f^*(t; f_0,\sigma_0)$ and $\sigma^*(t; f_0,\sigma_0)$ are the solutions of the underlying deterministic ordinary differential equations. In this case we can only use NSC (for technical reasons). In Fig.2 we compare the results of numerical evaluation of (4·3), within NSC;

in spite of the crude nature of the NSC approximation, the results agree qualitatively.

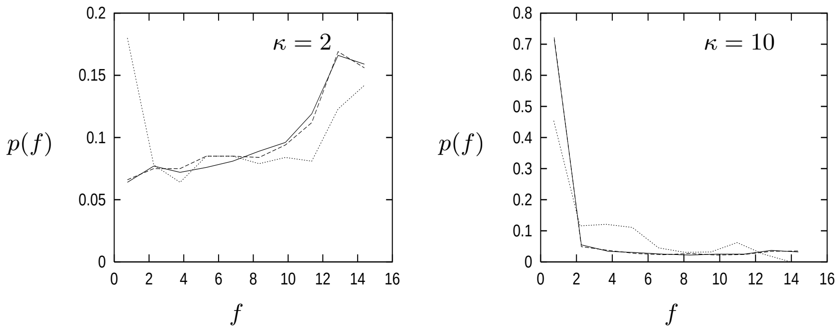

Fig. 2. The distribution $p(f)$ of antibody concentrations, for the finitely connected network with $\kappa = 2$ (left) and $\kappa = 10$ (right). We compare the solutions of the Liouville equation (two examples, solid and dashed) with the results of numerical simulations (at $N = 800$, dotted).

§5. Summary and discussion

In this paper we studied an idiotypic dynamical system immune network model with finite connectivity. We restricted ourselves to the simplified version, in which only the concentrations of antibodies change and those of B-cells remain fixed. Numerical simulations revealed that the distribution $p(f)$ of antibody concentrations can acquire a nontrivial shape as the number of clones N tends to ∞, except for small values of the interaction strength κ, where it converges to $\delta(f)$ (i.e. all antibodies disappear) and the system is meaningless as an immune system. We derived partial differential equation for $p(f)$, using the DRT formalism. Using the Liouville form of this equation, we could calculate $p(f)$ numerically within a specific approximation (NSC). We compared the distributions thus obtained with those measured in numerical simulations and obtained qualitatively good agreement. We also tried to solve the PDE for joint distribution of antibody concentrations and clone sensitivities $p(f, \sigma)$ numerically by using NSC and ANN approximations, unfortunately without finding numerical convergence yet; this is therefore left for future work.

It is a great pleasure for the authors to dedicate this paper to Professor Yoshiki Kuramoto on the occasion of his retirement from Kyoto University.

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