Assignment #4

Physics 498: Statistical Physics of Biological Complexity and Information

Development of Immune Response Models

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Introduction

Along with the nervous system, the immune system has served as prime examples of complex biological systems. Both have the capabilities of pattern recognition, learning, and memory. These complex tasks in the immune system involve cooperation among large number of different clones of cells that communicate via cell-cell contact and the secretion of molecules. Apart from this, the dynamical nature of the immune system imparts the capability of affinity maturation with time. In this work, an attempt has been made to develop quantitative immune response models to explain how the cells of the immune system behave and how they interact with each other to generate the coordinated activity observed. The immune system contains more than 10^7 different clones of cells that communicate via cell - cell contact and secretion of molecules that provide us with a basic defense against pathogenic organisms. The interactions among the components of the immune system are extremely intricate and not fully understood. Further, there are no equivalents of the Hodgkin-Huxley (1952) equations in neurophysiology. Yet the 'macroscopic behavior' of the immune system, as probed in a specific experiment, can be well characterized. The problem then arises of selecting the sample representation for the elementary interactions that would give rise to the organized behavior observed in the immune system.

Some of the most intriguing aspects of the immune system that manifest themselves at the macroscopic level :*Clonal Selection* (Clonal selection is the idea that only those cells that recognize the antigen proliferate, thus being selected against those which do not.) ; *Learning and Memory* (Learning in the immune system involves biasing the repertoire from random towards a repertoire that more clearly reflects the actual antigenic environment developed by previous encounters with the antigen) ; *Self and Non Self Discrimination* (The completeness of the repertoire presents a fundamental paradox for the immune system. Because all shapes can be recognized, the immune system can recognize molecules and cells of our body as well as foreign ones. For the immune system to function properly it needs to be able to distinguish between these two classes of molecules and cells, which are a priori indistinguishable, so as to avoid triggering an immune response against self antigens).

Network Models

Jerne (1974) hypothesized that the immune system, rather than being a set of discrete clones that respond only when triggered by antigen, is a regulated network of molecules and cells that recognize one another even in the absence of antigen. Because antibodies are created in part by random genetic mechanisms, they must look like novel molecules to the rest of the immune system and thus should be treated like antigens. The novel or idiosyncratic parts of an antibody are called idiotopes. The set of idiotopes that characterizes an antibody is called it's idiotype. Due to completeness of the repertoire, immune system should recognize the idiotopes on it's own antibodies and make antibodies against them. Jerne suggested that during an immune response antigen would directly elicit the production of the first set of antibodies Ab_1. These antibodies would then act as antigens and elicit the production of a second set of "anti-idiotypic" (anti-id) antibodies Ab_2 which recognize idiotopes of Ab_1.Similarly, a third set antibodies Ab_3 would be elicited that recognize Ab_2, and so forth.

The B cell model

It is one of the simplest models that can be conceived, yet it still exhibits interesting properties. We call it the B model since it deals only with B cells. The time evolution of -the population x, of clone *i* is described by the following differential equation:

$$\frac{dx_i}{dt} = m + x_i\left[pf\left(h_i\right) - d\right] \tag{1}$$

where *m* is a source term corresponding to newly generated cells coming into the system from the bone marrow, *p* is the rate of cell proliferation, the function $f(h_i)$ defines the fraction of cells proliferating as a

function of the "field" h_i, and d specifies the per capita rate of cell death. Because cells only proliferate when they are activated, $f(h_i)$ is called an activation function or sometimes proliferation function. For each clone i, the total amount of stimulation is considered to be a linear combination of the populations other interacting clones j. This linear combination is called the field h_i, acting on clone x_i, i.e.,

$$h_i = \sum_j J_{ij} x_i \tag{2}$$

where J_{ij} specifies the interaction strength (or affinity) between clones x_i, and x_j. The choice of a J matrix describes the topology of the network. For simplicity , J_{ij} values are typically chosen as 0 and 1. The most crucial feature of this model is the shape of activation function, $f(h_i)$, which is taken to be a log-shaped dose-response function [figure 1]

$$f(h_i) = \frac{h_i}{\theta_1 + h_i}\left(1 - \frac{h_i}{\theta_2 + h_i}\right) = \frac{h_i}{\theta_1 + h_i}\frac{\theta_2}{\theta_2 + h_i} \tag{3}$$

where θ_1 and θ_2 chosen such that $\theta_2 >> \theta_1$.

De Boer (1988), De Boer and Hogeweg (1989), Weisbuch, De Boer, and Perelson (1990), De Boer and Perelson (1991), Perelson and Weisbuch (1992), and Stadler, Schuster, and Perelson (1994), all considered variations of the following model for B-cell clonal dynamics.
In this paper, first I have considered the simplest network of two interacting populations for understanding the response of immune system models in the presence of an antigen A. Antigen is eliminated by reacting with antibody and hence as a simple model one might assume, where k is the rate constant.

$$\frac{dA}{dt} = -kAx_1 \tag{4}$$

Then, the robustness of the two clone model is checked for variation in initial size of Antigen A_0, rate constant of idiotype-antigen interaction (k), and production rate of B cells (m). Then, I tried simulating an idealistic immune topology with Cayley tree configuration [figure 2]. The immune response model equations were solved numerically using Fourth order Runga Kutta method with the help of XPP, freeware for solving simultaneous differential equations (Ermentrout, www.math.pitt.edu/~bard/xpp/).

Results and Discussions

The Two Clone Network simulations were based on model parameters estimated either from physiological properties and immunological assumptions or estimated so that the simulations match the selected nominal immune response.

The simulation of the set of equations (1), (2), (4) with the activation function calculated by equation (3) provided for the two clone model with the set of parameters estimated in. As reported previously in B cells models, that employ a log-bell-shaped activation function, three possible equilibrium levels for each B cell population have been identified:

1. a virgin, or unstimulated level, m/d.
2. a large population level corresponding to cells in an 'immune' state, that experience a low activating field, $(d/(p-d))\theta_1$, [figure 3(a)] and
3. an intermediate population level corresponding to the cells in a 'suppressed' or 'tolerant' state, that experience a high suppressive field, $((p-d)/d)\theta_2$ due to the high population of the anti-idiotype. [figure 3(b)]

The robustness analysis (Appendix C) along with the phase diagrams [figure 4] indicate that the immune response models are stable under physiological deviations in the values of antigen infection size A_0, rate constant of idiotype-antigen interaction (k), and production rate of B cells (m).

The Cayley tree configuration with 3 nodes with no loops and full rotational symmetry was studied to analysis the effect of the network topology on the attractors of the model proposed. The Cayley network also approaches, according to the parameter set-up, one of the following attractors:

- the virgin attractor, $X_i = m/d$;
- a vaccination attractor where $X_1 = H$, $X_2 = L/z$ and all other $X_i \sim m/d$. [figure 6(a)]
- a tolerant attractor where $X_1 \sim m/d$, $X_2 = H$, $X_3 = L/(z-I)$. [figure 6(b)]
- a percolation attractor, when the response to the antigen does not remain localized, but spreads and excites clones all over the network. A percolation configuration can be, for instance:
  $X_3 = X_7 = X_{11} = \ldots\ldots = H$
  $X_4 = X_8 = X_{12} = \ldots\ldots = L/(z-1)$
  and all other $X_i \sim m/d$. [figure 6(c)]

Conclusion

The mathematical or qualitative models proposed until now lack in comprehensively describing the immune system due to lack of experimental data. In this work, quantitative response models were analyzed and the influence of various parameters on the ultimate fate of the immune response was studied. Though many of the characteristics features of the immune system could be reproduced by these simple models, a lot questions remains to be answered. Immune network topology is one area, which requires an in-depth understanding by analysis of different models and experimental findings. The global behavior, which results from the complex interplay of the individual elements of the immune system, remains to be understood completely. Cellular and molecular biologists and immunologists have achieved great success in isolating and even in understanding many of the molecules and cells of the immune system. However, their reductionist techniques fail when one asks questions about the behavior of large collections of cells and molecules. Again, the dynamics have been studied in this work using models for the immune system. However, because of the difficulties in collecting data from one animal at many time points, dynamic experiments are rarely done, and when they are done they rarely have data taken at more than a few time points. Thus, questions about whether immune system operates at steady state, whether they are oscillatory, whether they chaotic, etc.

References

1. De Boer, R. J., 1988, in Theoretical Immunology, Part Two, edited by A. S. Perelson (Addison-Wesley, Redwood City, CA), p.265
2. De Boer, R. J., and P. Hogeweg, 1989, Bull. Math. Biol. 51, 381-408.
3. De Boer, R. J, and A. S. Perelson, 1991, J. Theo. Biol. 149, 381-424.
4. B. Ermentrout, http://www.math.pitt.edu/~bard/xpp/
5. Hodgkin, A. L, and A. F. Huxley, 1952, J. Physiol. (London) 117, 500-544.
6. N. Jerne, 1974, Annals of Immunology, 125(C):373--389**.**
7. Perelson, A. S., and G. Weisbuch, 1992, Eds., Theoretical and Experimental Insights into Immunology (Springer, Berlin).
8. Stadler, P.P., P. Schuster, and A. S. Perelson, 1994, J. Math. Biol. 33, 111-137.
9. Weisbuch, G., R. De Boer, and A. S. Perelson, 1990, J. Theo. Biol. 146, 483-499

Appendix A:
The activation function and the Cayley Tree configuration.

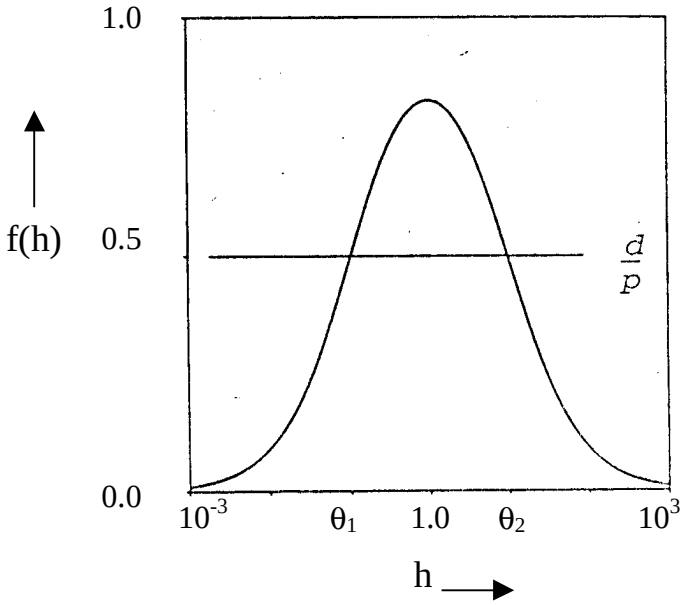


Figure 1. The log-bell-shaped activation function $f(h_i)$ defined by Eq.(3). As discussed in the text, when *m* is small, intersections of the line y = d/p with the bell-shaped curve define the activating and suppressive field values, L and H, respectively. For the parameters used here, p =1 and d =0.5, these intersections occur near the field values $\theta_1$and θ_2

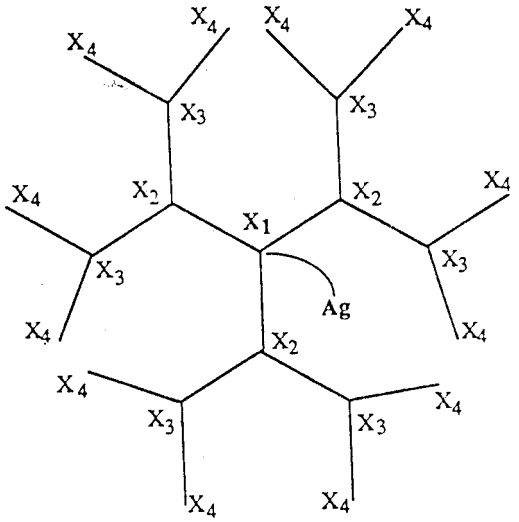


Figure 2. A Cayley Tree. This is a network without loops, in which each clone interacts fixed number of other clones. A Cayley tree with z = 3 is illustrated. Here only clone X_1 reacts with the antigen.

Appendix B:
Results of the Two Clone Immune Response Model

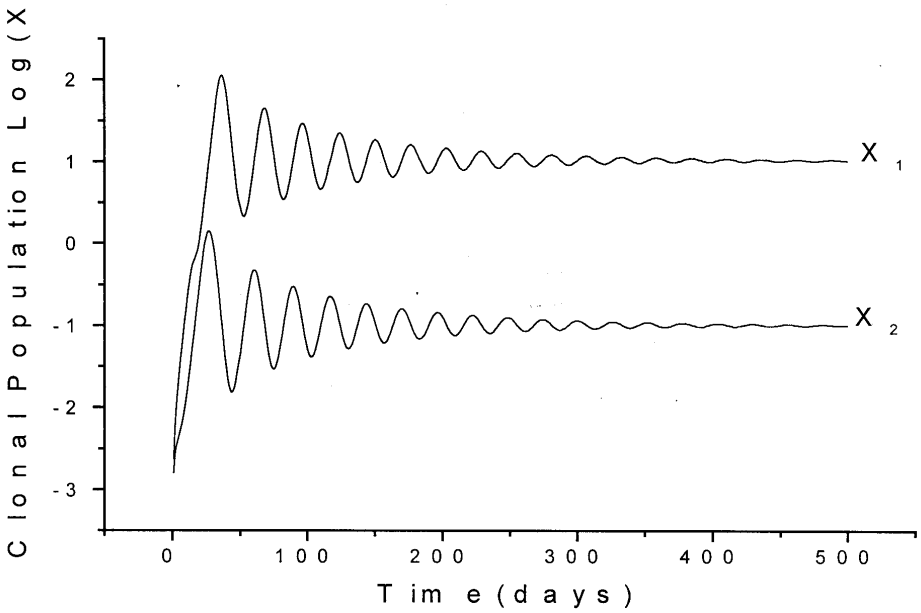


Figure 3(a). Dynamics of a response induced by injecting antigen A that results in the system approaching the immune attractor. The clone population sizes are plotted vs time in days. In the immune configuration the largest population is localized at the first level. X_1 is high (H) and is sustained by interacting with X_2, which is at a lower level(L).

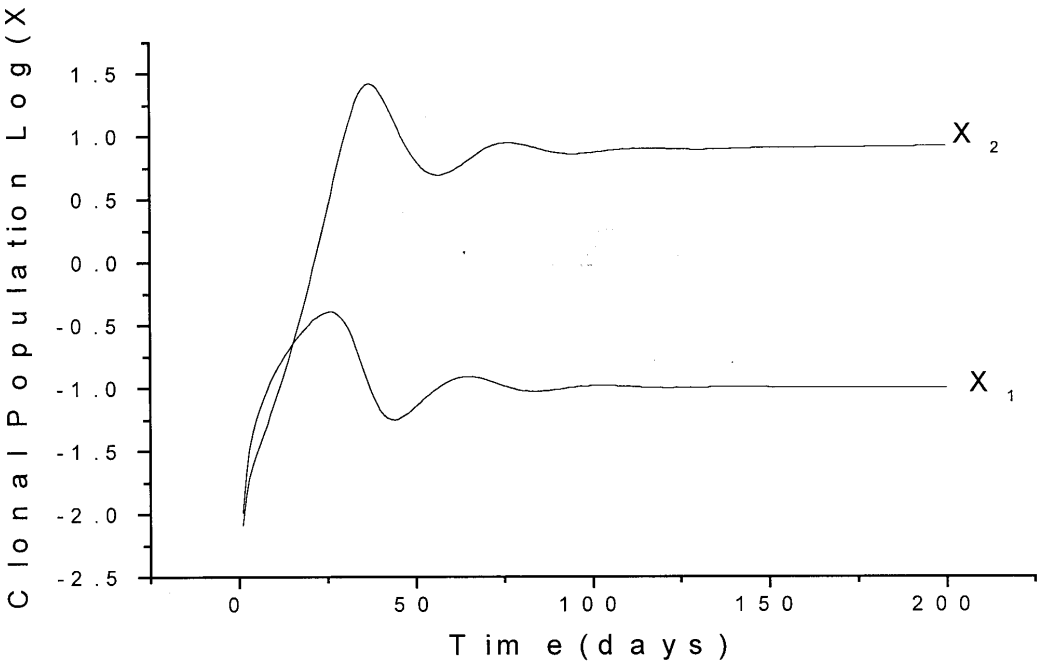


Figure 3(b). Dynamics of a response induced by antigen A that results in the system approaching the tolerant attractor. At the attractor, X_2 is high (H) and is sustained by X_1, which is at L.

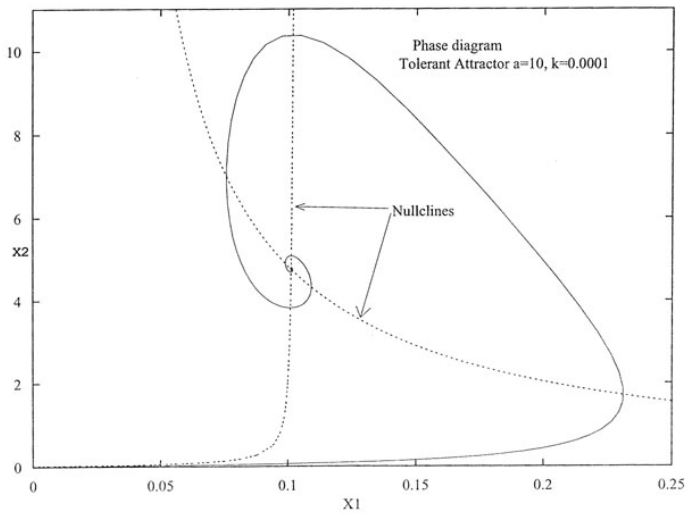


Figure 4(a). Phase portrait of the dynamics of interacting clones. The system approaching the tolerant attractor (x1, x2) ≈ (H,L). (x1 and x2 plotted on log-log scale for better representation)

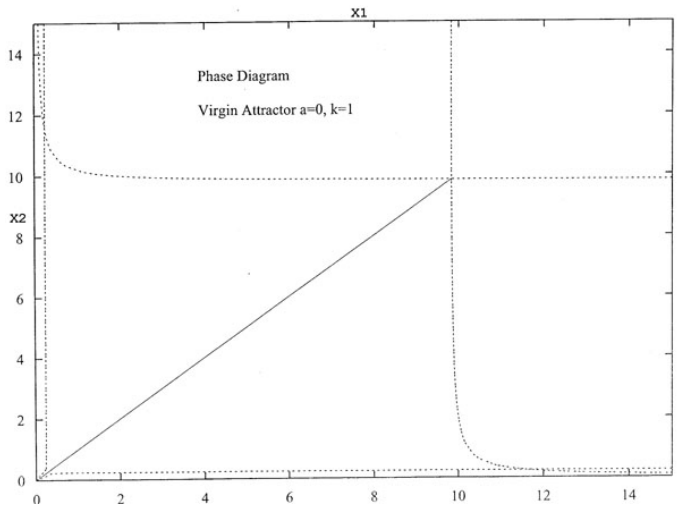


Figure 4(b). Phase portrait of the dynamics of interacting clones. The system approaching the virgin attractor (x1, x2) ≈ (L,L). (x1 and x2 plotted on log-log scale)

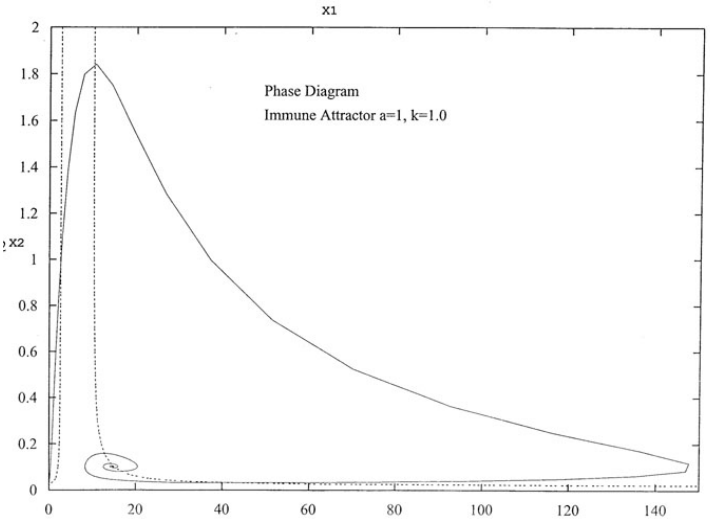


Figure 4(c). Phase portrait of the dynamics of interacting clones. The system approaching the immune attractor (x1, x2)≈ (L,H). (x1 and x2 plotted of the log-log scale)

Appendix C:

Robustness and Validation of the Two Clone Model

A good model of a physiological process should remain valid in the presence of small variations in the physiological circumstances. This is what is known as the robustness. The robustness and flexibility of the model equations (1), (2) and (4) in the presence of physiological variations from nominal behavior was considered with respect to variations in:

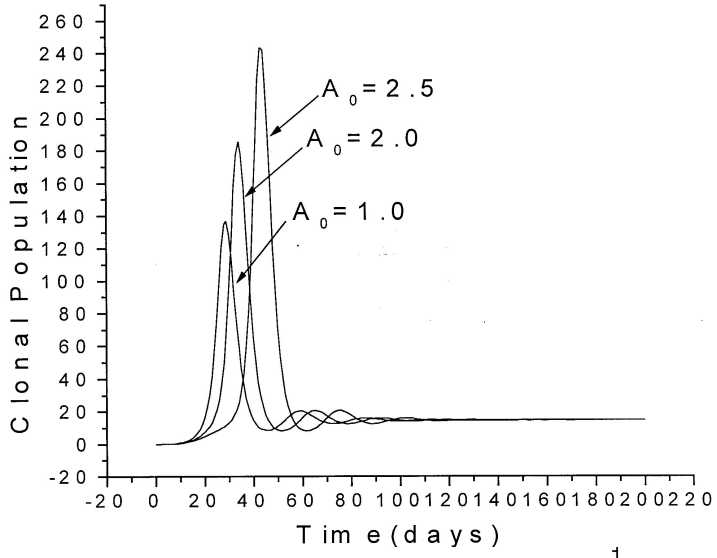


Figure 5(a). Variation in Infection size of the Antigen (A_0).

Minor variations in the initial infection dosage seldom evoke a radical change in the nominal immune response, as was the case with the presented model. The steady state values of the clonal population are stable even for significant variations in the initial infection size. A small difference occurs in the timing: the larger the initial infection the later the peak but with a higher and more wide spread (effective) initial simulation

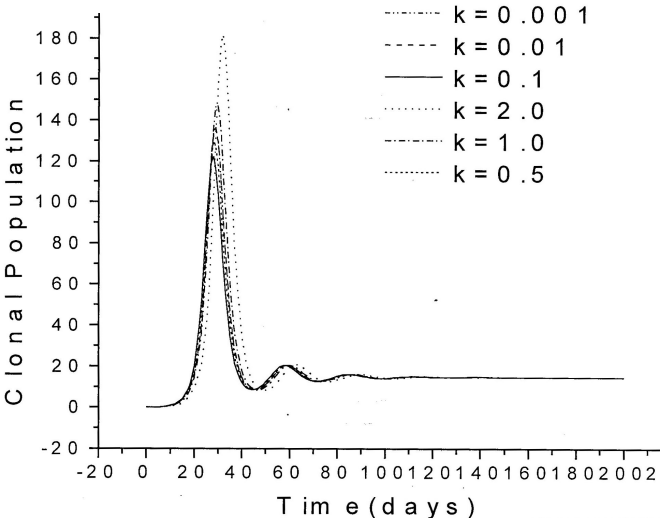


Figure 5(b). Variation in the rate constant of idiotype-antigen interaction (K).

The antibody-antigen reaction rate constant, K, determines the strength of interaction between antibody and antigen and the rate of removal of the antigen. Minor variations in K are expected under the physiological circumstances due to presence of idiotypes with slightly different conformations and hence having different rate constant. Increasing values of K results in a larger initial peak.

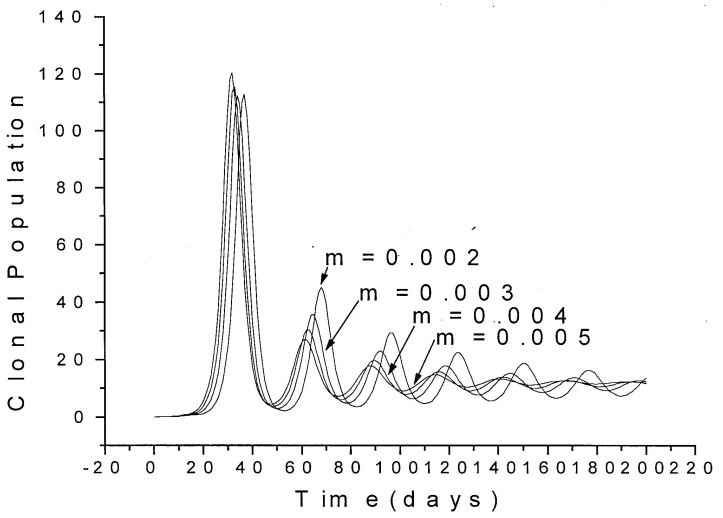


Figure 5(c). Variation of the production rate of the B cells (m).

The production rate of the B cells may vary with the physiological condition of the immune system and the health of the person. Nominal variations in m only results in subtle variations in the clonal population dynamics with a change observed in the frequency of the oscillations

Appendix D:
Results of the Cayley Tree Configuration simulations.

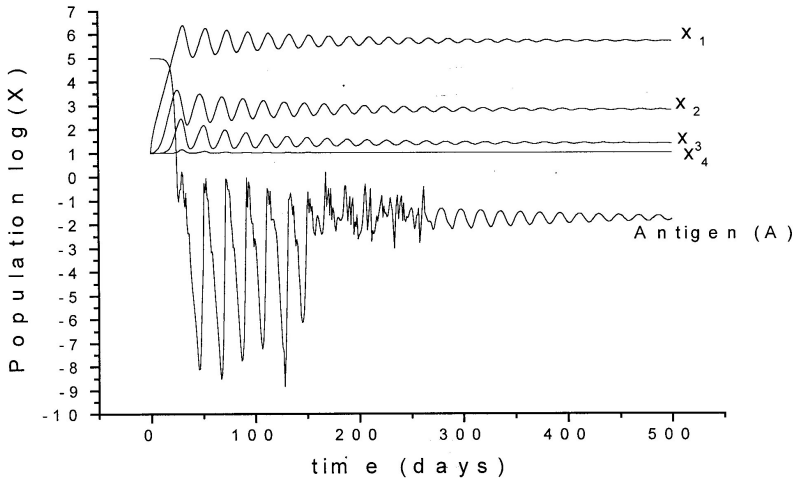
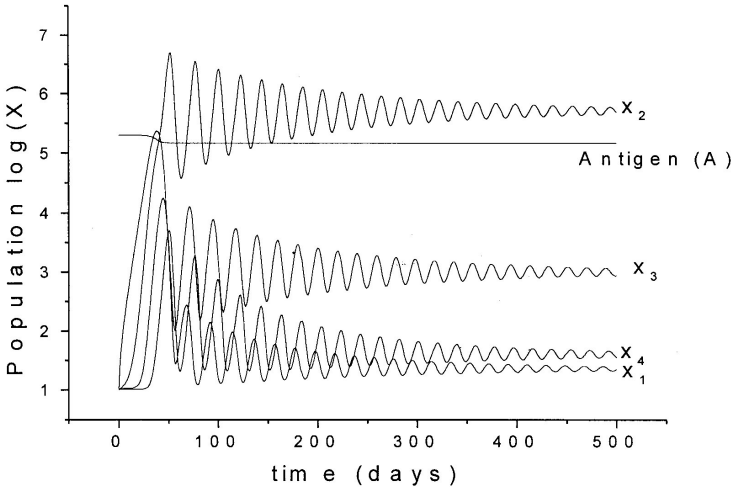


Figure 6(a). The vaccinated state is a localized state where the population X_1 is high (H) and sustained by an intermediate population (L) of X_2; X_2 suppressed by X_1. Dynamics leading to vaccination : X_1,the idiotypic clone, proliferates earlier than X_2 and suppresses it while eliminating the antigen. The parameters are: $k=10^{-5}$; $A_0=10^5$; d=1.0; p=1.5; z=3; m=10; $\theta_1=1000$; $\theta_2=10^6$.

Figure 6(b). The tolerant state is a localized state where X_z is high (H) and sustained by X_3 (L) which is suppressed by X_2. X_1 is over-suppressed by the zX_2 clones that it recognizes and therefore cannot eliminate the antigen. Dynamics leading to tolerance: X_2, the anti-idiotypic clone, proliferates faster thanX_1. X_3 is excited to a low level and sustains X_2 The parameters are: $k=10^{-7}$; $A_0=2*10^5$; d=1.0; p=1.5; z=3; m=10; $\theta_1=1000$; $\theta_2=10^6$.



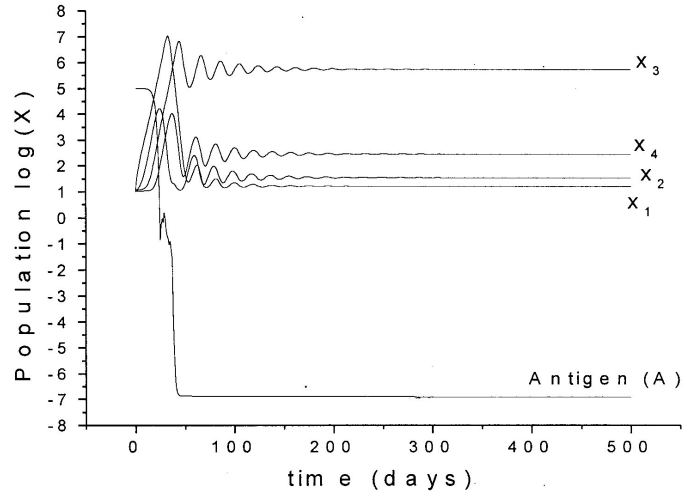


Figure 6(c). Percolation dynamics: first X_1 grows to H and X_2 to L; X_2 triggers X_3 and X_4, which then triggers the next couple and so on. When both X_1 and X_3 are high, X_2 is over suppressed and so X_1 cannot be sustained. The parameters are: $k=10^{-7}$; $A_0=2*10^5$; d=1.0; p=1.5; z=3; m=10; $\theta_1=1000$; $\theta_2=10^6$.