Chapter 11. Complexity and stability in network theory

A major problem for civilization is to wed the complexities of our society with stability. This is particularly pressing with respect to the civic disarray prevailing in many countries, the economy and the ecosystem. As society becomes more complex does it necessarily become more unstable? The immune system and the central nervous system are both very complex systems. How do they achieve their evident stabilities? Can they teach us anything in this regard? These are deep questions, and most people imagine that the systems are so different that we are unlikely to be able to use ideas from one system in thinking about another. However, analogy is an incredibly powerful mediator of "original" ideas, and we need all the original ideas we can muster for the above problems. The analogy between the brain and the immune system seems to have played an important role in Jerne's thinking when he formulated the idiotypic network hypothesis. In this chapter we will see that a more complex version of the symmetrical network theory is also viable. This immune network theory led to the formulation of a speculative neural network model, in which neurons exhibit hysteresis.[160]

So far in our immune network modelling we have focused mainly on only two representative complementary clones, that have some characteristic strength of interaction. The two-variable model can also be interpreted more broadly as simulating two classes of clones ("antigen-specific" and "antiidiotypic") that have some average or effective strength of interaction. We would now like to know what happens with a more extensive network, in which each clone interacts with several others, each with an individual interaction strength. If the interaction strength (say, the affinity) between a V region of a clone i and a V region of a clone j is K_{ij}, we have a clonal affinity matrix K_{ij}, with i and j going from 1 to N, where N is the number of clones. We might expect that most of the K_{ij} are zero, with each clone interacting with only a small fraction of all the rest. This is a realistic assumption if only high affinity interactions are important in regulation, but that has not been established. Different types of interactions are bound to have different affinity thresholds. For example, it is conceivable that low affinity interactions between the idiotypes of antigen-specific B cells and antiidiotypic helper T cell idiotypes are important in the development of the B cell repertoire, with higher affinity interactions being important for killing of lymphocytes by antiidiotypic antibodies.

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[160] G. W. Hoffmann, M. W. Benson, G. M. Bree and P. E. Kinahan (1986) A teachable neural network based on an unorthodox neuron. Physica 22D, 233-246.

The unpredictability axiom

It can be argued that the proper functioning of the network cannot be dependent on the initial detailed structure of the V region interaction matrix (K_{ij}). The germ line cannot reasonably have a structure that leads to a specific V-V interaction matrix structure in heterozygous animals. This follows from the following considerations:

• Consider a mouse which is the off-spring of a father of an inbred strain A and a mother of another inbred strain B. Half of its V region genes are from the A strain, and half are from the B strain. The V regions of the A strain have not been selected to interact specifically with B strain V regions, nor with the V regions of any of many other strains that may be present and available for mating.

• We cannot predict which V regions will all be present in the offspring of any mating of two heterozygous mice, except to say that about half of the genes used can be expected to come from the father and about half from the mother. Heavy chains encoded by V_H genes from the father can combine with V_L chains encoded by either parent, and similarly V_H genes from the mother can combine with V_L from either parent. The same is true for T cell receptors. Specific T cell receptors are formed using two genes with variable parts, namely T cell receptor α and β chains. Clonal selection of T cell V regions is strongly influenced by major histocompatability complex (MHC) genes, including both MHC class I and MHC class II, as elaborated in the next chapter. Furthermore, in the context of network theory, antibody V regions influence the expression of complementary V regions in both T cells and B cells. This is a complex situation, and yet the immune system functions satisfactorily with a wide range of combinations of V_H, V_L, T cell receptor α, T cell receptor β, MHC class I and MHC class II genes. We can reasonably conclude from this that the correct functioning of the system is not dependent on a particular fine structure of the V-V interaction matrices for B cells and/or T cells. For the time being, for simplicity we will use just one interaction matrix to model B cell V regions interacting with each other, for T cell V regions interacting with each other, and for B cell V regions interacting with T cell V regions.

• Many mutations in antibody V region genes ("somatic mutations") occur in the course of immune responses, and the selection of the resulting clones depends on their affinities for the antigen and their affinities for other V regions. These somatic mutations add to the unpredictability in the V region interaction matrix.

• If we have an F1 cross between two viable inbred strains A and B, one of which is a recent laboratory developed strain with a new, mutant V region, the mutation leads to new V-V interactions that could never have been selected

during evolution. An F1 hybrid AxB is typically more healthy and viable than the parent strains. (This phenomenon is called "hybrid vigour.") An abrupt change in the V-V matrix thus does not typically cause a problem for the immune system.

We conclude that the rules that govern the interactions in the network must be such that the network functions properly even if there is a significant element of randomness in the generation of the V region interaction matrix. As a model-building construct, we can take this one step further and define a class of models that satisfy the condition that they function satisfactorily even if the V region interaction matrix is generated by a random number generator. This class of models is said to satisfy the "unpredictability axiom" of immune network theory.

An attractive aspect of the unpredictability axiom is its simplicity. Another way of stating it is to say that acceptable models must be robust with respect to the fine structure of the V region interaction matrix K_{ij}.

Some models fail to satisfy the unpredictability axiom. For example, the Richter model requires that the interaction strengths between species Ab1, Ab2, Ab3, Ab4 and Ab5 are in narrowly defined limits.

The unpredictability axiom is an approximation

While the mechanisms we have discussed make the fine structure of the V region network unpredictable, the constraint of self-tolerance means that there must be reproducibility in the repertoire at another level. The combination of self antigens and dynamical V-V interactions must lead to a reproducible shape space network topography that ensures self-tolerance. An apt analogy may be that a mosaic (fine structure) can depict a single scene (overall picture) in a myriad of different ways. In particular, the positive selection of T cells by the MHC, as discussed in chapter 12, leads to a repertoire being selected that is reproducible in its bias. In fact, the T cell specificities selected depend more strongly on the MHC of the individual than on the T cell V region genes. The mature T cell repertoire is strongly biased to include mainly V regions that have some affinity for self MHC. Thus while the unpredictability axiom is a useful construct, the concept of a V region interaction matrix generated solely by a random number generator is not strictly applicable to T cells. It should however be legitimate to model the T cell repertoire by a process involving random generation combined with positive selection by self molecules, especially MHC molecules.

The formation of complete heavy and light chain genes involves linking DNA that encodes the constant regions with the DNA that encodes the variable (V_H and V_L) parts. The B cell repertoire evolves with time. Early in ontogeny, there is one pattern of V gene expression for B cells (V genes close

in the genome to the C genes are preferentially expressed), while in a mature animal there is more random expression. A plausible interpretation is that in the young animal V regions combine with C regions to form a complete gene for a heavy chain or light chain more easily if they are close together. In the mature animal the network of idiotypic specificities has developed further, and the expression of many quasi-randomly distributed V regions is suppressed. The system then utilizes whichever V regions are compatible with the rest of the network, which is then a stronger constraint than the constraint that the V regions are close in the genome to the C region gene.

In chapter 17 I will make the case that the repertoire of serum IgG antibodies is tightly regulated by T cells, with the result that the V region repertoire of these antibodies is far from random. The non-randomness is with respect to a shape space axis defined by MHC molecules. The repertoire can nevertheless be random with respect to other shape space axes, and the unpredictability axiom remains a useful construct.

How unique is the virgin state of the two-variable symmetrical model?

Before developing an N variable model with a random set of V-V interaction strengths, we revert briefly to the two-variable model. We address the question of whether the two-variable symmetrical network model, as formulated, is just one of many possibilities. A comprehensive analysis of all non-linear models is not feasible, but we can explore the question of uniqueness of the virgin state of the symmetrical network model. We first make the case that V-V interactions are operative in the virgin state. Then we use stability considerations to add to the case that the virgin state involves the postulated interactions.

We recall that, in the immune state of the model:

• Antigen-specific clones kill off the antiidiotypic clones.

• This leaves the antigen-specific clones relatively isolated from V-V interactions.

• There is a balance between influx and non-specific death for the antigen-specific clones.

In the virgin state meanwhile:

• The level of antigen-specific cells has to be lower in the virgin state than in the immune state.

• The virgin state then cannot also be a balance between influx and non-specific death, since this would lead to the same level of antigen-specific cells in the virgin and immune states.

• It follows that we need V-V interactions in the virgin state, to keep the level of antigen-specific clones in the virgin state lower than for their level in the immune state.

For any steady state, including the virgin state, we have of course a balance between birth and death rates. In addition to this balance, we have the requirement that the steady state be stable. In the context of the constraint that we need V-V interactions in the virgin state, we can ask what birth and death terms are feasible from the point of view of the virgin steady state being stable. We will again see that the constraint of stability is a powerful one in discriminating between models that can work and models that cannot work.

For antigen-specific cells, the rate of birth can reasonably be expected to have, on the basis of mass action kinetics, one of the following three forms:

• a constant influx term.

• a term that depends linearly on the number of antigen-specific cells, and which is independent of any interactions with antiidiotypic cells. This term, acting alone, would give an exponential increase in the number of x_1 (antigen-specific) cells. It could be ascribed to stimulation by a self antigen, that is present at a constant level.

• a term that likewise depends linearly on the number of antigen-specific cells, but which is also dependent on stimulatory interactions with antiidiotypic cells or their V region bearing products. This could involve interactions with single or multiple cells or cell products, and hence may be either linear or non-linear (more than linear) in x_2.

Similarly, the rate of death of antigen-specific cells can reasonably be expected to be given, on the basis of mass action kinetics, by one of the terms:

• a natural death term

• death mediated by antiidiotypic cells, with a rate that depends linearly on the cells being killed, and a linear or nonlinear dependence on antiidiotypic cells or their products. (A constant rate of death is not physically reasonable, since it could lead to negative population levels.)

The feasible virgin state terms may thus have one of the following forms (in which, without loss of generality, we use units of time and concentration such that the rate constants are unity):

$$\frac{dx_1}{dt} = 1 - x_1 x_2{}^{\nu}$$

$$\frac{dx_2}{dt} = 1 - x_2 x_1{}^{\nu} \qquad (11.1)$$

or

$$\frac{dx_1}{dt} = x_1 x_2{}^{\mu} - x_1 x_2{}^{\nu}$$
$$\frac{dx_2}{dt} = x_2 x_1{}^{\mu} - x_2 x_1{}^{\nu} \qquad (11.2)$$

Here μ is an integer greater than or equal to zero, and ν is an integer greater than or equal to 1. The steady state in all cases is at $x_1 = 1$, $x_2 = 1$.

Following the established procedure, we can then readily show that the eigenvalue equation at the steady state for the system (11.2) is:

$$\begin{pmatrix} -\lambda & -\nu+\mu \\ -\nu+\mu & -\lambda \end{pmatrix} = 0$$

The eigenvalues are then $\pm(\nu-\mu)$. We must have $\nu \neq \mu$, otherwise $\frac{dx_1}{dt} = \frac{dx_2}{dt}$ for all values of x_1 and x_2, and there is no regulation. Then one of the eigenvalues is positive, and the system is unstable.

In the case of equation (11.1) the eigenvalue equation is

$$\begin{pmatrix} -1-\lambda & -\nu \\ -\nu & -1-\lambda \end{pmatrix} = 0$$

and the eigenvalues are $-1 \pm \nu$. If $\nu > 1$ one of the states is unstable. If $\nu = 0$ we would have a putative virgin state that is a balance between the source term and the non-specific death term. This would give a level of x_1 in the virgin state that is the same as that in the immune state, which is unacceptable. The only remaining possibility is $\nu = 1$, in which case the eigenvalues are 0 and –2. The zero eigenvalue is indicative of neutral stability, which turns out not to be a problem. The reader can readily verify that the addition of even a very small non-specific death term (which we need anyway for the immune state) changes the zero eigenvalue to it having a negative value, and the steady state becomes a bona fide attractor. We will see below that in an *N*-variable generalization of the model we do not even need the non-specific death term for this purpose.

Table 11-1 summarizes the results we have obtained in this section.[161] (In the table "d.e." is an abbreviation for differential equation.) Stability analysis is seen here to be an extremely powerful method for identifying models that do not work, and by elimination, for finding at least one model that does work.

We conclude that the virgin state must have the form

$$\frac{dx_1}{dt} = S - k_2 x_1 x_2$$

$$\frac{dx_2}{dt} = S - k_2 x_1 x_2 \qquad (11.3)$$

That is, the virgin state is necessarily a balance between non-specific influx and killing that is linear in the concentration of the complementary cells.

A crucial caveat however remains. We have assumed in the above that the influx rates of x_1 and x_2 cells are identical. If we consider the more general case of influxes given by S_1 and S_2, with S_1 not necessarily equal to S_2, we have:

$$\frac{dx_1}{dt} = S_1 - k_2 x_1 x_2$$

$$\frac{dx_2}{dt} = S_2 - k_2 x_1 x_2$$

For $S_1 \neq S_2$ subtraction of the first equation from the second yields

$$\frac{dx_1}{dt} - \frac{dx_2}{dt} = S_1 - S_2 \neq 0$$

[161] G. W. Hoffmann (1982) The application of stability criteria in evaluating network regulation models. In "Regulation of Immune Response Dynamics" vol. I, C. DeLisi and J. R. J. Hiernaux, Eds., CRC Press, 137-162.

Table 11-1 Eigenvalues (λ) and stability characteristics of two-variable symmetric models. From G. W. Hoffmann (1982) in "Regulation of Immune Response Dynamics" vol. I, C. DeLisi and J. R. J. Hiernaux, Eds., CRC Press, 137-162.

	Dominant positive (birth) term in the differential equation for x_1			
	1	x_1	$x_1\ x_2$	$x_1 x_2^{\nu}\ (\nu > 1)$
Dominant negative (death) term in the d.e. for x_1				
x_1	λ = -1, -1 Stable	No regulation	λ = 1, -1 Unstable	$\lambda = \nu$, $-\nu$ Unstable
$x_1\ x_2$	λ = 0, -2 Stable	λ = 1, -1 Unstable	No regulation	$\lambda = \pm(\upsilon - 1)$ Unstable
$x_1 x_2^{\mu}\ (\mu > 1)$	λ = -1 - μ , -1 + μ Unstable	$\lambda = \mu$, $-\mu$ Unstable	$\lambda = \pm\ \mu$ -1 Unstable	If $\nu = \mu$ no regulation If $\nu \neq \mu$ $\lambda = \pm(\mu - \nu)$ Unstable

Integrating, we obtain $x_1 - x_2$ as a function of time:

$$x_1 - x_2 = (S_1 - S_2)t + c$$

where c is a constant of integration. Thus for $S_1 \neq S_2$ the difference $x_1 - x_2$ between the two population levels increases or decreases monotonically with time; if they are both to stay positive, one of them must go to infinity. Satisfying the condition $S_1 = S_2$ would be fortuitous; there is no reason why complementary clones (or groups of complementary clones) should be produced at precisely the same rates.

The bare bones virgin state of our two variable model, as it stands, is thus less than robust in this regard. The question then arises of whether making the network larger or having a greater density of network interactions would

increase our chances of having a stable network. The answer is yes, but this was a surprise for mathematicians working in the area of complex systems.

Stability versus complexity? Models with *N* variables

Some physicists have studied ecological network models (predator-prey models) that have some similarity to the immune system network models. Books by May[162] and Siljak[163] have made the case that as systems become more complex, they are likely to become less stable. For example, in support of this proposition, numerical studies by Gardner and Ashby[164] and an analytical study by May[165] showed that, in the following linear system, stability is opposed to complexity:

$$\frac{dx_i}{dt} = \sum_{j=1}^{N} a_{ij} x_j \tag{11.4}$$

The fraction of the matrix elements a_{ij} that are non-zero is called the connectance. The probability of stability decreases with the connectance, and with the size of the system (N). That is, the probability of stability for the system decreases as its complexity increases. May suggests that this is a *general* property of complex systems; the theme of his book is that complexity is opposed to stability.

On the other hand, the following N dimensional generalization of the interactions operative in the virgin state of our symmetrical network theory provides a counter-example to May's thesis:

$$\frac{d x_i}{dt} = S - x_i \sum_{j=1}^{N} K_{ij} x_j \tag{11.5}$$

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162 R. M. May (1974) "Stability and Complexity in Model Ecosystems", 2nd edition, Princeton University Press.

163 D. D. Siljak (1978) "Large-Scale Dynamic Systems: Stability and Structure," North-Holland, New York.

164 M. R. Gardner and W. R. Ashby (1970) "Connectance of large dynamic (cybernetic) systems: critical values for stability." Nature 228, 784.

165 R. M. May (1972) "Will a large complex system be stable?" Nature, 238, 413-414.

where $K_{ij} = K_{ji}$. This equation is an N clone version of equation (11.3) above. The fraction of non-zero terms in $\mathbf{K}$, the matrix with elements K_{ij}, is the connectance, and we denote it by C. The larger the value of N, and the higher the value of C, the more likely this system is stable, as shown in Figure 11-1, which shows the probability $P_{SS}(N,C)$ of the system having a stable steady state as a function of C for three values of N, as determined by numerical integration. Hence the more complex this system is, the more likely it is to be stable. By numerical integration of equation (11.5) I showed that, for large N, there is a sharp transition from the system being certainly unstable to being certainly stable, as C increases.[166] The threshold connectance needed for a system with N clones to have a stable steady state, $C_T(N)$ is defined as the value of C for which there is a 50% probability of stability. Figure 11-2 shows $C_T(N)$ as a function of N, the number of clones. The value of $C_T(N)$ for $P_{SS}(N,C)$ is roughly equal to $N^{-0.7}$. It can also be seen in Figures 11-1 and 11-2 that, to a good approximation, each clone must interact with at least two others for the system to be stable. Put another way, every clone needs at least two "enemies" (or regulators) for the system as a whole to be stable.

Another feature of this system, first established numerically, is that when the connectance is high enough to yield a stable steady state that solution is unique, even though the system is highly dimensioned (many clones) and the $\mathbf{K}$ matrix (the matrix with elements K_{ij} with $K_{ij} = K_{ji}$) is generated by a random number generator. The evidence for this is that the same steady state solution that is found is independent of the initial values of the x_i. This fits well with the finding that immune responses that involve IgM but not IgG do not exhibit memory. In such responses the system is perturbed from its initial steady state, but reverts to that same steady state after the antigen is eliminated.

The system (11.5) has also been investigated analytically by Spouge, who emphasized that for this system, unstable subsystems can be combined to yield a stable, more complex system.[167]

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166 G. W. Hoffmann (1982) The application of stability criteria in evaluating network regulation models. In Regulation of Immune System Response Dynamics, C. DeLisi and J. R. J. Hiernaux (Eds.) vol. I, 137-162.

167 J. L. Spouge (1986) Increasing stability with complexity in a system composed of unstable subsystems. J. Math. Analysis and Applications 118, 502-518.

Figure 11-1. The probability $P_{SS}(N,C)$ of the system (11.5) having a stable steady state as a function of the size of the system (value of N) and the connectance (fraction of non-zero terms in the matrix $\mathbf{K}$). Also shown is the probability $P_2(N,C)$, of all the clones in the system having non-zero interactions with two or more other clones.

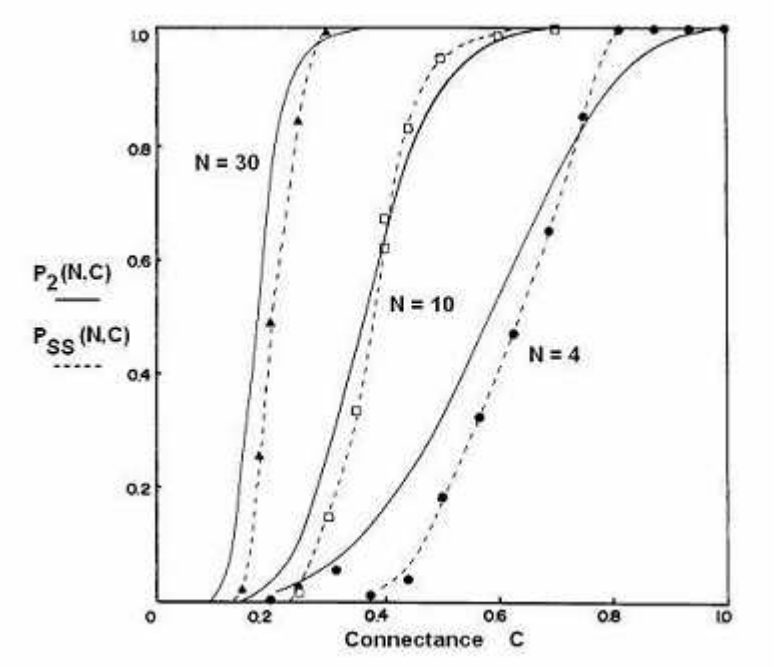
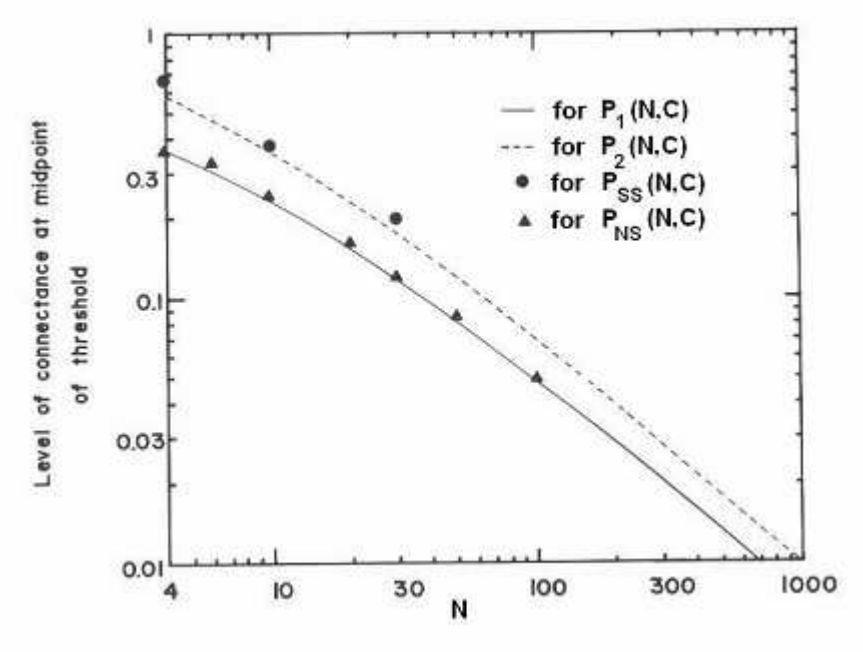


Figure 11-2. The threshold level of connectance, $P_{SS}(N,C)$, required for the system (11.5) to be stable, as a function of N, as determined by numerical integration. The threshold is defined as the level at which there is a 50% probability of the system being stable. Also shown are thresholds for each clone interacting with at least one other clone, $P_1(N,C)$, at least two other clones, $P_2(N,C)$, and for the matrix of interaction strengths being non-singular, $P_{NS}(N,C)$. Values used for determining $P_1(N,C)$ and $P_2(N,C)$ were obtained analytically. The value of $P_{SS}(N,C)$ is seen to be well-approximated by the threshold for each clone interacting with at least two other clones.



Perturbing the system with IgM antibody

The system (11.5) models non-specific influx and killing by IgM. It suggests that adding IgM of some specificity would shift the steady state of this system. Such an effect has been observed by Forni and colleagues, who found that injecting mice with IgM specific for sheep red blood cells or specific for dextran resulted in the production of antibodies with the same specificity.[168] This was without any injection of the antigen. The IgM was either immune serum that was depleted of IgG, or monoclonal IgM antibodies. As little as 40ng of IgM induced a 4-fold increase in anti-SRBC plaque forming cells. This amount compares with the normal total level of IgM in mice of about 200μg/ml. Since this system is relatively simple, more quantitative analysis may prove to be fruitful.

Stability of systems with symmetric versus asymmetric interactions

Another idea developed by May in his book is that symmetric interactions are more destabilizing than asymmetric interactions.[162] This can be made plausible by considering the following two matrices:

$$\mathbf{A} = \begin{pmatrix} a & b_1 \\ b_2 & a \end{pmatrix}$$

and

$$\mathbf{B} = \begin{pmatrix} a & b_1 \\ -b_2 & a \end{pmatrix}$$

where a, b_1, and b_2 are real, and b_1 and b_2 have the same sign. The matrix $\mathbf{A}$'s eigenvalues are $a \pm \sqrt{b_1 b_2}$, so $\mathbf{A}$ is stable if and only if $a < 0$ and $\sqrt{b_1 b_2} < a$. That is, there are two conditions to be fulfilled. $\mathbf{B}$'s eigenvalues are $a \pm i\sqrt{b_1 b_2}$, so $\mathbf{B}$ is stable if and only if $a < 0$. That is, there is only one condition to be fulfilled. It is more probable that just one condition is satisfied than two, so the more symmetric system is less likely to be stable.

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168 L. Forni, A. Coutinho, G. Köhler and N. K. Jerne (1980) IgM antibodies induce the production of antibodies of the same specificity. Proc. Nat. Acad. Sci. (USA) 77, 1125-1128.

Our virgin state system is however stable even though it is completely symmetric, so also in this regard it is a counter-example to the generalizations proposed by May.

How many stable states?

The number of different stable states of an immune system is potentially very large. For example, even if there are only 1000 different, independently regulated antigens (which is not known to be the case, and may be too low), and if the system can be in any one of at least 3 stable states (virgin, immune and suppressed) for each one, then we would have 3 to the power 1000 (about 10^{470}) different stable states of the system as a whole, a greater-than-astronomical number.

Dynamics of an *N*-variable model displayed in two dimensions

A significant conceptual barrier to the further development of the symmetrical network theory was the problem of finding a way to depict the dynamics of an N -dimensional system on a two-dimensional page. A solution was found with the realization that each clone with population size x_i can be associated with an antiidiotypic field, Y_i, where

$$Y_i = \sum_{j=1}^{N} K_{ij} x_j \tag{11.6}$$

I have called Y_i the connectivity of the clone i, which is not to be confused with the connectance of the system (the fraction of non-zero elements in $\mathbf{K}$)[169]. The dynamics of the N -variable system (11.5) can then be represented by N trajectories in the x_i / Y_i phase plane as shown in Figure 11-3. The parameters for this example yield a stable steady state, with all of the N trajectories converging onto points on the line

$$x_i Y_i = S \tag{11.7}$$

which is a *locus of equilibrium* for the system.

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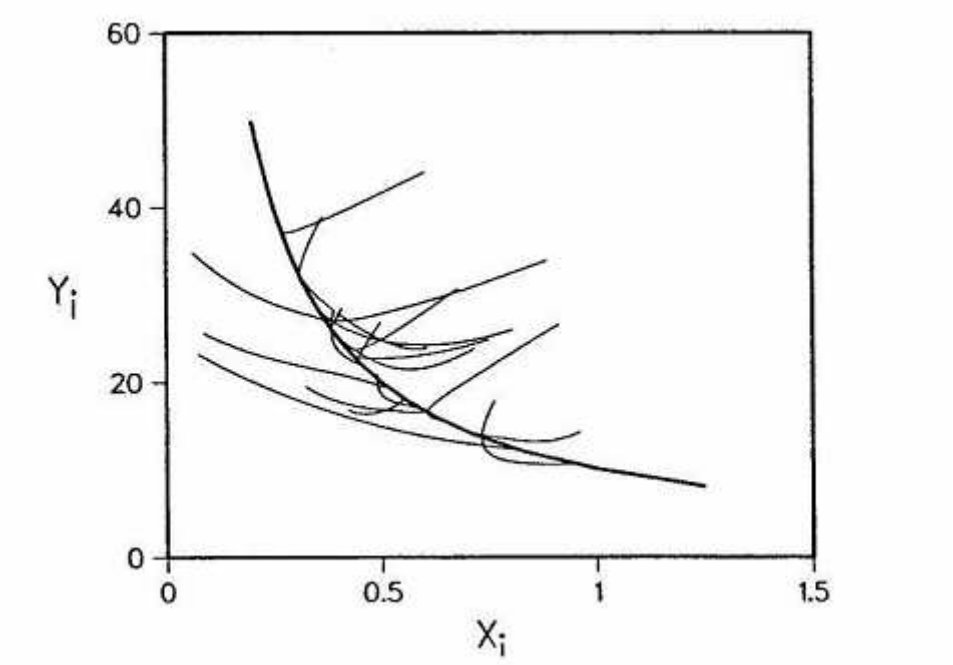
169 G. W. Hoffmann, T. A. Kion, R. B. Forsyth, K. G. Soga and A. Cooper-Willis (1988) in "Theoretical Immunology, Part Two", A. S. Perelson, Ed., Addison Wesley Publishing Company, Redwood City, California, 291-319.

Figure 11-3. Phase plane dynamics for the system (11.5), a simple model of the interactions of clones in the virgin state. Each clone has a population size x_i and a field Y_i, where $Y_i = \sum_{j=1}^{N} K_{ij} x_j$. Providing the size of the system (number of clones, equals the value of N) and the connectance C (fraction of non-zero K_{ij}) are large enough, all the trajectories converge onto the line $x_i Y_i = S$, which is a locus of equilibrium. Otherwise some clone population levels go to zero, while others increase without limit. The parameters here are N = 20, S = 10, C = 0.5, non-zero K_{ij} values randomly distributed between 0.0 and 1.0, and initial values of the x_i randomly distributed between 0.0 and 1.0. Reproduced from G. W. Hoffmann et al. (1988) in "Theoretical Immunology, Part Two", A. S. Perelson, Ed., Addison Wesley Publishing Company, Redwood City, California, 291-319.



Following this approach, the two-variable system of equation (10.2), that includes a constant source term, IgM killing, IgG killing, non-specific death, and sharp thresholds for inhibition by specific T cell factors, can be very simply generalized to N dimensions by replacing x_1 by x_i, and replacing x_2 by the field (connectivity) of clone i, namely Y_i (with $i=1$ to N):

$$\frac{dx_i}{dt} = S - k_2 x_i Y_i e_{2i} - k_3 x_i Y_i^2 e_{3i} - k_4 x_i \tag{11.8a}$$

with

$$e_{qi} = 1 \text{ for } x_i Y_i < C_q$$

and (11.8b)

$$e_{qi} = 0 \text{ for } x_i Y_i > C_q$$

for i = 1 to N and $q =$ 2 and 3. The x_i / Y_i phase plane is then divided into three regions by the lines $x_i Y_i = C_2$ and $x_i Y_i = C_3$; see Figure 11-4 for an example with parameters that satisfy the inequalities:

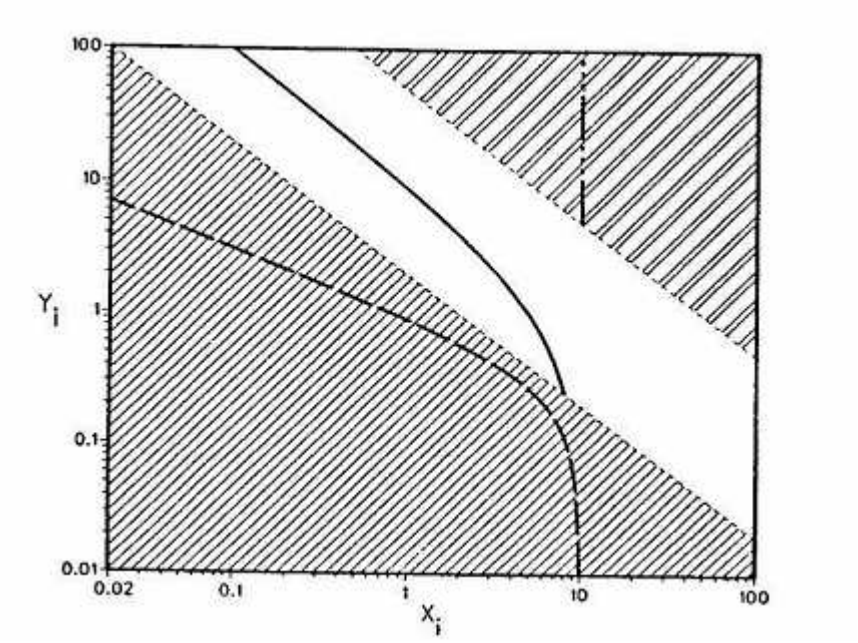
$$\frac{k_4}{k_3} < C_3 < \frac{S}{k_2} < C_2 < \left(\frac{S}{k_4}\right)^2$$

This set of inequalities corresponds to one of the two regions of parameter space derived for the two-dimensional model; see the inequalities (10.15a) in the previous chapter. Each of the three regions contains a locus of equilibrium, that is obtained by setting $\frac{dx_i}{dt} = 0$.

The locus for the immune and anti-immune states is:

$$x_i = \frac{S}{k_2 Y_i + k_3 Y_i^2 + k_4} \tag{11.9}$$

Figure 11-4. The three regions in the x_i / Y_i phase plane of the N-dimensional model, that each contain a locus of equilibrium. The regions are bounded by the lines $x_i Y_i = C_2$ and $x_i Y_i = C_3$. The equations of the loci of equilibrium are (11.15) (immune and anti-immune states – – –); (11.16) (virgin state ——); and (11.17) (suppressed state – – – –). Parameters: k_2 = 1, k_3 = 10, k_4 = 1, S = 10, C_2 = 50, C_3 = 2. Reproduced from G. W. Hoffmann et al. (1988) in "Theoretical Immunology, Part Two", A. S. Perelson, Ed., Addison Wesley Publishing Company, Redwood City, California, 291-319.



The locus for the virgin state is

$$x_i = \frac{S}{k_2 Y_i + k_4} \tag{11.10}$$

and the locus for the suppressed state is

$$x_i = \frac{S}{k_4} \tag{11.11}$$

At a stable steady state for the entire system, the coordinates of each of the clones in the x_i / Y_i phase plane is situated on one of the loci of equilibrium. Figure 11-5 shows a simulation in which 25 clones are all given equal low initial clone sizes, and some of them go to the virgin state while others go to the immune/anti-immune locus. Antigenic stimuli perturb the clones from the loci of equilibrium. Figure 11-6 shows trajectories of clones, that are initially all in the virgin state, following a small transient perturbation. (Here we added a transient term simulating antigen to the differential equation.) The clones all return to the locus of equilibrium for the virgin state. This response models what happens with stimulation by a T independent antigen; the response has no associated memory. A larger perturbation (Figure 11-7) results in some of the clones switching to the suppressed state locus, with the clones that return to the virgin locus now returning to new (x_i, Y_i) coordinates, because of changes in their fields caused by clones that switched. This mathematical model does not include the role played by the A cell, and hence we do not see any clones switching to the immune state.

It is possible in this model to simultaneously have clones in all four of the virgin, immune, anti-immune and suppressed states. The immune and anti-immune states are along one locus of equilibrium, with immune state clones being at high x_i and anti-immune state clones being at low x_i. Clones are then all initially at one of the steady states and are perturbed to various degrees by a transient pulse of antigen. The antigen causes an increase in the level of the x_i and a decrease in Y_i for clones in the immune state.

The system (11.8) is a simple generalization of the two-variable model, and provides a representation of N -variable immune network dynamics on a two-dimensional page. It can however be argued that the model fails to accurately model the symmetry of the theory in one respect. The interactions between a clone i and a clone j should be equally inhibitable by clone i specific T cell factors and clone j specific T cell factors. If we model the concentration of

Figure 11-5. Trajectories in the x_i / Y_i phase plane for the system (11.8). In this example 25 clones are randomly connected with a connectance of 0.3. All clones are given initial x_i values of 0.1. Here some clones veer to low x_i and large Y_i (anti-immune state), while others go to large x_i and small Y_i (immune state), both of which are on the locus of equilibrium for the immune and anti-immune states, equation 11.15. The non-zero K_{ij} are random numbers in the range 0.0 to 1.0. All of the other parameters are the same as for Figure 11-4. Reproduced from G. W. Hoffmann et al. (1988) in "Theoretical Immunology, Part Two", A. S. Perelson, Ed., Addison Wesley Publishing Company, Redwood City, California, 291-319.

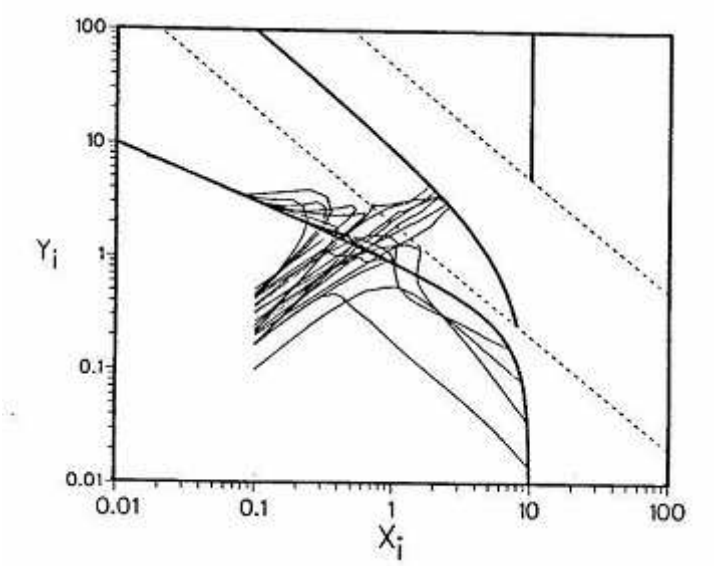


Figure 11-6. Another example of trajectories in the x_i / Y_i phase plane for the system (11.8). In this case all of the clones are initially in the virgin state (on the locus of equilibrium for the virgin state). A small transient perturbation by antigen causes the clones to leave the locus of equilibrium, and they then return to it. This simulates the effect of a T independent antigen that stimulates many clones, but does not cause an immune response with memory. The parameters are the same as for Figure 11-5. Reproduced from G. W. Hoffmann et al. (1988) in "Theoretical Immunology, Part Two", A. S. Perelson, Ed., Addison Wesley Publishing Company, Redwood City, California, 291-319.

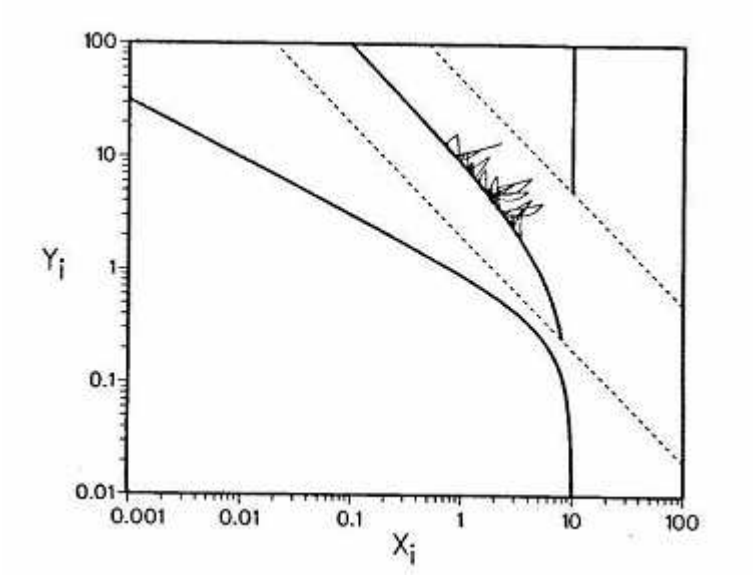
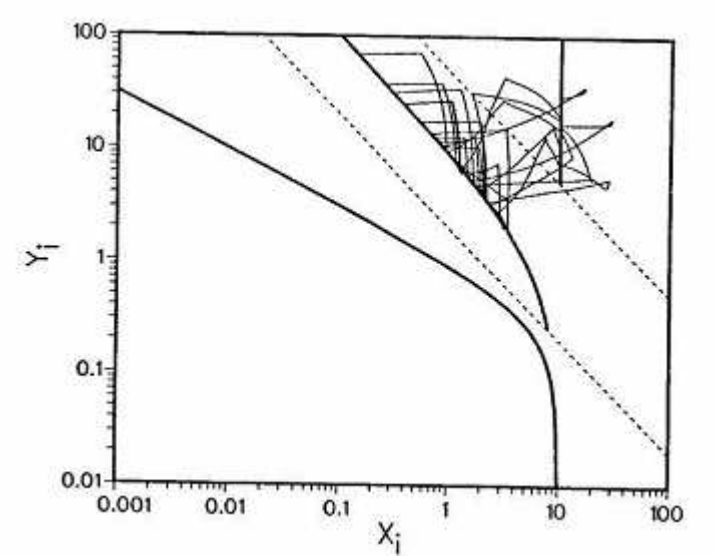


Figure 11-7. A third example of trajectories in the x_i / Y_i phase plane for the system (11.8). A larger pulse of antigen takes some clones into the zone of attraction of the suppressed state. The clones that do not switch return to new points on the locus of equilibrium for the virgin state, since their fields Y_i have changed. The parameters are the same as for Figure 11-4. Reproduced from G. W. Hoffmann et al. (1988) in "Theoretical Immunology, Part Two", A. S. Perelson, Ed., Addison Wesley Publishing Company, Redwood City, California, 291-319.



the former by $x_i Y_i$, perhaps we should model the latter by $x_j Y_j$. Our expression for e_q includes the former but not the latter. This is equivalent to saying that the model should include not only antigen-specific (x_i) and antiidiotypic cells (Y_i), but also anti-antiidiotypic cells, since the x_j would be antiidiotypic to x_i, and the Y_j would be antiidiotypic to the x_j clones. There are some experiments involving T cell regulation that demonstrate roles for three levels of T cells being involved in suppression, namely Ts1 that are antigen-specific and express a defined idiotype, Ts2 that are antiidiotypic, and Ts3 that bear the same idiotype as Ts1, and may or may not be antigen-specific.[170] When the antigen is introduced, it selects an antigen-specific population which in turn selects an antiidiotypic population, and there is a positive feedback loop between these two populations. If the Ts3 clones are not antigen-specific, we might expect the positive feedback loop between Ts1 and Ts2 to be dominant (because it is activated first), and the role of the next positive feedback loop, between Ts2 and Ts3 to be of secondary importance. On the other hand, if Ts2 and Ts3 are from populations of T cells that have a high initial level of connectivity to each other, the Ts2-Ts3 loop may also be important. We will describe a model that incorporates Ts1, Ts2 and Ts3 cells in chapter 17. At this stage, however, we will keep the model as simple as possible.

In light of the above considerations, one way in which the model can be kept reasonably simple and potentially improved is by replacing $x_i Y_i$ in the expressions for e_2 and e_3 by $X_i Y_i$, where X_i is a weighted sum of the clone i together with clones that are similar to clone i. In order to do this we need to have a quantitative measure of similarity of clones for each other. This similarity can for example be in the context of the set of V regions in the system. If the V region of a clone i binds to the V region of a clone k with an affinity K_{ik}, and the clone k has an affinity K_{kj} for clone j, then in the context of clone k, the similarity of clones i and j is proportional to K_{ik} and to K_{kj}. The significance of this similarity is furthermore proportional to the size of the clone k, namely x_k. The similarity S_{ij} of clones i and j in the context of all N clones in the system is then given by

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[170] R. N. Germain and B. Benacerraf (1981) Hypothesis. A single major pathway of T-lymphocyte interactions in antigen-specific immune suppression. Scand. J. Immunol. 13, 1-10.

$$S_{ij} = \sum_{k=1}^{N} K_{ik} K_{kj} x_k$$

The greatest similarity of a clone is with itself, so the S_{ij} matrix can be expected to be diagonally dominant. We use S_{ij} to define X_i according to

$$X_i = \sum_{j=1}^{N} S_{ij} x_j$$

We then have the system

$$\frac{dx_i}{dt} = S - k_2 x_i Y_i e_{2i} - k_3 x_i Y_i^2 e_{3i} - k_4 x_i \qquad \text{for } i = 1 \text{ to } N$$

with

$e_{qi} = 1$ for $X_i Y_i < C_q$

and for $i = 1$ to N and $q = 2$ and 3

$e_{qi} = 0$ for $X_i Y_i > C_q$

The reader may wish to explore the dynamical properties of this system.