STABILITY OF SYMMETRIC IDIOTYPIC NETWORKS— A CRITIQUE OF HOFFMANN'S ANALYSIS

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Hoffmann (1982) analysed a very simple model of suppressive idiotypic immune networks and showed that idiotypic interactions are stabilizing. He concluded that immune networks provide a counterexample to the general analysis of large dynamic systems (Gardner and Ashby, 1970; May, 1972). The latter is often verbalized as: an increase in size and/or connectivity decreases the system stability. We here analyse this apparent contradiction by extending the Hoffmann model (with a decay term), and comparing it to an ecological model that was used as a paradigm in the general analysis. Our analysis confirms that the neighbourhood stability of such idiotypic networks increases with connectivity and/or size. However, the contradiction is one of interpretation, and is not due to exceptional properties of immune networks. The contradiction is caused by the awkward normalization used in the general analysis.

Introduction. Immunologists have argued that the basic mode of idiotypic interactions should be suppression because this would guarantee network stability (Jerne, 1974; Cooper *et al.*, 1984). The stability criteria of large dynamic systems (Gardner and Ashby, 1970; May, 1972) however seem to invalidate this argument. An equilibrium point of a large dynamic system is almost certainly unstable if the number of variables (here idiotypes) and/or the connectance (here idiotypic interactions) exceeds a certain threshold. Because idiotypic networks comprise an extremely large number of variables ($>10^7$ clones), and because the number of idiotypic partners per clone (the connectance) may be high (Holmberg *et al.*, 1984, 1986; Vakil and Kearny, 1986; Novotny *et al.*, 1987), idiotypic networks are expected to have very few (or no) stable equilibrium points.

The converse was however suggested by Hoffmann (1982). Analysing a simple model with only suppressive idiotypic interactions he concluded that network stability (1) requires a minimum connectance and (2) increases with increasing connectance. Hoffmann's analysis was extended and confirmed analytically by Spouge (1986). We here investigate this apparent contradiction between the Hoffmann (1982) analysis and the, more general, Gardner and Ashby (1970) and May (1972) analysis.

The Hoffmann model is extended with a cell decay term, and compared with the symmetric ecological competition model used by May (1974), under

external equivalence (Irvine and Savageau, 1985) conditions. Analysis of the Jacobian matrix in the equilibria demonstrates that the Gardner and Ashby (1970) and May (1972) method cannot predict the increase in stability in these "extended Hoffmann" models. Thus the above contradiction hinges upon the method of analysis, and is not typical only of idiotypic networks (i.e. various other systems can also be expected to increase in stability if connectance increases).

Results.   Hoffmann (1982) proposed a very simple model defining an influx (S_i) for each clone X_i and a number of negative anti-idiotypic interactions with the clones X_j:

$$\frac{dX_i}{dt} = S_i - X_i \sum_{j=1}^{n} \mathbf{A}_{ij} X_j. \tag{1}$$

The matrix $\mathbf{A}$ is the affinity matrix; it is composed of random numbers that are uniformly distributed between zero and one (Hoffmann, 1982). All the S_i terms were set to one (Hoffmann, 1982). Idiotypic interactions are assumed to be symmetric (Hoffmann, 1979; 1980; 1982); it thus follows that $\mathbf{A}_{ij} = \mathbf{A}_{ji}$. Clones never recognize themselves: $\mathbf{A}_{ii} = 0$ (in the original Gardner and Ashby (1970) analysis all $\mathbf{A}_{ii}$ elements were negative). The connectance of the network can easily be varied by varying the number of non-zero elements in the $\mathbf{A}$ matrix. Hoffmann concluded from this model [equation (1)] that the probability of stability increases if both the connectance and/or the number of variables (n) increases. A highly connected idiotypic network thus appears to be a viable possibility (Hoffmann, 1982).

In the absence of idiotypic interactions (i.e. all $\mathbf{A}_{ij} = 0$), the Hoffmann (1982) model [equation (1)] is unstable: all clones then expand at a rate S_i (the original Gardner and Ashby (1970) analysis corresponded to individually stable parts). Stability thus at least requires one connection per clone. Therefore the Hoffmann (1982) result can best be rephrased into: an immune system that has no stable equilibrium can obtain one by negative idiotypic interactions. If the Hoffmann (1982) model is extended with a simple decay term, a non-connected network has a stable equilibrium point whatever the magnitude of such a term (i.e. even the smallest decay term alters Hoffmann's conclusion). Moreover, we think that normal turnover of lymphocytes is an essential property of immune regulation (De Boer and Hogeweg, 1985; 1986; 1987a; 1987b). We therefore extend equation (1) with a decay term:

$$\frac{dX_i}{dt} = S_i - DX_i - X_i \sum_{j=1}^{n} \mathbf{A}_{ij} X_j. \tag{2}$$

In the absence of idiotypic interactions each clone (X_i) equilibrates at S_i/D; the largest eigenvalue in that equilibrium point equals $-D$. Thus, in the absence of idiotypic interactions, such a decay term ensures stability. A minimum connectance (Hoffmann, 1982) is no longer required. We call equation (2) the "extended Hoffmann' (EH) model.

To pinpoint more closely the aberrant stability requirements of these (suppressive) immune networks, we compare networks based on equation (2) with the symmetric (ecological) competition model analysed by May (1974):

$$\frac{dX_i}{dt} = RX_i - BX_iX_i - X_i \sum_{j=1}^{n} A_{ij}X_j. \tag{3}$$

Populations grow exponentially at a rate R until a stable density R/B (the carrying capacity) is reached: this is the logistic equation [we call equation (3) the LC (logistic competition) model]. In the absence of connections the largest eigenvalue equals $-R$. Matrix A now defines the competition interactions with all other clones (all $A_{ii} = 0$).

Compare the stability of the equilibrium points of equations (2) and (3). This comparison is facilitated by parameter constraints, i.e. by external equivalence (Irvine and Savageau, 1985). Thus, we require equality in the absence of interactions for both stability $(D = A)$ and for the stable population size $(S/D = R/B)$. We compare the effect of increasing the connectance by providing identical A-matrices for both systems [internal equivalence (Irvine and Savageau, 1985)]. Now consider the diagonal elements of the respective Jacobian matrices [the off-diagonal elements of equations (2) and (3) are identical: $A_{ij}X_i$]. The diagonal elements of the EH model are:

$$-D - \sum_{j=1}^{n} A_{ij}X_j, \tag{4}$$

whereas those of the LC system are:

$$R - 2BX_i - \sum_{j=1}^{n} A_{ij}X_j, \tag{5}$$

and if we substitute the equilibrium value of X_i:

$$-R + \sum_{j=1}^{n} A_{ij}X_j. \tag{6}$$

In the absence of interactions (all $A_{ij} = 0$) the eigenvalues of equations (4) and (6) are identical: $-D = -R$. [Note that we have not substituted the equilibrium values in equation (4). Because these values are always positive,

this does not influence the following argument]. If connectance increases, the diagonal elements of the EH model [equation (4)] become more strongly negative, whereas those of LC systems [equation (6)] increase (and may become positive).

Thus, diagonal elements in the equilibrium situation: (1) depend on the connectance; (2) have an opposite response to a change in connectance in EH and LC systems. The original analysis of Gardner and Ashby (1970) and May (1972) was entirely defined on the Jacobian matrix. The diagonal elements were however constant (e.g. -1), i.e. were independent of the connectance. Thus the essential difference between the EH and the LC model is masked in the general Gardner and Ashby (1970) and May (1972) analysis. Application of their general results requires the rescaling of the Jacobian matrix relative to the model's interactions, see e.g. Rappoldt and Hogeweg (1980). If we were to rescale the Jacobian matrices (for each connectance) in order to scale the diagonal elements to a constant value [e.g. -1 (May, 1972)], we would have to decrease the off-diagonal elements of the EH systems. This however would mean decreasing the average interaction strength, which is known to increase the stability (May, 1972). Hence, if applied properly, the general May (1972) formula would predict an increase in the stability of equilibria if connectance increases in EH systems. We conclude that: (1) stability does indeed increase in EH systems, this largely confirms Hoffmann's (1982) result, but (2) that this is correctly predicted by the general May (1972) formula. Hence, the counter-example does not contradict these general results, but merely pinpoints the difficulties in their biological interpretation.

We also compared these two systems in a simulation study (under external equivalence conditions, e.g. $S_i = 100$ and $D = 1$ [equation (2)] plus $R = 1$ and $B = 0.01$ [equation (3)]). This allows us to analyse the stability of "attainable" [and hence stable and feasible (Roberts, 1974)] equilibrium points. In fact, it is not the percentage of stable equilibrium points in which we should be interested, but the likelihood that at least one (n-D) equilibrium is stable. Simulation (of a 50-D system) was performed by numerical integration using Adams Moulton's algorithm implemented in ACSL (Mitchell and Gauthier, 1986).

This simulation analysis confirmed the above results. The stability (measured by the largest eigenvalue) of the equilibria attained by EH systems increases if the network connectance is increased. In LC systems stability decreases in identical circumstances. Moreover, in the equilibria reached by the LC systems part of the populations is absent, i.e. is excluded by competition. Interestingly, in a system intermediate to the EH and LC system, ie one with a constant influx (S) and a squared self-limitation (BX_iX_i), stability first decreases but later increases if connectance is increased. [This system could also be made externally equivalent to the above systems (i.e. $S = 50$, $B = 0.005$).]

Discussion. The present paper solves the contradiction put forward by Hoffmann (1982). Simultaneously, it confirms Hoffmann's (1982) analysis (apart from the minimum connectance result): equilibria of suppressive idiotypic networks do indeed increase in stability if connectance increases. Hoffmann (1982) however concluded that, because equilibria are expected to be stable, strongly connected immune networks are viable possibility. We doubt the correctness of this conclusion for two reasons.

Firstly, the degree of stability of an idiotypic network is expected to affect the capacity of the system to respond to perturbations by external (non-idiotypic) antigens. In strongly connected networks an immune reaction would thus be impossible. This trade-off between stability and controllability is discussed in more detail by Segel and Perelson (1988); they deliberately define "nearly unstable" immune networks. Thus, although a strongly connected network may be viable (Hoffmann, 1982), it is expected to be unresponsive and hence non-functional.

Secondly, the present suppressive idiotypic networks omit proliferation, ie they omit an immune reaction. Incorporation of proliferation in these models requires the introduction of an exponential growth term (similar to that of the logistic equation) in the (extended) Hoffmann equation. Such terms have a destabilizing effect. We have previously analysed idiotypic networks that incorporate proliferation and suppression (De Boer, 1988; De Boer and Hogeweg, 1989). In such systems it was shown that the stability of equilibria first decreases and later increases if connectance is increased. Interestingly, these networks are only responsive to external antigens in the region where stability decreases. An increase of the network connectance does not only influence stability, but also disrupts the switching behaviour and responsiveness of the system. We think (De Boer, 1988; De Boer and Hogeweg, submitted) that these disruptive effects seriously question the viability of strongly connected idiotypic networks.

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