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Resilience and Variability in Pathogens and Hosts

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Adaptability by means of phenotype variability in host–pathogen systems is studied using a model that resembles a class of array systems known as cellular automata. Each automaton in this model is characterized by a network of $n \times m$ processors that process the information contained in levels 0 to m. The effect of the automaton's architecture on its ability to satisfy variations in constraints is analysed, and automata-evolution experiments are described. Increasing the number of organization levels in the automaton is shown to increase its efficiency in buffering external changes, and the mechanism of modulating the processing rules appears more efficient than the mechanism of controlling the mutation rate. Analogy with biological systems suggests that hosts and pathogens evolve towards increasing modulation of their genomic information processing and that single mature lymphocytes should be able to generate more than one antigen receptor. These hypotheses can provide an explanation for the sequential ordered expression of different antigen genes in trypanosomes, as well as for immunosuppression and autoimmune phenomena.

Keywords: automata; host–pathogen systems; antigenic diversity.

1. Introduction

THE IMMUNE system is capable of performing nontrivial tasks that today are referred to as 'learning', 'memory', and 'pattern recognition'. This machinery is thought to be so efficient that its methods are suggested as basic algorithms in solving fundamental problems in artificial intelligence (Farmer *et al.*, 1986).

Notwithstanding its 'cognitive' sophistication, it should be borne in mind that our immune system is outsmarted by simple organisms such as RNA viruses and protozoa. Of particular interest is the fact that, in spite of the seemingly limitless array of antibody types (Langman & Cohn, 1986), pathogens such as the HIV and the influenza viruses *Plasmodium falciparum* and *Trypanosoma brucei* evade immune surveillance by means of antigenic diversity and antigenic variation (Ratner *et al.*, 1985; Laver *et al*, 1981; Marsh & Howard, 1986; Van der Ploeg *et al.*, 1986).

Phenotypic variability seems to be the strategy of both parties in this type of confrontation, with no obvious advantage to the very complex host or the very simple pathogen. This may run counter to one's intuition that the phenotypic repertoire of organisms should somehow be related to their level of complexity.

The present work is concerned with adaptation in host–pathogen systems. This

problem has a physical aspect (infectious diseases) and nonphysical aspects (adaptation, variability, resilience, and complexity). These latter properties can be shared by objects with no physical basis in common and, hence, characterize both natural and artificial systems. This may justify the embodiment of these two sets of systems in a single unified theory (Holland, 1975), or at least the use of knowledge attained in one of the two sets to further the understanding of the other.

The latter approach is adopted in the present work. Adaptation by means of variability and resilience is studied in an automata model, and hypotheses concerning the efficiency of different mechanisms for the generation of phenotypic variability are suggested (Section 2). These hypotheses are tested in automata-evolution experiments described in Section 3, and the applications to natural host–pathogen systems are discussed in section 4.

2. The model

Our model organisms are cylindrical networks of $n \times m$ processors. A simpler rectangular form is studied elsewhere (Agur & Kerszberg, 1987). The 0-level information, represented by a cyclic binary string (to be denoted *ring*) of n bits, is transformed by n processors to produce a new n-bit ring at level 1, which is further processed to produce a third ring, and so on to level m.

Each ring of size n represents one level of organization of the automaton. The genomic information is represented by the top ring while the bottom ring represents the phenotype. The maximal number of ring configurations at level 0 is called *the genomic repertoire* $R_{0,n}$; the maximal number of ring configurations at the bottom level m is called *the phenotypic repertoire* $R_{m,n}$.

2.1 *The Processing Rules*

The processors in our model are described as Boolean functions that may assume a large variety of operations. Let $a_{i,j}$ be the memory value contained in the processor located in the ith row and jth column. Let $a_{i-1,j-r}$, $a_{i-1,j-r+1}, \ldots, a_{i-1,j+r}$ be the input values to this element and $a_{i,j}$ be the output. The new output of each element is then computed as a function of the input:

$$a_{i,j} = \Phi(a_{i-1,j-r}, a_{i-1,j-r+1}, \ldots, a_{i-1,j+r}),$$

where Φ stands for the processing rule and $r > 0$.

Nonlinear processing of macromolecules is a universal phenomenon, characterizing the whole spectrum of biological complexity from viruses to eukaryotes (see, for example, Leder *et al.*, 1980, and Reanney, 1982; for a more detailed description of the general character of the biological processing rules, see Agur & Kerszberg, 1987). The natural nonlinear processing activity is represented in our model by the *fail-safe* and the *majority* rules. In spite of their extreme simplicity, these rules incorporate some of the most fundamental properties of biological information handling, namely, an error-damping activity and a many/one and one/many type of hierarchy.

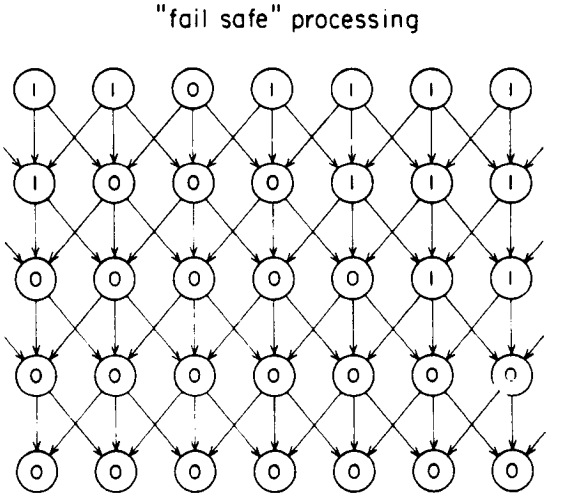

FIG. 1. A small subset of the information-processing automaton. Each circle represents a processor operating by the *fail-safe* rule (equation (1)). Its function is to receive from each of its three upper neighbours ($r = 1$) their information content in the form of a bit (either 0 or 1) and to generate from these an output bit that will be 1 if and only if the three input bits are 1 (and 0 otherwise). The top processors contain the bits which constitute the 'genetic message', while the bottom layer of processors generates a string of bits called the 'phenotype'.

The *fail-safe* rule (see equation (1) below) recognizes errors in the input and corrects them if they are not too large. This rule represents editing activity such as that of the DNA polymerase, polIII holoenzyme, whose proof-reading capacity may be inhibited by lesion-induced activity of recA (Lu *et al.*, 1986).

Let the bit 1 represent a sequence mutation. Under *fail-safe* processing, this mutation is transferred to the subsequent level if and only if all other bits that belong to the same controlling sequence, the size of which is $2r + 1$ $(r > 0)$, have mutated as well (see Fig. 1). Thus,

$$a_{i,j} = \begin{cases} 1 & \text{for } \sum_{l=-r}^{r} a_{i-1,j+l} = 2r + 1, \\ 0 & \text{for } \sum_{l=-r}^{r} a_{i-1,j+l} < 2r + 1. \end{cases} \tag{1}$$

The *majority* rule does not recognize errors as such. Rather, it damps down the effect of any minority in the controlling sequence (see Fig. 2). This rule mimics a rather common biological mechanism of error damping, in which random mutations in the genome are transcribed but not expressed phenotypically when relatively rare. An instance of this phenomenon is the multiple tandem repeats in many protein antigens of the malaria parasite. Their redundant expression is said to enhance the probability of cooperativity in the interaction with a mobile multimeric receptor by reducing the impact of harmful mutational events (Nussenzweig & Nussenzweig, 1984).

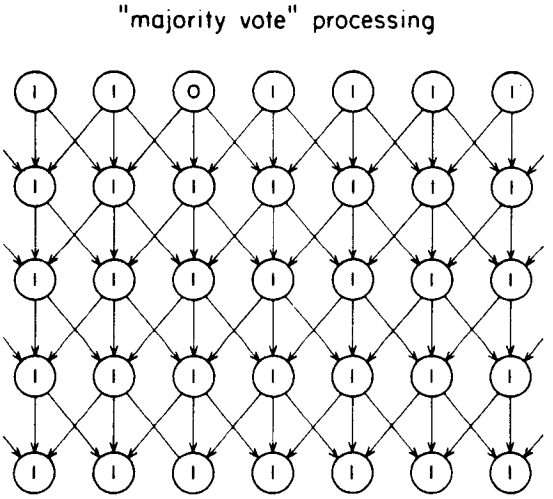

FIG. 2. A small subset of the information processing automaton, operating by the *majority* rule (equation (2)). This rule specifies that the output bit is 0 or 1 according to whether a majority of 0 or 1 is present in the input triplet ($r = 1$).

Under the *majority* rule $r > 0$ and

$$a_{i,j} = \begin{cases} 1 & \text{for } \sum_{l=-r}^{r} a_{i-1,j+l} > \tfrac{1}{2}(2r+1), \\ 0 & \text{for } \sum_{l=-r}^{r} a_{i-1,j+l} < \tfrac{1}{2}(2r+1). \end{cases} \tag{2}$$

In *linear* processing $r = 0$ (see Fig. 3) and

$$a_{i,j} = a_{i-1,j}. \tag{3}$$

2.2 *The Phenotypic Repertoire*

While the genomic repertoire depends only on the automaton's length, and is given by

$$R_{0,n} = 2^n,$$

the phenotypic repertoire depends on the automaton's size, $n \times m$, and on the processing rules.

Consider first a fully linear information transfer. In this case, it is clear that the phenotype is an exact reflection of the genotype. Hence, we obtain the following property.

Property 1. The phenotypic repertoire for 2^n different genotypes in automata operating by fully linear processing is given by $R_{m,n} = 2^n$ for all m and n.

Consider next the nonlinear processing rules, that is, $r > 0$, $n \geq 3$. When all processors act by the *fail-safe* rule, the phenotypic repertoire decreases with increasing depth of the automaton (see Table 1). For $r = 1$, we obtain the following property, the proof of which is immediate.

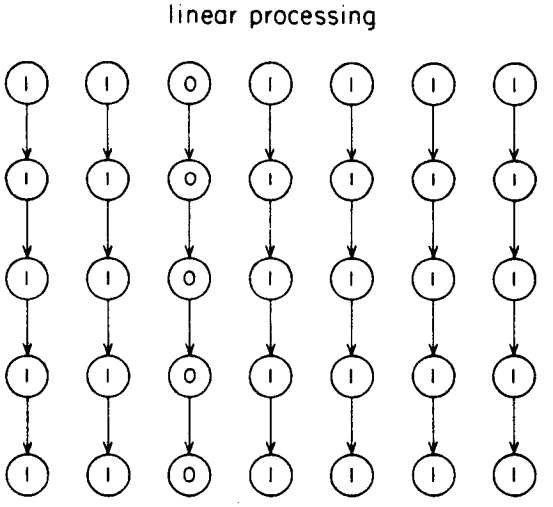

FIG. 3. A small subset of an automaton with a *linear* information transfer (equation (3)). The information is identical through all levels of organization.

Property 2. The asymptotic phenotypic repertoire, $R_{\infty,n}$ for 2^n different genotypes in automata operating by *fail-safe* processing is

$$R_{\infty,n} = R_{\lceil \frac{1}{2}(n-1) \rceil,n} = 2 \quad \text{for all } n \geq 3.$$

In physical terms, one may say that this system strongly contracts in phase space. This global contraction in phase space results from the strong local error correction embedded in each *fail-safe* processor. Phase-space contraction reflects the automaton's resilience, that is, perturbations at level 0 are seldom expressed phenotypically. Resilience can be therefore measured by the ratio between the genomic repertoire and the phenotypic repertoire.

TABLE 1
The number of different ring configurations as a function of the organization level m and the processing rule. The automaton's width is n = 7

Level	Processing rule		
	Fail safe	*Majority*	*Linear*
0	128	128	128
1	30	58	128
2	16	44	128
3–∞	2	30	128

In *majority* automata the phenotypic repertoire also decreases with increasing depth, but phase-space contraction is weaker than in *fail-safe* automata, and the asymptotic phenotypic repertoire is a function of n. The phenotypic repertoire is evaluated using the following lemma.

LEMMA. *A cyclic binary string is invariant under the* majority *rule with* $r = 1$, *if and only if it contains no single* 0 *between two* 1's *and no single* 1 *between two* 0's.

From the above lemma, it follows that the asymptotic phenotypic repertoire of *majority* automata is given by the number of different rings of size n in which there appears no single 0 between two 1's and no single 1 between two 0's. The answer to this problem is given by the following theorem, the proof of which is due to Agur *et al.* (1987).

THEOREM *The asymptotic phenotypic repertoire for* 2^n *genotypes of length* n *in automata operating by the* majority *rule is*

$$R_{\infty,n} = R_{\lfloor \frac{1}{2}(n-1) \rfloor,n} = p^n + \hat{p}^n + (-1)^{\lfloor \frac{1}{3}(n+1) \rfloor}\left(2 - \lceil \tfrac{1}{2}(n \bmod 3) \rceil\right), \tag{4}$$

where $p = \frac{1}{2}(1 + \sqrt{5})$ *and* $\hat{p} = 1 - p$; *the symbolism* $\lfloor x \rfloor$ *and* $\lceil x \rceil$ *denotes the largest integer* $\leq x$ *and the smallest integer* $\geq x$, *respectively*; *and* $n \bmod k$ *denotes the remainder of the division of* n *by* k.

Since $\hat{p}^n$ tends rapidly to zero, and the last term is a small correction, equation (4) is approximated by $R_{\infty,n} = p^n$ for large n. The special nonconvergent ring, ... 10101010 ..., with even n, is excluded from (4).

From these results it is clear that, for $m \geq \frac{1}{2}(n-1)$, a genomic repertoire of size $R_{0,n} = 2^n$ can yield a phenotypic repertoire, the size of which varies from $R_{m,n} = 2$ to $R_{m,n} = 2^n$, depending on the processing rules.

2.3 *Complexity*

The aim of this section is to show that complexity of the organism can be represented by the number of layers of information processing in the individual automaton.

An interesting attempt to give a formal global measurement of complexity is made by Hogg & Huberman (1986). Their measure (HH complexity) is based on examining the diversity of a given structure as determined by the number of different kinds of interactions among the parts that exist in the corresponding hierarchy at all levels. In order to measure the HH complexity of our automata, their generic form, that of a matrix, has to be replaced by a form of an unlabelled tree. The following considerations enable us to do this. When error damping is embedded in the processing rules of our automata, each phenotypic ring can be generated by more than one ring on level $m - 1$; each of these can be generated by more than one ring on level $m - 2$; and so on. To each phenotype is thus attached a tree whose leaves are the different genotypes by which it can be generated. These leaves are said to be the *domain of attraction* of the phenotype (Agur & Kerszberg, 1987). By clustering all the phenotypic trees of a given genomic repertoire in a single structure, one can measure the automaton's complexity. Hence, it seems intuitive that the HH complexity of nonlinear automata increases with increasing number of organization levels m for $m \leq \frac{1}{2}(n-1)$.

2.4 *Conclusions*

The above considerations give rise to the following statements.

1. When error damping processors are employed, resilience increases with increasing depth of the automaton, i.e. with increasing complexity. Lower complexity automata have a weaker capacity of damping down the effect of alterations at level 0, and hence have a larger phenotypic repertoire than higher complexity automata.

2. Highly resilient automata populations may be phenotypically homogeneous but still harbour individuals that largely vary in their evolutionary potential. Automata located near the boundaries of their domain of attraction may pass to a new domain upon small changes in their 0-level configuration. Such a transition may involve a large phenotypic change (see also Agur & Kerszberg, 1987).

3. Relatively complex automata of fixed size can control their phenotypic repertoire by modulating their processing rules. Such modulation endows them with the capacity of switching between a state of strong resilience, where a large variety of genomic configurations yields similar phenotypes, and a state of a large phenotypic repertoire with many genomic alterations being reflected phenotypically.

Suppose we are to build an automaton capable of buffering changes in external constraints. The hypotheses suggested here are that more complex automata will be more efficient in doing this and that automata that modulate their processing rules will satisfy the above prerequisite most efficiently. An alternative hypothesis is that changes in external constraints can be most efficiently buffered by controlling the realized genomic repertoire rather than the processing rules.

3. Automata evolution

Computer experiments were conducted to check the above hypotheses. To this end, the evolution of automata populations was followed in a fluctuating limited environment. The initial genomic make-up of each individual in the populations was chosen at random, and the mutation and the death processes were also stochastic. Under these conditions, natural selection type processes should have been set in motion, and the populations were expected to evolve towards dominance of the more efficient automata.

The experimental parameters were as follows:

- t duration of the experiment;
- n width of the individual automaton;
- m depth of the individual automaton;
- K maximal population size;
- μ mutation rate (probability of a single-bit alteration);
- Λ the fitness function (fitness is measured by the number of offspring of an automaton characterized by its phenotype; in the experiments reported here, the individual fitness was linearly related to the number of 1's in the mth ring);
- ϕ probability of transition to a new environmental state (two extreme

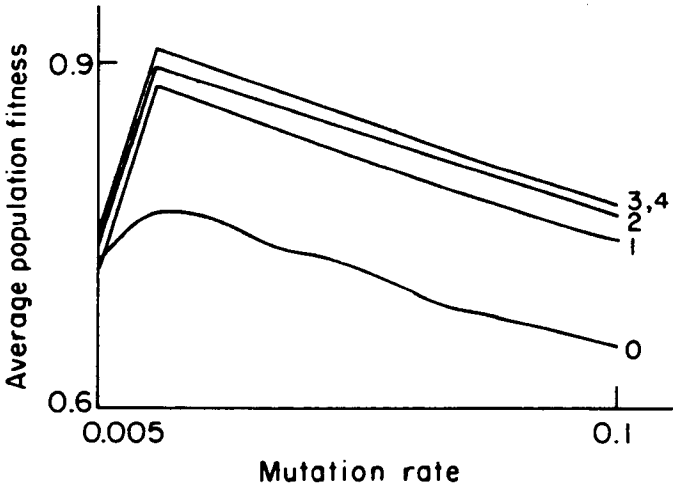

FIG. 4. Automata evolution (Experiment 1). Each curve represents one population characterized by the number of organization levels of its constituents m: the curve marked 0, for example, represents a population of automata whose 0-level information is linearly transferred; the curve marked 3 represents a population of automata with 3 levels of *majority* processing. Population fitness, averaged over 20 experiment iterations, is plotted as a function of mutation rate μ, with $t = 100$, $n = 7$, and $K = 100$.

environmental states were considered: state $\mathscr{E}_1$ allotting maximal fitness to automata whose mth ring contained n bits of 1; and state $\mathscr{E}_2$ allotting maximal fitness to automata whose mth ring contained n bits of 0;

Φ processing rules employed by the automaton;

Θ modulation mechanism employed by each automaton as a reaction to a stress signal acting on the individual level;

α magnitude of mutation rate acceleration.

Experiment 1. Effect of automata complexity on their ability to buffer changes in constraints.

Each population in this experiment was characterized by the complexity of its constituents, i.e. by the number of levels of *majority* processing in the individual automaton. Average population fitness was measured as a function of mutation rate μ. Environmental transition occurred deterministically in the 33rd time unit. Results (Fig. 4) show that when environmental perturbation occurs once in a period of 100 time units, (a) there exists one optimal 'universal' mutation rate, maximizing average fitness of populations that differ in complexity, and (b) under these conditions, fitness increases with increasing number of levels of *majority* processing from 0 to 3. These results support our hypothesis that higher complexity automata are more efficient in handling changes in the system's constraints.

Experiment 2. Effect of modulation type Θ.

In this experiment, the evolution of modulation types was simulated. All individuals had the same initial architecture: 7×5 *majority* processors. Their

0-level ring, i.e. their *genome*, was constructed using a random number generator. A stress-detection mechanism, similar in all automata, was assumed: before reproduction takes place, each individual automaton estimates its potential number of offspring under current environmental conditions; if this is less than a given proportion (50% in the present experiment) of its maximal number of offspring, then this individual 'reads' a stress signal. Automata differed in modulation type Θ: processing rules modulation (PRUM) automata (50% of initial population) reacted to a stress signal by modulating their processing rules, replacing the *majority* processing by *linear* processing; mutation acceleration mechanism (MAM) automata reacted to a stress signal by accelerating their mutation rate, and hence increasing their genomic repertoire.

Owing to constraints related to computer time, population size was limited to 100 individuals in a single experiment. Moreover, as was mentioned above, a significant 'demographic' stochasticity was allowed for in the mutation and death processes. These factors were expected to generate a 'genetic drift', realized in some cases of exclusion of the more efficient automata. It is assumed that 'genetic drift' was responsible for part of the cases in which MAM automata were not excluded from the system. Yet, results of this experiment clearly indicate that the PRUM mechanism has a competitive advantage when environmental perturbation frequency and mutation rate are not too low (Table 2). This experiment supports our hypothesis that changes in constraints are more efficiently buffered by modulating the processing rules than by adjusting the genomic repertoire.

Adaptability of individuals is a basic prerequisite in harshly varying environments of the type simulated in our experiments. This property is characterized by the ability to satisfy variations in constraints with minimal changes in structure (Hogg & Huberman, 1985). PRUM automata with their flexible transformation rules can control their phenotypic repertoire with no change in their basic structure. MAM automata have a flexible mutation rate, but any increase in mutation rate causes a change in the basic structure, that of the genome. This change in structure has a significant cost: the loss of evolutionary memory. Thus, whereas PRUM automata can be preadapted to multiple environmental states, this is not the case for MAM automata. However, competition results may perhaps be inversed when fine tuning of the genome is generally more advantageous than its coarse tuning, that is, in environments where harsh changes are infrequent.

4. Application to host–pathogen interaction

The experiments described above were intended to compare the efficiency of two different mechanisms in reaction to changes in external constraints: the mechanism of processing rules modulation, PRUM, and the mutation acceleration mechanism, MAM. The experimental design attempted to incorporate some of the most essential universal biological properties. Thus, the model organism, the automaton, undergoes multilevel information processing, with processing rules allowing for different types of nonlinearity and error damping, as well as for many/one and one/many types of hierarchy. Evolution in these experiments is based on a limited environmental carrying capacity and on a variable, phenotype

TABLE 2

Automata evolution (Experiment 2). Competition between automata that modulate their processing rules, PRUM, and those controlling their mutation rate, MAM. PRUM automata react to a stress signal by replacing the majority *processing by a* linear *processing; MAM automata react to a stress signal by accelerating their mutation rate. Final proportion of MAM automata is averaged over 20 iterations of the experiment for each set of parameters. Average initial proportion of MAM automata is 0·5, with $t = 100$, $n = 7$, $m = 5$, and $K = 100$*

Probability of environmental perturbation, ϕ	Mutation rate, μ	Proportion of MAM automata
0·05	0·005	0·55
	0·006	0·45
	0·007	0·42
	0·008	0·15
	0·009	0·12
	0·010	0·28
0·10	0·005	0·45
	0·006	0·31
	0·007	0·20
	0·008	0·35
	0·009	0·42
	0·010	0·28
0·20	0·005	0·25
	0·006	0·19
	0·007	0·28
	0·008	0·28
	0·009	0·06
	0·010	0·05
0·25	0·005	0·35
	0·006	0·20
	0·007	0·20
	0·008	0·10
	0·009	0·15
	0·010	0·22

determined, individual fitness. It should be noted, though, that owing to the model's simplicity it must have incorporated a certain degree of arbitrariness, and the possibility that other plausible models could have yielded different results cannot be altogether excluded. Nevertheless, it is hoped that the analogy between our automata and biological organisms is justified so that some hypotheses concerning natural processes can be put forward. Although the work was motivated by the need to clarify host–pathogen interactions, it contains no assumptions that are unique to such interactions. For this reason, the hypotheses presented below have a general speculative character; adaptation of the model to specific host–pathogen processes will be discussed elsewhere.

Our model implies that global resilience is weak in lower complexity pathogens and that the antigenic repertoire is constantly large. Higher complexity organisms should be more resilient, and a simple translation to phenotypic properties of randomly occurring mutations cannot be the main source of their antigenic diversity. The origin of special mechanisms for the generation of antigenic variability should therefore mark the switching point in the balance between resilience and the *basic* phenotypic variability in pathogens.

Owing to the continuous changes in constraints imposed by both the pathogen and the host, adaptability is a primary prerequisite in this system. The automata-evolution experiments imply that organisms which modulate their processing rules *on several organization levels* should be more adaptable to environmental perturbations than those modulating their mutation rate. Hence, it is suggested that hosts and pathogens have evolved towards increasing modulation of their processing rules, with the most advanced modulation presumably found in the immune system of mammals. Changes on various levels of antigen-receptor processing are therefore expected to occur in mature lymphocytes, triggered by the introduction of new antigens. Owing to these changes, more than one antigen receptor may be generated by a single lymphocyte. Such multiple employment of the existing mature lymphocyte population can provide rapid and economic defence for the host. Antigen-triggered proliferation and terminal differentiation of selected B cell clones may come into action in later stages of the process, or when the current population fails to produce the adequate antigen receptor.

Our model thus suggests that the immune reaction to the introduction of new antigens is a non-Markovian process, determined by the lymphocyte population history. This contrasts with the current opinion, holding that the process is Markovian in the sense that each invasion of a new pathogen generates a completely new active lymphocyte population.

The above considerations can suggest possible explanations for some as yet unexplained history-dependent phenomena in host–pathogen systems. A sequential, ordered, expression of a large series of different antigen genes has been domonstrated in *Trypanosoma brucei* (Gray, 1965; Van der Ploeg *et al.*, 1986). The present work implies that this order is regulated by the mature lymphocyte population structure, excluding new variants for which antigen receptors are instantaneously produced by processing rules modulation. Another, nonexclusive, explanation is given by Van der Ploeg *et al.* (1986).

The above hypotheses may aid in clarifying some cases of stalemate in host–pathogen confrontation. Thus, it is further assumed that, under some circumstances, the advantage of the PRUM mechanism may turn out to be a major impediment to its successful use. Our conjecture that the phenotypic repertoire can be controlled with no changes in the organism structure also means that no large structural changes are necessary for the disruption of this control. Hence, a pathogen capable of hindering the modulation in the immune system of the host can prevent the production of specific receptors; 'linearizing' the processing rules in the host (for example, by disrupting the activity of a splicing enzyme) should result in a polyclonal antigen-receptor activation and a specific-receptor suppression. The latter is a well-documented immunosuppression phenomenon in

trypanosomiasis (Hudson *et al.*, 1976; Albright & Albright, 1980). Also consistent with our hypothesis is the appearance of *autoantibodies* in trypanosomiasis, directed against normal tissue antigens (Mansfield & Kreier, 1972; Mackenzie & Boreham, 1974).

Partial processing of precursor mRNA has been documented for *T. cruzi*, where northern blot analysis reveals a ladder of molecules larger than the 'mature' mRNA (Lizardi *et al.*, 1986). In higher animals, there exists a powerful PRUM mechanism in the central nervous system (Douglass *et al.*, 1984). Peptides that convert neural signals into physiological responses are originally synthesized in the form of large precursors. Some of these precursors are the source of as many as eight bioactive peptides that may act in concert in the complex behavioural responses. Such a polyfunctional action has not been documented in lymphocytes. Rather, it is currently believed that each mature lymphocyte generates only one type of antigen receptor (Jerne, 1975). In view of our model, and the explanations it provides for some immunopathological problems, it seems justified to suggest that the possibility of 'one lymphocyte/many antigen receptors' is reconsidered.

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