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Fixed Points of Majority Rule Cellular Automata with Application to Plasticity and Precision of the Immune System

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Abstract. Signal processing in the immune system is studied in a theoretical multilayered network. The elements in the network have regular connectivities, with the level of connectivity reflecting the level of signal (cytokine) multifunctionality. Each element operates by the same nonlinear *majority* rule. An exact formula for the number of fixed points is derived as a function of the network's size n (n odd) and connectivity r, as well as a general upper-bound estimate for the number of fixed points for all n and r. Results show that increasing connectivity enhances resilience by strengthening the global error damping capacity of the system. Its cost is diminished general memory storage space, reflecting diminished phenotypic plasticity. Laboratory experiments are suggested for verifying the implications of the results for pathogenesis and immunosuppression.

The duration and amplitude of the immune response is regulated by a group of peptides called *cytokines* that bind to the cell surface and ultimately lead to a change in its phenotypic state, that is, its proliferative or functional behavior. In the past, each step in the immune process was thought to be controlled by a unique single-purpose molecule. Today it is realized that cytokine activity is characterized by pleiotropism and redundancy: individual cytokines are pleiotropic in having multiple overlapping cell regulatory actions (denoted a *one/many* property), while different cytokines can have a similar action (*many/one* property). Moreover, the ultimate response of a cell usually depends on two or more different messages received concurrently at the cell surface; these are selected from a larger repertoire of cytokines [1–3]. It thus appears that the processing rules in this system, whose state transitions are determined by a combination of elements each of which is insufficient and unnecessary on its own, are of the *majority vote* type.

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Given our current knowledge, it is difficult to understand the complexity of the cytokine network, and the question "Why so many cytokines with so many activities?" is reiterated in the literature [1 3]. It has been suggested that individual cytokines are the equivalent of characters in a language alphabet: the use of combinations of a large number of signaling molecules increases the amount of information that can be transmitted [1]. However, language is *positionally structured*, every word being determined by the order of its characters. In contrast, a state transition of an immune system cell is an outcome of the composition of signals present at its surface in a given moment. This network is therefore *compositionally*, rather than *positionally*, structured, so that the above mentioned analogy cannot hold, and the effect of cytokine multifunctionality on the system's efficiency still remains to be verified. It seems, however, that this collective behavior is too complex to be captured merely by a phenomenological description of cytokine activity, whereas a formal analysis, by voluntarily neglecting the details and by abstracting and generalizing, may provide insight to its essential features.

This work investigates the effect of signal multifunctionality on information storage capacity and response precision in a network whose properties are those characterizing the cytokine network. The model is minimalistic in structure, so as to be analytically tractable and, hence, general and robust in its predictions. By verifying our predictions in laboratory experiments, their relevance to the cytokine network will hopefully be established.

Our minimalistic description of the information processing in the immune system incorporates the general information content of the system at any specific moment and the rule by which this information is processesed (see [5, 6] for a general discussion of this model of biological information processing). This rule is taken to be analogous to stimulation of the cytokines. In most cases the information processing leads to a *fixed point* a new state of the system (described by its information content) that remains invariant under further processing of the same type. The number of fixed points reflects the general memory storage capacity of the system. A system with many fixed points can store a large amount of information, or, in biological terms, has a large phenotypic repertoire. Our aim in this work is to examine how the level of cooperativity, or connectivity, in the system affects the number of fixed points.

Let the information content of the system at the initiation of the processing (level 0) be represented by a binary string of n-bits, A_0. To avoid the need for the definition of boundary conditions we consider the strings as cyclic, so that the first and last bits are neighbors. This string is processed according to a certain rule Φ, producing a new string of n-bits, $A_1 = \Phi(A_0)$, which describe the first transient state of the system during the processing. The process is repeated a sufficient number of times, that is, $A_m = \Phi(A_{m-1})$ for $m \geq 1$, for a fixed point to be reached. The system operates by the majority rule, so the state of an element in level m in the processing is determined by its closest $2r + 1$ neighbors in level $m - 1$, by a simple majority vote. Thus,

if

$$\begin{aligned} A_m &= a_0 \dots a_{n-1} \\ A_{m+1} &= b_0 \dots b_{n-1} \end{aligned}$$

and

$$A_{m+1} = \Phi A_m$$

then

$$b_i = \begin{cases} 1 & \text{if } \sum_{\ell=-r}^{r} a_{i+\ell} > (2r+1)/2, \\ 0 & \text{if } \sum_{\ell=-r}^{r} a_{i+\ell} < (2r+1)/2, \quad 0 \le i < n. \end{cases} \tag{1}$$

Here, all additions and subtractions on indices are carried out modulo n. The parameter r measures the connectivity of the system: a larger r means that a larger number of inputs from the previous level cooperate in determining the present state of each element, and that each output affects the state of a larger number of elements in the subsequent level.

Consider a binary string of size n. $A_m = (a_0, a_1, \dots, a_{n-1})$, and define a *run* as a maximal substring of consecutive like bits in the string. Let k be the number of runs in A_m, and let their sizes be $t_1, t_2, \dots, t_k$ (where $\sum_{i=1}^{k} t_i = n$). Note that, since the strings are cyclic, the origin may be chosen such that k is odd, in which case $a_0 = a_{n-1}$ (except for the two strings $1010\dots10$ and $0101\dots01$). Every string A_0, varying under Φ, leads either to a cycle of period 2, or to a *fixed point*, namely a string A_∞ and an integer $m_0 \le \frac{1}{2}n$ such that [4,7]

$$A_\infty = \Phi^{m_0}(A_0) \quad \text{and} \quad \Phi(A_\infty) = A_\infty. \tag{2}$$

We derive the exact formula for the number of fixed points $f(n, r)$ in networks operating under (1) for n odd. When n is even additional fixed points exist, but we show that these fixed points are highly unstable in the sense that any single-bit perturbation in them will drive the system, under further operation of the majority rule, to one of the *stable* fixed points, whose number is calculated below. Being susceptible to any level of noise in the system the unstable fixed points seem to be of no biological relevance. For this reason they are excluded from the calculation.

Let $D_{n,r} = \{A : A \text{ has } n \text{ bits and } \Phi A = A\}$ be the set of fixed points of Φ, where Φ is defined in (1). We evaluate the number of elements in $D_{n,r}$ using the following properties of the majority-rule fixed point.

Lemma 1. *If A_∞ is invariant under Φ and contains a run u such that*

$$t_u \ge r + 1,$$

then, if k is even, A_∞ maintains

$$t_i \geq r+1, \quad i = 1, \ldots, k.$$

Otherwise

$$t_i \geq r+1, \ i = 2, \ldots, k-1 \quad \textit{and} \quad t_1 + t_k \geq r+1.$$

Lemma 2. *If A_m contains a run u such that $t_u = r$, then A_m is not a fixed point under Φ.*

The proofs of Lemmas 1 and 2 are straightforward.

Conjecture. If A_∞ is invariant under Φ, and A_∞ contains a run u such that

$$t_u < r,$$

then A_∞ is even and contains an equal number of 0s and 1s.

Theorem 1. *If A_∞ is invariant under Φ, and A_∞ contains a run u such that*

$$t_u < r,$$

then any string A_m that differs from A_∞ in one bit will have a fixed point $A'_\infty \neq A_\infty$, A'_∞ being a homogenous string of only 0s or only 1s.

Proof. Consider any run transition in $A_\infty, \ldots, e_j, f_{j+1}, \ldots$, with e representing the 0 bits and f representing the 1 bits, or vice versa. From Lemma 1 and Lemma 2 it follows that A_∞ must maintain $t_i < r$, $i = 1, \ldots, k$. Thus each run transition in A_∞ is the center of a substring of size $2r+2$, whose form is

$$(e_{j-r} \ldots f_{j-x}, e_{j-x+1} \ldots e_j, f_{j+1} \ldots f_{j+y}, e_{j+y+1} \ldots f_{j+1+r}) \qquad (x, y < r), \tag{3}$$

with exactly $r+1$ es and $r+1$ fs.

Now consider another string A_m, differing from A_∞ in one bit so that, without loss of generality, we may consider A_m as having the form (4):

$$\ldots, e_{j-r} \ldots f_{j-x}, e_{j-x+1} \ldots e_j, f_{j+1} \ldots e_{j+z} \ldots f_{j+y}, \\ e_{j+y+1} \ldots f_{j+1+r}, \ldots \tag{4}$$

The sequences of size $2r+1$ in A_m that are symmetric around f_{j+1} and around f_{j+y} have a majority of es. Thus, under Φ, we get the following transformations in (4):

$$\begin{aligned} f_{j+1} &\to e_{j+1}, \\ f_{j+y} &\to e_{j+y}. \end{aligned} \tag{5}$$

It is easy to show by induction that these transformations will be followed, under further operation of Φ, by successive transformations of all f bits in

(4), located at the runs extrema, until the string becomes a homogeneous string of es.

The instability of the fixed points containing runs $t_i < r$ to any single-bit perturbation renders them meaningless as a model for the information content of the biological network. Moreover, Moran [8] proves that the fraction of initial string configurations that maps on the unstable fixed points and on the *period 2* strings measures less than $n^{-1/2}$. This fraction is negligible for n being large enough. For these reasons we omit the unstable fixed points as well as the *period 2* strings in the evaluation of the number of fixed points in our model for biological information processing, as described hereafter. Note however that by adding this fraction to the formula (7) below, we obtain a general upper-bound estimate for the number of fixed points under the majority rule for all n and r. ∎

Corollary. A cyclic binary string of size n (n odd) is invariant under Φ if and only if the following holds:
if k is even then

$$t_i \geq r+1, \quad i = 1, \ldots, k,$$

otherwise (6)

$$t_i \geq r+1, \; i = 2, \ldots, k-1 \quad \text{and} \quad t_1 + t_k \geq r+1.$$

Theorem 2. *The number $f(n,r)$ of elements of $D_{n,r}$ for $n \geq 5$ (n odd and $r \leq (n-1)/2$) is*

$$f(n,r) = 2\left(1 + \sum_{\ell=1}^{\lfloor \frac{n}{2(r+1)} \rfloor} \left(\frac{n}{n-2\ell r}\binom{n-2\ell r}{2\ell}\right)\right) \tag{7}$$

Proof. Let s_i be the number of "excess" bits in an invariant string satisfying (6), in the sense that

$$s_i = \begin{cases} t_i - (r+1-t_1) & \text{if } t_1 < r+1,\ i = k \text{ and } k \text{ is odd}, \\ 0 & \text{if } t_1 < r+1,\ i = 1 \text{ and } k \text{ is odd}, \\ t_i & \text{if } t_1 \geq r+1,\ i = k \text{ and } k \text{ is odd}, \\ t_i - (r+1) & \text{otherwise.} \end{cases} \tag{8}$$

Taking $k = 2\ell + 1$, (8) is equivalent to

$$\sum s_i = n - (k-1)(r+1),$$

and the number of different arrangements of $\sum s_i$ bits is

$$\sum_{t_1=1}^{r} \binom{\sum s_i + k - 2}{k-2} = r\binom{n-2\ell r-1}{2\ell-1} \qquad \text{for } t_1 < r+1 \tag{9}$$

and

$$\binom{\sum s_i + k - 1}{k-1} = \binom{n - 2\ell r}{2\ell} \qquad \text{for } t_1 \geq r+1 \tag{10}$$

Note that (10) also counts the invariant strings with an even number of runs ($t_k = s_k = 0$; $k = 2\ell + 1$).

Introducing the following constraint on ℓ,

$$\frac{n}{2(r+1)} \geq \ell \geq 1,$$

and adding (10) to (9) we get

$$\sum_{\ell=1}^{\lfloor \frac{n}{2(r+1)} \rfloor} \left(r \binom{n - 2\ell r - 1}{2\ell - 1} + \binom{n - 2\ell r}{2\ell} \right) = \sum_{\ell=1}^{\lfloor \frac{n}{2(r+1)} \rfloor} \left(\frac{n}{n - 2\ell r} \binom{n - 2\ell r}{2\ell} \right).$$

By adding 1 for $k = 1$, and multiplying by 2 for symmetry, we obtain equation (7). ∎

Note that the combinatorial analysis that appears in [7] is a special case of Theorem 2, for $r = 1$. From Theorem 2 we conclude that $f(n, r)$ decreases nonlinearly with r. In general, the number of *stable fixed points* (maintaining (6)), and hence the global memory storage capacity of a system operating under the majority rule, decreases with increasing connectivity. Larger connectivity yields larger average differences between the fixed points, so that starting from rather similar initial configurations the system may end up in very different final configurations. Thus a network that *a priori* seems fuzzy, due to largely overlapping signal functions, is in fact a powerful mechanism for generating very distinct final states. The system's resilience, defined as the probability that the fixed points are unaltered by input perturbations at the different processing levels, can be estimated by relating the number of fixed points of Φ to the size of the set of A_0 [5]:

$$R(n, r) = 1 - f(n, r)/2^n. \tag{11}$$

This measure is comparable with the results of computer simulations, showing that the probability of a fixed point remaining unchanged by a single-bit inversion at any processing layer increases with increasing connectivity.

The model analyzed in this work makes minimal assumptions about the network's properties, so that its conclusions should be applicable to many different natural and artificial systems with similar properties. Note, however, that it still remains to be shown that the results presented here for one-dimensional information processing can be generalized to networks with a more complex architecture. By the same token, it still remains to be shown that the model's conclusions are applicable to the real-life cytokine network, whose richness is not yet fully unraveled. But if the main properties of this network are indeed those suggested above – namely many/one and one/many,

error damping, and information processing—our results should throw some light on the role of cytokine multifunctionality in the immune response. These results can be interpreted as suggesting that increasing connectivity in the immune system, by increasing cooperation among immunoregulators, improves the error-damping capacity and the response precision. The cost is diminished phenotypic plasticity. Based on these results it may be speculated that blockage of a given cytokine, whose activity is essentially cooperative, should *increase* the repertoire of the immune responses. Since the pool of immune cells is limited, increasing diversity of response may hamper its efficiency. This speculation may bear upon the general "confusion" of the immune response associated with African sleeping sickness (*trypanosomiasis*). This disease is characterized by immunosuppression, as well as by the production of a wide spectrum of autoimmune antibodies and by poly-clonal immune cell (B-cell) activation [9]. Based on the conclusions of the present analysis, it seems interesting to check the possibility that the above phenomena may be due to the suppression of cytokine activity: suppression of cytokine (IL-2) production has been observed during murine trypanosome (*T. cruzi*) infection [9].

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