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Percolation on General Trees and HIV Modeling

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Percolation on a general tree is studied. A general tree is used to model the transition from HIV infection into AIDS and to explain the large differences of the transition time from one patient to another. HIV has some autoimmune effects due to its low antigenic mutants. Fuzzy mathematics is used to explain these effects.

1. BASIC CONCEPTS

Percolation (Aharony and Stauffer, 1992) on homogeneous trees, where the number of nearest neighbors Z_i is independent of the site ($Z_i = z$), is an important problem, with many applications. However, some cases need to be modeled on general trees. In this section this problem is studied. In Section 2 it will be applied to the transition from HIV (human immunodeficiency virus) disease to AIDS (acquired immune deficiency syndrome). In Section 3 some autoimmune aspects of HIV will be studied using fuzzy concepts (Klir and Folger, 1988).

We begin by giving some basic definitions:

A *vertex set* is a set of points (objects) called sites.

An *edge* or *branch* is a pair of distinct vertices (sites). Therefore any two vertices (sites) in a graph a, b are either connected by a set of edges, e.g., $ac_1, c_1c_2, \ldots, c_nb$ (in this case they are called connected) or not (in this case they are called disconnected or disjoint). If $b = a$, then the set of edges $ac_1, c_1c_2, \ldots, c_na$ is called a *loop*.

A *tree* is a graph with no loops. The coordination number Z_s of a site s is the number of edges of the form sa. If $Z_s = Z$ for all sites in a tree, then it is called a *homogeneous* (Cayley) tree, otherwise it is called an *inhomogeneous* one. Examples are shown in Fig. 1.

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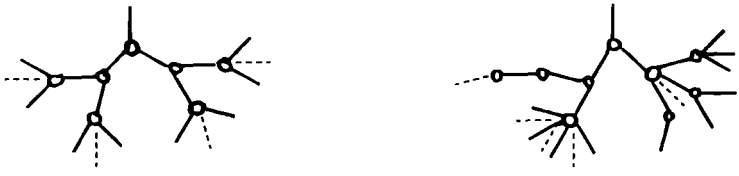

(a) (b)

Fig. 1. (a) An example of a homogeneous ($Z = 3$) tree. (b) An inhomogeneous tree.

In percolation (Aharony and Stauffer, 1992), a flow (e.g., of a fluid, electric current, infectious disease, etc.) on a graph is studied. The sites of the graph are either conducting (or occupied) with probability p or nonconducting (empty).

The question is whether or not the flow can cross the graph. If p is small, then most of the sets are empty, hence the flow cannot cross the graph. The critical concentration p_c is the minimum value of p for which the graph becomes conducting.

To evaluate the critical concentration p_c, we use the number of outgoing branches from site i, $Z_i - 1$; hence the average number of open branches from site i is $p(Z_i - 1)$. In order for the site to belong to an infinite cluster this quantity should exceed unity, thus the critical concentration is

$$p_c = \max_i \{1/(z_i - 1)\} \tag{1}$$

To find the probability that an occupied site belongs to an infinite cluster Ω, let Q_j be the probability that the site j does not belong to an infinite cluster along a given branch, where site j is a nearest neighbor (nn) to site i, then

$$Q_j = 1 - p + p \prod_{k \neq i} Q_k \tag{2}$$

where p is the probability that a site is occupied and k runs over the set of all nn of j other than i. The quantity $p - \Omega$ is the probability that a site is occupied and belongs to a finite cluster; therefore

$$p - \Omega = p \prod_j Q_j \tag{3}$$

Equations (2) and (3) determine Ω.

When $Z_i = z$ the familiar equations for Q are regained,

$$Q = 1 - p + pQ^{z-1}, \qquad p - \Omega = pQ^z \tag{4}$$

2. GENERAL TREES AND MODELING HIV–AIDS TRANSITION

Recent evidence (Nowak and McMichail, 1995) indicates that one of the reasons HIV is able to defeat the immune system (IS) is its high ability to mutate. Consequently, although the IS is able initially to combat HIV, some mutants with low antigenicity are able to escape (at least for a while). Therefore the IS response to these mutants is both delayed and diluted (as will be discussed in the next section) while the virus continues infecting T-helper cells. This process is continued until the number of T-helper cells is reduced to approximately 20% of their normal level, where HIV infection becomes full-blown AIDS.

We use general trees to model this transition as follows: we model IS clones by sites of a tree. Assume that clone j has recognized the HIV virus. To avoid the IS effects, the virus mutates. The mutant with highest survival probability is one that corresponds to nn of site j with lowest number of nn of its own. Mathematically it corresponds to the site k which is nn of site j and

$$\min_{v \neq j}(Z_v) < \min_{u \neq k}(Z_u) \tag{5}$$

where $v(u)$ runs over all nn of $k(j)$.

It is known (de Boer and Perelson, 1991) that approximately 80% of IS sites have 10–40 nn, while the remaining 20% have much fewer. We call them relatively isolated. Therefore it is almost always possible for a mutant to reach one of these relatively isolated sites where the mutants overcome the IS. Using the language of percolation, it is required to study the time needed to go from an arbitrary point in the cluster to its peripheral.

We do not know of any analytical study of this problem; therefore computer simulation will be used.

The system is simulated by assigning numbers of nn randomly to one-dimensional sites such that the probability of having $10 < Z < 40$ is 80%, which agrees with observations. Mutants are allowed to move to nn until a relatively isolated site is reached. The number of moves is a measure of the transition time from HIV infection to AIDS. The results are given in Table I. It shows that the transition times vary greatly from one case to another. This agrees with observations (Nowak and McMichail, 1995).

Table I

Number of Moves	1	2	3	4	5	≥6
Frequency	45%	20%	9%	7%	9%	10%

3. LOW ANTIGENICITY, AUTOIMMUNITY, AND FUZZY CONCEPTS

Impression and uncertainty are intrinsic concepts in biosystems. Immunology (Benjamini and Leskowitz, 1989) is no exception. One of the most important tasks of the immune system is pattern recognition, i.e., distinguishability between self and nonself. However, it is known that some foreign antigens have the ability to mimic self ones. This is one of the proposed mechanisms for autoimmune responses (AIR) of the immune system. A similar case appears for tumors with low antigenicity. Therefore pattern recognition should be considered as a fuzzy process.

Fuzzy pattern recognition has been studied mathematically (Bezdek and Pal, 1992); however it has not been applied to immunology. In this work such an application is attempted.

In ordinary sets an element x either belongs or does not belong to a given set A. In fuzzy sets (Klir and Folger, 1988) there is a membership map $0 < m(x) < 1$ which determines how much x belongs to A. A value $m(x) = 0$ (1) means that x does not (does) belong to A. This fuzzy concept agrees more with our everyday terminology, e.g., high, low, similar, dissimilar etc. Most operations on ordinary sets can be generalized to fuzzy ones.

Now let us apply the fuzzy concept to the discrete model for the IS of Chowdhury *et al.* (1990). There are five variables A, B, H, S, and V representing the concentrations of antibody, B-cells, helper cells, suppressors, and the antigen, respectively. Here we consider only the lymphocyte clone with highest affinity to the antigen. Using a cellular automaton approach, we have that these variables usually take two values, 0 (low concentration) and 1 (high or normal concentration). The equations are

$$\begin{aligned} A &= V \text{ and } B \text{ and } H \\ S &= S \text{ or } H \\ H &= [V \text{ and (not } S)] \text{ or } H \\ B &= (V \text{ or } B) \text{ and } H \\ V &= V \text{ and not } A \end{aligned} \tag{6}$$

In this model it is implicitly assumed that the antigen is totally nonself. But what about antigens with some self characters? A similarity grade $0 \leq m(V) \leq 1$ is attributed to the antigen V such that $m(V) = 0$ (1) means that the antigen is totally foreign (self). The fuzzy case $m(V) = 0.5$ will be considered. It represents an antigen trying to mimic self antigen or an immune tumor trying to evade immune response. The equations for the fuzzy case $0 < m(V) < 1$ are

$$\begin{aligned} A &= \min\{V, B, H\} \\ V &= V\delta_{A,0} \\ S &= \max\{S, H\} \\ B &= \min\{H, \max(V, B)\} \\ H &= \max\{H, V\delta_{S,0}\} \end{aligned} \tag{7}$$

where δ is the Kronecker delta function,

$$\delta_{i,j} = \begin{cases} 1, & i = j \\ 0, & i \neq j \end{cases}$$

For the nonfuzzy case $m(V) = 0$ or 1 the five steady states of Chowdhury *et al.* are regained. They are [denoted by (V, B, H, S, A)] (1) the virgin (0, 0, 0, 0, 0), (2) low-dose paralysis (0, 0, 0, 1, 0), (3) vaccinated (0, 0, 1, 1, 0), (4) memory (0, 1, 1, 1, 0), and (5) high-dose paralysis (1, 0, 0, 1, 0) states.

For the fuzzy case $m(V) = 0.5$ two additional pathogenic steady states have been found: (6) (0, 0, 0.5, 0.5, 0), which we expect to be related to autoimmune diseases, since suppression is below normal, which allow self-reactive cells to operate, and (7) (0, 0.5, 1, 1, 0), which represents normal level for T-lymphocytes but below normal for B ones. It will be interesting to relate these additional states to known diseases.

4. SUMMARY

Percolation on a general tree has been studied and used to model the HIV–AIDS transition. The model shows the observed wide range of transition times. The low antigenicity of HIV mutants (Nowak, 1995) causes some autoimmune effects that can be explained using fuzzy concepts.

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