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Fuzzy Cellular Automata Models in Immunology

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The self–nonself character of antigens is considered to be fuzzy. The Chowdhury *et al.* cellular automata model is generalized accordingly. New steady states are found. The first corresponds to a below-normal help and suppression and is proposed to be related to autoimmune diseases. The second corresponds to a below-normal B-cell level.

KEY WORDS: Fuzzy; immunology; cellular automata.

Imprecision and uncertainty are intrinsic concepts in biosystems. Immunology[1] is no exception. One of the most important tasks of the immune system (IS) is pattern recognition, i.e., to distinguish 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 some tumors. Therefore pattern recognition in immunology should be considered a fuzzy process.

Fuzzy pattern recognition has been studied mathematically.[2] However, it has not been applied to immunology. This work offers such an application.

In ordinary sets an element x either belongs or does not belong to a given set A. In fuzzy sets[4] there is a membership map $0 \leqslant m(x) \leqslant 1$ 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.

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Now let us apply the fuzzy concept to the Chowdhury *et al.*[3] discrete model for IS. 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 the cellular automata approach these variables usually take two values 0 (low concentration) and 1 (high concentration). The equations are

$$\begin{aligned} A &= V \text{ and } B \text{ and } H \\ S &= S \text{ or } H \\ H &= [V \text{ and not } S] \text{ or } H \\ B &= (V \text{ or } B) \text{ and } H \\ V &= V \text{ and not } A \end{aligned} \tag{1}$$

In this model it is implicity assumed that the antigen is totally nonself. But what about antigens with some self characters? A similarity grade $0 \ll m(V) \leqslant 1$ 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 or an immune tumor trying to evade immune response. Hence in the fuzzy case the range of variables is (0, 0.5, 1). The proposed equations are

$$\begin{gathered} A = \min(V, B, H), \qquad V = V\delta_{A,0} \\ S = \max(S, H), \qquad H = \max(H, V\delta_{S,0}) \\ B = \min(H, \max(B, V)) \end{gathered} \tag{2}$$

where δ is the Kronecker delta function. It is clear that for the nonfuzzy case, Eq. (2) are equivalent to (1).

Five nonfuzzy steady states appear: $(V, B, H, S, A) =$ (1) (0, 0, 0, 0, 0), the virgin state; (2) (0, 0, 0, 1, 0), low-dose paralysis; (3) (0, 0, 1, 1, 0), vaccinated state; (4) (0, 1, 1, 1, 0), memory; (5) (1, 0, 0, 1, 0), high-dose paralysis. In addition, fuzzy pathogenic states appear: (6) (0, 0, 0, 0.5, 0), (0, 0, 0.5, 0.5, 0), and (0, 0.5, 0.5, 0.5, 0), which correspond to low suppression—this allows autoimmunity; (7) (0.5, 0, 0, 1, 0), (1, 0, 0, 0.5, 0), and (0.5, 0, 0, 0.5, 0), which correspond to chronic diseases; and (8) (0, 0, 0.5, 1, 0), (0, 0.5, 0.5, 1, 0), and (0, 0.5, 1, 1, 0), whose meaning is not clear yet.

It well be interesting to relate all these states to known diseases.

Next, fuzzy pattern recognition is applied to the continuous model of Kuznetsov *et al.*[5] which studies IS–tumor interaction. Again we consider

the process of identifying the tumor Ag (TAg) to be fuzzy. Hence there is a function $1 \gg m(\text{TAg}) \gg 0$ which specifies how much TAg resembles self. Tumors with low (high) antigenicity will correspond to m being close to 1 (0). Since this fuzzy concept affects only IS–tumor interaction, we propose the following modification to the Kuznetsov *et al.* model:

$$\begin{aligned} dE/dt &= s + p(1-m)\,ET/(g+T) - q(1-m)\,ET - dE \\ DT/dt &= aT(1-bT) - n(1-m)\,ET \end{aligned} \tag{3}$$

where $E(T)$ is the number density of immune effector (tumor) cells, $q(n)$ is a measure of the removal of effector (tumor) cells due to the tumor–IS interaction, d is the rate of natural death of effectors, and a is a measure of the tumor growth. It is interesting to see that the factor $(1-m)$ cannot be removed by rescaling. Also, for the pure self state, $m=1$, the two equations decouple and the normal state ($E=s/d$, $T=1/b$) is recovered.

A steady state of the fuzzy model (3) is $T=0$, $E=s/d$, which is the normal state. We also have

$$\begin{aligned} a(1-bT) - n(1-m)\,E &= 0 \\ s + p(1-m)\,ET/(g+T) - q(1-m)\,ET - dE &= 0 \end{aligned} \tag{4}$$

Equations (4) illustrate the effect of the fuzzy Ag recognition, namely it dilutes the IS reaction. This can be seen by comparing the first equation of (4) with its nonfuzzy ($m=0$) counterpart $a(1-bT) - nE = 0$. Thus a fixed concentration of immune effectors will correspond, in the fuzzy case, to a higher fraction of the tumor. Alternatively a higher concentration of effectors will be needed to keep the tumor at a certain level.

It is also expected that this factor will enhance the sneaking through phenomenon where a tumor grows rapidly (exponentially) while the immune response is weak or diluted. When the IS regains its effectiveness, the tumor has already become too large to be affected.

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