# Dynamical and critical behavior of a simple discrete model of the cellular immune system

A. Brass,* A. J. Bancroft, M. E. Clamp, R. K. Grencis, and K. J. Else
*School of Biological Sciences, University of Manchester, 2.205 Stopford Building, Oxford Road, Manchester M13 9PT, United Kingdom*
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A simple cellular automata model has been constructed to investigate the interactions between the two T-helper subset cell types ($T_H1$ and $T_H2$) in a lymph node during chronic parasitic infection. The model exhibits behavior similar to a phase transition as a function of the antigenic burden placed on the host. At low antigen density the behavior of the model resembles that of a "paramagnetic" phase in which both T-helper cell subset cells can coexist. Above a threshold antigen density then one or other of the $T_H$ subset cells becomes dominant and forms a single, connected, infinite cluster (equivalent to a "ferromagnetic" phase). Much of the phenomenological behavior of the model is seen to be in good agreement with that observed in animal models of parasitic infection.

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## INTRODUCTION

The immune system is made up of a complex array of different cell types which communicate via a large number of direct and indirect interactions to help protect the body against disease. The immune response mounted against a particular pathogen can be conveniently divided into humoral and cellular components. The humoral component consists of antibody-mediated defense mechanisms, for example the production of antibodies by B cells to bind to and neutralize a pathogen. The cellular response consists of the effector cells which either directly interact with pathogens, e.g., via phagacytosis, or produce factors which orchestrate and control the nature of the immune response mounted. Both arms of the immune system must work together to combat infection effectively.

Recent studies have highlighted the importance of one part of the cellular immune system, the T-helper ($T_H$) cell, in orchestrating both the cellular and humoral immune responses. $T_H$ cells interact with fragments of antigen presented to them by specialized antigen presenting cells. Once activated by antigen $T_H$ cells produce a range of soluble factors (cytokines) which play a critical role in orchestrating the type of immune response directed against the pathogen. $T_H$ cells that have not yet been presented with antigen are known as $T_H0$ cells. After chronic exposure to antigen $T_H0$ cells can develop into either $T_H1$ or $T_H2$ cells. These two types of $T_H$ cells can be distinguished by the cocktail of soluble factors (cytokines) they produce, and the effect that these cytokines have on the rest of the immune system [1].

The observation that $T_H$ cells can be split into two distinct classes has greatly improved our understanding of many disease states. In particular, it has become clear that whether or not an individual is resistant or susceptible to a range of chronic infections depends critically on which class of $T_H$ cells eventually predominates. Although both $T_H1$ and $T_H2$ responses can sometimes be observed at the onset of infection in a given individual, by the later stages of infection the response will either be entirely $T_H1$ or entirely $T_H2$. An example of this occurs in the mouse model for the tropical disease *leishmaniasis*. All *leishmania*-infected strains of mouse in which the $T_H1$ cells finally predominate are resistant to the parasite, whereas all mouse strains in which the $T_H2$ cells predominate are totally susceptible to the parasite [2]. The opposite set of responses is seen in mice infected with the nematode parasite *Trichuris muris*. In this case mice that generate a $T_H2$ response are resistant to parasitic infection whereas mice that generate a $T_H1$ response are totally susceptible to the parasite [3]. It is now known that this phenomenon of $T_H$ cell polarization plays an important role in many diseases (listed in Table I [4]).

There is much interest in immunology in determining the mechanisms which govern $T_H$ cell polarization, as this process has important implications in determining resistance and susceptibility to many diseases. $T_H$ cells are found densely packed in the lymph nodes and communicate via short range, directional interactions [5]. These properties mean that cellular immune responses can be conveniently modeled using a cellular automata (CA) [6]. Although cellular immune responses have been modeled using differential equations [7,8], one advantage in using a CA to model $T_H$ cell behavior is that it can specifically consider the role of the spatial organization within the lymph node in determining the immune

TABLE I. Pathogens which cause $T_H$ cell polarization [4].

| Pathogen | $T_H$ polarization and immune status |
|---|---|
| Mycobacterium leprae | $T_H1$ (protection) |
| Leishmania major | $T_H1$ (protection): $T_H2$ (susceptibility) |
| Toxoplasma gondii | $T_H1$ (protection) |
| Trichinella spiralis | $T_H2$ (resistance) |
| Trichuris muris | $T_H1$ (susceptibility): $T_H2$ (protection) |
| Measles | $T_H1$ (protection) |

*Author to whom correspondence should be addressed.

 

response. To this end we have previously devised a simple cellular automata model of $T_H$ cell interactions [9]. The behavior of this model was seen to be in good agreement with the observed experimental data on cellular immune response during chronic parasitic infection. In this paper we consider dynamic and critical responses of a simplified version of this model, and examine the significance of these behaviors on the control of the immune response.

## METHODS

### The system

The model immune system was studied using the program CAT$_H$IE (cellular automata for $T_H$ induction and expansion). This program models the behavior of a simplified lymph node (LN) containing T cells interacting on a cubic lattice, and an antigen source which distributes a fixed amount of antigen at random to cells in the LN. The LN was made up of 13 824 sites arranged in a cubic $24\times24\times24$ grid with periodic boundary conditions. Every site in the LN was defined as having six neighbors (in the $\pm x$, $\pm y$, and $\pm z$ directions). Three different T cell types were included in the CA: T0 cells (equivalent to $T_H0$ cells), T1 cells (equivalent to $T_H1$ cells), and T2 cells (equivalent to $T_H2$ cells). At the start of the simulations a single T0 cell was placed at every site on the LN.

### Antigen interactions

In one time unit of the simulation $N_A$ units of antigen were simultaneously distributed at random to sites with the LN. There is experimental evidence to suggest that the way in which antigen is presented to a T cell (the type of antigen presentation cell used) determines whether a T0 cell becomes a T1 or T2 cell. In the CA this is modeled by the inclusion of two different antigen presentation routes (equivalent to two populations of antigen presenting cells). Antigen presented by the first route (labeled A1) elicited a T1 response; antigen presented via the second route (labeled A2) elicited a T2 response. The parameter $a$ defined the proportions of $A1$ and $A2$ antigen produced: in one time unit $aN_A$ units of $A1$ antigen and $(1-a)N_A$ units of $A2$ antigen were distributed among the sites in the LN.

### T cell interactions

In nature it is known that $T_H1$ cells produce factors that promote the growth of $T_H1$ cells and suppress the growth of $T_H2$ cells. Similarly $T_H2$ cells produce factors that promote the growth of other $T_H2$ cells and suppress the growth of $T_H1$ cells. Therefore in the model every T1 cell produced a factor which supported T1 cells and suppressed T2 cells in the six-nearest-neighbor sites and vice versa. $A1$ antigen presented to a T0 cell at a site turned it into a mature T1 cell unless the T0 cell had a majority of T2 neighbors, in which case induction of the T0 cell into the T1 pathway was suppressed and the T0 cell remained in its original state. Similar rules applied to T0 cells presented with T2 antigen. A T1 cell with a majority of T2 neighbors was suppressed, i.e., although remaining a T1 cell it became unable to produce any factors to suppress neighboring T2 cells or support neighboring T1 cells. A similar rule was used for T2 cells with a majority of T1 neighbors. A counter recorded the time since each T1 or T2 cell was last stimulated by the appropriate antigen. A cutoff value $N_T$ was set such that cells not restimulated within this time died, to be replaced with T0 cells. The model immune system with all the various cytokine interactions is shown in Fig. 1.

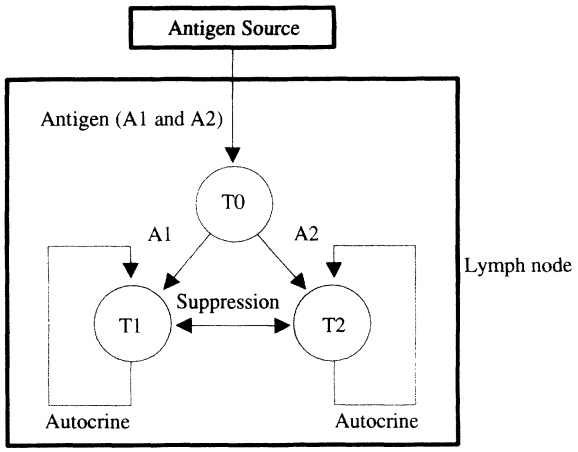


FIG. 1. A simple diagrammatic representation of the CA model of a lymph node. Antigen is distributed at random to cells within the lymph node from an external antigen source. Two types of antigen are produced: $A1$, which induces T0 cells along the T1 pathway, and $A2$, which induces T0 cells along the T2 pathway. T1 cells produce factors which support neighboring T1 cells (autocrine factor) and suppress neighboring T2 cells. Similarly T2 cells produce factors which support neighboring T2 cells and suppress neighboring T1 cells.

### Model parameters

The variables $N_T$ (the time needed before a cell not restimulated by the appropriate antigen died) and $N_A$ (the number of units of antigen distributed in each time unit) are not independent. The probability that a given cell will die in a given unit of time is related to the probability that a T cell has not been restimulated in the past $N_T$ time steps. If $N_A$ units of antigen are distributed each step then the probability that a T1 cell will not be stimulated by $A1$ antigen is given by $p=(1-aN_A/24^3)$. The probability that a cell dies, i.e., is not restimulated after $N_T$ iterations, is then simply given by $d=p^{N_T}$. In most of the interesting regimes of the model the quantity $aN_A/24^3$ is small, so that to a good approximation $d=(1-N_TaN_A/24^3)$, i.e., if $N_T$ is doubled and $N_A$ is halved the behavior of the model is equivalent. In this study we have therefore examined the behavior of the CA with respect to the two control parameters $a$ and $d$. At each iteration of the automata the total number of T0

cells, active T1 and T2 cells, and suppressed T1 and T2 cells was recorded. After every simulation the final configuration of the LN was studied to examine the topology of the T cell clusters. A cluster counting program was used which determined the sizes of all the connected clusters of cells in the network.

## RESULTS

In Fig. 2 the number of activated T1 and T2 cells is plotted as a function of time for simulations with $a=0.5$ and $d=0.2$ [Fig. 2(a)] or $d=0.6$ [Fig. 2(b)]. For simulations run at low values of $d$ [Fig. 2(a)] the number of T1 and T2 cells rose at the start of the simulation before one population of cells began to dominate. At equilibrium the majority of the dominant cell population was found in a single infinite cluster. For simulations run at high values of $d$ the number of T1 and T2 cells in the node rose rapidly and quickly reached a stable state in which both T1 and T2 cells were present [Fig. 2(b)]. Analysis of the T1 and T2 clusters created in the LN at equilibrium showed that all connected clusters of T1 and T2 cells were finite. The noise spectrum of the number of T1 and T2 cells as a function of the number of iterations showed a $1/f^2$ behavior. All simulations performed in this study, irrespective of the values of $d$ and $a$ at which they were run, showed a similar $1/f^2$ noise spectrum.

Figures 3(a) and 3(b) show the equilibrium number of T1 and T2 cells as a function of $d$ for simulations run at various values of $a$. For simulations run at $a=0.5$ the ground state of the system was degenerate, i.e., for simulations at low values of $d$ either the T1 or T2 cell type could dominate. For consistency with the other data the T1 curve presented for $a=0.5$ is defined by min(T1,T2) and the T2 curve by max(T1,T2). One of the interesting features of these curves is the peak seen in the number of T1 cells as a function of $d$. For small values of $d$ the LN is made up exclusively of T2 cells; however, as the value of $d$ is increased the number of T1 cells in the node also increases. The value of $d$ at which this peak occurs and its height are a function of $a$.

The behavior of the node can be clarified by examining the final equilibrium value for $\langle |N_{T2}-N_{T1}| \rangle$, i.e., the mean difference between the number of T1 and T2 cells in the LN at equilibrium, as a function of $d$ (Fig. 4). The values of $\langle |N_{T2}-N_{T1}| \rangle$ as a function of $d$ at $a=0.5$ resembled those seen for an order parameter at a phase transition. If the midpoint of the transition is denoted as $d_c$, then it was found that for all simulations run with the value of $d$ below $d_c$ there existed an infinite cluster of

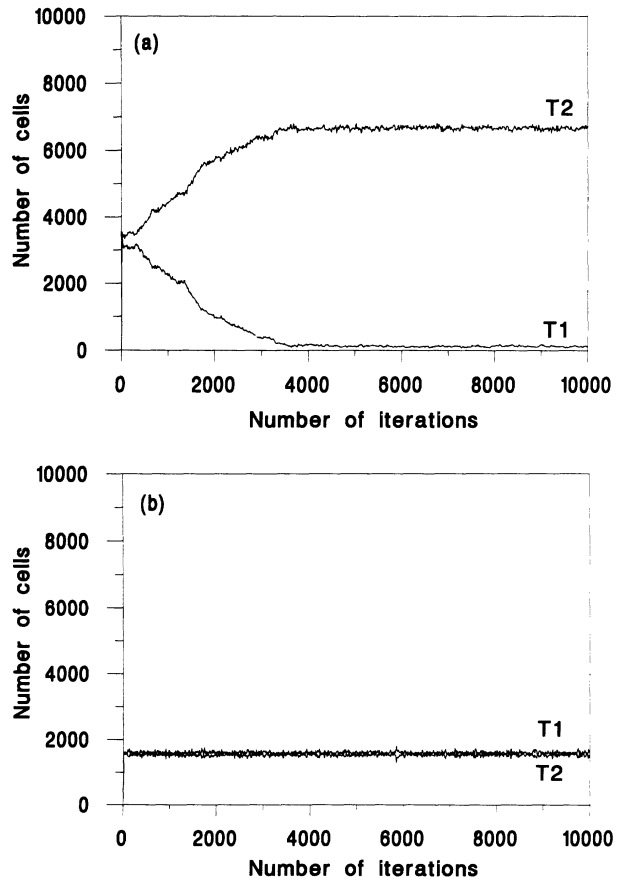


FIG. 2. The total number of activated T1 and T2 cells contained within the LN as a function of the number of iterations of the CA for runs with $a=0.5$. (a) A run with $d=0.2$. (b) A run with $d=0.6$.

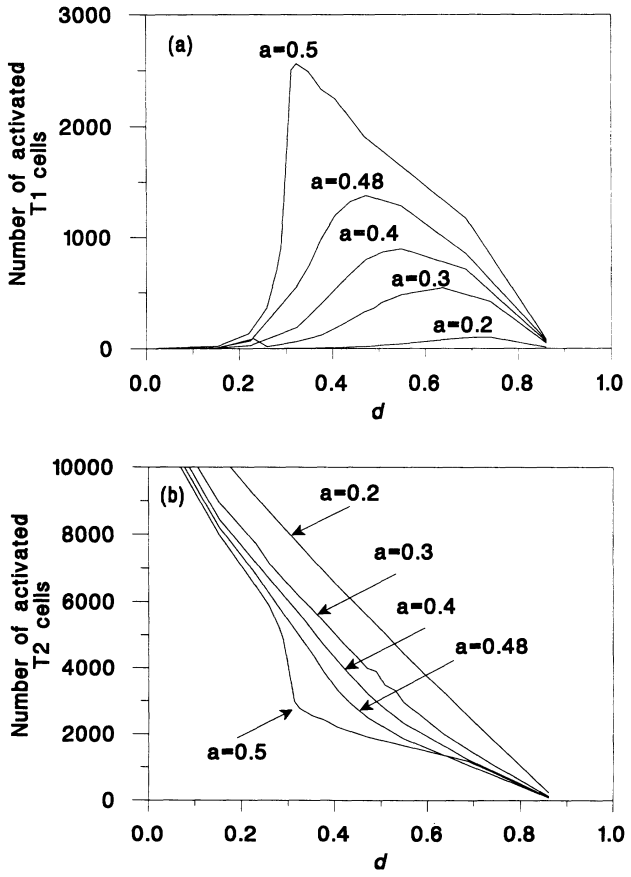


FIG. 3. (a) The average number of activated T1 cells in the lymph node at equilibrium as a function of $d$ plotted for different values of the parameter $a$. (b) The average number of activated T2 cells in the lymph node at equilibrium as a function of $d$ plotted for different values of the parameter $a$ (note that the two scales for these graphs are different).

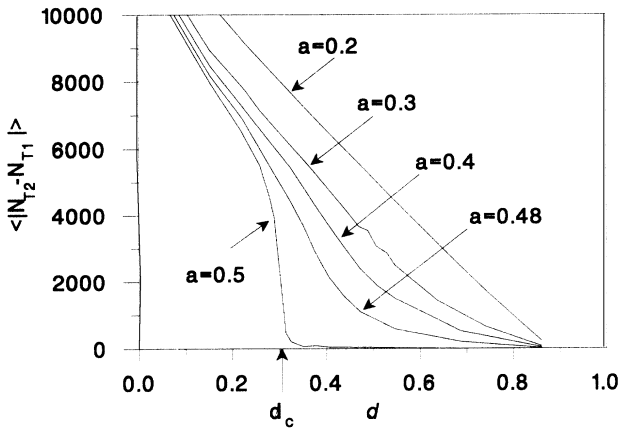


FIG. 4. The average value of $\langle |N_{T2}\text{-}N_{T1}| \rangle$ in the lymph node at equilibrium as a function of $d$ plotted for different values of the parameter $a$ where $N_{T1}$ and $N_{T2}$ are the number of T1 and T2 cells in the node. The position of the midpoint of the transition is marked on the $x$ axis by $d_c$, where $d_c \approx 0.31$.

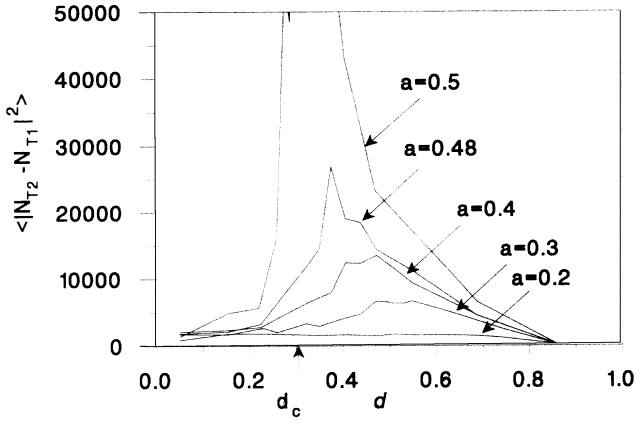


FIG. 5. The average value of $\langle |N_{T2}\text{-}N_{T1}|^2 \rangle$ in the lymph node at equilibrium as a function of $d$ plotted for different values of the parameter $a$. The value $d_c$ marks the midpoint in the transition observed in the values of $\langle |N_{T2}\text{-}N_{T1}| \rangle$ as a function of $d$.

connected T2 cells, whereas for simulations run for values of $d$ greater than $d_c$ there was no infinite cluster of connected T2 cells.

Figure 5 shows the value average of $\langle |N_{T2}\text{-}N_{T1}|^2 \rangle$ as a function of $d$ for simulations performed at different values of $a$. For simulations run at $a = 0.5$ there was a strong peak in the value of $\langle |N_{T2}\text{-}N_{T1}|^2 \rangle$ at a value of $d \approx d_c$. For values of $a$ away from 0.5 the size of the peak in $\langle |N_{T2}\text{-}N_{T1}|^2 \rangle$ as a function of $d$ was much smaller and shifted to higher values of $d$.

## DISCUSSION AND CONCLUSIONS

In this paper we have described a simple model to describe the behavior of T-helper cell subsets in chronic infection. The model has concentrated on studying the effects of the highly directional, competing nearest-neighbor interactions between two $T_H$ cell subsets in a compact lymph node.

To understand the behavior of this model it is helpful to draw a crude analogy between the CA and a magnetic system in an external field. The parameter $d$ can be thought of as playing a role equivalent to temperature: when $d$ is small then T1 cells rarely die to be replaced by T2 cells and vice versa; similarly, when $d$ is large it is common for T1 and T2 cells to die to be replaced by cells of the other subset. Therefore for simulations run at high values of $d$ the T cell subset at a site will be constantly changing ("high temperature") whereas for simulations run at low values of $d$ the T cell subset represented at a site will stay much more constant ("low temperature"). The parameter $a$ defines the likelihood that an antigen from the pathogen will induce a cell into the T1 lineage. When $a = 0.5$ there is no bias of the system toward a ground state in which either T1 or T2 cells dominate. If $a > 0.5$ then the T1 cells will dominate, for $a < 0.5$ then T2 cells will dominate. Therefore the parameter $a$ plays a role similar to that of an external magnetic field.

At low values of $d$ the LN is dominated by an infinite connected cluster of one particular T cell subset ("ferromagnetic" phase). For $a = 0.5$ (i.e., no "external field") the ferromagnetic phase is degenerate and either T1 or T2 cells can dominate. For $a \neq 0.5$ the ferromagnetic phase is no longer degenerate and the dominant T cell subset is determined by whether $a$ is greater or less than 0.5. For high values of $d$ (low antigen density) the model demonstrates a "paramagnetic" phase in which both T1 and T2 cells can coexist and all the connected clusters are finite.

With two simple assumptions it is possible to draw analogies between the behavior of the CA and the immune responses of mice with chronic *T. muris* infection. First, different strains of mice show different immune responses to infection. In the model this effect can be reflected in the value of the parameter $a$, i.e., different strains of mice will vary in their inherent levels or efficiency of antigen presenting cells capable of inducing $T_H1$ and $T_H2$ responses. Second, in the experimental models of *T. muris* infection different responses are seen with different levels of parasite load. In the model we can include this effect via the parameter $d$, with low values of $d$ corresponding to high-level infections and high values of $d$ corresponding to low-level infections. Using these assumptions in the CA model then several predictions can be made about the immune response to parasitic infection.

(i) For high-level infections the LN should be in the "ferromagnetic" phase—i.e., mice should always become all $T_H1$ or all $T_H2$. For strains with $a \neq 0.5$ the final dominant T cell type should always be the same. However, it may be possible for a strain with $a \approx 0.5$ to show a differential response—i.e., in the same set of genetically identical mice all given a similar infection, some individuals will mount a $T_H1$ response whereas others mount a $T_H2$ response.

(ii) For low-level infections the LN should be in the "paramagnetic" phase and the immune response mounted should be qualitatively different to that seen in high-level infections; for example, it may be possible to see both $T_H1$ and $T_H2$ responses in the same animal.

(iii) There should be a sudden switch in the immune response to parasitic infection when the parasite burden is slowly increased from a low level to a higher level as the response switches from the "paramagnetic" to the "ferromagnetic" phase, i.e., there should be a threshold effect with respect to the level of parasite burden.

Interestingly, there is experimental evidence to support each of these predictions from experiments on mice infected with *T. muris* and *leishmania*. In experiments in which mice were given a high-level infection of *T. muris* [3], it was found that some strains of mice always mounted a $T_H1$ response, other strains always mounted a $T_{H2}$ response, and one strain (B10.D2n) was a differential responder (meaning that if a batch of the genetically identical B10.D2n mice were infected with *T. muris* around half the mice mounted a $T_H1$ response and half a $T_H2$ response even though they all receive the same dose of parasite [10]). In terms of the model these results are consistent with the "ferromagnetic" phase of the immune response, as would be expected for high antigen density (low values of $d$), in which the B10.D2n strain had a value of $a$ close to 0.5.

Mice normally resistant to a high-level infection of the parasite *T. muris* were found to be susceptible to a low-level infection. In terms of the model we would predict that for very low doses of the parasite the immune response is within the "paramagnetic" phase. In the paramagnetic phase the LN cannot mount a full protective $T_H2$ response and this allows the parasite to survive immune attack. Similar responses have also been seen in the *leishmania* system [11], except in this case mice that were normally susceptible to high doses of the parasite (mounting an ineffective $T_H2$ response) became resistant to low levels of the parasite.

Evidence for the existence of a threshold could be seen in experiments in which mice normally resistant to high-level infections with *T. muris* were exposed to a trickle infection (i.e., given a gradually increasing worm burden). For very low levels of infection the mice were unable to expel the parasite; however, as the level of infection increased the mice suddenly became able to expel the parasite [Bancroft, Else, and Grencis (unpublished)]. These data are consistent with the prediction that there is a critical value $d_c$ which must be reached before a full protective $T_H2$ response can be mounted. It is interesting to speculate that this threshold phenomenon may be partly responsible for the age-dependent parasite loads seen in the human populations infected with *Trichuris trichiura* [12]. It is known that *T. trichiura* parasite loads are highest in young children and decrease with age. These data would be consistent with the model that human populations are exposed to a constant low-level infection with the parasite to which they will initially be susceptible (because the immune response is "paramagnetic"), but as they get older the parasite burden will increase to the point where the immune response enters the "ferromagnetic" phase and they will be able to expel the parasite.

From these data we would therefore suggest that it is useful to think of the immune response as a many-body phenomenon capable of showing many of the behaviors (such as phase transitions) associated with such systems, and that simple physical models of the immune response have a useful role to play in developing an understanding of the immune system as a whole.

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