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Theoretical Immunology

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1. Introduction

The immune system is a genuine example of an information processing system. Information in the immune system is present in the form of antigens (self and non-self) and receptor molecules. These are information-bearing structures that interact upon complementary matching. Embedded in a universe of $>10^5$ self antigens, the immune system is able to pick up novel information (i.e., foreign antigen) and is able to remember it specifically (i.e., immunological memory). These information-processing (or cognitive [1]) properties of the immune system arise somehow from the cellular and molecular interactions between the components of the system. The immune system is composed of many different cell types and molecules. This enormous complexity hampers our understanding of the "functioning" (or information processing) of the immune system.

Theoretical immunology aims to tackle this problem. By coupling the interactions described by immunologists in theoretical models, one is able to study the (possibly coordinate) behaviour that emerges. Because the structure of the immunological interactions in such models can be manipulated easily, the "functioning" of simple model immune systems can usually be understood completely. By understanding the interplay of interactions in these models we gain insight into the possible mechanisms by which the immune system might function in terms of the cellular and molecular interactions. It usually turns out that relatively simple models can account for a number of the complex informational properties that are described for the immune system (see [2] for a recent overview).

For a number of reasons it is important that theoretical models should be kept simple. Adequate understanding of a model requires that the model be sufficiently simple. Complex models will fail to contribute much to our understanding of the even more complex immune system. Secondly, through the development of minimal models, immunological phenomena can be understood in terms of the minimal set of realistic assumptions required for obtaining them. A minimal model often outperforms one which incorporates a maximum of immunological information. Thus models always ignore a number of important facts, and are always "wrong" from an immunological point of view. It is the art of the field to find out what it is best to ignore and what it is best to incorporate in the model.

2. *Overview and Summary*

The aim of the Utrecht symposium was to introduce the field of *theoretical immunology* to theoretical biologists and experimental immunologists. One main focus of attention during the symposium was idiotypic networks. The networks behaviour that arises as the result of coupling millions of different clones by means of receptor–receptor interactions is one of the main issues in the field. Five different approaches to modelling the idiotype network were presented and compared. These network approaches all consider the immune system as a well-mixed system. The last paper, by contrast, studies the spatial patterns that arise by cell–cell interactions in lymph nodes.

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Hoffmann (Vancouver) presented a concept of similarity coefficients for sera containing antibody. Two antibodies (or two sera) are similar to one another when they have similar interactions with a third party antibody (or serum). In his contribution to these proceedings [3], Hoffmann suggested various diagnostic applications of these ideas. The similarity between the different clones in an idiotypic network was also used to extend his previous symmetric network model of two clones (i.e. 2-D) to one of many clones (i.e. n-D); see the discussion in [4].

Another network contribution [5] was made by Segel (Rehovot) who presented the shape space approach which he developed with Perelson (Los Alamos). In the shape space all idiotypes are ordered according to their shapes. Ab1's and Ab3's, which are expected to be similar, should therefore be located more or less adjacently in the shape space.

De Boer (Utrecht) tested ideas of idiotypic repertoire selection during early ontogeny [6]. The theoretical idiotypic networks mature in the presence or absence of self antigens that are either stimulatory or inhibitory. He analysed how these differences in the self environment are reflected in the idiotypic repertoire, and whether this is interpretable in terms of self tolerance.

Based on the hypothesis that the immune system is not antigen-driven, but instead is autonomously active, Varela (Paris) presented his n-D idiotypic network model incorporating B cells, antibodies and a special recruitment for naive B cells [1]. Reducing this model to a skeleton level by ignoring recruitment and B cell dynamics, he was able to show that the network would always settle into a steady state (Varela, F. J. and Stewart, J., in prep.). When B cell dynamics and recruitment were incorporated, however, the network showed sustained oscillations [7] that resemble the variations in natural IgM concentrations that were described recently [8]. The interaction matrix of this model was based on empirical data for connectivity; a re-ordering of these data revealed the presence of distinct groups each of which has different network dynamics [7].

The focus of the symposium then turned from n-D idiotypic networks to models with just a few components of the immune system.

Kaufman (Brussels) has been working for several years now on models of which the core is an idiotypic interaction between T helper and T suppressor cells which regulates the humoral immune response [9–11]. Her work revealed the presence of multiple steady states which include a virgin state, a memory state, and a suppressed state. These states were found by combining a novel discrete (i.e. logical) approach with the more conventional continuous approach (i.e. differential equations). By dynamic introduction into the model of antigen in increasing doses, she was able to establish the presence of a virgin region, a low dose paralysis region, an immunity region and a high dose paralysis region [10].

Hogeweg (Utrecht), applying the technique of cellular automata, analysed the diffusion of IL-2 molecules and T-B cell interaction in lymph nodes [12]. The results stress the importance of spatial models in immunology. It is shown that germinal centres with the characteristic separation into B and T cell areas in lymph nodes develop spontaneously due to the T-B cell interactions.

We hope that the achievements made in this field will arouse further interest. It is our conviction that if the functioning of the enormously complex immune system is to be properly understood, one needs to adopt a formal modelling approach. If this modelling goes hand in hand with the new developments in experimental immunology, it is our hope that once we have finished identifying the components of the system we will indeed be able to *understand* the system.

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