

Immune Network Theory

Geoffrey W. Hoffmann

The University of British Columbia

For many years we have known that the immune system can sense the presence of foreign things in the body. The immune system reacts to foreign substances by making antibodies, and thus rids the body of intruders. We now know that the immune system also has the ability to sense its own components. It is an inward-looking system, in addition to being a defensive system against intruders. This perspective leads to a unified theory, called the symmetrical network theory, that is based on a small number of postulates, and covers many aspects of the regulation of the adaptive immune system.

Table of Contents

Outline	iii
Chapter 1. Immunology: many facts, few theories	1
Chapter 2. Antibodies	8
Chapter 3. Clonal selection	20
Chapter 4. Immune responses to foreign antigens	25
Chapter 5. Specificity	34
Chapter 6. Regulation: T cells and B cells	40
Chapter 7. Non-specific components	57
Chapter 8. Early network findings and ideas	63
Chapter 9. First symmetry	78
Chapter 10. Introduction to the symmetrical network theory	86
Chapter 11. Complexity, stability and network theory	133
Chapter 12. MHC restriction and network theory	152
Chapter 13. The I-J phenomenon	162
Chapter 14. Second symmetry	175
Chapter 15. Self-nonsel self discrimination and autoimmunity	185
Chapter 16. HIV and AIDS pathogenesis	190
Chapter 17. Synthesis	202
Chapter 18. Outlook	217
Index	221

Outline

Immune network theory has been developed since the 1970s, and has been previously published in journals and in book chapters including conference proceedings. This monograph presents and extends the scope of a version of immune network theory called the symmetrical network theory.

There has been a problem for students and even many scholars of immunology of not being able to see the wood for the trees. The subject of immune system regulation is huge, and the selection of facts provided by conventional textbooks is not geared to understanding the immune system in terms of immune network theory. In a typical immunology textbook the network "idea" is summarily dealt with in a few paragraphs, and most of today's immunology graduates are not aware of the extensive experimental and theoretical literature that exists on network immunology.

Chapter 1 describes the general role of theory in biology and specifically in immunology. How do we build theories, and how we know when we have a good one? The pivotal role of mathematical modelling in theoretical biology is outlined. Another key component is to identify any paradoxes that exist within a reigning paradigm, and to seek and find ways to resolve them.

Chapters 2 to 7 introduce some basic concepts of immunology, the building blocks that the theorist has to work with. Much of this material can be found also in introductory texts on immunology. The main difference is that almost no more detail is given here than is necessary for the development of network theory in the subsequent chapters.

Chapter 2 begins with a thumbnail sketch of antibodies, the protein molecules that are highly diverse and can be highly specific in their interactions with substances that are foreign to the body (antigens).

Chapter 3 describes the clonal selection theory. This fundamental law of immunology describes how antibodies are produced by lymphocytes.

Chapter 4 describes some of the forms of the response of the immune system that can be observed following stimulation by various foreign antigens. This chapter concludes with the question of whether the many different immune response phenomena are the result of a corresponding diversity of mechanisms (which tends to be the conventional view) or whether a unifying model can be found that accounts for a wide range of diverse phenomena. The latter is the aim of immune network theory.

The specificity of antibodies and lymphocytes is the subject of Chapter 5. While the "exquisite" specificity of antibodies is a cliché, antibodies actually have variable parts called V regions with multiple sites for potentially binding to antigens, and antibodies are consequently multispecific.

The regulation of specific B cell and T cell responses is the most fascinating aspect of the immune system, and some of the main phenomena are described in Chapter 6. Of particular importance are the ways in which T cells can be shown to help and suppress immune responses. These are the most basic phenomena that a theory of regulation of the immune system needs to account for, so this chapter sets the stage for the later development of network theory.

While network regulation deals mostly with molecules that have V regions and hence are called specific, there are also some cells and molecules without V regions that play a role, and some of these non-specific mediators are described in Chapter 7.

Niels Jerne's network hypothesis is introduced in Chapter 8, and states that interactions between the V regions of antibodies (and similarly interactions involving other molecules and receptors with V regions) play a key role

in the regulation of the system. The hypothesis did not spell out many details of how this might occur; that came later with the explicit network models that have been developed. The hypothesis is firmly based on clonal selection, and involves clones recognizing each others' V regions, instead of being independent of each other. Mutual recognition of clones means that the immune system is introspective, with self-recognition being at least as important as the recognition of foreign things. The first explicit network model to be developed was formulated by Peter Richter. It is also discussed in Chapter 8.

Chapter 9 documents an important symmetry in the immune system, that was recognized in 1975 and led to the symmetrical network theory, which is the main focus of this book. "First symmetry" was the starting point for the theory that provides us with a way of fitting many pieces of the immunological puzzle into a coherent whole.

The symmetrical network theory is introduced in Chapter 10. This chapter describes how much of the important phenomenology can be understood in terms of this most complete version of network theory. The central role of mathematical modelling in finding a self-consistent theory is also made clear in this chapter. The clones specific for a given antigen include two main classes, namely those that have complementarity to the antigen and those that resemble the antigen to a greater extent than the extent to which they are complementary to the antigen. A two-variable mathematical model of the population levels of these clones simulates some of the main ideas of the theory. Non-specific accessory cells play a role in switching between stable states of the system.

Chapter 11 extends the two-variable mathematical model (two classes of clones) developed in chapter 10 to an N-variable model, and the question of how the added complexity can be compatible with the system being stable is explored. A central aspect of the system is unusual as a mathematical system. It is robustly stable even when there are a very large number of interconnected clones; in fact the stability increases with the complexity of the system. Most dynamical systems become less stable as they become more complex.

Chapter 12 describes a phenomenon that was discovered around the time that network theory was invented, namely "MHC (major histocompatibility complex) restriction." T cells are selected to recognize the MHC molecules of the individual in addition to having specificity for foreign antigens, and thus they appear to have a dual specificity. The interpretation of this phenomenon is straightforward in the context of the symmetrical network theory.

Chapter 13 relates how, in 1982, one of the pieces in the puzzle appeared not to fit. This became known as the "I-J paradox". The I-J phenomenon had been discovered in 1976, and appeared to be central to an understanding of immunoregulation. The I-J paradox concerned what seemed to be a missing gene, a discrepancy between serological mapping of a presumed protein(s) called I-J and molecular genetic mapping. The discrepancy unfortunately caused many immunologists to lose interest in the entire area. It was shown in 1988 that the conundrum could be solved in terms of the symmetrical network theory, but by then the waves caused by the paradox had caused many immunologists to be sceptical of a large section of immunoregulatory phenomena and theory, including suppressor T cells, I-J and network theory, and they threw out the baby with the bathwater. It is time to revisit a largely forgotten story. In this chapter we describe the I-J paradox and show how it is important and can be resolved in the context of the symmetrical network theory.

Chapter 14 discusses antibodies that are found in the serum of animals that have been immunized with cells from animals of the same species, but of a different strain. When we take account of antibodies that are specific for receptors of foreign lymphocytes that recognize self antigens, an intriguing new symmetry emerges, that we call "second symmetry". This symmetry also has implications for our understanding of I-J.

Chapter 15 addresses the question of how the immune system distinguishes between self and non-self structures. The question of how the system can go wrong, and make an immune response against self components (autoimmunity) is explored.

Chapter 16 describes an idiotypic network model of HIV pathogenesis. In this model HIV triggers autoimmunity. The theory is based on the model of I-J described in chapter 13. The theory is furthermore based on the fact that HIV preferentially infects HIV-specific helper T cells. The theory predated the experimental demonstration that this is the case. The theory leads to a potential vaccine based strategy for the prevention of HIV infection.

Chapter 17 describes a more detailed idiotypic network models of regulatory T cells that includes the influence of self MHC class II on Th1, Th2, Ts1, Ts2 and Ts3 cells and serum IgG. Phenomena called I-J restriction and Igh restriction of suppressor T cells are described and explained in the context of the model. Serum IgG is ascribed a role in the maintenance of self tolerance. The inverse relationship between antibody immune responses and delayed type hypersensitivity is ascribed to competition between suppressor T cells and contrasuppressor T cells. The model is then extended to include all self antigens and IgM secreting and IgG secreting B cells.

Chapter 18 assesses what has been achieved in immune network theory, and where the field needs to go from here.