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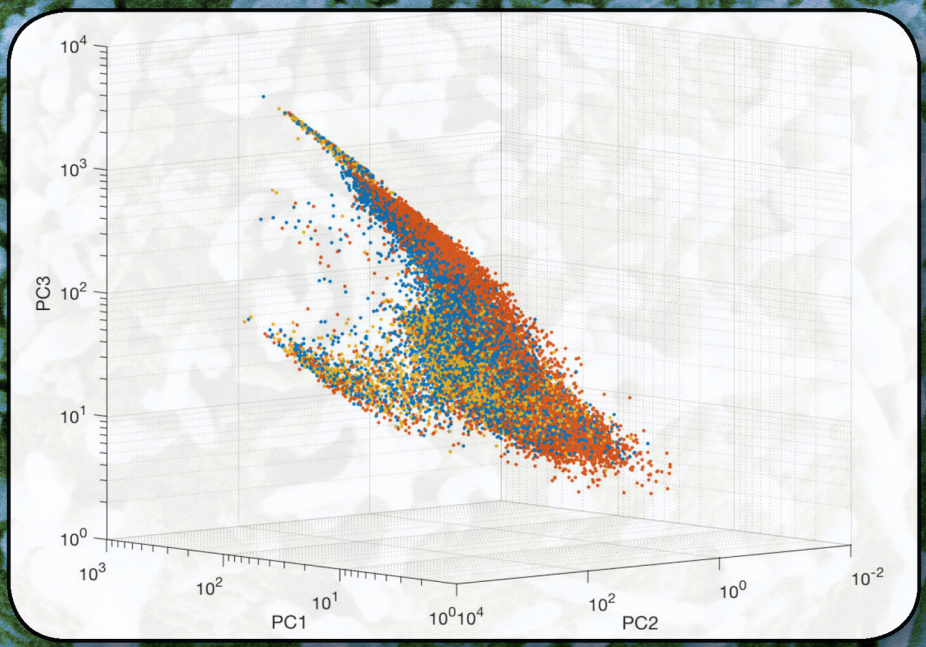
SYSTEMS IMMUNOLOGY

An Introduction to Modeling Methods for Scientists



EDITED BY

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An Introduction to Modeling Methods for Scientists

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Systems Immunology
An Introduction to Modeling Methods for Scientists

Edited by
Jayajit Das
Ciriyam Jayaprakash

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To my parents and teachers.

Jayajit Das

To Fernand Hayot, scientist, scholar, and friend.

Ciriyam Jayaprakash

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Series preface

Biophysics encompasses the application of the principles, tools, and techniques of the physical sciences to problems in biology, including determination and analysis of structures, energetics, dynamics, and interactions of biological molecules. Biochemistry addresses the mechanisms underlying the complex reactions driving life, from enzyme catalysis and regulation to the structure and function of molecules. Research in these two areas is having a huge impact in pharmaceutical sciences and medicine.

These two highly interconnected fields are the focus of this book series. It covers both the use of traditional tools from physical chemistry such as nuclear magnetic resonance (NMR), x-ray crystallography, and neutron diffraction, as well as novel techniques including scanning probe microscopy, laser tweezers, ultrafast laser spectroscopy, and computational approaches. A major goal of this series is to facilitate interdisciplinary research by training biologists and biochemists in quantitative aspects of modern biomedical research, and teaching core biological principles to students in physical sciences and engineering.

Proposals for new volumes in the series may be directed to Lou M Chosen, Executive Editor (lou.chosen@taylorandfrancis.com).

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Foreword

It is becoming increasingly clear that the immune system is critically important for maintaining health and is implicated in mediating various states of disease. The desire to combat infectious diseases since antiquity, the more recent interest in deploying the immune system to combat cancer, the untold amount of suffering caused by autoimmune diseases, and the desire to understand how the remarkable immune system works has led to a great deal of experimental and clinical research aimed toward understanding how immunity is regulated. Some spectacular discoveries have been made over the years. In spite of these major advances, our understanding of how a systemic immune response develops, and how it can be mis-regulated to cause diverse diseases remains incomplete. The ability to collect large amounts of data in a high throughput manner combined with computational inference of patterns in this data, mechanistic modeling to generate appropriate hypotheses to explain these patterns, and experimental/clinical tests of these hypotheses is beginning to change this situation. This convergence of approaches and people from different disciplines may lead us to a future where a person's immune health can be monitored, corrected when it goes awry, and manipulated for therapeutic and prophylactic purposes with precision. This edited book reviews progress in some aspects of ongoing work pertinent to this goal. The first chapter by Salvatore Valitutti and co-workers aims to introduce the basics of how the immune system works to individuals not trained as biologists. There is also an interesting chapter by Steven R. Abel that summarizes the various approaches that are being pursued to construct theoretical and computational models of processes pertinent to the immune system across a range of spatio-temporal scales. Other chapters discuss topics that cover a wide range that includes statistical analyses methods, rule-based modeling of immune cell signaling, characterizing vulnerabilities of mutable viruses to immune attack, importance of spatial heterogeneities in regulating immune responses across scales, the key challenges that remain in understanding immune synapses, etc. Taken together, the body of information contained in this book provides readers with a bird's-eye view of different aspects of exciting work at the convergence of disciplines that will ultimately lead to a future where we understand how immunity is regulated, and how we can harness this knowledge toward practical ends that reduce human suffering. I commend the editors for putting this volume together.

Arup K. Chakraborty
MIT

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Preface

I have done this to illustrate that the approach being used is not meaningless speculation but has real possibilities of suggesting experiments that may lead to its modification or rejection.

Frank M. Burnet
Nobel lecture, 1960

The discipline of immunology has undergone transformative changes in the last few decades. Driven by intense research efforts aimed at combating infectious diseases such as HIV infection and by technological advances in experimental approaches our knowledge of the immune system now spans from the scales of single molecules to human communities. To put the above range of scales in a perspective, a similar range in length scale relates the size of a human to the average distance of Saturn from the Sun. The major challenges in immunology are usually multiscale problems where dynamical processes occurring on such a wide range of scales interact with each other to generate responses that affect our health. Take the example of the progression of an epidemic where interactions between viral peptides and immune receptors in the microscale propagate to larger scales infecting individuals and then human communities residing in many geographical regions. The complexity and the multi-scale nature of the immune system have necessitated the use of sophisticated modeling and theoretical techniques to construct mechanistic and data-driven models and then use the models to make predictions and design experiments or hypotheses. Techniques from physical and engineering sciences, in particular physics, have been proven valuable for building such models. Some of these models have led to the development of life saving clinical strategies besides providing basic understanding of the underlying biochemical processes. This interdisciplinary effort has led to a small but steadily growing field loosely designated as computational immunology or systems immunology.

However, it is still difficult for a researcher with a background in physical sciences or immunology to readily start working in this interdisciplinary area. On the one hand, a researcher from physical sciences is often overwhelmed by the vast immunology literature; on the other hand, biologists are intimidated by mathematical jargon and seemingly complicated computational methods. Another common difficulty is that even a well-trained Ph. D. in the physical and mathematical sciences will not know all of the different mathematical techniques required in modeling immunology. Some of these issues are dealt with in review articles published in professional journals; however, these reviews often have a very narrow focus depending on the target audience of the specific journal and fail to provide a holistic picture of the entire field. Thus, there is an acute need for a book that can be used by physical scientists or biologists who are interested in using quantitative methods to develop predictive mechanistic models in immunology.

This book is designed to address some of the above problems and provide a solid foundation for students and researchers in physical and biological sciences who would like to start working in the interdisciplinary field of systems or computational immunology. The nineteen chapters, written by leading experts in the field, cover a wide range of computational and mathematical methods employed in mechanistic and data driven modeling of immune responses at the scales of single cells to organs to individual organisms to populations. In addition, a basic introduction to the immune system is provided to help a newcomer get started. The chapters on fundamentals of statistical data analysis, and, on the approximations and assumptions that are usually made in mechanistic modeling should help students critically assess models presented in the literature where such discussions are often omitted.

Graduate students and advanced undergraduate students in physics, biophysics, chemistry, applied mathematics, chemical engineering, bioengineering, systems biology, ecology, molecular biology, and immunology

departments will find this book useful as a textbook for courses pertaining to quantitative methods in immunology or biology. We hope the book will also serve as a useful introduction for modeling approaches to researchers with physical sciences or biology background.

We appreciate the time and effort of the authors who made room in their busy schedules to contribute to this effort. The book would not have been possible without the valuable help from Rhonda Purcell and Gail White, who assisted us with organizing the chapters and coordination between the contributors, the editors, and the publisher.

Jayajit Das
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1

Introduction to basic concepts in immunology

ROXANA KHAZEN AND SALVATORE VALITUTTI

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1.1 SUMMARY

The immune system is a complex network of cells and soluble mediators that evolved to defend its host organism from pathogenic microbes. Since immune responses are endowed with high complexity and plasticity, the understanding of complex immunological networks can strongly benefit from the interdisciplinary work of physicists, applied mathematicians, and experimental immunologist. For successful interdisciplinary collaboration, it is of primary importance that basic concepts are shared in a simplified fashion. In this chapter, we outline some basic concepts to introduce immunology to non-biologists. We provide fundamental knowledge and nomenclature, which is essential to understand the complexity of immunological networks. For a more complete understanding of immunology, the readers can refer to excellent reference texts (Abbas et al., 2015; Murphy et al., 2012; Paul, 2012). We detail T cell antigen recognition and cytotoxic T lymphocyte (CTL) function more than other aspects of immunology. These topics are chosen as examples to illustrate the complexity of the molecular and cellular interactions taking place in the immune system.

1.2 INTRODUCTION

1.2.1 General view of the immune system

The immune response is based on interactive networks of numerous cellular and molecular effectors that evolved to protect a host against infections, to control tumor growth, as well as to maintain the homeostasis of tissues.

1.2.1.1 CELLS

Development of cells of the immune system starts in the bone marrow from a common precursor cell (called pluripotent hematopoietic stem cell) that then differentiates into more specialized cells to form a heterogeneous group of immune cells called leukocytes, or white blood cells (Figure 1.1).

1.2.1.2 CYTOKINES AND CHEMOKINES

Cytokines and *chemokines* are essential components of the immune system. They can be considered "molecular messengers" that cells of the immune system exchange among each other. More than one hundred different cytokines have been identified so far. Cytokines are secreted in the extracellular milieu or are bound on the surface of the cell. They are responsible for complex intercellular communication since each cytokine can be produced by more than one type of cell and acts on different cells of the immune system (remarkably, each cytokine can exert different effects on different cells). Different types of cytokines include: tumor necrosis factor-α (*TNF*-α), interferons (*IFN*-α, *IFN*-β, and *IFN*-γ), interleukins (*IL-1, IL-2, IL-3*, etc.), and chemokines. All cytokines accomplish their functional role by binding to specific receptors expressed on the surface of a cell. Some cytokines, such as TNF-α and interferons, have the role of alerting the immune system and of promoting immune responses. Others, such as TGF-β and IL-10, are instead inhibitory cytokines and suppress immune responses.

The chemokines are a family of small cytokines involved in *chemotaxis* (directed movement) of cells. Chemokines are therefore chemotactic cytokines. The main role of chemokines is to guide the migration of immune system cells so they may reach the organs or tissues where their function is required.

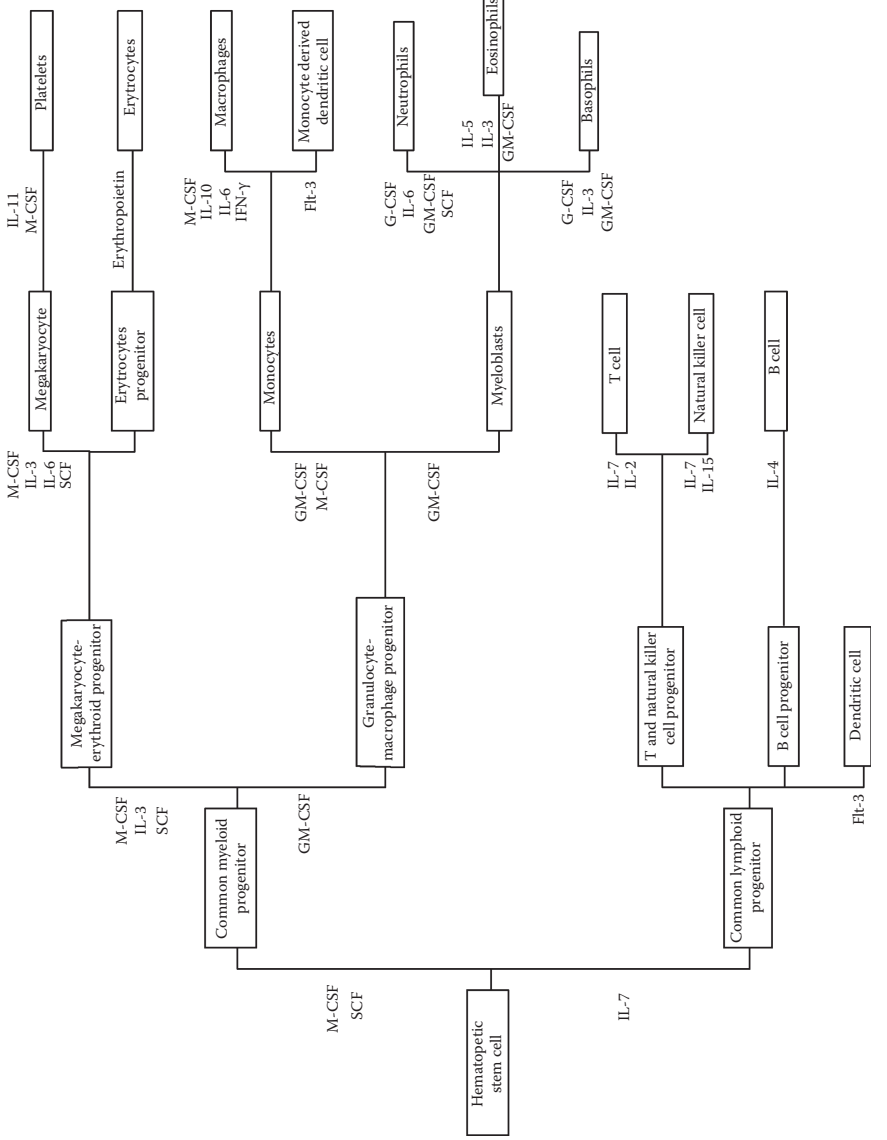

Figure 1.1 Development of cells of the immune system. Development starts from a common pluripotent hematopoietic precursor cell that differentiates into more specialized progenitor cells in the bone marrow to form a heterogeneous group of immune cells called leukocytes, or white blood cells. The main cytokines involved in the differentiation of the different immune cells are indicated in blue. Neutrophils, monocytes, macrophages, and immature dendritic cells (DC) originate from common myeloid precursor cells, whereas B and T lymphocytes and natural killer (NK) cells arise from common lymphoid progenitors.

1.2.2 The innate immune response

Studies over the past three to four decades characterize the immune system as consisting of two main categories: innate immunity and adaptive immunity. Although these two components of the immune response mainly differ in terms of specificity, rapidity, duration, and biological functions, they are complementary and deeply interconnected.

Innate immunity plays an essential role in the immediate defense of the host organism. It allows the discrimination of *self/nonself* by a system that consists of soluble proteins and relatively invariant cellular receptors. By *self*, immunologists mean the molecular patterns that the immune system has learned to recognize as components of the host organism. The immune system does not react against these components. This phenomenon is named *immunological tolerance*. By *nonself,* immunologists mean the molecular structures that do not belong to the host organism and that therefore trigger immune responses when penetrating the organism.

Innate immunity is composed of three layers of defense: (1) the physical barriers composed of epithelial cells and antimicrobial agents; (2) cells such as neutrophils, macrophages, and dendritic cells (*DC*), which uptake pathogens and cell fragments and release antimicrobial agents, and natural killer cells (*NK*), which kill virus-infected cells; and (3) plasma proteins, including cytokines, chemokines, and the *complement system*.

It is important to note that macrophages and DC do not only intervene in early steps of innate immune responses but also present antigenic ligands to T lymphocytes, therefore acting as a bridge between innate and adaptive immune responses (see the legend to Figure 1.2). Other cells that are implicated in the initial protection against pathogens and that play a functional role at the interface between innate and adaptive immune responses are basophils, eosinophils, mast cells, and innate lymphoid cells (*ILC*) as well as some subpopulations of lymphocytes including B-1 B cells, natural killer T cells (*NKT*), and γδT cells.

Cells that are part of the innate immunity category reside in various parts of the body and are in particular located at potential entry sites of pathogens, such as skin and mucous membranes, where they are ready to rapidly respond upon recognition of danger signals. The danger signals are common structural patterns of microbes (pathogen-associated molecular patterns, *PAMP*) or endogenous byproducts of damaged or dying cells (damage-associated molecular patterns, *DAMP*); these patterns are recognized by evolutionary conserved receptors named pattern recognition receptors (*PRR*). Among these receptors, an important family is represented by the Toll-like receptors (*TLR*s) that are expressed by various cells of the immune system.

A peculiar characteristic of the innate immune cells is that they rapidly respond against pathogens, but they do not "learn" from previous encounters with a given pathogen and therefore respond evenly to repeated exposure to an infectious agent.

A typical innate immune response is depicted in Figure 1.2. The legend of Figure 1.2 summarizes, in a schematic fashion, the cascade of cellular and molecular steps constituting innate immune responses.

1.2.3 The adaptive immune response

Adaptive immunity is characterized by the proliferation and differentiation of specific cells called *lymphocytes* that recognize antigens. The main feature of adaptive immune responses is the usage of antigen specific receptors expressed by the two main subsets of lymphocytes, the B and T lymphocytes. Pathogens, infected cells, and tumor cells express on their surface antigens that are recognized by B and T lymphocytes. An *antigen* is defined as a molecule that is recognized by the adaptive immune system. More precisely, the receptors expressed by B and T lymphocytes recognize, with high specificity, a small molecular structure named *epitope* within the antigen. A pathogen, such as bacteria, can therefore be seen as a mosaic of antigens (each antigen is made of various epitopes) that triggers different B and T lymphocytes, each one expressing on their surface approximately 30,000-50,000 identical antigenreceptors that are specific for a given epitope.

Adaptive immunity takes longer to get involved when compared to innate immunity and constitutes the second line of the host organism's defense. Although adaptive immunity requires several days or weeks to develop, it can eventually elicit the specific elimination of antigens, infected cells, and cancerous cells. It is