Antigen-Antibody Interaction

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Abstract-The clonal selection theory of acquired immunity provides a relatively graceful to comprehend explanation for the diversity and specificity of the acquired immune system. This easy of comprehension is deceptive as much of the specific details that underlie the theory are abstracted. This work provides a brief review of some of the physiological and immunochemical aspects of antigen-antibody interaction with a special focus on antibody bound to the surface of lymphocyte cells (B-cell receptors), and their role in the clonal selection theory of acquired immunity.

Keywords-Antibody, Antigen, Clonal Selection Theory, Artificial Immune System, Acquired Immunity, Interaction, B-Cell Receptor, Immunoglobulin

I. Introduction

The clonal selection theory of acquired immunity [5,6,9,10] provides an explanation for the diversity and specialisation of antibodies. The theory describes the selection of B lymphocytes by antigen, and the resulting clonal expansion and affinity maturation by hypermutation [17,18]. In view of the clonal selection theory, this work reviews some relevant detail of antigen-antibody interaction, specifically antigenlymphocyte interaction that is central to the theory of acquired immunity.

Section II provides some background by introducing some immunological physiology, in particular the ways in which antigen-antibody interaction is described in immunology, the classes of antibody (immunoglobulin) and membrane bound antibody on B lymphocytes. Section III addresses the problem of antigen arrival, specifically the types of antigen, and the ways in which pathogen may enter the host. Section IV addresses the concern of antigen selection of antibody, in particular the selection of membrane-bound antibody on B-lymphocytes. Discussed are the physio-chemical forces involved, the specificity and generality of the binding and the types of interactions that may result. Section V discusses the two principle ways to measure the closeness of the selection and binding: affinity and avidity. Finally, section VI briefly discusses what happens to antibodies directly after the binding.

This work reviews the principles of antigen-antibody interaction, with artificial immune systems and algorithm design in mind. The subject has its roots in immunology and immunochemistry, for a more detailed treatment see [4,8,13,14]. This brief review was inspired by a section of Lord's Masters Thesis [3] that described

for method for considering antigen-antibody interaction (section 2.2 pages 11-12).

II. SOME PHYSIOLOGY

This section provides a brief introduction into the physiology of antigen-antibody interaction, in particular from the host perspective. A quintessential antigenantibody interaction depiction is presented which is reused throughout this work. See the glossary at the end of this work for some terms and definitions.

A. Antibody-Antigen Interaction

Antigen-antibody interaction is referred to by many terms involving many different actors. Some examples include:

Antigen	Antibody
Epitope	Paratope
Ligand	Receptor
Antigenic Determinant	Combining Site
Protein	Binding Site

Table 1 - Summary of some of the terms used to describe antigen-antibody interaction

An antibody is a protein molecule (immunoglobulin) that has one or more combining sites called paratopes. An antigen is a general term for a molecule that may trigger **anti**body **gen**eration, with potentially many different features surface. Antigenic determinants are those surfaces features of the antigen that are complementary to an antibodies combining site.

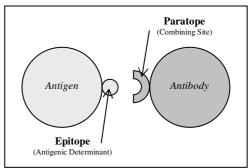


Figure 1 - Depiction of an antigens epitope and an antibodies paratope

B. Immunoglobulin

Antibody belongs to a type of protein molecules called immunoglobulin (Ig), which in humans consists of a heterogeneous population of five different classes or isotypes. Each class of immunoglobulin has generally

different functional behaviours, and different a half-life. Ig may be found in secreted form in fluid, or bound to the surface of a cell, such as a B lymphocyte. A type of B lymphocyte called plasma B-lymphocytes are responsible for the secretion of all five types of antibody, which occurs as apart of the clonal response in the clonal selection process. Table 2 summarises the five immunoglobulin types, for a more detailed treatment see [13] (pages 25-28), [14] (pages 69-80) and [7] (chapter 4).

Class	Additional Info	Functional Description
IgG	IgG1-IgG4	Predominant antibody found in blood and lymph. Predominant antibody involved in material immunity.
IgA	IgA1 (serum), IgA2 (secretory)	Predominant antibody found in saliva, tears, sweat, milk, intestinal secretions, and colostrum
IgM	Macroglobulin	First antibody type produced during a clonal response. Bound to lymphocytes and in serum
IgD	Surface bound	Bound to the surface of lymphocytes, very low concentrations in serum
IgE	Parasite Protection	Has a role in the protection from parasites. Low levels in serum

Table 2 - Summary of human immunoglobulin types (isotypes)

C. Membrane-Bound Immunoglobulin

The immunoglobulin bound to the surface of Blymphocytes is a central feature of the clonal selection theory. That is the selection of cell lines that ultimately: (1) provide the defensive capability in secretion of soluble antibody of the same specificity as the cells receptor, and (2) remembering and refining the cells receptor as a clone of cells for future exposure to the antigen. A single has many Ig receptors, as many as 10⁴ or 10^5 [7], [13] (page 34). Not all B-lymphocyte have surface bound Ig (typically called B-cell Receptors -BCR). Naïve B-cells (antigen independent) express IgM and IgD in approximately equal numbers. Plasma B cells do not express immunoglobulin but rather secrete it, specifically the isotypes IgG, IgE, and IgA. Memory B cells may express one of each of these three secreted isotypes. For more information see [15] (page 30-33), and [7] (Chapter 7).

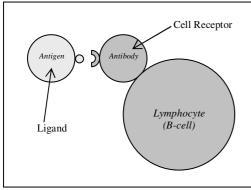


Figure 2 - Depiction of a receptor on a cell and a ligand

III. ANTIGEN (PATHOGEN) ARRIVAL

Antigen are also critical to the theory, without antigen, there is no immunity for the acquired immune system to respond to and learn. This section summarises various different antigen types and the ways in which an exogenous antigen may penetrate the host.

A. Antigen Types

Antigens are macromolecules with one or more antigenic determinants. They are also called immunogens because they result in an immune response. Smaller molecules called haptens are antigenic determinants, although they are too small and must be bound to the surface of larger molecules. Antigens are typically phrased as molecules of external origin (exogenous), although they may also originate from within the host (endogenous). Steward ([13] provides a table of various different antigen types (see Table 3).

Class	Origin	Examples	
		Example Type	Specific Example
Natural	Plants, Bacteria, Animals	Particulate	Blood cells, bacteria, viruses
		Soluble	Toxins, toxoids, proteins, carbohydrates, glycoproteins. Liproproteins
Artificial	Chemically modified natural antigens	Iodinated conjugates	proteins, protein-hapten
Synthetic	Chemically synthesized molecules	Polypeptide multichain a	s, polyaminoacids, aminoacid copolymers

Table 3 - Summary of different antigen types, examples, and their origins (taken from [13] page 9)

External antigens that may cause disease in the host organism are called pathogens. Pathogens are typically microorganisms like viral, bacterial, and parasite antigens. Auto-antigens or self-antigens are tissues of the host that trigger an immune response and may be a signal of autoimmune disease. Tumour antigens are self-antigens that can cause harm to the host. Foreign host tissues may be antigens in the example of tissue or blood transplants where the transplanted tissue is rejected by the hosts' immune system. Vaccines are antigens that result in immunity to an antigenic determinant shared by the vaccine and the pathogen.

An allergen is an antigen (such as pollen) that results in an extreme immune response called an allergic reaction. A tolerogen is an antigen results in tolerance rather than an immune response in the host. An example of natural tolerogens is the self-tissues of the host. Foreign antigens may be tolerogens if they are introduced to the host early in its development such as before the immune system has fully developed.

B. Host Penetration Methods

Exogenous antigens, typically pathogens must circumvent the physical barriers and defence of the innate immune system before interacting with the acquired immune system. Some general methods for penetrating the host includes injection, inhalation, ingestion, and contact (skin or wound). Once within the host, the antigen is filtered from the blood or drawn from the tissue in the lymph and stored in secondary lymphoid tissues, awaiting exposure to B-lymphocytes [1,12]. The behaviour of a pathogen after penetrating the host is referred to as intra-host or in-host dynamics [11,19].

There are many factors of the antigen that influence the immune response. For example, a relatively large or small dose may result in tolerance to the antigen, whereas an intermediate dose may trigger immunization. The method of penetration defines the route the pathogen will take. Arrival or interaction with different tissues of the acquired immunity result in different responses, for examples inhalation or ingestion results in mucosal immunity and injection results in systemic immunity. Other factors include the nature of the antigen such as whether the antigen is a particulate or soluble, and the timing of the exposure. See [7] (page 221-223) for further discussion.

IV. SELECTION

Selection refers to the choosing of antibodies and B-cell receptors (to bind to) by antigens in the clonal selection theory. The selection of antibodies occurs in solution such as in the blood and lymph. The selection of lymphocytes receptors typically occurs in the secondary lymphoid tissues such as the spleen, and lymph nodes. Selection is a competitive event, where there are multiple antigenic determinants for immunoglobulin to attempt to bind with and multiple immunoglobulins seeking to chemically bind.

A. Intermolecular Forces

The selection of immunoglobulins by antigen is governed firstly by the spatial and temporal properties of both. Assuming that such properties of each coincide, selection in a mixed solution of antigen and antibodies is governed by the physical and chemical properties of their interaction, the so-called intermolecular forces. The molecules are mixed and come into contact with each. If the combination of attractive and repulsive forces (affinity) between the antigenic determinant and the antibodies combining site are more attractive than repulsive and strong enough, the antigen and antibody form a chemical bond. This bond is like a key and lock relationship where the antigen is the key, and the antibody is the lock. The amount of energy required to separate the bond is referred to as the bond energy. See Table 4 for a summary of the forces involved, and [14] (page 37-39) for a more in-depth treatment.

Force	Summary	
Hydrogen Bonds	Bonding with hydrogen atoms	
Ionic (coulombic)	Oppositely charged groups	
Van der Walls	Electron clouds interact	
Apolar (hydrophobic)	Seeking minimum energy state in the absence of water	
Steric factor/steric repulsive	Basis of discrimination, non-complementary electron cloud resulting in repulsive force	

Table 4 - Summary of the chemical and physical forces involved in antigenantibody bonding

B. Antigenicity and Specificity

The capability of an antigen to trigger an immune response, the reactivity, and likelihood that it will bind to an antibody is called the antigenicity or immunogenicity of the antigen. The ability or likelihood of an antibody or B-cell receptor to bind with an antigen is referred to as the antibody's or receptors specificity.

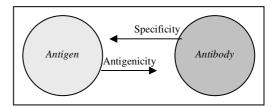


Figure 3 – The specificity and antigenicity between a single antigen and antibody

These general terms are defined by, and abstract the chemical properties of the antigenic determinant and binding site respectively. The specificity of an antibody may be relevant to other antibodies and may be relative to antigenic determinants. Equally, the antigen's immunogenicity may be relative to other antigens, other antigenic determinants, or to antibodies.

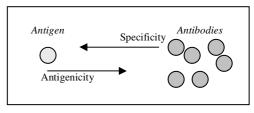


Figure 4 – Specificity and antigenicity may also refer to an antigen and a group of antibodies

C. Cross-Reactivity

The generalization of an antibodies specificity is referred to as cross-reactivity. It is the capability of an antibody to react with other antigens. There are two primary examples of cross-reactivity:

- 1) Other antigens possess the same antigenic determinant, thus antibodies raised for the determinant will react to other antigens with the same determinant.
- 2) Other antigens possess a similar antigenic determinant to the determinant used to raise the antibodies, thus a partial (good enough) binding may occur.

Specificity and cross-reactivity may be thought of as opposite effects. The more specific a combining site to an antigenic determinant, the more specialised the knowledge acquired by the immune system and the more efficient the response. The lower the specificity of the response, the more generalized the knowledge acquired by the immune system, and the border the defensive coverage of the response. Specificity and cross-reactivity provide a trade-off in narrow efficiency and broad general coverage in the immune response.



Figure 5 - Depiction of the opposite effects of specificity and cross-reactivity

D. Monoclonal versus Polyclonal Interaction

A population of antibodies is polyclonal, meaning that the molecules originate from plasma cells of different genetic lines, thus have varied specificity. The antibodies secreted from a single plasma cell are monoclonal, meaning they all have the same specificity. A typical clonal selection immune response is oligoclonal meaning that a few high-specificity clones are selected by antigen and are responsible for the exponential increase in antibody produced during the response. A typical response is specific and is monoclonal, or polyclonal to a small degree.

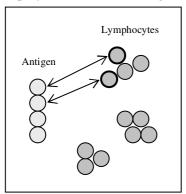


Figure 6 - Depiction of a monoclonal (oligoclonal) interaction to a typical antigen

In the same manner that an antibody or B-cell receptor may have high specificity or high cross-reactivity, an antigen may have the same effect on a pool of B-cells. A super-antigen¹ may possess general antigenic determinants that trigger a much larger percentage of the lymphocyte pool in what is called the hyper-activation of the immune response. Rather than a specific monoclonal or small polyclonal response, the response is large and strongly polyclonal.

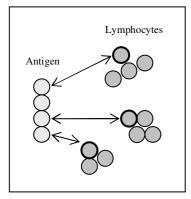


Figure 7 - Depiction of a polyclonal interaction to a super-antigen $\,$

V. Interaction Measures

The two common measures of the interaction between an antigen and an antibody are affinity and avidity. This section provides a summary of these measures and their meaning the context of their interaction.

A. Affinity

Affinity defines the sum of the attractive and repulsive physical and chemical forces between an antigens antigenic determinant and an immunoglobulins combining site. Affinity measures the binding strength

between the epitope and the paratope, and is typically used to qualitatively measure the specificity of an immunoglobulin for an antigenic determinant. In theoretical immunology, affinity is used as the basis of an 'affinity landscape' formalism [2,16] as the response surface for various receptors (and their genetic basis) to an antigenic determinant.

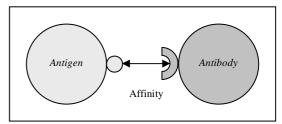


Figure 8 - Affinity refers to the strength of the interaction between a antigenic determinant and an combining region

B. Valence

Valence refers to the number of paratopes of an immunoglobulin or the number of epitopes on an antigen. It defines the theoretical number of chemical bonds that may occur between an antigen and an antibody. A typically antibody has a valence of two, although some isotypes have more such as IgM. An antigen is typically highly polyvalent (meaning a typical antigen has many antigenic determinants). A typical Blymphocyte is also highly polyvalent, as already mentioned, it may have up to 10⁵ receptors.

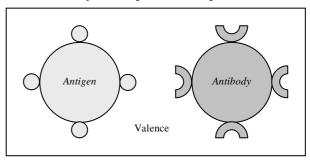


Figure 9 – Depiction of the antigens multivalence and the antibodies multivalence

C. Avidity

Avidity provides a measure of the stability of the complex that forms are a result of the binding of an antigen and antibody or an antigen and a receptor. A measure of avidity includes the sum of the affinities for the multivalent interaction. In addition to the sum of affinities, avidity measures the general strength of the binding, taking into account additional considerations such as the structural arrangement of both molecules.

¹ Super-antigens and their effect typically refer to T lymphocyte cells that detect and respond to parts of antigen presented to them, rather than antigen in their natural form.

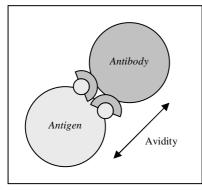


Figure 10 - Avidity as more than the sum of the affinities between an antigen and antibody

VI. WHAT HAPPENS AFTER

The result of the interaction between an antigen and an immunoglobulin is an immune complex. A complex is formed by the aggregation of a number of smaller antigen-antibody complexes into a larger structure. The result is the neutralization and ultimately destruction (ingestion) of the antigen. In measuring immune responses, one may measure the complexes formed and the amount of left-over free antigen and antibodies.

The result of the interaction between an antigen and a B cell receptor is that the lymphocyte ingests the antigen and becomes activated, triggering the start of the clonal selection and expansion process that ultimately results in cell division, differentiation and the secretion of antibodies with the same specificity for the antigenic determinant as the receptor. Activation may be dependant on co-stimulation of the cell by a T lymphocyte (cell mediated immunity, the most common form of activation), or may not require such mediation.

GLOSSARY OF TERMS

Term	Summary
Agonist	A molecule that can bind with a receptor on a cell and produce a physiologic reaction typical for that substance
Antibody	Generic term used to describe immunoglobulin proteins produced by B lymphocyte cells.
Antigen	A substance that can trigger anti body gen eration. Examples include bacteria, viruses, and foreign cells.
Antigenic Determinant	A localised region (specific epitope) on an antigen that defines the specificity of an antigen-antibody reaction. An antigen, such as a protein, may have many determinants.
Binding Site	The place on a molecule where a ligand binds. Also known as the active site. The binding site of an antibody is referred to its paratope.
Concentration	Relative quantities of two substances in a mixture. Defines how often molecules collide in solution.
Epitope	A localised region on the surface of an antigen that may elicit an immune response. It may refer to a feature in the shape in an antigen proteins tertiary structure.
Hapten	A molecule that acts as an antigenic determinant although must be bound to a larger carrier molecule like a protein
Ligand	An effector molecule that has an affinity to bind to another molecule or atom. When a protein binds to another molecule, the other molecule may be referred to as a ligand for the protein.
Molecule	A small particle or structure that consists of two or more atoms held together by chemical forces.
Paratope	(Antibody combining site) The localised region of an

	antibody that makes physical contact with an antigenic determinant (specific epitope).	
Protein	Large molecules constructed from a chain of amino acids. Examples include antigens and antibodies	
Receptor	Molecular structure on the surface of a cell that binds with a specific substance. Immunoglobulin proteins act may act as receptors on the surface of lymphocyte cells	

Table 5 - Summary of terms used in immunology and immunochemistry

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