# The 'shape-space' and 'affinity landscape' Immunological Paradigms

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Abstract- The 'shape-space' formalism and fitness-inspired affinity landscape are two geometric paradigms of theoretical and computational immunity that have found popular application in the field of artificial immune systems. This work reviews the inception and early application of these paradigms in theoretical immunology and reviews a framework that unifies both ideas for use investigating artificial immune systems with regard to general application not limited to pattern recognition.

Keywords- Immune System, Formalism, Paradigms, Shape Space, Affinity Landscape, Affinity Maturation, Clonal Selection

## I. INTRODUCTION

What is the shape-space formalism and what is the relationship of this formalism with affinity landscapes?

The 'shape-space' formalism and its sibling the 'affinity landscape' are two popular geometric paradigms (so called patterns of thought) from computational immunology, both of which have had a recent revival and reapplication in the related field of Artificial Immune Systems (AIS). The intent of this work is to survey the history of these terms briefly in the context of computational immunology, and consider their pervasive application in AIS.

Section II introduces the shape space formalism of antibody-antigen interaction, highlighting the related precursor idea of sequence space, and a number of seminal works in computational immunology that employ the formalism. Section III discusses the related affinity landscape paradigm for considering the usefulness of an antibody molecule (in a sequence space such as shape space) for detecting a specific antigen. Finally, section IV briefly discusses the exploitation of both computational immunology paradigms in the field of artificial immune systems, focusing on the framework of de Castro and Timmis [32].

## II. SHAPE-SPACE

In their theoretical investigation of antibody repertoire size and reliable recognition, Perelson and Oster [5] introduced the shape space formalism. Given antibody (ab) and antigen (ag), the authors discretised the physical aspects of the antibodies combining site and the antigenic determinant into a vector of n so called 'shape' parameters. The parameters may include the geometric structure, electrostatic charge, hydrogen

binding, van der Waals interactions, and any other features important to the ab-ag recognition. This abstraction of a ab and ag molecule's shape was later referred to as their 'generalised shape' [4]. Thus, ag and ab may be defined as points in an n-dimensional Euclidean vector space called 'shape space' S. The authors suggest that given an adequate method of defining molecule shape, the dimensionality of such a space could be as low as five. Further, the formalism ignores the complementarity nature of ab-ag interactions, thus rather than the convention ab!=ag, we consider ab=ag as representing a perfect match. Given this adjustment, the formalism defines distances between ab and ag in this space as the 'degree of complementarity' or 'affinity' of the interaction.

Shape space is a finite hypercube, with a volume V of uniform density. In their application of the model, random distributions of ag and ab were used, and selfantigens were ignored. Further, each antibody is defined with a local recognition region in the shape space ( $\varepsilon$ ), with a Gaussian falloff. An ab-ag interaction only occurs if the ag is above an affinity threshold, within the triggering hyper-sphere of the ab.

**Shape-Space** – An n-dimensional space where the dimensions are taken as the generalised properties involved in antigen and antibody interaction, thus permitting the antigens and antibodies to be considered points within this space. Antibodies possess a hyper-region of recognition within this space in which antigens may trigger an immune response. The complementary nature of antigen-antibody interactions may be ignored such that distance measures of similarity may model the affinity between any two given molecules within the space.

Figure 1 - A general definition of the shape space formalism

This fundamental ag-ab interaction paradigm was throughout the late 1980's and predominantly in theoretical works modelling clonal selection and various aspects of Jerne's idiotypic network theory. Some seminal applications of the formalism in this era include: modelling in a onedimensional Euclidean shape-space [33], investigating the stability of the idiotypic model [4], investigating cross-reactivity and stability [30], dynamics and scaling properties [18], Hamming shape-space with contigious bit regionsas a matching function [41], a twodimensional shape space used with an asynchronous cellular automata [43], complementary matching in a large-scale model of the immune system [40], shape space in higher dimensions (up to ten) [16], investigation of the probabilistic diversity of the system [42], and shape space with self-antigens [55].

### **Generalized Affinity Function**

 $c_{ii} = f(x_i, x_i)$ 

where  $c_{ij}$  is the affinity between the molecules i and j, and  $x_i$  and  $x_j$  are vectors representing the molecules in shape space, f is an appropriate affinity function.

Figure 2 - Mathematical definition of an affinity function for two molecules

Carneiro and Stewart [22] criticise the shape space formalism, focusing on the simplicity of the abstracted space and the shortcomings of the simple affinity functions. They caution the extrapolation of results from the abstraction to the real shape space, highlighting that the dimensionality of the space should be much higher (at least 10, and as high as 20), and that the affinity mapping function would have to be irregular and discontinuous. They support their claims observations from simulated docking of molecules based on crystallographic structures. They propose a splitting of the formalism into a 'realistic shape space' in which real molecules can be evaluated, and an abstracted 'inversion space' as a tool for modelling.

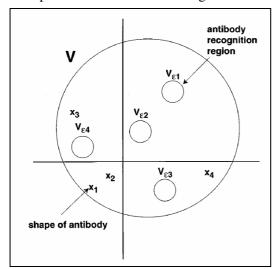


Figure 3 - Diagram of the shape space formalism taken from [6] page 1225. Here,  $x_i$  represents antibodies with corresponding complementary recognition volumes  $v \, \boldsymbol{\varepsilon}_i$ .

Some additional interesting and more recent works are provided. Monte Caro simulations in shape space [51] and [15], self-identity in shape space [24], modelling in so called 'real space' [7], yet another stochastic idiotypic model [52], modelling germinal centre and lymphocytes in a shape space [34], on deriving parameters such as dimensions, matching influence, etc, from shape space [14], investigation of antibody-pathogen matching rules using a genetic algorithm [36], investigating the shape space model of antibody gene library evolution [44], an immune network with a continuous shape space [1], review of shape-space based models [21], T-cell shape space models [19,27,28] and complex networks in shape-space [20]. Finally modelling real molecules in shape space to better understand interrelationships of molecules [2].

Finally, it is useful to consider that although the

shape-space formalism provides a geometric way to consider molecule interactions (in the context of the immune system), it was not the first of such approaches. Write [48] considered a genotypic space for possible gene combinations and a mapping onto the now ubiquitous 'fitness landscape'. Smith [29] considered the idea of 'protein space' and 'sequence space' for gene-toamino acid-to-protein relations and adaptive walks in such spaces. Macken and Perelson [3,12] consider a 'sequence space' for peptides (sequences of amino acids) and their mapping onto rugged protein landscapes. Schuster, Fontana, et al. [39] investigate the mapping of proteins sequence space to a shape space which describes RNA's secondary structure (much like Perelson's generalised shape space for immunological molecules). Cupal, Kopp, et al. [25] also use shape space in this manner to investigate the structure of evolutionary topology, that is the relations between phenotypes and genotypes.

Edgington [47] on his discussion of biopharmaceuticals provides a useful summary of such 'spaces' and mapping to resultant 'landscapes'. Kauffman furiously investigated various molecular spaces and resultant landscapes, not limited to the 'catalytic task space' [49] for enzymatic reactions, and the 'affinity landscape' which will be considered in the next section.

### III.AFFINITY LANDSCAPE

It is typical in physics for systems to minimise some utility in the context of a response surface, whereas in biology it common for systems to maximise some utility. This is highlighted by the already mentioned evolutionary fitness landscape paradigm introduced by Wright [48] in conceptualising gene combinations. In the immune system, one may consider the utility of an antibody as its affinity in binding a specific antigen. Perhaps the first to refer to this conceptualisation as an 'affinity landscape' was Kaffman and Weinberger [45,46] who used this geometric paradigm in the field of theoretical immunology to investigate and describe the effects of affinity maturation. They investigated adaptive walks on the affinity landscape based on antibody sequences or so called 'antibody space' in response to a given antigen. They used Kauffman's NK model to explore such adaptive walks. Kauffman and others used this model to investigate various molecular sequence spaces and the corresponding response surfaces (not limited to [23,49,50]).

**Affinity Landscape** – An affinity (degree of complementarity) response surface for a given collection of antigen detecting agents (lymphocyte cells, antibody, etc), for a given antigenic determinant. Abstractions of this surface considered in theoretical immunological are typically continuous, the topology of which consists of many local optima. Detecting agents may navigate this response surface through the process of affinity maturation, which involves mutations to genotypic sequence information.

Figure 4 – A general definition of the affinity landscape formalism

The affinity landscape is a simple yet important conception, and although Kauffman et al. were perhaps the first to apply such a name, the geometric formalism was no doubt in the mind of Perelson and others in the early days of theoretical and computational

immunology. The formalism plays an important role in conceptualising and formalising 'affinity maturation' of the immune response by hypermutation (examples not limited to [13,35,37,38]), which is a critical aspect of the clonal selection theory of antibody diversity.

George and Gray [9,10] use the affinity landscape as a crutch in describing their theories on receptor editing, which are generalised very effectively on a simple twodimensional affinity graph.

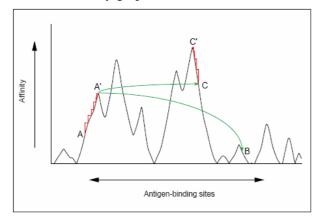


Figure 5 – Theory of receptor editing providing long jumps in the affinity landscape, from [9]

### IV. ARTIFICIAL IMMUNE SYSTEMS

The shape space and affinity landscape immunological geometric paradigms have been widely used in the field of artificial immune systems. Some examples include the quintessential binary shape space used in negative selection and immune network algorithms [17,54], the recognition region and threshold used in data mining and classification algorithms [8,11,53], and the affinity landscape cost functions navigated by optimization algorithms [26,31].

The usage of these paradigms is unified in an artificial immune systems framework proposed by de Castro and Timmis [32]. The framework encompasses more than shape space and resultant fitness landscapes, to abstractions of the various processes that may occur in the context of these formalisms. Thus, given the generality of their abstractions, the framework may be considered a useful tool when investigating artificial immune systems.

One may interpret three components from de Castro and Timmis' framework relevant to this discussion:

**Representation** – Extending the shape-space paradigm, the sequence, or search space is considered essentially a representation domain. Examples provided include real-valued, binary, integer and symbolic.

Mapping – From their framework, one may consider a mapping function from the representation space to an affinity surface. Distance and matching within the shape space are the mapping functions discussed with a number of appropriate suggestions for the various shape spaces listed. A point in one of these spaces may have a 'recognition region', and a 'cross-reactive threshold'. Thus, de Castro and Timmis suggest that such a mapping function may be complemented with an additional threshold binding function, perhaps to convert a scalar affinity into a decision variable.

**Affinity** – Affinity is further abstracted from the degree of complementarity in an antibody-antigen interaction, to a more general definition. Affinity may be

a measure of quality of a molecule in a specific environment or in the context of a specific requirement.

Figure 6 - Summary of three foundational components of de Castro and Timmis' [32] AIS framework

This more general geometric interpretation and relation of 'shape space' to 'affinity landscape' paradigms provides an open framework for investigating immunological principles in domains, not limited to the pattern recognition problem. As unifying as it is, one may consider further geometric conceptions related to affinity maturation in immune system that lack a suitable formalism, let alone an abstraction for use in artificial immune systems. Two examples may include; (1) the aggregation of multiple affinity landscapes, that is the affinity of a repertoire in the context of an antigenic environment not limited to one antigen, and (2) the temporal and spatial aspects to affinity throughout the host organism in the context of lymphocyte and antibody mobility.

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