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Induction of broadly neutralizing antibodies in Germinal Centre simulations

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Vaccines against mutating pathogens such as influenza, HIV, or plasmodium are poorly protective towards new evolving strains. Rare individuals naturally mount broadly neutralizing antibodies covering most strains, but the requirements for their induction are unknown. The antibody response to vaccination has been recapitulated by *in silico* models that proposed two opposite schemes: A theory of 'frustration' where one epitope at a time leads to optimal antibody breadth through sequential immunizations, that was proven successful for HIV vaccination in primates. Another theory supports vaccination with cocktails of multiple representative epitopes in a unique prime and boost, which succeeded for influenza in mice. We discuss how *in silico* models differ in their assumptions, with particular focus on protein affinity representation.

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Introduction

The efficiency of a vaccine relies on the production of highly affine and diverse antibodies by B cells [1••]. Activated B cells can mutate their B Cell Receptor (BCR), later secreted as antibody, through a process called Somatic Hypermutation (SHM). As a consequence, new receptors are generated with increased or decreased affinity towards the target antigen. SHM occurs inside anatomical structures called Germinal Centres (GC), where B cells bind and internalize antigens presented on Follicular Dendritic Cells (FDC). Later, B cells compete for costimulation from T follicular helper cells (Tfh), based on the amount of antigen they internalized and presented on their MHC [2]. After many days of successive cycles of proliferation, SHM, selection and recycling in GCs, the emerging BCRs (and therefore antibodies) show a highly increased affinity towards the pathogenic antigens, a process called Affinity Maturation (AM).

In the context of mutating pathogens, vaccination strategies are challenged by the generation of new strains that escape the initial immune response. Strikingly, a few individuals develop broadly neutralizing antibodies (bnABs) that recognize a wide range of strains during the chronic infection phase. bnABs have been described for HIV [3], influenza [4], HCV [5] and plasmodium [6,7]. In some cases, prior administration of these bnABs confers protection [8,9]. How to explain that the body develops in a few individuals what vaccines are craving to induce for years?

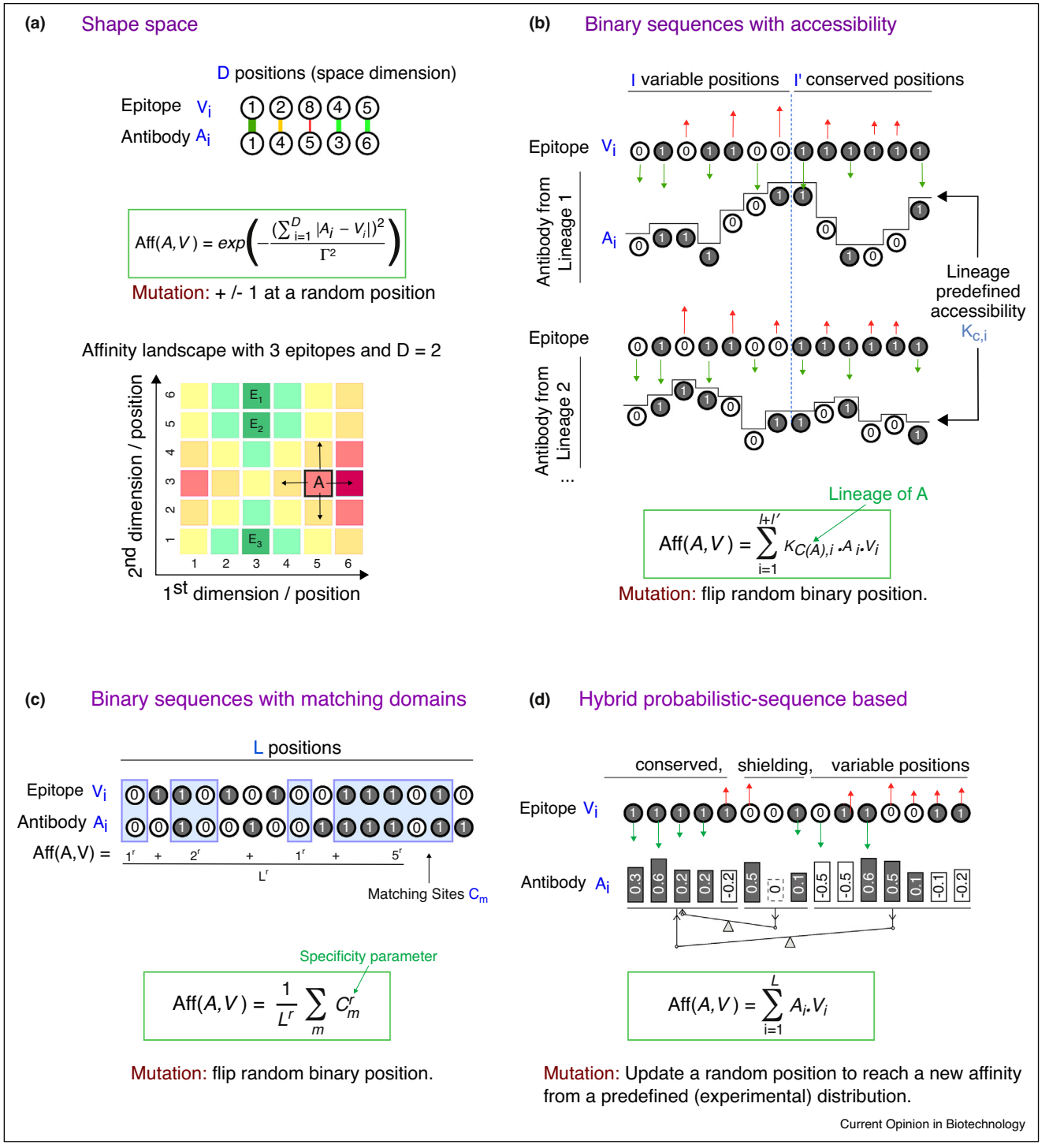
Here, we describe the recent advances in mathematical modelling published in the last four years, which investigate the requirements for a broad vaccine response to multiple epitopes or strains. The chosen representations of affinities between antibodies and multiple antigens are particularly important in the light of cross-reactivity and viral evolution. We discuss their design and implications, and compare the proposed theories to recent experimental developments.

In silico representations of antibody-antigen affinity

Classical mathematical models for AM in GC have been developed in the last 15 years based on a unique target epitope [10–16]. In the context of pathogens with multiple or evolving epitopes, an explicit representation of sequence affinity and SHM is required. Despite the development of structural databases and predictive threading models, the sequences generated by SHM are very diverse, and there exists no reliable folding prediction method for antibody-epitope affinity. Instead, several abstract models have been developed (Figures 1 and 2), and it is critical to dissect the consequence of their design onto the predicted outcome of AM.

Shape space. An initial affinity representation for GC models [10,17,18,19••] is the 'shape space', where

Figure 1



In silico representations of antibody-epitope binding affinities (Part I: abstract and facing representations). **(a)** Shape space: (Top) Antigens and antibodies are represented as points in an abstract multidimensional Euclidian grid [20], whose dimensions each represent an abstract property. Affinity is chosen with a decreasing Gaussian depending on the summed distance in each dimension, meaning that the optimal antibody positions are the epitope positions. (Bottom) Example of an affinity landscape with 2 dimensions and 3 epitopes. Mutations happen by moving to a neighbour position on the grid (black arrows). **(b–d)** Binary representations. Antibody and antigens are represented with the same size as facing residues with a binary property, such as their polarity. Matching residues with the same binary polarity attract each other (green arrows) while opposite ones decrease the overall affinity (red arrows). Mutations occur by flipping a random position, while binding affinity is a combination of the affinity raised by the facing residues. (b) Lineage accessibilities: The study of B cell lineages is made possible by fixing a pre-defined accessibility profile for each lineage, showed as the staircase line, which is included as coefficients $K(C)$ specific for lineage C in the affinity