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Type	Oral communication
Session	Structural Bioinformatics
Title	A moments-based analysis of shape and electrostatics in molecular recognition: the case of antibodies.
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Motivation

The interaction between antibody and antigen is a central event during the immune response and its accurate description is crucial to our understanding of molecular recognition processes; indeed, given the very high affinity and specificity that antibodies exhibit towards their antigens, they offer a paradigmatic model of molecular binding. Antibody specificity arises from the sequence and structure variability of its binding site, which is composed by six regions, appropriately named “hypervariable loops” or Complementary Determining Regions (CDRs). At the molecular interface a very dense network of non-bonded interactions is responsible for the binding between two molecules. This is a very complex picture, its interpretation is often not straightforward and therefore the application of a more compact and synthetic model can make the analysis of molecular complexes easier.

Methods

Here we present a novel superposition-free method, able to accurately compare antibody and antigen surfaces according to shape and physico-chemical characteristics of their binding sites. Identified the amino acids involved in contacting the molecular partner, two 3d functions are built in order to describe the geometrical shape and electrostatic potential of the cognate portion of external solvent accessible surface. Each of these 3D functions is then expanded in the basis of Zernike polynomials, and the coefficients of this expansion, from which Zernike descriptors are calculated, are uniquely determined by the analyzed function. This new approach allow us to summarize the surface characteristics of a protein patch in a very compact and standardized numerical representation. The shape and electrostatic Zernike descriptors, invariant for translation and rotation, can be easily compared even when surfaces very different in terms of size or orientation are taken into account.

Results

The implementation of the Zernike formalism on one hand make possible the comparison between antibodies in terms of their binding site shape and electrostatic potential, removing the preliminary need of structural superposition, and on the other hand allows the analysis of shape and electrostatic complementarity with their different properties in stabilizing antibody-antigen complexes.
To test the method we collected a dataset of 326 antibodies in complex with antigens solved with good accuracy in x-ray cristallography.
Starting from the hypothesis that antibodies with similar binding sites are likely to bind similar antigens, we preliminary show that, using a Zernike-based classification of the binding sites, knowing the structure of the antibody we can predict if the bound antigen is or not a protein with an overall accuracy of 80%. Moreover it is interesting to note that the best performance in this prediction is achieved when are considered with the same weight both the shape and the electrostatic similarity, proving the interplay that these 2 factors have in antigen recognition.
Furthermore, working with both paratope and epitope surfaces, we show that a maximum shape complementarity is reached considering short-range interactions while longer-range interactions account for optimal electrostatic complementarity. This is because the shape complementarity is expression of the vdW forces, important only when two atoms are very close, while the Coulomb forces accountable for electrostatic complementarity can be considerable even between two very far atoms.
Based on this findings, we studied the difference in complementarity when using the real epitope region or random antigenic surface regions (decoys). Fixed the x-ray paratope, we designed the decoys to be as similar as possible to the x-ray epitope in terms of solvent accessibility, size and amino acid composition. Working with the real structural epitope and such similar surface regions, it is therefore possible to obtain a rank of the most complementary antigenic regions. The real epitope region is ranked by Zernike formalism is in the top 5 patches in the 49% of the complexes for shape and in 25% for the electrostatic, results that are in line with the state of art software. These results represent a step towards the very elusive goal of

predicting antibody specificity and further shed light on the well known, but still intriguing, ability of antibodies to find and bind their antigen.

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Availability	-

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