Structural Bioinformatics Based Method for Predicting the Initial Adsorbed Protein Orientation on a Surface

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Statement of Purpose: Prior to conducting a molecular simulation of protein-surface interactions, it is first necessary to decide on the starting orientation of the protein on the surface. However, the identification of low-energy orientations of a protein on a surface is a very challenging problem in its own right. While various molecular simulation methods have been developed to address this problem, these methods are generally computationally expensive and time consuming, especially for large molecules [1]. However, the adsorption free energy of the initial interaction between a protein and a surface can be considered to be a function of the types of amino acid residues on the face of the protein that are close enough to interact with the surface. Thus, estimates of adsorption free energy as a function of protein orientation on a surface should be able to be made using a structural bioinformatics based approach by mapping out the compositional distribution and characteristics of amino acids over the surface of a protein. The objective of this research was therefore to develop a fast structural bioinformatics-based method to predict low-energy orientations of a protein on a surface.

Methods: Protein models were obtained from the Protein Data Bank (PDB) and were corrected by moving the global coordinate system to the center of mass (COM).

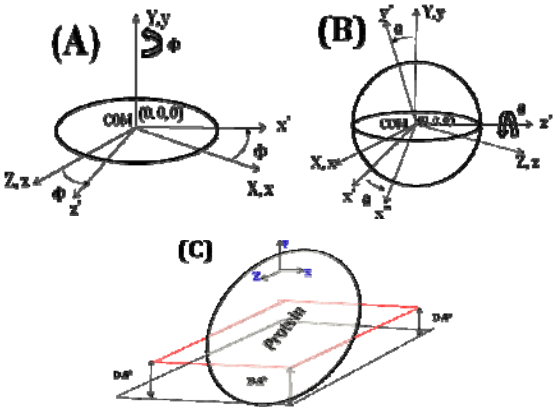

Fig. 1. Depiction of the two angles (Φ, θ) used to track the orientation of the protein relative to a global coordinate system. (A) Rotation of the protein about the Y axis (Φ). (B) Rotation of the protein about the z' axis (θ) following the Y-axis rotation. (C) Interfacial depth,'D' for characterizing the amino acids expected to interact with the surface.

Rotations of the protein are shown in Fig 1. The value of Φ varies from 0° to 360°, while, θ varies from 0° to 180°, and the interaction depth that determines which amino acids on the protein's surface interact with the adsorbent surface was set at 10 Å. Buried residues were ignored from the analysis. The amino acids interacting with the surface were categorized into one of the three groups: hydrophobic, hydrophilic and charged. Glycine and histidine residues were grouped separately due to their unique characteristics. The algorithm was implemented through a customized script in MATLAB®, with protein visualization implemented through external interfacing of MATLAB® with RasMol v2.6 [2].

Results: Analysis has been performed for both large (> 300 kDa) and small (< 20 kDa) proteins with total runtime (i.e., iterations required for rotating the protein and analyzing the amino acid composition over the surface) typically taking only a few minutes per protein. Selected results for the topographical mapping of hen egg-white lysozyme (PDB: 1gxv, 14.3 kDa) are shown below.

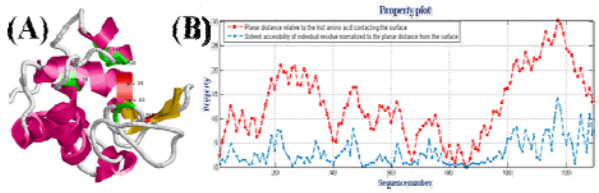

Fig. 2. Topographical map of lysozyme surface. (A) The initial orientation (0°, 0°) in which the molecule was retrieved from the PDB. (B) The property plot for the initial orientation of the protein. The red line indicates the planar distance of each amino acid residue relative to the residue closest to the surface. The blue line indicates the predicted solvent accessibility of each amino acid residue when adsorbed in this orientation.

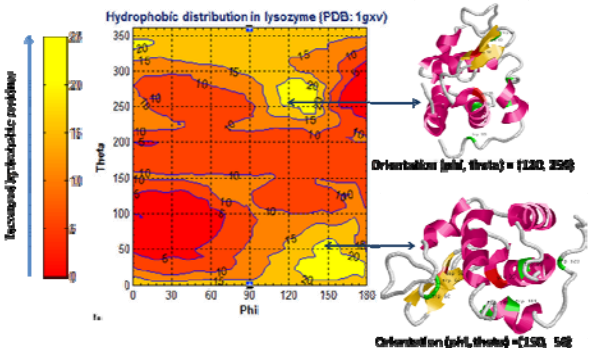

Fig. 3: Topographical map of lysozyme. Surface hydrophobicity of lysozyme for different orientations (contour number scale with increased hydrophobicity). Two orientations are shown which are predicted to have maximum hydrophobic interactions.

For each orientation, the contacting surface area, planar distance of residues, effective accessible area, and the likely interactions were characterized. The results of the current studies are consistent with previous results [3, 4].

Conclusions: A rapid and computationally inexpensive method for predicting low-energy orientations of a protein on a surface has been developed with application to select the initial orientation of a protein on a surface for subsequent molecular simulations to study protein-surface interactions. Besides the intended applications for the support of molecular simulations, this program also has general application for surface design to control the bioactive state of adsorbed proteins.

References: 1) Agashe M et al. Langmuir 2005, 21:1103-1117. 2) Sayle et al. Trends Biochem Sci 1995, 20: 374. 3) Sun Y. et al. Langmuir 2005, 21:5616-5626. 4) Fears KP et al. Langmuir 2009, 25: 9319 – 9327.