A simplified 1-D representation of electrostatic surface properties of modeled protein structures enables screening for evolutionary adaptive protein sites

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We have developed a novel way of simplifying the comparison of the electrostatic molecular surfaces of proteins to the comparison of 1-D "electrostatic surface profiles". To generate a 1-D surface profile for a given protein model, per-atom charges are first calculated in the context of the 3D-structure [1]. The electrostatic surface is then essentially apportioned to individual residues by summing up the charge over all solvent-exposed atoms in each residue. The resulting profile format enables fast, large-scale comparisons either between the modelled surfaces of homologous proteins. In my talk I will discuss how predictions of new protein-protein interactions can be made from the 1-D surface profile comparisons. The rationale is that some new, or changing, protein interaction sites have been subject to adaptive (positive) evolution. Our approach aims to discover greater-than-expected electrostatic change that may reflect such adaptation. By contrast to many other methods no knowledge of the interaction partner is required.

An application of this idea to the human immune-regulating protein Complement Receptor 1 (CR1) illustrates how functionally important domains within a set of homologous domains in the same protein, are pinpointed through screening of their 1-D surface profiles.

While CR1 is known to be involved in protein-protein interactions with several partners at several sites along its length (1998 amino acids), not all partners are known and the location of the binding sites on different domains, with respect to their common structural scaffold, can differ. Comparing the surface profiles of the models of the 30 homologous domains in CR1 [2] to each other, by reference to their sequence similarity, suggests which domain surfaces seem to have changed more than would be expected - which may reflect the acquisition of new interaction partners during evolution. Our results agree well with visual inspection of GRASP [3] pictures and can be compared to those of other methods for electrostatic surface comparison. In addition they are corroborated by positive evolution signals in the encoding gene sequences, as established by tertiary windowing of non-synonymous (Kₐ) versus synonymous (Kₛ) mutation rates [4] (Figure 1). Thus, while experimental information about interactions between CR1 and other proteins is scarce, the sites pinpointed by our comparisons seem to have been subjected to adaptive evolution. Our results are compatible with current biological knowledge of CR1 function and suggest a new interaction site of interest in connection with CR1’s role in the manifestation of malaria.

Interaction sites predicted on Complement Receptor 1 modules CR1~02 and CR1~24. CR1~16 and CR1~17 (top row) are the most closely homologous CR1 modules to CR1~02 and CR1~24, respectively, and are displayed to visualize the adaptive differences (circled). The striking electrostatic differences (GRASP representation; top and middle rows) are corroborated by high non-synonymous mutation rates in the encoding genes (bottom row). While the interaction site on CR1~02 has been characterized experimentally, the putative interaction site on CR1~24 is a new discovery.
References

