A computational approach to the analysis and comparison of protein functional surfaces

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Surface comparison is a useful tool for the understanding of biomolecular functions, since it may help in identifying determinants that are not dependent on protein sequence or secondary structure. Protein surfaces are critically involved in selective binding, recognition and interaction with molecular partners, therefore methods for surface comparison may give new insights into protein function analysis.
Large scale surface comparison experiments have not been attempted yet, due to the calculation time required. Our goal is the creation of a database of surface patches of functional interest to be used in an all-versus-all comparison. Functional sites are often localized on protein surfaces, and the residues involved in the function represent usually a limited set. It has been shown [1] that functional sites correspond very often to surface clefts and cavities; with an automated procedure (SURFNET, [2]) we have identified such surface cavities for all the proteins with known structure in the PDB database, and we have calculated the protein residues that define them, obtaining a collection of patches.
Once such surface regions have been calculated, information about their function can be derived from different sources, such as sequence or functional pattern databases (PROSITE; SWISS-PROT etc.). Moreover, several proteins with known structure have been crystallized together with a ligand (i.e. a substrate, an inhibitor, etc.); this information can be used to annotate patches binding ability. A new surface comparison method will allow the comparison of each patch with the whole patches database, identifying not obvious functional site similarities. Results will be integrated in the annotated patches DB, which will be a useful resource in the characterization of proteins. The construction of a surface patches databases, together with the possibility to compare them, will lead to the identification of similarities not easily detectable with sequence or structure comparison methods, moreover focalizing the attention on putative functional sites. The patches database will be accessible on-line to the users: for each patch a list of similar surface patches will be reported, together with the detected ligand interaction ability and sequence-derived information. This application can therefore be a powerful tool for the analysis of protein functions, considering the great number of uncharacterized structures that will be solved in the structural genomic era.

[1] Laskowski R.A., Luscombe N.M., Swindells M.B., Thornton J.M. Protein clefts in molecular recognition and function. Protein Sci 1996 Dec;5(12):2438-52.
[2] Laskowski R.A. SURFNET: a program for visualizing molecular surfaces, cavities, and intermolecular interactions.J Mol Graph. 1995 Oct;13(5):323-30, 307-8.