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

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Methods for surface comparison are more complicated than sequence or structure comparison, but may give a better understanding of biomolecular functions, since they can identify determinants that are independent from sequence or secondary structure. Evolution can lead sequences to diverge or structures to change topology; nevertheless, surface determinants that are essential to protein function itself may be maintained. Moreover, different molecules could converge to similar functions by gaining specific surface determinants (Via et al., 2000). In such cases, sequence or structure comparisons are likely to be inadequate in describing or identifying all the protein functions and evolutionary relationships among proteins. Since protein surfaces are critically involved in selective binding, recognition and interaction with molecular partners, methods for surface comparison may give new insights into protein function analysis. The 3D Profile method (de Rinaldis et al., 1998) for surface comparison is a powerful tool dedicated to the analysis of functional sites. The method is suitable for two possible applications: i) surface comparison of a subset of proteins and ii) database search of proteins with similar local surfaces.

The surface comparison among all the proteins with known structure is a difficult and time-consuming task, but may be a rich source of information. Our goal is the creation of a database of surface patches of functional interest to be eventually used in an all-versus-all comparison. Our approach is based on the identification of potential functional surface sites. The SURFNET algorithm (Laskowski, 1995) can locate clefts and cavities on protein surfaces, and can calculate their volumes and geometric centres. In the great majority of the examined cases (Laskowski et al., 1996), the bigger cleft on a protein surface corresponds to the functional site (Laskowski et al., 1996). We define a surface patch as the exposed residues belonging to a 10 angstrom spheroid centred in the cavity centre. The database of surface patches will be calculated from all the PDB surface clefts with sufficiently wide volume. Then, the 3D Profile method will allow us the comparison of each patch with the whole patches database, identifying functional sites similarities. Using patches instead of the whole surface focuses the attention on hypothetical functional sites, moreover reducing database search calculation time.

Possible aims of this project are:

1) the identification of new functional sites on the surface of proteins of known function (proteins of known function may contain not yet identified functional regions);
2) the recognition of functional sites in proteins produced by structural genomic projects;
3) the identification of new ‘attractors’ of uncharacterized function in the space of protein surfaces;
4) the analysis of the different problems approachable with methods of sequence, structure or surface comparison. Has natural selection ever explored the possibility of using two different folds to achieve the same “surface function”.

References:

De Rinaldis, M., Ausiello, G., Cesareni, G. & Helmer Citterich, M. (1998). Three-dimensional profiles: a new tool to identify protein surface similarities. J.Mol.Biol., 284, 1211-1221.

Laskowski, R.A. (1995). SURFNET: A program for visualizing molecular surfaces, cavities and intermolecular interactions. J. Mol. Graph., 13, 323-330.

Laskowski, R.A., Luscombe, N.M., Swindells, M.B. & Thornton, J.M. (1996) Protein clefts in molecular recognition and function. Protein Sci 5, 2438-2452.

Via, A., Ferrè, F., Brannetti, B., Valencia, A. & Helmer Citterich, M. (2000). Three-dimensional view of the surface motif associated with the P-loop structure: cis and trans cases of convergent evolution. J. Mol. Biol. 303, 455-465.