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Comparative Analysis of Protein - Protein Interface Methods

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CONTEXT

In the cells, proteins are never alone. All proteins interact with other molecules to become functional. Protein-Protein interactions (PPIs) are essential for a broad range of cellular processes including signal transduction, cell-to-cell communication, transcription, replication, and membrane transport. So, studying PPIs is crucial to understand the relationship between different protein partners and their functions. These interactions result in physical contacts of high specificity as a result of biochemical events steered by electrostatic forces including hydrophobic effect. Residues close in space determine protein contacts and computational approaches finding these residues are interesting for PPI studies.

GOAL OF THE PROJECT

- 4742 non-redundant complex proteins from InterEvol database
- 3743 homo-dimers versus 999 hetero-dimers
- 3145 X-ray structures (79 % < 2.5 Å)
- 289 NMR structures
- 8177 unique protein chains from 3434 PDB codes

RESULTS & DISCUSSION

DataSet

- Threshold method dependent of an heavy atom distance value, in general ranging from 4.5 to 6.5 Å (5.0 Å in this study)
- Threshold method defines only atom/residue contacts
- ASA method dependent of the radius of the probe
- ASA method defines interface area
- No contact definition with ASA
- VIP dependent of an environment (in general water)
- VIP defines both atom/residue contacts and interfaces

Discussion

VIP versus ASA Method

- VIP identifies more hydrophobic contacts, i.e. F/A/I/V/L, whereas threshold method identifies more contacts between polar pairs (O,H,P,N) – polar residue contacts may be screened by water molecules in VIP approach
- Using both metrics, specific residues contribute mostly in the difference between both methods

Applications for VIP (Dimer of DXR)

- MMPBSA
- Water Structure

VIP versus Threshold Method

- Threshold method identifies most of the time less residues than other methods (except E,R,K where the % is higher compared with VIP)

Conclusion

VIP is an extension of VLDP software [1-6] and is an open source program available on request. Depending on scientific community interest, a webserver could be developed. Intraspecifically, VIP identifies the nearest neighbouring residue (contacts) and an interface that does not suffer from the limitations of standard methods. For example, an arbitrary distance parameter must be defined in the threshold method, and results of the ASA method depend on the choice of probe sphere radius. One limitation of VIP could be the atom weight assignments, which can be verified by slightly varying the values and checking for any network changes (contacts). Moreover, further addition of solvent, for example, from a dynamics trajectory, is important in analyses of the environment in protein complexes. This comparative analysis showed that VIP is particularly promising as both common and supplementary types of residues not found by other metric methods (threshold and ASA) or MMPBSA energy calculations could be identified. To conclude, VIP is a powerful, mathematically robust and efficient, geometric tool for analysing interface and environments in protein complexes.