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Alexandre de Brevern, Jérémy Esque. Comparative Analysis of Protein -Protein Interface Methods. Groupe Graphisme Modélisation Moléculaire (GGMM), May 2017, Reims, France. inserm-01586501

HAL Id: inserm-01586501

https://inserm.hal.science/inserm-01586501

Submitted on 12 Sep 2017

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Comparative Analysis of Protein - Protein Interface Methods

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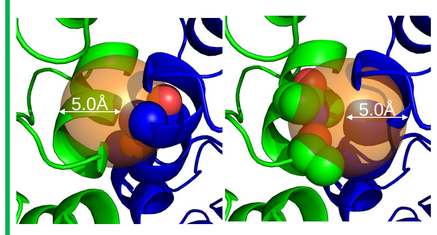
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CONTEXT

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 better 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.

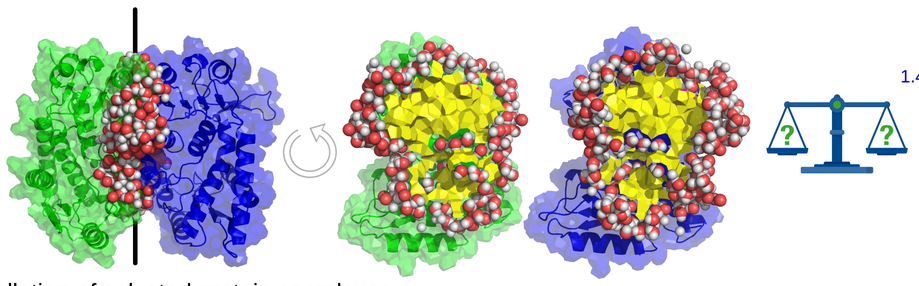
GOAL OF THE PROJECT

Threshold Method



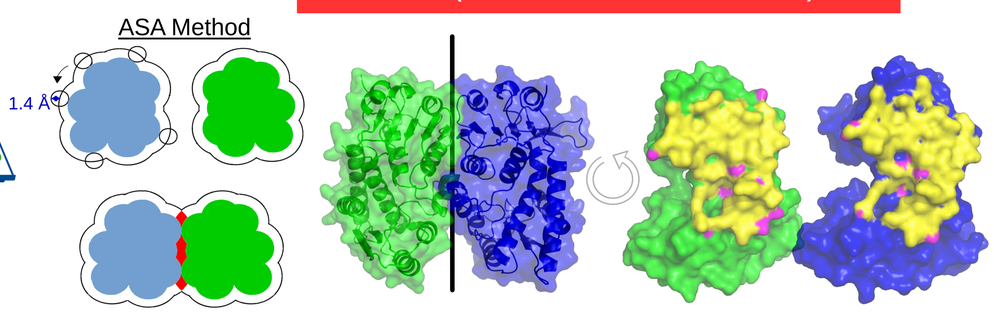
Distance Based Method

ViP (Voronoï Interface Protein) [1-3]



Tessellation of solvated protein complexes

ASA (Accessible Surface Area)



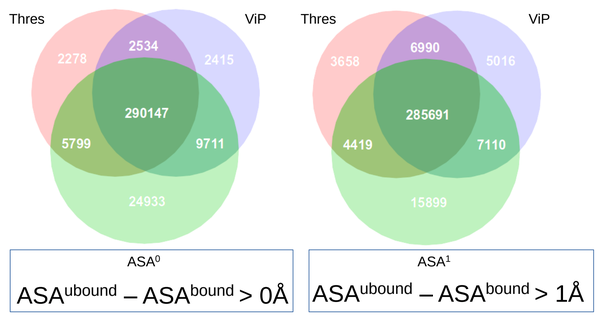
RESULTS & DISCUSSION

DataSet

- **4742** non-redundant complex proteins from InterEvol database [4]
- **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

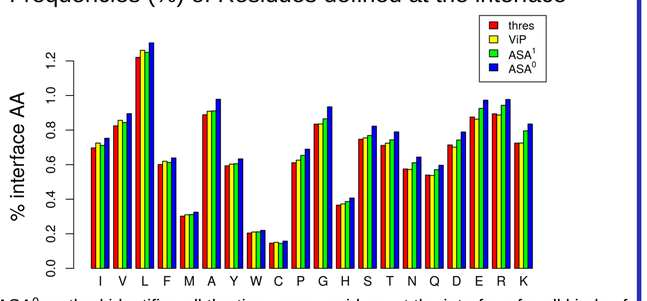
Global View

Venn Diagram of Residues defined at the interface



~ 90 % residues in common in all methods

Frequencies (%) of Residues defined at the interface



- ASA^0 method identifies all the time more residues at the interface for all kinds of residues.
- Threshold Method identifies most of the time less residues than other methods (except D,E,R,K where the % is higher compared with ViP)

Discussion

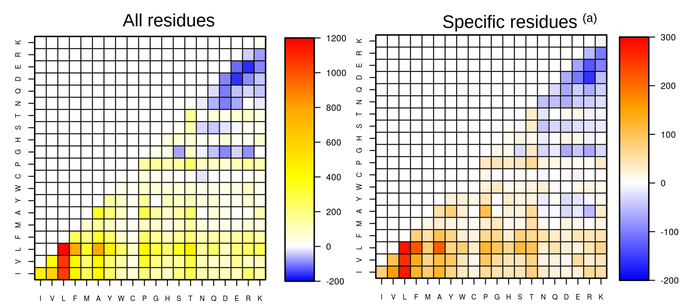
- **Threshold method dependent of an heavy atom distance** value, in general ranging from 4.5 to 5.5 Å (**5,0 Å** in this study)
- **Threshold** method defines **only atom/residue contacts**

- **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**

ViP *versus* Threshold Method

Differences of **Residue Pairs** (**Contacts**)

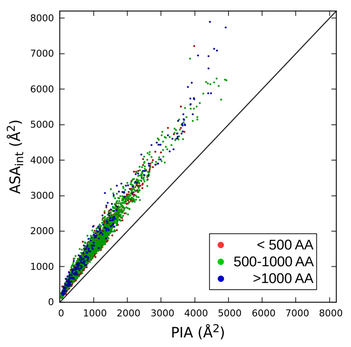


(a) Specific Residues = Residue found at the interface in only one of both methods

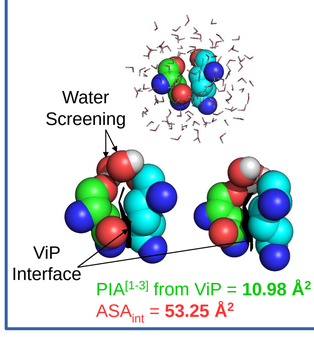
- ViP identifies more hydrophobic contacts, i.e. F/A/I/V/L-L, whereas threshold method identifies more contacts between polar pairs (D,E,R,K) → polar residue contacts may be Screened by water molecules in ViP approach
- Comparing both matrices, specific residues contribute mostly in the difference between both methods

ViP *versus* ASA Method

Differences of **Interface Area**



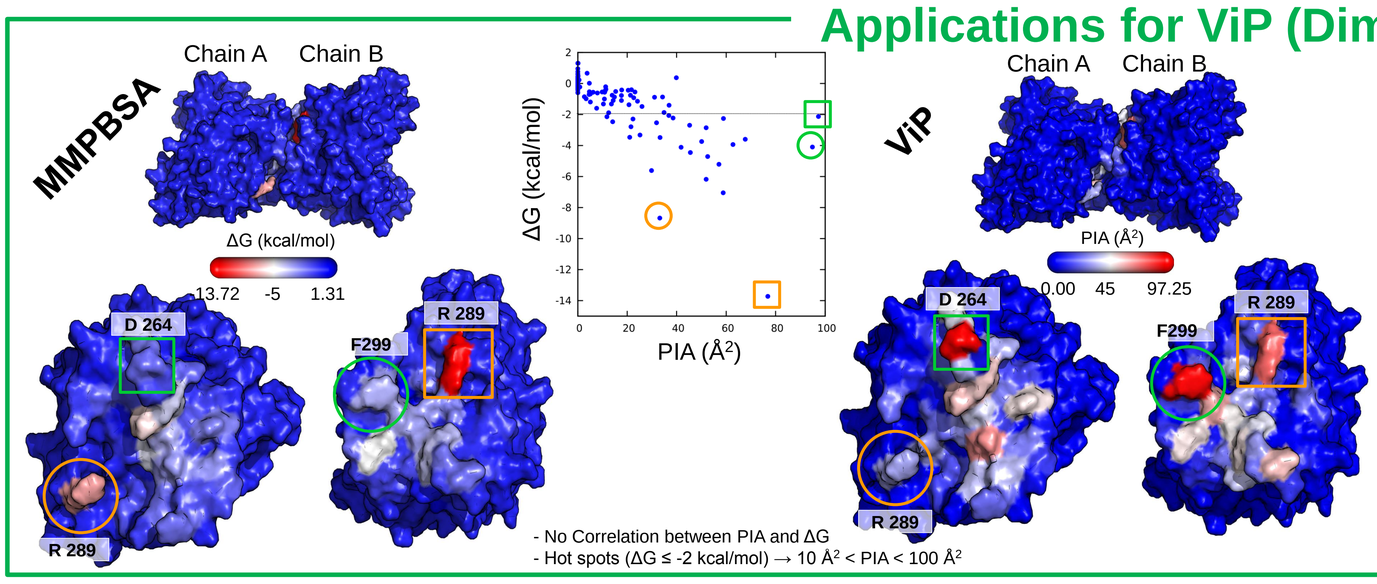
Test Case



PIA[1-3] from ViP = **10.98 Å²**
ASA_{int} = **53.25 Å²**

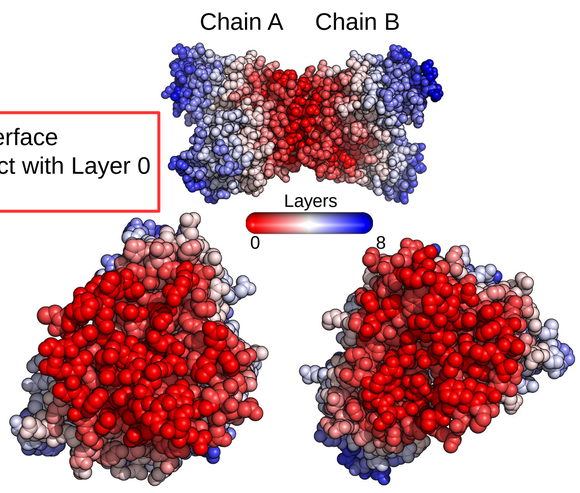
- Interface from ASA method is all the time higher than PIA (Polyhedral Interface Area) from ViP
- PIA defines the interface from **"direct contacts"** between two chains unlike ASA → **(ASA may overestimate the interface area)**
- **Water in ViP approach plays a role in the surroundings and interface definition (cf test case)**

Applications for ViP (Dimer of DXR)



- No Correlation between PIA and ΔG
- Hot spots (ΔG ≤ -2 kcal/mol) → 10 Å² < PIA < 100 Å²

Stratification from VIP Network



Conclusion

ViP is an extension of VLDP software [1-3] and is an open source program available on request. Depending on scientific community interest, a webserver could be developped. Instrinsically, 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.**

[1] *Esque J, Oguey C and AG de Brevern. A novel evaluation of residue and protein volumes by means of Laguerre tessellation. J. Chem. Inf. Mod. (2010) 50:947-60*
[2] *Esque J, Oguey C and AG de Brevern. Comparative analysis of threshold and tessellation methods for determining protein contacts. J. Chem. Inf. Mod. (2011) 51:493-507*
[3] *Esque J, Léonard S, AG de Brevern and Oguey C. VLDP web server : a powerful geometric tool for analysing protein structures in their environment. NAR (2013) 41:W373-8*
[4] *Faure G, Andreani J and Guerois R. InterEvol database : Exploring the structure and evolution of protein complex interfaces. NAR (2012) 40:D847-56*