ViewContacts

A superior tool for chemists, modelers and crystallographers for improved understanding of non-covalent interactions in protein-ligand complexes

ViewContacts Advantages

- **Data Driven**. Created by industry experts, ViewContacts is accurate and comprehensive in finding the many different types of hydrogen bonds, polar interactions, and lipophilic contacts in binding sites

- **Rule Based**. ViewContacts ensures interactions are correctly identified by using an extensive range of rigourously tested rules. These rules form the basis of a superior algorithm, developed from the latest findings in structural biology, molecular modeling, molecular recognition and database mining studies.

- **Visualisation**. ViewContacts creates scripts that allow fast and easy exploration of the key protein-ligand interactions determining binding affinity

- **Handling Water Molecules.** Rank scores provide easy identification of bound water molecules for targeting in ligand design experiments

- Identifies Unfavourable Interactions. ViewContacts allows for the detection of desolvation penalties that negatively affect target binding.

- **Ease Of Use**. Enables both experts and non-experts to make the best use of protein crystallography in structure based drug design

Overview of Interaction Types

- ViewContacts identifies commonly occurring interactions types:
  - hydrogen bonding
  - ionic pairs
  - van der Waals contacts

- ViewContacts identifies many, less well understood interactions types:
  - cation-pi
  - hydrogen bonding to pi-systems
  - halogen bonding
  - orthogonal dipolar alignment
  - dipolar antiperiplaner interactions
  - pi-stacking
  - pi edge-to-face contact
  - hydrogen bonding involving CH groups

Pair Interaction Definitions

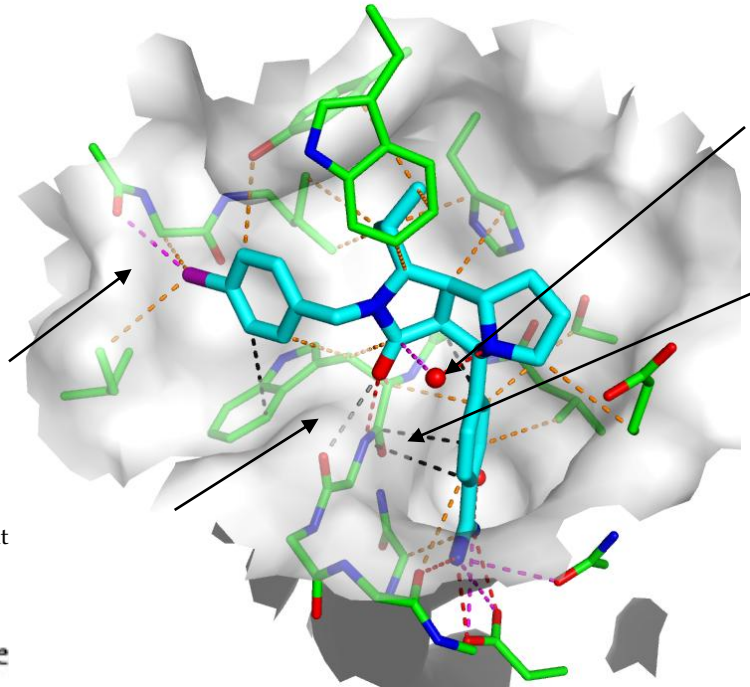
Automatic assignment of SMARTS-based atom types and detection of different types of favourable and unfavourable interactions (with distance & angle constraints, pruning of excess contacts)

Classification of interaction types:

1. hydrogen bond
2. metal
3. ionic
4. cation-dipole
5. cation-pi
6. diploar
7. σ–hole bond
8. h_donor-pi
9. pi-pi
10. vdW

11. unfavourable of 1, 2, 3, 6
12. polar and nonpolar clashes
13. polar-nonpolar mis-matches

Ex. 2cf8 (thrombin)



ViewContacts creates PyMol scripts that allow fast and easy exploration of the key protein-ligand interactions determining binding affinity

Handling of Water Molecules

- Scoring of water replacement potential based on deviation from ideal tetrahedral coordination of protein-bound water molecules

$$Rank = \sum_{n} \left\{ \left(2.80A / r_n\right) + \left[\sum_{m} \cos\left(\Theta_{Td} - \Theta_{nm}\right) \right] / 6 \right\}$$

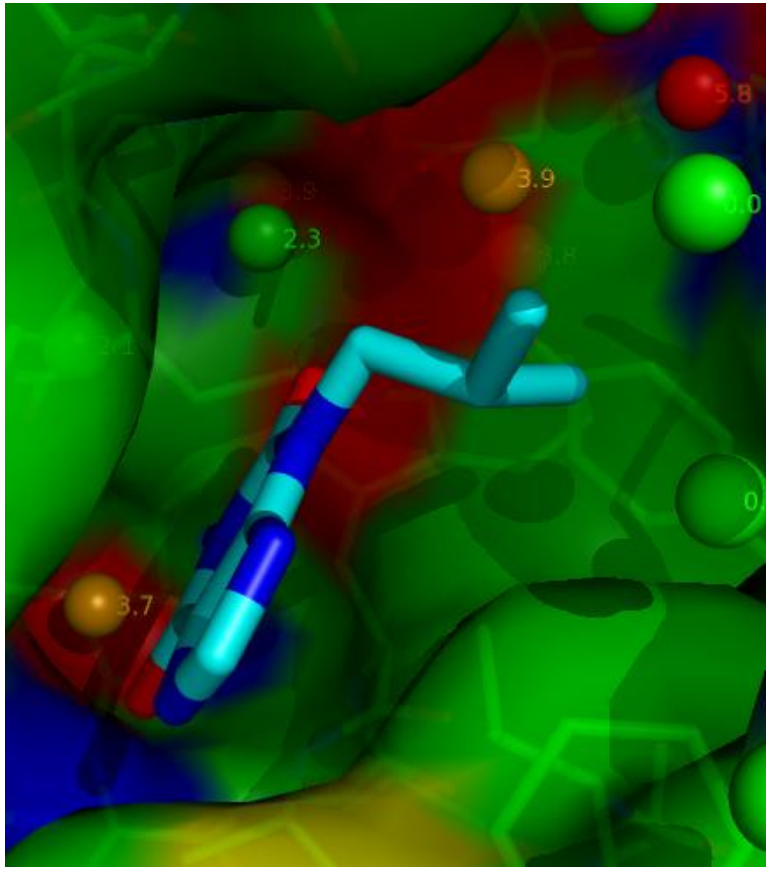
- Rank scores:
  - 1 ideal H-bond: 1
  - 2 ideal H-bonds: 2.3
  - 3 ideal H-bonds: 4.0
  - tetrahedral coordination: 6.0

- Maximum of 4 protein atoms is counted (≤ 2 donors and ≤ 2 acceptors). Any angle less than 60° is rejected

Color-coding of Rank score in PyMol:

1. **green: 0 - 2.3 (easy to replace)**
2. **amber: 2.3 - 4.0 (possible to replace with suitable polar functionalities)**
3. **red: 4.0 - 6.0 (unlikely to replace)**

Ex. 2r8q (PDE-B1)



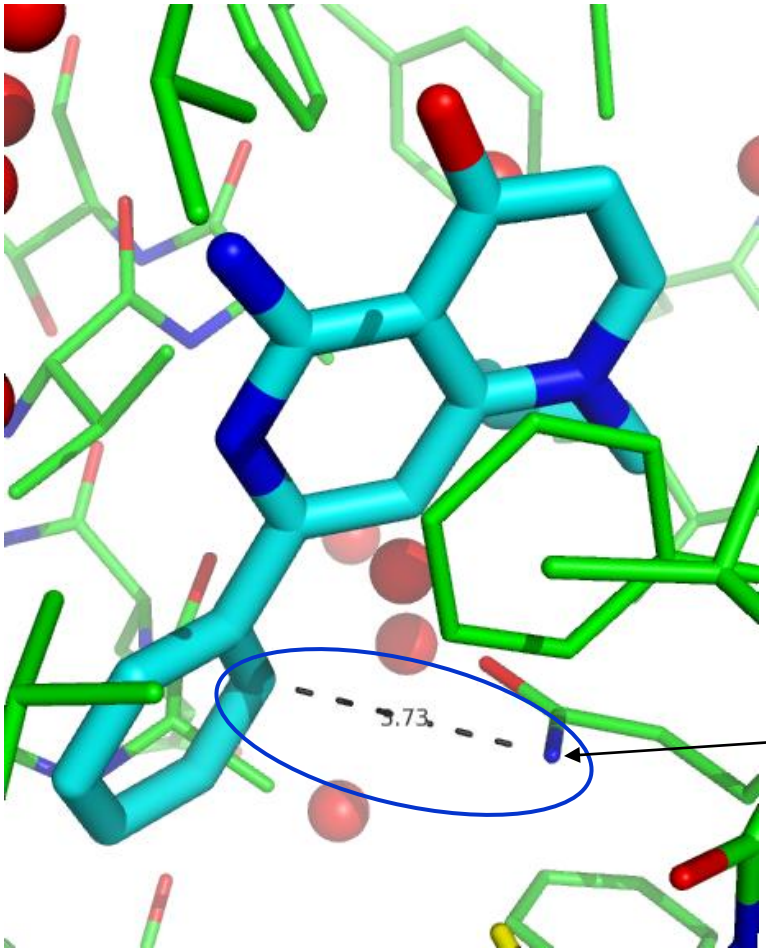
Rank scores provide easy identification of bound water molecules that can be targeted in ligand design experiments

Identification of Unfavourable Interactions

- Unfavourable contact if aploar ligand atom replaced by a water molecule fulfills hydrogen bonding requirements

- Distances and angles are checked for all polar/apolar close-contact pairs

- Solvent exposure of each atom is taken into account when testing for unfavourable contacts



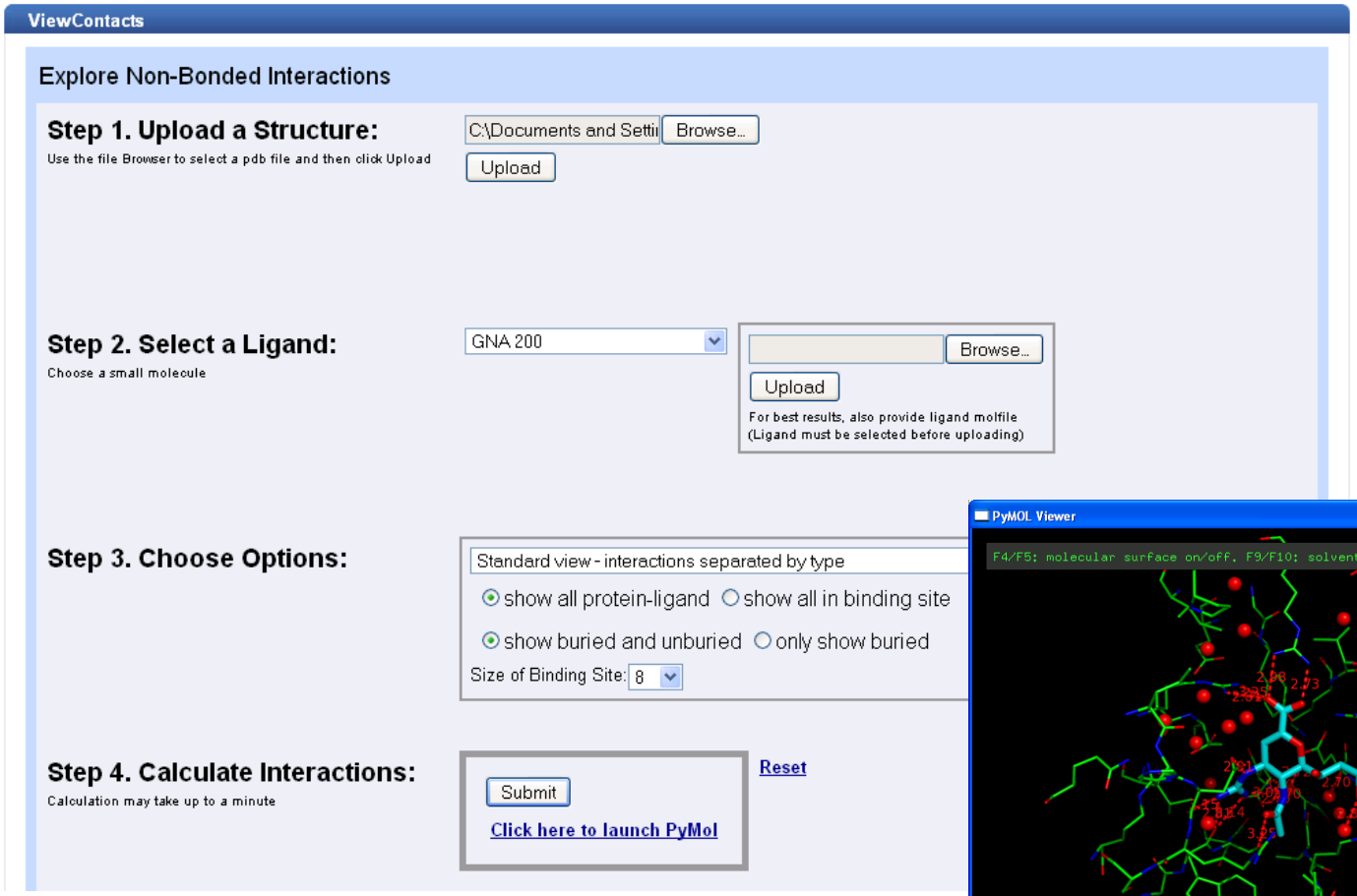
Ex. 3hdz (PDE-5)

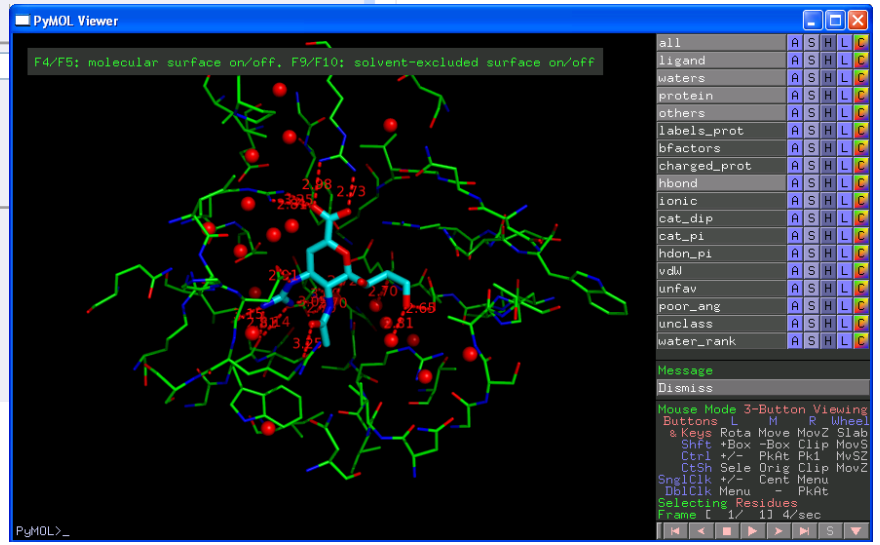
No hydrogen bond partner for this buried N atom in the binding site → contact highlighted as an unfav. interaction

Allows for the detection of desolvation penalties that negatively affect target binding

VCWeb

VCWeb is an easy-to-use web based application for running ViewContacts





VCWeb runs highly optimized javascript which is fast to load and fast to execute in all popular browsers

Additional Features

- Any HET group in any domain of any pdb file can be explored
- Size of viewed binding site can be modified
- Interactions can be grouped into different schemes, according to requirements
- Interactions can be further sub-divided into strong/weak
- All interactions within a binding site can be viewed
- Buried contacts can be viewed separately from solvated contacts
- Water mediated hydrogen bonds can be highlighted
- Can easily read results from docking studies, with poses stored in sdf file(s)
- PyMol script creates molecular surface, solvent excluded surface, short-cuts for viewing temperature factors and much more
- Bond orders from input sdf file, cif library, or detected using automated methods
- SMARTS definitions can handle tautomers
- SMARTS definitions and the angle and distance constraints, can be easily customized/extended
- Easily linked with Proasis2 and Proasis3, DesertSci's Protein Structure Database and Visualization System, including viewing of interactions in overlayed complexes
- Available as both a web based system and a command line tool for Linux systems

References

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