Scorpion™ *… innovation*

Network Cooperativity and Binding Affinity in Protein-Ligand Complexes

Scorpion is a completely new approach to protein-ligand molecular recognition based on network concepts and cooperativity.

Scorpion combines covalent and non-covalent interactions to create a single network similar to a small-world network. Through the implementation and understanding of network properties and cooperativity, Scorpion offers you completely **new insights** into important molecular recognition phenomena and their impact on drug discovery.

Scorpion software for drug discovery provides you with:

- a new computational description of molecular recognition
- new tools for understanding atomic contributions to binding in protein-ligand complexes
- new binding affinity scoring based on the presence of networks

Inclusions

Scorpion includes ViewContacts software, a powerful tool for finding, classifying, and visualising SMARTs based protein-ligand non-covalent interactions and geometric water rank score.

You can run Scorpion from either the command line or using our intuitive web interface, ScorpionWeb.

The software can be fully integrated into DesertSci's Protein Structure Database and Visualisation System, Proasis3, providing you with a powerful and intuitive suite of tools for your research needs.

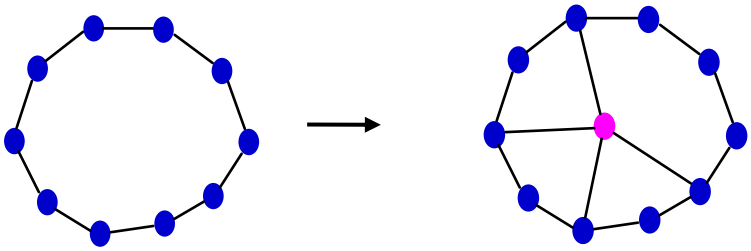
Scorpion Features

- ligand atoms in a complex can be colour-coded according to their contribution to binding
- multiple complexes/poses can be ranked by calculated scores
- exploration of protein-ligand non-covalent interactions
- careful treatment of both explicit and implicit solvation
- water molecules can be colour-coded according to geometric water rank score
- command line tools and web gui
- computes results from multi mol sdf files
- read raw pdb files, no pre-processing required
- writes estimated binding affinity, with contributions from interactions and network
- writes atom and bond contributions to binding affinity
- search text files of output obtained from running Scorpion on all inhouse and public domain structures
- finds pairs of favourable ligand atoms that are connected by a short network motif
- provides scripts for viewing in PyMOL and/or MOE

Theory and concepts

Scorpion's key concept is that no longer should we separate non-covalent and covalent bonds but rather we need to combine them into one **network of nodes and edges**.

Scorpion models the whole protein-ligand complex as a **small world network** in which the nodes are atoms and the edges are **all** close contacts (both covalent and favourable non-covalent).



The blue nodes denote protein binding site groups; the pink node represents the ligand; and an edge represents a non-covalent favourable or covalent interaction. The addition of just one new node and a few extra edges leads to shorter path lengths between many pairs of nodes in the network. This arrangement is analogous to the way ligands fit into binding site cavities. In the small world network model of Scorpion, ligand binding leads to the formation of a number of favorable protein-ligand interactions, and **tight ligand binding is a consequence of this enhanced network stability**.

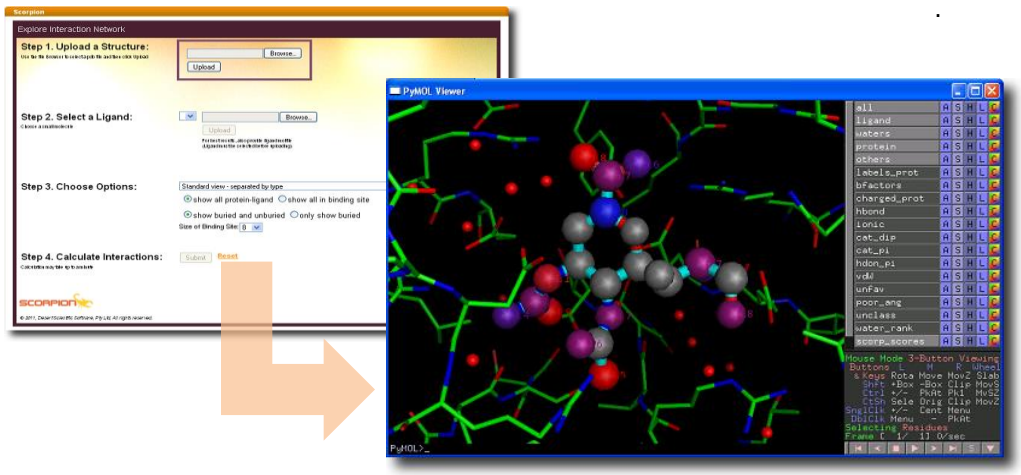
A complete description of the method and scoring function is available in our publication J. Chem. Inf. Mod., 2011, 51(12), pp3180-3198 (http://dx.doi.org/10.1021/ci200319e.)

Scorpion … *In Action*

Scorpion treats a protein-ligand complex as an interaction network to predict binding affinity. Specifically, the nodes of the network are formed by amino acids, water molecules and ligands. The edges of the network are formed by covalent bonds and non-covalent interactions. Scorpion encodes local cooperativity effects and considerably improves the quality of predicted binding affinities.

Colour Coding based on Calculated Affinity

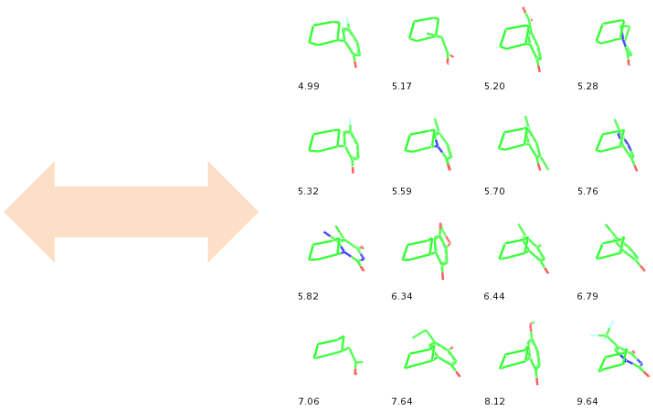
Using the Scorpion interaction network, network parameters that increase local tight binding are identified and calculated. High scoring atoms are coloured red (in PyMOL and/or MOE) to indicate tight binding.



Scorpion Scoring

Scorpion scores binding affinity based on a derived scoring function which incorporates network terms in addition to terms for favourable and unfavourable interactions. Genetic algorithm optimization using high quality training sets resulted in parameters for each individual interaction type and the corresponding network term. Only strongly networked interactions are included in the final scoring function. Total scores and individual contributions are saved in sdf format, which can be viewed either in a table or spreadsheet, including the depictions.

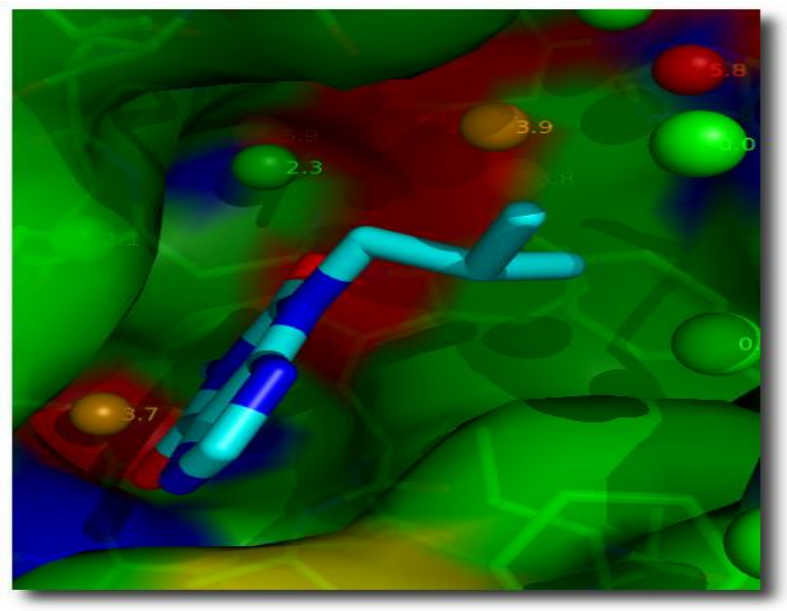
	A	B	C	D	E	F	G	H	I	J
1	TOTAL	VDW	VDW_NW	HBOND	HBOND_NW	PI	PI_NW	UNFAV_HBOND	UNFAV_VDW2	UNFAV_VDW3
2	4.69	3.1	0.34	0.95	0.08	0	0	-0.39	0	0
3	4.75	4.13	0.57	0.47	0.03	0.19	0.48	0	0	-1.15
4	4.84	2.58	0	1.42	0.64	0.19	0	0	0	0
5	4.85	3.1	0.36	0.95	0.1	0.56	0.91	0	0	-1.15
6	4.99	2.58	0.41	1.42	0.19	0.38	0	0	0	0
7	5.17	2.06	0.54	1.89	1.44	0	0	-0.77	0	0
8	5.2	3.1	0.56	1.89	0.23	0.38	0	0	0	-1.15
9	5.28	4.13	0.5	0.95	0.08	0	0	-0.39	0	0
10	5.32	3.1	0.42	1.42	0.19	0.19	0	0	0	0
11	5.59	3.1	0.89	0.95	0.08	0.38	0	0	0	0
12	5.7	3.61	0.71	1.42	0.2	0.38	0	0	0	-1.15
13	5.76	3.1	1.06	0.95	0.09	0.19	0	0	0	0
14	5.82	2.58	1.07	1.42	0.13	0.56	0	0	0	-1.15
15	6.34	2.58	0	1.42	0.19	0.19	0	0	0	0
16	6.44	4.13	1.15	0.95	0.09	0.56	0	0	0	-1.15
17	6.79	3.61	1.06	0.95	0.08	0.56	0	0	0	0
18	7.06	2.06	0.59	2.37	2.29	0	0	-0.77	0	0
19	7.64	5.16	1.68	0.95	0.09	0.38	0	0	0	-1.15
20	8.12	4.13	0.72	1.42	0.19	0.19	0	0	0	0
21	9.64	7.23	2.5	0.47	0.03	0.38	0.53	0	-0.9	-1.15



Geometric Water Score

Structural water molecules are classified according to their interactions with neighboring protein atoms and other water molecules. The water rank score is a measure of the deviation from ideal tetrahedral coordination.

The colour coding of rank score is: green (easy to replace); amber (possible to replace with suitable polar functionalities); red (unlikely to replace)



Installation

Scorpion server software runs under Linux and end users access the system using either ScorpionWeb or command line scripts. Structures are viewed using PyMOL or MOE.

Software requirements:

Scorpion software requires the following components:

On the server machine:

- Python - version 2.7 is recommended (version 2.4 minimum requirement)
- Python add-on modules networkx (version networkx-1.0.1.tar.gz recommended) and egenix-mx-base (version egenix-mx-base-3.1.3.tar.gz recommended)

For end users:

- PyMOL (Incentive version recommended) for viewing protein ligand complexes, non-covalent interactions, and atoms highlighted by Scorpion scores and water ranks.
- MOE version 2010 or above

Acknowledgements

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