Scorpion™....*innovation*

FIRSTLY

WHAT IS SCORPION?

Scorpion is a our proprietary 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 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

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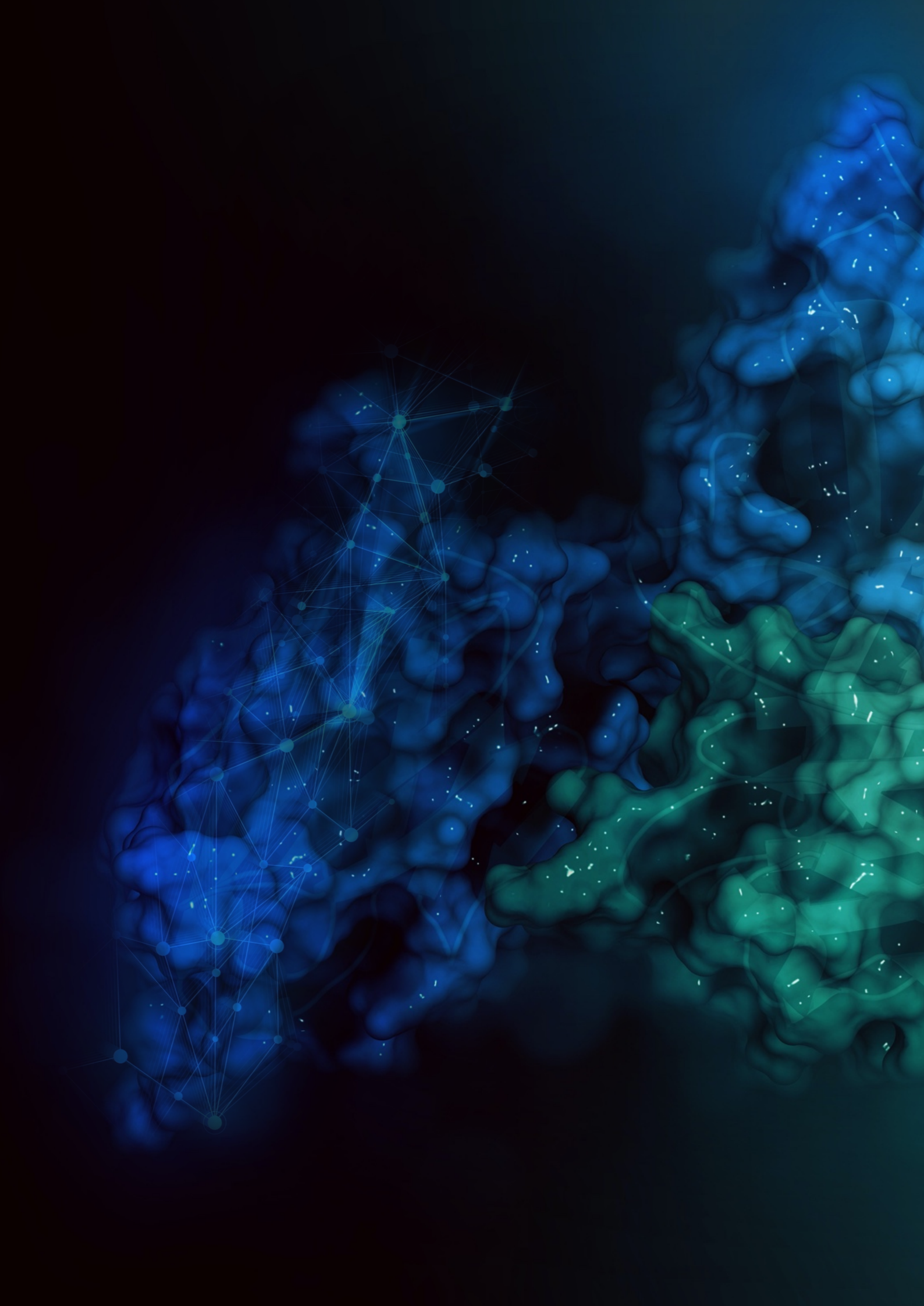


INCLUSIONS

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

Scorpion is fully integrated into DesertSci's Protein Structure Database and Visualisation System, Proasis4, providing a powerful and inituitive suite of tools for research needs.

Scorpion can also be run using command line tools or using API resources.

SCORPION FEATURES

multiple complexes/poses can be ranked by calculated scores

ligand atoms in a complex can be colour-coded according to their contribution to binding

exploration of protein-ligand non-covalent interactions

reads raw pdb files - no pre-processing required

treatment of explicit and implicit solvation, water molecules colour-coded according to geometric water rank score

computes results from multi mol sdf files

finds pairs of favourable ligand atoms connected by a short network motif

writes estimated binding affinity including contributions from interactions and network

writes atom and bond contributions to binding affinity

data mine output from Scorpion on all inhouse and public domain structures

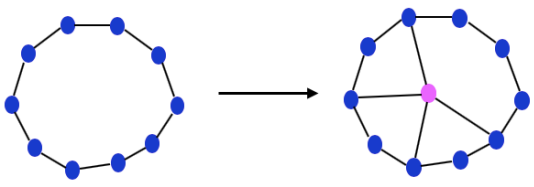
command line tools and api resources available

scripts provided for viewing in Proasis4 and third-party applications

THEORY & CONCEPTS

Scorpion's key concept is that non-covalent and covalent bonds shouldn't be separated but rather combined 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 signify protein binding site groups
→ the pink node represents the ligand
→ 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 favourable 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 treats a protein-ligand complex as an interaction network to predict binding affinity.

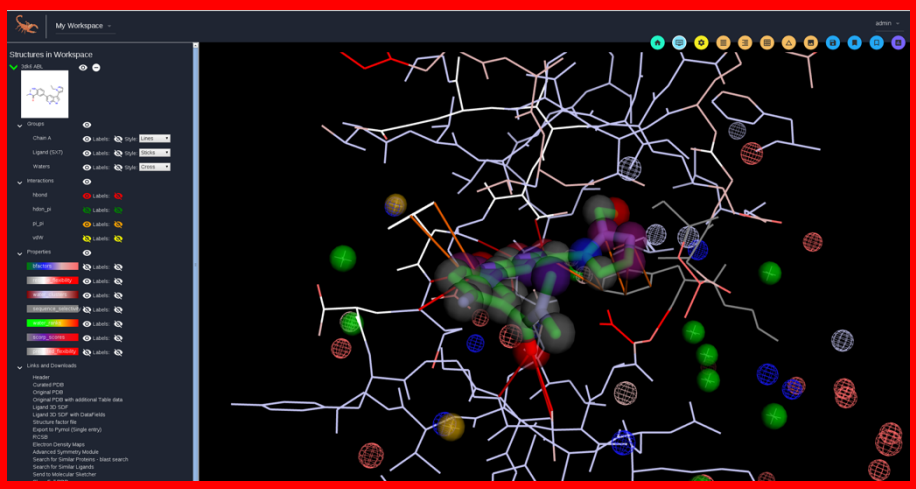
Specifically, the nodes of the network are formed by amino acids, water molecules and ligands.

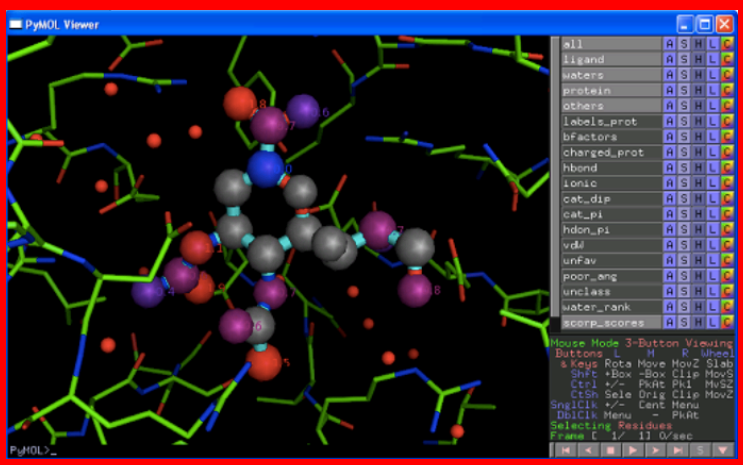
The edges of the network are formed by covalent bonds and non-covalent interactions. Scorpion encodes local cooperativity effects and considerably improves the quality of predicted binding affinities.

COLOUR CODING BASED ON CALCULATED AFFINITY

Using the Scorpion interaction network, we can identify and calculate the network parameters that increase local tight binding.

High scoring atoms are coloured red (in Proasis4, PyMol, MOE) to indicate tight binding. Lower scoring atoms are rendered with darker colours. This guides design by highlighting where ligands should be modified to enhance binding.





SCORPION SCORING

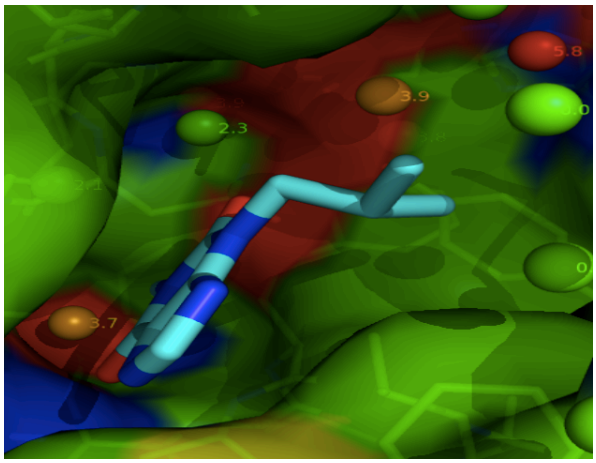
Genetic algorithm optimisation using high quality training sets resulted in parameters for each individual interaction type and network term.

Scorpion scores binding affinity based on a derived scoring function. The scoring function incorporates network terms, in addition to terms for favourable and unfavourable interactions. Total scores and individual contributions are saved in sdf format, which can be viewed either in a table or spreadsheet, including depictions.

GEOMETRIC WATER SCORE

Structural water molecules are classified according to their interactions with neighbouring 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

& Software Requirements

INSTALLATION

Scorpion server software runs under Linux and end users access the system using command line scripts or Proasis4.

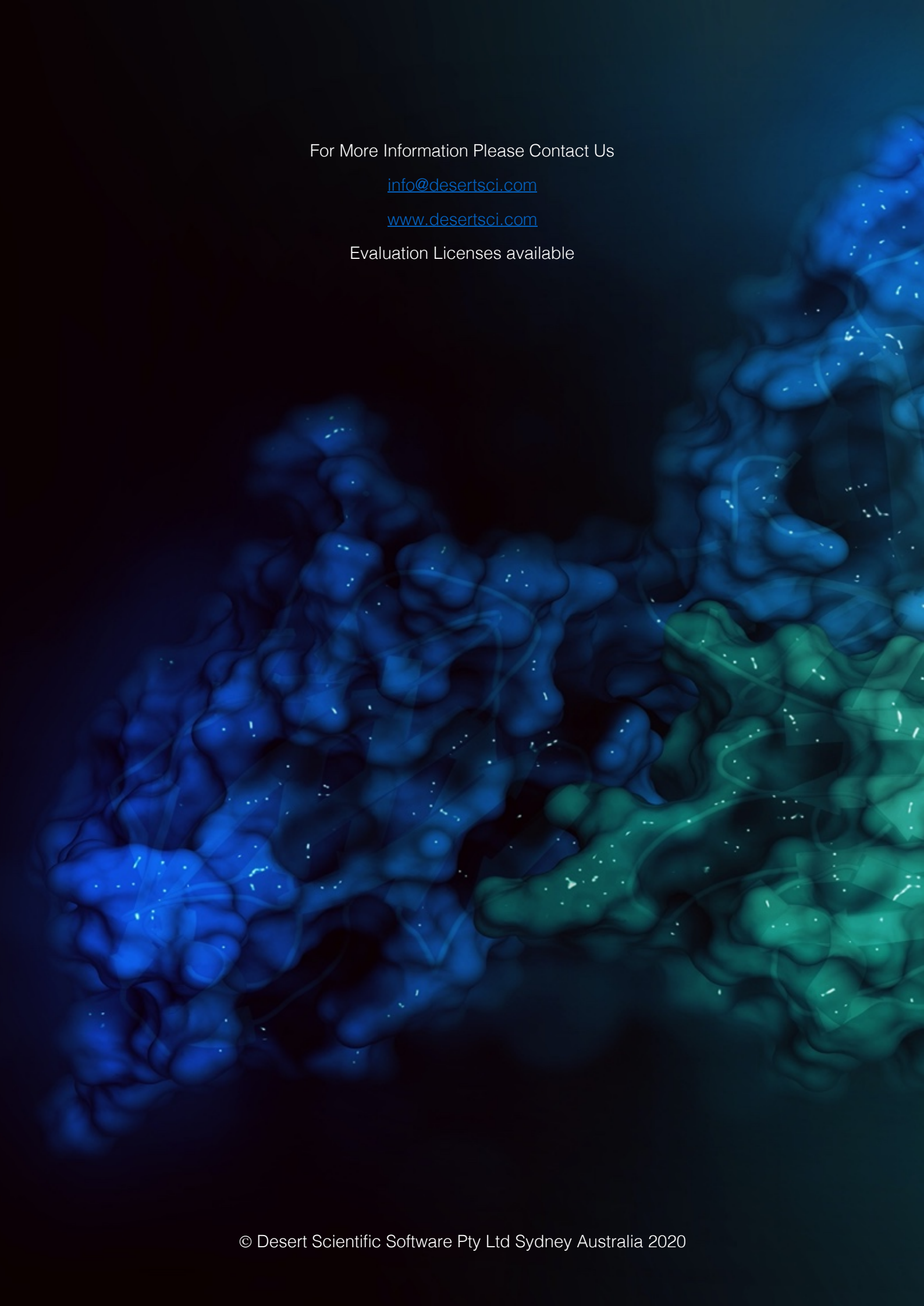
SOFTWARE REQUIREMENTS

On the server machine:

- Python version 2.7 is required
- Python add on modules - networkx (version networkx-1.8.1.tar.gz recommended)
- Openbabel - latest version 2.3.0 or later is recommended

For end user viewing:

- Proasis4 web application
- other third-party modelling applications



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