...applying innovation

FIRSTLY

WHAT IS VIPER?

Viper is DesertSci's powerful new ligand design software suite based on Scorpion technology.

Viper is a completely new approach for designing tight binding ligands. It identifies areas for improving protein-ligand interaction networks and cooperativity using pharmacophore searching and fragment scanning.

With Viper you can identify new ligand substituents that substantially improve binding affinities without having to add large groups.

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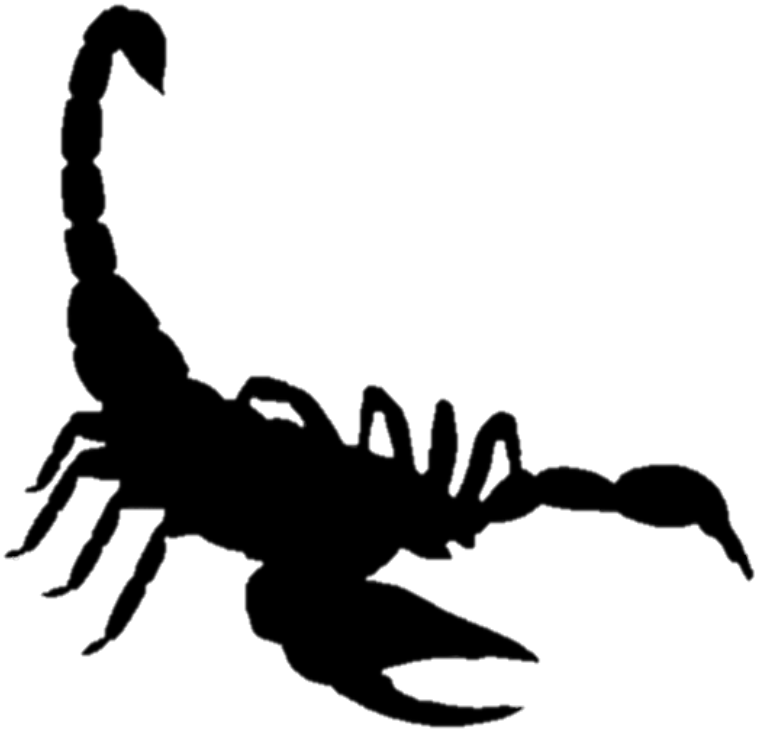
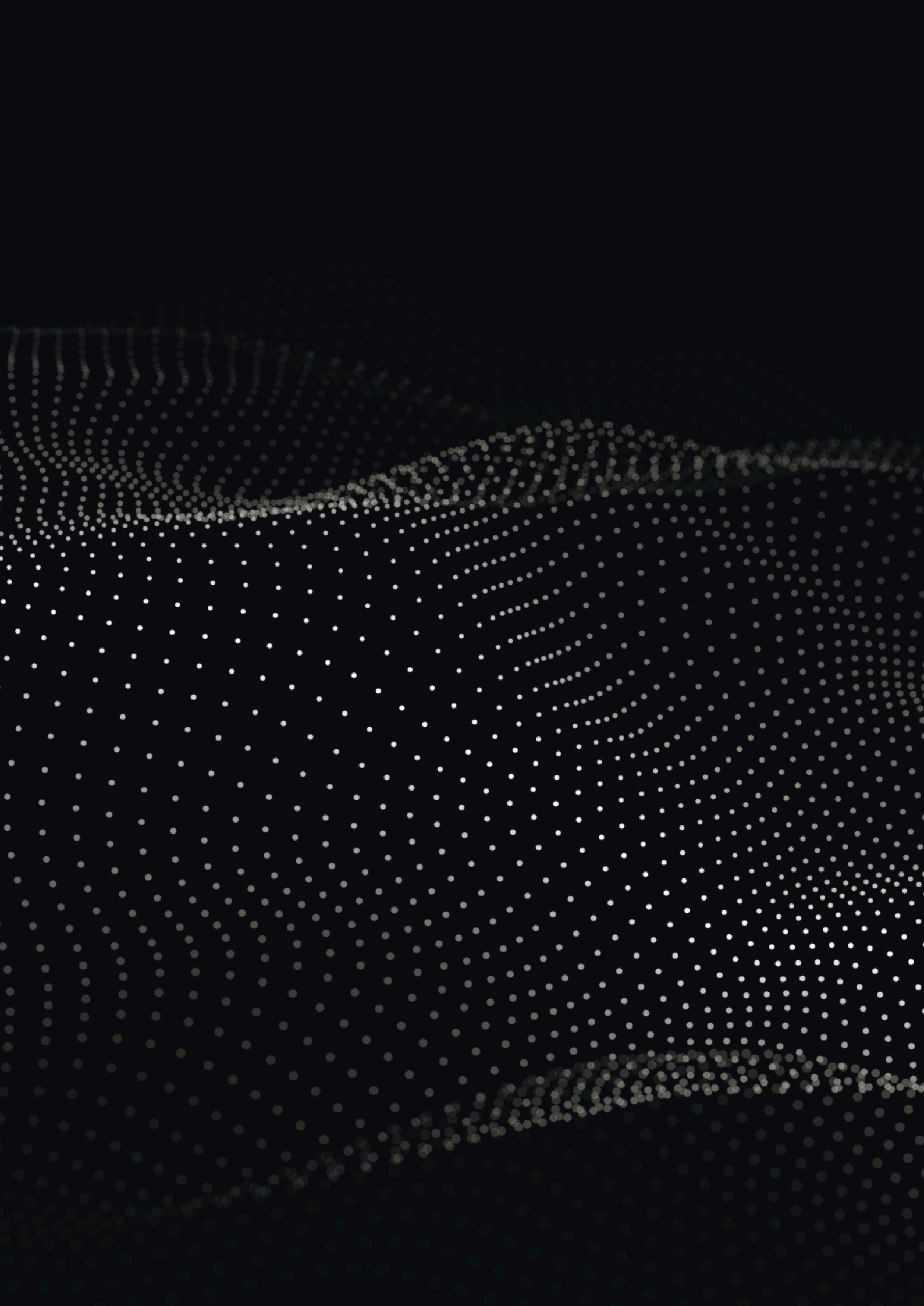


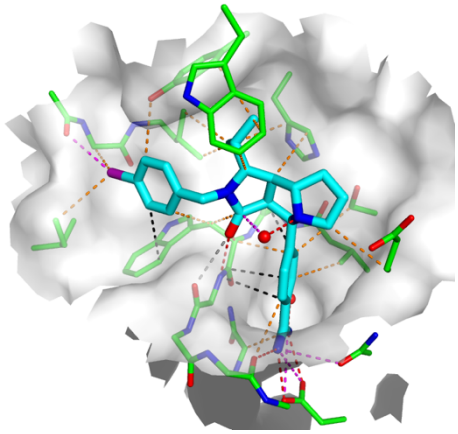


1 | INCLUSIONS

Viper software provides the following ligand design functionality:

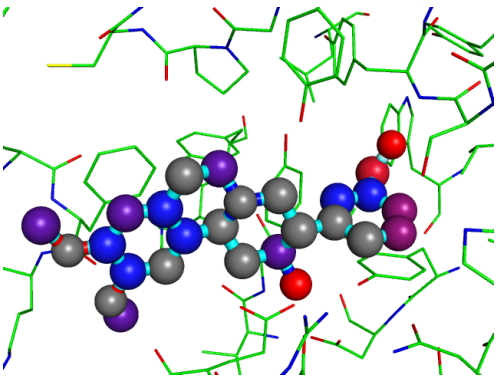
- → **Fragment scanning** – extending off an atom or replacing a substituent
- → **Atom scanning** – such as halide or methyl scan
- → **SMIRKS scanning** – chemical transformations involving atoms, small groups and ring modifications

The Viper software suite also includes:



ViewContacts *for automatically classifying non-covalent interactions, finding commonly occurring and less-commonly occurring atom close-contacts. The system detects desolvation penalties and other sub-optimal close contacts; and rank scores bound water molecules. A wide range of visualisation options are available*

Scorpion *for ligand affinity prediction based on ViewContacts interaction types, water rank scores, and novel network descriptors. It provides easy visualisation of ligand atoms, colour-coded according to predicted binding affinity*



Viper is **fully integrated** into DesertSci's Protein Structure Database and Visualisation System, **Proasis4**, providing a powerful and intuitive suite of tools for the needs of research. The Viper GUI is designed to allow for fast, exploratory ligand design experiments to be run, followed by more exhaustive scans with bigger libraries and more comprehensive scoring of hits.

Proasis allows for **fully automated ligand design**, where complete all-atom scanning is performed for all deposited inhouse protein-ligand complexes.

Viper can be run using command line tools or using API resources.

2 VIPER FEATURES

highlight of pharmacophores for strong protein-ligand interaction networks and cooperativity

grid sampling of a binding site based on combinations of ViewContacts interaction types

multiple atom scanning around ligand based on the Scorpion scoring function

able to scan fragment library at any ligand position, and rank with Scorpion

able to scan fragment library guided by network hotspots

interactions from each pharmacophore site to neighbouring protein atoms are easily explored in PyMOL

chemistry knowledge built into fragment linking

identification of favourable water binding sites

WHAT IS SCORPION TECHNOLOGY?

Using Viper with its incorporated Scorpion technology provides you with:

- a new computational description of molecular recognition
- new tools for exploring binding in protein-ligand complexes
- a completely new approach for designing tight binding ligands

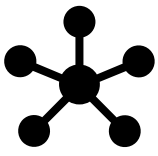
Scorpion technology underpins our modeling software by providing a new computational description of molecular recognition. Specifically, Scorpion technology uses a small world network approach to rationalise binding in protein-ligand complexes.

It is based on the concept of cooperativity and offers you new insights into molecular recognition phenomena and rational drug design.

4

VIPER

.....IN ACTION



A typical fragment scan computation is done in three stages:

- pharmacophore search
- fragment scan
- full Scorpion scoring

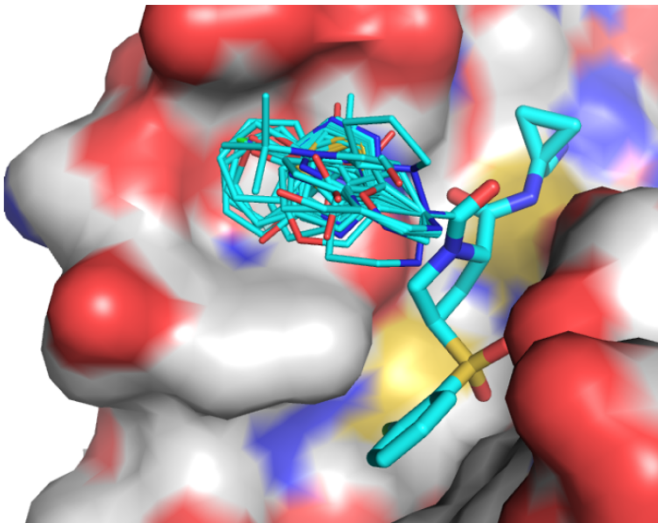
Multiple fragment scan computations can be done using the results from a single pharmacophore search. The search for explicit ligand substituents can be directed to maximize total binding affinity or be fine-tuned in a wide variety of ways; for example, to optimize local hydrogen bonding cooperativity.

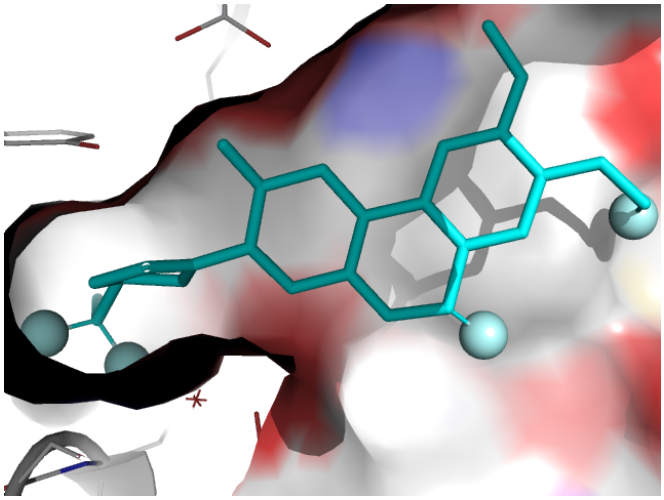
4 VIPER
..... In Action

FRAGMENT SCANNING

Fragment scanning guided by network hotspots enables the optimisation of ligand binding affinity. Explicit ligand substituents from a fragment library are linked to the template, taking account of the allowed chemistry and ligand strain. Substituents that provide improved interactions, including those with high network scores, are saved.

An example of 16 high scoring fragments from the BRICS library (http://www.zbh.uni-hamburg.de/BRICS), calculated for DPP4 (pdb id 3kwf), as seen in the image opposite to indicate a subset of the output calculated by Viper.





ATOM SCANNING

Atom scanning identifies explicit single atom substituent patterns that lead to high network scores in binding sites. Viper checks for all possible substitution sites then orders the new ligand designs from lowest to highest affinity. Halide scans are particularly powerful for optimising molecules during lead development.

Viper atom scan results typically reproduce experimental results, as seen opposite for pdb entry 3kwf. The primary amine nitrogen in the ligand was predicted by Viper to be the highest scoring nitrogen position. The results shown highlight the most favourable positions for fluorine substitution.

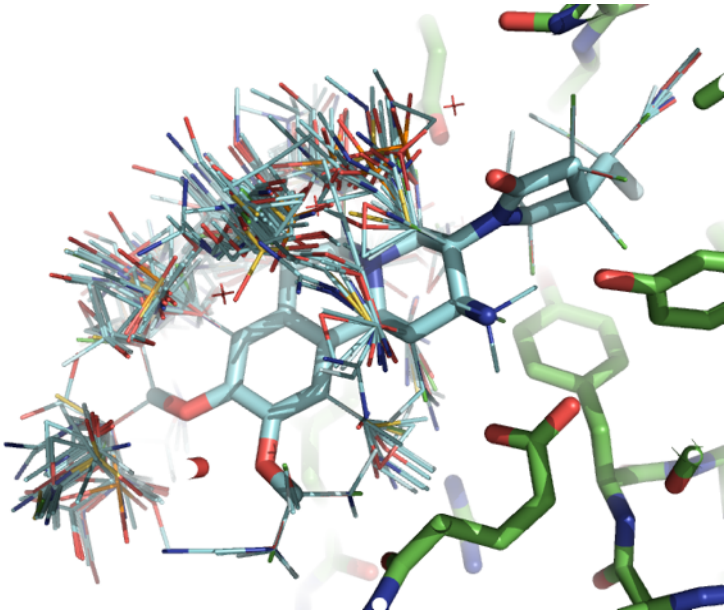
SMIRKS SCANNING

SMIRKS scanning greatly extends the power of fragment-based ligand design by enabling a wider range of chemical transformations and facilitating low-molecular weight fragment extensions. It allows for designers to encode their favourite set of fragments, such as those from matched molecular pair analyses.

SMIRKS scanning allows for a wide range of on-the-fly chemical transformations:

[#6:1][H:2]>>[#6:1][C:2]([F])([F])[F]
[O:1][H:2]>>[#O:1]CC
[c:1]1[a][a][a][a][a]1>>[n:1]1[a][a][a][a][a]1
[#6:1][H:2]>>[#6:1][O:2][CH3]
[N:1][H:2]>>[N:1]CC
[n:1]1[a][a][a][a][a]1>>[c:1]1[a][a][a][a][a]1

DesertSci provides a number of SMIRKS libraries of different sizes, obtained from a statistical analysis of all small substituents extracted from retro-synthetic analyses.



SMIRKS scanning *automatically scans every atom in a ligand, in the environment of the protein binding site, identifying the optimal low-molecular weight substitutions and chemical transformations that can lead to tighter ligand binding*

5 INSTALLATION
& Software Requirements

INSTALLATION

Viper server software runs under Linux and end users access the system using command line scripts or Proasis4.
Viewing of hits can be done within Proasis4 or using PyMOL. Other third-party modelling applications can also be used.

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) and rdkit (version 2012_06_1 or later) for running SMIRKS scans
- Openbabel - latest version 2.3.0 or later is recommended
- For end users viewing:
  - protein ligand complexes
  - non-covalent interactions
  - atoms highlighted by Scorpion scores
  - network hotspots
  - results from fragment scans
- Proasis4 web application
- PyMOL
- Other desktop modelling applications

For more information please contact us at

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