Predicting drug polypharmacology using a novel surface property similarity-based approach

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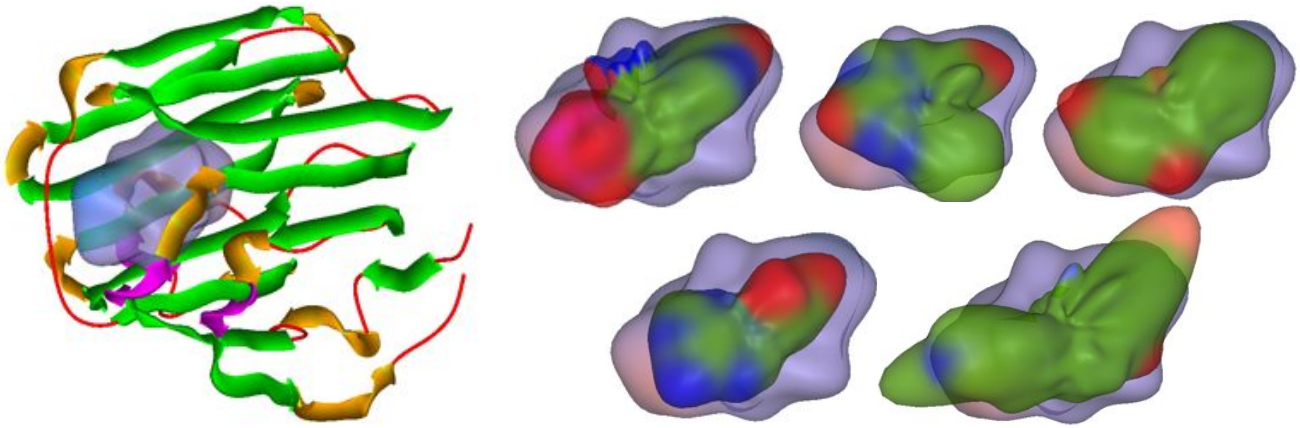

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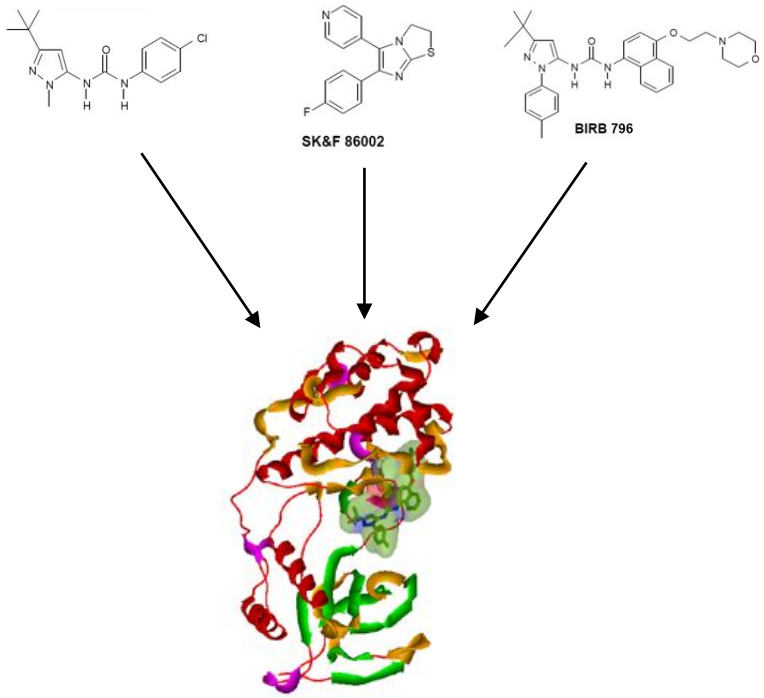
Polypharmacology

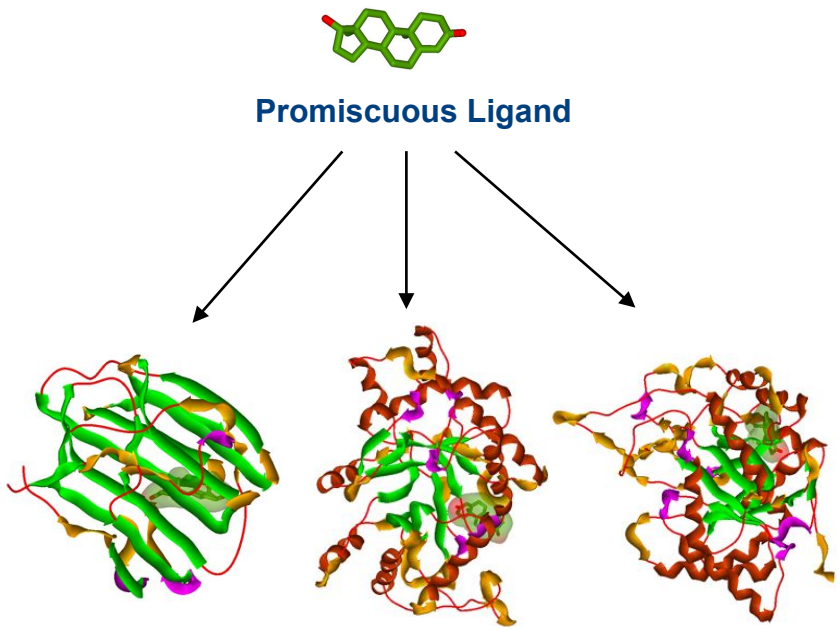
Polypharmacology (Drug selectivity)

Multiple drugs bind to a given target (promiscuous targets)



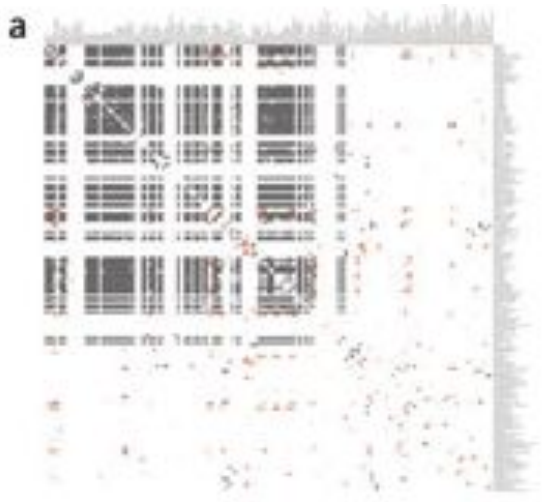
Promiscuous Target

A given drug binds to more than one target (promiscuous ligands)

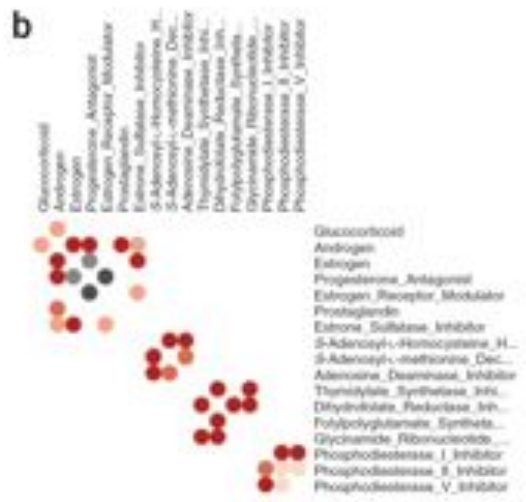


Previous work

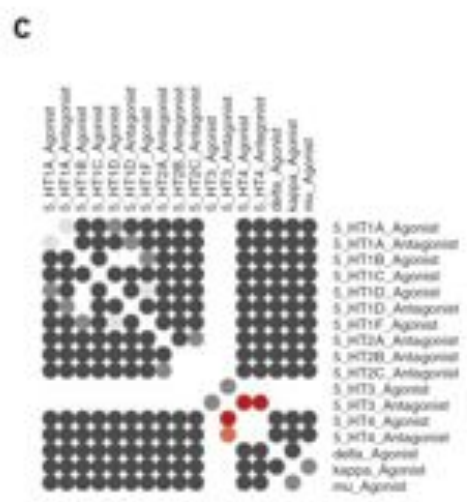
Relate receptors to each other quantitatively based on the similarity in the:



Ligand space
(chemical fingerprints)



Sequence space



Binding pocket space
(pharmacophoric descriptors)

•Keiser *et al*. *Nature Biotechnol.* **2007**, *25*, 197-206. Similarity Ensemble Approach (SEA) relates proteins based on the set-wise chemical similarity among their ligands.

•Vidal & Mestres. *Mol. Inf.* **2010**, 29, 543. PHRAG, FPD, SHED molecular descriptors.

•Weskamp *et al. Proteins* **2009**, *76*, 317-330. Similarity amongst binding pockets extracted by LIGSITE algorithm.

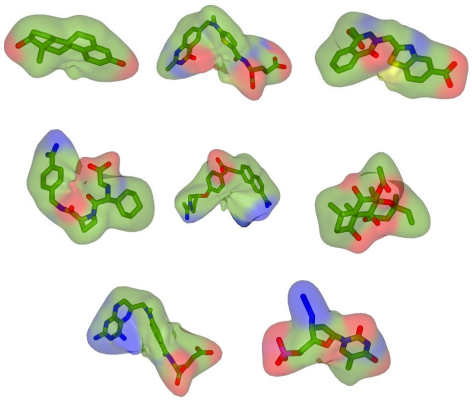
•Milletti, F.; Vulpetti, A. *J. Chem. Inf. Model.,* **2010**, *50*, 1418–143. Binding pocket comparison using four-point pharmacophoric descriptors based on GRID.

Our approach

3D spherical harmonic (SH) shape-based approach to compare molecular surfaces and key surface properties very fast and efficiently.

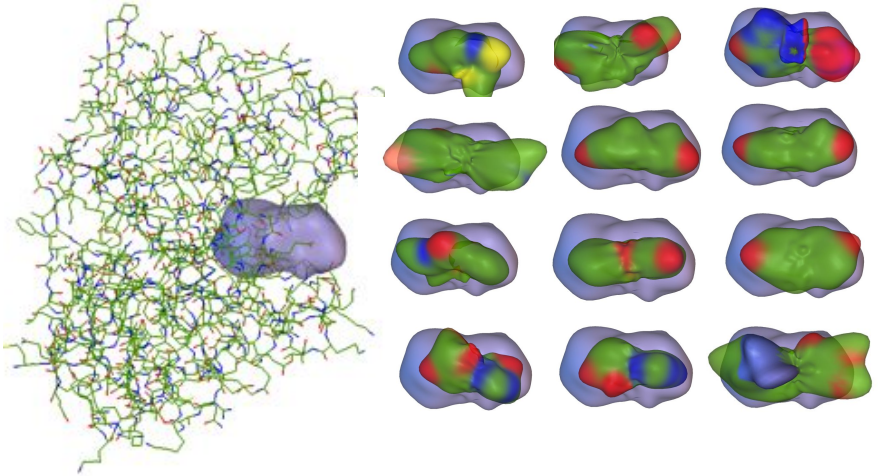
Ligand space

Ligand SH shape similarity

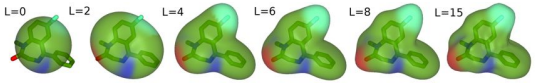


Binding pocket space

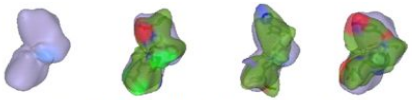
Binding pocket SH shape similarity



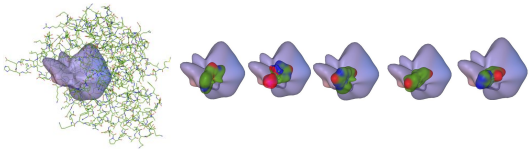
Methodology



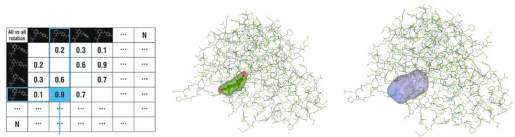
1. Calculating SH Shapes



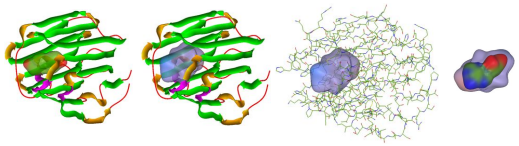
2. Calculating SH Consensus Shapes



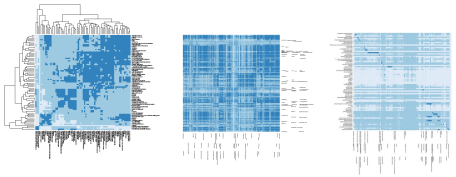
3. SH Consensus Pockets



4. Predicting promiscuity using SH shape-based similarity

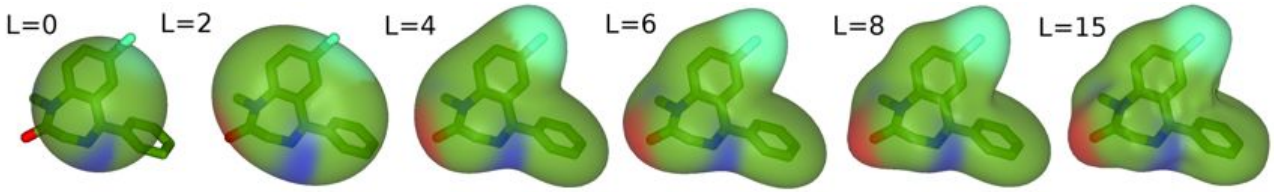


5. Data processing



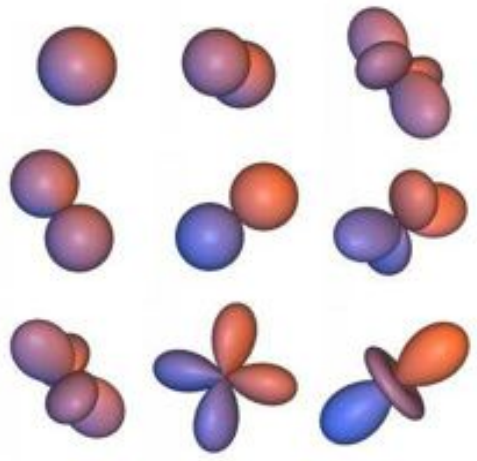
6. Cross interaction matrices

1. Calculating SH Shapes



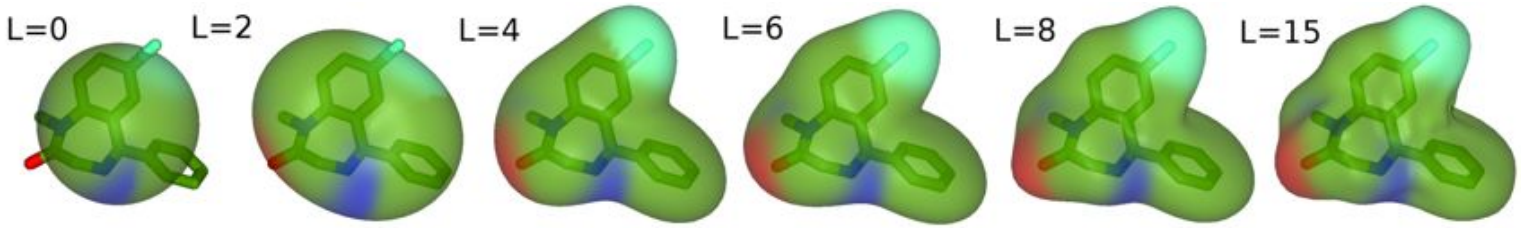
Spherical Harmonic Surfaces

Surface shapes are represented as radial distance expansions of the molecular surface with respect to the center of the molecule.



- **Real SHs:** $y_{lm}(\theta, \phi)$
- **Coefficients:** a_{lm}
- **Encode radial distances from origin as SH series…**
- **Solve coefficients by numerical integration…**

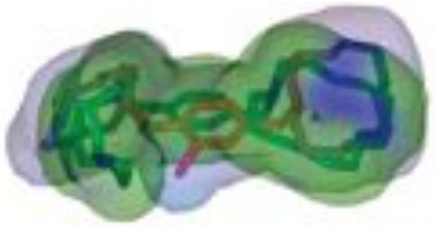
$$r(\theta, \phi) = \sum_{l=0}^{15} \sum_{m=-l}^{l} a_{lm} y_{lm}(\theta, \phi)$$



Ritchie, D.W. and Kemp, G.J.L. *J. Comp. Chem.* **1999**, 20, 383–395.

ParaFit

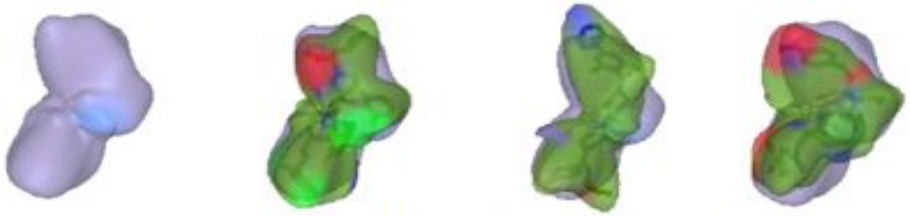
ParaFit calculates superpositions between pairs of molecules by exploiting the special rotational properties of the SH functions



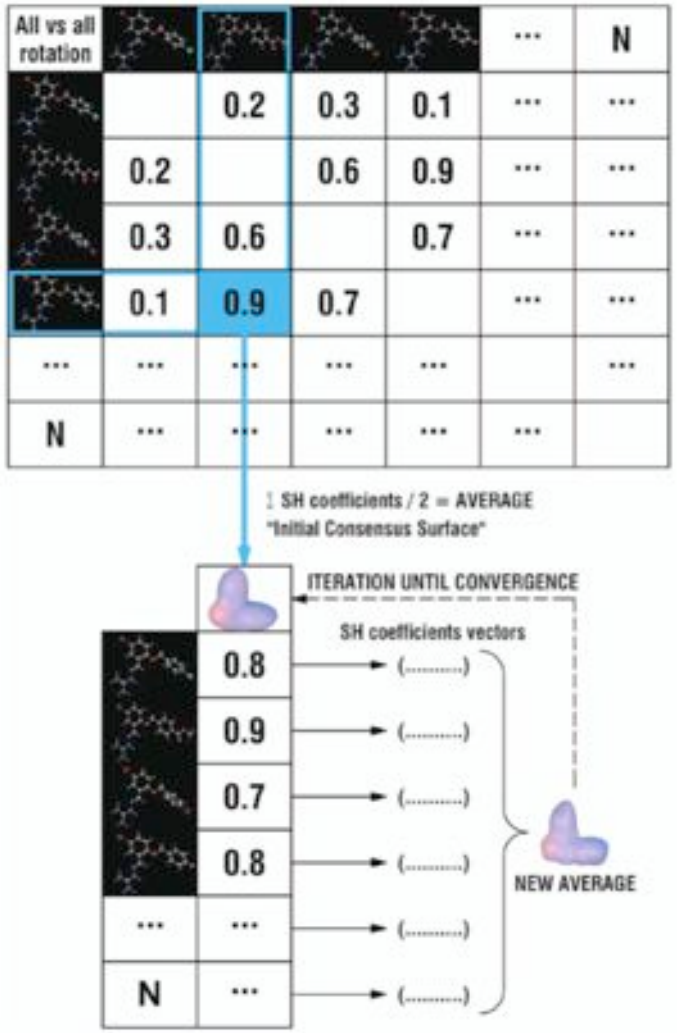
- **Distance:** $D = \int (r_A(\theta,\phi) - r_B(\theta,\phi)')^2 \mathrm{d}\Omega$
- **Orthogonality:** $D = |\underline{a}|^2 + |\underline{b}|^2 - 2\underline{a}.\underline{b}'$
- **Rotation:** $b'_{lm} = \sum_{m'} R^{(l)}_{mm'}(\alpha,\beta,\gamma) b_{lm'}$
- **Carbo:** $S = \underline{a}.\underline{b}'/(|\underline{a}|.|\underline{b}|)$
- **Hodgkin:** $S = 2\underline{a}.\underline{b}'/(|\underline{a}|^2 + |\underline{b}|^2)$
- **Tanimoto:** $S = \underline{a}.\underline{b}'/(\underline{a}|^2 + |\underline{b}|^2 - \underline{a}.\underline{b}')$
- **Multi-property:** $Q = pS + qS^{\mathrm{MEP}} + rS^{\mathrm{IE_L}} + \ldots$

Ritchie, D.W. and Kemp, G.J.L. *J. Comp. Chem.* **1999**, 20, 383–395.

2. Calculating SH Consensus Shapes



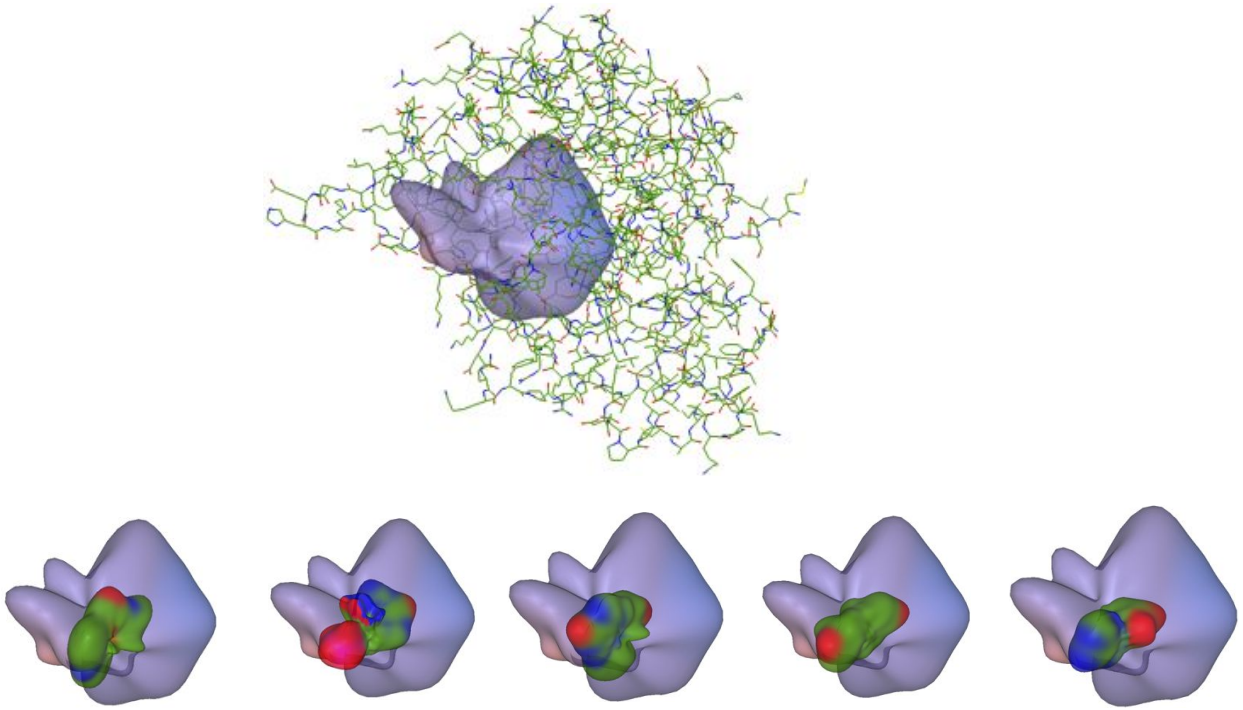
Calculating Consensus Shapes



1. Do all-v-all SH comparison
2. Find best pair-wise match
3. Calculate SH average of pair
4. Treat average as new seed
5. Superpose all onto seed
6. Compute new average seed
7. Rotate all onto new seed
8. Iterate until convergence...
9. Result = SH pseudo-molecule

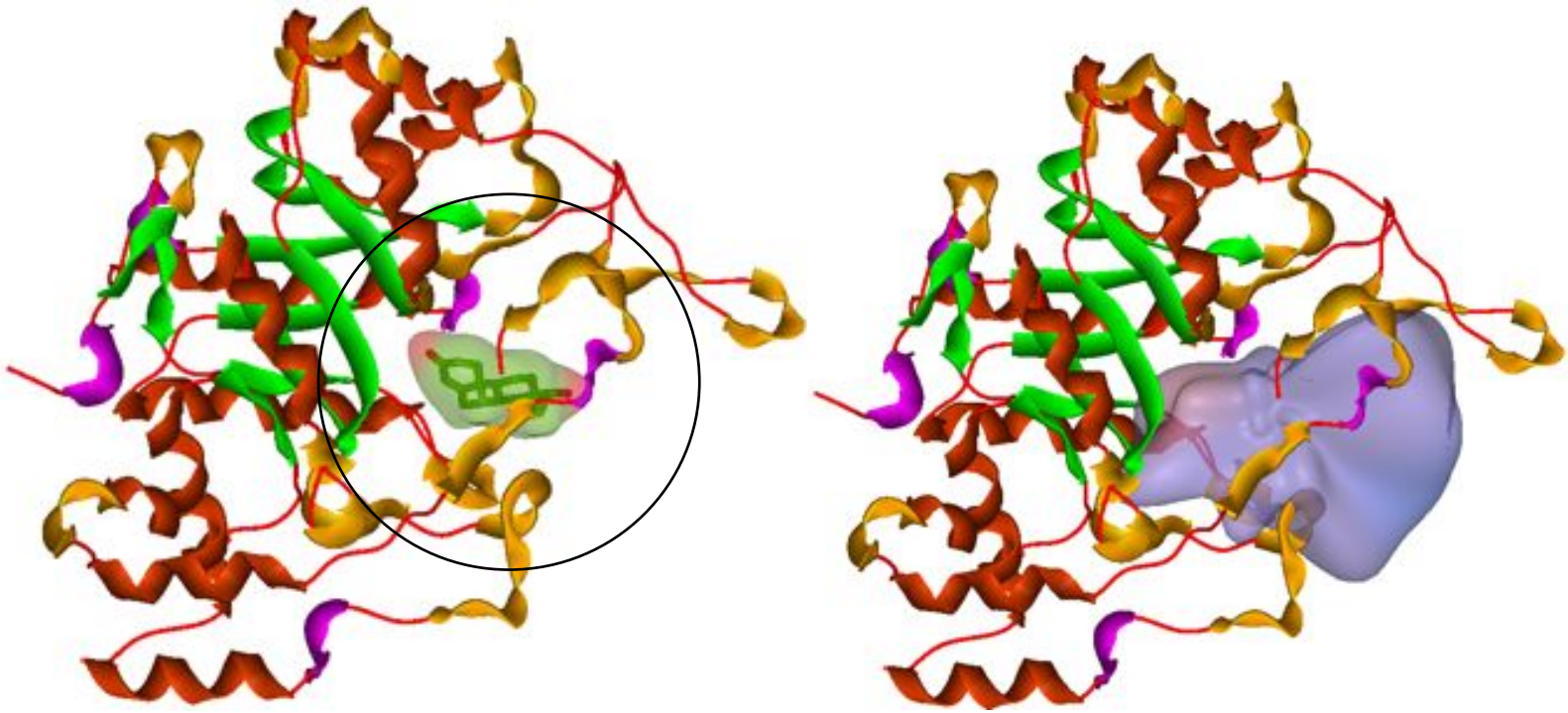
Pérez-Nueno *et al*. *J. Chem. Inf. Model.* **2008**, *48*, 2146–2165.

3. SH Consensus Pockets



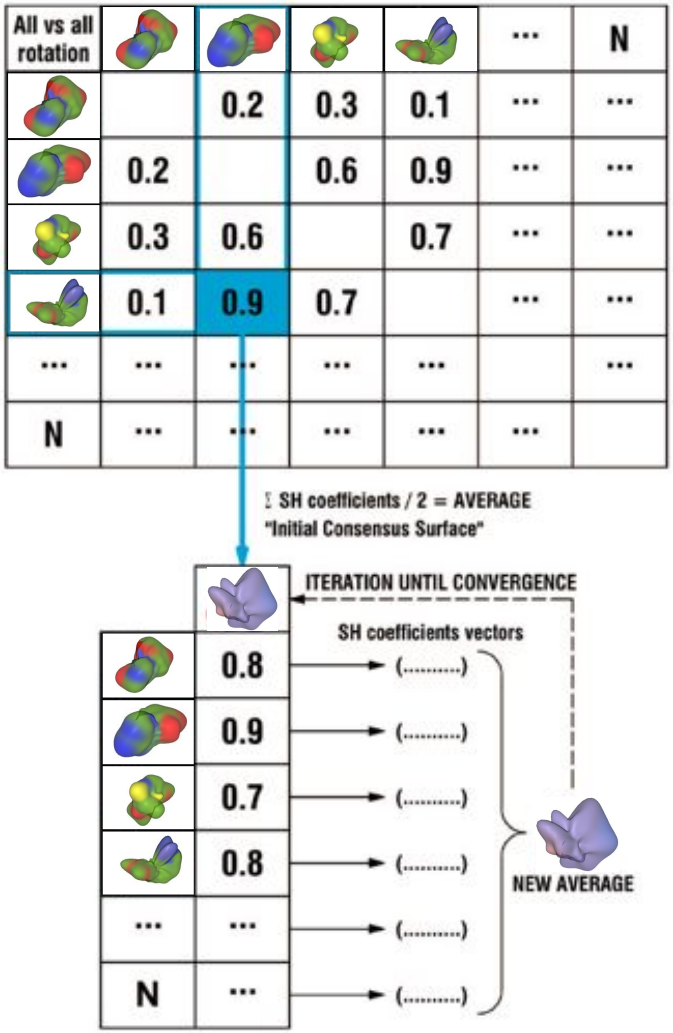
SH Consensus Pockets

1. **Calculate SH coefficients of the binding pockets with MSSH. Each cavity surface is calculated around the bound ligand coordinates taking a radius cutoff of 20 Å.**

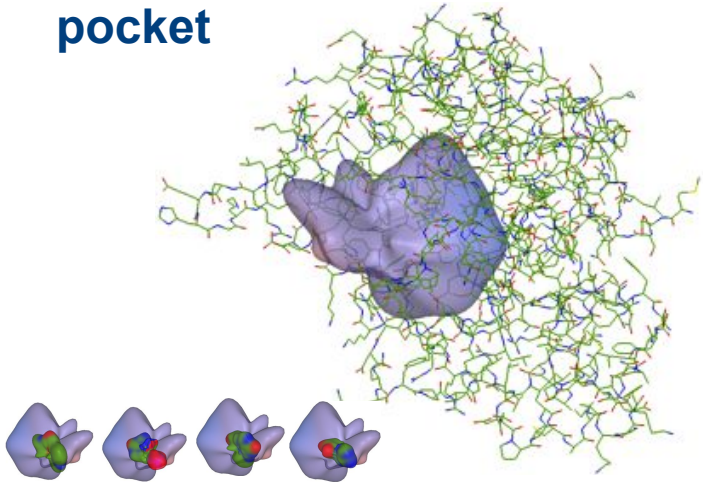


MSSH: Beautrait A., Maigret B. *et al. J. Mol. Model.* **2008**, *14*, 135–148. http://www.harmonicpharma.com/"

SH Consensus Pockets

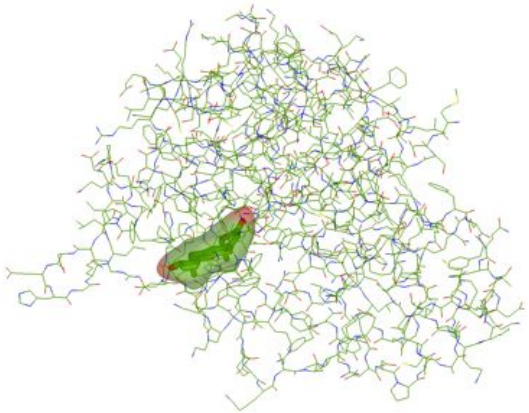


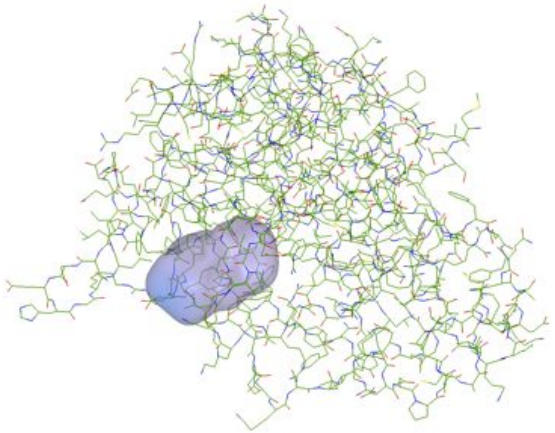
2. Do all-v-all SH comparison
3. Find best pair-wise match
4. Calculate SH average of pair
5. Treat average as new seed
6. Superpose all onto seed
7. Compute new average seed
8. Rotate all onto new seed
9. Iterate until convergence...
10. Result = SH consensus pocket



4. Predicting promiscuity using SH shape-based similarity

All vs all rotation					...	N
		0.2	0.3	0.1	...	...
	0.2		0.6	0.9	...	...
	0.3	0.6		0.7	...	...
	0.1	0.9	0.7		...	...
...	...	...	...	...		...
N	...	...	...	...	...	



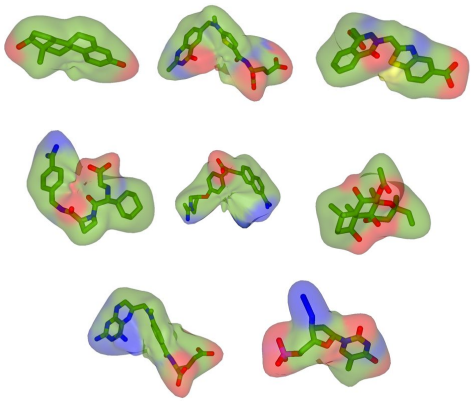


Predicting promiscuity using SH shape-based similarity

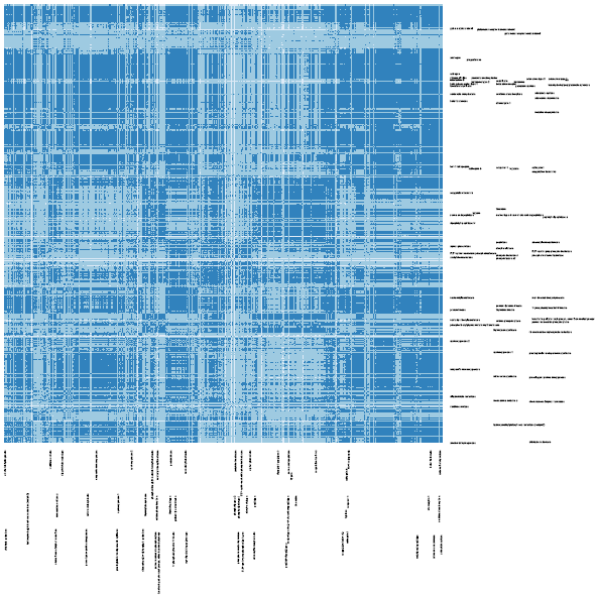
Ligand SH shape similarity

Shape similarity of each ligand to each target's ligand set quantified by Tanimoto

The all vs all ligand interaction matrix is analyzed by setting 3 Tanimoto thresholds



Tanimoto shape similarity score
Tanimoto ≥ 0.9 *Dark blue*
0.7 ≤ Tanimoto < 0.9 *Blue*
Tanimoto < 0.7 *Light blue*

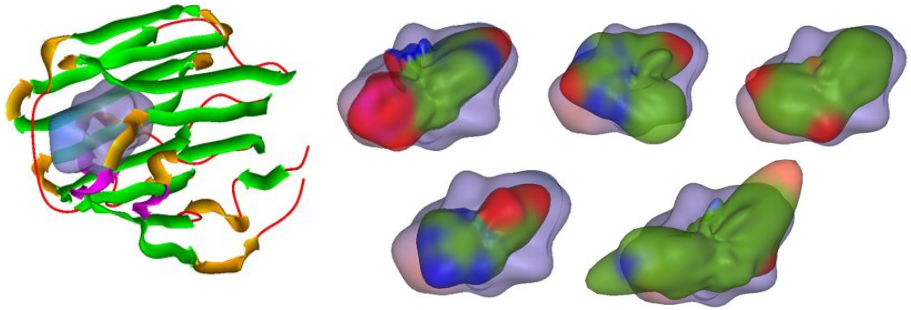


Predicting polypharmacology using SH shape-based similarity

Binding pocket SH shape similarity

Consensus of the targets pockets' belonging to the same annotation (biological function)

Shape similarity of each consensus pocket to each annotation consensus pocket quantified by Tanimoto
The all vs all pocket interaction matrix is analyzed by setting 3 Tanimoto thresholds



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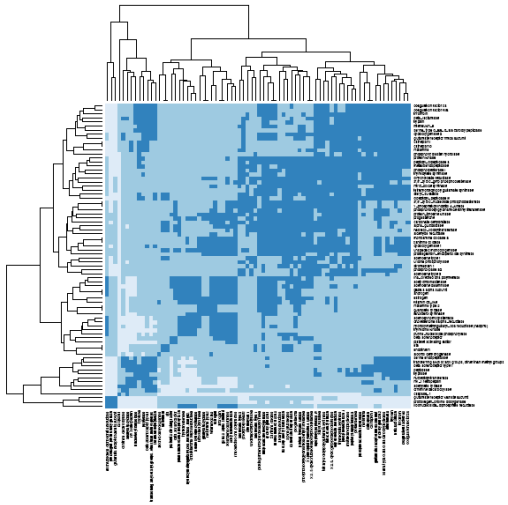
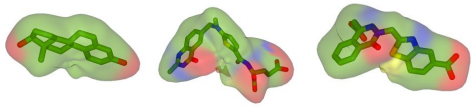
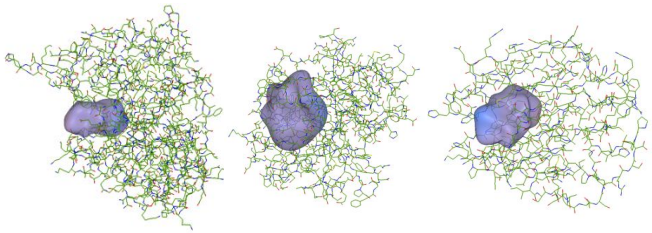


Predicting polypharmacology using SH shape-based similarity

Ligand vs Binding pocket SH shape similarity

Shape similarity of each ligand to each annotation consensus pocket quantified by Tanimoto

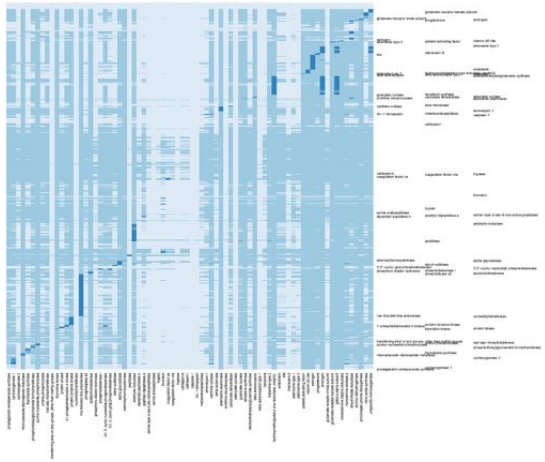




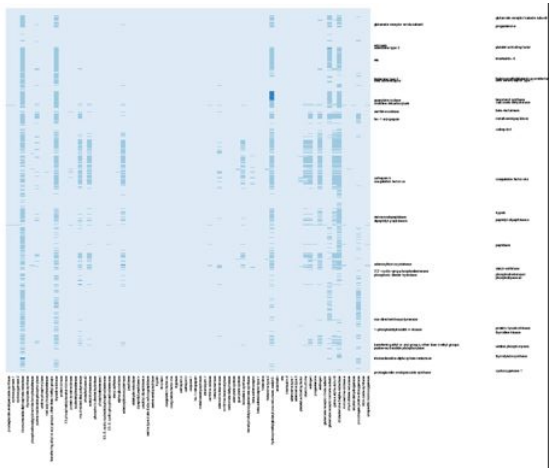
The interaction matrix is color coded for different Tanimoto thresholds (0.9, 0.85, 0.8, 0.75, 0.7) according to:

- L – P shape similarity found & PDB existence *Dark blue*
- L –P shape similarity found & no PDB existence *Blue*
- L - P shape not similarity found *Light blue*

Tanimoto 0.7

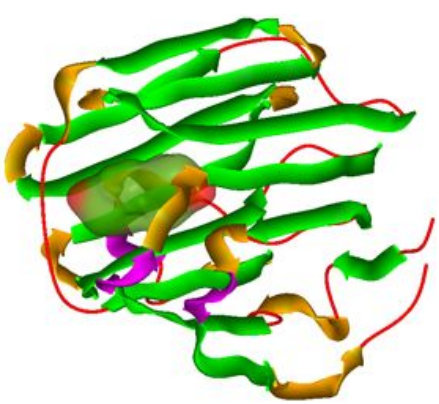


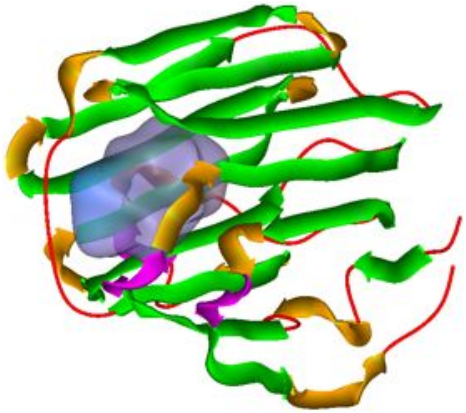
Tanimoto 0.9

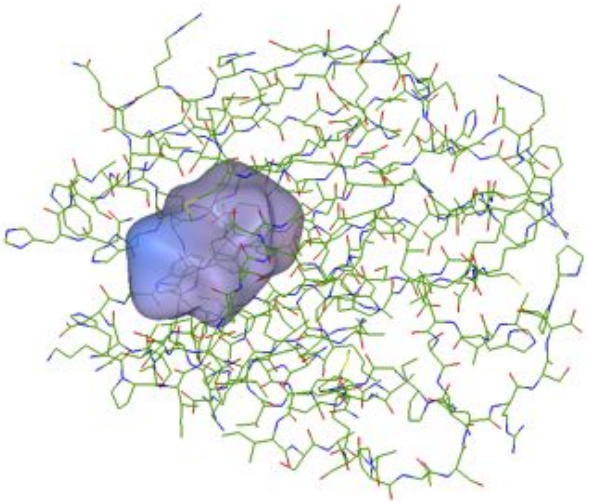


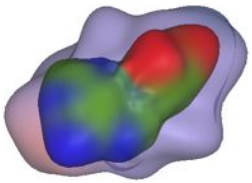
The plot that highlights the confirmed interactions (PDB) is selected

5. Data processing









MDDR 2010.2 (MDL Drug Data Report)

MDDR Schuffenhauer subset *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 947-955

<ACTIVE_INDEX>	ACT_KEY	ACT_DESCRIPTION	<ACTIVE_CLASS>	INTRINSIC_ACTIVITY	TARGET_KEY
	01129	Opioid Agonist		agonist	3953
	01131	kappa Agonist		agonist	3955
	01132	delta Agonist		agonist	3954
	01133	mu Agonist		agonist	3956
	01140	Enkephalinase Inhibitor		inhibitor	2816
	01141	Aminopeptidase Inhibitor		inhibitor	2577
	01150	Opioid Mixed Agonist-Antagonist		agonist	3953
	01210	PGE2 Antagonist		antagonist	4035
	01221	Neurotensin-Based Analgesic		agonist	3984
	02110	Anaphylatoxin Receptor Antagonist		antagonist	3918
	02451	IL-1beta Converting Enzyme Inhibitor		inhibitor	2765
	02456	IL-6 Inhibitor		inhibitor	3976
	02520	Bradykinin Antagonist		antagonist	3915
	02521	Bradykinin B1 Antagonist		antagonist	3916
	02522	Bradykinin B2 Antagonist		antagonist	3917
	02630	Complement Inhibitor		inhibitor	2459
	03200	Xanthine Oxidase Inhibitor		inhibitor	284
	06210	Benzodiazepine		agonist	4285
	06211	Benzodiazepine Agonist		agonist	4285
	06212	Benzodiazepine Agonist/Antagonist		agonist	4285
	06213	Benzodiazepine Antagonist		antagonist	4285
	06214	GABA A/Benzodiazepine Receptor Complex-Related Drug		agonist	4285
	06215	CRF Antagonist		antagonist	4083
	06216	Benzodiazepine Inverse Agonist		inverse agonist	4285
	06217	Benzodiazepine Partial Inverse Agonist		partial inverse agonist	4285
	06230	5 HT Antagonist		antagonist	3893
	06232	5 HT2 Antagonist		antagonist	3900
	06233	5 HT3 Antagonist		antagonist	4309
	06234	5 HT1 Agonist			
	06235	5 HT1A Agonist			
	06236	5 HT1B Agonist			
	06237	5 HT1C Agonist			
	06238	5 HT1C Antagonist			
	06239	5 HT1C/2 Antagonist			
	06240	5 HT1A Antagonist			
	06241	5 HT4 Agonist			
	06242	5 HT4 Antagonist			
	06243	5 HT3 Agonist			
	06246	5 HT1D Agonist			
	06247	5 HT1D Antagonist			
	06248	5 HT2A Antagonist			

We apply our approach to the Schuffenhauer subset of the *MDL* Drug Data Report (MDDR) database containing 65367 compounds distributed over 249 diverse pharmacological targets for which experimental binding information is known.

MDDR 2010.2 (MDL Drug Data Report)

MDDR Schuffenhauer subset *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 947-955

Annotation schemes for pharmaceutical ligands present in MDDR

In Schuffenhauer MDDR subset, all ligands are annotated, when attribution was possible, according to the activity class provided in MDDR.

An annotated set is one where a function, such as “dihydrofolate reductase inhibitor” or “anticancer agent”, is assigned to the ligands in it.

MDDR processing

ACT_KEY	ACT_DESCRIPTION	INTRINSIC_ACTIVITY	TARGET_KEY
01129	Opioid Agonist	agonist	3953
01131	kappa Agonist	agonist	3955
01132	delta Agonist	agonist	3954
01133	mu Agonist	agonist	3956
01140	Enkephalinase Inhibitor	inhibitor	2816
01141	Aminopeptidase Inhibitor	inhibitor	2577
01150	Opioid Mixed Agonist-Antagonist	agonist	3953
01210	PDE2 Antagonist	antagonist	4035
01221	Neurotensin-Based Analgesic	agonist	3984
02110	Anaphylatoxin Receptor Antagonist	antagonist	3918
02451	IL-1beta Converting Enzyme Inhibitor	inhibitor	2765
02456	IL-6 Inhibitor	inhibitor	3976
02520	Bradykinin Antagonist	antagonist	3915
02521	Bradykinin BK1 Antagonist	antagonist	3916
02522	Bradykinin BK2 Antagonist	antagonist	3917
02630	Complement Inhibitor	inhibitor	2659
03200	Xanthine Oxidase Inhibitor	inhibitor	286
06210	Benzodiazepine	agonist	4285
06211	Benzodiazepine Agonist	agonist	4285
06212	Benzodiazepine Agonist/Antagonist	agonist	4285
06213	Benzodiazepine Antagonist	antagonist	4285
06214	GABA A/Benzodiazepine Receptor Complex-Related Drug	agonist	4285
06215	CRF Antagonist	antagonist	4083
06216	Benzodiazepine Inverse Agonist	inverse agonist	4285
06217	Benzodiazepine Partial Inverse Agonist	partial inverse agonist	4285
06230	5 HT Antagonist	antagonist	3893
06232	5 HT2 Antagonist	antagonist	3900
06233	5 HT3 Antagonist	antagonist	4309
06234	5 HT1 Agonist	agonist	3894
06235	5 HT1A Agonist	agonist	3895
06236	5 HT1B Agonist	agonist	3896
06237	5 HT1C Agonist	agonist	3897
06238	5 HT1C Antagonist	antagonist	3897
06239	5 HT1C/2 Antagonist	antagonist	3897
06240	5 HT1A Antagonist	antagonist	3895
06241	5 HT4 Agonist	agonist	3904
06242	5 HT4 Antagonist	antagonist	3904
06243	5 HT3 Agonist	agonist	4309
06244	5 HT1D Agonist	agonist	3898
06247	5 HT1D Antagonist	antagonist	3898
06248	5 HT2A Antagonist	antagonist	3901

```
-------------------------------------------------------------------------------
ATARGET: 1002
RETREG: 245646
RACT_CLASS: Xanthine Oxidase Inhibitor; HMG A Inhibitor; Lipid Peroxidation Inhibitor; Antiobesity; Antipsoriatic; Antineoplastic; Chemopre
ective; Cyclooxygenase-1 Inhibitor;
RACT_INDEX: 00200; 00410; 12453; 52000; 59300; 75000; 75040; 75045; 78453;
RLIG: SAL
RPDB: 1EX2; 1HP5; 1S8D; 1U8W; 1Z1F; 3C8L;
RETREG: 210861
RACT_CLASS: Cyclooxygenase-1 Inhibitor; Cyclooxygenase-2 Inhibitor;
RACT_INDEX: 78453; 78454;
RLIG: LCF
RPDB: 1PYX;
RETREG: 093347
RACT_CLASS: Analgesic, Non-Opioid; Antiinflammatory; Cyclooxygenase-1 Inhibitor; Cyclooxygenase-2 Inhibitor;
RACT_INDEX: 01200; 02100; 78453; 78454;
RLIG: IMM
RPDB: 1S2A; 2B3X; 2B3M; 2B3Q; 2HM6; 2H1N; 2Z8B; 3F87; 4COX;
RETREG: 133190
RACT_CLASS: Analgesic, Non-Opioid; Antiarthritic; Antiinflammatory; Antimigraine; Cyclooxygenase-1 Inhibitor; Cyclooxygenase-2 Inhibitor;
RACT_INDEX: 01200; 02000; 02100; 12342; 78453; 78454;
RLIG: IBP
RPDB: 1EQG; 2B3Q; 2PYS;
RETREG: 093347
RACT_CLASS: Analgesic, Non-Opioid; Antipyretic; Antiinflammatory; Neuronal Injury Inhibitor; Antianginal; Nitric Oxide Donor; Platelet Anti
oiegic Agent; Chemopreventive; Cyclooxygenase-1 Inhibitor;
RACT_INDEX: 01200; 01260; 02100; 12452; 30000; 30020; 37200; 38300; 75040; 78453;
RLIG: AIH
RPDB: 1H3H; 1TGN;
-------------------------------------------------------------------------------
ATARGET: 1003
RETREG: 172050
RACT_CLASS: Antiarthritic; Nitric Oxide Synthase Inhibitor; Antiallergic/Antiasthmatic; Antiinflammatory, Topical; Chemopreventive; Tyrosin
 Kinase Inhibitor; Cyclooxygenase-2 Inhibitor;
RACT_INDEX: 02000; 12464; 27200; 59200; 75040; 78370; 78454;
RLIG: PIT
```

MDDR_2D_SDF **309**

EXTREG No
ACTIVITY KEY
ACTIVITY CLASS

Remove duplicates

SCHUFFENAHUER'S DATA **213**

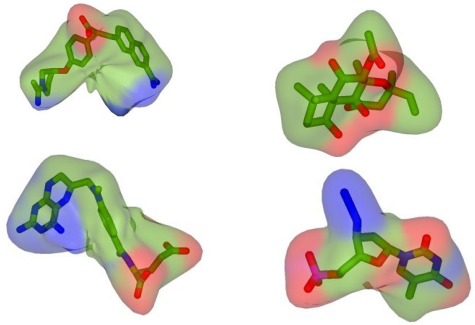
17 non Activity key correspondences between Schuffenhauer version and the new MDDR version

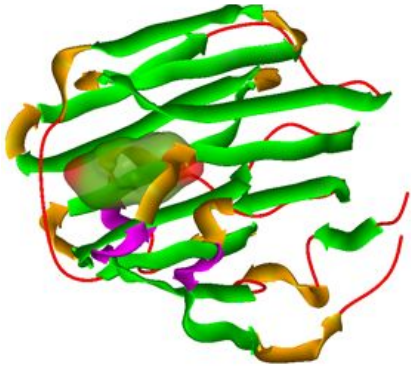
UNIQUE ANNOTATIONS **196**

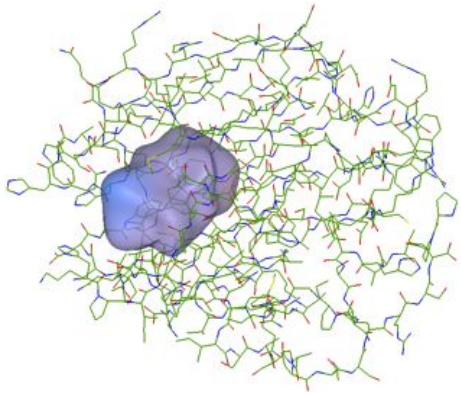
Search in the PDB Heteroatom dictionary the corresponding ligand 3 letter code names for the list of ligands in each Schuffenhauer annotation

UNIQUE ANNOTATIONS comprising at least one ligand found in the PDB Heteroatom dictionary (3 letter code ligand) **93**

MDDR processing







3 LETTER CODE LIGANDS 424
corresponding to the 93 Schuffenhauer annotations

Search the PDB to retrieve the pdb files associated with those 3 letter code ligands

PDB codes 957

Removed structures solved by NMR

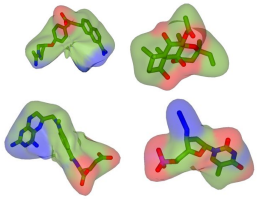
952

Remove structures without CATH code, which implies removing proteins with low resolution and structures that belong to the same complex

PDB codes 687
(kept one chain for each PDB)

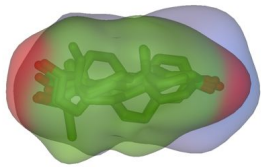
MDDR processing

LIGANDS



Extract all the ligands from the PDBs

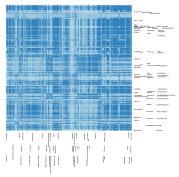
687



Superpose all ligands onto the origin (the canonical orientation) with PARASURF/PARAFIT

677

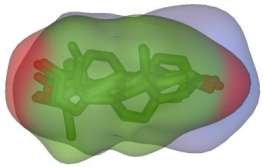
10 compounds fail when calculating Parasurf (CoG outside molecule)



Calculate ligand SH shape-similarity with PARAFIT

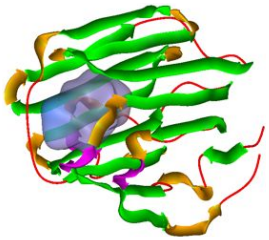
ALL VS ALL LIGAND INTERACTION MATRIX
According to Tanimoto score (thresholds 0.9 and 0.7)

BINDING POCKETS



Align complexes into the ligand canonical orientation

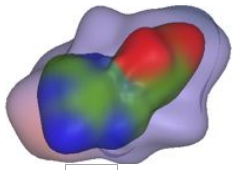
677



Calculate binding pocket SH shape with MSSH

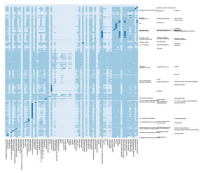
10 compounds fail when calculating MSSH

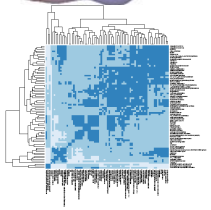
670



Consensus of the pockets belonging to the same annotation with PARAFIT

76



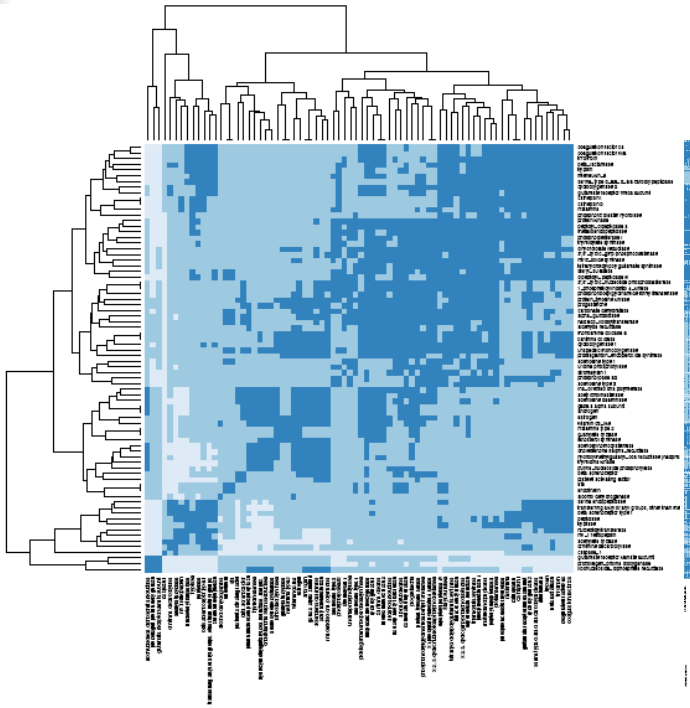


Calculate binding pocket SH shape-similarity of the consensus pockets

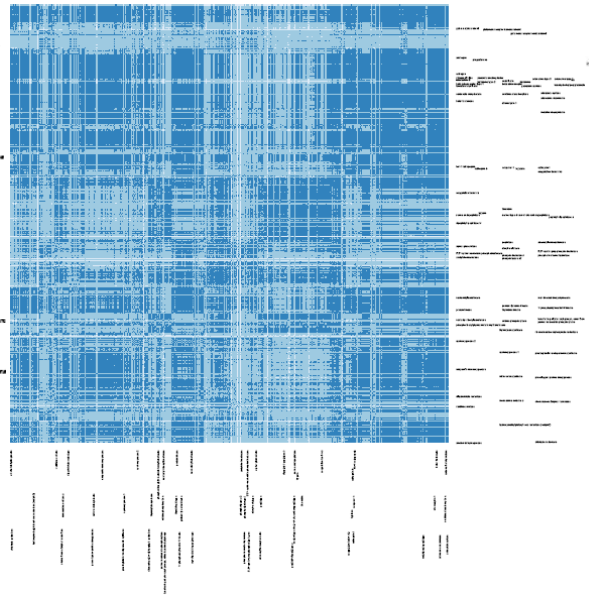
LIGAND VS BINDING POCKET INTERACTION MATRIX (677x76)

ALL VS ALL BINDING POCKET INTERACTION MATRIX
According to Tanimoto score (thresholds 0.9 and 0.7)

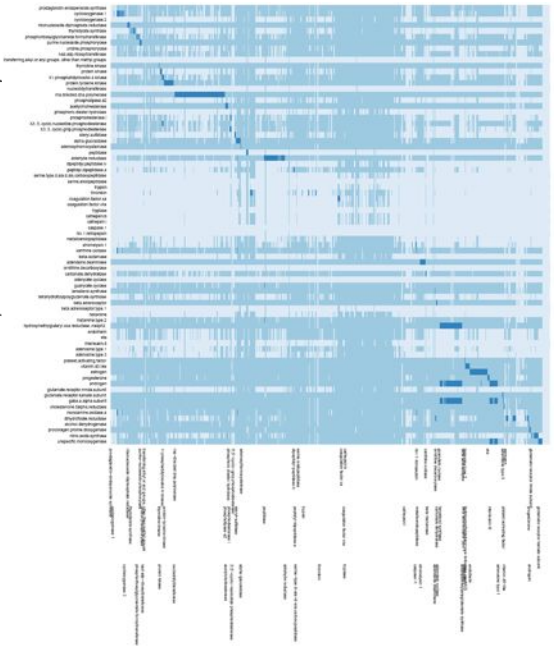
6. Cross interaction matrices



BP - BP



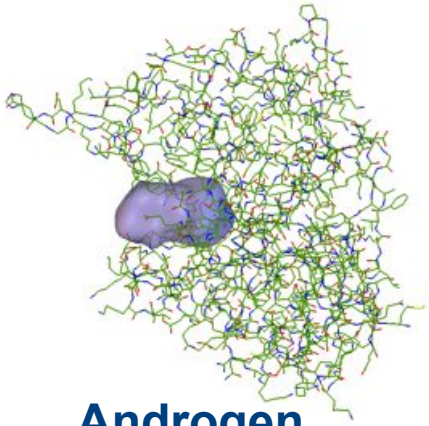
L - L

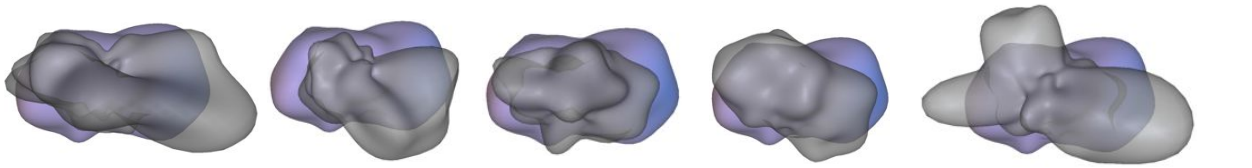


L - BP

Binding Pocket-Binding Pocket interaction matrix

Correlated pockets

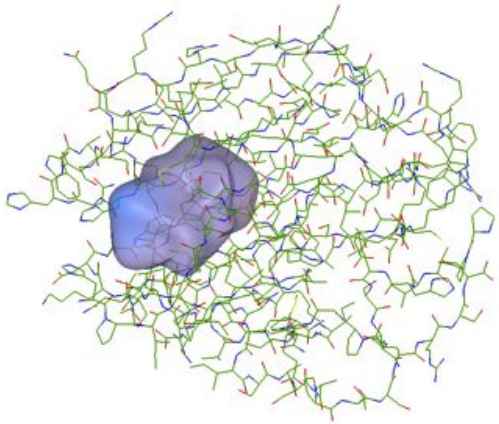


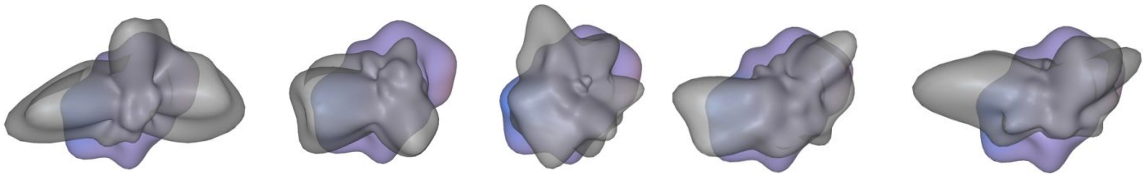


β adrenoreceptor | Purine nucleoside phosphorilase | Thimidine kinase | Hydroxymethyl glutaryl coa reductase | Adenosylhomocysteinase

Androgen

Related activity classes: androgen, aromatase inhibitor, antiandrogen





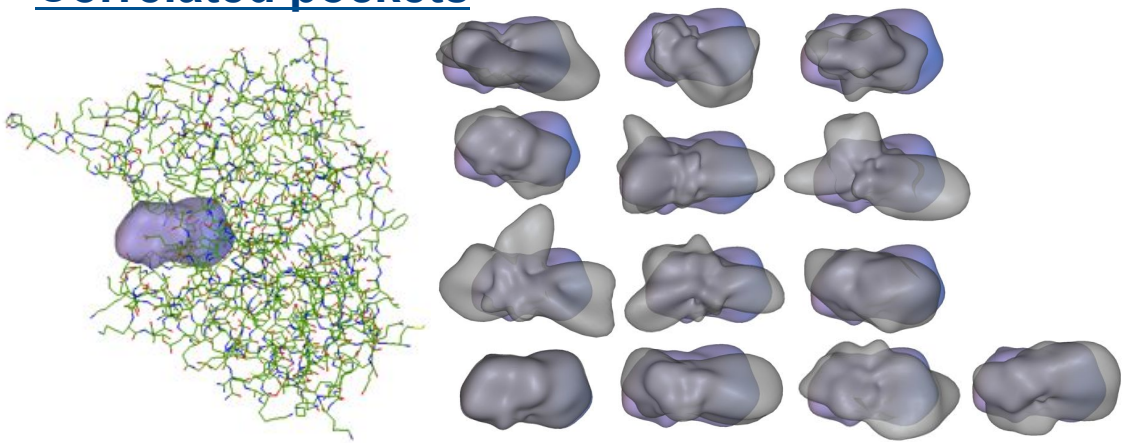
Lanosterol synthase | Purine nucleoside phosphorilase | Thimidine kinase | Cholestenone 5α reductase | Adenosylhomocysteinase

Hydroxymethylglutaryl coa reductase

Related activity classes: hypolipidemic, HMG-CoA Reductase (beta) Inhibitor

Binding Pocket-Binding Pocket interaction matrix

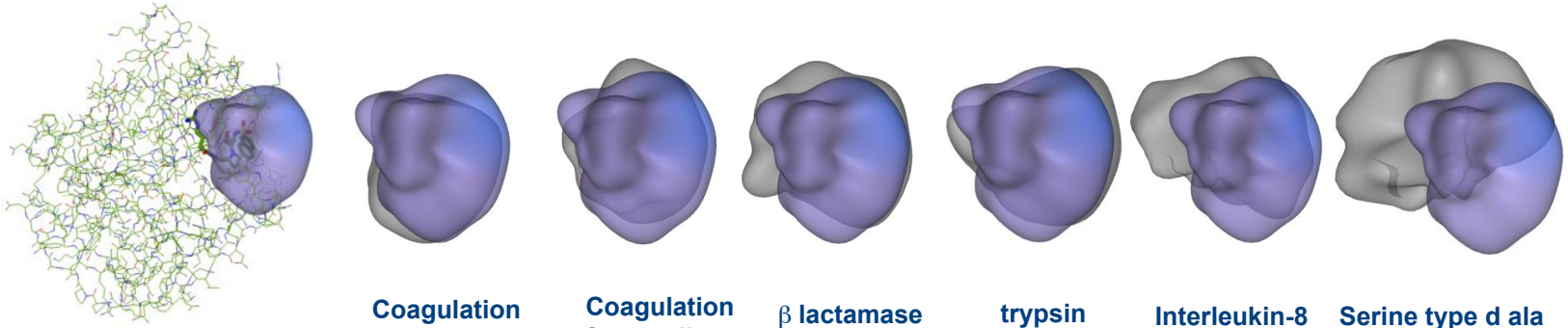
Correlated pockets



β Adrenoreceptor
Purine nucleoside phosphorilase
Thimidine kinase
Hydroxymethylglutaryl coa reductase
Cholestenone 5 alpha reductase
Adenosylhomcysteinase
Lanosterolsynthase
Vitamin 3d like
Estrogen
Androgen
Adenosindeaminase
Acetylcholinesterase
Rna directed dna polymerase

Gaba a alpha subunit

Related activity classes: non opioid analgesic, GABA A/benzodiazepine receptor, sedative/hypnotic, anxiolytic, agent for sleep disorders, benzodiazepine agonist, acohol deterrent, anticonvulsant, agent for premedication, antimigraine, intravenous anesthetic



Coagulation factor xa
Coagulation factor viia
β lactamase
trypsin
Interleukin-8
Serine type d ala carboxypeptidase

Thrombin

Related activity classes: anticoagulant, thrombin inhibitor, Factor Xa Inhibitor, Trypsin inhibitor, protease inhibitor

Binding Pocket-Binding Pocket interaction matrix

Loria | INRIA centre de recherche NANCY - GRAND EST

76 x 76 annotation consensus pockets

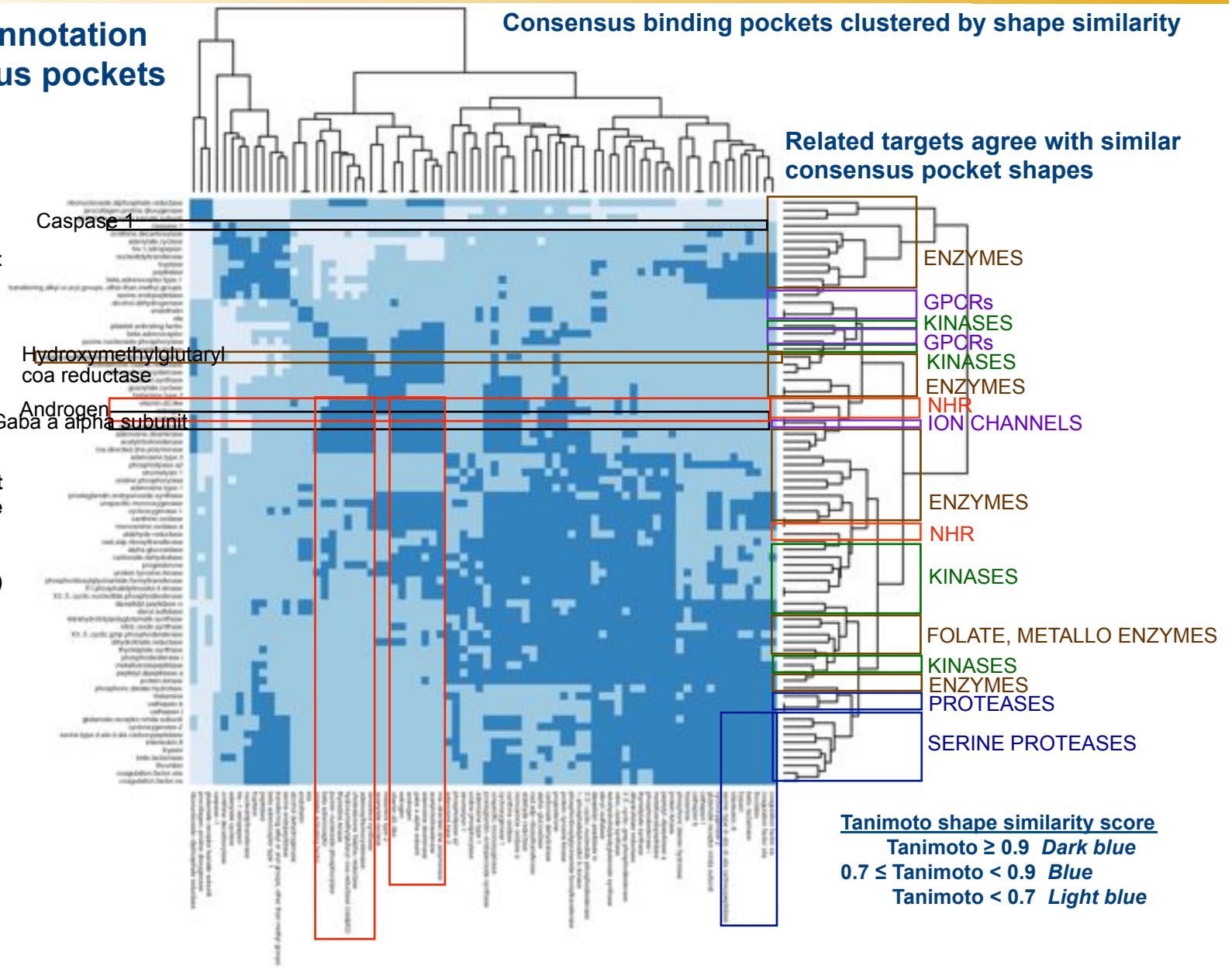
Consensus binding pockets clustered by shape similarity

Related targets agree with similar consensus pocket shapes

Diagonal: every annotation consensus pocket matches with itself.

Very promiscuous targets:
Gaba a alpha subunit
Androgen
Hidroxymethylglutaryl coa reductase

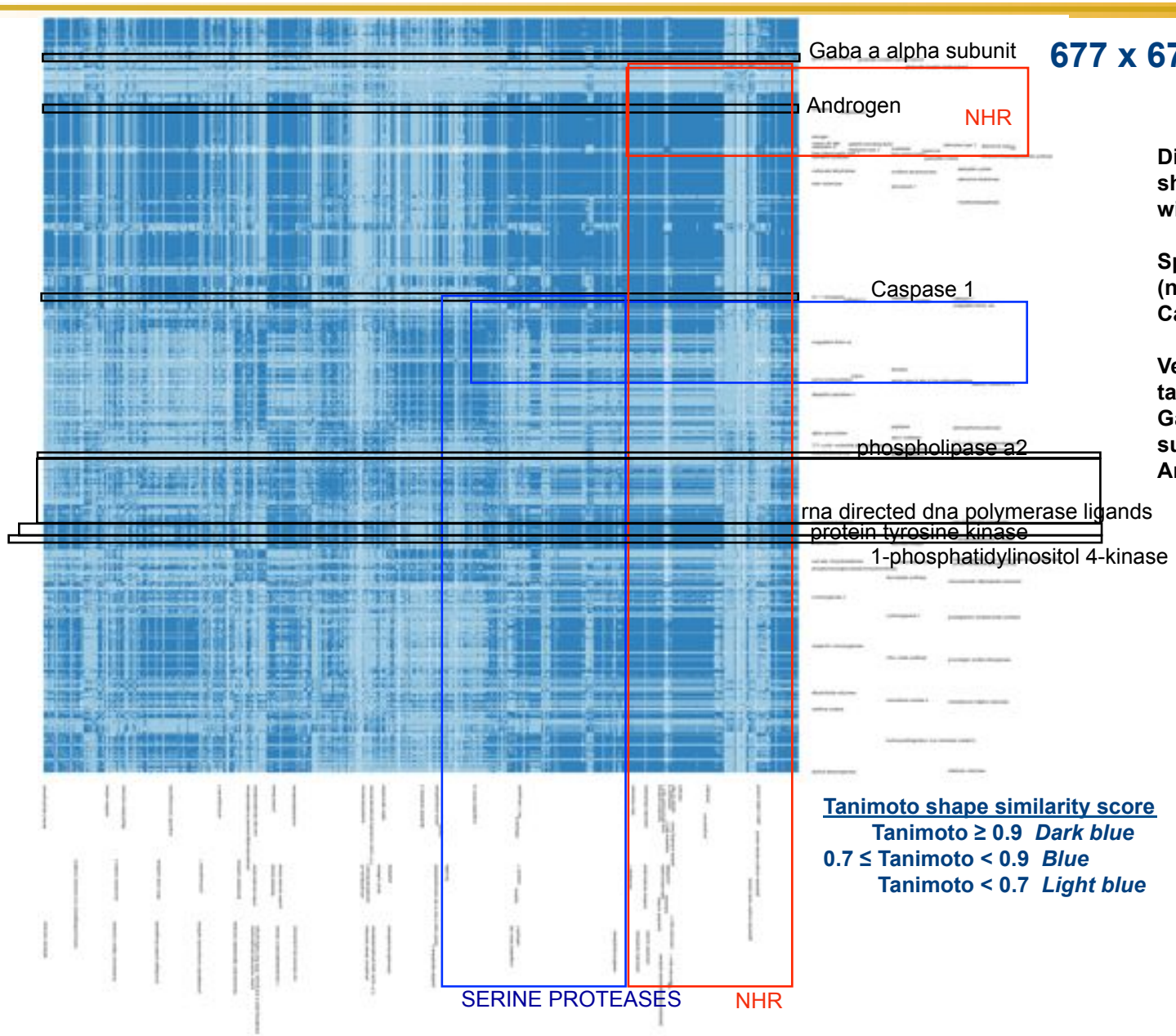
Specific targets (not promiscuous)
Caspase 1



Tanimoto shape similarity score

Tanimoto ≥ 0.9 ***Dark blue***
0.7 ≤ Tanimoto < 0.9 ***Blue***
Tanimoto < 0.7 ***Light blue***

Ligand-Ligand interaction matrix



677 x 677 ligands

Diagonal: ligand shape matches with itself.

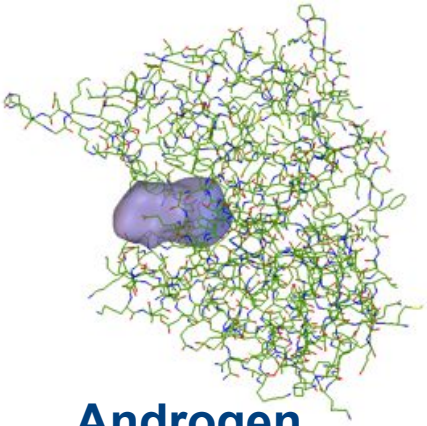
Specific targets (not promiscuous)
Caspase 1

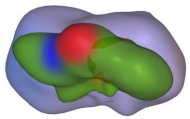
Very promiscuous targets:
Gaba a alpha subunit
Androgen

Tanimoto shape similarity score
Tanimoto ≥ 0.9 ***Dark blue***
0.7 ≤ Tanimoto < 0.9 ***Blue***
Tanimoto < 0.7 ***Light blue***

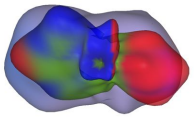
Binding Pocket-Ligand interaction matrix

Correlated pocket and ligand shapes

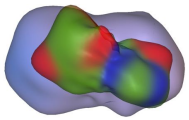




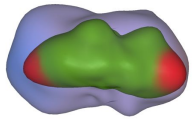
β adrenoreceptor



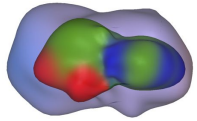
Purine nucleoside phosphorilase



Thimidine kinase



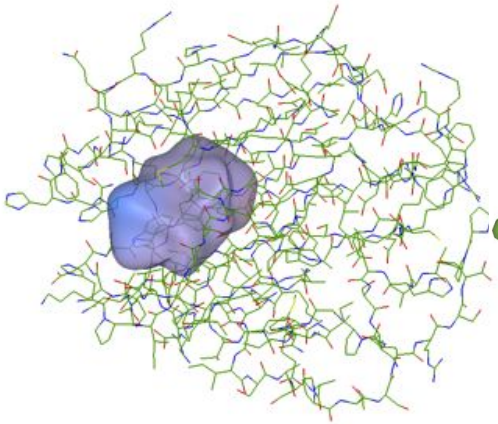
Hydroxymethyl glutaryl coa reductase

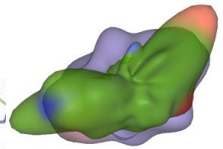


Adenosylhomocysteinase

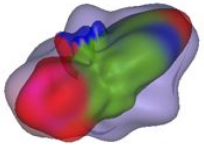
Androgen

Related activity classes: androgen, aromatase inhibitor, antiandrogen

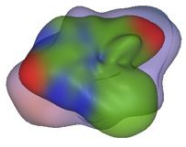




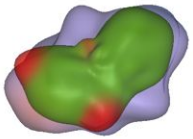
Lanosterol synthase



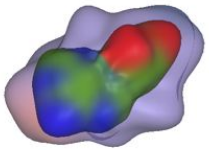
Purine nucleoside phosphorilase



Thimidine kinase



Cholestenone 5α reductase



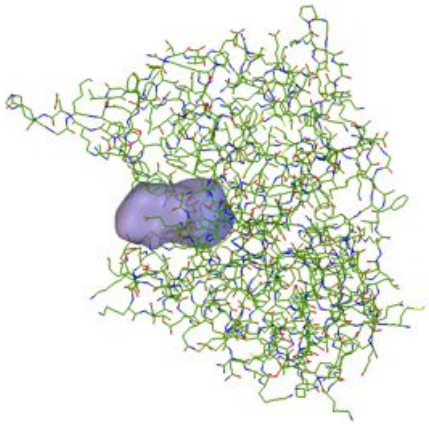
Adenosylhomocysteinase

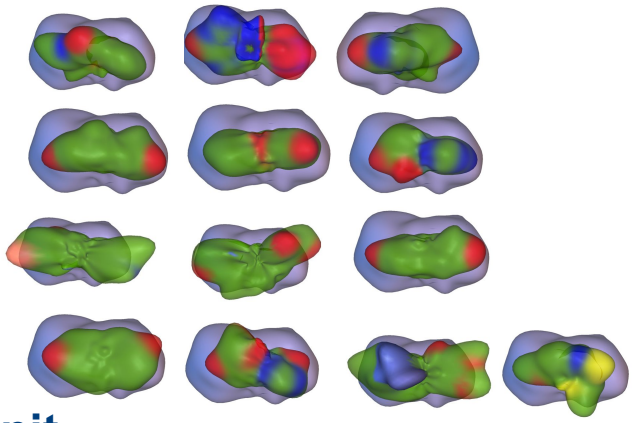
Hydroxymethylglutaryl coa reductase

Related activity classes: hypolipidemic, HMG-CoA Reductase (beta) Inhibitor

Binding Pocket-Ligand interaction matrix

Correlated pocket and ligand shapes

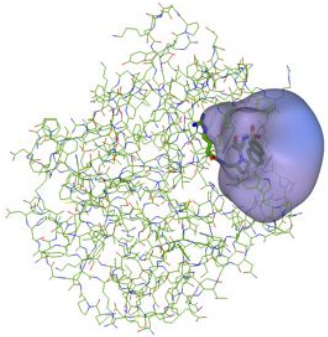


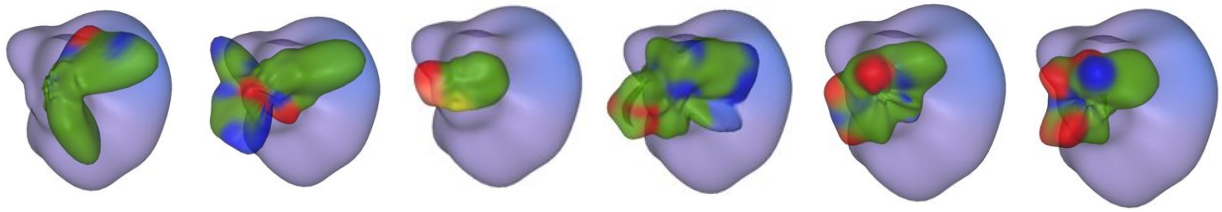


β Adrenoreceptor
Purine nucleoside phosphorilase
Thimidine kinase
Hydroxymethylglutaryl coa reductase
Cholestenone 5 alpha reductase
Adenosylhomcysteinase
Lanosterolsynthase
Vitamin 3d like
Estrogen
Androgen
Adenosindeaminase
Acetylcholinesterase
Rna directed dna polymerase

Gaba a alpha subunit

Related activity classes: non opioid analgesic, GABA A/benzodiazepine receptor, sedative/hypnotic, anxiolytic, agent for sleep disorders, benzodiazepine agonist, acohol deterrent, anticonvulsant, agent for premedication, antimigraine, intravenous anesthetic





Coagulation factor xa
Coagulation factor viia
β lactamase
trypsin
Interleukin-8
Serine type d ala carboxypeptidase

Thrombin

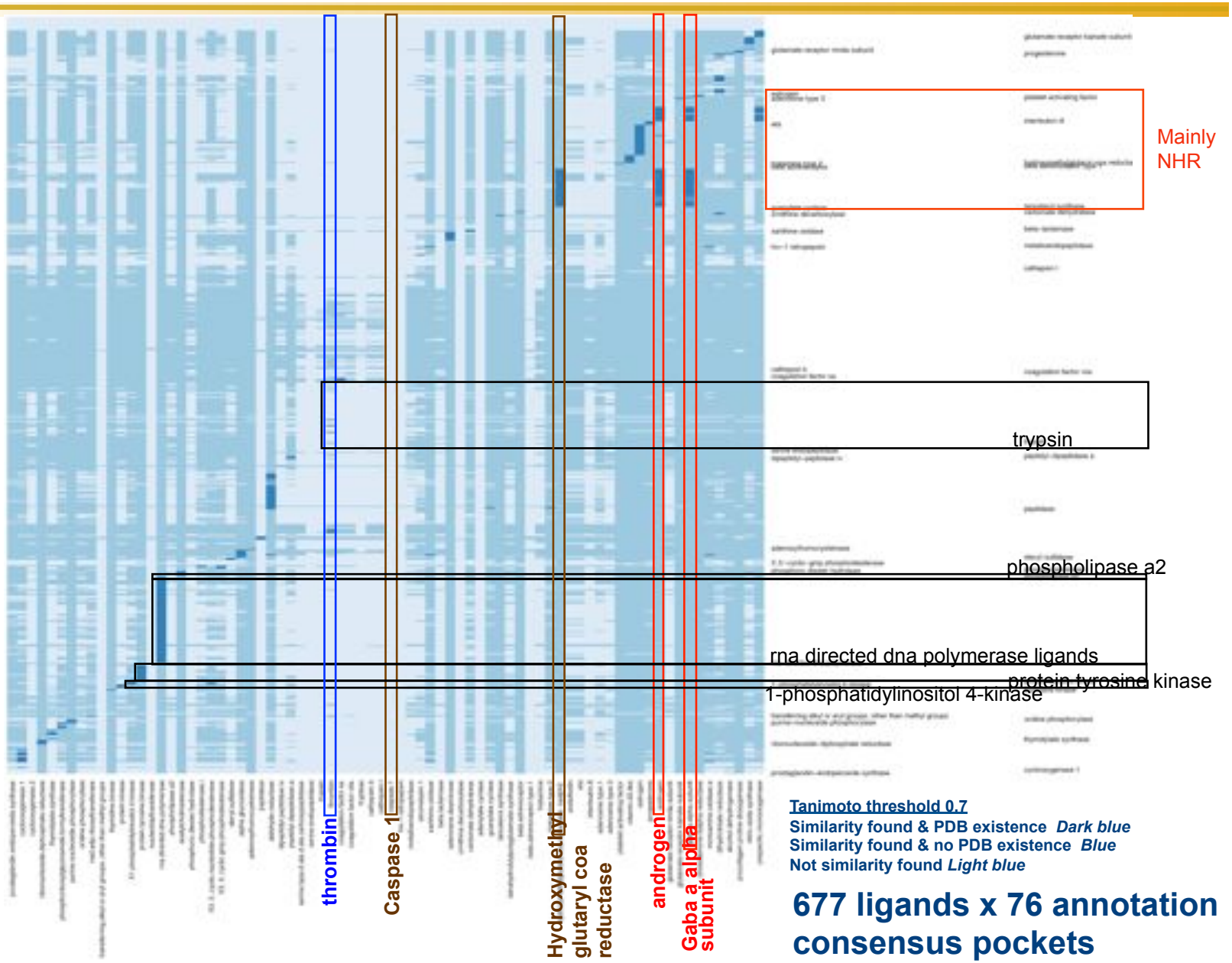
Related activity classes: anticoagulant, thrombin inhibitor, Factor Xa Inhibitor, Trypsin inhibitor, protease inhibitor

Ligand-Binding Pocket interaction matrix

Diagonal: every annotation consensus pocket matches with the ligands related to the annotation

Very promiscuous targets:
Gaba a alpha subunit
Androgen

Specific targets (not promiscuous)
Caspase 1



Tanimoto threshold 0.7
Similarity found & PDB existence *Dark blue*
Similarity found & no PDB existence *Blue*
Not similarity found *Light blue*

677 ligands x 76 annotation consensus pockets

In silico vs *in vitro* interaction matrices

Available biological activities have been compiled from *Binding DB* database for the compounds in Schuffenhauer MDDR subset used for the analysis. The *in silico* vs *in vitro* interaction matrices are compared

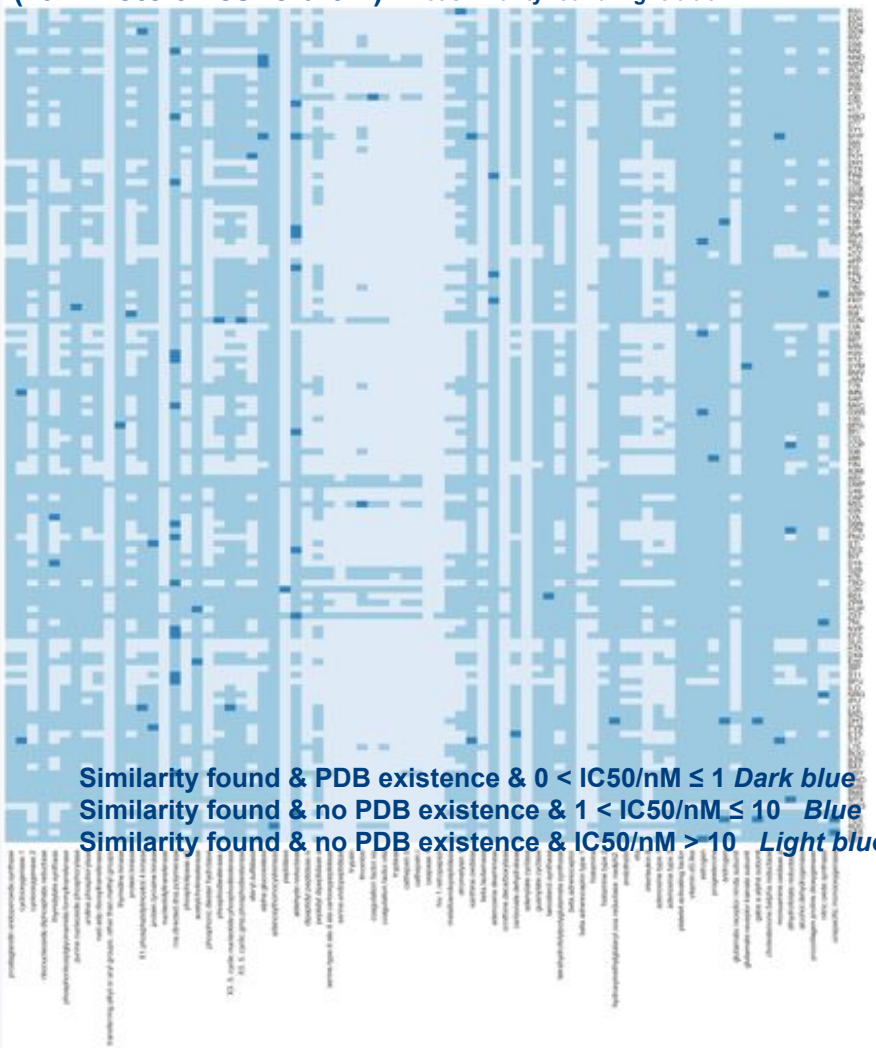
In silico
(Tanimoto threshold 0.7)

Similarity found & PDB existence *Dark blue*
Similarity found & no PDB existence *Blue*
Not similarity found *Light blue*

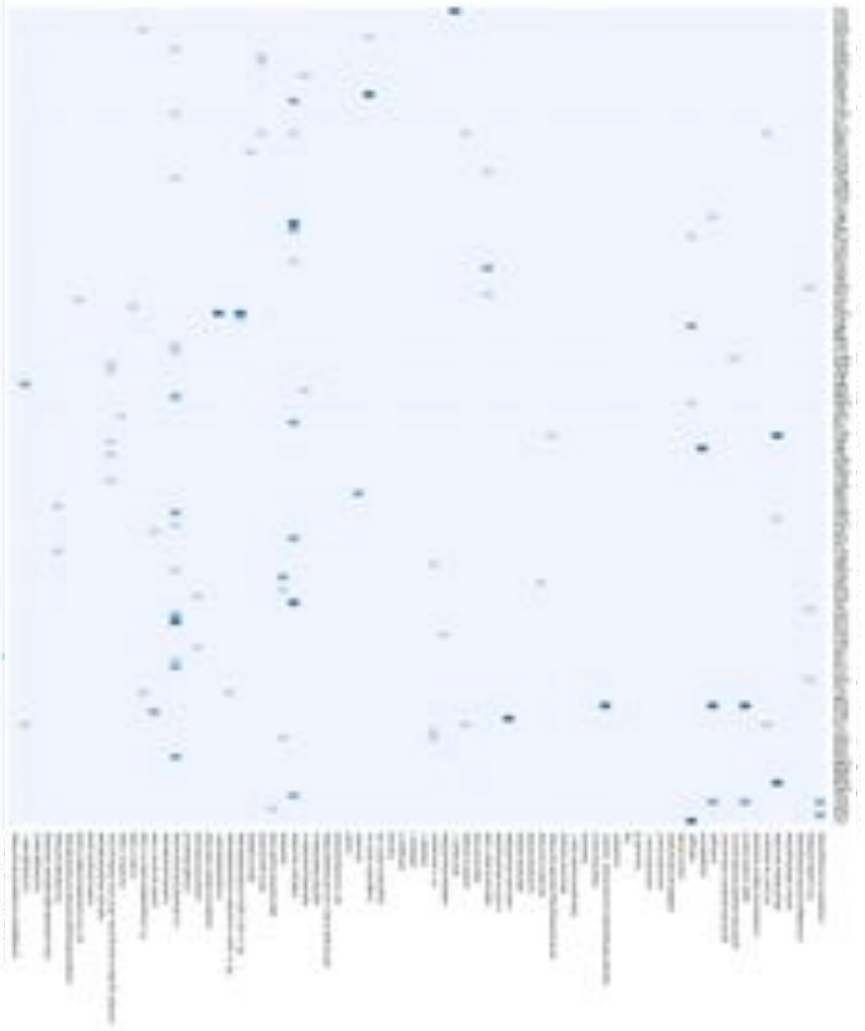
***In vitro* vs *in silico* matches**

***In vitro* (IC50/nM)**

0 < IC50/nM ≤ 1 *Dark blue*
1 < IC50/nM ≤ 10 *Blue*
IC50/nM > 10 *Light blue*



Similarity found & PDB existence & 0 < IC50/nM ≤ 1 *Dark blue*
Similarity found & no PDB existence & 1 < IC50/nM ≤ 10 *Blue*
Similarity found & no PDB existence & IC50/nM > 10 *Light blue*



Conclusions

- Our 3D shape-based approach relates receptors to each other based on the SH similarity of their ligands and their binding pockets.
- Ligand and binding pocket shapes similarity matrices return nearly the same information.
- Ligand vs consensus pockets interaction matrix agree with the existence of PDBs for promiscuous ligands/targets.
- In silico polypharmacology results follow a similar trend than experimental results.
- Future work: statistical analyses (E value) of the ligand and pocket shape similarity matrices for promiscuity predictions.

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Papers: http://www.loria.fr/~pereznue/
http://www.loria.fr/~ritchied/

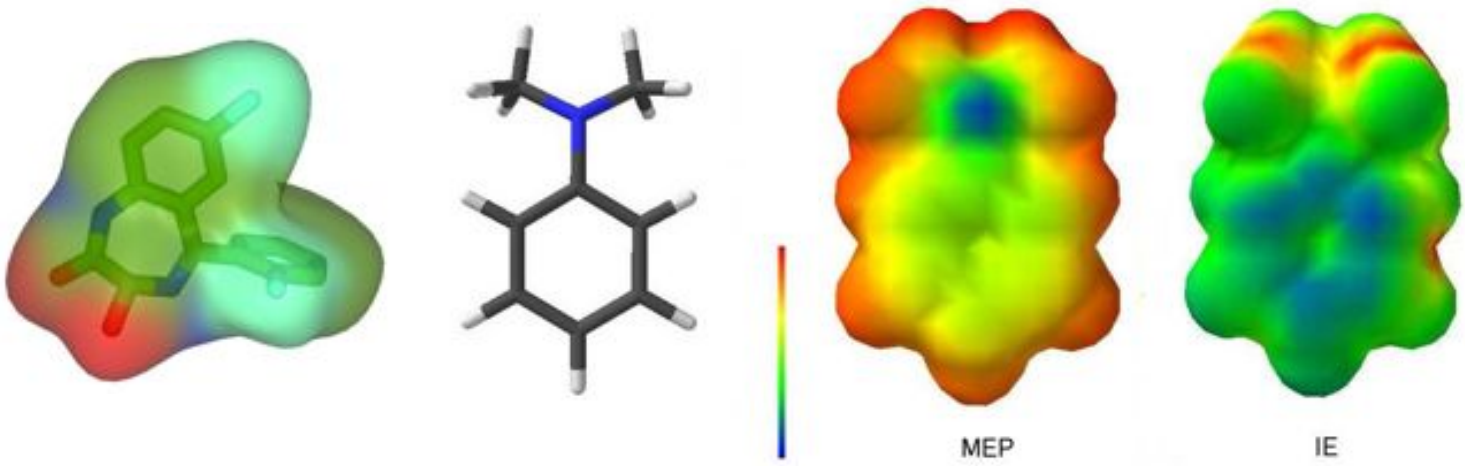
ParaSurf + ParaFit: http://www.ceposinsilico.de/

Thank you!

ParaSurf

Shapes/Properties From Semi-Empirical QM

- From MOPAC or VAMP, calculate:
  - Density contours of 2x10-4e/A3 (i.e. approx = SAS)
  - MEP – electrostatic potential
  - IEL – ionization energy
  - EAL – electron affinity
  - aL – polarizability
- Encode as Spherical Harmonic expansions to order L=15…



Lin, J.-H. and Clark, T. J. *Chem. Inf. Model.* **2005**, 45, 1010–1016.