DOCK: where it is and where its going

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Tuesday, June 20th 12:00pm EDT

Upcoming Webinars:
July 25th: BioXTAS RAW with Jesse Hopkins
October 3rd: SPHIRE with Toshio Moriya
November 4th: EMAN2 with Steven Ludtke

SBGrid CONSORTIUM

Events are posted on SBGrid Google Calendar (to join visit http://sbgrid.org/calendar)

Systems Check

Outline

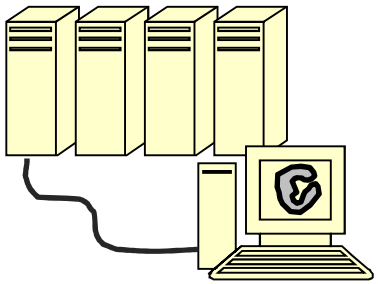
- Introduction to docking and DOCK
- DOCK 3.7
  - Resources
  - How DOCK 3.7 works
  - Tutorial on how to run it
  - Features
- DOCK 6.8
  - Resources
  - Anchor-&-grow algorithm (how DOCK 6.8 works)
  - Many scoring functions
  - Features

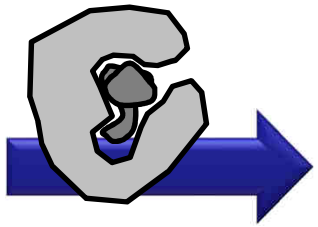
Docking is Ligand Discovery Tool

ZINC

~4M molecules

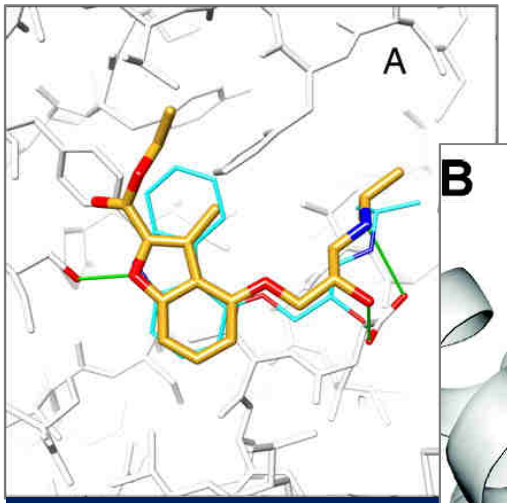
DOCK



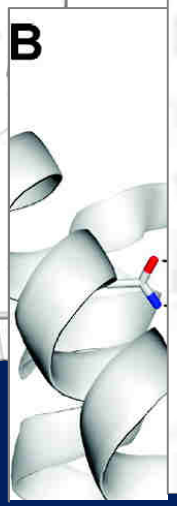


best

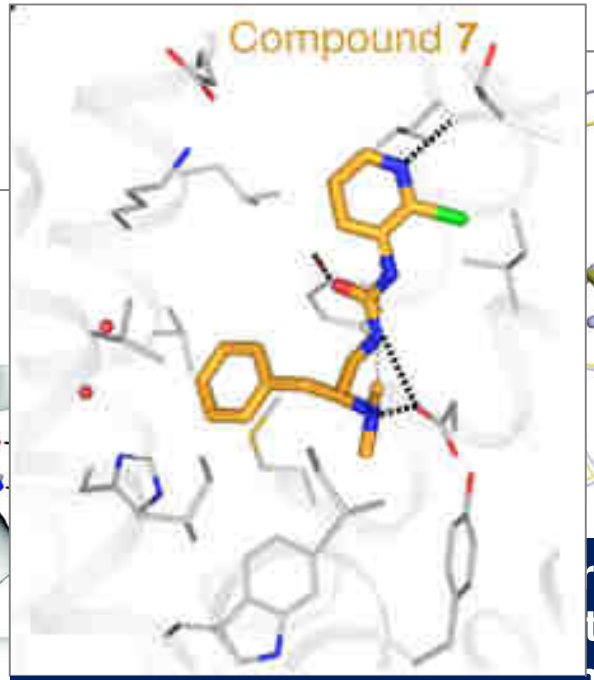
worst



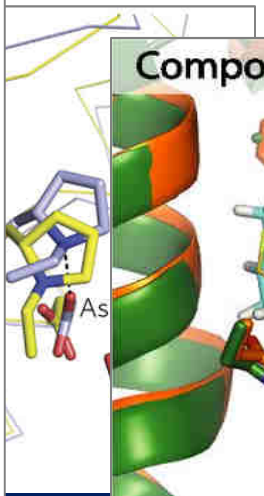
β2-adrenergic receptor
24% hit rate; 9 nM
Kolb, *PNAS* 2009



A_{2A} ade
35% h
Carlssor



μ-Opioid receptor
30% hit rate; 2.3μM
Manglik et al., Nature 2016



recep
te; 30
nodel
200nl
m Biol

M2/M3 muscarinic receptor
58% hit rate; 400 nM
Kruse, *Mol Pharm* 2013

Why use Dock?

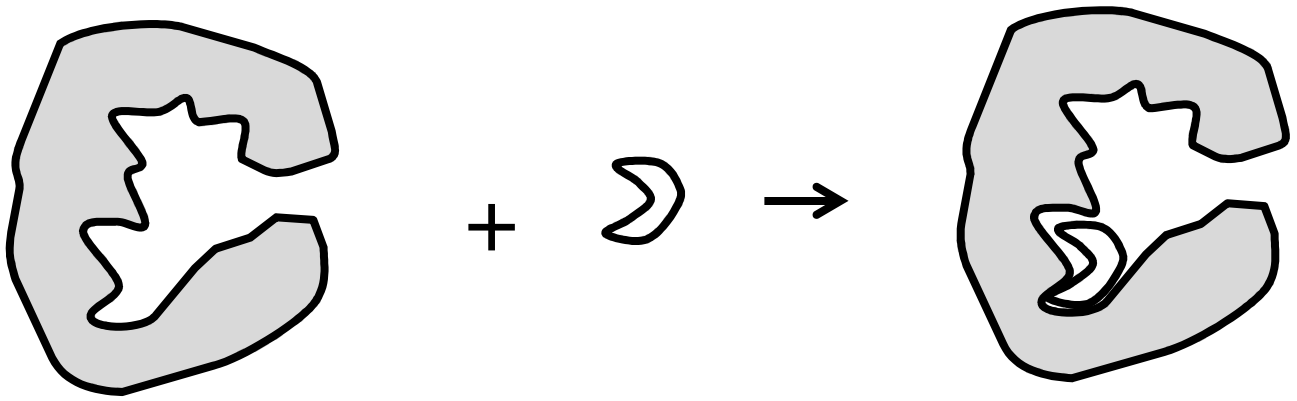
Applications of docking

- Virtual Screening given a protein and database of molecules find those that bind.
- Give a molecule and a protein predict how that molecule binds to the receptor

Docking Tasks

- Sampling
  - Generate all possibilities including the correct geometry
- Scoring
  - Rank order all the possibilities, rank the correct pose first
  - Rank the binders better than decoys
- Balance of speed and accuracy, docking has to be fast.

DOCK 3.7 is among the fastest docking programs

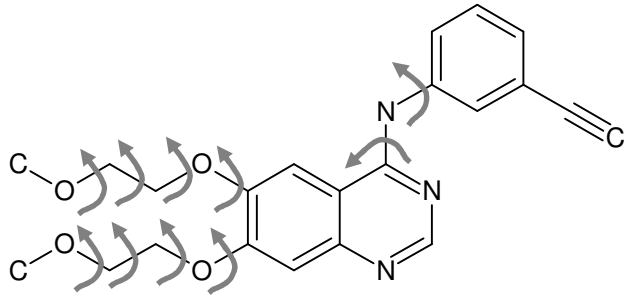


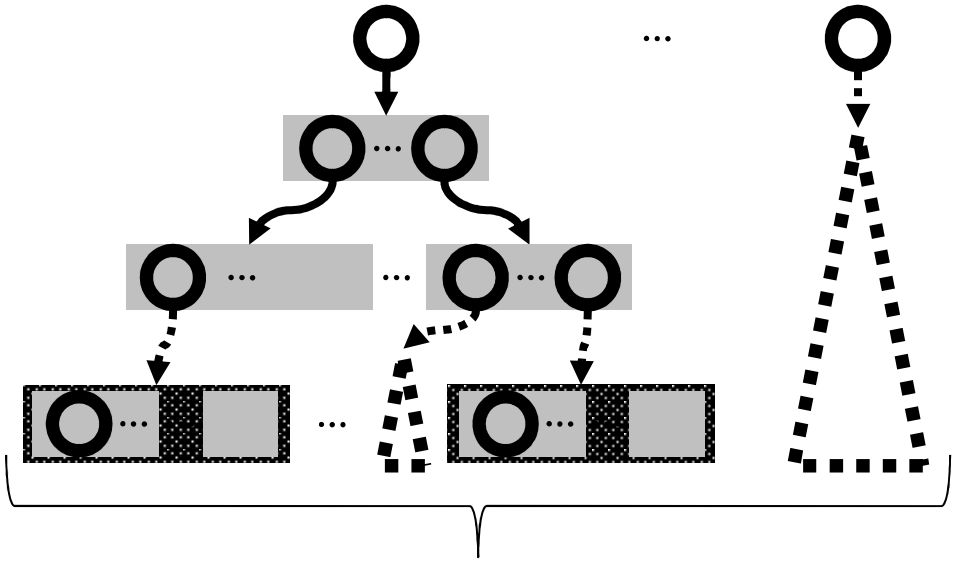
How to use DOCK 3.7

How DOCK 3.7 works

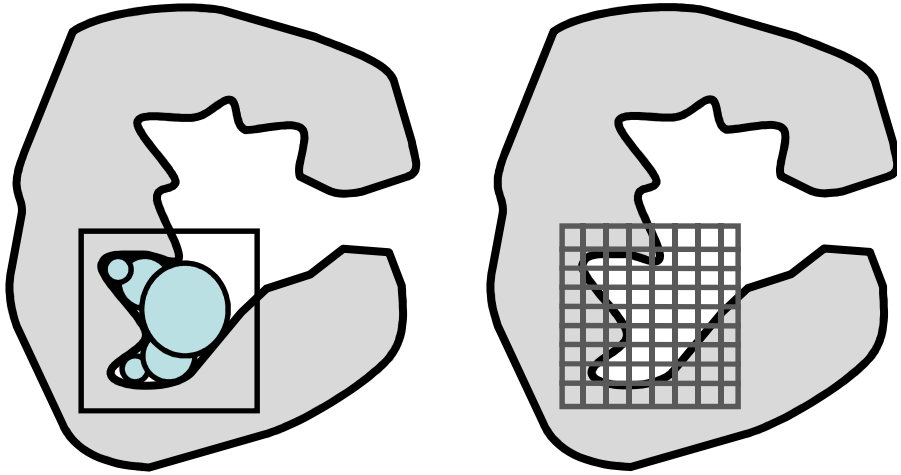
Preparation, Sampling, and Scoring

Ligand Sampling done outside of
DOCK 3.7 – database construction





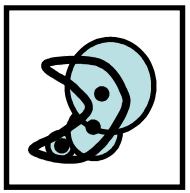
Dockable database file

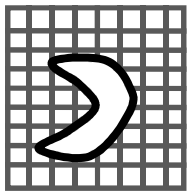


DOCKING

orient

score





Scoring using a grid to speed up
the calculations

DOCK 3.7 Scoring Function

$$E_{score} = E_{VDW} + E_{ES} + E_{lig,desol}$$

- VDW term is based on the AMBER united-atom force field
- Electrostatics term
  - PB calculation using DELPHI or QNIFFT
  - Binding site has low dielectric by including spheres.
- Ligand Desolvation
  - desolvation grid value times by the polar and nonpolar terms in ligand file
  - General Born approximation
- What's Missing ?

Meng, et al J. Comput. Chem. 1992, 13, 505– 524
Mysinger and Shoichet J Chem Inf Model. 2010, 50(9):1561-73

Resources for DOCK 3.7

- BKS lab wiki: http://wiki.bkslab.org/index.php/DOCK_3.7

- DOCK-fans email archive (list to search for solutions to problems or submit questions): http://mailman.docking.org/pipermail/dock-fans/

- Database of small molecules:

  http://zinc15.docking.org/

- DUD-E databases and decoy generator

  http://dude.docking.org/

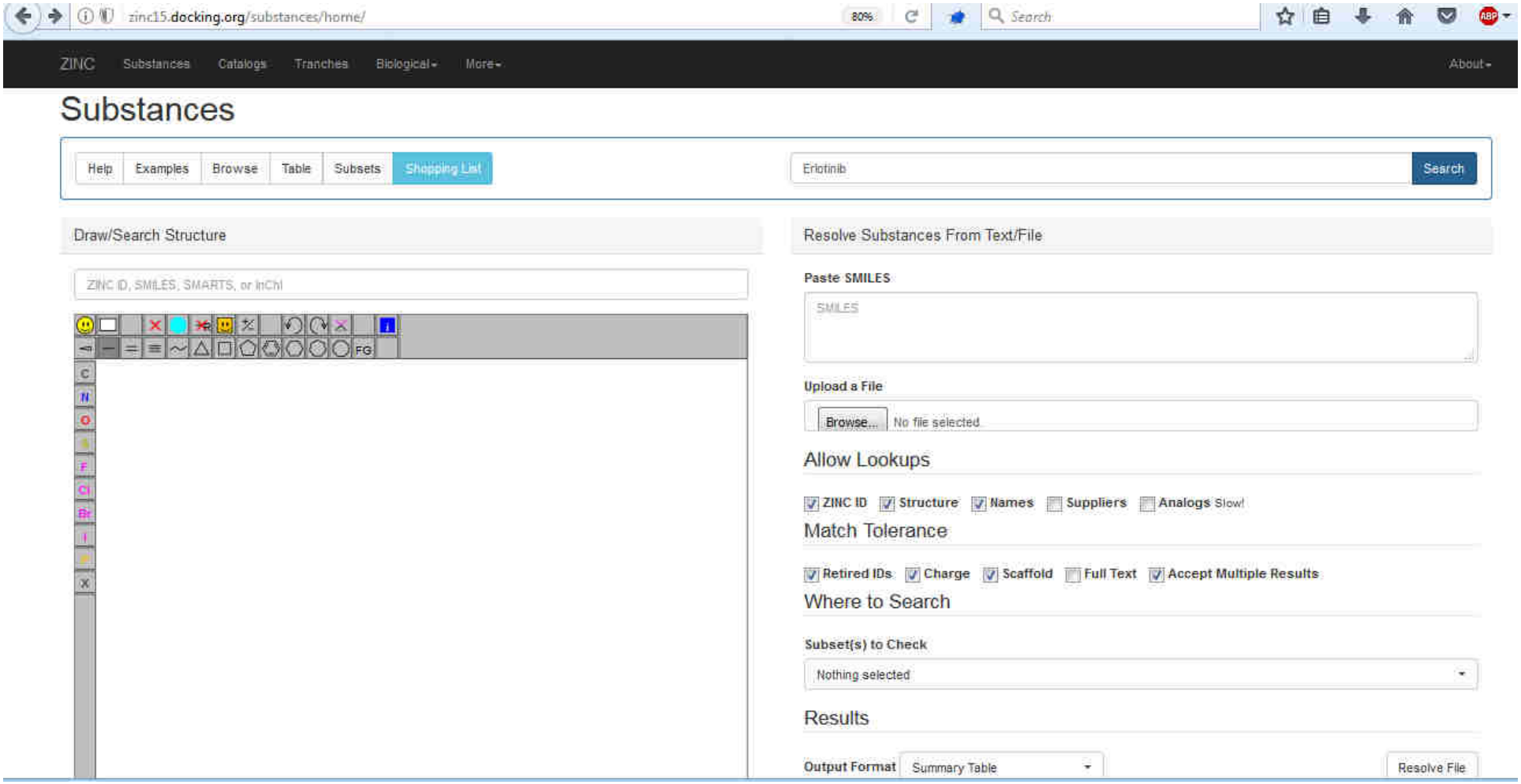
  http://dude.docking.org/generate

  http://autodude.docking.org/

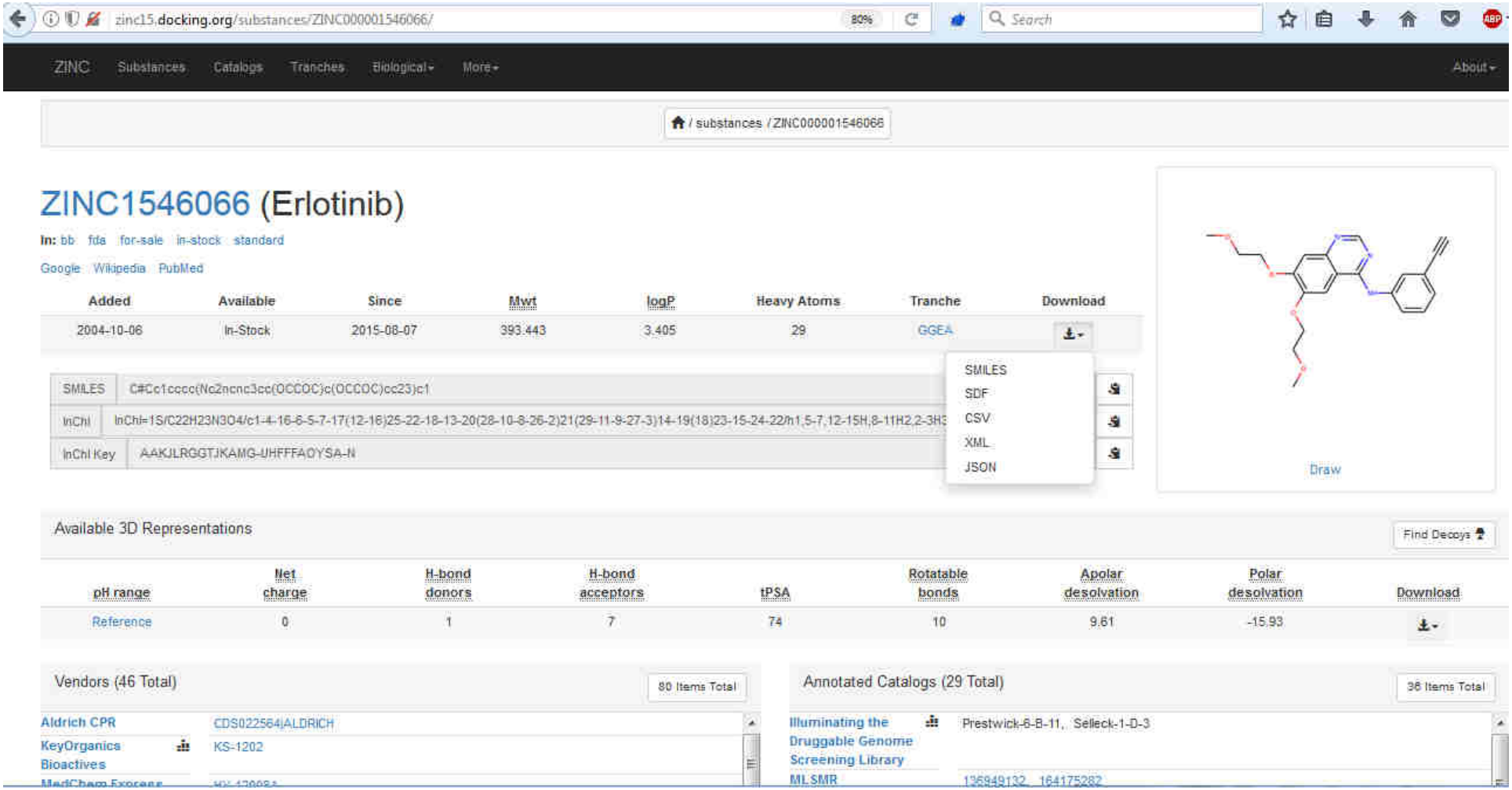
Tutorial

Scenario 1:
Use docking to predicted how Erlotinib (an approved drug) binds to the Epidermal Growth Factor Receptor

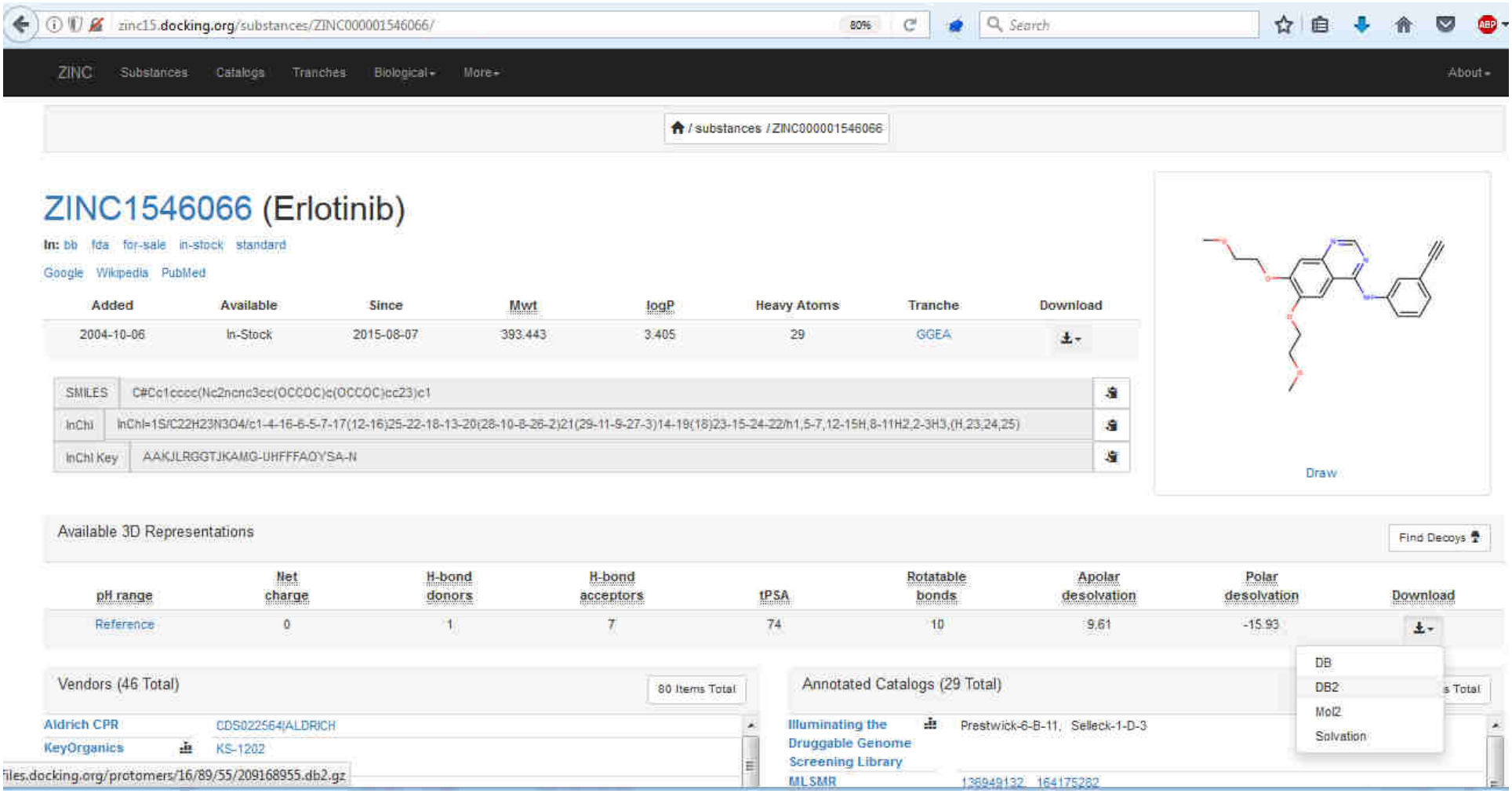
Search for Your Molecule in ZINC



Get 2D Files from ZINC



Get Files for Docking from ZINC




```
wget http://files.docking.org/protomers/16/89/55/209168955.db2.gz

ls /path/tutorial_for_webinar/dock3.7/209168955.db2.gz > ligands.sdi
```

Get Files Needed for Docking

Get the link from the zinc webpage and us wget to download:

```
wget http://files.docking.org/protomers/16/89/55/209168955.db2.gz
```

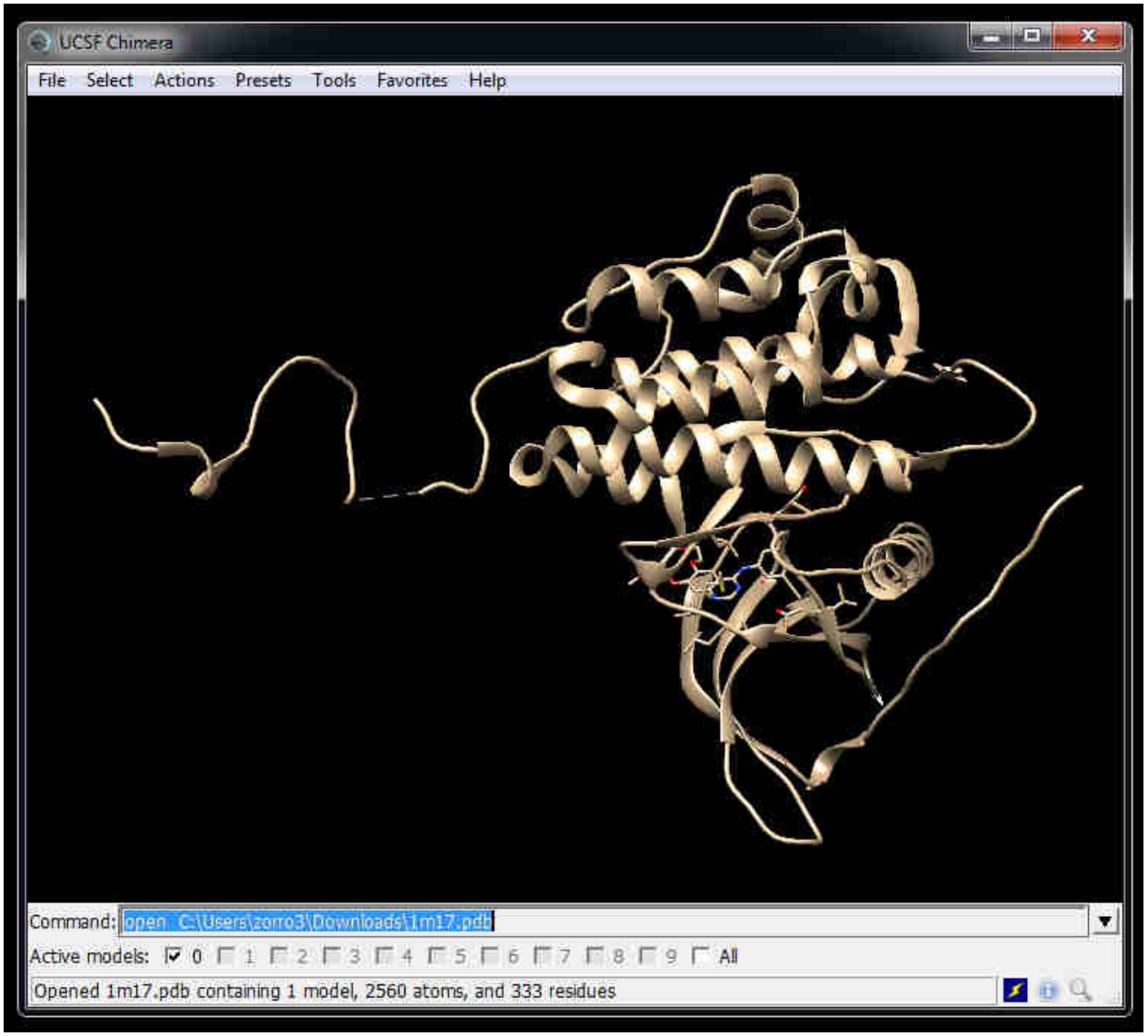
Put the path of the downloaded database into the split database index file (this file usually contain many db2 file):

```
ls /path/tutorial_for_webinar/dock3.7/209168955.db2.gz > ligands.sdi
```

Get the receptor structure from the PDB website

```
wget https://files.rcsb.org/download/1M17.pdb --no-check-certificate
```

Break Xtal into Receptor and Ligand Files



You may use a program like Chimera for this

Receptor file must be called: rec.pdb

Ligand file: xtal-lig.pdb

What if the crystal does not have a ligand:

Place atoms in the site were you want to dock. One way is to run sphgen and selecting spheres near residues in the site convert to pdb

Prepare Receptor for Docking

Make the recptor file (remove alternative side chains):

```
grep "^ATOM" 1M17.pdb | grep -v ^................B > rec.pdb
```

Make ligand file:

```
grep AQ4 1M17.pdb | sed -e 's/HETATM/ATOM  /g' > xtal-lig.pdb
```

Run blastermaster: input rec.pdb, xtal-lig.pdb and makes all receptor file need for docking.

```
python $DOCKBASE/proteins/blastermaster/blastermaster.py --addhOptions="
-HIS -FLIPs "  -v
```

This command may take several minutes to run.

Prepare Receptor for Docking Output

-rw-r--r--. 1 tbalius bks 3163 Jun 17 12:27 INDOCK

dockfiles/:
total 30388
-rw-r--r--. 1 tbalius bks 1206051 Jun 17 12:27 ligand.desolv.heavy
-rw-r--r--. 1 tbalius bks 1206051 Jun 17 12:27 ligand.desolv.hydrogen
-rw-r--r--. 1 tbalius bks   3376 Jun 17 12:27 matching_spheres.sph
-rw-r--r--. 1 tbalius bks   908086 Jun 17 12:27 trim.electrostatics.phi
-rw-r--r--. 1 tbalius bks 3121095 Jun 17 12:27 vdw.bmp
-rw-r--r--. 1 tbalius bks   1653 Jun 17 12:27 vdw.parms.amb.mindock
-rw-r--r--. 1 tbalius bks 24660016 Jun 17 12:27 vdw.vdw

Modifying INDOCK File

```
match_goal                      5000
```

How much orienting to do
Reduce 1000 if docking takes to long

```
number_save                     1
number_write                    1
```

Number of poses to write out
Consider writing out 100

```
#                       MINIMIZATION
minimize                        no
sim_itmax                       500
sim_trnstep                     0.2
sim_rotstep                     5.0
sim_need_to_restart             1.0
sim_cnvrge                      0.1
min_cut                         1.0e15
iseed                           777
```

Minimize the 6 degrees for the poses written out (3 rotation, 3 translation)
All molecules written out will be minimized

Run Docking Calculations

Make perpare docking directories.

```
 $DOCKBASE/docking/setup/setup_db2_zinc15_file_number.py ./ ligand
ligand.sdi 500 count
```

Submit jobs to queue (we use SGE queuing system):

```
$DOCKBASE/docking/submit/submit.csh
```

To analyze the results we need to combine the results and then get poses

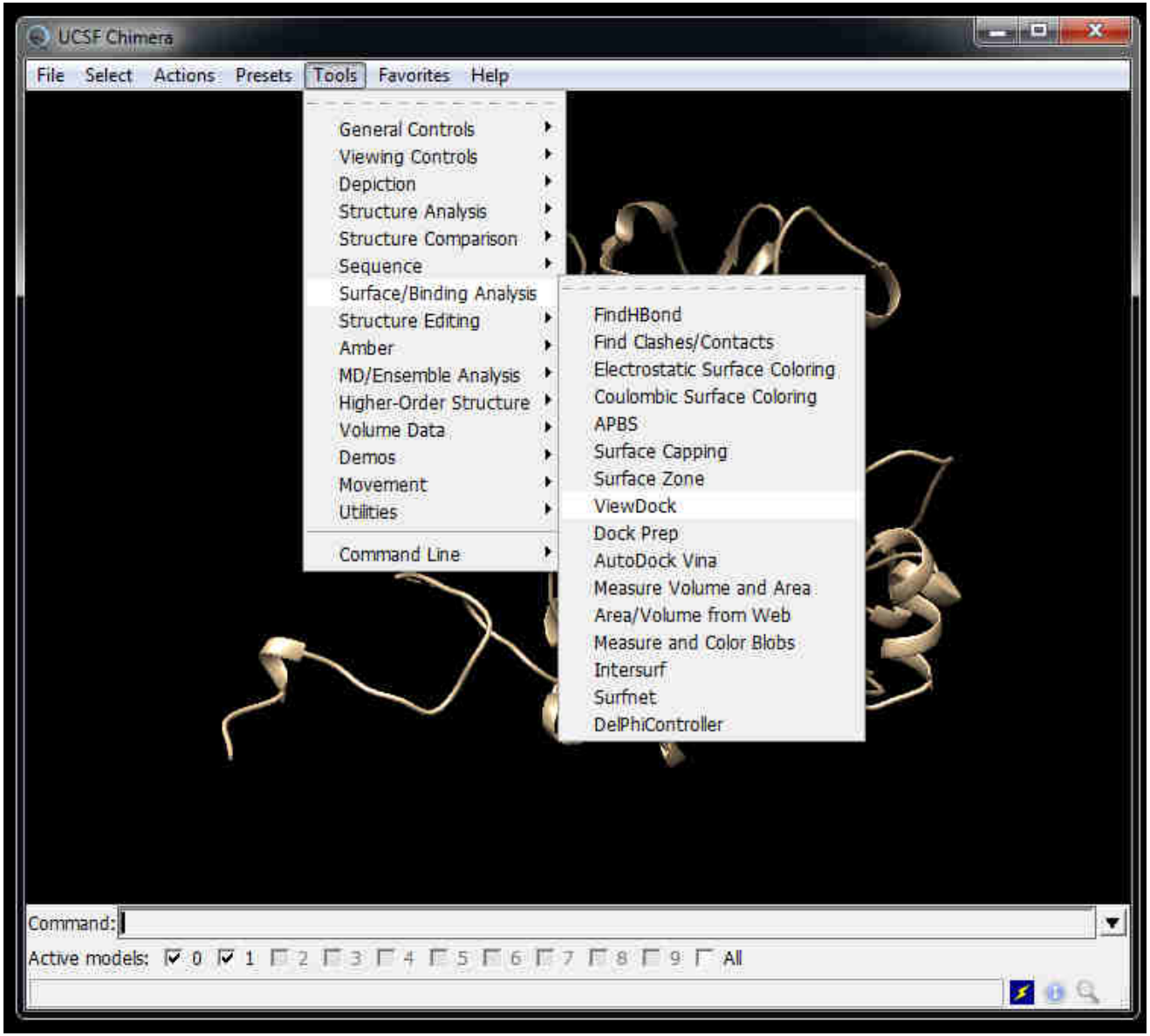
```
$DOCKBASE/analysis/extract_all.py
$DOCKBASE/analysis/getposes.py
```

It is also possible to run dock locally:

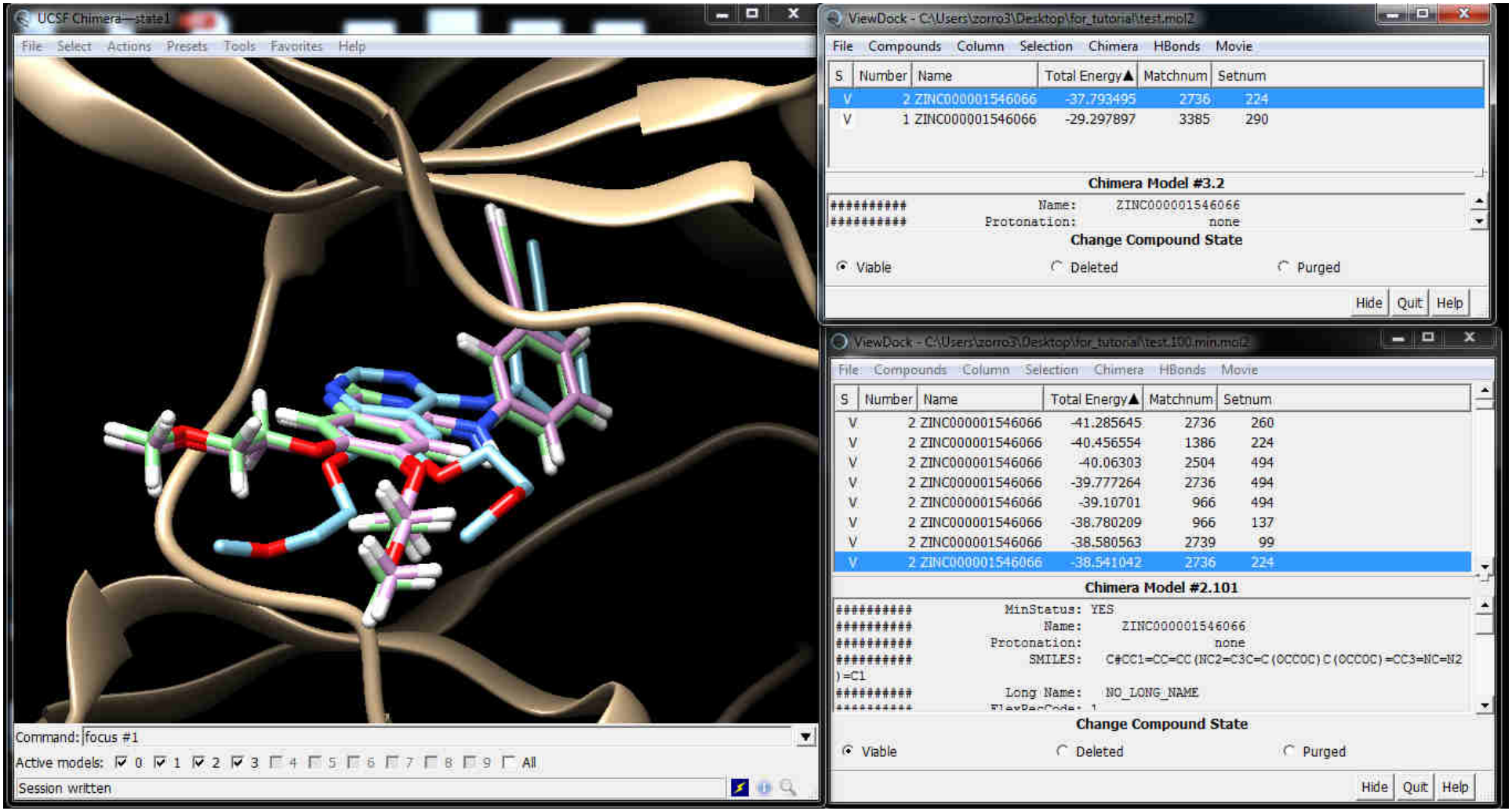
```
$DOCKBASE/docking/DOCK/bin/dock64
```

Output: OUTDOCK and test.mol2.gz

Visualize poses in Chimera with Viewdock

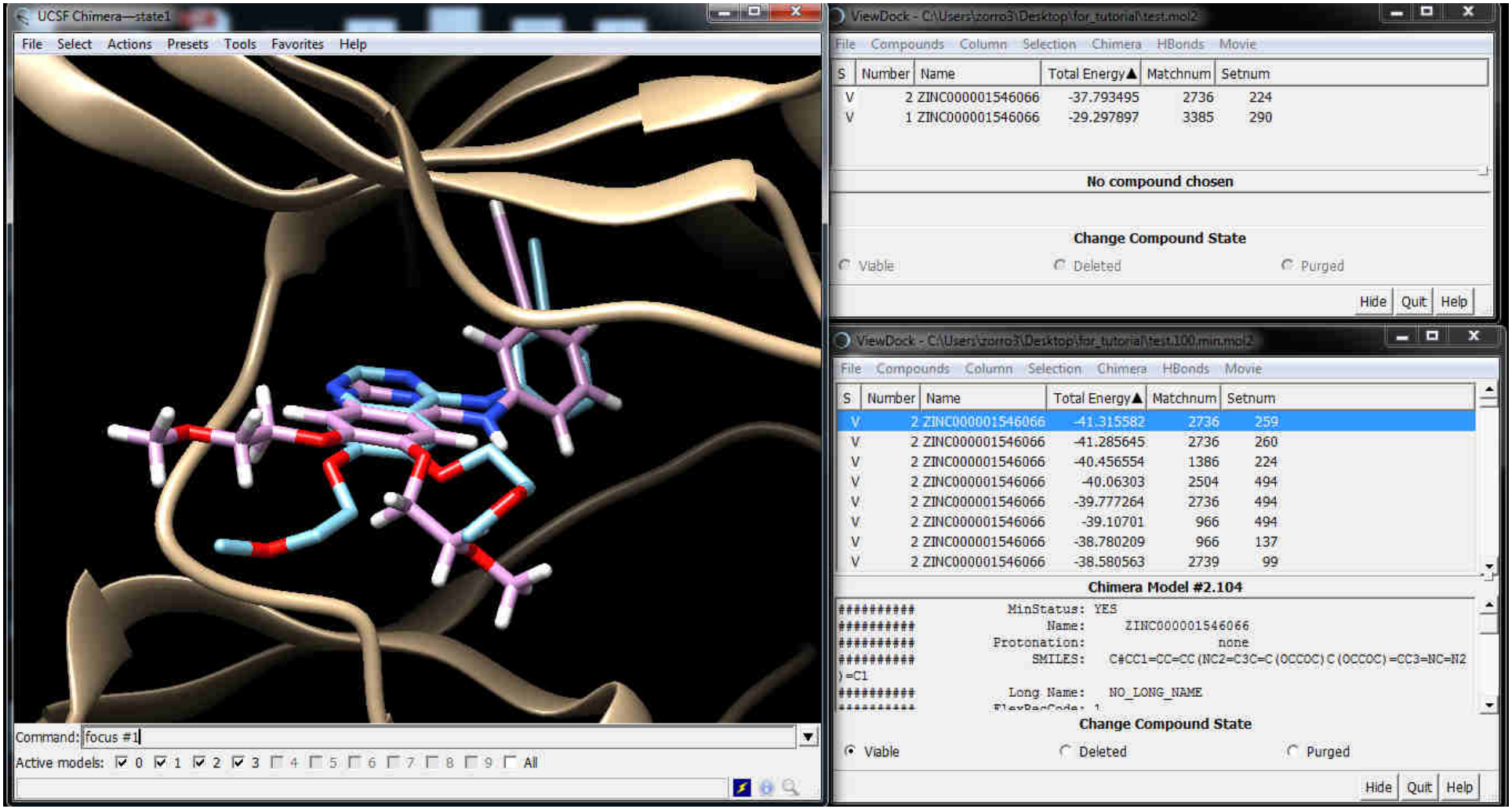


Visualize Poses in Chimera with Viewdock



Pose with and without minimization: Energy -37.79 -> -38.54

Visualize Poses in Chimera with Viewdock

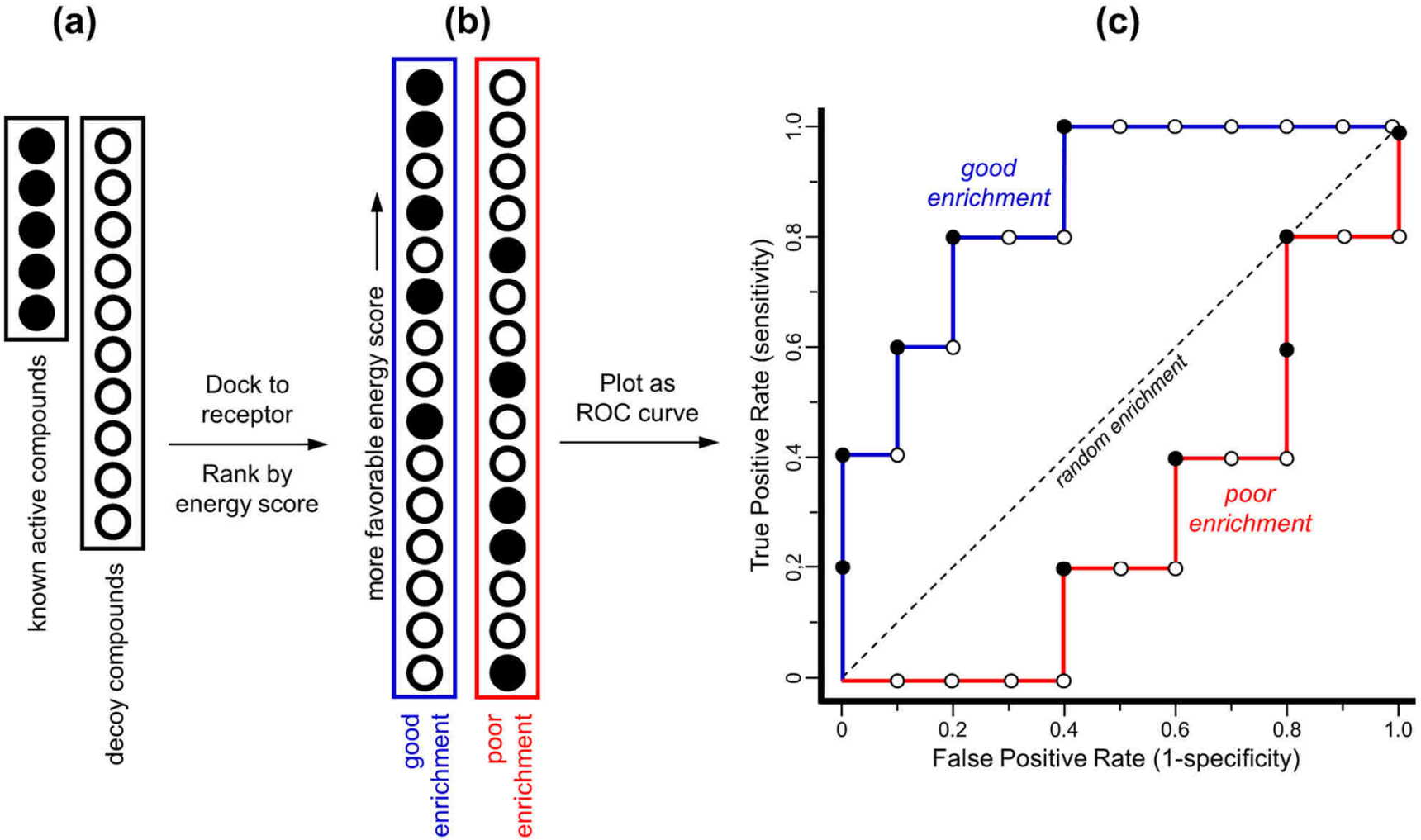


Best pose out of the top 100 after min: Energy -41.31

Tutorial

Scenario 2:
Use docking to test enrichment capabilities of Epidermal Growth Factor Receptor using 12 ligands and DUD-E property matched decoys

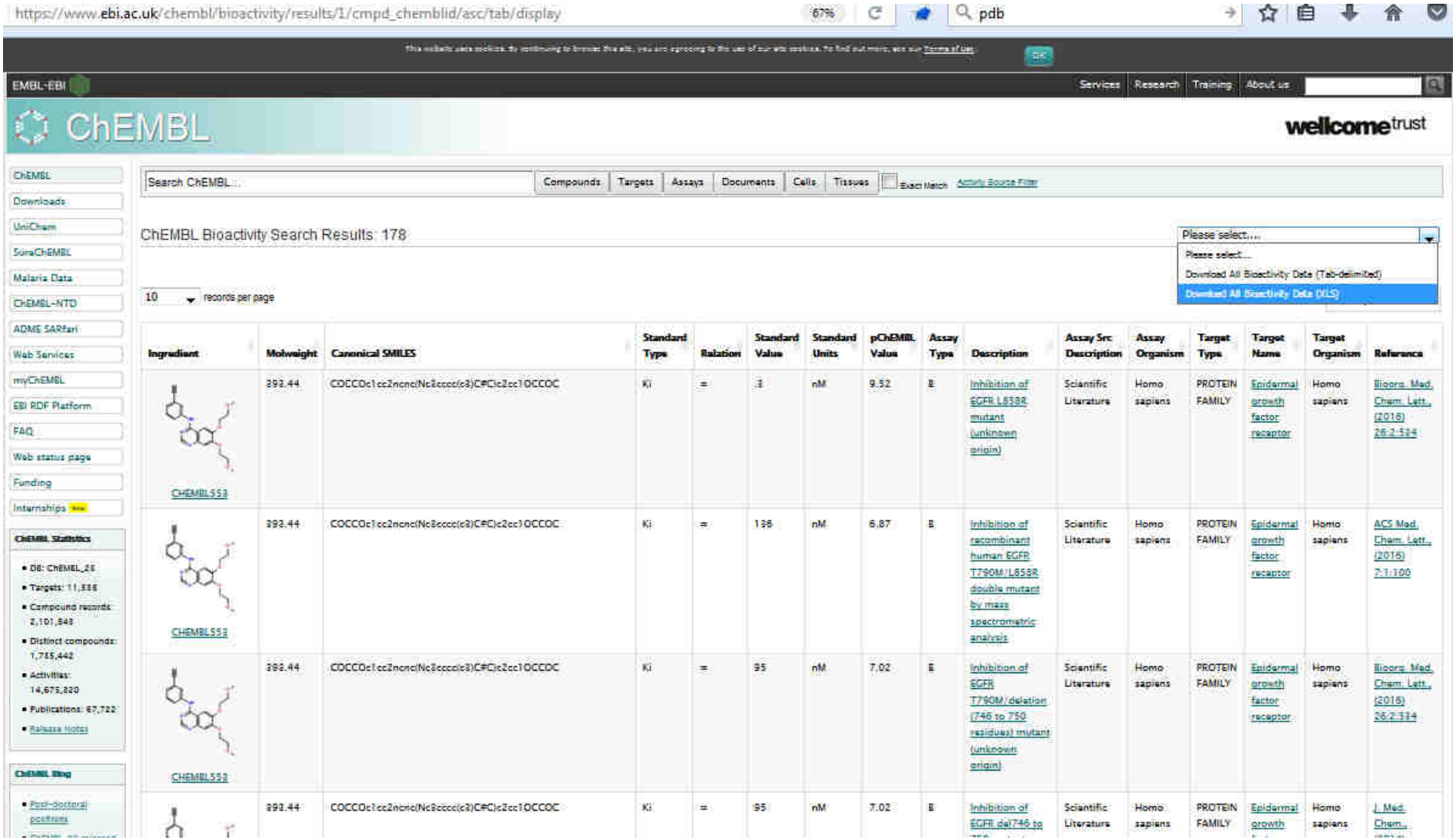
Enrichments: ROC Cuves



Get Known Ligands for Docking

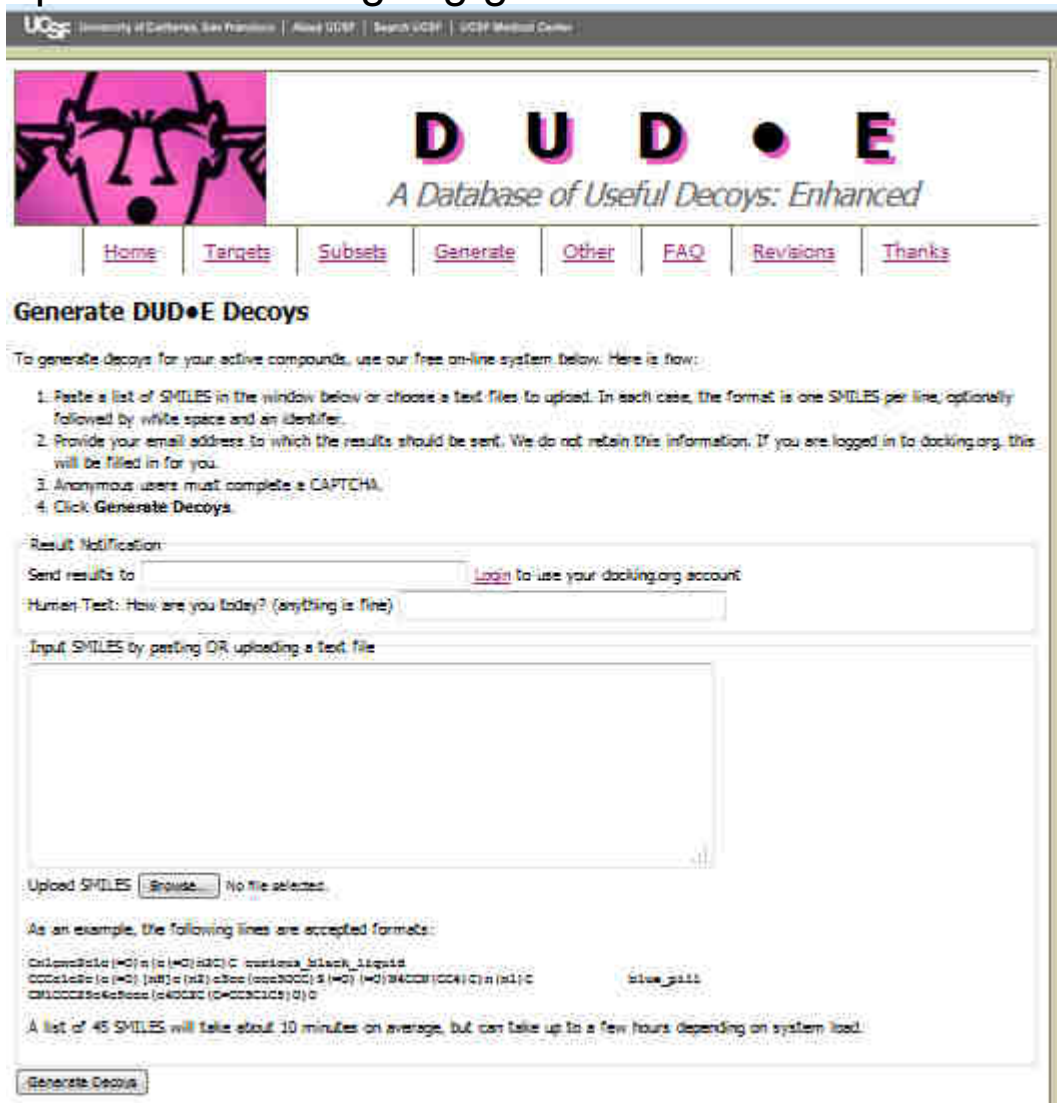
https://www.ebi.ac.uk/chembl/target/inspect/CHEMBL203

Get Known Ligands for Docking



Generate Decoy Smiles File

http://dude.docking.org/generate



Building Databases Locally

If the system is in DUD-E, You may download ready to dock databases here:
http://autodude.docking.org/

Here I just used the first 12 ligands from Chembl

Generated decoys using DUD-E webserver
Use the link in email:

wget http://dude.docking.org/generate/results/4094969748/dude-decoys.tar.gz
tar -xzvf dude-decoys.tar.gz

grep -v ligand dude-decoys/decoys/decoys.P*.picked | awk -F: '{print $2}' | awk '{print $1 " " $2}' > ! decoys.smi

${DOCKBASE}/ligand/generate/build_database_ligand.sh -H 7.4 ligands_12_from_chembl.smi

csh wraper_queue_build_smiles_ligand_mod_corina.csh decoys.smi
http://wiki.docking.org/index.php/Ligand_preparation_-_20170424

Perform Enrichment Calculations

Make a list of all the databases:

ls /path/databases/ligands_12_from_chembl/CHEMBL*/*.db2.gz
/path/databases/decoys/sgejob_*/finished/C*/*.db2.gz > ! ligands_decoys.sdi

awk '{print $2}' databases/ligands_12_from_chembl.smi >
databases/ligands_names.txt
awk '{print $2}' databases/decoys.smi > databases/decoys_names.txt

Make directories for docking:

$DOCKBASE/docking/setup/setup_db2_zinc15_file_number.py ./ ligands_decoys
databases/ligands_decoys.sdi 100 count

Submit docking jobs:
$DOCKBASE/docking/submit/submit.csh

Perform Enrichment Calculations

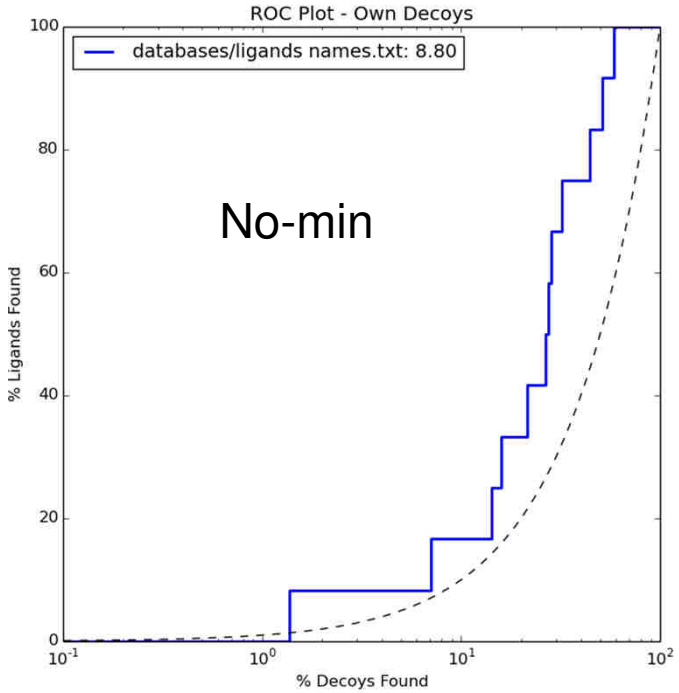
Process results combining results and get the best poses:

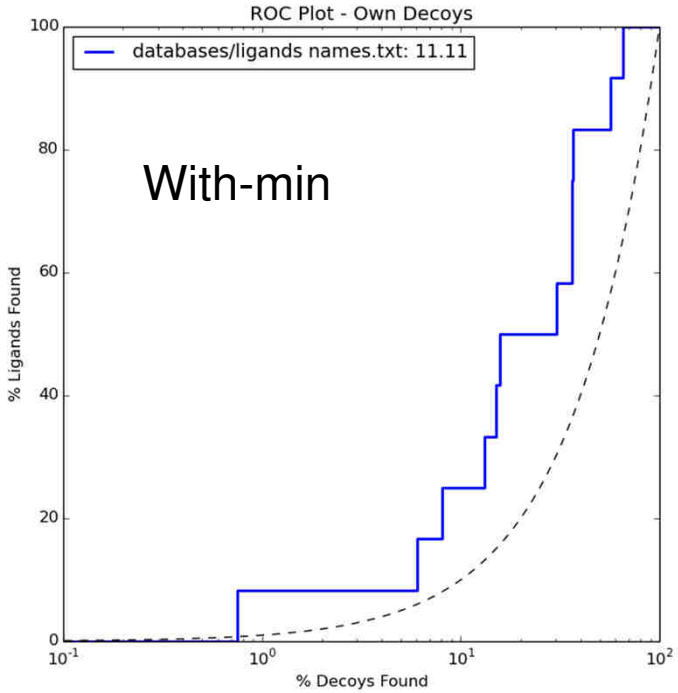
$DOCKBASE/analysis/extract_all.py
$DOCKBASE/analysis/getposes.py

Calculate enrichments:

$DOCKBASE/analysis/enrich.py -i . -l databases/ligands_names.txt -d databases/decoys_names.txt
$DOCKBASE/analysis/plots.py -i . -l databases/ligands_names.txt -d databases/decoys_names.txt

Perform Enrichment Calculations

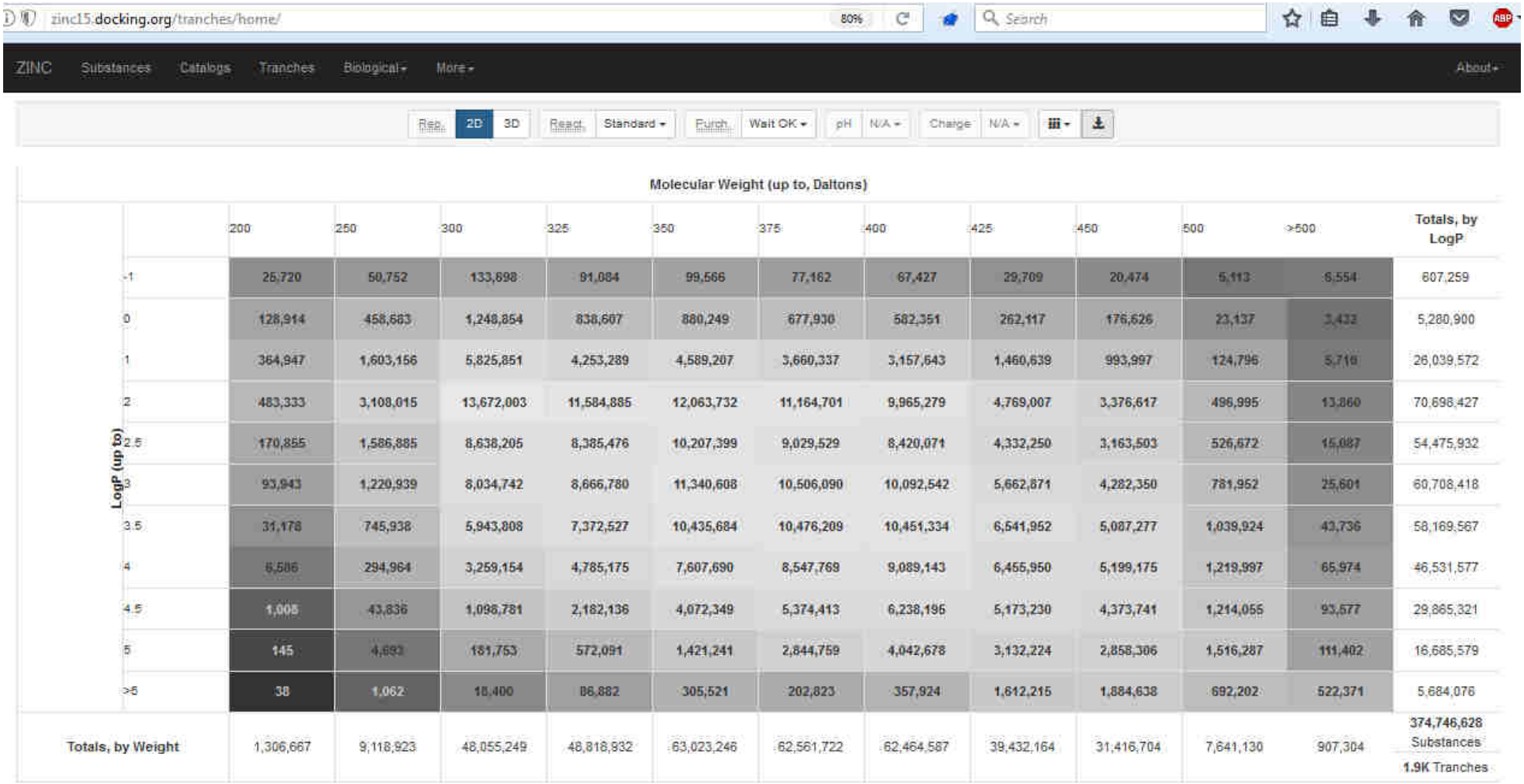




Using ZINC for Drug Discovery

Once you are happy with the retrospective sanity checks now we can do screening.

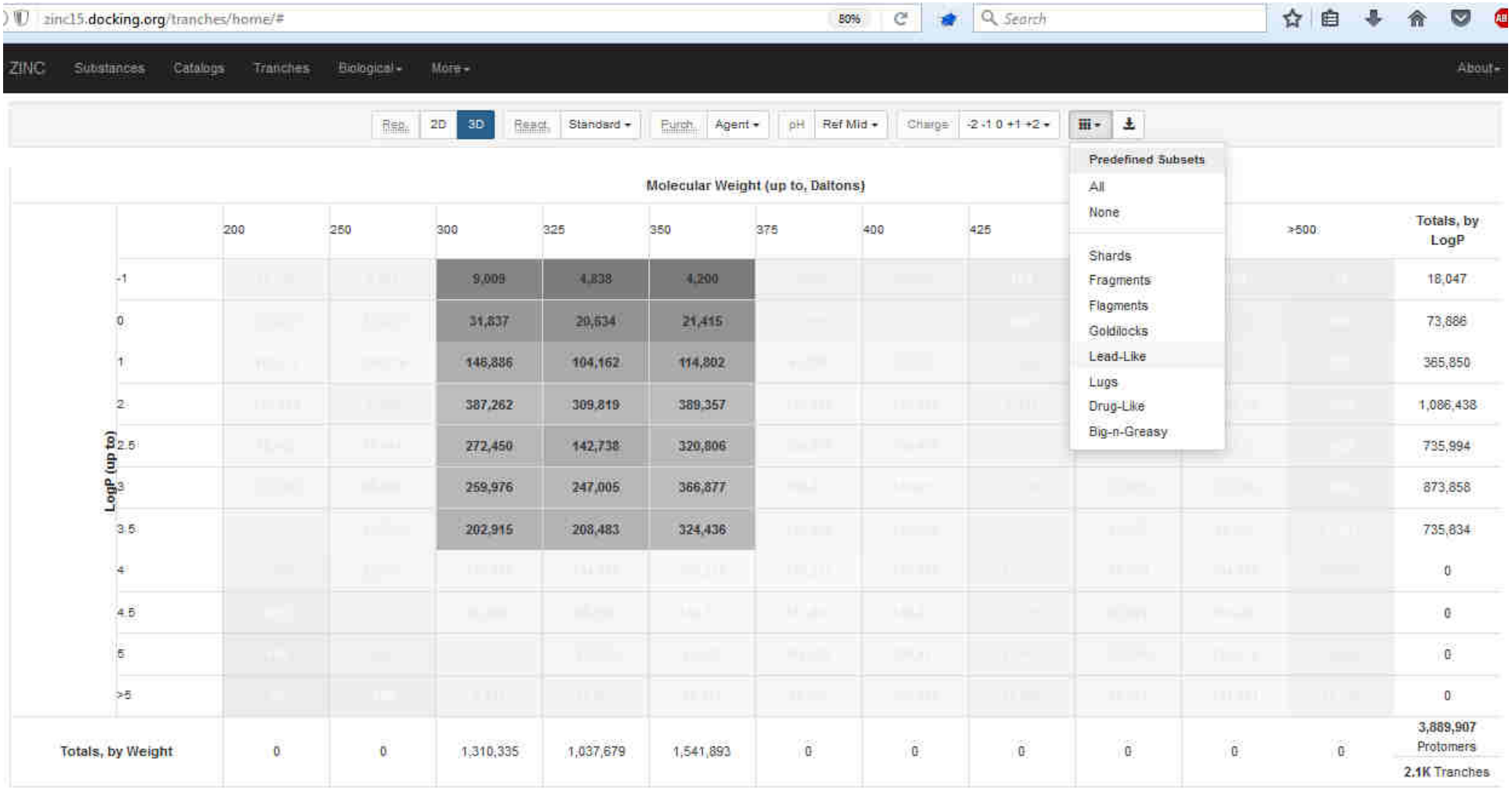
Get Lead-like Molecules to DOCK



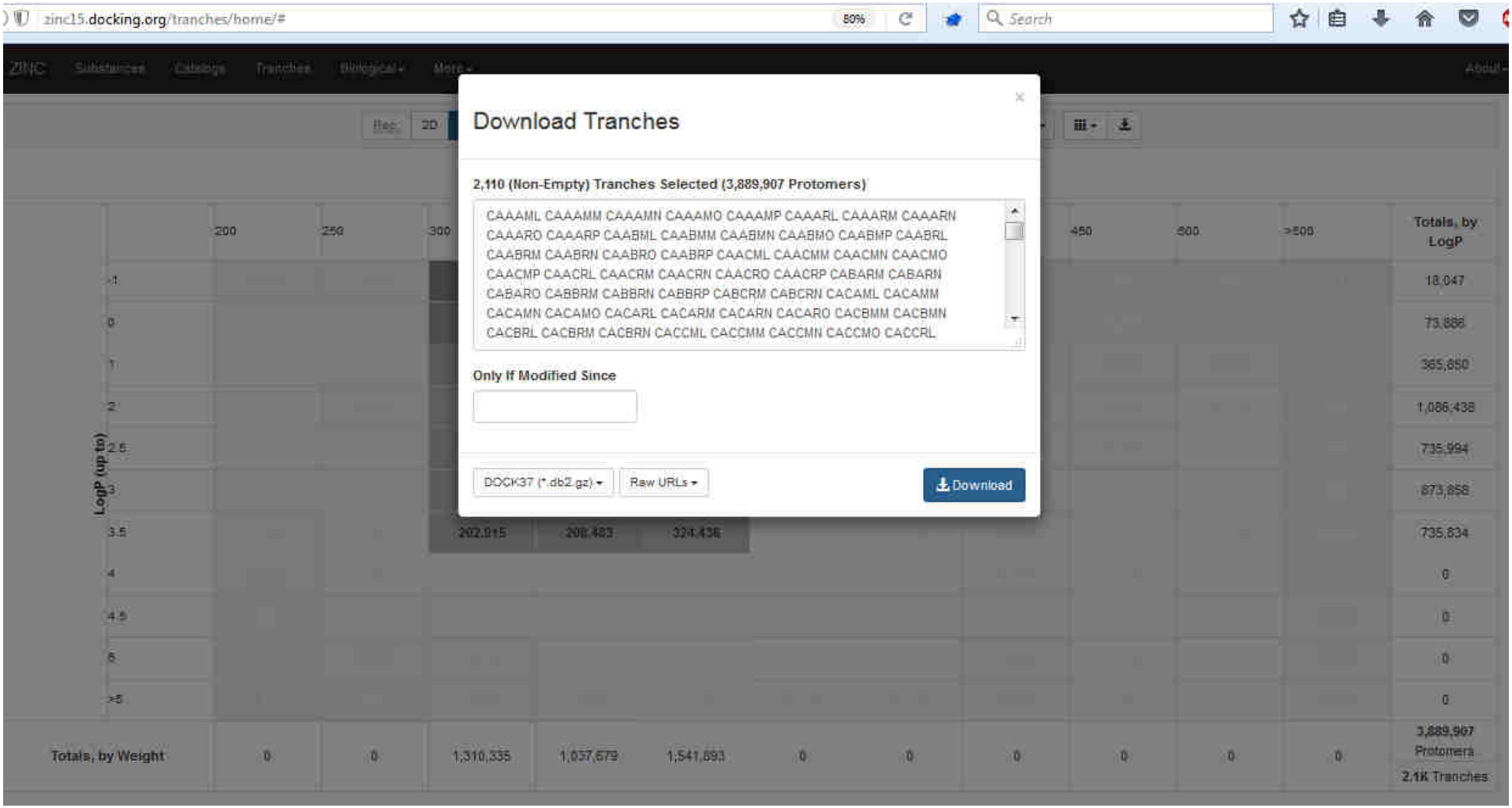
Molecular Weight (up to, Daltons)

LogP (up to)	200	250	300	325	350	375	400	425	450	500	>500	Totals, by LogP
-1	25,720	50,752	133,698	91,084	99,566	77,162	67,427	29,709	20,474	5,113	8,554	607,259
0	128,914	458,663	1,248,854	838,607	880,249	677,930	582,351	262,117	176,626	23,137	3,432	5,280,900
1	364,947	1,603,156	5,825,851	4,253,289	4,589,207	3,660,337	3,157,643	1,460,639	993,997	124,796	5,710	26,039,572
2	483,333	3,108,015	13,672,003	11,584,885	12,063,732	11,164,701	9,965,279	4,769,007	3,376,617	496,995	13,860	70,698,427
2.5	170,855	1,586,885	8,638,205	8,385,476	10,207,399	9,029,529	8,420,071	4,332,250	3,163,503	526,672	15,087	54,475,932
3	93,943	1,220,939	8,034,742	8,666,780	11,340,608	10,506,090	10,092,542	5,662,871	4,282,350	781,952	25,601	60,708,418
3.5	31,178	745,938	5,943,808	7,372,527	10,435,684	10,476,209	10,451,334	6,541,952	5,087,277	1,039,924	43,736	58,169,567
4	6,586	294,964	3,259,154	4,785,175	7,607,690	8,547,769	9,089,143	6,455,950	5,199,175	1,219,997	65,974	46,531,577
4.5	1,008	43,836	1,098,781	2,182,136	4,072,349	5,374,413	6,238,195	5,173,230	4,373,741	1,214,055	93,677	29,865,321
5	145	4,693	181,753	572,091	1,421,241	2,844,759	4,042,678	3,132,224	2,858,306	1,516,287	111,402	16,685,579
>5	38	1,062	15,400	86,882	305,521	202,823	357,924	1,612,215	1,884,638	692,202	522,371	5,684,076
Totals, by Weight	1,306,667	9,118,923	48,055,249	48,818,932	63,023,246	62,561,722	62,464,587	39,432,164	31,416,704	7,641,130	907,304	374,746,628 Substances 1.9K Tranches

Get Lead-like Molecules to DOCK



Get Lead-like Molecules to DOCK



Features in DOCK 3.7

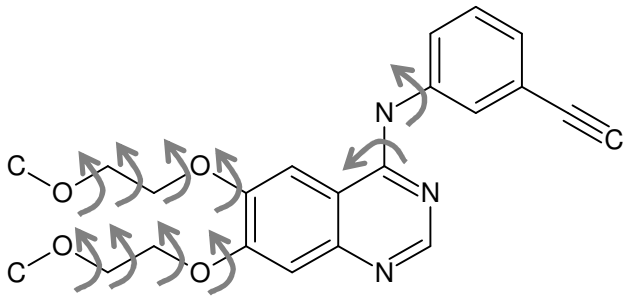
- DOCKovalent – used to screen databases of reactive molecules
- Receptor Desolvation – incorporated
- Minimization
- DOCK 3.7 is among the fastest docking software
- Purchasable chemical space continues to grow (Dock 100 million molecules)

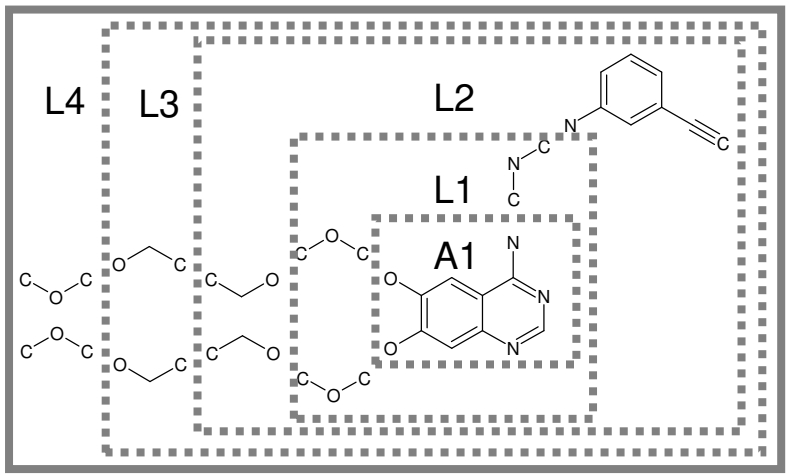
Information About DOCK 6.8

Resources for DOCK 6.8

- Manual: http://dock.compbio.ucsf.edu/DOCK_6/dock6_manual.htm
- Tutorials: http://dock.compbio.ucsf.edu/DOCK_6/tutorials/index.htm
- Rizzo lab wiki: http://ringo.ams.sunysb.edu/index.php/DOCK_Tutorials
- DOCK-fans email archive (list to search for solutions to problems or submit questions): http://mailman.docking.org/pipermail/dock-fans/
- Email dock-fans when you need advise or assistance:

  dock-fans@docking.org





Sampling using Anchor-&-Grow

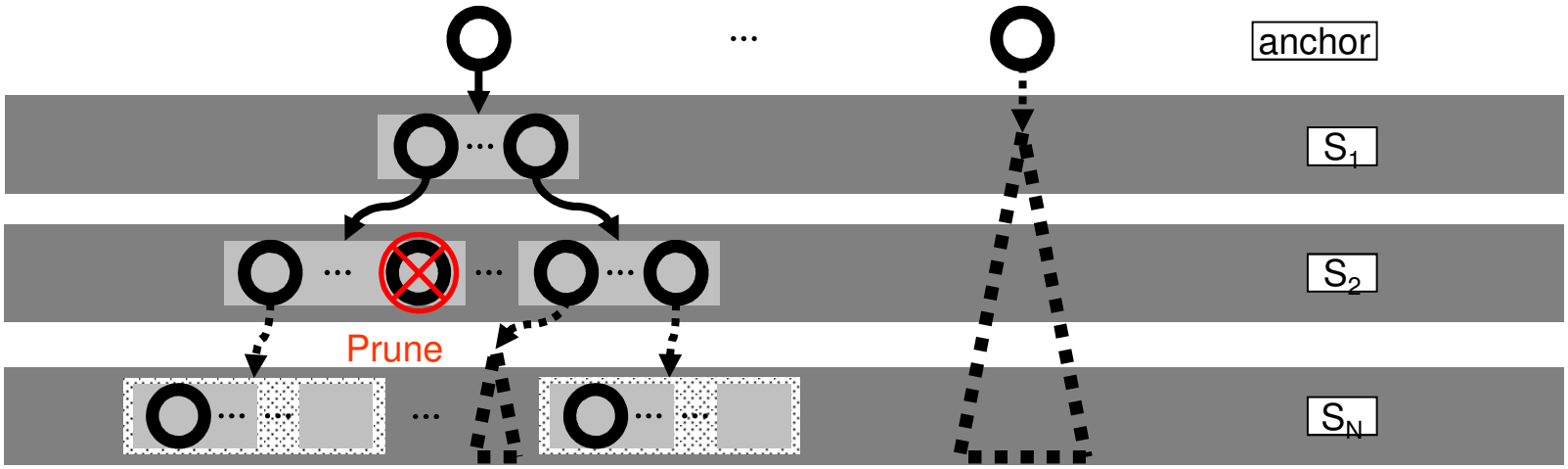
Start from anchor orient

Arrange segments by layer about anchor center

Grow each segment one at a time

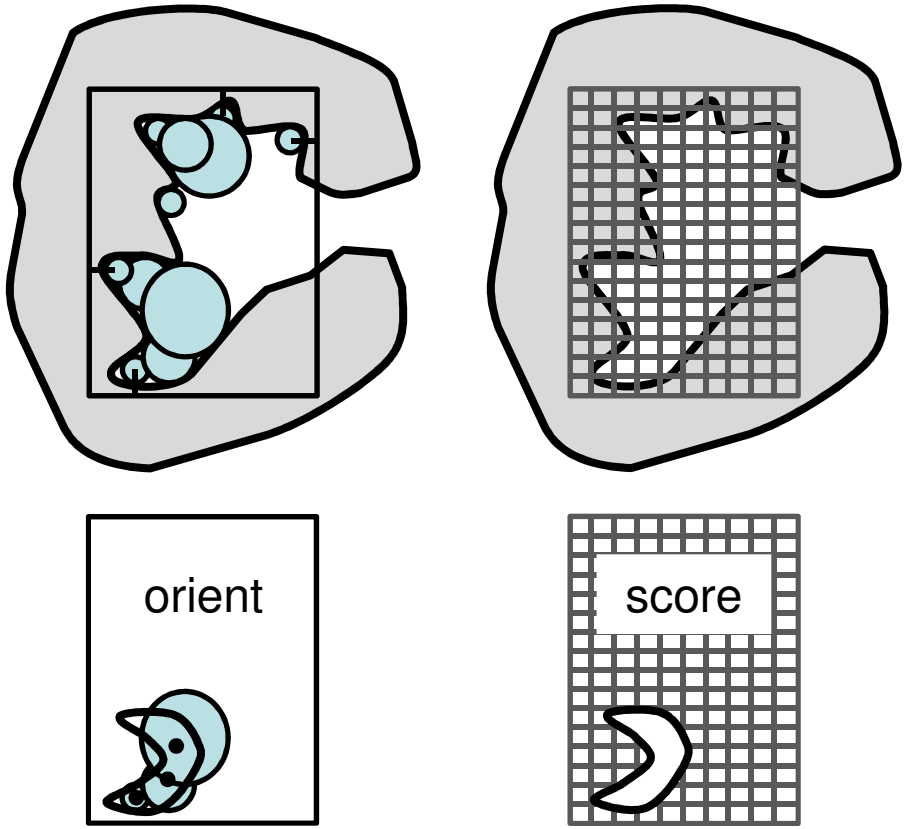
Grow segments in Layer 1

Grow segments in Layer 2 and so on

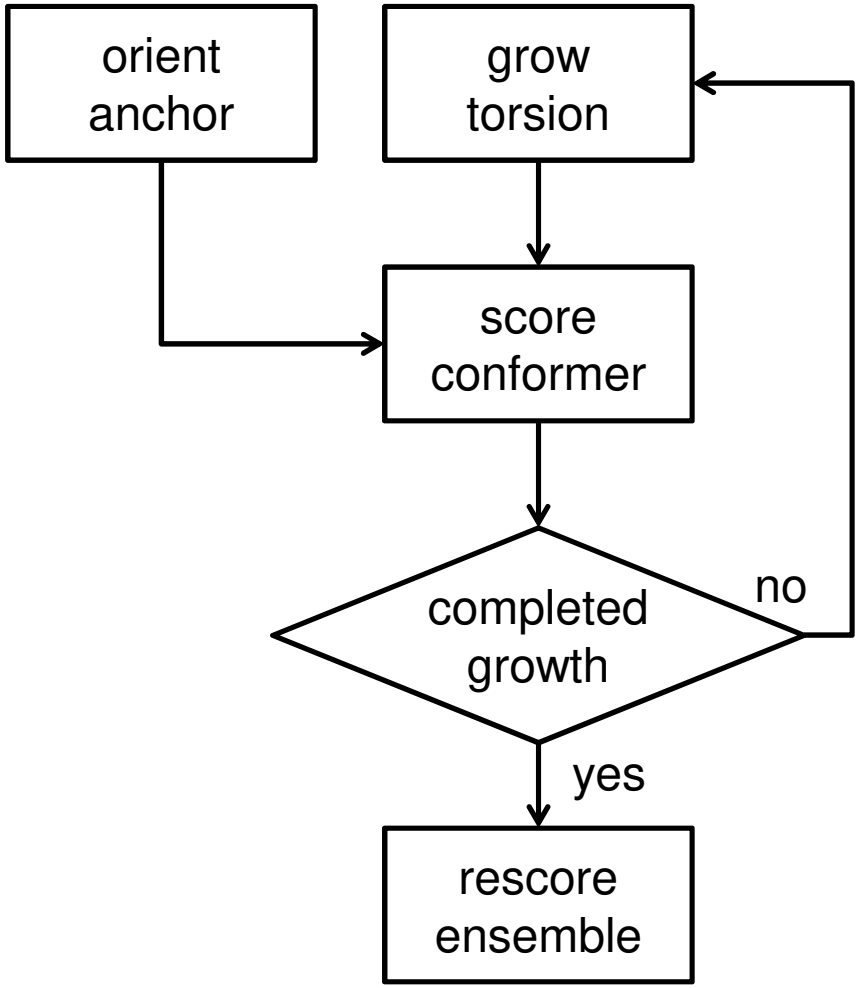


Sampling and Scoring

DOCK preparation



Scoring using a grid to speed up the calculations



DOCK 6 is a parallel program using MPI

DOCK6 Has Many Scoring Functions

- Bump Filter
- Contact Score
- Grid-Based Score

$$E_{Grid} = E_{VDW} + E_{ES}$$

- DOCK 3.5 Score
- Continuous Score
- Zou GB/SA Score
- Hawkins GB/SA Score
- PB/SA Score
- AMBER Score
- Footprint Score
- MultiGrid FPS Score
- Pharmacophore Matching Similarity Score
- SASA Score
- Descriptor Score
  - Tanimoto Score
  - Hungarian Matching Similarity Score
  - Volume Overlap Score

Features in DOCK 6.8

- Array of Scoring Function
  - New is Descriptor Score, Pharmacophore Score
- *De novo* design (will be released in future versions)
- Modular
- MPI parallel implementation

DOCK: where it is and where its going

Trent Balius, Ph.D.
Postdoctoral Scholar, Shoichet Lab
University of California, San Francisco

Tuesday, June 20th 12:00pm EDT

Upcoming Webinars:
July 25th: BioXTAS RAW with Jesse Hopkins
October 3rd: SPHIRE with Toshio Moriya
November 4th: EMAN2 with Steven Ludtke

SBGrid CONSORTIUM

Events are posted on SBGrid Google Calendar (to join visit http://sbgrid.org/calendar)

Extra Slides

Rescoring: Footprint Similarity

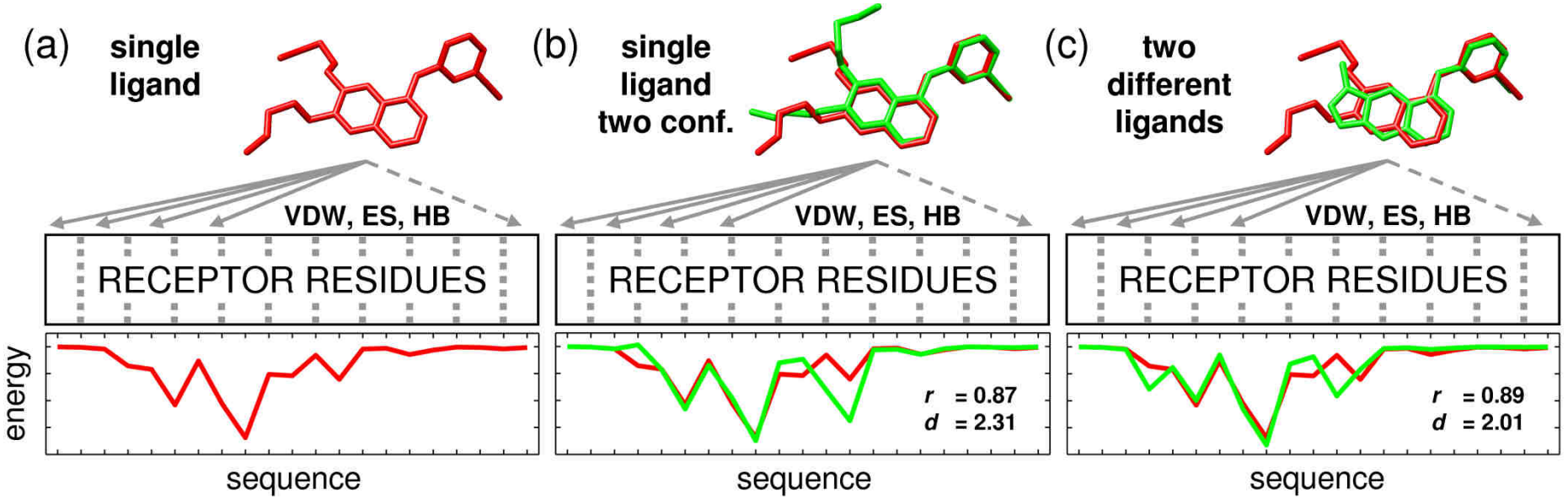


Table I. Examples of possible reference types to derive molecular footprints.

Reference Types	**Description**
Known inhibitor	FDA-approved drug or experimental inhibitor validated to bind
Natural substrate	Native peptide or cofactor
Transition state	Predicted transition state geometry for a chemical reaction
Modified structure	Key functionality/substructure (side-chain mediating protein-protein interactions)
Text file footprint	Modified entries to increase/decrease importance of select residues (resistance mutations)
Ensemble-weighted	Averaged footprints derived from MD/MC simulations

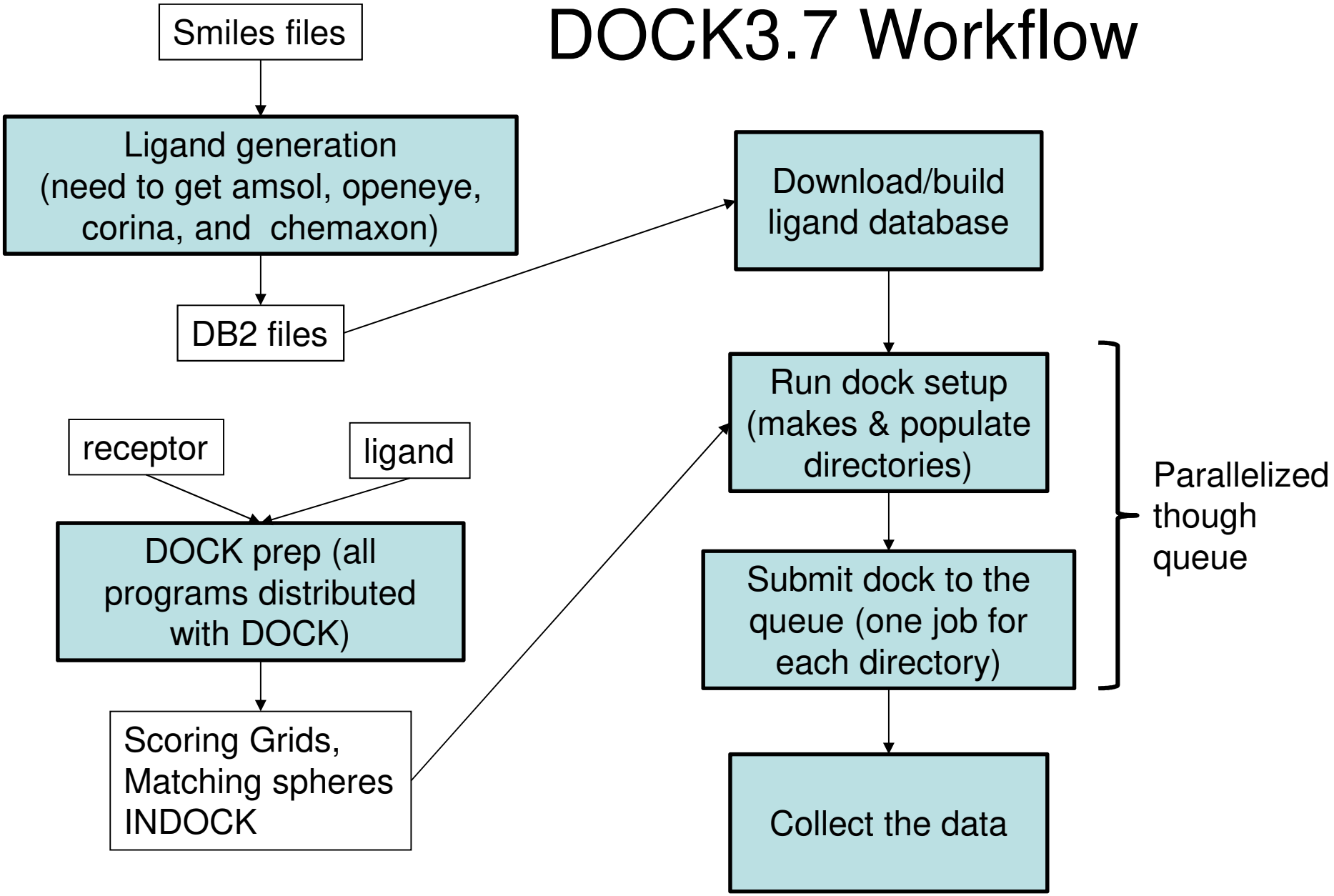
DOCK: Where it is and where its going

SBGrid Lunch Break

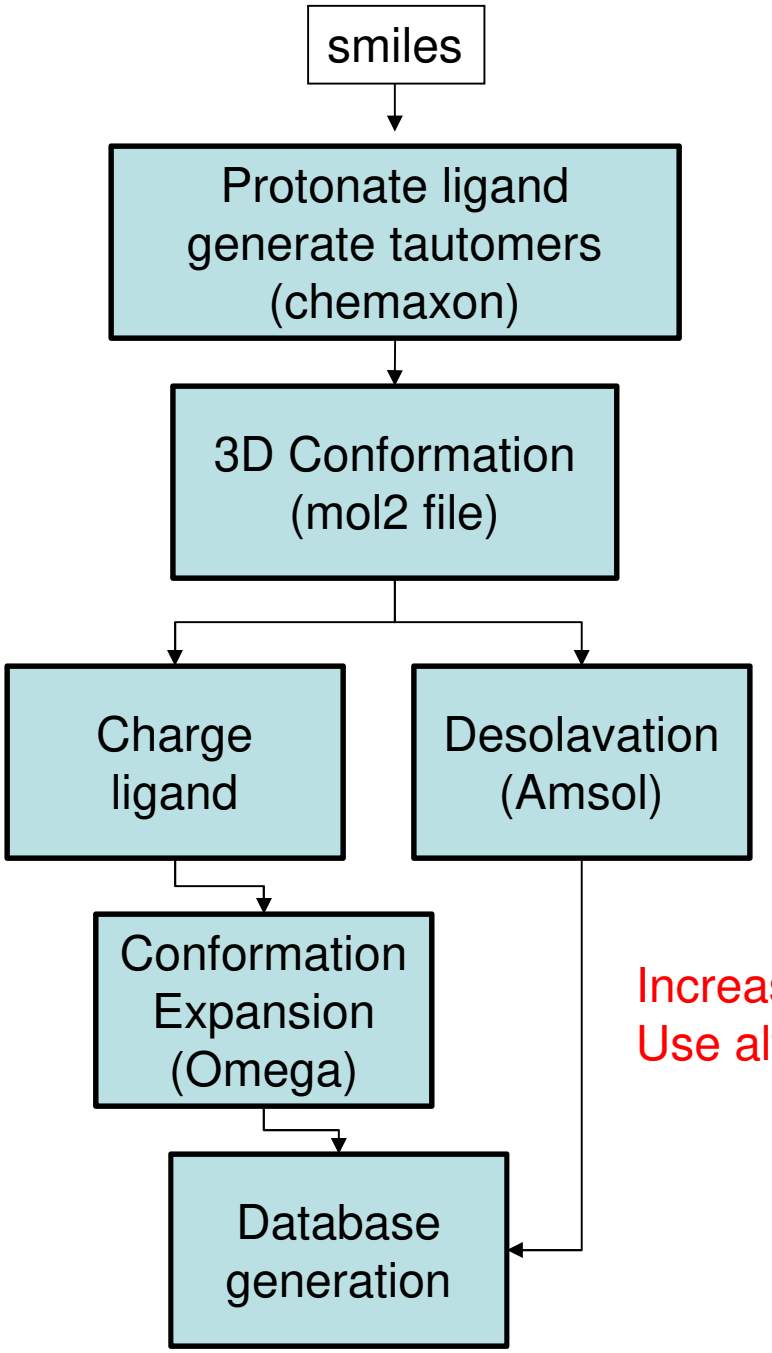
Trent Balius

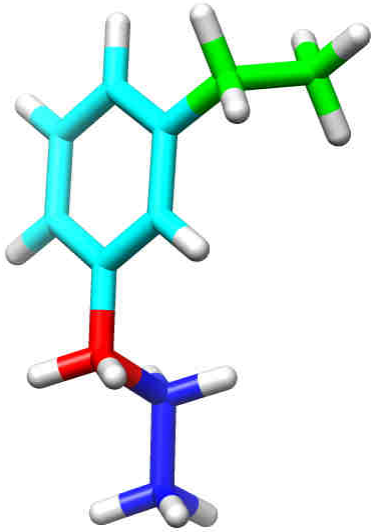
June 20, 2017

DOCK3.7 Workflow



Ligand Preparation

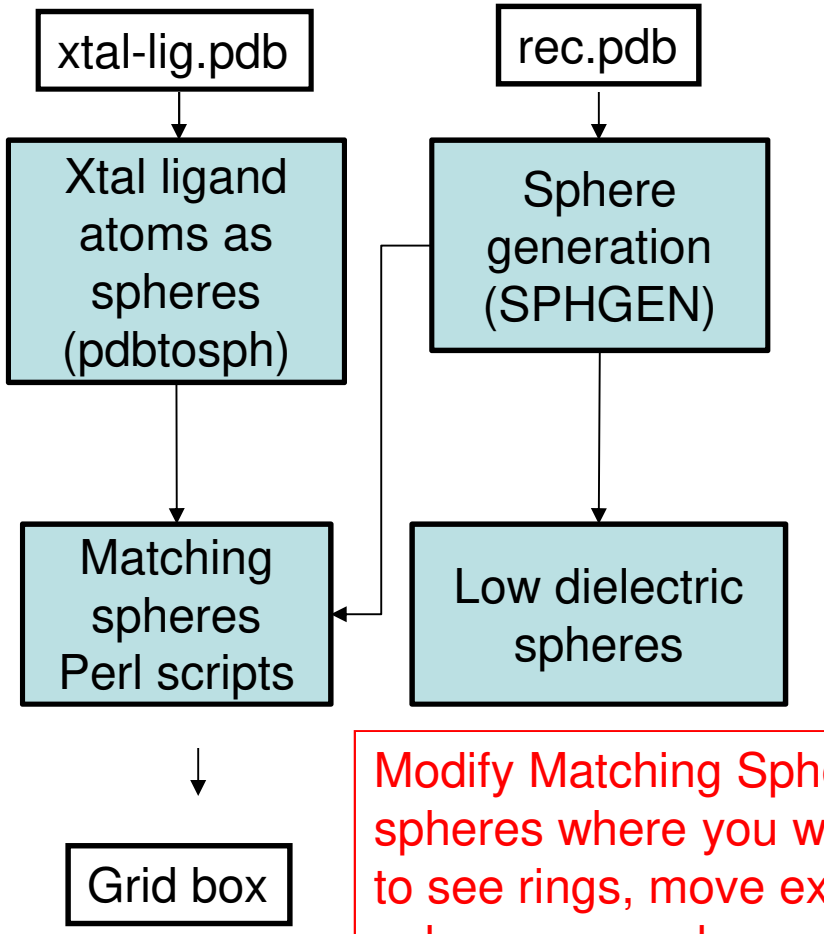


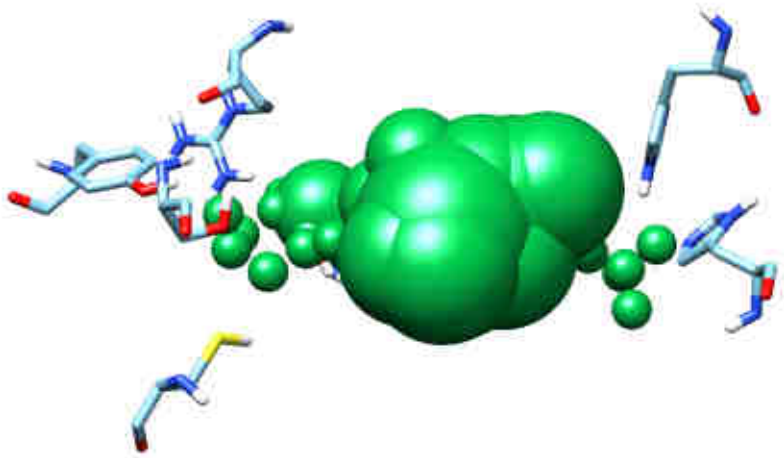


DOCKable Ligand databases are available through ZINC15

Increase sampling (turn nobles in omega)
Use alternative sampling engines.

Sphere Generation: Receptor Prep.

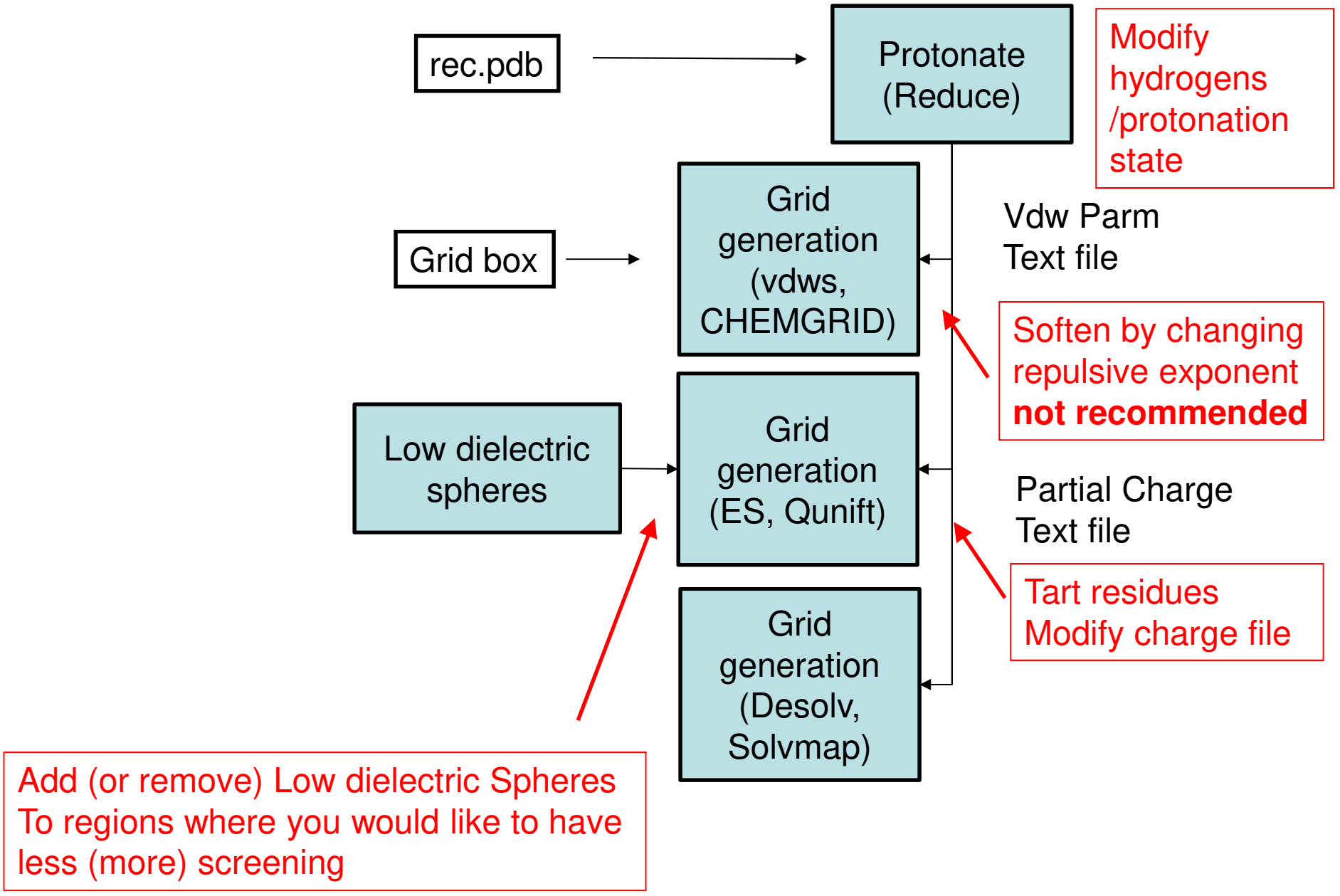




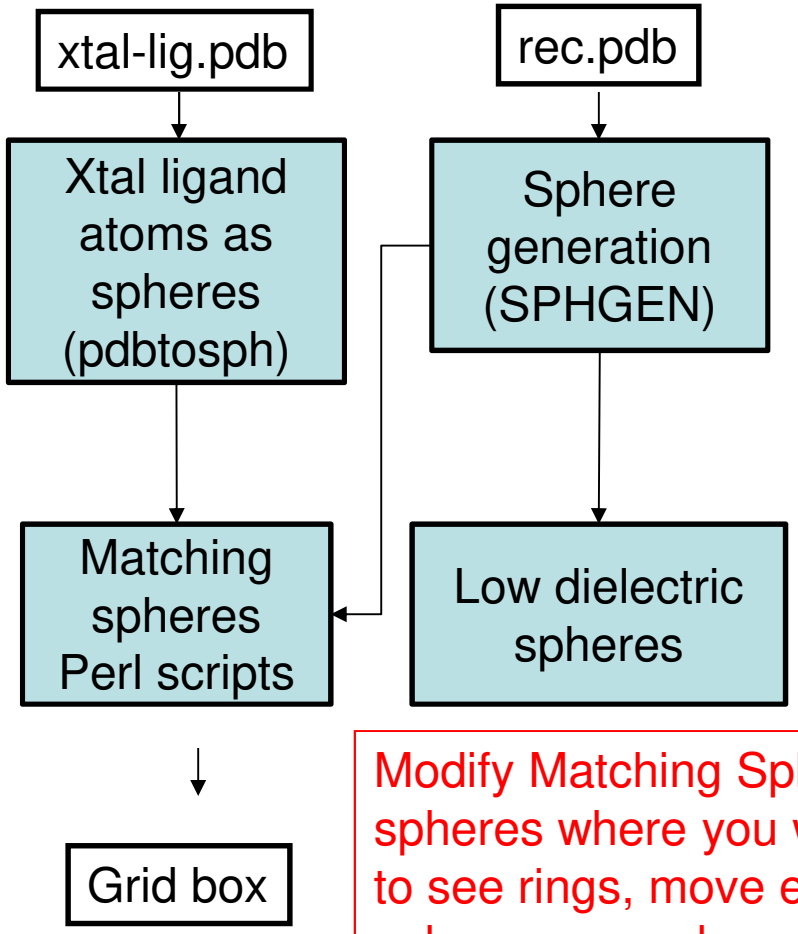
Modify Matching Spheres: add spheres where you would like to see rings, move existing spheres around

Add (or remove) Low dielectric Spheres To regions where you would like to have less (more) screening

Grid Generation: Receptor preparation



Sphere Generation

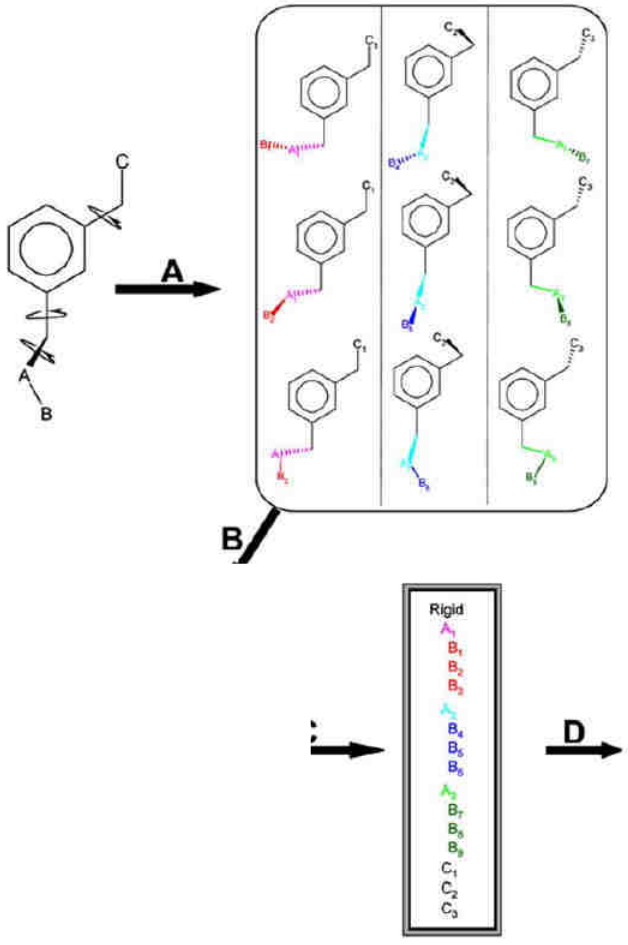


Modify Matching Spheres: add spheres where you would like to see rings, move existing spheres around

Add (or remove) Low dielectric Spheres To regions where you would like to have less (more) screening

How Sampling Works (Internal)

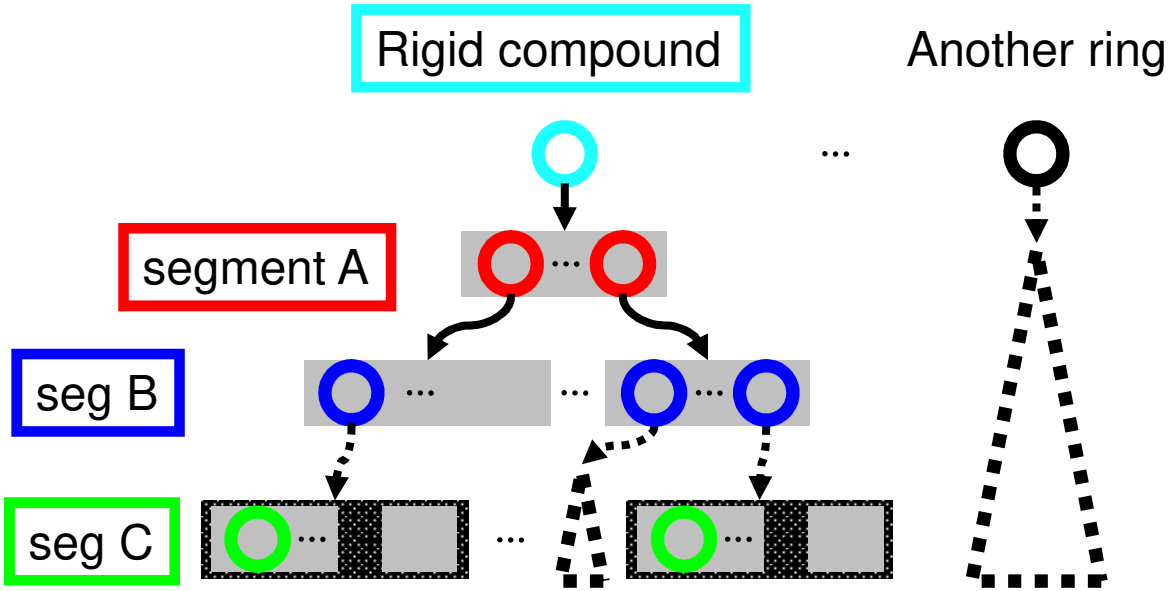
Hierarchical docking of databases

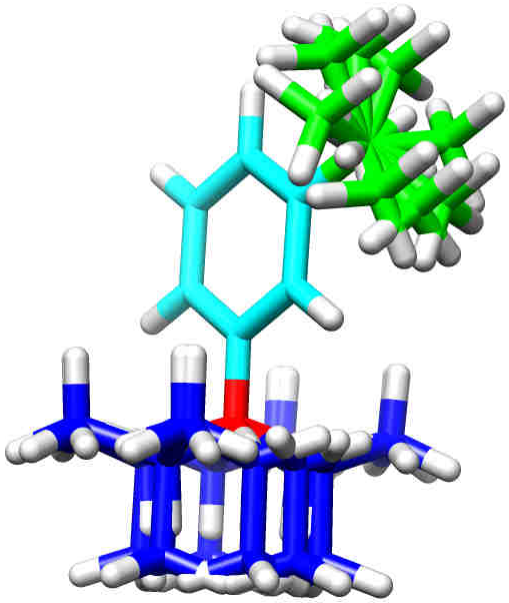


	Atom		
conf #	A	B	C
1	1	1	1
2	1	2	1
3	1	3	1
4	2	4	1
5	2	5	1
6	2	6	1
7	3	7	1
8	3	8	1
9	3	9	1
10	1	1	2
11	1	2	2
12	1	3	2
13	2	4	2
14	2	5	2
15	2	6	2
16	3	7	2
17	3	8	2
18	3	9	2
19	1	1	3
20	1	2	3
21	1	3	3
22	2	4	3
23	2	5	3
24	2	6	3
25	3	7	3
26	3	8	3
27	3	9	3

Lorber DM and Shoichet BK., Curr Top Med Chem. 2005;5(8):739-49.

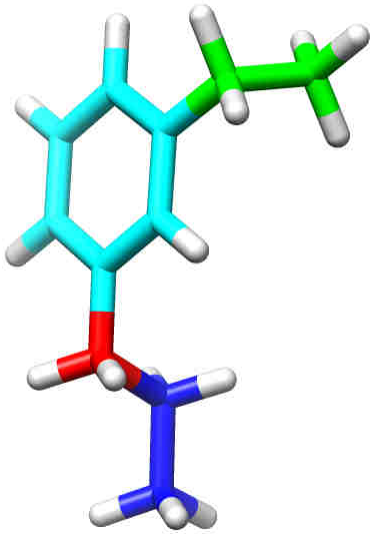
Ligand Sampling – Database Construction





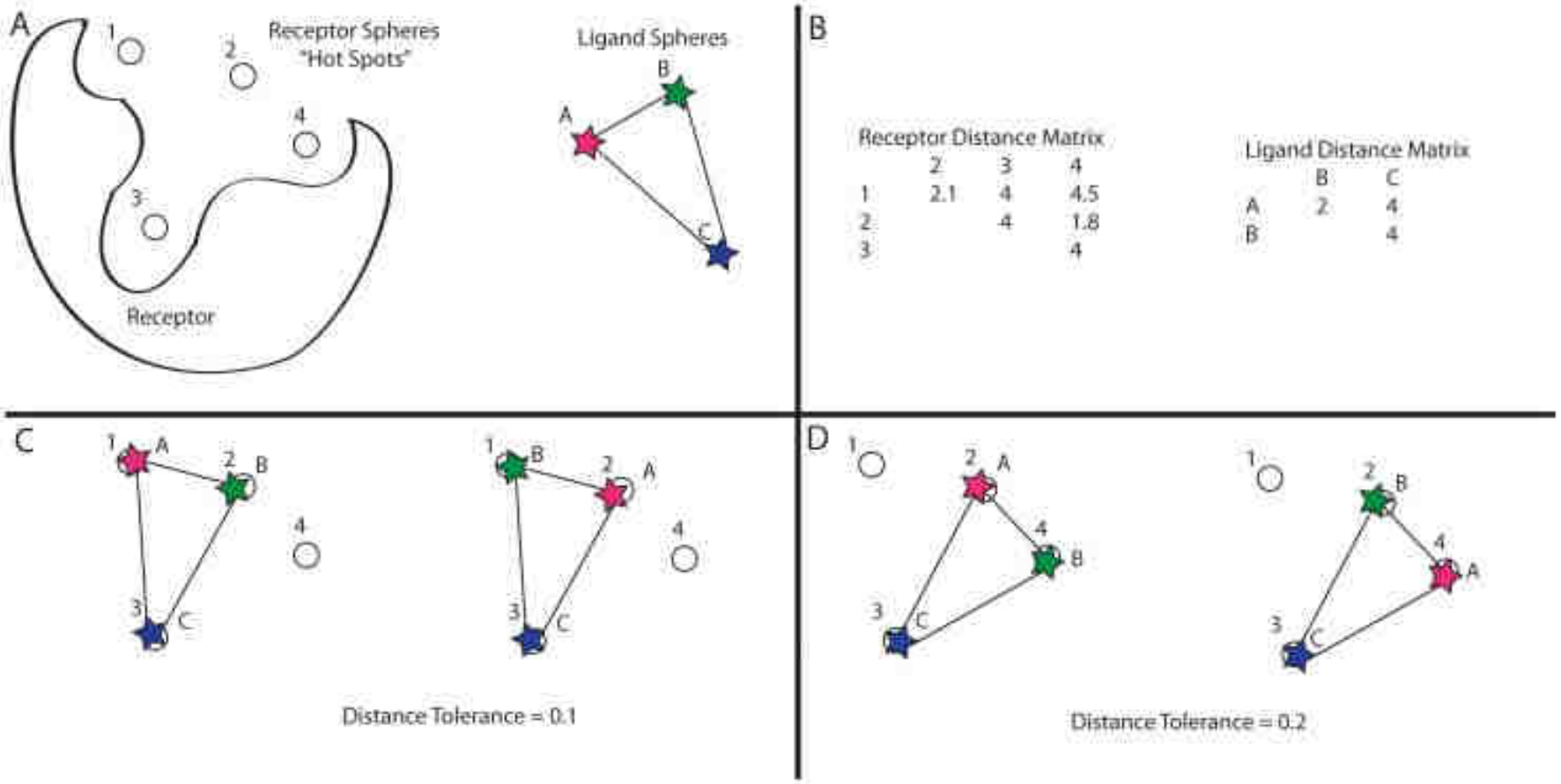
Fully Grown Conformers

Branch
(conformer)

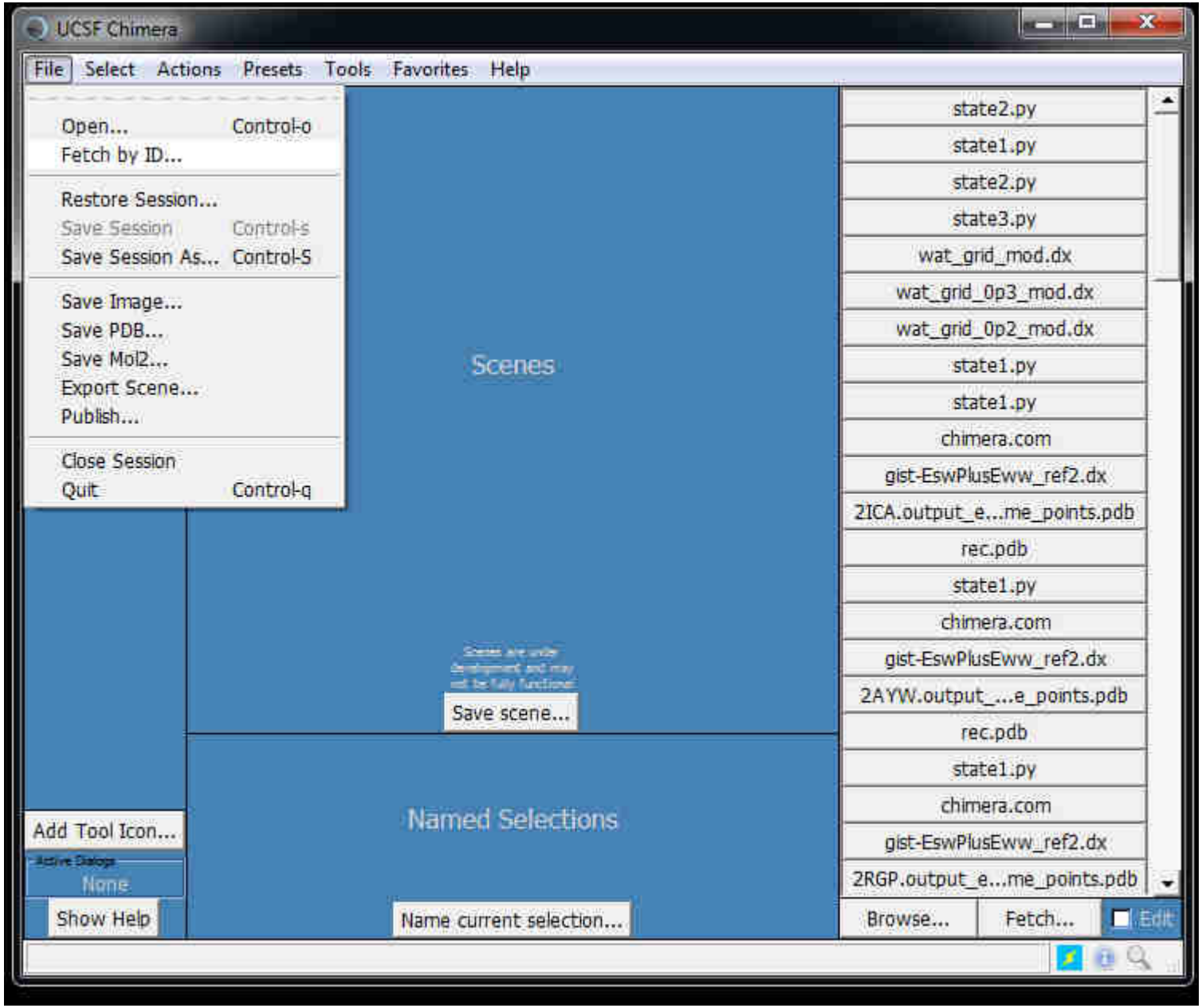


How Sampling Works (Orientational)

A toy example illustrating the matching sphere orientational matching algorithm



Coleman, RG et al. PLoS One. 2013; 8(10): e75992.


UCSF Chimera
File
Select
Actions
Presets
Tools
Favorites
Help
Open... Control-o
Fetch by ID...
Restore Session...
Save Session Control-s
Save Session As... Control-S
Save Image...
Save PDB...
Save Mol2...
Export Scene...
Publish...
Close Session
Quit Control-q
Scenes
Save scene...
Named Selections
Name current selection...
Add Tool Icon...
None
Show Help
state2.py
state1.py
state2.py
state3.py
wat_grid_mod.dx
wat_grid_0p3_mod.dx
wat_grid_0p2_mod.dx
state1.py
state1.py
chimera.com
gist-EswPlusEww_ref2.dx
2ICA.output_e...me_points.pdb
rec.pdb
state1.py
chimera.com
gist-EswPlusEww_ref2.dx
2AYW.output_...e_points.pdb
rec.pdb
state1.py
chimera.com
gist-EswPlusEww_ref2.dx
2RGP.output_e...me_points.pdb
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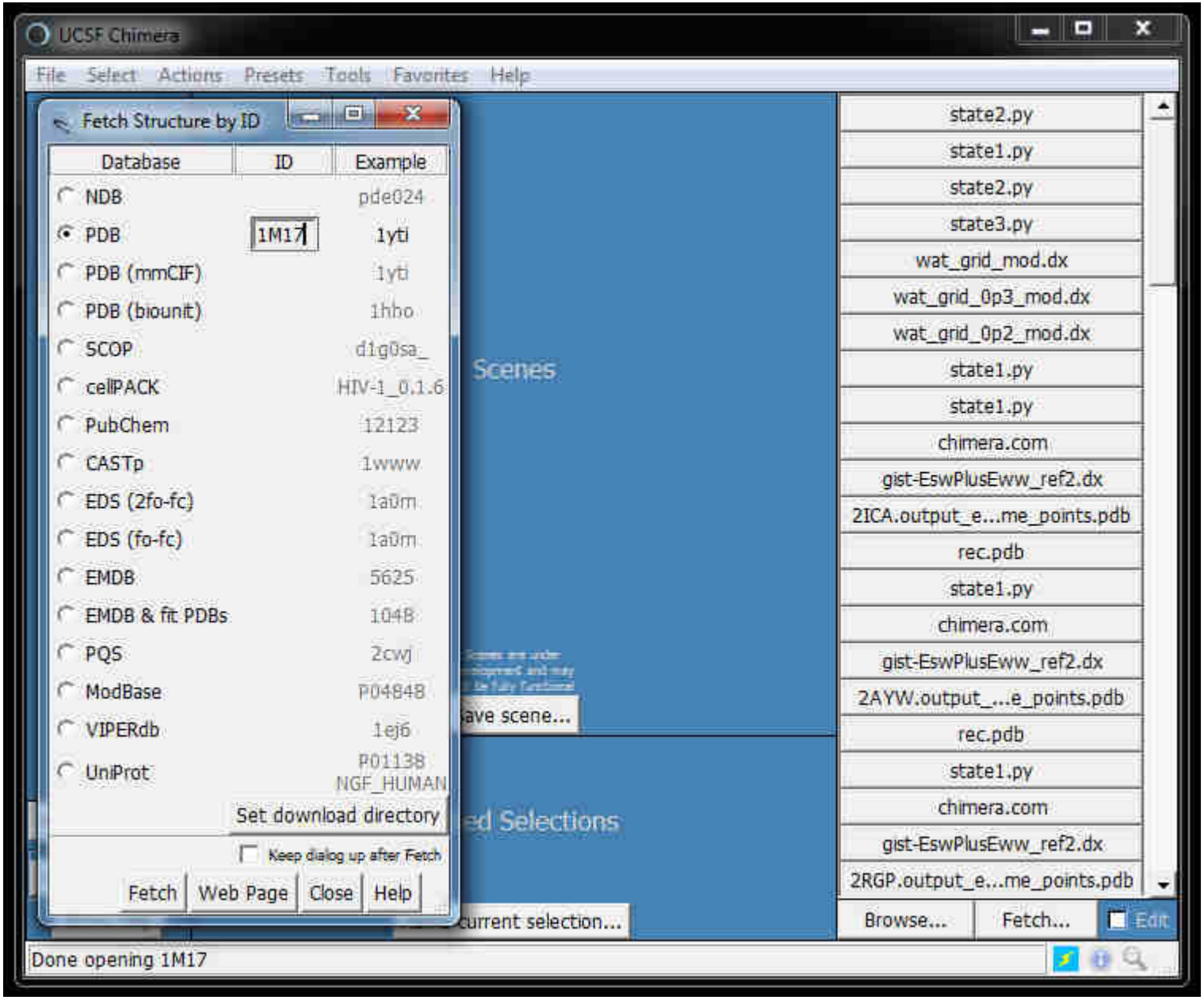
Fetch...
Edit


UCSF Chimera
File Select Actions Presets Tools Favorites Help
Fetch Structure by ID
Database ID Example
NDB pde024
PDB 1M17 1yti
PDB (mmCIF) 1yti
PDB (biounit) 1hho
SCOP d1g0sa_
cellPACK HIV-1_0.1.6
PubChem 12123
CASTp 1www
EDS (2fo-fc) 1a0m
EDS (fo-fc) 1a0m
EMDB 5625
EMDB & fit PDBs 1048
PQS 2cwj
ModBase P04848
VIPERdb 1ej6
UniProt P01138 NGF_HUMAN
Set download directory
Keep dialog up after Fetch
Fetch Web Page Close Help
Scenes
ave scene...
ed Selections
current selection...
state2.py
state1.py
state2.py
state3.py
wat_grid_mod.dx
wat_grid_0p3_mod.dx
wat_grid_0p2_mod.dx
state1.py
state1.py
chimera.com
gist-EswPlusEww_ref2.dx
2ICA.output_e...me_points.pdb
rec.pdb
state1.py
chimera.com
gist-EswPlusEww_ref2.dx
2AYW.output_...e_points.pdb
rec.pdb
state1.py
chimera.com
gist-EswPlusEww_ref2.dx
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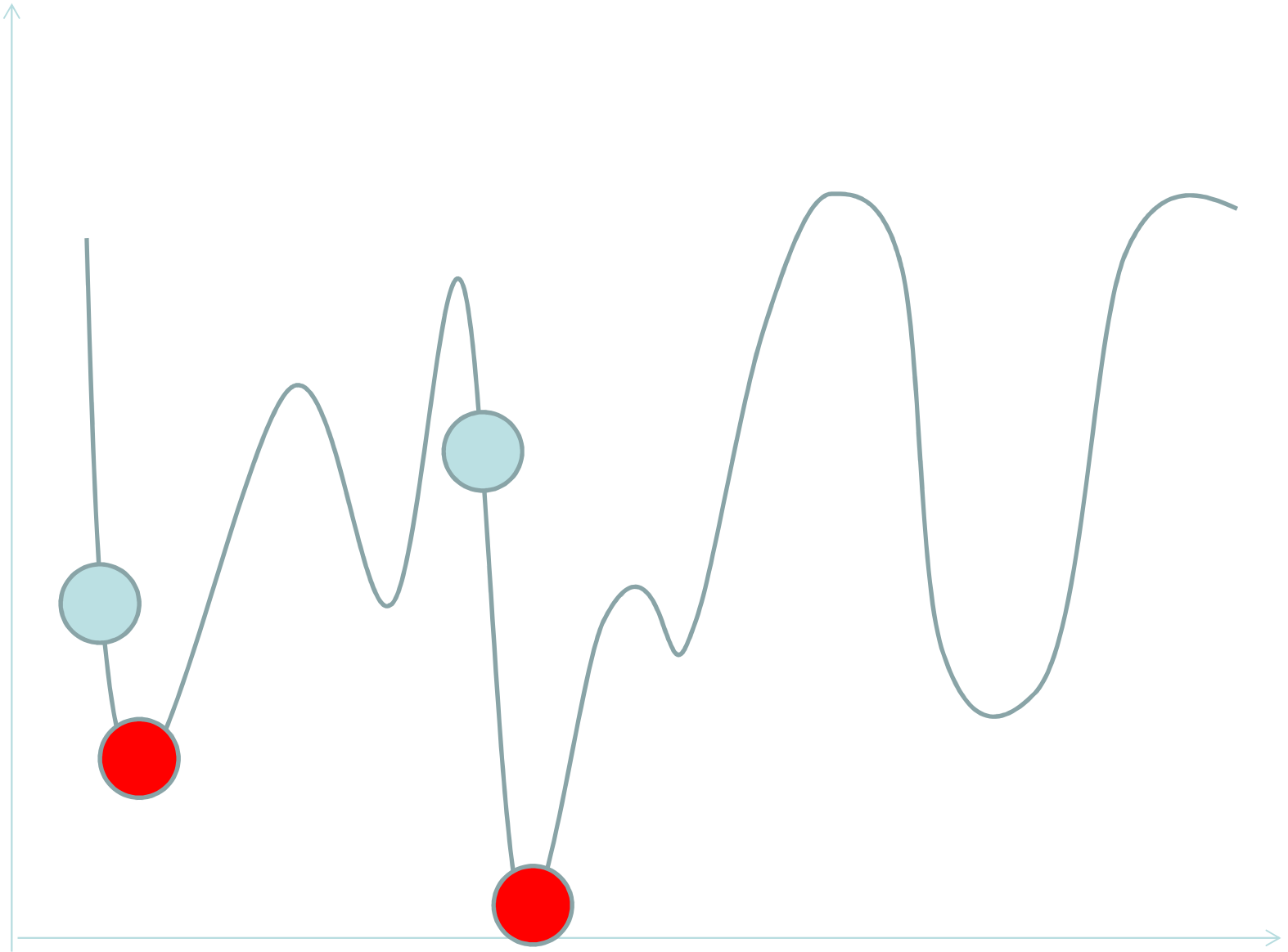
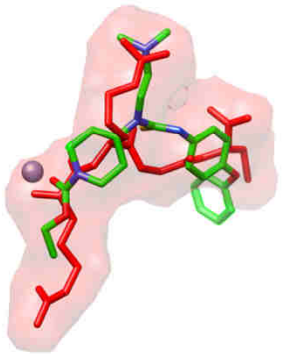
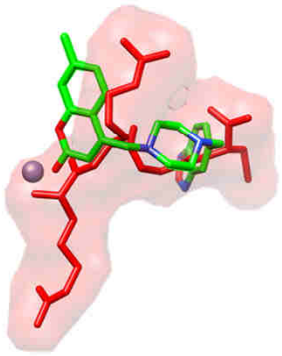


Lab Projects Employing FPS: Bot NT/A

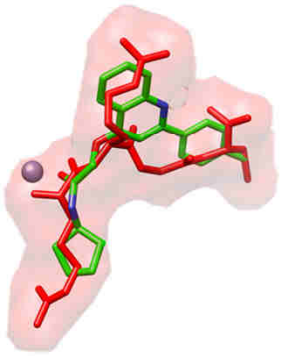
~900,000 screened → 99 purchased → 5 active (picked using FPS)



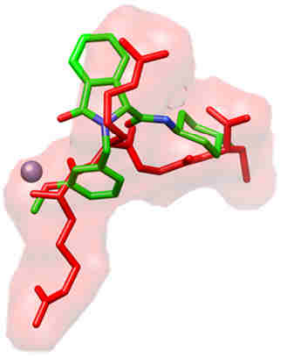
IC_{50} = 6 (μM)
DCE = -73.78
FPS = 0.89



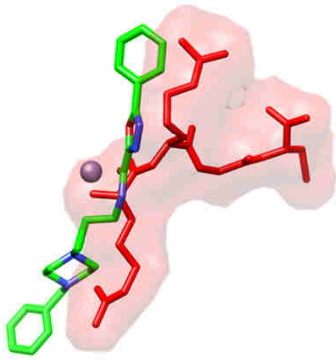
IC_{50} = 16 (μM)
DCE =-60.57
FPS = 0.89



IC_{50} = 18 (μM)
DCE = -60.98
FPS =0.92



IC_{50} = 18 (μM)
DCE = -62.53
FPS = 0.86



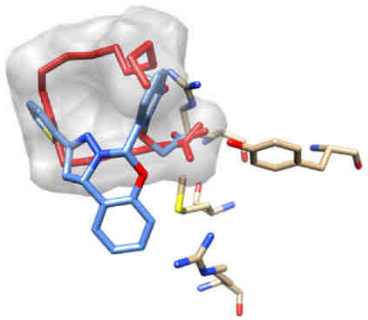
IC_{50} = 18 (μM)
DCE = -67.97
FPS = 1.63

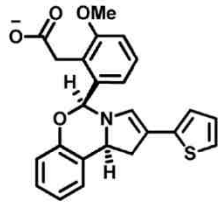
Preliminary results, work in progress: Bill Berger, Trent Balius, Eduard Melief, Peter Tonge, Subramanyam Swaminathan, Iwao Ojima, and Robert Rizzo

Y.-H. G Teng et al. Bioorg. Med. Chem. 23 (2015) 5489–5495

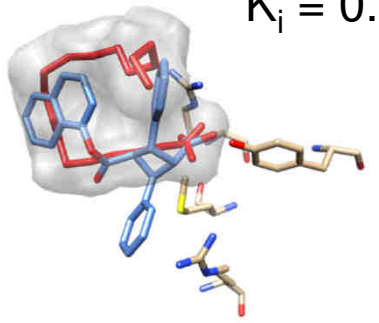
Lab Projects Employing FPS: FABP

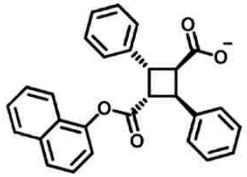
K_i = 0.93±0.08 µM



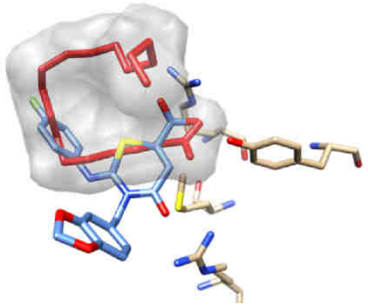


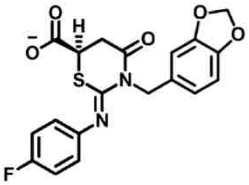
SB-FI-19
(ChemDiv 5511-0235)



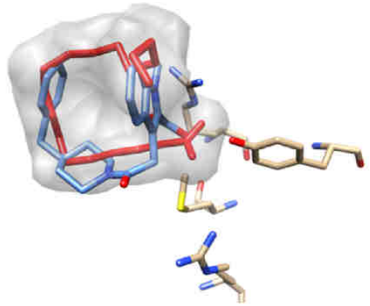


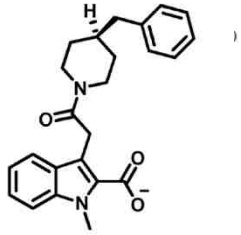
SB-FI-26
(ChemDiv 8009-2334)



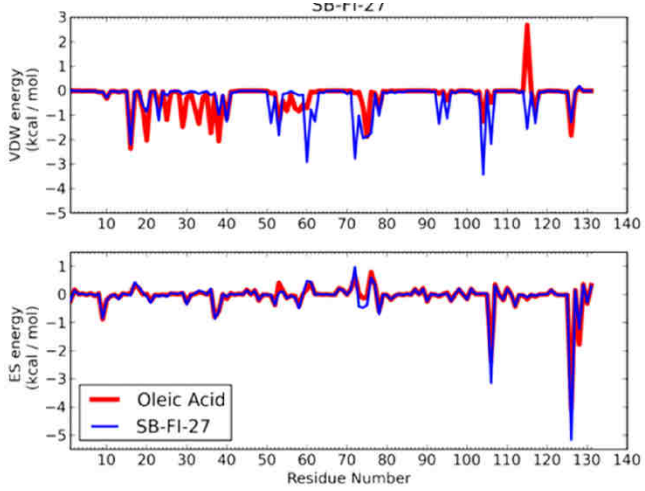


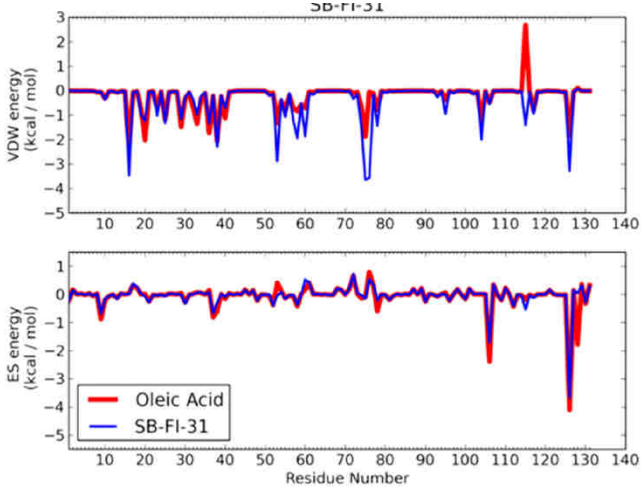
SB-FI-27
(ChemDiv 8009-7646)





SB-FI-31
(ChemDiv C075-0064)

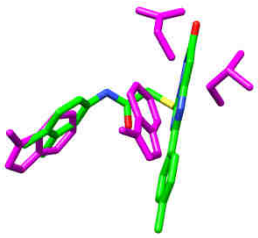




Berger et al. PloS one 7 (12), e50968

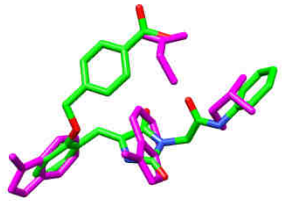
Lab Projects Employing FPS: HIVgp41

~500,000 screened → 115 purchased → 7 active (3 / 7 picked using FPS)

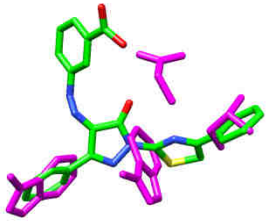


sum_fp
Ki = 0.46 (μM)

es_fp
Ki = 4.45 (μM)



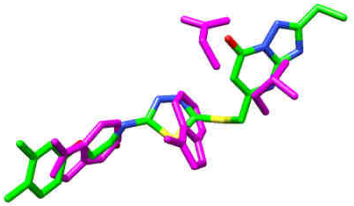
tots
Ki = 7.1 (μM)



tots
Ki = 0.20 (μM)

tots
Ki = 1.6 (μM)

es_fp
Ki = 13 (μM)

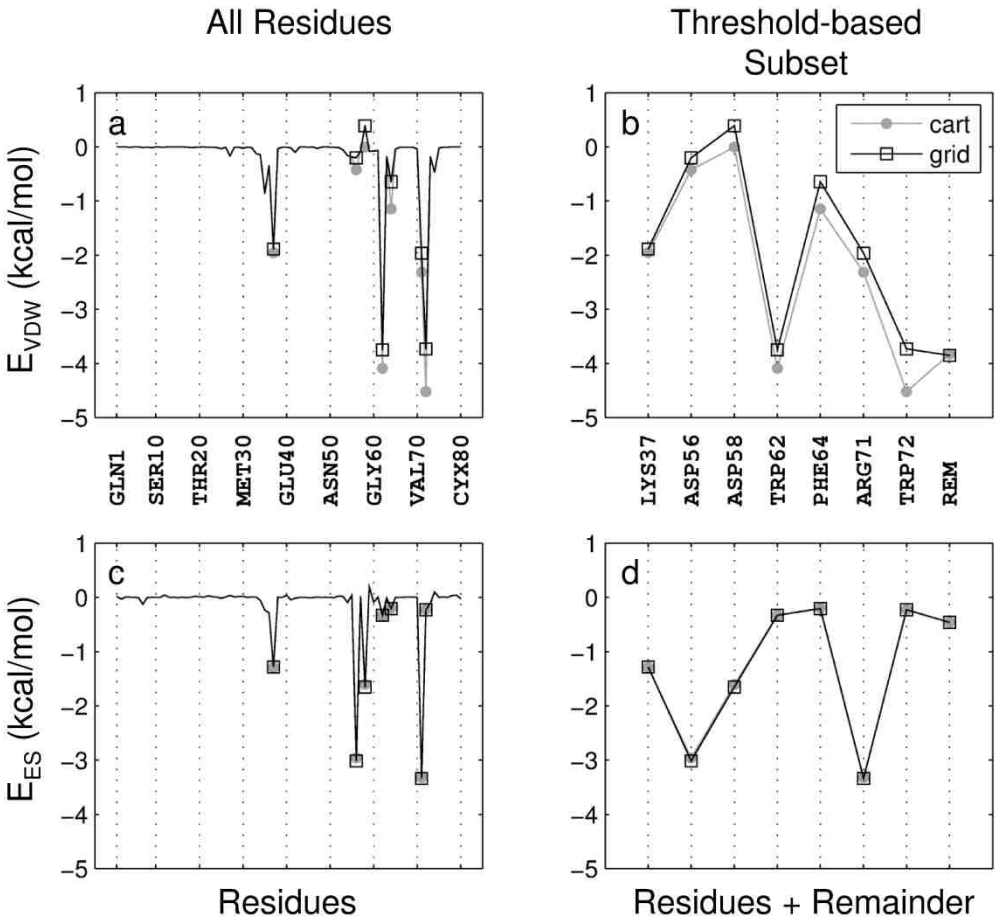


tots
Ki = 2.55 (μM)

Patrick M. Holden, Harmeet Kaur, Miriam Gochin, and Robert C. Rizzo

Holden et al., . Bioorg. Med. Chem. (2012) doi: 10.1016/j.bmcl.2012.02.017

Grid-Based Footprints



Grid are faster than Cart

Per-residues may be abstracted to a grid

Grid-based and Cartesian footprints show good agreement

Plasminogen kringle-4 protein which is an important protein in blood clotting (pdb code 2PK4)

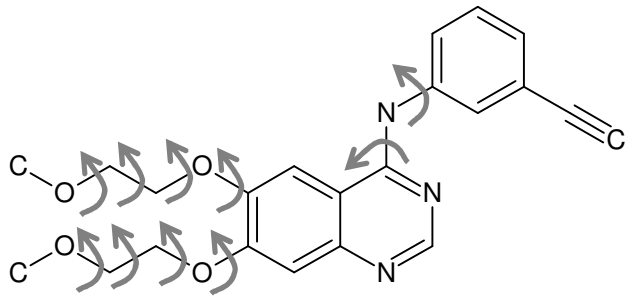
2PK4 consists of 80 residues

All 80 shown on the left, Subset shown on right

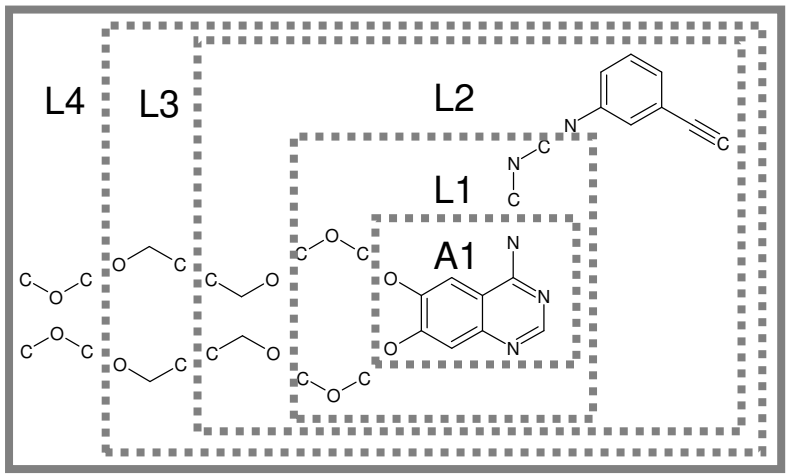
VDW on top, ES on bottom

A remainder grid is calculated to insure that the FP sum = total

a



b



Sampling using Anchor-&-Grow

Start from anchor orient

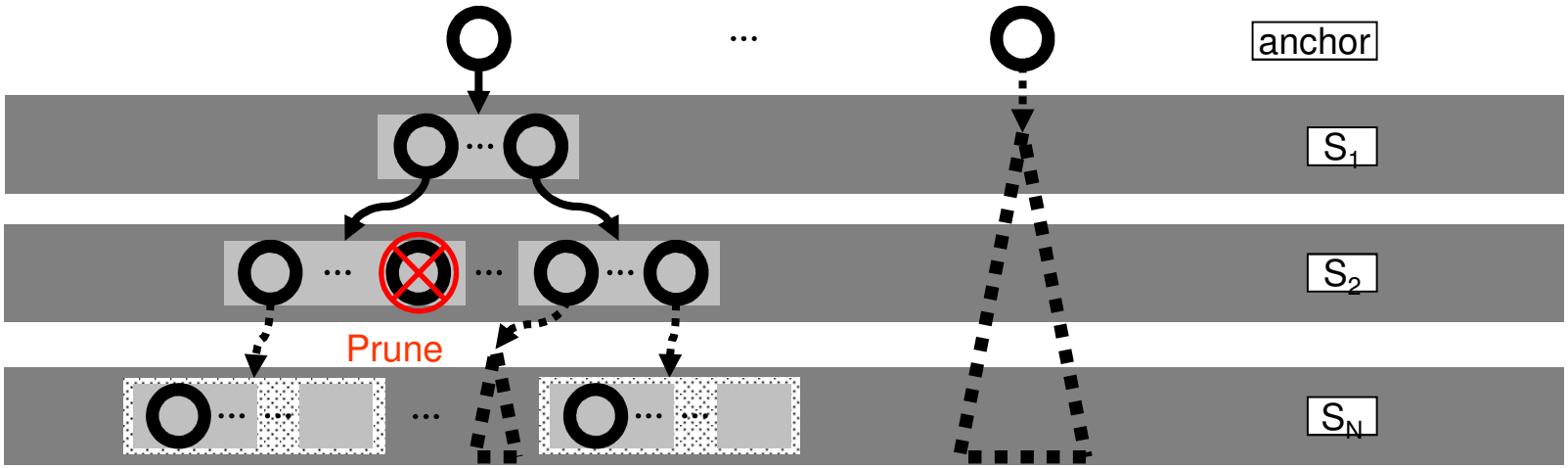
Arrange segments by layer about anchor center

Grow each segment one at a time

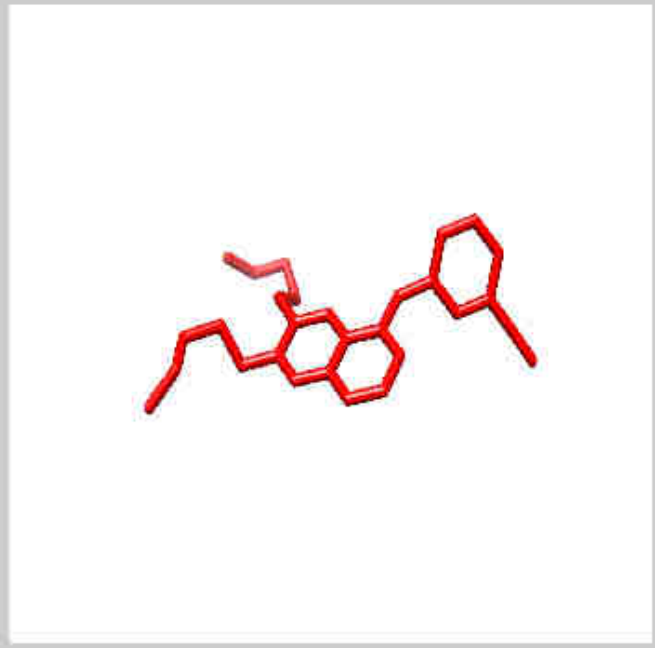
Grow segments in Layer 1

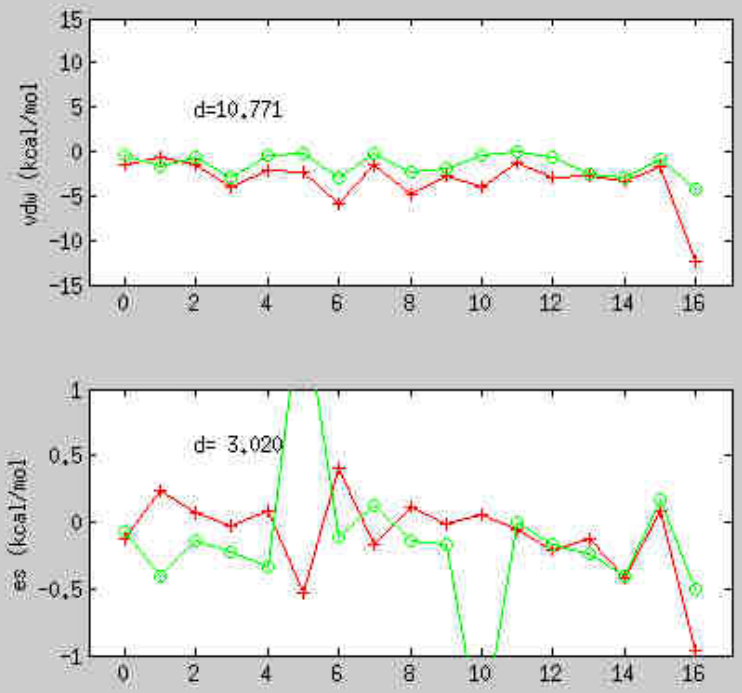
Grow segments in Layer 2 and so on

c

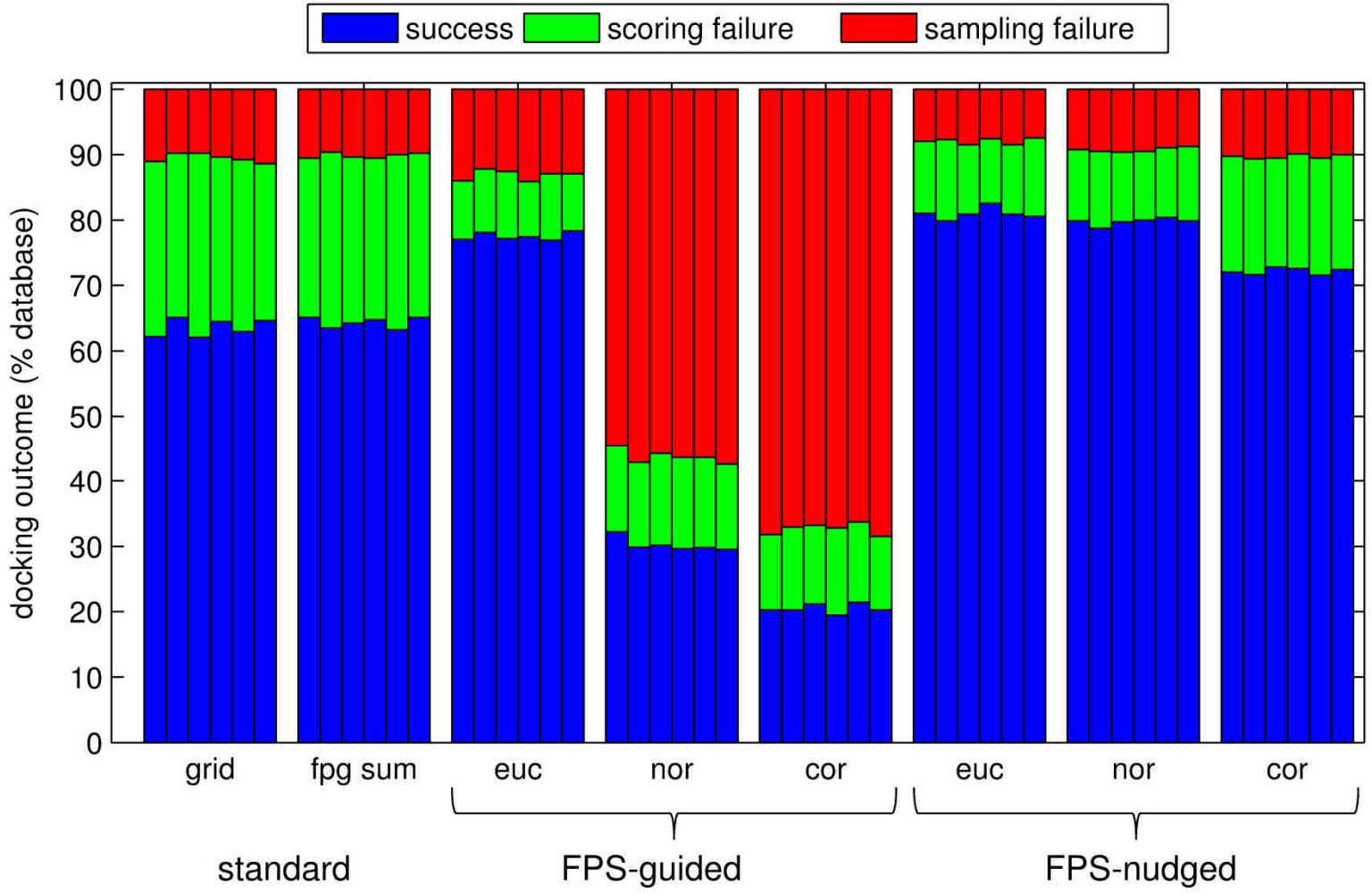


Footprint-Guided Growth





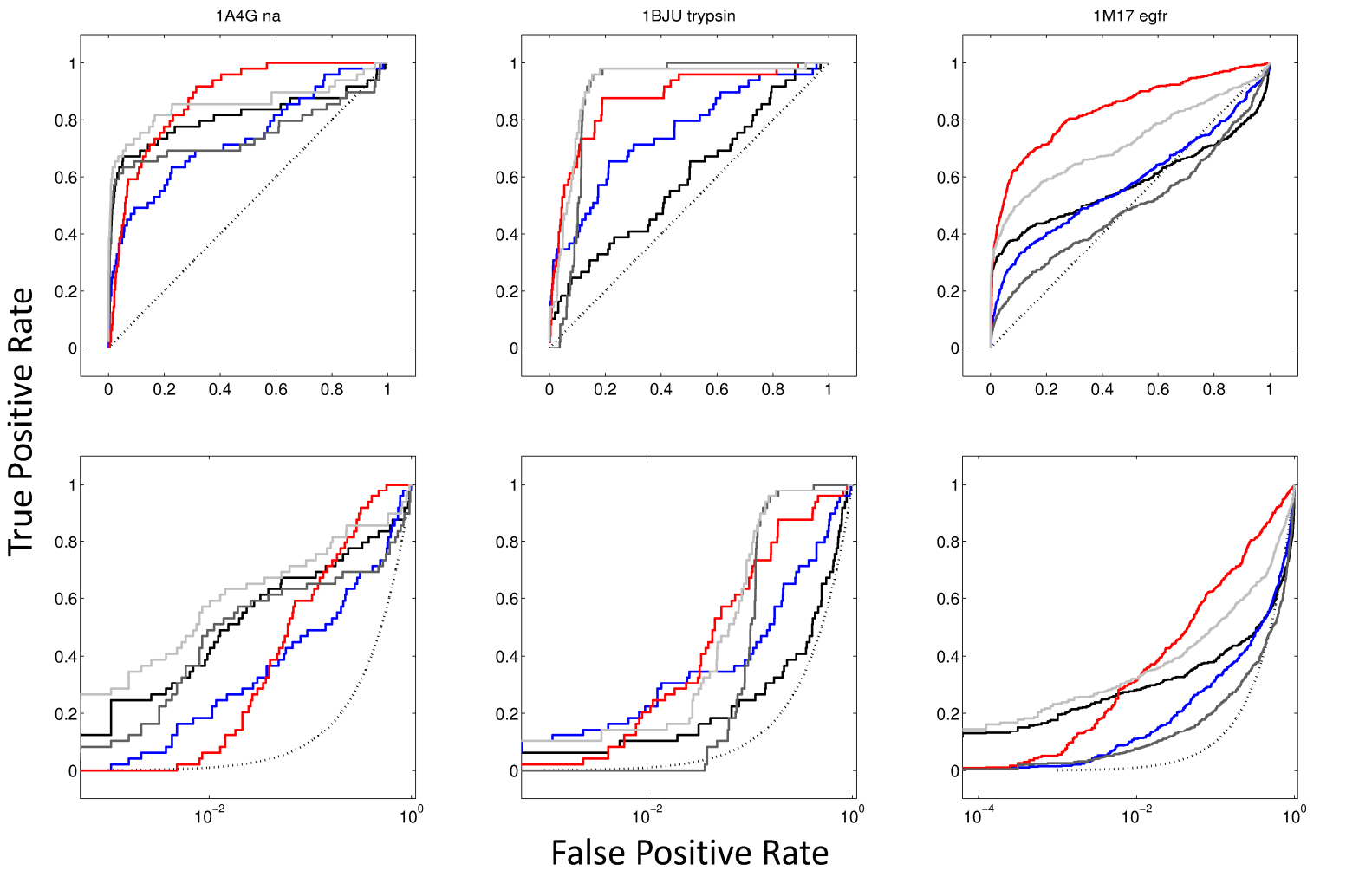
Grid-Based Footprints



Grid is O(N), Multi-grid is O(N*M), Cartesian O(N*K) M << K
Multi-grid is about 5 times slower

Effect of scoring function on sampling

d = driven; s = stared; r = rescored



DOCK Input File

```
DOCK 3.7 parameter
#####################################################
# NOTE: split_database_index is reserved to specify a list of files
ligand_atom_file               split_database_index
#####################################################
#                               OUTPUT
output_file_prefix             test.
#####################################################
#                               MATCHING
match_method                   2
distance_tolerance             0.05
match_goal                     5000
distance_step                  0.05
distance_maximum               0.5
timeout                        10.0
nodes_maximum                  4
nodes_minimum                  4
bump_maximum                   50.0
bump_rigid                     50.0
#####################################################
#                               COLORING
chemical_matching              no
case_sensitive                 no
#####################################################
#                               SEARCH MODE
atom_minimum                   4
atom_maximum                   100
number_save                    1
molecules_maximum              100000
check_clashes                  yes
do_premax                      no
do_clusters                    no
```

Increase for more sampling

Max is 4. To go higher you have to change the code.

Allowing clashes can help sampling

DOCK Input File (continued)

```
#######################################################
#                               SCORING
ligand_desolvation              volume
vdw_maximum                     1.0e10
electrostatic_scale             1.0
vdw_scale                       1.0
internal_scale                  0.0
#######################################################
# INPUT FILES / THINGS THAT CHANGE
receptor_sphere_file            ../dockfiles/matching_spheres.sph
vdw_parameter_file              ../dockfiles/vdw.parms.amb.mindock
delphi_nsize                    81
flexible_receptor               no
total_receptors                 1
############## grids/data for one receptor
rec_number                      1
rec_group                       1
rec_group_option                1
solvmap_file                    ../dockfiles/ligand.desolv.heavy
hydrogen_solvmap_file           ../dockfiles/ligand.desolv.hydrogen
delphi_file                     ../dockfiles/trim.electrostatics.phi
chemgrid_file                   ../dockfiles/vdw.vdw
bumpmap_file                    ../dockfiles/vdw.bmp
############## end of INDOCK
```

Delphi_nsize is electrostatic grid size

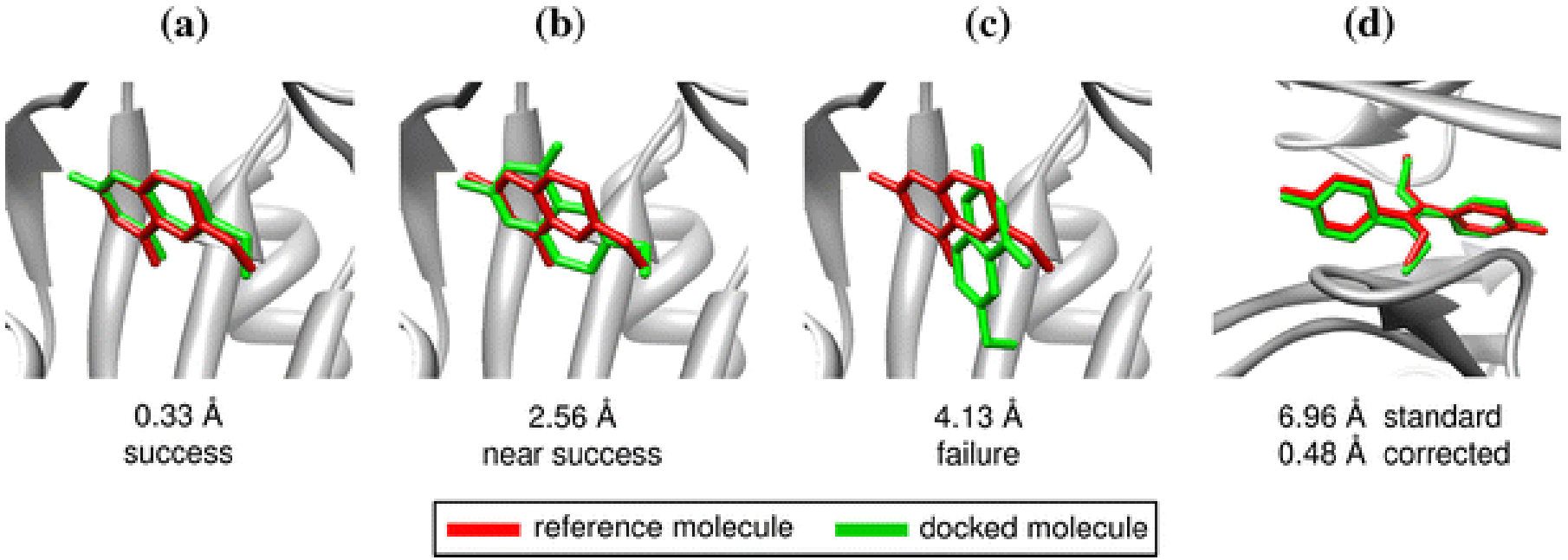
Things are structured differently in Github

```
ls -l ~/zzz.github/DOCK/
total 32
-rw-r--r--.  1 tbalius bks 2737 Aug 28 14:09 README.md
drwxr-xr-x.  2 tbalius bks 4096 Aug 27 11:22 analysis
drwxr-xr-x.  2 tbalius bks 4096 Aug 28 14:50 common
drwxr-xr-x.  7 tbalius bks 4096 Sep 11 16:53 docking
drwxr-xr-x.  3 tbalius bks 4096 Aug 27 11:22 install
drwxr-xr-x.  9 tbalius bks 4096 Aug 28 14:09 ligand
drwxr-xr-x. 19 tbalius bks 4096 Aug 27 11:22 proteins
drwxr-xr-x.  3 tbalius bks 4096 Aug 27 11:23 test
```

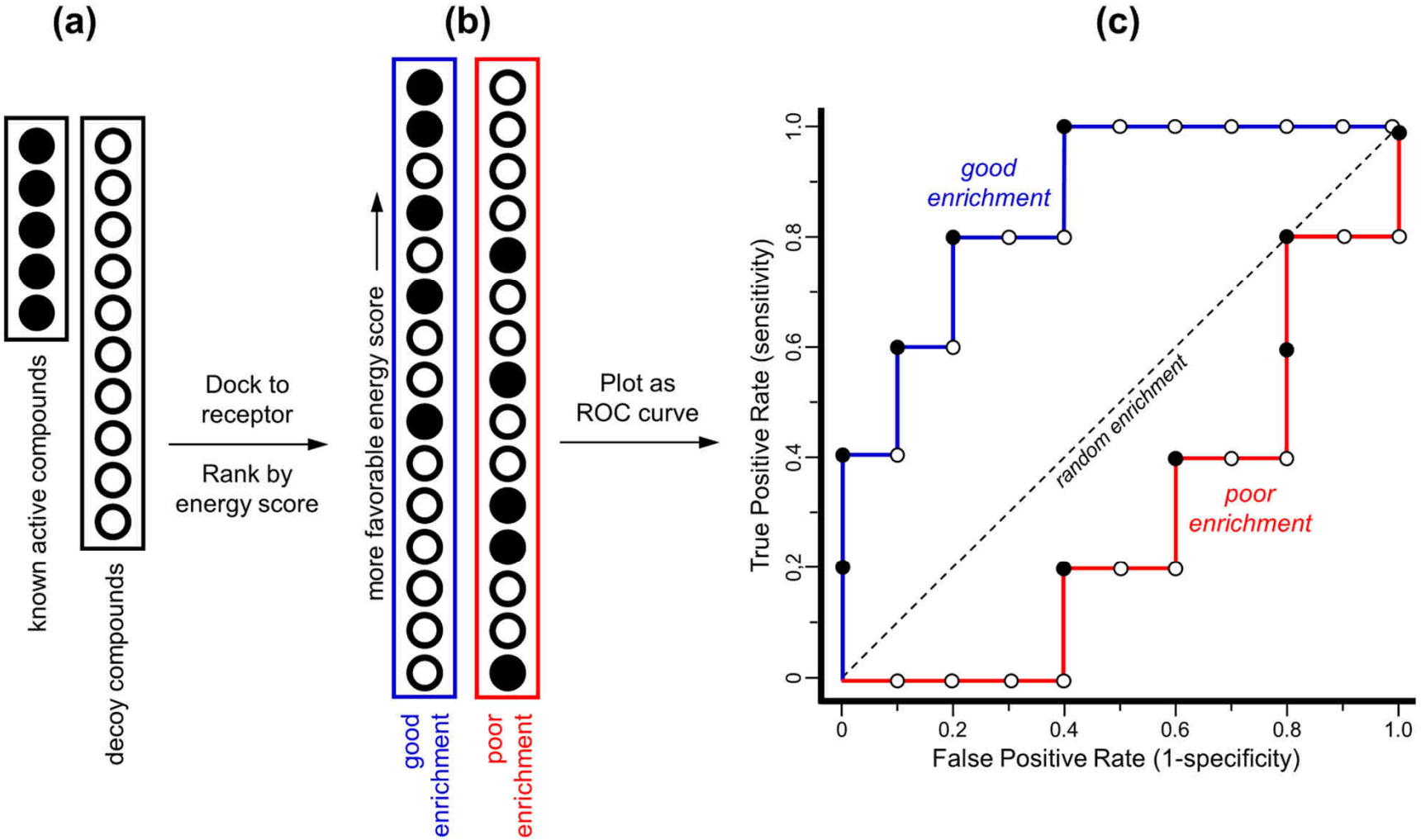
Work done by Teague and Ryan.

Evaluation Methods

- Pose Reproduction (cognate docking, cross docking)
- Enrichment calculations
- Prospective testing of predictions



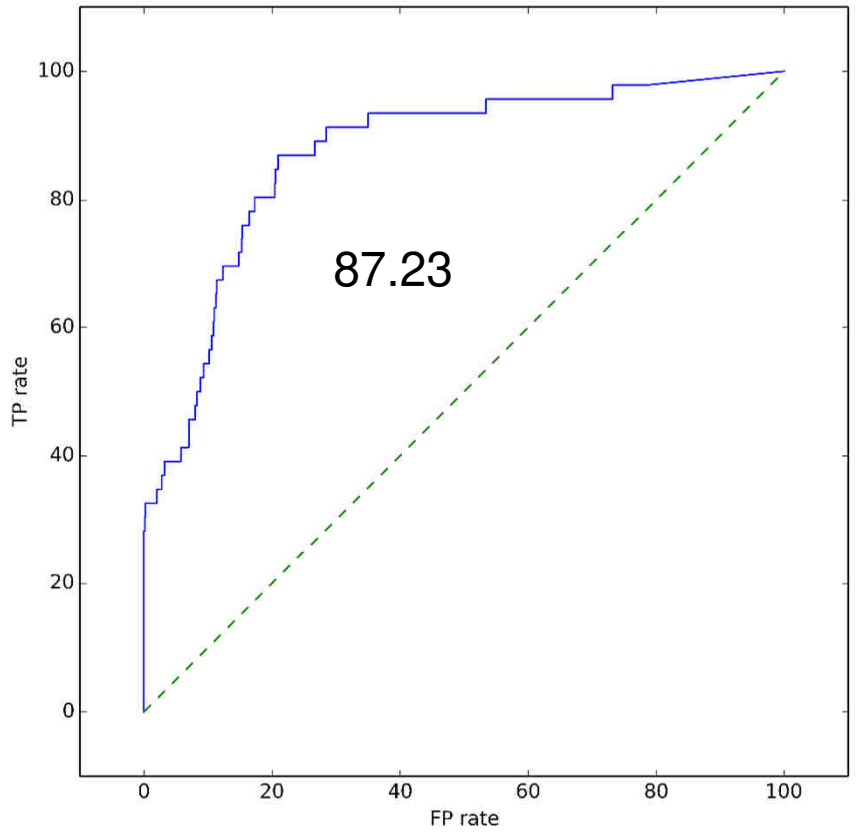
Enrichments: ROC Cuves



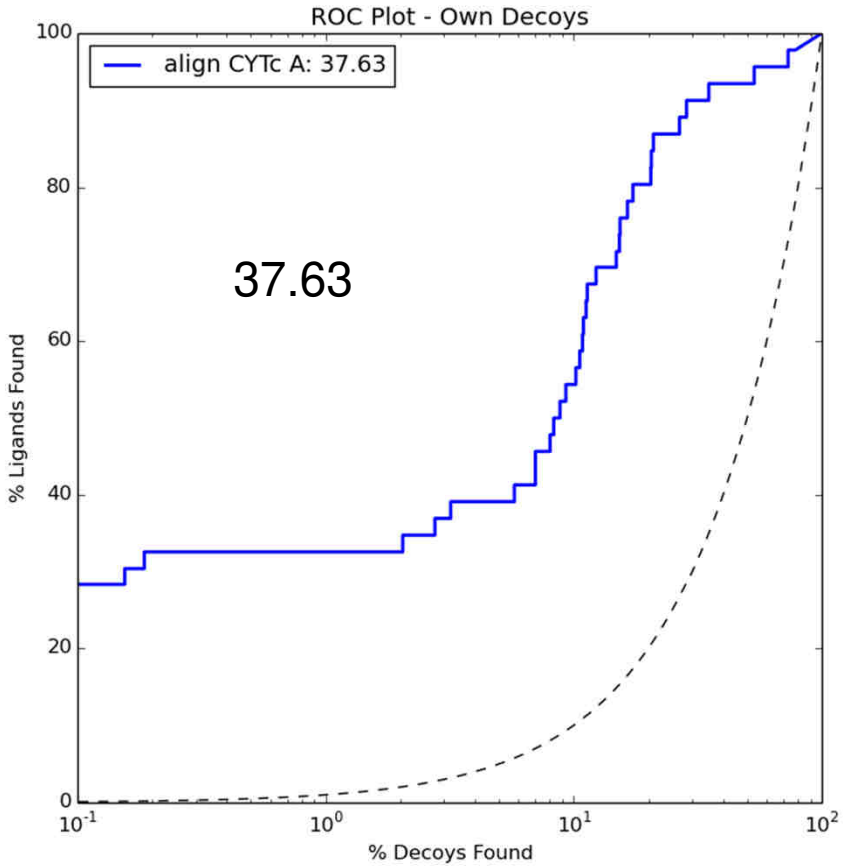
Log-adjusted AUC: Early Enrichment Weighted More

CcP conformation A

ROC curve

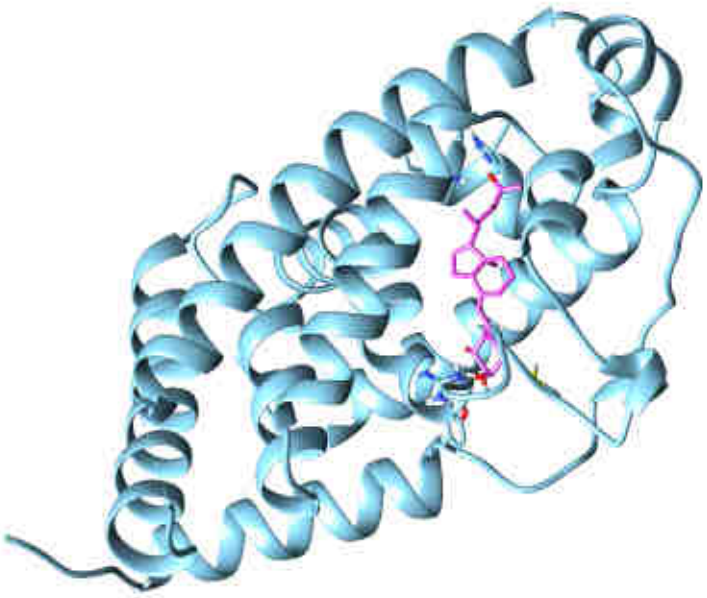


Log adjusted ROC curve

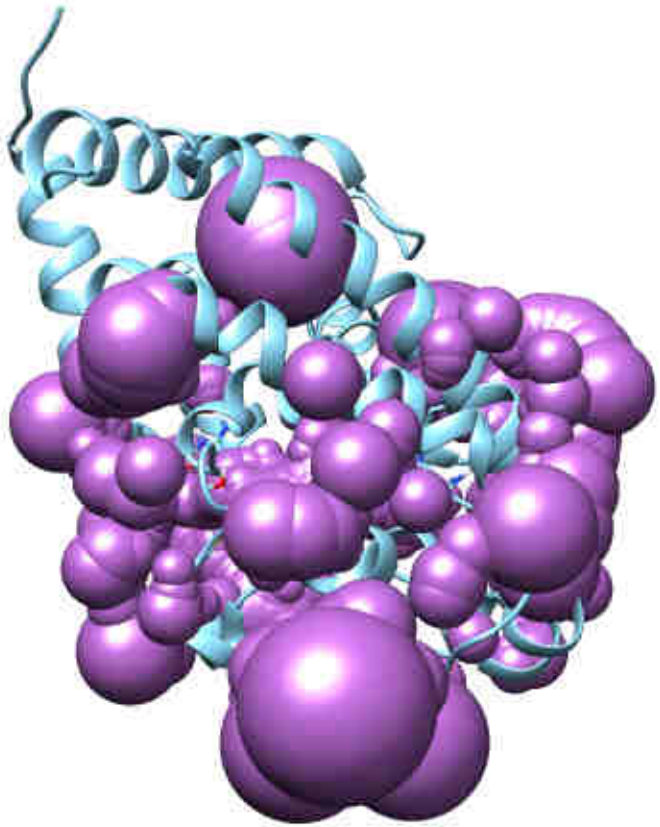


Tweaking your set up – Spheres

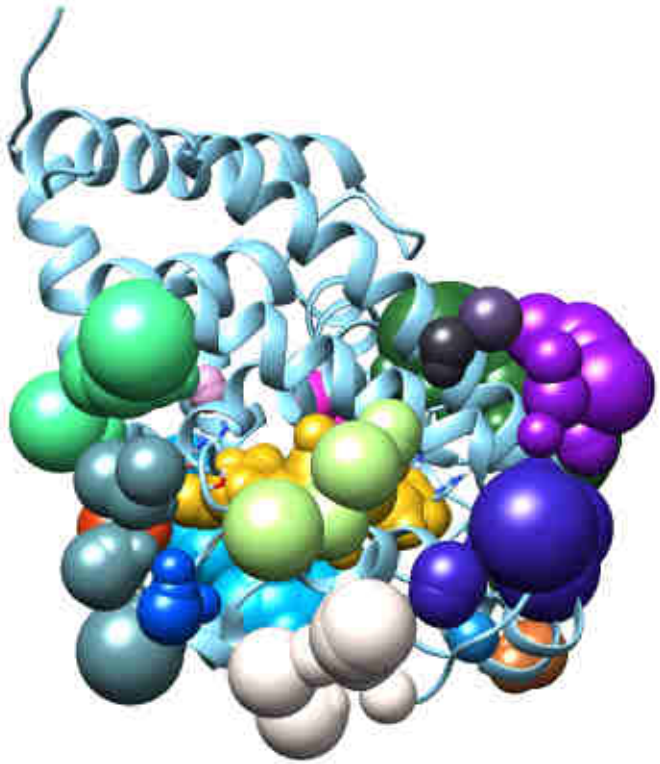
- Place spheres were you want your rings to go
- Use previous screens for ideas



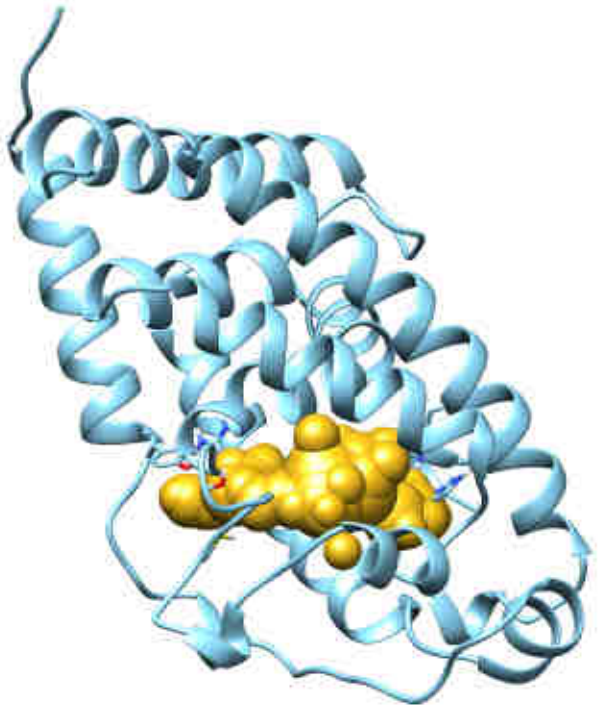
SPHGEN Spheres



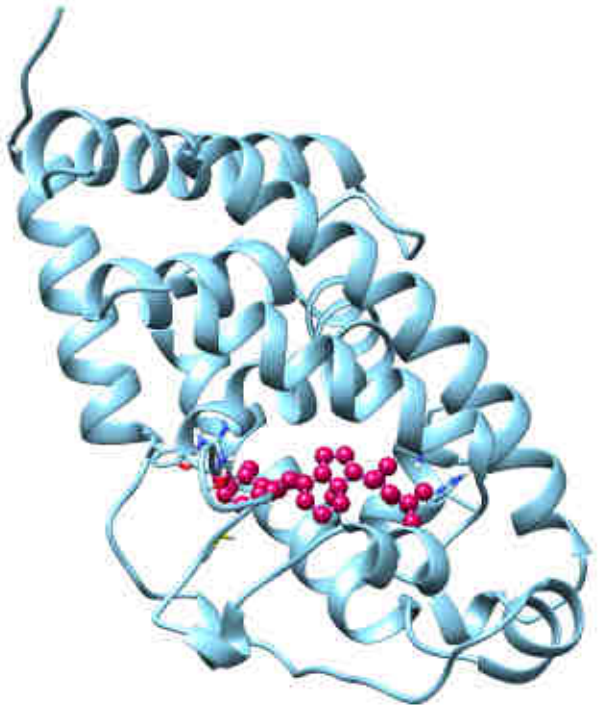
SPHGEN Sphere Clusters



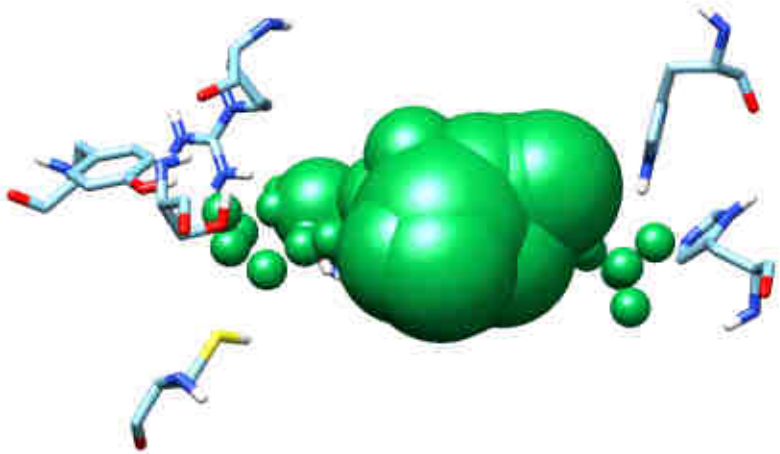
SPHGEN Cluster1 Spheres



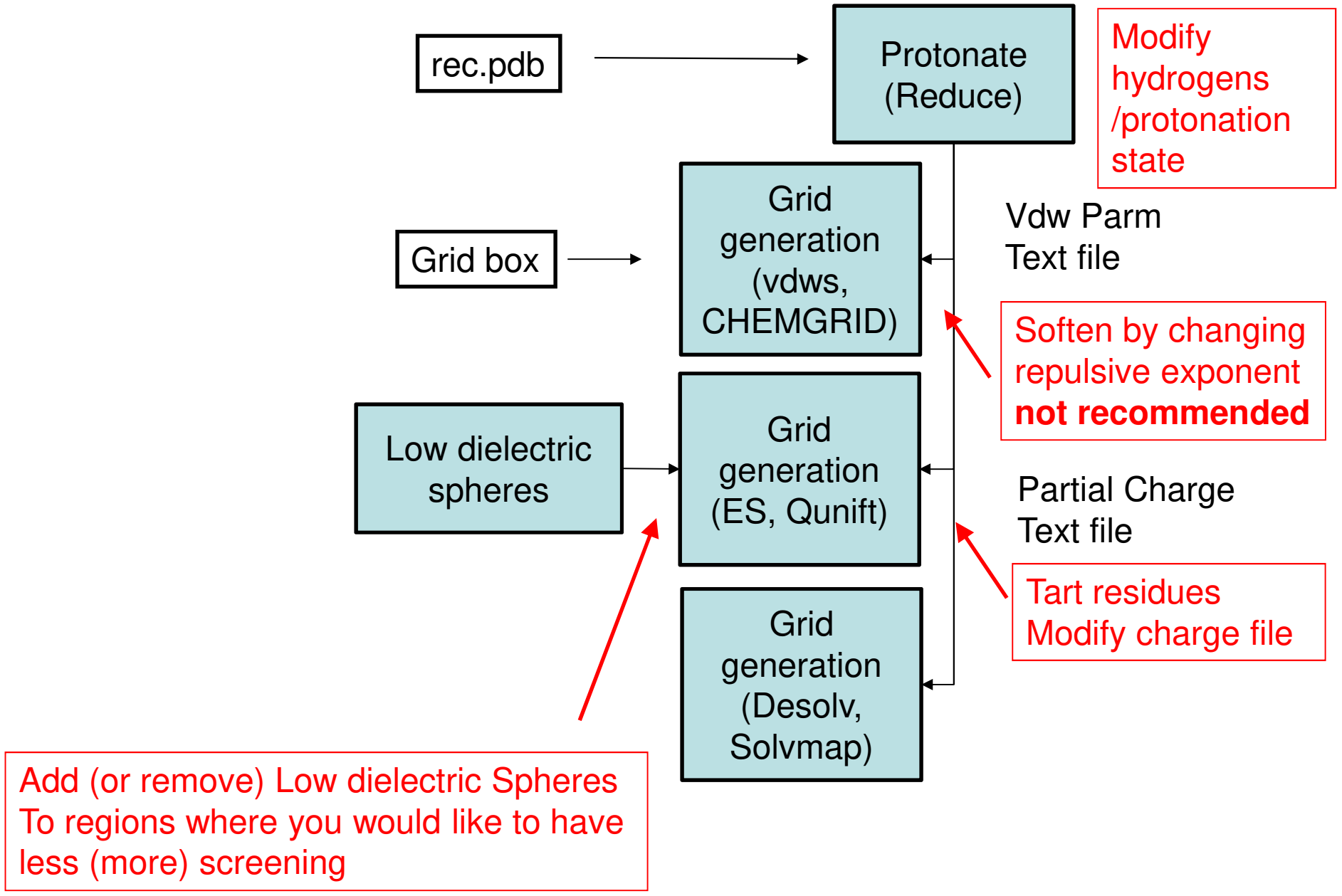
Ligand Atoms Spheres



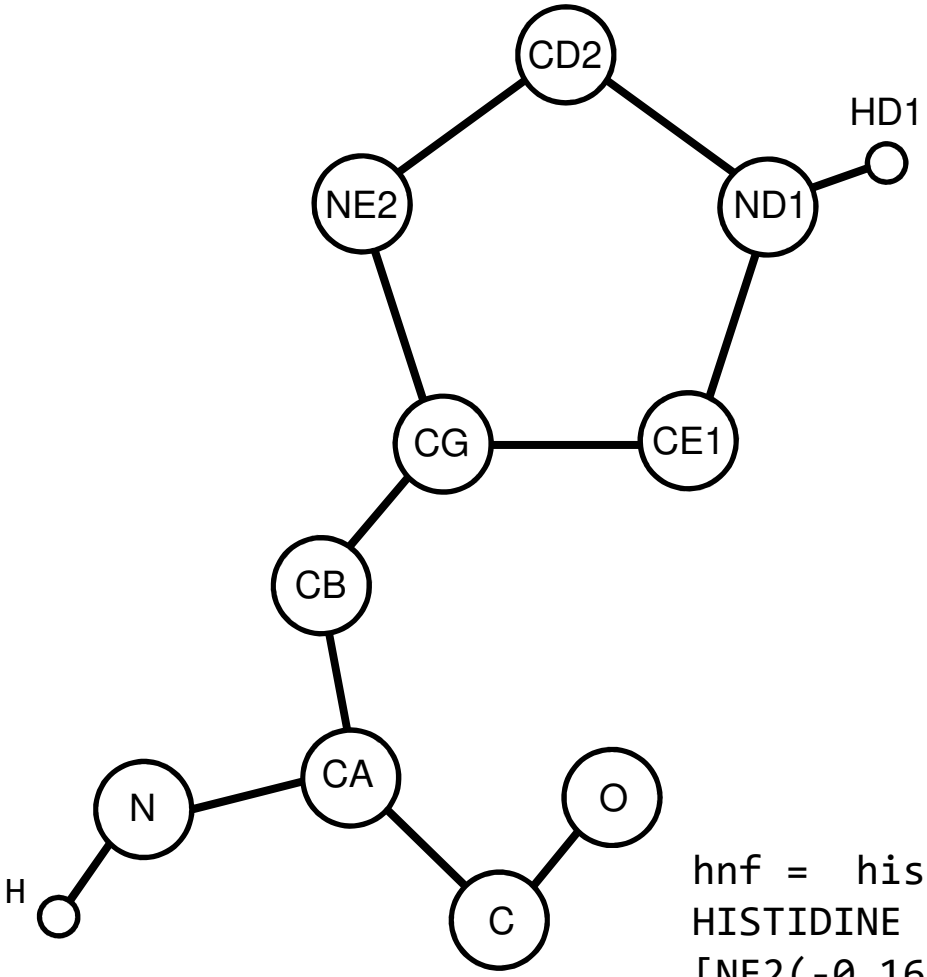
Matching Spheres



Receptor preparation



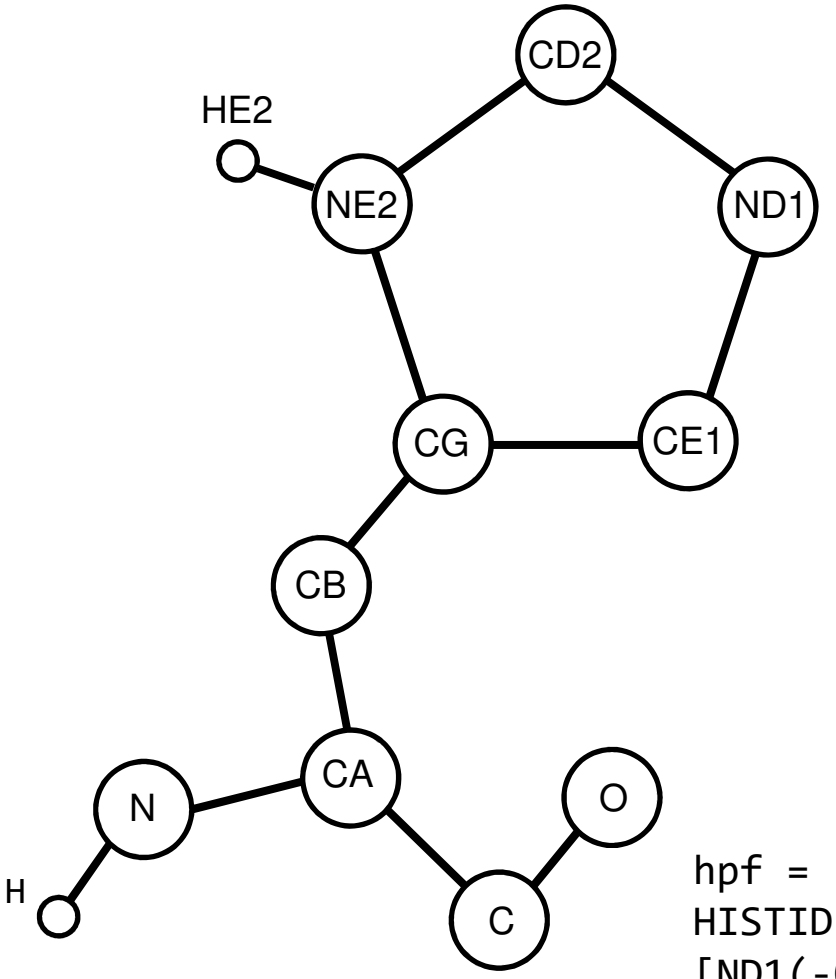
HISTIDINE neutral delta proton [tart2]



N	-0.520	N	-0.520	
C	0.526	C	0.526	
O	-0.500	O	-0.500	
CA	0.219	CA	0.219	
CB	0.060	CB	0.060	
CG	0.089	CG	0.089	
CD2	0.145	CD2	0.145	
CE1	0.384	CE1	0.384	
ND1	-0.444	ND1	-0.364	+0.08
NE2	-0.527	NE2	-0.687	-0.16
H	0.248	H	0.248	
HD1	0.320	HD1	0.400	+0.08

hnf = his negative epsilon nitrogen
HISTIDINE neutral delta proton, but more polar
[NE2(-0.16) --> ND1 (+0.08), HD1(+0.08)]

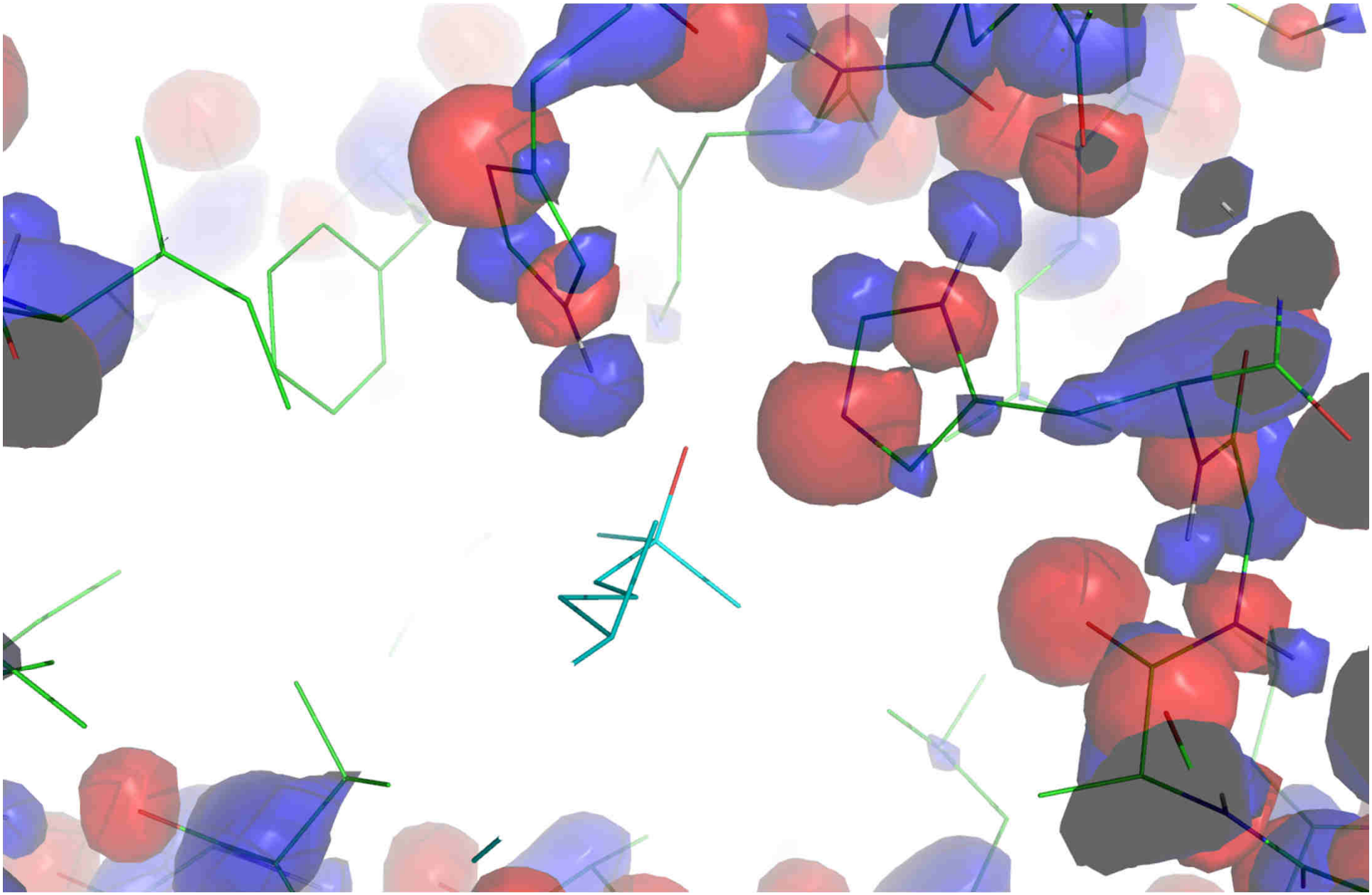
HISTIDINE neutral epsilon proton [tart2]



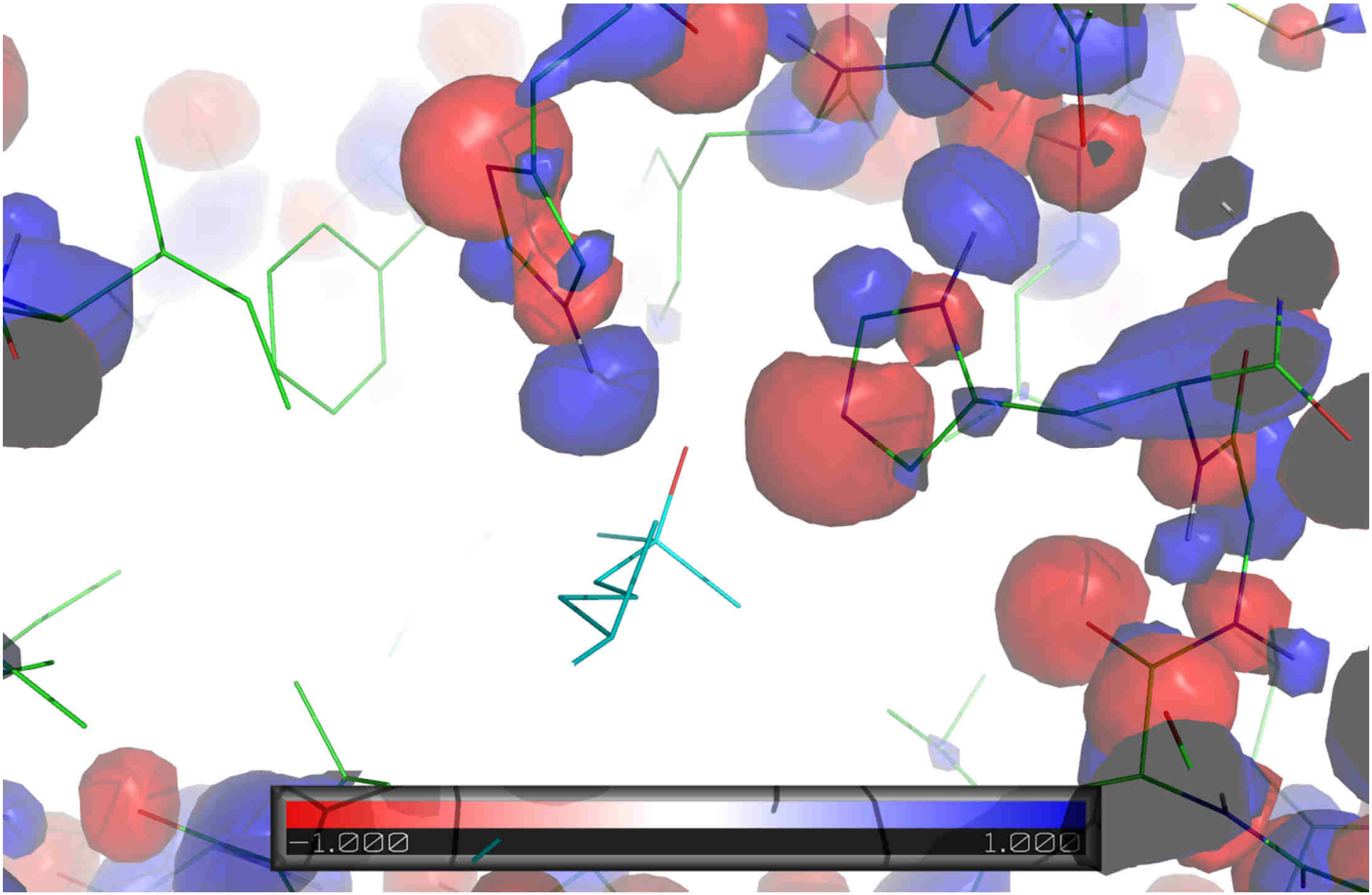
N	-0.520	N	-0.520	
C	0.526	C	0.526	
O	-0.500	O	-0.500	
CA	0.219	CA	0.219	
CB	0.060	CB	0.060	
CG	0.112	CG	0.112	
CD2	0.122	CD2	0.122	
CE1	0.384	CE1	0.384	
ND1	-0.527	ND1	-0.607	-0.08
NE2	-0.444	NE2	-0.524	-0.08
H	0.248	H	0.248	
HE2	0.320	HE2	0.480	+0.16

hpf = his positive epsilon hydrogen
HISTIDINE neutral epsilon proton, but more polar
[ND1(-0.08), NE2 (-0.08) --> HE2(+0.16)]

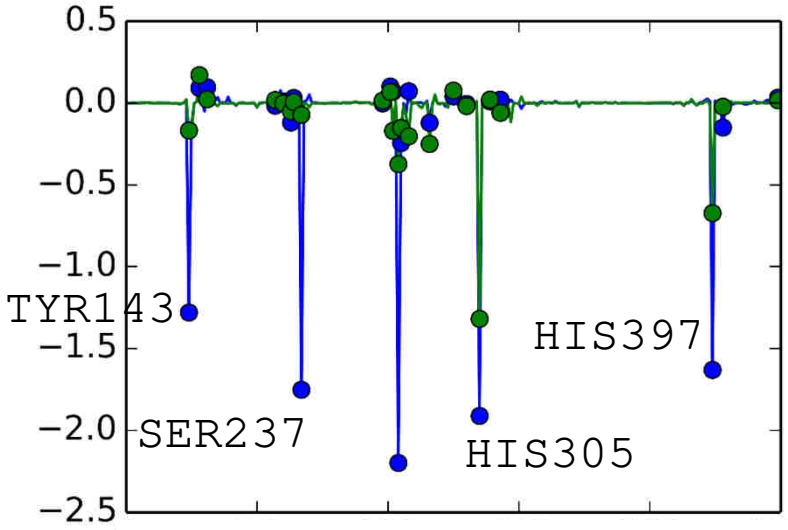
Original partial charges

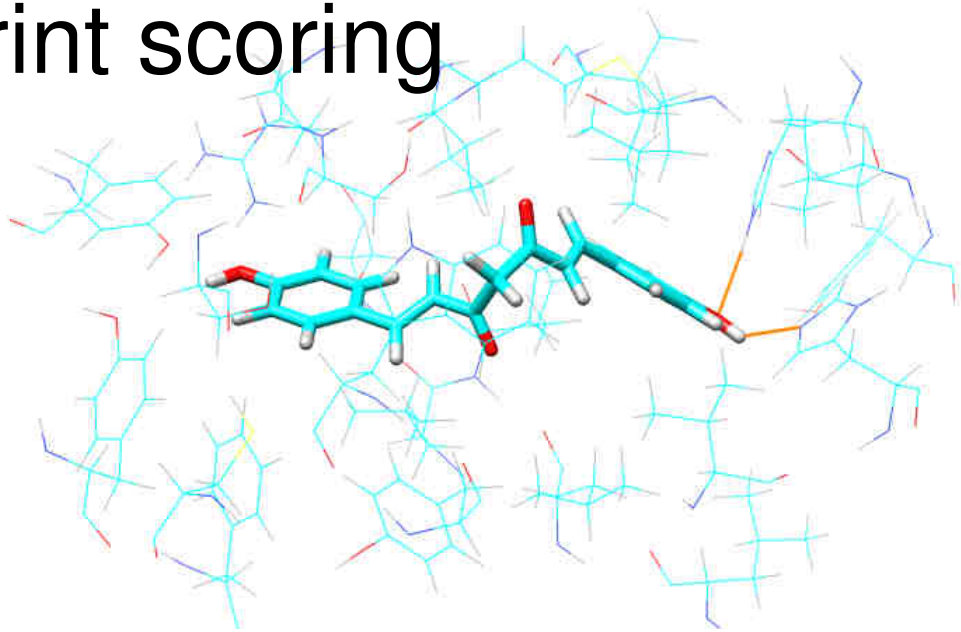


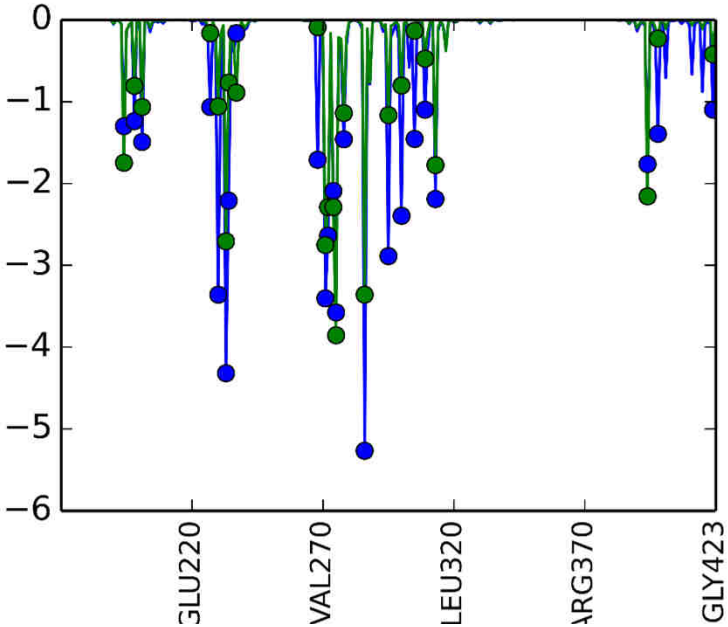
More polar (tart2) partial charges

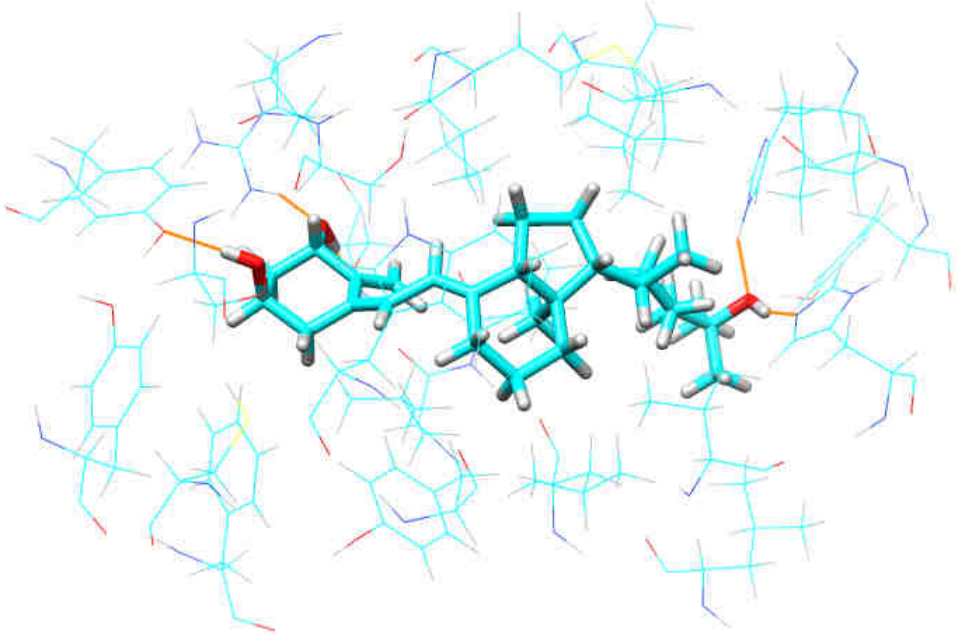


Footprint scoring





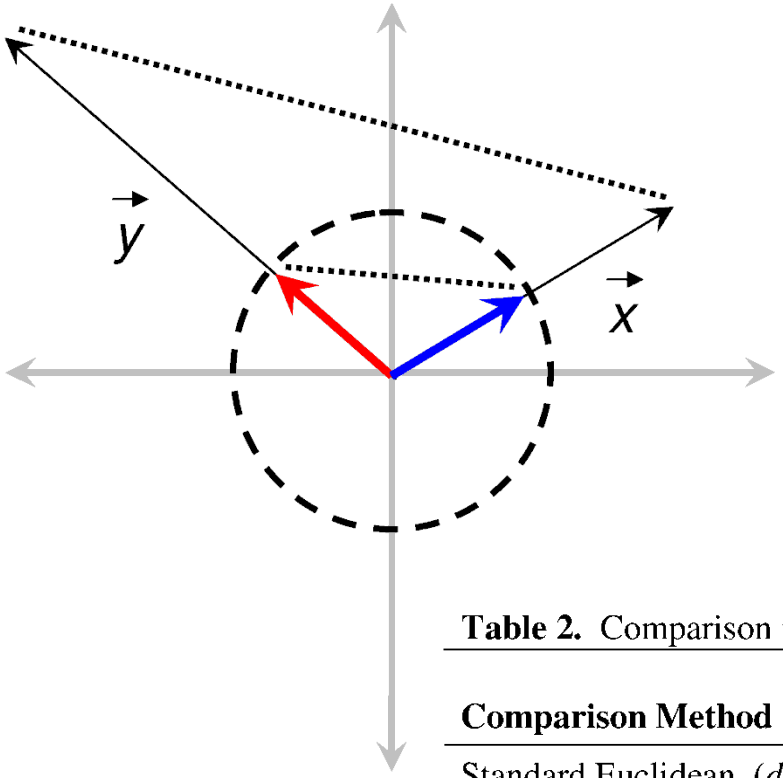




Footprint Similarity Nomenclature

- DCE -- Dock Cartesian Energy (Standard Energy function)
- Cartesian energy decompositions of VDW, ES and H-bonds
- FPS_{VDW} -- quantifies the similarity between 2 VDW footprints
- FPS_{ES} -- quantifies the similarity between 2 ES footprints
- FPS_{HB} -- quantifies the similarity between 2 H-bond footprints
- $FPS_{VDW+ES} = FPS_{VDW} + FPS_{ES}$ (consensus score)

Methods for Quantifying Similarity



$$d = \left\|\vec{x} - \vec{y}\right\| = \sqrt{\sum (x_i - y_i)^2}$$

$$d_{norm} = \left\|\vec{X} - \vec{Y}\right\| \quad \vec{X} = \vec{x}/\left\|\vec{x}\right\| \quad \vec{Y} = \vec{y}/\left\|\vec{y}\right\|$$

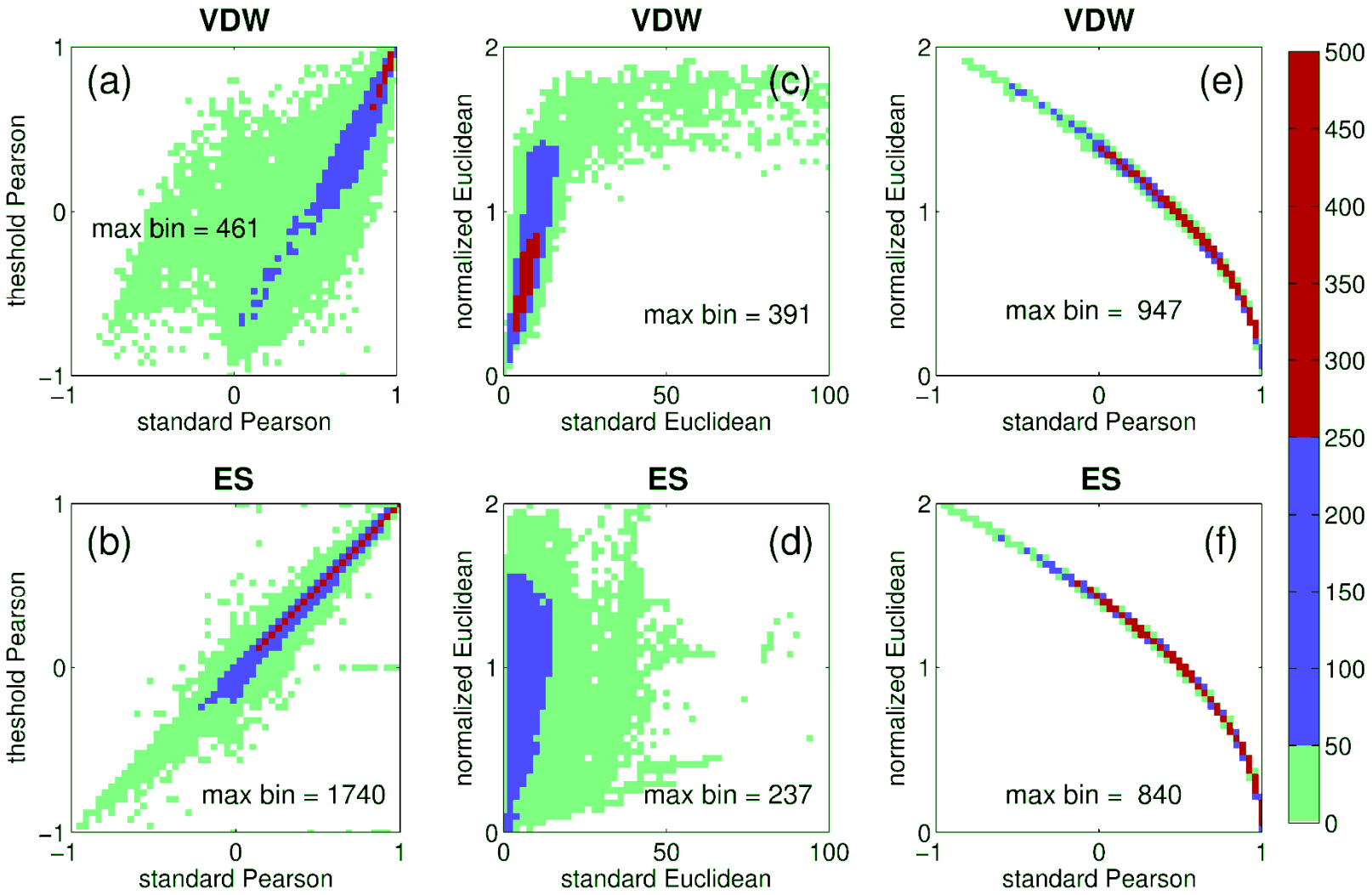
$$r = \frac{\mathrm{cov}(\vec{x}, \vec{y})}{\sqrt{\mathrm{var}(\vec{x})}\sqrt{\mathrm{var}(\vec{y})}}$$

Table 2. Comparison methods and corresponding ranges for footprint similarity (FPS) scores.

Comparison Method	Ranges[a] FPS_{VDW}, FPS_{ES}, FPS_{HB}	FPS_{VDW+ES}	$FPS_{VDW+ES+HB}$
Standard Euclidean (d)	[0, ∞)	[0, ∞)	[0, ∞)
Normalized Euclidean (d_{norm})	[0, 2]	[0, 4]	[0, 6]
Standard Pearson (r)	[-1, 1]	[-2, 2]	[-3, 3]
Threshold Pearson (r_{thresh})	[-1, 1]	[-2, 2]	[-3, 3]

[a]The most favorable score possible for each method is underlined.

Functional Relationships



$$r = \cos(\theta) = \frac{\vec{x}^{\mu} \cdot \vec{y}^{\mu}}{\left\|\vec{x}^{\mu}\right\| \left\|\vec{y}^{\mu}\right\|} \approx \frac{\vec{x} \cdot \vec{y}}{\left\|\vec{x}\right\| \left\|\vec{y}\right\|} = \cos(\theta^*) \qquad d_{norm} = \sqrt{2(1-\cos(\theta^*))} \approx \sqrt{2(1-r)}$$

Functional Relationships

$$r = \cos(\theta) = \frac{\vec{x}^{\mu} \cdot \vec{y}^{\mu}}{\left\|\vec{x}^{\mu}\right\| \left\|\vec{y}^{\mu}\right\|} \approx \frac{\vec{x} \cdot \vec{y}}{\left\|\vec{x}\right\| \left\|\vec{y}\right\|} = \cos(\theta^*) \qquad d_{norm} = \sqrt{2(1-\cos(\theta^*))} \approx \sqrt{2(1-r)}$$

Corollary 1: if $\vec{u}$ and $\vec{v}$ are unit vectors, then $\left\|\vec{u}-\vec{v}\right\| = \sqrt{2(1-\cos(\theta))}$, where θ is the angle between $\vec{u}$ and $\vec{v}$.

Proof:

Let $\vec{u}$ and $\vec{v}$ be unit vectors. Then,

$$\cos(\theta) = \frac{\vec{u} \cdot \vec{v}}{\left\|\vec{u}\right\| \left\|\vec{v}\right\|} = \vec{u} \cdot \vec{v} \qquad (\because \quad \left\|\vec{u}\right\| = 1)$$

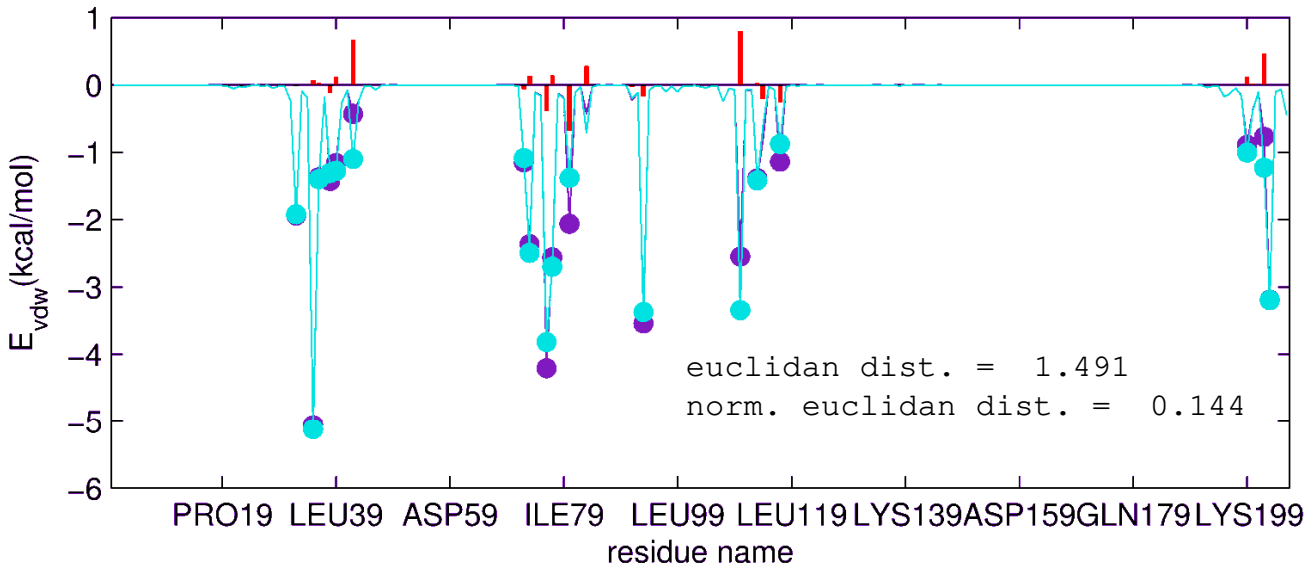
$$\left\|\vec{u}-\vec{v}\right\| = \sqrt{\sum (u_i - v_i)^2} = \sqrt{\sum u_i^{\,2} + \sum v_i^{\,2} - 2\sum u_i v_i}$$

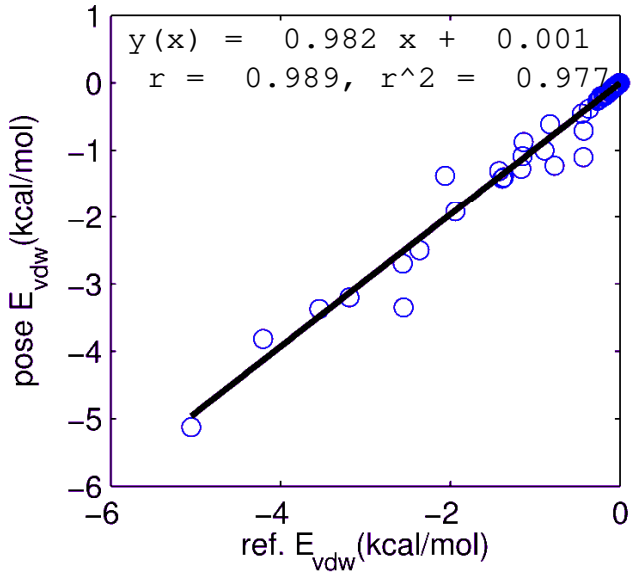
$$= \sqrt{1+1-2\sum u_i v_i} \qquad (\because \quad \left\|\vec{u}\right\|^2 = \sum u_i^{\,2} = 1)$$

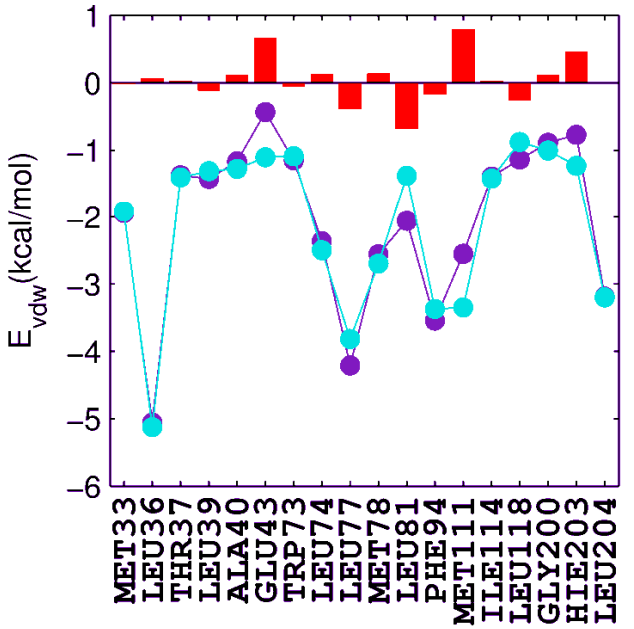
$$= \sqrt{2(1-\vec{u} \cdot \vec{v})}$$

Therefore, $\left\|\vec{u}-\vec{v}\right\| = \sqrt{2(1-\cos(\theta))}$

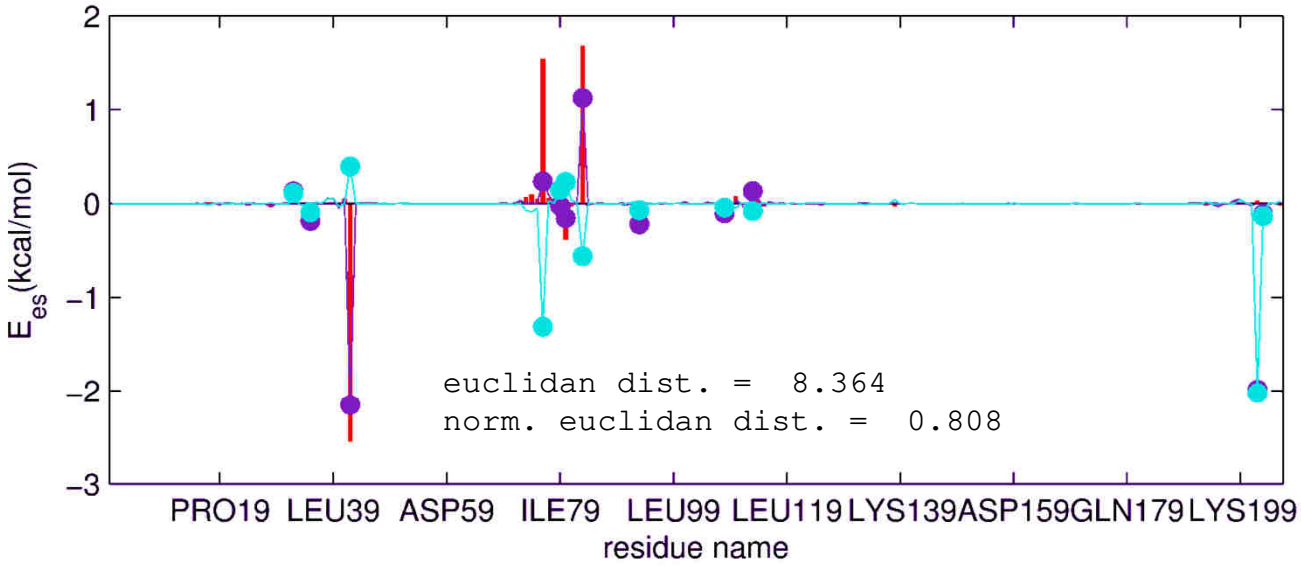
2QE4 van der Waals Footprint (Good Comparison)

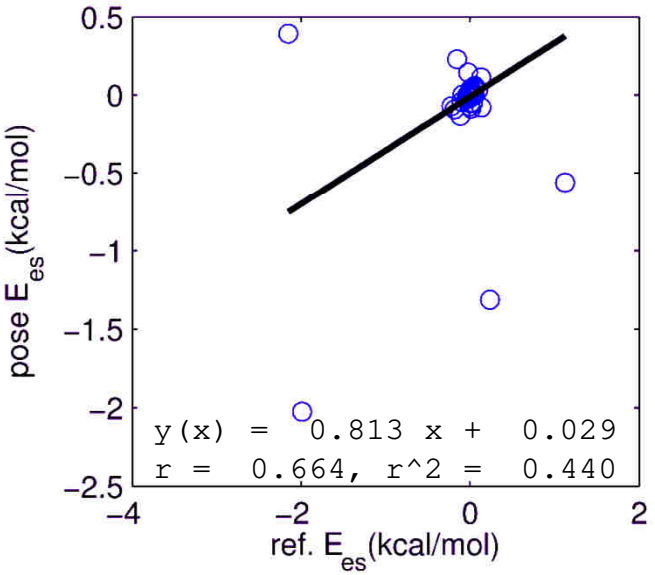


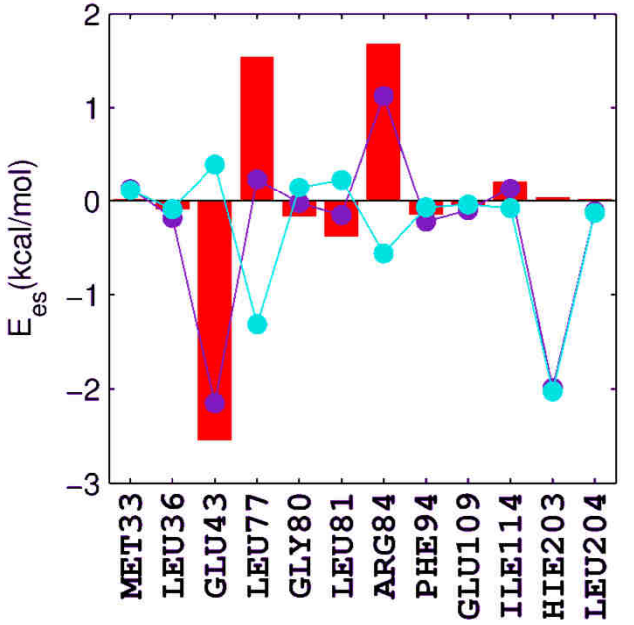




2QE4 Electrostatics Footprint (Bad Comparison)



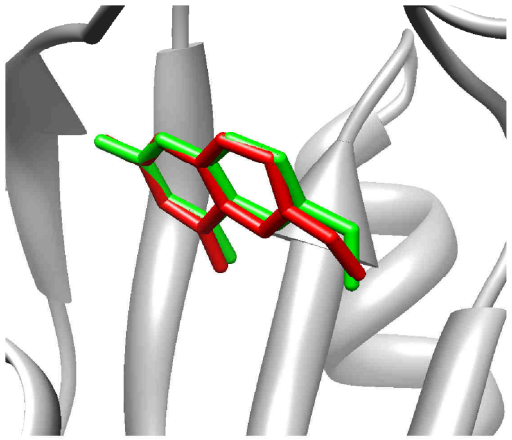




Structural Comparisons using rmsd

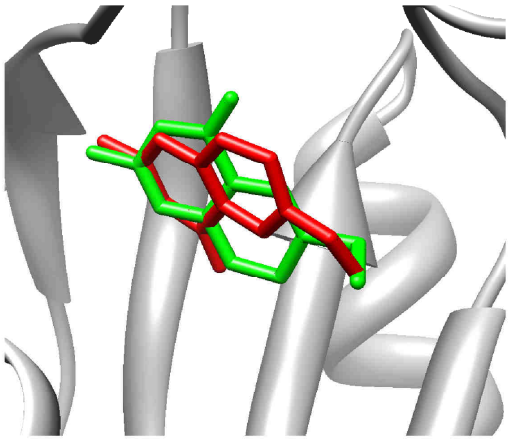
reference molecule docked molecule

(a)



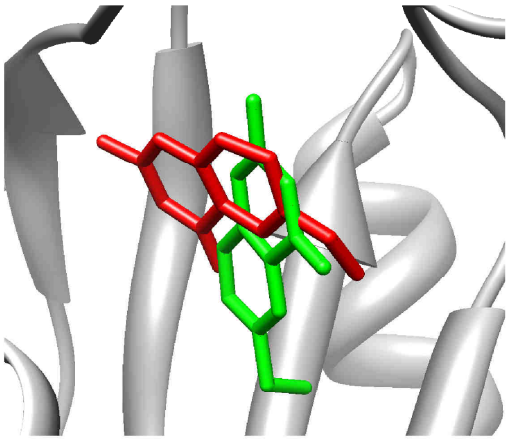
0.33 Å
success

(b)



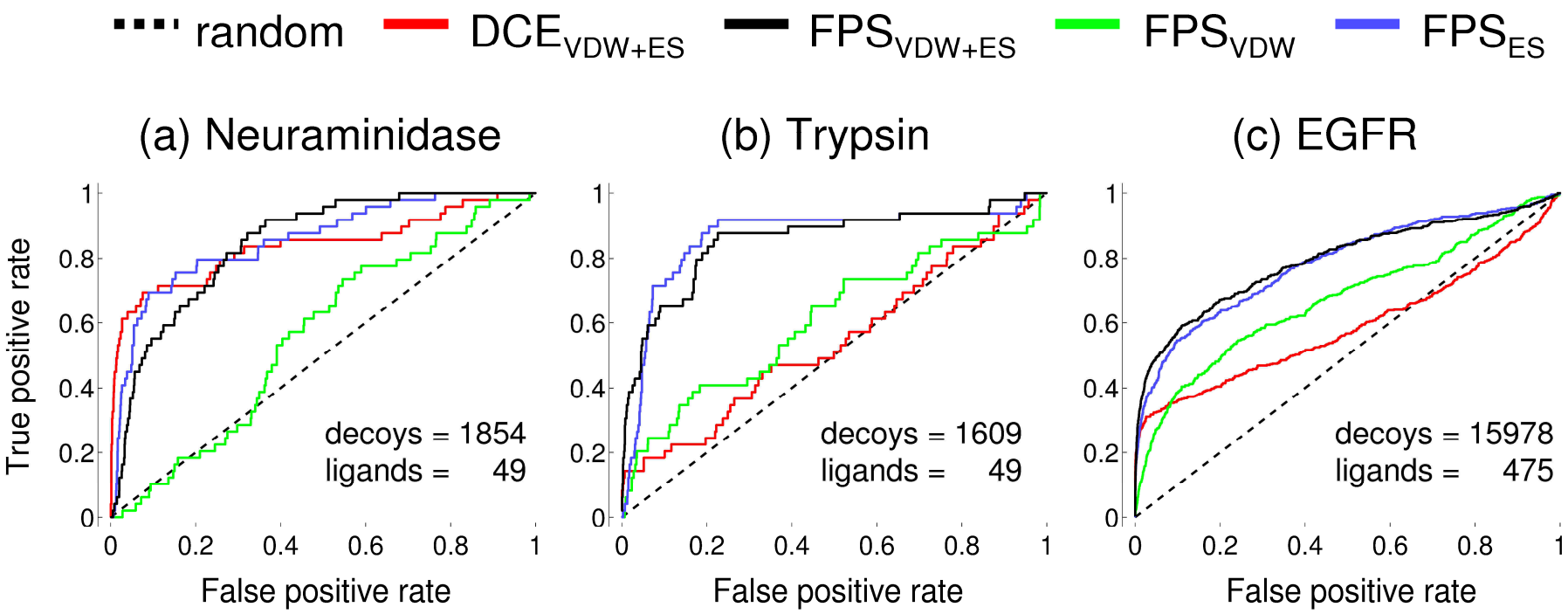
2.56 Å
near success

(c)

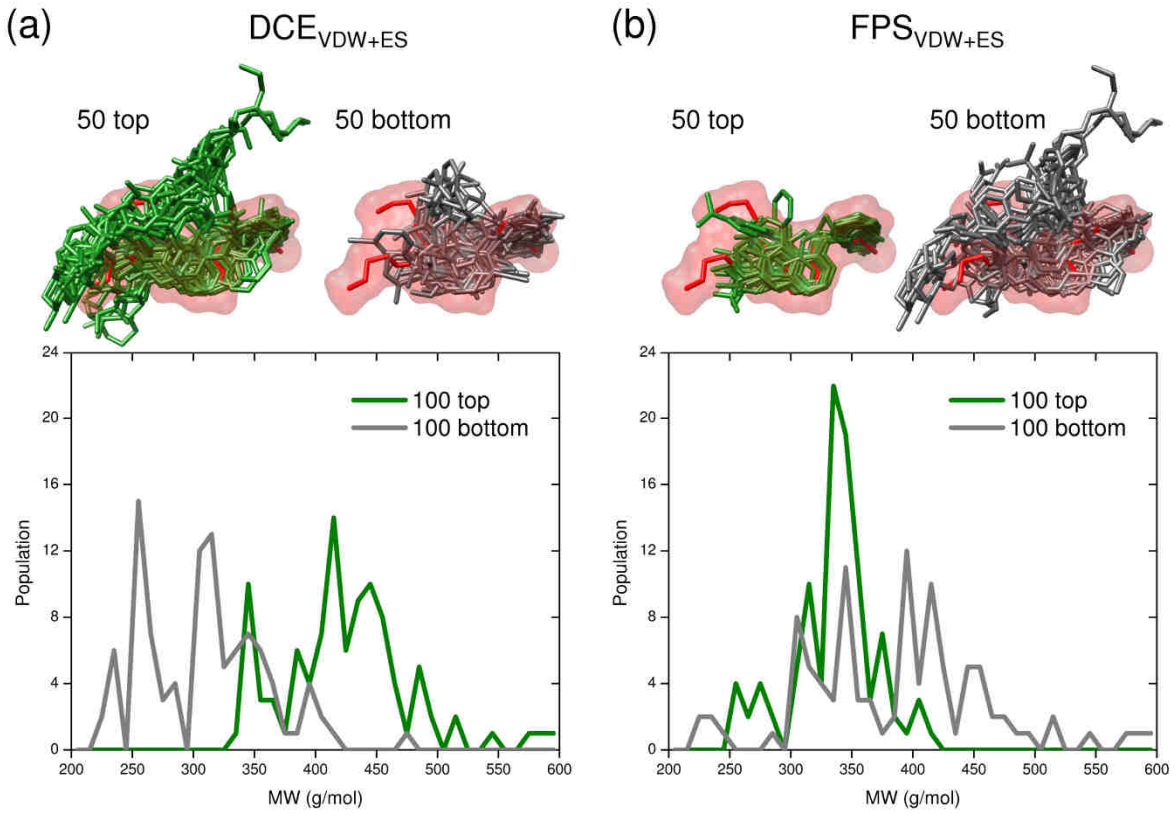


4.13 Å
failure

Enrichment (ROC Curves)

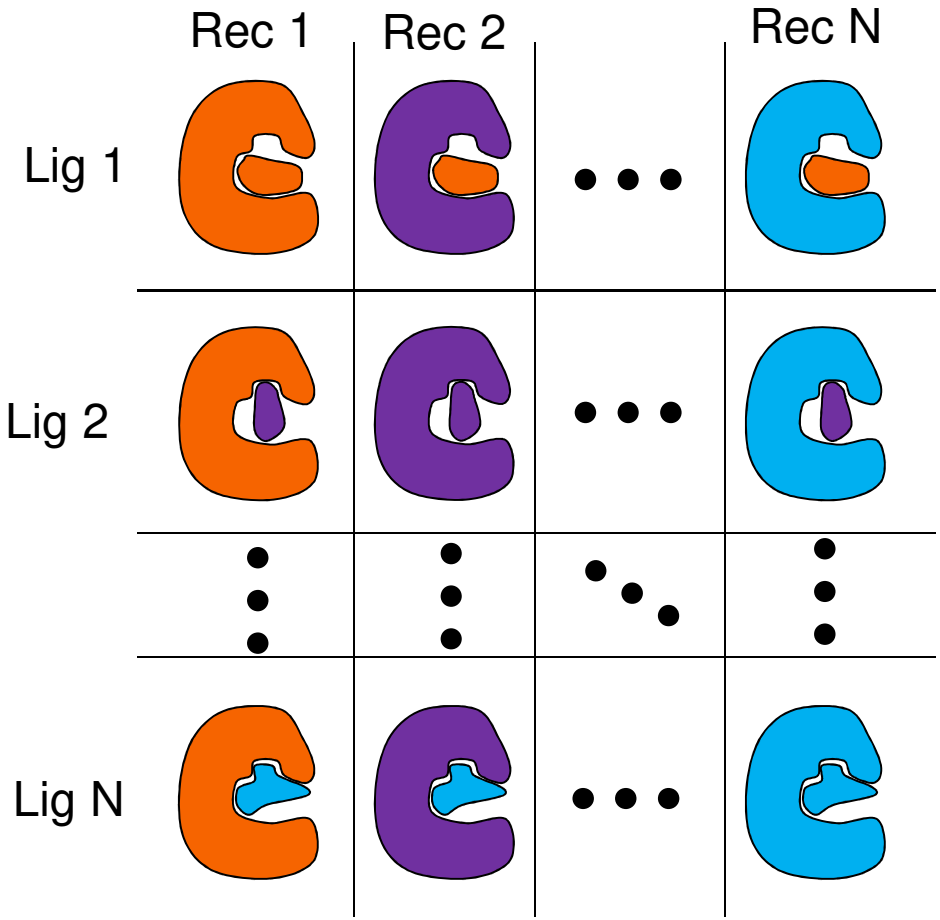


Enrichment (Molecular Weight Bias)



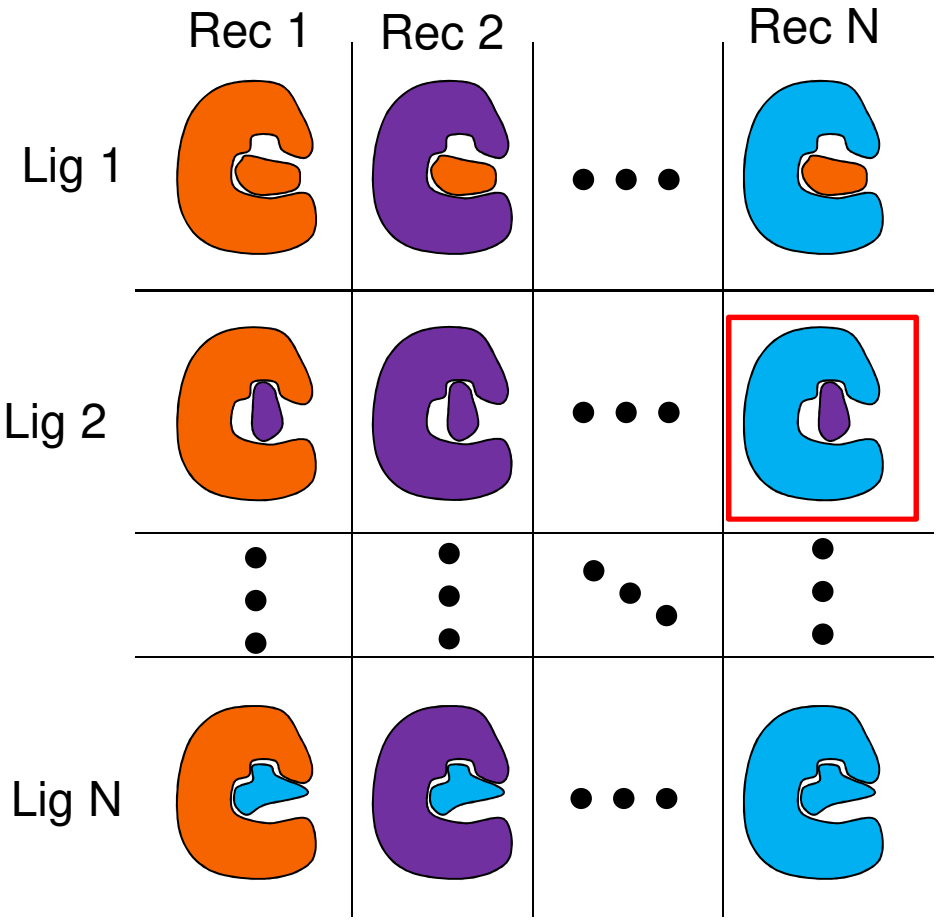
- DCE prefers larger ligands
- FPS prefers molecular weight close to that of erlotinib (393.44 g/mol)

Cross-Docking



Dock every ligand into every receptor

Cross-Docking



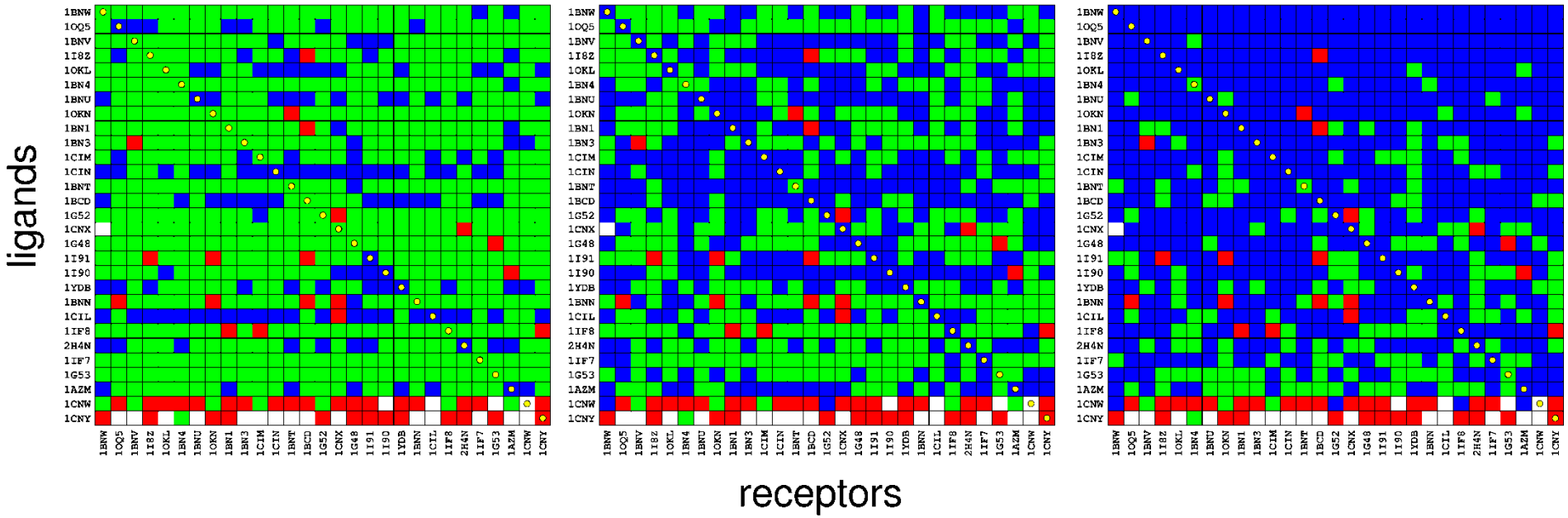
Dock every ligand into every receptor

Docking ligand 2 in to receptor N

[dock lig i in rec j]

Carbonic Anhydrase Crosdocking

(a) DCE_{VDW+ES} (b) FPS_{VDW+ES} diag (c) FPS_{VDW+ES} all



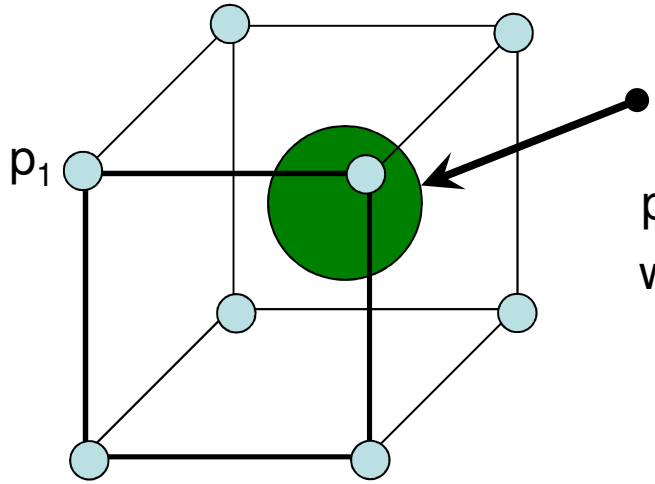
- success, blue; scoring failure, green; sampling failure, red; incomplete growth, white
- (a) standard DCE_{VDW+ES},
- (b) FPS_{VDW+ES} in which cognate ligands (diagonals) were used as the footprint-reference corresponding to each receptor
- (c) FPS_{VDW+ES} in which footprint-references were derived by minimizing each ligand in each receptor and every matrix element used a unique reference

$$E = \sum_{i \in L} \left(\sqrt{A_{i,i}} \sum_{j \in R} \frac{\sqrt{A_{j,j}}}{r_{i,j}^{\ a}} - \sqrt{B_{i,i}} \sum_{j \in R} \frac{\sqrt{B_{j,j}}}{r_{i,j}^{\ b}} + 332 q_i \sum_{j \in R} \frac{q_j}{D r_{i,j}} \right)$$

$$G_{av}(p) = \sum_{l \in R} \frac{\sqrt{A_{l,l}}}{r_{p,l}^{\ a}}$$

$$G_{rv}(p) = \sum_{l \in R} \frac{\sqrt{B_{l,l}}}{r_{p,l}^{\ b}}$$

$$G_{es}(p) = 332 \sum_{l \in R} \frac{q_l}{D r_{p,l}}$$



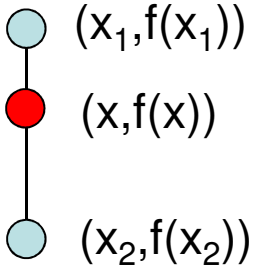
http://dock.compbio.ucsf.edu/DOCK_6/dock6_manual.htm#Grid

$$E \approx \sum_{i \in L} \begin{pmatrix} \sqrt{A_{i,i}}\,\mathrm{interp}[G_{av}(p_1), \cdots, G_{av}(p_8)] \\ -\sqrt{B_{i,i}}\,\mathrm{interp}[G_{rv}(p_1), \cdots, G_{rv}(p_8)] \\ +332 q_i\,\mathrm{interp}[G_{es}(p_1), \cdots, G_{es}(p_8)] \end{pmatrix}$$

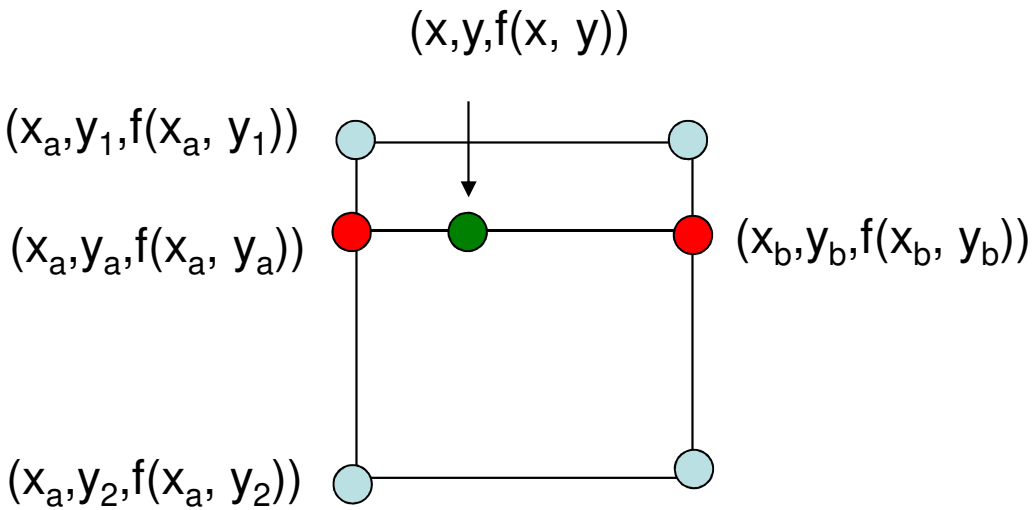
Interpolation

linear

$$f(x) \approx \frac{(x - x_1) f(x_2) + (x_2 - x) f(x_1)}{(x_2 - x_1)}$$



bilinear: Perform 3 linear Interpolations: 2 to calculate red (from cyan); and 1 to calculate green (from red)



Trilinear: for a cube, perform 7 linear interpolations: 4 to calculate red (from the cyan); 2 to calculate green (from red); and 1 to calculate the atomic approximation (from green)

http://en.wikipedia.org/wiki/Trilinear_interpolation

Decomposition for the grid

grid point

$$G_X\left(\overset{\downarrow}{p}\right) = \sum_{l \in R} E_X(p,l)$$

$$= \sum_{l \in SC_1} E_X(p,l) + \sum_{l \in SC_2} E_X(p,l) + \cdots + \sum_{l \in SC_M} E_X(p,l)$$

$$= \sum_{k \in [1,M]} \sum_{l \in SC_k} E_X(p,l)$$

$$= \sum_{k \in [1,M]} G_{X,SC_k}(p)$$

$R = [1, N]$

set of receptor atoms

receptor has N atoms

receptor has M residues

DOCK program

- DOCK develop in 1980's in group of Irwin"Tack" D. Kuntz

  Kuntz et al., *Journal of molecular biology* **161** (2): 269–88 (1982).

- Anchor-&-grow for ligand sampling (DOCK 4, 5, and 6)

  Ewing et al., *Journal of computer-aided molecular design* **15** (5): 411–28 (2001) .

  Moustakas et al., *Journal of computer-aided molecular design* **20** (10–11): 601–19 (2006) .

DOCK: A History