Schrödinger Workshop 2013

Structure Based Virtual Screening

- Various Approaches

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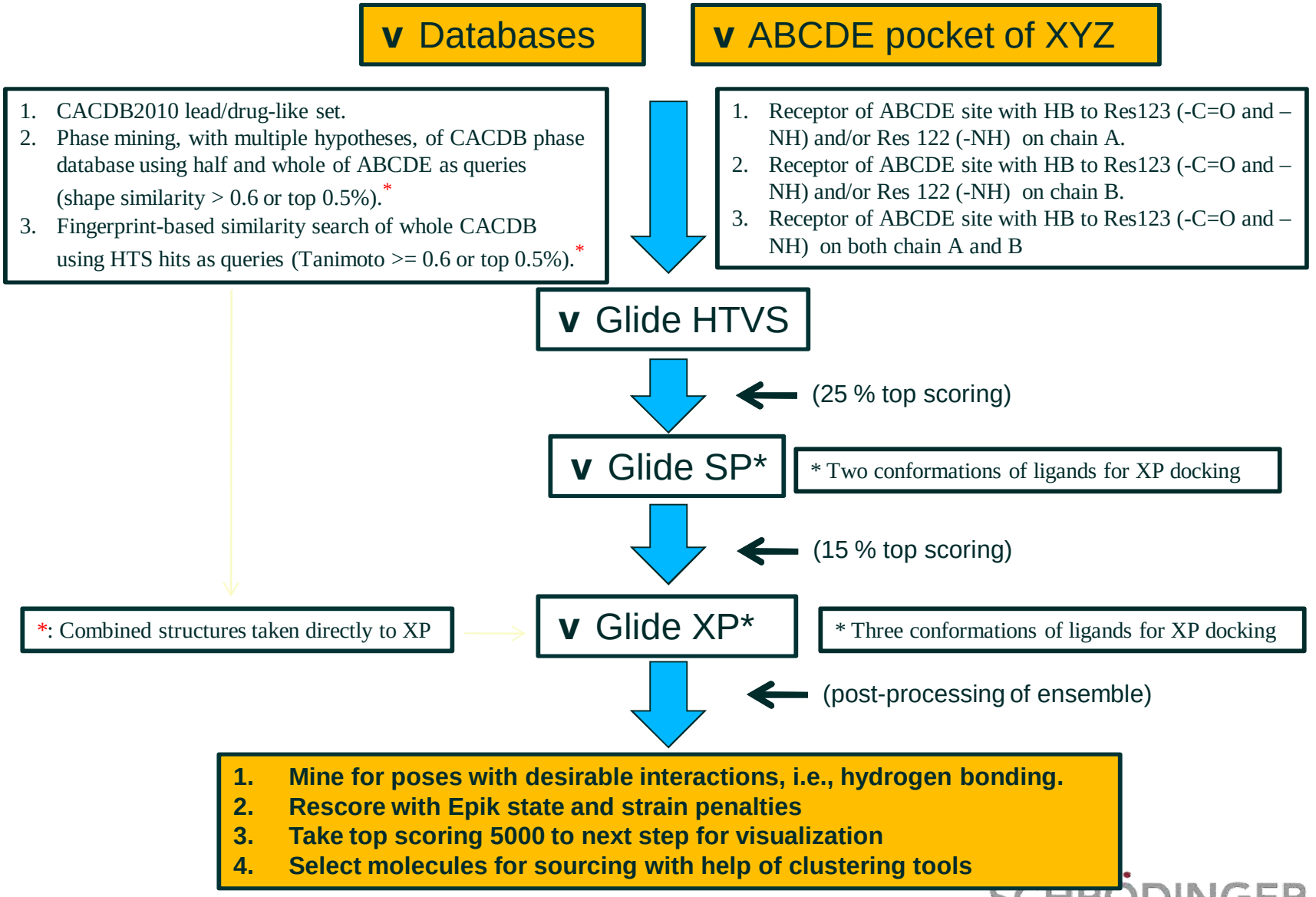
Today's Protocol



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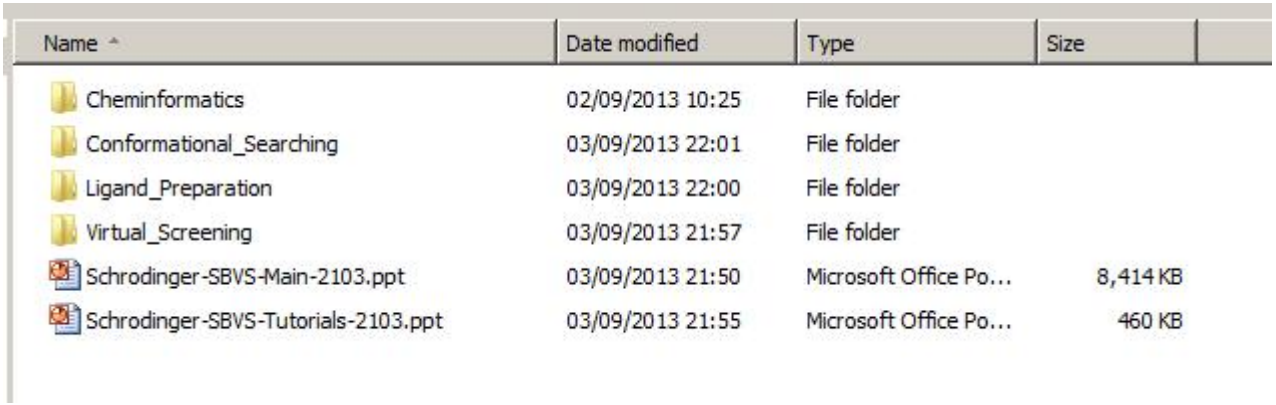
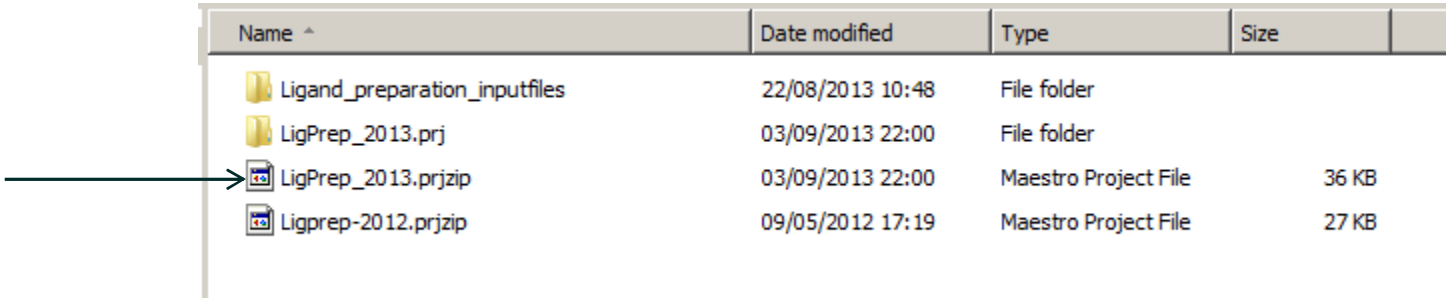
Your Files for Today

- 4 main directories



Name	Date modified	Type	Size
Cheminformatics	02/09/2013 10:25	File folder	
Conformational_Searching	03/09/2013 22:01	File folder	
Ligand_Preparation	03/09/2013 22:00	File folder	
Virtual_Screening	03/09/2013 21:57	File folder	
Schrodinger-SBVS-Main-2103.ppt	03/09/2013 21:50	Microsoft Office Po...	8,414 KB
Schrodinger-SBVS-Tutorials-2103.ppt	03/09/2013 21:55	Microsoft Office Po...	460 KB

- Open the latest *prjzip file for pre-generated results
  - E.g. /Ligand_Preparation



Name	Date modified	Type	Size
Ligand_preparation_inputfiles	22/08/2013 10:48	File folder	
LigPrep_2013.prj	03/09/2013 22:00	File folder	
LigPrep_2013.prjzip	03/09/2013 22:00	Maestro Project File	36 KB
Ligprep-2012.prjzip	09/05/2012 17:19	Maestro Project File	27 KB

- Raw files for import are all also in each dir

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Exercise 1
Fast Screening Using 2D Approaches (.../Cheminformatics)

- Create a Canvas project and import 'FXA_all_initial_data.sdf' / *ligprep.out
  - Note you may want to start from different points
    - 2D filtering > 3D preparation > 2D Filtering .....
    - 3D preparation > Shape filtering > 2D Filtering .....
- Generate molecular properties
  - Applications -> Molecular properties
- Incorporate the results
- Filter by properties using
  - Data -> Property Filter
  - Scatter plots
- *Similarity Searches if you have data on known ligands*
- *Clustering data with different Clustering methods*

Exercise 2
Preparing 3D Ligands for 3D Screening *(.../Ligand preparation)*

- In Maestro import a simple example of starting ligands
  - Import 2D_variations.sdf
  - In the first structure note, it has two ionisable groups, an ammonium counter ion and there are three chiral centres (two marked)
- Run LigPrep
  - Default options
  - Start and Append new entries as a new group
- Observe results in Maestro
  - Tile and label the structures to see them individually
  - In the first structure note, carboxylate is unprotonated, pyridine is both protonated and unprotonated, the variety of R/S chiralities

- In Maestro import FXA_ligprep-out.mae
  - Only import the first few ligands using the Advanced options. We do not need to see the entire file as it is very large.

Exercise 3 (.../Virtual Screening)
Preparing a PDB Structure for Virtual Screening

- Download 1FJS structures in Protein preparation wizard.
  - Extra: go to EDS (http://eds.bmc.uu.se/eds/) and download the CNS format map (2mFo-DFc) for 1FJS; Examine the electron density
  - Notes on electron density: do the residues ligand protein water sit in the electron density or is there an anomoloy? ...
- Prepare 1FJS
- Set up Glide grids (Applications -> Glide -> Receptor grid generation)

Exercise 4 (.../Virtual Screening)
Property Mapping the Xtal Structure

- Run Sitemap for 1FJS
  - Try ”Evaluate...” Tasks.
- Analyse the results. Where are the hydrophobic areas and polar areas? * Is the target druggable?
- Sitemap has been parameterized such that :

Rule of thumb

average value:	
undruggable	0.631
difficult	0.871
druggable	1.108

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Exercise 5
Virtual Screening: Docking and Visualising Poses

- Generate the Glide Grid for 1fjs
  - Use the fully prepared protein and co-crystralised ligand as starting point for Glide > Receptor Grid Generation
  - Define the ligand inside the Grid panel
  - Start the job (1-2 minutes)
  - ’1fjs-grid-2013.zip’ is the pre-generated output

- Dock the 1fjs ligand using this Grid file
  - In Glide > Ligand Docking, Settings tab > browse for the 1fjs grid file, choose SP mode
  - In Ligands tab > choose selected entry and ensure the ’1fjs ligand only’ is highlited in the Project Table
  - Start the job
  - ’Selfdock-1fjs-sp-pv.mae’ is the pre-generated output

- Use Maestro to view the result(s)... Overlay Sitemap result!

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Exercise 6
Post-Docking Analysis; SIFTs and Clustering

Using the Workspace Style toolbar is an easy way to visualize the docked poses, along with 'view poses' option with a 'right click' to the Group in the PT. While eye-balling is crucial, the SiFTS interface makes identifying key interactions easy

- Run the script on VSW results output (96 - VSW 1FOR results) and analyse the interaction pattern
  - Scripts->Cheminformatics->Interaction fingerprints
- Perform Clustering, chosing the number of 'desired clusters'

Exercise 7
Understanding Extra Precision Docking, XPVisuliaser

- Do Glide 'Score in Place' with the co-crystalized ligand IFJS using XP and toggle on "Write XP descriptor information"
- Examine the XP descriptors in Applications-> Glide -> XP Visualizer (read in your *xp pv file)
  - A pre-generated file can be used "ScoreInPlace_1FJS_XP_pv.maegz"
- Use 'Help...' To understand the terms in the scoring function
- ...
- Leads to Exercise 4b

Exercise 8
Generating a Structure Based Pharmacophore for Screening

- *... In the PT Group **** E-PH4s*****, the XP ligand can be used to generate e-Pharmacophore with Scripts->Post-docking processing-> e-Pharmacophore (< 1 min)*
  - *Single ligand option*
  - *Create hypothesis*
    - *Note, the input is a 'glide-dock-XP-SIP-2013-pv.maegz' pose-viewer file normally.*
- *Search the Phase database using Applications -> Phase -> Advanced Pharmacophore Screening(< 1 min for search)*
  - *Database: /Conf_database/FXA_db.phdb (latest 2013 format)*
  - *Choose hypothesis in workspace (or selected entry)*
  - *Use existing conformations*
- *View results in Maestro*
  - *Fitness is the output column*
  - *Use 'right click fix' on highlited row to fix the original pharmacophore in the workspace. Arrow-through results.*

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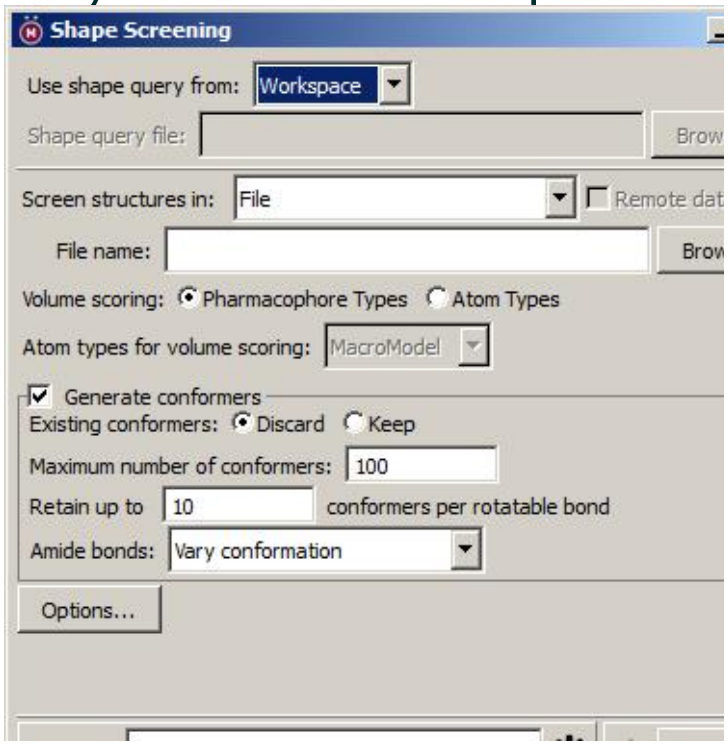
Exercise 9 (if you have energy!)
Shape Based Searching

- Use the VDW shape of a ligand to search for molecules of a similar shape. The 1FJS xtal ligand is the template.
- Applications > Shape Screening...
  - Use Shape query from workspace
  - Generate conformations during search
  - Drop-down options give you more stringency in addition to shape
  - “Shape sim” is the output column
  - View results in Maestro as before



Summary

- Virtual screening needs careful planning and preparation
- Post-process the results using different tools and re-score, re-rank
- Products and tools that have been discussed today:
  - PrimeX, Prime, Macromodel, Sitemap, Glide, Epik, Canvas, Phase, *Prime MM-GBSA*, Interaction fingerprint, Spectral clustering, *Strain rescore*, Pose filter, e-Pharmacophore

Thanks to you All !

Thanks to the Organisers

Thanks to the Audience !

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