Computer Aided Drug Design

Docking and other Virtual Screening Methods
Drug Design Lingo:

- **Target**: any macromolecule whose function can be manipulated/altered to result in disease treatment!

- **Ligand**: compound (typically small molecule) that may bind to a target, with hopes of it serving as a treatment

- **HTS**: High Throughput Screening; experimental method of assaying many (thousands) of compounds for activity

- **Binding Mode**: orientation of ligand in a binding site
Goals/objectives of CADD:

- Find/design *ligands* to bind/regulate target *macromolecules*
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- Find/design **ligands** to bind/regulate target **macromolecules**
  
- Virtual High Throughput Screening
  - Thousands+ of ligands/1-2 targets
  
- Target Structure/Binding Site Prediction
  - 1-2 targets
  
- Off-path Target Screening
  - 10-20 ligands/10-20 targets
  
- Binding Mode Analysis/Prediction
  - 10-20 ligands/1-2 targets
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**Docking, Pharmacophore Modeling**

**Homology Modeling, Binding Site Prediction**

**Binding Site Comparison, Cross-Docking**

**Flexible Docking**
An Example of CADD Success!


<table>
<thead>
<tr>
<th>technique</th>
<th>compds tested</th>
<th>hits with IC_{50} &lt; 100 μM</th>
<th>hits with IC_{50} &lt; 10 μM</th>
<th>hit rate (%)</th>
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<tbody>
<tr>
<td>HTS</td>
<td>400 000</td>
<td>85</td>
<td>6</td>
<td>0.021</td>
</tr>
<tr>
<td>docking</td>
<td>365</td>
<td>127</td>
<td>21</td>
<td>34.8(^a)</td>
</tr>
</tbody>
</table>

\(^a\) We define hit rate for the docked molecules as 100 times the number of bioactive docked molecules divided by the total number of docked molecules that were bioassayed.
What functionality are you looking for?

- What information do you have??
- What information do you want??
- Directory of Computer Aided Drug Design Tools
  - (very great link! cross references functionality by software!)c
What functionality are you looking for?

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You know the structure of the target binding site!

Saturday Morning!!

You know a ligand confirmed to bind target!
What functionality are you looking for?

- What information do you have??
- What information do you want??
- Directory of Computer Aided Drug Design Tools
  - (very great link! cross references functionality by software!)

Let’s take 5 minutes, to all follow this link separately... you might find something that interests you!
Molecular Docking Simulations:
Introduction and Tutorial
Docking... What is it??
“In the field of molecular modeling, **docking** is a method which **predicts the preferred orientation** of one molecule to a second when bound to each other to **form a stable complex**. Knowledge of the preferred orientation in turn may be used to predict the **strength of association or binding affinity** between two molecules using, for example, **scoring functions**.” (from Wikipedia)
“In the field of molecular modeling, **docking** is a method which predicts the preferred orientation of one molecule to a second when bound to each other to **form a stable complex**. Knowledge of the preferred orientation in turn may be used to predict the **strength of association or binding affinity** between two molecules using, for example, **scoring functions**.” (from Wikipedia)
Docking Goals:

1. Identify false positives and false negatives before experimental screening (narrow compound library)

2. Predict binding modes & relative binding affinity

3. Suggest possible successful compounds
Docking can predict binding modes as well as possible binders!

<table>
<thead>
<tr>
<th>Number of Compound</th>
<th>Ligand PubChem ID Number</th>
<th>Docking Score (kcal/mol)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>5287509</td>
<td>-14.70727</td>
</tr>
<tr>
<td>2</td>
<td>49837867</td>
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<tr>
<td>5</td>
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<tr>
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<tr>
<td>8</td>
<td>10436120</td>
<td>-12.08685</td>
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<tr>
<td>9</td>
<td>6398761 (Maxacalcit)</td>
<td>-11.69114</td>
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<td>10</td>
<td>ChemSpider ID: 146693</td>
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<tr>
<td>11</td>
<td>11352536</td>
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<td>12</td>
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<td>13</td>
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<td>15</td>
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</table>
There are many docking programs....

<table>
<thead>
<tr>
<th>1-Click Docking</th>
<th>FLIPDock</th>
<th>PatchDock</th>
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<tbody>
<tr>
<td>AADS</td>
<td>FLOG</td>
<td>PLANTS</td>
</tr>
<tr>
<td>ADAM</td>
<td>FRED</td>
<td>PLATINUM</td>
</tr>
<tr>
<td>AutoDock</td>
<td>FTDOCK</td>
<td>PRODOCK</td>
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<tr>
<td>AutoDock Vina</td>
<td>GEMDOCK</td>
<td>PSI-DOCK</td>
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<td>BetaDock</td>
<td>GOLD</td>
<td>PSO@AUTODOCK</td>
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<tr>
<td>Blaster</td>
<td>GPCRautomodel</td>
<td>PythDock</td>
</tr>
<tr>
<td>BSP-SLIM</td>
<td>HADDOCK</td>
<td>Q-Dock</td>
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<td>CIF-DOCK</td>
<td>ICM-Dock</td>
<td>QXP</td>
</tr>
<tr>
<td>DARWIN</td>
<td>idTarget</td>
<td>rDock</td>
</tr>
<tr>
<td>DIVALI</td>
<td>iScreen</td>
<td>SANDOCK</td>
</tr>
<tr>
<td>DOCK</td>
<td>Lead Finder</td>
<td>Score</td>
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<td>DockingServer</td>
<td>LigandFit</td>
<td>smina</td>
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<td>DockVision</td>
<td>LigDockCSA</td>
<td>SODOCK</td>
</tr>
<tr>
<td>EADock</td>
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<td>eHITS</td>
<td>MCDock</td>
<td>Surflex-Dock</td>
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<tr>
<td>EUUDOC</td>
<td>MOE</td>
<td>SwissDock</td>
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<td>MolDock</td>
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<td>FlexAIS</td>
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<td>YUCCA</td>
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<tr>
<td>FlexPepDock</td>
<td>ParDOCK</td>
<td></td>
</tr>
<tr>
<td>FlexX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Why so many different docking programs??

• **Protein, Ligands, etc.**
  - **Ligand**
    - Whole molecule
    - Fragment Based
  - **Protein**
    - Rigid Docking
    - Flexible Receptor Docking
    - Semi-flexible docking
    - Full Protein Flexible Docking
  - **Water / co-factors / metals**
    - Explicit
    - Implicit

• **Scoring Function**
  - Empirical
  - Force Field
  - Knowledge Based
  - Consensus

\[ \Delta G_{\text{score}} = E_{\text{protein}}^{\text{intra}} + E_{\text{ligand}}^{\text{intra}} + E_{\text{van}} + E_{\text{elec}} + \Delta G_{\text{complex}} + \Delta G_{\text{complex}} \]
The Specifics: What do we need to predict a binding mode?

- **Ligand of Interest**
- **Conformational Search Algorithm**
- **Energetic Scoring Function**
- **Predicted Binding Mode**
The Specifics: What do we need to predict a binding mode?

- Conformational Search Algorithm
  - Molecular Dynamics Simulations
  - Genetic Algorithm
  - Systematic Searching (i.e., rotamer libraries and such)

- Energetic Scoring Function

**Ligand of Interest**

*may be a database of ligands....*

**Predicted Binding Mode**
AutoDock Vina: A Rigid, Grid-based Docking Procedure

Vina represents shape and properties of the receptor as a grid of points, where each point in space is assigned a value in a field! (ligand = flexible, protein = rigid)

(draw grid here on board)

The non-bonded energetic terms of a docked ligand are then minimized within this grid/field, rather minimized via explicit atom-atom calculations.
Is “rigid” the best model for receptor/ligand interaction?
Is “rigid” the *best* model for receptor/ligand interaction?
## Results: “Canonical” Cross Docking Test Set

<table>
<thead>
<tr>
<th>Enzyme Family</th>
<th>Cross-dockings</th>
<th>Schrödinger</th>
<th>Accelrys</th>
<th>SCARE</th>
<th>Flexley</th>
<th>CIF Dock</th>
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<tbody>
<tr>
<td></td>
<td>PDB</td>
<td>Ligand</td>
<td>Protein</td>
<td>Rigid</td>
<td>IFD</td>
<td>RMSD’s (Å)</td>
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<td>Aldose Reductase</td>
<td>1AH3</td>
<td>2ACR</td>
<td>0.9</td>
<td>0.9</td>
<td>-</td>
<td>1.1</td>
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<td>Antibody DB3</td>
<td>1DBB</td>
<td>1DBA</td>
<td>7.6</td>
<td>0.3</td>
<td>-</td>
<td>0.7</td>
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<tr>
<td></td>
<td>1DM2</td>
<td>1BUH</td>
<td>6.4</td>
<td>1.1</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>1AQ1</td>
<td>1AQ1</td>
<td>0.6</td>
<td>0.8</td>
<td>0.9</td>
<td>1.0</td>
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<tr>
<td></td>
<td>1DM2</td>
<td>1DM2</td>
<td>6.2</td>
<td>0.8</td>
<td>0.7</td>
<td>0.6(5)</td>
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<tr>
<td>COX-2</td>
<td>1C2X</td>
<td>3PCG</td>
<td>1.1</td>
<td>1.0</td>
<td>1.9</td>
<td>1.0</td>
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<tr>
<td></td>
<td>3PCG</td>
<td>1C2X</td>
<td>0.6</td>
<td>0.5</td>
<td>2.0</td>
<td>0.9</td>
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<tr>
<td>Estrogen Receptor</td>
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<td>1.0</td>
<td>1.2</td>
<td>1.5</td>
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<td>1IXA</td>
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<td>1.5</td>
<td>2.0</td>
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<td>1IXA</td>
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<td>1.5</td>
<td>2.0</td>
<td>0.5</td>
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<td>1CTR</td>
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<td>2.5</td>
<td>-</td>
<td>1.2(6)</td>
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<td>1.6</td>
<td>0.8</td>
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<td>2PRG</td>
<td>2PRG</td>
<td>9.1</td>
<td>1.8</td>
<td>-</td>
<td>1.7(3)</td>
</tr>
<tr>
<td></td>
<td>1FM9</td>
<td>1FM9</td>
<td>9.8</td>
<td>1.5</td>
<td>-</td>
<td>1.6</td>
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<td>1KJ6</td>
<td>3.5</td>
<td>3.2</td>
<td>3.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1KJ6</td>
<td>1KJ6</td>
<td>1.1</td>
<td>1.5</td>
<td>1.2</td>
<td>-</td>
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<tr>
<td>Thymidine Kinase</td>
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<td>1K41</td>
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<td>0.4</td>
<td>1.2</td>
<td>0.5</td>
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<tr>
<td></td>
<td>1K41</td>
<td>1K41</td>
<td>0.5</td>
<td>1.2</td>
<td>1.2</td>
<td>1.3</td>
</tr>
</tbody>
</table>
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“Hand and glove” model $\Rightarrow$ implies receptor and ligand are both flexible

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Thus we need:
“Lock and key” → implies some element of rigidity

“Hand and glove” model → implies receptor and ligand are both flexible

Thus we need: Flexible ligand/flexible receptor docking!
Induced Fit Docking (IFD) in Schrödinger:

Initial ligand docking with Glide SP (using reduced vdw radii, can mutate large side-chains to alanine)

Prime (protein structure prediction tool) used for each initial pose to predict multiple receptor conformations

Glide XP “redocking” into different receptor conformers

GlideScore calculated and complexes ranked, XP descriptors written
CHARMM-based Flexible Receptor Docking

CHARMM-based Flexible Receptor Docking
So is rigid docking useless?

• NO! Use it to identify *false positives* and *false negatives* before further screening!
  • *rigid docking is computationally inexpensive*...
  • *narrow the library before using expensive tools*...

• Use flexible docking to predict binding modes and affinities
Tutorial: Docking with AutoDock Vina

AutoDock Vina Publication
1. Navigate to the PDB website (http://www.rcsb.org/pdb) and search for the PDB ID 1MVC (http://www.rcsb.org/pdb/explore/explore.do?structureId=1MVC)

2. Click “Download Files > PDB Format”, this will download the 1MVC structure (a human RxR) with bound BMS649 agonist.
This is PyRx, a GUI for AutoDock Vina!

The **Navigator Panel** is where you can load and organize molecules for jobs. The **View Panel** is where you can view molecules, documents, plots and charts! You can also make plots, documents and charts. The **Controls** section has a Vina wizard, an AutoDock Wizard, a Babel wizard, and a python shell, as well as an error log.

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1. From the top toolbar in PyRx, click the “Load Molecule” icon.

2. A ‘Finder’ window (or windows equivalent) will open. Navigate to the downloads folder, select “1mvc.pdb” to open.

3. The macromolecule is now loaded in the 3D Scene!
Now we need to modify the 1mvc.pdb file so that we can have the macromolecule (1mvc) and the ligand (bms649) in separate pdb files.

1. In the “View” Panel, select the “Documents” Tab.
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![Finder window opening 1mvc.pdb file]
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3. This is what it should look like after opening the 1mvc.pdf file in documents!
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3. This is what it should look like after opening the 1mvc.pdf file in documents!

4. Scroll to nearly the bottom of 1mvc.pdb, looking for lines that start with the word “HETATM”

The lines of interest are:

```
HETATM 1773  O1  BM6 A ...
......
HETATM 1800  C24 BM6 A ...
```

Ctrl + C (copy) these lines of the pdb file!
5. Make a new document, this will be the BMS649 ligand file, by clicking the “New” Icon (looks like a piece of paper).
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6. Paste the copied BM6 lines into this new untitled document.
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7. Click the yellow floppy disk icon to save the new document.
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6. Paste the copied BM6 lines into this new untitled document.

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10. Click “Save As” (blue floppy-disk) icon, and while saving, rename the file to “1mvc-mod.pdb” just to distinguish it from the original file downloaded from the PDB.
11. Now, we need to remove the original 1mvc.pdb from the Navigation Pane, so that we can instead include the separate macromolecule and ligand files.
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12. With a newly cleared Navigation Pane, load 1mvc-mod.pdb and bms649.pdb into PyRx (as done in steps 1-2). You can see, ligands (as well as some elements of the macromolecular structure) will be represented in “ball-and-stick; while the protein is represented in “lines”. If you toggled between structures in the Navigation Pane (by checking and unchecking boxes) you can verify that the ligand and protein are in fact in separate files.
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14. Right click on it in the navigation pane, select “AutoDock > Make Ligand”
11. Now, we need to remove the original 1mvc.pdb from the Navigation Pane, so that we can instead include the separate macromolecule and ligand files.

12. With a newly cleared Navigation Pane, load 1mvc-mod.pdb and bms649.pdb into PyRx (as done in steps 1-2). You can see, ligands (as well as some elements of the macromolecular structure) will be represented in “ball-and-stick; while the protein is represented in “lines”. If you toggled between structures in the Navigation Pane (by checking and unchecking boxes) you can verify that the ligand and protein are in fact in separate files.


14. Right click on it in the navigation pane, select “AutoDock > Make Ligand”

15. Now everything is ready for re-docking with AutoDock Vina!
Re-docking with AutoDock Vina!

Re-docking is a technique in which a ligand with an already known binding mode in a binding site (such as from successful co-crystalization or other structural methods) is docked into the binding site to verify that the docking process can replicate the known binding mode.

1. Click on the “Vina Wizard” in the “Controls” section below, and press the “Start” button in the lower right corner.
Re-docking with AutoDock Vina!

Re-docking is a technique in which a ligand with an already known binding mode in a binding site (such as from successful co-crystalization or other structural methods) is docked into the binding site to verify that the docking process can replicate the known binding mode.

1. Click on the “Vina Wizard” in the “Controls” section below, and press the “Start” button in the lower right corner.

2. AutoDock Vina will now prompt you to select a macromolecule and a ligand. Use the “+ Add Ligand” and “+ Add Macromolecule” buttons on the bottom left, make sure that bms649.pdbqt is loaded under the “Ligands” tab, and “1mvc-mod” is loaded under the macromolecule tab. Select them by clicking on them. After making sure the macromolecule and ligands are selected properly, click “Forward” in the bottom right corner.
Re-docking with AutoDock Vina! (cont.)

3. The next step is generating a grid for flexible ligand docking. In the 3D Scene you should now see a cube as well as a 3D axis definition.

Click and hold the white spheres that border the 3D axes to extend the size of the grid. For redocking, make sure that the grid encompasses the volume in which bms649 is known to bind.
Re-docking with AutoDock Vina! (cont.)

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Click and hold the white spheres that border the 3D axes to extend the size of the grid. For redocking, make sure that the grid encompasses the volume in which bms649 is known to bind.

4. The center of the receptor grid can also be moved by click, holding, and dragging the center sphere on the 3d axes. Move the center of the receptor grid to the center of bms649. Click “Forward” in the bottom right corner once you have the grid appropriately placed.
Re-docking with AutoDock Vina! (cont. 2)

5. Clicking “Forward” in the prior step will start the docking procedure! Output from the docking procedure will be displayed in the “3D Scene” window until the job is complete! You should have two resulting predicted binding modes! One that nearly matches the crystal structure alignment, and one that has some rotation.
Docking with CHARMMing!

https://www.charmming.org/charmming/
ProBiS: Protein Binding Site Comparison

• Compare your protein (3D) structure to all other known 3D protein structures in the PDB!

• ProBiS Ligands allows you to collect ligands that bind in other similar binding sites!
What can you do with ProBiS?? Virtually search for ligands!

<table>
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3. Once done you will get results organized as on the right here!
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2. While searching you will get updates about progress!

3. Once done you will get results organized as on the right here!

4. Take a look at the Predicted Ligands! ProBiS searches and finds ligands that are likely to bind for you!!
Pharmacophore Modeling Basics:

- Ligand Based vs. Structure Based Pharmacophore Models
- Pharmacophore model = simplified representation of interaction types
- Screen ligands by comparing predicted pharmacophore models (very fast)
- Software: Pharmer, MedChem Studio, Phase ($$)

https://en.wikipedia.org/wiki/Pharmacophore
Quantitative Structure Activity Relationship (QSAR) Basics:

• Regression models: predictor X leads to response Y
• In chemical modeling the predictor X might be some structural element (side chains, physiochemical properties, etc.) and response might be predicted experimental values (binding affinity, biological activity)
• using the regression model allows you to quickly predict values of interest without simulation, just by correlation
