Introduction to Molecular Docking

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Agenda

- What is Medicinal Chemistry?
- What is Cheminformatics?
- What is Virtual Screening?
- What is Molecular Docking?
- Molecular Docking Algorithms
- Molecular Docking using DOCK 6.4
- Hands on: UCSF Chimera an Extensible Molecular Modeling System
- A Practical Guide to DOCK 6.4
- Hands on
  - Preparing Molecules for Docking
  - Generating Spheres
  - Generating the Grid
  - Rigid and Flexible Docking
Computational Chemistry and Biology

**Applications Classification**

**Sciences**
- Chemical

**Specialties**
- Computational Chemistry
- Materials

**Subdivisions**
- Quantum Chemistry
- Molecular Mechanics/Molecular Dynamics
- Sequence Analysis

**Life**
- Computational Biology
- Bioinformatics
- Proteomics
- Structural Biology
- X-Ray Crystallography
- Docking
- Pharmacokinetics

**Medicinal Chemistry**
What is Medicinal Chemistry?

Medicinal Chemistry

- Chemists attempt to design and synthesize a medicine or a pharmaceutical agent
- Agent will benefit humanity
- Called a ‘drug

- Graham L Patrick, An Introduction to Medicinal Chemistry
What Are Drugs?

Drugs are compounds that interact with a biological system to produce a biological response.

No drug is totally safe

- Drugs have side effects.

The dose level of a compound determines whether it will act as a medicine or a poison.

A therapeutic index is a measure of a drug’s beneficial effect at low dose versus its harmful effects at higher dose.

- High therapeutic indicates a large safety margin between beneficial and toxic doses.

Graham L Patrick, An Introduction to Medicinal Chemistry
Where Do Drugs Interact?

Drugs act in at different locations

Drugs target:
- Lipids
- Carbohydrates
- Proteins
- Nucleic Acids

Graham L Patrick, An Introduction to Medicinal Chemistry
Drug Interaction

Drugs interact with macromolecules in a process called “binding”.

The area in the macromolecule where it takes place is the binding site.

Graham L Patrick, An Introduction to Medicinal Chemistry
What Is Cheminformatics?

Cheminformatics or chemical informatics:

- Computer and informational techniques
  - “Chemoinformatics is the mixing of those information resources to transform data into information and information into knowledge for the intended purpose of making better decisions faster in the area of drug lead identification and optimization.” F. K. Brown

- Utilized by pharmaceutical companies in the process of drug discovery

Cheminformatics 101
Virtual screening:

- It is a computational technique used in drug discovery.
- It involves the rapid \textit{in silico} assessment of large libraries.
- It is used to identify top structures that bind to a drug target.
  - Protein receptor or enzyme.
There are two broad categories of screening techniques:

- **Ligand-based**
  - Given a set of structurally diverse ligands that binds to a receptor, a model of the receptor can be built based on what binds to it
    - Pharmacophore models
  - Chemical similarity analysis methods to scan a database of molecules against one active ligand structure

- **Structure-based**
  - Structure-based virtual screening involves docking of candidate ligands (small molecules) into a protein target

http://en.wikipedia.org/wiki/Virtual_screening
Why Virtual Screening?

It is crucial when testing from hundredths to millions of compounds.

It is also crucial when testing multiple targets.

Low cost compared to experiment.

Faster compared to experiment.
Molecular Docking

It is a computer simulation used to try to predict optimal conformations between a small molecule and a receptor

- Ligand-protein complex
- Binding site
Computers in Drug Discovery

Target Identification and Selection

Target Isolation and Purification

Structure Determination

Analyze Structure for Potential Ligand Binding Sites

Docking of Small Molecules using Computational Methods

Biochemical Assays and further Testing

Lead Optimization to Improve Potency

Cytotoxicity Tests, Pharmacokinetics Studies, and Toxicological Investigations

Drug Candidate

Image source: http://en.wikibooks.org/wiki/Proteomics/Proteomics_and_Drug_Discovery
Initial Requirements: Target & Library

Target Databases:
- RCSB Protein Data Bank (PDB)
- Worldwide Protein Data Bank (wwPDB)
- PDBBIND
- PLD
- AffinDB
- BindDB

Small Molecules Databases:
- ZINC
- PubChem
- ChemDB
- DrugBank
Virtual Screening Flow

Small molecule library

Target X-Ray structure

Prepare Target

PDB

Rigid-docking

Top ranking molecules

Flexible-docking

Top ranking molecules

Molecular Dynamics

Further refinement
CHIMERA

http://www.cgl.ucsf.edu/chimera/
Lab: What Are You Going to Learn?

Manipulate PDB files within Chimera

- Manipulation, Selection, and Chains
- Select Structures
- Adding Labels
- Adding Color
- Molecular Representations and Surfaces
- Display Styles
Lab: Obtain PDB Files

Where do you get the PDB file?

The following PDB files are required:

- 1ABE = L-arabinose-binding protein
- 1d86 = D(CGCE6G)AATTCGCG)-Netropsin Complex
- 1zik = General Control Protein GCN4
Lab: Open Chimera

1. Open Chimera (on Windows, double click the Chimera icon)

2. Now open a structure
   1. Choose **File**→**Open** from the menu
   2. locate 1zik.pdb (the **File type** should be set to all (guess type) or PDB)

3. Use the Favorites menu to show the Side View
   1. Try moving the eye position (the small square) and the clipping planes (vertical lines) with the left mouse button
   2. Try moving the structure with the mouse in the main graphics window
   3. Hovering the mouse cursor over an atom or bond (without clicking any buttons) will show identifying information in a pop-up "balloon." The balloon will disappear when the cursor is moved away
1. **Selection** specifies atoms, bonds, residues, *etc.* for subsequent operations with the Actions menu.
   1. Selection include using the **Select** menu or picking from the screen
   2. **Actions** menu applies to whatever is selected, but when nothing is selected, the **Actions** menu applies to everything
      - Hide the water (red dots):
      - **Select** → **Structure** → solvent
      - **Actions** → **Atoms/Bonds** → hide
      - Clear the selection and display only the chain trace:
      - **Select** → **Clear Selection**
      - **Actions** → **Atoms/Bonds** → **backbone only** → **chain trace**
Lab: Select Structures from the Screen

Picking from the screen is done by:

● Clicking on the atom or bond of interest with the left mouse button while holding down the Ctrl key.

● To add to an existing selection, also hold down the Shift key.

● Try picking two atoms, one from each peptide (Ctrl-click the first, Ctrl-Shift-click the second). The selection is highlighted in green, and its contents are reported on the button near the lower right corner of the main window.
Lab: Adding Labels

Label the atoms you have selected, first by atom name and then by residue name and number:

Actions → Label → name
Actions → Label → off
Actions → Label → residue → name + specifier
Each residue label is of the form:

- \textit{res\_name res\_number.chain} One peptide is chain A and the other is chain B.

Clear the selection and undisplay the residue labels:

Select → Clear Selection
Actions → Label → residue → off
Lab: Adding Color

Color the two chains different colors:
Select → Chain → A
Actions → Color → cyan

Repeat the process to color chain B yellow.

Display its full backbone:
Actions → Atoms/Bonds → backbone only → full

Display all atoms of chain A only:
Actions → Atoms/Bonds → show only

Display all atoms and color them by element:
Select → Clear Selection
Actions → Atoms/Bonds → show
Actions → Color → by element
Lab: Exit Chimera

File → Quit
File → Open.

- 1d86.pdb. It contains the molecule netropsin bound to double-helical DNA

Undisplay the water:
Select → Structure → solvent
Actions → Atoms/Bonds → hide

Color the different nucleotides different colors. For example, color the adenine deoxynucleotides blue:
Select → Residue → DA
Actions → Color → blue

Analogously, color cytosine deoxynucleotides (DC residues) cyan, guanine deoxynucleotides (DG residues) yellow, and thymine deoxynucleotides (DT residues) magenta. Clear the selection with
Select → Clear Selection
Try some different display styles, or representations. Multiple styles can be combined with each other and with surfaces (more on surfaces below)

Actions $\rightarrow$ Ribbon $\rightarrow$ show
Actions $\rightarrow$ Ribbon $\rightarrow$ edged
Actions $\rightarrow$ Ribbon $\rightarrow$ rounded
Actions $\rightarrow$ Ribbon $\rightarrow$ hide
Actions $\rightarrow$ Atoms/Bonds $\rightarrow$ stick
Actions $\rightarrow$ Atoms/Bonds $\rightarrow$ sphere

Change the representation of only one of the DNA strands:
Select $\rightarrow$ Chain $\rightarrow$ A
Actions $\rightarrow$ Atoms/Bonds $\rightarrow$ stick
Select $\rightarrow$ Clear Selection

Change everything to a ball-and-stick representation:
Actions $\rightarrow$ Atoms/Bonds $\rightarrow$ ball & stick
Ctrl-click to pick one of the atoms in netropsin
Label the residue:
Actions → Label → residue → name
- Showing that it is named NT
- The residue label might not be near the selected atom. The first submenu under Label controls individual atom labels, while the second controls residue labels. Actions → Label → name would have shown the name of the atom instead of the name of the residue

Clear the selection and undisplay the residue label:
Select → Clear Selection (or Ctrl-click in empty space)
Actions → Label → residue → off
Lab: Playing with Surfaces

Have some fun with surfaces. There are built-in categories within structures such as main and ligand; when nothing is selected, Actions → Surface → show displays the surface of main

Actions → Surface → show
Actions → Surface → hide
Select → Structure → ligand
Actions → Surface → show
Actions → Surface → mesh
References

**Medicinal Chemistry:**

**Docking Algorithms:**

**Chimera:**
- [http://www.cgl.uchsf.edu/chimera/](http://www.cgl.uchsf.edu/chimera/)

**DOCK 6.5:**