Medicinal Chemistry/ CHEM 458/658

Chapter 4- Computer-Aided Drug Design

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Computer Aided Drug Design - Introduction

- Development of computers
  - hardware
  - algorithms – softwares
  - computation chemists
  - representation

(a) Stick model of aspirin.  
(b) Space fill model of aspirin (CPK model)

(c) Stick model of Vitamin E.  
(d) Space fill model of vitamin E.
Computer Aided Drug Design - Introduction

- Models

- Molecular modelling methods
  - Molecular or quantum mechanics
  - Semiempirical vs ab initio methods
  - Cartesian and polar coordinates

(a) Coordinates are x, y and z

(b) Coordinates are r, θ and φ.
Computer Aided Drug Design - Introduction

- Computer graphics
  - space fill, CPK (Corey-Pauling-Koultoum), stick, stick and ball, mesh, ribbon, surface, molecular dynamics etc.
Molecular Mechanics

- Basis: $E_{\text{total}} = \Sigma$ attractive + repulsive forces

- mechanical method – atoms are “balls” with respective atomic masses

![Diagram of molecular mechanics with equilibrium, stretched, and compressed bond lengths.](image)
\( E_{\text{total}} = \sum E_{\text{stretching}} + \sum E_{\text{bend}} + \sum E_{\text{torsion}} + \sum E_{\text{vdW}} + \sum E_{\text{coulombic}} \)
Molecular Mechanics

- Creating a molecular model using molecular mechanics
  - Joining fragments from program database
  - Prepare 2D structure and convert it to 3D structure
  - Converting an existing model from the database

**Step 1:** The selection of the structure fragments from the database of the INSIGHT II program. The molecule with the relevant functional group and/or structure is selected.

The INSIGHT II models of these structures

**Step 2:** The fragments are linked together. Fragments are joined to each other by removing hydrogen atoms (see shaded boxes in step 1) at the points at which the fragments are to be linked.

**Step 3:** The force field of the model is minimised to give the final structure.
Molecular Dynamics

- Creating a dynamic molecular model
  - atomic coordinates (twist, bend, stretch etc.)
  - conformational analysis
Quantum Mechanics

- Schrödinger equation, Born-Oppenheimer approximation
  - simplification
  - Hartree-Fock approximation
  - Density Functional Theory

Practice
- Gaussian 03 (or 98) *ab initio* methods
- Gamess

Walter Kohn
"for his development of the density-functional theory"

John A. Pople
"for his development of computational methods in quantum chemistry"

The Nobel Prize in Chemistry 1998
Docking

- Produce and investigate the complex of large biomolecule (host) and the drug (or candidate) (ligand)

\[ E_{\text{binding}} = E_{\text{target}} + E_{\text{ligand}} - E_{\text{target-ligand}} \]

Global \( E_{\text{min}} \rightleftharpoons \) Bioactive conformer
Docking

- De novo design
  Using docking programs to design **new** lead structures

The template method

The component fragment method
Docking

• A case study
  Inhibition of FBPase (Kimberly Stieglitz)

  Start: - build and optimize the drug candidate
  ChemDraw and import to Gaussian
  or get crystal structure (CCD)

  - get protein (enzyme or receptor) structure
  PDB
Docking

- A case study

Inhibition of FBPase - list of compounds

Schematic representation of the inhibitor candidates used in this study.
Docking

• A case study

Inhibition of FBPase - protein structure

Figure 1. (a) The FBPase is a homotetramer. The three potential targets are shown: (1) the active site of FBPase, (2) the allosteric binding site of AMP, (3) the tetrameric allosteric inhibitor site. PDB coordinates 1KZ8\textsuperscript{13,14} were used. The figure was drawn using POVS\textsuperscript{script+}.\textsuperscript{37} (b) A closeup of the AMP binding pocket is shown. The three programs used are Dock6, Autodock4, and Surf\textsuperscript{flex} and were tested using the crystallographic ligand AMP moved out of the binding pocket (as explained in results section). This figure was drawn using POVS\textsuperscript{script+}.\textsuperscript{37} The three conformers of AMP were superimposed with a rmsd of <2.0 Å\textsuperscript{5} from actual AMP atoms in the crystallographic structure.
Docking

- A case study
Inhibition of FBPase - docking

Table 1. Results of Docking Studies and the Experimental IC₅₀ Data of the Molecules Utilized in the Inhibition of FBPase

<table>
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<tr>
<th>entry</th>
<th>inhibitor</th>
<th>Dock6 energy score</th>
<th>Autodock, estimated inhibition constant, $K_i$</th>
<th>Surflex, energy score</th>
<th>$K_d$</th>
<th>final binding energy (kcal/mol)</th>
<th>IC₅₀ (µM)</th>
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Docking

- A case study
  Inhibition of FBPase - enzyme inhibition assays

Figure 3. Effect of inhibitor concentration on the activity of FBPase for IC\textsubscript{50} determination of the three inhibitor lead compounds and the natural inhibitor AMP: (◊) AMP; (△) 1; (□) 7; (○) 21.
Docking

• A case study
  Inhibition of FBPase - visualization

Figure 4. Comparison of AMP (A) in the AMP binding pocket of FBPase, PDB code 1FTA, with the docking results of the three best actual inhibitors (B) 21; (C) 7, and (D) 1 from Table 1: carbon, gray; fluorine, magenta; nitrogen, blue; oxygen, red; phosphorus, yellow.
Docking

Figure 2 Schematic representation of the library of pyrrole, pyrazole and indole-based potential FBPase inhibitor candidates used in this study (for individual structures, see Supporting Information)
Docking

### Table 1. Docking data of AMP and the 13 best inhibitor candidates

<table>
<thead>
<tr>
<th>compound</th>
<th>Surflex 2 Energy score</th>
<th>Dock 6 Energy score</th>
<th>Autodock 4 Final Docked Energy</th>
<th>X-Score Energy Score</th>
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</table>
Docking

IC_{50} = 991 \text{nM}

IC_{50} = 1.34

IC_{50} = 32 \text{nM}

IC_{50} = 135 \text{nM}

IC_{50} = 575 \text{nM}
Comparing 3D Structure by Overlays

- Binding small molecules to the active sites
  - design a linker between them
  - use an active compound to design a new one
Comparing 3D Structure by Overlays

- Case study

```
Lead obtained by HTS (see section 5.6)

(a)

Lead obtained from a screen carried out at Eli-Lilly

(b)

Active analogue LY235656

Key: Thick lines = Losartan
Thin lines = LY235656
```
Pharmacophores

- Pharmacophore – biologically active ligand
  - a tool to search new active compounds
    structurally diverse compounds – same pharmacophores
    3D map

- HR X-ray crystallography and NMR
  PDB!

- Analysis of the structures of ligands
  frequently used when there is no information about the target
  analysis – 3D overlays (DISCO, HipHop)
  potential binding group – 3D map - perceived pharmacophore
Pharmacophores

A case study
Inhibition of AChE  -  Marianna Torok, Seema Bag
Typical pharmacophore features are:
- Hydrophobic
- Aromatic
- Hydrogen bond donor/acceptor
- Cation/anion

The features need to match different chemical groups with similar properties, in order to identify novel ligands.

Ligands receptor interactions are typically “polar positive”, “polar negative” or “hydrophobic”.

A well-defined pharmacophore model includes both hydrophobic volumes and hydrogen bond vectors.
Pharmacophores

Select molecules: 50 – 100 highly active molecules

Training set + test set

PHASE Version 3.0

Find common pharmacophore using binary decision tree

Prepare Ligands

Create pharmacophoric sites

Screen/design for more potent analogs

Alignment

Build QSAR model

$r^2$ & $q^2$ value
Pharmacophores

Pharmacophoric points on active molecules
Pharmacophores

Interpretation

H-donor

Hydrophobic
Pharmacophores

Actual vs Predicted Activity for training set of the molecules

Actual vs Predicted Activity for the test set of molecules
Pharmacophores

galanthamine

dihydrocodeine

morphine
Modelling Protein Structures

- Protein structure - required

- Template based approach
  
  template should have similar structure
  template must have an X-ray or NMR structure available
  section of template structure should match

bacteriorhodopsin
Modeling Protein Structures

Solvent Mapping (Sandor Vajda, BU)

16 solvents: ethanol, acetaldehyde, acetonitrile, benzaldehyde, isopropanol, methanol, dimethyl ether, urea, benzene, t-butanol, isobutanol, cyclohexane, methanamine, acetamide, phenol, acetone, dimethylformamide and ethane)

will be used in rigid-body fragment docking
Modeling Protein Structures
3D QSAR

- Similar structures, common pharmacophore - same activities, different potency