Protein – Ligand Modeling

Lynn F. Ten Eyck
San Diego Supercomputer Center
and
Department of Pharmacology
University of California at San Diego

Lecture Overview

- *This lecture addresses the problem of predicting interactions of small molecules with proteins.*
- *Developing (and in many cases, using) the programs designed for this purpose combines knowledge and techniques from biology, chemistry, physics, mathematics, and computer science.*
- *General principles are illustrated with examples drawn from three programs.*
  - DOCK *(Professor I. D. Kuntz, UCSF)*
  - AutoDock *(Professor Arthur Olson, The Scripps Research Institute)*
  - DOT *(San Diego Supercomputer Center)*

Why Do We Care?

- *Find lead compounds for drug discovery*
- *Study conformational possibilities for molecules known to interact*
- *Identify binding determinants*
- *Deduce mechanism of action for molecules known to have biological activity*
- *Study binding process by simulation for insight*

Junction of Fields

- *Biology*
  - *You need to choose you problems so that somebody cares about the answer!*
  - *You also need to screen for relevance . . .*
- *Chemistry and Physics*
  - *There is nothing unique about the forces and energies in biological systems.*
- *Mathematics is the natural language for describing the Chemistry and Physics*
- *Computer Science*
  - *Global Optimization problems are challenging.*

Links to Resources Discussed in this Lecture

- *The best descriptions of the overall problem and the approaches taken are in the web sites, program manuals, and papers describing specific software packages.*
  - *The DOCK web site is at http://www.cmpharm.ucsf.edu/kuntz/dock.html*
  - *The AutoDock web site is at http://www.scripps.edu/pub/olson-web/doc/autodock*
  - *The paper describing DOT is at http://www.sdsc.edu/CCMS/Papers/DOT_sc95.html*

First Example: DOCK

- *DOCK was designed primarily to screen for possible lead compounds in the drug discovery process.*
  - *Overview*
  - *Details*
- *The process of preparing your data is common to all docking problems, but differs in details.*
  - *Locate or build a model of the receptor*
  - *Locate or build a model of the ligand*
  - *Locate or compute all parameters required for an energy calculation or scoring function*

Features of DOCK

- *Characterization of the binding site*
  - *Packing spheres to describe shape*
- *Geometric matching by binding site descriptors*
- *Direct search for optimum fit*
  - *Energy evaluation by table lookup in a grid (Goodford's affinity grid)*
  - *Search localized to binding site*
- *Optimization for searching compound libraries*

Second Example: AutoDock

- *AutoDock was designed to dock flexible ligands into receptor binding sites.*
  - *The AutoDock home page is at http://www.scripps.edu/pub/olson-web/doc/autodock/*
- *Essential features:*
  - *Energy calculation by Goodford affinity grids*
  - *Global optimization by genetic algorithm or simulated annealing*
  - *Explicit ligand flexibility*
- *The strongest feature of AutoDock is the optimization algorithm.*

Third Example: DOT

- *DOT was described briefly by Dr. Mitchell in the previous lecture as a tool for protein-protein docking.*
- *The basic paper on DOT can be found at http://www.sdsc.edu/CCMS/Papers/DOT_sc95.html.*
- *Essential features of DOT:*
  - *Rigid body docking*
  - *'Nearly' Poisson-Boltzman electrostatic energy model*
  - *Simplified contact potentials*
  - *Exhaustive search*
  - *Partition Function calculated assuming the DOT energy model*

DOT (continued)

- *The Partition Function gives an estimate of Free Energy with position. This is more useful for small molecule docking than macromolecular docking because there are more feasible positions over which to integrate.*

DOT (continued)

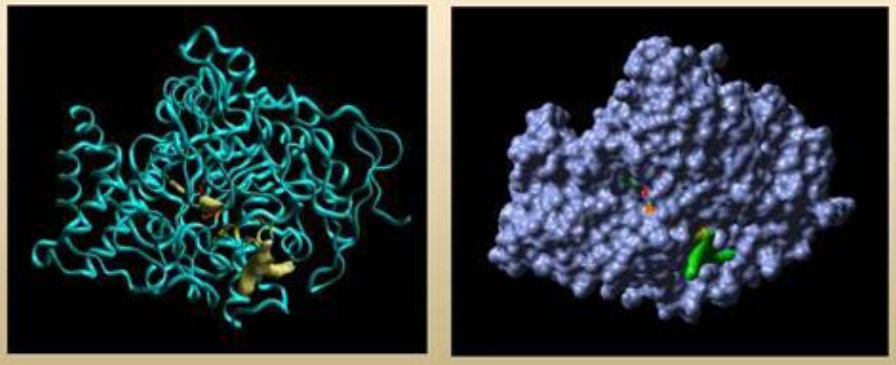
- *Acteylcholinesterase – Acetylcholine (and Choline)*
  - *AChE splits the neurotransmitter ACh into acetate and choline in the neuromuscular junctions*
  - *Fasciculin blocks access to the active site*
  - *Fasciculin-Blocked AChE still retains significant residual activity, even to rather large inhibitors*
  - *A "back door" has been postulated, and molecular dynamics calculations indicate it is possible.*

Front and Back Door?

- *AChE with Fasciculin and paths for ACh to enter by either front or back door*
  - *Red is with FAS*
  - *White is without FAS*
- *Explains some of the experimental difficulties . . .*

AChE - Ach Free Energy Map

The Free Energy Map clearly shows a previously unknown binding site for ACh at the Back Door.



Pointers to Further On-Line Information

- *The NIH Molecular Modeling Software List*
  http://cmm.info.nih.gov/software.html
- *The Amber Parameter Database*
  http://pharmacy.man.ac.uk/amber
- *CMS Molecular Biology Resource*
  http://restools.sdsc.edu

Points for Discussion

- *Why is it difficult to add flexibility of the receptor to any of these programs?*
- *What other programs for these purposes do you know of or can you find by searching the Web?*
- *How would you design an improved method for ligand docking?*
  - *Which improvements are most needed?*
    - *Energy model?*
    - *Algorithms?*
    - *Data representation?*
  - *Would you look first in Computer Science, Mathematics, Chemistry, or Biology? Why?*