Computer-Aided Drug Design: A Practical Guide

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History of Drug Design

• Natural Products-Ebers Papyrus, 1500 B.C. documents over 700 plant based products used to treat a variety of illnesses
• The rise of Organic Chemistry, middle or the 20th Century, semi-synthetic and synthetic drugs
• Computers emerge in the late 1980s, CADD with minimal impact
• Automation in the 1990s, High Through-put Screening and Robotics, Compound Libraries
• CADD has continued to advance since its introduction with improving capabilities
Computational Chemistry

• Ab initio calculations

• Semi-empirical calculations

• Molecular Mechanics
Molecular Mechanics

\[ U = \sum_{i<j} \sum 4\varepsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \sum_{i<j} \sum \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \]

\[ + \sum_{\text{bonds}} \frac{1}{2} k_b (r - r_0)^2 \]

\[ + \sum_{\text{angles}} \frac{1}{2} k_a (\theta - \theta_0)^2 \]

\[ + \sum_{\text{torsions}} k_\phi \left[ 1 + \cos(n\phi - \delta) \right] \]
Global Minimum
Force Fields

- MM2, MM3, MM4
- MMFF
- AMBER
- CHARM
- OPLS
Finding the Global Minimum

• Systematic Search
• Monte Carlo Methods
• Simulated Annealing
• Quenched Dynamics
Minor Groove Binders
Computer-Aided Drug Design

• Structure Based Design
  – Docking
  – Molecular Dynamics
  – Free Energy Perturbation

• Ligand Based Design-QSAR
  – COMFA
  – Pharmacophore Modeling
  – Shape Based Methods
Docking-The Receptor

• X-Ray Crystal Structures
  – RCSB Protein Data Bank (https://www.rcsb.org/)
  – Private Data
• Homology Modeling
• Nuclear Magnetic Resonance
Docking - The Ligand

- Proprietary Ligands
- Databases
  - Real Databases
    - FDA approved drugs- (http://chemoinfo.ipmc.cnrs.fr/MOLDB/index.html)
    - Purchasable compounds
      - Zinc 15, currently 100 million compounds (http://zinc15.docking.org/)
  - Virtual Databases- Enamines Real Database 720 million
    - https://enamine.net/hit-finding/compound-collections/real-database
Docking-Preparation

• Prepare the receptor
  – Add hydrogens
  – Remove water?
  – Check ionization
  – Add missing sidechains and atoms
  – Deal with metals/subunits
  – Minimize
  – Create the grid

• Prepare the ligands
  – Check ionization, tautomers, atom types
Docking-The Process

• Typical time to dock 1-100 sec/cmpd/cpu
  – Size of the active site
  – Size of the ligand
  – Number of rotatable bonds

• Typically only bonds in the ligand are allowed to rotate

• Induced fit docking increases docking time to 20 min/cmpd/cpu
Docking-The Results

• A series of poses for each compound
  – Typically programs can redock ligands the protein was crystallized with very well (RMSD= 0-2 angstroms)

• A docking score
  – Docking scores do not generally correlate well with experimental binding data

• A ranking of the docked poses
  – Since the scores do not correlate with binding data, the ranking does not either
Docking - The Results

Overlay of HDAC inhibitor
PDB ID 4LY1
Green = experimental
Gray = predicted by Glide
RMSD = 0.44 Angstroms
Docking-The Results

Ligand Interaction Diagram - experimental

Ligand Interaction Diagram - predicted
Experimental vs Predicted

CB2 Agonists binding (best result) $R^2 = 0.49$

CB1 Agonists binding (typical result) $R^2 = 0.01$
Enrichment

• What docking studies are best suited for is compound enrichment
• Known actives are docked against either known inactives or decoys
• DUDE-Database of useful decoys: http://dude.docking.org

• Docking of known CB2 agonists (15 cmpds) + DUDE database (750 cmpds) with CB2 receptor
Modeling Programs

• Academic
  – Autodock Vina: http://vina.scripps.edu
  – Autodock: http://autodock.scripps.edu
  – Dock: http://dock.compbio.ucsf.edu/

• Commercial
  – Schrodinger: https://www.schrodingerc.com
  – MOE: https://www.chemcomp.com
Docking Servers

- Dock Blaster: http://blaster.docking.org
- Swissdock: http://www.swissdock.ch
- Z Dock Server: http://zdock.umassmed.edu
Homology Modeling

• Homology modeling allows for the creation of structural models when a protein has not been crystallized but the primary sequence is known.

• Sequence homology should be greater than 30%

• G-Protein Coupled Receptors can be especially difficult and exist in both agonist and antagonist forms
Homology Modeling

Homology Servers

• I-Tasser: https://zhanglab.ccmb.med.umich.edu/I-TASSER/

• Swiss-Model: https://swissmodel.expasy.org/

Manual Homology edit

• Modeller: https://salilab.org/modeller/download_installation.htm
Free Energy Perturbation

• Addresses many of the problems associated with static docking
  – Uses molecular dynamics so the protein is allowed to move
  – May simulate the receptor existing in the cell membrane, e.g. GPCRs
  – Incorporates the solvent in the calculation
  – Works best for solved crystal structures and congeneric series of ligands.
FEP Theory

From Schrodinger, Inc.

- Calculates the relative free energy of converting ligand 1 to ligand 2 in the solvent and then calculates the relative free energy of converting 1 to 2 bound to the receptor.
FEP Results

• Errors typically in the 1-3 kcal/mole
• Run on GPUs but a single run may take 24 hours
Molecular Dynamics and FEP Programs

• Desmond: https://www.deshawresearch.com/downloads/download_desmond.cgi

• NAMD: https://www.ks.uiuc.edu
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