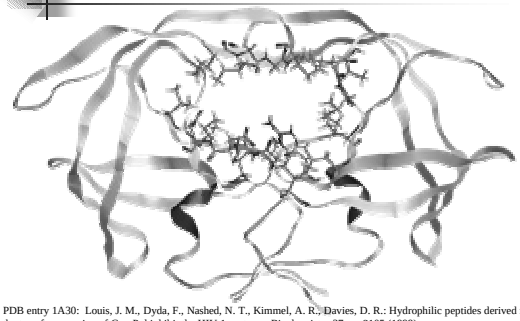
De Novo Design and Pharmacophore Analysis

The Research Problem

- To design or find structures that will bind to a particular biomolecular target of known structure
- Approaches
  - De novo design
    - Outside-in (start from perimeter of site and build in)
    - Inside-out (start randomly in binding site and build out)
    - Fill site with fragments and connect after optimization
  - Database searching
    - Often follows pharmacophore elucidation to find new molecules with similar 3D arrangement of functionality

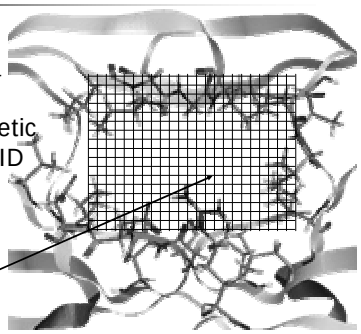
A Binding Site (HIV Protease)



PDB entry 1A30: Louis, J. M., Dyda, F., Nashed, N. T., Kimmel, A. R., Davies, D. R.: Hydrophilic peptides derived from the transframe region of Gag-Pol inhibit the HIV-1 protease. Biochemistry 37 pp. 2105 (1998)

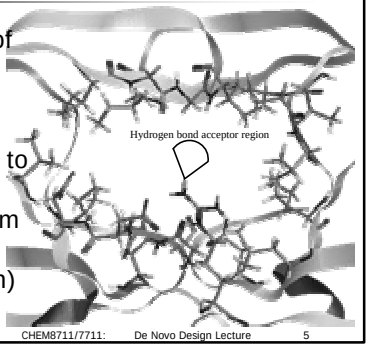
Defining the Binding Site - I

- Grid points explored with a probe atom to compute energetic interaction (GRID program, Peter Goodford)



Defining the Binding Site - II

- Identification of hydrogen bonding functionality, with extension to location an interacting atom should be (Yvonne Martin)



Outside-in Approaches

- Caveat (Paul Bartlett)
  - database search finds scaffold to connect fragments
- Sprout (Peter Johnson)
  - templates are used to connect site points – atom identities added later

Inside-out Approaches

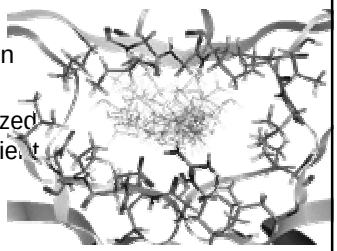
- Ludi (Hans-Joachim Böhm)
  - Rules determine substitutents to add to a core to improve binding
- GenStar (Mark Murcko)
  - Sequential growth of sp^3 carbons
  - Post-modification replaces carbons with appropriate heteroatoms

Fragment-based Approaches

- Multiple Copy Simultaneous Search (MCSS, Martin Karplus)
  - Many copies of identical fragments optimized in the binding site
  - Fragments are not energetically influenced by each other
- Concepts (David Pearlman)
  - Multiple atoms in binding site are optimized
  - Bonds break and form based on distances between atoms

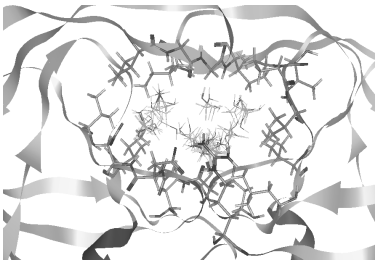
Multiple Fragment Search in MOE

- Methanol fragments
- 100 copies
- Starting position in HIV protease
- Fragments optimized to 0.01 RMS gradient

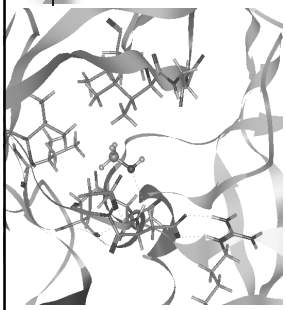


Optimized Positions

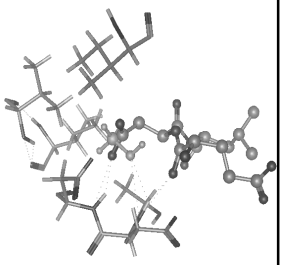
- 68 unique positions
  - many have similar oxygen positions
- Calculation took < 1 hour



Best Interacting Fragment



superimposed with inhibitor



The Combinatorial Problem

- De Novo Design Methods can generate thousands of diverse structures
- Synthetic efforts should be saved for the more promising structures
- Designed compounds need to be scored or ranked

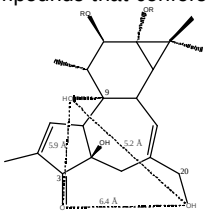
Ranking Criteria

- Likelihood of activity (binding affinity) – same methods as used in ranking docking results
  - Most rigorous: Free Energy Perturbation
  - Grid-based
  - Force field-based
  - Other empirical functions
- Ease of synthesis
  - Often estimated with heuristics
    - Stereocenters are difficult
    - Rings are easy
    - Adjacent heteroatoms are difficult (often not stable)

Examples

Pharmacophore Analysis

- Goal
  - To find the 3D positioning of functional groups common to a set of lead compounds that confers a particular activity
- The Challenge
  - Conformational flexibility!



Approaches - I

- Constrained search (Garland Marshall)
  - Select the least flexible molecule and generate accessible conformations
  - Find conformations of the next molecule that place corresponding pharmacophoric features in the same 3D locations
  - Continue repetitively until very few possibilities remain

Approaches - II

- Ensemble methods
  - Distance geometry
  - Molecular dynamics
    - Force field modified so that molecules do not interact
    - Restraints applied on corresponding atoms or functional groups in the different molecules
    - Generally requires high temperatures

Approaches - III

- MOE: Optimization of similarity/internal energy functions
  - RIPS-style conformational changes
  - Subsequent optimization of similarity function : -kT log F + U
  - F is a function expressing similarity, U is the average internal energy of the molecules

Class Exercise

- Construct three molecules that have similar functional groups, but do not have obvious 3D similarity to you (make sure to use molecules with adequately defined parameters)
- Perform a flexible alignment of the molecules
- Examine the results visually

Reading

- Second Edition
  - Section 12.3-12.4
  - Section 12.11
- Additional references
  - Chapters 1 & 2 from volume 11 of Reviews in Computational Chemistry

Homework Assignment

- Before November 7 (yes, that is a Sunday):
  - use the multiple fragment simultaneous search (MFSS) in MOE (or its equivalent in other software) to investigate optimal interactions between at least one type of fragment and a molecule of interest to you (protein, metal complex, I don't care what you pick)
  - email me a MOE file of the lowest dE fragment interacting with your molecule and describe the calculation you did (fragment types used, # placed, unique positions resulting…)