

Pharmacophore Modeling and Database Searching



Process



- Collect set of high-affinity ligands for target (from literature)
- Analyze conformations of each (start from least flexible)
- Superpose pharmacophore elements to identify bioactive conformation
- Examine lower affinity ligands to identify disallowed volume

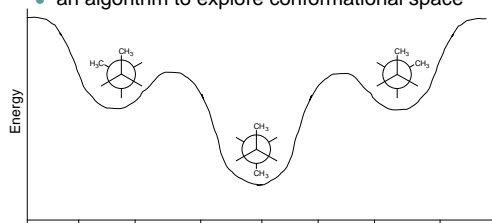
Why > 1 Conformation?



Conformational Analysis



- Requires:
 - a method to calculate (relative) energies
 - an algorithm to explore conformational space



Computing Energies







Energies can be calculated at several levels of theory

- *Ab Initio* – PC Spartan
 - Most theoretically rigorous
 - Energies calculated from electronic structure
 - Requires no experimental parameters
- Semi-Empirical – PC Spartan
 - Simplifying assumptions made
 - Experimental parameters compensate
- Molecular Mechanics – MOE and PC Spartan
 - Electrons essentially ignored
 - Many experimental parameters required

Molecular Mechanics



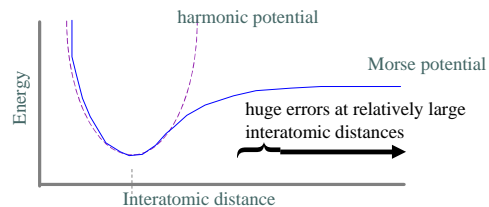
- Energy broken down into terms
 - Bond stretching 
 - Angle bending 
 - Torsional potential 
 - Non-bonded interactions
 - Van derWaals, electrostatic, dipolar interactions 

Force Fields

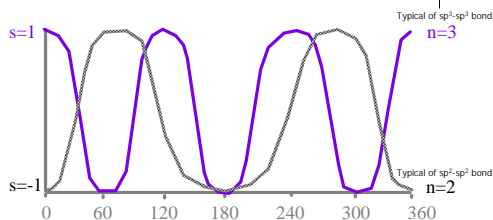
- The combination of mathematical formulae and parameters used to represent the energy of a chemical system
- Different forcefields are optimized for different problems:
 - **MMFF94**: optimized for small organic compounds - wide structural variety
 - **AMBER94**: optimized for proteins - often missing parameters for other organics
 - **PEFSAC95**: optimized for carbohydrates

Bond Stretching

- Approximated with a harmonic potential
- $V = k_s (r - r_0)^2$
- Two parameters per pair of atom types



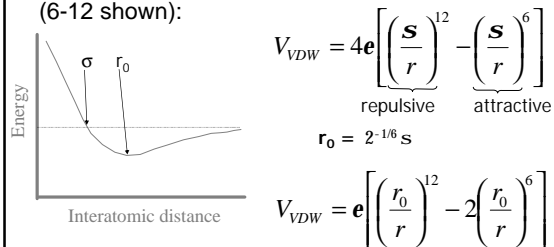
Torsional Potential



- $E_{\omega} = V_n (1 + s \cos n\omega)$
(Two-fold term added to compensate for non-equivalent minima)
- **Three parameters needed for each combination of atom types**

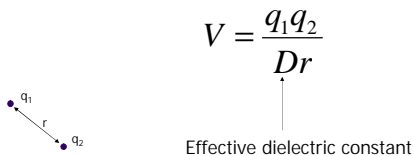
Van derWaals

- Usually expressed as a Lennard-Jones potential (6-12 shown):



Ionic Interactions

- Generally approximated using partial point charges



Conformational Search Algorithms

- Torsion angle driving
- Monte Carlo
- Artificial Intelligence
- Molecular Dynamics
- Simulated Annealing
- Poling
- Etc.

Monte Carlo

- Uses a random kick of coordinates followed by minimization to find new minima
 - More effective on highly flexible molecules
 - Not exhaustive -> heuristics used to define end point:
 - if each of the lowest energy conformations has been found ~10 times, the search has probably found all the interesting ones
 - if duplicate conformations are found ~20 times in a row, the interesting conformations have probably all been found
 - (actual numbers to use depend on the flexibility of the system and your interest in a nearly exhaustive search!)
- In MOE there are two methods that include this
 - Compute -> Conformations -> Stochastic Search
 - Compute -> Conformations -> Hybrid Monte Carlo



Exercise

- Build a structure for morphine and perform a stochastic conformational search
 - Use Window->Potential Control to activate the MMFF94 force field
 - Use default conditions (your choice on output database name) to run the search
- Analyze your results
 - How many conformations?
 - What energy range?
 - How different are they (might try Edit->Interactive Superpose)



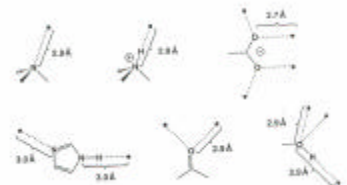
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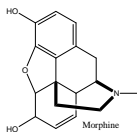
Pharmacophore Element Representations

- While a pharmacophore is defined based on ligand structure, activity occurs due to an interaction with a receptor
- Pharmacophore elements can be represented as:
 - Ligand Points
 - Site Points



Morphine Pharmacophore Elements

- Choose a conformation of morphine from your search as the 'bioactive' conformation
- What are the distances between potential pharmacophore elements?



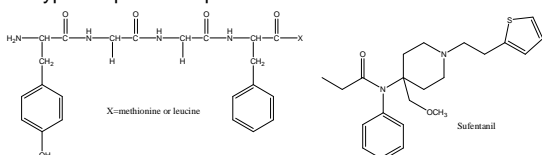
Refining a Pharmacophore

- Most pharmacophore modeling cases do not include a molecule as inflexible as morphine
- These cases require consideration of several structures to identify a most likely bioactive conformation for each
- Compute->Flexible Alignment can be used to find superimpositions of several structures based on types of pharmacophore element



Exercise – Flexible Alignment

- Use flexible alignment to superimpose one of the flexible structures below on your selected conformation of morphine (fix morphine atoms using Edit->Fix)
- Compute->Flexible Alignment can be used to find superimpositions of several structures based on types of pharmacophore element



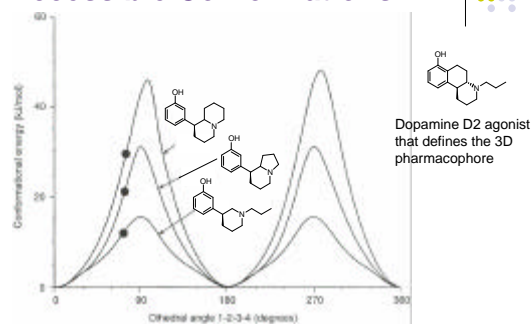
Using a Pharmacophore

- Distances between pharmacophore elements can be used as input to 3D database searches
- Public 3D database searching available through the National Cancer Institute (link on course home page)
 - Pharmacophore elements can be drawn
 - Distance ranges can be specified
 - Additional constraints (MW range, properties) can be used to reduce number of potential hits

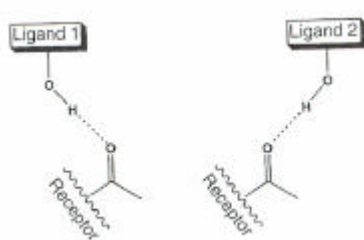
Why Distance Ranges?

1. 3D databases contain a limited set of representative conformations, not every accessible conformation
2. Queries defined by ligand points are overly restrictive

Accessible Conformations



Ligand Point Restriction



Exercise

- Go to the NCI database
- Define a query using the morphine pharmacophore (and any other limitations you like)
- What do you find?

Related Reading



- The Organic Chemistry of Drug Design and Drug Action
 - Chapter 2.2A
 - Problems 2.4: 3
- Textbook of Drug Design and Discovery
 - Chapter 4