Forcefield Optimization

Homayoun Valafar
Department of Computer Science and Engineering, USC
Forcefield Optimization

• Structure can be modified to optimize a forcefield
• Can use programs such as Xplor-NIH, CNS, DYANA, CYANA, Amber, Charm, etc.
• Most use local optimization techniques such as Gradient Descent
• Most have methods of implementing Simulated Annealing to overcome limitations of GD
• We will use Xplor-NIH
• Xplor-NIH used to minimize total empirical energy
• We will use Minimize.inp as the starting seed script
Topology and Parameter Files

• Topology
  – Indicates and describes the topology of macromolecules
    • DNA, RNA, Carbohydrates, Lipids and Proteins.
    • What atoms are present in an amino acid.
    • What atoms are connected to each other.

• Parameter
  – Empirical information
    • Van Der Waals Radii
    • Charge files
    • Bond angles
    • Etc.
Powell Minimization

• General Structure of a Powell minimization:
• Force field description:
  – flags exclude * include bond angl impr end
• Powell minimization:
  – minimize powell
  – nstep= 1000
  – nprint=100
  – drop=1
  – tolgradient=0.01
  – debug=False
  – end
Constraint Minimization

• Use constraint directive to fix coordinates of a region
• Example:
  – constraints fix=(resid 1:8 or resid 13:20) end
• Will fix residues 1-8 and 13-20 and will minimize 9-12.
• Demonstrate example.
Manipulation of Weights

- Can turn energy terms on or off by “flags” statement.
- May terms on but with different importance.
- Use “weights” term.
- Example:
  - constraints fix=(resid 1:8 or resid 13:20)
  - weights
  -  * 1.0
  -  bond 2.0
  -  end
  -  end

\[
E_{\text{Total}} = \sum \left[ w_{\text{BOND}}^p E_{\text{BOND}} + w_{\text{ANGL}}^p E_{\text{ANGL}} + w_{\text{DIHE}}^p E_{\text{DIHE}} + w_{\text{IMPR}}^p E_{\text{IMPR}} + w_{\text{VDW}}^p E_{\text{VDW}} + w_{\text{ELEC}}^p E_{\text{ELEC}} \right]
\]
Rigid Body Minimization

• May want to fix the relative structure of a region (not the coordinates).
• Use “minimize rigid” term
  – minimize rigid
  – drop=1
  – group=(residue 1:7)
  – group=(residue 14:20)
  – nprint=10
  – nstep= 100000
  – tolerance=0.0001
  – end
Rigid Body Minimization

• Here the structure of residues 1-7 and 14-20 will remain unchanged.

• The total energy term will depend on
  – All variables for the none groups.
  – Six parameters for each group.
    • \((\alpha, \beta, \gamma, \Delta x, \Delta y, \Delta z)\)

• Demonstration
Effective Energy Term

- Remember that:
  - \( E_{\text{Total}} = E_{\text{Empirical}} + E_{\text{Effective}} \)
  - \( E_{\text{Empirical}} \): energy of the molecule as a function of the atomic coordinates
  - \( E_{\text{Effective}} \): restraining energy terms that use experimental information.

- Xplor allows the inclusion of relevant experimental data.
  - Experimental data can be collected by X-ray crystallography or NMR spectroscopy.
  - Dihedral restraints: set \( \phi_{15} \) to \(-120^\circ \pm 30^\circ\)
  - Distance restraints: set dist(HN15, O43) = 3.5Å ± 1.5Å
  - Residual Dipolar Couplings restraints.
  - And many more…