BCB 569: Bioinformatics III

Lecture 5:
Empirical Models and Force Fields

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Atoms and Physical Laws

- The physical universe is made of atoms
- The physical laws govern how atoms interact
  - the four basic forces

Proteins, atoms, forces

- Proteins are made of atoms
- The behavior (dynamics, functions etc.) of a protein is influenced by atomic interactions
  - local interactions: e.g., covalent bonds
  - long range interactions: e.g., electrostatic

- To apply theoretical approaches to study the behaviors of a protein, we need
  - a model of the protein (and surrounding water)
  - a model of atomic interactions, or force fields

Why Empirical Force Fields

- The most accurate model for atomic interactions is quantum-mechanics based methods
  - normally applicable only to systems with a small number of atoms

- Empirical: something relying on experience and observation, not on theory

Empirical Models

- Each atom is treated as a point mass centered on the nucleus
- The interactions among atoms are approximated so that they have simple mathematical forms, expressible as a potential function
  - each conformation is related to a potential energy
  - The interacting forces are derivatives of the potential
- This greatly facilitates the computer simulation of such a system

Conformation and conformation space

- conformation (or configuration): structural arrangement
- For a protein, a conformation may be represented by the phi/psi angles of its residues, and possibly the chi angles of the side chains

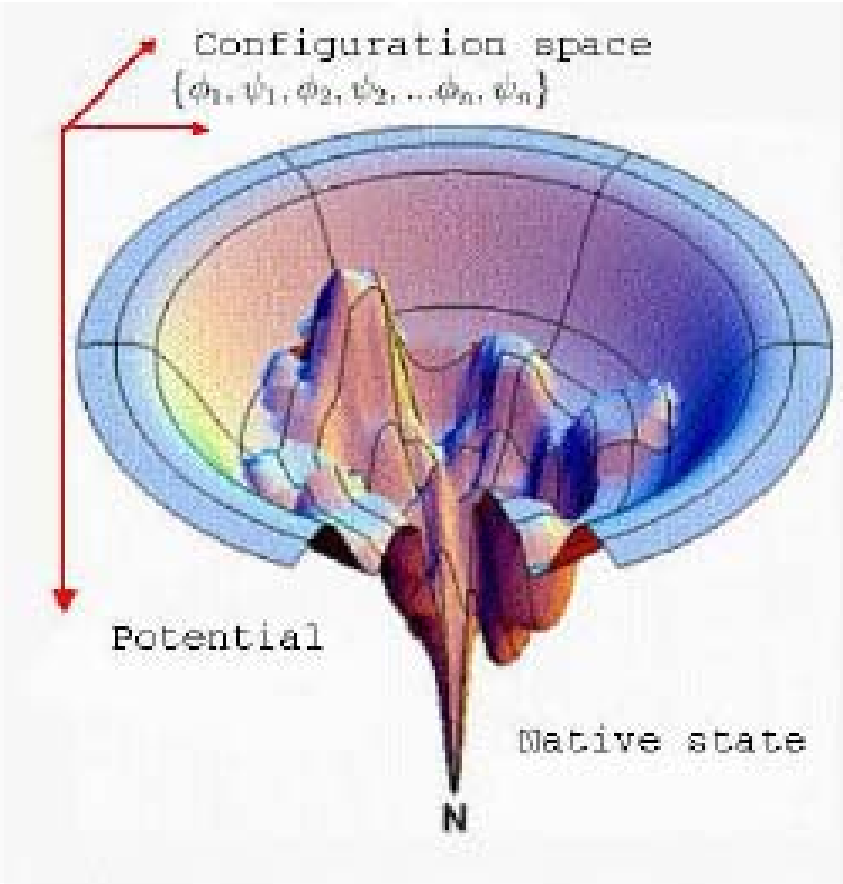
- The conformation space is a space of all the possible conformations
  - e.g. all the possible combinations of the phi/psi angles

Potential Energy Landscape

- for each conformation, we can compute its potential energy by using the empirical potential function

- So, as we take a tour of the conformation space, we see the potential energy goes up and down. That shows the energy landscape of the conformation space

Conformation space and energy landscape



Potential energy function

- The interacting forces are derivatives of the potential
- The forces can be used to determine the equation of motions
- Protein molecules like to stay at conformations with low potentials

What potential energy function looks like

$$PEF(R) = \sum_{\text{bonds}} K_b \{b(R) - b_{eq}\}^2 + \sum_{\text{angles}} K_\theta \{\theta(R) - \theta_{eq}\}^2 +$$

$$\sum_{\text{dihedrals}} \frac{K_\phi}{2} \{1 + \cos[n\phi(R) - \gamma]\} +$$

$$\sum_{\substack{\text{non-bonded} \\ \text{atom pairs i,j}}} \left[\frac{A_{ij}}{r_{ij}(R)^{12}} - \frac{B_{ij}}{r_{ij}(R)^{6}} + \frac{q_i q_j}{\varepsilon_r \varepsilon_0 r_{ij}(R)} \right] \quad (1)$$

- bond stretching
- bond angle
- torsional angles
- van der Waals
- electrostatic

Determining the parameters in potential

- Parameters are optimized based on reproducing a set of target data, especially on small molecules (such as *N*-methylacetamide CH3-CO-NH-CH3 and the alanine dipeptide)

- Target data ideally come from experimental data, but also may come from quantum mechanics calculations
  - geometry from experimental structure
  - vibration frequencies

Considering the solvent

- Explicit models
  - models the water molecules explicitly
  - may include tens of thousands of water molecules in one simulation
  - Water models: TIP3P, TIP4P, SPC, F3C, etc.
- Implicit models
  - only consider the effect of the solvent, not explicitly modeled
  - Possian-Boltzmann Model, Generalized Born model
  - Advantage: smaller system, faster simulation

Water models

- http://en.wikipedia.org/wiki/Water_model

All atoms versus united atoms

- united atom model
  - nonpolar hydrogen atom are treated part of a carbon atom (e.g. CH3 -> C’), being approximated by a carbon atom of a slightly larger diameter
  - hydrogen atoms participate in hydrogen bonds kept

The limitation of empirical potential functions

- They are approximations, therefore the parameters are subject to more testing and improvement

- There are limitations that cannot be overcome because of the inaccuracy of the model itself

Recommended Readings

- All-Atom Empirical Potential for Molecular Modeling and Dynamics Studies of Proteins

  J. Phys. Chem. B **1998,** *102,* 3586-3616

  - a fine paper on CHARMM empirical potential

- Read the information on the website about potential function

  – http://www.ch.embnet.org/MD_tutorial