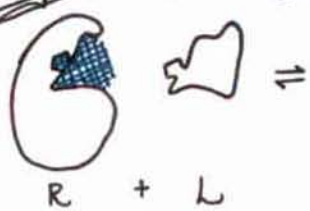
LECTURE 5: BINDING & DOCKING MOLECULAR DYNAMICS SIMULATION

BINDING & DOCKING



R + L ⇌ C

GEOMETRIC HASHING Fischer et al J Mol Biol 240:459-477 (1995)

BASIC STRATEGY

1.) Molecular Surface: Ligand & Receptor
2.) Identify "critical points" on each surface
- Centers of convex patches on ligand
- Centers of concave patches on receptor

} & surface normals

3.) Create total orientations
- In each orientation, line up 2 critical points & their avg. surface normal from ligand with 2 more & avg. surface normal from receptor
- In each orientation, count number of other critical point coincidences

4.) Collect high scorers (based on geometry alone) & evaluate with energy function

TIMING: $2\binom{m}{2}\cdot\binom{n}{2} \sim m^2n^2$ trial orientations

$m \cdot n$ → # of distances to measure in each orientation

$\sim m^2n^2$ Total → quite bad

EFFICIENT IMPLEMENTATION

1.) For each pair of critical points on ligand, transform into "standard orientation"
- mark positions of other critical points in space & store in hash table
  - index by voxel of critical point → store the current ligand transformation

2.) For each pair of critical points on the receptor, carry out the complementary transformation
- look up each receptor critical point's voxel in hash table. Add a vote for each ligand transformation with a critical point in that voxel.
- tally votes for each ligand transformation
- pass high scorers on to energy function

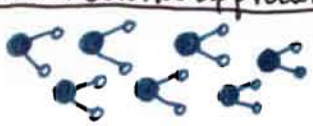
TIMING:
1.) $\binom{m}{2}$ pairs of ligand points; $\mathcal{O}(m)$ operations on each ⇒ m^3
2.) $2\binom{n}{2}$ pairs of receptor points $\mathcal{O}(n)$ operations on each ⇒ $\sim n^3$

$\sim m^3 + n^3$ Total

MOLECULAR DYNAMICS

- TWO USERS: Biologists & Mat Sci
- VMD, NAMD2
- Formulation of equations — Hamiltonian
- Discretization in time

Material Science approach



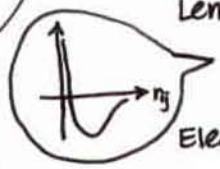
track thousands of molecules

Ask Questions like:
- Extract Diffusion Constants or flow rates, density
- Temperature, Pressure
- Ensemble Averages

} Extraction of Continuum Properties

Important Forces — Non-bonded

Lennard-Jones:



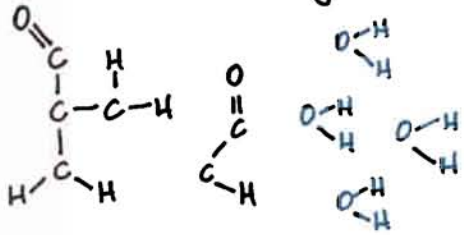
$$\sum_{i>j} \frac{B_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^{6}}$$ ← Potential functions

Electrostatics:

$$\sum_{i>j} \frac{D_{ij}}{r_{ij}}$$

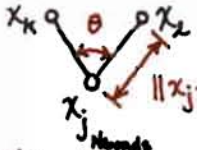
Look at VMD simulator

One or two molecules interacting (with water or salt)



QUESTIONS:
- Conformational changes
- Different foldings
- How hard are they to pull apart

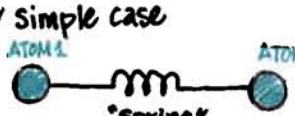
More Important Forces.. (bonded/covalent)



$$E(\vec{x}) = \sum_{i=1}^{N_{bonds}} \frac{1}{2}k(\vec{x}_i - \vec{x}_j)^2 + \sum \frac{1}{2}k_{\theta,i}(\theta_j - \theta_i)^2 + \dots$$

Move an atom

Simple case



Force between A1 & A2: $k\|\vec{x}_1 - \vec{x}_2\|$

$k_b(\|\vec{x}_1 - \vec{x}_2\| - d_{eq})$

0 don't worry

derivative relative two

Spring potential energy $\frac{1}{2}k_b(\|\vec{x}_1 - \vec{x}_2\|)^2$

Molecular Dynamics

Force on atom $i = \frac{-\partial}{\partial x_i}\Big|_{xyz} E(\vec{x})$ ← all atom positions

$F(\vec{x}) = -\nabla_{\vec{x}} E(\vec{x})$

HAMILTONIAN POINT OF VIEW

$$H(q,p) = \frac{1}{2}\sum_i \frac{1}{m_i}\vec{p}_i\vec{p}_i + E(\vec{q})$$

Potential Energy; position; momentum (mv); Kinetic energy; bonds, angle, VDW, Es

$$\frac{d}{dt}\begin{bmatrix}\vec{q}\\ \vec{p}\end{bmatrix} = \begin{bmatrix}\frac{\partial}{\partial p} H(p,q)\\ -\frac{\partial}{\partial q} H(p,q)\end{bmatrix}$$

$M = [m_1 \dots m_n]$

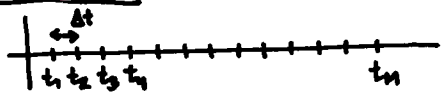
$$\frac{d}{dt}\vec{q} = M^{-1}\vec{p} = \frac{\partial}{\partial p}H(q,p)$$

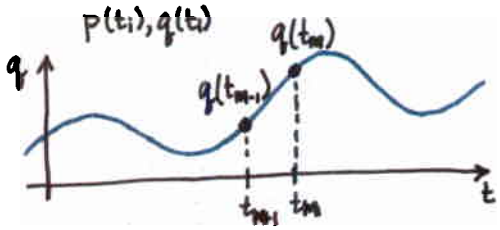
$$\frac{d}{dt}\vec{p} = \frac{-\partial}{\partial q}H(p,q) = \frac{-\partial}{\partial q}E(q)$$

Invariant: $H(p,q) = \text{const.}$

THURSDAY
25 FEB 06

DISCRETIZE TIME





$$\frac{d}{dt}q \cong \frac{q_f(t_m) - q_f(t_{m-1})}{\Delta t}$$

FORWARD EULER

$$\begin{cases} q_f(t_{m+1}) = q_f(t_m) + \Delta t \frac{\partial}{\partial q} H(q_f(t_m), p(t_m)) \\ p(t_{m+1}) = p(t_m) + \Delta t \frac{\partial}{\partial p} H(q_f(t_m), p(t_m)) \end{cases}$$

known

$$q_f(t_1) = q_f(t_0) + \Delta t\, H(q_f(t_0), p(t_0))$$
$$p(t_1) = \ldots$$

BACKWARD EULER

$$q_f(t_{m+1}) = q_f(t_m) + \Delta t \frac{\partial}{\partial q} H(q_f(t_{m+1}), p(t_{m+1}))$$
$$p(t_{m+1}) = \ldots$$