1. Miscellaneous Points
2. Molecular Mechanics and Simulation

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A Drug Sold as a Racemate

- Several antimalarial drugs have activity in multiple enantiomeric forms
- Mefloquine
  - Developed in the 1970s by Army as a chemical synthetic similar to quinine
  - Psychotropic side effects, vestibular damage
  - Sold as mixture of (+/-) R*,S* enantiomers
  - Some research suggests that one enantiomer is more effective against malaria, another binds to adenosine receptors in the central nervous system
Alternatives to Tanimoto

- Continuous form of Tanimoto (Jaccard coefficient) ranges from -1/3 to +1
- Soergel distance is 1 minus Tanimoto coefficient, measures dissimilarity
- Others
  - Hamming
  - Euclidean
  - Dice
Protein Structure Determination

- Nuclear magnetic resonance (NMR) and X-ray crystallography
  - Online repository of structures at www.pdb.org
- Remember proteins are not rigid
- Crystallization is not always easy
  - GPCRs, for example
  - Alternative approaches when no structure

Nobel winner Emil Fischer. One may hear, ”He must have a whisker from Fischer's beard,” when someone crystallizes a difficult compound.
Molecular Mechanics and Dynamics

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“Jigglings and Wigglings”

“...all things are made of atoms, and that everything that living things do can be understood in terms of the jigglings and wigglings of atoms.”

- Richard Feynman
Motivations

- Same as we’ve discussed for other computational techniques

- Easier/faster than experiment

- Complements experiment
  - Get atomistic resolution
  - Also finer time resolution
Uses of MD

- Sampling conformational space
  - Often need a Boltzmann or equilibrium sampling
  - We’ll talk about later, along with other methods also appropriate for that (like Monte Carlo)

- Observing a process
  - Opening and closing of active sites
  - Flexibility of RNA
  - Ligand entrance or exit into heme protein
  - Protein folding
  - Protein aggregation
  - Much more
Molecular Dynamics

Integrate Newton’s laws of motion over a short time interval, update atom positions, repeat over and over
Forcefields

- Need a model to use for computing forces
- Numerous all atom “forcefields” have been developed, with charge, radius, etc. parameters for each atom type
- Example potential:

\[
\sum_{\text{bonds}} K_b (b - b_0)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 \\
+ \sum_{\text{dihedrals}} K_\chi (1 + \cos(n \chi - \delta)) \\
+ \sum_{\text{nonbonded-pairs}, i,j} \left[ \frac{q_i q_j}{4 \pi e_0 r_{ij}} - \varepsilon_{ij} \left\{ \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^6 \right\} \right]
\]
Obstacle

Time. Each time step has to be small (order of fs). This is so small that many molecular processes are very slow in comparison.

Using protein folding for context:

If you could simulate 1 ns a day, a 1 ms simulation would take 3000 years.
How to Go Longer

- More computational power (processors, grids)
- Faster models and approximations (implicit water, cutoffs for nonbonded interactions, etc.)
- Intelligent combination of a number of shorter trajectories
  - With Markov models, for example
Is it Right?

- Have to compare to experiment wherever possible. Is the model working?
- But not as many comparisons possible as we’d like
  - Experiment hasn’t seen as short times as we can simulate, and we haven’t been able to simulate to the length experiment can see
  - Changing, with better simulation techniques and newer experimental methods
Papers

- Dissociation of an antiviral compound from the internal pocket of human rhinovirus 14 capsid. (PNAS, 2005)

- LINCS: A linear constraint solver for molecular simulations (Hess, et. al., J.C.C., 1997)

- HIV–1 protease molecular dynamics of a wild–type and of the V82F/I84V mutant: Possible contributions to drug resistance and a potential new target site for drugs (Perryman, et. al., Prot. Sci.)