1. Miscellaneous Points
2. Molecular Mechanics and Simulation

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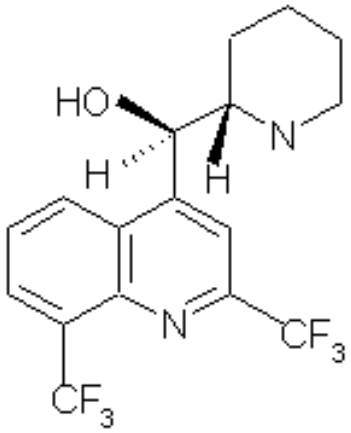
A Drug Sold as a Racemate

- 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.

Experiment and theory for heterogeneous nucleation of protein crystals in a porous medium

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Molecular Mechanics and Dynamics

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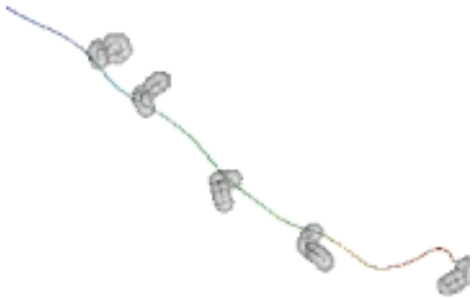
“Jigglings and Wigglings”

“…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:

$$\sum_{\text{bonds}} K_b(b - b_0)^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_o)^2$$

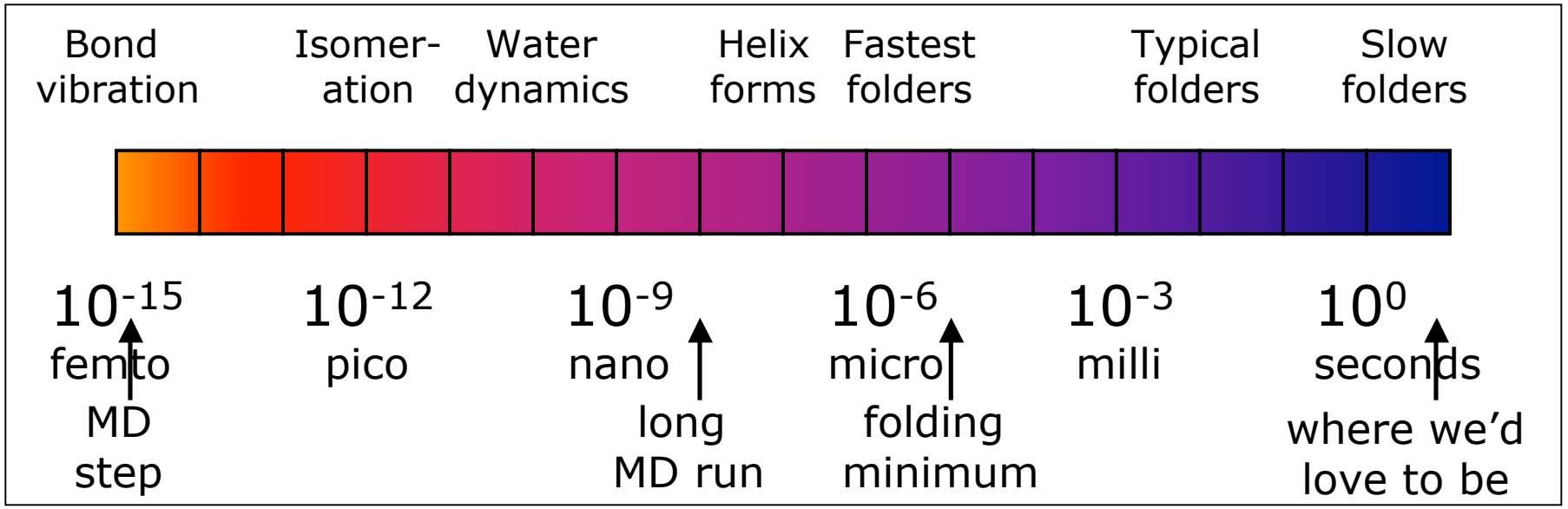
$$+ \sum_{\text{dihedrals}} K_\chi(1 + \cos(n\chi - \delta))$$

$$+ \sum_{\text{nonbonded-pairs}, i,j} \left[\frac{q_i q_j}{4\pi e_o r_{ij}} - \varepsilon_{ij} \left\{ \left(\frac{R_{\min ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{\min ij}}{r_{ij}} \right)^{6} \right\} \right]$$

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.)