Molecular dynamics simulation

CS/CME/BioE/Biophys/BMI 279

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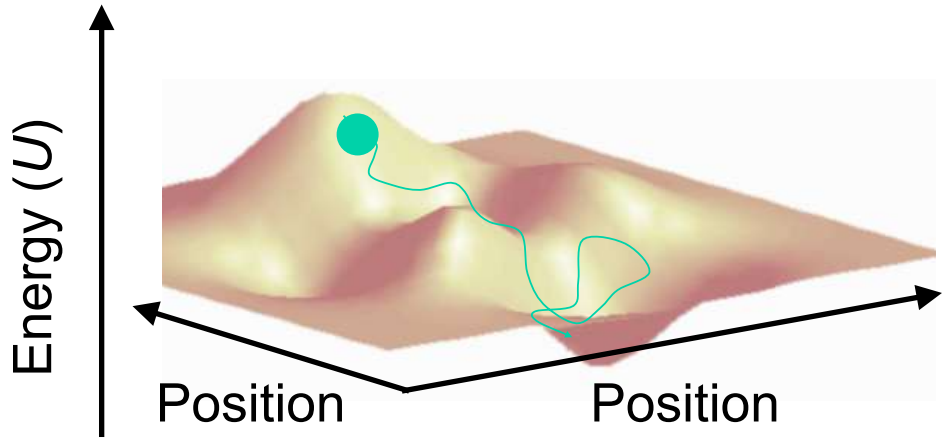
Outline

- Molecular dynamics (MD): The basic idea
- Equations of motion
- Key properties of MD simulations
- Sample applications
- Limitations of MD simulations
- Software packages and force fields
- Accelerating MD simulations
- Monte Carlo simulation

Molecular dynamics: The basic idea

The idea

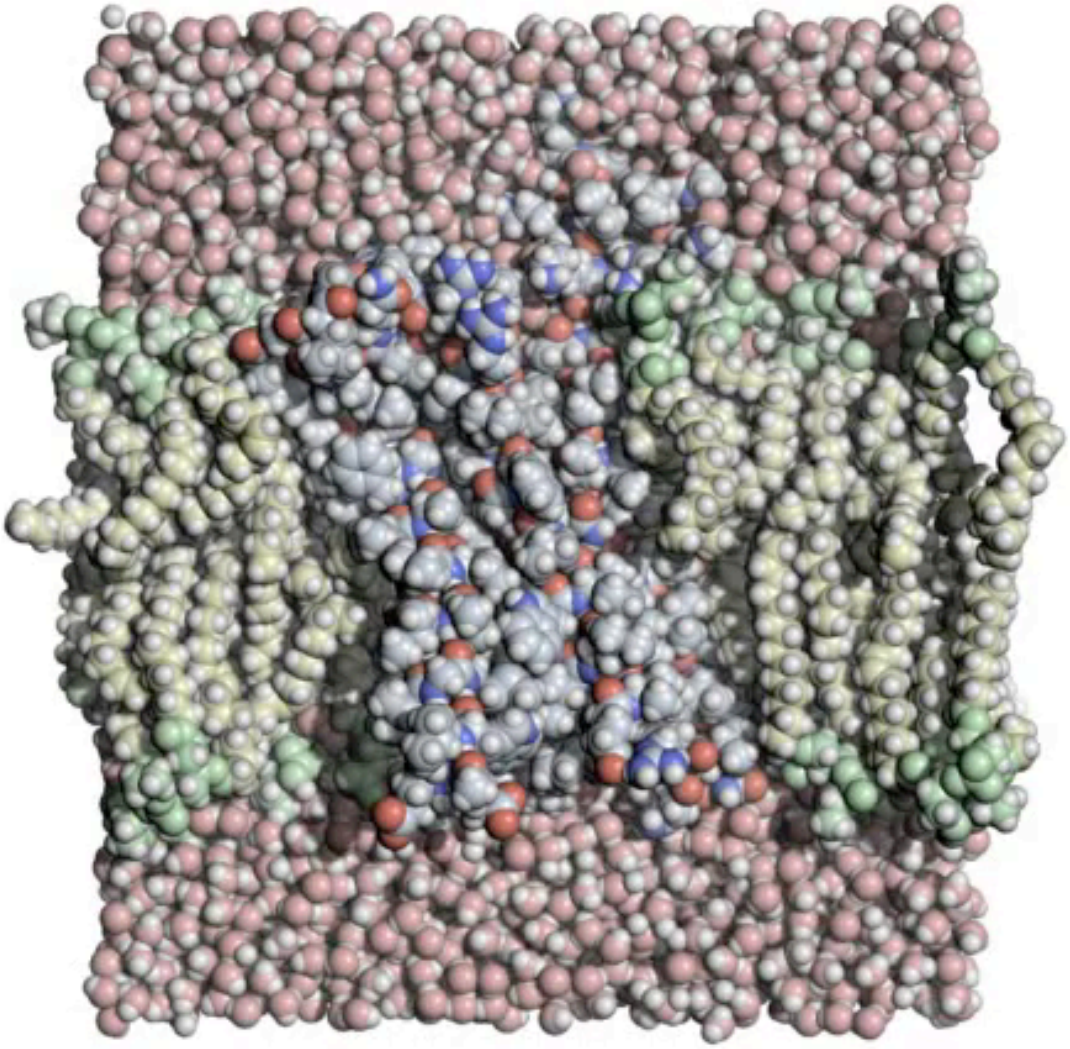
- Mimic what atoms do in real life, assuming a given potential energy function
  - The energy function allows us to calculate the force experienced by any atom given the positions of the other atoms
  - Newton's laws tell us how those forces will affect the motions of the atoms



Basic algorithm

- Divide time into discrete time steps, no more than a few femtoseconds (10^{-15} s) each
- At each time step:
  - Compute the forces acting on each atom, using a molecular mechanics force field
  - Move the atoms a little bit: update position and velocity of each atom using Newton's laws of motion

Molecular dynamics movie



Equations of motion

Specifying atom positions

- For a system with *N* atoms, we can specify the position of all atoms by a single vector ***x*** of length 3*N*
  - This vector contains the *x*, *y*, and *z* coordinates of every atom

$$\mathbf{x} = \begin{pmatrix} x_1 \\ y_1 \\ z_1 \\ x_2 \\ y_2 \\ z_2 \\ \vdots \\ x_N \\ y_N \\ z_N \end{pmatrix}$$

Specifying forces

- A single vector ***F*** specifies the force acting on every atom in the system
- For a system with *N* atoms, ***F*** is a vector of length 3*N*
  - This vector lists the force on each atom in the *x*-, *y*-, and *z*- directions
- Notation:
  - Force on atom 1 in the *x*-direction: $F_{1,x}$
  - Potential energy: $U(\mathbf{x})$
  - How quickly potential energy changes as one moves atom 1 in the *x*-direction: $\frac{\partial U}{\partial x_1}$

$$\mathbf{F} = \begin{pmatrix} F_{1,x} \\ F_{1,y} \\ F_{1,z} \\ F_{2,x} \\ F_{2,y} \\ F_{2,z} \\ \vdots \\ F_{N,x} \\ F_{N,y} \\ F_{N,z} \end{pmatrix} = -\nabla U(x) = -\begin{pmatrix} \frac{\partial U}{\partial x_1} \\ \frac{\partial U}{\partial y_1} \\ \frac{\partial U}{\partial z_1} \\ \frac{\partial U}{\partial x_2} \\ \frac{\partial U}{\partial y_2} \\ \frac{\partial U}{\partial z_2} \\ \vdots \\ \frac{\partial U}{\partial x_N} \\ \frac{\partial U}{\partial y_N} \\ \frac{\partial U}{\partial z_N} \end{pmatrix}$$

Equations of motion

- Newton's second law: $\boldsymbol{F} = m\boldsymbol{a}$
  - where $\boldsymbol{F}$ is force on an atom, m is mass of the atom, and $\boldsymbol{a}$ is the atom's acceleration
- Recall that: $F(\boldsymbol{x}) = -\nabla U(\boldsymbol{x})$
  - where $\boldsymbol{x}$ represents coordinates of all atoms, and U is the potential energy function
- Velocity is the derivative of position, and acceleration is the derivative of velocity Velocity is speed + direction of motion
- We can thus write the equations of motion as:

$$\frac{d\boldsymbol{x}}{dt} = \boldsymbol{v}$$

$$\mathbf{a} = \quad \frac{d\boldsymbol{v}}{dt} = \frac{F(\boldsymbol{x})}{\boldsymbol{m}}$$

Solving the equations of motion

$$\frac{d\boldsymbol{x}}{dt} = \boldsymbol{v}$$

$$\mathbf{a} = \frac{d\boldsymbol{v}}{dt} = \frac{F(\boldsymbol{x})}{\boldsymbol{m}}$$

- This is a system of ordinary differential equations
  - For *N* atoms, we have 3*N* position coordinates and 3*N* velocity coordinates
- "Analytical" (algebraic) solution is impossible
- Numerical solution is straightforward

$$\boldsymbol{x}_{i+1} = \boldsymbol{x}_i + \delta_t \boldsymbol{v}_i$$

$$\boldsymbol{v}_{i+1} = \boldsymbol{v}_i + \delta_t F(\boldsymbol{x}_i) / \boldsymbol{m}$$

  - where δ_t is the time step

Numerically means we start at a particular point in time *i* where we know the position and velocity of each atom, then we step a little bit through time and update the positions/velocities for time *i*+1

Typically, we use the experimentally determined structure as starting positions of the atoms and assign velocities randomly from a probability distribution based on the temperature of the system

Solving the equations of motion

- Straightforward numerical solution:

$$\boldsymbol{x}_{i+1} = \boldsymbol{x}_i + \delta_t \boldsymbol{v}_i$$

$$\boldsymbol{v}_{i+1} = \boldsymbol{v}_i + \delta_t F(\boldsymbol{x}_i) / \boldsymbol{m}$$

- In practice, people use “time symmetric” integration methods such as “Leapfrog Verlet”

$$\boldsymbol{x}_{i+1} = \boldsymbol{x}_i + \delta_t \boldsymbol{v}_{i+1/2}$$

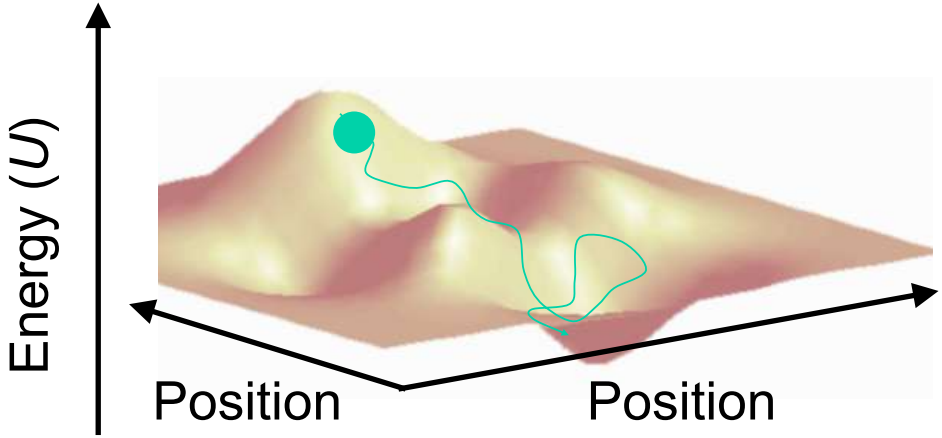
$$\boldsymbol{v}_{i+1/2} = \boldsymbol{v}_{i-1/2} + \delta_t F(\boldsymbol{x}_i) / \boldsymbol{m}$$

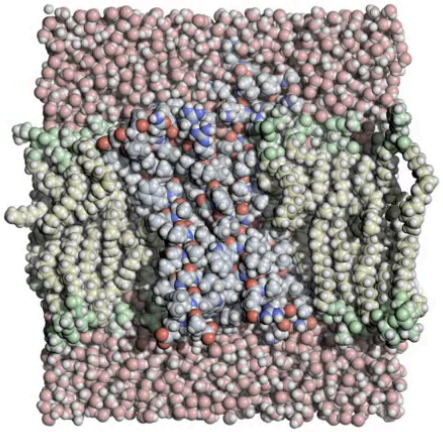
  - This gives more accuracy
  - You’re not responsible for this

Key properties of MD simulations

Atoms never stop jiggling

- In real life, and in an MD simulation, atoms are in constant motion.
  - They will *not* simply go to an energy minimum and stay there
- Given enough time, the simulation samples the Boltzmann distribution
  - That is, the probability of observing a particular arrangement of atoms is a function of the potential energy
  - In reality, one often does not simulate long enough to reach all energetically favorable arrangements
  - This is not the only way to explore the energy surface (i.e., sample the Boltzmann distribution), but it's a pretty effective way to do so





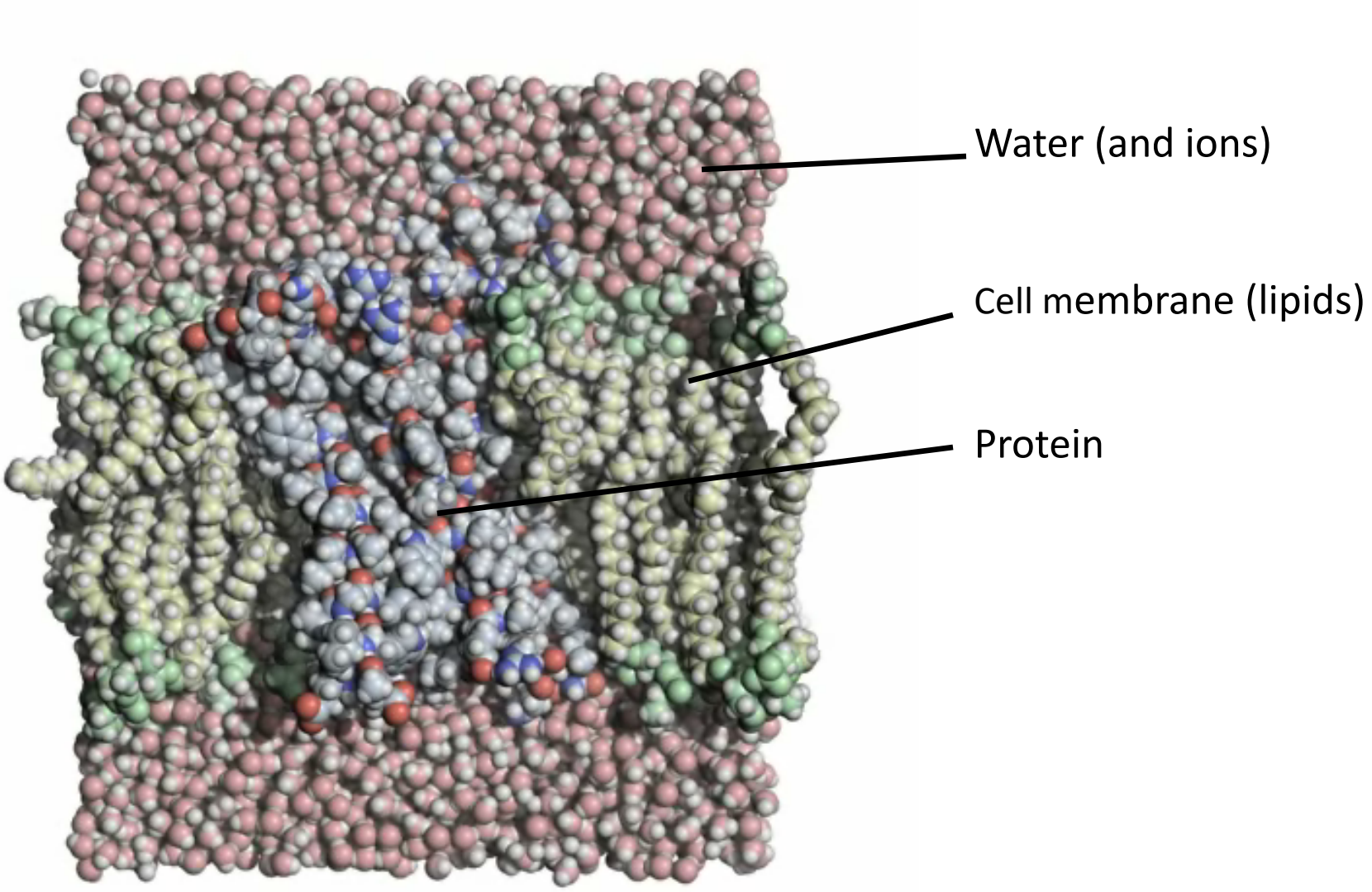
Energy conservation

- Total energy (potential + kinetic) should be conserved in closed system
  - In atomic arrangements with lower potential energy, atoms move faster
  - In practice, total energy tends to grow slowly with time due to numerical errors (rounding errors) which means temperature also goes up
  - In many simulations, one adds a mechanism to keep the temperature roughly constant (a “thermostat”)

Water is important

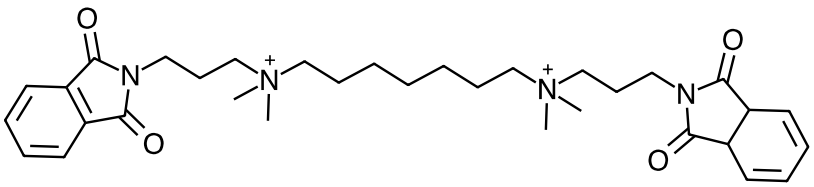
- Ignoring the solvent (the molecules surrounding the molecule of interest) leads to major artifacts
  - Surrounding molecules include: Water, salt ions (e.g., sodium, chloride), lipids of the cell membrane
- Two options for taking solvent into account
  - Explicitly represent solvent molecules
    - High computational expense but more accurate
    - Usually assume periodic boundary conditions (a water molecule that goes off the left side of the simulation box will come back in the right side, like in PacMan)
  - Implicit solvent
    - Mathematical model to approximate average effects of solvent
    - Less accurate but faster

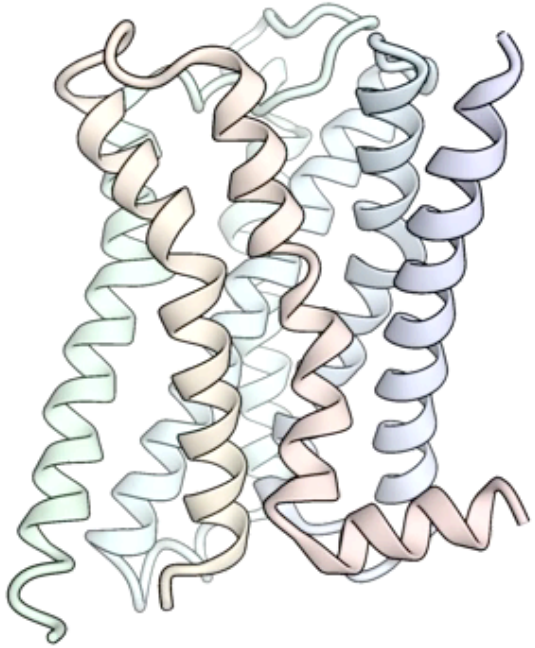
Explicit solvent



Sample applications

Determining where drug molecules bind, and how they exert their effects





Acetylcholine receptor

We used simulations to determine where this molecule binds to its receptor, and how it changes the binding strength of molecules that bind elsewhere (in part by changing the protein's structure). We then used that information to alter the molecule such that it has a different effect.

Dror et al., *Nature* 2013

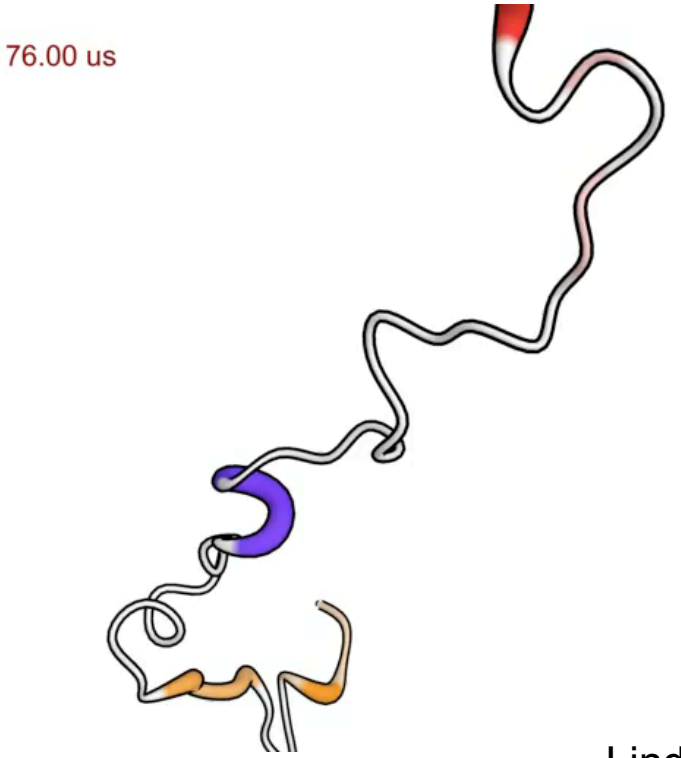
Determining functional mechanisms of proteins

Simulation started from active structure vs.
Inactive structure

- We performed simulations in which an adrenaline receptor transitions spontaneously from its active structure to its inactive structure
- We used these to describe the mechanism by which drugs binding to one end of the receptor cause the other end of the receptor to change shape (activate)

Rosenbaum et al., *Nature* 2010; Dror et al., *PNAS* 2011

Understanding the *process* of protein folding



Lindorff-Larsen et al., *Science* 2011

- For example, in what order do secondary structure elements form?
- But note that MD is generally not the best way to predict the folded structure

Increasingly, MD is used together with experimental approaches to address more complicated problems

Example:
Suomivuori, Latorraca, …, Dror, *Science*, 2020
"Molecular mechanism of biased signaling in a prototypical G protein–coupled receptor"

Collaboration with Lefkowitz lab (Duke), Kruse lab (Harvard)

Supercomputer Research Redesigns Drugs Without the Side Effects

By Staff report

June 9, 2020

We've all heard the commercials: a drug promises amazing results for treating a disease, and then the remainder of the commercial is filled with a mind-numbingly long list of potential side effects. Side effects plague prescription drugs, sometimes prompting drug approval agencies to reject the drug or making patients wonder if the cure can be worse than the disease. Now,

Source: *HPCWire*

Note: The most challenging part of many MD studies is analyzing the data that the simulations produce

MD simulation isn't just for proteins

- Simulations of other types of molecules are common
  - All of the biomolecules discussed in this class
  - Materials science simulations

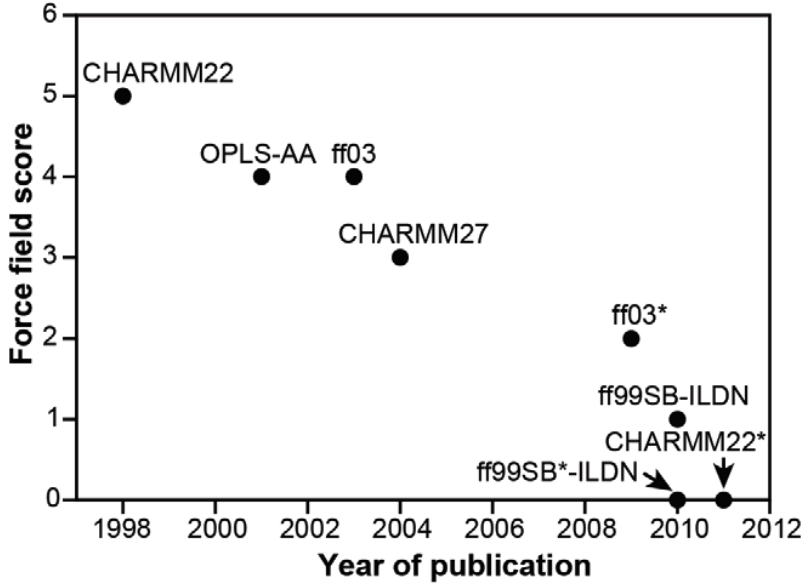
Limitations of MD simulations

Timescales

- Simulations require short time steps for numerical stability
  - 1 time step ≈ 2 fs (2×10^{-15} s)
- Structural changes in proteins can take nanoseconds (10^{-9} s), microseconds (10^{-6} s), milliseconds (10^{-3} s), or longer
  - Millions to trillions of sequential time steps for nanosecond to millisecond events (and even more for slower ones)
- Until recently, simulations of 1 microsecond were rare
- Advances in computer power have enabled microsecond simulations, but simulation timescales remain a challenge
- Enabling longer-timescale simulations is an active research area, involving:
  - Algorithmic improvements
  - Parallel computing
  - Hardware: GPUs, specialized hardware

Force field accuracy

- Molecular mechanics force fields are inherently approximations
- They have improved substantially over the last decade, but many limitations remain



Here force fields with lower scores are better, as assessed by agreement between simulations and experimental data. Even the force fields with scores of zero are imperfect, however!

Lindorff-Larsen et al., *PLOS One*, 2012

- In practice, one needs some experience to know what to trust in a simulation

Covalent bonds cannot break or form during standard MD simulations

- Once a protein is created, most of its covalent bonds do not break or form during typical function.
- A few covalent bonds do form and break more frequently (in real life):
  - Disulfide bonds between cysteines
  - Acidic or basic amino acid residues can lose or gain a hydrogen (i.e., a proton)
- Various more advanced techniques do allow simulations to capture breaking or formation of at least some covalent bonds

Software packages and force fields

(These topics are not required material for this class, but they'll be useful if you want to do MD simulations)

Software packages

- Multiple molecular dynamics software packages are available; their core functionality is similar
  - GROMACS, AMBER, NAMD, Desmond, OpenMM, CHARMM
- Dominant package for visualizing results of simulations: VMD (“Visual Molecular Dynamics”)

Force fields for molecular dynamics

- Three major force fields are used for MD
  - CHARMM, AMBER, OPLS-AA
    - Multiple versions of each
  - Do not confuse CHARMM and AMBER force fields with CHARMM and AMBER software packages
- They all use strikingly similar functional forms
  - Common heritage: Lifson's "Consistent force field" from mid-20th-century

Accelerating MD simulations

MD simulations of biomolecules consume about one-third of U.S. supercomputer resources (for which usage data is available)

Why is MD so computationally intensive?

- Many time steps (millions to trillions)
- Substantial amount of computation at every time step
  - Dominated by non-bonded interactions, as these act between *every* pair of atoms.
    - In a system of N atoms, the number of non-bonded terms is proportional to N^2
  - Can we ignore interactions beyond atoms separated by more than some fixed cutoff distance?
    - For van der Waals interactions, yes. These forces fall off quickly with distance.
    - For electrostatics, no. These forces fall off slowly with distance.

Non-bonded interactions: hydrogen bond, van der waals, etc.

How can one speed up MD simulations?

- Reduce the amount of computation per time step
- Reduce the number of time steps required to simulate a certain amount of physical time
- Reduce the amount of physical time that must be simulated
- Parallelize the simulation across multiple computers
- Redesign computer chips to make this computation run faster

I want you to understand why simulations are computationally expensive and slow, and to have a sense of the types of things people try to speed them up. You are not responsible for the details of these speed-up methods.

How can one speed up MD simulations?

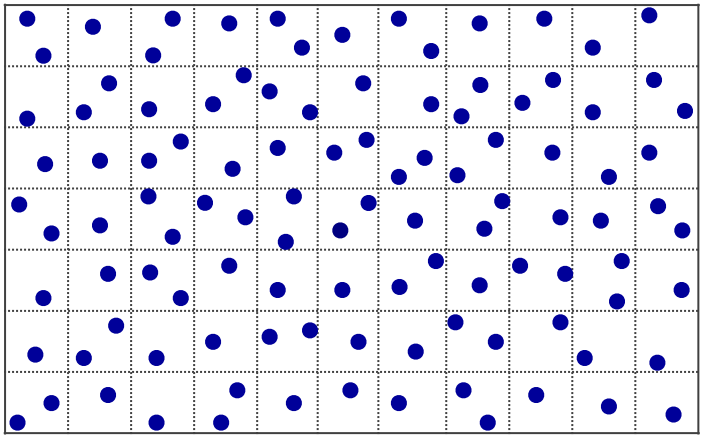
- Reduce the amount of computation per time step
  - Faster algorithms
  - Example: fast approximate methods to compute electrostatic interactions, or methods that allow you to evaluate some force field terms every other time step.

Most commonly used fast approximate methods involve Fourier transform, and can compute the interactions much faster than order N^2 of the number of atoms

- Reduce the number of time steps required to simulate a certain amount of physical time
  - One can increase the time step several fold by freezing out some very fast motions (e.g., certain bond lengths).
- Reduce the amount of physical time that must be simulated
  - A major research area involves making events of interest take place more quickly in simulation, or making the simulation reach all low-energy conformational states more quickly.
  - For example, one might apply artificial forces to pull a drug molecule off a protein, or push the simulation away from states it has already visited.
  - Each of these methods is effective in certain specific cases.

Parallelize the simulation across multiple computers

- Splitting the computation associated with a single time step across multiple processors requires communication between processors.



  - Usually each processor takes responsibility for atoms in one spatial region.
  - Algorithmic improvements can reduce communication requirements.
- Alternative approach: perform many short simulations
  - One research goal is to use short simulations to predict what would have happened in a longer simulation.

Redesign computer chips to make this computation run faster

- GPUs (graphics processor units) are now widely used for MD simulations. They pack more arithmetic logic on a chip than traditional CPUs, and give a substantial speedup.
  - Parallelizing across multiple GPUs is difficult.
- Several projects have designed chips especially for MD simulation
  - These pack even more arithmetic logic onto a chip, and allow for parallelization across multiple chips.

GPU

Specialized chip

Monte Carlo simulation

Monte Carlo simulation

- An alternative method to discover low-energy regions of the space of atomic arrangements
- Instead of using Newton's laws to move atoms, consider *random* moves

"moves" is any way you might update the position of atoms

  - For example, consider changes to a randomly selected dihedral angle, or to multiple dihedral angles simultaneously
  - Examine energy associated with resulting atom positions to decide whether or not to "accept" (i.e., make) each move you consider

Metropolis criterion ensures that simulation will sample the Boltzmann distribution

- The Metropolis criterion for accepting a move is:
  - Compute the potential energy difference (ΔU) between the pre-move and post-move position
    - $\Delta U < 0$ if the move would *decrease* the energy
  - If $\Delta U \leq 0$, accept the move
  - If $\Delta U > 0$, accept the move with probability $e^{-\Delta U / k_B T}$

For $\Delta U > 0$, you also sometimes accept the move with probability that depends on ΔU. The larger ΔU it is, the less likely you will accept the move

Why do we want to accept move that increases energy? to escape from the local energy minimum (including global energy minima) so we can explore the conformational space

- After you run such a simulation for long enough, the probability of observing a particular arrangement of atoms is given by the Boltzmann distribution

$$p(\boldsymbol{x}) \propto \exp\left(-U(\boldsymbol{x}) / k_B T\right)$$

This important property is also shared by the molecular dynamic simulation

- If one gradually reduces the temperature T during the simulation, this becomes a *minimization* strategy ("simulated annealing").

A completely different approach

- A recent research direction is using machine learning to directly identify low-energy conformations
  - More specifically, to sample from the Boltzmann distribution without moving between nearby arrangements of atoms
- Such techniques cannot capture dynamics (i.e., produce a movie), but at least in certain cases, they produce huge speedups

Prominent example: Noé et al., *Science* 2019
"Boltzmann generators: Sampling equilibrium states of many-body systems with deep learning"