A lightning-fast introduction to molecular dynamics

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What are MD simulations?

- Basic idea: simulate molecules in time by calculating forces at each instant and applying Newton's second law
- Do this over and over…usually 10^6 to 10^{12} steps
- Underlying assumption: $\bar{\Theta}_t = \langle \Theta \rangle$

  (ergodic hypothesis)

A basic MD integration scheme

- Supposing we have initial coordinates and velocities:

  $\{\vec{x}_i(t_0)\}$ and $\{\vec{v}_i(t_0)\}$

- Integration scheme (how to propagate in time):

$$\vec{x}_i(t_0+\Delta t) = \vec{x}_i(t_0) + \left.\frac{\partial \vec{x}_i}{\partial t}\right|_{t_0} \Delta t + \frac{1}{2}\left.\frac{\partial^2 \vec{x}_i}{\partial t^2}\right|_{t_0} \Delta t^2 + \ldots = \vec{x}_i(t_0) + \vec{v}_i(t_0)\Delta t + \frac{1}{2}\vec{a}_i(t_0)\Delta t^2$$

$$\vec{a}_i(t_0) = \frac{1}{m_i}\vec{F}_i(t_0) = -\frac{1}{m_i}(\nabla U)_i$$

  …and then increment by another Δt

What do you need to run MD?

- Initial coordinates of atoms (3D structure)
- Topology (which atoms are connected to each other and how)
- Force field (to calculate energies/forces)
- Integrator (to propagate in time)

…and some fancier things

- Suppose we want to carry out a simulation at constant temperature (e.g., NVT): thermostats can modify atomic velocities accordingly
- Suppose we want to carry out a simulation at constant pressure (e.g., NPT): barostats can modify system volumes accordingly

How big should our timestep be?

- How big is Δt? Typically 1 fs (due to X-H bond vibration frequencies).
- Want a larger Δt?
  - Constrain X-H bonds: 2 fs
  - Repartition mass from heavy atoms to H atoms: 4 fs
- Moral of the story: For all-atom MD simulations, we're stuck using atomic timescales.

The sampling problem

- If you really want to speed up sampling in your simulations, you'll need an *enhanced sampling* method (e.g., replica exchange MD, accelerated MD, or metadynamics).

- Additionally, there are *multiple time step* methods (e.g., Margul and Tuckerman, *JCTC* 2016) that can effectively lengthen Δt by 1-2 orders of magnitude.

Challenges for MD

- Sampling problem
- Force field accuracy
- We want to sample all relevant states, and make sure we are accurately representing the features that matter

Diagram of classes in OpenMM 6.0