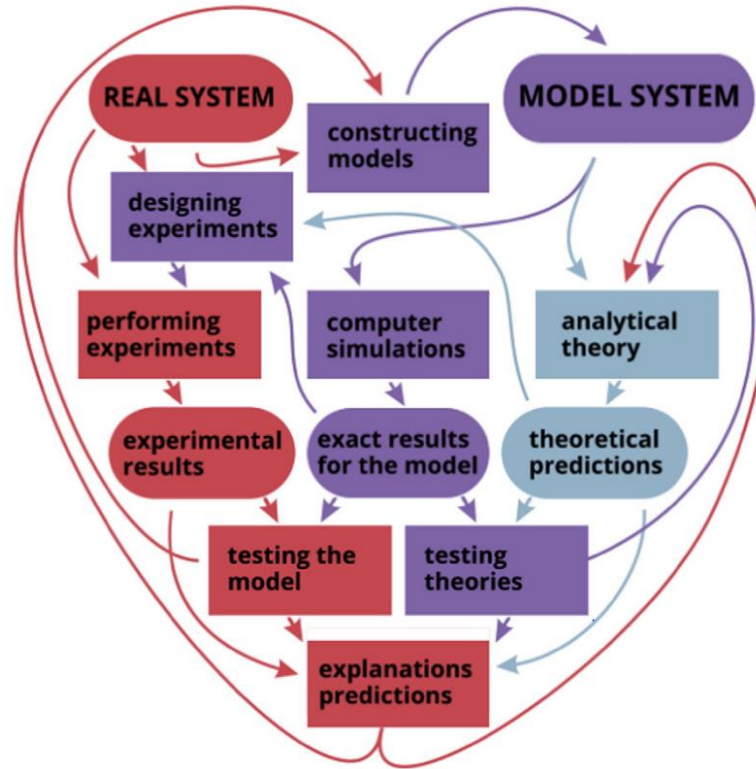# Constant Ensemble Simulation

2024 Winter Son Lab Seminar

January 26th, 2024

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Why we focus on NVT, NPT not NVE ?

 In real condition, we can measure temperature, pressure almost every case, but energy is not.

 And we can connect velocity and temperature, so we can do much thing.

 For example, N polyatomic system we have that :

$$\langle K \rangle = \frac{3}{2} N k_B T$$

To conserve the temperature of the system we need to make sure that the average kinetic energy is fixed, while the instantaneous K is allowed to fluctuate.

$$K = \frac{1}{2} \sum_i m_i v_i^2$$

One possible way to alter the temperature of the system so that it stays constant is **to scale the velocities**.

How we fix "Temperature" ?

Thermostat is introduced to modulate the temperature of a system in some fashion.

The various of thermostat methods are available to add and remove energy from the boundaries of an MD system in realistic way, **approximating the canonical ensemble**.

The goal of thermostat is not to keep the temperature constant, to ensure that the average temperature of a system be the desired one.

Key : Aim of fixing T in NVT or NPT ensemble is just keep target temperature with thermal fluctuations , not fixing the total kinetic energy.

Thermostat's pros and cons

Pros

Drift during equilibration

Drift as a result of force truncation and integration errors

Heating due to external or frictional forces

Cons

 For larger systems, errors in ensemble averages and structural properties incurred by using temperature control to remove slow drifts in temperature appear to be negligible, but **no completely comprehensive comparisons have been carried out, and some caution must be taking in interpreting the results**.
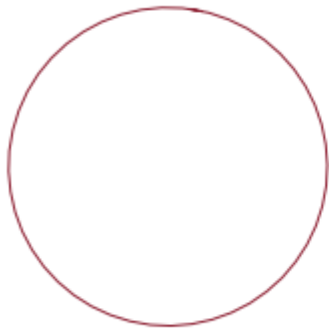
Thermostat's key property

Drift during equilibration

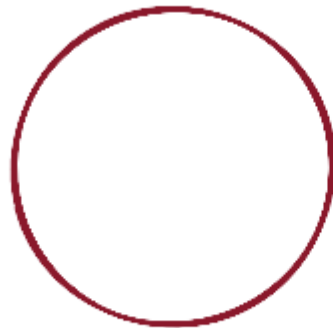Drift as a result of force truncation and integration errors

Heating due to external or frictional forces
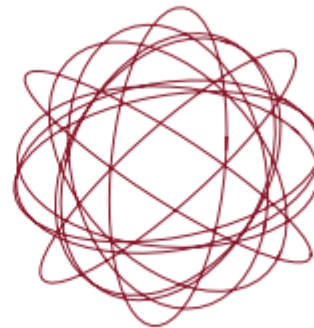
Ergodicity must be guaranteed.

Energy fluctuation must be shown.

Microcanonical Nosé-Hoover Andersen Langevin

The types of thermostat

1. Andersen Thermostat
Wall thermostat without the wall

 Each molecule undergoes impulsive "collisions" with a heat bath which is imposed the desired temperature at random intervals.

 Anderson thermostat perform the simulation with two parameters: T and v.

T : desired Temperature
v: The frequency of stochastic collisions which determine the strength of the coupling to the heat bath

$$P(t:v) = v e^{-vt}$$

2. Berendsen

One main problem of velocity-rescaling method is that it does NOT allow temperature fluctuations which are present in the canonical ensemble.

To overcome this problem, a weak coupling method to an external bath which now is called Berendsen thermostat.

Trying to correct the deviations of the actual temperature T

$$\frac{dT}{dt} = \frac{1}{\tau}(T_0 - T) \rightarrow T = T_0 - Ce^{-t/\tau}$$

This lead to a modification of the momenta $p_i \rightarrow \lambda p_i$ where λ is the scaling factor

$$\lambda^2 = 1 + \frac{\Delta t}{\tau_T}\left(\frac{T_0}{T} - 1\right)$$

Actually, Berendsen thermostat can't capture "Energy fluctuations" correctly. Moreover, it does not generate a correct canonical ensemble, even for the configurational degrees of freedom, and results in notable pathologies for system.

3. Nose-Hoover Thermostat: Extended System Method

We need some mechanism for introducing the energy fluctuations in order to simulate such a system.

Nose invent an extended Lagrangian , assume the system is of N particles with coordinates q_i', masses m_i, potential energy $\phi(q')$, and momenta p_i'. An additional degree of freedom s is introduced acting as an external system on the simulated system.

Virtual variable (q_i, p_i, t) are related to the real variable (q', p', t') .

$$q_i' = q_i, p_i' = \frac{p_i}{s}, t' = \int_0^t \frac{dt}{s} \Rightarrow \frac{dq_i'}{dt'} = s\frac{dq_i'}{dt} = s\frac{dq_i}{dt}$$

$$L_{Nose} = \sum_{i=1}^{N} \frac{m_i}{2}s^2\dot{q}_i^2 - \phi(q) + \frac{Q}{2}\dot{s}^2 - gkT\ln s$$

$$p_i = \frac{\partial L_{Nose}}{\partial \dot{q}_i} = m_i s^2 \dot{q}_i \ , \ p_s = \frac{\partial L_{Nose}}{\partial \dot{s}} = Q\dot{s}$$

$$H_{Nose} = \sum_{i=1}^{N} \frac{p_i^2}{2m_i s^2} + \phi(q) + \frac{p_s^2}{2Q} + gkT\ln s$$

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4. Nose-Hoover Chain Thermostat: Extended System Method
Unfortunately, the Nose-Hoover dynamics is not ergodic for small or stiff system.

Due to conservation of probability to show that the distribution

$$f(p, q, p_s, s) \propto \exp[-\frac{1}{kT}(V(q) + \sum_{i=1}^{N} \frac{p_i^2}{2m_i} + \frac{p_s^2}{2Q})]$$

The Hamiltonian of the extended system along the equation only for "ergodic systems"

➔ Chaining variables behaves better for small or stiff cases

• A modification of the Nosé-Hoover thermostat which includes not a single thermostat variable but a chain of variables with different "masses".
• Chaining variables with different masses helps to suppress oscillations.

The types of thermostat

5. Langevin

$$\dot{p} = -\nabla V(q) - \gamma p + \sigma \xi_i, \sigma = \sqrt{2m\gamma kT}$$

In langevin thermostat, the smaller particles create a damping force to the momenta, $-\gamma p_i$, as the large particles push the smaller ones out of the way.
The smaller particles also move with kinetic energy and give random kicks to the large particles.

$$\Delta p_i = \left(\frac{\partial \phi(q)}{\partial q_i} - \gamma p_i + \delta p \right) \Delta t$$

δp is a Gaussian distributed random number with probability

$$\rho(\delta p) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left(-\frac{|\delta p|^2}{2\sigma^2} \right)$$

The random fluctuating force represents the thermal kicks from the small particles.
The damping factor and the random force combine to give the correct canonical ensemble.

The types of thermostat

5. Langevin
Benefit

Typical advantage for Langevin thermostat is that we need fewer computations per time step since **we eliminate many atoms and include them implicitly by stochastic terms**.

Besides, we can choose a relatively large time step Δt, 2-3 times larger than in MD due to dissipative term, because damping term stabilizes the equations of motion.

Langevin thermostat replace the fastest frequency motions in the real system by stochastic terms, Δt is now chosen to resolve the slower degrees of freedom, and thus Δt is several hundred times larger than in the original MD. (➔ Large Frequency !)

```
inittimestep = 1.*femtosecond
timestep = 1.*femtosecond
freq = 1/picosecond
```

```
integ_eq = LangevinIntegrator(temperature, freq, inittimestep)
```

The types of thermostat

5. Langevin
Drawbacks

Excluded volume effects of solvent not included

Not trivial to implement drag force for non-spherical particles since the friction coefficient γi is related to the particle radius $\gamma_i = 6\pi\eta r_i/m_i$

For the solute-solvent system, solvent molecules must be small compared to the smallest molecules explicitly considered

Thermostats-necessary evil

1. The "Flying ice cube" effect and what to do about it

 Velocity rescaling using standard protocols can **systematically change the proportion of total kinetic energy found in motions** associated with the various degrees of freedom.

 High-frequency motions drain to low-frequency modes and eventually the system freezes and becomes a flying ice cube.

 A particularly pathological form of this problem occurs if one does not periodically remove the net translation of and rotation about the center of mass.

 In this case, almost all of the kinetic energy is converted into these two kinds of motion, producing a system with **almost no kinetic energy associated with the internal degrees of freedom**.

  The flying ice cube artifact is a violation of the equipartition principle and is not pecific to any simulation package but rather solely due to velocity rescaling a technique applied by global thermostats including the commonly used Berendsen weak coupling method and Nosé-Hoover.

Thermostats-necessary evil

2. The effect of thermostat in transport properties and kinetics

We can consider dynamic processes occurring on different time scales by measuring translational and rotational self-diffusion , shear viscosity of water, diffusion of a small molecule, etc…

All of theses properties are significantly dampen by thermostat algorithms which randomize particle velocities when strong coupling is used.

Algorithms which operate by scaling the velocities, such as the Berendsen thermostat and the Nose-Hoover thermostat, yield transport properties that are statistically indistinguishable from the microcanonical ensemble.
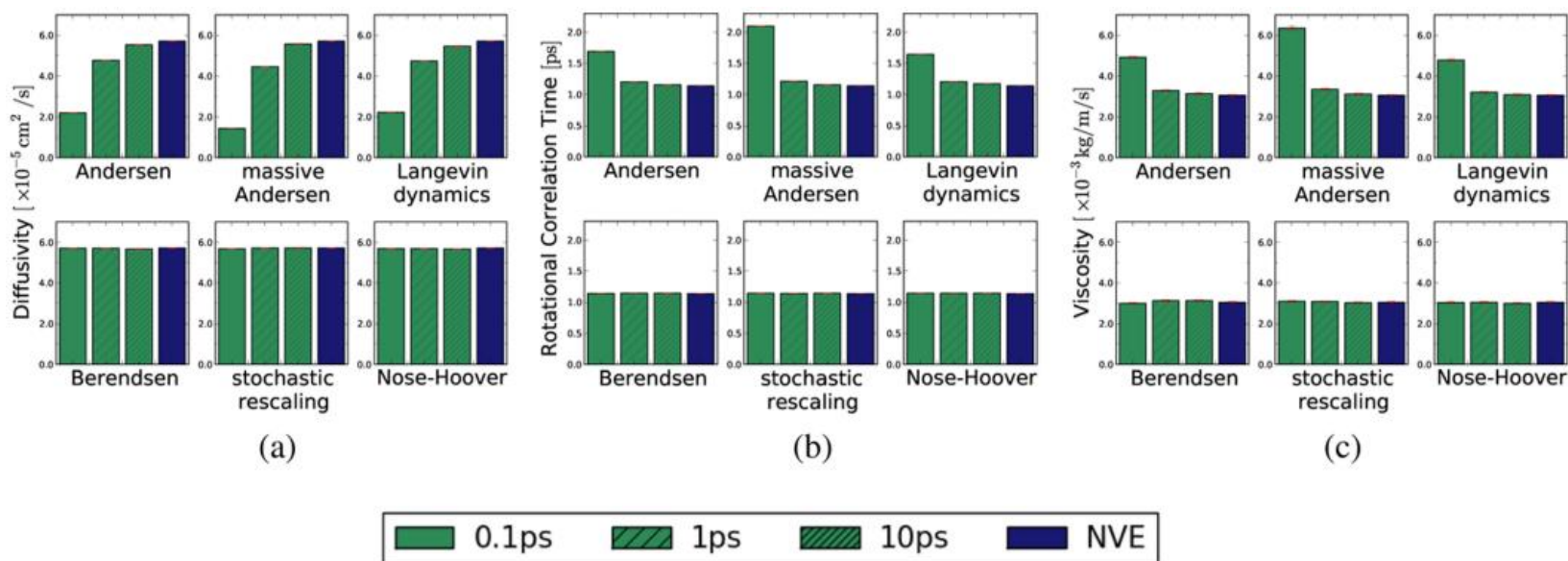
Thermostats-necessary evil

2. The effect of thermostat in transport properties and kinetics

The thermostatting algorithms alter the velocities of the particles and thus modify the dynamics of the system with respect to the microcanonical ensemble.

Because of the principle of few thermostat, it potentially lead to dynamical artifacts.

So we want to figure out which variance could vary the dynamics and the

Thermostats-necessary evil

3. Hot solvent - cold solute problem

Furthermore, using a single thermostat for an inhomogeneous solute-solvent system can lead to stationary temperature gradients.

To avoid this "hot solvent/cold solute" problem, two separate thermostats are frequently applied, one to the solute and one to the solvent.

However, such a separate temperature control will perturb the dynamics of the macromolecule much more strongly than a global one and, therefore, can introduce large artifacts into its conformational dynamics.

The simplest solution is indeed to apply thermostats separately the solute and solvent. In practice, the simulated system may consist of macromolecules and water, and a separate thermostat can perturb the dynamics of the micromolecule much more strongly than single global control.

Thermostats-necessary evil

4. The effect of treatment of thermostat on protein folding in the replica exchange molecular dynamics (REMD) simulations
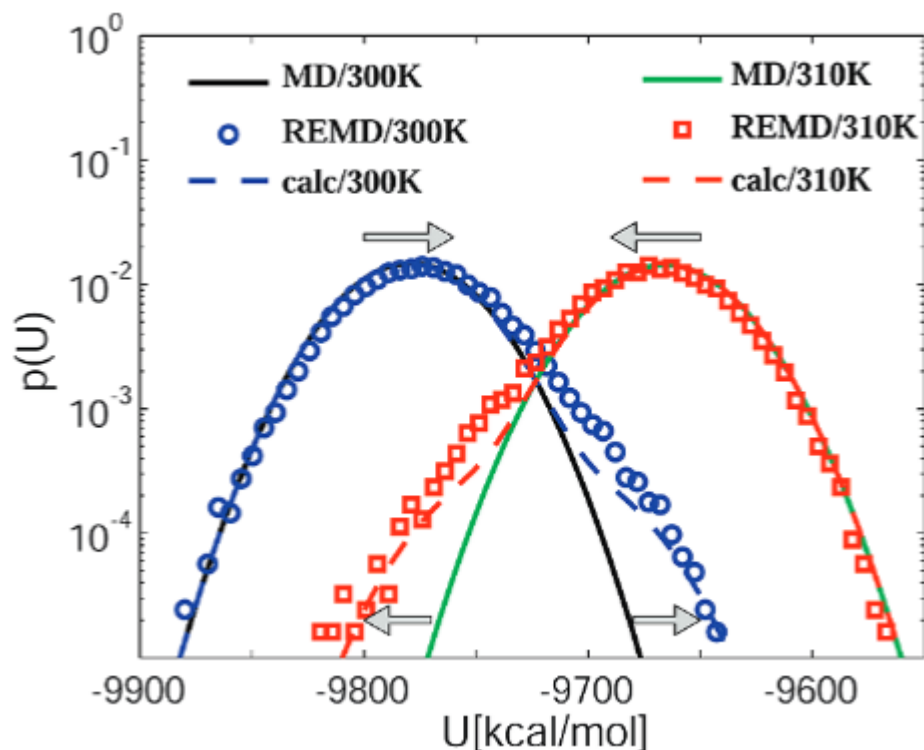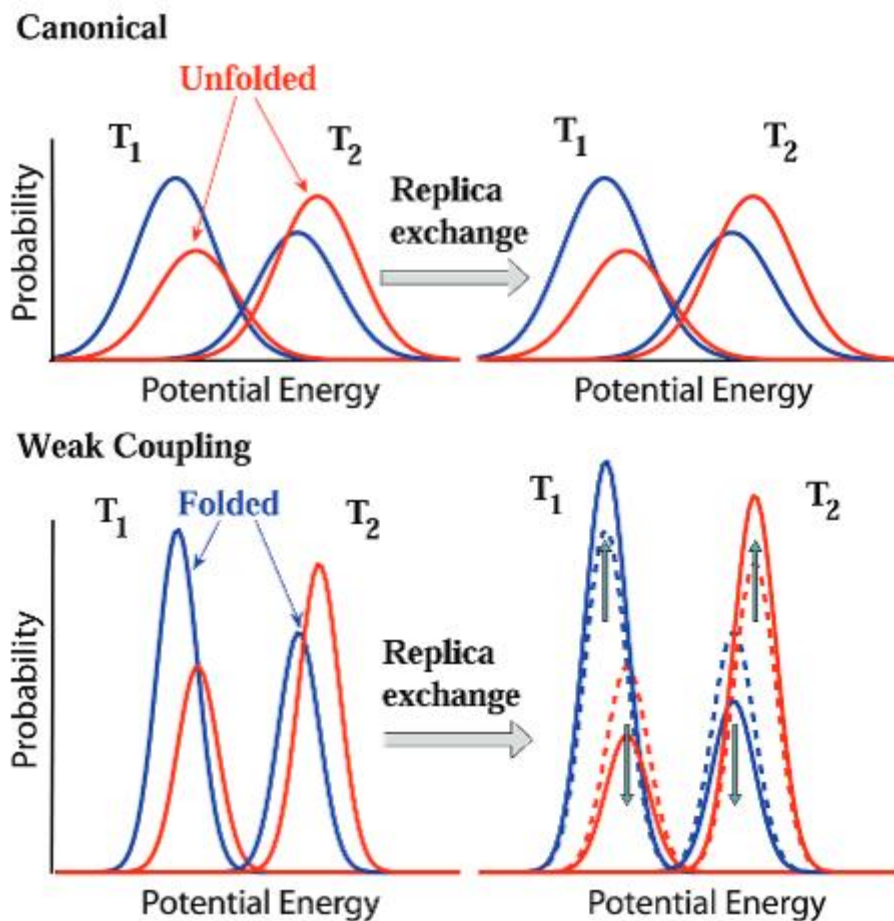
If the thermostats do not produce a canonical ensemble, REMD simulations are found to distort the configuration-space distributions.
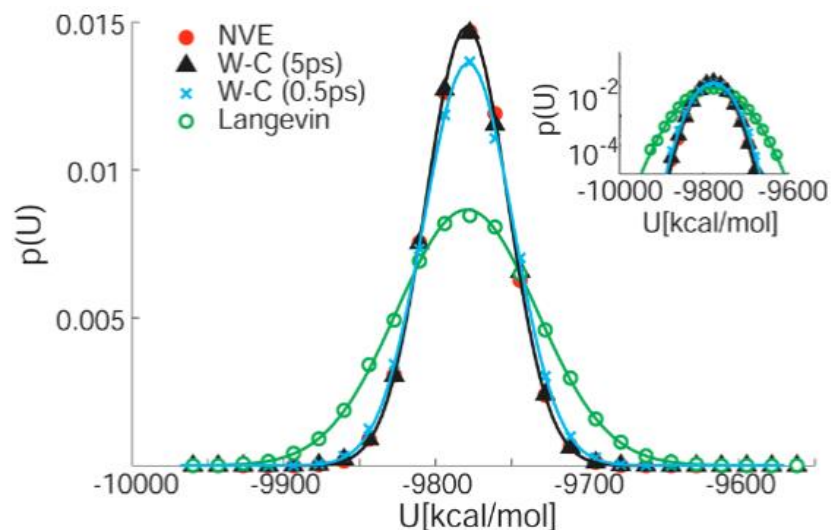
Thermostats-necessary evil

4. The effect of treatment of thermostat on protein folding in the replica exchange molecular dynamics (REMD) simulations
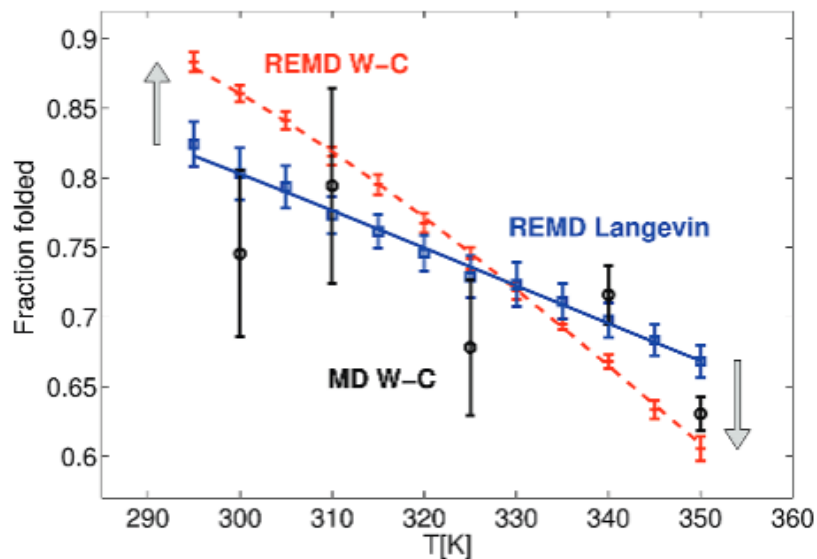In canonical Simulations / Non canonical simulations

Thermostats-necessary evil

4. The effect of treatment of thermostat on protein folding in the replica exchange molecular dynamics (REMD) simulations

2) In noncanonical Simulaions

Q&A