

An Introduction to Molecular Dynamics

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Why do molecular modeling?

- Why do we bother doing molecular modeling?
- Much of engineering is about modeling a system well enough to make predictions about how to design and control the system.
- So why not model at a **molecular** level?

Why do molecular modeling?

- What can we get out of molecular simulations?
- Thermodynamics
 - Ensemble averages of configurations
 - Free energy related quantities
 - Distributions of molecular configurations
- Kinetics/transport
 - Dependent on the paths that molecules take
 - Rates of transfer between configurations
 - Diffusion, viscosity, protein conformations, polymer aging

Molecular dynamics simulations are classical approximations to the QM equations

- Closest to truth: relativistic, time-dependent, Schrödinger equation
 - Assumption #1: Almost always with molecules, you can ignore relativity
 - Even then, anything more complex than a few atoms cannot be handled at this level of theory
- Assumption #2: We can assume that the nuclei move like classical point masses (Born-Oppenheimer approximation)
- We can then make many, many more numerical approximations that make it faster
- This allows us to do *Ab Initio* Molecular Dynamics (AIMD)
 - Use some approximation for Schrodinger's equations to solve for the electronic wavefunction,
 - Then use Coulomb's law to describe how the electron forces move nuclei around
- STILL VERY, VERY SLOW!!

Molecular dynamics simulations are classical approximations to the QM equations

- But what if we just give up on modeling the electrons, and instead **average out the electronic degrees of freedom**?
- A type of coarse-graining, where we just model the nuclei and electrons **lumped together**
- Approximate the interactions of the electrons and nuclei TOGETHER?
- And model the physics of THIS system?
- This is **classical molecular dynamics**.

Classical MD simulation

- Cons:
 - As we average out electron behavior more and more, we lose accuracy
 - Usually, have to add in bonds making/breaking by hand.
 - Interactions like pi-cations really hard to model.
 - No understanding of interaction of light with models.
- Pros:
 - Orders of magnitude faster 10^3 - 10^9
 - Actually more accurate for many problems in condensed phase solutions
 - Converging QM to high levels of accuracy is HARD, sometimes you can do better by picking an approximate interaction term.
 - It's a model - you use **the model that works for your questions.**

A classical system follows Newton's equations of motion

$$m\vec{a}_i(t) = \vec{F}_i(\vec{x}(t)) = -\nabla U(\vec{x}_i) = -\left[\frac{\partial U}{\partial x_i}, \frac{\partial U}{\partial y_i}, \frac{\partial U}{\partial z_i}\right]$$

$$\frac{\partial^2 x_i}{\partial t^2} = -\frac{1}{m} \nabla U(\vec{x})$$

- General strategy:
 - Pick an energy function $U(x)$
 - **IMPORTANT CHOICE!**
 - Specify the positions and velocities at time t .
 - Approximate the positions and velocities at time $t+\Delta t$ using the differential equation
- How we get "good" initial positions and velocities?
 - **IMPORTANT CHOICE!**

Go to the notebook!

- Simple_MD.ipynb
- We will discuss:
 - Taylor series solution
 - Verlet and higher order solutions
 - Energy drift
 - Shadow Hamiltonians
 - Stiffness

What sort of ensemble does MD generate?

- MD simulates the NVE ensemble (it conserves energy!)
- With a bit of tweaking, MD can also allow us to capture canonical (NVT) and isobaric-isothermal (NPT) ensembles

What comes out of an MD simulation?

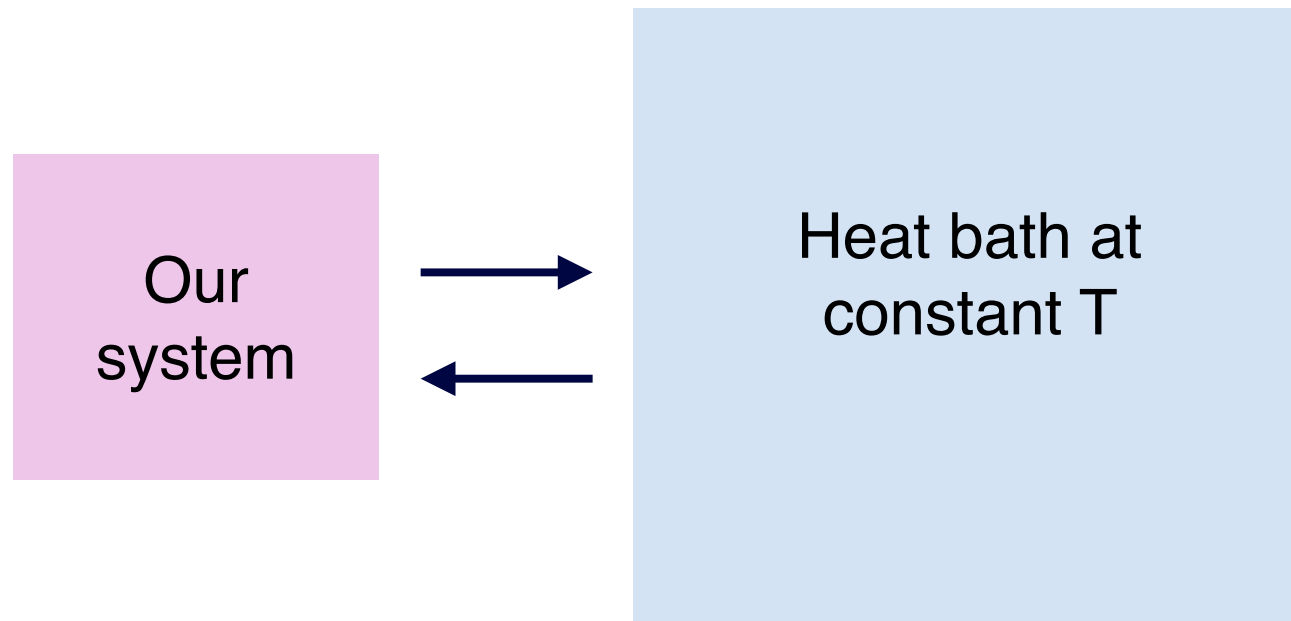
- Time series of the energies and forces (+ other derived quantities like pressure, etc).
- Time series of the coordinates/velocities
- This is sufficient to estimate **pretty much any corresponding experimental observable**.
 - What are some of these observables?
- The **key problem of MD analysis** is how to **extract data of interest** when you have $3N \times$ number of frames data points!

Why do we need thermostats for molecular dynamics?

- Molecular dynamics gives:
 - Solutions to the initial value partial differential equations defined by Newton's equation of motion
- Newton's laws of motion conserve **energy**
- Therefore this gives ensembles
 - constant number of particles
 - constant volume
 - **constant energy**
- But we want answers at, say 300 K?

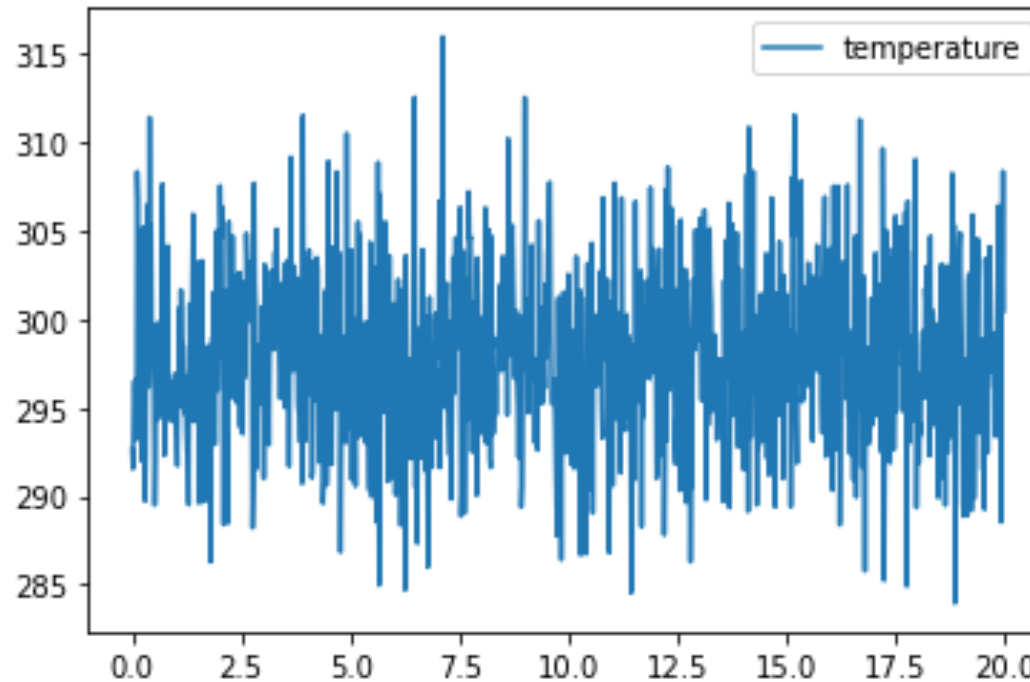
We want to simulate properties at constant T

What does it mean to be a constant T ensemble?



Exchange thermal energy
until at equilibrium

What does it mean if you see a graph like this from a simulation?



- This is actually a graph of $\frac{2KE}{N_{DOF}k_B}$
- $T = \frac{2\langle KE \rangle}{N_{DOF}k_B}$, but T is constant in an NVT simulation.

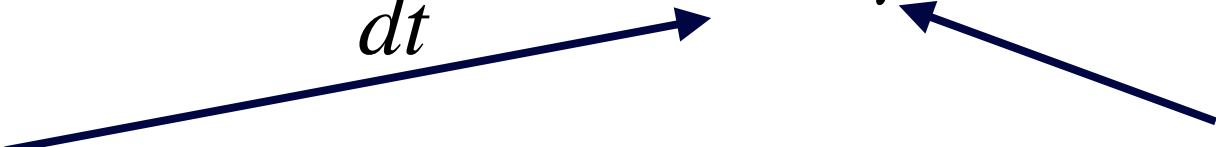
How does REAL LIFE thermal equilibration happen?

- Our system is surrounded by other molecules
- They bang into our system, and exchange kinetic energy
 - If they are hotter than the system average, then energy goes into the system, and it heats up
 - If they are cooler than the system average, then energy goes out of the system, and it cools down
 - Until it is in thermal equilibrium with the surroundings

A very simple thermostat (Andersen)

- "Thermo" = temperature, "stat" - keeps the same
- With some probability p (or frequency N), our particles collide
 - (With what? Some imaginary particle from the multiverse)
 - And we randomize their velocity to the Maxwell-Boltzmann distribution
- This is the Andersen thermostat
- In GROMACS, `tcoupl = anderson-massive`
- Need to set `ref_t` as well!
- Go to the notebook `Example_NVT`!

Langevin dynamics

$$m \frac{dv}{dt} = F + R - \gamma v$$


- Add thermal energy by adding random noise
 - Like a particle colliding!
 - But, all of the particles are colliding, even ones inside your system...
- Suck excess thermal energy away with a friction term
 - Like moving through a fluid, which doesn't not necessarily make sense; the simulation IS the fluid . . .
- Balance the friction loss and random noise to be equal when you are at the right T $\langle R \rangle = 0 \quad \langle R^2 \rangle = 2k_B T \gamma$
 - Implemented as `integrator = sd` in gromacs.
 - Very good stability!
 - If you add too much random noise, and suck out too much velocity, it **slows the dynamics**.

How else could we get thermal energy into and out of the system?

- We modify the kinetic energies of the particles
- First guess:
 - If the average thermal energy is too **high**, decrease the velocity of **all** particles
 - If the average thermal energy is too **low**, increase the velocity of **all** particles
- This is the weak coupling thermostat
- In GROMACS, `tcoupl = berendsen`
- Need to set `ref_t` as well!

How quickly do we pump energy in or out?

- Let's say the system has 110 kJ mol. At the temperature you specified, it should have 100 kJ/mol on average
 - Do you take out 10 kJ/mol each step?
 - Or do you take out 1 kJ/mol each step?
- We need to define a **rate** at which excess kinetic energy is removed

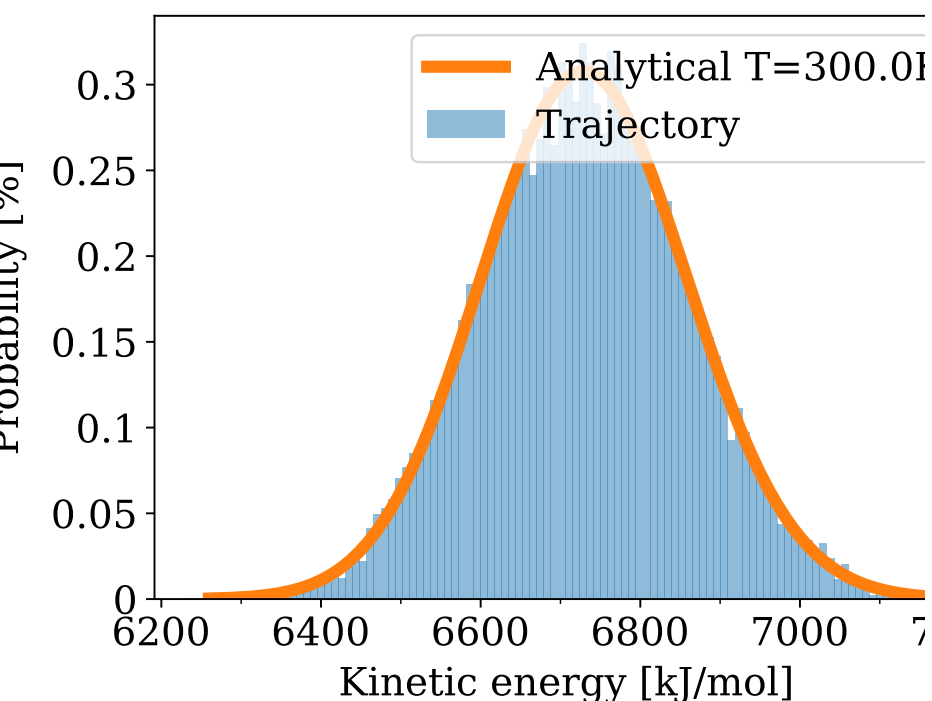
$$\frac{dKE}{dt} = k(KE_0 - KE)$$

- k has units of $1/\text{time} = 1/\tau$
- In GROMACS, this is `tau_t`.

There's a problem with Berendsen!

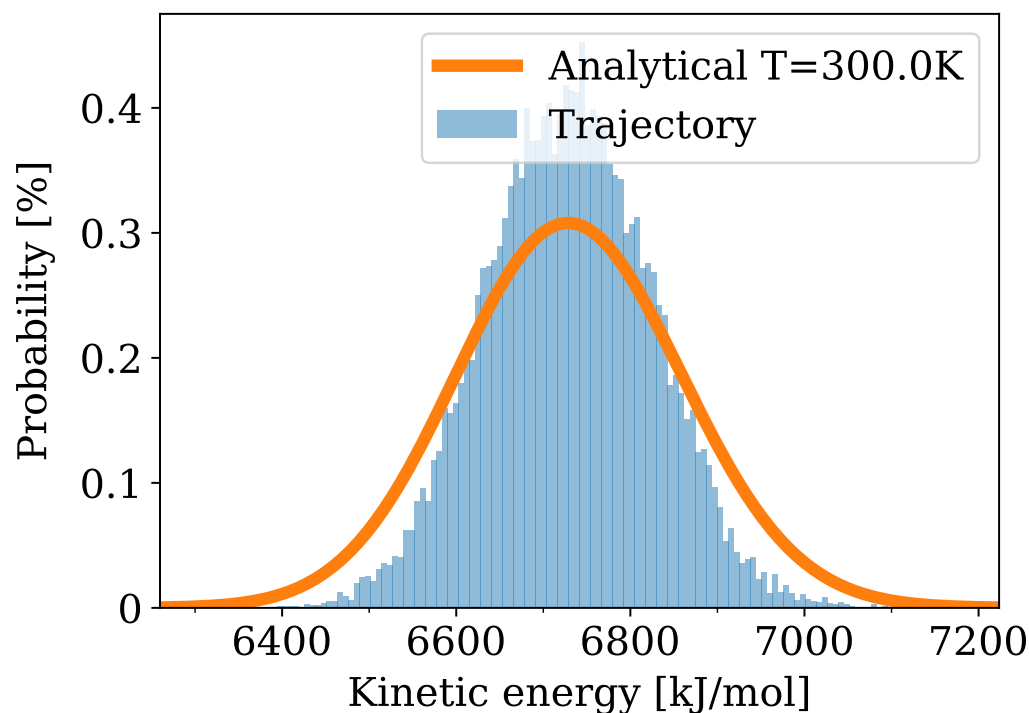
- It suppresses fluctuations!

True thermostat



$T_{\mu} = 299.94 \pm 0.04 \text{ K}$
 $T_{\sigma} = 301.01 \pm 1.47 \text{ K}$
 $p = 0.214045$

Berendsen thermostat



$T_{\mu} = 299.99 \pm 0.03 \text{ K}$
 $T_{\sigma} = 222.60 \pm 1.16 \text{ K}$
 $p = 8.42116 \times 10^{-83}$

Bussi-Parrinello

- A simulation should not have a single target kinetic energy. It should have a **Maxwell-Boltzmann kinetic energy distribution**.
- Don't target a **fixed** kinetic energy K . Target at **random** K , chosen from the Maxwell-Boltzmann distribution
- This gives a **correct distribution of kinetic energies**
- **Rigorously consistent** with KE NVT distribution

$$\frac{dKE}{dt} = k(KE_{\text{Maxwell-Boltzmann}} - KE)$$

In GROMACS, `tcoupl = v-rescale`

Nosé-Hoover thermostat

- Also a scaling thermostat:
 - If kinetic energy K is too big, make all particles slower
- Math is too complicated for today
- **But** it is essentially a **second-order** thermostat

$$\frac{dKE}{dt} = k(KE_0 - KE)^2$$

- Relaxes to right K **faster** than Berendsen
- BUT can oscillate back and forth
 - This can be bad for solids
- *Almost always* gives the right NVT

Do I need a thermostat?

- Unless you are measuring transport properties, almost certainly yes.
- It is VERY EASY to start a simulation at too high a total E. Need to maintain T!
- If your simulation is SLIGHTLY not obeying $F=ma$, it will also keep the simulation from accumulating or losing much energy

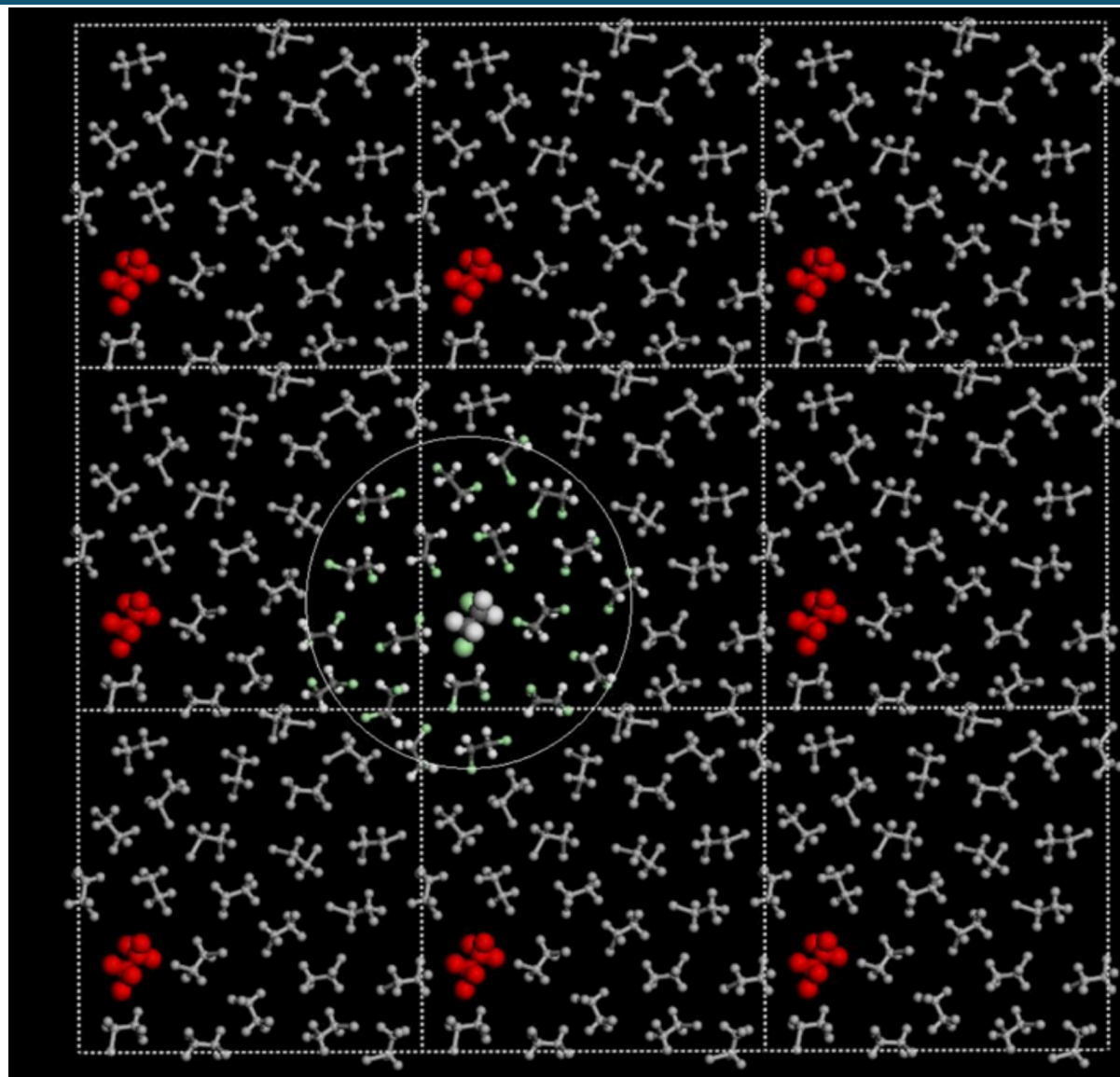
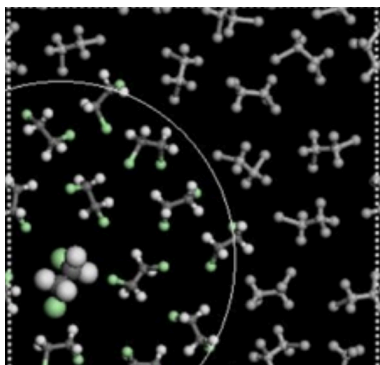
Thermostat recommendations

- Langevin is most stable, but slows system down a bit, especially at large friction values
 - Anderson is slows things down a bit more.
 - The ONLY ones you should use for gases
- Bussi-Parrinello is simple and usually very good
- Parrinello-Rahman is OK for liquids, not so good for gases/solids
- Berendsen (weak coupling) is only good to equilibrate a system.

How do we simulate bulk properties?

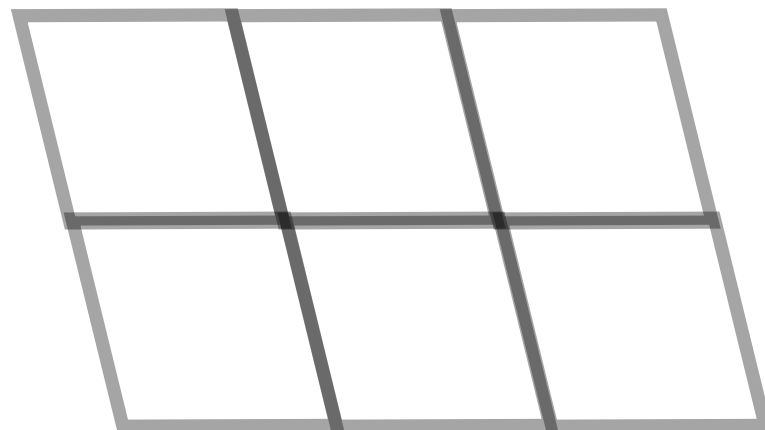
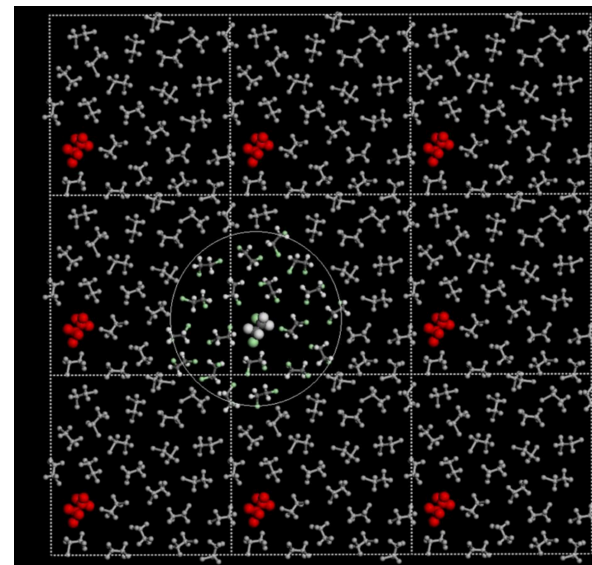
- Our simulation box is usually only a few nanometers across!
- We could simulate with infinitely hard walls, or simulate a droplet
 - But surface effects are at **least** 1-2 nanometers.
- Periodic boundary conditions:
 - We model the bulk by REPEATING the simulation cell.
- When a particle goes **out** one side, it comes **back** on the other.
- To calculate forces, we calculate the force from **the neighboring copies**.

Periodic Boundary Conditions



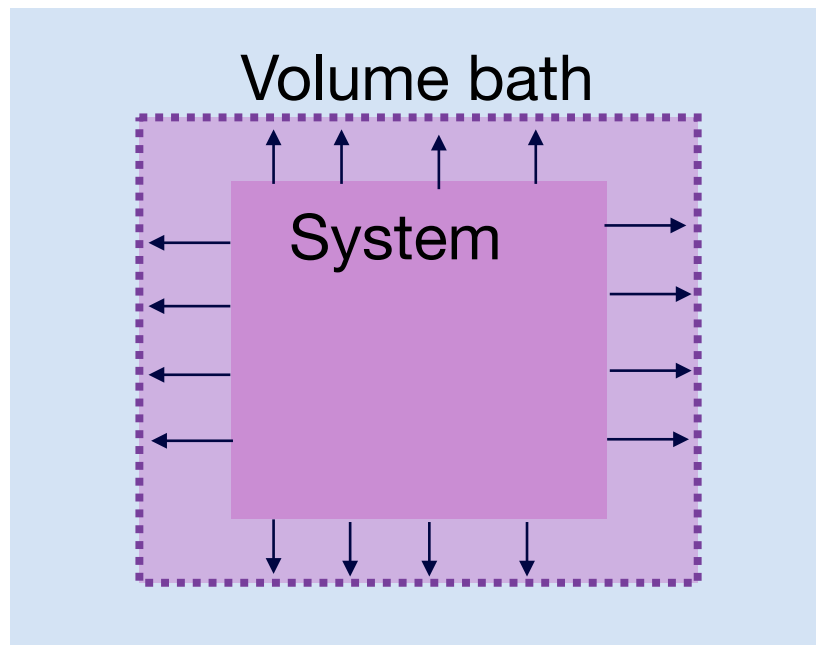
Periodic Boundary Conditions

- Minimum image convention
 - Means box can't be smaller than 2x the longest energy cutoff
- Boxes can be cubic or tilted
- When not to use:
 - Single molecule
 - Droplet
- Molecules can't be longer than the box, or you get weirdness.



Barostats

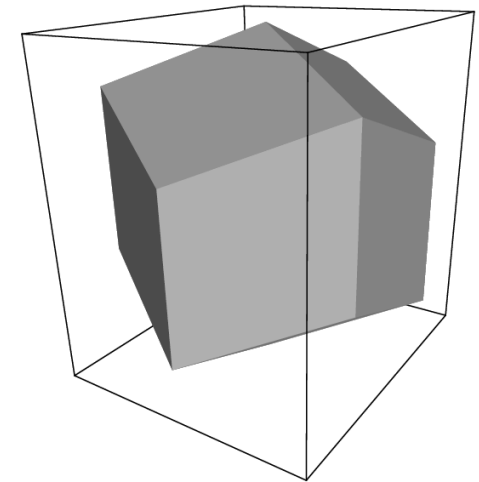
- So: We know how to
 - Handle thermal equilibrium
 - What box volume means for a periodic system
- What about **NPT**
 - Where the volume is not constant?



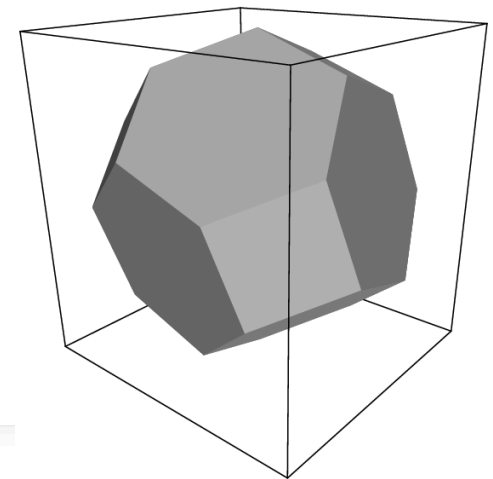
- System exchanges volume with the surroundings until in mechanical equilibrium with its environment.

Possible ways to tile 3d space

box type	image distance	box volume	box vectors			box vector angles		
			a	b	c	$\angle bc$	$\angle ac$	$\angle ab$
cubic	d	d^3	d	0	0	90°	90°	90°
			0	d	0			
			0	0	d			
rhombic dodcahdron (xy-square)	d	$\frac{1}{2}\sqrt{2}d^3$ $0.707d^3$	d	0	$\frac{1}{2}d$	60°	60°	60°
			0	d	$\frac{1}{2}d$			
			0	0	$\frac{1}{2}\sqrt{2}d$			
rhombic dodcahdron (xy- hexagon)	d	$\frac{1}{2}\sqrt{2}d^3$ $0.707d^3$	d	$\frac{1}{2}d$	$\frac{1}{2}d$	60°	60°	60°
			0	$\frac{1}{2}\sqrt{3}d$	$\frac{1}{6}\sqrt{3}d$			
			0	0	$\frac{1}{3}\sqrt{6}d$			
truncated octahedron	d	$\frac{4}{9}\sqrt{3}d^3$ $0.770d^3$	d	$\frac{1}{3}d$	$-\frac{1}{3}d$	71.53°	109.47°	71.53°
			0	$\frac{2}{3}\sqrt{2}d$	$\frac{1}{3}\sqrt{2}d$			
			0	0	$\frac{1}{3}\sqrt{6}d$			



rhombic dodecahedron

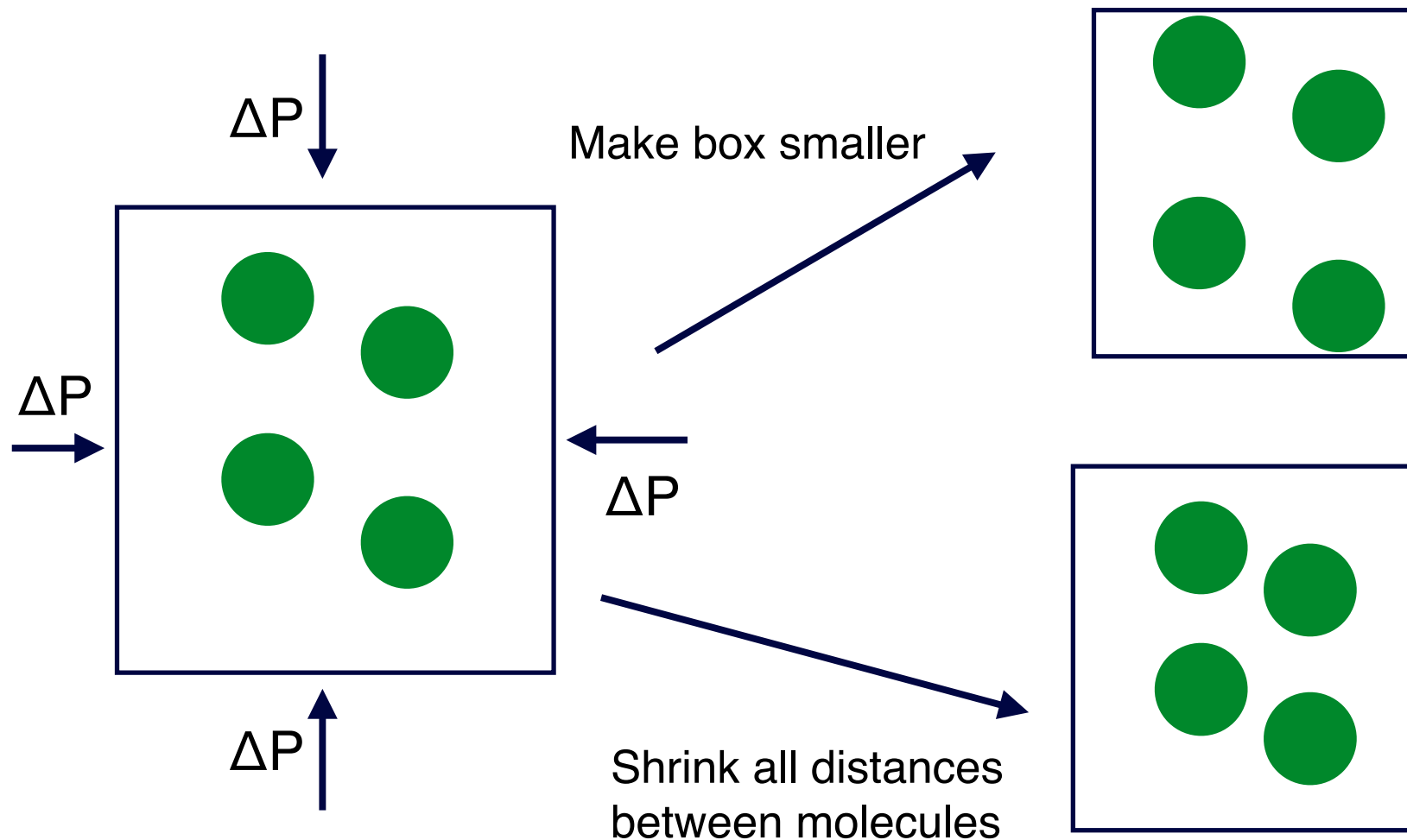


truncated octahedron

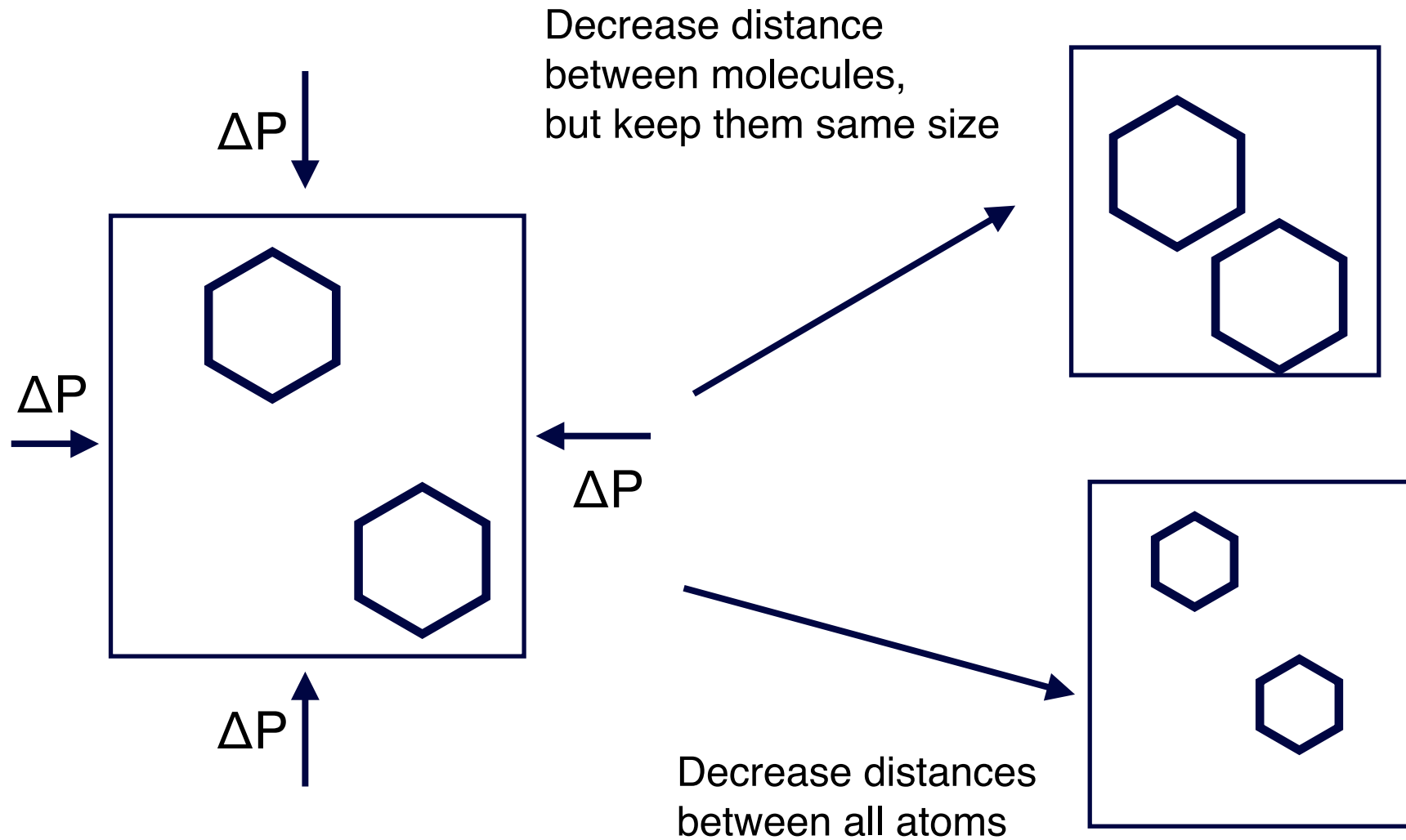
How does a real life barostat work?

- Outside particles collide with your system.
 - If there are lots of hard collisions with your system, it pushes your system together
 - If there are few hard collisions with your system, your system pushes out.
- How can we model that in a periodic boundary system?
 - There is no **outside**. . .

How does an MD barostat work?



Do we shrink molecules??



How do we know whether to shrink or grow?

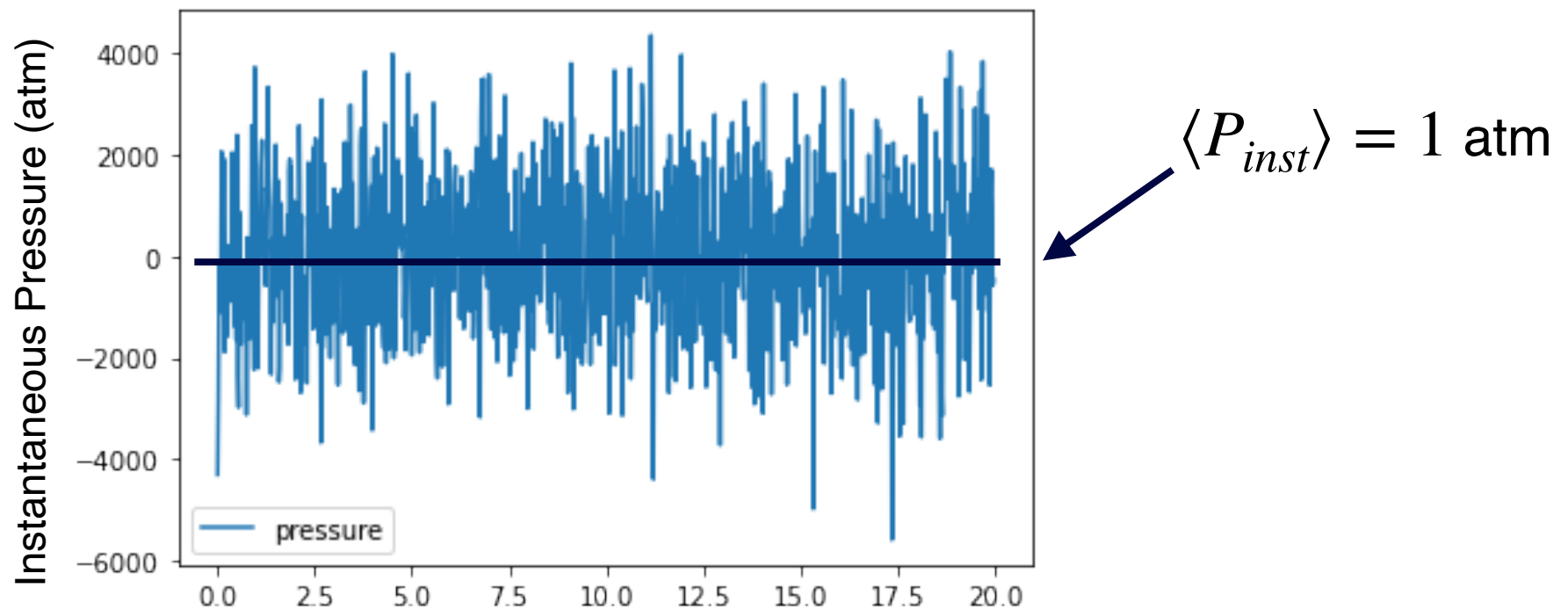
$$P = \left\langle \frac{1}{V} \left(2KE + \frac{1}{3} \sum_{i>j} r_{ij} \cdot F(r_{ij}) \right) \right\rangle$$

- The **virial** compares the "pushing out" of the kinetic energy with the "pulling in" of the forces
- This is an "instantaneous pressure" not the external pressure. The pressure is constant.
- We compare the quantity inside the averages to P
- If it's too big, we shrink!
- If it's too small, we grow!

Properties of "instantaneous pressure"

$$P = \left\langle \frac{1}{V} \left(2KE + \frac{1}{3} \sum_{i>j} r_{ij} \cdot F(r_{ij}) \right) \right\rangle$$

- Can oscillate wildly (like, several 1000 atm!)



How a simple barostat works

- " P "_{estimate} > P _{desired}
 - Shrink box by some factor s
- " P "_{estimate} < P _{desired}
 - Expand box by some factor s
- HOW BIG should s be?
- Let's make s is proportional to $P_{\text{target}} - P_{\text{instant}}$
- What is the constant of proportionality, i.e. how QUICKLY does one respond to differences in pressure?
- If we say: $V_{\text{new}}/V_{\text{old}} = k(P_{\text{target}} - P_{\text{instant}})$
 - in GROMACS, τ_p sets k
- Berendsen's weak coupling barostat
- `pcouple=Berendsen`, and set `ref_p` as well!
- **Guess what!** Weak coupling suppresses true

Parrinello-Rahman barostat

- Parrinello-Rahman barostat
 - Similar theory to Nosé-Hoover thermostat
 - 2nd order, so approaches true answer with some oscillations
 - Common in most MD packages
 - Rigorously* gives NPT
 - Has some minor errors if you have *constraints*, like rigid water, hydrogen bond constraints
 - Tends to be somewhat numerically unstable, especially for small systems
- `pcoupl = Parrinello-Rahman`

Cell-resizing thermostat

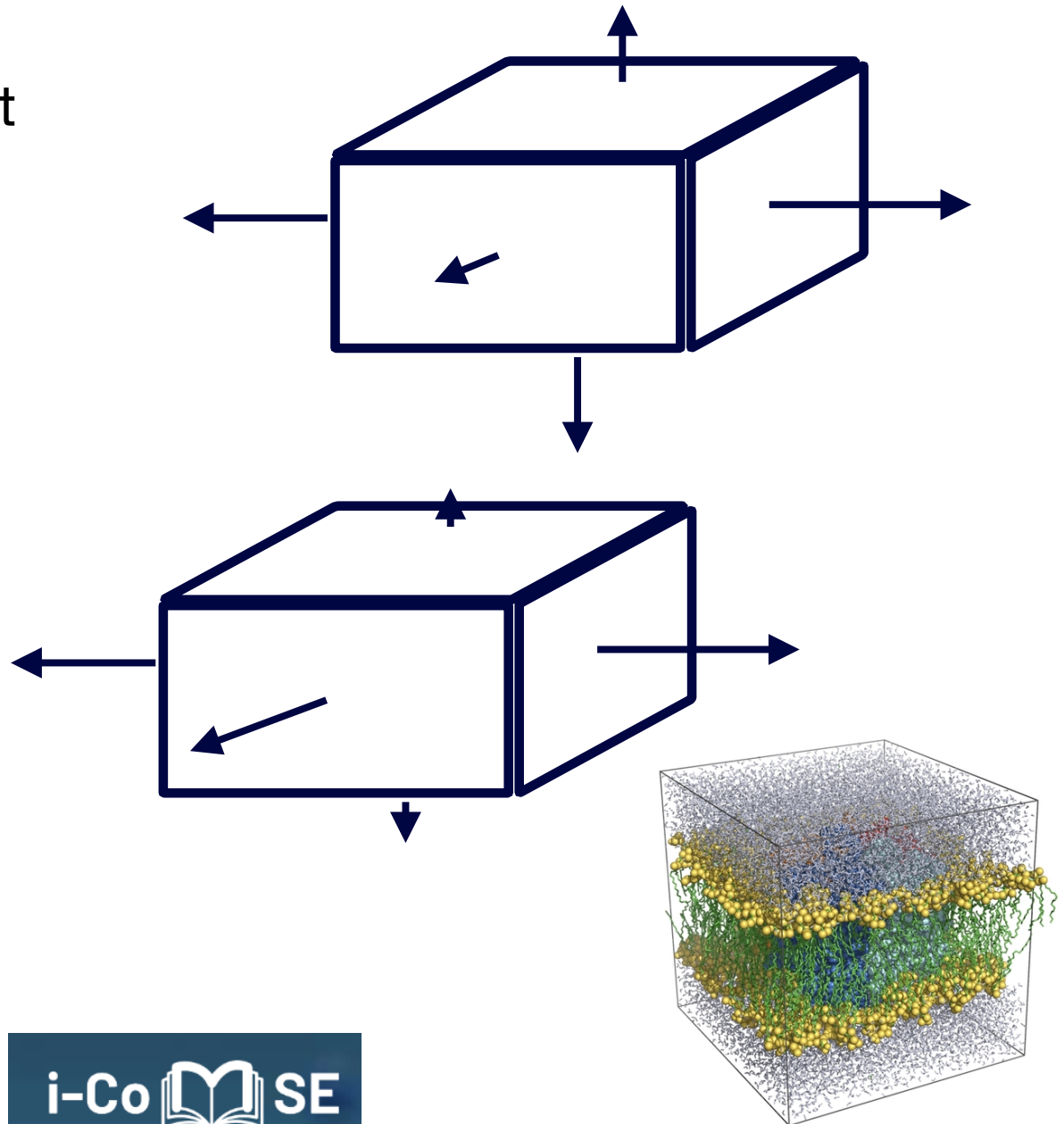
- Very new!
- Similar theory to Bussi-Parrinello thermostat
- Like Berendsen, but with added fluctuations to get NPT right.
- Rigorously gives NPT
- Not that well understood where it might fail, but in theory it should be the best barostat
- `pcoupl = c-rescale`

Monte Carlo Barostat

- Change the system volume by a random small amount
 - If $U+PV$ is lower, then accept the change
 - If $U+PV$ is higher, then roll a random number to accept
 - If change is accepted, then shrink/expand the box
- Gives correct NPT volume distributions!
 - implemented in OpenMM
- Doesn't this breaks the dynamics
- Barostats **already** break the dynamics, since particles don't magically move together and apart in nature without direct action from other molecules

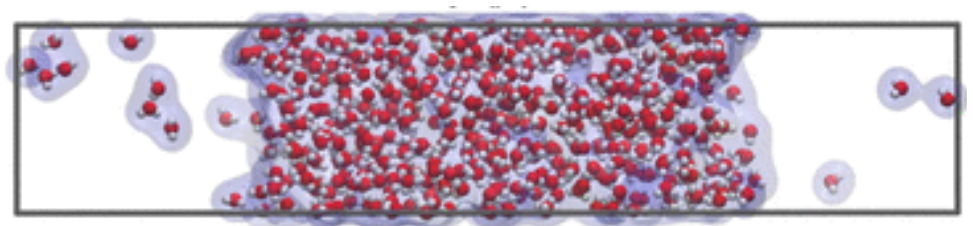
Other possibilities for a barostat

- Isotropic
 - Box side ratios do not change
- Anisotropic:
 - All box sides can move independently.
 - The ratio of the sides can change
- Semiisotropic
 - x and y isotropically, but not z
 - Common for bilayer/lamellar simulations



What can go wrong with a barostat?

- The systems of equations for MD are significantly less stable than MD alone or MD + barostat
 - Because particles can get "scaled" into each other!
- More likely to crash.
 - If you start from a bad configuration.
 - If the system is poorly equilibrated
 - If the system is very small.
 - If there is some sort of phase separation or self-assembly



Do I need a barostat?

- You almost certainly need a barostat to relax your simulation to the equilibrium volume.
 - You don't want to run at a density that is too high or too low
 - Like running at 1000 atm, or bubbles could form.
- BUT if your system is **highly incompressible**,
 - You may not need to run your simulation at NPT once it reaches the right P
 - You could average the volume over the last 100 ps, find the average volume, and pick a frame with that average volume, and run with that barostat
- OFTEN results are OK with the Berendsen barostat

Some guidelines

- **Thermostats:**

- For equilibration, have a SHORT τ_t
 - 0.1 to 1 ps
- For production, have a LONGER τ_t
 - 5 or 10 ps

- **Barostats:**

- Instantaneous pressure will frequently oscillate between +/- 1000 atm for a low compressibility fluid. THIS IS NORMAL!
- Generally, keep τ_p about 5x τ_t
- If the simulation crashes because of volume fluctuations, try a somewhat longer τ_p (2x-5x). Results will be valid as long as τ_p is < 0.1-1% of the simulation run.