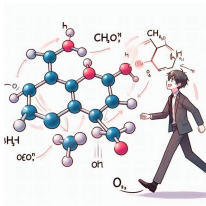# Molecular Dynamics Short Course @CCB

Sonya M. Hanson & Chris Edelmaier

Flatiron Institute, NY, NY

Wednesday, October 30, 2024

COURSE SUMMARY as we hit course 3 of 8

Part I

Oct 16. Introduction & Integrators
Oct 22. Probability & Thermodynamics
Oct 30. (TODAY) MD Basics

Part II

Nov 6. Advanced forcefields & Enhanced Sampling (Miro)
Nov 13. Infinite range forces (Chris)
Nov 20. Coarse Graining (Abhilash)
Dec 4. Super Coarse Graining and Continuum Models (Chris)
Dec 11. Bonus Session (leftover material/personal projects)

FLATIRON
INSTITUTE

This Lecture - Molecular Dynamics Basics

1. Overview of Integrators
2. Overview of Thermostats
3. Intro to Barostats
4. MD in practice
5. Periodic Boundary Conditions
6. Lennard-Jones and Truncation of Interactions
7. Bonded and Non-Bonded Terms
8. TUTORIAL with OpenMM and PyMOL
X. Some slides on the Liouville formalism

FLATIRON
I N S T I T U T E

Molecular Dynamics Basics - Introduction

Recall from our first lecture:
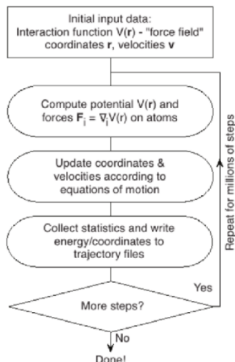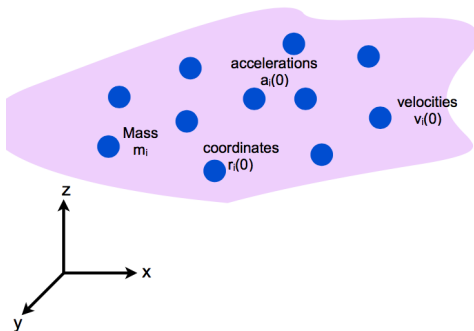
Solution: A discretized time step (Δt).

For numerical stability this time step is usually very small ~ 2 fs $(2 \times 10^{-15} s)$.

$$r_i(t_0) \longrightarrow r_i(t_0+\Delta t) \longrightarrow r_i(t_0+2\Delta t) \longrightarrow r_i(t_0+3\Delta t) \longrightarrow r_i(t_0+n\Delta t)$$

The first molecular simulation - Metropolis Monte Carlo.

- At its simplest the Monte Carlo technique is just random sampling.

- It is not in general possible to evaluate our integral by direct Monte Carlo simulation (using e.g. quadrature), instead what Metropolis et al[1] showed an efficient Monte Carlo scheme to evaluate a RATIO of two integrals.

- Using this scheme Metropolis et al studied a two dimensional rigid sphere system using the MANIAC.

Recall also from our first lecture:
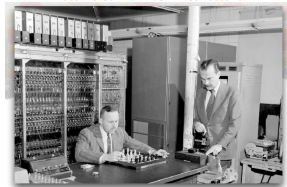
1952 - The MANIAC computer at Los Alamos

---

[1] Metropolis, Rosenbluth, Rosenbluth, Teller, & Teller. 'Equation of state calculations by fast computing machines.' *J. Chem. Phys.*, 21:1087-1092, 1953.

The first molecular simulation - Metropolis Monte Carlo.

- At its simplest the Monte Carlo technique is just random sampling.

- It is not in general possible to evaluate our integral by direct Monte Carlo simulation (using e.g. quadrature), instead what Metropolis et al[1] showed an efficient Monte Carlo scheme to evaluate a RATIO of two integrals.

- Using this scheme Metropolis et al studied a two dimensional rigid sphere system using the MANIAC.

- Conventional quadrature vs. Metropolis sampling:

  - In the Metropolis scheme, a random walk is constructed through that region of space where the integrand is nonnegligible.
  - A trial move is rejected if it takes you out of the water and is accepted otherwise.
  - After every trial move (accepted or not), the depth of the water is measured.

Recall also from our first lecture:
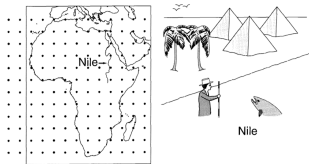

1952 - The MANIAC computer at Los Alamos

Figure 3.1: Measuring the depth of the Nile: a comparison of conventional quadrature (left), with the Metropolis scheme (right).

---

[1] Metropolis, Rosenbluth, Rosenbluth, Teller, & Teller. 'Equation of state calculations by fast computing machines.' *J. Chem. Phys.*, 21:1087-1092, 1953.

MD vs. MC

Molecular dynamics (MD) differs from Monte Carlo (MC) simulations in that in MD we are calculating time-dependent dynamics.
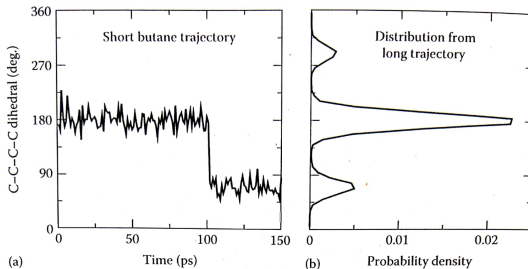
What makes a good integrator?

A good Molecular Dynamics program requires a good choice of algorithm to integrate Newton's equations of motion.

What makes a *good* algorithm?

- **Speed:** Not so important because the fraction of time spent integrating the equations of motion is small compared to that spent evaluating the forces.

- **Accuracy for large time steps:** The longer the time step, the fewer evaluations of the forces are needed per unit time. Tends to be a compromise between error and time step length.

- **Memory:** Usually not crucial except for higher-order algorithms and very large systems.

- **Energy conservation:** It is critical to avoid overall energy drifts for long simulation times. Verlet-style algorithms have little long-term drift, though they have moderate short-term energy conservation.

FLATIRON
INSTITUTE

Velocity Verlet (review)

Example 2: Velocity Verlet Algorithm[2]

We can also cast the Verlet algorithm in a form that yields positions, r^N, and velocities, v^N, computed at equal times.

$$r_j(t + \Delta t) = r_j(t) + v_j(t)\Delta t + \frac{f(t)}{2m}\Delta t^2$$

(like the Euler scheme) i.e. looks like Taylor expansion of coordinates

$$v_j(t + \Delta t) = v_j(t) + \frac{f(t + \Delta t) + f(t)}{2m}\Delta t$$

(unlike Euler) time reversible: past and future coordinates enter symmetrically.

---

[2]Swope, Andersen, Berens, & Wilson, 'A computer simulation method for the calculation of equilibrium constants for the formation of physical clusters of molecules: Applications to small water clusters.' *J. Chem. Phys.*, 76,1:637-649, 1982.

Velocity Verlet (review)

Example 2: Velocity Verlet Algorithm[2]
We can also cast the Verlet algorithm in a form that yields positions, r^N, and velocities, v^N, computed at equal times.

$$r_j(t + \Delta t) = r_j(t) + v_j(t)\Delta t + \frac{f(t)}{2m}\Delta t^2$$

(like the Euler scheme) i.e. looks like Taylor expansion of coordinates

$$v_j(t + \Delta t) = v_j(t) + \frac{f(t + \Delta t) + f(t)}{2m}\Delta t$$

(unlike Euler) time reversible: past and future coordinates enter symmetrically.

This expression for the velocity comes directly from the expression for r_j:

$$r_j(t - \Delta t) = r_j(t) - v_j(t)\Delta t + \frac{f(t)}{2m}\Delta t^2$$

Substitution: $t' = t - \Delta t$

$$r_j(t') = r_j(t' + \Delta t) - v_j(t' + \Delta t)\Delta t + \frac{f(t' + \Delta t)}{2m}\Delta t^2$$

---

[2]Swope, Andersen, Berens, & Wilson, 'A computer simulation method for the calculation of equilibrium constants for the formation of physical clusters of molecules: Applications to small water clusters.' *J. Chem. Phys.*, 76,1:637-649, 1982.

Velocity Verlet (review)

Example 2: Velocity Verlet Algorithm[2]
We can also cast the Verlet algorithm in a form that yields positions, r^N, and velocities, v^N, computed at equal times.

$$r_j(t + \Delta t) = r_j(t) + v_j(t)\Delta t + \frac{f(t)}{2m}\Delta t^2$$

(like the Euler scheme) i.e. looks like Taylor expansion of coordinates

$$v_j(t + \Delta t) = v_j(t) + \frac{f(t + \Delta t) + f(t)}{2m}\Delta t$$

(unlike Euler) time reversible: past and future coordinates enter symmetrically.

- equivalent to the original Verlet scheme
- error in velocity is $\mathcal{O}(\Delta t^3)$

---

[2]Swope, Andersen, Berens, & Wilson, 'A computer simulation method for the calculation of equilibrium constants for the formation of physical clusters of molecules: Applications to small water clusters.' *J. Chem. Phys.*, 76,1:637-649, 1982.

FLATIRON

Lyapunov Instability

Something that could have been in the What makes a good integrator? section.

Notice we didn't ask: Which integrator makes the most accurate prediction of the trajectory of the particles?

Lyapunov Instability

Something that could have been in the What makes a good integrator? section.

Notice we didn't ask: Which integrator makes the most accurate prediction of the trajectory of the particles?

To illustrate the extreme sensitivity of trajectories to small differences in initial conditions, let us consider a small perturbation, ϵ, of the momenta, such that

$$r(t) = f[r^N(0), p^N(0); t]$$
$$r'(t) = f[r^N(0), p^N(0) + \epsilon; t]$$

Lyapunov Instability

Something that could have been in the What makes a good integrator? section.

Notice we didn't ask: Which integrator makes the most accurate prediction of the trajectory of the particles?

To illustrate the extreme sensitivity of trajectories to small differences in initial conditions, let us consider a small perturbation, ϵ, of the momenta, such that

$$r(t) = f[r^N(0), p^N(0); t]$$
$$r'(t) = f[r^N(0), p^N(0) + \epsilon; t]$$

The difference between $r(t)$ and $r'(t)$ is denoted by $\Delta r(t)$, and for sufficiently short times $\Delta r(t)$ is linear in ϵ. However, the coefficient of linear dependence diverges exponentially. That is,

$$|\Delta r(t)| \sim \epsilon e^{\lambda t}$$

where λ is the Lyapunov exponent (or the largest of 6N exponents, which dominates the long-time exponential divergence of initially close trajectories).

FLATIRON
INSTITUTE

Lyapunov Instability

Something that could have been in the *What makes a good integrator?* section.

Notice we didn't ask: Which integrator makes the most accurate prediction of the trajectory of the particles?

To illustrate the extreme sensitivity of trajectories to small differences in initial conditions, let us consider a small perturbation, ϵ, of the momenta, such that

$$r(t) = f[r^N(0), p^N(0); t]$$
$$r'(t) = f[r^N(0), p^N(0) + \epsilon; t]$$

The difference between $r(t)$ and $r'(t)$ is denoted by $\Delta r(t)$, and for sufficiently short times $\Delta r(t)$ is linear in ϵ. However, the coefficient of linear dependence diverges exponentially. That is,

$$|\Delta r(t)| \sim \epsilon e^{\lambda t}$$

where λ is the Lyapunov exponent (or the largest of 6N exponents, which dominates the long-time exponential divergence of initially close trajectories).

Two simulations will diverge, we can consider it caused by the integration error in the algorithm - the Lyapunov instability.

Lyapunov Instability - Why it's okay.

How close are MD simulations to the 'true trajectories'?

- There is considerable evidence[3], though no proof, that our simulated trajectories are representative of the true trajectory.

- Writing down the time-discretized formulations of the Verlet algorithm, gives us the 'true trajectory' indicating that the Verlet algorithm is indeed an approximation of true dynamics[4].

- This 'true trajectory' is often called the 'shadow trajectory'. Evidence even points to a better behavior of these shadow trajectories for systems in which small differences in the initial conditions lead to exponential divergence, than for simpler systems for which this divergence isn't there[4].

[3]Quinlan & Tremaine. 'On the reliability of gravitational n-body integrations.' *Mon. Not. R. Astron. Soc.*, 259:505-518, 1992.
[4]Olender & Elber. 'Calculation of classical trajectories with a very large time step: Formalism and numerical examples.' *J. Chem. Phys.*, 105:9299-9315, 1996.

Beyond NVE.

With a good integrator we can simulate the natural time evolution of a classical system of N particles in a volume V, in which the total energy E is a constant of motion, NVE, or the microcanonical ensemble.

However, it is often desirable to simulate in the NVT (canonical) or NPT ensembles, as these more directly match the conditions in an experiment.

For example, if we are comparing our simulations to experimental results on a system in a test tube with a constant number of particles, N, a constant volume, V, and a constant temperature, T.

To simulate in these other ensembles we use Thermostats and Barostats.

The flying ice cube

In the 90s, Harvey et al[5] found that a violation of energy equipartion in velocity rescaling lead to a pathology dubbed 'The flying ice cube', which occurs if one does not periodically remove the net translation of the center of mass.

⇒ Almost all of the kinetic energy is converted into translational motion (hence 'flying'), resulting in a system with almost no kinetic energy associated with internal degrees of freedom (hence 'ice cube').

In the 2000s, Bussi et al[6] developed a new v-rescaling algorithm, sometimes dubbed canonical sampling through velocity rescaling (CSVR), which does not have this artifact because it is consistent with the canonical ensemble, and not the 'isokinetic ensemble' like Berendsen.

⇒ Despite the clear advantage of doing velocity rescaling with the Bussi thermostat, the Berendsen thermostat is still being used to the surprise and consternation of many[7].

---
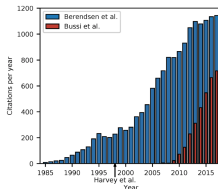
[5] Harvey, Tan, & Cheatham. 'The Flying Ice Cube: Velocity Rescaling in Molecular Dynamics Leads to Violation of Energy Equipartition.' *J. Comput. Chem.*, 19:726-740, 1998.

[6] Bussi, Donadio, & Parrinello. 'Canonical Sampling Through Velocity Rescaling.' *J. Chem. Phys.*, 126:014101, 2007.

[7] Braun, Moosavi, & Smit. 'Anomalous Effects of Velocity Rescaling Algorithms: The Flying Ice Cube Effect Revisited.' *J. Chem. Theory Comput.*, 14:5262-5272, 2018.

FLATIRON
INSTITUTE

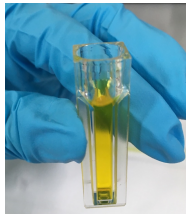# Thermostating algorithms

A useful table summarizing popular thermostats [8]:

Table 1. Basic summary of popular thermostats. ✗ indicates that the thermostat does not fulfill the statement, ✓ indicates that the thermostat does fulfill the statement, and (✓) indicates that the thermostat fulfills the statement under certain circumstances.

Thermostat	Ensemble	Deterministic/ Stochastic	Global/ Local	Physical?	Correct Structural Properties?	Correct Dynamical Properties?
None	Microcanonical	Deterministic		✓	✓	✓
Gaussian	Isokinetic	Deterministic	Global	✗	✓	✗
Simple Velocity Rescaling	Undefined	Deterministic	Global	✗	✗	✗
Berendsen	Undefined	Deterministic	Global	✗	✗	✗
Bussi	Canonical	Stochastic	Global	✗	✓	(✓)
Andersen	Canonical	Stochastic	Local	✗	✓	✗
Langevin	Canonical	Stochastic	Local	✗	✓	✗
Nosé-Hoover	Canonical	Deterministic	Global	✗	✓	(✓)

---

[8]Braun, Gilmer, Mayes, Mobley, Monroe, Prasad, & Zuckerman. 'Best Practices for Foundations in Molecular Simulation [Article v1.0]' *Living J. Comp. Mol. Sci.*, 1(1): 5957, 2019.

Motivation for constant pressure simulations

⇒ Typically, thermodynamic properties of interest are measured under open-air conditions in a laboratory, which (for short timescales) means that they are measured at essentially constant temperature (RT) and pressure (1 atm).

- Note though, that barostat algorithms control only pressure. So if we want to simulate in the isothermal-isobaric (NPT) ensemble, they must be applied with a thermostat. If only a barostat is applied, the ensemble that is simulated is the isoenthalpic-isobaric (NPH) ensemble.

Barostating algorithms

Different ways of simulating constant pressure:

1. Strong coupling method: volume rescaling
   $\rightarrow$ scale volume to give exact desired value
2. Weak coupling method: Berendsen barostat
   $\rightarrow$ scale volume in the direction of the desired value
3. Extended system dynamics: Andersen barostat
   $\rightarrow$ uses extended degrees of freedom to control the volume item
   Ext. sys. dynamics with support for anisotropy: Parinello-Rahman
   $\rightarrow$ uses extended degrees of freedom while supporting anisotropy

$\Rightarrow$ **Barostats alter volumes.**
   $\rightarrow$ The Andersen (3) and Parinello-Rahman (4) barostats alter volumes
      such that trajectories sample the correct ensemble.

How do we define pressure in a microscopic system?

- For the purpose of molecular modeling, consider a hypothetical system that is being compressed and/or expanded by a fictitious piston.
- The mass of the piston can be tuned to change the compression of the system, which will change how often the particles in the system interact with it.
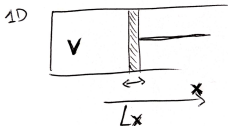
**Container with volume V, enclosed by a piston area A**

How do we define pressure in a microscopic system?

- For the purpose of molecular modeling, consider a hypothetical system that is being compressed and/or expanded by a fictitious piston.
- The mass of the piston can be tuned to change the compression of the system, which will change how often the particles in the system interact with it.

Container with volume V, enclosed by a piston area A

Pressure $P = -\dfrac{\langle K \rangle}{A}$

where $\langle K \rangle$ is the average force on the particles due to the piston.

How do we define pressure in a microscopic system?

- For the purpose of molecular modeling, consider a hypothetical system that is being compressed and/or expanded by a fictitious piston.
- The mass of the piston can be tuned to change the compression of the system, which will change how often the particles in the system interact with it.

Container with volume V, enclosed by a piston area A
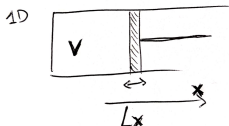
Pressure $P = -\dfrac{\langle K \rangle}{A}$

where $\langle K \rangle$ is the average force on the particles due to the piston.
Wall potential:

$$V^{wall} = V^{\infty} \sum_{i=1}^{N} \theta(x_i - L_x)$$

where V^{∞} is large and corresponds to the thermal energy.

How do we define pressure in a microscopic system?

Hamiltonian:

$$H = \sum \frac{1}{2} m v_i^2 + \sum_{i+1}^{N} V(r_1 - r_N) + V^{wall}$$

How do we define pressure in a microscopic system?

Hamiltonian:

$$H = \sum \frac{1}{2} m v_i^2 + \sum_{i+1}^{N} V(r_1 - r_N) + V^{wall}$$

$$K = \sum_{i+1}^{N} K_i = -\sum_{i+1}^{N} \frac{\partial V^{wall}}{\partial x_i} = \frac{\partial}{\partial L_x} \sum_{i+1}^{N} V^{wall} = \frac{\partial H}{\partial L_x}$$

How do we define pressure in a microscopic system?

Hamiltonian:

$$H = \sum \frac{1}{2} m v_i^2 + \sum_{i+1}^{N} V(r_1 - r_N) + V^{wall}$$

$$K = \sum_{i+1}^{N} K_i = - \sum_{i+1}^{N} \frac{\partial V^{wall}}{\partial x_i} = \frac{\partial}{\partial L_x} \sum_{i+1}^{N} V^{wall} = \frac{\partial H}{\partial L_x}$$

$$P = -\frac{\langle K \rangle}{A} = -\langle \frac{\partial H}{\partial L_x} \rangle \frac{1}{A} = -\langle \frac{\partial H}{\partial V} \underbrace{\frac{\partial V}{\partial L_x}}_{L_y L_z} \rangle \frac{1}{L_y L_z} = -\langle \frac{\partial H}{\partial V} \rangle$$

How do we define pressure in a microscopic system?

Hamiltonian:

$$H = \sum \frac{1}{2} m v_i^2 + \sum_{i+1}^{N} V(r_1 - r_N) + V^{wall}$$

$$K = \sum_{i+1}^{N} K_i = -\sum_{i+1}^{N} \frac{\partial V^{wall}}{\partial x_i} = \frac{\partial}{\partial L_x} \sum_{i+1}^{N} V^{wall} = \frac{\partial H}{\partial L_x}$$

$$P = -\frac{\langle K \rangle}{A} = -\langle \frac{\partial H}{\partial L_x} \rangle \frac{1}{A} = -\langle \frac{\partial H}{\partial V} \underbrace{\frac{\partial V}{\partial L_x}}_{L_y L_z} \rangle \frac{1}{L_y L_z} = -\langle \frac{\partial H}{\partial V} \rangle$$

$$P \cdot V = \langle \frac{\partial H}{\partial V} \rangle V = -\langle \frac{\partial H}{\partial L_x} L_x \rangle \overset{\text{(isotropic)}}{=} -\frac{1}{3} \langle \underbrace{\frac{\partial H}{\partial L_x} L_x}_{} + \frac{\partial H}{\partial L_y} L_y + \frac{\partial H}{\partial L_z} L_z \rangle$$

$$\langle \frac{\partial V^{wall}}{\partial L_x} L_x \rangle = \langle -\sum_{i+1}^{N} \frac{\partial V^{wall}}{\partial x_i} x_i \rangle$$

Note: $\frac{\partial V^{wall}}{\partial L_x} = V^{\infty} \sum_{i=1}^{N} \delta(x_i - L_x)$

How do we define pressure in a microscopic system?

Hamiltonian:

$$H = \sum \frac{1}{2}mv_i^2 + \sum_{i+1}^{N} V(r_1 - r_N) + V^{wall}$$

$$K = \sum_{i+1}^{N} K_i = -\sum_{i+1}^{N} \frac{\partial V^{wall}}{\partial x_i} = \frac{\partial}{\partial L_x} \sum_{i+1}^{N} V^{wall} = \frac{\partial H}{\partial L_x}$$

$$P = -\frac{\langle K \rangle}{A} = -\langle \frac{\partial H}{\partial L_x} \rangle \frac{1}{A} = -\langle \frac{\partial H}{\partial V} \underbrace{\frac{\partial V}{\partial L_x}}_{L_y L_z} \rangle \frac{1}{L_y L_z} = -\langle \frac{\partial H}{\partial V} \rangle$$

$$P \cdot V = \langle \frac{\partial H}{\partial V} \rangle V = -\langle \frac{\partial H}{\partial L_x} L_x \rangle \stackrel{\text{(isotropic)}}{=} -\frac{1}{3} \langle \underbrace{\frac{\partial H}{\partial L_x} L_x}_{} + \frac{\partial H}{\partial L_y} L_y + \frac{\partial H}{\partial L_z} L_z \rangle$$

$$\langle \frac{\partial V^{wall}}{\partial L_x} L_x \rangle = \langle -\sum_{i+1}^{N} \frac{\partial V^{wall}}{\partial x_i} x_i \rangle$$

Note: $\frac{\partial V^{wall}}{\partial L_x} = V^\infty \sum_{i=1}^{N} \delta(x_i - L_x)$

Thus: $PV = +\frac{1}{3} \langle \underbrace{\sum_{i+1}^{N} \nabla r_i V^{wall}}_{\text{External force due to walls, } -f_i^{ext}} \cdot r_i \rangle = \frac{1}{3} - \langle \sum_{i+1}^{N} f_i^{ext} r_i \rangle$

How do we define pressure in a microscopic system?

Ideal gas equation of state:

$$P = \frac{N k_B T}{V} = \rho k_B T$$

How do we define pressure in a microscopic system?

Ideal gas equation of state:

$$P = \frac{Nk_BT}{V} = \rho k_B T$$

Real system:

$$P = k_B T(\rho + \rho^2 B_2(T) + \mathcal{O}(\rho^3))$$

where B_2 is the second Virial coefficient, and $\mathcal{O}(\rho^3)$ is expressed in terms of microscopic properties.

Derive pressure from simulations: Virial equation.

FLATIRON
INSTITUTE

Virial theorem

In mechanics, the virial theorem provides a general equation that relates the average over time of the total kinetic energy of a stable system of discrete particles, bound by potential forces, with that of the total potential energy of the system.

Virial theorem

In mechanics, the virial theorem provides a general equation that relates the average over time of the total kinetic energy of a stable system of discrete particles, bound by potential forces, with that of the total potential energy of the system.

Virial G is defined as (in classical mechanics)

$$G_i = \sum_{i=1}^{N} r_i p_i$$

with time derivative

$$\frac{d}{dt} G = \frac{d}{dt} \left(\sum_{i=1}^{N} r_i p_i \right) \overset{\text{(chain rule)}}{=} \underbrace{\sum_{i=1}^{N} \frac{2}{2m} p_i^2}_{2 \cdot E_{kin} = 2 \cdot N \cdot 3 \cdot \frac{1}{2} k_B T} + \sum_{i=1}^{N} r_i f_i$$

where f_i the total force is the external force from the walls $+$ the internal forces due to interactions

$$f_i = f_i(r^N) = \nabla r_i V(r^N) - \nabla r_i V^{wall}(r^N)$$

Virial theorem

<u>Ensemble average</u>
Since G is finite (conservation of phase space volume): $\langle \frac{d}{dt} G \rangle = 0$

$$\langle \frac{d}{dt} G \rangle = 2 \cdot \langle E_{kin} \rangle + \langle \overbrace{\sum_{i+1}^{N} r_i \underbrace{(-\nabla r_i V(r^N))}_{\text{internal forces}}} \rangle + \langle \overbrace{\sum_{i+1}^{N} r_i (-\nabla r_i V^{wall})}^{\text{external forces}=-3PV} \rangle$$

Virial theorem

Ensemble average

Since G is finite (conservation of phase space volume): $\langle \frac{d}{dt} G \rangle = 0$

$$\langle \frac{d}{dt} G \rangle = 2 \cdot \langle E_{kin} \rangle + \langle \overbrace{\sum_{i+1}^{N} r_i \left(-\nabla r_i V(r^N) \right)}^{\text{internal forces}} \rangle + \langle \overbrace{\sum_{i+1}^{N} r_i (-\nabla r_i V^{wall})}^{\text{external forces} = -3PV} \rangle$$

$\rightarrow$ Virial theorem: provides connection between average kinetic energy and average potential energy

$$P = \underbrace{\frac{2}{3V} \overbrace{\langle E_{kin} \rangle}^{\frac{1}{2} k_B T \cdot 3N}}_{\frac{Nk_B T}{V} \text{(eq. of state for ideal gas)}} + \underbrace{\frac{1}{3V} \langle -\sum_{i+1}^{N} r_i \nabla r_i V(r^N) \rangle}_{\chi_{int}: \text{ virial correction} \atop \text{to ideal gas (inner Virial)}}$$

Virial theorem

<u>Ensemble average</u>

Since G is finite (conservation of phase space volume): $\langle \frac{d}{dt} G \rangle = 0$

$$\langle \frac{d}{dt} G \rangle = 2 \cdot \langle E_{kin} \rangle + \overbrace{\langle \sum_{i+1}^{N} r_i (-\nabla r_i V(r^N)) \rangle}^{\text{internal forces}} + \overbrace{\langle \sum_{i+1}^{N} r_i (-\nabla r_i V^{wall}) \rangle}^{\text{external forces}=-3PV}$$

$\rightarrow$ <u>Virial theorem:</u> provides connection between average kinetic energy and average potential energy

$$P = \underbrace{\frac{2}{3V} \overbrace{\langle E_{kin} \rangle}^{\frac{1}{2} k_B T \cdot 3N}}_{\frac{N k_B T}{V} \text{(eq. of state for ideal gas)}} + \underbrace{\frac{1}{3V} \langle -\sum_{i+1}^{N} r_i \nabla r_i V(r^N) \rangle}_{\substack{\chi_{int}: \text{ virial correction} \\ \text{to ideal gas (inner Virial)}}}$$

$\rightarrow$ The instantaneous pressure is given by

$$P_{inst} = \frac{2}{3V} E_{kin} + \frac{1}{3V} \chi_{int}$$

Virial theorem

Since G is finite (conservation of phase space volume): $\langle \frac{d}{dt} G \rangle = 0$

$$\langle \frac{d}{dt} G \rangle = 2 \cdot \langle E_{kin} \rangle + \overbrace{\langle \sum_{i+1}^{N} r_i \left(-\nabla_{r_i} V(r^N) \right) \rangle}^{\text{internal forces}} + \overbrace{\langle \sum_{i+1}^{N} r_i \left(-\nabla_{r_i} V^{wall} \right) \rangle}^{\text{external forces} = -3PV}$$

$\rightarrow$ <u>Virial theorem:</u> provides connection between average kinetic energy and average potential energy

$$P = \underbrace{\frac{2}{3V} \overbrace{\langle E_{kin} \rangle}^{\frac{1}{2} k_B T \cdot 3N}}_{\frac{N k_B T}{V} \text{ (eq. of state for ideal gas)}} + \underbrace{\frac{1}{3V} \langle -\sum_{i+1}^{N} r_i \nabla_{r_i} V(r^N) \rangle}_{\substack{\chi_{int}: \text{ virial correction} \\ \text{to ideal gas (inner Virial)}}}$$

$\rightarrow$ The instantaneous pressure is given by

$$P_{inst} = \frac{2}{3V} E_{kin} + \frac{1}{3V} \chi_{int}$$

$\rightarrow$ **Regardless of the barostat, the Virial is used to define the pressure in simulations.**

FLATIRON

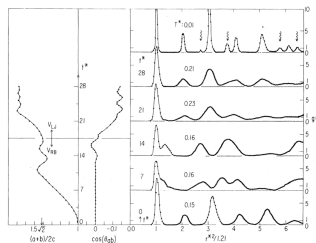# Parinello-Rahman: The recommended ext. sys. barostat

- In this barostat developed by Parinello and Rahman later in 1980[9], they modified Andersen's barostat to allow for changes in volume *and* shape of the MD cell.

---
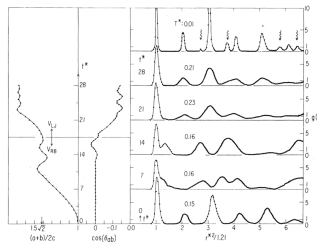
[9]Parrinello & Rahman. 'Crystal Structure and Pair Potentials: A Molecular-Dynamics Study.' *Phys. Rev. Lett.*, 45(14): 1196-1199, 1980.

Parinello-Rahman: The recommended ext. sys. barostat

- In this barostat developed by Parinello and Rahman later in 1980[9], they modified Andersen's barostat to allow for changes in volume *and* shape of the MD cell.

- In this scheme the extended part of the Lagrangian takes the form $\frac{1}{2}W\text{Tr}(\dot{h}'\dot{h}) - p\Omega$ where h is the matrix formed by $\{\vec{a}, \vec{b}, \vec{c}\}$ the box vectors, p is the hydrostatic pressure imposed on the system, and W is a constant of proportionality that has the dimension of mass.

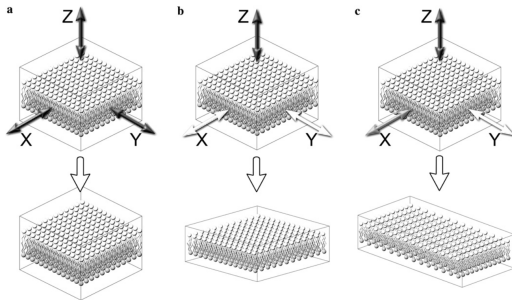[9]Parrinello & Rahman. 'Crystal Structure and Pair Potentials: A Molecular-Dynamics Study.' *Phys. Rev. Lett.*, 45(14): 1196-1199, 1980.

FLATIRON INSTITUTE

Parinello-Rahman: The recommended ext. sys. barostat

- In this barostat developed by Parinello and Rahman later in 1980[9], they modified Andersen's barostat to allow for changes in volume *and* shape of the MD cell.

- In this scheme the extended part of the Lagrangian takes the form $\frac{1}{2}W\mathrm{Tr}(\dot{h}'\dot{h}) - p\Omega$ where h is the matrix formed by $\{\vec{a}, \vec{b}, \vec{c}\}$ the box vectors, p is the hydrostatic pressure imposed on the system, and W is a constant of proportionality that has the dimension of mass.

- Using this new barostat they investigated a 500 particle system using the Lennard-Jones 6-12 potential with parameters suitable for a rubidium metal (results to the right).
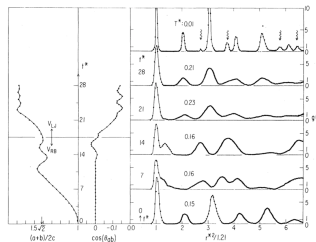
[9]Parrinello & Rahman. 'Crystal Structure and Pair Potentials: A Molecular-Dynamics Study.' *Phys. Rev. Lett.*, 45(14): 1196-1199, 1980.

FLATIRON
I N S T I T U T E

The practical importance of anisotropy in a barostat

Anisotropy is the property of substances to exhibit variations in physical properties along different molecular axes.

- Unlike the Andersen barostat, Parrinello-Rahman supports the scaling schemes of the size and shape of the simulation box other than isotropic.

- **Anisotropic scaling** scaling can be quite useful in solid simulations, where phase changes can be shape changes in a crystal lattice.
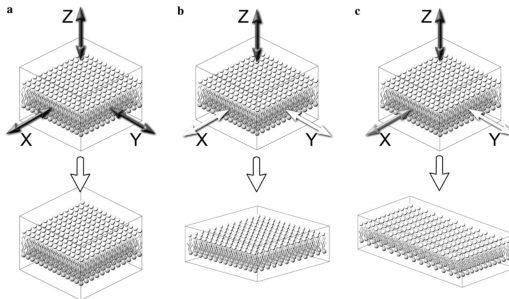

10

10 Kandt, Ash, & Tieleman. 'Setting up and running MD simulations of membrane proteins.' *Methods*, 41: 475-488, 2007.

FLATIRON
INSTITUTE

The practical importance of anisotropy in a barostat

Anisotropy is the property of substances to exhibit variations in physical properties along different molecular axes.

- Unlike the Andersen barostat, Parrinello-Rahman supports the scaling schemes of the size and shape of the simulation box other than isotropic.

- **Anisotropic scaling** scaling can be quite useful in solid simulations, where phase changes can be shape changes in a crystal lattice.

- For simulations of lipid bilayers **semi-isotropic pressure coupling** is preferred as bilayer surface area fluctuations are allowed.

10

[10] Kandt, Ash, & Tieleman. 'Setting up and running MD simulations of membrane proteins.' *Methods*, 41: 475-488, 2007.

FLATIRON INSTITUTE

This Lecture - Molecular Dynamics Basics

1. Overview of Integrators
2. Overview of Thermostats
3. Intro to Barostats
4. **MD in practice**
5. Periodic Boundary Conditions
6. Lennard-Jones and Truncation of Interactions
7. Bonded and Non-Bonded Terms
8. TUTORIAL with OpenMM and PyMOL
X. Some slides on the Liouville formalism

Periodic Boundary Conditions

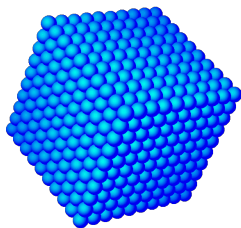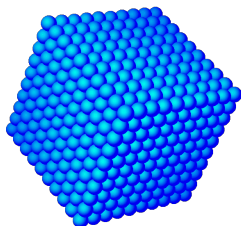If we take a small volume of fluid, it is a bad representation of the bulk fluid because interfacial effects will dominate.

Periodic Boundary Conditions

If we take a small volume of fluid, it is a bad representation of the bulk fluid because interfacial effects will dominate.

$\rightarrow$ In a 3D N-particle system with boundaries, the fraction of all molecules at the surface is proportional to $N^{-1/3}$.

Periodic Boundary Conditions

If we take a small volume of fluid, it is a bad representation of the bulk fluid because interfacial effects will dominate.

$\rightarrow$ In a 3D N-particle system with boundaries, the fraction of all molecules at the surface is proportional to $N^{-1/3}$.

$\rightarrow$ For instance, in a simple cubic crystal of 1000 atoms, $\sim 49\%$ of all atoms are at the surface!

Periodic Boundary Conditions

If we take a small volume of fluid, it is a bad representation of the bulk fluid because interfacial effects will dominate.

$\rightarrow$ In a 3D N-particle system with boundaries, the fraction of all molecules at the surface is proportional to $N^{-1/3}$.

$\rightarrow$ For instance, in a simple cubic crystal of 1000 atoms, $\sim 49\%$ of all atoms are at the surface!

$\rightarrow$ Even for 10^6 atoms this only decreases to 6%.

Periodic Boundary Conditions

If we take a small volume of fluid, it is a bad representation of the bulk fluid because interfacial effects will dominate.
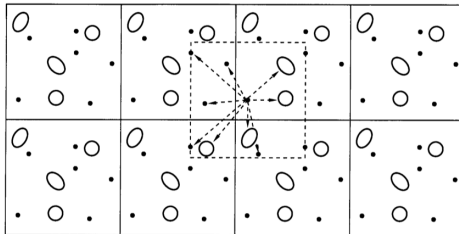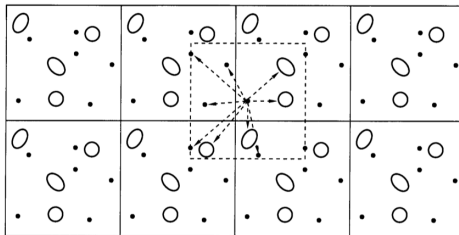

Figure 3.2: Schematic representation of periodic boundary conditions.

To mimic a macroscopic fluid (i.e. a large infinite system) we use periodic boundary conditions (PBC).

- The system is repeated periodically as a lattice with lattice constant L.

Periodic Boundary Conditions

If we take a small volume of fluid, it is a bad representation of the bulk fluid because interfacial effects will dominate.
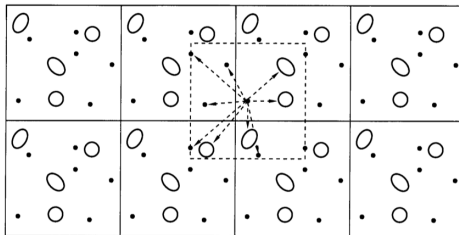

Figure 3.2: Schematic representation of periodic boundary conditions.

To mimic a macroscopic fluid (i.e. a large infinite system) we use periodic boundary conditions (PBC).

- The system is repeated periodically as a lattice with lattice constant L.
- A given particle, i, now interacts with all other particles
- The total potential energy of N particles in a box m becomes an infinite sum.

Periodic Boundary Conditions

If we take a small volume of fluid, it is a bad representation of the bulk fluid because interfacial effects will dominate.
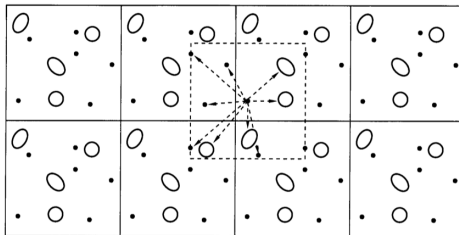

Figure 3.2: Schematic representation of periodic boundary conditions.

To mimic a macroscopic fluid (i.e. a large infinite system) we use periodic boundary conditions (PBC).

- The system is repeated periodically as a lattice with lattice constant L.
- A given particle, i, now interacts with all other particles
- The total potential energy of N particles in a box m becomes an infinite sum.

$\rightarrow$ Need to define a cutoff distance, r_c.

Periodic Boundary Conditions

If we take a small volume of fluid, it is a bad representation of the bulk fluid because interfacial effects will dominate.

Figure 3.2: Schematic representation of periodic boundary conditions.

To mimic a macroscopic fluid (i.e. a large infinite system) we use periodic boundary conditions (PBC).

- The system is repeated periodically as a lattice with lattice constant L.

    $\rightarrow$ After defining a cutoff distance $r_c \leq L/2$

- We consider only the interactions of particle i with the nearest periodic image of particle j
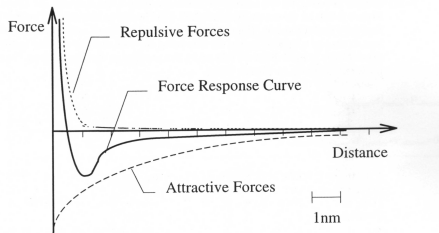
Truncation of Interactions

Truncation can be tricky, though:
Even though $|V(r)|$ decreases with r, the number of neighbors rapidly increases as a function of r. In fact it increases asymptotically as r^{d-1}, where d is the dimensionality of the system.

Truncation of Interactions

Truncation can be tricky, though:

Even though $|V(r)|$ decreases with r, the number of neighbors rapidly increases as a function of r. In fact it increases asymptotically as r^{d-1}, where d is the dimensionality of the system.

Example: The Lennard-Jones fluid

Let us compute the effect of truncating the pair potential for the simple example system of a fluid of *neutral particles* described by the Lennard-Jones pair potential:

$$V_{ij}^{LJ}(r_{ij}) = 4\epsilon \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 \right] \text{ where } r_{ij} = |r_i - r_j|$$

Truncation of Interactions

Example: The Lennard-Jones fluid

Let us compute the effect of truncating the pair potential for the simple example system of a fluid of *neutral particles* described by the Lennard-Jones potential:

$$V_{ij}^{LJ}(r_{ij}) = 4\epsilon \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^{6} \right] \text{ where } r_{ij} = |r_i - r_j|$$

The average potential energy of any given particle i is given by

$$\langle V \rangle = \frac{1}{2} 4\pi \int_0^\infty dr \, r^2 \rho(r) V_{ij}^{LJ}(r)$$

where $\rho(r)$ denotes the average number denisty at a distance r from a given particle i, and the factor $(1/2)$ corrects for double counting of intermolecular interactions. If we truncate the potential at r_c, we ignore the tail contribution

$$\langle V_{tail} \rangle = \frac{1}{2} 4\pi \int_{r_c}^\infty dr \, r^2 \rho(r) V_{ij}^{LJ}(r)$$

Truncation of Interactions

Example: The Lennard-Jones fluid - Simple truncation at r_c.
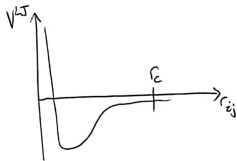We can solve this integral for $\langle V_{tail} \rangle$

$$\langle V_{tail} \rangle = \frac{1}{2} 4\pi \int_{r_c}^{\infty} dr \, r^2 \rho(r) V_{ij}^{LJ}(r)$$

$$= \frac{1}{2} 16\pi\rho\epsilon \int_{r_c}^{\infty} dr \, r^2 \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^{6} \right]$$

$$= \frac{8}{3} \pi\rho\epsilon\sigma^3 \left[\frac{1}{3} \left(\frac{\sigma}{r_c} \right)^{9} - \left(\frac{\sigma}{r_c} \right)^{3} \right].$$

FLATIRON
I N S T I T U T E

Truncation of Interactions

Example: The Lennard-Jones fluid - Simple truncation at r_c.
We can solve this integral for $\langle V_{tail} \rangle$

$$\langle V_{tail} \rangle = \frac{1}{2} 4\pi \int_{r_c}^{\infty} dr \, r^2 \rho(r) V_{ij}^{LJ}(r)$$

$$= \frac{1}{2} 16\pi\rho\epsilon \int_{r_c}^{\infty} dr \, r^2 \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^{6} \right]$$

$$= \frac{8}{3} \pi\rho\epsilon\sigma^3 \left[\frac{1}{3} \left(\frac{\sigma}{r_c} \right)^{9} - \left(\frac{\sigma}{r_c} \right)^{3} \right].$$

This means that for a cutoff distance of $r_c = 2.5\sigma$ the potential decays to a value of $1/60$th of the well depth, which seems small, but is in fact non-negligible.

For instance, at a density $\rho\sigma^3 = 1$, we find $\langle V_{tail} \rangle = -0.535\epsilon$, this ends up being 10% of the total potential energy per atom at a typical liquid density.
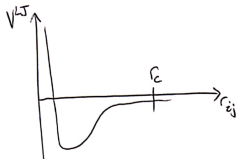
FLATIRON

Truncation of Interactions - Other options.
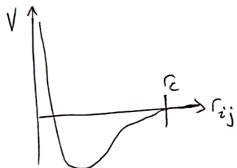
1. ~~Simple truncation~~

Truncation of Interactions - Other options.
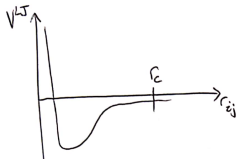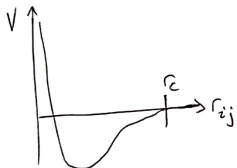
❶ ~~Simple truncation~~

❷ Truncation and shift

$$V_{ij}(r_{ij}) = V_{ij}^{LJ}(r_{ij}) - V_{ij}^{LJ}(r_c) \text{ for } r_{ij} \leq r_c$$

$\rightarrow$ Force discontinuous.

Truncation of Interactions - Other options.

❸ Smooth switching of the potential

❶ ~~Simple truncation~~

$$V_{ij}(r_{ij}) = \begin{cases} V_{ij}^{LJ}(r_{ij}) & \text{for } r_{ij} \leq r_s \\ S_V(r_{ij})V_{ij}^{LJ}(r_{ij}) & \text{for } r_s < r_{ij} \leq r_c \\ 0 & \text{otherwise} \end{cases}$$

with S_V as the potential switching function.

❷ Truncation and shift

$V_{ij}(r_{ij}) = V_{ij}^{LJ}(r_{ij}) - V_{ij}^{LJ}(r_c)$ for $r_{ij} \leq r_c$

$\rightarrow$ Force discontinuous.

Truncation of Interactions - Other options.

① ~~Simple truncation~~

② Truncation and shift

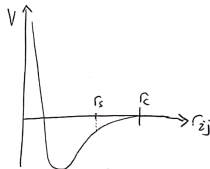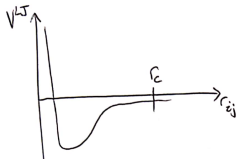$$V_{ij}(r_{ij}) = V_{ij}^{LJ}(r_{ij}) - V_{ij}^{LJ}(r_c) \text{ for } r_{ij} \leq r_c$$

→ Force discontinuous.

③ Smooth switching of the potential

$$V_{ij}(r_{ij}) = \begin{cases} V_{ij}^{LJ}(r_{ij}) & \text{for } r_{ij} \leq r_s \\ S_V(r_{ij})V_{ij}^{LJ}(r_{ij}) & \text{for } r_s < r_{ij} \leq r_c \\ 0 & \text{otherwise} \end{cases}$$

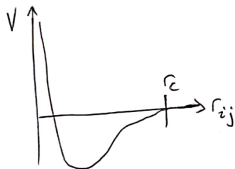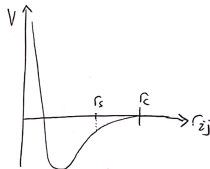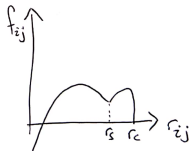with S_V as the potential switching function.

→ Removes the discontinuity in the force, but now there is an unphysical bulge between r_s and r_c.

Truncation of Interactions - Force switching.

4. Force switching!

$$V_s(r) = \int_r^{\infty} f_s(x)\,dx$$

The switched force f_s can generally be written as:

$$f_s(r) = \begin{cases} f_\alpha(r) & \text{for } r < r_s \\ f_\alpha(r) + S_f(r) & \text{for } r_s < r \leq r_c \\ 0 & \text{otherwise} \end{cases}$$

Where f_α is the force for a pure Lennard-Jones interaction, and the switching function $S_f(r)$ is smooth at the boundaries, such that
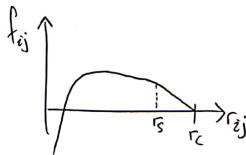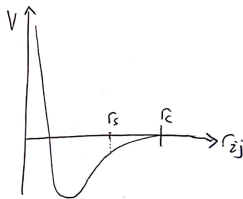
$$S_f(r_s) = 0 \text{ and } S_f'(r_s) = 0$$

$$S_f(r_c) = -f_\alpha(r_c) \text{ and } S_f'(r_c) = -f_\alpha'(r_c)$$

A 3rd degree polynomial of the form

$$S_F(r) = A(r - r_1)^2 + B(r - r_1)^3$$

fulfills these requirements.

Truncation of Interactions - In summary.

What options do we have for truncating long-distance interactions such that they don't become infinitely compounded by our periodic boundary conditions?

1. Simple truncation
   - Potentially discontinuous
   - Singularity in force (or at least discontinuity)
   - Severe artifacts are possible

2. Truncation and shift
   - Better but force still discontinuous

3. Smooth switching of the potential
   - Switching the function smoothly and gradually alters the potential in the region $r_s < r_{ij} \leq r_c$
   - Removes the discontinuity in the force but the force has unphysical bulge between r_s and r_c
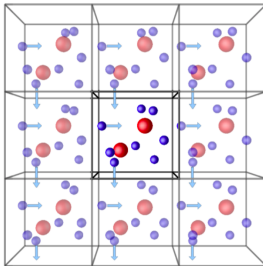   - Dangerous!

4. Force switching (The best choice)
   - Force is smoothly attenuated between r_s and r_c
   - The potential is obtained by integrating from large to small r_{ij}
   - Beware: This is close but not exactly the LJ potential.

$\Rightarrow$ If you observe novel effects in your simulation, always check for cutoff effects!

The Coulomb interaction cannot be truncated.

- Lennard-Jones fluids consist of *neutral* spheres, for which we only need to take Van der Waals interactions into account.
- If there are any *charges*, as is very often the case in biological systems, we need to consider Coulomb interactions as well.
- For Coulomb interactions, we cannot use a cutoff, and must consider the contributions from all periodic images.

The Coulomb interaction cannot be truncated.

- Lennard-Jones fluids consist of *neutral* spheres, for which we only need to take Van der Waals interactions into account.
- If there are any *charges*, as is very often the case in biological systems, we need to consider Coulomb interactions as well.
- For Coulomb interactions, we cannot use a cutoff, and must consider the contributions from all periodic images.
- Usually this is done using the smooth Particle-Mesh-Ewald (SPME) method, in which charges are assigned to a grid, which is then Fourier transformed to speed up the calculation. This 'reciprocal sum' is never cut-off, but a distance cut-off is still applied for the closer range 'direct sum' interactions.

---

[11]Rocklin, Mobley, Dill, & Huenenberger. 'Calculating the binding free energies of charged species based on explicit-solvent simulations employing lattice-sum methods: An accurate correction scheme for electrostatic finite-size effects.' *J. Chem. Phys.*, 139:184103, 2013.

The Coulomb interaction cannot be truncated.

- Lennard-Jones fluids consist of *neutral* spheres, for which we only need to take Van der Waals interactions into account.
- If there are any *charges*, as is very often the case in biological systems, we need to consider Coulomb interactions as well.
- For Coulomb interactions, we cannot use a cutoff, and must consider the contributions from all periodic images.
- Usually this is done using the smooth Particle-Mesh-Ewald (SPME) method, in which charges are assigned to a grid, which is then Fourier transformed to speed up the calculation. This 'reciprocal sum' is never cut-off, but a distance cut-off is still applied for the closer range 'direct sum' interactions.

Note: Finite-size effects can still cause problems: A relatively recent correction scheme was introduced when free energy of binding of charged ligands to a target protein were found to be box-size dependent[11].

---

[11] Rocklin, Mobley, Dill, & Huenenberger. 'Calculating the binding free energies of charged species based on explicit-solvent simulations employing lattice-sum methods: An accurate correction scheme for electrostatic finite-size effects.' *J. Chem. Phys.*, 139:184103, 2013.

FLATIRON
INSTITUTE

How to choose a potential energy function?

Which forces are present in biomolecular system, and how can we describe these forces?

- So far: $\rightarrow$ Assumed that we know the forces or the interaction potential.
- Interaction potential: $\rightarrow$ Interaction within biomolecule and with the surrounding water.
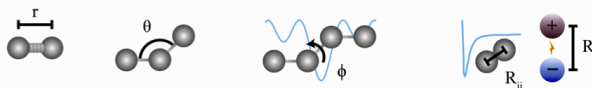- Interaction potential $=$ force field
- Important: Accuracy of our simulation

How to choose a potential energy function?

Which forces are present in biomolecular system, and how can we describe these forces?

- So far: $\rightarrow$ Assumed that we know the forces or the interaction potential.
- Interaction potential: $\rightarrow$ Interaction within biomolecule and with the surrounding water.
- Interaction potential $=$ force field
- Important: Accuracy of our simulation

How do we derive the forces?

A force field is composed of several components and is defined by the analytical form of each of these components and the parameters characterizing them:

$$E_{total} = \sum_{bonds} K_r(\mathbf{r} - \mathbf{r}_{eq})^2 + \sum_{angles} K_\theta(\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]$$

Non-bonded interactions

There are two major types of non-bonded interactions:
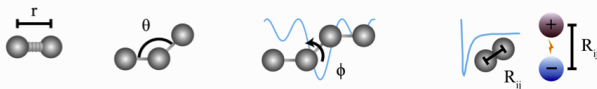
1. Van der Waals interaction / Lennard Jones pair potential
2. Coulomb interaction

$$E_{total} = \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]$$
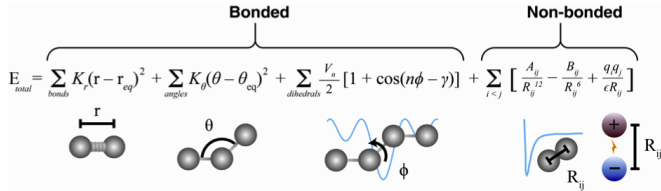
Bonded interactions

Bonded interactions are interactions between covalently bonded atoms, and occur between a fixed number of atoms (≤ 4 atoms):

1. Bond stretching (2 body)
2. Bond angle (3 body)
3. Dihedral angle (4 body)

$$E_{total} = \underbrace{\sum_{bonds} K_r(\mathbf{r} - \mathbf{r}_{eq})^2 + \sum_{angles} K_\theta(\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)]}_{\text{Bonded}} + \underbrace{\sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}} \right]}_{\text{Non-bonded}}$$

Slides to clarify course 1: The Liouville formulation

We have seen that Newton's equations of motion are time reversible. They also conserve the magnitude of the phase space volume element. A *good integrator* should have the same properties.

In the 90s Tuckerman et al[12] have shown how to systematically derive time-reversible, area-preserving MD algorithms from the Liouville formulation of classical mechanics.

Let us consider an arbitrary function f that depends on all the coordinates and momenta of the N particles in our system: $f(\mathsf{p}^N(t), \mathsf{r}^N(t))$. The time derivate of f (if f does not depend explicitly on t) is given as:

$$\dot{f} = \dot{\mathsf{r}} \frac{\partial f}{\partial \mathsf{r}} + \dot{\mathsf{p}} \frac{\partial f}{\partial \mathsf{p}} \equiv iLf$$

The last part of this equation defines the *Liouville operator*:

$$iL = \dot{\mathsf{r}} \frac{\partial}{\partial \mathsf{r}} + \dot{\mathsf{p}} \frac{\partial}{\partial \mathsf{p}}$$

---

[12]Tuckerman, Berne, & Martyna. 'Reversible multiple time scale molecular dynamics.' *J. Chem. Phys.*, 97:1990-2001, 1992.

![FLATIRON INSTITUTE]

The Liouville formulation

Let us consider an arbitrary function f that depends on all the coordinates and momenta of the N particles in our system: $f(p^N(t), r^N(t))$. The time derivative of f (if f does not depend explicitly on t) is given as:

$$\dot{f} = \dot{r}\frac{\partial f}{\partial r} + \dot{p}\frac{\partial f}{\partial p} \equiv iLf$$

The last part of this equation defines the *Liouville operator*:

$$iL = \dot{r}\frac{\partial}{\partial r} + \dot{p}\frac{\partial}{\partial p}$$

Integrating $\dot{f}$ the formal solution reads:

$$f(p^N(t), r^N(t)) = e^{iLt}f(p^N(0), r^N(0))$$

Or with timestep Δt in our numerical scheme:

$$f(p^N(t + \Delta t), r^N(t + \Delta t)) = e^{iL\Delta t}f(p^N(t), r^N(t))$$

The Liouville formulation

So now we have:

$$f(\mathsf{p}^N(t + \Delta t), \mathsf{r}^N(t + \Delta t)) = e^{iL\Delta t} f(\mathsf{p}^N(t), \mathsf{r}^N(t))$$

Unfortunately, evaluating $e^{iL\Delta t}$ is equivalent to the exact integration of the classical equations of motion. Fortunately, there are some cases for which we can evaluate terms with the Liouville operator exactly. For example:

$$iL_r \equiv \dot{\mathsf{r}} \frac{\partial}{\partial \mathsf{r}} \quad \text{and} \quad iL_p \equiv \dot{\mathsf{p}} \frac{\partial}{\partial \mathsf{p}}$$

where $iL = iL_r + iL_p$, such that we can now define:

$$f(\mathsf{p}^N(t + \Delta t), \mathsf{r}^N(t + \Delta t)) = e^{i(L_r + L_p)\Delta t} f(\mathsf{p}^N(t), \mathsf{r}^N(t))$$

But we have another problem: iL_r and iL_p are noncommuting operators:

$$e^{i(L_r + L_p)\Delta t} \neq e^{iL_r \Delta t} e^{iL_p \Delta t}$$

The Liouville formulation

So now we have:
$$f(p^N(t + \Delta t), r^N(t + \Delta t)) = e^{i(L_r + L_p)\Delta t} f(p^N(t), r^N(t))$$

But with the problem: iL_r and iL_p are noncommuting operators:
$$e^{i(L_r + L_p)\Delta t} \neq e^{iL_r \Delta t} e^{iL_p \Delta t}$$

$\Rightarrow$ We can use the following <u>Trotter identity</u>:
$$e^{(A+B)} = \lim_{P \to \infty} \left(e^{A/2P} e^{B/P} e^{A/2P} \right)^P,$$

which for large, but finite P, can be restated as
$$e^{(A+B)} = \left(e^{A/2P} e^{B/P} e^{A/2P} \right)^P e^{\mathcal{O}(1/P^2)}.$$

Giving us
$$e^{i(L_r + L_p)\Delta t} \approx e^{iL_p \frac{\Delta t}{2}} e^{iL_r \Delta t} e^{iL_p \frac{\Delta t}{2}}$$

FLATIRON
INSTITUTE

The Liouville formulation

So now we have:

$$f(p^N(t + \Delta t), r^N(t + \Delta t)) = e^{iL_p \frac{\Delta t}{2}} e^{iL_r \Delta t} e^{iL_p \frac{\Delta t}{2}} f(p^N(t), r^N(t))$$

First, we'll apply $e^{iL_p \frac{\Delta t}{2}}$ to f and obtain:

$$e^{iL_p \frac{\Delta t}{2}} f(p^N(0), r^N(0)) = f\left\{ \left[p(0) + \frac{\Delta t}{2}\dot{p}(0) \right]^N, r^N(0) \right\}$$

Then, we can apply $e^{iL_r \Delta t}$ to this result:

$$e^{iL_r \Delta t} f\left\{ \left[p(0) + \frac{\Delta t}{2}\dot{p}(0) \right]^N, r^N(0) \right\} = f\left\{ \left[p(0) + \frac{\Delta t}{2}\dot{p}(0) \right]^N, [r(0) + \Delta t \dot{r}(\frac{\Delta t}{2})]^N \right\}$$

And finally we'll apply $e^{iL_p \frac{\Delta t}{2}}$ once more to obtain a final expression:

$$f\left\{ \left[p(0) + \frac{\Delta t}{2}\dot{p}(0) + \frac{\Delta t}{2}\dot{p}(\Delta t) \right]^N, [r(0) + \Delta t \dot{r}(\frac{\Delta t}{2})]^N \right\}$$

Note that the shift in r is a function of p only (because $\dot{r} = p/m$), while the shift is p is a function of r only (because $\dot{p} = F(r^N)$). The Jacobian of the transformation from $\{p^N(0), r^N(0)\}$ to $\{p^N(\Delta t), r^N(\Delta t)\}$ is simply the product of the Jacobians of the three elementary transformations. But, as each of these Jacobians is equal to 1, the overall Jacobian is also equal to 1.

In other words, the algorithm is <u>area preserving</u>.

FLATIRON
INSTITUTE

The Liouville formulation

If we now consider the overall effect of this sequence of operations on the positions and momenta, we find the following:

$$p(0) \rightarrow p(0) + \frac{\Delta t}{2}(F(0) + F(\Delta t))$$
$$r(0) \rightarrow r(0) + \Delta t \dot{r}(\frac{\Delta t}{2}) = r(0) + \Delta t \dot{r}(0) + \frac{\Delta t^2}{2m}F(0)$$

Thus the Liouville formalism allows us to derive the Velocity Verlet algorithm as a special case of the Trotter expansion of the time-evolution operator.

$\rightarrow$ The past and future coordinates enter symmetrically into the algorithm.
  $\Rightarrow$ Velocity Verlet is time reversible.
$\rightarrow$ Conservation of phase space density.

$\rightarrow$ For $\Delta t \rightarrow 0$ a proper Liouville operator is obtained and thus the system obeys Hamiltonian dynamics.
$\rightarrow$ For finite Δt, a shadow Hamiltonian exists that differs from the exact one, by $\mathcal{O}(\Delta t^3)$ and which is conserved.
  $\Rightarrow$ No energy drift.

The Liouville formulation
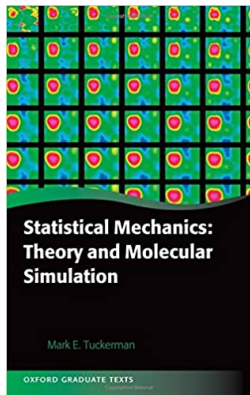
Statistical Mechanics: Theory and Molecular Simulation
by Mark E. Tuckerman