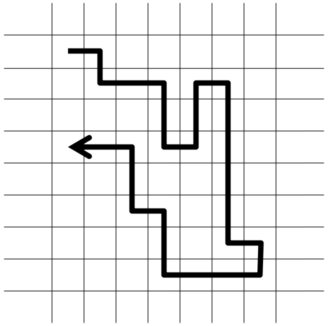
Monte Carlo and MD simulations

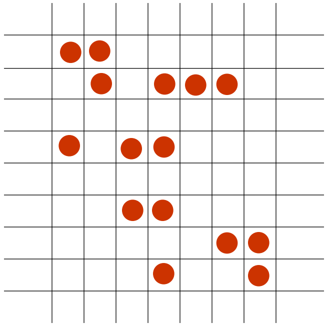
What we observe in any system ?

- averages of observables (pressure, energy, density)

Given enough time system will visit all states



time



random
hopping

My observable A

$$A_{obs} = \frac{1}{b-a}\int_a^b A_t dt$$

$$A_{obs} = \frac{1}{N_{obs}}\sum_{i=1}^{N_{obs}} A_i$$

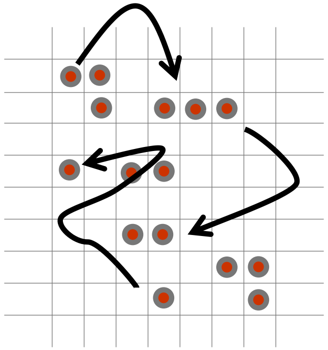
Time and space averages

If we believe $A_{obs} = \frac{1}{N_{obs}} \sum_{i=1}^{N_{obs}} A_i$

then

$$A_{obs} = \sum_{j}^{states} p_j A_j$$

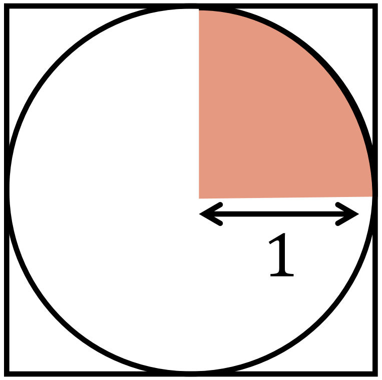
$$\equiv \langle A \rangle$$



- $\langle A \rangle$ is ensemble average and usually $\bar{A}$ is time average
- if sample with correct probability, we can find A_{obs}
- order of visiting states does not matter

Monte Carlo

How to calculate π with random numbers



$$\frac{points_{red}}{points_{square}} = \frac{{}^{1}/_{4}\,\pi r^2}{\text{area in square}}$$

$$\pi = 4\,\frac{points_{red}}{points_{square}}$$

```
while ( not converged)
    pick random $x, y$
    $n_{square}$++
    if (($x^2$+$y^2$) < 1)
        $n_{red}$++
print 4 $\frac{n_{red}}{n_{square}}$
```

diagram loosely from Allen, MP and Tildesley, DJ

Generating distributions / Monte Carlo

Generating points in a circle ? (generating function)

$$p_{in\_circle} = \begin{cases} 1 & x^2 + y^2 \leq 1 \\ 0 & x^2 + y^2 > 1 \end{cases}$$

- we could work out the area of a circle (integrate) by picking random numbers

What does Monte Carlo simulation mean ?

- generating points according to some distribution to find an average or integral
- what is our distribution in physical systems ?
  - Boltzmann distribution

Monte Carlo and Boltzmann distributions

Boltzmann probability distribution

$p_i = \frac{e^{\frac{-E_i}{kT}}}{\sum_j e^{\frac{-E_j}{kT}}}$ often written as $p_i = \frac{e^{\frac{-E_i}{kT}}}{Z}$

- if we could generate this distribution, we could reproduce most properties of a system
- leads to a scheme (not possible)

correct, but not practical scheme

```
while (not happy)
    generate configuration $\mathbf{r}_i$ (conformation of protein, …)
    calculate $p_i$                (number between 0 and 1)
    generate random number x
    if ($x < p_i$)
        accept $\mathbf{r}_i$
    else
        reject $\mathbf{r}_i$
```

$$p_i = \frac{e^{\frac{-E_i}{kT}}}{\sum_j e^{\frac{-E_j}{kT}}}$$

- result ? a set of $\mathbf{r}_i$ with Boltzmann distribution
- problem ? we do not know $\sum_j e^{\frac{-E_j}{kT}}$

a better scheme

We cannot generate points from $p_i = \frac{e^{\frac{-E_i}{kT}}}{\sum_j e^{\frac{-E_j}{kT}}}$

What if we have two configurations ?

$$\frac{p_i}{p_j} = \frac{e^{\frac{-E_i}{kT}}}{Z} \quad \frac{Z}{e^{\frac{-E_j}{kT}}}$$

$$= \frac{e^{E_j - E_i}}{kT}$$

$$= e^{\frac{-\Delta E}{kT}}$$

a better scheme

$$\frac{p_i}{p_j} = e^{\frac{-\Delta E}{kT}}$$

If we have one configuration to start

- we can work out the relative probability of a second

- convenient convention
  - going from old→new $\Delta E < 0$
    - $E_{new} - E_{old} < 0$ energy is better / more negative

Metropolis Monte Carlo

- generating a distribution $\frac{p_i}{p_j} = e^{\frac{-\Delta E}{kT}}$
- if $\Delta E < 0$, new is likely (more than 1)
- if $\Delta E > 0$, old is p_{new} is possible

```
• generate starting configuration $\mathbf{r}_o$
  while (not happy)
      generate $\mathbf{r}_{new}$
      calculate $E_{new}$ and $\Delta E$
      if $\Delta E < 0$
          set $\mathbf{r}_o$ to $\mathbf{r}_{new}$
      else
          x = rand [0:1]
          if$\left( x \le e^{-\Delta E / kT} \right)$
              set $\mathbf{r}_o$ to $\mathbf{r}_{new}$
```

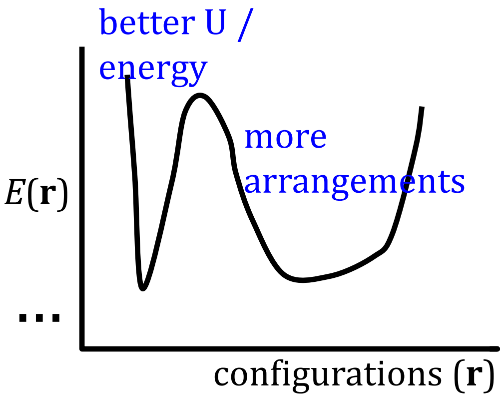
- what if ΔE slightly > 0 ?
    - 0.0000000001
- what if $\Delta E = 10^6$?
- small uphill moves are OK
- bigger moves are less likely

Properties of Monte Carlo

The set of $\mathbf{r}_o$ is a valid distribution (ensemble)

- for some property A

$$A_{obs} = \langle A \rangle = \frac{1}{N_{visited}} \sum_{i}^{N_{visited}} A_i$$



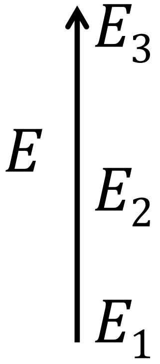
- A could be density, structural property, E, …
- only works for one temperature T

- look at picture.. could I calculate entropy / free energy ?
  - for simple systems

Equilibrium

MC results (observables / averages)

- only for system at equilibrium
- Simulations generate system at equilibrium



What happens for a system out of equilibrium ?

- Toy system with 3 states
- for some *T*, at equilibrium
- p_1 = ⅝ p_2 = ¼ p_3 = ⅛
- if I have 80 copies of the system, most are in state$_1$

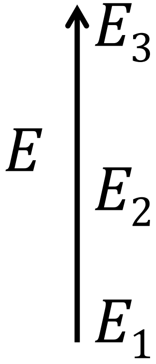
Reaching equilibrium

System wants $p_1 = 5/8$ $p_2 = 1/4$ $p_3 = 1/8$

50 : 20 : 10

- start it with 5 : 70 : 5

- all moves 2→1 are accepted (large flux)
- the flux from 1 → 2
  - 1→ 2 moves are not always accepted
  - there are less particles in state$_1$



- moving to equilibrium depends on
  - population
  - probability

Detailed balance

For any two states (state$_i$ and state$_j$)

Flow $i \rightarrow j$ must equal $j \rightarrow i$

- otherwise ?

Flow $i \rightarrow j$ depends on

- population N_i
- probability $\pi(i \rightarrow j)$

Detailed balance

$$N_i \pi(i \rightarrow j) = N_j \pi(j \rightarrow i)$$

- detailed balance must apply for any pair i, j

all textbooks use π for probability here

Ergodic

Assumptions

- I can do integrals because
  - I will visit every state
  - I can calculate p_i for all states
- I will visit every state

alternatively

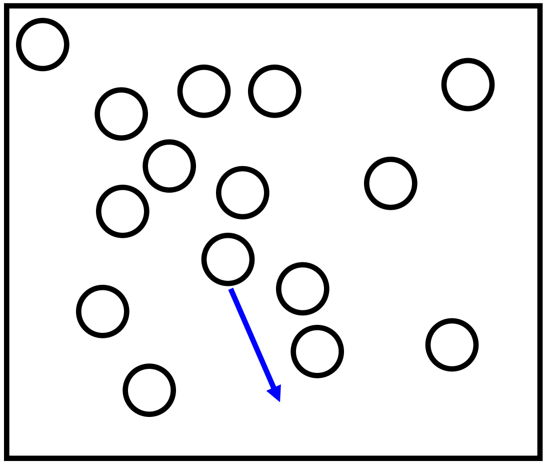
For any i, j

- $\pi(i \rightarrow j) > 0$
- may require a finite number of steps: $i \rightarrow k \rightarrow m \rightarrow j$
- must be satisfied

Moves

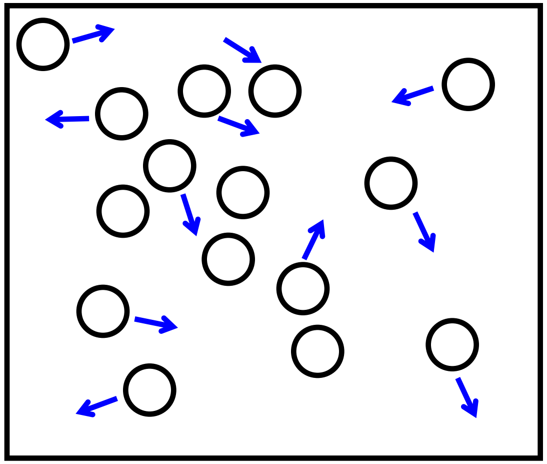
version 1

- decide on r_{max}
- pick a particle at random
- pick random $\Delta x, \Delta y, \Delta z$
    - $0 < \Delta a < r_{max}$
- apply move
- accept / reject move



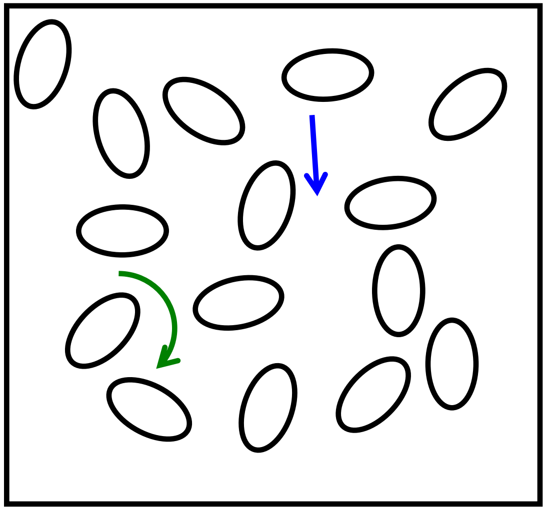
version 2

- decide on smaller r_{max}
- foreach particle
    - pick random $\Delta x, \Delta y, \Delta z$
        - $0 < \Delta a < r_{max}$
- apply move
- accept / reject



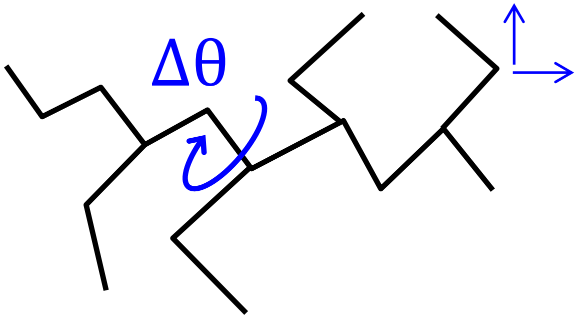
Moves

- both kinds of move OK
- note
  - "accept / reject"
- more generally,
  - how big is r_{max} ?
  - big
    - system moves faster
    - more moves rejected
- what if my particles are not spheres ?
  - rotations also necessary



- time has no meaning

Bonded systems



Protein (lipid, polymer, ..)

Random $\Delta\, x$?

- nearly all will stretch a bond
    - high energy : rejected move
- only feasible method
    - random rotations $\Delta\theta$

In general

- most kinds of simple moves OK
- must maintain detailed balance, ergodicity
- question of efficiency
    - high rejection rate means lots of wasted calculations

More moves – *N* particles

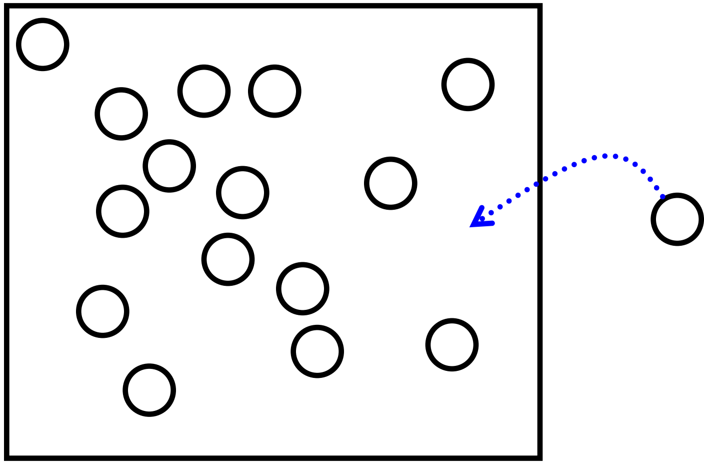
$\frac{p_{new}}{p_{old}} = e^{-\Delta E/_{kT}}$

I have defined temperature

- and $N_{particles}$ and V
- called NVT simulation

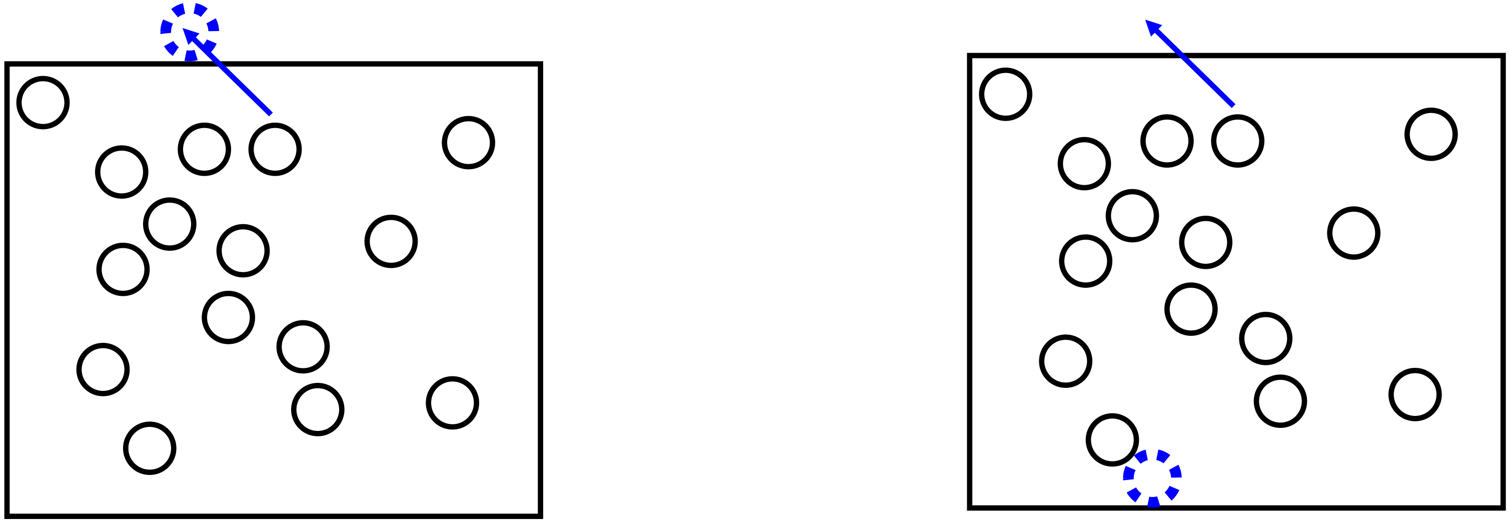
Vould I have varied something else ?

- what if I tried to put particles in / take out ?
    - sometimes energy ↑sometimes↓
- system will fluctuate around $\langle N \rangle$
- this would not be NVT

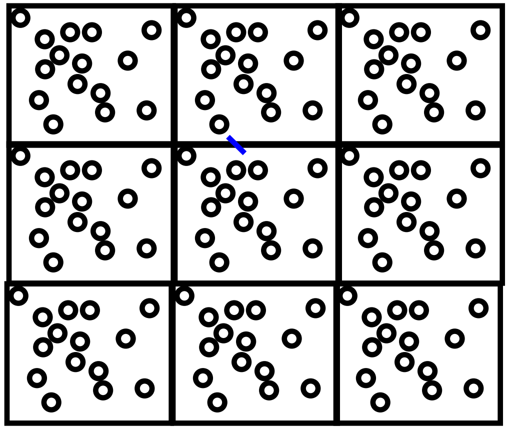


Periodic Boundary Conditions

Technical point relevant to gases, proteins in water…



Behaves like an infinite system

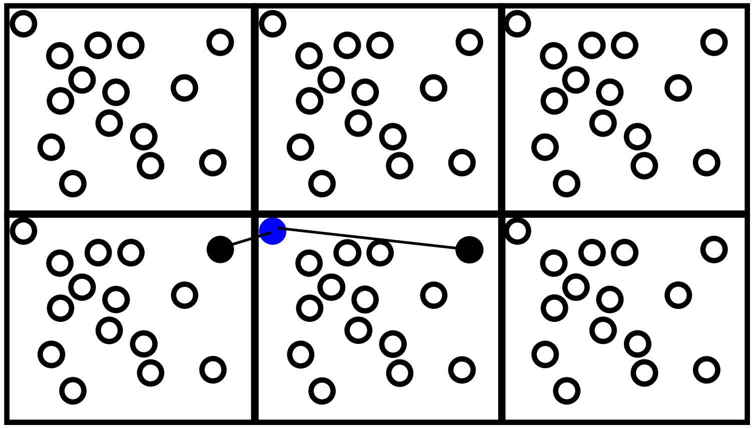


Infinite interactions ?

Neighbours of blue particle

- only use the nearer
- not really an infinite system

- volume defined by box



Problems with Monte Carlo

```
while (not happy)
    propose move
    accept / reject move
```

Small steps ?

- system moves slowly: long time to visit all states

Big steps ?

- calculate energy
- reject move
  - no progress, wastes time

Dense Systems and Monte Carlo

Random moves ?

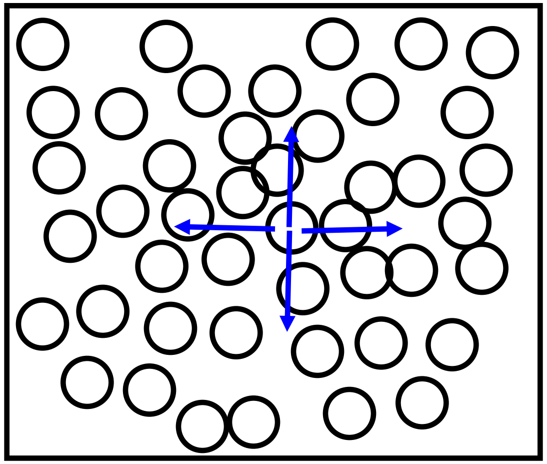
- most moves rejected

Dense systems ?

- liquids
- proteins, polymers, …

Solutions

- cleverer MC moves (later)
- MD



Why do molecular dynamics simulations ?

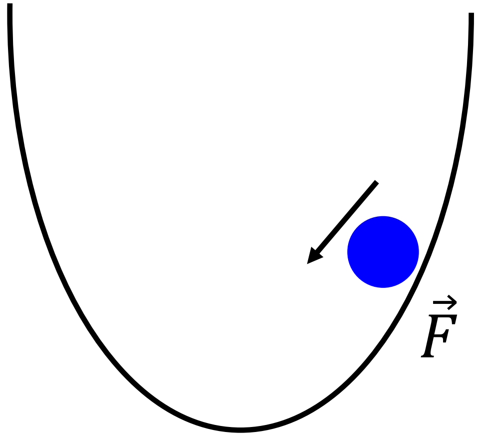
Real world

- box of gas, molecule in space, protein molecule in water
- atoms hit each other,
  - share energy, box expands/contracts, ..
  - soon reaches equilibrium
  - visits low energies (often), high energies (less often)
  - visits entropically favoured regions
- we stick in a thermometer
- measure density, …

What have the atoms done ?

- feel forces and move
- an MD simulation just copies this

What do we expect ? Molecular Dynamics



$$\vec{F} = -\frac{\partial U}{\partial \vec{r}}$$

one particle in a well

Unlike MC, particles have kinetic energy E_{kin}

Kinetic and potential energy

Our system is isolated (no work done)

E_{tot} never changes

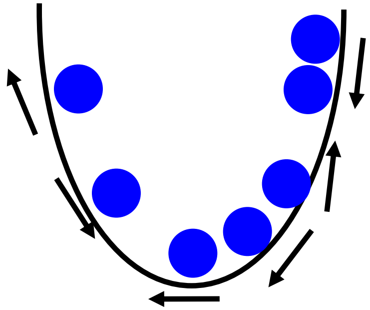
- conserves energy (no work done on system)

$$E_{tot} = E_{pot} + E_{kin}$$

E_{kin}	small	E_{kin}	big
E_{pot}	big	E_{pot}	small

For one particle $E_{tot} = E_{pot} + E_{kin}$ = constant

Lots of particles



Particles hitting each other

- exchanging energy

Total system

- conserves energy

One particle ?

- maybe at bottom but moving slow (E_{kin} + E_{pot} small)
- per particle energy no longer conserved (may gain or lose)

Many particles

  - distribution of velocities
  - distribution of potential energies

Boltzmann distribution in real world

One version of real world (N, V, T)

- constant number of particles, volume, temperature
- today $E = E_{kin} + E\_pot$
- Z is partition function
- earlier $Z = \sum_i e^{\frac{-\Delta E_i}{kT}}$

But now we have kinetic energy $E_{kin}(\boldsymbol{p})$

- where $\boldsymbol{p} = m\dot{\boldsymbol{x}}$
    - potential energy $E_{pot}(\mathbf{r})$
- if we write in continuous form …

Partition function for MD

Usually write $H(\mathbf{p}, \mathbf{r}) = E_{kin}(\mathbf{p}) + E_{pot}(\mathbf{r})$

- "Hamiltonian"

All the states are defined by all possible momenta and coordinates

- sum over these: $Z(N, V, T) \propto \int d\mathbf{p} \int d\mathbf{r}\, e^{\frac{-H(p,r)}{kT}}$

often see $\mathcal{H}(\mathbf{p}, \mathbf{r})$ or $\mathcal{H}(\mathbf{\Gamma})$

MD Method

For any particle we can calculate forces

Newtons law

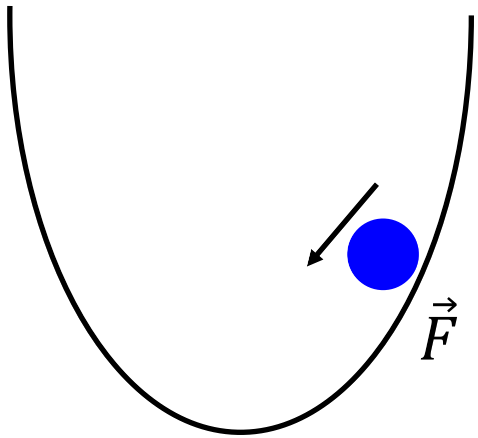
$F = ma$ often better written $\ddot{\vec{x}} = \vec{F} m^{-1}$

If we know acceleration

- we can get velocity

from velocity

- can get coordinates



$$\vec{F} = -\frac{\partial U}{\partial \vec{r}}$$

```
while (nstep < max_step)
     calculate forces
     integrate to get new coordinates
     nstep ++
```

averaging,
sampling,
…

Starting system

Initial coordinates

- protein model
- protein from protein data bank (PDB)
- protein + proposed ligand
- box of liquid

Do initial coordinates matter ?

- in principle: no – infinitely long simulation visits all configurations, reaches equilibrium
- in practice: yes
  - bad examples
    - no simulation is long enough to predict protein conformation
  - take water configuration and run at ice temperature

Initial velocities

First consider temperature – reflects kinetic energy

$$\left\langle \frac{1}{2} m v_\alpha^2 \right\rangle = \frac{1}{2} kT$$

where v_α^2 could be v_x, v_y, v_z

leads to definition

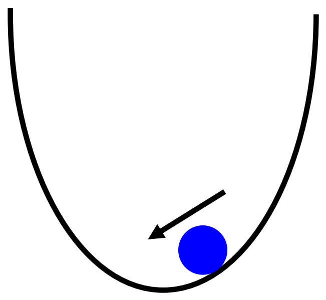
$$T(t) = \sum_{i=1}^{N} \frac{m_i v_i^2(t)}{k N_f}$$

- where N_f is number degrees of freedom $\approx 3N$
- we could use this to get initial velocities $\langle v_\alpha^2 \rangle = \frac{kT}{m}$

Initial velocities

Would one $<v^2>$ be OK ?

- not very good
    - E_{kin} correlated with E_{pot}



Either

- use more sophisticated distribution
- do not worry
    - system will go to equilibrium
        - velocities will reach sensible values

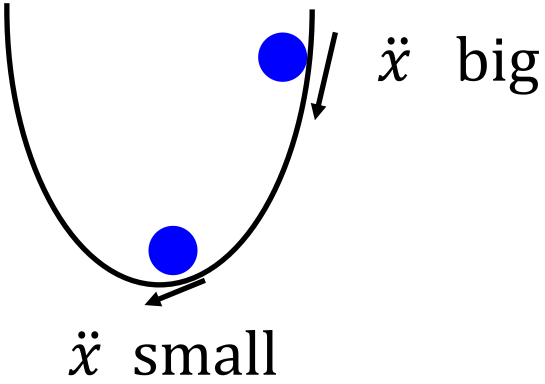
Getting new velocities / coordinates

constant acceleration

$$x_t = x_0 + vt + \frac{1}{2}at^2$$

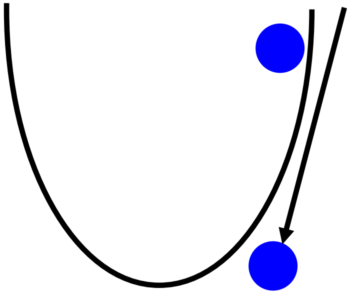
or

$$x_t = x_0 + \dot{x} + \frac{1}{2}\ddot{x}t^2$$

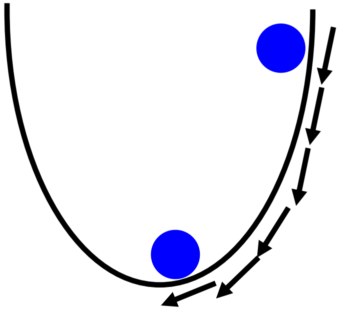


OK for constant acceleration

- try to use formula to predict future time



big Δt / step
big error



small Δt / step
small error
slow

Fundamental problem with integration

- We want to use big Δt (speed)
- We must use small Δt (accuracy)

All Δt will give us some error

- numerical integration is never perfect

How small is Δt ?

- depends on fastest frequency / steepest walls in energy
  - usually bonds
- for proteins at room temperature
  - $\Delta t \approx 1$ fs (femtosecond 10^{-15}s)
- high temperature Δt should be smaller

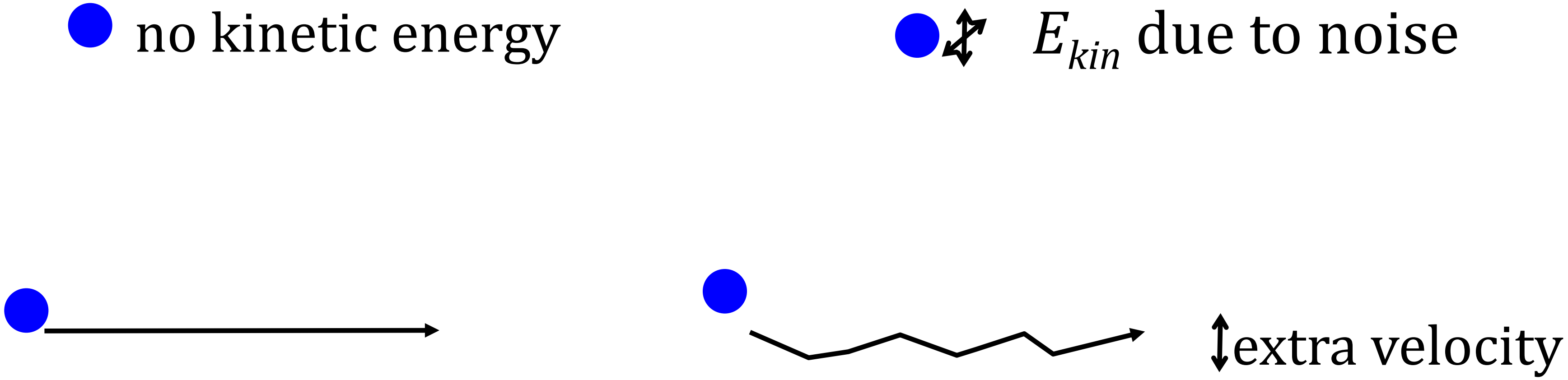
Practical integrators

- remove velocity – slightly more sophisticated

Noise and heating

General rule

- noise heats the system
- formally difficult to prove
- $E_{kin} = \frac{1}{2} mv^2$



no kinetic energy

E_{kin} due to noise

↕extra velocity

Noise-free Simulation

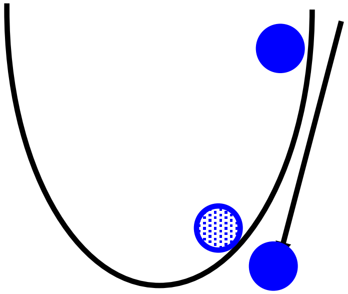
Energy conservation : Absolute rule $E_{pot} = f(\mathbf{r})$

- no time component
- invariant under translation, rotation

When violated ?

- $(\mathbf{r})$ does not change, but E_{pot} changes: E_{tot} changes

Noise Sources

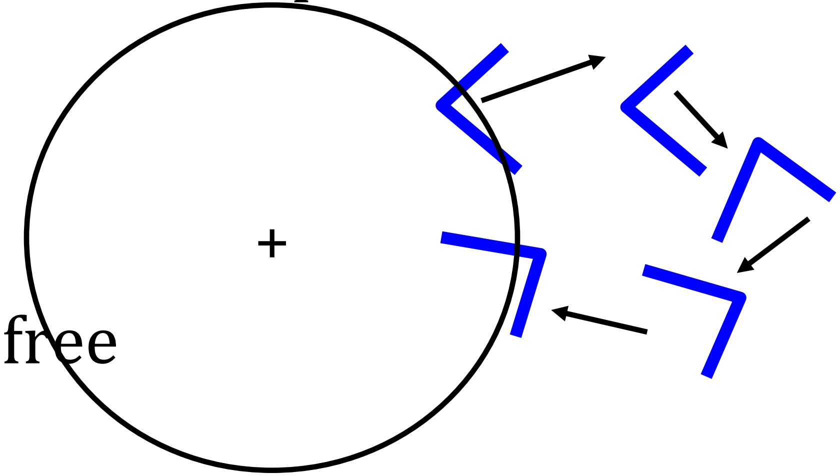


Integrator

- coordinates do not match velocity
  E_{kin} wrong: $\left(E_{kin} + E_{pot}\right) \neq$ constant
- energy not conserved

Numerical noise

- $E_{pot} = f(\mathbf{r})$
- initial coordinates ($\mathbf{r}$) quoted to 3 decimal places
- really less accurate



Cutoffs

- within cutoff rotation restricted
- outside cutoff rotation suddenly free

Result

- heating

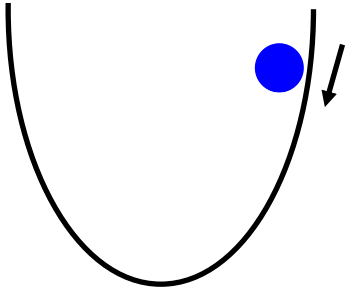
Equilibrium

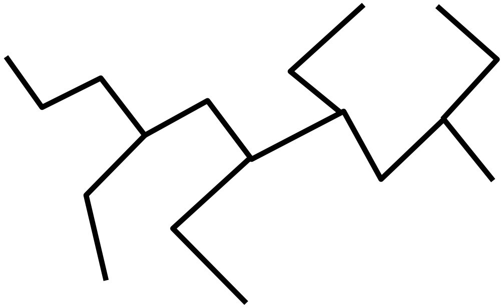
Remember MC story

- system not at equilibrium ? eventually equilibrates

MD

- start in high energy E_{pot}
- E_{pot} converted to E_{kin}





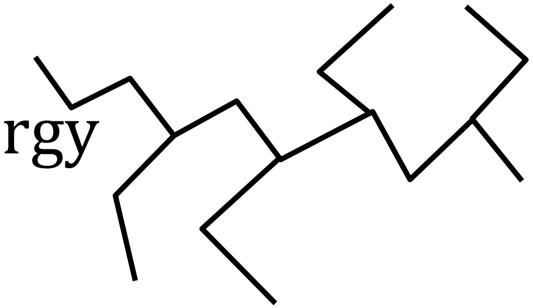
Some high energy conformation

- relaxes
- E_{pot} converted to E_{kin}

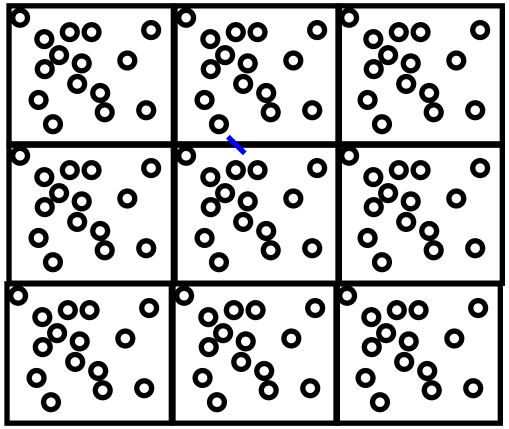
MD system will not

- really find low energy
- known temperature

MD in a closed system



- An isolated molecule should not lose energy
- A repeated box will not lose energy
- Formally system is
  - NVE (constant $N_{particles}$, volume, energy)



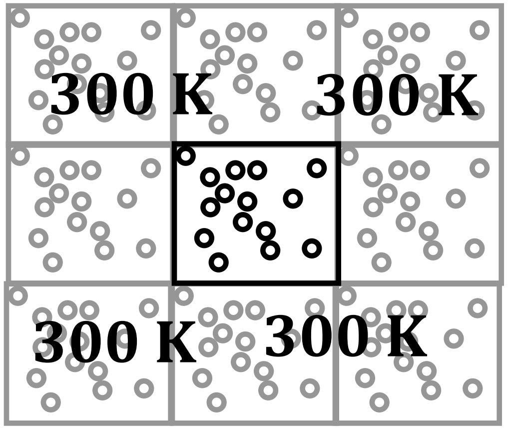
Problems

- we want to set the temperature of the system
- we may have noise / heat creating energy

Cure

  - thermostat

Bath



imagine infinite bath at desired temperature

- heat will flow in or out
- at equilibrium no flow of heat
  - maybe removal of noise/heat

How to implement ? Many ways

Occasionally:

1. introduce a fake particle desired temperature / collide
2. pick a particle at random / give average *v* for temperature
3. Easy method –weak coupling…

Weak Coupling

Remember temperature* $E_{kin} = \sum_i^N \frac{1}{2} m_i v_i^2 = \frac{3}{2} NkT$

Heat leaves system depending on how wrong temperature is

$$\frac{dT(t)}{dt} = \frac{T_0 - T(t)}{\tau_T}$$

- T_0 is reference temperature
- τ_t is a coupling / relaxation constant
  - τ_t tiny, heat moves fast. τ_t big, …
- to implement this idea ? Multiply velocities

*Slight simplification of formula

Classic reference: Berendsen, HJC, Postma, JPM, van Gunsteren, WF, DiNola, A, Haak, JR, "Molecular dynamics with coupling to an external bath", J. Chem Phys, 81, 3684, (1984)

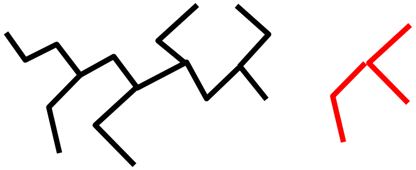
Implementation of weak coupling

Scale velocities, $v_{new} = \lambda\, v_{old}$ and $\lambda = \left(1 + \frac{\Delta t}{\tau_T}\left(\frac{T_0}{T} - 1\right)\right)^{1/2}$

Intuitively

- Δt (time step) big ? temperature will change more
- what if $T_0 = T$?
- square root ?
    - wrong T reflects a difference in v^2

Can we break this ?



- scaling is applied to whole system
    - what if part is hot ?
    - it may remain hotter than black part

Importance of heat baths

Does not conserve energy

In principle

- bring a system to equilibrium for temperature

In practice

- avoid damage due to numerical errors / approximations

For a system at equilibrium

- heat bath should do nothing

Does allow artificial tricks

- gently heat a system and watch behaviour
- gently cool a system and "anneal" it (more later)
- Extension to other properties
  - analogous reasoning for pressure bath

Summary of MD

Philosophy

- natural way to copy/model/simulate nature

Lets one model processes in real time

MC	MD
• any cost/energy OK	requires continuous $E_{pot}(\mathbf{r})$
• time usually invalid	gives time scales
• most moves OK	physical trajectories
• Temperature enforced by acceptance	has explicit E_{kin}

both yield a Boltzmann distribution

both include entropy