

# Molecular dynamics and Monte Carlo methods

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# Today's topics

- Equations of motion
- Molecular dynamics (MD) methods
  - Exercise 1
- Comparability with experimental data
- Monte Carlo methods
  - Exercise 2
- Constant-temperature MD methods

# Review of classical mechanics

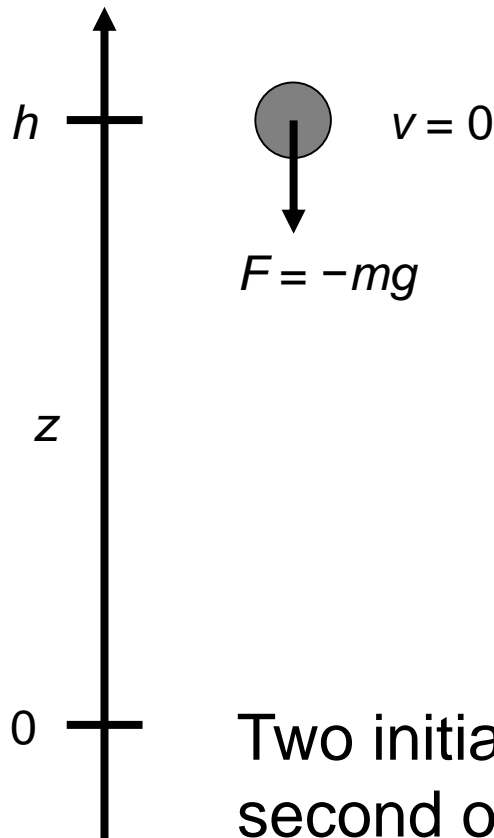
- Newton's equations of motion  
 $\mathbf{F} = m\mathbf{a}$     $\mathbf{F}$ : force,  $m$ : mass,  $\mathbf{a}$ : acceleration  
 $\mathbf{F}$  and  $\mathbf{a}$  are 3D vectors → bold  
 $m$  is a scalar number → italic
- $\mathbf{a}$  is second derivative of  $\mathbf{r}$  with respect to  $t$ .

$$\mathbf{v} = \frac{d\mathbf{r}}{dt} = \left( \frac{dx}{dt}, \frac{dy}{dt}, \frac{dz}{dt} \right)$$

$$\mathbf{a} = \frac{d\mathbf{v}}{dt} = \frac{d^2\mathbf{r}}{dt^2} = \left( \frac{d^2x}{dt^2}, \frac{d^2y}{dt^2}, \frac{d^2z}{dt^2} \right)$$

# Solution of equations of motion (1)

- Release a ball with a mass of  $m$



$$m \frac{d^2 z}{dt^2} = -mg \quad \rightarrow \quad \frac{d^2 z}{dt^2} = \frac{dv_z}{dt} = -g,$$

$$v_z(t) = -gt + C, \quad v_z(0) = 0 \quad \rightarrow \quad C = 0$$

$$\frac{dz}{dt} = v_z(t) = -gt, \quad z(t) = -\frac{1}{2}gt^2 + D$$

$$z(0) = h \quad \rightarrow \quad D = h \quad \rightarrow$$

$$z(t) = -\frac{1}{2}gt^2 + h$$

Two initial conditions are necessary to solve second order differential equations

# Solution of equations of motion (2)

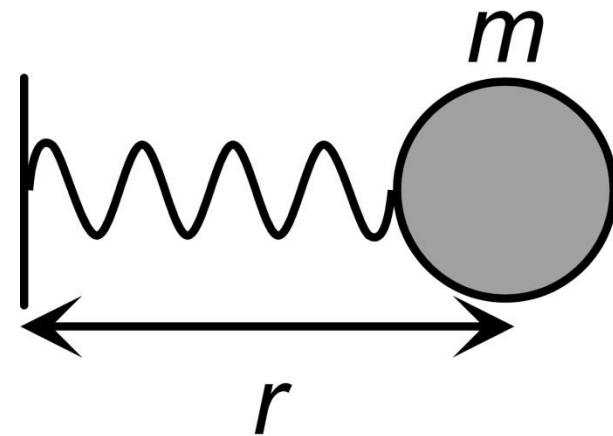
- Motion of a spring

Mass:  $m$

Spring length:  $r$

Equilibrium length:  $r_0$

Spring constant:  $k$



$$F = -k(r - r_0)$$

$$F = -kq$$

$$m \frac{d^2 r}{dt^2} = -k(r - r_0)$$

$$\xrightarrow{q = r - r_0}$$

$$m \frac{d^2 q}{dt^2} = -kq$$

# Solution of equation of motion (3)

$$\frac{d^2 q}{dt^2} = -\frac{k}{m} q = -\omega^2 q, \quad \omega = \sqrt{\frac{k}{m}}$$

$$q(t) = A \cos \omega t + B \sin \omega t \quad (\text{General solution})$$

$$q(0) = q_0, \quad dq/dt|_{t=0} = v(0) = 0 \quad (\text{Initial conditions})$$

$$A = q_0, \quad B = 0$$

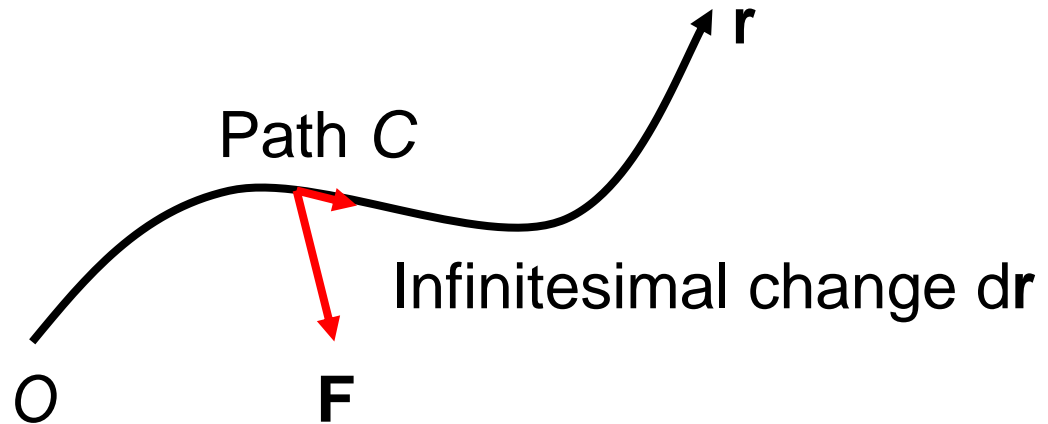
$$q(t) = q_0 \cos \omega t, \quad r = q_0 \cos \omega t + r_0$$

# Potential energy and force (1)

Definition of potential energy  $E(\mathbf{r})$  at position  $\mathbf{r}$

$$E(\mathbf{r}) = -\int_C \mathbf{F} \cdot d\mathbf{r}$$

Integrate the dot product of  $\mathbf{F}$  and  $d\mathbf{r}$  along path  $C$



# Potential energy and force (2)

Change of  $E(\mathbf{r})$  by an infinitesimal change in  $\mathbf{r}$

$$\begin{aligned} E(\mathbf{r} + \Delta\mathbf{r}) - E(\mathbf{r}) &= E(x + \Delta x, y + \Delta y, z + \Delta z) - E(x, y, z) \\ &= E(x + \Delta x, y + \Delta y, z + \Delta z) - E(x, y + \Delta y, z + \Delta z) \\ &\quad + E(x, y + \Delta y, z + \Delta z) - E(x, y, z + \Delta z) \\ &\quad + E(x, y, z + \Delta z) - E(x, y, z) \\ &= \frac{\partial E}{\partial x} \Delta x + \frac{\partial E}{\partial y} \Delta y + \frac{\partial E}{\partial z} \Delta z = \nabla E \cdot \Delta\mathbf{r} \end{aligned}$$

From the definition,

$$E(\mathbf{r} + \Delta\mathbf{r}) - E(\mathbf{r}) = -\mathbf{F} \cdot \Delta\mathbf{r}$$

The comparison gives the following:

$$\mathbf{F} = -\nabla E$$

Force is calculated from potential energy function.



# Energy conservation law (1)

- The sum of potential energy  $E$  and kinetic energy  $K$  ( $H = E + K$ ) is conserved in an isolated system.

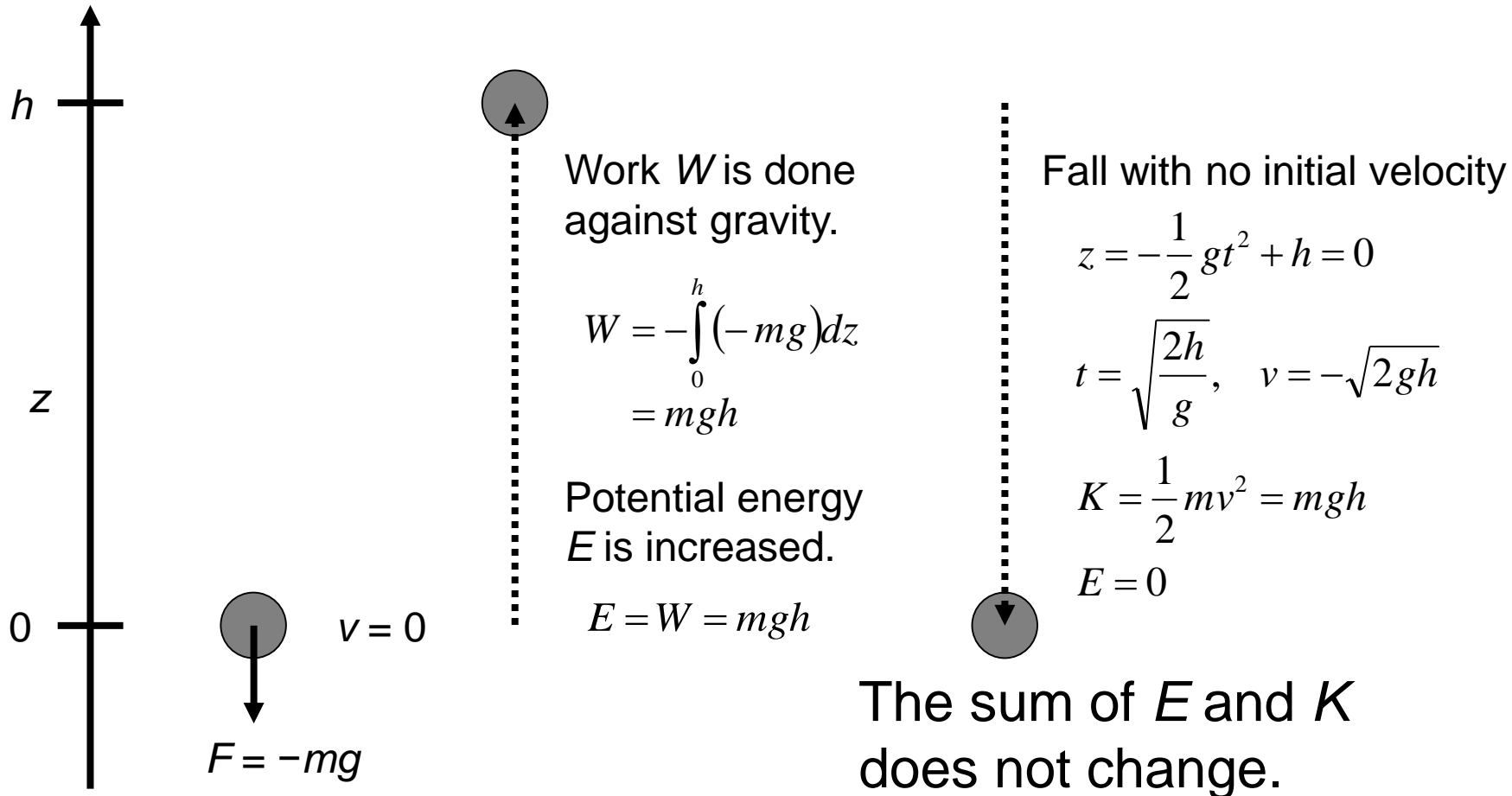
- Kinetic energy

$$K = \frac{1}{2} m |\mathbf{v}|^2$$

- Proof

$$\begin{aligned} \frac{dH}{dt} &= \frac{dK}{dt} + \frac{dE}{dt} = m\mathbf{v} \cdot \frac{d\mathbf{v}}{dt} + \frac{d\mathbf{x}}{dt} \cdot \frac{\partial E}{\partial \mathbf{x}} \\ &= m\mathbf{v} \cdot \mathbf{a} - \mathbf{v} \cdot \mathbf{F} = \mathbf{v} \cdot (m\mathbf{a} - \mathbf{F}) = 0 \end{aligned}$$

# Energy conservation law (2)



# Energy conservation law (3)

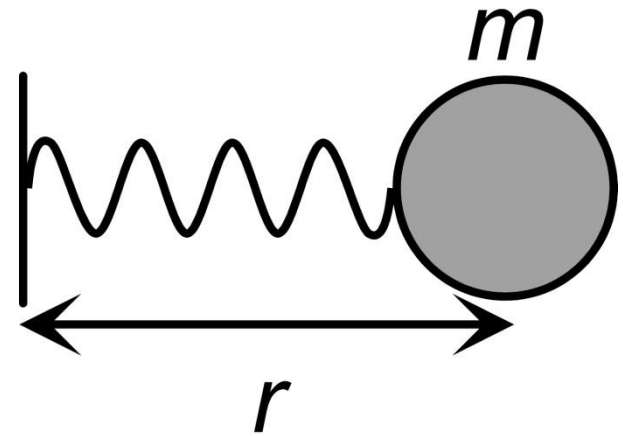
Motion of a spring

$$r(t) = q_0 \cos \omega t + r_0$$

$$v(t) = dr(t)/dt = -q_0 \omega \sin \omega t$$

$$E(r) = -\int_{r_0}^r -k(r' - r_0) dr' = \frac{k}{2} (r - r_0)^2$$

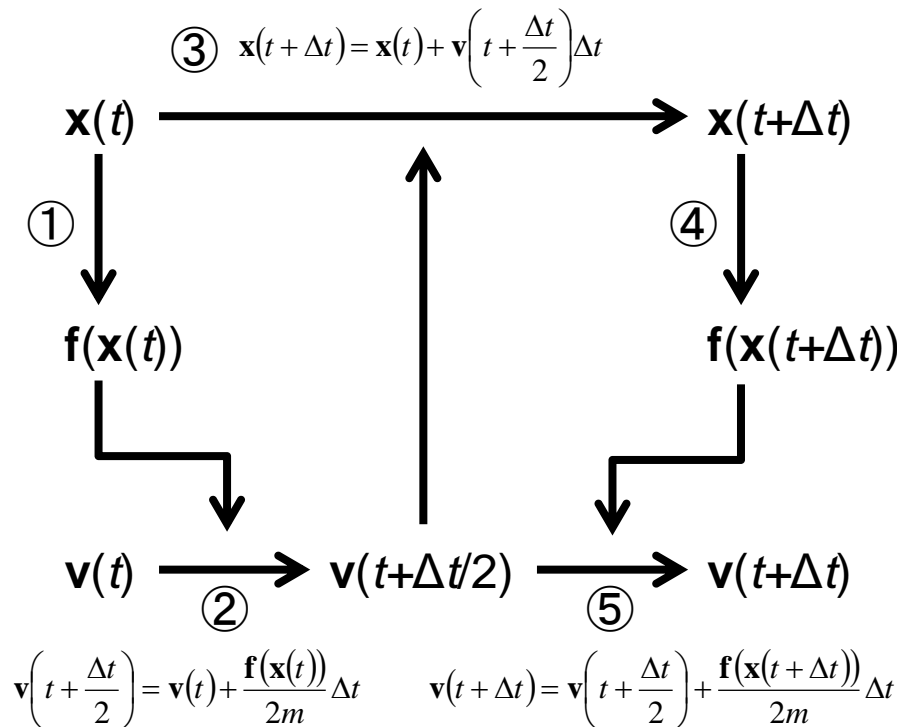
$$\begin{aligned} H &= \frac{m}{2} [v(t)]^2 + \frac{k}{2} [r(t) - r_0]^2 \\ &= \frac{mq_0^2 \omega^2}{2} \sin^2 \omega t + \frac{kq_0^2}{2} \cos^2 \omega t = \frac{1}{2} kq_0^2 \end{aligned}$$



# Molecular dynamics methods

- In the molecular dynamics (MD) methods, the force exerted on each atom is calculated from the potential energy function and the time evolutions of its position and velocity are calculated according Newton's equations of motion.
- The equations of motion cannot be solved analytically for the system composed of three or more atoms.  
→Use of numerical methods
- In the numerical methods, the position and the velocity of each atom are successively calculated at small intervals of time (time step:  $\Delta t$ ).
- Accuracy is measured by the deviation of the energy from the initial value.

# The velocity Verlet method



- ① Calculate the force for the position at  $t$ .
- ② Calculate the velocity at  $t + \Delta t/2$ .
- ③ Calculate the position at  $t + \Delta t$ .
- ④ Calculate the force for the position at  $t + \Delta t$ .
- ⑤ Calculate the velocity at  $t + \Delta t$ .
- ⑥ Return to ② and repeat.

# A harmonic oscillator (1)

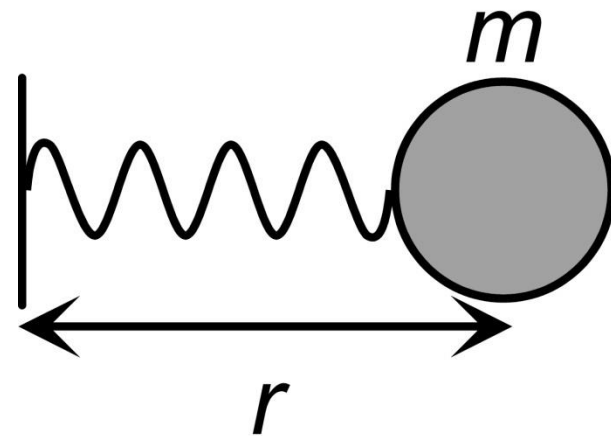
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$$\xrightarrow{q = r - r_0}$$

$$m \frac{d^2 q}{dt^2} = -kq$$

# A harmonic oscillator (2)

- Analytical solution

Initial position:  $q_0$ , initial velocity: 0

$$q(t) = q_0 \cos \omega t, \quad v(t) = -q_0 \omega \sin \omega t$$

- A perl script implementing velocity Verlet (osc.pl)

```
$q=1.0;$v=0.0;
$m=1.0;$k=1.0;
$dt=0.01;$nstep=100;
sub calc_force {
    my $q=$_[0];
    my $f=-$k*$q;
    my $e=0.5*$k*$q**2;
    return ($e,$f);
}
open(OUT,">osc$dt.csv");
```

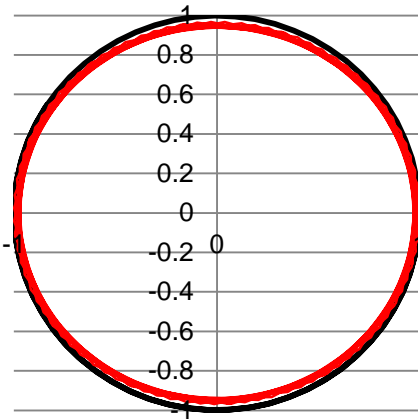
```
($e,$f)=calc_force($q);
for($i=1;$i<=$nstep;$i++) {
    $v+=0.5*$f/$m*$dt;
    $q+=$v*$dt;
    ($e,$f)=calc_force($q);
    $v+=0.5*$f/$m*$dt;
    $H=0.5*$m*$v**2+$e;
    print OUT $i*$dt,",",,$q,
        ",",$v,",",,$H,"¥n";
}
```

# Exercise 1

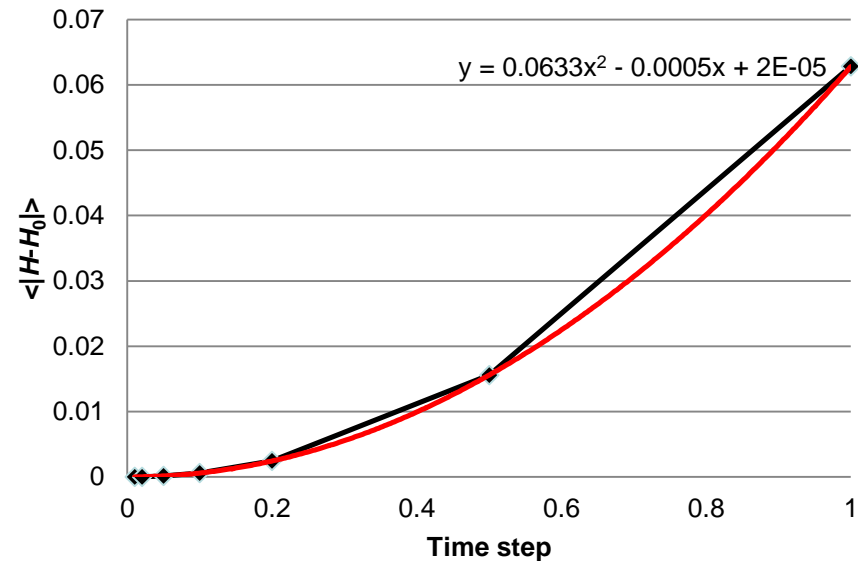
1. Download `osc.pl` and `osc.xlsx` from the web page of this lecture and run `osc.pl` with different  $\Delta t$  values (0.01, 0.02, 0.05, 0.1, 0.2, 0.5, and 1.0).
2. For each  $\Delta t$  value, calculate the average of absolute difference,  $\langle |H - H_0| \rangle$ , between the total energy  $H$  and its initial value  $H_0 = 0.5$ .
3. Plot  $\langle |H - H_0| \rangle$  as a function of  $\Delta t$  using `osc.xlsx`.
4. Discuss how  $\langle |H - H_0| \rangle$  changes as  $\Delta t$  increases.



# Time step vs. error



Trajectories of  $(q, v)$  in the simulations with  $\Delta t$  of 0.1 (black) and 0.5 (red).



Plot of  $\langle |H - H_0| \rangle$  as a function of  $\Delta t$

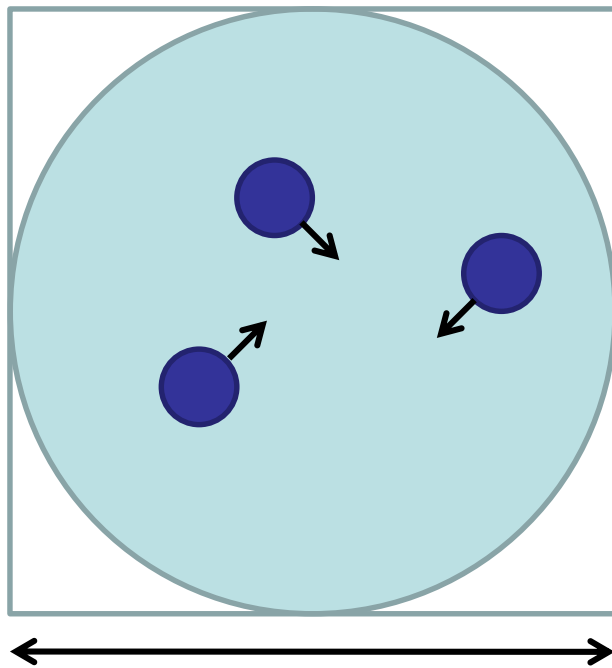
$$H = \frac{mv^2}{2} + \frac{kq^2}{2} = 0.5 \quad \Rightarrow \quad v^2 + q^2 = 1 \quad |H - H_0| \text{ corresponds to the deviation from the circle.}$$

# Appropriate choice of time step

- The smaller deviation of the total energy is obtained with the smaller time step.
- In general, the time step should be 1/10–1/20 of the cycle of the fastest motion.
- As for the case of proteins, the fastest motion is the X–H bond stretching motion (X = C, N, O, or S). The frequency is about  $3000\text{ cm}^{-1}$  and the cycle is about 10 fs.
- Therefore, 0.5–1.0 fs is used for  $\Delta t$ .

# A multi-particle system (1)

- A multi-particle system with van der Waals interaction (vdw.pl)



\$width

```
$natom=3;           # Number of particles
$width=10.0;        # Width of initial
                    # particle distribution
$scale=1.0;         # Scaling factor for
                    # initial velocity
$fcap=1.0;          # Force constant for
                    # spherical boundary
$sigma=1.0;         # Atom radius
$epsilon=1.0;       # Well depth
$mass=1.0;          # Atomic mass
$nstep=100000;     # Number of MD steps
$nsave=100;         # Frequency of saving
                    # trajectory
$dt=0.001;          # Time step
$seed=170615;       # Random seed
```

# A multi-particle system (2)

- Initial placement
  - Particles are randomly placed within a cube of side length \$width centered on the origin.
- Initial velocities
  - Randomly assigned (parameter: \$scale)
- Potential energy function

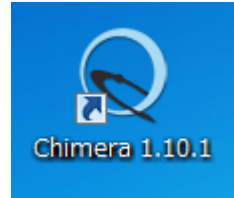
$$E = \sum_{i=1}^N \sum_{j=i+1}^N 4\epsilon \left( \frac{\sigma^{12}}{r_{ij}^{12}} - \frac{\sigma^6}{r_{ij}^6} \right) + \sum_{i=1}^N E_{\text{cap}}(r_i)$$

$$E_{\text{cap}}(r_i) = \begin{cases} 0 & r_i < r_{\text{cut}} \\ f_{\text{cap}}(r_i - r_{\text{cut}})^2 & r_i \geq r_{\text{cut}} \end{cases}$$

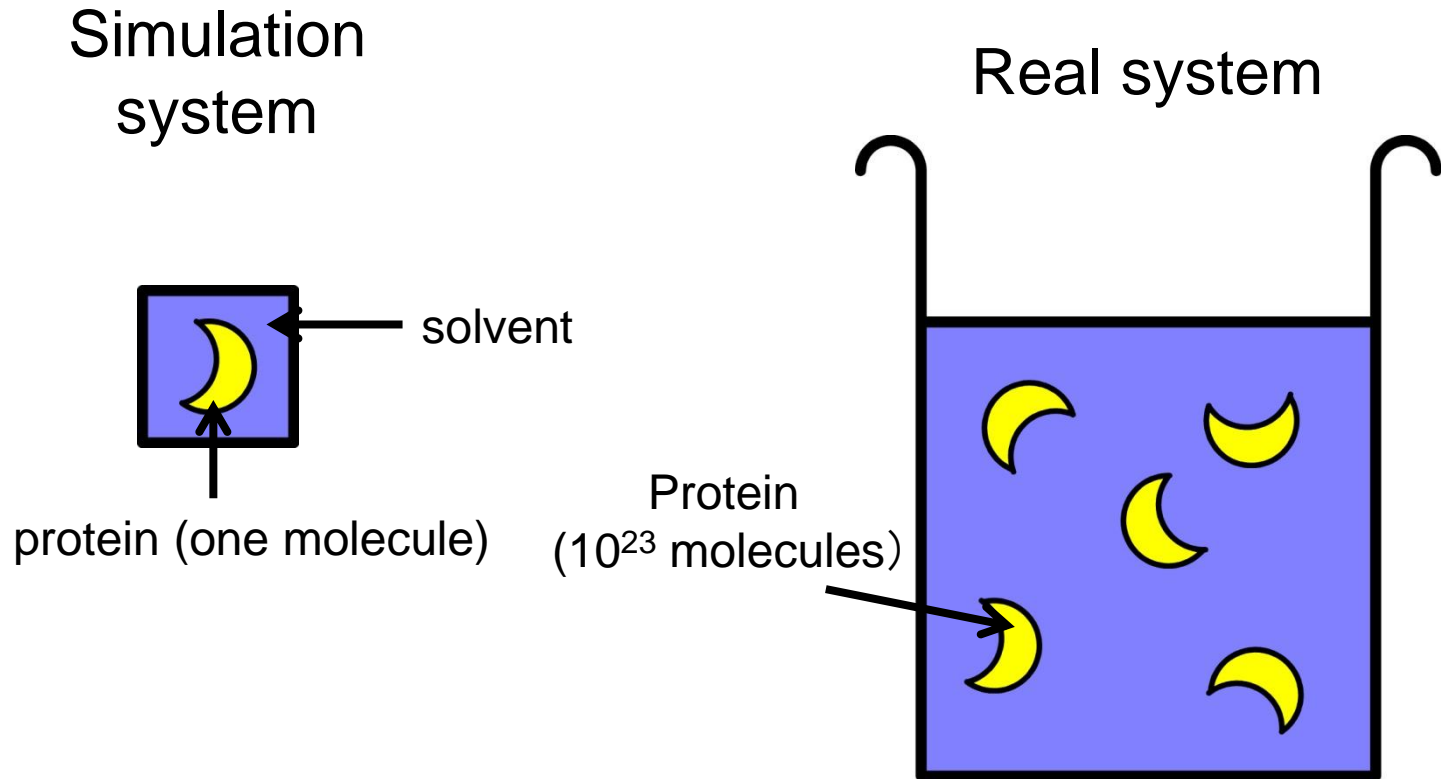
$r_i$ : distance from the origin  
 $r_{\text{cut}}$ : half of \$width

# A multi-particle system (3)

- Visualize the result with UCSF Chimera.
- Start Chimera.
- Choose “Tools” → “MD/Ensemble Analysis” → “MD Movie”, select “PDB” as Trajectory format, select “Single file” as PDB frames contained in, specify “vdw.pdb” on the Desktop as the file, and “OK.”
- Click the play button to start animation.
- Examine how the motion changes when the parameters change.

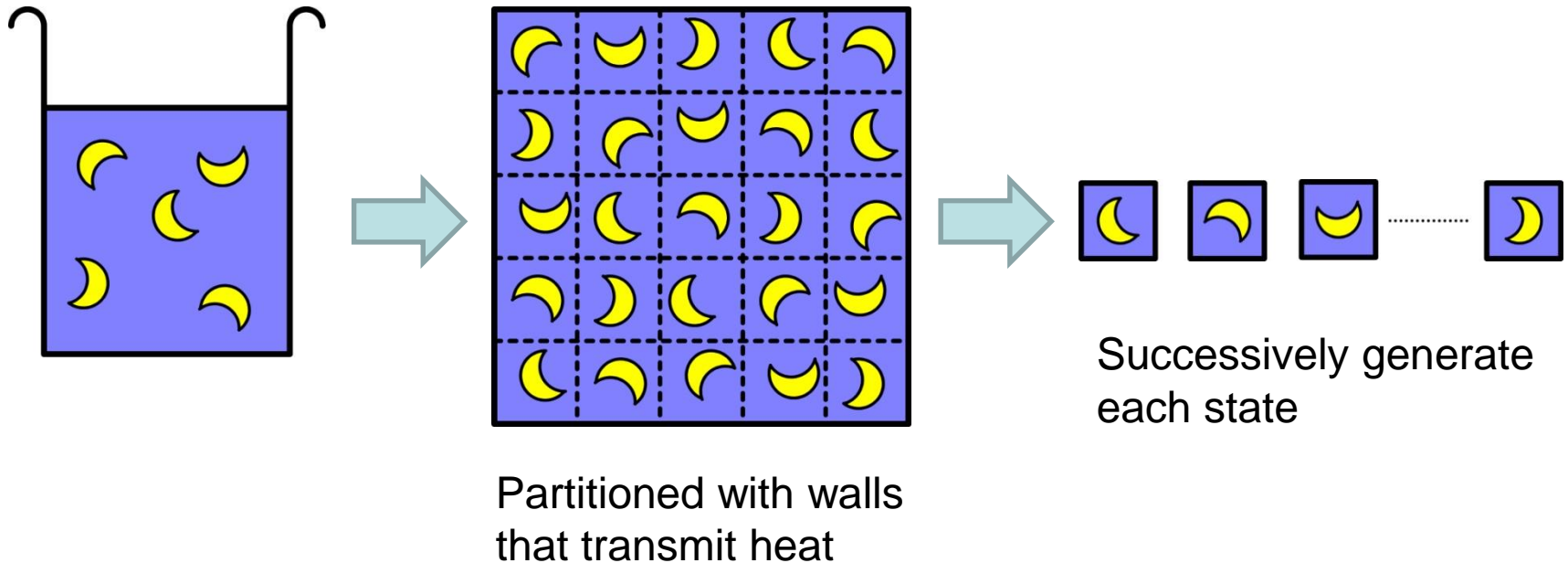


# Comparability with experimental data (1)



- Is the result of a molecular simulation comparable with the experimental data?

# Comparability with experimental data (2)



- The real system can be reproduced by successively generating each state in a molecular simulation, but how to generate it?

# Comparability with experimental data (3)

- Experimental data is the weighted average of the observable over the states.

$$\langle A \rangle = A_i \rho_i, \quad \sum_i \rho_i = 1 \quad \rho_i: \text{probability of state } i$$

- Probability of each state follows the canonical distribution.

$$\rho_i = Z^{-1} \exp(-e_i/k_B T) \quad e_i: \text{energy of state } i$$

$$Z = \sum_i \exp(-e_i/k_B T) \quad Z: \text{partition function}$$

→Generate each state following the canonical distribution.



# A harmonic oscillator (1)

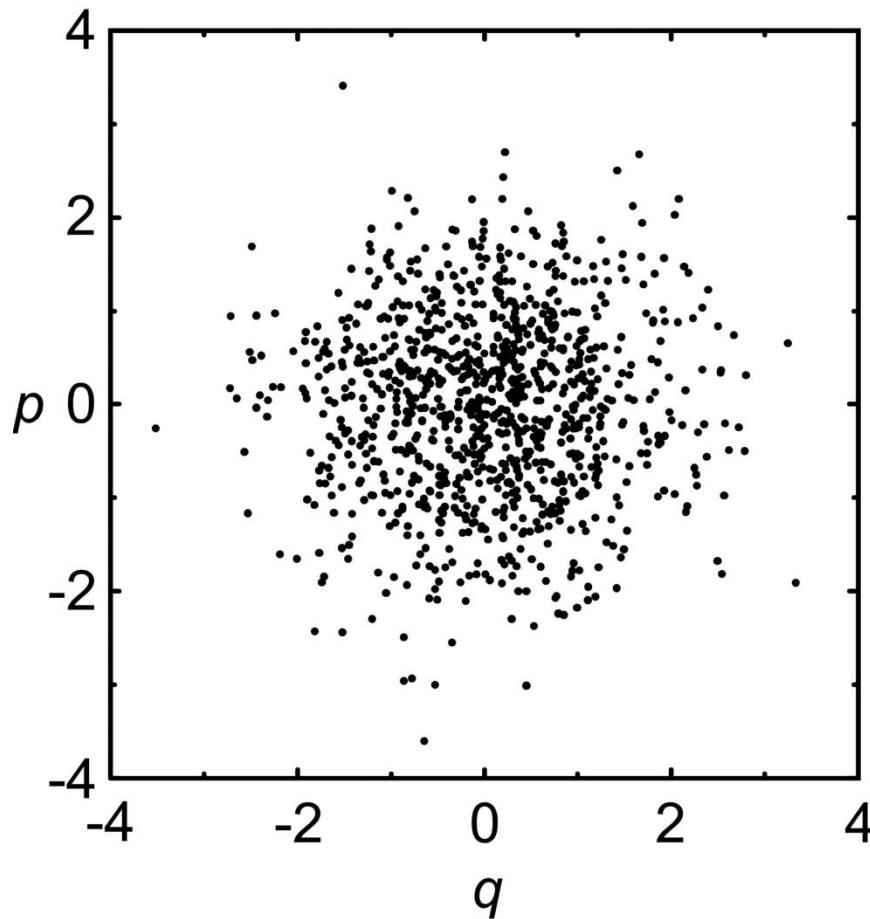
- The canonical distribution of  $(q, p)$

$$H(q, p) = \frac{p^2}{2m} + \frac{k}{2}q^2, \quad \rho(q, p) = \frac{\exp\left[-\frac{H(q, p)}{k_B T}\right]}{\int \exp\left[-\frac{H(q, p)}{k_B T}\right] dq dp}$$

- Generate  $(q, p)$  following this distribution
  - Evaluate the accuracy using the average of the total energy

$$\langle H \rangle = \int H(q, p) \rho(q, p) dq dp = k_B T$$

# A harmonic oscillator (2)



- When  $m = k = k_B T = 1$ , this corresponds with the normal distribution.

$$\rho(q, p) = \frac{1}{2\pi} \exp\left(-\frac{q^2 + p^2}{2}\right)$$

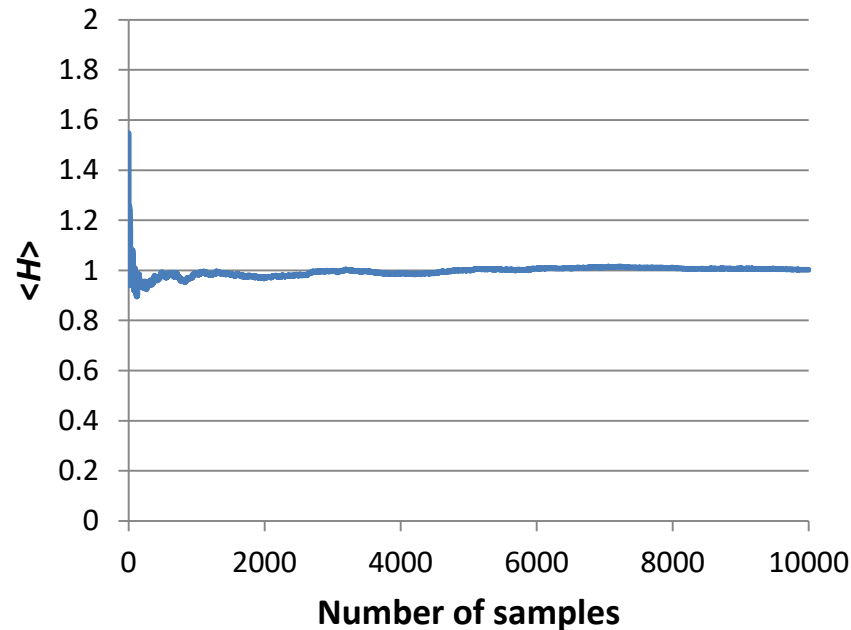
- Check the convergence of  $\langle H \rangle$  by increasing the number of samples.

# An example program

```
$kT=1.0;
$pi=atan2(1.0,1.0)*4.0;
$npt=10000;

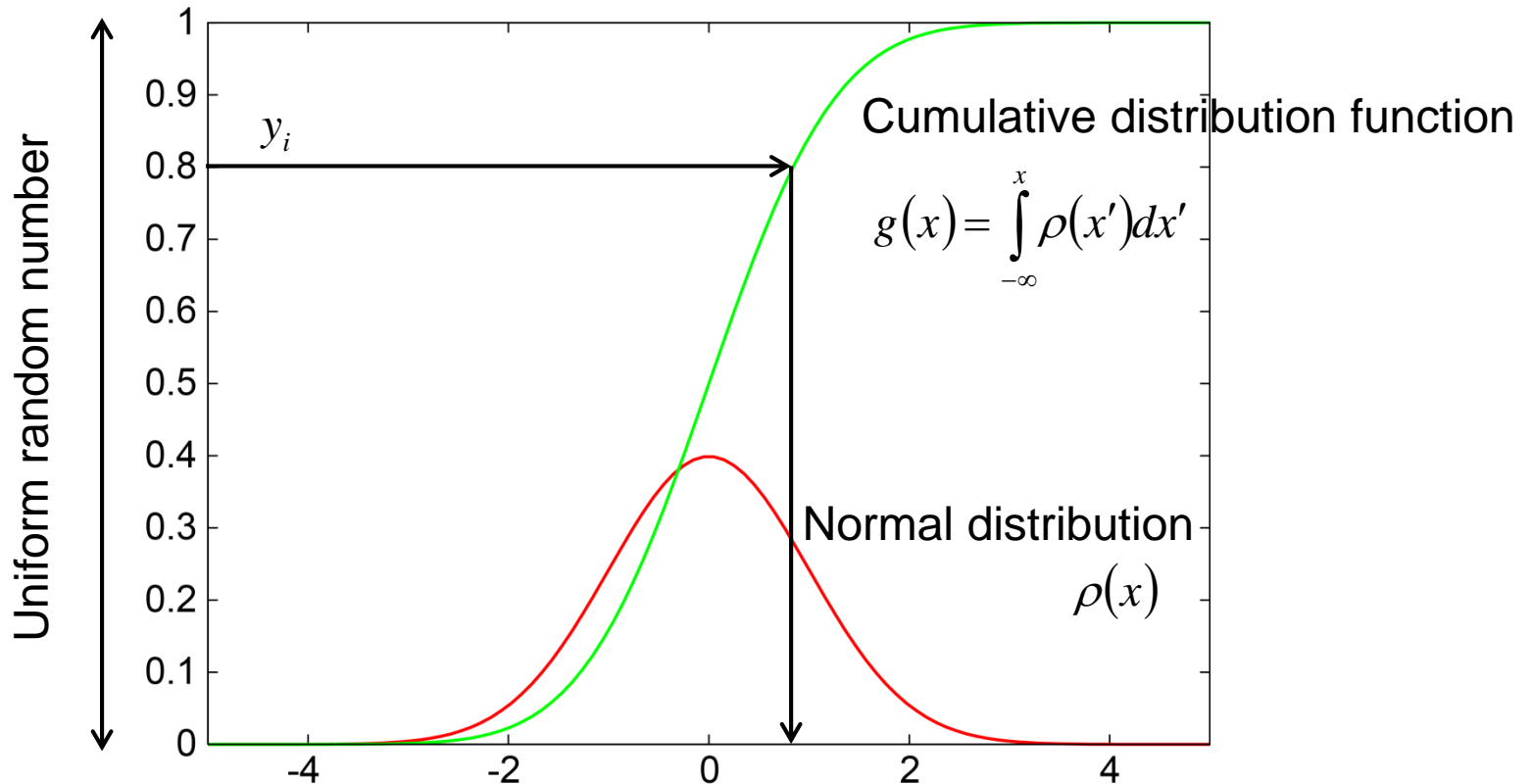
open(OUT,">normal.csv");
$val1=0.0;
for($i=1;$i<=$npt;$i++) {
    $x1=rand;
    $x2=rand;
    #Convert uniform dist. into normal dist.
    $q=sqrt(-2.0*$kT*log($x1))*cos(2.0*$pi*$x2);
    $p=sqrt(-2.0*$kT*log($x1))*sin(2.0*$pi*$x2);
    $H=0.5*$q**2+0.5*$p**2;
    $val1+=$H;           #Average of total energy
    if($i % 100 == 0) {
        printf(OUT "%d,%f¥n",$i,$val1/$i);
    }
}
```

# A harmonic oscillator (3)



- $\langle H \rangle$  quickly converges to the theoretical value, 1.

# Sample generation (1)



Convert the number into the one following the normal distribution

$$g(x_i) = y_i, \quad x_i = g^{-1}(y_i)$$

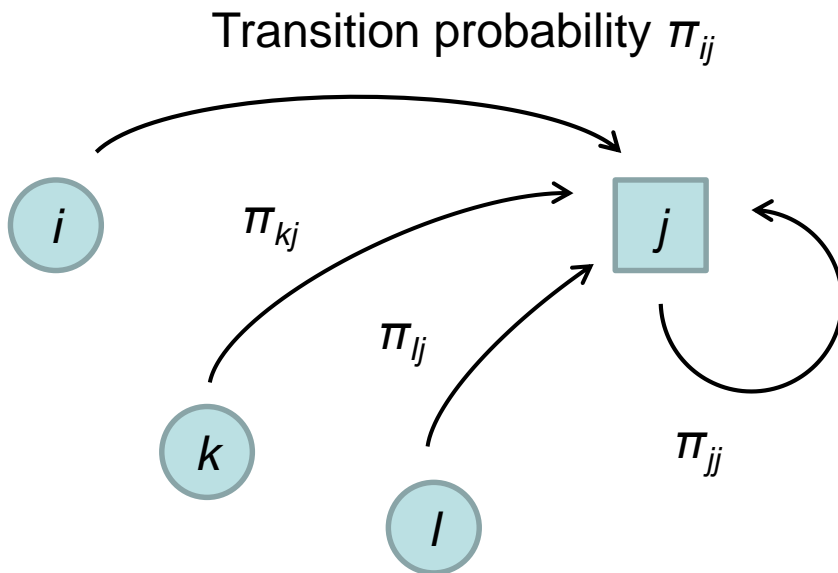
# Sample generation (2)

- The above-mentioned method is only applicable to the cases where the cumulative probability function is computable.
- As for the biomacromolecular systems, the relation between bonded and non-bonded interactions is so complex that it is impossible to analytically compute the cumulative probability function.
- Due to the large internal degree of freedom, numerical calculation is also impossible.



Use of Markov chain

# Markov chain



- Let  $\pi_{ij}$  be the transition probability from state  $i$  to state  $j$ .
- Let  $\rho_i^0$  be the probability of state  $i$  before transition. Then, the probability of state  $j$  after transition is:

$$\rho_j^1 = \sum_i \rho_i^0 \pi_{ij}$$

- The transition probability matrix satisfies:

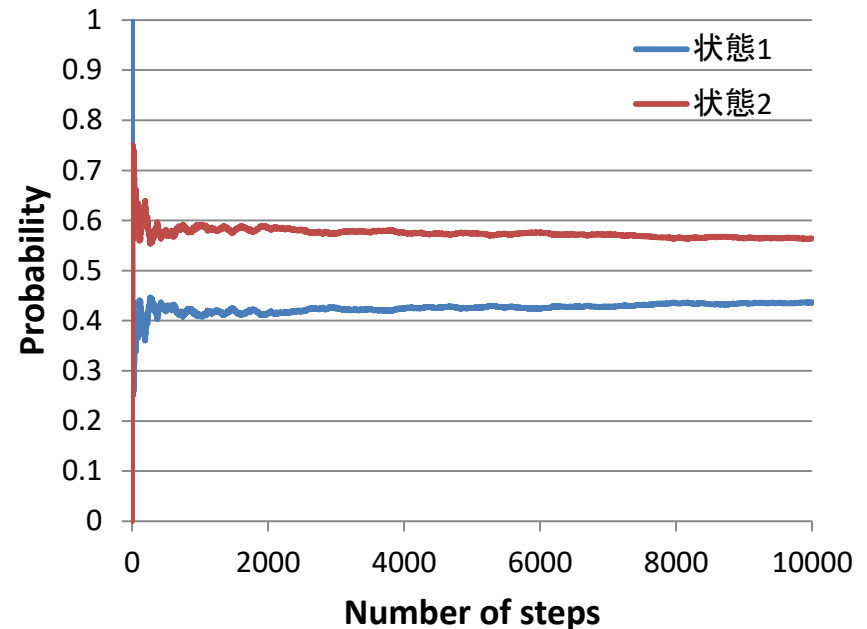
$$\sum_j \pi_{ij} = 1$$

# An example (1)

- Consider two states.
- The transition probabilities are:

$\pi_{11} = 0.6$	$\pi_{12} = 0.4$
$\pi_{21} = 0.3$	$\pi_{22} = 0.7$

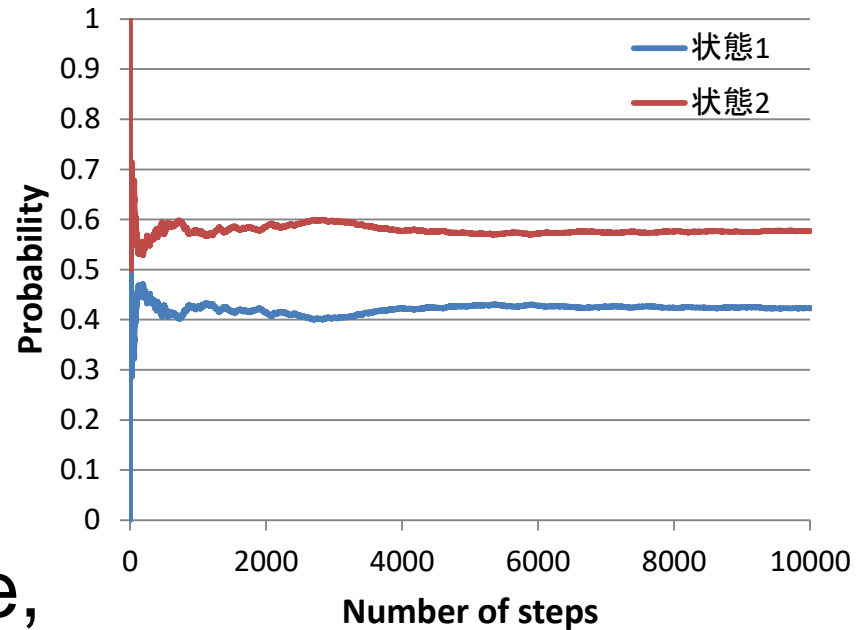
- The plot shows the result of the simulation starting with state 1.





# An example (2)

- The probabilities converge to the same values if the simulation starts with state 2.



- Upon the convergence, the equation,  $\boldsymbol{\rho} = \boldsymbol{\rho}\boldsymbol{\pi}$ , holds.
- $\boldsymbol{\rho}$  is an eigenvector of  $\boldsymbol{\pi}$ .  
→ Uniquely determined for a given  $\boldsymbol{\pi}$ .

# The Metropolis method (1)

- We want to find  $\boldsymbol{\pi}$  from  $\boldsymbol{\rho}$ .
- If the detailed balance condition holds,  $\boldsymbol{\rho} = \boldsymbol{\rho}\boldsymbol{\pi}$  holds.

$$\rho_i \pi_{ij} = \rho_j \pi_{ji} \Rightarrow \sum_i \rho_i \pi_{ij} = \sum_i \rho_j \pi_{ji} = \rho_j \sum_i \pi_{ji} = \rho_j$$

- Metropolis *et al.* proposed the following:

$$\begin{cases} \pi_{ij} = \alpha_{ij} & \text{if } \rho_j \geq \rho_i \text{ and } i \neq j \\ \pi_{ij} = \alpha_{ij} (\rho_j / \rho_i) & \text{if } \rho_j < \rho_i \text{ and } i \neq j \end{cases}$$

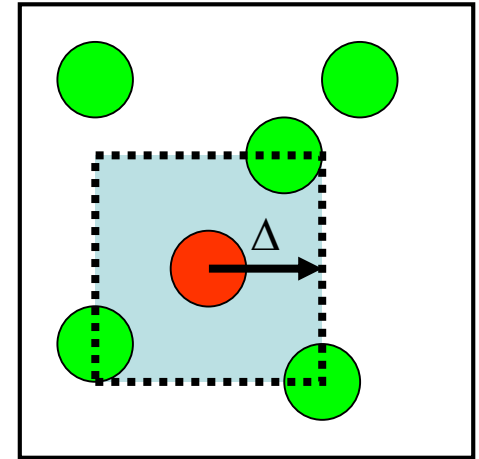
$$\alpha_{ij} = \alpha_{ji}, \quad \sum_{j \neq i} \alpha_{ij} = 1, \quad \pi_{ii} = 1 - \sum_{j \neq i} \pi_{ij}$$

# The Metropolis method (2)

1. Move an atom of interest randomly within a cube with side length  $2\Delta$  centered on the atom.

$$\alpha_{ij} = \frac{1}{N_{\Delta}} \quad \text{Within the cube}$$

$$\alpha_{ij} = 0 \quad \text{Outside the cube}$$



2. If the energy of the destination state,  $e_j$ , is lower than that of the original state,  $e_i$ , accept the movement. If not, accept it with the following probability:

$$\rho_j / \rho_i = \exp[-(e_j - e_i) / k_B T] = \exp(-\Delta e_{ji} / k_B T)$$

3. If not accepted, use the original state as the new state.

$$\pi_{ii} = 1 - \sum_{j \neq i} \pi_{ij} = \sum_{j \neq i} (\alpha_{ij} - \pi_{ij}) = \sum_{\substack{j \neq i \text{ and} \\ \rho_j < \rho_i}} \alpha_{ij} (1 - \rho_j / \rho_i)$$

# Exercise 2

1. Download metropolis.pl from the web page of this lecture and run it.
2. Plot  $\langle H \rangle$  as a function of the sample number and ascertain that  $\langle H \rangle$  approaches to 1 as the sample number increases.
3. Run metropolis.pl with  $\$delta = 0.1$  and plot the result similarly.
4. How does the plot change by using a smaller  $\$delta$  value? Discuss the reason for the change.

# metropolis.pl

```
$nstep=10000; #Number of steps
($q,$p)=(0.0,0.0); #Initial conditions
$delta=1.0; #Maximum displacement
$kT=1.0;$m=1.0;$k=1.0; #kT, mass, force constant
$delta_q=$delta/sqrt($k);
$delta_p=$delta*sqrt($m);

open(OUT,">metropolis$delta.csv"); #Output file

$save=0.0;
$H=&calc_H($q,$p); #Initial energy
for($i=1;$i<=$nstep;$i++) {
    $q_new=$q+2.0*$delta_q*(rand()-0.5); #Trial
    $p_new=$p+2.0*$delta_p*(rand()-0.5); #Trial
    $H_new=&calc_H($q_new,$p_new);
    $probability=exp(($H-$H_new)/$kT);
    if($probability >= 1.0 || $probability >= rand()) { #Judgement
        $q=$q_new;$p=$p_new;$H=$H_new;
    }
    $save+=$H;
    printf(OUT "%d,%f\n", $i, $save/$i) if($i % 100 == 0);
}
close(OUT);

sub calc_H { #Energy function
    my ($q,$p)=@_;
    return 0.5*$p*$p/$m+0.5*$k*$q*$q;
}
```

# Application to biomacromolecules

- “State” corresponds to “structure.”
- The Metropolis method can be performed by moving an arbitrary chosen atom.
- However, moving an atom changes the bond length and the energy increases in most cases.  
→The trial is rarely accepted.
- To solve this problem, only dihedral angles are changed without changing the bond lengths and angles. But, there are still difficulties.  
→Application to a multiple molecular system is difficult.  
→In the protein core where atoms are densely packed, changing a dihedral angle tends to cause overlapping of atoms.

# Constant-temperature MD (1)

- Sampling from the canonical distribution is enabled by keeping the temperature constant in the MD simulation.

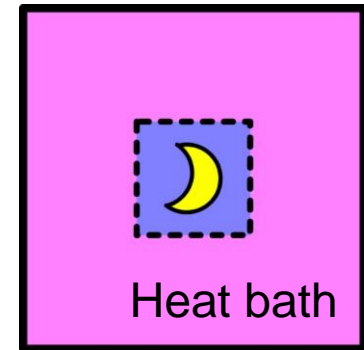
$$\frac{3}{2} Nk_{\text{B}}T = \sum_{i=1}^N \frac{m_i |\mathbf{v}_i|^2}{2}$$

- Since MD simulations are conducted in the Cartesian coordinate system, they are more easily applied to biomacromolecules.
- The average is taken over time.

# Constant-temperature MD (2)

- Nosé's method
- Nosé-Hoover chain method
  - An improved method
- Constraint method
  - Only the distribution of the coordinates is canonical.
- Langevin dynamics
  - Temperature is controlled by random force and friction.
- Berendsen's weak coupling method
  - Distribution is not canonical.
  - But frequently used because of its easiness and stability

} Considers degree of freedom of heat bath





# Langevin dynamics

- Exchange of energy between the real system and the heat bath occurs by the collision between the atoms of the real system and randomly moving fictitious particles of the heat bath.
  - If the real system is hot, the energy is transmitted toward the heat bath and vice versa.

- Equations of motion

$$m\mathbf{a} = \mathbf{F}(\mathbf{x}) - \gamma\mathbf{v} + \mathbf{R}(t)$$

friction force by collision with fictitious particles

- $\mathbf{R}$  satisfies the following conditions:

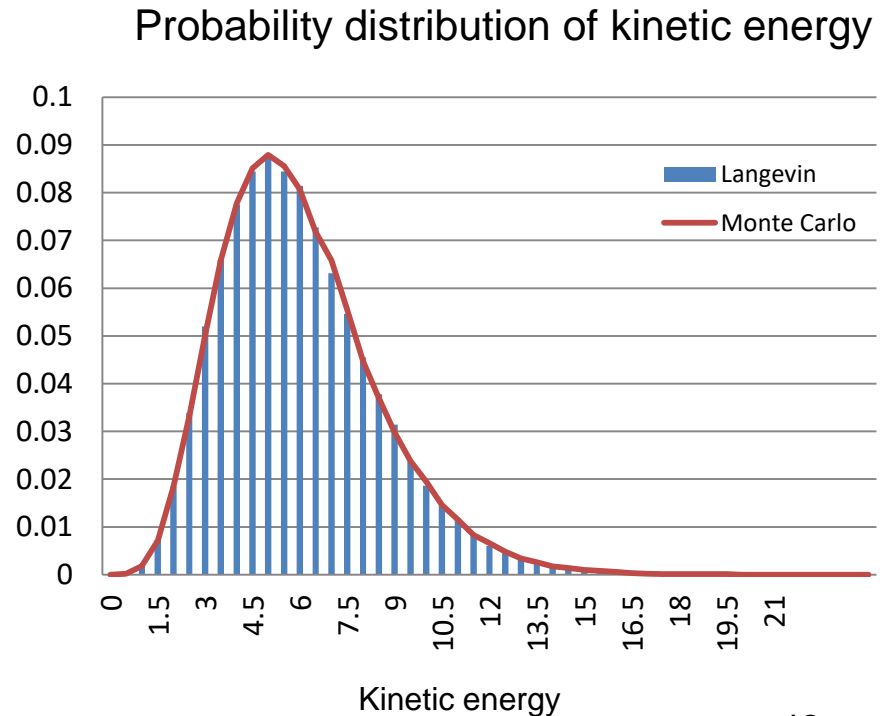
$$\langle \mathbf{R}(t) \rangle = 0, \quad \langle \mathbf{R}(t) \cdot \mathbf{R}(t') \rangle = 6k_B T \gamma \delta(t - t')$$

average variance-covariance

# An example

- A multi-particle system with van der Waals interaction (vdw\_langevin.pl)

```
$natom=4;           # Number of particles
$width=10.0;        # Width of initial
                    # particle distribution
$fcap=1.0;          # Force constant for
                    # spherical boundary
$sigma=1.0;         # Atom radius
$epsilon=1.0;       # Well depth
$mass=1.0;          # Atomic mass
$nstep=100000;     # Number of MD steps
$nsave=100;         # Frequency of saving
                    # trajectory
$dt=0.001;          # Time step
$seed=170615;       # Random seed
$gamma=10.0;        # friction coefficient
$kT=1.0;
```



# Berendsen's weak coupling

1. Calculate instantaneous temperature  $T'$  after each step of velocity Verlet

$$\frac{3}{2} Nk_{\text{B}}T' = \sum_{i=1}^N \frac{m_i |\mathbf{v}_i|^2}{2}$$

2. Scale the velocity by a factor of  $\chi$ . Parameter  $\tau$  controls the speed of adaptation.

$$\chi = \left[ 1 + \frac{\Delta t}{\tau} \left( \frac{T}{T'} - 1 \right) \right]^{1/2}$$

# Instructions for submission

- Put the results and discussion of the exercises in the slides of a PowerPoint file.
- Send the PowerPoint file as an attachment to email.
- Put “Molecular modeling” in the Subject field.
- Be sure to put your name and ID card number (if you are a student) in the body of the email.
- Send the email to Prof. Tohru Terada (tterada@iu.a.u-tokyo.ac.jp).