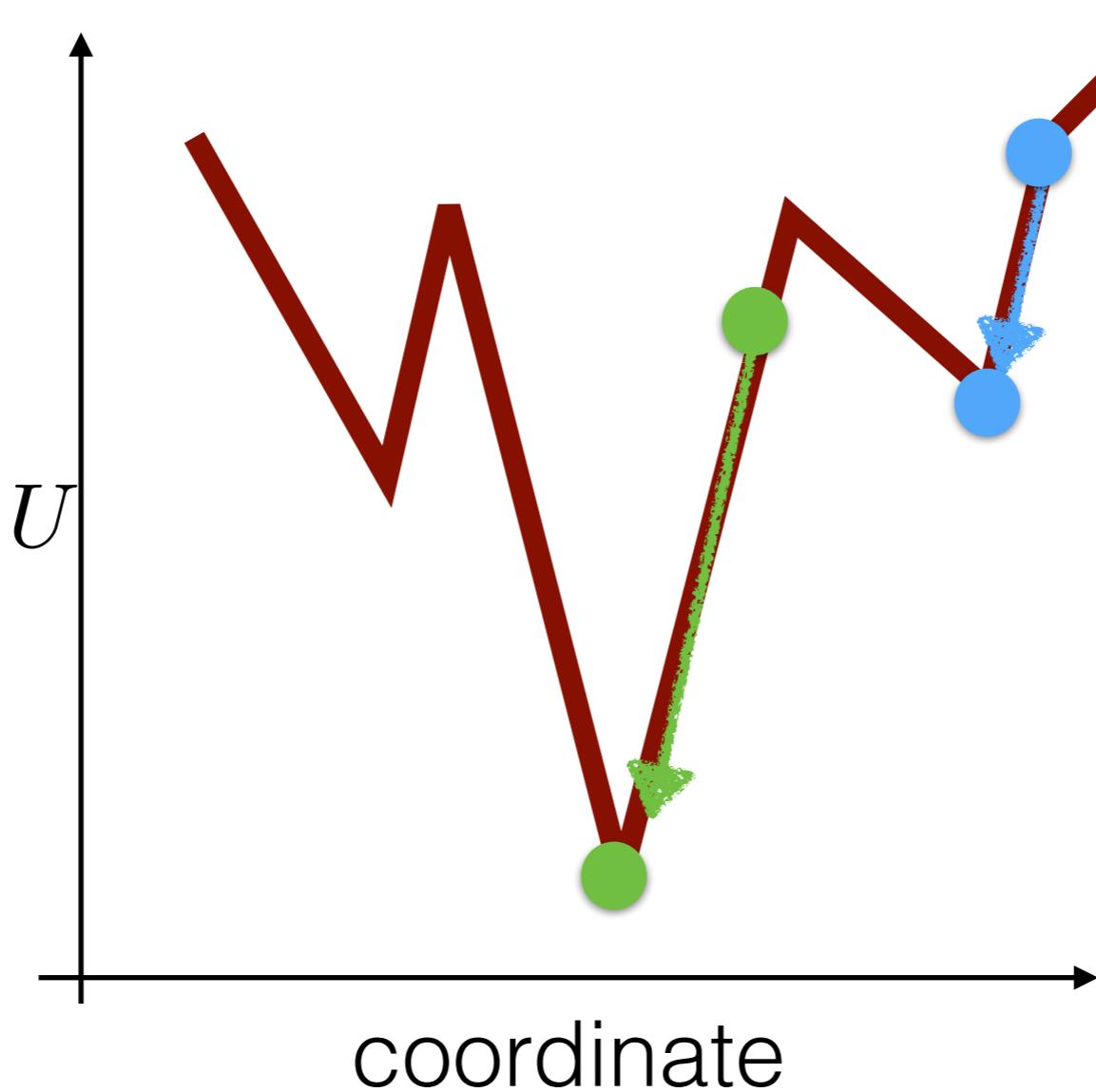


CHM695

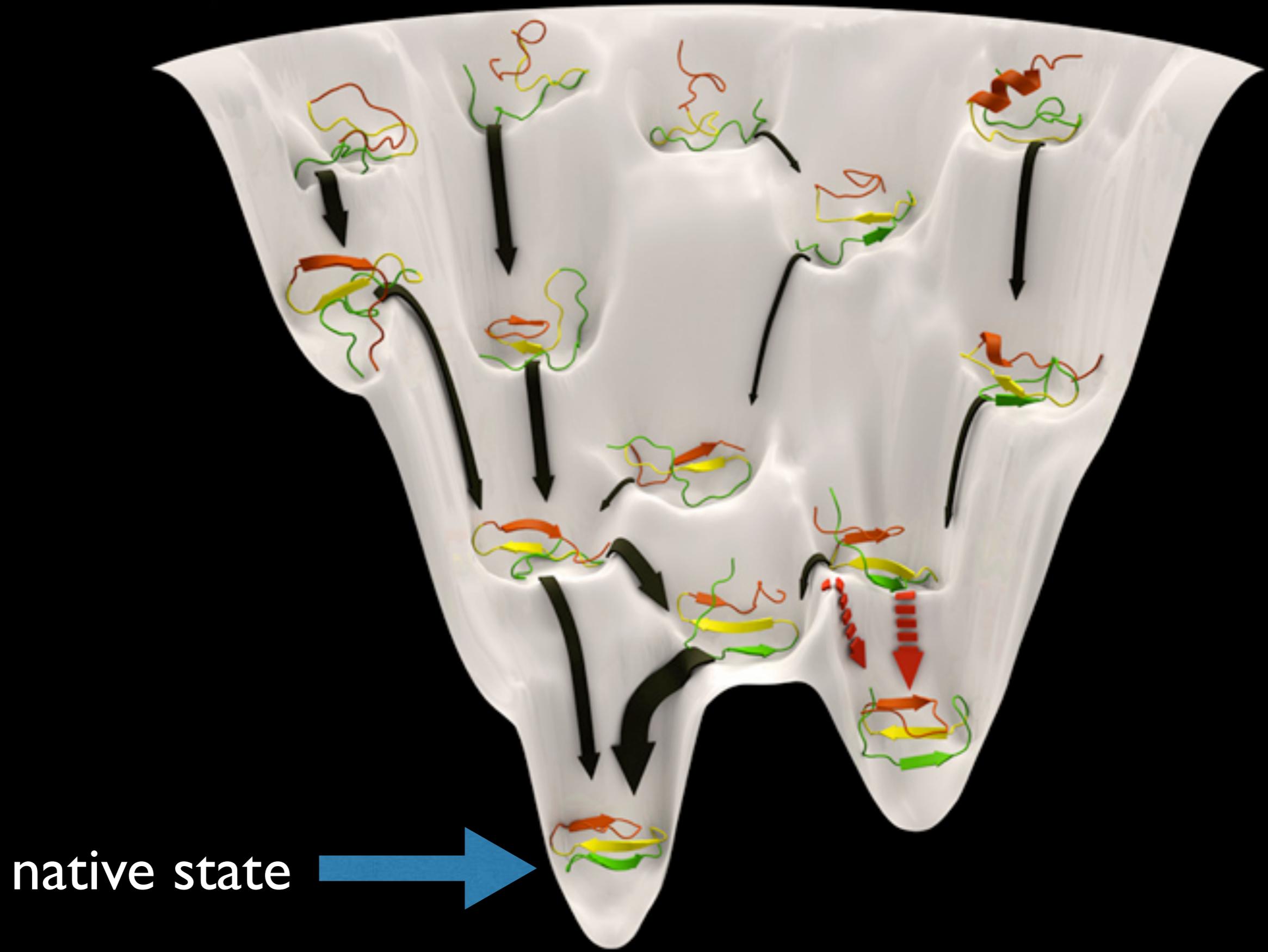
Lecture 6

Geometry optimisations are local optimisations

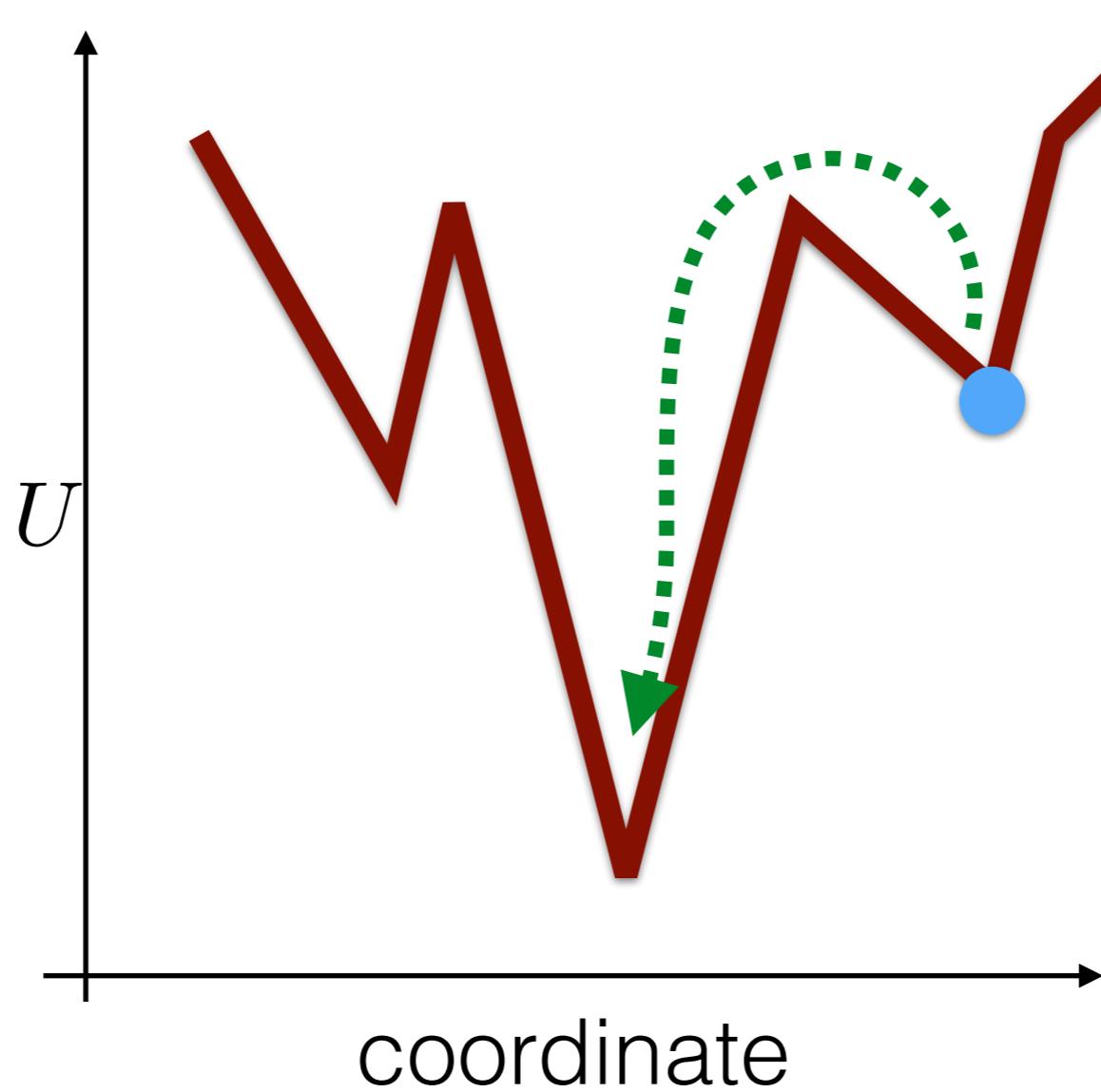


How to predict the global minimum?

Protein Folding

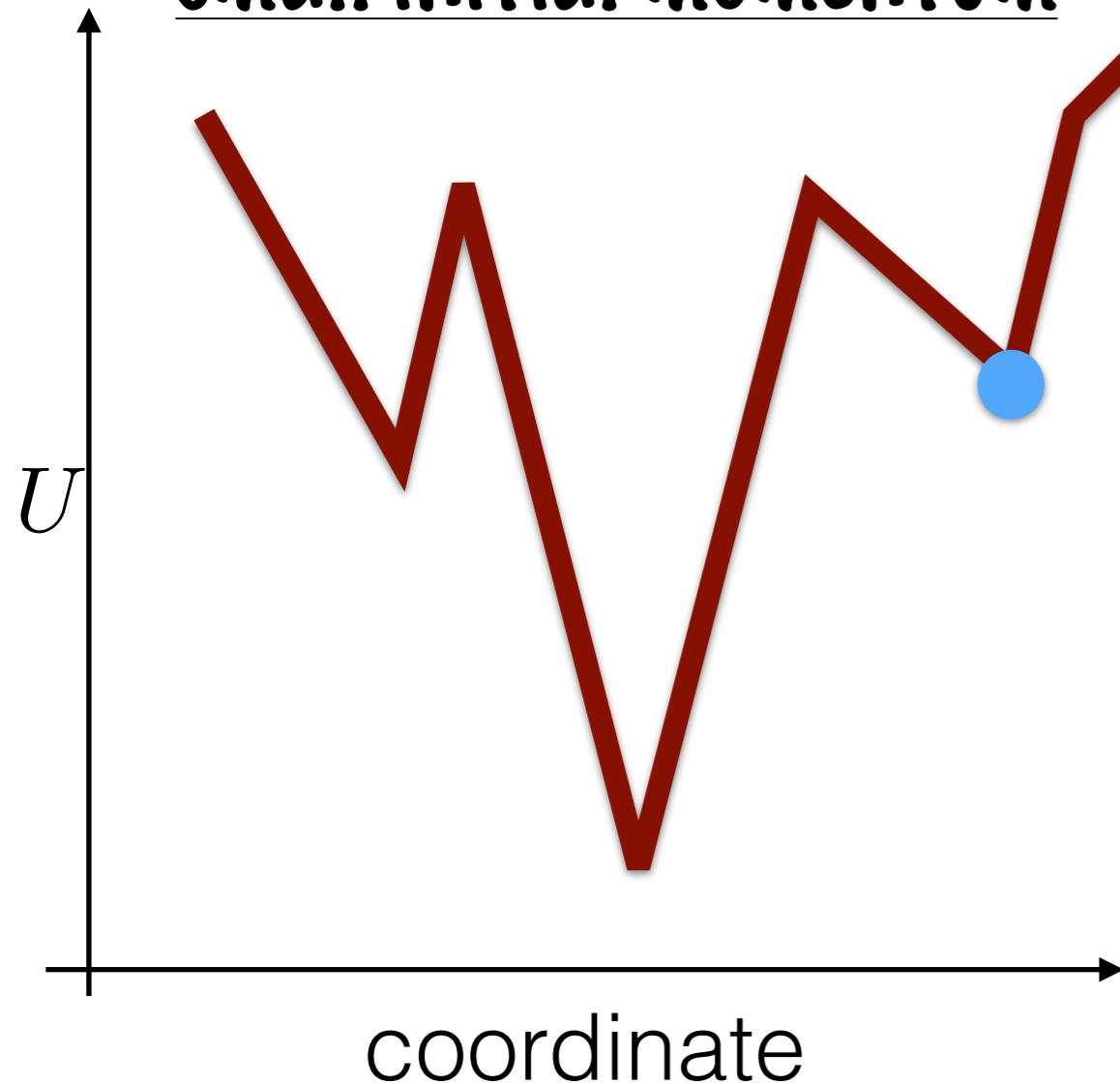


We need a technique to jump over the barriers!

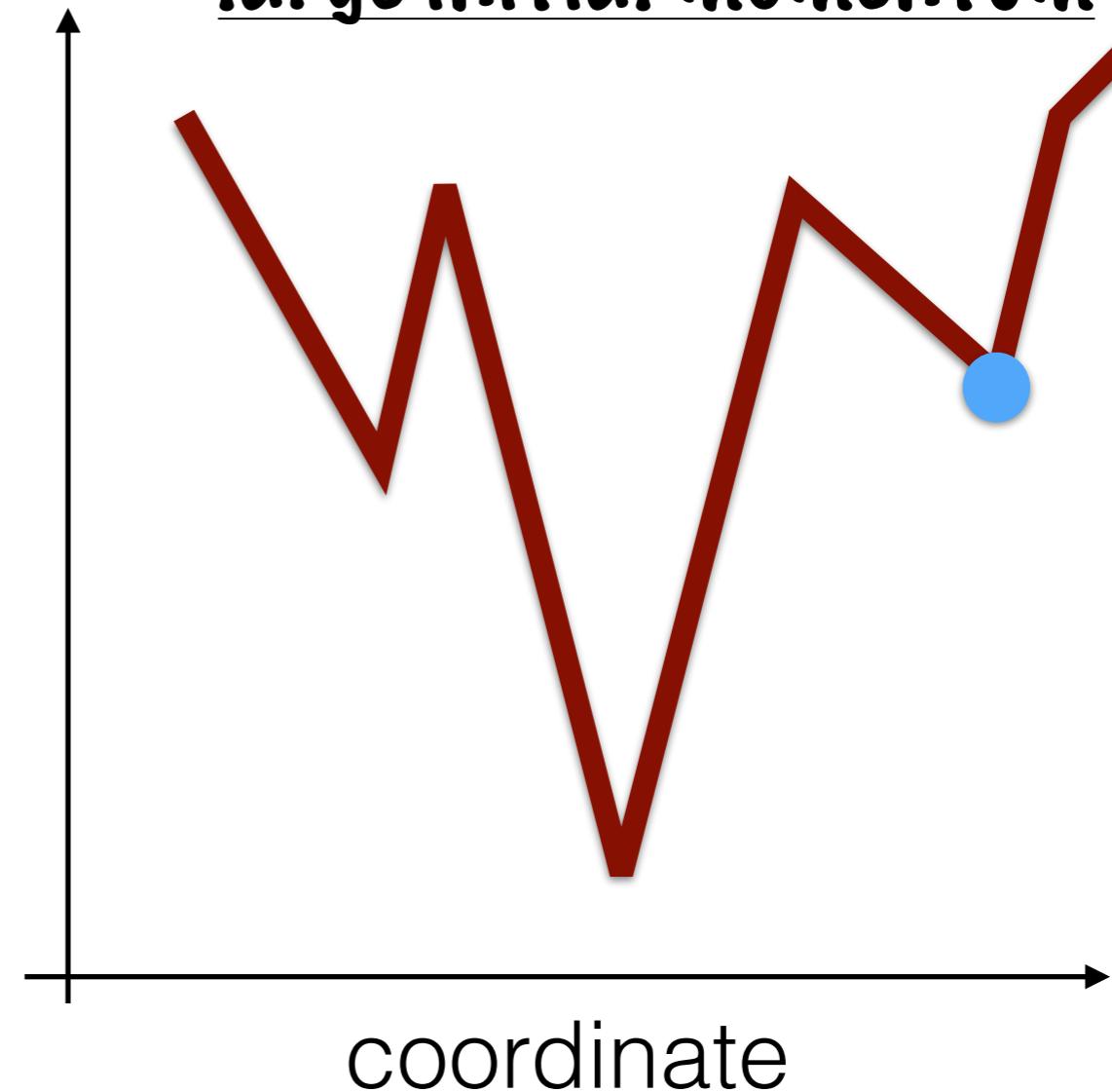


Dynamics: large momentum to escape?

small initial momentum



large initial momentum



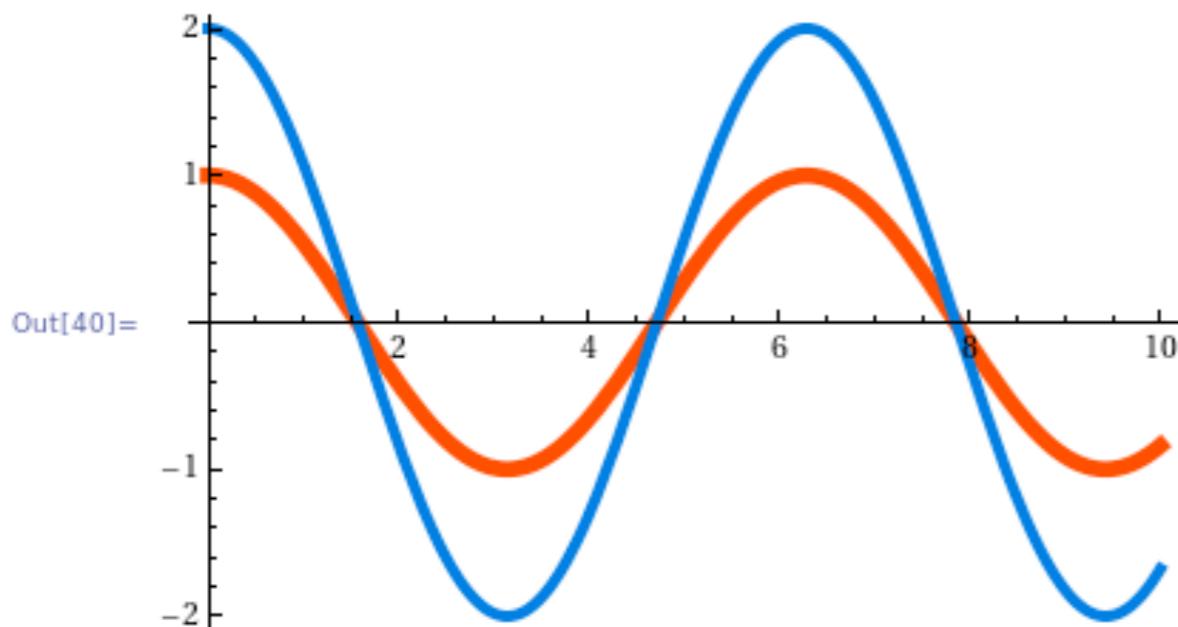
How can we do “molecular dynamics” (MD)?

Integrating Classical Equations of Motion

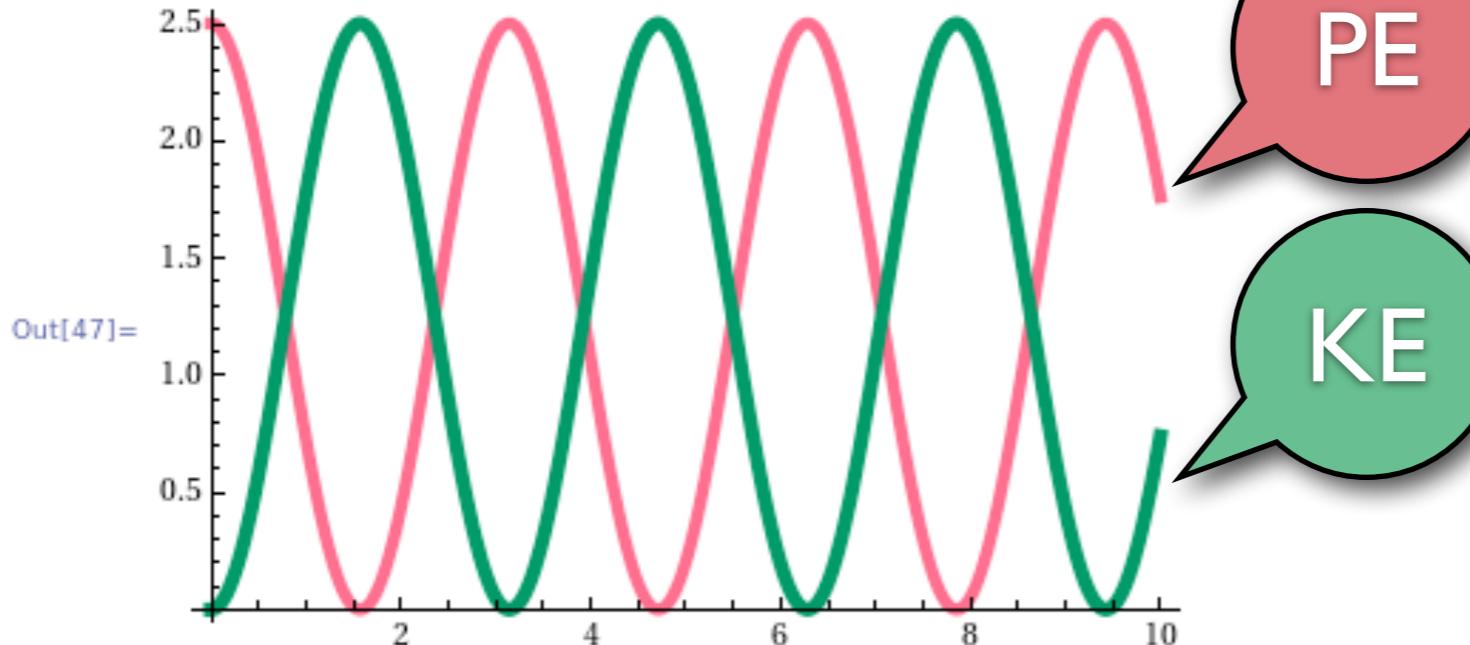
```
In[46]:= DSolve[{y'''[t] + y[t] == 0, z'''[t] + z[t] == 0, y[0] == 1, y'[0] == 0, z[0] == 2, z'[0] == 0}, {y, z}, t]
```

```
Out[46]= {{y → Function[{t}, Cos[t]], z → Function[{t}, 2 Cos[t]]}}
```

```
In[40]:= Plot[Evaluate[{y[t], z[t]} /. %], {t, 0, 10}]
```



```
In[47]:= Plot[Evaluate[{0.5*y[t]^2 + 0.5*z[t]^2, 0.5*y'[t]^2 + 0.5*z'[t]^2} /. %], {t, 0, 10}]
```



Harmonic oscillator example:
You can do this easily
(with paper-pencil or by Mathematica/Matlab)

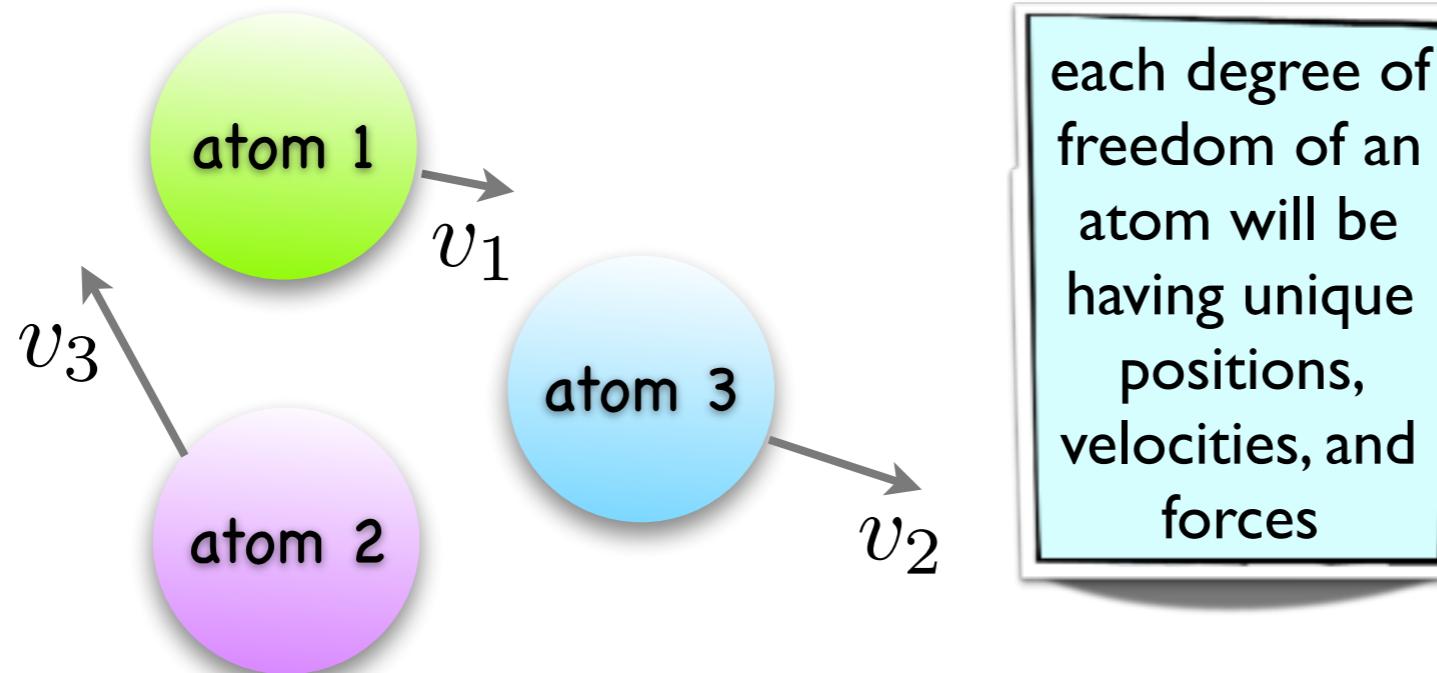
How about atoms?

- Classical mechanics? or quantum mechanics?
- It is a good assumption to treat the atomic motions classically

$$F_i = m_i \frac{d^2 x_i}{dt^2}$$

i=1,3N

N=number of particles



- Each degree of freedom has an equation of motion (classical) as you have seen for a 2D-harmonic oscillator (before)

For e.g. consider two atoms:

For atom 1

$$F_{x_1} = M_1 \frac{d^2 x_1}{dt^2}$$

$$F_{y_1} = M_1 \frac{d^2 y_1}{dt^2}$$

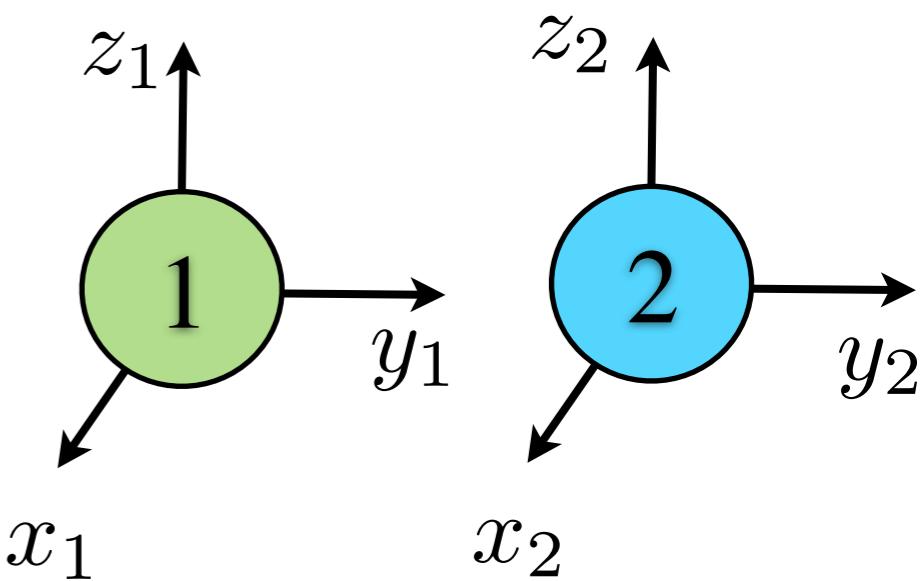
$$F_{z_1} = M_1 \frac{d^2 z_1}{dt^2}$$

For atom 2

$$F_{x_2} = M_2 \frac{d^2 x_2}{dt^2}$$

$$F_{y_2} = M_2 \frac{d^2 y_2}{dt^2}$$

$$F_{z_2} = M_2 \frac{d^2 z_2}{dt^2}$$



6 Eq. of motion to solve independently

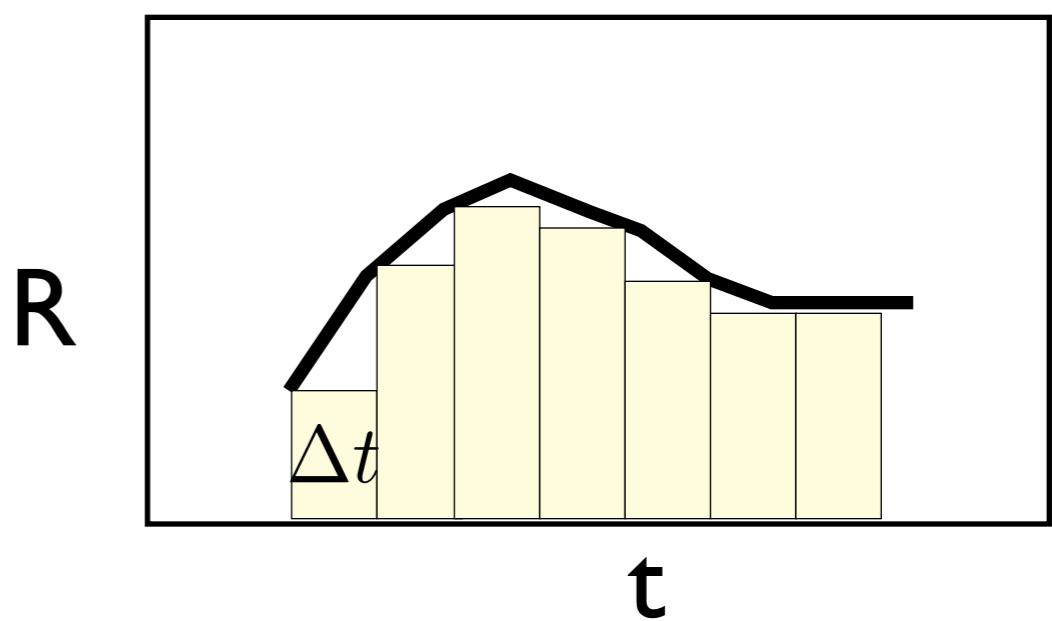
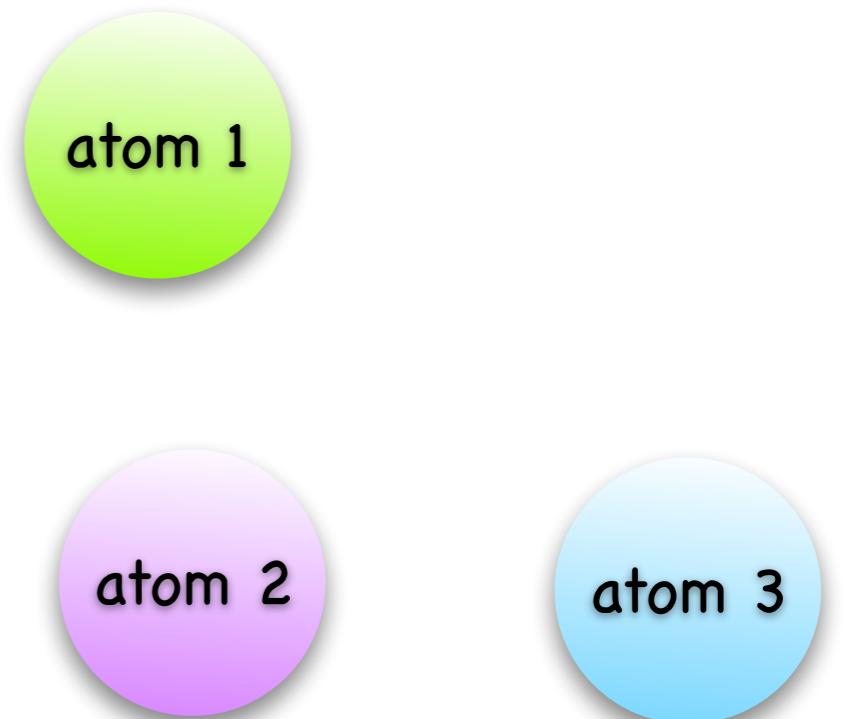
- The force acting on each degree of freedom of every atom has the information about the inter-atomic interactions
- Interatomic interactions are governed by the potential energy surface (as negative of the gradient of the potential energy is the force)

Numerical Integration

$$\mathbf{V}_I(t) = \mathbf{V}_I(0) + \int_0^t d\tau \frac{\mathbf{F}_I(\tau)}{M_I}$$

$$\mathbf{R}_I(t) = \mathbf{R}_I(0) + \int_0^t d\tau \mathbf{V}_I(\tau)$$

many body
interactions within the
force: numerical
integration is required



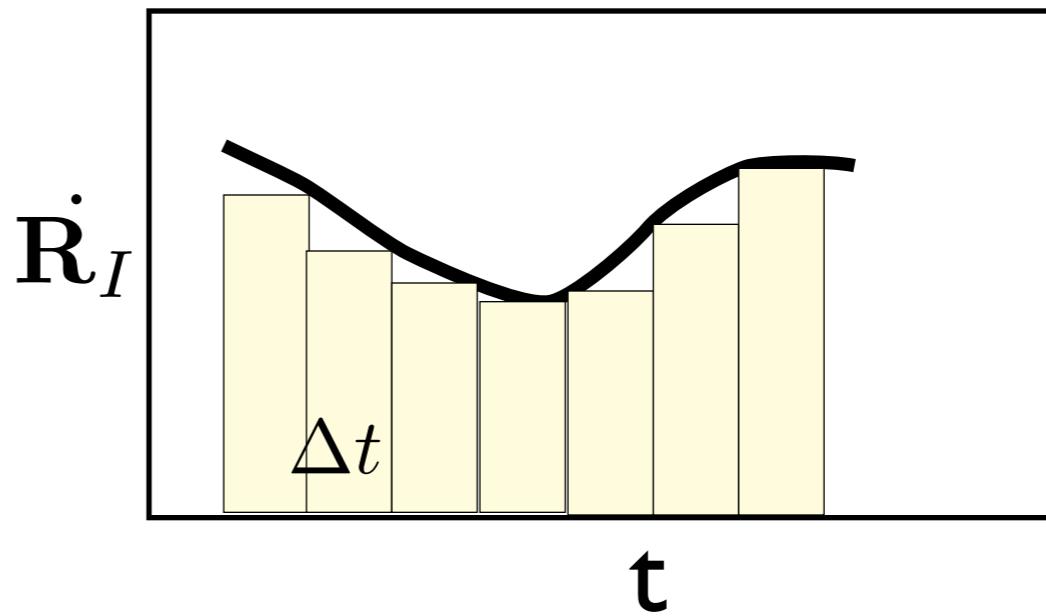
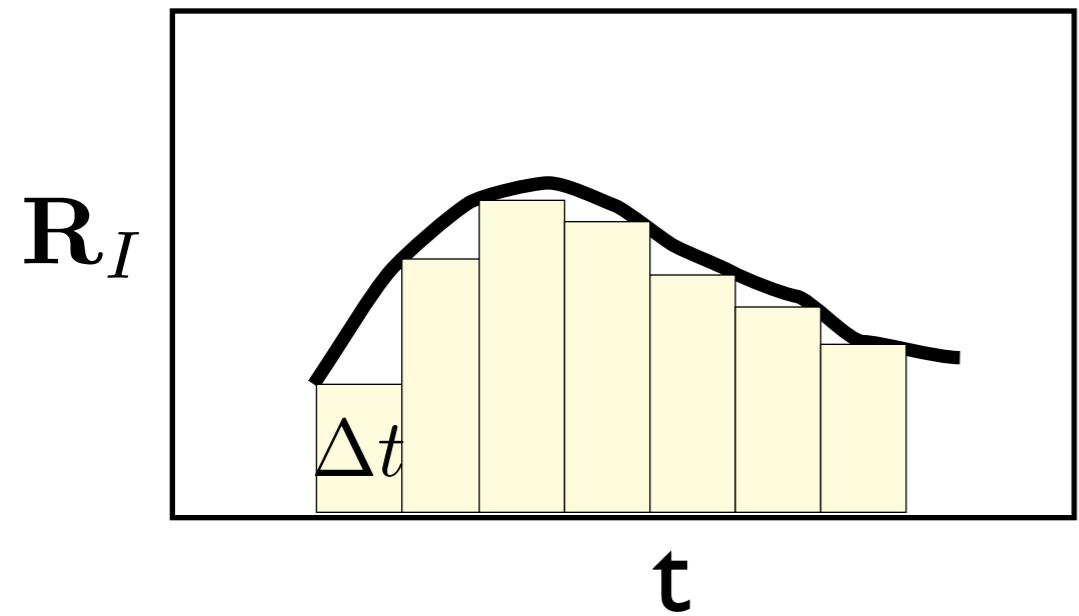
Velocity Verlet Algorithm

$$\mathbf{R}_I(t + \Delta t) = \mathbf{R}_I(t) + \dot{\mathbf{R}}_I(t)\Delta t + \frac{1}{2}\ddot{\mathbf{R}}_I(t)\Delta t^2 + \mathcal{O}(\Delta t^3)$$

$$U_{\text{LJ}} (\mathbf{R}_1(t), \dots, \mathbf{R}_N(t))$$

$$U_{\text{LJ}} (\mathbf{R}_1(t + \Delta t), \dots, \mathbf{R}_N(t + \Delta t))$$

$$\dot{\mathbf{R}}_I(t + \Delta t) = \dot{\mathbf{R}}_I(t) + \frac{\Delta t}{2} [\ddot{\mathbf{R}}_I(t) + \ddot{\mathbf{R}}_I(t + \Delta t)] + \mathcal{O}(\Delta t^2)$$



$\{\mathbf{R}_I(0), \dot{\mathbf{R}}_I(0)\}$ $\{\mathbf{R}_I(\Delta t), \dot{\mathbf{R}}_I(\Delta t)\}$ $\{\mathbf{R}_I(2\Delta t), \dot{\mathbf{R}}_I(2\Delta t)\}$

trajectory



History

- Alder & Wainwright
(JCP, 1957)

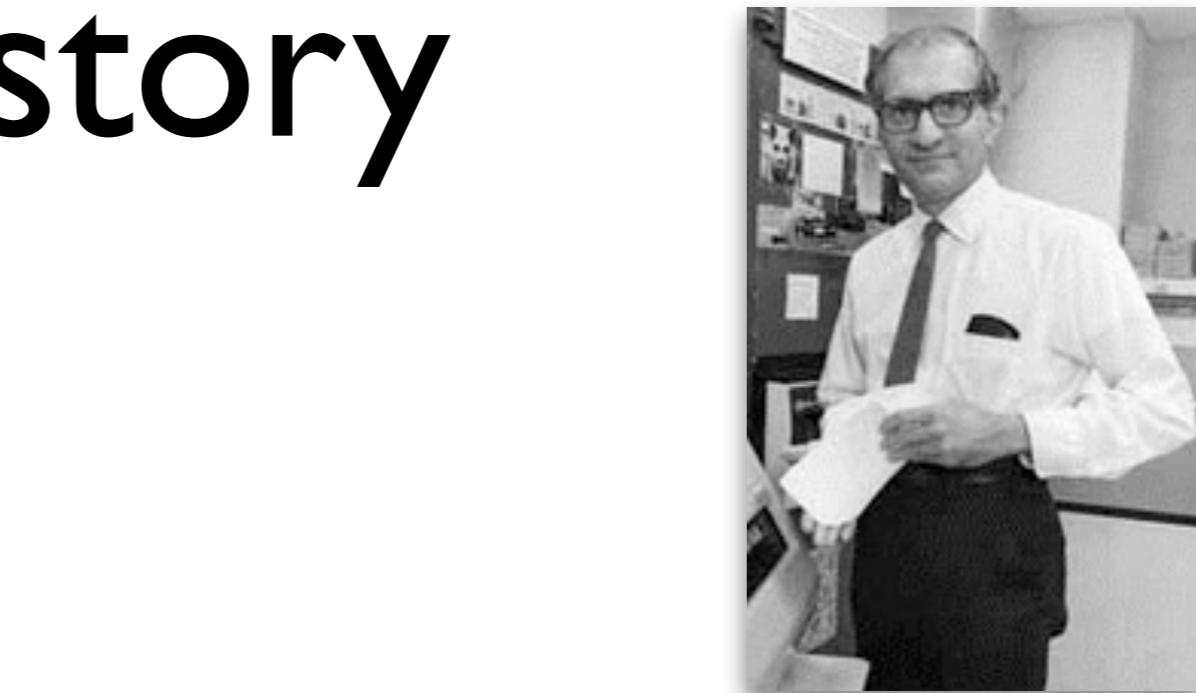
Phase Transition for a Hard Sphere System

B. J. ALDER AND T. E. WAINWRIGHT

University of California Radiation Laboratory, Livermore, California

(Received August 12, 1957)

A CALCULATION of molecular dynamic motion has been designed principally to study the relaxations accompanying various nonequilibrium phenomena. The method consists of solving exactly (to the number of significant figures carried) the simultaneous classical equations of motion of several hundred particles by means of fast electronic computers. Some of the details as they relate to hard spheres and to particles



- A. Rahman (Phys. Rev. 1964)

PHYSICAL REVIEW

VOLUME 136, NUMBER 2A

19 OCTOBER 1964

Correlations in the Motion of Atoms in Liquid Argon*

A. RAHMAN

Argonne National Laboratory, Argonne, Illinois

(Received 6 May 1964)

A system of 864 particles interacting with a Lennard-Jones potential and obeying classical equations of motion has been studied on a digital computer (CDC 3600) to simulate molecular dynamics in liquid argon at 94.4°K and a density of 1.374 g cm⁻³. The pair-correlation function and the constant of self-diffusion are found to agree well with experiment; the latter is 15% lower than the experimental value. The spectrum of the velocity autocorrelation function shows a broad maximum in the frequency region $\omega = 0.25(k_B T/\hbar)$. The shape of the Van Hove function $G_s(r,t)$ attains a maximum departure from a Gaussian at about $t = 3.0 \times 10^{-12}$ sec and becomes a Gaussian again at about 10^{-11} sec. The Van Hove function $G_d(r,t)$ has been compared with the convolution approximation of Vineyard, showing that this approximation gives a too rapid decay of $G_d(r,t)$ with time. A delayed-convolution approximation has been suggested which gives a better fit with $G_d(r,t)$; this delayed convolution makes $G_d(r,t)$ decay as t^4 at short times and as t at long times.

first MD

first realistic MD



History

- Liquid Water Simulation
(Stillinger & Rahman, 1974)

JOURNAL OF CHEMICAL PHYSICS VOLUME 55, NUMBER 7 1 OCTOBER 1971

Molecular Dynamics Study of Liquid Water*

ANNE SUR RAHMAN

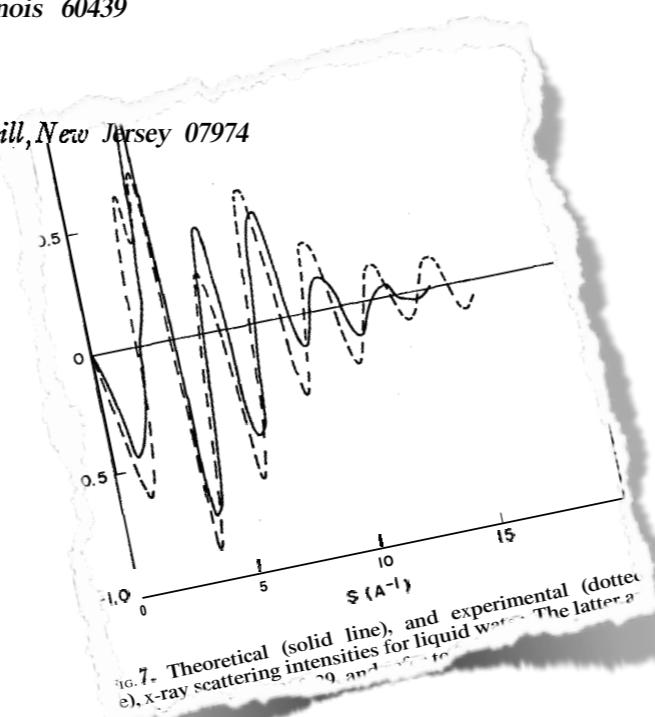
Argonne National Laboratory, Argonne, Illinois 60439

AND

FRANK H. STILLINGER

Bell Telephone Laboratories, Incorporated, Murray Hill, New Jersey 07974

(Received 6 May 1971)



Nature 267, 585 - 590 (16 June 1977); doi:10.1038/267585a0

Dynamics of folded proteins

J. Andrew McCammon, Bruce R. Gelin & Martin Karplus

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

The dynamics of a folded globular protein (bovine pancreatic trypsin inhibitor) have been studied by solving the equations of motion for the atoms with an empirical potential energy function. The results provide the magnitude, correlations and decay of fluctuations about the average structure. These suggest that the protein interior is fluid-like in that the local atom

MD & expt

MD for bio!

MD Algorithm

$$\mathbf{R}_I(t + \Delta t) = \mathbf{R}_I(t) + \dot{\mathbf{R}}_I(t)\Delta t + \frac{1}{2}\ddot{\mathbf{R}}_I(t)\Delta t^2$$

$$\dot{\mathbf{R}}_I(t + \Delta t) = \dot{\mathbf{R}}_I(t) + \frac{\Delta t}{2} [\ddot{\mathbf{R}}_I(t) + \ddot{\mathbf{R}}_I(t + \Delta t)]$$

- 
- a) Initialize coordinates and velocities & compute force
 - b) Velocity Verlet-1: $\mathbf{R}(t) \rightarrow \mathbf{R}(t+\Delta t)$
 - c) Compute force (acceleration) for $\mathbf{R}(t+\Delta t)$
 - d) Velocity Verlet-2: $\mathbf{V}(t) \rightarrow \mathbf{V}(t+\Delta t)$
 - e) Go to step (b) or stop

Time Step

fastest motion
determines the
time step

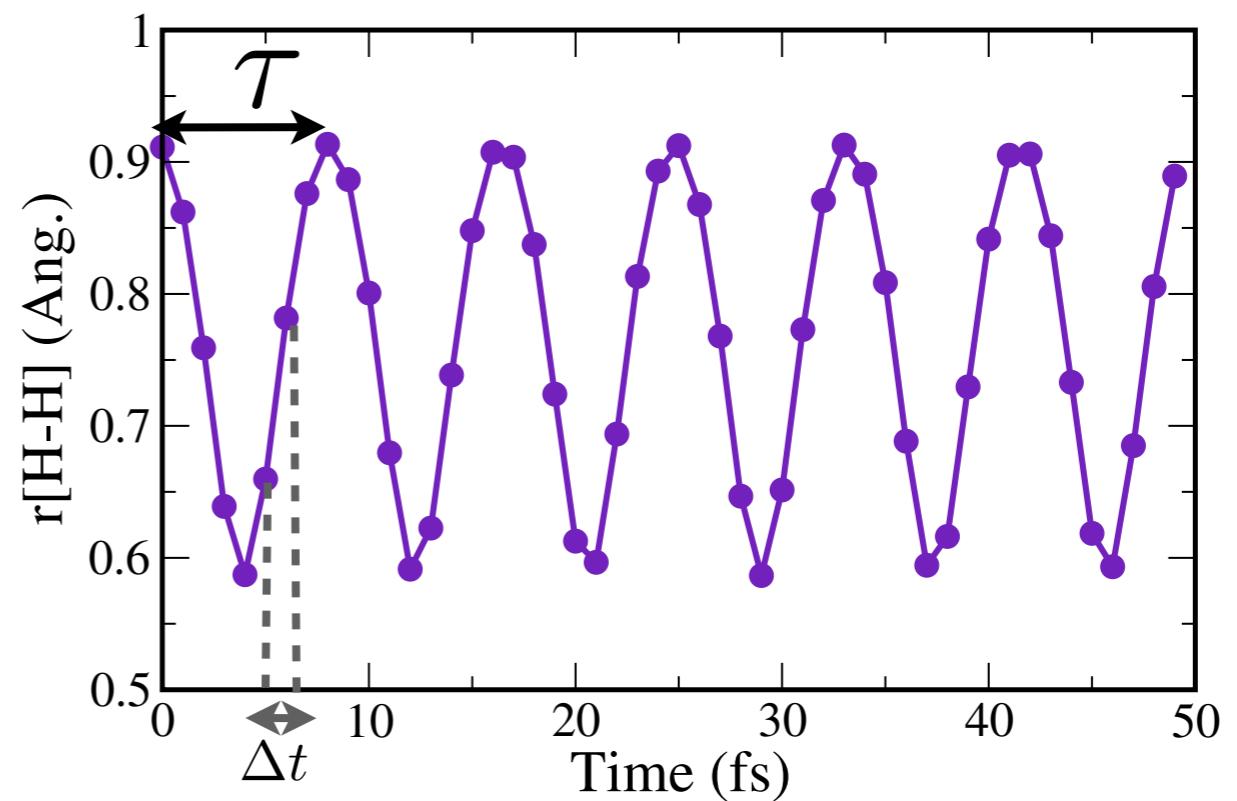
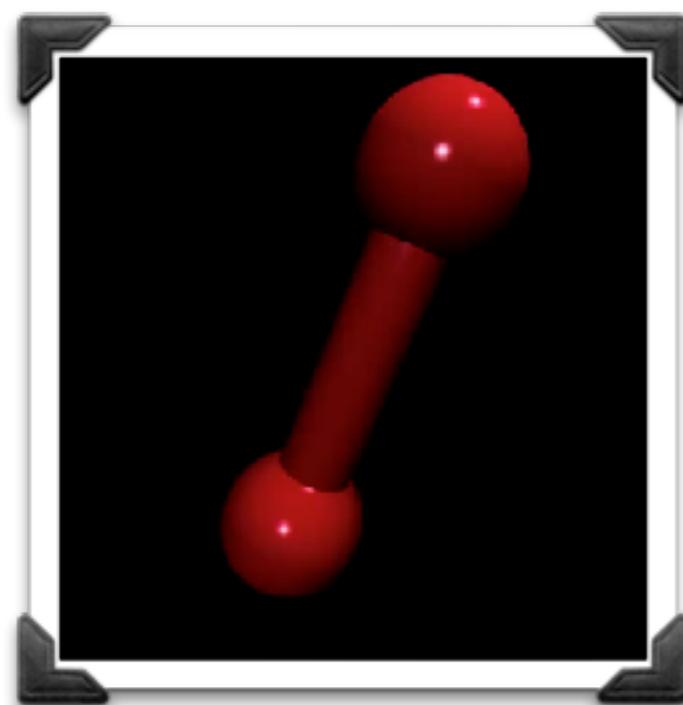
$$\nu = \frac{1}{\tau} = c\bar{\nu}$$

vibrational freq. of H_2 : $\bar{\nu} = 4000 \text{ cm}^{-1}$

period of oscillation of H_2 : $\Rightarrow \tau = 8.33 \times 10^{-15} \text{ s} \approx 10 \text{ fs}$

Time step should at least (equally) divide a period
for better capture of the features of the dynamics

$$\Delta t \approx \tau/10 = 1 \text{ fs}$$



Initial State

- **Initial coordinates:** X-ray structure, chemical intuition, arbitrary/random structures
- **Initial velocities:** from Boltzmann distribution of velocities for a given initial temperature $T_0 \rightarrow$ this can be generated from Box-Muller sampling (see next page)

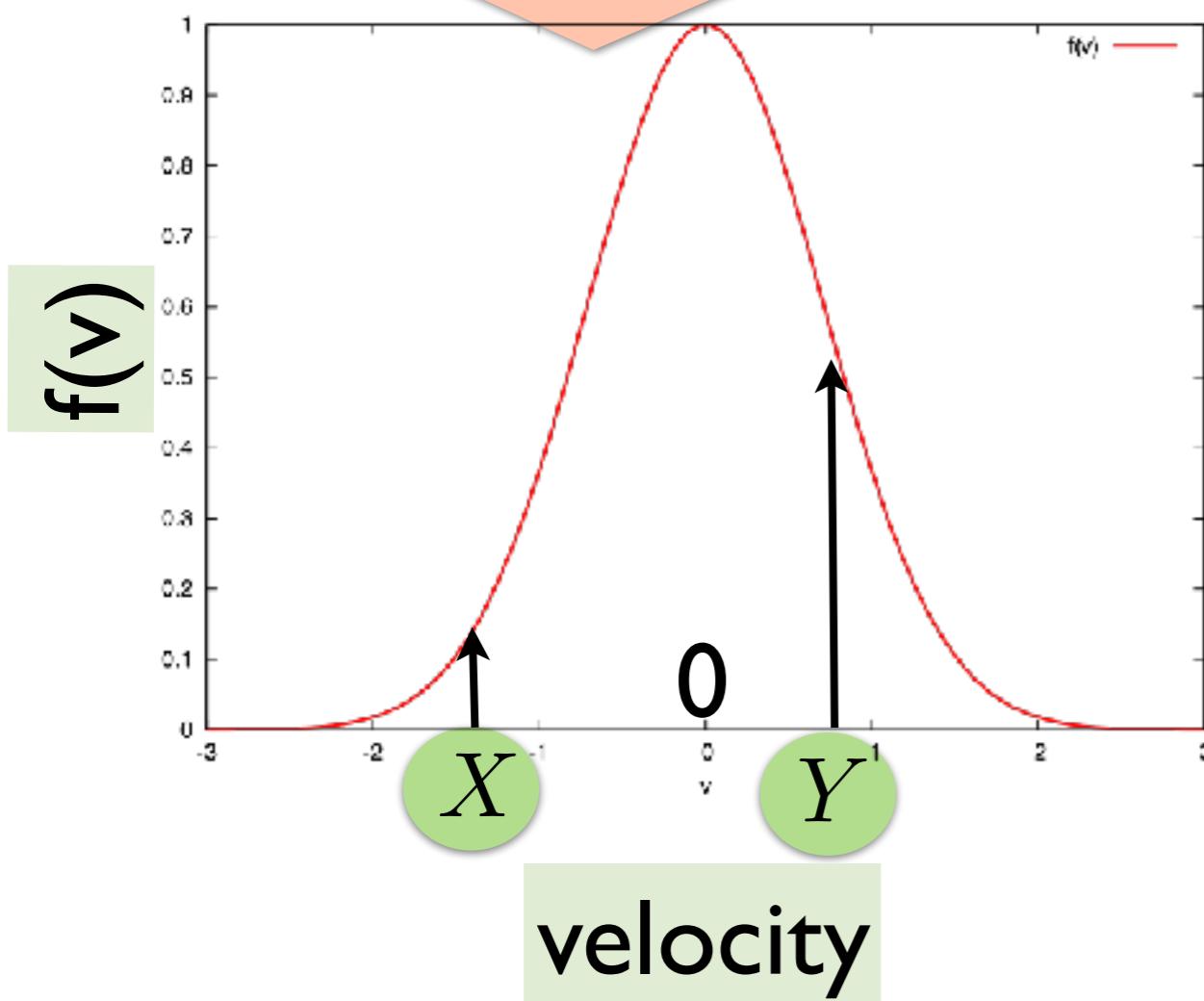
Box-Muller Sampling

Maxwell distribution of velocities:

$$f(v) = \left(\frac{M}{2\pi k_B T} \right)^{1/2} \exp \left(-\frac{Mv^2}{2k_B T} \right)$$

all quantities are known for a given system; M is the mass of an atom

This is a gaussian with standard deviation $\sigma = \sqrt{k_B T/M}$



uniform rand.
numbers
between 0 & 1

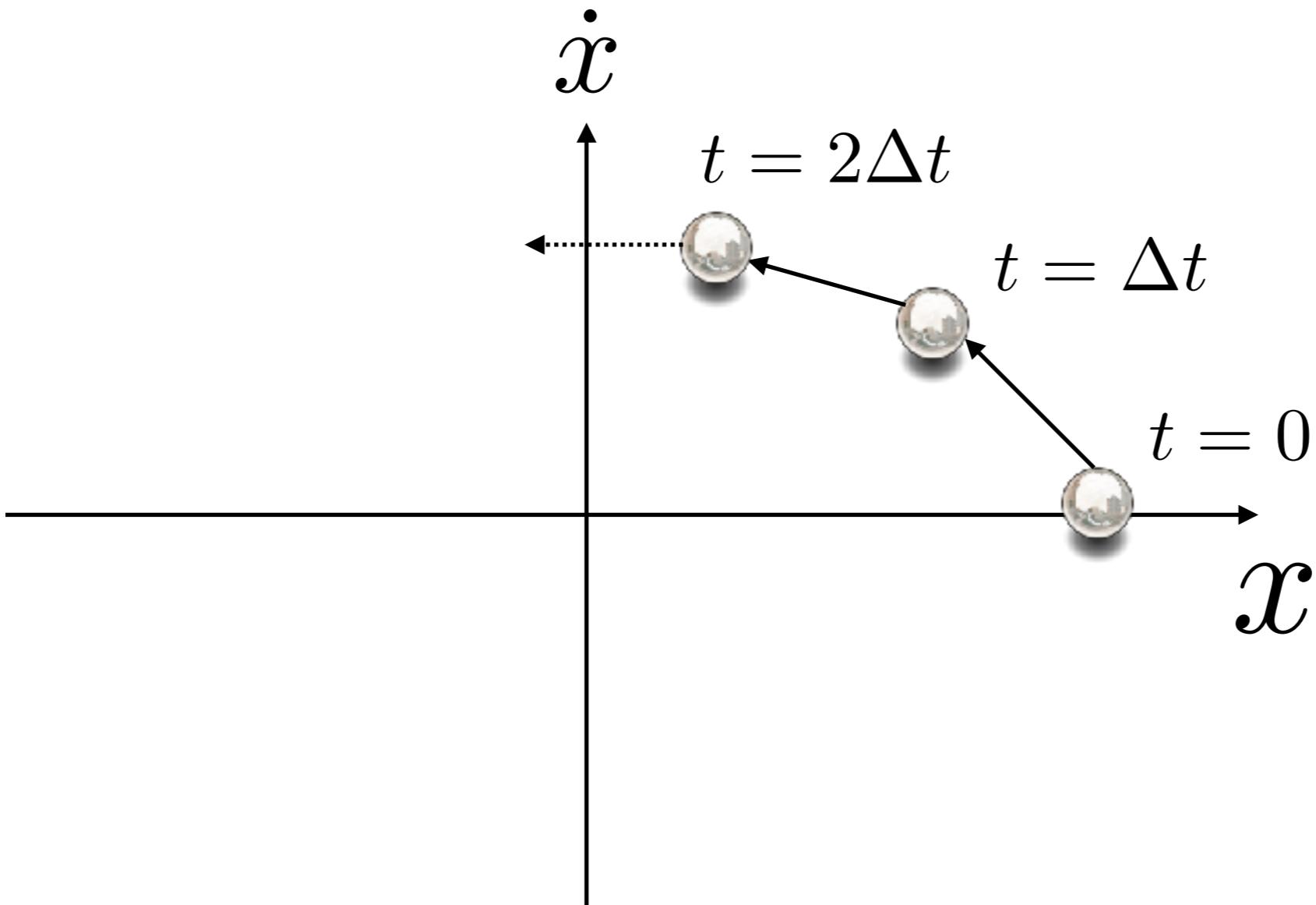
$$X = \sigma \sqrt{-2 \ln \xi'_2} \cos(2\pi\xi_1)$$

$$Y = \sigma \sqrt{-2 \ln \xi'_2} \sin(2\pi\xi_1)$$

X and Y are two random velocities obtained by picking randomly from the distribution $f(v)$

- If you have two atoms, we require 6 values of velocities (each for a degree of freedom)
- For this, we generate 6 uniform random numbers from computers: ξ_1, \dots, ξ_6
- Substituting these random numbers in the two Box-Muller equations above [a pair at a time], we obtain, 6 values for velocities (with a probability according to Boltzman distribution): $X_1, Y_1, X_2, Y_2, X_3, Y_3$
- Assign these values of X and Y to each degree of freedom (in any order that you like)

- In other words, if we take a histogram (or distribution) of all the velocities $\{X, Y\}$, generated using Box-Muller sampling, we will get a Boltzmann distribution



Phase space: vector space of positions and velocities

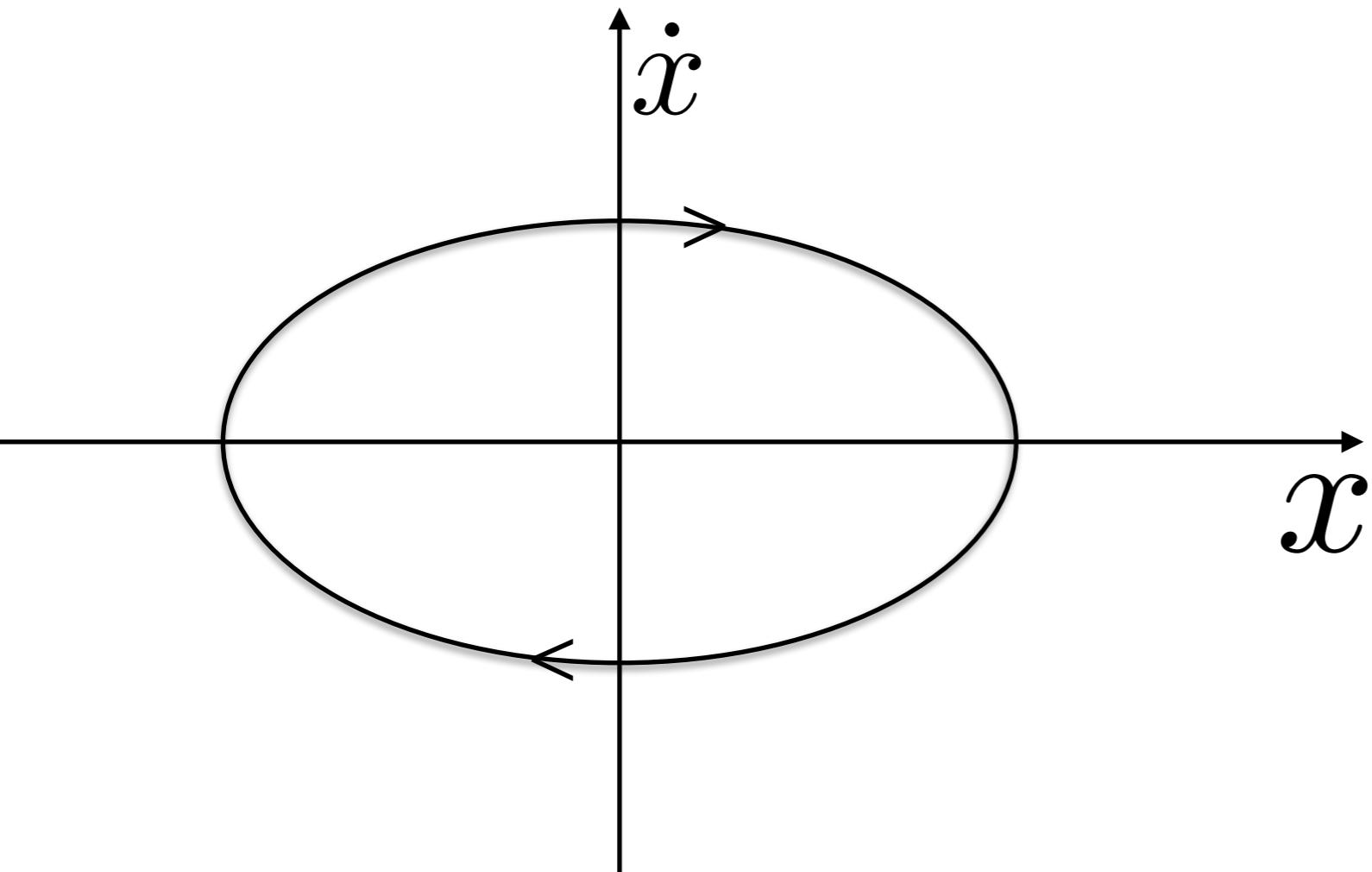
Trajectory along the phase space: set of positions and momentum obtained by integration of EOMs

Phase space of a 1D Harmonic Oscillator

Remember: total energy will be conserved here:

$$E = \frac{1}{2}m\dot{x}(t)^2 + \frac{1}{2}m\omega^2x(t)^2$$

Show that it is an ellipse.



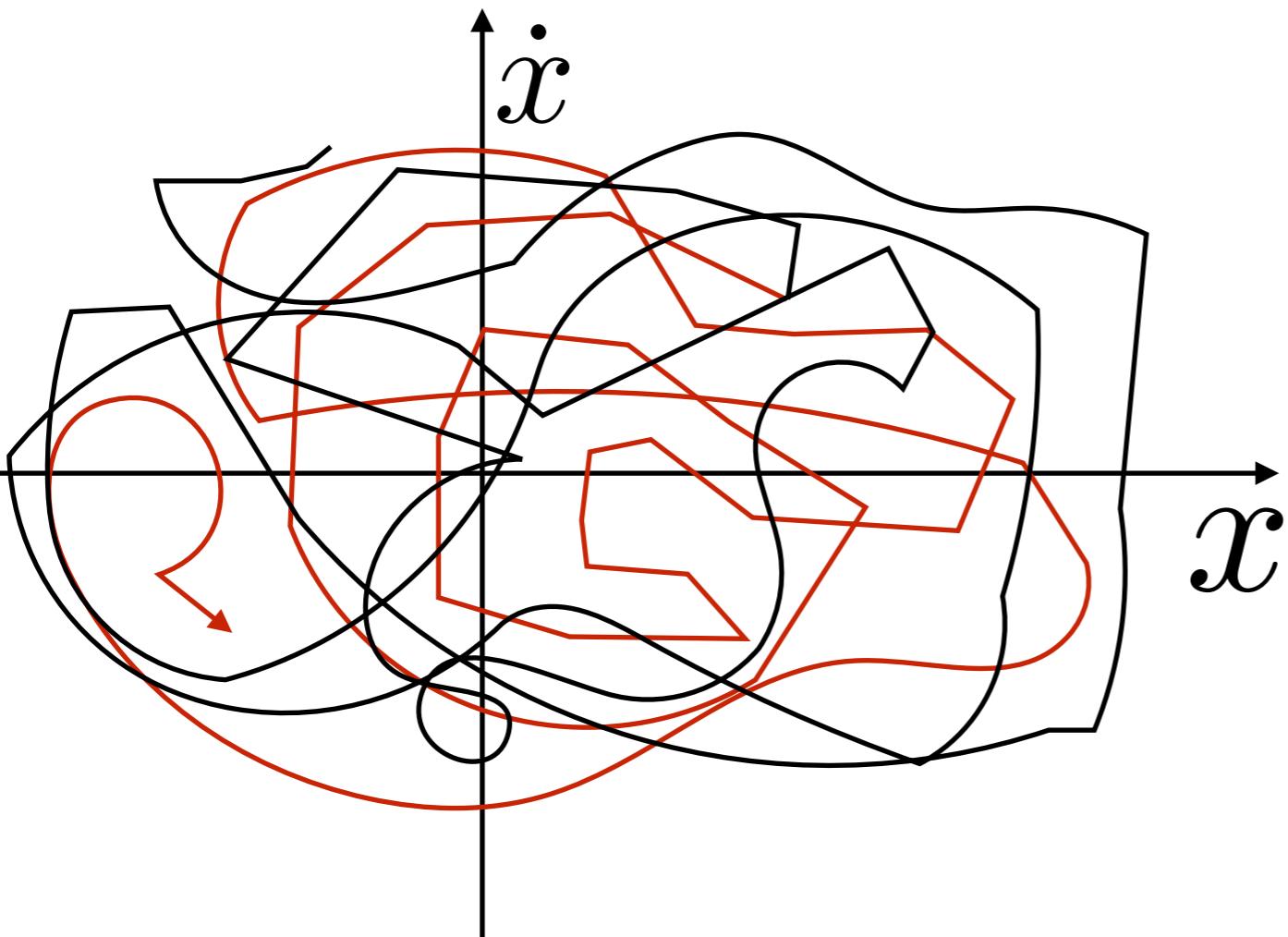
When will it be a circle?

What is the area of the ellipse signify here?

What about the directions of arrows?

Ensemble

Different (microscopic) trajectories (due to different initial conditions), but giving same macroscopic property
(For e.g. same total energy)



Collection of all possible trajectories with same macroscopic properties is an “**ensemble**”

Ensemble average

$$A = \frac{1}{\mathcal{N}} \sum_i a_i$$

number of members of the ensemble

microscopic
property

The diagram consists of two arrows. One arrow points from the text "number of members of the ensemble" to the fraction $\frac{1}{\mathcal{N}}$. Another arrow points from the text "microscopic property" to the term a_i .

E.g.: NVE or micro canonical ensemble
NVT or canonical ensemble

Lagrangian Formulation of Classical Mechanics

Lagrangian:

$$\mathcal{L}(\mathbf{R}^N, \dot{\mathbf{R}}^N) = K(\dot{\mathbf{R}}^N) - U(\mathbf{R}^N)$$

remember
this eqn.

Euler Lagrange Equation:

$$\frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{\mathbf{R}}_I} \right) - \frac{\partial \mathcal{L}}{\partial \mathbf{R}_I} = 0$$

remember
this eqn.

$$\frac{\partial \mathcal{L}}{\partial \dot{\mathbf{R}}_I} = \frac{\partial}{\partial \dot{\mathbf{R}}_I} \left(\frac{1}{2} \sum_I^N M_I \dot{\mathbf{R}}_I^2 \right) \\ = M_I \ddot{\mathbf{R}}_I$$

$$\frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{\mathbf{R}}_I} \right) = M_I \ddot{\mathbf{R}}_I$$

$$\frac{\partial \mathcal{L}}{\partial \mathbf{R}_I} = - \frac{\partial U}{\partial \mathbf{R}_I}$$

$$= \mathbf{F}_I$$

Then,

$$\frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{\mathbf{R}}_I} \right) - \frac{\partial \mathcal{L}}{\partial \mathbf{R}_I} = M_I \ddot{\mathbf{R}}_I - \mathbf{F}_I \\ = 0$$

$$\frac{dE}{dt} = \frac{d}{dt} \left[\sum_{I=1}^N \frac{1}{2} M_I \dot{\mathbf{R}}_I^2 + U(\mathbf{R}^N) \right]$$

$$= \sum_{I=1}^N M_I \dot{\mathbf{R}}_I \cdot \ddot{\mathbf{R}}_I + \sum_{I=1}^N \frac{dU}{d\mathbf{R}_I} \cdot \frac{d\mathbf{R}_I}{dt}$$

$$= \sum_{I=1}^N \dot{\mathbf{R}}_I \cdot [M_I \ddot{\mathbf{R}}_I - \mathbf{F}_I]$$

$$= 0$$

Total energy conservation