# Chemical dynamics & molecular interaction

overall goal: micro to macro

molecular structure

quantum mechanics

molecular interactions

quantum mechanics

molecular dynamics

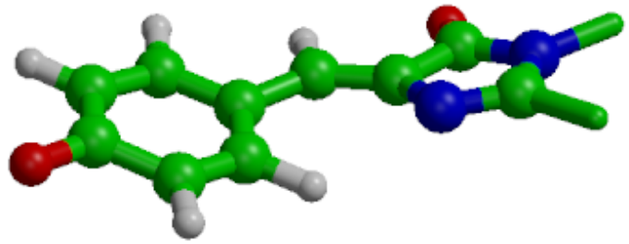
sampling

configuration space

partition functions

statistical thermodynamics

free energy



# Chemical dynamics & molecular interaction

overall goal: micro to macro

molecular structure

quantum mechanics

molecular interactions

quantum mechanics

molecular dynamics

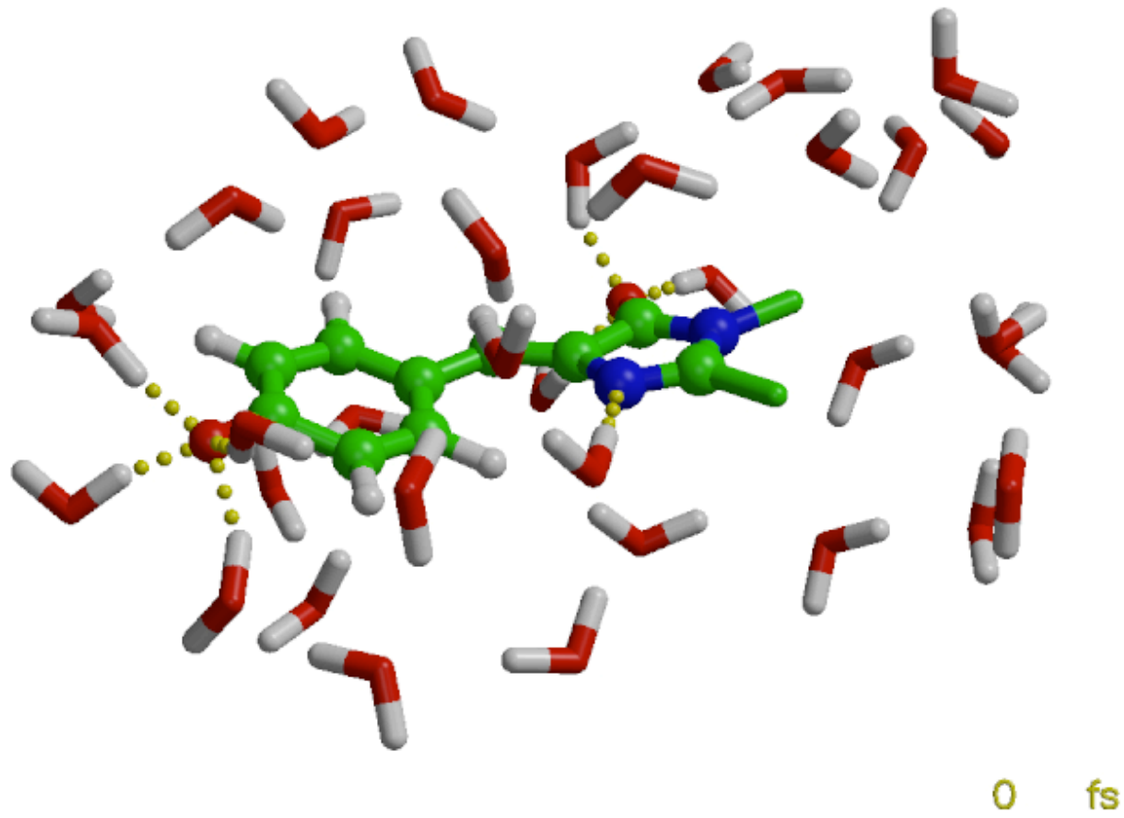
sampling

configuration space

partition functions

statistical thermodynamics

free energy



# Chemical dynamics & molecular interaction

overall goal: micro to macro

molecular structure

quantum mechanics

molecular interactions

quantum mechanics

molecular dynamics

sampling

configuration space

partition functions

statistical thermodynamics

free energy

thermodynamics

molecule-free

# Chemical dynamics & molecular interaction

two options

basic: 3 credits

lectures

homework exercises

exam

advanced: 3 additional credits

project

written report

oral presentation

# Chemical dynamics & molecular interaction

content (could be changed still)

I thermodynamics refresher

equation of state of ideal gas

first & second laws of thermodynamics

Carnot engine

'discovery' of entropy

demonstration (maybe)

efficiency of steam engine

molecule-free

# Chemical dynamics & molecular interaction

content (could be changed still)

## 2 statistical mechanics/thermodynamics

from micro (molecules) to macro (bulk)

micro state

macro sate

statistical weight

Boltzman definition of entropy

partition function

free energy

ensembles

micro-canonical

canonical

grand-canonical

# Chemical dynamics & molecular interaction

content (could be changed still)

## 3. molecular interactions

### intramolecular interactions

### intermolecular interactions

electrostatic

dispersion

hydrogen bonds

### evaluating intermolecular interactions

Ewald summation: energy of crystal

### partition function

classical statistics

phase space

# Quantum Mechanics (KEMS406)

lecture 3:

## Dirac quantum conditions

### Poisson bracket

free energy

equilibrium constant

### rates

reaction coordinates

Arrhenius' law

Eyring's transition state theory

Krames' theory

# Chemical dynamics & molecular interaction

content (could be changed still)

5. difficult stuff

quantum statistics

black body radiation

hydrophobic effect

self-aggregation

fluctuations & non-equilibrium processes

jarzynski/Crooks theorema

....

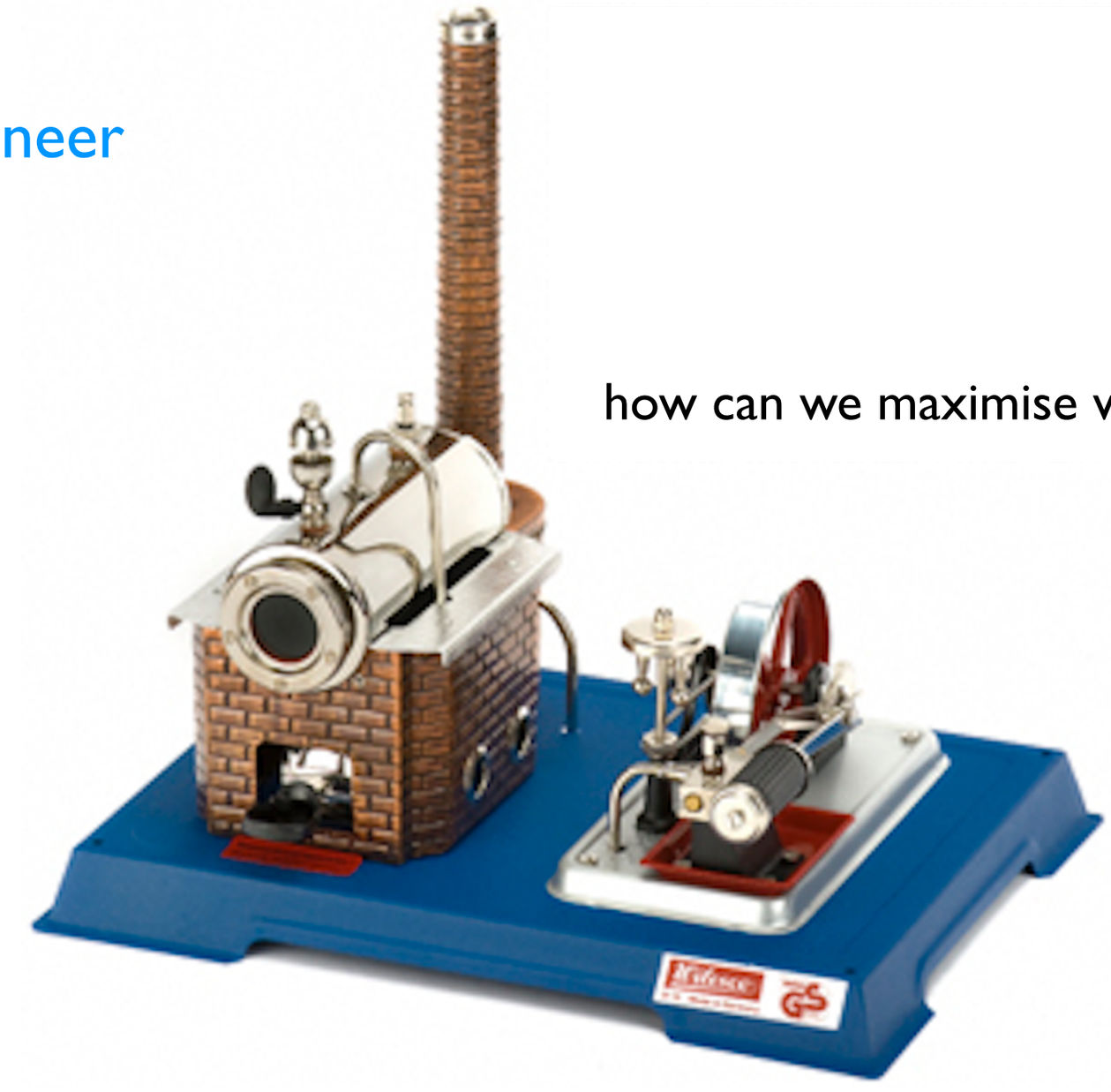
# Thermodynamics

first law: conservation of energy

second law: direction of spontaneous change

important

if you're an engineer



how can we maximise work?

$$(-W_{\mathrm{u}}) \leq -\Delta A = -\left[\Delta U - T\Delta S\right]$$

# Thermodynamics

## Helmholtz free energy

internal energy

entropy

$$A = U - TS$$

extensive properties

# Thermodynamics

## Helmholtz free energy

internal energy

entropy

$$A = U - TS$$

extensive properties

chemical/physical change at constant temperature

$$\Delta A = \Delta U - T\Delta S \qquad \Delta A = -T\Delta S^{\mathrm{tot}}$$

spontaneous

$$\Delta A < 0$$

equilibrium

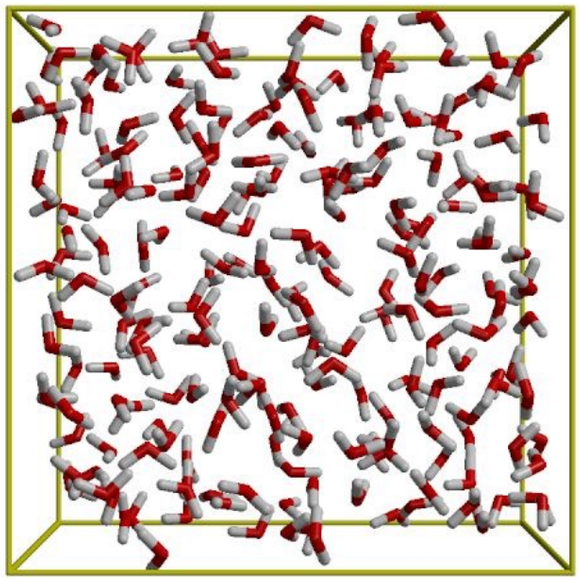
$$\Delta A = 0$$

# Thermodynamics

## entropy of isolated system

### micro-states (realisations)

### box with 216 waters:



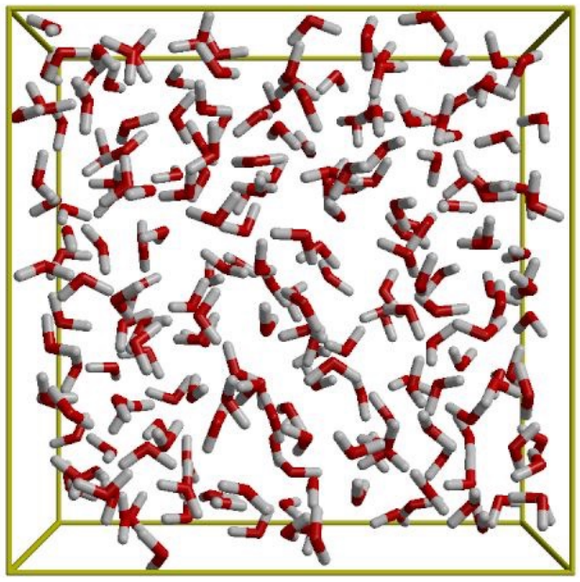
microstate 1

# Thermodynamics

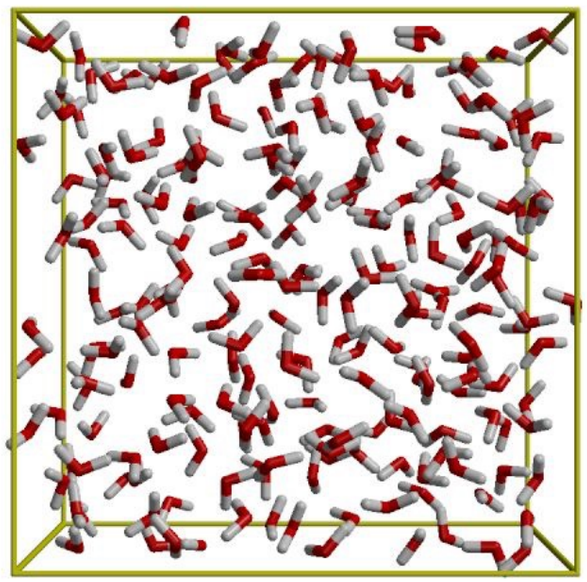
entropy of isolated system

micro-states (realisations)

box with 216 waters:



microstate 1



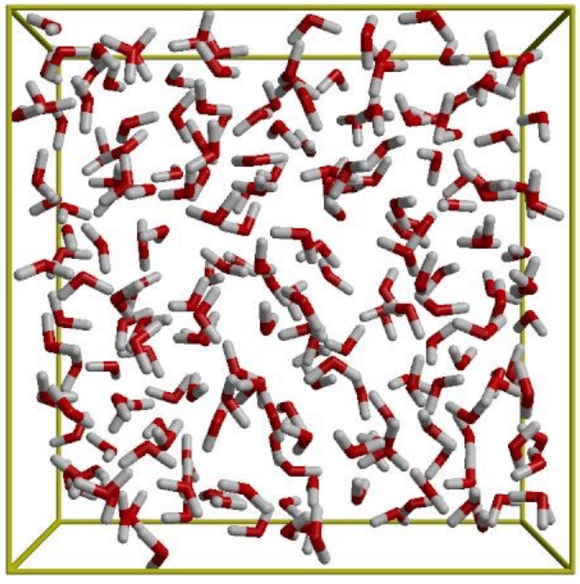
microstate 2

# Thermodynamics

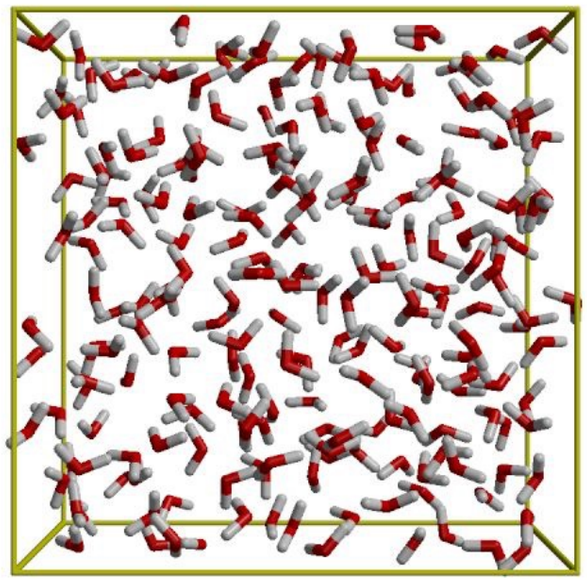
## entropy of isolated system

### micro-states (realisations)

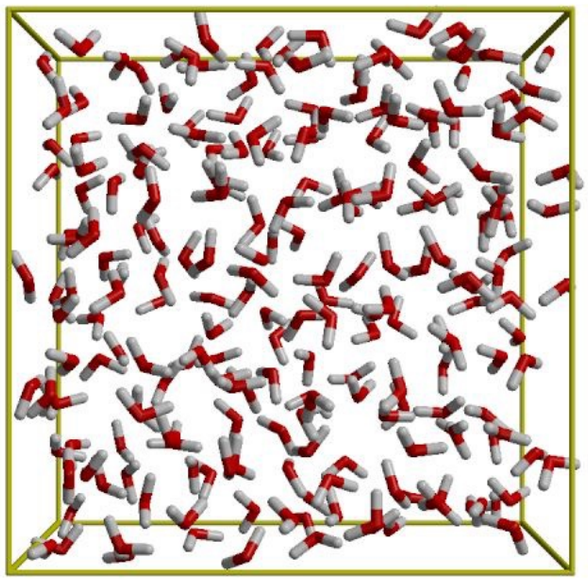
### box with 216 waters:



microstate 1



microstate 2



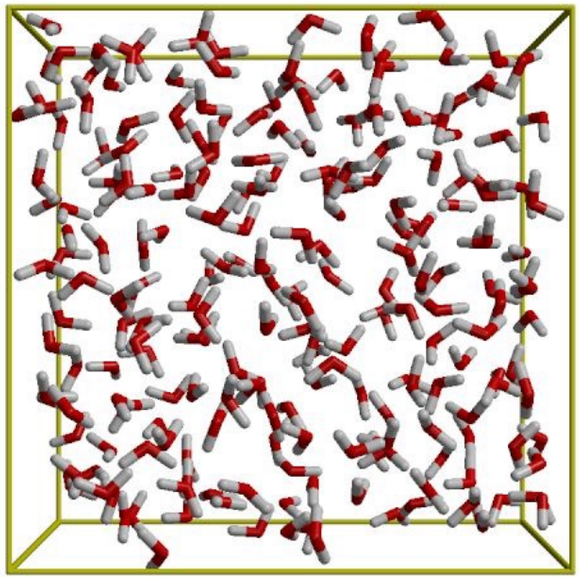
microstate 3

# Thermodynamics

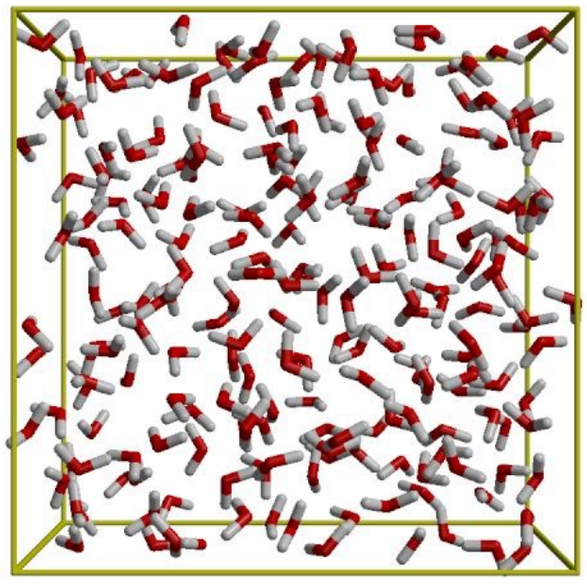
## entropy of isolated system

### micro-states (realisations)

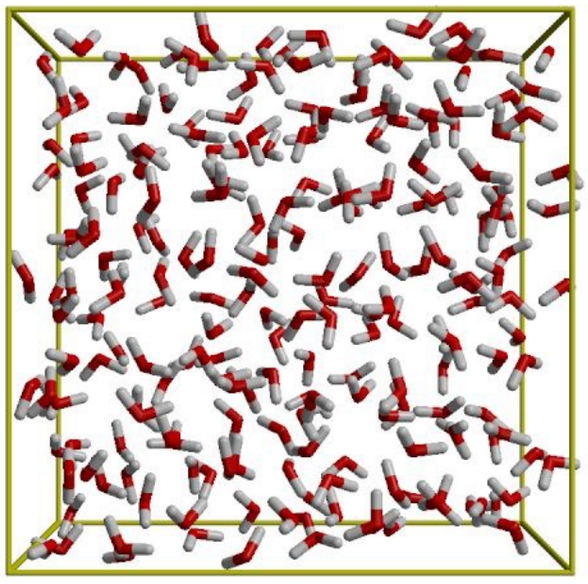
### box with 216 waters:



microstate 1



microstate 2



microstate 3

### total number of micro-states (realisations)

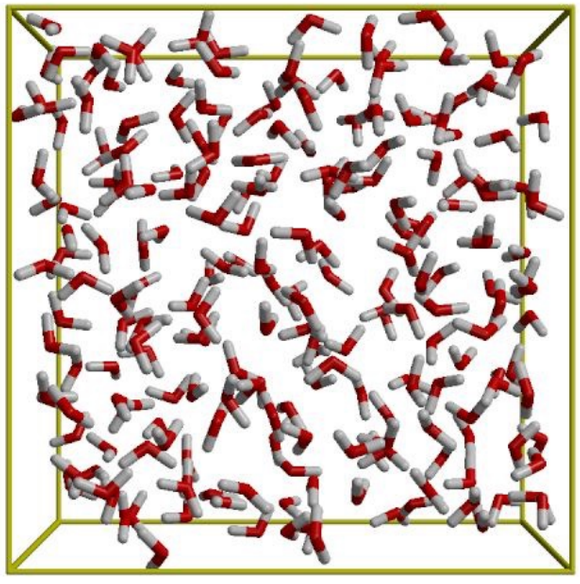
$\Omega$

# Thermodynamics

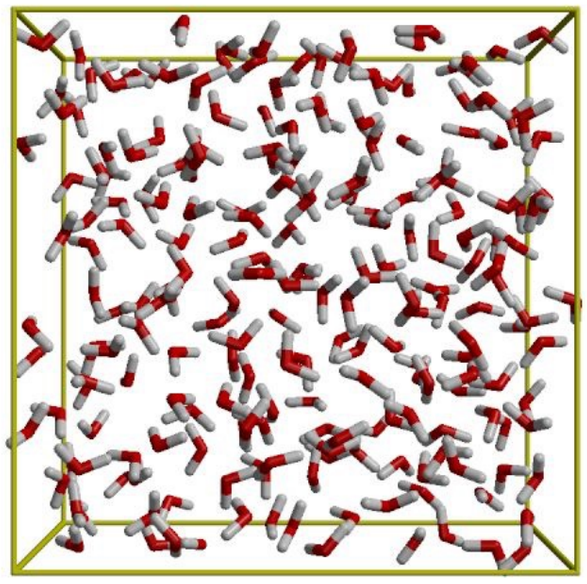
## entropy of isolated system

### micro-states (realisations)

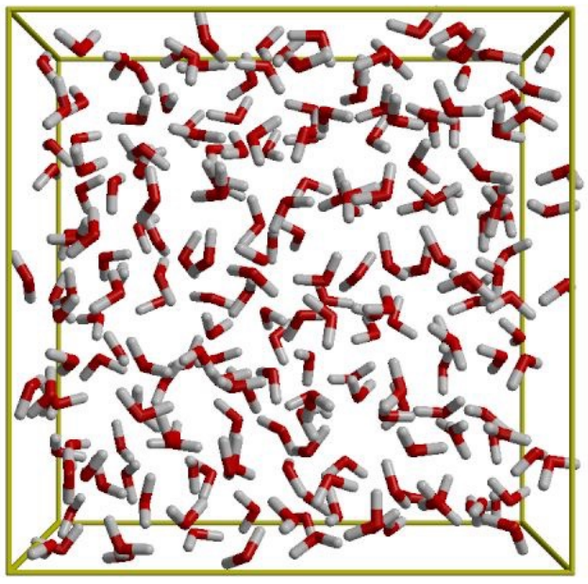
### box with 216 waters:



microstate 1



microstate 2



microstate 3

### total number of micro-states (realisations)

$\Omega$

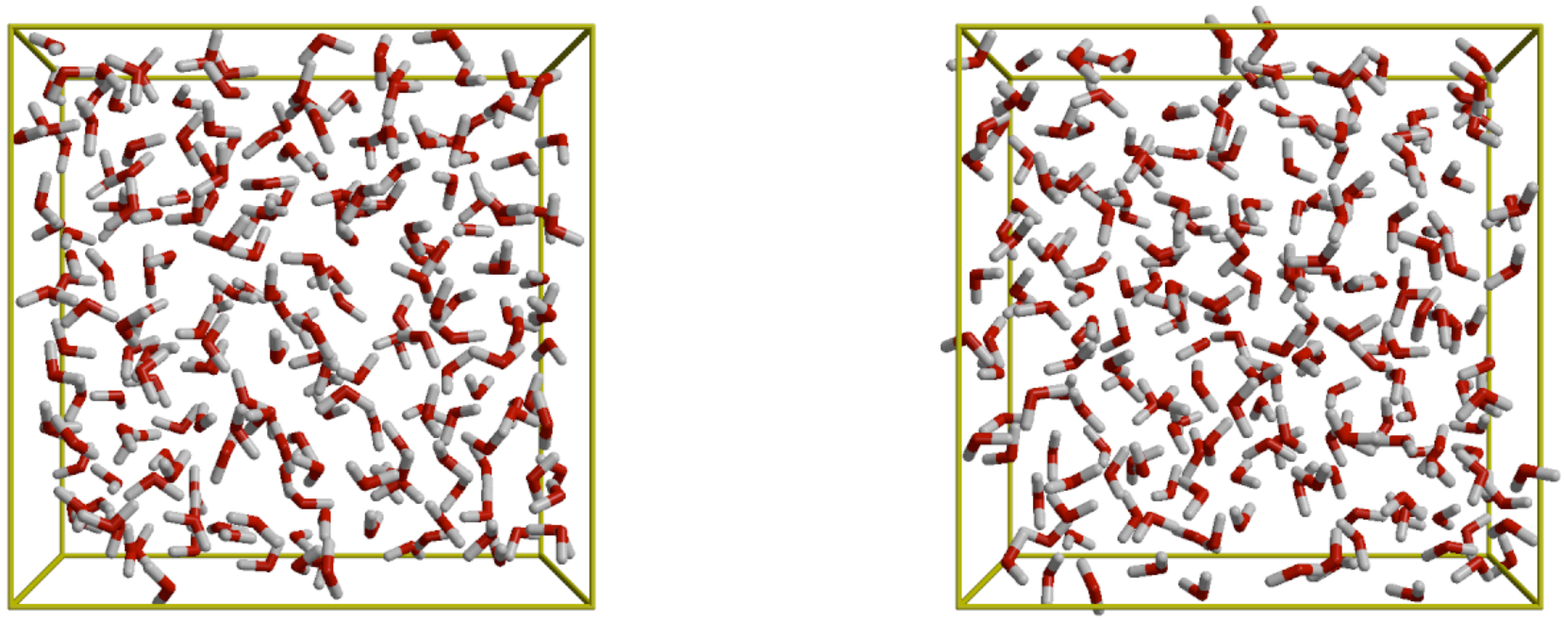
if you know how many, you pass the course today!

# Thermodynamics

## entropy of isolated system

### micro-states (realisations)

### two boxes of water:



box 1 box 2

### total number of micro states (realisations)

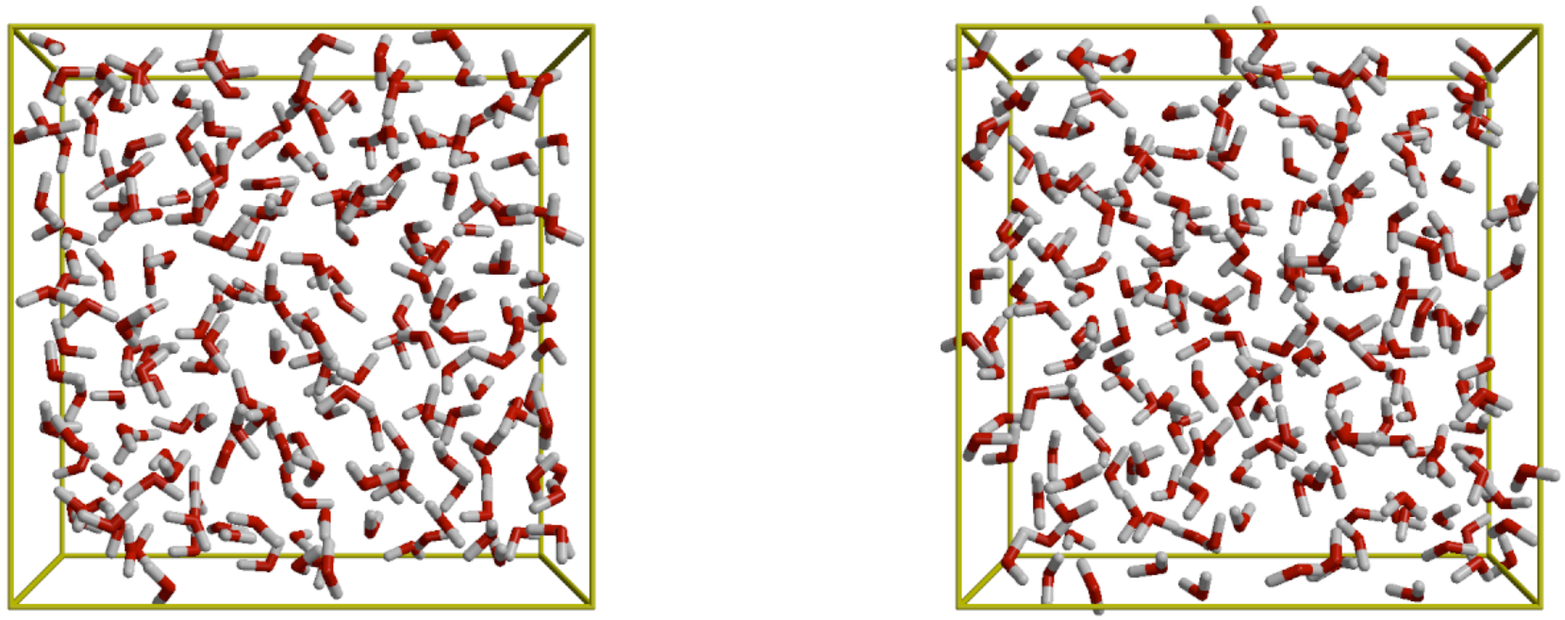
$$\Omega^{\mathrm{tot}} =$$

# Thermodynamics

## entropy of isolated system

### micro-states (realisations)

### two boxes of water:



box 1



box 2

### total number of micro states (realisations)

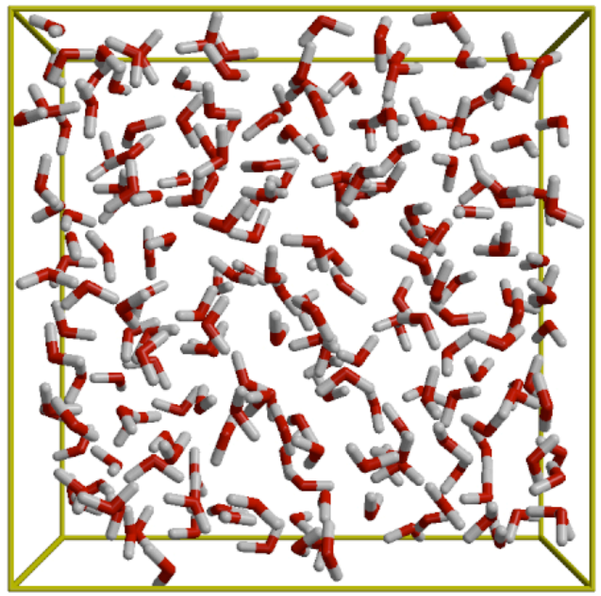
$$\Omega^{\mathrm{tot}} = \Omega_1 \cdot \Omega_2$$

# Thermodynamics

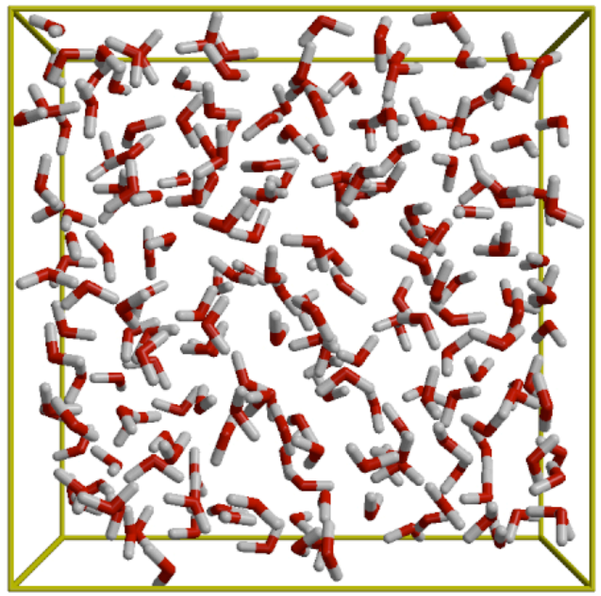
## entropy of isolated system

### micro-states (realisations)

### two boxes of water:



box 1



box 2

### total number of micro states (realisations)

$$\Omega^{\mathrm{tot}} = \Omega_1 \cdot \Omega_2$$

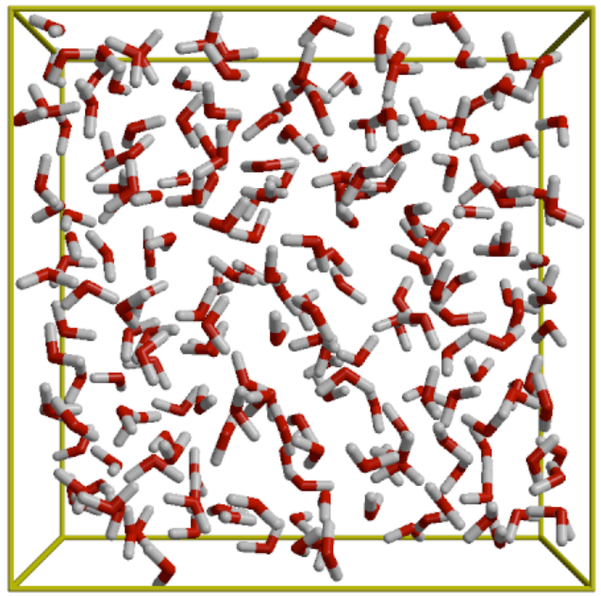
### entropy is extensive, so should be sum:

# Thermodynamics

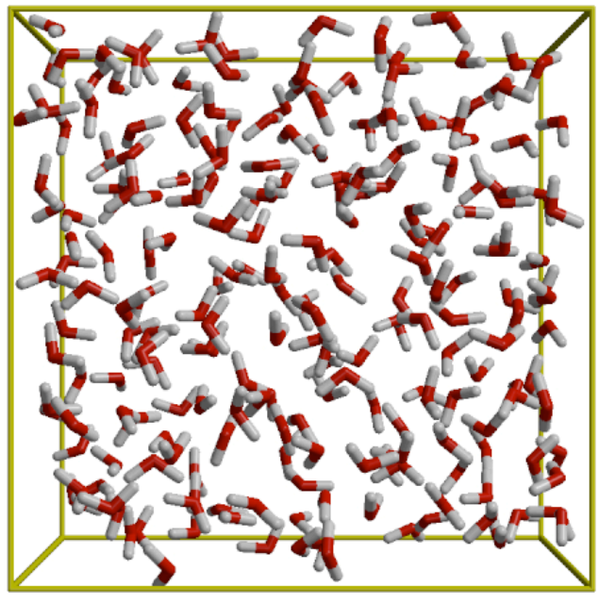
## entropy of isolated system

### micro-states (realisations)

### two boxes of water:



box 1



box 2

### total number of micro states (realisations)

$$\Omega^{\mathrm{tot}} = \Omega_1 \cdot \Omega_2$$

### entropy is extensive, so should be sum:

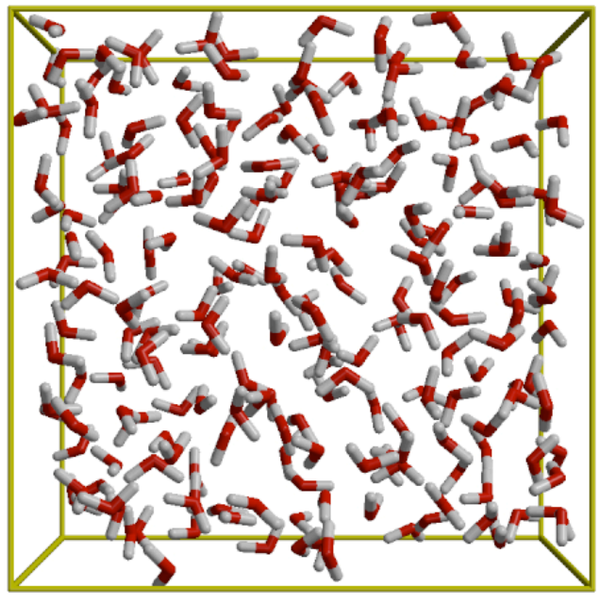
$$S = k \ln \Omega$$

# Thermodynamics

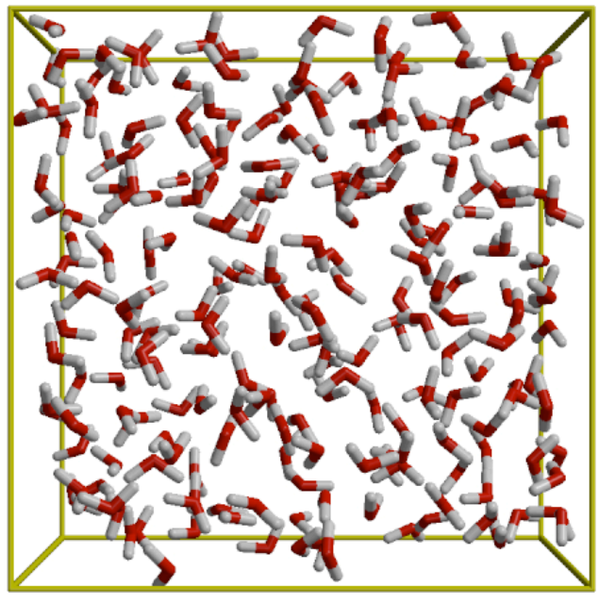
## entropy of isolated system

### micro-states (realisations)

### two boxes of water:



box 1



box 2

### total number of micro states (realisations)

$$\Omega^{\mathrm{tot}} = \Omega_1 \cdot \Omega_2$$

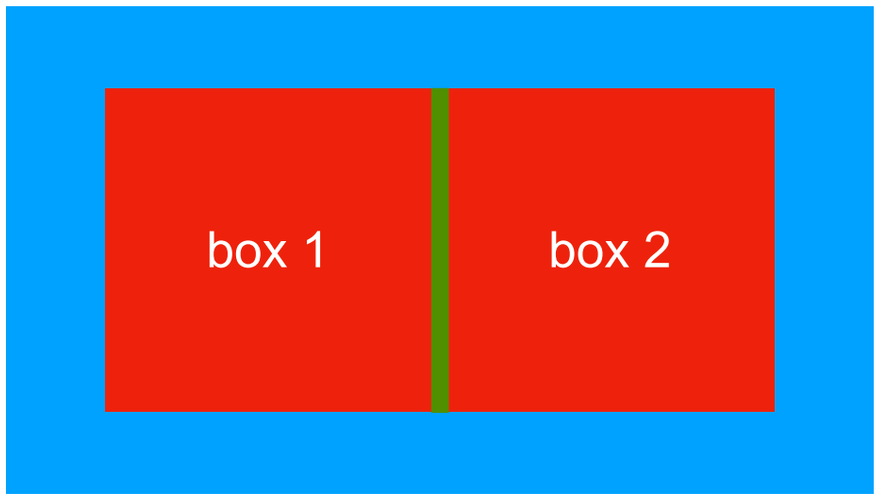
### entropy is extensive, so should be sum:

$$S^{\mathrm{tot}} = k \ln[\Omega_1 \cdot \Omega_2] = k \ln \Omega_1 + k \ln \Omega_2 = S_1 + S_2$$

# Thermodynamics

two systems in thermal equilibrium, isolated from world

diathermic walls (only energy can transfer)




$$N_1 + N_2 = N$$

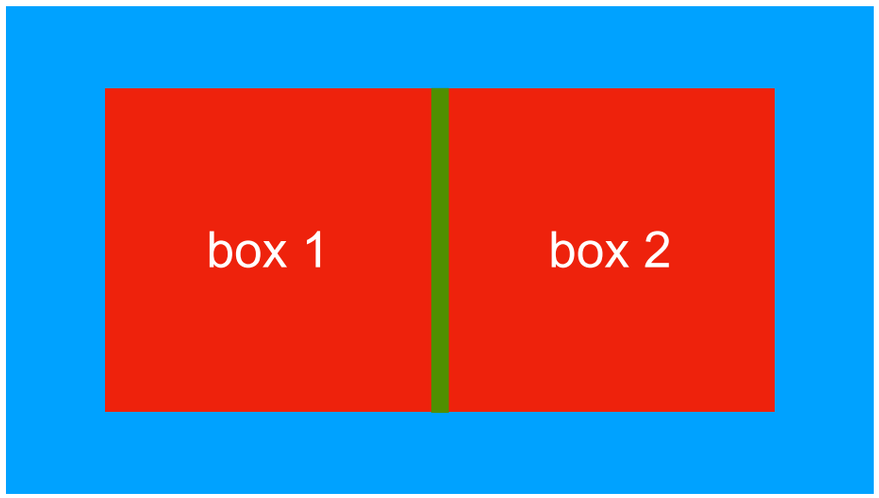
$$E_1 + E_2 = E$$

$$\frac{dE_2}{dE_1} = -1$$

# Thermodynamics

two systems in thermal equilibrium, isolated from world

diathermic walls (only energy can transfer)




$$N_1 + N_2 = N$$

$$E_1 + E_2 = E$$

$$\frac{dE_2}{dE_1} = -1$$

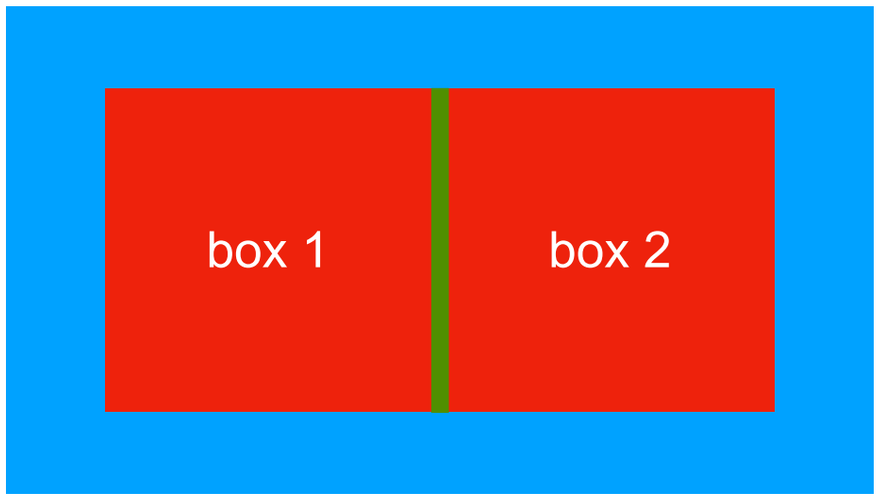
equilibrium: no net changes in total entropy

$$\frac{\partial S^{\rm tot}}{\partial E_1} = \frac{\partial S_1}{\partial E_1} + \frac{\partial S_2}{\partial E_2}\frac{dE_2}{dE_1} = 0$$

# Thermodynamics

two systems in thermal equilibrium, isolated from world

diathermic walls (only energy can transfer)




$$N_1 + N_2 = N$$

$$E_1 + E_2 = E$$

$$\frac{dE_2}{dE_1} = -1$$

equilibrium: no net changes in total entropy

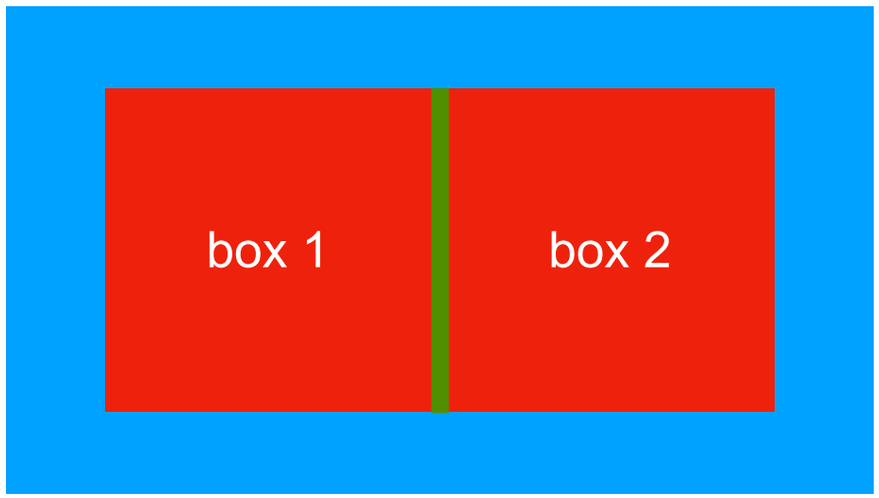
$$\frac{\partial S^{\mathrm{tot}}}{\partial E_1} = \frac{\partial S_1}{\partial E_1} + \frac{\partial S_2}{\partial E_2}\frac{dE_2}{dE_1} = 0$$

$$\frac{\partial S_1}{\partial E_1} = \frac{\partial S_2}{\partial E_2}$$

# Thermodynamics

two systems in thermal equilibrium, isolated from world

diathermic walls (only energy can transfer)




$$N_1 + N_2 = N$$

$$E_1 + E_2 = E$$

$$\frac{dE_2}{dE_1} = -1$$

equilibrium: no net changes in total entropy

$$\frac{\partial S^{\mathrm{tot}}}{\partial E_1} = \frac{\partial S_1}{\partial E_1} + \frac{\partial S_2}{\partial E_2}\frac{dE_2}{dE_1} = 0$$

$$\frac{\partial S_1}{\partial E_1} = \frac{\partial S_2}{\partial E_2}$$

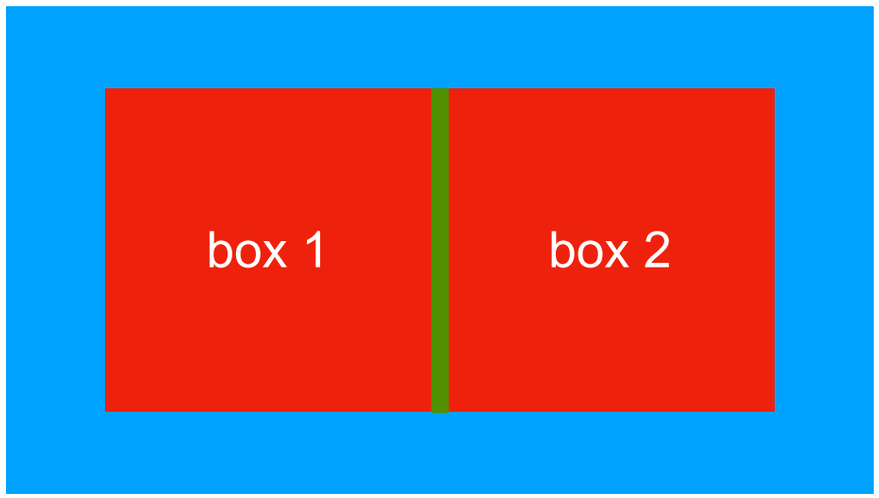
definition of temperature:

$$\frac{\partial S_1}{\partial E_1} = \frac{1}{T_1}$$

# Thermodynamics

two systems in thermal equilibrium, isolated from world

diathermic walls (only energy can transfer)




$$N_1 + N_2 = N$$

$$E_1 + E_2 = E$$

no equilibrium: total entropy must increase

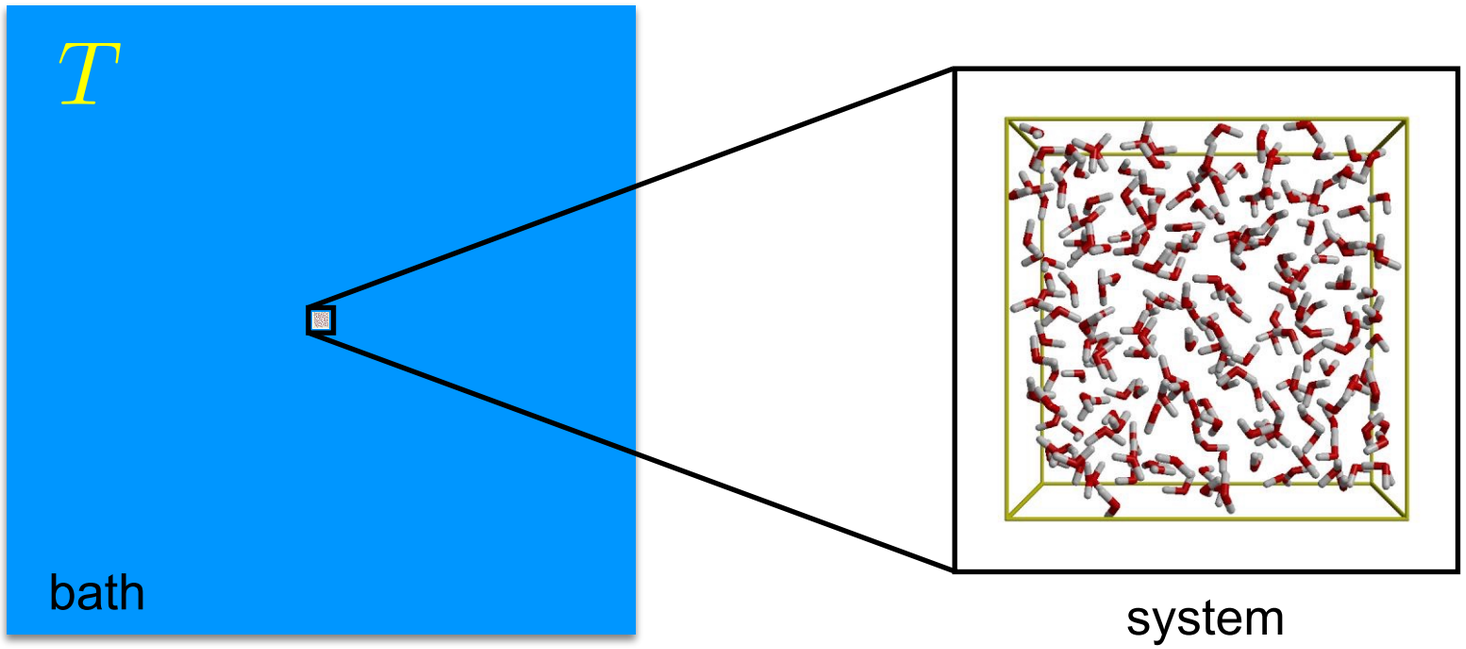
$$\frac{dS^{\rm tot}}{dt} = \left(\frac{1}{T_1} - \frac{1}{T_2}\right)\frac{dE_1}{dt} > 0$$

energy flows from higher to lower temperature

# Statistical mechanics

## canonical ensemble

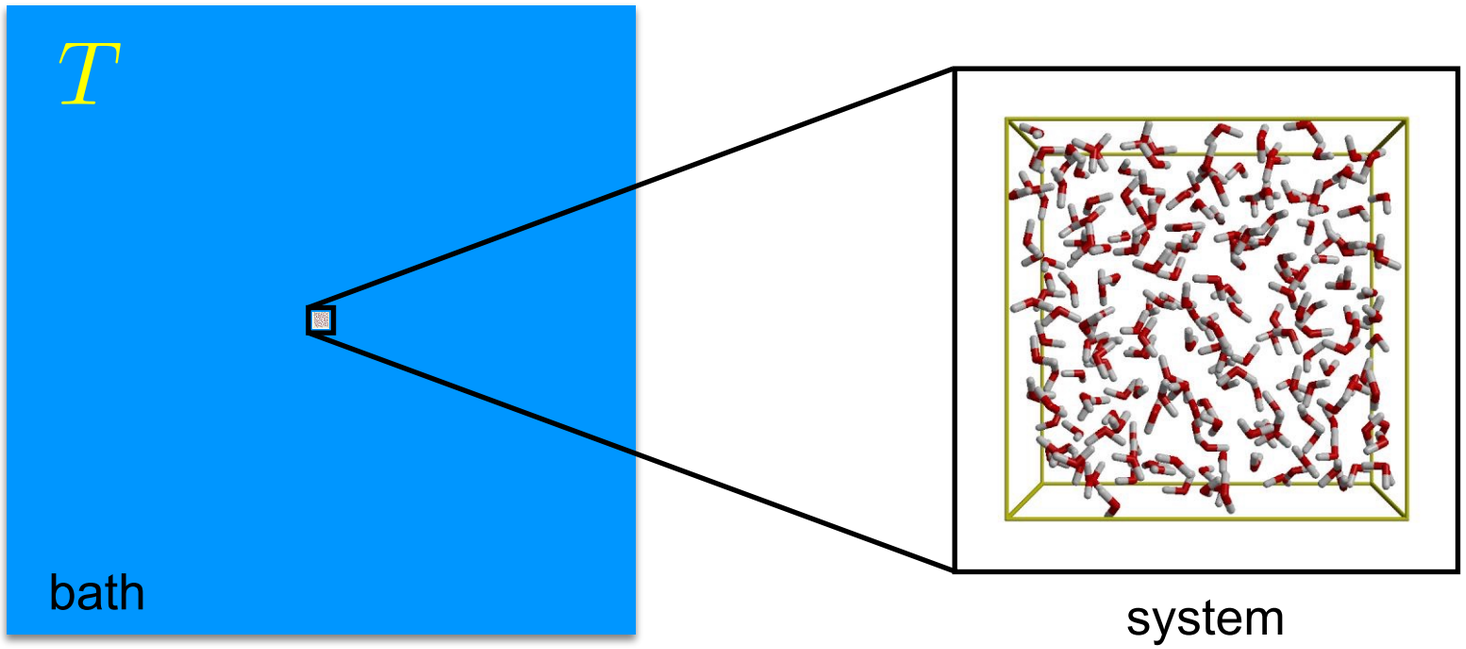
### system in thermal equilibrium with bath



# Statistical mechanics

## canonical ensemble

### system in thermal equilibrium with bath




### micro-states of system

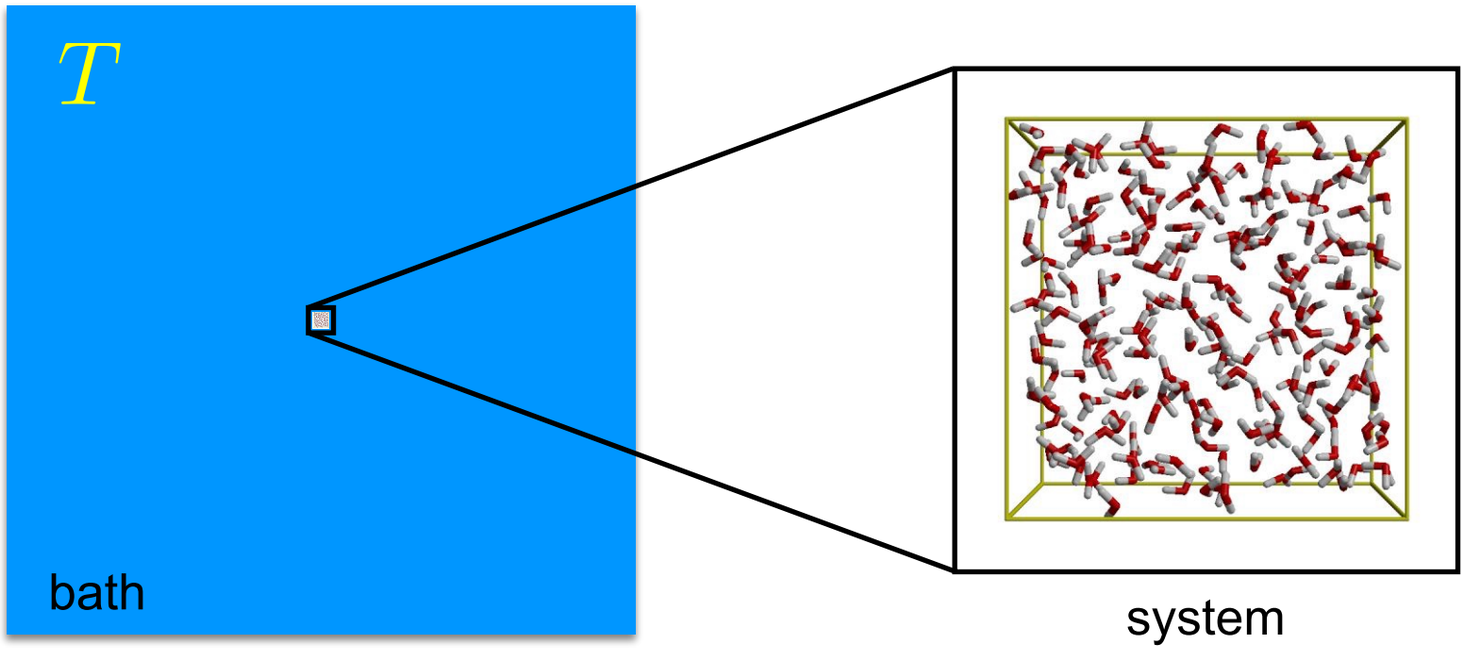
#### each with different energy

$$E_1 \leq E_2 \leq E_3 \leq ... \leq E_i \leq ...$$

# Statistical mechanics

## canonical ensemble

### system in thermal equilibrium with bath




### micro-states of system

each with different energy

$$E_1 \leq E_2 \leq E_3 \leq ... \leq E_i \leq ...$$

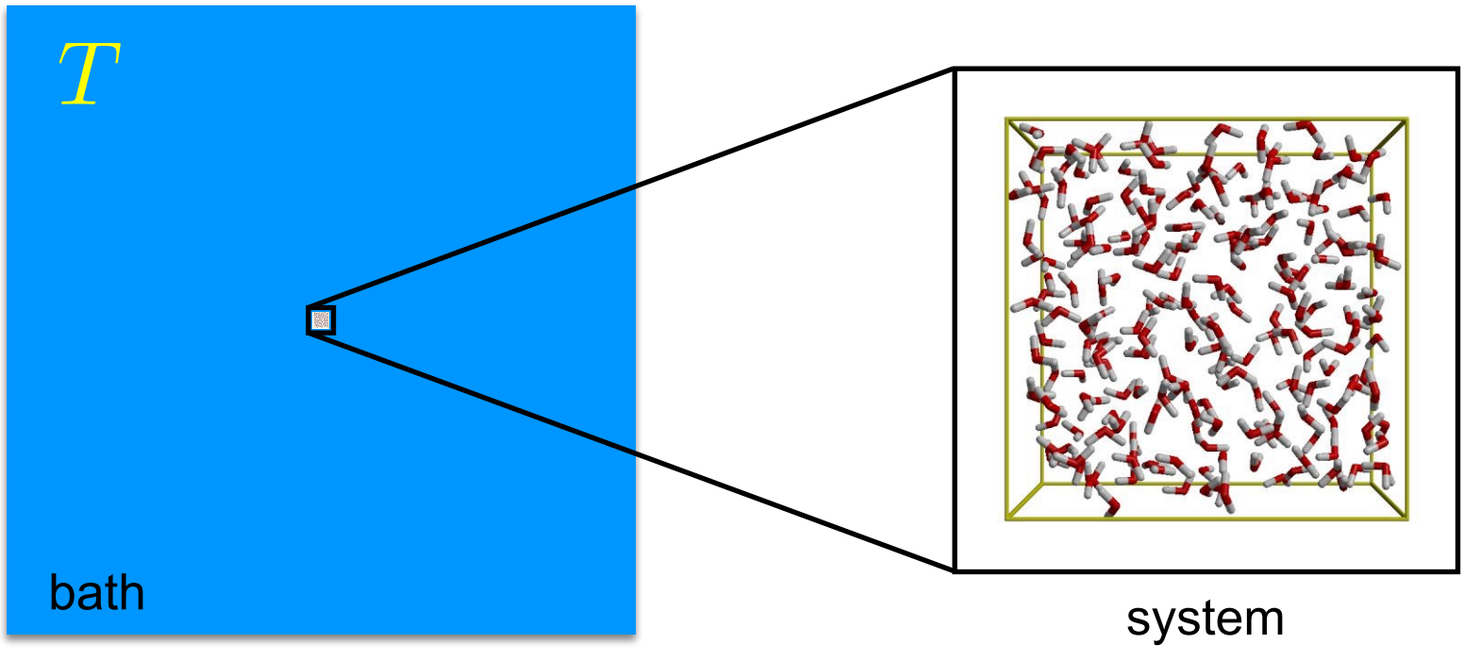
probability of micro state $i$ proportional to number of micro states of bath

$$p_i = \text{const} \cdot \Omega_{\text{bath}}(E^{\text{tot}} - E_i)$$

# Statistical mechanics

## canonical ensemble

### system in thermal equilibrium with bath




### micro-states of system

each with different energy

$$E_1 \leq E_2 \leq E_3 \leq ... \leq E_i \leq ...$$

probability of micro-state $i$ proportional to number of micro states of bath

$$p_i = \text{const} \cdot \Omega_{\text{bath}}(E^{\text{tot}} - E_i)$$

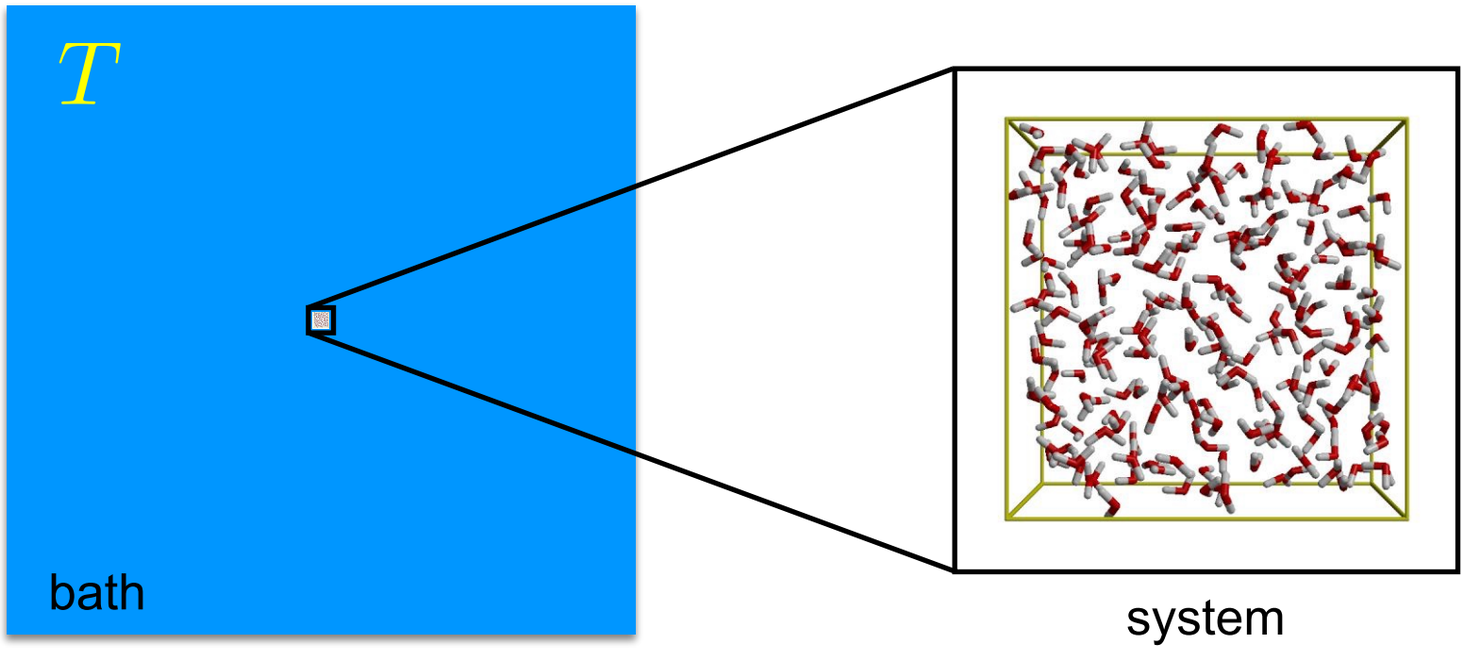
normalisation (const):

$$p_i = \frac{\Omega_{\text{bath}}(E^{\text{tot}} - E_i)}{\sum_i \Omega_{\text{bath}}(E^{\text{tot}} - E_i)}$$

# Statistical mechanics

## canonical ensemble

### system in thermal equilibrium with bath




### micro-states of system

probability of micro-state $i$ proportional to number of micro states of bath

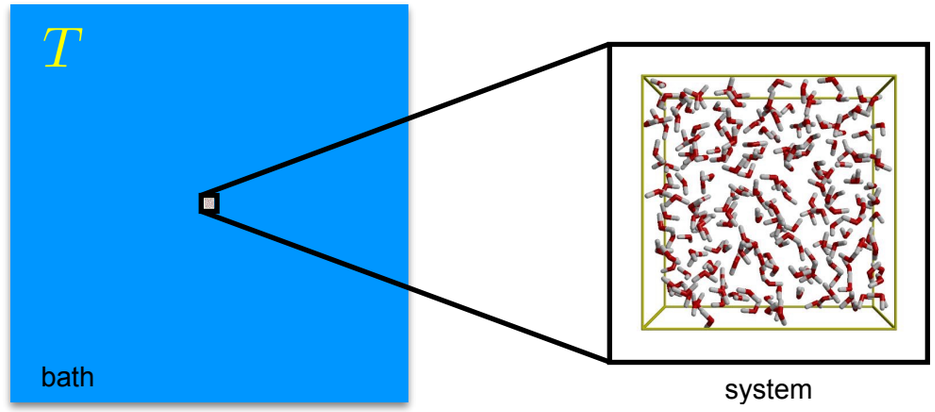
$$p_i = \text{const} \cdot \Omega_{\text{bath}}(E^{\text{tot}} - E_i)$$

normalisation (const):

$$p_i = \frac{\Omega_{\text{bath}}(E^{\text{tot}} - E_i)}{\sum_i \Omega_{\text{bath}}(E^{\text{tot}} - E_i)}$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

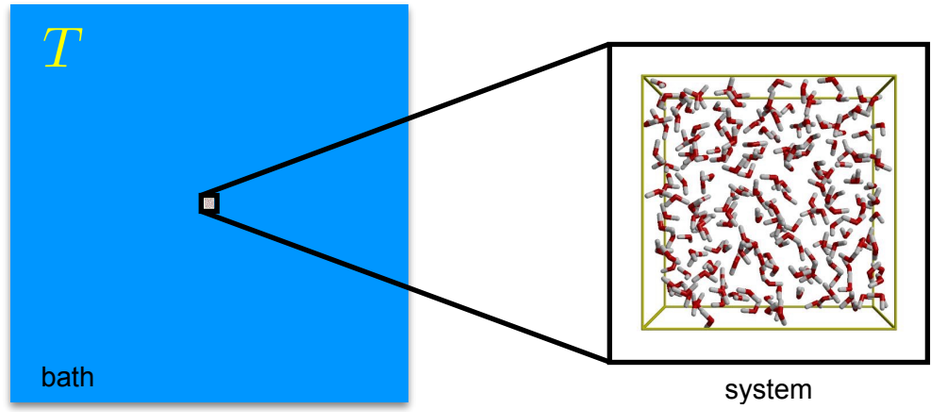
micro-states of system

probability of micro state $i$ proportional to number of micro-states of bath

$$p_i = \text{const} \cdot \Omega_{\text{bath}}(E^{\text{tot}} - E_i)$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro state $i$ proportional to number of micro-states of bath

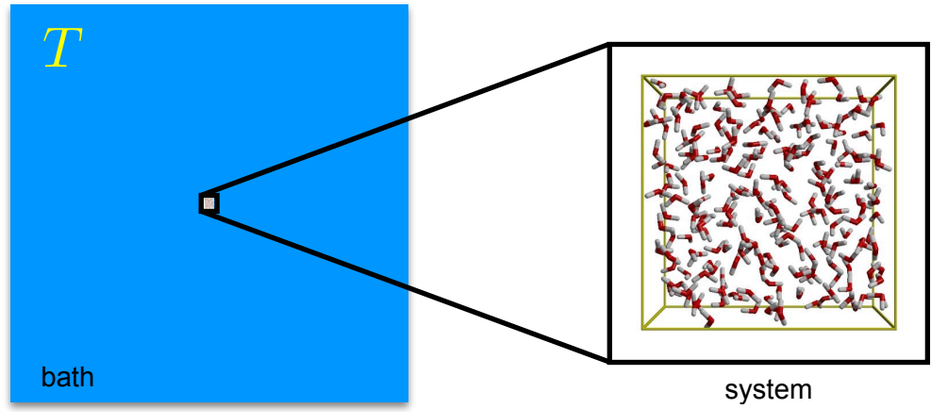
$$p_i = \text{const} \cdot \Omega_{\text{bath}}(E^{\text{tot}} - E_i)$$

with definition of entropy: $S = k \ln \Omega$

$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro state $i$ proportional to number of micro-states of bath

$$p_i = \text{const} \cdot \Omega_{\text{bath}}(E^{\text{tot}} - E_i)$$

with definition of entropy: $S = k \ln \Omega$

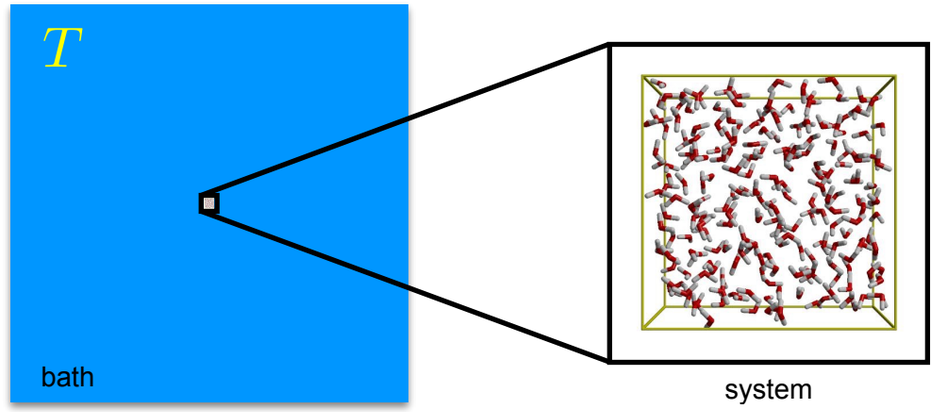
$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

bath much larger than system:

$$E^{\text{tot}} \gg E_i$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro state $i$ proportional to number of micro states of bath

$$p_i = \text{const} \cdot \Omega_{\text{bath}}(E^{\text{tot}} - E_i)$$

with definition of entropy: $S = k \ln \Omega$

$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

bath much larger than system:

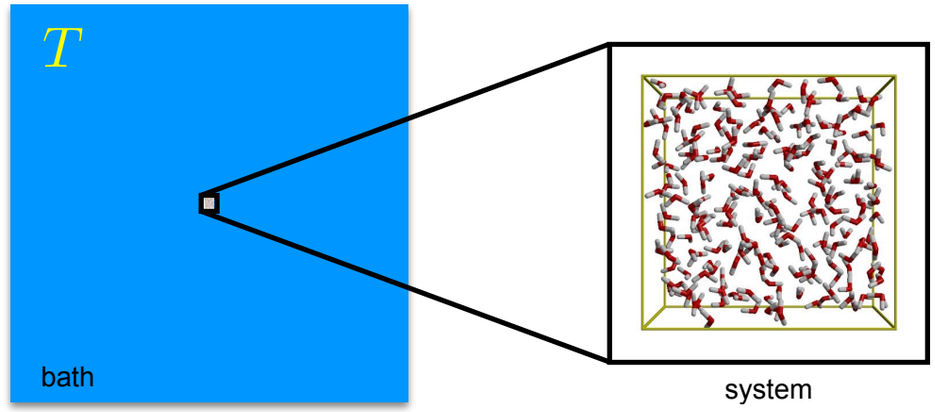
$$E^{\text{tot}} \gg E_i$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \frac{E_i}{k} \left. \frac{\partial S_{\text{bath}}(E)}{\partial E} \right|_{E=E^{\text{tot}}} + \ldots$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro state $i$ proportional to number of micro-states of bath

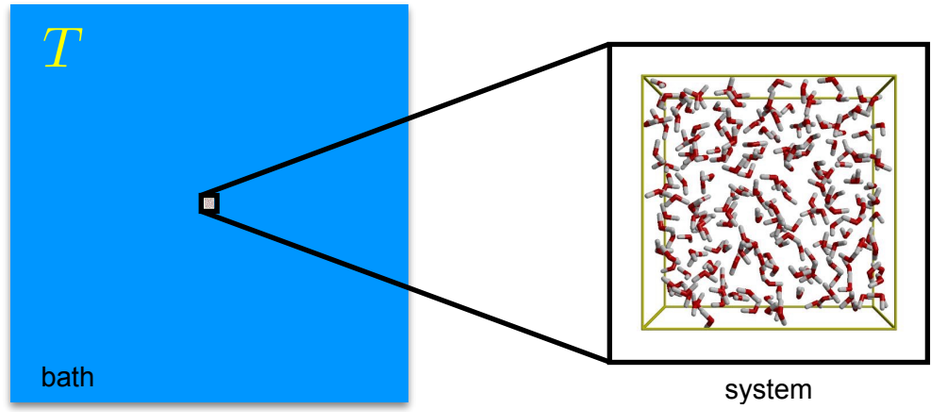
$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \frac{E_i}{k} \left. \frac{\partial S_{\text{bath}}(E)}{\partial E} \right|_{E=E^{\text{tot}}} + \ldots$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro state $i$ proportional to number of micro-states of bath

$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \frac{E_i}{k} \left. \frac{\partial S_{\text{bath}}(E)}{\partial E} \right|_{E=E^{\text{tot}}} + \ldots$$

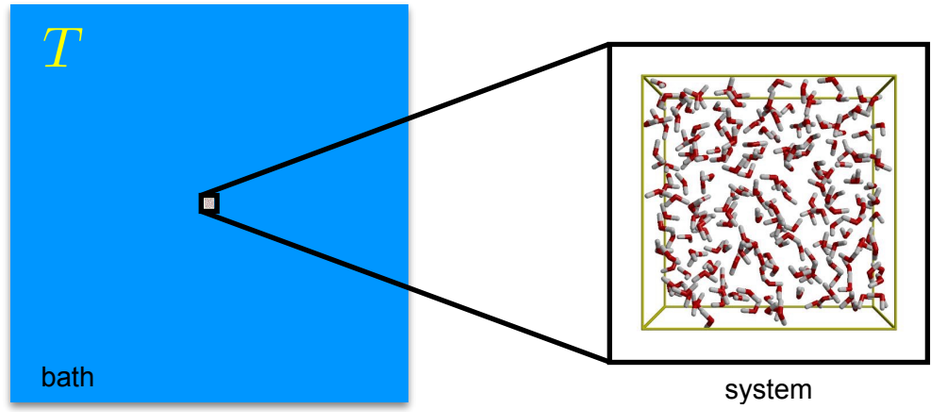
with definition of temperature

$$\frac{\partial S}{\partial E} = \frac{1}{T}$$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \frac{1}{kT} E_i$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro-state $i$ proportional to number of micro-states of bath

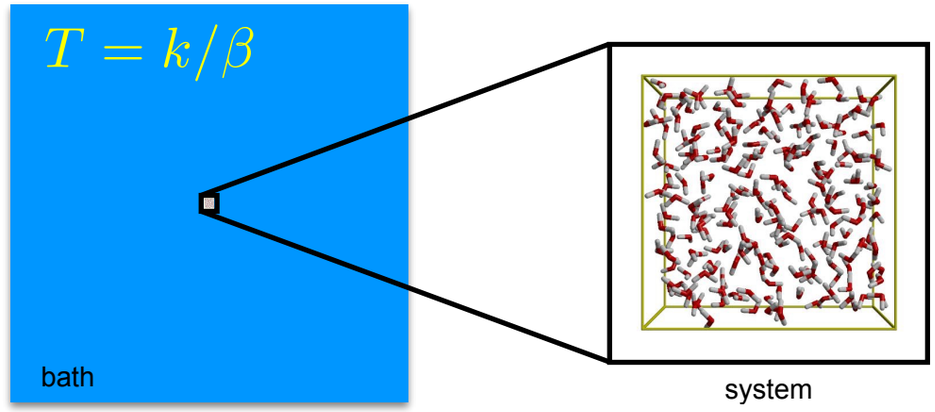
$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \frac{1}{kT} E_i$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro-state $i$ proportional to number of micro-states of bath

$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \frac{1}{kT} E_i$$

define

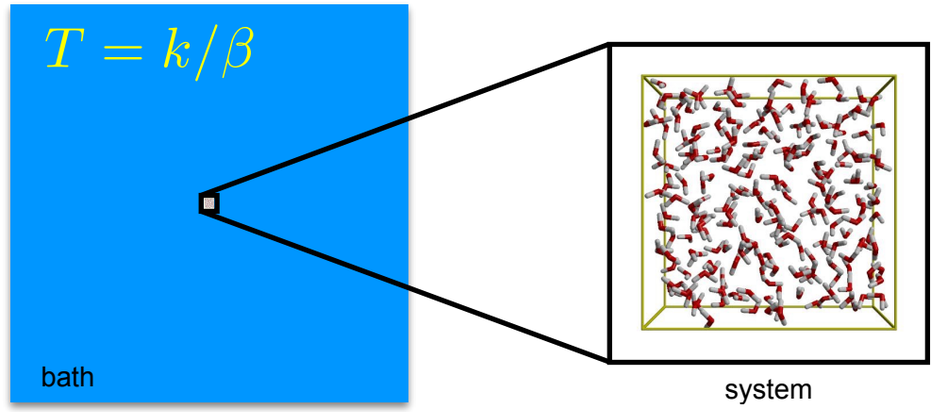
$$\beta \equiv \frac{1}{kT}$$

# Statistical mechanics

## canonical ensemble

system in thermal equilibrium with bath

micro-states of system




probability of micro-state $i$ proportional to number of micro-states of bath

$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \frac{1}{kT} E_i$$

define

$$\beta \equiv \frac{1}{kT}$$

so that

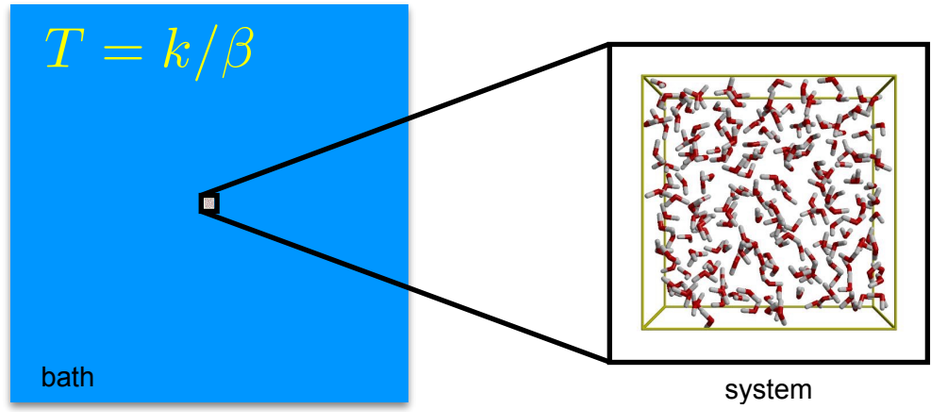
$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \beta E_i$$

# Statistical mechanics

## canonical ensemble

system in thermal equilibrium with bath

micro-states of system




probability of micro state $i$ proportional to number of micro-states of bath

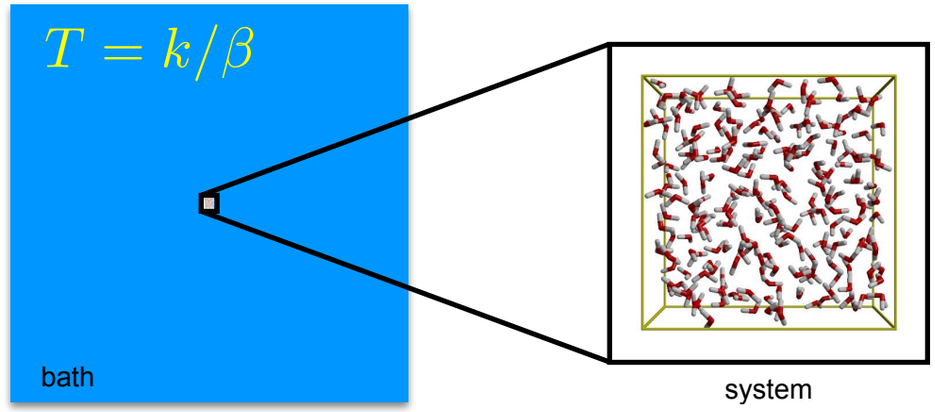
$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \beta E_i$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro state $i$ proportional to number of micro-states of bath

$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \beta E_i$$

probability of micro-state $i$

Boltzmann distribution

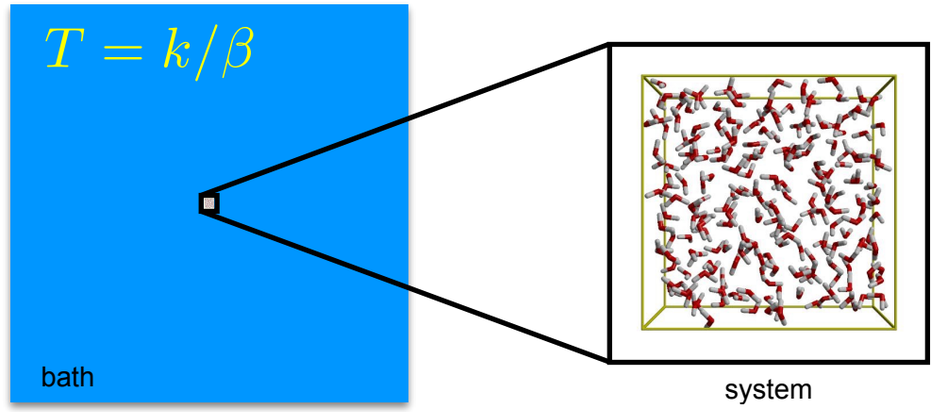
$$p_i = \frac{1}{Z} e^{-\beta E_i}$$

# Statistical mechanics

## canonical ensemble

system in thermal equilibrium with bath

micro-states of system




probability of micro state $i$ proportional to number of micro-states of bath

$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \beta E_i$$

probability of micro-state $i$

Boltzmann distribution

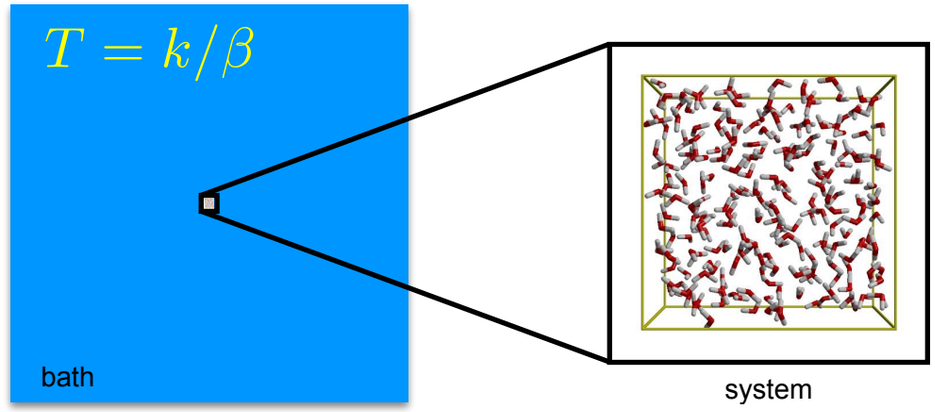
$$p_i = \frac{1}{Z} e^{-\beta E_i}$$

partition function

$$Z = \sum_i e^{-\beta E_i}$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

micro-states of system

probability of micro state $i$ proportional to number of micro-states of bath

$$p_i = \text{const} \cdot \exp[S_{\text{bath}}(E^{\text{tot}} - E_i)/k]$$

Taylor expansion of $S_{\text{bath}}$ around $E^{\text{tot}}$

$$\frac{1}{k} S_{\text{bath}}(E^{\text{tot}} - E_i) = \frac{1}{k} S_{\text{bath}}(E^{\text{tot}}) - \beta E_i$$

probability of micro state $i$

Boltzmann distribution

$$p_i = \frac{1}{Z} e^{-\beta E_i}$$

partition function

$$Z = \sum_i e^{-\beta E_i}$$

from microscopic to macroscopic with partition function

# Statistical mechanics

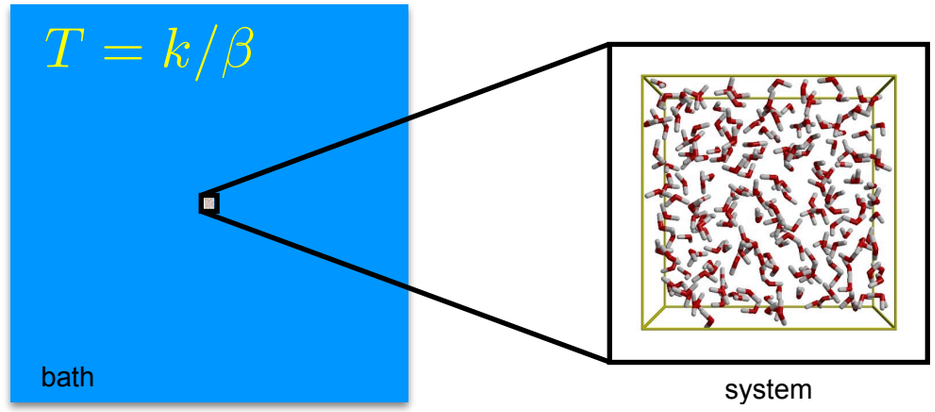
## canonical ensemble

### system in thermal equilibrium with bath

### entropy of system

#### probability of micro-state $i$

$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum_i e^{-\beta E_i}$$



# Statistical mechanics

## canonical ensemble

system in thermal equilibrium with bath

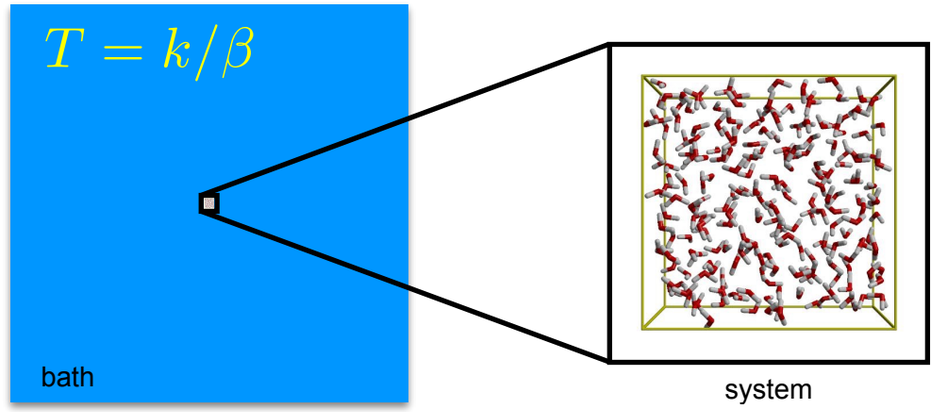
entropy of system

probability of micro-state $i$

$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum_i e^{-\beta E_i}$$

average energy of system

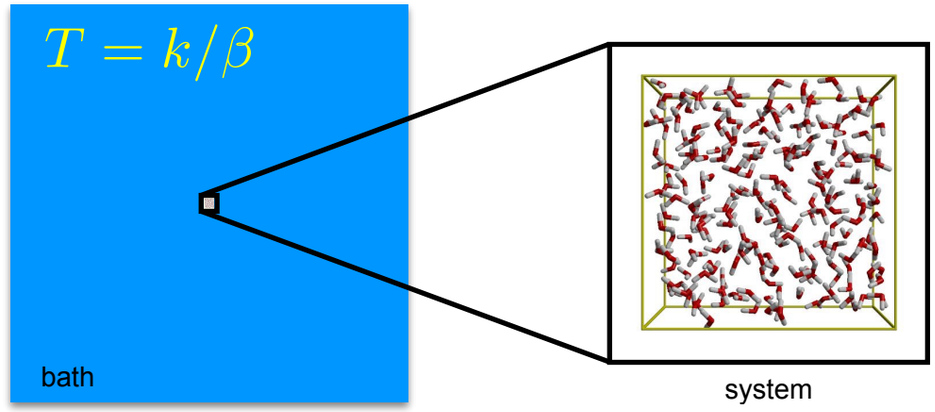
$$\langle E \rangle =$$



# Statistical mechanics

## canonical ensemble

### system in thermal equilibrium with bath




### entropy of system

#### probability of micro-state $i$

$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum_i e^{-\beta E_i}$$

#### average energy of system

$$\langle E \rangle = \sum_i p_i E_i$$

# Statistical mechanics

## canonical ensemble

system in thermal equilibrium with bath

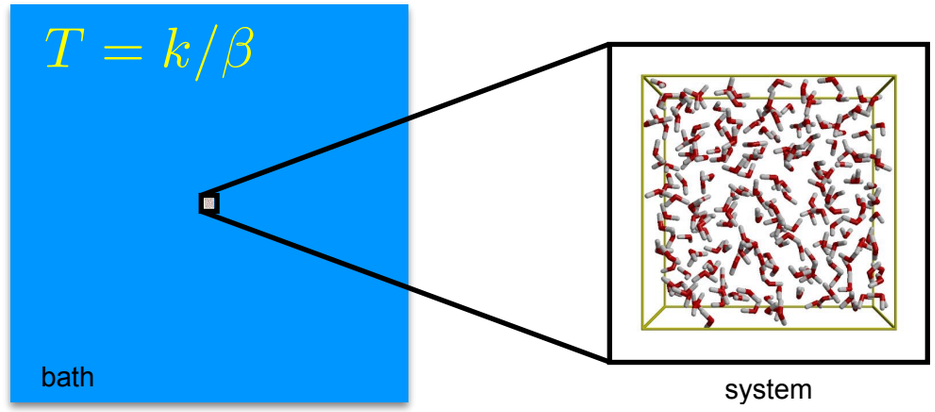
entropy of system

probability of micro-state $i$

$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum_i e^{-\beta E_i}$$

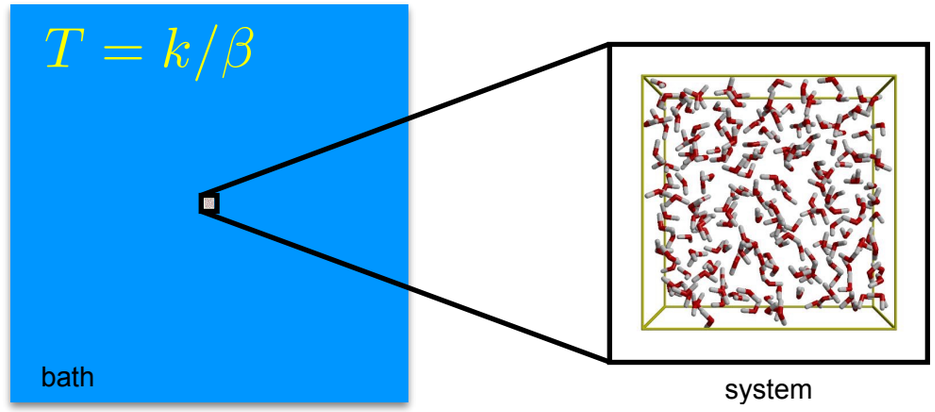
average energy of system

$$\langle E \rangle = \sum_i p_i E_i = \frac{\sum_i E_i e^{-\beta E_i}}{\sum_i e^{-\beta E_i}}$$



# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

entropy of system

probability of micro-state $i$

$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum_i e^{-\beta E_i}$$

average energy of system

$$\langle E \rangle = \sum_i p_i E_i = \frac{\sum_i E_i e^{-\beta E_i}}{\sum_i e^{-\beta E_i}} = -\frac{\partial \ln Z}{\partial \beta}$$

# Statistical mechanics

## canonical ensemble

system in thermal equilibrium with bath

entropy of system

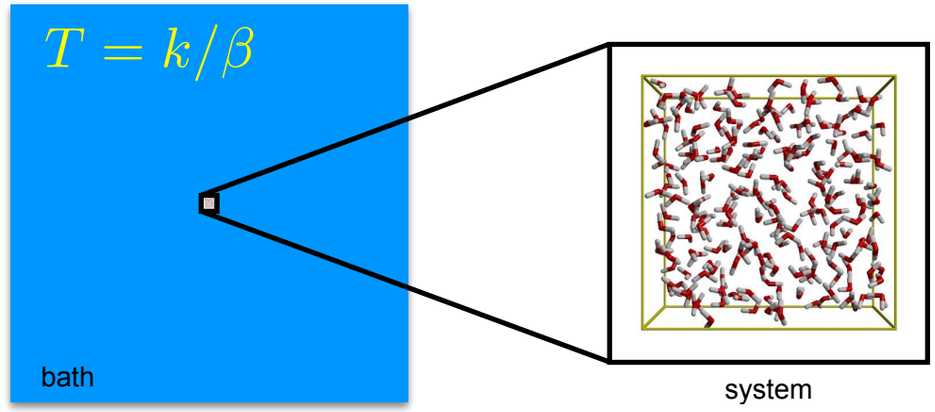
probability of micro state $i$

$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum_i e^{-\beta E_i}$$

average energy of system

$$\langle E \rangle = \sum_i p_i E_i = \frac{\sum_i E_i e^{-\beta E_i}}{\sum_i e^{-\beta E_i}} = -\frac{\partial \ln Z}{\partial \beta}$$

what about entropy?



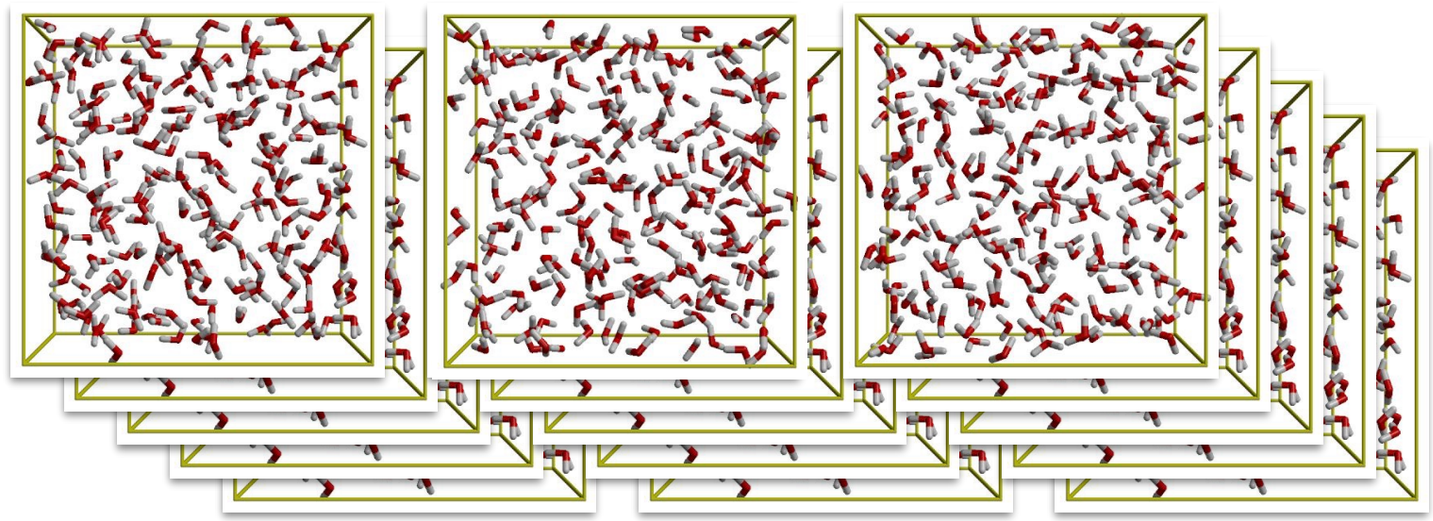
# Statistical mechanics

entropy

general ensemble

replicate many time

ensemble of *N* replicas



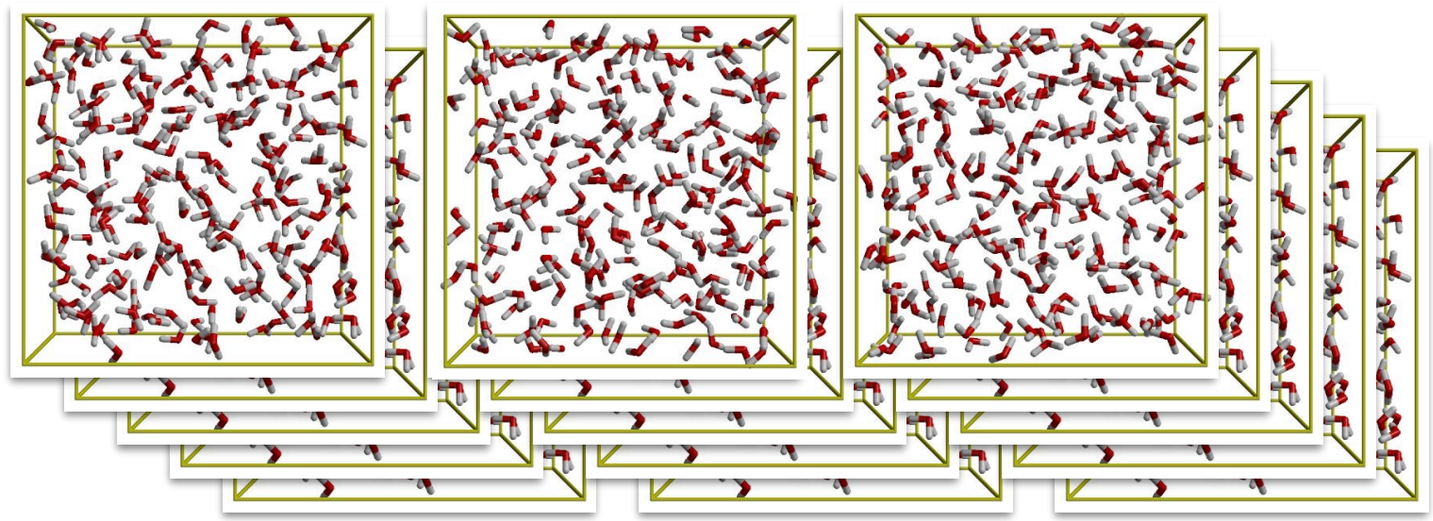
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

ensemble of *N* replicas



number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

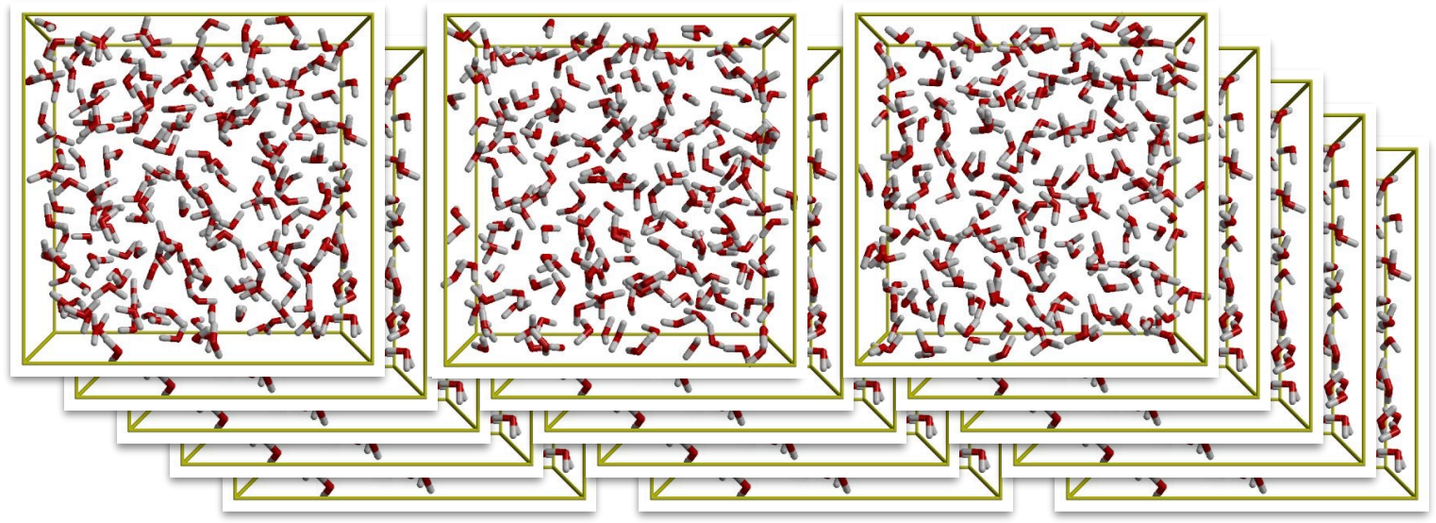
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

ensemble of *N* replicas



number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

total number of micro-states

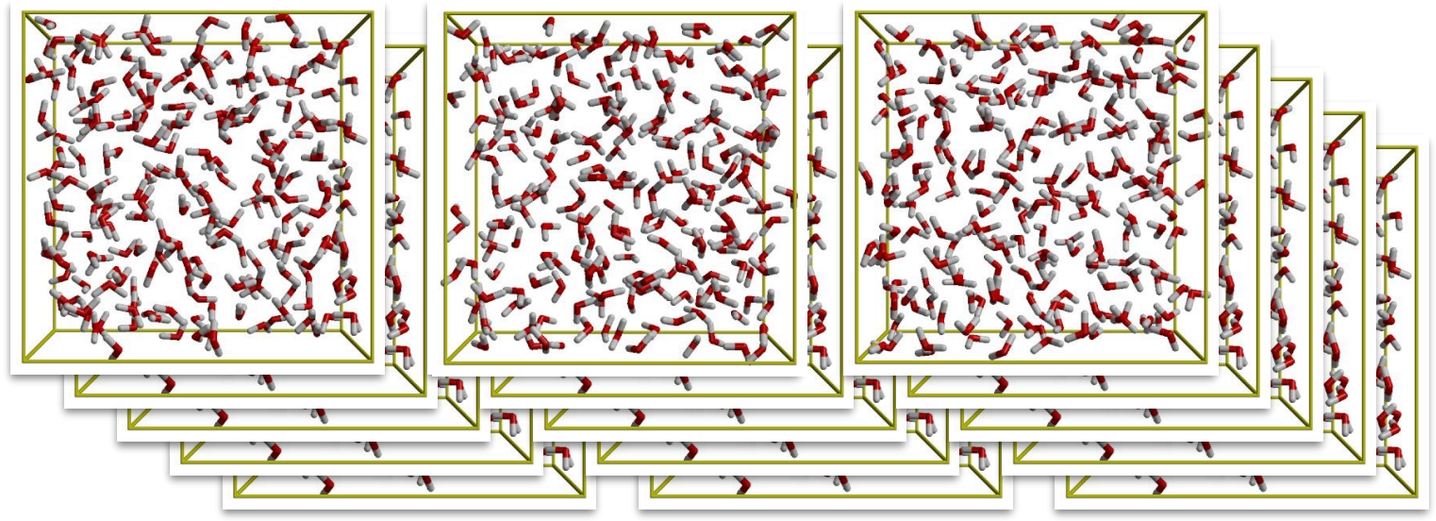
$$\Omega_N = \frac{N!}{n_1! n_2! \ldots n_i! \ldots}$$

# Statistical mechanics

## entropy

### general ensemble

### replicate many time



ensemble of *N* replicas

number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

total number of micro-states

$$\Omega_N = \frac{N!}{n_1! n_2! \ldots n_i! \ldots}$$

entropy of ensemble

$$S_N = k \ln \Omega_N = k \ln \left[ \frac{N!}{n_1! n_2! \ldots n_i! \ldots} \right]$$

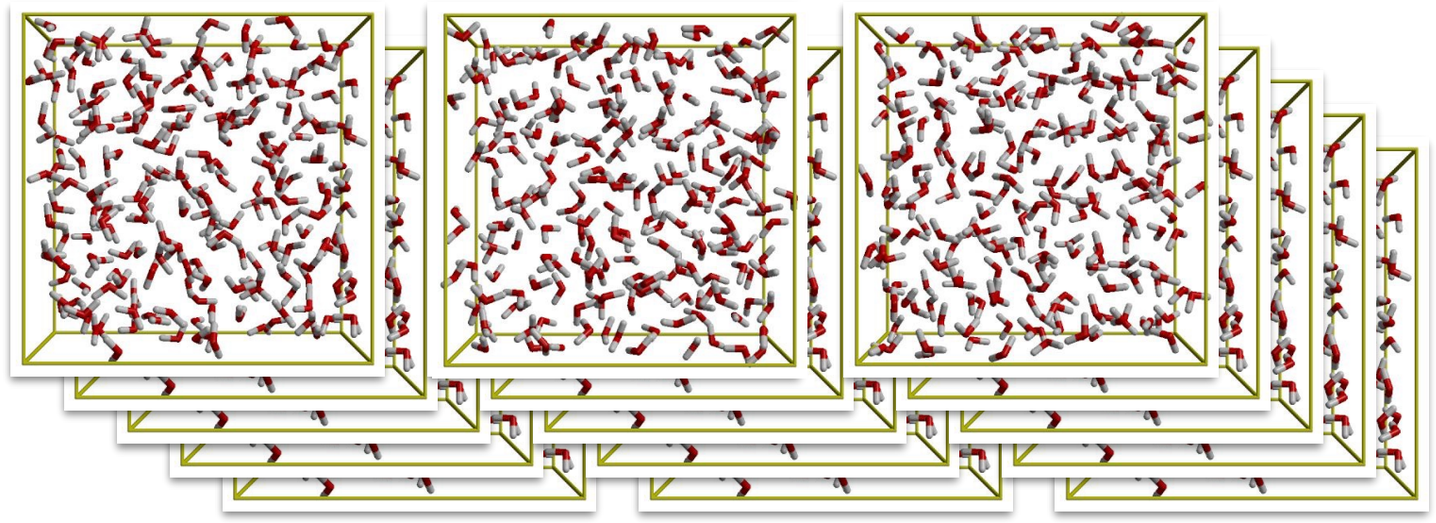
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

ensemble of *N* replicas



number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

total number of micro-states

$$\Omega_N = \frac{N!}{n_1! n_2! \ldots n_i! \ldots}$$

entropy of ensemble

$$S_N = k \ln \Omega_N = k \ln \left[ \frac{N!}{n_1! n_2! \ldots n_i! \ldots} \right]$$

Stirling approximation:

$$\lim_{x \to \infty} \ln x! = x \ln x - x$$

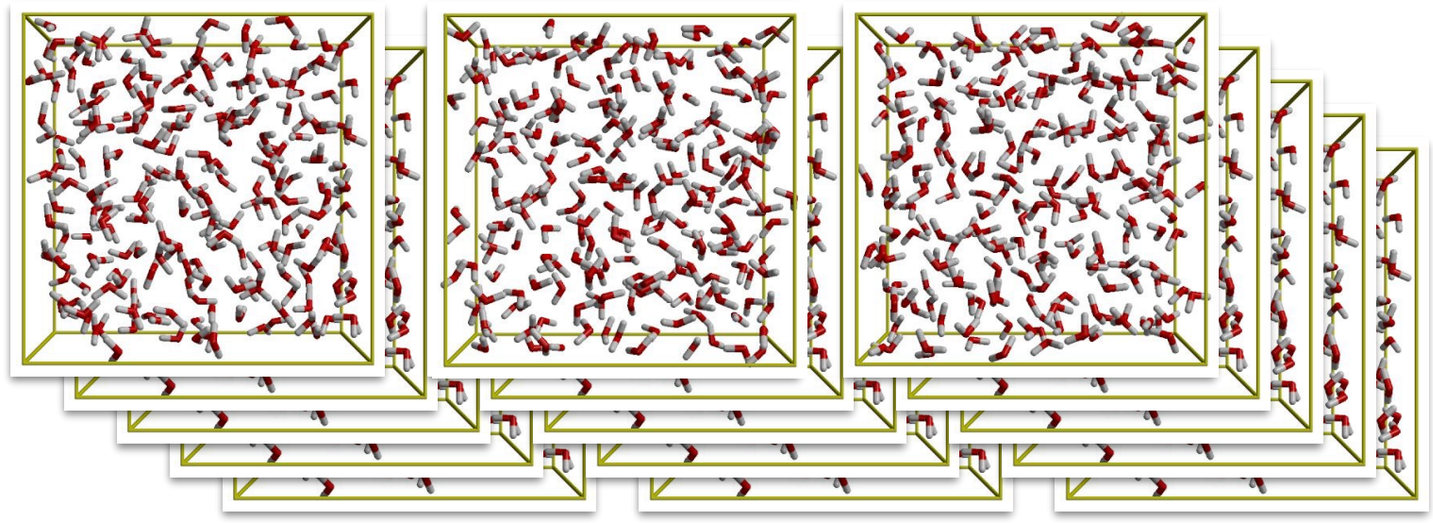
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

#### ensemble of *N* replicas



#### number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

#### entropy of ensemble

$$S_N = k \ln \Omega_N = k \ln \left[ \frac{N!}{n_1! n_2! \ldots n_i! \ldots} \right]$$

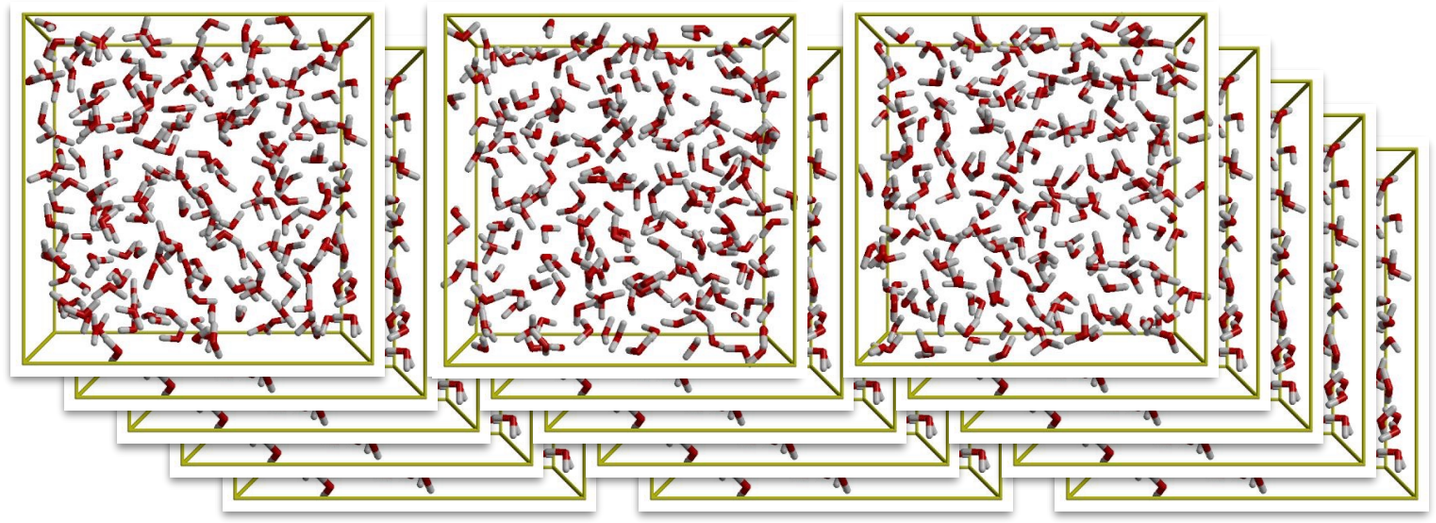
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

#### ensemble of *N* replicas



#### number of replicas in micro-state *i*

$$n_i = N p_i \qquad \sum_i p_i = 1$$

#### entropy of ensemble

$$S_N = k \ln \Omega_N = k \ln \left[ \frac{N!}{n_1! n_2! \ldots n_i! \ldots} \right]$$

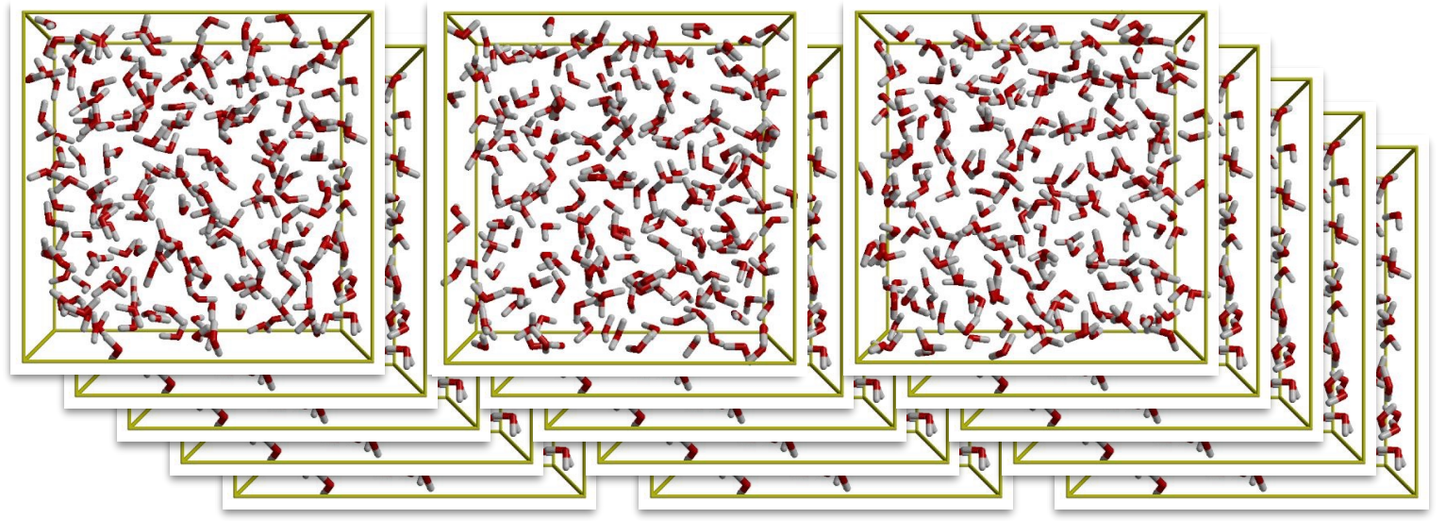
$$S_N = k \left[ N \ln N - N - \sum_i (n_i \ln n_i - n_i) \right]$$

# Statistical mechanics

## entropy

### general ensemble

### replicate many time



#### ensemble of *N* replicas

#### number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

#### entropy of ensemble

$$S_N = k \ln \Omega_N = k \ln \left[ \frac{N!}{n_1! n_2! \ldots n_i! \ldots} \right]$$

$$S_N = k \left[ N \ln N - N - \sum_i (n_i \ln n_i - n_i) \right]$$

$$S_N = k \left[ N \ln N - N - N \sum_i (p_i \ln [N p_i] - p_i) \right]$$

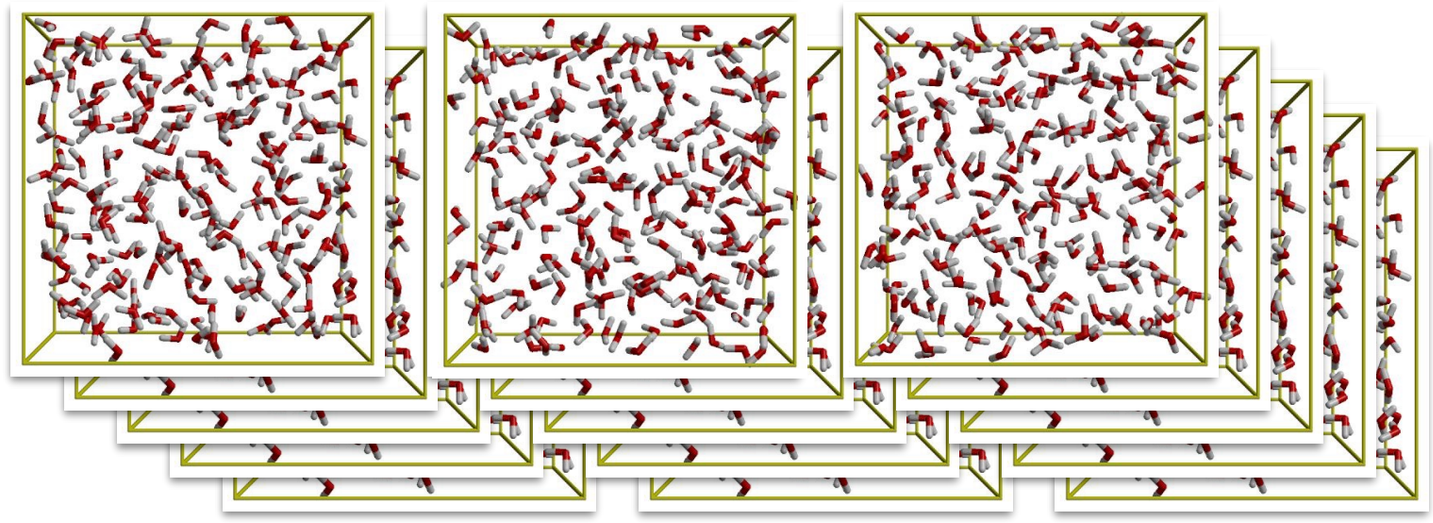
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

ensemble of *N* replicas



number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

entropy of ensemble

$$S_N = k \left[ N \ln N - N - N \sum_i (p_i \ln[N p_i] - p_i) \right]$$

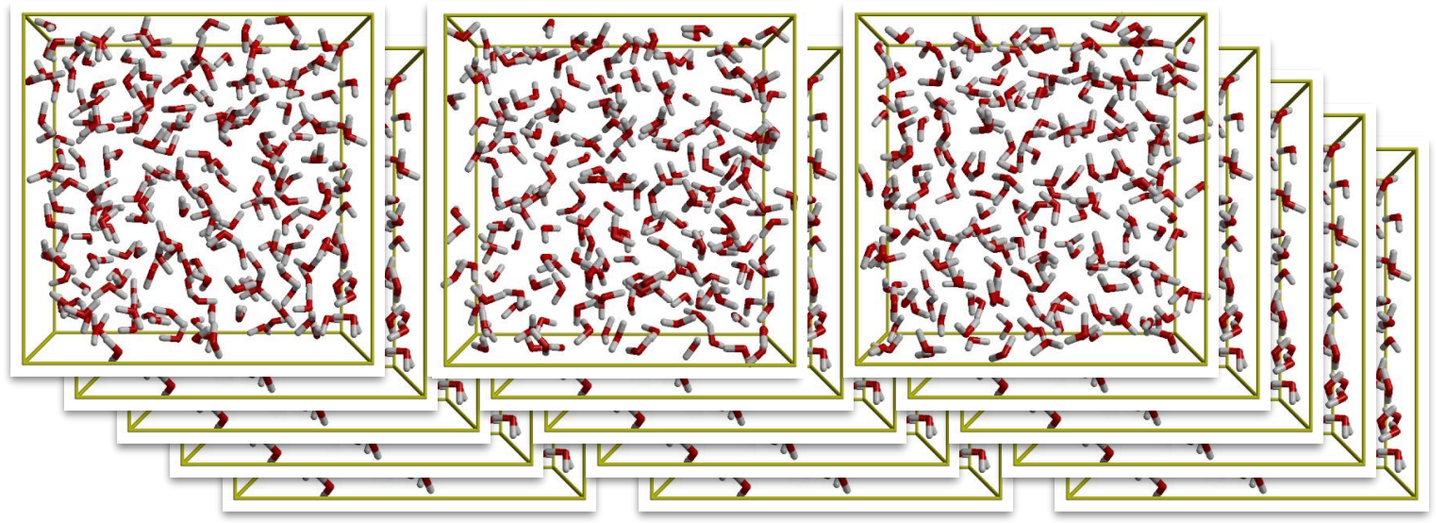
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

#### ensemble of *N* replicas



#### number of replicas in micro-state *i*

$$n_i = N p_i \qquad \sum_i p_i = 1$$

#### entropy of ensemble

$$S_N = k \left[ N \ln N - N - N \sum_i (p_i \ln[N p_i] - p_i) \right]$$

$$S_N = k \left[ N \ln N - N - N \ln N - N \sum_i p_i \ln p_i - N \right]$$

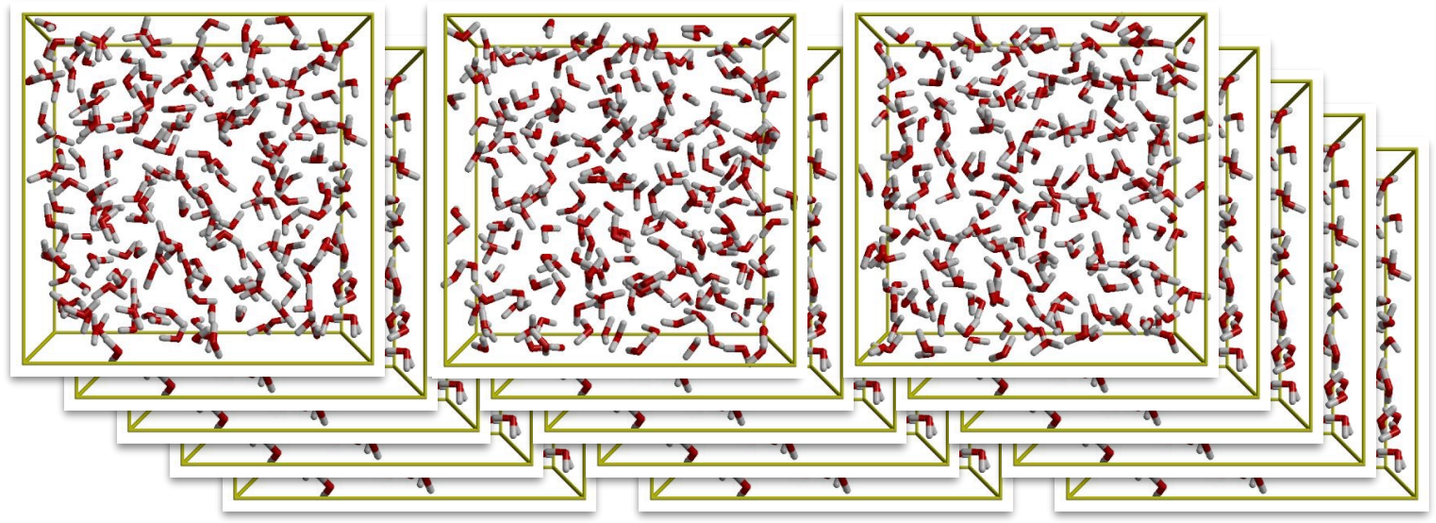
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

#### ensemble of *N* replicas



#### number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

#### entropy of ensemble

$$S_N = k \left[ N \ln N - N - N \sum_i (p_i \ln[N p_i] - p_i) \right]$$

$$S_N = k \left[ \cancel{N \ln N} - \cancel{N} - \cancel{N \ln N} - N \sum_i p_i \ln p_i - \cancel{N} \right]$$

$$S_N = -N k \sum_i p_i \ln p_i$$

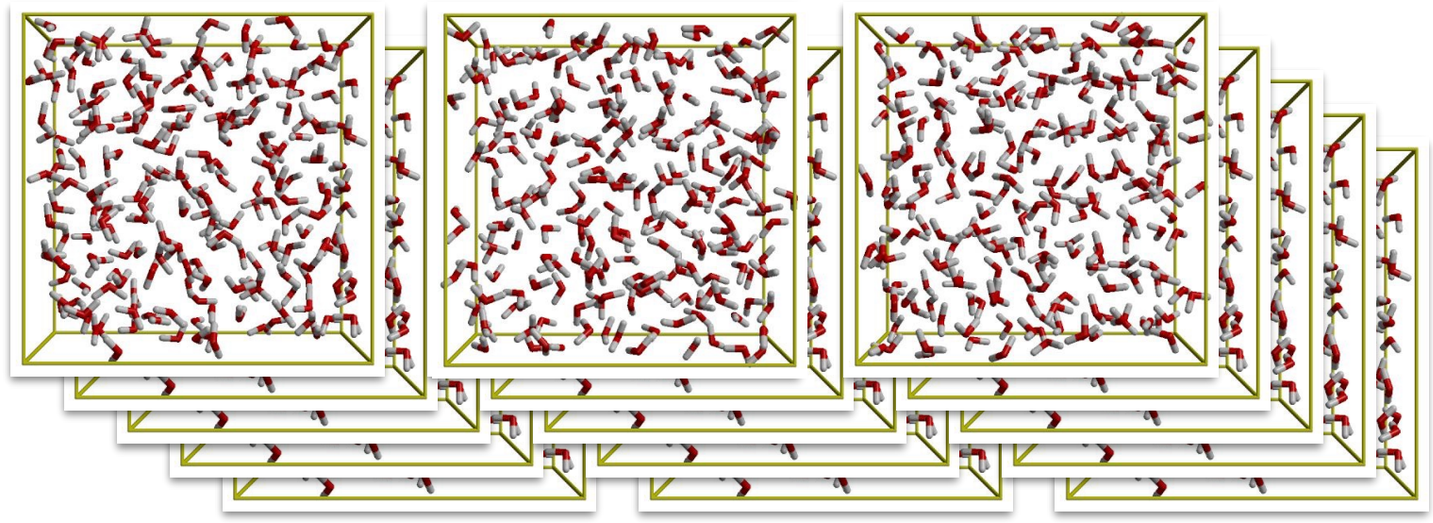
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

#### ensemble of *N* replicas



#### number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

#### entropy of ensemble

$$S_N = -Nk \sum_i p_i \ln p_i$$

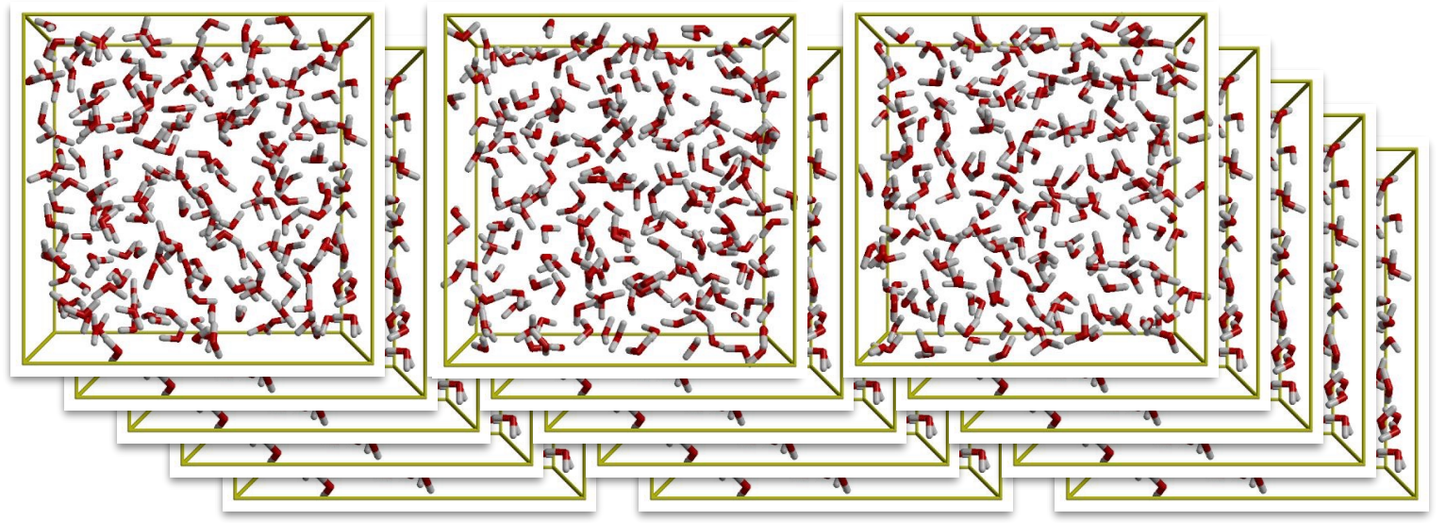
# Statistical mechanics

## entropy

### general ensemble

### replicate many time

#### ensemble of *N* replicas



#### number of replicas in micro-state $i$

$$n_i = N p_i \qquad \sum_i p_i = 1$$

#### entropy of ensemble

$$S_N = -Nk \sum_i p_i \ln p_i$$

#### entropy of replica

$$S = -k \sum_i p_i \ln p_i$$

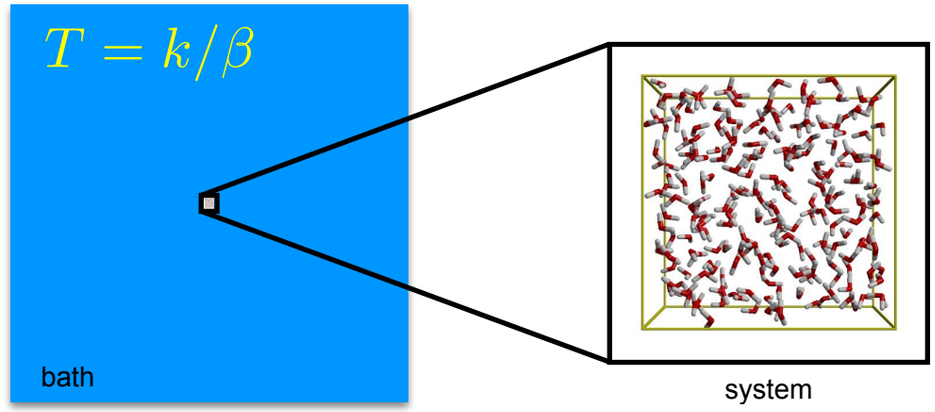
# Statistical mechanics

## canonical ensemble

system in thermal equilibrium with bath

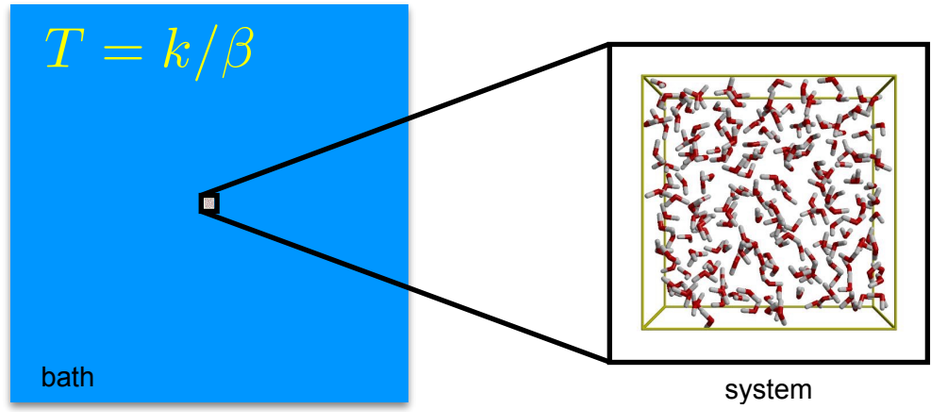
entropy of system

$$S = -k \sum_i p_i \ln p_i$$



# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

entropy of system

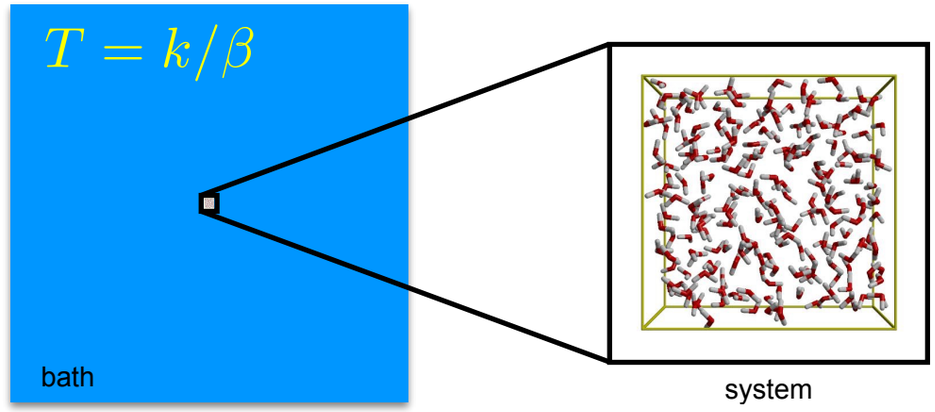
$$S = -k \sum_i p_i \ln p_i$$

Boltzmann distribution

$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum_i e^{-\beta E_i} \qquad \beta \equiv \frac{1}{kT}$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

entropy of system

$$S = -k \sum_i p_i \ln p_i$$

Boltzmann distribution

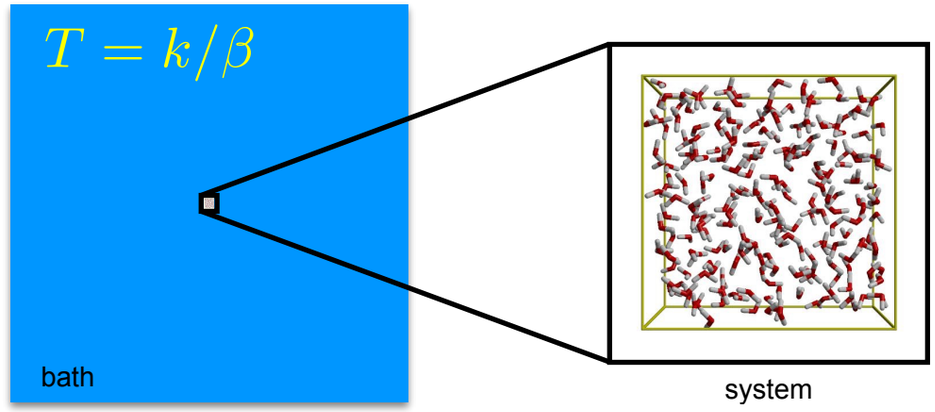
$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum e^{-\beta E_i} \qquad \beta \equiv \frac{1}{kT}$$

substituting and rearranging

$$S = \frac{k}{Z} \sum_i e^{-\beta E_i} \beta E_i + \frac{k}{Z} \sum_i e^{-\beta E_i} \ln Z$$

# Statistical mechanics

## canonical ensemble




system in thermal equilibrium with bath

entropy of system

$$S = -k \sum_i p_i \ln p_i$$

Boltzmann distribution

$$p_i = \frac{1}{Z} e^{-\beta E_i} \qquad Z = \sum e^{-\beta E_i} \qquad \beta \equiv \frac{1}{kT}$$

substituting and rearranging

$$S = \frac{k}{Z} \sum_i e^{-\beta E_i} \beta E_i + \frac{k}{Z} \sum_i e^{-\beta E_i} \ln Z$$

an almost familiar expression

$$S = \frac{1}{T} \langle E \rangle + k \ln Z$$

# Statistical mechanics

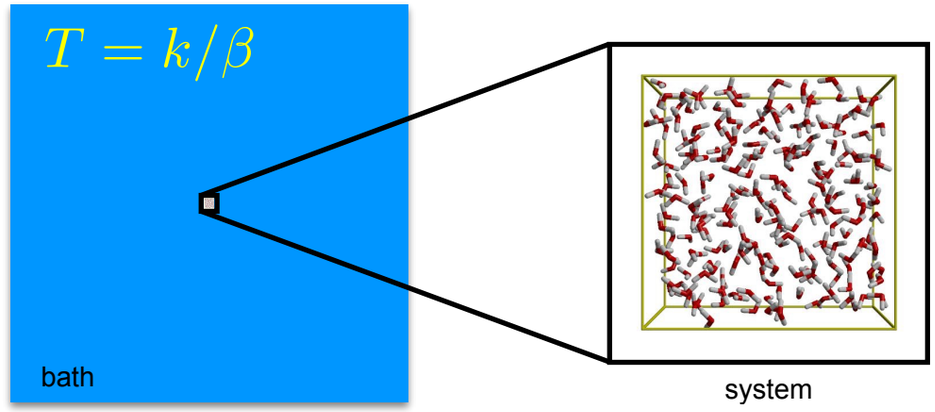
## canonical ensemble

### system in thermal equilibrium with bath

### free energy of system

#### microscopic entropy

$$S = \frac{1}{T}\langle E \rangle + k \ln Z$$



# Statistical mechanics

## canonical ensemble

### system in thermal equilibrium with bath

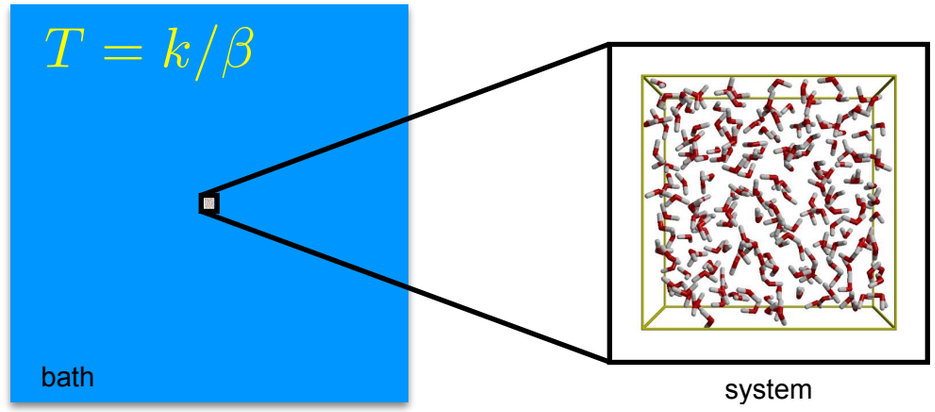
### free energy of system

#### microscopic entropy

$$S = \frac{1}{T}\langle E \rangle + k \ln Z$$

#### microscopic free energy

$$-kT \ln Z = \langle E \rangle - TS$$



# Statistical mechanics

## canonical ensemble

### system in thermal equilibrium with bath

### free energy of system

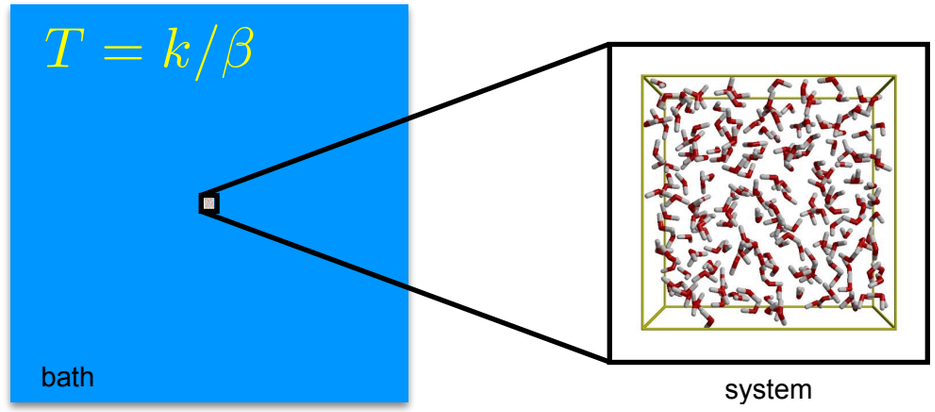
#### microscopic entropy

$$S = \frac{1}{T}\langle E \rangle + k \ln Z$$

#### microscopic free energy

$$-kT \ln Z = \langle E \rangle - TS$$

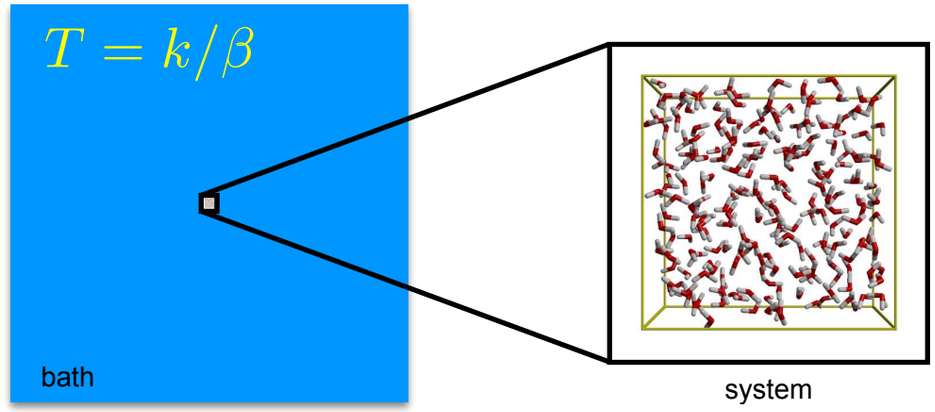
$$A = -kT \ln Z$$



# Statistical mechanics

## canonical ensemble

### system in thermal equilibrium with bath




### free energy of system

#### microscopic entropy

$$S = \frac{1}{T}\langle E \rangle + k \ln Z$$

#### microscopic free energy

$$-kT \ln Z = \langle E \rangle - TS$$

$$A = -kT \ln Z$$

#### macroscopic free energy

$$A = U - TS$$

# Statistical mechanics

## canonical ensemble

system in thermal equilibrium with bath

free energy of system

microscopic entropy

$$S = \frac{1}{T}\langle E \rangle + k \ln Z$$

microscopic free energy

$$-kT \ln Z = \langle E \rangle - TS$$

$$A = -kT \ln Z$$

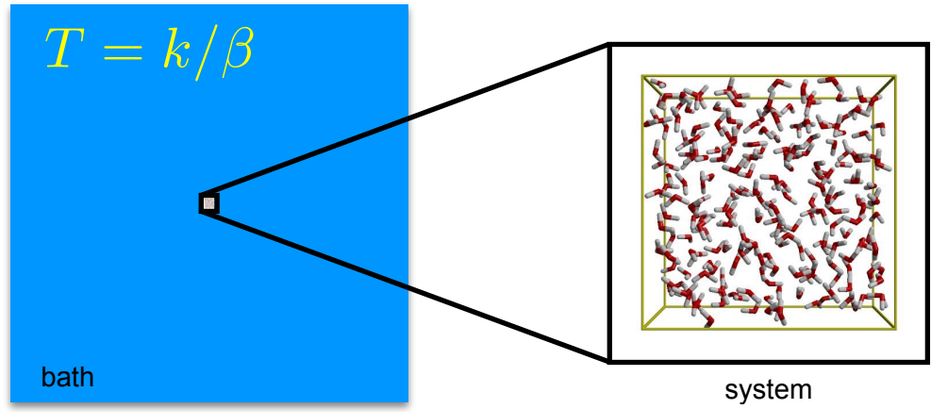
macroscopic free energy

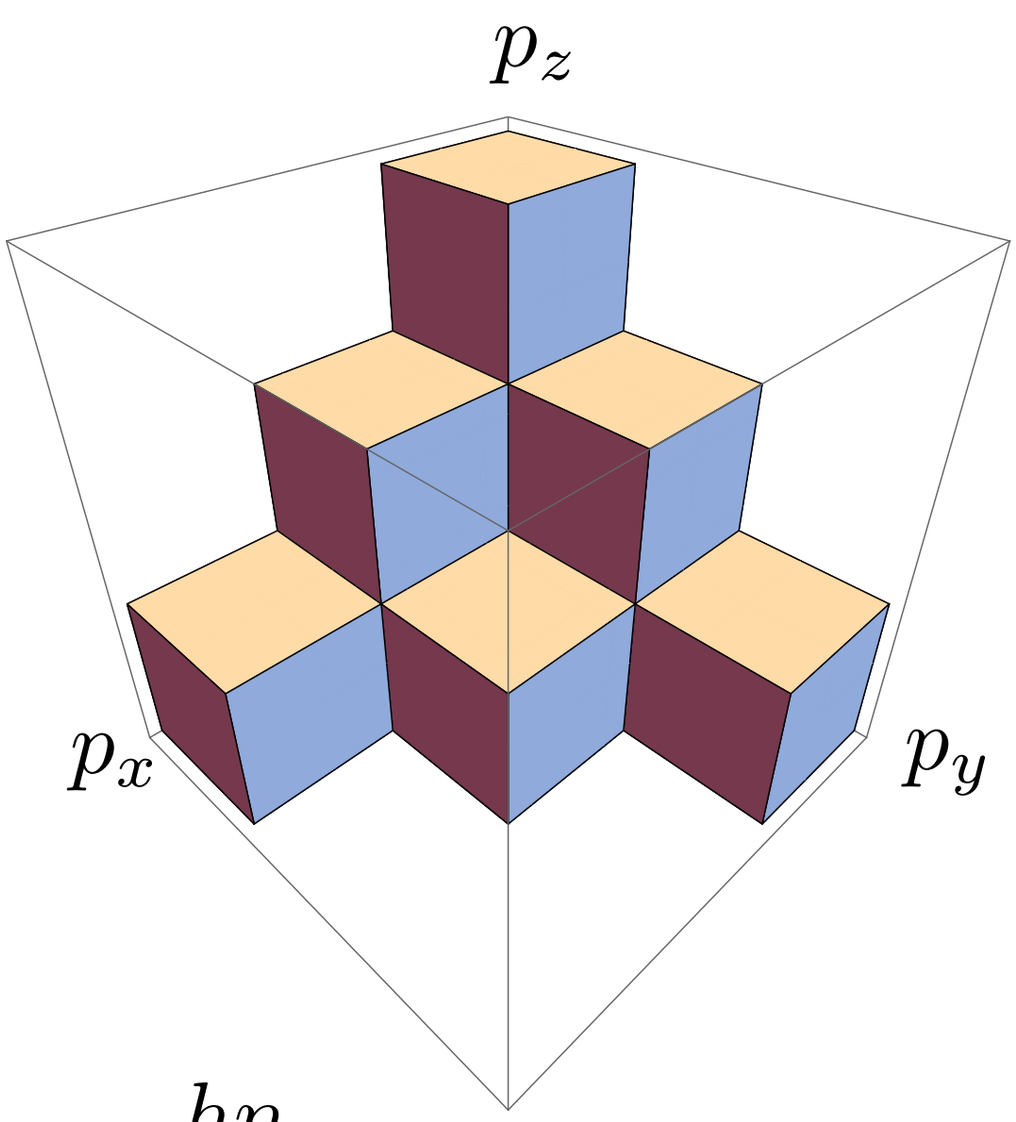
$$A = U - TS$$

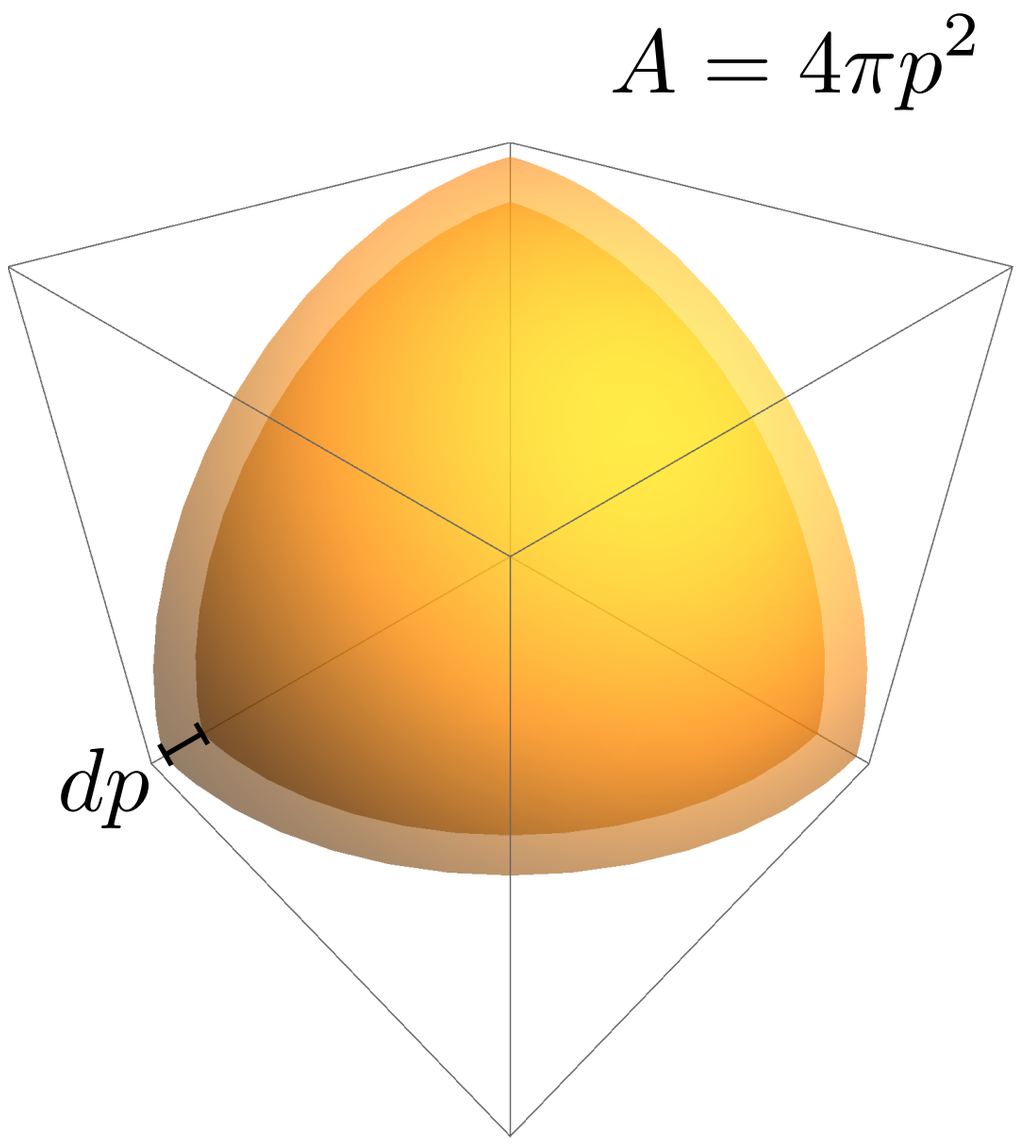
from micro to macro: generate partition function

Monte Carlo

molecular dynamics simulations






$$p_x = \frac{hn_x}{2L}$$

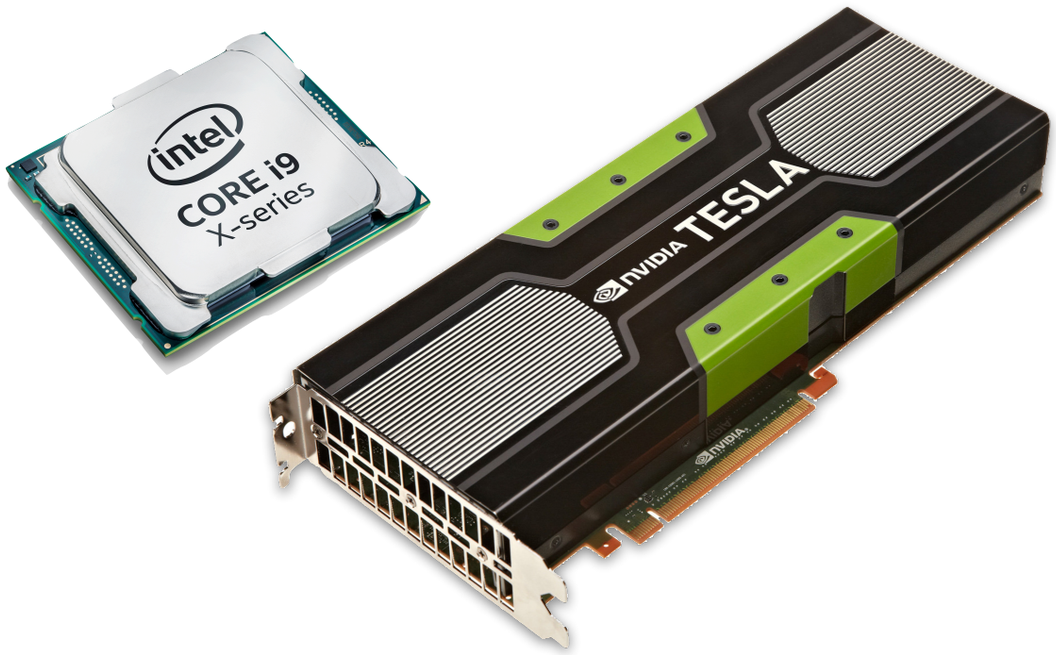
$$p_y = \frac{hn_y}{2L}$$

$$p_z = \frac{hn_z}{2L} \qquad n_x, n_y, n_z = 1, 2, 3, ...$$

$$V(p + \delta p) = 4\pi p^2 dp$$

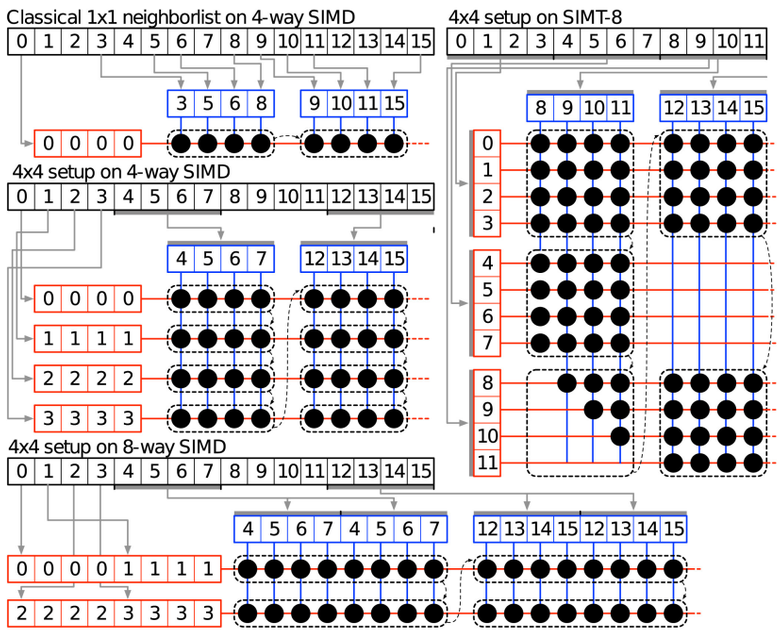
# Statistical mechanics on a computer

## modern computer hardware

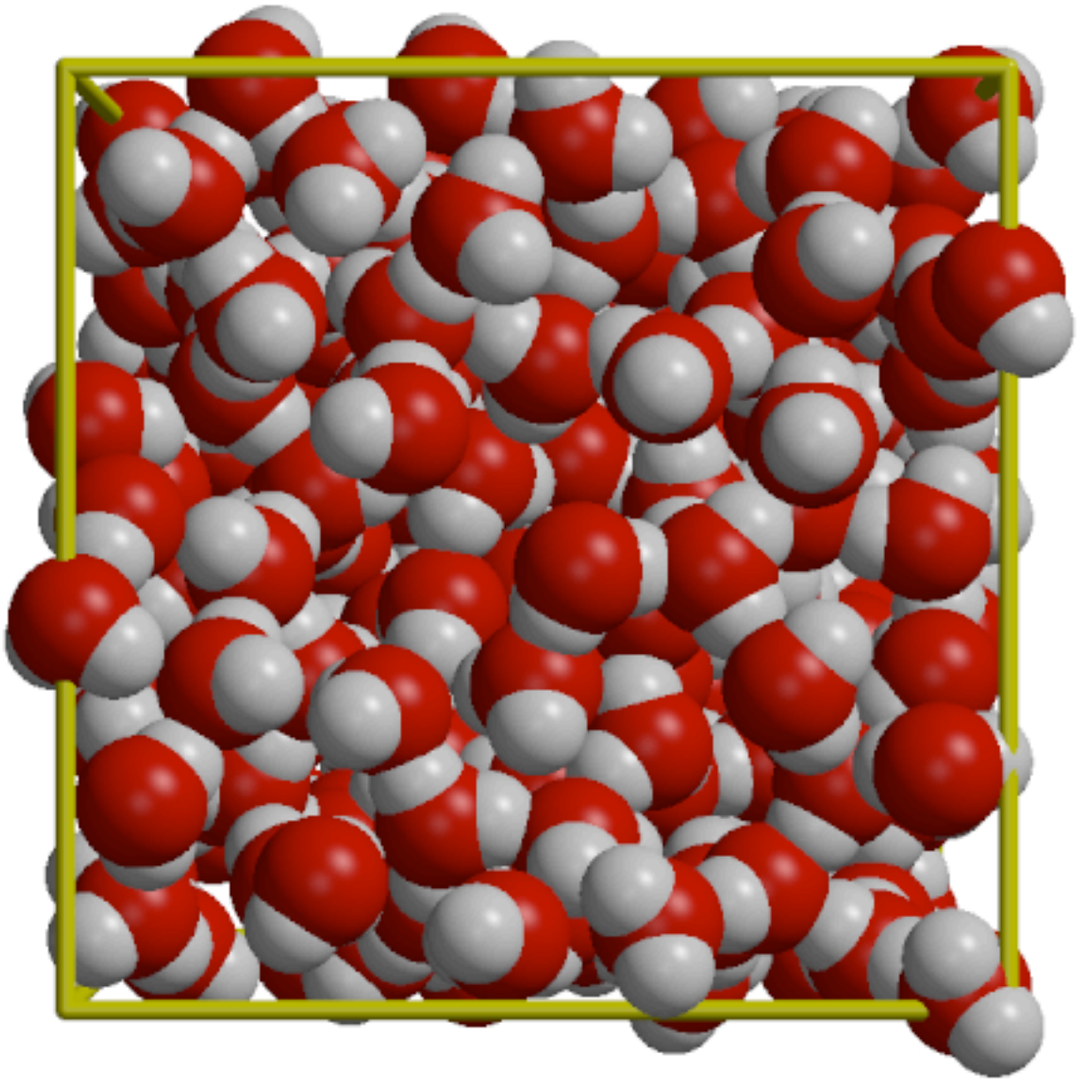



## modern software

### Gromacs




www.gromacs.org



some water

10,000,000,000,000 X ▶▶

## approximations

cannot be derived from first-principles

compare with experiment instead

# The very basics

molecules & matter

electrons (-e), protons (e) & neutrons

Ernest Rutherford

Niels Bohr

# The very basics

molecules & matter

electrons (-e), protons (e) & neutrons

Coulomb interaction

keeps molecules together

$$V(\mathbf{r}_1, \mathbf{r}_2) = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{|\mathbf{r}_2 - \mathbf{r}_1|}$$

Ernest Rutherford

Niels Bohr

Charles de Coulomb

# The very basics

## molecules & matter

### electrons (-e), protons (e) & neutrons

## Coulomb interaction

### keeps molecules together

$$V(\mathbf{r}_1, \mathbf{r}_2) = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{|\mathbf{r}_2 - \mathbf{r}_1|}$$

## Quantum mechanics

### non-relativistic time-dependent Schrödinger equation (1926)

$$i\hbar \frac{\partial}{\partial t} \Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...) = \hat{H} \Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...)$$

Ernest Rutherford

Niels Bohr

Charles de Coulomb

Erwin Schrödinger

# The very basics

## molecules & matter

### electrons (-e), protons (e) & neutrons

## Coulomb interaction

### keeps molecules together

$$V(\mathbf{r}_1, \mathbf{r}_2) = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{|\mathbf{r}_2 - \mathbf{r}_1|}$$

## Quantum mechanics

### non-relativistic time-independent Schrödinger equation (1926)

$$\hat{H}\Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...) = E\Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...)$$

Ernest Rutherford

Niels Bohr

Charles de Coulomb

Erwin Schrödinger

# The very basics

## molecules & matter

### electrons (-e), protons (e) & neutrons

## Coulomb interaction

### keeps molecules together

$$V(\mathbf{r}_1, \mathbf{r}_2) = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{|\mathbf{r}_2 - \mathbf{r}_1|}$$

Ernest Rutherford

Niels Bohr

Charles de Coulomb

## Quantum mechanics

### non-relativistic time-independent Schrödinger equation (1926)

$$\hat{H}\Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...) = E\Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...)$$

### Hamilton operator

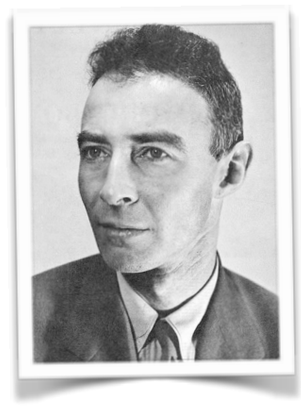
$$\begin{aligned}
\hat{H} &= \hat{T}(\dot{\mathbf{R}}_1, \dot{\mathbf{R}}_2, ..., \dot{\mathbf{r}}_1, \dot{\mathbf{r}}_2, ...) + \hat{V}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...) \\
&= \textstyle\sum_A \frac{1}{2} m_A \dot{\mathbf{R}}_A^2 + \sum_a \frac{1}{2} m_e \dot{\mathbf{r}}_a^2 \\
&+ \frac{e^2}{4\pi\epsilon_0} \sum_A \sum_B \frac{Z_A Z_B}{|\mathbf{R}_B - \mathbf{R}_A|} - \frac{e^2}{4\pi\epsilon_0} \sum_A \sum_a \frac{Z_A}{|\mathbf{r}_a - \mathbf{R}_A|} + \frac{e^2}{4\pi\epsilon_0} \sum_a \sum_b \frac{1}{|\mathbf{r}_b - \mathbf{r}_a|}
\end{aligned}$$

Erwin Schrödinger

# Approximate methods of applying QM

## Born-Oppenheimer approximation (1927)

Max Born



Robert Oppenheimer

separate electronic and nuclear degrees of freedom

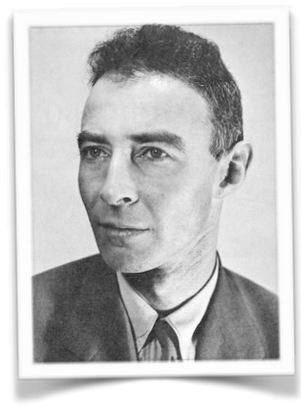
$$m_e << m_{\mathrm{H}+}$$

$$\Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...) = \Xi(\mathbf{R}_1, \mathbf{R}_2, ...)\Phi(\mathbf{r}_1, \mathbf{r}_2, ...)$$

# Approximate methods of applying QM

## Born-Oppenheimer approximation (1927)

Max Born



Robert Oppenheimer

separate electronic and nuclear degrees of freedom

$$m_e << m_{\mathrm{H}+}$$

$$\Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...) = \Xi(\mathbf{R}_1, \mathbf{R}_2, ...)\Phi(\mathbf{r}_1, \mathbf{r}_2, ...)$$

separate Schrödinger equations for nuclei & electrons

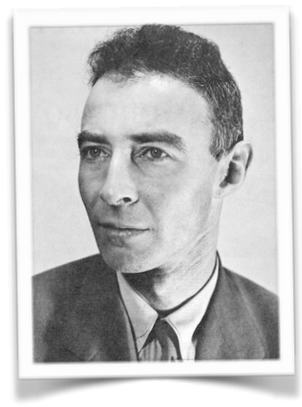
$$\begin{aligned} \hat{H}_e\Phi(\mathbf{r}_1, \mathbf{r}_2, ...) &= \left[\hat{T}_e(\dot{\mathbf{r}}_1, \dot{\mathbf{r}}_2, ...) + \hat{V}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...)\right]\Phi(\mathbf{r}_1, \mathbf{r}_2, ...) \\ &= V_e(\mathbf{R}_1, \mathbf{R}_2, ...)\Phi(\mathbf{r}_1, \mathbf{r}_2, ...) \end{aligned}$$

$$\hat{H}\Xi(\mathbf{R}_1, \mathbf{R}_2, ...) = \left[\hat{T}_n(\dot{\mathbf{R}}_1, \dot{\mathbf{R}}_2, ...) + V_e(\mathbf{R}_1, \mathbf{R}_2, ...)\right]\Xi(\mathbf{R}_1, \mathbf{R}_2) = E\Xi(\mathbf{R}_1, \mathbf{R}_2)$$

# Approximate methods of applying QM

## Born-Oppenheimer approximation (1927)

Max Born



Robert Oppenheimer

separate electronic and nuclear degrees of freedom

$$m_e << m_{\mathrm{H}+}$$

$$\Psi(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...) = \Xi(\mathbf{R}_1, \mathbf{R}_2, ...)\Phi(\mathbf{r}_1, \mathbf{r}_2, ...)$$

separate Schrödinger equations for nuclei & electrons

$$\begin{aligned} \hat{H}_e\Phi(\mathbf{r}_1, \mathbf{r}_2, ...) &= \left[\hat{T}_e(\dot{\mathbf{r}}_1, \dot{\mathbf{r}}_2, ...) + \hat{V}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{r}_1, \mathbf{r}_2, ...)\right]\Phi(\mathbf{r}_1, \mathbf{r}_2, ...) \\ &= V_e(\mathbf{R}_1, \mathbf{R}_2, ...)\Phi(\mathbf{r}_1, \mathbf{r}_2, ...) \end{aligned}$$

$$\hat{H}\Xi(\mathbf{R}_1, \mathbf{R}_2, ...) = \left[\hat{T}_n(\dot{\mathbf{R}}_1, \dot{\mathbf{R}}_2, ...) + V_e(\mathbf{R}_1, \mathbf{R}_2, ...)\right]\Xi(\mathbf{R}_1, \mathbf{R}_2) = E\Xi(\mathbf{R}_1, \mathbf{R}_2)$$

electronic potential energy surface

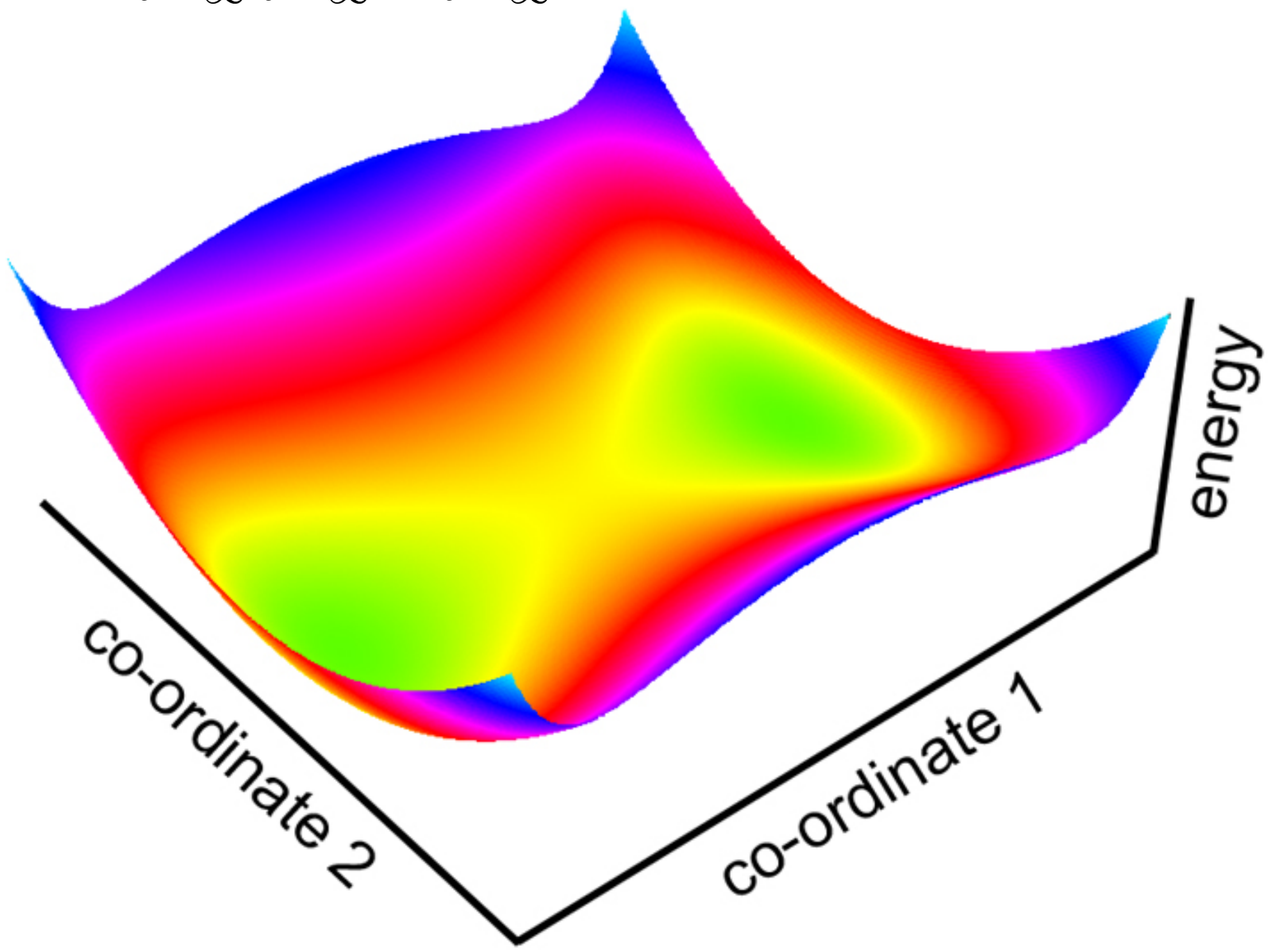
$$V_e(\mathbf{R}_1, \mathbf{R}_2, ...) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}...\int_{-\infty}^{\infty}\Phi^*(\mathbf{r}_1, \mathbf{r}_2, ...)\hat{H}_e\Phi(\mathbf{r}_1, \mathbf{r}_2, ...)d\mathbf{r}_1 d\mathbf{r}_2 ... d\mathbf{r}_n$$

# Approximate methods of applying QM

## Born-Oppenheimer approximation (1927)

potential energy surface on which nuclei move

$$V_e(\mathbf{R}_1, \mathbf{R}_2, ...) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} ... \int_{-\infty}^{\infty} \Phi^*(\mathbf{r}_1, \mathbf{r}_2, ...) \hat{H}_e \Phi(\mathbf{r}_1, \mathbf{r}_2, ...) d\mathbf{r}_1 d\mathbf{r}_2 ... d\mathbf{r}_n$$

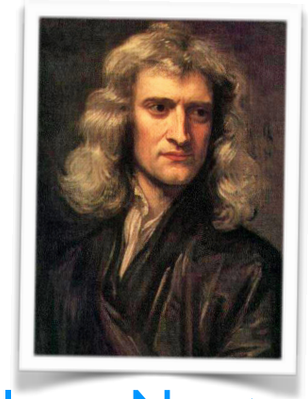


# Approximate methods of applying QM

## classical approximation for nuclei

### Newton's equations of motion

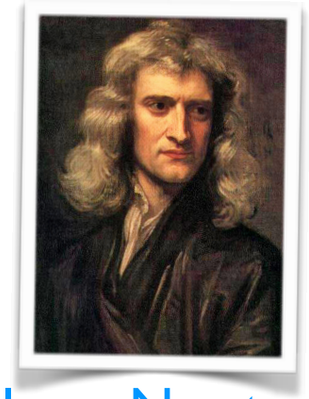
$$F_B = m_B \mathbf{a}_B = -\nabla_{\mathbf{R}_B} V_e(\mathbf{R}_1, \mathbf{R}_2, ...)$$



Isaac Newton

# Approximate methods of applying QM

## classical approximation for nuclei

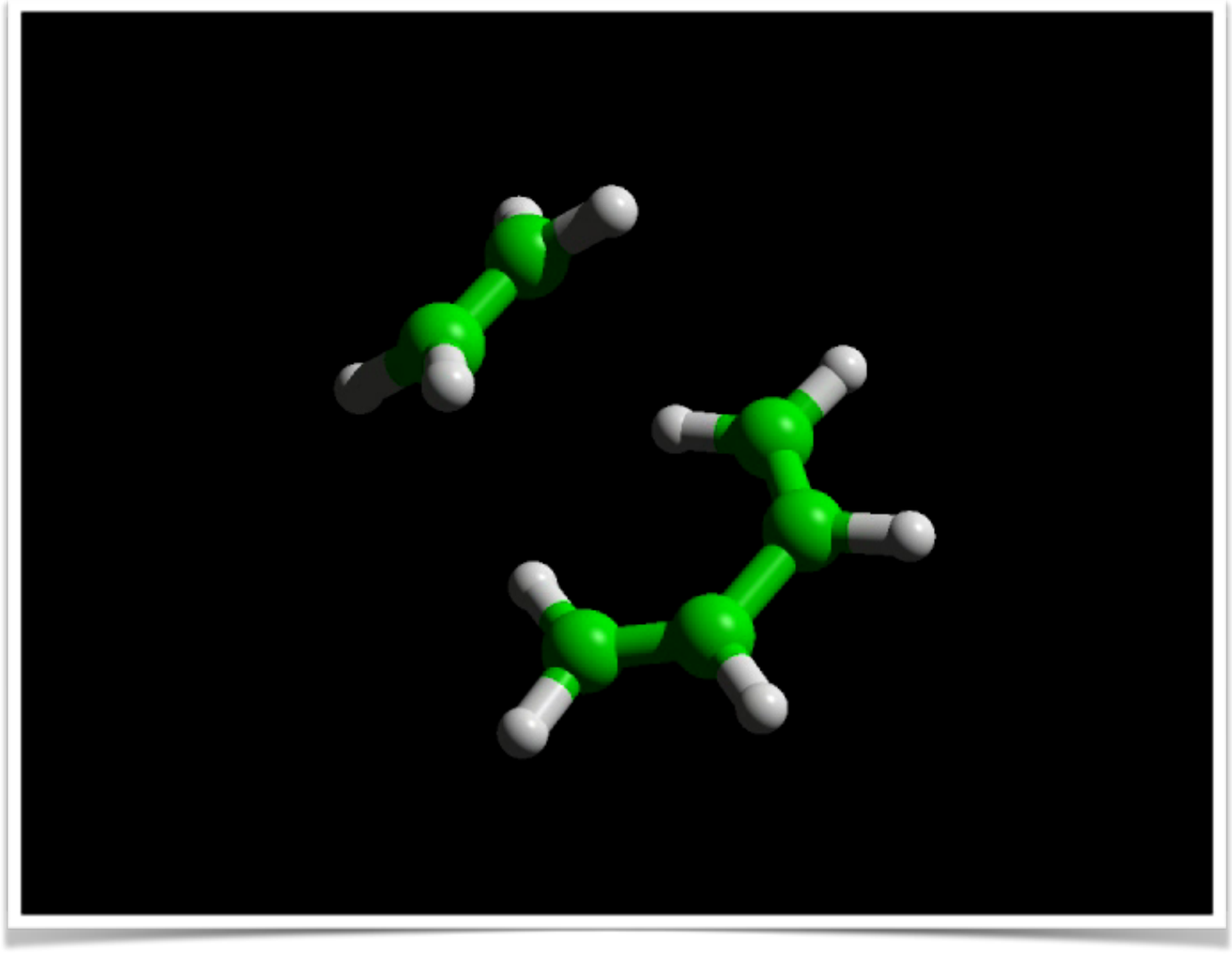


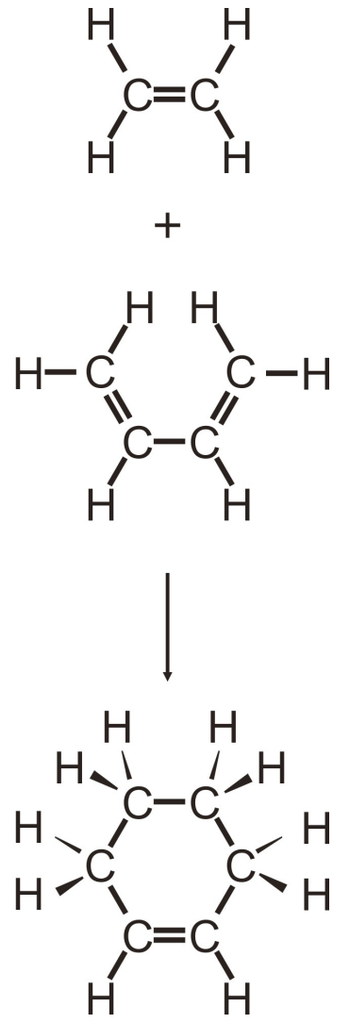
Isaac Newton

### Newton's equations of motion

$$F_B = m_B \mathbf{a}_B = -\nabla_{\mathbf{R}_B} V_e(\mathbf{R}_1, \mathbf{R}_2, ...)$$

### example: Diels-Alder reaction





# Approximate methods of applying QM

## approximations for electronic wave function

### Hartree Fock & beyond (1927)

$$\Phi(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_n) = \hat{A}\phi_1(\mathbf{r}_1)\phi_2(\mathbf{r}_2)...\phi_n(\mathbf{r}_n)$$

3N dimensions

10 - 1000 atoms


Douglas Hartree | Vladimir Fock | John Slater

# Approximate methods of applying QM

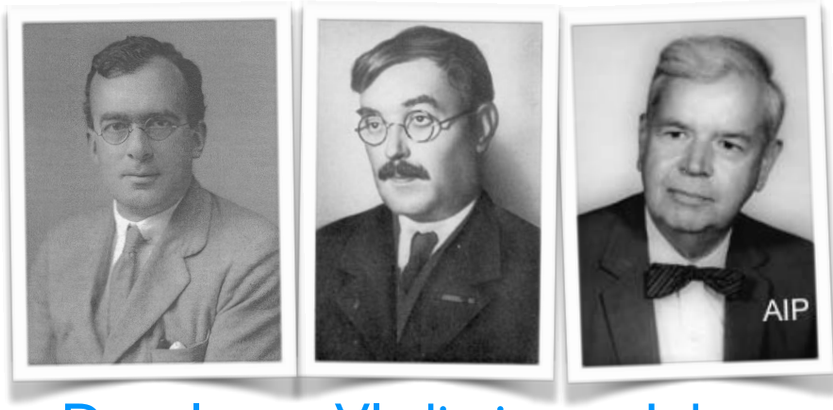
## approximations for electronic wave function

### Hartree Fock & beyond (1927)

$$\Phi(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_n) = \hat{A}\phi_1(\mathbf{r}_1)\phi_2(\mathbf{r}_2)...\phi_n(\mathbf{r}_n)$$

3N dimensions

10 - 1000 atoms



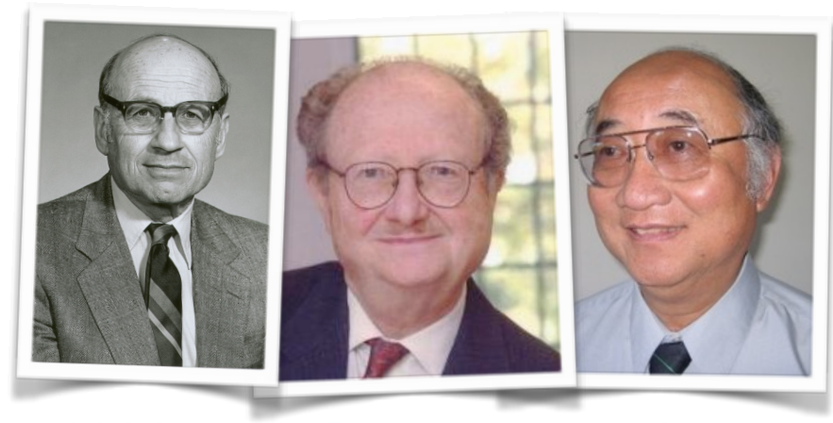

Douglas Hartree | Vladimir Fock | John Slater

### density functional theory (1964)

$$\rho(\mathbf{r}) \Longrightarrow \Phi_0(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_n)$$

3 dimensions

100 - 10000 atoms



Walter Kohn | Pierre Hohenberg | Lu Sham

# Approximate methods of applying QM

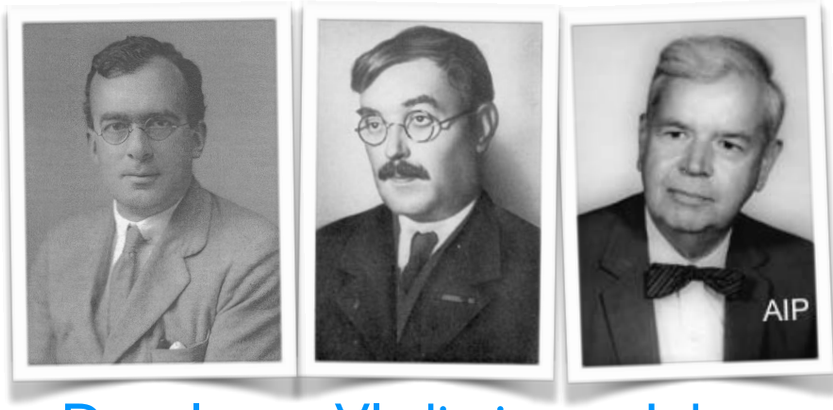
## approximations for electronic wave function

### Hartree Fock & beyond (1927)

$$\Phi(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_n) = \hat{A}\phi_1(\mathbf{r}_1)\phi_2(\mathbf{r}_2)...\phi_n(\mathbf{r}_n)$$

3N dimensions

10 - 1000 atoms



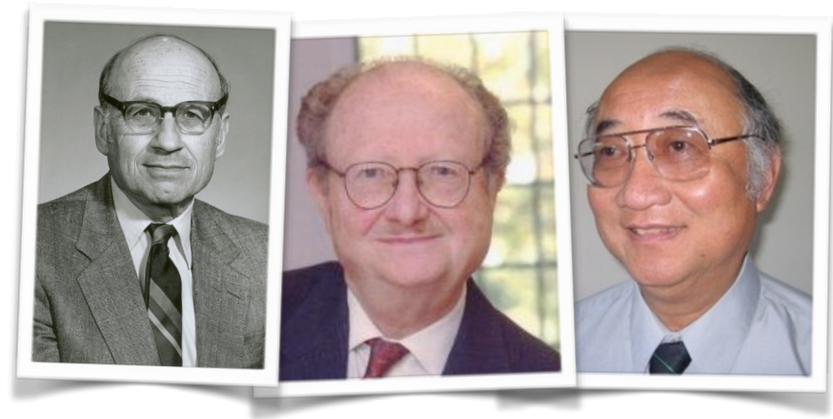

Douglas Hartree | Vladimir Fock | John Slater

### density functional theory (1964)

$$\rho(\mathbf{r}) \Longrightarrow \Phi_0(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_n)$$

3 dimensions

100 - 10000 atoms



Walter Kohn | Pierre Hohenberg | Lu Sham

### molecular mechanics force field (1970's)

forget about electrons!!!

low-dimensional functions & parameters

$$V^{\mathrm{MM}}(R_1, R_2, ..., R_N) = \sum_k v_k(R_i, R_j, R_k, R_l; \{p_k\})$$

Martin Karplus | Michael Levitt | Arieh Warshel

# Molecular Mechanics Force Field

throw away the electrons!!!

low-dimensional functions

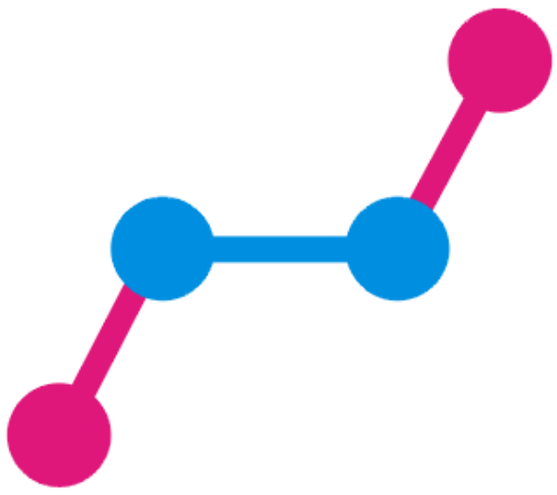
empirical parameters

experimental data & *ab initio* calculations

$$V^{\mathrm{MM}}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = \sum_k v_k(\mathbf{R}_A, \mathbf{R}_B, \mathbf{R}_C, \mathbf{R}_D; \mathbf{p}_k)$$

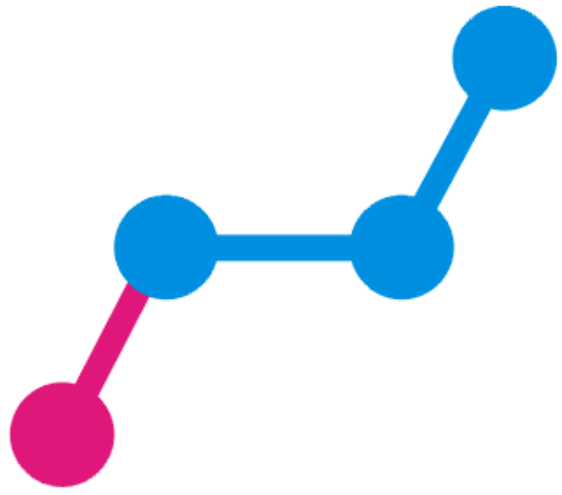
covalent interactions

bond



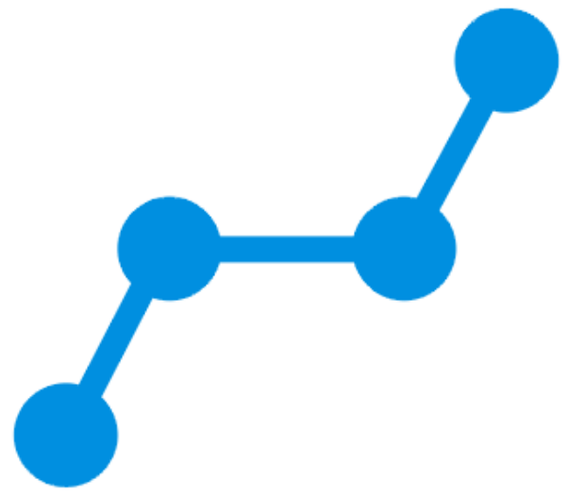
$$v_{\mathrm{b}}(\mathbf{R}_A, \mathbf{R}_B) = \frac{1}{2} k_b (R_{AB} - r_0)^2$$

angle



$$v_{\mathrm{a}}(\mathbf{R}_A, \mathbf{R}_B, \mathbf{R}_C) = \frac{1}{2} k_a (\theta_{ABC} - \theta_0)^2$$

torsion



$$v_{\mathrm{d}}(\mathbf{R}_A, \mathbf{R}_B, \mathbf{R}_C, \mathbf{R}_D) = \sum_n^5 k_n (\cos(\varphi_{ABCD}))^n$$

# Molecular Mechanics Force Field

throw away the electrons!!!

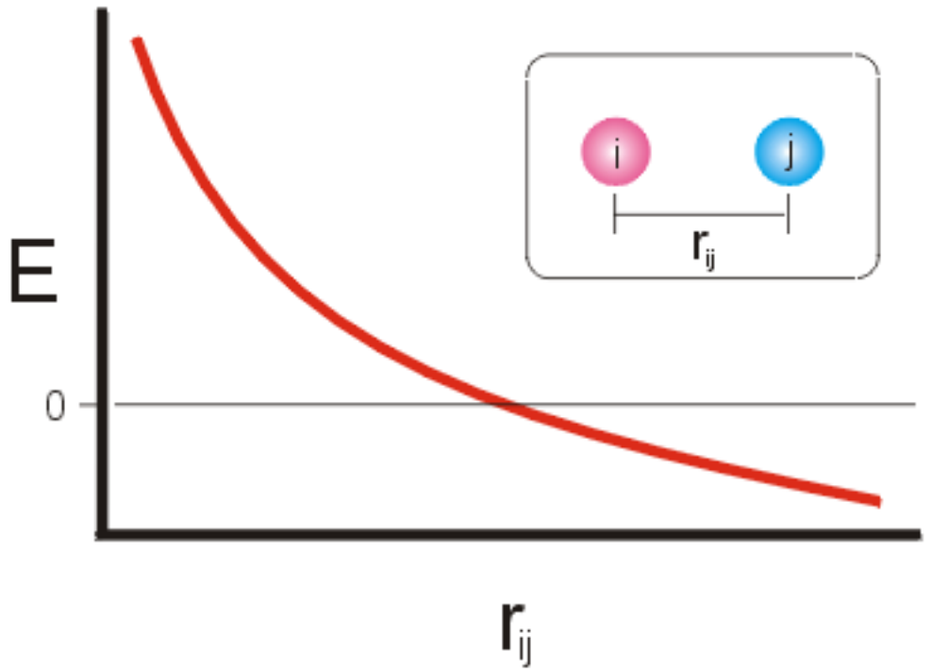
low-dimensional functions

empirical parameters

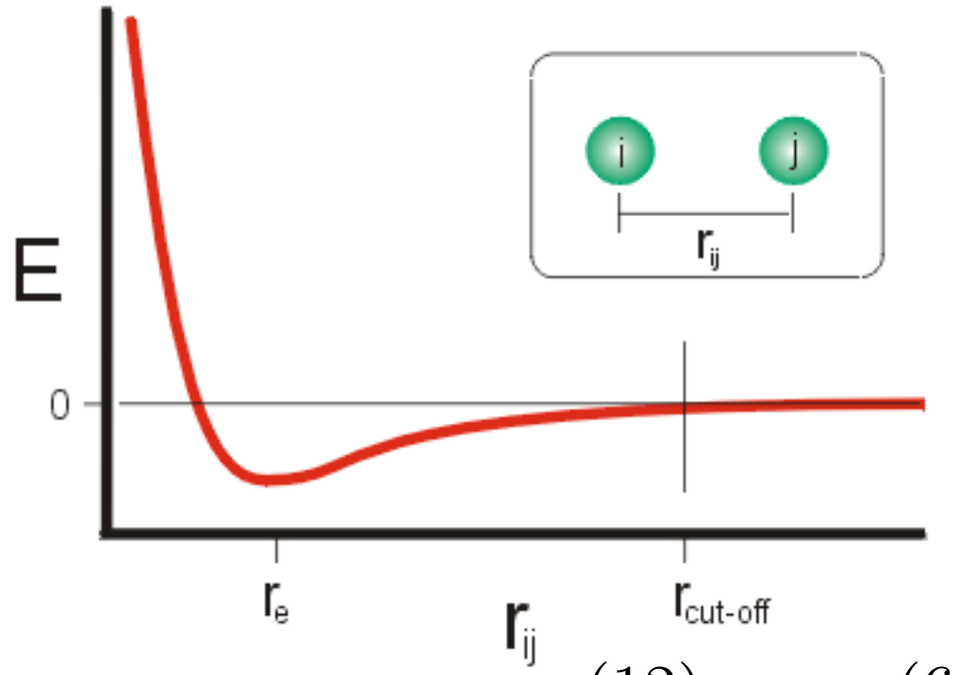
experimental data & *ab initio* calculations

$$V^{\mathrm{MM}}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = \sum_k v_k(\mathbf{R}_A, \mathbf{R}_B, \mathbf{R}_C, \mathbf{R}_D; \mathbf{p}_k)$$

non-covalent interactions

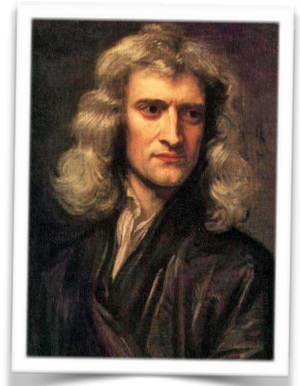



$$v_{\mathrm{Coul}}(\mathbf{R}_A, \mathbf{R}_B) = \frac{e^2 q_A q_B}{4\pi\epsilon_0 R_{AB}}$$




$$v_{\mathrm{LJ}}(\mathbf{R}_A, \mathbf{R}_B) = \frac{C_{AB}^{(12)}}{R_{AB}^{12}} - \frac{C_{AB}^{(6)}}{R_{AB}^{6}}$$

# Molecular dynamics simulations

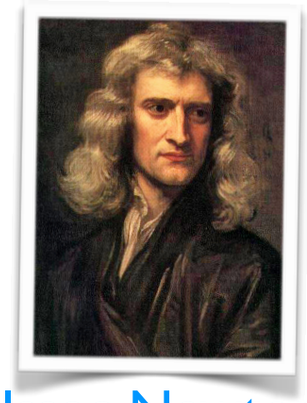


Isaac Newton

classical nuclei

$$\mathbf{F}_i = -\nabla_{\mathbf{R}_i} V(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = m_i \frac{d^2}{dt^2} \mathbf{R}_i$$

# Molecular dynamics simulations



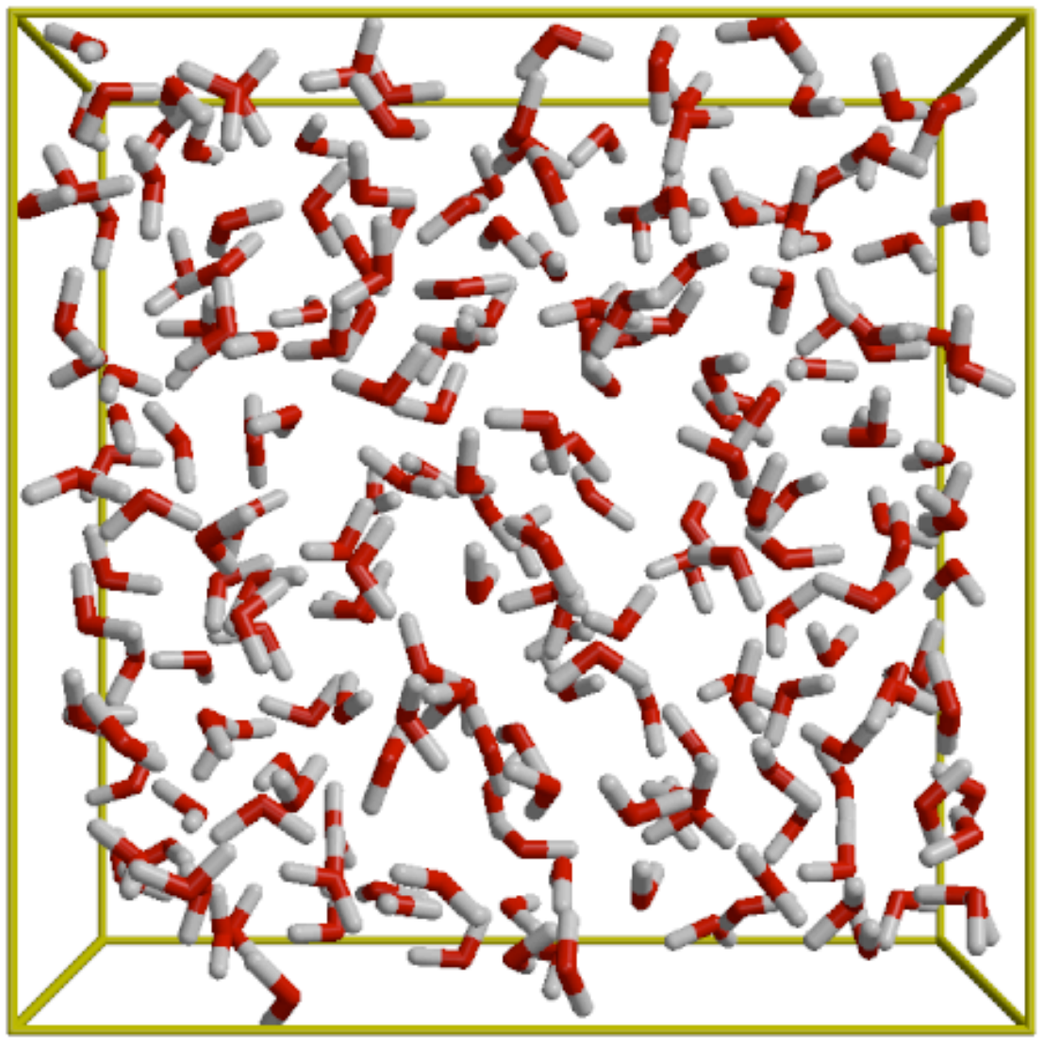
Isaac Newton

classical nuclei

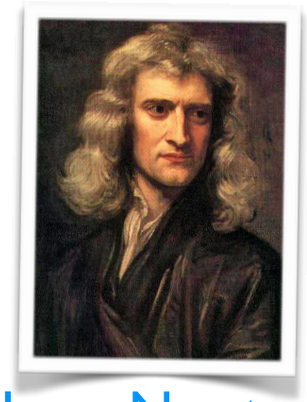
$$\mathbf{F}_i = -\nabla_{\mathbf{R}_i} V(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = m_i \frac{d^2}{dt^2} \mathbf{R}_i$$

trajectory

jiggling & wiggling



# Molecular dynamics simulations



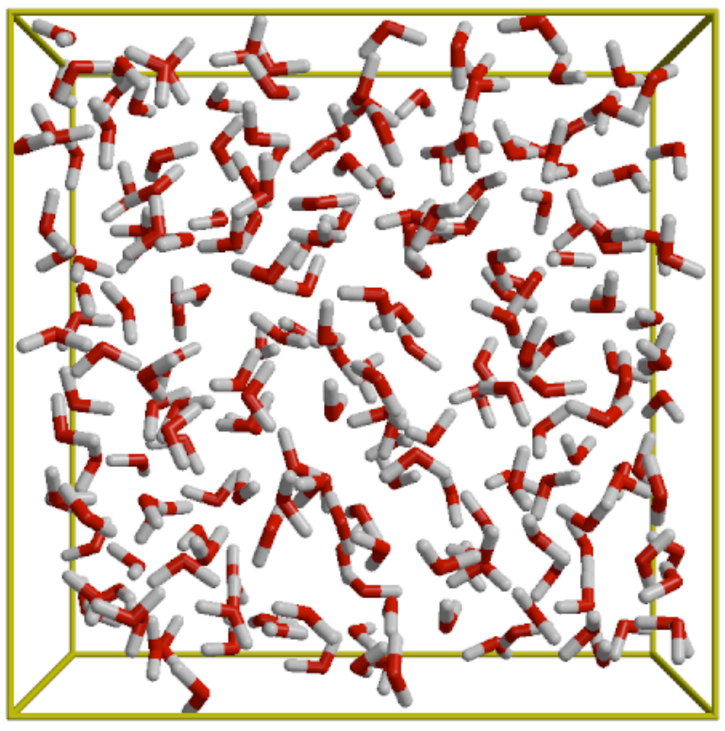
Isaac Newton

classical nuclei

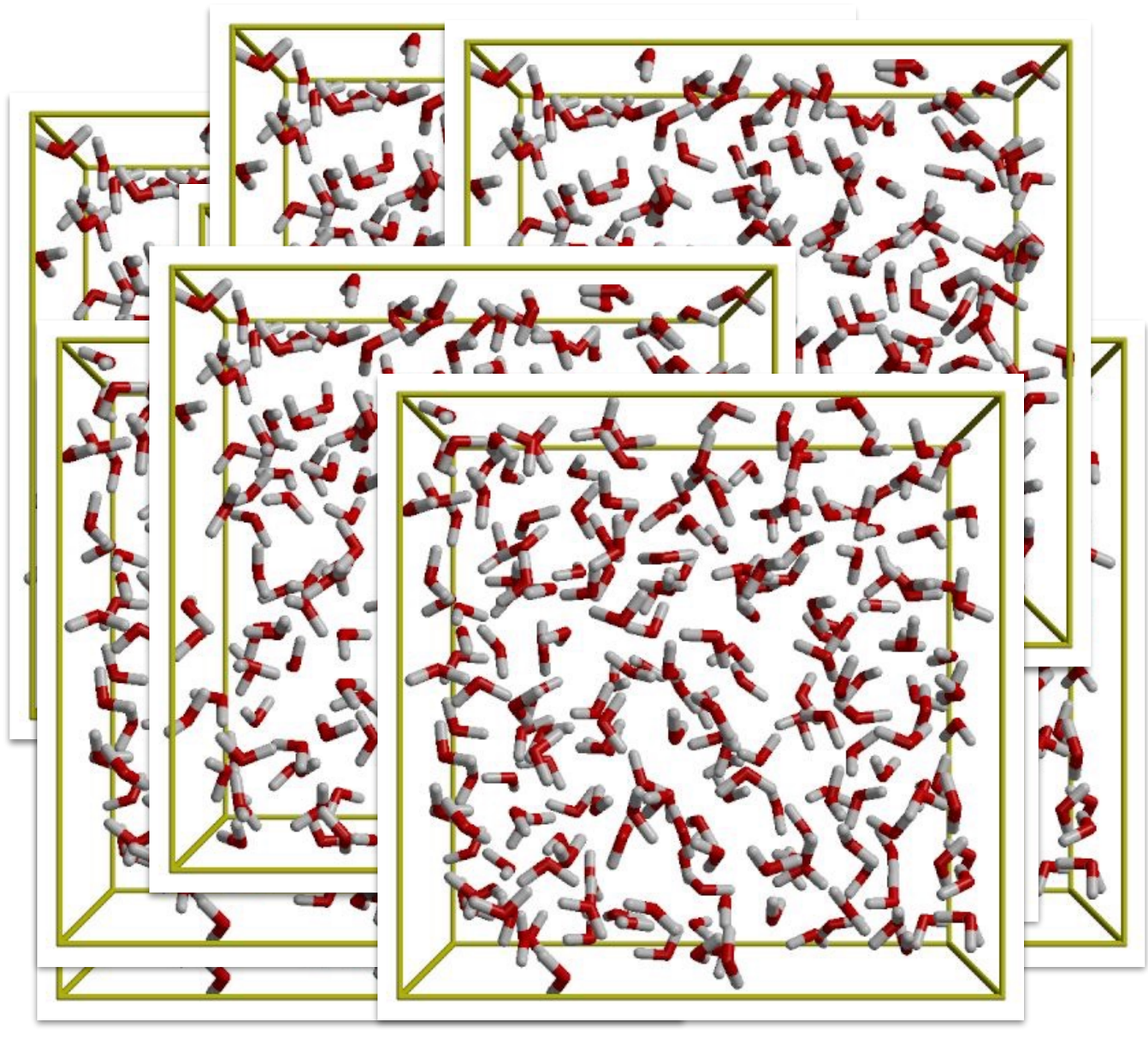
$$\mathbf{F}_i = -\nabla_{\mathbf{R}_i} V(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = m_i \frac{d^2}{dt^2} \mathbf{R}_i$$

trajectory

ergodicity



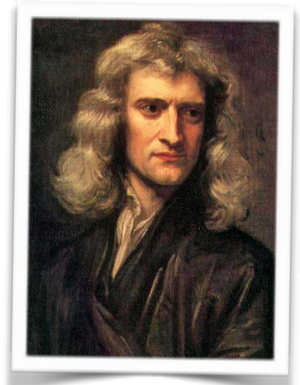
≡



trajectory

ensemble

# Molecular dynamics simulations



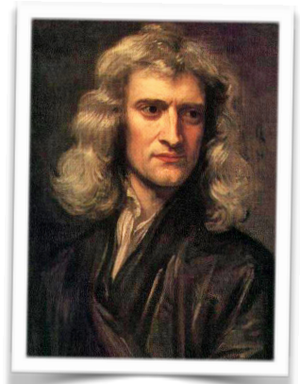
Isaac Newton

classical nuclei

$$\mathbf{F}_i = -\nabla_{\mathbf{R}_i} V(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = m_i \frac{d^2}{dt^2} \mathbf{R}_i$$

potential energy functions

# Molecular dynamics simulations



Isaac Newton

classical nuclei

$$\mathbf{F}_i = -\nabla_{\mathbf{R}_i} V(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = m_i \frac{d^2}{dt^2} \mathbf{R}_i$$

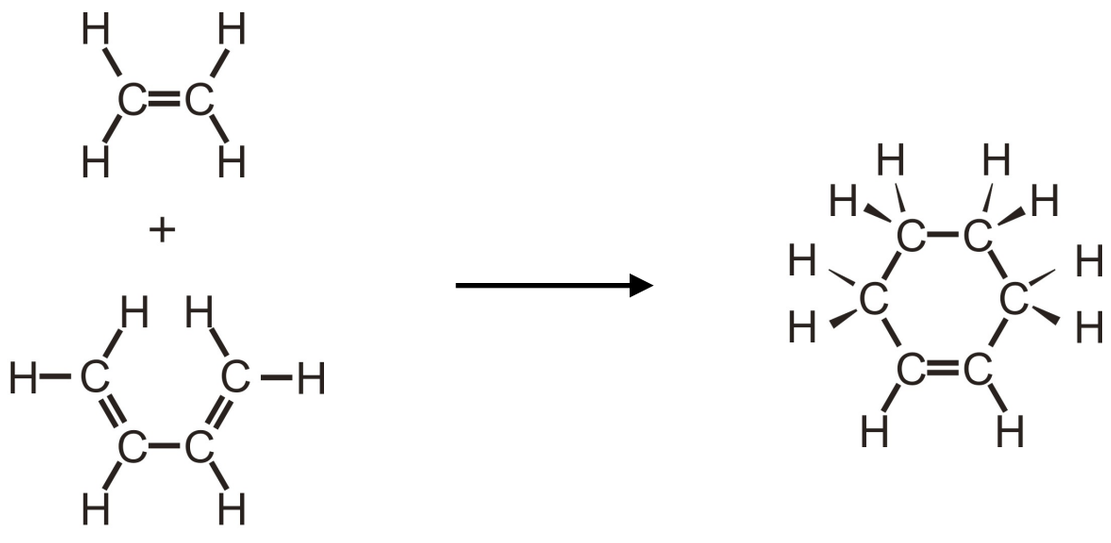
potential energy functions

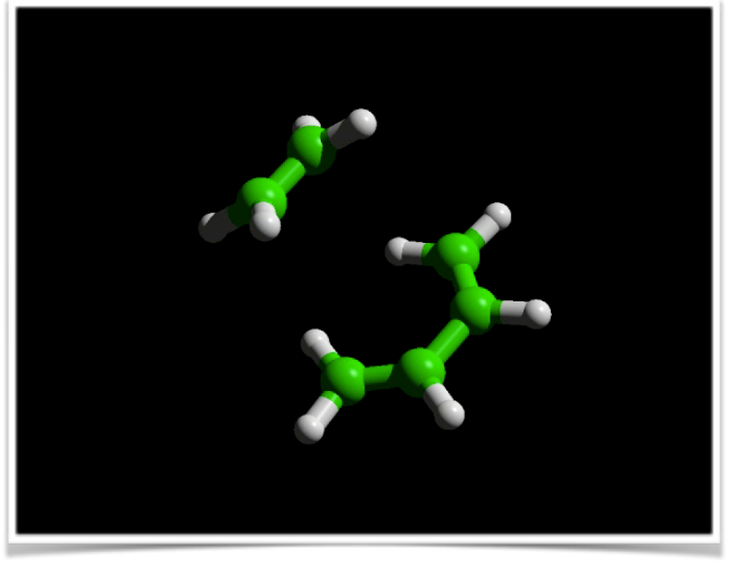
quantum chemistry (QM)

Erwin Schrödinger

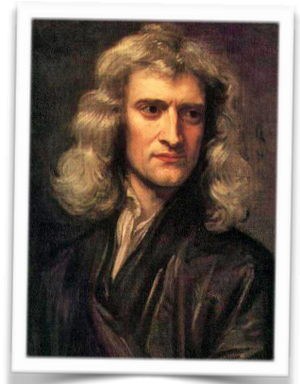
$$V^{\mathrm{QM}}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) =$$

$$\langle \Psi_e(\mathbf{r}_1, \mathbf{r}_2, ...\mathbf{r}_n) | \hat{H}_e(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) | \Psi_e(\mathbf{r}_1, \mathbf{r}_2, ...\mathbf{r}_n) \rangle$$





# Molecular dynamics simulations



Isaac Newton

classical nuclei

$$\mathbf{F}_i = -\nabla_{\mathbf{R}_i} V(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = m_i \frac{d^2}{dt^2} \mathbf{R}_i$$

potential energy functions

quantum chemistry (QM)

Erwin Schrödinger

$$V^{\mathrm{QM}}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) =$$

$$\langle \Psi_e(\mathbf{r}_1, \mathbf{r}_2, ...\mathbf{r}_n) | \hat{H}_e(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) | \Psi_e(\mathbf{r}_1, \mathbf{r}_2, ...\mathbf{r}_n) \rangle$$

molecular mechanics (MM)

empirical functions with parameters

$$V^{\mathrm{MM}}(R_1, R_2, ..., R_N) = \sum_k v_k(R_i, R_j, R_k, R_l; \{p_k\})$$

# Molecular Mechanics Force Field

throw away the electrons!!!

low-dimensional functions

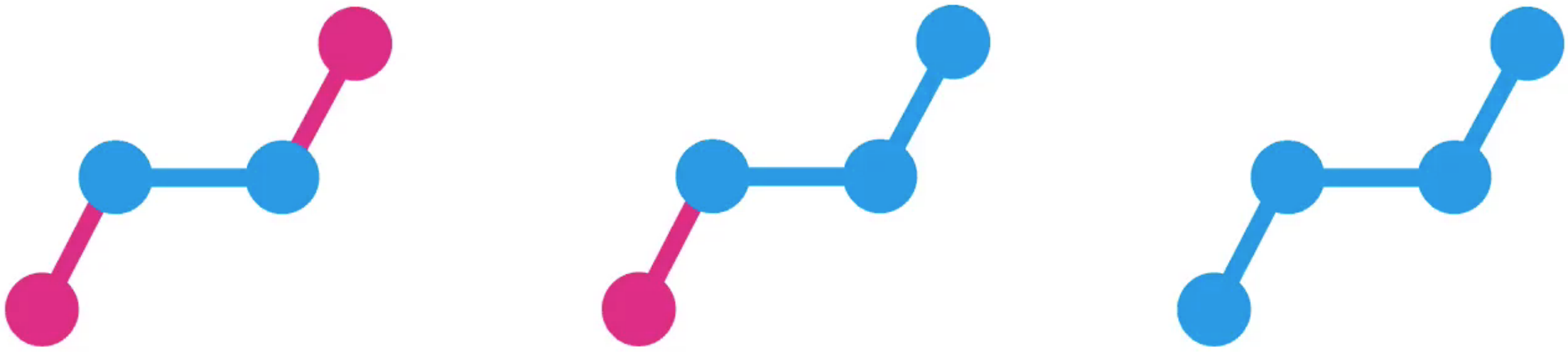
empirical parameters

experimental data & *ab initio* calculations

Martin Karplus | Michael Levitt | Arieh Warshel

$$V^{\mathrm{MM}}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = \sum_k v_k(\mathbf{R}_A, \mathbf{R}_B, \mathbf{R}_C, \mathbf{R}_D; \mathbf{p}_k)$$

bonded interactions



$$v_{\mathrm{b}}(\mathbf{R}_A, \mathbf{R}_B) = \frac{1}{2} k_b (R_{AB} - r_0)^2 \quad v_{\mathrm{a}}(\mathbf{R}_A, \mathbf{R}_B, \mathbf{R}_C) = \frac{1}{2} k_a (\theta_{ABC} - \theta_0)^2 \quad v_{\mathrm{d}}(\mathbf{R}_A, \mathbf{R}_B, \mathbf{R}_C, \mathbf{R}_D) = \sum_n^5 k_n (\cos(\varphi_{ABCD}))^n$$

# Molecular Mechanics Force Field

throw away the electrons!!!

low-dimensional functions

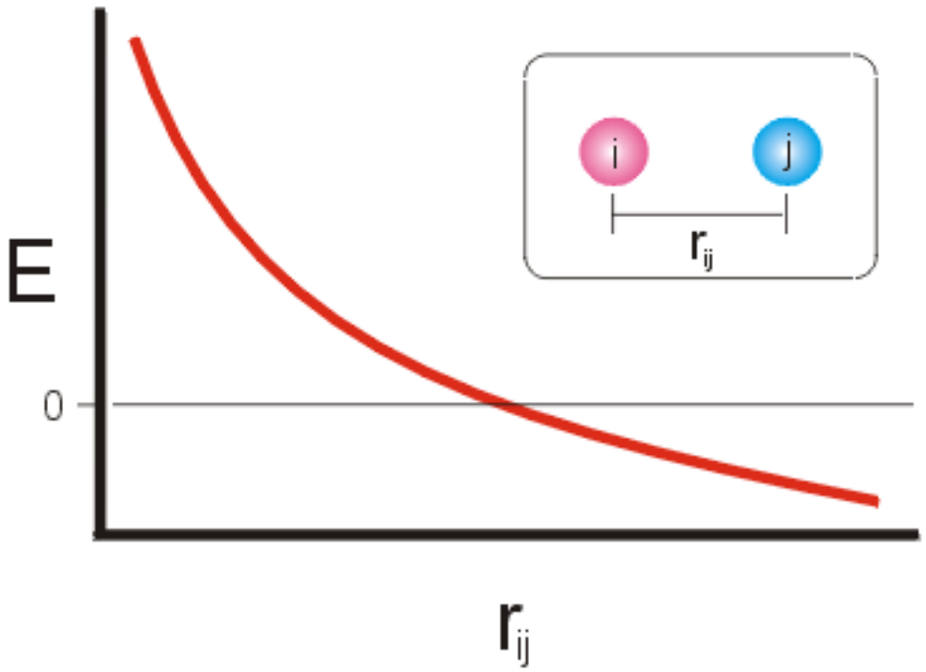
empirical parameters

experimental data & *ab initio* calculations

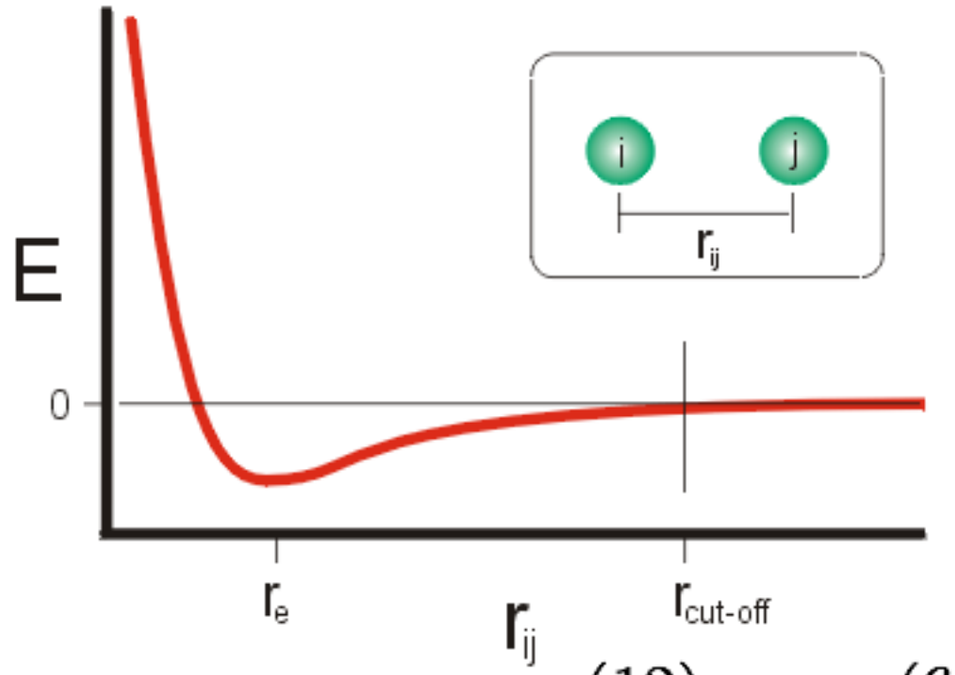
Martin Karplus | Michael Levitt | Arieh Warshel

$$V^{\mathrm{MM}}(\mathbf{R}_1, \mathbf{R}_2, ..., \mathbf{R}_N) = \sum_k v_k(\mathbf{R}_A, \mathbf{R}_B, \mathbf{R}_C, \mathbf{R}_D; \mathbf{p}_k)$$

bonded interactions




$$v_{\mathrm{Coul}}(\mathbf{R}_A, \mathbf{R}_B) = \frac{e^2 q_A q_B}{4\pi\epsilon_0 R_{AB}}$$

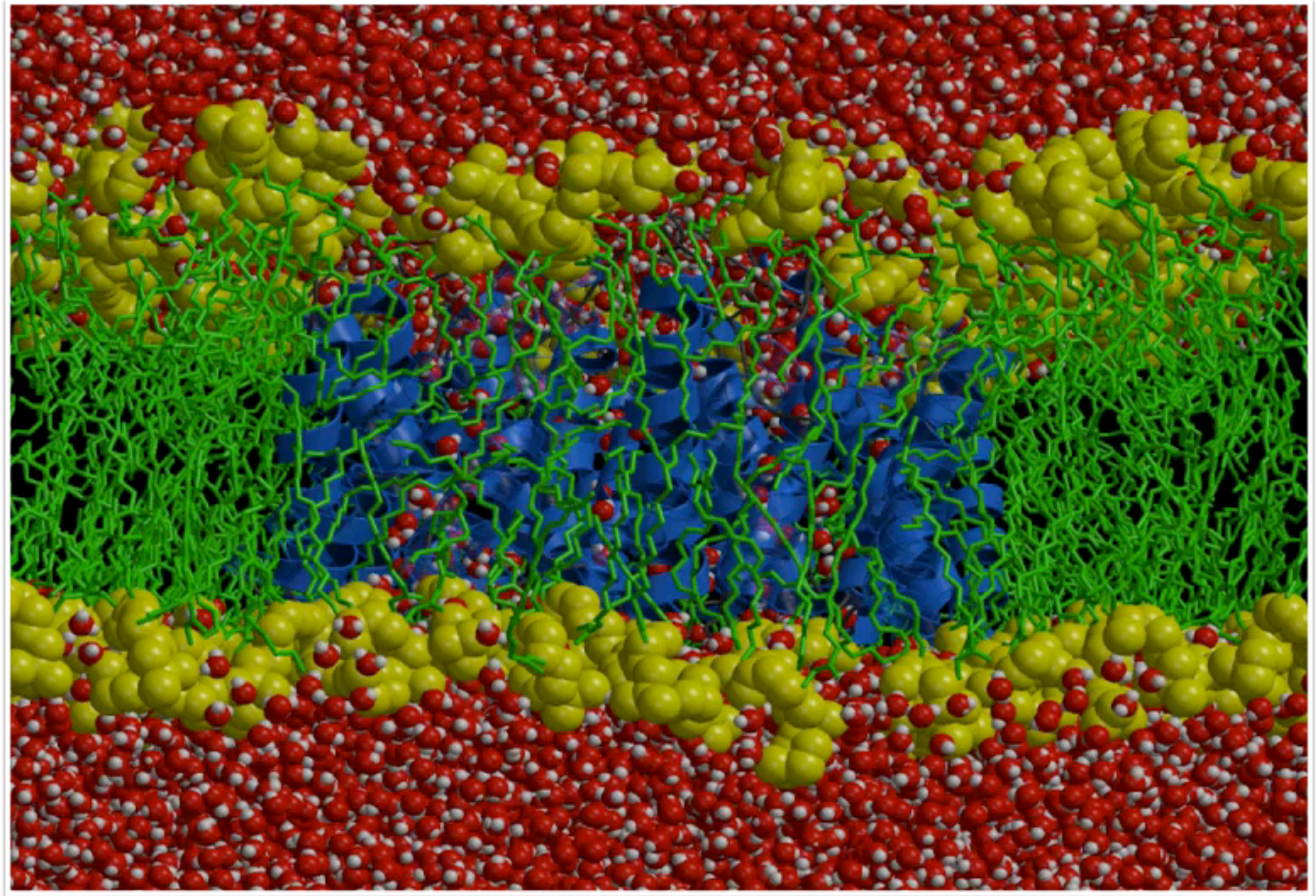



$$v_{\mathrm{LJ}}(\mathbf{R}_A, \mathbf{R}_B) = \frac{C_{AB}^{(12)}}{R_{AB}^{12}} - \frac{C_{AB}^{(6)}}{R_{AB}^{6}}$$

# Chemistry without test-tubes

observe jiggling and wiggling

MD simulation of aqua-porin water channel

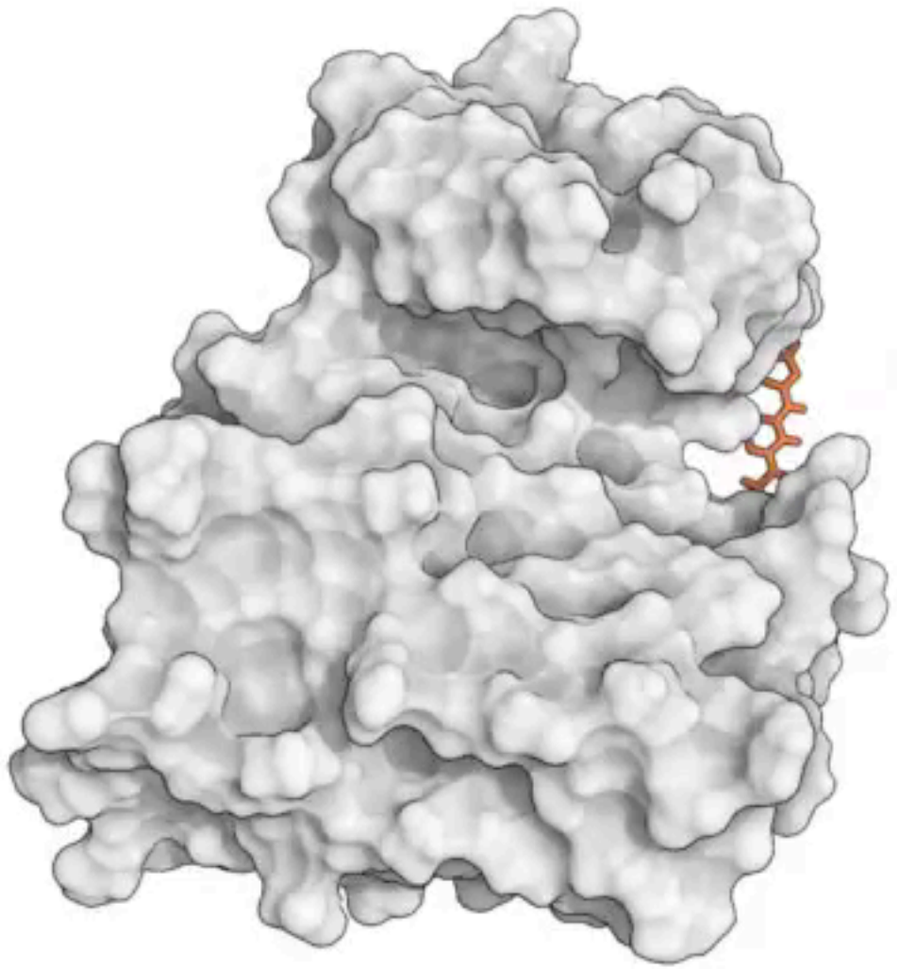


B. L. de Groot & H. Grubmüller. Science 294 (2001): 2353

# Chemistry without test-tubes

## how drugs bind their targets

all-atom simulations of 2.3 μs (in total 35 μs)



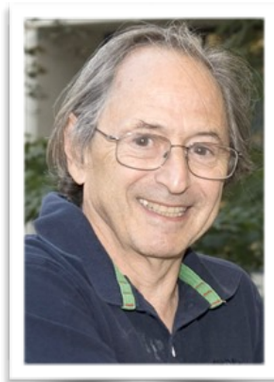
Y Shan, E. T. Kim, M. P. Eastwood, R. O. Dror, M. A. Seeliger & D. E. Shaw: *J. Am. Chem. Soc.* **133** (2011): 9181

# Chemistry without test-tubes

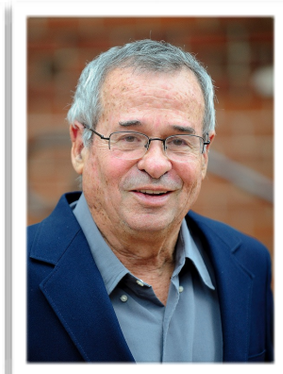
hybrid quantum mechanics /molecular mechanics

active site: quantum mechanics for electrons

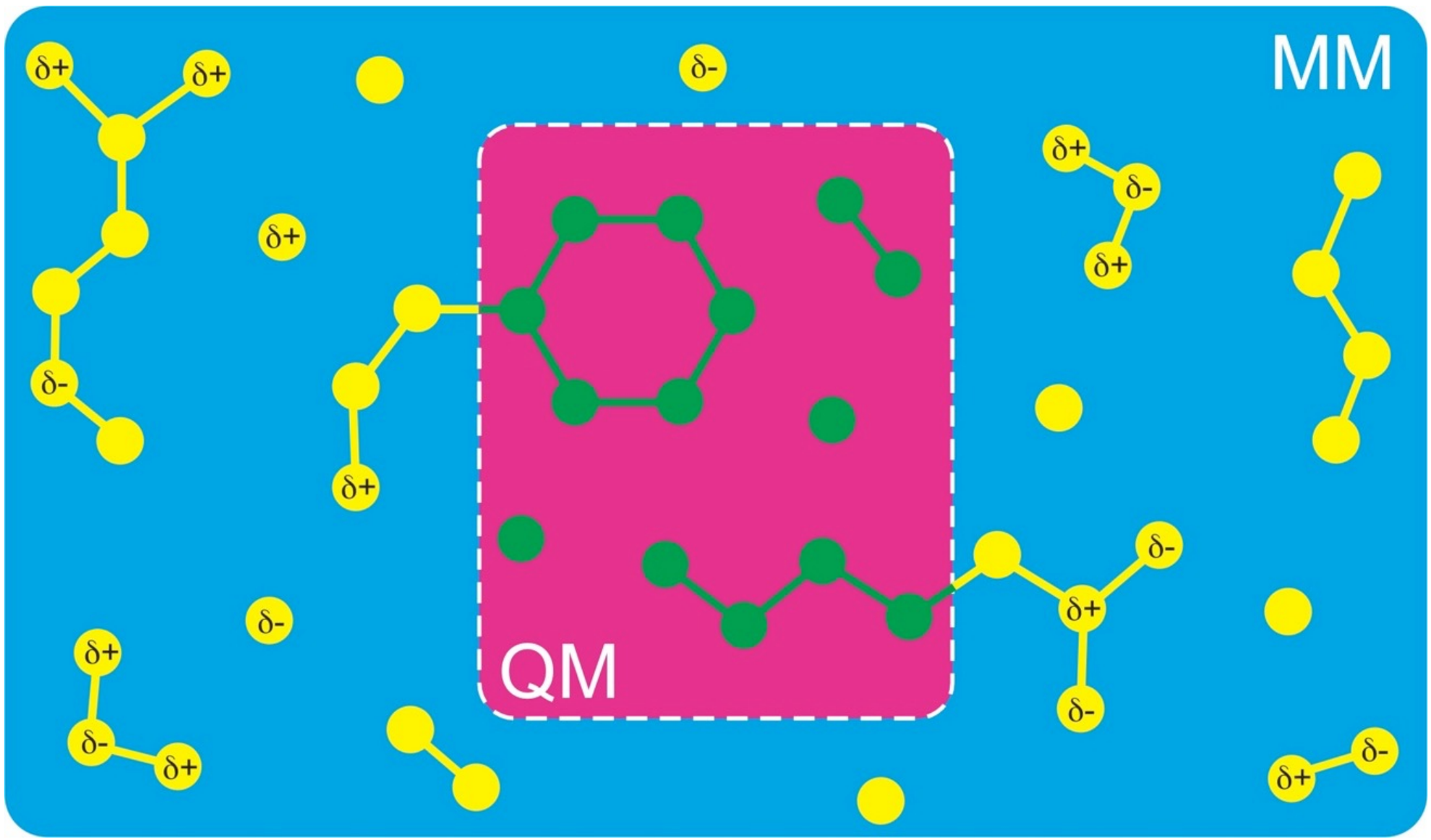
rest: molecular mechanics force field



Michael Levitt



Arieh Warshel



# Chemistry without test-tubes

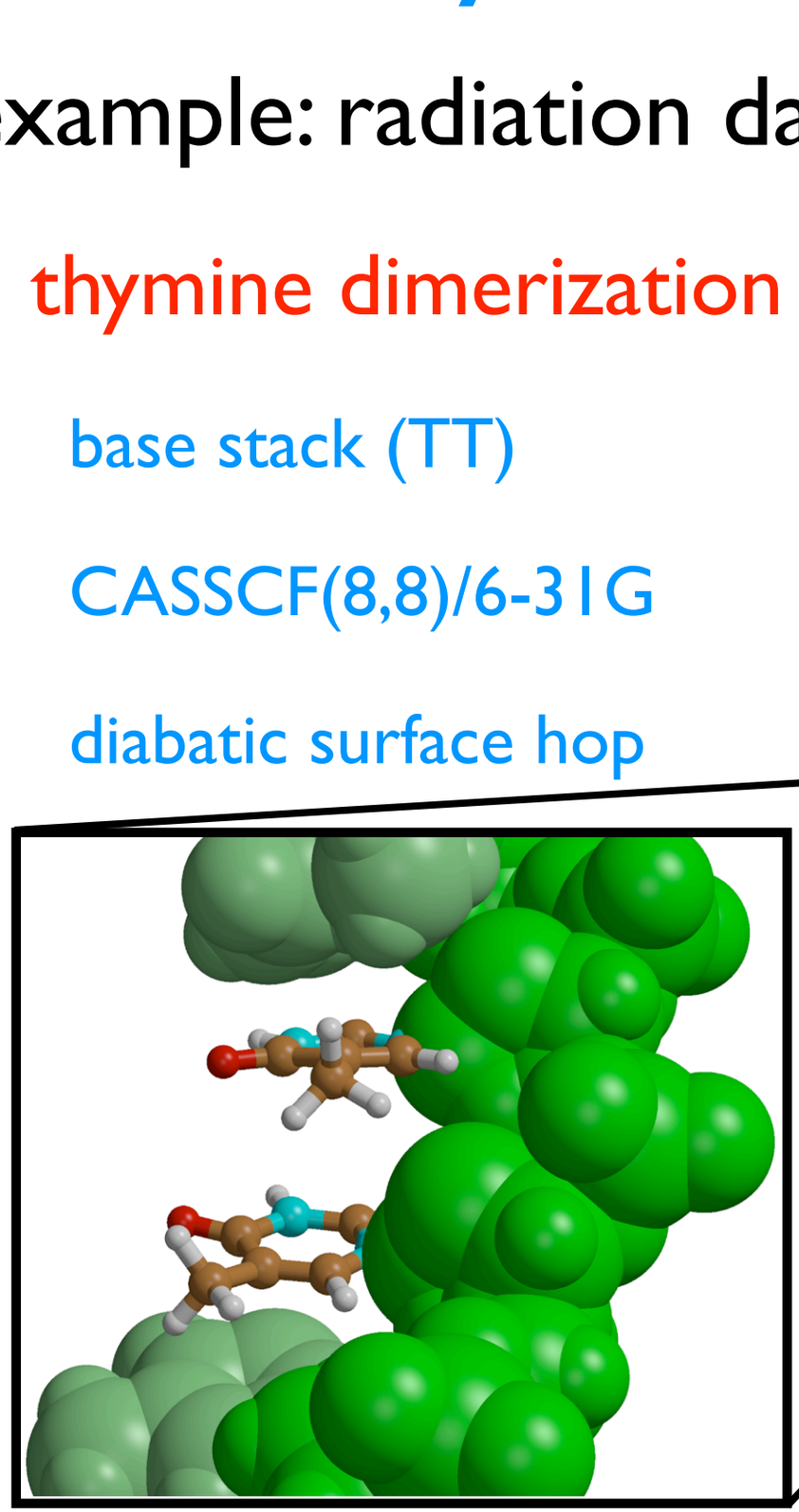
example: radiation damage in DNA

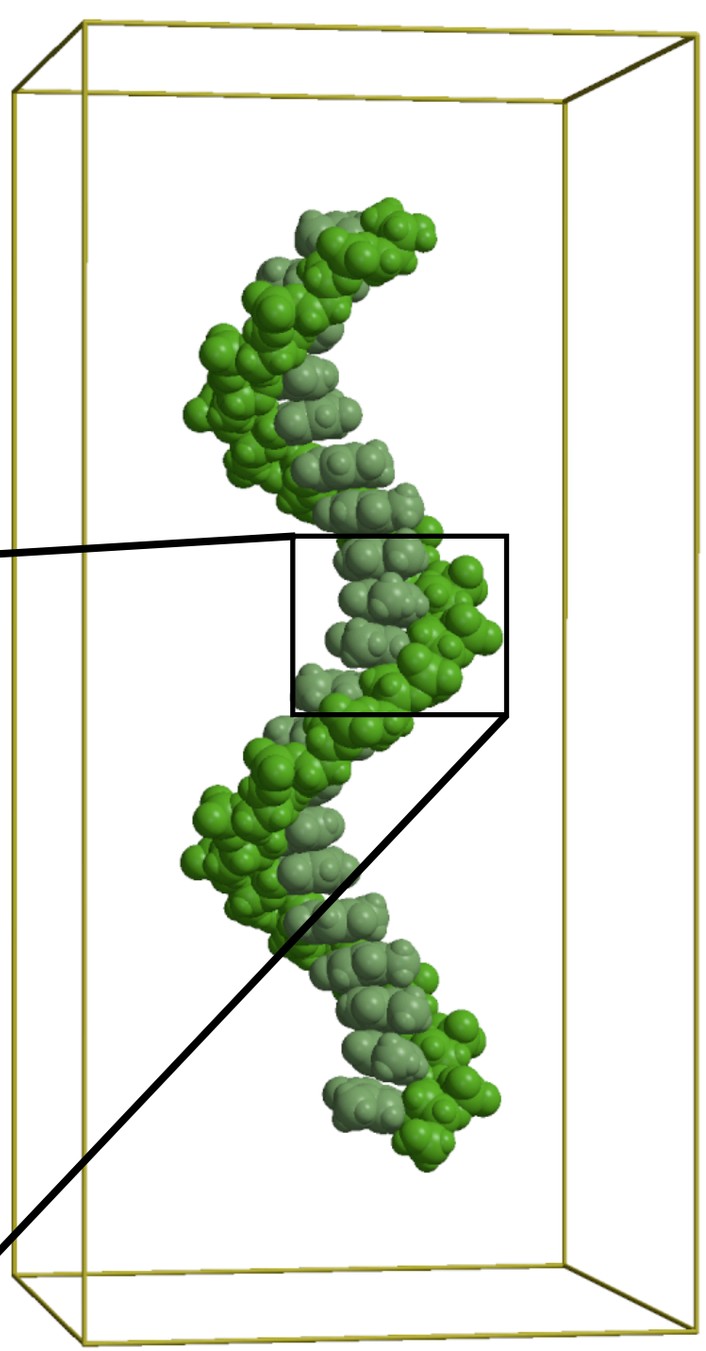
thymine dimerization

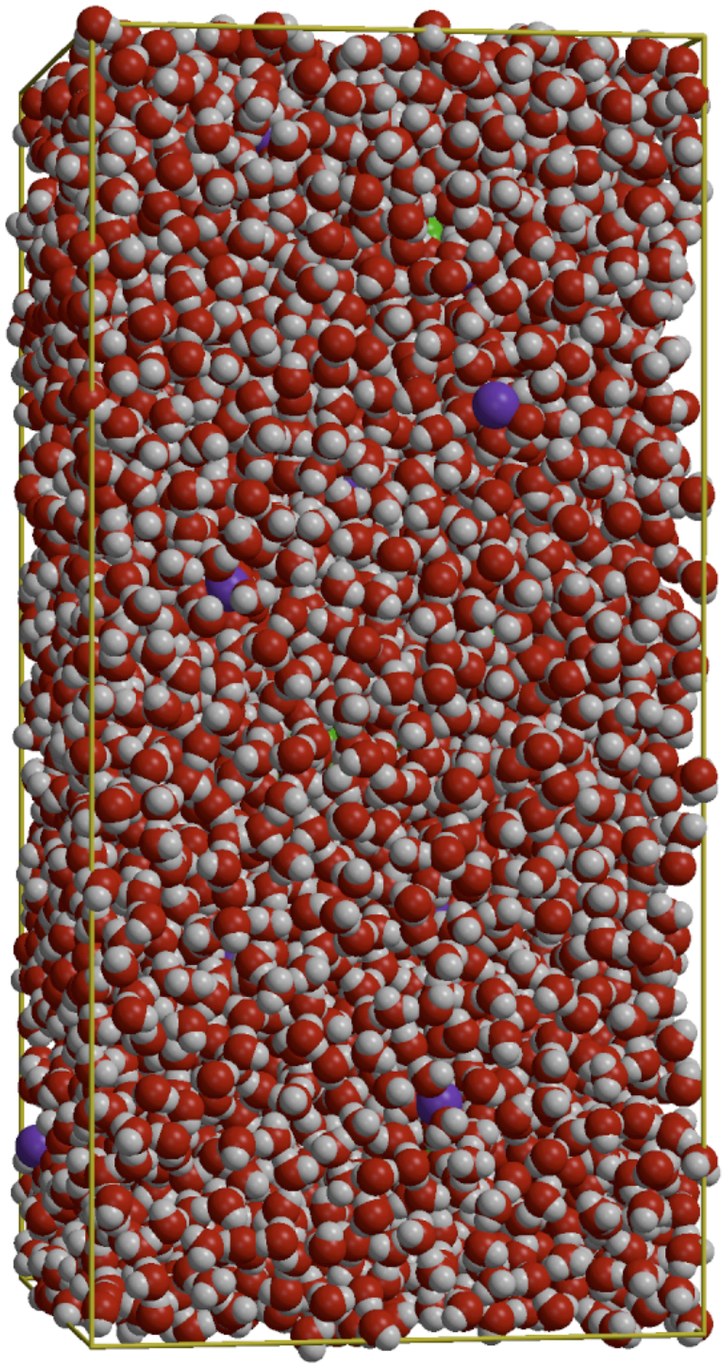
base stack (TT)

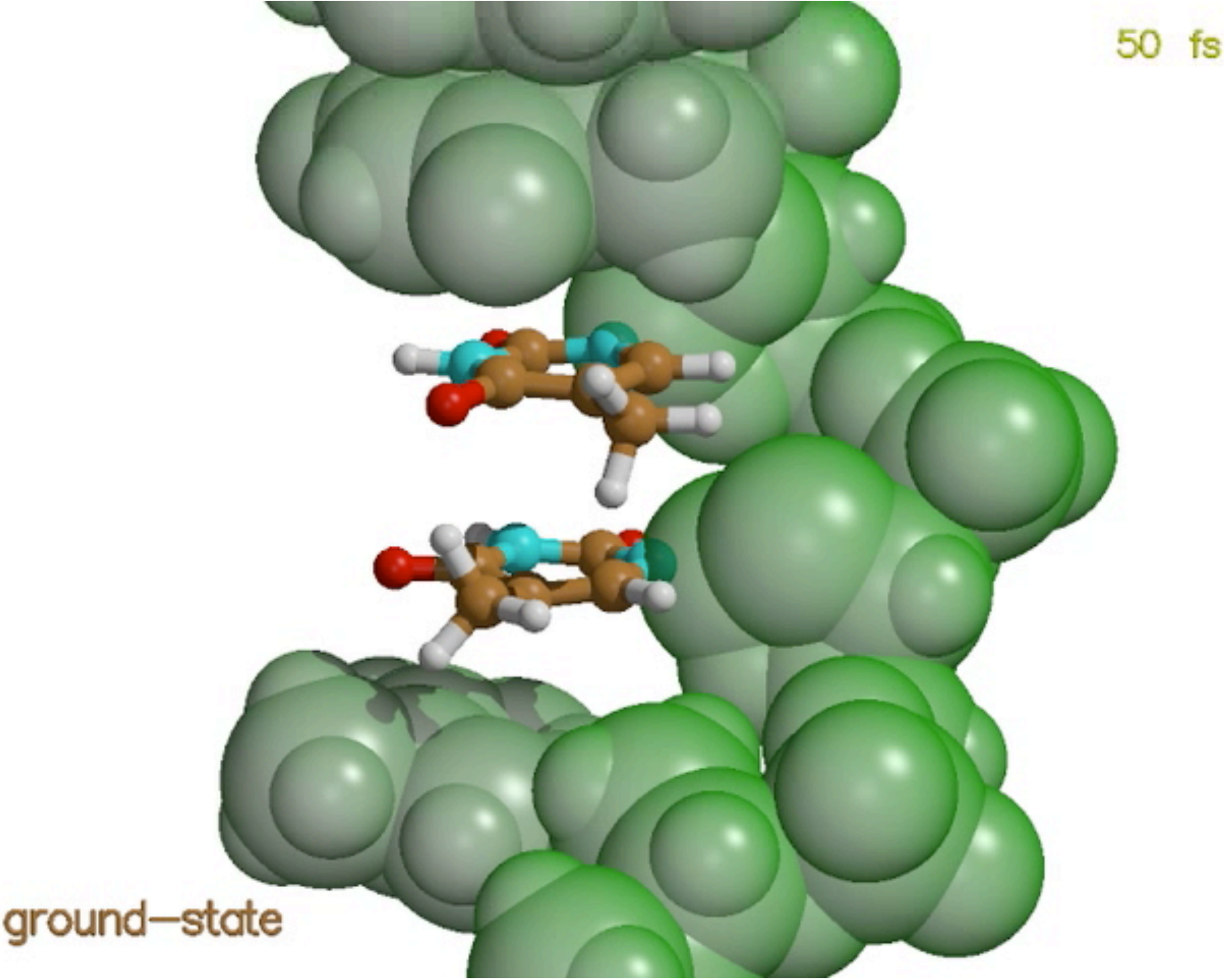
CASSCF(8,8)/6-31G

diabatic surface hop





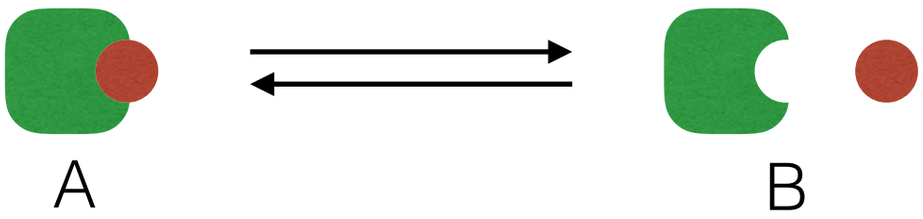



50 fs
ground–state

# Chemistry without test-tubes

## calculating free energies in MD simulations

e.g. binding



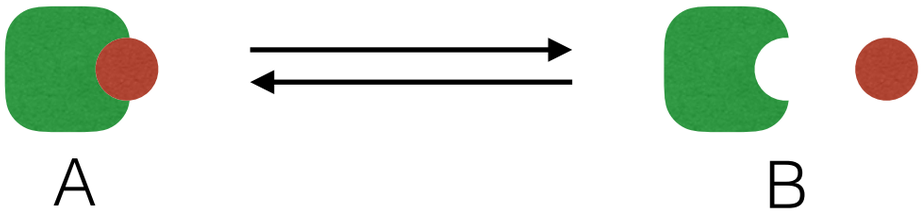

$$G_A = -kT \ln Z_A \qquad G_B = -kT \ln Z_B$$

$$\Delta G = G_B - G_A = -kT \ln Z_B / Z_A$$

# Chemistry without test-tubes

## calculating free energies in MD simulations

e.g. binding



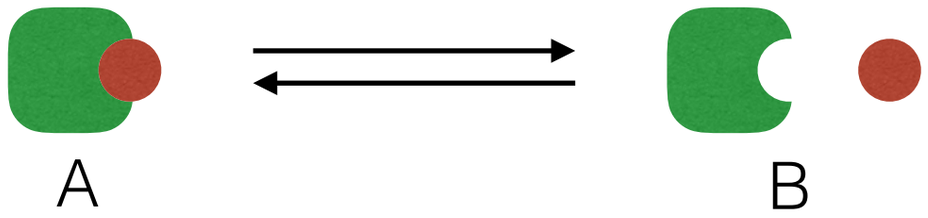

$$G_A = -kT \ln Z_A \qquad G_B = -kT \ln Z_B$$

$$\Delta G = G_B - G_A = -kT \ln Z_B/Z_A$$

# Chemistry without test-tubes

## calculating free energies in MD simulations

e.g. binding



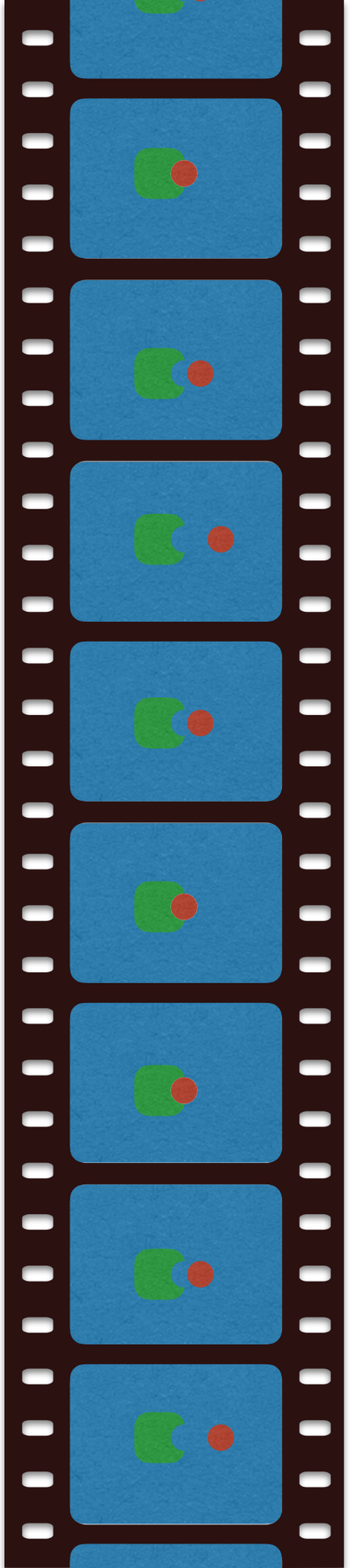

$$G_A = -kT \ln Z_A \qquad G_B = -kT \ln Z_B$$

$$\Delta G = G_B - G_A = -kT \ln Z_B/Z_A$$

most naive approach: counting

ergodicity: time average same as ensemble average

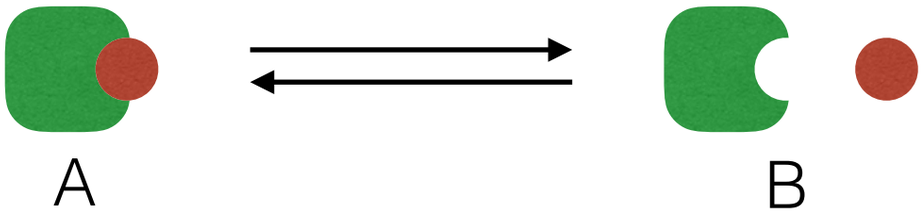
sort frames of a trajectory and compute probabilities



# Chemistry without test-tubes

## calculating free energies in MD simulations

e.g. binding



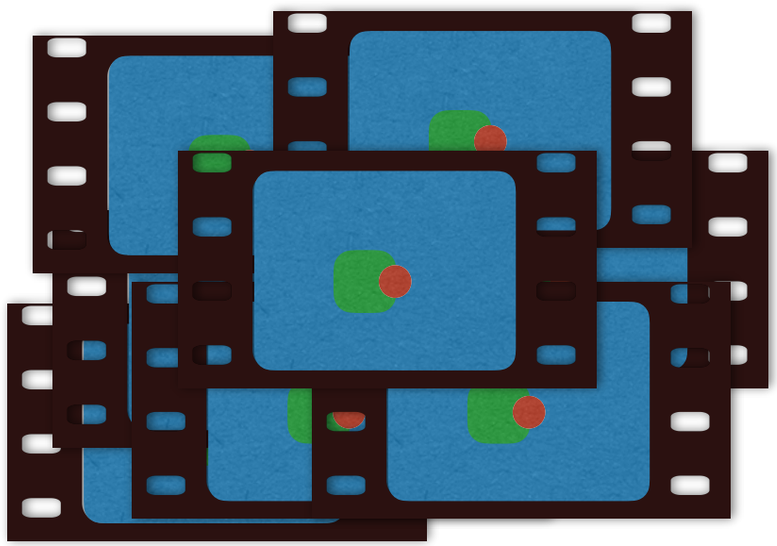

$$G_A = -kT \ln Z_A \qquad G_B = -kT \ln Z_B$$

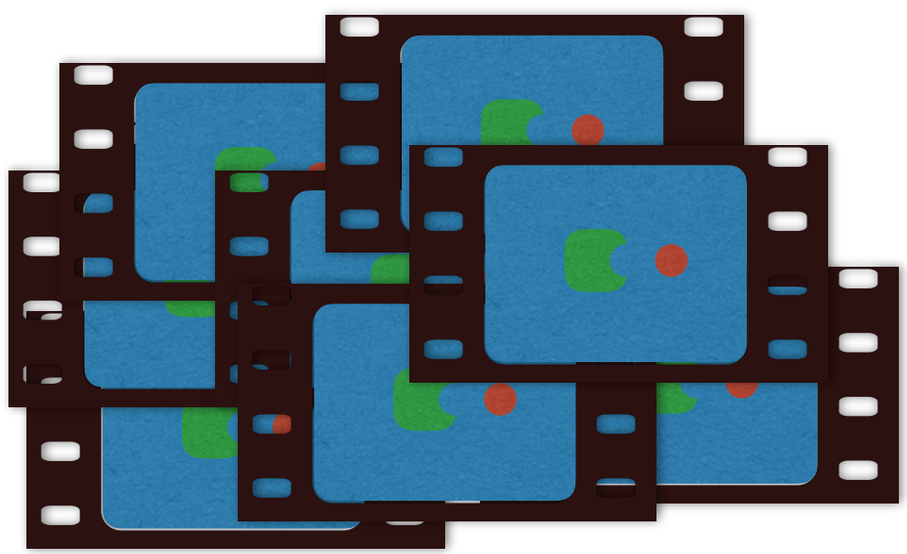
$$\Delta G = G_B - G_A = -kT \ln Z_B/Z_A$$

most naive approach: counting

ergodicity: time average same as ensemble average

sort frames of a trajectory and compute probabilities

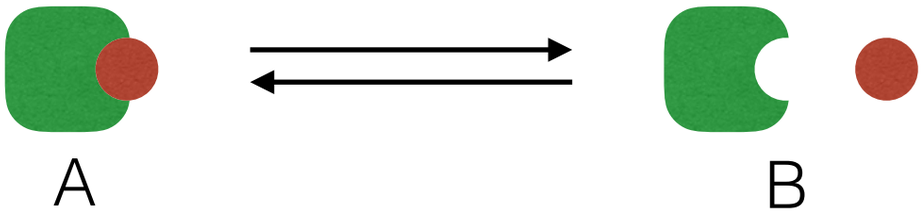




# Chemistry without test-tubes

## calculating free energies in MD simulations

e.g. binding



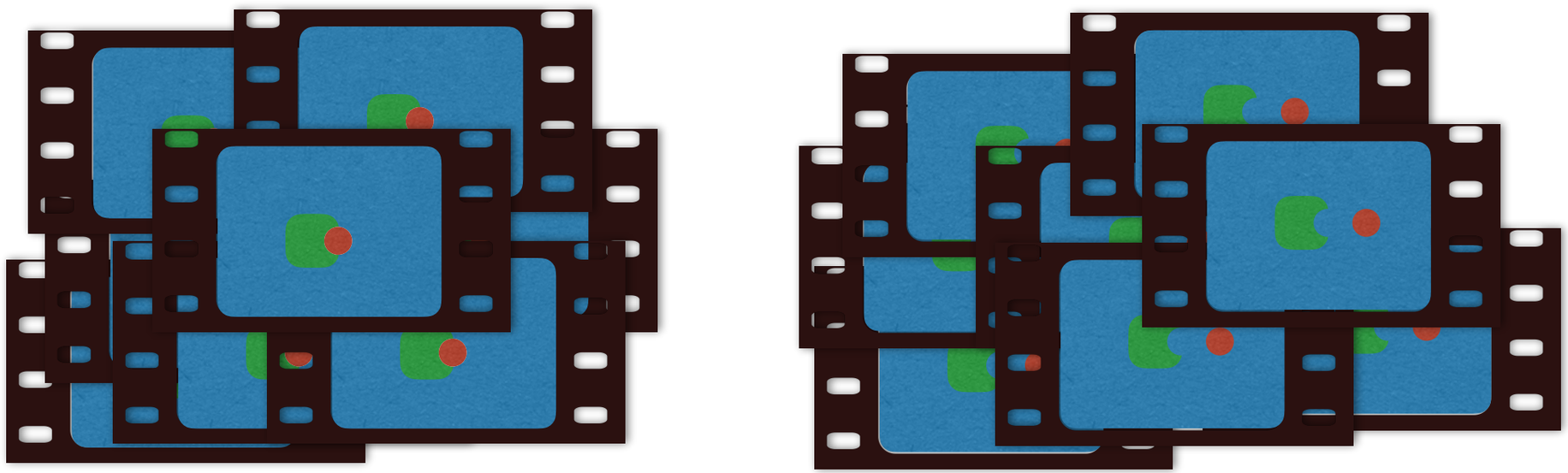

$$G_A = -kT \ln Z_A \qquad G_B = -kT \ln Z_B$$

$$\Delta G = G_B - G_A = -kT \ln Z_B/Z_A$$

most naive approach: counting

ergodicity: time average same as ensemble average

sort frames of a trajectory and compute probabilities

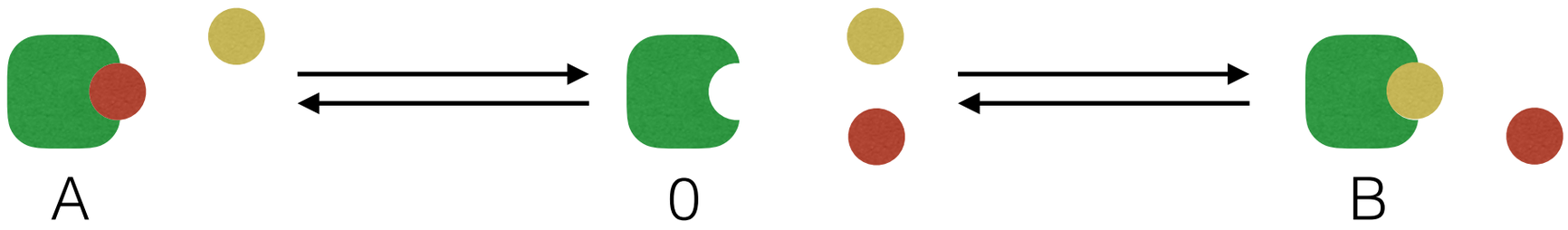


$$\frac{Z_B}{Z_A} = \frac{\sum_{i\in B} e^{-\beta E_i}}{\sum_{i\in A} e^{-\beta E_i}} = \frac{\sum_{i\in B} p_i}{\sum_{i\in A} p_i} = \frac{N_B^{\text{snapshot}}}{N_A^{\text{snapshot}}}$$

# Chemistry without test-tubes

calculating free energy differences in MD simulations

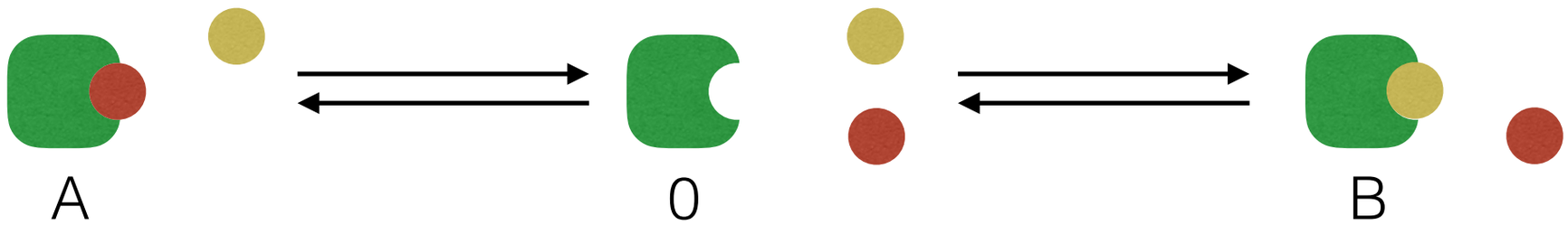
e.g. competitive binding



# Chemistry without test-tubes

## calculating free energy differences in MD simulations

### e.g. competitive binding



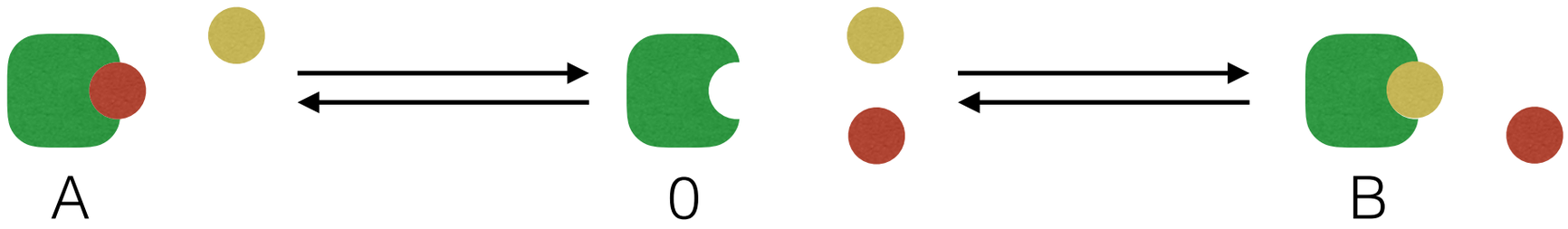

$$G_A = -kT \ln Z_A \qquad G_0 = -kT \ln Z_0 \qquad G_B = -kT \ln Z_B$$

$$\Delta\Delta G_{AB} = (G_B - G_0) - (G_A - G_0) = -kT \ln[\frac{Z_B}{Z_0}\frac{Z_0}{Z_A}] = -kT \ln Z_B/Z_A$$

# Chemistry without test-tubes

## calculating free energy differences in MD simulations

### e.g. competitive binding



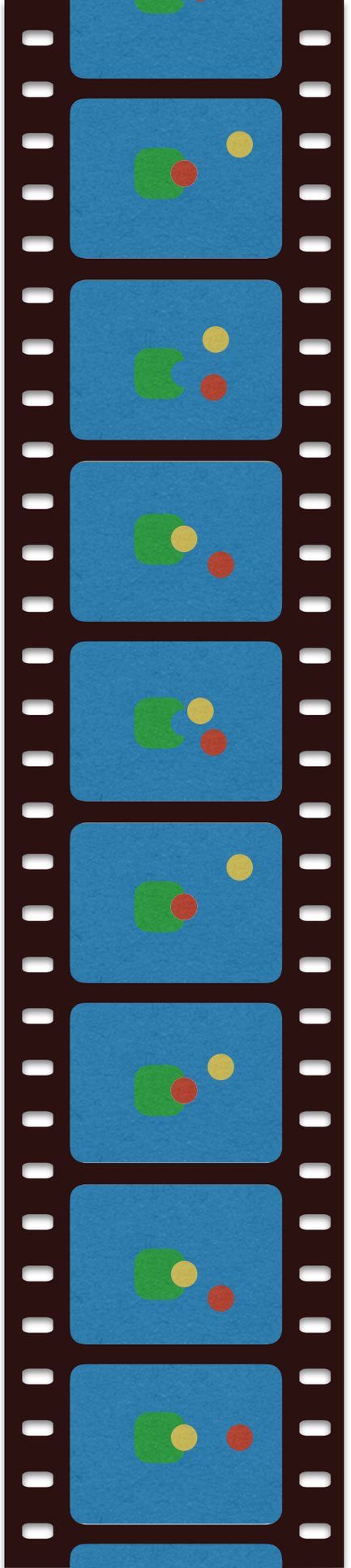

$$G_A = -kT \ln Z_A \qquad G_0 = -kT \ln Z_0 \qquad G_B = -kT \ln Z_B$$

$$\Delta\Delta G_{AB} = (G_B - G_0) - (G_A - G_0) = -kT \ln[\frac{Z_B}{Z_0}\frac{Z_0}{Z_A}] = -kT \ln Z_B/Z_A$$

### most naive approach: counting

ergodicity: time average same as ensemble average

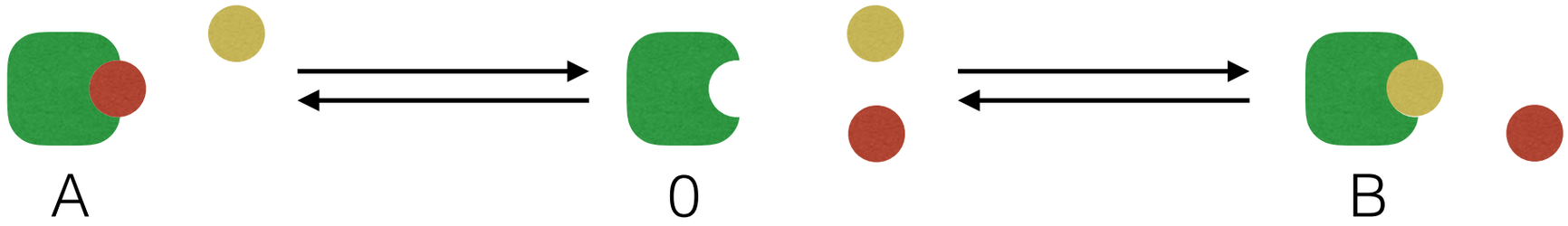
sort frames of a trajectory and compute probabilities



# Chemistry without test-tubes

## calculating free energy differences in MD simulations

### e.g. competitive binding



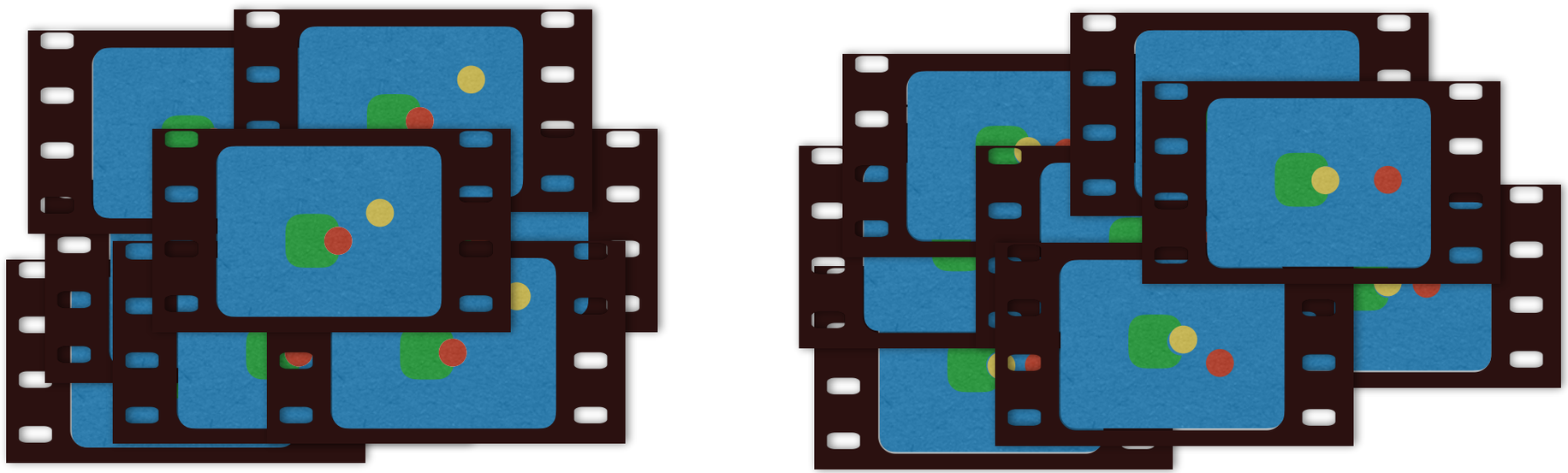

$$G_A = -kT \ln Z_A \qquad G_0 = -kT \ln Z_0 \qquad G_B = -kT \ln Z_B$$

$$\Delta\Delta G_{AB} = (G_B - G_0) - (G_A - G_0) = -kT \ln[\frac{Z_B}{Z_0}\frac{Z_0}{Z_A}] = -kT \ln Z_B/Z_A$$

### most naive approach: counting

ergodicity: time average same as ensemble average

sort frames of a trajectory and compute probabilities

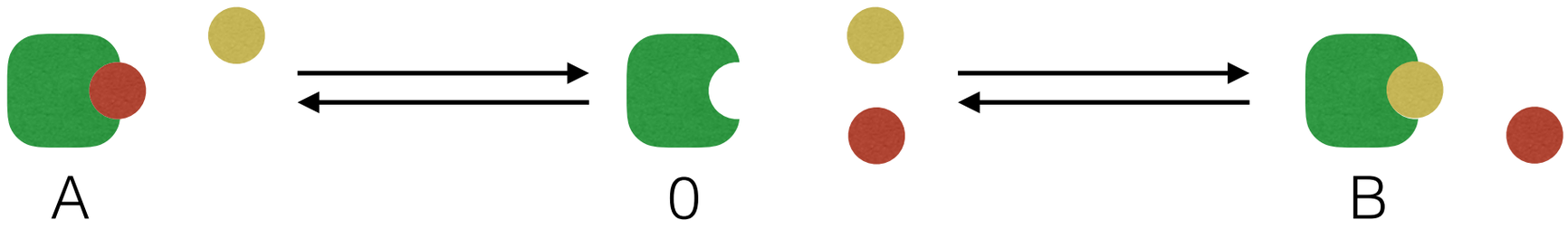


$$\frac{Z_B}{Z_A} = \frac{\sum_{i\in B} e^{-\beta E_i}}{\sum_{i\in A} e^{-\beta E_i}} = \frac{\sum_{i\in B} p_i}{\sum_{i\in A} p_i} = \frac{N_B^{\text{snapshot}}}{N_A^{\text{snapshot}}}$$

# Chemistry without test-tubes

## calculating free energy differences

### e.g. competitive binding




$$G_A = -kT \ln Z_A \qquad G_0 = -kT \ln Z_0 \qquad G_B = -kT \ln Z_B$$

$$\Delta\Delta G_{AB} = (G_B - G_0) - (G_A - G_0) = -kT \ln[\frac{Z_B}{Z_0}\frac{Z_0}{Z_A}] = -kT \ln Z_B/Z_A$$

### most naive approach: counting

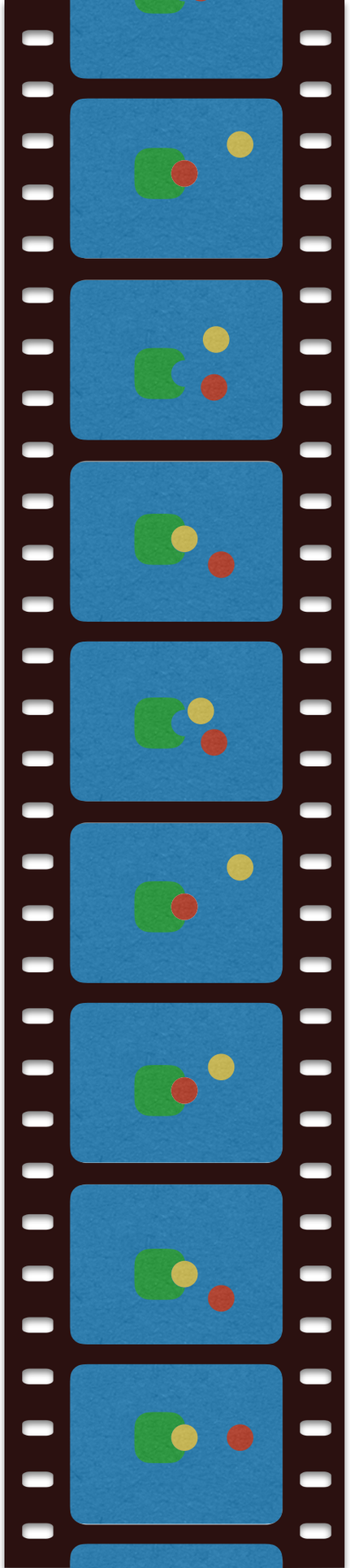
ergodicity: time average same as ensemble average

sort frames of a trajectory and compute probabilities

### converged MD ensemble?

sufficiently long trajectory

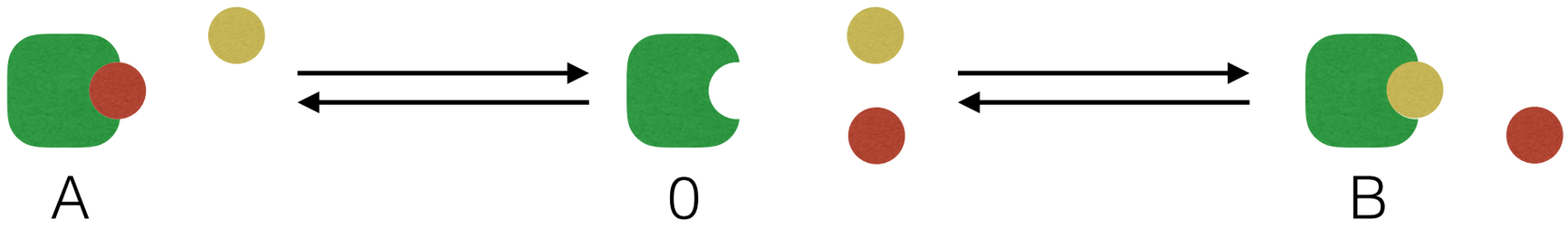
very difficult in practice



# Chemistry without test-tubes

## calculating free energy differences

### e.g. competitive binding




$$G_A = -kT \ln Z_A \qquad G_0 = -kT \ln Z_0 \qquad G_B = -kT \ln Z_B$$

$$\Delta\Delta G_{AB} = (G_B - G_0) - (G_A - G_0) = -kT \ln[\frac{Z_B}{Z_0}\frac{Z_0}{Z_A}] = -kT \ln Z_B/Z_A$$

### most naive approach: counting

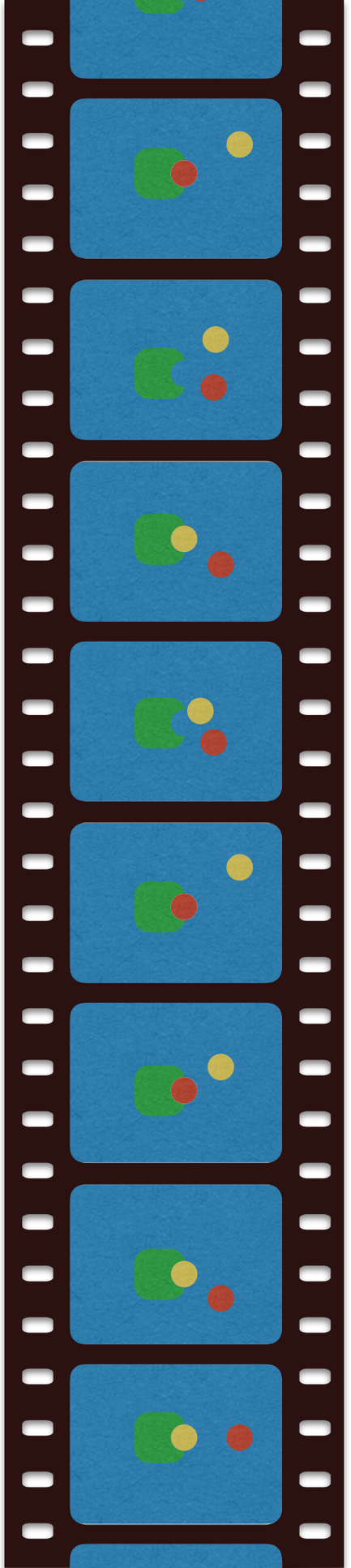
- ergodicity: time average same as ensemble average
- sort frames of a trajectory and compute probabilities

### converged MD ensemble?

- sufficiently long trajectory
- very difficult in practice

### alternative approaches

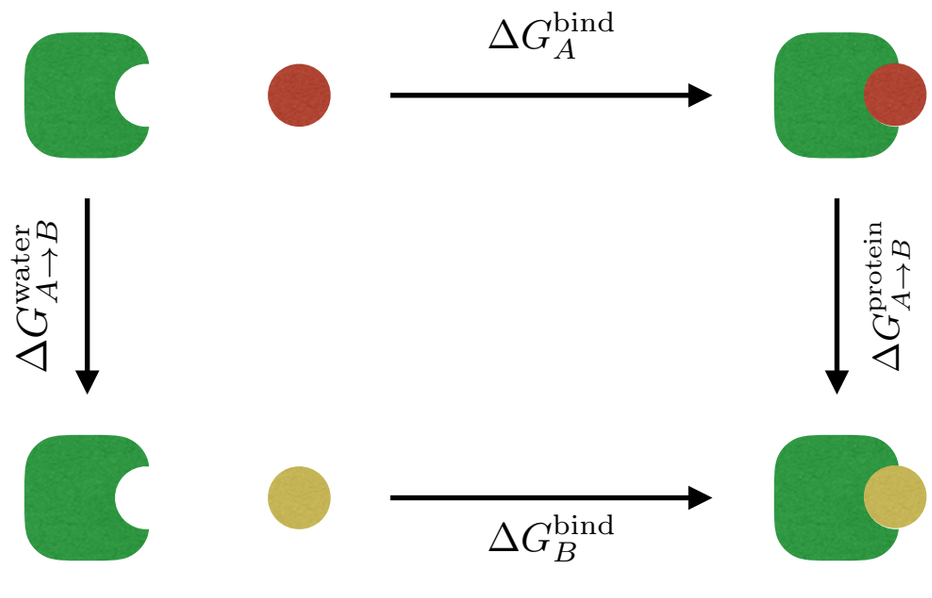
- thermodynamic integration



# Thermodynamic integration

## calculating free energy differences

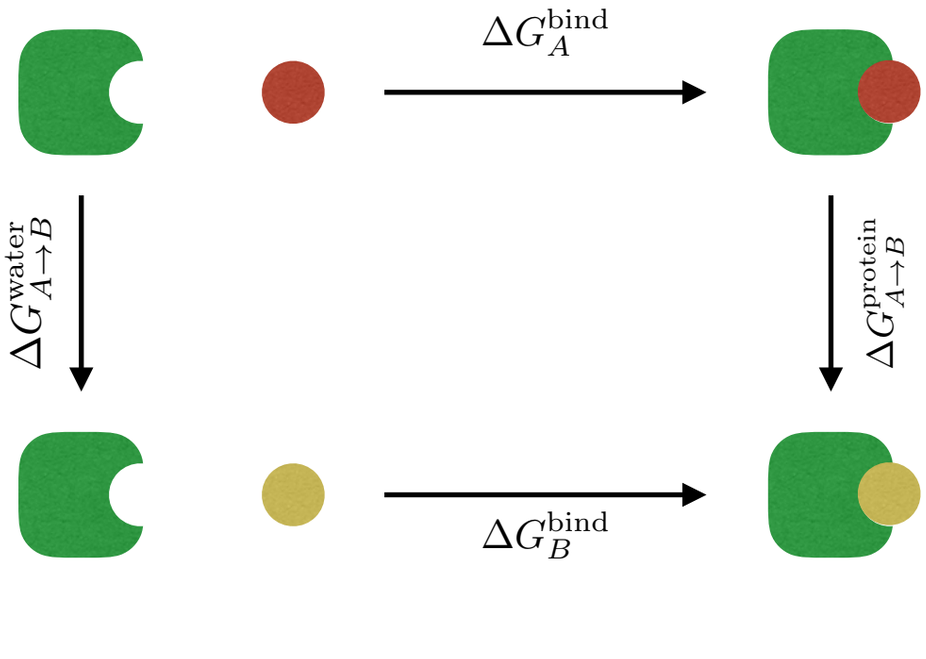
### thermodynamic cycle



# Thermodynamic integration

## calculating free energy differences

### thermodynamic cycle




$$\Delta\Delta G_{AB}^{\text{bind}} = \Delta G_B^{\text{bind}} - \Delta G_A^{\text{bind}}$$

$$= \Delta G_{A\to B}^{\text{protein}} - \Delta G_{A\to B}^{\text{water}}$$

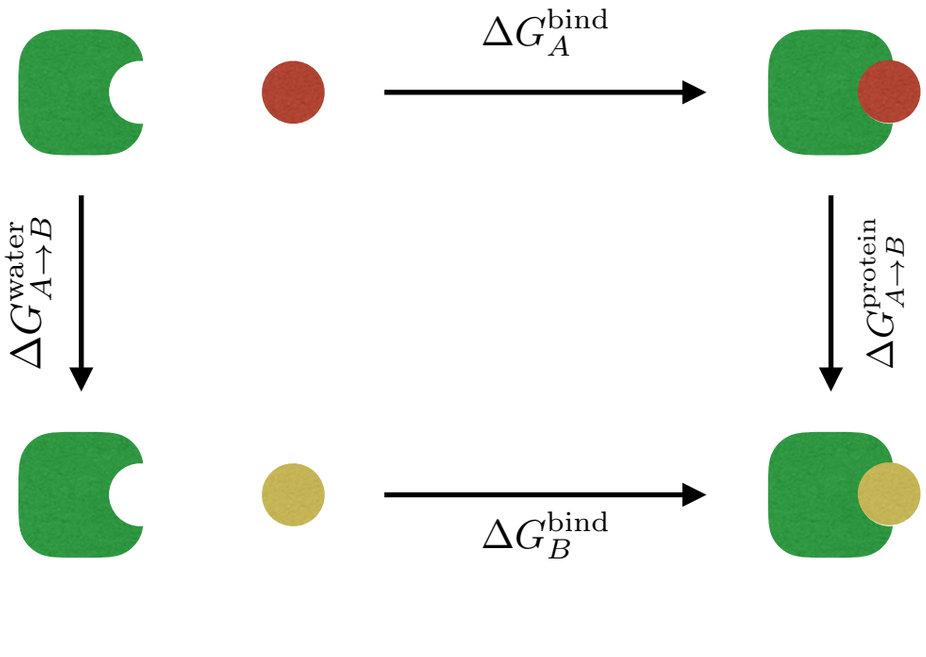
free energy is a state function: independent of path

$$\Delta G_A^{\text{bind}} + \Delta G_{A\to B}^{\text{protein}} = \Delta G_{A\to B}^{\text{water}} + \Delta G_B^{\text{bind}}$$

# Thermodynamic integration

## calculating free energy differences

### thermodynamic cycle




$$\Delta\Delta G_{AB}^{\mathrm{bind}} = \Delta G_B^{\mathrm{bind}} - \Delta G_A^{\mathrm{bind}}$$

$$= \Delta G_{A\to B}^{\mathrm{protein}} - \Delta G_{A\to B}^{\mathrm{water}}$$

free energy is a state function: independent of path

$$\Delta G_A^{\mathrm{bind}} + \Delta G_{A\to B}^{\mathrm{protein}} = \Delta G_{A\to B}^{\mathrm{water}} + \Delta G_B^{\mathrm{bind}}$$

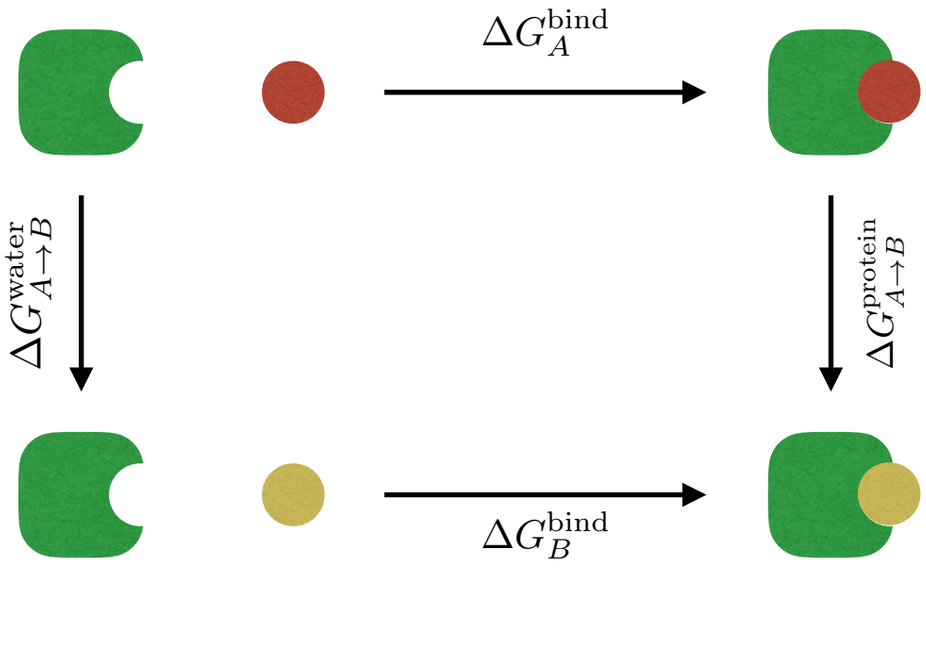
difficult to evaluate with MD simulations

$$\Delta G_A^{\mathrm{bind}} \qquad \Delta G_B^{\mathrm{bind}}$$

# Thermodynamic integration

## calculating free energy differences

### thermodynamic cycle




$$\Delta\Delta G_{AB}^{\mathrm{bind}} = \Delta G_B^{\mathrm{bind}} - \Delta G_A^{\mathrm{bind}}$$

$$= \Delta G_{A\to B}^{\mathrm{protein}} - \Delta G_{A\to B}^{\mathrm{water}}$$

free energy is a state function: independent of path

$$\Delta G_A^{\mathrm{bind}} + \Delta G_{A\to B}^{\mathrm{protein}} = \Delta G_{A\to B}^{\mathrm{water}} + \Delta G_B^{\mathrm{bind}}$$

difficult to evaluate with MD simulations

$$\Delta G_A^{\mathrm{bind}} \qquad \Delta G_B^{\mathrm{bind}}$$

'easy' (sometimes) to evaluate with MD simulations

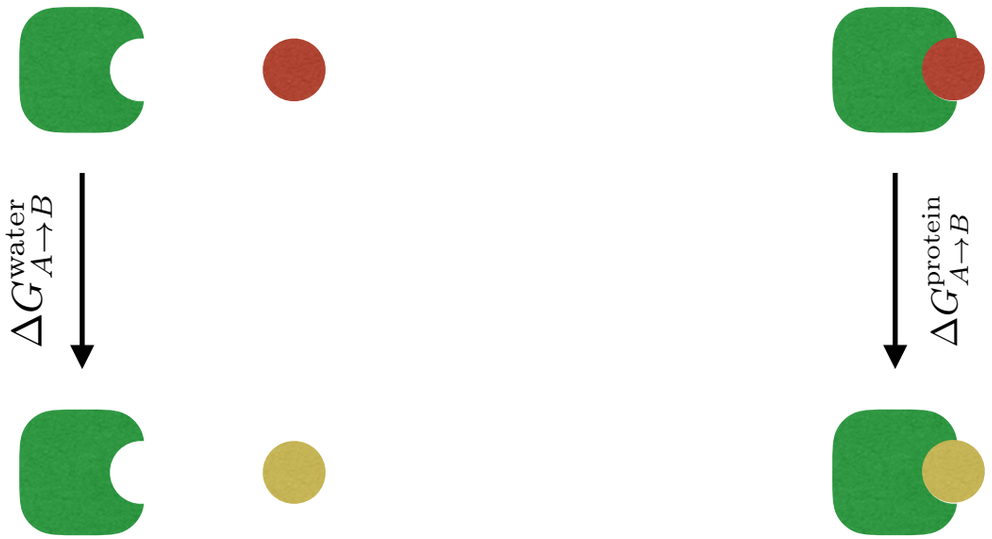
$$\Delta G_{A\to B}^{\mathrm{water}} \qquad \Delta G_{A\to B}^{\mathrm{protein}}$$

# Thermodynamic integration

## why ‘easy’?

### interpolate the energy function

*in silico* everything is possible

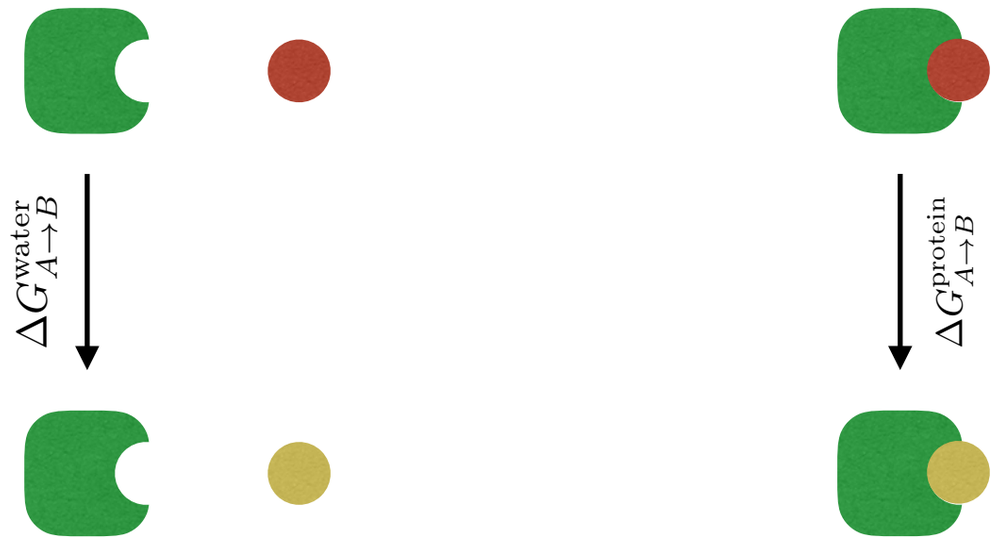



# Thermodynamic integration

## why 'easy'?

### interpolate the energy function

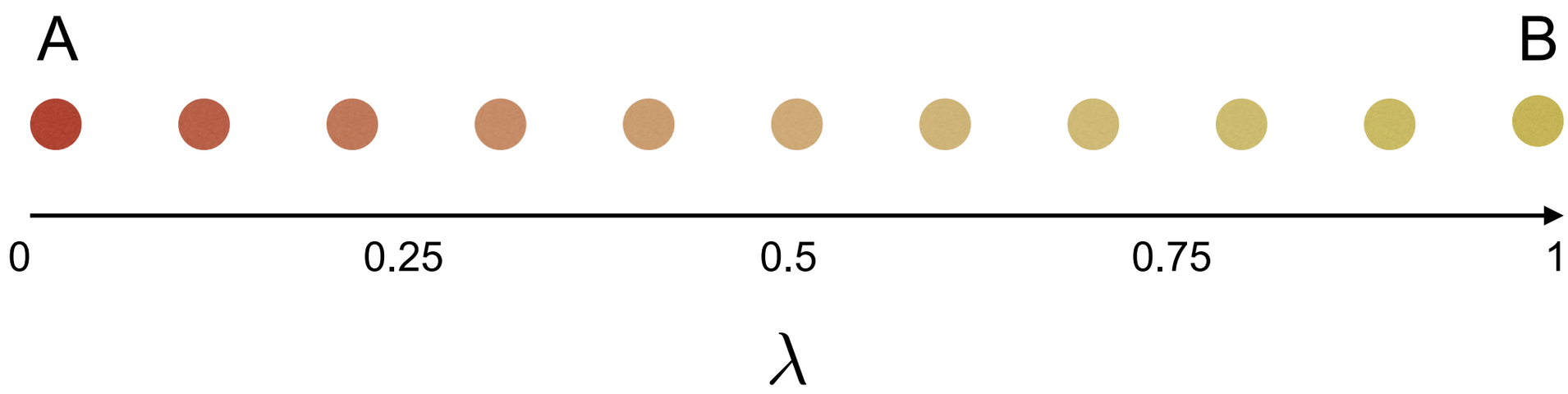
*in silico* everything is possible




$$E^A(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

$$E^B(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

$$E(\lambda, \mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2) = (1-\lambda)E^A(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2) + \lambda E^B(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

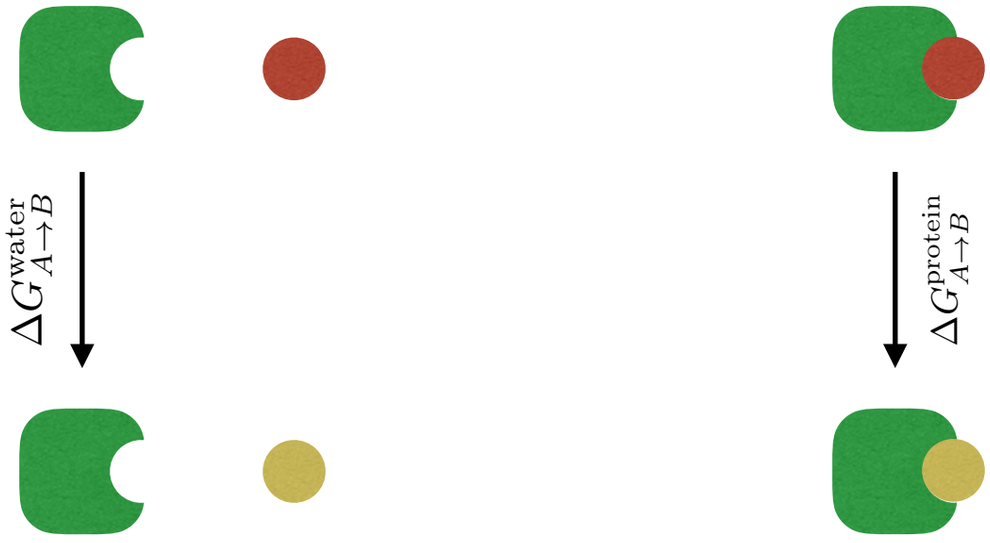


# Thermodynamic integration

## why 'easy'?

### interpolate the energy function

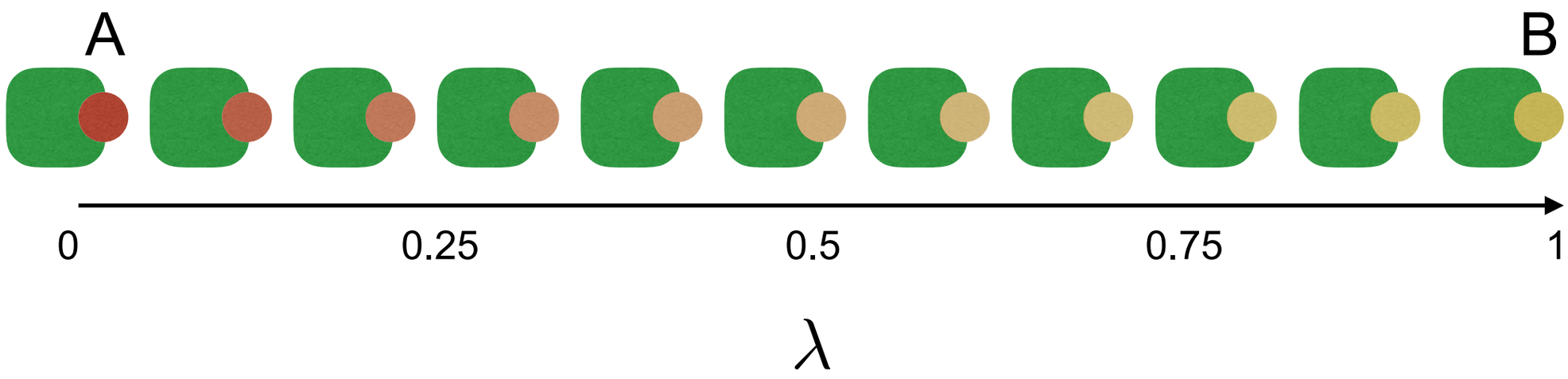
*in silico* everything is possible




$$E^A(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

$$E^B(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

$$E(\lambda, \mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2) = (1-\lambda)E^A(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2) + \lambda E^B(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

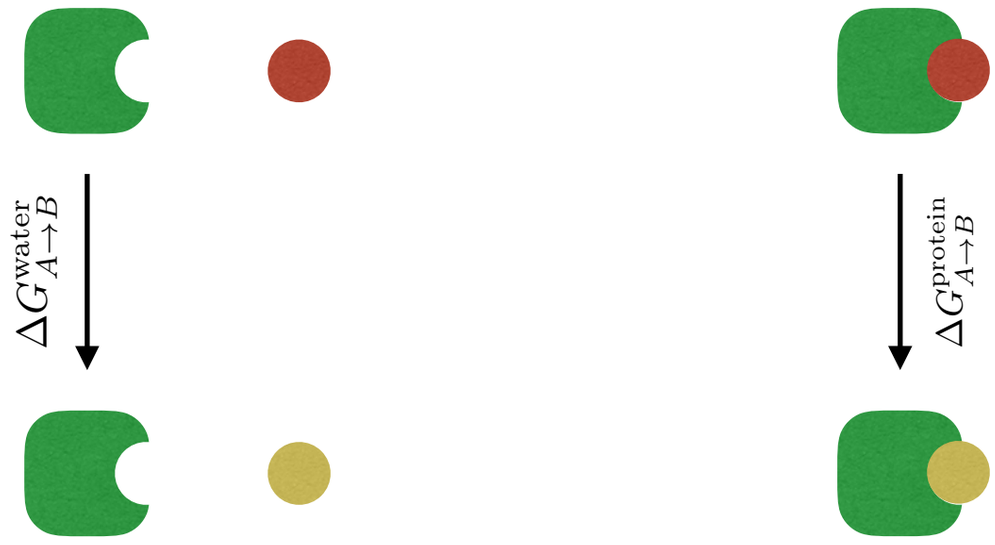


# Thermodynamic integration

## why 'easy'?

### interpolate the energy function

*in silico* everything is possible




$$E^A(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

$$E^B(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

$$E(\lambda, \mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2) = (1-\lambda)E^A(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2) + \lambda E^B(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

### partition function

$$\begin{aligned} Z(\lambda) &= \sum_i e^{-\beta E(\lambda, \mathbf{P}_i, \mathbf{R}_i)} \\ &= \sum_i e^{-\beta[(1-\lambda)E^A(\mathbf{P}_i, \mathbf{R}_i) + \lambda E^B(\mathbf{P}_i, \mathbf{R}_i)]} \end{aligned}$$

$$\mathbf{P}_i \equiv \begin{pmatrix} \mathbf{p}_1 \\ \mathbf{p}_2 \\ \cdots \\ \mathbf{p}_N \end{pmatrix}_i \qquad \mathbf{R}_i \equiv \begin{pmatrix} \mathbf{r}_1 \\ \mathbf{r}_2 \\ \cdots \\ \mathbf{r}_N \end{pmatrix}_i$$

# Thermodynamic integration

## why 'easy'?

### interpolate the energy function

*in silico* everything is possible


$$E^A(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

$$E^B(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

$$E(\lambda, \mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2) = (1-\lambda)E^A(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2) + \lambda E^B(\mathbf{p}_1, \mathbf{p}_2, .., \mathbf{r}_1, \mathbf{r}_2)$$

### partition function

$$\begin{aligned} Z(\lambda) &= \sum_i e^{-\beta E(\lambda, \mathbf{P}_i, \mathbf{R}_i)} \\ &= \sum_i e^{-\beta[(1-\lambda)E^A(\mathbf{P}_i, \mathbf{R}_i) + \lambda E^B(\mathbf{P}_i, \mathbf{R}_i)]} \end{aligned}$$

$$\mathbf{P}_i \equiv \begin{pmatrix} \mathbf{p}_1 \\ \mathbf{p}_2 \\ \cdots \\ \mathbf{p}_N \end{pmatrix}_i \qquad \mathbf{R}_i \equiv \begin{pmatrix} \mathbf{r}_1 \\ \mathbf{r}_2 \\ \cdots \\ \mathbf{r}_N \end{pmatrix}_i$$

### free energy

$$G(\lambda) = -kT \ln Z(\lambda)$$

how does this help?

# Thermodynamic integration

why 'easy'?

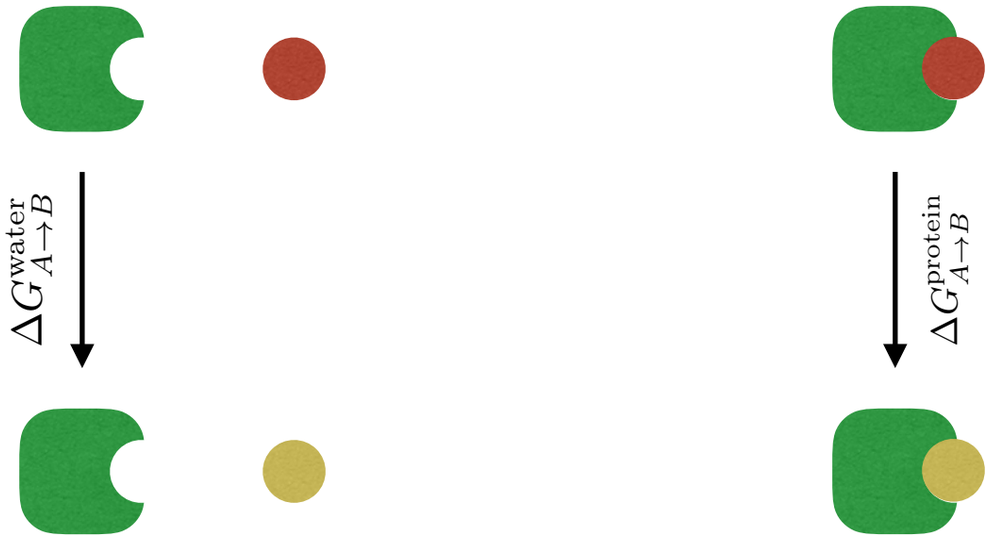
interpolate the energy function

partition function

replace sum by integration (classical)

$$Z(\lambda) = \sum_i e^{-\beta E(\lambda,\mathbf{P}_i,\mathbf{R}_i)}$$

$$= \int\int e^{-\beta E(\lambda,\mathbf{P},\mathbf{R})} d\mathbf{P} d\mathbf{R}$$




$$\mathbf{P} \equiv \begin{pmatrix} \mathbf{p}_1 \\ \mathbf{p}_2 \\ \dots \\ \mathbf{p}_N \end{pmatrix} \qquad \mathbf{R} \equiv \begin{pmatrix} \mathbf{r}_1 \\ \mathbf{r}_2 \\ \dots \\ \mathbf{r}_N \end{pmatrix}$$

# Thermodynamic integration

why 'easy'?

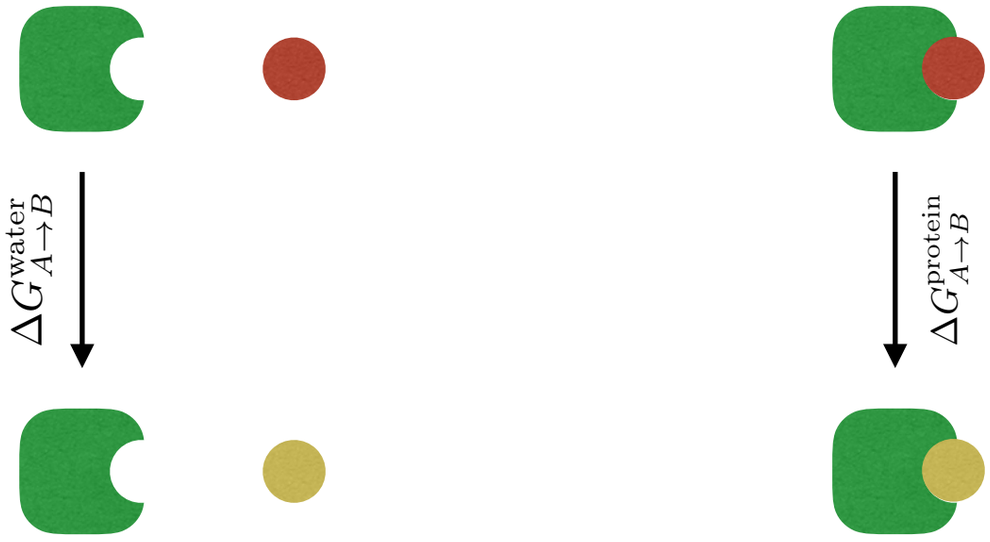
interpolate the energy function

partition function

replace sum by integration (classical)

$$Z(\lambda) = \sum_i e^{-\beta E(\lambda,\mathbf{P}_i,\mathbf{R}_i)}$$

$$= \int\int e^{-\beta E(\lambda,\mathbf{P},\mathbf{R})} d\mathbf{P} d\mathbf{R}$$




free energy

$$G(\lambda) = -kT \ln Z(\lambda)$$

$$\mathbf{P} \equiv \begin{pmatrix} \mathbf{p}_1 \\ \mathbf{p}_2 \\ \dots \\ \mathbf{p}_N \end{pmatrix} \qquad \mathbf{R} \equiv \begin{pmatrix} \mathbf{r}_1 \\ \mathbf{r}_2 \\ \dots \\ \mathbf{r}_N \end{pmatrix}$$

# Thermodynamic integration

## why 'easy'?

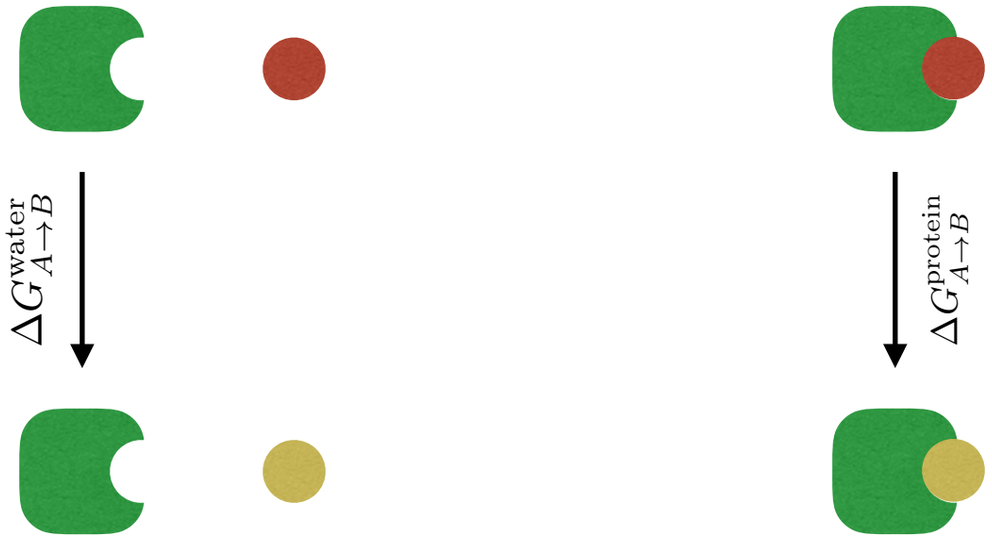
interpolate the energy function

partition function

replace sum by integration (classical)

$$Z(\lambda) = \sum_i e^{-\beta E(\lambda,\mathbf{P}_i,\mathbf{R}_i)}$$

$$= \int\int e^{-\beta E(\lambda,\mathbf{P},\mathbf{R})} d\mathbf{P} d\mathbf{R}$$




free energy

$$G(\lambda) = -kT \ln Z(\lambda)$$

$$\mathbf{P} \equiv \begin{pmatrix} \mathbf{p}_1 \\ \mathbf{p}_2 \\ \dots \\ \mathbf{p}_N \end{pmatrix} \qquad \mathbf{R} \equiv \begin{pmatrix} \mathbf{r}_1 \\ \mathbf{r}_2 \\ \dots \\ \mathbf{r}_N \end{pmatrix}$$

derivative of free energy

$$\frac{\partial G}{\partial \lambda} = -\frac{kT}{Z(\lambda)} \frac{\partial Z}{\partial \lambda}$$

$$= \int\int \frac{\partial E(\lambda)}{\partial \lambda} \frac{e^{-\beta E(\lambda,\mathbf{P},\mathbf{R})}}{Z} d\mathbf{P} d\mathbf{R}$$

$$= \left\langle \frac{\partial E(\lambda)}{\partial \lambda} \right\rangle_\lambda$$

# Thermodynamic integration

why ‘easy’?

interpolate the energy function

derivative of free energy

$$\frac{\partial G}{\partial \lambda} = -\frac{kT}{Z(\lambda)}\frac{\partial Z}{\partial \lambda}$$

$$= \int\int \frac{\partial E(\lambda)}{\partial \lambda}\frac{e^{-\beta E(\lambda,\mathbf{P},\mathbf{R})}}{Z} d\mathbf{P}d\mathbf{R}$$

$$= \left\langle \frac{\partial E(\lambda)}{\partial \lambda} \right\rangle_{\lambda}$$

# Thermodynamic integration

why 'easy'?

interpolate the energy function

derivative of free energy

$$\frac{\partial G}{\partial \lambda} = -\frac{kT}{Z(\lambda)}\frac{\partial Z}{\partial \lambda}$$

$$= \int\int \frac{\partial E(\lambda)}{\partial \lambda}\frac{e^{-\beta E(\lambda,\mathbf{P},\mathbf{R})}}{Z} d\mathbf{P}d\mathbf{R}$$

$$= \left\langle \frac{\partial E(\lambda)}{\partial \lambda} \right\rangle_{\lambda}$$


free energy

$$\Delta G_{A\to B} = \int_0^1 \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$

# Thermodynamic integration

## why 'easy'?

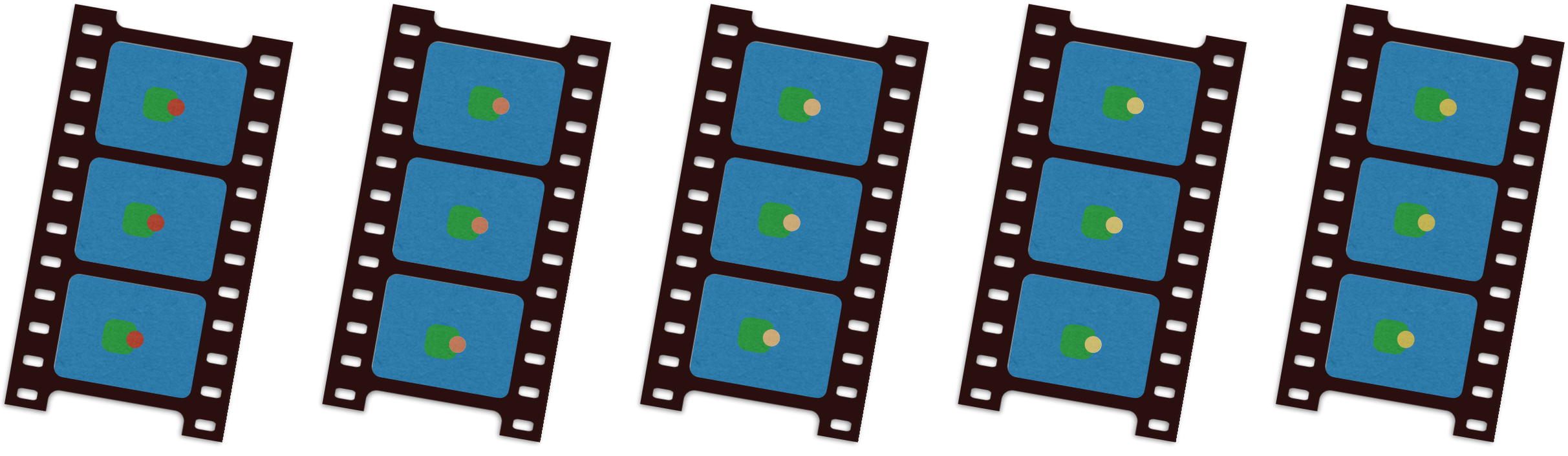
interpolate the energy function

free energy

$$\Delta G_{A\to B} = \int_0^1 \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_\lambda d\lambda$$

multiple MD trajectories


$$\Delta G^{\text{protein}}_{A\to B}$$



$$\left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=0.0} \quad \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=0.25} \quad \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=0.50} \quad \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=0.75} \quad \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=1.0}$$

# Thermodynamic integration

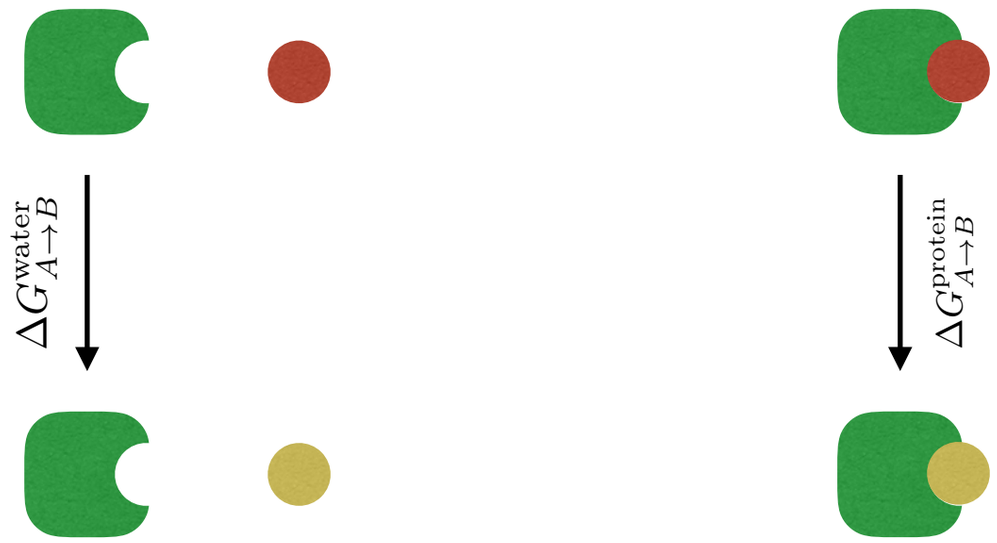
## why ‘easy’?

interpolate the energy function

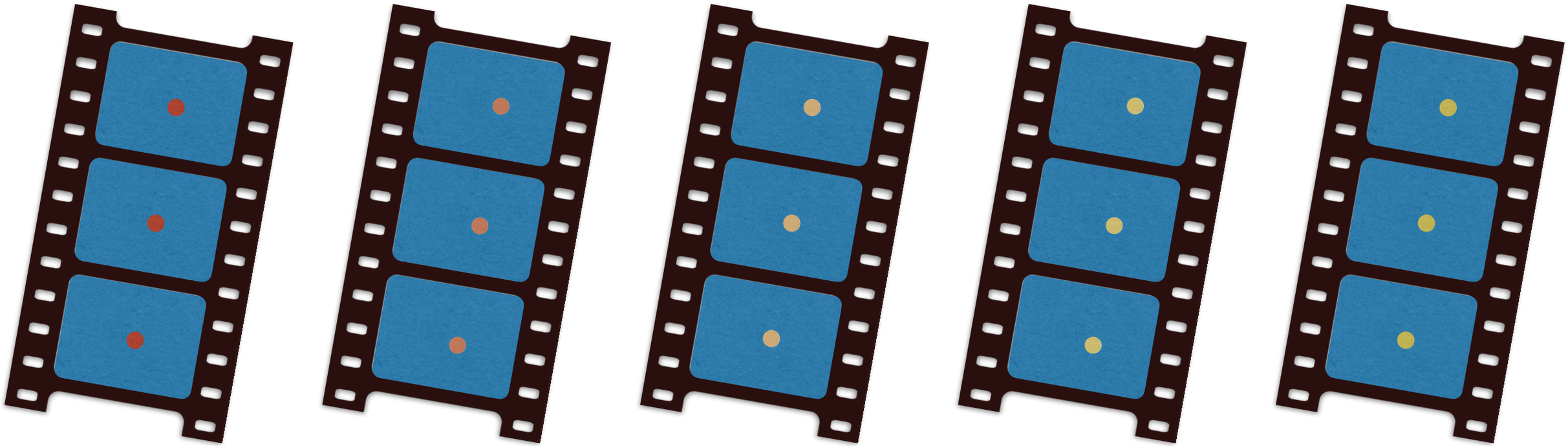
free energy

$$\Delta G_{A\to B} = \int_0^1 \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_\lambda d\lambda$$

multiple MD trajectories




$\Delta G^{\text{water}}_{A\to B}$



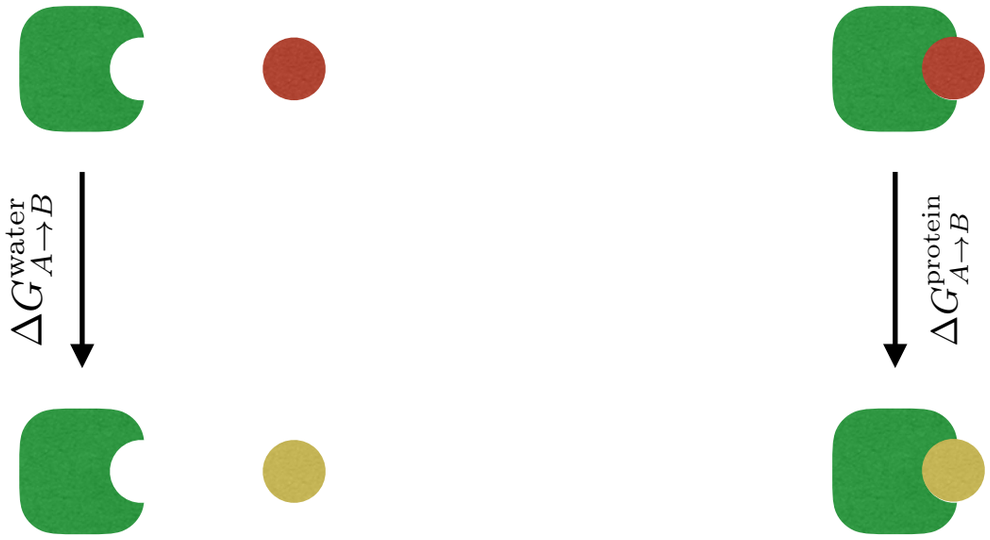
$\left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=0.0}$ $\left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=0.25}$ $\left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=0.50}$ $\left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=0.75}$ $\left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda=1.0}$

# Thermodynamic integration

## in practice

### energy function (Hamiltonian)

$$E = H = E_{\text{kin}} + E_{\text{pot}}$$



# Thermodynamic integration

## in practice

### energy function (Hamiltonian)

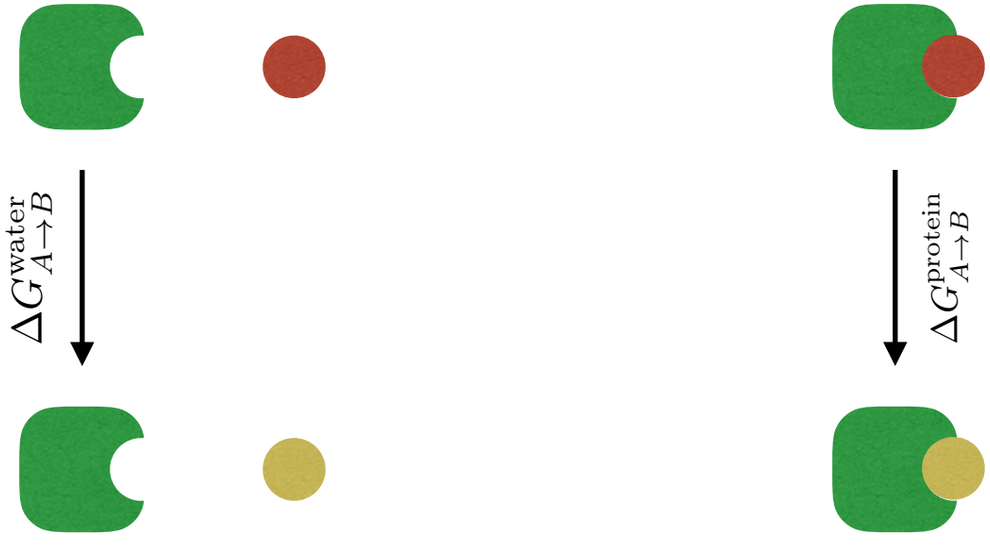
$$E = H = E_{\text{kin}} + E_{\text{pot}}$$

### leave kinetic energy untouched

$$E_{\text{kin}} = \frac{1}{2} \sum_{i}^{N} \frac{p_i^2}{m_i}$$

### interpolate only potential energy

$$E_{\text{pot}} = V(\mathbf{r}_1, \mathbf{r}_2, .., \mathbf{r}_N, \lambda)$$



# Thermodynamic integration

## in practice

### energy function (Hamiltonian)

$$E = H = E_{\text{kin}} + E_{\text{pot}}$$

### leave kinetic energy untouched

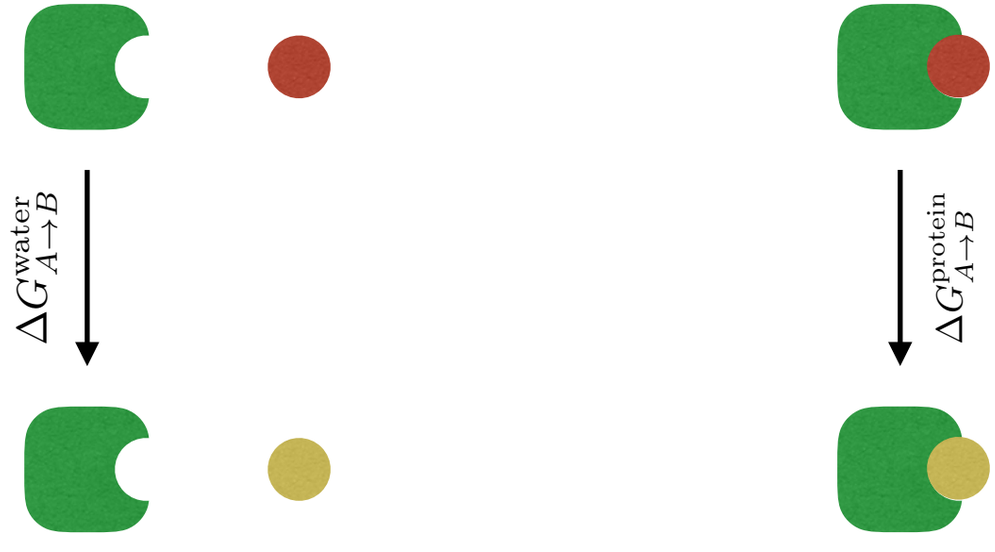
$$E_{\text{kin}} = \frac{1}{2}\sum_{i}^{N}\frac{p_i^2}{m_i}$$

### interpolate only potential energy

$$E_{\text{pot}} = V(\mathbf{r}_1, \mathbf{r}_2, .., \mathbf{r}_N, \lambda)$$

### partition function

$$Z(\lambda) = \underbrace{\int e^{-\beta E_{\text{kin}}(\mathbf{p}_1,\mathbf{p}_2,..,\mathbf{p}_N)} d\mathbf{p}_1 d\mathbf{p}_2 .. d\mathbf{p}_N}_{\text{always same!}} \cdot \int e^{-\beta E_{\text{pot}}(\mathbf{r}_1,\mathbf{r}_2,..,\mathbf{r}_N,\lambda)} d\mathbf{r}_1 d\mathbf{r}_2 .. d\mathbf{r}_N$$



# Thermodynamic integration

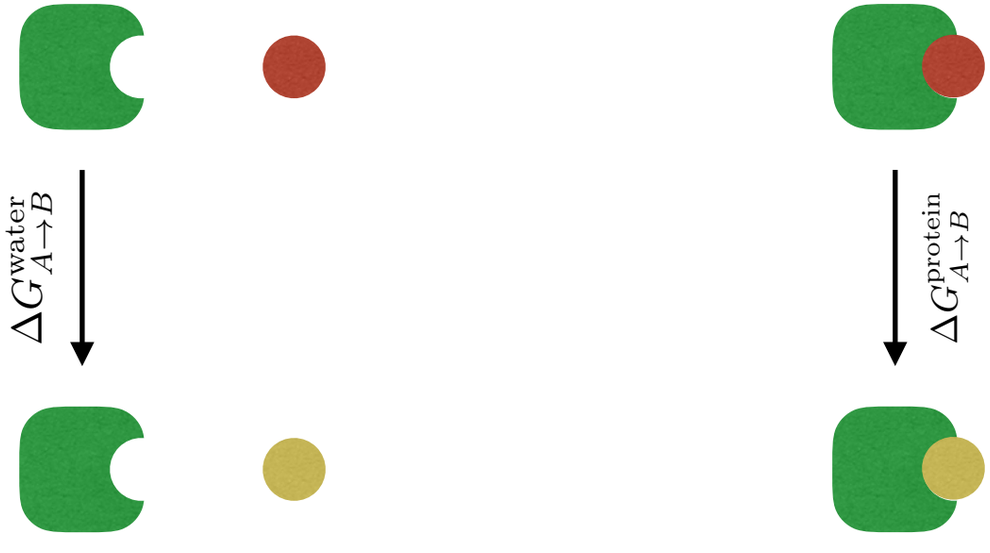
## in practice

### energy function (Hamiltonian)

$$E = H = E_{\text{kin}} + E_{\text{pot}}$$

### leave kinetic energy untouched

$$E_{\text{kin}} = \frac{1}{2}\sum_{i}^{N}\frac{p_i^2}{m_i}$$




### interpolate only potential energy

$$E_{\text{pot}} = V(\mathbf{r}_1, \mathbf{r}_2, .., \mathbf{r}_N, \lambda)$$

### partition function

$$Z(\lambda) = \underbrace{\int e^{-\beta E_{\text{kin}}(\mathbf{p}_1,\mathbf{p}_2,..,\mathbf{p}_N)} d\mathbf{p}_1 d\mathbf{p}_2 .. d\mathbf{p}_N}_{\text{always same!}} \cdot \int e^{-\beta E_{\text{pot}}(\mathbf{r}_1,\mathbf{r}_2,..,\mathbf{r}_N,\lambda)} d\mathbf{r}_1 d\mathbf{r}_2 .. d\mathbf{r}_N$$

### derivative of free energy

$$\frac{\partial G}{\partial \lambda} = \left\langle \frac{\partial V(\lambda)}{\partial \lambda} \right\rangle_{\lambda}$$