Understanding Molecular Simulations

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This is a heavy burden the shoulders of "chemistry":

The "rest" amounts to the quantitative description of the world around us and the prediction of all every-day phenomena ranging from the chemical reactions of small molecules to the integrated description of living organisms.

for a given intermolecular potential "exactly" predict the thermodynamic and transport properties of the system

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We assume the interactions between the particles are known!



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Pressure Heat capacity Heat of adsorption Structure

for a given intermolecular potential "exactly" predict the thermodynamic and transport properties of the system

Diffusion coefficient Viscosity

If one could envision an experimental system of these particles that interact with the potential.

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...making these approaches untractable. What was the alternative at the time ?

- Smart tricks ("theory")
 Only works in special cases: the Ising model: the ideal gas, etc etc
- 2. Constructing a model ("molecular lego").



J.D. Bernal's ball-bearing model of an atomic liquid



Watson and Crick's model of DNA double helix

The computer age



With computers we can follow the behavior of hundreds to hundreds of millions of molecules.

Increment of power since 1950's

Microprocessor Transistor Counts 1971-2011 & Moore's Law



Molsim 2012

Super computer performance development







Molsim 2012

Uses of Molecular Simulations

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- Mimic the real world:
 - Predicting properties of (new) materials
 - Computer 'experiments' at extreme conditions
 - Understanding phenomena on a molecular scale

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- Mimic the real world:
 - Predicting properties of (new) materials
 - Computer 'experiments' at extreme conditions
 - Understanding phenomena on a molecular scale
- Model systems
 - test theory using same simple model
 - explore consequences of model
 - explain poorly understood phenomena in terms of essential physics

Properties of materials

Critical properties of long chain hydrocarbons





Properties of materials

Critical properties of long chain hydrocarbons





To *predict* the thermodynamic properties (boiling points) of the hydrocarbon mixtures it is convenient to know the critical points of the hydrocarbons.

Hydrocarbons intermolecular potential

United-atom model

- Fixed bond length
- Bond-bending
- Torsion
- Non-bonded: Lennard-Jones



$$u(r) = 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r} \right)^{12} - \left(\frac{\sigma_{ij}}{r} \right)^6 \right]$$



Vapour-liquid equilibria




Computational issues:

How to compute vapour-liquid equilibrium?

Molsim 2012



- How to compute vapour-liquid equilibrium?
- How to deal with long chain hydrocarbons?



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Properties at extreme conditions

- Carbon phase behavior at very high pressure and temperature
- Empirical pair potential depending on carbon coordination

$$E_{b} = \frac{1}{2} \sum_{i,j}^{N} \left(f_{c,ij} V_{ij}^{SR} + (1 - f_{c,ij}) V_{ij}^{LR} \right)$$
$$V_{ij}^{SR} = V_{R}(r_{ij}) - \overline{b}_{ij} V_{A}(r_{ij})$$
coordination number

$$V_R(r) = Ae^{-\alpha r}$$

$$V_A(r) = B_1 e^{-\beta_1 r} + B_2 e^{-\beta_2 r}$$

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$$U_{A}(r) = B_{1} e^{-\beta_{1}r} + B_{2} e^{-\beta_{1}r} + B_{2} e^{-\beta_{1}r}$$

$$U_{A}(r) = B_{1} e^{-\beta_{1}r} + B_{2} e^{-\beta_{1}r}$$

60

Pressure [GPa]

- Protein conformational change with Molecular dynamics
- Empirical potential, including bonds, angles dihedrals

Course on MD

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- Transition path sampling



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Course on

rare events

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Leads to insight and new hypotheses

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Your hypothesis is **WRONG** it disagrees with the experiments



Testing theories with simp

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Your hypothesis is **WRONG** it disagrees with the experiments My hypothesis is **RIGHT**: but this experimentalist refuses to use molecules that do not have any attractive interactions

that molecules with only r



An older Alder

 Bernie Alder *et al.* carried out Molecular Dynamics simulations of the freezing of hard spheres



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- But, did the scientific community accept this computer results as evidence ...?



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- But, did the scientific community accept this computer results as evidence ...?
- ... during a New Jersey conference in 1957 it was proposed to vote on it ...
- ... and it was voted against the results of Alder!



An older Alder

Experiments are now possible

.. not on molecules but on colloids



from :Yethiraj and van Blaaderen Nature 421, 513-517 (2003)

and show that hard spheres indeed crystallize at high density

• Trans membrane peptides



 Coarse-grained model of a membrane to study the interactions between peptides in a membrane

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 Coarse-grained model of a membrane to study the interactions between peptides in

Course on coarse graining

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Understanding in terms of essential physics

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- Make simple lattice model with essential physics of proteins
 - polymer connectivity
 - heteropolymer sequence
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Course on lattice models

compact states

 (10^{10})

- 11

transition states (10³)

native state (1)

С

unfolded states (10¹⁶

The limits of Molecular Simulation

- Brute-force simulations can never bridge all the scales between \bullet microscopic (nanometers/picoseconds) and macroscopic (cells, humans, planets).
- Need different levels of ٠ description ("coarse mm graining") - and we need Pluid mechanics input from experiments hybrid at many different levels length AA/CG to validate our models. μm QM/MM nm rare event methods fs

ps

ns

μs

ms

time

S

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- Simulations are becoming an integral part of the analysis of experimental data.

Understanding Molecular Simulation

Molecular simulations are based on the framework of statistical mechanics/thermodynamics

Hence:

Understanding Molecular Simulation

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Hence:

An introduction (or refresher) of Statistical Thermodynamics

Outline

- Basic Assumption
 - micro-canonical ensemble
 - relation to thermodynamics
- Canonical ensemble
 - free energy
 - thermodynamic properties
- Other ensembles
 - constant pressure
 - grand-canonical ensemble

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- Consequence:
 ALL of equilibrium Statistical Mechanics and Thermodynamics

Simpler example: standard statistics

Draw N balls from an infinite vessel that contains an equal number of red and blue balls



Number of possibilities to draw N_R red balls and N_B blue balls: $\Omega(N_R, N_B) = \frac{N!}{N_R!N_B!}$.





















Molecular consequence of basic assumption









$$E_1$$
 $E_2 = E - E_1$



Systems I and 2 are weakly coupled such that they can exchange energy.

What will be E_l ?



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$$\Omega(E_1, E - E_1) = \Omega_1(E_1) \times \Omega_2(E - E_1)$$



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BA: each configuration is equally probable; but the number of states that give an energy E_1 is not (yet) known.



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What will be E_1 ?

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BA: each configuration is equally probable; but the number of states that give an energy E_1 is not (yet) known.

The most likely E_{I_1} is the E_{I_2} that maximizes $\Omega_{I_1}(E_{I_2}) \times \Omega_{I_2}(E_{I_2})$

$$\Omega(E_1, E - E_1) = \Omega_1(E_1) \times \Omega_2(E - E_1)$$

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$$\begin{split} \Omega\left(E_{1}, E - E_{1}\right) &= \Omega_{1}\left(E_{1}\right) \times \Omega_{2}\left(E - E_{1}\right) \\ \ln \Omega\left(E_{1}, E - E_{1}\right) &= \ln \Omega_{1}\left(E_{1}\right) + \ln \Omega_{2}\left(E - E_{1}\right) \\ &\left(\frac{\partial \ln \Omega\left(E_{1}, E - E_{1}\right)}{\partial E_{1}}\right)_{N_{1}, V_{1}} = 0 \\ \left(\frac{\partial \ln \Omega_{1}\left(E_{1}\right)}{\partial E_{1}}\right)_{N_{1}, V_{1}} + \left(\frac{\partial \ln \Omega_{2}\left(E - E_{1}\right)}{\partial E_{1}}\right)_{N_{2}, V_{2}} = 0 \\ &\left(\frac{\partial \ln \Omega_{1}\left(E_{1}\right)}{\partial E_{1}}\right)_{N_{1}, V_{1}} = \left(\frac{\partial \ln \Omega_{2}\left(E - E_{1}\right)}{\partial E_{2}}\right)_{N_{2}, V_{2}} \end{split}$$





Indeed this is the condition for thermal equilibrium: "no spontaneous heat flow between I and 2" Normally, thermal equilibrium means: equal temperatures

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Then, thermal equilibrium is equivalent to:

$$\beta_1 = \beta_2$$

This suggests that β is a function of T.

Relation to thermodynamics

Conjecture:

Almost right.

Good features:

- Extensivity
- Third law of thermodynamics comes for free

Bad feature:

It assumes that entropy is dimensionless but (for unfortunate, historical reasons, it is not...)

Relation to thermodynamics

Conjecture: $S = \ln \Omega$

Almost right.

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$$S = k_B \ln \Omega(E)$$

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$$\left(\frac{\partial S}{\partial E}\right)_{N,V} = \frac{1}{T} \qquad \qquad dE = TdS - pdV + \sum_{i=1}^{n} \mu_i dN_i$$

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In thermodynamics, the absolute (Kelvin) temperature scale was defined such that

$$\left(\frac{\partial S}{\partial E}\right)_{N,V} = \frac{1}{T}$$

But we found (defined):

$$3 = \left(\frac{\partial \ln \Omega(E)}{\partial E}\right)_{N,V}$$

And this gives the "statistical" definition of temperature:

$$\frac{1}{T} \equiv k_B \left(\frac{\partial \ln \Omega(E)}{\partial E} \right)_{N,V}$$

with

$$\beta = \frac{1}{k_B T}$$

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with

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In short:

Entropy and temperature are both related to the fact that we can COUNT states.

How large is Ω ?

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Macroscopic deviations from the second law of thermodynamics are not forbidden, but they are extremely unlikely.

Deviation from the 2nd law?

What is the probability that I mole of argon gas spontaneously lowers it entropy by 0.0000001% (=10⁻¹⁰)?

standard molar entropy of argon : $S_{argon} = 307.2 \text{ J/K mol}^{-1}$ slightly lower entropy $S_{argon,low} = 307.2 (1 - 10^{-10}) \text{ J/K mol}^{-1}$

probability of occurrence is

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$$P \approx \frac{\Omega_{argon,low}}{\Omega_{argon}} = \exp\left[\frac{S_{argon,low} - S_{argon}}{k_B}\right] = \exp\left[\frac{-3.07 \times 10^{-8}}{1.38 \times 10^{-23}}\right] \approx 10^{-10^{15}}$$

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A mathematical relation $:10^{-10^{15}} \neq 0$

A physical relation $: 10^{-10^{15}} = 0$

Consider a small system that can exchange heat with a big reservoir

$$E_i$$
 $E-E_i$

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$$\ln \Omega \left(E - E_i \right) = \ln \Omega \left(E \right) - \frac{\partial \ln \Omega}{\partial E} E_i + \cdots$$

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 $1/k_BT$

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$$E_{i} = E_{i}$$

$$E - E_{i}$$

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Partition function:
$$Q = \sum \exp(-E_{j}/k_{B}T)$$

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$$P(E_i) \propto \exp(-E_i/k_B T)$$
Canonical ensemble

Consider a small system that can exchange heat with a big reservoir

$$E_i$$
 $E-E_i$

$$\ln \Omega \left(E - E_i \right) = \ln \Omega \left(E \right) - \frac{\partial \ln \Omega}{\partial E} E_i + \cdots$$
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Hence, the probability to find E_i :

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"Low energies are more likely than high energies"

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We have assume quantum mechanics (discrete states) but we are interested in the classical limit

$$\sum_{i} \exp(-\beta E_{i}) \rightarrow \frac{1}{h^{3^{N}} N!} \iint d\mathbf{p}^{N} d\mathbf{r}^{N} \exp\left\{-\beta \left[\sum_{i} \frac{p_{i}^{2}}{2m_{i}} + U(r^{N})\right]\right\}$$

$$\frac{1}{N!}$$
Particles are indistinguishable
$$\frac{1}{h^{3^{N}}}$$
"volume of phase space"

Why does planck constant appear?

Easiest to look at translation partition function Q_x of particle in ID box

$$\varepsilon_{trans} = \frac{1}{2}mv^2 = \frac{p^2}{2m}$$

p= momentum m=mass



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$$\lambda = \frac{2L}{n} \qquad \qquad \varepsilon_{trans} = \frac{p^2}{2m} = \frac{\left(h/\lambda\right)^2}{2m} = \frac{n^2 h^2}{8mL^2}$$



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Postulate quantum mechanics: $p=h/\lambda$ met h Planck's constant Particle is standing wave with length

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now compare to classical integration without Planck's constant

$$Q_x = \int \int dp dr \exp(-\beta \frac{p^2}{2m} + U(r)) = L \int dp \exp(-\beta \frac{p^2}{2m}) = L \sqrt{\frac{2\pi m}{\beta}}$$

factor of h is missing for each degree of freedom.

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Integration over the momenta can be carried out for most systems:

$$\int d\mathbf{p}^{N} \exp\left\{-\beta \left[\sum_{i} \frac{p_{i}^{2}}{2m_{i}}\right]\right\} = \left[\int d\mathbf{p} \exp\left\{-\beta \frac{p^{2}}{2m}\right\}\right]^{3N} = \left(\frac{2\pi m}{\beta}\right)^{\frac{3}{2}N}$$

Define de Broglie wavelength:

$$\Lambda \equiv \left(\frac{h^2\beta}{2\pi m}\right)^{\frac{1}{2}}$$

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Free energy:

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Pressure:

Energy:

$$P = -\left(\frac{\partial F}{\partial V}\right)_T = \frac{N}{\beta V} \qquad \qquad E = \left(\frac{\partial \beta F}{\partial \beta}\right) = \frac{3N}{\Lambda} \frac{\partial \Lambda}{\partial \beta} = \frac{3}{2} N k_B T$$

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Chemical potential:

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$$\beta\mu = \ln\Lambda^3 + \ln\rho$$

$$\beta\mu^{IG} = \beta\mu^0 + \ln\rho$$

Heat capacity from energy fluctuation

$$C_{V} = \left(\frac{\partial E}{\partial T}\right)_{V,N} = \left(\frac{\partial E}{\partial \beta}\right)_{V,N} \left(\frac{\partial \beta}{\partial T}\right)$$

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$$k_{B}T^{2}C_{V} = -\left(\frac{\partial E}{\partial \beta}\right)_{V,N}$$
$$\left(\sum_{i} \sum_{i} E_{i} \exp(-\beta E_{i})\right)$$
$$\left(\langle E \rangle = \frac{\sum_{i} E_{i} \exp(-\beta E_{i})}{\sum_{i} \exp(-\beta E_{i})}\right)$$
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$$= \left\langle E^{2} \right\rangle - \left\langle E \right\rangle^{2} = \left\langle \left(E - \left\langle E \right\rangle\right)^{2} \right\rangle$$

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E

$$k_{B}T^{2}C_{V} = -\frac{\partial}{\partial\beta} \frac{\sum_{i} E_{i} \exp(-\beta E_{i})}{\sum_{i} \exp(-\beta E_{i})}$$

$$= \frac{\sum_{i} E_{i}^{2} \exp(-\beta E_{i})}{\sum_{i} \exp(-\beta E_{i})} - \left(\frac{\sum_{i} E_{i} \exp(-\beta E_{i})}{\sum_{i} \exp(-\beta E_{i})}\right)^{2} \qquad \mathsf{P}(\mathsf{E})$$
fluctuation in E grows as $1/\sqrt{\mathsf{N}}$

$$= \langle E^{2} \rangle - \langle E \rangle^{2} = \langle \left(E - \langle E \rangle\right)^{2} \rangle$$

Computing the pressure

$$P = -\frac{\partial F}{\partial V}$$

$$F = -kT \ln Q$$

$$Q(N,V,T) = \frac{1}{\Lambda^{3N} N!} \int d\mathbf{r}^{N} \exp\left[-\beta U(\mathbf{r}^{N})\right]$$

Introduce scaled coordinates ${f r}\equiv L{f s}$

$$Q(N, V, T) = \frac{V^N}{\Lambda^{3N} N!} \int d\mathbf{s}^N \, \exp[-\beta \mathcal{U}(\mathbf{s}^N; L)]$$

Computing the pressure

$$\frac{\partial F}{\partial V} = -P$$

$$\frac{\partial F}{\partial V} = k_B T \frac{\partial \ln Q}{\partial V}$$

$$P = k_B T \frac{\partial \ln V^N \int d\mathbf{s}^N \exp[-\beta \mathcal{U}(\mathbf{s}^N; L)]}{\partial V}$$

$$P = k_B T \frac{\partial \ln V^* \int d\mathbf{s}^* \exp[-\beta \mathcal{U}(\mathbf{s}^*; L)]}{\partial V}$$

$$P = \frac{Nk_BT}{V} + k_BT \frac{\partial \ln \int d\mathbf{s}^N \exp[-\beta \mathcal{U}(\mathbf{s}^N; L)]}{\partial V}$$

$$V = \frac{\partial V}{\partial V}$$

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$$\frac{\partial \mathcal{U}(\mathbf{s}^N; L)}{\partial V} = \sum_{i=1}^N \frac{\partial \mathcal{U}(\mathbf{r}^N)}{\partial \mathbf{r}_i} \frac{\partial \mathbf{r}_i}{\partial V}$$

$$\frac{\partial \mathbf{r}_i}{\partial V} = \frac{1}{3L^2} \frac{\partial L \mathbf{s}_i}{\partial L} = \frac{1}{3L^2} \mathbf{s}_i$$

$$\frac{\partial \mathcal{U}(\mathbf{s}^N; L)}{\partial V} = \sum_{i=1}^N \frac{\partial \mathcal{U}(\mathbf{r}^N)}{\partial \mathbf{r}_i} \cdot \frac{\mathbf{r}_i}{3V}$$

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$$P = \frac{Nk_BT}{V} - \frac{\int d\mathbf{s}^N \sum_{i=1}^N \frac{\partial \mathcal{U}(\mathbf{r}^N)}{\partial \mathbf{r}_i} \cdot \frac{\mathbf{r}_i}{3V} \exp[-\beta \mathcal{U}(\mathbf{s}^N; L)]}{\int d\mathbf{s}^N \exp[-\beta \mathcal{U}(\mathbf{s}^N; L)]}$$
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$$- \left\langle \sum_{i=1}^N \frac{\partial \mathcal{U}(\mathbf{r}^N)}{\partial \mathbf{r}_i} \cdot \frac{\mathbf{r}_i}{3V} \right\rangle = \frac{Nk_BT}{V} + \frac{1}{3V} \left\langle \sum_{i=1}^N \mathbf{f}_i \cdot \mathbf{r}_i \right\rangle$$

 $\frac{Nk_BT}{V} + \frac{1}{3V} \left\langle \sum_{i=1}^{N} \mathbf{f}_i \cdot \mathbf{r}_i \right\rangle$ it is can be written as ensemble average!

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 $\frac{BT}{T}$

$$P = \frac{Nk_BT}{V} + \frac{1}{3V} \left\langle \sum_{i=1}^{N} \mathbf{f}_i \cdot \mathbf{r}_i \right\rangle$$

For pairwise additive forces:

$$\mathbf{f}_i = \sum_{j \neq i} \mathbf{f}_{ij}$$

Then

$$P = \frac{Nk_BT}{V} + \frac{1}{3V} \left\langle \sum_{i,j=1,i\neq j}^{N} \mathbf{f}_{ij} \cdot \mathbf{r}_i \right\rangle$$

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i and *j* are dummy variable hence:

$$\sum_{i,j=1,i\neq j}^{N} \mathbf{f}_{ij} \cdot \mathbf{r}_i = \sum_{j,i=1,j\neq i}^{N} \mathbf{f}_{ji} \cdot \mathbf{r}_j$$

And we can write

$$\sum_{i,j=1,i\neq j}^{N} \mathbf{f}_{ij} \cdot \mathbf{r}_i = \frac{1}{2} \sum_{j,i=1,j\neq i}^{N} \left(\mathbf{f}_{ij} \cdot \mathbf{r}_i + \mathbf{f}_{ji} \cdot \mathbf{r}_j \right)$$

But as action equals reaction (Newton's 3rd law): $\mathbf{f}_{ij} = -\mathbf{f}_{ji}$

And hence

$$\sum_{j,i=1,j\neq i}^{N} \left(\mathbf{f}_{ij} \cdot \mathbf{r}_{i} + \mathbf{f}_{ji} \cdot \mathbf{r}_{j} \right) = \sum_{j,i=1,j\neq i}^{N} \mathbf{f}_{ij} \cdot (\mathbf{r}_{i} - \mathbf{r}_{j})$$

Inserting this in our expression for the pressure, we get:

$$P = \frac{Nk_BT}{V} + \frac{1}{6V} \left\langle \sum_{i,j=1,i\neq j}^{N} \mathbf{f}_{ij} \cdot \mathbf{r}_{ij} \right\rangle$$

Where $\mathbf{r}_{ij} \equiv \mathbf{r}_i - \mathbf{r}_j$

This is known as the virial expression

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What do you do if you can't use the virial expression?

$$P = -\frac{\partial F}{\partial V} \approx \frac{F(V - \Delta V) - F(V)}{\Delta V}$$

This will be the case e.g. with discontinuous potentials.

Partition function:

$$Q(N,V,E) = \frac{1}{h^{3N}N!} \iint d\mathbf{p}^N d\mathbf{r}^N \delta \left(H(\mathbf{p}^N,\mathbf{r}^N) - E \right)$$

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Probability to find a particular configuration $\Gamma = \{\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N\}$

$$P(\Gamma) \propto 1$$

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Entropy

$$S = k_B \ln Q_{N,V,E}$$

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For properties that only depend on the configurational part

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Ensemble average:

$$\langle A \rangle = \int d\Gamma A(\Gamma) P(\Gamma)$$

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Ergodicity theorem

suppose we have an ensemble average of a system defined by $U(\Gamma)$ obtained by MC

$$\langle A \rangle = \frac{1}{Q} \int d\Gamma A(\Gamma) \exp\left[-\beta U(\Gamma)\right]$$

Now suppose we have a NVT molecular dynamics trajectory for the same system A time average over the trajectory is simply

$$\bar{A} = \frac{1}{\mathcal{T}} \int_0^{\mathcal{T}} A(t) dt$$

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Ergodicity theorem states that for an 'ergodic system'

$$\bar{A} = \langle A \rangle$$

Ergodicity theorem

suppose we have an ensemble average of a system defined by $U(\Gamma)$ obtained by MC

$$\langle A \rangle = \frac{1}{Q} \int d\Gamma A (\Gamma) \exp \left[-\beta U (\Gamma) \right]$$

Now suppose we have a NVT molecular dynamics trajectory for the same system A time average over the trajectory is simply

$$\bar{A} = \frac{1}{\mathcal{T}} \int_0^{\mathcal{T}} A(t) dt$$

Ergodicity theorem states that for an 'ergodic system'

$$\bar{A} = \langle A \rangle$$

MC and MD give the same averages

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Course on MD and MC in different ensembles

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Other ensembles?

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But for doing this we need to know the Statistical Thermodynamics of the various ensembles.

Constant pressure simulations: N,P,T ensemble



Consider a small system that can exchange volume and energy with a big reservoir

Constant pressure simulations: N,P,T ensemble



Consider a small system that can exchange volume and energy with a big reservoir

$$\ln \Omega \left(V - V_{i,E} - E_{i} \right) = \ln \Omega \left(V, E \right) - \left(\frac{\partial \ln \Omega}{\partial E} \right)_{V} E_{i} - \left(\frac{\partial \ln \Omega}{\partial V} \right)_{E} V_{i} + \cdots$$

Constant pressure simulations: N,P,T ensemble



Constant pressure simulations: <u>NPT</u> ensemble

Thermo recall

Fundamental equation

$$dE = TdS - pdV + \sum_{i} \mu_{i} dN_{i}$$

 $\ln \Omega (V$

 V_i, E_i

$$-V_{i}$$
 Hence

T

and

$$\left(\frac{\partial S}{\partial V}\right)_{T,N} = \frac{\mu}{7}$$

 ∂S

 $\overline{\partial E}$

 p/k_BT can exchan volume with a bi reservoir $\left(\frac{\partial \ln' \Omega}{\partial V}\right)_{-} V_{i} + \cdots$




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Grand-canonical simulations: U.V.T ensemble

Thermo recall

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$$dE = TdS - pdV + \sum_{i} \mu_{i} dN_{i}$$

Hence

$$\ln \Omega \left(N - N_i \right)$$

 N_i, E_i

$$\frac{1}{T} = \left(\frac{\partial S}{\partial E}\right)_{V,N}$$

and

$$\left(\frac{\partial S}{\partial N_i}\right)_{T,V} = -\frac{\mu_i}{T}$$

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- MD also gives dynamical properties (viscosity, diffusion etc)
- Rest of the week: MC and MD in depth.

The end

