Statistical thermodynamics for MD and MC simulations

knowing 2 atoms and wishing to know 10^{23} of them

Marcus Elstner and Tomáš Kubař

22 June 2016

Thermodynamic properties of molecular systems

statistical mechanics: the way from the properties of particles
to the thermodynamic properties of ensembles
via the partition function

- how is the thermodynamic equilibrium characterized?
- which quantities are of interest?
- how may these be derived from the partition function?
- how to derive the ensemble partition function from the partition function of a single molecule?
- how is partition function connected to phase-space density?
- MD simulation provides an alternative way to thermodynamic quantities
- it is difficult to obtain free energies from normal simulations

Equilibrium and spontaneous processes

classical thermodynamics →
  thermodynamic equilibrium and spontaneous process
  says which quantites are maximized/minimized in equilibrium
    and show a definite change during spontaneous processes

microcanonical ensemble:
  equilibrium reached if entropy S maximized
  process spontaneously if entropy increases: $\Delta S > 0$

canonical ensemble – more complex, as we need
  to consider system of interest together with surroundings
  (to identify equilibrium and spontaneity)
to calculate anything for the supersystem
  – impossible – alternative needed

Free energy / enthalpy – fundamental property

How to keep our molecular system and drop the surroundings?
introduce a new thermodynamic function:

- Helmholtz free energy F in canonical ensemble
- Gibbs free energy/enthalpy G in NPT ensemble

$$F = U - TS \qquad\qquad G = H - TS = U + pV - TS$$

- $F = F(T, V)$ or $G = G(T, P)$ – depends on experimentally controllable variables T and V/P
- a 'stable' state of the system
  - – minimum of F or G rather than of U
  - – equivalent to maximization of entropy of universe
- F / G decreases in the course of spontaneous process
  - – holy grail of MD simulation

Microscopic definition of entropy

W – number of ways ('microstates')
in which a certain 'macrostate' may be realized
(a certain occupation of energy levels of the system)

microscopic entropy:

$$S = k_{\mathrm{B}} \cdot \ln W$$

(k_{B} – universal Boltzmann constant)

Microscopic definition of entropy

Ludwig Boltzmann – Austrian physicist

Microscopic definition of entropy

- S tells us something about the travel of the system through the configuration (phase) space
- equivalently, S can be related to the order in the system
- low entropy – few states are occupied
  - – only a small part of configuration space accessible
  - – ordered system
- high entropy – many states are visited
  - – extended regions of the configuration space covered
  - – less ordered system

Example – pile of books on a desk
Jan Černý (Charles University in Prague, Dept Cellular Biology):

anthropy – "entropy of human origin"

Introduction

"…series of molecular structures generated by an MD simulation with the Berendsen thermostat does not represent the correct canonical ensemble" – what does this mean?

The phase space may be sampled (walked through) in various ways
– just what is the correct way?

Closed system – canonical ensemble

system in thermal contact with the surroundings
– temperature rather than energy remains constant
– Boltzmann distribution of p_i applies:

$$p_i = \frac{\exp[-\beta \cdot \varepsilon_i]}{Q}$$

$$Q = \sum_j \exp[-\beta \cdot \varepsilon_j]$$

Q – canonical partition function (Zustandssumme)

derive the meaning of β – fall back to basic thermodynamics. . . :

$$\beta = \frac{1}{k_\mathrm{B} T}$$

Canonical partition function

Q – seems to be purely abstract…

but – to characterize the thermodynamics of a system
  Q is completely sufficient,
  all thermodynamic observables follow as functions of Q

how to obtain Q?
  – there will be 2 ways, depending on the system studied

partition function connects the microscopic and macroscopic world

Using the partition function

we can get all thermodynamic functions from Q:

$$\begin{aligned}
U &= \langle E \rangle = k_\mathrm{B} T^2 \frac{\partial \ln Q}{\partial T} \\
S &= k_\mathrm{B} T \cdot \frac{\partial \ln Q}{\partial T} + k_\mathrm{B} \cdot \ln Q \\
F &= -k_\mathrm{B} T \cdot \ln Q \\
P &= k_\mathrm{B} T \cdot \left(\frac{\partial \ln Q}{\partial V} \right)_T \qquad \text{(equation of state)} \\
H &= U + pV \\
G &= F + pV = H - TS
\end{aligned}$$

Michal Otyepka (Palacký University Olomouc, Dept Physical Chemistry):

> “Just grab the partition function at the tail, and then you have everything!”

2 ways to thermodynamic properties

- simple molecules with 1 or few minima of energy
  - calculate the partition function (trans+vib+rot)
    (probably employ approximations IG+HO+RR)
  - derive properties from Q

Discrete systems

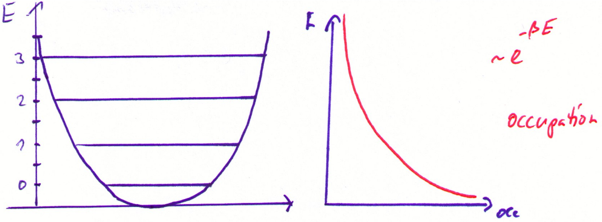
system with discrete energy levels E_i – partition function:

$$Q = \sum_i \exp[-\beta E_i]$$

Boltzmann distro function: (prob. of system in state E_i)

$$p_i = \frac{1}{Q}\exp[-\beta E_i]$$

example – HO: $E_i = \left(i + \frac{1}{2}\right) \cdot \hbar\omega$



Using the partition function of 1 molecule

partition function of a large system – simplifications possible:

- system of n identical and indistinguishable particles (gas):

$$Q = \frac{q^n}{n!}$$

- necessary effort reduced greatly!
  - get the molecular partition function q
    (calculate 1 molecule, or 2)
  - obtain the ensemble partition function Q
    and all thermodynamic quantities

Simple molecules

... with 1 or few well characterized minima
for a certain minimum – consider contributions to energy:

$$E = E^{\text{el}} + E^{\text{trans}} + E^{\text{rot}} + E^{\text{vib}}$$

partition function follows as

$$\begin{aligned} Q &= \exp\left[-\beta\left(E^{\text{el}} + E^{\text{trans}} + E^{\text{rot}} + E^{\text{vib}}\right)\right] = \\ &= \exp[-\beta E^{\text{el}}] \cdot \exp[-\beta E^{\text{trans}}] \cdot \exp[-\beta E^{\text{rot}}] \cdot \exp[-\beta E^{\text{vib}}] = \\ &= Q^{\text{el}} \cdot Q^{\text{trans}} \cdot Q^{\text{rot}} \cdot Q^{\text{vib}} \end{aligned}$$

or

$$\ln Q = \ln Q^{\text{el}} + \ln Q^{\text{trans}} + \ln Q^{\text{rot}} + \ln Q^{\text{vib}}$$

Electronic partition function

usually: quite high excitation energy
$\rightarrow$ electronic ground state only populated:

$$E^{\text{el}}(0) = 0 \qquad \text{arbitrarily}$$

electronic partition function:

$$Q^{\text{el}} = \exp[-\beta E^{\text{el}}(0)] + \exp[-\beta E^{\text{el}}(1)] + \ldots \approx 1 + 0 + \ldots = 1$$

so this may be neglected ☺

Translational partition function

calculated for quantum-mechanical particle (mass m) in a 3D box:

energy levels:

$$E_{n_x,n_y,n_z} = \frac{h^2}{8m}\left(\frac{n_x^2}{L_x^2} + \frac{n_y^2}{L_y^2} + \frac{n_z^2}{L_z^2}\right)$$

quantum numbers $n_i = 1, 2, \ldots$

partition function:

$$Q^{\text{trans}} = \left(\frac{2\pi m k_\text{B} T}{h^2}\right)^{\frac{3}{2}} \cdot V$$

Rotational partition function

calculated for a rigid rotor (moments of inertia I_x):

energy levels:

$$E_J = B \cdot J(J+1)$$

quantum number $J = 0, 1, 2, \ldots$, degeneracy of levels $2J+1$

rotational constant $B = \frac{h^2}{8\pi^2 I}$ (I – moment of inertia)

$$Q^{\mathrm{rot}} = \sum_{J=0}^{\infty} (2J+1) \exp\left[-J(J+1) \cdot \frac{B}{k_{\mathrm{B}} T}\right]$$

for asymmetric top with rotational constants B_x, B_y, B_z:

$$Q^{\mathrm{rot}} = \sqrt{\frac{\pi \left(k_{\mathrm{B}} T\right)^3}{B_x B_y B_z}}$$

Vibrational partition function

calculated with harmonic vibrational frequencies ω_k of the molecule
(computation of Hessian in the minimum of potential energy)
– each vibrational mode k is one harmonic oscillator

energy levels:

$$E_k^m = \left(m + \frac{1}{2}\right) \cdot \hbar\omega_k$$

where $E_k^0 = \frac{1}{2}\hbar\omega_k$ is zero point vibrational energy

partition function (using $\sum_{n=0}^{\infty} x^n = \frac{1}{1-x}$):

$$Q_k^{\mathrm{vib}} = \sum_{m=0}^{\infty} \exp\left[-\beta\left(m + \frac{1}{2}\right)\hbar\omega_k\right] = \frac{\exp\left[-\frac{1}{2}\beta\hbar\omega_k\right]}{1 - \exp\left[-\beta\hbar\omega_k\right]}$$

each molecule: $N - 6$ vibrational modes $=$ $N - 6$ HOs
example – H_2O: 3 modes (2 stretches, 1 bend)

Thermodynamic properties

for enthalpy – pV is needed – simple for IG:

$$pV = Nk_{\mathrm{B}}T$$

then, enthalpy and Gibbs free energy follow:

$$\begin{aligned} H &= U + pV = U + Nk_{\mathrm{B}}T \\ G &= F + pV = F + Nk_{\mathrm{B}}T \end{aligned}$$

thermal contributions – calculated by default
with many QCh and MD programs
whenever vibrational analysis is requested
reason – vibrational frequencies are computationally costly
while the thermodynamics is done ‘for free’

Example – vibrational contributions

$$\begin{aligned}
\ln Q_k &= -\frac{1}{2}\beta\hbar\omega_k - \ln\left[1 - \exp[-\beta\hbar\omega_k]\right] \\
U_k &= -\frac{\partial \ln Q_k}{\partial \beta} = \hbar\omega_k\left(\frac{1}{2} + \frac{1}{\exp[\beta\hbar\omega_k] - 1}\right)
\end{aligned}$$

consider this for all of $N-6$ vibrational DOFs, dropping ZPVE:

$$U^{\mathrm{vib}} = \sum_{k=1}^{N-6}\left(\frac{\hbar\omega_k}{\exp[\beta\hbar\omega_k] - 1}\right)$$

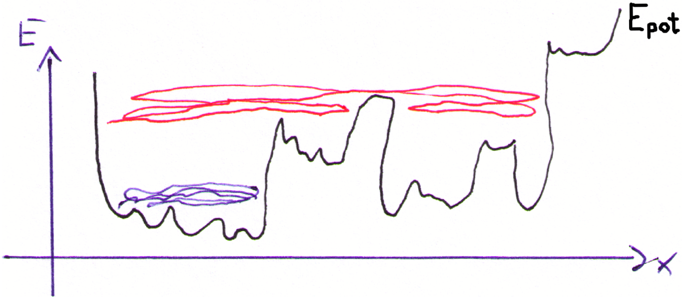
$$\begin{aligned}
F^{\mathrm{vib}} &= -k_{\mathrm{B}}T\ln Q^{\mathrm{vib}} = \sum_{k=1}^{N-6} k_{\mathrm{B}}T\ln\left[1 - \exp[-\beta\hbar\omega_k]\right] \\
\frac{S^{\mathrm{vib}}}{k_{\mathrm{B}}} &= \frac{U^{\mathrm{vib}} - F^{\mathrm{vib}}}{k_{\mathrm{B}}T} = \sum_{k=1}^{N-6}\left(\frac{\beta\hbar\omega_k}{\exp[\beta\hbar\omega_k] - 1} - \ln\left[1 - \exp[-\beta\hbar\omega_k]\right]\right)
\end{aligned}$$

2 ways to thermodynamic properties

- simple molecules with 1 or few minima of energy
  - calculate the partition function (trans+vib+rot)
    (probably employ approximations IG+HO+RR)
  - derive properties from Q
- flexible molecules, complex molecular systems
  - quantum mechanical energy levels cannot be calculated
  - a single minimum of energy not meaningful
  - do MD (MC) simulation instead, to sample phase space
  - evaluate time averages of thermodynamic quantities

Systems with continuous distribution of energy

dynamics of molecules – at different tot. energies or temperatures, differently extended regions of conformational space are sampled



complex energy landscape $E_{\text{pot}}(x)$
blue and red – trajectories at different total energies
– different phase-space densities

Continuous systems – canonical ensemble

- every point in phase space – a certain value of energy composed of $E_{\text{pot}} = E_{\text{pot}}(\vec{r})$ (force field), $E_{\text{kin}} = E_{\text{kin}}(\vec{p})$
- continuous energy levels – infinitesimally narrow spacing
- canonical probability distribution function
  – probability to find the system in state with E:

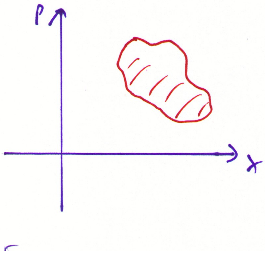
$$P(\vec{r},\vec{p}) = \rho(\vec{r},\vec{p}) = \frac{1}{Q} \cdot \exp\left[-\frac{E(\vec{r},\vec{p})}{k_{\text{B}}T}\right]$$

- perform MD simulation with a correct thermostat, or MC sim.
  – the goal is to obtain the right probability density ρ
- partition fction Q – integral over phase space rather than sum

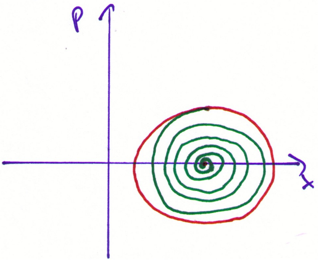
$$Q = \int \exp\left[-\frac{E(\vec{r},\vec{p})}{k_{\text{B}}T}\right] \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}$$

Thermodynamic quantities – sampling

$\rho(\vec{r},\vec{p})$ – gives the probability of finding the system at $(\vec{r},\vec{p})$
typically: system is sampling only a part of phase space ($P \neq 0$):



sampling in MD or MC



undamped and damped classical HO

Thermodynamic quantities – sampling

thermodynamic quantities – weighted averages:

$$\langle A \rangle = \frac{\int A \cdot \rho(\vec{r}, \vec{p})\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}}{\int \rho(\vec{r}, \vec{p})\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}}$$

why do MD? … obtain the correct phase-space density ρ

ergodic simulation – thermodynamic potentials U, H etc.
are obtained as time averages

$$\langle A \rangle = \frac{1}{t_1 - t_0} \int_{t_0}^{t_1} A(t)\, \mathrm{d}t$$

– valid only if the simulation has sampled the canonical ensemble
→ phase-space density is correct

– the density ρ is present in the the trajectory inherently
→ e.g. structure with high ρ occur more often

Thermodynamic quantities – sampling

Thus, we have the following to do:

- perform MD simulation (with correct thermostat!)
  $\rightarrow$ trajectory in phase space
  (simulation has 'taken care' of the phase-space density)
- get time averages of desired thermodynamic properties

$$\langle A \rangle = \frac{1}{t_1 - t_0} \int_{t_0}^{t_1} A(t)\,\mathrm{d}t$$

Thermodynamic quantities – sampling

we have to obtain the phase-space density with MD simulation

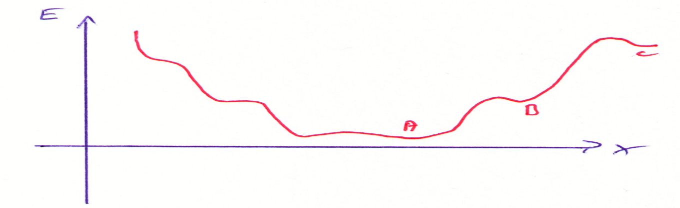
$$\rho(\vec{r},\vec{p}) = \frac{\exp[-\beta E(\vec{r},\vec{p})]}{Q} \qquad \vec{r} = \{r_1,\ldots,r_{3N}\}, \vec{p} = \{p_1,\ldots,p_{3N}\}$$

which is the probability of system occuring at point $(\vec{r},\vec{p})$

How long an MD simulation can we perform?
    1 ps → 1,000 points in trajectory
    10 ns → 10M points – we cannot afford much more

example – we have 1,000 points
  then, we have hardly sampled $(\vec{r},\vec{p})$ for which $\rho(\vec{r},\vec{p}) \leq \frac{1}{1000}$
  → points with high energy will be never reached!
    (while low-energy region may be sampled well)

Missing high-energy points in sampling



High-energy points B and C may be sampled badly

– a typical problem in MD simulations of limited length
– the corresponding large energies are missing in averaging
– when does this matter?

– no serious error for the internal energy – exponential dependence of phase-space density kills the contribution

$$\rho(\vec{r}, \vec{p}) = \frac{\exp[-\beta E(\vec{r}, \vec{p})]}{Q}$$

Missing high-energy points in sampling

Free energies

- determine the spontaneity of process
- NVT canonical – Helmholtz function F
- NPT ‘canonical’ – Gibbs function G
- the relevant quantity always obtained depending on whether NVT or NPT simulation is performed
- much more pronounced sampling issues than e.g. for internal energy!

Missing high-energy points in sampling

$$
\begin{aligned}
F &= -k_\mathrm{B} T \ln Q = k_\mathrm{B} T \ln \frac{1}{Q} = \\
&= k_\mathrm{B} T \ln \frac{c^{-1} \cdot \iint \exp[\beta E(\vec{r},\vec{p})] \cdot \exp[-\beta E(\vec{r},\vec{p})] \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}}{Q} = \\
&= k_\mathrm{B} T \ln \iint \exp[\beta E(\vec{r},\vec{p})] \cdot \rho(\vec{r},\vec{p}) \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p} - \ln c \\
&= k_\mathrm{B} T \cdot \ln \left\langle \exp\left[\frac{E}{k_\mathrm{B} T}\right] \right\rangle - \ln c
\end{aligned}
$$

serious issue – the large energy values enter an exponential,
and so the high-energy regions may contribute significantly!
→ if these are undersampled, then free energies are wrong

– calculation of free energies impossible! special methods needed!