Free energy simulations

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Motivation

a physical quantity that is of most interest in chemistry?

free energies – Helmholtz F or Gibbs G
– holy grail of computational chemistry,
both for their importance
and because they are difficult to calculate

Convergence issue

– especially desperate for free energies:

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

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!

Tackling the issue

two fundamental approaches:
free energy perturbation and thermodynamic integration

several computational tricks for particular types of reactions:
alchemical simulations or umbrella sampling

important: not necessary to find the absolute value of free energy;
it is important to know merely the free energy difference $\Delta F / \Delta G$ between the involved states (reactant A and product B).

"reaction" – not necessarily chem. bonds created or broken

- ligand binding to a protein
- passage of a molecule through membrane
- protein folding. . .

Tackling the issue

Note on ΔF vs. ΔG:

ΔF is obtained in NVT simulations
ΔG is obtained in NPT simulations
– automatically, with otherwise identical simulation protocols

In this presentation, F is written.
Everything applies to G as well.

Free energy perturbation

states with energies $E_A(\vec{r},\vec{p})$, $E_B(\vec{r},\vec{p})$ and partition fns Q_A, Q_B

$$\begin{aligned}
\Delta F &= F_B - F_A = -k_\mathrm{B} T \ln \frac{Q_B}{Q_A} = -k_\mathrm{B} T \ln \frac{\iint \exp[-\beta E_B] \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}}{\iint \exp[-\beta E_A] \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}} = \\
&= -k_\mathrm{B} T \ln \frac{\iint \exp[-\beta E_B] \, \exp[\beta E_A] \, \exp[-\beta E_A] \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}}{\iint \exp[-\beta E_A] \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}} = \\
&= -k_\mathrm{B} T \ln \frac{\iint \exp[-\beta E_B] \, \exp[\beta E_A] \, \exp[-\beta E_A] \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}}{\iint \exp[-\beta E_A] \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}} = \\
&= -k_\mathrm{B} T \ln \iint \exp[-\beta E_B] \exp[\beta E_A] \cdot \rho_A(\vec{r},\vec{p}) \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p} = \\
&= -k_\mathrm{B} T \ln \iint \exp[-\beta (E_B - E_A)] \cdot \rho_A(\vec{r},\vec{p}) \,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}
\end{aligned}$$

The working equation

$$\Delta F = -k_\mathrm{B} T \ln \iint \exp[-\beta(E_B - E_A)] \cdot \rho_A(\vec{r}, \vec{p})\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}$$

The integral has the form of an average of a property S taken with the phase space density of state A

$$\langle S \rangle_A = \iint S(\vec{r}, \vec{p}) \cdot \rho_A(\vec{r}, \vec{p})\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}$$

and so we can write equivalently

$$\begin{aligned} \Delta F(A \to B) &= -k_\mathrm{B} T \ln \langle \exp[-\beta(E_B - E_A)] \rangle_A \\ \Delta F(B \to A) &= -k_\mathrm{B} T \ln \langle \exp[-\beta(E_A - E_B)] \rangle_B \end{aligned}$$

– free energy formula by Zwanzig (1954)
– the essence of the FEP method

How to use it

$$\Delta F(A \to B) = -k_\mathrm{B} T \ln \left\langle \exp[-\beta(E_B - E_A)] \right\rangle_A$$

What does it mean?

It is possible to perform a simulation of state A
and obtain the free energy
by averaging the exponential of the difference
of energies of states B and A, or vice versa.

Practically:

- perform an MD in state A to get the phase space density ρ_A
- evaluate the difference $E_A - E_B$ along the trajectory

Advantage of FEP over free simulation

- free MD simulation – direct evaluation of free energies:
  two simulations, one for each state A and B:

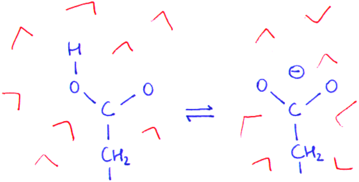
  $$\Delta F(A \to B) = k_\mathrm{B}T \ln \left\langle \exp[\beta E_B] \right\rangle_B - k_\mathrm{B}T \ln \left\langle \exp[\beta E_A] \right\rangle_A$$

  $\Delta F(A \to B)$ is a small difference of extremely large energies
  → the subtraction leads to a huge relative error

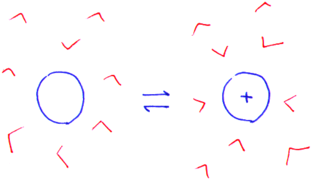
- FEP – evaluate the difference directly in one simulation
  – not necessary to sample the parts of the molecular system
  that do not change (thus, do not contribute to $E_B - E_A$)
- FEP – a much smaller region of phase space to be sampled thoroughly → the required simulation length becomes feasible

Examples of use

deprotonation of amino acid



ionization of molecule



Examples of use

Free energy of deprotonation (pK_a)
of an amino acid side chain in a protein

- run a simulation for the protonated species
- evaluate the energy difference between protonated and unprotonated species to get the average of $\exp[-\beta(E_B - E_A)]$
- only works if the conformations of the protein and the configuration of water molecules, sampled along the MD, are very similar with both forms
- usually not the case, unfortunately

Examples of use

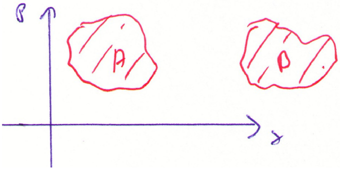
The ionization of a molecule

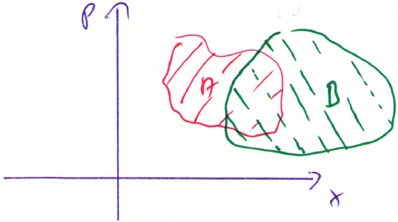
- perform a simulation of the neutral species
- evaluate the energy differences along the trajectory
- problem:
  the configuration of water would be quite different here, too
  $\rightarrow$ very small overlap of phase space densities
  of the reactant and the product

FEP in use – requirements

overlap in phase space or overlap of phase space densities

the more similar the states A and B are,
the more similar are the corresponding phase space densities,
and they may overlap:





FEP in use – requirements

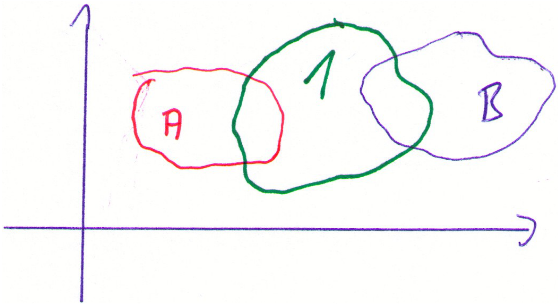
If the phase space densities for states A and B overlap
$\rightarrow$ the low-energy regions of state B may be sampled well
even in the simulation of state A,
and the free energy difference $\Delta F(A \rightarrow B)$ may converge

What happens if this is not the case?
The simulation of state A hardly samples the region
of phase space where the state B has low energy
$\rightarrow$ this region is undersampled,
the averaging of the energy E_B is wrong,
and the calculation will not converge

FEP in use – connecting the end states

How to overcome this problem?

insert an intermediate state that overlaps with both A and B:



How does this help?

free energy is a state function, and so

$$\Delta F(A \rightarrow B) = \Delta F(A \rightarrow 1) + \Delta F(1 \rightarrow B)$$

FEP in use – connecting the end states

We can perform two MD simulations,
one for each of the states A and 1,
and evaluate free energies for the two reactions.

These may be expected to converge better,
and their sum gives the free energy of $A \to B$:

$$\begin{aligned}\Delta F = & - k_\mathrm{B} T \ln \left[\frac{Q_1}{Q_A} \cdot \frac{Q_B}{Q_1} \right] = \\ = & - k_\mathrm{B} T \ln \left\langle \exp[-\beta(E_1 - E_A)] \right\rangle_A \\ & - k_\mathrm{B} T \ln \left\langle \exp[-\beta(E_B - E_1)] \right\rangle_1\end{aligned}$$

FEP in use – connecting the end states

more than one intermediate state may be inserted between $A - B$, if these differ exceedingly

for N intermediate states $1, 2, \ldots, N$:

$$\begin{aligned}\Delta F = & - \quad k_\mathrm{B} T \ln \left[\frac{Q_1}{Q_A} \cdot \frac{Q_2}{Q_1} \cdot \ldots \cdot \frac{Q_B}{Q_N} \right] = \\ = & - \quad k_\mathrm{B} T \ln \left\langle \exp[-\beta(E_1 - E_A)] \right\rangle_A - k_\mathrm{B} T \ln \left\langle \exp[-\beta(E_2 - E_1)] \right\rangle_1 \\ & - \quad \ldots - k_\mathrm{B} T \ln \left\langle \exp[-\beta(E_B - E_N)] \right\rangle_N\end{aligned}$$

and we have to perform $N + 1$ simulations of states $A, 1, 2, \ldots, N$:

$$\Delta F = \Delta F(A \to 1) + \Delta F(1 \to 2) + \ldots + \Delta F(N \to B)$$

FEP in use

- may look complicated, but it is rather straightforward
- FEP is used with common simulation packages conveniently

- We can change the chemical identities of atoms
  or functional groups – computational alchemy
- use a parameter λ to interpolate the force-field parameters
  between those of state A and those of state B:

$$E_\lambda = (1 - \lambda) \cdot E_A + \lambda \cdot E_B$$

Examples

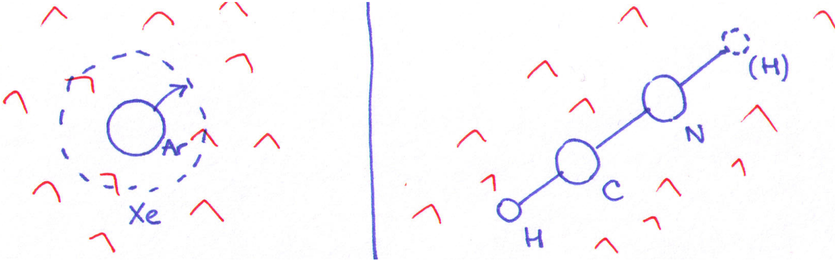
The hydration free energy difference of argon and xenon

- Ar and Xe differ only in the vdW parameters
  – the well depth ε and the radius σ
- interpolate between the parameters for the two elements:

$$\begin{aligned}\varepsilon_\lambda &= (1-\lambda)\cdot\varepsilon_{\mathsf{Ar}} + \lambda\cdot\varepsilon_{\mathsf{Xe}}\\ \sigma_\lambda &= (1-\lambda)\cdot\sigma_{\mathsf{Xe}} + \lambda\cdot\sigma_{\mathsf{Xe}}\end{aligned}$$

- start a simulation from $\lambda = 0$ (i.e. an argon atom), and change it in subsequent steps to 1
- for each step (λ value, or window), perform an MD simulation with corresponding ε_λ and σ_λ, and calculate the free energy difference

Examples



Examples

A true chemical reaction: HCN → CNH

- more complicated – need the topologies of both molecules
  – dual-topology simulation
- both molecules are present simultaneously in the simulation
- they do not interact with each other
- the interactions of one species with the solvent
  are switched off gradually,
  while the other is being switched on

Thermodynamic integration

TI – an alternative way to free energies.

energy E is a function of λ,
so free energy also becomes dependent on λ:

$$F = F(\lambda)$$

with $F(\lambda = 0) = F(A)$ and $F(\lambda = 1) = F(B)$

Therefore:

$$\Delta F = F(B) - F(A) = \int_0^1 \frac{\partial F(\lambda)}{\partial \lambda} \mathrm{d}\lambda$$

with

$$F(\lambda) = -k_{\mathrm{B}} T \ln Q(\lambda)$$

TI – working principle

$$\begin{aligned}
\frac{\partial F}{\partial \lambda}(\lambda) &= -k_B T \frac{\partial \ln Q}{\partial \lambda}(\lambda) = -k_B T \frac{1}{Q(\lambda)} \cdot \frac{\partial Q}{\partial \lambda}(\lambda) \\
&= -k_B T \frac{1}{Q(\lambda)} \cdot \frac{\partial}{\partial \lambda} \iint \exp[-\beta E_\lambda] \, \mathrm{d}\vec{r} \, \mathrm{d}\vec{p} = \\
&= -k_B T \frac{1}{Q(\lambda)} \cdot \iint (-\beta) \exp[-\beta E_\lambda] \cdot \frac{\partial E_\lambda}{\partial \lambda} \, \mathrm{d}\vec{r} \, \mathrm{d}\vec{p} = \\
&= -k_B T \cdot (-\beta) \cdot \iint \frac{\exp[-\beta E_\lambda]}{Q(\lambda)} \cdot \frac{\partial E_\lambda}{\partial \lambda} \, \mathrm{d}\vec{r} \, \mathrm{d}\vec{p} \\
&= 1 \cdot \iint \rho_\lambda(\vec{r}, \vec{p}) \cdot \frac{\partial E_\lambda}{\partial \lambda} \, \mathrm{d}\vec{r} \, \mathrm{d}\vec{p} = \\
&= \left\langle \frac{\partial E_\lambda}{\partial \lambda} \right\rangle_\lambda
\end{aligned}$$

TI – working principle

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

Essence of TI:

the derivative of free energy F with respect to λ
is calculated as the average of derivative of total energy E,
which can be directly evaluated in the simulation

The free energy difference follows simply as

$$\Delta F = \int_0^1 \left\langle \frac{\partial E_\lambda}{\partial \lambda} \right\rangle_\lambda \mathrm{d}\lambda$$

How to do it practically

We perform a MD simulation for each chosen value of λ:
usually, equidistant values in the interval (0,1) are taken:
0, 0.05, . . . , 0.95 and 1.

Each of these simulations produces a value of $\left\langle \frac{\partial E}{\partial \lambda} \right\rangle_\lambda$, so
we obtain the derivative of F in discrete points for $\lambda \in (0, 1)$.

This function is then integrated numerically,
and the result is the desired free energy difference ΔF.

Example

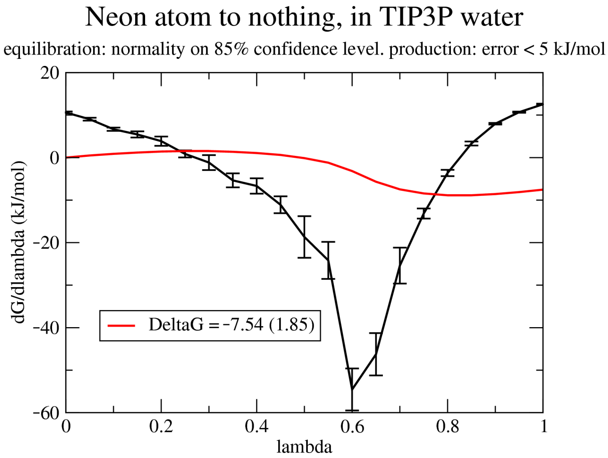
Free energy of hydration of rare gas (neon)

in the course of an NPT simulation,
vdW parameters of the neon atom are being
switched off by means of λ gradually,
so that the atom is effectively disappearing

The derivative of total energy with respect to λ
is evaluated for 21 values of λ ranging from 0 to 1.
Then, TI gives the Gibbs energy difference of two states:

- a neon atom in water
- no neon atom in water $\equiv$
  $\equiv$ a neon atom outside of the solution, in vacuo

Example


Neon atom to nothing, in TIP3P water
equilibration: normality on 85% confidence level. production: error < 5 kJ/mol
dG/dlambda (kJ/mol)
20
0
-20
-40
-60
0
0.2
0.4
0.6
0.8
1
lambda
DeltaG = -7.54 (1.85)

Choice of reaction coordinate

Both FEP and TI require a coupling parameter λ
– the reaction coordinate (reactant $\lambda = 0$, product $\lambda = 1$)

Free energy is a state function
→ the result is independent of the chosen path
between the reactant and the product

We are free to use even an unphysical process
as the reaction coordinate
– e.g., a change of chemical identity of one or more atoms
(in the alchemical simulations)

Choice of the number of windows

- we would like to have as few as possible,
  without compromising numerical precision of the calculation
- the factors affecting the choice are different in FEP and in TI

FEP: The assumption is that while simulating the state A,
the low-energy regions of state B are sampled well.
The closer the windows are, the better this condition is met.

TI: The free energy derivative is always evaluated for one λ-value,
and the problem present in FEP does not occur here.
However, numerical inaccuracy may arise due to
the numerical integration of the free energy derivative.

TI – limits

major limitation of TI using equilibrium simulations for discrete λs
– very slow convergence of $\partial G/\partial\lambda$
when the alchemical change becomes large.

It is perfectly possible to mutate of a single amino acid side chain in a protein (when the structure of the protein remains the same), but larger reactions are getting impossible to simulate.

Non-equilibrium simulations

recent development – use of non-equilibrium simulations

The usual “equilibration” of the system
for every of the selected values of λ is not performed

Instead, a non-equilibrium simulation consists of n MD steps,
where λ starts at 0 and increases by $1/n$ in every MD step.

This way, the simulation never describes the system in equilibrium,
as the external parameter λ is changing all the time.

Principle

A single simulation of this kind would be of no value...

... but when we perform an ensemble of such simulations, we can use Jarzynski's equality to obtain the free energy:

$$\exp[-\beta \Delta F] = \langle \exp[-\beta W] \rangle$$

W – values of irreversible work obtained from the individual non-equilibrium simulations:

$$W = \int_0^1 \left(\frac{\partial E}{\partial \lambda} \right) \mathrm{d}\lambda$$

(difference from TI: no equilibrated values of $\partial E / \partial \lambda$)

The individual non-equilibrium simulations can be very short

Practice and analysis

Where is the sampling problem? (it is always somewhere. . .)
– large statistical weight carried by rarely occuring simulations
(unfavorable averaging in Jarzynski's equality)

A more general expression than the Jarzynski equality
– Crooks fluctuation theorem (CFS):

the distributions of forward and reverse work are related like

$$\frac{P_f(W)}{P_r(-W)} = \exp[\beta(W - \Delta F)]$$

This can be applied in two slightly different ways:

CFS – first possibility

Once we have obtained well-converged distributions P_f and P_r from an equal number of forward and reverse simulations, we can apply Bennett's acceptance ratio:

$$\left\langle \frac{1}{1+\exp[\beta(W-\Delta F)]} \right\rangle_f = \left\langle \frac{1}{1+\exp[-\beta(W-\Delta F)]} \right\rangle_r$$

(implicit equation for ΔF)

CFS – second possibility

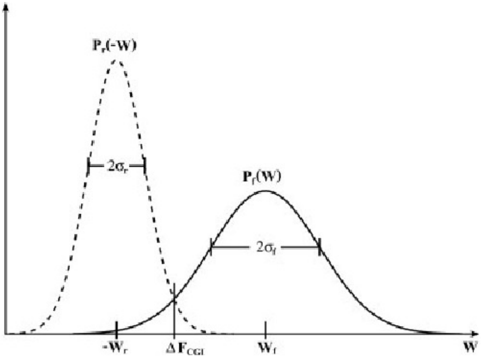
A more direct application of CFS:

The free energy corresponds to the value of work W
for which the probabilities P_f and P_r are equal
– the intersection point of the distributions.

We can search for the intersection point,
after fitting each of the distributions with a Gaussian function
– possibly large errors that may occur when the distributions
have little overlap (are 'far from each other')
are reduced

The assumption of normality of work distributions holds
for a system with a large number of degrees of freedom

CFS – second possibility



(from Goette and Grubmüller 2009)

Differences of differences

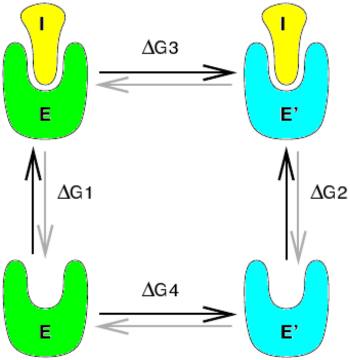
Often – we are interested not in the absolute free energies
and not even in the reaction free energies,
but rather in the difference (Δ) of reaction free energies (ΔF)
of two similar reactions:

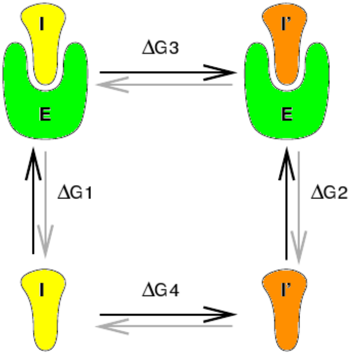
$$\Delta\Delta F \text{ or } \Delta\Delta G$$

Reaction free energy difference

Example left: binding of an inhibitor molecule I to an enzyme E, difference of binding free energies to similar enzymes E and E′:

$$\begin{array}{rcll} \mathrm{E} + \mathrm{I} & \rightleftharpoons & \mathrm{EI} & \quad \Delta G_1 \\ \mathrm{E}' + \mathrm{I} & \rightleftharpoons & \mathrm{E}'\mathrm{I} & \quad \Delta G_2 \end{array}$$





Reaction free energy difference

ligand binding itself – very difficult to simulate
reason – possible structural changes in the enzyme upon binding

Solution:

- do not simulate the reaction of binding
- rather, simulate alchemical transmutation of enzyme E to E′
- E and E′ are very similar, so this may be easy to do
- (example: mutation of a single AA, e.g. leucine to valine)
- The structure of complexes EI and E′I may be similar,
  → the simulation may provide converged free energy

Reaction free energy difference

Free energy is a state function → the sum of free energies
around a thermodynamic cycle vanishes:
(e.g. clockwise in figure left):

$$\Delta G_1 + \Delta G_3 - \Delta G_2 - \Delta G_4 = 0$$

The difference of binding free energies equals
the difference of free energies calculated in alchemical simulations:

$$\Delta\Delta G = \Delta G_1 - \Delta G_2 = \Delta G_3 - \Delta G_4$$

Reaction free energy difference

Similarly, it is possible to calculate the free energy difference of binding of two similar ligands to the same enzyme (fig. right),

or the difference of solvation energy of two similar molecules.

In the latter case, two alchemical simulations would be performed: one in vacuo and the other in solvent.

(Example – the neon case shown earlier in this lecture)

Geometric reaction coordinate

Sometimes, we need to know how the free energy changes
along a certain interval of a geometric reaction coordinate q

The free energy is then a function of q
while it is integrated over all other degrees of freedom

Such a function $F(q)$ is called the potential of mean force

Geometric reaction coordinate

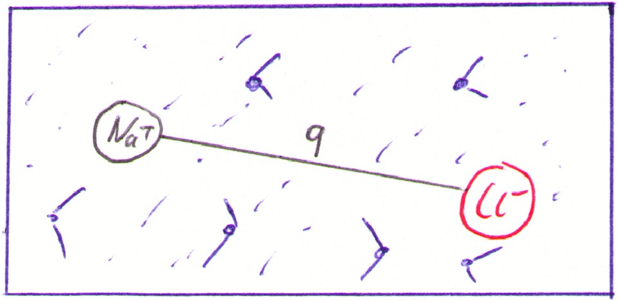
Examples:

- distance between two particles in a dissociating complex
- the position of a proton for a reaction of proton transfer
- the dihedral angle when dealing with conformational changes

Looking for the free energy at a certain value of q,
remaining degrees of freedom are averaged over (integrated out)
One could think of performing an MD simulation
and sampling all degrees of freedom except for q.

Example

free energy of formation of an ion pair Na^+–Cl^- in solution:



MD simulation would be performed to calculate the free energy for every value of the reaction coordinate q: $F = F(q)$

Foundations

$$F = -k_\mathrm{B} T \ln \iint \exp[-\beta E(\vec{r}, \vec{p})] \, \mathrm{d}\vec{r} \, \mathrm{d}\vec{p}$$

We need to evaluate F for q taking a certain value of q_0.
How do we consider ('pick') that particular value?

Dirac delta function $\delta(q - q_0)$:

- an infinitely sharp peak that bounds a unit area
- $\delta(x)$ is zero everywhere, except at $x = 0$
- at $x = 0$, it rises above bounds so that its integral is 1

$$F(q = q_0) = -k_\mathrm{B} T \ln \iint \delta(q - q_0) \exp[-\beta E(\vec{r}, \vec{p})] \, \mathrm{d}\vec{p} \, \mathrm{d}\vec{u} \, \mathrm{d}q$$

($\vec{u}$ are all coordinates except q)

Foundations

The free energy for the fixed reaction coordinate q_0 is

$$\begin{aligned}
F(q_0) &= -k_\mathrm{B}T\ln\iint\delta(q-q_0)\exp[-\beta E(\vec{r},\vec{p})]\,\mathrm{d}\vec{p}\,\mathrm{d}\vec{u}\,\mathrm{d}q \\
&= -k_\mathrm{B}T\ln\left[Q\cdot\iint\delta(q-q_0)\frac{\exp[-\beta E(\vec{r},\vec{p})]}{Q}\,\mathrm{d}\vec{p}\,\mathrm{d}\vec{u}\,\mathrm{d}q\right] \\
&= -k_\mathrm{B}T\ln\left[Q\cdot\iint\delta(q-q_0)\cdot\rho(\vec{r},\vec{p})\,\mathrm{d}\vec{p}\,\mathrm{d}\vec{u}\,\mathrm{d}q\right] \\
&= -k_\mathrm{B}T\ln\left[Q\cdot\langle\delta(q-q_0)\rangle\right] \\
&= -k_\mathrm{B}T\ln Q - k_\mathrm{B}T\ln\langle\delta(q-q_0)\rangle
\end{aligned}$$

Meaning: $\langle\delta(q-q_0)\rangle$ counts the occurrences $q=q_0$,
thus $\langle\delta(q-q_0)\rangle = \mathcal{P}(q_0)$,
which is the probability that q takes the value of q_0

$$F(q_0) = C - k_\mathrm{B}T\ln\mathcal{P}(q_0)$$

Foundations

in the example of the ion pair Na^+–Cl^-:

We perform an MD simulation for the system,
and then count how many times q takes the value q_0:
we obtain the probability $\mathcal{P}(q_0)$ of finding the system at q_0.

Then, the free energy difference of two states A and B is

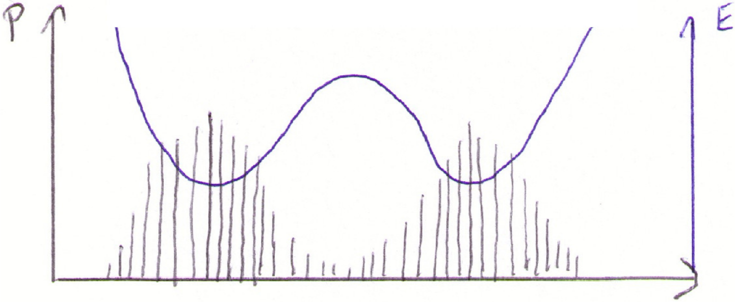
$$F_B - F_A = -k_\mathrm{B} T \ln \frac{\langle \delta(q - q_B) \rangle}{\langle \delta(q - q_A) \rangle} = -k_\mathrm{B} T \ln \frac{\mathcal{P}(q_B)}{\mathcal{P}(q_A)}$$

which actually leads to the equilibrium constant

$$K_{AB} = \frac{\mathcal{P}(B)}{\mathcal{P}(A)}$$

Foundations

Perform an MD simulation, specify a reaction coordinate, and build a histogram – i.e., count how many times each specified value of the reaction coordinate occurs
The ratio of these values gives the free energy difference!



Problem and solution

If a high barrier has to be crossed to come from A to B,
a usual, unbiased MD simulation will hardly make it
– the simulation is not ergodic
Even if it does, the high-energy region will be sampled poorly

A straightforward solution – umbrella sampling:
apply an additional, biasing potential energy function V
to restrain the system to region/s of phase space
that would otherwise remain undersampled.

The biasing potential shall depend only on the reaction coord.,
$V = V(q)$, and it becomes a component of the force field used

Note: a previously mentioned, similar solution – metadynamics

Working principle

What will be the free energy in such a biased case?

$$
\begin{aligned}
F(q_0) &= -k_\mathrm{B} T \ln \left(\frac{\iint \delta(q-q_0)\, \exp[-\beta E]\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}}{\iint \exp[-\beta E]\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}} \right) \\
&= -k_\mathrm{B} T \ln \left(\frac{\iint \delta(q-q_0)\, \exp[\beta V]\, \exp[-\beta(E+V)]\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}}{\iint \exp[-\beta(E+V)]\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}} \cdot \frac{\iint \exp[-\beta(E+V)]\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}}{\iint \exp[-\beta E]\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}} \right) \\
&= -k_\mathrm{B} T \ln \left(\langle \delta(q-q_0) \exp[\beta V] \rangle_{E+V} \cdot \frac{\iint \exp[-\beta(E+V)]\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}}{\iint \exp[\beta V]\, \exp[-\beta(E+V)]\, \mathrm{d}\vec{r}\, \mathrm{d}\vec{p}} \right) \\
&= -k_\mathrm{B} T \ln \left(\langle \delta(q-q_0) \exp[\beta V] \rangle_{E+V} \cdot \frac{1}{\langle \exp[\beta V] \rangle_{E+V}} \right) \\
&= -k_\mathrm{B} T \ln \left(\exp[\beta V(q_0)]\, \langle \delta(q-q_0) \rangle_{E+V} \cdot \frac{1}{\langle \exp[\beta V] \rangle_{E+V}} \right) \\
&= -k_\mathrm{B} T \ln \langle \delta(q-q_0) \rangle_{E+V} - V(q_0) + k_\mathrm{B} T \ln \langle \exp[\beta V \rangle_{E+V} \\
&= -k_\mathrm{B} T \ln \mathcal{P}^*(q_0) - V(q_0) + k_\mathrm{B} T \ln \langle \exp[\beta V] \rangle_{E+V}
\end{aligned}
$$

Working principle

. . . free energy follows as function of reaction coordinate, or PMF:

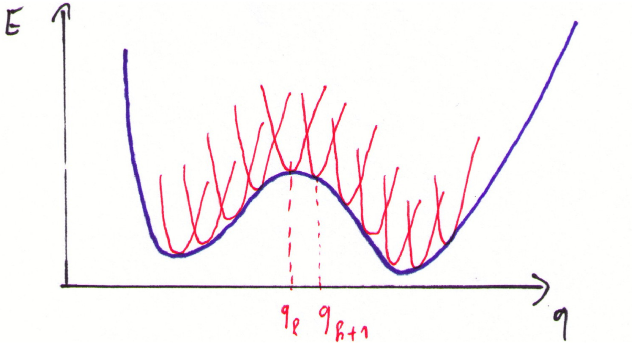
$$F(q) = -k_{\mathrm{B}} T \ln \mathcal{P}^*(q) - V(q) + K$$

Interesting:

- an arbitrary potential $V(q)$ was added
- we consider averages with the biased potential, $\langle\rangle_{E+V}$
- we obtain the biased probability $\mathcal{P}^*(q)$ of finding the system at the value of reaction coordinate for the ensemble $E + V$
- $\mathcal{P}^*(q)$ differs from the unbiased probability $\mathcal{P}(q)$, obviously
- still, the right, unbiased free energy $F(q)$ can be recovered:
  - take the biased $\mathcal{P}^*(q)$ and subtract the potential $V(q)$ (the constant K has to be determined yet)

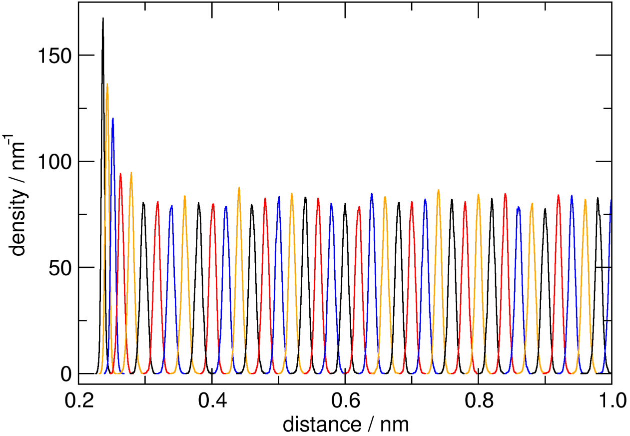
Practical PMF

We can use this scheme efficiently, by way of moving a biasing harmonic potential along the reaction coordinate:



Practical PMF

Example – ion pair Na^+–Cl^- in solution – biased histograms $\mathcal{P}_k^*$

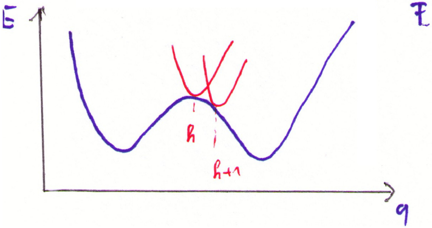


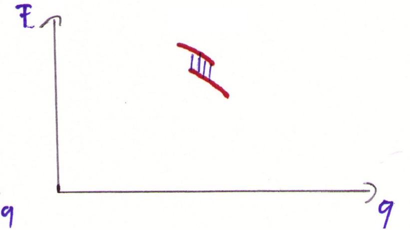
Practical PMF

We perform k simulations with biasing potentials V_k, and for each

- extract the probability $\mathcal{P}_k^*(q)$ – i.e., build histogram
- calculate $V^k(q)$
- then, free energy: $F_k(q) = -k_\mathrm{B} T \ln \mathcal{P}_k^*(q) - V_k(q) + K_k$

  where the constant shift K_k is undetermined



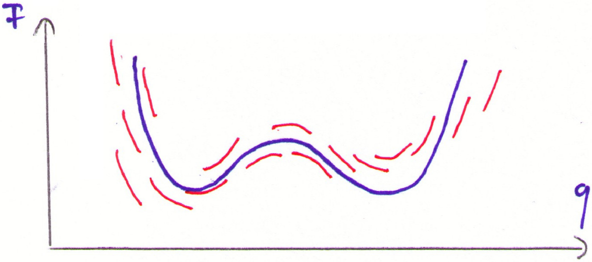


$F_k(q)$ and $F_{k+1}(q)$ are offset by a constant related to $K_{k+1} - K_k$

Practical PMF

Final task – find K_k, i.e. match the pieces of the curve together

Requirement – $F_k(q)$ and $F_{k+1}(q)$ must 'overlap' sufficiently
– can be judged by the overlap of biased histograms $\mathcal{P}_k^*(q)$



may be solved by means of Weighted Histogram Analysis Method

Practical PMF – WHAM

The unknowns

- unbiased probabilities $\mathcal{P}(q_j)$ of coordinate q falling into the j-th bin of the histogram – i.e., the unbiased free energy $F(q)$
- the previously undetermined shifts K_i

are found with self-consistent solution of a set of equations

$$\mathcal{P}(q_j) = \frac{\sum\limits_{\text{simulations } i} n_i(q_j) \, \exp[-\beta V_i(q_j)]}{\sum\limits_{\text{simulations } i} N_i \, \exp[-\beta(V_i(q_j) - K_i)]}$$

$$K_i = -k_\mathrm{B} T \, \log \sum_{\text{bins } j} \mathcal{P}(q_j) \, \exp[-\beta V_i(q_j)]$$

N_i – number of frames in the i-th simulation

$n_i(q_j)$ – number of hits in bin j of histogram from i-th simulation

Practical PMF – WHAM

Example – ion pair Na^+–Cl^- in solution – result