A diagram of a molecular structure, possibly a protein or a nanoscale device, is shown on the left side of the slide. It consists of a network of red and grey spheres connected by lines, forming a complex, interconnected shape.
$$U_s = \frac{1}{2}b\dot{x}^2$$
$$F_s = -\nabla U_s$$

? ? ? ? ?

You just can't do that!

- Friction is not a conservative force!
- U_s is not even a potential, it is a force multiplied by a velocity (power)

Specifically, U_s it's the (1D) Rayleigh dissipation function, which gives the actual friction force F_s via the *velocity* gradient as:

$$F_s = -\nabla_{\dot{x}} U_s$$

Then, you can write down Newton equations of motion as:

$$m\ddot{x} + b\dot{x} + kx = 0$$



In this way we have not specified a Lagrangian,
nor we have used the Eulero-Lagrange equations...

Can we write down a Lagrangian containing a friction term?

Yes - by basically cheating, and modifying the way in which we write the kinetic energy. For instance, the following Lagrangian:

$$\mathcal{L}(x, \dot{x}) = \frac{1}{2} e^{\mu t} (m \dot{x}^2 - k x^2), \quad \mu = \frac{b}{m}$$

Gives exactly the same equations of motions as above

However...

The “correct” way to proceed when you have some non conservative force in your system is:

- Write the Lagrangian as usual, omitting the terms originating from the non conservative force
- Solve the **modified** Eluero-Lagrange equation:

$$\frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{\mathbf{x}}} \right) - \frac{\partial \mathcal{L}}{\partial \mathbf{x}} = \Xi$$

Where Ξ includes every non conservative force you have in your system.

Again, you end up with the same equations of motions, this time avoiding to modify the Lagrangian

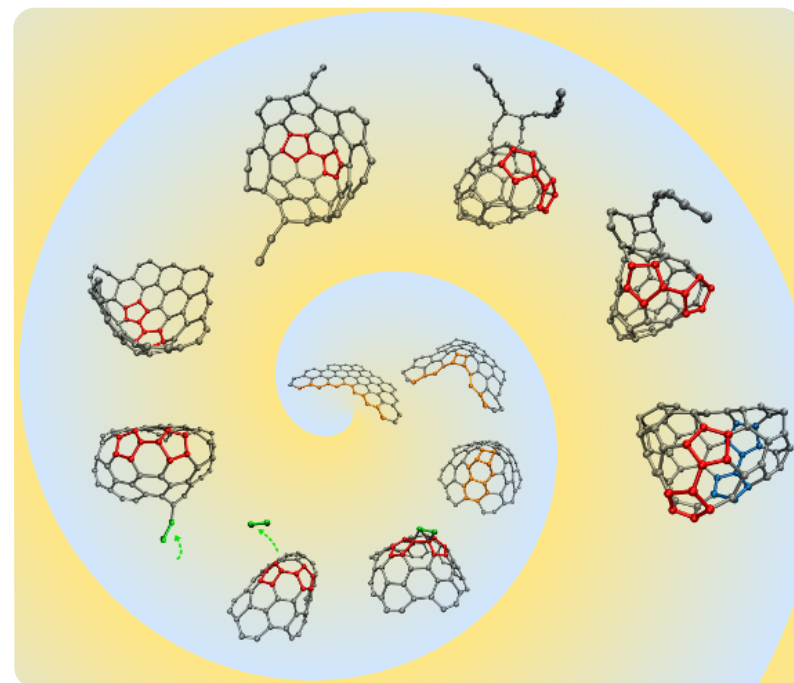
Electronic Structure Methods for Materials Modelling

A peek into the wondrous realm of the

Enhanced Sampling (Vol.1)

- Learning Outcomes
 - Coarse graining the phase space: *The concept of Collective Variable*
 - The basics of *free energy-based enhanced sampling methods*

- Why do we need enhanced sampling methods?
 - Rare events
 - Free energy vs path sampling methods
- Thermodynamic integration
- Order parameters (collective variables)
- Blue Moon ensemble
- Umbrella Sampling
- Path sampling methods



Next: Enhanced sampling (Vol.2)

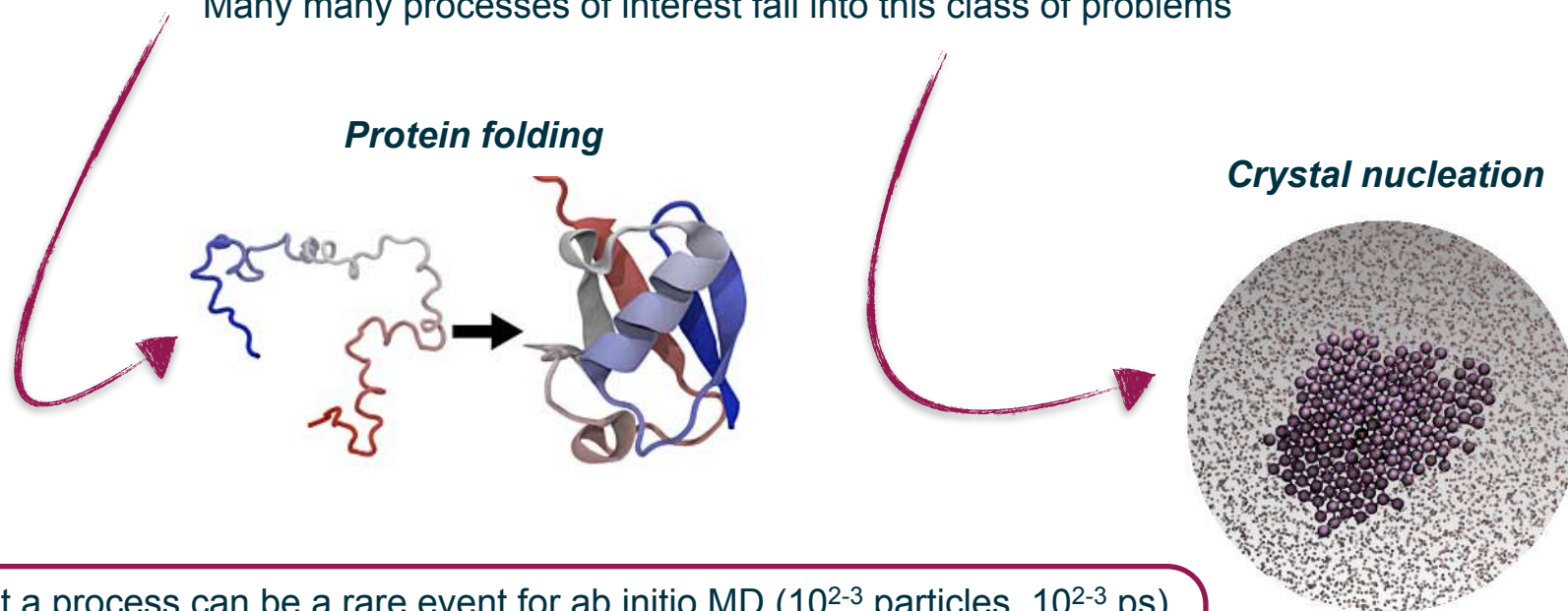
Rare events

And why they matter

What is a rare event?

In molecular dynamics, a rare event is something that happens on a timescale much longer than the one you can afford

Many many processes of interest fall into this class of problems



Note that a process can be a rare event for ab initio MD (10^{2-3} particles, 10^{2-3} ps) but not for classical MD (10^{5-6} particles, 10^{5-6} ps).

For example, the structural relaxation of a supercooled liquid

What do you do when you want to simulate something that would never (well, maybe several decades...) happen in your MD simulation?

Enhanced Sampling

Free energy based vs path sampling methods

Enhanced sampling methods:

The goal:

Simulate the rare event of interest disrupting as little as possible the actual dynamics of the system

A typical scenario:

Natural fluctuations of the system

Free energy barrier

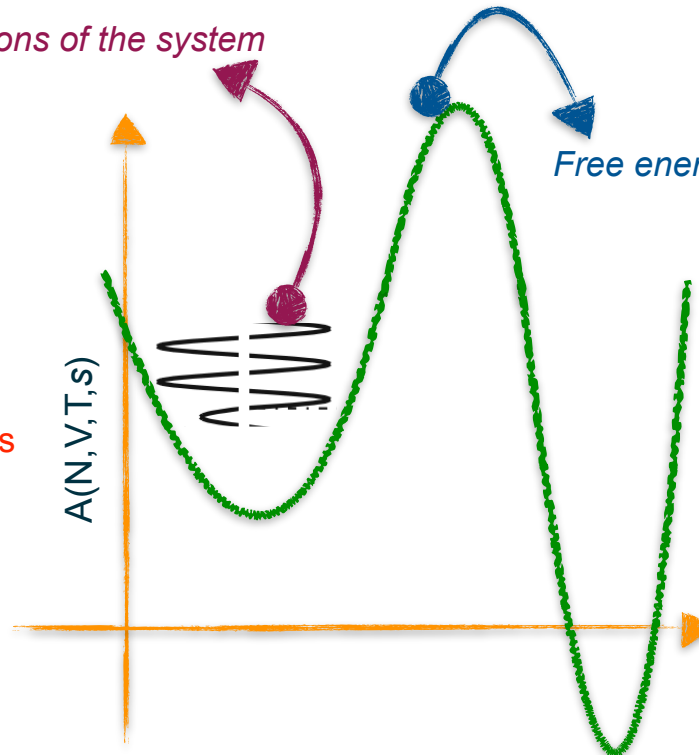
Free energy methods

They try to reconstruct the free energy surface

Tell a lot about thermodynamics (kinetics it's tricky)

Doable ab initio

(with some effort)



Path sampling methods

They meddle with the way in which the system evolves in time

Tell a lot about kinetics (and thermodynamics as well)

Still far beyond the reach of ab initio MD

*s - same order parameter
(more on that later...)*

The basic goal

Obtaining Free Energies

In principle, we know that (in e.g. NVT)...

$$P = \langle p(x) \rangle = \frac{1}{Q(N, V, T)} \cdot \int p(x) \cdot e^{-\beta H(x)} dx$$

For the (Helmoltz) free energy $A=E-TS$, though...

$$A = \langle E - TS \rangle = \frac{1}{Q(N, V, T)} \cdot \int (E - T\textcolor{red}{S}) \cdot e^{-\beta H(x)} dx$$

The problem with evaluating entropy...

- Does not depend on x (position, momenta) only!
- Cannot be evaluated by an ensemble average
- It is related to the on the available volume of accessible phase space (i.e. the partition function!)

$$S = k_B \ln[\Omega(N, V, E)]$$

In fact...

$$A(N, V, T) = -k_B T \ln[Q(N, V, T)]$$

Thermodynamic integration

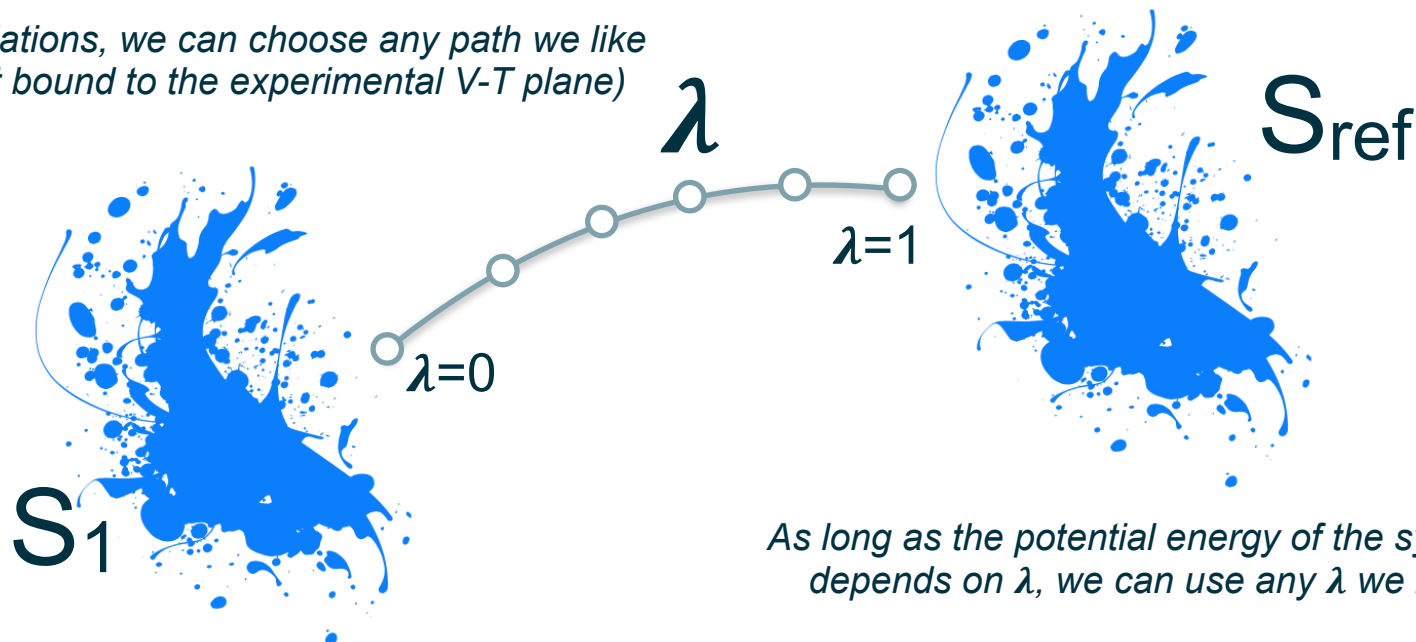
The idea

As it happens, experiments can't get free energies directly as well.
They measure **derivatives of free energies**, such as:

$$\left(\frac{\partial A}{\partial V}\right)_{NT} = -P \quad \text{or} \quad \left(\frac{\partial A/T}{\partial 1/T}\right)_{VN} = E$$

Thus, we should do the same! Let us find a path in the V-T plane connecting the system in which we are interested in (S_1) with another system of which we know the free energy already (S_{ref})

*We do simulations, we can choose any path we like
(we are not bound to the experimental V-T plane)*



As long as the potential energy of the system depends on λ , we can use any λ we like

Thermodynamic integration

The math

Then, we just integrate along the path, obtaining the free energy

$$\Delta A(N, V, T) = \int_{\lambda=0}^{\lambda=1} \left(\frac{\partial A(N, V, T, \lambda)}{\partial \lambda} \right)_{N, V, T} d\lambda$$

$$A(N, V, T, \lambda) = -k_B T \ln[Q(N, V, T, \lambda)]$$



$$\left(\frac{\partial A(N, V, T, \lambda)}{\partial \lambda} \right)_{N, V, T} = ??$$

$$\Delta A(N, V, T) = \int_{\lambda=0}^{\lambda=1} \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$

Now these are ensemble averages!

You can get them from a series of MD runs for different values of λ
- if you have a reference state, as you need the derivative!

Keep in mind:

The path must be reversible! If we encounter a phase transition in between, we are doomed!

There are very few systems we can use as S_{ref}

- **Liquids** → LJ liquid
- **Solids** → Einstein crystal (non interacting particles harmonically coupled with their lattice sites)

Thermodynamics integration is relatively inexpensive for classical MD

Only recently feasible via AIMD

Recent Developments in *ab initio* Thermodynamics

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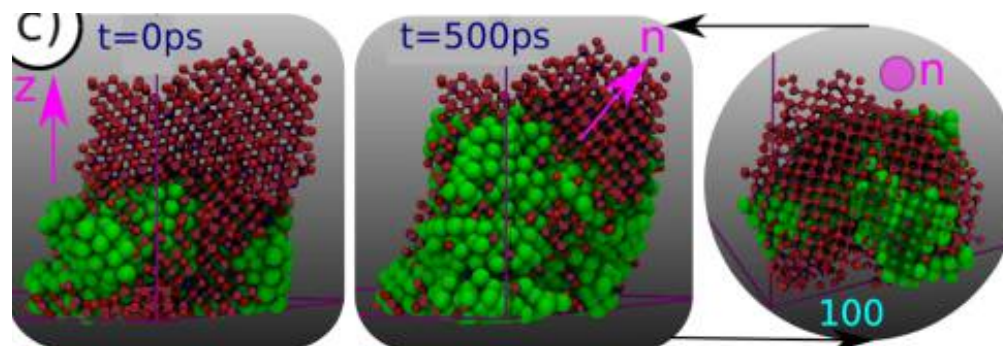
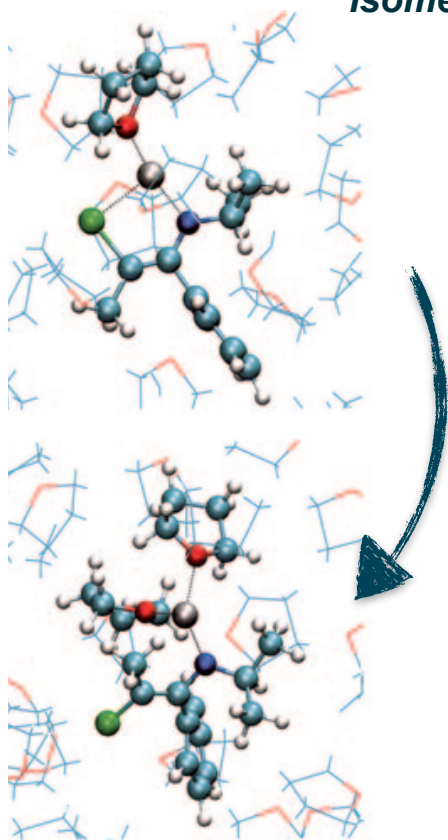
From λ to a generic CV

Order parameters

Rare events are literally everywhere: chemical reaction, phase transitions...
Every time you have a free energy barrier larger than $k_B T$ you are in trouble

We need some λ , some order parameters, or collective variables (CV) or (careful here) reaction coordinates to describe the particular phenomenon we are interested in

Isomerization: angles



Crystal nucleation:
Steinhardt parameters

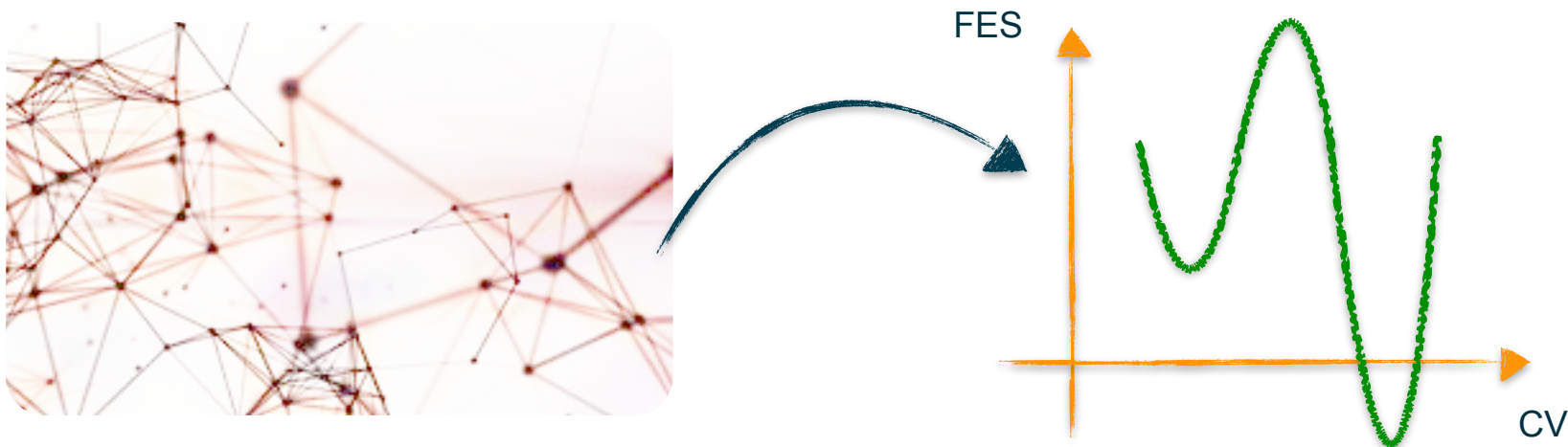
Word of caution:
Even a set of CVs is a serious simplification of the rare event

From λ to a generic CV

The Free Energy Surface

Dimensionality reduction:

The true free energy surface (FES) of the process is a multidimensional hyper surface



- We remap the problem on to a - manageable - number of CVs, so that:
- It's easier to understand what's going on
 - We can do enhanced sampling

Remember:

One is allowed to identify a CV as the actual reaction coordinate only very simple cases

From λ to a generic CV

A matter of partition functions

How do we get the free energy surface (say, in the canonical ensemble) with respect to a CV?

Let's assume we are interested in a single CV:

$$CV = f(\{\mathbf{r}\})$$

Recall that thanks to the partition function we can get any property we like as:

$$\mathcal{P} = \langle p(x) \rangle = \frac{1}{\mathcal{Z}} \int p(x) \mathcal{F}(\mathcal{H}(x)) dx \quad \text{where} \quad \mathcal{Z} = \int \mathcal{F}(\mathcal{H}(x)) dx$$

Thus, the probability for the CV to be equal to a value s is (within the canonical ensemble!):

$$\begin{aligned} P(s) &= \frac{1}{Q(N, V, T)} \int \delta(f(\{\mathbf{r}\}) - s) \cdot e^{-\beta \mathcal{H}(\{\mathbf{r}, \mathbf{p}\})} d\mathbf{r} d\mathbf{p} \\ &= \frac{1}{Q(N, V, T)} \frac{1}{\lambda^{3N}} \int \delta(f(\{\mathbf{r}\}) - s) \cdot e^{-\beta \mathcal{H}(\{\mathbf{r}\})} d\mathbf{r} \end{aligned}$$

Thermal
average

This is a *configurational* canonical partition function

$$\mathcal{Z}(N, V, T, s) = \int \delta(f(\{\mathbf{r}\}) - s) \cdot e^{-\beta \mathcal{H}(\{\mathbf{r}\})} d\mathbf{r}$$

From λ to a generic CV

A matter of partition functions

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From λ to a generic CV

The magic formula

As such:

$$A(N, V, T, s) = -k_B T \log(\mathcal{Z}(N, V, T, s))$$

The Helmholtz free energy of the system associated with the collective variable s is related á la Boltzmann to the configurational partition function with respect to s

However, remember, remember: as a rule,

$$A(N, V, T, s) \neq A(N, V, T)$$



Free energies from histograms

Sometimes you don't need enhanced sampling

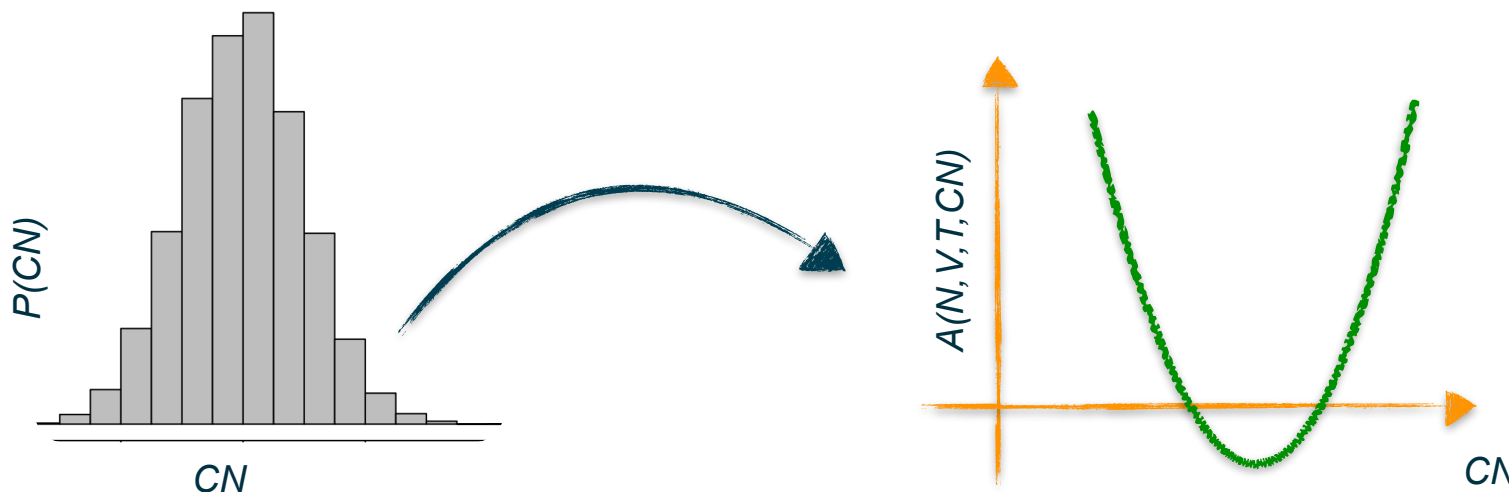
In many cases, you can use the natural fluctuations of your system to build a free energy surface for a specific quantity

Say, you run a simulation of a liquid in which the atoms are - on average - four coordinated. What is the free energy associated with the coordination number (CN)?

$$A(N, V, T, CN) = -k_B T \ln \mathcal{Z}(N, V, T, CN)$$

Provided your simulation is long enough...

The configurational partition function \mathcal{Z} can be obtained from the normalised histogram of CN
Just one MD run, and you can already say something about it!



The idea

As all the enhanced sampling methods, the Blue Moon Ensemble (BME) deals with rare events (which happens *once in a Blue Moon*)

- Not particularly popular as we speak
- It is used in ab initio simulations
- Possibly the most evocative name of them all

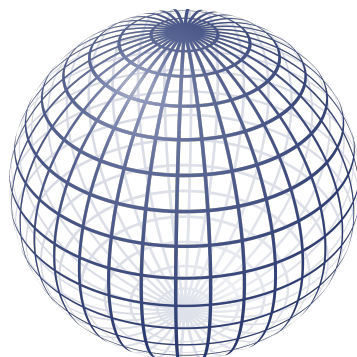


A “blue moon” refers to the occurrence of thirteen full moons in a calendar year as opposed to the usual twelve. The extra full moon, which occurs roughly every 2.72 years, is called a blue moon.

BME provides an elegant example of constrained molecular dynamics

Constraints → Remove some degree of freedom

Holonomic constraints → Depend exclusively on positions (at given times), but e.g. not on momenta



For instance. A particle that instead of moving randomly can only sample the surface of a sphere is subject to the holonomic constraint:

$$x^2 + y^2 + z^2 - R^2 = 0$$

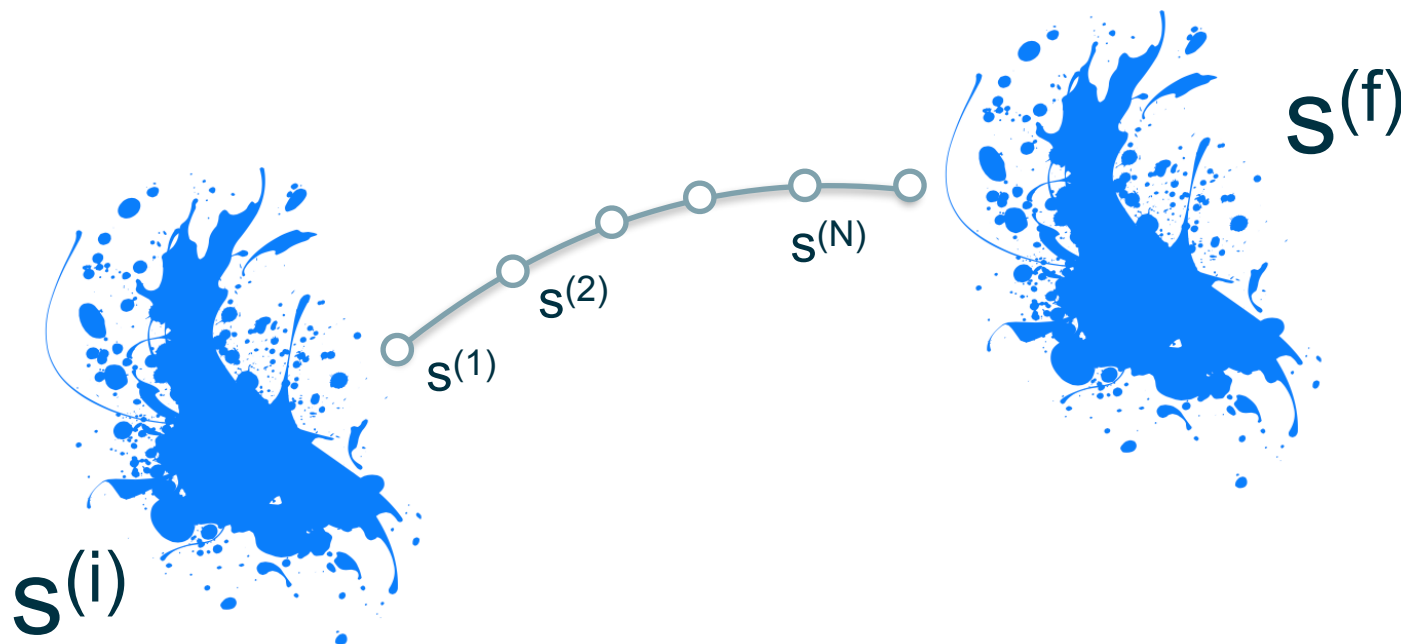
If the particle is subject to gravity as well → non holonomic

The idea

Consider an holonomic constraint σ acting on a given CV:

$$\sigma(CV) = \sigma(f(\{\mathbf{r}\}))$$

Much like in a thermodynamic integration fashion, the BME consists in a series of constrained MD runs for different values s of the CV



Hence, we reason again terms of free energy *differences*,
as the BME yields the derivative of $A(N, V, T, s)$ with respect to s

$$\begin{aligned}\frac{\partial A(N, V, T, s)}{\partial s} &= -k_B T \frac{\partial}{\partial s} \log(\mathcal{Z}(N, V, T, s)) \\ &= -k_B T \frac{1}{\mathcal{Z}(N, V, T, s)} \int \frac{\partial}{\partial s} \delta(f(\{\mathbf{r}\}) - s) \cdot e^{-\beta \mathcal{H}(\{\mathbf{r}\})} d\mathbf{r}\end{aligned}$$



It can be shown (not really an intuitive demonstration, see e.g. Tuckerman...)

$$\Delta A(N, V, T, s) = \int_{s^{(i)}}^{s^{(f)}} \frac{\partial A(N, V, T, s)}{\partial s} ds$$

Which is basically equivalent to what we have obtained for thermodynamic integration

(The actual implementation of the BME is not *that* easy...)


Constraints vs restraints

- **Constraint:** prepare the system/CV in a certain state/value and force it to stay there e.g. fixing bond lengths or angles... SHAKE, LINKS...
- **Restraint:** push the system/CV toward a particular state/value by means of some bias e.g. harmonic potential restraining atomic positions or energy bias acting on a CV

Blue Moon ensemble → **constraints** the CV
Umbrella Sampling → **restraints** the CV

Usually, an harmonic restraint (an harmonic potential W) pushing the system toward a specific value s^* of the CV is added to the actual potential energy of the system

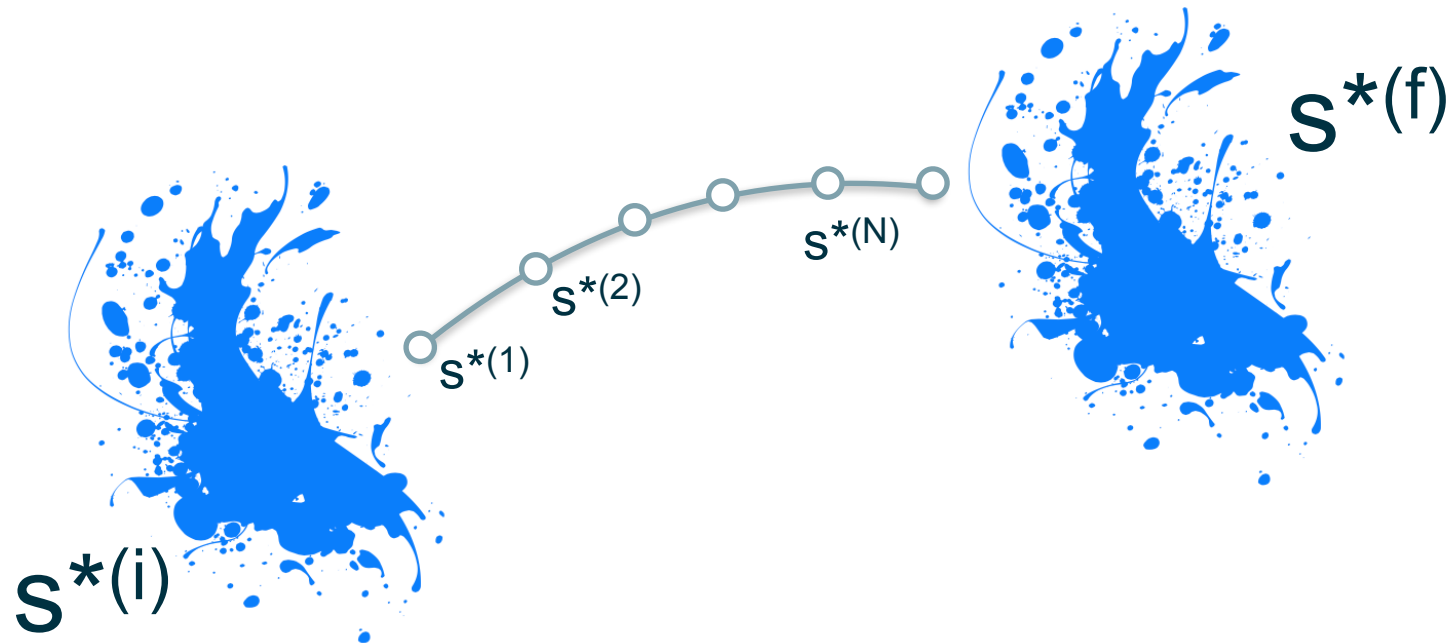
$$U_{tot}(\mathbf{r}) = U_{unbiased}(\mathbf{r}) + W(s(\mathbf{r}), s^*(\mathbf{r}))$$

$$W(s(\mathbf{r}), s^*(\mathbf{r})) = \frac{1}{2} \kappa (s(\mathbf{r}) - s^*(\mathbf{r}))^2$$


Umbrella Sampling

Building a collection of probabilities

Again, you run several MD runs, each one for a given value of s^*



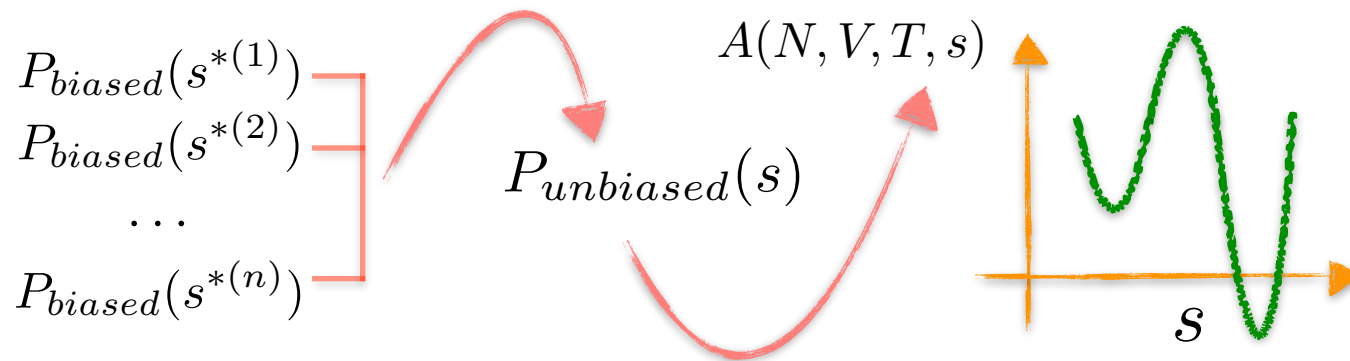
Now, from each MD run you get a **biased** probability distribution for the CV $s^{*(i)}$

$$s^{*(i)} \rightarrow P_{biased}(s^{*(i)})$$

Umbrella Sampling

Reweight

However, we need the *total* unbiased probability distribution to get the free energy profile $A(s)$.



The most common way of doing that → the Weighted Histogram Analysis Method, aka



We get the unbiased $P(s)$ from the biased $P(s)$ as:

$$P_{unbiased}(s^{*(i)}) = P_{biased}(s^{*(i)}) \cdot e^{-\beta \left[\underbrace{A(N,V,T,W(s,s^{*(i)}))}_{\substack{\text{Free energy associated to} \\ \text{the bias potential} \\ \text{We don't know it - yet...}}} - \underbrace{W(s,s^{*(i)})}_{\text{Bias potential}} \right]}$$

The WHAM write the total unbiased probability as a linear combination (weighted sum) of the unbiased probabilities

$$P_{unbiased}(s) \propto \sum_{i=1}^{N_{MDruns}} m_i(s^{*(i)}) \cdot P_{unbiased}(s^{*(i)})$$

Where the weights have to:

- Be normalised
- Minimise the statistical error with respect to the total unbiased probability

$$\sum_{i=1}^{N_{MDruns}} m_i(s^{*(i)}) = 1$$

$$\frac{\partial(\sigma^2[P_{unbiased}(s)])}{\partial m_i(s^{*(i)})} = 0$$

In order to obtain the weights $m_i(s^{*(i)})$ we have to minimise a function $\sigma^2[P_{unbiased}(s)]$ taking into account the following constraint:

$$\sum_{i=1}^{N_{MD \text{ runs}}} m_i(s^{*(i)}) = 1$$

This problem can be solved using Lagrange multipliers to give

$$P_{unbiased}(s) \propto \sum_{i=1}^{N_{MD \text{ runs}}} \frac{\sum_{j=1}^{N_{MD \text{ runs}}} \sigma^2[P_{unbiased}(s^{*(j)})]}{\sigma^2[P_{unbiased}(s^{*(i)})]} P_{unbiased}(s^{*(i)})$$

Some other manipulations can be done. In particular:

$$\sigma^2[P_{unbiased}(s^{*(i)})] \propto \sigma^2[P_{biased}(s^{*(i)})] \cdot e^{2\beta[A(N,V,T,W(s,s^{*(i)})) - W(s,s^{*(i)})]}$$

We don't know $A(N,V,T,W)$!



As such, the WHAM actually involves a set of equations to be solved in a self consistent fashion

- Rare events are ubiquitous and important
- Because of the timescales involved we have to use enhanced sampling methods (*in ab initio MD, free energy based methods*)
- We cannot compute the free energy directly but we can get free energy differences via the derivative of the free energy (**Thermodynamic Integration**)
- It is useful to describe the free energy in terms of few order parameters to get a low dimensional free energy surface
- Many methods exist to explore that low dimensional surface
 - ★ **Blue Moon Ensemble**: constraints the order parameter
 - ★ **Umbrella Sampling**: restraints the order parameter
- Learning Outcomes
 - Coarse graining the phase space: ***The concept of Collective Variable***
 - The basics of ***free energy-based enhanced sampling methods***

Next: metadynamics - a very efficient way to reconstruct free energy surfaces