Session 3. Enhanced sampling techniques and free energy methods 1: Umbrella Sampling & Metadynamics simulations

TCCM 2021-2022 Cecam School: Computational Biochemistry.
Efficient Tools to fight Diseases

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Outline

- Motivation
  - Sampling limitations & timescale problem
- Classification of enhanced sampling / free energy methods
  - Methods based on CVs
  - Methods independent of CVs
  - Alchemical Methods
- Umbrella Sampling
- Metadynamics
- Advantages & Disadvantages of Umbrella Sampling & Metadynamics
- Examples of application to real problems

Reminder of some magnitudes

- Partition function

$$Z = \int \exp[-\beta E(\mathbf{r})] d\mathbf{r}$$

- Beta (inverse of temperature in energy units, proportional to thermal energy)

$$\beta = (k_B T)^{-1}$$

- Free Energy

$$F = -\frac{1}{\beta} \ln Z$$

- Ensemble average of an observable A

$$\langle A \rangle = \frac{\int A \exp[-\beta E(\mathbf{r},\mathbf{p})] d\boldsymbol{\tau}}{\int \exp[-\beta E(\mathbf{r},\mathbf{p})] d\boldsymbol{\tau}}$$

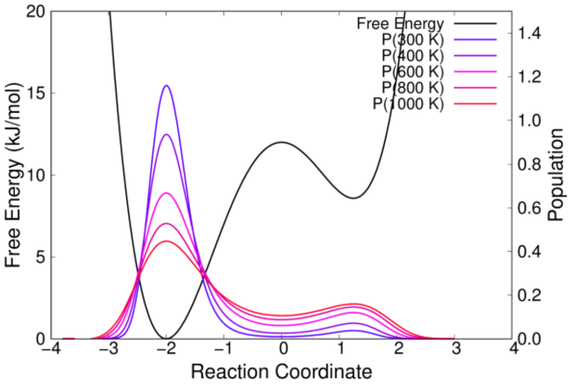
Motivation: Time scale Problem

At $T > 0$ the dynamics is governed by the free energy surface F

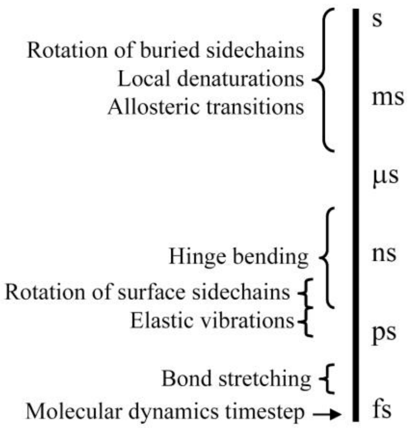
The population of a given state $P(\mathbf{s})$ decreases exponentially with $F(\mathbf{s})$

$$P(\mathbf{s}) = \exp(-\beta F(\mathbf{s}))$$

In a computer simulation (MD or MC), states with $F(\mathbf{s}) >> k_B T$ are not (or very rarely) sampled



Motivation: Time scale Problem



- •Protein Folding - milliseconds/seconds (10^{-3}-1s)
- •Ligand Binding - micro/milliseconds (10^{-6}-10^{-3} s)
- •Enzyme catalysis-micro/milliseconds (10^{-6}-10^{-3} s)
- •Conformational transitions - pico/nanoseconds (10^{-12}-10^{-9} s)
- •Collective vibrations -1 picosecond (10^{-12} s)
- •Bond vibrations - 1 femtosecond (10^{-15} s)

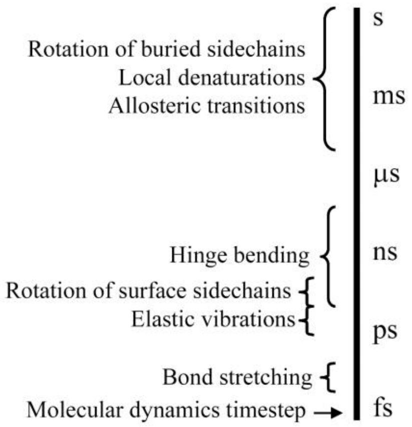
Motivation: Time scale Problem

*e.g. if an event takes place in a timescale of 1 ms and we run 1 µs of simulation, there is ~1/1000 probability of observing the event

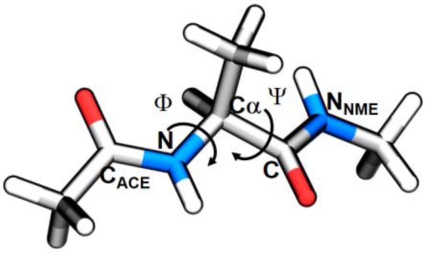
Solution 1: better hardware

Solution 2: methods based on statistical mechanics to enhance the sampling of high energy regions

Solution 3: Optimize the sampling of standard MD (e.g. with Markov State Models)



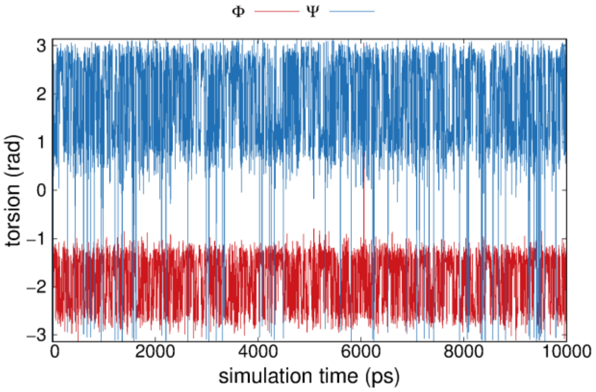
Motivation: Time scale Problem



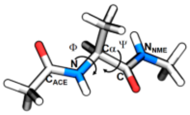
Alanine dipeptide

10 ns in vacuum 300 K

Evolution of ϕ and Ψ in a standard MD simulation

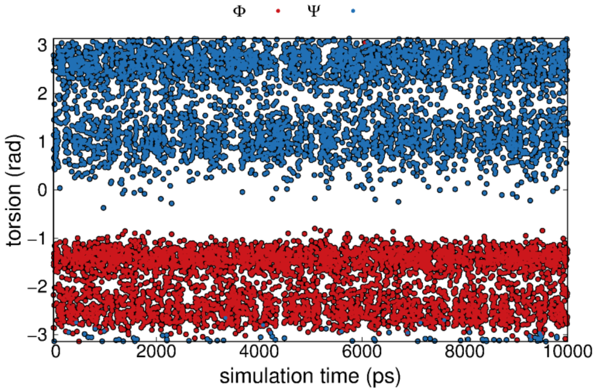


Motivation: Time scale Problem



Alanine dipeptide

10 ns in vacuum 300 K



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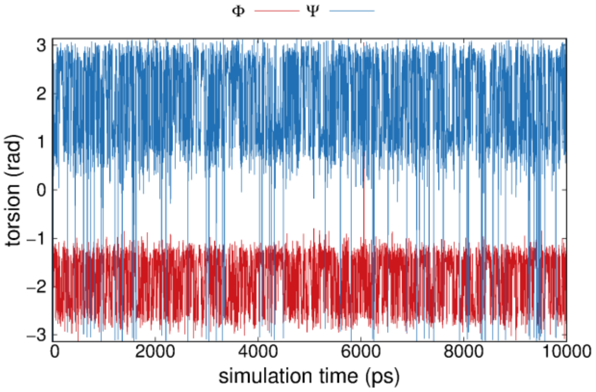
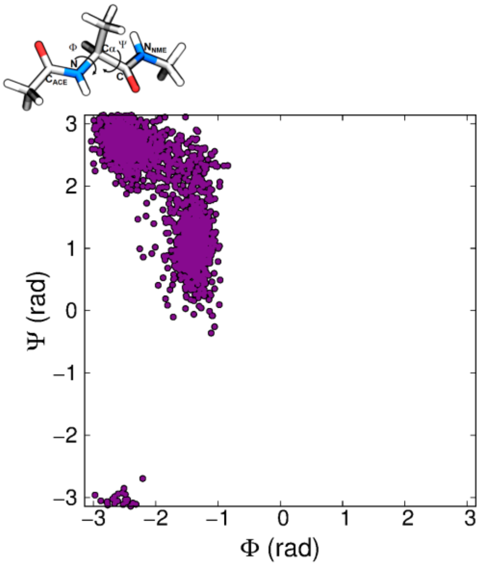
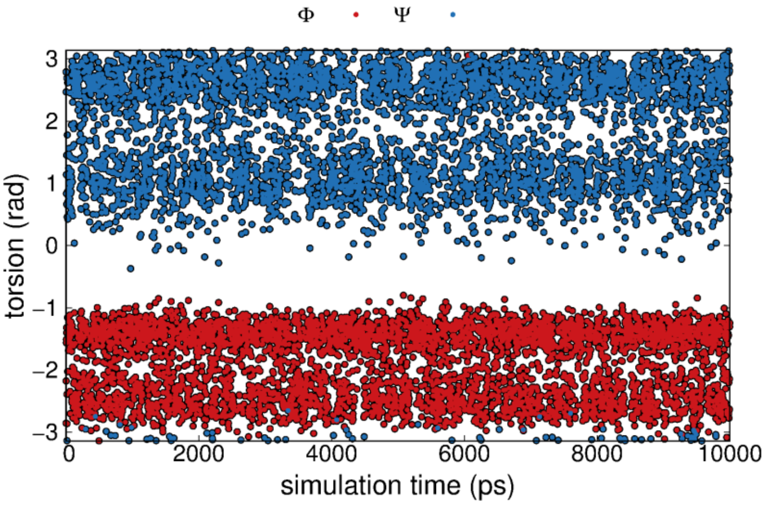
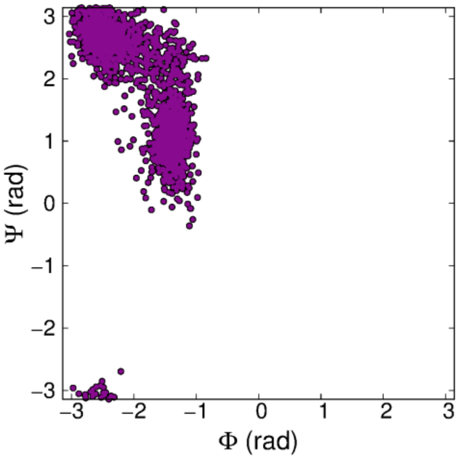


Motivation: Time scale Problem

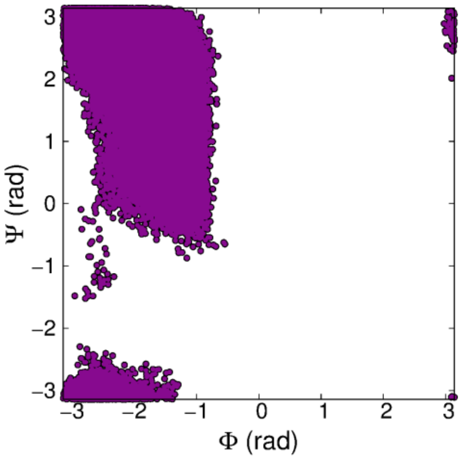




Motivation: Time scale Problem



(1/40 data)



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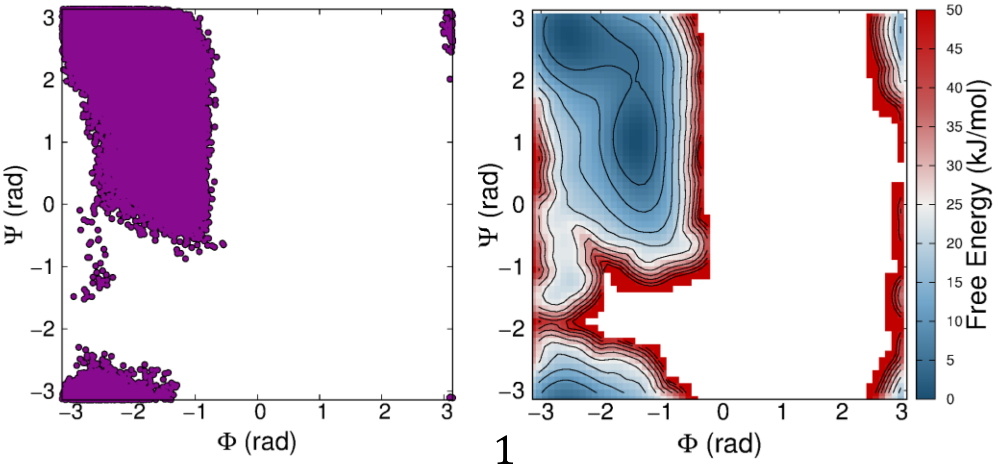
Motivation: Time scale Problem



$$F(\mathbf{s}) = -\frac{1}{\beta}\ln P(\mathbf{s})$$

A classification of Enhanced Sampling Methods

- Methods based on Collective Variables
  - Umbrella Sampling
  - Metadynamics
  - Steered Molecular Dynamics
  - Conformational flooding
  - Local elevation
  - …
- Methods independent of Collective Variables
  - Replica Exchange
  - Accelerated MD
  - …
- Alchemical methods
  - Alchemical Free energy perturbation

Methods based on Collective Variables

- **State**: Region of the phase space in which the system resides a significant amount of time.
- **Reaction Coordinate**: ensemble of multidimensional paths connecting two or more states, which has the highest transition probability.
- **Collective Variable**: coarse-grained representation of the Reaction Coordinate expressed in terms of one or few “simple” order parameters.

Main idea of collective variable-based enhanced sampling methods: Add external energy (bias) to a collective variable to accelerate transitions between states.

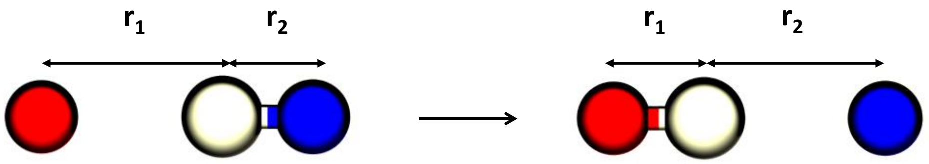
More on Collective Variables

- The CV(s) is a function (or few functions) that should discriminate between states and describe the path between them.
- The CVs should be continuous and derivable to calculate the forces associated to them acting on the system during the MD.
- The CV or set of CVs should include **all** the slow degrees of freedom relevant to the event or transition.
- Simple CVs: distances, angles, torsions…
- More complex CVs: RMSD, pathCVs
- Not geometrical CVs: potential energy as CV

More on Collective Variables

The CV or set of CVs should include all the slow degrees of freedom relevant to the event or transition.

Reaction A + B-C → A-B + C with E_a=7.0 kcal/mol.

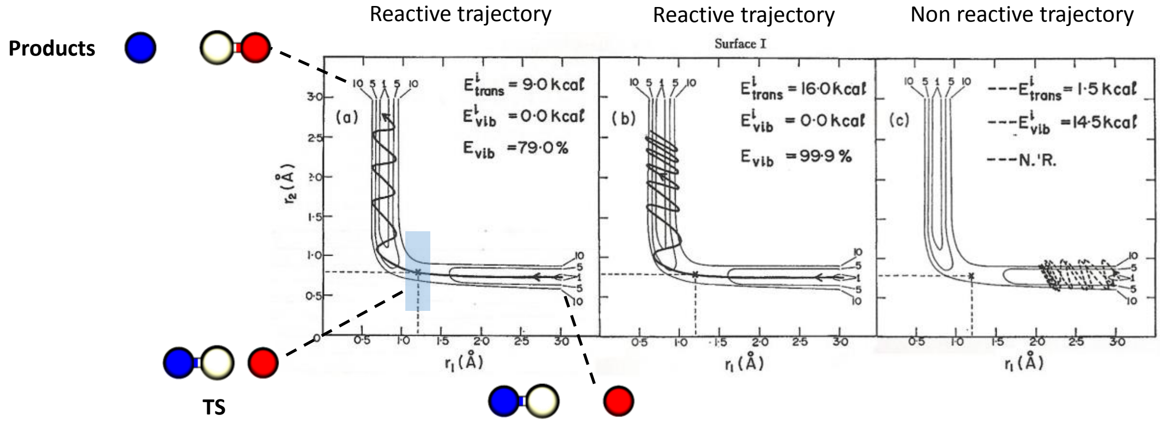


Collective variables: r_1 (distance AB), r_2 (distance BC)

Start collision trajectories with different initial translational ($\mathbf{r_1}$) and vibrational ($\mathbf{r_2}$) energies. Apart from the bias, the efficiency of the collision strongly depends on the position of the energy barrier.

More on Collective Variables

Case A) The energy barrier is orthogonal to r_1. Reactive trajectories show enough energy on r_1 to cross the barrier (AB relative translational kinetic energy)



TS
A···B is forming (energetically costly event)
B-C is unaltered

Reactants

J.C. Polanyi, W.H. Wong, J. Chem. Phys. (1969) 51, 1439-1450;
M.H. Mok, J.C. Polanyi, J. Chem. Phys. (1969) 51, 1451-1469;
J.C. Polanyi, Acc. Chem. Res. (1972) 5, 161-168

More on Collective Variables

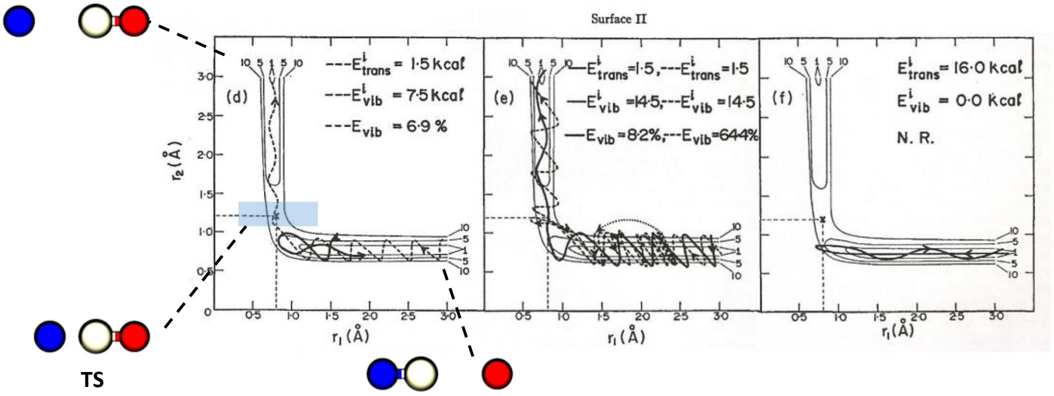
Case B) The energy barrier is orthogonal to r_2. Reactive trajectories show enough energy on r_2 to cross the barrier (BC vibrational energy)

Reactive trajectory

Reactive trajectory

Non reactive trajectory

Products



TS
A-B is already formed
B···C is breaking (energetically costly event)

Reactants

J.C. Polanyi, W.H. Wong, J. Chem. Phys. (1969) 51, 1439-1450;
M.H. Mok, J.C. Polanyi, J. Chem. Phys. (1969) 51, 1451-1469;
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More on Collective Variables

To sample a rare event successfully all the slow degrees of freedom should be included in the CVs so that they are biased!

Umbrella Sampling

Probability distribution along the CV $\mathbf{s}(\mathbf{r})$

$$Z(\mathbf{s}) = \frac{\int \delta[\mathbf{s}(\mathbf{r}) - \mathbf{s}] \exp[-\beta E(\mathbf{r})] d\mathbf{r}}{\int \exp[-\beta E(\mathbf{r})] dr}$$

*The Dirac delta $\delta[\mathbf{s}(\mathbf{r})\text{-}\mathbf{s}]$ in the integral extracts the **s** degree of freedom (i.e. integrate out all the degrees of freedom apart from **s**)

Free Energy along the CV $\mathbf{s}(\mathbf{r})$

$$F(s) = -\frac{1}{\beta} \ln Z(s)$$

Umbrella Sampling

In the ergodic limit $P(\mathbf{s}) = Z(\mathbf{s})$

$$\langle P(\mathbf{s}) \rangle = \frac{1}{N} \sum P(\mathbf{s}) = \frac{1}{t} \sum P(\mathbf{s}(t)) \Delta t$$

$$Z(\mathbf{s}) = \lim_{t \to \infty} \frac{1}{t} \int_0^t P(\mathbf{s}(t)) dt$$

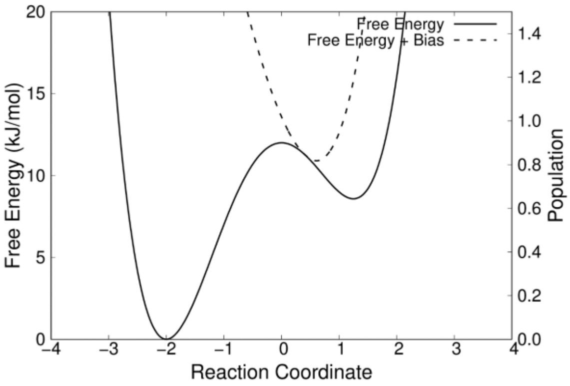
In practice $Z(\mathbf{s})$ cannot be sampled in a computer simulation due to the presence of high free energy barriers (i.e. the system will not be ergodic)

Umbrella Sampling

Addition of an external bias along the CV to increase the sampling in high energy regions

$$E^b(\mathbf{r}) = E^u(\mathbf{r}) + V_i(\mathbf{s}(\mathbf{r}))$$

b and u denote biased and unbiased quantities, respectively



Umbrella Sampling

Addition of an external bias to increase the sampling in high energy regions

$$E^b(\mathbf{r}) = E^u(\mathbf{r}) + V_i(\mathbf{s}(\mathbf{r}))$$

$$P^u(\mathbf{s}) = \frac{\int \delta[\mathbf{s}(\mathbf{r}) - \mathbf{s}] \exp[-\beta E(\mathbf{r})] d\mathbf{r}}{\int \exp[-\beta E(\mathbf{r})] d\mathbf{r}}$$

$$+V_i(\mathbf{s}(\mathbf{r})) \Big\downarrow$$

$$P^b(\mathbf{s}) = \frac{\int \delta[\mathbf{s}(\mathbf{r}) - \mathbf{s}] \exp[-\beta \{E(\mathbf{r}) + V_i(\mathbf{s}(\mathbf{r}))\}] d\mathbf{r}}{\int \exp[-\beta \{E(\mathbf{r}) + V_i(\mathbf{s}(\mathbf{r}))\}] d\mathbf{r}}$$

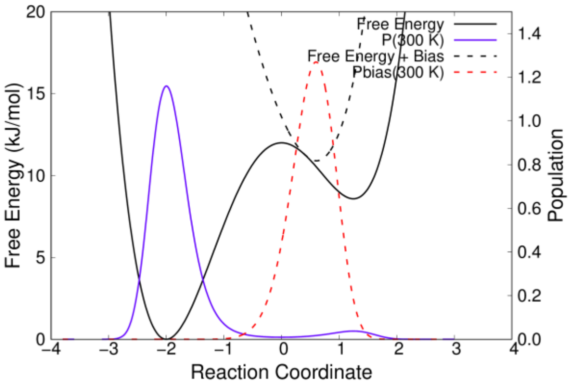
Umbrella Sampling

Addition of an external bias to increase the sampling in high energy regions

$$E^b(\mathbf{r}) = E^u(\mathbf{r}) + V_i(\mathbf{s}(\mathbf{r}))$$

$$P^b(\mathbf{s}) = \frac{\int \delta[\mathbf{s}(\mathbf{r}) - \mathbf{s}] \exp[-\beta\{E(\mathbf{r}) + V_i(\mathbf{s}(\mathbf{r}))\}] d\mathbf{r}}{\int \exp[-\beta\{E(\mathbf{r}) + V_i(\mathbf{s}(\mathbf{r}))\}] d\mathbf{r}}$$

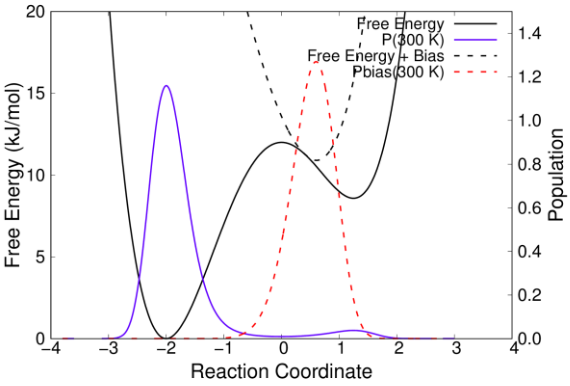
Any region of $\mathbf{s}(\mathbf{r})$ can be sampled thoroughly by choosing $V_i(\mathbf{s}(\mathbf{r}))$ properly



Umbrella Sampling

However, we are interested in studying the unbiased probability distributions $P^u(\mathbf{s})$ and not $P^b(\mathbf{s})$

How can $P^u(\mathbf{s})$ be calculated from biased simulations?



Umbrella Sampling

$$P^b(\mathbf{s}) = \frac{\int \delta[\mathbf{s}(\mathbf{r})-\mathbf{s}]\exp[-\beta\{E(\mathbf{r})+V_i(\mathbf{s}(\mathbf{r}))\}]d\mathbf{r}}{\int \exp[-\beta\{E(\mathbf{r})+V_i(\mathbf{s}(\mathbf{r}))\}]d\mathbf{r}}$$

$$= \exp[-\beta V_i(\mathbf{s}(\mathbf{r}))]\frac{\int \delta[\mathbf{s}(\mathbf{r})-\mathbf{s}]\exp[-\beta E(\mathbf{r})]d\mathbf{r}}{\int \exp[-\beta\{E(\mathbf{r})+V_i(\mathbf{s}(\mathbf{r}))\}]d\mathbf{r}}$$

V_i only depends on $\mathbf{s}(\mathbf{r})$

$$= \exp[-\beta V_i(\mathbf{s}(\mathbf{r}))]\frac{P^u(\mathbf{s})\int \exp[-\beta E(\mathbf{r})]d\mathbf{r}}{\int \exp[-\beta\{E(\mathbf{r})+V_i(\mathbf{s}(\mathbf{r}))\}]d\mathbf{r}}$$

$$P^u(\mathbf{s}) = \frac{\int \delta[\mathbf{s}(\mathbf{r})-\mathbf{s}]\exp[-\beta E(\mathbf{r})]d\mathbf{r}}{\int \exp[-\beta E(\mathbf{r})]d\mathbf{r}}$$

$$P^u(\mathbf{s}) = P^b(\mathbf{s})\exp[\beta V_i(\mathbf{s}(\mathbf{r}))]\frac{\int \exp[-\beta\{E(\mathbf{r})+V_i(\mathbf{s}(\mathbf{r}))\}]d\mathbf{r}}{\int \exp[-\beta E(\mathbf{r})]d\mathbf{r}}$$

Umbrella Sampling

$$P^u(\mathbf{s}) = P^b(\mathbf{s})\exp[\beta V_i(\mathbf{s}(\mathbf{r}))]\frac{\int \exp[-\beta\{E(\mathbf{r})+V_i(\mathbf{s}(\mathbf{r}))\}]d\mathbf{r}}{\int \exp[-\beta E(\mathbf{r})]d\mathbf{r}}$$

$$P^u(\mathbf{s}) = P^b(\mathbf{s})\exp[\beta V_i(\mathbf{s}(\mathbf{r}))]\left\langle \exp[-\beta V_i(\mathbf{s}(\mathbf{r}))]\right\rangle$$

Unbiased free energy

$$F_i^u(\mathbf{s}) = -\frac{1}{\beta}\ln P_i^b(\mathbf{s}) - V_i(\mathbf{s}) - \frac{1}{\beta}\ln\left\langle \exp[-\beta V_i(\mathbf{s}(\mathbf{r}))]\right\rangle$$

$$-\frac{1}{\beta}\ln\left\langle \exp[-\beta V_i(\mathbf{s}(\mathbf{r}))]\right\rangle = F_i = ct.$$

P^b is sampled in the simulation
V_i is known
What about F_i?

Umbrella Sampling

It is unnecessary to know F_i to calculate free energy differences of the same biased simulation

$$F_i^u(\mathbf{s}_2) - F_i^u(\mathbf{s}_1) = -\frac{1}{\beta}\ln\frac{P_i^b(\mathbf{s}_2)}{P_i^b(\mathbf{s}_1)} - \{V_i(\mathbf{s}_2) - V_i(\mathbf{s}_1)\} + F_i - F_i$$

If we were able to design a bias $V_i(\mathbf{s})$ that enables the sampling along the entire CV space, we would not need to determine F_i

e.g. for $V_i(\mathbf{s}) = -F_i^u(\mathbf{s})$; $P_i^b = ct.$

The problem is, we don't know $F_i^u(\mathbf{s})$. It is what we want to calculate!

Umbrella Sampling

Alternative: run multiple simulations (windows) with a simple bias (e.g. harmonic)

Then, combine the unbiased F_i^u of all the windows to obtain the F_i^u along the entire $\mathbf{s}(\mathbf{r})$.

$$F_i^u(\mathbf{s}) = -\frac{1}{\beta}\ln P_i^b(\mathbf{s}) - V_i(\mathbf{s}) + F_i$$

This implies calculating F_i for each window (i.e. to align all the F_i^u)

Weighted Histogram Analysis Method (WHAM)

$$P^u(\mathbf{s}) = \sum_i^{windows} p_i(\mathbf{s}) P_i^u(\mathbf{s})$$

$p_i(\mathbf{s})$ weight of the distribution P_i^u from window *i*

Weighted Histogram Analysis Method (WHAM)

$$\frac{\partial \sigma^2(P^u(\mathbf{s}))}{\partial p_i(\mathbf{s})} = 0$$

Find the weights that minimize the variance (i.e. error) of the global unbiased distribution built from the independent simulations

$$\sum_i^{windows} p_i(\mathbf{s}) = 1$$

Restricted optimization (Normalization condition)

$$p_i = \frac{N_i \exp[-\beta V_i(\mathbf{s}) + \beta F_i]}{\sum N_i \exp[-\beta V_i(\mathbf{s}) + \beta F_i]}$$

N_i number of data in window i

Weighted Histogram Analysis Method (WHAM)

$$P^u(\mathbf{s}) = \sum_i^{windows} p_i(\mathbf{s}) P_i^u(\mathbf{s}) \qquad p_i = \frac{N_i \exp[-\beta V_i(\mathbf{s}) + \beta F_i]}{\sum N_i \exp[-\beta V_i(\mathbf{s}) + \beta F_i]}$$

Remember:

$$P^u(\mathbf{s}) = P^b(\mathbf{s}) \exp[\beta V_i(\mathbf{s}(\mathbf{r}))] \langle \exp[-\beta V_i(\mathbf{s}(\mathbf{r}))] \rangle$$

$$P^u(\mathbf{s}) = P^b(\mathbf{s}) \exp[\beta V_i(\mathbf{s}(\mathbf{r}))] \exp[-\beta F_i]$$

P^u depends on F_i through p_i, but F_i depends on P^u -> iterative solution

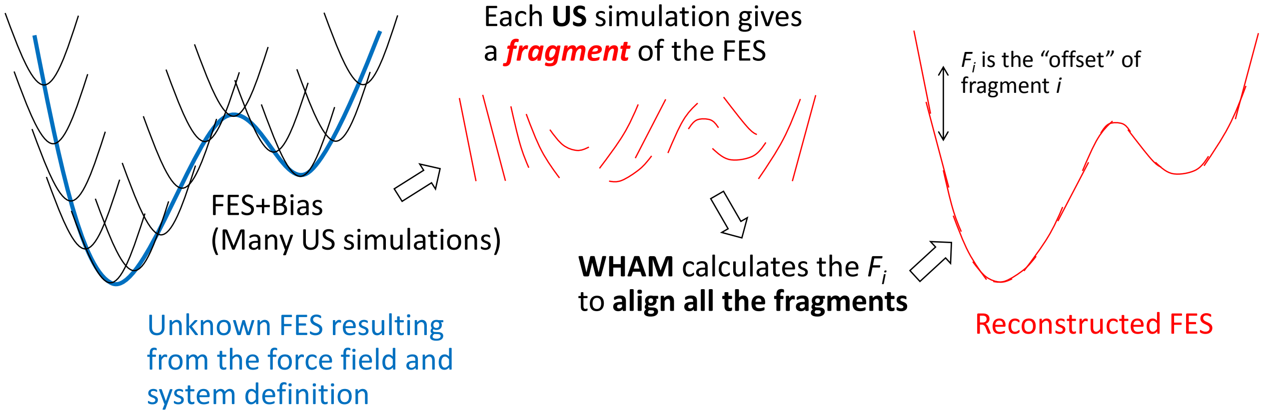
Once P^u and F_i are converged, we can calculate F^u

In Umbrella Sampling, the Free Energy Surface is usually called **Potential of Mean Force** (**PMF**).

Summary Umbrella Sampling & WHAM

Umbrella sampling -> allows sampling all over the CV space (we get multiple *fragment* of the FES)

WHAM -> reconstructs the complete FES from the *fragments*



FES+Bias
(Many US simulations)

Unknown FES resulting
from the force field and
system definition

Each **US** simulation gives
a ***fragment*** of the FES

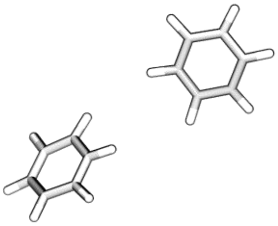
WHAM calculates the F_i
to **align all the fragments**

F_i is the “offset” of
fragment *i*

Reconstructed FES

US + WHAM Example: Benzene dimer

Objective: Calculation of the association/dissociation
free energy profile (Potential of Mean Force)



Procedure:

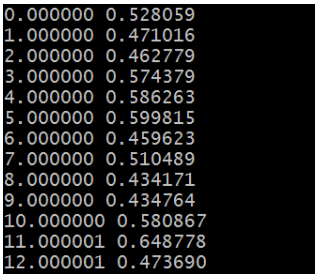
1. Selection of a CV: distance between centers of mass of each molecule
2. Decide CV space (range of distances to study): from 0.20 to 1.30 nm
3. Divide CV space in “windows”: create one window every 0.05 nm -> 23 windows
4. Run one MD simulation with a restraint per window
5. Create one histogram of the sampled CV per window
6. Calculate PMF and sampling errors with WHAM

US + WHAM Example: Benzene dimer

Result of the restrained MD (harmonic restraint k=500 kJ/mol·nm^2, s_0=0.50 nm)

Raw data:

Simulation time, CV



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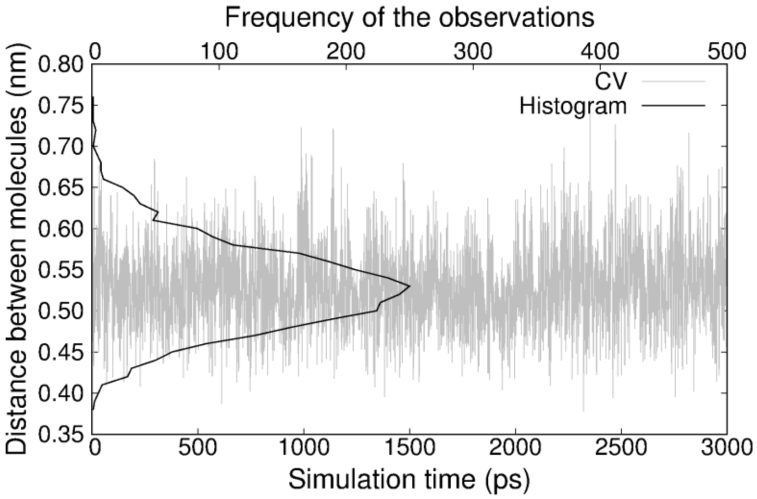
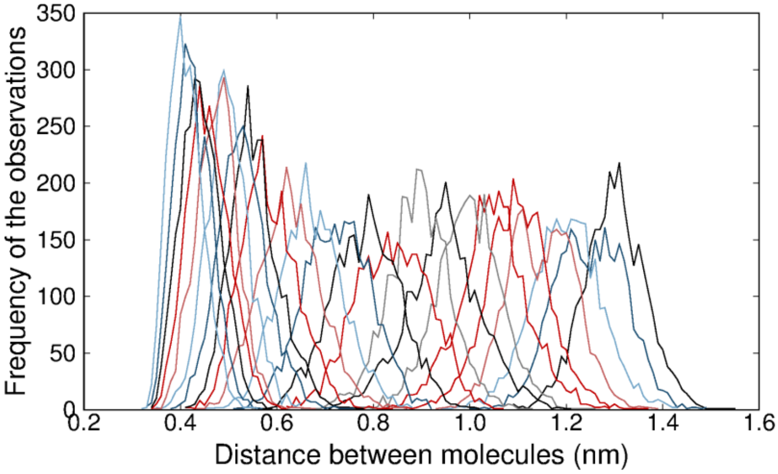
0.000000 0.528059
1.000000 0.471016
2.000000 0.462779
3.000000 0.574379
4.000000 0.586263
5.000000 0.599815
6.000000 0.459623
7.000000 0.510489
8.000000 0.434171
9.000000 0.434764
10.000000 0.580867
11.000001 0.648778
12.000001 0.473690
```



US + WHAM Example: Benzene dimer

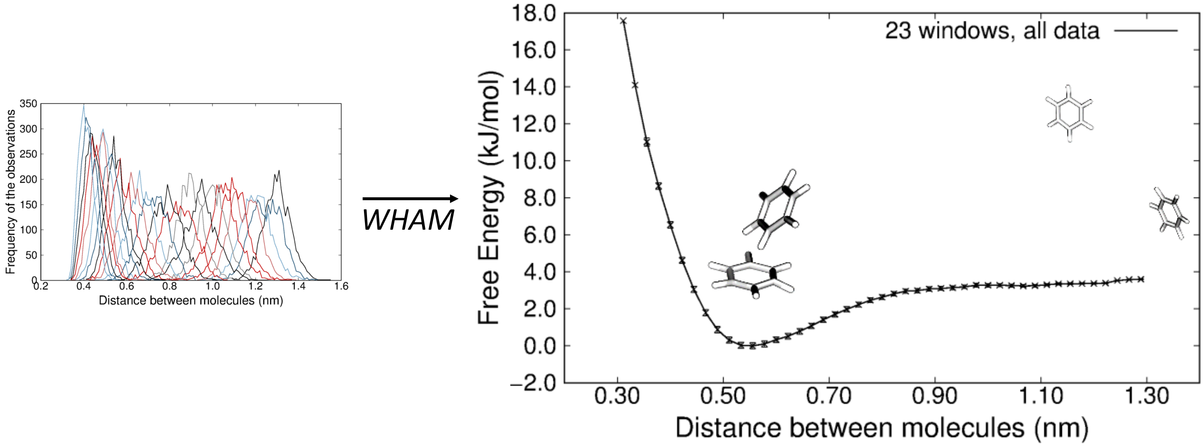
Analyze histograms

1. There should be data in all the CV space
2. The histograms should overlap



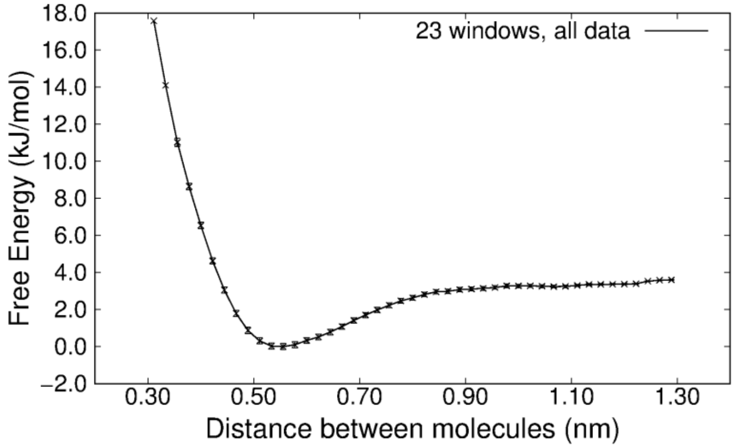
US + WHAM Example: Benzene dimer

Create Free Energy Profile (PMF)



US + WHAM Example: Benzene dimer

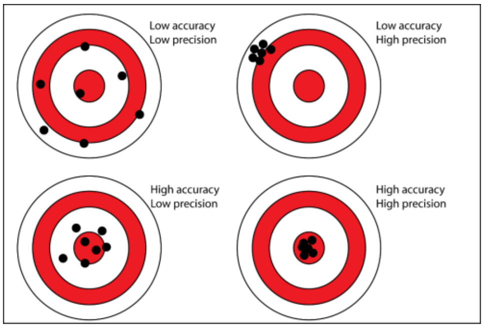
Beware! The error bars indicate the statistical error of the sampling. They **do not** indicate errors with respect to the true free energy profile!

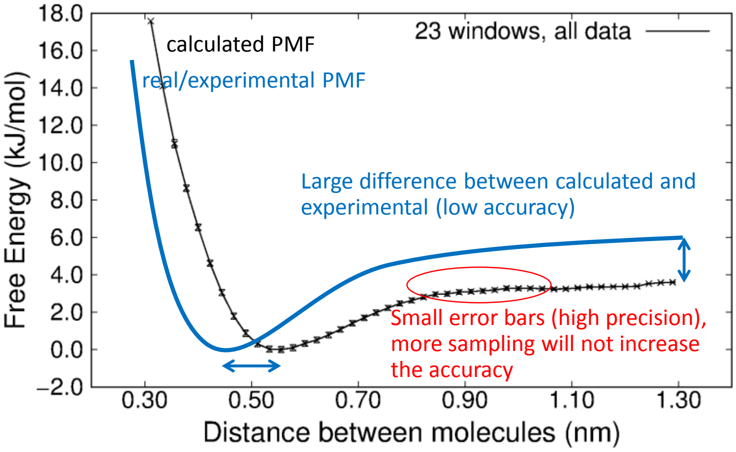


US + WHAM Example: Benzene dimer

Statistical error (due to sampling) -> precision

Error with respect to the real/experimental value (due to the method) -> accuracy





Large difference between calculated and experimental (low accuracy)

Small error bars (high precision), more sampling will not increase the accuracy

US + WHAM Example: Benzene dimer

If we have limited computational resources, What is more important?

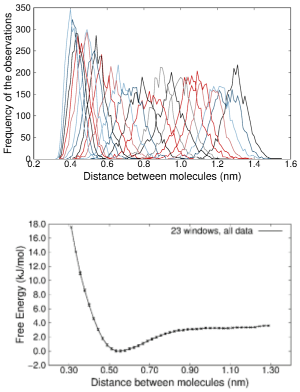
a) More windows, less data per window

b) Fewer windows, more data per window

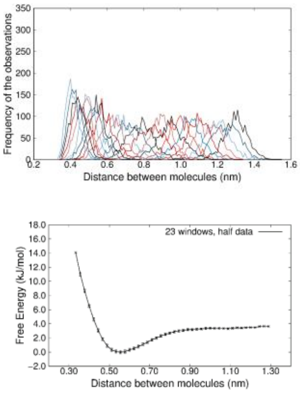
US + WHAM Example: Benzene dimer

a) More windows, less data per window

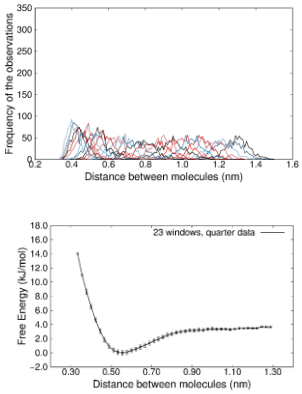
23w, 100% data



23w, 50% data



23w, 25% data



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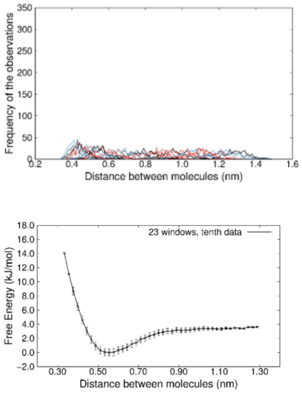
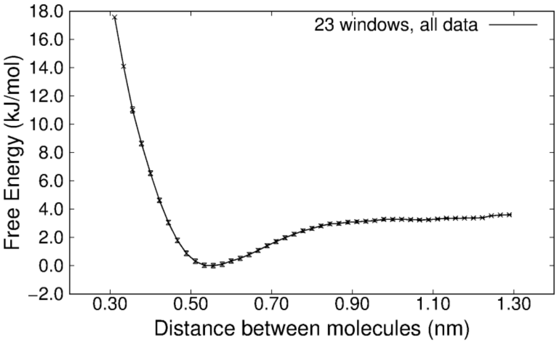


US + WHAM Example: Benzene dimer

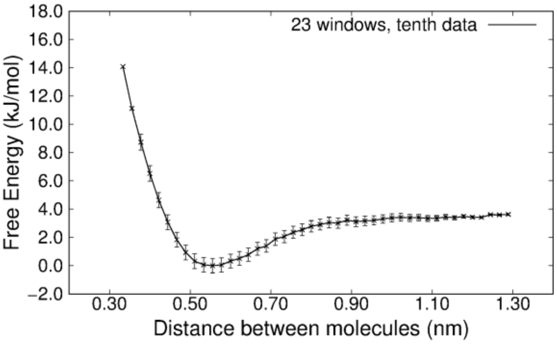
a) More windows, less data per window

The statistical error increases but the PMF is very similar

23w, 100% data



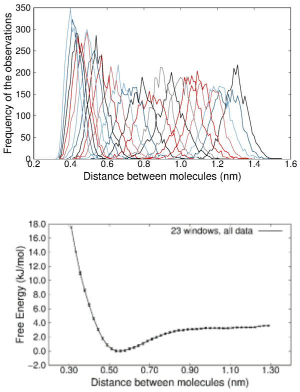
23w, 10% data



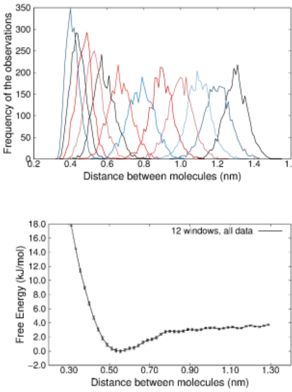
US + WHAM Example: Benzene dimer

b) Fewer windows, more data per window

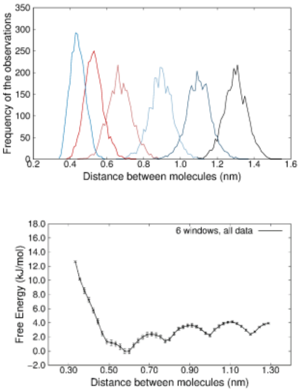
23w, 100% data



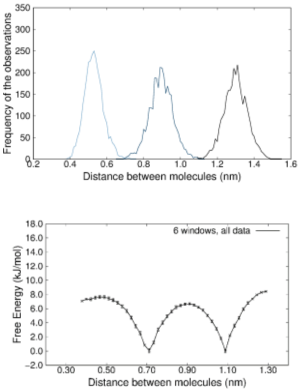
12w, 100% data



6w, 100% data



3w, 100% data



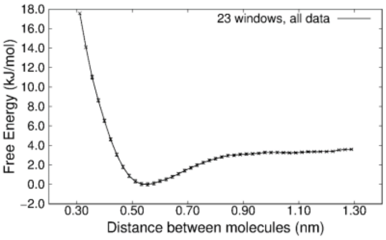
US + WHAM Example: Benzene dimer

If we have limited computational resources, What is more important?

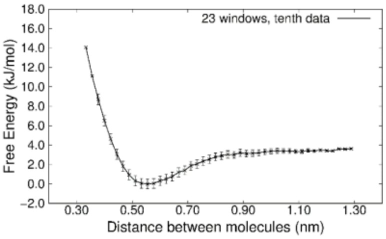
a) More windows, less data per window

b) Fewer windows, more data per window

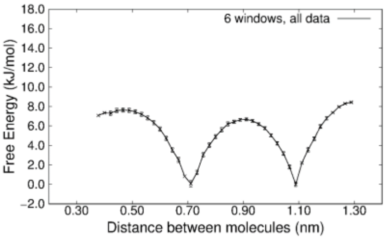
23w, 100% data



23w, 10% data



3w, 100% data



US & WHAM Selected References

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- WHAM original paper: S. Kumar, J. M. Rosenberg, D. Bouzida, R. H. Swendsen, P. A. Kollman, *J. Comput. Chem*. **1992**, *13*, 1011–1021.
- WHAM Grossfield's implementation: http://membrane.urmc.rochester.edu/content/wham
- Review: J. Kästner, *WIREs Comput. Mol. Sci*., **2011**, *1*, 932–42
- Umbrella Integration (other method to build P^u from multiple simulations): J. Kästner, W. Thiel, *J. Chem. Phys.*, **2005**, *123*, 144104.

Metadynamics

Remember: Addition of an external bias to increase the sampling in high energy regions

$$E^b(\mathbf{r}) = E^u(\mathbf{r}) + V_i(\mathbf{s}(\mathbf{r}))$$

Leads to

$$F^u(\mathbf{s}) = -\frac{1}{\beta}\ln P^b(\mathbf{s}) - V(\mathbf{s}) + F$$

*In a single simulation, we don't need to know F to calculate relative free energies (i.e. we would not need WHAM)

Metadynamics

In a single simulation, we don't need F to calculate relative free energies.

In metadynamics $V(\mathbf{s})$ is built during the simulation (i.e. $V(\mathbf{s},t)$) by the periodic addition of biasing kernel potentials (normally, gaussian-shaped).

At time t of the simulation, $V(\mathbf{s},t)$:

$$V(\mathbf{s},t)=\sum_{\tau}^{k\tau<t} w\exp\left(-\frac{(\mathbf{s}-\mathbf{s}_0(k\tau))^2}{2\sigma^2}\right)$$

ω gaussian height

σ gaussian width

τ deposition period

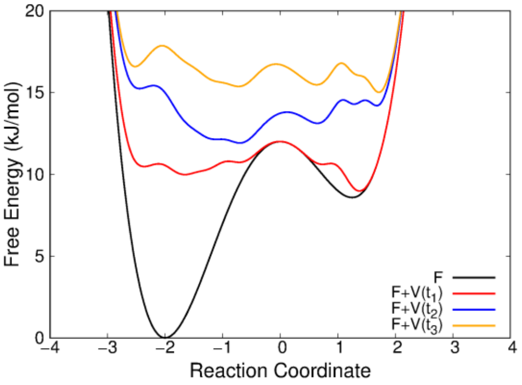
Metadynamics

At time t of the simulation

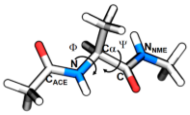
$$V(\mathbf{s},t)=\sum_{\tau}^{k\tau<t} w\exp\left(-\frac{(\mathbf{s}-\mathbf{s}_0(k\tau))^2}{2\sigma^2}\right)$$

At the end, the bias counteracts the underlying Free Energy Surface

$$\lim_{t\to\infty} V(s,t)=-F(s)$$

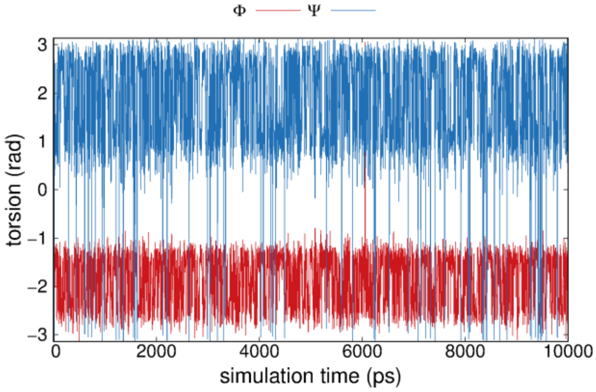


Metadynamics on alanine dipeptide



Standard Molecular Dynamics

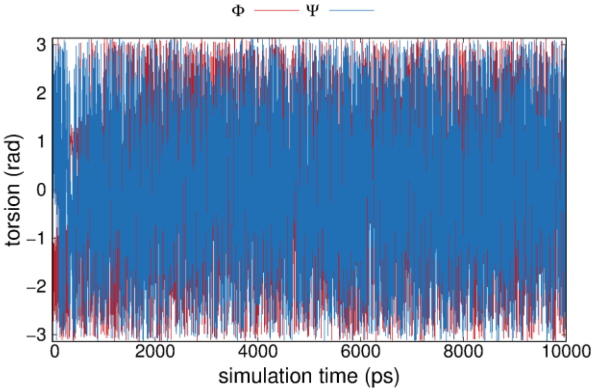
10 ns in vacuum 300 K



Φ and Ψ explore **limited** areas of the CV space

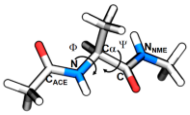
Metadynamics

10 ns in vacuum 300 K,τ=1 ps, w=1.2 kJ/mol, σ=0.35 rad



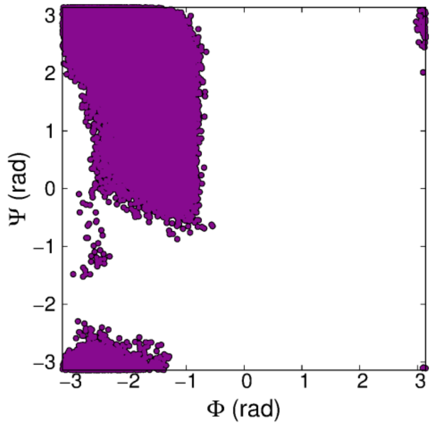
Φ and Ψ explore **all** the CV space

Metadynamics on alanine dipeptide



Standard Molecular Dynamics

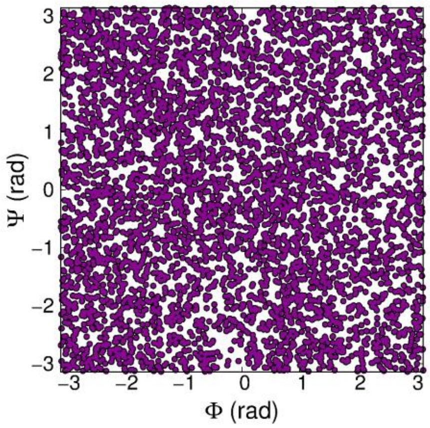
10 ns in vacuum 300 K



Φ and Ψ explore **limited** areas of the CV space

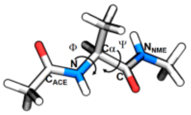
Metadynamics

10 ns in vacuum 300 K,τ=500 ps, w=1.2 kJ/mol, σ=0.35 rad



Φ and Ψ explore **all** the CV space

Metadynamics on alanine dipeptide



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Metadynamics

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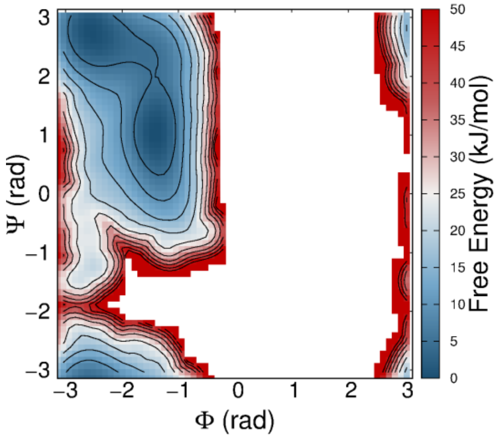
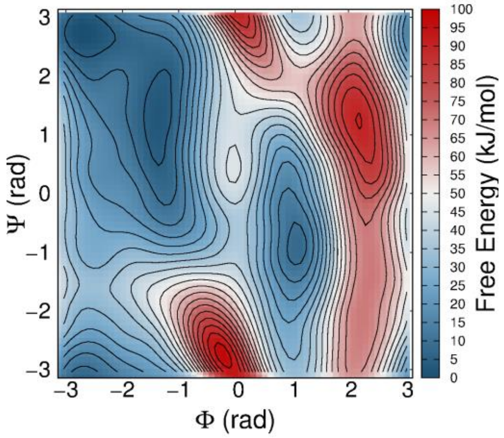


Φ and Ψ explore **limited** areas of the CV space



Φ and Ψ explore **all** the CV space

Well-Tempered Metadynamics

In practice it is convenient that the height of the hills is reduced as the space $\mathbf{s}(\mathbf{r})$ is revisited to ensure convergence of the Free Energy Surface

$$V_{k\tau}(\mathbf{s}) = V_{(k-1)\tau}(\mathbf{s}) + w\exp\left(-\frac{(\mathbf{s}-\mathbf{s}_0(k\tau))^2}{2\sigma^2}\right)\exp\left(-\frac{1}{\gamma-1}\beta V_{(k-1)\tau}(\mathbf{s})\right)$$

This bias converges asymptotically to $$V(\mathbf{s},t) = -\left(1-\frac{1}{\gamma}\right)F(\mathbf{s}) + c(t)$$

Well-Tempered Metadynamics

A note on the gamma factor

let $$(\gamma - 1)\beta^{-1} = k_B \Delta T$$

then $$\gamma = \frac{\Delta T + T}{T}$$

*Performing WT-metadynamics is "like" sampling the CV at a temperature $T + \Delta T$, while the other degrees of freedom are sampled at temperature T and the free energy is obtained at T

Well-Tempered Metadynamics

$$V(\mathbf{s},t) = -\left(1 - \frac{1}{\gamma}\right)F(\mathbf{s}) + c(t)$$

where $$c(t) = \frac{1}{\beta}\log\frac{\int \exp[-\beta F(\mathbf{s})]d\mathbf{s}}{\int \exp[-\beta\{F(\mathbf{s}) + V(\mathbf{s})]d\mathbf{s}}$$

It can be shown:

$$F(\mathbf{s}) = -\left(\frac{\gamma}{\gamma - 1}\right)V(\mathbf{s},t) + \frac{1}{\beta}\log\int \exp\left[\frac{\gamma}{\gamma - 1}\beta V(\mathbf{s},t)\right]d\mathbf{s}$$

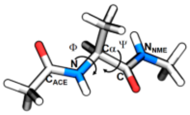
independent of time!

Well-Tempered Metadynamics

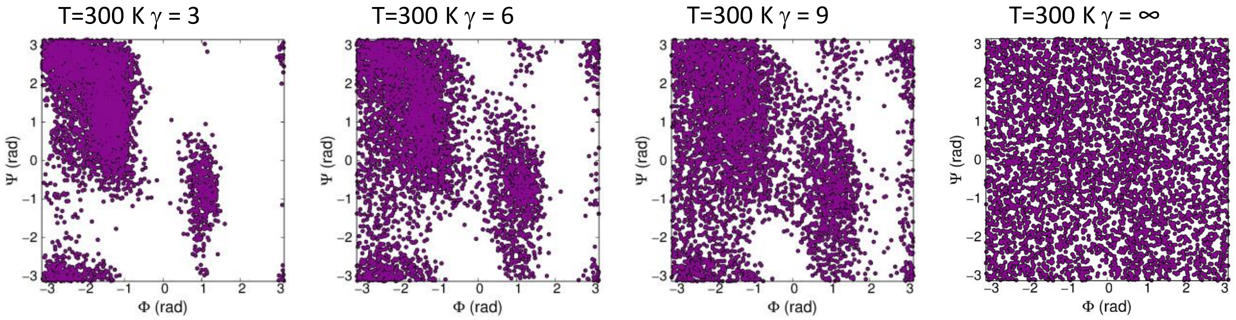
Once $c(t)$ is known, we can calculate the average of the observable $O(\mathbf{r})$ in the unbiased ensemble from the metadynamics trajectory

$$\langle O(\mathbf{r})\rangle = \langle O(\mathbf{r})\exp[\beta\{V(\mathbf{s}(\mathbf{r}),t)-c(t)\}]\rangle_V$$

Well-Tempered Metadynamics on alanine dipeptide



As the γ factor increases, the system explores higher energy regions


T=300 K γ = 3

T=300 K γ = 6

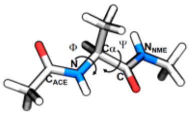
T=300 K γ = 9

T=300 K γ = ∞

*Well-tempered metadynamics with γ = ∞ is like standard metadynamics

**Well-tempered metadynamics with γ = 0 is like standard MD

Well-Tempered Metadynamics on alanine dipeptide



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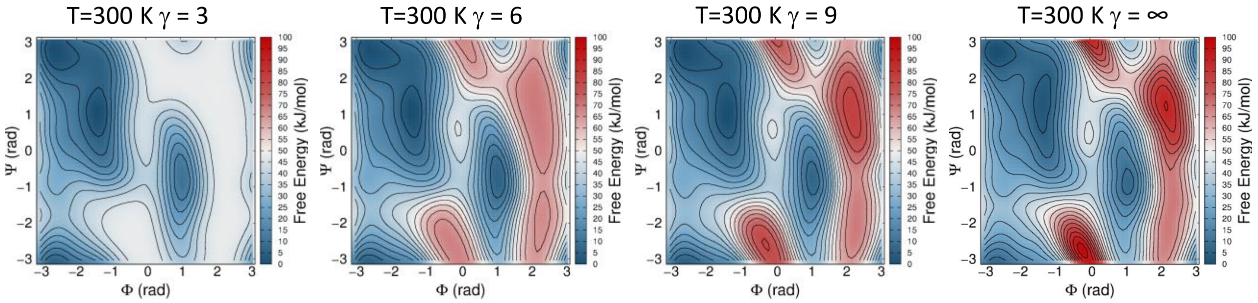


*Well-tempered metadynamics with γ = ∞ is like standard metadynamics

**Well-tempered metadynamics with γ = ∞ is like standard MD

Good and Bad CVs

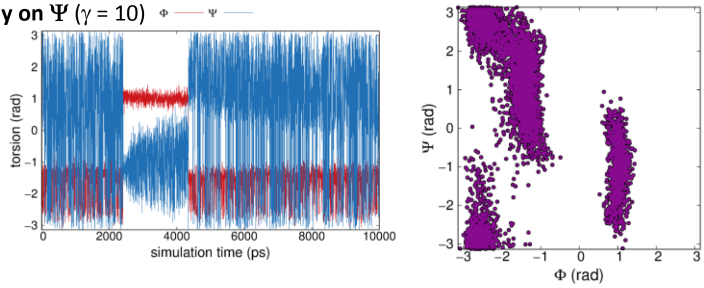
Remember: The CVs should include all the slow degrees of freedom relevant to the transition

What happens if we **miss** one slow degree of freedom on our metadynaics simulation?

→ Sampling of the rare event and convergence of the FES will be difficult (or impossible)

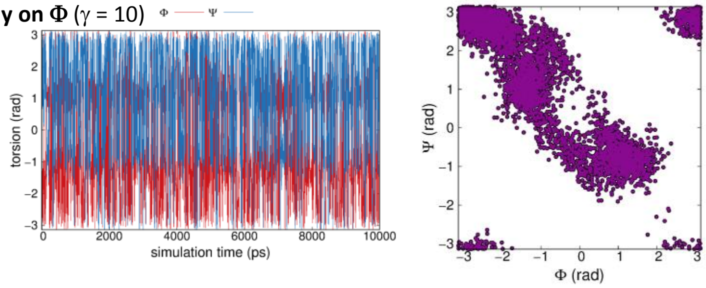
Good and Bad CVs

Bias **only on** Ψ (γ = 10)

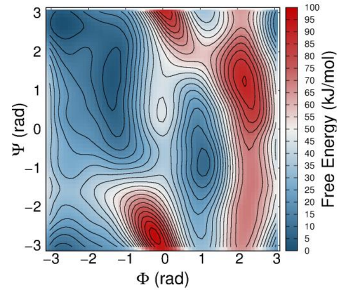


High energy barriers along a slow degree of freedom will not be crossed efficiently (and properly sampled) if we do not apply bias on such degree of freedom.

Bias **only on** Φ (γ = 10)

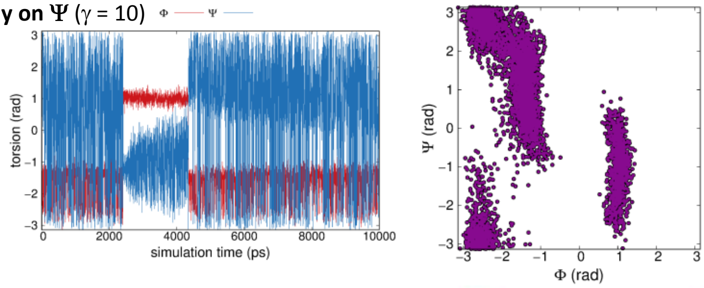


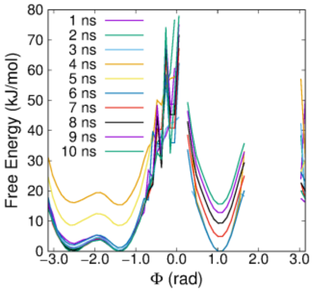
Bias on Ψ **and** Φ



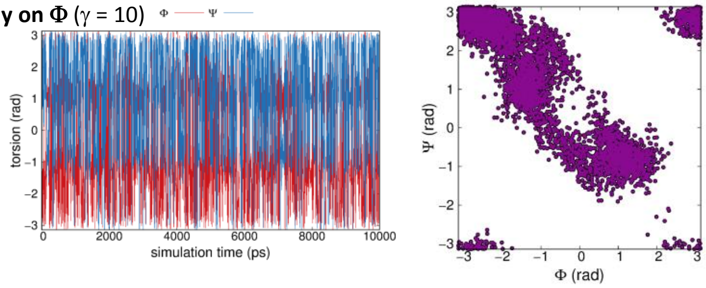
Good and Bad CVs

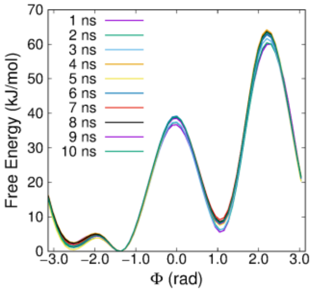
Bias **only on** Ψ (γ = 10)





Bias **only on** Φ (γ = 10)





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- Reweighting: P. Tiwary, M. Parrinello *J. Phys. Chem. B*, **2015**, *119*, 736–42; A. Barducci, M. Bonomi, M. Parrinello *WIREs Comput. Mol. Sci*., **2011**, *1*, 826–43.
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- PLUMED: http://www.plumed.org/

Metadynamics vs. Umbrella Sampling

Umbrella Sampling is used mostly for 1 CV problems. Sampling exhaustively 2 or more CVs is normally computationally very expensive.

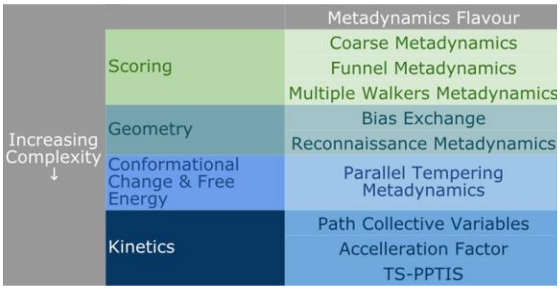
Metadynamics is faster exploring multidimensional sets of CVs because the sampling occurs preferentially along the regions of minimal free energy.

Umbrella Sampling is better for dissociation/association type of events. Metadynamics is good to sample dissociation but not so good for association as this is driven by entropy

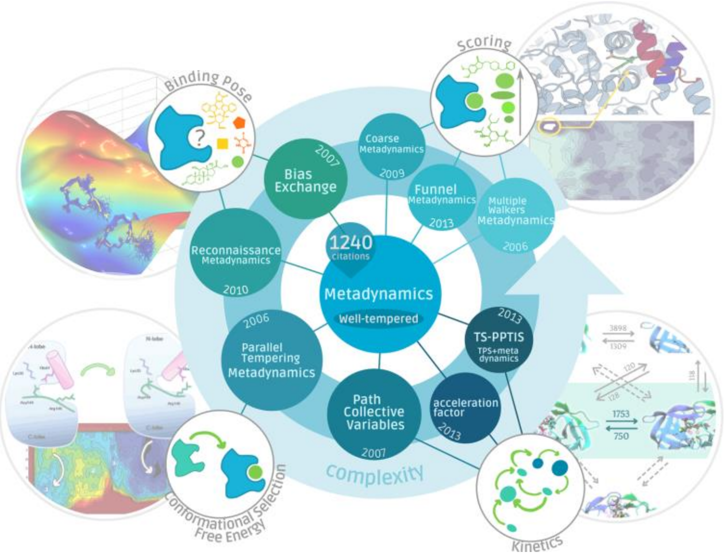
Normally, it is easier to control convergence in umbrella sampling.

In special cases, it is posible to recover the real dynamics from metadynamics simulations.

Metadynamics for drug target interaction

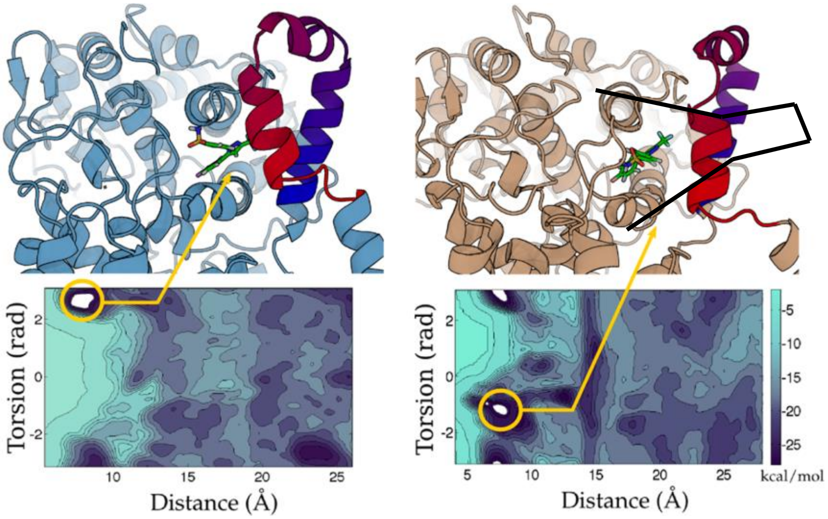


		Metadynamics Flavour
Increasing Complexity ↓	Scoring	Coarse Metadynamics
		Funnel Metadynamics
		Multiple Walkers Metadynamics
	Geometry	Bias Exchange
		Reconnaissance Metadynamics
	Conformational Change & Free Energy	Parallel Tempering Metadynamics
	Kinetics	Path Collective Variables
		Accelleration Factor
		TS-PPTIS



A. Cavalli, A. Spitaleri, G. Saladino, F. L. Gervasio, *Acc. Chem. Res.*, **2015**, *48*, 277-285

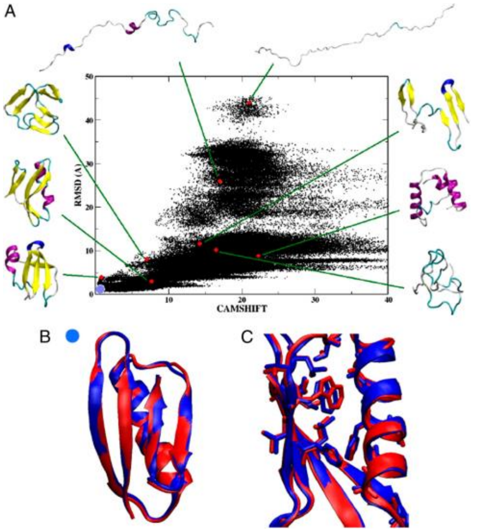
Funnel Metadynamics for drug target interaction

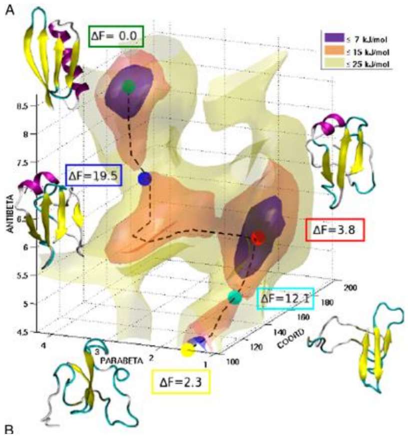


A. Cavalli, A. Spitaleri, G. Saladino, F. L. Gervasio, *Acc. Chem. Res.*, **2015**, *48*, 277-285

V. Limongelli, M. Bonomi, M. Parrinello, *Prod. Natl. Acad. Sci. USA*, **2013**, *110*, 6358-6363

NMR-Guided MTD for protein free energy landscapes





D. Granata, C. Camilloni, M. Vendruscolo, A. Laio, *Proc. Natl. Acad. Sci.*, **2013**, *110*, 6917-6822