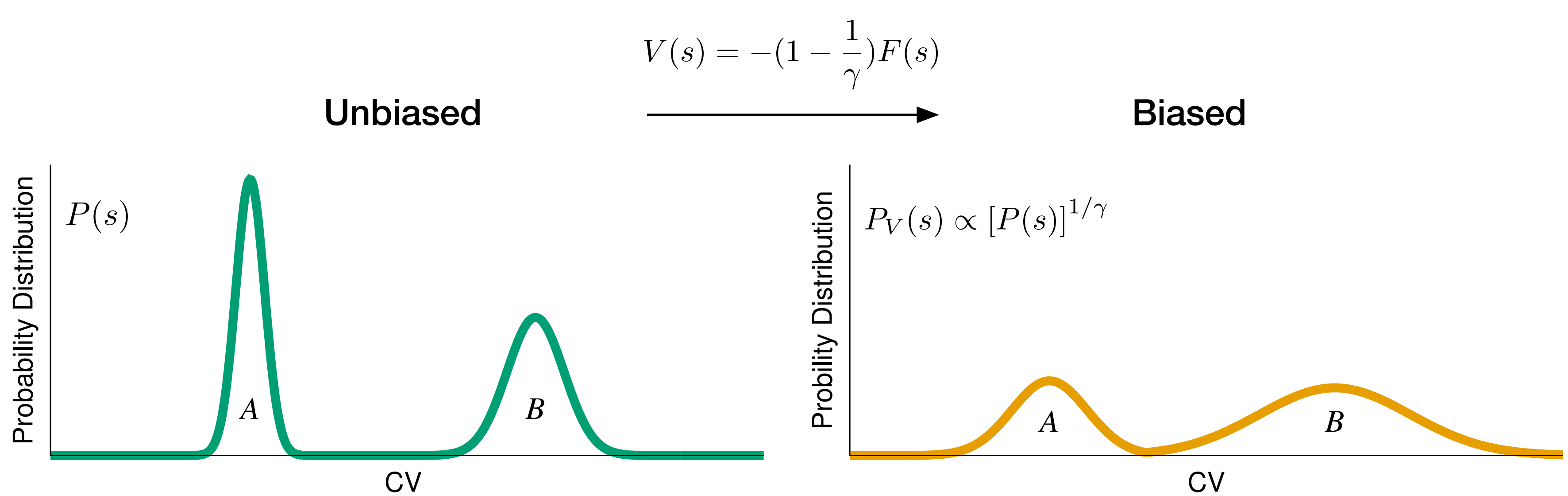
Enhanced Sampling Methods for Soft Matter Simulations:

Metadynamics



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TRR 146 IRTG School 2020

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Suggested Readings

Annual Review of Physical Chemistry 2016, 67:159-84

Enhancing Important Fluctuations: Rare Events and Metadynamics from a Conceptual Viewpoint

Omar Valsson,[1,2] Pratyush Tiwary,[3] and Michele Parrinello[1,2]

http://doi.org/10.1146/annurev-physchem-040215-112229

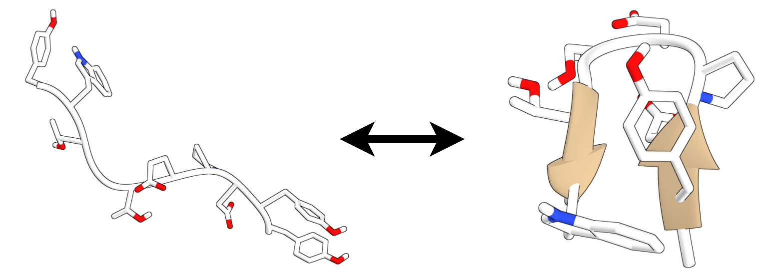
Other useful reviews:
https://doi.org/10.1038/s42254-020-0153-0
https://doi.org/10.1007/978-3-319-44677-6_49
https://doi.org/10.1007/978-1-4939-9608-7_21 (also https://arxiv.org/abs/1812.08213)

Time Scale Problem in Molecular Simulations

Time Scale Problem in Molecular Simulations

fs ps ns µs

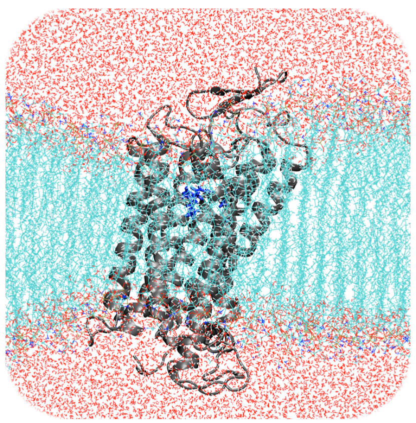
Atomistic (classical)



~ 100 ns/day on 1 hybrid GPU/CPU node
(200 atoms and 2000 water molecules)

fs ps

Ab initio



~ 1 ps/day on 2 nodes (48 cores)
(QM/MM with 73 QM atoms)

fs ps ns µs ms s

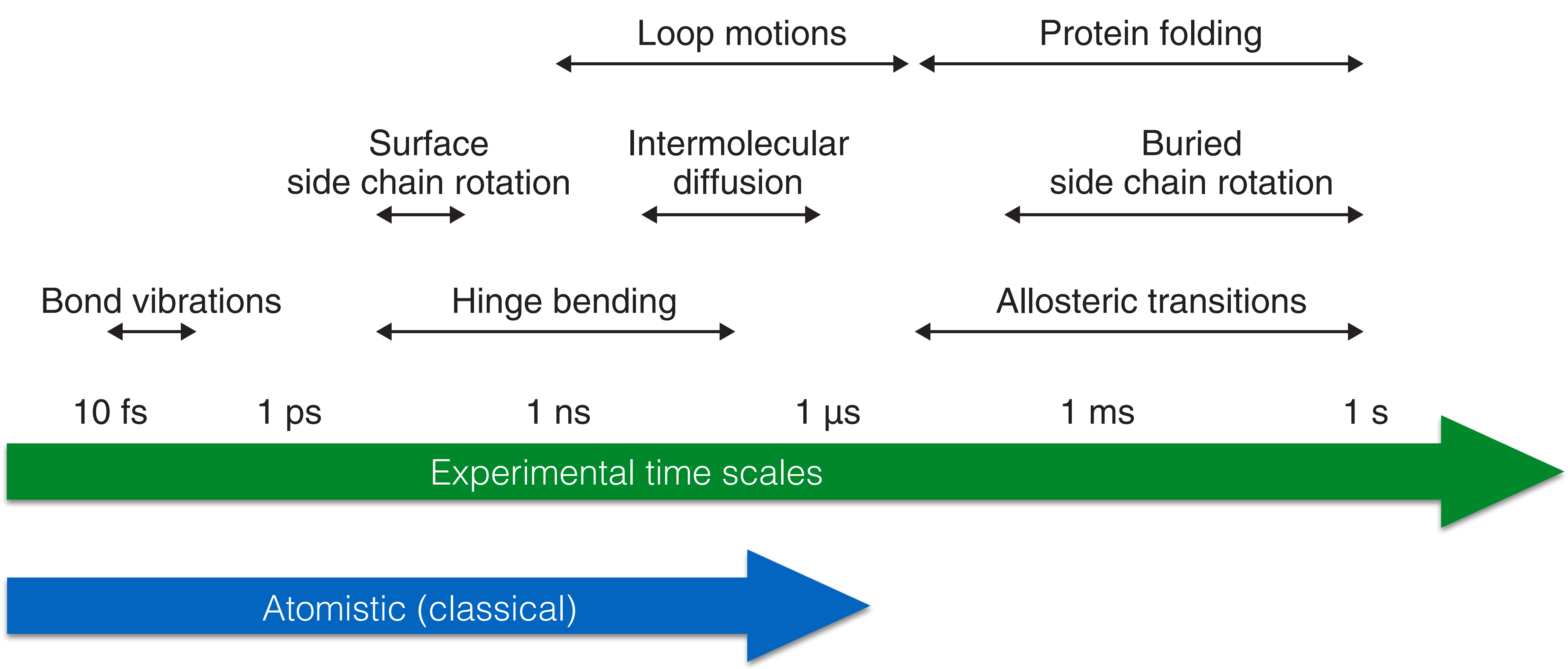
Experimental time scales

Conventional molecular simulations suffer from a **severe time scale problem**

Time Scale Problem in Molecular Simulations

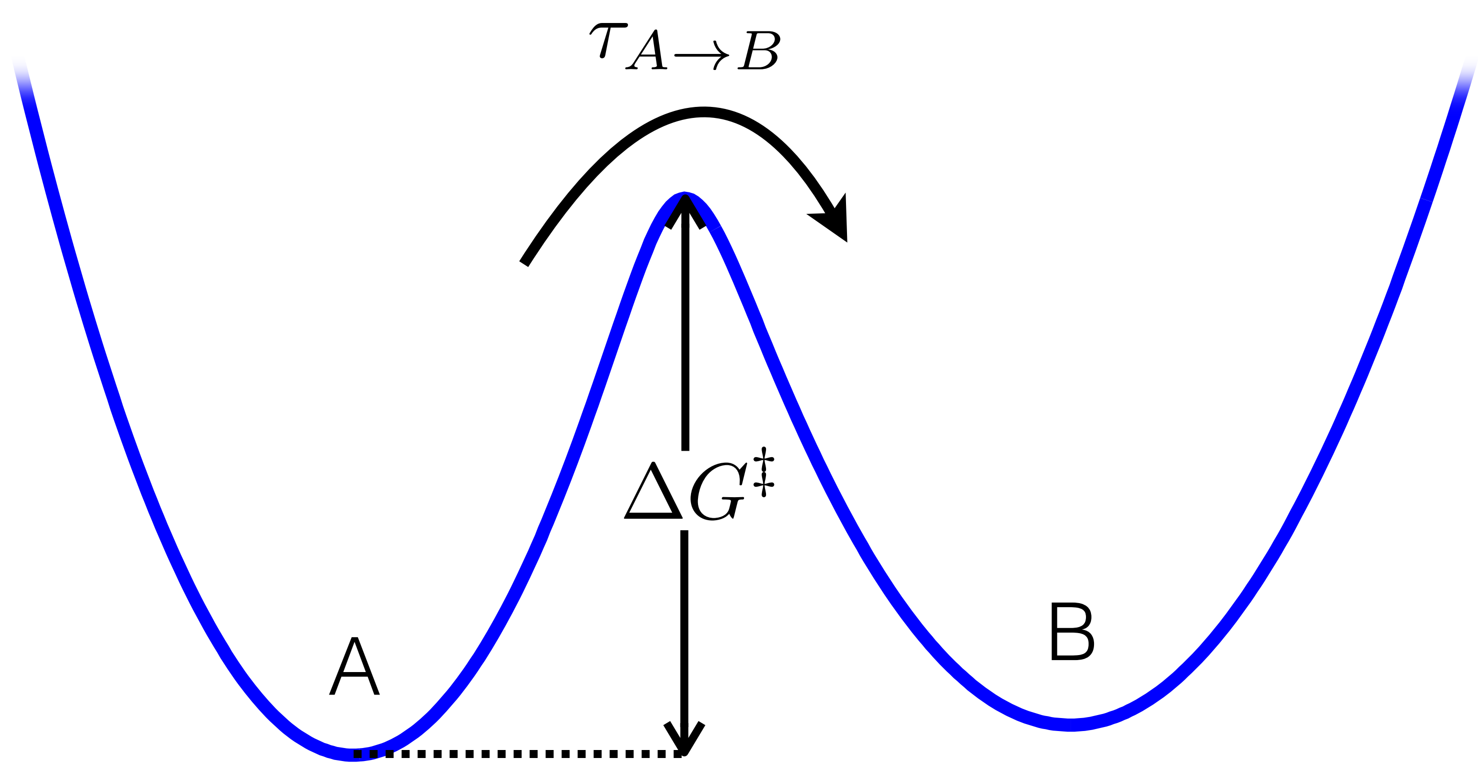
e.g. typical protein motions

Curr. Opin. Pharma. 10 745 (2010)



Time Scale Problem in Molecular Simulations

Physical system characterized by many metastable states
separated by high free energy barriers

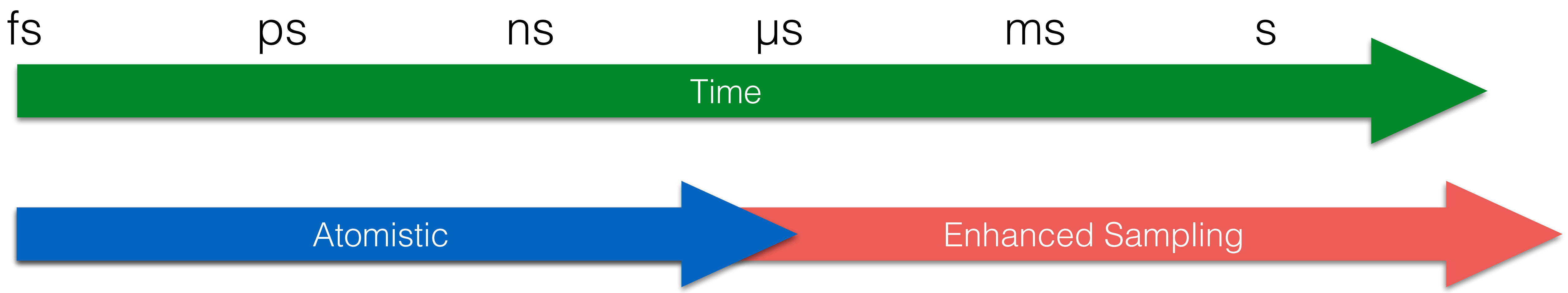


$$\tau_{A\to B} = \frac{1}{\nu_0\, e^{-\Delta G^{\ddagger}/k_{\mathrm{B}}T}} \propto e^{+\Delta G^{\ddagger}/k_{\mathrm{B}}T}$$

$\Delta G^{\ddagger} >> k_{\mathrm{B}}T$ ➡ trapped in a metastable state

barrier crossings are **rare events** on the timescales we can afford

Advanced sampling method needed to bridge time scales



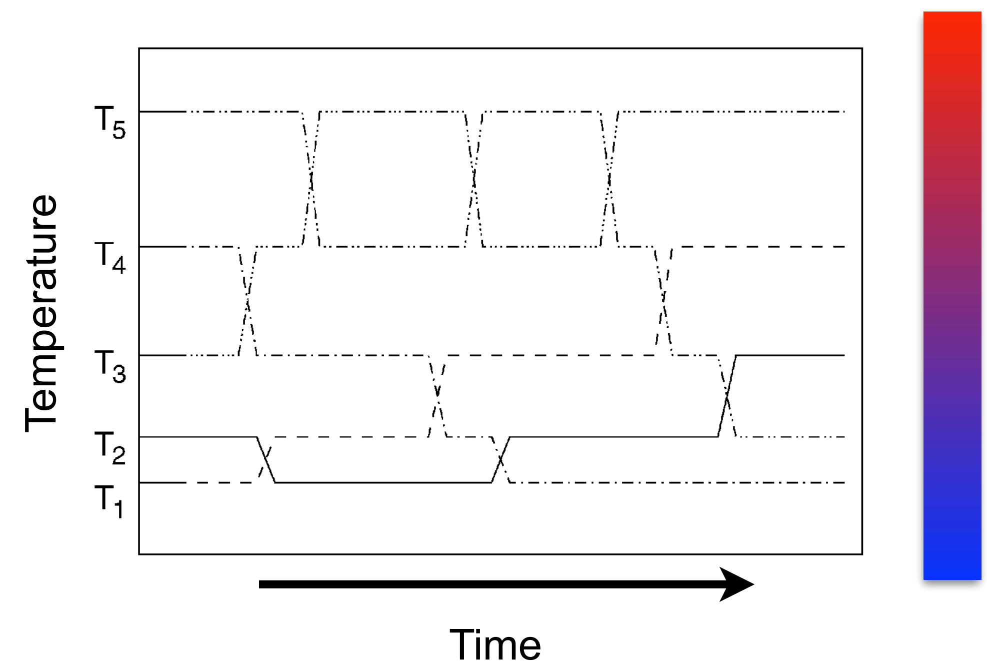
Solving the Time Scale Problem

Parallel tempering: cross barriers by heating and cooling

(or more generally replica exchange)

requires generally little information about the system

but expensive as we often need many replicas, especially for solvated systems

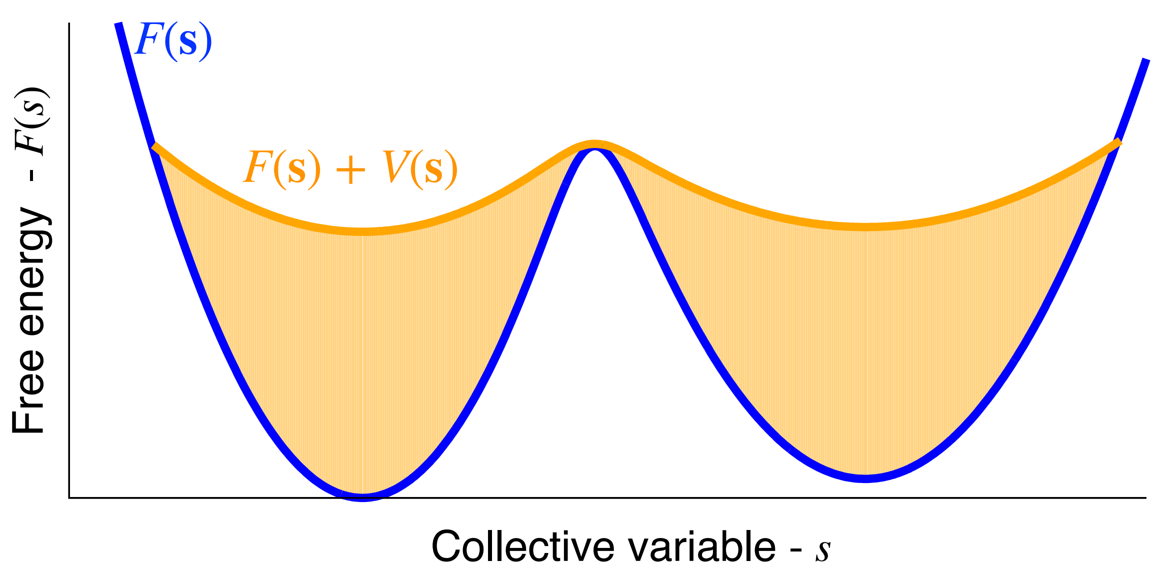


Focus on few relevant slow degrees of freedom

i.e. collective variable based methods

generally less expensive

but requires knowledge about the system



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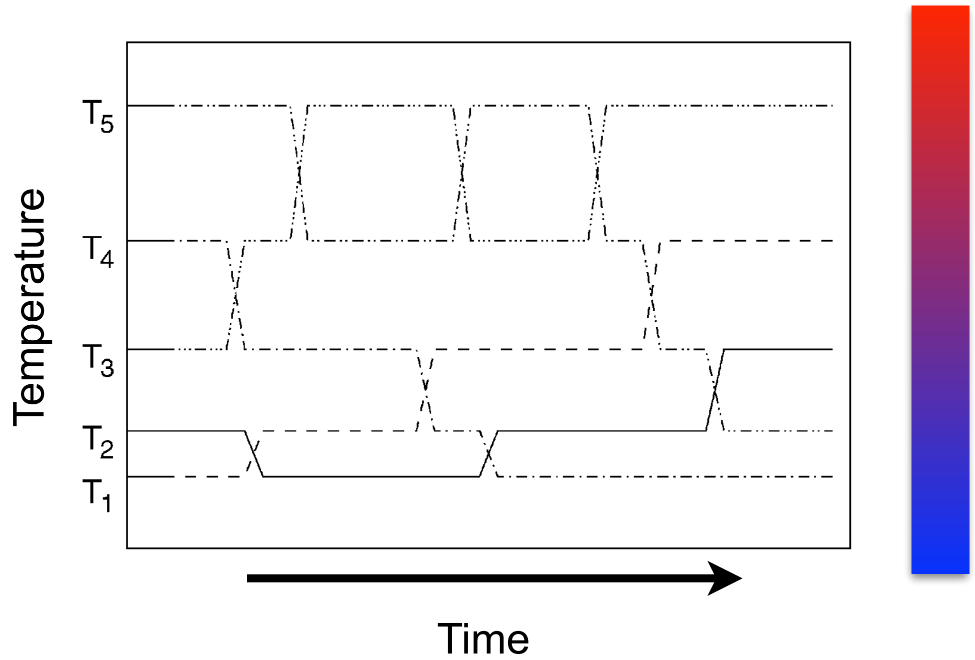

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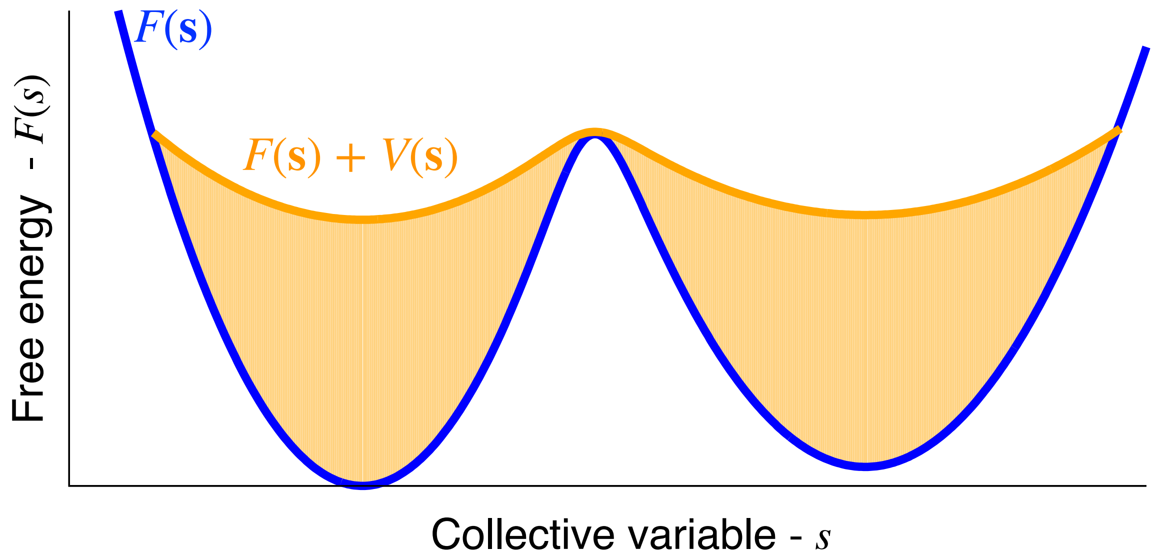


Collective Variables (CVs) and CV-based Enhanced Sampling Methods

Mapping to a Lower Dimension

Start by reducing the description of the problem to a reduced number of variables

$$\mathbf{R} = (\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \ldots, \mathbf{r}_N) \in \mathbb{R}^{3N}$$

high-dimensional space (~ 10^4-10^6)
hard to understand

$$\mathbf{s}(\mathbf{R}) = (s_1(\mathbf{R}), s_2(\mathbf{R}), \ldots, s_d(\mathbf{R})) \in \mathbb{R}^d \qquad d \ll 3N$$

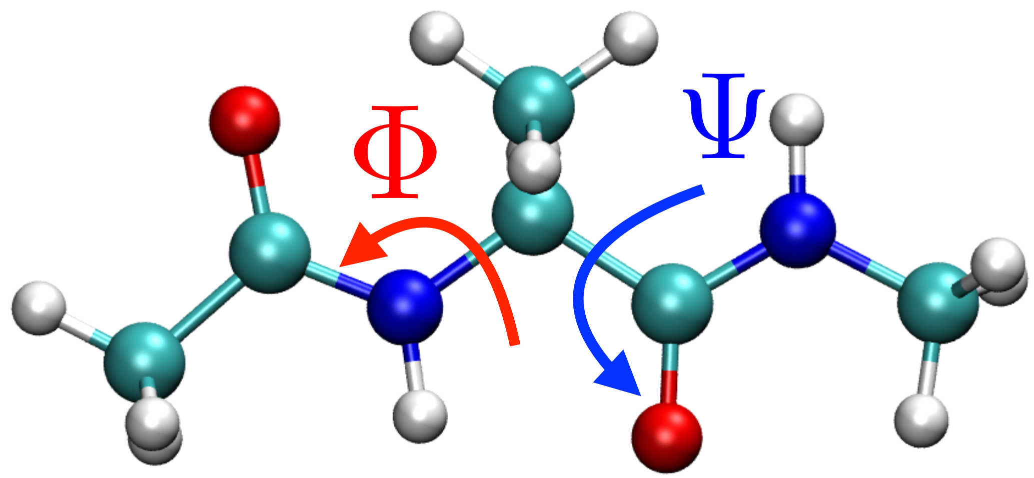
(generally ~1-3)

Coarse-grained descriptors or order parameters, generally called
collective variables (CVs)

Often highly non-linear functions of $\mathbf{R}$

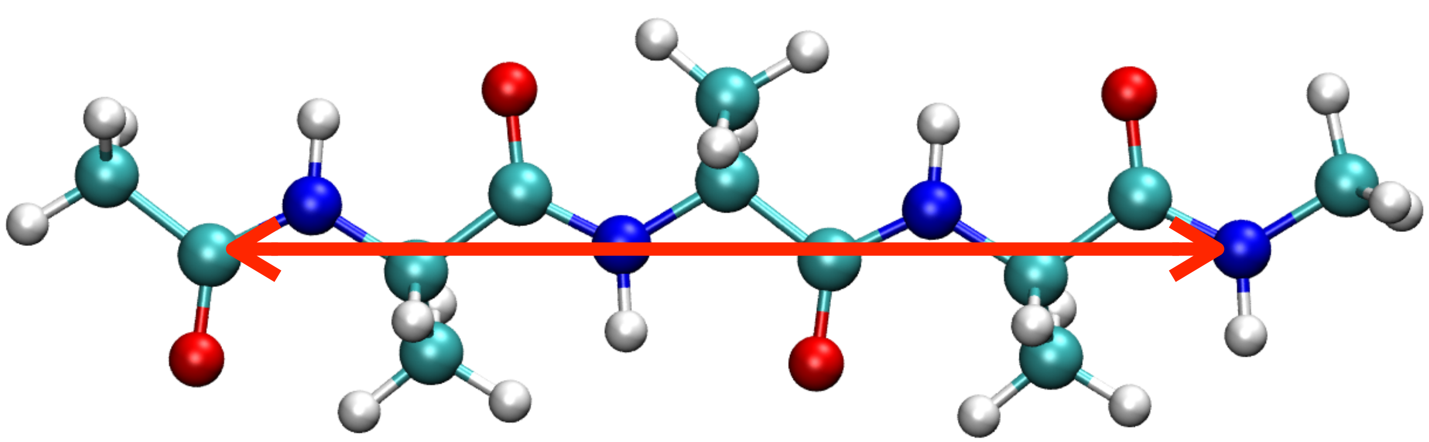
Examples of Collective Variables

Dihedral angles



Distances

$$d_{i,j} = ||\mathbf{r}_i - \mathbf{r}_j||$$



Examples of Collective Variables

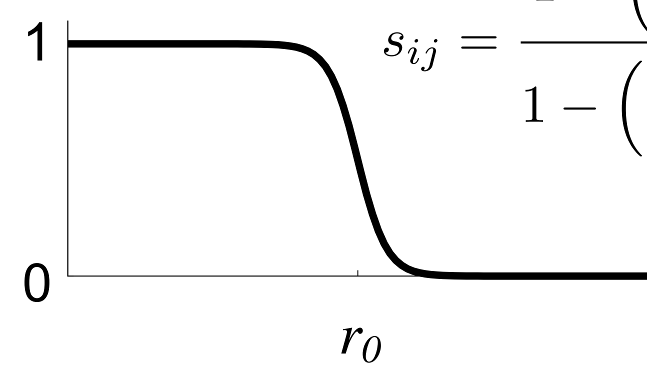
Root mean square deviation (RMSD) from a reference structure

$$RMSD = \sqrt{\frac{1}{n}\sum_{i}^{n} ||\mathbf{r}_i - \mathbf{r}_i^{ref}||^2}$$

continuous switching function

Coordination numbers (e.g. number of hydrogen bond)

$$CN = \sum_{i \in A} \sum_{j \in B} \frac{1 - \left(\frac{|\mathbf{r}_i - \mathbf{r}_j|}{r_0}\right)^6}{1 - \left(\frac{|\mathbf{r}_i - \mathbf{r}_j|}{r_0}\right)^{12}}$$



$$s_{ij} = \frac{1 - \left(\frac{|\mathbf{r}_i - \mathbf{r}_j|}{r_0}\right)^6}{1 - \left(\frac{|\mathbf{r}_i - \mathbf{r}_j|}{r_0}\right)^{12}}$$

Radius of gyration

$$R_g = \left(\frac{\sum_i m_i |\mathbf{r}_i - \mathbf{r}_{\mathrm{COM}}|^2}{\sum_i m_i}\right)^{1/2} \qquad \mathbf{r}_{\mathrm{COM}} = \frac{\sum_i m_i \mathbf{r}_i}{\sum_i m_i}$$

And many more ….

Mapping to a Lower Dimension

Boltzmann distribution

$$P(\mathbf{R}) = \frac{e^{-\beta U(\mathbf{R})}}{\int d\mathbf{R}\, e^{-\beta U(\mathbf{R})}} \qquad \beta = \frac{1}{k_{\mathrm{B}} T}$$

Mapping to a Lower Dimension

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Distribution (marginal) of **CVs** obtained by integrating over all other degrees of freedom

$$P(\mathbf{s}) = \int d\mathbf{R}\, \delta\left[\mathbf{s} - \mathbf{s}(\mathbf{R})\right]\, P(\mathbf{R}) = \langle \delta\left[\mathbf{s} - \mathbf{s}(\mathbf{R})\right] \rangle$$

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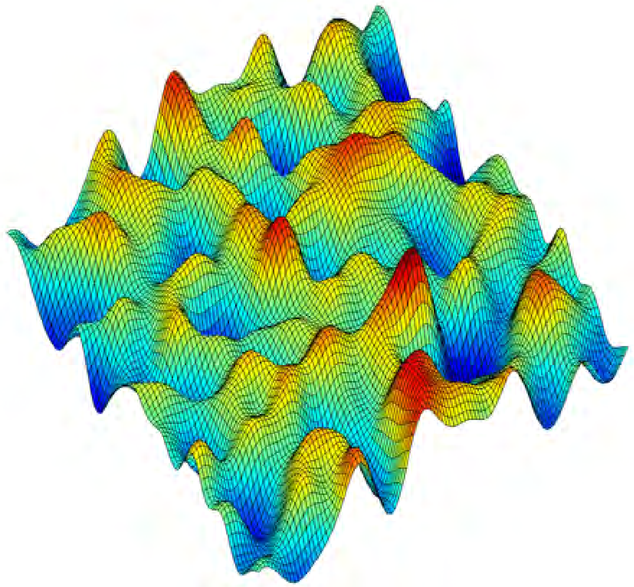
so-called **Free Energy Surface (FES)** given by the negative logarithm

$$F(\mathbf{s}) = -\frac{1}{\beta} \log P(\mathbf{s}) = -\frac{1}{\beta} \log \int d\mathbf{R}\, \delta\left[\mathbf{s} - \mathbf{s}(\mathbf{R})\right]\, e^{-\beta U(\mathbf{R})} + C$$

Mapping to a Lower Dimension



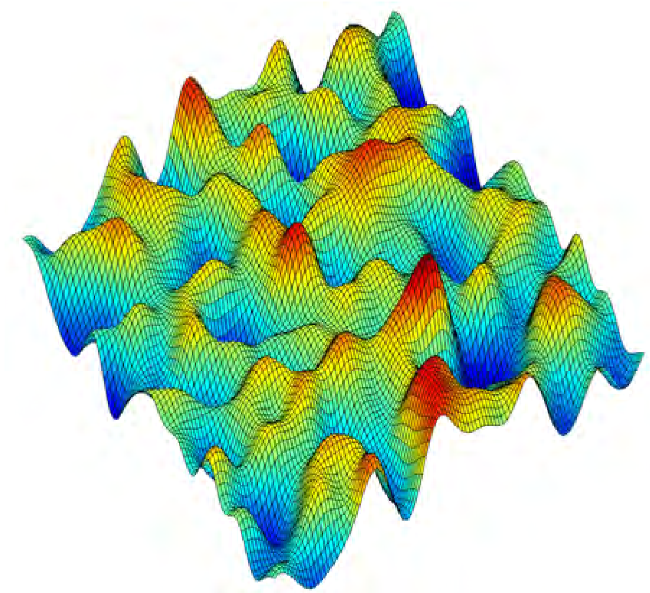
C. Dellago

Potential Energy Surface $U(\mathbf{R})$

➡ High-dimensional, $\mathbf{R} \in \mathbb{R}^{3N}$

➡ Rugged

Mapping to a Lower Dimension



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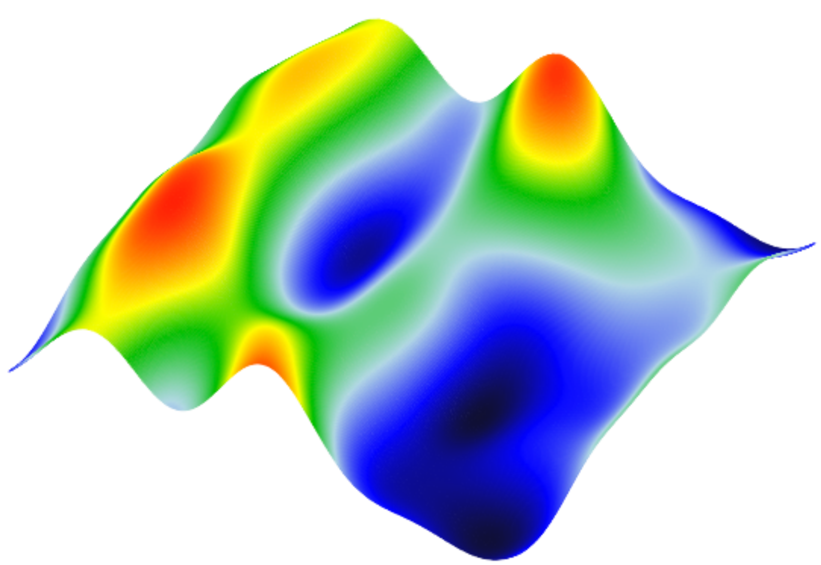
CVs $\quad \mathbf{s}(\mathbf{R}) = (s_1(\mathbf{R}), s_2(\mathbf{R}), \ldots, s_d(\mathbf{R}))$



Free Energy Surface $F(\mathbf{s})$

➡ Low-dimensional, $\mathbf{s} \in \mathbb{R}^d$

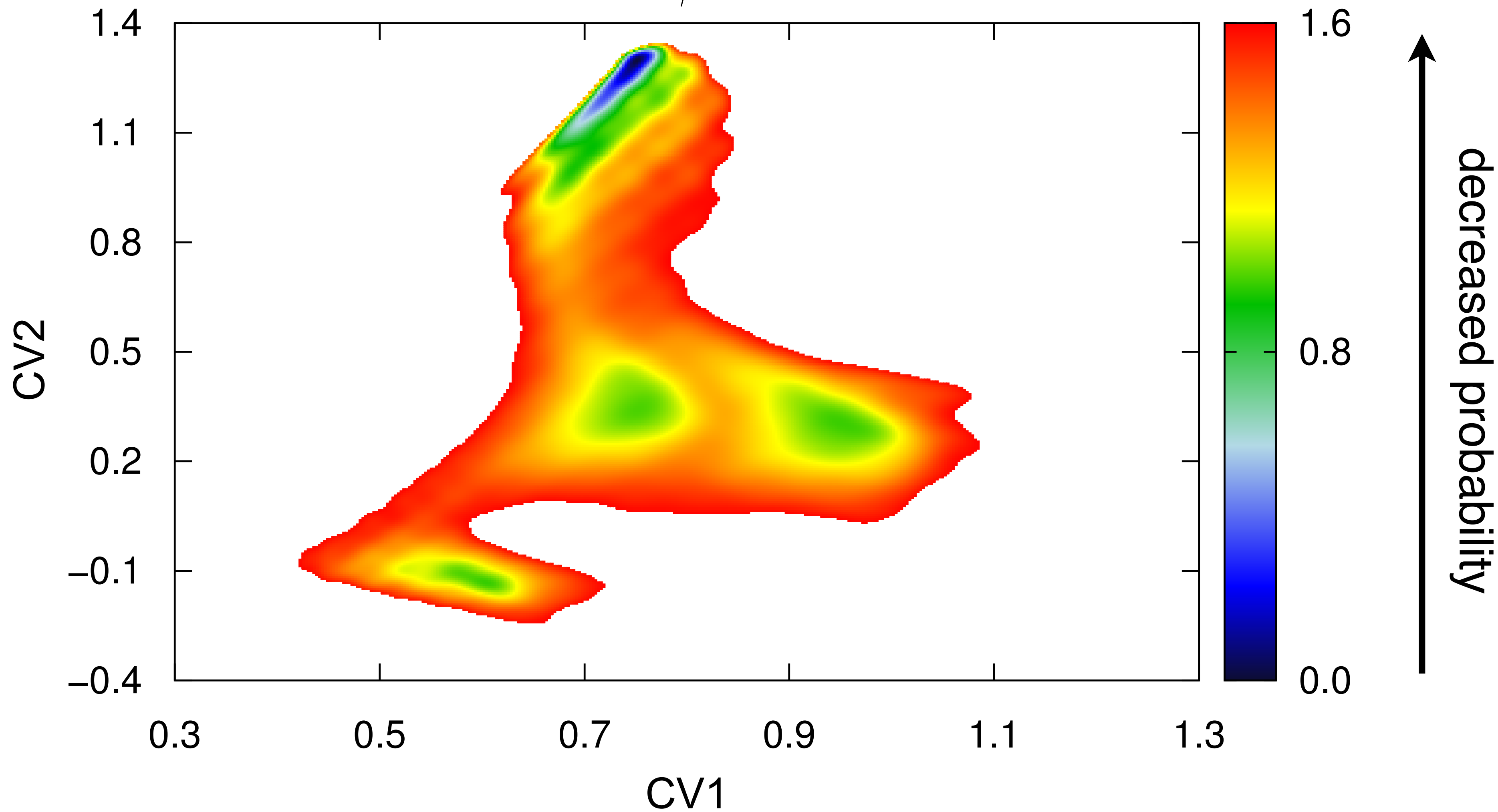
➡ Smooth

Free Energy Surface

The FES normally what we are interested in obtaining

gives information about metastable states, their relative stability, and the free energy barriers

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



Estimating the Free Energy Surface

The FES is also defined as

$$F(\mathbf{s}) = -\frac{1}{\beta} \lim_{t \to \infty} \log N(\mathbf{s}, t)$$

where $N(\mathbf{s},t)$ is a normalized histogram

$$N(\mathbf{s}, t) = \frac{1}{t} \sum_{t'}^{t} \delta \left[\mathbf{s} - \mathbf{s}(\mathbf{R}(t')) \right]$$

Therefore, should be possible to estimate the FES from histogram accumulated in a unbiased simulation of finite length

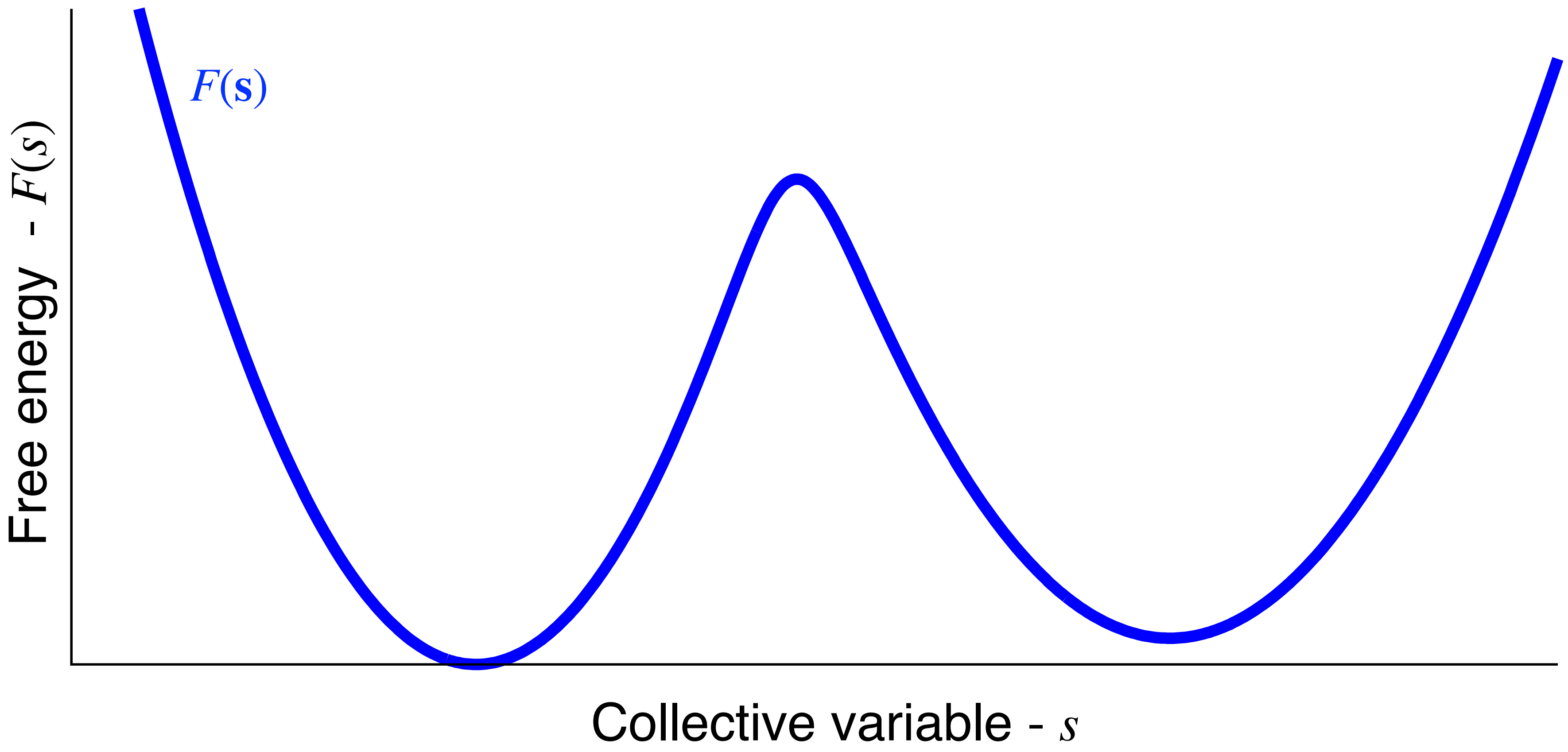
$$F(\mathbf{s}) = -\frac{1}{\beta} \log N(\mathbf{s}, t)$$

However, this rarely works due to sampling problems

Umbrella Sampling

Torrie and Valleau, J. Comp. Phys. 1977

The basic idea behind many enhanced sampling methods



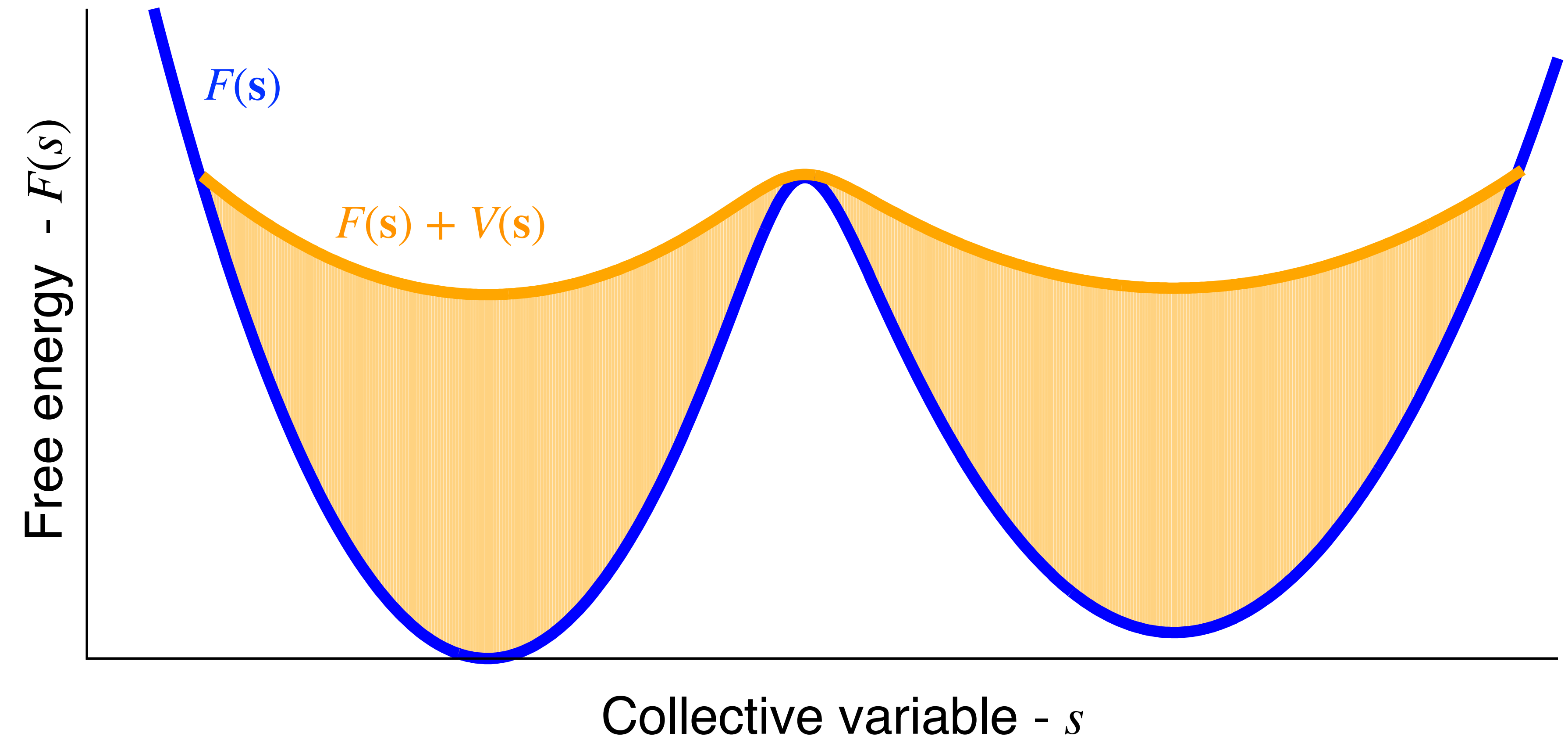
Umbrella Sampling

Torrie and Valleau, J. Comp. Phys. 1977

The basic idea behind many enhanced sampling methods

Introduce a bias potential $V(\mathbf{s})$ that acts in the space spanned by the slow CVs

$$U(\mathbf{R}) \quad \longrightarrow \quad U(\mathbf{R}) + V(\mathbf{s}(\mathbf{R}))$$



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Sample a “easier” biased distribution

$$P_V(\mathbf{R}) = \frac{e^{-\beta[U(\mathbf{R})+V(\mathbf{s}(\mathbf{R}))]}}{\int d\mathbf{R}\, e^{-\beta[U(\mathbf{R})+V(\mathbf{s}(\mathbf{R}))]}} \propto P(\mathbf{R}) e^{-\beta V(\mathbf{s}(\mathbf{R}))}$$

The biased CV distribution is then

$$P_V(\mathbf{s}) = \int d\mathbf{R}\, \delta\left[\mathbf{s} - \mathbf{s}(\mathbf{R})\right] \, P_V(\mathbf{R}) \propto e^{-\beta[F(\mathbf{s})+V(\mathbf{s})]}$$

Umbrella Sampling - Reweighting

Can obtain unbiased ensemble averages by weighting each configuration by the bias acting on it

$$P(\mathbf{R}) \propto P_V(\mathbf{R})\, e^{\beta V(\mathbf{s}(\mathbf{R}))}$$

$$\langle O(\mathbf{R}) \rangle = \frac{\left\langle O(\mathbf{R}) e^{\beta V(\mathbf{s}(\mathbf{R}))} \right\rangle_V}{\left\langle e^{\beta V(\mathbf{s}(\mathbf{R}))} \right\rangle_V}$$

e.g. the FES for any CVs

$$F(\tilde{\mathbf{s}}) = -\frac{1}{\beta} \log \left\langle \delta\left[\tilde{\mathbf{s}} - \tilde{\mathbf{s}}(\mathbf{R})\right] e^{+\beta V(\mathbf{s}(\mathbf{R}))} \right\rangle_V$$

Note that these relation are only valid if the bias is stationary
(i.e. does not change with time)

How to Select a Good Bias Potential

Assume that we can take the bias potential as

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

where $\gamma \geq 1$ is a parameter

Inserting this $V(\mathbf{s})$ into

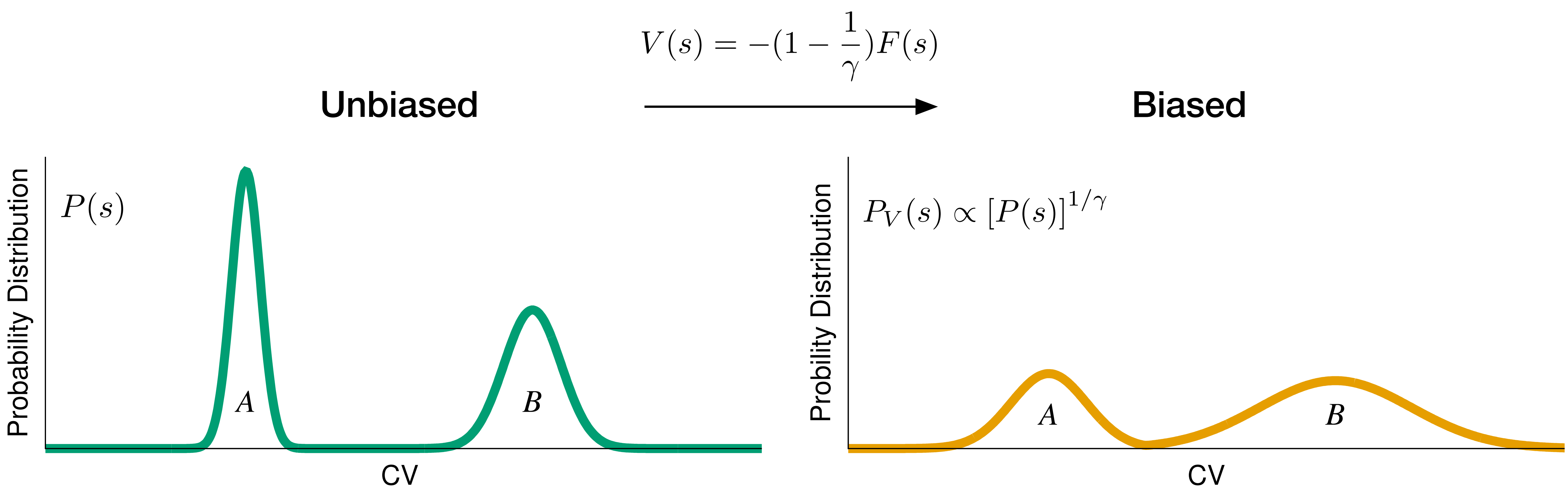
$$P_V(\mathbf{s}) \propto e^{-\beta[F(\mathbf{s})+V(\mathbf{s})]}$$

gives

$$P_V(\mathbf{s}) \propto [P(\mathbf{s})]^{1/\gamma}$$

so called well-tempered distribution

Well-Tempered Distribution



Enhanced fluctuations of the CVs ➡ easier to cross barriers

Flatten the sampling as compared to unbiased distribution $P(\mathbf{s})$

Well-Tempered Distribution

By using

$$P_V(\mathbf{s}) \propto [P(\mathbf{s})]^{1/\gamma} \qquad \text{and} \qquad F_V(\mathbf{s}) = -\frac{1}{\beta}\log P_V(\mathbf{s})$$

we obtain

$$F_V(\mathbf{s}) = \frac{1}{\gamma}F(\mathbf{s})$$

(ignoring unimportant additive constants)

sampling on an effective FES where barriers have been reduced by a factor of γ

optimal γ such that effective barriers are around few $k_{\mathrm{B}}T$ and easily crossed

Uniform Distribution

Taking the limit $\gamma \to \infty$ gives

$$V(\mathbf{s}) = -F(\mathbf{s})$$

$$P_V(\mathbf{s}) \propto 1$$

Uniform sampling of CVs

Complete disappearance of free energy barriers

Many enhanced sampling ("flat histogram") methods aim to achieve such a bias potential

but, generally not optimal

- ➡ spend a lot of time sampling irrelevant regions high in free energy
- ➡ better to just enhance CV fluctuations with a finite value of γ

Constructing the Bias Potential

However cannot use directly

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

as it depends on the FES $F(\mathbf{s})$ which is the very quantity we want to obtain

Can instead iteratively on the fly build a bias potential that in the long-time limit gives this solution

Metadynamics

Laio and Parrinello, Proc. Natl. Acad. Sci. U.S.A. 2002,

Barducci, Bussi, and Parrinello, Phys. Rev. Lett. 2008

Variationally Enhanced Sampling

Valsson and Parrinello, Phys. Rev. Lett. 2014

General Requirements on CVs

The CVs that are biased must generally:

- be few in number (~1-3)
  although there some extensions that allow for overcoming this
- have continuous derivatives
  technical requirement for MD to have continuous forces
- distinguish all the relevant metastable states
- include all slow modes of the system
  not always possible, but there are ways to tackle this

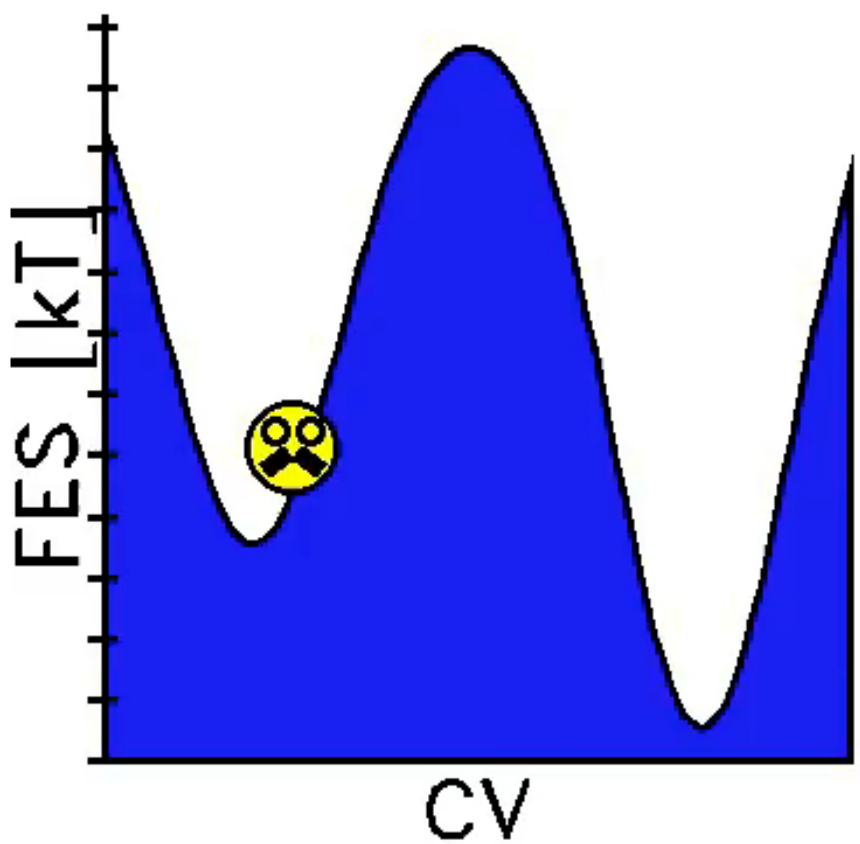
Metadynamics

Metadynamics

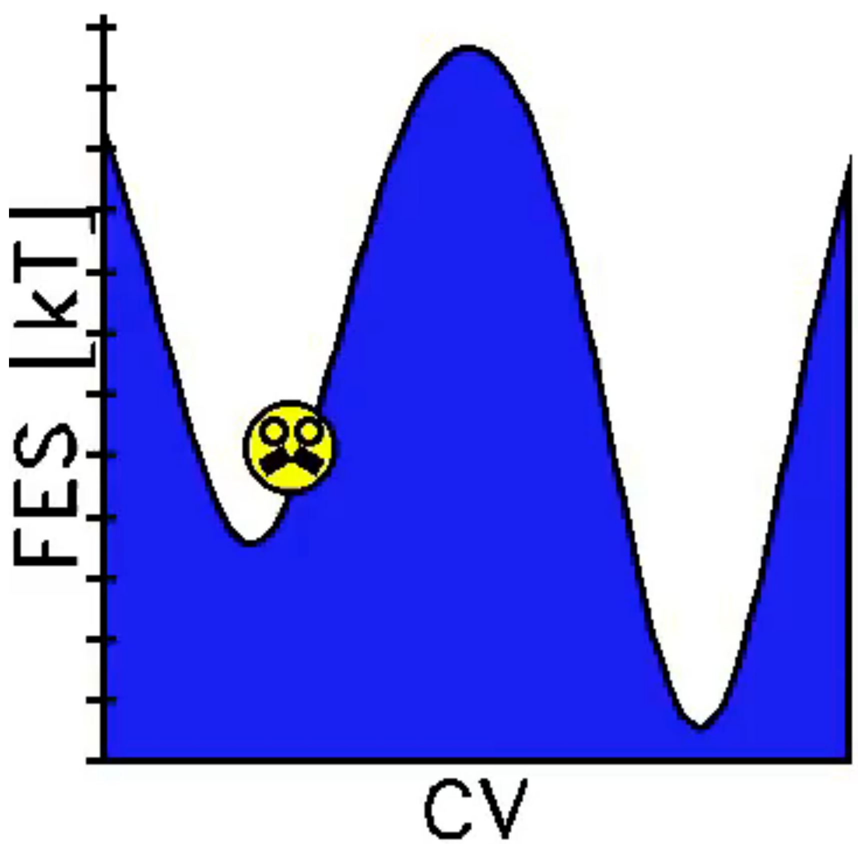
Deposit repulsive Gaussian biasing kernels everywhere you go in CV space

➡ pushes you over the barriers

Unbiased Molecular Dynamics



Metadynamics



Movies from Giovanni Bussi

Well-Tempered Metadynamics

Iteratively builds a bias by periodically updating it according to

$$V_n(\mathbf{s}) = V_{n-1}(\mathbf{s}) + G(\mathbf{s}, \mathbf{s}_n)\ \exp\left[-\frac{1}{\gamma - 1}\,\beta V_{n-1}(\mathbf{s}_n)\right]$$

where

$$G(\mathbf{s}, \mathbf{s}_n) = W_0 \exp\left(-\sum_i^d \frac{(s_i - s_{n,i})^2}{2\sigma_i^2}\right)$$

is a Gaussian biasing kernel of height W_0 that is centered at the current CV location $\mathbf{s}_n = (s_{n,1}, s_{n,2}, \ldots, s_{n,d})$ and scaled by

$$\exp\left[-\frac{1}{\gamma - 1}\,\beta V_{n-1}(\mathbf{s}_n)\right]$$

Well-Tempered Metadynamics

The update is performed every N_G steps

between updating steps n and $n+1$ the bias reads

$$V_n(\mathbf{s}) = \sum_{k=1}^{n} W_k \exp\left(-\sum_i \frac{(s_i - s_{k,i})^2}{2\sigma_i^2}\right)$$

where W_k is the Gaussian height for the Gaussian deposited at step k

$$W_k = W_0 \exp\left[-\frac{1}{\gamma - 1}\,\beta V_{k-1}(\mathbf{s}_k)\right].$$

Well-Tempered Metadynamics

The scaling factor in the update

$$V_n(\mathbf{s}) = V_{n-1}(\mathbf{s}) + G(\mathbf{s}, \mathbf{s}_n)\ \exp\left[-\frac{1}{\gamma - 1}\,\beta V_{n-1}(\mathbf{s}_n)\right]$$

decreases to zero as $1/n$

$$\exp\left[-\frac{1}{\gamma - 1}\,\beta V_{n-1}(\mathbf{s}_n)\right] \sim \frac{1}{n}$$

The bias thus reaches a quasi-stationary state (i.e. does not change with time), this is important for reweighting

Well-Tempered Metadynamics

Can be rigorously proven that in the long-time limit the bias fulfills

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

constant independent of $\mathbf{s}$

$$\Downarrow$$

$$P_V(\mathbf{s}) \propto [P(\mathbf{s})]^{1/\gamma}$$

thus, in the long time limit we obtain the well-tempered distribution

furthermore, can directly obtain the FES from the constructed bias

Well-Tempered Metadynamics - Reweighting

Need to account for time-dependence of bias when reweighting

$$P(\mathbf{R},t) = P_V(\mathbf{R})\, e^{\beta[V(\mathbf{s}(\mathbf{R}),t)-c(t)]}$$

$$\langle O(\mathbf{R})\rangle = \left\langle O(\mathbf{R}) e^{\beta[V(\mathbf{s}(\mathbf{R}))-c(t)]} \right\rangle_V$$

where the time-dependent constant $c(t)$ is calculated as[a]

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

valid when the bias has reached a quasi-stationary state

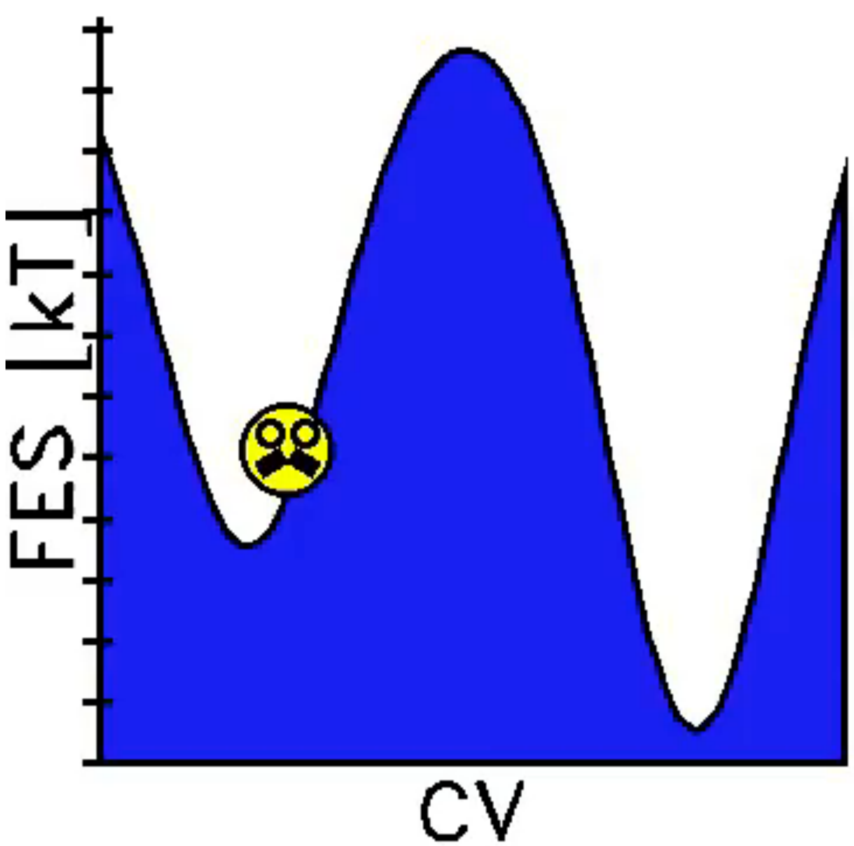
[a]Tiwary and Parrinello, JPCB, 2014

Metadynamics

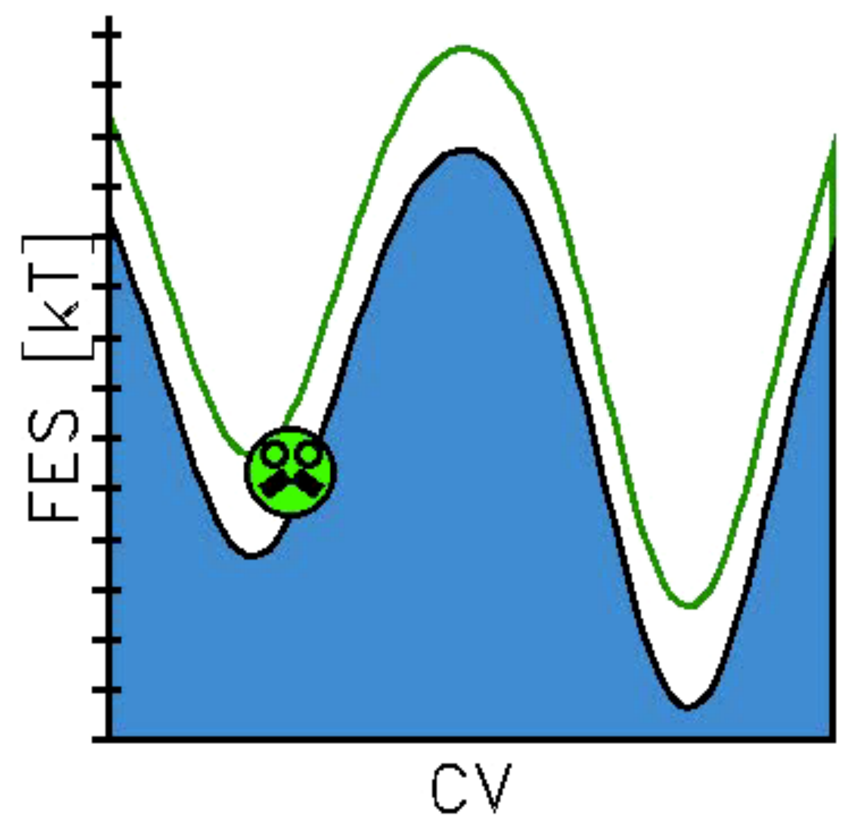
In the original version of Metadynamics the biasing kernel was not scaled this corresponding to the $\gamma \rightarrow \infty$ limit and $V(\mathrm{s}) = -F(\mathrm{s})$ (flat histogram)

However, hard to converge

Original Metadynamics



Well-Tempered Metadynamics

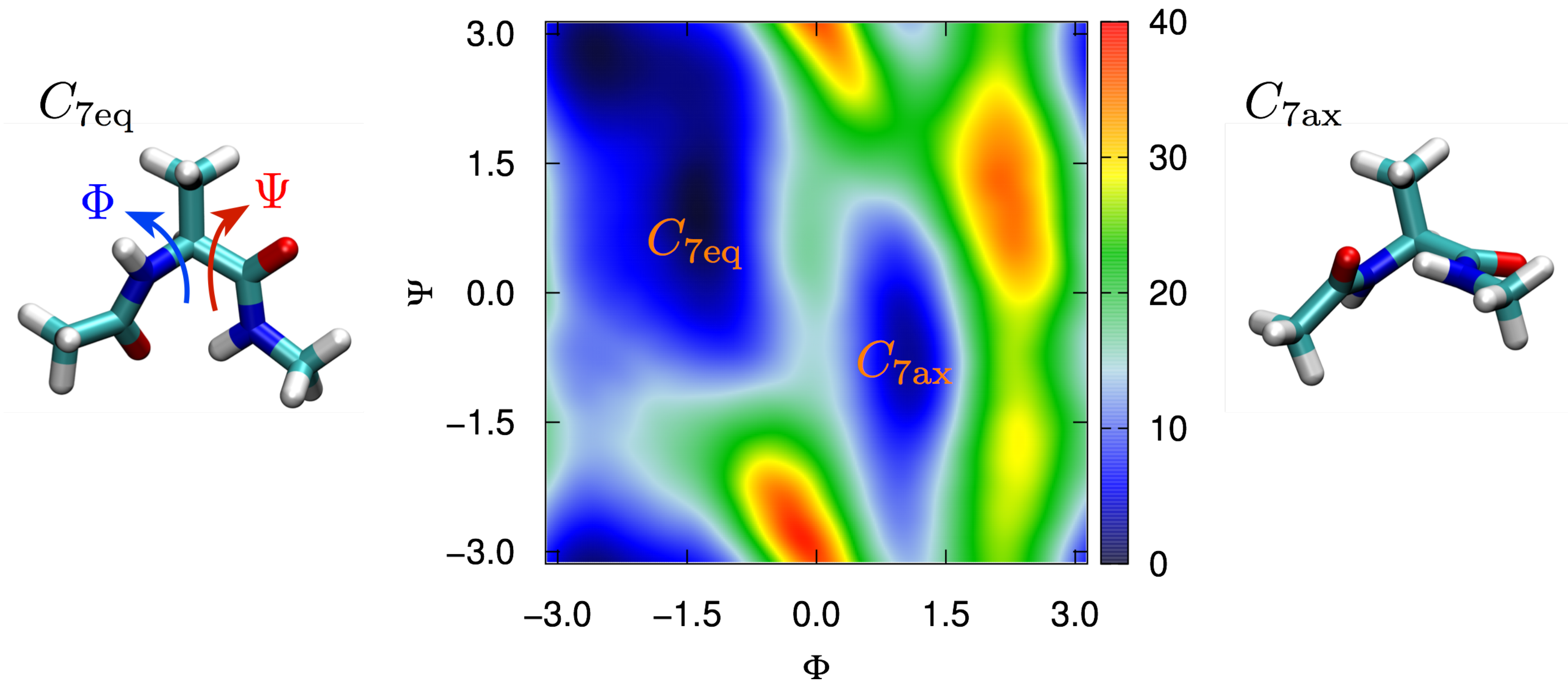


Convergence greatly improved by the well-tempered version described here

Movies from Giovanni Bussi

Exemplifying System - Alanine Dipeptide

Alanine dipeptide in vacuum - Backbone dihedral angles Φ, Ψ as CVs

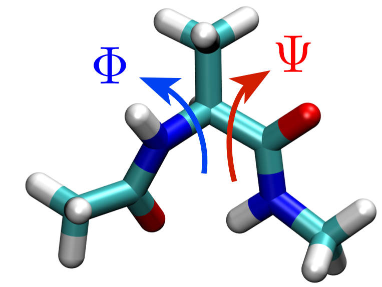


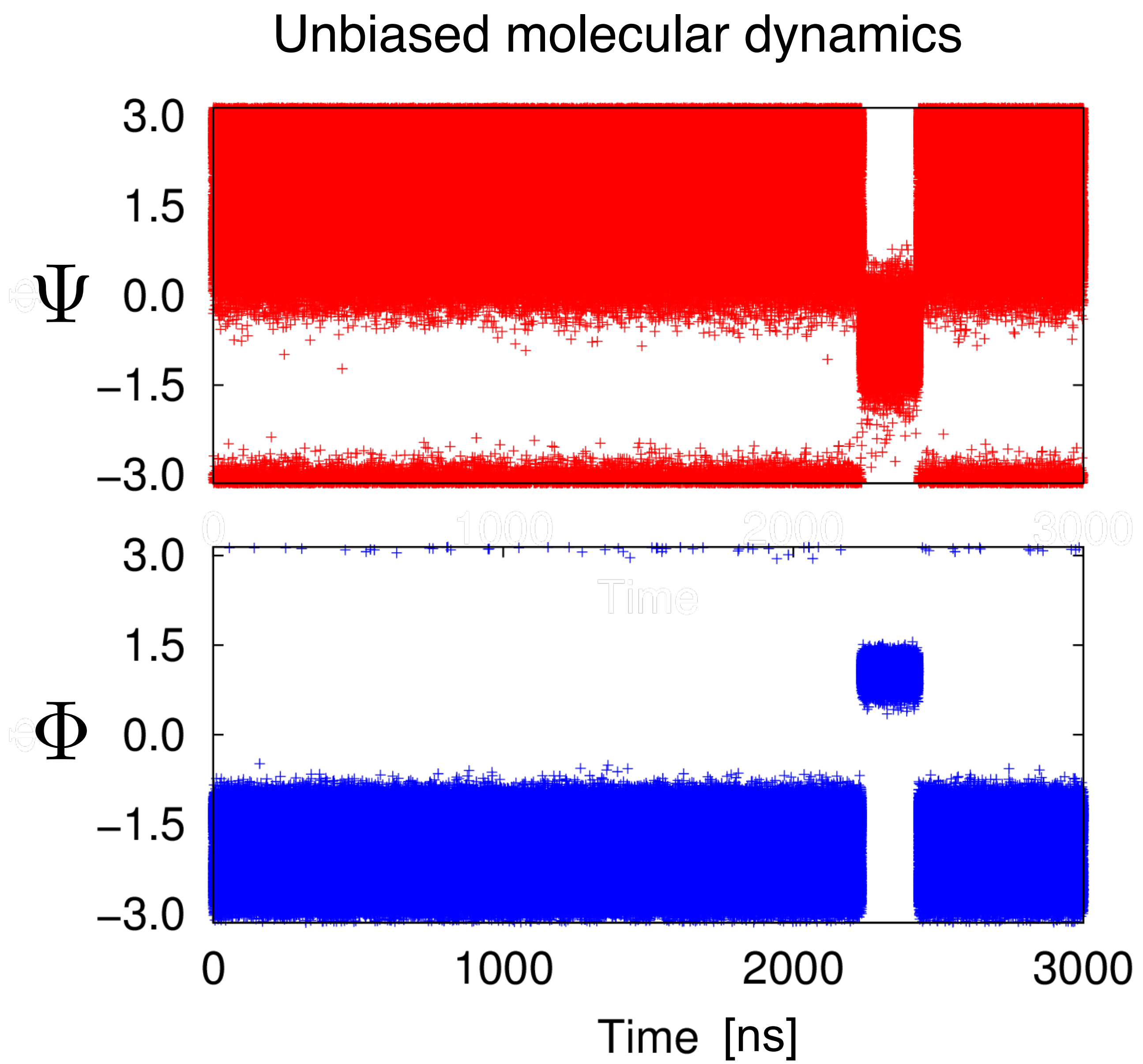
Two metastable basins, C_{7eq} and C_{7ax}

barrier around 34 kJ/mol (16 $k_{\mathrm{B}}T$)

mean transition time around 28 μs

Exemplifying System - Alanine Dipeptide





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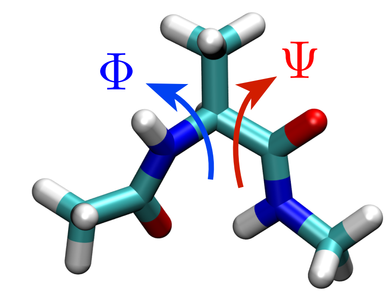
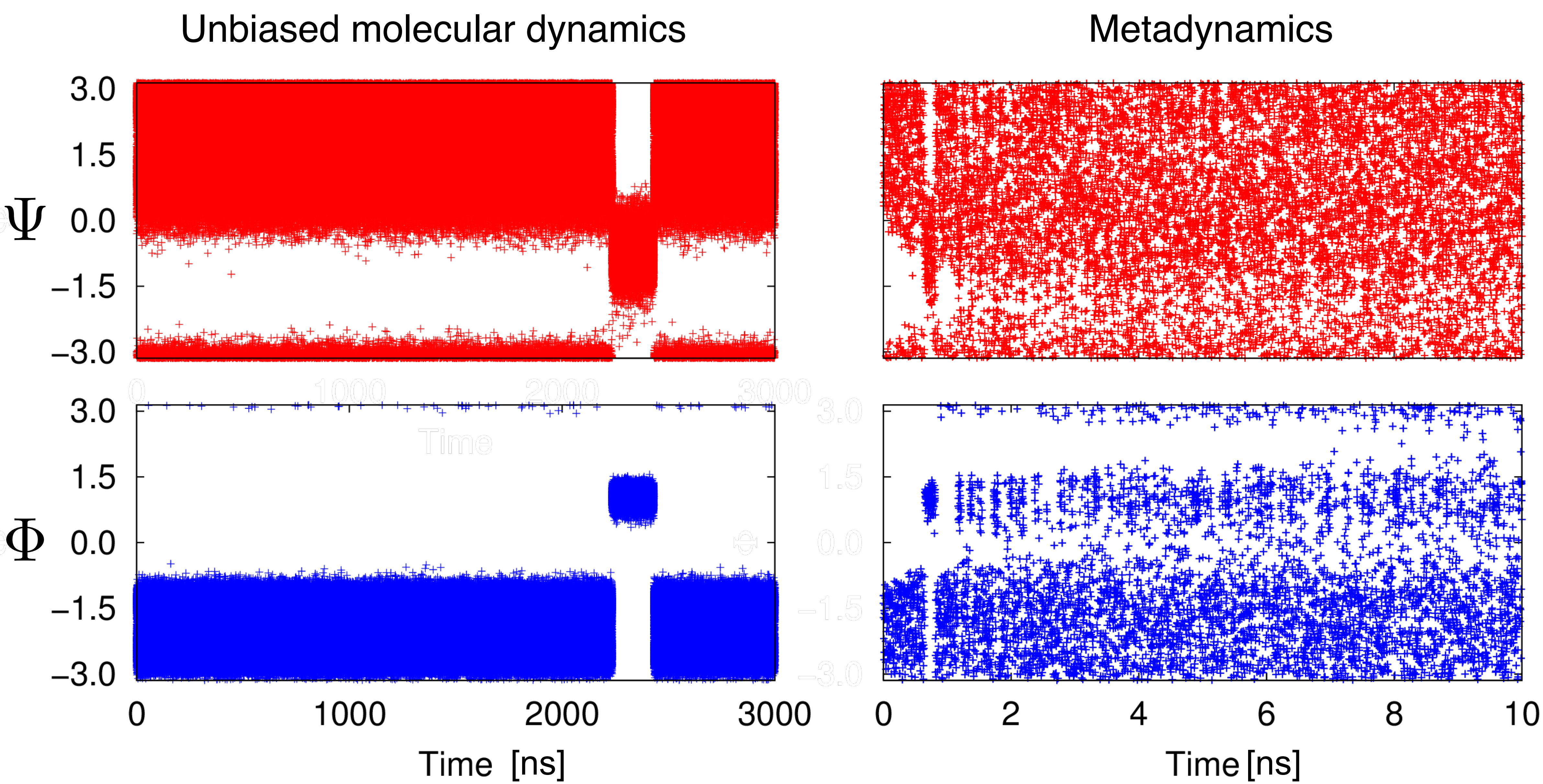
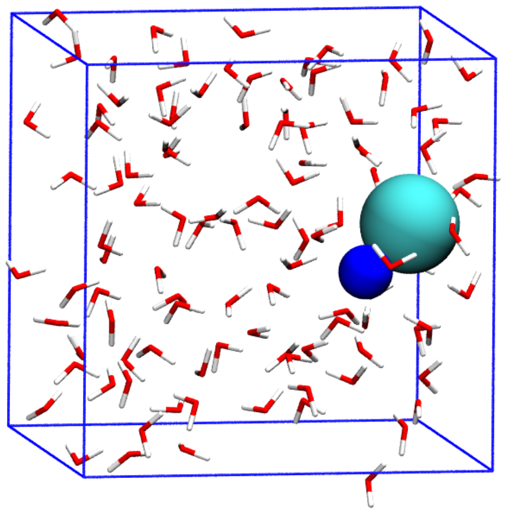




Note the difference of 300 in the time scale!

Metadynamics Reweighting

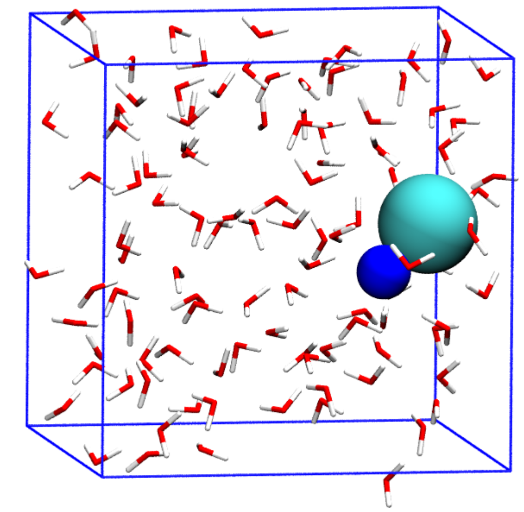


Can use reweighting to obtain FESs for CVs not biased

Example: association/dissociation of NaCl in acqueous solution
(from a tutorial in the VES code, see later)

Biased CV: Na-Cl distance

Metadynamics Reweighting

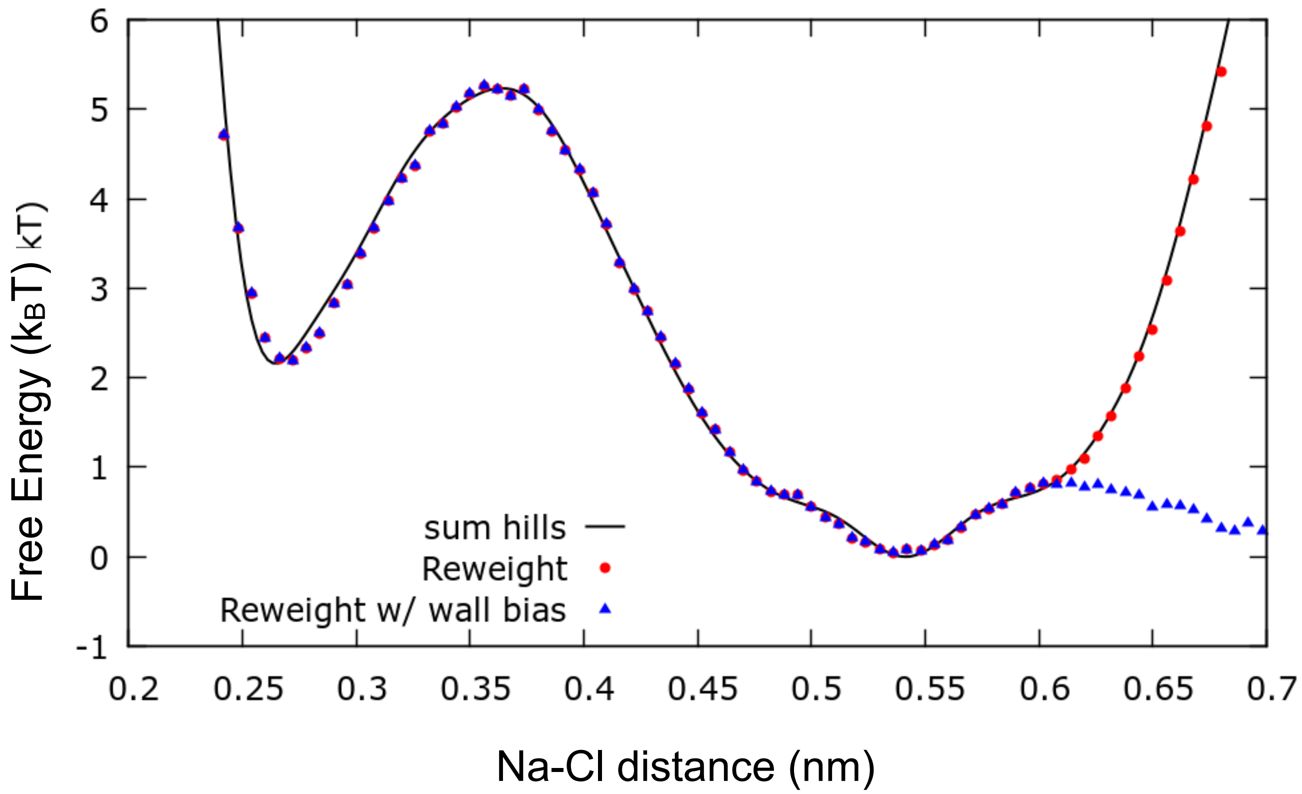


Can use reweighting to obtain FESs for CVs not biased

Example: association/dissociation of NaCl in acqueous solution
(See later in tutorial)

Biased CV: Na-Cl distance

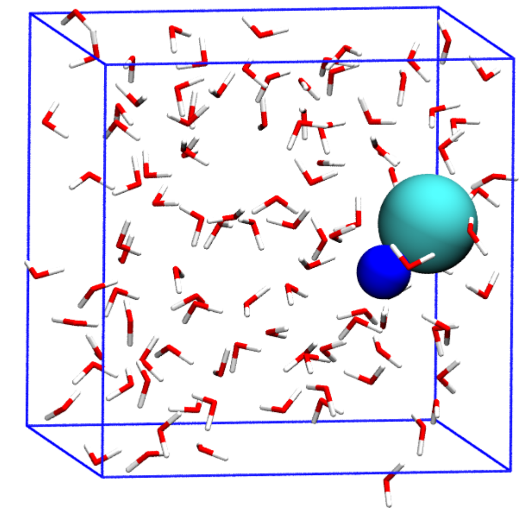
FES for Na-Cl distance



Reweighting can also be used to check the results,
or to correct for the usage of constrains

Metadynamics Reweighting

Can use reweighting to obtain FESs for CVs not biased



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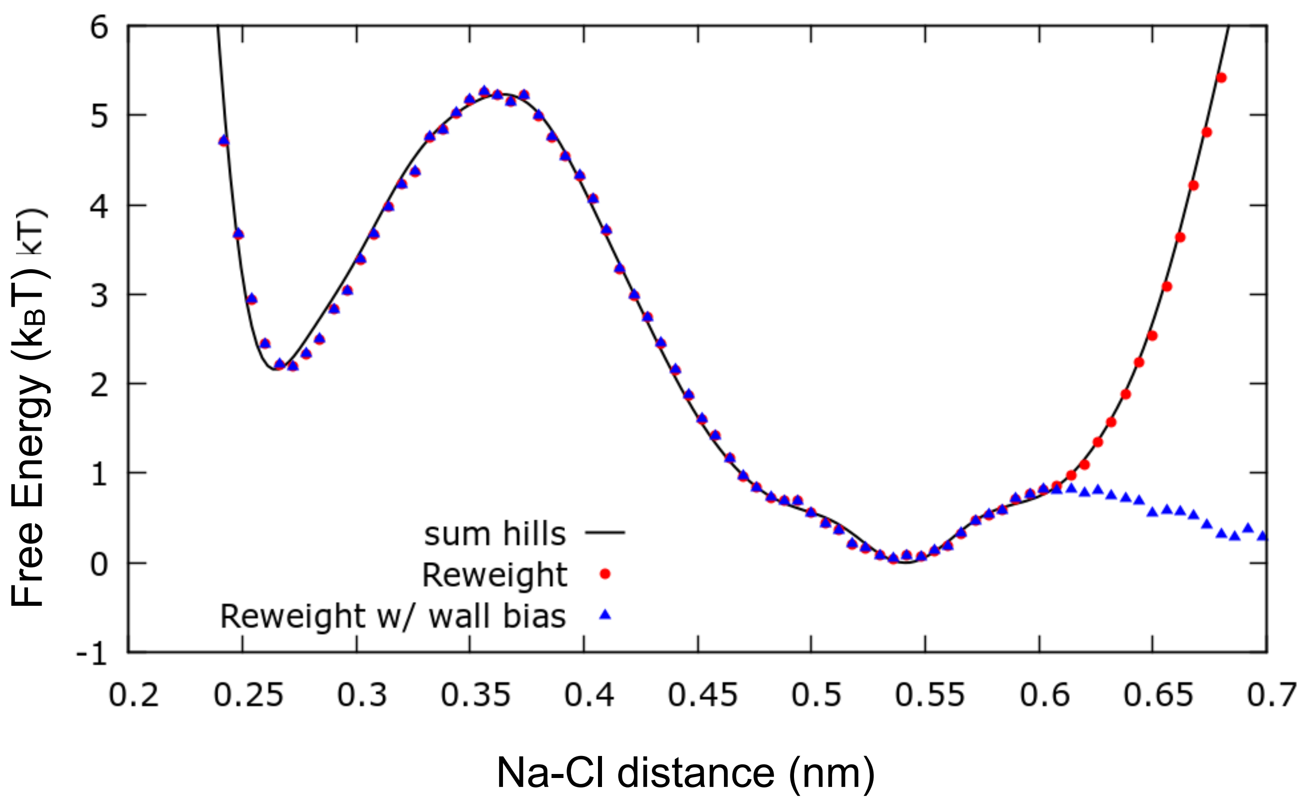
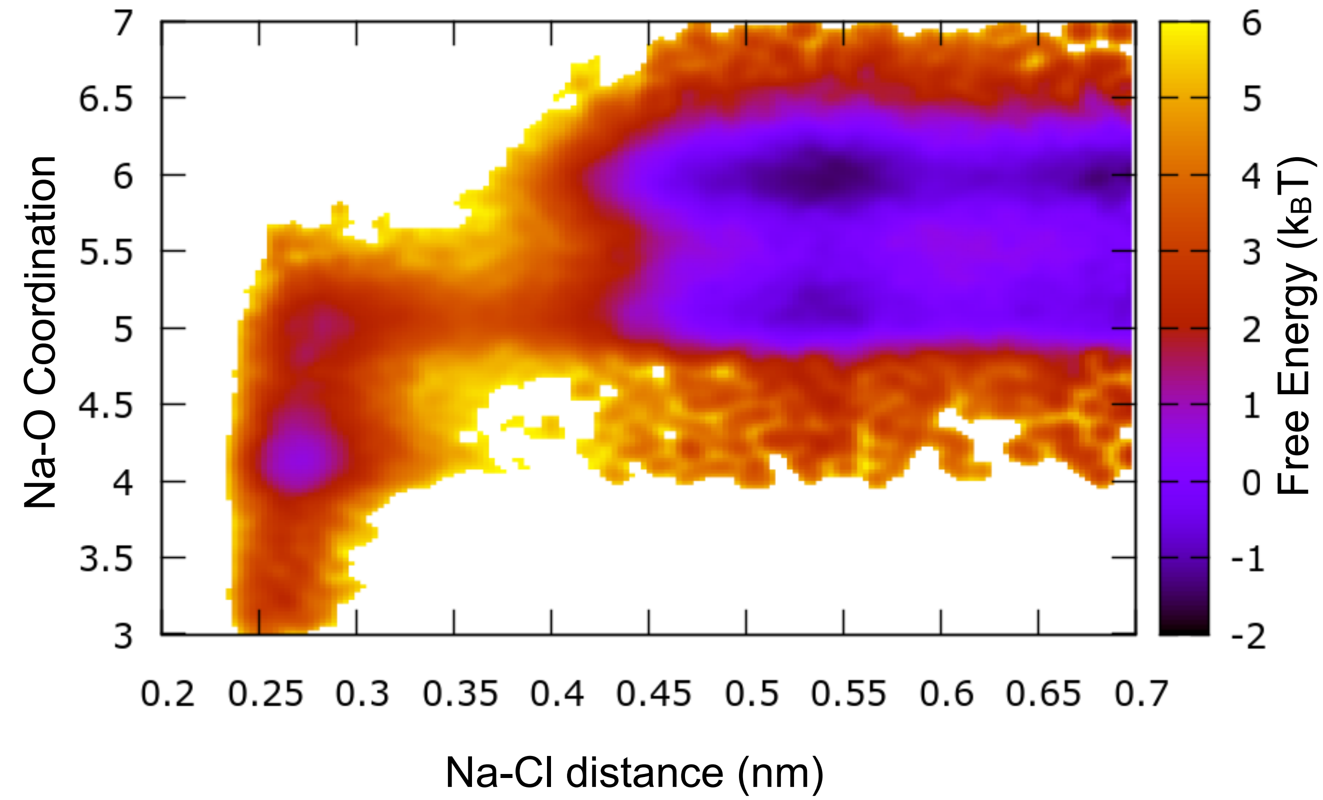


FES for Na-Cl distance + Na-O Coordination



Reweighting can also be used to check the results,
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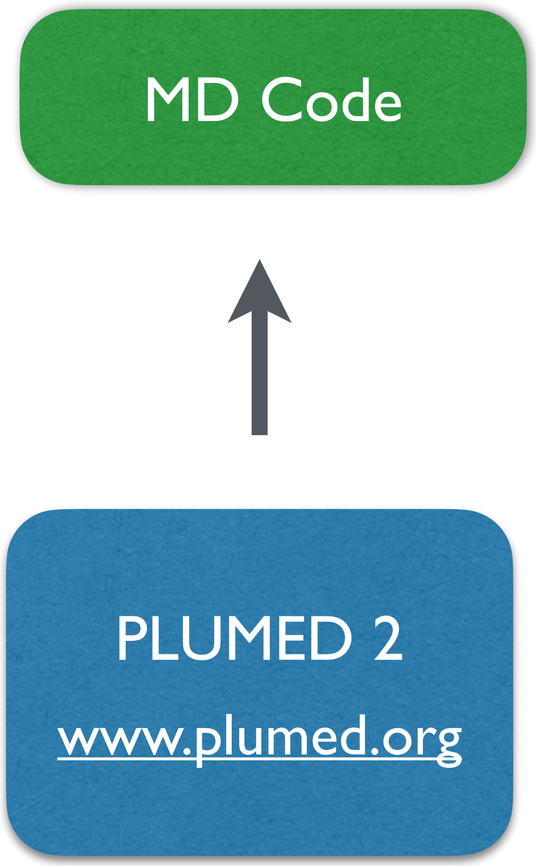
Extensions of Metadynamics

- Parallel-Tempering MetaD
  Helps sampling missing slow CVs
- Well-Tempered Ensemble
  Can be used to reduce the number of replicas needed for parallel-tempering
- Bias Exchange MetaD
  Employ many CVs via replica exchange strategy
- Parallel-Bias MetaD
  Employ many CVs within one replica via 1D potentials
- Multiple Walkers MetaD
  Shared bias between multiple copies, reduces human time needed for convergence
- Adaptive Gaussians MetaD
  Gaussian whose shape adapt to the FES
- Infrequent MetaD for obtaining kinetics
  Obtain kinetics of rare event from biased simulations

See Ann. Rev. Phys. Chem. 2016, 67:159-84 for further information and original references

PLUMED



e.g. Gromacs, LAMMPS, CP2K, OpenMM, …

PLUgin for **M**ol**E**cular **D**ynamics (open source)

wide range of collective variables available

metadynamics, umbrella sampling, steered MD, …

easy to use, extensive tutorials, …

Well-Tempered Metadynamics

the input parameters for a metadynamics simulations are

N_G	how often we deposit Gaussians
W_0	the initial Gaussian height
γ	bias factor
σ_i	width (standard deviations) of deposited Gaussians

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Well-Tempered Metadynamics

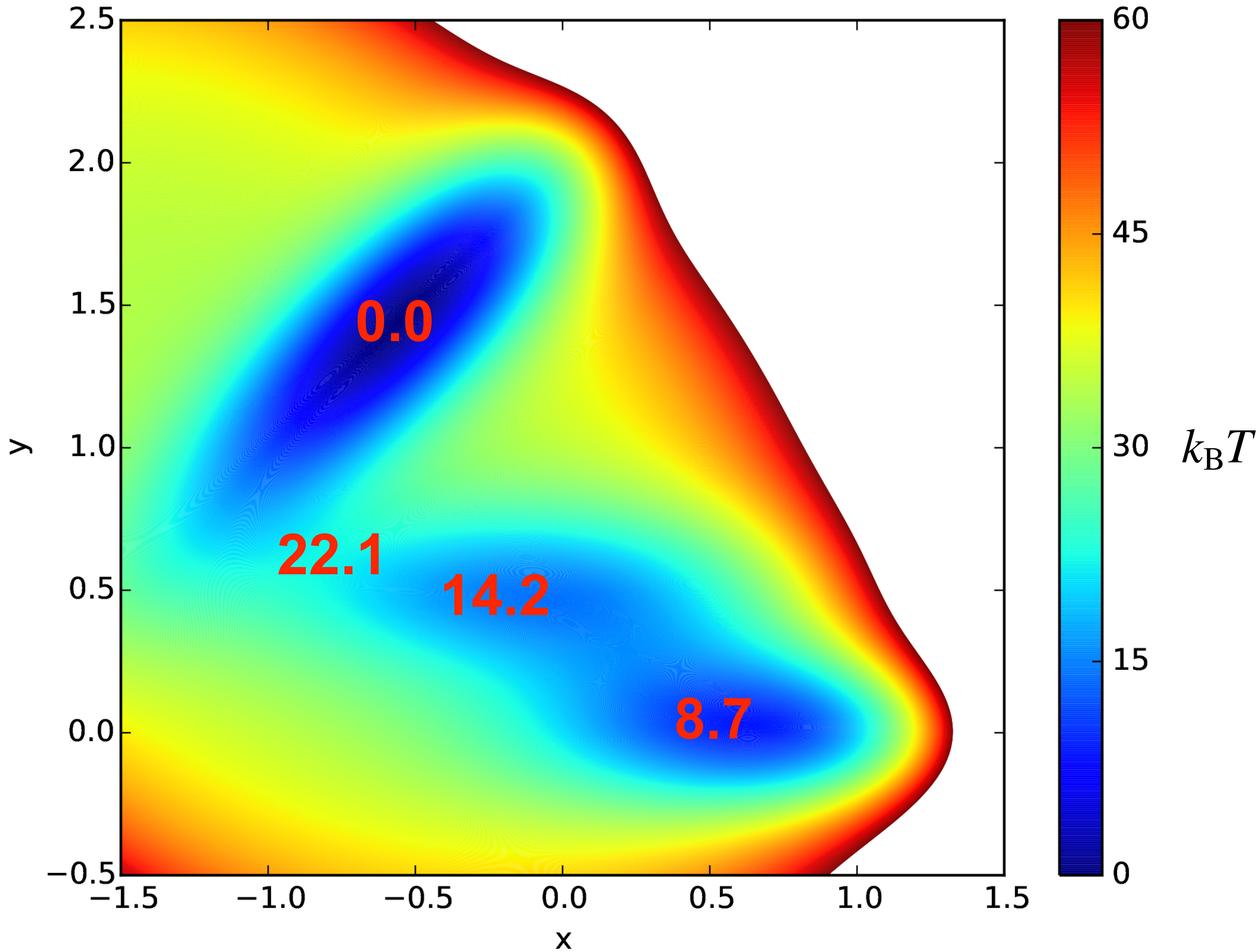
typical values

N_G	~ 500-1000 steps for molecular dynamics simulation ~ 1-10 steps for Monte Carlo simulation if each MC move is not too “small”
W_0	fraction or around $k_{\mathrm{B}}T$, e.g. 0.1*$k_{\mathrm{B}}T$ to 1.0*$k_{\mathrm{B}}T$
γ	ideally a value that makes the effective free energy barriers to be on the order of few $k_{\mathrm{B}}T$ too low value will not enhance the sampling enough while too large value will lead to slow convergence
σ_i	on the order of the fluctuation (i.e. standard deviations) of the CVs observed in unbiased simulations, e.g. 0.5-1.0 of the unbiased fluctuations

Exemplifying System - Mueller Brown Potential

One particle on a two-dimensional potential energy surface

$$U(x,y) = \sum_{i=1}^{4} A_i \, \exp\left[a_i(x-x_0)^2 + b_i(x-x_0)(y-y_0) + c_i(y-y_0)^2\right] + C_0$$

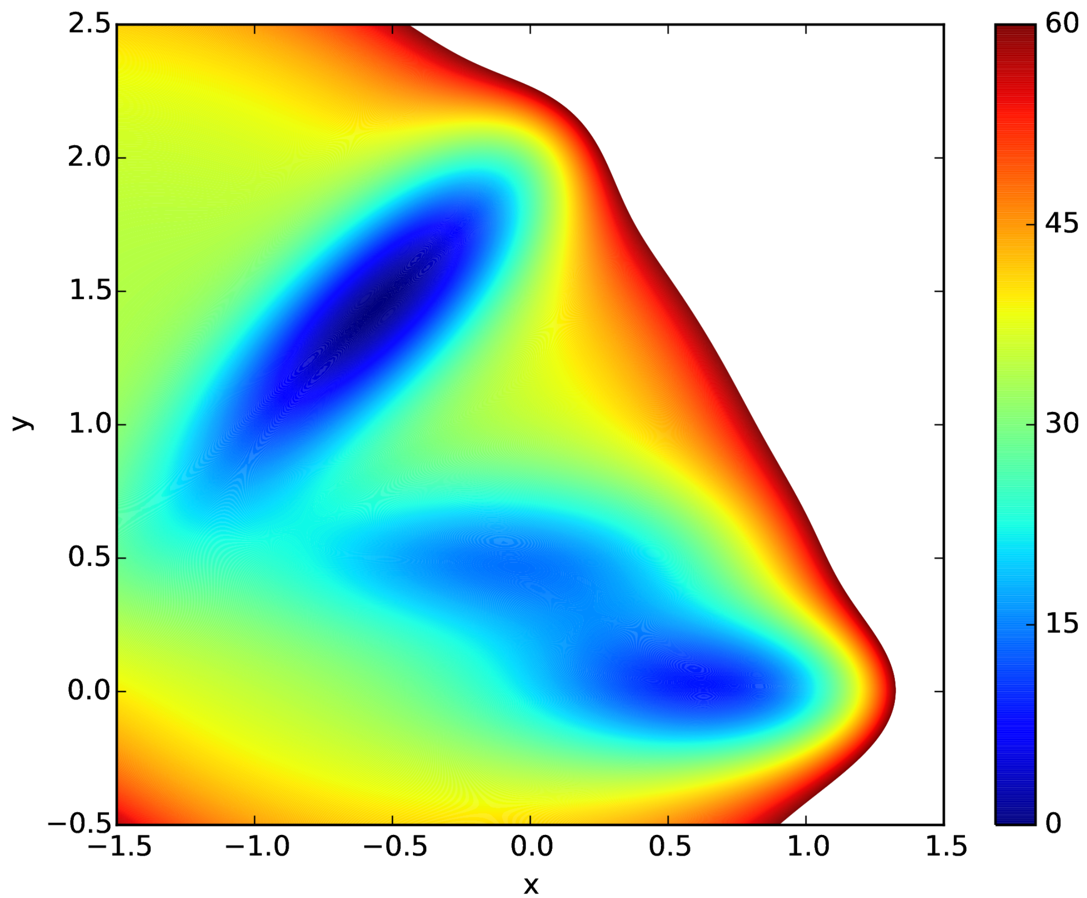


Exemplifying System - Mueller Brown Potential

$$F(\mathbf{s}) = -\frac{1}{\beta}\log\int d\mathbf{R}\,\delta\left[\mathbf{s}-\mathbf{s}(\mathbf{R})\right]\,e^{-\beta U(\mathbf{R})}$$

x and y as CVs ➡ the FES is just given by $U(x,y)$

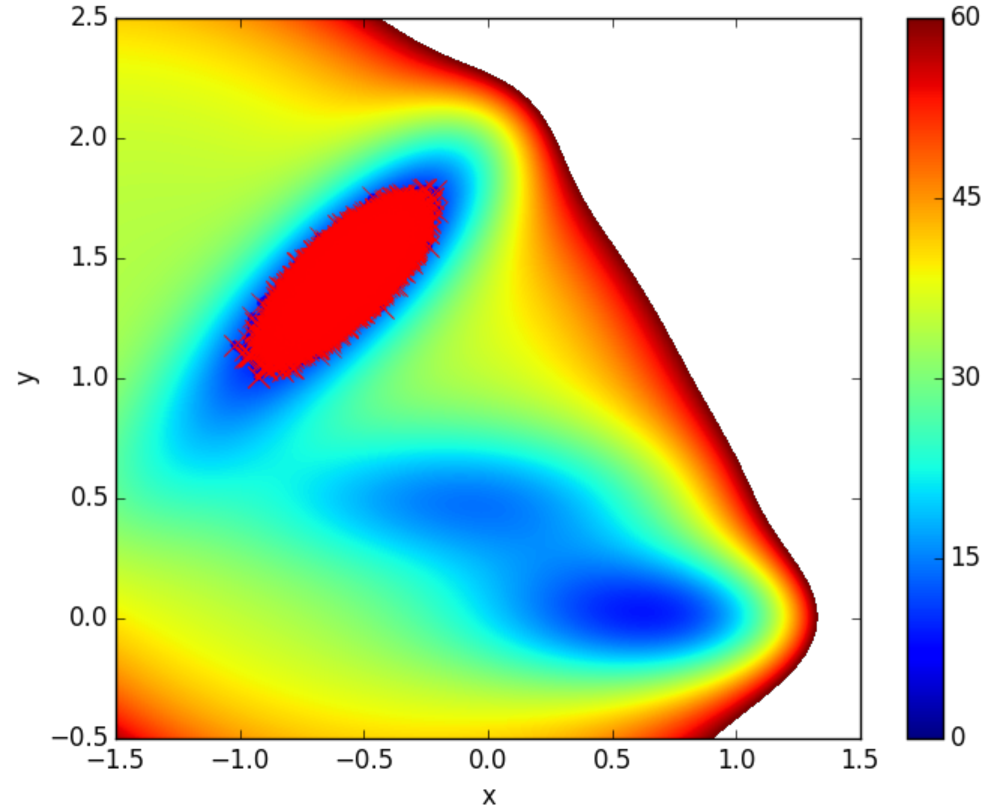
$$F(x,y) = U(x,y)$$

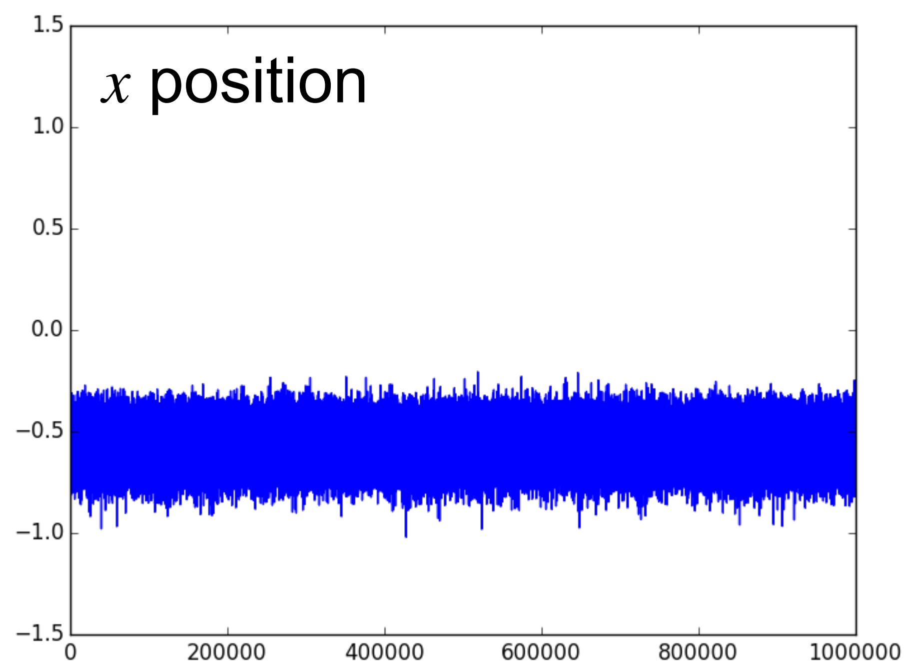


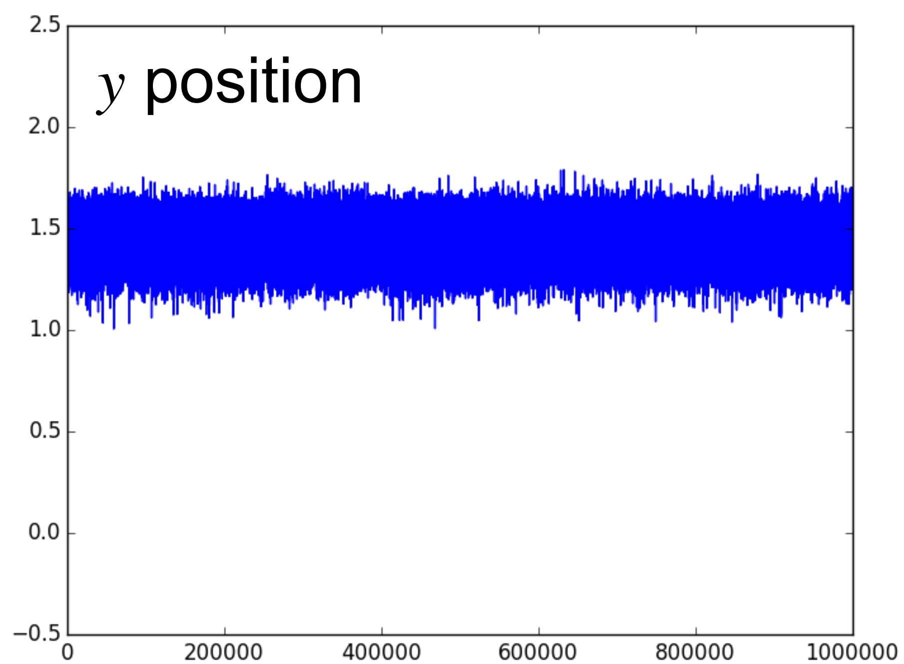
Unbiased Monte Carlo Simulations

Unable (or rare) to cross barriers in unbiased MC simulations

10^6 MC step







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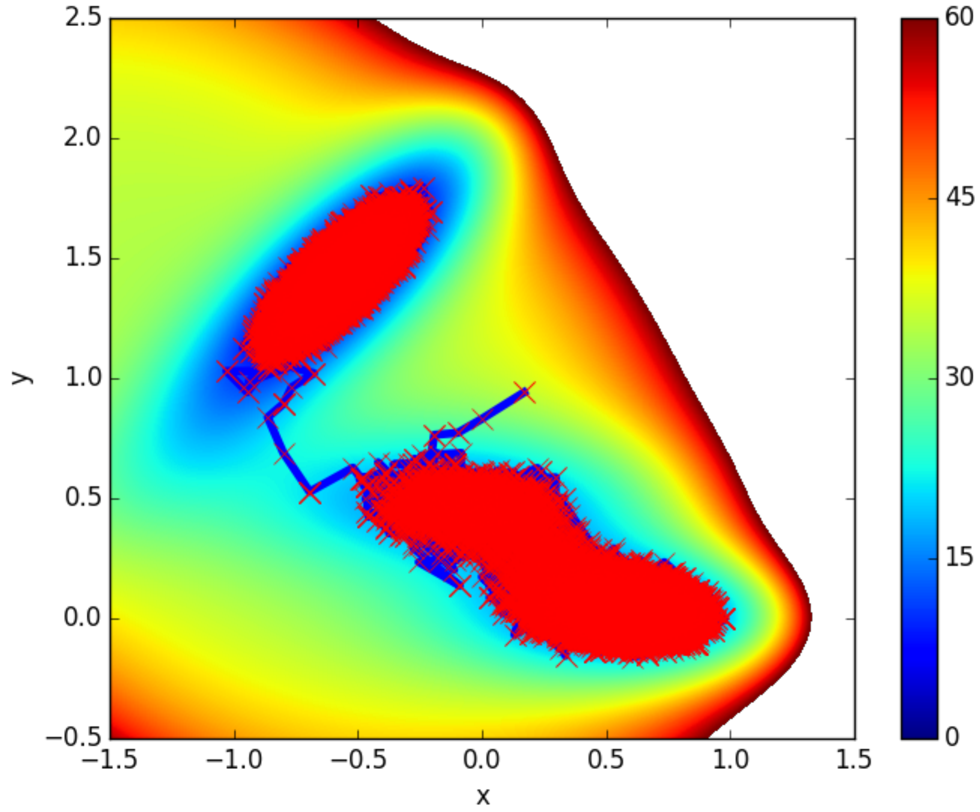
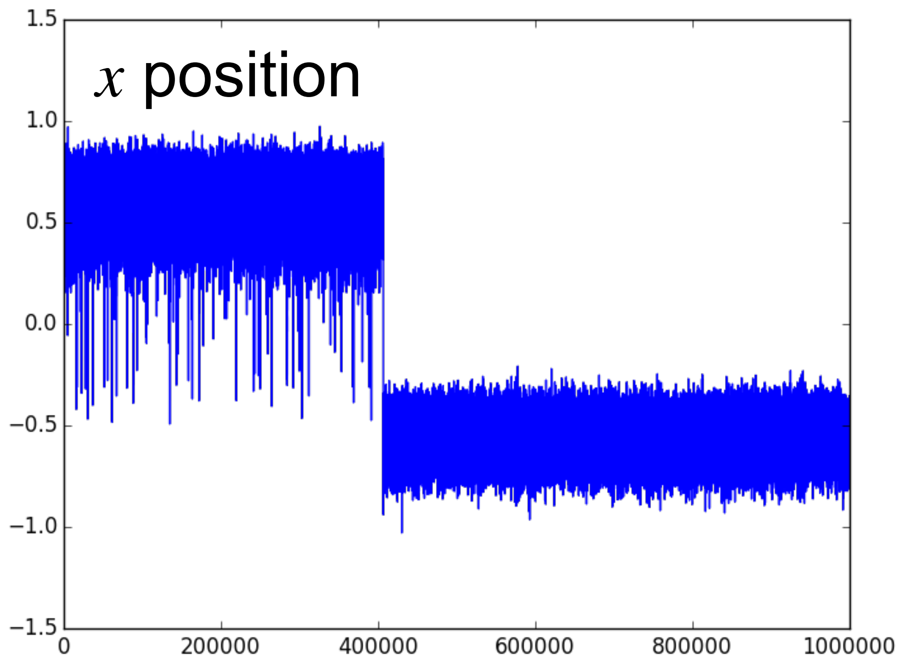
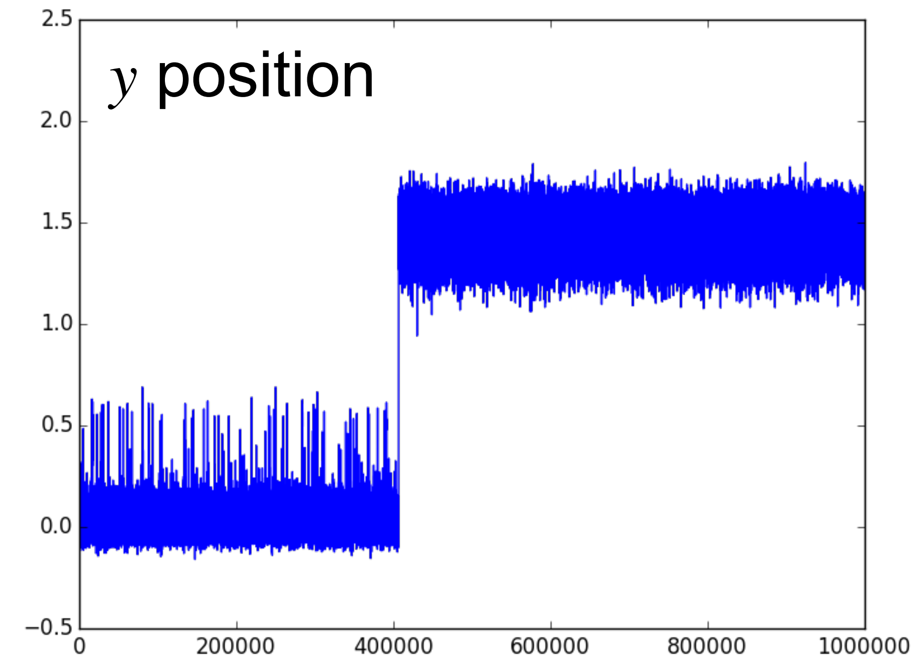


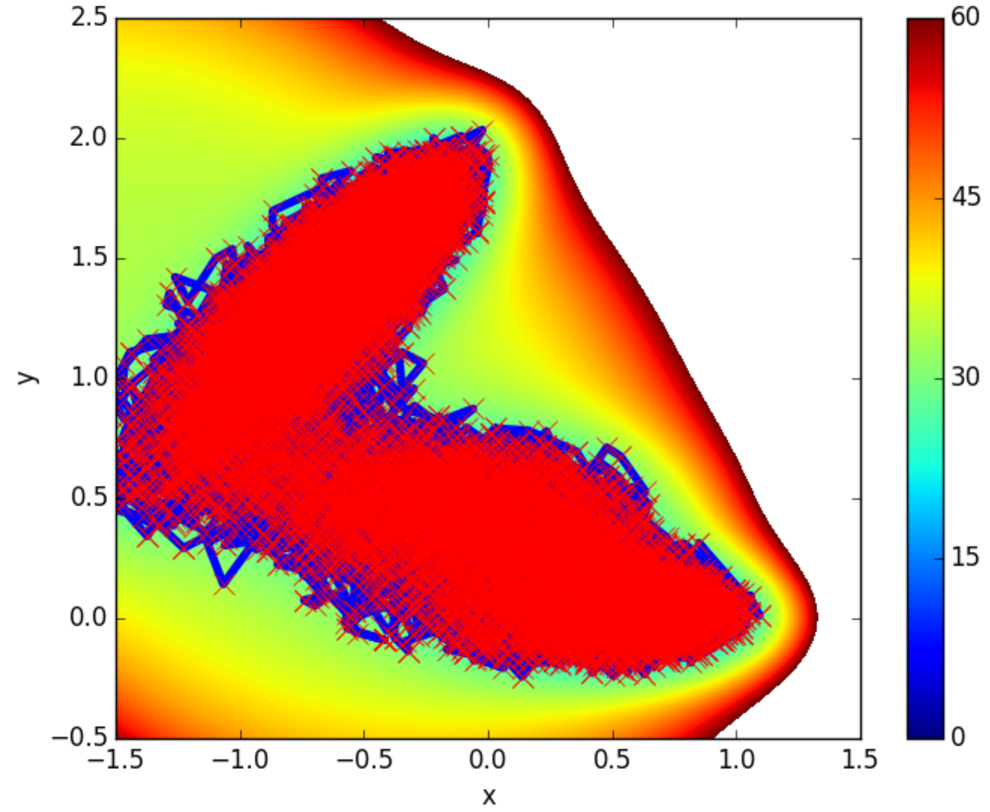
10^6 MC step





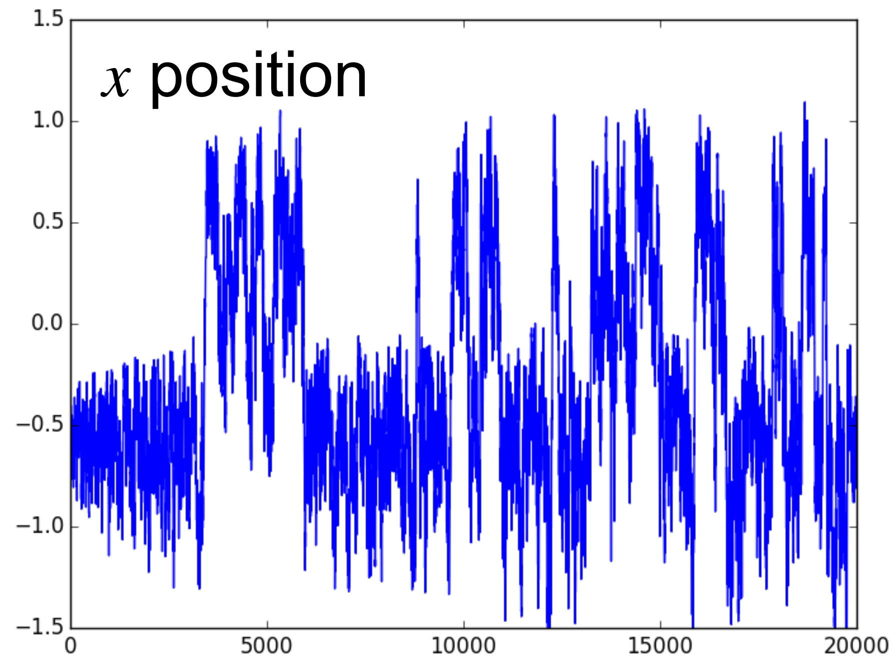
Metadynamics Simulations

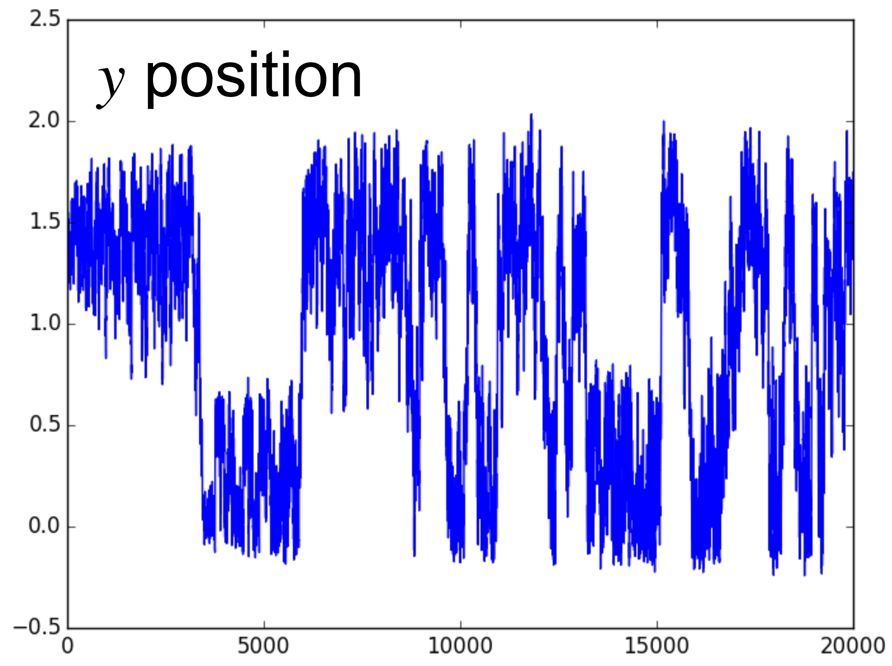
Greatly enhanced barrier crossings with Metadynamics



2*10^4 MC step

much less than for the unbiased run before!



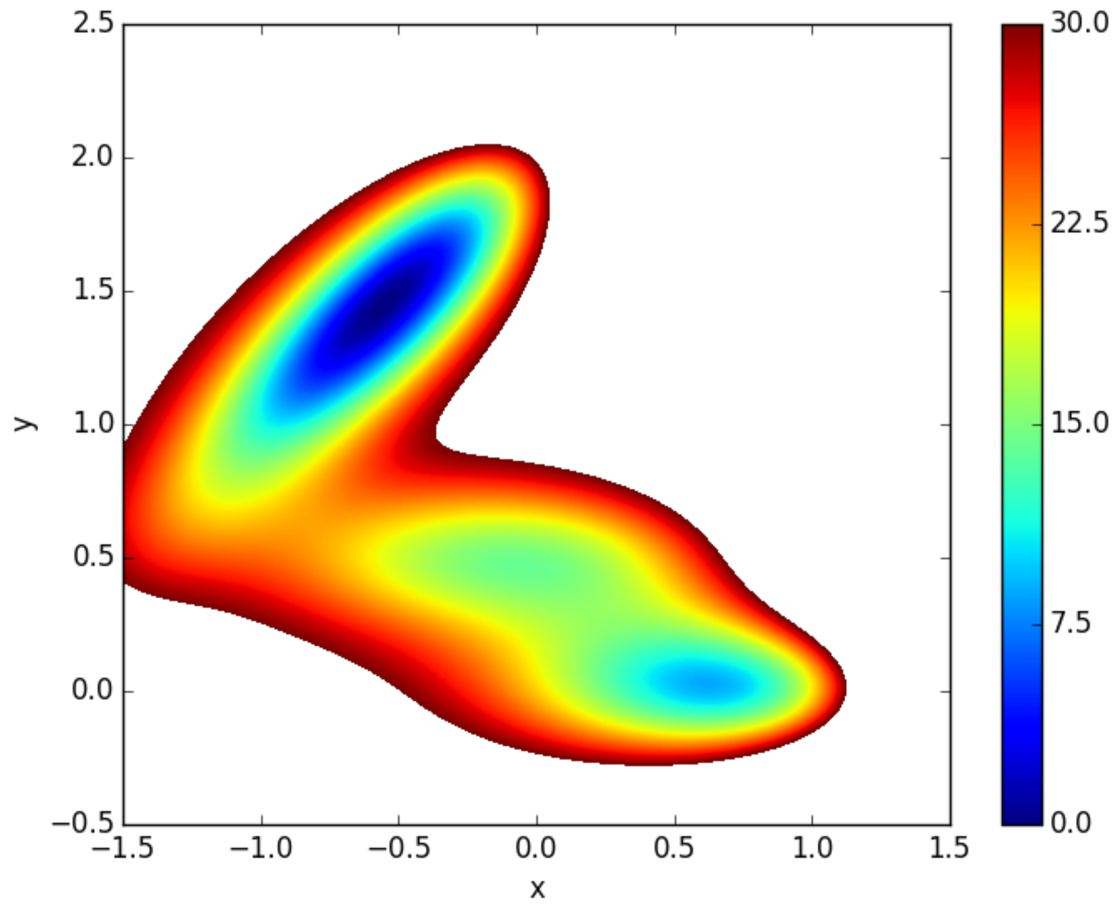


Metadynamics Simulations

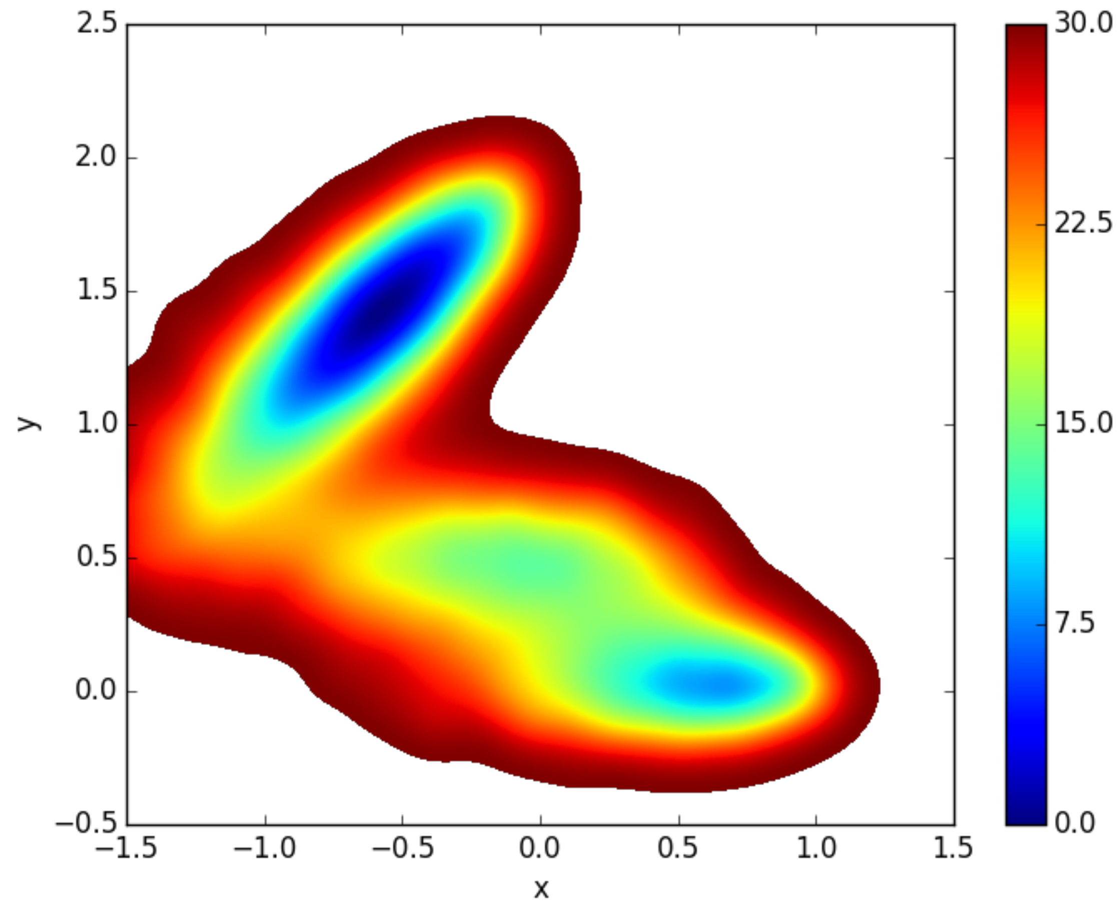
FES/PES from Metadynamics in good agreement with the exact potential

2*10^4 MC step

Exact Potential

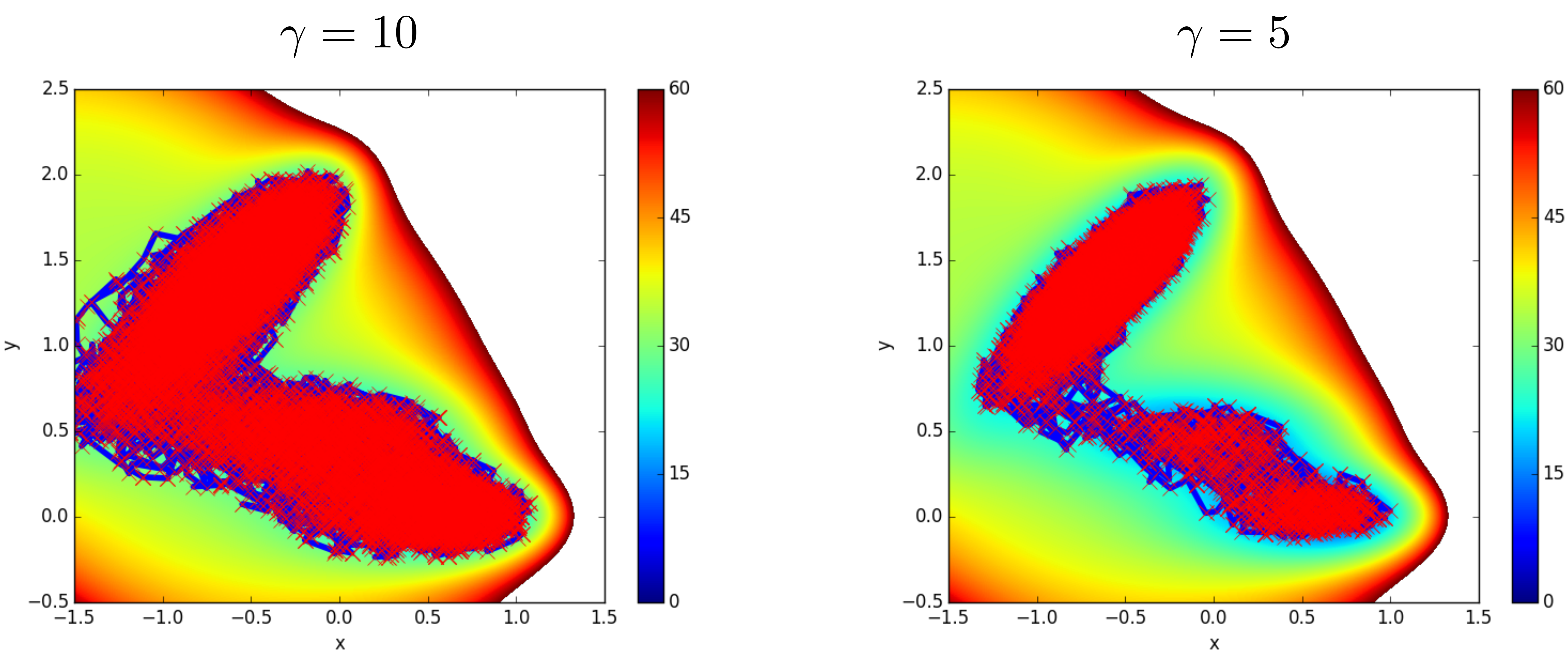


Estimate from Metadynamics



Metadynamics Simulations

Effect of the bias factor



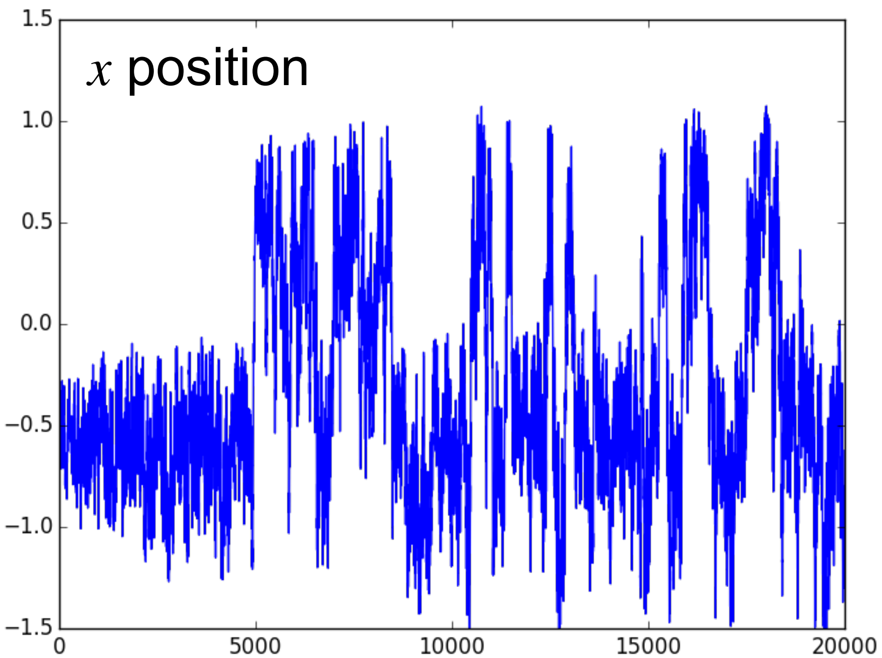
Metadynamics Simulations

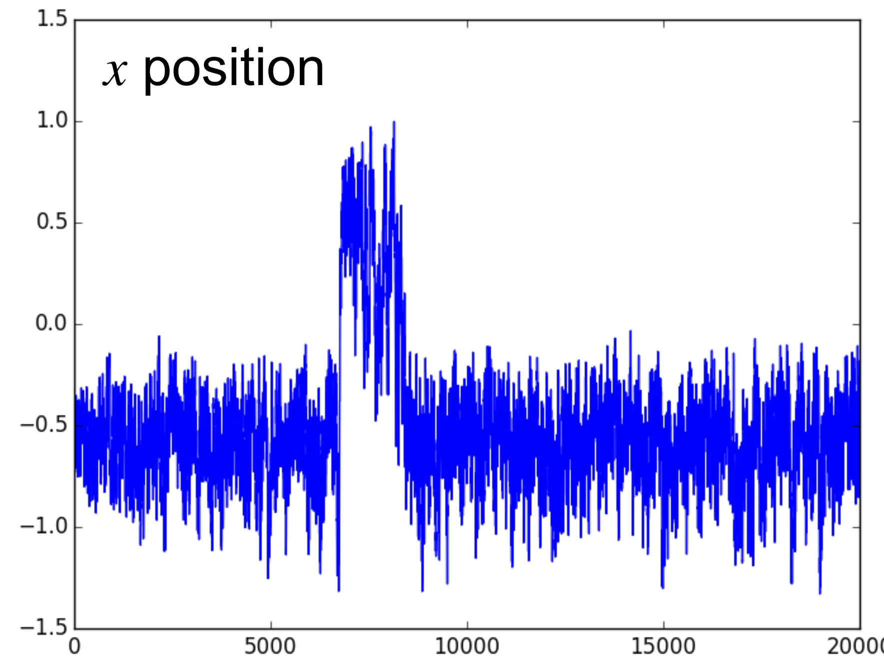
Effect of the bias factor

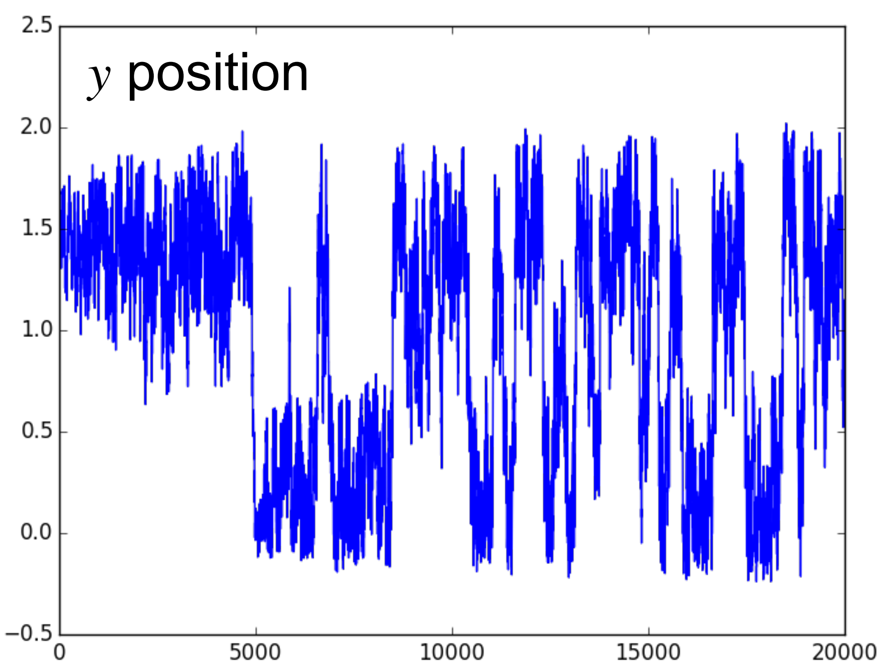
value of 5 not sufficient to overcome barriers

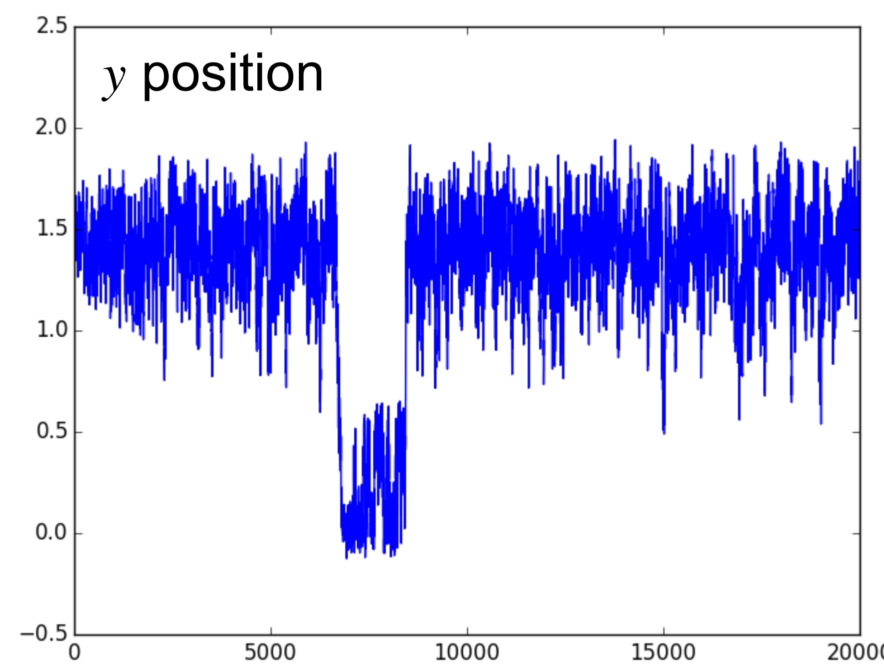
$$\gamma = 10$$

$$\gamma = 5$$

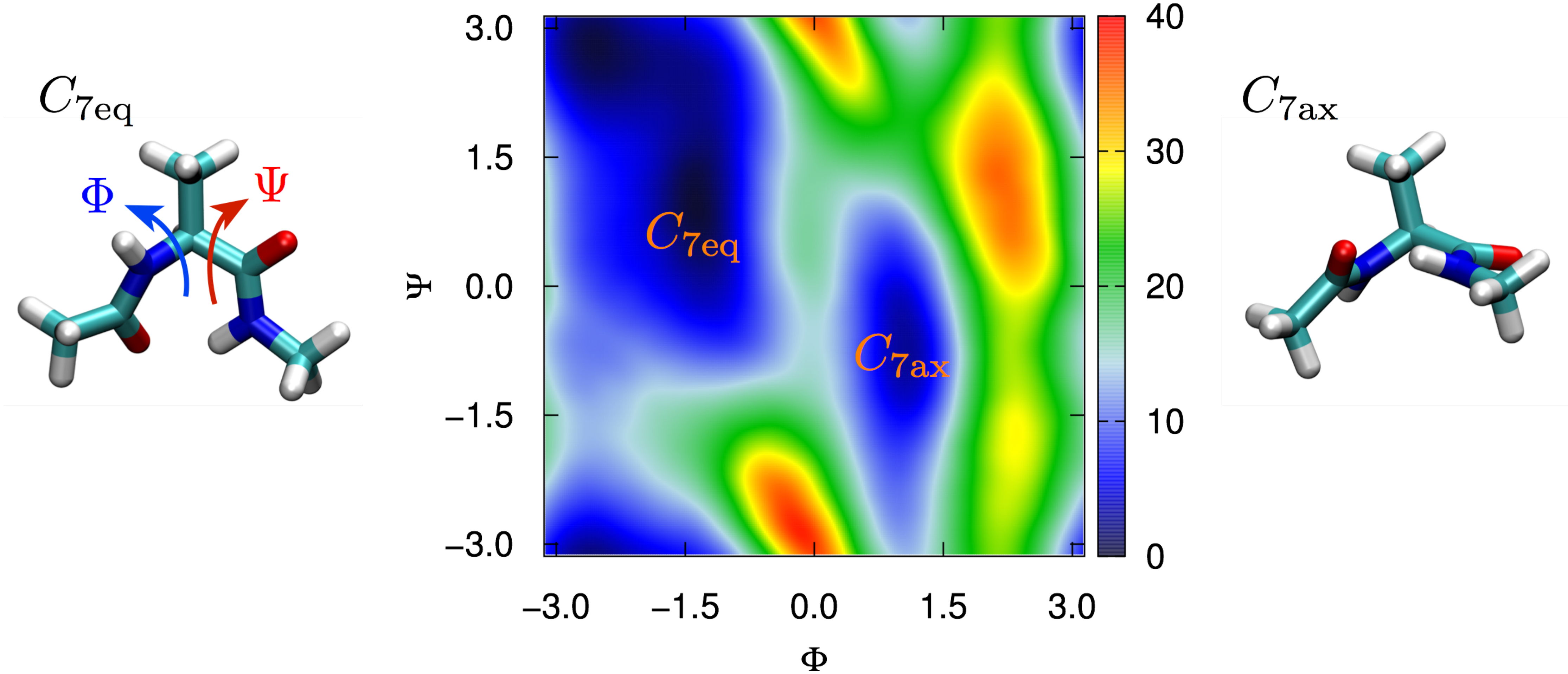








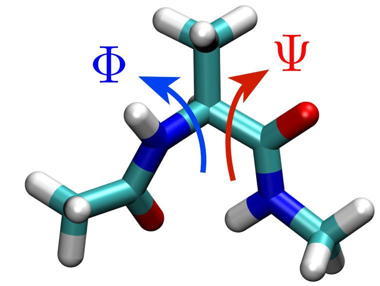
Missing Slow CVs



Ψ fast CV

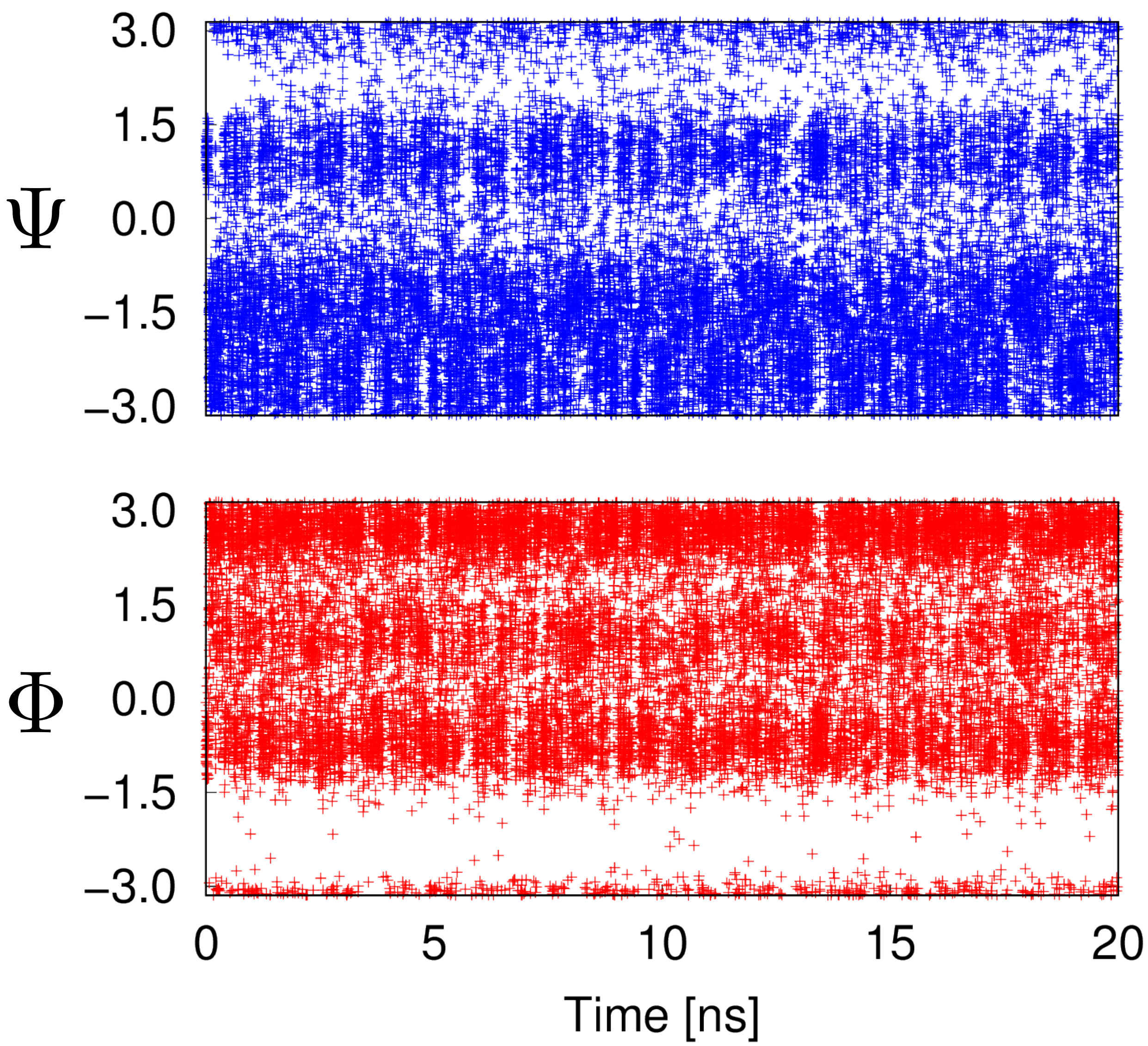
Φ slow CV

Missing Slow CVs

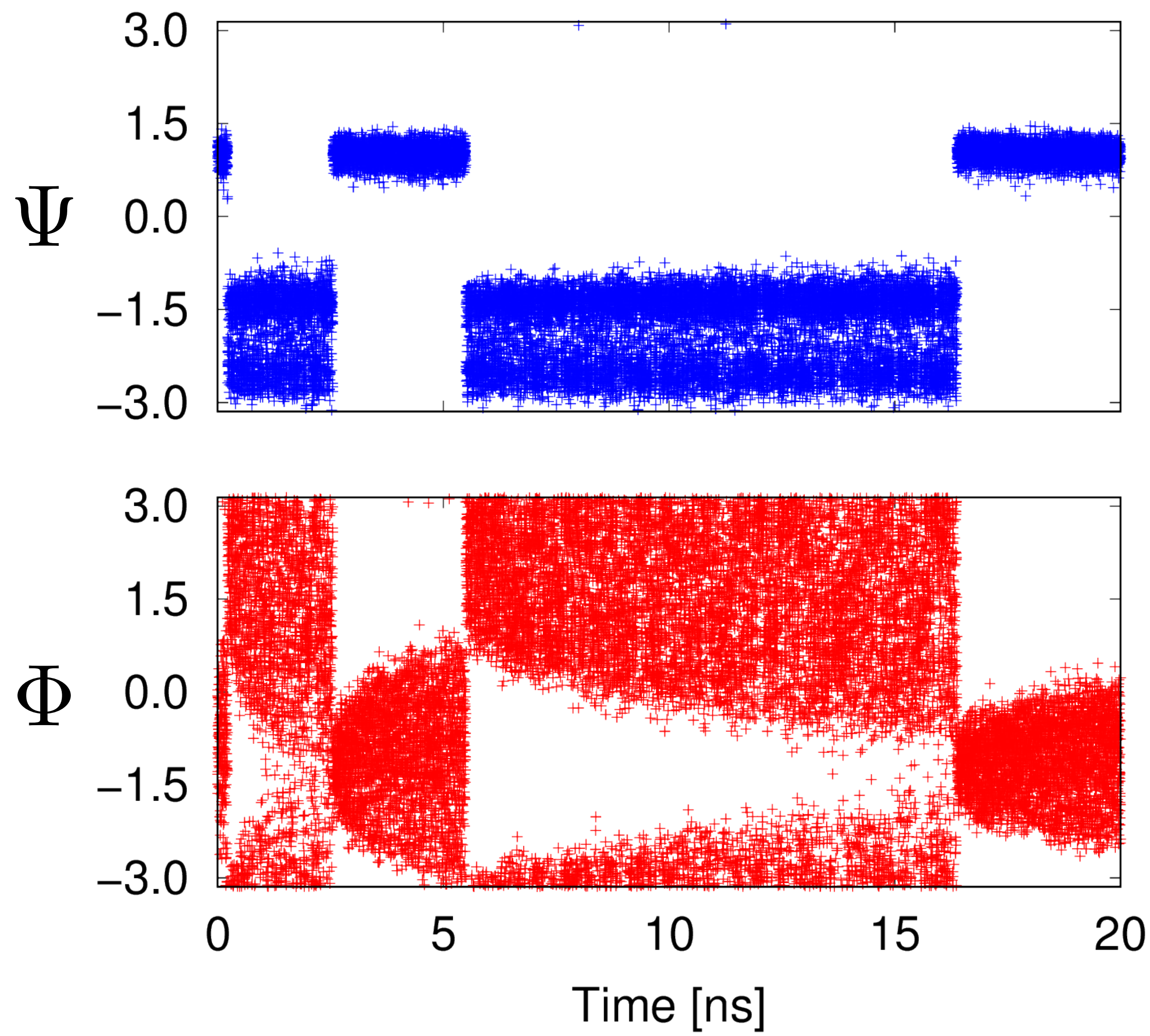


Φ slow CV / Ψ fast CV

biasing only slow CV Φ



biasing only fast CV Ψ

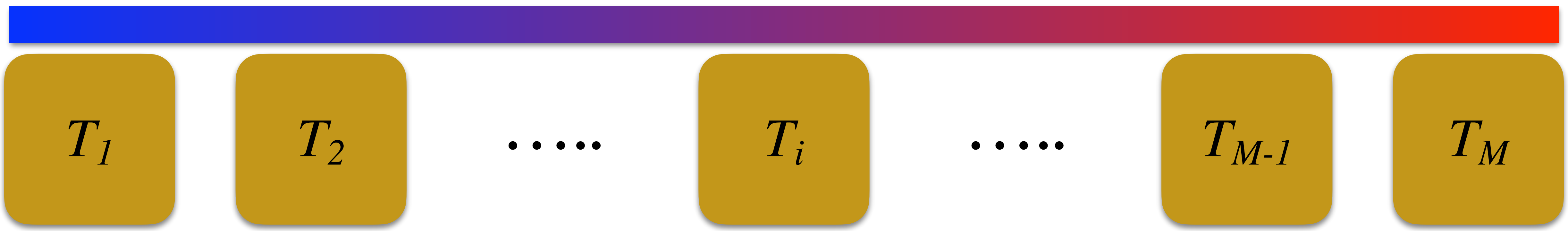


hysteresis behavior in Ψ if we are missing slow CV Φ

such behavior is quite general

Parallel-Tempering + Metadynamics

Can combine Metadynamics with parallel-tempering (or other replica exchange method)



Reduces the requirement on the quality of the metadynamics CVs as parallel-tempering will help sampling the slow degrees of freedom not included in the CV set.

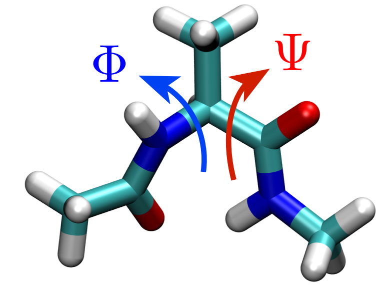
Metadynamics will also assist in sampling transitions states and higher lying metastable free energy basins that are generally poorly sampled in parallel-tempering (as it reproduces canonical sampling)

However, parallel-tempering can require a large number of replicas, especially for solvated biomolecules. One why to circumvent this is to employ the so-called well-tempered ensemble (PT-WTE)

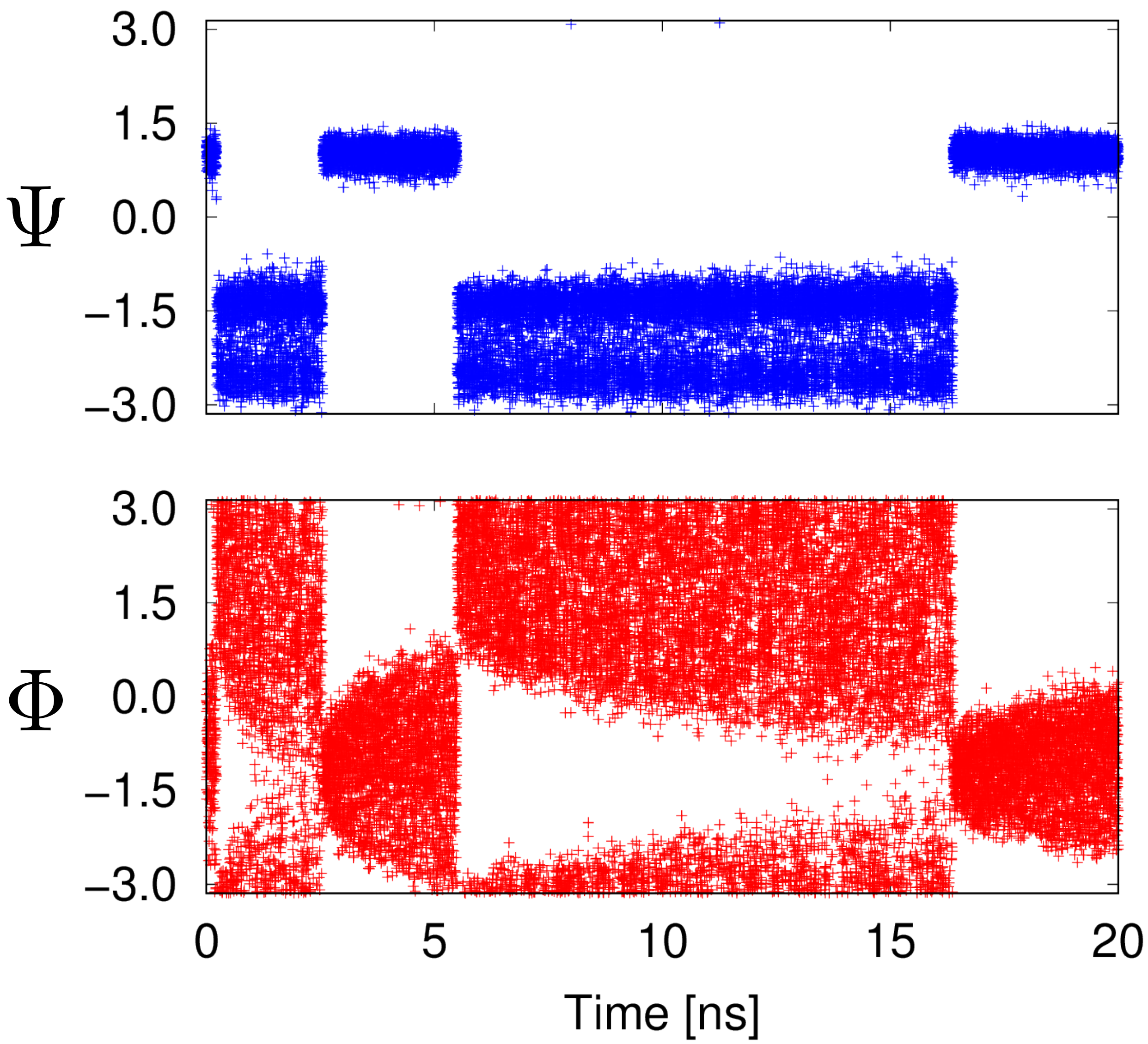
Bussi, Gervasio, Laio, and Parrinello, JACS 2006

PT+MetaD Helps with Missing Slow CVs

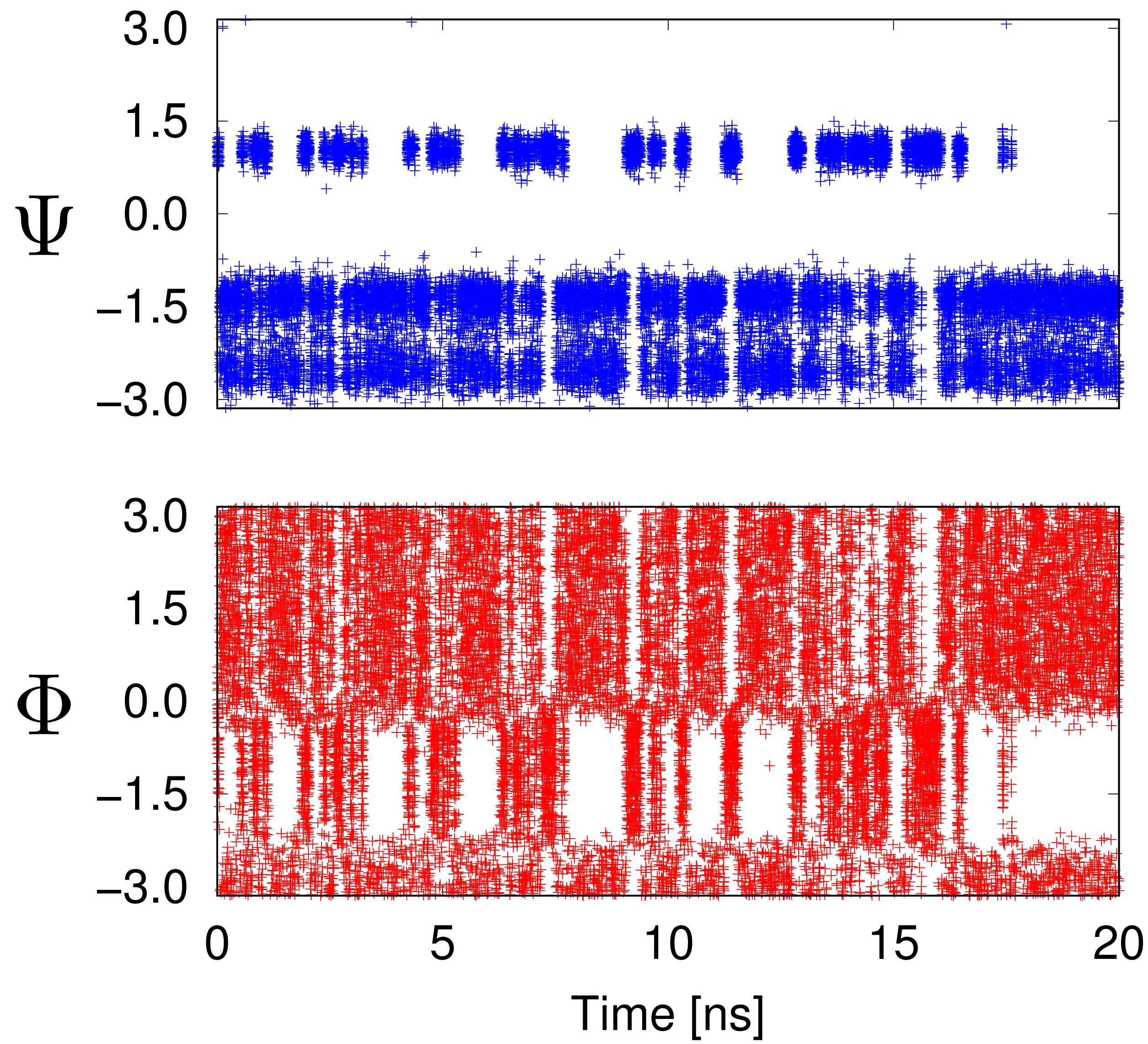
Φ slow CV / **Ψ** fast CV



Metadynamics
biasing only fast CV **Ψ**



Metadynamics + PT
biasing only fast CV **Ψ**



Combing with parallel-tempering mends hysteresis behavior