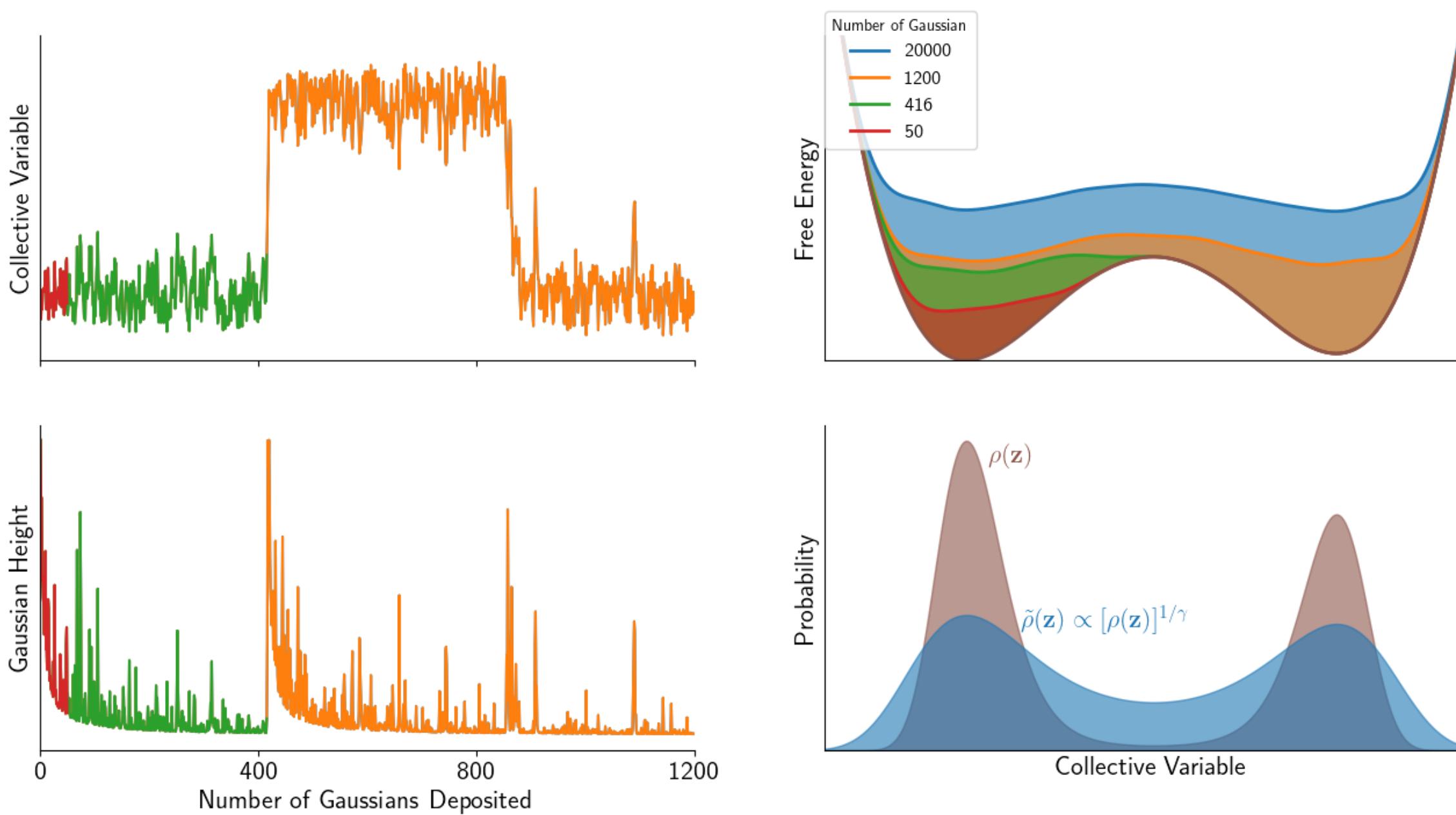


# Enhanced Sampling Methods for Molecular Dynamics Simulations



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# Valsson Research Group @ University of North Texas

## Method Development

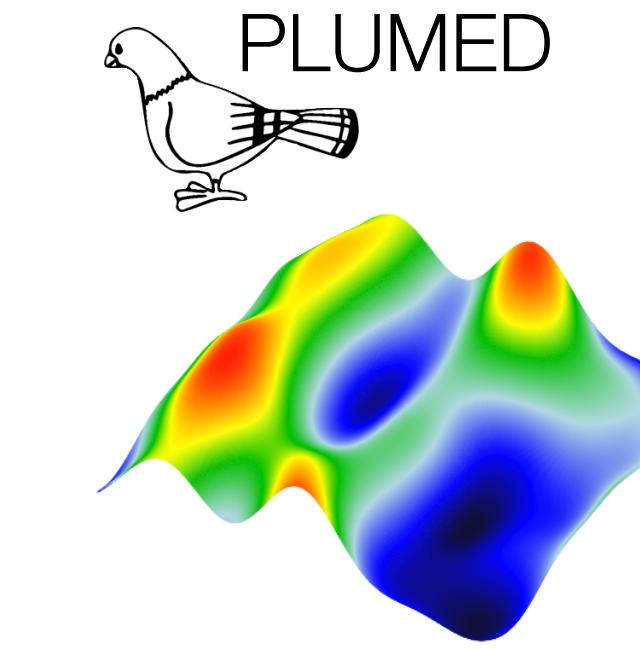
### Enhanced Sampling Methods

$$\Omega[V] = \frac{1}{\beta} \log \frac{\int d\mathbf{s} e^{-\beta[F(\mathbf{s})+V(\mathbf{s})]}}{\int d\mathbf{s} e^{-\beta F(\mathbf{s})}} + \int d\mathbf{s} p(\mathbf{s})V(\mathbf{s})$$

$$\Omega(\alpha) \quad \nabla \Omega(\alpha)$$

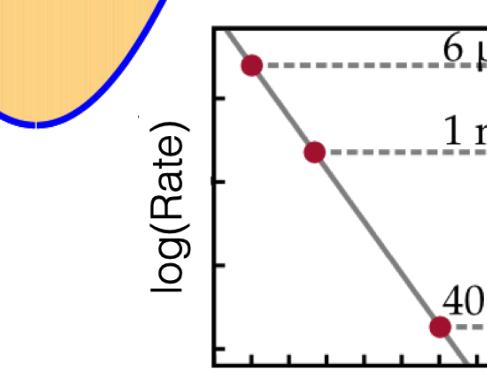
### Variationally Enhanced Sampling

PLUMED



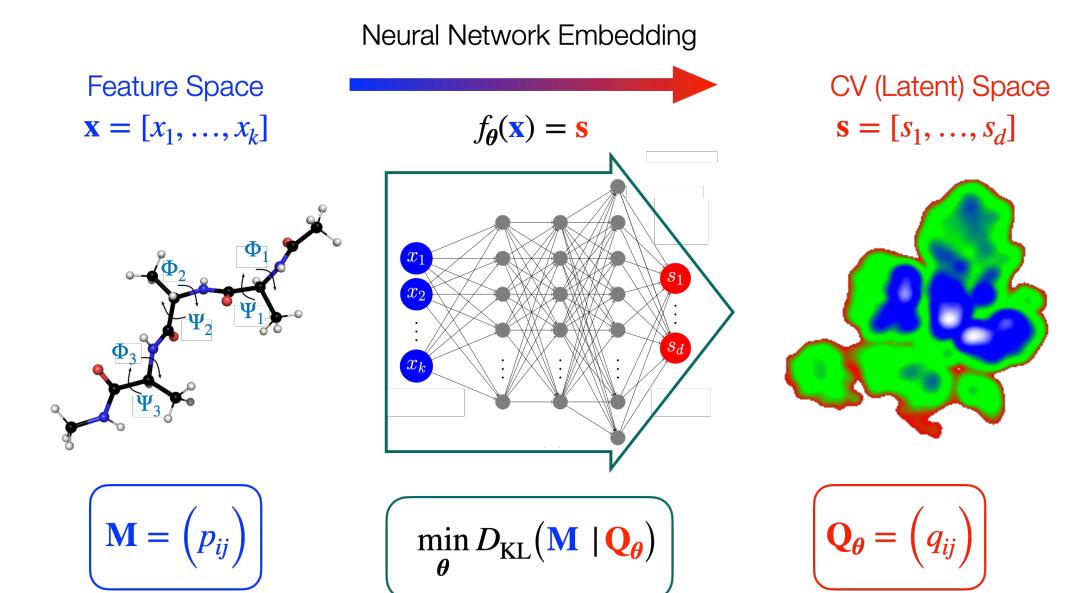
### Thermodynamic Properties Free Energy Landscapes

$\tau_{A \rightarrow B}^V$



1/T  
Kinetic Rates

### Machine Learning

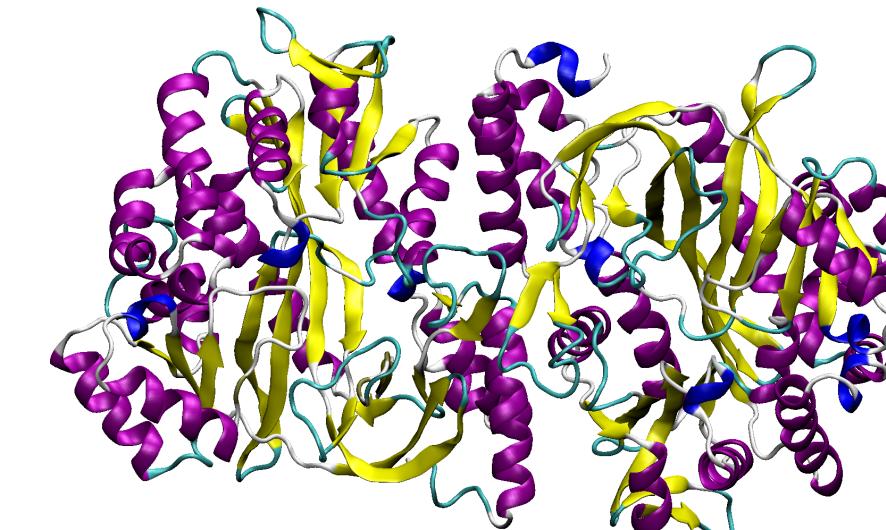
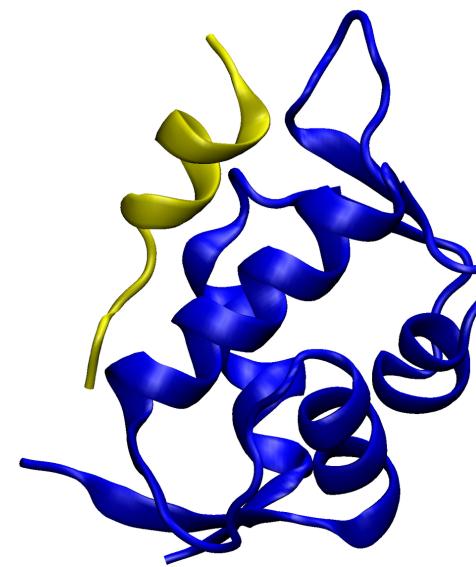


### Multiscale Reweighted Stochastic Embedding

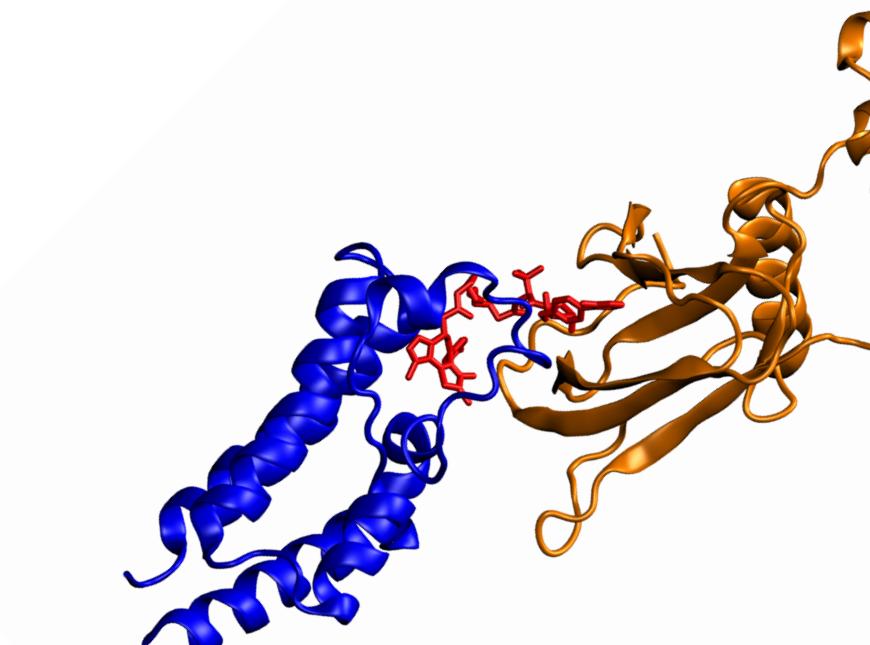
## Application Domains

### Biomolecular Systems

#### Protein-Protein Interactions

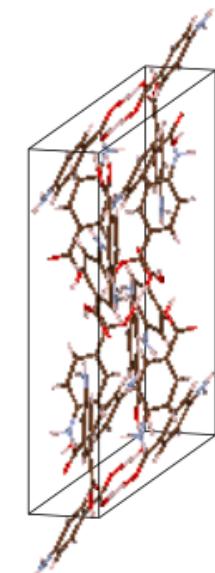
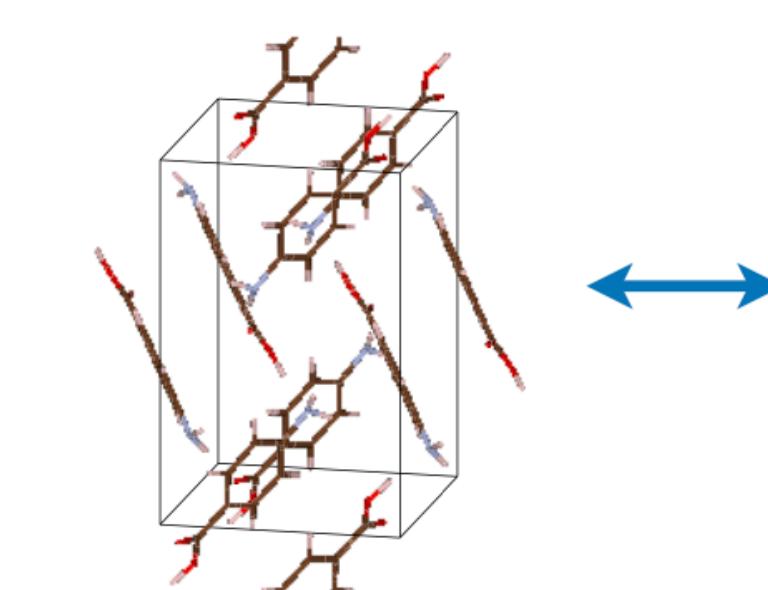


#### Protein Degradation (PROTACs)

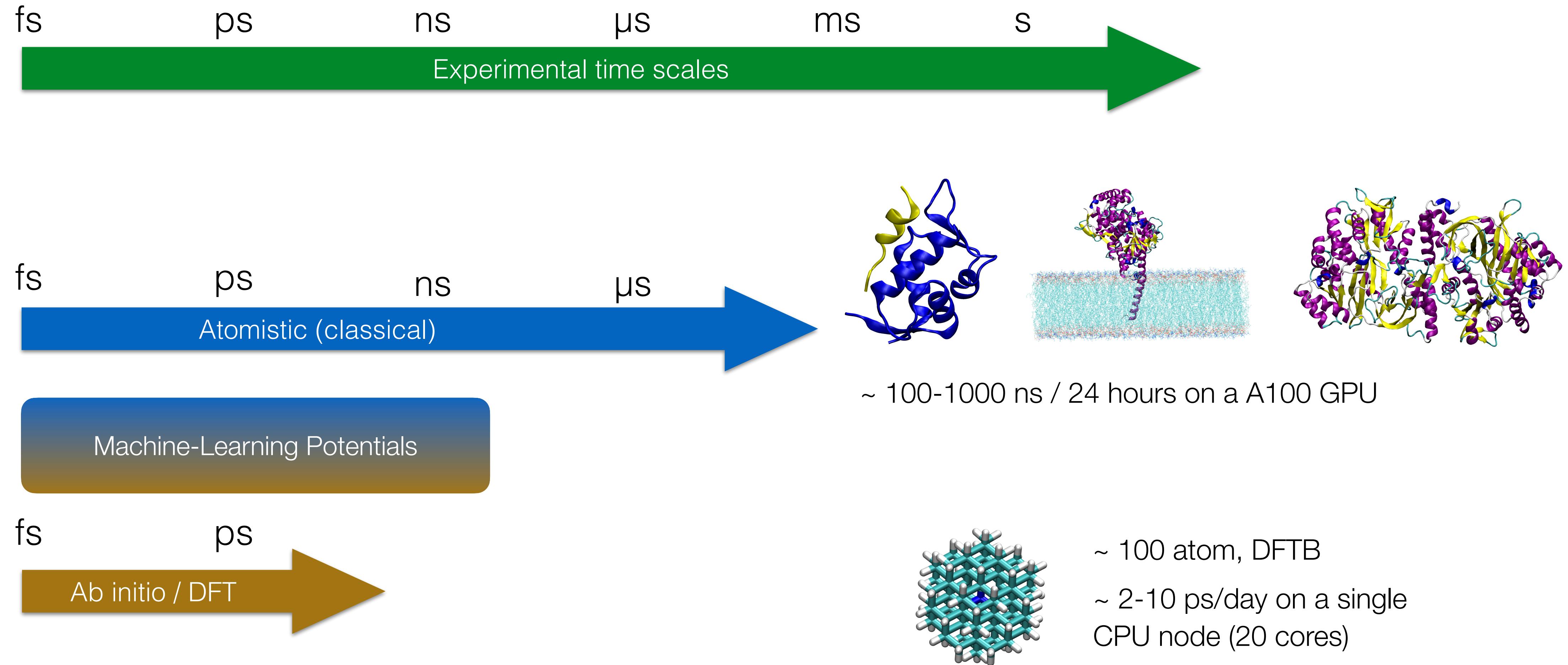


### Molecular Crystals

#### Polymorphic transitions



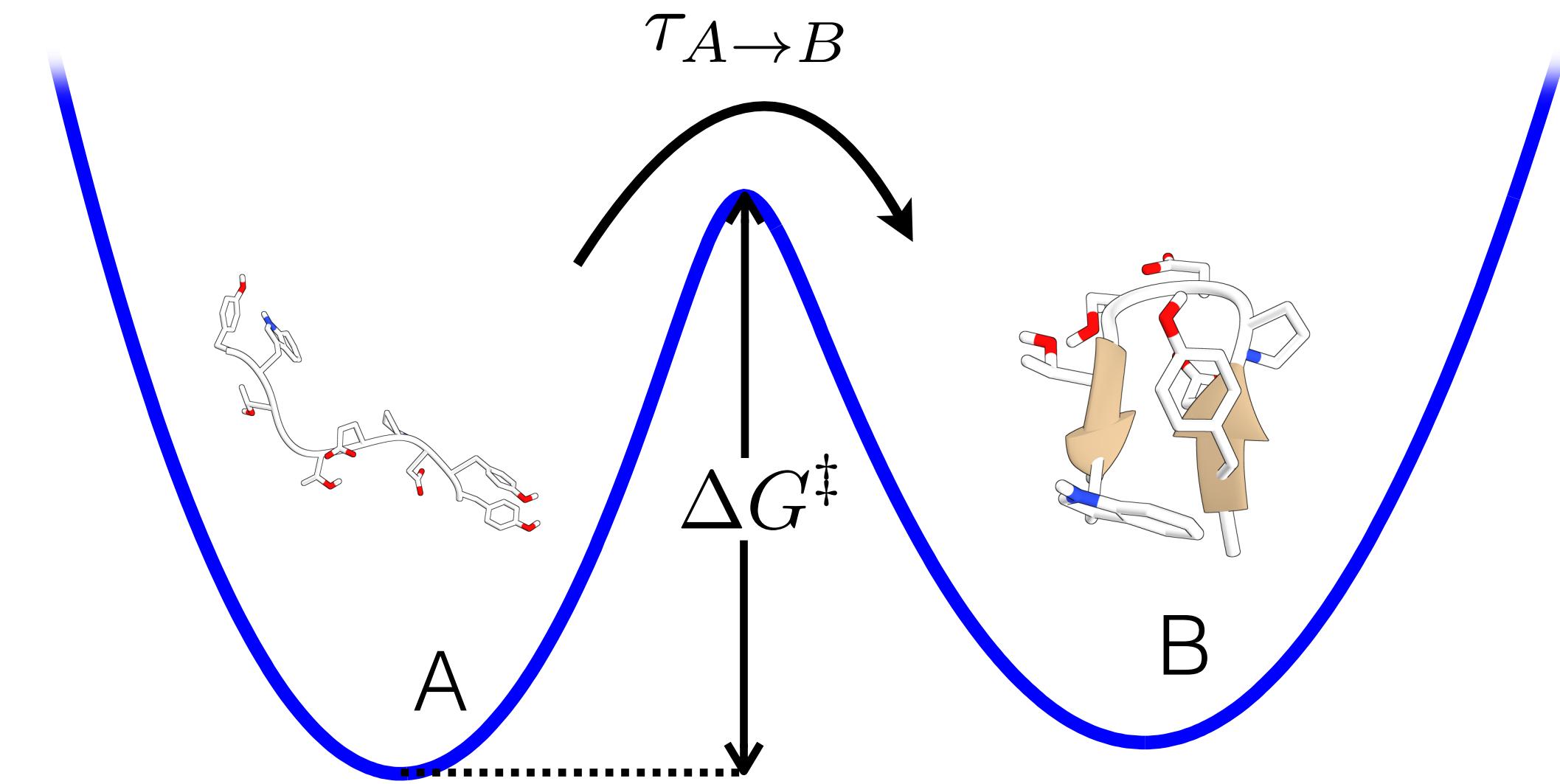
# Time Scale Problem in Atomistic Simulations



Disparity between the fastest processes and the long-time scale phenomenon we are interesting in

# Time Scale Problem in Atomistic Simulations

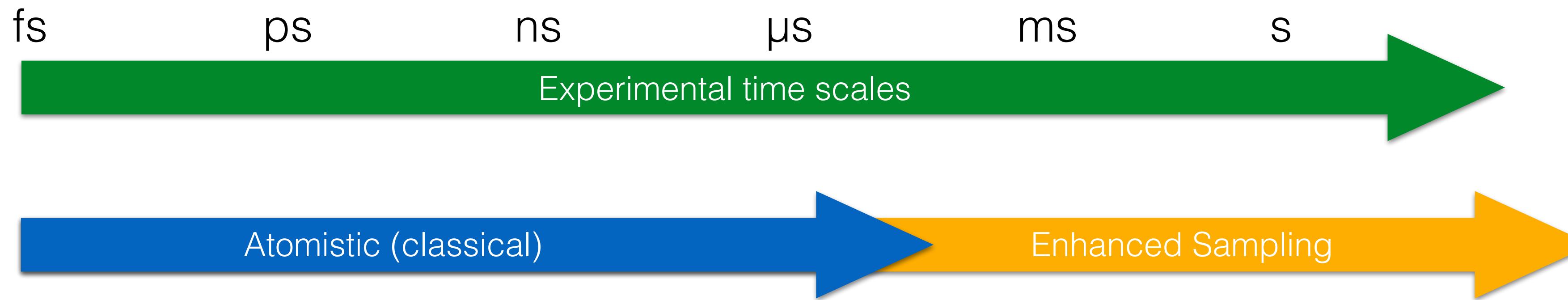
Physical system characterized by many metastable states  
separated by high free energy barriers



$$\tau_{A \rightarrow B} = \frac{1}{\nu_0 e^{-\Delta G^\ddagger/k_B T}} \propto e^{+\Delta G^\ddagger/k_B T}$$

$\Delta G^\ddagger \gg k_B T \rightarrow$  trapped in a metastable state

Advanced sampling method needed to overcome barriers and bridge time scales



# Wide Range of Enhanced Sampling Methods Available

## Enhanced Sampling Methods for Molecular Dynamics Simulations [Article v1.0]

Jérôme Hénin<sup>1\*</sup>, Tony Lelièvre<sup>2\*</sup>, Michael R. Shirts<sup>3\*</sup>, Omar Valsson<sup>4,5\*</sup>, Lucie Delemotte<sup>6\*</sup>

<sup>1</sup>Université Paris Cité, Laboratoire de Biochimie Théorique, CNRS UPR 9080, Paris, France; <sup>2</sup>CERMICS, Ecole des Ponts ParisTech, INRIA, Marne-la-Vallée, France;

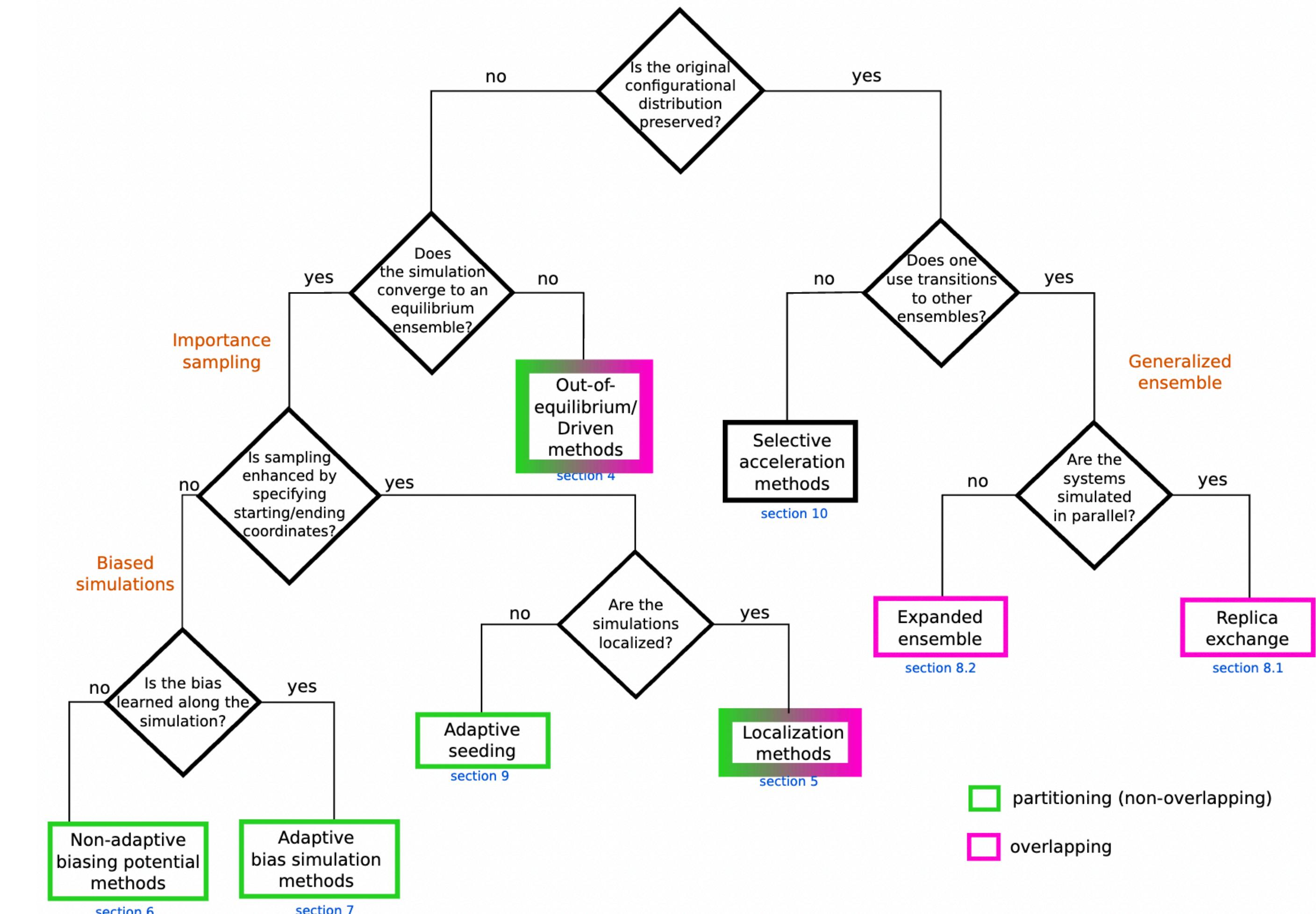
<sup>3</sup>Department of Chemical and Biological Engineering, University of Colorado Boulder, Boulder, CO, USA, 80309; <sup>4</sup>University of North Texas, Department of Chemistry, Denton, TX, USA; <sup>5</sup>Max Planck Institute for Polymer Research, Mainz, Germany; <sup>6</sup>KTH Royal Institute of Technology, Science for Life Laboratory, Stockholm, Sweden

Living Journal of Computational Molecular Science

LiveCoMS. 4, 1583 (2022)

DOI: [10.33011/livecoms.4.1.1583](https://doi.org/10.33011/livecoms.4.1.1583)

An attempt at classifying enhanced sampling schemes



## Other Suggested Readings

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

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

Omar Valsson,<sup>1,2</sup> Pratyush Tiwary,<sup>3</sup>  
and Michele Parrinello<sup>1,2</sup>

<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/10.1007/978-3-319-44677-6_49)

[https://doi.org/10.1007/978-1-4939-9608-7\\_21](https://doi.org/10.1007/978-1-4939-9608-7_21) (also <https://arxiv.org/abs/1812.08213>)

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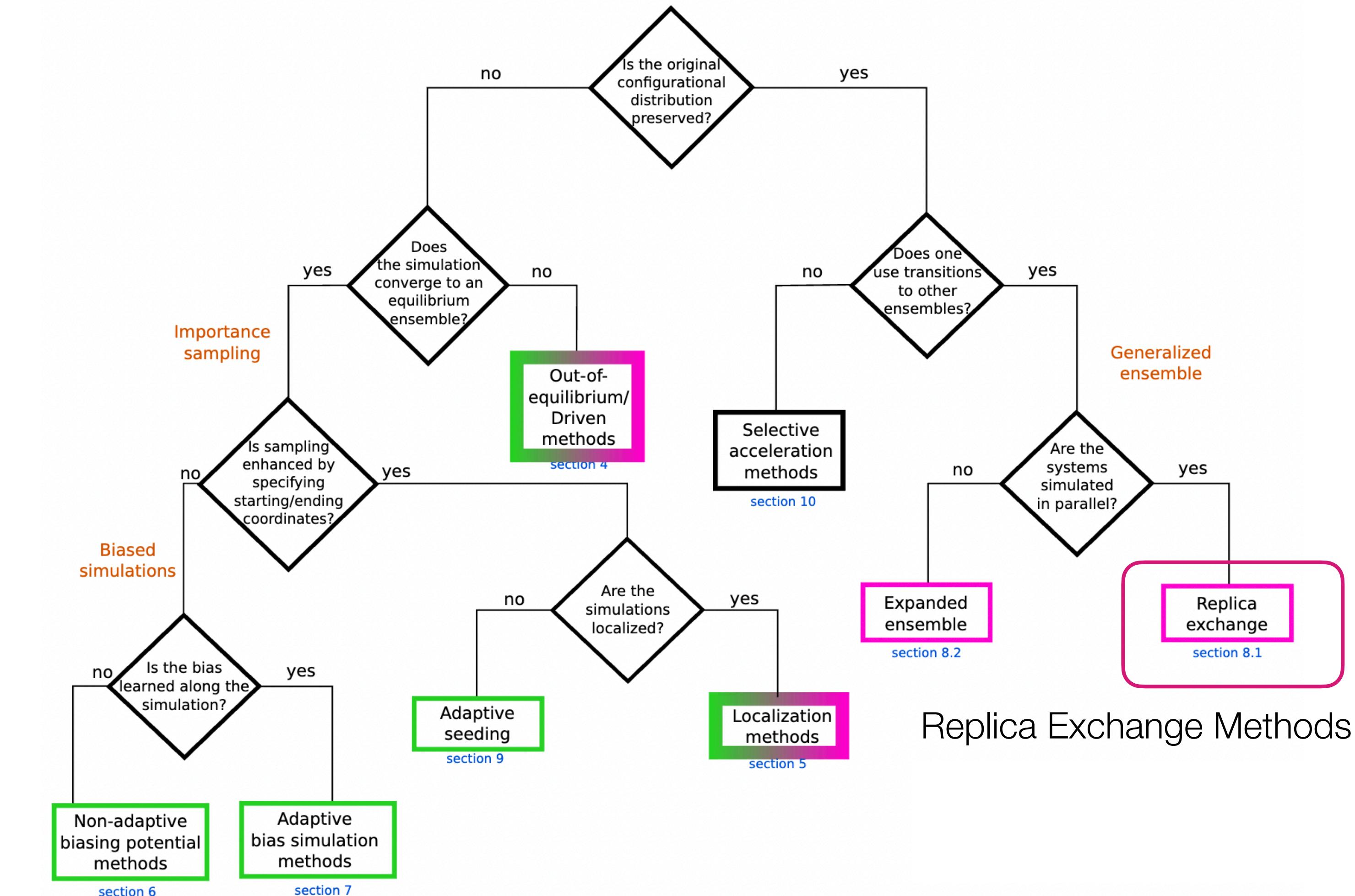
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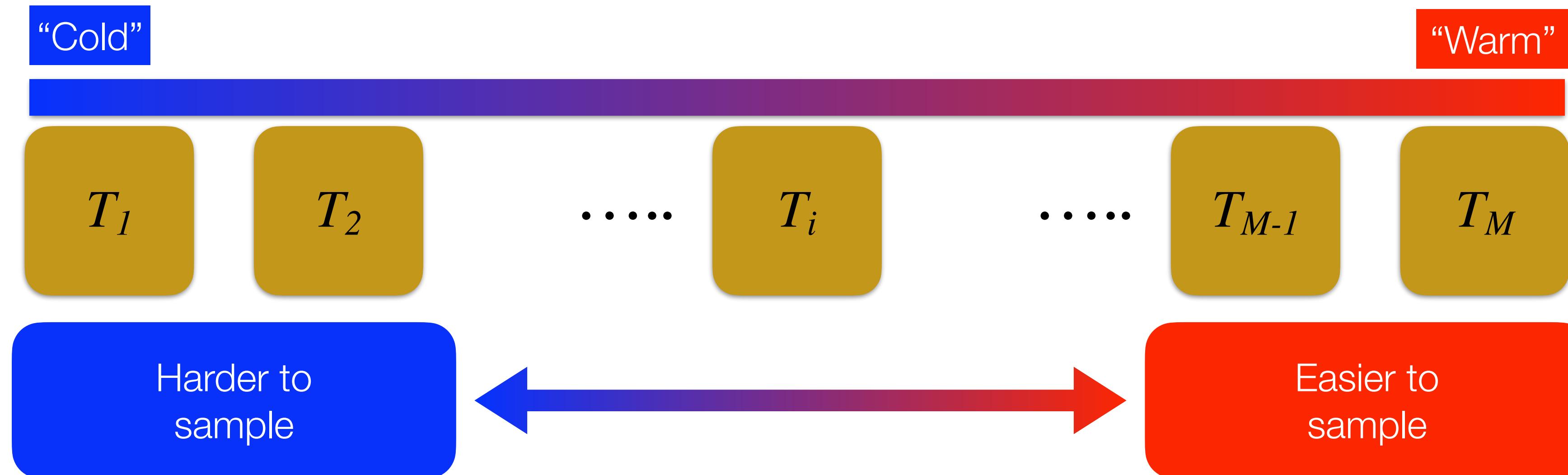
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An attempt at classifying enhanced sampling schemes



# Replica Exchange

Parallel-tempering (i.e., temperature replica exchange method)



Run multiple replicas in parallel with periodic exchanges of configurations

Simulation trajectory can overcome barriers by going up in temperature, where the sampling is easier, and then going down to the temperature of interest

However, parallel-tempering can require a large number of replicas, especially for solvated biomolecules. Ways to circumvent (e.g., solute tempering, well-tempered ensemble (PT-WTE), etc.)

Hamiltonian replica exchange: generalization of this idea, with replicas where you have the original Hamiltonian, and a series of replicas with Hamiltonians where the sampling is easier

# Wide Range of Enhanced Sampling Methods Available

## Enhanced Sampling Methods for Molecular Dynamics Simulations [Article v1.0]

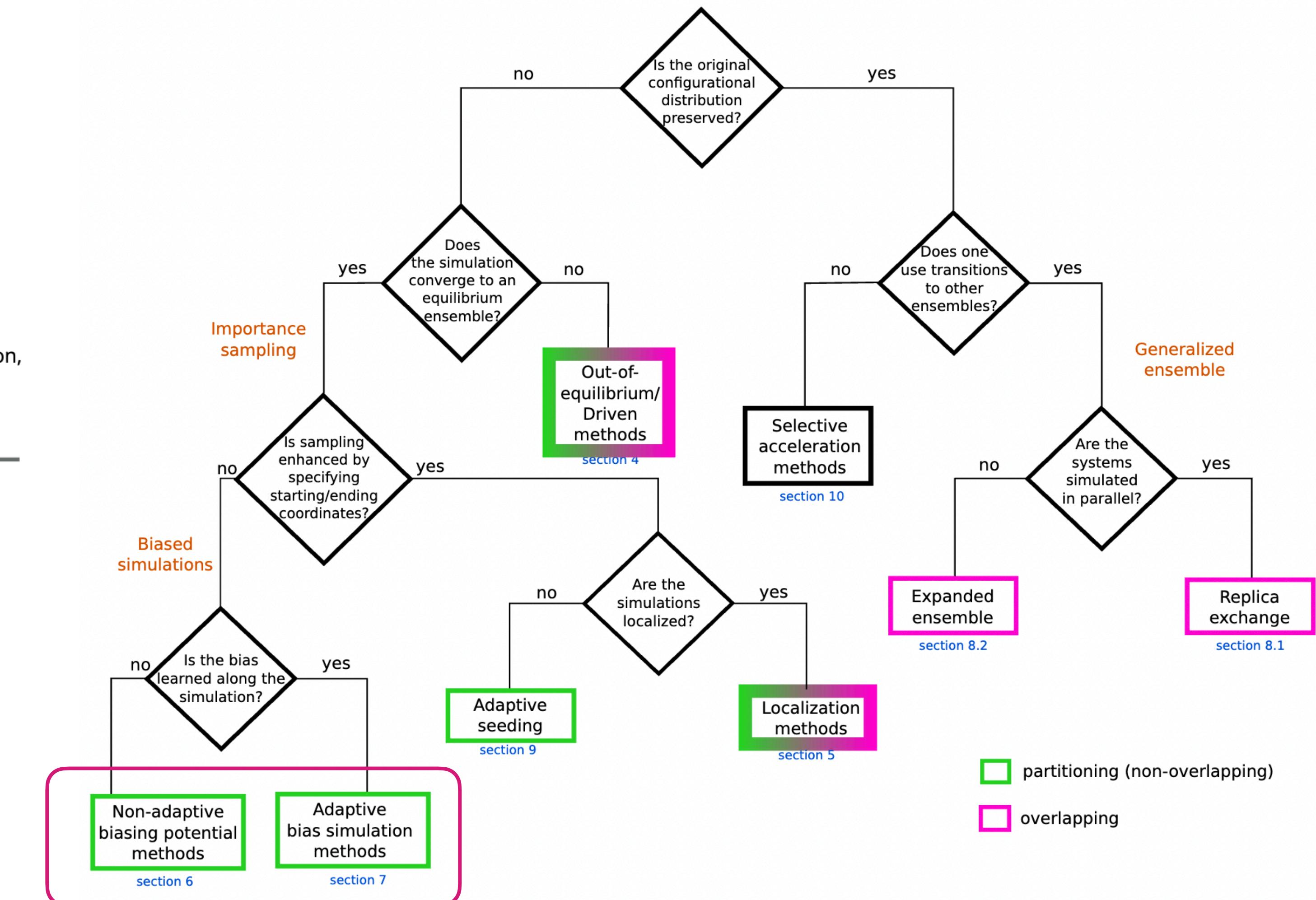
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An attempt at classifying enhanced sampling schemes



partitioning (non-overlapping)

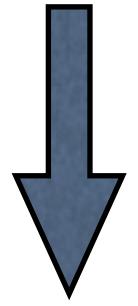
overlapping

## Mapping the Problem to a Lower Dimension

Atomistic coordinates

$$\mathbf{R} = [\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \dots, \mathbf{r}_N] \in \mathbb{R}^{3N}$$

high-dimensional space ( $\sim 10^4\text{-}10^6$ )  
hard to understand



Collective Variables

$$\mathbf{s}(\mathbf{R}) = [s_1(\mathbf{R}), s_2(\mathbf{R}), \dots, s_d(\mathbf{R})] \in \mathbb{R}^d$$

$d \ll 3N$     (generally  $\sim 1\text{-}3$ )

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

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

# Mapping the Problem to a Lower Dimension

Identify few important coarse-grained variables that describe the problem

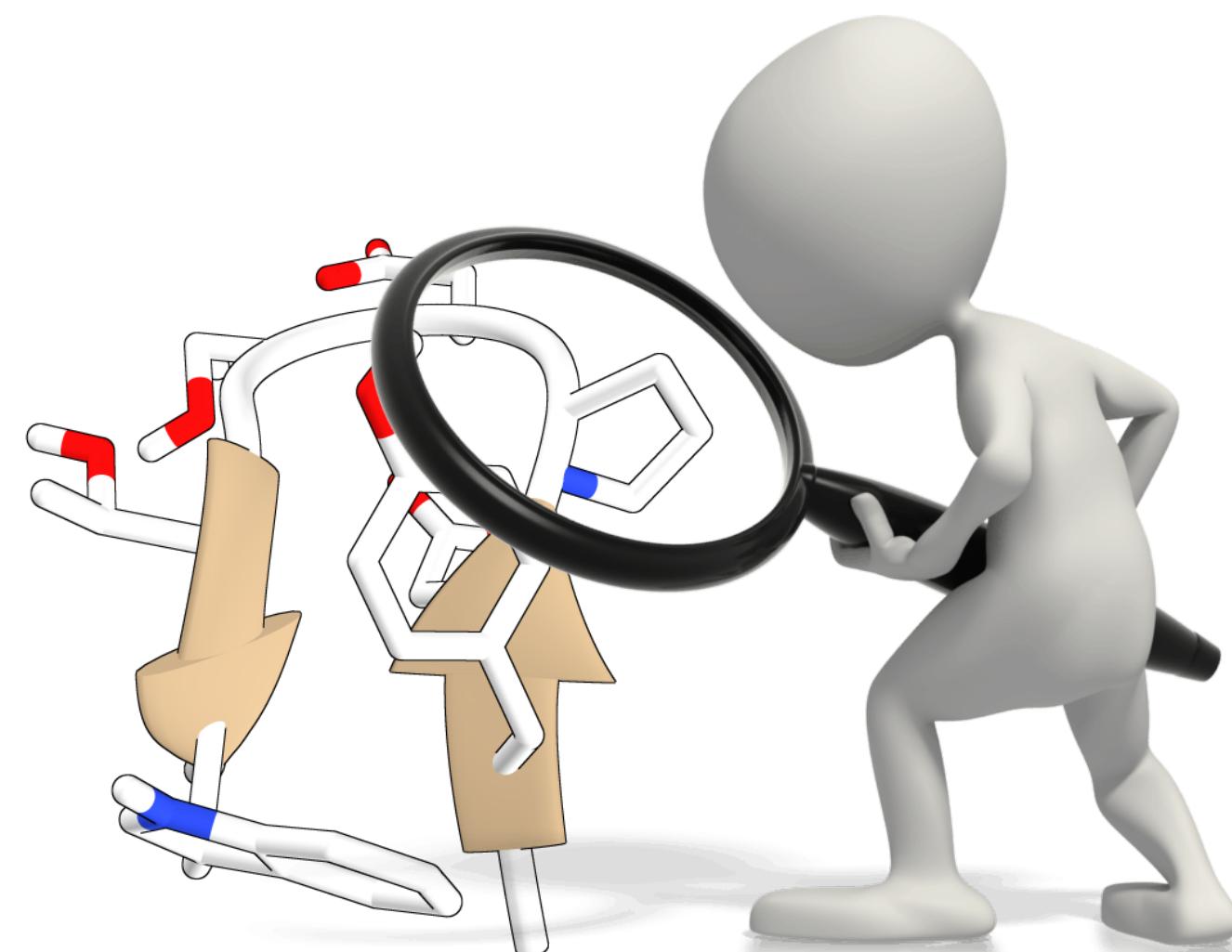
- Distinguish the relevant metastable states
- Include the slow degrees of freedom

Large number of generally applicable CVs available  
e.g. distances, dihedral angles, coordination numbers, contacts maps, RMSD, path CV, ....

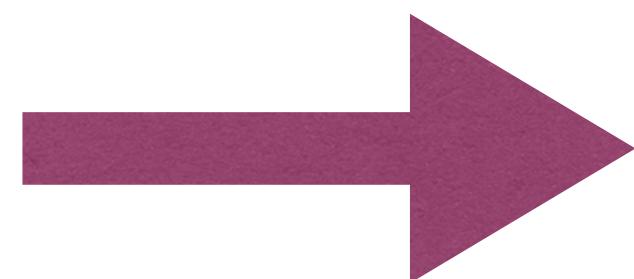
So-called **Collective Variables (CVs)** (or reaction coordinates)

$$\mathbf{s}(\mathbf{R}) = [s_1(\mathbf{R}), s_2(\mathbf{R}), \dots, s_d(\mathbf{R})]$$

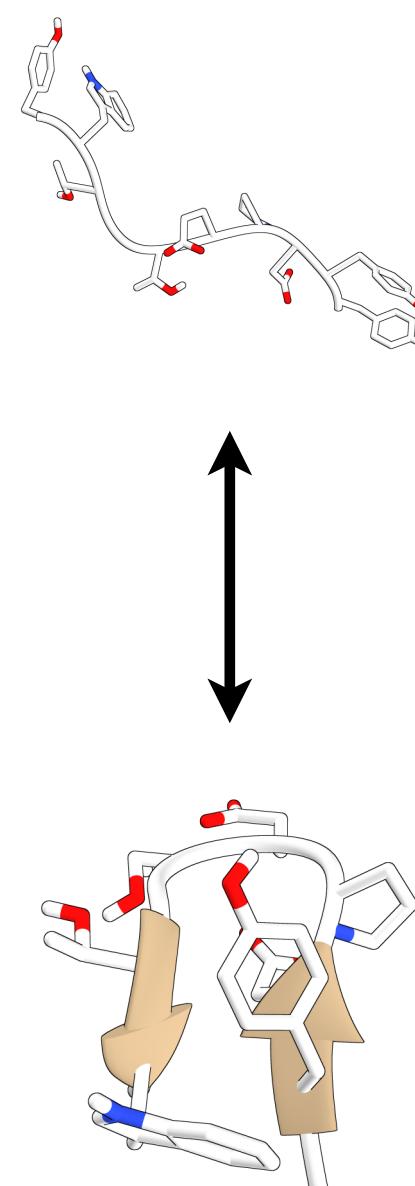
functions of the atomistic coordinates  $\mathbf{R}$



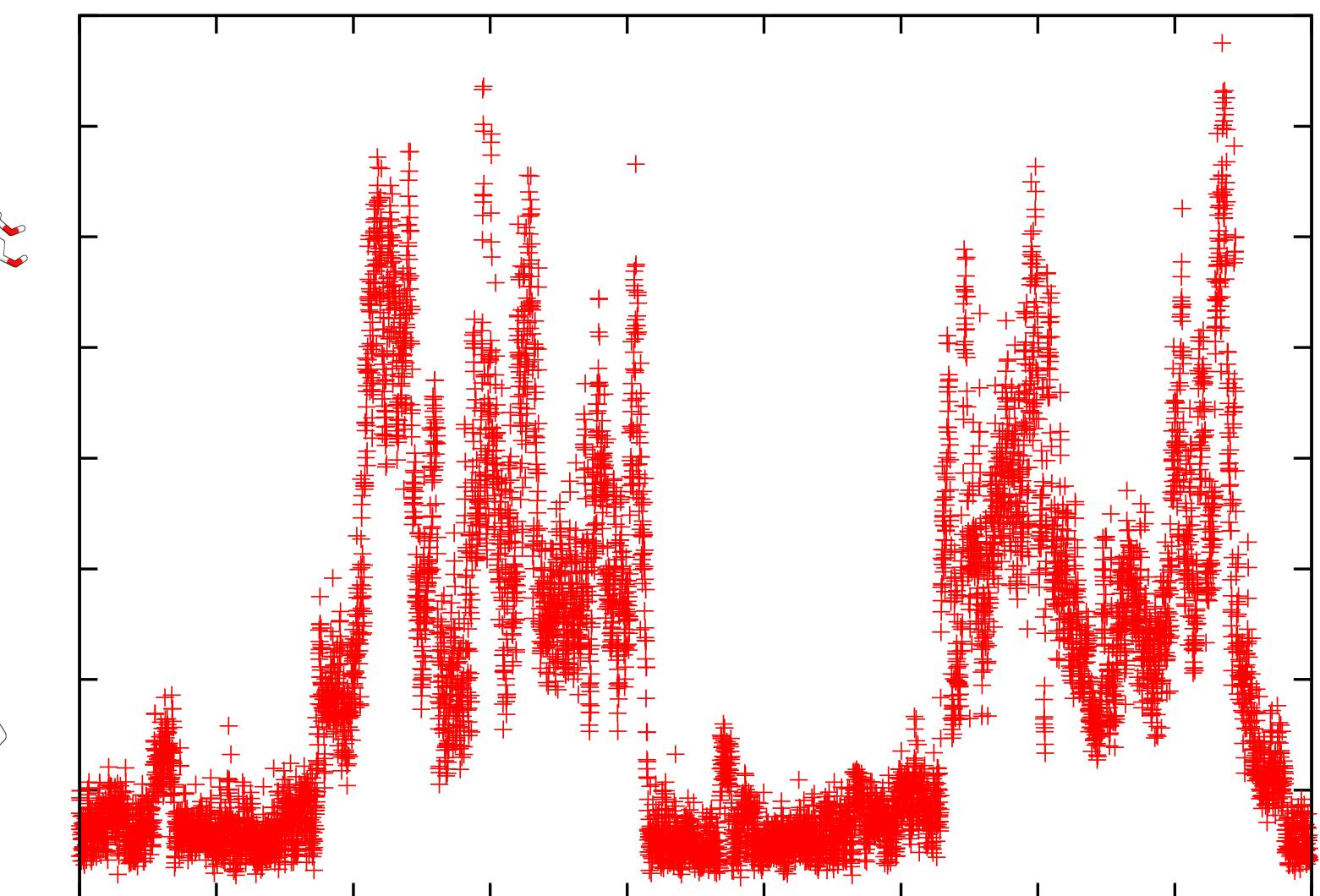
Collective Variables



$$\mathbf{s} = [s_1, \dots, s_d]$$

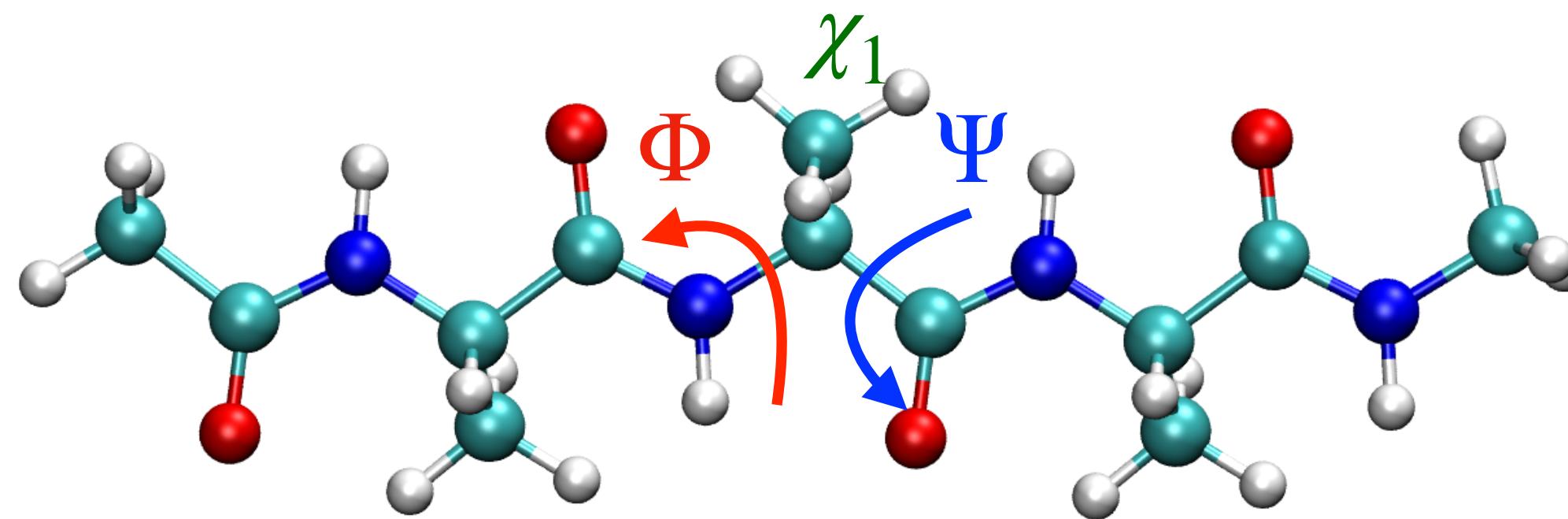


Root-mean-square deviation



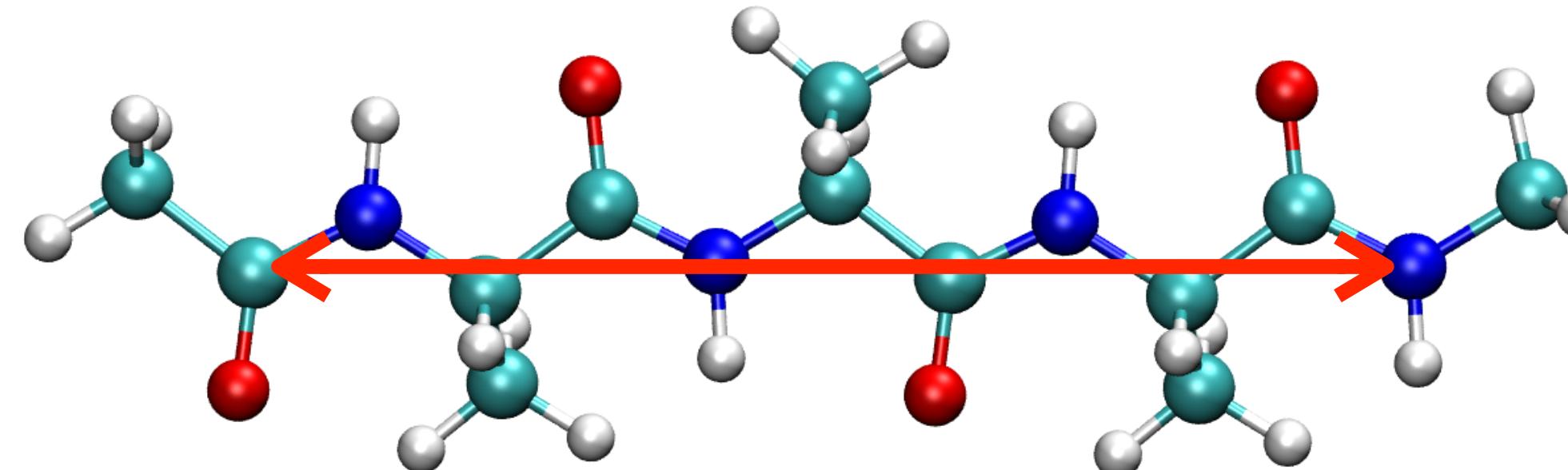
## Examples of Collective Variables

Dihedral angles



Distances

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

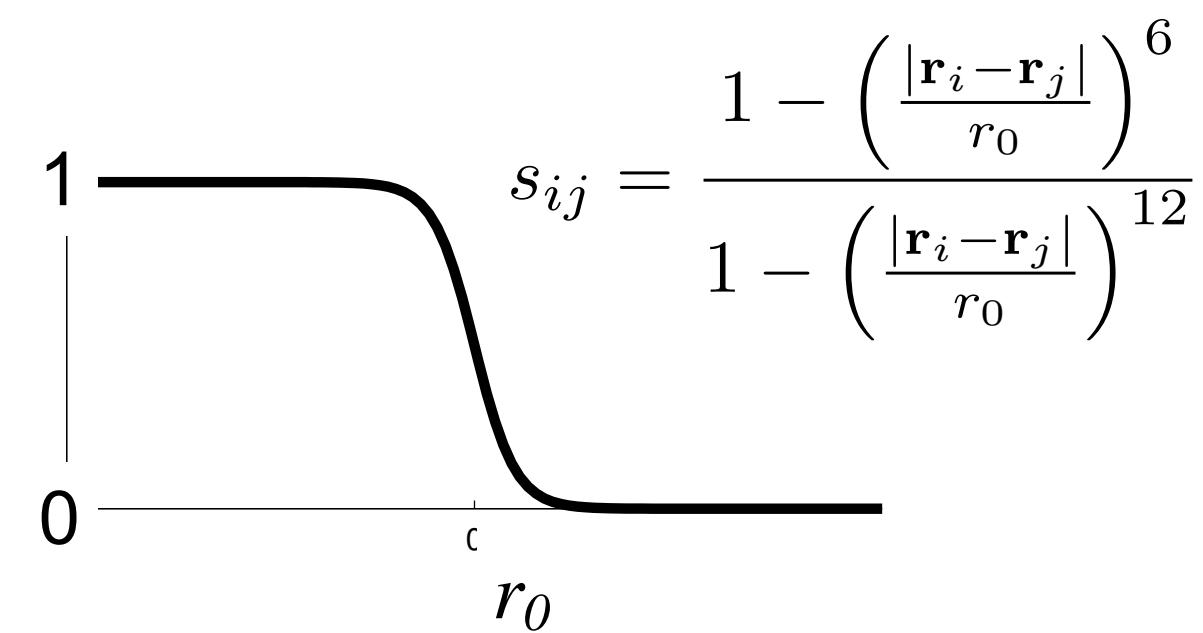


# Examples of Collective Variables

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

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

continuous (rational) switching function



Root mean square deviation (RMSD) from a reference structure

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

Graph of a rational switching function

Radius of gyration

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

$$\mathbf{r}_{COM} = \frac{\sum_i m_i \mathbf{r}_i}{\sum_i m_i}$$

# Examples of Collective Variables

## CV Documentation

The following list contains descriptions of a number of the colvars that are currently implemented in PLUMED.

<b>ADAPTIVE_PATH</b>	Compute path collective variables that adapt to the lowest free energy path connecting states A and B.
<b>ALPHABETA</b>	Measures a distance including pbc between the instantaneous values of a set of torsional angles and set of reference values.
<b>ALPHARMSD</b>	Probe the alpha helical content of a protein structure.
<b>ANGLE</b>	Calculate an angle.
<b>ANTIBETARMSD</b>	Probe the antiparallel beta sheet content of your protein structure.
<b>CELL</b>	Calculate the components of the simulation cell
<b>CONSTANT</b>	Return one or more constant quantities with or without derivatives.
<b>CONTACTMAP</b>	Calculate the distances between a number of pairs of atoms and transform each distance by a switching function.
<b>COORDINATION</b>	Calculate coordination numbers.
<b>DHENERGY</b>	Calculate Debye-Hückel interaction energy among GROUPA and GROUPB.
<b>DIHCOR</b>	Measures the degree of similarity between dihedral angles.
<b>DIMER</b>	This CV computes the dimer interaction energy for a collection of dimers.
<b>DIPOLE</b>	Calculate the dipole moment for a group of atoms.
<b>DISTANCE</b>	Calculate the distance between a pair of atoms.
<b>DISTANCE_FROM_CONTOUR</b>	Calculate the perpendicular distance from a Willard-Chandler dividing surface.
<b>EEFSOLV</b>	Calculates EEF1 solvation free energy for a group of atoms.
<b>ENERGY</b>	Calculate the total potential energy of the simulation box.
<b>ERMSD</b>	Calculate eRMSD with respect to a reference structure.
<b>EXTRACV</b>	Allow PLUMED to use collective variables computed in the MD engine.
<b>FAKE</b>	This is a fake colvar container used by cttools or various other actions that supports input and period definitions
<b>GHBFIX</b>	Calculate the GHBFIX interaction energy among GROUPA and GROUPB using a potential defined in Kührová et al., Improving the performance of the AMBER RNA force field by tuning the hydrogen-bonding interactions, JCTC, 2019. Essentially it is a switching function being -1 for small distances and 0 for large distances with a smooth interpolation in the middle. This can be scaled as desired by specifying interaction scaling parameters and energy units.
<b>GPROPERTYMAP</b>	Property maps but with a more flexible framework for the distance metric being used.
<b>GYRATION</b>	Calculate the radius of gyration, or other properties related to it.
<b>PARABETARMSD</b>	Probe the parallel beta sheet content of your protein structure.
<b>PATH</b>	Path collective variables with a more flexible framework for the distance metric being used.
<b>PATHMSD</b>	This Colvar calculates path collective variables.
<b>PCAVARS</b>	Projection on principal component eigenvectors or other high dimensional linear subspace
<b>POSITION</b>	Calculate the components of the position of an atom.
<b>PROJECTION_ON_AXIS</b>	Calculate a position based on the projection along and extension from a defined axis.
<b>PROPERTYMAP</b>	Calculate generic property maps.
<b>PUCKERING</b>	Calculate sugar pseudorotation coordinates.
<b>TEMPLATE</b>	This file provides a template for if you want to introduce a new CV.
<b>TORSION</b>	Calculate a torsional angle.
<b>VOLUME</b>	Calculate the volume of the simulation box.

## Mapping to a Lower Dimension

Boltzmann distribution

$$P(\mathbf{R}) = \frac{e^{-\beta U(\mathbf{R})}}{\int d\mathbf{R} e^{-\beta U(\mathbf{R})}} \quad \beta = \frac{1}{k_B T}$$

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

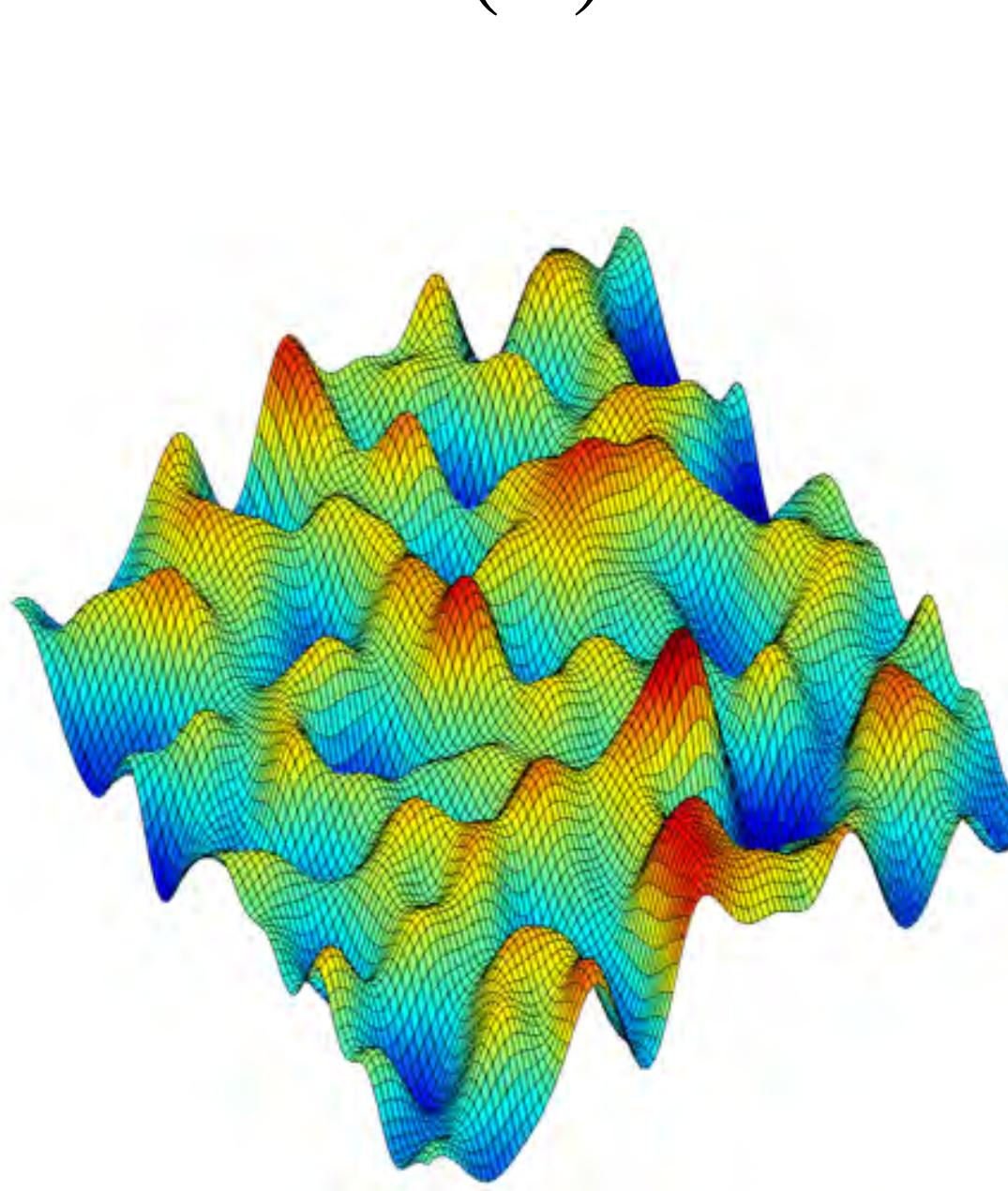
$$P(\mathbf{s}) = \int d\mathbf{R} \delta [\mathbf{s} - \mathbf{s}(\mathbf{R})] P(\mathbf{R}) = \langle \delta [\mathbf{s} - \mathbf{s}(\mathbf{R})] \rangle$$

The **Free Energy Surface (FES)** given by the negative logarithm multiplied by  $k_B T = \beta^{-1}$

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

# Mapping the Problem to a Lower Dimension

Potential Energy Surface



High-dimensional / Rugged

$$\mathbf{R} \in \mathbb{R}^{3N}$$

Free Energy Landscape/Surface

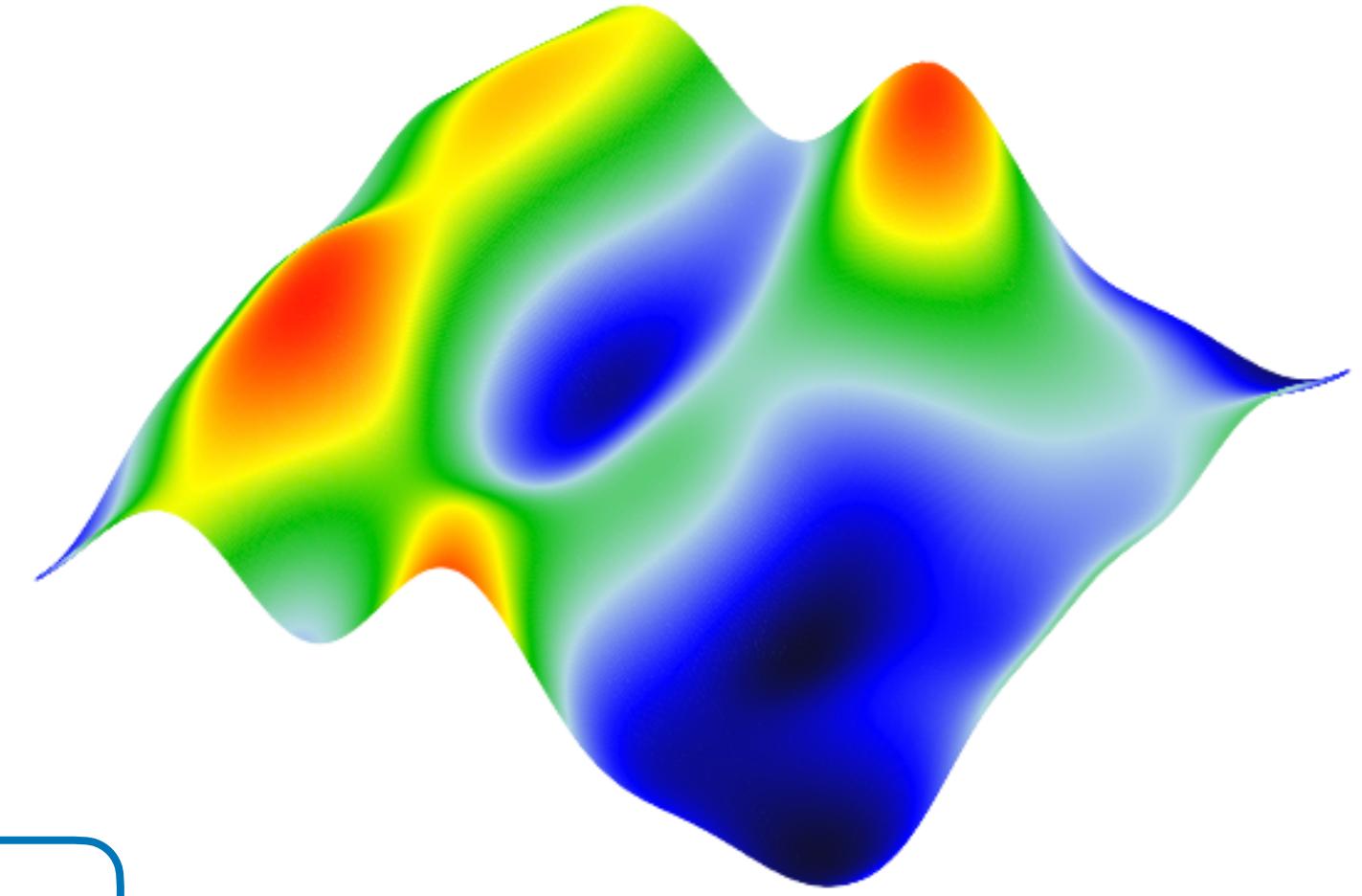
(i.e. logarithm of the marginal distribution)

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

Collective Variables



$$\mathbf{s}(\mathbf{R}) = [s_1(\mathbf{R}), s_2(\mathbf{R}), \dots, s_d(\mathbf{R})]$$



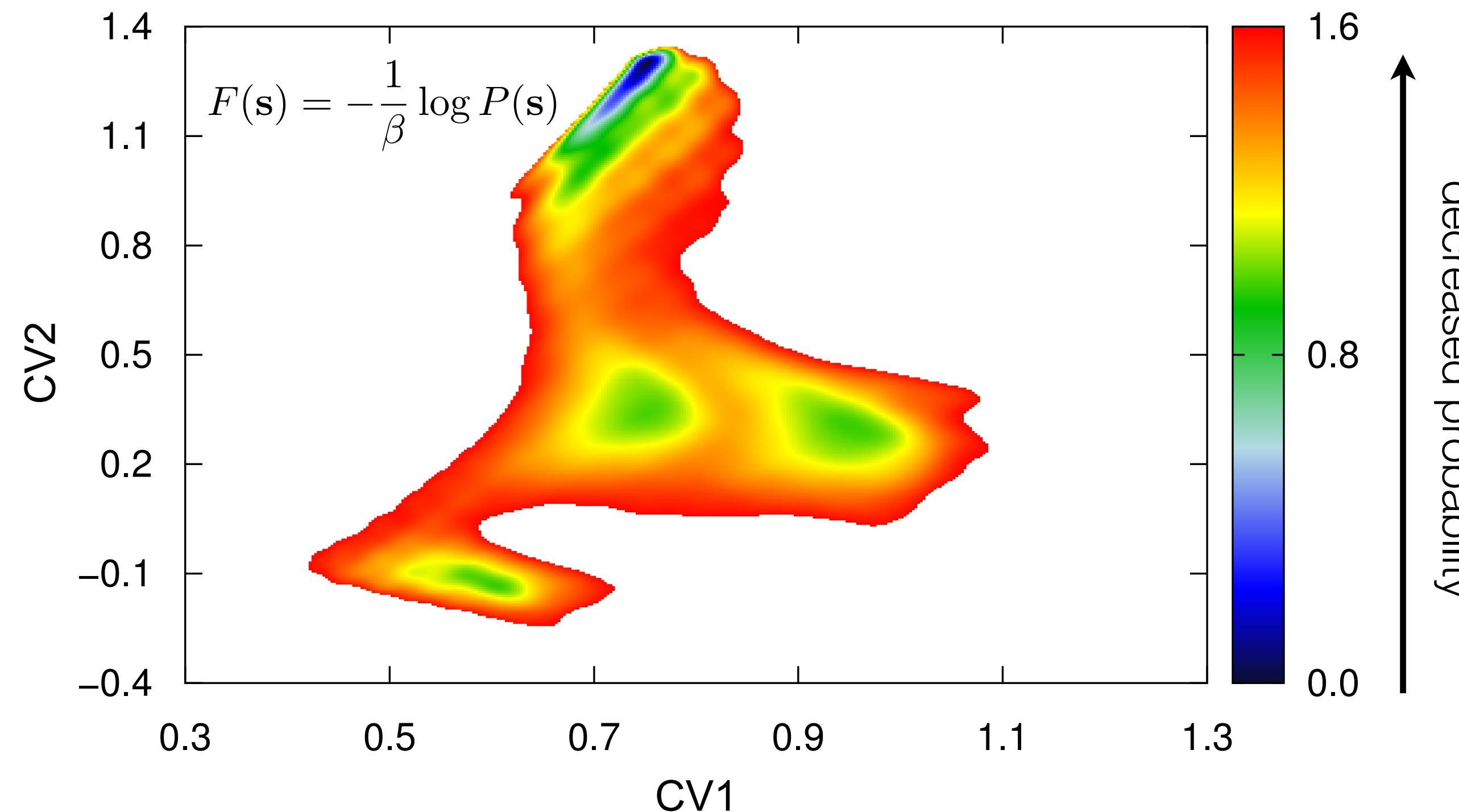
Use the collective variables to both  
**represent** and **drive the sampling**  
of the free energy landscape

Low-dimensional / Smooth

$$\mathbf{s} \in \mathbb{R}^d \quad d \ll 3N$$

## Free Energy Surface/Landscape

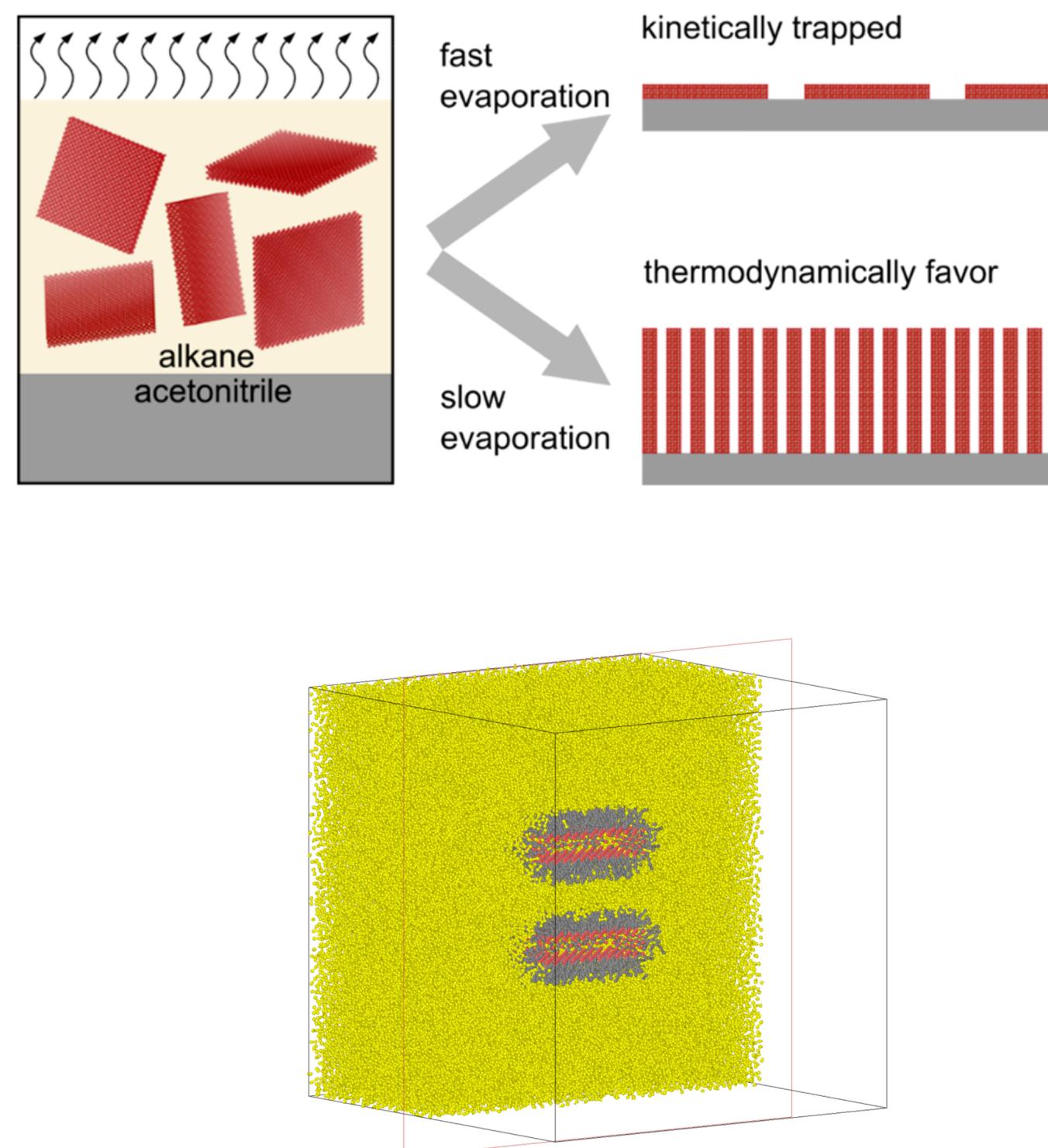
The FES normally what we are interested in obtaining gives information about metastable states, their relative stability, and the free-energy barriers<sup>A</sup>



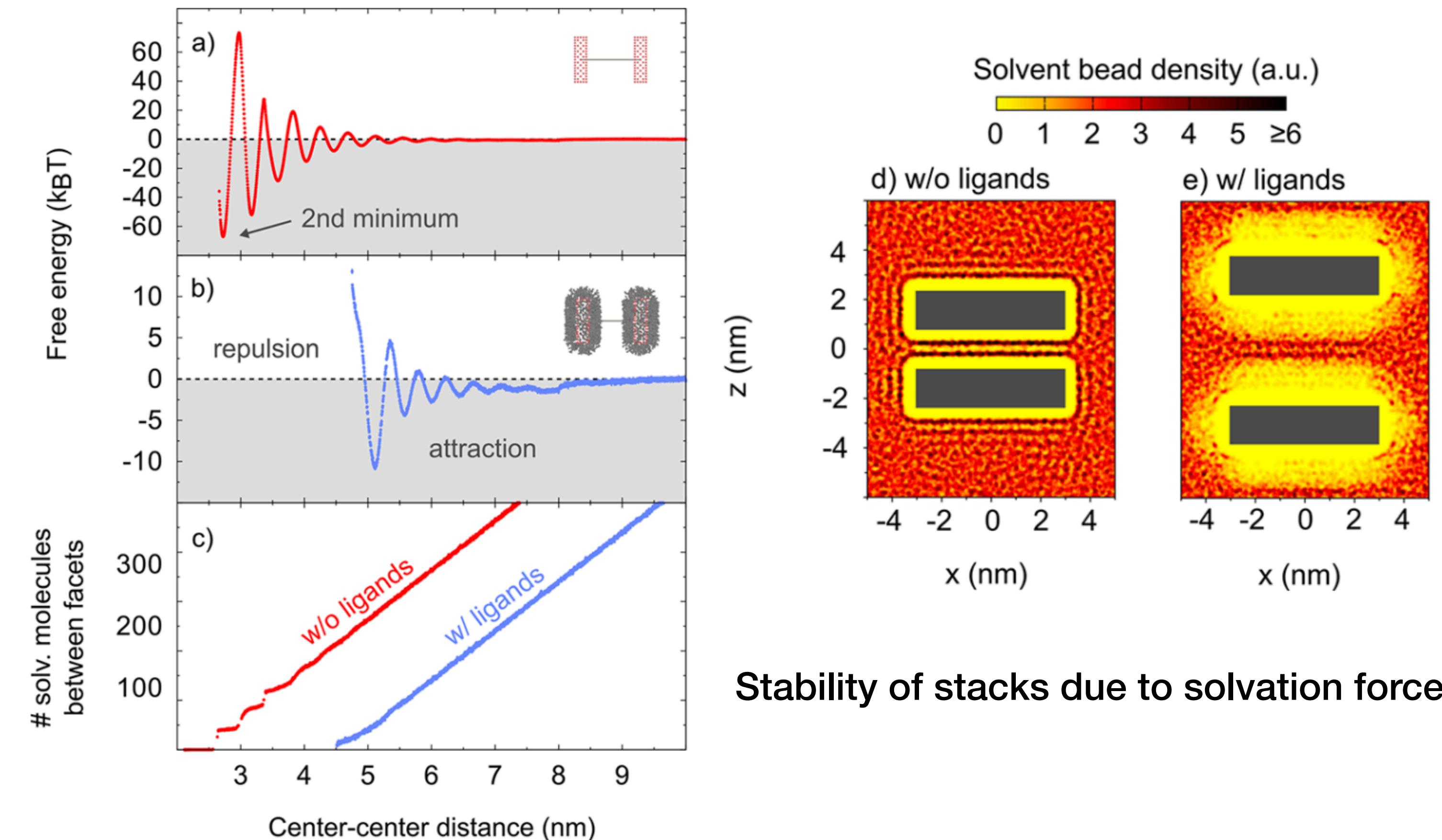
<sup>A</sup> Caveat: the FES is not invariant with respect to the CVs, so the connection of free-energy barriers to activation free energies and kinetics is not always clear, see [10.1063/5.0020240](https://doi.org/10.1063/5.0020240), [10.1063/5.0102075](https://doi.org/10.1063/5.0102075), and [10.1063/5.0083423](https://doi.org/10.1063/5.0083423)

# Example: Nanoplatelet Interactions

Looking at interactions of CdSe nanoplatelets and why they tend to form stable stacks in experiments



Use Martini coarse-grained FF and multiple window umbrella sampling



**Stability of stacks due to solvation forces**

Currently looking into how other parameter such as solvent length/type modulate the solvation force

## Estimating the Free Energy Surface

The FES is also defined as

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

Valid for ergodic systems, which are most system we are interested in

(Note: ergodicity is a theoretical notion that characterizes asymptotic behavior over infinitely long times)

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

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

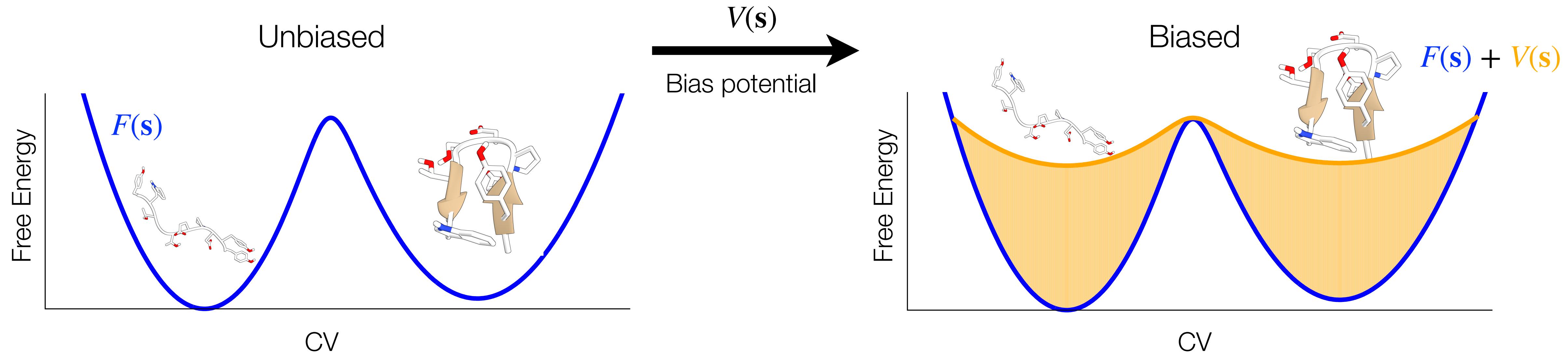
Therefore, should be possible to estimate the FES from histogram accumulated in a unbiased simulation of finite length

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

However, this rarely works due to sampling problems => the system will be stuck in single metastable state

# CV-based Based Enhanced Sampling Method

Introduce a bias potential  $V(s)$  that acts in the space spanned by the **slow** CVs  
(originally suggested in umbrella sampling<sup>@</sup>)



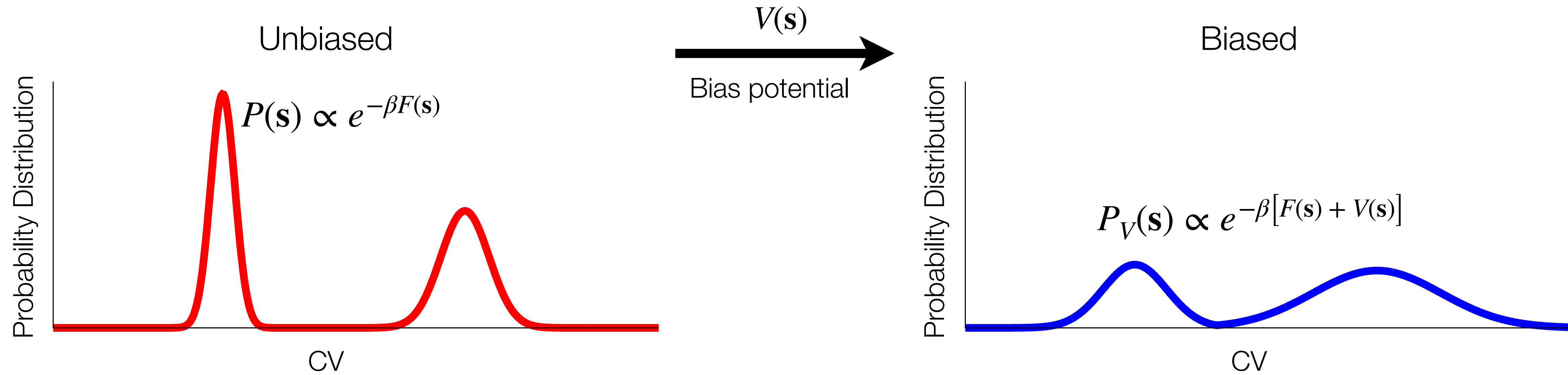
Reduce free energy barriers → easier to move between metastable states

Note: the original paper on umbrella sampling<sup>@</sup> only considered a single bias potential designed by hand. The idea of using multiple windows, each biased by a harmonic potential came later on and combining the results using weighted histogram analysis method (WHAM) came later on.

## CV-based Based Enhanced Sampling Method

Can also be viewed as enhancing CV fluctuations

Go to a biased distribution that is easier to sample



## CV-based Based Enhanced Sampling Method

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

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

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

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

## CV-based Based Enhanced Sampling Method - Reweighting

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

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

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

e.g. the FES for any CVs

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

Reweighted histogram

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

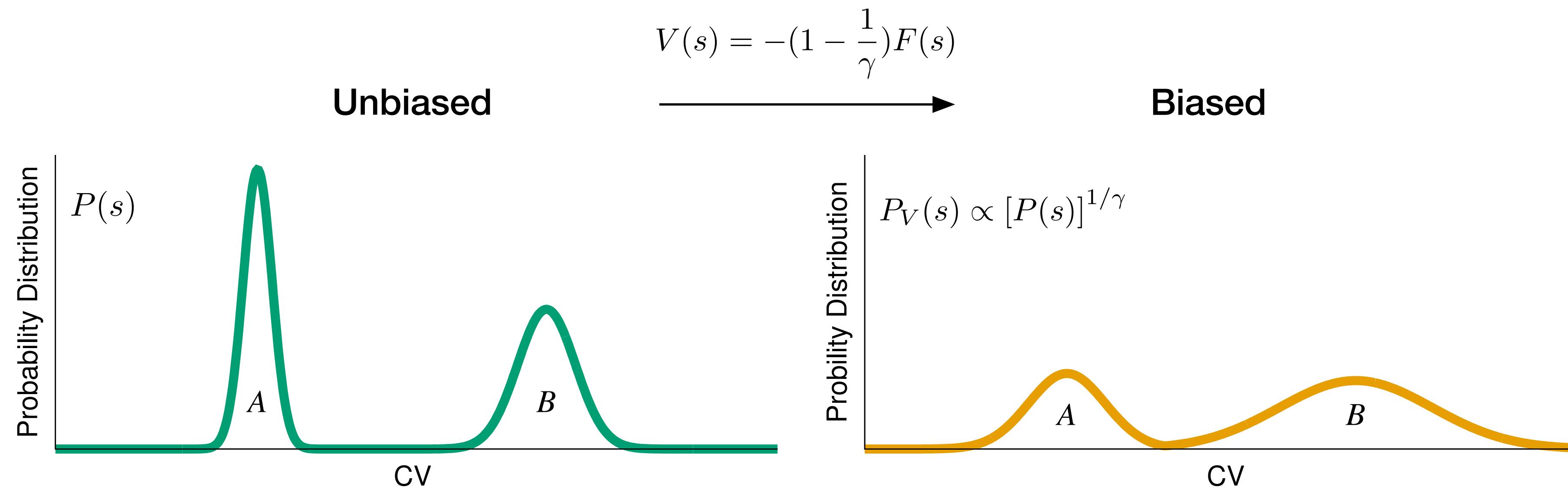
$$P_V(\mathbf{s}) \propto e^{-\beta[F(\mathbf{s})+V(\mathbf{s})]}$$

gives

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

so called **Well-Tempered Distribution**

## Well-Tempered Distribution



Enhanced fluctuations of the CVs  $\Rightarrow$  easier to cross barriers

Flatten the sampling as compared to unbiased distribution  $P(s)$

## Well-Tempered Distribution

By using

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

we obtain

$$F_V(\mathbf{s}) = \frac{1}{\gamma} F(\mathbf{s}) \quad (\text{ignoring unimportant additive constants})$$

The WT distribution can be viewed as sampling on an effective FES where barriers have been reduced by a factor of  $\gamma$

Optimal  $\gamma$  such that effective barriers are around few  $k_B T$  and easily crossed

The WT distribution can also be view as sampling the biased CVs at a higher effective temperature  $T + \Delta T = \gamma T$  (with a fixed FES  $F(\mathbf{s})$ )

## Uniform Distribution

Taking the limit  $\gamma \rightarrow \infty$  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  $\gamma$

# 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

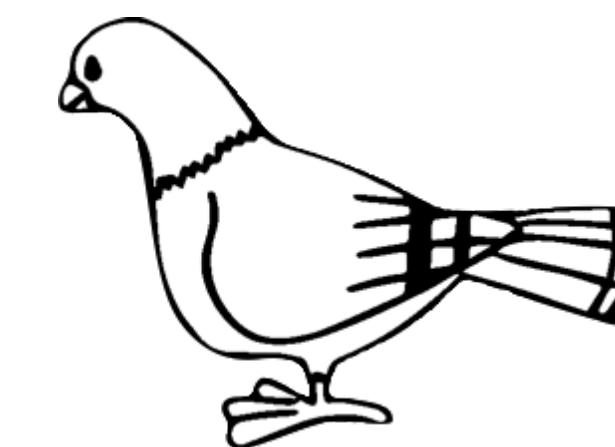
Laio & Parrinello, Proc. Natl. Acad. Sci. U.S.A. 2002,

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

Variationally Enhanced Sampling

Valsson & Parrinello, Phys. Rev. Lett. 2014

All available in PLUMED!



OPES (On-the-fly Probability Enhanced Sampling)

Invernizzi & Parrinello, J. Phys. Chem. Lett. 2020

Invernizzi, Piaggi, & Parrinello, Pays. Rev. X 2020

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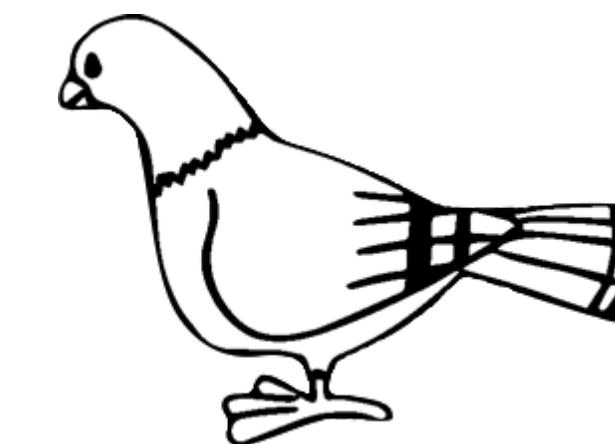
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Laio & Parrinello, Proc. Natl. Acad. Sci. U.S.A. 2002,

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## General Requirements on CVs

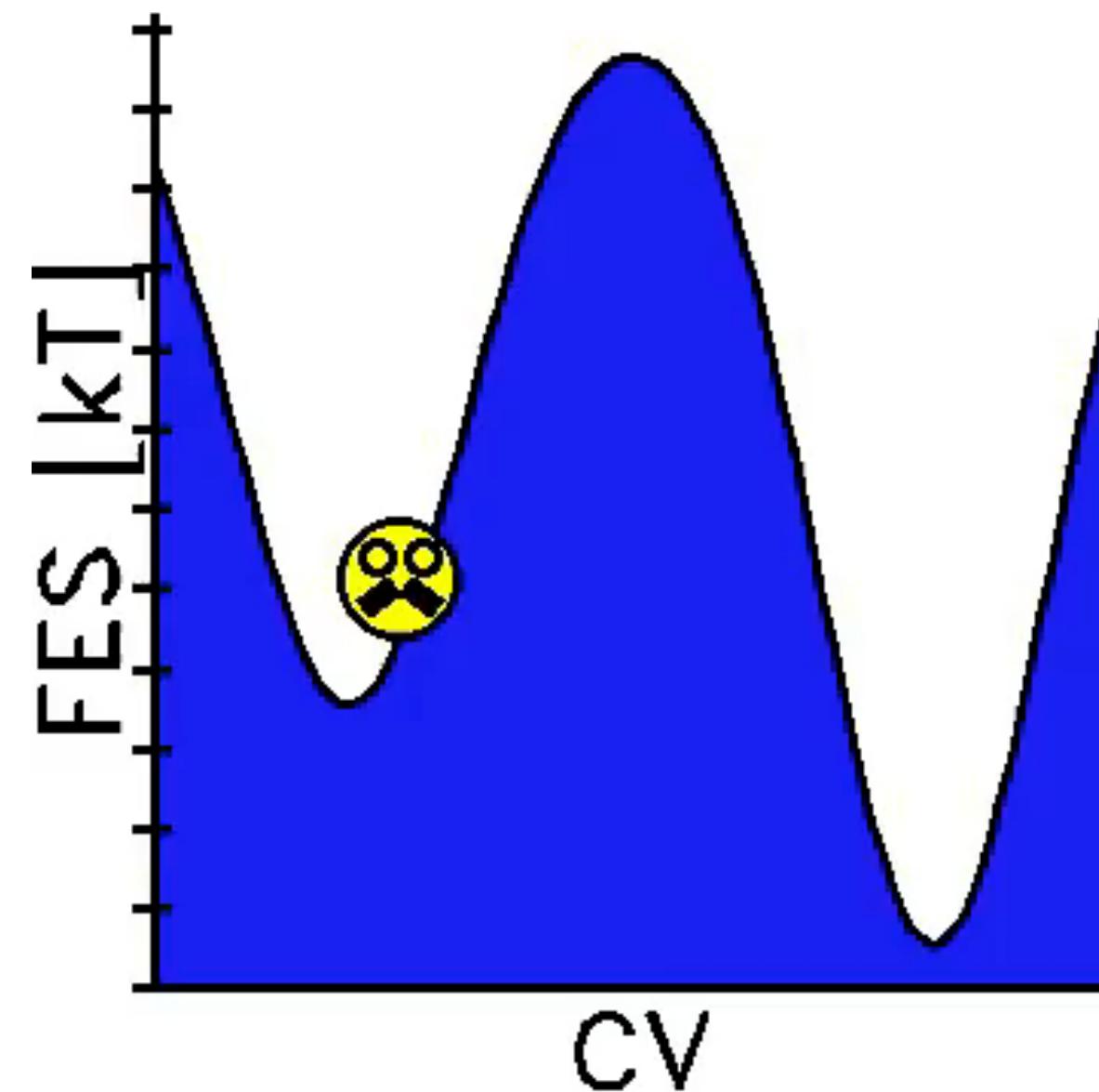
The CVs that are biased must generally:

- 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

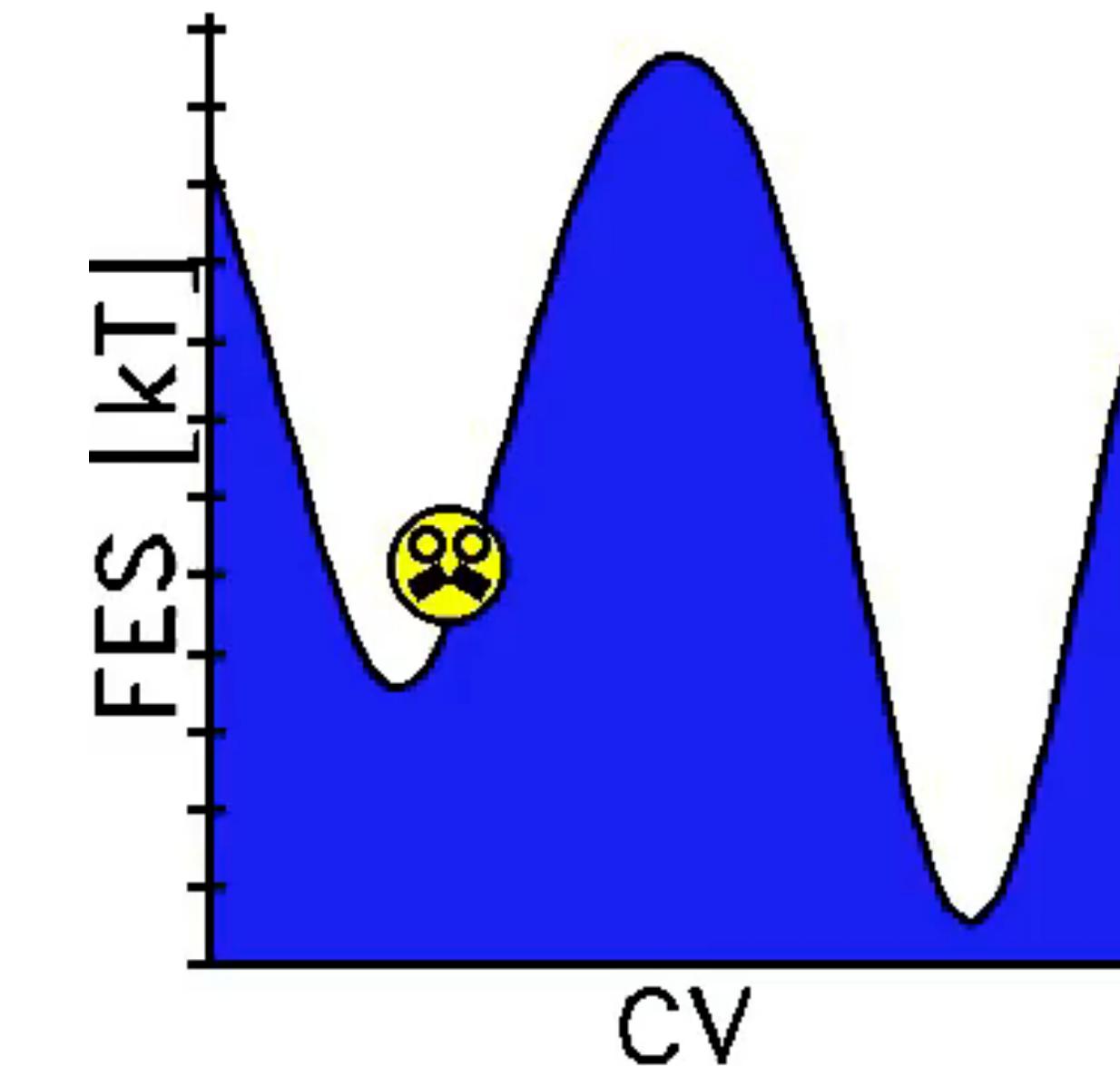
## Metadynamics

Deposit repulsive Gaussian biasing kernels everywhere you go in CV space  
→ pushes you over the barriers

Unbiased Molecular Dynamics



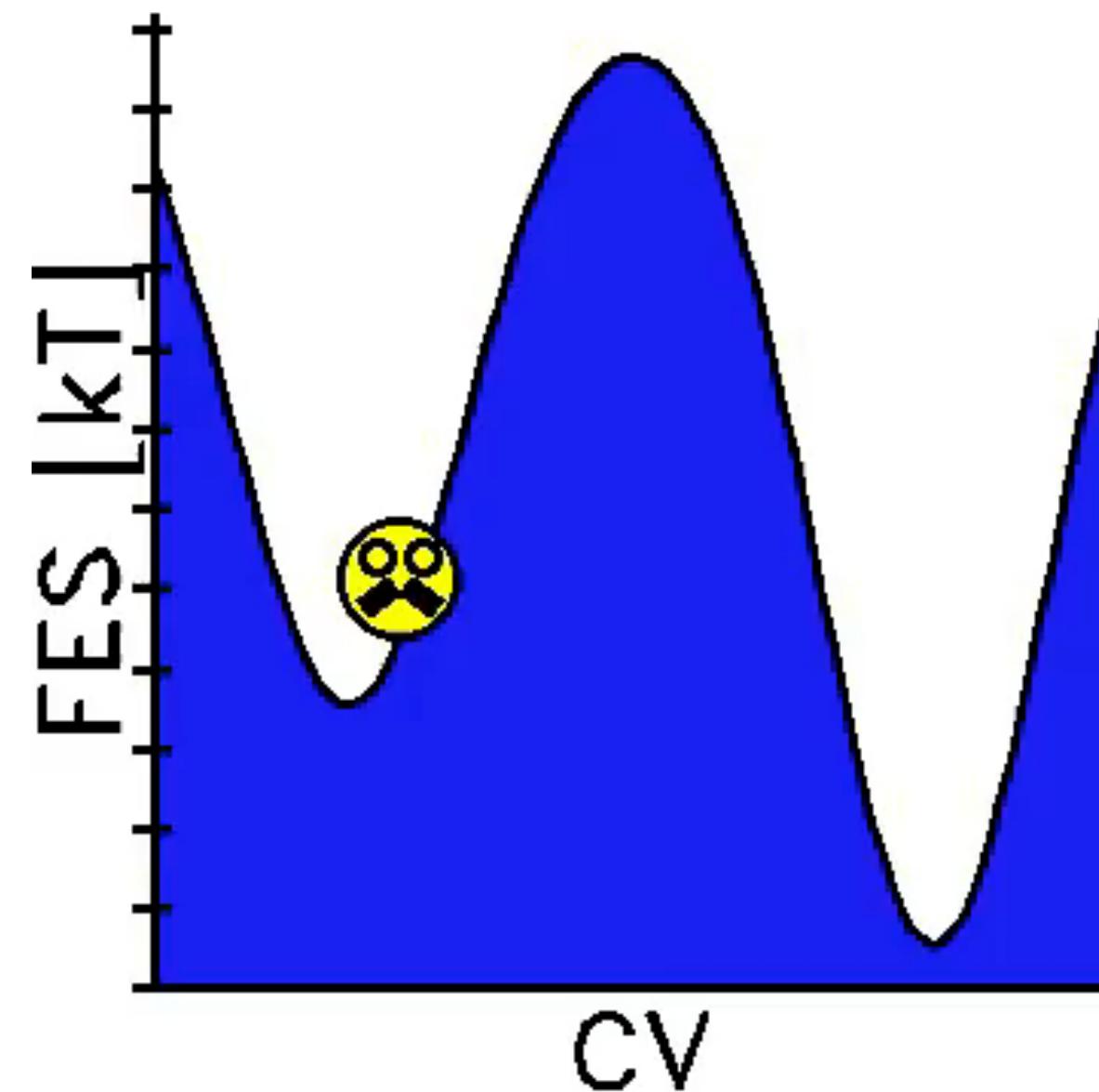
Metadynamics



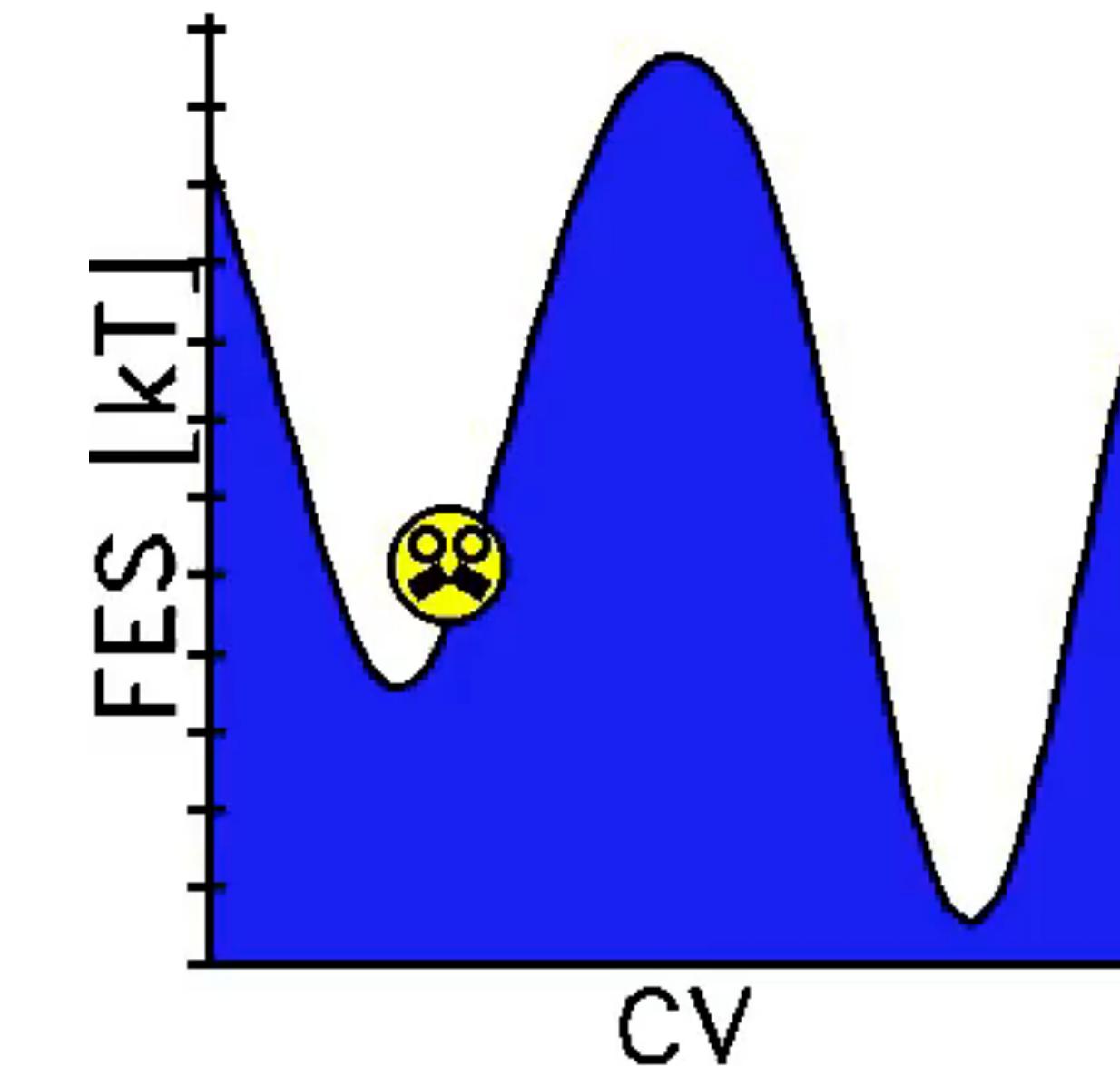
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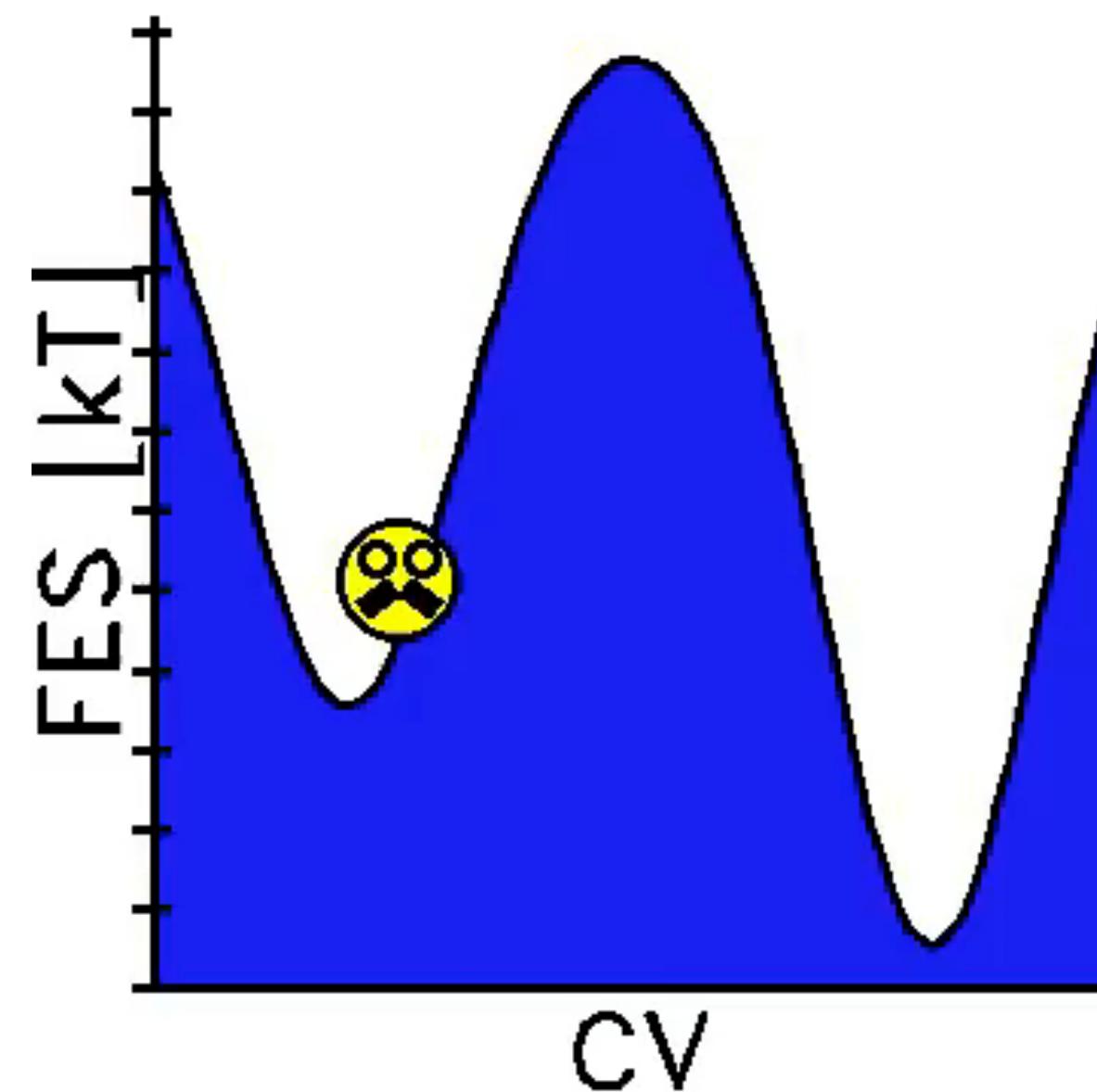
Metadynamics



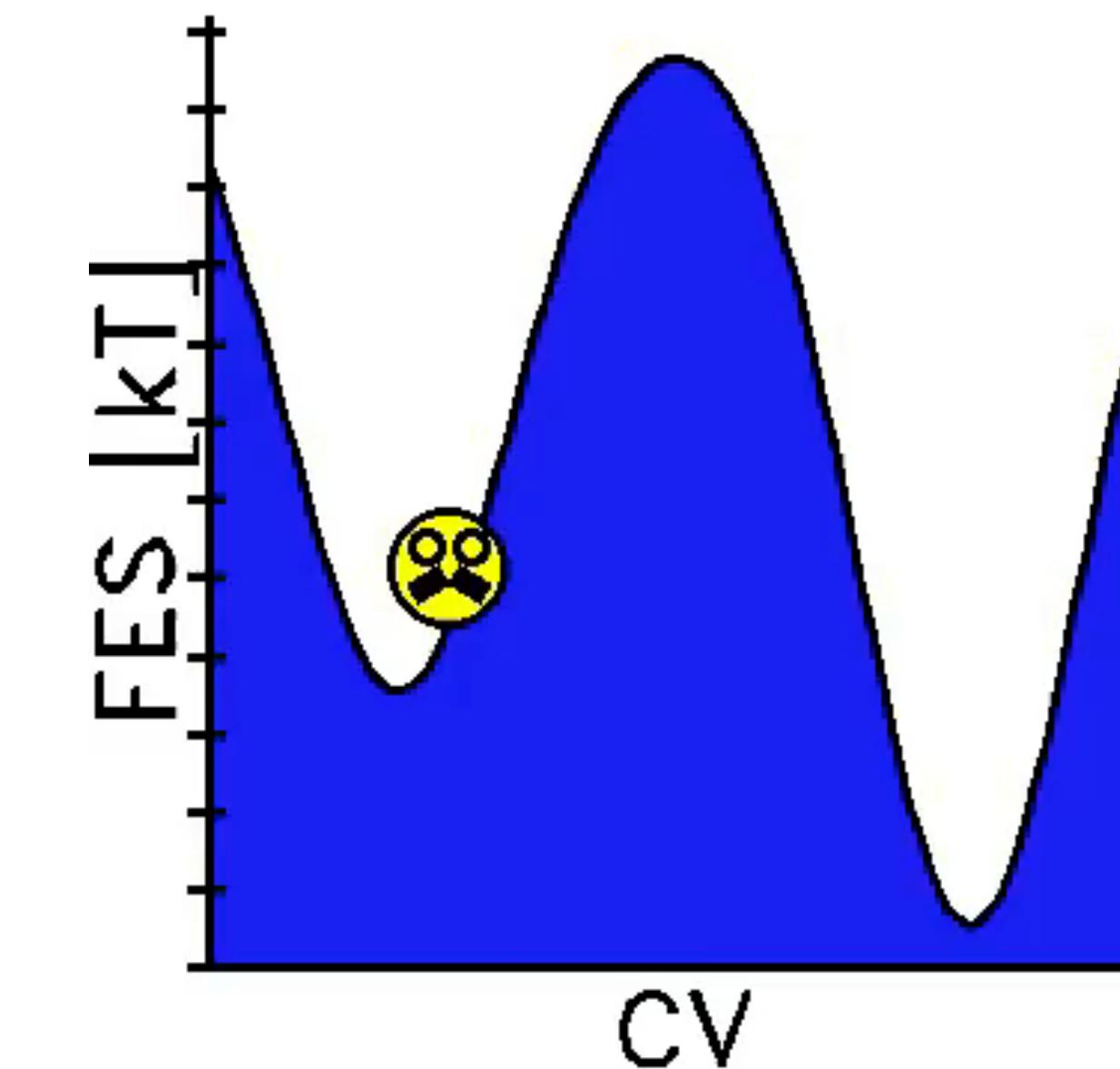
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Deposit repulsive Gaussian biasing kernels everywhere you go in CV space  
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Unbiased Molecular Dynamics



Metadynamics



## 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  $\mathbf{s}_n$  and scaled by

$$\exp \left[ -\frac{1}{\gamma - 1} \beta V_{n-1}(\mathbf{s}_n) \right] \quad \mathbf{s}_n = (s_{n,1}, s_{n,2}, \dots, s_{n,d})$$

## Well-Tempered Metadynamics

The update is performed every  $N_G$  steps

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

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

sum of repulsive Gaussian kernels

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, so it does not change with time (apart from a time-dependent constant) => This is important for reweighting

## Well-Tempered Metadynamics

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

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

↑  
constant independent of  $\mathbf{s}$   
that grows with time

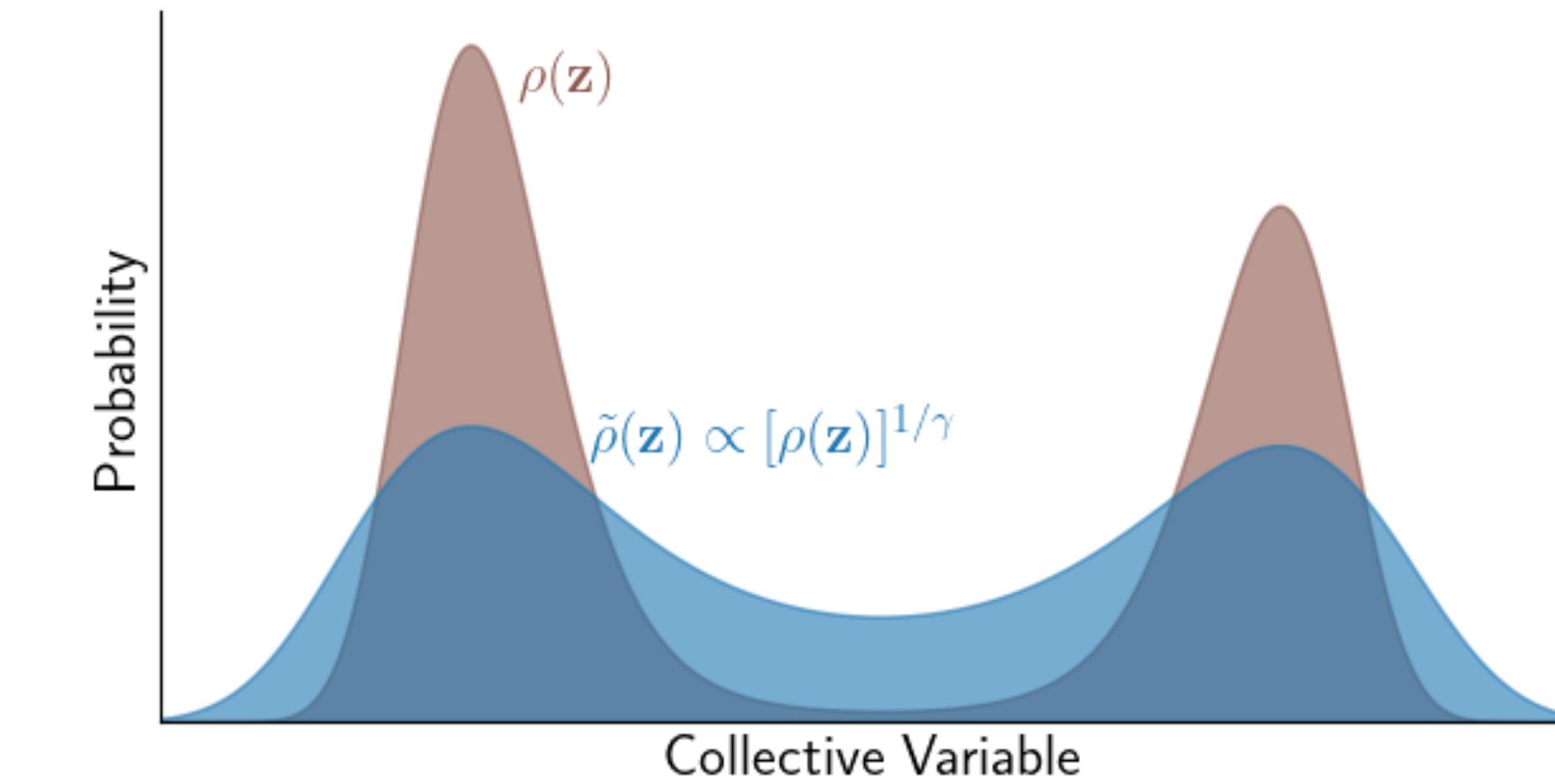
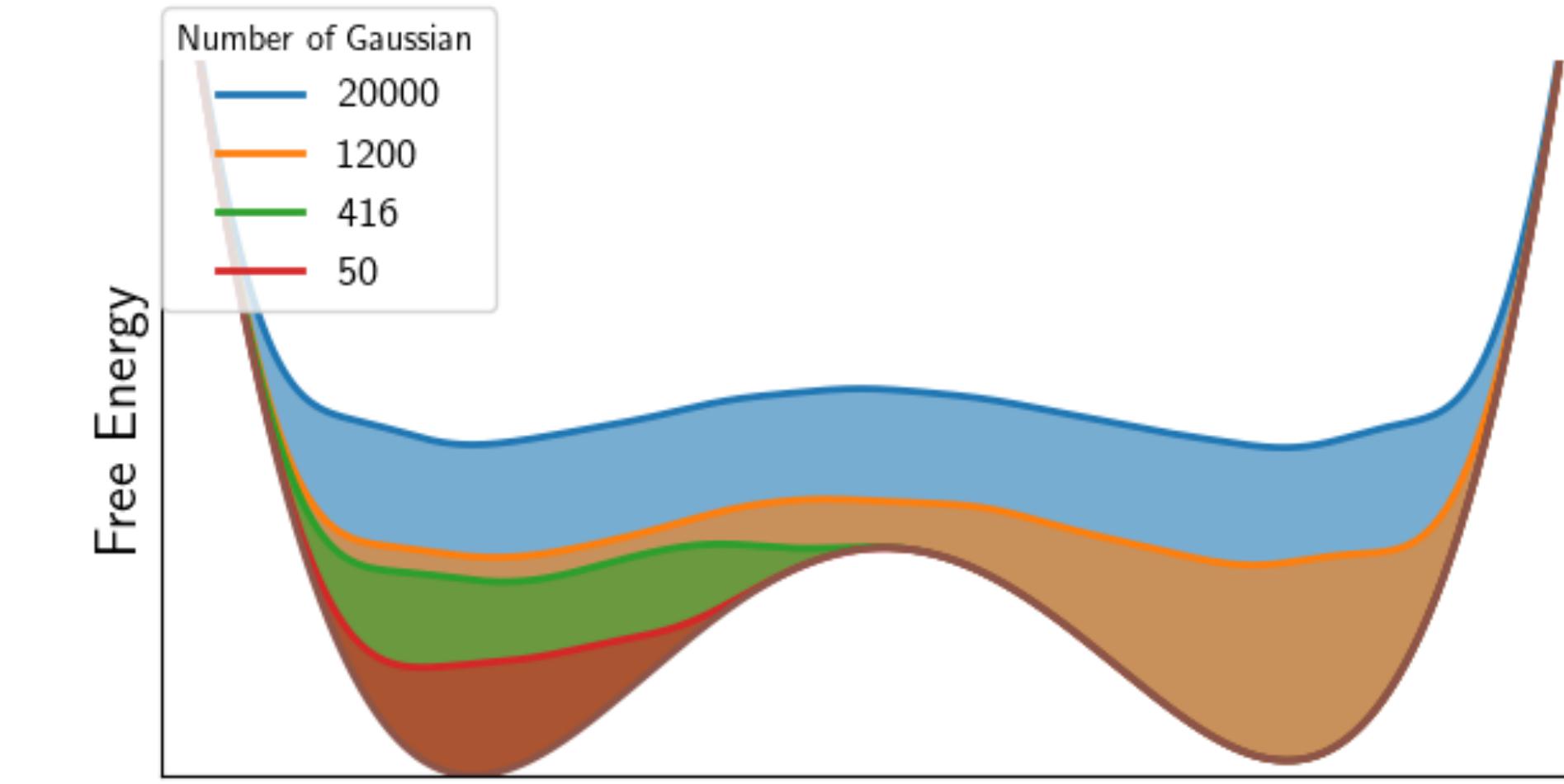
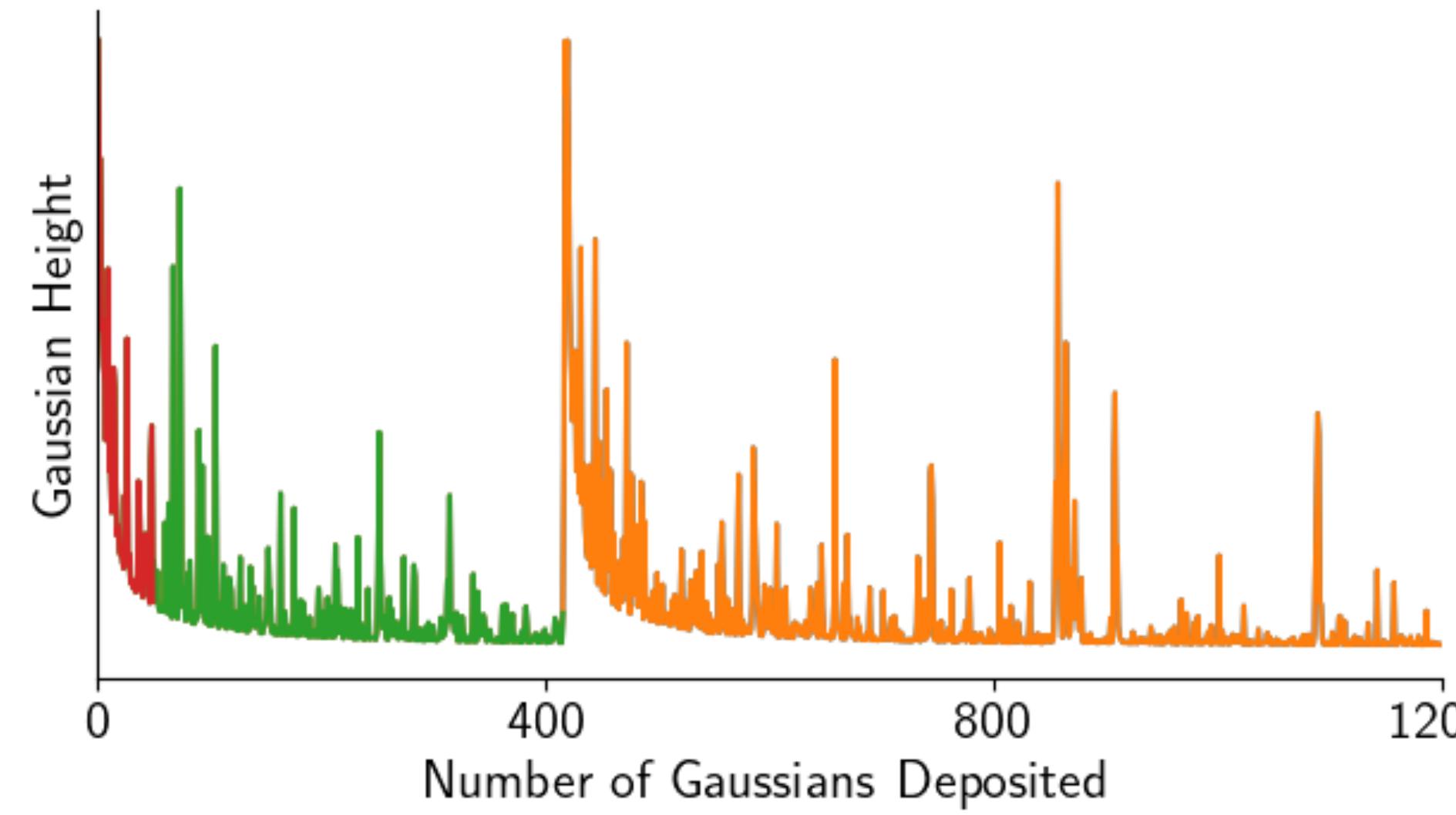
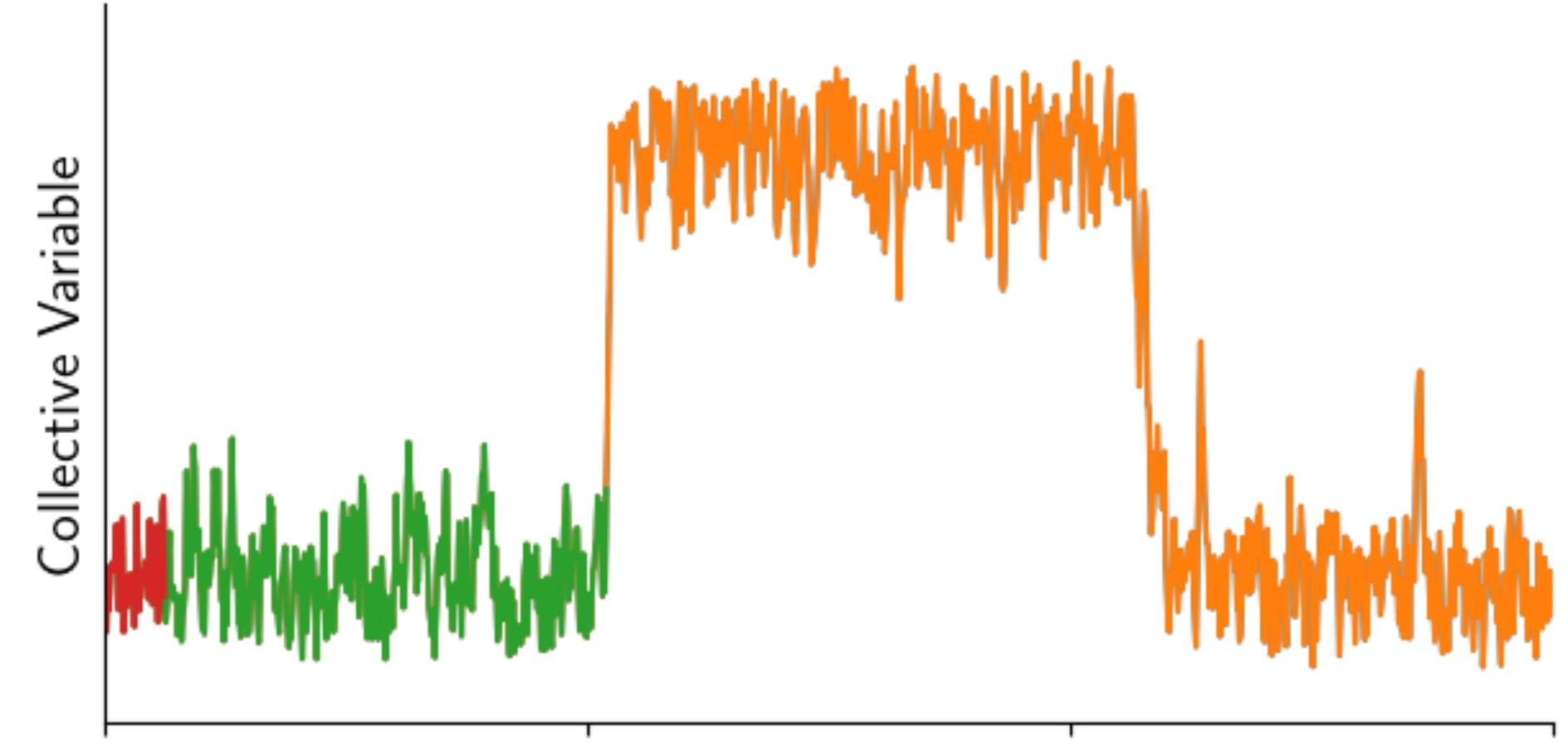


$$P_V(\mathbf{s}) \propto [P(\mathbf{s})]^{1/\gamma}$$

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

**Can directly obtain the FES from the constructed bias**

# Well-Tempered Metadynamics



## Well-Tempered Metadynamics - Reweighting

Need to account for time-dependence of bias when reweighting

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

Can view this as a re-normalized bias potential used for reweighing

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

$$\tilde{V}(\mathbf{s}, t) = V(\mathbf{s}, t) - c(t)$$

where the time-dependent constant  $c(t)$  is calculated as<sup>a</sup>

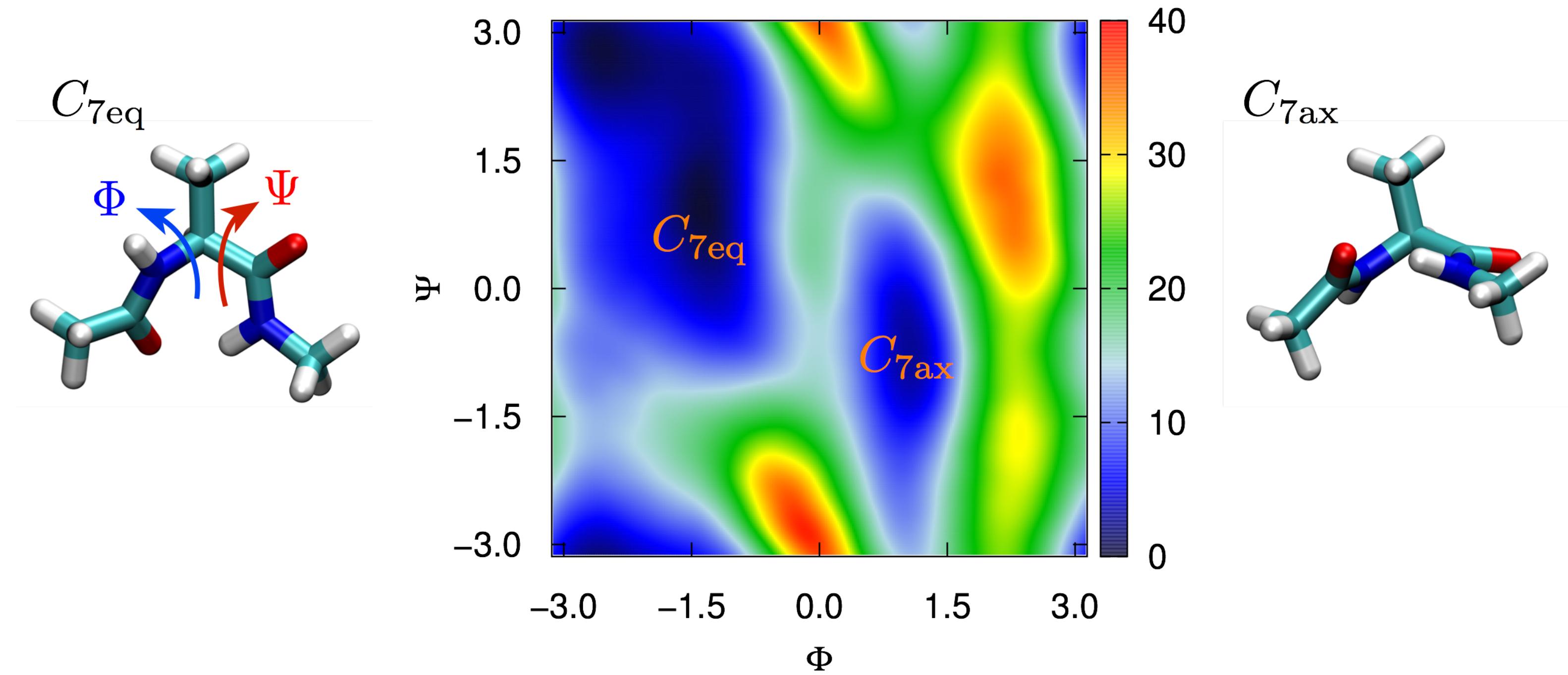
$$c(t) = \frac{1}{\beta} \log \frac{\int d\mathbf{s} \exp \left[ \frac{\gamma}{\gamma-1} \beta V(\mathbf{s}, t) \right]}{\int d\mathbf{s} \exp \left[ \frac{1}{\gamma-1} \beta V(\mathbf{s}, t) \right]}$$

valid when the bias has reached a quasi-stationary state

Alternative: last-bias reweighting, see [10.33011/livecoms.4.1.1583](https://doi.org/10.33011/livecoms.4.1.1583)

## Exemplifying System - Alanine Dipeptide

Alanine dipeptide in vacuum - Backbone dihedral angles  $\Phi, \Psi$  as CVs

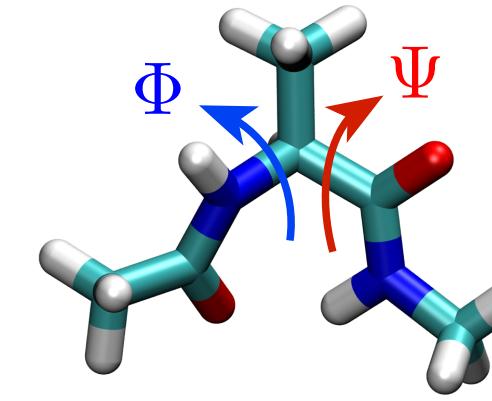


Two metastable basins,  $C_{7\text{eq}}$  and  $C_{7\text{ax}}$

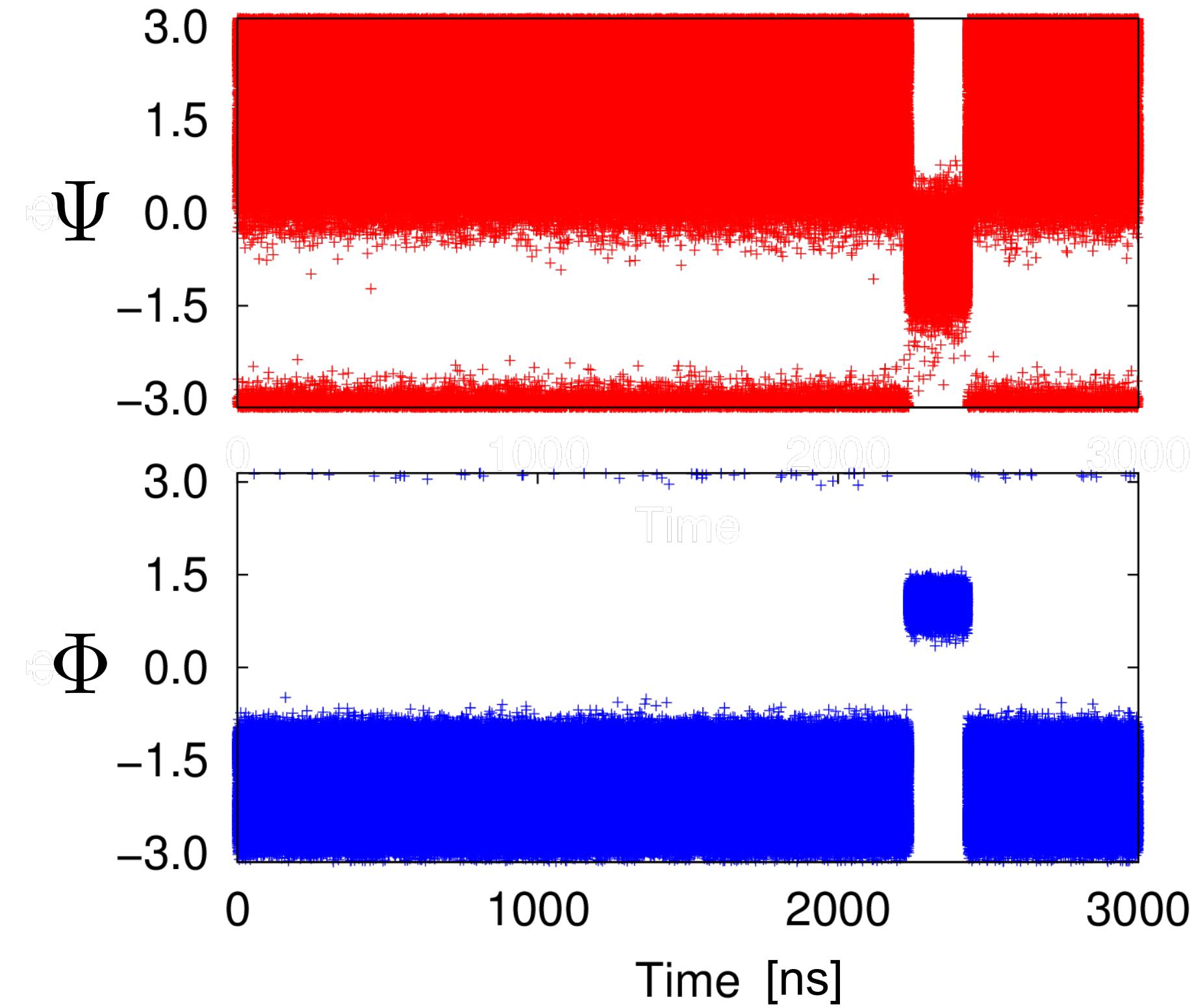
barrier around 34 kJ/mol ( $16 k_B T$ )

mean transition time around 28  $\mu\text{s}$

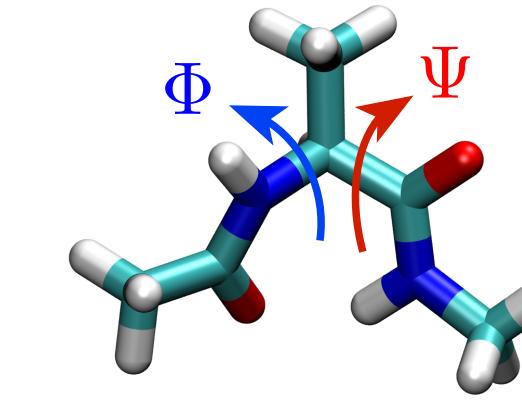
## Exemplifying System - Alanine Dipeptide



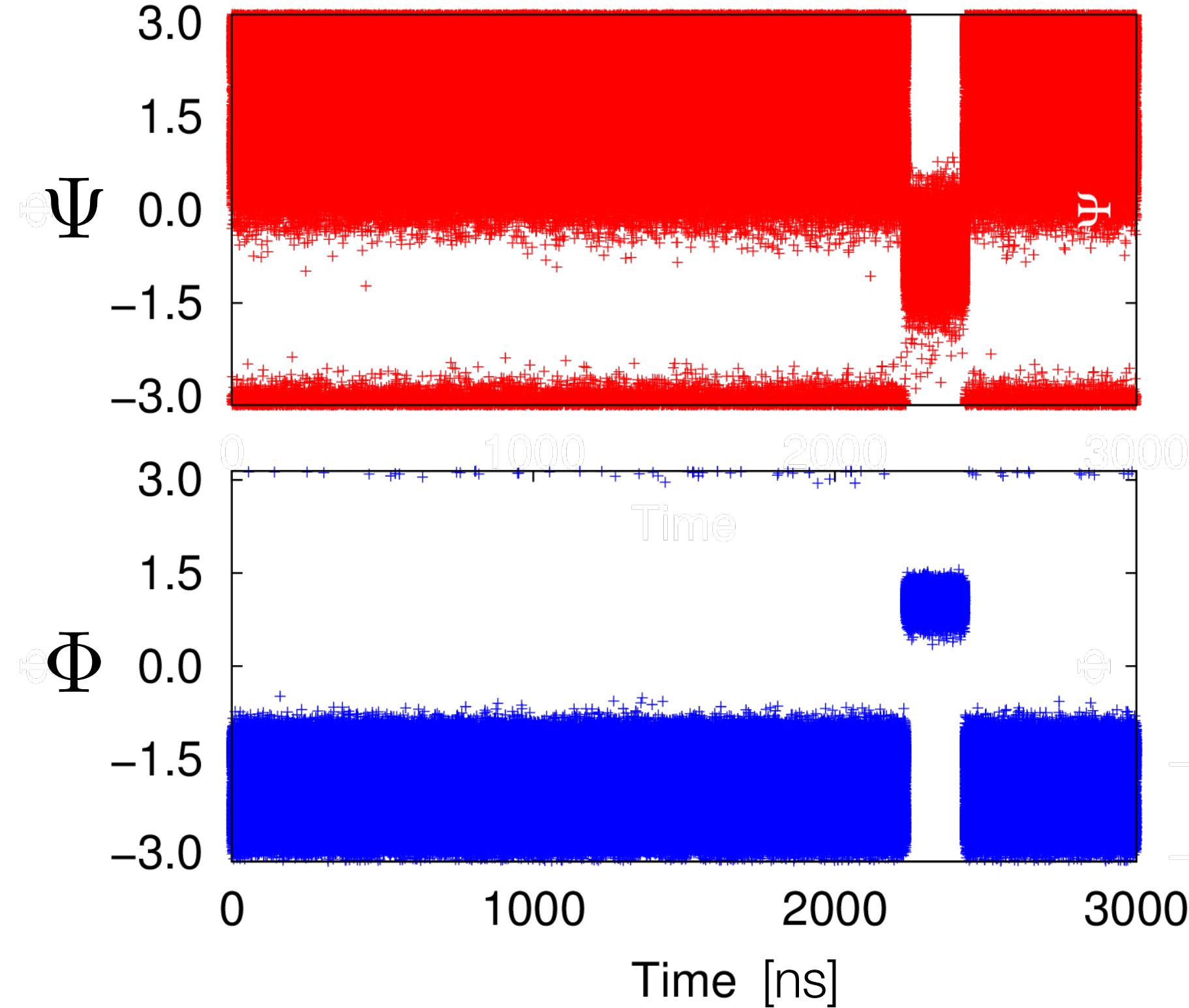
Unbiased molecular dynamics



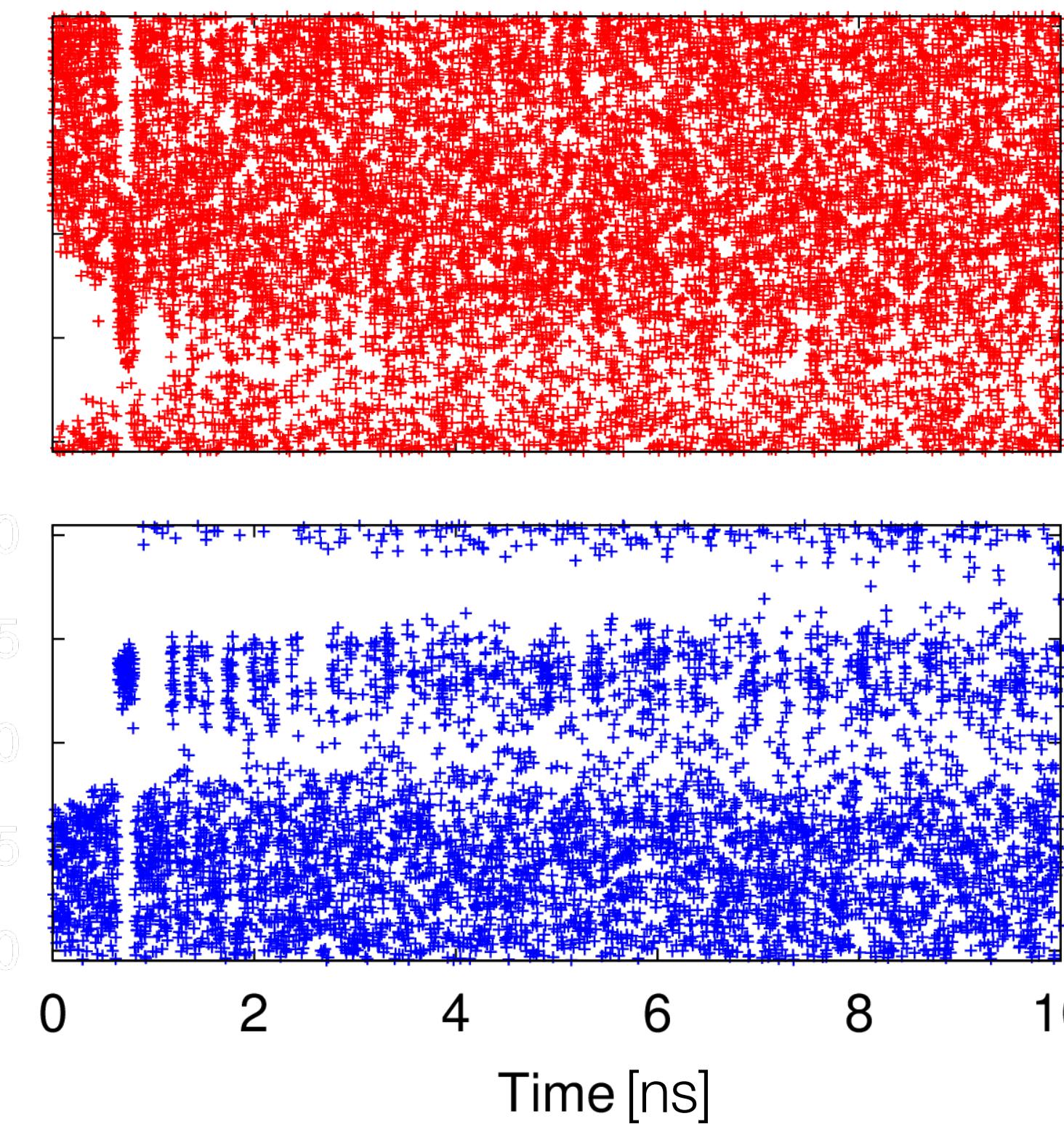
## Exemplifying System - Alanine Dipeptide



Unbiased molecular dynamics



Metadynamics



Note the difference of 300 in the time scale!

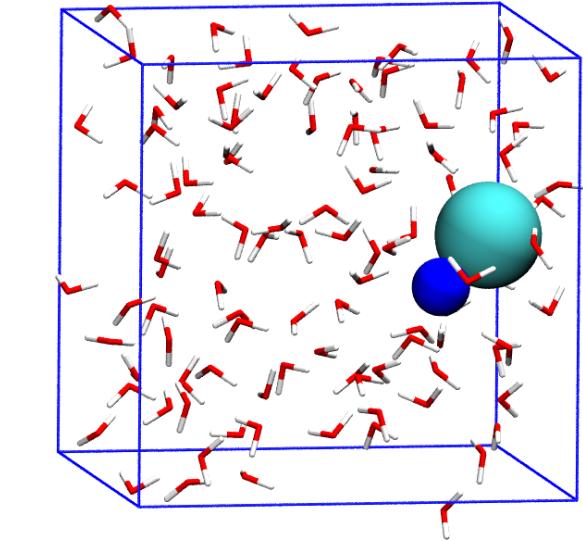
# Metadynamics Reweighting

The ability to reweight Metadynamics simulations is a powerful post-processing tool

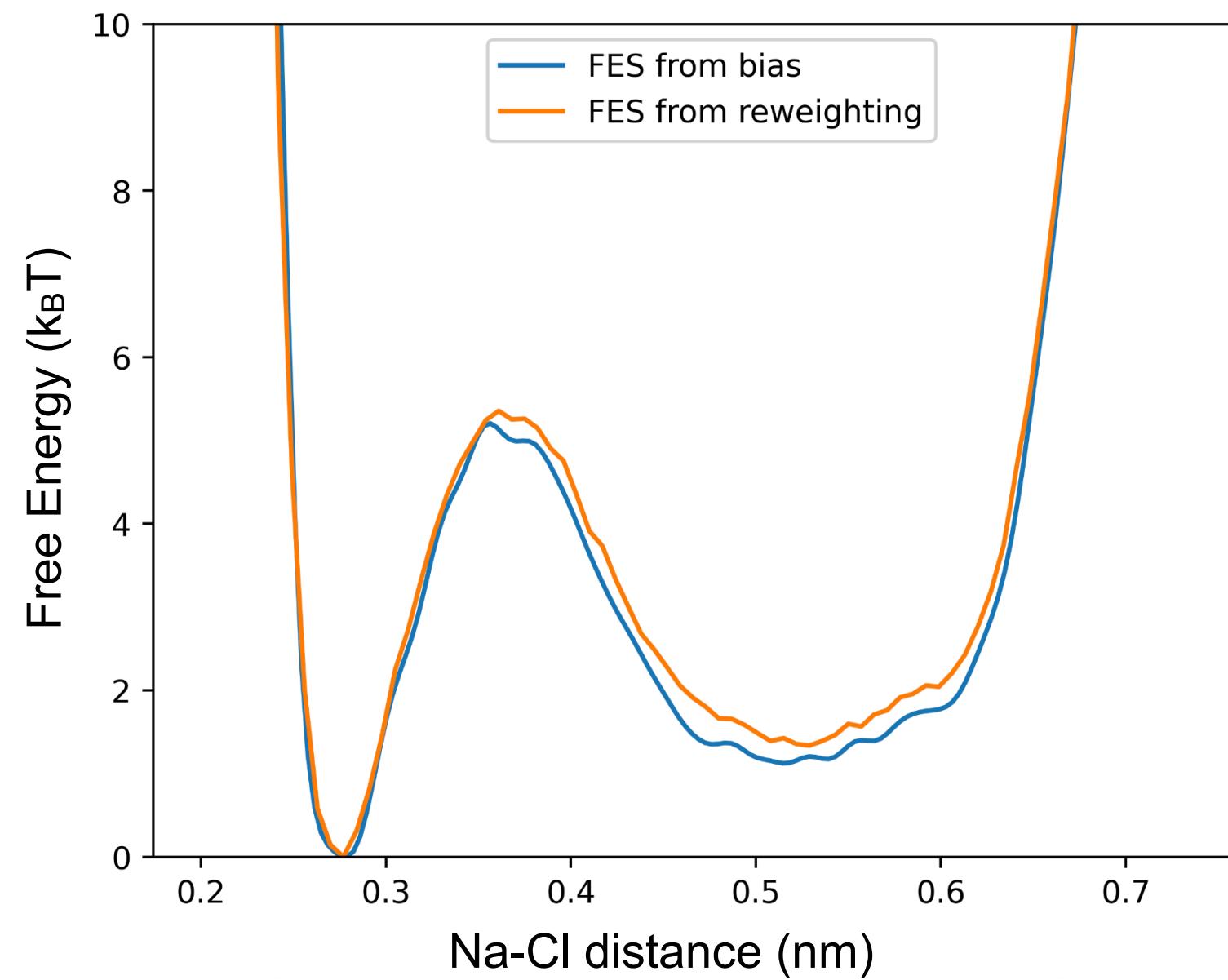
- Can check convergence by comparing FES obtained directly from bias and from reweighting (recommend practice)
- Can obtain the FES for CVs that were not biased in the Metadynamics simulations

Example: association/dissociation of NaCl in aqueous solution (from [this tutorial](#))

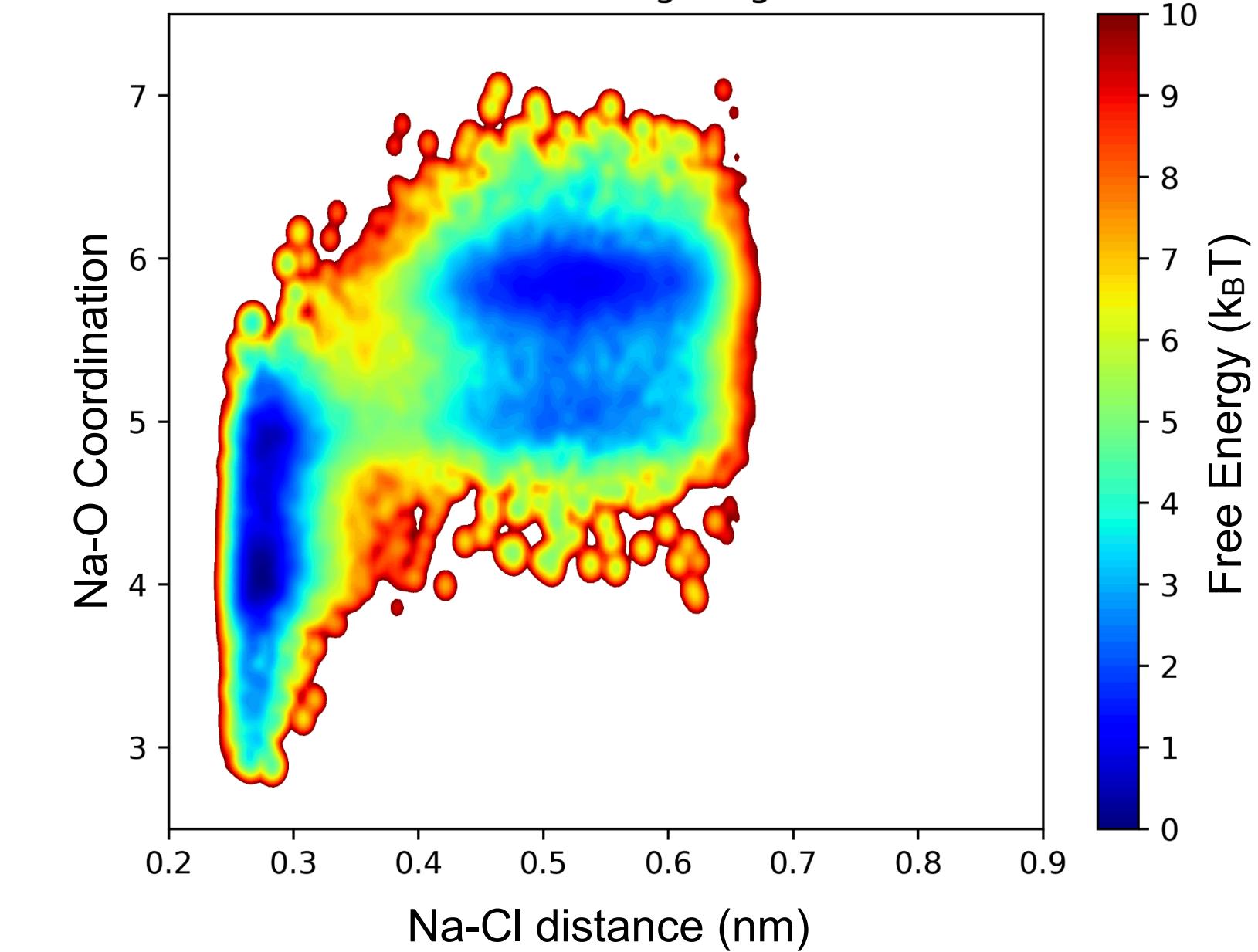
Biased CV: Na-Cl distance



FES for Na-Cl distance



FES for Na-Cl distance + Solvation of Na



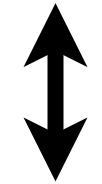
## Extensions of Metadynamics

- Multiple Walkers MetaD  
Shared bias between multiple copies, reduces human time needed for convergence
- 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 a replica exchange strategy
- Parallel-Bias MetaD  
Employ many CVs within one replica via 1D potentials
- Adaptive Gaussians MetaD  
Gaussian whose shape adapt to the FES
- Infrequent MetaD for obtaining kinetics  
Obtain kinetics of rare event from biased simulations

# PLUMED + MD Code of Choice

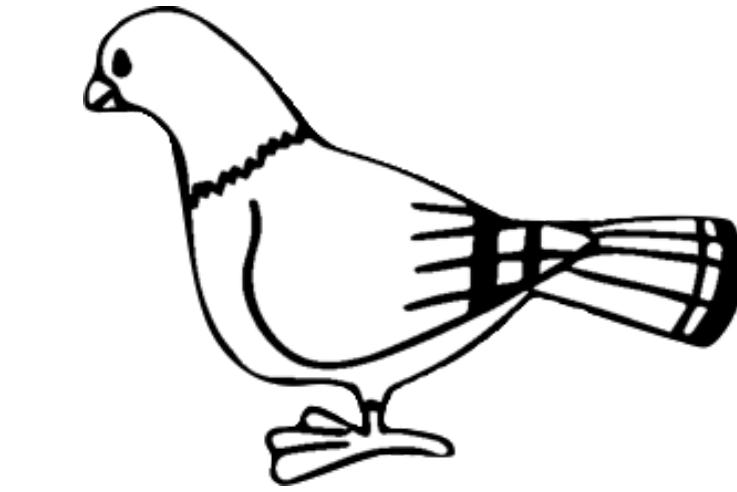
MD Code

e.g. Gromacs, **LAMMPS**, CP2K, OpenMM, Amber, NAMD, ESPResSo++, ...



PLUMED 2  
[www.plumed.org](http://www.plumed.org)

**PLU**gin 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

Keywords in a **METAD** action in PLUMED

$N_G$  how often we deposit Gaussians **PACE**

$W_0$  the initial Gaussian height **HEIGHT**

$\gamma$  bias factor **BIASTATOR**

$\sigma_i$  width (standard deviations) of deposited Gaussians **SIGMA**

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**BIASTHRESHOLD**

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## Well-Tempered Metadynamics

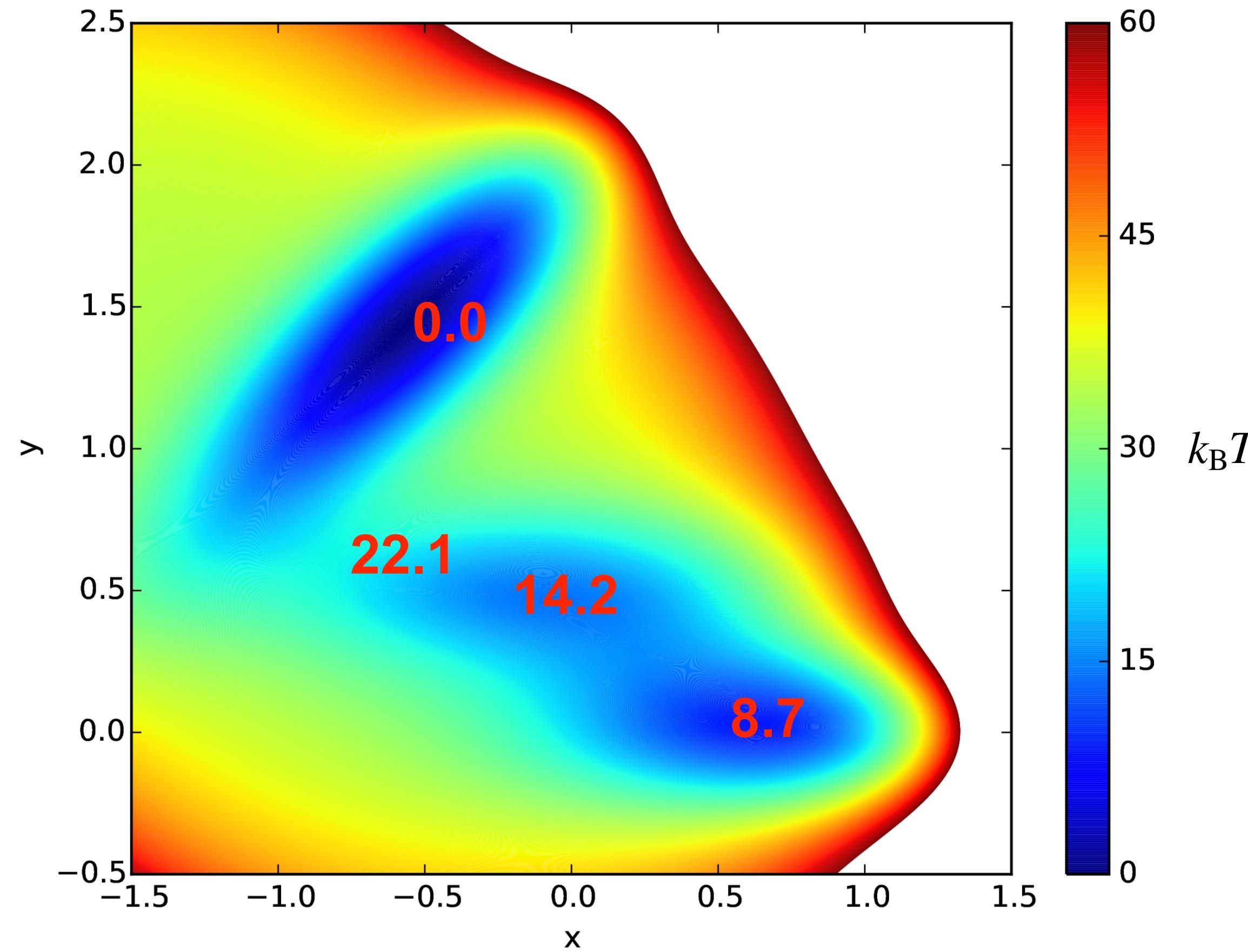
typical values

$N_G$	~ 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 $k_B T$ , e.g. $0.1^*k_B T$ to $1.0^*k_B T$
$\gamma$	ideally a value that makes the effective free energy barriers to be on the order of few $k_B T$ too low value will not enhance the sampling enough while too large value will lead to slow convergence
$\sigma_i$	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

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

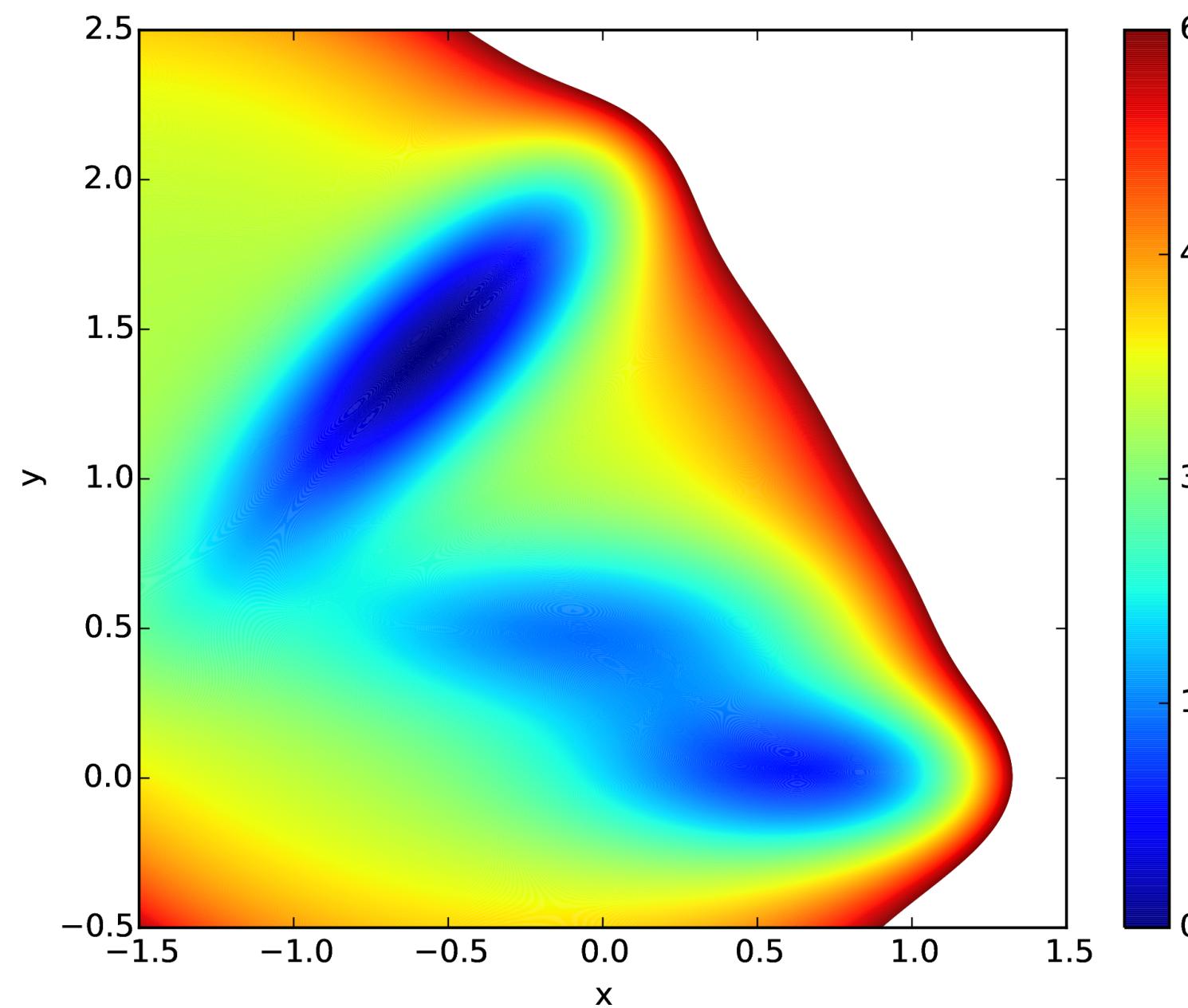


## Exemplifying System - Mueller Brown Potential

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

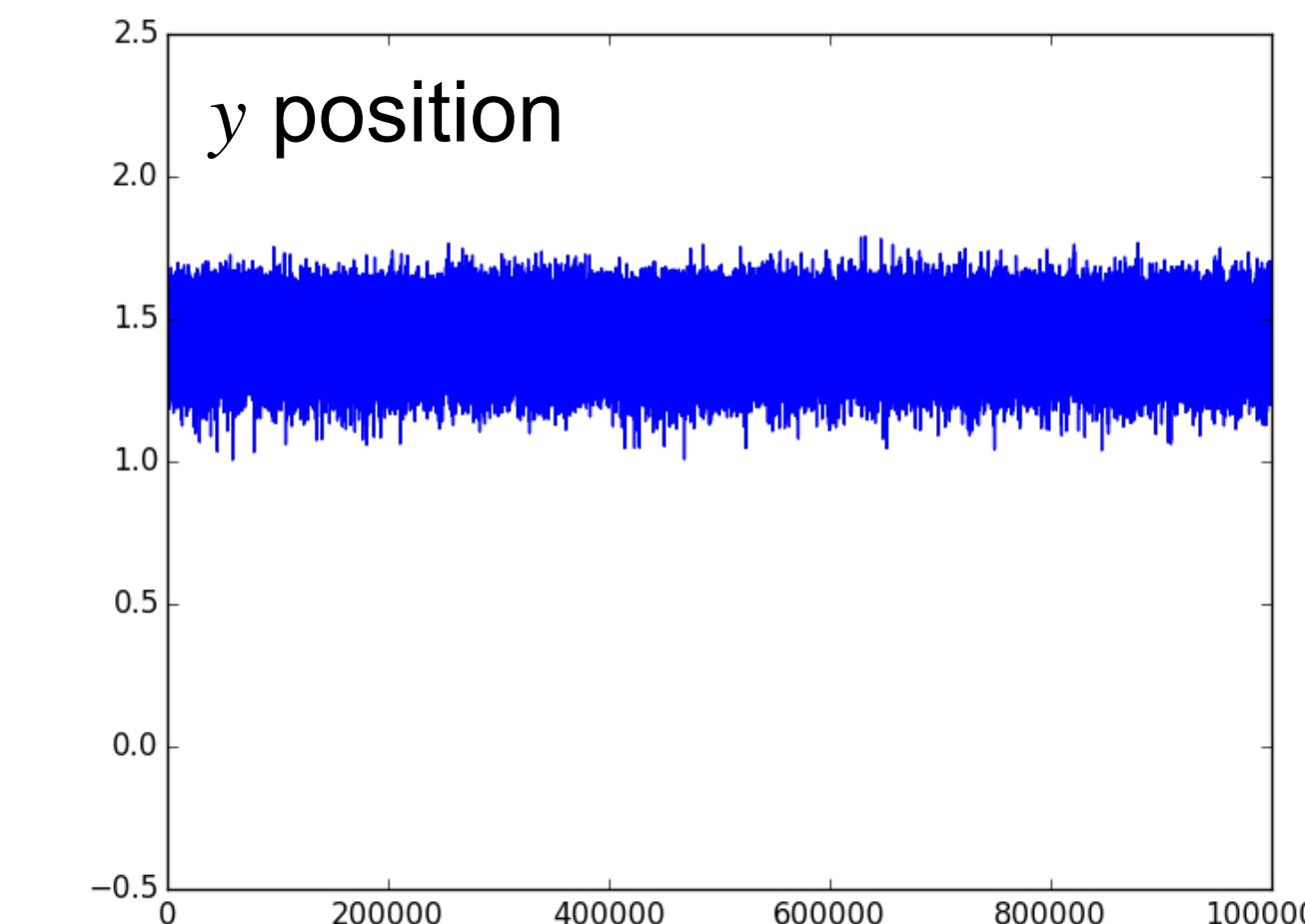
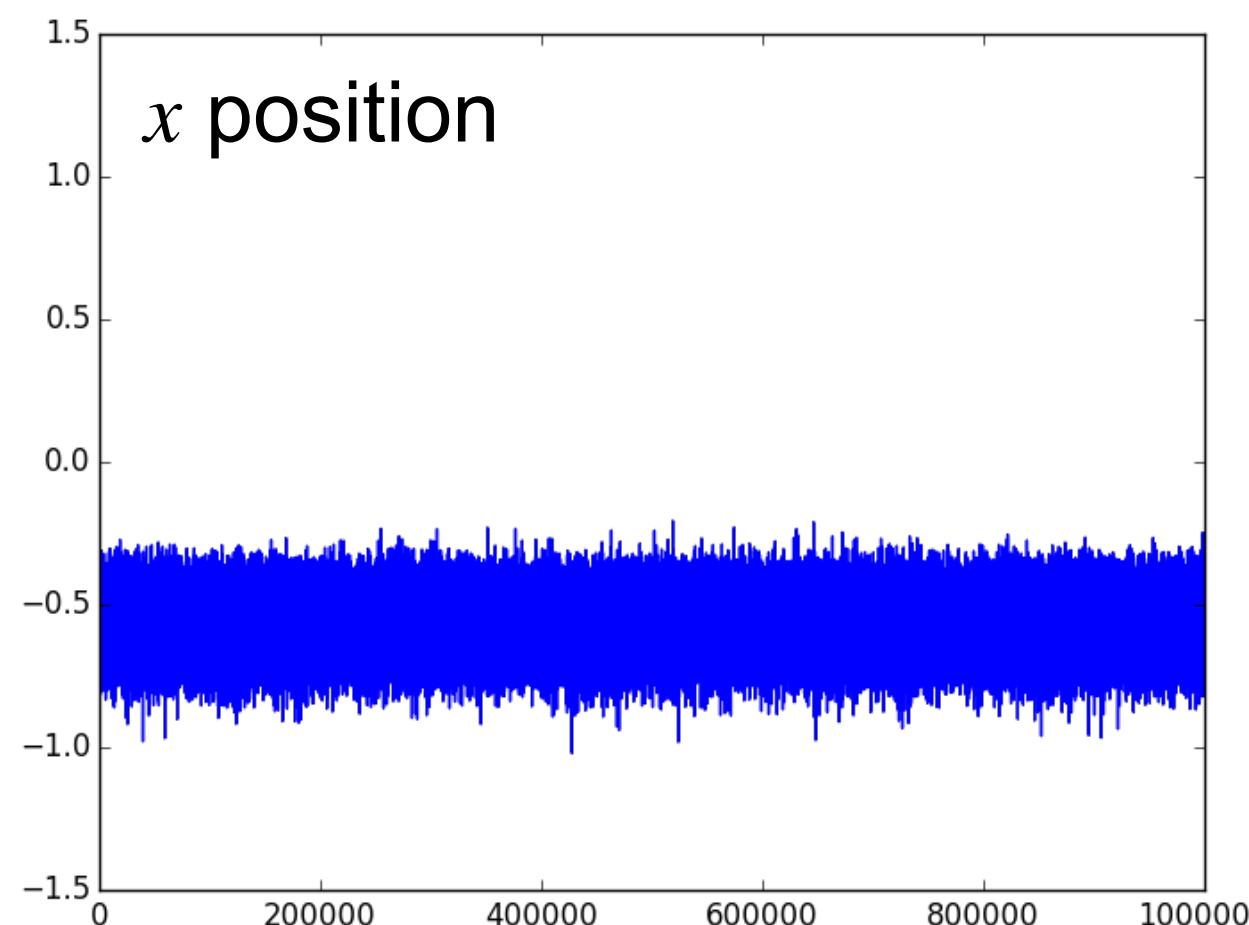
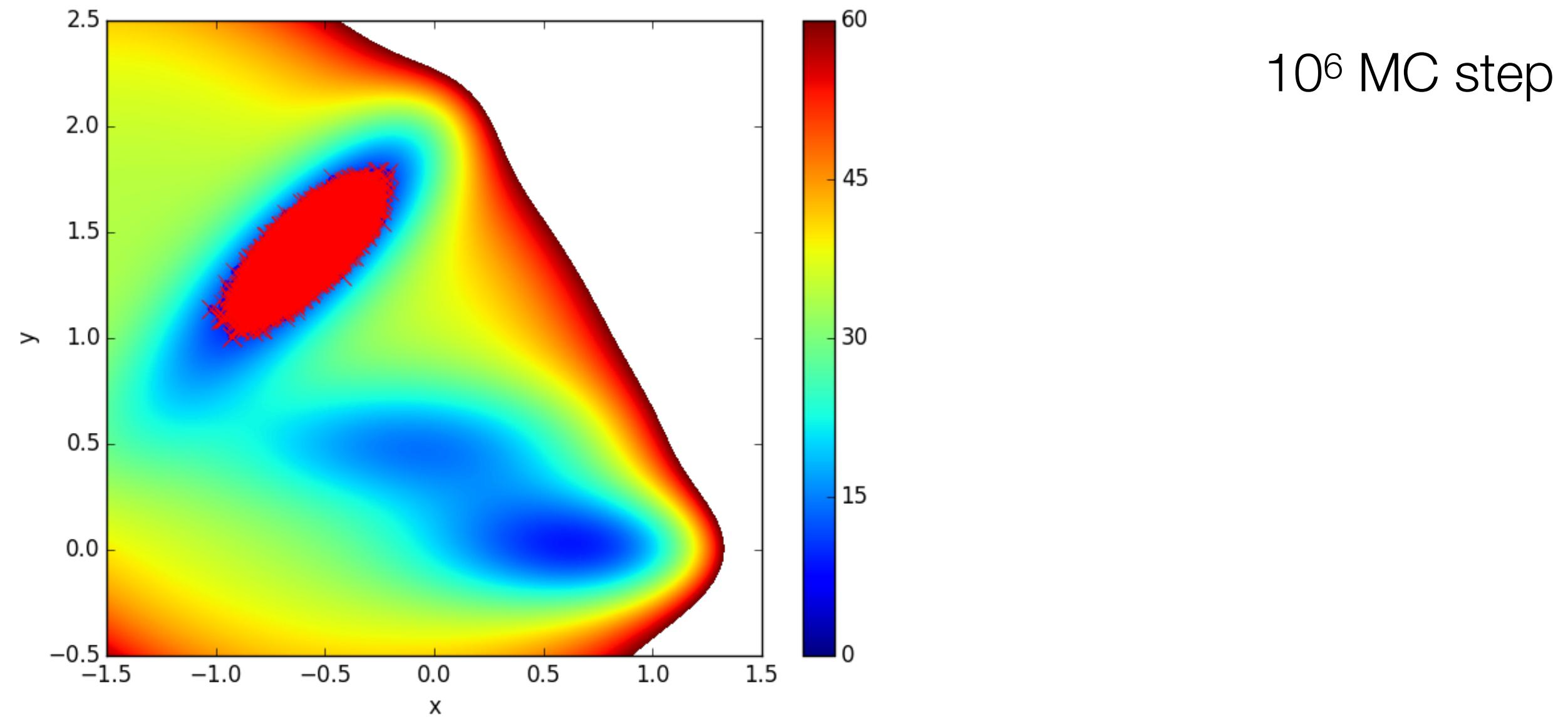
$x$  and  $y$  as CVs  $\rightarrow$  the FES is just given by  $U(x,y)$

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



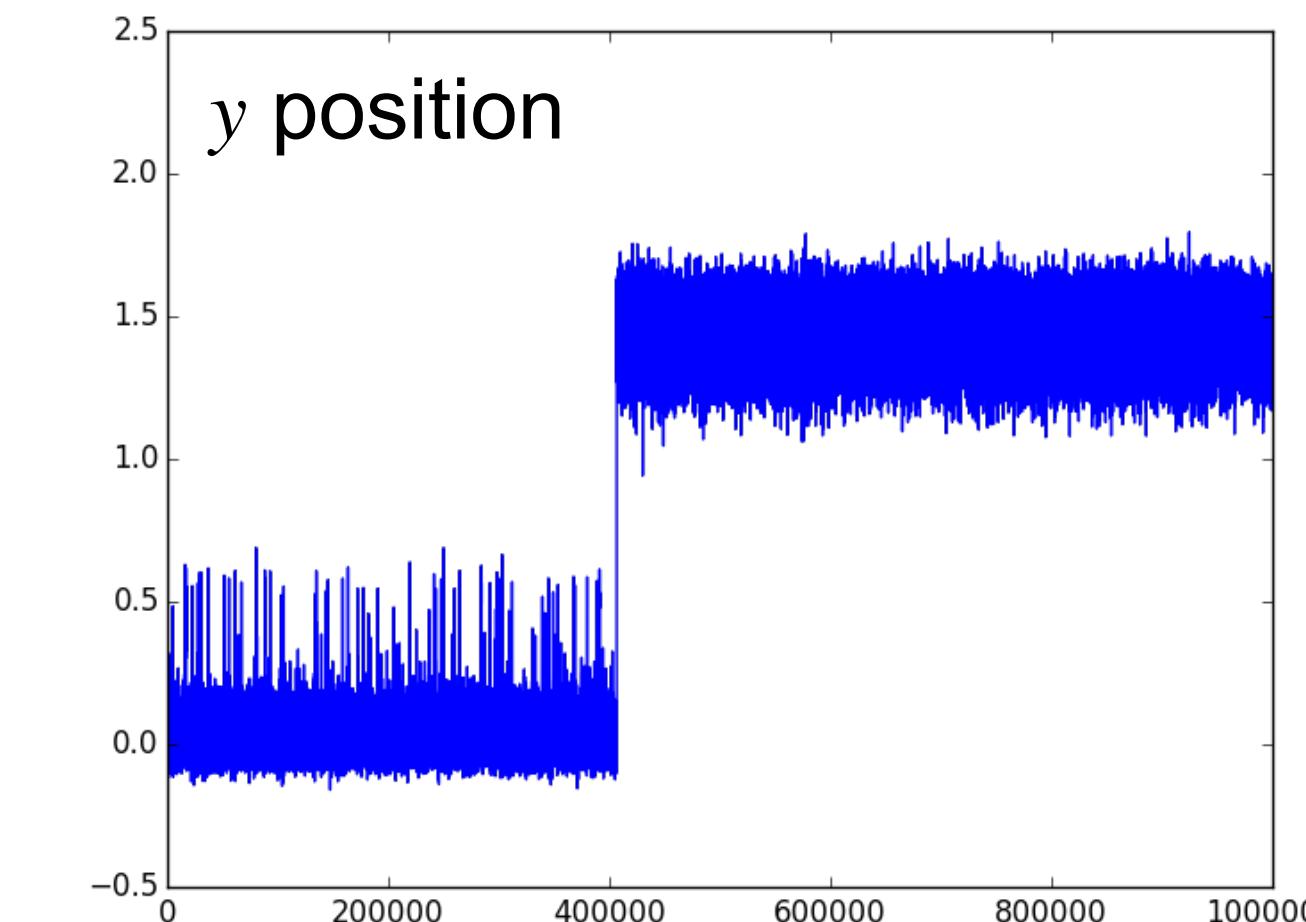
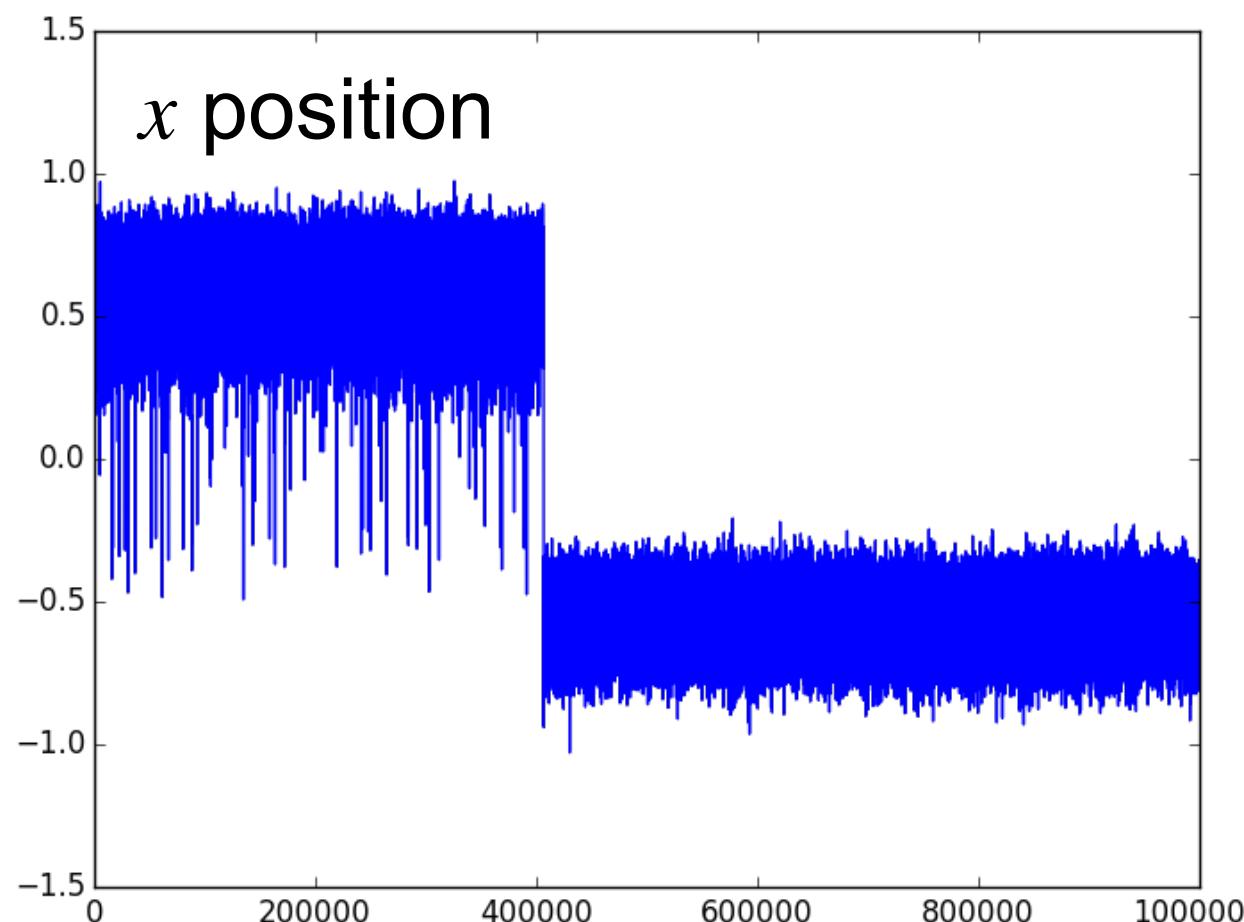
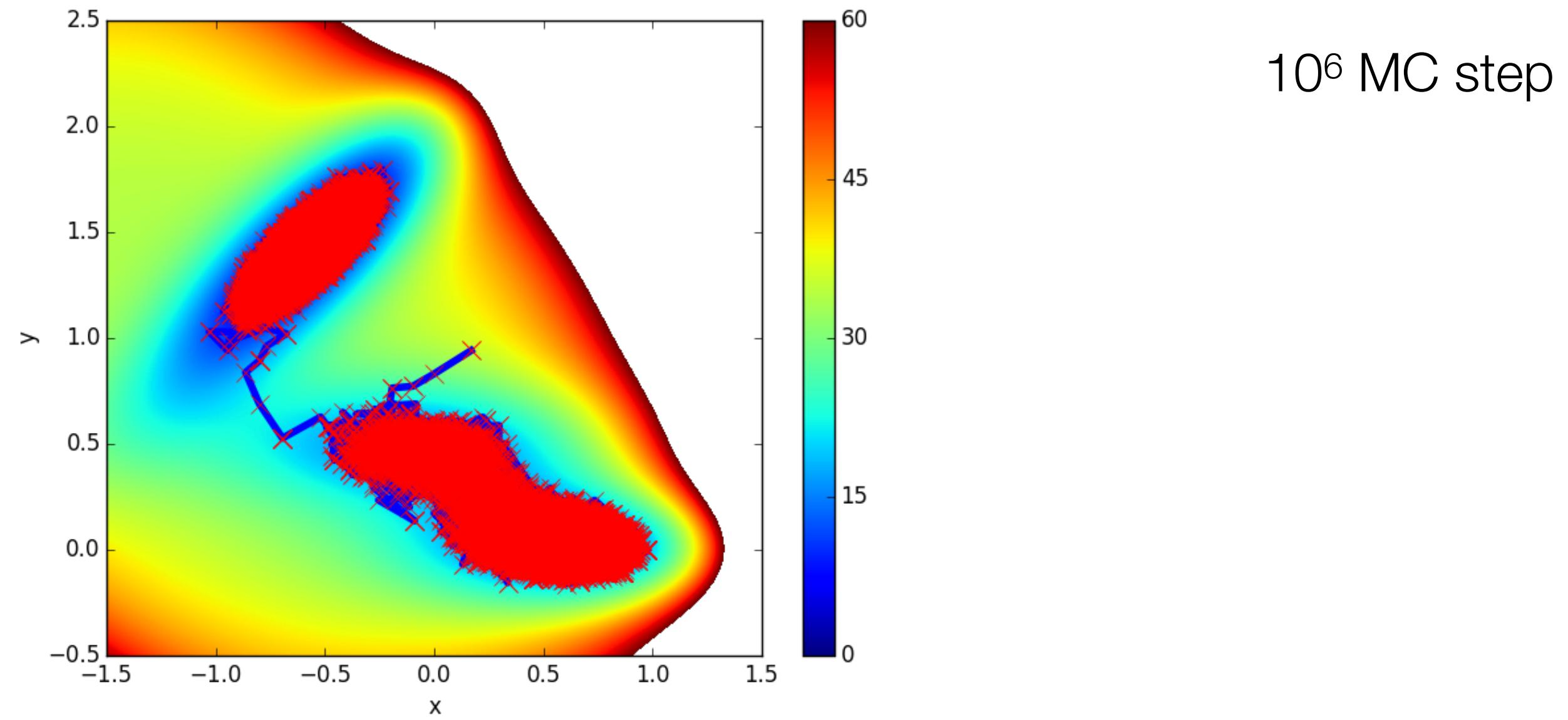
# Unbiased Monte Carlo Simulations

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



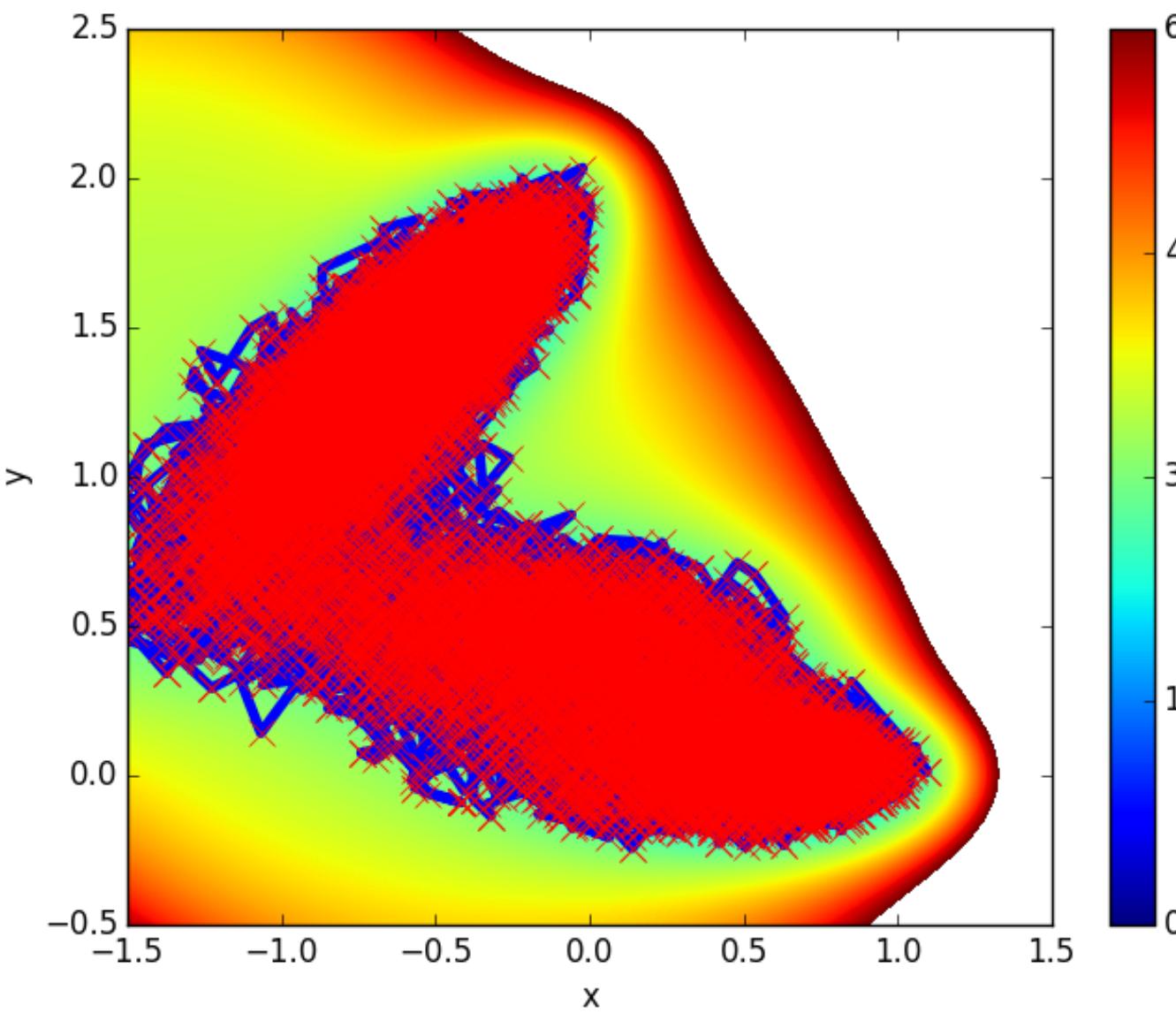
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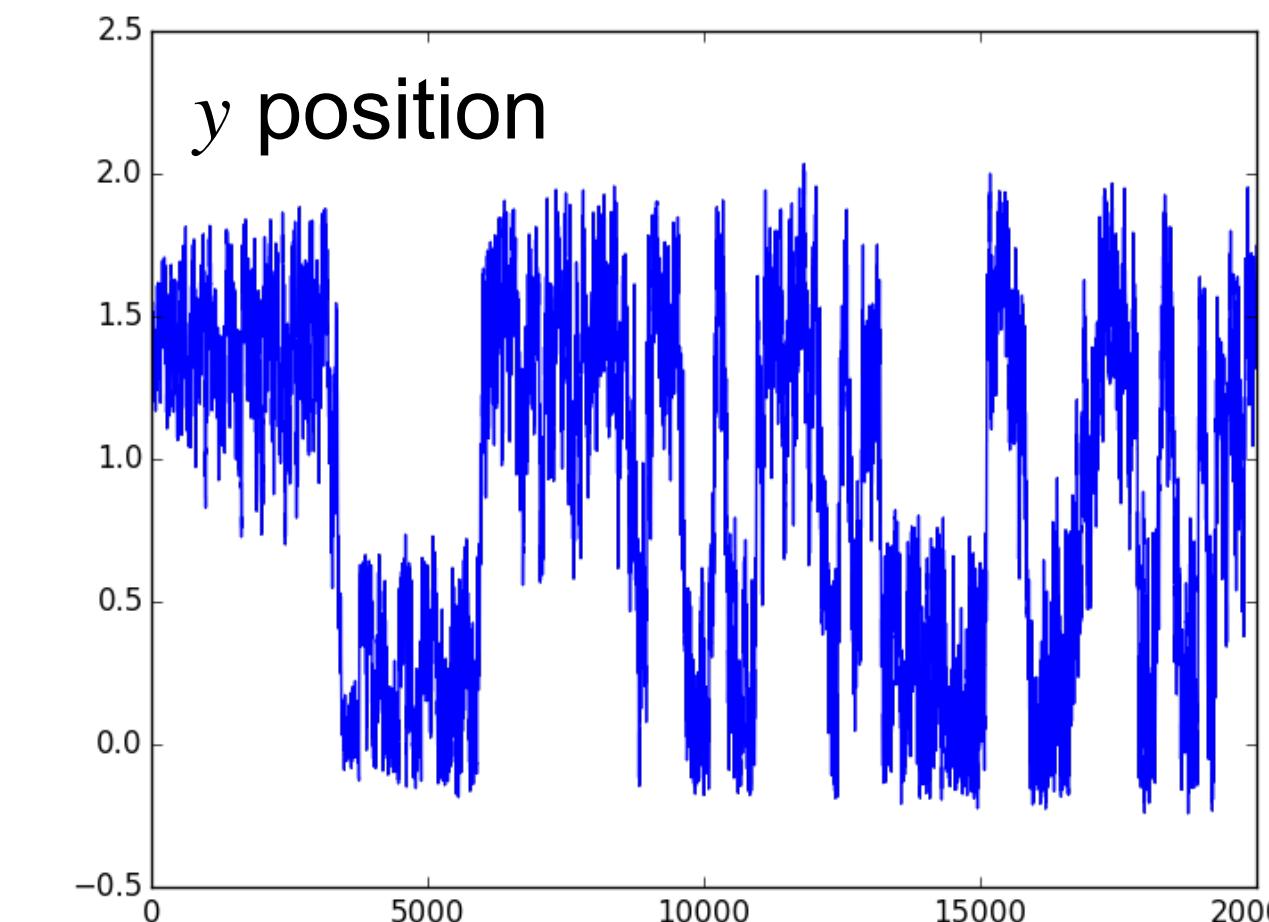
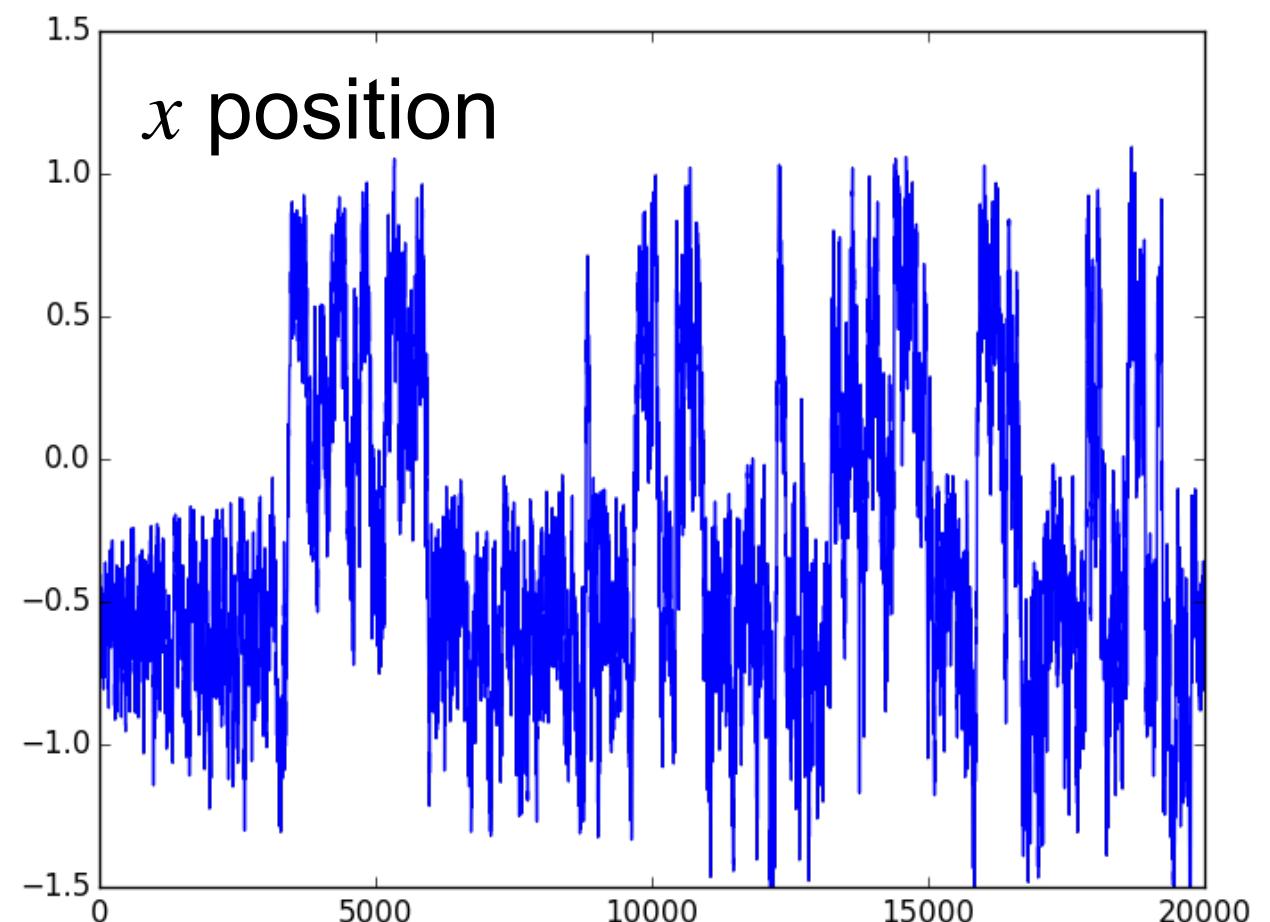


# Metadynamics Simulations

Greatly enhanced barrier crossings with Metadynamics



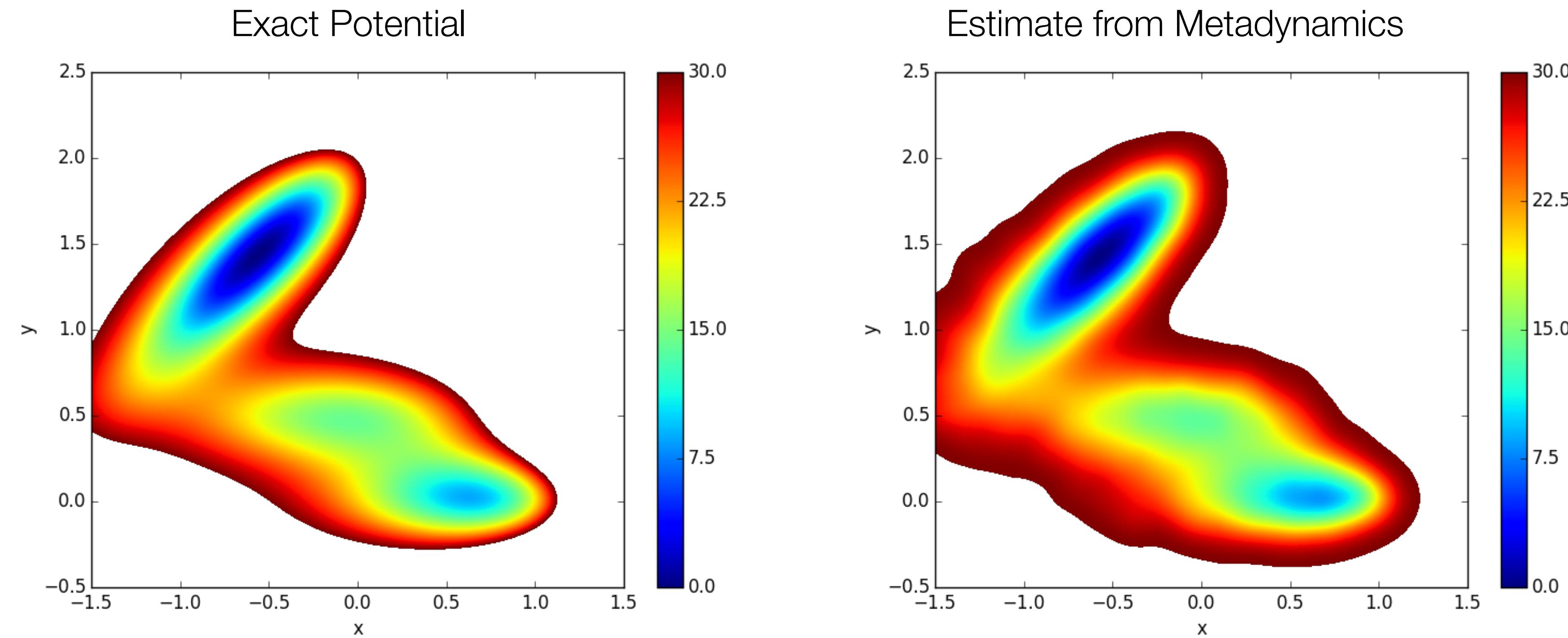
$2 \times 10^4$  MC step  
much less than for the  
unbiased run before!



# Metadynamics Simulations

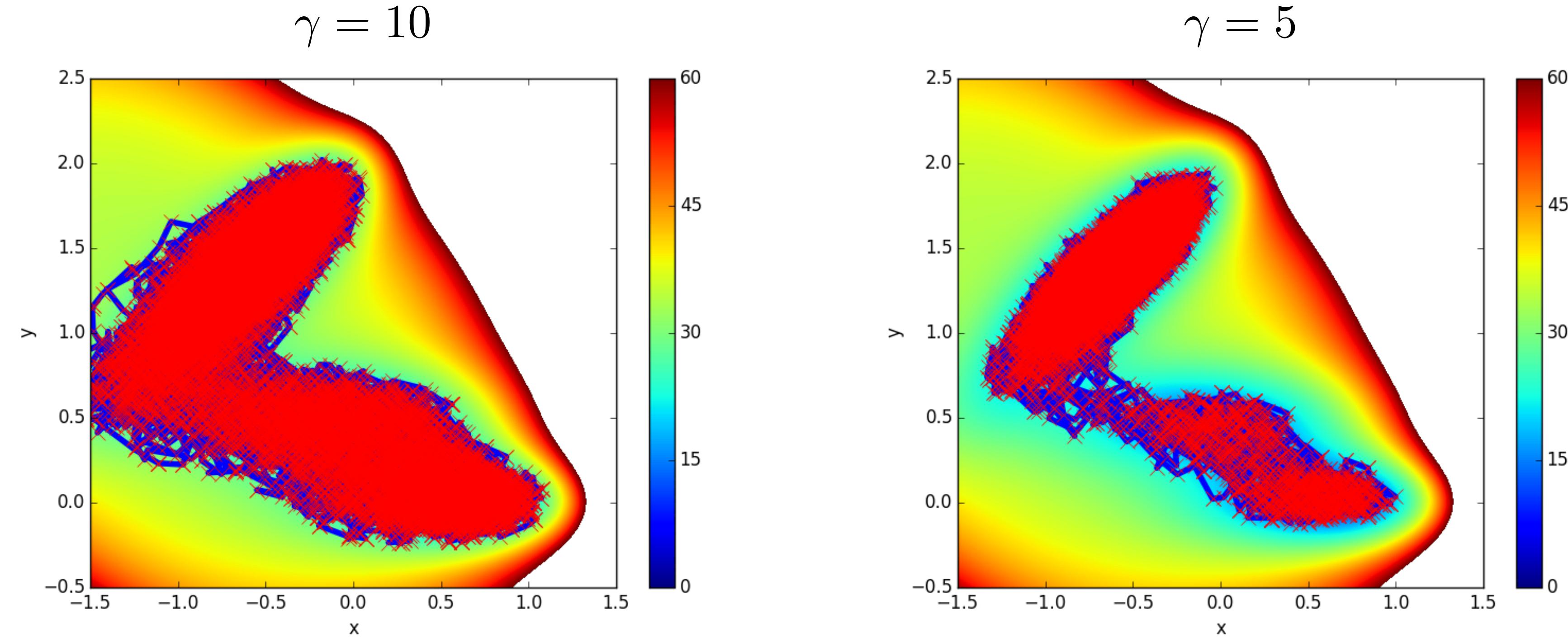
FES/PES from Metadynamics in good agreement with the exact potential

$2 \times 10^4$  MC step



# Metadynamics Simulations

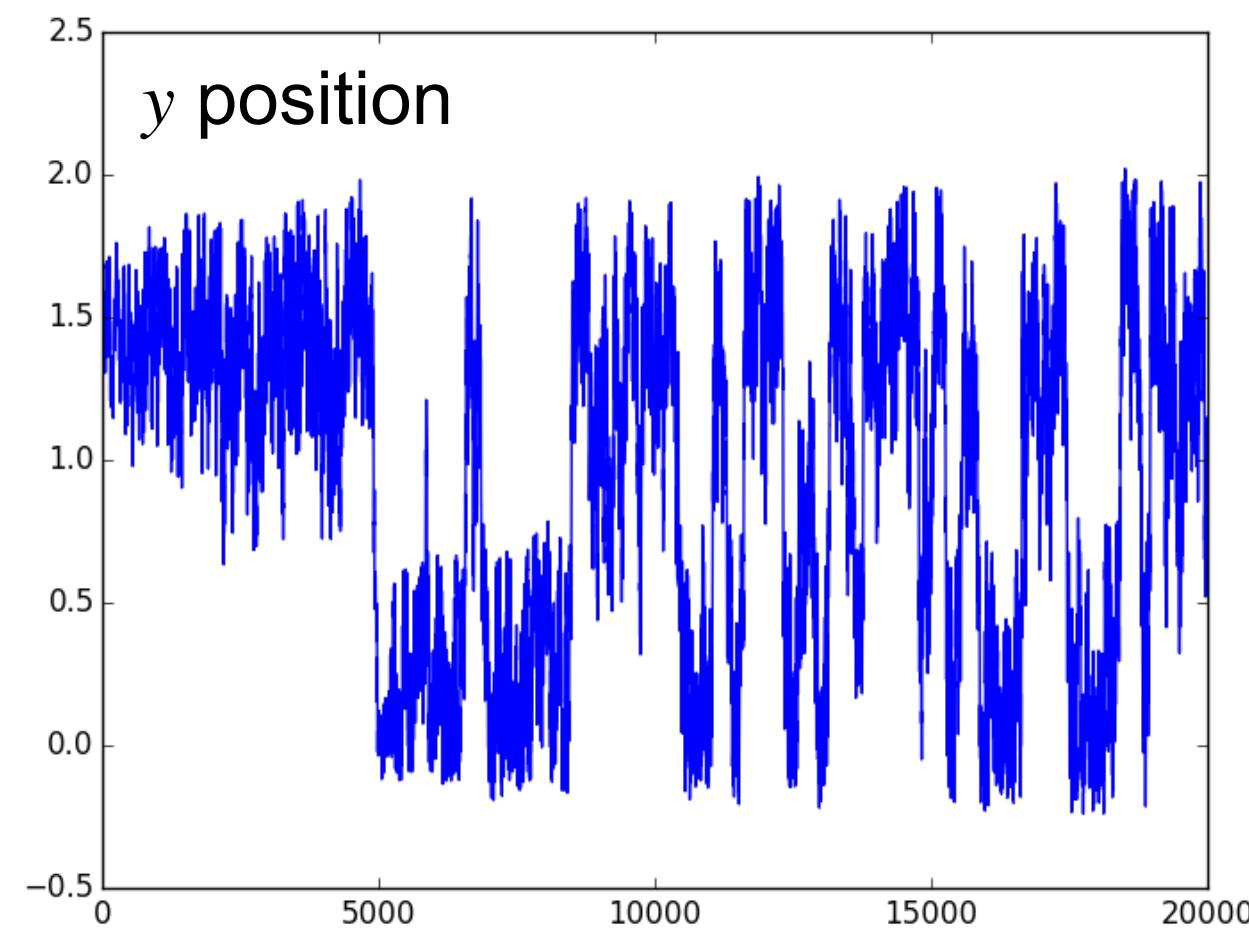
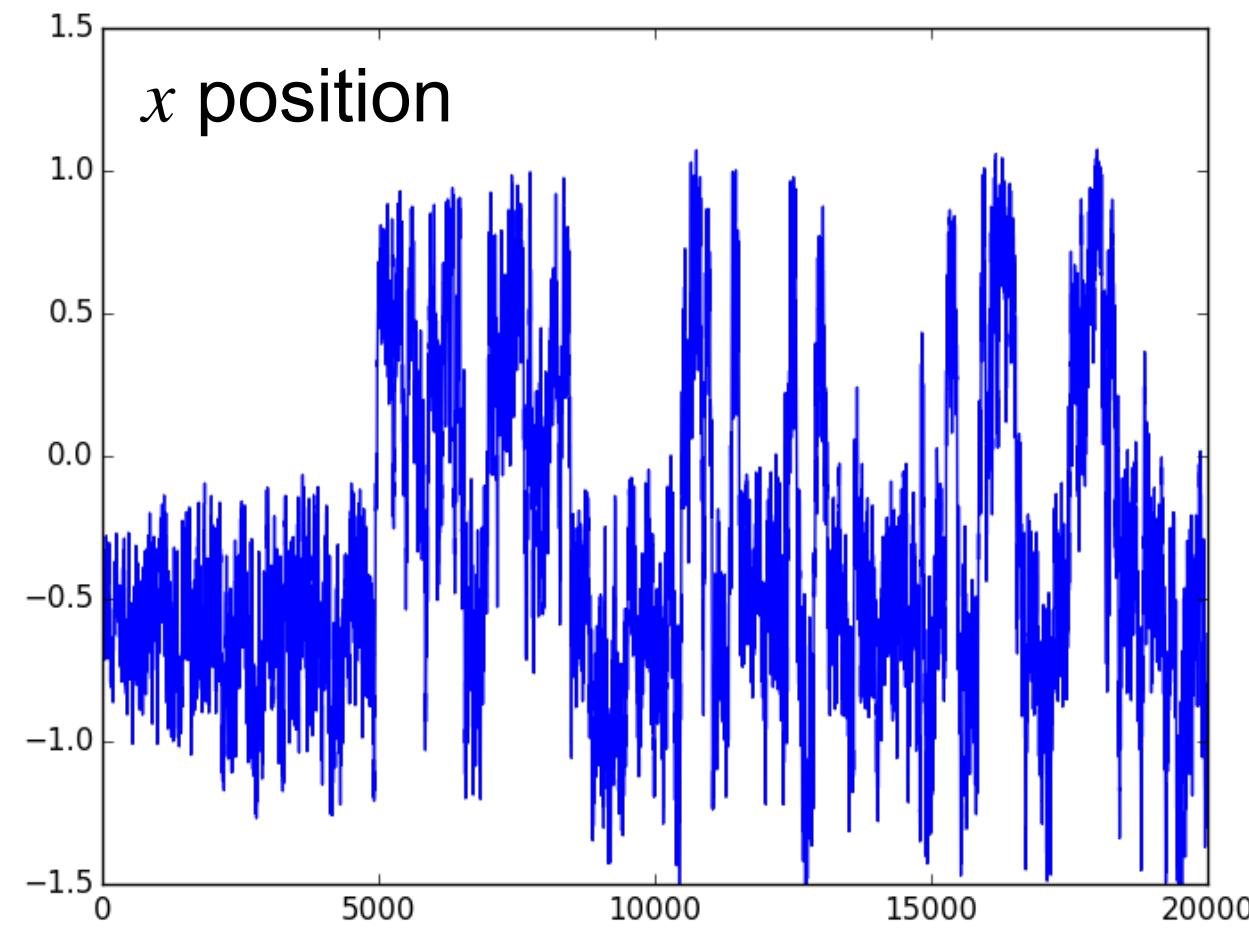
Effect of the bias factor



# Metadynamics Simulations

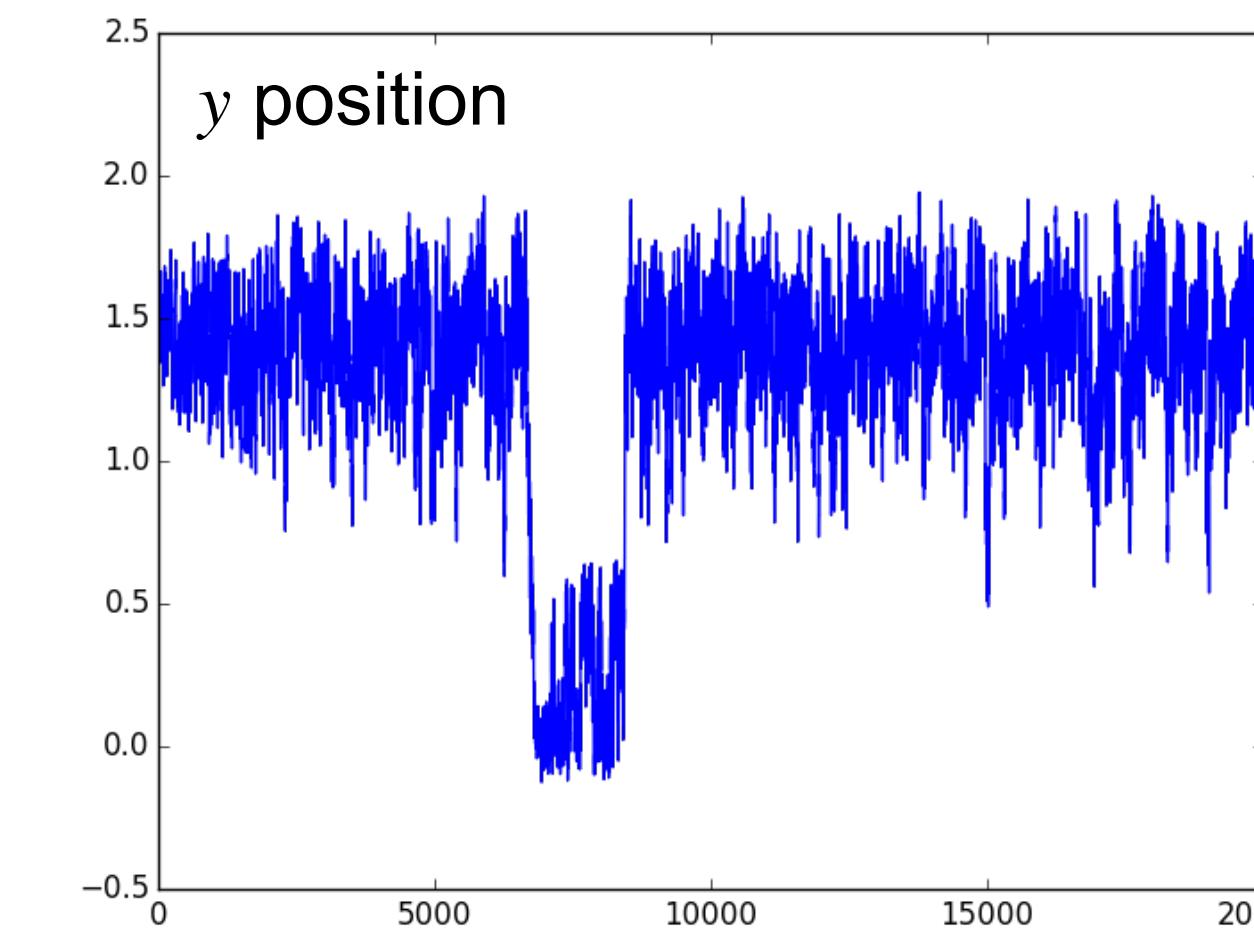
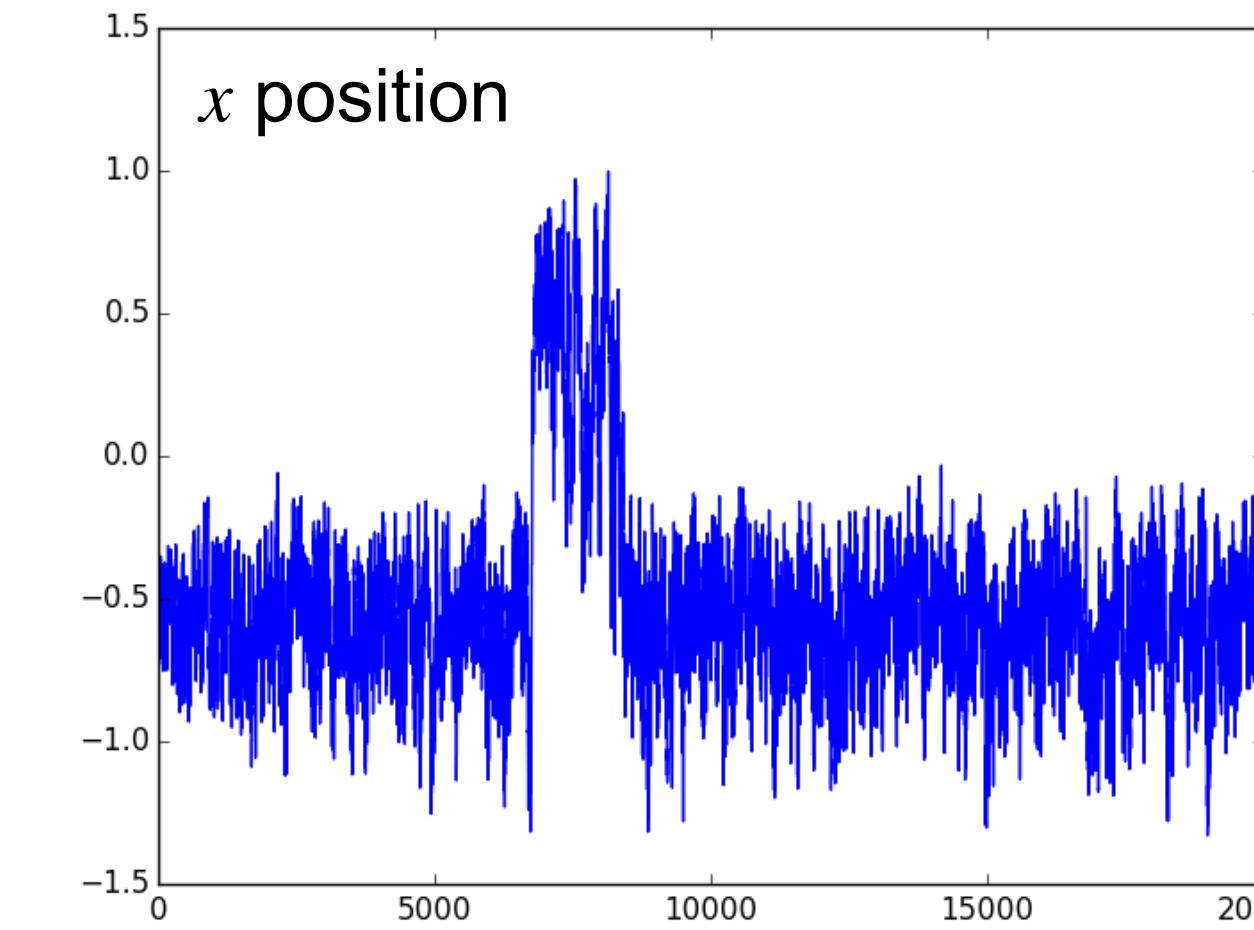
Effect of the bias factor

$$\gamma = 10$$

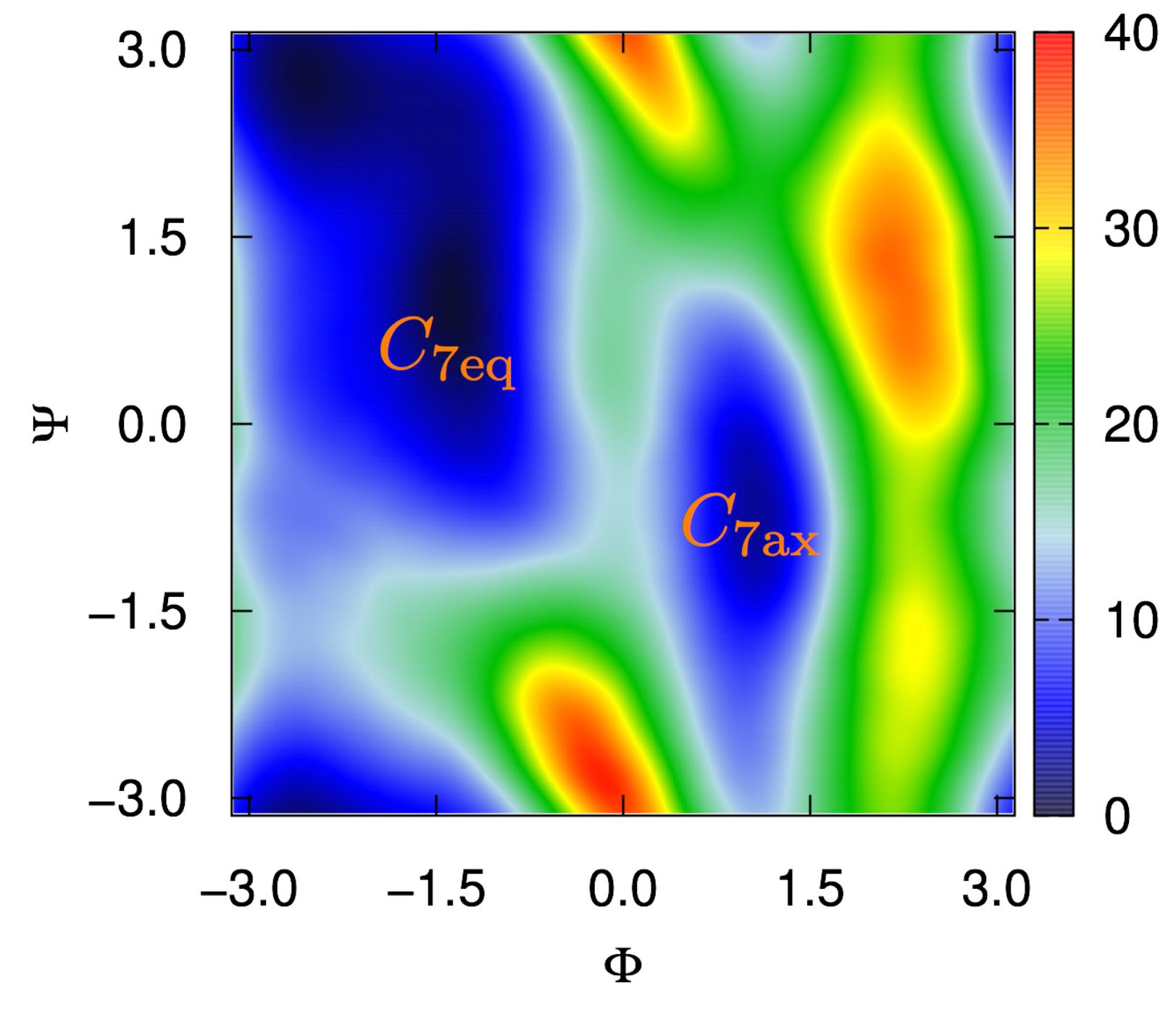
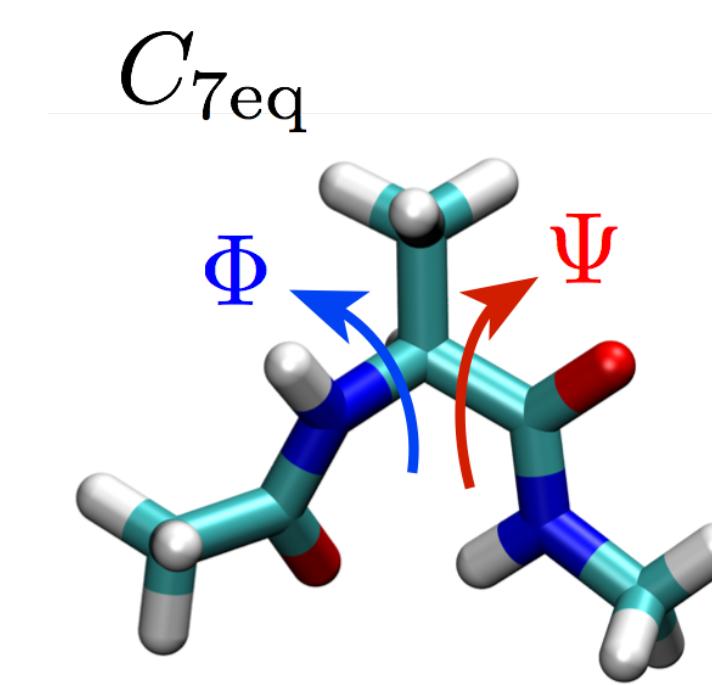


value of 5 not sufficient to overcome barriers

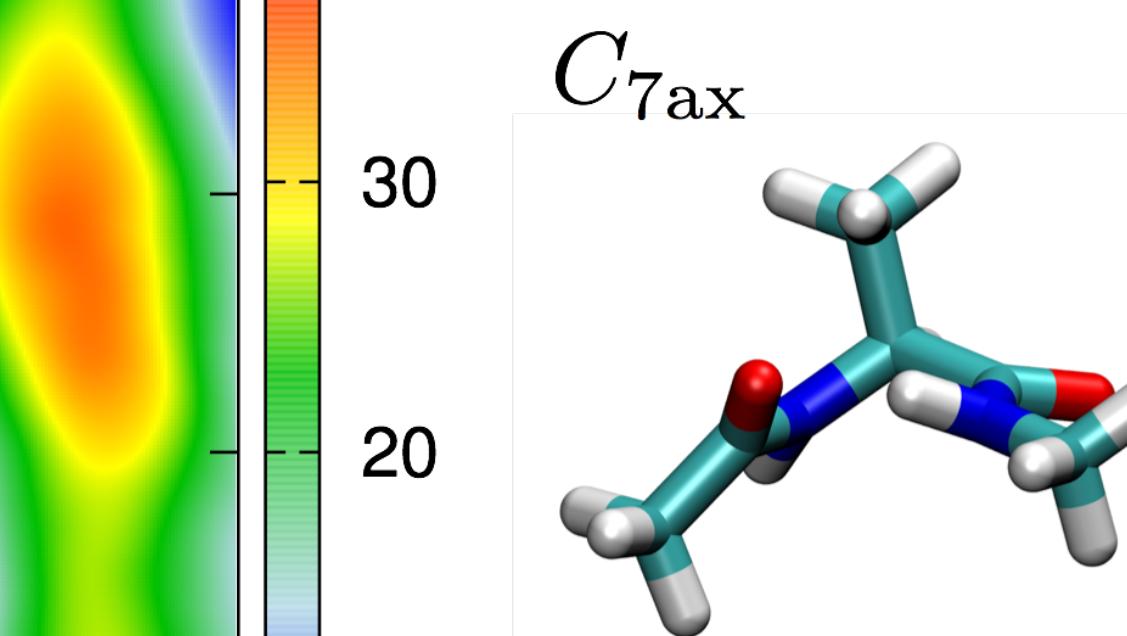
$$\gamma = 5$$



## Missing Slow CVs

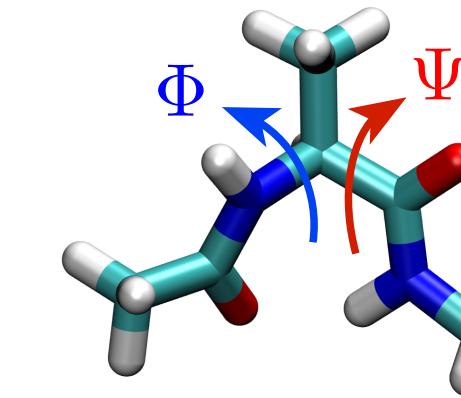


$\Psi$  fast CV

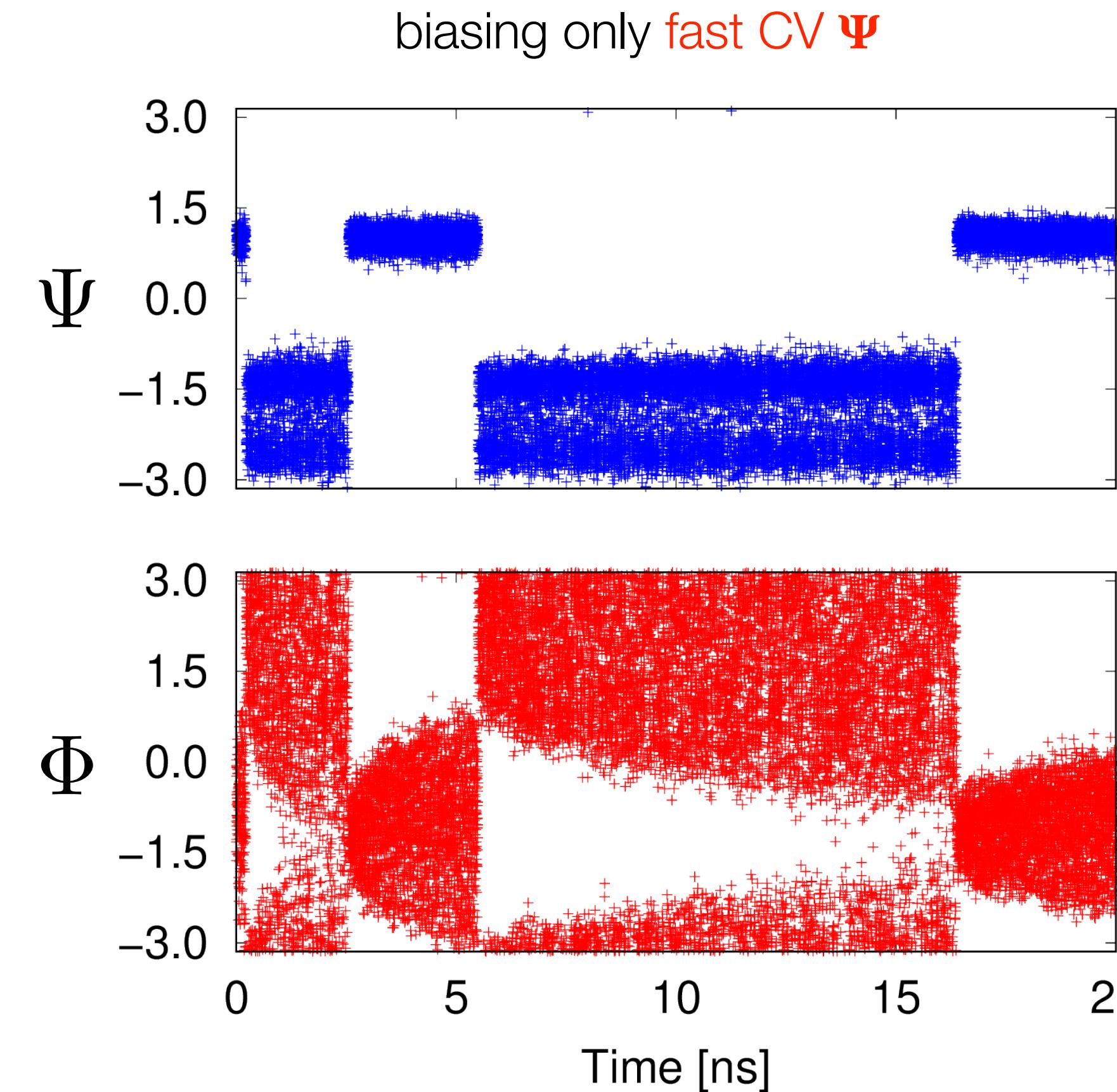
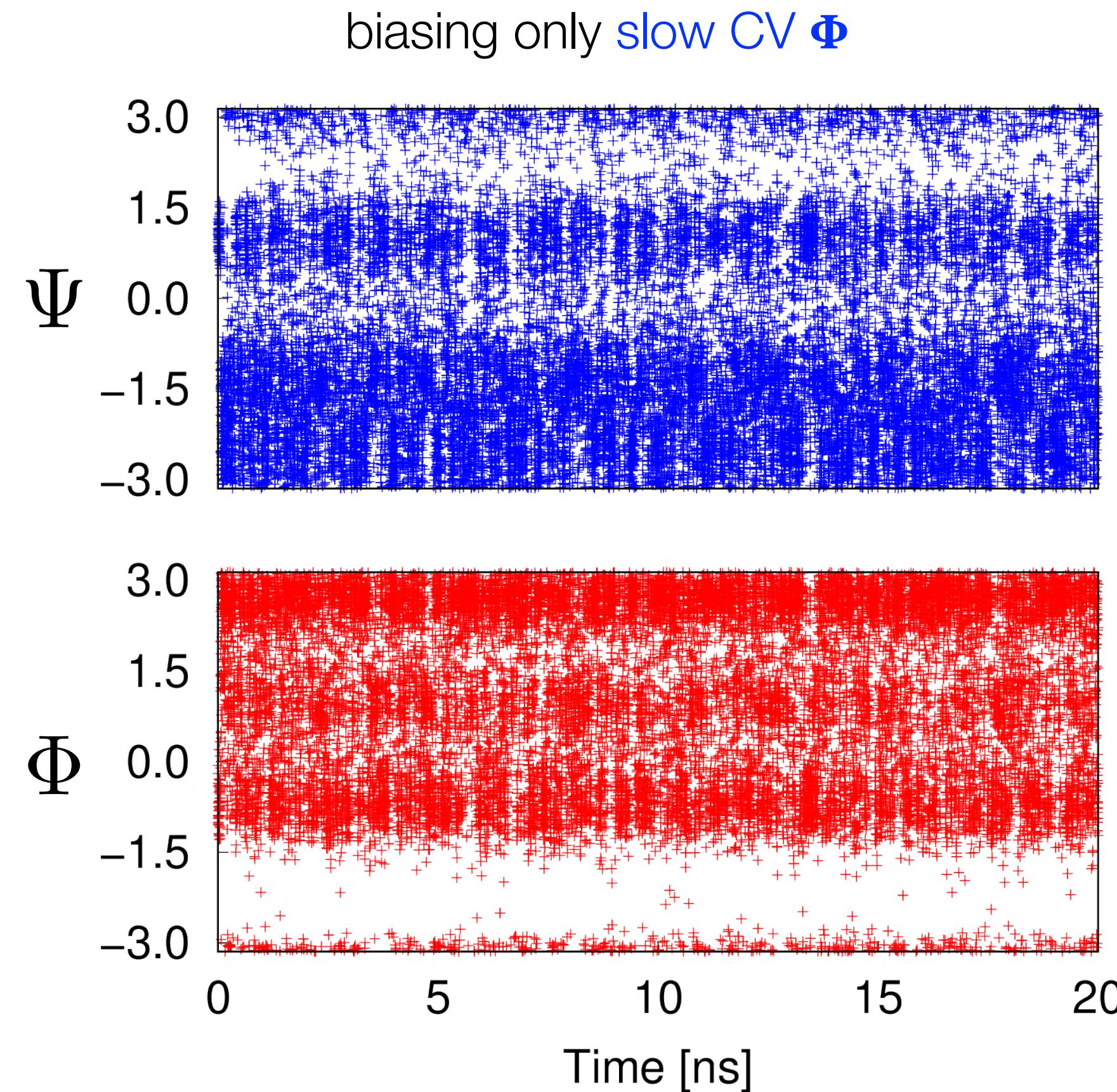


$\Phi$  slow CV

## Missing Slow CVs



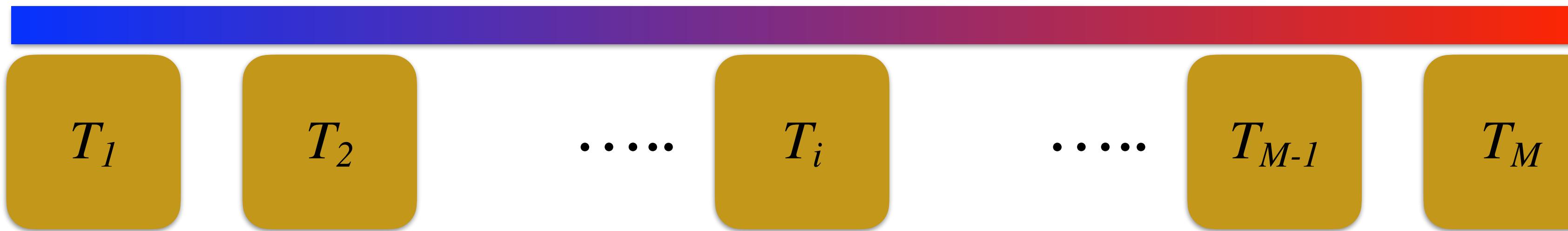
$\Phi$  slow CV /  $\Psi$  fast CV



hysteresis behavior in  $\Psi$  if we are missing slow CV  $\Phi$   
such behavior is quite general

## Parallel-Tempering + Metadynamics

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

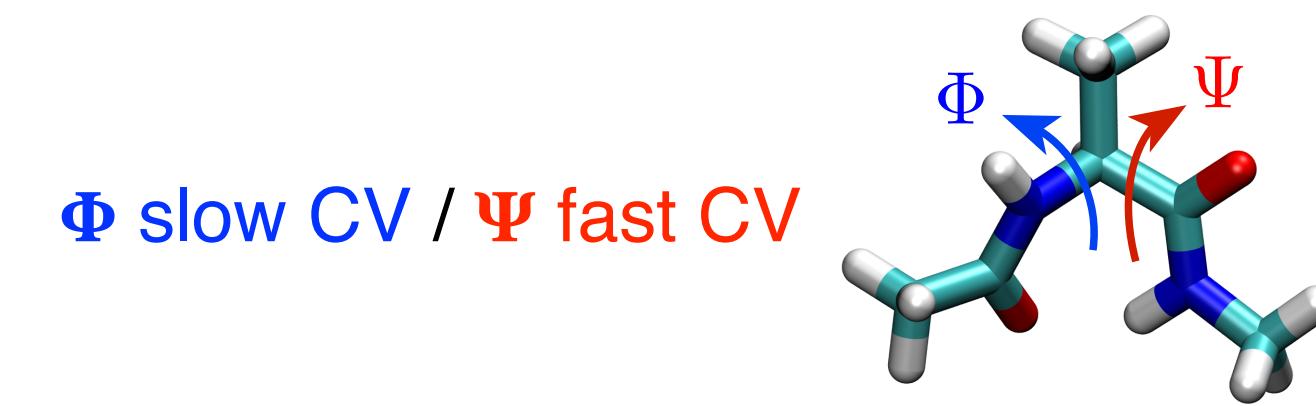


Reduces the requirement on the quality of the metadynamics CVs as parallel-tempering will help sampling the slow degrees of freedom not included in the CV set.

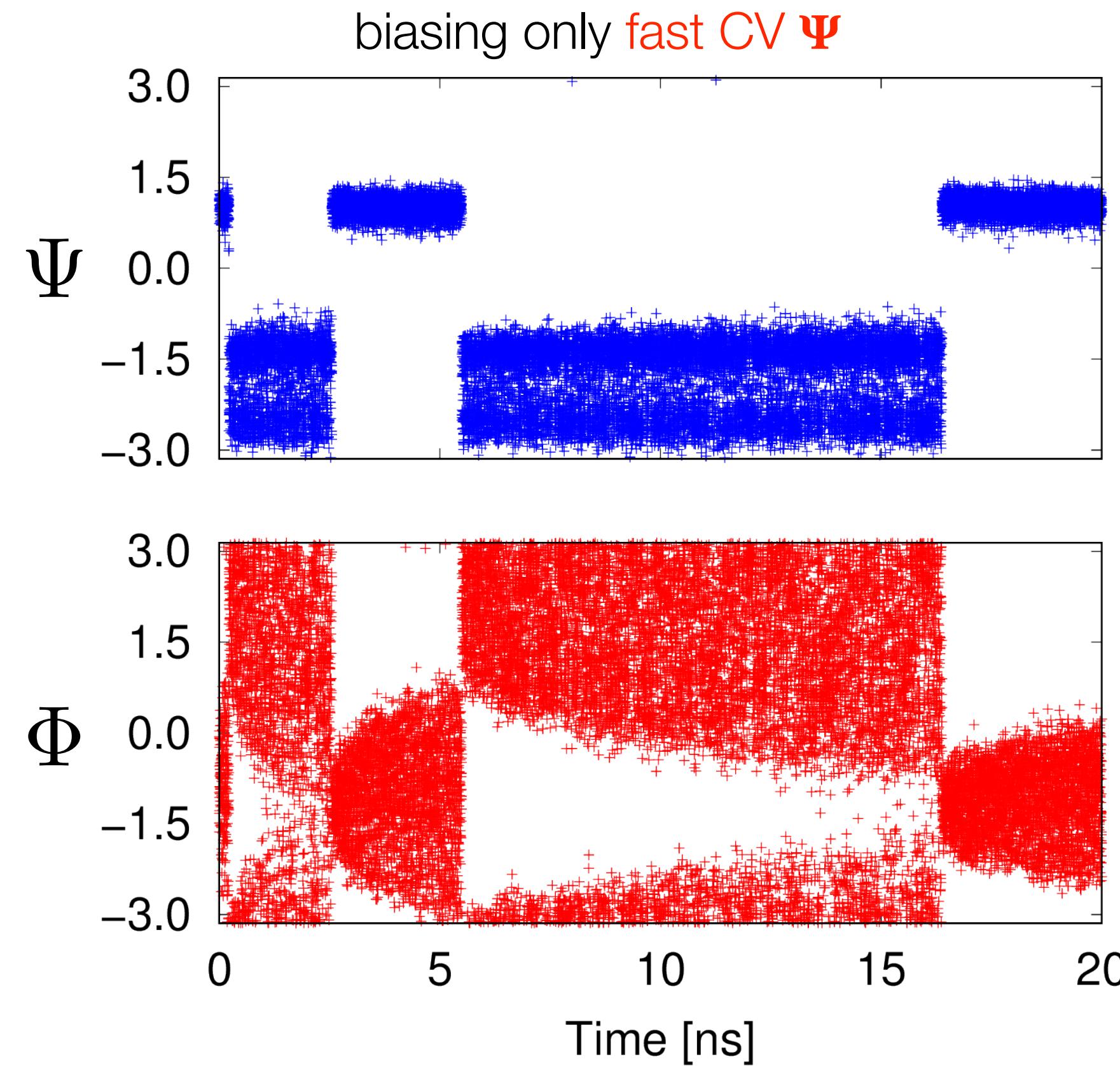
Metadynamics will also assist in sampling transition states and higher lying metastable free energy basins that are generally poorly sampled in parallel-tempering (as it reproduces canonical sampling)

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

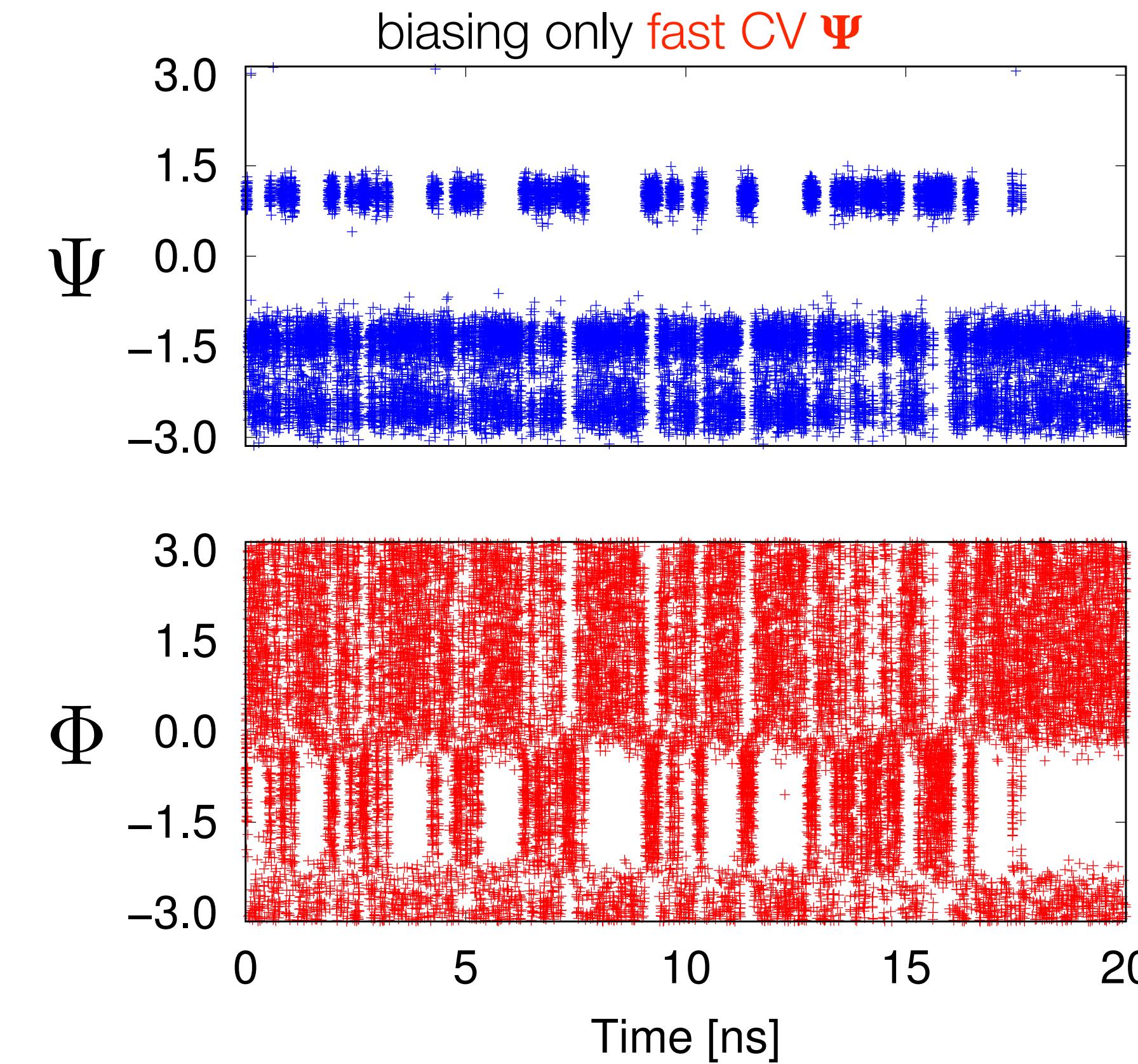
# PT+MetaD Helps with Missing Slow CVs

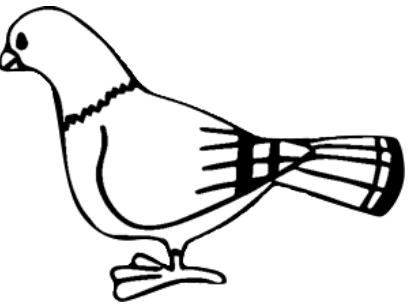


Metadynamics



Metadynamics + PT





## Variationally Enhanced Sampling

CV-based enhanced sampling method based on a **variational principle**

Effective bias potential  $V(\mathbf{s})$  in CV space constructed by minimizing a convex functional

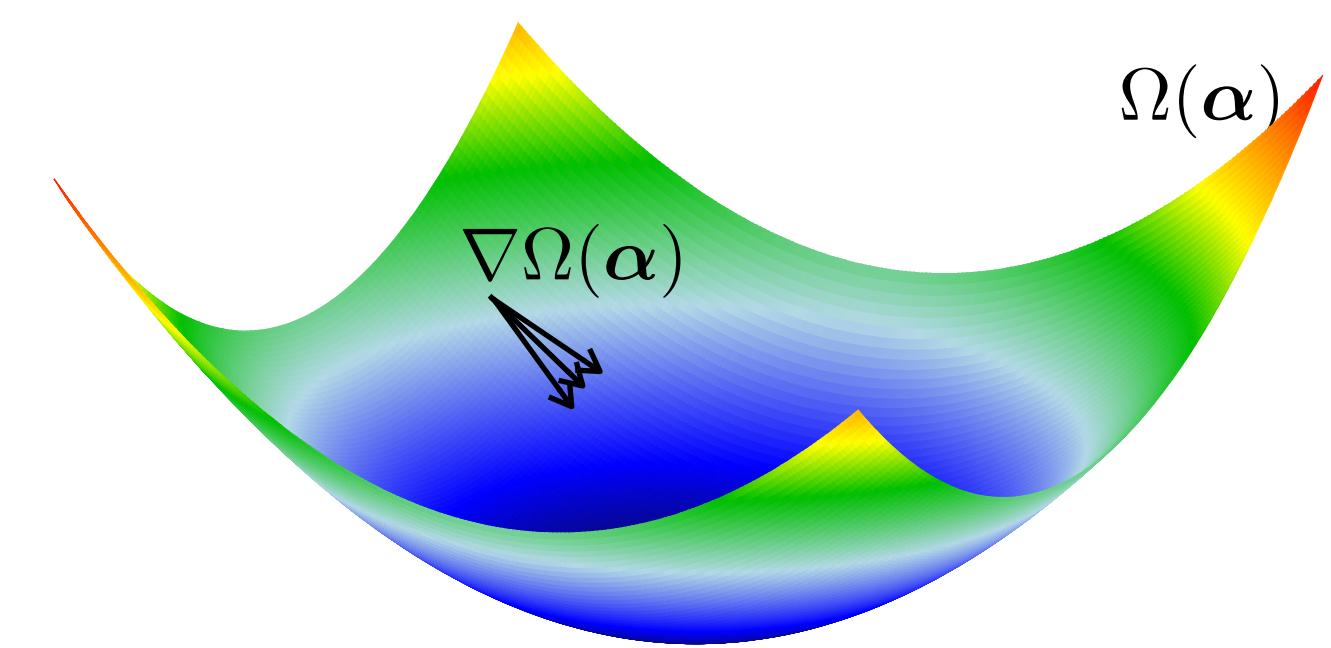
$$\Omega[V] = \frac{1}{\beta} \log \frac{\int d\mathbf{s} e^{-\beta[F(\mathbf{s}) + V(\mathbf{s})]}}{\int d\mathbf{s} e^{-\beta F(\mathbf{s})}} + \int d\mathbf{s} p(\mathbf{s})V(\mathbf{s})$$

$$\min_V \Omega[V] \quad \rightarrow \quad V(\mathbf{s}) = -F(\mathbf{s}) - \frac{1}{\beta} \log p(\mathbf{s}) + C$$

Linear bias expansion

$$V(\mathbf{s}; \boldsymbol{\alpha}) = \sum_{\mathbf{k}} \alpha_{\mathbf{k}} \cdot f_{\mathbf{k}}(\mathbf{s})$$

Convex optimization problem



Offers interesting possibilities in the form of the bias potential and the sampling that can be achieved

Completely general → can applied to a wide range of problems

Noisy gradients → stochastic optimization

Tutorial - PLUMED Masterclass-22-11

<https://github.com/valsson-group/masterclass-22-11>

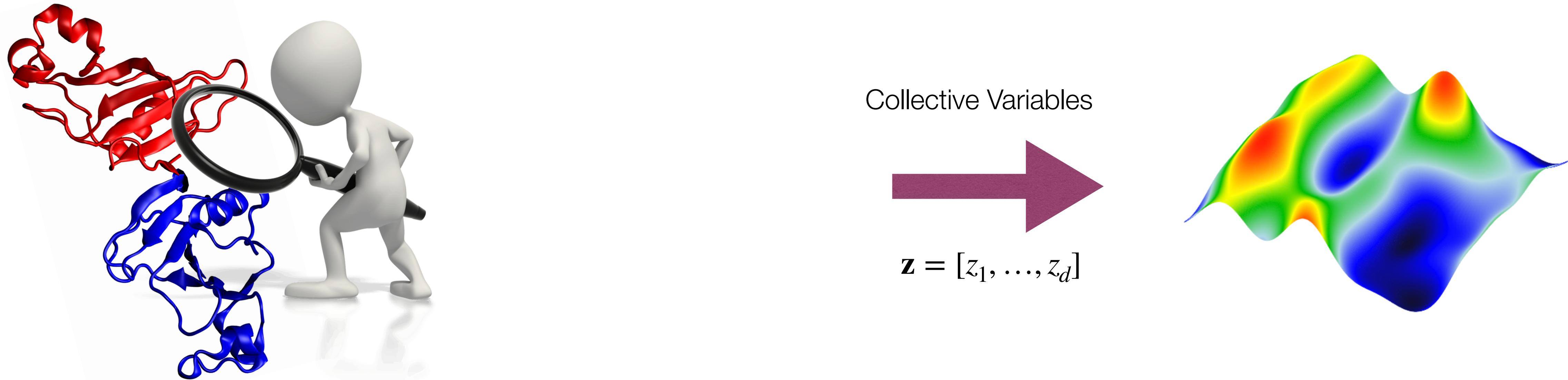
## The Issue of the Collective Variables

The performance of CV-based enhanced sampling methods heavily on the quality of the chosen CVs

Effective CVs should:

- Discriminate between the relevant metastable states
- Include most of the slow degrees of freedom
- Be few in number

Typically, the CVs are constructed manually by using physical and chemical intuition,



## The Issue of the Collective Variables

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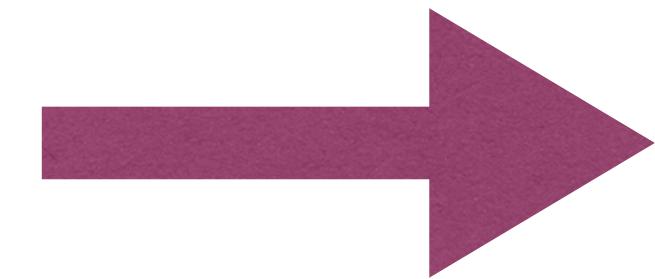
Effective CVs should:

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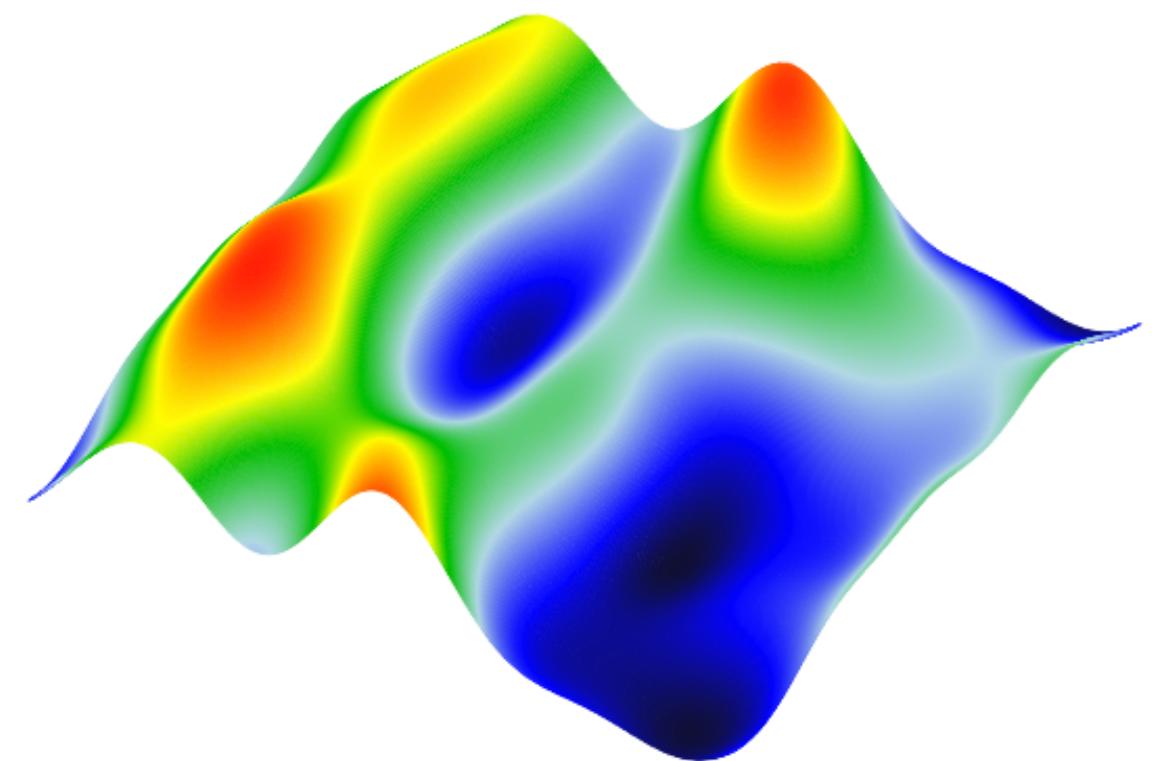
Typically, the CVs are constructed manually by using physical and chemical intuition,



Collective Variables



$$\mathbf{z} = [z_1, \dots, z_d]$$



However, can be far from trivial to find a set of CVs that quantify all the essential characteristics of a system

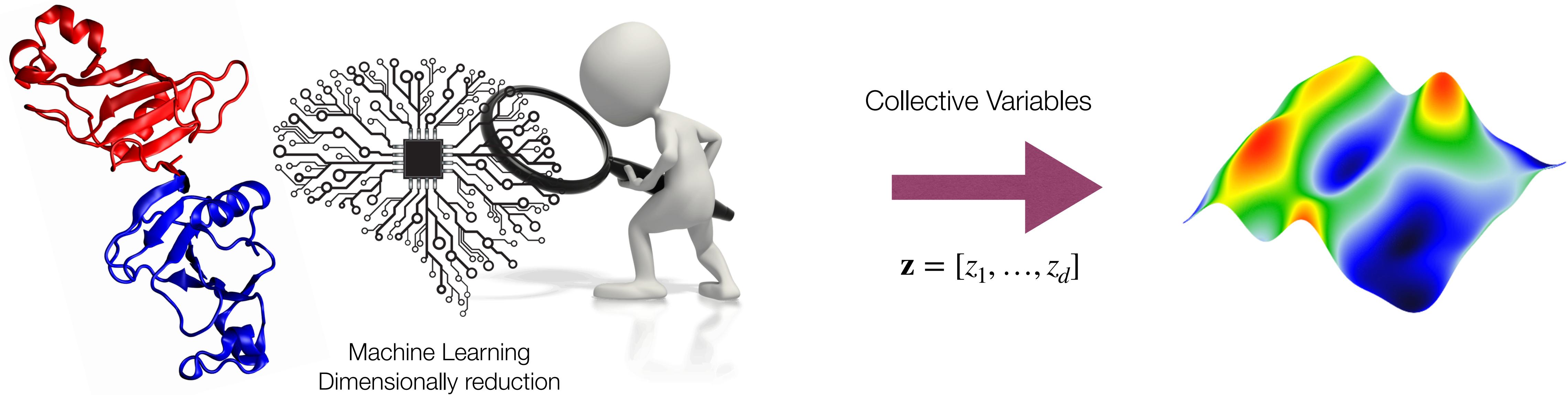
## The Issue of the Collective Variables

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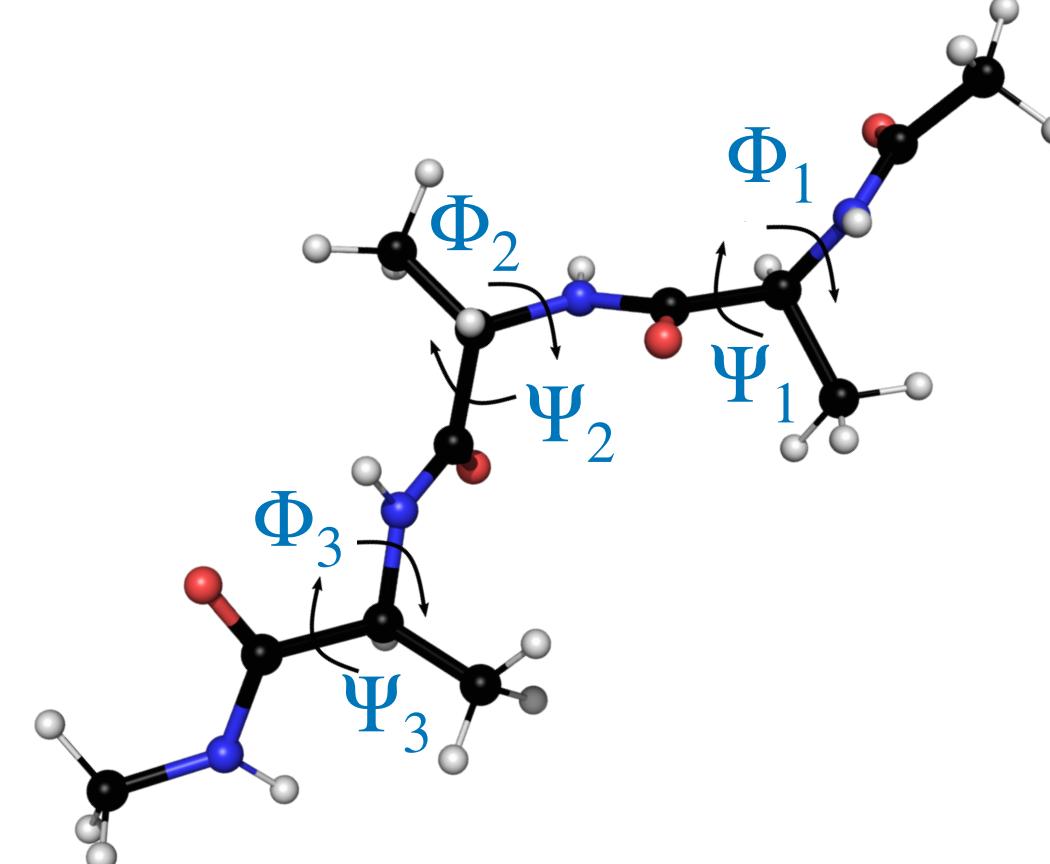
Thus, considerable interest in the field to use **machine learning** to automatically find/construct CVs

# Machine Learning for Constructing Collective Variables

Feature Space

High-dimensional,  $k \sim 10-1000$

$$\mathbf{x} = [x_1, \dots, x_k]$$



Distances  
Dihedral angles  
Backbone atom positions (aligned)  
Coordinate numbers  
Symmetry functions  
.....

Target Mapping / Embedding

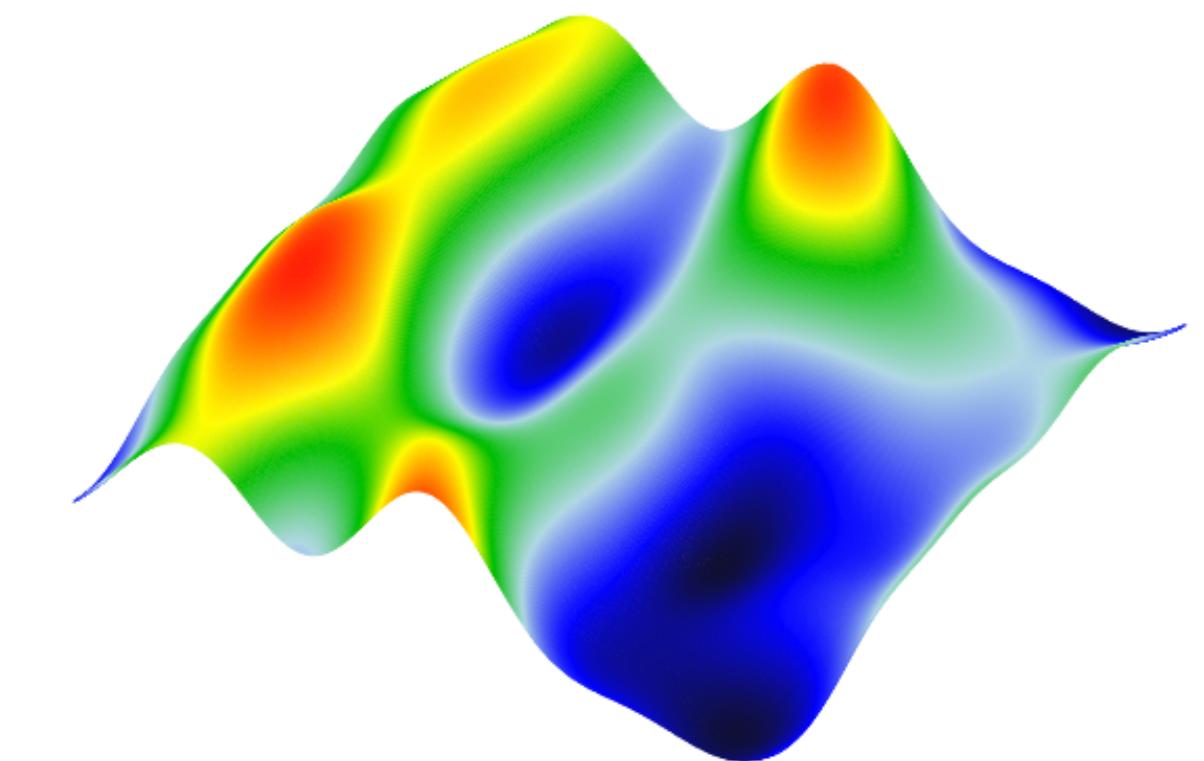
$$f_{\theta}(\mathbf{x}) = \mathbf{z}$$



CV (Latent) Space

Low-dimensional,  $d \sim 1-3$

$$\mathbf{z} = [z_1, \dots, z_d]$$



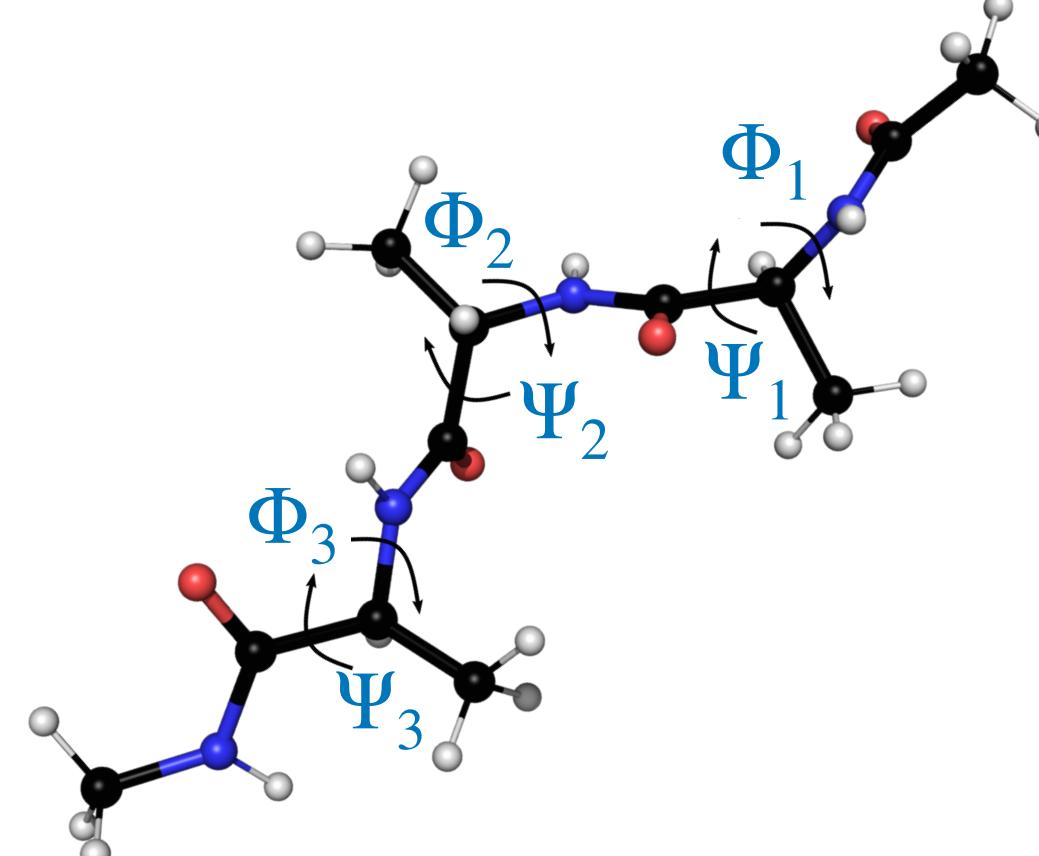
Construct/learn the mapping/embedding given some training data obtained from MD simulations (unbiased or biased)

# Machine Learning for Constructing Collective Variables

## Feature Space

High-dimensional,  $k \sim 10-1000$

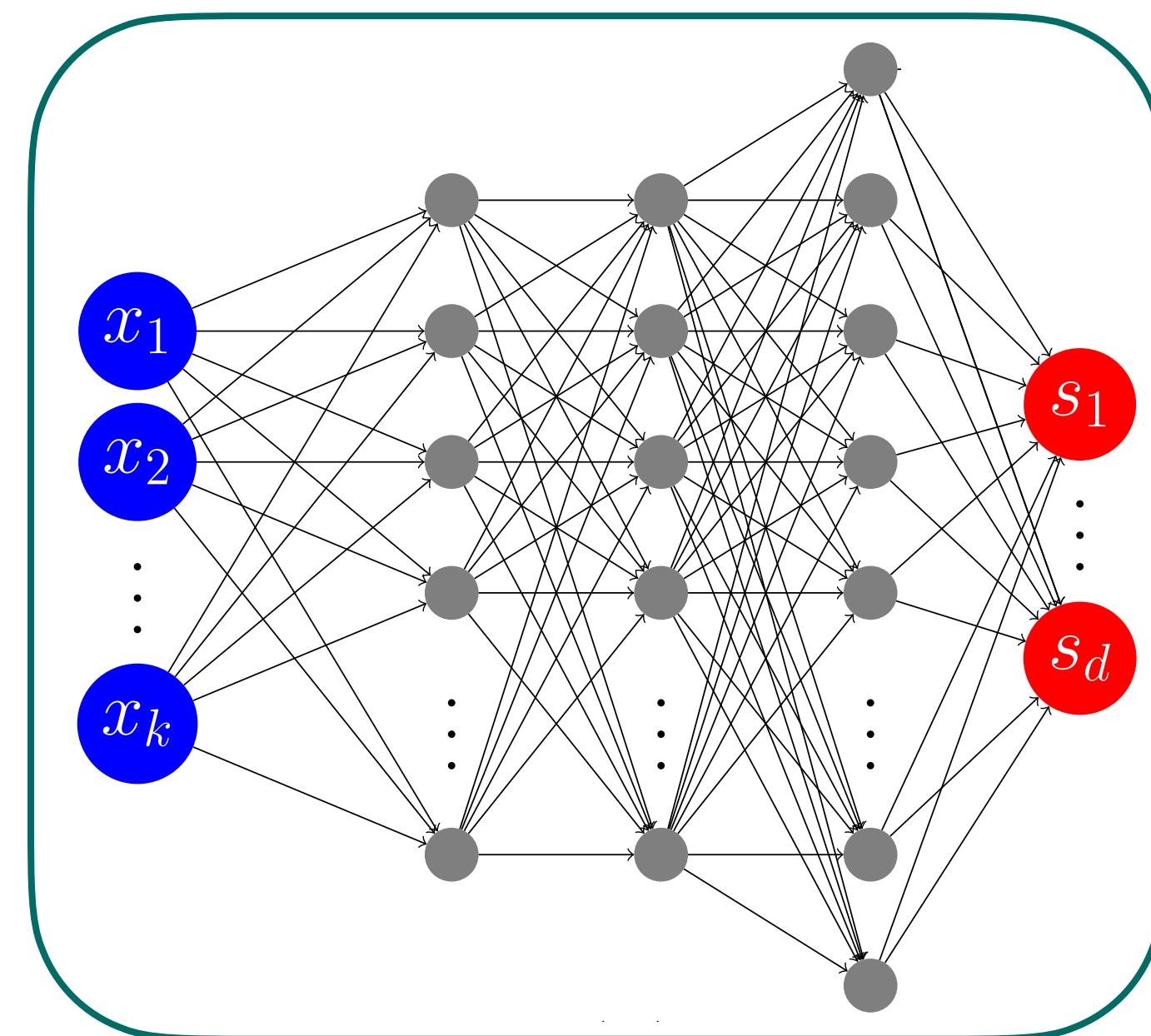
$$\mathbf{x} = [x_1, \dots, x_k]$$



- Distances
- Dihedral angles
- Backbone atom positions (aligned)
- Coordinate numbers
- Symmetry functions
- .....

## Neural Network Embedding

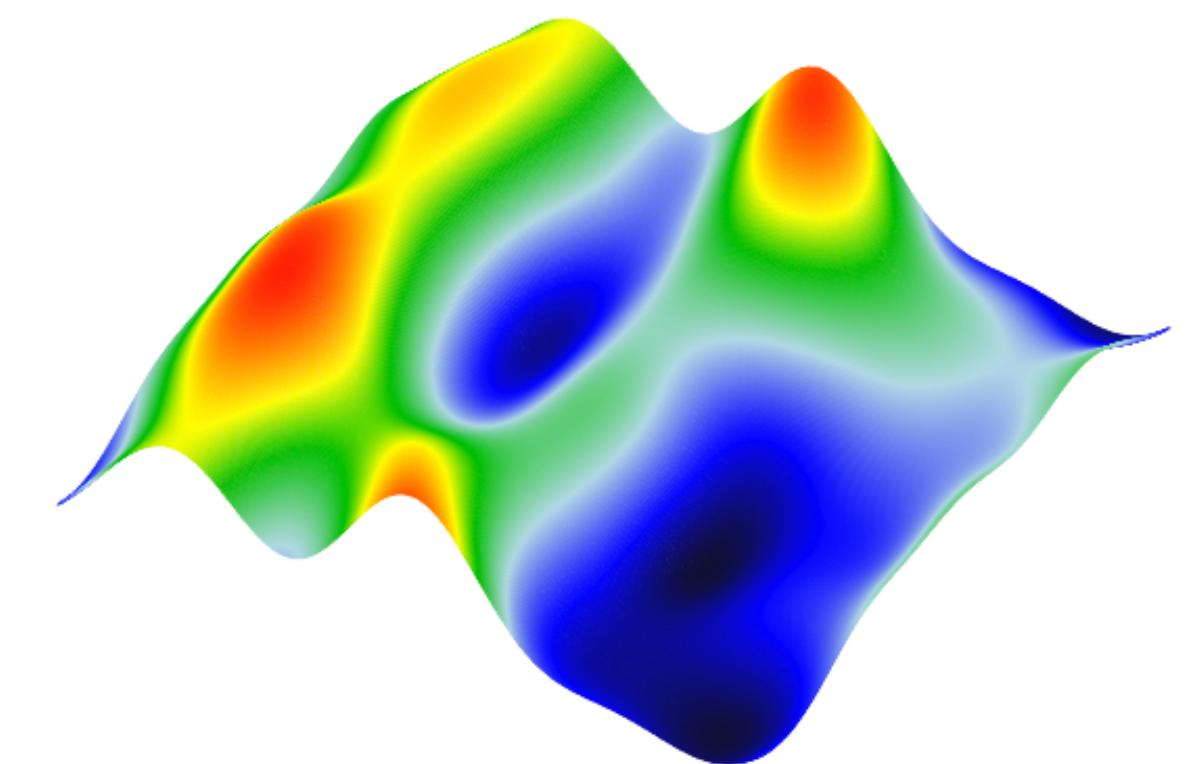
$$f_{\theta}(\mathbf{x}) = \mathbf{z}$$



## CV (Latent) Space

Low-dimensional,  $d \sim 1-3$

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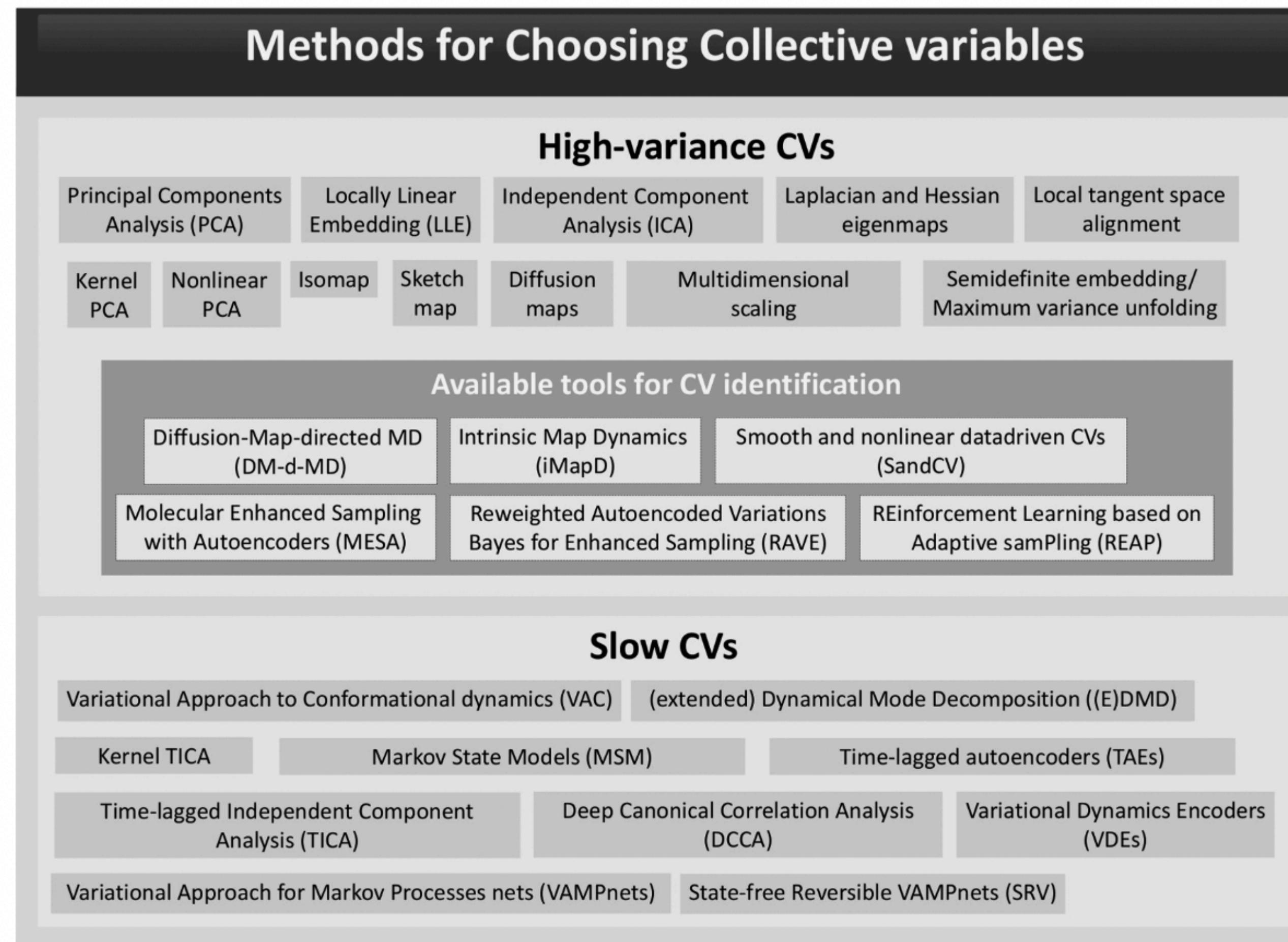
Construct/learn the mapping/embedding given some training data obtained from MD simulations (unbiased or biased)

# Machine Learning for Constructing Collective Variables

Journal of Chemical Theory and Computation

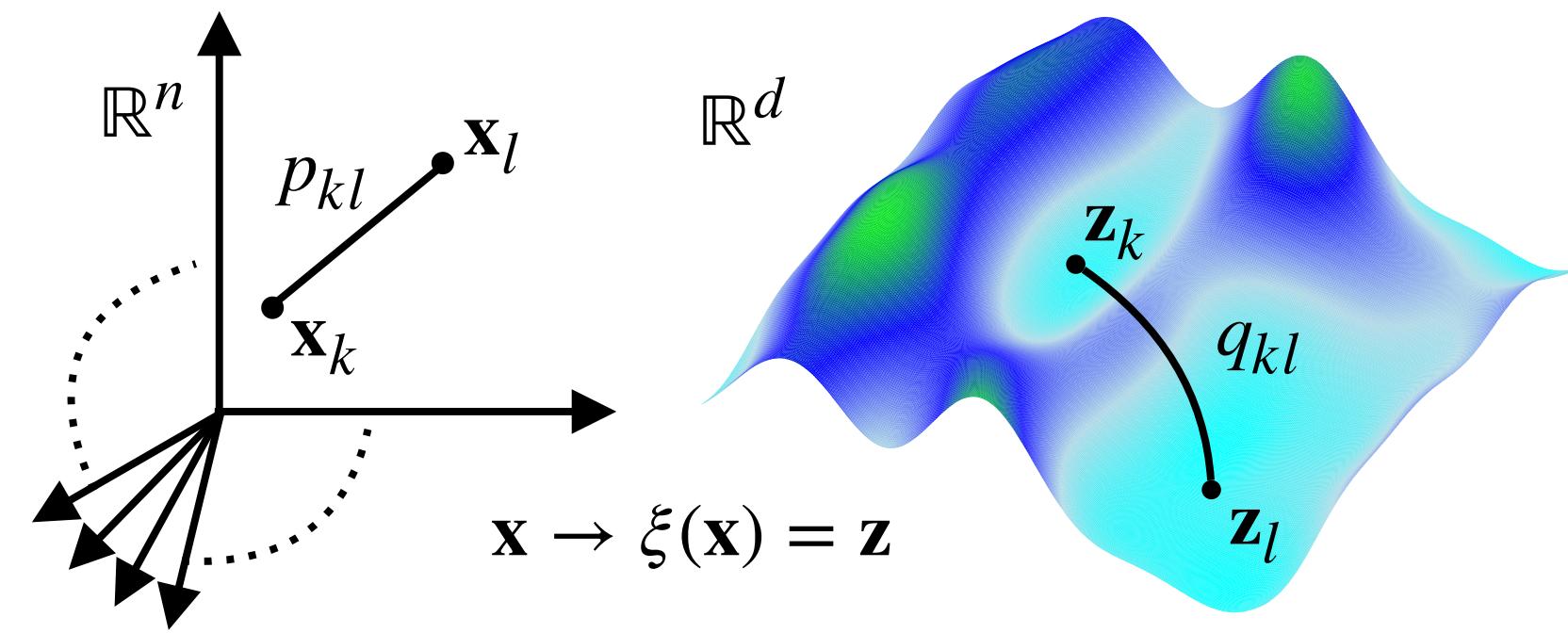
pubs.acs.org/JCTC

Perspective



**Figure 2.** Representative methods for CV identification. All related citations are in the main text.

# Manifold Learning for Constructing Collective Variables



Manifold hypothesis:

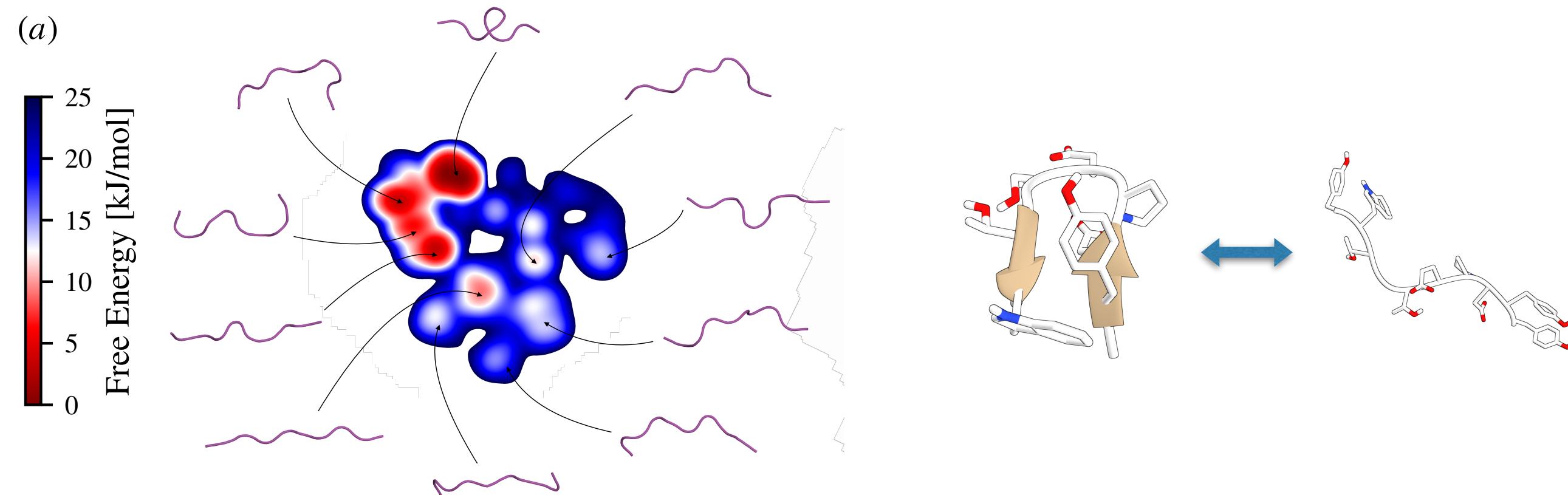
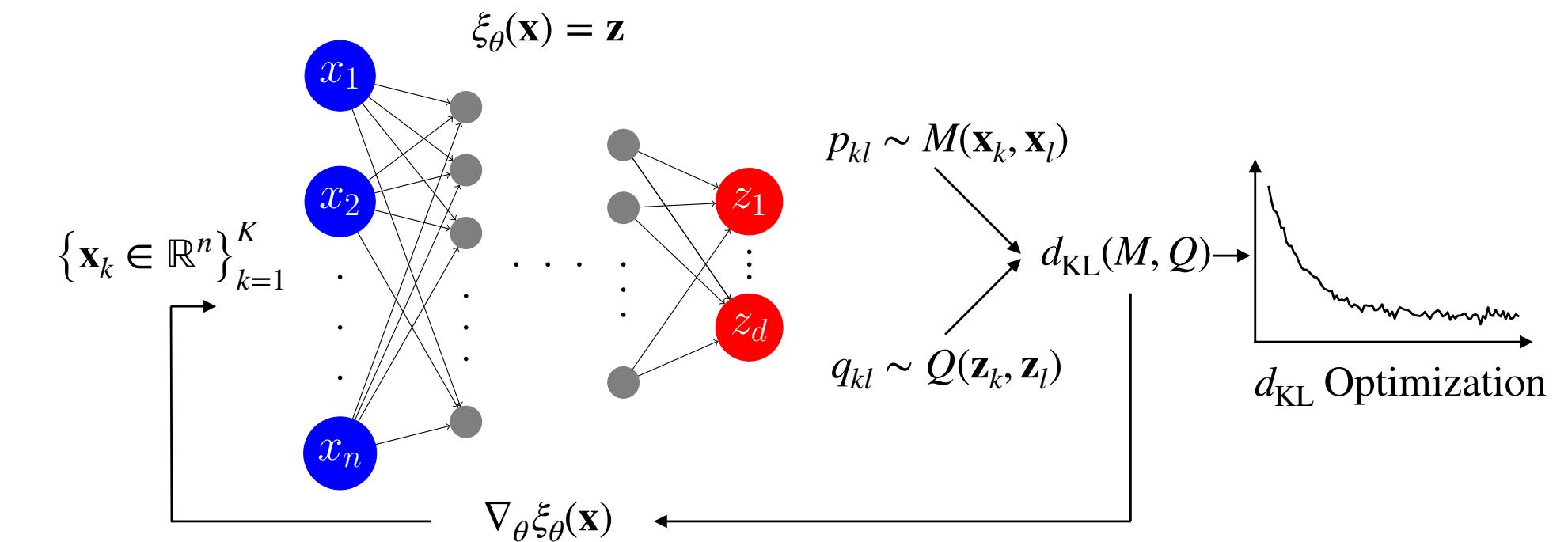
the dynamics effectively evolves on the low-dimensional manifold  
(i.e., subspace) embedded in the high-dimensional space<sup>A,B</sup>

Review forthcoming in ML:ST: Rydzewski, Chen, [Valsson](#), arXiv:[2303.08486](#)

# Multiscale Reweighted Stochastic Embedding

Manifold learning method for constructing CVs based on stochastic neighbor embedding

- Gives parametric embedding via a neural network  $\rightarrow$  can use CVs for biasing
- Multiscale representation  $\rightarrow$  parameter-free method (no perplexity as in *t*-SNE)
- Supports learning from biased data (e.g., from enhanced sampling simulation)



## References:

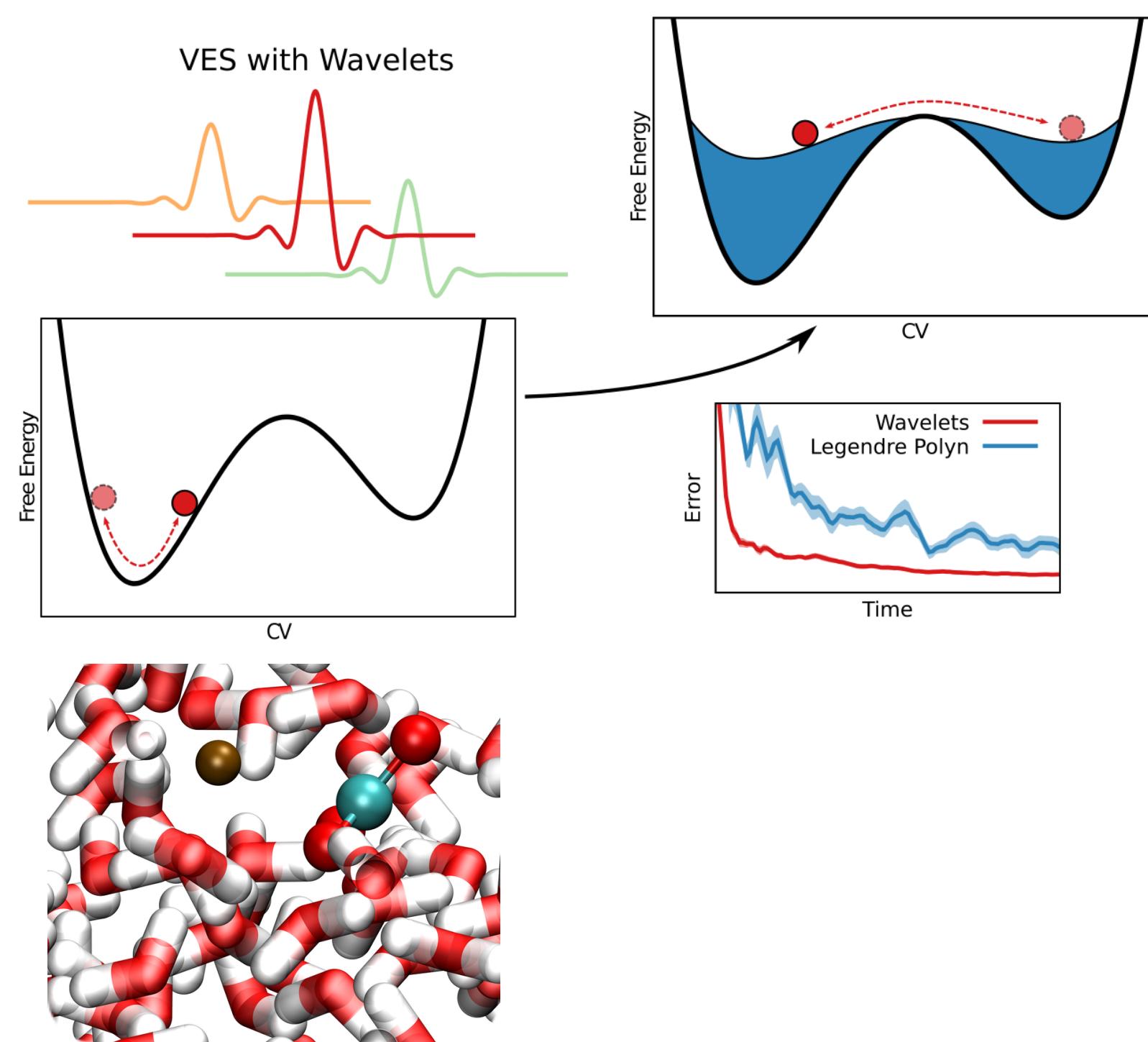
- Rydzewski and Valsson, J Phys Chem A 2021
- Rydzewski, Chen, Ghosh, and Valsson, JCTC 2022
- Rydzewski, Chen, and Valsson, arXiv:2303.08486 - Review on Manifold learning methods for CVs  $\Rightarrow$  Forthcoming in ML:ST

# Recent Publications on Enhanced Sampling from the Valsson Group

## Wavelet (Localized) Based Bias Potentials for Variationally Enhanced Sampling

Pampel & **Valsson**

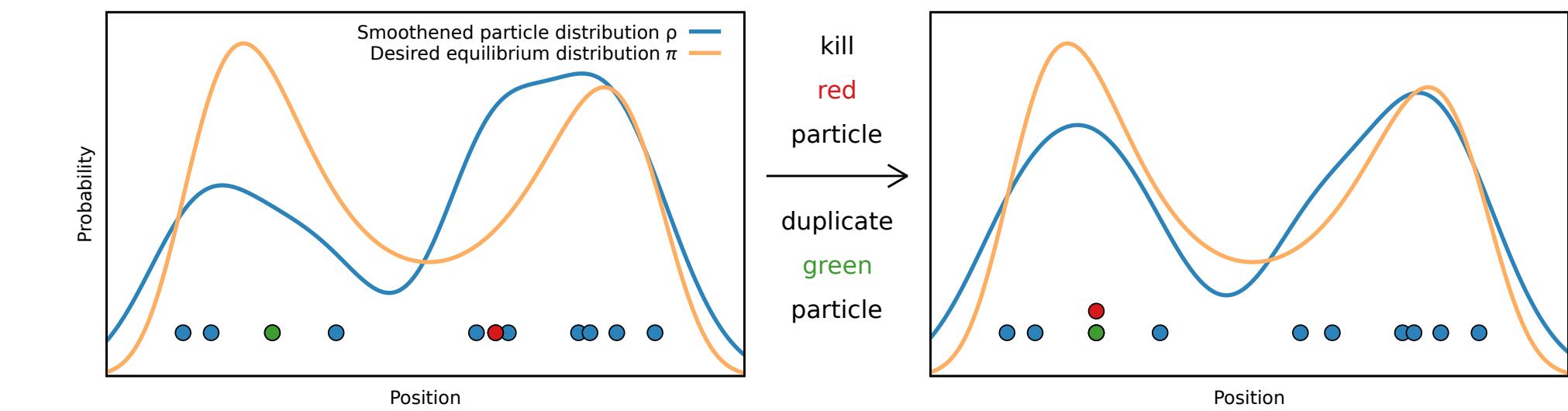
J. Chem. Theory Comput. 18, 4127-4141 (2022)



## Sampling Rare Event Energy Landscapes via Birth-Death Augmented Dynamics

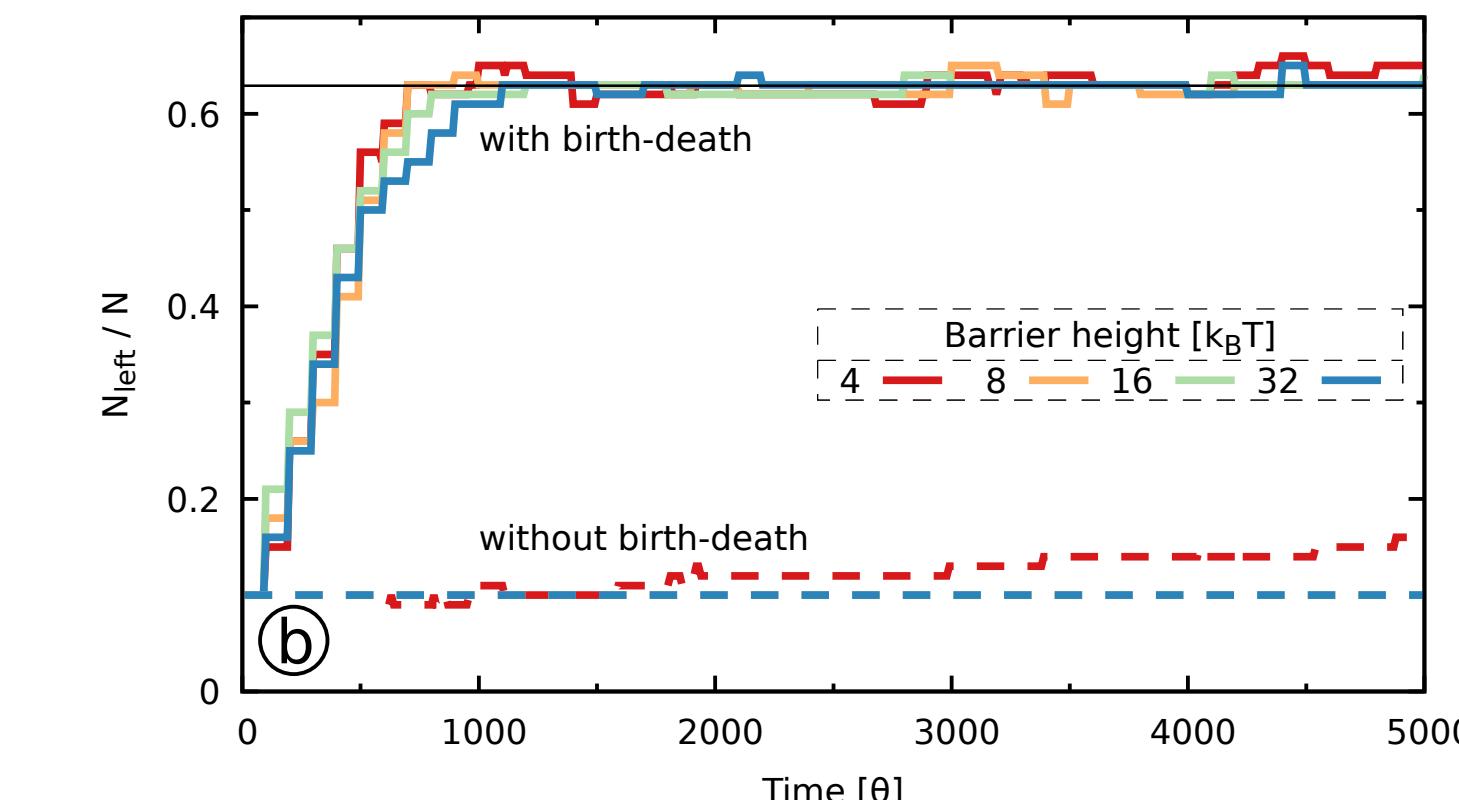
Pampel, Holbach, Hartung, & **Valsson**

Phys. Rev. E 107, 024141 (2023)



Fokker-Planck-Birth-Death Equation

$$\partial_t \rho_t(x) = L^* \rho_t(x) - \tau_\alpha \alpha_\pi(\rho_t) \rho_t$$



## Review Papers

Reviews on Enhanced Sampling and Metadynamics:

- <http://doi.org/10.33011/livecoms.4.1.1583>
- <http://doi.org/10.1146/annurev-physchem-040215-112229>
- <https://doi.org/10.1038/s42254-020-0153-0>
- [https://doi.org/10.1007/978-3-319-44677-6 49](https://doi.org/10.1007/978-3-319-44677-6_49)
- [https://doi.org/10.1007/978-1-4939-9608-7 21](https://doi.org/10.1007/978-1-4939-9608-7_21) (also <https://arxiv.org/abs/1812.08213>)

Reviews on Collective Variables for Crystallization

- <https://doi.org/10.1021/acsomega.2c06310>
- <https://doi.org/10.1103/physreve.107.l012601>

Reviews on Machine Learning for Finding Collective Variables

- <https://doi.org/10.48550/arXiv.2303.08486>
- <https://doi.org/10.1021/acs.jctc.0c00355>
- <https://doi.org/10.1080/00268976.2020.1737742>
- <https://doi.org/10.1017/qrd.2022.23>
- <https://doi.org/10.1016/j.sbi.2019.12.016>
- <https://arxiv.org/abs/2306.09111>

## PLUMED Resources

The official manual for PLUMED version v2.8 can be found [here](#)

### PLUMED Masterclass Tutorials

- Corresponding YouTube videos with lectures and solutions found [here](#)
- [Masterclass 21.1: PLUMED syntax and analysis](#)
- [Masterclass 21.2: Statistical errors in MD](#)
- [Masterclass 21.3: Umbrella sampling](#)
- [Masterclass 21.4: Metadynamics](#)
- [Masterclass 21.5: Simulations with multiple replicas](#)
- [Masterclass 21.6: Dimensionality reduction](#)
- [Masterclass 21.7: Optimizing PLUMED performances](#)
- [Masterclass 22.3: OPES method](#)
- [Masterclass 22.11: Variationally enhanced sampling with PLUMED](#)

Various other PLUMED tutorial can be found in the [manual](#)



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[omar.valsson@unt.edu](mailto:omar.valsson@unt.edu)

Thanks for your attention!  
Questions?