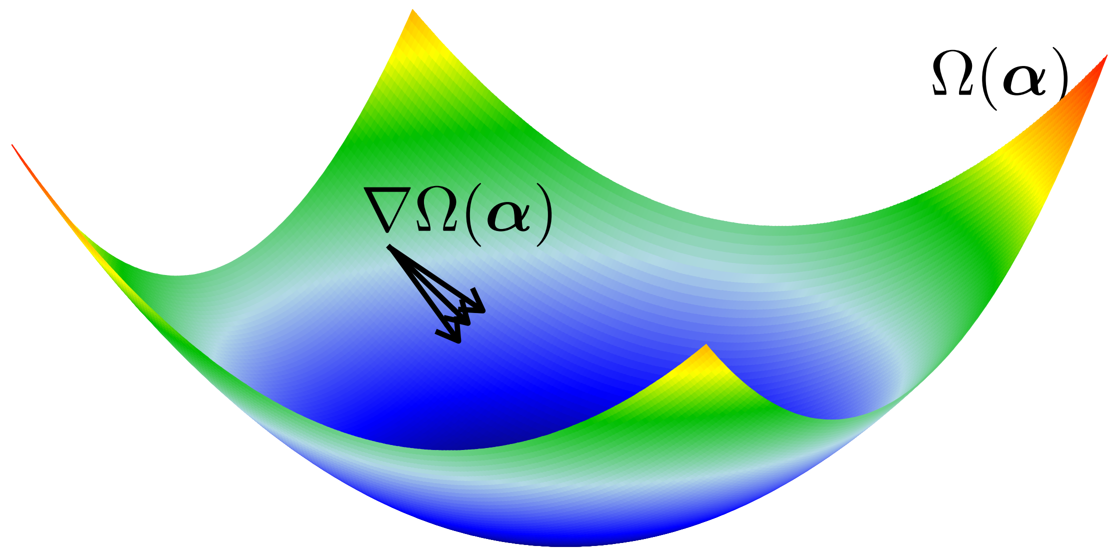
VES Code: Module for Performing Variationally Enhanced Sampling Simulations within PLUMED



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Max Planck Institute for Polymer Research

THEORY GROUP

PLUMED Meeting, Trieste, May 22, 2017

* since April, 2017

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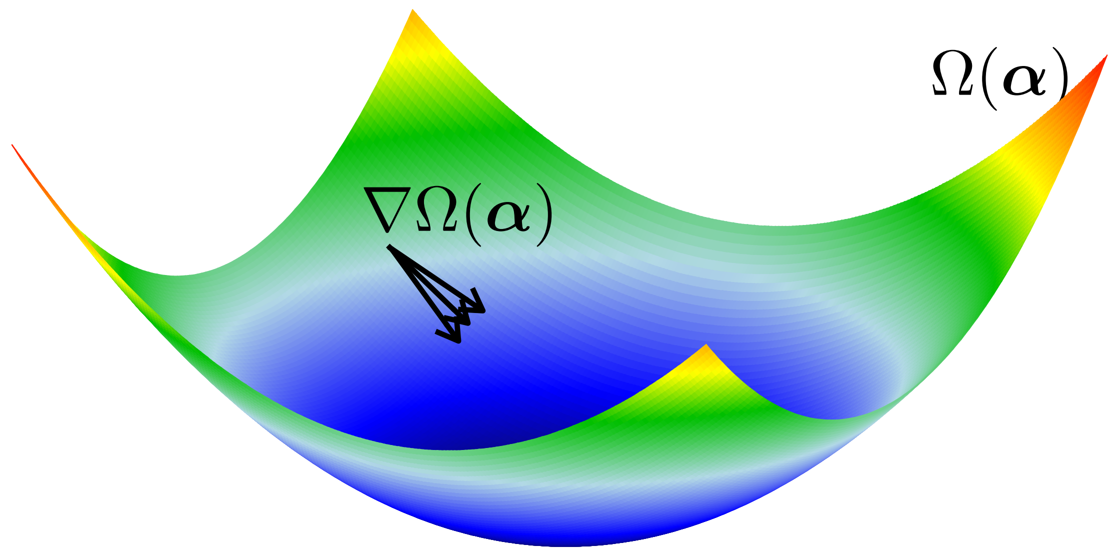

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MARVEL

NATIONAL CENTRE OF COMPETENCE IN RESEARCH

FNSNF

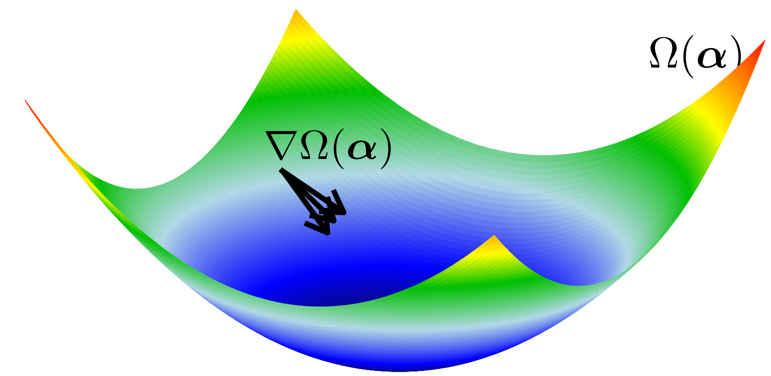
SWISS NATIONAL SCIENCE FOUNDATION

PLUMED Meeting, Trieste, May 22, 2017

* until March, 2017

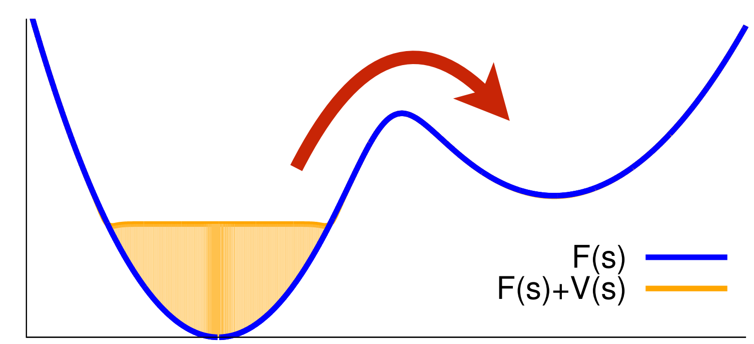
Outline

Variationally Enhanced Sampling (VES)



Extensions of VES

- Kinetics, …

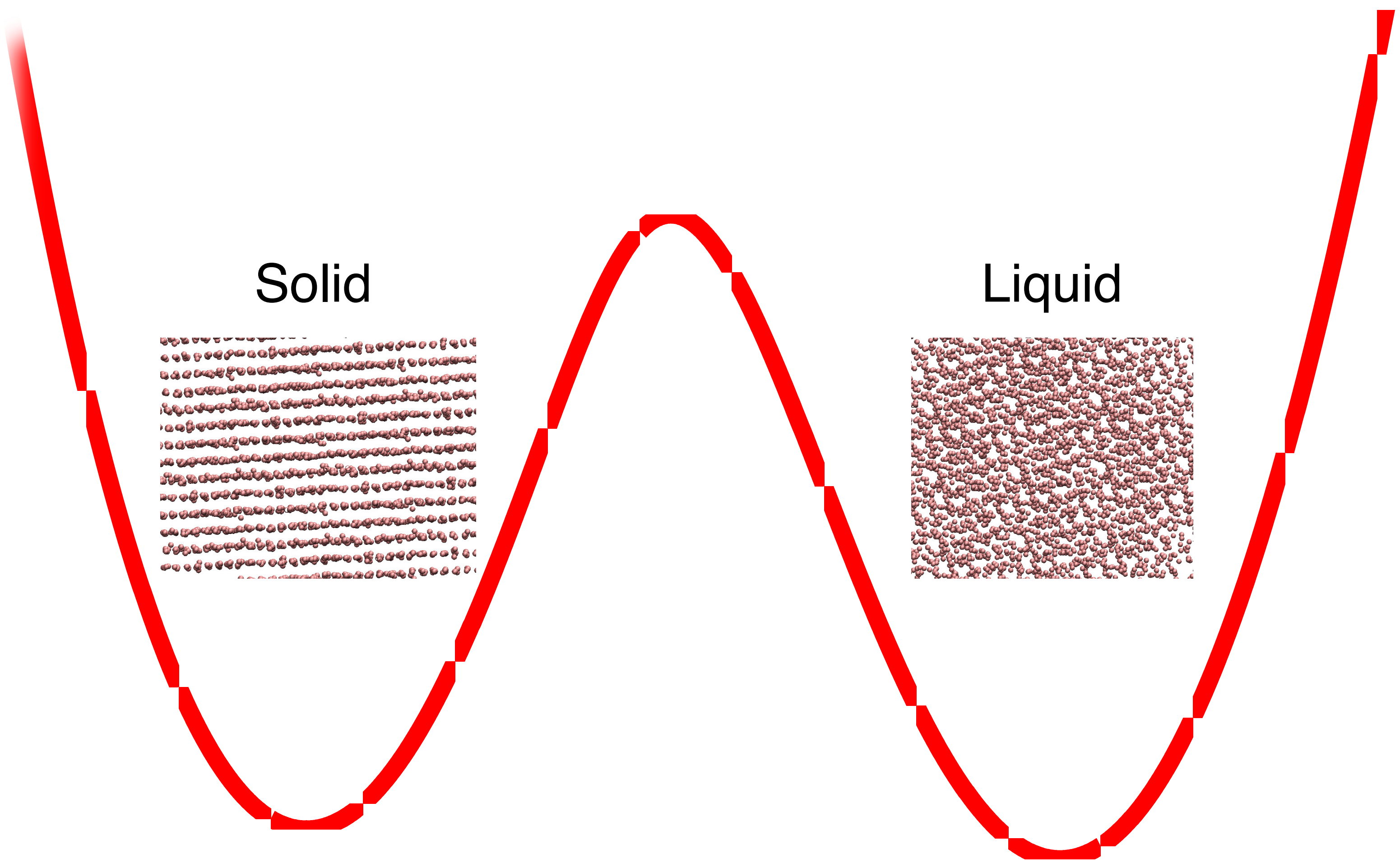


Implementation

PLUMED + VES Code → MD

The Sampling Problem in Molecular Simulations

Physical systems generally characterized by many metastable states separated by high free energy barriers



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

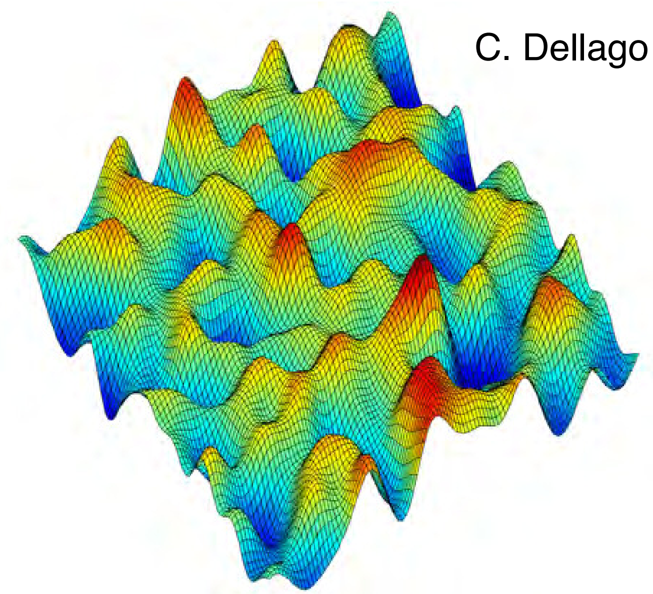
➡ need to employ enhanced sampling methods

Mapping the Problem to a Lower Dimension

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

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

➡ Rugged

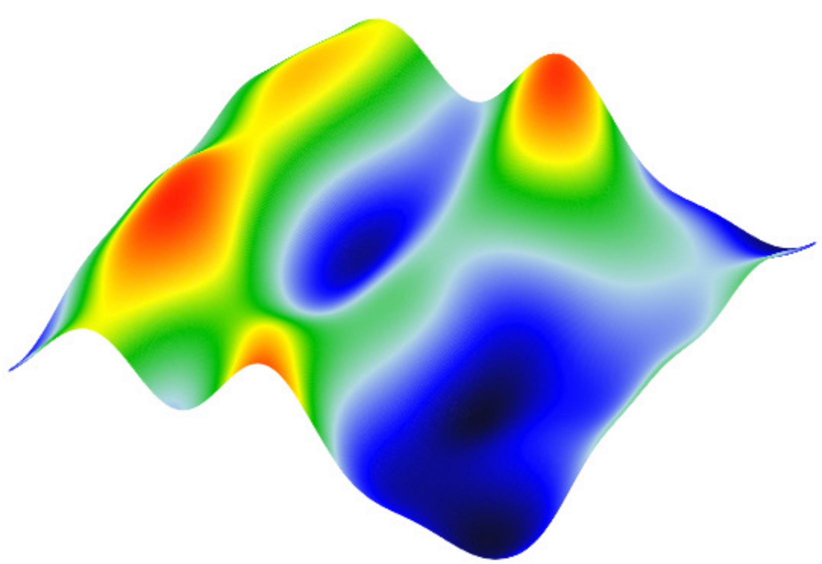


CVs $\mathbf{s}(\mathbf{R}) = (s_1(\mathbf{R}), s_2(\mathbf{R}), \ldots, s_d(\mathbf{R}))$

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

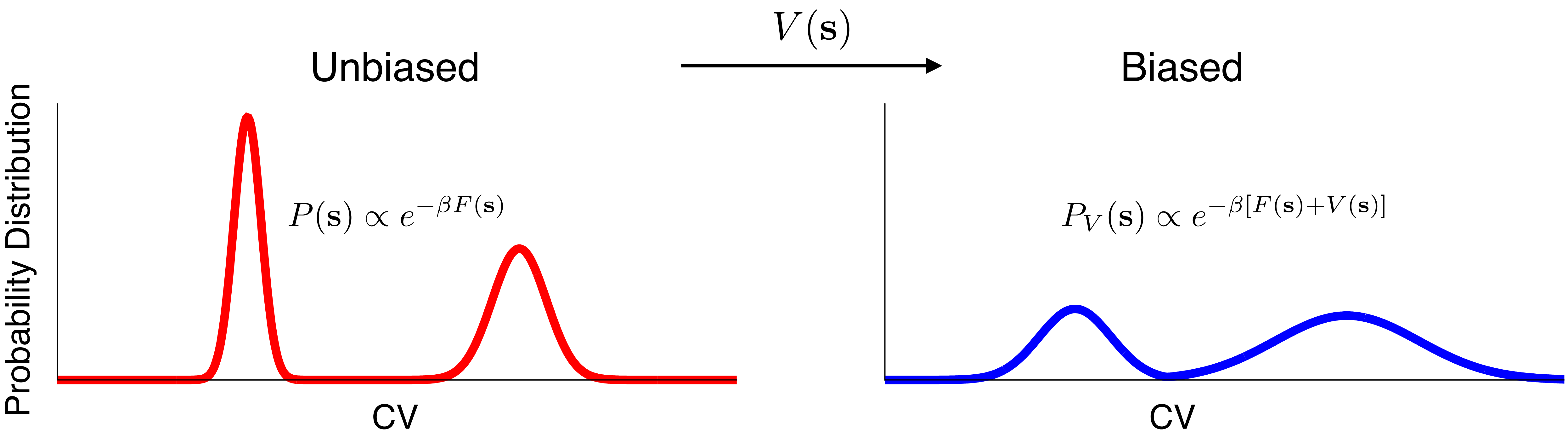
➡ Low-dimensional, $\mathbf{s} \in \mathbb{R}^d$

➡ **Smooth**



Enhancing CV Fluctuations

introduce a bias potential $V(\mathbf{s})$ that acts in the space spanned by the CVs
(originally suggested within umbrella sampling[a])



enhance CV fluctuations ➡ easier to overcome barriers

various methods which adaptively build $V(\mathbf{s})$ during the simulation

- e.g. Local Elevation, Adaptive Biasing Force, Metadynamics, …

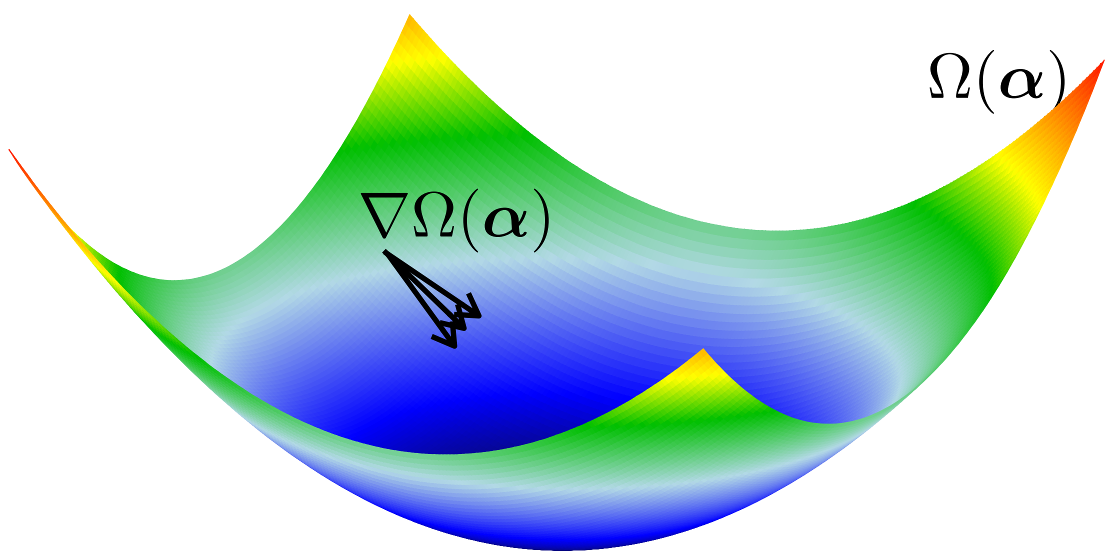
[a] Torrie and Valleau, J. Comp. Phys. 1977

Variationally Enhanced Sampling (VES)

New CV based enhanced sampling method

Based on a variational principle

$V(\mathbf{s})$ constructed by minimizing a convex functional



Offers many interesting possibilities in the form of $V(\mathbf{s})$

Can tailor the sampling of the CVs

Valsson and Parrinello, Phys. Rev. Lett. 2014

Variational Principle

introduce a functional $\Omega[V]$ of an external bias potential $V(\mathbf{s})$

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

$p(\mathbf{s})$ predefined probability distribution

$$\int d\mathbf{s}\, p(\mathbf{s}) = 1$$

can be shown that $\Omega[V]$ is a convex functional, i.e. fulfills

$$\Omega\left[\frac{V_1 + V_2}{2}\right] \leq \frac{1}{2}\Omega[V_1] + \frac{1}{2}\Omega[V_2]$$

Variational Principle

minimum of $\Omega[V]$ is fulfills

$$0 = \frac{\partial \Omega[V]}{\partial V(\mathbf{s})} = -\frac{e^{-\beta[F(\mathbf{s})+V(\mathbf{s})]}}{\int d\mathbf{s} e^{-\beta[F(\mathbf{s})+V(\mathbf{s})]}} + p(\mathbf{s})$$

which is solved by

$$V(\mathbf{s}) = -F(\mathbf{s}) - \frac{1}{\beta} \log p(\mathbf{s}) + C$$

minimum of $\Omega[V]$ directly related to $F(\mathbf{s})$

➡ can obtain the FES by finding the bias that minimizes $\Omega[V]$

global minimum as $\Omega[V]$ is convex

Target Distribution

CVs sampled according to the target distribution $p(\mathbf{s})$ at the minimum

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

can choose the target distribution $p(\mathbf{s})$ as we want

➡ can precisely tune the sampling of phase space

➡ brings a lot of flexibility to the method

simplest choice uniform distribution, but generally non-optimal

does not need to be known a-priori ➡ can be iteratively updated[a]

[a] Valsson and Parrinello, JCTC 2015

Recap of the Main Idea Behind VES

Variational principle to enhanced sampling

based on a functional $\Omega[V]$

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

which is minimized by

$$V(\mathbf{s}) = -F(\mathbf{s}) - \frac{1}{\beta} \log p(\mathbf{s}) + C$$

can enhance the sampling and obtain $F(\mathbf{s})$ by
finding the $V(\mathbf{s})$ that minimizes $\Omega[V]$

the resulting CV distribution determined by the target distribution $p(\mathbf{s})$,
which we can choose freely

convex functional ➡ easy optimization problem

Valsson and Parrinello, PRL 2014

VES in Practice

assume some functional form for the bias $V(\mathbf{s};\boldsymbol{\alpha})$ that depends on a set of variational parameters $\boldsymbol{\alpha} = (\alpha_1,\alpha_2,\ldots,\alpha_K)$

minimize the convex function $\Omega(\boldsymbol{\alpha}) = \Omega[V(\boldsymbol{\alpha})]$ using a gradient-based optimization algorithm

the gradient $\nabla\Omega(\boldsymbol{\alpha})$ is defined by the elements

$$\frac{\partial\Omega(\boldsymbol{\alpha})}{\partial\alpha_i} = -\left\langle \frac{\partial V(\mathbf{s};\boldsymbol{\alpha})}{\partial\alpha_i} \right\rangle_{V(\boldsymbol{\alpha})} + \left\langle \frac{\partial V(\mathbf{s};\boldsymbol{\alpha})}{\partial\alpha_i} \right\rangle_{p}$$

$\Downarrow$ averages sampled in a biased MD simulation

$\Downarrow$ averages over $p(\mathbf{s})$

Linear Basis Set Expansion

most straightforward to expand the bias linearly in a set of basis functions

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

such expansions can represent any general FES

the gradient then simplifies to averages of $f_{\mathbf{i}}(\mathbf{s})$

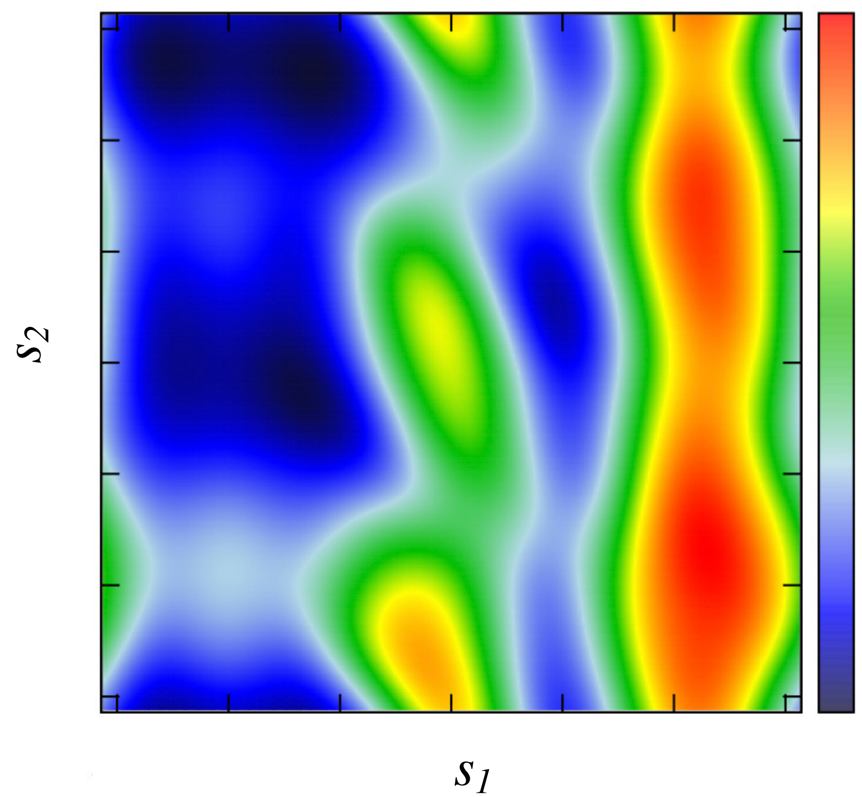
$$\frac{\partial \Omega(\boldsymbol{\alpha})}{\partial \alpha_{\mathbf{i}}} = -\left\langle f_{\mathbf{i}}(\mathbf{s}) \right\rangle_{V(\boldsymbol{\alpha})} + \left\langle f_{\mathbf{i}}(\mathbf{s}) \right\rangle_{p}$$

Linear Basis Set Expansion

Periodic CV

Fourier series (i.e. plane waves)

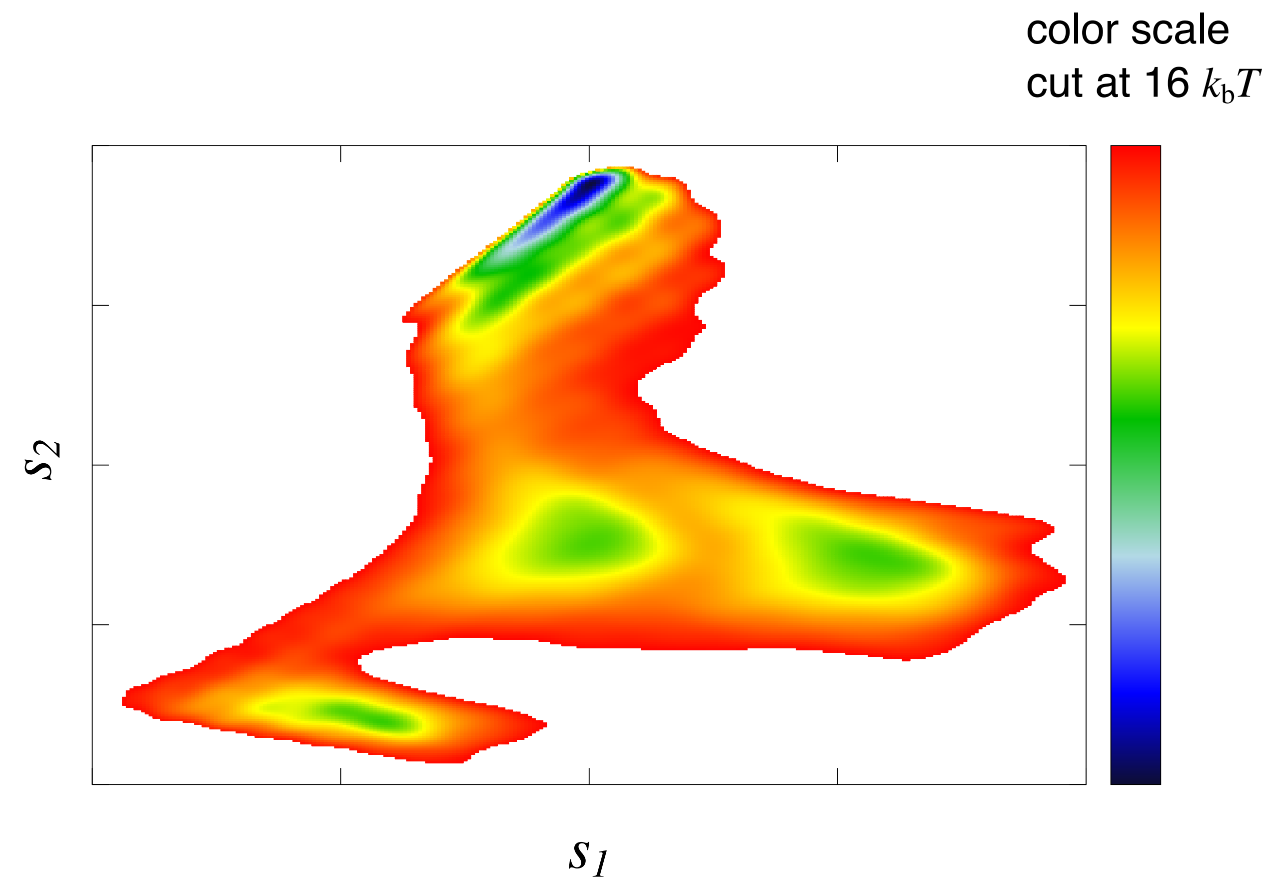
$$V(s_1, s_2) = \sum_{k_1,k_2} \alpha_{k_1,k_2}\, e^{ik_1\tilde{s}_1} \cdot e^{ik_2\tilde{s}_2}$$



Non-Periodic CV

Legendre or Chebyshev polynomials

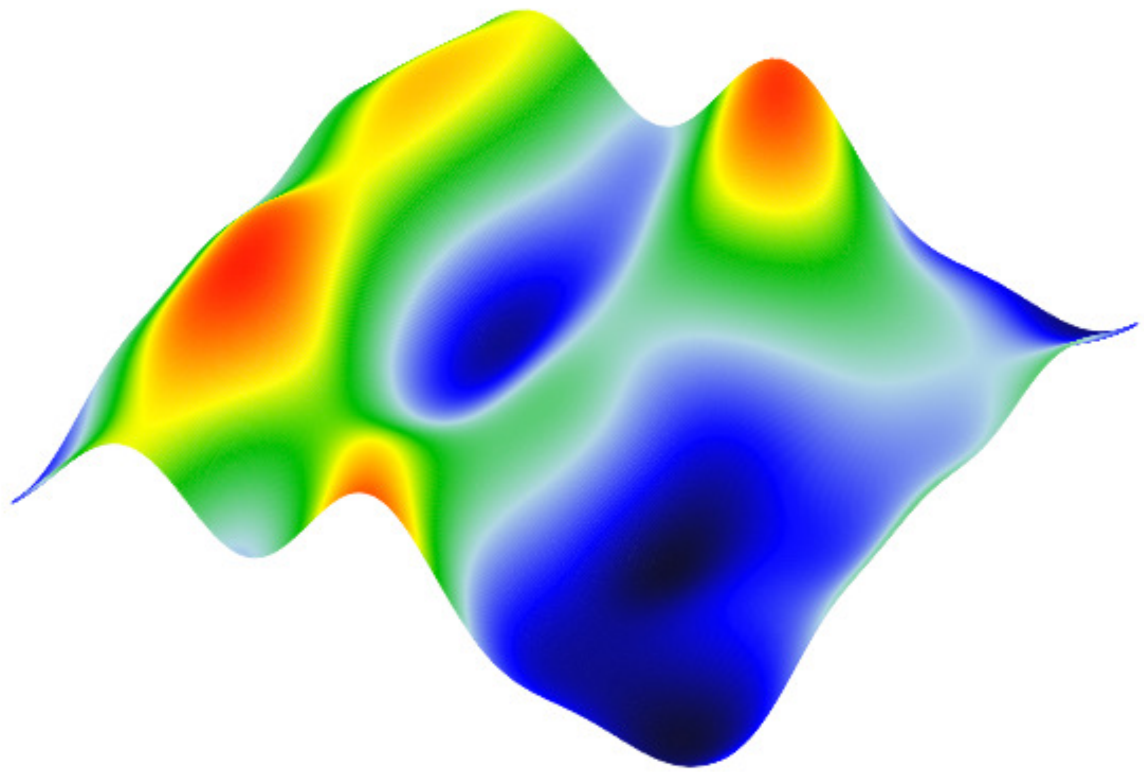
$$V(s_1, s_2) = \sum_{k_1,k_2} \alpha_{k_1,k_2}\, T_{k_1}(\tilde{s}_1) \cdot T_{k_2}(\tilde{s}_2)$$



many other possibilities: e.g. other orthonormal polynomials, splines, wavelets, ….

$F(\mathbf{s})$ normally smooth

➡ generally do not need many terms in the linear expansion



~100 basis functions in two dimensions

~1000 basis functions in three dimensions

Gradient-based Optimization

the gradient $\nabla\Omega(\boldsymbol{\alpha})$ is defined by the elements

$$\frac{\partial\Omega(\boldsymbol{\alpha})}{\partial\alpha_{\mathbf{i}}} = \boxed{-\left\langle f_{\mathbf{i}}(\mathbf{s})\right\rangle_{V(\boldsymbol{\alpha})}} + \left\langle f_{\mathbf{i}}(\mathbf{s})\right\rangle_{p}$$

known analytically or numerically

sampled in a biased MD simulation ➡ noisy!

long sampling time needed to get accurate gradients if we wanted to employ deterministic optimization methods ➡ not optimal

employ stochastic optimization methods instead

Averaged Stochastic Gradient Descent[a]

consider two sets of coefficients, instantaneous and **averaged**

instantaneous coefficients updated according to

$$\boldsymbol{\alpha}^{(n+1)} = \boldsymbol{\alpha}^{(n)} - \mu \left[\nabla\Omega(\bar{\boldsymbol{\alpha}}^{(n)}) + \mathbf{H}(\bar{\boldsymbol{\alpha}}^{(n)})[\boldsymbol{\alpha}^{(n)} - \bar{\boldsymbol{\alpha}}^{(n)}] \right]$$

where gradient and Hessian are obtained using **averaged** coefficients

$$\bar{\boldsymbol{\alpha}}^{(n)} = \frac{1}{n+1} \sum_{k=0}^{n} \boldsymbol{\alpha}^{(k)}$$

the bias acting on the system depends on **averaged** coefficients

➡ smooth convergence of bias and estimated FES

➡ allows very short sampling time for each iteration (~ 1000 MD steps)

[a] F. Bach and E. Moulines, NIPS, 2012

Averaged Stochastic Gradient Descent

Now we need also the (stochastic) Hessian $\mathbf{H}(\boldsymbol{\alpha})$

For a linear expansion it is defined by

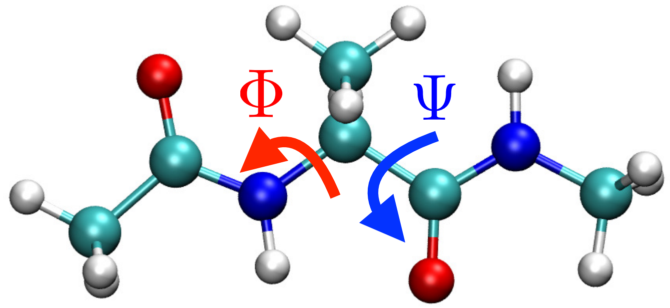
$$\frac{\partial^2 \Omega(\boldsymbol{\alpha})}{\partial \alpha_{\mathbf{j}} \partial \alpha_{\mathbf{i}}} = \beta \cdot \mathrm{cov}\left[f_{\mathbf{i}}(\mathbf{s}), f_{\mathbf{j}}(\mathbf{s}) \right]_{V(\mathbf{s};\boldsymbol{\alpha})}$$

i.e. covariance of the basis functions

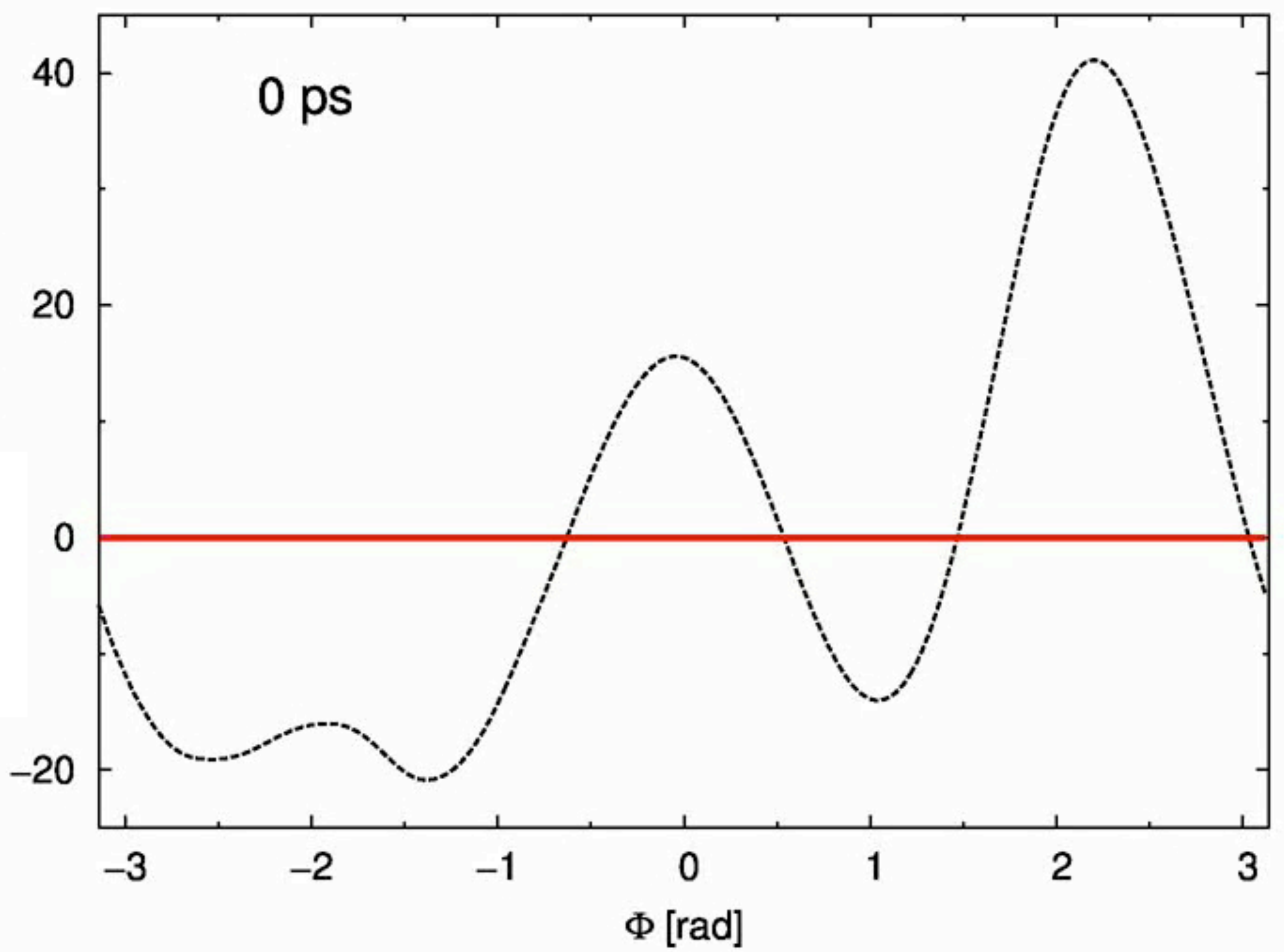
In practice it is often sufficient to consider only the diagonal part of the Hessian

Example of Time Evolution

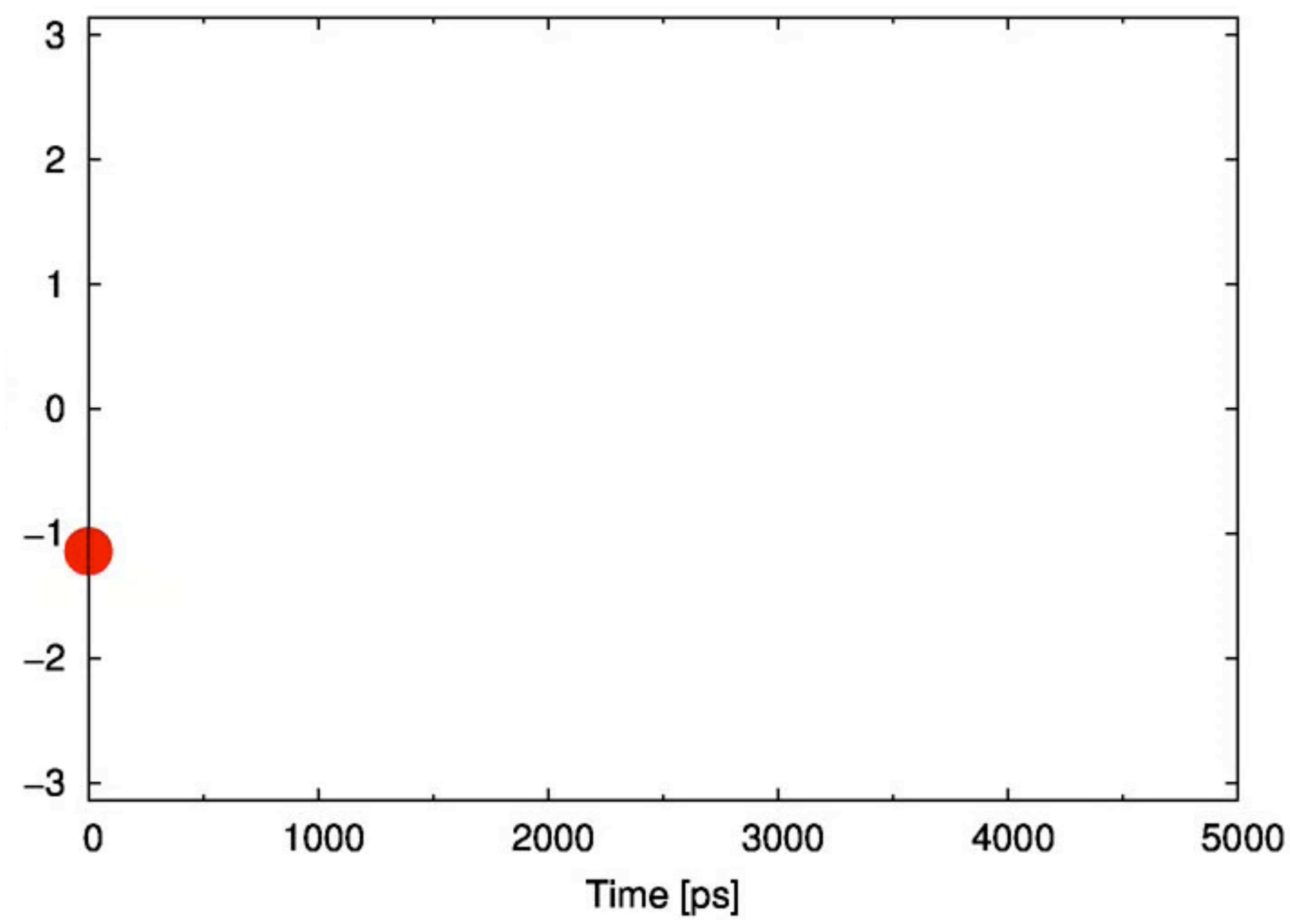
Alanine dipeptide, biasing only the Φ dihedral angle



$F(\Phi) = -V(\Phi)$ [kJ/mol]



Φ [rad]



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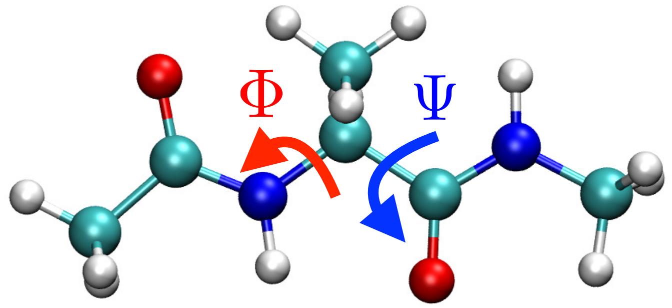
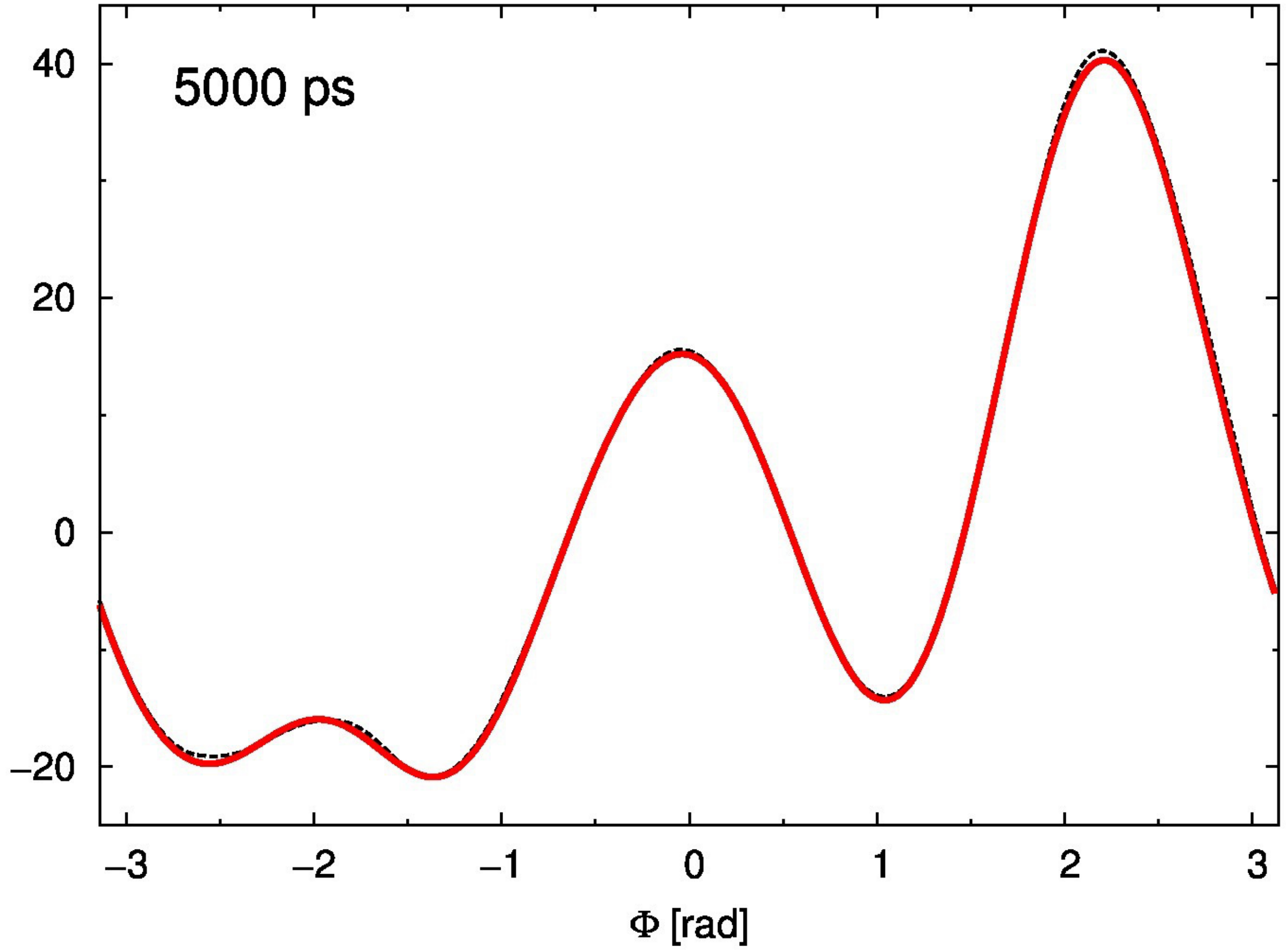
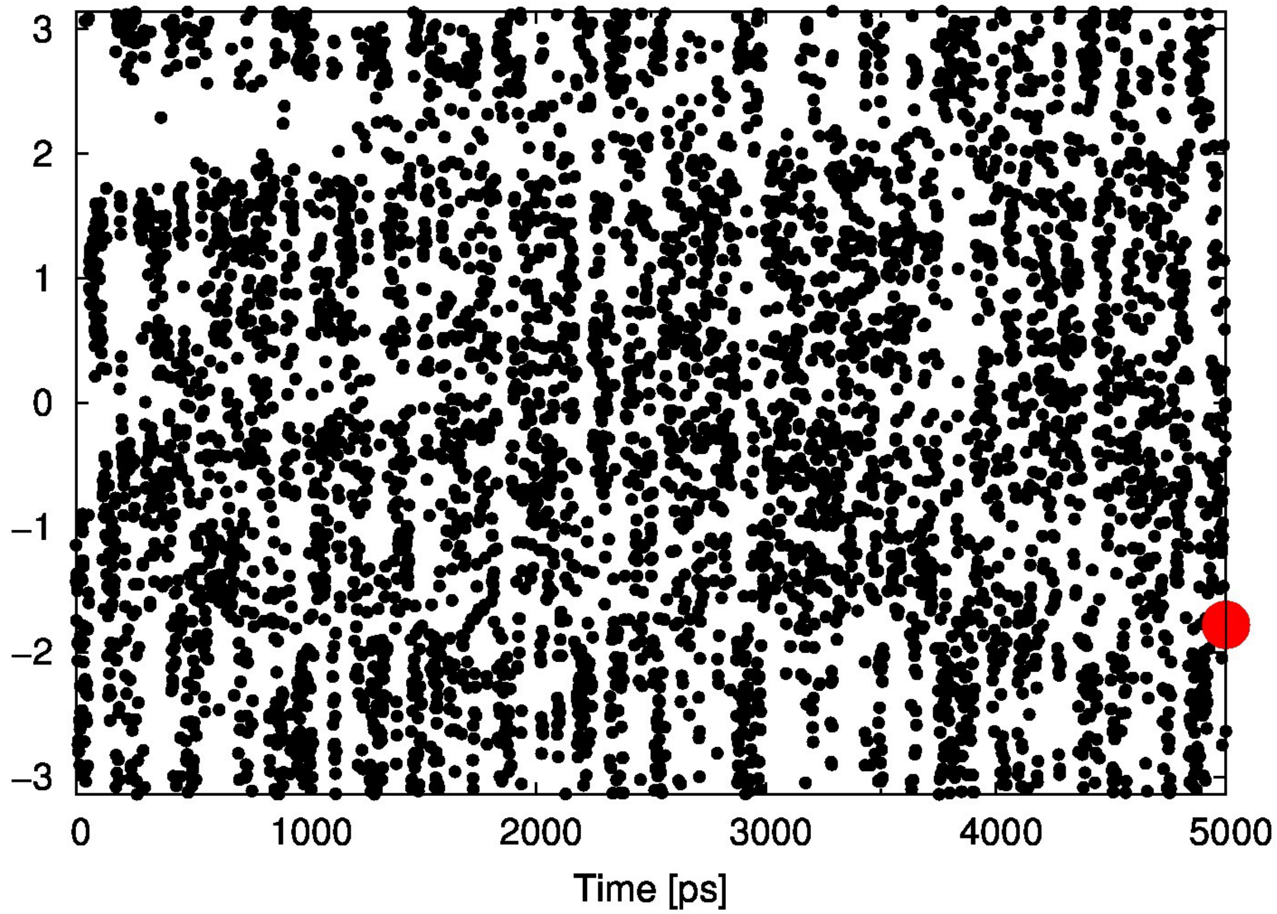


$F(\Phi) = -V(\Phi)$ [kJ/mol]

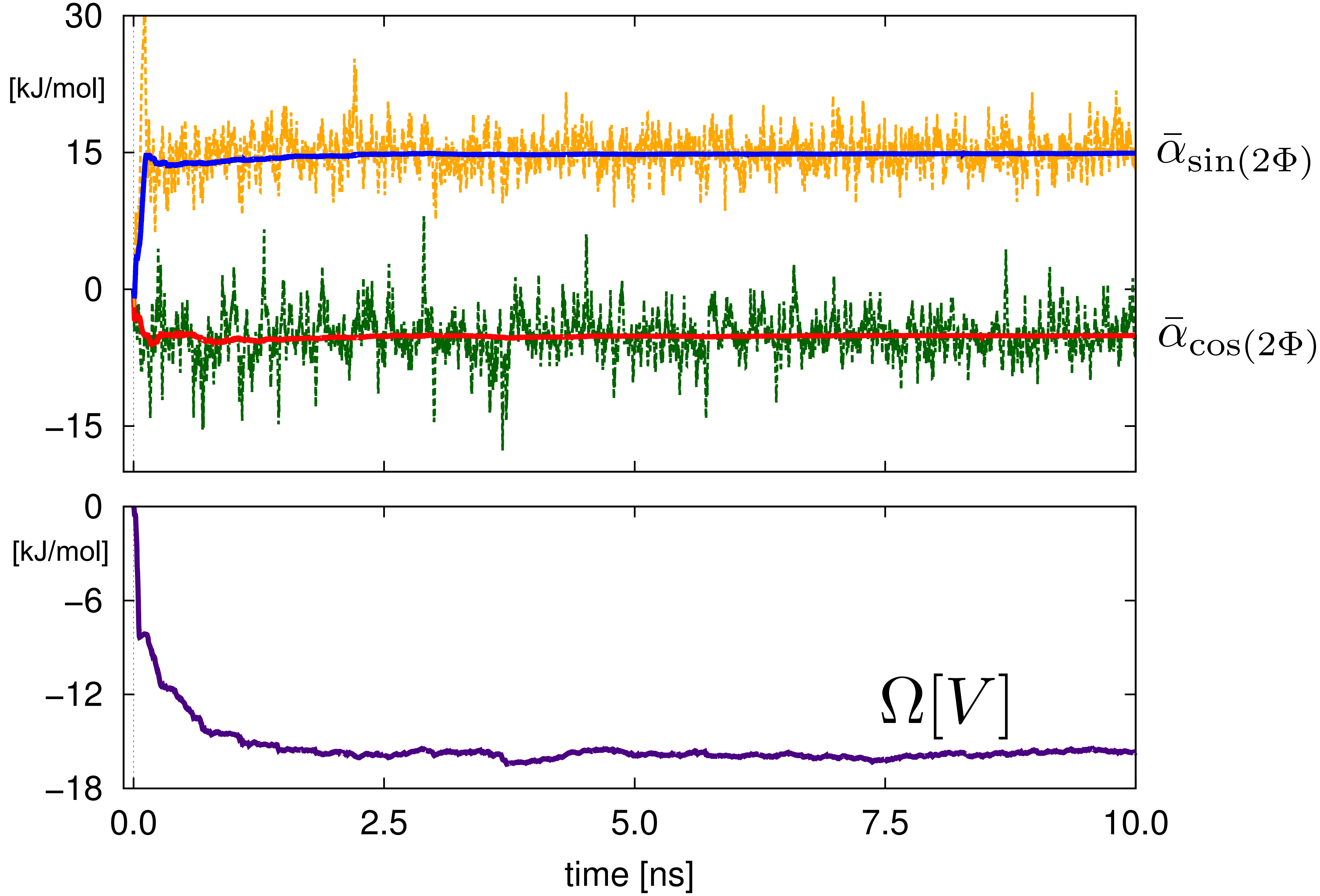


Φ [rad]



Example of Time Evolution

Clear convergence behavior observed for
variational parameters and $\Omega[V]$

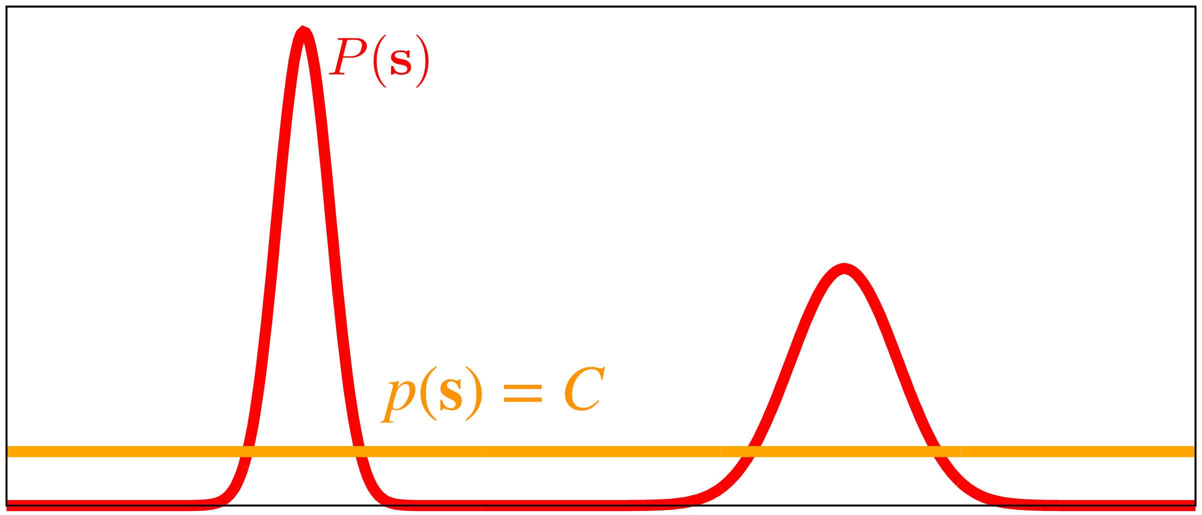


Choice of the Target Distribution

Uniform Target Distribution

the simplest choice for the target distribution $p(\mathbf{s})$ is to take it as uniform

$$p(\mathbf{s}) = \frac{1}{\int d\mathbf{s}} = C \quad \Rightarrow \quad V(\mathbf{s}) = -F(\mathbf{s}) \qquad \text{(modulo constant)}$$



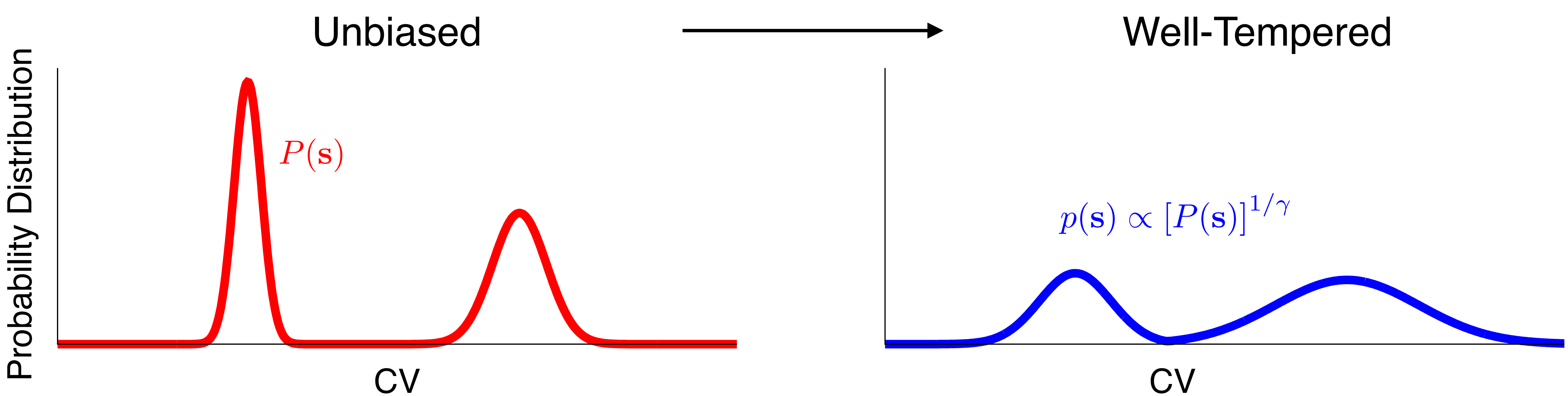
but generally rather non-optimal

➡ spend a lot of time sampling irrelevant regions high in free energy

instead better to focus the sampling towards the low-lying regions

Well-Tempered Target Distribution

$$p(\mathbf{s}) = \frac{e^{-(1/\gamma)\beta F(\mathbf{s})}}{\int d\mathbf{s}'\, e^{-(1/\gamma)\beta F(\mathbf{s}')}} \propto [P(\mathbf{s})]^{1/\gamma} \quad \Rightarrow \quad V(\mathbf{s}) = -\left(1-\frac{1}{\gamma}\right)F(\mathbf{s})$$



enhanced CV fluctuations ➡ easier to overcome barriers

can control free energy exploration through the bias factor γ

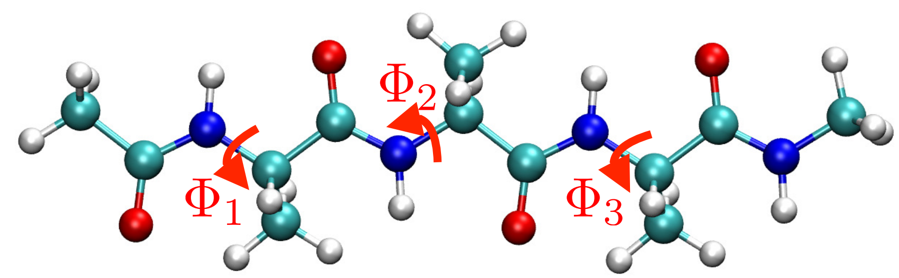
$F(\mathbf{s})$ is of course a priori unknown ➡ achieved through a iterate scheme[b]

[a] Barducci, Bussi, and Parrinello, PRL 2008

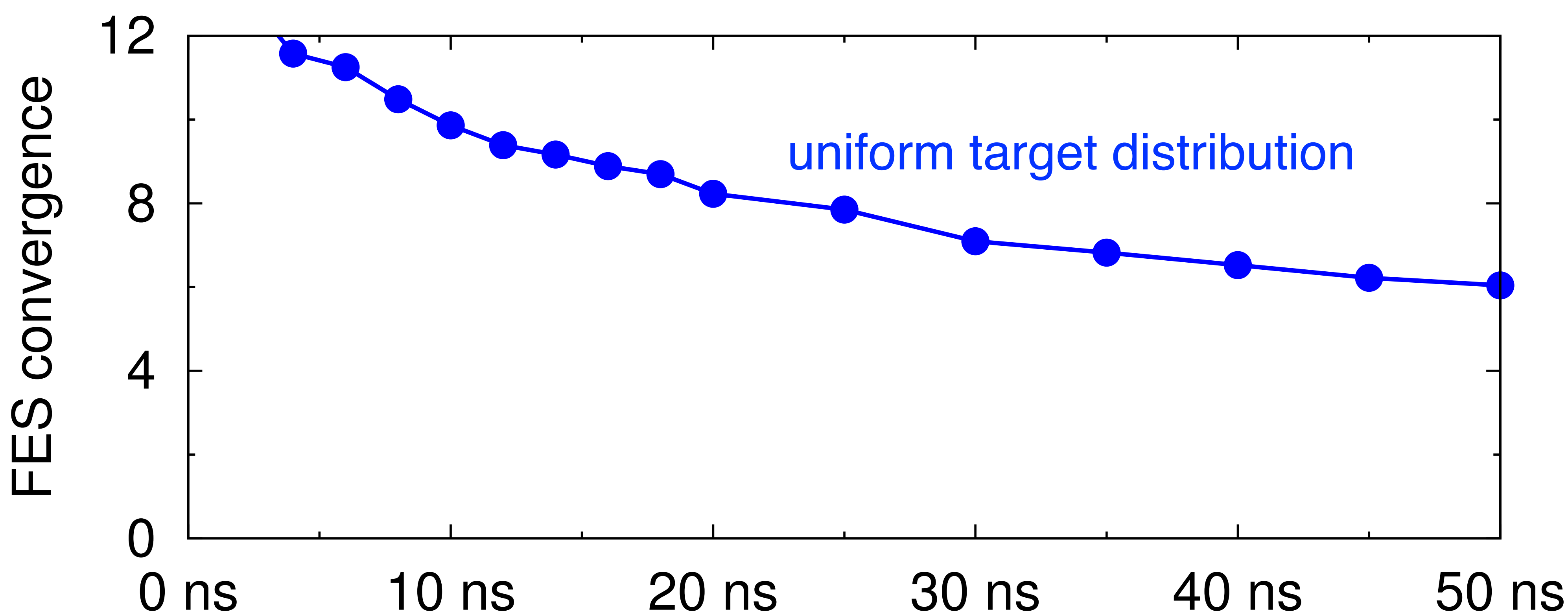
[b] Valsson and Parrinello, JCTC 2015

Choice of the Target Distribution and Convergence

Alanine tetrapeptide



3 CVs ➡ ~2000-10000 basis functions



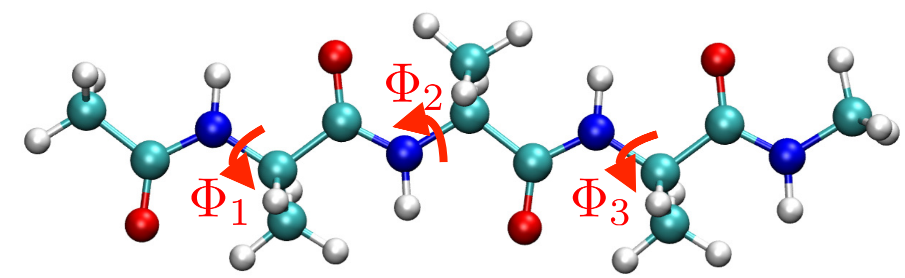
very slow convergence with a uniform $p(\mathbf{s})$

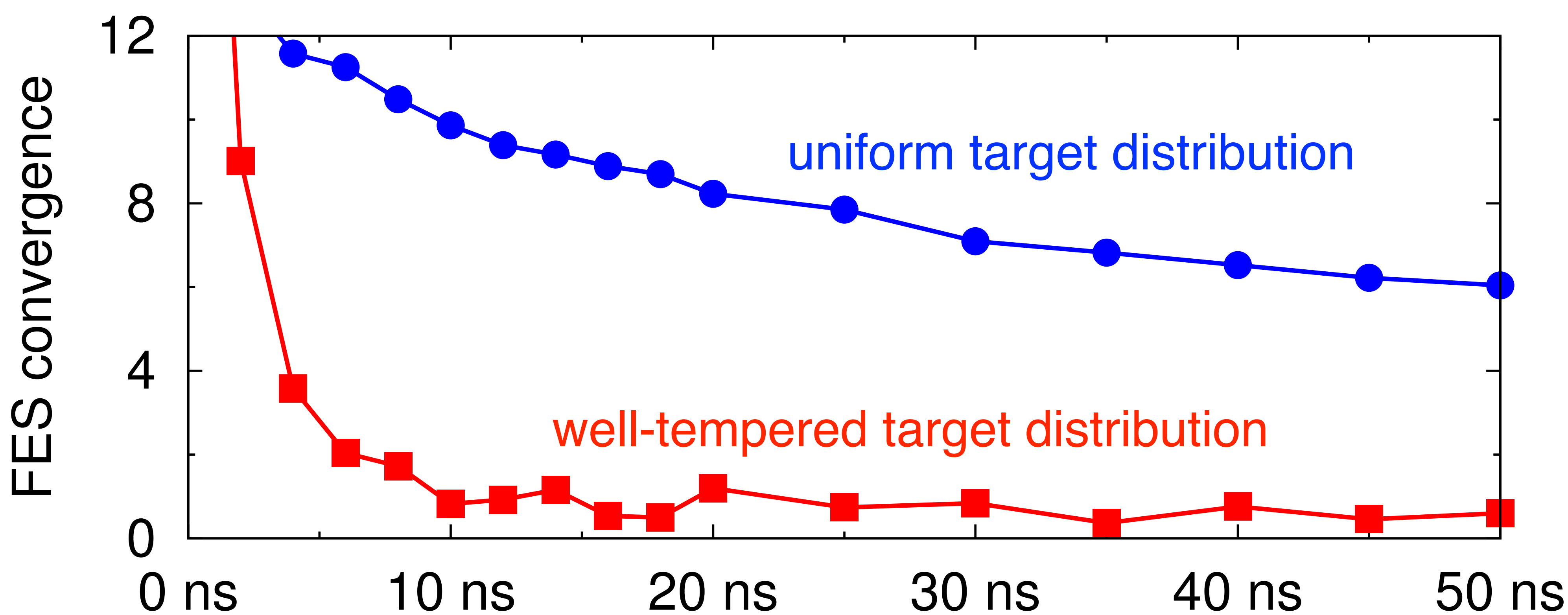
Valsson and Parrinello, JCTC 2015

Choice of the Target Distribution and Convergence

3 CVs ➡ ~2000-10000 basis functions

Alanine tetrapeptide





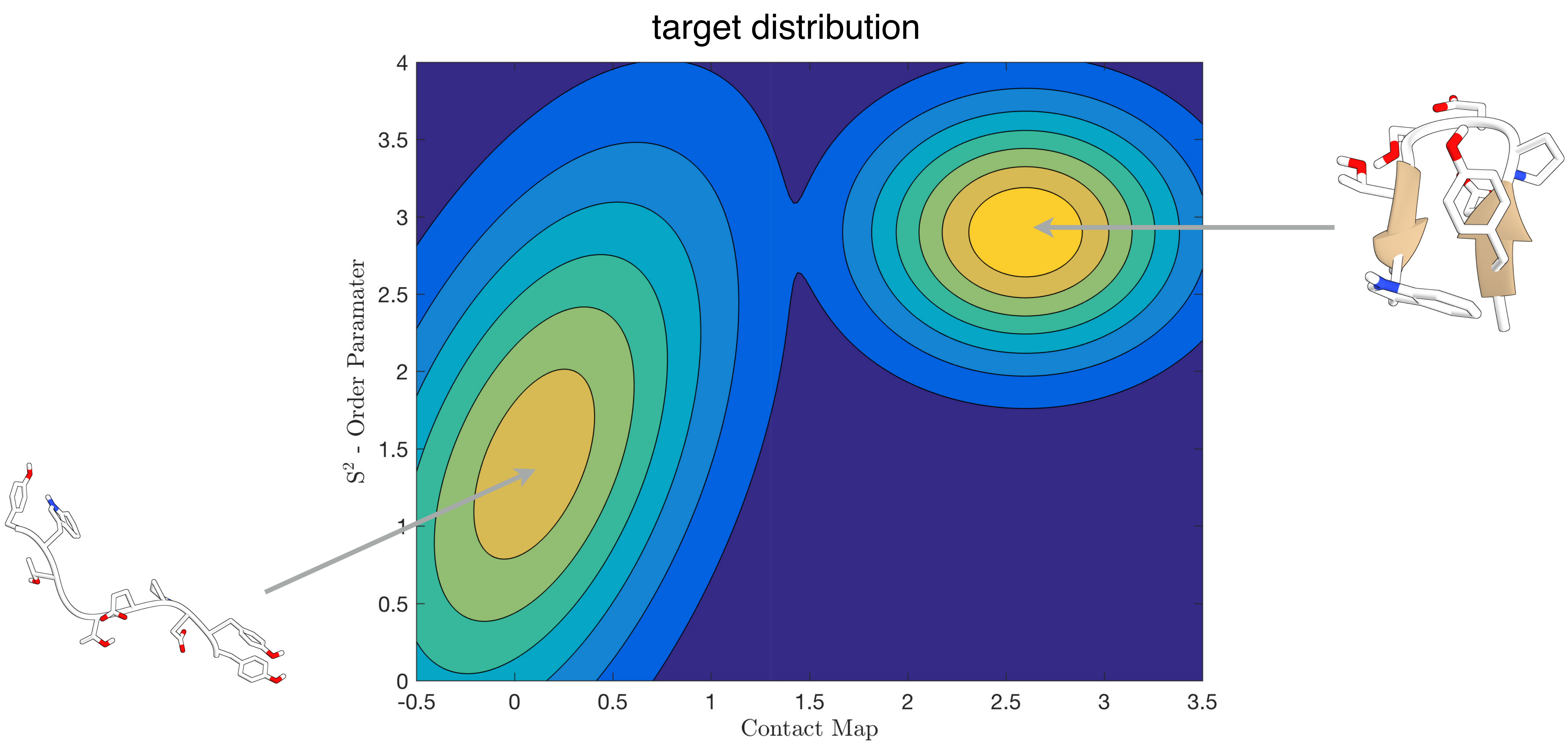
significant improvement in convergence with a well-tempered $p(\mathbf{s})$

Valsson and Parrinello, JCTC 2015

Localized Target Distribution

Can also use the target distribution to localize the sampling

$$p(\mathbf{s}) = w_f\, p_f(\mathbf{s}) + w_u\, p_u(\mathbf{s}),$$



Ferruccio, Valsson, Parrinello, submitted 2017

Various Extensions

can employ directly many extensions from metadynamics

- multiple walkers[a]

  share $V(\mathbf{s})$ and cooperatively sample the averages needed for $\nabla\Omega(\boldsymbol{\alpha})$

  observed to significantly improve convergence for difficult cases

- combine with replica exchange schemes[b]

  i.e. parallel-tempering, parallel-tempering in the well-tempered ensemble, solute-tempering, …

  helps with sampling missing orthogonal CVs

- bias-exchange[c]

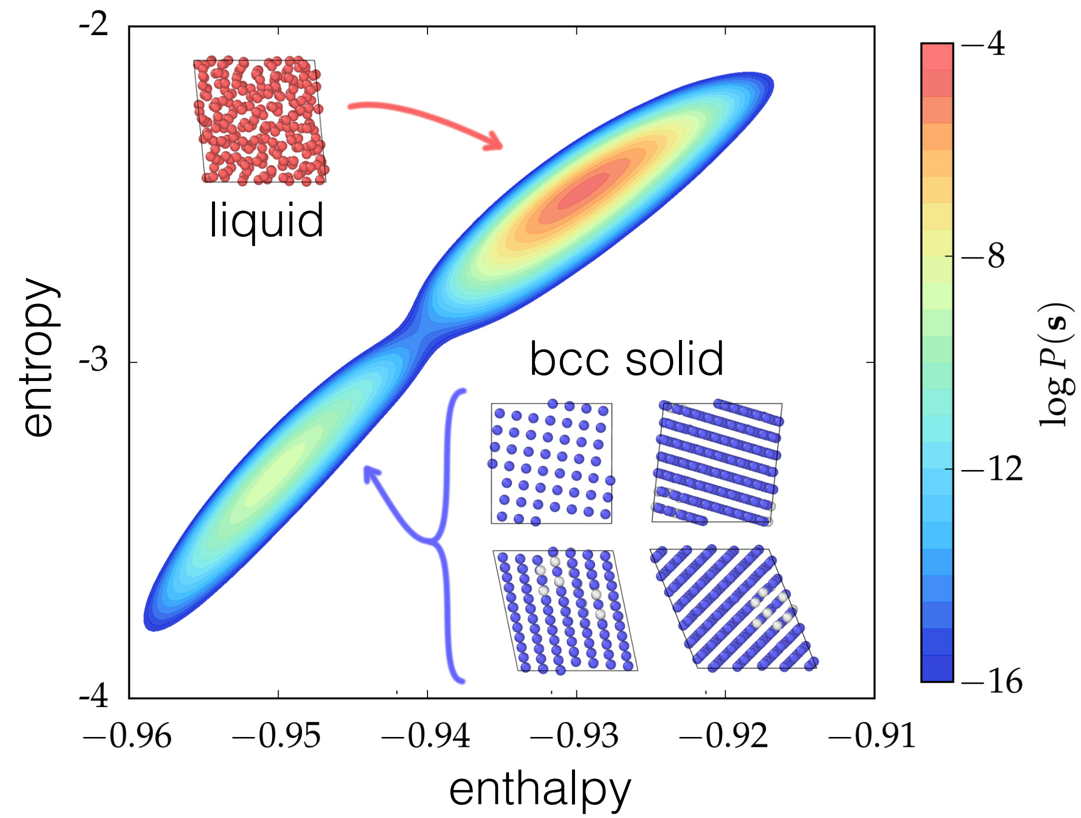
[a] Raiteri, Laio, Gervasio, Micheletti, and Parrinello, JPCB 2006

[b] Bussi, Gervasio, Laio, and Parrinello, JACS 2006

[c] Piana and Laio, JPCB 2007

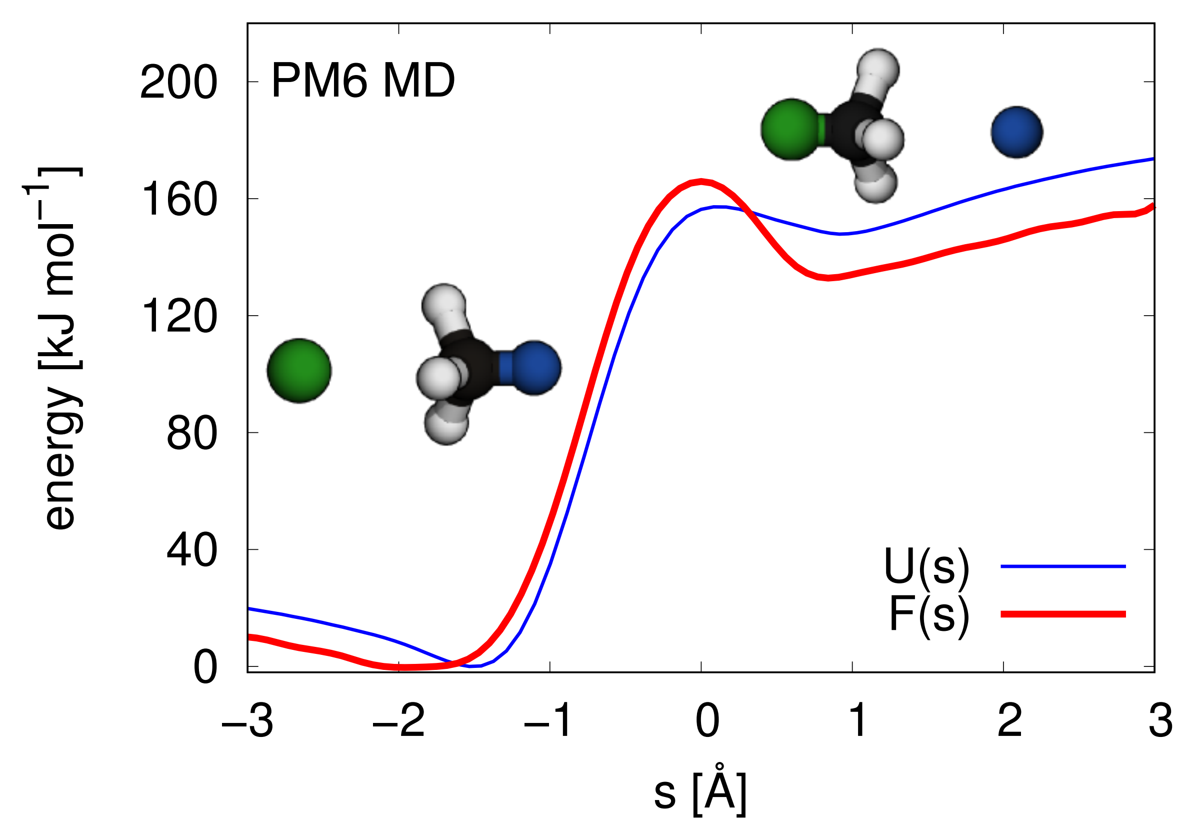
Examples

Crystallization of sodium



Piaggi, Valsson, Parrinello, PRL, submitted 2017

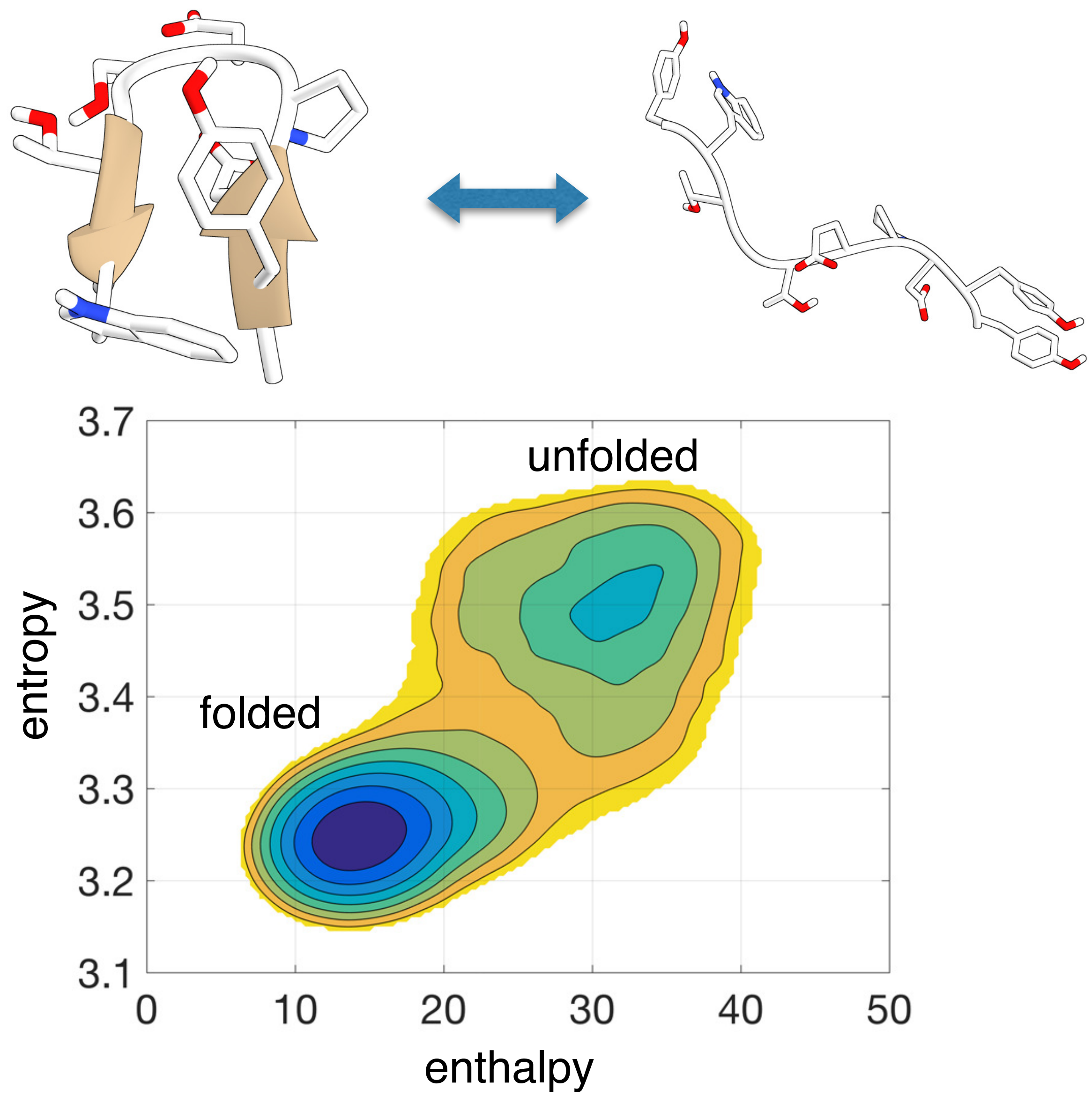
S_N2 reaction - $CH_3F + Cl^- \rightleftharpoons CH_3Cl + F^-$



Piccini, McCarty, Valsson, Parrinello, J. Phys. Chem. Lett., 2017

Examples

Protein Folding (chignolin)



Ferruccio, Valsson, Parrinello, submitted 2017

Using the Variational Property of $\Omega[V]$ in Innovative Ways

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

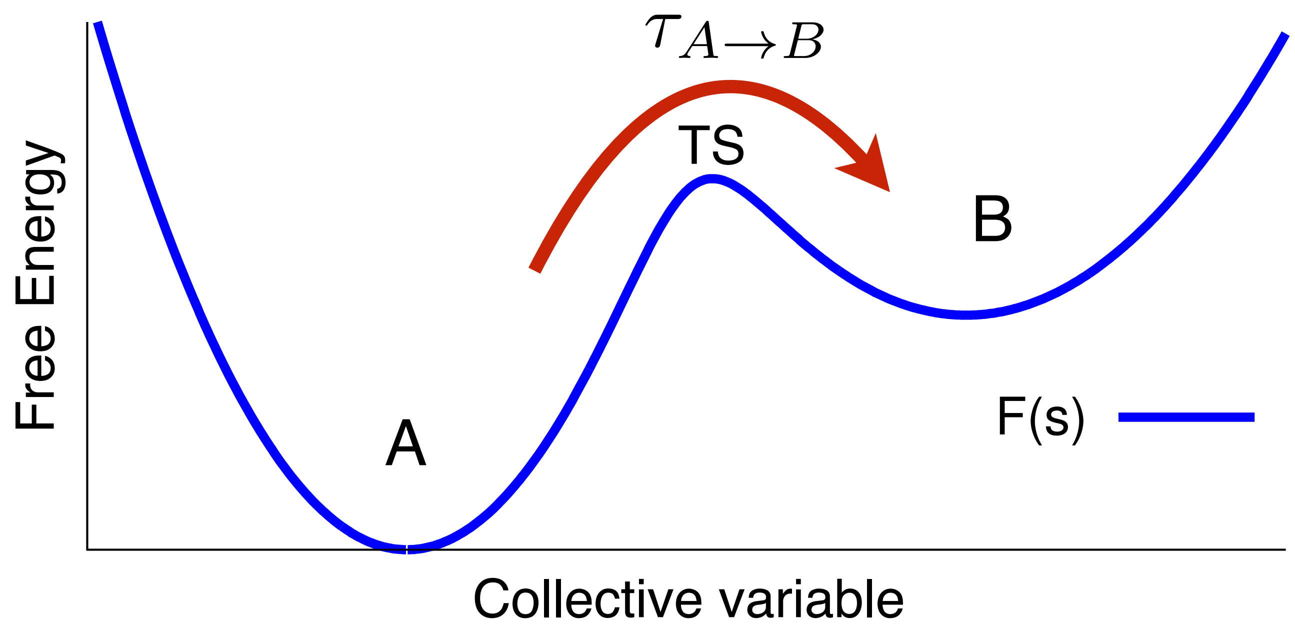
Complete flexility in the form of the bias potential $V(\mathbf{s})$

Can precisely tune the sampling via the target distribution $p(\mathbf{s})$

Variational ➡ obtain the best results given our choice

Can make use of this in many innovative ways

Kinetics from Variationally Enhanced Sampling

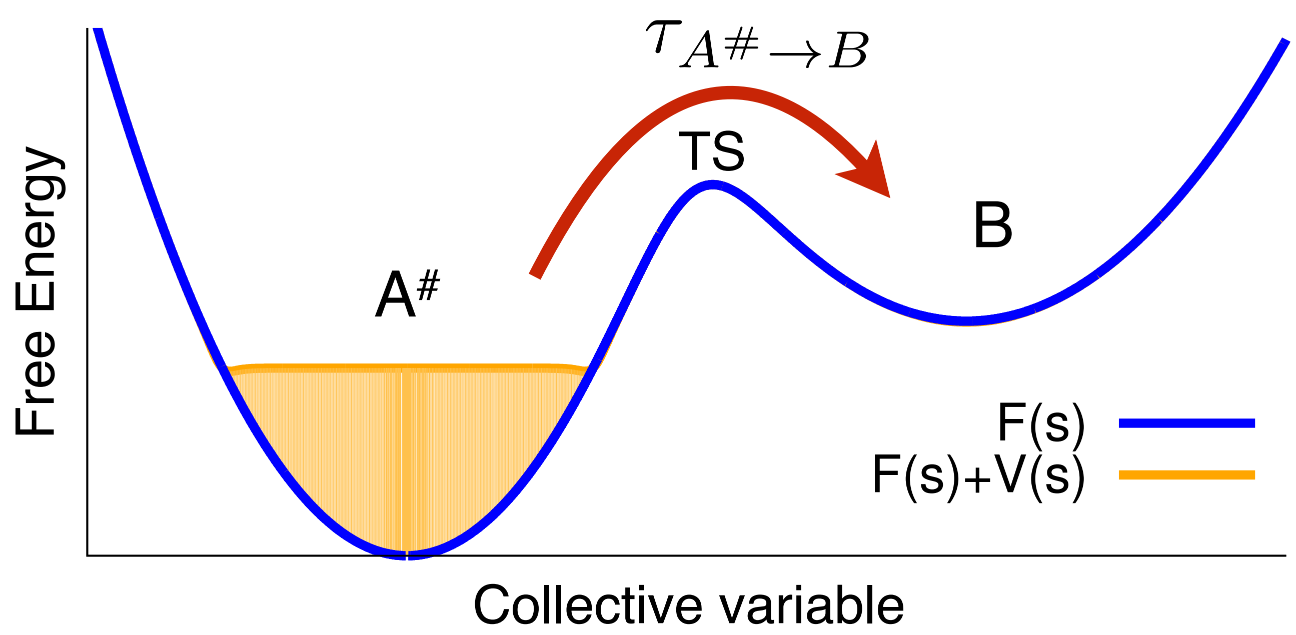


Often interested in kinetics of rare events

e.g. how much time (on average) does it take to go between metastable states A and B

McCarty, Valsson, Tiwary, Parrinello, Phys. Rev. Lett. 2015

Kinetics from Variationally Enhanced Sampling



Often interested in kinetics of rare events

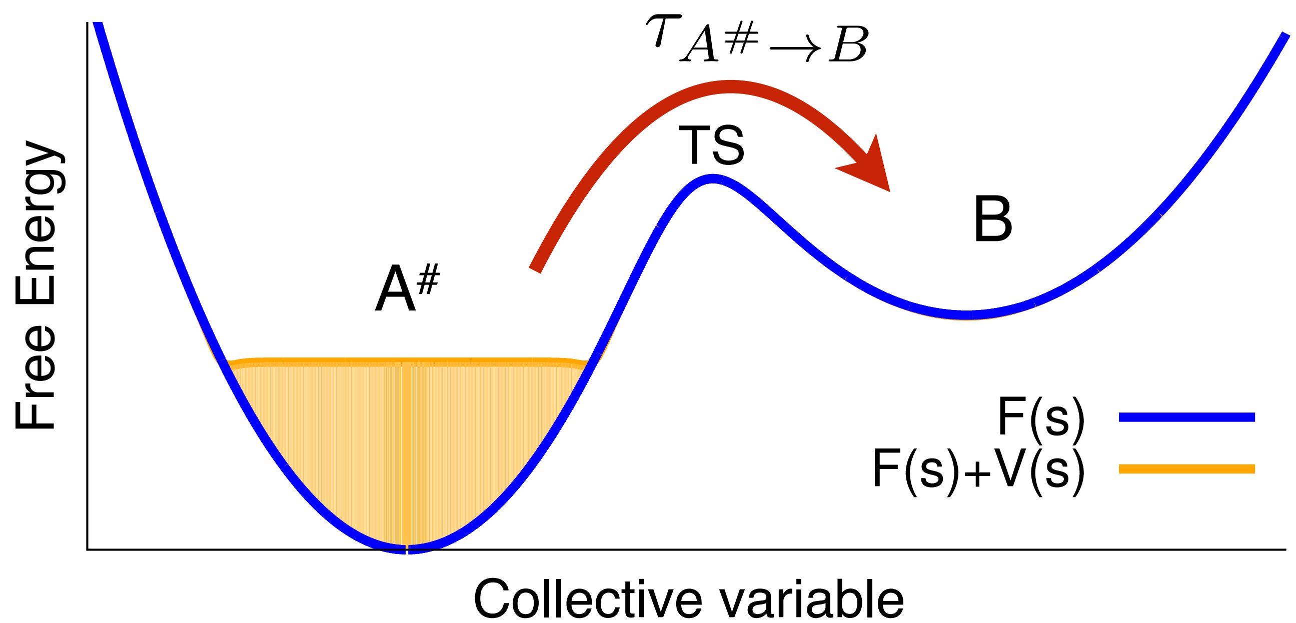
e.g. how much time (on average) does it take to go between metastable states A and B

biasing will accelerate this (which is of course what we want)

$$\tau_{A\# \rightarrow B} \ll \tau_{A \rightarrow B}$$

McCarty, Valsson, Tiwary, Parrinello, Phys. Rev. Lett. 2015

Kinetics from Variationally Enhanced Sampling



Real kinetics can be obtained from biased MD simulation through the hyperdynamics formalism[a,b]

$$\tau_{A\to B} = \tau_{A\#\to B} \cdot < e^{\beta V(\mathbf{s})} >_{V(\mathbf{s})}$$

valid if the transition state (TS) is **bias-free**

➡ can f.ex. be achieved through infrequent metadynamics[b]

use VES to construct a bias that fulfills this condition

McCarty, Valsson, Tiwary, Parrinello, Phys. Rev. Lett. 2015

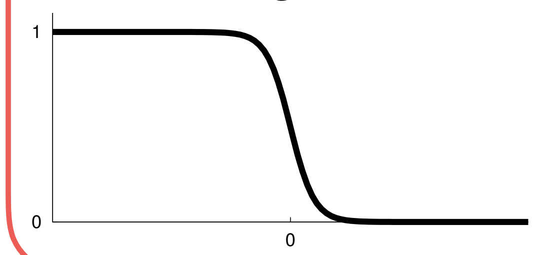
[a] Voter, PRL 1997; Grubmueller PRE 1995

[b] Tiwary and Parrinello, PRL 2013

linear expansion

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

switching function



$$V(\mathbf{s};\boldsymbol{\alpha}) = \boxed{v(\mathbf{s};\boldsymbol{\alpha})} \cdot \boxed{\mathcal{S}(-v(\mathbf{s};\boldsymbol{\alpha}) - F_c)}$$

optimize $V(\mathbf{s})$ using the target distribution

$$p(\mathbf{s}) = \frac{\mathcal{S}(F^*(\mathbf{s}) - F_c)}{\int d\mathbf{s}\, \mathcal{S}(F^*(\mathbf{s}) - F_c)} \qquad F^*(\mathbf{s}) \approx -v(\mathbf{s})$$

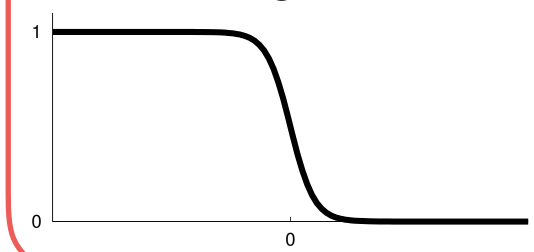
(iteratively updated)

McCarty, Valsson, Tiwary, and Parrinello, Phys. Rev. Lett. 2015

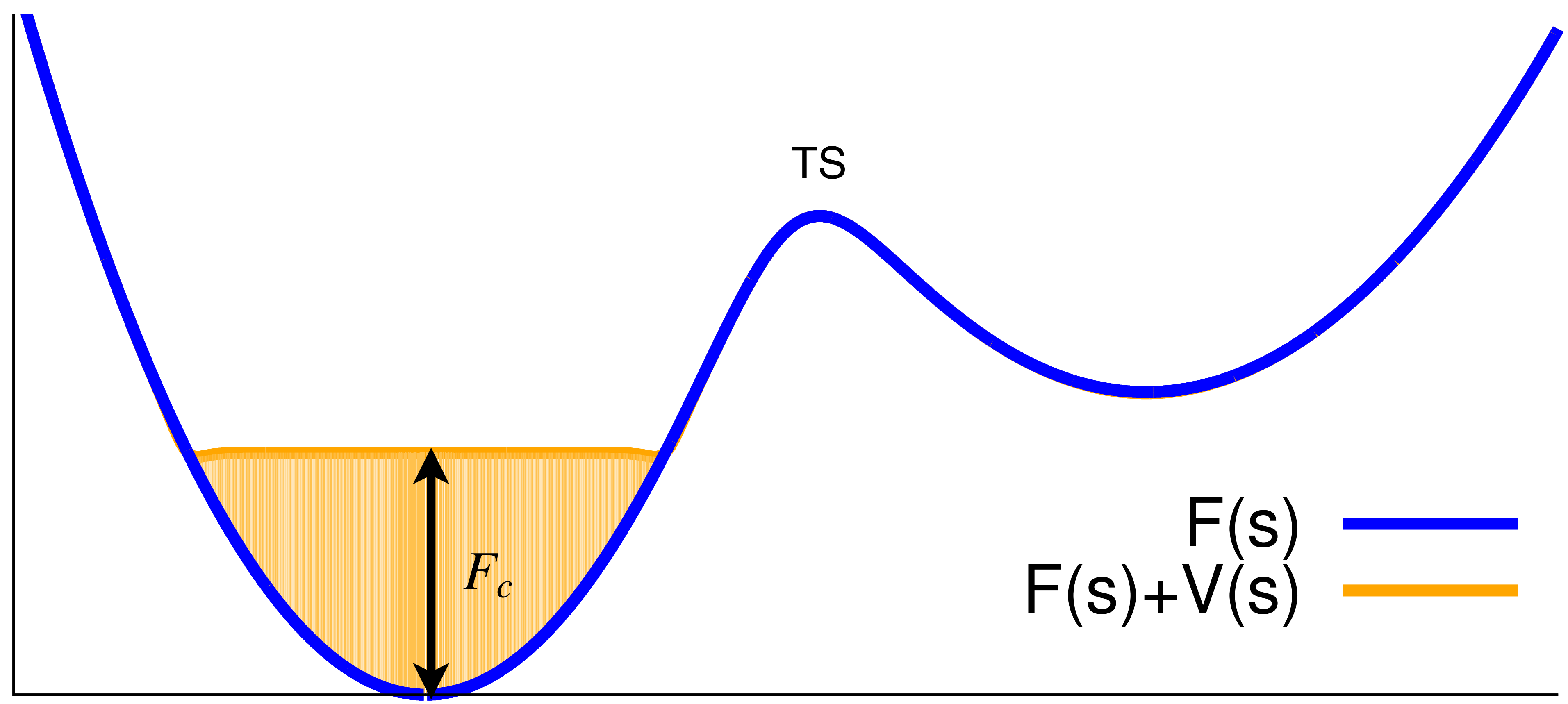
linear expansion

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

switching function



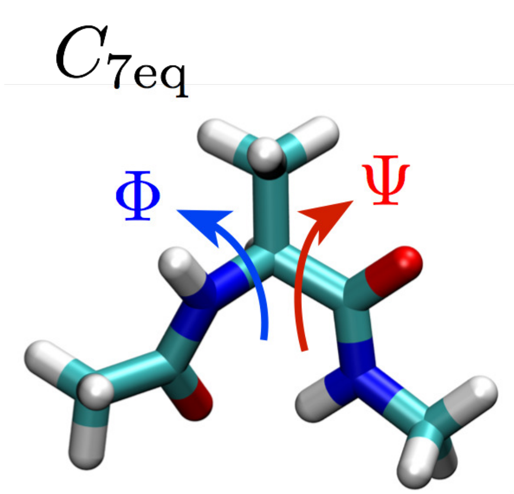
$$V(\mathbf{s};\boldsymbol{\alpha}) = \boxed{v(\mathbf{s};\boldsymbol{\alpha})} \cdot \boxed{\mathcal{S}(-v(\mathbf{s};\boldsymbol{\alpha}) - F_c)}$$

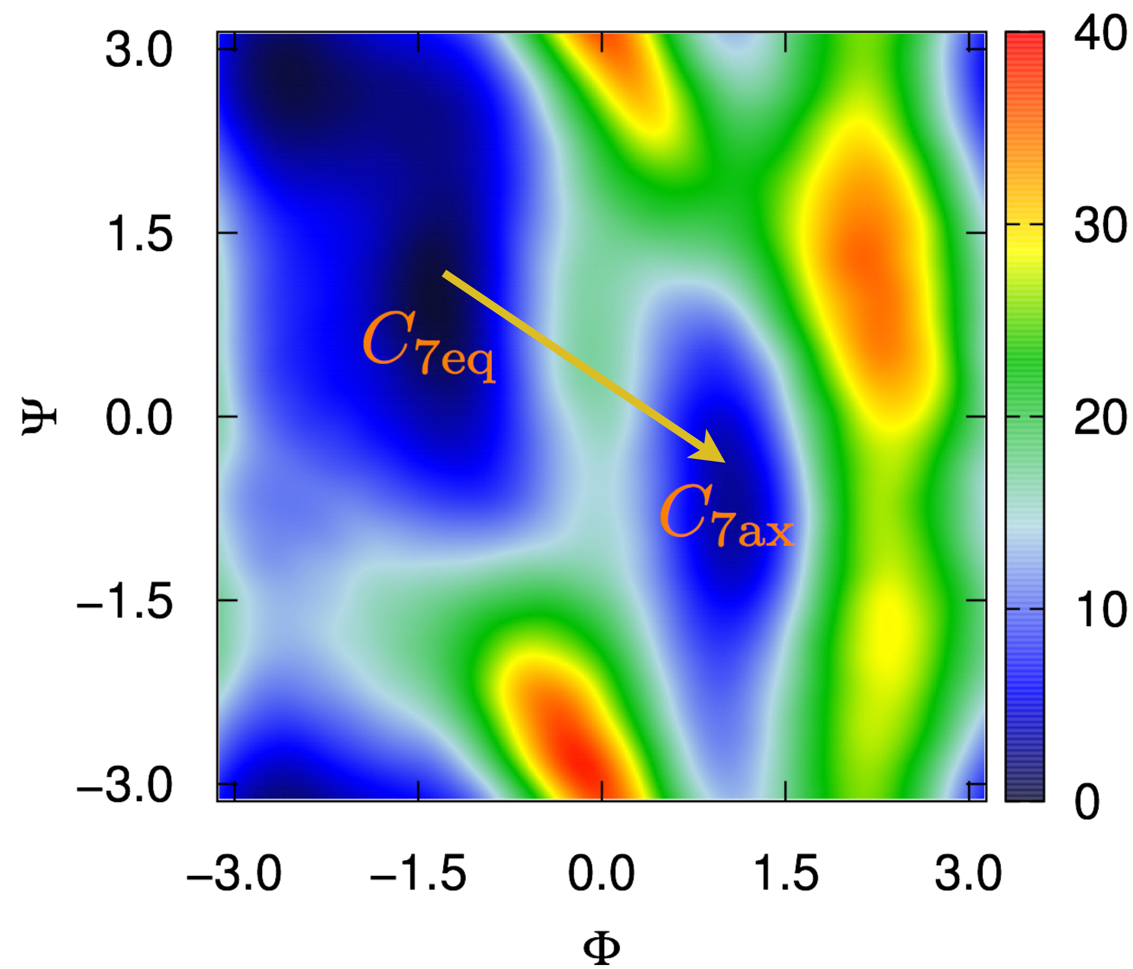


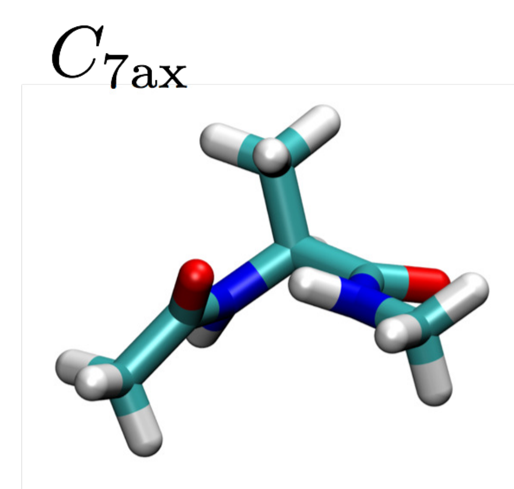
McCarty, Valsson, Tiwary, and Parrinello, Phys. Rev. Lett. 2015

Kinetics from VES: Example

C_{7eq} to C_{7ax} transition in alanine dipeptide in vacuum at 250 K





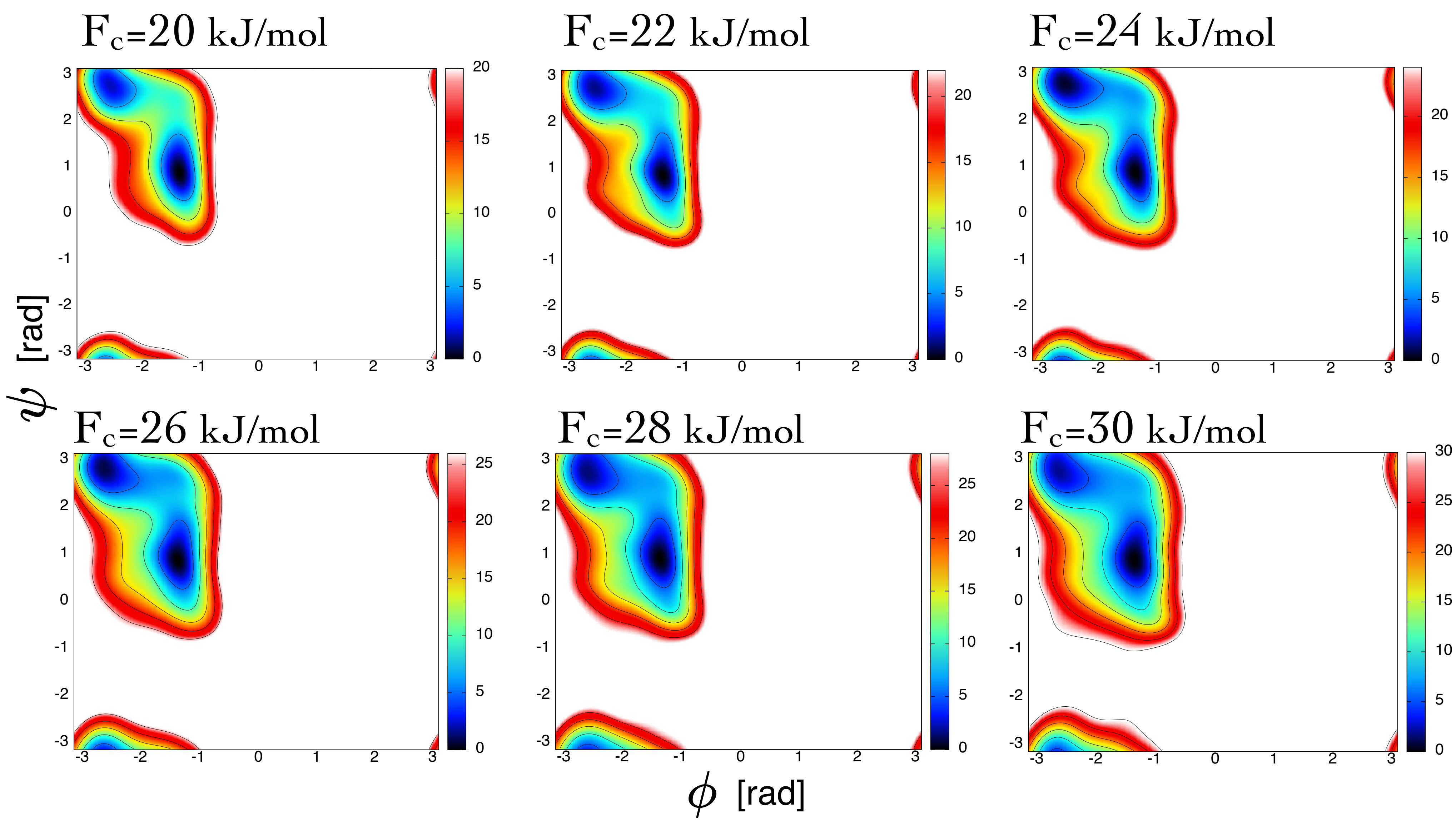


barrier around 34 kJ/mol (16 $k_B T$)

mean transition time around 28 μs

McCarty, Valsson, Tiwary, and Parrinello, Phys. Rev. Lett. 2015

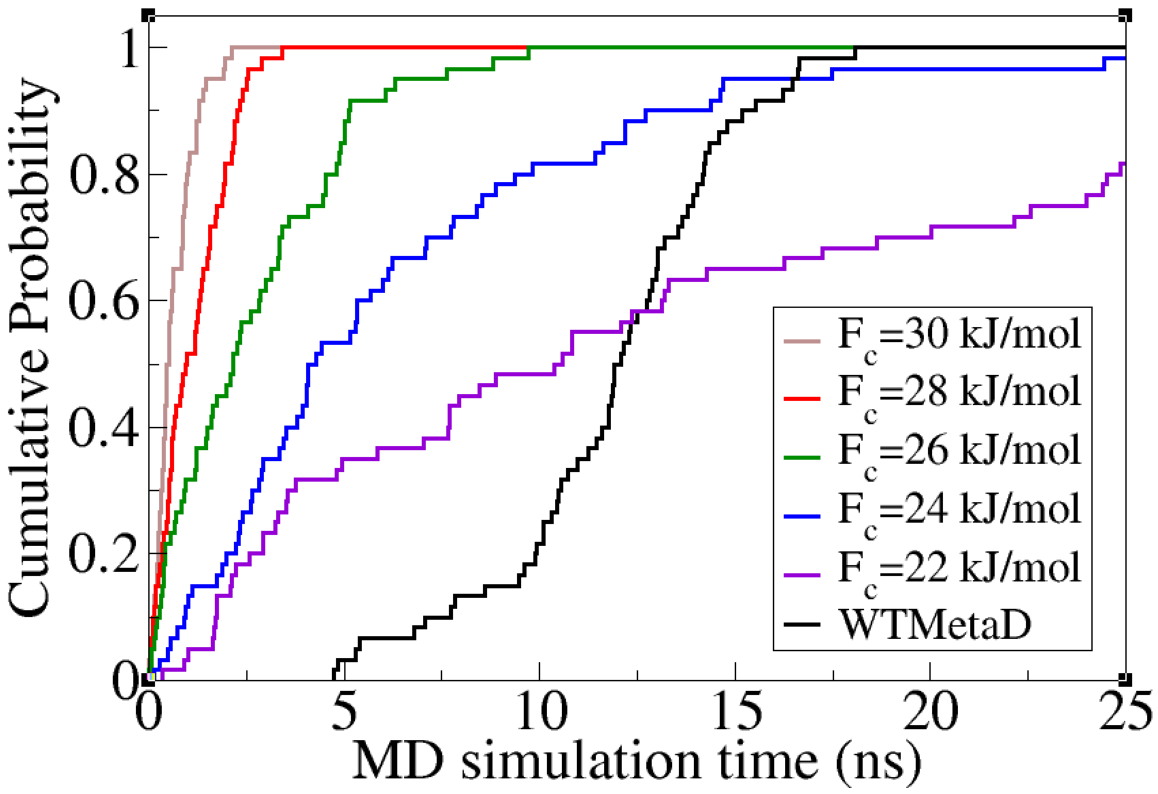
generate bias potentials with different F_c values from 20 to 30 kJ/mol



McCarty, Valsson, Tiwary, and Parrinello, Phys. Rev. Lett. 2015

launch 60 independent runs for each F_c values (static bias potentials)

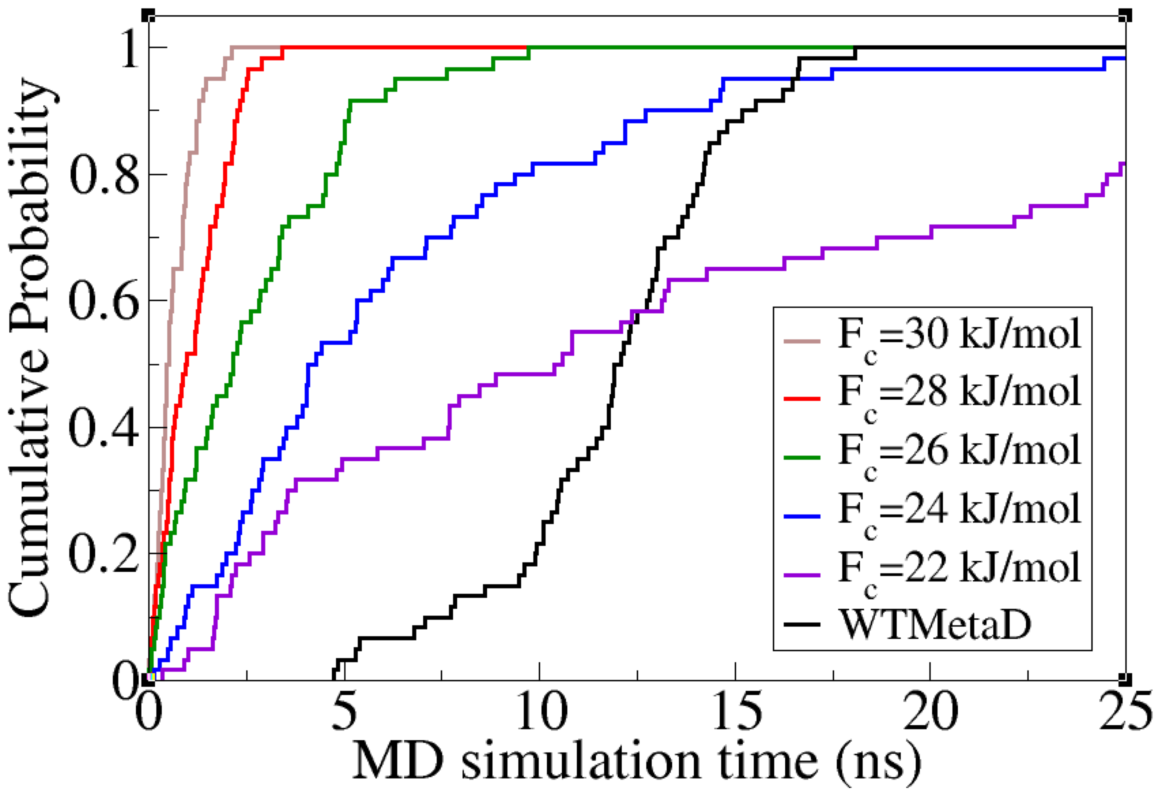
unscaled MD times



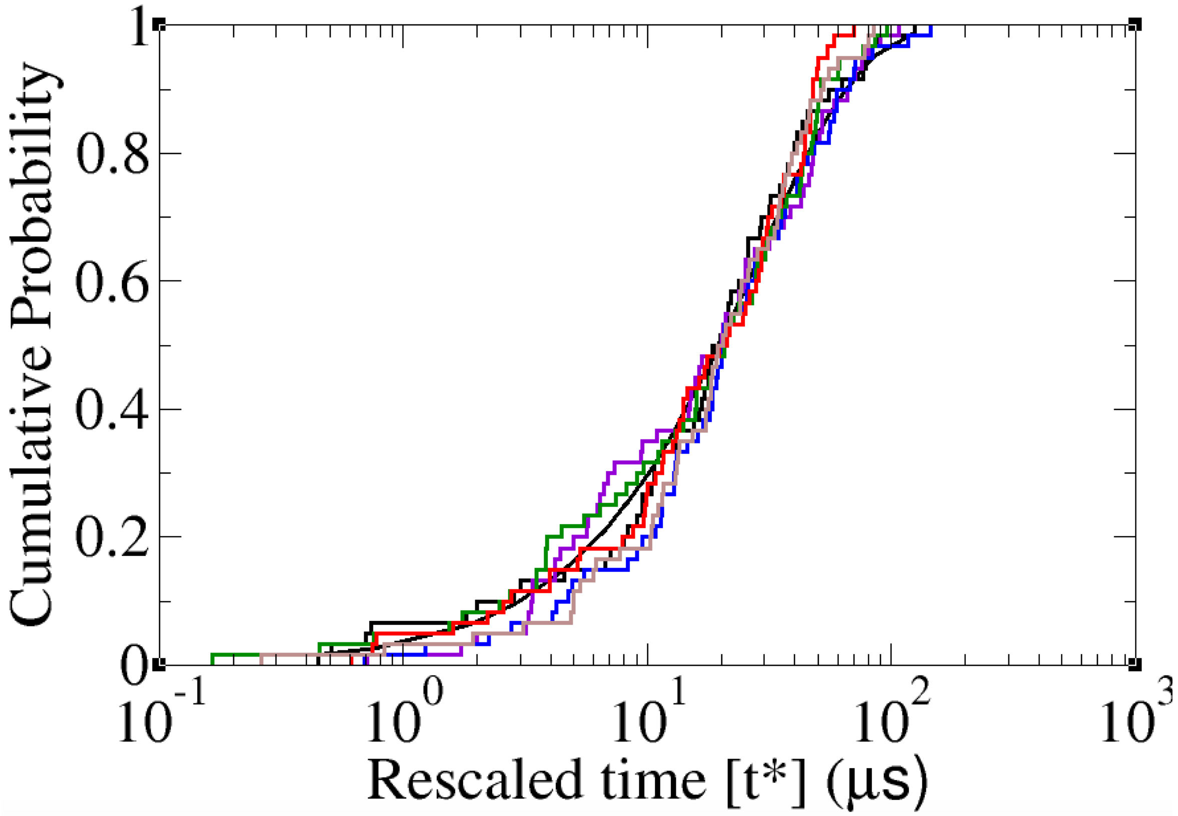
McCarty, Valsson, Tiwary, and Parrinello, Phys. Rev. Lett. 2015

rescale times according to $\tau = \tau_V^* \cdot \langle e^{\beta V(\mathbf{s})} \rangle_V$

unscaled MD times

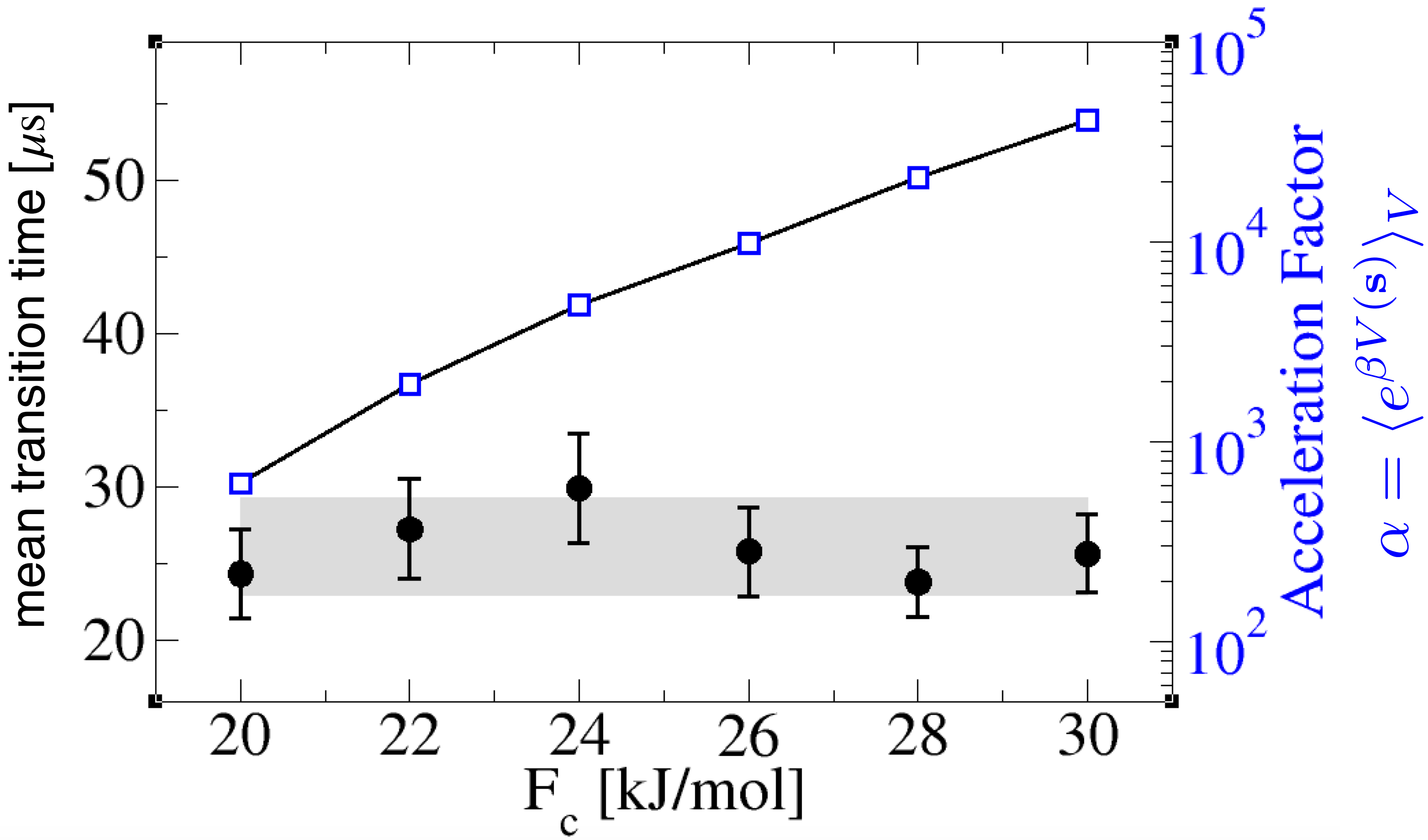


real times



different F_c values always yield the correct distribution

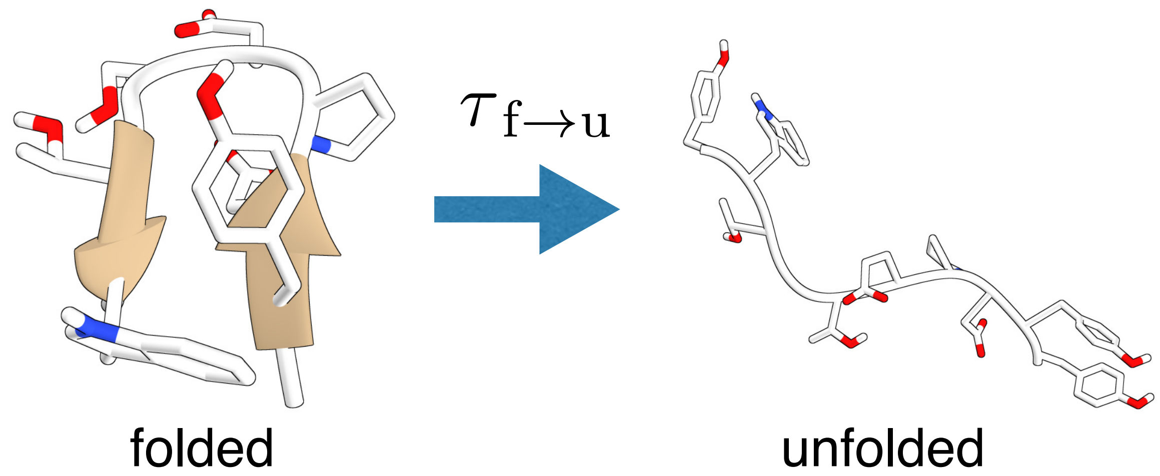
McCarty, Valsson, Tiwary, and Parrinello, Phys. Rev. Lett. 2015

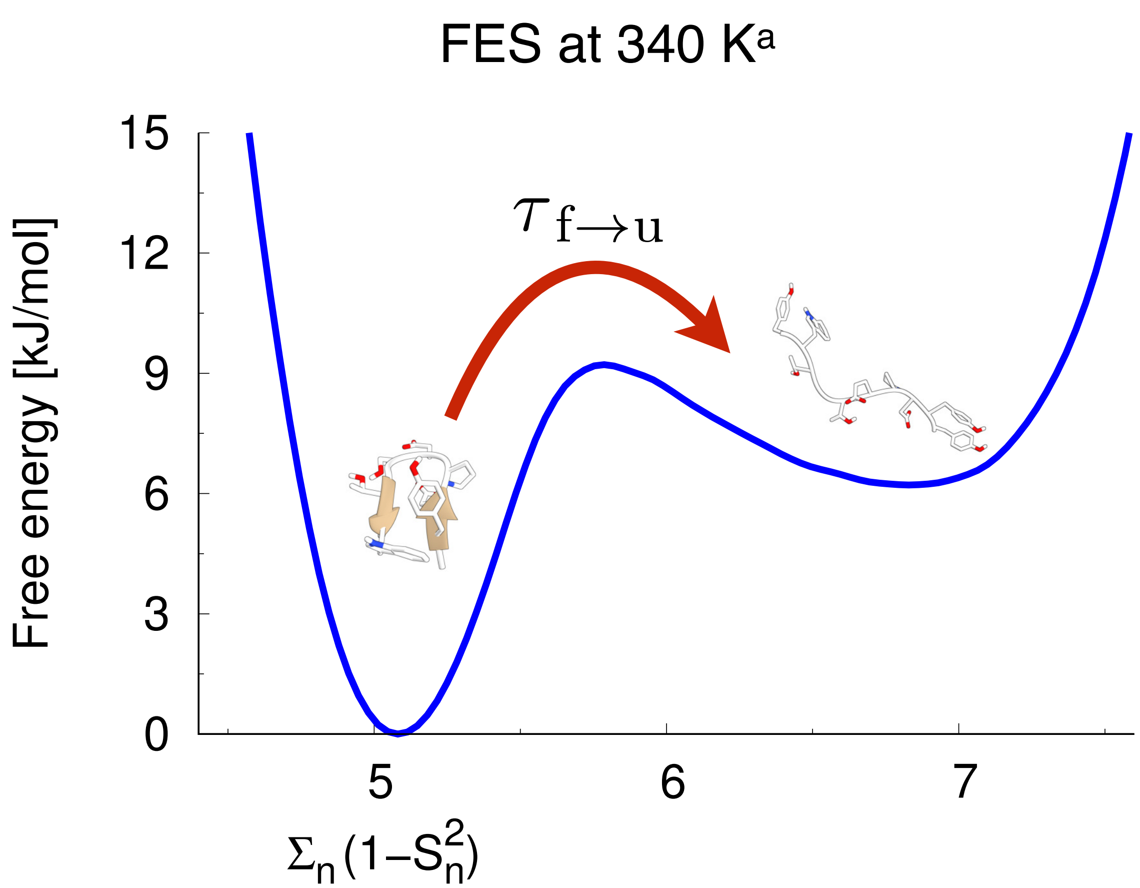


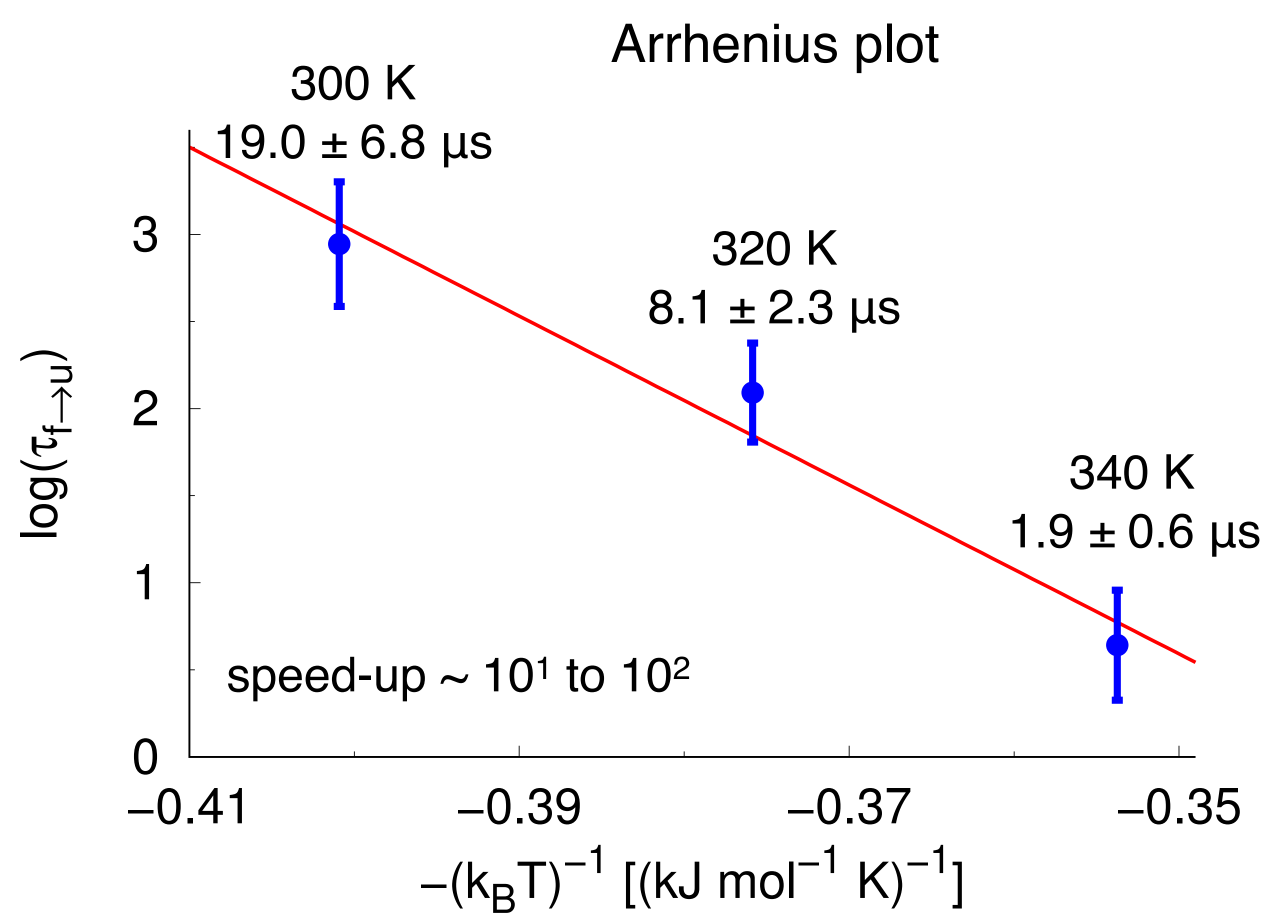
speedup of up to 10^4-10^5 compared to unbiased simulations

McCarty, Valsson, Tiwary, and Parrinello, Phys. Rev. Lett. 2015

Unfolding times of chignolin



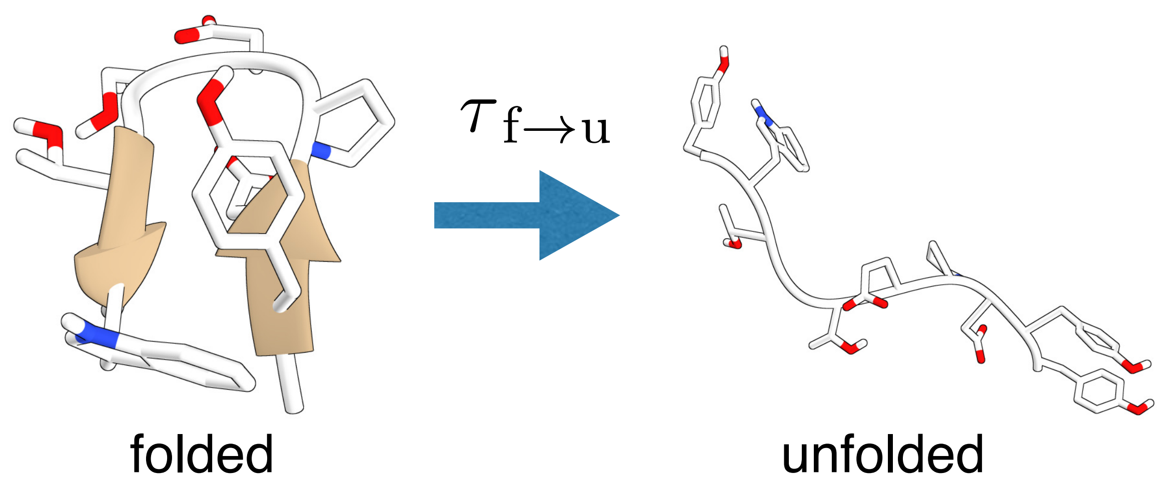




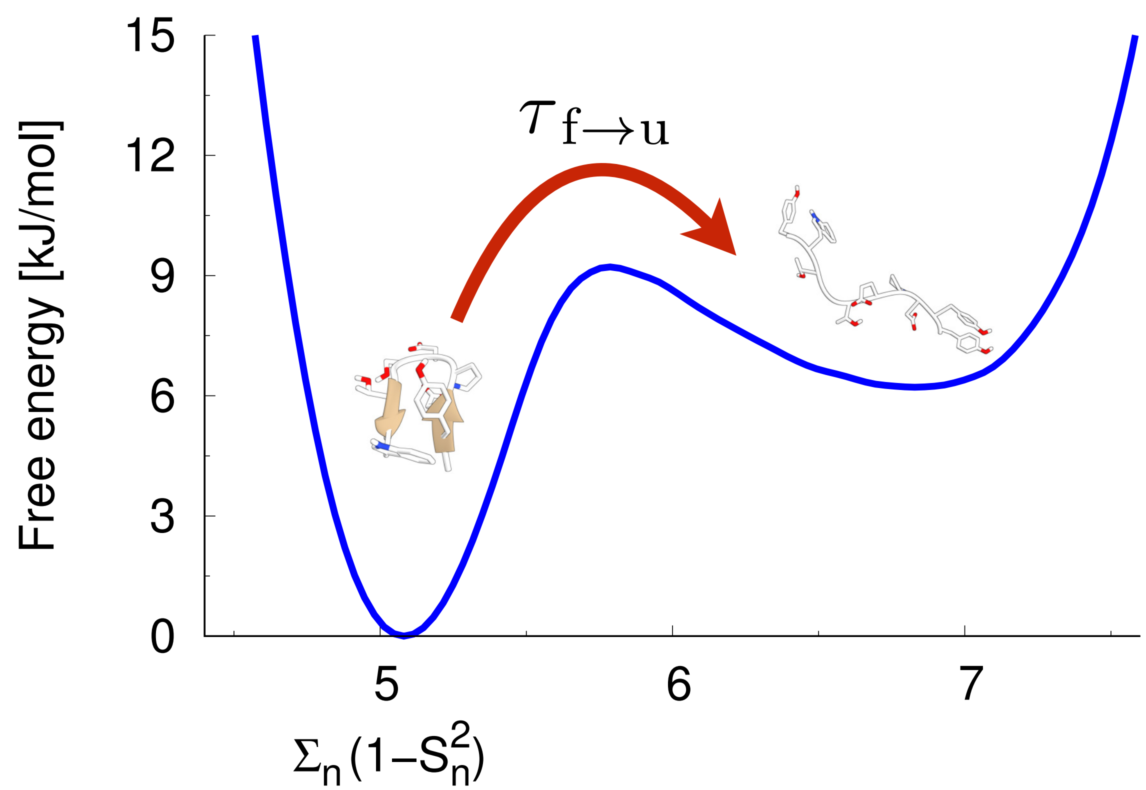
Ferruccio, Valsson, Parrinello, submitted

[a]Lindorff-Larsen, Piana, Dror, and Shaw, Science 2011

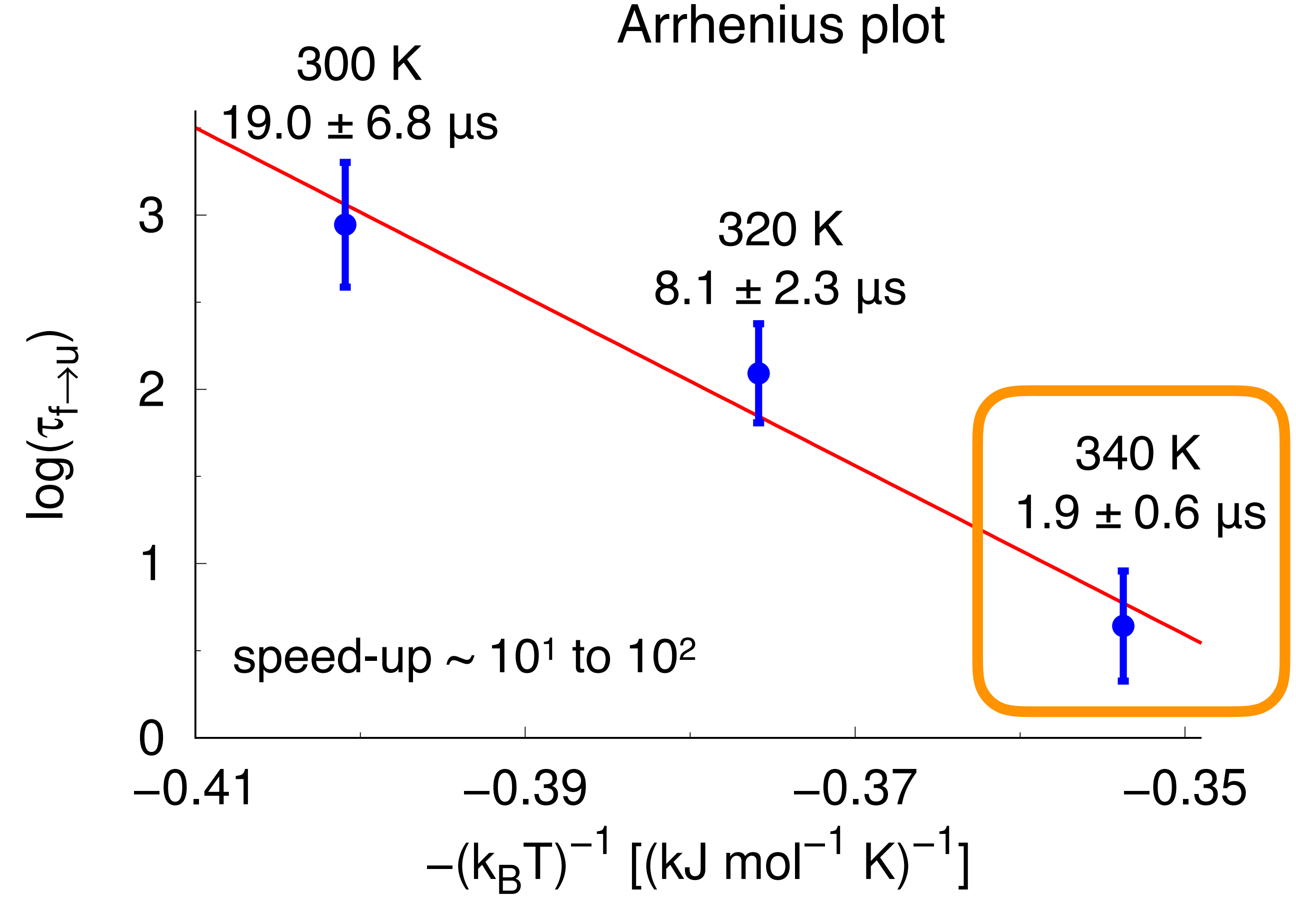
Unfolding times of chignolin



FES at 340 K[a]



Arrhenius plot



Unbiased MD at 340K[a]: 2.4 ± 0.4 μs

Ferruccio, Valsson, Parrinello, submitted

[a]Lindorff-Larsen, Piana, Dror, and Shaw, Science 2011

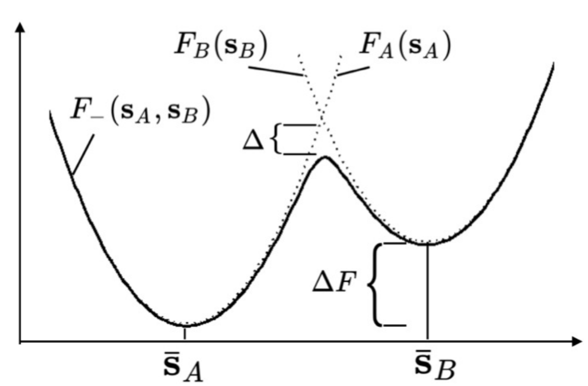
Other Examples

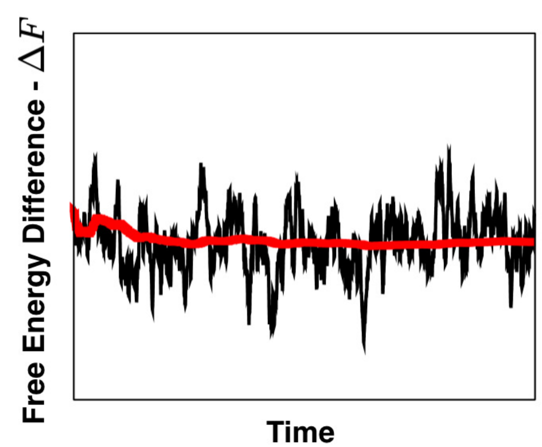
Approximate bias potentials

$$V\left(s_1, s_2, \ldots, s_d; \boldsymbol{\alpha}\right) = \sum_{i,j} V(s_i, s_j; \boldsymbol{\alpha}^{(i,j)}),$$

Shaffer, Valsson, Parrinello, PNAS, 2016

Bespoke Bias for Obtaining Free Energy Differences





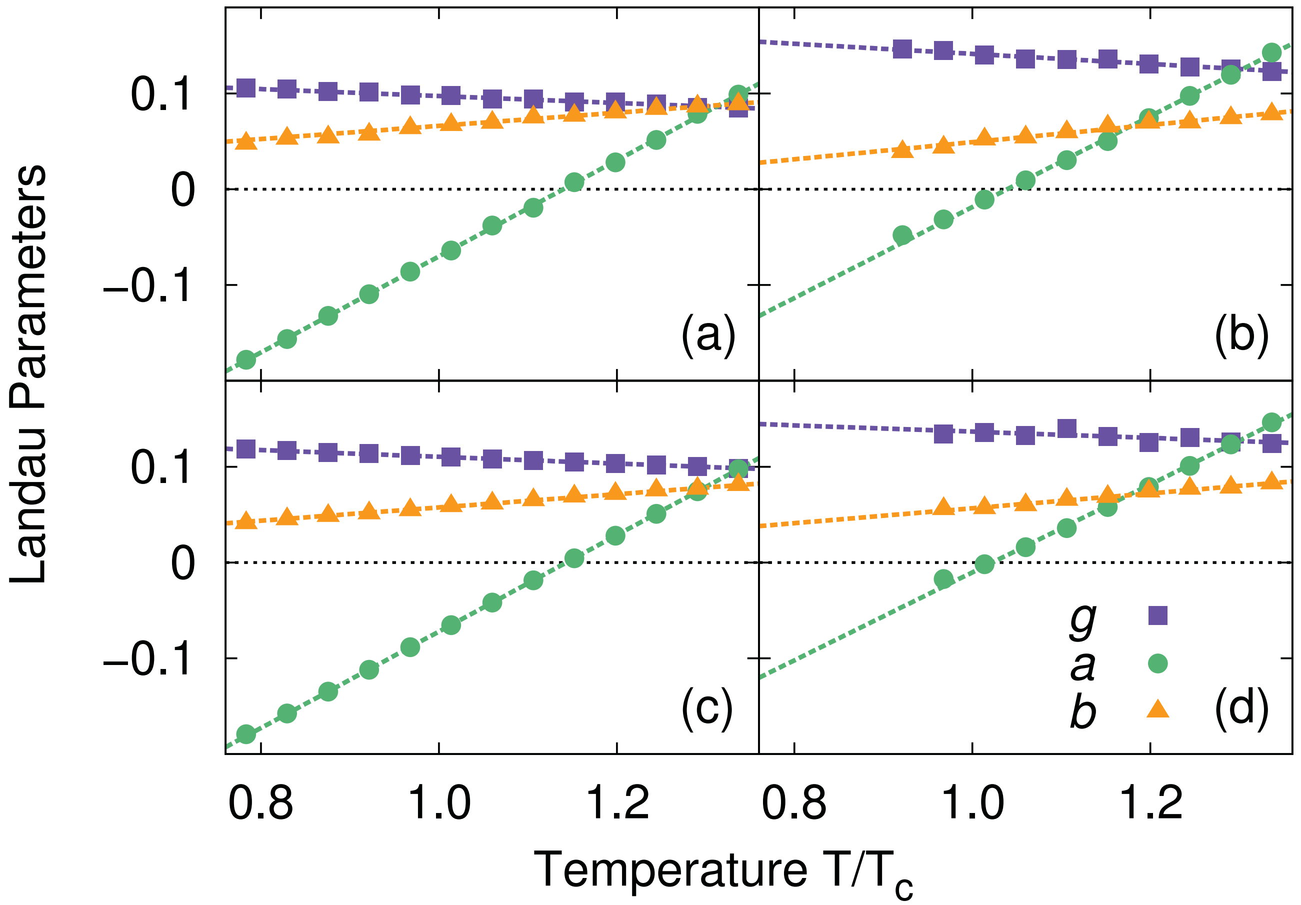
$$F_-(\mathbf{s}_A, \mathbf{s}_B) = \frac{F_A(\mathbf{s}_A) + F_B(\mathbf{s}_B)}{2} - \sqrt{\left(\frac{F_A(\mathbf{s}_A) - F_B(\mathbf{s}_B) - \Delta F}{2}\right)^2 + \Delta^2}$$

McCarty, Valsson, and Parrinello, JCTC 2016

Calculations of parameters for phenomenological coarse-grained models

$$F[\psi] = g \int |\nabla\psi(\vec{r})|^2 d^3r + a \int \psi^2(\vec{r}) d^3r + b \int \psi^4(\vec{r}) d^3r$$

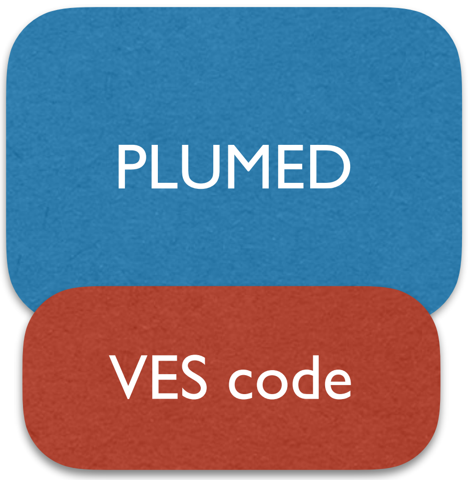
e.g. Ginzburg-Landau model for second order phase transitions



Invernizzi, Valsson, Parrinello, PNAS 2017

VES code

Module for PLUMED 2 that implements methods based on VES



Modular design - easy to add new features (basis functions, target distribution, optimizers, …)

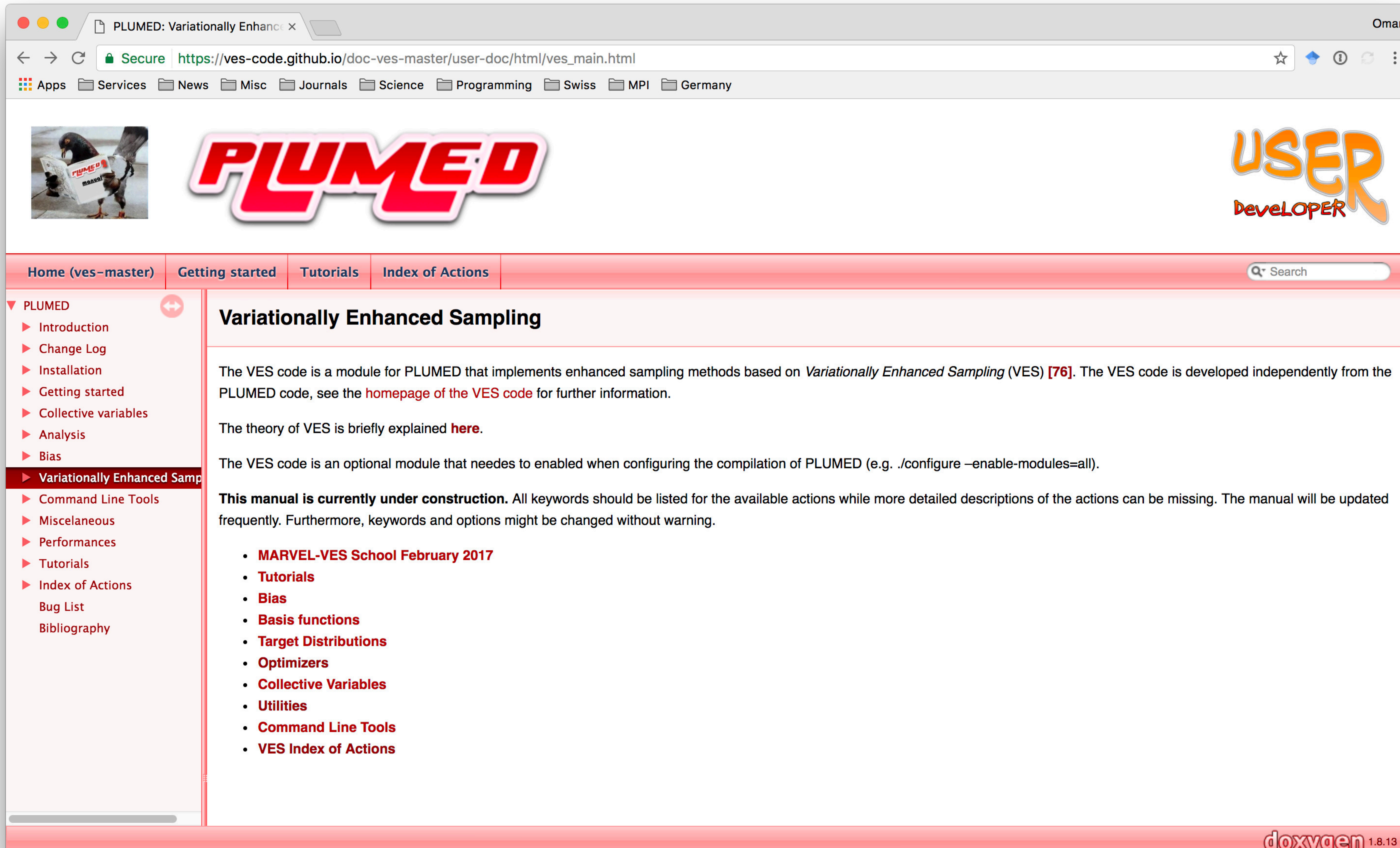
Available in a public fork on Github - https://github.com/ves-code/plumed2-ves

- Kept in sync with master branch
- Regtests: ~80% coverage

Will be contributed as a module to version 2.4 of PLUMED

Manual

https://ves-code.github.io/doc-ves-master



Tutorials available

MARVEL-VES tutorial (Lugano Feb 2017): VES 1	Introduction to VES, using different target distributions and basis sets.
MARVEL-VES tutorial (Lugano Feb 2017): VES 2	VES, well-tempered target distribution and 2 dimensional biases.
MARVEL-VES tutorial (Lugano Feb 2017): Kinetics	How to obtain kinetics from biased molecular simulations using VES.

MARVEL

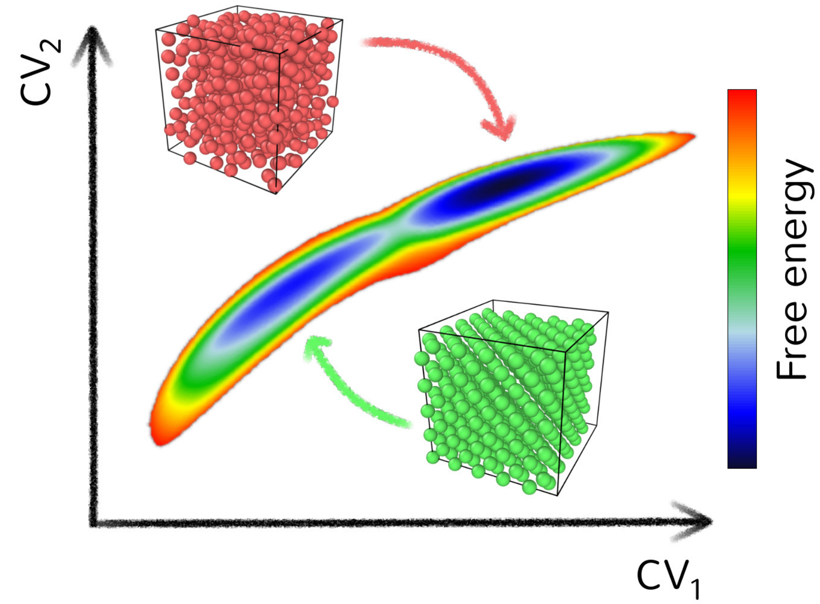
NATIONAL CENTRE OF COMPETENCE IN RESEARCH

SCHOOL ON VARIATIONALLY ENHANCED SAMPLING

Lugano, February 14-17 2017

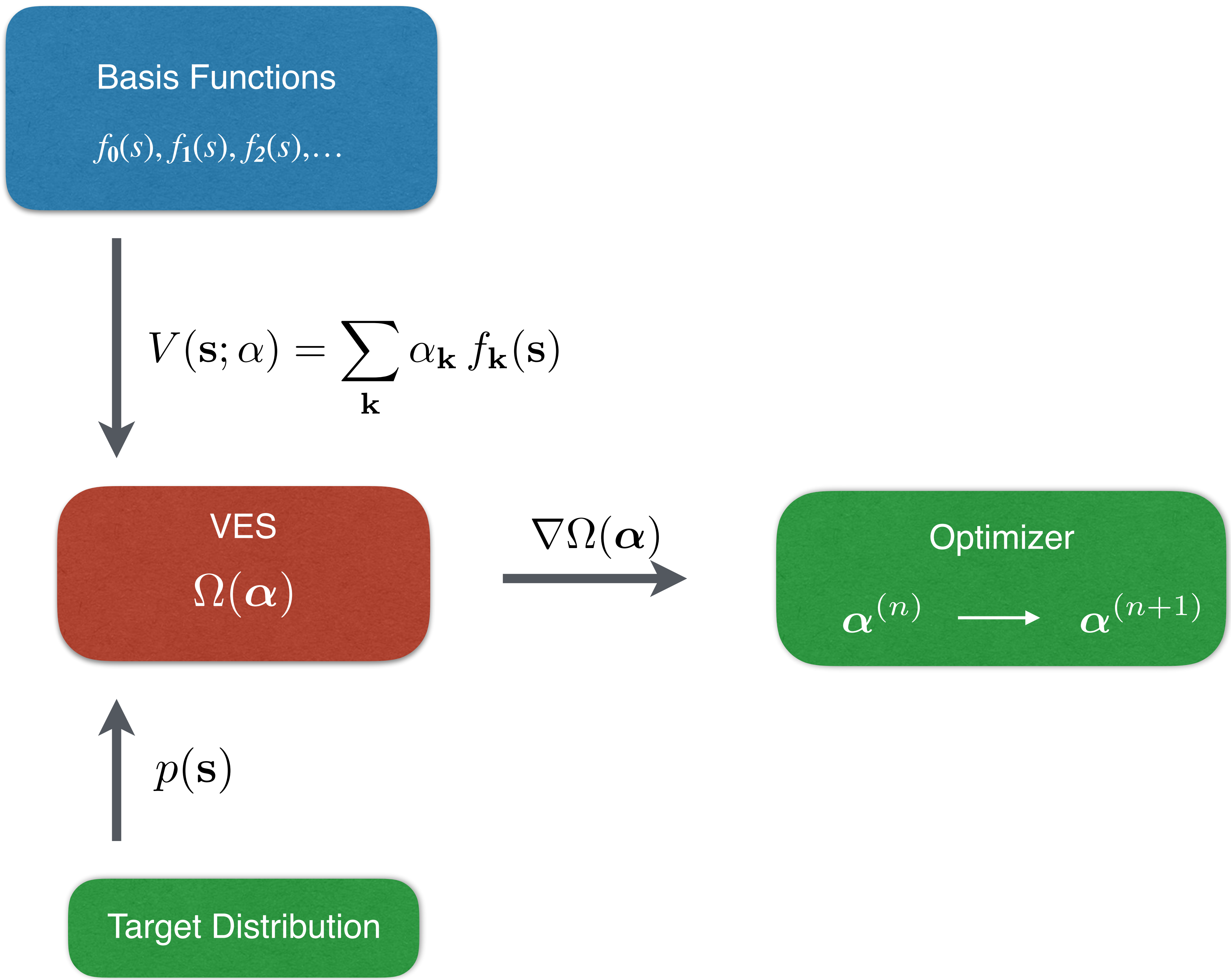
Università della Svizzera italiana

ETH zürich



FNSNF SWISS NATIONAL SCIENCE FOUNDATION

The National Centres of Competence in Research (NCCR) are a research instrument of the Swiss National Science Foundation



Basis Functions
$f_0(s), f_1(s), f_2(s), \ldots$
$V(\mathbf{s};\alpha) = \sum_{\mathbf{k}} \alpha_{\mathbf{k}} f_{\mathbf{k}}(\mathbf{s})$
VES
$\Omega(\boldsymbol{\alpha})$
$\nabla\Omega(\boldsymbol{\alpha})$
Optimizer
$\boldsymbol{\alpha}^{(n)} \longrightarrow \boldsymbol{\alpha}^{(n+1)}$
$p(\mathbf{s})$
Target Distribution

Currently supports biases written as a product of 1-dimensional basis functions

$$V(\mathbf{s};\boldsymbol{\alpha}) = \sum_{i_1,i_2} \alpha_{i_1,i_2}\, f_{i_1}(s_1)\, g_{i_2}(s_2)$$

BF_CHEBYSHEV	Chebyshev polynomial basis functions.
BF_COMBINED	Combining other basis functions types
BF_COSINE	Fourier cosine basis functions.
BF_FOURIER	Fourier basis functions.
BF_LEGENDRE	Legendre polynomials basis functions.
BF_MATHEVAL	Basis functions given by matheval expressions.
BF_POWERS	Polynomial power basis functions.
BF_SINE	Fourier sine basis functions.

+ many other hidden and untested options

very easy to add new basis functions types

Target distributions

GAUSSIAN	Target distribution given by a sum of Gaussians (static).
GRID_DIST	Target distribution from an external grid file (static).
LINEAR_COMBINATION	Target distribution given by linear combination of distributions (static or dynamic).
MATHEVAL_DIST	Target distribution given by a matheval parsed function (static or dynamic).
PRODUCT_COMBINATION	Target distribution given by product combination of distributions (static or dynamic).
PRODUCT_DISTRIBUTION	Target distribution given by a separable productof one-dimensional distributions (static or dynamic).
UNIFORM	Uniform target distribution (static).
VON_MISES	Target distribution given by a sum of Von Mises distributions (static).
WELL_TEMPERED	Well-tempered target distribution (dynamic).

+ many other hidden and untested options

very easy to add new target distributions

Optimizers

AVERAGED_SGD	Averaged stochastic gradient decent with fixed step size.
FAKE_OPTIMIZER	Dummy optimizer for debugging.
ROBBINS_MONRO_SGD	Robbins-Monro stochastic gradient decent.

basis functions

```
bf1: BF_LEGENDRE ORDER=20 INTERVAL_MIN=0.0 INTERVAL_MAX=10.0
```

bias

```
VES_LINEAR_EXPANSION ...
 ARG=cv1
 BASIS_FUNCTIONS=bf1
 LABEL=ves1
 TEMP=300.0
 GRID_BINS=100
... VES_LINEAR_EXPANSION
```

optimizer

```
AVERAGED_SGD ...
  BIAS=ves1
  STRIDE=500
  LABEL=o1
  STEPSIZE=0.5
  FES_OUTPUT=100
  BIAS_OUTPUT=500
  COEFFS_OUTPUT=10
... AVERAGED_SGD
```

basis functions

```
bf1: BF_LEGENDRE ORDER=20 INTERVAL_MIN=0.0 INTERVAL_MAX=10.0
bf2: BF_FOURIER  ORDER=10 INTERVAL_MIN=-pi INTERVAL_MAX=pi
```

bias

```
VES_LINEAR_EXPANSION ...
 ARG=cv1,cv2
 BASIS_FUNCTIONS=bf1,bf2
 LABEL=ves1
 TEMP=300.0
 GRID_BINS=100,100
 TARGET_DISTRIBUTION={WELL_TEMPERED BIASFACTOR=10}
... VES_LINEAR_EXPANSION
```

optimizer

```
AVERAGED_SGD ...
  BIAS=ves1
  STRIDE=500
  LABEL=o1
  STEPSIZE=0.5
  FES_OUTPUT=100
  BIAS_OUTPUT=500
  COEFFS_OUTPUT=10
... AVERAGED_SGD
```

basis functions

```
bf1: BF_LEGENDRE ORDER=20 INTERVAL_MIN=-4.0 INTERVAL_MAX=+4.0
bf2: BF_LEGENDRE ORDER=20 INTERVAL_MIN=-4.0 INTERVAL_MAX=+4.0
```

bias

```
VES_LINEAR_EXPANSION ...
 ARG=cv1,cv1
 BASIS_FUNCTIONS=bf1,bf2
 LABEL=ves1
 TEMP=300.0
 GRID_BINS=100,100
 TARGET_DISTRIBUTION={GAUSSIAN
                      CENTER1=-1.5,+1.5 SIGMA1=0.8,0.3
                      CENTER2=+1.5,-1.5 SIGMA2=0.3,0.8
                      WEIGHTS=1.0,4.0
                     }
... VES_LINEAR_EXPANSION
```

optimizer

```
AVERAGED_SGD ...
  BIAS=ves1
  STRIDE=500
  LABEL=o1
  STEPSIZE=0.5
  FES_OUTPUT=100
  BIAS_OUTPUT=500
  COEFFS_OUTPUT=10
... AVERAGED_SGD
```

basis functions

```
bf1: BF_LEGENDRE ORDER=20 INTERVAL_MIN=-4.0 INTERVAL_MAX=+4.0
bf2: BF_LEGENDRE ORDER=20 INTERVAL_MIN=-4.0 INTERVAL_MAX=+4.0
```

bias

```
VES_LINEAR_EXPANSION ...
 ARG=cv1,cv2
 BASIS_FUNCTIONS=bf1,bf2
 LABEL=ves1
 TEMP=300.0
 GRID_BINS=100,100
 TARGET_DISTRIBUTION={MATHEVAL_DIST
                      FUNCTION=1.0
                               *exp(-0.5*((s1+1.5)/0.8)^2)
                               *exp(-0.5*((s2-1.5)/0.3)^2)
                               +4.0
                               *exp(-0.5*((s1-1.5)/0.3)^2)
                               *exp(-0.5*((s2+1.5)/0.8)^2)
                     }
... VES_LINEAR_EXPANSION
```

optimizer

```
AVERAGED_SGD ...
  BIAS=ves1
  STRIDE=500
  LABEL=o1
  STEPSIZE=0.5
  FES_OUTPUT=100
  BIAS_OUTPUT=500
  COEFFS_OUTPUT=10
... AVERAGED_SGD
```

Matheval defined target distribution

```
# Shifted Maxwell-Boltzmann distribution
TARGET_DISTRIBUTION={MATHEVAL_DIST
                     FUNCTION=(s1+20)^2*exp(-(s1+20)^2/(2*10.0^2))}

# Generalized error distribution
TARGET_DISTRIBUTION={MATHEVAL_DIST
                     FUNCTION=exp(-(abs(s1-20.0)/5.0)^4.0)}

# Frechet distribution
TARGET_DISTRIBUTION={MATHEVAL_DIST
                     FUNCTION=(3.0/10.0)
                              *((s1+20.0001)/10.0)^(-1.0-3.0)
                              *exp(-((s1+20.0001)/10.0)^(-3.0))}

# Well-Tempered with gamma=10
TARGET_DISTRIBUTION={MATHEVAL_DIST FUNCTION=exp(-(beta/10.0)*FE)}
```

can also define basis functions via matheval

```
BF_MATHEVAL ...
 TRANSFORM=(t-(min+max)/2)/((max-min)/2)
 FUNC1=x
 FUNC2=(1/2)*(3*x^2-1)
 FUNC3=(1/2)*(5*x^3-3*x)
 FUNC4=(1/8)*(35*x^4-30*x^2+3)
 FUNC5=(1/8)*(63*x^5-70*x^3+15*x)
 FUNC6=(1/16)*(231*x^6-315*x^4+105*x^2-5)
 INTERVAL_MIN=-4.0
 INTERVAL_MAX=4.0
 LABEL=bf1
... BF_MATHEVAL
```

same as

```
BF_LEGENDRE ...
 ORDER=6
 INTERVAL_MIN=-4.0
 INTERVAL_MAX=+4.0
 LABEL=bf2
... BF_LEGENDRE
```

Acknowledgements

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Fellow group members

- Patrick Shaffer
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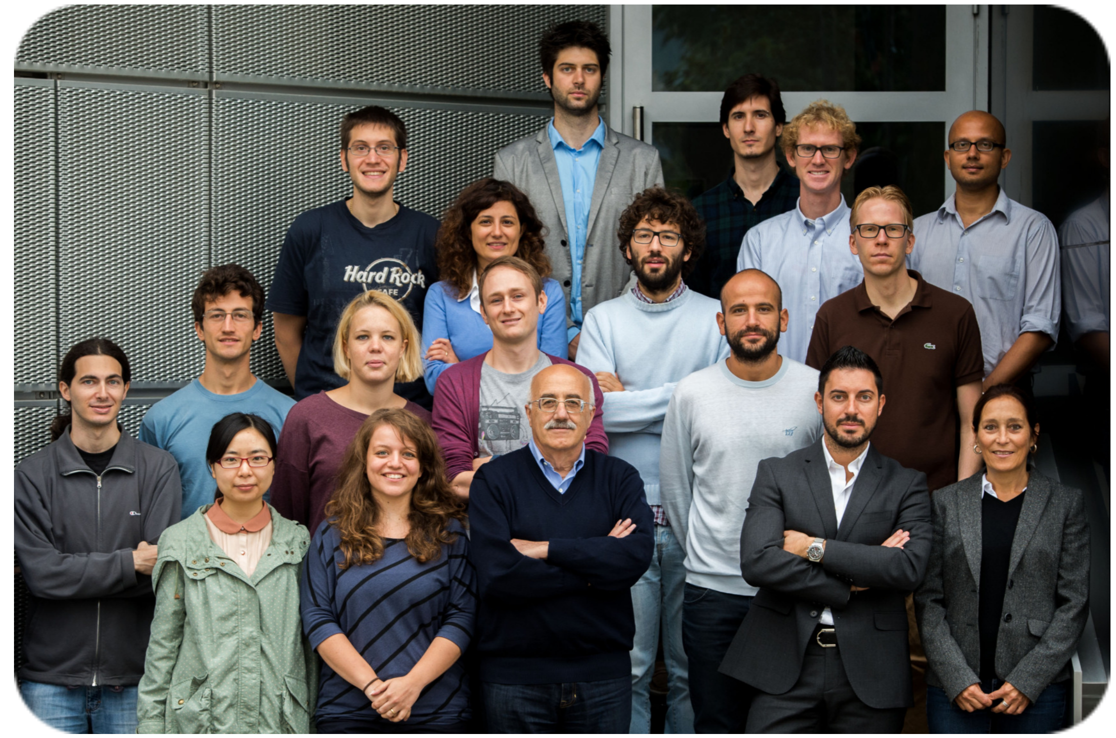
- Vincenzo Verdolino
- Giovanni Piccini

Pratyush Tiwary

NCCR MARVEL for funding



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Thanks for your attention!

Questions?