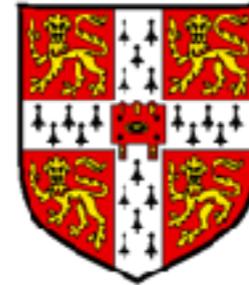




Atomistic  
Simulation  
Centre



# Metadynamics

**Max Bonomi**  
Gareth Tribello  
Carlo Camilloni  
Giovanni Bussi

**PLUMED**



<http://www.plumed.org>

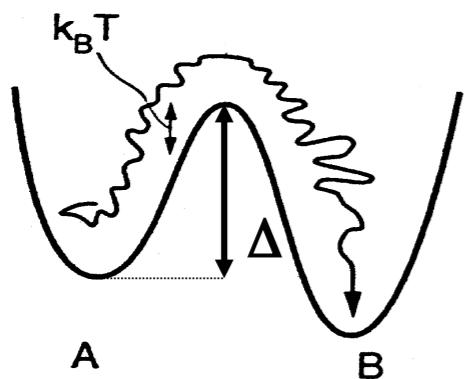
# Objectives

- Metadynamics theoretical background
- Practical guidelines to setup metadynamics simulations with PLUMED and to wisely choose all the parameters
- Estimating free energy from metadynamics simulations
- Reweighting metadynamics simulations
- Assessing convergence and calculating errors

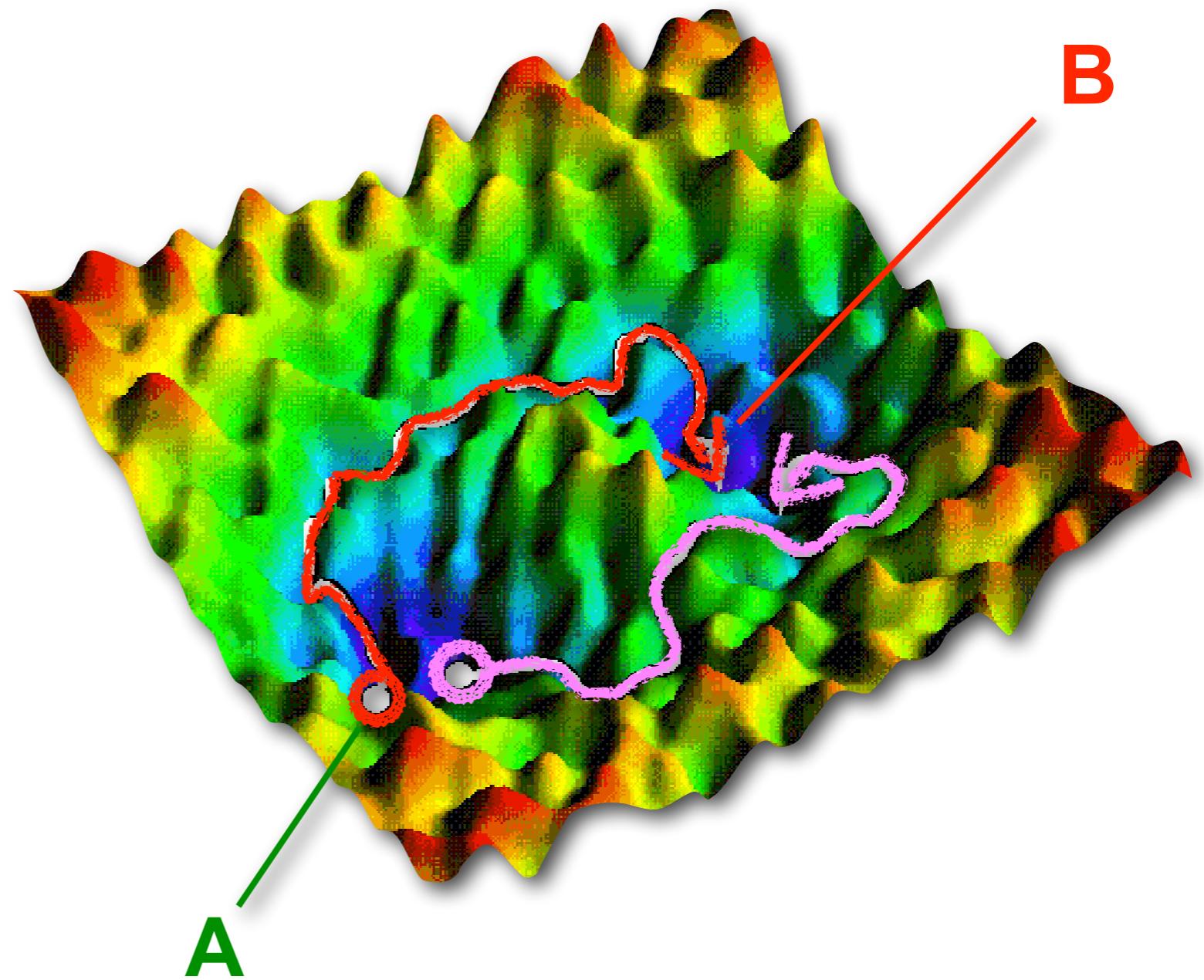
# A time scale problem

Sampling capability of MD and MC is limited by the time scale accessible in “standard” simulations:

★ Activated events



★ Slow diffusion



# Dimensional reduction

It is often possible to describe a physical/chemical process in terms of a small number of coarse descriptors of the system:

$$\mathbf{S} = \mathbf{S}(\mathbf{R}) = (S_1(\mathbf{R}), \dots, S_d(\mathbf{R}))$$

Key quantity of thermodynamics is the free energy as a function of these variables:

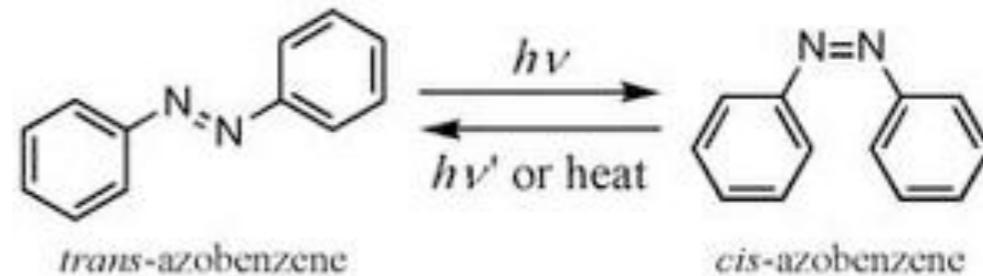
$$F(\mathbf{S}) = -\frac{1}{\beta} \ln P(\mathbf{S}) \quad \text{where} \quad \beta = \frac{1}{k_B T}$$

canonical  
ensemble

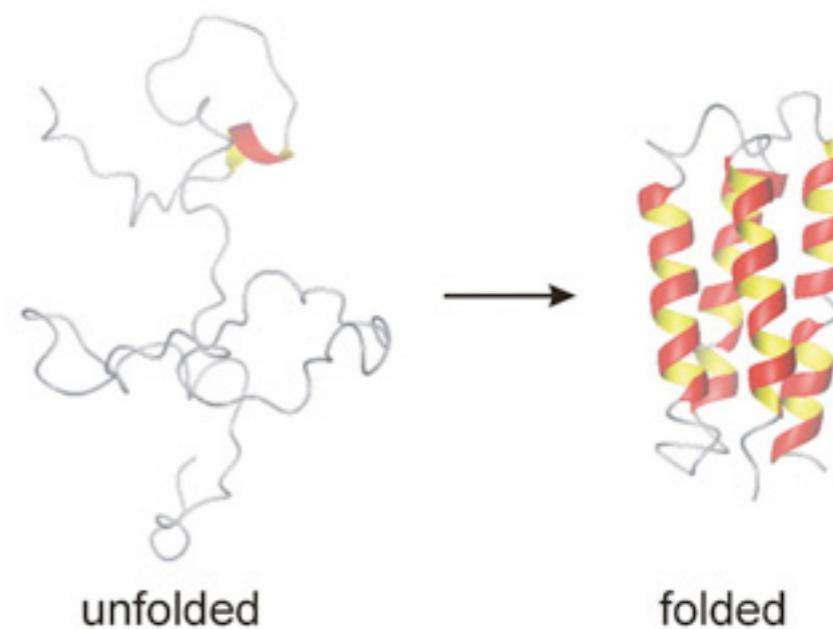
$$P(\mathbf{S}) = \frac{\int d\mathbf{R} \delta(\mathbf{S} - \mathbf{S}(\mathbf{R})) e^{-\beta U(\mathbf{R})}}{\int d\mathbf{R} e^{-\beta U(\mathbf{R})}}$$

# Examples

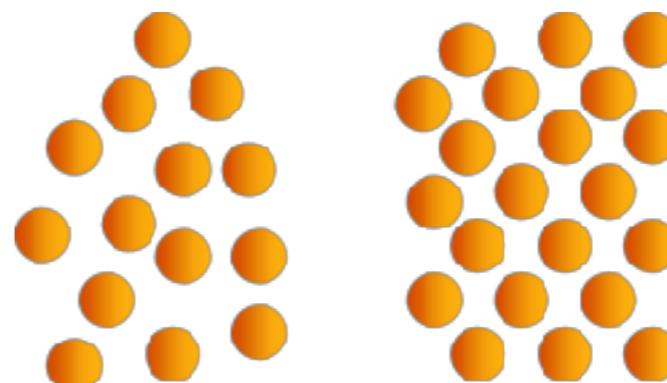
Isomerization:  
dihedral angle



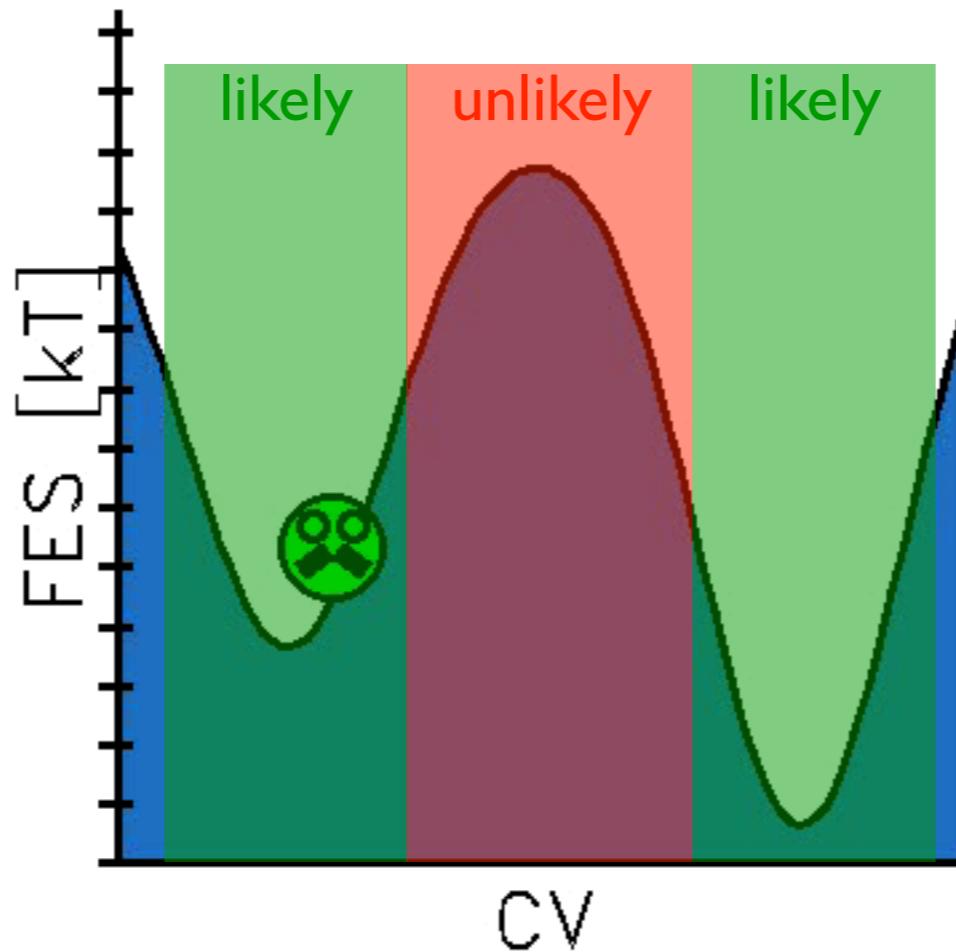
Protein folding:  
gyration radius,  
number of contacts,  
...



Phase transitions:  
lattice vectors,  
bond order parameters,  
...



# Rare events simplified



How can we estimate a free energy difference if we never see a transition?

$$F(A) - F(B) = -k_B T \ln \frac{N_A}{N_B}$$

## Biased sampling

The idea is to add a bias potential that acts on the collective variables:

$$U(\mathbf{R}) \rightarrow U(\mathbf{R}) + V(\mathbf{S}(\mathbf{R}))$$

In this biased ensemble the free energy becomes:

$$F'(\mathbf{S}) = -\frac{1}{\beta} \ln P'(\mathbf{S}) + C$$

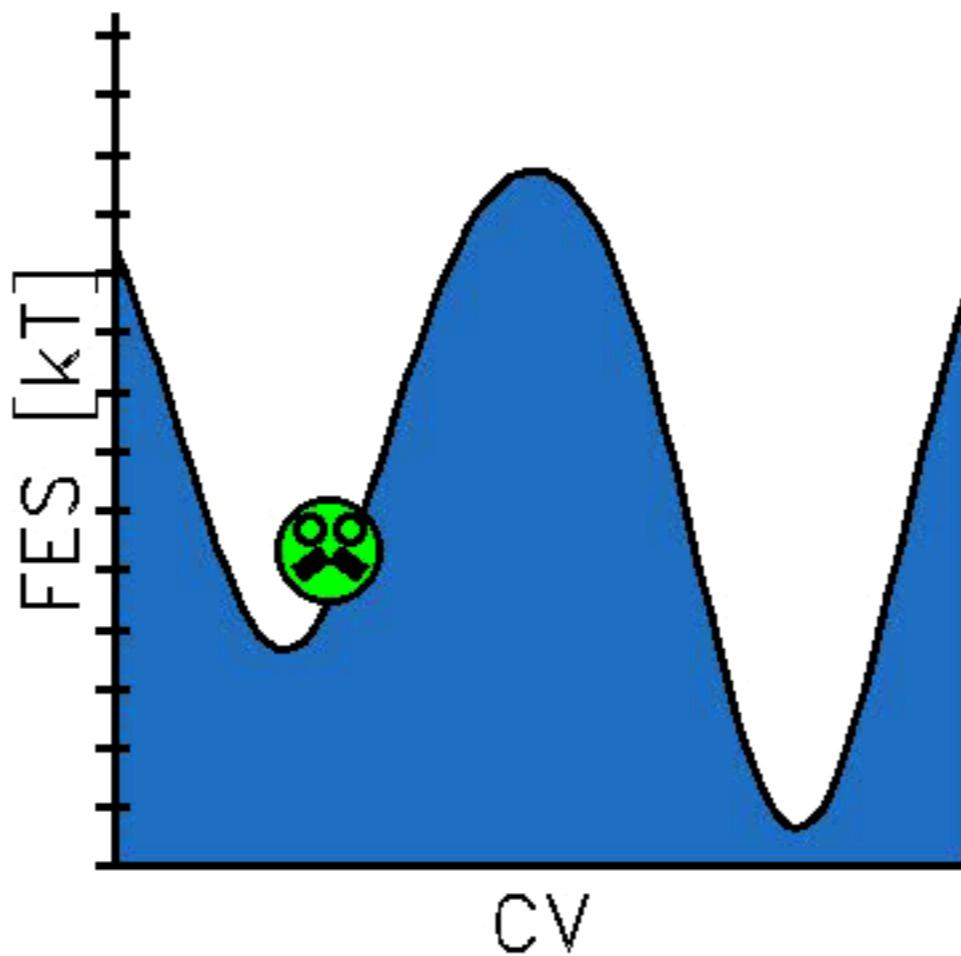
where  $P'(\mathbf{S}) = \frac{\int d\mathbf{R} \delta(\mathbf{S} - \mathbf{S}(\mathbf{R})) e^{-\beta[U(\mathbf{R})+V(\mathbf{S}(\mathbf{R}))]}}{\int d\mathbf{R} e^{-\beta[U(\mathbf{R})+V(\mathbf{S}(\mathbf{R}))]}}$

which leads to:

$$F'(\mathbf{S}) = F(\mathbf{S}) + V(\mathbf{S})$$

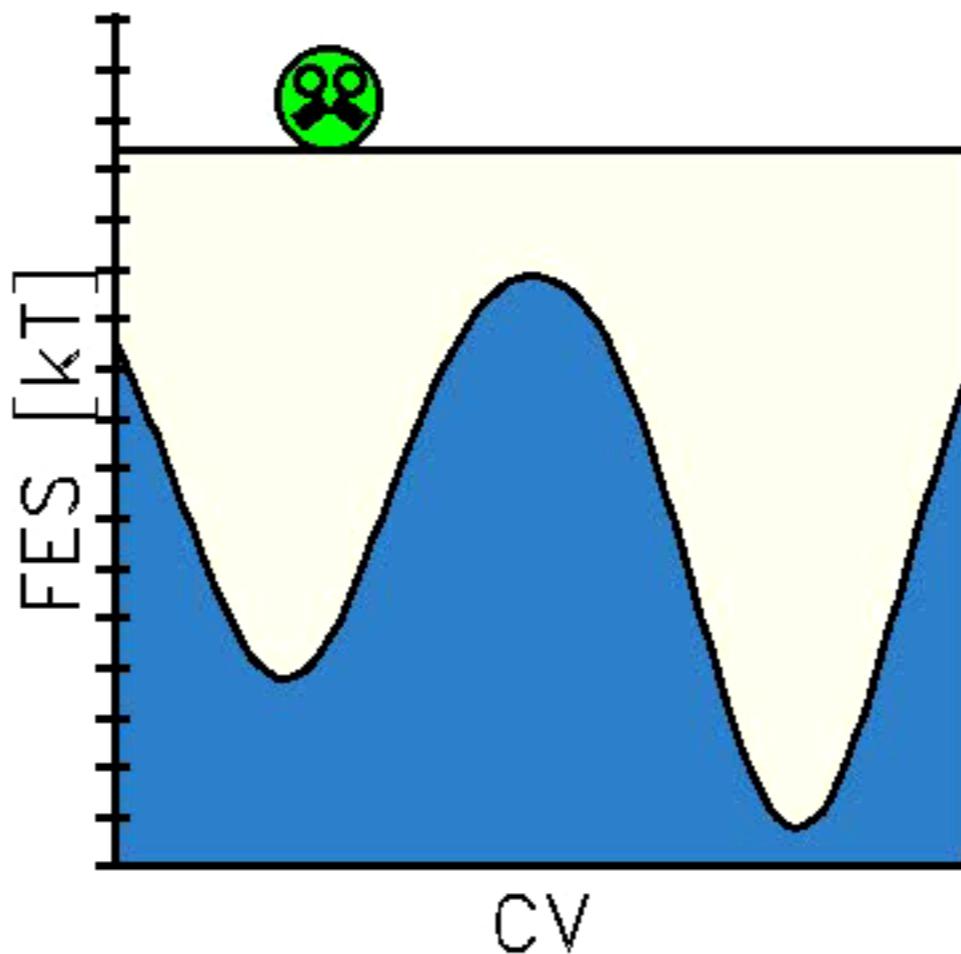
# Umbrella sampling

What is a good choice of bias potential?



# Umbrella sampling

What is a good choice of bias potential?



The one that leads to  $F'(\mathbf{S}) = 0 \rightarrow V(\mathbf{S}) = -F(\mathbf{S})$

Let's use an approximation of the free energy as bias potential

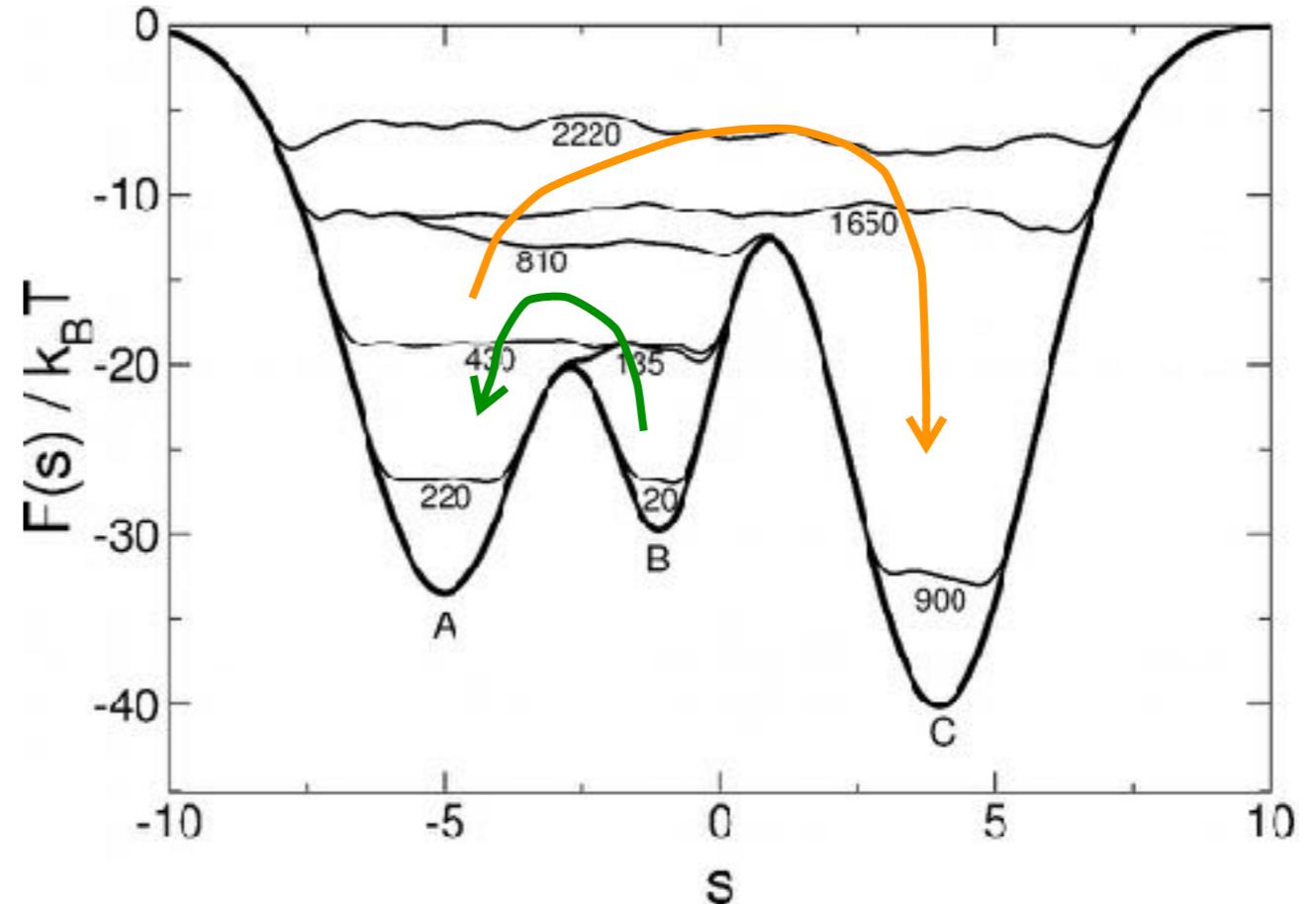
# Metadynamics

History-dependent bias potential acting on selected degrees of freedom or Collective Variables (CVs)

$$S = (S_1(\mathbf{R}), \dots, S_d(\mathbf{R}))$$

$$V_G(\mathbf{S}, t) = W \sum_{t'=\tau_G, 2\tau_G, \dots}^{t' < t}$$

$$\exp \left( - \sum_{i=1}^d \frac{(S_i - S_i(\mathbf{R}(t')))^2}{2\sigma_i^2} \right)$$



Laio & Parrinello PNAS (2002)

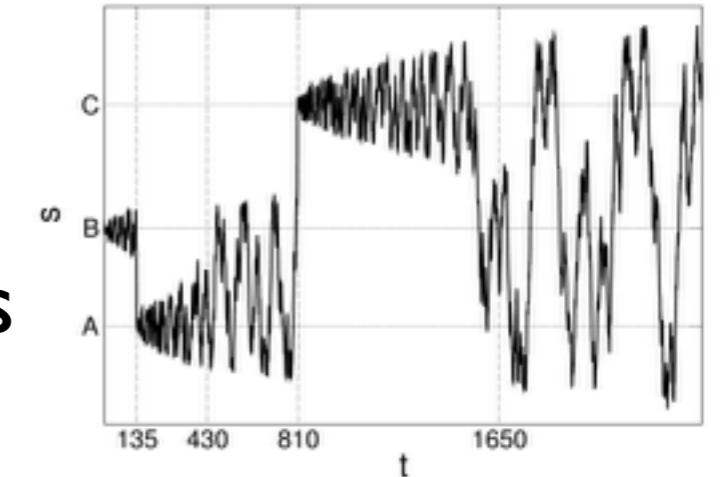
REVIEW: Barducci, Bonomi, Parrinello WIREs Comput Mol Sci (2011)

# Pros and Cons

## Advantages

- Enhanced sampling along the CVs
- Reconstruction of the FES:

$$V_G(S, t \rightarrow \infty) = -F(S) + C$$



Bussi, Laio, Parrinello PRL (2006)

- *A priori* knowledge of the landscape not required

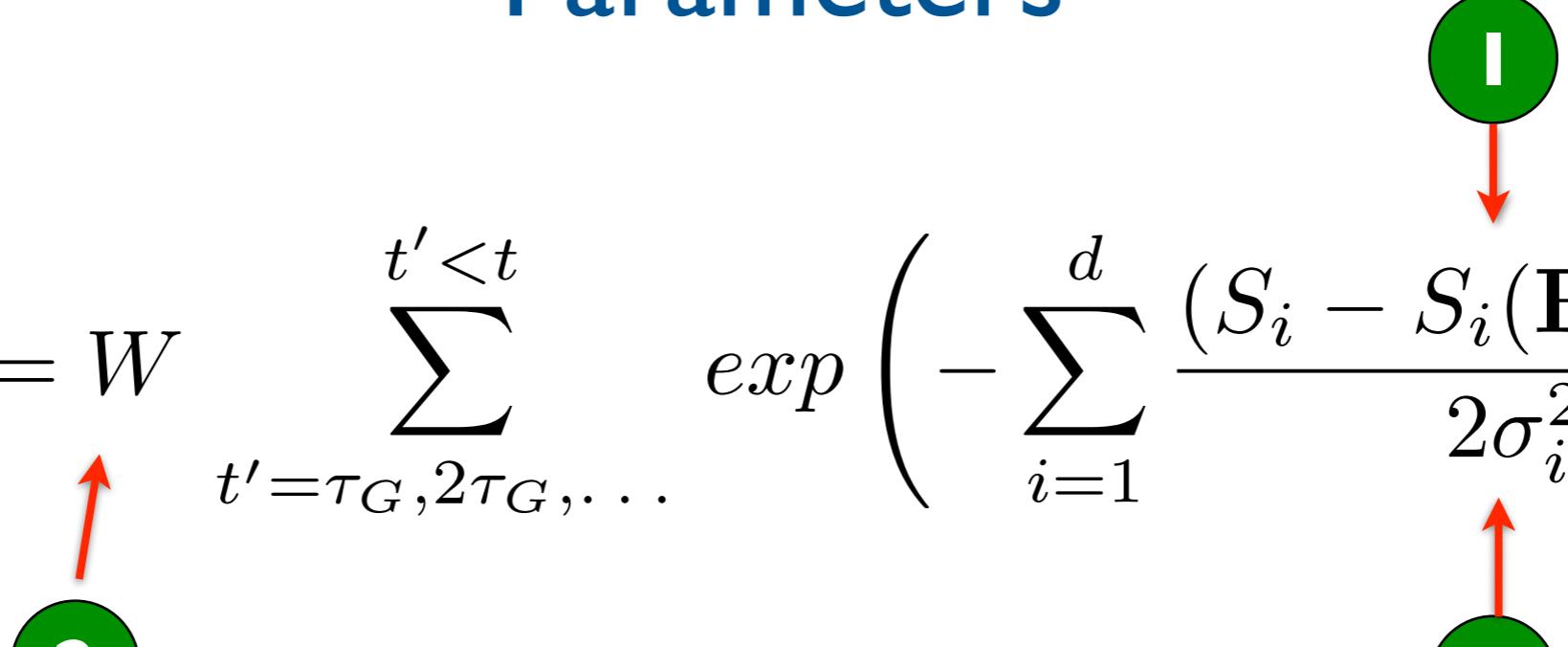


## Disadvantages



- Lack of convergence in a single run
- Overfilling
- The choice of the CVs is not trivial

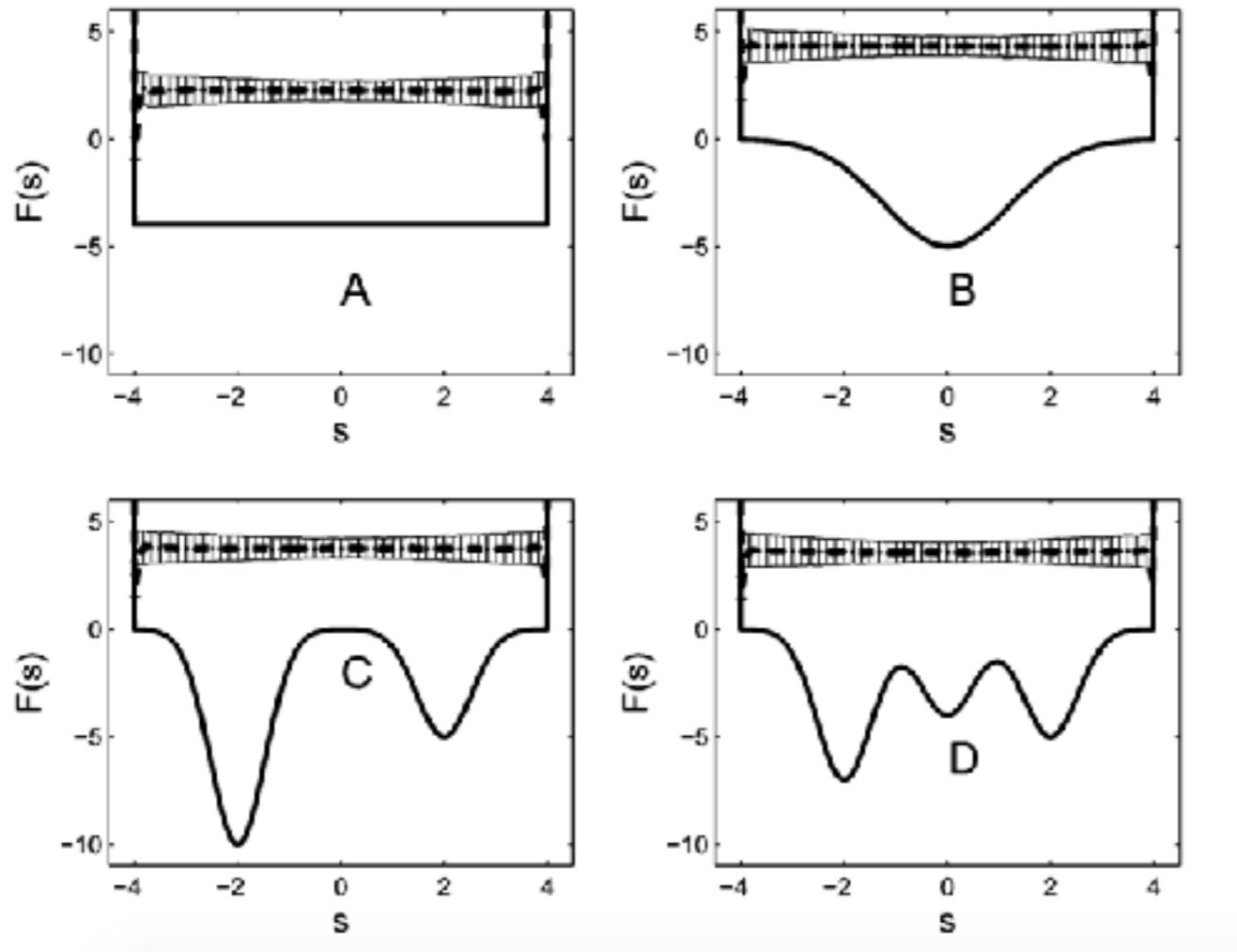
# Parameters

$$V_G(\mathbf{S}, t) = W \sum_{t'=\tau_G, 2\tau_G, \dots}^{t' < t} \exp \left( - \sum_{i=1}^d \frac{(S_i - S_i(\mathbf{R}(t')))^2}{2\sigma_i^2} \right)$$


What do we need to choose?

- 1 Collective variables  $S = (S_1(\mathbf{R}), \dots, S_d(\mathbf{R}))$
- 2 Energy rate  $\omega = \frac{W}{\tau_G}$
- 3 Gaussian width

# Assessing the accuracy of metadynamics



$$\epsilon^2 \propto \frac{W}{\tau_G} \sigma$$

Reducing the error by time-averaging different profiles:

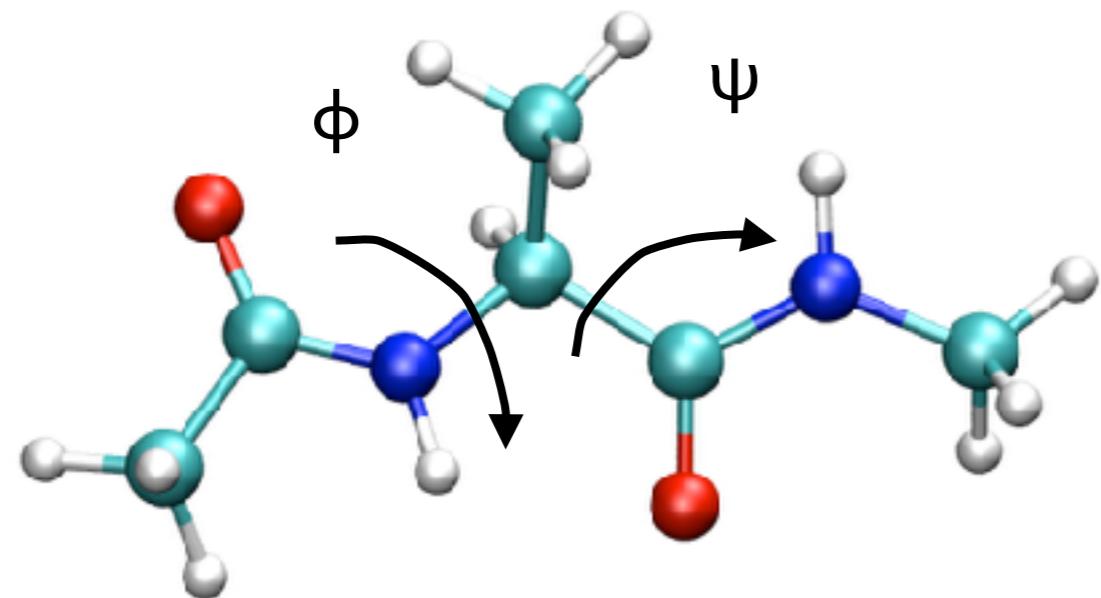
$$F_{\text{meta}}(s, t_{\text{tot}}) = -\frac{1}{t_{\text{tot}} - t_F} \int_{t_F}^{t_{\text{tot}}} V_G(s, t) dt.$$

Laio et al, JPCB (2005)

Micheletti, Laio, Parrinello PRL (2004)

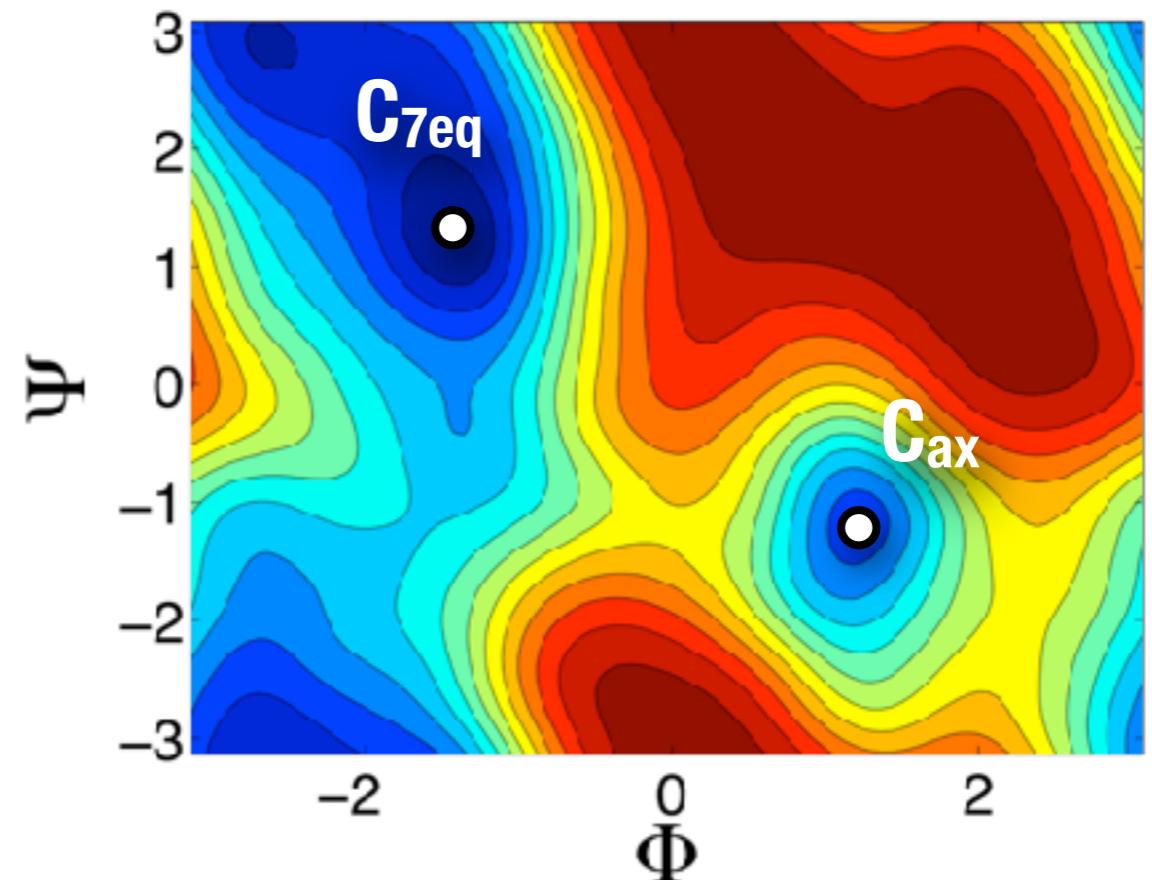
# MetaD with PLUMED

Alanine dipeptide in vacuo: two metastable states in the Ramachandran plot



$$(\Phi, \Psi)_{C_{7eq}} = (-1.45, 1.30)$$

$$(\Phi, \Psi)_{C_{ax}} = (1.22, -1.22)$$



The isomerization is a rare event: barrier of 6-8 kcal/mol at 300K (CHARMM27 force field)

# MetaD with PLUMED

```
# declare collective variables
phi: TORSION ATOMS=5,7,9,15
psi: TORSION ATOMS=7,9,15,17

# activate metadynamics
metad: METAD ARG=phi,psi HEIGHT=1.2 SIGMA=0.35,0.35 PACE=500

# print out collective variables and metadynamics bias
PRINT ARG=phi,psi,metad.bias STRIDE=100 FILE=COLVAR
```

## Units of measure:

- Height in kJoule/mol
- Stride in time steps
- Sigma in CV units

# MetaD with PLUMED

The main output is the HILLS file

```
#! FIELDS time phi psi sigma_phi sigma_psi height biasf  
#! SET multivariate false  
#! SET min_phi -pi  
#! SET max_phi pi  
#! SET min_psi -pi  
#! SET max_psi pi
```

HEADER

1.0000	1.1087	-0.8443	0.3500	0.3500	1.2000	-1.0000
2.0000	0.8819	-0.4241	0.3500	0.3500	1.2000	-1.0000
3.0000	1.2015	-0.2560	0.3500	0.3500	1.2000	-1.0000
4.0000	1.0359	-0.1549	0.3500	0.3500	1.2000	-1.0000
5.0000	0.9848	-0.6522	0.3500	0.3500	1.2000	-1.0000
6.0000	0.9970	-1.2823	0.3500	0.3500	1.2000	-1.0000
7.0000	0.8488	-1.0816	0.3500	0.3500	1.2000	-1.0000
8.0000	0.6605	-1.2918	0.3500	0.3500	1.2000	-1.0000
9.0000	1.1637	-1.4699	0.3500	0.3500	1.2000	-1.0000
10.0000	1.0504	-0.6997	0.3500	0.3500	1.2000	-1.0000
11.0000	1.0553	-0.8905	0.3500	0.3500	1.2000	-1.0000
12.0000	0.9541	-0.4194	0.3500	0.3500	1.2000	-1.0000

Time (ps)	CV (rad)	Sigma (rad)	Height (kJ/mol)	Bias Factor
--------------	-------------	----------------	--------------------	----------------

# Well-Tempered Metadynamics

Idea. New form for the bias potential:

$$V(\mathbf{S}, t) = k_B \Delta T \ln \left( 1 + \frac{\omega N(\mathbf{S}, t)}{k_B \Delta T} \right)$$

histogram  
collected during  
the simulation

“CV temperature”

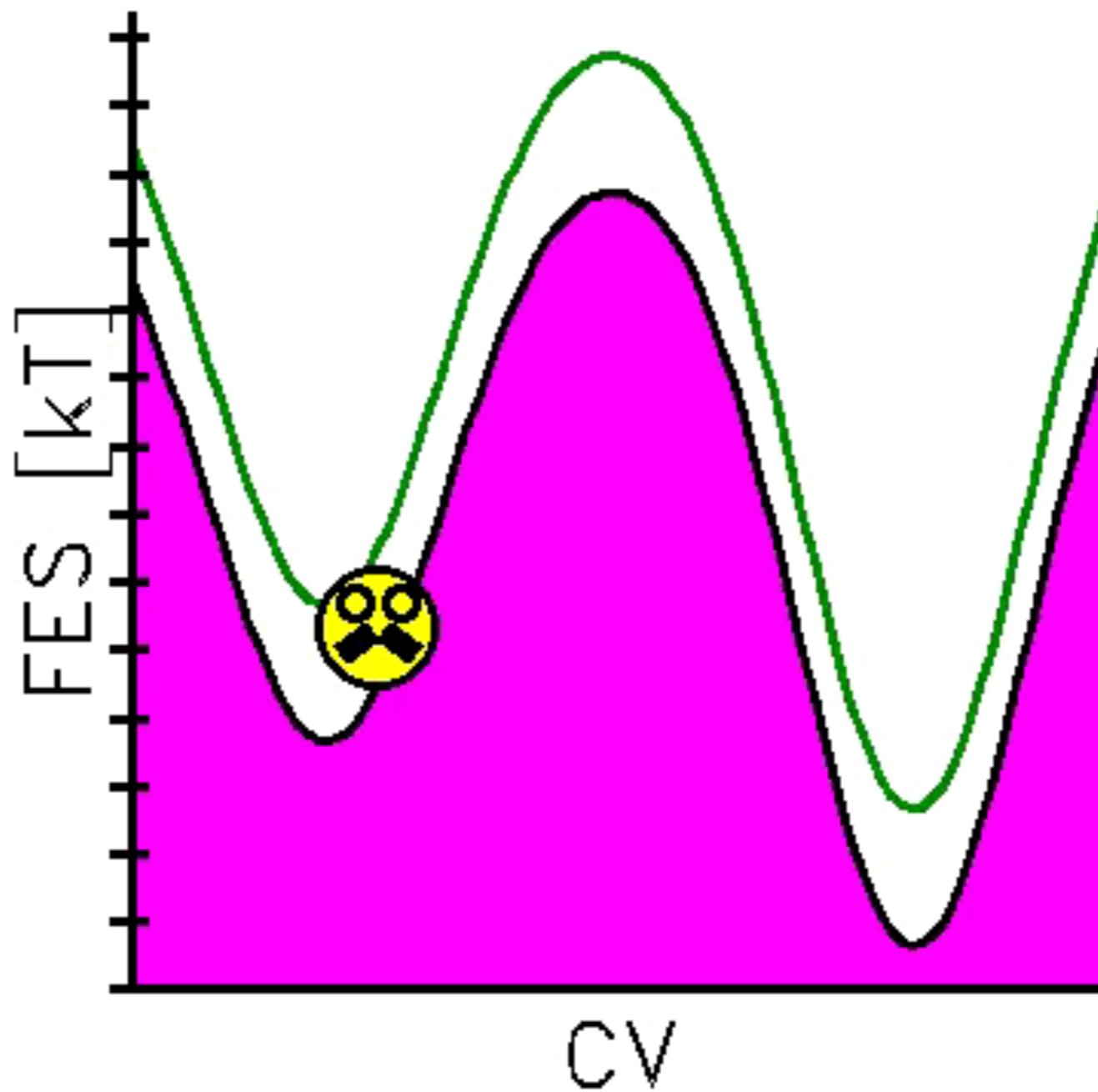
$$\dot{V}(\mathbf{S}, t) = \frac{\omega \delta_{\mathbf{S}, \mathbf{S}(t)}}{1 + \frac{\omega N(\mathbf{S}, t)}{k_B \Delta T}} = \omega e^{-\frac{V(\mathbf{S}, t)}{k_B \Delta T}} \delta_{\mathbf{S}, \mathbf{S}(t)}$$

Implementation.

Rescale the Gaussian height:

$$W = \omega \tau_G e^{-\frac{V_G(\mathbf{S}, t)}{k_B \Delta T}}$$

# Well-Tempered Metadynamics



movie by G. Bussi

- Single run convergence:

$$V_G(\mathbf{S}, t \rightarrow \infty) = -\frac{\Delta T}{T + \Delta T} F(\mathbf{S}) + C$$

- Overfilling issue solved.  $\Delta T$  to limit the exploration to the physically relevant regions.
- Error goes to zero in a single run:  $\epsilon(t) \propto 1/\sqrt{t}$
- The dynamics of all the microscopic variables becomes closer to equilibrium as the simulation proceeds:

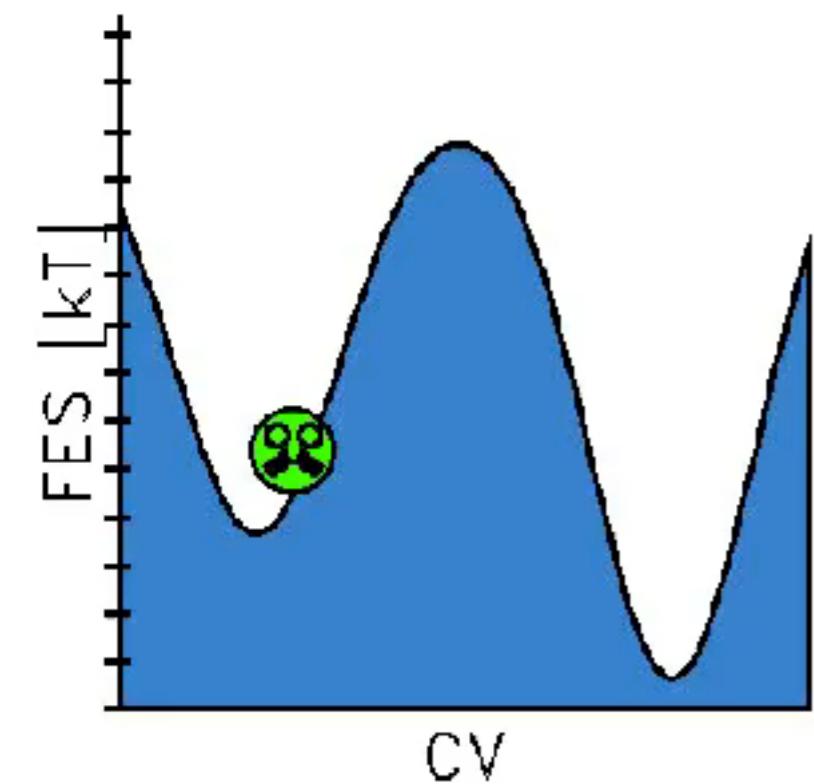
$$\dot{V}_G(\mathbf{S}, t \rightarrow \infty) \propto 1/t \rightarrow 0$$

- Distribution of variables other than the CVs can be easily reconstructed

Bonomi, Barducci, Parrinello *J. Comp. Chem.* (2009)  
 Branduardi, Bussi, Parrinello *JCTC* (2012)  
 Tiwary, Parrinello *JPCB* (2015)

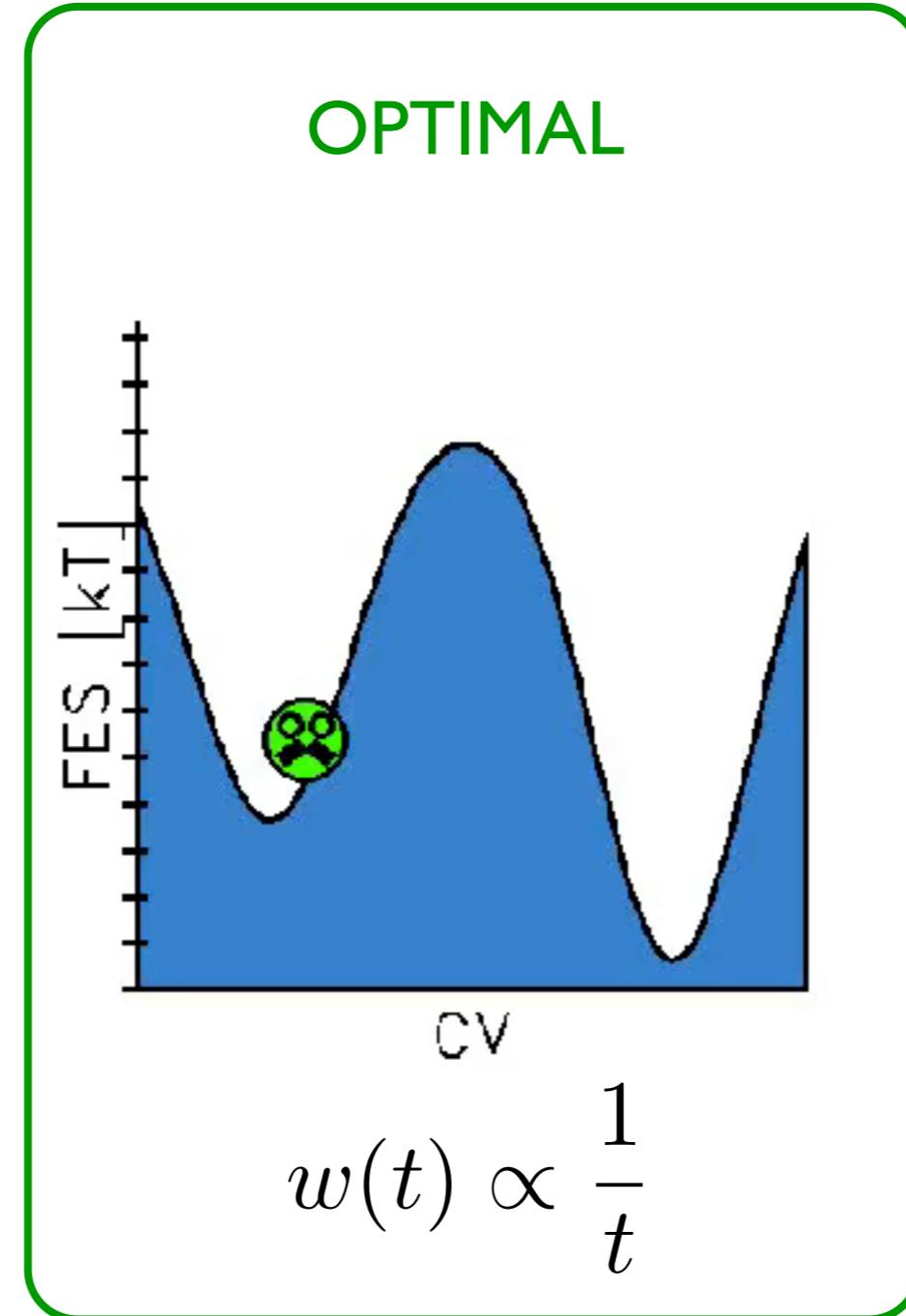
# An optimal recipe

TOO SLOW



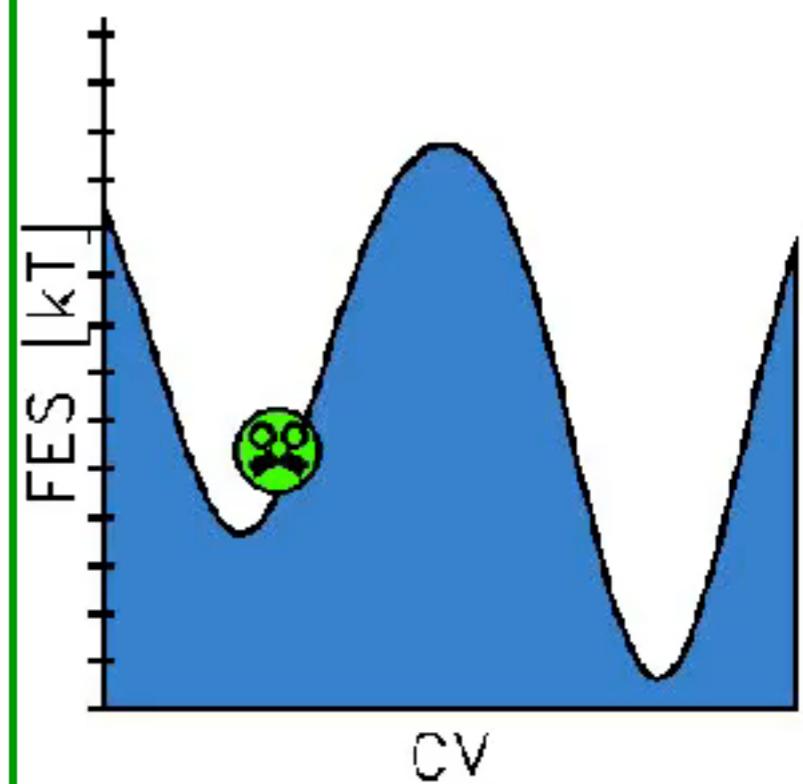
$$w(t) \propto \frac{1}{\log t}$$

OPTIMAL



$$w(t) \propto \frac{1}{t}$$

TOO FAST



$$w(t) \propto \frac{1}{t^2}$$

# Parameters

$$W = \omega \tau_G e^{-\frac{V_G(S,t)}{k_B \Delta T}}$$


1      2

1 Initial Gaussian height + deposition stride

2 How fast the amount of bias added decreases to zero

$$\left\{ \begin{array}{l} T + \Delta T \\ \frac{T + \Delta T}{T} \end{array} \right.$$

CV  
TEMPERATURE

BIAS  
FACTOR

# WT-MetaD with PLUMED

```
# declare collective variables
phi: TORSION ATOMS=5,7,9,15
psi: TORSION ATOMS=7,9,15,17

# activate well-tempered metadynamics
metad: METAD ARG=phi,psi HEIGHT=1.2 SIGMA=0.35,0.35 PACE=500 BIASFACTOR=8

# print out collective variables and metadynamics bias
PRINT ARG=phi,psi,metad.bias STRIDE=100 FILE=COLVAR
```

# WT-MetaD with PLUMED

The main output is the HILLS file

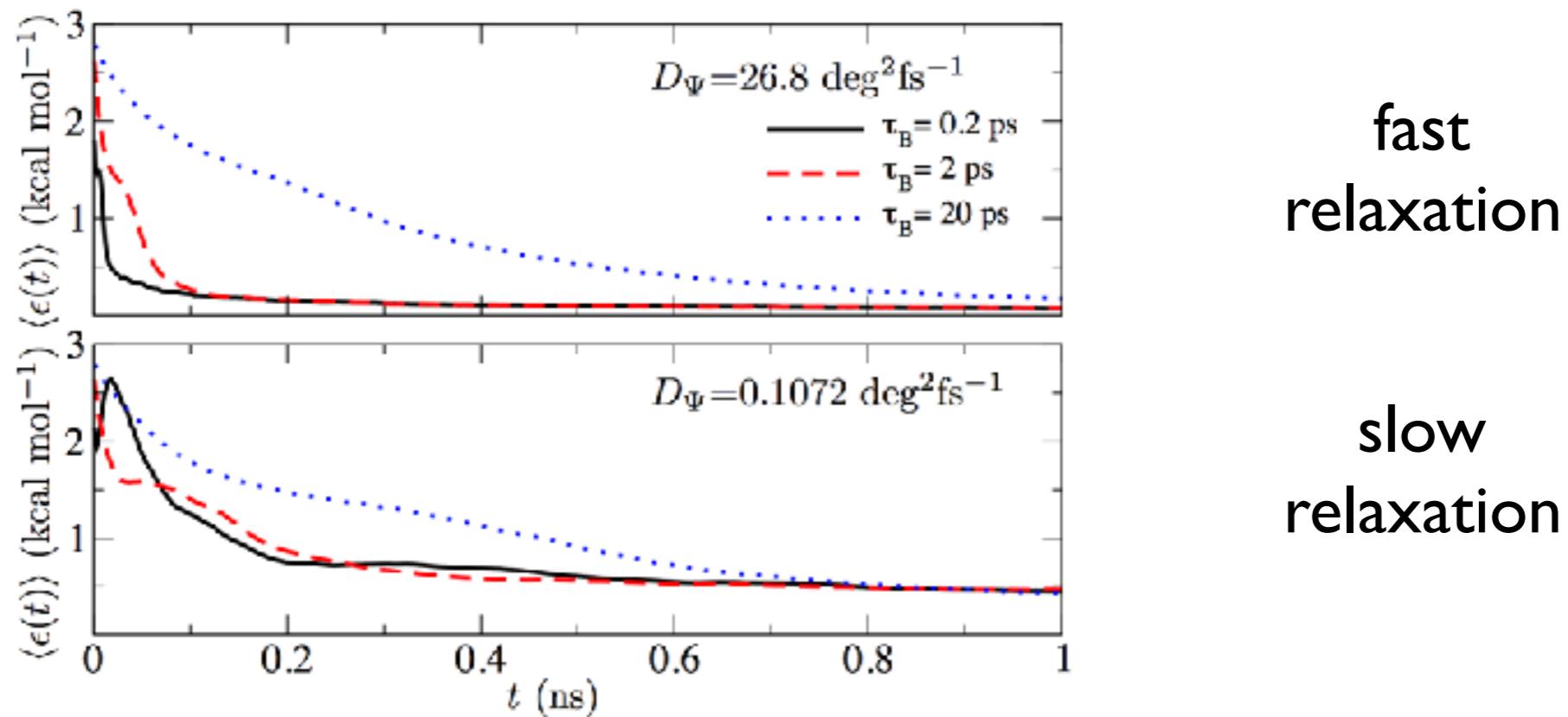
```
#! FIELDS time phi psi sigma_phi sigma_psi height biasf
#! SET multivariate false
#! SET min_phi -pi
#! SET max_phi pi
#! SET min_psi -pi
#! SET max_psi pi
```

1.0000	1.1087	-0.8443	0.3500	0.3500	1.3714	8.0000
2.0000	0.8819	-0.4241	0.3500	0.3500	1.3348	8.0000
3.0000	1.1897	-0.2275	0.3500	0.3500	1.3007	8.0000
4.0000	0.9427	-0.0746	0.3500	0.3500	1.2513	8.0000
5.0000	0.9916	-0.7114	0.3500	0.3500	1.1933	8.0000
6.0000	1.1558	-1.1060	0.3500	0.3500	1.2525	8.0000
7.0000	1.1366	-0.7487	0.3500	0.3500	1.0996	8.0000
8.0000	1.0933	-1.0890	0.3500	0.3500	1.1288	8.0000
9.0000	1.0794	-0.7793	0.3500	0.3500	1.0000	8.0000
10.0000	1.1538	-0.4934	0.3500	0.3500	1.0038	8.0000
11.0000	0.7173	-0.7677	0.3500	0.3500	1.0751	8.0000
12.0000	1.0673	-0.3857	0.3500	0.3500	0.9596	8.0000

Time (ps)	CV (rad)	Sigma (rad)	Height (kJ/mol)	Bias Factor
--------------	-------------	----------------	--------------------	----------------

$$V_G(\mathbf{S}, t \rightarrow \infty) = -\frac{\Delta T}{T + \Delta T} F(\mathbf{S}) + C$$

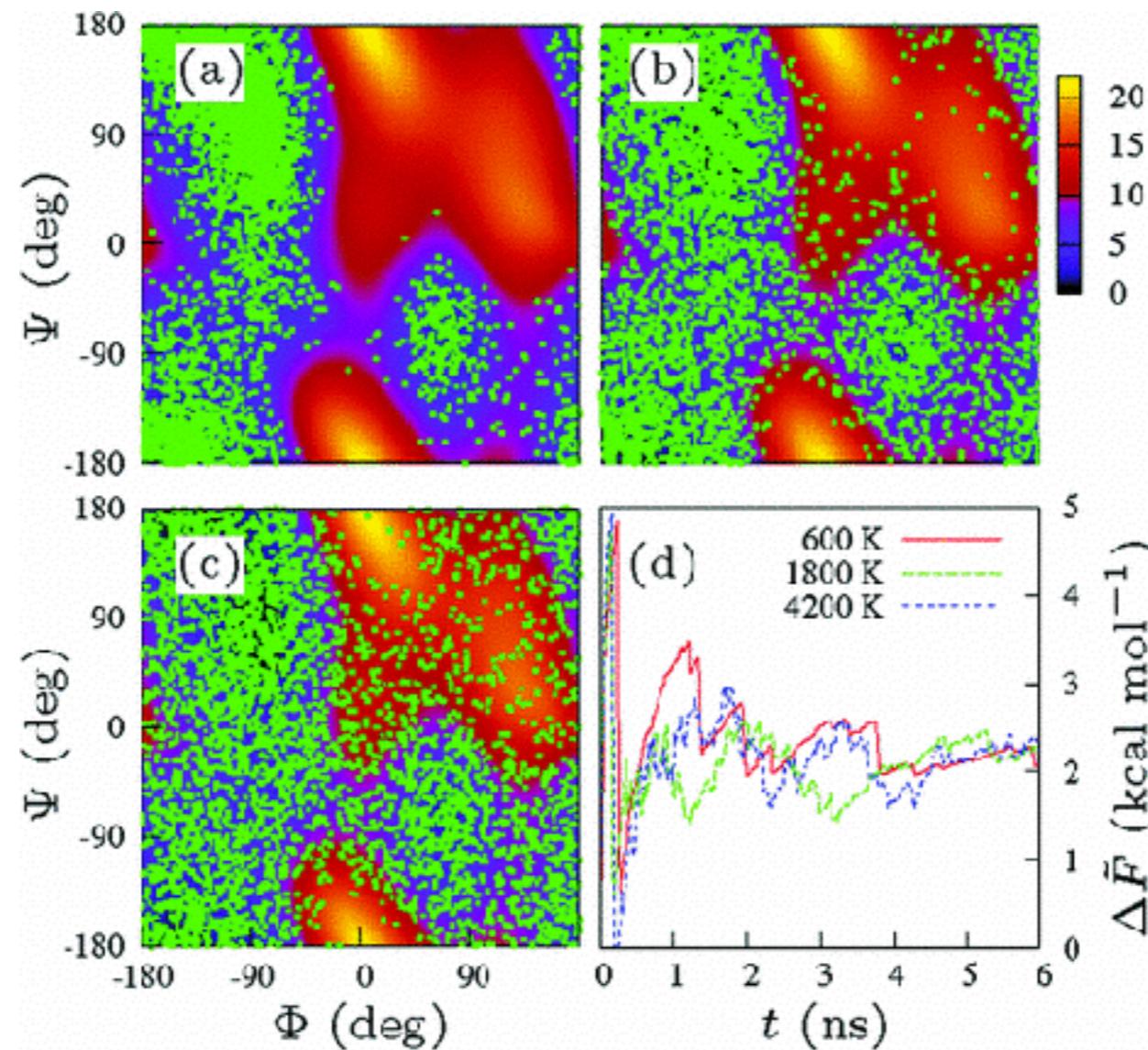
# Guidelines for choosing the initial deposition rate



The initial deposition rate affects the transient period

Typical value for biological applications  $\sim 0.5\text{-}1.0 \text{ k}_\text{B}\text{T}$  per ps

# Guidelines for choosing the biasfactor



Determine the extent of free-energy exploration

Typical value for biological applications  $\sim 10$

# Guidelines for choosing the biasfactor

From another point of view: WT-MetaD enhances the fluctuations of the collective variables.

$$P(\mathbf{S}) \longrightarrow P_\gamma(\mathbf{S}) = P(\mathbf{S})^{\frac{1}{\gamma}}$$

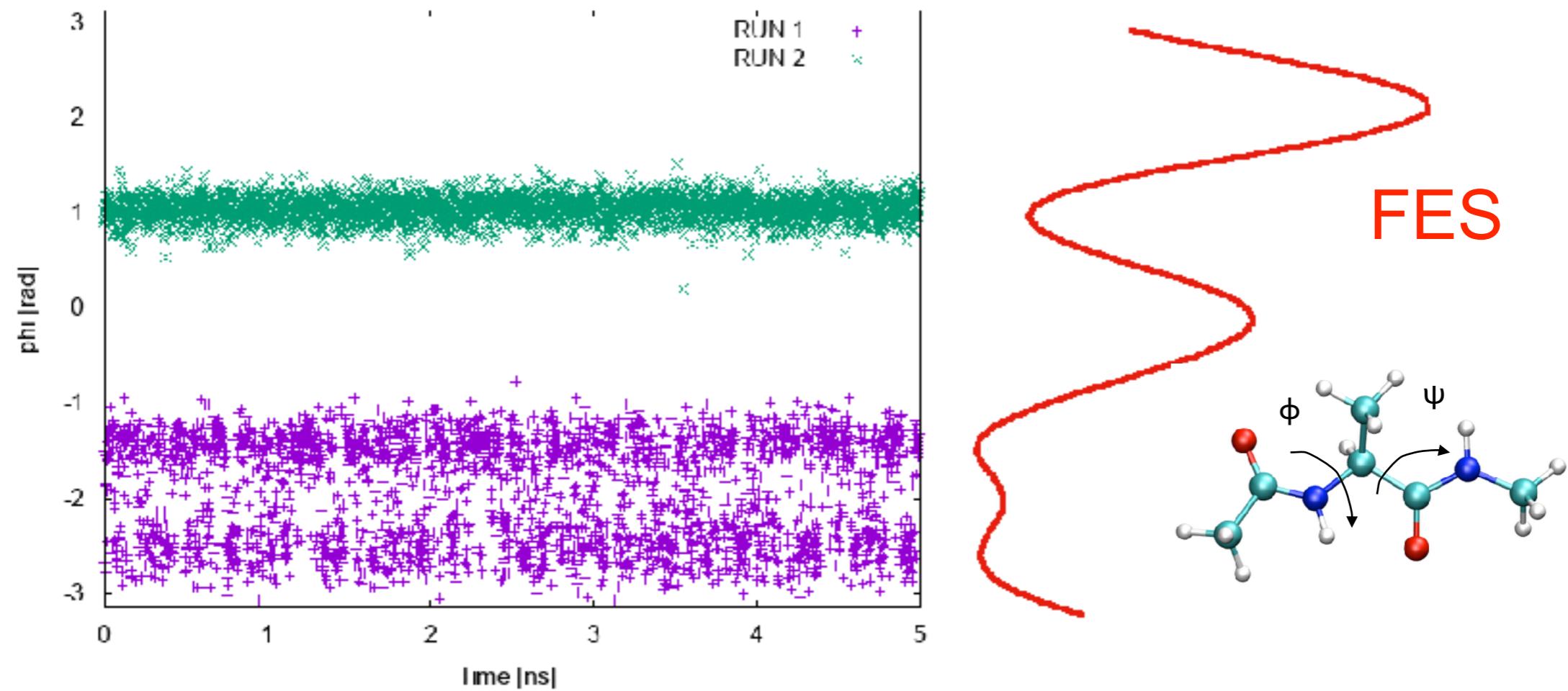
This is particular clear when biasing the potential energy of the system (Well-Tempered Ensemble), whose unbiased probability distribution is often Gaussian:

$$P(U) \propto e^{-\frac{(U - \langle U \rangle)^2}{2\Delta U^2}} \longrightarrow e^{-\frac{(U - \langle U \rangle)^2}{2\Delta U_\gamma^2}}$$
$$\Delta U_\gamma^2 = \gamma \cdot \Delta U^2$$

# Guidelines for choosing sigma

The width of the Gaussian should be commensurate to the typical size of the “features” of the free energy landscape

Typically, the Gaussian width is estimated from the fluctuations of the collective variables in an unbiased run:



# Adaptive Gaussians

Branduardi, Bussi, Parrinello JCTC (2015)

Automatic way to determine Gaussian sigma that accounts for

- fluctuations varying across the free-energy landscape
- CVs being correlated

It uses multivariate, non-diagonal  
Gaussians:

$$\begin{aligned}\dot{V}(s, t) = & \omega e^{-V(s(t), t)/\Delta T} \\ & \times \exp\left(-\frac{1}{2} \sum_{ij} [s_i - s_i(t)] \sigma_{ij}^{-2} [s_j - s_j(t)]\right)\end{aligned}$$

with covariance-matrix elements determined by:

$$\bar{s}_i(t) = \frac{1}{\tau_D} \int_0^t dt' s_i(t') e^{-(t-t')/\tau_D}$$

and

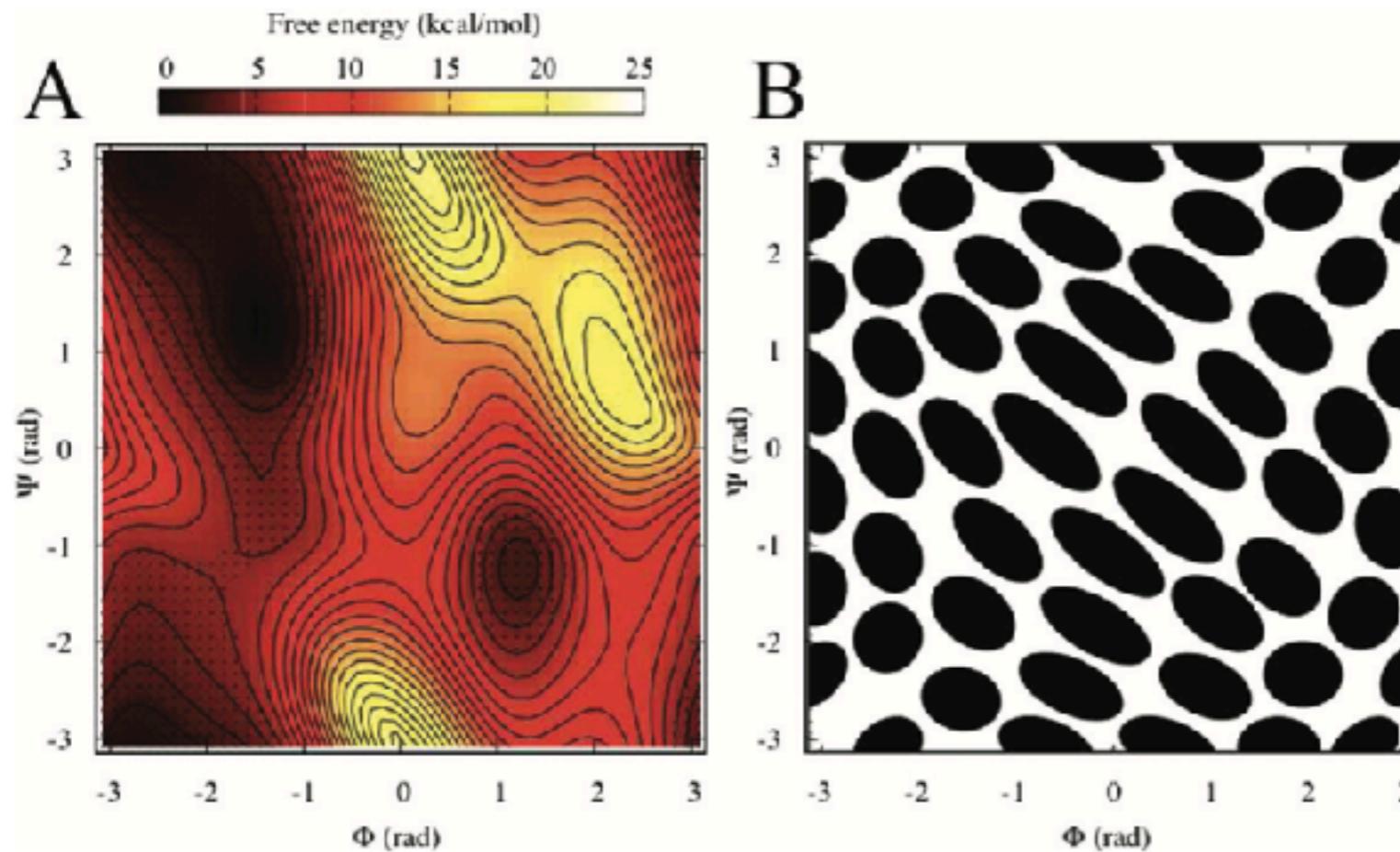
$$\begin{aligned}\sigma_{ij}^2(t) = & \frac{1}{\tau_D} \int_0^t dt' [s_i(t') - \bar{s}_i(t')] [s_j(t') - \bar{s}_j(t')] \\ & \times e^{-(t-t')/\tau_D}\end{aligned}$$

dynamically-adapted

or

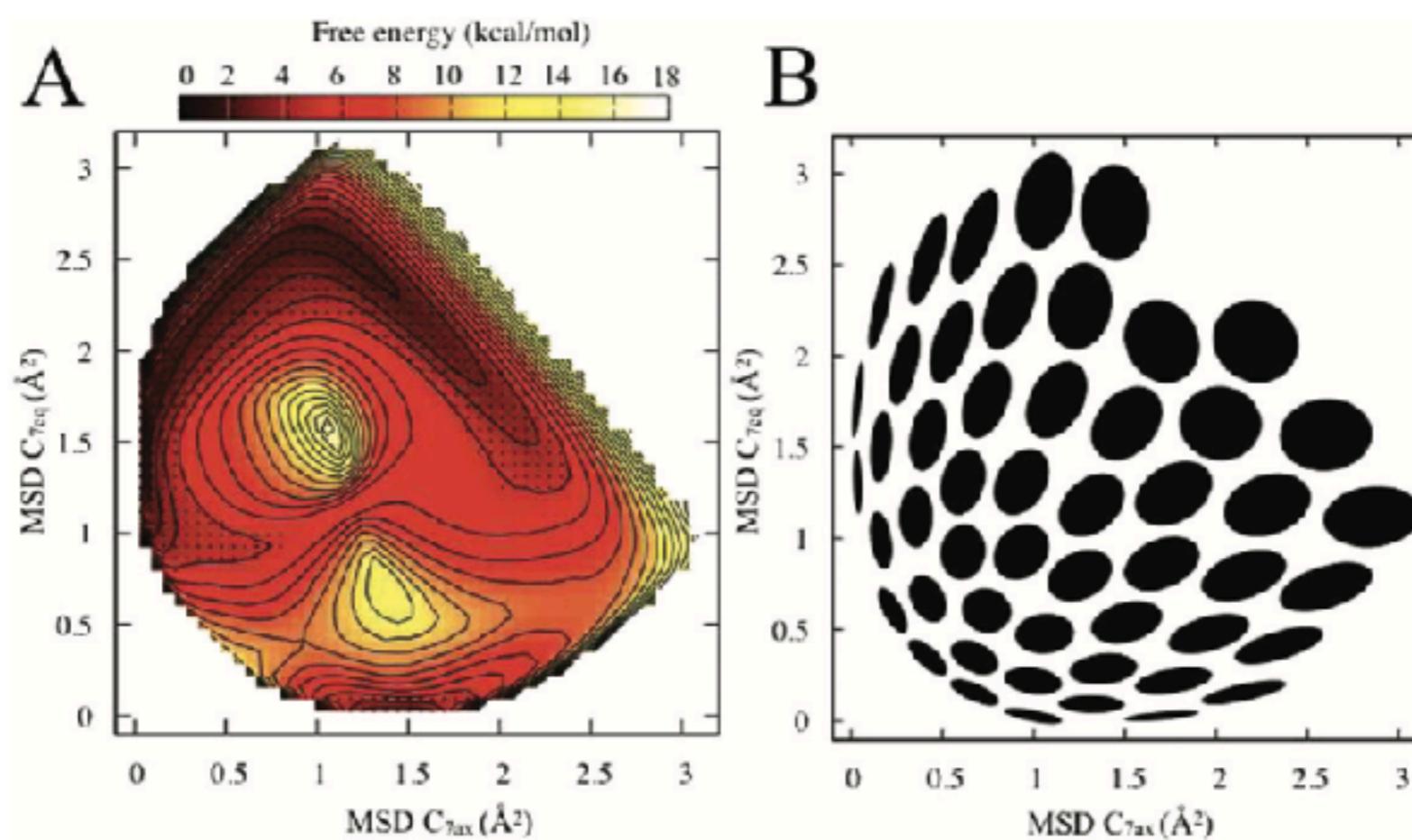
$$\sigma_{ij}^2(q) = \sigma_G^2 \sum_\alpha \frac{\partial s_i}{\partial q_\alpha} \frac{\partial s_j}{\partial q_\alpha}$$

geometrically-adapted



CVs

backbone  
dihedrals



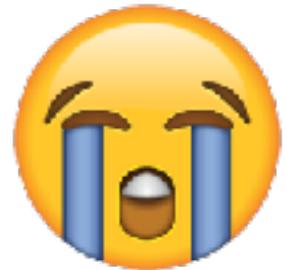
MSD from  
local minima

# Guidelines for choosing the CVs

A good set of CVs for metadynamics (and other biasing techniques) should:

- Discriminate between relevant metastable states
- Include all the slow modes of a process
- Be as small as possible

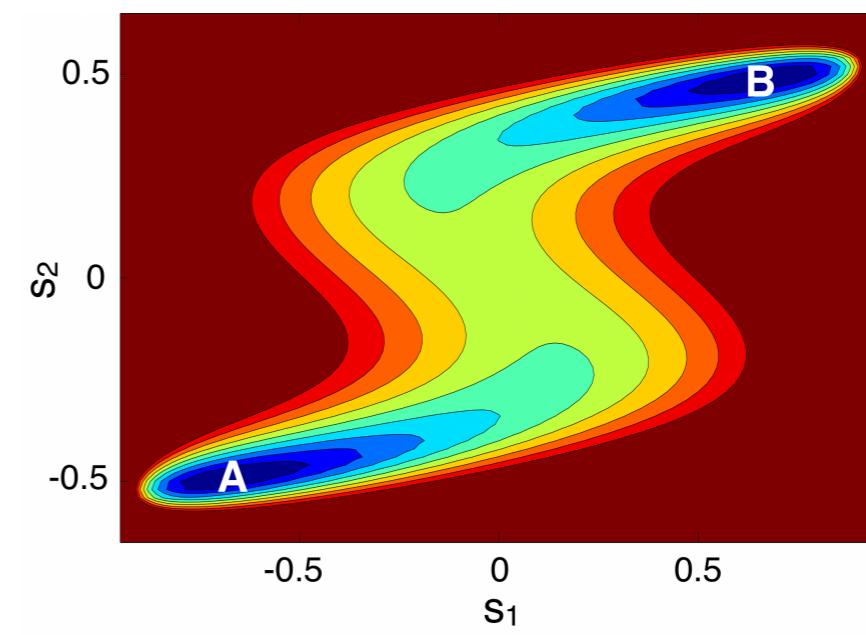
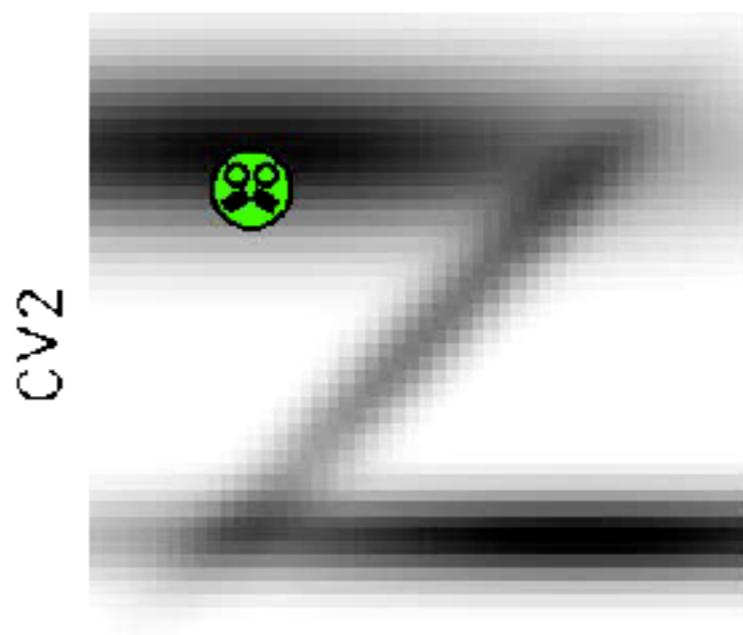
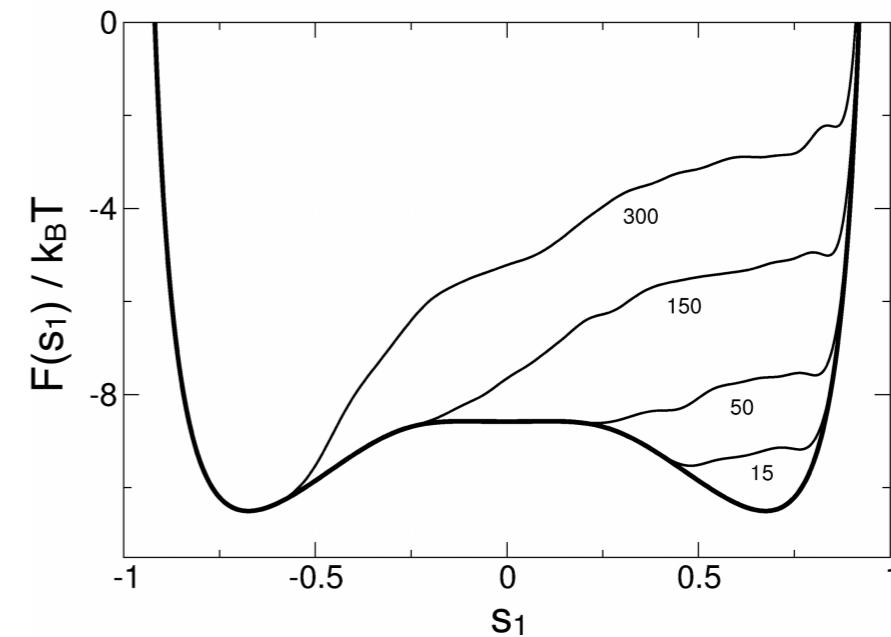
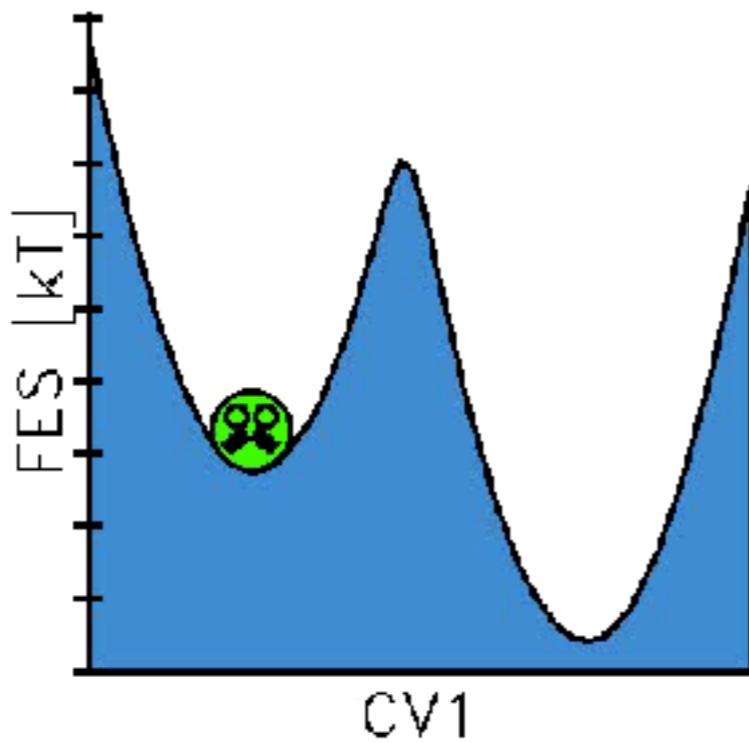
Metadynamics is inefficient with a large number of CVs.



Possible strategies:

- design smart CVs
- devise automatic protocols to find good CVs
- improve metadynamics to deal with a large number of CVs
- couple metadynamics with other methods, such as REM

# Hidden degrees of freedom



# Path Collective Variables

Branduardi, Gervasio, Parrinello *JCP* (2007)

Map a configuration in terms of:

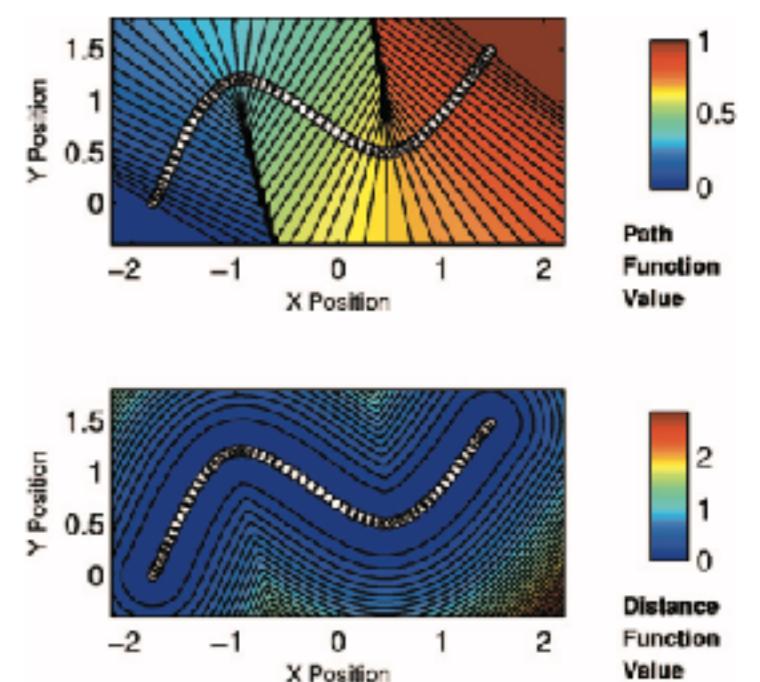
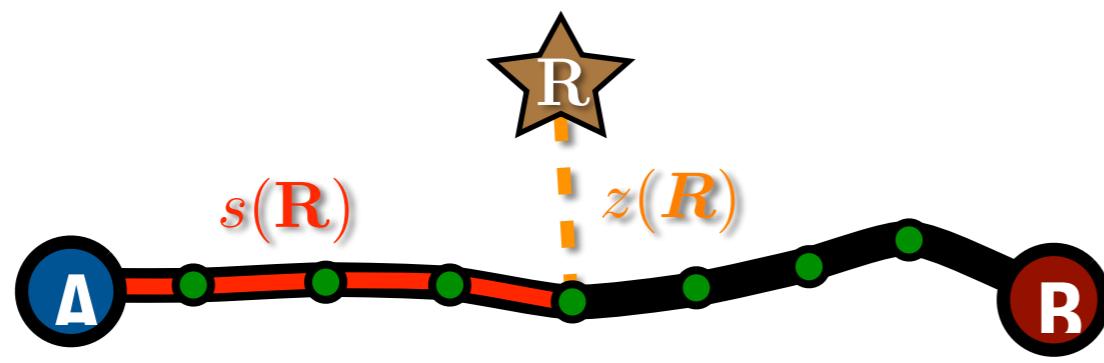
→ PROGRESS

$$s(\mathbf{R}) = \frac{1}{P-1} \frac{\sum_{l=1}^P (l-1) e^{-\lambda \|S(\mathbf{R}) - S(l)\|^2}}{\sum_{l=1}^P e^{-\lambda \|S(\mathbf{R}) - S(l)\|^2}}$$

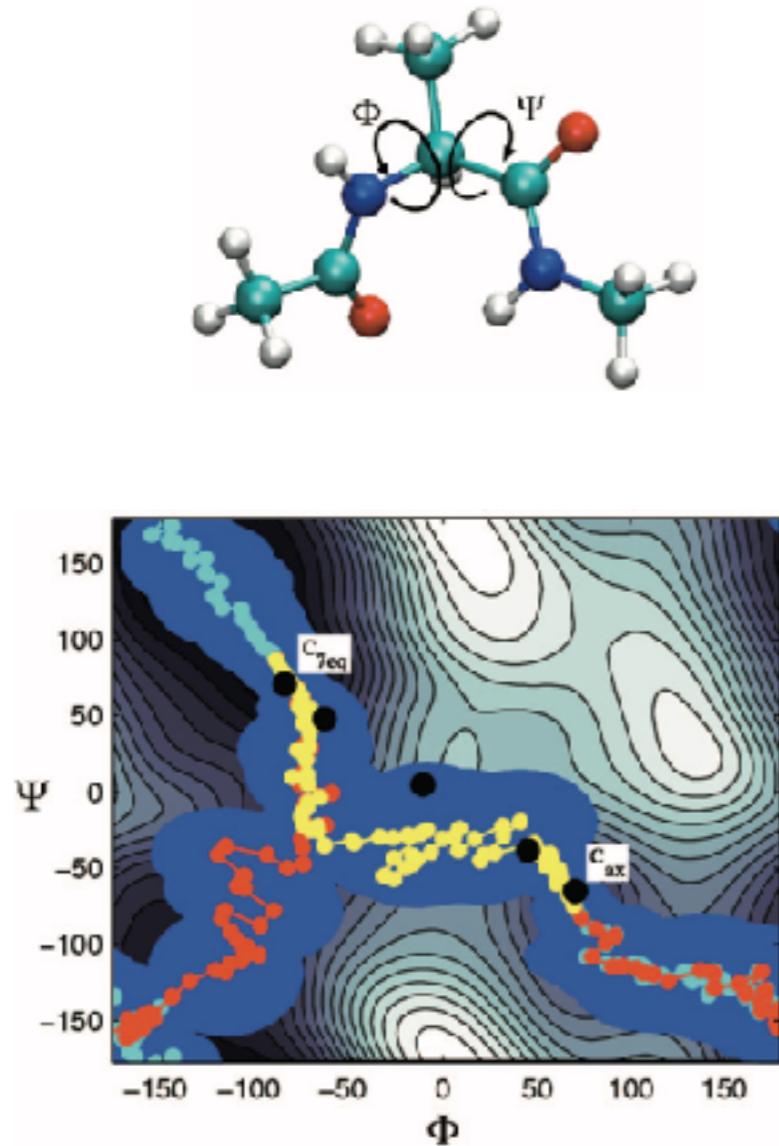
→ DISTANCE

$$z(\mathbf{R}) = -\frac{1}{\lambda} \ln \left( \sum_{l=1}^P e^{-\lambda \|S(\mathbf{R}) - S(l)\|^2} \right)$$

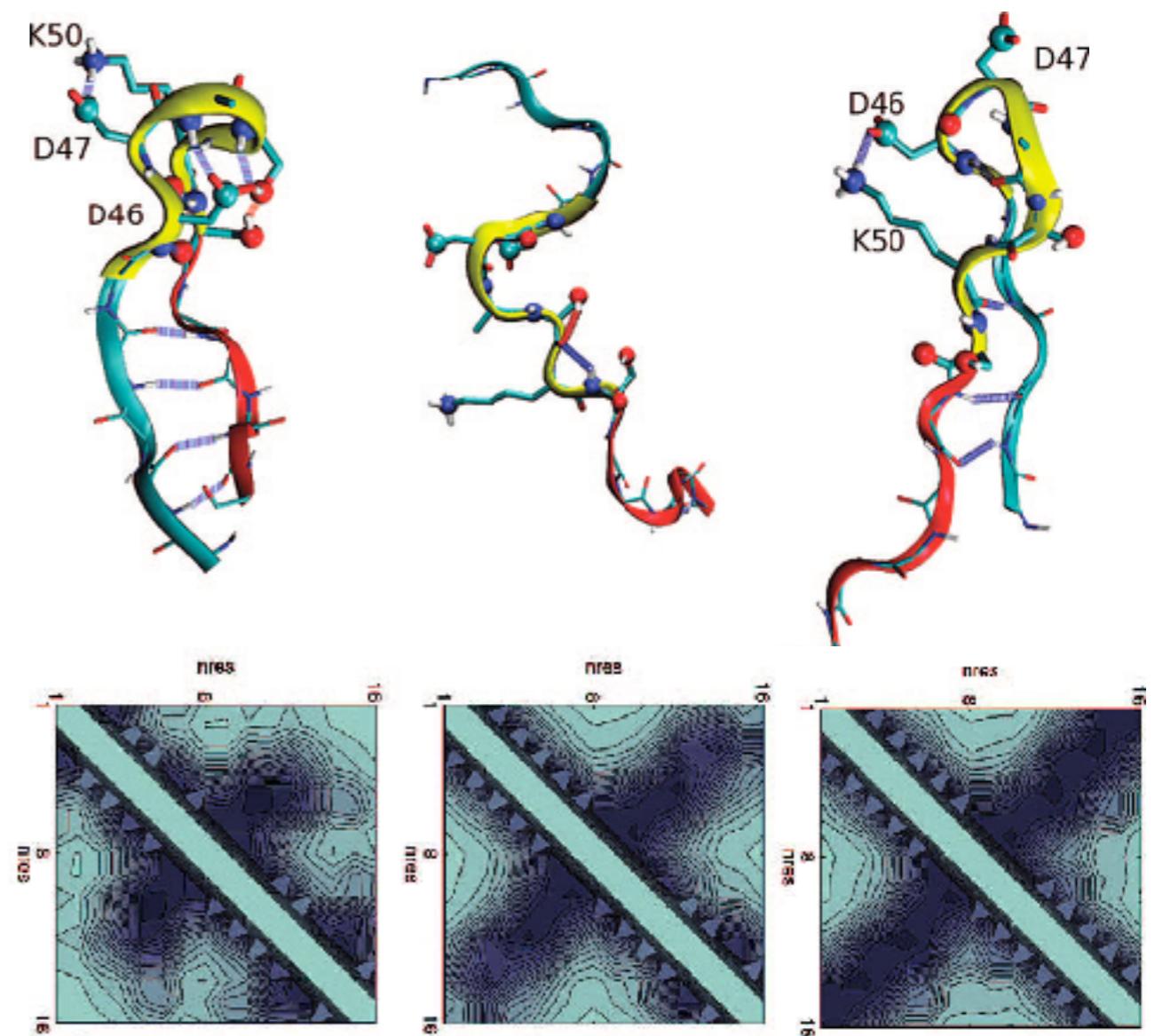
with respect to a reference path going from A to B



# RMSD path variables



# Contact Map path variables



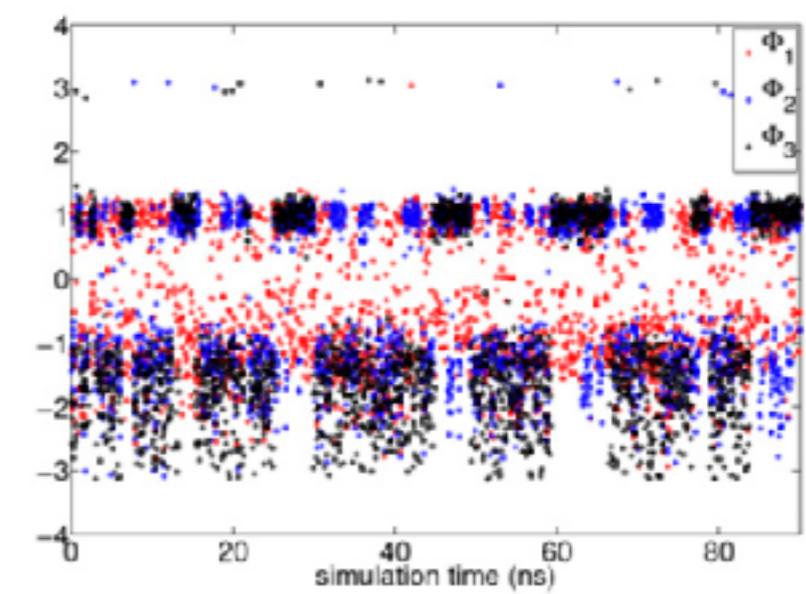
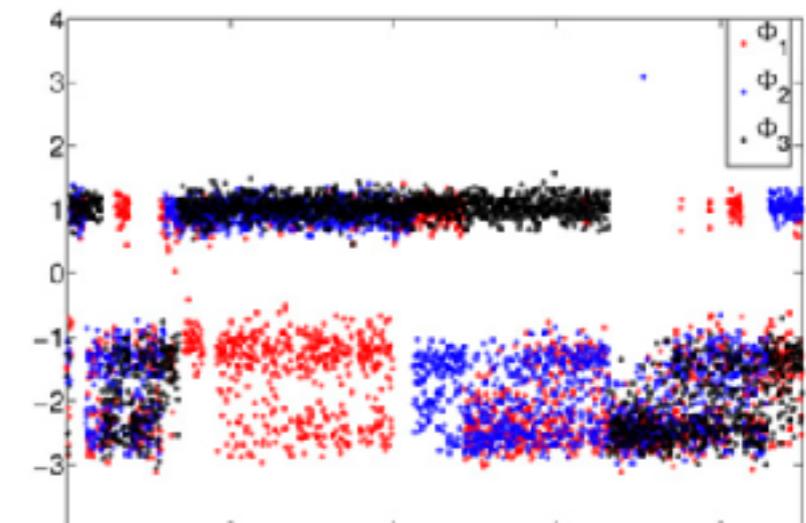
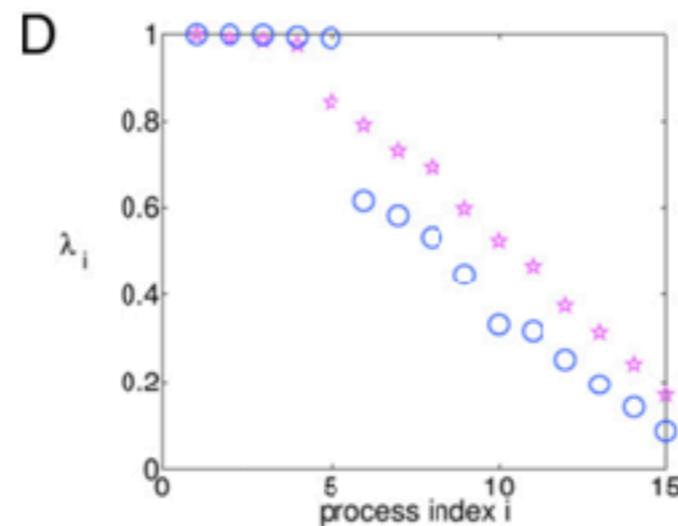
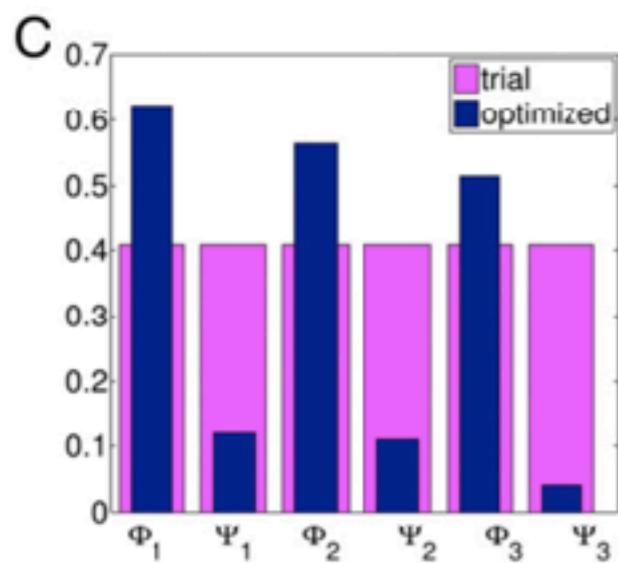
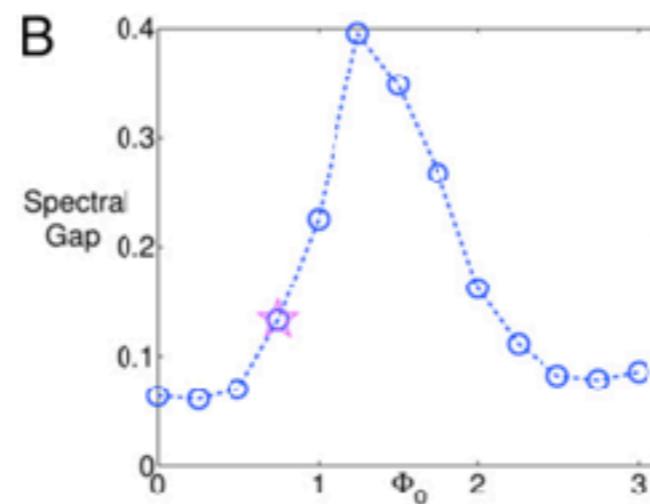
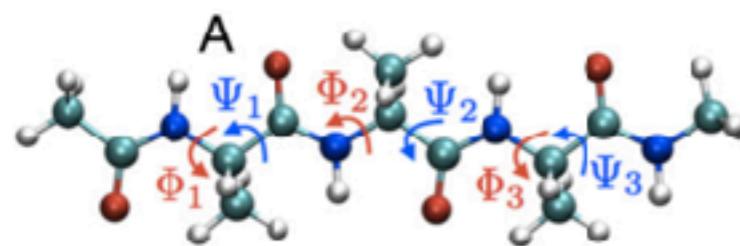
Branduardi, Gervasio, Parrinello *JCP* (2007)

Bonomi, Branduardi, Gervasio, Parrinello *JACS* (2008)

# Spectral-gap optimized Collective Variables

Toward & Berne PNAS (2016)

Optimize the mixing coefficients of a large set of CVs



# Parallel Bias Metadynamics

Pfaendtner & Bonomi JCTC (2015)

Biasing a large number of CVs with WTMetaD is inefficient

In PBMetaD we apply multiple low-dimensional bias potentials:

$$V(S_1, t), \dots, V(S_N, t)$$

one at a time:

$$P_t(\mathbf{R}, \eta) \propto \exp \left[ -\beta \left( U(\mathbf{R}) + \sum_i \eta_i V(S_i, t) \right) \right]$$

where  $\eta = (\eta_1, \dots, \eta_N)$  switches on and off (and allows updating) one bias potential at a time

Each bias potential converges to the corresponding free energy:

$$V(S_i, t) \rightarrow -\frac{\Delta T}{T + \Delta T} F(S_i)$$

# Parallel Bias Metadynamics

Pfaendtner & Bonomi JCTC (2015)

Since we are not interested in the  $\eta$ -distribution, we can marginalize this variable:

$$P_t(\mathbf{R}) = \int d\eta P_t(\mathbf{R}, \eta) \propto \exp [-\beta (U(\mathbf{R}) + V_{PB}(\mathbf{S}, t))]$$

where:

$$V_{PB}(\mathbf{S}, t) = -\frac{1}{\beta} \log \sum_{i=1}^N \exp - [\beta V(S_i, t)]$$

In order for each bias potential to converge to the corresponding free energy, we need a new rescaling rule:

$$\omega_i = \omega_{0,i} e^{-\frac{V(S_i, t)}{k_B \Delta T_i}} P(\eta_i = 1 | \mathbf{R})$$

where:

$$P(\eta_i = 1 | \mathbf{R}) = \frac{\exp [-\beta V(S_i, t)]}{\sum_{j=1}^N \exp [-\beta V(S_j, t)]}$$

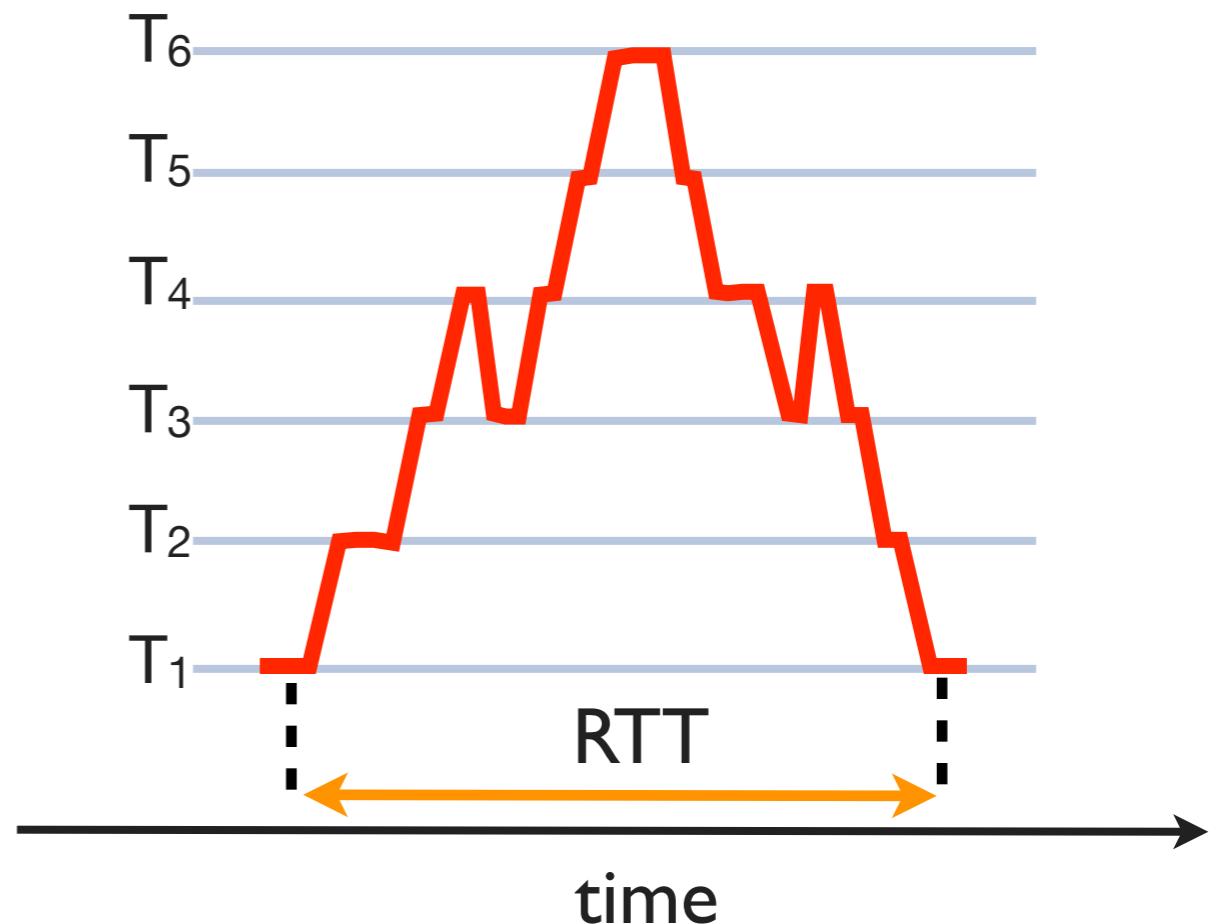
# Parallel Tempering and...

- N replicas at different  $T_i$
- Exchange configurations with a Metropolis criteria:

$$p(j \rightarrow k) = \min\{1, e^{\Delta_{j,k}}\}$$

with:

$$\Delta_{j,k} = (\beta_j - \beta_k)(U(\mathbf{R}_j) - U(\mathbf{R}_k))$$



- Prevent cold replicas to get trapped in local energy minima

Hansmann, Chem. Phys. Lett. (1997)  
Sugita and Okamoto, Chem. Phys. Lett. (1997)

# ... Metadynamics together

Bussi, Gervasio, Laio, Parrinello *JACS* (2006)

- N replicas at different T
- Same CVs, different bias potential
- Modified exchange probability:

$$\begin{aligned}\Delta_{j,k} = & (\beta_j - \beta_k)(U(\mathbf{R}_j) - U(\mathbf{R}_k)) \\ & + \beta_j[V_G^{(j)}(\mathbf{S}(\mathbf{R}_j), t) - V_G^{(j)}(\mathbf{S}(\mathbf{R}_k), t)] \\ & + \beta_k[V_G^{(k)}(\mathbf{S}(\mathbf{R}_k), t) - V_G^{(k)}(\mathbf{S}(\mathbf{R}_j), t)]\end{aligned}$$

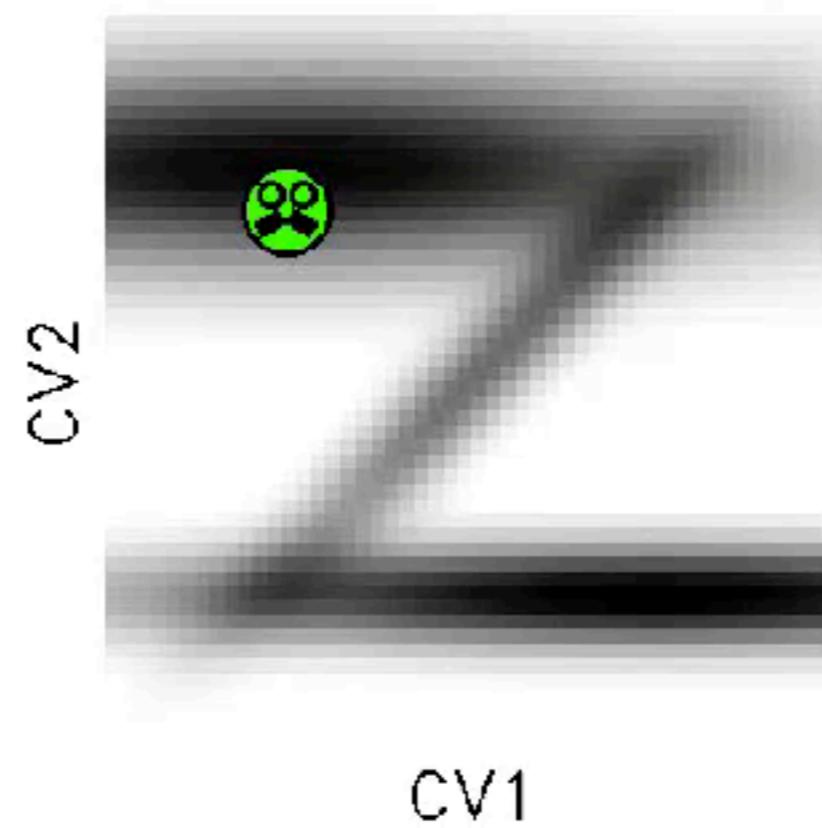
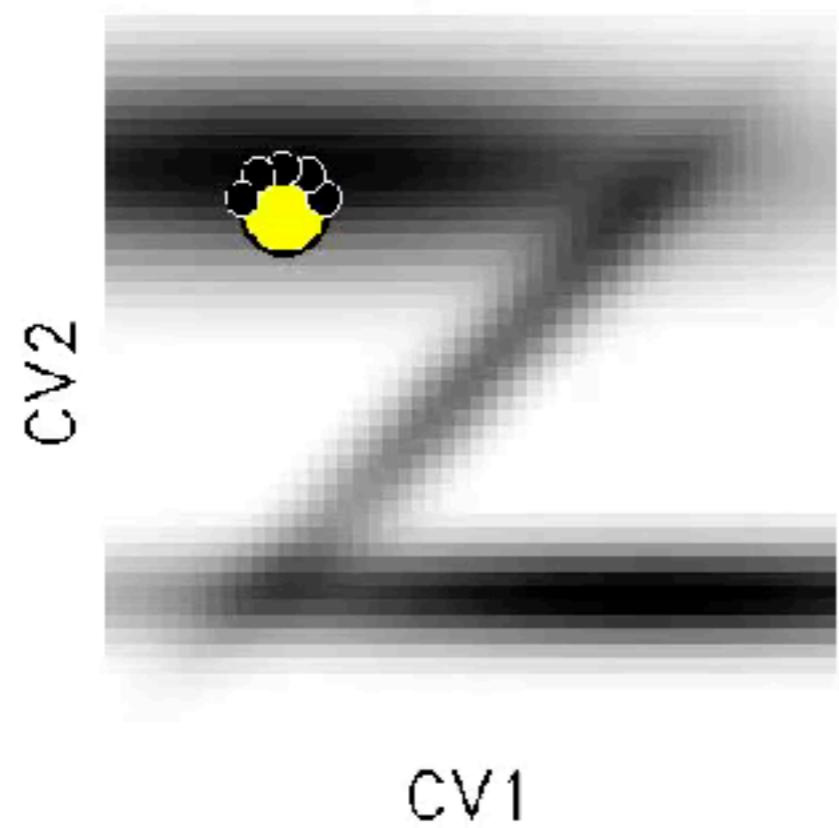
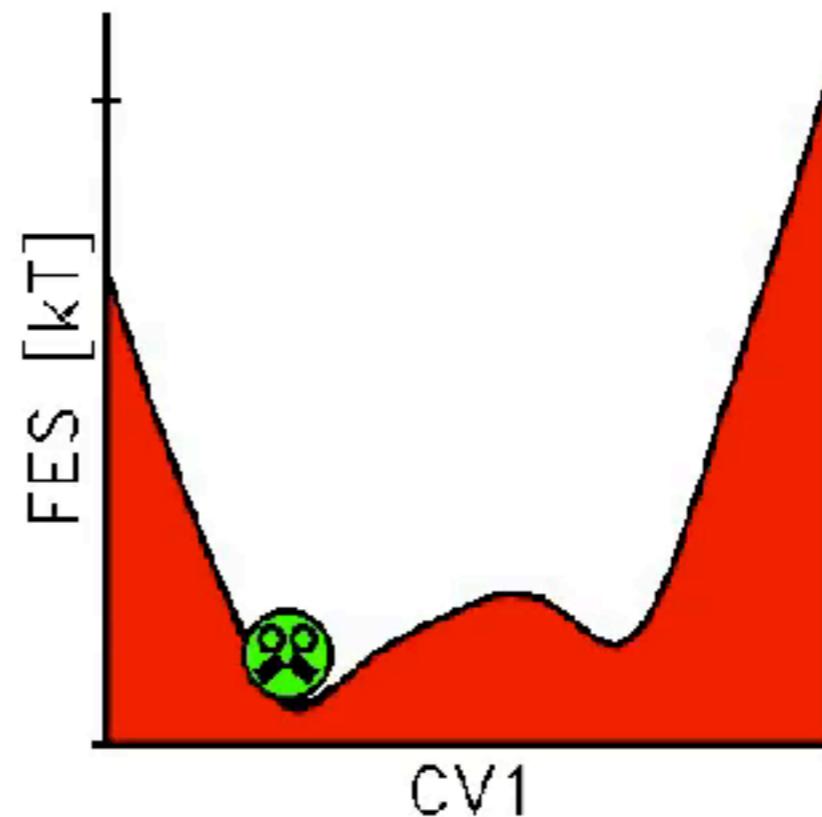
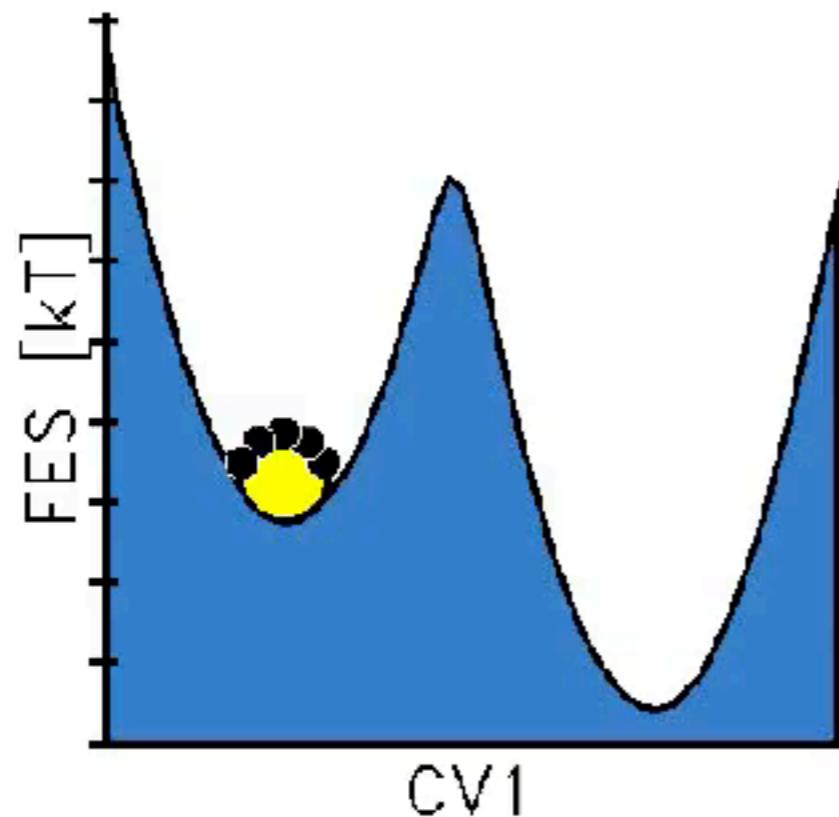
**MetaD**: cross high barriers in a few selected degrees of freedom



**PT**: cross moderate barriers along all degrees of freedom



The combination improves both methods!



movie by G. Bussi

# How to calculate free-energies

## Free-energy reconstruction with SUM\_HILLS

$$V(S, t \rightarrow \infty) = -\frac{\Delta T}{T + \Delta T} F(S) + C$$

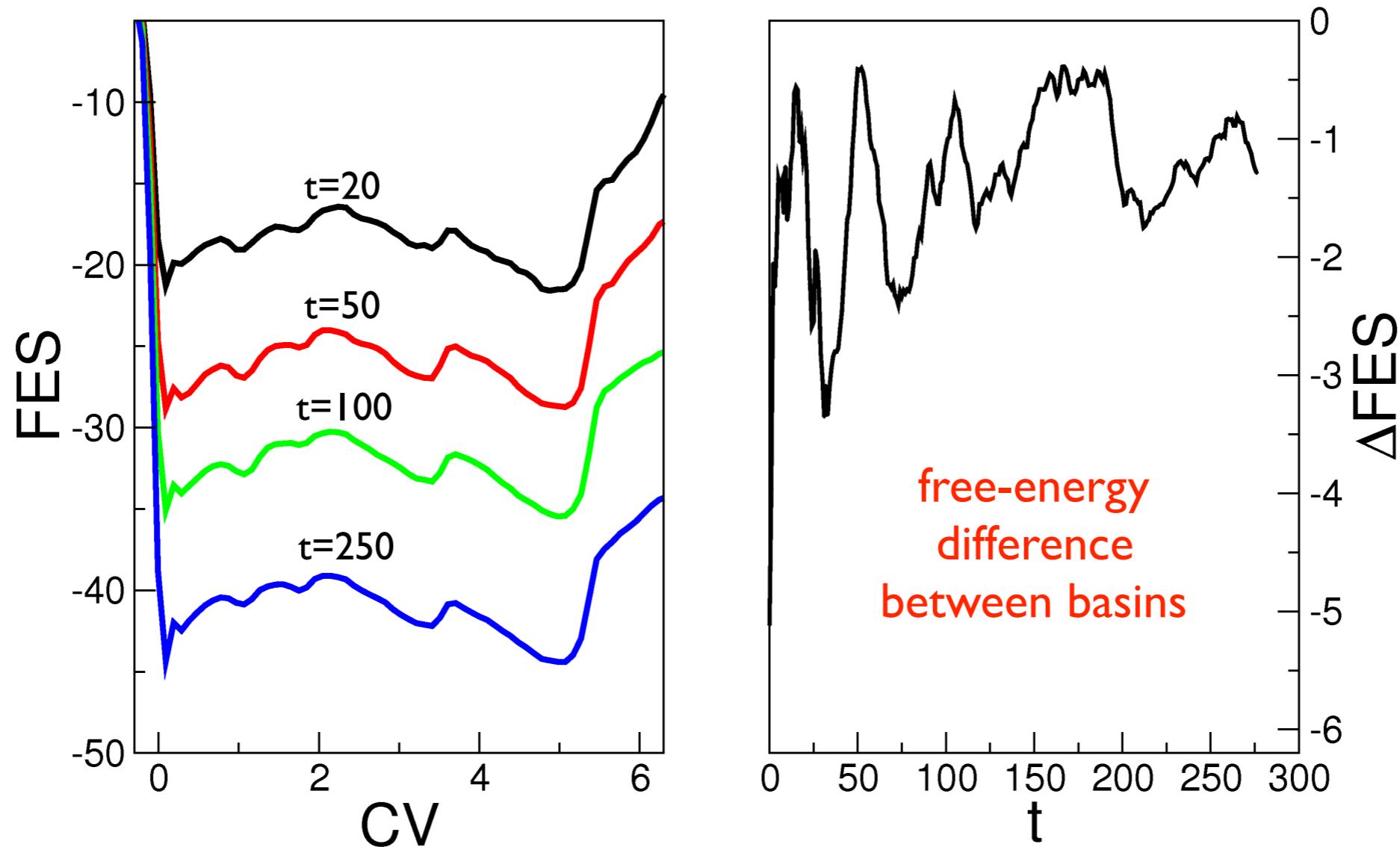
Usage: `sum_hills [options]`

The following options are available

```
--help/-h - ( default=off ) print this help
--help-debug - ( default=off ) print special options that can be used to
               create regtests
--negbias - ( default=off ) print the negative bias instead of the free
               energy (only needed with welltempered runs and flexible hills)
--nohistory - ( default=off ) to be used with --stride: it splits the
               bias/histogram in pieces without previous history
--mintozero - ( default=off ) it translate all the minimum value in
               bias/histogram to zero (usefull to compare results)
--hills - specify the name of the hills file
--histo - specify the name of the file for histogram a colvar/hills
          file is good
--stride - specify the stride for integrating hills file (default
          0=never)
```

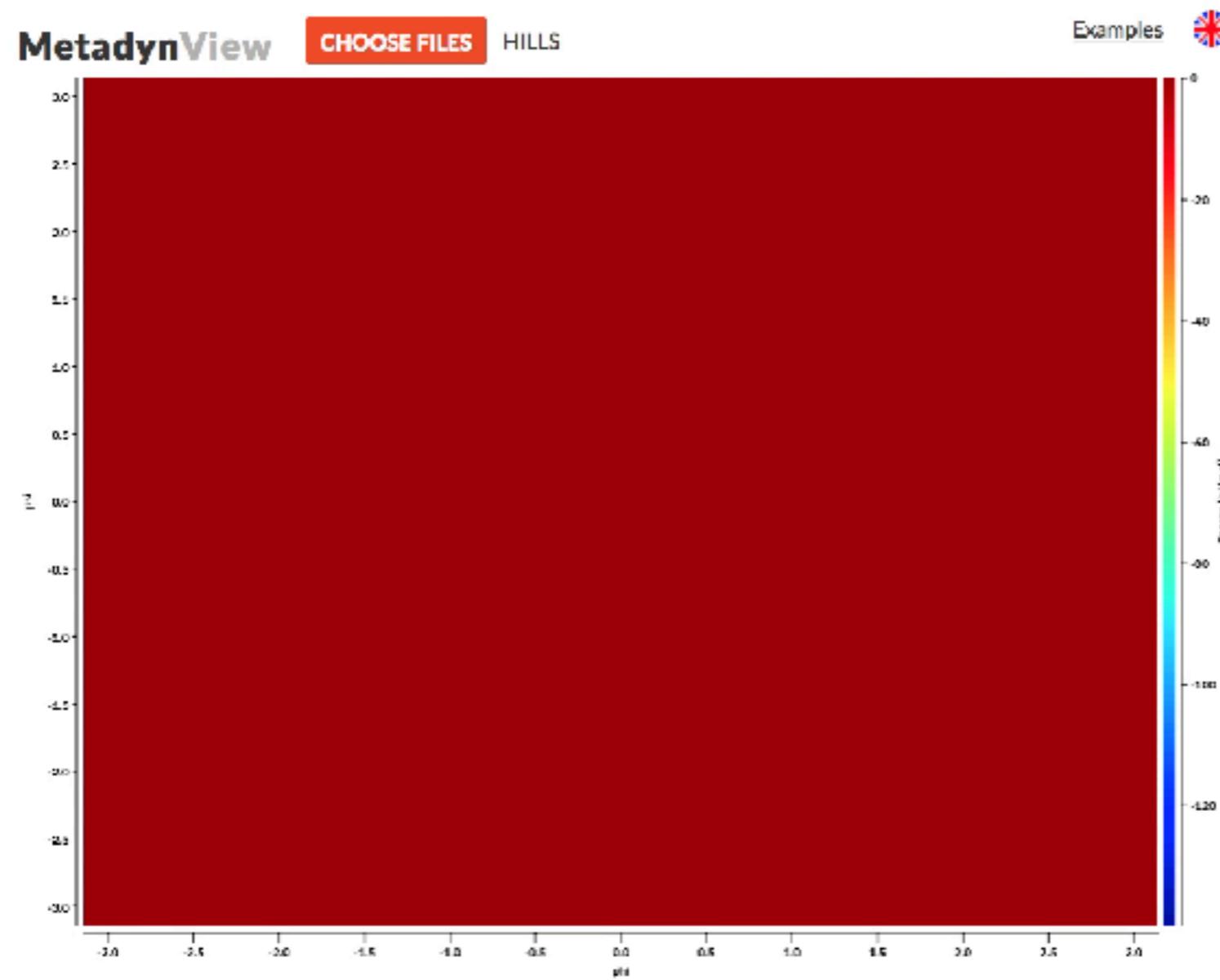
# How to monitor convergence

Qualitative indication of convergence from the analysis of the free-energy estimate as a function of time



# How to monitor convergence

or with a cool web server, like Metadyn View



# How to quantitatively estimate convergence

We need a quantitative measure of convergence

**ANY IDEAS?**

# Reweighting WT-MetaD simulations

At convergence, we have  $F(\mathbf{S})$

From this, the ensemble average of any function of the CVs can be calculated:

$$P_B(\mathbf{S}) \propto e^{-\beta F(\mathbf{S})} \quad \langle g(\mathbf{S}) \rangle = \frac{\int d\mathbf{S} g(\mathbf{S}) e^{-\beta F(\mathbf{S})}}{\int d\mathbf{S} e^{-\beta F(\mathbf{S})}}$$

What about the other “fast” degrees of freedom?

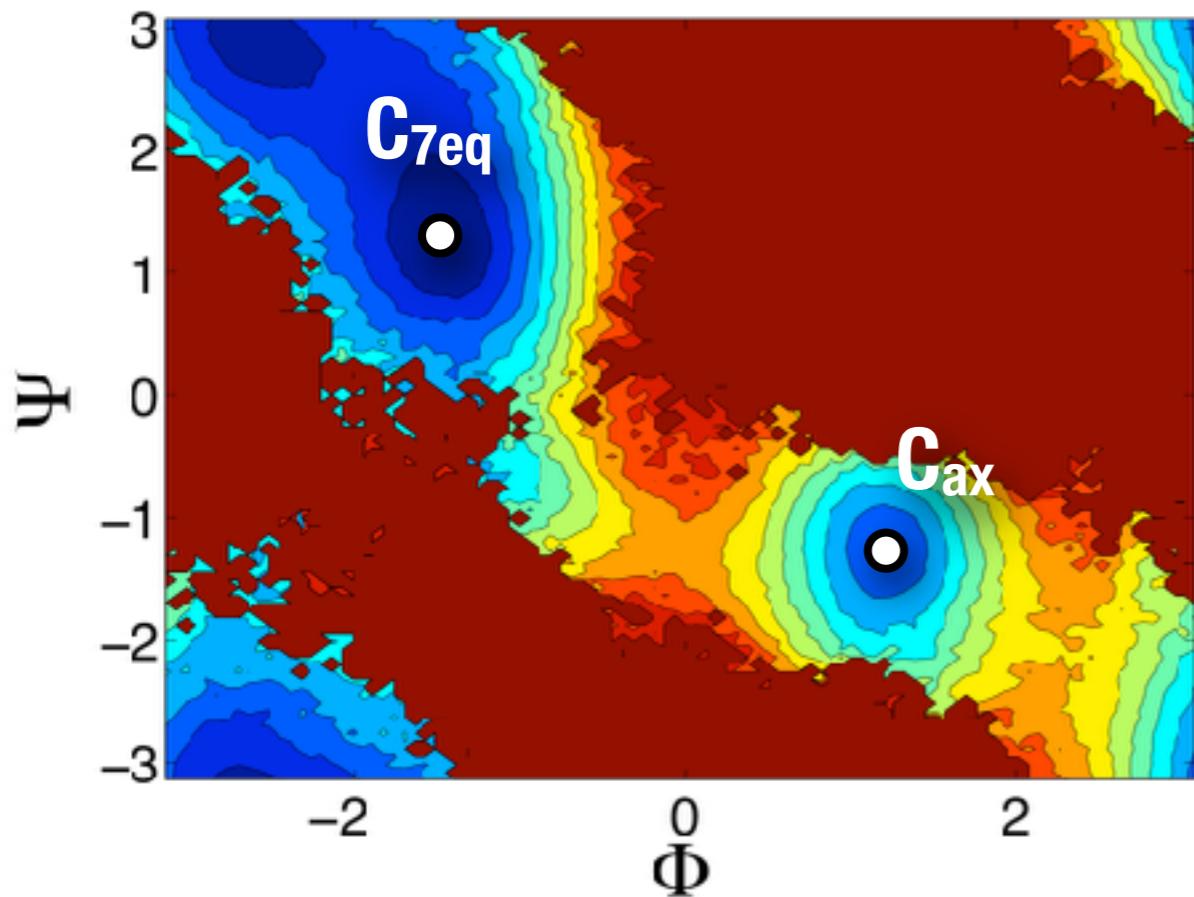
Their probability distribution is distorted in a non-trivial way

- With a static bias:  $P_B(\mathbf{R}) \propto P(\mathbf{R}) e^{\beta V(S(\mathbf{R}))}$
- MetaD bias is time-dependent!

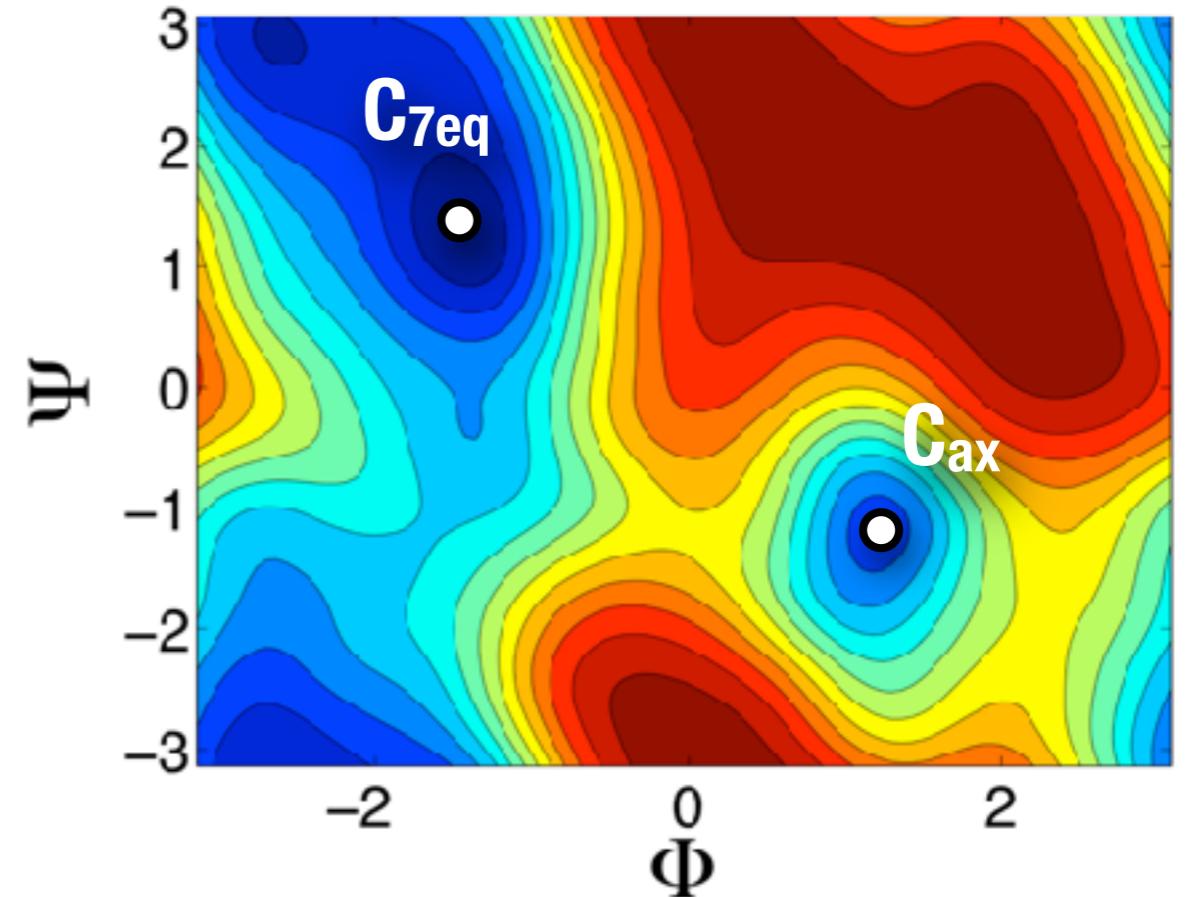


# Reweighting WT-MetaD simulations

1 CV + reweight



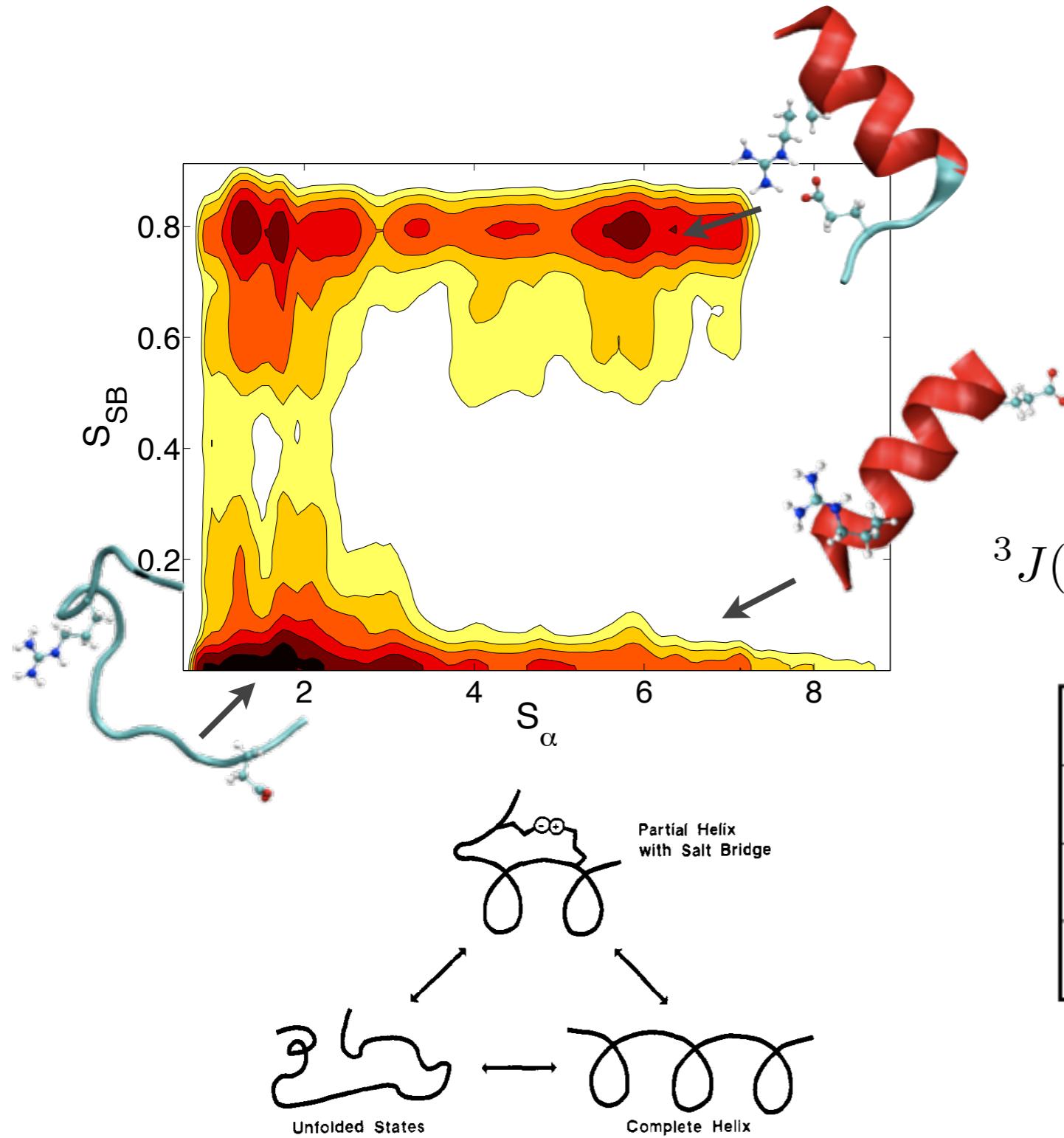
2 CVs



A two-dimensional free energy is obtained from a well-tempered metadynamics simulation using only one CV

Reweighting is useful in several situations!

# Linking simulations with experiments



Calculate average scalar  
couplings  ${}^3J$  from WT-MetaD  
simulations

$${}^3J(\Phi) = A\cos^2(\Phi + \Delta) + B\cos(\Phi + \Delta) + C$$

	$\chi^2$
PTMetaD Open	0.88
PTMetaD Closed	0.92
$\langle MD \rangle$	3.29

Caballero et al. *Biophys. J.* (2005)

Barducci, Bonomi and Parrinello *Biophys. J.* (2010)

# Reweighting schemes

## Three possible approaches for WT-MetaD\*

### Reconstructing the Equilibrium Boltzmann Distribution from Well-Tempered Metadynamics

JCC 2009

M. BOINOMI, A. BARDUCCI, M. PARRINELLO

*Computational Science, Department of Chemistry and Applied Biosciences, ETH Zurich,  
c/o USI Campus, via Buffi 13, CH-6900 Lugano, Switzerland*

2

### A Time-Independent Free Energy Estimator for Metadynamics

Pratyush Tiwary\* and Michele Parrinello

Department of Chemistry and Applied Biosciences, ETH, 8092 Zurich, Switzerland  
Facoltà di Informatica, Istituto di Scienze Computazionali, Università della Svizzera Italiana, Via G. Buffi 13, 6900 Lugano, Switzerland

JPCB 2014

3

### Metadynamics with Adaptive Gaussians

Davide Branduardi,<sup>†</sup> Giovanni Bussi,<sup>\*‡</sup> and Michele Parrinello<sup>§||</sup>

<sup>†</sup>Theoretical Molecular Biophysics Group, Max Planck Institute for Biophysics, Max-von-Laue strasse 5, 60438, Frankfurt am Main, Germany

<sup>‡</sup>SISSA - Scuola Internazionale Superiore di Studi Avanzati, via Bonomea 265, 34136, Trieste, Italy

<sup>\*</sup>Department of Chemistry and Applied Biosciences, ETH Zurich, Via G. Buffi 13, 6900, Lugano, Switzerland

<sup>§</sup>Facoltà di Informatica, Istituto di Scienze Computazionali, Università della Svizzera Italiana, Via G. Buffi 13, 6900, Lugano, Switzerland

JCTC 2012

# Plumed 1.3

# Method I

Assuming a slow-growth regime, we evolve the “biased” probability distribution during the simulation:

$$P(\mathbf{R}, t + \Delta t) = e^{-\beta (\dot{V}_G(\mathbf{S}(\mathbf{R}), t) - \langle \dot{V}_G(\mathbf{S}(\mathbf{R}), t) \rangle) \Delta t} P(\mathbf{R}, t)$$

↑      ↑  
 the new Gaussian      average  
 calculated in the biased ensemble

Finally we estimate the Boltzmann probability distribution like in umbrella sampling reweighting:

$$P_B(\mathbf{R}) \propto e^{+\beta V_G(S(\mathbf{R}), t)} P(\mathbf{R}, t)$$

## Plumed 2

## Method 2

The average of any function of the microscopic coordinates is obtained from the bias potential and a reweighing factor:

$$\langle O(\mathbf{R}) \rangle_0 = \langle O(\mathbf{R}) e^{\beta(V(s(\mathbf{R}, t) - c(t)))} \rangle$$

where the reweighing factor is obtained from the bias potential:

$$\begin{aligned} e^{\beta c(t)} &\approx \frac{\tau(t + \Delta t) - \tau(t)}{\Delta t} = \frac{k_B \Delta T}{\gamma \omega \Delta t (2\pi)^{d/2} \det \sigma} \\ &= \int d\mathbf{s} [e^{\gamma V(s, t + \Delta t) / k_B \Delta T} - e^{\gamma V(s, t) / k_B \Delta T}] \end{aligned}$$

## Plumed 2

## Method 3

This method is based on the following relation between free energy, bias potential, and histogram accumulated in the biased ensemble:

$$\begin{aligned}\tilde{F}_N(s, t) = & -T \ln N(s, t) - V(s, t) \\ & + T \ln \int ds' N(s', t)\end{aligned}$$

Strictly-true when bias is time-independent and coincides with the umbrella-sampling reweighting recipe

In practice, the bias at the end of the simulation (at convergence) is used to reweigh all conformations generated by the metadynamics simulation using the relation above

# How to quantitatively estimate convergence

We seeks to quantify the error in the estimated free energy if we stop the simulation at a given time

We use a reweighing approach to estimate the free energy as a function of the metadynamics CV

Methods 2 and 3 are more convenient, as they provide the “unbiasing weight” for each conformation

We use block analysis to estimate the error in the reconstructed free energy

# Summary

- Theory of metadynamics and its well-tempered variant
- Setup a metadynamics simulation with PLUMED:
  - the PLUMED input file
  - choosing the basic parameters
  - choosing the collective variables
- Calculate free energies
- Overview of methods to reweigh metadynamics simulations
- Block analysis and assessing convergence

# Tutorial instructions



[plumed.github.io/doc-master/user-doc/html/trieste-4.html](https://plumed.github.io/doc-master/user-doc/html/trieste-4.html)