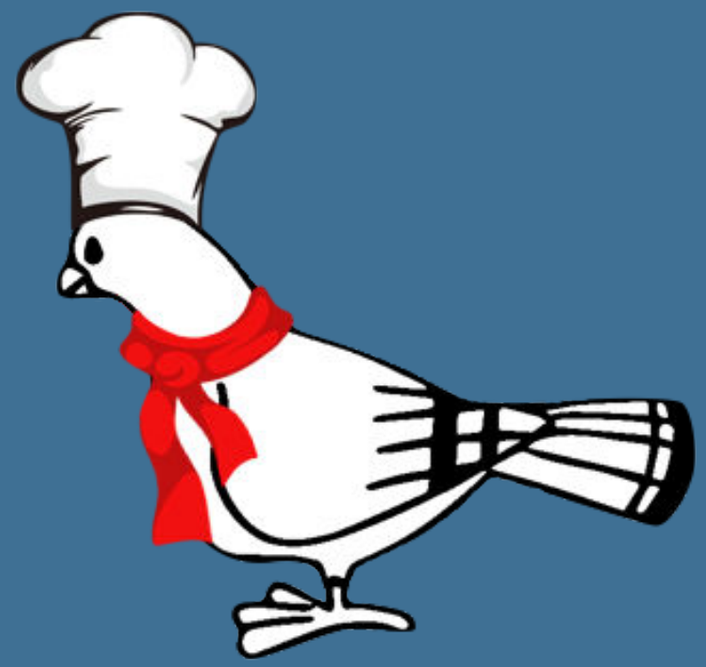


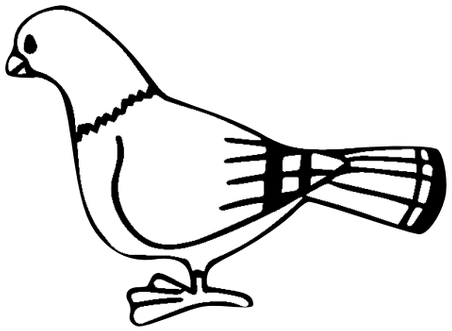
PLUMED Masterclass

21.4: Metadynamics

Max Bonomi
Institut Pasteur - CNRS
mbonomi@pasteur.fr
@BonomiMax

INSTITUT PASTEUR

cnrs



PLUMED

open-source
freely-available
C++ library

- enhanced-sampling methods
- free-energy methods
- analysis MD data

www.plumed.org

@plumed_org

Bonomi *et al.* CPC 2009
Tribello *et al.* CPC 2014

Gareth Tribello

Max Bonomi

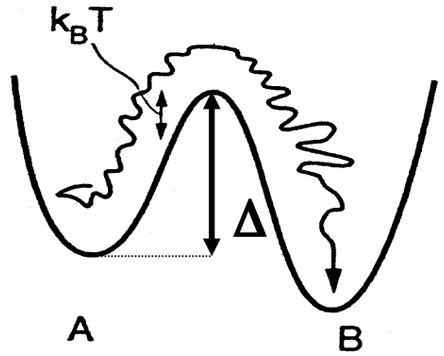
Carlo Camilloni

Giovanni Bussi

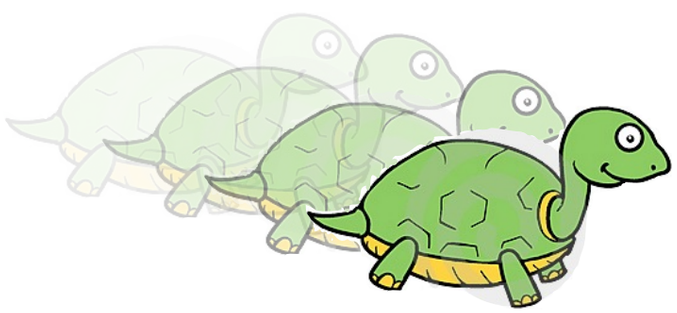
The time scale problem

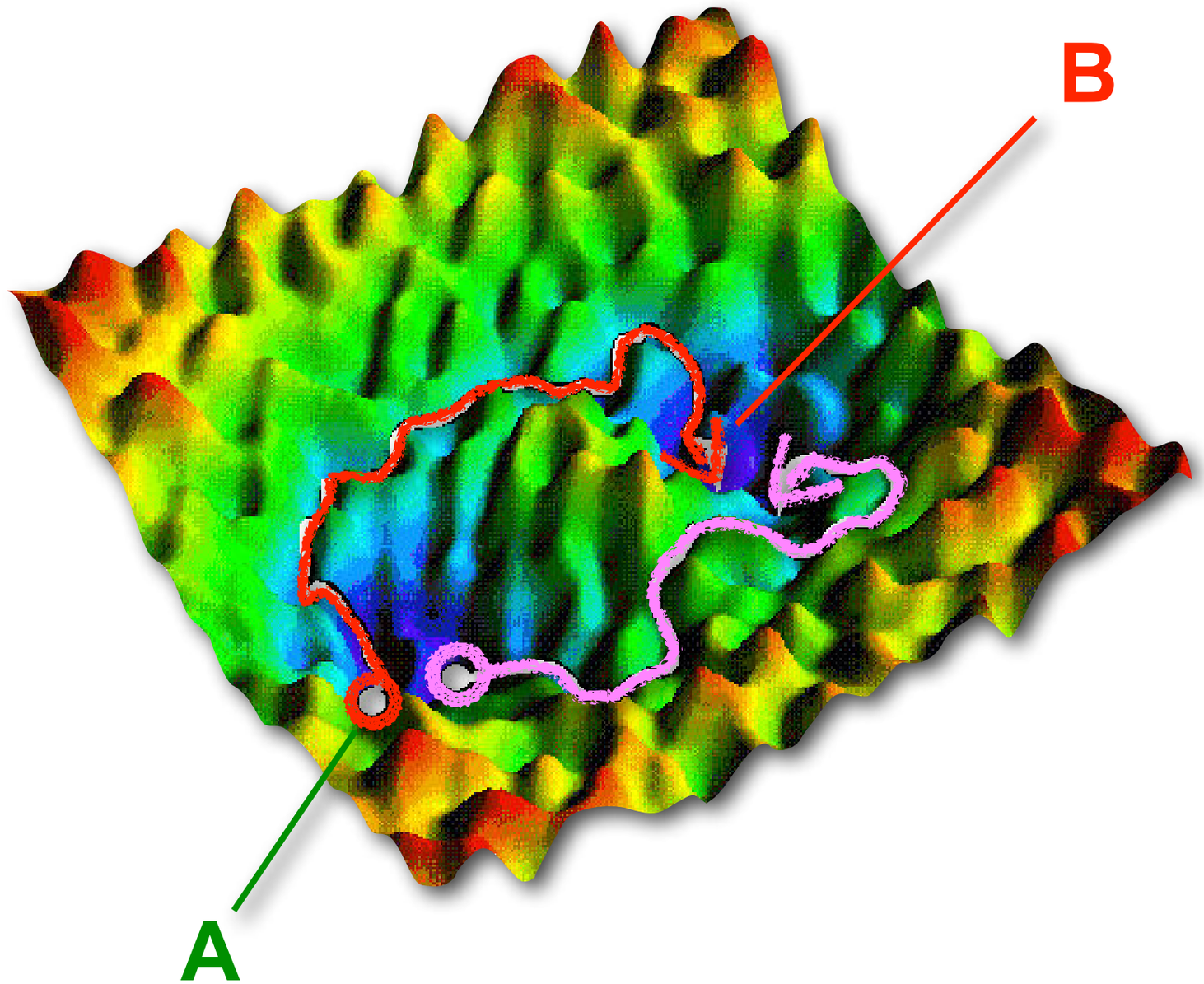
Sampling capability of MD and MC is limited by the time scale accessible in "standard" simulations:

★ Activated events



★ Slow diffusion





Dimensionality reduction

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

$$\boldsymbol{S} = \boldsymbol{S}(\boldsymbol{R}) = (S_1(\boldsymbol{R}), \ldots, S_d(\boldsymbol{R}))$$

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

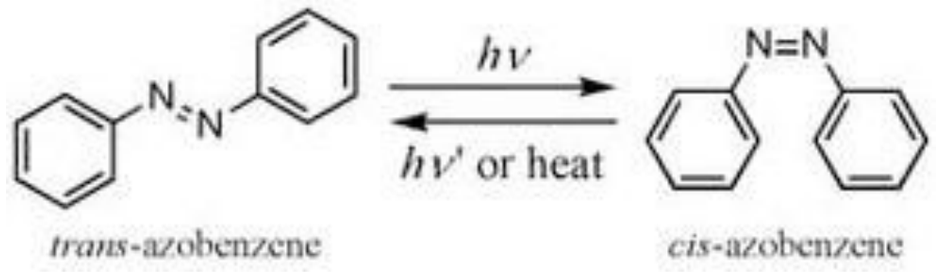
$$F(\boldsymbol{S}) = -\frac{1}{\beta} \ln P(\boldsymbol{S}) \quad \text{where} \quad \beta = \frac{1}{k_B T}$$

canonical ensemble

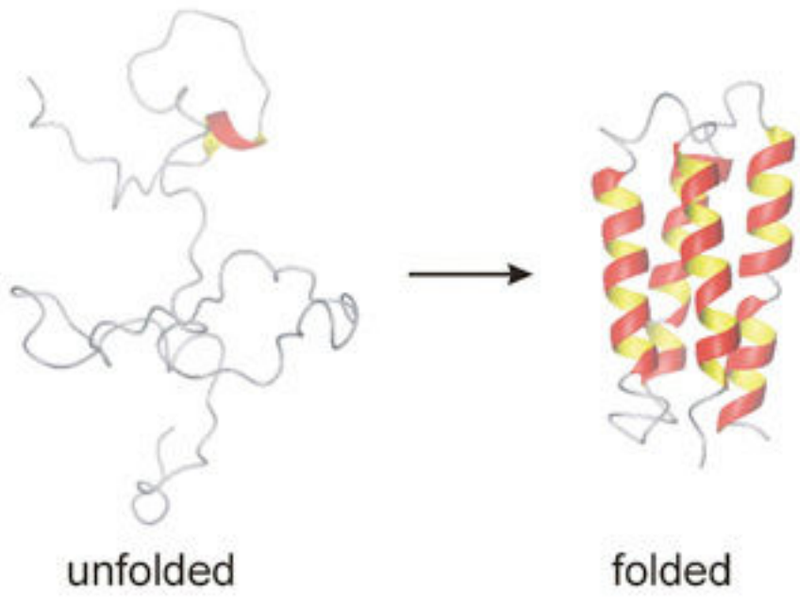
$$P(\boldsymbol{S}) = \frac{\int d\boldsymbol{R}\, \delta(\boldsymbol{S} - \boldsymbol{S}(\boldsymbol{R}))\, e^{-\beta U(\boldsymbol{R})}}{\int d\boldsymbol{R}\, e^{-\beta U(\boldsymbol{R})}}$$

Examples

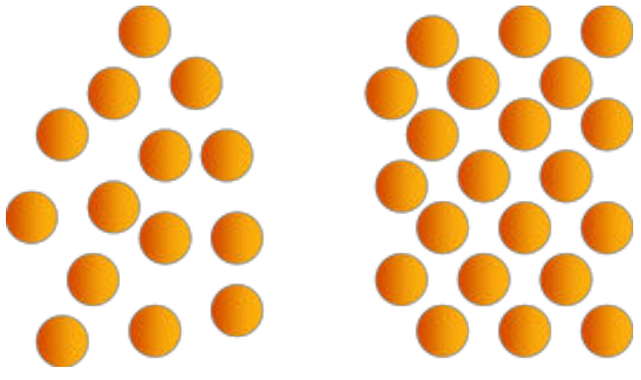
Isomerization:
dihedral angle



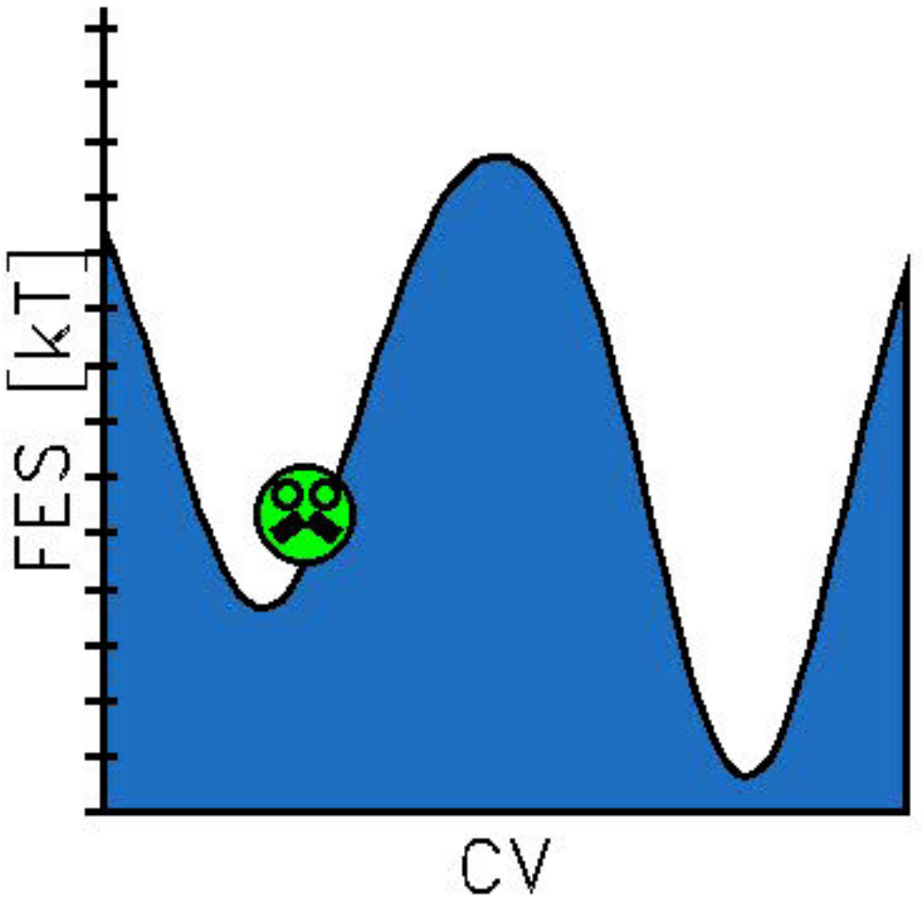
Protein folding:
gyration radius,
number of contacts,
...



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



Biased sampling



Movies by
G. Bussi

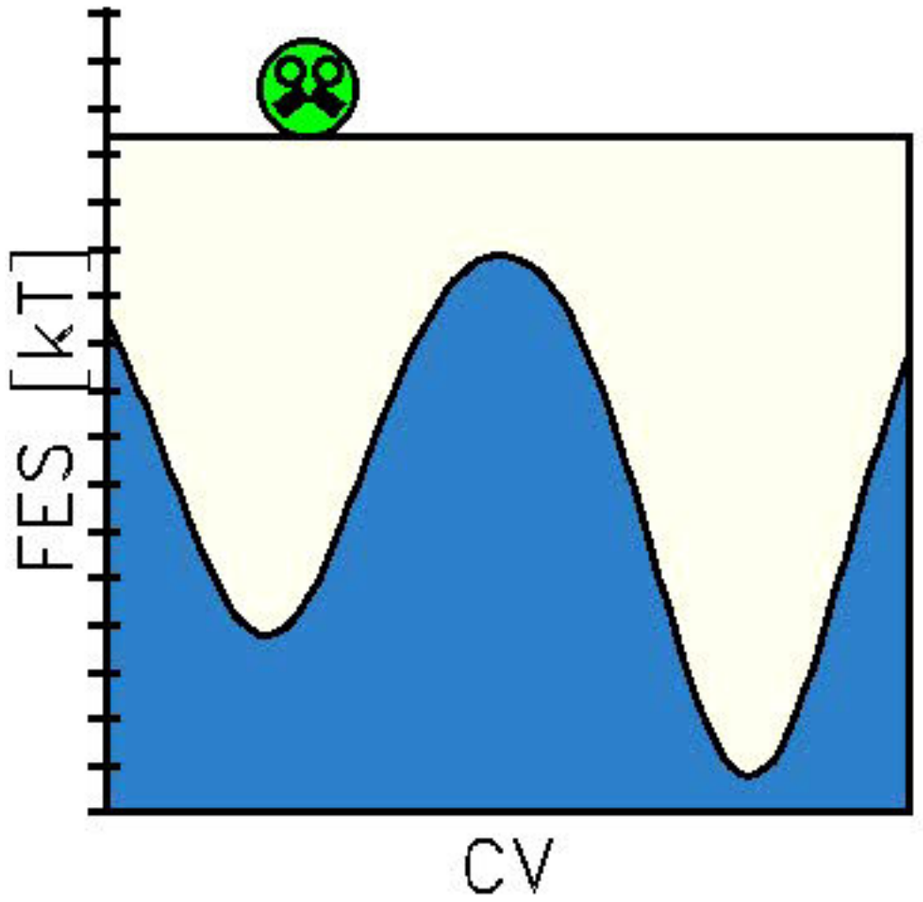
The idea is to add a bias potential that acts on the collective variables:

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

What is a good choice of bias potential?

Umbrella sampling

What is a good choice of bias potential?



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

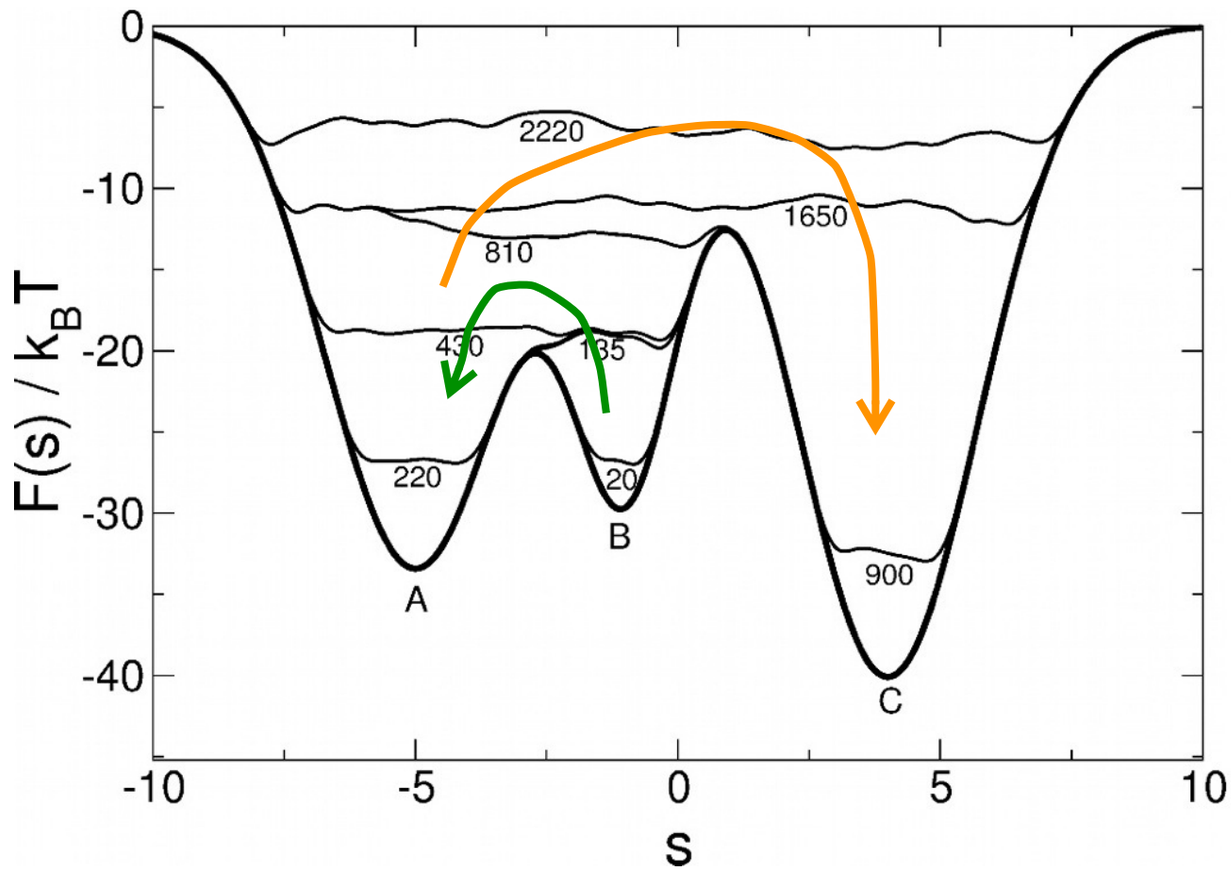
Metadynamics idea: build on-the-fly an approximation of the free energy and use it as bias potential

Torrie & Valleau JCP (1977)

Metadynamics: the actual equations

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

$$\boldsymbol{S} = (S_1(\boldsymbol{R}), ..., S_d(\boldsymbol{R}))$$



and built as a sum of Gaussians:

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

Laio & Parrinello PNAS 2002

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

Metadynamics parameters

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

1 2 3

Which parameters do we need to choose?

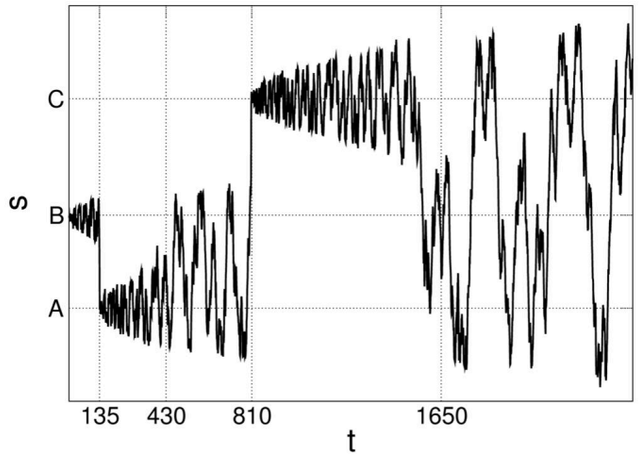
1. Collective variables $\boldsymbol{S} = (S_1(\boldsymbol{R}), ..., S_d(\boldsymbol{R}))$
2. Energy rate W, τ_G
3. Gaussian width σ_i

Pros and Cons

Advantages

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

$$V_G(\boldsymbol{S}, t \to \infty) = -F(\boldsymbol{S}) + C$$



Bussi, Laio, Parrinello PRL (2006)

- *A priori* knowledge of the landscape not required

Disadvantages

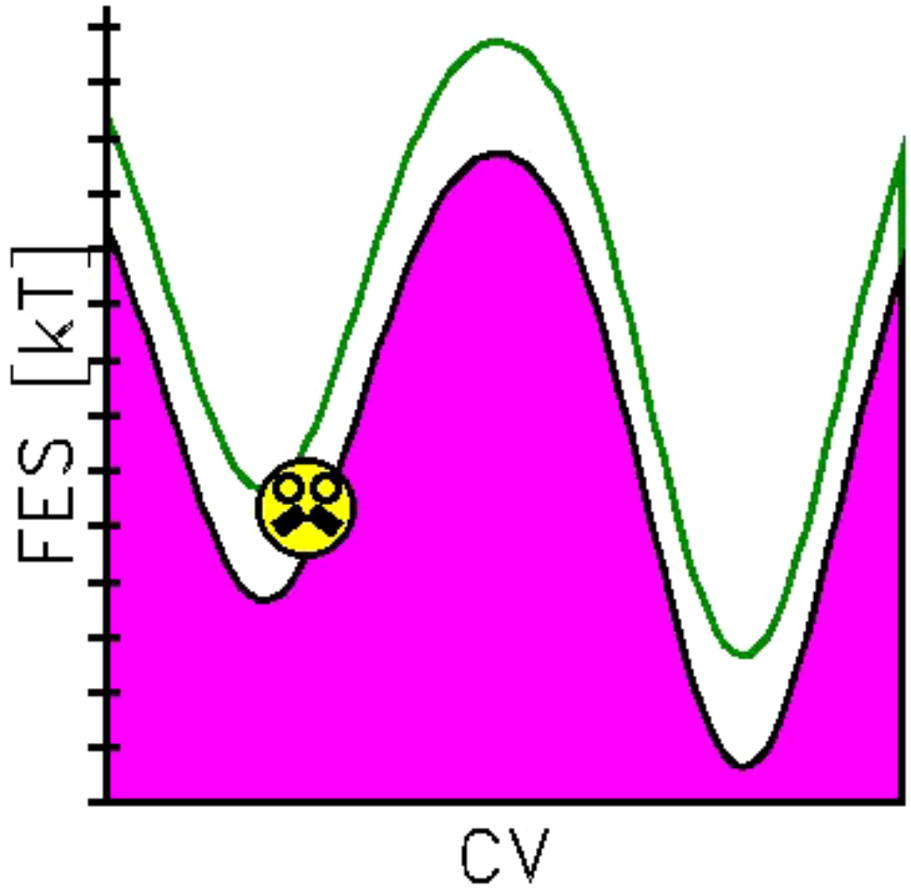
- Lack of convergence in a single run
- Overfilling
- The choice of the CVs is not trivial

Well-Tempered Metadynamics

The initial Gaussian height W_0 is rescaled during the simulation:

$$W = W_0 \, e^{-\frac{V_G(\mathbf{s},t)}{k_B \Delta T}}$$

where $T + \Delta T$ is a fictitious CV temperature.



- Convergence and overfilling issues solved:

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

- ΔT can be used to tune the extent of exploration

Barducci, Bussi, Parrinello PRL 2008

Well-Tempered Metadynamics parameters

$$W = W_0 \, e^{-\frac{V_G(\mathbf{S},t)}{k_B \Delta T}}$$

1

2

1. Initial Gaussian height W_0

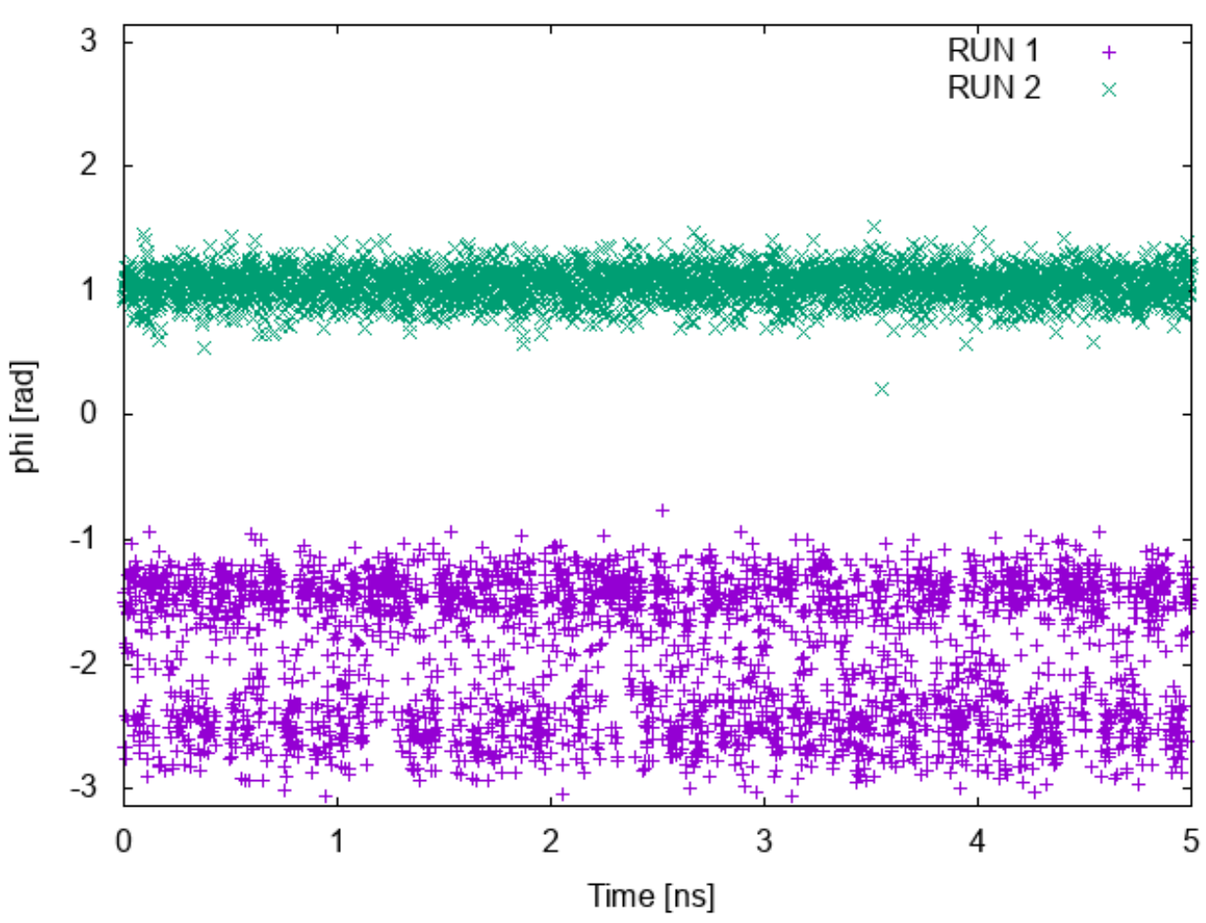
2. How fast the amount of bias added decreases to zero

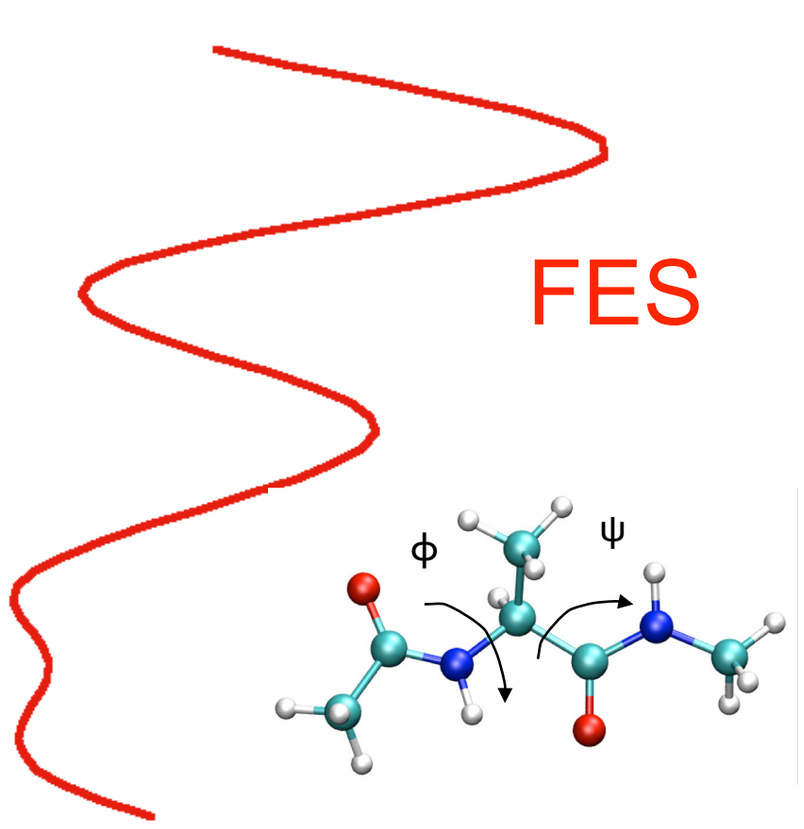
$$\begin{cases} T + \Delta T & \text{CV TEMPERATURE} \\ \dfrac{T + \Delta T}{T} & \text{BIAS FACTOR} \end{cases}$$

Guidelines for choosing sigma

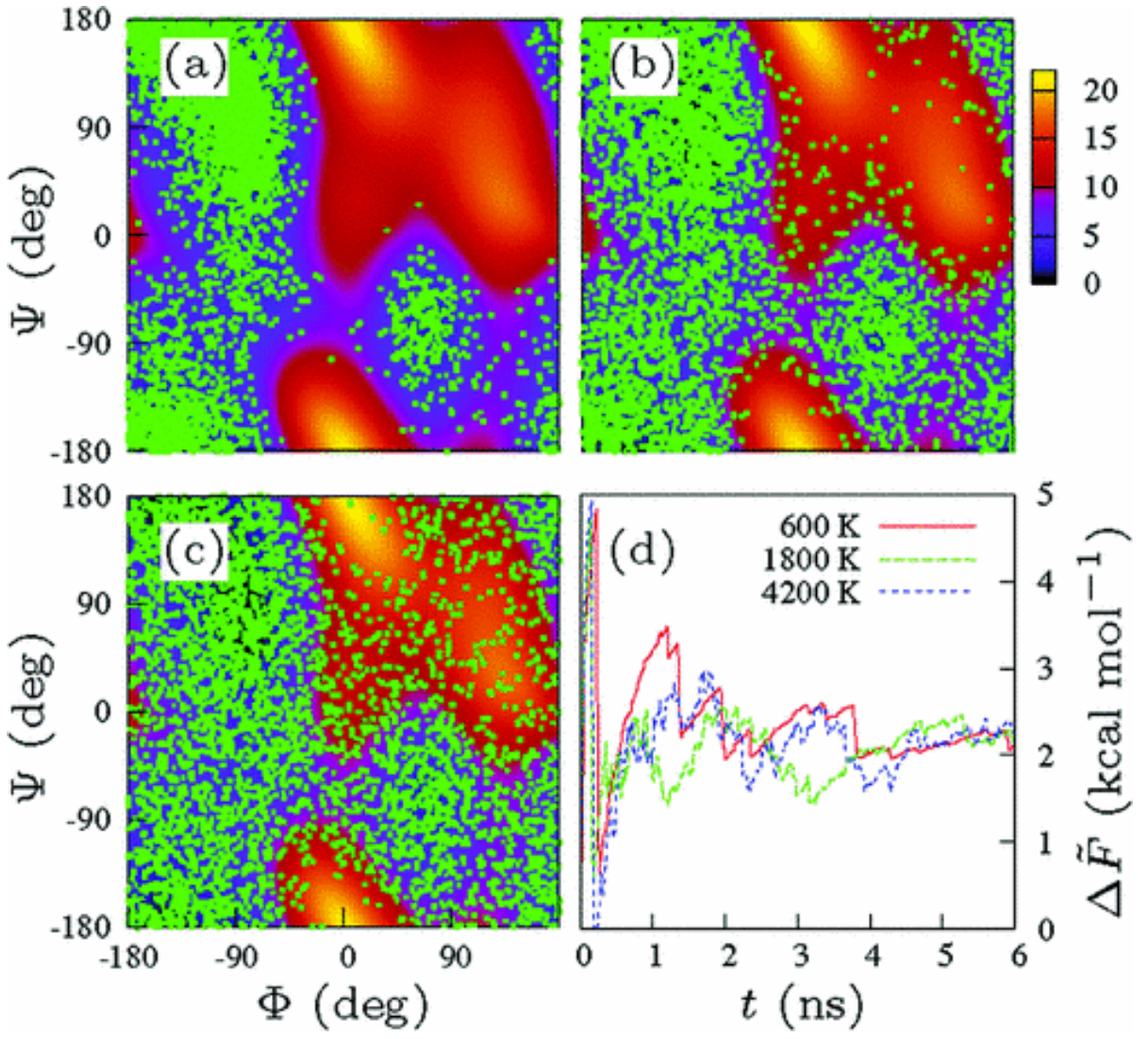
The width of the Gaussian should be commensurate to the typical size of the "features" of the free energy landscape

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





Guidelines for choosing the biasfactor



Determine the extent of free-energy exploration: it should be comparable to the typical free-energy barriers

Typical value for biological applications ~ 10

Barducci, Bussi, Parrinello PRL 2008

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

Reweighting WT-MetaD simulations

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

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

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

What about the other "fast" degrees of freedom?
Their probability distribution is distorted in a non-trivial way

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

Reweighting schemes

(At least) 4 possible approaches

1

Reconstructing the Equilibrium Boltzmann Distribution from Well-Tempered Metadynamics

M. BONOMI, 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

JCC 2009

2

Metadynamics with Adaptive Gaussians

Davide Branduardi,[†] Giovanni Bussi,[*,‡] and Michele Parrinello[§,∥]

[†]Theoretical Molecular Biophysics Group, Max Planck Institute for Biophysics, Max-von-Laue strasse 5, 60438, Frankfurt am Main, Germany

[‡]SISSA - Scuola Internazionale Superiore di Studi Avanzati, via Bonomea 265, 34136, Trieste, Italy

[§]Department of Chemistry and Applied Biosciences, ETH Zurich, Via G. Buffi 13, 6900, Lugano, Switzerland

[∥]Facoltà di Informatica, Istituto di Scienze Computazionali, Università della Svizzera Italiana, Via G. Buffi 13, 6900, Lugano, Switzerland

JCTC 2012

3

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

4

Iterative Unbiasing of Quasi-Equilibrium Sampling

F. Giberti,[*,†] B. Cheng,[‡] G. A. Tribello,[§] and M. Ceriotti[*,†]

[†]Laboratory of Computational Science and Modeling, Institute of Materials, École Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland

[‡]Trinity College, University of Cambridge, Cambridge CB2 1TQ, United Kingdom

[§]Atomistic Simulation Centre, School of Mathematics and Physics, Queen's University Belfast, Belfast, BT14 7EN, United Kingdom

JCTC 2020

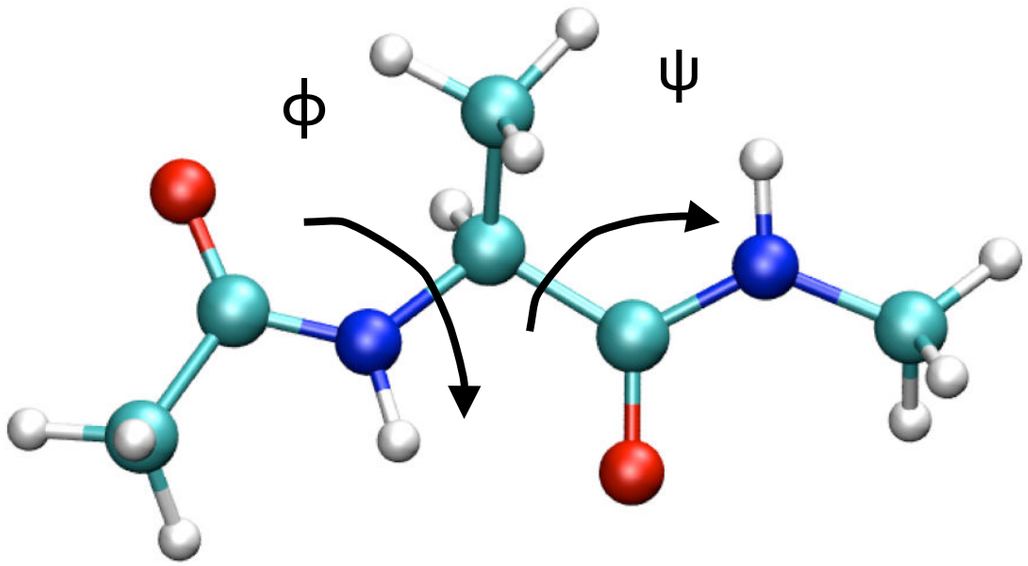
Instructions

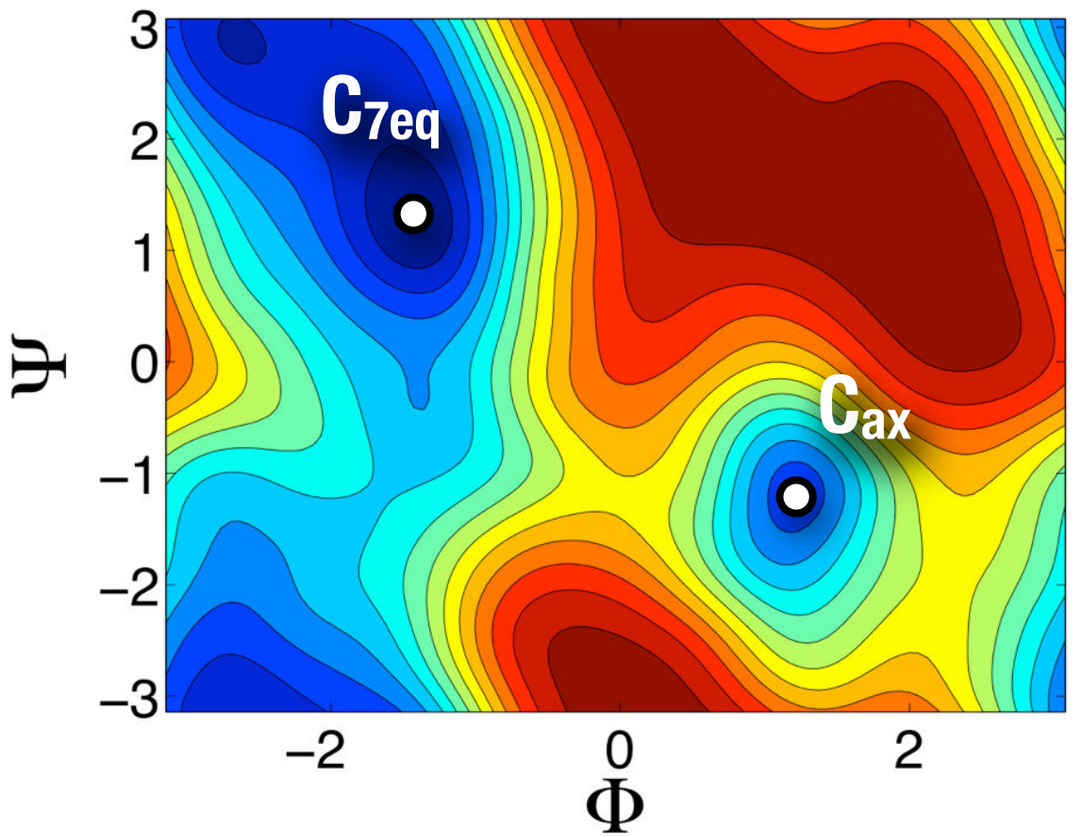
Class	Topic	Lecture I	Lecture II	Instructor
21.1	PLUMED syntax and analysis	January 18, 2021	January 25, 2021	M. Bonomi
21.2	Statistical errors in MD	February 1, 2021	February 8, 2021	G. Tribello
21.3	Umbrella sampling	February 15, 2021	February 22, 2021	G. Bussi
21.4	Metadynamics	March 1, 2021	March 8, 2021	M. Bonomi
21.5	Replica exchange methods	March 15, 2021	March 22, 2021	G. Bussi
21.6	Dimensionality reduction	April 12, 2021	April 19, 2021	G. Tribello
21.7	Performance optimization	April 26, 2021	May 3, 2021	M. Bonomi
21.8	Poster session	May 10, 2021		

1. Go to www.plumed.org
2. Click on the Masterclass tab
3. Click on the Topic of class 21.4
4. 1 week to complete the exercises
5. Questions/discussions on Slack channel masterclass-21-4
6. Lecture I and II available on YouTube

The molecule of the day

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