

Adaptively Biased Molecular Dynamics

Volodymyr Babin, Christopher Roland and Celeste Sagui

Department of Physics, NC State University,
Raleigh, NC 27695-8202

The Talk Outline:

- Problem statement
- Metadynamics (+ Applications)
- ABMD (+ Applications)

Problem Statement:

- Collective Variable

$$\sigma : \mathbb{R}^{3N} \mapsto \mathbb{Q}$$

- Its probability distribution

$$p(\xi) = \langle \delta[\xi - \sigma(\mathbf{r}_1, \dots, \mathbf{r}_N)] \rangle$$

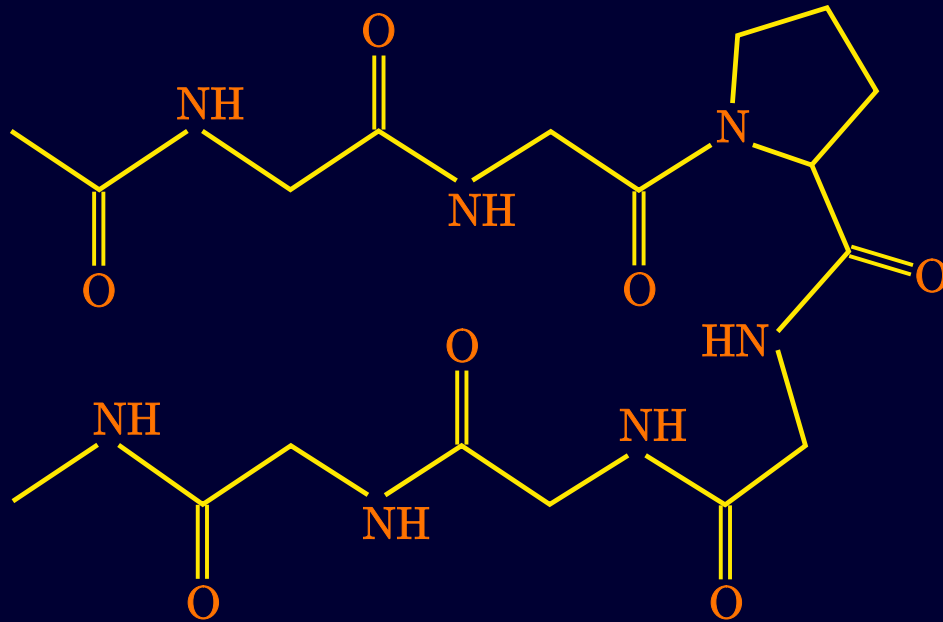
- Corresponding Free Energy (logdensity of ξ)

$$f(\xi) = -k_B T \ln p(\xi), \xi \in \mathbb{Q}$$

The Free Energy $f(\xi)$:

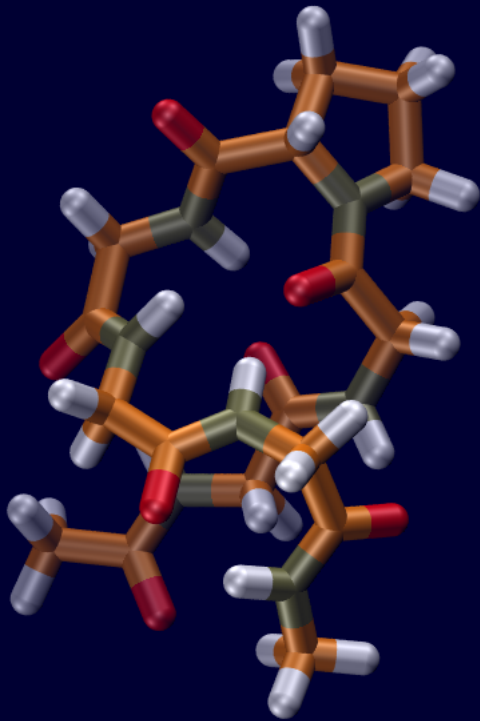
- Describes the relative stability of different states.
- Provides useful insights into the transitions between these states.

An Example:

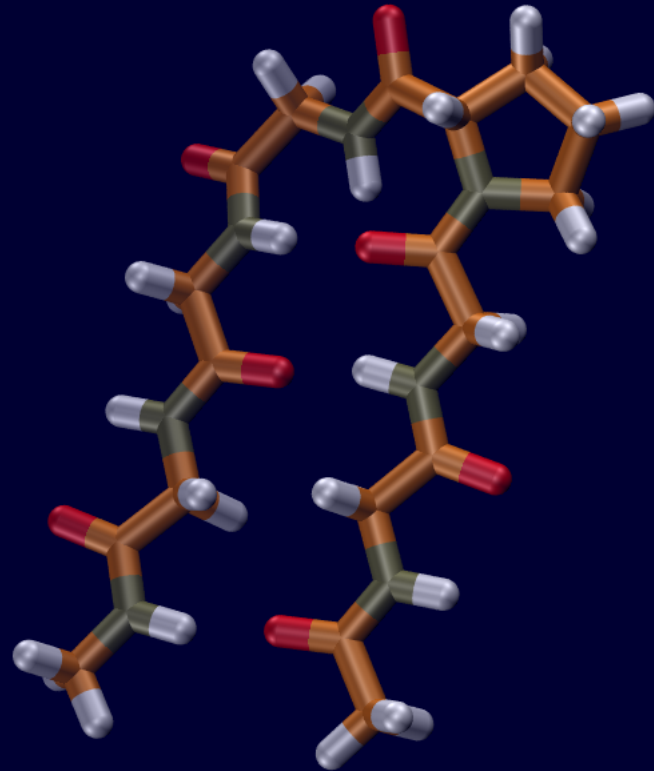


$\text{Ace}-(\text{Gly})_2\text{-Pro}-(\text{Gly})_3\text{-Nme}$

Long-Lived Conformations:



Globule



β -turn

Collective Variable:

(radius of gyration)

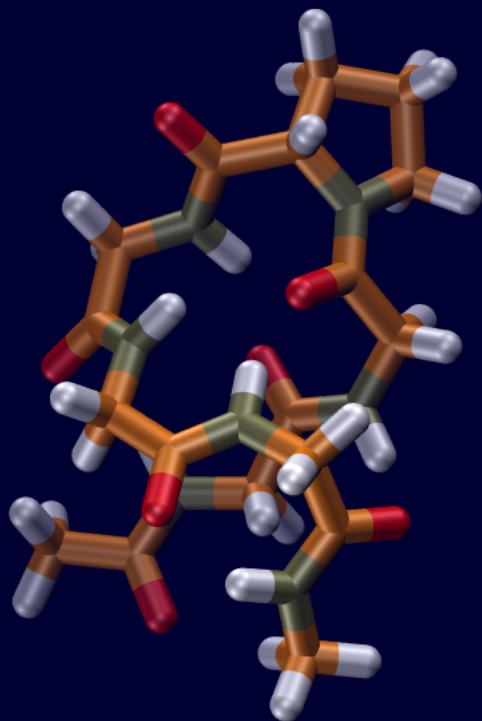
$$R_g = \sqrt{\sum_a \frac{m_a}{M_\Sigma} (\mathbf{r}_a - \mathbf{R}_\Sigma)^2}$$

$$\mathbf{R}_\Sigma = \sum_a \frac{m_a}{M_\Sigma} \mathbf{r}_a, \quad M_\Sigma = \sum_a m_a$$

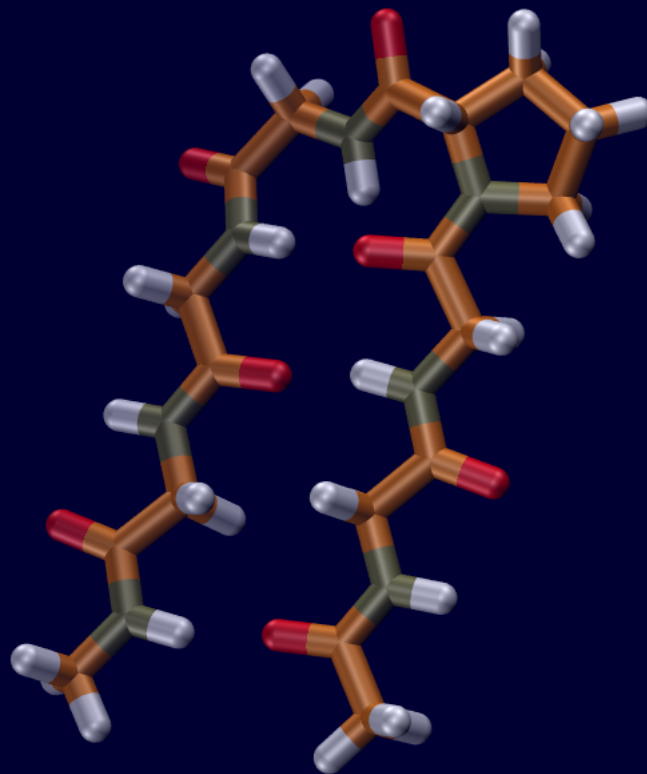
Why the R_g ?

- It provides a sensible description of the conformations in terms of just one number.

The Conformations:

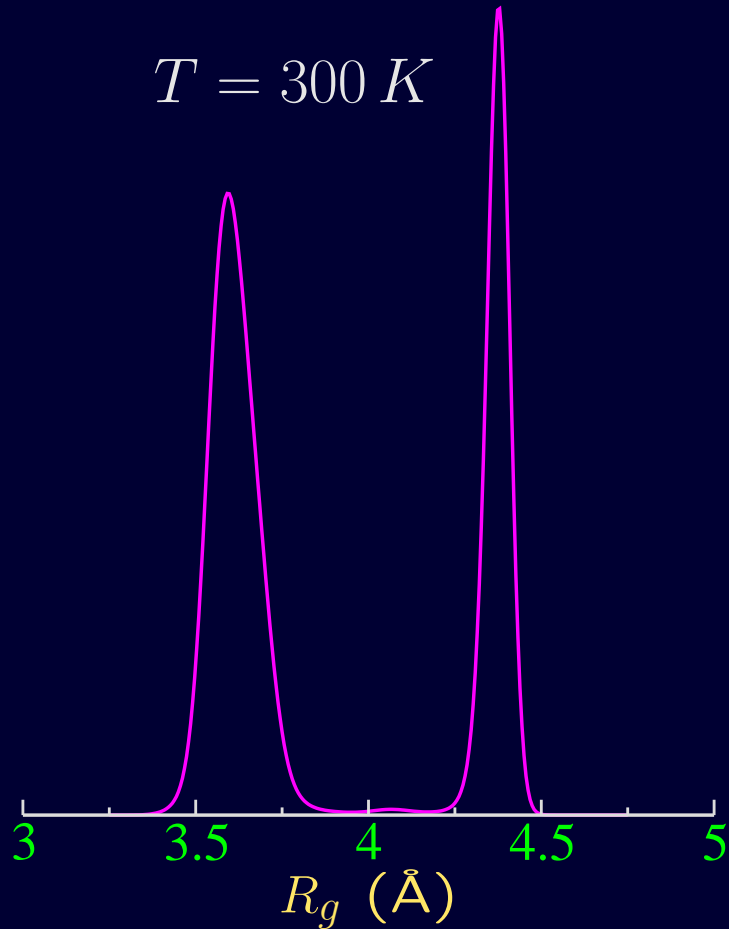


$$R_g \approx 3.6\text{\AA}$$



$$R_g \approx 4.4\text{\AA}$$

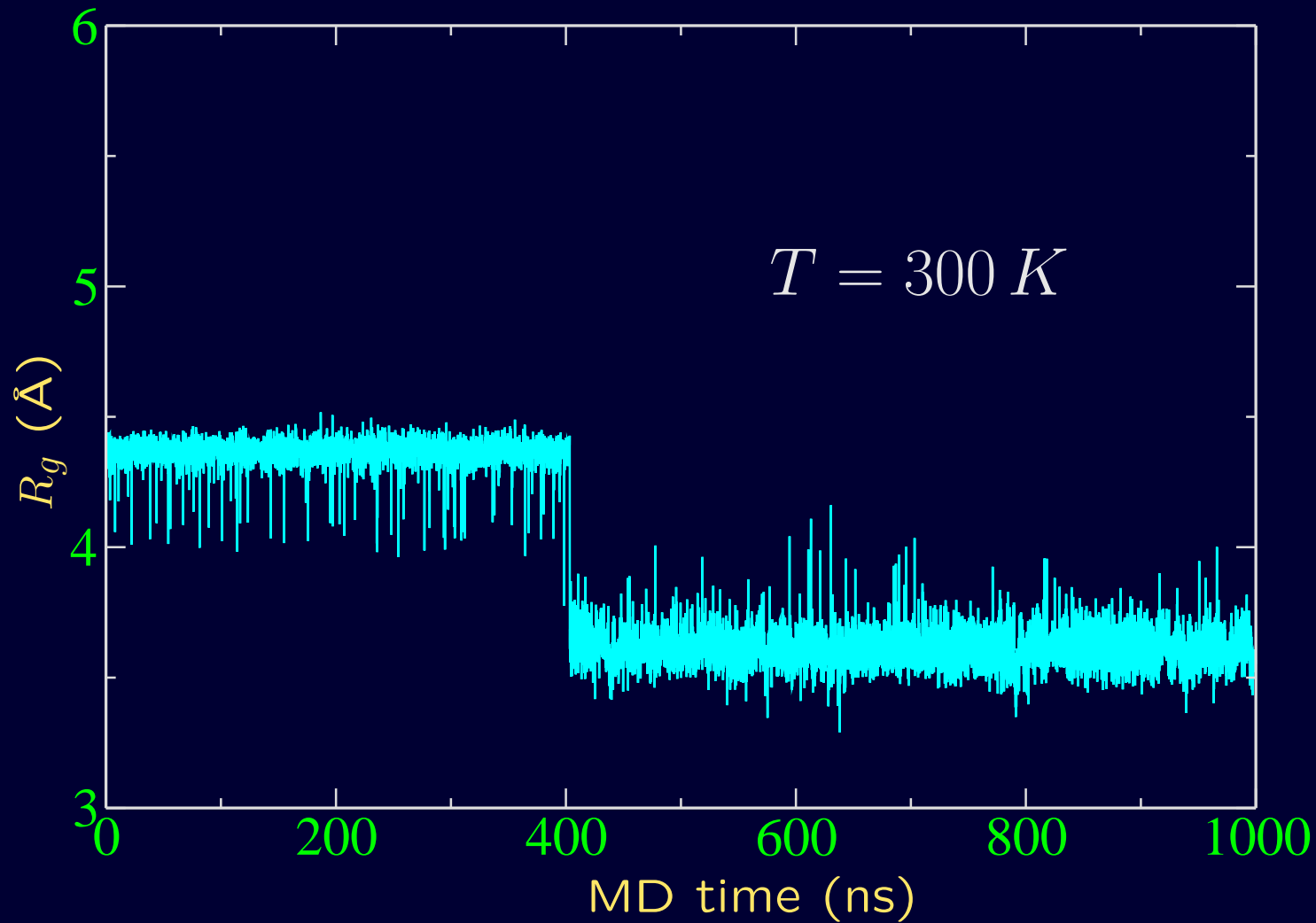
The Probability Density:



Canonical Ensemble

$$p(\mathbf{r}_1, \dots, \mathbf{r}_N) \propto \exp \left[-\frac{1}{k_B T} E(\mathbf{r}_1, \dots, \mathbf{r}_N) \right]$$

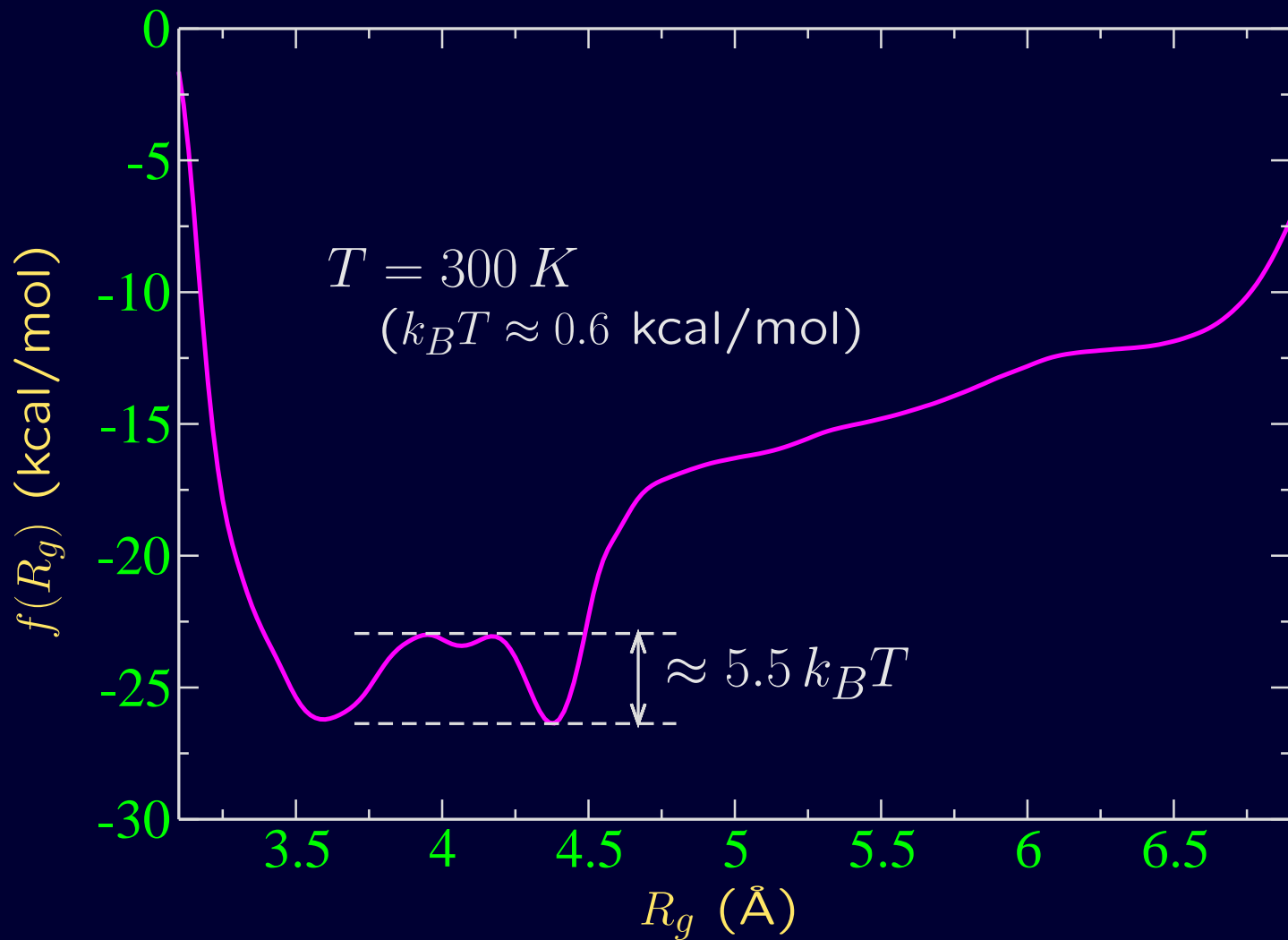
Molecular Dynamics



The Problems:

- MD trajectory rarely jumps through the barriers (i.e., the MD is bad for sampling from the canonical distribution; this can be “cured” by using, e.g., *parallel tempering*).
- MD trajectory is trapped near the free energy minima (canonical ensemble).

The Free Energy



“Classical” Remedies:

- Better ways of sampling from the canonical distribution (replica exchange).
- Sampling from a biased distribution with the bias that can be “undone” afterwards (umbrella sampling).

Non-Equilibrium Methods

- Local Elevation (MD context)

T. HUBER, A. E. TORDA, AND W. F. VAN GUNSTEREN, *Local elevation: a method for improving the searching properties of molecular dynamics simulation*, J. Comput. Aided. Mol. Des., 8 (1994), pp. 695–708.

- Wang-Landau (MC context)

F. WANG AND D. P. LANDAU, *Efficient, multiple-range random walk algorithm to calculate the density of states*, Phys. Rev. Lett., 86 (2001), pp. 2050–2053.

Non-Equilibrium Methods

- Adaptive Force Bias

E. DARVE AND A. POHORILLE, *Calculating free energies using average force*, J. Chem. Phys., 115 (2001), pp. 9169–9183.

J. HÉNIN AND C. CHIPOT, *Overcoming free energy barriers using unconstrained molecular dynamics simulations.*, J. Chem. Phys., 121 (2004), pp. 2904–2914.

- Metadynamics

M. IANNUZZI, A. LAIO, AND M. PARRINELLO, *Efficient exploration of reactive potential energy surfaces using Car-Parrinello molecular dynamics*, Phys. Rev. Lett., 90 (2003), pp. 238302–1.

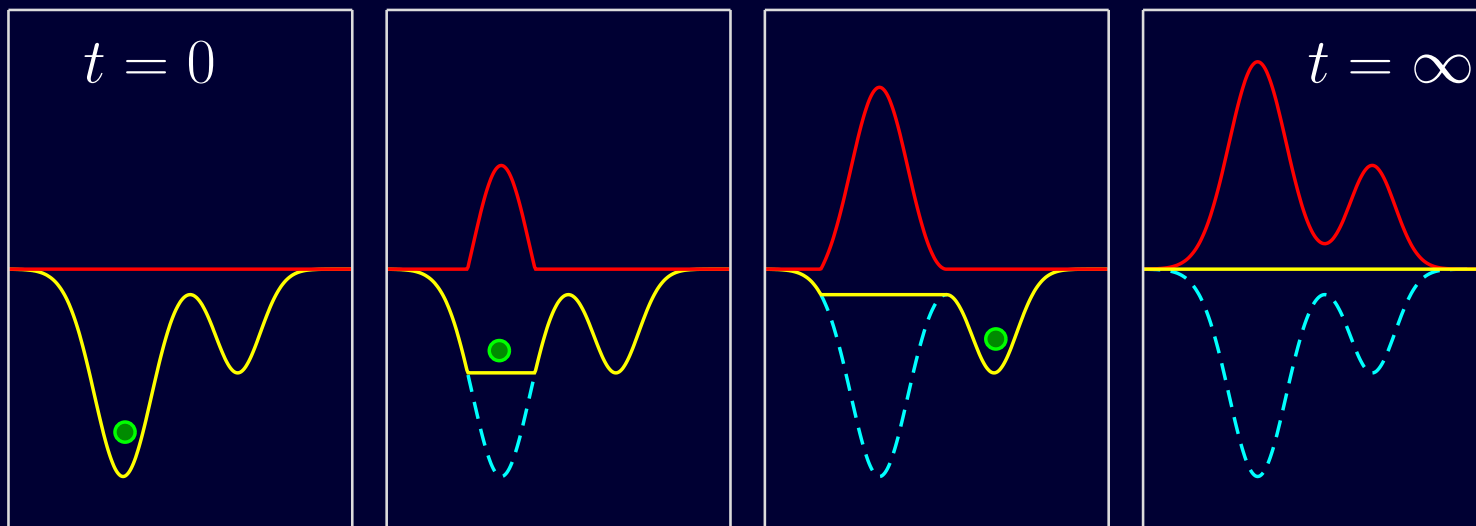
Ingredients of a Non-Equilibrium Method:

- Sampling Device (typically Molecular Dynamics or Replica-Exchange Molecular Dynamics).

and

- Non-stationary Biasing potential.

Evolving Biasing Potential:



- – biasing potential
- – “flattened” free-energy

Metadynamics References

A. LAIO AND M. PARRINELLO, *Escaping free-energy minima*, Proc. Natl. Acad. Sci., 99 (2002), pp. 12562–12566.

M. IANNUZZI, A. LAIO, AND M. PARRINELLO, *Efficient exploration of reactive potential energy surfaces using Car-Parrinello molecular dynamics*, Phys. Rev. Lett., 90 (2003), pp. 238302–1.

Metadynamics Equations

$$M\ddot{\xi} + K\left(\xi - \sigma[\mathbf{r}_1, \dots, \mathbf{r}_N]\right) = -\frac{\partial}{\partial \xi} V_h(\xi, t)$$

$$m_a \ddot{\mathbf{r}}_a - K\left(\xi - \sigma[\mathbf{r}_1, \dots, \mathbf{r}_N]\right) \frac{\partial}{\partial \mathbf{r}_a} \sigma[\mathbf{r}_1, \dots, \mathbf{r}_N] = \mathbf{F}_a[\mathbf{r}_1, \dots, \mathbf{r}_N]$$

ξ – additional dynamical variable harmonically coupled to the collective variable ($\sigma[\mathbf{r}_1, \dots, \mathbf{r}_N]$)

$V_h(\xi, t)$ – the “hills” potential

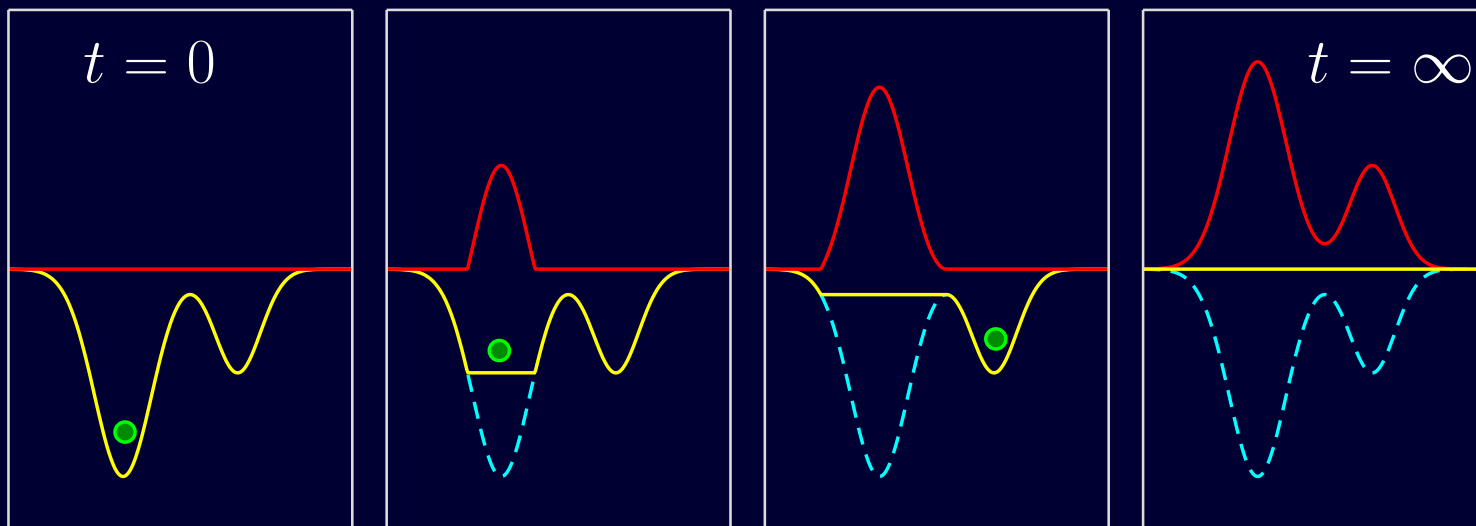
$$M\ddot{\xi} + K\left(\xi - \sigma[\mathbf{r}_1, \dots, \mathbf{r}_N]\right) = 0$$

If the dynamics of ξ is much **slower** than the dynamics of \mathbf{r}_a and the harmonic coupling (K) is strong enough, the motion of ξ is driven by the **free energy** gradient:

$$\delta(\xi - \sigma[\mathbf{r}_1, \dots, \mathbf{r}_N]) \approx \exp\left[-\frac{K}{2}(\xi - \sigma[\mathbf{r}_1, \dots, \mathbf{r}_N])^2\right]$$

$$\frac{\partial}{\partial \xi} f(\xi) \propto \frac{1}{T} \int_t^{t+T} d\tau (\xi - \sigma[\mathbf{r}_1(\tau), \dots, \mathbf{r}_N(\tau)])$$

“Umbrella” Potential $V_h(\xi, t)$



$$V_h(\xi, t) = \sum_{\tau < t} G[\xi - \xi(\tau)]$$

the metadynamics’ “hills” potential is a sum of tiny bumps placed along the $\xi(t)$ trajectory

As-Is Metadynamics is $O(t^2)$:

- The number of terms (bumps) in $V_h(\xi, t)$ (the “hills” potential) at time t is proportional to t .
- $V_h(\xi, t)$ must be computed at every MD step.

Metadynamics / Applications

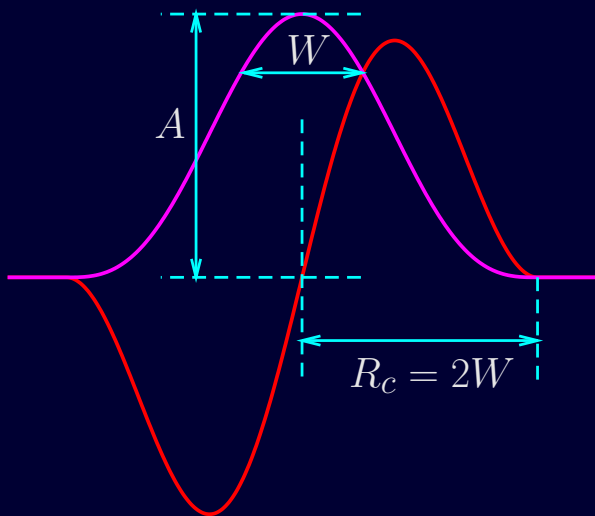
E. ASCIUTTO AND C. SAGUI, *Exploring Intramolecular Reactions in Complex Systems with Metadynamics: The Case of the Malonate Anions*, J. Phys. Chem. A, 109 (2005), pp. 7682–7687.

J. G. LEE, E. ASCIUTTO, V. BABIN, C. SAGUI, T. A. DARDEN AND C. ROLAND, *Deprotonation of Solvated Formic Acid: Car-Parrinello and Metadynamics Simulations*, J. Phys. Chem. B, 110 (2006) pp. 2325–2331.

V. BABIN, C. ROLAND, T. A. DARDEN AND C. SAGUI, *The free energy landscape of small peptides as obtained from metadynamics with umbrella sampling corrections*, J. Chem. Phys., 125 (2006), pp. 204909.

- Metadynamics for AMBER (classical MD: significant entropy contributions require long runs).
- Fast implementation using *kd*-trees for the “hills” potential (faster than naïve $O(t^2)$, but still not fast enough).
- An equilibrium follow-up run to assess and improve the “raw” metadynamics free energy.

The Hills Potential



$$V_h(\xi, t) = \sum_n A_n G \left[R(\xi \mid \xi_n^{(0)}, s_n) / W_n \right] / G(0)$$

$$R(\xi \mid \xi^{(0)}, s) = \sqrt{\sum_{\alpha} \left(\frac{\xi_{\alpha} - \xi_{\alpha}^{(0)}}{s_{\alpha}} \right)^2}$$

$$G(R) = \begin{cases} \exp\left(-\frac{1}{2}R^2\right) + P(R) \exp\left(-\frac{1}{2}R_c^2\right), & R < R_c \\ 0, & R \geq R_c \end{cases}$$

$$P(R) = \frac{1}{2}R^2 \left(1 + \frac{1}{2}R_c^2 - \frac{1}{4}R^2 \right) - \frac{1}{2}R_c^2 \left(1 + \frac{1}{4}R_c^2 \right) - 1$$

How to check the accuracy ?

Corrective Follow-Up:

1. Get the (equilibrium) biased probability density:

$$E_B(\mathbf{r}_1, \dots, \mathbf{r}_N) = E(\mathbf{r}_1, \dots, \mathbf{r}_N) + V_h[\sigma(\mathbf{r}_1, \dots, \mathbf{r}_N)]$$

$$p_B(\xi) = \langle \delta[\xi - \sigma(\mathbf{r}_1, \dots, \mathbf{r}_N)] \rangle_B$$

2. Use it to correct the free energy:

$$\Delta f(\xi) = -k_B T \ln p_B(\xi)$$

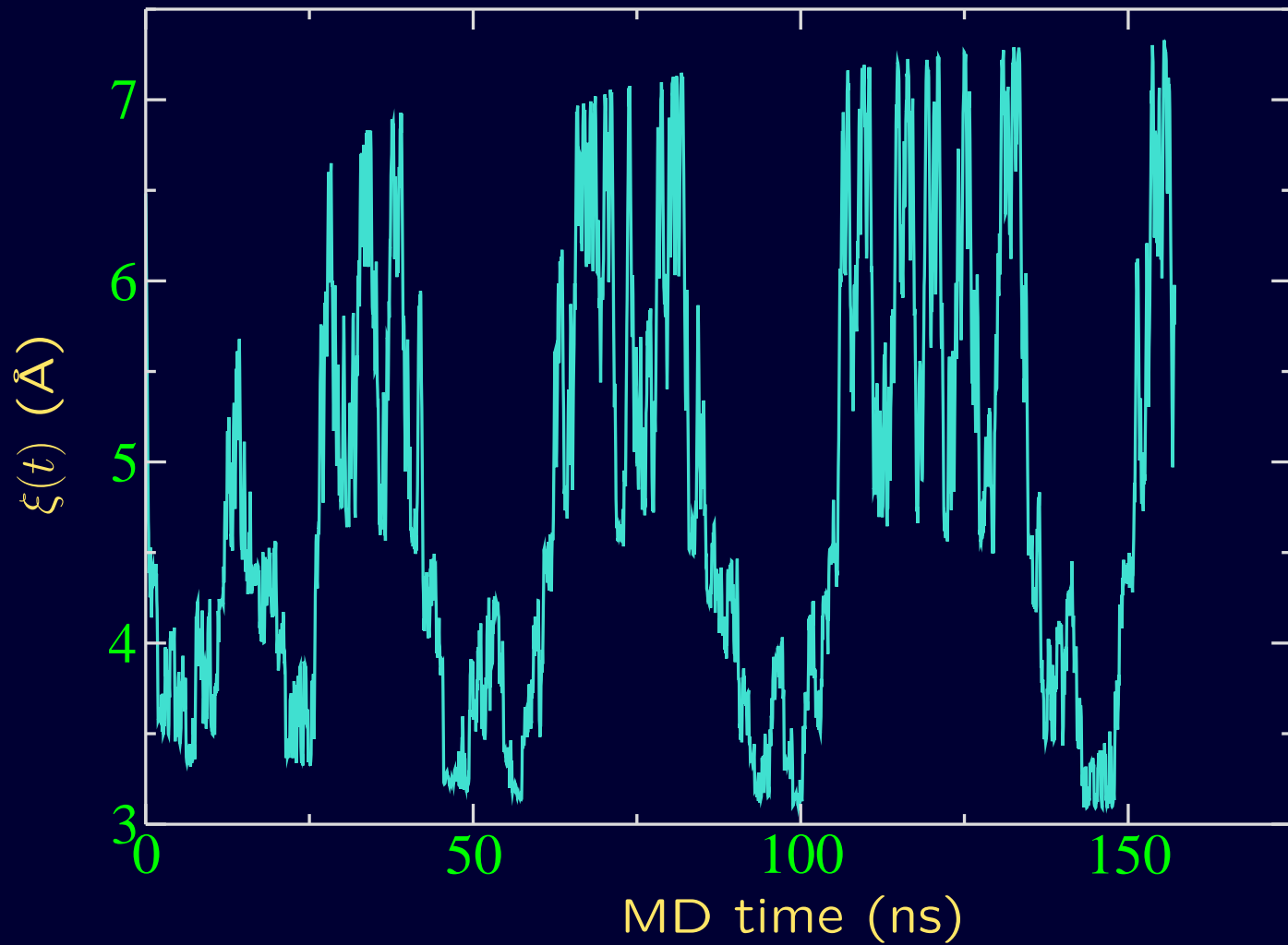
$$f(\xi) = -V_h(\xi) + \Delta f(\xi)$$

Ace-(Gly)₂-Pro-(Gly)₃-Nme

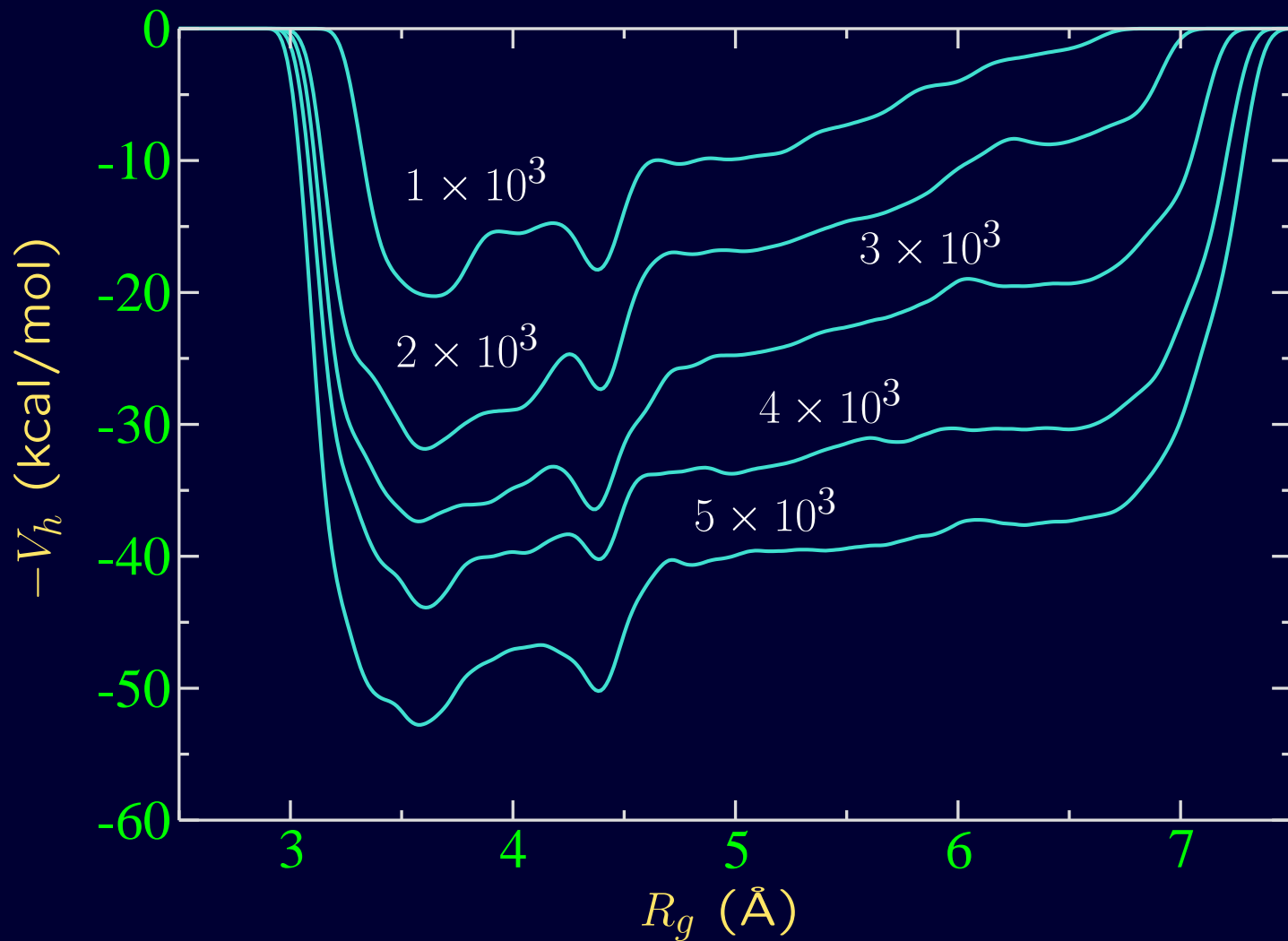


(using R_g as the collective variable)

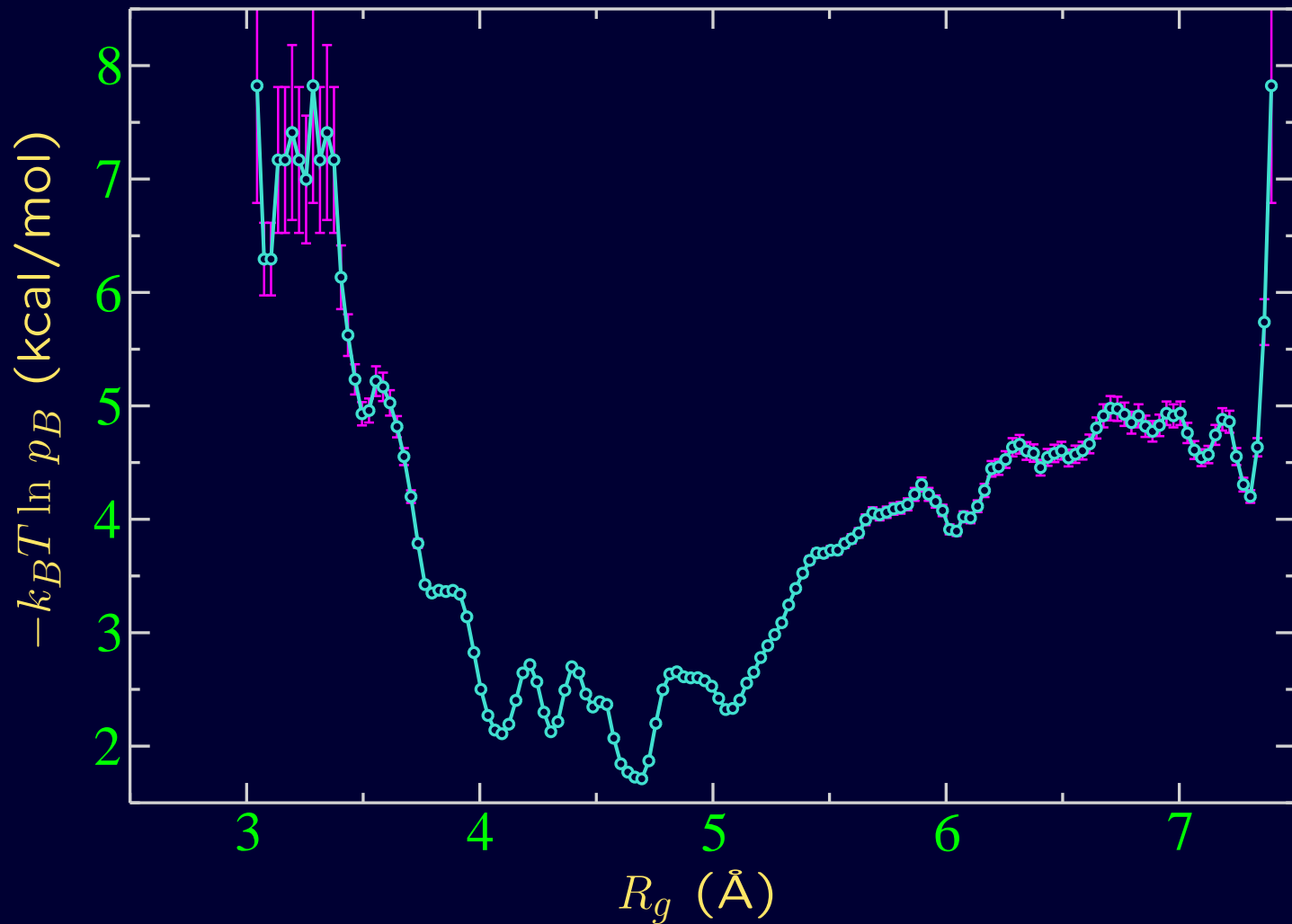
Metadynamics Trajectory:



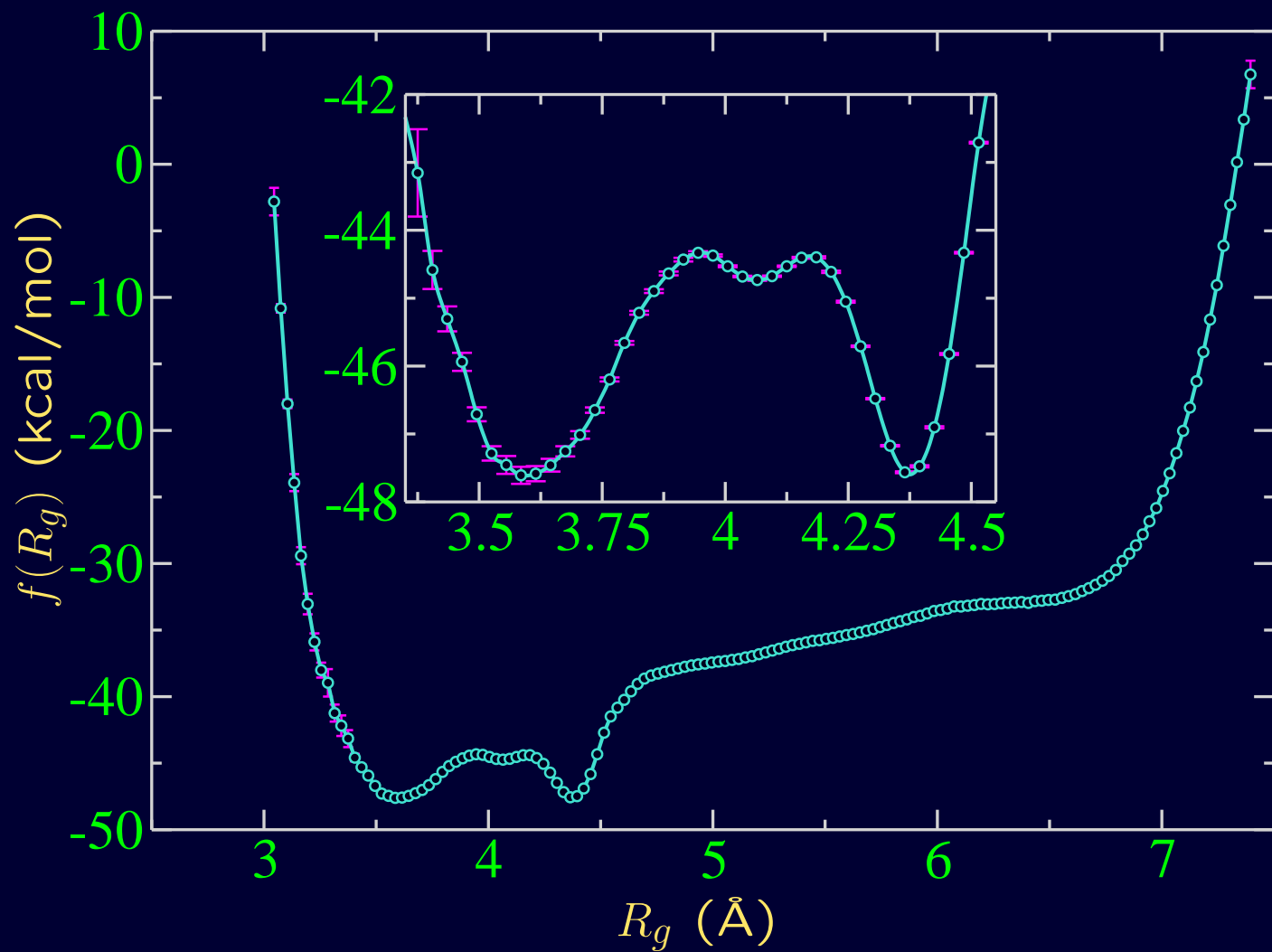
“Raw” Metadynamics:



“Raw” Metadynamics Error:

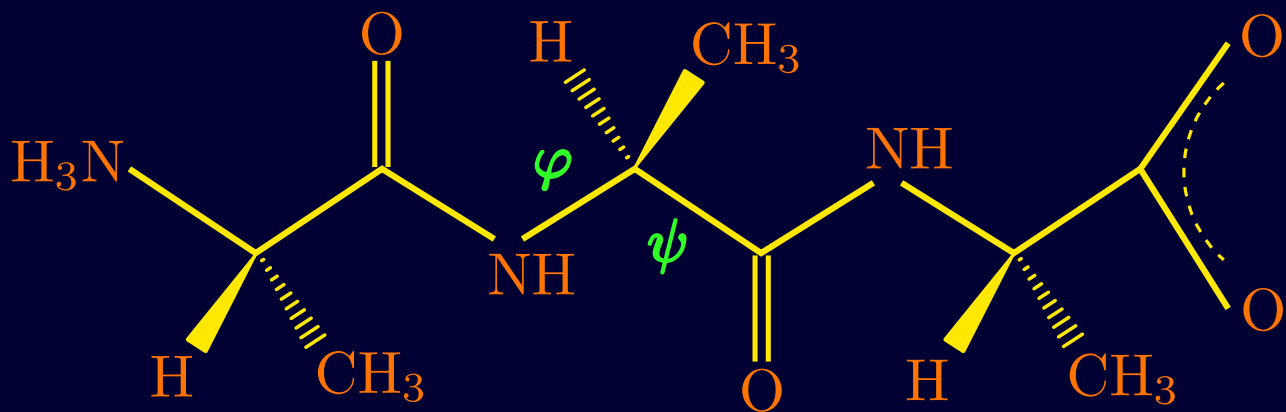


“Raw” + “Correction”:



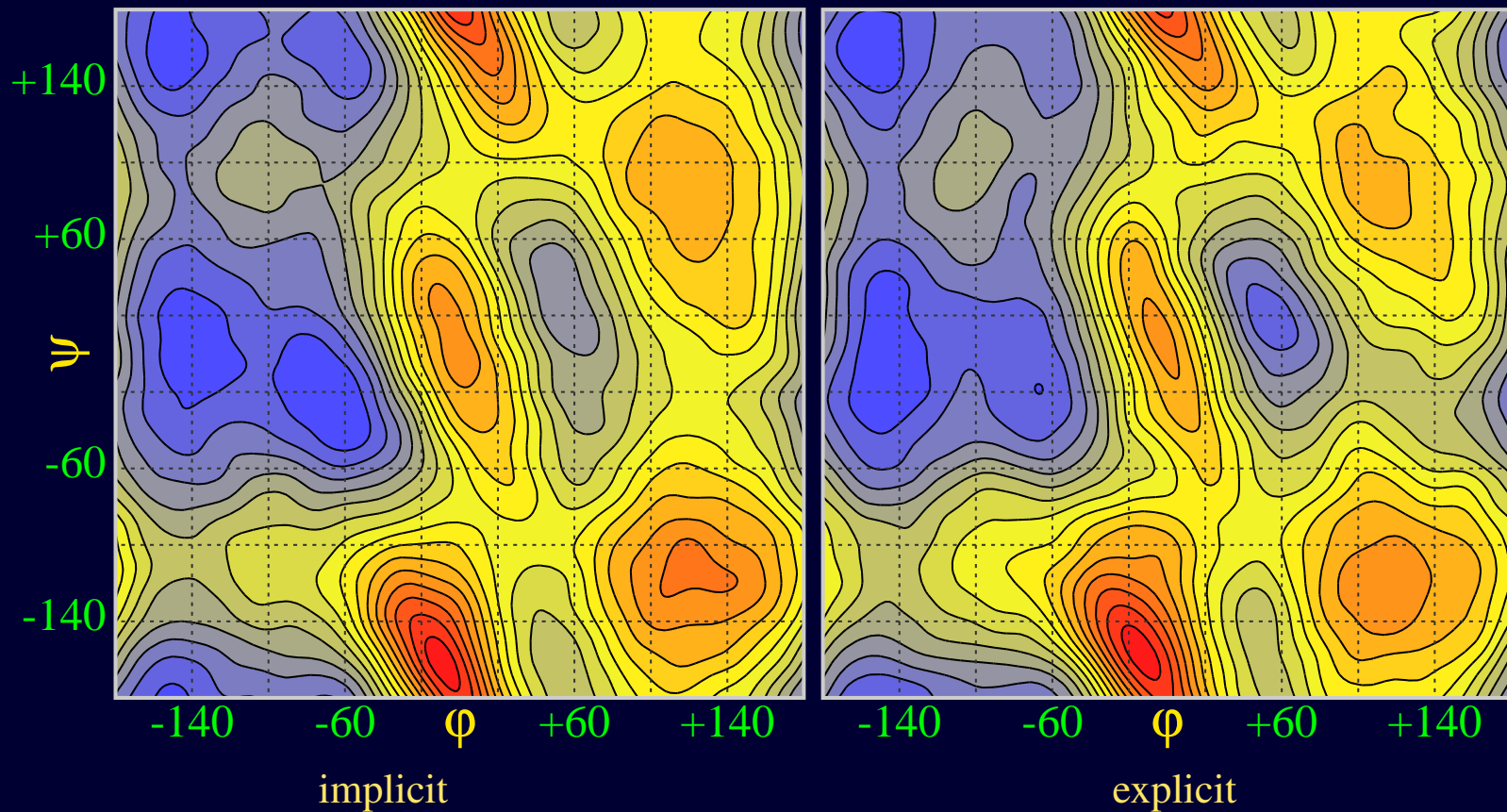
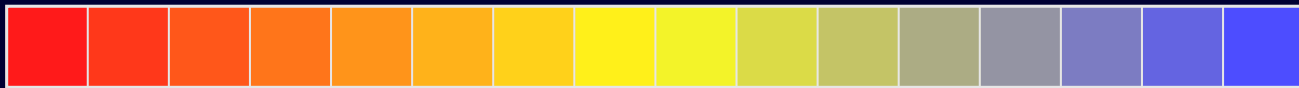
The “raw” error of $\approx 5k_B T$ is unacceptable (it is comparable with the barrier height)! The equilibrium follow-up is therefore crucial to get accurate results.

Tri-Alanine



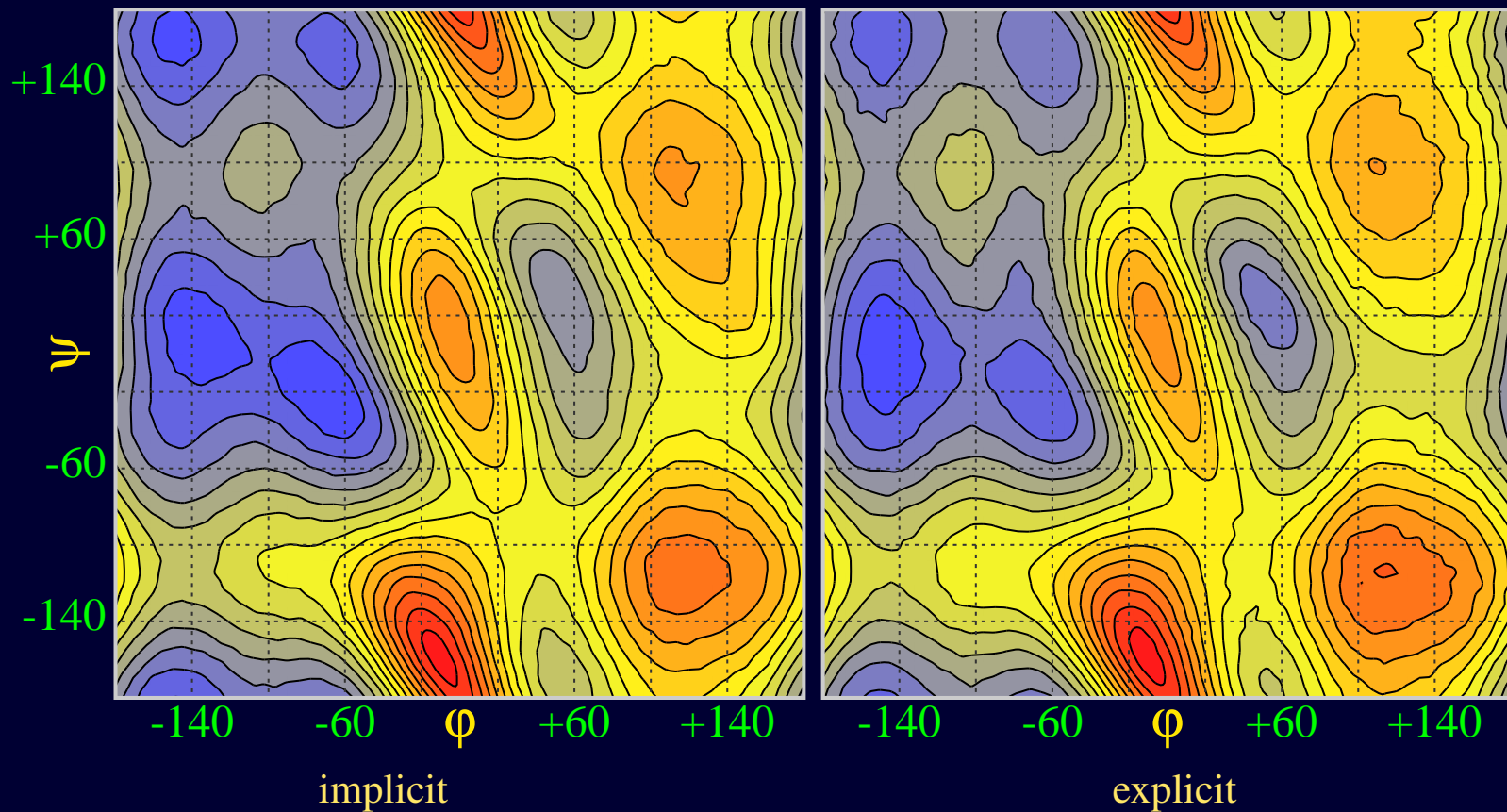
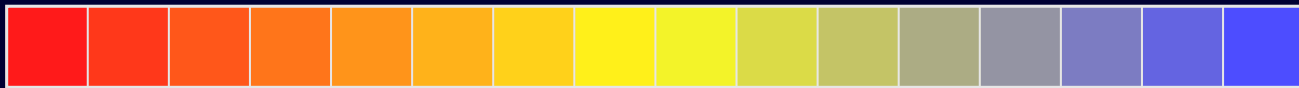
"Raw":

-0.5
-1.5
-2.5
-3.5
-4.5
-5.5
-6.5
-7.5
-8.5
-9.5
-10.5
-11.5
-12.5
-13.5
-14.5



"Raw" + "Correction":

-0.5 -1.5 -2.5 -3.5 -4.5 -5.5 -6.5 -7.5 -8.5 -9.5 -10.5 -11.5 -12.5 -13.5 -14.5



Can we do better ?

Vectors of Improvement:

- Different biasing strategies (e.g., smoother in both time and in Q biasing potential).
- Better “sampling devices” (e.g., replica exchange).

V. BABIN, C. ROLAND, AND C. SAGUI, *Adaptively biased molecular dynamics for free energy calculations*, J. Chem. Phys., 128 (2008), p. 134101.

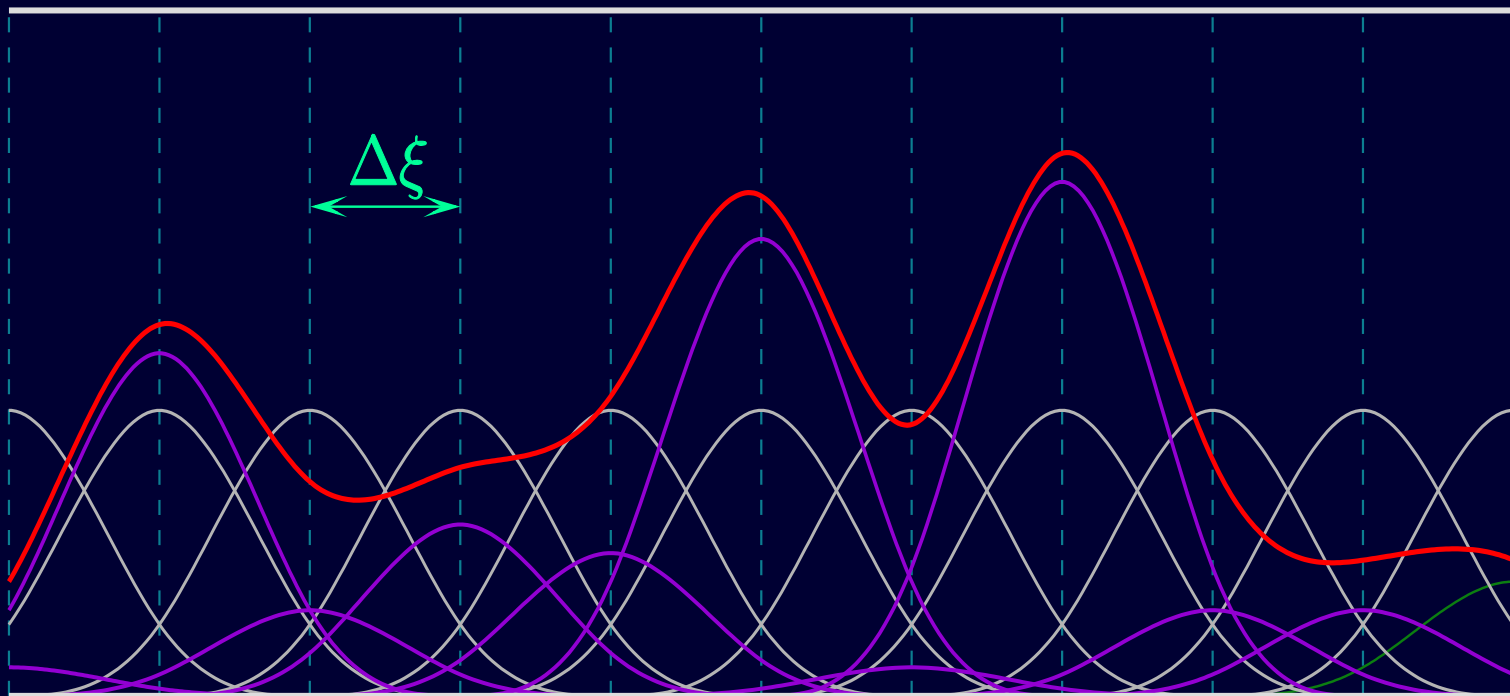
$$m_a \frac{d^2 \mathbf{r}_a}{dt^2} = \mathbf{F}_a - \frac{\partial}{\partial \mathbf{r}_a} U [t | \sigma (\mathbf{r}_1, \dots, \mathbf{r}_N)]$$

$$\frac{\partial U(t | \xi)}{\partial t} = \frac{k_B T}{\tau_F} G [\xi - \sigma (\mathbf{r}_1, \dots, \mathbf{r}_N)]$$

T. LELIÈVRE, M. ROUSSET, AND G. STOLTZ, *Computation of free energy profiles with parallel adaptive dynamics*, J. Chem. Phys., 126 (2007), p. 134111.

Discretization in \mathbb{Q}

$$U(t|\xi) = \sum_{m \in \mathbb{Z}^D} U_m(t) B(\xi / \Delta\xi - m)$$



Discretization in Time

$$U_m(t + \Delta t) = U_m(t) + \Delta t \frac{k_B T}{\tau_F} G[\sigma(t)/\Delta\xi - m]$$

$$G(\xi) = \frac{48}{41} \begin{cases} \left(1 - \xi^2/4\right)^2, & -2 \leq \xi \leq 2 \\ 0, & \text{otherwise} \end{cases}$$

Advantages of the ABMD

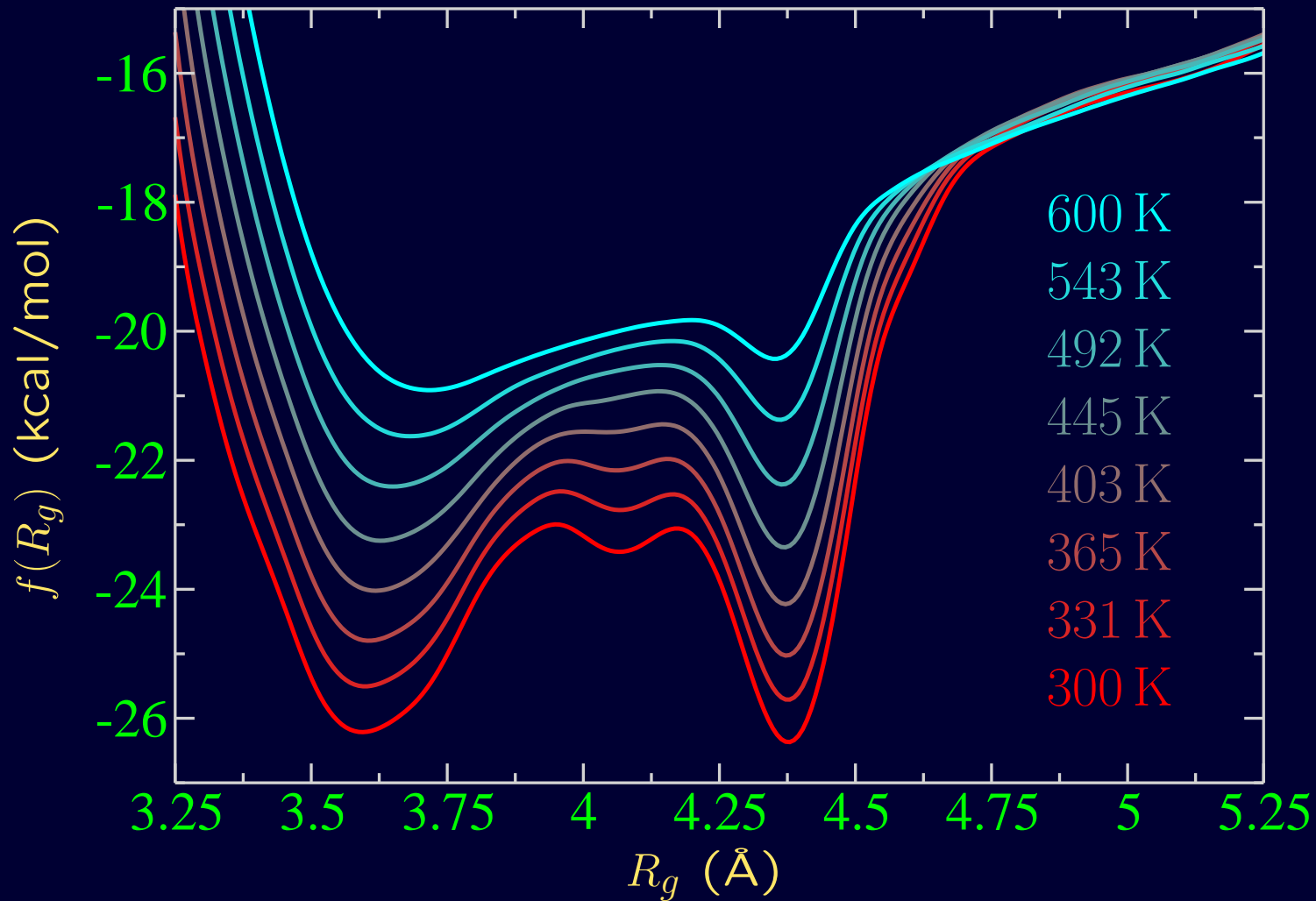
- It is fast: goes as $O(t)$ since the numerical cost of the $U(t|\xi)$ does not depend on time t (it is $O(1)$).
- It is memory efficient (if sparse arrays are used for the $U_m(t)$).
- It is convenient (only two parameters: $\Delta\xi$ and τ_F).

Ace-(Gly)₂-Pro-(Gly)₃-Nme



(using R_g as the collective variable)

Reference Free Energies:



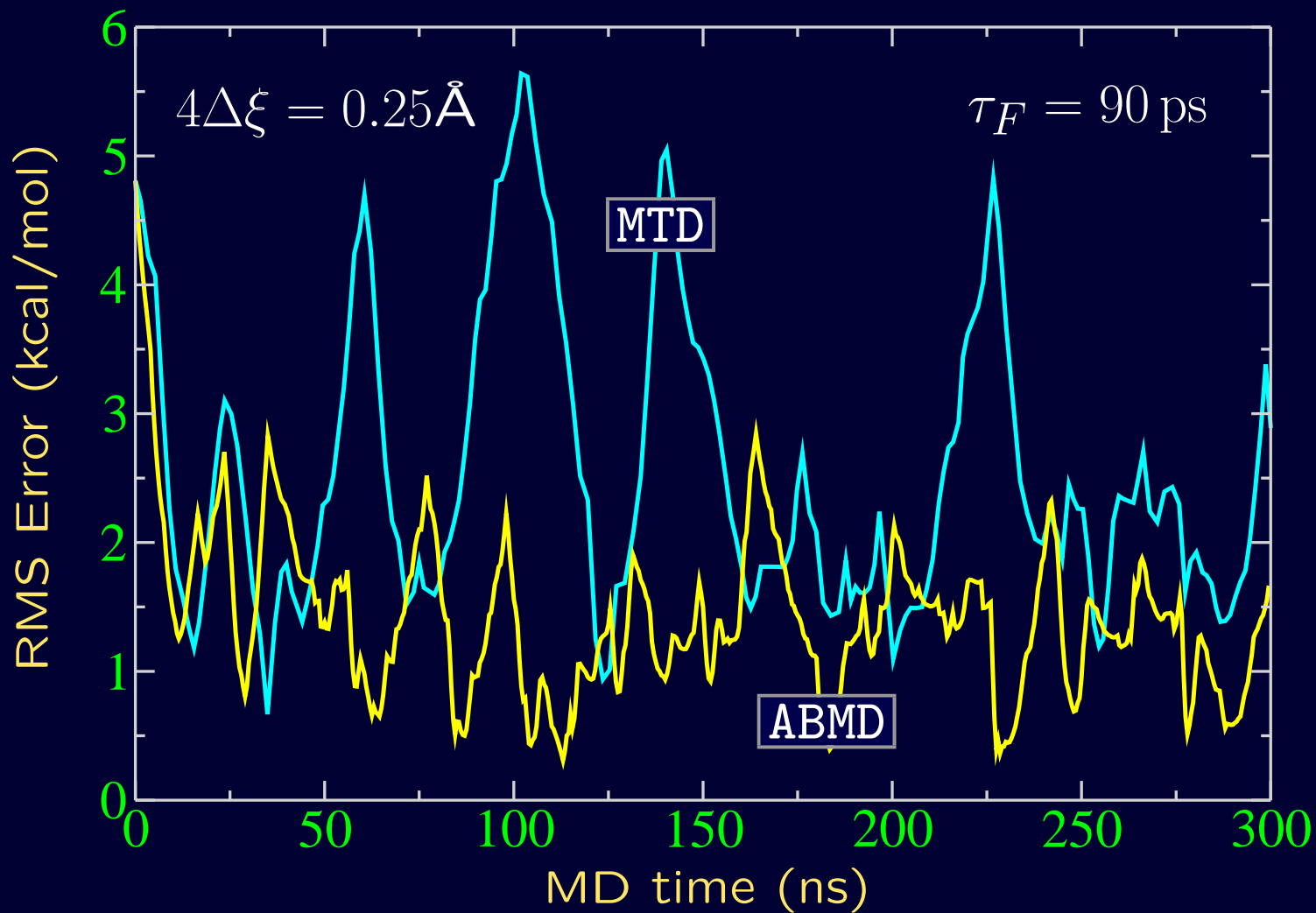
The RMS Free Energy Error:

$$E_{RMS} = \sqrt{\frac{1}{b-a} \int_a^b d\xi \left(f_1(\xi) - f_2(\xi) - \Delta \right)^2}$$

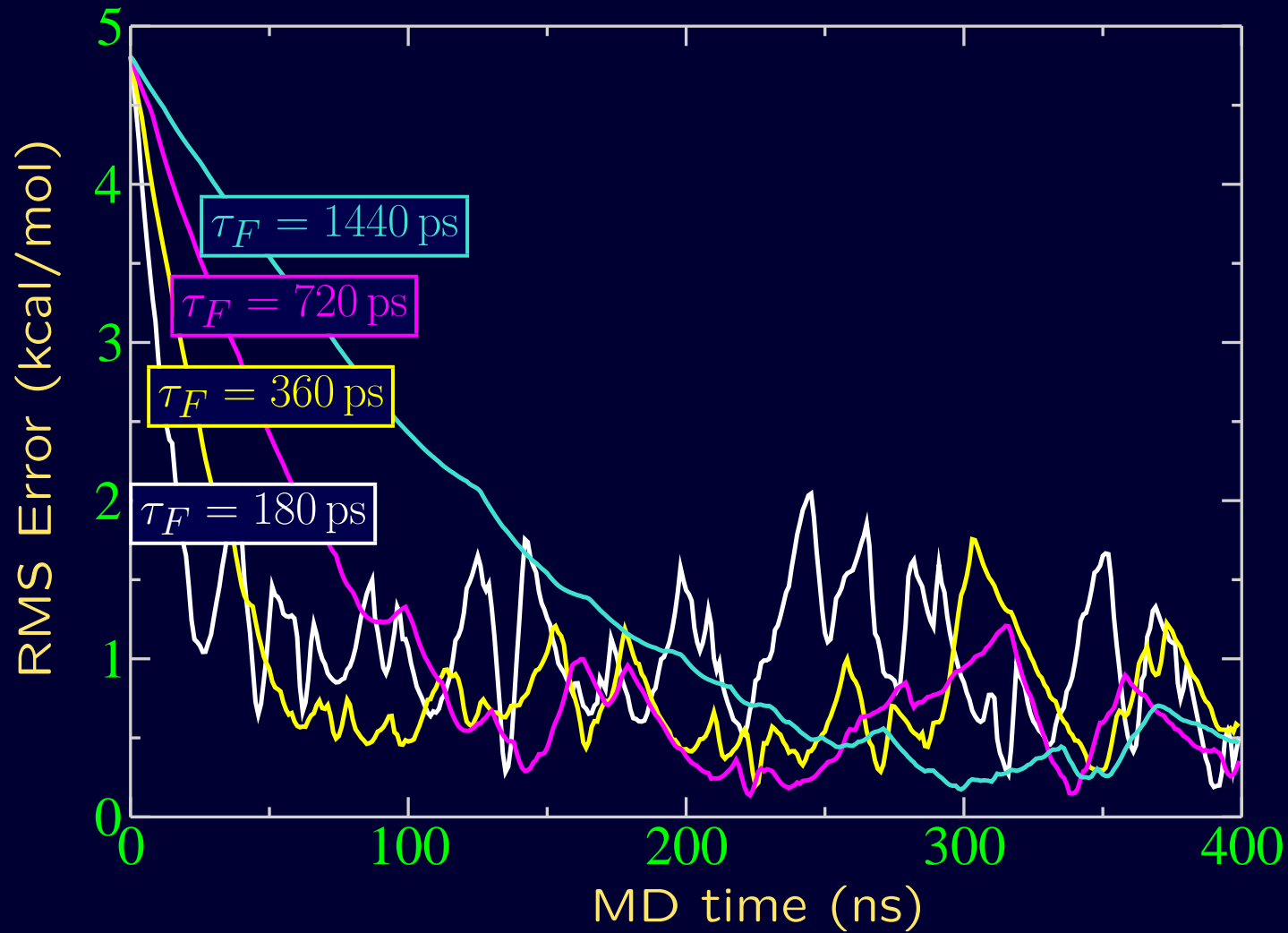
where

$$\Delta = \frac{1}{b-a} \int_a^b d\xi \left(f_1(\xi) - f_2(\xi) \right)$$

ABMD vs Metadynamics:



The slower, the better:

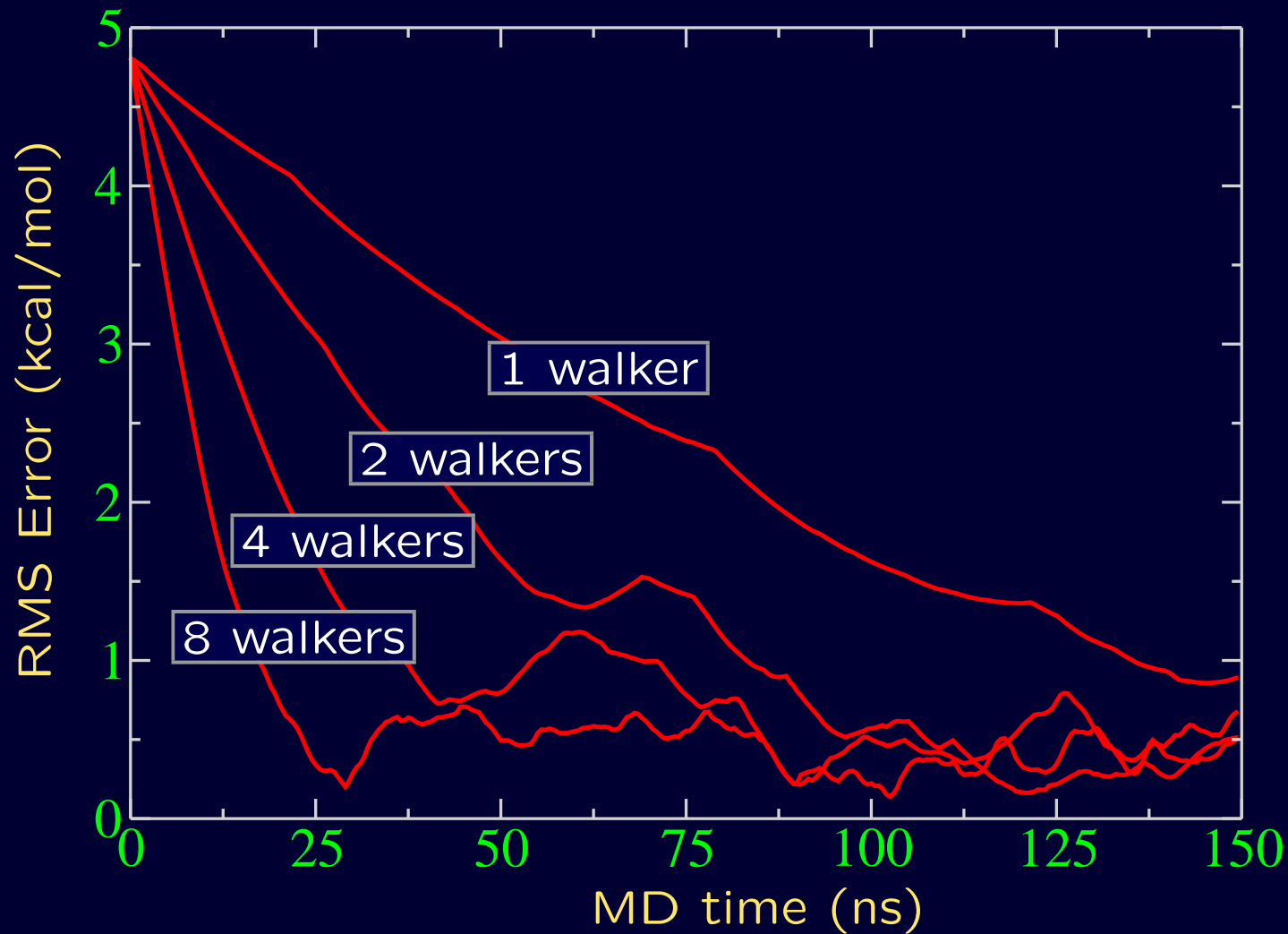


Multiple Walkers

$$\frac{\partial U(t|\xi)}{\partial t} = \frac{k_B T}{\tau_F} \sum_{\alpha} G[\xi - \sigma(\mathbf{r}_1^{\alpha}, \dots, \mathbf{r}_N^{\alpha})]$$

(the sum runs over different MD trajectories)

P. RAITERI, A. LAIO, AND F. L. GERVASIO, C. MICHELETTI AND M. PARINELLO, *Efficient Reconstruction of Complex Free Energy Landscapes by Multiple Walkers Metadynamics*, J. Phys. Chem. B, 110 (2006), pp. 3533–3539.

Multiple Walkers for Fixed τ_F :

Replica Exchange – A Better “Sampling Device”

Y. SUGITA, A. KITAO AND Y. OKAMOTO, *Multidimensional replica-exchange method for free-energy calculations*, J. Chem. Phys., 113 (2000), pp. 6042–6051.

- N copies (replicas) in parallel.
- Each replica may have different temperature and/or collective variable.
- Either stationary ($\tau_F = \infty$) or evolving biasing potential on per-replica basis.

Exchange Probability:

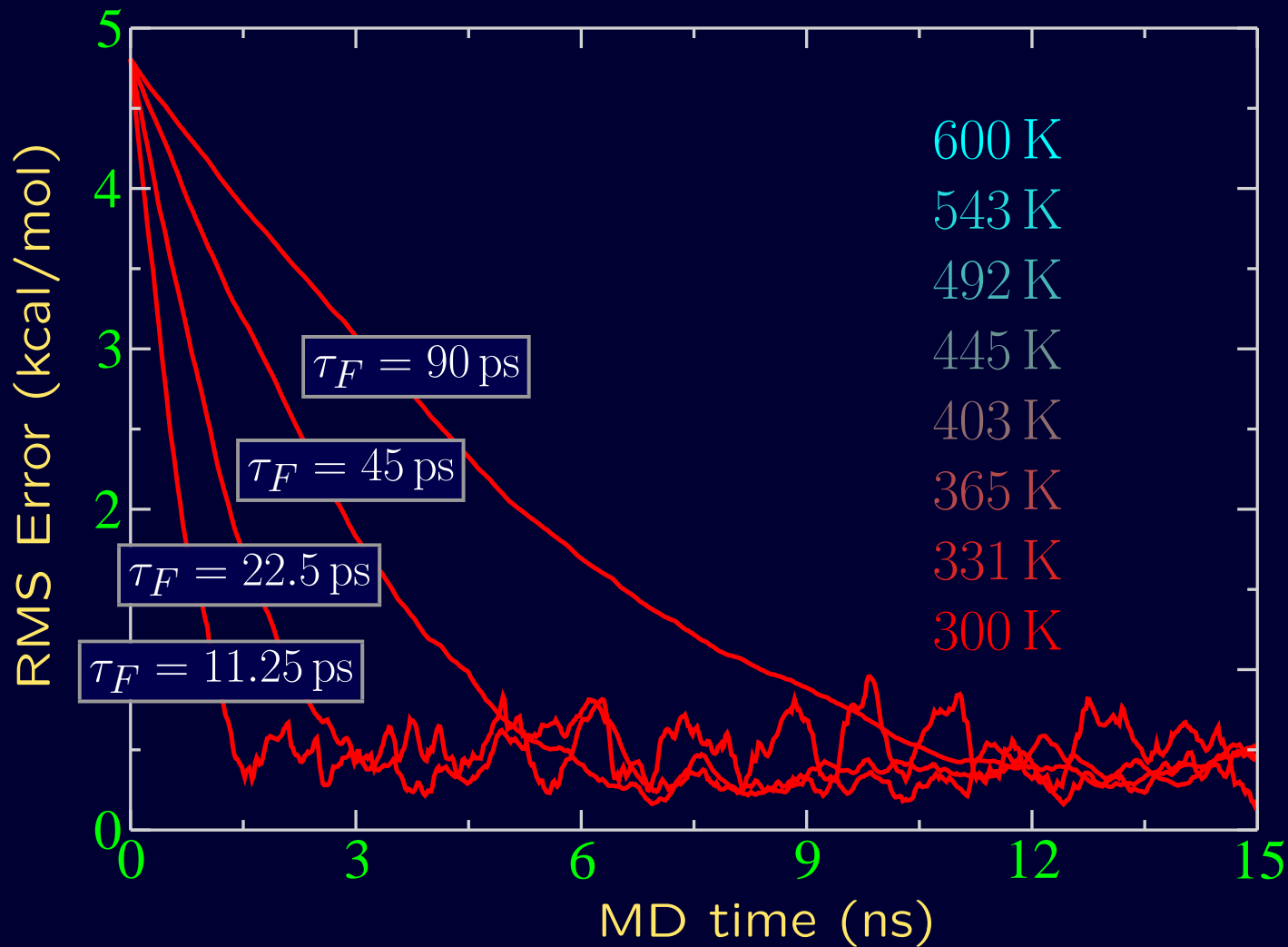
$$w(m|n) = \begin{cases} 1, & \Delta \leq 0 \\ \exp(-\Delta), & \Delta > 0 \end{cases}$$

$$\begin{aligned} \Delta = & \left(\frac{1}{k_B T_n} - \frac{1}{k_B T_m} \right) (E_p^m - E_p^n) \\ & + \frac{1}{k_B T_m} [U^m(\xi^n) - U^m(\xi^m)] \\ & - \frac{1}{k_B T_n} [U^n(\xi^n) - U^n(\xi^m)] \end{aligned}$$

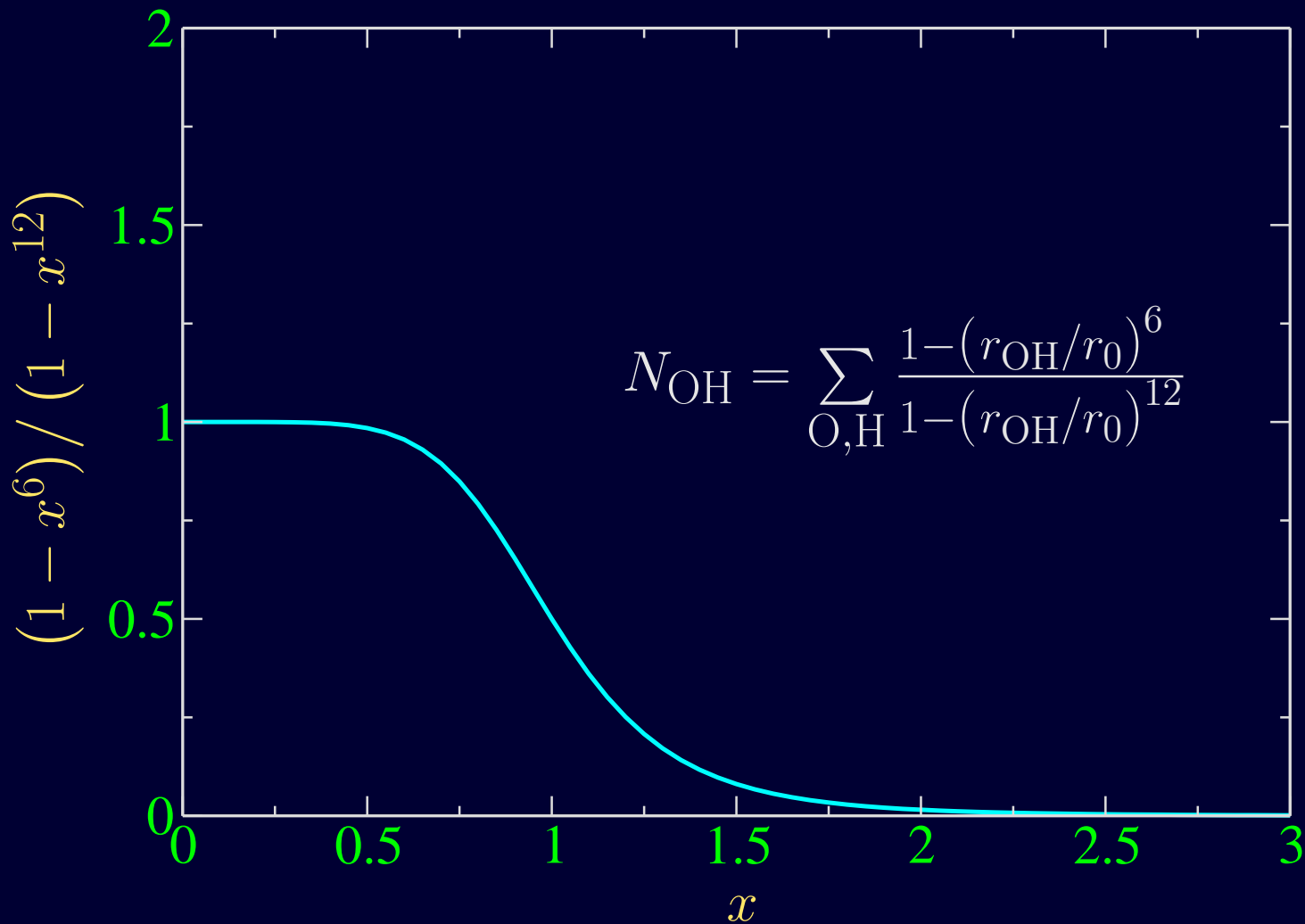
Parallel Tempering ABMD

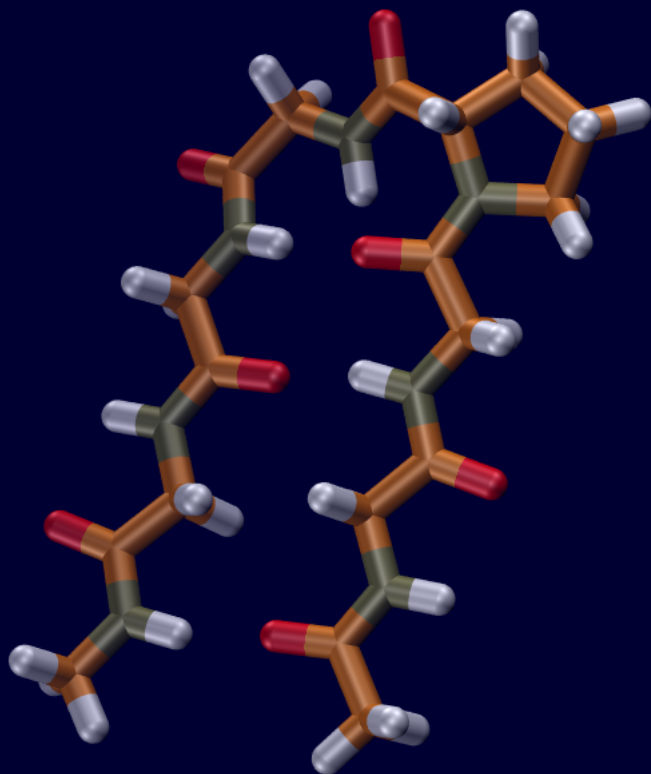
- Different temperatures.
- Same collective variable(s) in all replicas.

Parallel Tempering ABMD



Another Collective Variable:

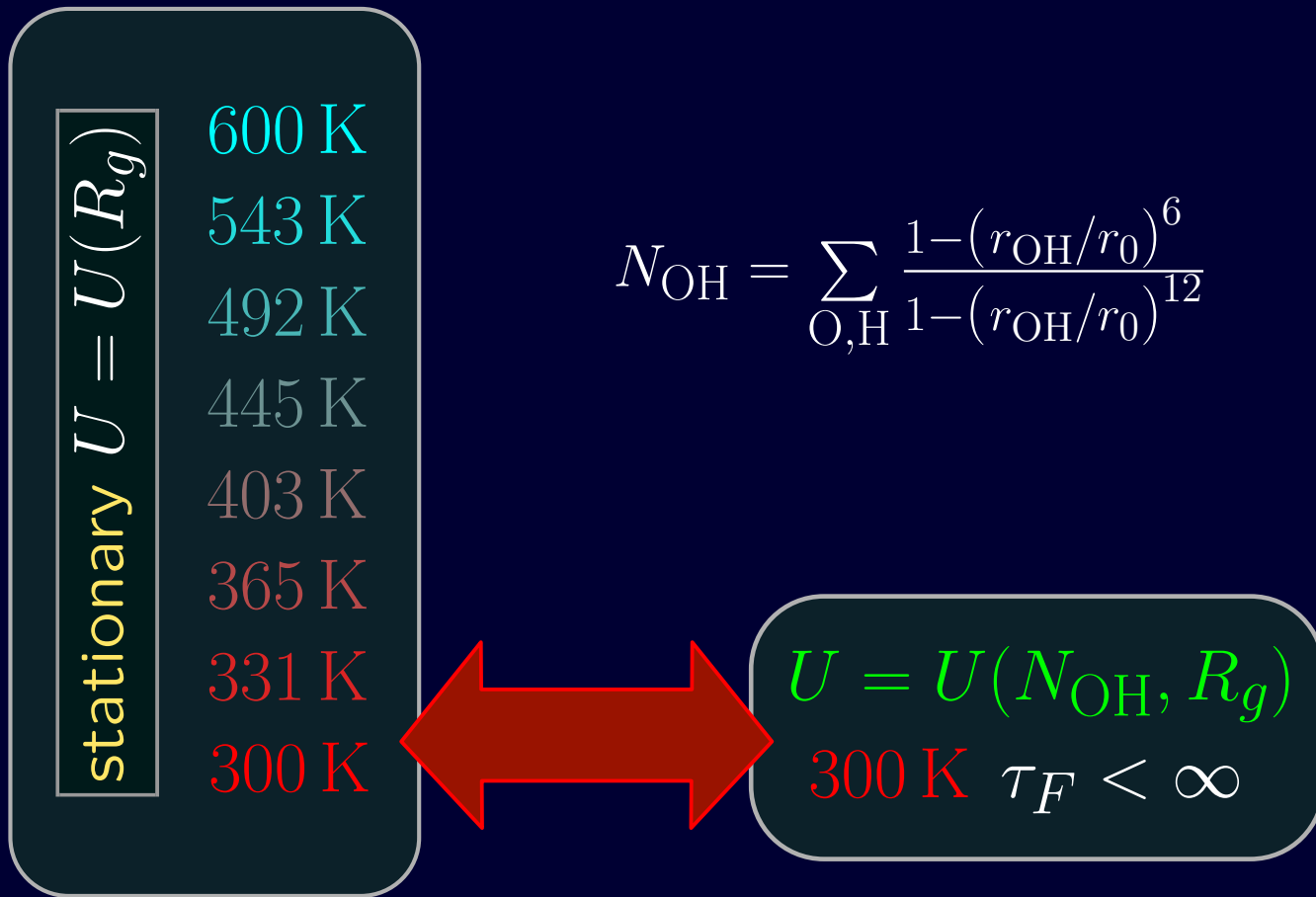


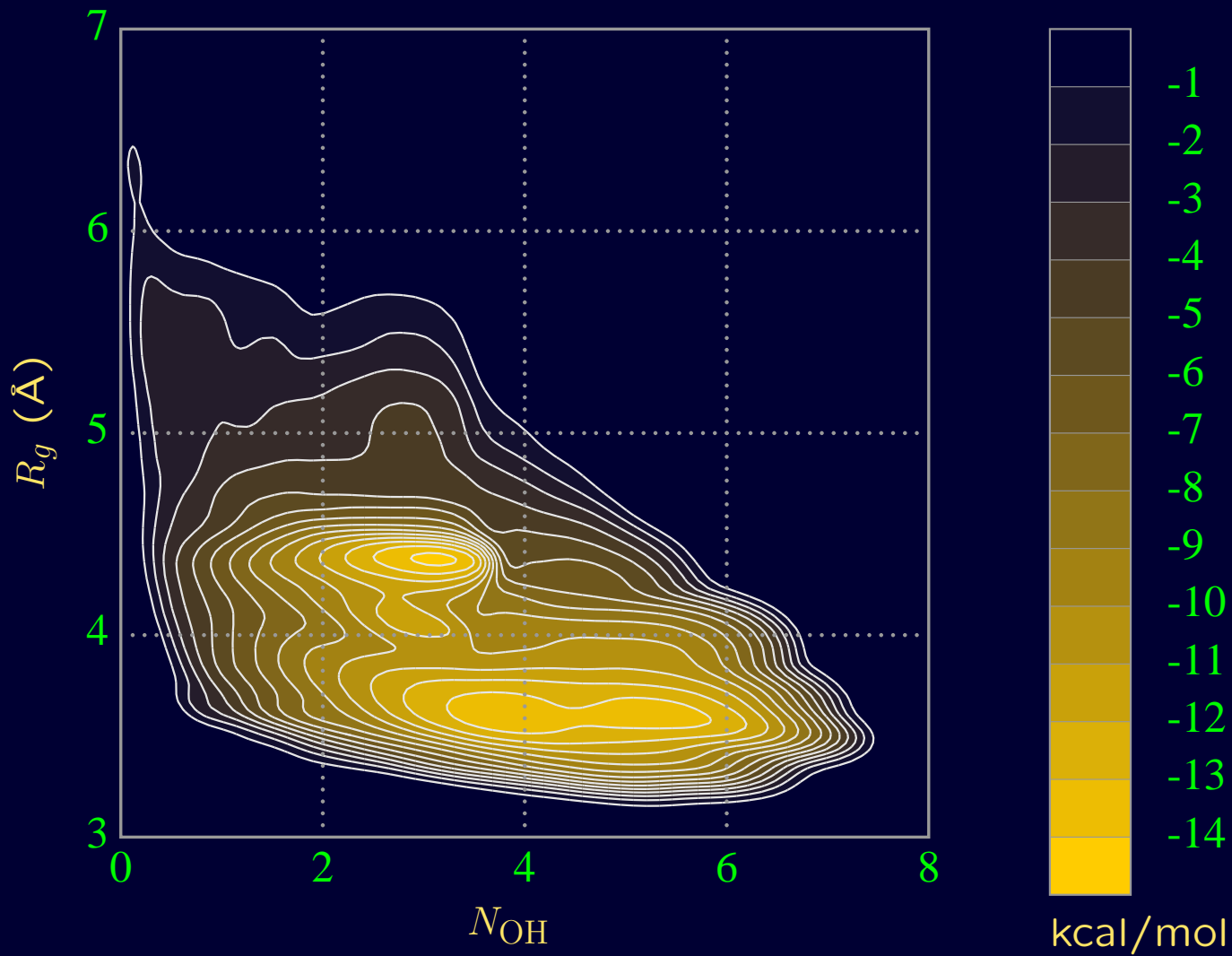


$$r_0 = 2.5\text{\AA}$$

$$N_{\text{OH}} \approx 3$$

Hamiltonian Replica Exchange: 8 + 1

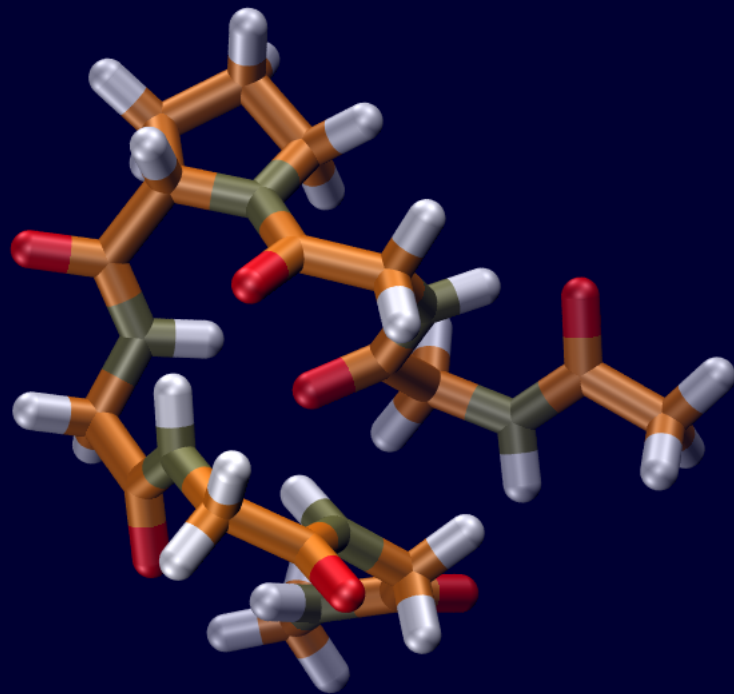




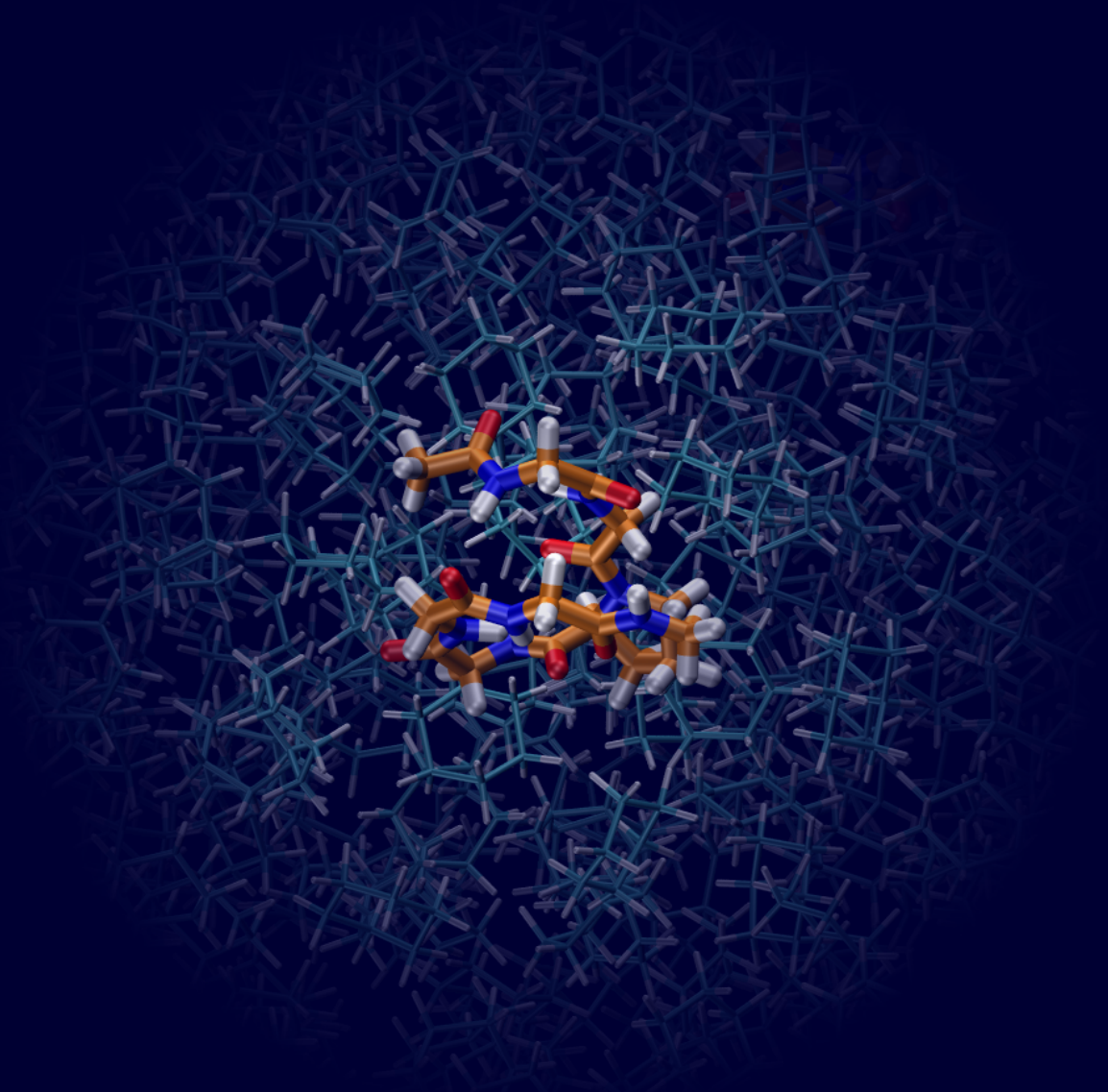
Globular Conformations:



$R_g \approx 3.8\text{\AA}$, $N_{\text{OH}} \approx 3.7$



$R_g \approx 3.6\text{\AA}$, $N_{\text{OH}} \approx 6.0$



Exchange Probability:

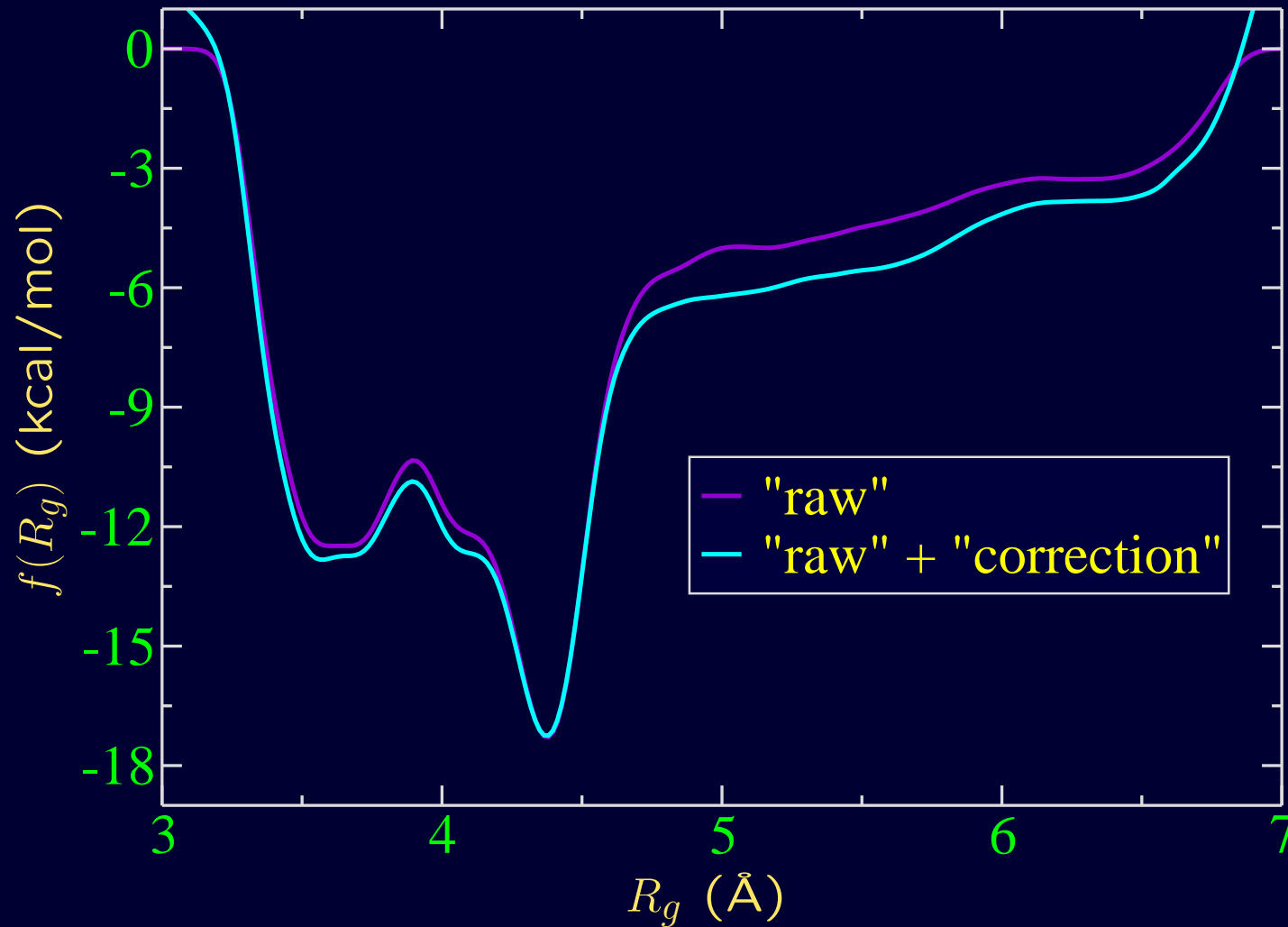
$$w(m|n) = \begin{cases} 1, & \Delta \leq 0 \\ \exp(-\Delta), & \Delta > 0 \end{cases}$$

$$\begin{aligned} \Delta = & \left(\frac{1}{k_B T_n} - \frac{1}{k_B T_m} \right) (E_p^m - E_p^n) \\ & + \frac{1}{k_B T_m} [U^m(\xi^n) - U^m(\xi^m)] \\ & - \frac{1}{k_B T_n} [U^n(\xi^n) - U^n(\xi^m)] \end{aligned}$$

Hamiltonian Replica Exchange: Explicit Solvent

- All replicas at $T = 300$ K.
- 10 replicas with $U = U(r_{ab})$ (distances between the carbon atoms separated by at least two amino-acids).
- 11th replica with $U = U(R_g)$

The Free Energy:



Applications in Progress:

- $B \leftrightarrow Z$ DNA
(Vadzim Karpusenka and Mahmoud Moradi)
- Left – Handed \leftrightarrow Right – Handed polyproline
(Mahmoud Moradi)
- $\alpha \leftrightarrow 3_{10} \leftrightarrow \pi$ helices by $AAAAA(AAARA)_3A$
(Vadzim Karpusenka)

The ABMD is included in AMBER 10
(and freely available for AMBER 9)

Collaborators:

NCSU

Volodymyr Babin
Christopher Roland
Celeste Sagui

NIEHS

Thomas Darden

NCSU (students)

Vadzim Karpusenka
Mahmoud Moradi