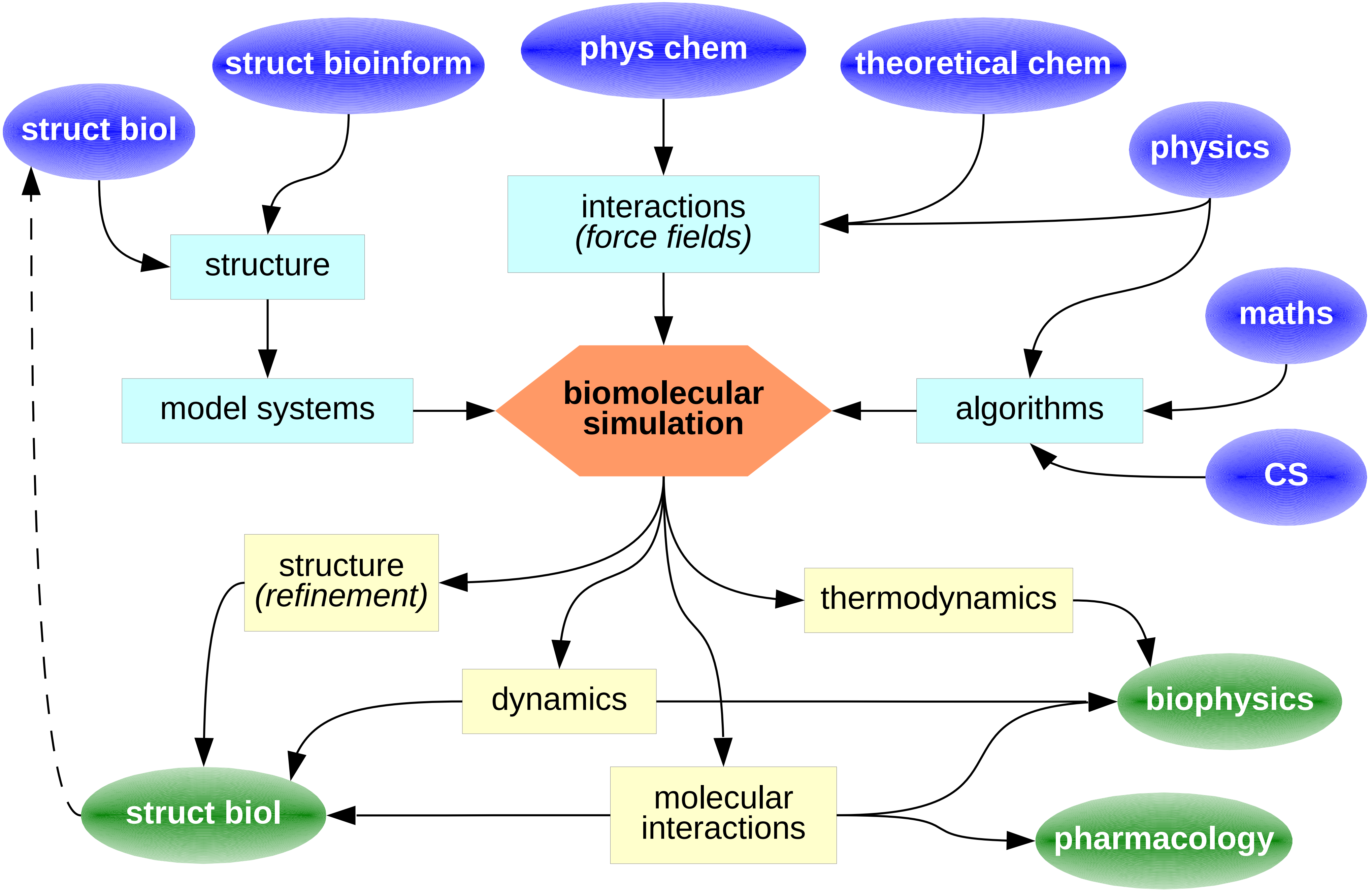
Sampling the free energy surfaces of collective variables

Jérôme Hénin

Enhanced Sampling
and Free-Energy Calculations
Urbana, 12 September 2018

Please interrupt!



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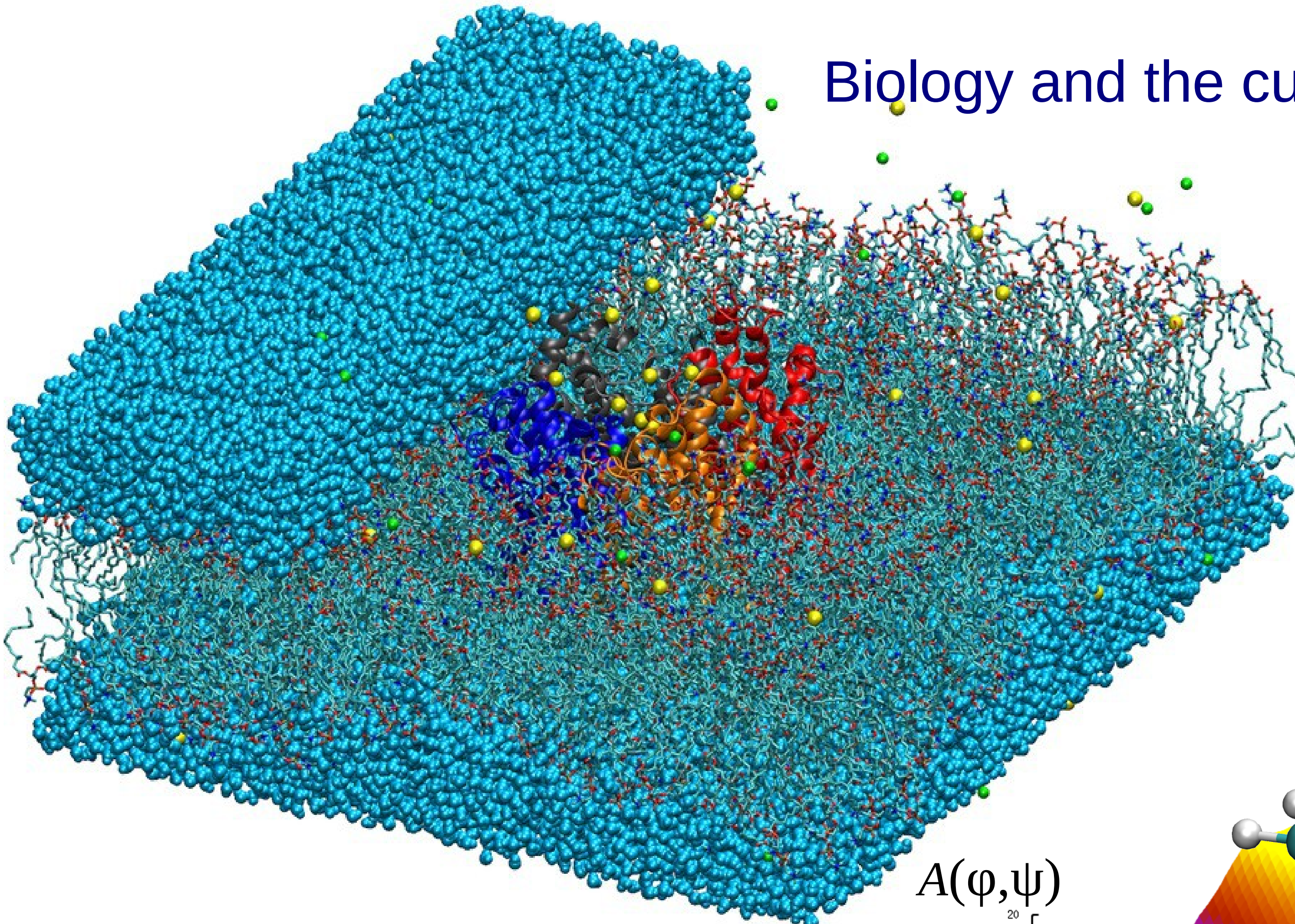
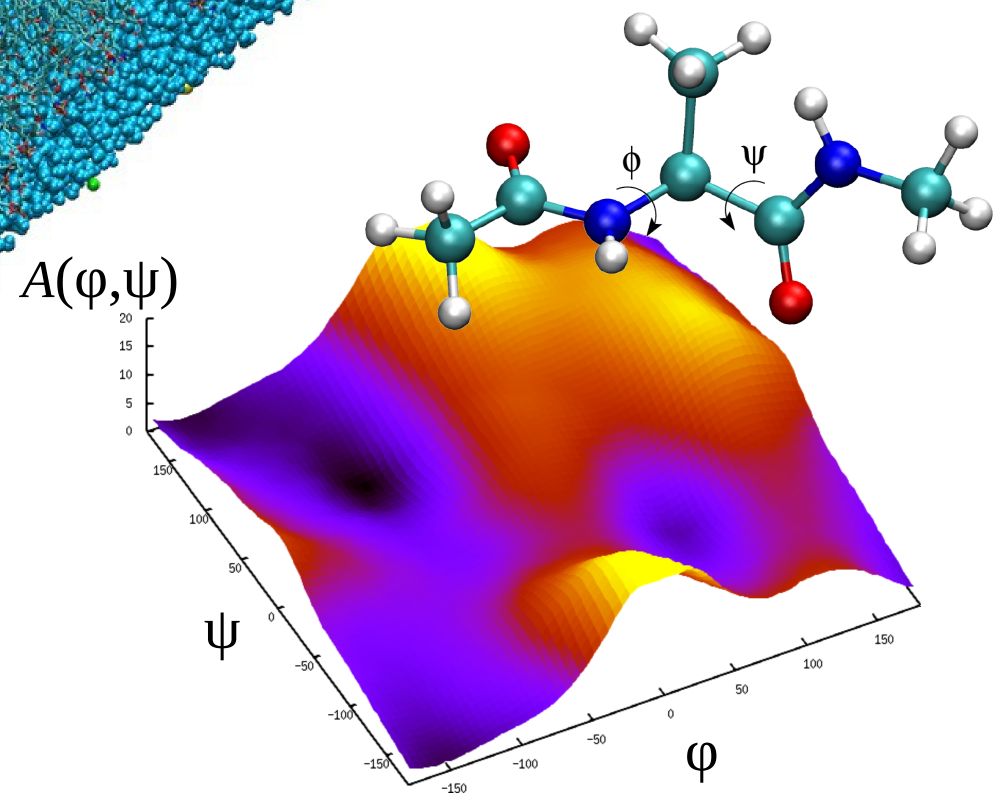
Biology and the curse of dimensionality





we need reduced representations made of few selected coordinates

- for human intuition
- for importance sampling

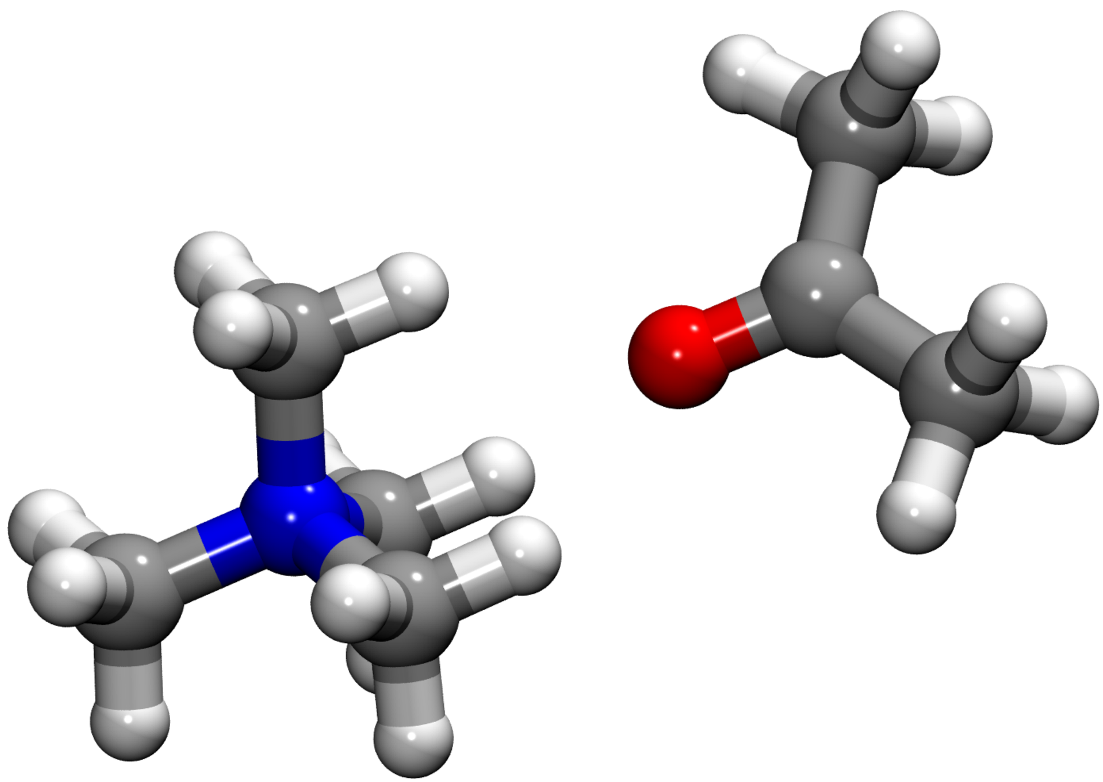
Outline

- Free energy
- Collective variables
- Free energy landscapes

- Methods to compute (estimate) FE landscapes
  - from probability distribution (histograms)
  - from forces (thermodynamic integration)
  - from adapted biasing potential (metadynamics)

- Methods to sample FE landscapes
  - umbrella sampling
  - metadynamics : adaptive biasing potential
  - adaptive biasing force

Tetramethylammonium – acetone binding



Free energy

- **free energy differences ↔ probability ratios**

$$\Delta F_{AB} = F_B - F_A = -k_B T \ln\left(\frac{P_B}{P_A}\right)$$

$$\Delta F_{AB} > 0 \iff P_B < P_A$$

$$\Delta F_{AB} = 0 \iff P_B = P_A$$

- ***macrostates*** (A, B) are collections of ***microstates*** (atom coordinates *x*)
- →probabilities of macrostates are sums (integrals) over microstates

$$P_A = \int_A p(x)dx$$

- probabilities of microstates follow ***Boltzmann distribution***

$$p(x) = \frac{\exp(-V(x)/k_B T)}{Z} = \frac{1}{Z}e^{-\beta V(x)}$$

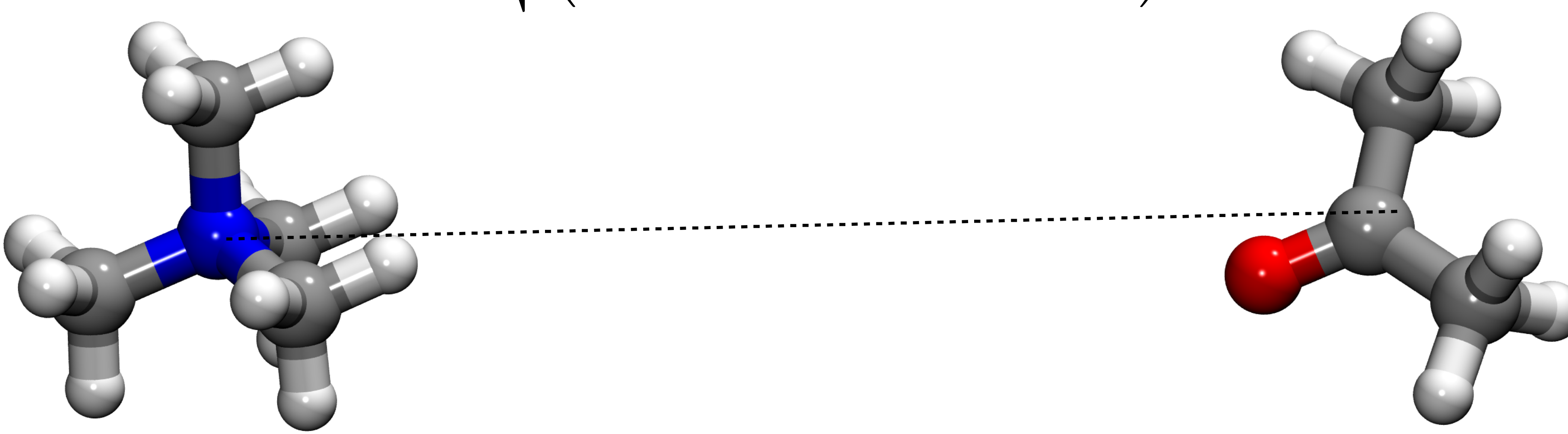
Collective variables

- geometric variables that depend on the positions of several atoms (hence "collective")
- mathematically: functions of atomic coordinates $z = \xi(x_i, y_i, z_i ...)$
- example: distance between two atoms

$$d_{12} = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2} = \sqrt{(r_2 - r_1)^2}$$

- distance between the centers of mass of groups of atoms G_1, G_2

$$d_{G1,G2} = \sqrt{\left(\frac{\sum_{i \in G_2} m_i r_i}{\sum_{i \in G_2} m_i} - \frac{\sum_{i \in G_1} m_i r_i}{\sum_{i \in G_1} m_i} \right)^2}$$



Probability distribution of a collective variable

- we know the 3N-dimensional probability distribution of atom coordinates *x:*

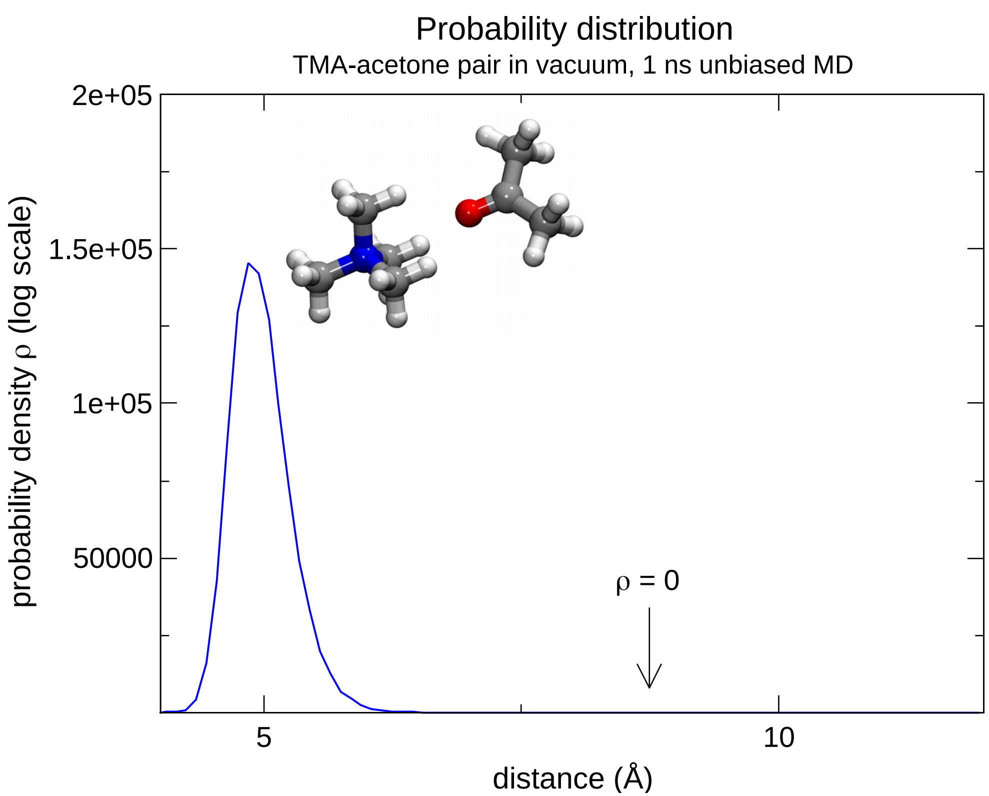
$$p(x) = \frac{\exp(-V(x)/k_B T)}{Z}$$

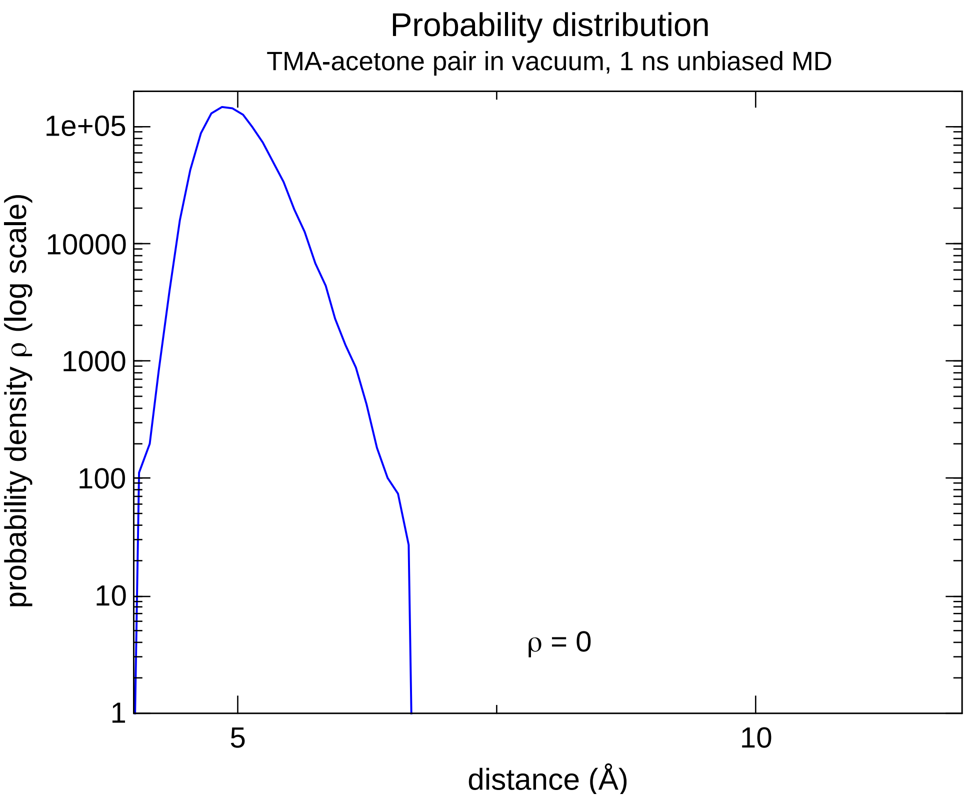
- what is the probability distribution of $z = \xi(x)$
- theory: sum (integral) over all the values of *x* corresponding to a value of *z*

$$\rho(z) = \int p(x)\delta(\xi(x) - z)dx$$

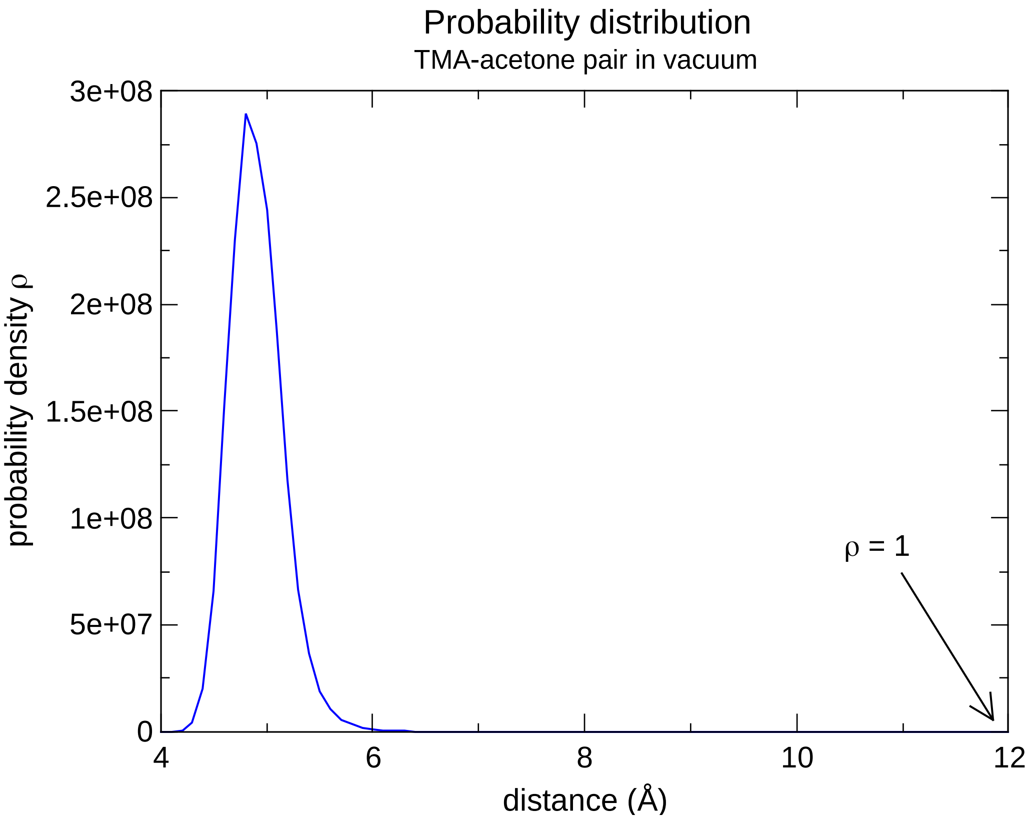
- in simulations: sample and calculate a **histogram** of coordinate *z*

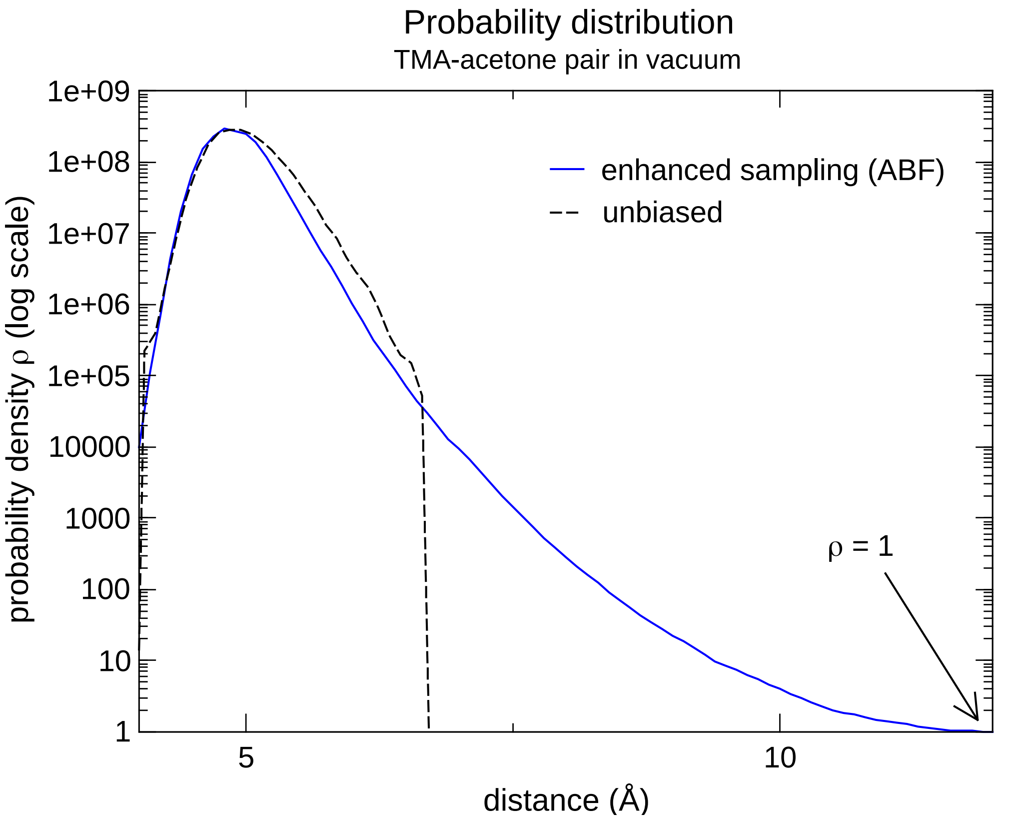
Probability distribution of a collective variable
(1) from unbiased simulation



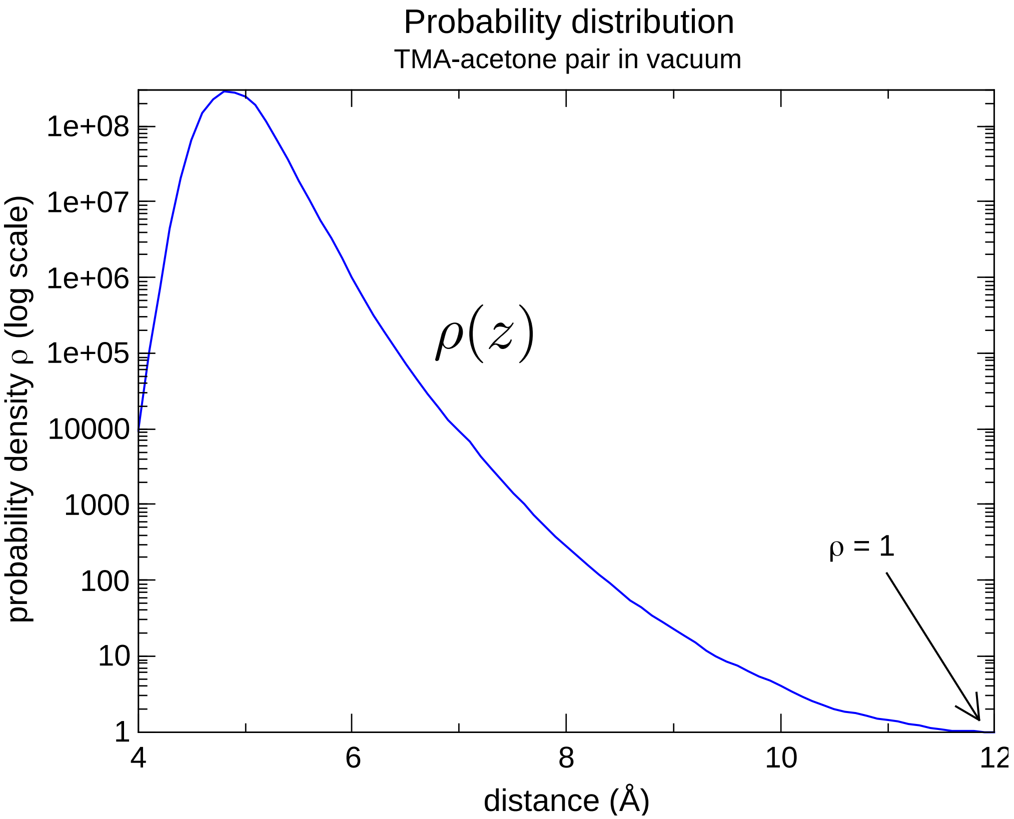


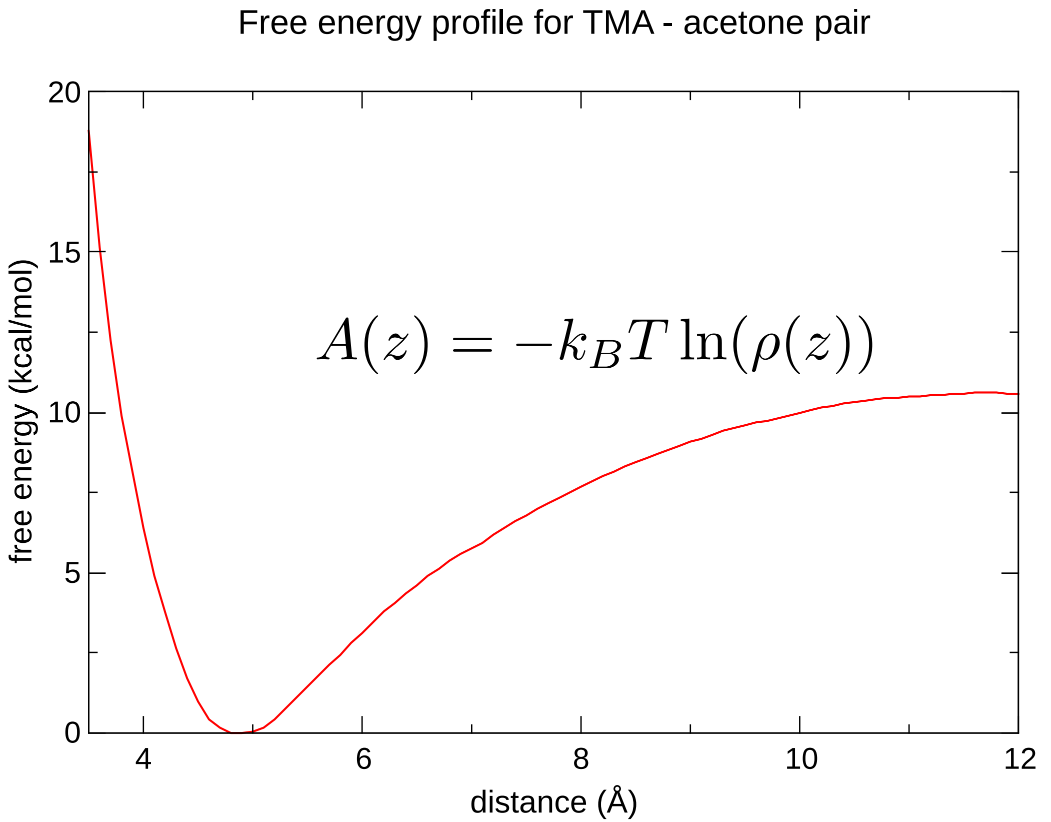
Probability distribution of a collective variable (2) with enhanced sampling





From probability to free energy





Ways to calculate the free energy

- from unbiased histogram $A(z) = -k_B T \ln(\rho(z)) + C$

- from biased histogram (*importance sampling*) with bias $V^{bias}(z)$

$$A(z) = -k_B T \ln(\rho(z)) - V^{\mathrm{bias}}(z) + C$$

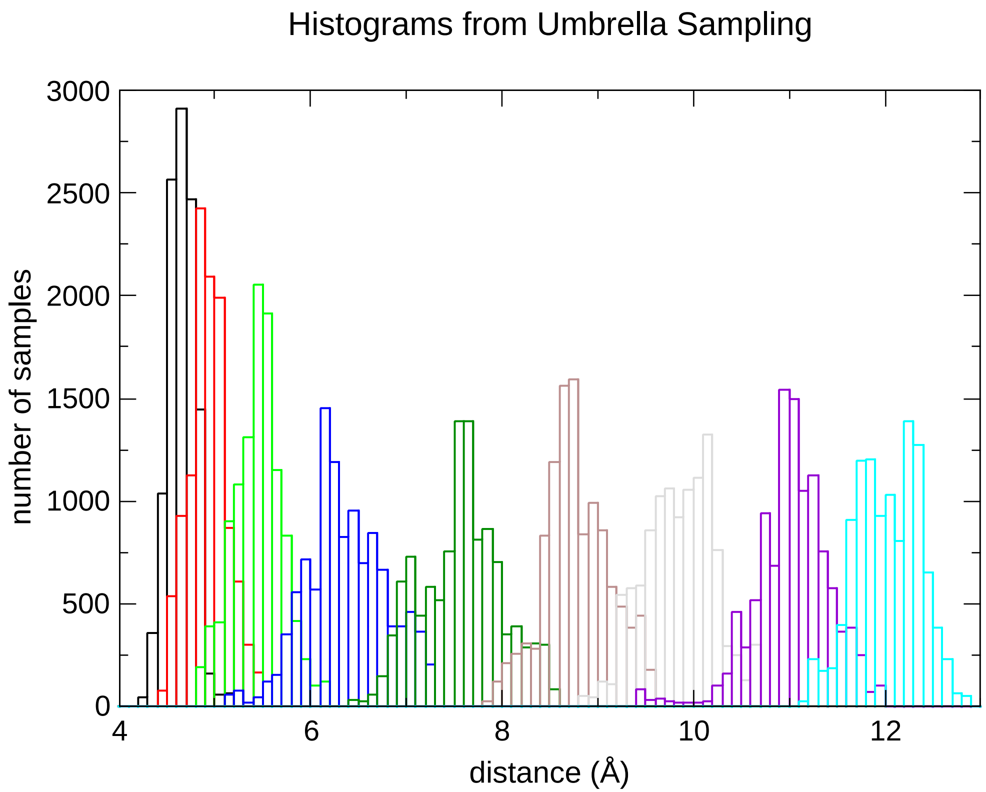
  - in Umbrella Sampling, need to find values of *C!*

- estimate and integrate free energy derivative (gradient): *Thermodynamic Integration*

$$A(z) = \int_0^z A'(z^*) dz^* + A(0)$$

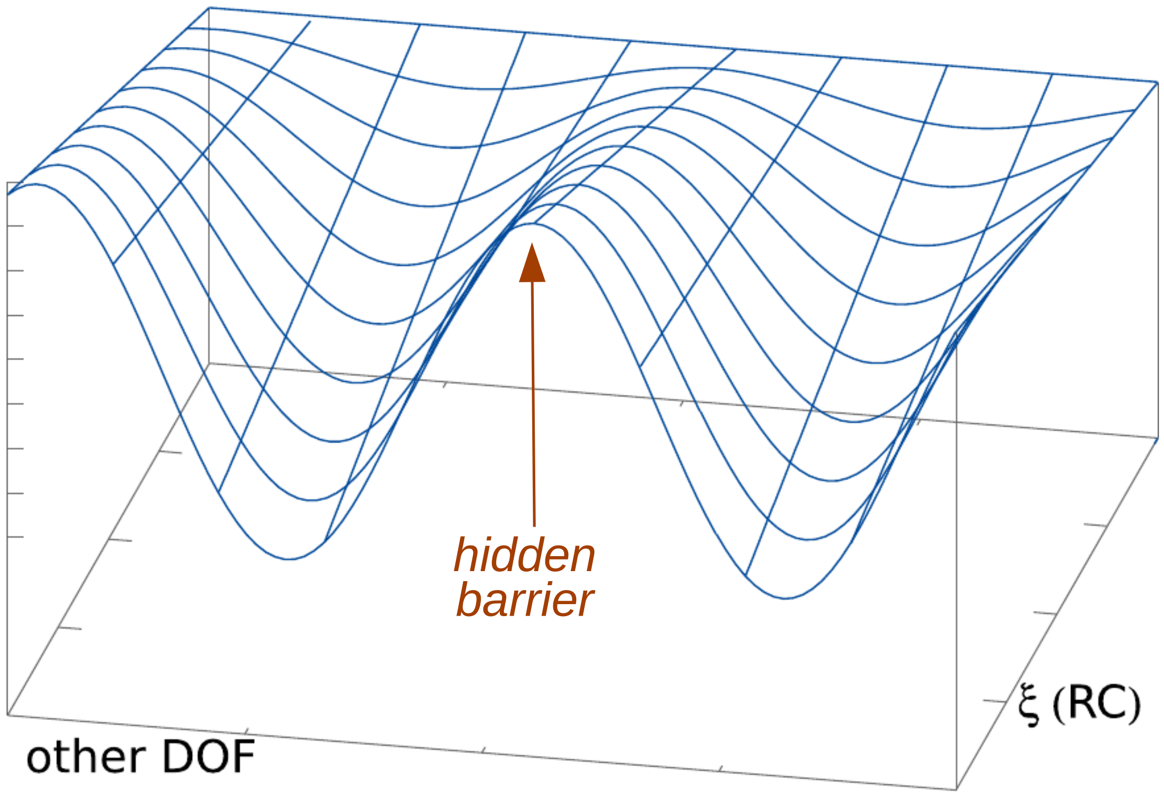
$$A'(z) = \left\langle \frac{\partial V}{\partial z} - k_B T \frac{\partial \ln |J|}{\partial z} \right\rangle_{\xi(x)=z}$$

Umbrella sampling

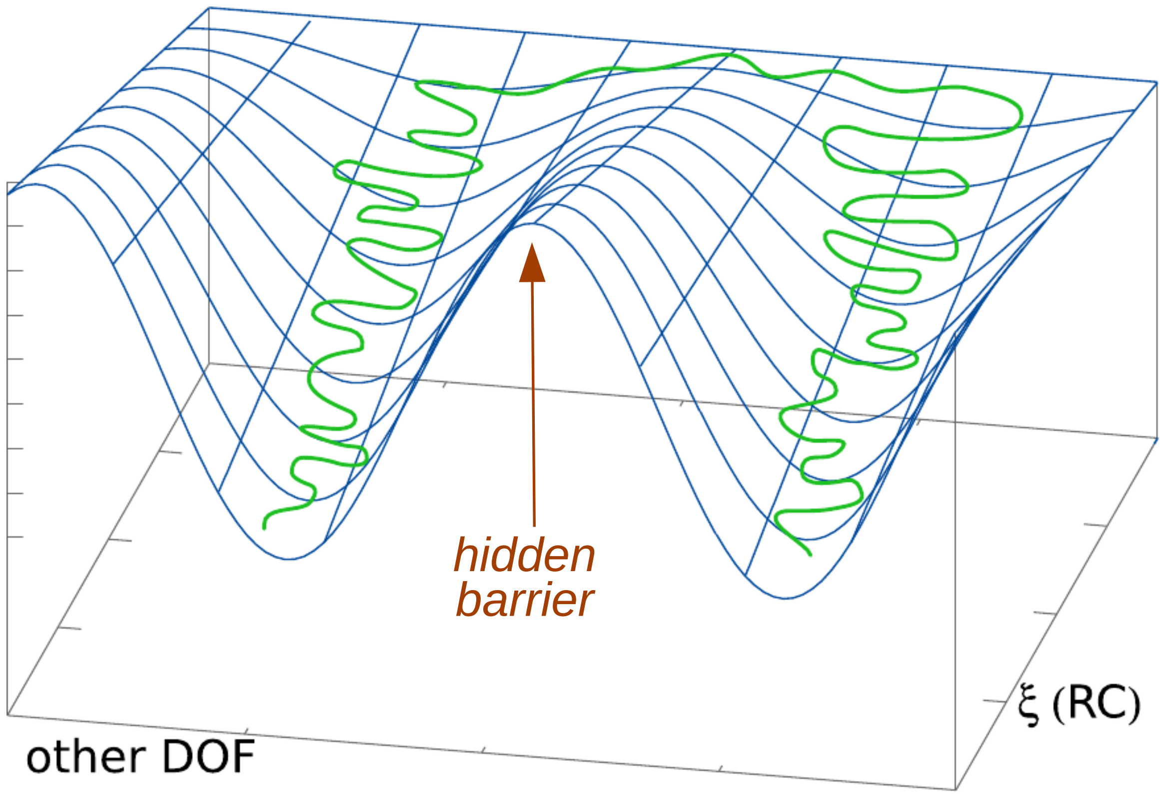


- distribute (*stratify*) sampling using multiple confinement restraints
- combine partial information of each histogram by computing relative free energies
  - WHAM (weighted histogram analysis method)
  - MBAR (multistate Bennett's acceptance ratio)
- requires overlap between sampling in adjacent windows

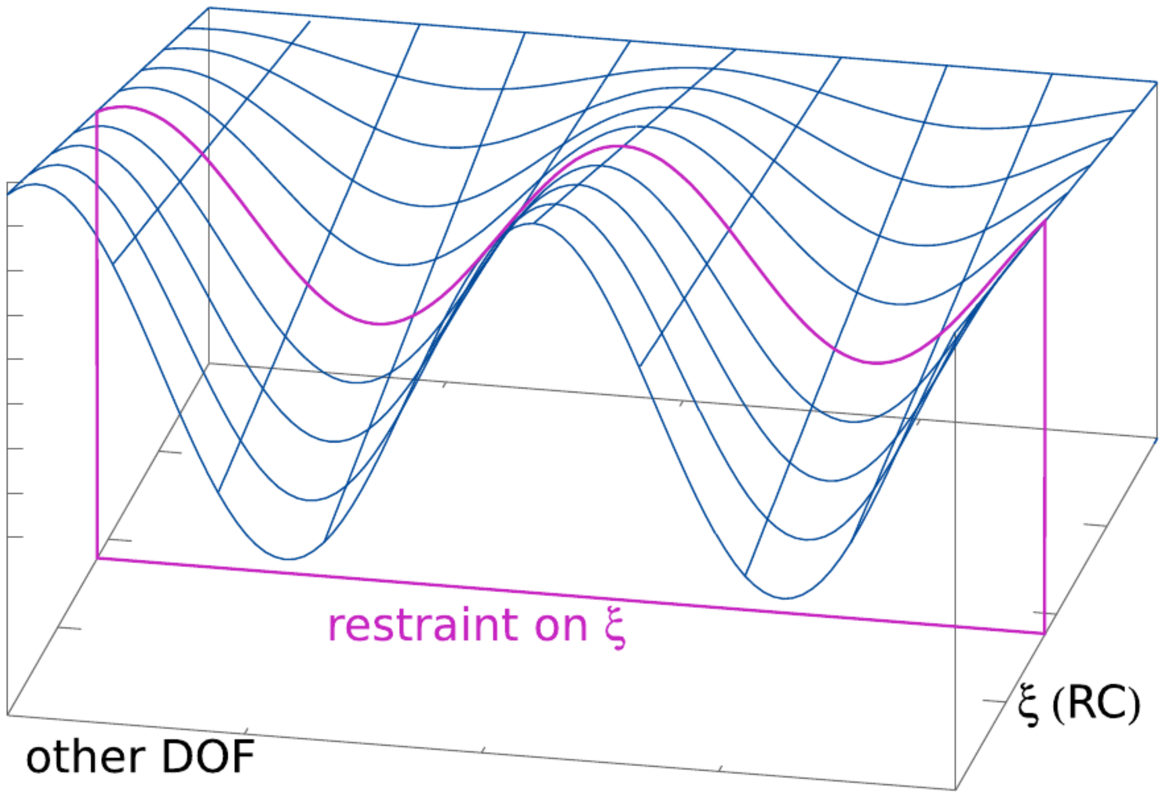
Multi-channel free energy landscape



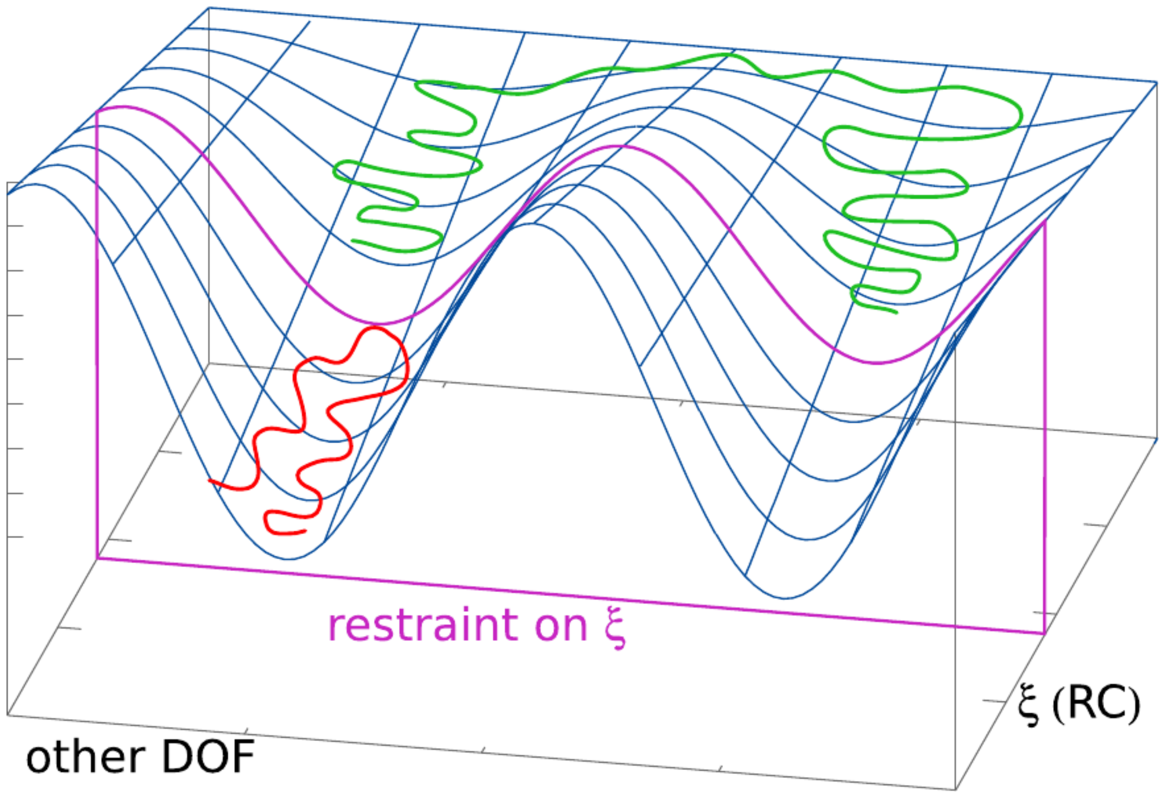
Multi-channel free energy landscape



Umbrella Sampling: *stratification*

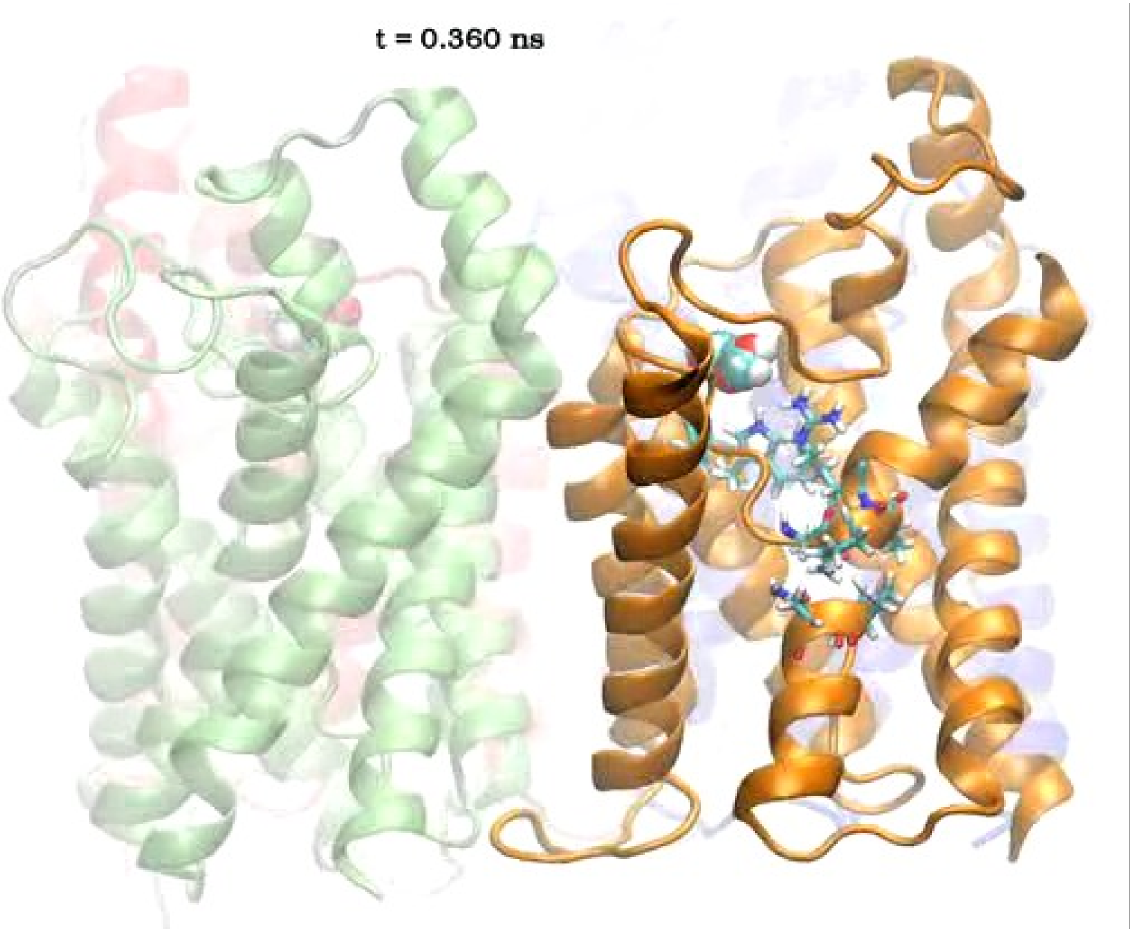


Umbrella *Sampling or Not Sampling?*



benefit of adaptive sampling methods: no stratification needed

Orthogonal relaxation in ABF



Hénin, Tajkhorshid, Schulten & Chipot, Biophys J. 2008

Adaptive sampling 1: adaptive biasing potential

Free energy profile *A(z)* is linked to distribution of transition coordinate:

$$e^{-\beta A(z)} \propto \rho(z) \propto \int e^{-\beta V(x)} \delta(\xi(x) - z)\, dx$$

ABP: time-dependent biased potential

$$\tilde{V}_t(x) = V(x) - A_t(\xi(x))$$ where A_t converges to A

Long-time biased distribution: $\tilde{\rho}_\infty(z) \propto e^{-\beta(A(z) - A_\infty(z))}$

that is, a **uniform distribution**.

Adaptive Biasing Potential : Metadynamics

- adaptive bias is sum of Gaussian functions created at current position
- pushes coordinate away from visited regions
- convergence requires careful tuning of time dependence of the bias (“well-tempered” metadynamics)

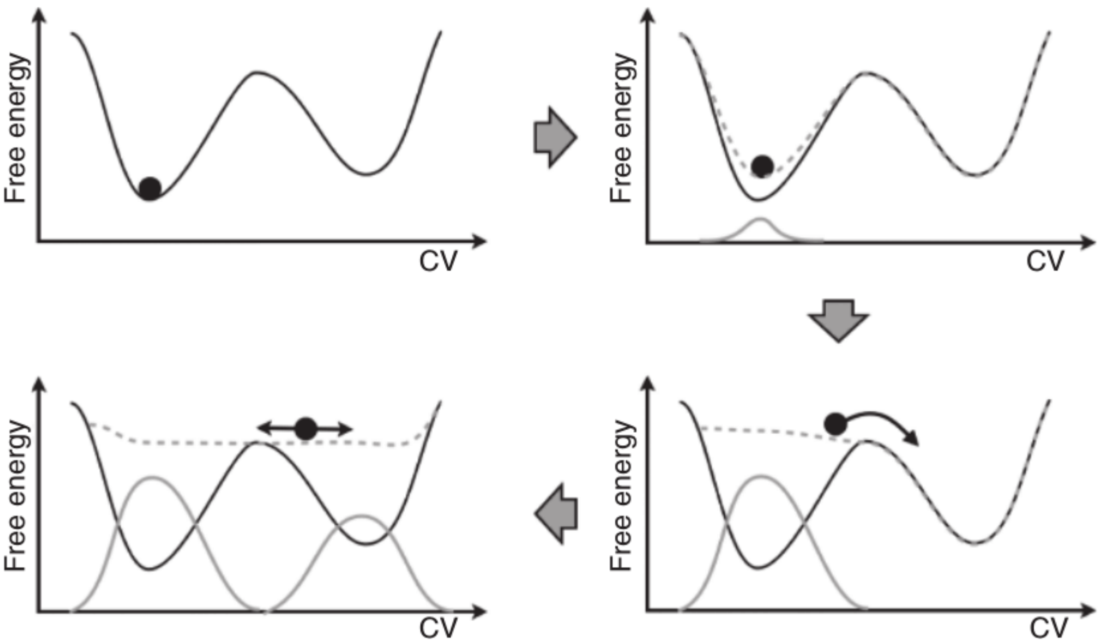


Illustration: Parrinello group, ETH Zürich

Adaptive sampling 2: Adaptive Biasing Force (ABF)

- ABF: time-dependent biasing force

$$\tilde{F}_t(x) = -\nabla V(x) + A'_t(\xi(x))\nabla\xi$$ where A'_t converges to A'

- long-time biased distribution is uniform, as in ABP
- how do we estimate A'?

Free energy derivative is a mean force

$$A(z) = -k_B T \ln \left(\int e^{-\beta V(x)} \delta(\xi(x) - z) dx \right)$$

$$A'(z) = \left\langle \frac{\partial V}{\partial z} - k_B T \frac{\partial \ln |J|}{\partial z} \right\rangle_{\xi(x)=z}$$

$-\dfrac{\partial V}{\partial z}$ is a projected force (defined by coordinate transform)

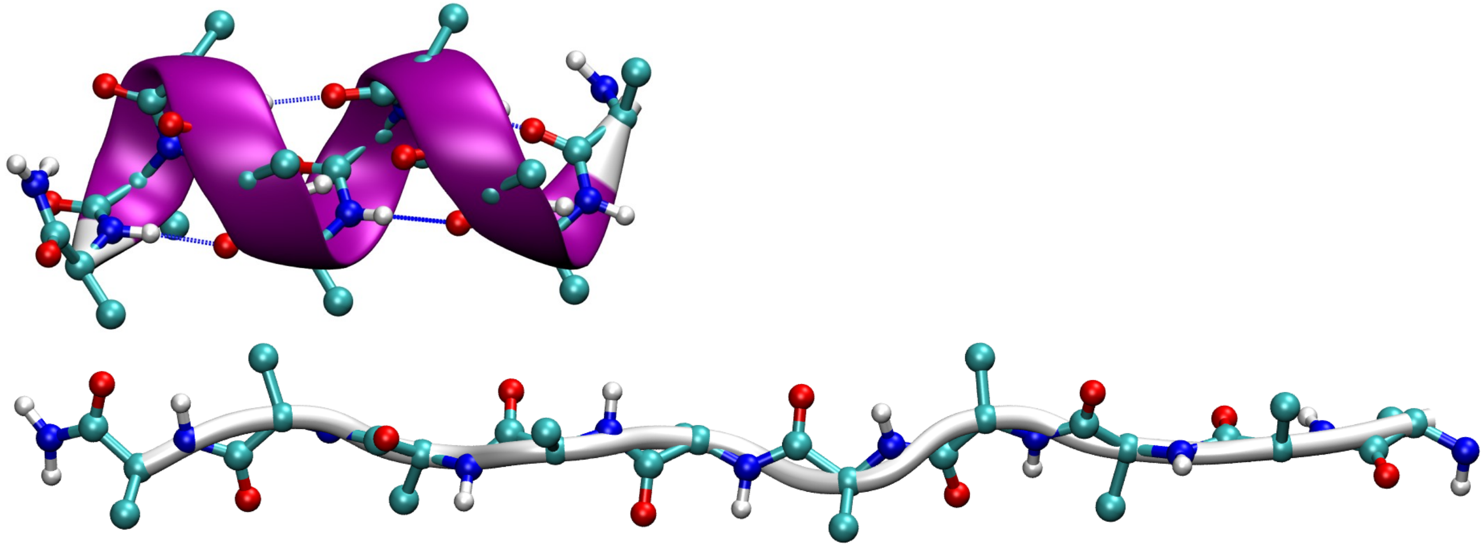
$\dfrac{1}{\beta} \dfrac{\partial \ln |J|}{\partial z}$ is a geometric (entropic) term

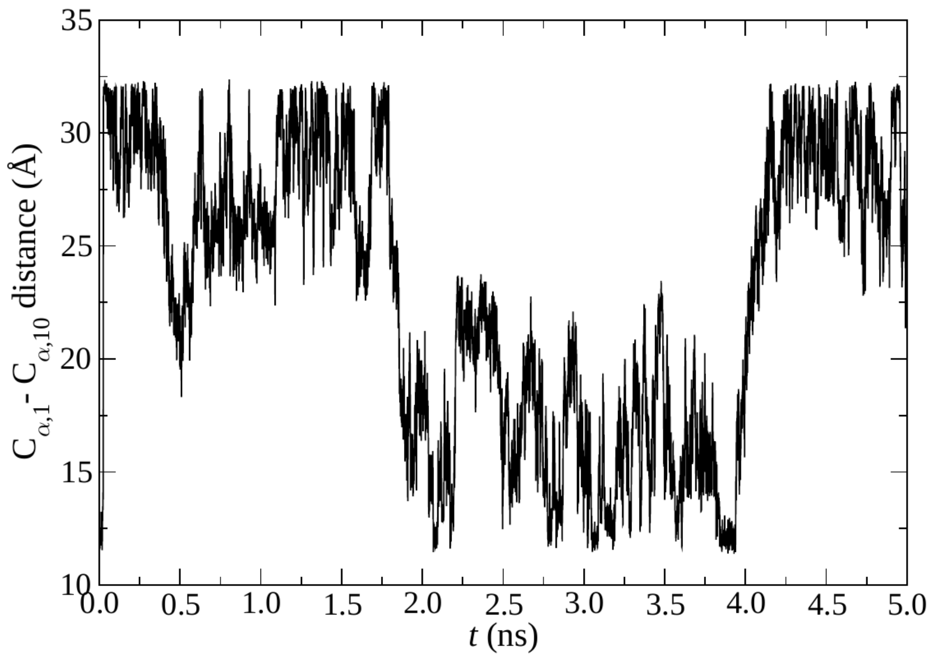
den Otter J. Chem. Phys. 2000

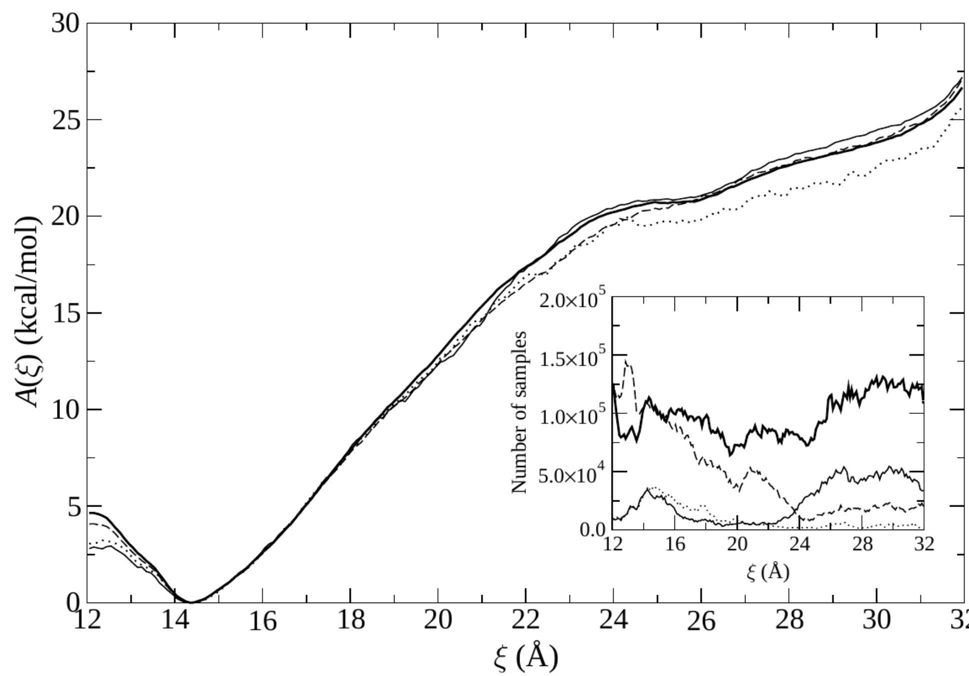
Simpler estimator of free energy gradient

- for each variable ξ_i, force is measured along arbitrary vector field $v_i(x)$ *(Ciccotti et al. 2005)*
- orthogonality condition: $v_i \cdot \nabla_x \xi_j = \delta_{ij}$
- free energy gradient: $\partial_i A(z) = \langle v_i \cdot \nabla_x V - k_B T \nabla_x \cdot v_i \rangle_{\xi(x)=z}$
- there are other estimators:
  - from constraint force (original ABF, Darve & Pohorille 2001)
  - from time derivatives of coordinate (Darve & Pohorille 2008)

1. Stretching deca-alanine

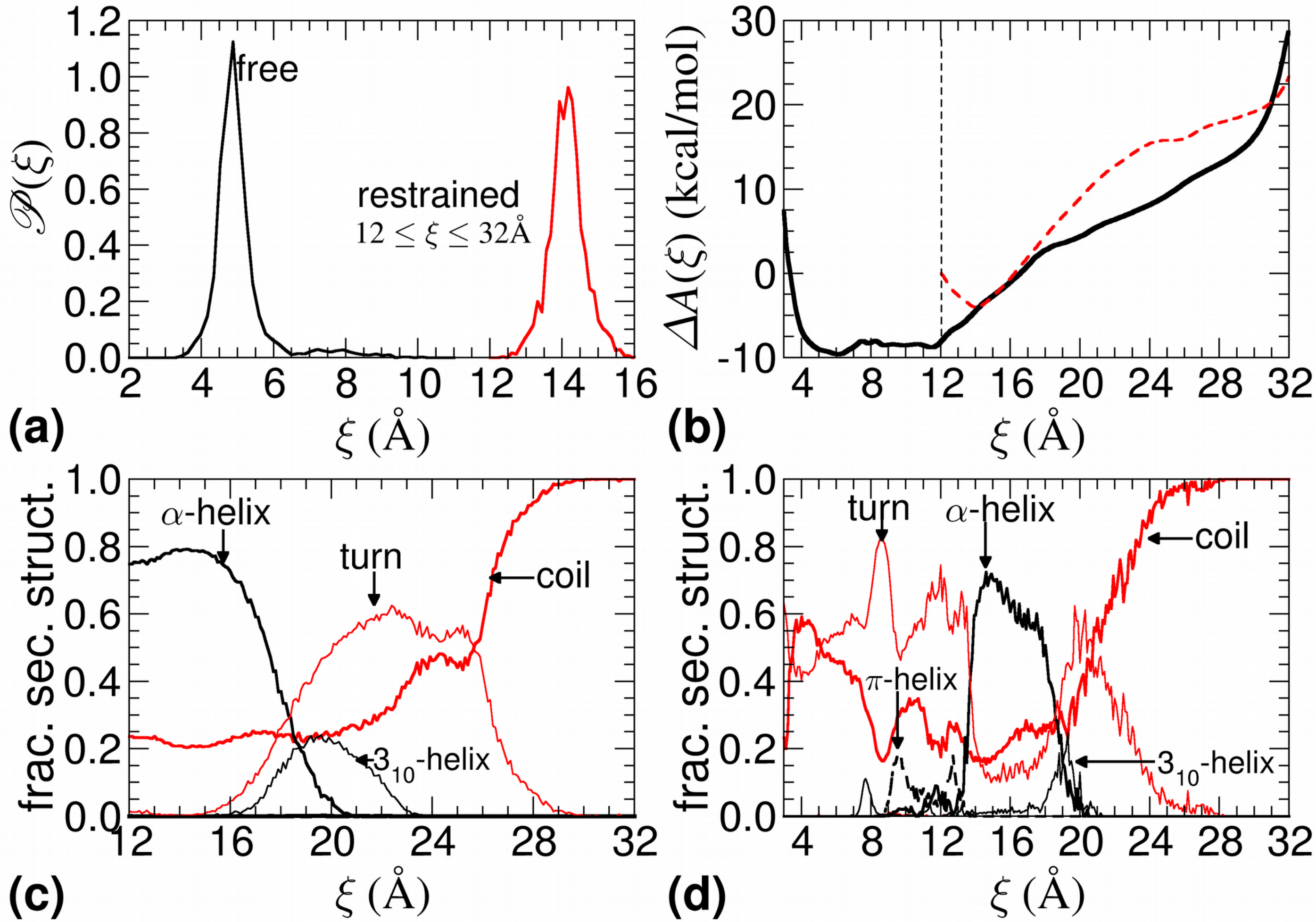


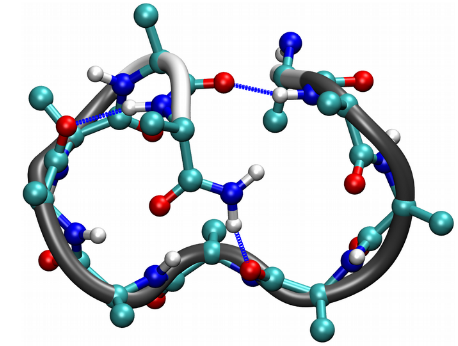


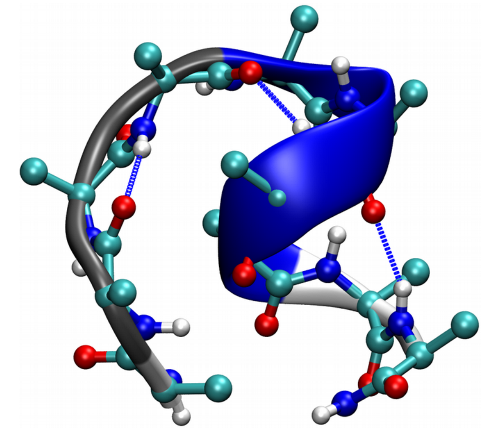


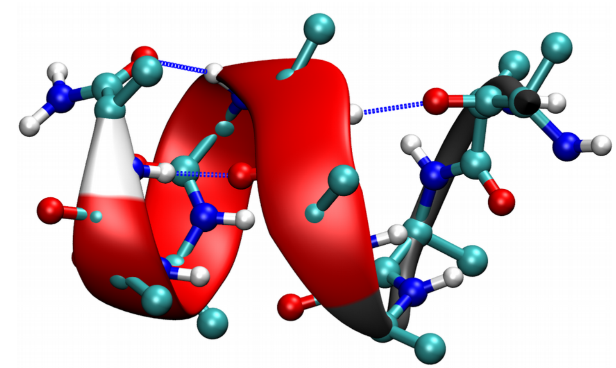
Hénin & Chipot JCP 2004

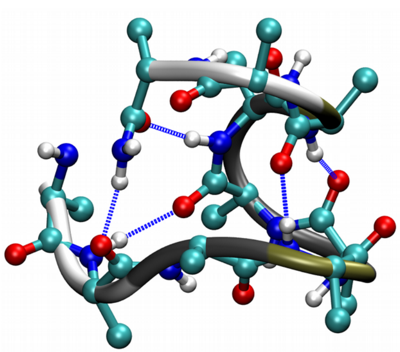
2. Sampling deca-alanine?

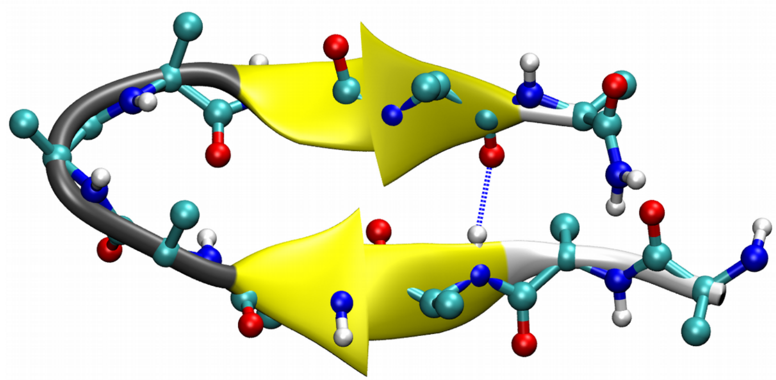






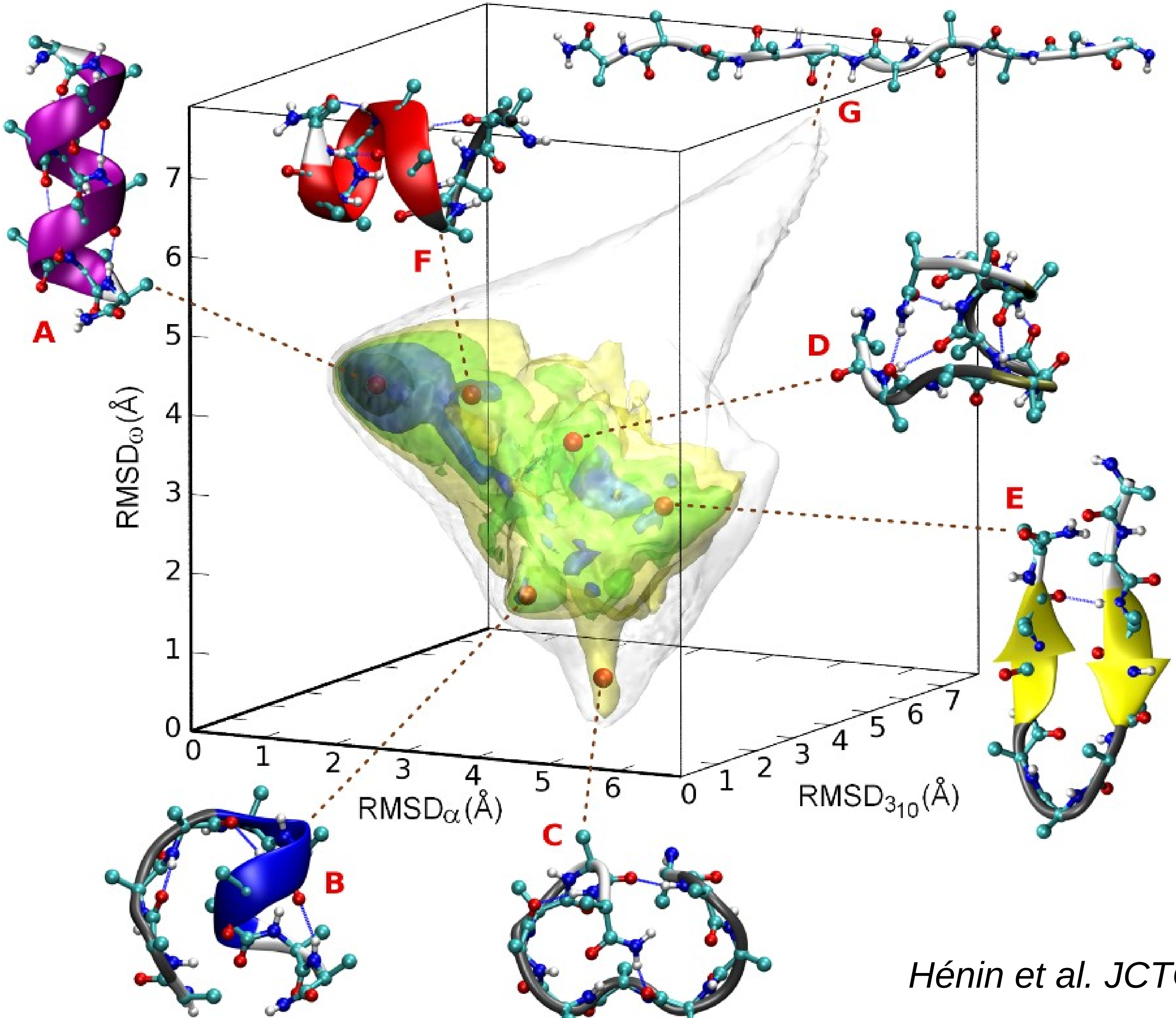






Chipot & Hénin JCP 2005

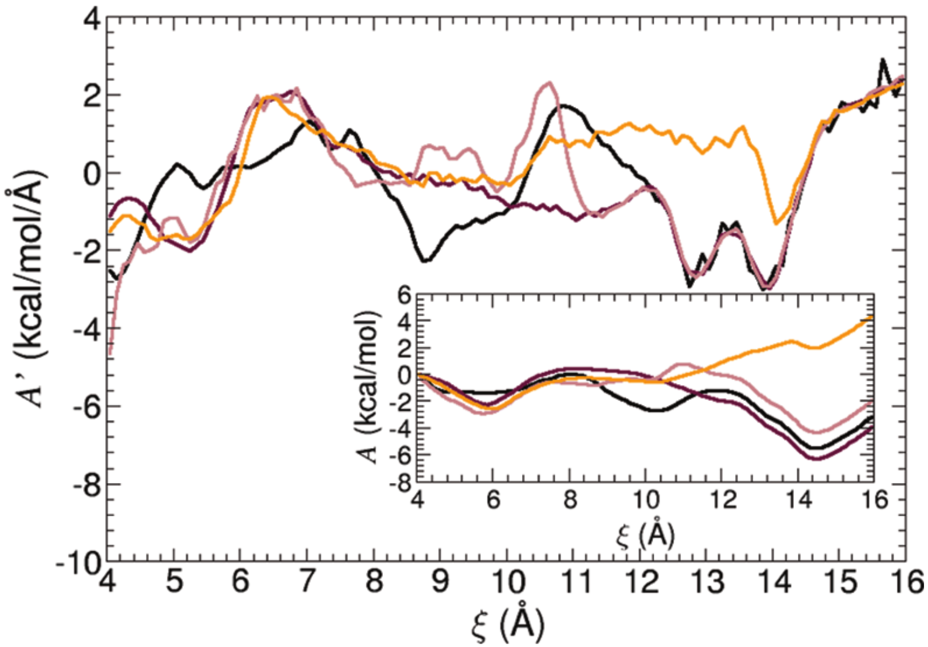
3. Sampling in higher dimension



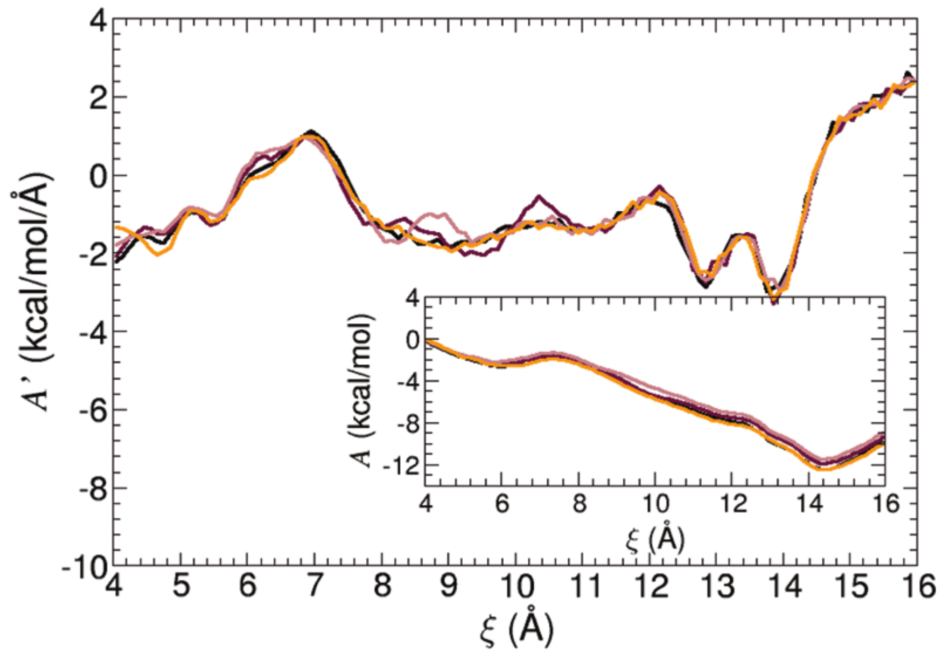
Hénin et al. JCTC 2010

4. More robust sampling for poor coordinates: Multiple-Walker ABF

- good performance with *hidden barriers* (Minoukadeh, Chipot, Lelièvre 2010)
- can sample systems using incomplete set of collective variables?



ABF, 1 x 100 ns



MW-ABF, 32 x 3 ns

ABF: a tale of annoying geometry

Estimator of free energy gradient:

- for each variable ξ_i, force is "measured" along arbitrary vector field v_i *(Ciccotti et al. 2005)*
- orthogonality conditions: $\begin{cases} \boldsymbol{v}_i \cdot \boldsymbol{\nabla}_{\boldsymbol{x}} \xi_j = \delta_{ij} \\ \boldsymbol{v}_i \cdot \boldsymbol{\nabla}_{\boldsymbol{x}} \sigma_k = 0 \end{cases}$

- free energy gradient: $\partial_i A(z) = \langle v_i \cdot \nabla_x V - k_B T \nabla_x \cdot v_i \rangle_{\xi(x)=z}$

- geometric calculations are sometimes intractable
(e.g. second derivatives of elaborate coordinates)
- orthogonality conditions are additional constraints
- in practice, many cases where **ABF is unavailable**

extended-system Adaptive Biasing Force (eABF)

- idea: Lelièvre, Rousset & Stoltz 2007
- implementation: Fiorin, Klein & Hénin 2013

Get rid of geometry by watching an unphysical variable λ ,
harmonically coupled to our geometric coordinate:

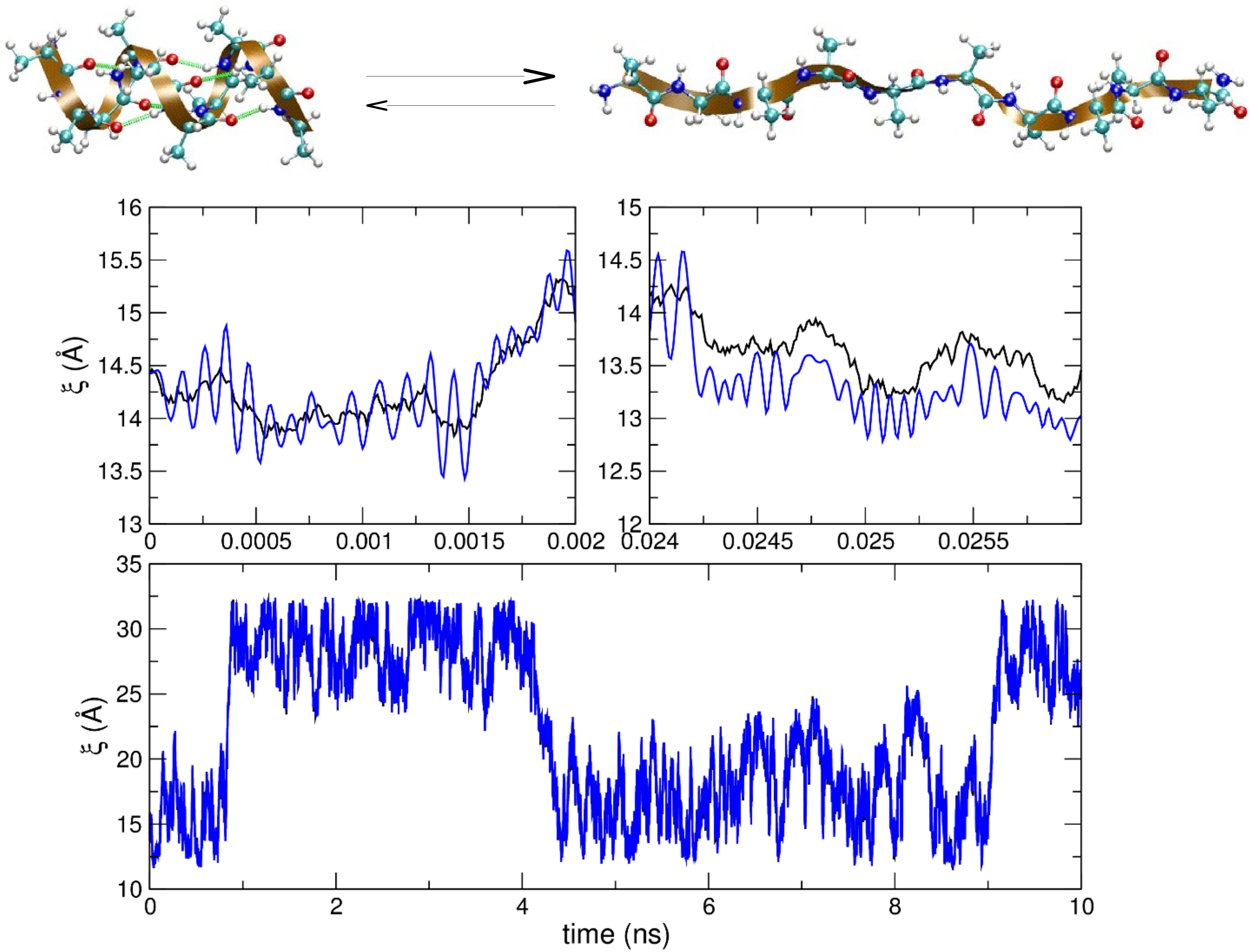
$$V^k(x,\lambda) = V(x) + \frac{1}{2}k\left(\xi(x) - \lambda\right)^2$$

λ undergoes Langevin dynamics with mass m.
Mass and force constant based on desired fluctuation and period:

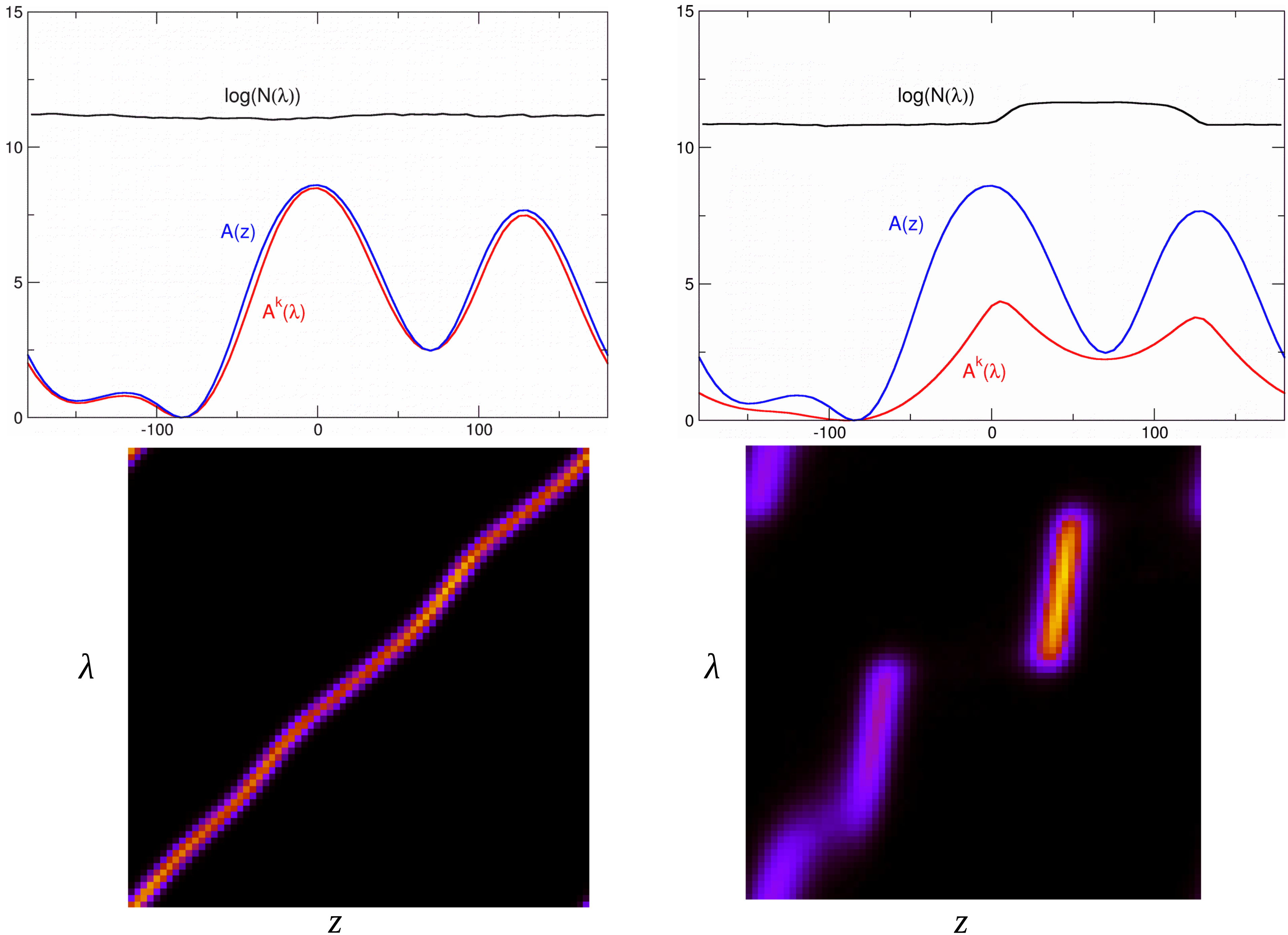
$$\sigma = \sqrt{\frac{k_B T}{k}}$$

$$\tau = 2\pi\sqrt{\frac{m}{k}}$$

eABF trajectories



Tight vs. loose coupling



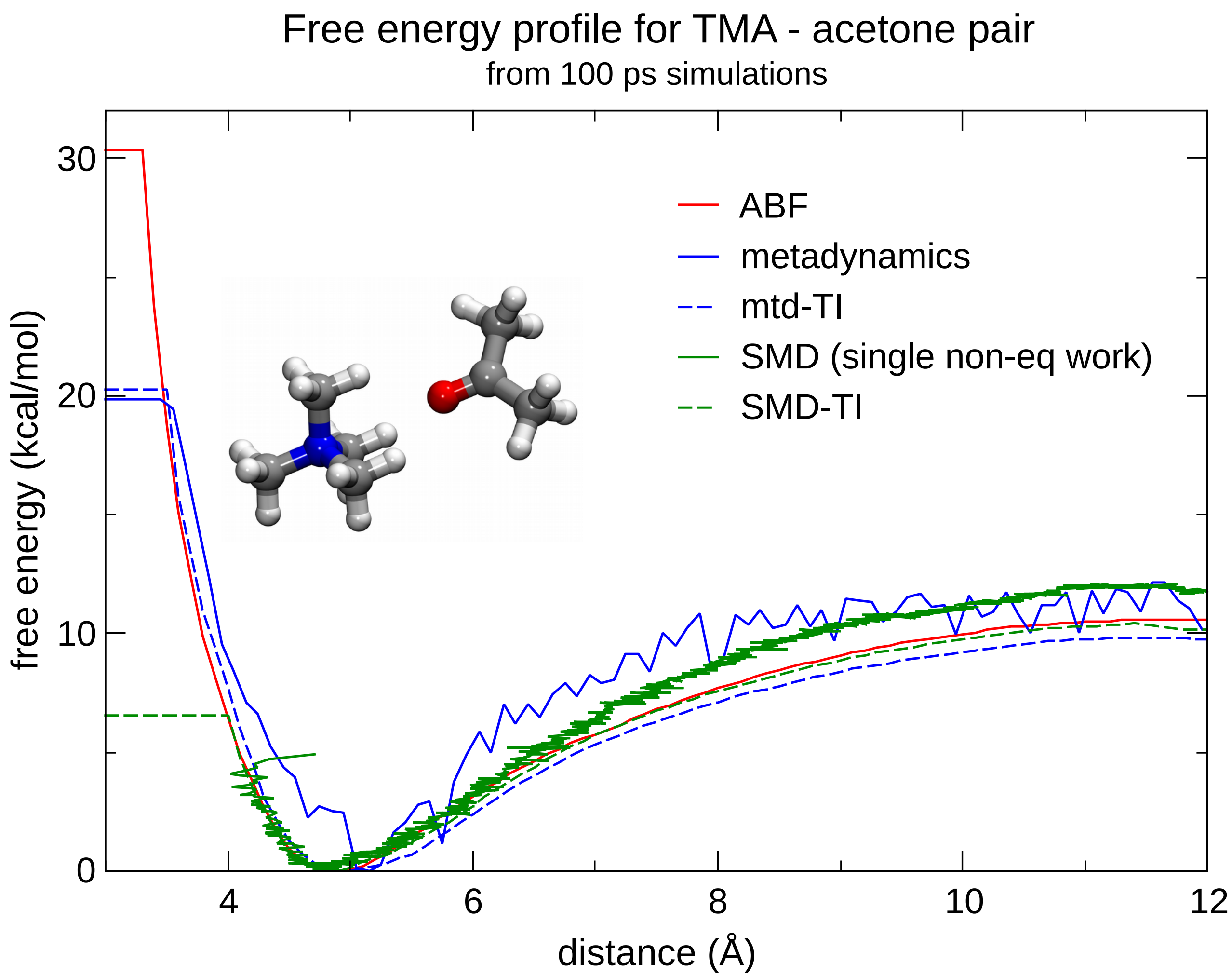
Free energy estimators for eABF

- A^k is an estimator of free energy A, asymptotically accurate **for high *k***
- other estimators lift this “stiff spring” requirement:
  - umbrella integration (Kästner & Thiel 2005, Zheng & Yang 2012, Fu, Shao, Chipot & Cai 2016)
  - CZAR (Lesage, Lelièvre, Stoltz & Hénin 2017)
- using these estimators, eABF is a **hybrid adaptive method** (free energy estimate is separate from bias)

Hybrid methods

- adaptive sampling combines free energy estimation and enhanced sampling
- hybrid methods: bias based on one estimator, use another estimator to compute final free energy
- examples:
  - unbiased sampling with thermodynamic integration
  - metadynamics with thermodynamic integration
  - eABF dynamics with UI or CZAR estimator

Different estimates at very short sampling times



- same long-time results, but different short-time convergence!
- caution: may be system-dependent
- efficiency of sampling vs. biases in short-time estimates

  → benefit of hybrid methods

Thank you!

Questions?