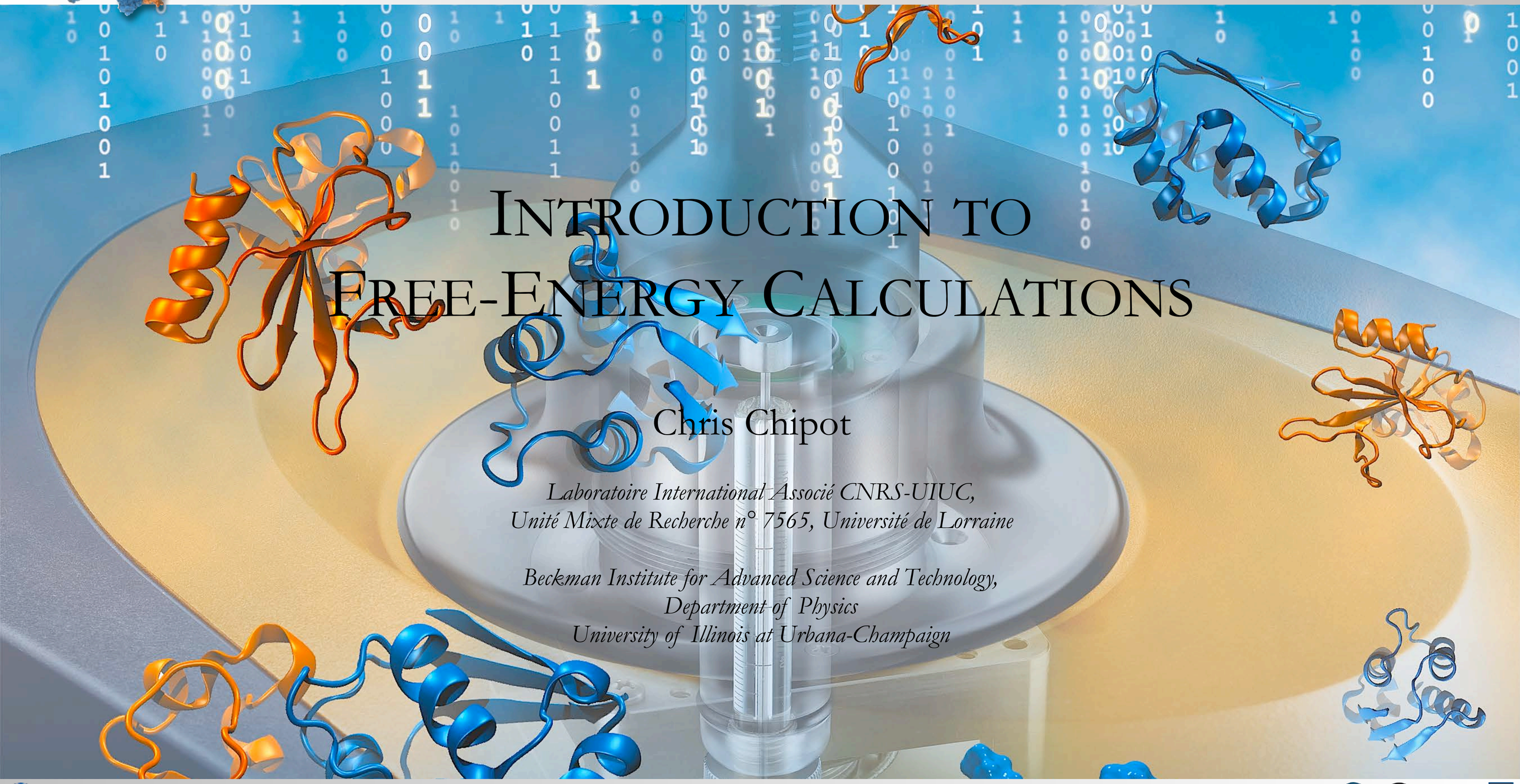

Introduction to Free-Energy Calculations

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Beckman Institute for Advanced Science and Technology,
Department of Physics
University of Illinois at Urbana-Champaign

Introduction

The race for longer and larger simulations
What is the best method for a given problem?

Alchemical free-energy calculations

- A tool to address host-guest chemistry questions
- Good practices, guidelines and recommendations
- The long-standing protein-ligand problem

Geometrical free-energy calculations

- What is a good reaction-coordinate model?
- A host of methods to measure free-energy changes
- Potentials of mean force and transport phenomena
- Potentials of mean force and recognition and association phenomena
- What about non-equilibrium work computer experiments?

Ongoing challenges at the frontiers of free-energy calculations

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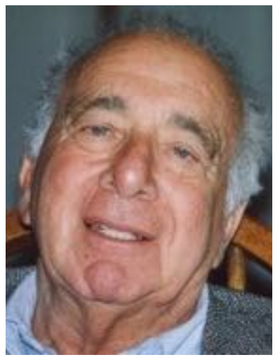
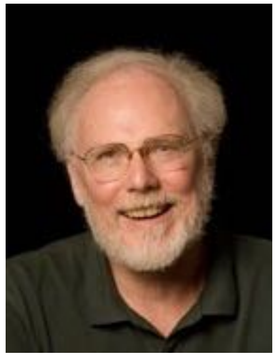


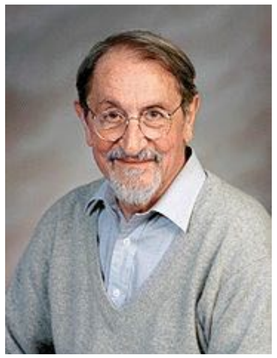
First molecular dynamics simulation. Phase transition in model liquids.

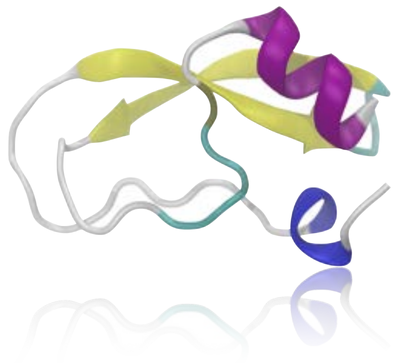
$$\begin{cases} m_i \dfrac{\mathrm{d}^2 x_i}{\mathrm{d}t^2} &= F_i \\ F_i &= -\dfrac{\partial U(\mathbf{x})}{\partial x_i} \end{cases}$$



A turning point in computational structural biology

First molecular dynamics simulation applied to a small protein, BPTI, over 8 ps.





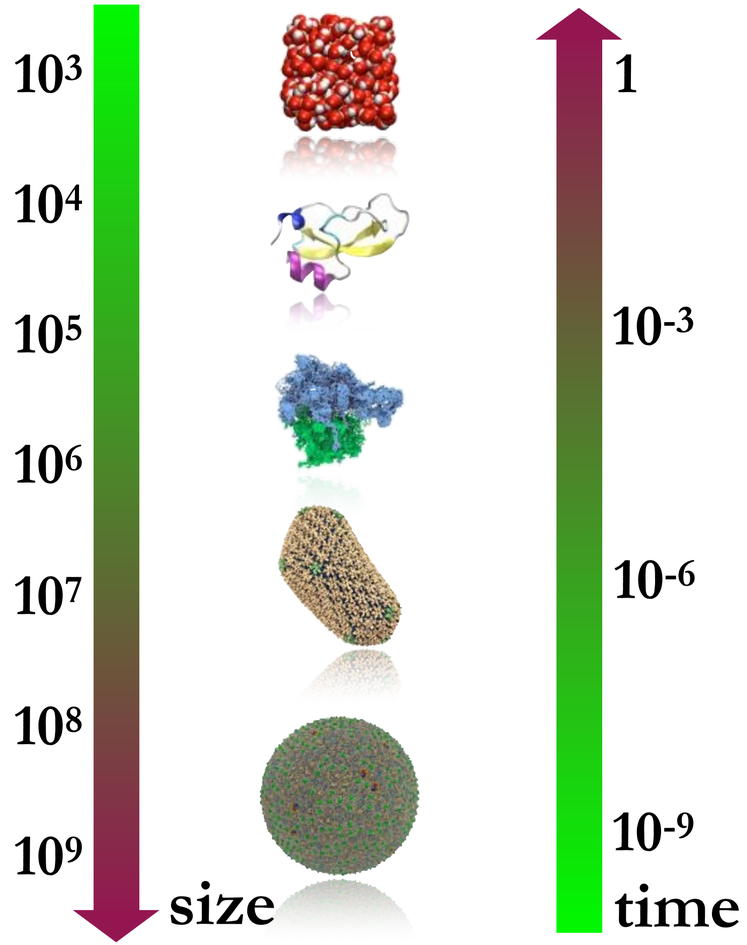
Alder, B. J.; Wainwright, T. E. *J. Chem. Phys.*, **1957**, *27*, 1208-1209

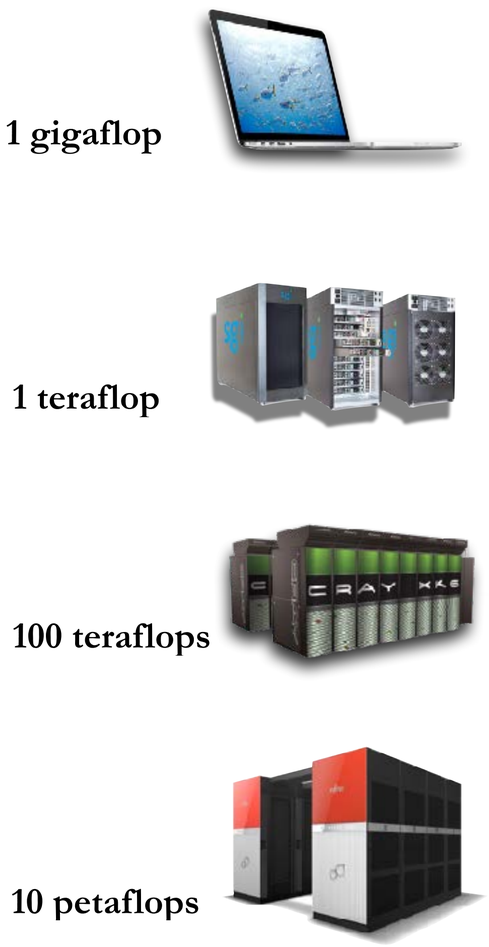
McCammon, J. A.; Gelin, B. R.; Karplus, M. *Nature*, **1977**, *267*, 585-590

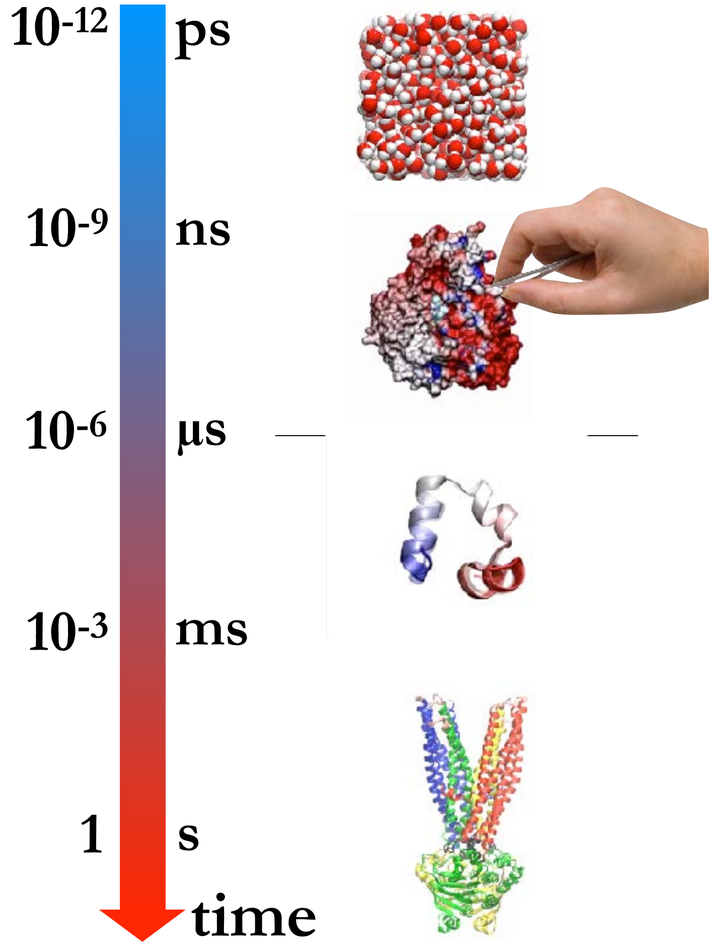
THE RACE FOR LONGER AND LARGER SIMULATIONS

Brute-force simulations struggling to bridge the gap between time and size scales

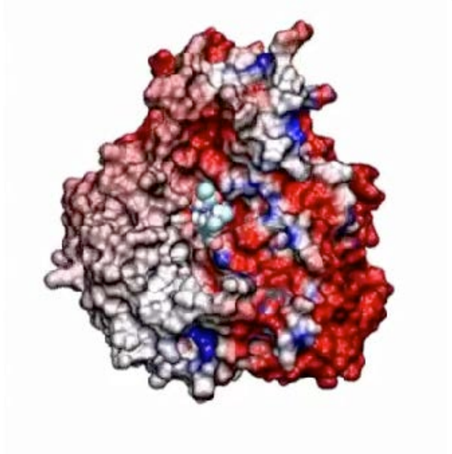
Free-energy calculations are computational tweezers to anatomize and explore relevant degrees of freedom



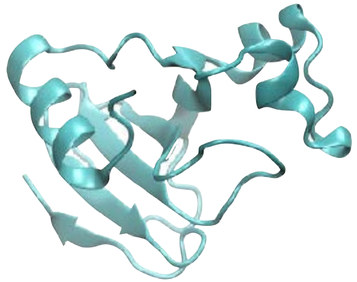


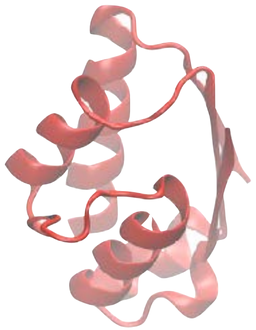


WHAT ARE FREE-ENERGY CALCULATIONS COMMONLY USED FOR ?

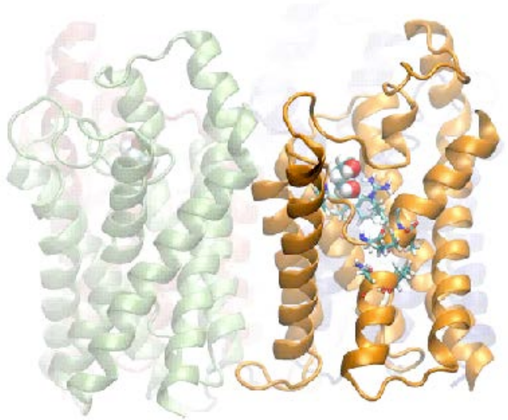


Recognition and association phenomena

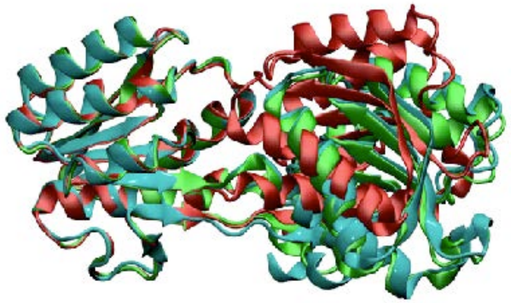




- protein-ligand binding
- site-directed mutagenesis
- protein-protein binding
- partition coefficients
- permeabilities
- activation barriers
-structural modifications



Transport phenomena

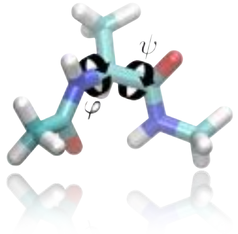


Conformational transitions

WHAT IS THE BEST METHOD FOR A GIVEN PROBLEM ?

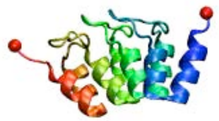
Free-energy differences can be estimated computationally following four possible routes

(1) Methods based on histograms



$$\Delta A(\xi) = -\frac{1}{\beta} \ln P(\xi) + \Delta A_0$$

(2) Non-equilibrium work simulations

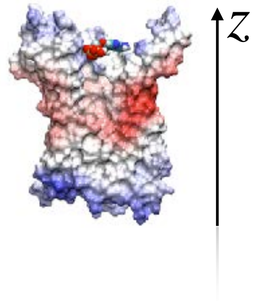


$$\exp(-\beta \Delta A) = \langle \exp(-\beta w) \rangle$$

(3) Perturbation theory

$$\exp(-\beta \Delta A) = \langle \exp(-\beta \Delta U) \rangle_0$$

(4) Measuring the derivative and integrating it



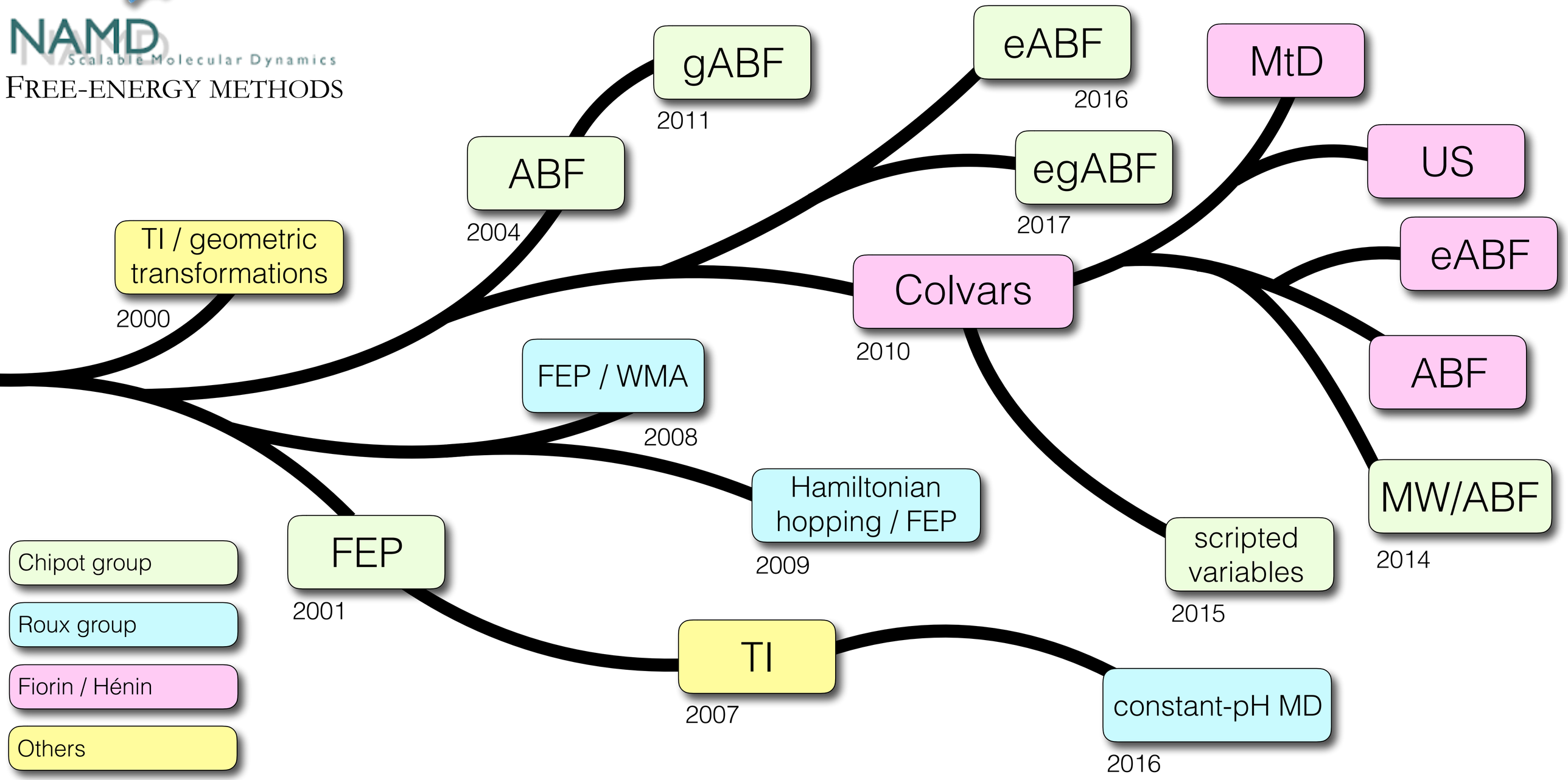
$$\frac{\mathrm{d}A(\xi)}{\mathrm{d}\xi} = \left\langle \frac{\partial U}{\partial \xi} - \frac{1}{\beta} \frac{\partial \ln |J|}{\partial \xi} \right\rangle_\xi$$

Torrie, G. M.; Valleau, J. P. *Chem. Phys. Lett.* **1974**, *28*, 578-581
Widom, B. *J. Chem. Phys.* **1963**, *39*, 2808-2812
Israelewitz, B.; Gao, M.; Schulten, K. *Curr. Opin. Struct. Biol.* **2001**, *11*, 224-230
Jarzynski, C. *Phys. Rev. Lett.* **1997**, *78*, 2690-2693

Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420-1426
Pohorille, A.; Jarzynski, C.; Chipot, C. *J. Phys. Chem. B* **2010**, *114*, 10235-10253
Kirkwood, J. G. *J. Chem. Phys.* **1935**, *3*, 300-313
Carter, E. et al. *Chem. Phys. Lett.* **1989**, *156*, 472-477

NAMD
Scalable Molecular Dynamics

Free-energy methods



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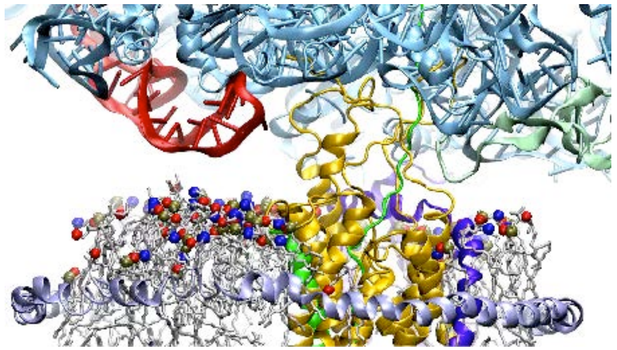
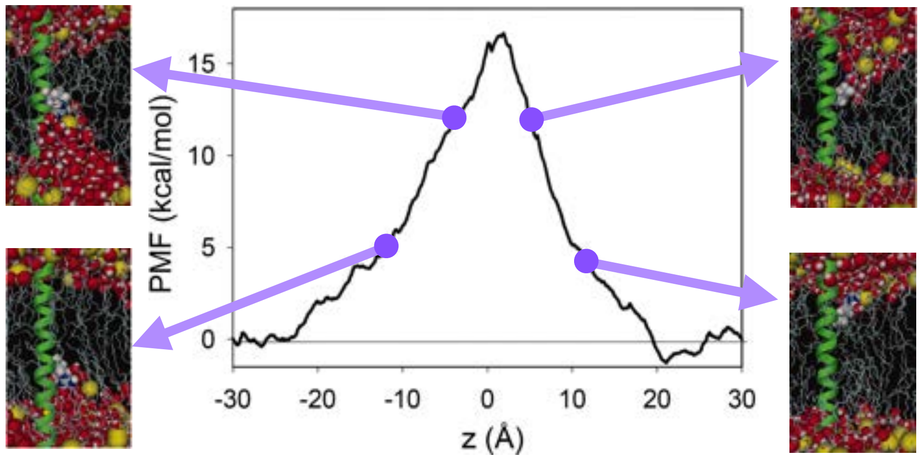
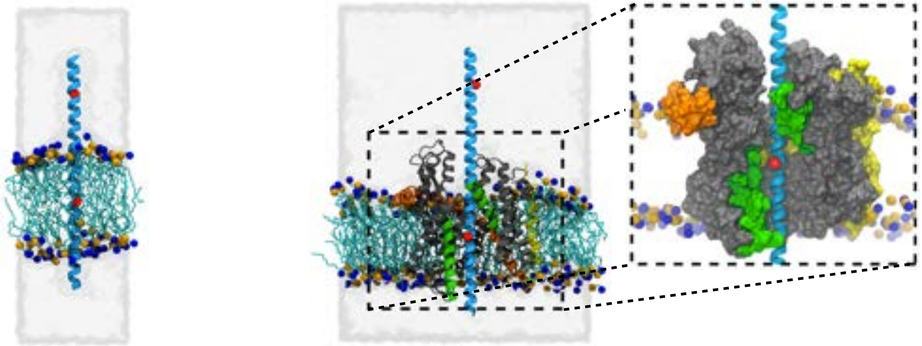


Nascent membrane proteins typically insert into the membrane via the Sec-translocon.

Membrane insertion of arginine, for instance, requires 14–17 kcal/mol according to molecular dynamics simulations, but only 2–3 kcal/mol according to experiment.



How does the translocon reduce the energetic cost and gain that accompanies insertion?



Becker, T. et al. *Science* **2009**, *326*, 1369-1373

Dorairaj, S.; Allen, T. W. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 4943-4948

Hessa, T. et al. *Nature* **2007**, *450*, 1026-1030

Gumbart, J. C.; Chipot, C.; Schulten, K. *Proc. Natl Acad. Sci. USA* **2011**, *108*, 3596-3601

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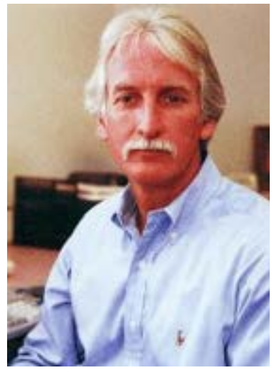


Transforming between chemical species, exploiting the malleability of the potential energy function.

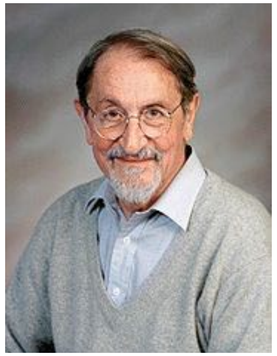
First alchemical transformation: Methanol to ethane (6.7 vs. 6.9 kcal/mol in experiment).

Single-topology paradigm:

- A common-denominator topology for the end states of the transformation.
- The non-bonded terms are a function of a general-extent parameter, λ.
- Necessity to correct for the change of bond length — if shaken bonds.
- Requires electrostatic decoupling.

Jorgensen, W. L.; Ravimohan, C. *J. Chem. Phys.* **1985**, *83*, 3050-3054
Postma, J. P. M.; Berendsen, H. J. C.; Haak, J. R. *Faraday Symp. Chem. Soc.* **1982**, *17*, 55-67
Bash, P. A. et al. *Science* **1987**, *236*, 564-568
Bash, P. A. et al. *Science* **1987**, *235*, 574-576

A tool to address host-guest chemistry problems



Free energy is a state function.

The free-energy difference between the end states is independent from the path followed to calculate it.

Dual-topology paradigm:

- The end states are defined explicitly.
- An exclusion list prevents them from seeing each other.
- The interaction of the perturbed state with its environment is a function of a general-extent parameter, λ.
- Prone to end-point catastrophes.
- Branching requires particular care.

Gao, J.; Kuczera, K.; Tidor, B.; Karplus, M. *Science* **1989**, *244*, 1069-1072

A tool to address host-guest chemistry problems

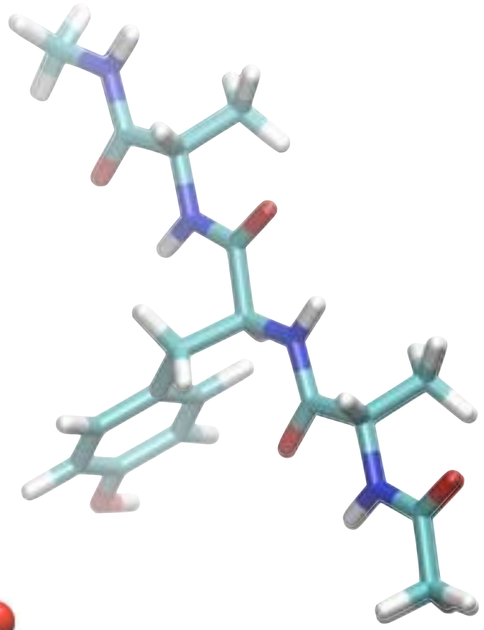
Free-energy perturbation

$$\exp(-\beta\Delta A) = \langle \exp(-\beta\Delta U) \rangle_0$$

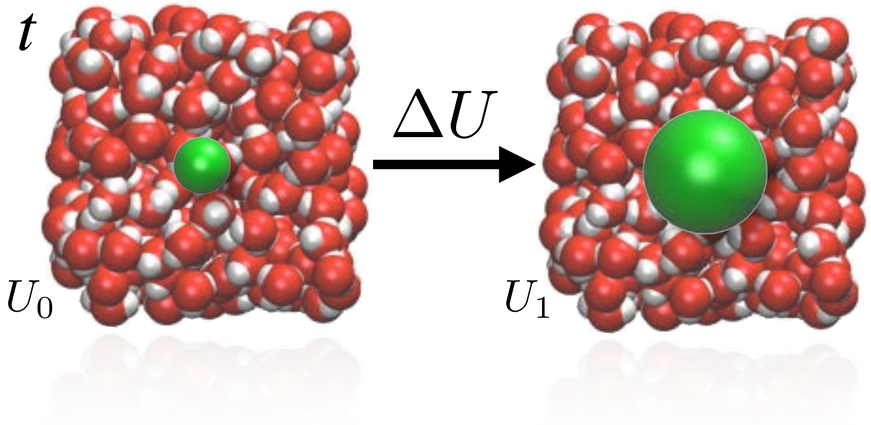
- Requires the sole knowledge of the reference state.
- Formally exact for any perturbation.
- Importance-sampling method.

Thermodynamic integration

$$\Delta A = \int \mathrm{d}\lambda \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda$$



$$\Delta U(\lambda) = \lambda U_1 + (1-\lambda) U_0$$



Landau, L. D. Statistical physics, **1938**

Zwanzig, R. W. J. *Chem. Phys.* **1954**, *22*, 1420-1426

Kirkwood, J. G. *J. Chem. Phys.* **1935**, *3*, 300-313

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

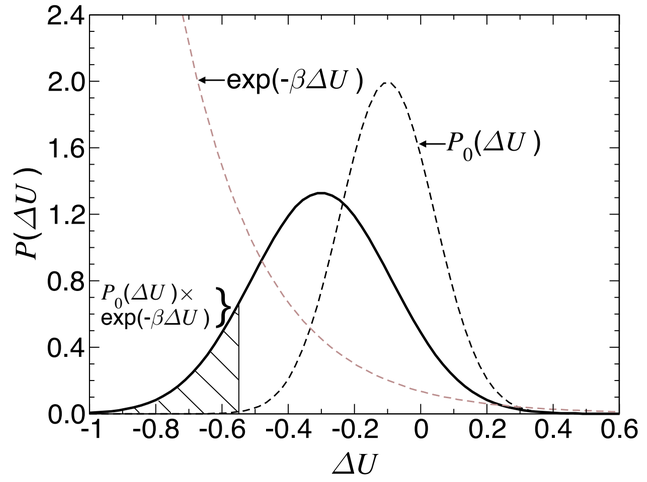
How to deal with large perturbations ?

$$\Delta A = -\frac{1}{\beta} \ln \int \mathrm{d}\Delta U \; P_0(\Delta U) \; \exp(-\beta \Delta U)$$

$$P_0(\Delta U) = \frac{1}{\sqrt{2\pi\sigma_0^2}} \; \exp\left[-\frac{(\Delta U - \langle \Delta U \rangle_0)^2}{2\sigma_0^2}\right]$$

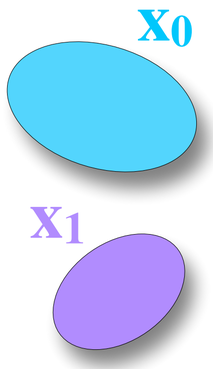
$\Delta A \leq \langle \Delta U \rangle_0$

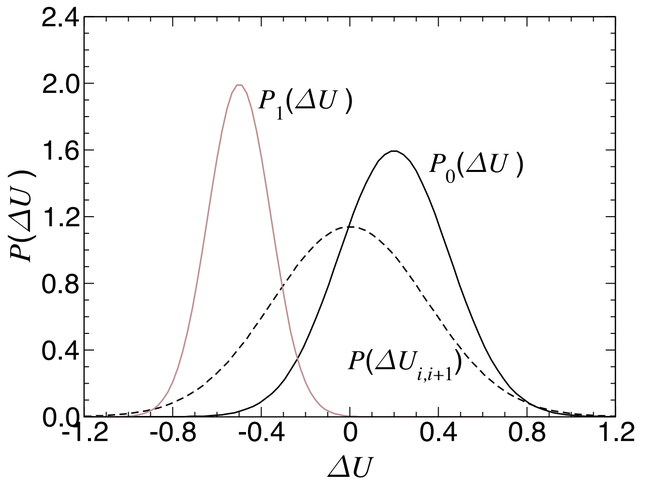
$$\Delta A = \langle \Delta U \rangle_0 - \frac{1}{2}\beta\sigma_0^2$$



Stratification strategies

$$\Delta A = -\frac{1}{\beta} \sum_i \ln \langle \exp(-\beta \Delta U_{i,i+1}) \rangle_i$$





Valleau, J. P.; Card, D. N. *J. Chem. Phys.* **1972**, *57*, 5457-5462

Chipot, C.; Pohorille, A. Free energy calculations. Theory and applications in chemistry and biology, **2007**

Lelièvre, T.; Stoltz, G.; Rousset, M. Free energy computations: A mathematical perspective, **2010**

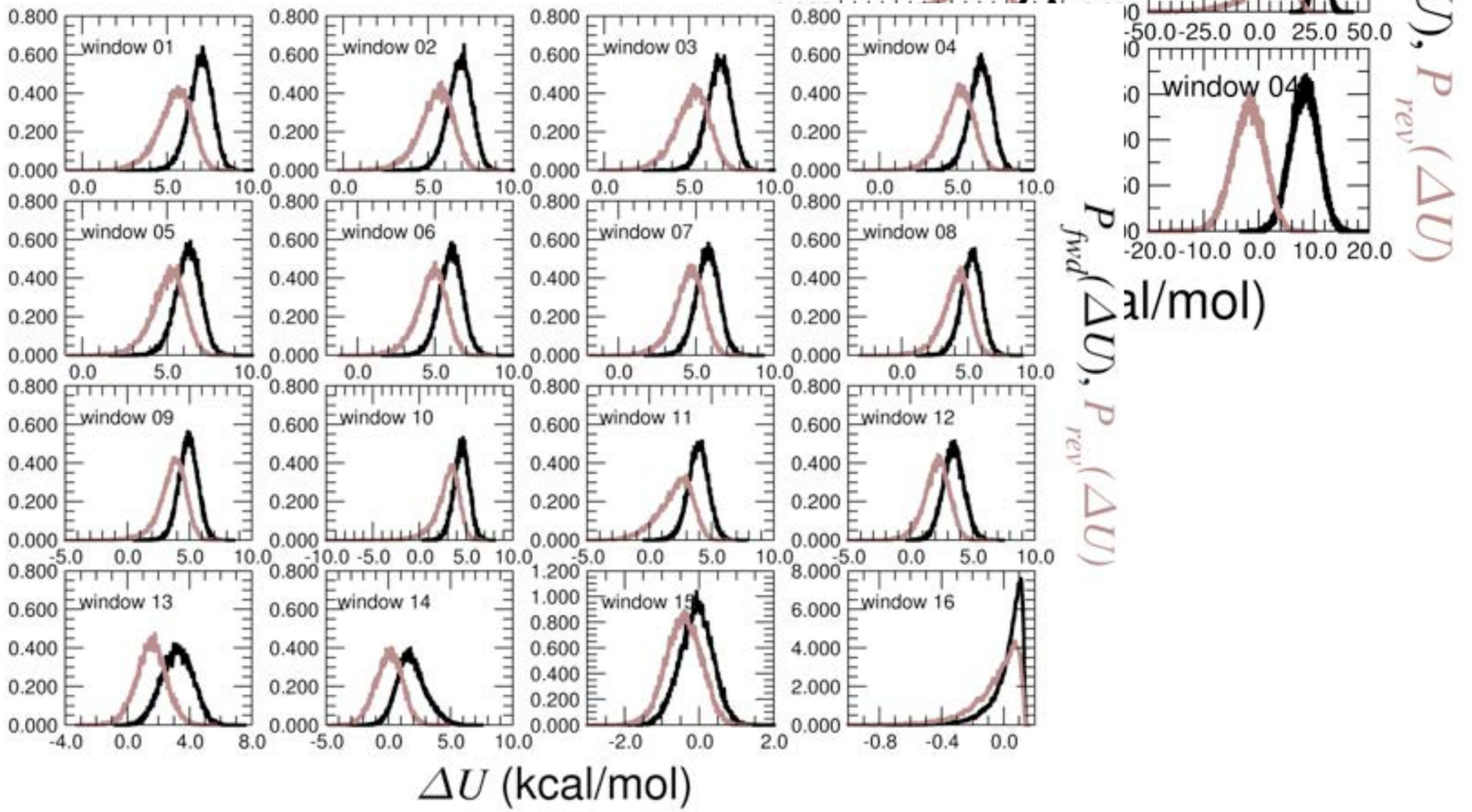
GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

How many strata should I choose ?

Stratification will impact the accuracy of the free-energy calculation.

In the NAMD lingo:

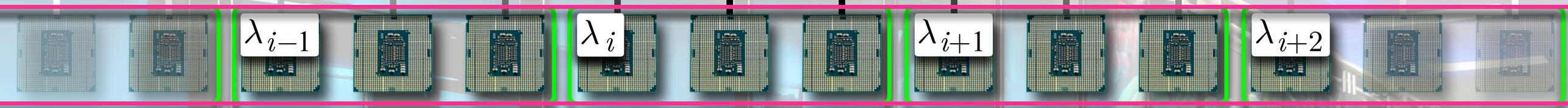
```
runFEP   0.0   1.0   0.0625   $nSteps
```

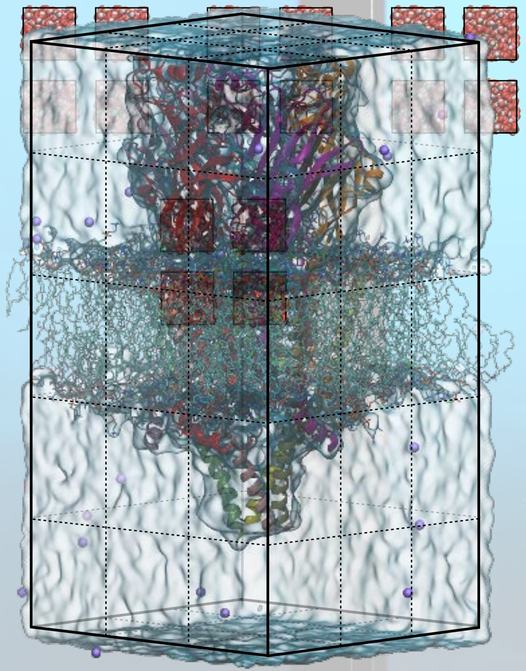


Valleau, J. P.; Card, D. N. *J. Chem. Phys.* **1972**, *57*, 5457-5462

Pohorille, A.; Jarzynski, C.; Chipot, C. *J. Phys. Chem. B* **2010**, *114*, 10235-10253

Good practices, guidelines and recommendations





Different strategies for harnessing petascale architectures

Domain decomposition molecular dynamics.

One λ-state at a time.

Many, if not all λ-states concomitantly.

Valleau, J. P.; Card, D. N. *J. Chem. Phys.* **1972**, *57*, 5457-5462

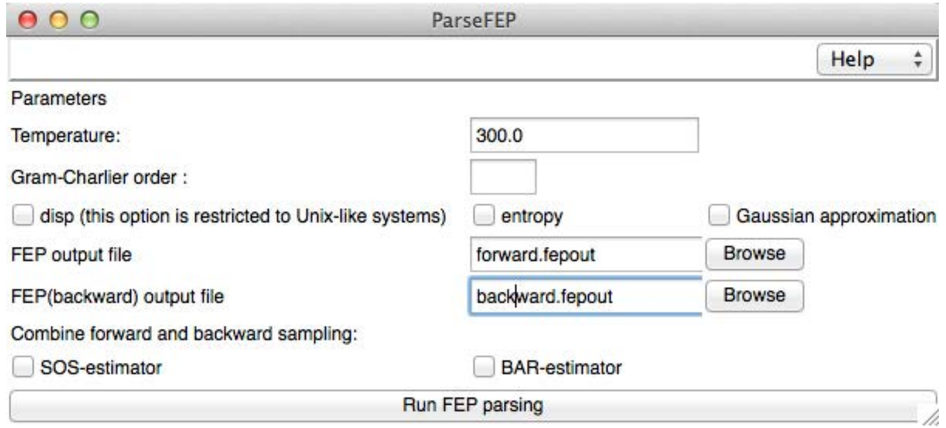
Pohorille, A.; Jarzynski, C.; Chipot, C. *J. Phys. Chem. B* **2010**, *114*, 10235-10253

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

Combining forward and backward transformations

Maximum-likelihood estimator of the free-energy change.

Guarantees the minimum variance.



$$\begin{cases} \exp\left(\beta\Delta\hat{A}^{\mathrm{BAR}}\right) = \dfrac{\langle f\left[-\beta\left(\Delta U - c\right)\right]\rangle_1}{\langle f\left[+\beta\left(\Delta U - c\right)\right]\rangle_0}\ \exp\left(+\beta c\right) \\ c = \Delta\hat{A}^{\mathrm{BAR}} + \dfrac{1}{\beta}\ln\dfrac{N_1}{N_0} \qquad f(x) = 1/[1+\exp\left(x\right)] \end{cases}$$

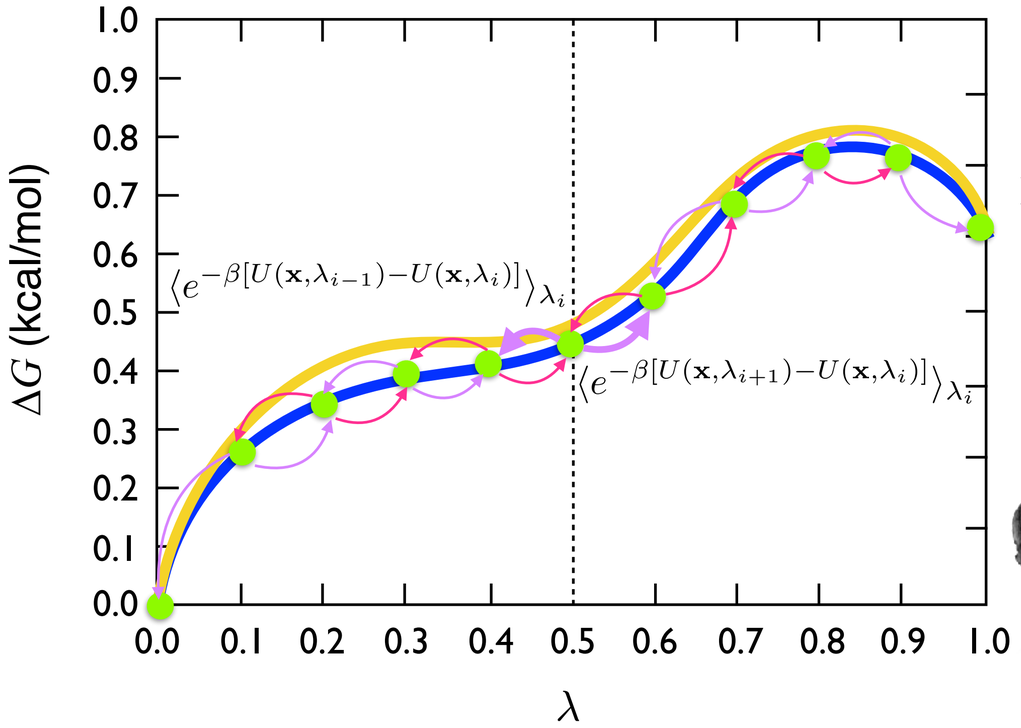
$$\sigma^2_{\Delta A}{}^{\mathrm{BAR}} = \frac{1}{N_0\beta^2}\left[\frac{\langle f^2(x)\rangle_0}{\langle f(x)\rangle_0^2} - 1\right] + \frac{1}{N_1\beta^2}\left[\frac{\langle f^2(-x)\rangle_1}{\langle f(-x)\rangle_1^2} - 1\right]$$

Bennett, C. H. *J. Comp. Phys.* **1976**, *22*, 245–268.

Pohorille, A.; Jarzynski, C.; Chipot, C. *J. Phys. Chem. B* **2010**, *114*, 10235-10253

Hahn, A. M.; Then, H. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **2009**, *80*, 031111

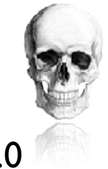
GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



Double-wide sampling

Ensemble averages carried out with respect to the initial state, λ_i.

More effective than two independent free-energy calculations.



Possible Hamiltonian lag requires proper thermalization at each stratum.

Readily supplies the relevant information for Bennett acceptance ratio analysis.

Readily supplies the hysteresis of the transformation.

Jorgensen, W. L.; Ravimohan, C. *J. Chem. Phys.* **1985**, *83*, 3050-3054

Pearlman, D. A.; Kollman, P. A. *J. Chem. Phys.* **1989**, *91*, 7831-7839

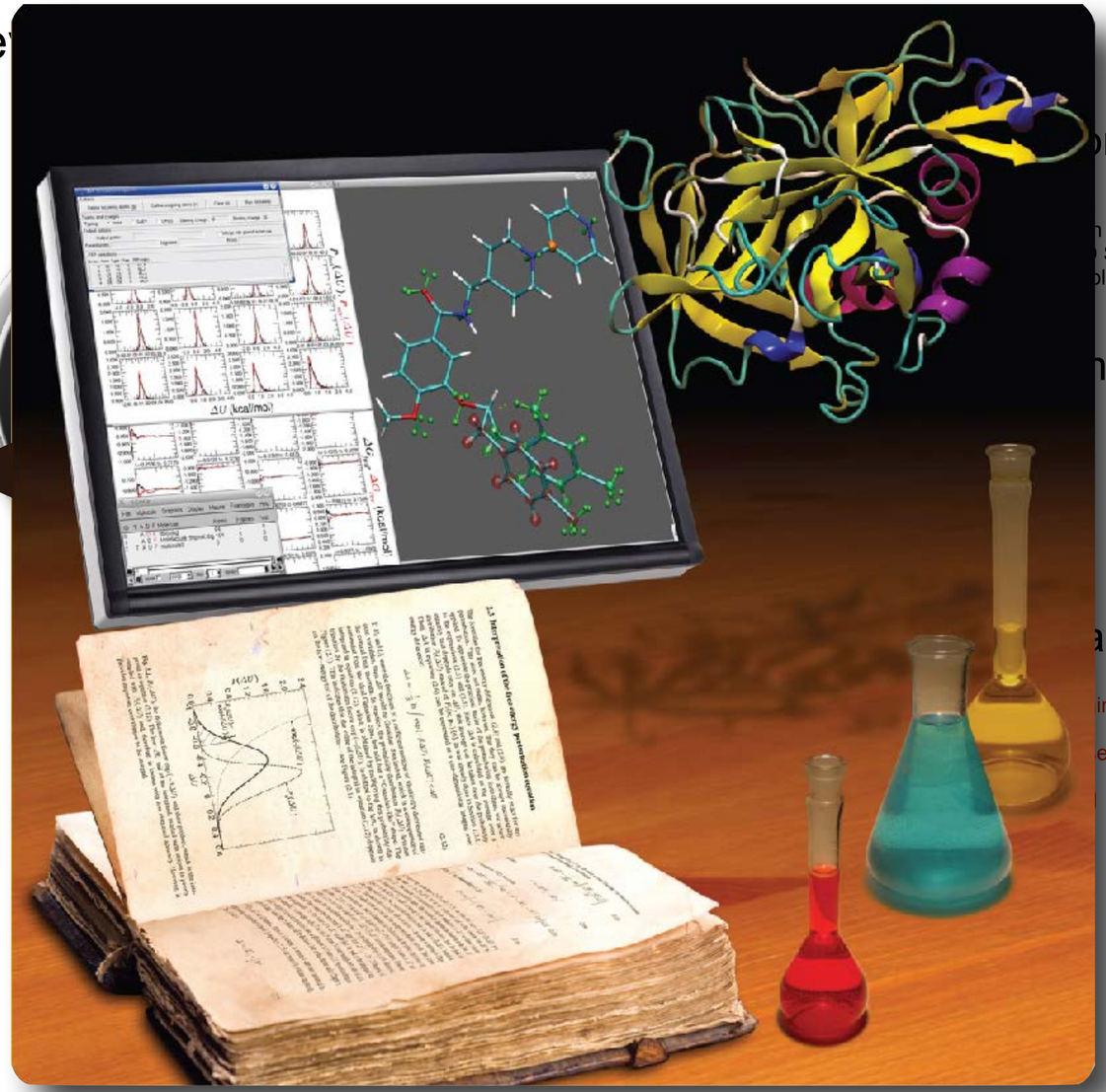
Berendsen, H. J. C. in Renugopalakrishnan, V.; et al. Eds. *Proteins, Structure, Dynamics and Design* ESCOM, **1991**, 384-392

VMD Plugins

Advanced Tools de

Analysis

APBSRun
CatDCD
Contact Map
GofRGUI
HeatMapper
ILSTools
IRSpecGUI
MultiSeq
NAMD Energy
NAMD Plot
NetworkView
NMWiz
ParseFEP
PBCTools
PMEpot
PropKa GUI
RamaPlot
RMSD Tool
RMSD Trajectory Tool
RMSD Visualizer Tool
Salt Bridges
Sequence Viewer
Symmetry Tool
Timeline
VolMap



ration

Shared Views

nport and Plotting

I/O Plugins

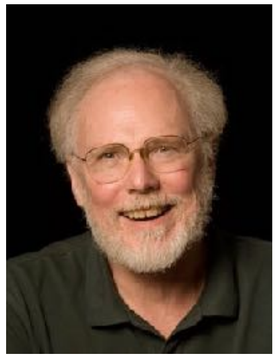
ally Hosted Plugins

ins

ential Dynamics

Liu, P.; Dehez, F.; Cai, W.; Chipot, C. *J. Chem. Theor. Comput.* **2012**, *8*, 2606-2616

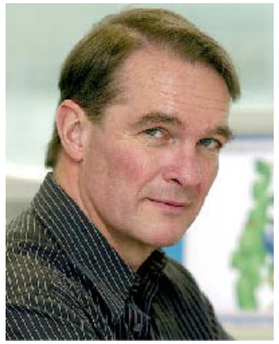
GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



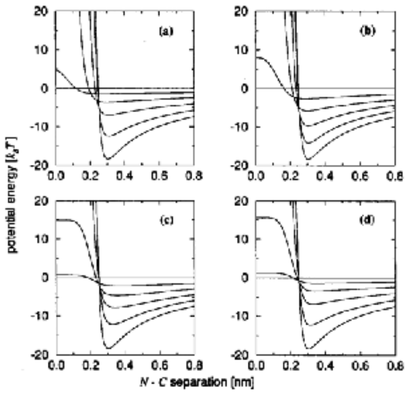
What about end-point catastrophes ?

Avoid singularities in the van der Waals potential as particles appear.

$$U^{\mathrm{vdW}}(r_{ij};\lambda) = 4\epsilon_{ij}(1-\lambda)\left[\left(\frac{\sigma_{ij}^2}{r_{ij}^2+\alpha\lambda}\right)^6 - \left(\frac{\sigma_{ij}^2}{r_{ij}^2+\alpha\lambda}\right)^3\right]$$



$$U^{\mathrm{vdW}}(r_{ij};\lambda) = 4\epsilon_{ij}(1-\lambda)^n\left\{\frac{1}{\left[\alpha\lambda^2+\left(\frac{\sigma_{ij}}{r_{ij}}\right)^6\right]^2} - \frac{1}{\alpha\lambda^2+\left(\frac{\sigma_{ij}}{r_{ij}}\right)^6}\right\}$$



In the NAMD lingo:

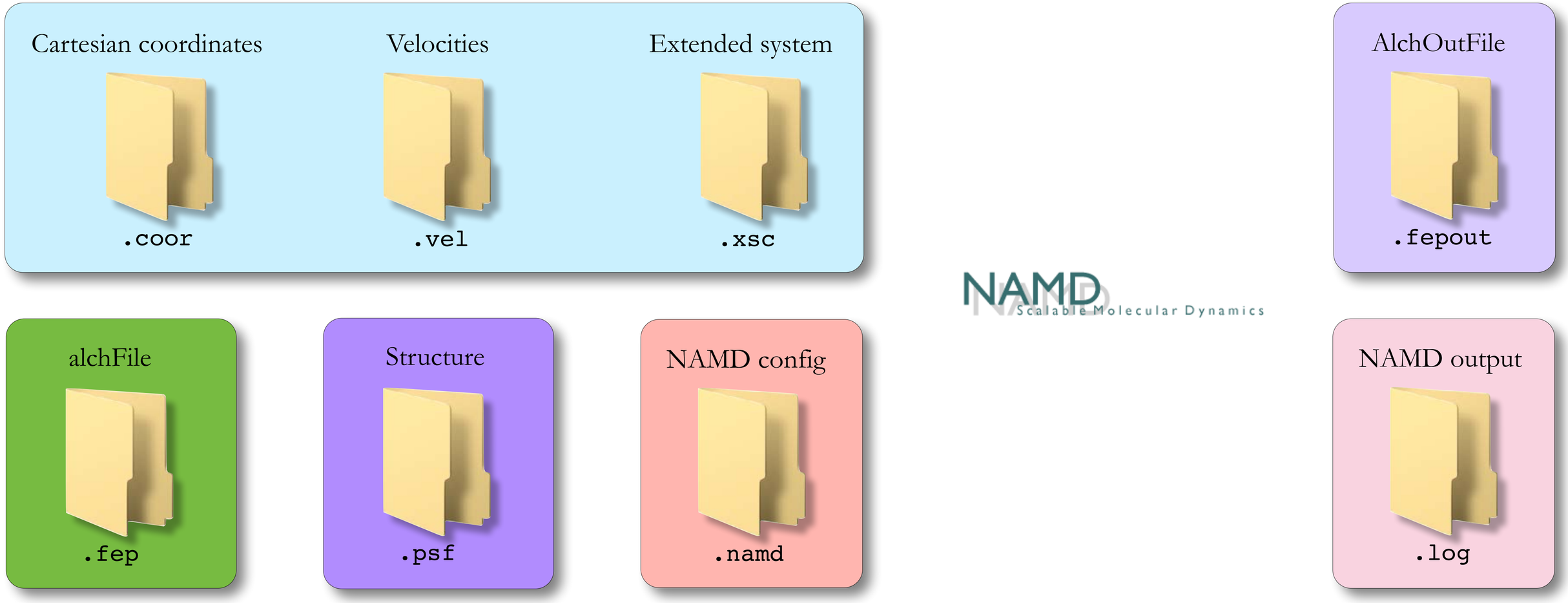
```
alchVdWShiftCoeff     4.0
```

Zacharias, M.; Straatsma, T. P.; McCammon, J. A. *J. Chem. Phys.* **1994**, *100*, 9025-9031

Beutler, T. C.; Mark, A. E.; van Schaik, R. C.; Gerber, P. R.; van Gunsteren, W. F. *Chem. Phys. Lett.* **1994**, *222*, 529-539

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

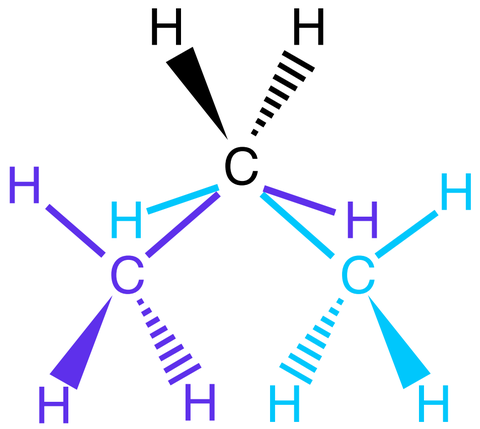
Equilibration simulation



Phillips, J. C. et al. *J. Comput. Chem.* **2005**, *26*, 1781-1802

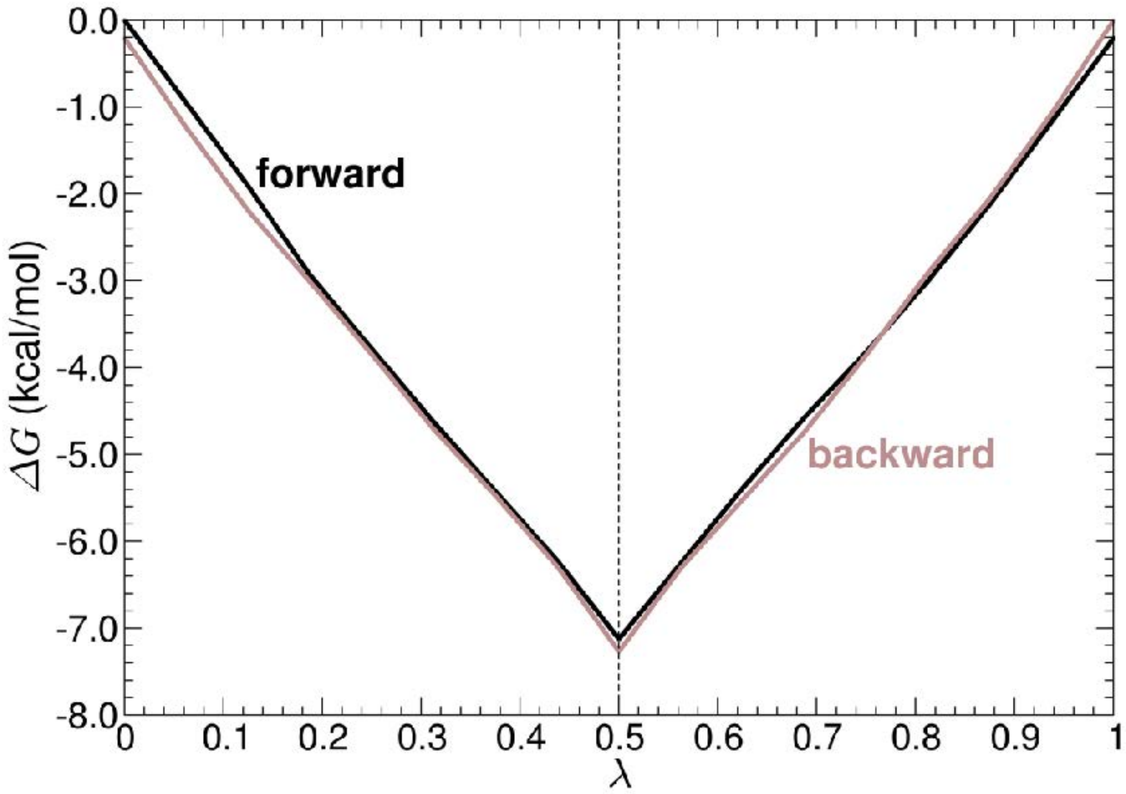
Bhandarkar, M. et al. NAMD user's guide, version 2.9, **2012**

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



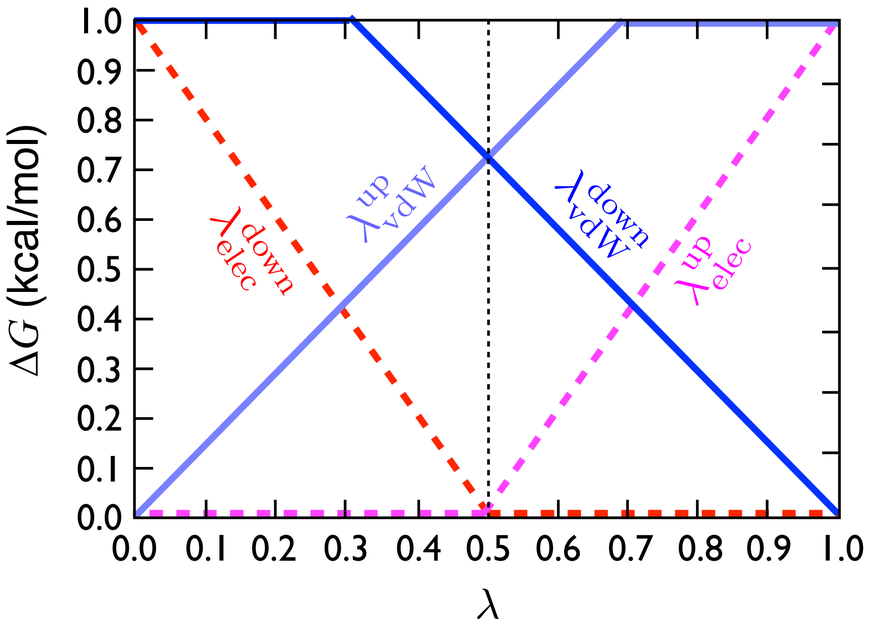

```
RESI ZERO         0.00       !  ethane -> ethane
GROUP                        !
ATOM CI    CT3   -0.27       !
ATOM HI1   HA     0.09       !
ATOM HI2   HA     0.09       !
ATOM HI3   HA     0.09       !
GROUP                        !   HI1        HM1    HF2  HF3
ATOM CM    CT3   -0.27       !      \         |     |  /
ATOM HM1   HA     0.09       !       \HF     |     | /
ATOM HM2   HA     0.09       !         CI----CM----CF
ATOM HI    HA     0.09       !        / |     |     HI\
ATOM HF    HA     0.09       !       /  |     |        \
GROUP                        !   HI2  HI3   HM2        HF1
ATOM CF    CT3   -0.27       !
ATOM HF1   HA     0.09       !
ATOM HF2   HA     0.09       !
ATOM HF3   HA     0.09       !
BOND      CI  HI1        CI  HI2        CI   HI3        ! ethane 1
BOND      CF  HF1        CF  HF2        CF   HF3        ! ethane 2
BOND      CI  CM         CF  CM                         ! common
BOND      CM  HM1        CM  HM2                        ! common
BOND      CM  HI                                        ! ethane 1
BOND      CM  HF                                        ! ethane 2
```

Zero free-energy change transformation



Pearlman, D. A.; Kollman, P. A. *J. Chem. Phys.* **1991**, *94*, 4532-4545

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



Scheduling the electrostatic decoupling:

Outgoing particles

	beginning	end
electrostatics	0	$1 - \lambda_{\mathrm{elec}}^{\mathrm{start}}$
van der Waals	$1 - \lambda_{\mathrm{vdW}}^{\mathrm{end}}$	1

Incoming particles

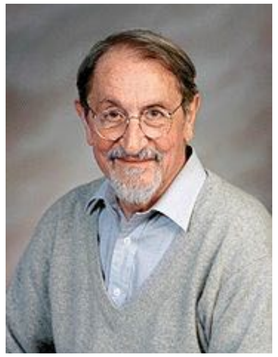
	beginning	end
electrostatics	$\lambda_{\mathrm{elec}}^{\mathrm{start}}$	1
van der Waals	0	$\lambda_{\mathrm{vdW}}^{\mathrm{end}}$

Decoupling in the NAMD lingo:

```
alchVdwLambdaEnd          0.7
alchElecLambdaStart       0.5
```

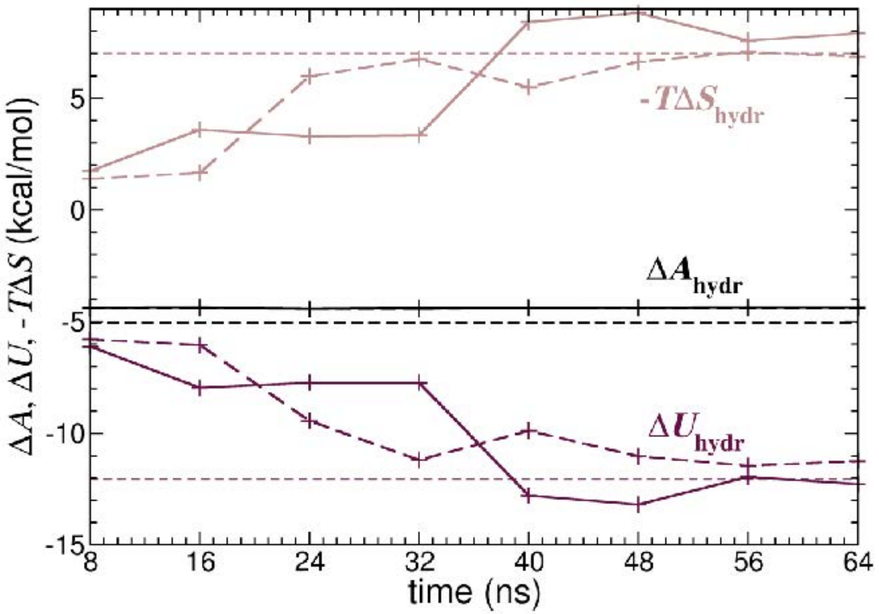
Pearlman, D. A.; Kollman, P. A. *J. Chem. Phys.* **1991**, *94*, 4532-4545

HOW ABOUT THE ENTROPY ?



Appreciably more challenging to estimate on account of averages over U_0 and U_1.

$$\Delta S = \frac{1}{T}\left(\frac{\langle U_1 \exp(-\beta\Delta U)\rangle_0}{\langle \exp(-\beta\Delta U)\rangle_0} - \langle U_0\rangle_0\right) + k_B \ln\langle \exp(-\beta\Delta U)\rangle_0$$



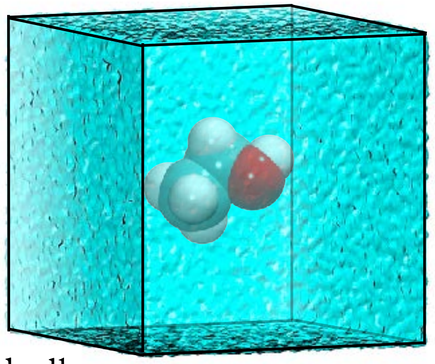
Alternate route:

$$\Delta S = -\left(\frac{\partial \Delta A}{\partial T}\right)_{N,V}$$

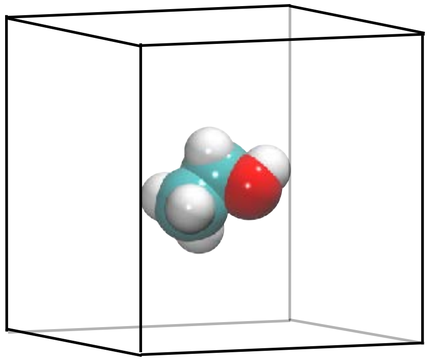
Wan, S.; Stote, R. H.; Karplus, M. *J. Chem. Phys.* **2004**, *121*, 9539–9548

Kubo, M. M.; Gallicchio, E.; Levy, R. M. *J. Phys. Chem. B* **1997**, *101*, 10527-10534

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

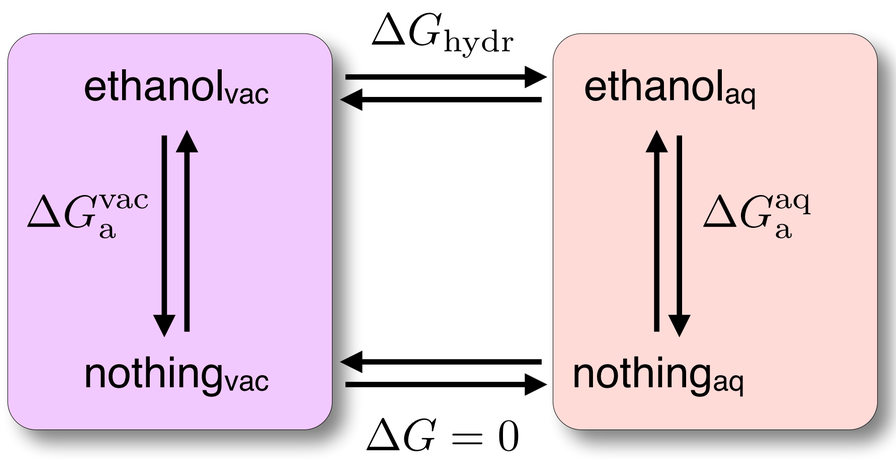


bulk



vacuum

Ethanol hydration



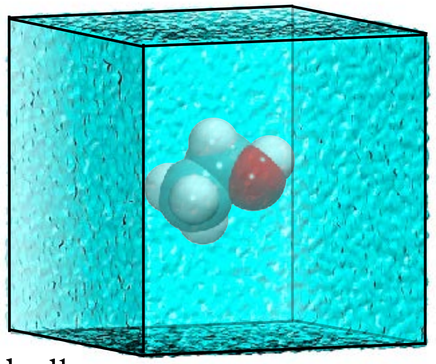
Why do I need to complete the full thermodynamic cycle ?

In different dielectric environments, molecules may adopt very different conformations, corresponding to distinct intramolecular interactions.

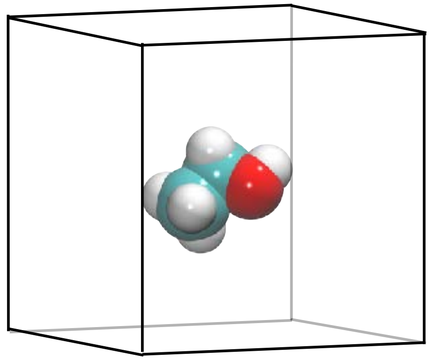
In NAMD lingo: `AlchDecouple off`

Not a free-energy calculation in vacuum per se, but in a periodic cell bereft of solvent.

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

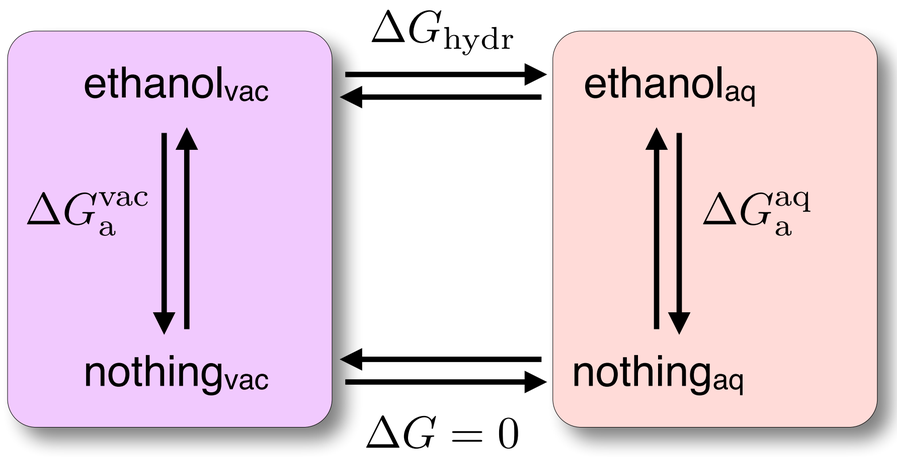


bulk



vacuum

Exercise 2. Ethanol hydration



	ΔG (kcal/mol)		
	annihilation	creation	BAR
vacuum	+5.1	-5.3	-5.2
water	+9.5	-9.6	-9.6
hydration	+4.4	-4.3	-4.4

experiment: -5.1 kcal/mol

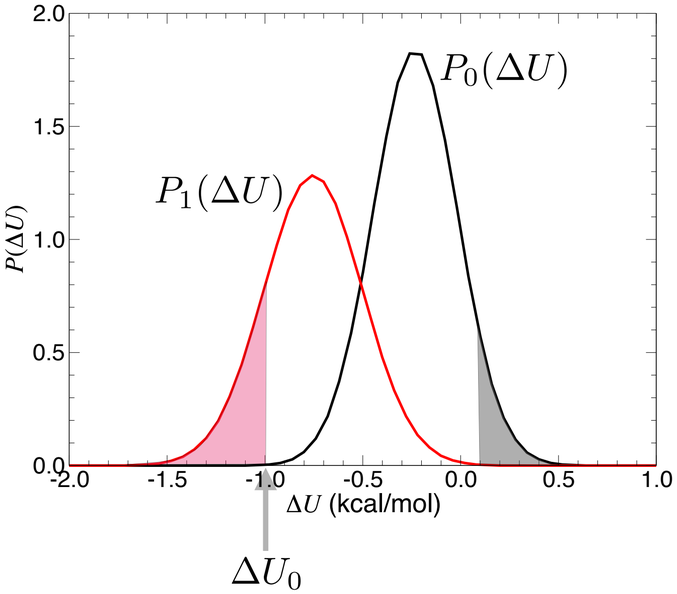
Ben-Naim, A.; Marcus, Y. *J. Chem. Phys.* **1984**, *81*, 2016-2027

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

All free-energy calculations should be accompanied by an error estimate. A distinction between statistical and systematic error ought to be made.

Since the reliability of free-energy estimates depends on the overlap between $P_0(\Delta U)$ and $P_1(\Delta U)$, these distributions should be monitored to assess the degree of overlap.

$$\frac{\delta\epsilon_{\Delta A}}{\exp(-\beta\Delta A)} = -\int_{-\infty}^{\Delta U_0} \mathrm{d}\Delta U \; P_1(\Delta U)$$



Stratification provides an effective, general method for reducing the variance and improving overlap at each stage.

Combining forward and backward simulations using, for instance, the BAR estimator is strongly recommended.

Kofke, D.; Cummings, P. *Fluid Phase Equil.* **1998**, *150*, 41-49

Chipot, C.; Pohorille, A. Free energy calculations. Theory and applications in chemistry and biology, **2007**

Pohorille, A.; Jarzynski, C.; Chipot, C. *J. Phys. Chem. B* **2010**, *114*, 10235-10253

Introduction

The race for longer and larger simulations
What is the best method for a given problem?

Alchemical free-energy calculations

- A tool to address host-guest chemistry questions
- Good practices, guidelines and recommendations
- The long-standing protein-ligand problem

Geometrical free-energy calculations

- What is a good reaction-coordinate model?
- A host of methods to measure free-energy changes
- Potentials of mean force and transport phenomena
- Potentials of mean force and recognition and association phenomena
- What about non-equilibrium work computer experiments?

Ongoing challenges at the frontiers of free-energy calculations

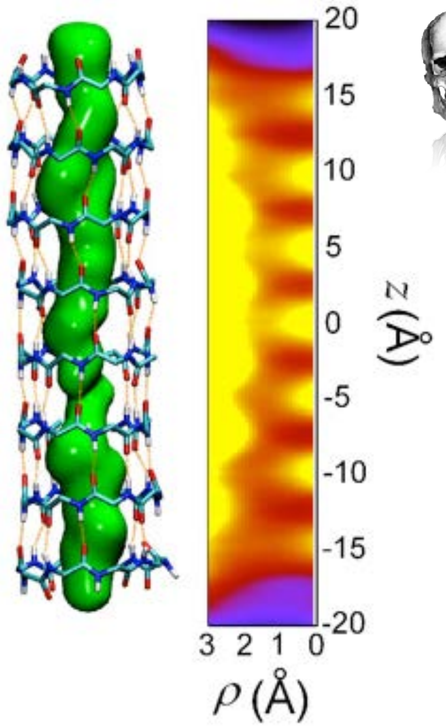
Concluding remarks and questions

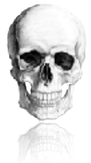
WHAT IS A GOOD REACTION-COORDINATE MODEL ?

The *true* reaction coordinate generally refers to a unique mathematical object on $\mathbb{R}^{3N}$.

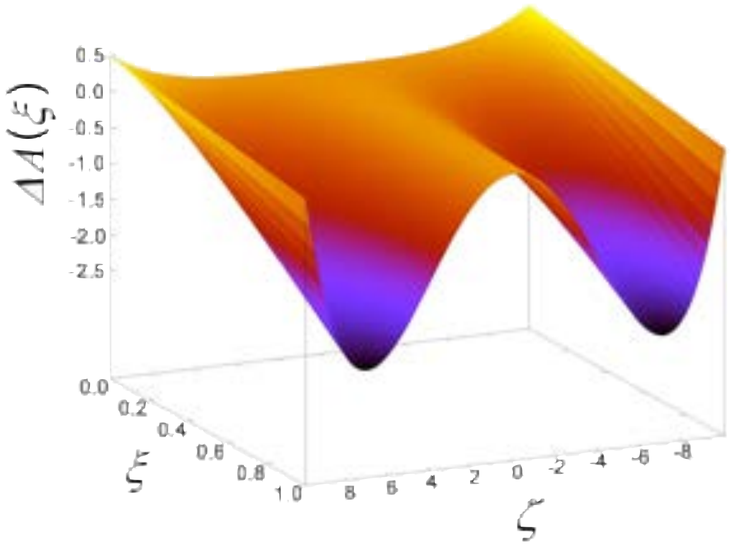
It defines the minimum free-energy pathway connecting the reference state to the target state of the transformation.

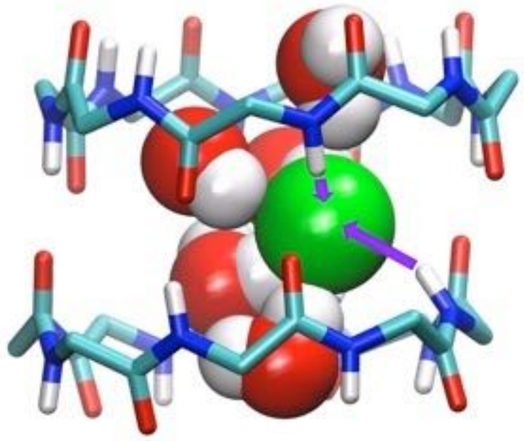
Committor — The probability to reach the target state before returning to the reference state.





A one-dimensional order parameter, namely the long axis of the cavity, is not enough to describe ion conduction in a synthetic channel.



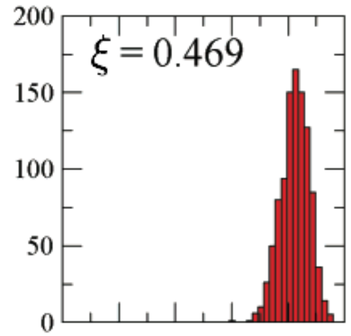


Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5877-5882

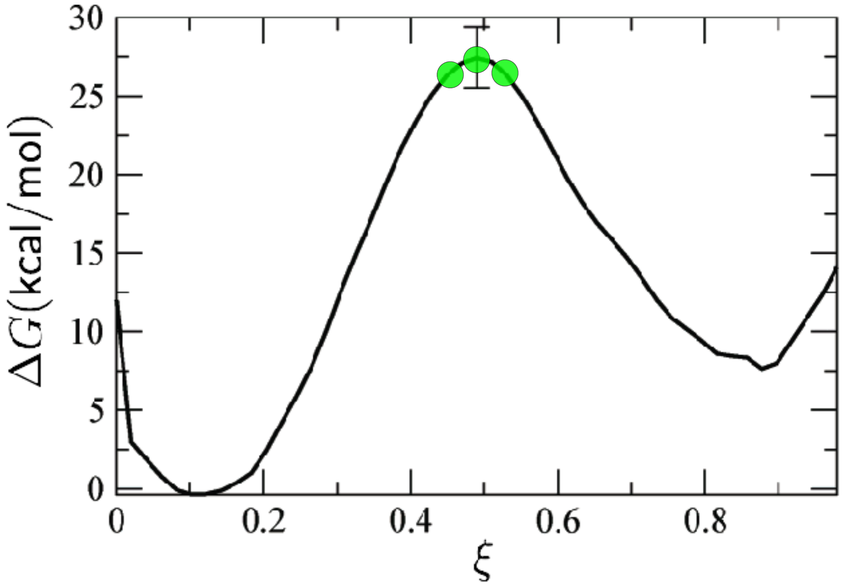
Bolhuis, P. G.; Chandler, D.; Dellago, C.; Geissler, P. *Ann. Rev. Phys. Chem.* **2002**, *59*, 291-318

WHAT IS A GOOD REACTION-COORDINATE MODEL ?

While the choice of the reaction-coordinate model does not impact the thermodynamics of the process at hand, it modulates its kinetics.



Option: Determine $N(p_A)$, the distribution of the committor probability, p_A, for the model of the reaction coordinate, ξ.



Run a series of molecular dynamics simulations from the putative maximum of the free-energy barrier and infer $N(p_A)$.

Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5877-5882

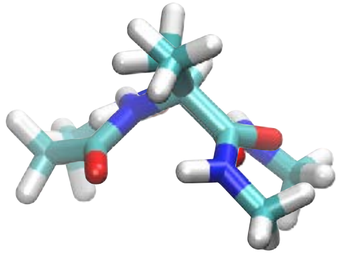
Bolhuis, P. G.; Chandler, D.; Dellago, C.; Geissler, P. *Ann. Rev. Phys. Chem.* **2002**, *59*, 291-318

WHAT IS A GOOD REACTION-COORDINATE MODEL ?

low collectivity

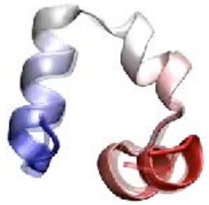
`distance`
`distanceZ`
`distanceXY`

`angle`

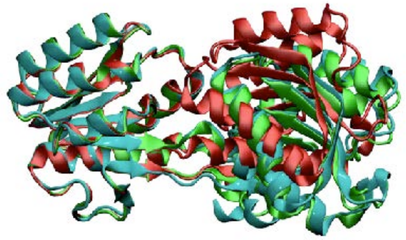


`dihedral`

`rmsd`
`gyration`



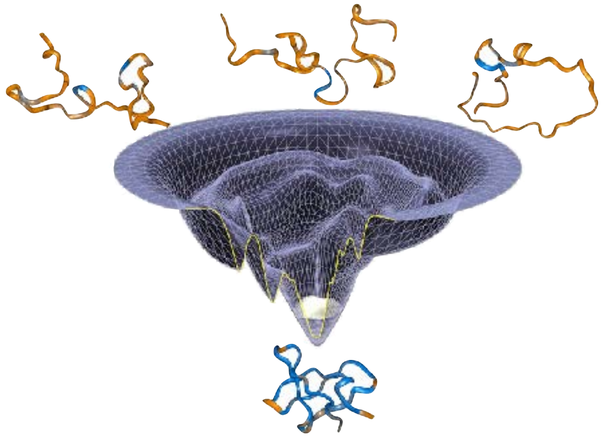
`eigenvector`



high collectivity

Possible linear combination of variables

Degenerate variable

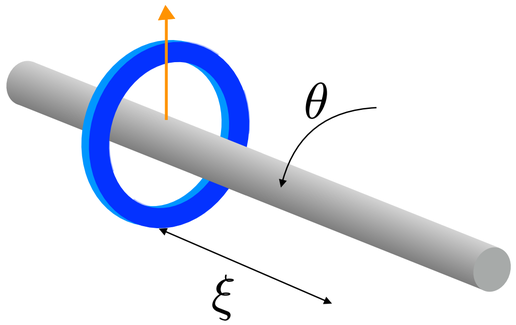


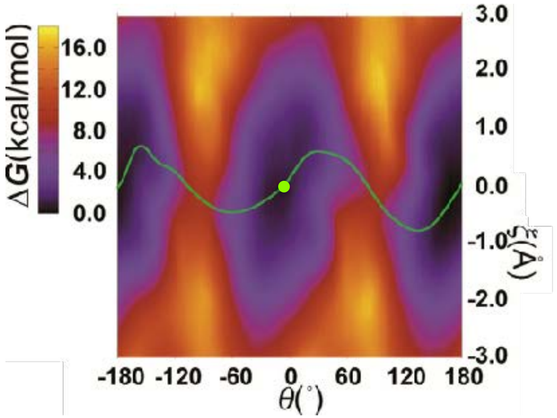
From normal mode or principal component analysis

Hénin, J.; Forin, G.; Chipot, C.; Klein, M. L. *J. Chem. Theor. Comput.* **2010**, *6*, 35-47

Fiorin, G.; Klein, M. L.; Hénin, J. *Mol. Phys.* **2013**, *111*, 3345-3362

WHAT IS A GOOD REACTION-COORDINATE MODEL ?





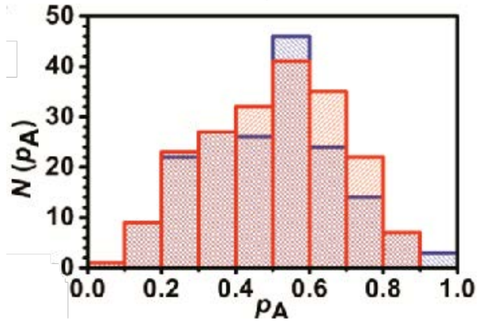
Movements in molecular objects can be more complex than suggested by chemical intuition.

Define reaction coordinate model based on chemical intuition

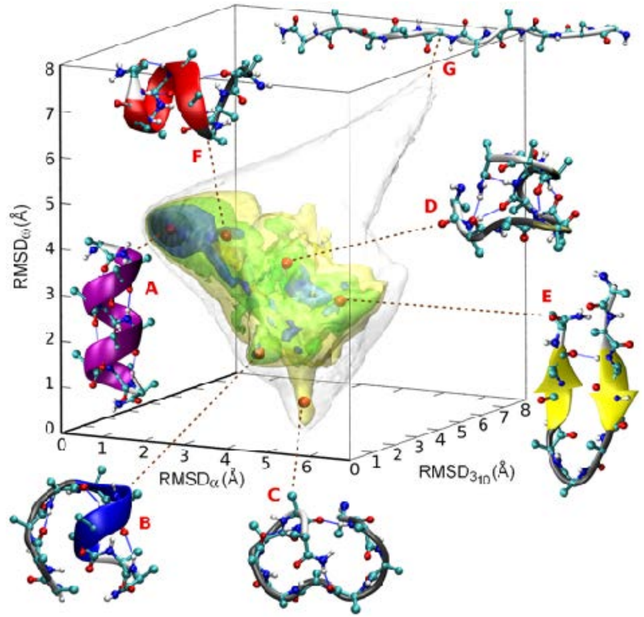
↓

Ascertain that the reaction coordinate model is a committor function

↓



- Increase dimensionality of the model
- Turn to ergodic-sampling algorithms
- Search for a minimum-action path



Liu, P.; Shao, X.; Chipot, C.; Cai, W. *Chem. Sci.* **2015**

Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5877-5882

THE STRING METHOD WITH SWARMS OF TRAJECTORIES

Let us assume some minimum-action (most probable) transition path connecting two basins of a free-energy landscape defined by a set of collective variables $\mathbf{z}$. Let us also consider the potential of mean force along this path,

$$\exp[-\beta w(z)] = \frac{\int \mathrm{dx}\ \delta[\mathbf{z} - \mathbf{z}'(\mathbf{x})]\ \exp[-\beta U(\mathbf{x})]}{\int \mathrm{dx}\ \exp[-\beta U(\mathbf{x})]}$$

Let us further assume that the collective variables evolve on the free-energy landscape according to non-inertial Brownian dynamics,

$$z_i(\delta t) = z_i(0) + \sum_j \left\{\beta D_{ij}[\mathbf{z}(0)] F_j[\mathbf{z}(0)] + \nabla_{z_j} D_{ij}[\mathbf{z}(0)]\right\} \delta t + R_i(0) \qquad \text{where} \qquad F_i = -\nabla_i w(\mathbf{z})$$

$$\langle R_i(0) R_i(\delta t)\rangle = 2 D_{ij} \delta t$$

Let us consider a path $\mathbf{z}(\alpha)$ connecting the two basins, such that α varies between 0 and 1,

$$z_i(\alpha) = z_i(\alpha') + \sum_j \left\{\beta D_{ij}[\mathbf{z}(0)] F_j[\mathbf{z}(0)] + \nabla_{z_j} D_{ij}[\mathbf{z}(0)]\right\} \delta t$$

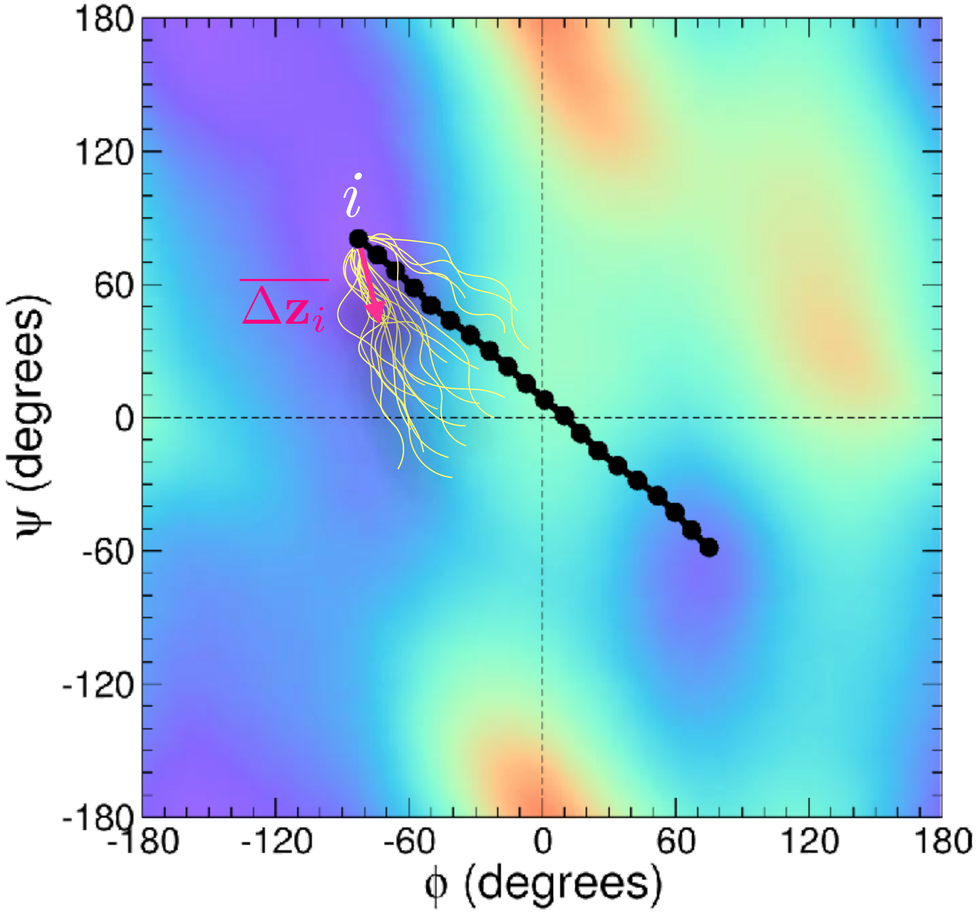
Average drift from an ensemble of unbiased trajectories of length δt,

$$\overline{z_i(\delta t)} = \overline{z_i(\delta t) - z_i(0)} = \sum_j \left\{\beta D_{ij}[\mathbf{z}(0)] F_j[\mathbf{z}(0)] + \nabla_{z_j} D_{ij}[\mathbf{z}(0)]\right\} \delta t$$

Ren, W.; Vanden-Eijnden, E.; Maragakis, P.; E, W. *J. Chem. Phys.* **2005**, *123*, 134109

Pan, A. C.; Sezer, D.; Roux, B. *J. Phys. Chem. B* **2008**, *112*, 3432-3440

THE STRING METHOD WITH SWARMS OF TRAJECTORIES



Prepare a configuration for each one of the P images of the string, the corresponding collective variables of which are close to $\mathbf{z}_i$, for $i = 1,\ldots, P$.

Generate an equilibrium trajectory for each image with $\mathbf{z}$ restrained around $\mathbf{z}_i$.

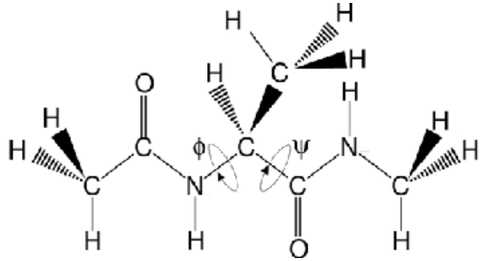
From the equilibrium trajectory, generate a large number of short, unbiased trajectories for each image.

Use the resulting average displacement, $\overline{\Delta \mathbf{z}_i}$, to determine the position of the P images.

Parameterize the string to ensure that the images are equidistant in collective-variable space.

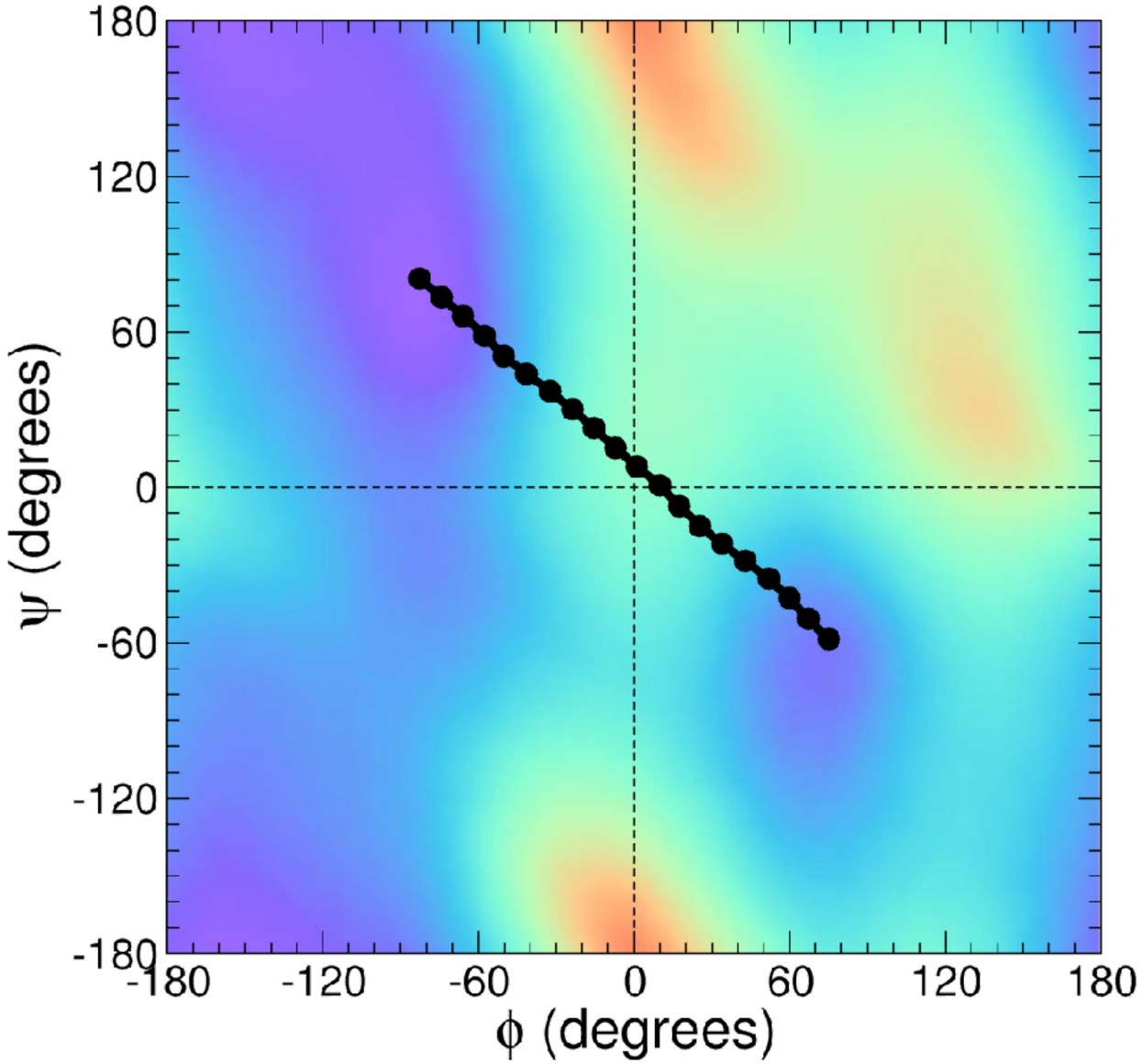
$\{$ C_{7eq} : -81°, +81°

C_{7ax} : +63°, -81°

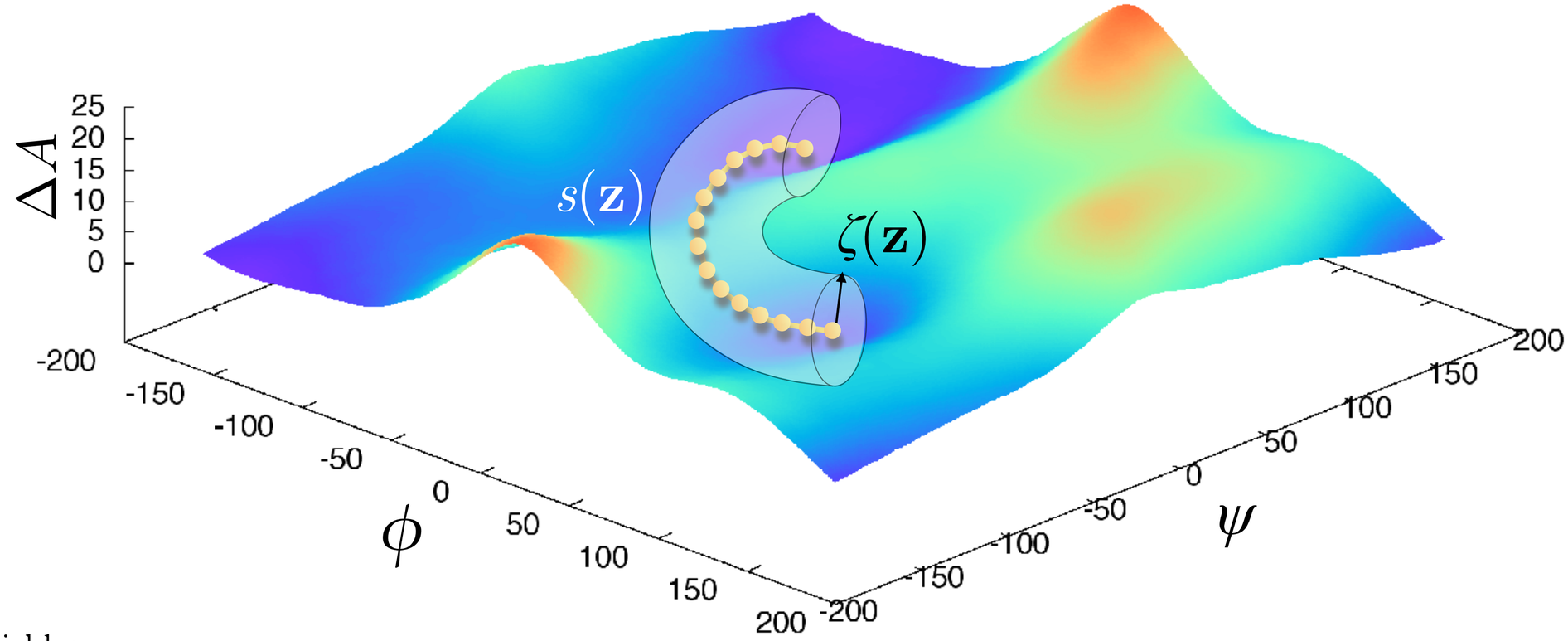


Pan, A. C.; Sezer, D.; Roux, B. *J. Phys. Chem. B* **2008**, *112*, 3432-3440

THE STRING METHOD WITH SWARMS OF TRAJECTORIES



THE STRING METHOD WITH SWARMS OF TRAJECTORIES

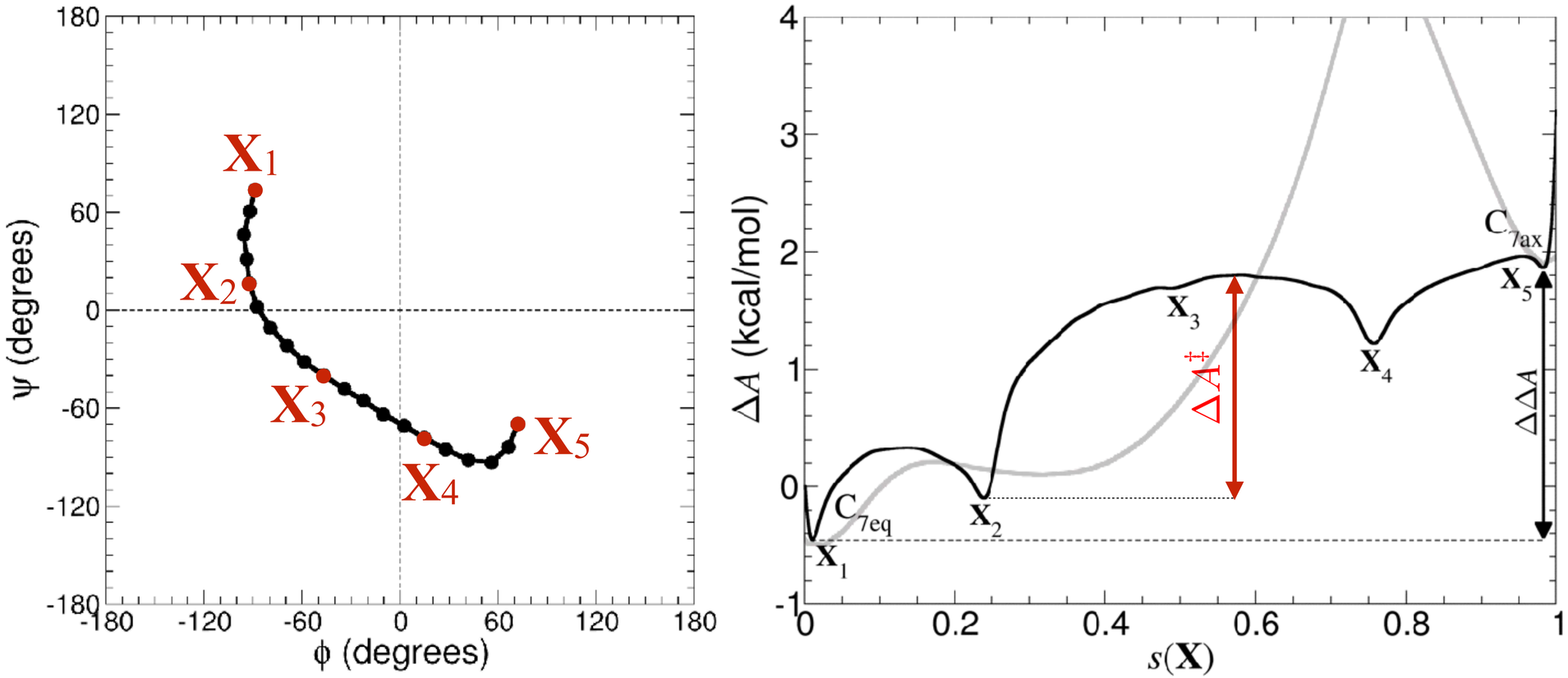


Path collective variables:

$$s(\mathbf{z}) = \lim_{\lambda\to\infty} \frac{\int_0^1 \mathrm{d}t\ t\ \exp\{-\lambda[\mathbf{z}-\mathbf{z}(t)]^2\}}{\int_0^1 \mathrm{d}t\ \exp\{-\lambda[\mathbf{z}-\mathbf{z}(t)]^2\}} \qquad \zeta(\mathbf{z}) = \lim_{\lambda\to\infty} -\frac{1}{\lambda}\int_0^1 \mathrm{d}t\ \exp\{-\lambda[\mathbf{z}-\mathbf{z}(t)]^2\}$$

Branduardi, D.; Gervasio, F. L.; Parrinello, M. *J. Chem. Phys.* **2007**, *126*, 054103

THE STRING METHOD WITH SWARMS OF TRAJECTORIES

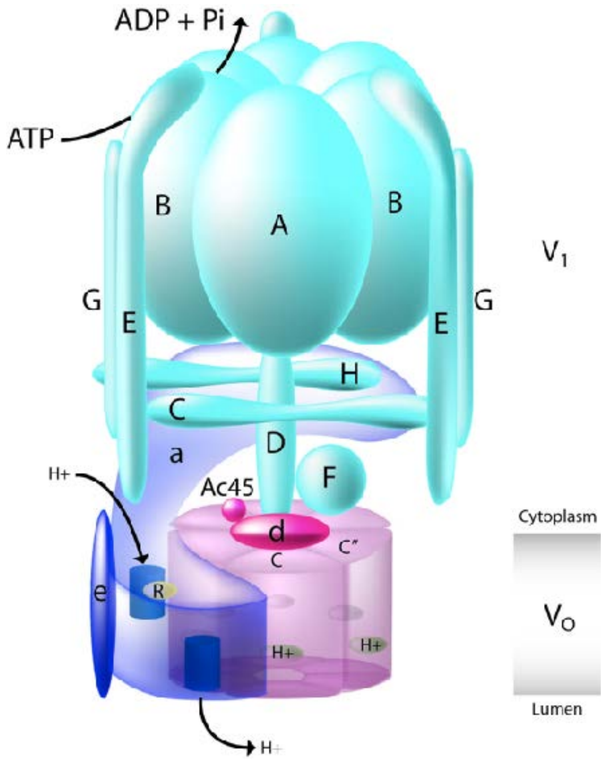


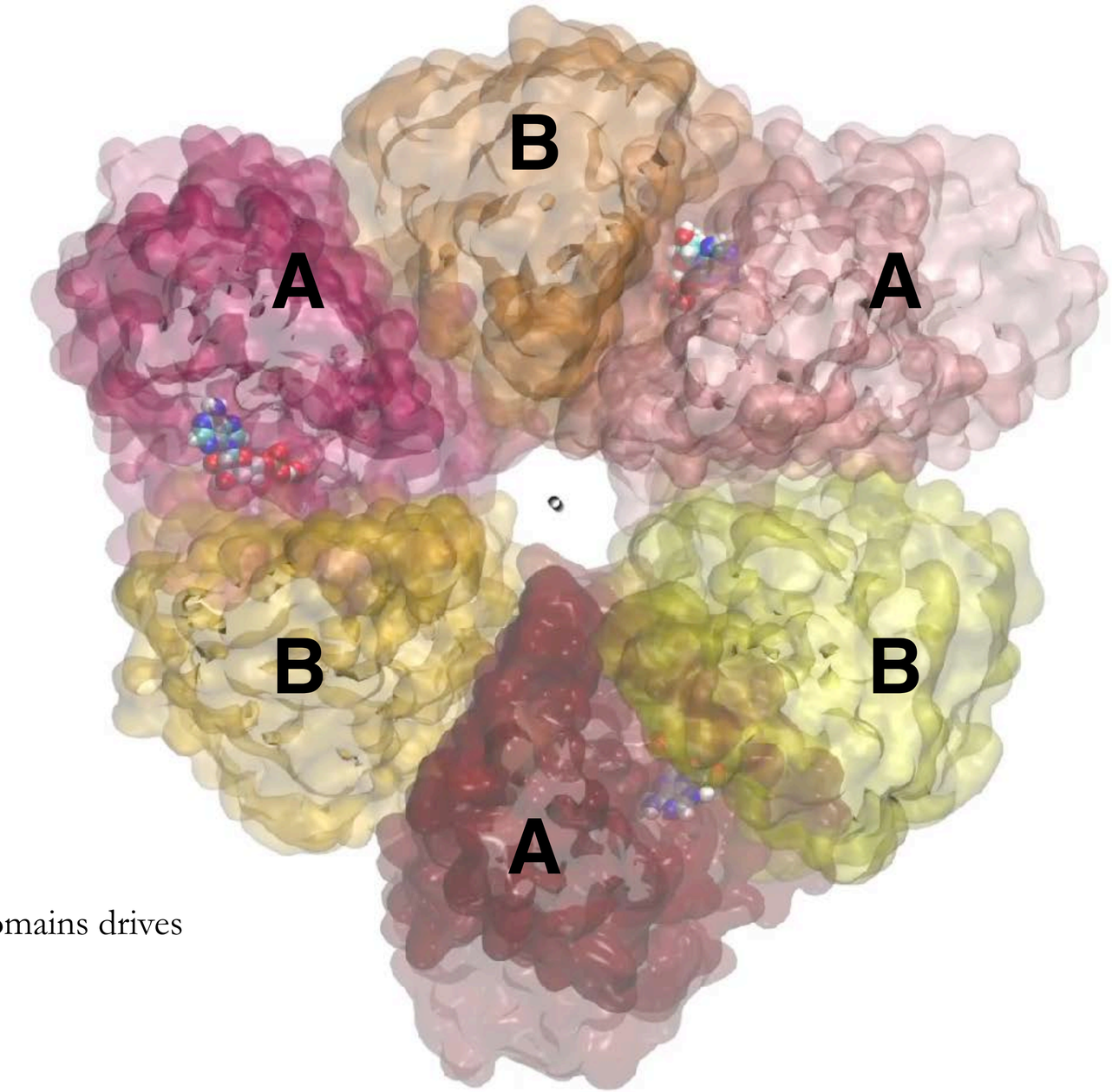
From the integration of C_{7eq} and C_{7ax} basins, $\Delta\Delta A = 2.5$ kcal/mol.

From the difference of RMSD's, $\Delta A^{\ddagger} = 5.6$ kcal/mol.

Hénin, J.; Fiorin, G.; Chipot, C.; Klein, M. L. *J. Chem. Theor. Comput.* **2010**, *6*, 35-47

THE STRING METHOD WITH SWARMS OF TRAJECTORIES





ATP hydrolysis-driven conformational transitions in the A_3B_3 domains drives rotation of the central stalk.

Singharoy, A.; Chipot, C.; Moradi, M.; Schulten, K. *J. Am. Chem. Soc.* **2017**, *139*, 293-310

A host of methods to measure free-energy changes



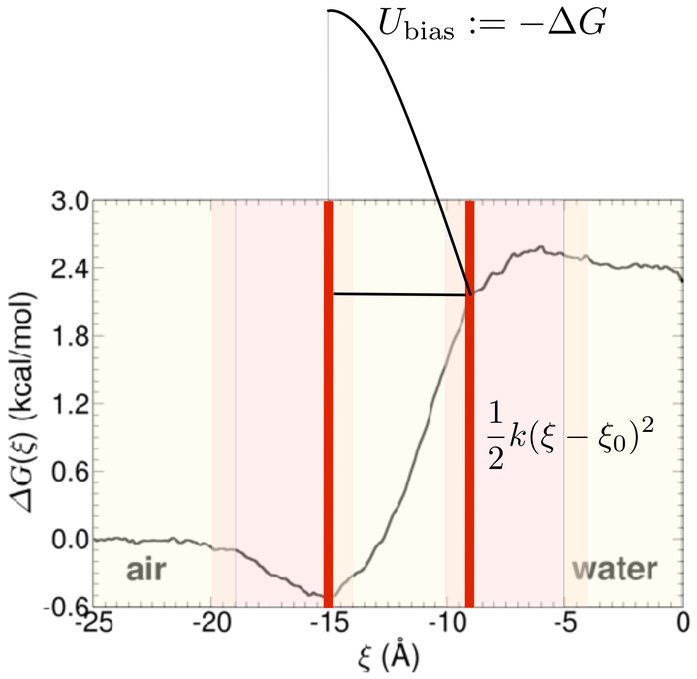
- Conformational flooding.
- Local elevation.
- Metadynamics.


- Umbrella sampling.
- Staging.

$$\Delta G(\xi) = -\frac{1}{\beta} \ln P(\xi) - U_{\text{bias}} + \Delta G_0$$

Weighted histogram analysis method:

$$\begin{cases} P_\lambda(\xi) = \dfrac{\sum_j N_j(\xi) \exp\left(-\beta \sum_i \lambda_i U_{\text{bias},i}\right)}{\sum_k n_k \exp\left(\Delta A_k - \beta \sum_i \lambda_i U_{\text{bias},i}\right)} \\ \exp(-\Delta A_i) = \sum_{U_{\text{bias}}} P_\lambda(\xi) \end{cases}$$



Grubmüller, H. *Phys. Rev. E* **1995**, *52*, 2893-2906
Huber, T. et al. *J. Comput. Aided Mol. Des.* **1994**, *8*, 695-708
Laio, A.; Parrinello, M. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 12562-12565
Torrie, G. M.; Valleau, J. P. *J. Comput. Phys.* **1977**, *23*, 187-199
Valleau, J. P. ; Card, D. N. *J. Chem. Phys.* **1972**, *57*, 5457-5462
Ferrenberg, A. M.; Swendsen, R. H. *Phys. Rev. Lett.* **1989**, *63*, 1195-1198

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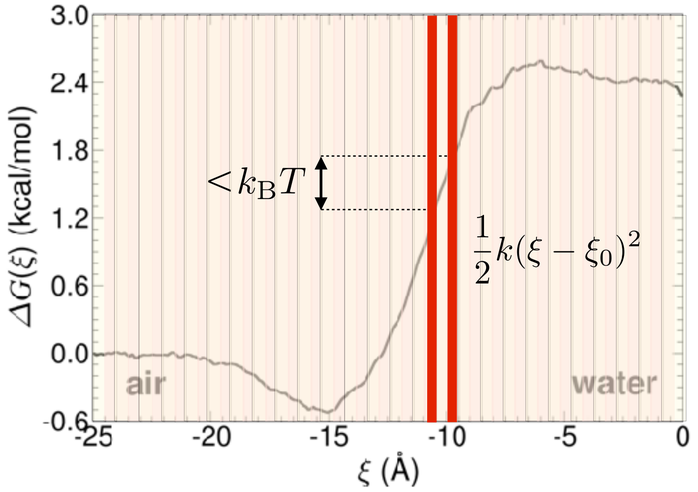


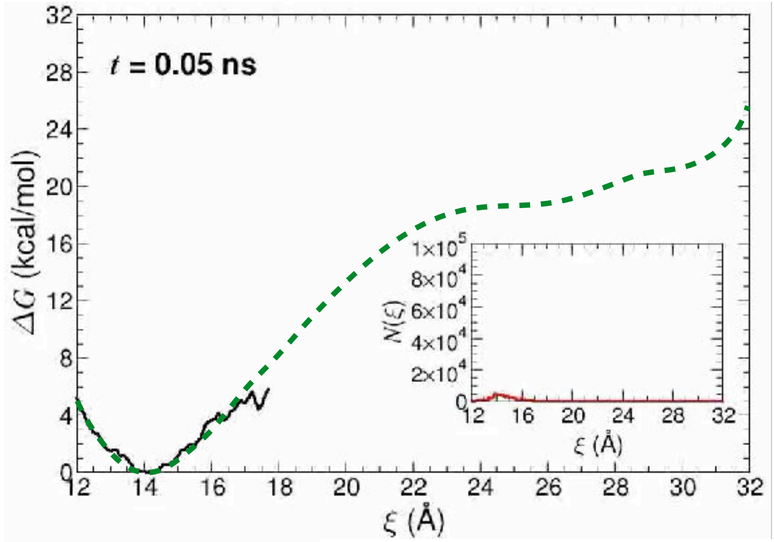
Grubmüller, H. *Phys. Rev. E* **1995**, *52*, 2893-2906
Huber, T. et al. *J. Comput. Aided Mol. Des.* **1994**, *8*, 695-708
Laio, A.; Parrinello, M. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 12562-12565
Torrie, G. M.; Valleau, J. P. *J. Comput. Phys.* **1977**, *23*, 187-199
Valleau, J. P. ; Card, D. N. *J. Chem. Phys.* **1972**, *57*, 5457-5462
Ferrenberg, A. M.; Swendsen, R. H. *Phys. Rev. Lett.* **1989**, *63*, 1195-1198

A HOST OF METHODS TO MEASURE FREE-ENERGY CHANGES

The derivative of the free energy with respect to the order parameter may be expressed as a sum of configurational averages at constant ξ :

$$\begin{cases} \nabla A(z) := \mathbb{E}\{F(\mathbf{x})|\xi(\mathbf{x}) = z\} \\ F(\mathbf{x}) = \dfrac{\nabla U(\mathbf{x}) \cdot \nabla\xi}{|\nabla\xi|^2} - \dfrac{1}{\beta} \cdot \nabla\left(\dfrac{\nabla\xi}{|\nabla\xi|^2}\right) \end{cases}$$

$\mathbf{v}_{i,i\in[1,\ldots,n]}$ are arbitrarily chosen vector fields of $\mathbb{R}^{3N} \rightarrow \mathbb{R}^{3N}$, which verify $\mathbf{v}_i \cdot \nabla_{\mathbf{x}}\xi_j = \delta_{ij}, \forall i, j$.



The i-th partial derivative of the free energy surface is calculated as the ensemble average of the thermodynamic force:

$$\nabla A(z) = \left\langle \mathbf{v}_i \cdot \nabla U(\mathbf{x}) - \frac{1}{\beta}\nabla \cdot \mathbf{v}_i \right\rangle$$

Carter, E. et al. *Chem. Phys. Lett.* **1989**, *156*, 472-477

Darve, E.; Pohorille, A. *J. Chem. Phys.* **2001**, 115, 9169-9183

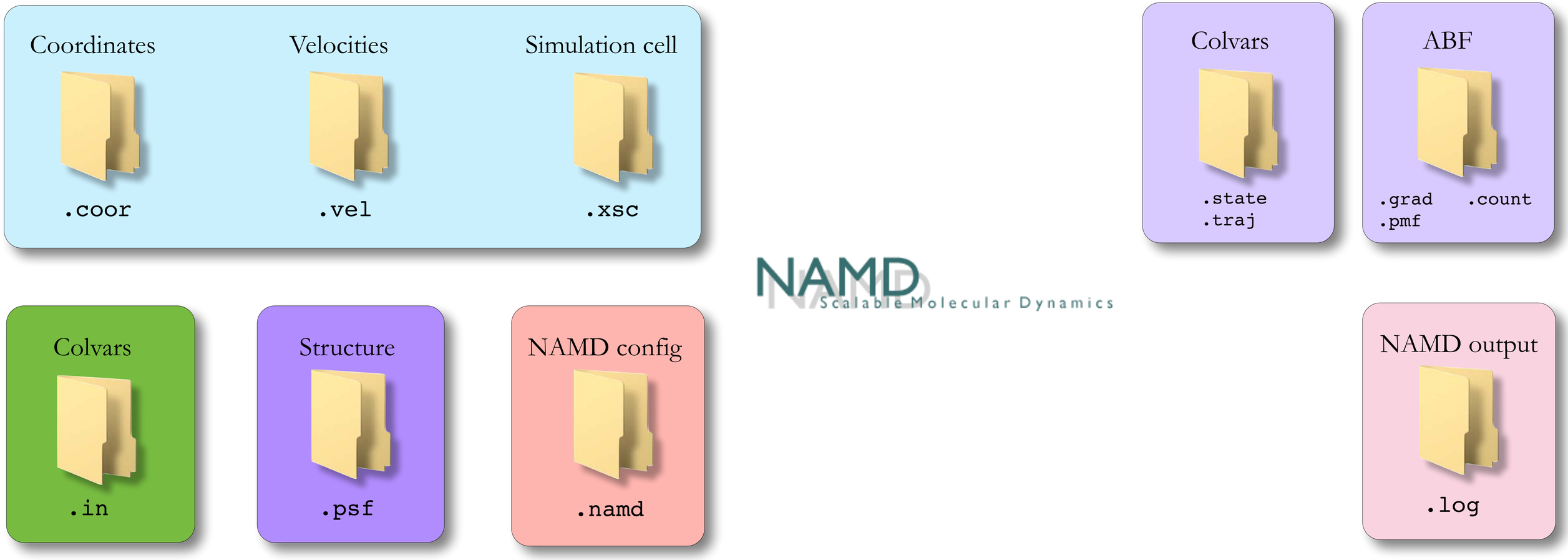
Hénin, J.; Chipot, C. *J. Chem. Phys.* **2004**, *121*, 2904-2914

Den Otter, W. *J. Chem. Phys.* **2000**, *112*, 7283-7292

Comer, J.; Gumbart, J. C.; Hénin, J.; Lelièvre, T.; Pohorille, A.; Chipot, C. *J. Phys. Chem. B* **2015**, *119*, 1129-1151

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

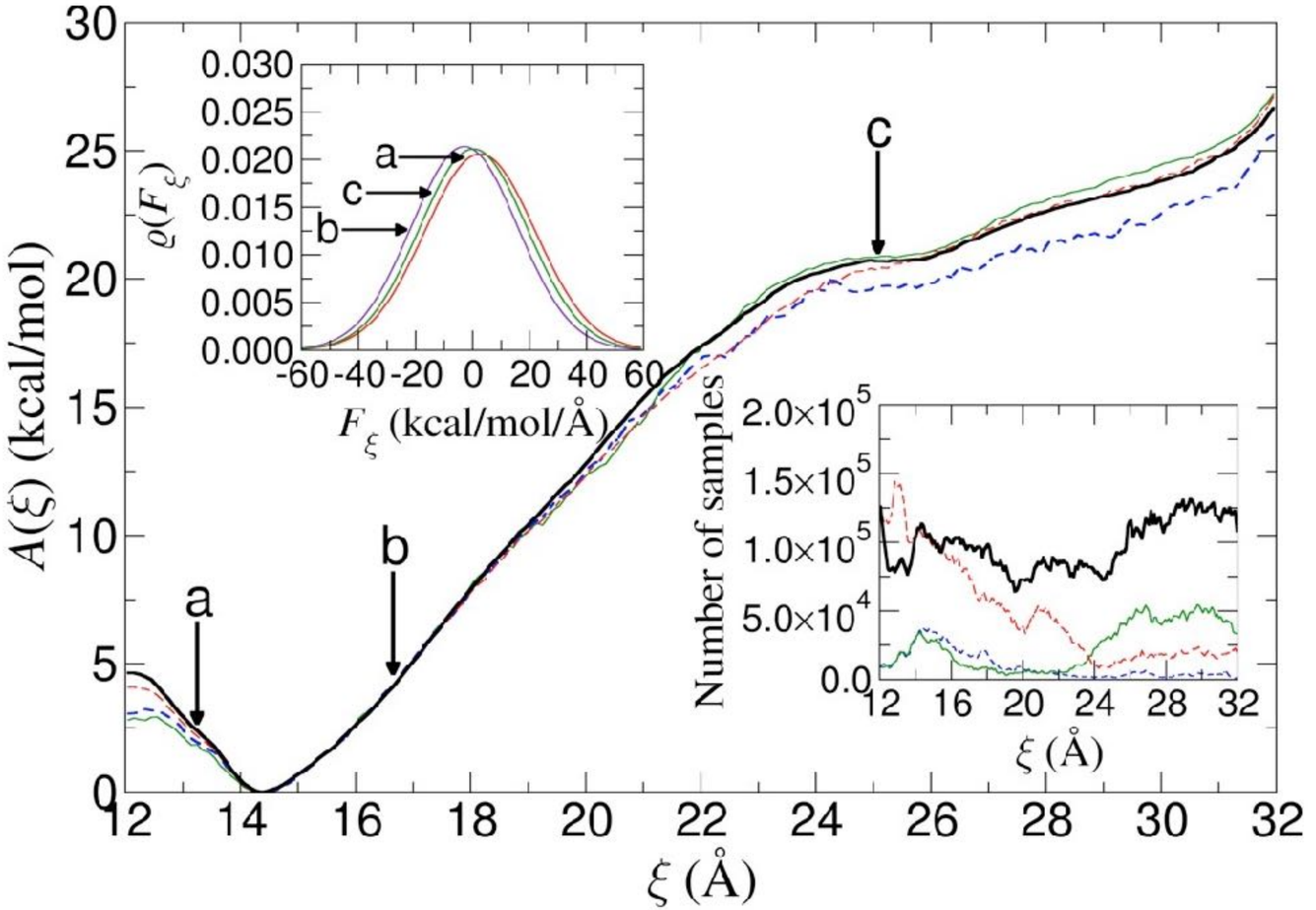
Equilibration simulation



Phillips, J. C. et al. *J. Comput. Chem.* **2005**, *26*, 1781-1802

Bhandarkar, M. et al. NAMD user's guide, version 2.9, **2012**

Reversible unfolding of decaalanine



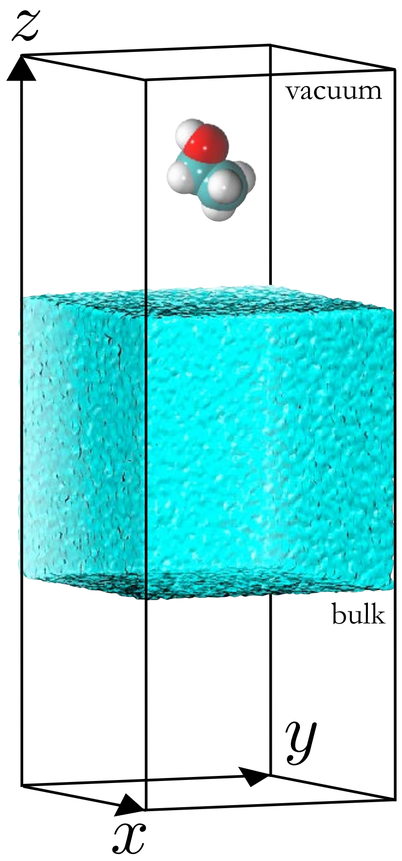

```
colvar {
   name EndToEndDistance

   width 0.2

   lowerboundary 12.0
   upperboundary 32.0

   lowerwallconstant 100.0
   upperwallconstant 100.0

   outputSystemForce   yes
   outputAppliedForce  yes

   distance {
      group1 {
         atomnumbers { 10 }
      }
      group2 {
         atomnumbers { 92 }
      }
   }
}
```

Avoid possible contamination by shaken/rattled degrees of freedom.

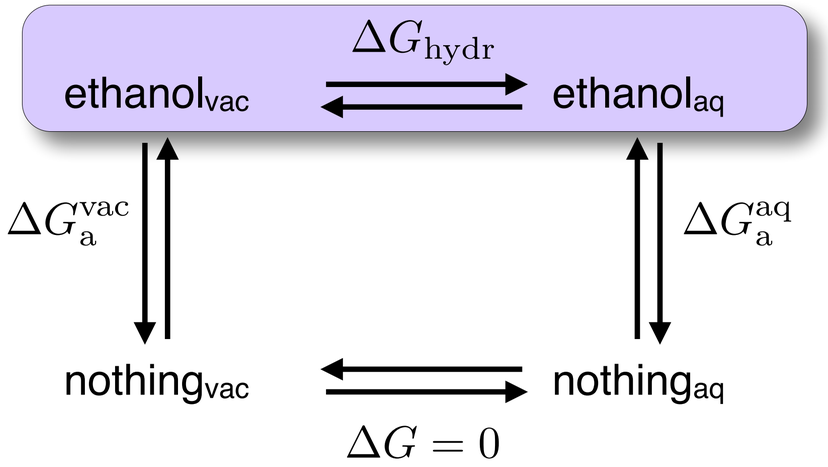
Park, S.; Khalili-Araghi, F.; Tajkhorshid, E.; Schulten, K. *J. Chem. Phys.* **2003**, *119*, 3559-3566

Hénin, J.; Chipot, C. *J. Chem. Phys.* **2004**, *121*, 2904-2914

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



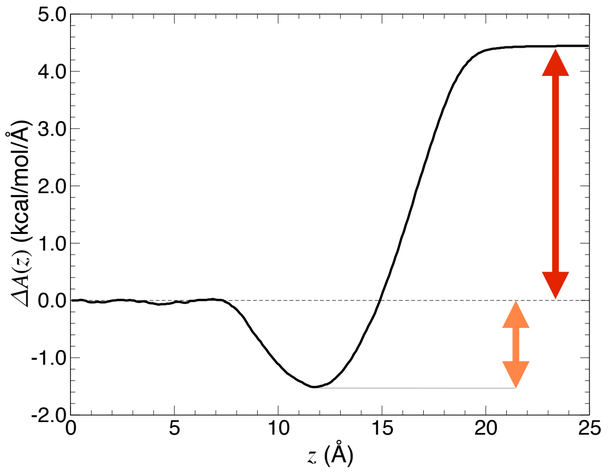
Back to exercise 2. Ethanol hydration



Access to both hydration and adsorption (experiment: +2.5 kcal/mol) free energies.

Decomposition of $\nabla_z A$ and projection onto z yields free-energy contributions.

```
colvar {
   name ProjectionZ
   width 0.1
   lowerboundary  0.0
   upperboundary  5.0
   lowerwallconstant 100.0
   upperwallconstant 100.0

   distanceZ {
      ref {
         atomsFile reference.pdb
         atomsCol B
      }
      main  {
         atomnumbers { 1 2 3 4 5 6 7 8 9 }
      }
   }
}

abf {
  colvars ProjectionZ
  fullSamples    1000
}
```



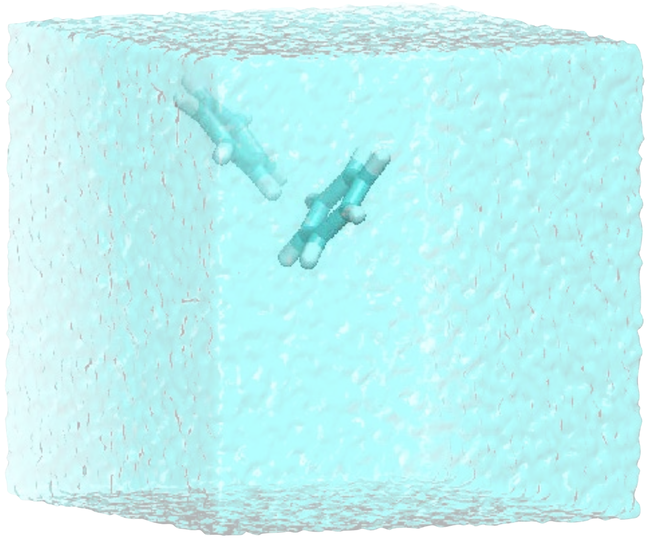
Chipot, C.; Pohorille, A. Free energy calculations. Theory and applications in chemistry and biology, **2007**

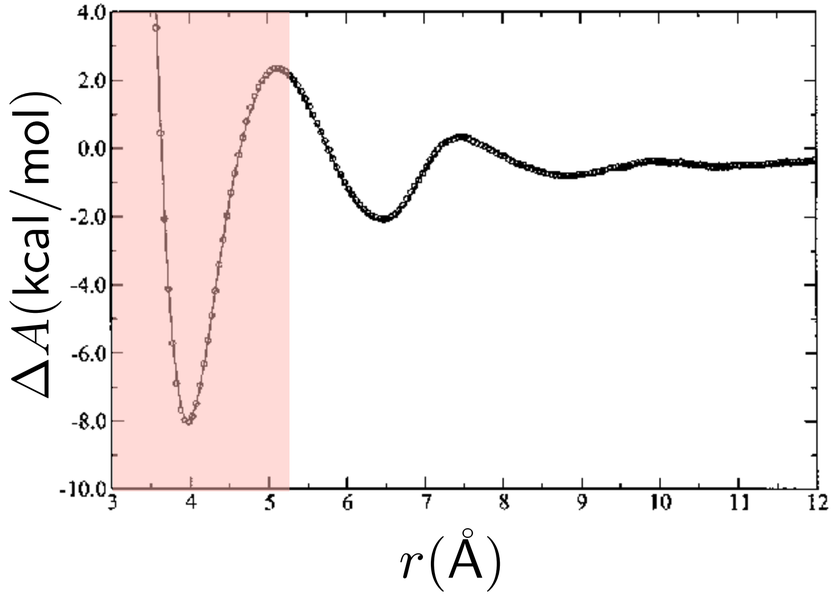
Wilson, M. A.; Pohorille, A. *J. Phys. Chem. B* **1997**, *101*, 3130-3135

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

Measuring binding constants from one-dimensional separation potentials of mean force is justified in the limit of all other degrees of freedom being appropriately sampled. This is true for small, fast-relaxing molecular species.

$$K_a = 4\pi \int_0^{R_c} \mathrm{d}r \; r^2 \; \exp[-\beta \Delta A(r)]$$





Shoup, D.; Szabo, A. *Biophys. J.* **1982**, *40*, 33-39

Woo, H. J.; Roux, B. *Proc. Natl. Acad. Sci. USA* **2005**, 102, 6825-6830

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

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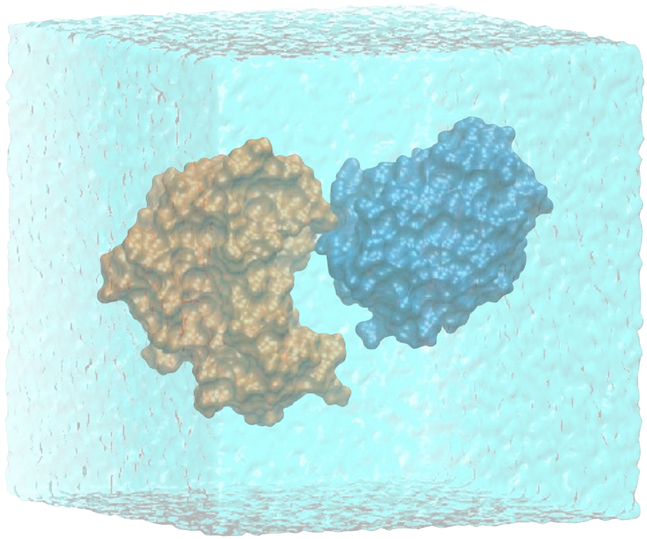
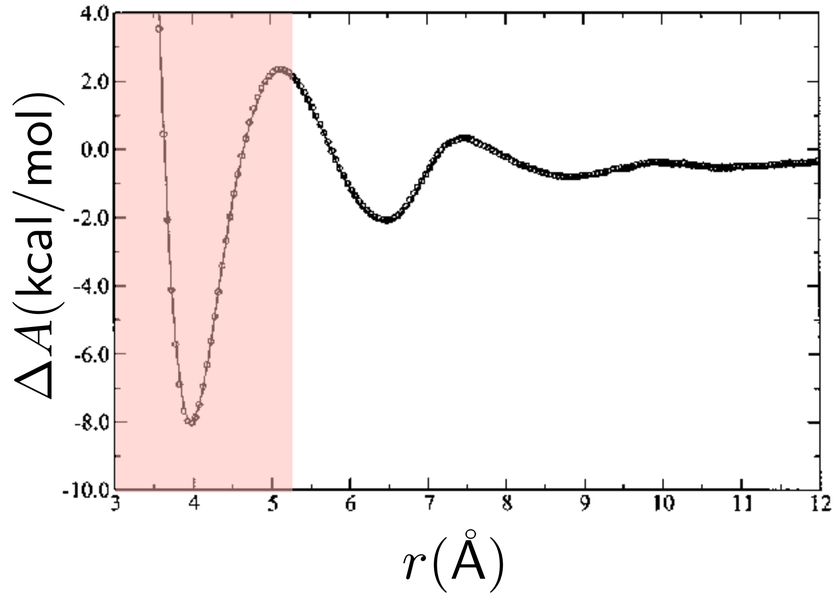
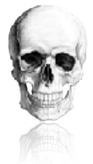






In more complex molecular assemblies, e.g., protein-ligand complexes, the partners acquire upon separation additional configurational - i.e., conformational, positional and orientational entropy, not easily captured over timescales amenable to molecular dynamics.

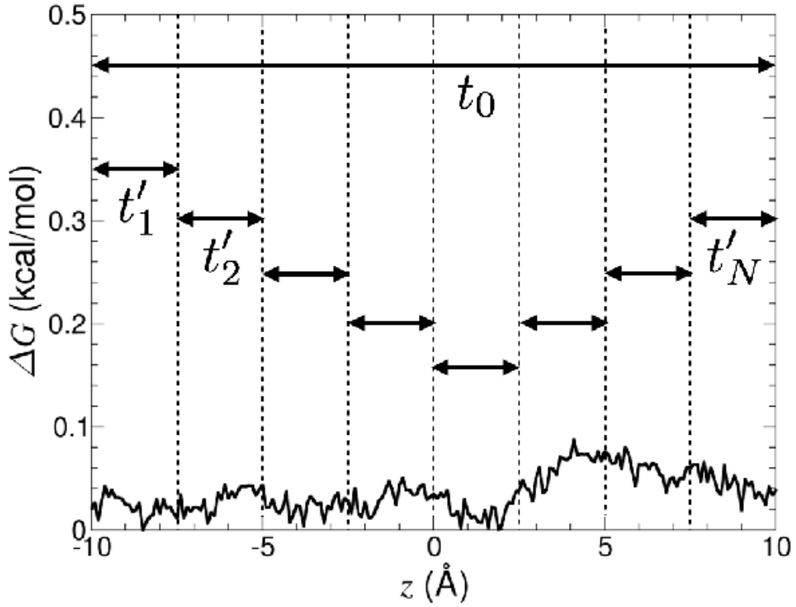
Shoup, D.; Szabo, A. *Biophys. J.* **1982**, *40*, 33-39

Gumbart, J. C.; Roux, B.; Chipot, C. *J. Chem. Theor. Comput.* **2013**, *9*, 3789-3798

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

ξ ought to be completely decoupled from degrees of freedom to which holonomic constraints are applied.

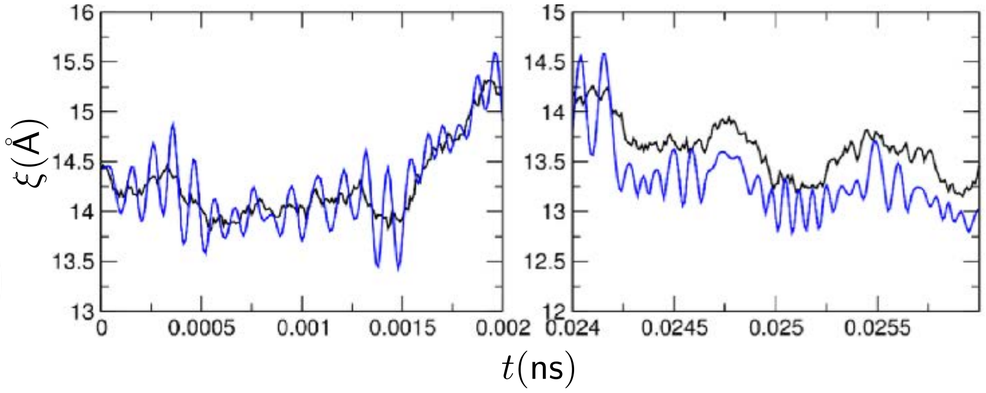
As a matter of principle, ξ ought to be stratified: $t_0 > \sum_i t'_i$



Turn to the extended-Lagrangian formulation of ABF in the event geometrical restraints are coupled to ξ.

```
ExtendedLagrangian    on
```

$$F(\mathbf{x}) = \frac{\nabla U(\mathbf{x}) \cdot \nabla \xi}{|\nabla \xi|^2} - \frac{1}{\beta} \cdot \nabla \left(\frac{\nabla \xi}{|\nabla \xi|^2} \right)$$

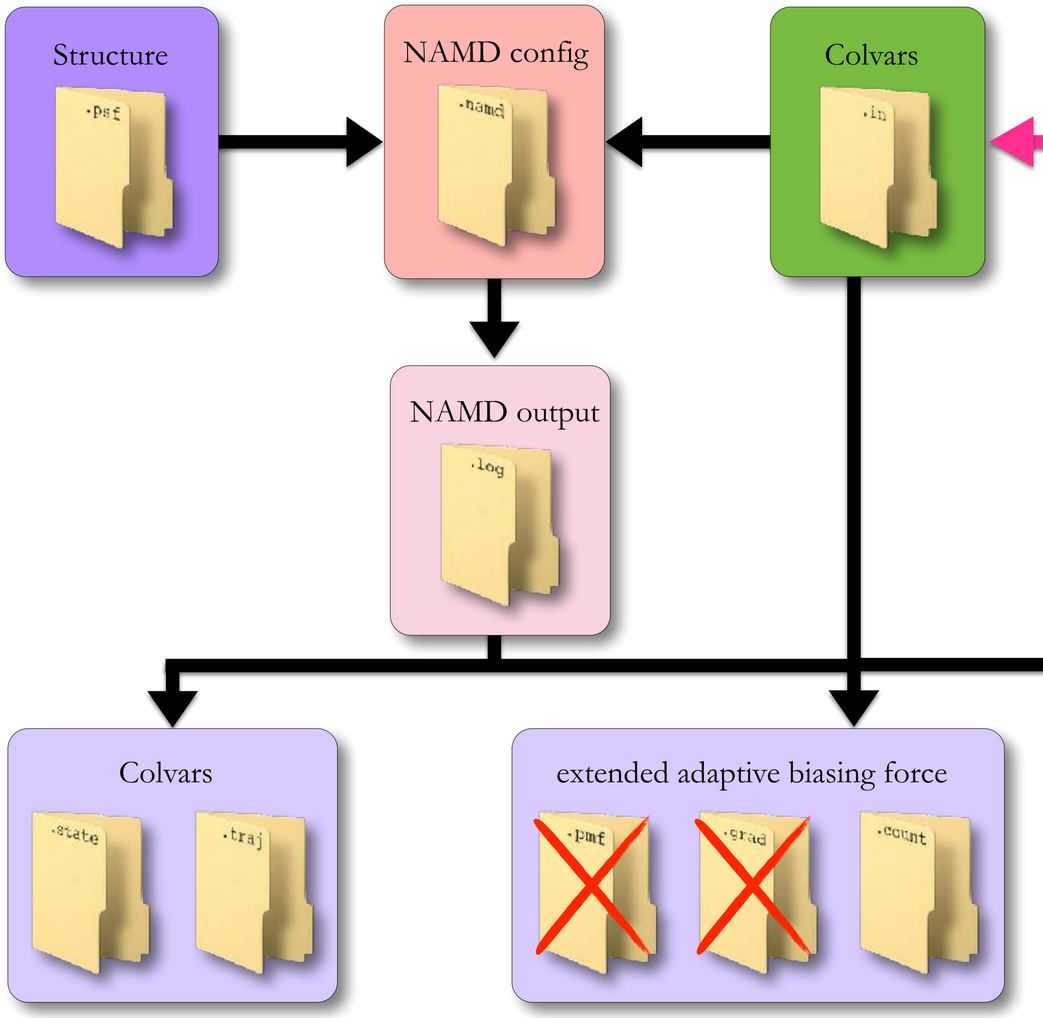


Chipot, C.; Pohorille, A. Free energy calculations. Theory and applications in chemistry and biology, **2007**

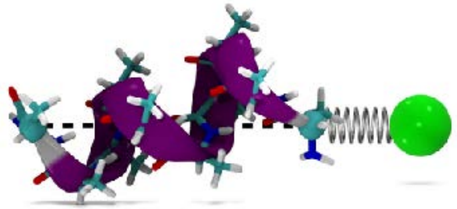
Lelièvre, T.; Stoltz, G.; Rousset, M. Free energy computations: A mathematical perspective, **2010**

Comer, J.; Gumbart, J. C.; Hénin, J.; Lelièvre, T.; Pohorille, A.; Chipot, C. *J. Phys. Chem.* **2014**

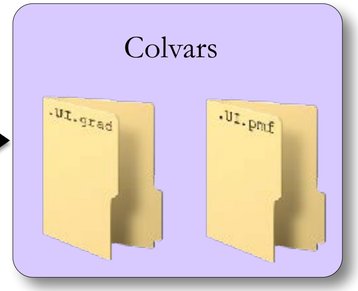
GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS




```
colvar {
  name R
  width 1.0
  lowerboundary 0.0
  upperboundary 40.0
  lowerwallconstant 100.0
  upperwallconstant 100.0
  extendedLagrangian on
  distance {
    forceNoPBC yes
    group1 {
      atomnumbers { 367 368 369 370 384 385 }
    }
    group2 {
      atomnumbers { 949 950 951 952 958 959 }
    }
  }
}
```



$$\left(\frac{\mathrm{d}G}{\mathrm{d}\xi}\right)_{\xi'} = \frac{\sum_{\Xi'} N(\xi',\Xi')\left[\frac{(\xi'-\langle\xi_{\Xi'}\rangle)}{\beta\sigma^2_{\Xi'}} - K_\xi(\xi'-\Xi')\right]}{\sum_{\Xi'} N(\xi',\Xi')}$$

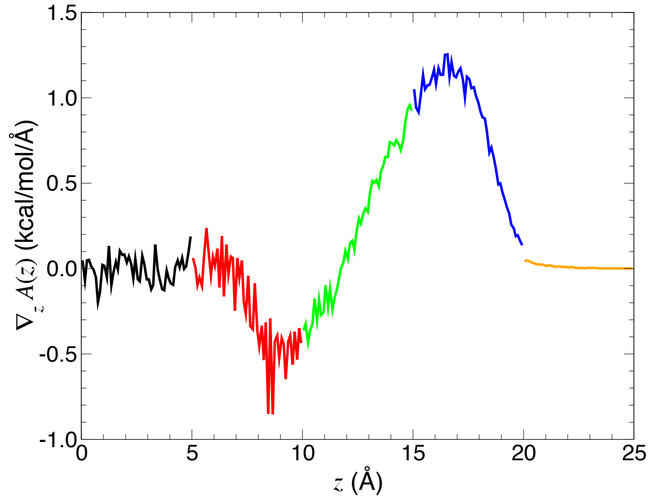


UIestimator

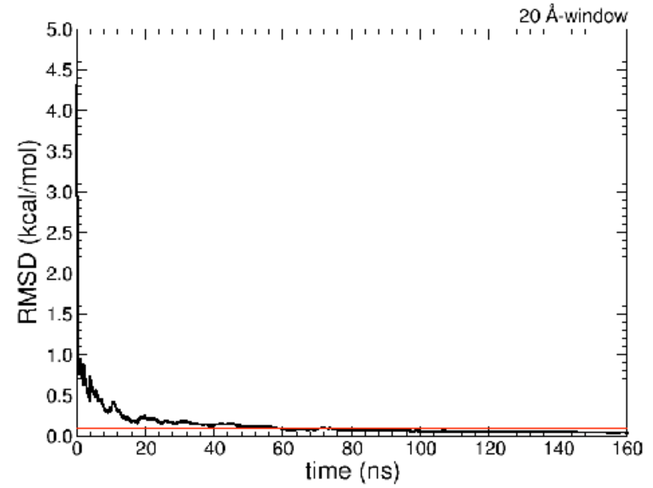
Zheng, L.; Yang, W. *J. Chem. Theory Comput.* **2012**, *8*, 810-823.
Zheng, L.; Chen, M.; Yang, W. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 20227-20232.
Fu, H.; Shao, X.; Chipot, C.; Cai, W. *J. Chem. Theory Comput.* **2016**, *12*, 3506–3513.
Lesage, A.; Lelièvre, T.; Stoltz, G.; Hénin, J. *J. Phys. Chem. B* **2017**, *121*, 3676–3685.

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

In stratified ABF calculations, continuity of the average force ought to be verified.



Free-energy profiles ought to be provided with error bars, $\sigma_{\Delta A} \simeq \frac{\sigma}{N^{1/2}}(1+2\kappa)^{1/2}$



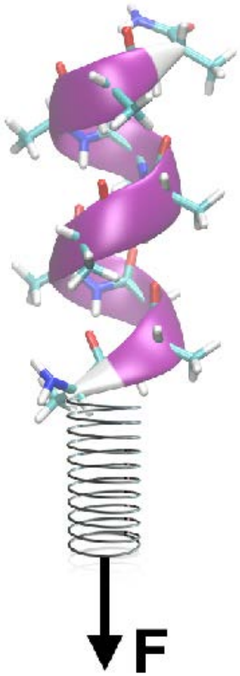
Assess convergence, for instance, by breaking down the free-energy calculations in multiple sub-runs and compute a root mean-square deviation with respect to the last one.

Chipot, C.; Pohorille, A. Free energy calculations. Theory and applications in chemistry and biology, **2007**

Lelièvre, T.; Stoltz, G.; Rousset, M. Free energy computations: A mathematical perspective, **2010**

Comer, J.; Gumbart, J. C.; Hénin, J.; Lelièvre, T.; Pohorille, A.; Chipot, C. *J. Phys. Chem.* **2014**

WHAT ABOUT NON-EQUILIBRIUM WORK COMPUTER EXPERIMENTS ?

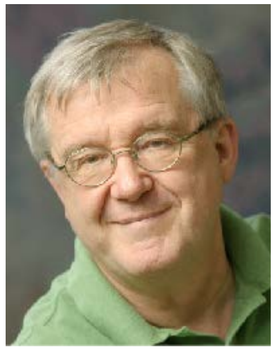


$$\exp(-\beta\Delta A) = \langle \exp(-\beta w) \rangle$$

Pulling simulations are usually carried out at a velocity about 10^3 greater than that of experiment.

$$\frac{P_0(+w)}{P_1(-w)} = \exp[+\beta(w - \Delta A)]$$

Akin to BAR, combine the forward and backward transformations to reduce the variance.



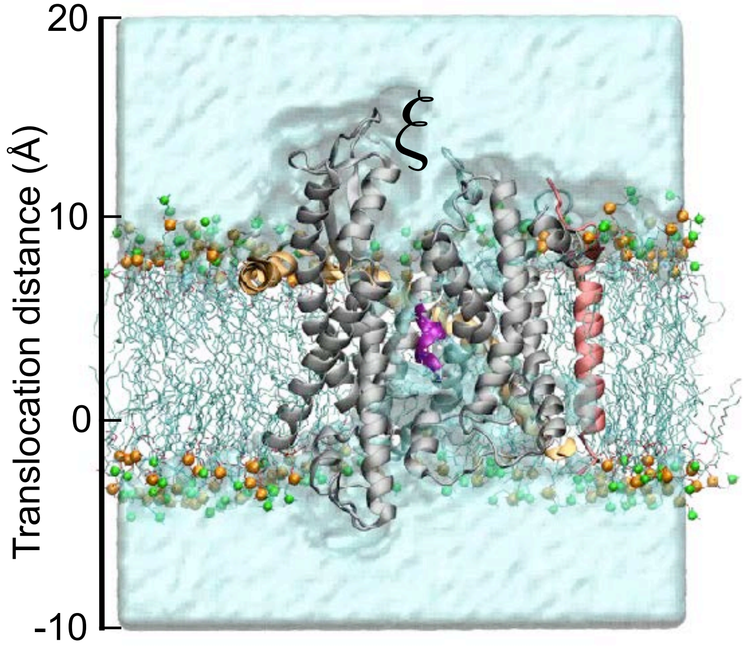
Though cumulant expansions help, the non-equilibrium work route to free-energy differences requires near-equilibrium conditions to converge.

In general, there is no fundamental reason to resort to non-equilibrium work experiments if the free-energy change can be estimated at equilibrium.

Jarzynski, C. *Phys. Rev. Lett.* **1997**, *78*, 2690-2693

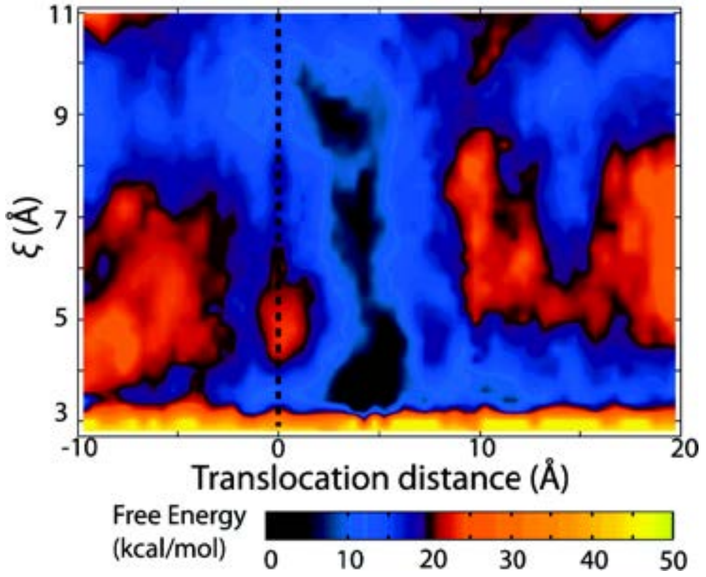
Crooks, G. *J. Stat. Phys.* **1998**, *90*, 1481-1487

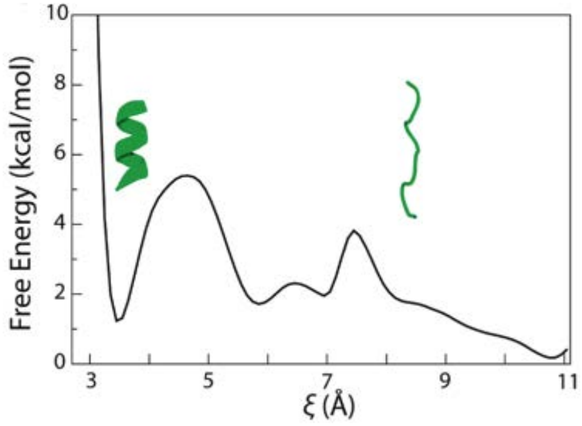
Park, S.; Khalili-Araghi, F.; Tajkhorshid, E.; Schulten, K. *J. Chem. Phys.* **2003**, *119*, 3559-3566



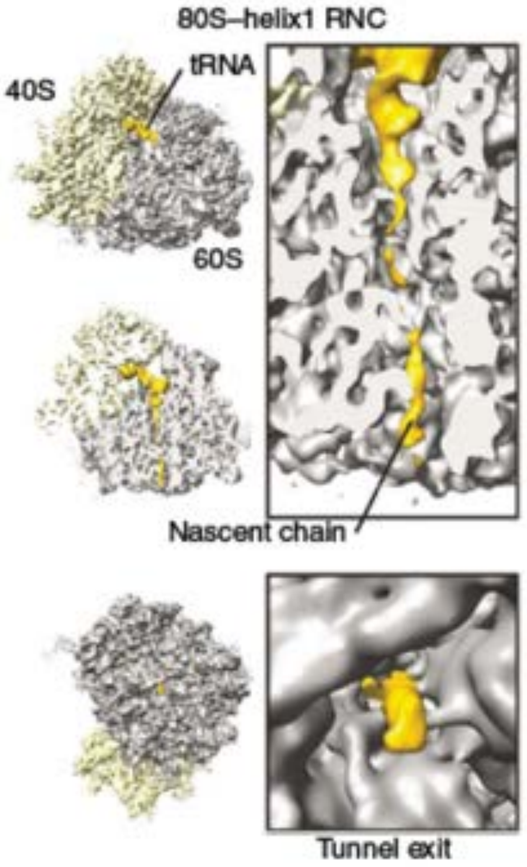
Two-dimensional reaction coordinate: Translation in SecY plus the concerted folding of the peptide chain (ξ).

Translocation of proteins supposes partial opening of SecY.





Control simulation:
Folding in bulk water.



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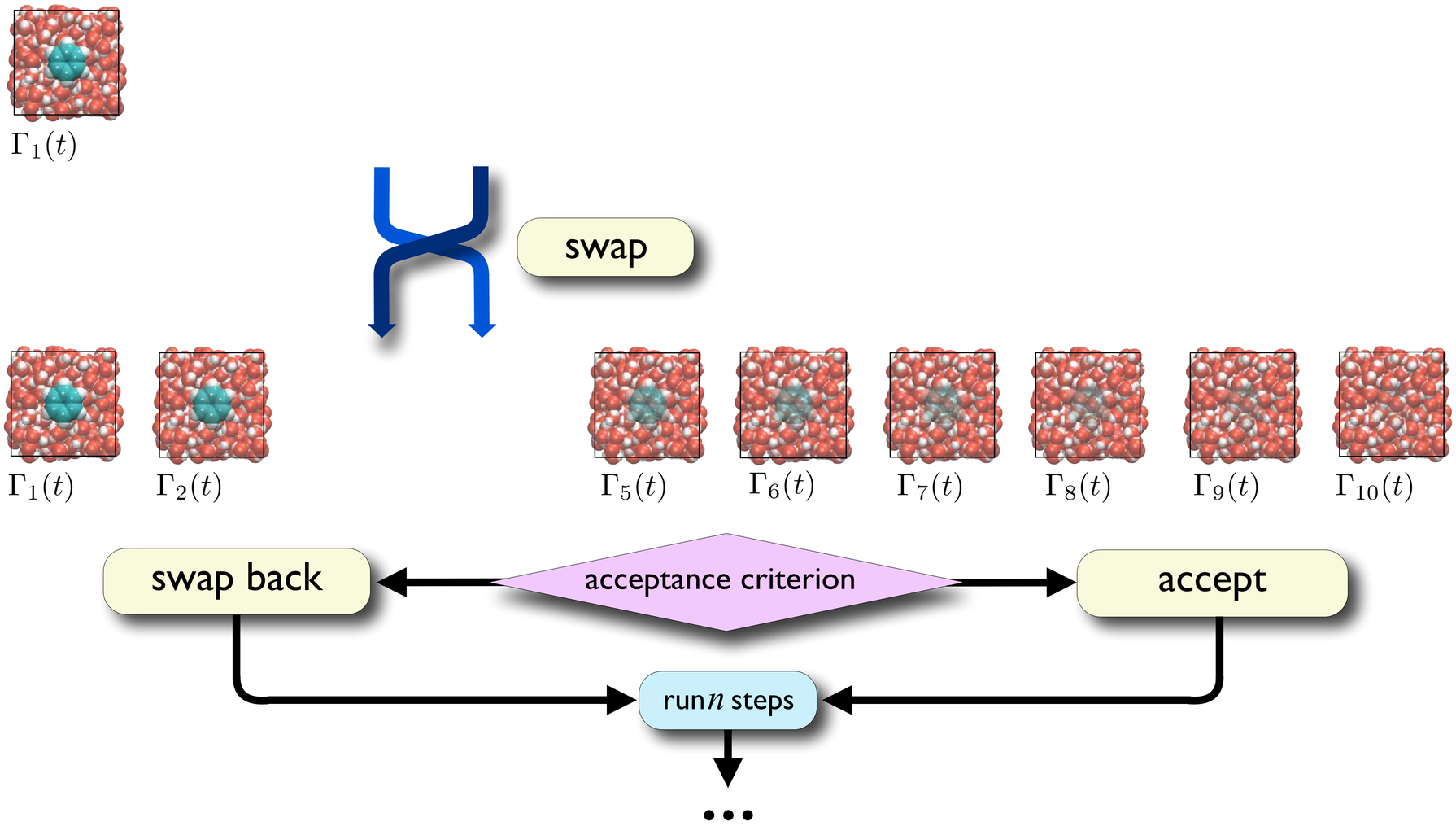
Concluding remarks and questions

TOWARDS ERGODIC SAMPLING

$$p(\lambda_i \to \lambda_j) = \min\left\{1; \mathrm{e}^{-\beta\{[U^j(\mathbf{x},\lambda_j)-U^i(\mathbf{x},\lambda_j)]+[U^i(\mathbf{x},\lambda_i)-U^j(\mathbf{x},\lambda_i)]\}}\right\}$$



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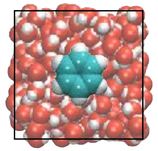
Comer, J.; Roux, B.; Chipot, C. *Mol. Sim.* **2014**, *40*, 218-228

TOWARDS ERGODIC SAMPLING

$$p(T_i \to T_j) = \min\left(1; \mathrm{e}^{(\beta_j - \beta_i)[U^j(\mathbf{x},\lambda_j) - U^i(\mathbf{x},\lambda_i)]}\right)$$

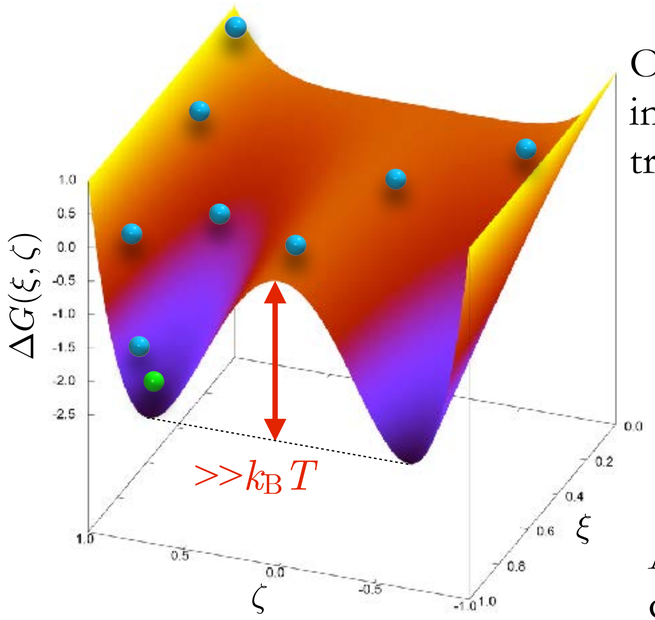


$\Gamma_1(t)$

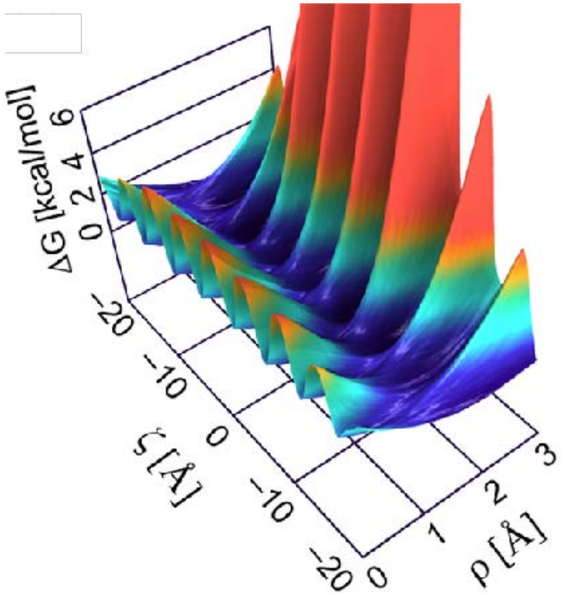
TOWARDS ERGODIC SAMPLING

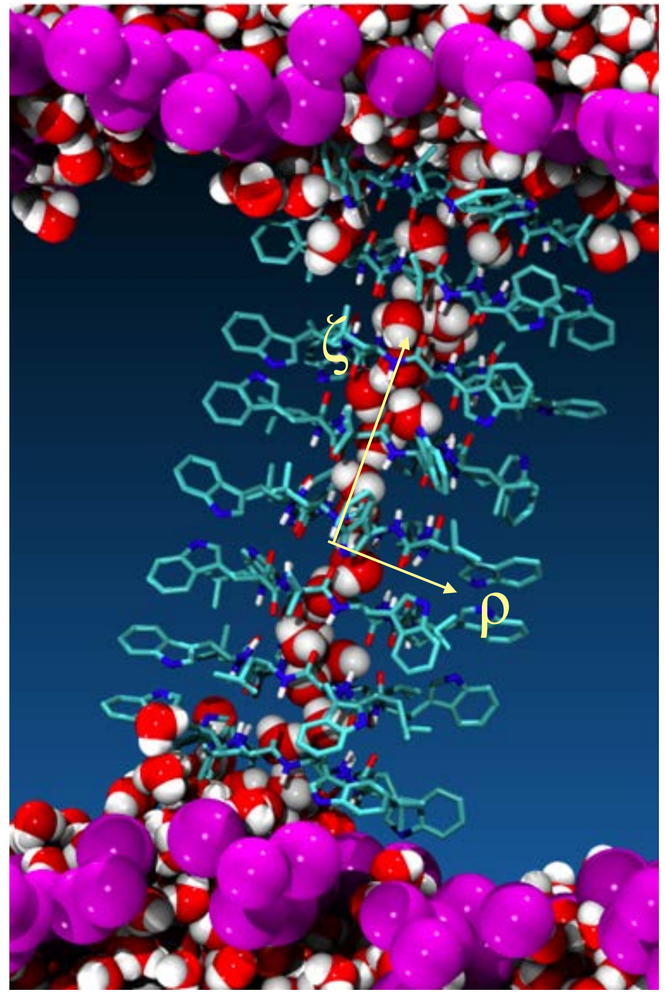
Non-ergodicity scenarios are often related to hidden barriers in orthogonal space.

Such non-ergodicity scenarios generally arise from too naïve a view of what the reaction coordinate is and how we represent it in a low-dimensional collective-variable space.



One possible remedy consists in increasing the dimensionality of the transition coordinate.





Another remedy consists in exploiting the ability of large computer architectures to handle many walkers concomitantly.

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Beyond thermodynamics

$$\Delta Z = \beta D(Z_t)F(Z_t,t)\Delta t + \nabla D(Z_t)\Delta t + \sqrt{2D(Z_t)\Delta t}\ g_t$$

Let: $\begin{cases} \mu = \beta D(Z_t)F(Z_t,t)\Delta t + \nabla D(Z_t)\Delta t \\ \sigma^2 = 2D(Z_t)\Delta t \end{cases}$

Then: $\Delta Z = \mu + \sigma\ g_t$

$$P[\Delta Z|w(z),D(z)] = \frac{1}{\sigma\sqrt{2\pi}}\exp\left(-\frac{(\Delta Z-\mu)^2}{2\sigma^2}\right)$$

Probability over the entire trajectory, given the parameters:

$$P[Z(t)|w(z),D(z)] = \prod_i \frac{1}{\sigma_i\sqrt{2\pi}}\exp\left(-\frac{(\Delta Z_i-\mu_i)^2}{2\sigma_i^2}\right)$$

(1) The molecular dynamics supplies the trajectory of the collective variable, $Z(t)$.

(2) The molecular dynamics supplies also, $f_{\text{bias}}(t)$.

(3) Pick trial parameters, $w(z)$ and $D(z)$.

(4) Assume a propagator, e.g., Brownian dynamics.

(5) Calculate the probability of the trajectory given the parameters.

(6) Bayes's theorem: Get the probability of the parameters given the trajectory.

(7) Optimize the parameters to yield the greatest probability.

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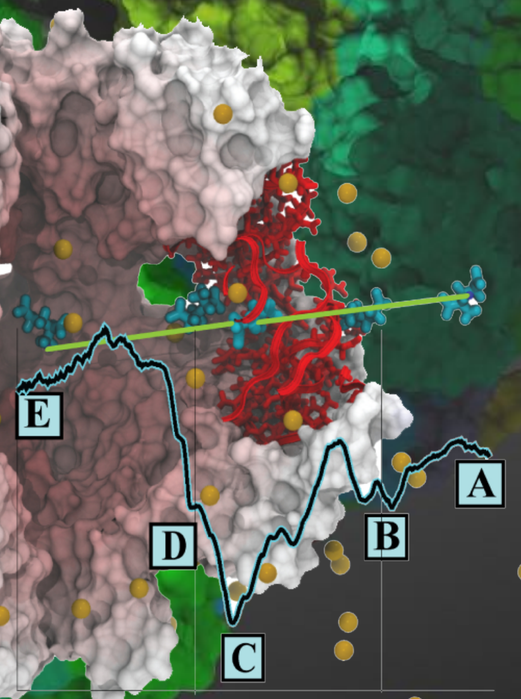
Kinetic models

Bacteria resist osmotic stress by means of MscS, but why does the latter include a balloon-like, water filled cytoplasmic domain?

CD acts as an entropic filter that prevents Glu^- from reaching the pores, but once Glu^- enters a pore, it passes unhindered by virtue of a reduced enthalpic barrier preventing clogging.



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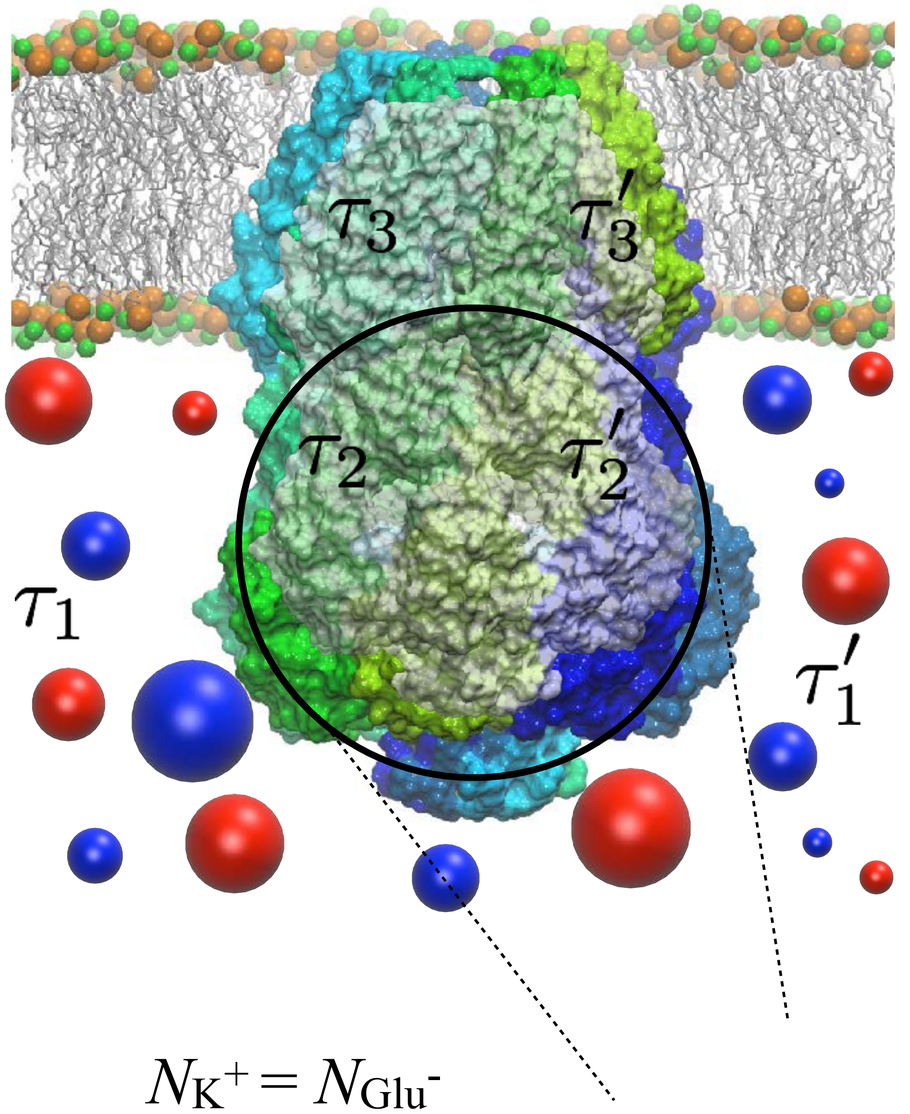
Determine τ_1, τ_2 and τ_3 for Glu^- and K^+ :

$$\tau = \int_a^b \mathrm{d}z \ \exp[\beta \Delta G(z)] D^{-1}(z) \int_a^z \mathrm{d}\zeta \ \exp[-\beta \Delta G(\zeta)]$$

CD maintains an overall balance of electrolytes to preclude collapse of the transmembrane potential whilst over-coming osmotic shock.



$$N_{K^+} = N_{Glu^-}$$

Martinac, B. et al. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 2297-2301

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Institut de Biologie Physico-Chimique

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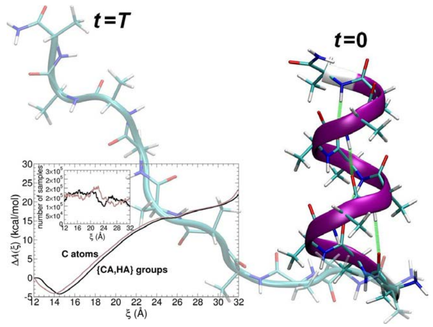
Theoretical and Computational Biophysics Group

Free energy calculations along a reaction coordinate: A tutorial for adaptive biasing force simulations



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November 3, 2014

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introduction to free-energy perturbation calculations

introductory tutorial

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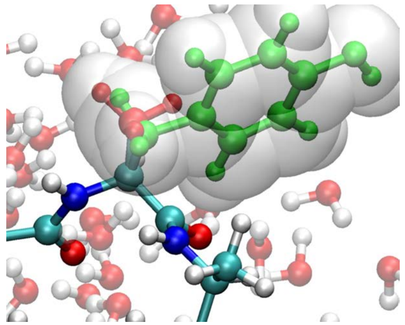
In silico alchemy: A tutorial for alchemical free-energy perturbation calculations with NAMD



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standard binding free energies

geometric free-energy calculations
alchemical free-energy calculations

advanced tutorial

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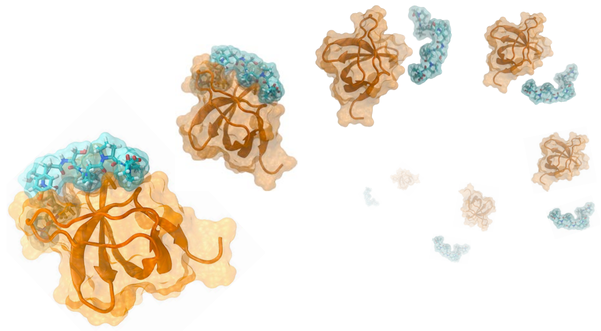
Protein:ligand standard binding free energies: A tutorial for alchemical and geometrical transformations



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path sampling

string method with swarm of trajectories, free-energy calculations along a path-collective variable

advanced tutorial

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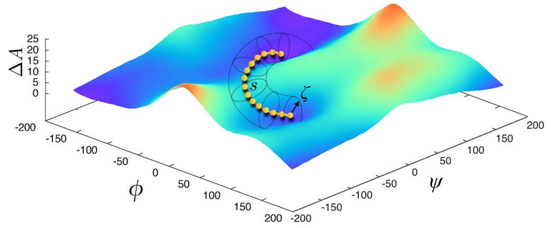
String method with swarms of trajectories: A tutorial for free-energy calculations along a minimum-action path



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Contributors: Gumbart, J. C.; Hénin, J.; Fajer, M.; Roux, B.; Chipot, C.

WHAT DO I NEED FOR THIS WORKSHOP ?

- An up-to-date version of NAMD

- An up-to-date version of VMD, featuring the ParseFEP plugin

- The bundle of hands-on exercises, which can be downloaded from:

```
http://www.ks.uiuc.edu/Training/Tutorials
```