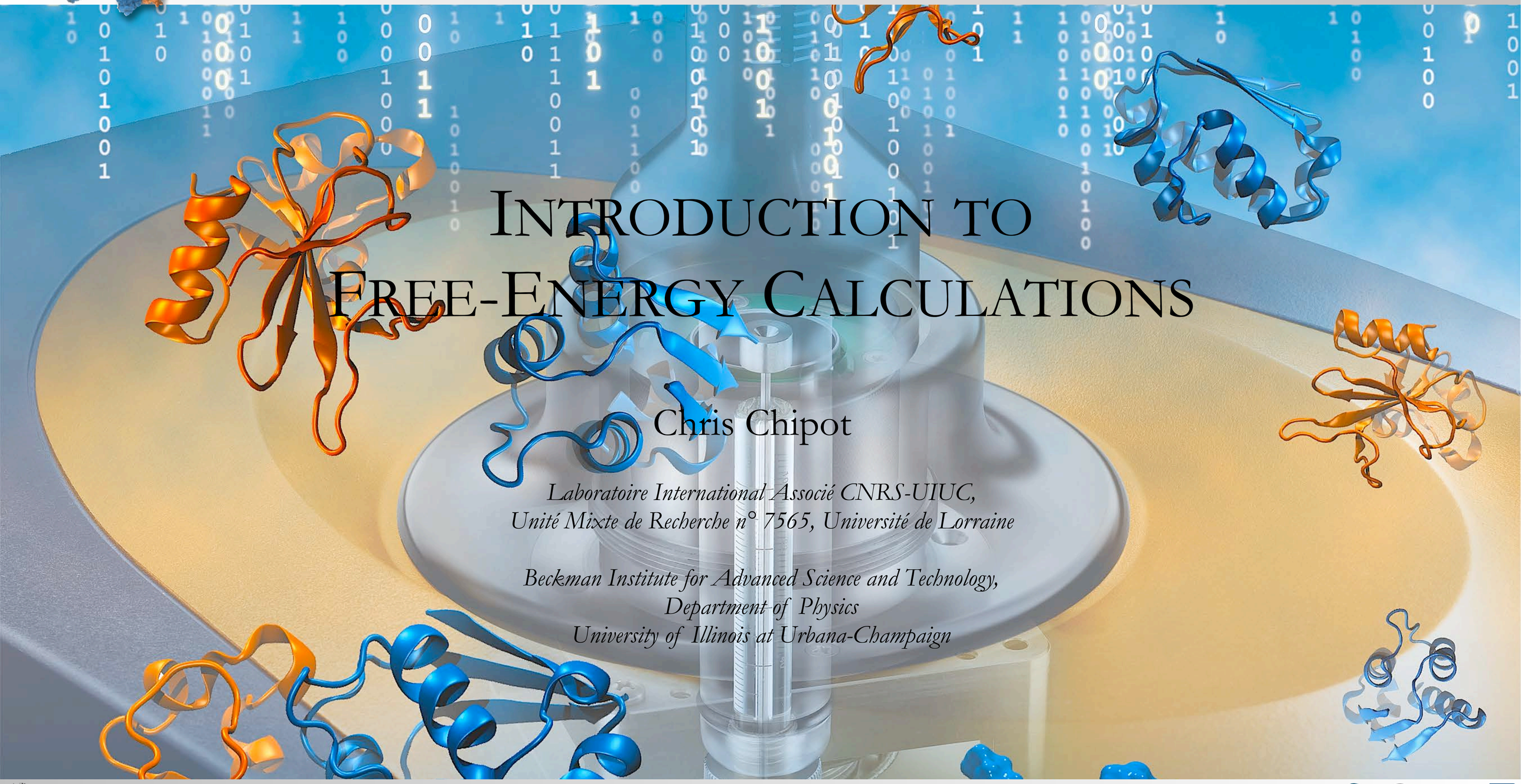

Introduction to Free-Energy Calculations

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Unité Mixte de Recherche n° 7565, Université de Lorraine

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

Geometrical free-energy calculations

- Potentials of mean force and transport phenomena
- Potentials of mean force and recognition and association phenomena
- What about non-equilibrium work computer experiments?

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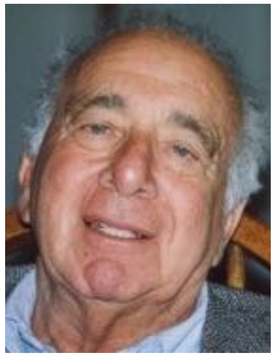
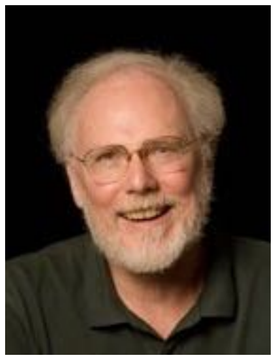
The race for longer and larger simulations



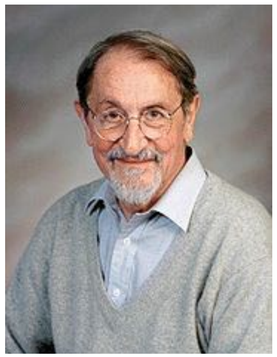
First molecular dynamics simulation. Phase transition in model liquids.

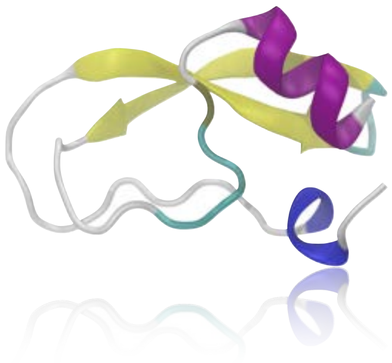
$$\begin{cases} m_i \dfrac{\mathrm{d}^2 x_i}{\mathrm{d}t^2} &= F_i \\ F_i &= -\dfrac{\partial U(\mathbf{x})}{\partial x_i} \end{cases}$$



A turning point in computational structural biology

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





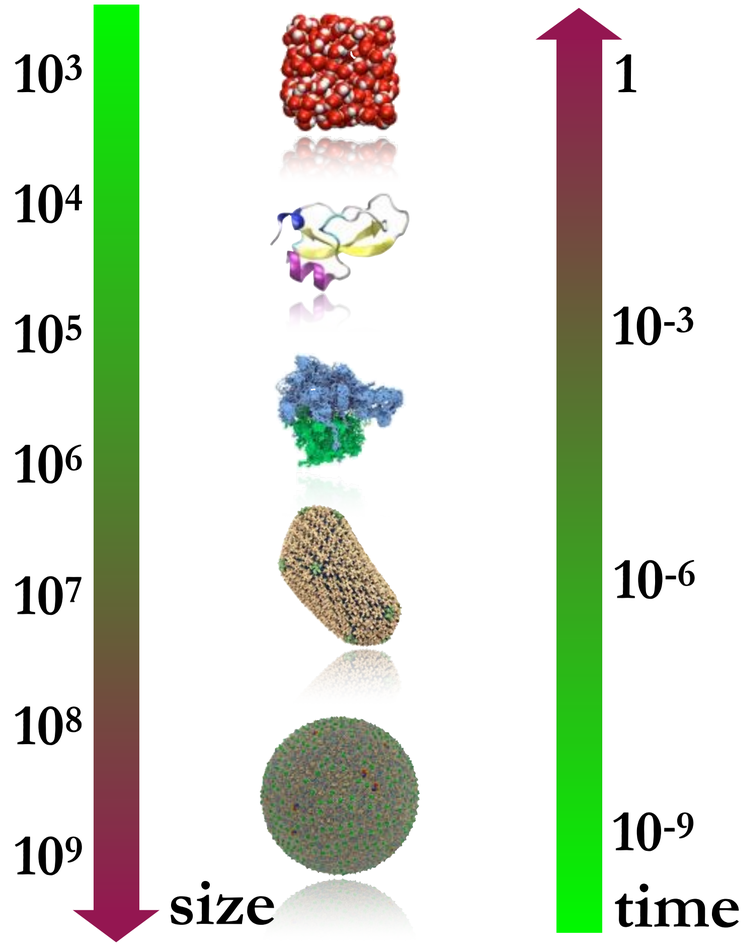
Alder, B. J.; Wainwright, T. E. *J. Chem. Phys.*, **1957**, *27*, 1208-1209

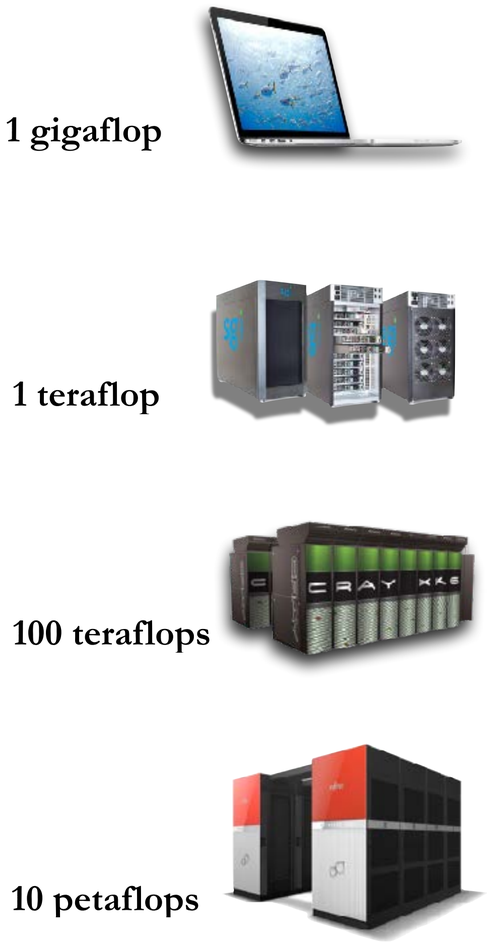
McCammon, J. A.; Gelin, B. R.; Karplus, M. *Nature*, **1977**, *267*, 585-590

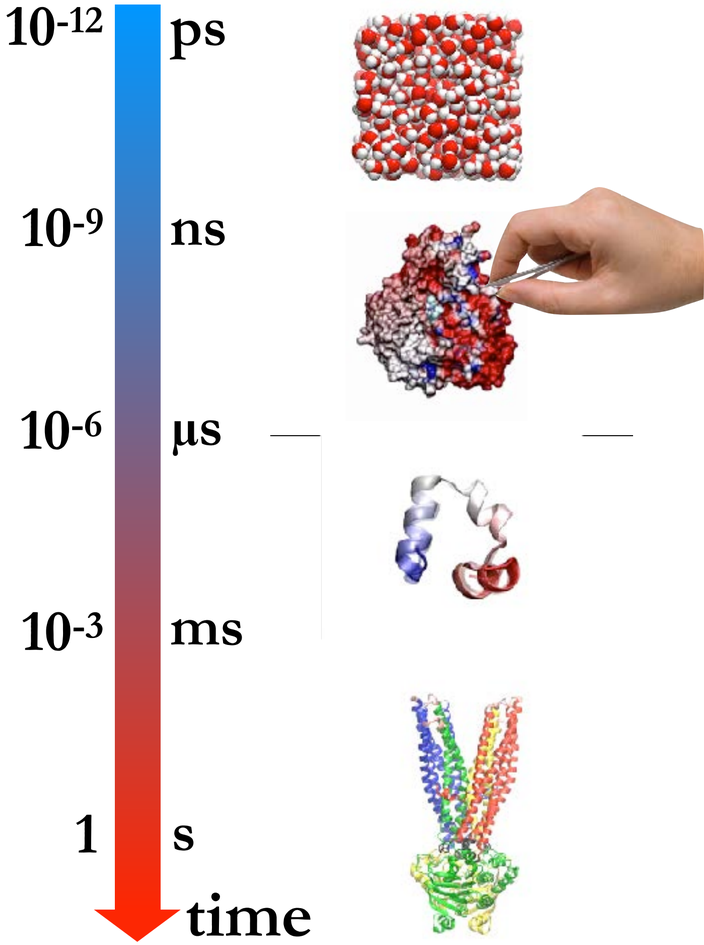
THE RACE FOR LONGER AND LARGER SIMULATIONS

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

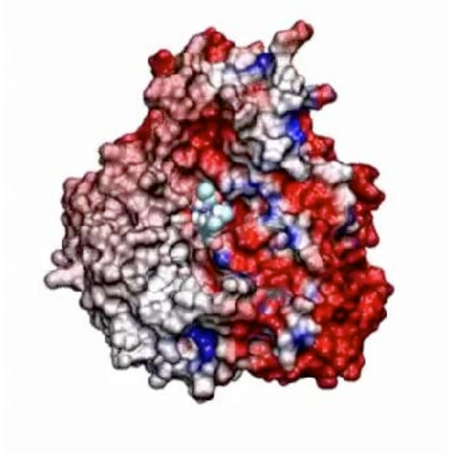
Free-energy calculations are computational tweezers to anatomize and explore relevant degrees of freedom



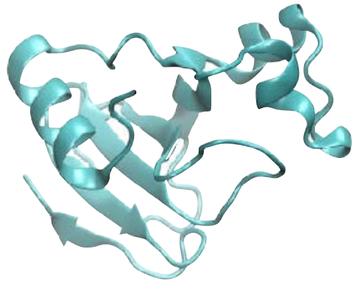


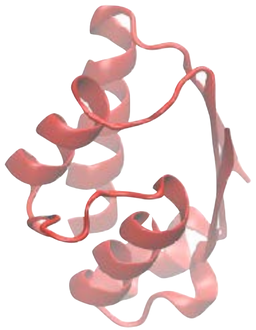


WHAT ARE FREE-ENERGY CALCULATIONS COMMONLY USED FOR ?

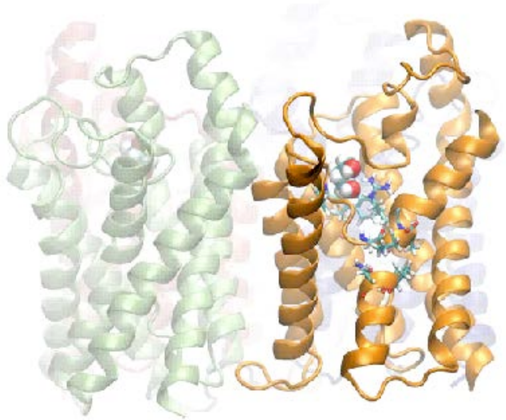


Recognition and association phenomena

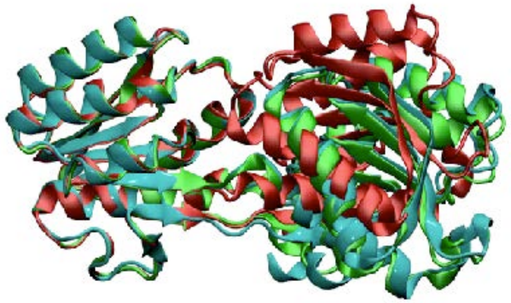




- protein-ligand binding
- site-directed mutagenesis
- protein-protein binding
- partition coefficients
- permeabilities
- activation barriers
-structural modifications



Transport phenomena

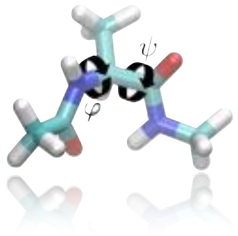


Conformational transitions

WHAT IS THE BEST METHOD FOR A GIVEN PROBLEM ?

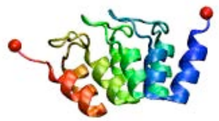
Free-energy differences can be estimated computationally following four possible routes

(1) Methods based on histograms



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

(2) Non-equilibrium work simulations

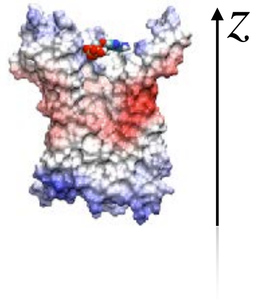


$$\exp(-\beta \Delta A) = \langle \exp(-\beta w) \rangle$$

(3) Perturbation theory

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

(4) Measuring the derivative and integrating it

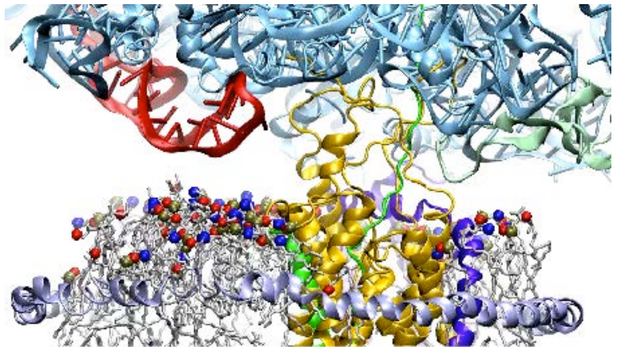


$$\frac{\mathrm{d}A(\xi)}{\mathrm{d}\xi} = \left\langle \frac{\partial U}{\partial \xi} - \frac{1}{\beta} \frac{\partial \ln |J|}{\partial \xi} \right\rangle_\xi$$

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

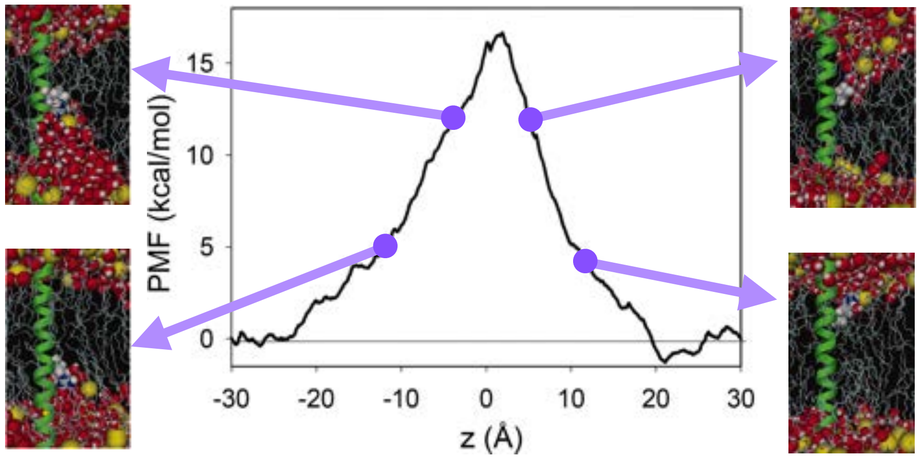
WHAT IS THE BEST METHOD FOR A GIVEN PROBLEM ?

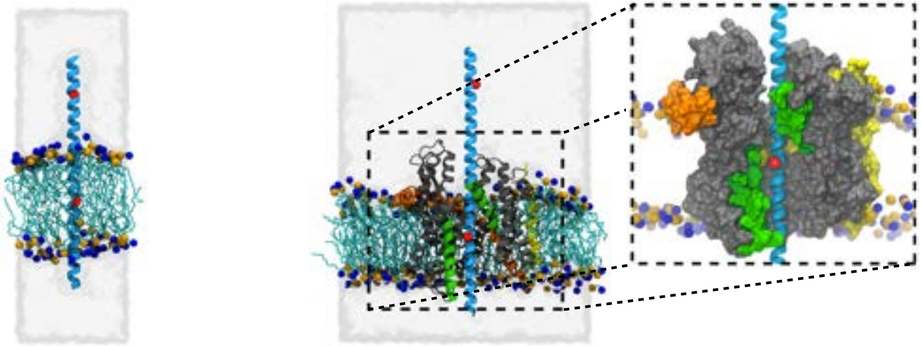


Nascent membrane proteins typically insert into the membrane via the Sec-translocon.

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

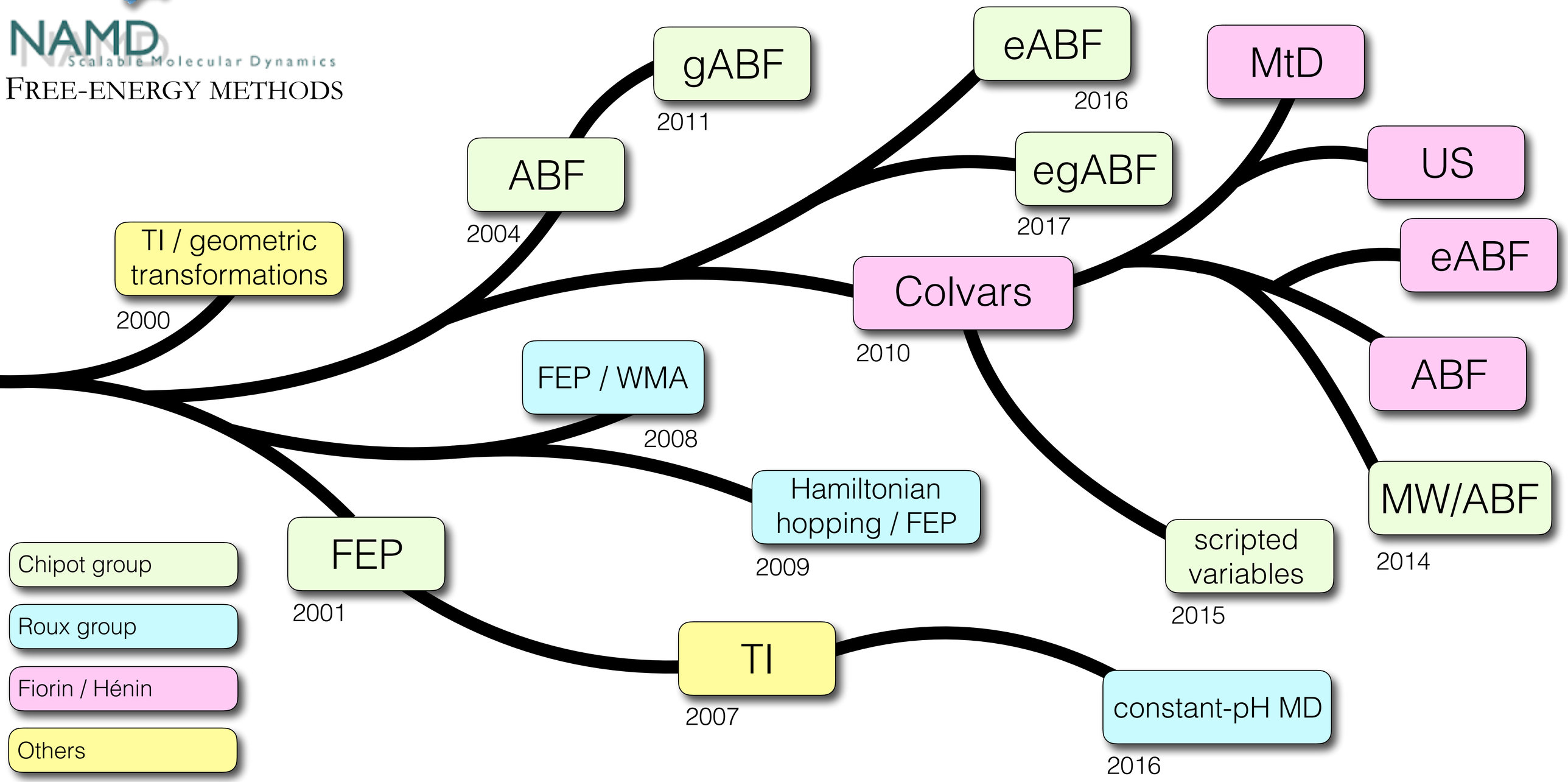
Dorairaj, S.; Allen, T. W. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 4943-4948

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

NAMD
Scalable Molecular Dynamics

Free-energy methods



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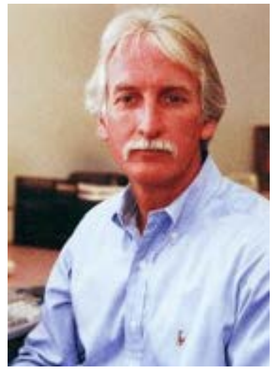
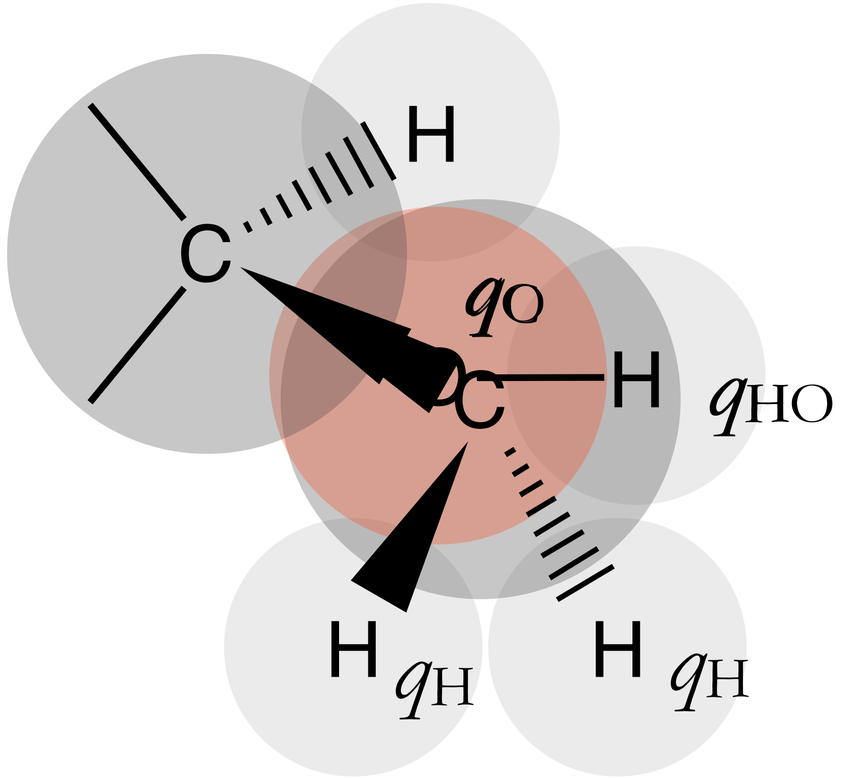
A tool to address host-guest chemistry problems



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).

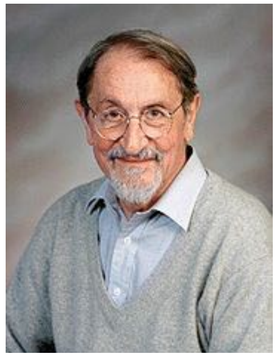


Single-topology paradigm:

- 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.

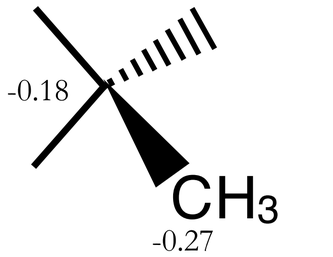
Jorgensen, W. L.; Ravimohan, C. *J. Chem. Phys.* **1985**, *83*, 3050-3054
Postma, J. P. M.; Berendsen, H. J. C.; Haak, J. R. *Faraday Symp. Chem. Soc.* **1982**, *17*, 55-67
Bash, P. A. et al. *Science* **1987**, *236*, 564-568
Bash, P. A. et al. *Science* **1987**, *235*, 574-576

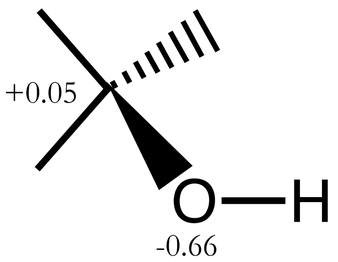
A tool to address host-guest chemistry problems

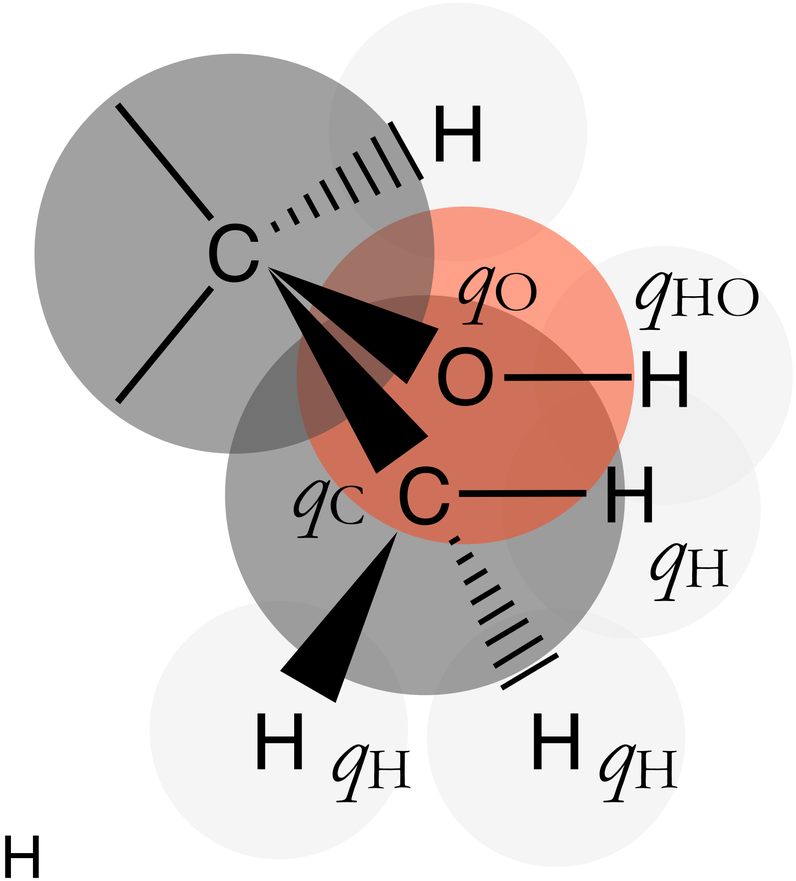


Free energy is a state function.

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

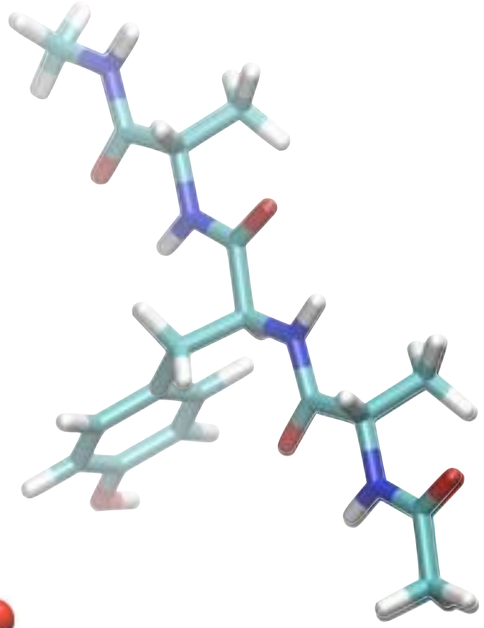
Free-energy perturbation

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

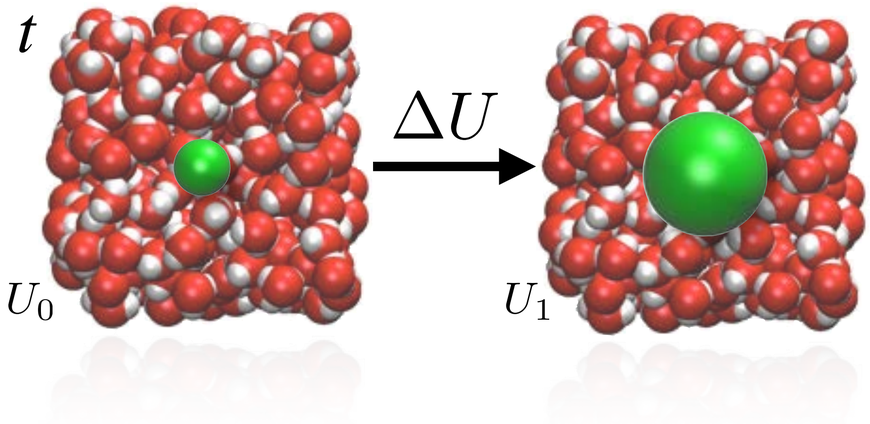
- Requires the sole knowledge of the reference state.
- Formally exact for any perturbation.
- Importance-sampling method.

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

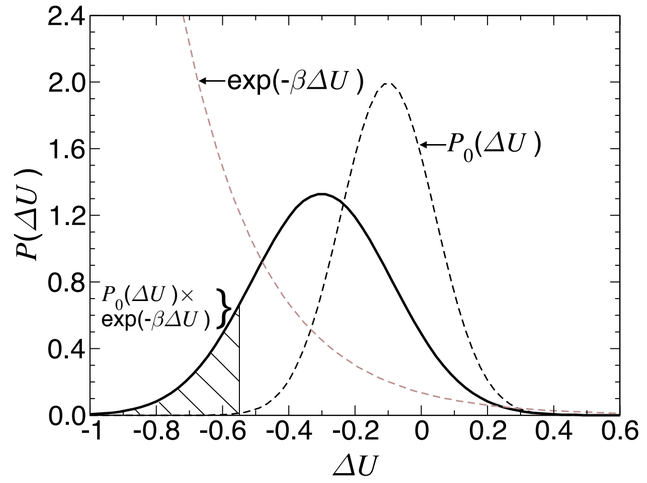
How to deal with large perturbations ?

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

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

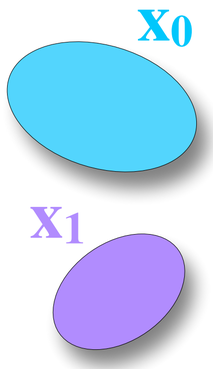
$\Delta A \leq \langle \Delta U \rangle_0$

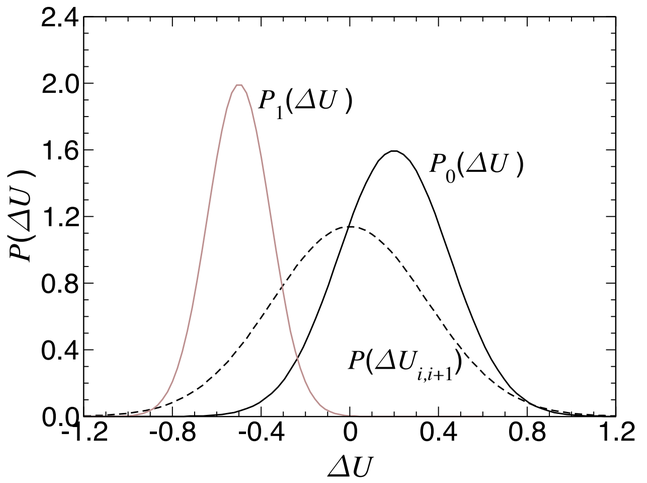
$$\Delta A = \langle \Delta U \rangle_0 - \frac{1}{2}\beta\sigma_0^2$$



Stratification strategies

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



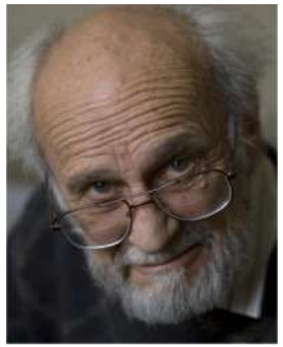


Valleau, J. P.; Card, D. N. *J. Chem. Phys.* **1972**, *57*, 5457-5462

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

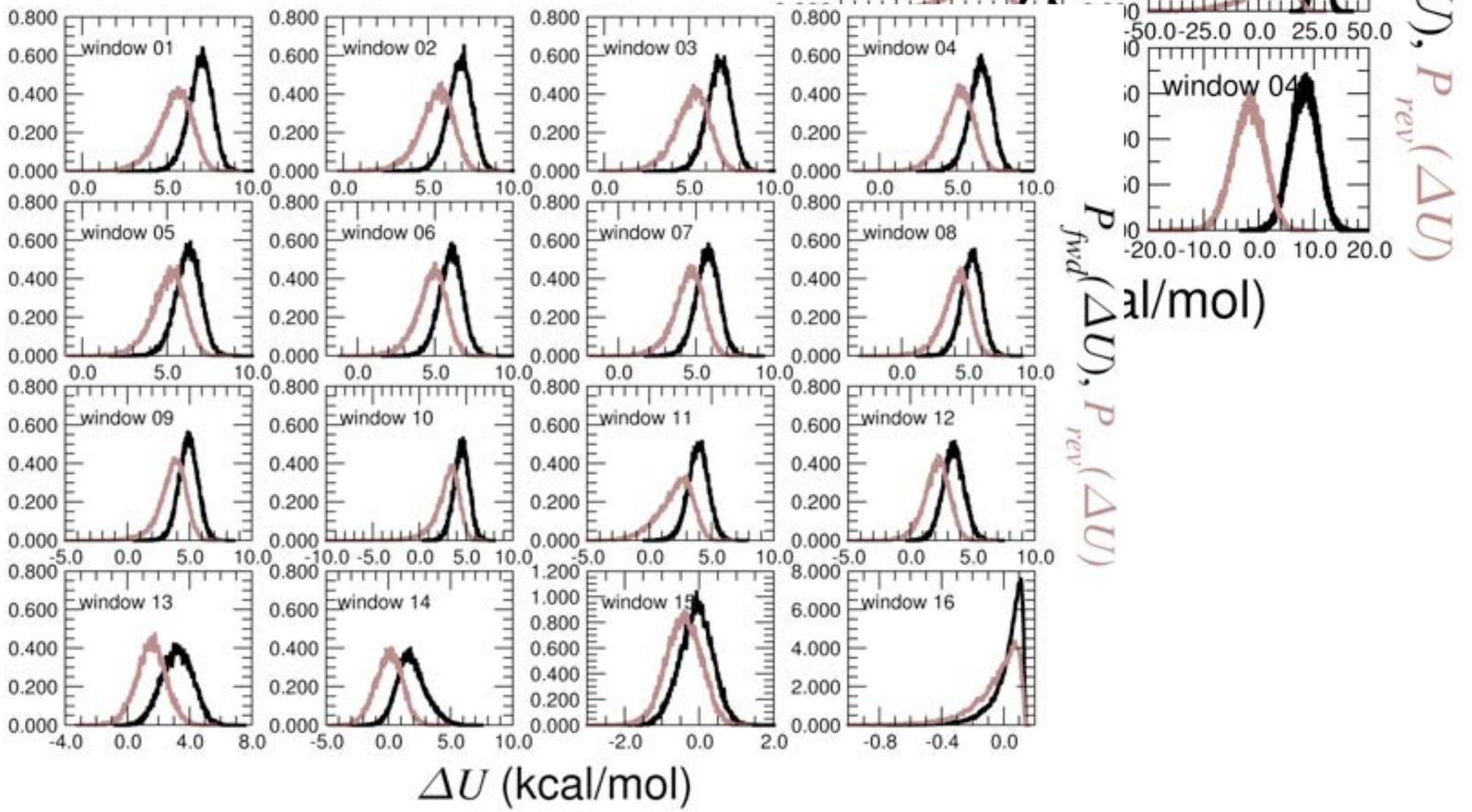


How many strata should I choose ?

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

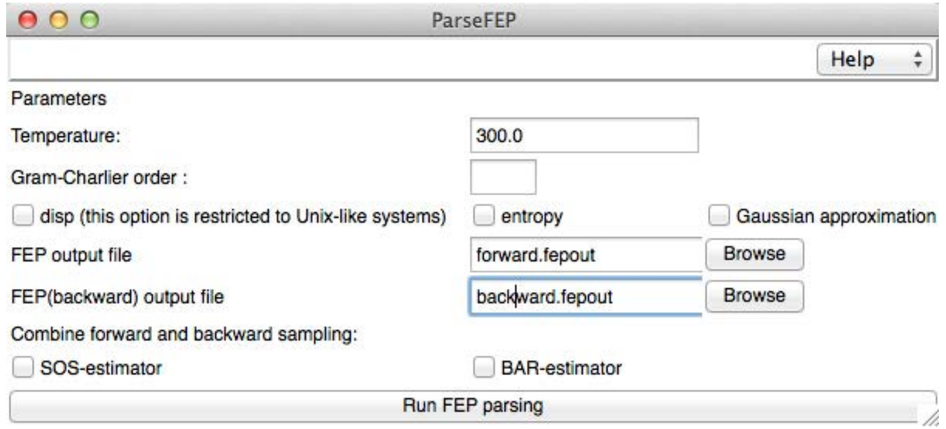
Pohorille, A.; Jarzynski, C.; Chipot, C. *J. Phys. Chem. B* **2010**, *114*, 10235-10253

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

Combining forward and backward tranformations

Maximum-likelihood estimator of the free-energy change.

Guarantees the minimum variance.



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

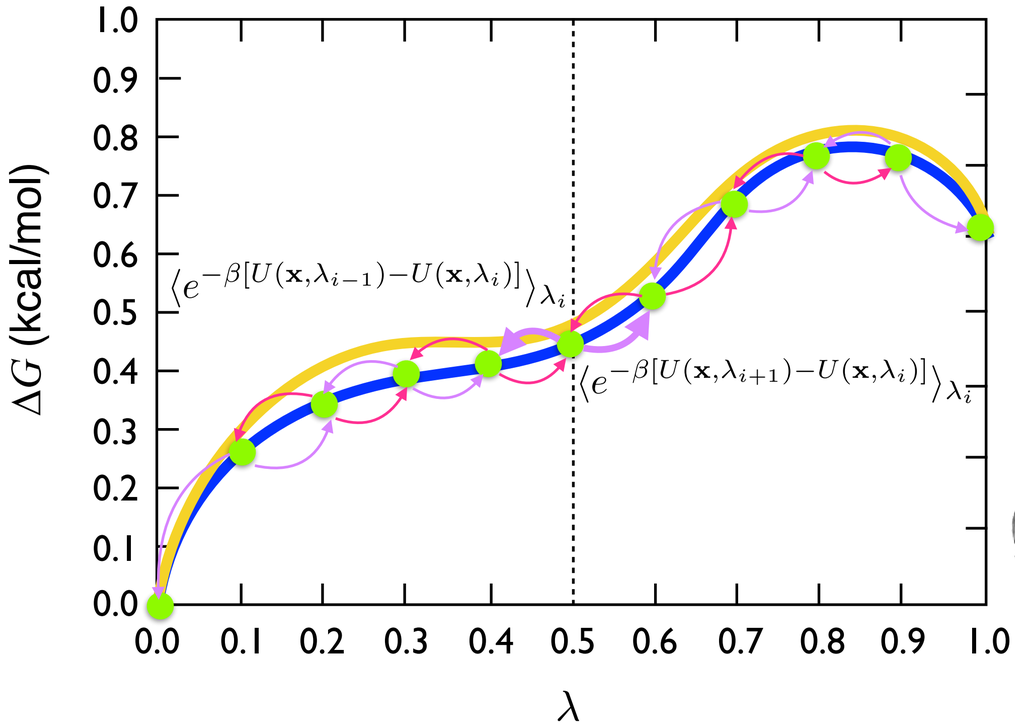
$$\sigma^2_{\Delta A}{}^{\mathrm{BAR}} = \frac{1}{N_0\beta^2}\left[\frac{\langle f^2(x)\rangle_0}{\langle f(x)\rangle_0^2} - 1\right] + \frac{1}{N_1\beta^2}\left[\frac{\langle f^2(-x)\rangle_1}{\langle f(-x)\rangle_1^2} - 1\right]$$

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

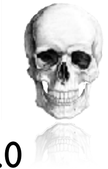
GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



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

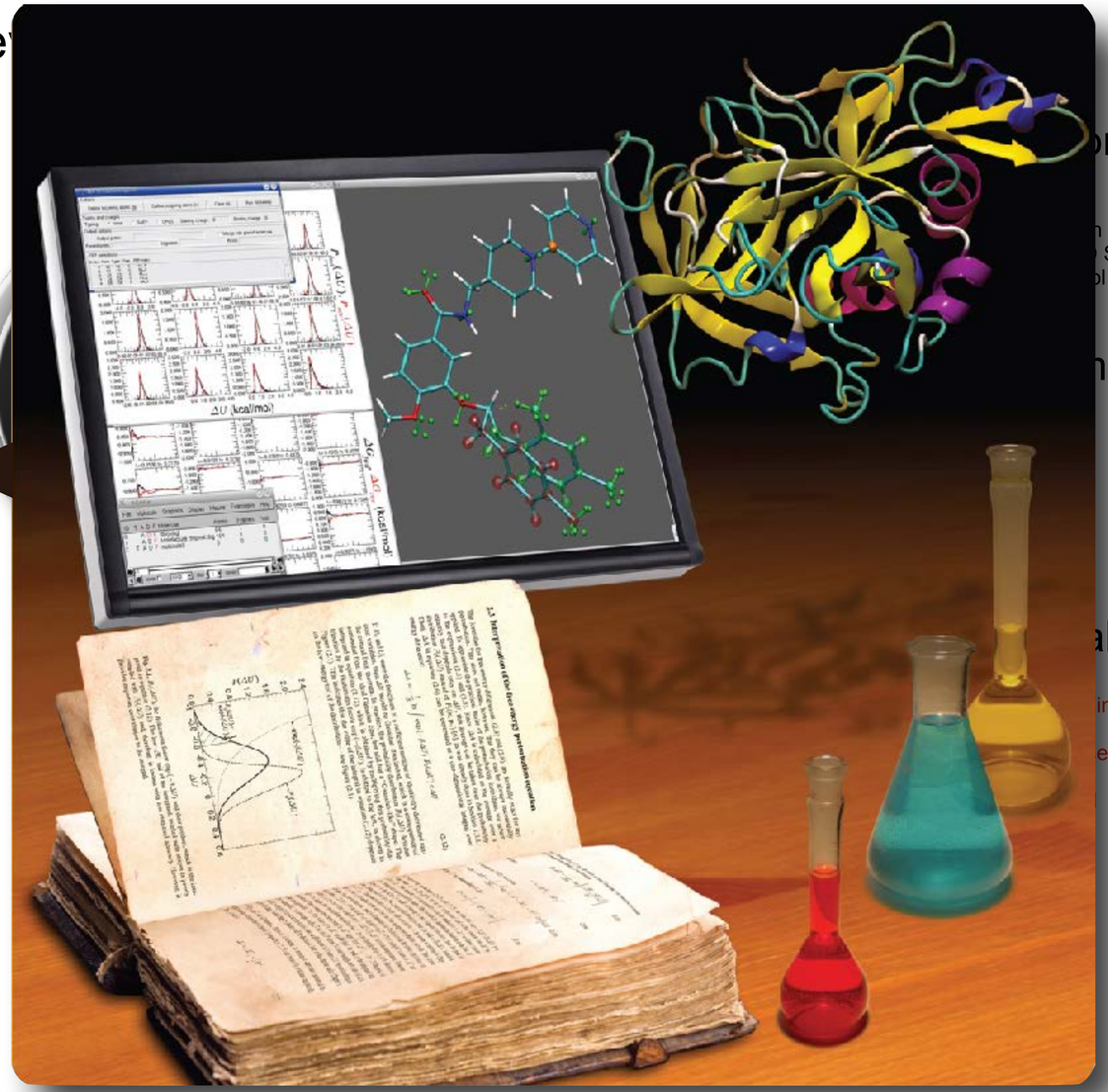
Berendsen, H. J. C. in Renugopalakrishnan, V.; et al. Eds. *Proteins, Structure, Dynamics and Design* ESCOM, **1991**, 384-392

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

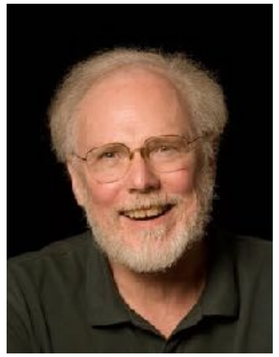
ally Hosted Plugins

ins

ential Dynamics

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

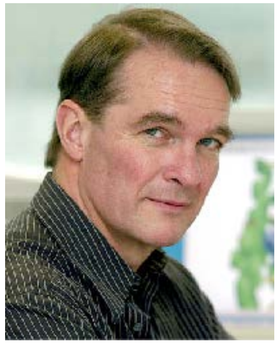
GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



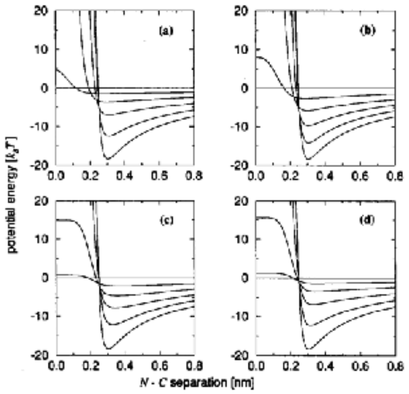
What about end-point catastrophes ?

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:

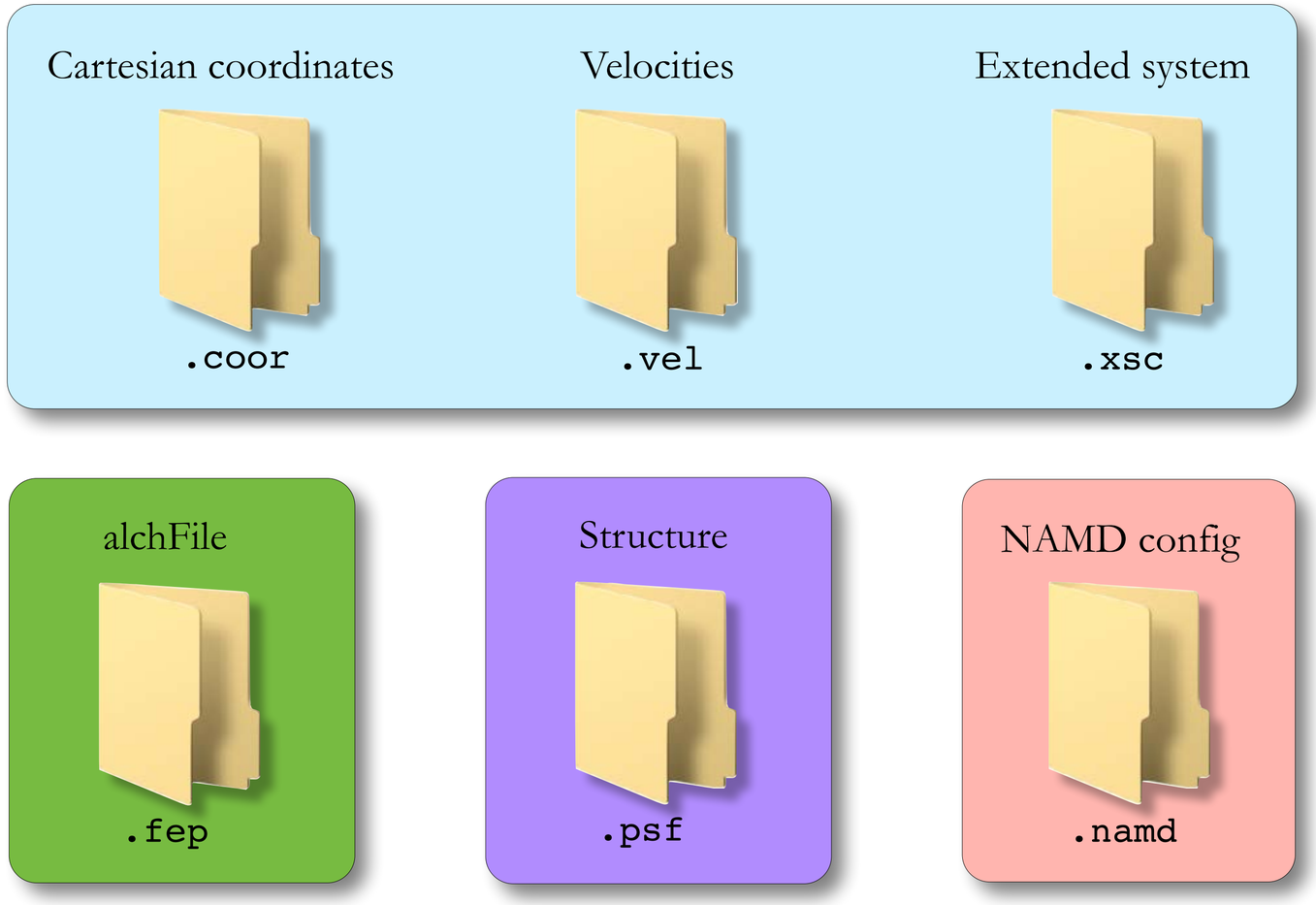
```
alchVdWShiftCoeff     4.0
```

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

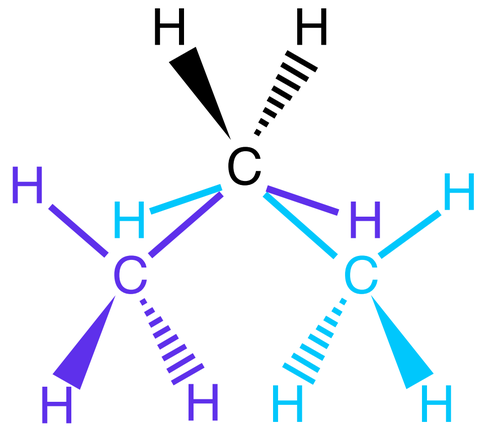
Equilibration simulation



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

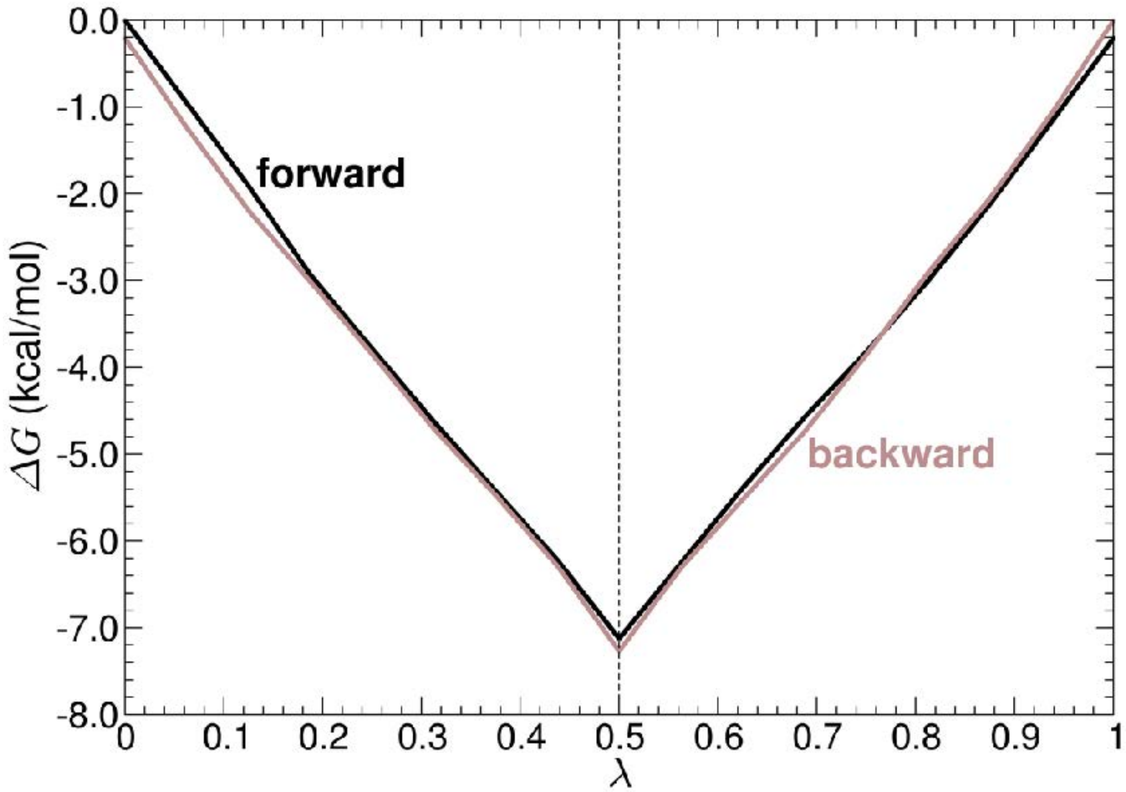
Bhandarkar, M. et al. NAMD user's guide, version 2.9, **2012**

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



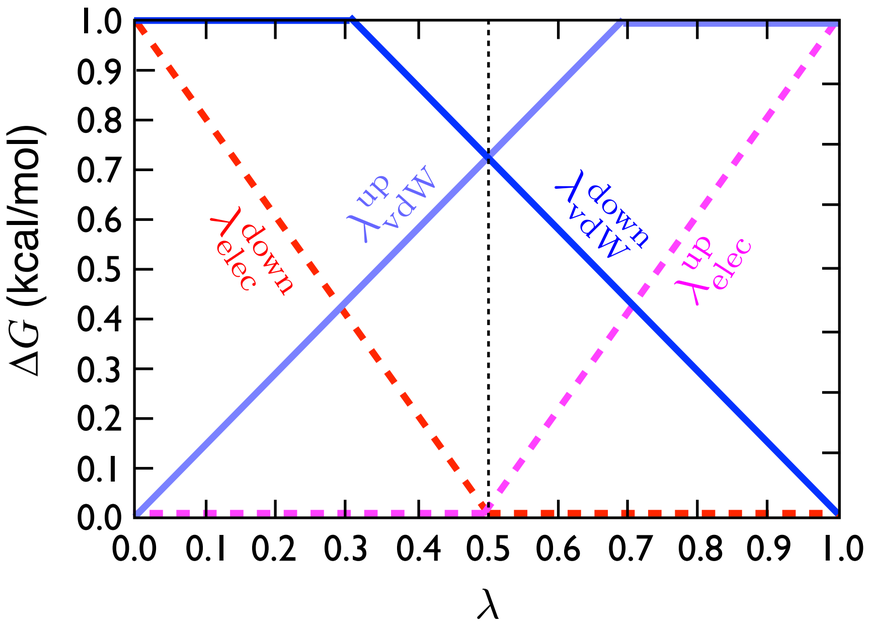

```
RESI ZERO         0.00       !  ethane -> ethane
GROUP                        !
ATOM CI    CT3   -0.27       !
ATOM HI1   HA     0.09       !
ATOM HI2   HA     0.09       !
ATOM HI3   HA     0.09       !
GROUP                        !   HI1        HM1    HF2  HF3
ATOM CM    CT3   -0.27       !      \         |     |  /
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

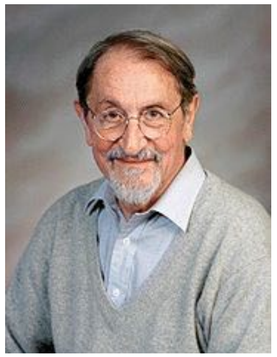
	beginning	end
electrostatics	$\lambda_{\mathrm{elec}}^{\mathrm{start}}$	1
van der Waals	0	$\lambda_{\mathrm{vdW}}^{\mathrm{end}}$

Decoupling in the NAMD lingo:

```
alchVdwLambdaEnd          0.7
alchElecLambdaStart       0.5
```

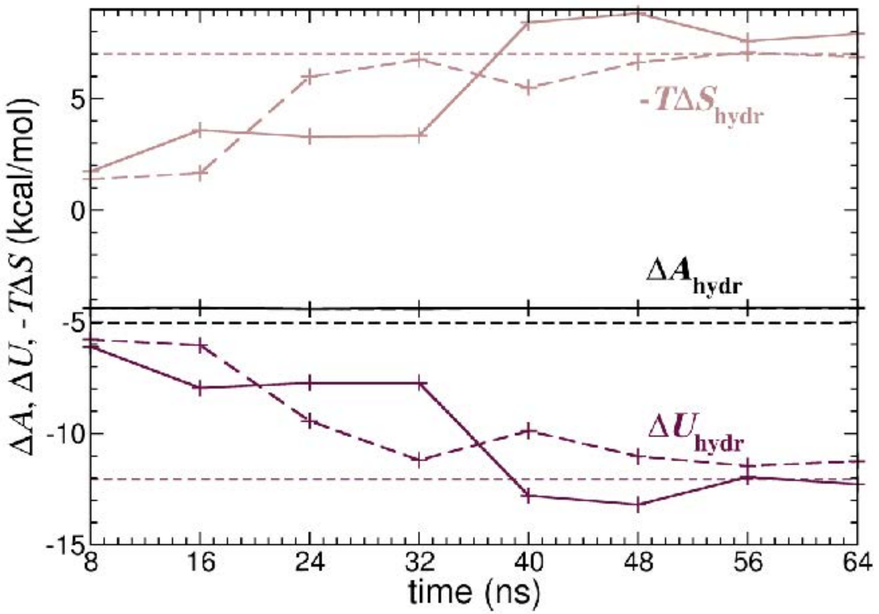
Pearlman, D. A.; Kollman, P. A. *J. Chem. Phys.* **1991**, *94*, 4532-4545

HOW ABOUT THE ENTROPY ?



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

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



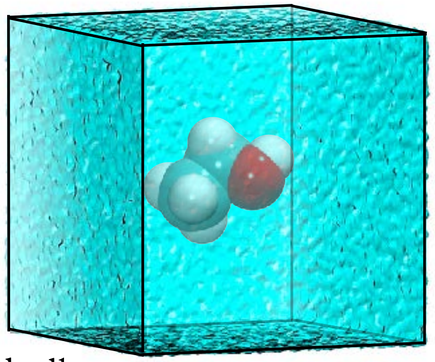
Alternate route:

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

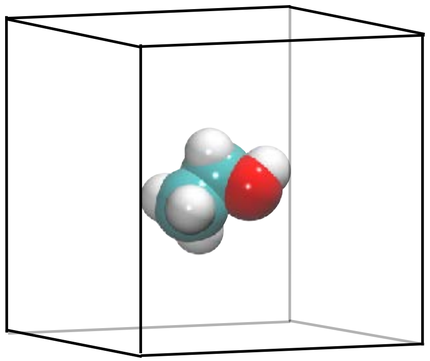
Wan, S.; Stote, R. H.; Karplus, M. *J. Chem. Phys.* **2004**, *121*, 9539–9548

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

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

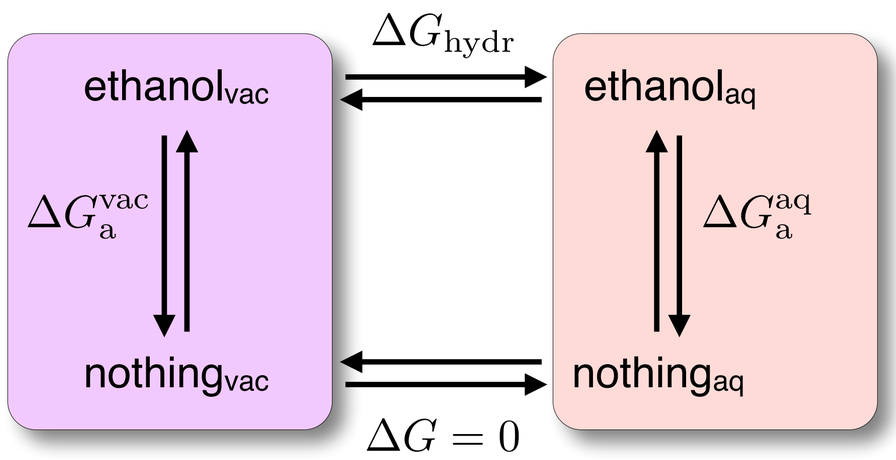


bulk



vacuum

Ethanol hydration



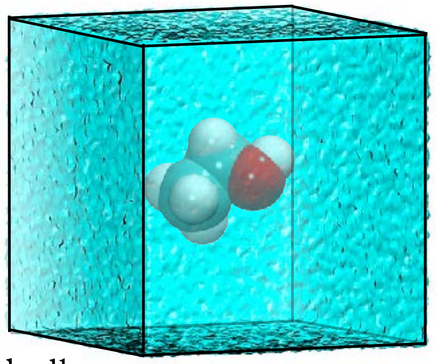
Why do I need to complete the full thermodynamic cycle ?

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

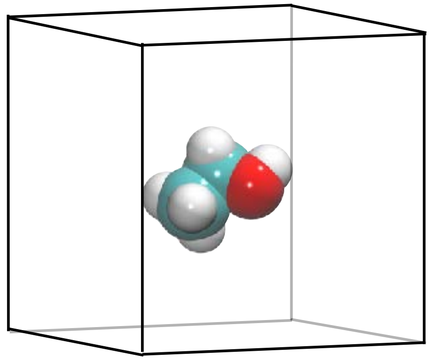
In NAMD lingo: `AlchDecouple off`

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

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

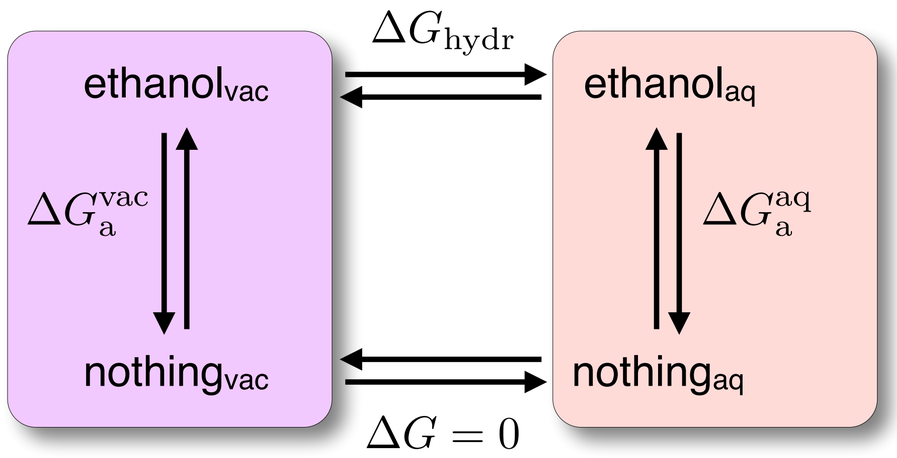


bulk



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

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

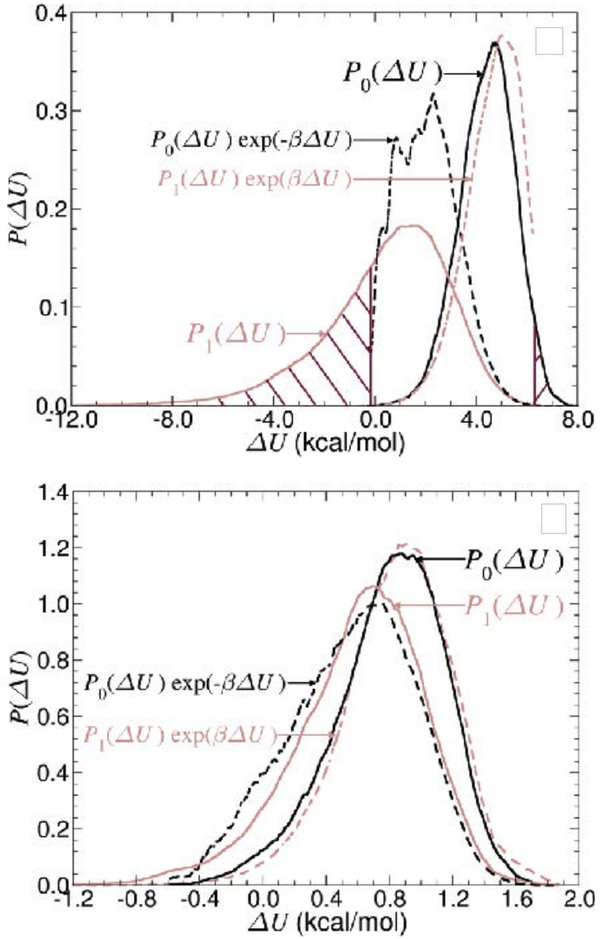
$$\exp\left(-\beta\Delta U\right)P_0\left(\Delta U\right) = \exp\left(-\beta\Delta A\right)P_1\left(\Delta U\right)$$

What should be the optimum number of strata and how much sampling per stratum is required?

$$D\left(P_0^{\mathrm{eq}}||P_1^{\mathrm{eq}}\right) = \int P_0^{\mathrm{eq}} \ln\left(\frac{P_0^{\mathrm{eq}}}{P_1^{\mathrm{eq}}}\right) \geq 0$$

$$W^0_{\mathrm{dissipative}} \equiv \langle \Delta U \rangle_0^{\mathrm{eq}} - \Delta A$$

$$\begin{cases} N_0 \sim \exp\left(\beta W^1_{\mathrm{dissipative}}\right) \\ N_1 \sim \exp\left(\beta W^0_{\mathrm{dissipative}}\right) \end{cases}$$



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**

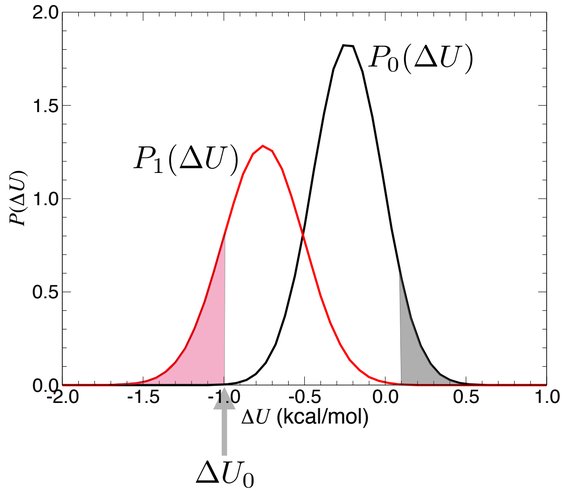
Pohorille, A.; Jarzynski, C.; Chipot, C. *J. Phys. Chem. B* **2010**, *114*, 10235-10253

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

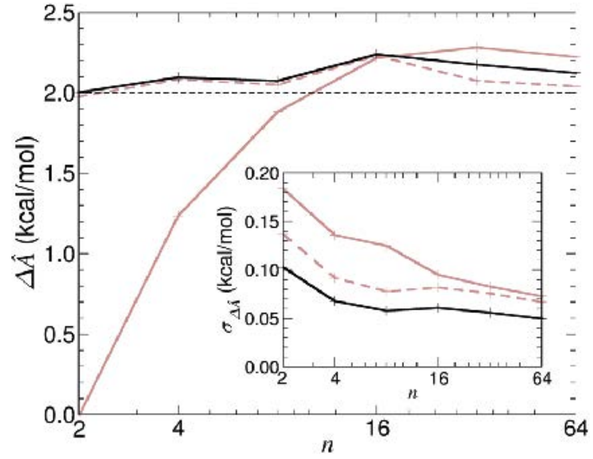
All free-energy calculations should be accompanied by an error estimate. A distinction between statistical and systematic error ought to be made.

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, or lack thereof, as a measure of inaccuracy:

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



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

GEOMETRICAL FREE-ENERGY CALCULATIONS

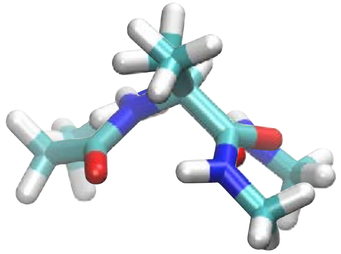
- Potentials of mean force and transport phenomena
- Potentials of mean force and recognition and association phenomena
- What about non-equilibrium work computer experiments?

A variety of variables of tailored collectivity

low collectivity

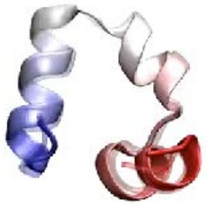
`distance`
`distanceZ`
`distanceXY`

`angle`

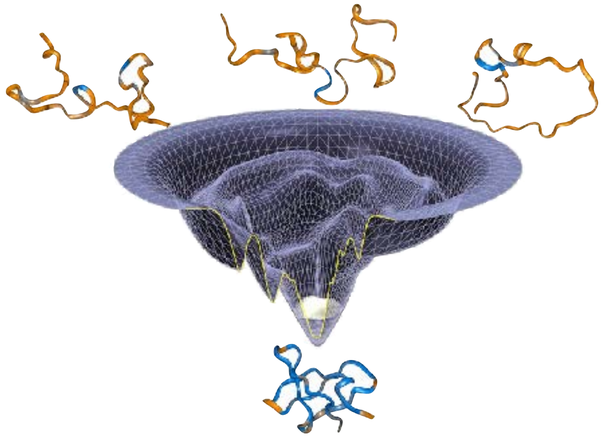


`dihedral`

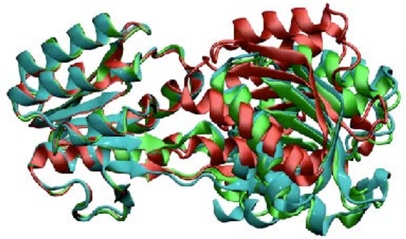
`rmsd`
`gyration`



Degenerate variable



`eigenvector`



From normal mode or principal component analysis

high collectivity

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

A host of methods to measure free-energy changes



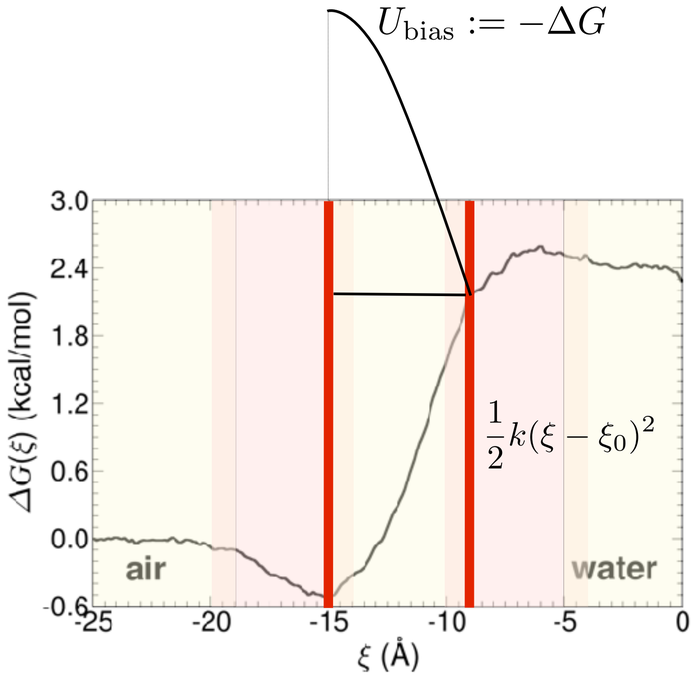
- Conformational flooding.
- Local elevation.
- Metadynamics.


- 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

A host of methods to measure free-energy changes



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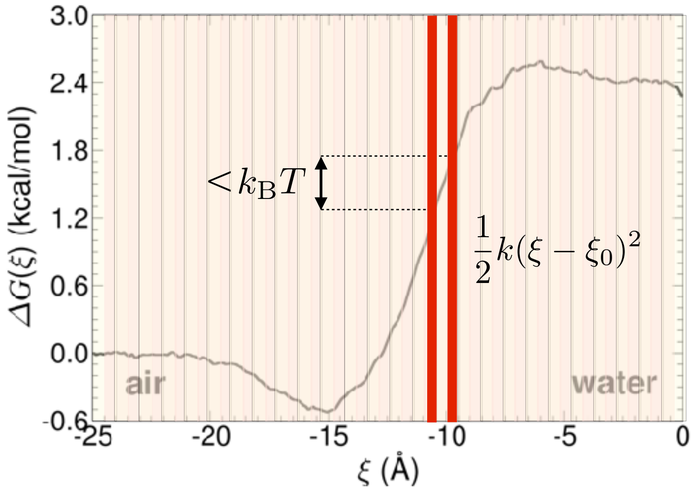


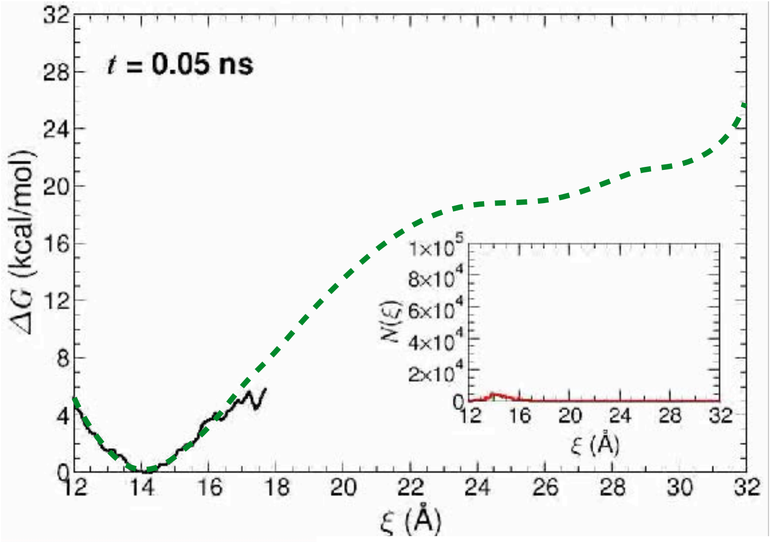
Grubmüller, H. *Phys. Rev. E* **1995**, *52*, 2893-2906
Huber, T. et al. *J. Comput. Aided Mol. Des.* **1994**, *8*, 695-708
Laio, A.; Parrinello, M. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 12562-12565
Torrie, G. M.; Valleau, J. P. *J. Comput. Phys.* **1977**, *23*, 187-199
Valleau, J. P. ; Card, 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

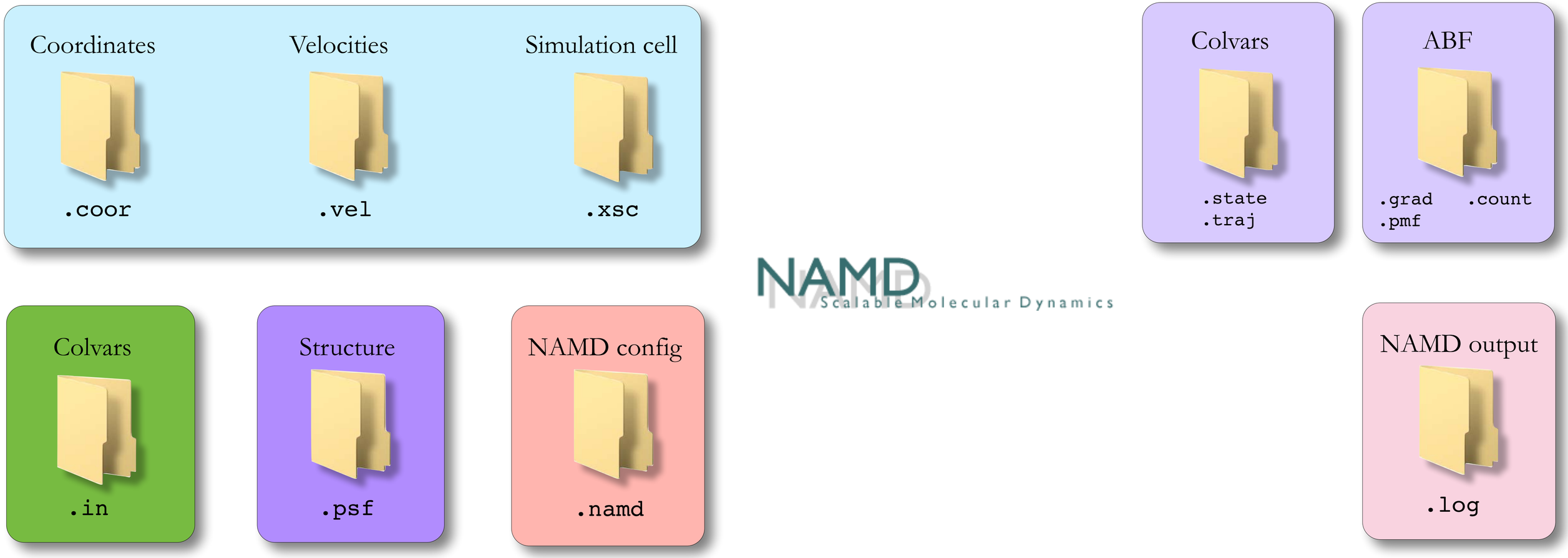
Hénin, J.; Chipot, C. *J. Chem. Phys.* **2004**, *121*, 2904-2914

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

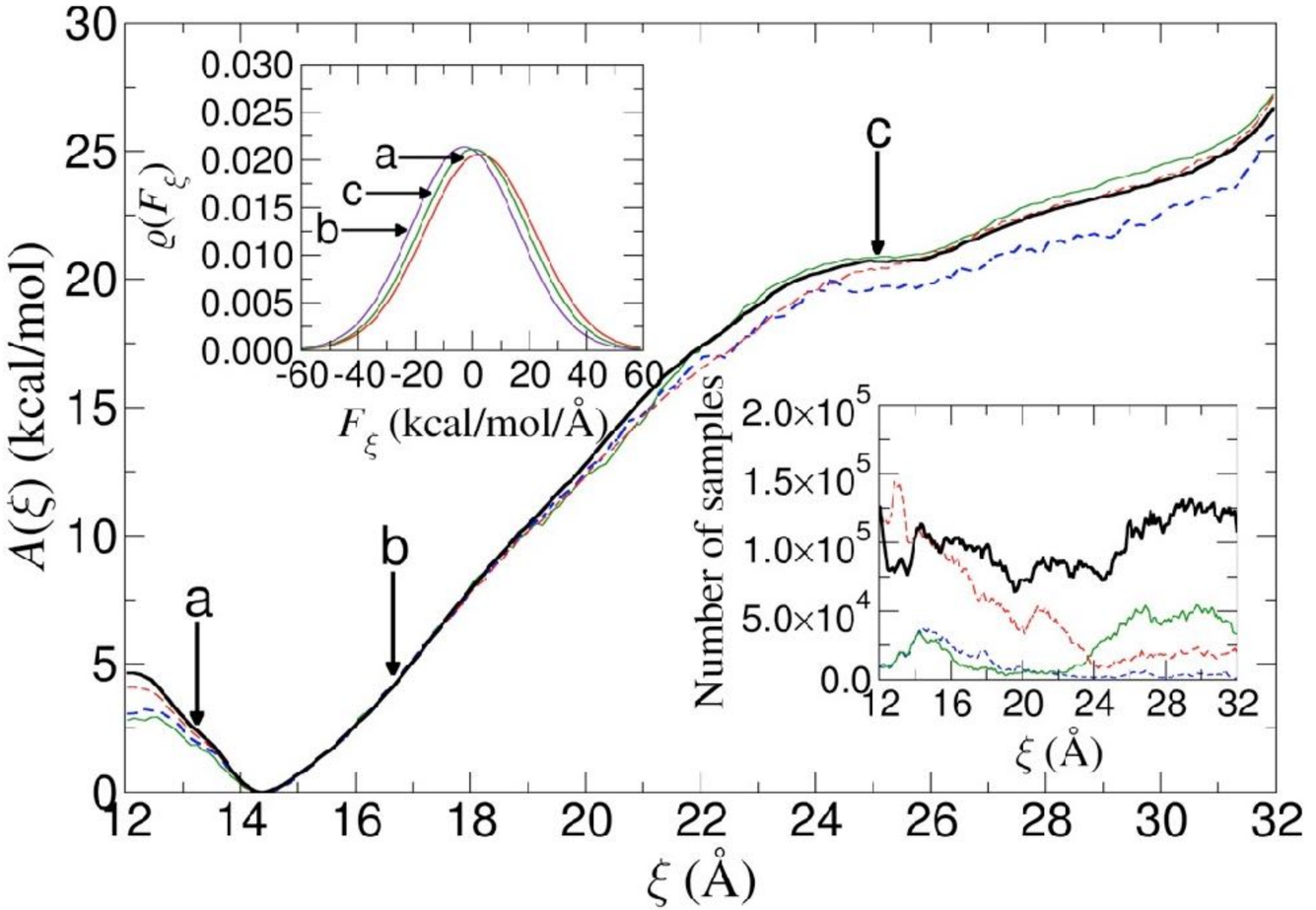
Equilibration simulation



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



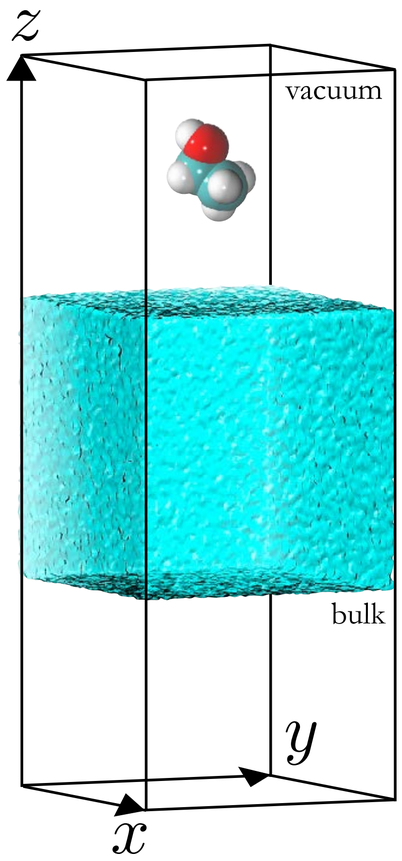

```
colvar {
   name EndToEndDistance

   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. Issue solved in NAMD 2.12

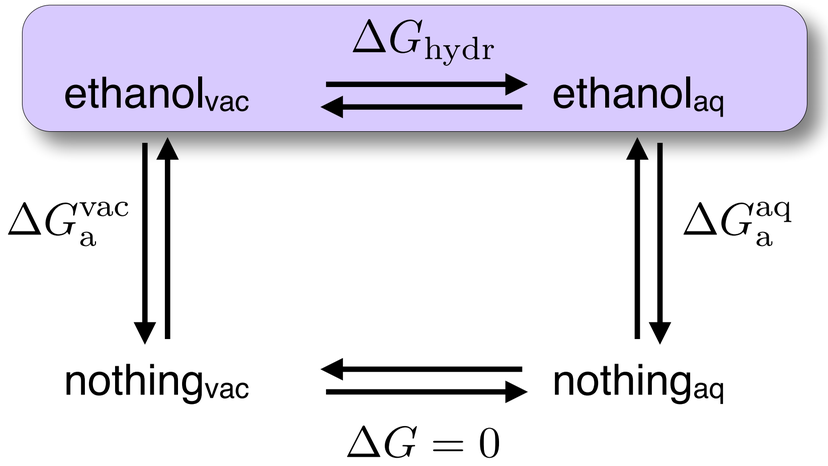
Park, S.; Khalili-Araghi, F.; Tajkhorshid, E.; Schulten, K. *J. Chem. Phys.* **2003**, *119*, 3559-3566

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

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS



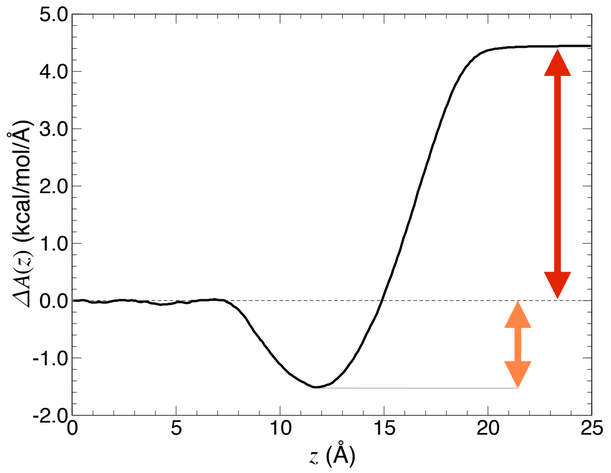
Back to exercise 2. Ethanol hydration



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
}
```



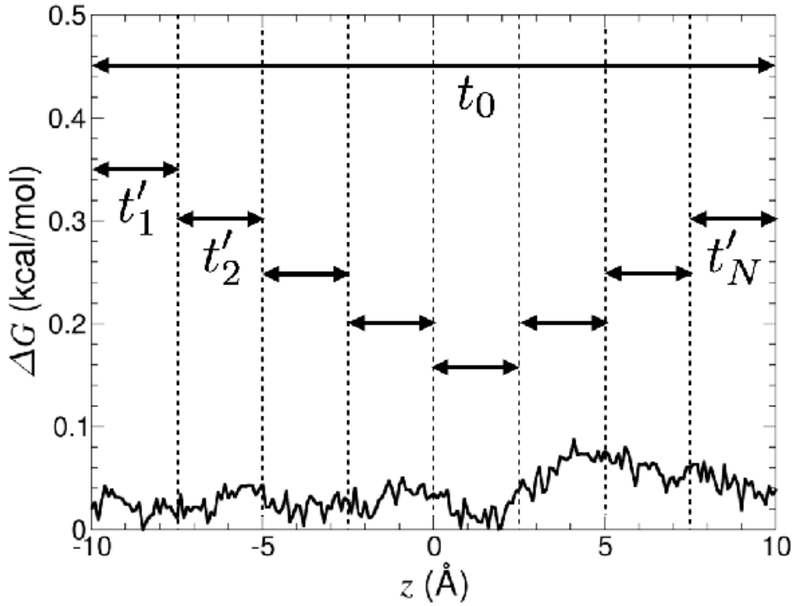
Chipot, C.; Pohorille, A. Free energy calculations. Theory and applications in chemistry and biology, **2007**

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

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

ξ ought to be completely decoupled from degrees of freedom to which holonomic constraints are applied. Issue solved in NAMD 2.12.

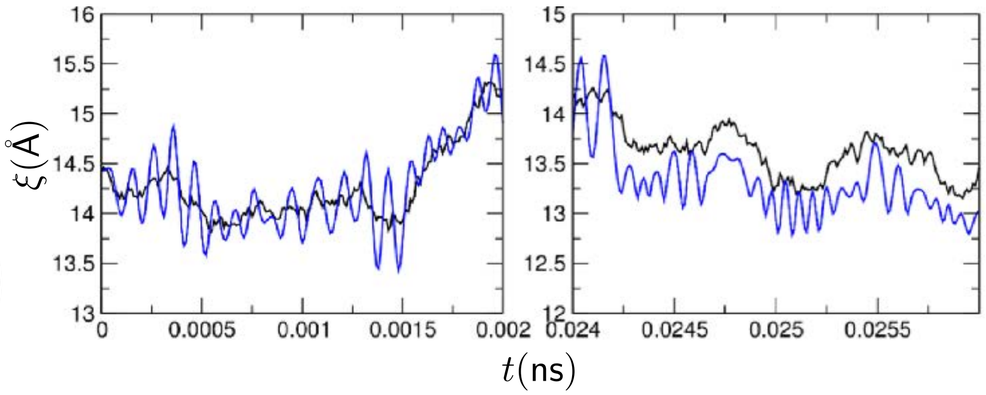
As a matter of principle, ξ ought to be stratified: $t_0 > \sum_i t'_i$



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

```
ExtendedLagrangian    on
```

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

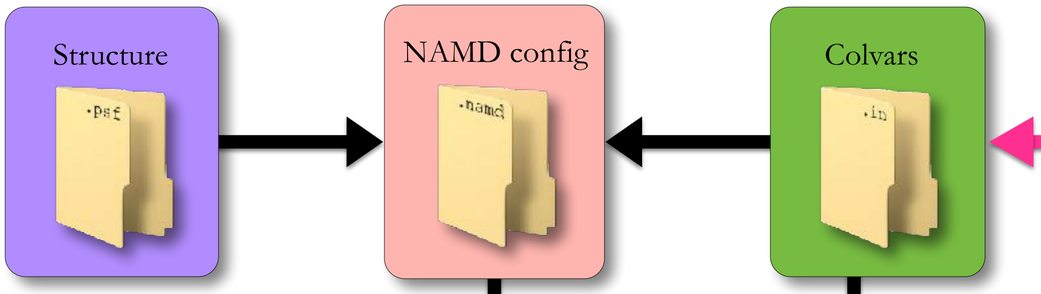


Chipot, C.; Pohorille, A. Free energy calculations. Theory and applications in chemistry and biology, **2007**

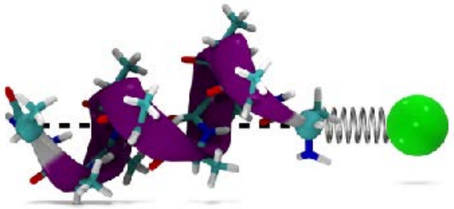
Lelièvre, T.; Stoltz, G.; Rousset, M. Free energy computations: A mathematical perspective, **2010**

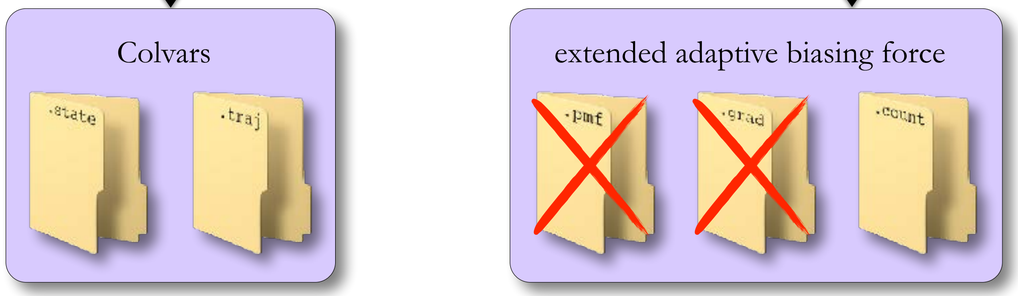
Comer, J.; Gumbart, J. C.; Hénin, J.; Lelièvre, T.; Pohorille, A.; Chipot, C. *J. Phys. Chem.* **2014**

GOOD PRACTICES, GUIDELINES AND RECOMMENDATIONS

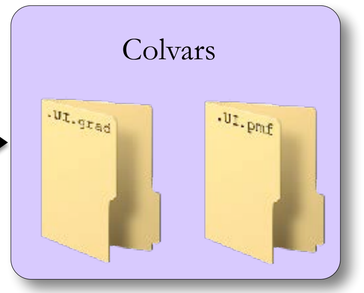



```
colvar {
  name R
  width 1.0
  lowerboundary 0.0
  upperboundary 40.0
  lowerwallconstant 100.0
  upperwallconstant 100.0
  extendedLagrangian on
  distance {
    forceNoPBC yes
    group1 {
      atomnumbers { 367 368 369 370 384 385 }
    }
    group2 {
      atomnumbers { 949 950 951 952 958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





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

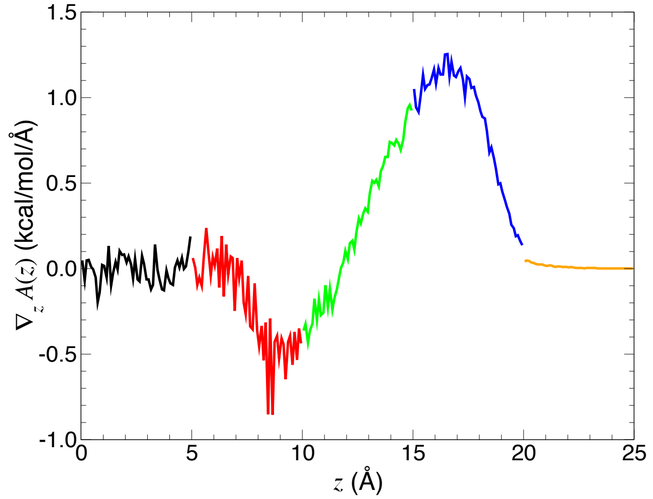


UIestimator

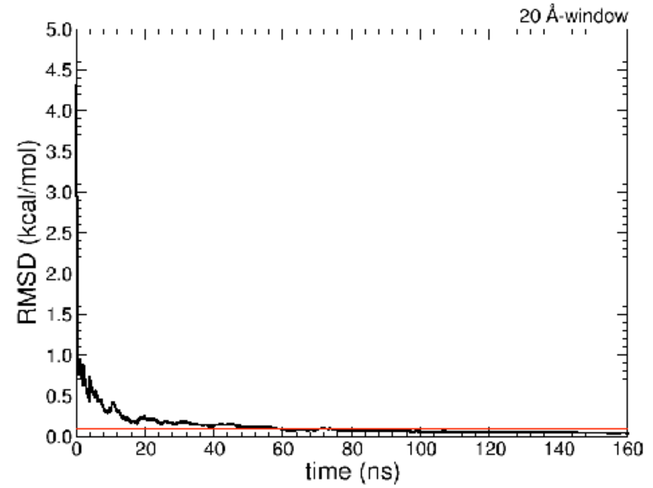
Zheng, L.; Yang, W. *J. Chem. Theory Comput.* **2012**, *8*, 810-823.
Zheng, L.; Chen, M.; Yang, W. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 20227-20232.
Fu, H.; Shao, X.; Chipot, C.; Cai, W. *J. Chem. Theory Comput.* **2016**, *12*, 3506–3513.
Lesage, A.; Lelièvre, T.; Stoltz, G.; Hénin, J. *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, $\sigma_{\Delta A} \simeq \frac{\sigma}{N^{1/2}}(1+2\kappa)^{1/2}$



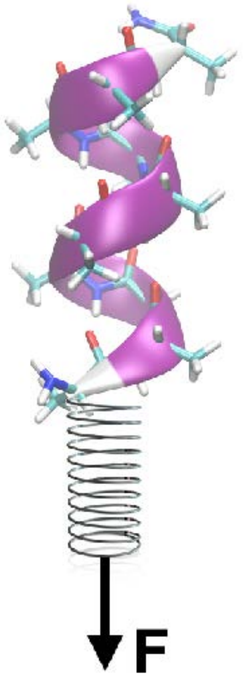
Assess convergence, for instance, by breaking down the free-energy calculations in multiple sub-runs and compute a root mean-square deviation with respect to the last one.

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 ?

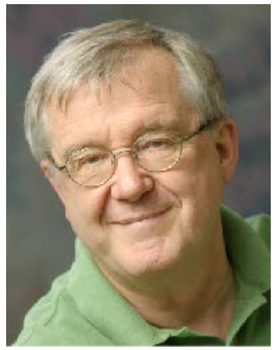


$$\exp(-\beta\Delta A) = \langle \exp(-\beta w) \rangle$$

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.



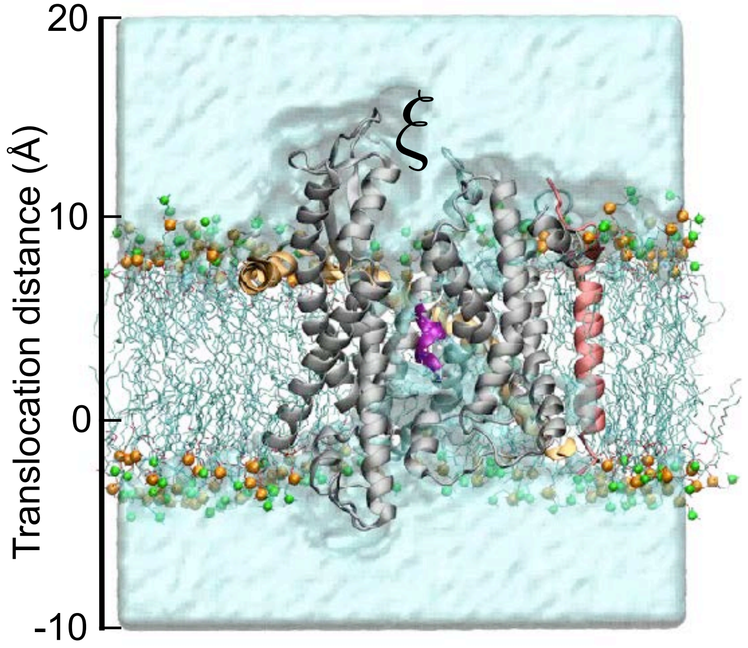
Though cumulant expansions help, the non-equilibium work route to free-energy differences requires near-equilibrium conditions to converge.

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

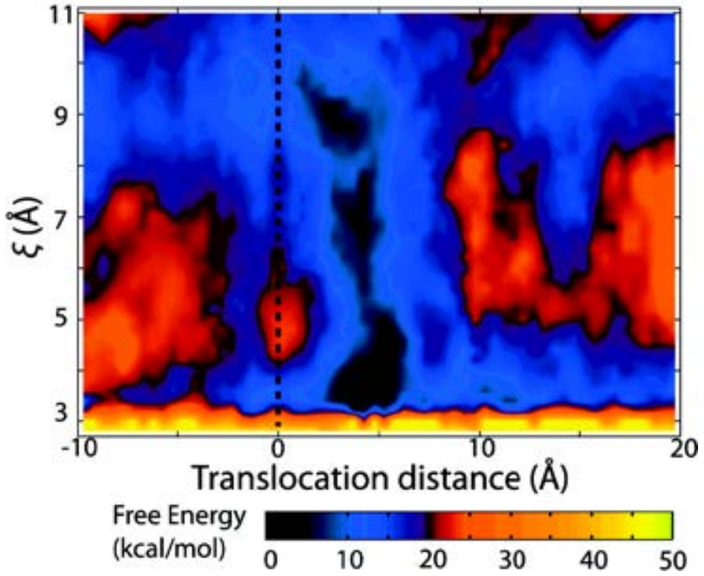
Crooks, G. *J. Stat. Phys.* **1998**, *90*, 1481-1487

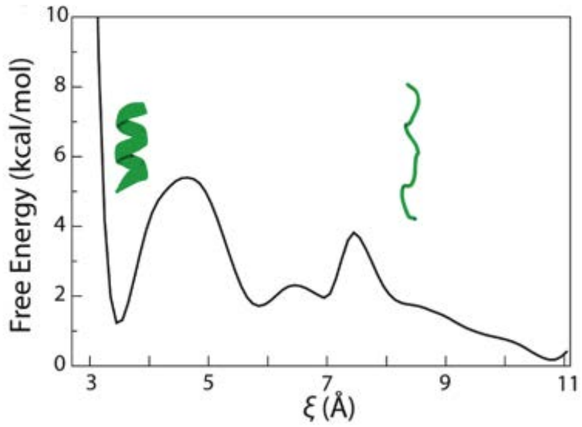
Park, S.; Khalili-Araghi, F.; Tajkhorshid, E.; Schulten, K. *J. Chem. Phys.* **2003**, *119*, 3559-3566



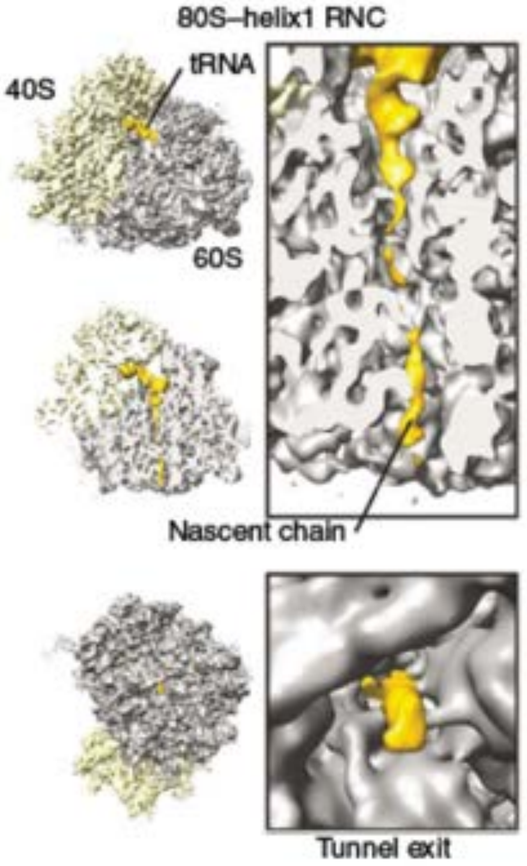
Two-dimensional reaction coordinate: Translation in SecY plus the concerted folding of the peptide chain (ξ).

Translocation of proteins supposes partial opening of SecY.





Control simulation:
Folding in bulk water.



Mingarro, I.; Nilsson, I.; Whitley, P.; von Heijne, G. *BMC Cell Biol.* **2000**, *1*, 3

Lu, J.; Deutsch, C. *Nat. Struct. Mol. Biol.* **2005**, *12*, 1123-1129

Gumbart, J. C.; Chipot, C.; Schulten, K. *J. Am. Chem. Soc.* **2011**, *133*, 7602-7607

geometric free-energy calculations

introduction to the adaptive biasing force algorithm

introductory tutorial

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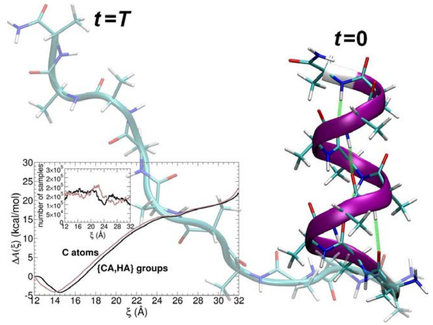
Laboratoire International Associé CNRS-University of Illinois

Centre National de la Recherche Scientifique
Institut de Biologie Physico-Chimique

University of Illinois at Urbana-Champaign
Beckman Institute for Advanced Science and Technology
Theoretical and Computational Biophysics Group

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



Jérôme Hénin
James Gumbart
Christophe Chipot

November 3, 2014

Current editor: Lela Vuković (Lvukov1@ks.uiuc.edu)

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alchemical free-energy calculations

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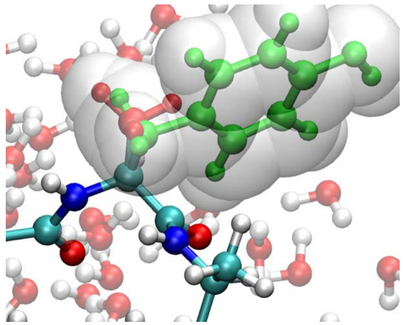
In silico alchemy: A tutorial for alchemical free-energy perturbation calculations with NAMD



Jérôme Hénin
James Gumbart
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November 4, 2014

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standard binding free energies

geometric free-energy calculations

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advanced tutorial

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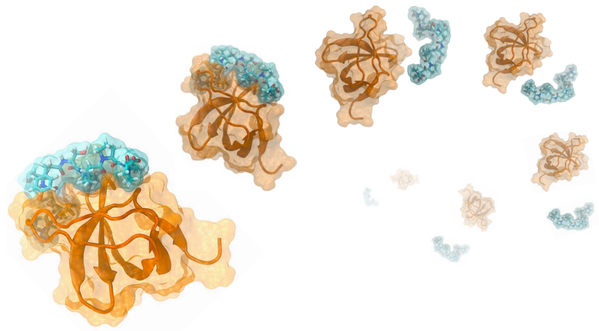
Protein:ligand standard binding free energies: A tutorial for alchemical and geometrical transformations



James Gumbart
Benoît Roux
Christophe Chipot

July 4, 2013

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path sampling

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

advanced tutorial

Department of Biochemistry and Molecular Biology
Gordon Center for Integrative Science
The University of Chicago

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Université de Lorraine

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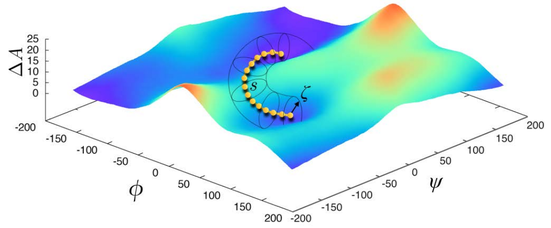
Theoretical and Computational Biophysics Group

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



Mikolai Fajer
Jérôme Hénin
Benoît Roux
Christophe Chipot

August 19, 2015

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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
```