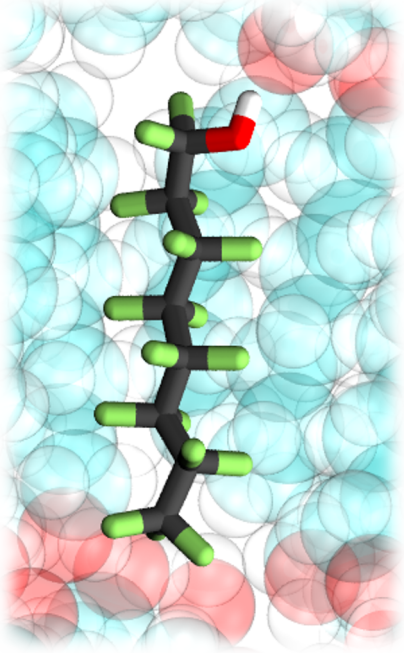
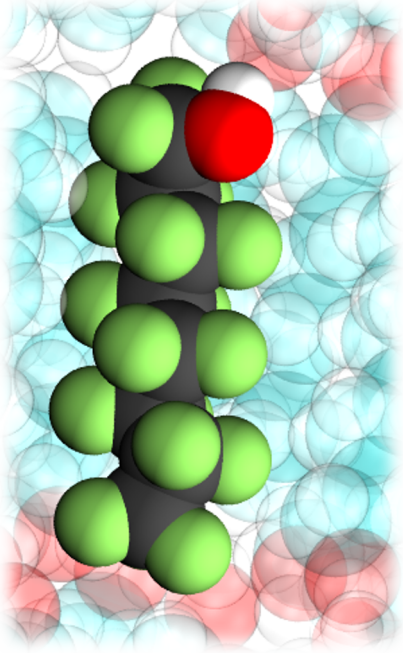
Overview of Free Energy Methods and Collective Variables in NAMD





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University of Illinois at Urbana-Champaign

Computational Biophysics Virtual Workshop, 2020

Outline:

Introduction

- Free energy applications

Alchemical free energy calculations

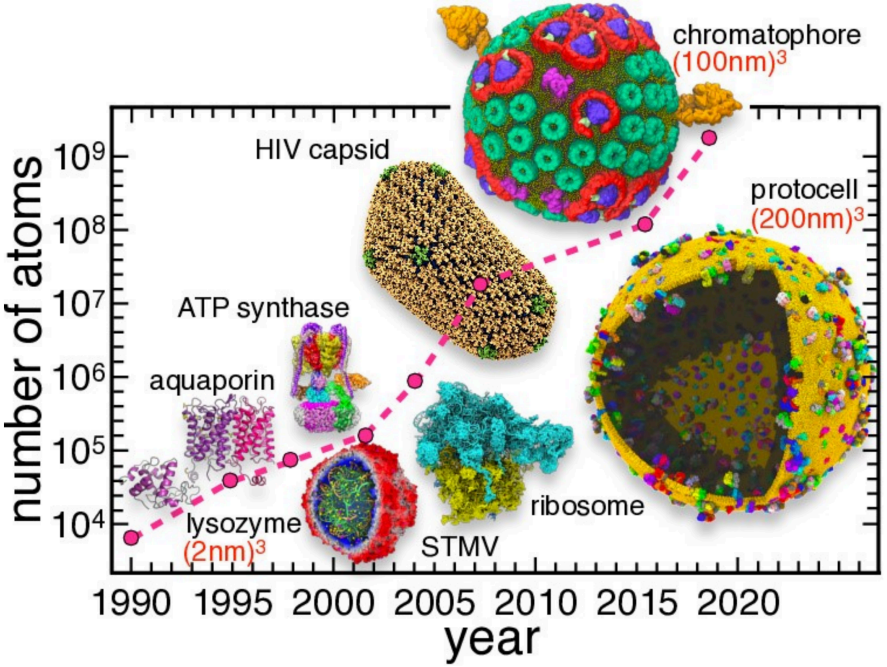
- Free Energy Perturbation (FEP)
- Thermodynamic Integration (TI)
- FEP in NAMD and VMD

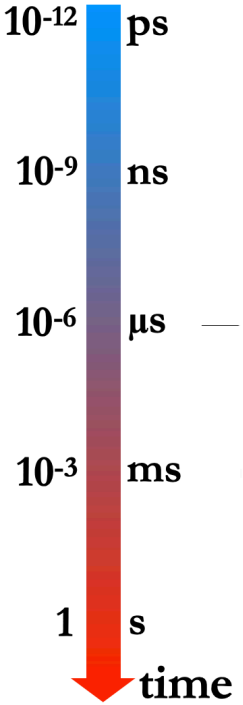
Geometrical free-energy calculations

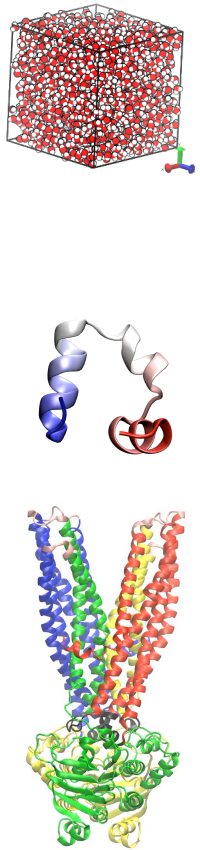
- Steered Molecular Dynamic (SMD)
- Adaptive Biasing Potential
  - Metadynamics (MtD)
  - Well-tempered metadynamics (WT-MtD)
- Adaptive Biasing Force (ABF)
- Extended-system Adaptive Biasing Force (eABF)

Introduction: Free energy applications

1. Time scale requires for adequate sampling
2. Force field approximation

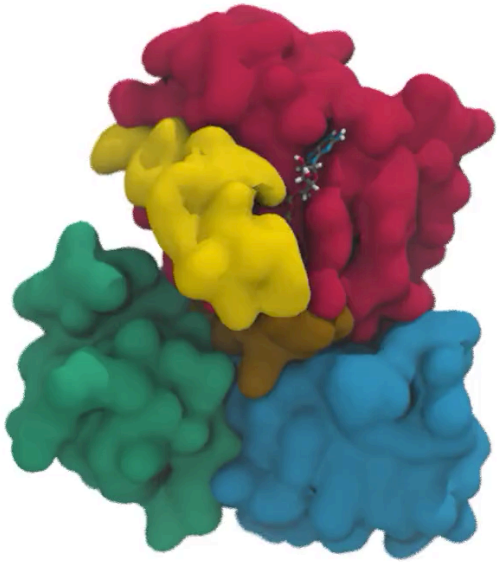


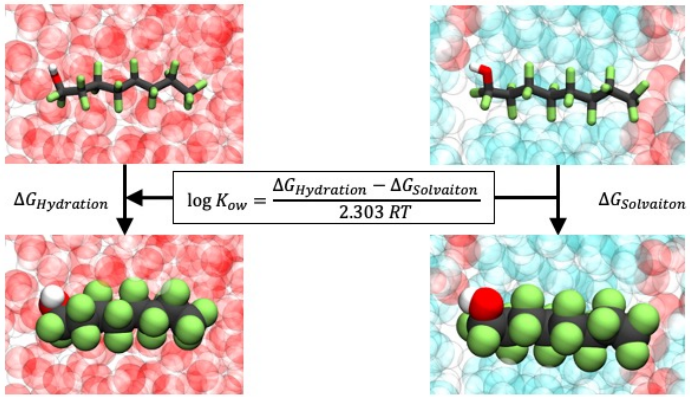




Introduction: Free energy applications

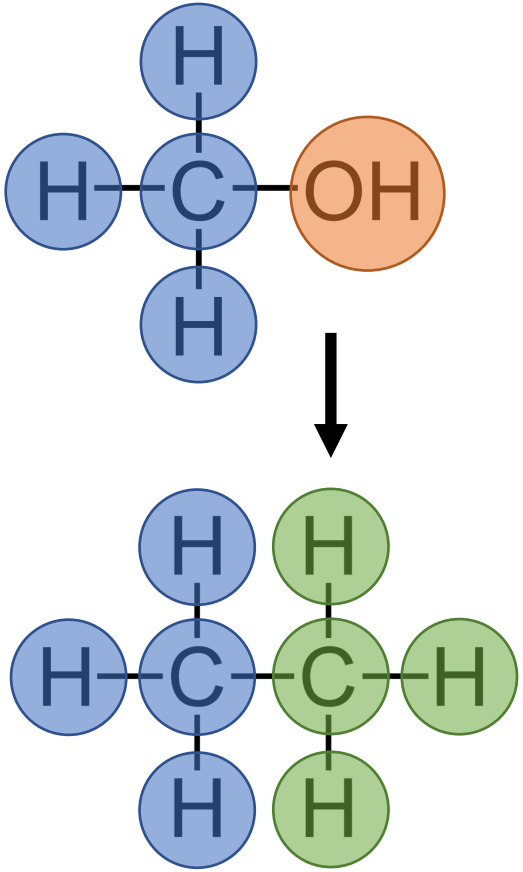
- Partition coefficients
- Protein-ligand binding
- Protein-protein
- Binding permeabilities
- Activation barriers
- Site-directed mutagenesis
- Structural modifications

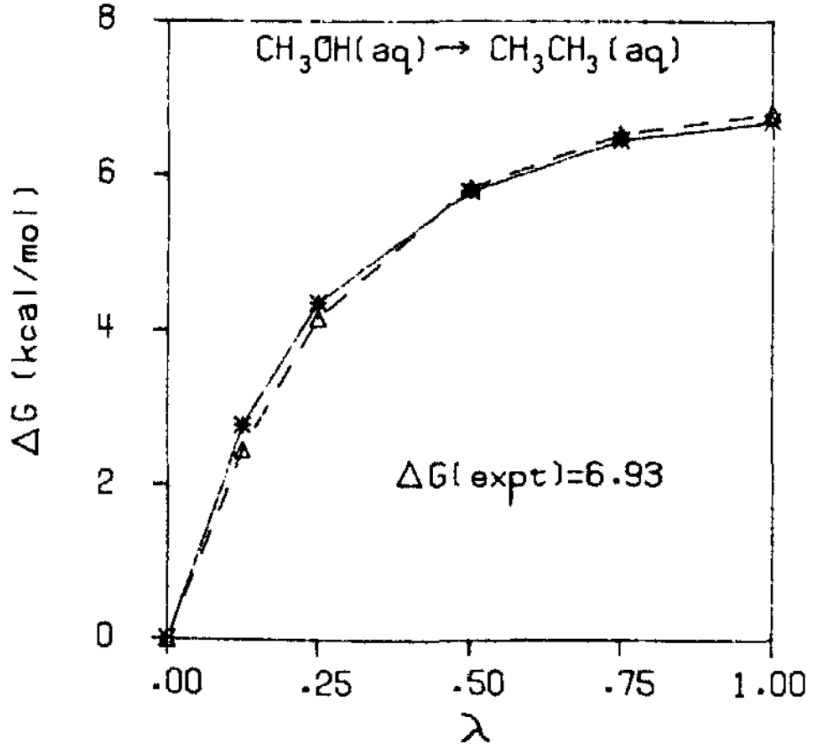




Lai, J., Ghaemi, Z., Luthey-Schulten, Z., 2017, Biochemistry, 56, 45, 5972–5979
M Soroush Barhaghi, C Luyet, JJ Potoff. Mol. Phys 117 (23-24), 3827-3839

Alchemical free energy calculation: FEP





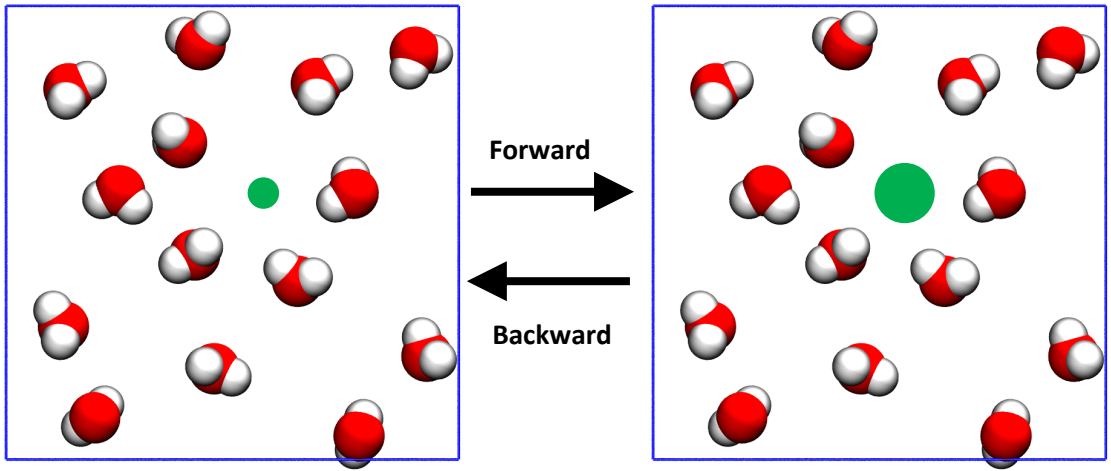
Jorgensen, W. L.; Ravimohan, C. J. Chem. Phys. 1985, 83, 3050-3054

Alchemical free energy calculation: FEP

$$\Delta F(A \longrightarrow B) = -\frac{1}{\beta}\ln\langle\exp\left(-\beta(U_B - U_A)\right)\rangle_A \qquad \beta = \frac{1}{k_{\mathrm{B}}T}$$

$$\Delta F(\mathrm{B} \longrightarrow A) = -\frac{1}{\beta}\ln\langle\exp\left(-\beta(U_A - U_B)\right)\rangle_B$$

$$\Delta F(A \longrightarrow B) = -\Delta F(\mathrm{B} \longrightarrow A)$$



$\boldsymbol{A = Na^+}$ $\boldsymbol{B = K^+}$

Jorgensen, W. L.; Ravimohan, C. J. Chem. Phys. 1985, 83, 3050-3054
Landau, L. D. Statistical physics, 1938
Zwanzig, R. W. J. Chem. Phys. 1954, 22, 1420-1426

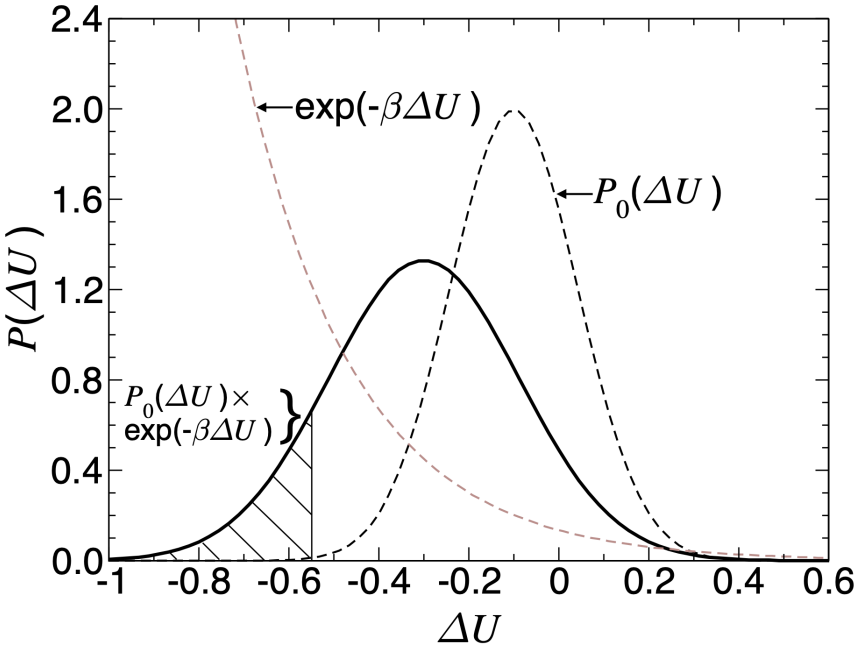
Alchemical free energy calculation: Stratification

$$\Delta F(A \longrightarrow B) = -\frac{1}{\beta}\ln\langle\exp(-\beta\Delta U)\rangle_A$$

$$\Delta F = -\frac{1}{\beta}\ln\int P_A(\Delta U)\exp(-\beta\Delta U)\, d\Delta U$$

$$P_A(\Delta U) = \frac{1}{\sqrt{2\pi\,\sigma^2}} exp\left[-\frac{(\Delta U\ -\ \langle\Delta U\rangle_A)^2}{2\sigma^2}\right]$$

$$\Delta F = \langle\Delta U\rangle_A - \frac{1}{2}\beta\sigma^2$$



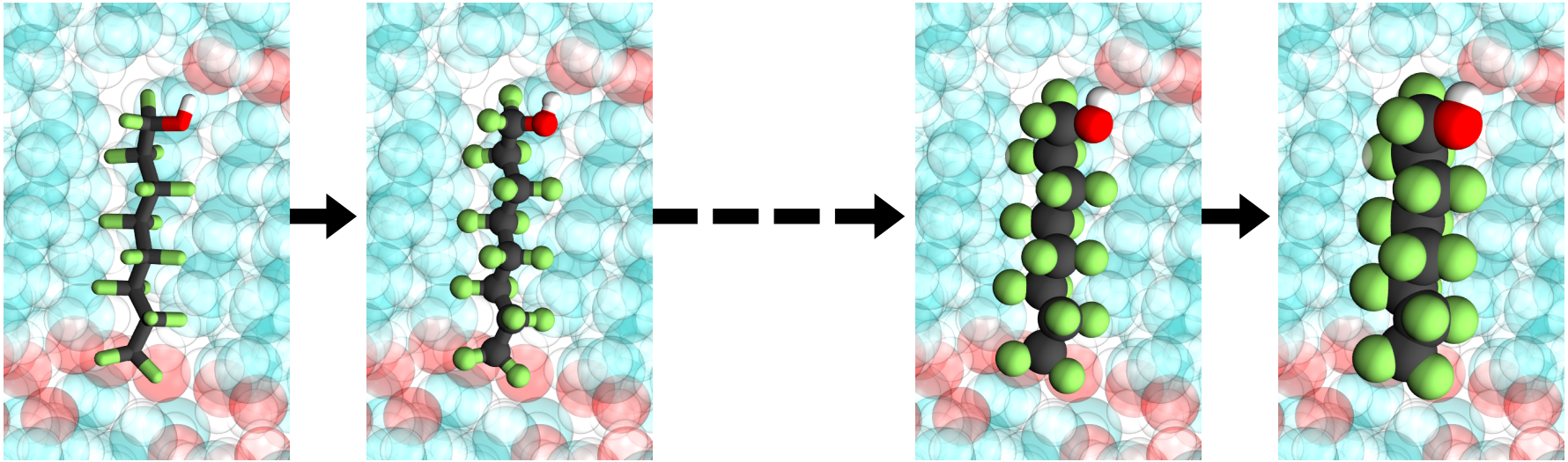
Valleau, J. P.; Card, D. N. J. Chem. Phys. 1972, 57, 5457-5462

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

Alchemical free energy calculation: Stratification

$$U(\lambda) = \lambda U_B + (1-\lambda)U_A \qquad \Delta F(A \longrightarrow B) = -\frac{1}{\beta}\sum_{i=0}^{N-1} \ln\langle \exp[-\beta(U(\lambda_{i+1}) - U(\lambda_i))]\rangle_i$$

$$A(\lambda_0 = 0) \quad < \quad \lambda_1 \quad < \ . \ . \ . \ . < \quad \lambda_{N-1} \quad < \quad B(\lambda_N = 1)$$



M Soroush Barhaghi, C Luyet, JJ Potoff. Mol. Phys 117 (23-24), 3827-3839

Alchemical free energy calculation: Stratification

$$\Delta F(A \longrightarrow B) = -\frac{1}{\beta}\sum_{i=0}^{N-1} \ln\langle \exp[-\beta(U(\lambda_{i+1}) - U(\lambda_i))]\rangle_i$$

$$U(\lambda) = \lambda U_B + (1-\lambda)U_A$$

$$\lambda U_B\left(r_{ij},\lambda\right) = \lambda_{LJ}\epsilon_{ij}\left[\left(\frac{R_{min}^2}{r_{ij}^2 + \alpha\left(1-\lambda_{LJ}\right)}\right)^6 - \left(\frac{R_{min}^2}{r_{ij}^2 + \alpha\left(1-\lambda_{LJ}\right)}\right)^3\right] + \lambda_{Elect}\frac{q_i q_j}{\epsilon r_{ij}}$$

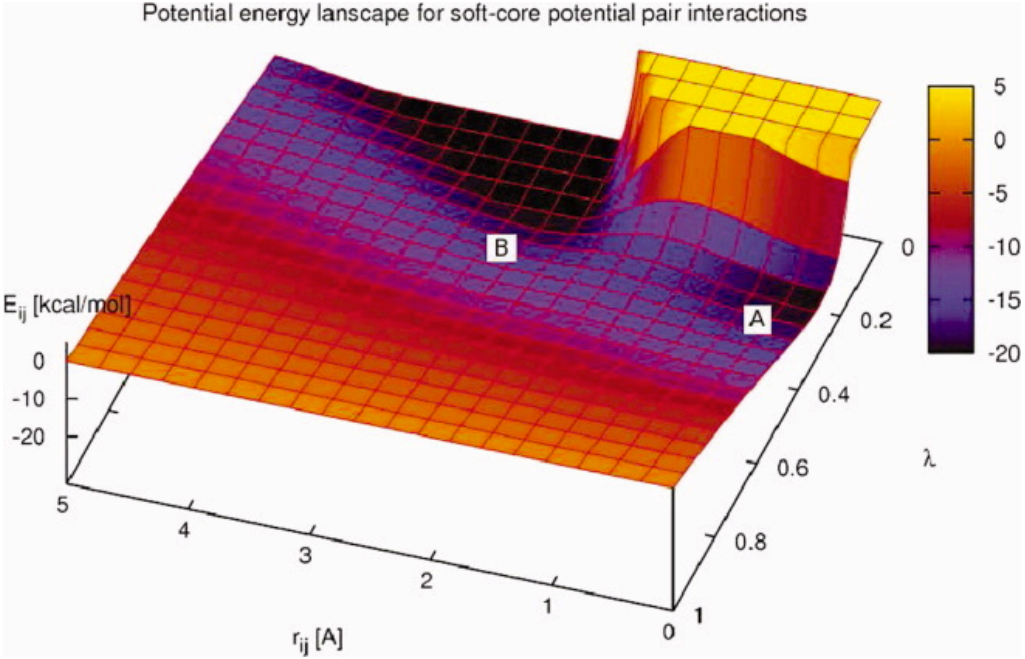
$$(1-\lambda)U_A\left(r_{ij},\lambda\right) = \left(1-\ \lambda_{LJ}\right)\epsilon_{ij}\left[\left(\frac{R_{min}^2}{r_{ij}^2 + \alpha\lambda_{LJ}}\right)^6 - \left(\frac{R_{min}^2}{r_{ij}^2 + \alpha\lambda_{LJ}}\right)^3\right] + (1-\ \lambda_{Elect})\frac{q_i q_j}{\epsilon r_{ij}}$$

Alchemical free energy calculation: TI

$$\Delta F(A \longrightarrow B) = \int_{\lambda=0}^{\lambda=1} \langle \frac{dU}{d\lambda} \rangle_\lambda \, d\lambda$$

$$U(\lambda) = \lambda U_B + (1-\lambda) U_A$$

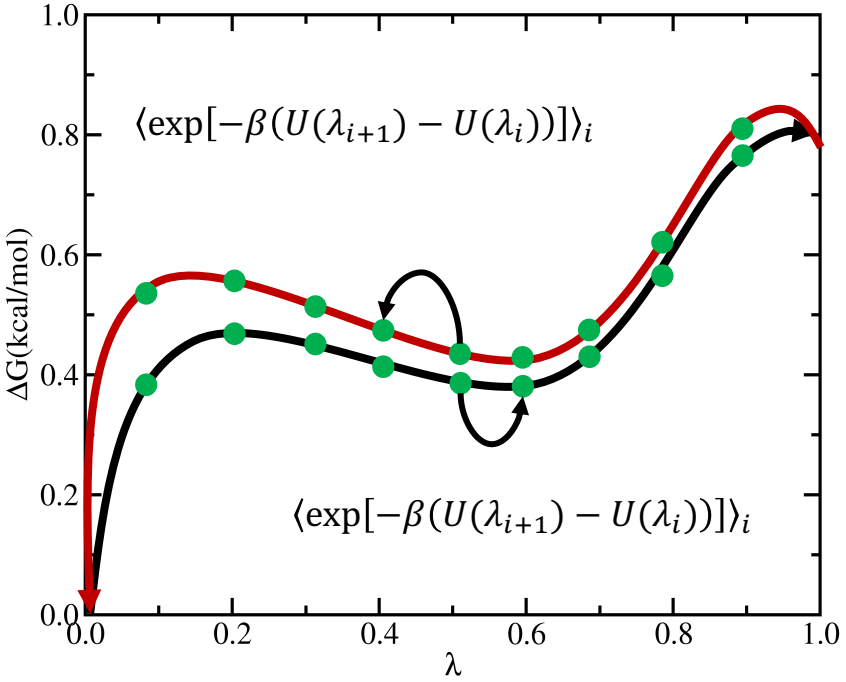
$$\frac{dU}{d\lambda} = U_B - U_A + \lambda \frac{dU_B}{d\lambda} + (1-\lambda) \frac{dU_A}{d\lambda}$$



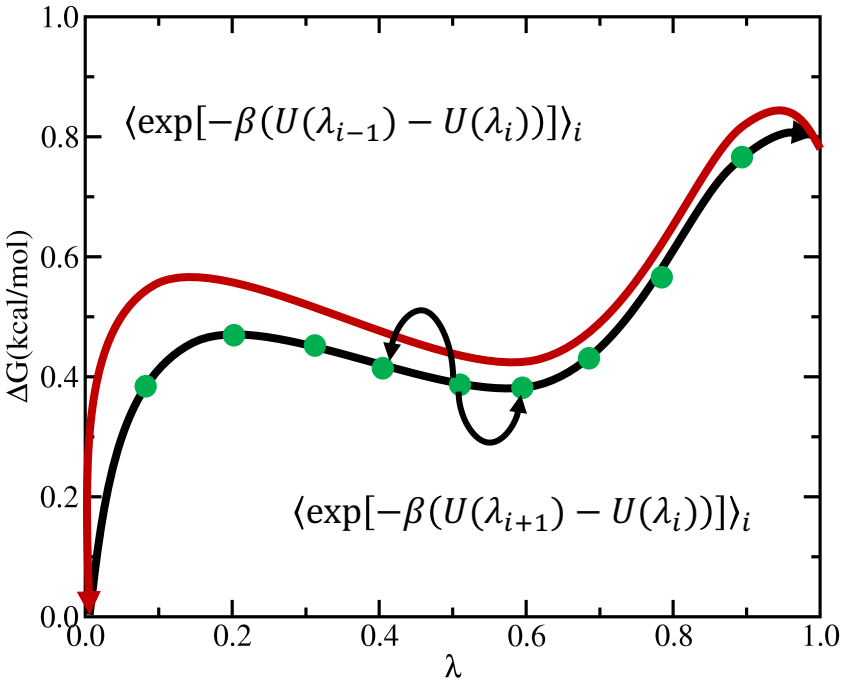
T. Steinbrecher, I. Joung, and D. A. Case, *J. Comput. Chem.* **32** (15), 3253 (2011).
J. G. Kirkwood. J. Chem. Phys. 1935, 3, 300-313 .

Alchemical free energy calculation: Sampling

forward & backward

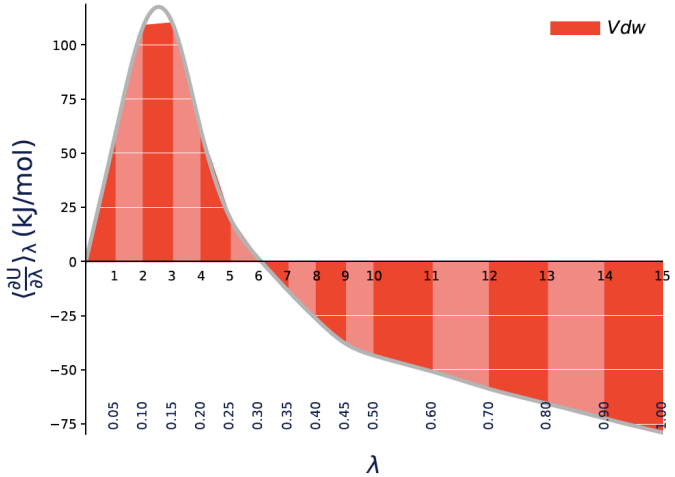


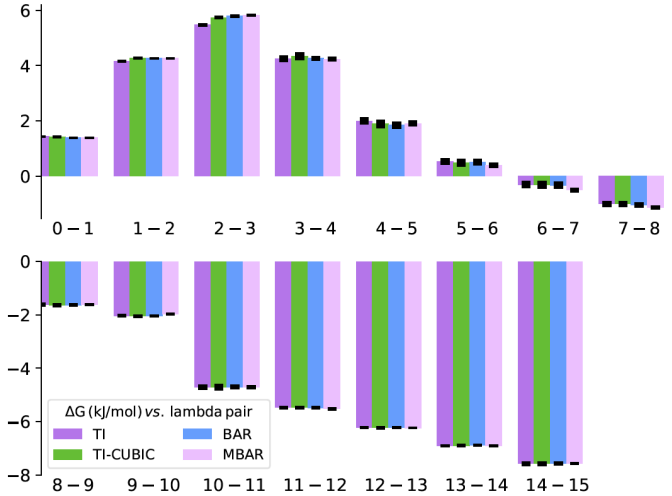
double-wide sampling



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

Alchemical free energy calculation: BAR



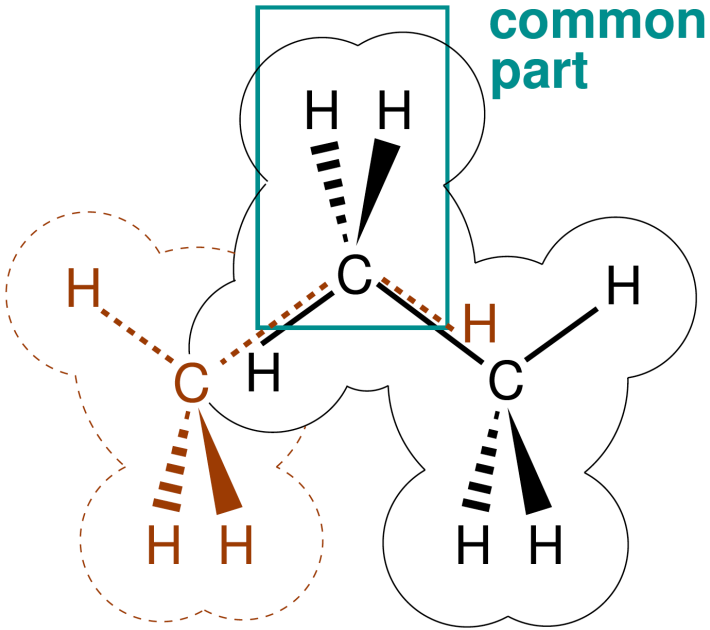


$$\begin{cases} \exp\left(\beta \hat{A}^{BAR}\right) = \dfrac{\langle f[-\beta(\Delta U - c)]\rangle_1}{\langle f[+\beta(\Delta U - c)]\rangle_0} \exp(\beta c) \\ c = \Delta \hat{A}^{BAR} + \dfrac{1}{\beta} \ln \dfrac{N_1}{N_0} \quad , f(x) = \dfrac{1}{1+\exp(x)} \end{cases}$$

Maximum-likelihood estimator of the free-energy change.
Guarantees the minimum variance.

Bennett, C. H. J. Comp. Phys. 1976, 22, 245–268.
Shirts, M.R., and Chodera, J.D. 2008, J. Chem. Phys. 129, 124105.

Alchemical free energy calculation: Dual-topology

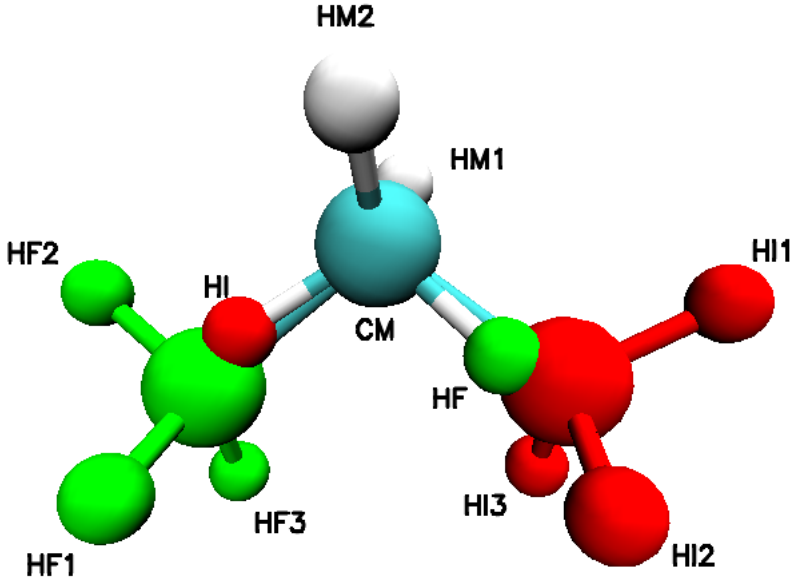



```
* Topology for ethane-to-ethane transformation
27 1    ! pretend we are CHARMM27_1

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

! No patching
PATCHING FIRST NONE LAST NONE
END
```

Alchemical free energy calculation: Dual-topology




```
ATOM      1  CI   ZERO    1      -1.167   0.224   0.034  1.00 -1.00
ATOM      2  HI1  ZERO    1      -2.133  -0.414   0.000  1.00 -1.00
ATOM      3  HI2  ZERO    1      -1.260   0.824   0.876  1.00 -1.00
ATOM      4  HI3  ZERO    1      -1.258   0.825  -0.874  1.00 -1.00
ATOM      5  CM   ZERO    1       0.001  -0.652  -0.002  1.00  0.00
ATOM      6  HM1  ZERO    1       0.000  -1.313  -0.890  1.00  0.00
ATOM      7  HM2  ZERO    1       0.005  -1.308   0.889  1.00  0.00
ATOM      8  HI   ZERO    1       1.234   0.192   0.000  1.00 -1.00
ATOM      9  HF   ZERO    1      -1.237   0.190   0.000  1.00  1.00
ATOM     10  CF   ZERO    1       1.289   0.150  -0.078  1.00  1.00
ATOM     11  HF1  ZERO    1       2.149  -0.425  -0.001  1.00  1.00
ATOM     12  HF2  ZERO    1       1.256   0.837  -0.893  1.00  1.00
ATOM     13  HF3  ZERO    1       1.131   0.871   0.940  1.00  1.00
ATOM     14  OH2  TIP3    1      -5.574  -5.971  -9.203  1.00  0.00
ATOM     15  H1   TIP3    1      -5.545  -5.020  -9.301  1.00  0.00
...
```

Alchemical free energy calculation: NAMD FEP/TI

```
# FEP PARAMETERS FOR FORWARD

source                  ../tools/fep.tcl

alch                    on
alchType                FEP
alchFile                zero.fep
alchCol                 B
alchOutFile             forward-shift.fepout
alchOutFreq             10

alchVdwLambdaEnd        1.0
alchElecLambdaStart     0.5
alchVdWShiftCoeff       6.0
alchDecouple            yes

alchEquilSteps          100
set numSteps            500

runFEP 0.0 1.0 0.0625 $numSteps
```

```
# FEP PARAMETERS FOR BACKWARD

source                  ../tools/fep.tcl

alch                    on
alchType                FEP
alchFile                zero.fep
alchCol                 B
alchOutFile             backward-shift.fepout
alchOutFreq             10

alchVdwLambdaEnd        1.0
alchElecLambdaStart     0.5
alchVdWShiftCoeff       6.0
alchDecouple            yes

alchEquilSteps          100
set numSteps            500

runFEP 1.0 0.0 -0.0625 $numSteps
```

Alchemical free energy calculation: NAMD FEP/TI

```
source                  ../tools/fep.tcl

alch                    on
alchType                FEP
alchFile                zero.fep
alchCol                 B
alchOutFile             forward-shift.fepout
alchOutFreq             10

alchVdWShiftCoeff       6.0
alchDecouple            yes

alchEquilSteps          100
set numSteps            500


runFEP 0.0 1.0 0.0625 $numSteps
```

```
ATOM      1  CI   ZERO    1      -1.167   0.224   0.034  1.00 -1.00
ATOM      2  HI1  ZERO    1      -2.133  -0.414   0.000  1.00 -1.00
ATOM      3  HI2  ZERO    1      -1.260   0.824   0.876  1.00 -1.00
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ATOM      5  CM   ZERO    1       0.001  -0.652  -0.002  1.00  0.00
ATOM      6  HM1  ZERO    1       0.000  -1.313  -0.890  1.00  0.00
ATOM      7  HM2  ZERO    1       0.005  -1.308   0.889  1.00  0.00
ATOM      8  HI   ZERO    1       1.234   0.192   0.000  1.00 -1.00
ATOM      9  HF   ZERO    1      -1.237   0.190   0.000  1.00  1.00
ATOM     10  CF   ZERO    1       1.289   0.150  -0.078  1.00  1.00
ATOM     11  HF1  ZERO    1       2.149  -0.425  -0.001  1.00  1.00
ATOM     12  HF2  ZERO    1       1.256   0.837  -0.893  1.00  1.00
ATOM     13  HF3  ZERO    1       1.131   0.871   0.940  1.00  1.00
ATOM     14  OH2  TIP3    1      -5.574  -5.971  -9.203  1.00  0.00
ATOM     15  H1   TIP3    1      -5.545  -5.020  -9.301  1.00  0.00
...
```

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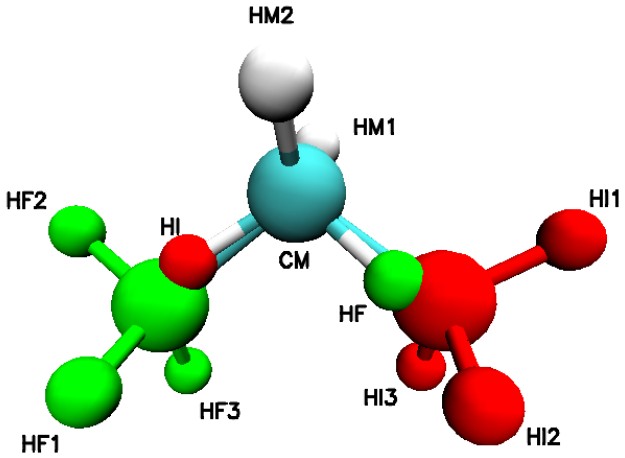
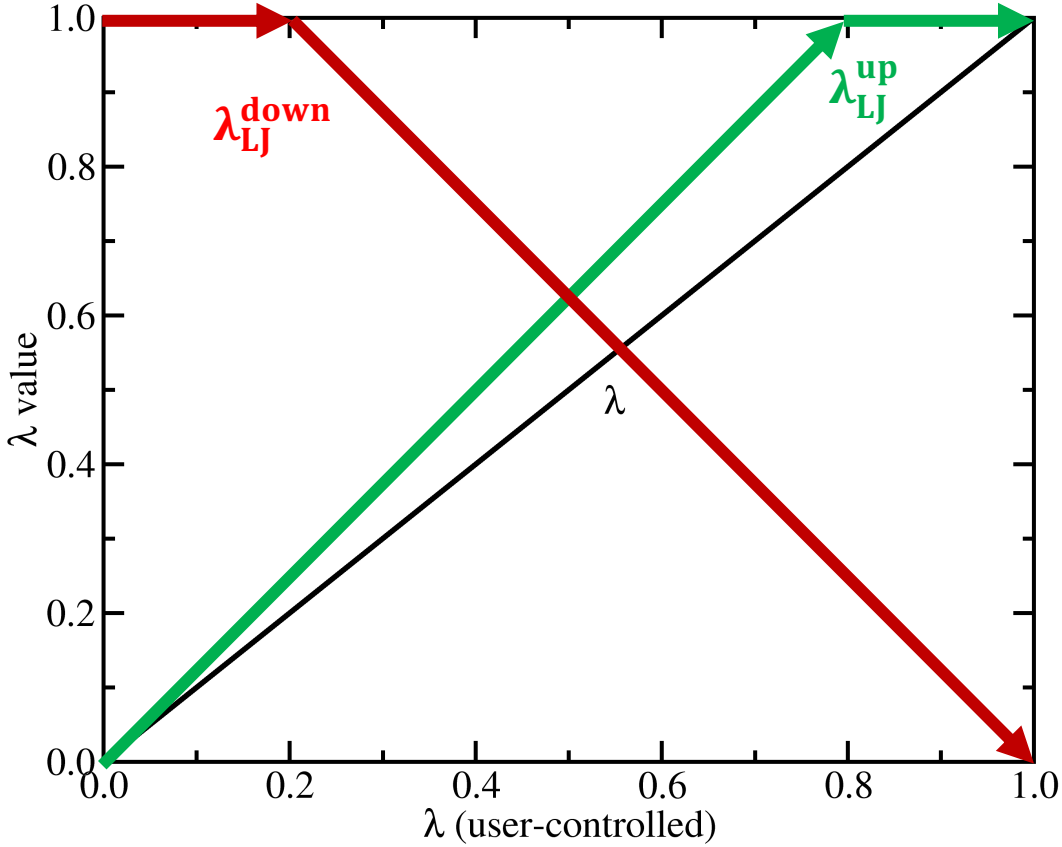
Alchemical free energy calculation: NAMD FEP/TI

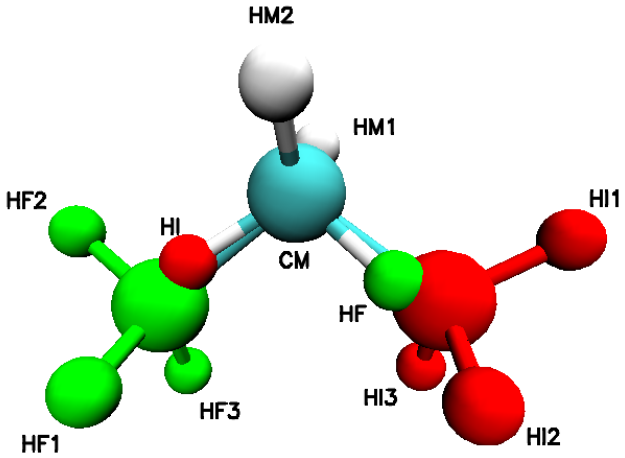
```
alchVdwLambdaEnd          0.8

alchElecLambdaStart       0.5
```

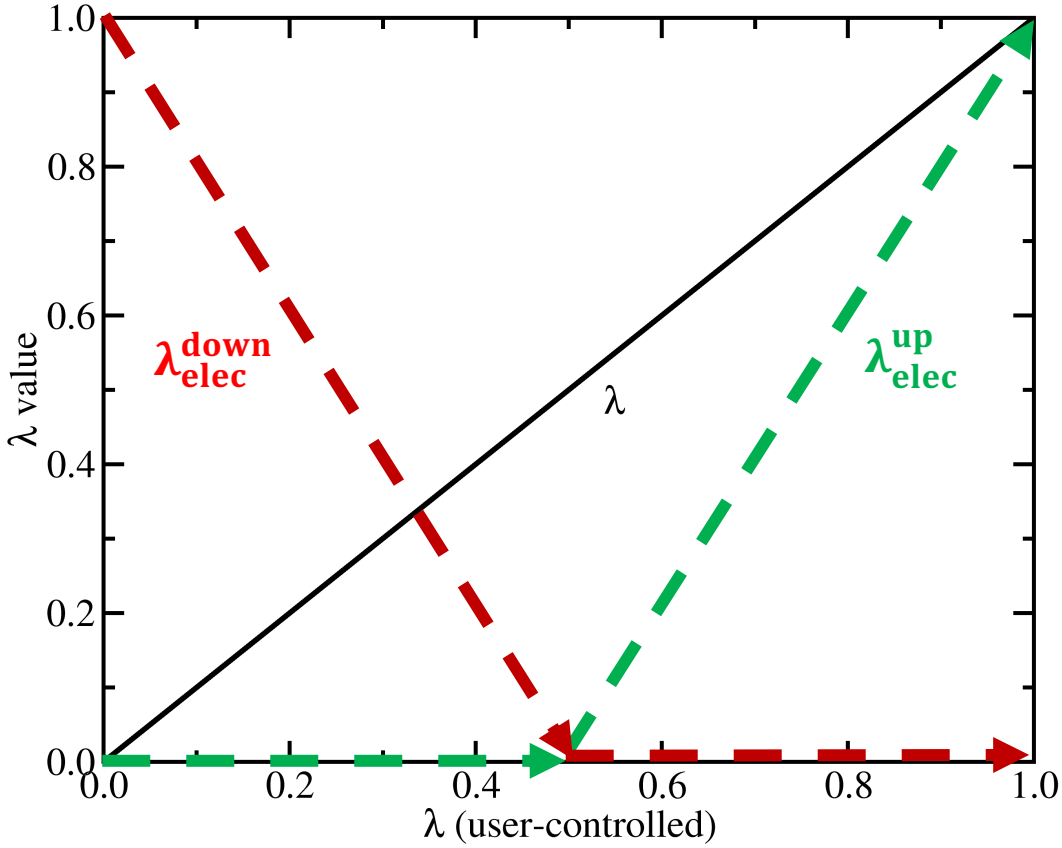




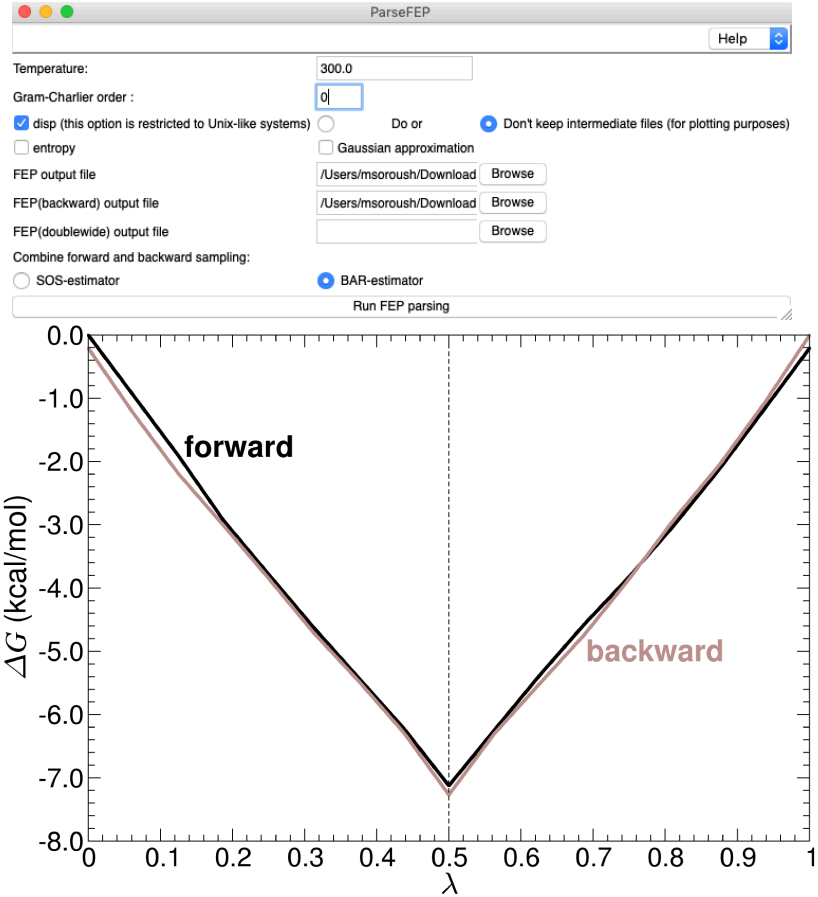
Alchemical free energy calculation: NAMD FEP/TI

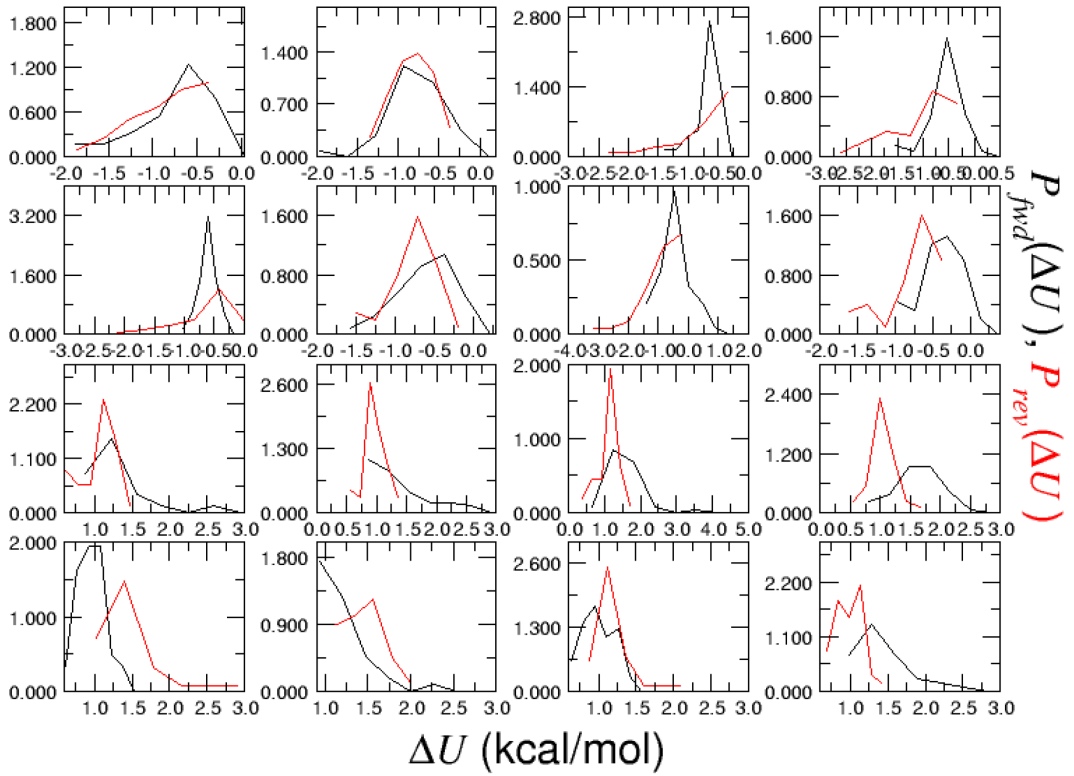
```
alchVdwLambdaEnd          0.8

alchElecLambdaStart       0.5
```





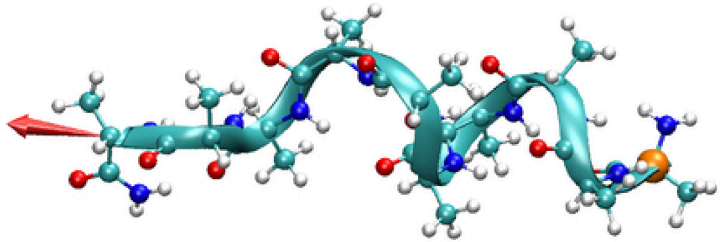
Alchemical free energy calculation: VMD FEP Analysis





Geometrical free energy calculation: Steered MD simulation

$$E(\boldsymbol{S},t)=\frac{1}{2}k(t)[\boldsymbol{S}-\boldsymbol{S}(t)]^2, \qquad \boldsymbol{S}(t)=\boldsymbol{S}_0+vt$$



$$W=\int_0^t \frac{dE(\boldsymbol{S},t')}{dt'}\,dt'$$

$$W=\int_0^t -k(t)[\boldsymbol{S}-\boldsymbol{S}(t)]v\,dt'+\int_0^t \frac{1}{2}[\boldsymbol{S}-\boldsymbol{S}(t)]^2\frac{dk(t')}{dt'}\,dt'$$

$$\Delta F=-\frac{1}{\beta}\ln\langle\exp(-\beta \mathrm{W})\rangle$$

If pulling process is reversible, it is possible to obtain free energy surfaces from **repeated non-equilibrium experiments**.

C. Jarzynski, Phys. Rev. Lett. 1997, 78, 2690
C. Jarzynski, Phys. Rev. E, 1997, 56, 5018

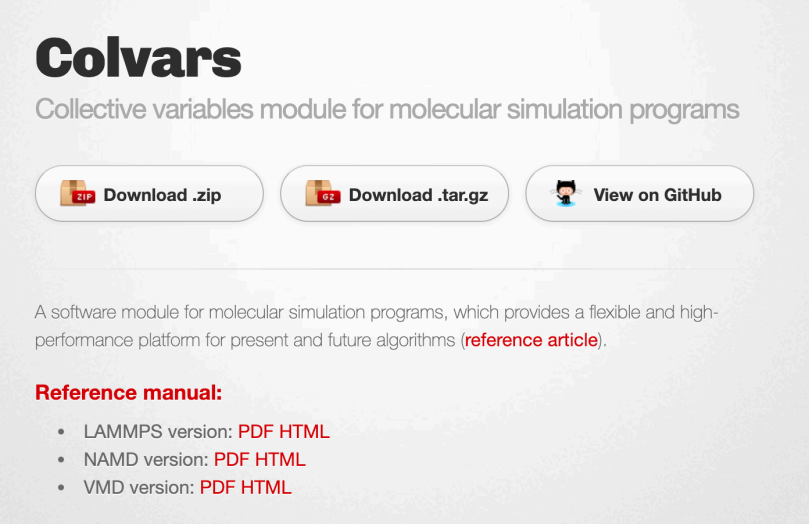
Geometrical free energy calculation: Collective variables

A colvar S is as a differentiable function of the vector atomic Cartesian coordinates $\boldsymbol{r}$.

$$\boldsymbol{S}(r) = S(\boldsymbol{r_1}, \boldsymbol{r_2}, \ldots, \boldsymbol{r_N})$$

Depending on the structure of the system, $S(r)$ is often a function of much fewer arguments than 3*N*, or can be expressed as a combination of such functions

$$\boldsymbol{S}(r) = S(z^1(\boldsymbol{r}), z^2(\boldsymbol{r}), \ldots)$$



These features are contributed to NAMD by Giacomo Fiorin (NIH) and Jérôme Hénin (CNRS, France)

https://colvars.github.io/
https://github.com/Colvars/colvars
https://www.ks.uiuc.edu/Research/namd/2.14/ug/node53.html

Geometrical free energy calculation: Collective variables

Component

Scalar

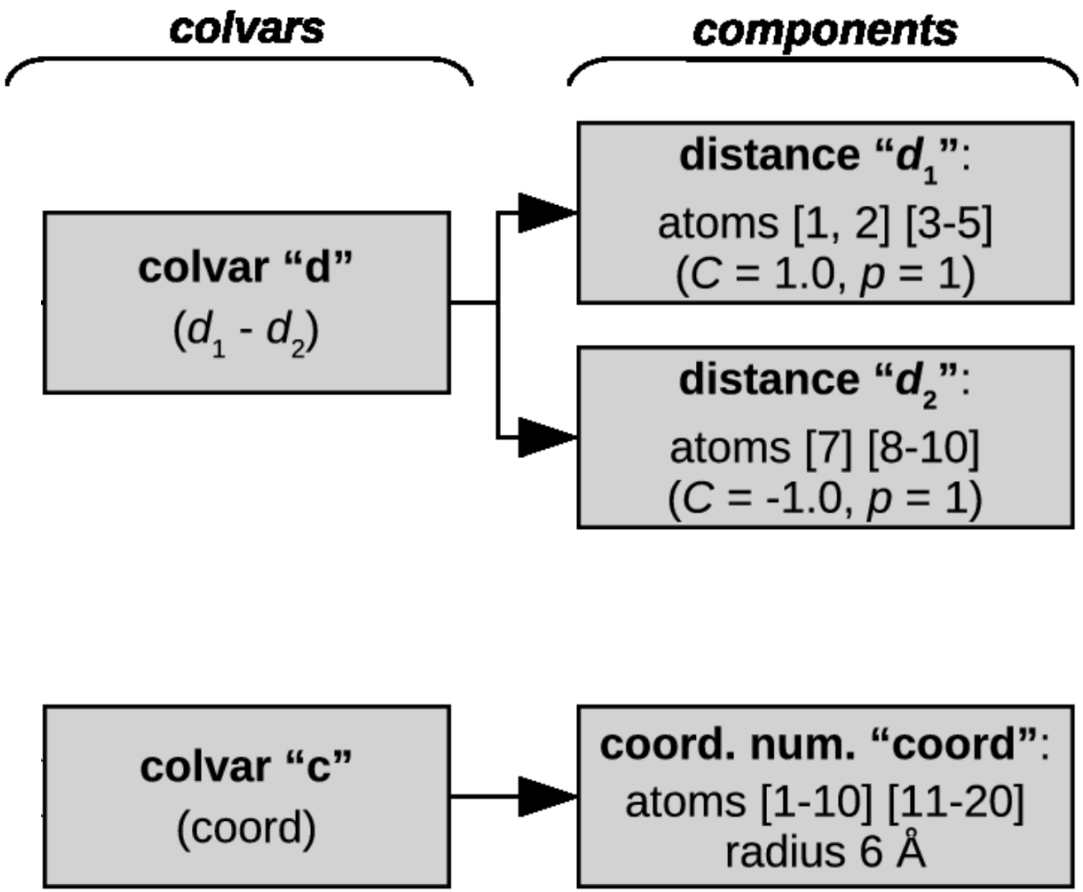
1. distance
2. Distance z
3. Distance xy
4. Polar theta
5. Polar phi
6. Distance inverse
7. Distance pairs
8. Dipole magnitude
9. Angle
10. Dipole angle
11. dihedral
12. Coordinate number
13. Self coordinate number
14. Group coordinate number
15. Hydrogen bond
16. RMSD
17. Orientation angle
18. Orientation projection
19. tilt
20. Spin angle
21. gyration
22. inertia
23. Inertia z
24. Eigen vector
25. Alpha dihedrals
26. Alpha angles
27. Dihedral Principle Component

Non-scalar

1. Distance vector
2. Distance direction
3. cartesian
4. orientation

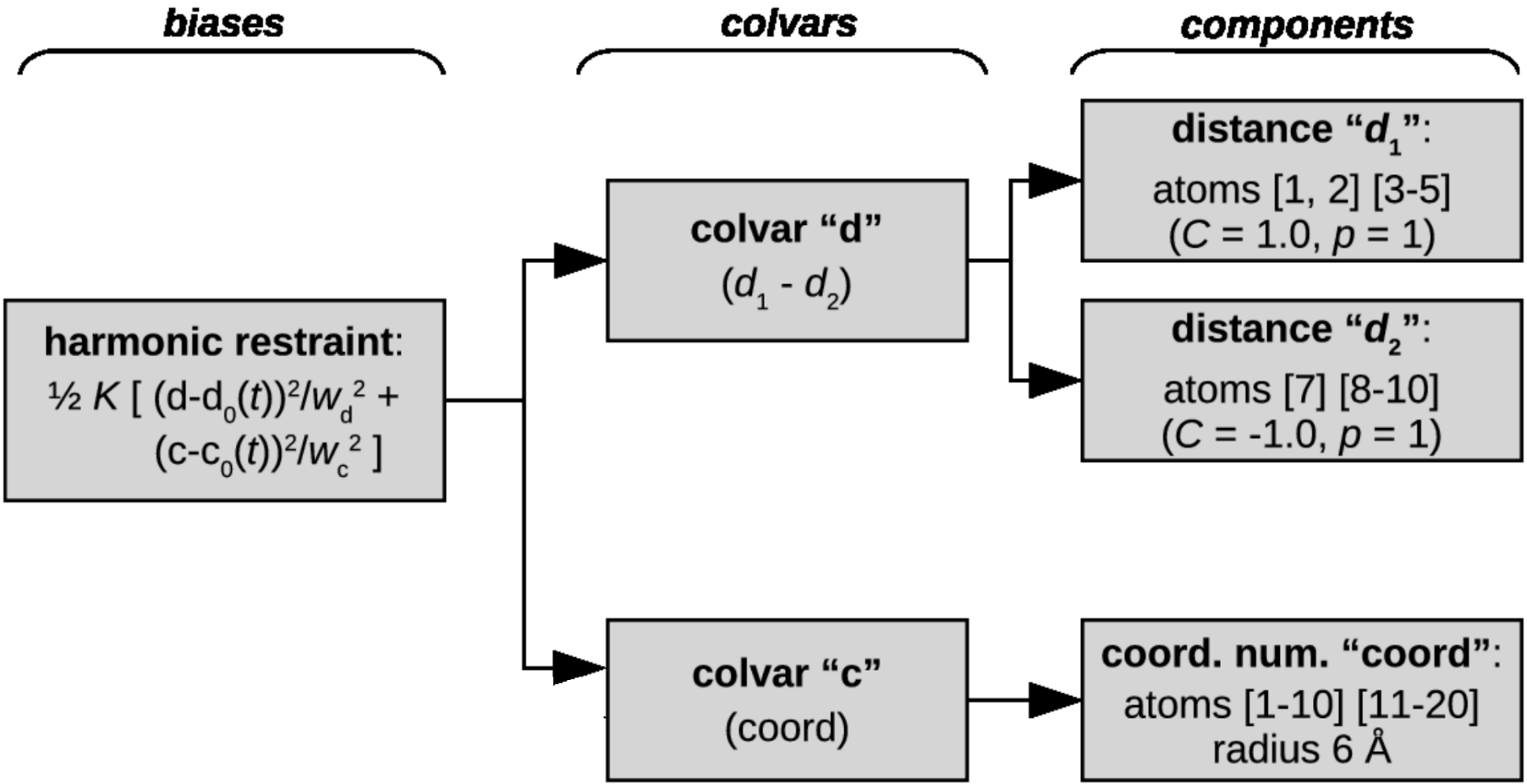
Biases

1. Thermodynamic Integration
2. Adaptive Biasing Force
3. Extended-system Adaptive Biasing Force
4. Metadynamics
   a. Ensemble-Biased Metadynamics
   b. Well-tempered metadynamics
   c. Multiple-walker metadynamics
5. Harmonic restraints
   a. Moving restraints: SMD
   b. Moving restraints: US
   c. Changing force constant
6. Harmonic wall restraints
7. Linear restraints
8. Adaptive Linear Bias
9. Multidimensional histograms
10. Probability distribution-restraints




```
colvar {
  name d

  distance {
    componentCoeff 1.0
    group1 { atomNumbers 1 2 }
    group2 { atomNumbers 3 4 5 }
  }
  distance {
    componentCoeff -1.0
    group1 { atomNumbers 7 }
    group2 { atomNumbers 8 9 10 }
  }
}
```

```
colvar {
  name c

 coordNum {
    cutoff 6.0
    group1 { atomNumbersRange 1-10 }
    group2 { atomNumbersRange 11-20 }
  }
}
```


biases
colvars
components
harmonic restraint:
½ K [(d-d0(t))²/wd² +
(c-c0(t))²/wc²]
colvar "d"
(d1 - d2)
distance "d1":
atoms [1, 2] [3-5]
(C = 1.0, p = 1)
distance "d2":
atoms [7] [8-10]
(C = -1.0, p = 1)
colvar "c"
(coord)
coord. num. "coord":
atoms [1-10] [11-20]
radius 6 Å

Geometrical free energy calculation: Unbiased simulation

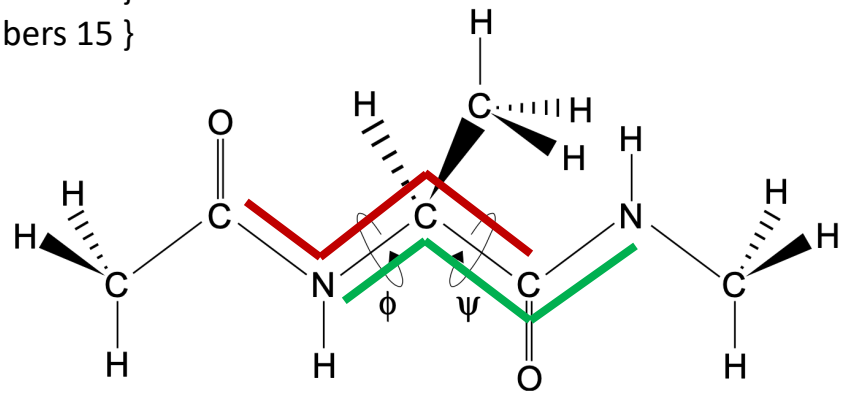
```
colvar { name phi
    dihedral {
    group1 { atomnumbers 13 }
    group2 { atomnumbers 15 }
    group3 { atomnumbers 17 }
    group4 { atomnumbers 1 }
}
```

```
colvar { name psi
dihedral {
    group1 { atomnumbers 3 }
    group2 { atomnumbers 1 }
    group3 { atomnumbers 17 }
    group4 { atomnumbers 15 }
}
```

$$-180 \leq \phi, \psi < 180$$

$$F(\boldsymbol{S}) = -\frac{1}{\beta} \ln \int e^{-\beta U(\boldsymbol{r})}\, \delta\big(\boldsymbol{S} - \boldsymbol{S}(\boldsymbol{r})\big) d\boldsymbol{r} + C$$

$$F(\boldsymbol{S}) = -\frac{1}{\beta} \ln N(\boldsymbol{S}) + C$$



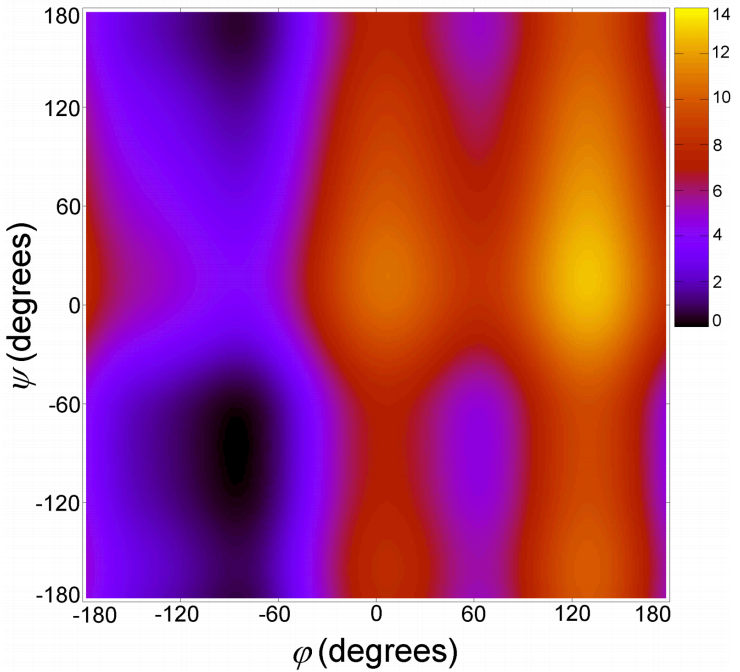
N–acetyl–*N*′–methyl–L–alanylamide (NANMA)

Need to perform: Simulated tempering , parallel tempering , and Hamiltonian replica exchange

Y. Sugita, Y. Okamoto, Chem. Phys. Lett. 314 (1999) 141.
H. Fukunishi, O. Watanabe, S. Takada, J. Chem. Phys. 116 (2002) 9058.
E. Marinari, G. Parisi, Europhys. Lett. 19 (1992) 451.
U.H.E. Hansmann, Chem. Phys. Lett. 281 (1997) 140.

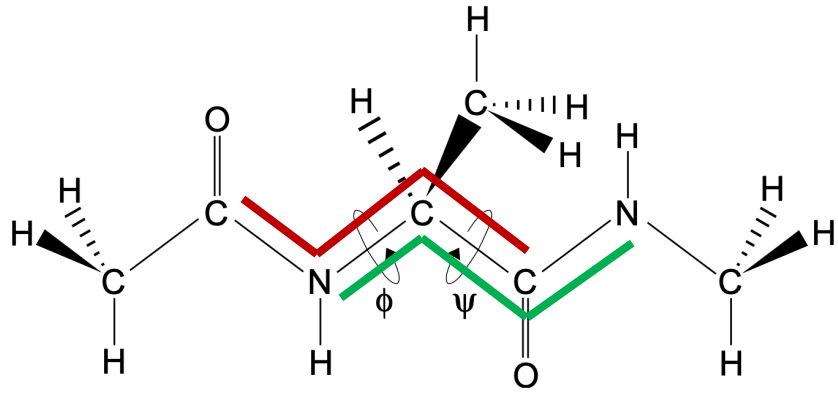
Geometrical free energy calculation: Biased simulation

```
metadynamic {
        colvars phi psi
        hillwidth 2
        hillweight 0.01
}
```




```
colvar { name phi
    dihedral {
    group1 { atomnumbers 13 }
    group2 { atomnumbers 15 }
    group3 { atomnumbers 17 }
    group4 { atomnumbers 1 }
}
```

```
colvar { name psi
dihedral {
    group1 { atomnumbers 3 }
    group2 { atomnumbers 1 }
    group3 { atomnumbers 17 }
    group4 { atomnumbers 15 }
```



$$F(\boldsymbol{S}) = -\frac{1}{\beta}\ln N(\boldsymbol{S}) - E(\boldsymbol{S}) + C$$

Geometrical free energy calculation: Adaptive Biasing Potential

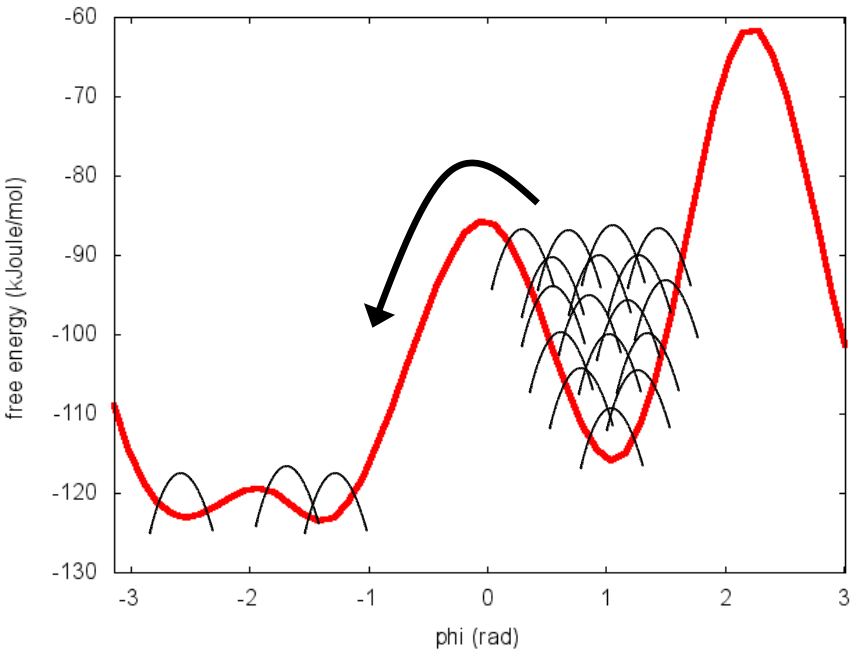
Metadynamics

The bias potential is built as a sum of Gaussian functions centered on the previously visited configurations in the CVs space.

$$E(\boldsymbol{S},t) = \sum_{t'=\tau,2\tau,\ldots}^{t'<t} W \exp\left(-\sum_{i=1}^{i<N_{cv}} \frac{\left(\boldsymbol{S}_i(t') - \boldsymbol{S}_i(t^0)\right)^2}{2\sigma_i^2}\right)$$

$$F(\boldsymbol{S}) = -\frac{1}{\beta}\ln N(\boldsymbol{S}) - E(\boldsymbol{S}) + C$$

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



D. Cvijovic, J. Klinowski, Science 267 (1995) 664.

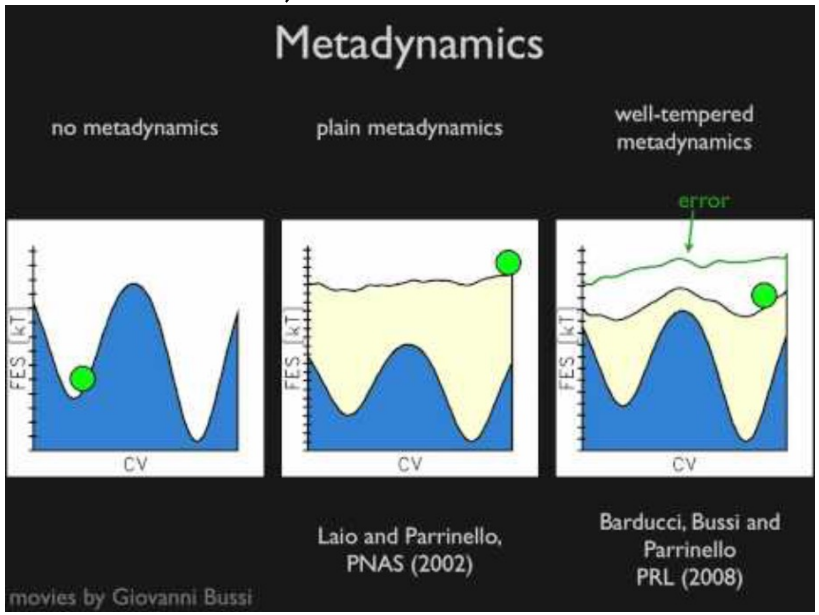
Geometrical free energy calculation: Adaptive Biasing Potential

Well-tempered Metadynamics

$$E(\boldsymbol{S},t) = \sum_{t'=\tau,2\tau,\ldots}^{t'<t} W(t')\exp\left(-\sum_{i=1}^{i<N_{\mathrm{cv}}} \frac{\left(\boldsymbol{S}_i(t') - \boldsymbol{S}_i(t^0)\right)^2}{2\sigma_i^2}\right) \qquad W(t') = \exp\left(\frac{E(\boldsymbol{S},t')}{\Delta T}\right)$$

$$F(\boldsymbol{S}) = -\frac{1}{\beta}\ln N(\boldsymbol{S}) - E(\boldsymbol{S}) + C$$

$$\lim_{t\to\infty} E(\boldsymbol{S},t) = -\frac{T+\Delta T}{\Delta T}F(\boldsymbol{S})$$



Barducci, G. Bussi, M. Parrinello, Phys. Rev. Lett. 100 (2008) 020603.
Viedo by Giovanni Bussi

Geometrical free energy calculation: Adaptive Biasing Force

ABF

$$\Delta F(\boldsymbol{S}) = \int_{s_0}^{s_1} \frac{dF(\boldsymbol{S})}{d\boldsymbol{S}}\, d\boldsymbol{S}$$

$$\frac{dF(\boldsymbol{S})}{d\boldsymbol{S}} = \left\langle \frac{\partial \mathcal{H}}{\partial \boldsymbol{S}} \right\rangle_{\boldsymbol{S}}$$

Ensemble average of an instantaneous force, acting on the reaction parameter $\boldsymbol{S}$.

$$\frac{\partial F(\boldsymbol{S})}{\partial \boldsymbol{S}} = \left\langle \frac{\partial U}{\partial \boldsymbol{S}} - k_B T \frac{\partial \ln |J|}{\partial \boldsymbol{S}} \right\rangle_{\boldsymbol{S}}$$

Force acting along $\boldsymbol{S}$

Geometric entropic contribution

The term $|J|$ is upon changing from Cartesian to generalized coordinates.

$$\frac{\partial U}{\partial \boldsymbol{S}} = \frac{\partial U}{\partial \boldsymbol{r}} \times \frac{\partial \boldsymbol{r}}{\partial \boldsymbol{S}}$$

Need a full set of generalized coordinates!

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

Geometrical free energy calculation: Adaptive Biasing Force

$$\frac{\partial F(\boldsymbol{S})}{\partial \boldsymbol{S}} = \left\langle \frac{\partial U}{\partial \boldsymbol{S}} - k_B T \frac{\partial \ln|J|}{\partial \boldsymbol{S}} \right\rangle_{\boldsymbol{S}}$$

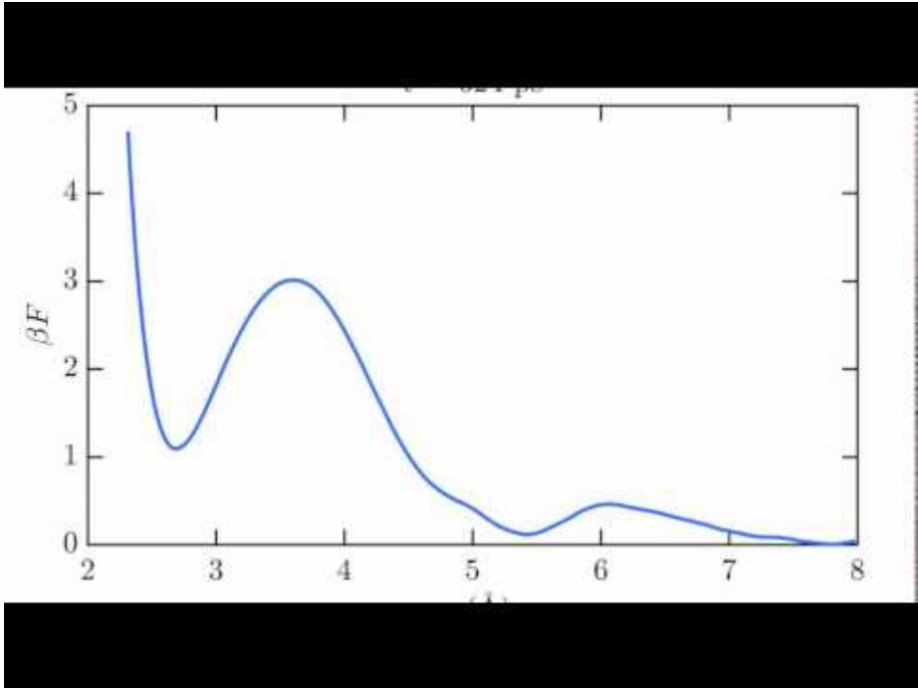
For an arbitrary vector field $\boldsymbol{w}$ such that $\boldsymbol{w}_i . \nabla \mathbf{S}_j \neq 0$

$$\frac{\partial F(\boldsymbol{S})}{\partial \boldsymbol{S}} = \left\langle \nabla U . \frac{\boldsymbol{w}_i}{\boldsymbol{w}_i . \nabla \boldsymbol{S}} - k_B T \nabla . \frac{\boldsymbol{w}_i}{\boldsymbol{w}_i . \nabla \boldsymbol{S}} \right\rangle_{\boldsymbol{S}}$$

If we assume: $\boldsymbol{w}_i . \nabla \mathbf{S}_j = \delta_{ij}$

$$\frac{\partial F(\boldsymbol{S})}{\partial \boldsymbol{S}} = \langle \nabla U . \boldsymbol{w}_i - k_B T \nabla . \boldsymbol{w}_i \rangle_{\boldsymbol{S}}$$

PMF between an NaCl ion pair in water



M. J. Ruiz-Montero, D. Frenkel, and J. J. Brey. Mol. Phys., 90:925–941, 1997.
Montero, M. J.; Frenkel, D.; Brey, J. J. Mol. Phys. 1997, 90, 925–941
W. K. den Otter. J. Chem. Phys., 112:7283–7292, 2000.
G. Ciccotti, R. Kapral, and E. Vanden-Eijnden. Chem Phys Chem, 6(9):1809–1814, 2005

Viedo by Giovanni Bussi

Geometrical free energy calculation: Adaptive Biasing Force (eABF)

Extended-system ABF

Bias is not applied directly to the collective variable!

Bias is applied to an extended fictitious coordinate (λ) that evolves dynamically according to Newtonian or Langevin dynamics.

$$E^{extended}(\boldsymbol{S}, \lambda) = U(r) + \frac{k}{2}(\boldsymbol{S} - \lambda)^2$$

$$\sigma = \sqrt{\frac{k_B T}{k}} \qquad \tau = 2\pi\sqrt{\frac{m}{k}}$$

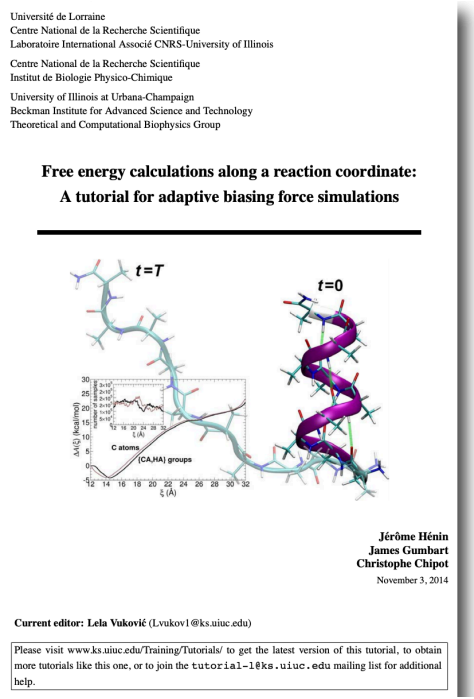
Corrected z-averaged restraint (CZAR) estimator of the free energy

$$\frac{\partial F(\boldsymbol{S})}{\partial \boldsymbol{S}} = -\frac{1}{\beta}\frac{\partial \ln N(\boldsymbol{S})}{\partial \boldsymbol{S}} + k(\langle\lambda\rangle_{\boldsymbol{S}} - \boldsymbol{S})$$

A. Lesage, T. Lelièvre, G. Stoltz, and J. Hénin. *J. Phys. Chem. B*

Free energy tutorials

http://www.ks.uiuc.edu/Training/Tutorials/#freeenergymethods



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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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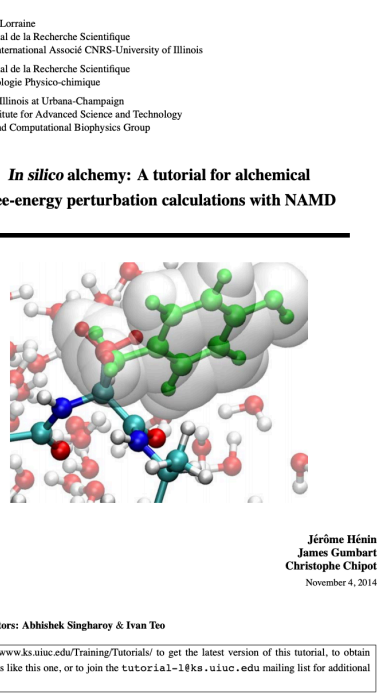

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***In silico* alchemy: A tutorial for alchemical free-energy perturbation calculations with NAMD**

Jérôme Hénin
James Gumbart
Christophe Chipot
November 4, 2014

Current editors: Abhishek Singharoy & Ivan Teo

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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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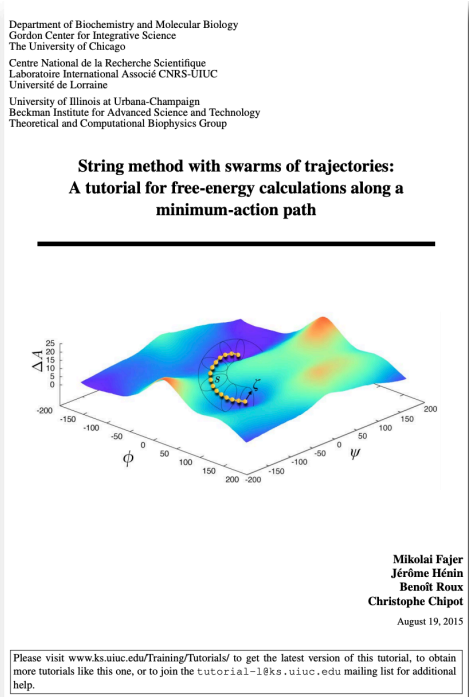

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String method with swarms of trajectories: A tutorial for free-energy calculations along a minimum-action path

Mikolai Fajer
Jérôme Hénin
Benoît Roux
Christophe Chipot
August 19, 2015

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A. Lesage, T. Lelièvre, G. Stoltz, and J. Hénin. *J. Phys. Chem. B*

Acknowledgement

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Prof. Chris Chipot
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