Applying the Accelerated Weight Histogram method to alchemical transformations

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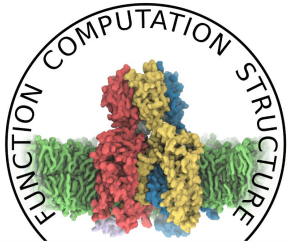


MOLECULAR BIOPHYSICS STOCKHOLM

ERCO PHARMA

Outline

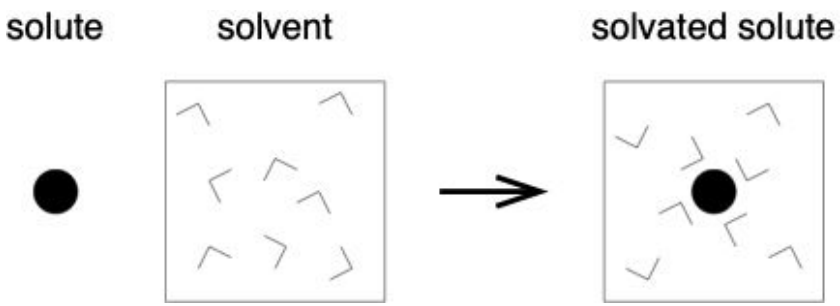
- Short introduction to alchemical free energy calculations
- The basics of AWH
- Examples of applications
- How to set up AWH free energy calculations in practice

Alchemical free energy calculations

Free energies differences give the relative population of states A and B:

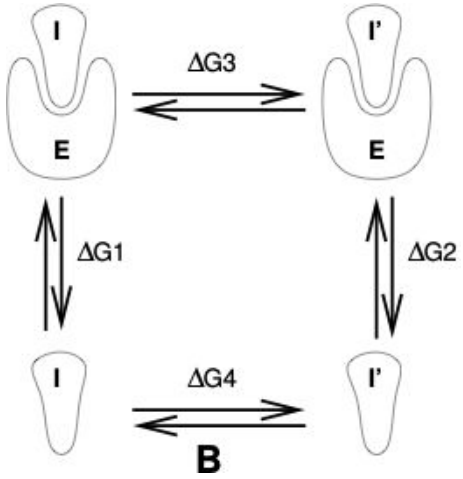
$P_A / P_B = \exp(\Delta G / k_B T)$, free energy difference $\Delta G = G_2 - G_1$

Solvation free energy



Differences in binding free-energy

$\Delta\Delta G = \Delta G_1 - \Delta G_2$
$= \Delta G_3 - \Delta G_4$



How to couple states A and B?

Coupling parameter approach

- Add a coupling parameter λ to the Hamiltonian:

$$H = H(p,q;\lambda)$$

$$H(p,q;0) = H_A(p,q)\ ,\ H(p,q;1) = H_B(p,q)$$

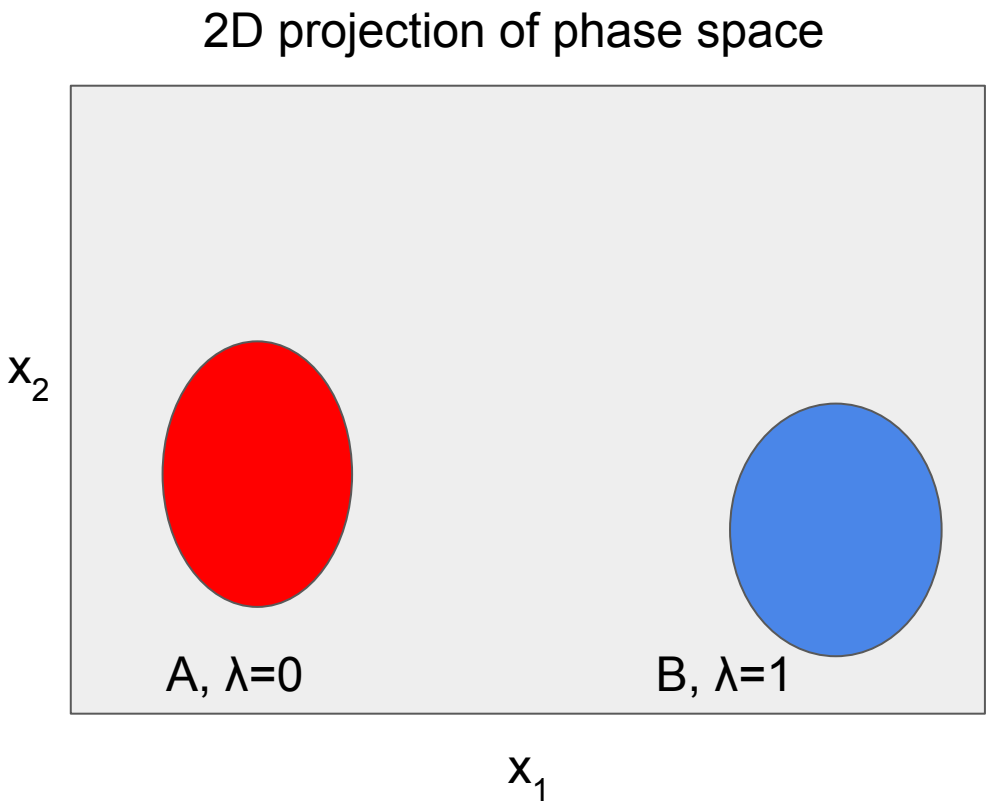
- Free energy is then given by:

$$G_B(p,T) - G_A(p,T) = \int_0^1 \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_{NPT;\lambda} d\lambda$$

There is often no overlap between the end states

In most cases the phase space distributions of states A and B have no overlap

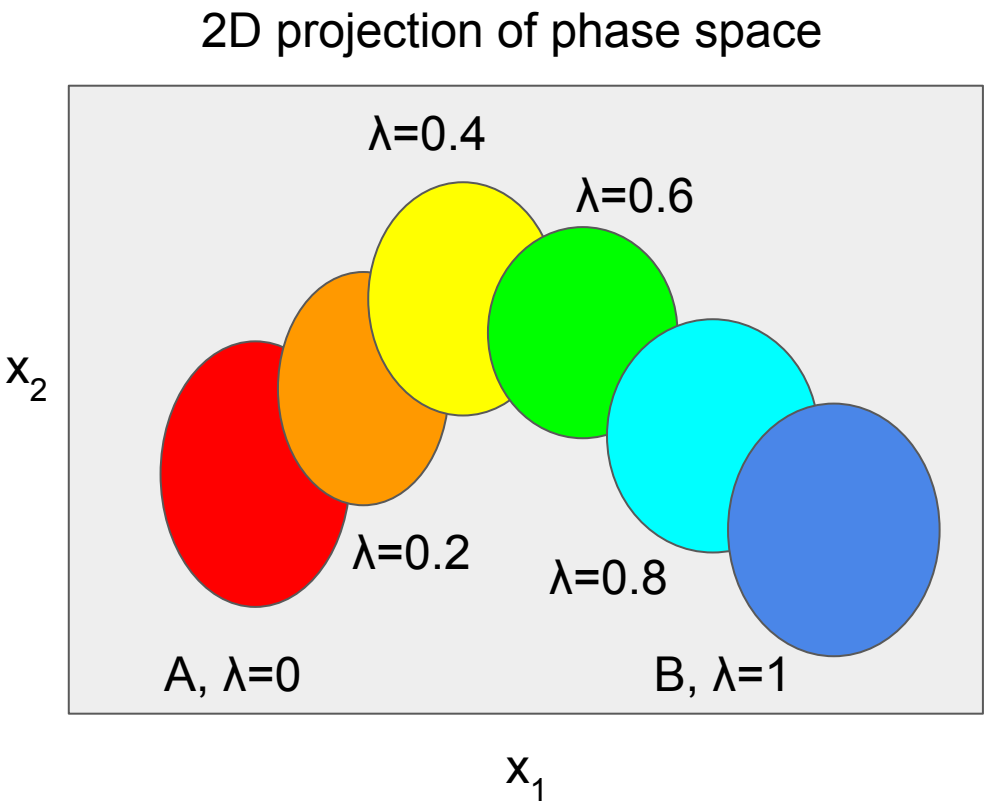
One could compute dH/dλ in A and B, but dH/dλ might vary a lot in between



We need to create overlap

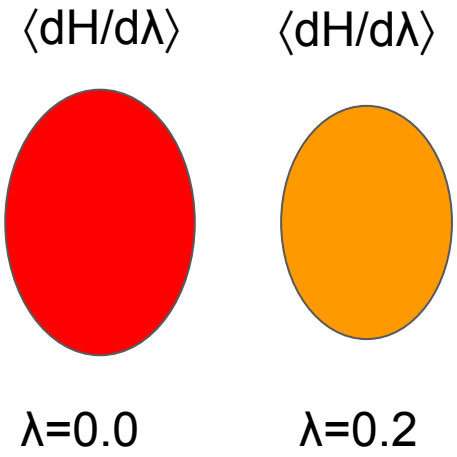
The λ-path is arbitrary, only the end states are given

- We need to choose an efficient path
- We need to choose points along the path

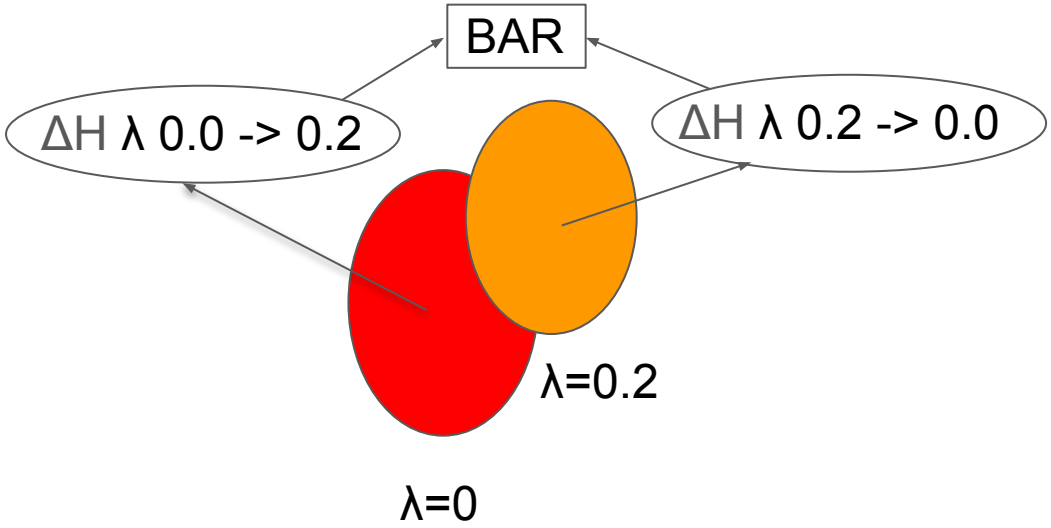


Computing the free energy differences

Thermodynamic integration
of dH/dλ, local operation, quadrature (integration) **error**



Bennett acceptance ratio
Uses Hamiltonian (energy) differences between two λ values both ways simultaneously



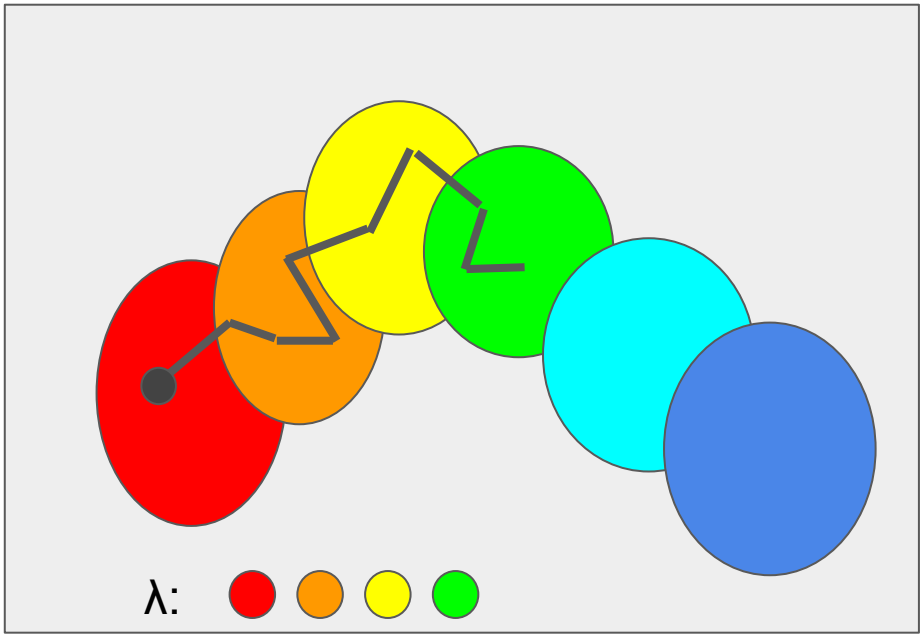
AWH moves λ dynamically

In a single simulation λ moves dynamically using Monte Carlo

A bias potential is added to λ to achieve uniform sampling

Hamiltonian differences are computed to all other λ values (like in MBAR)

2D projection of phase space



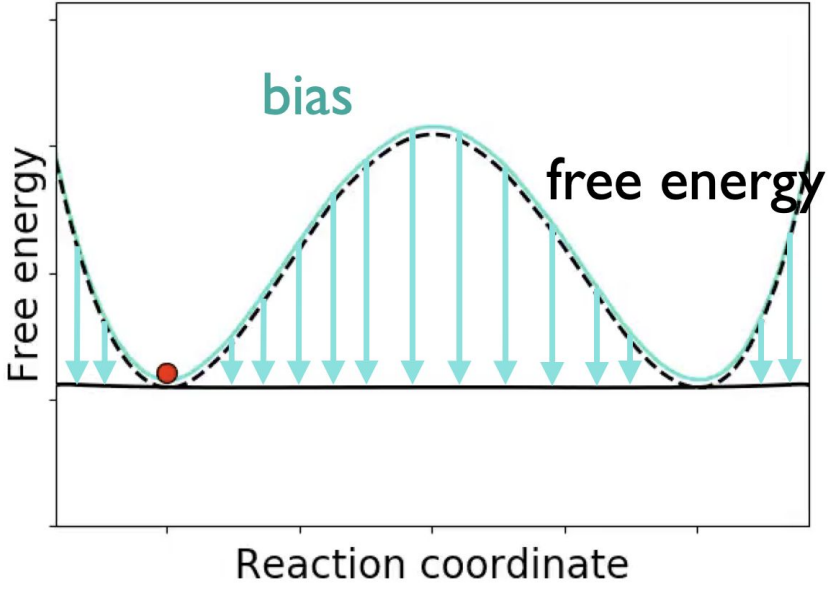
History of the Accelerated Weight Histogram method

- The method was originally developed as a general enhanced sampling method by Jack Lidmar "Improving the efficiency of extended ensemble simulations: The accelerated weight histogram method," Phys. Rev. E **85**, 056708 (2012). doi: 10.1103/PhysRevE.85.056708.
- Adapted for collective coordinates in MD and implemented in GROMACS by Viveca Lindahl V. Lindahl, J. Lidmar, and B. Hess, "Accelerated weight histogram method for exploring free energy landscapes," *The Journal of chemical physics*, **141** [4] 044110 (2014).
  BioExcel webinar in 2020: https://bioexcel.eu/webinar-accelerating-sampling-in-gromacs-with-the-awh-method-2019-09-24/
- A metric was devised for reaction coordinates V. Lindahl, J. Lidmar, and B. Hess, "Riemann metric approach to optimal sampling of multidimensional free-energy landscapes," Phys. Rev. E **98**, 023312 (2018). doi: 10.1103/PhysRevE.98.023312.
- A manuscript on AWH for alchemical free-energy calculations has been submitted (Magnus Lundborg, Jack Lidmar, Berk Hess)

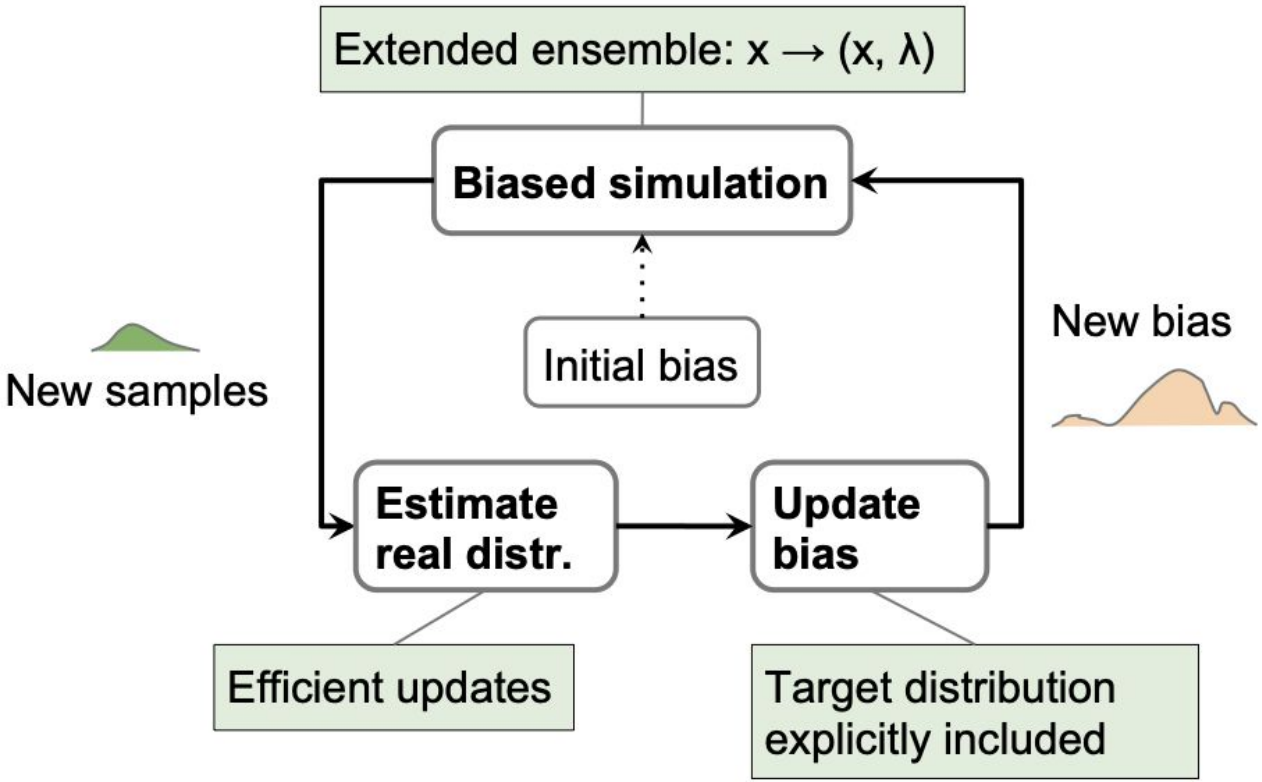
Flatten the free-energy landscape

Trick: add a bias potential to make the effective potential flat

Issue: the potential (or free-energy) is what we are after!



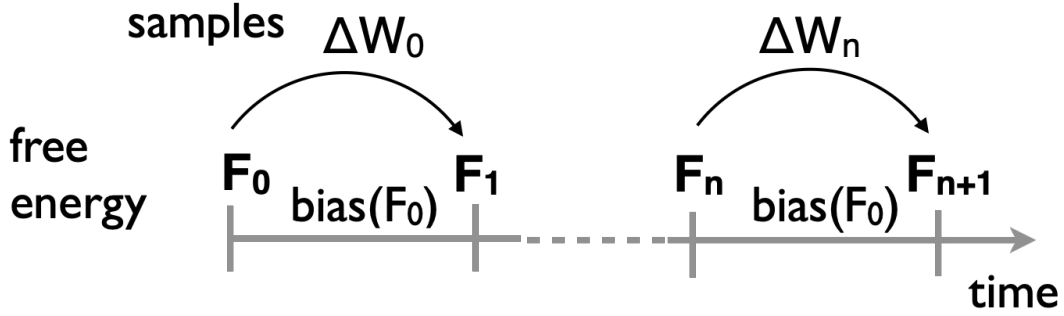
AWH schemetically



The Accelerated Weight Histogram method

Iterative scheme to solve for the unknown bias / free-energy:

- collect samples (using MD)
- update the free-energy estimate



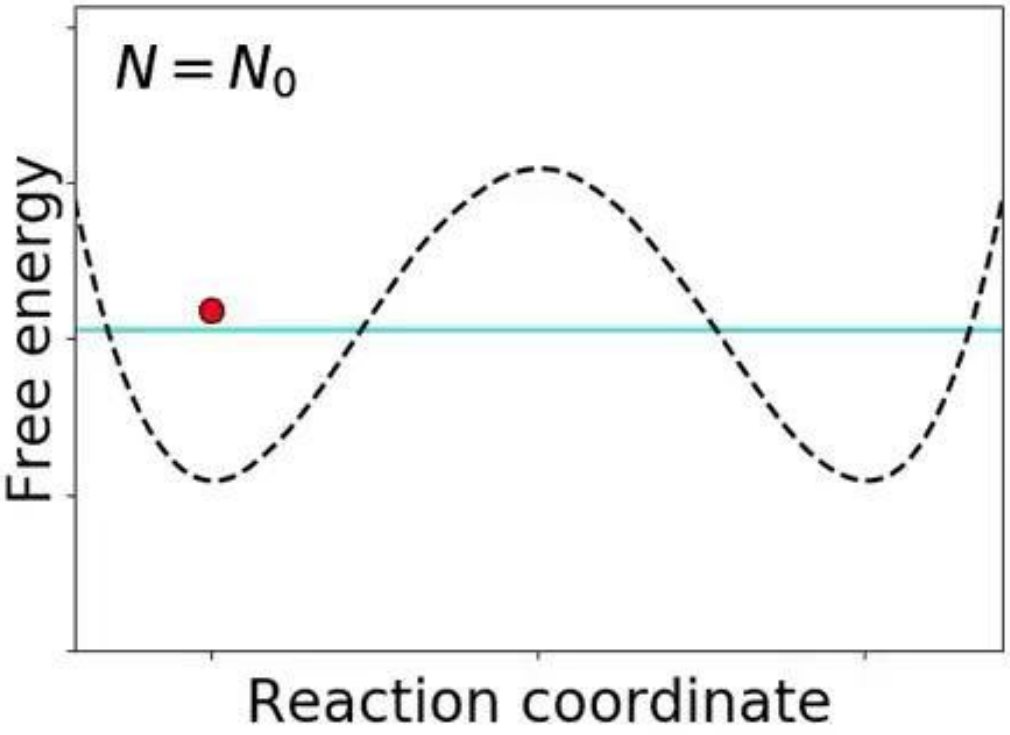
$$\Delta F_n(\lambda) = -\ln\left(1 + \frac{\Delta W_n(\lambda)}{N_n \pi(\lambda)}\right) \sim \frac{1}{N_n}$$

collected samples

prior number of samples

target distribution (flat)

AWH in action (on model double-well potential)



Ensemble parallelism using multiple “walkers”

AWH can be “trivially” parallelized by having multiple copies of the system, so called “walkers”, contribute to the same AWH bias

- Work for any number of walkers
- Reduces time to solution

Choices for AWH free energy calculations

There are few option / parameter choices to make:

- Number of walkers -> choose freely according to your resources
- Number of lambda points -> choose sufficiently many
- AWH diffusion coefficient / initial error -> choose 0.001 ps^{-1} / 10 kJ/mol

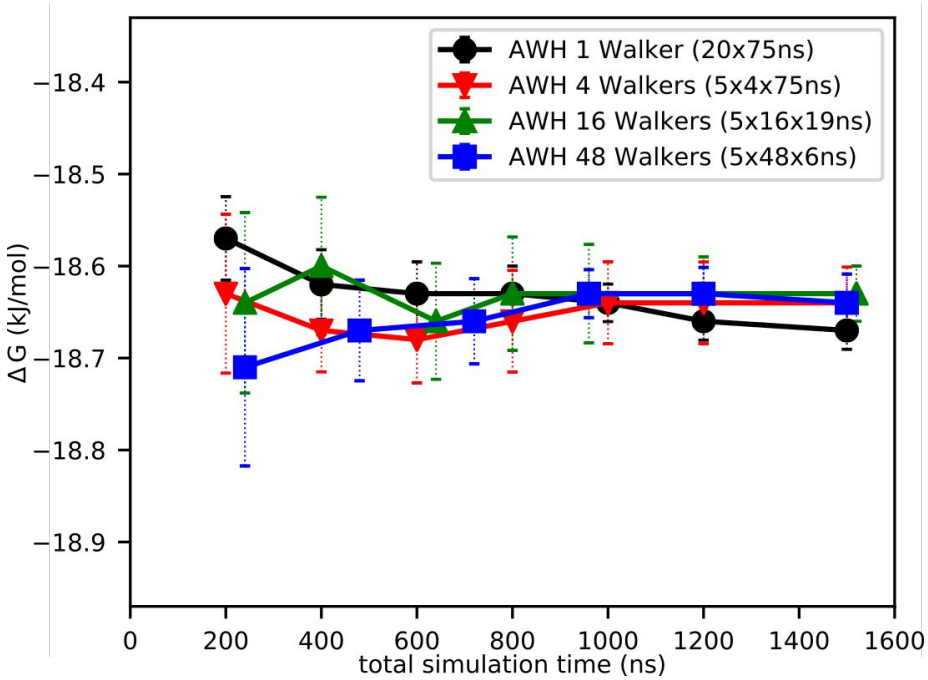
The initial update size for AWH needs to be set, we do this through a diffusion coefficient and initial error. These parameters are not sensitive

Advantages of AWH: easy to set up, no sensitive parameters!

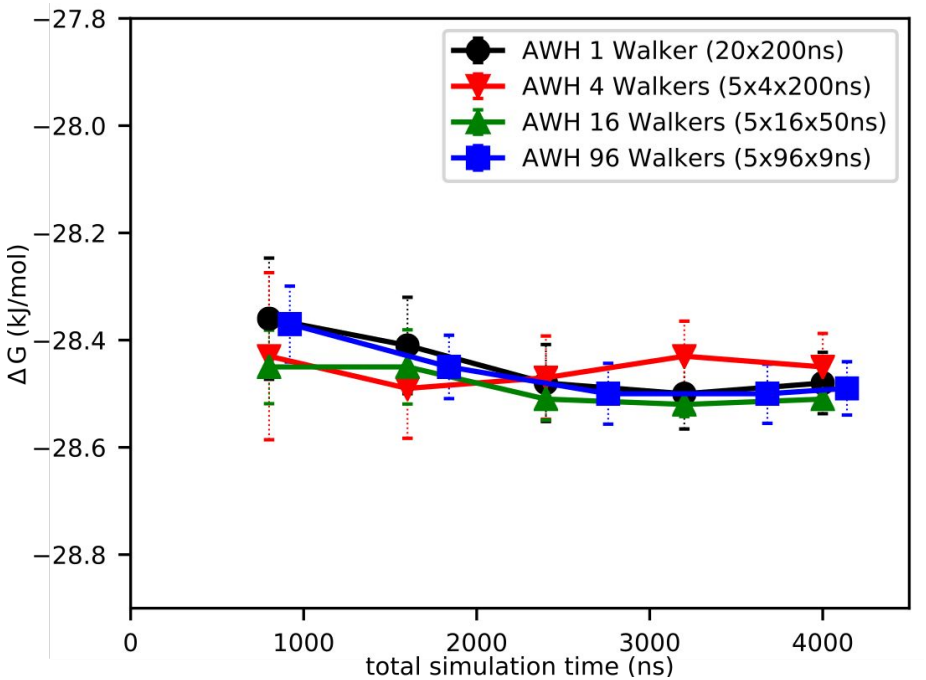
Some examples

Number of walkers

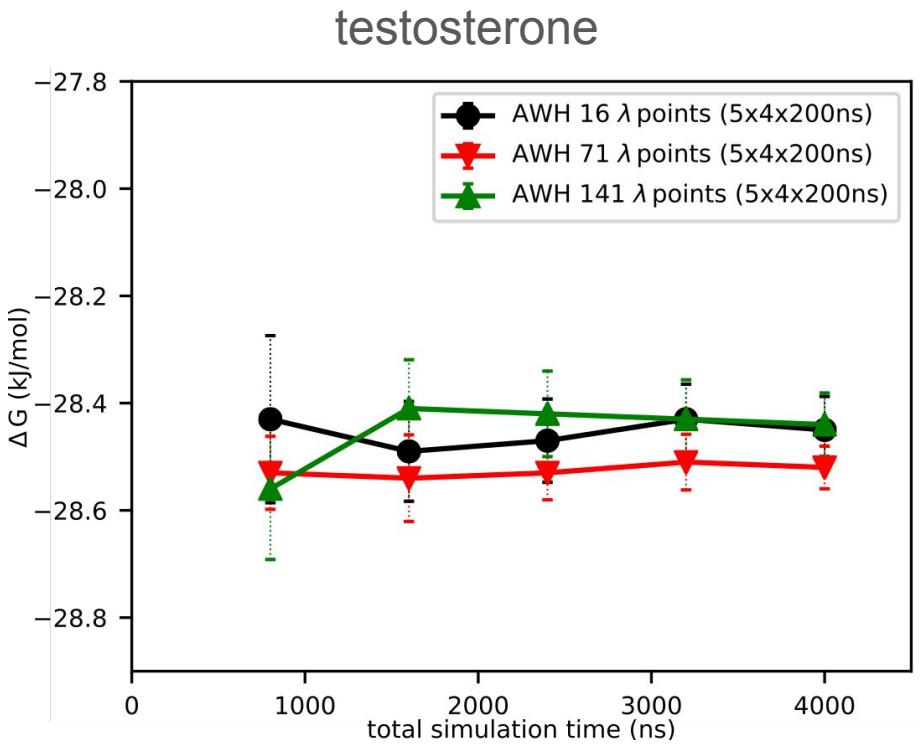
ethanol



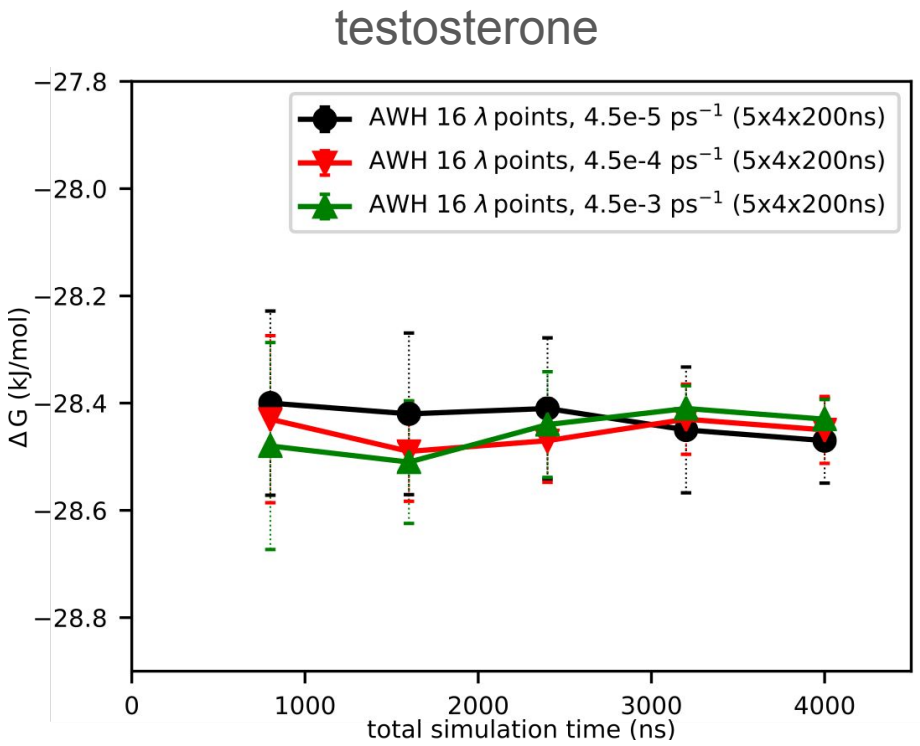
testosterone



Number of lambda points

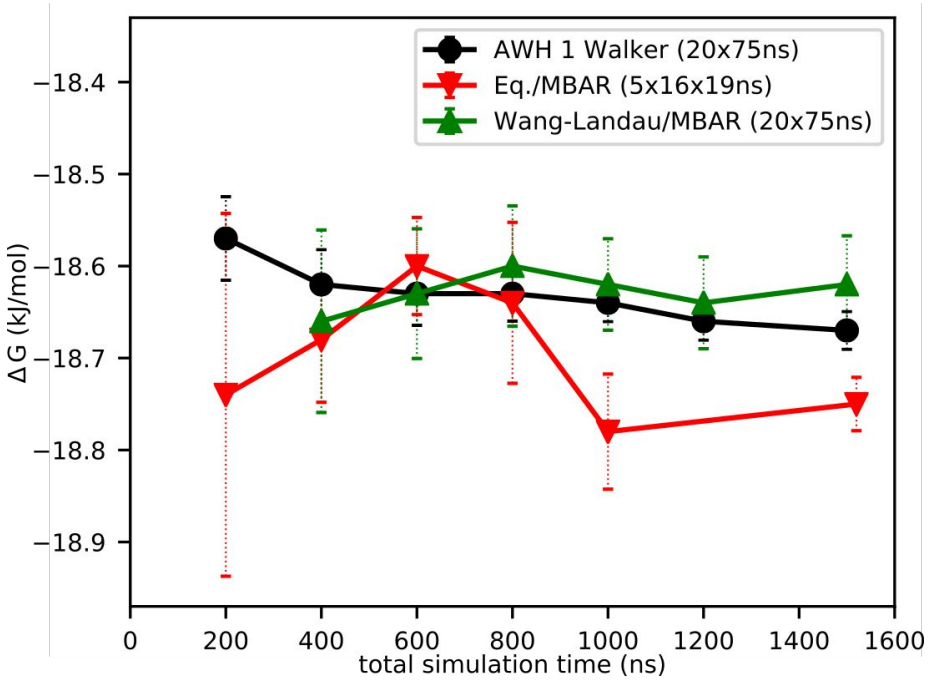


AWH diffusion coefficient



Convergence

ethanol



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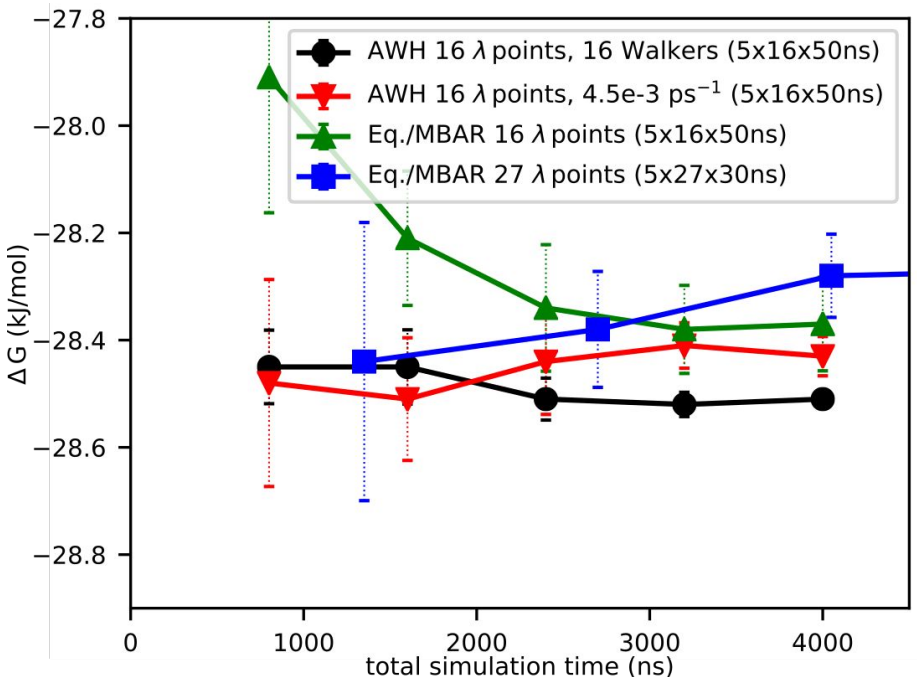
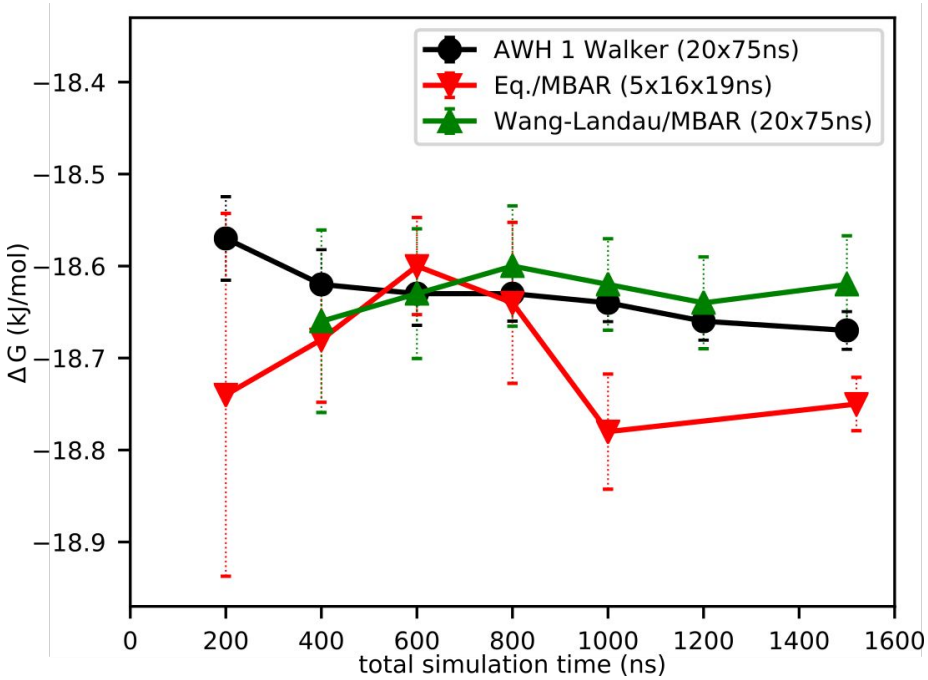


Convergence

ethanol



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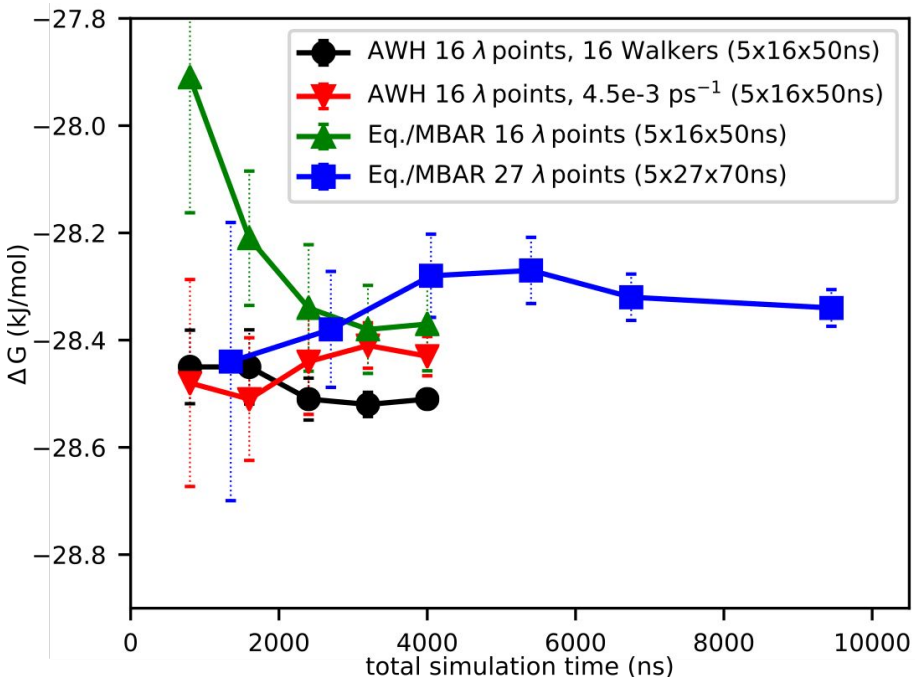
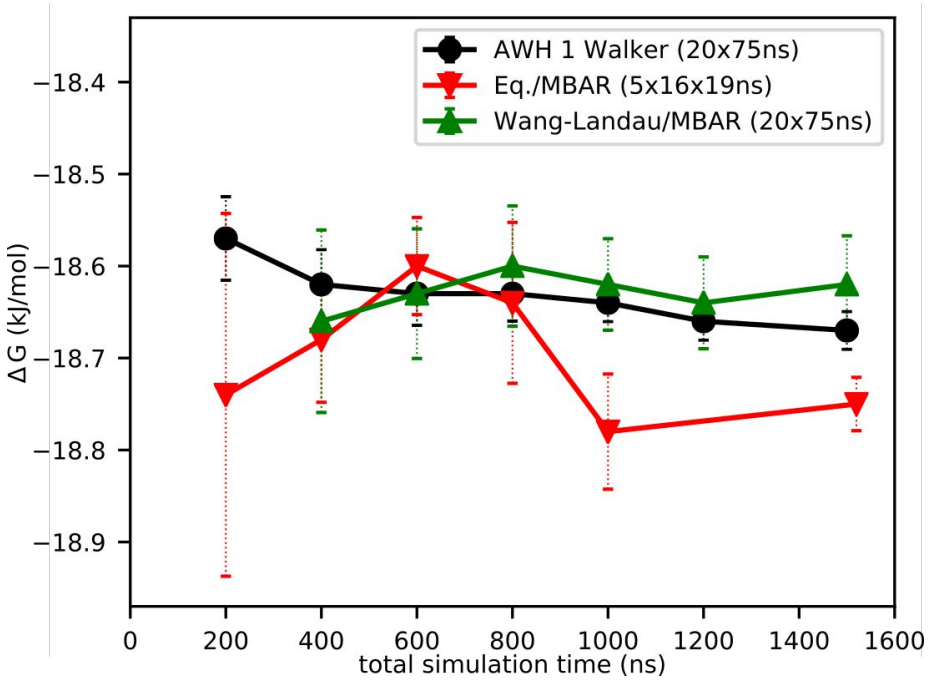


Convergence

ethanol



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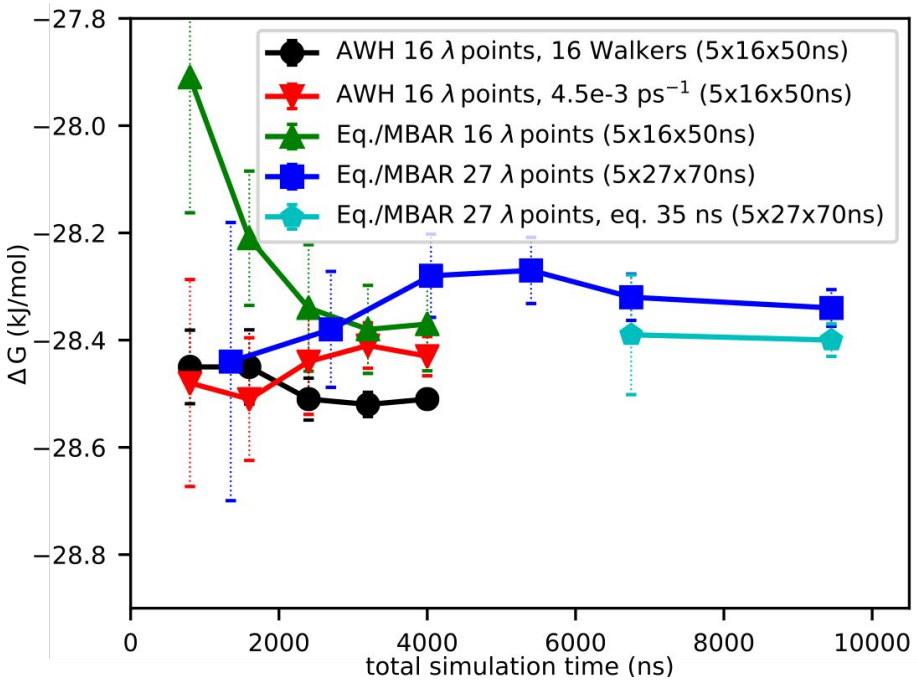

Permeability calculations through skin lipid barrier

- Complex Lipid system in near gel-state - slow diffusion through the system and slow convergence.

Lundborg et al., J. Struct. Biol. 2018, 203, 149-161

Permeability calculations through skin lipid barrier

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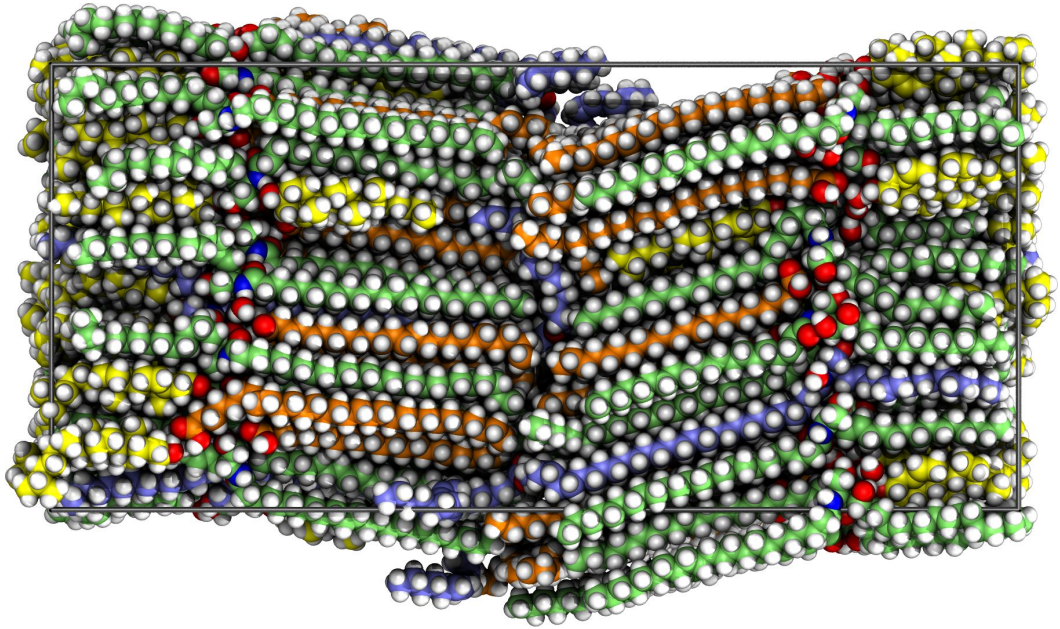
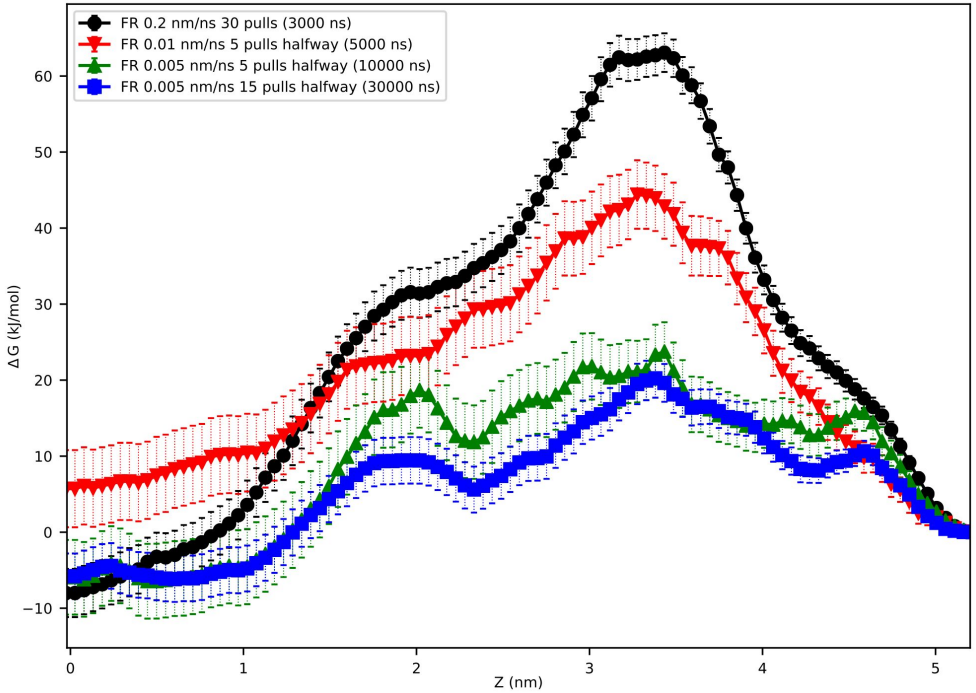


Permeability calculations through skin lipid barrier

- Nonequilibrium pulling (FR method) was sensitive to the pulling speed.

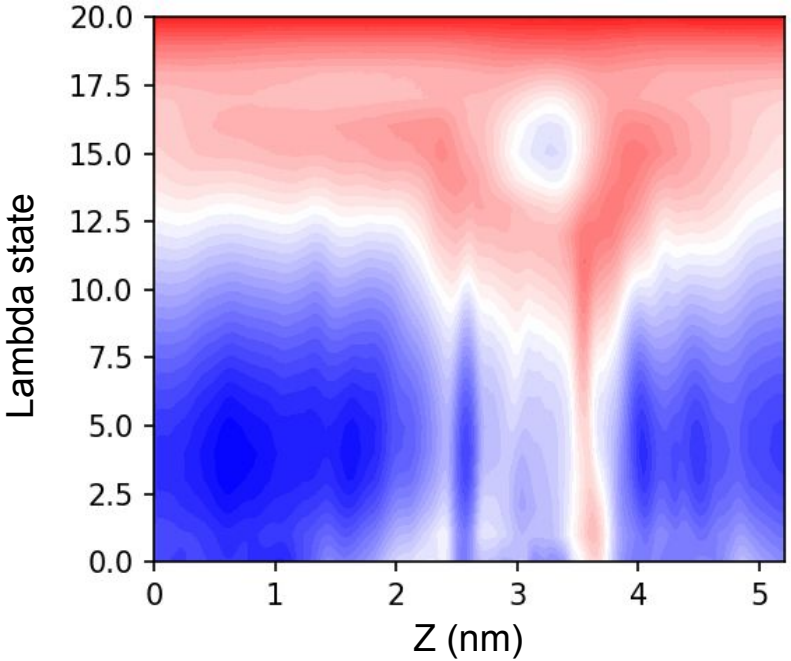


Permeability calculations through skin lipid barrier

- Umbrella sampling required very long simulations and long equilibration times.

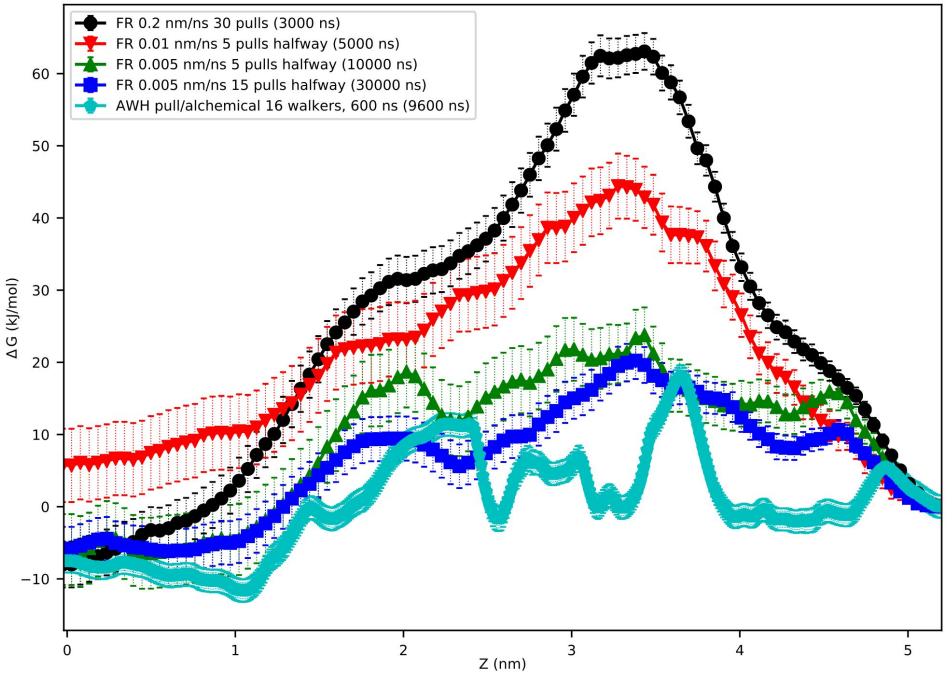
Permeability calculations through skin lipid barrier

- Combining an alchemical reaction coordinate dimension with a pull dimension.



Permeability calculations through skin lipid barrier

- Combining an alchemical reaction coordinate dimension with a pull dimension.



Error estimation

- No error estimation from the analysis.
- Repeat simulations
  - Most certain error estimate for equilibrium simulations as well.

Relevant GROMACS simulation parameters

- free-energy
  - Lambda states
    - Not necessary to optimize the lambda point distribution.
  - calc-lambda-neighbors = -1

Relevant GROMACS simulation parameters

- awh
  - awh-potential = umbrella
  - awh-nstsample : a multiple of nstcalcenergy
  - awh1-dim1-coord-provider = fep-lambda
  - awh1-dim1-start and -end : the indices of the first and last lambda points
  - awh1-dim1-diffusion : as high as “possible” (~10^{-2} to 10^{-4} ps^{-1})
  - awh1-equilibrate-histogram : recommended if running multiple walkers

Example mdp input (free-energy options)

```
free-energy             = yes
couple-lambda0          = none
couple-lambda1          = vdwq
couple-moltype          = ethanol
couple-intramol         = no
init-lambda-state       = 15
vdw-lambdas             = 1.0 1.00 1.00 1.00 1.00 1.00 0.90 0.80 0.70
0.60 0.50 0.40 0.30 0.20 0.10 0.00
coul-lambdas            = 1.0 0.80 0.60 0.40 0.20 0.00 0.00 0.00 0.00
0.00 0.00 0.00 0.00 0.00 0.00 0.00
calc-lambda-neighbors   = -1
separate-dhdl-file      = no
sc_alpha                = 0.5
sc_sigma                = 0.3
sc_power                = 1
sc_coul                 = no
```

Example mdp input (awh options)

```
awh                    = yes
awh-potential          = umbrella
awh-nstout             = 500000
awh-nbias              = 1
awh-nstsample          = 10
awh-nsamples-update    = 10
awh1-error-init        = 10
awh1-equilibrate-histogram = no
awh1-target            = constant
awh1-growth            = exp-linear
awh1-ndim              = 1
awh1-dim1-coord-provider = fep-lambda
awh1-dim1-coord-index = 1
awh1-dim1-start        = 0
awh1-dim1-end          = 15
awh1-dim1-diffusion    = 0.002
```

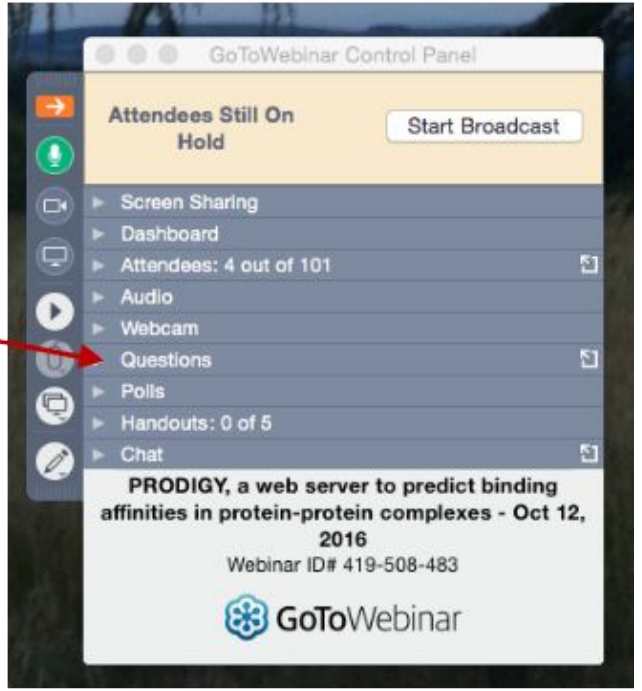
Summary

- AWH can be used for alchemical free energy calculations in GROMACS 2021
- Not very sensitive to the input parameters, such as the distribution, and number, of lambda states.
- Converges at least as quickly as equilibration simulations.
- Trivial parallelization with flexible number of copies of the system.
- Can be combined with other AWH reaction coordinates.

Audience Q&A session

- Please use the Questions function in GoToWebinar application
  - If you *don't have audio*, please mention that in the question.

- Any other questions or points to discuss after the live webinar? Join the discussions at http://ask.bioexcel.eu.



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