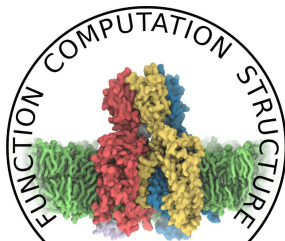


Applying the Accelerated Weight Histogram method to alchemical transformations

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MOLECULAR BIOPHYSICS STOCKHOLM



Outline

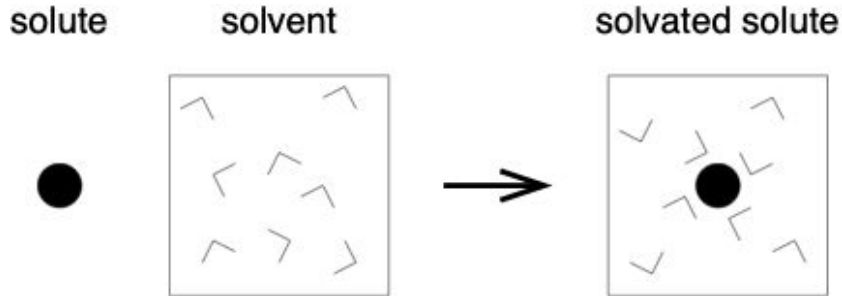
- Short introduction to alchemical free energy calculations
- The basics of AWH
- Examples of applications
- How to set up AWH free energy calculations in practice

Alchemical free energy calculations

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

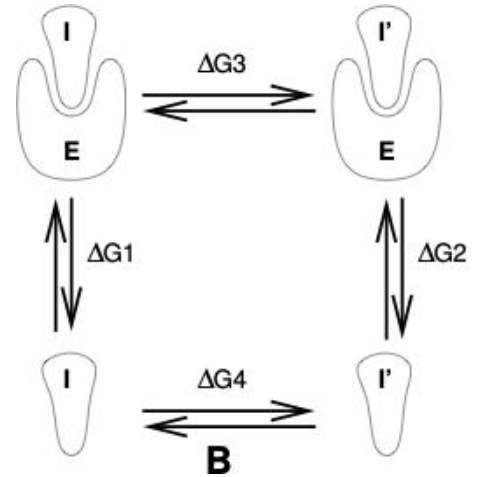
$$P_A / P_B = \exp(\Delta G / k_B T), \quad \text{free energy difference } \Delta G = G_2 - G_1$$

Solvation free energy



Differences in binding free-energy

$$\begin{aligned} \Delta\Delta G &= \Delta G_1 - \Delta G_2 \\ &= \Delta G_3 - \Delta G_4 \end{aligned}$$



How to couple states A and B?

Coupling parameter approach

- Add a coupling parameter λ to the Hamiltonian:

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

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

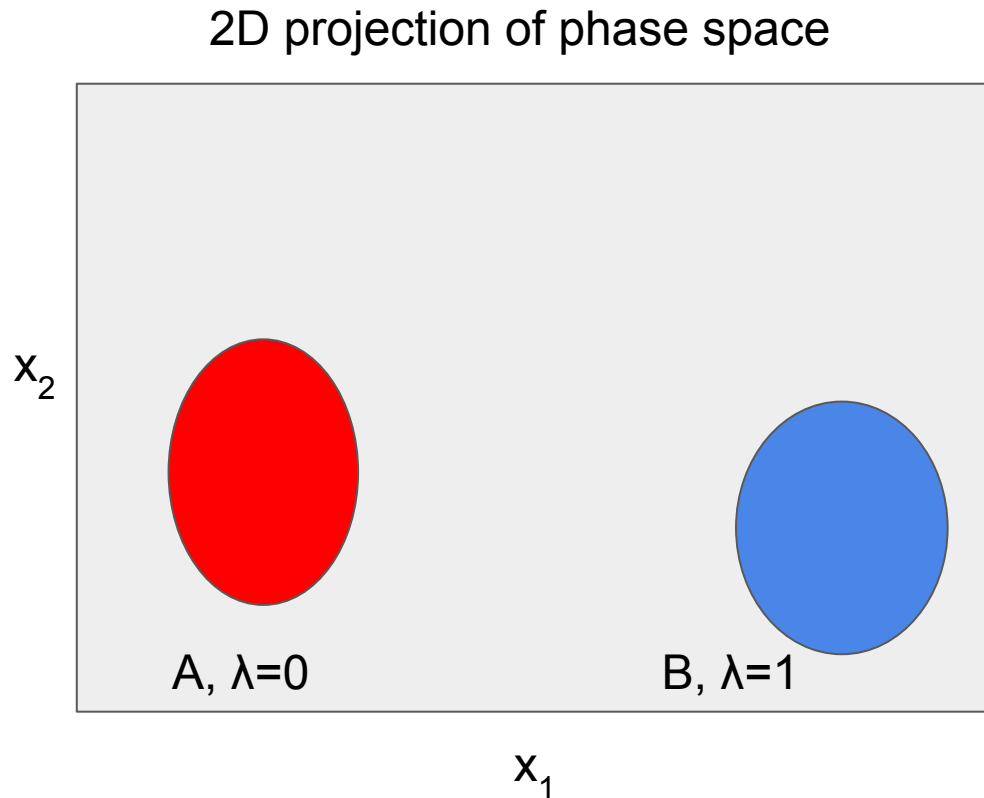
- Free energy is then given by:

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

There is often no overlap between the end states

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

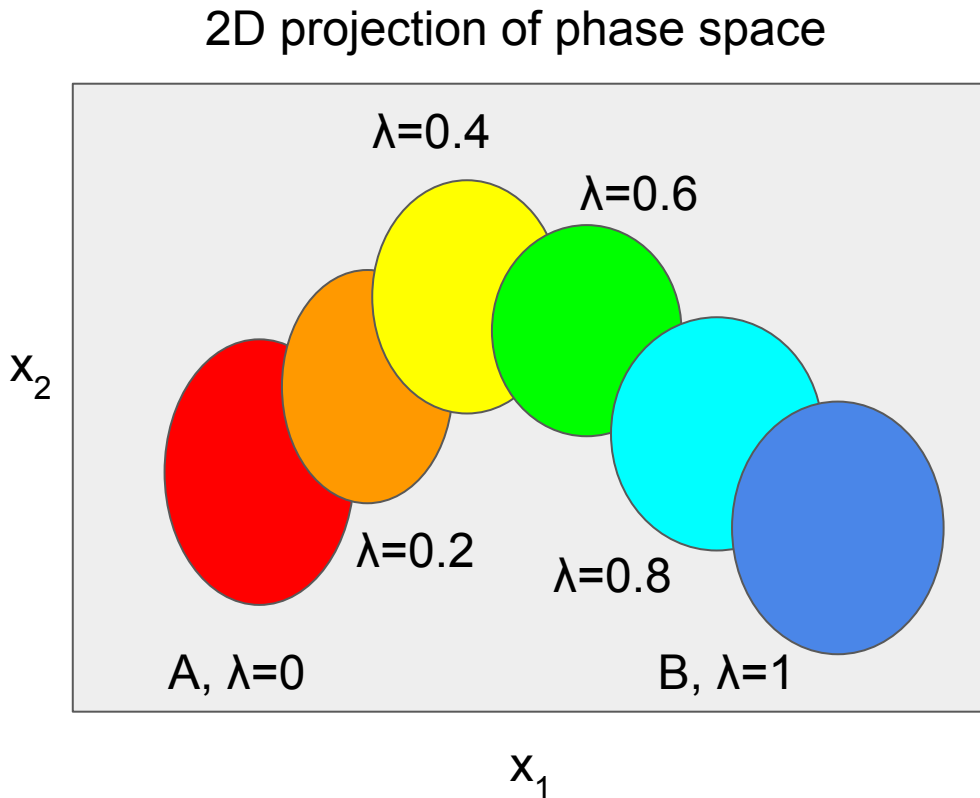
One could compute $dH/d\lambda$ in A and B, but $dH/d\lambda$ might vary a lot in between



We need to create overlap

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

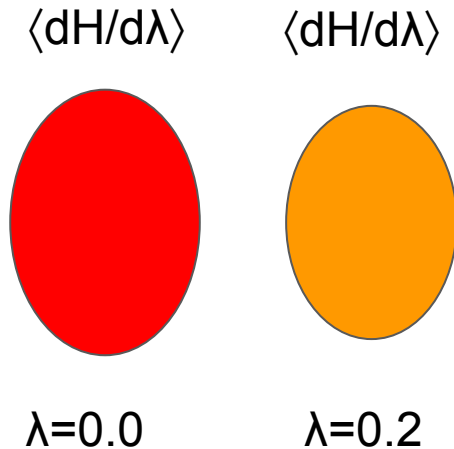
- We need to choose an efficient path
- We need to choose points along the path



Computing the free energy differences

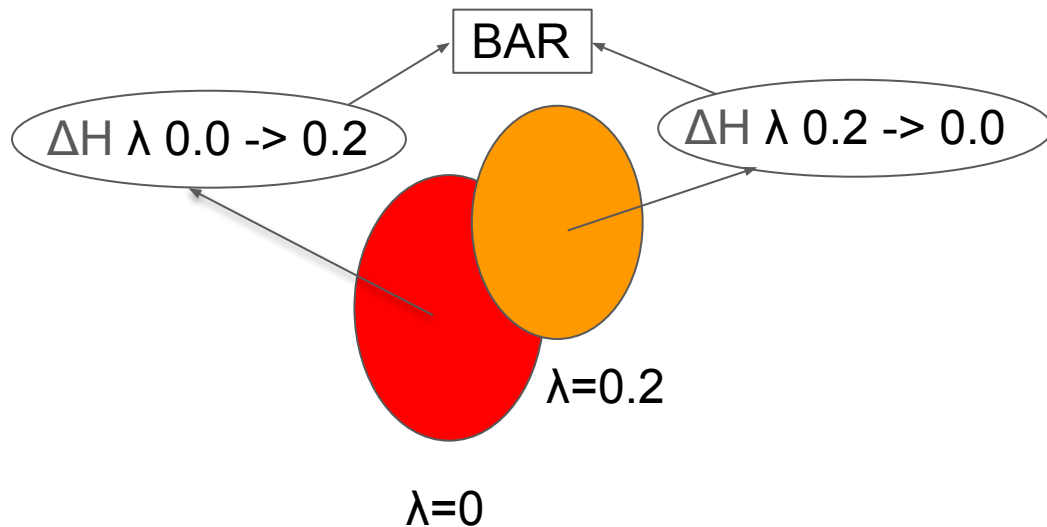
Thermodynamic integration

of $dH/d\lambda$, local operation,
quadrature (integration) **error**



Bennett acceptance ratio

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



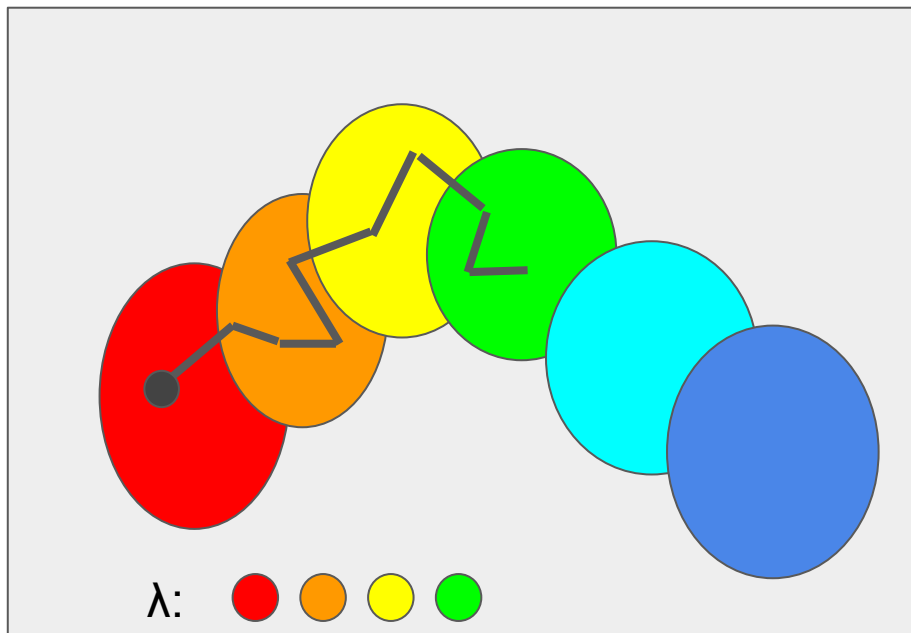
AWH moves λ dynamically

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



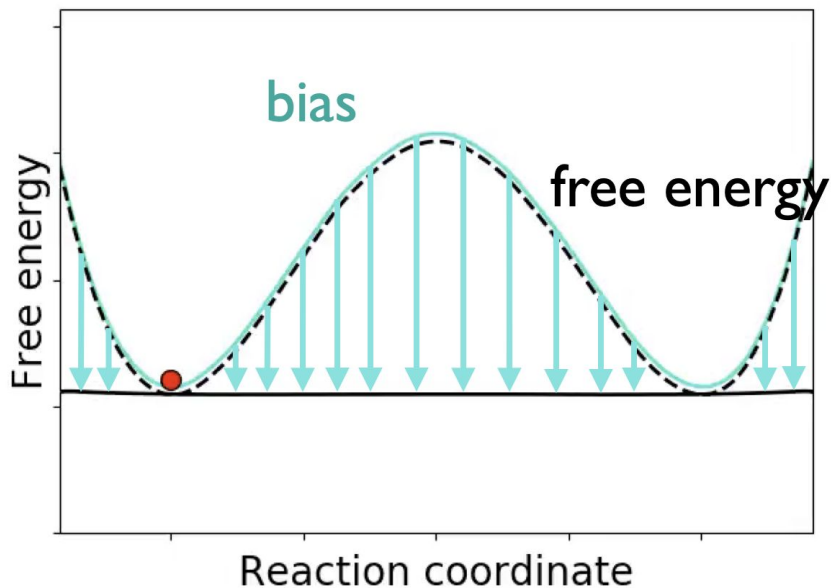
History of the Accelerated Weight Histogram method

- 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)

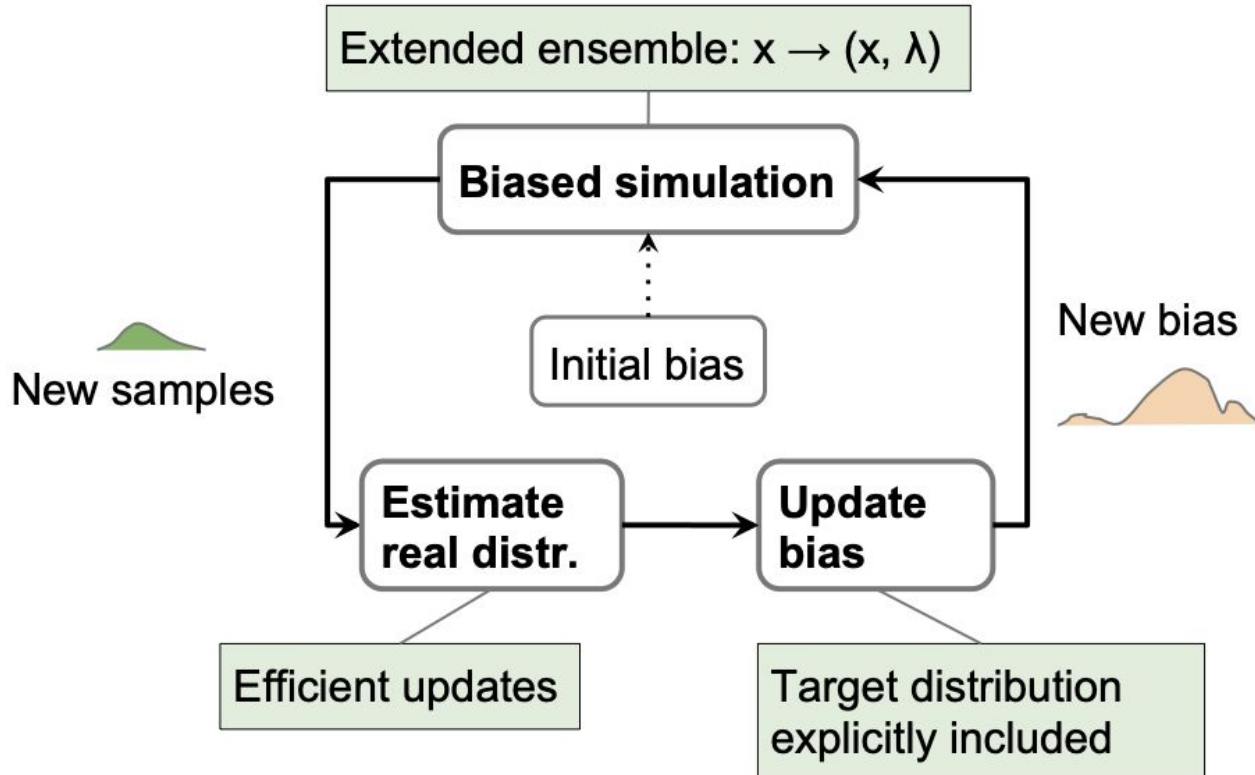
Flatten the free-energy landscape

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

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



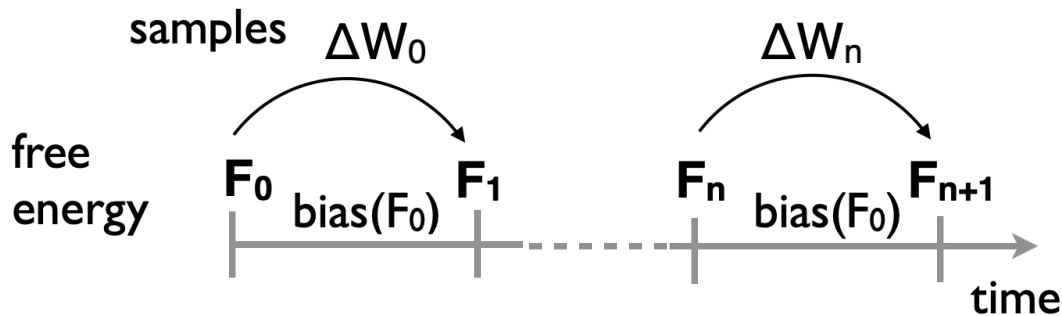
AWH schemetically



The Accelerated Weight Histogram method

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

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



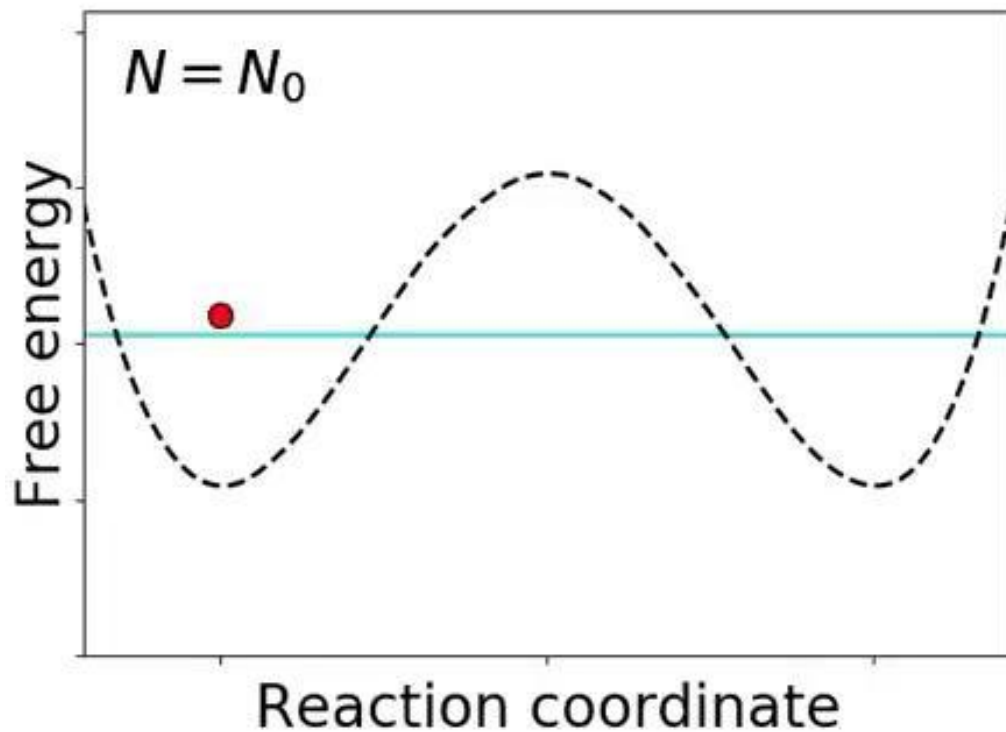
$$\Delta F_n(\lambda) = -\ln \left(1 + \frac{\Delta W_n(\lambda)}{N_n \pi(\lambda)} \right) \sim \frac{1}{N_n}$$

collected samples

prior number of samples

target distribution (flat)

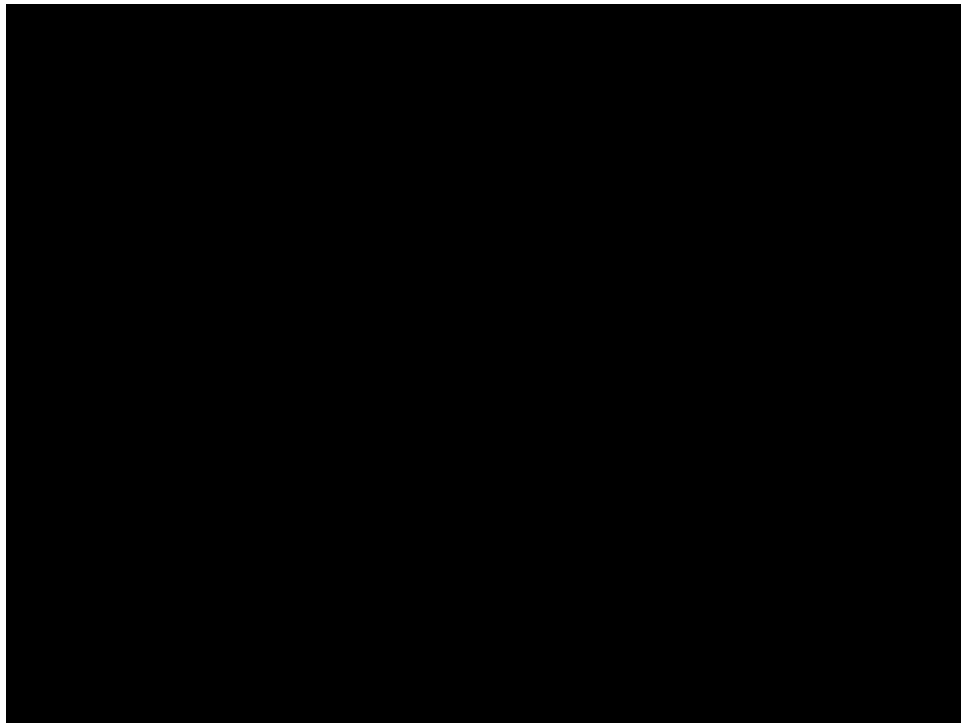
AWH in action (on model double-well potential)



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

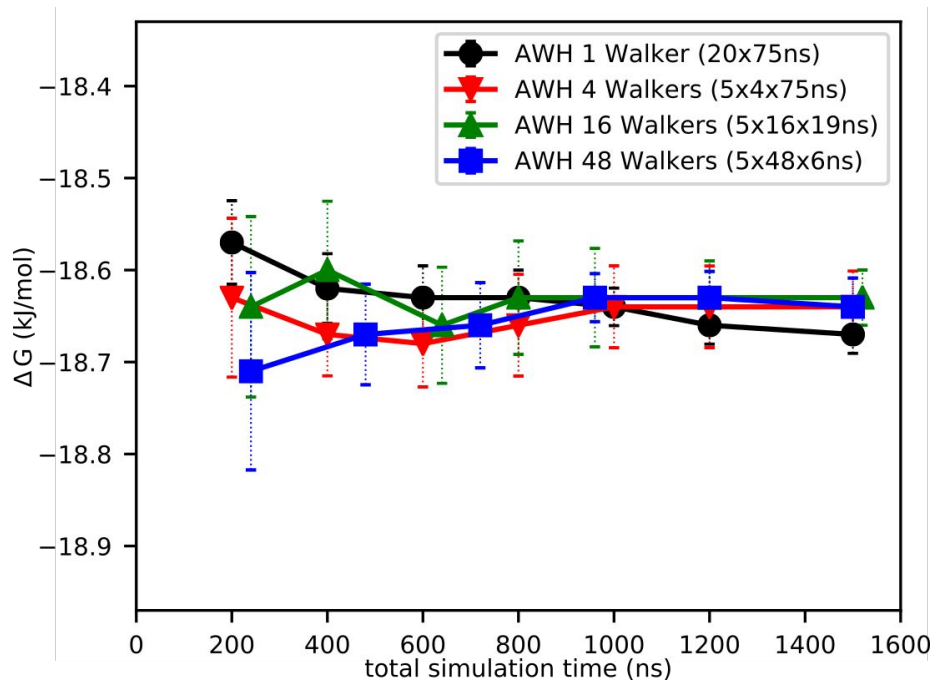
The initial update size for AWH needs to be set, we do this through a diffusion coefficient and initial error. These parameters are not sensitive

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

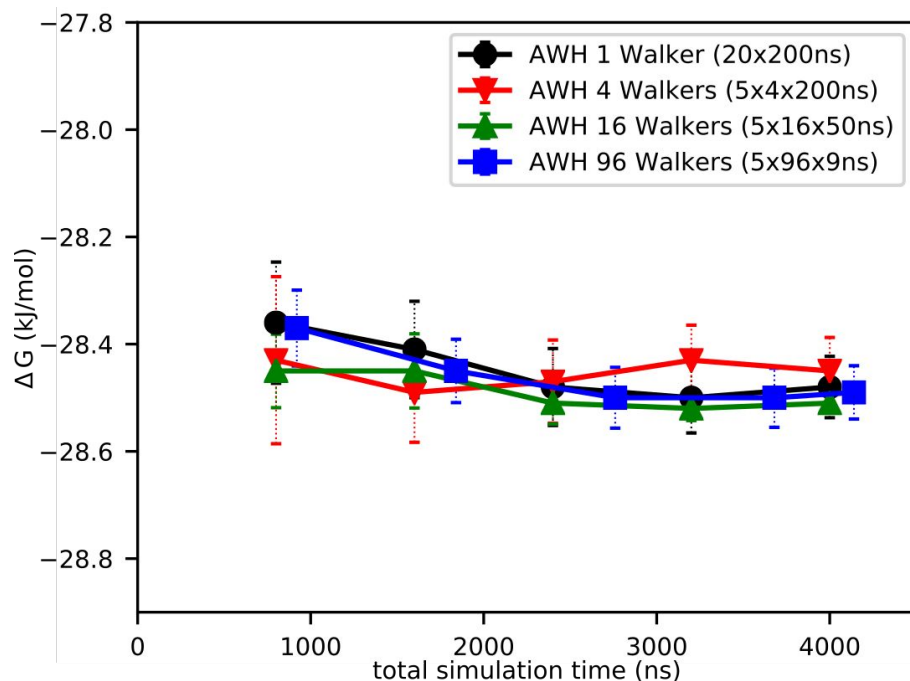
Some examples

Number of walkers

ethanol

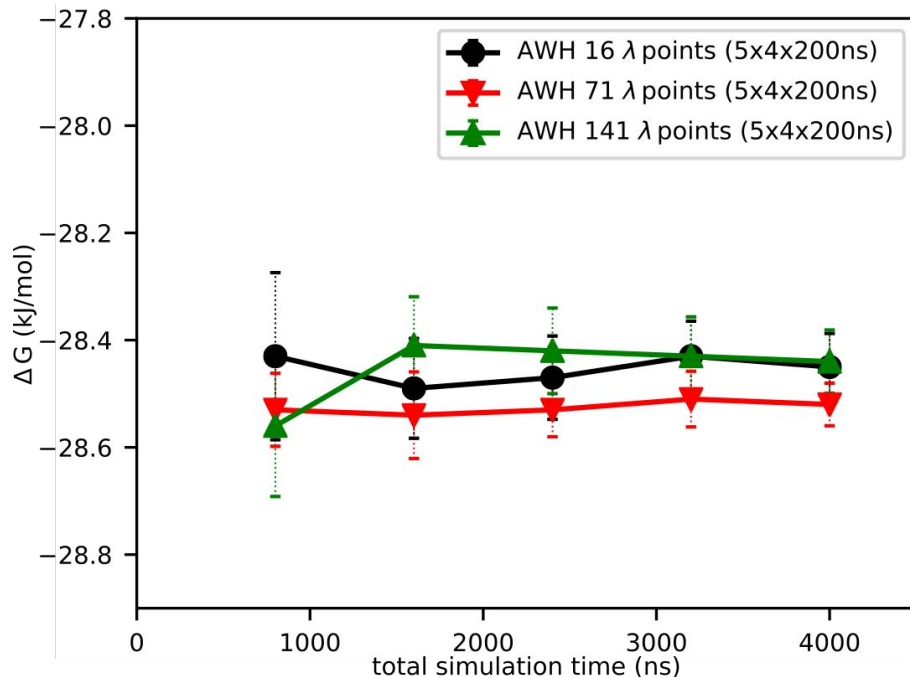


testosterone



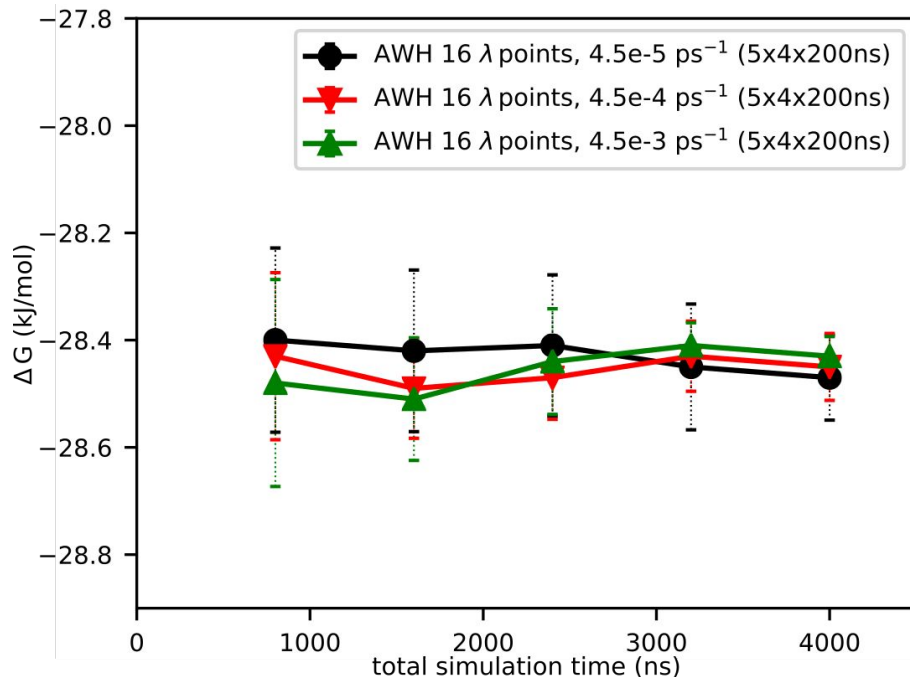
Number of lambda points

testosterone



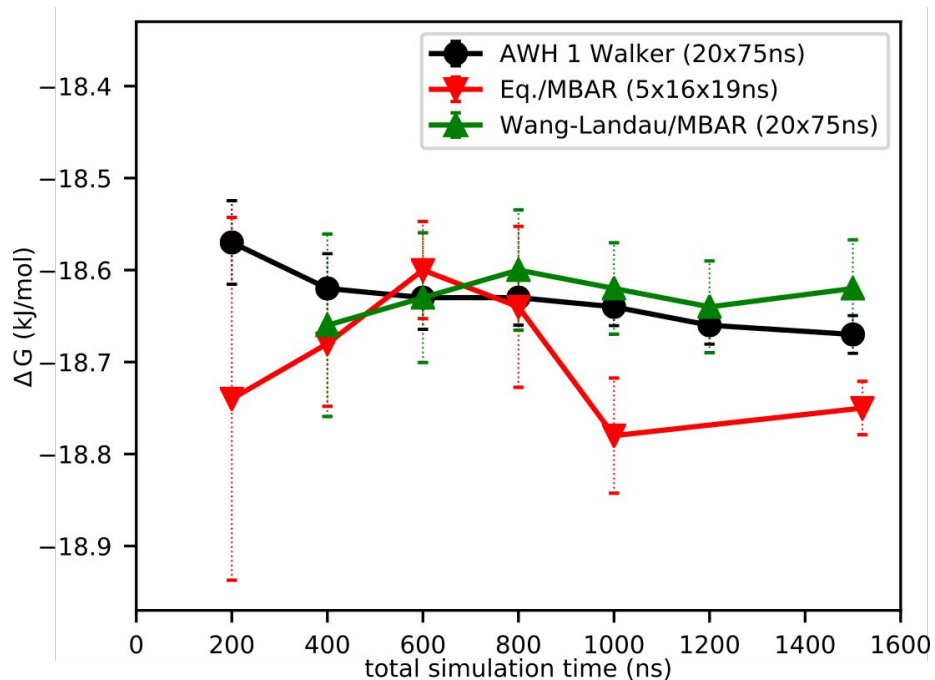
AWH diffusion coefficient

testosterone

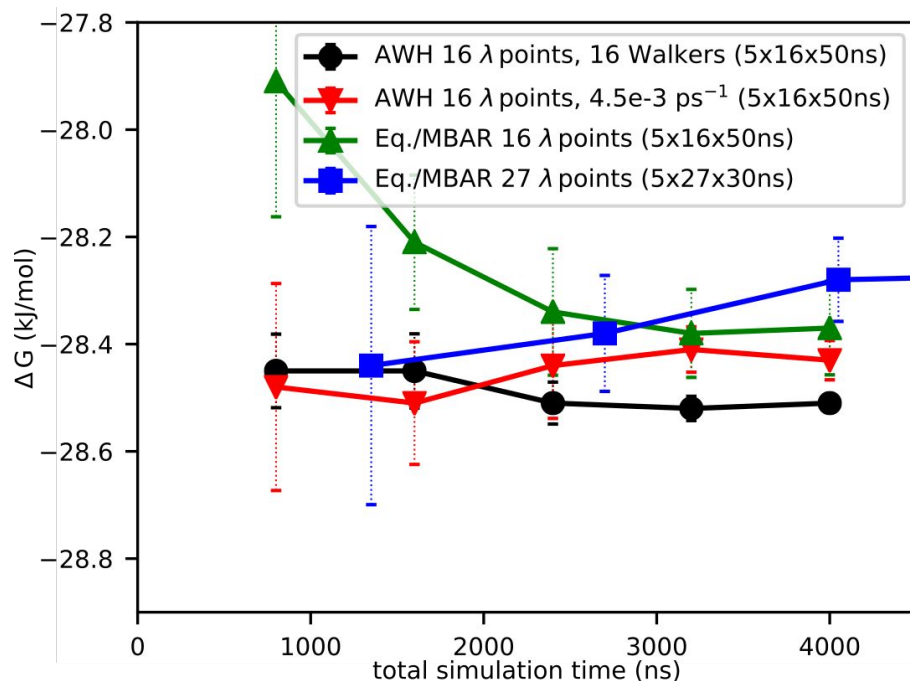


Convergence

ethanol

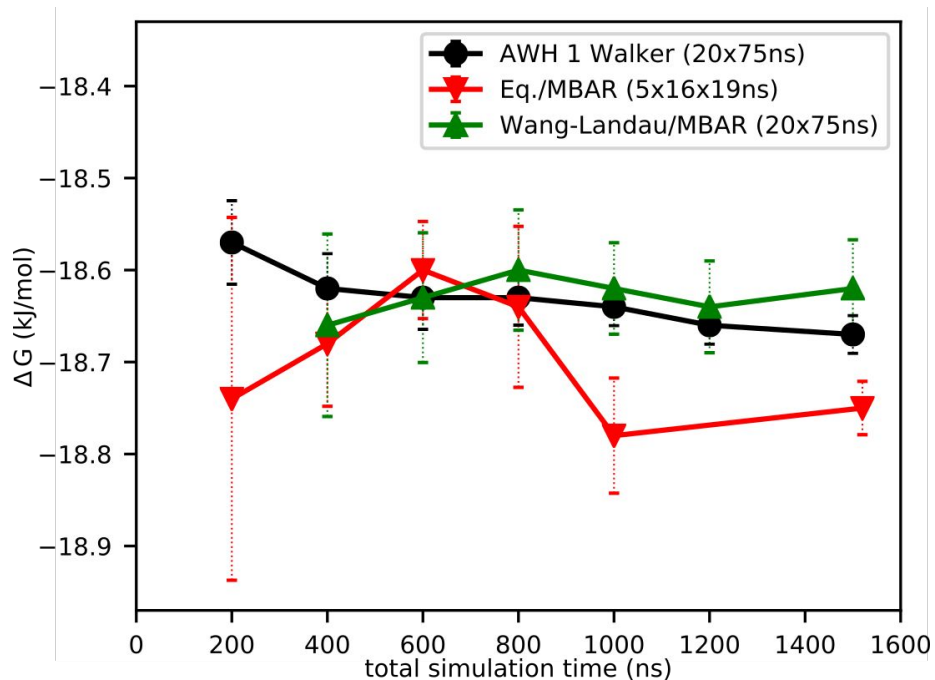


testosterone

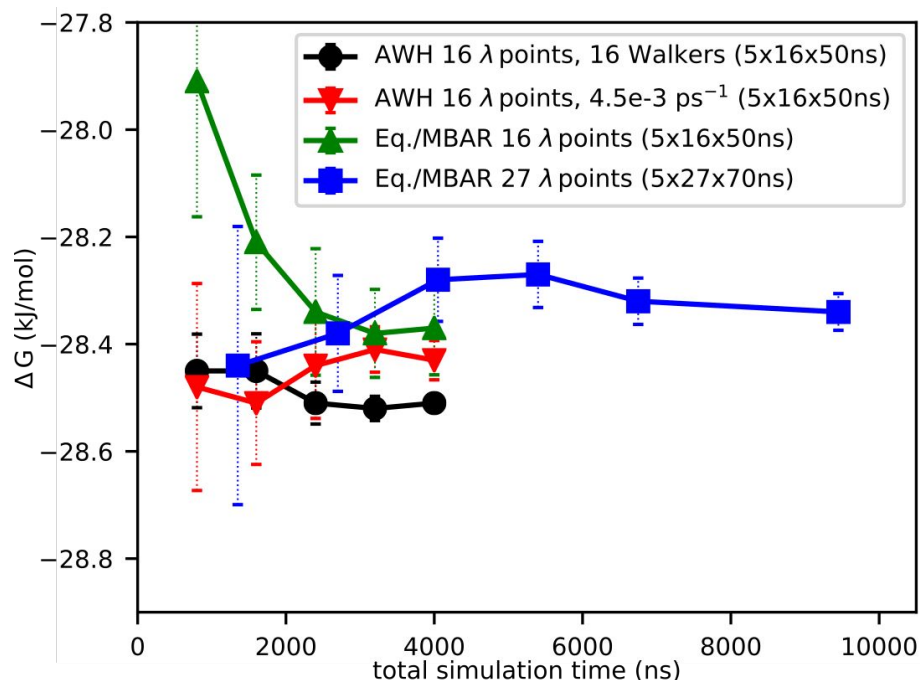


Convergence

ethanol

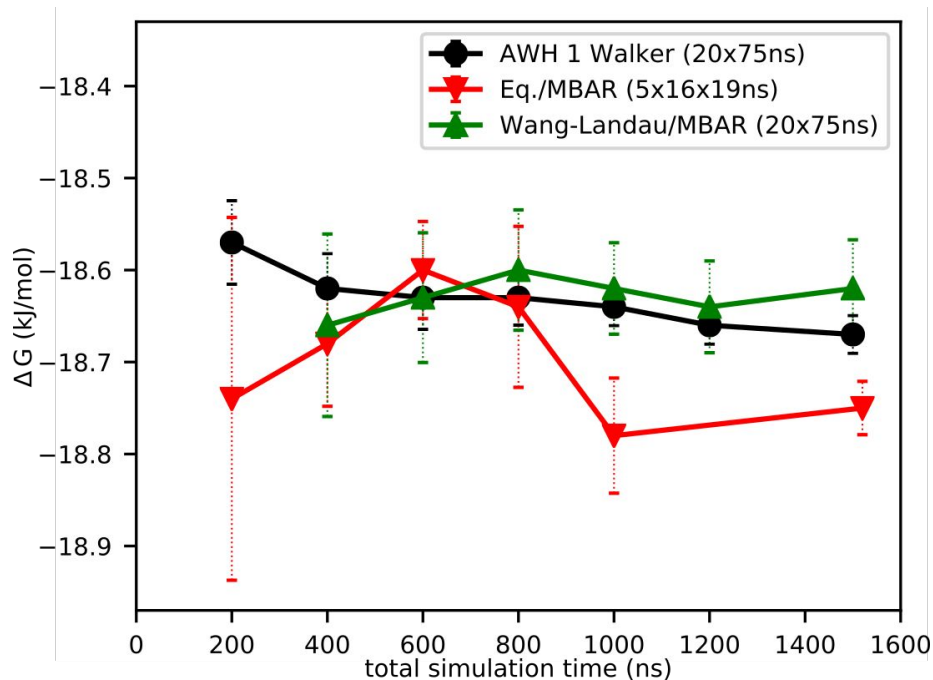


testosterone

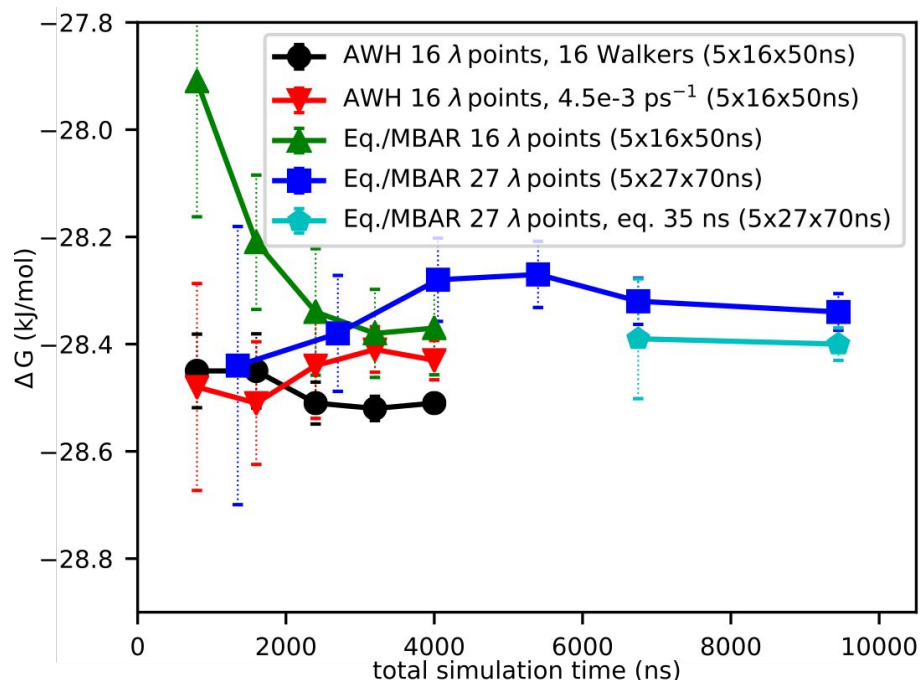


Convergence

ethanol

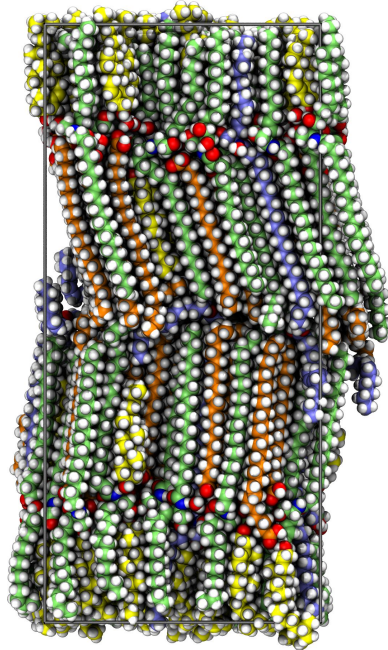


testosterone



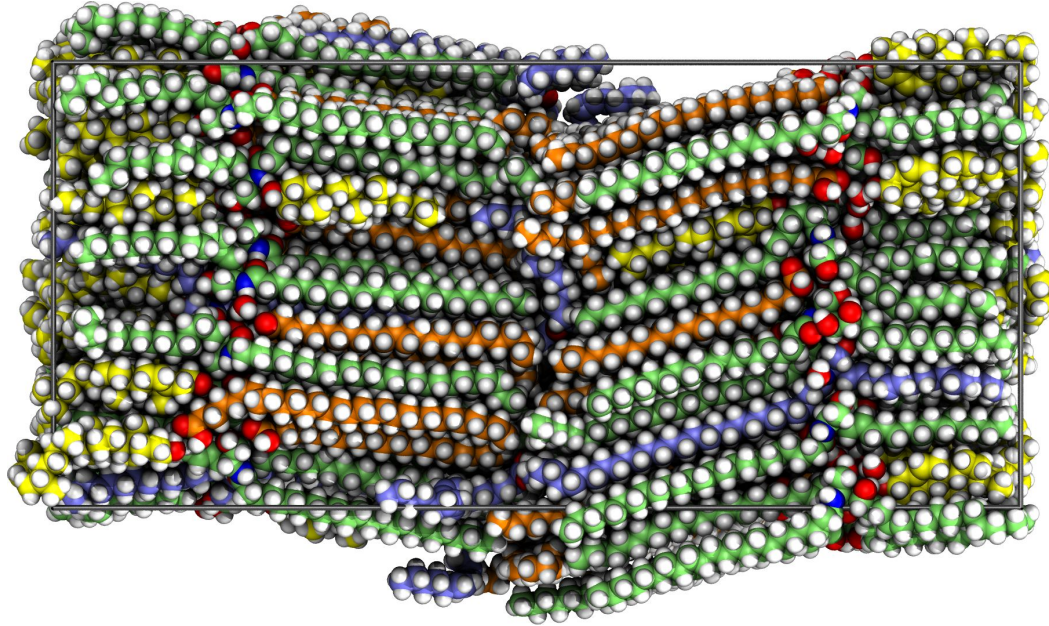
Permeability calculations through skin lipid barrier

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



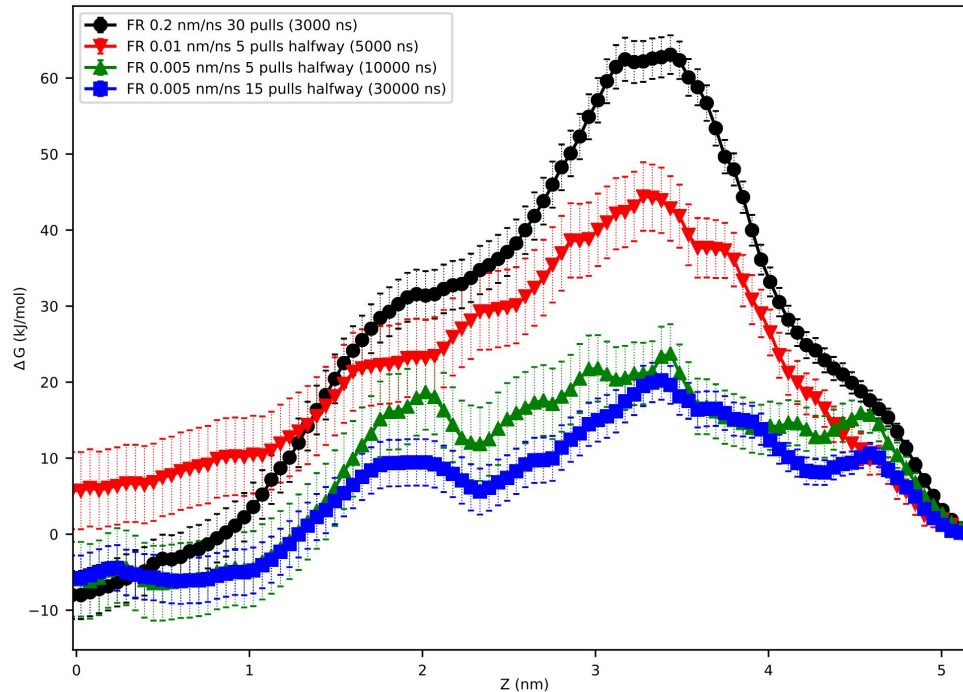
Permeability calculations through skin lipid barrier

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



Permeability calculations through skin lipid barrier

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

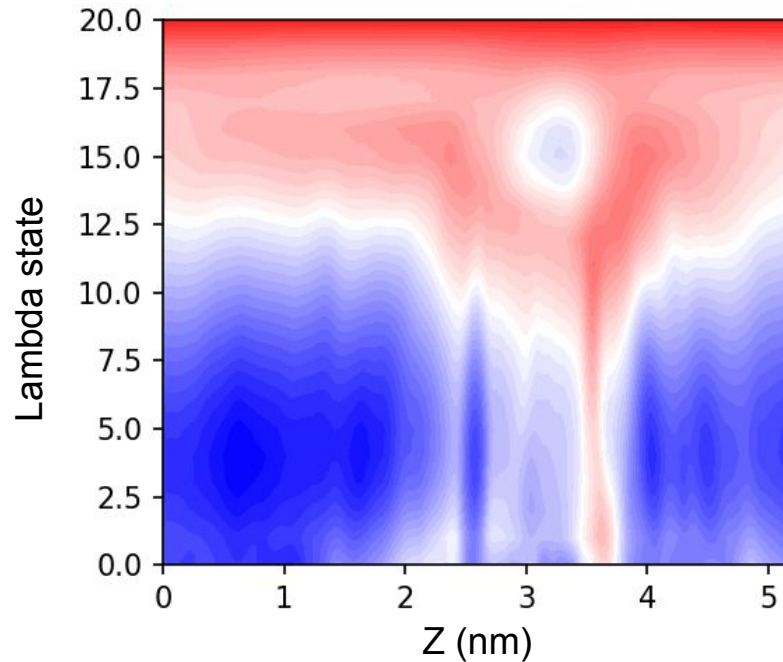


Permeability calculations through skin lipid barrier

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

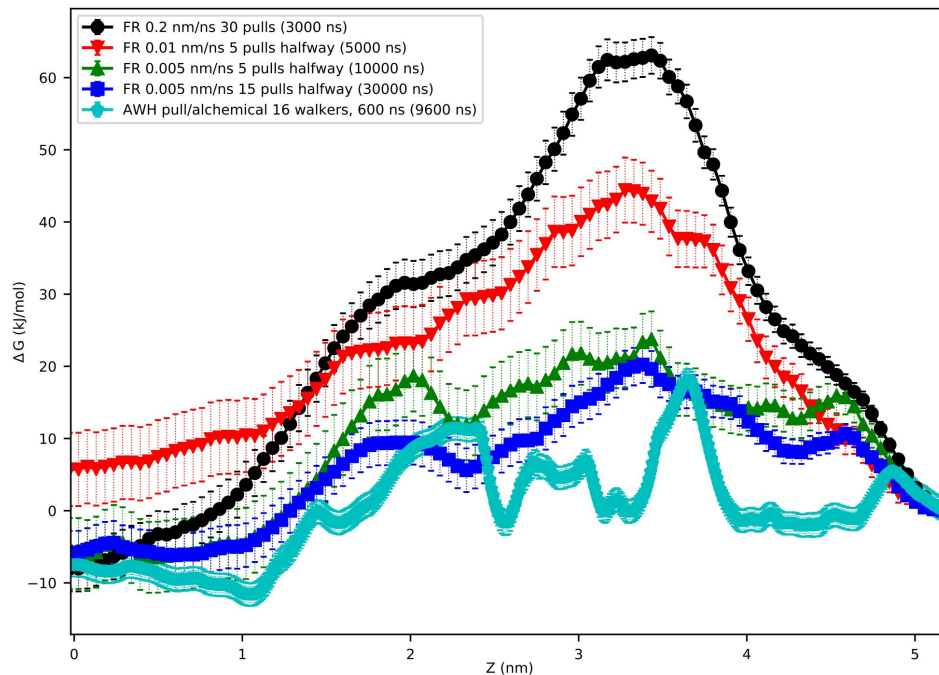
Permeability calculations through skin lipid barrier

- 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” ($\sim 10^{-2}$ 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 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)

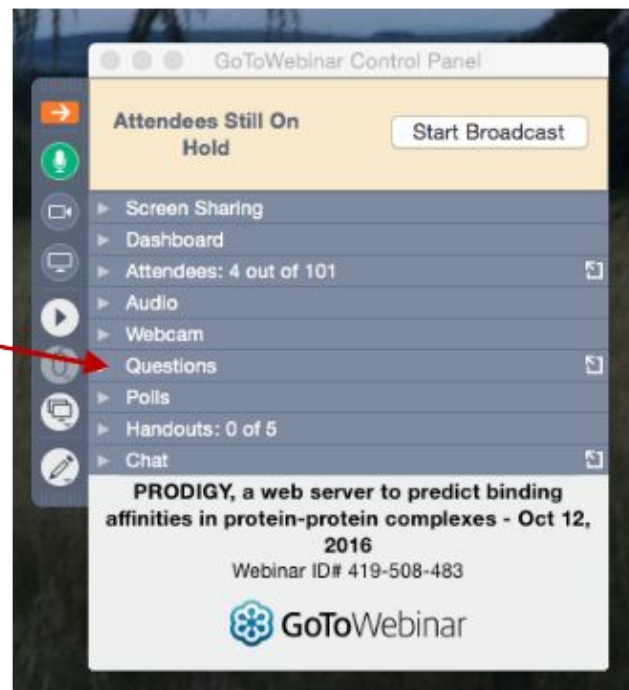
```
awh                                = yes
awh-potential                      = umbrella
awh-nstout                         = 500000
awh-nbias                         = 1
awh-nstsample                     = 10
awh-nsamples-update               = 10
awhl-error-init                   = 10
awhl-equilibrate-histogram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