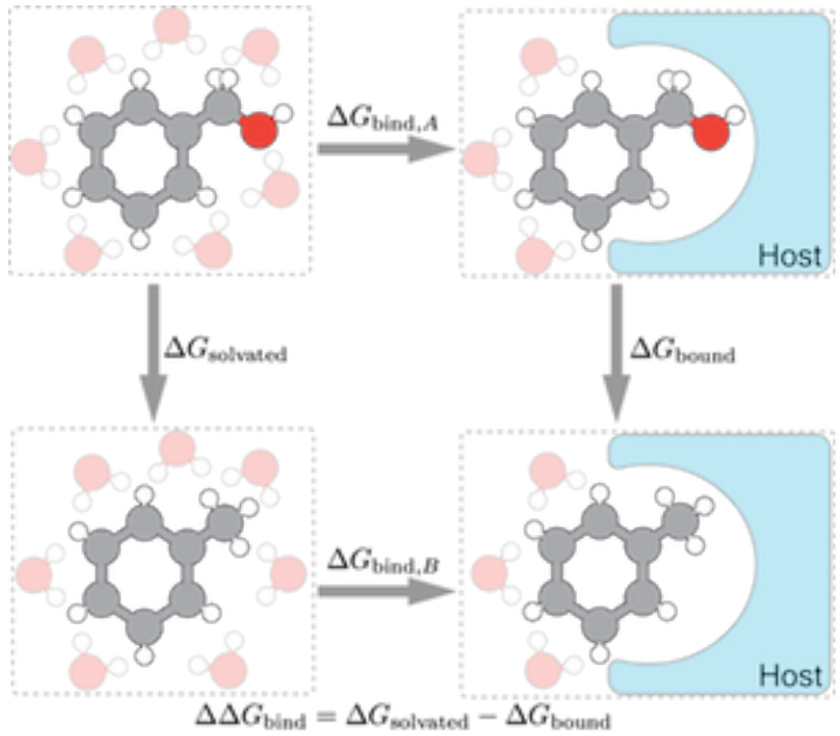
THE UNIVERSITY of EDINBURGH

Alchemical free energy simulations with BioSimSpace



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May 2019 – University of Bristol

The plan

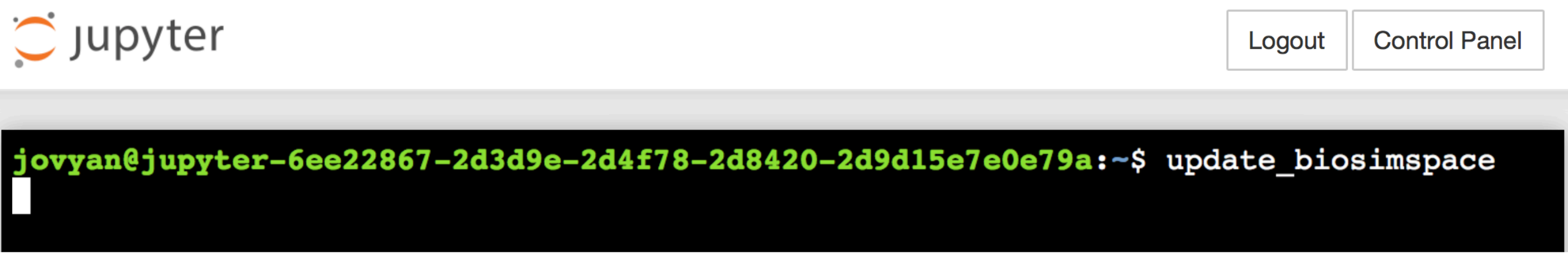
14:00 - 14:30	Introduction to Free Energy energy simulations
14:30 - 15:00	Exercise 01: Setting up an alchemical simulations
15:00 - 15:15	Coffee
15:15 - 15:30	Free energy analysis
15:30 - 16:00	Exercise 02: Free energy analysis
16:00 - 17:00	Exercise 03: Advanced free energy analysis

BioSimSpace server

notebook.biosimspace.org

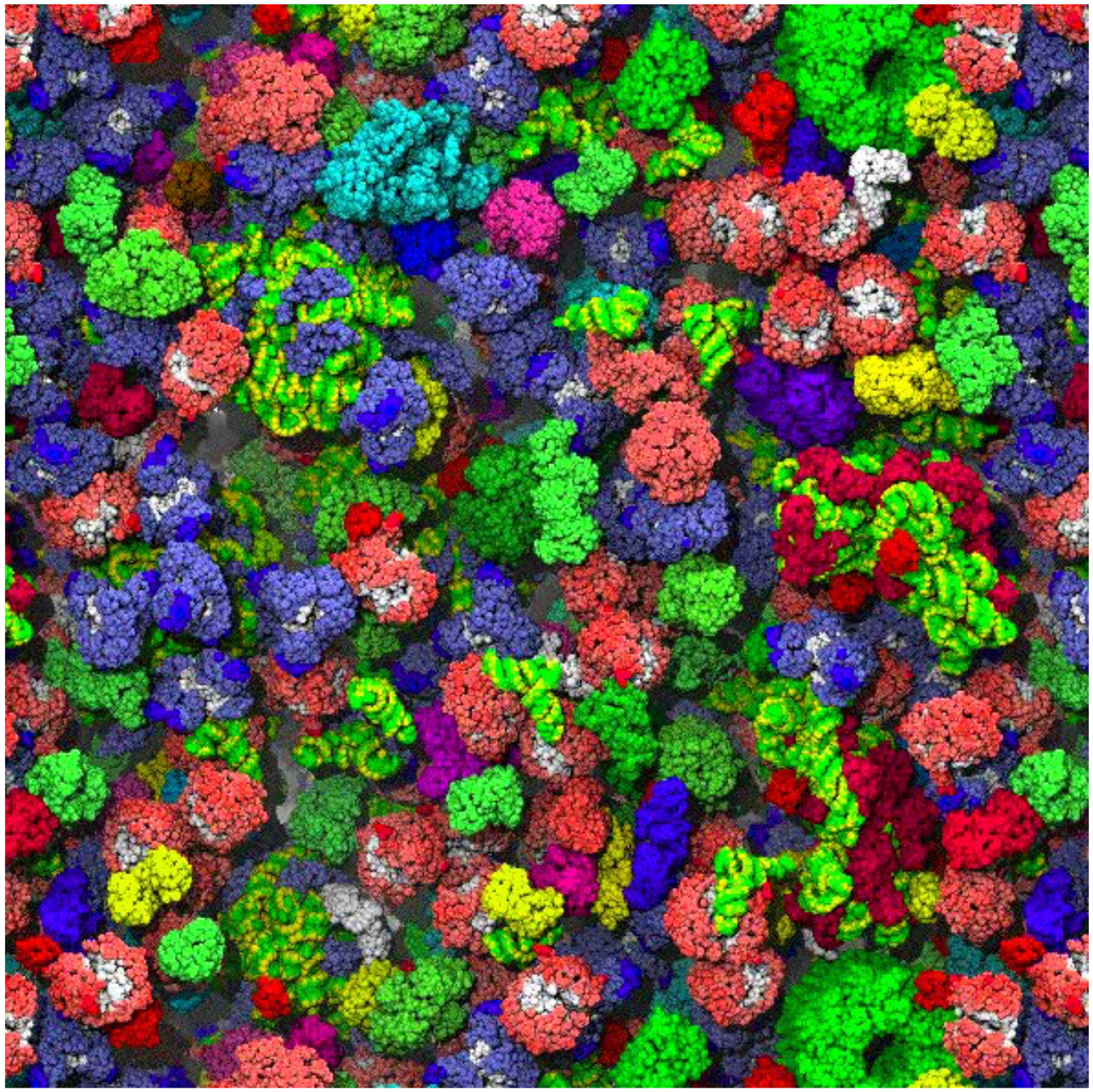
Update BioSimSpace

open terminal



The crowded cell

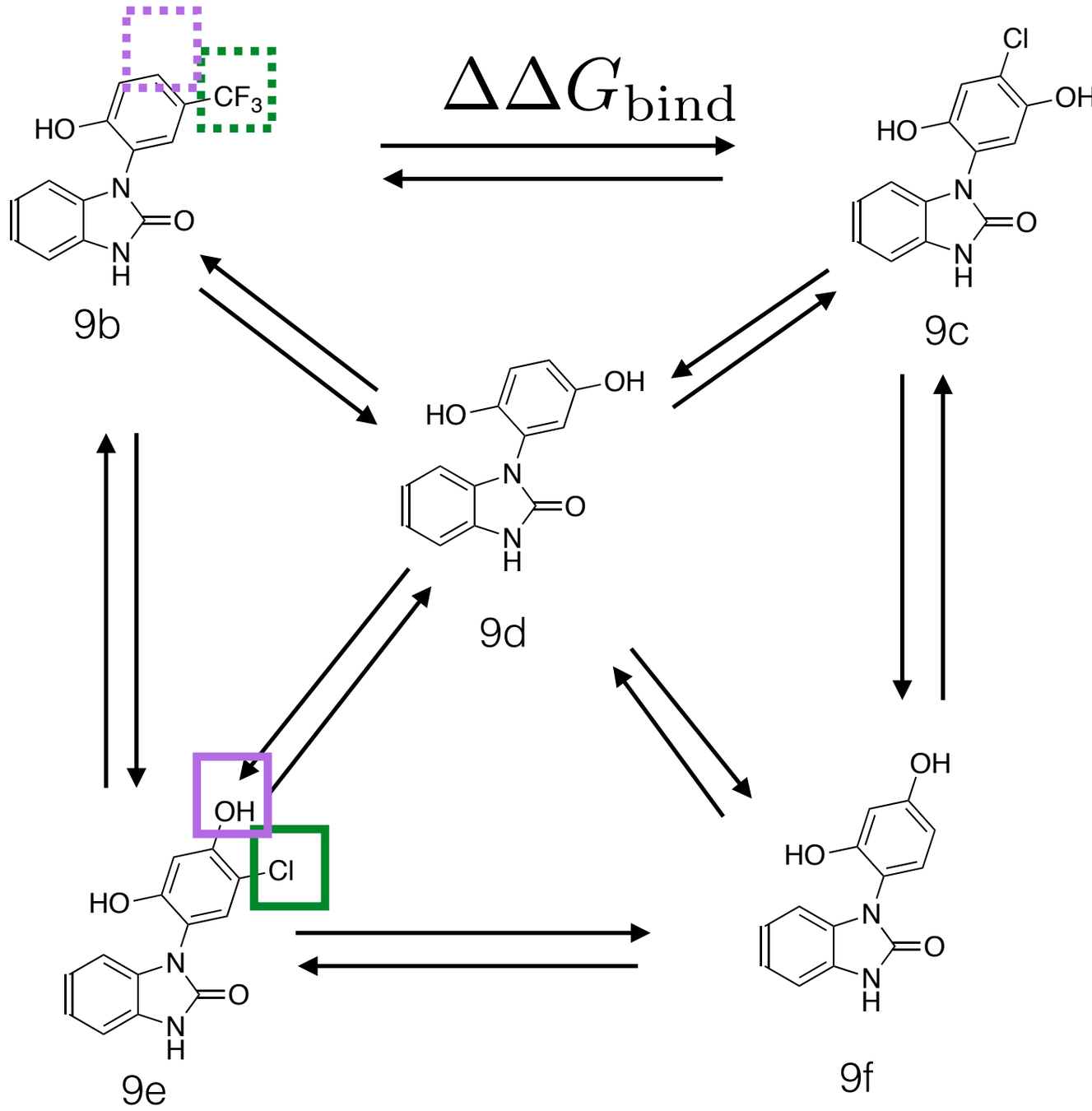
~2 million proteins in an E coli cell



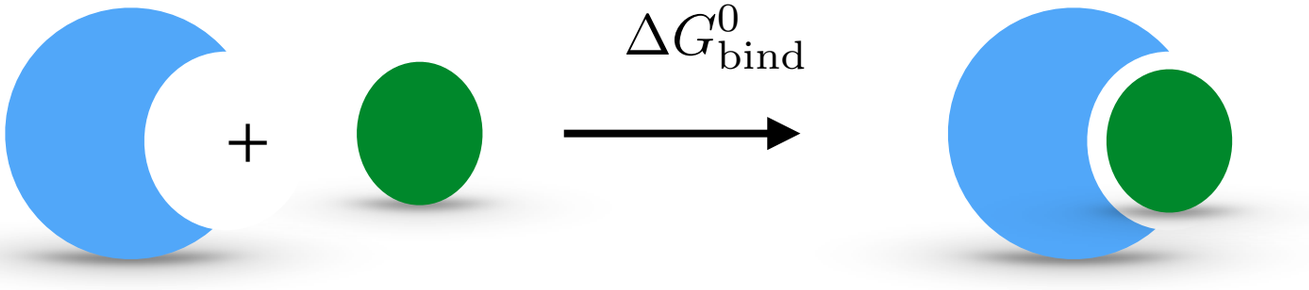
MCGuffee et al PLoS Comput Biol (2010)

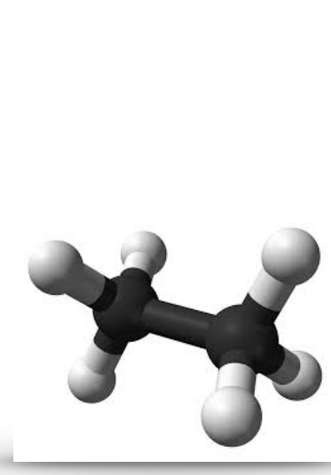
Free energy predictions

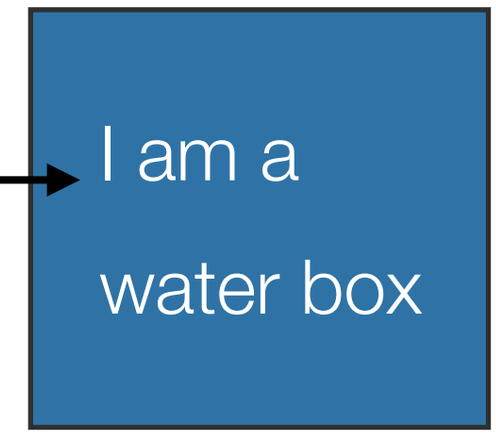
Dataset	Cresset/ UoE		Wang et al.[2]		Song et al.[3]	
	R	MUE	R	MUE	R*	MUE*
Thrombin	**0.88 ± 0.04**	**0.35 ± 0.04**	0.71 ± 0.24	0.76 ± 0.13	0.76	0.46
TYK2	**0.87 ± 0.02**	**0.60 ± 0.04**	0.89 ± 0.07	0.75 ± 0.11	0.57	1.07
PTP1B	**0.83 ± 0.04**	**0.84 ± 0.06**	0.80 ± 0.08	0.89 ± 0.12	0.71	1.06
JNK1	**0.81 ± 0.02**	**0.85 ± 0.04**	0.85 ± 0.07	0.78 ± 0.12	0.47	1.07
MCL1	**0.79 ± 0.02**	**1.30 ± 0.06**	0.77 ± 0.05	1.16 ± 0.10	0.65	1.52
CDK2	**0.69 ± 0.09**	**1.02 ± 0.08**	0.48 ± 0.19	0.91 ± 0.12	0.47	0.97
BACE	tbd	tbd	0.78 ± 0.07	0.84 ± 0.08	0.43	1.20
p38	tbd	tbd	0.65 ± 0.09	0.80 ± 0.08	0.38	1.20

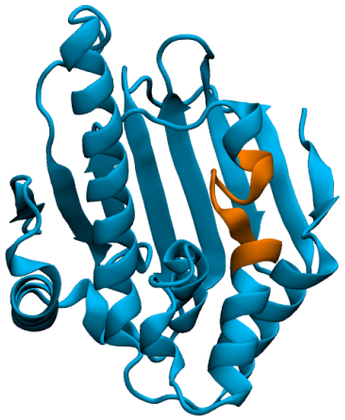


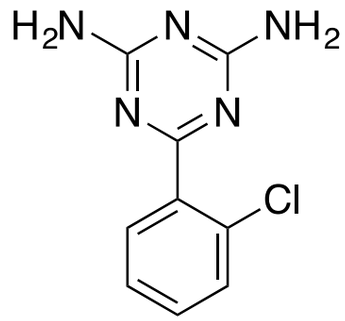
Problems we want to tackle









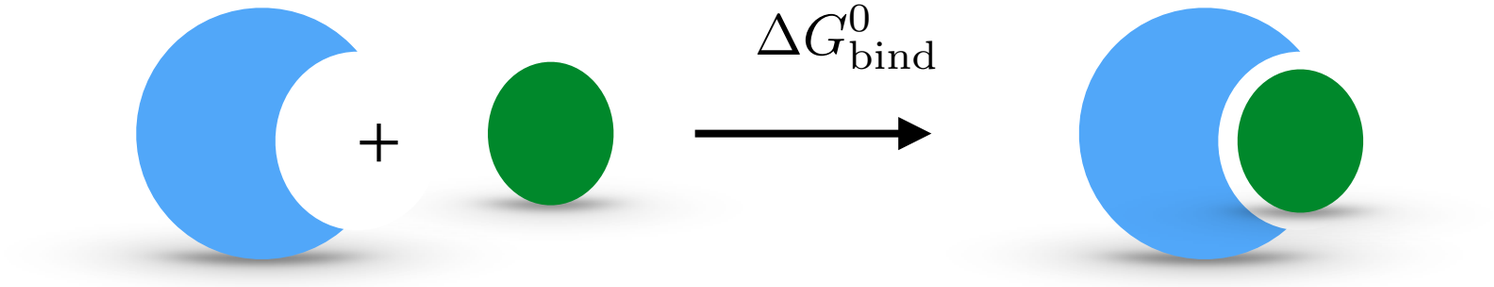


many ligand

Compute the free energy of hydration

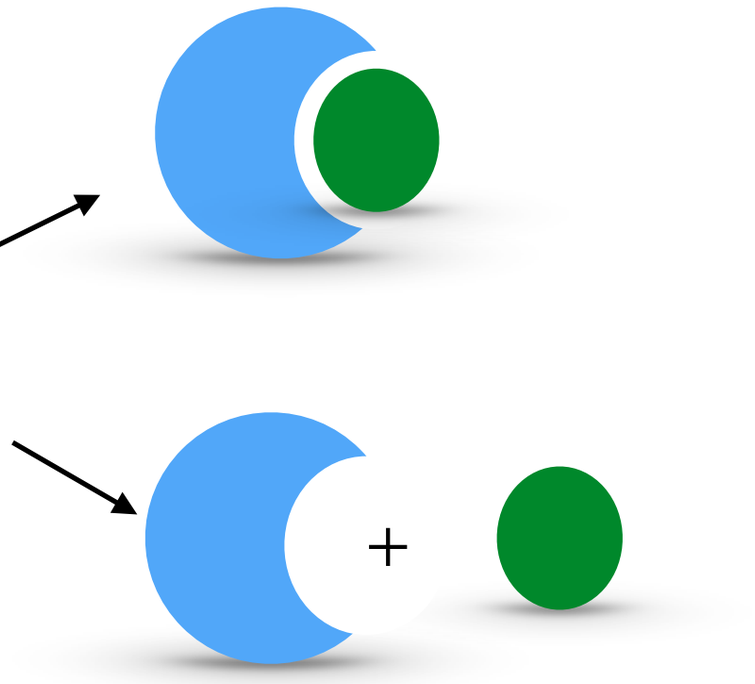
Predict affinity of a protein and ligand to bind

What is a free energy of binding?



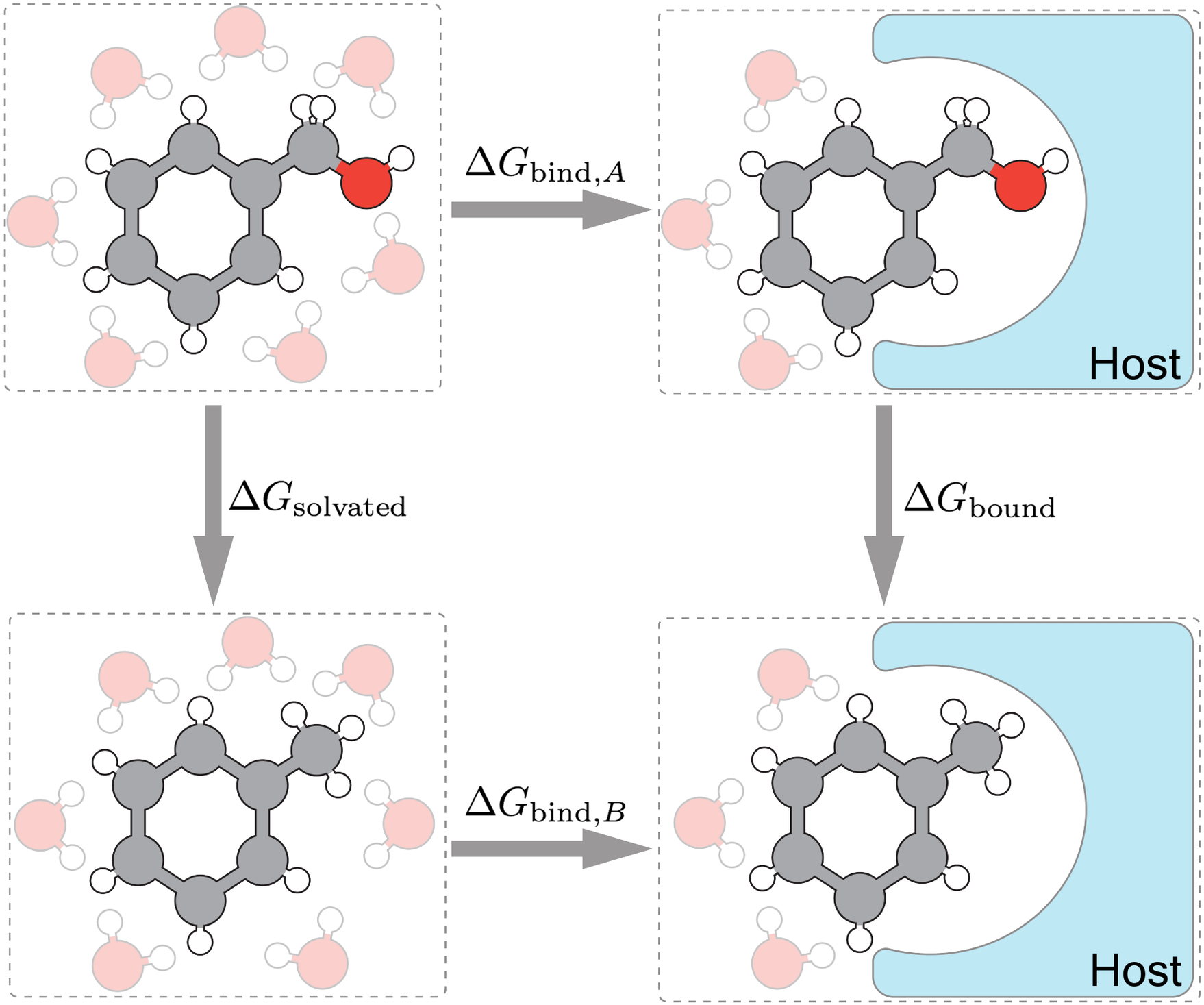
$$\Delta G_{\text{bind}} = -k_B T \ln K_b^\circ$$

$$K_b^\circ = \frac{\text{probability in bound state}}{\text{probability in unbound state}}$$



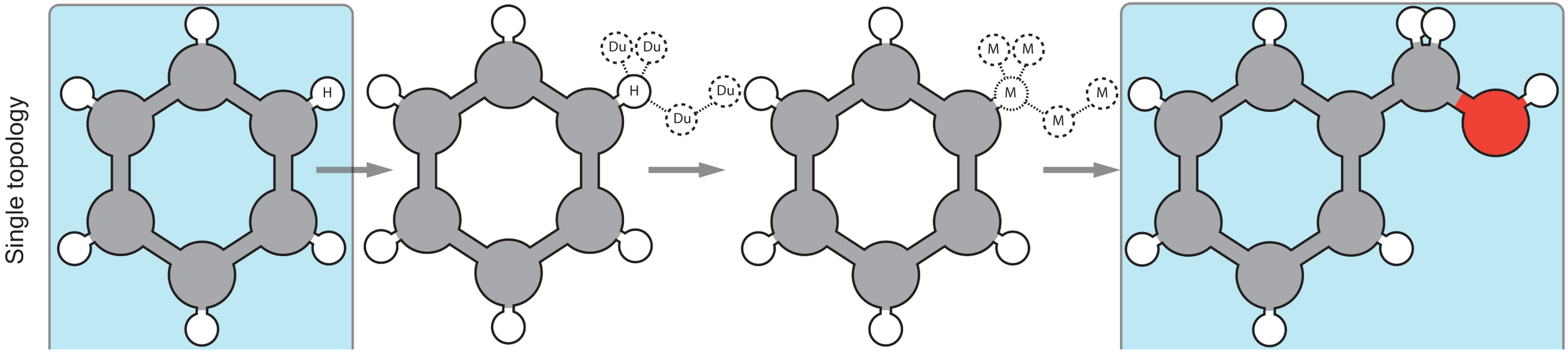
Sample this using Molecular dynamics?

The alchemical pathway



$$\Delta\Delta G_{\mathrm{bind}} = \Delta G_{\mathrm{bound}} - \Delta G_{\mathrm{solv}}$$

How do we sample this alchemical pathway?



Endpoint 1 $\lambda = 0$ $\lambda = 0.5$ Endpoint 2

$$U(\lambda, \mathbf{x}) = (1 - \lambda)U_0(\mathbf{x}) + \lambda U_1(\mathbf{x}) + U_{\text{unaffected}}$$

MD and forcefields

$$U = \sum_{\text{bonds}} \frac{1}{2} k_b (r - r_0)^2 + \sum_{\text{angles}} \frac{1}{2} k_a (\theta - \theta_0)^2 + \sum_{\text{torsions}} \frac{V_n}{2} [1 + \cos(n\phi - \delta)]$$

$$+ \sum_{\text{improper}} V_{imp} + \sum_{\text{LJ}} 4\epsilon_{ij} \left(\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^{6}}{r_{ij}^{6}} \right) + \sum_{\text{elec}} \frac{q_i q_j}{r_{ij}},$$

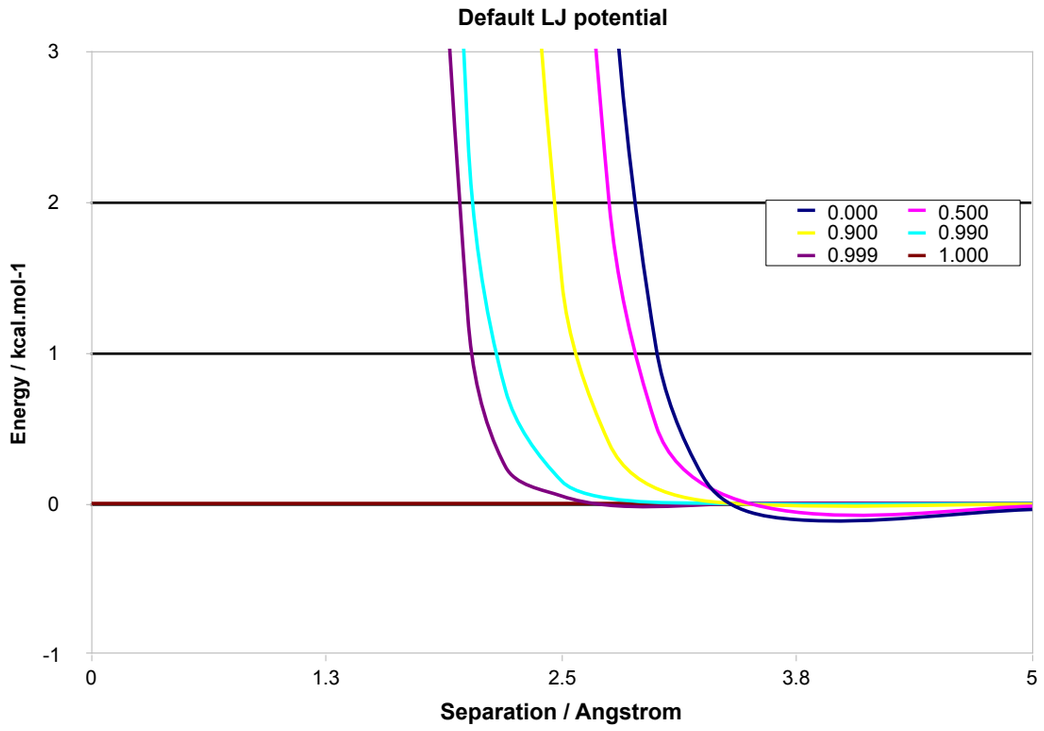
- The functional form and parameter set define a force field.
- Commonly used force fields include:
  CHARMM (Chemistry at Harvard Molecular Mechanics)
  AMBER (Assisted Model Building with Energy Refinement)
  OPLS (Optimised Potentials for Liquid Simulations)

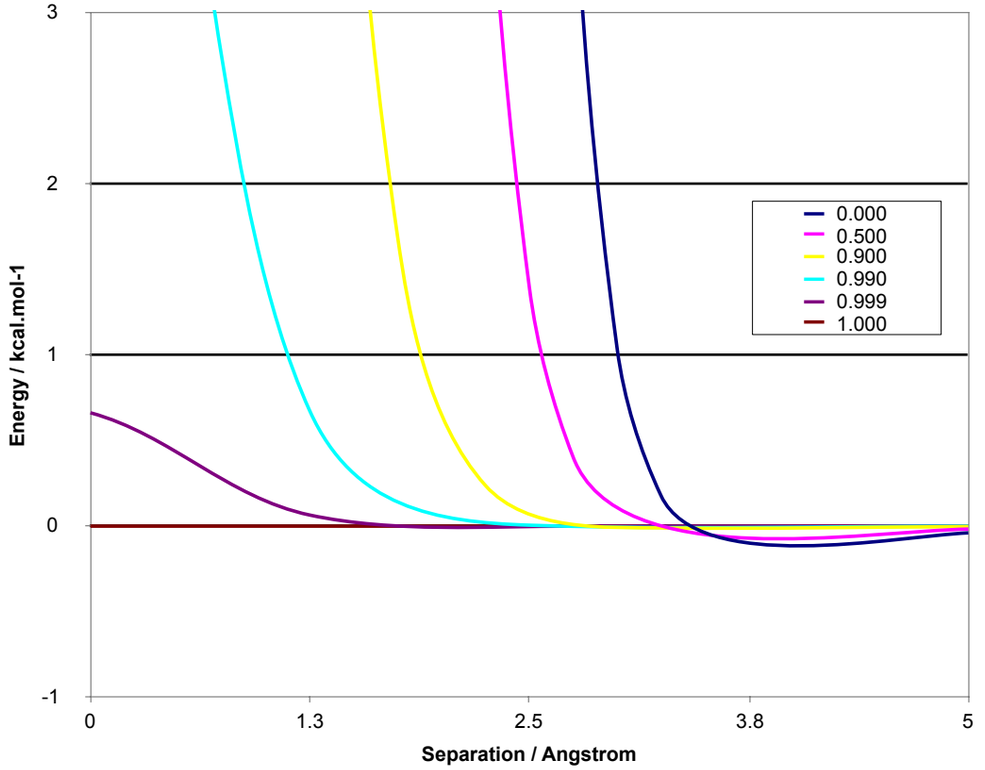
Softcore potential for dummy atoms

Zacharias et al. *J. Chem. Phys.* 100, 9025-, **1994**

$$U_{\text{nonbonded},\lambda} = (1-\lambda)4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}^{12}}{\left(\lambda\delta\sigma_{ij}+r_{ij}^2\right)^6}\right) - \left(\frac{\sigma_{ij}^{6}}{\left(\lambda\delta\sigma_{ij}+r_{ij}^2\right)^3}\right)\right] + \frac{(1-\lambda)^n q_i q_j}{4\pi\varepsilon_0\sqrt{\left(\lambda+r_{ij}^2\right)}}$$

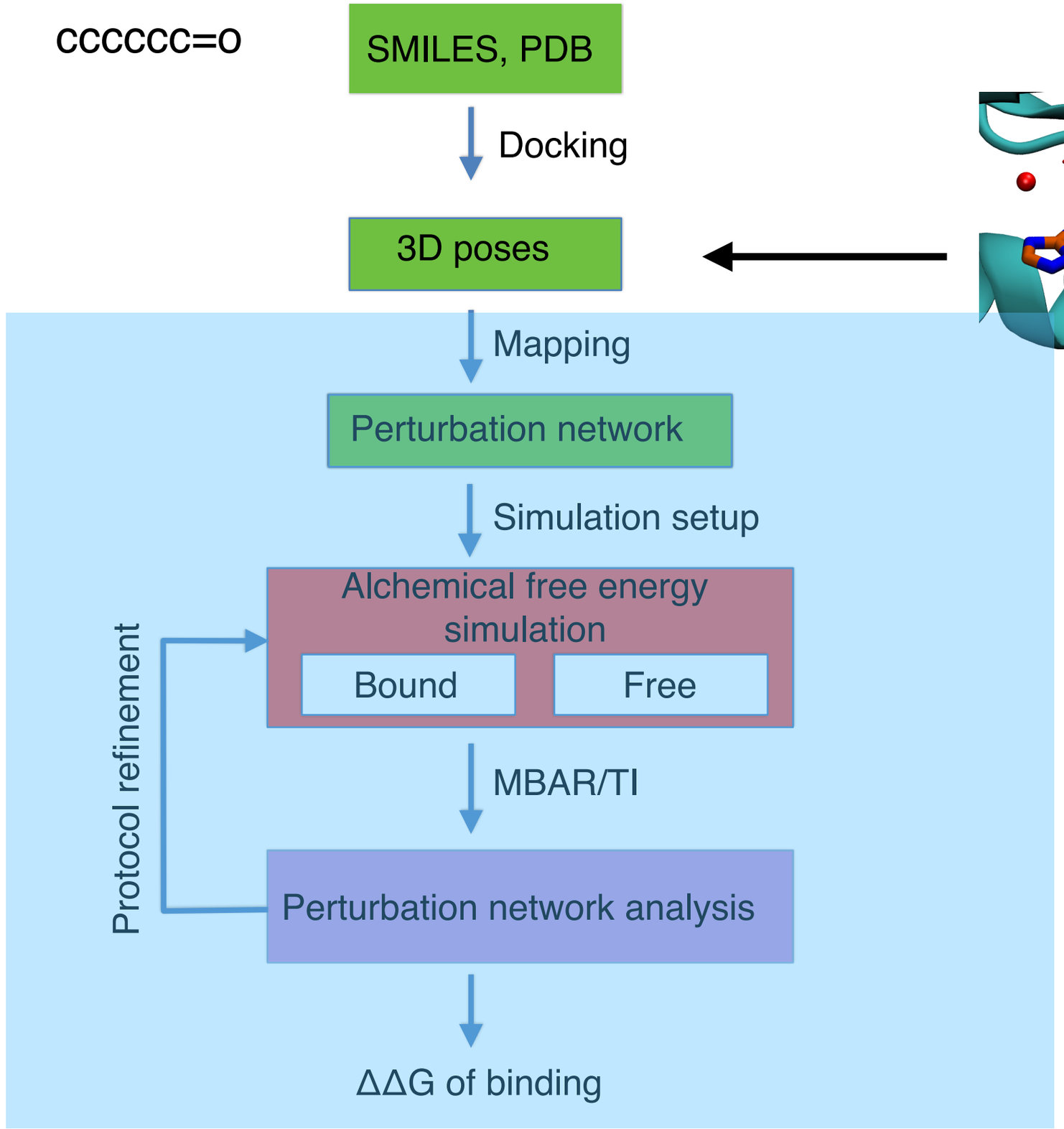
Dummy atoms!

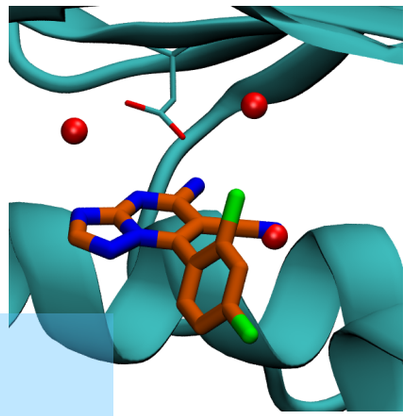




Binding free energies in practice

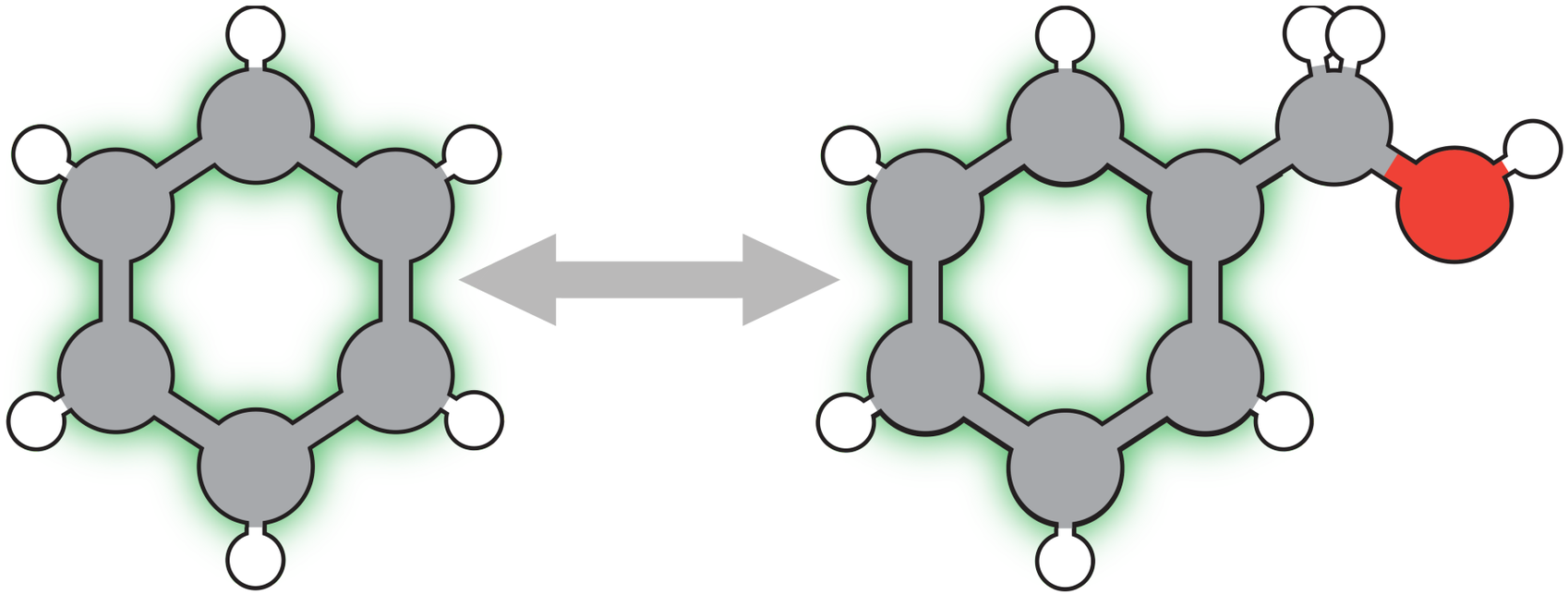
CCCCCC=O

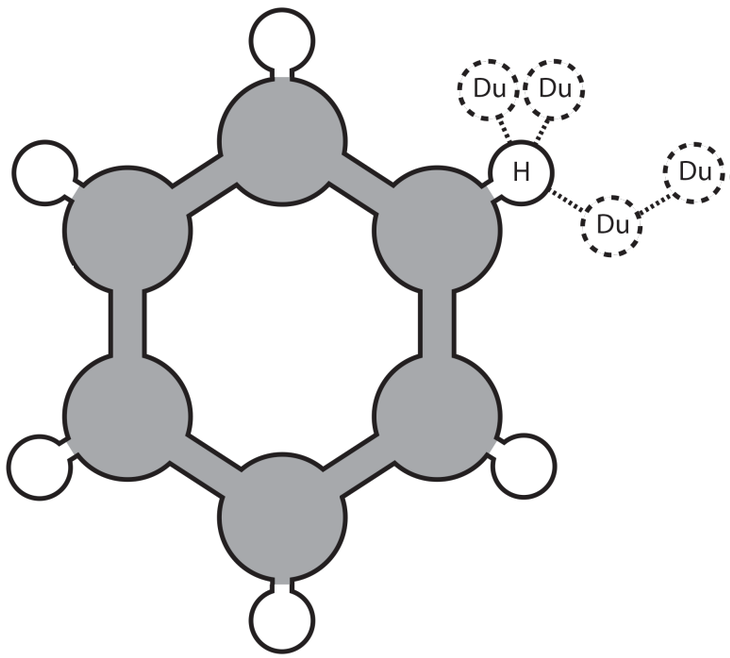




BioSimSpace

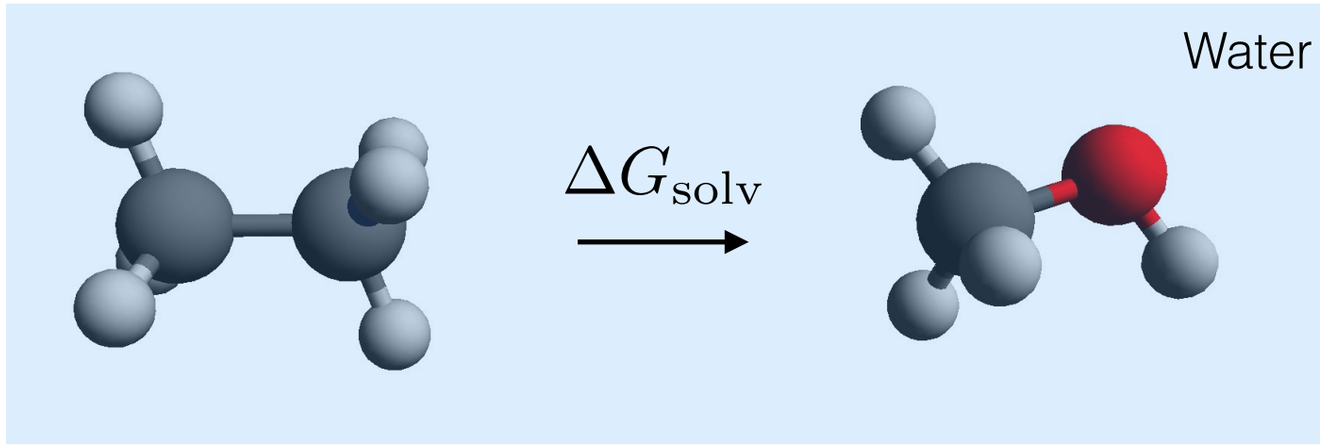
BioSimSpace can do the mapping between molecules

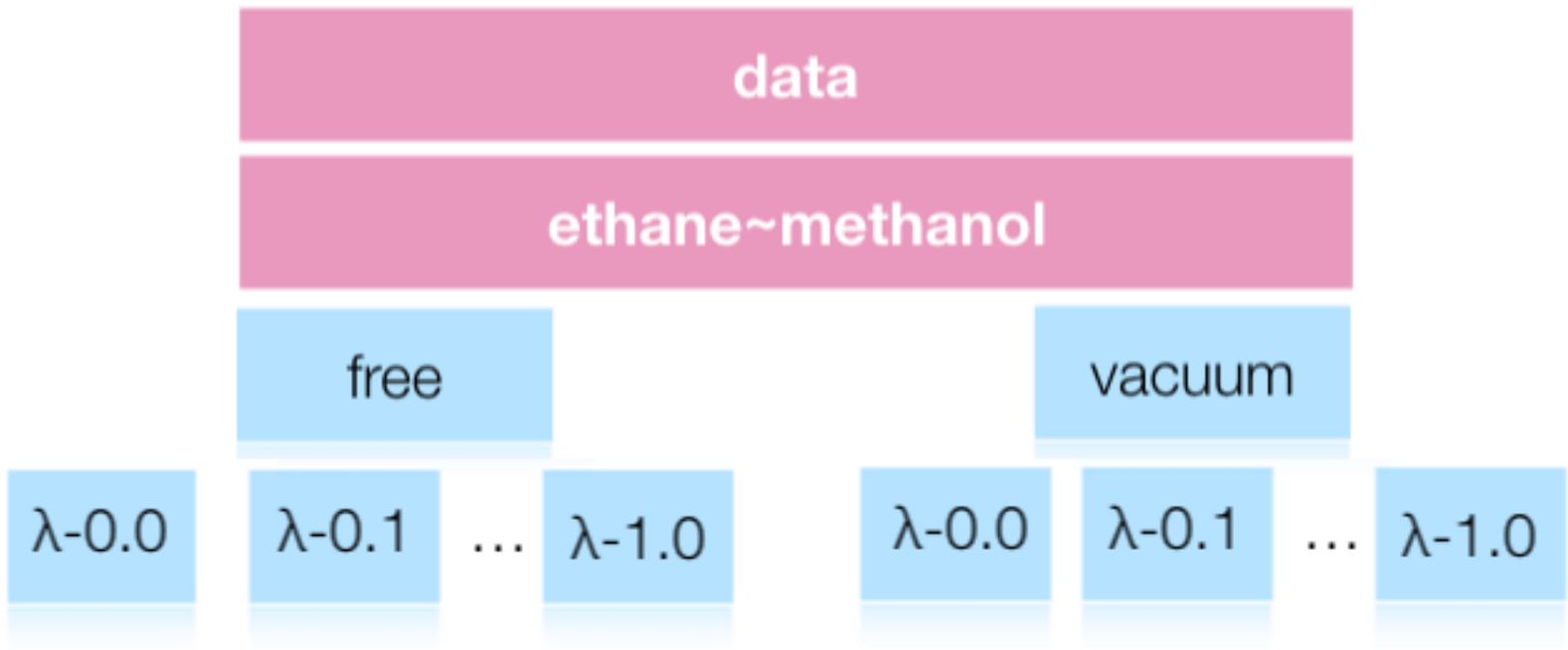




BioSimSpace holds a merged molecule and can write intermediates

BioSimSpace sets up all the simulation structure

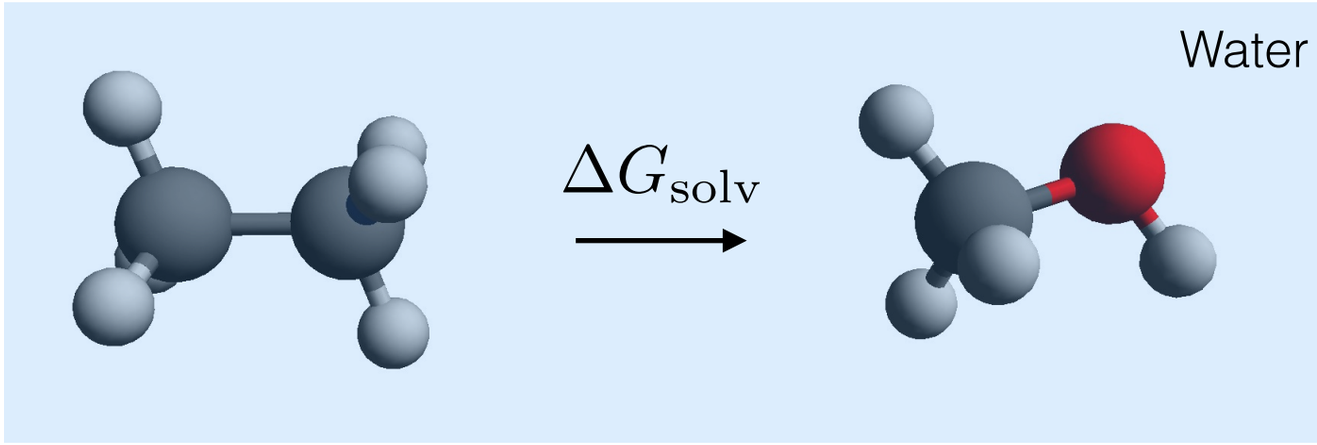


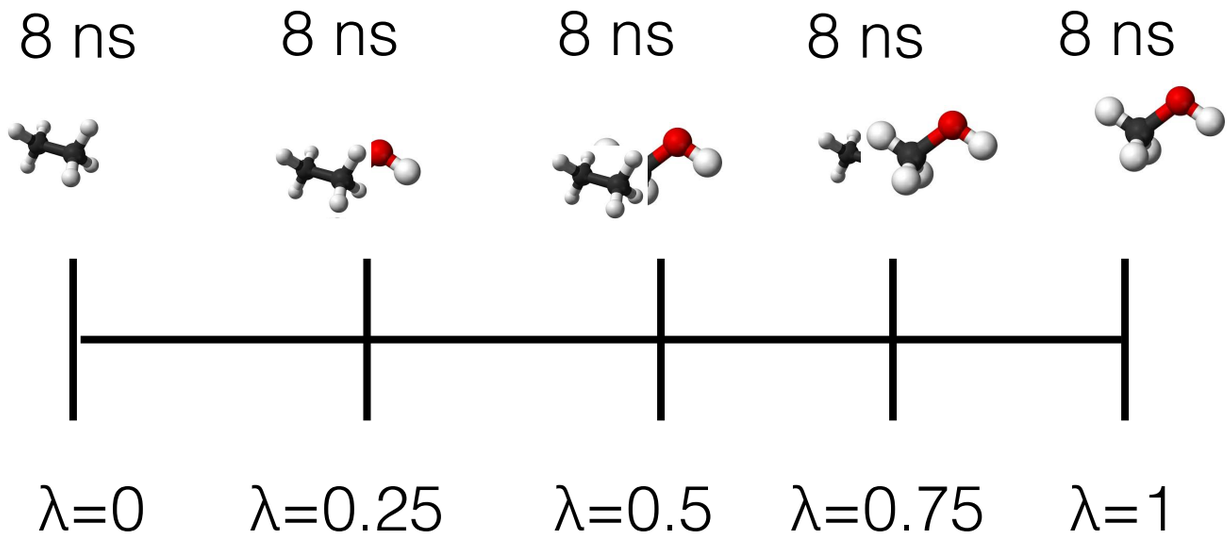


What methods have you heard about?

What do you know about them?

Analysis using the Zwanzig equation

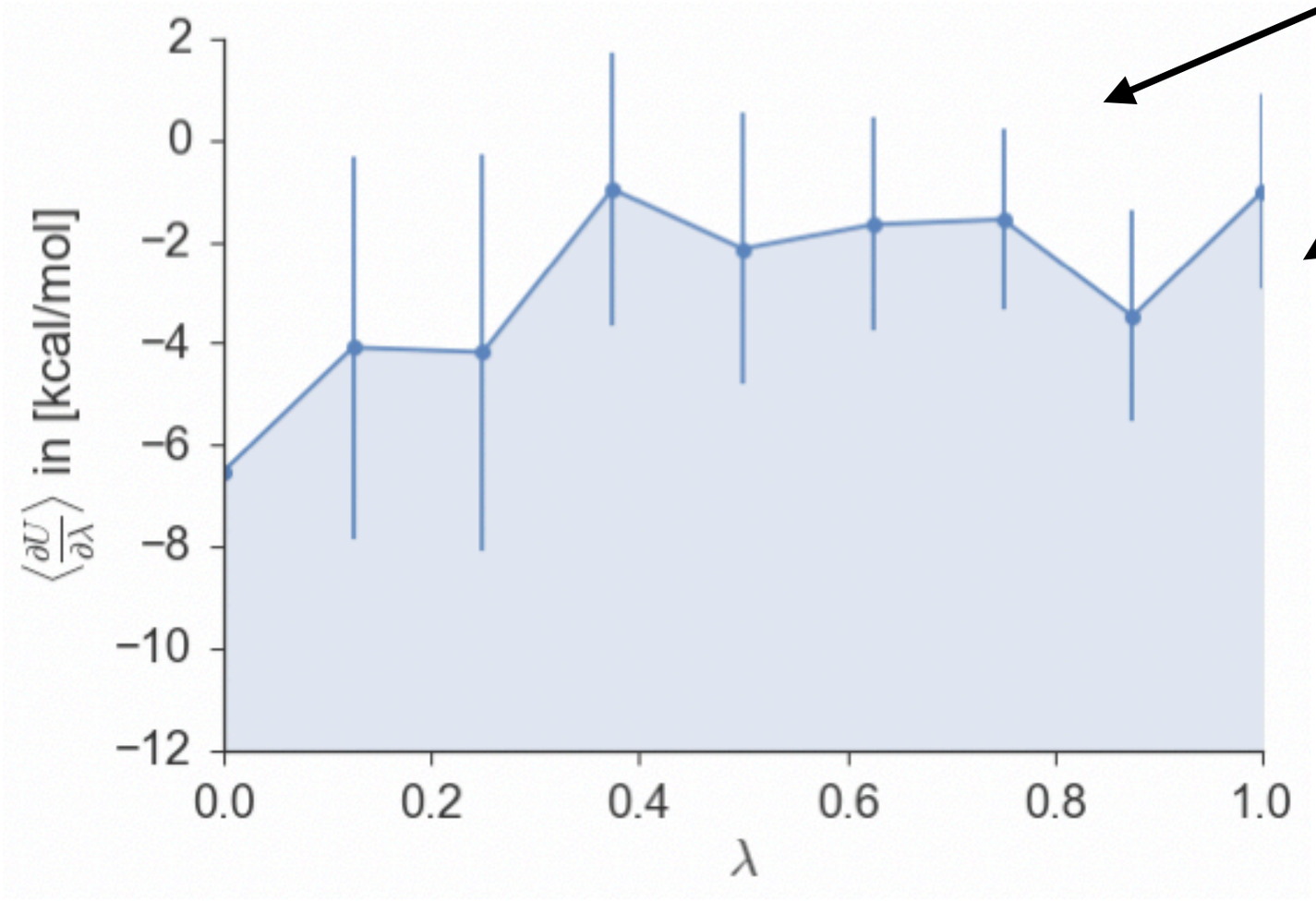




$$\Delta G_{AB} = G(A) - G(B) = -k_B T \ln \langle \exp(-\frac{U_B - U_A}{k_B T}) \rangle_A$$

Thermodynamic integration

$$\Delta\Delta G_{\text{bind}} = \Delta G_{\text{bound}} - \Delta G_{\text{solv}}$$



$$\Delta G = \int_{\lambda_0}^{\lambda_1} \frac{\partial G(\lambda)}{\partial \lambda} d\lambda$$

$$\Delta G = \int_{0}^{1} \langle \frac{\partial U}{\partial \lambda} \rangle d\lambda$$

The integral represents the area under the curve.
There are different ways in which one can numerically integrate.

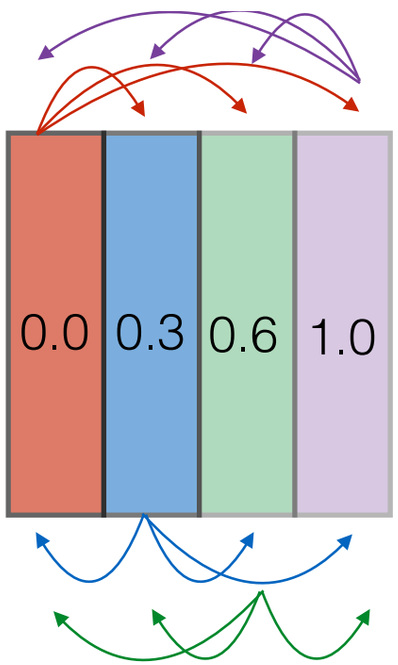
MBAR

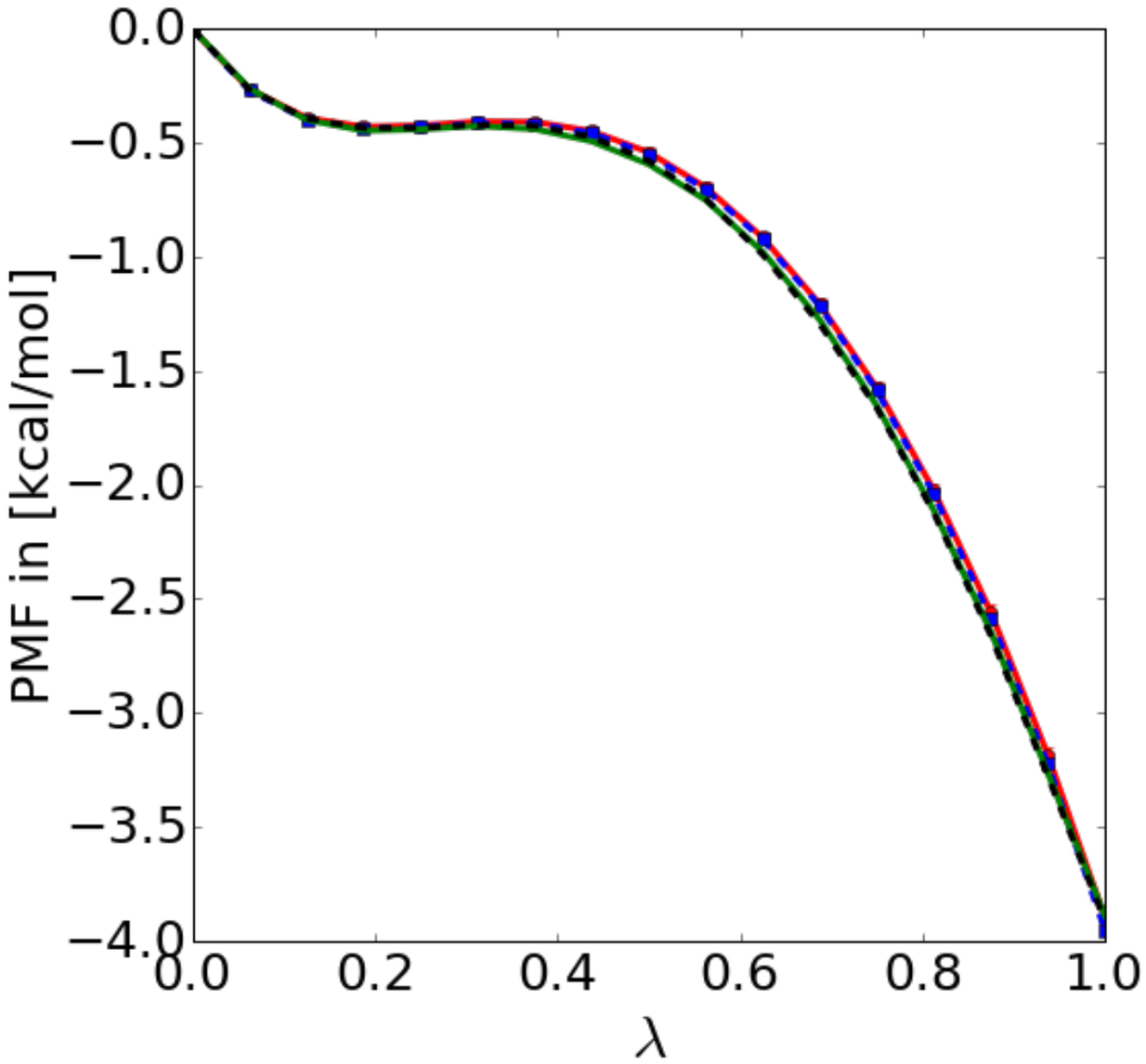
$$\mathcal{G}(\lambda_1) = -k_B T \ln \sum_{j=1}^{N} \sum_{n=1}^{K_j} \frac{\exp(-U(\lambda_i)/kT)}{\sum_{k=1}^{N} N_k \exp((\mathcal{G}(\lambda_k) - U(\lambda_k))/kT)}$$

MBAR is a reweighting estimator

The free energy is correct up to an additive constant, which will cancel out when evaluating free energy differences.

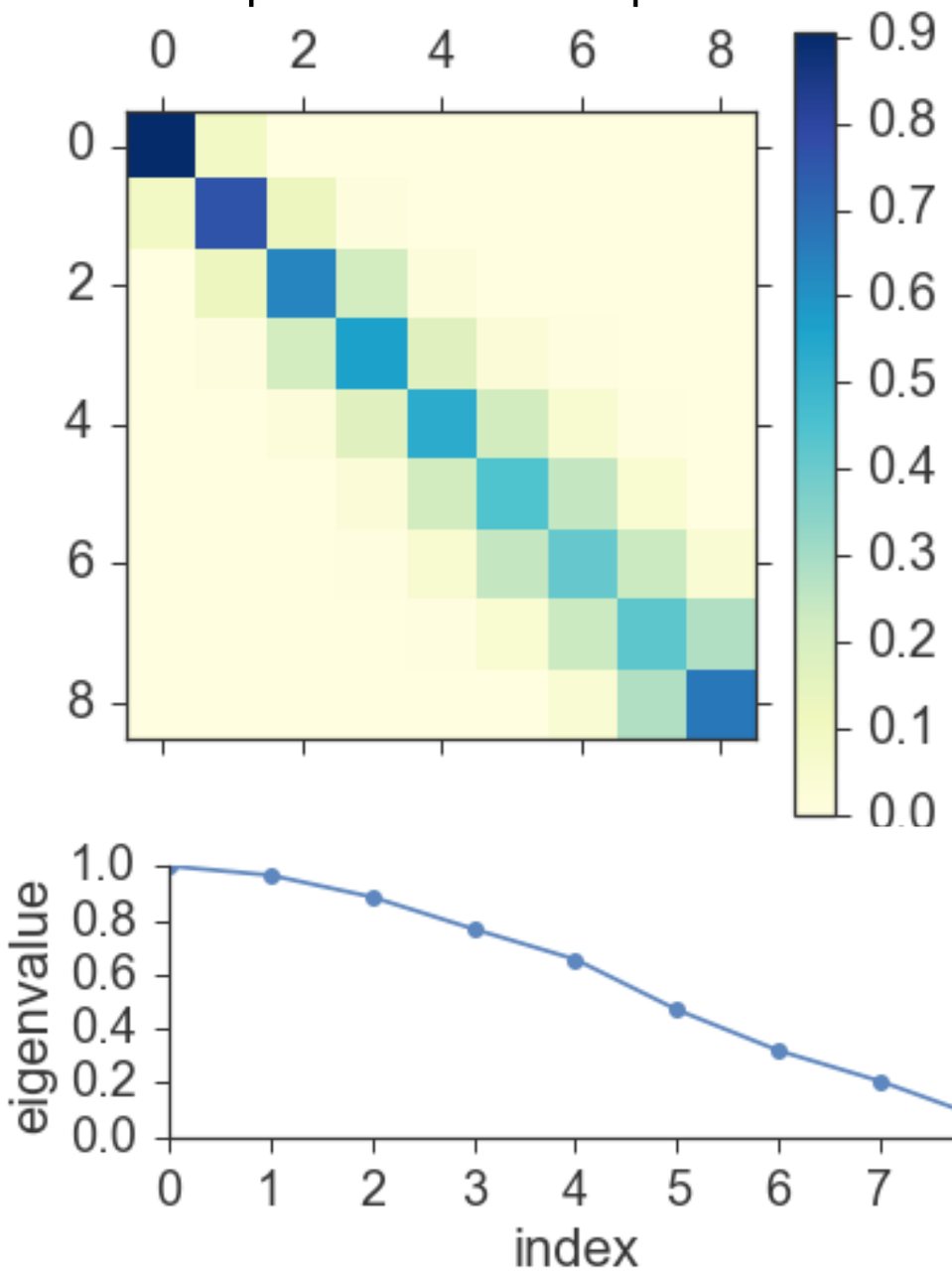
$$\Delta G_{AB} = G(\lambda_1) - G(\lambda_0)$$





Overlap

Overlap matrix estimates the phase space overlap



Define a weight matrix W containing the weight of each sample x_n.

$$W_{n,i}(x_n) = \frac{\exp(\beta F_i - U_i(x_n))}{\sum_{k=1}^{K} N_K \exp(\beta F_k - \beta U_k(x_n))}$$

Probability of $p_i(x_n)$ of x_n occurring at lambda window i.

$$\mathbf{O} = \mathbf{W^T W N}$$

N is a diagonal matrix with the number of samples collected at each lambda window.

Best Practices

- Overlap

- No element should be zero in the diagonal and above and below the main diagonal
- None zero elements should at least be > 0.03

- The number of samples needed for a good estimate will increase with a decrease in overlap.

- Many eigenvalues close to 1 are a bad sign for good overlap and a good free energy estimate.

- Compare different estimators
- Run multiple independent runs
- Subsample your data

Analysis in BioSimSpace

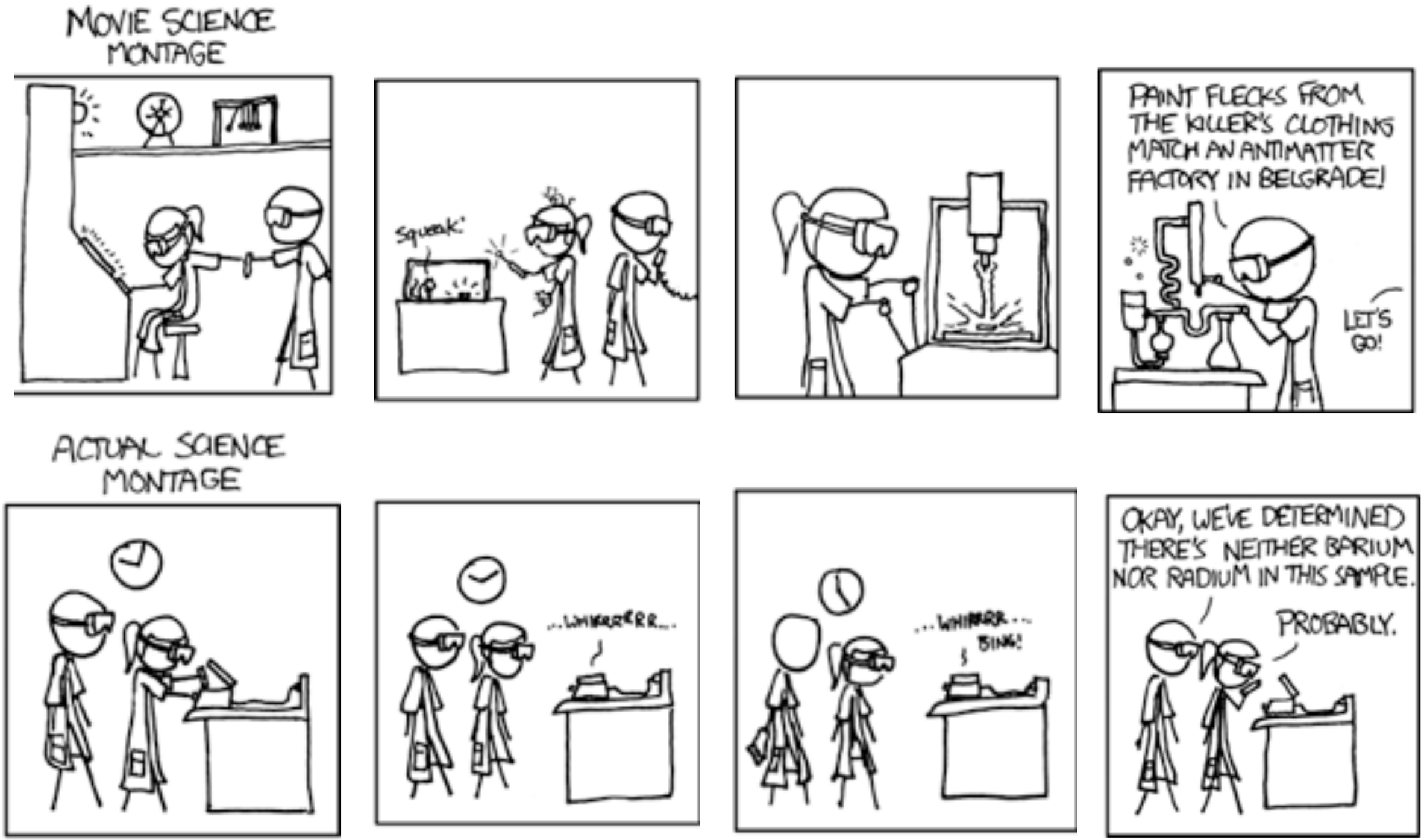
```
# Solvate in a 60 angstrom box of TIP3P water.
solvated = BSS.Solvent.tip3p(molecule=system, box=3*[60*BSS.Units.Length.angstrom])

# Create the free energy protocol.
protocol = BSS.Protocol.FreeEnergy(runtime=4*BSS.Units.Time.nanosecond, num_lam=9)

# Initialise the binding free energy object.
freenrg = BSS.FreeEnergy.Binding(solvated, protocol, work_dir="Binding_benzene_o_xylene" )
```

`freenrg.run()` ⟶ run the simulation

`freenrg.analyse()` ⟶ analyse the simulation

wraps around `analyse_freenrg mbar`

Thank you


MOVIE SCIENCE MONTAGE
Squeak!
PAINT FLECKS FROM THE KILLER'S CLOTHING MATCH AN ANTIMATTER FACTORY IN BELGRADE!
LET'S GO!
ACTUAL SCIENCE MONTAGE
...WHIRRRRR...
...WHIRR...
BING!
OKAY, WE'VE DETERMINED THERE'S NEITHER BARIUM NOR RADIUM IN THIS SAMPLE.
PROBABLY.