Alchemical Free Energy Methods with BioSimSpace

Julien Michel, Anna Herz, Finlay Clark, Lester Hedges, Christopher Woods

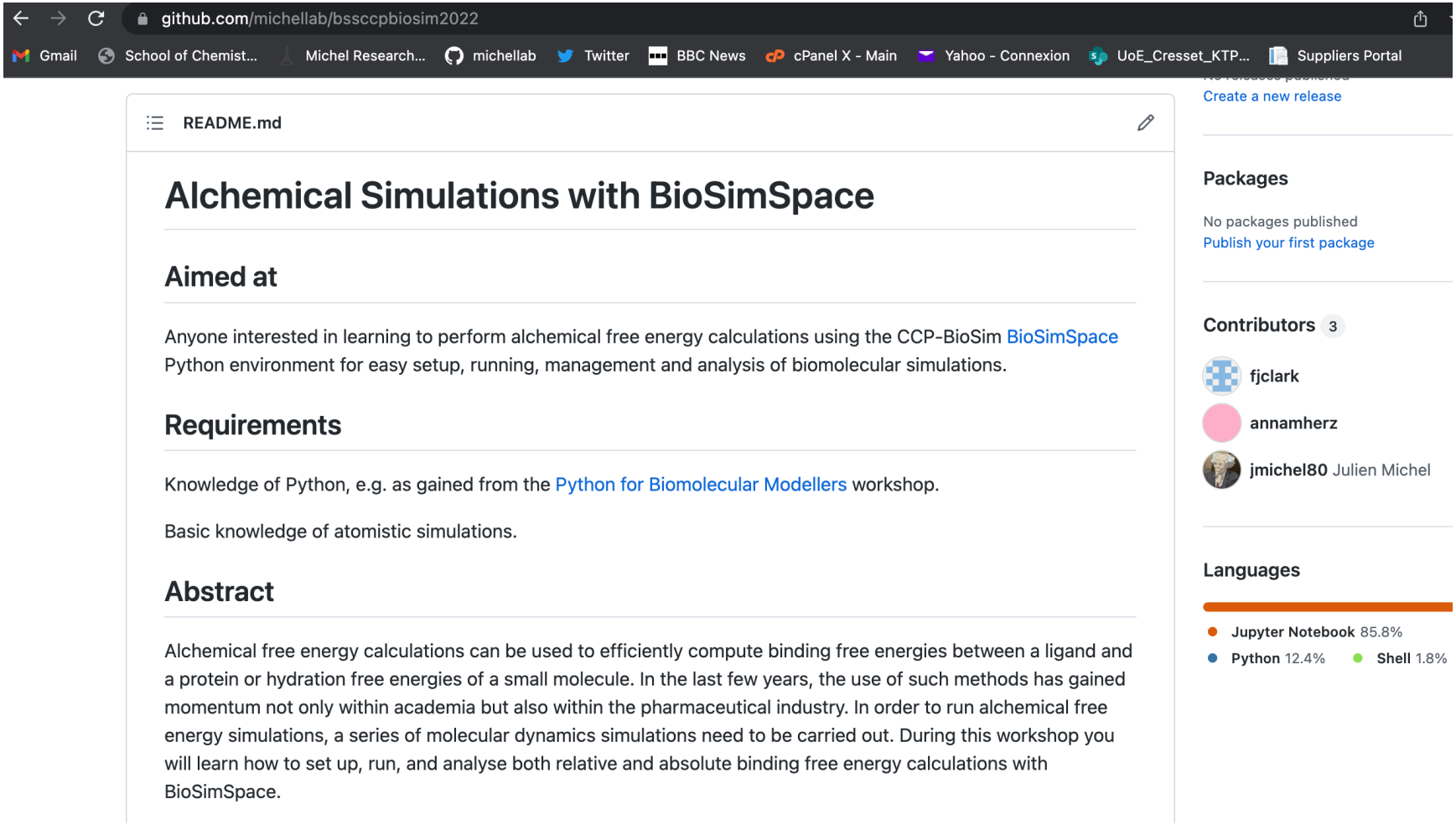
CCPBioSim Training Week – Leeds - 20/09/2022

Schedule

- 9.00 – 9.30 Set up & Lecture
- 9.30 – 10.15 Introduction to Alchemistry with BioSimSpace
- 10,15 - 10.30 Coffee Break
- 10.30 – 11.15 Relative Binding Free Energies with BioSimSpace
- 11.15 – 12.00 Absolute Binding Free Energies with BioSimSpace

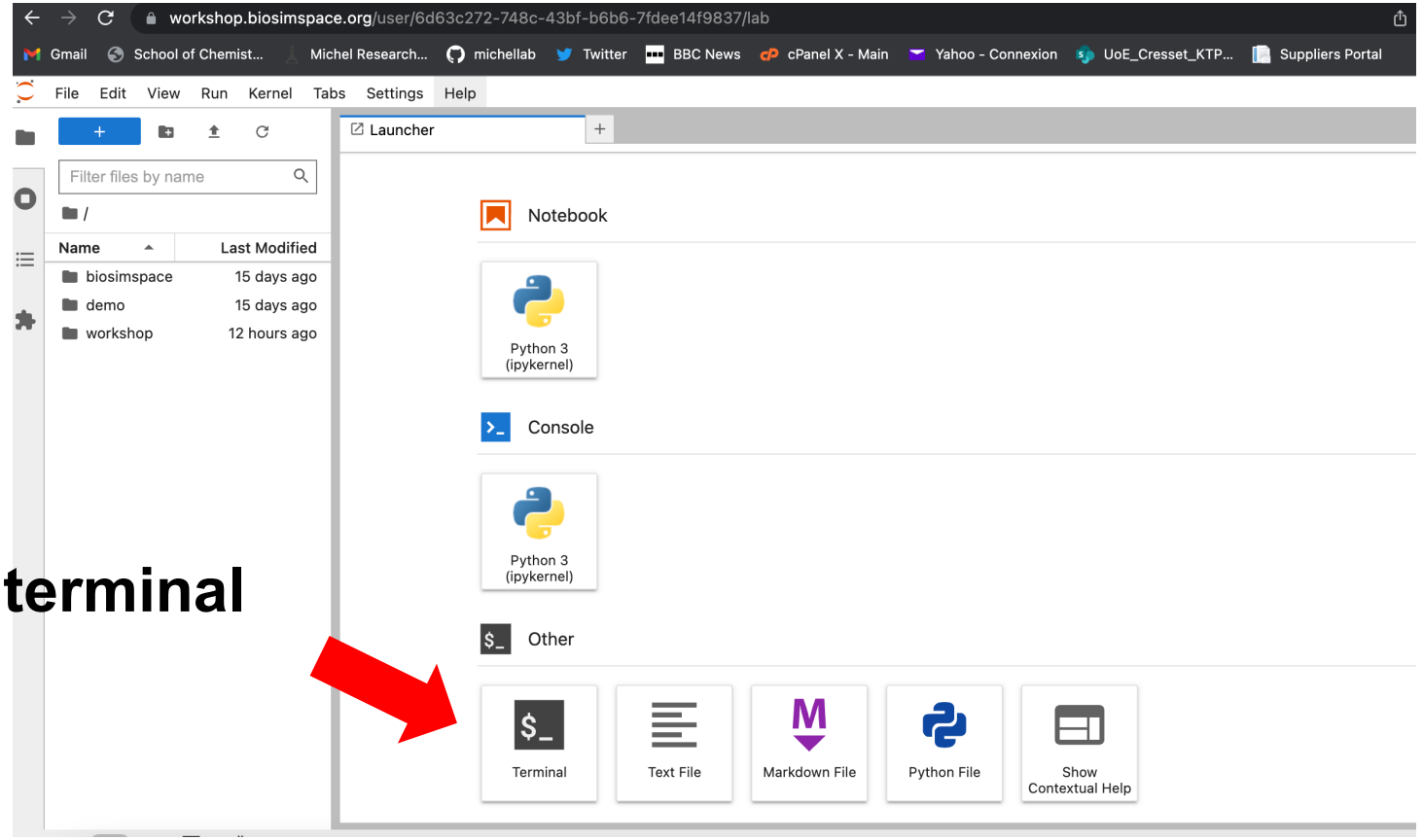
Workshop materials

github.com/michellab/bssccpbiosim2022



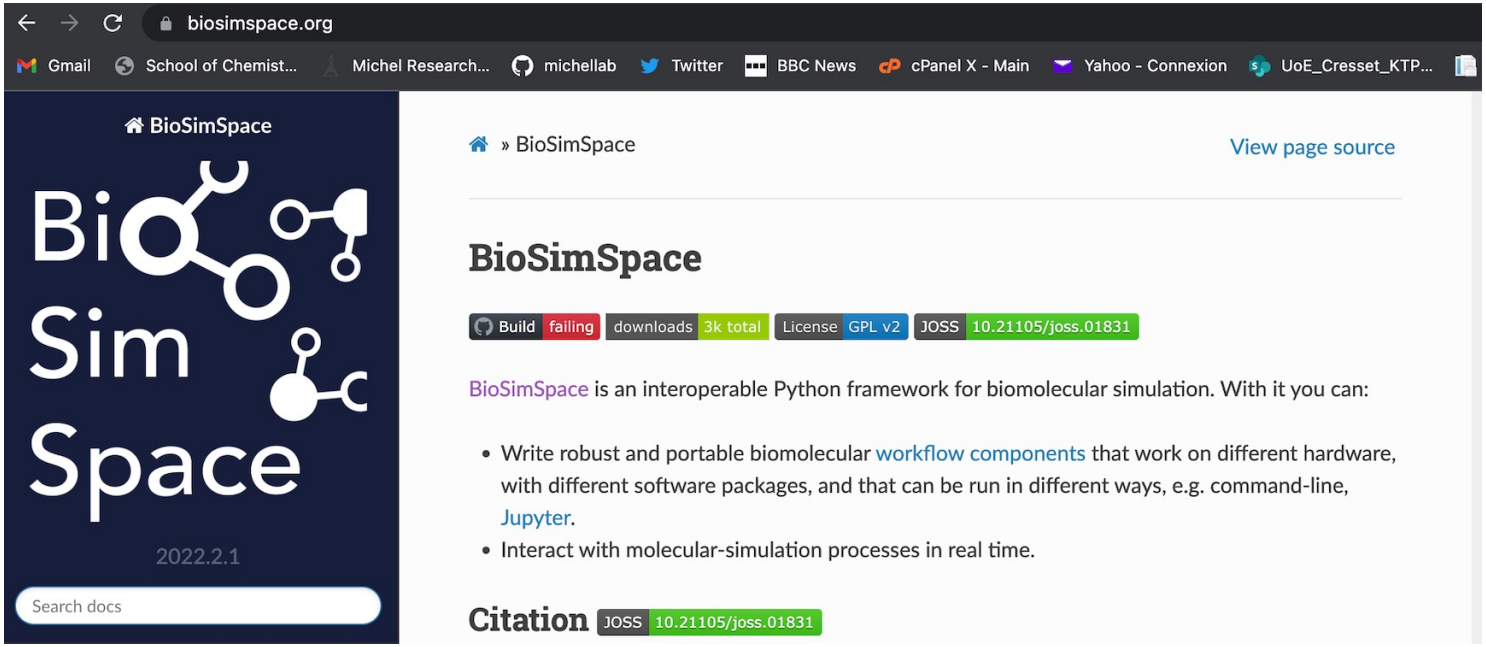
Accessing the workshop server

workshop.biosimspace.org



open terminal

What is BioSimSpace?

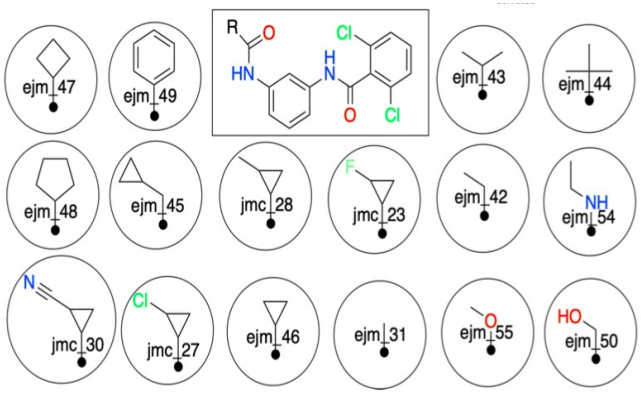


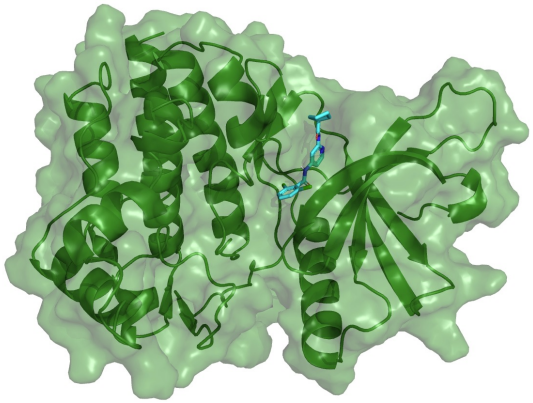
JOSS
The Journal of Open Source Software

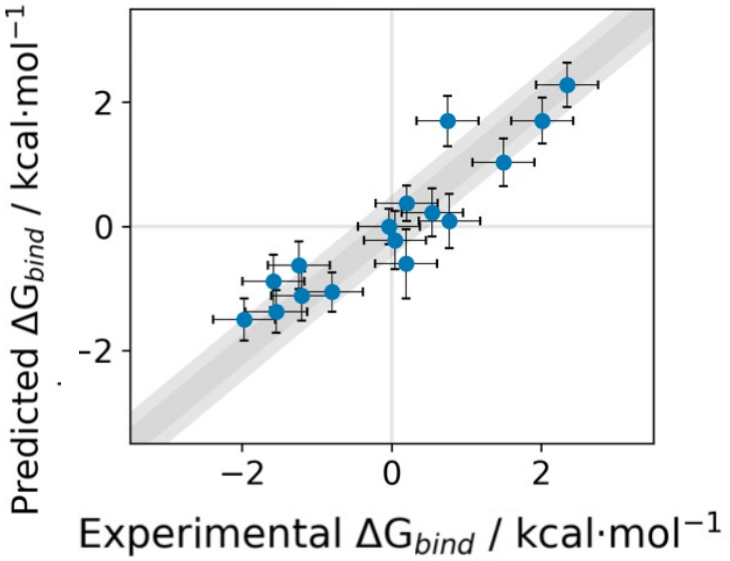
BioSimSpace: An interoperable Python framework for biomolecular simulation

Lester O. Hedges[1], Antonia S.J.S. Mey[2], Charles A. Laughton[3], Francesco L. Gervasio[4], Adrian J. Mulholland[5], Christopher J. Woods[1], and Julien Michel[2]

Alchemical free energy methods in drug design





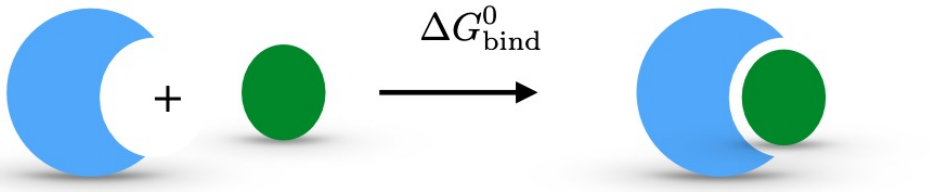


1930 — 1950 — 1980 — 2000 — 2020

Theoretical foundations → Enabling Technologies → Academic research → Industrial adoption

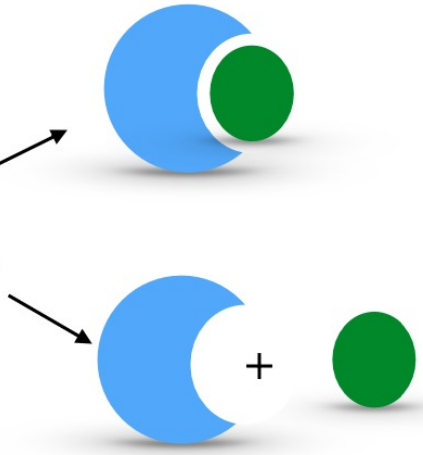
TI **FEP MM, MD, MC** **FEP+**

Free energy of binding



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

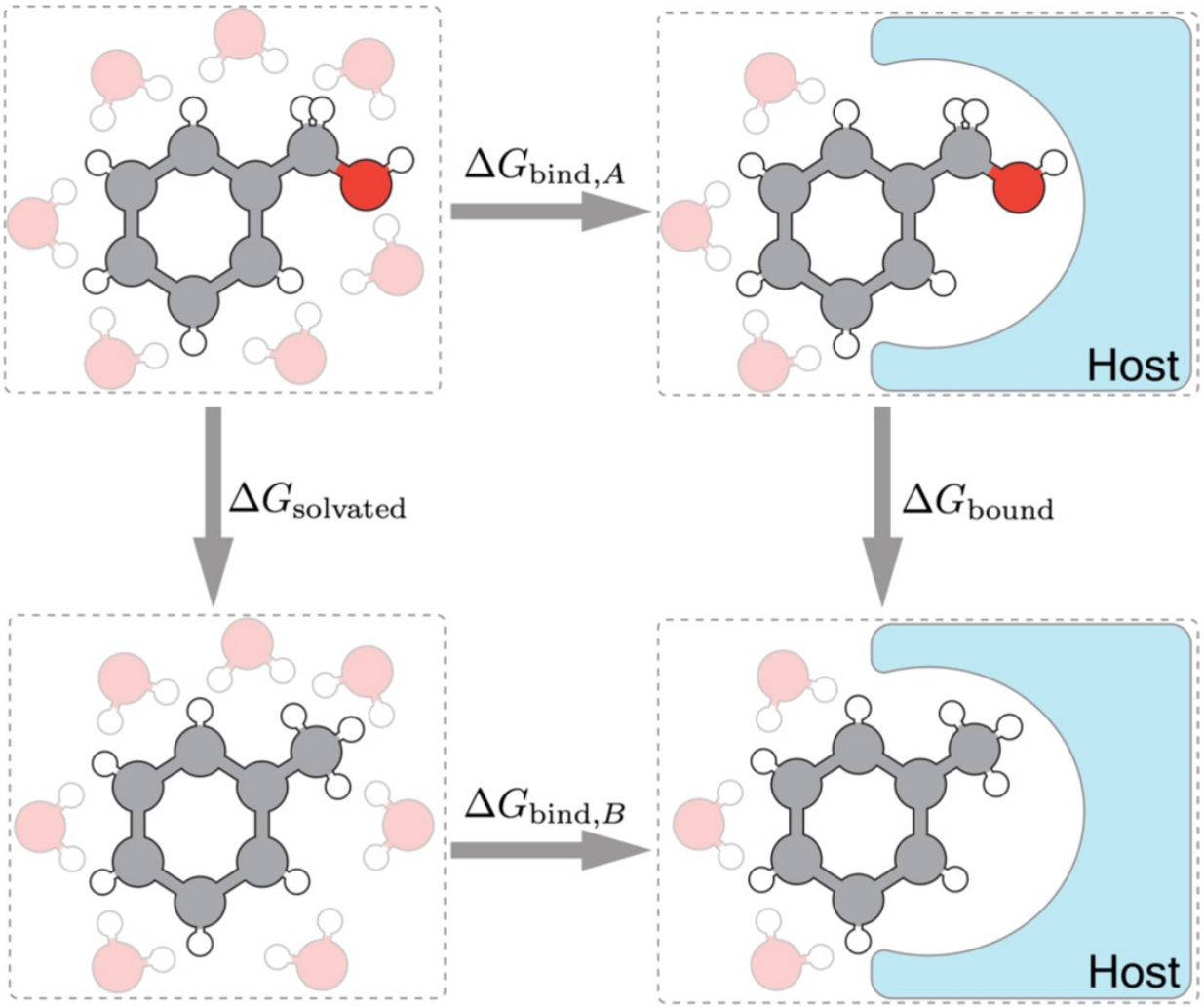
$$K_b^\circ = \frac{\text{probability in bound state}}{\text{probability in unbound state}}$$



Sample this using Molecular dynamics?

slide courtesy of Antonia Mey

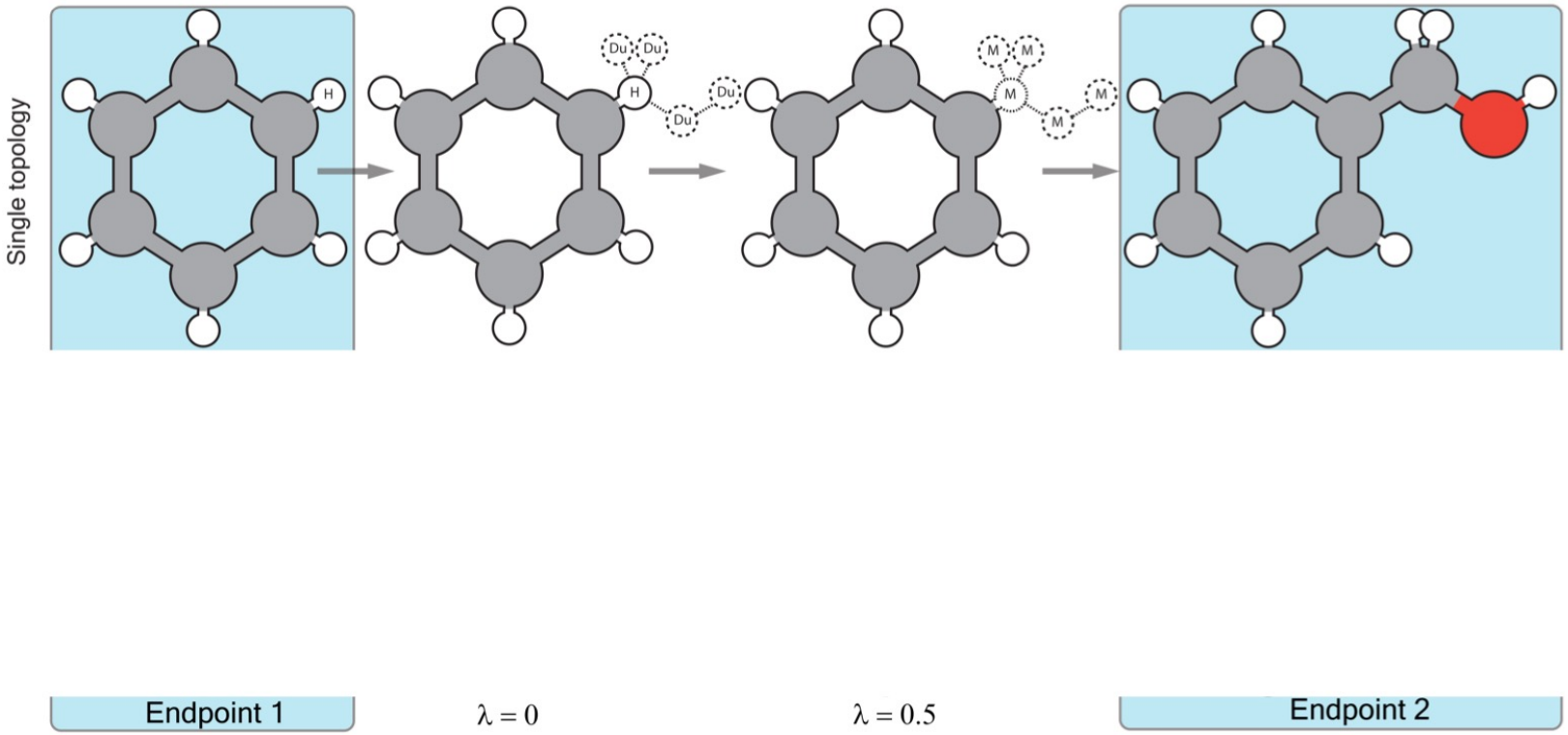
The alchemical pathway



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

slide courtesy of Antonia Mey

The lambda coordinate



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

Potential energy functions

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

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

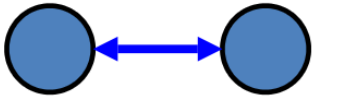
- The functional form and parameter set define a force field.
- Commonly used force fields include:
  CHARMM (Chemistry at Harvard Molecular Mechanics)
  AMBER (Assisted Model Building with Energy Refinement)
  OPLS (Optimised Potentials for Liquid Simulations)

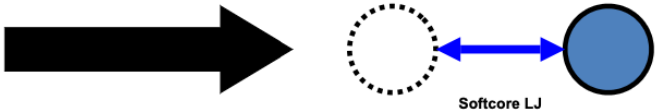
Softcore potentials

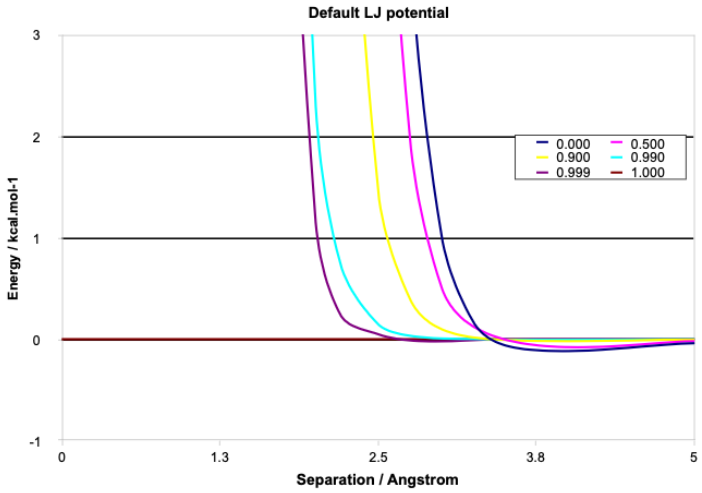
Zacharias et al. *J. Chem. Phys.* 100, 9025-, **1994**

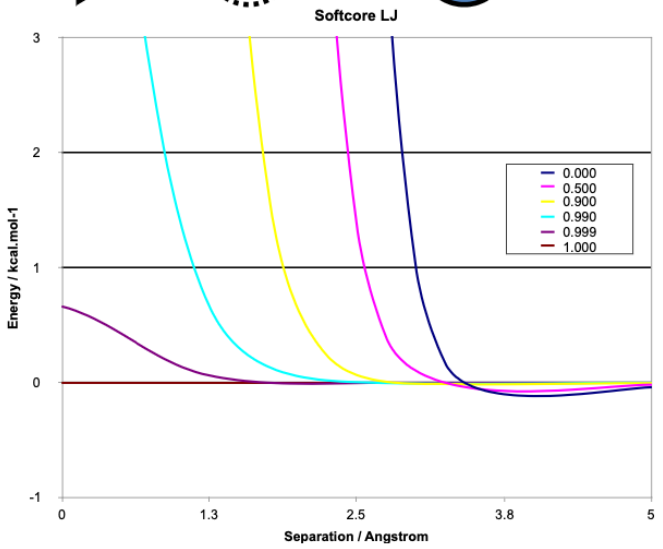
$$U_{\text{nonbonded},\lambda} = (1-\lambda)4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}^{12}}{\left(\lambda\delta\sigma_{ij}+r_{ij}^2\right)^6}\right) - \left(\frac{\sigma_{ij}^{6}}{\left(\lambda\delta\sigma_{ij}+r_{ij}^2\right)^3}\right)\right] + \frac{(1-\lambda)^n q_i q_j}{4\pi\varepsilon_0\sqrt{\left(\lambda+r_{ij}^2\right)}}$$

Dummy atoms!

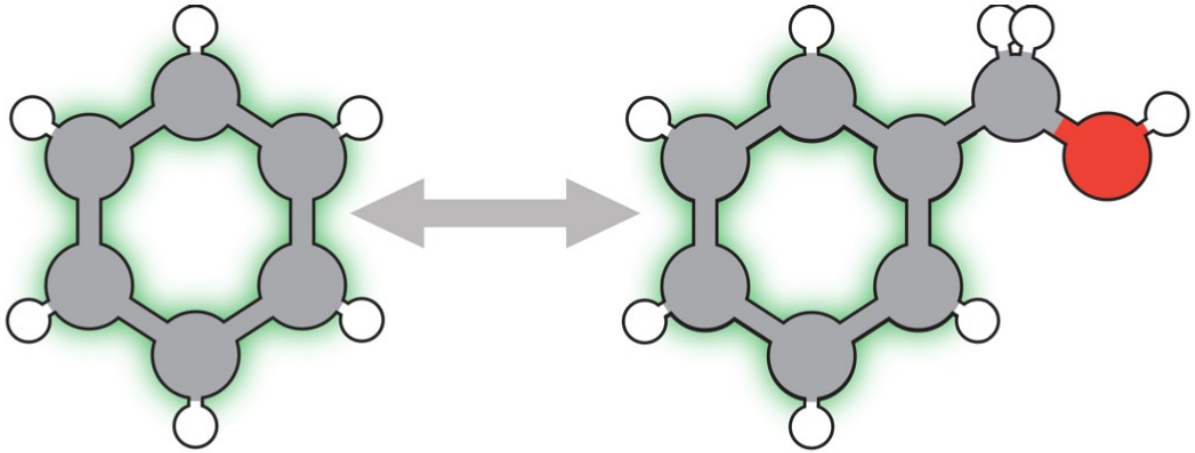


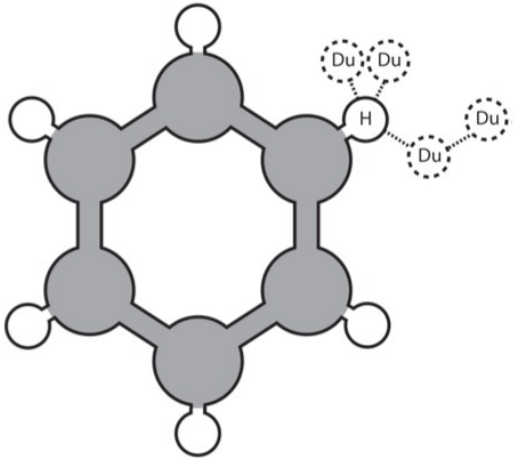






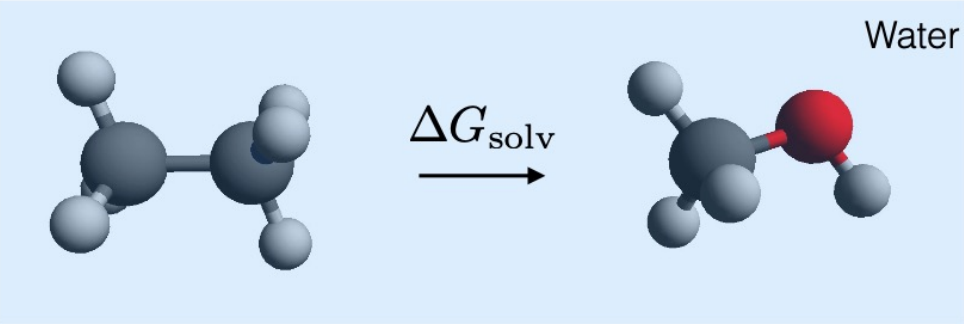
BioSimSpace merged molecules

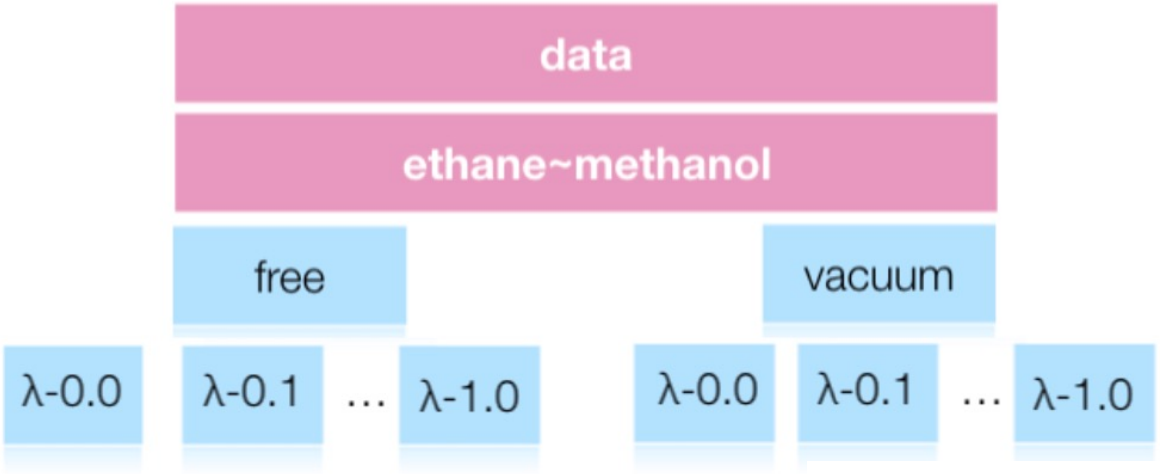




BioSimSpace holds a merged molecule and can write intermediates

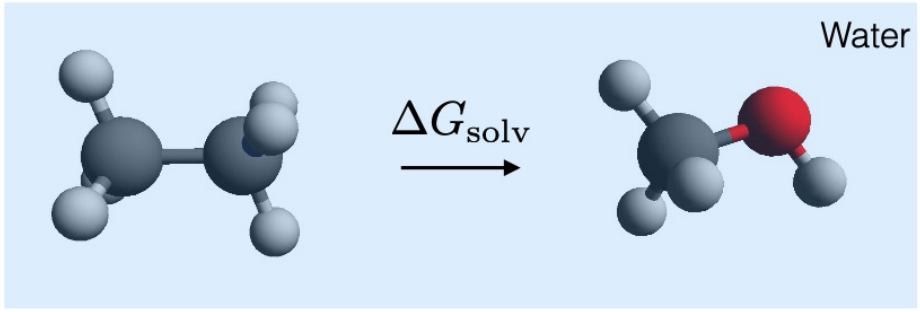
BioSimSpace setups inputs for different simulation engines

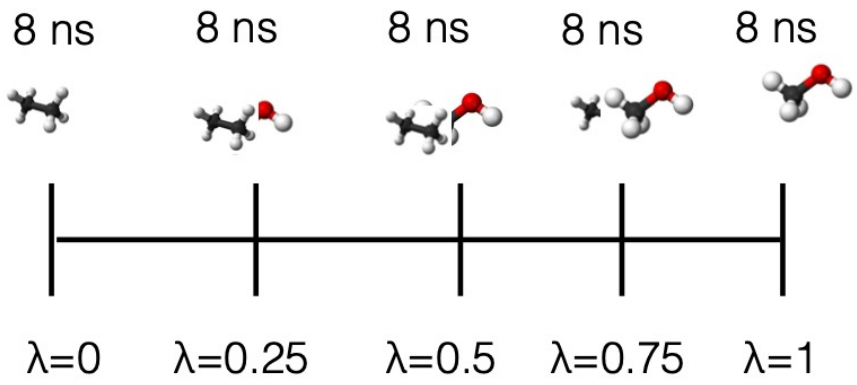




SOMD AMBER MD GROMACS FAST. FLEXIBLE. FREE.

BioSimSpace analyses simulation outputs



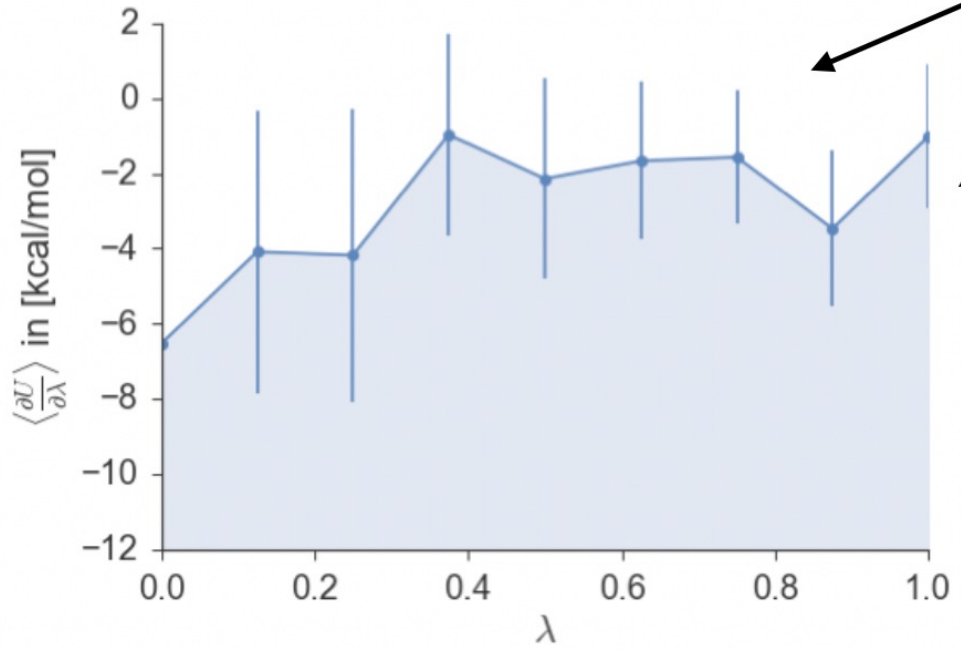


Zwanzig equation

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

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.

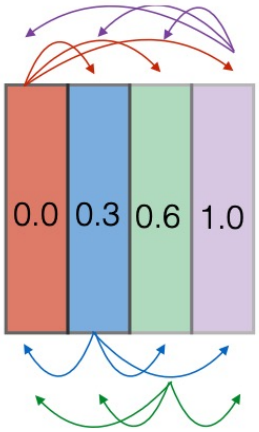
Multistate Bennett Acceptance Ratio (MBAR)

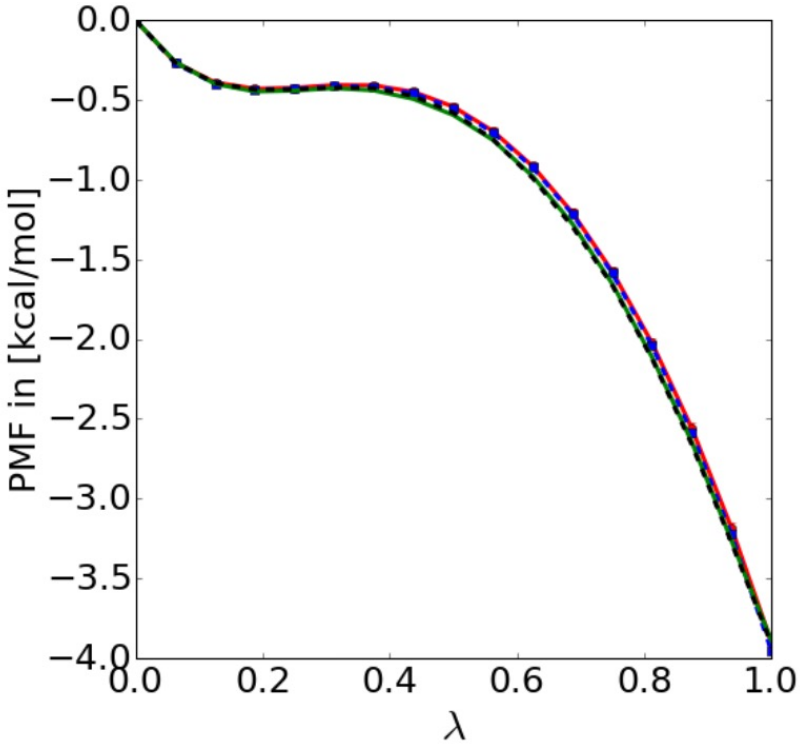
$$\mathcal{G}(\lambda_1) = -k_B T \ln \sum_{j=1}^{N} \sum_{n=1}^{K_j} \frac{\exp(-U(\lambda_i)/kT)}{\sum_{k=1}^{N} N_k \exp((\mathcal{G}(\lambda_k) - U(\lambda_k))/kT)}$$

MBAR is a reweighting estimator

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

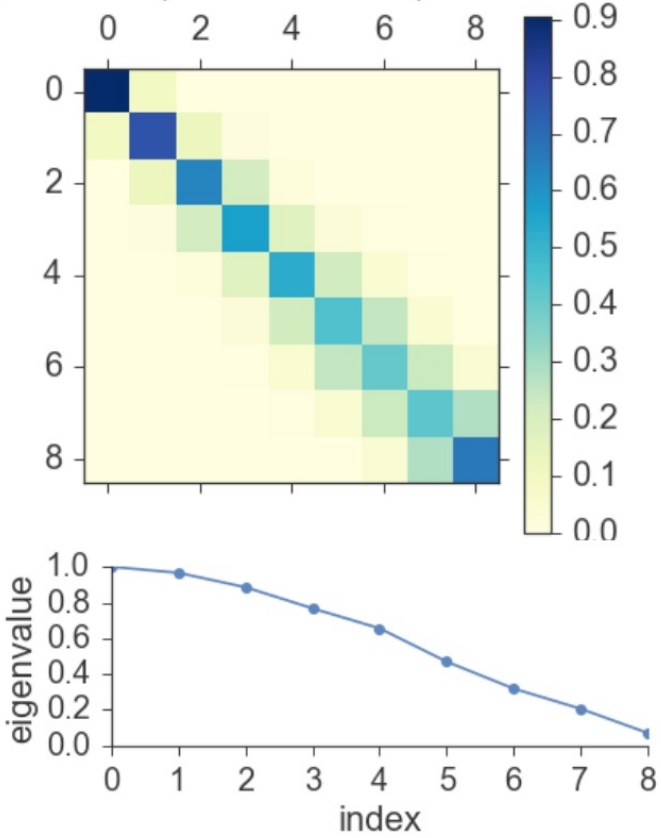
$$\Delta G_{AB} = G(\lambda_1) - G(\lambda_0)$$





Overlap matrix

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.

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

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

Let's get started