



Alchemical Free Energy Methods with BioSimSpace

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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

← → ↺

github.com/michellab/bssccpbiosim2022

🔑

🔗

Gmail

School of Chemist...

Michel Research...

🔗 michellab

🐦 Twitter

📺 BBC News

🔗 cPanel X - Main

📧 Yahoo - Connexion

🔗 UoE_Cresset_KTP...

📄 Suppliers Portal

📄 README.md

✎

Alchemical Simulations with BioSimSpace

Aimed at

Anyone interested in learning to perform alchemical free energy calculations using the CCP-BioSim [BioSimSpace](#) Python environment for easy setup, running, management and analysis of biomolecular simulations.

Requirements

Knowledge of Python, e.g. as gained from the [Python for Biomolecular Modellers](#) workshop.

Basic knowledge of atomistic simulations.

Abstract

Alchemical free energy calculations can be used to efficiently compute binding free energies between a ligand and a protein or hydration free energies of a small molecule. In the last few years, the use of such methods has gained momentum not only within academia but also within the pharmaceutical industry. In order to run alchemical free energy simulations, a series of molecular dynamics simulations need to be carried out. During this workshop you will learn how to set up, run, and analyse both relative and absolute binding free energy calculations with BioSimSpace.

Create a new release

Packages

No packages published
[Publish your first package](#)

Contributors 3

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Languages

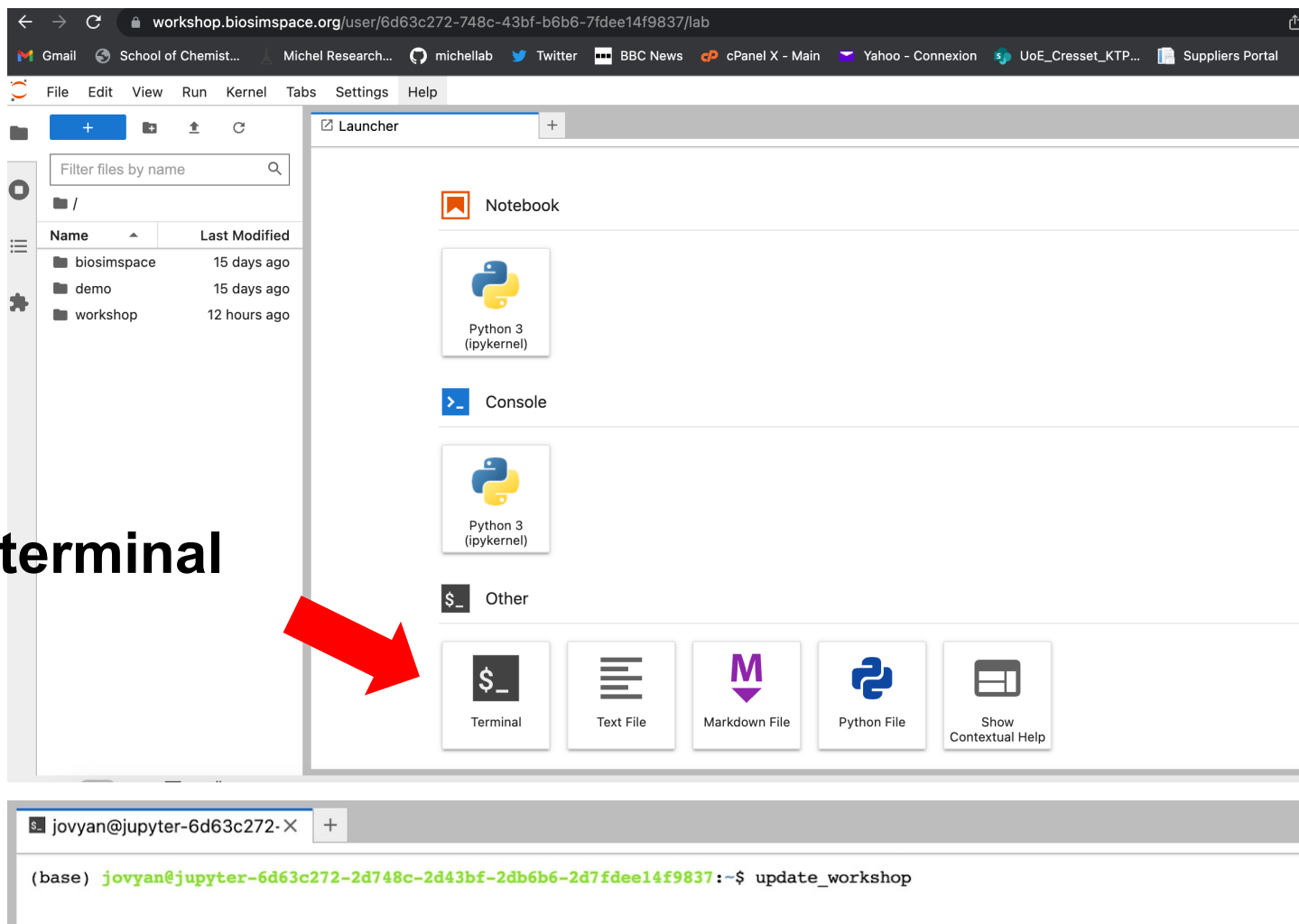
🟠 Jupyter Notebook 85.8%

🟢 Python 12.4%

🟢 Shell 1.8%

Accessing the workshop server

workshop.biosimspace.org



The screenshot shows the JupyterLab interface for a user on the workshop.biosimspace.org server. The left sidebar displays a file browser with a table of files:

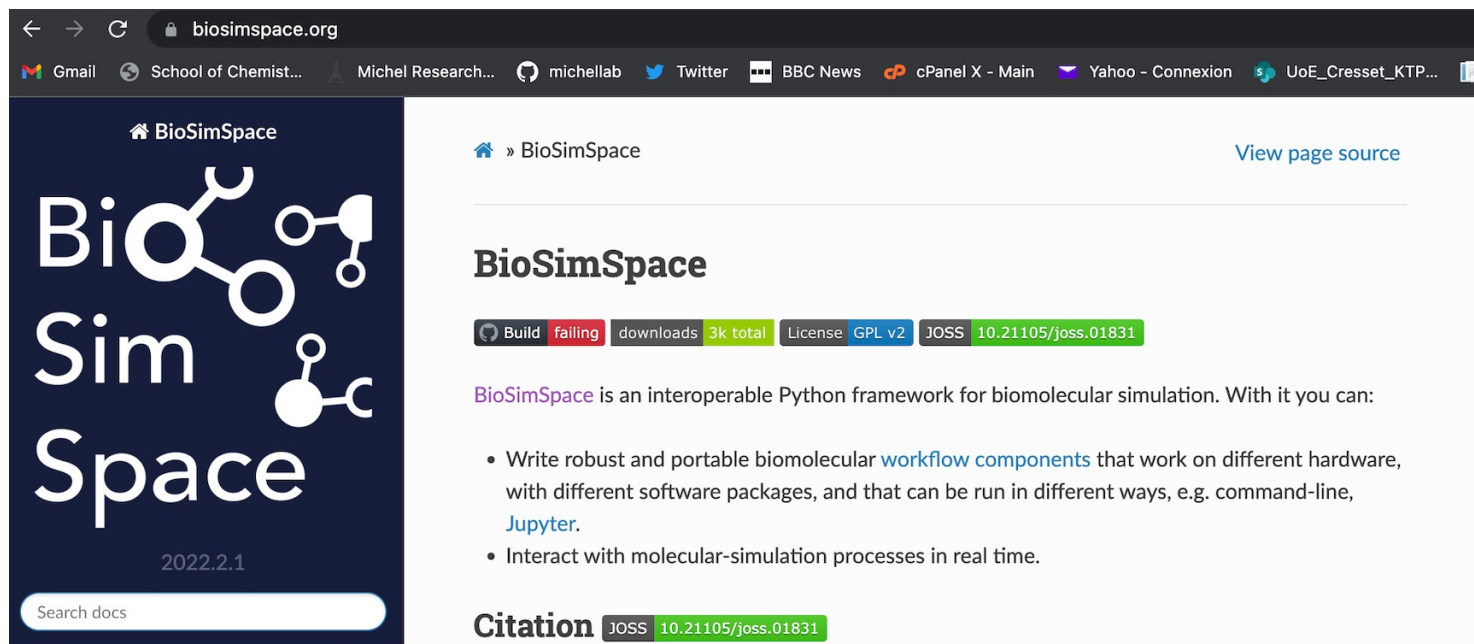
| Name | Last Modified |
|-------------|---------------|
| biosimspace | 15 days ago |
| demo | 15 days ago |
| workshop | 12 hours ago |

The main area shows the 'Launcher' view with several icons for opening new files or environments. A red arrow points to the 'Terminal' icon in the 'Other' section.

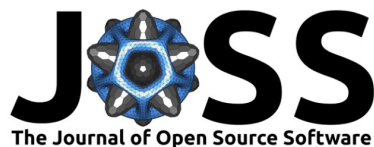
Below the Launcher view, a terminal window is open, showing the command prompt and the command being executed:

```
jovyan@jupyter-6d63c272-X  
(base) jovyan@jupyter-6d63c272-2d748c-2d43bf-2db6b6-2d7fdee14f9837:~$ update_workshop
```

What is BioSimSpace?



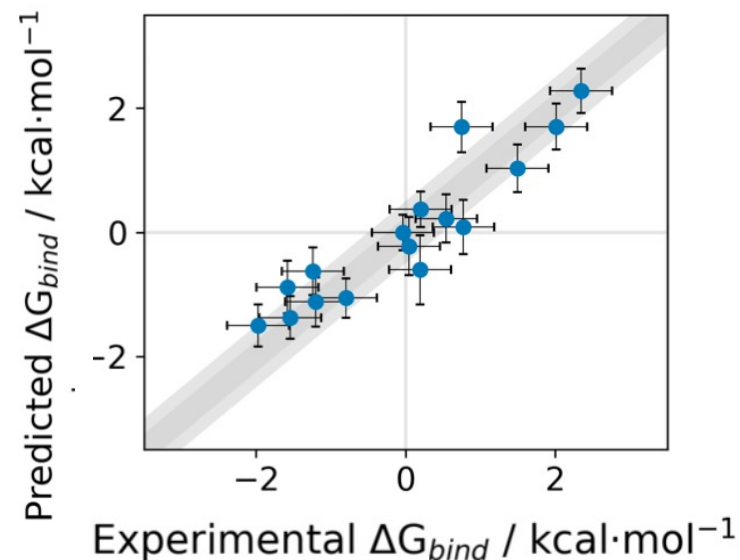
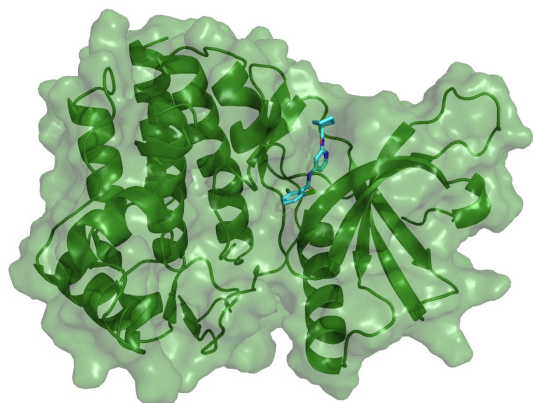
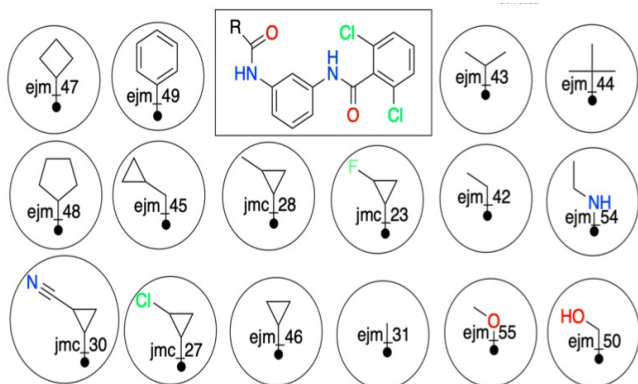
The screenshot shows the BioSimSpace website in a web browser. The browser's address bar displays 'biosimspace.org'. The website's header includes a 'BioSimSpace' logo and a 'View page source' link. The main content area features the title 'BioSimSpace' and a series of status badges: 'Build failing', 'downloads 3k total', 'License GPL v2', and 'JOSS 10.21105/joss.01831'. Below this, a paragraph describes BioSimSpace as an interoperable Python framework for biomolecular simulation. A bulleted list highlights its capabilities: writing robust and portable biomolecular workflow components that work on different hardware and software packages, and interacting with molecular-simulation processes in real time. A 'Citation' section provides the JOSS reference: 'JOSS 10.21105/joss.01831'. A search bar for documentation is located at the bottom left of the page.



BioSimSpace: An interoperable Python framework for biomolecular simulation

Lester O. Hedges¹, Antonia S.J.S. Mey², Charles A. Laughton³,
Francesco L. Gervasio⁴, Adrian J. Mulholland⁵, Christopher J. Woods¹,
and Julien Michel²

Alchemical free energy methods in drug design



1930

1950

1980

2000

2020

Theoretical
foundations

Enabling
Technologies

Academic
research

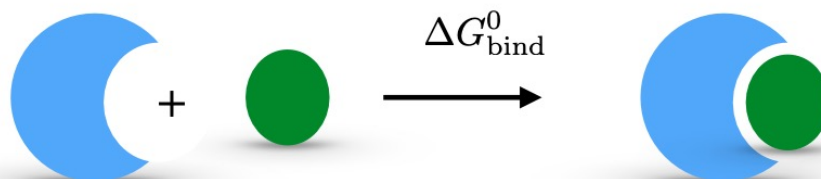
Industrial
adoption

TI

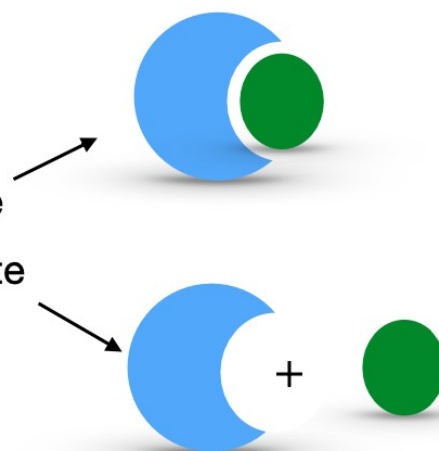
FEP MM, MD, MC

FEP+

Free energy of binding

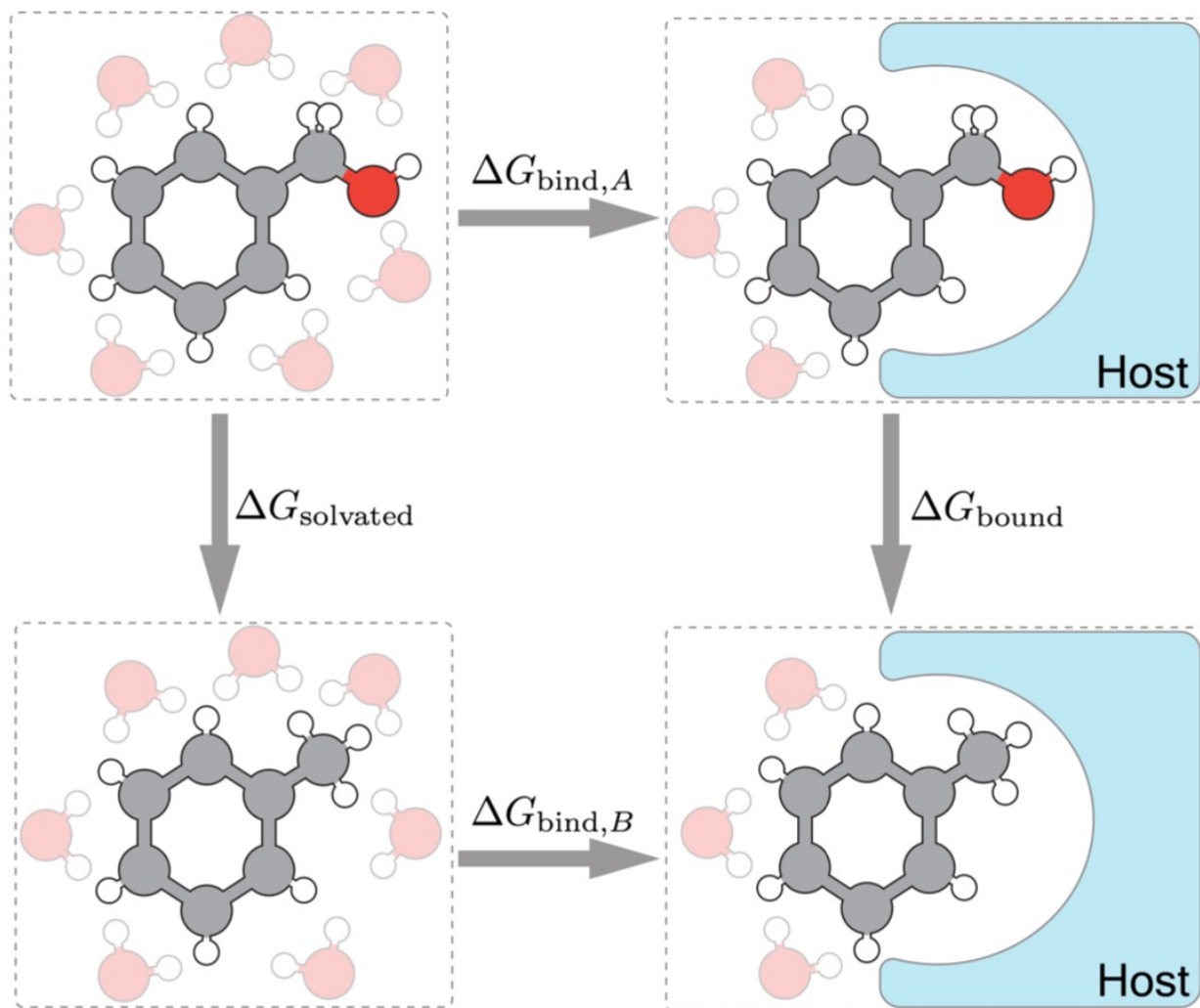


$$\Delta G_{\text{bind}} = -k_B T \ln K_b^{\circ}$$

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


Sample this using
Molecular dynamics?

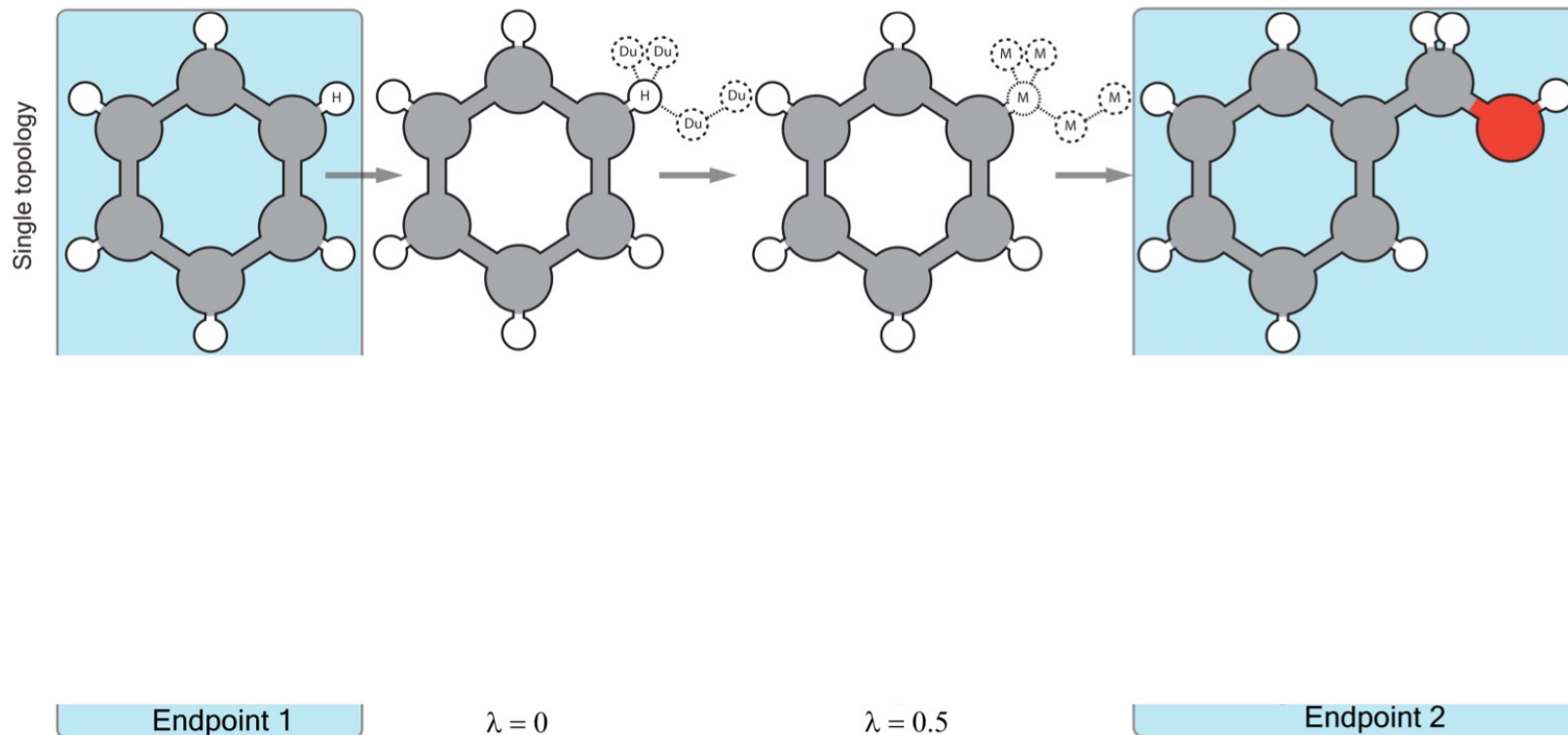
The alchemical pathway



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

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

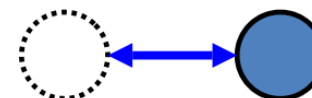
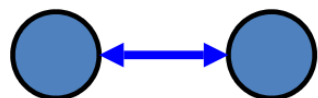
$$U = \sum_{\text{bonds}} \frac{1}{2} k_b (r - r_0)^2 + \sum_{\text{angles}} \frac{1}{2} k_a (\theta - \theta_0)^2 + \sum_{\text{torsions}} \frac{V_n}{2} [1 + \cos(n\phi - \delta)] \\ + \sum_{\text{improper}} V_{\text{imp}} + \sum_{\text{LJ}} 4\epsilon_{ij} \left(\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^6}{r_{ij}^6} \right) + \sum_{\text{elec}} \frac{q_i q_j}{r_{ij}},$$

- 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)

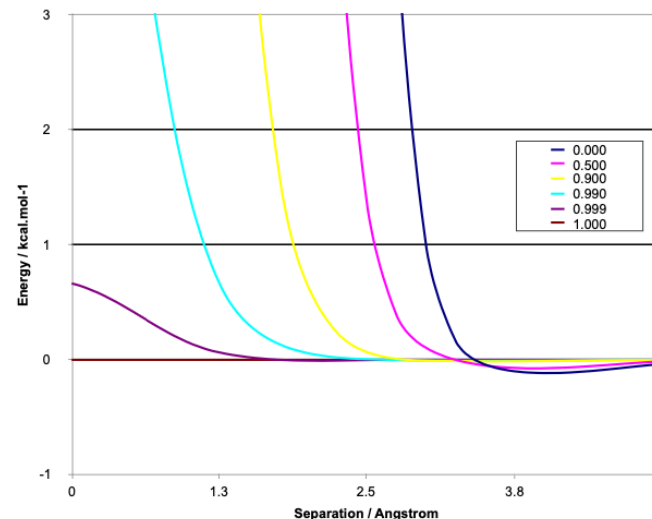
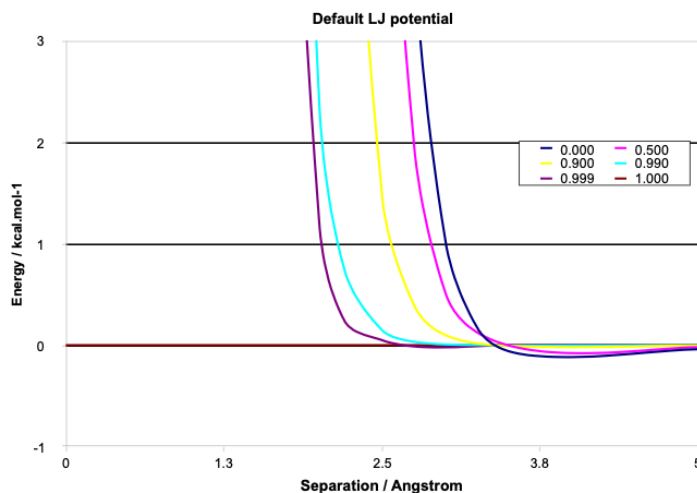
Softcore potentials

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

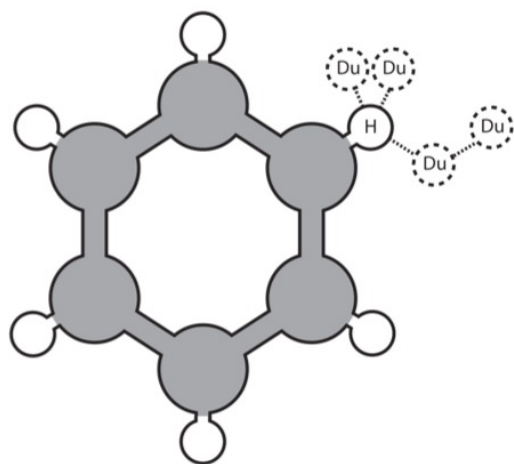
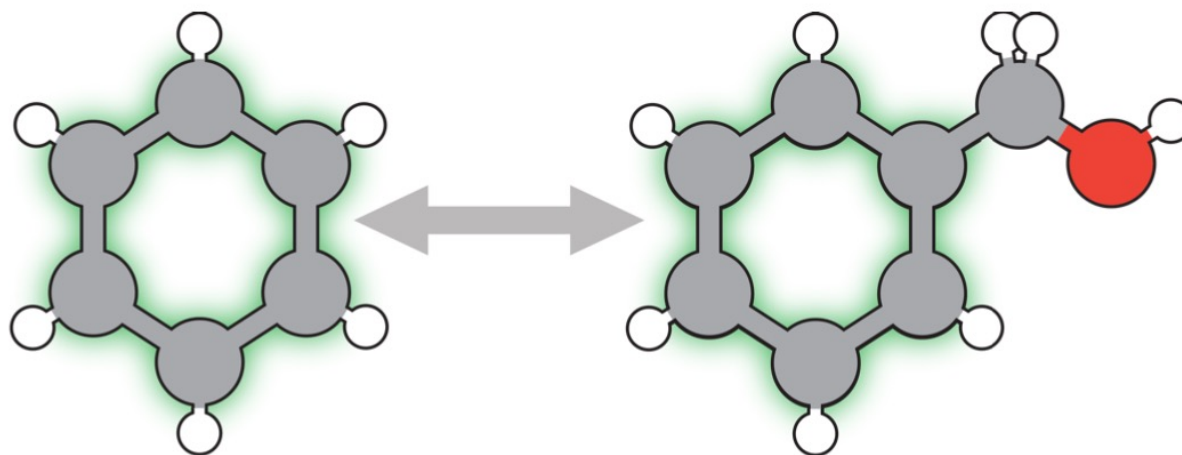
$$U_{\text{nonbonded},\lambda} = (1 - \lambda)4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}^{12}}{(\lambda\delta\sigma_{ij} + r_{ij}^2)^6} \right) - \left(\frac{\sigma_{ij}^6}{(\lambda\delta\sigma_{ij} + r_{ij}^2)^3} \right) \right] + \frac{(1 - \lambda)^n q_i q_j}{4\pi\varepsilon_0 \sqrt{(\lambda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



Softcore LJ

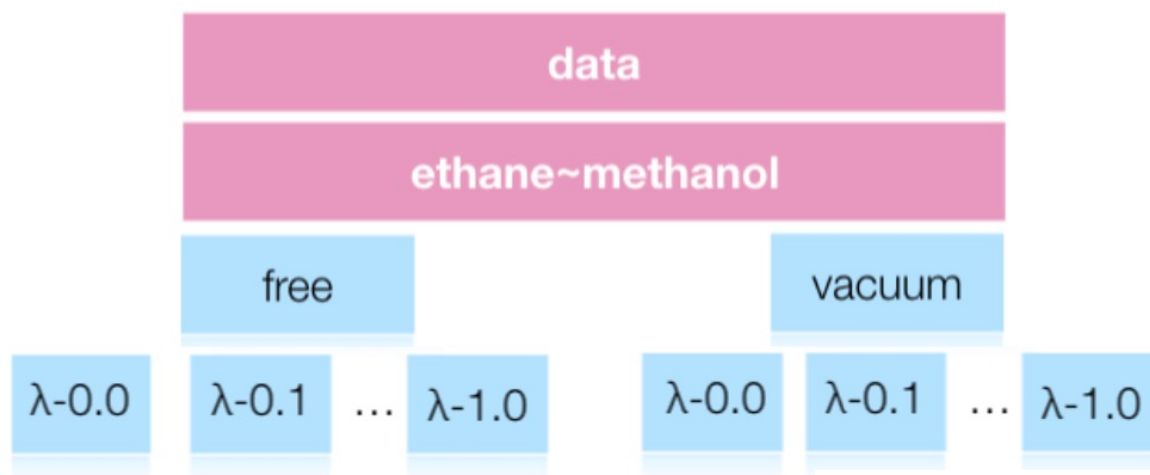
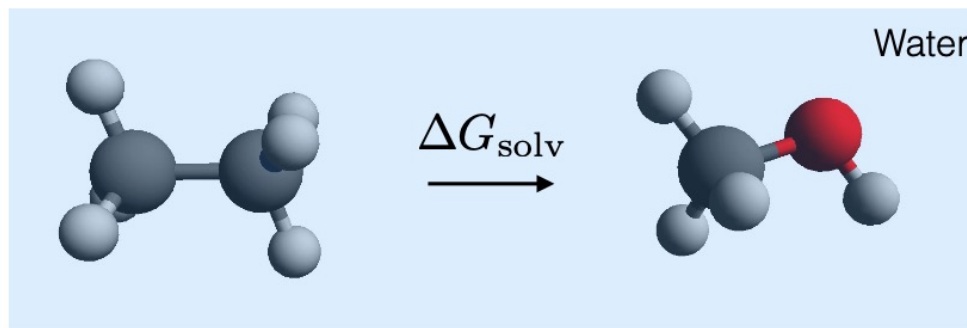


BioSimSpace merged molecules



BioSimSpace holds a merged molecule and can write intermediates

BioSimSpace setups inputs for different simulation engines



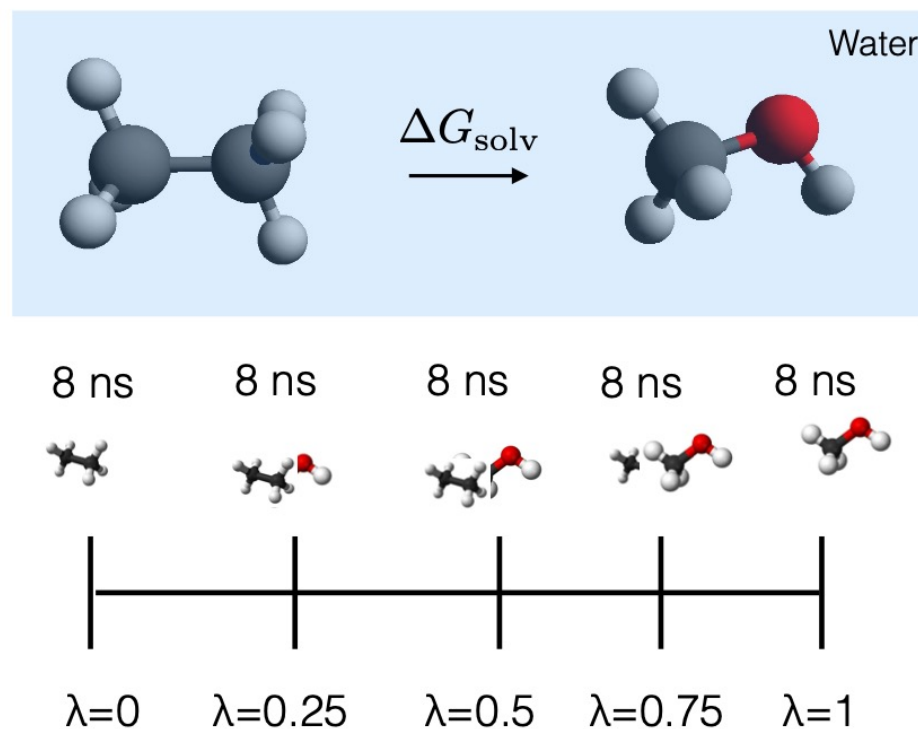
SOMD

AMBER MD

GROMACS
FAST. FLEXIBLE. FREE.



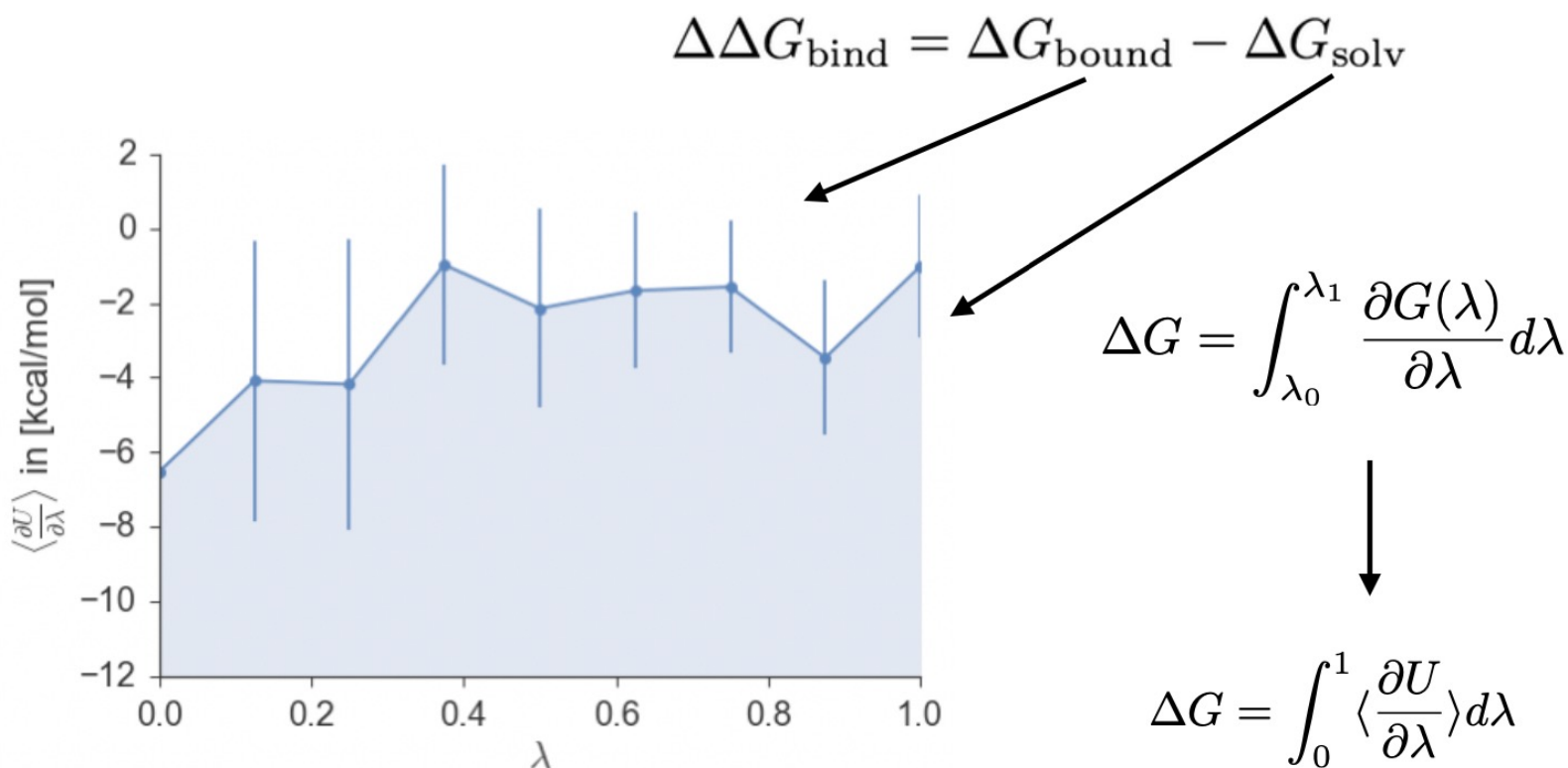
BioSimSpace analyses simulation outputs



Zwanzig equation

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

Thermodynamic integration



The integral represents the area under the curve.

There are different ways in which one can numerically integrate.

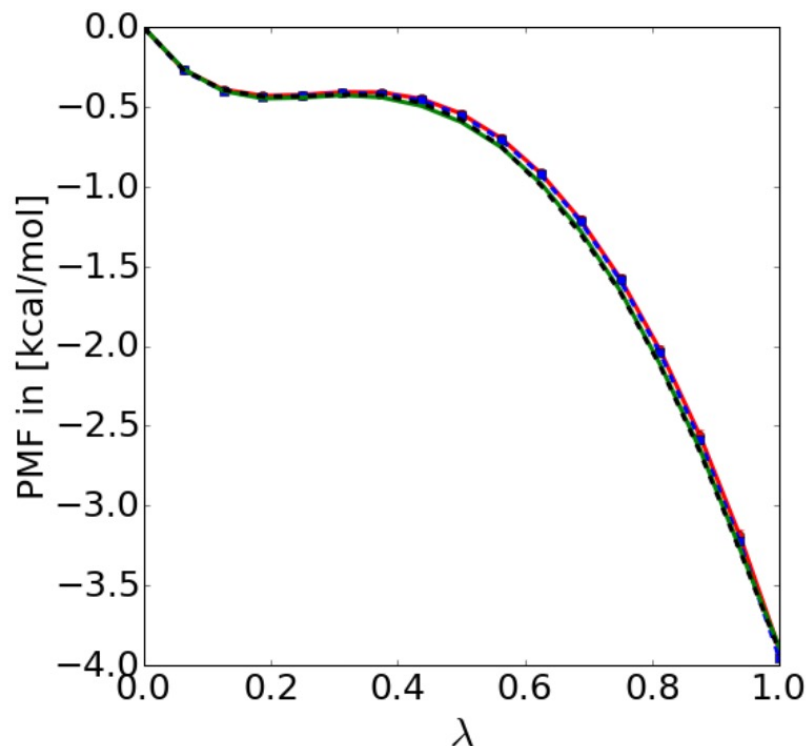
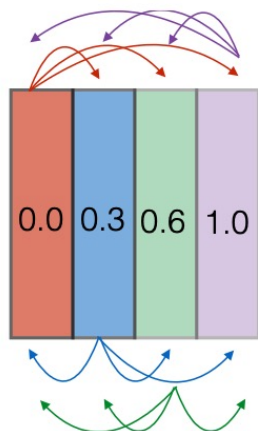
Multistate Bennett Acceptance Ratio (MBAR)

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

MBAR is a reweighting estimator

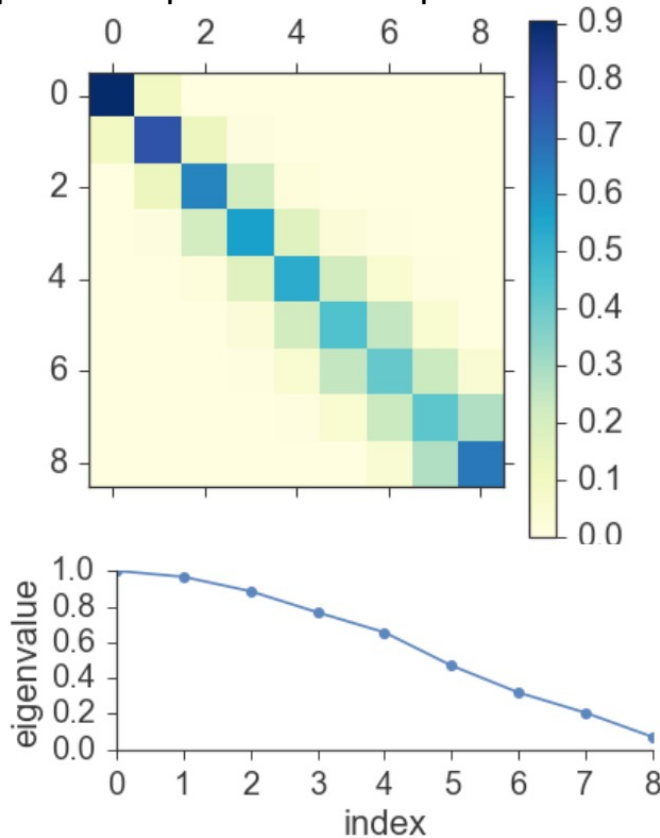
The free energy is correct up to an additive constant, which will cancel out when evaluating free energy differences.

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



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 .

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

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



Let's get started

The screenshot shows a JupyterLab environment. The left sidebar contains a file browser with a search bar and a list of files and folders. The main area displays a notebook titled 'alchemical_introduction.ipynb'.

File Browser:

| Name | Last Modified |
|---------------|---------------|
| answers | 12 hours ago |
| exercise_4... | 12 hours ago |
| images | 15 days ago |
| input | 15 days ago |
| o_xylene_... | 12 hours ago |
| slides | 12 hours ago |
| alchemical... | 12 hours ago |

Notebook Content:

Alchemical free energy setup

This jupyter notebook is an introduction alchemical free energy methods with BioSimSpace for the September 2022 CCPBioSim Workshop.

This notebook includes core as well as **extra** options. To ensure you have time to complete all notebooks, **we strongly recommend that you work through the notebooks to the end before returning to complete the extra sections.**

Authors

- [Antonia Mey](#) -- @ppxasjsm
- [Lester Hedges](#) -- @lohedges
- edited by [Finlay Clark](#) -- @fjclark
- expanded by [Anna Herz](#) -- @annamherz

Reading Time: ~ 30 mins