



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

← → ↺

github.com/michellab/bssccpbiosim2022

🔒

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UoE_Cresset_KTP...

Suppliers Portal

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✎

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

fjclark

annamherz

jmichel80 Julien Michel

Languages

Jupyter Notebook 85.8%

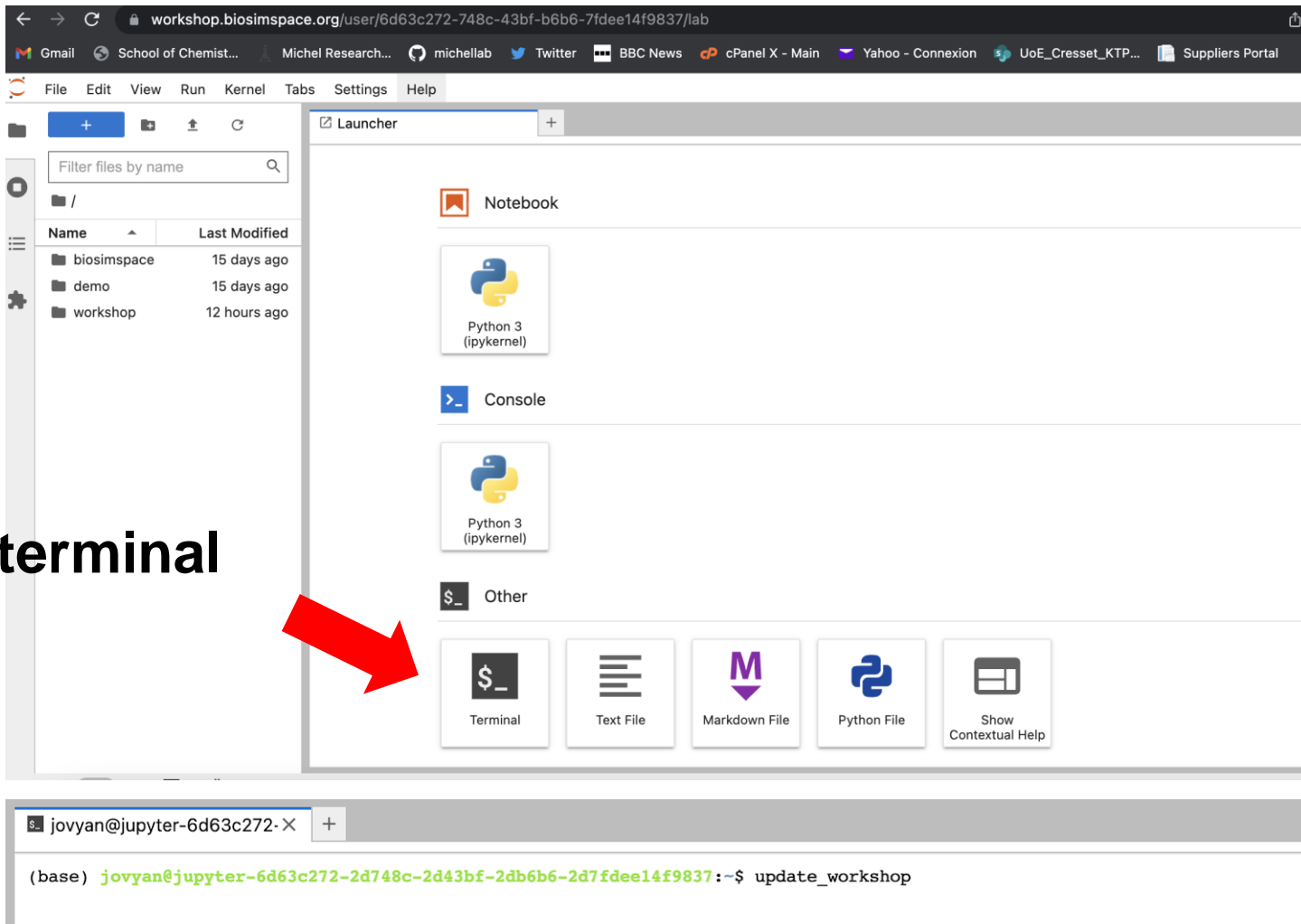
Python 12.4%

Shell 1.8%

Accessing the workshop server

workshop.biosimspace.org

open terminal



The screenshot shows the JupyterLab interface in a web browser. The address bar displays `workshop.biosimspace.org/user/6d63c272-748c-43bf-b6b6-7fdee14f9837/lab`. The left sidebar shows a file browser with a search bar and a table of files:

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

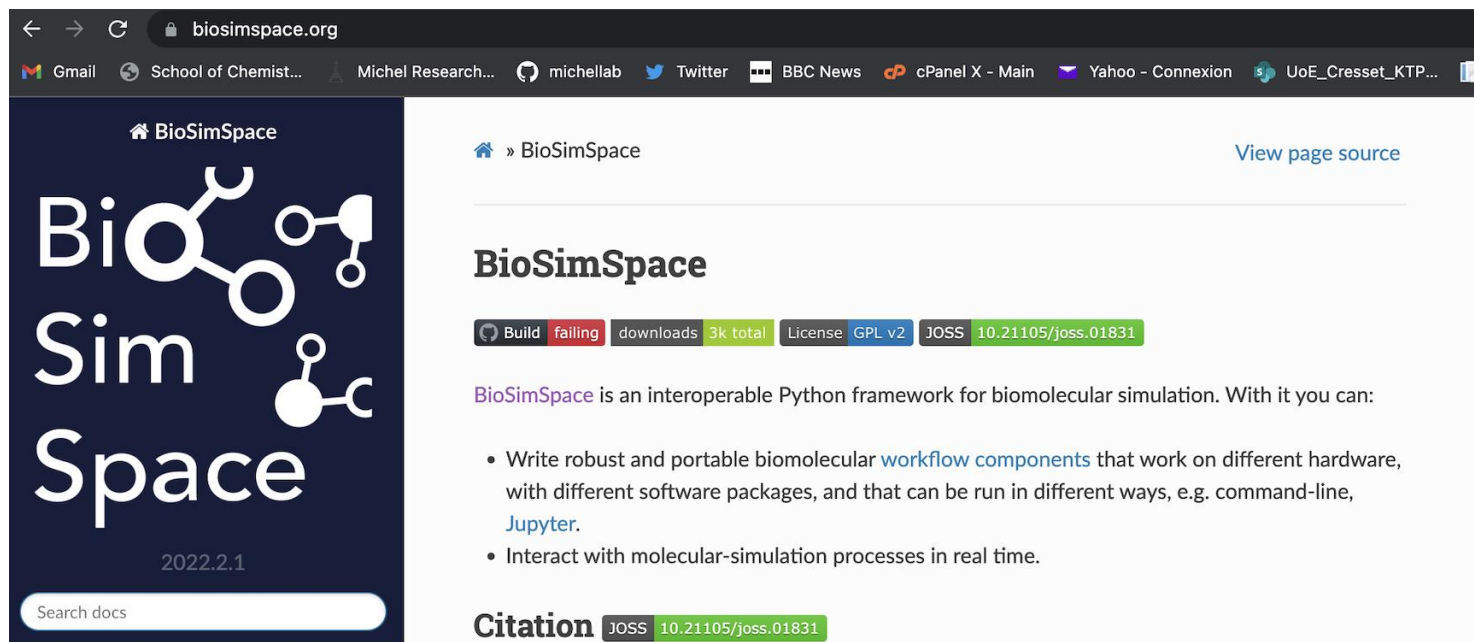
The main area is the 'Launcher' view, which contains several icons for opening different types of files or environments:

- Notebook
- Python 3 (ipykernel)
- Console
- Python 3 (ipykernel)
- Other
- Terminal
- Text File
- Markdown File
- Python File
- Show Contextual Help

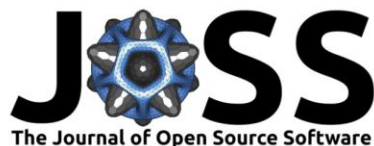
A red arrow points from the text 'open terminal' to the 'Terminal' icon in the 'Other' section.

Below the Launcher view, a terminal window is open, showing the command prompt `jovyan@jupyter-6d63c272-2d748c-2d43bf-2db6b6-2d7fdee14f9837:~$` and the command `update_workshop` being executed.

What is BioSimSpace?



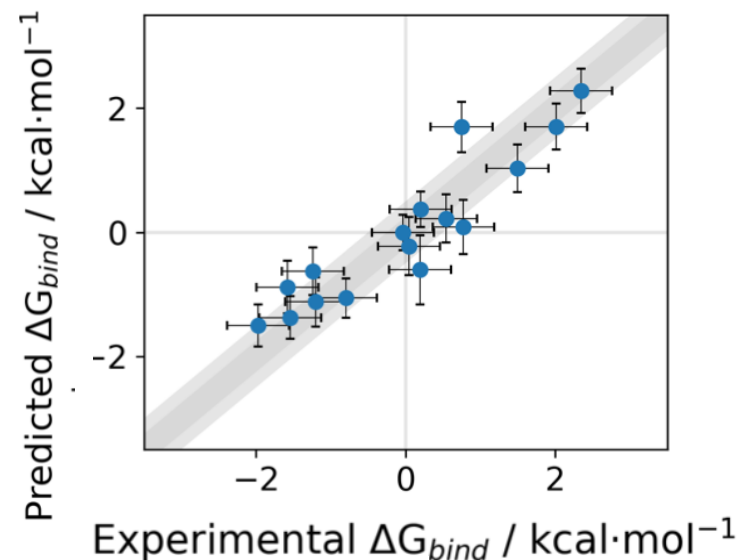
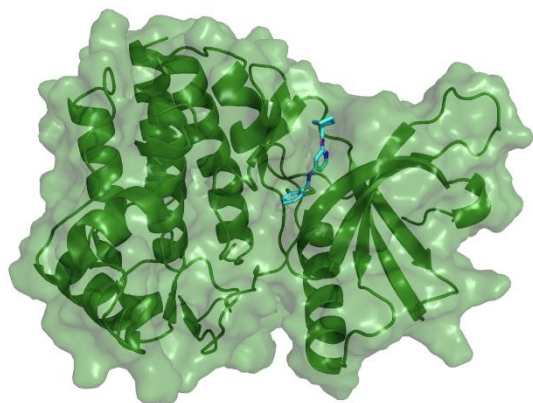
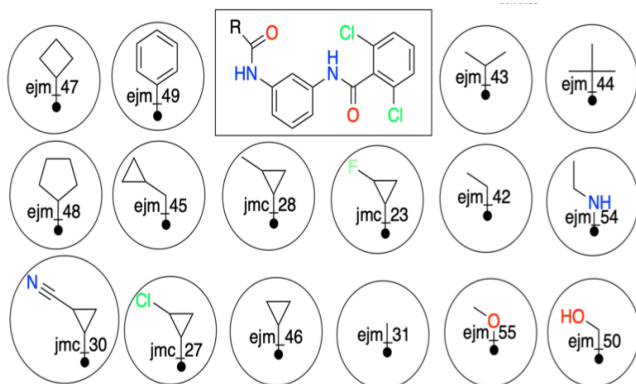
The screenshot shows the BioSimSpace website. The left sidebar features the BioSimSpace logo and the version number 2022.2.1. The main content area includes the BioSimSpace title, a navigation bar with links like Build, failing, downloads, 3k total, License, GPL v2, JOSS, and 10.21105/joss.01831. Below this, a description states: "BioSimSpace is an interoperable Python framework for biomolecular simulation. With it you can:" followed by a list of capabilities: "Write robust and portable biomolecular workflow components that work on different hardware, with different software packages, and that can be run in different ways, e.g. command-line, Jupyter." and "Interact with molecular-simulation processes in real time." A citation section at the bottom shows the JOSS citation: 10.21105/joss.01831.



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

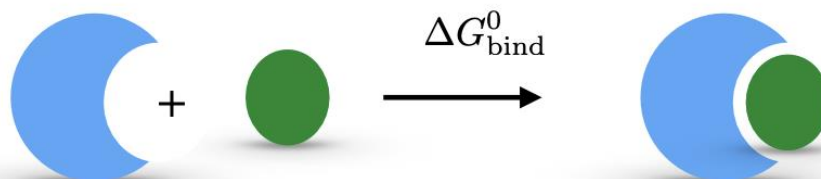
Industrial
adoption

TI

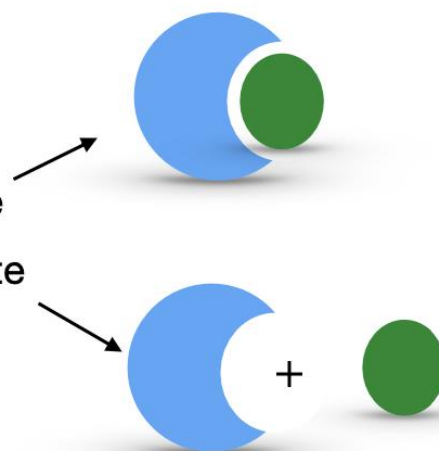
FEP MM, MD, MC

FEP+

Free energy of binding

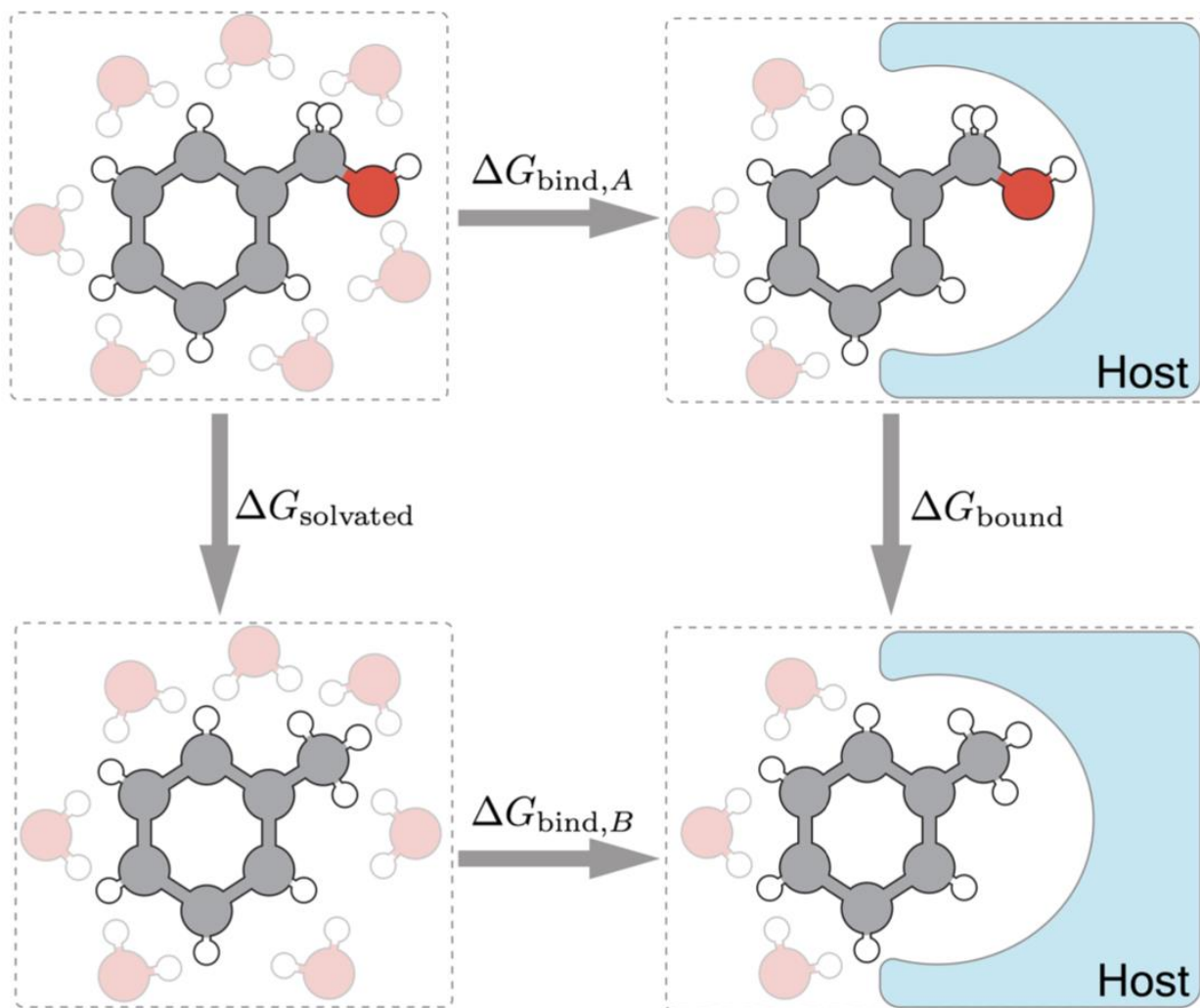


$$\Delta G_{\text{bind}}^{\circ} = -k_B T \ln K_b^{\circ}$$

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


Sample this using
Molecular dynamics?

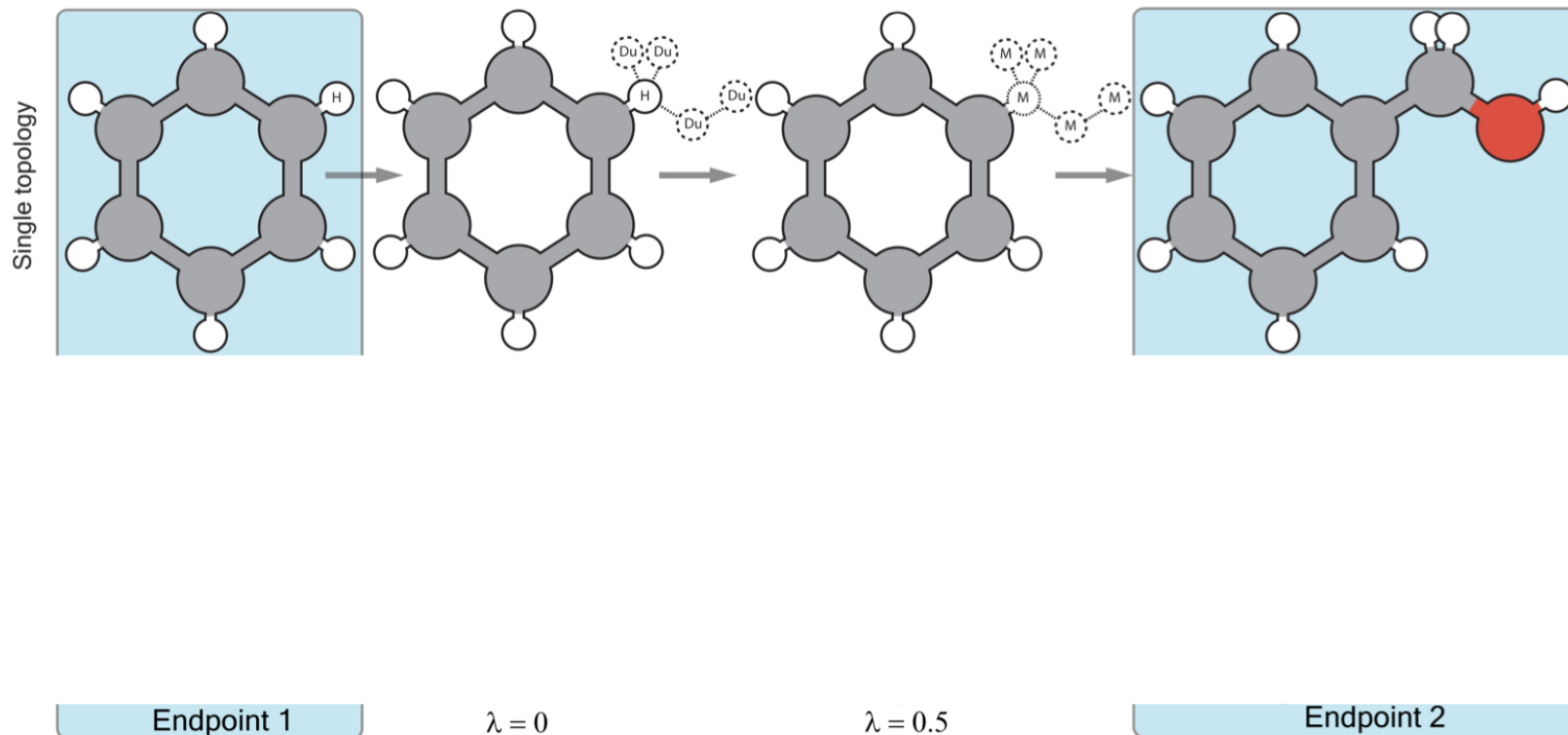
The alchemical pathway



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

slide courtesy of Antonia Mey

The lambda coordinate



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

slide courtesy of Antonia Mey

Potential energy functions

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

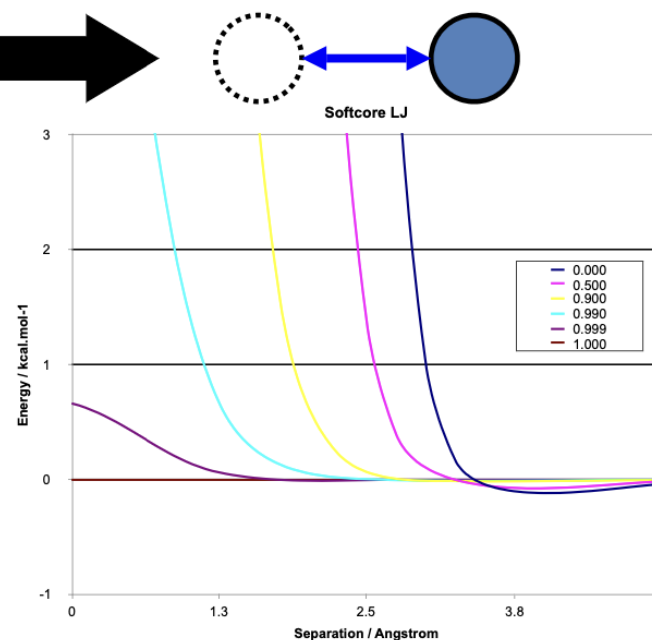
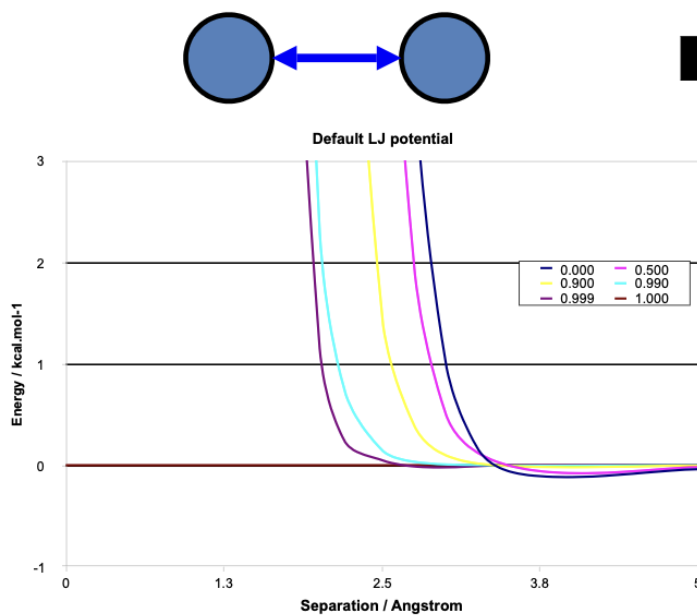
- The functional form and parameter set define a force field.
- Commonly used force fields include:
 - CHARMM (Chemistry at Harvard Molecular Mechanics)
 - AMBER (Assisted Model Building with Energy Refinement)
 - OPLS (Optimised Potentials for Liquid Simulations)

Softcore potentials

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

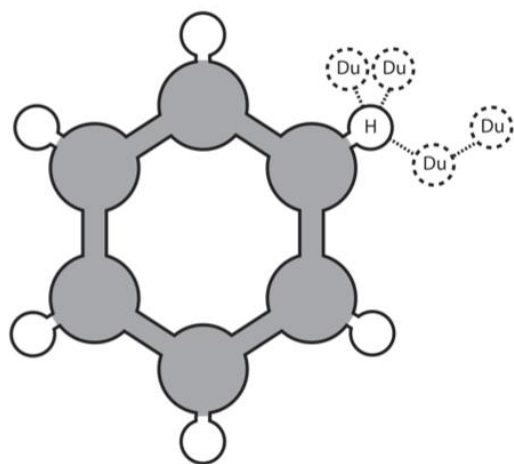
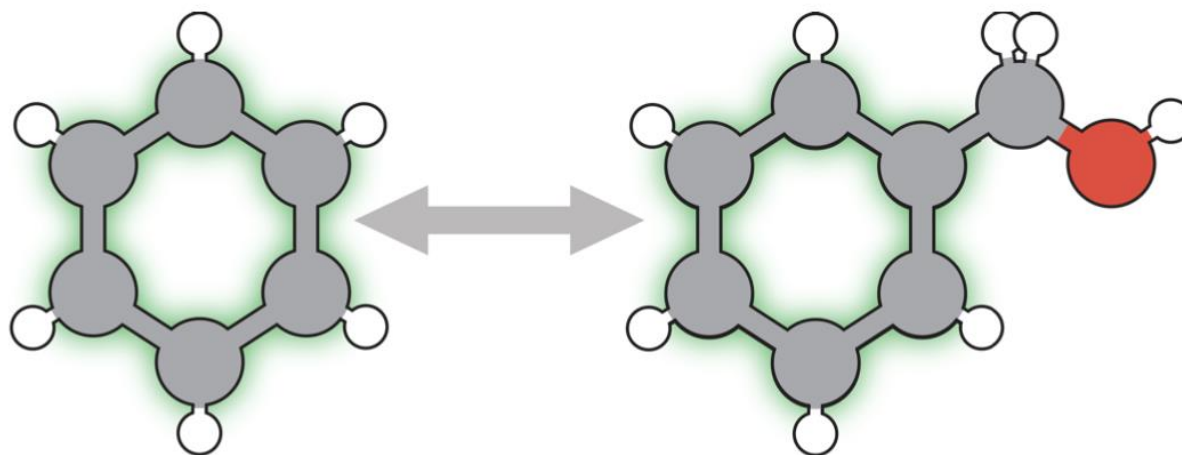
$$V_{\text{LJ}} = (1 - \lambda) \left[\frac{A}{(r^2 + \delta\lambda)^6} - \frac{B}{(r^2 + \delta\lambda)^3} \right]$$

Dummy atoms!



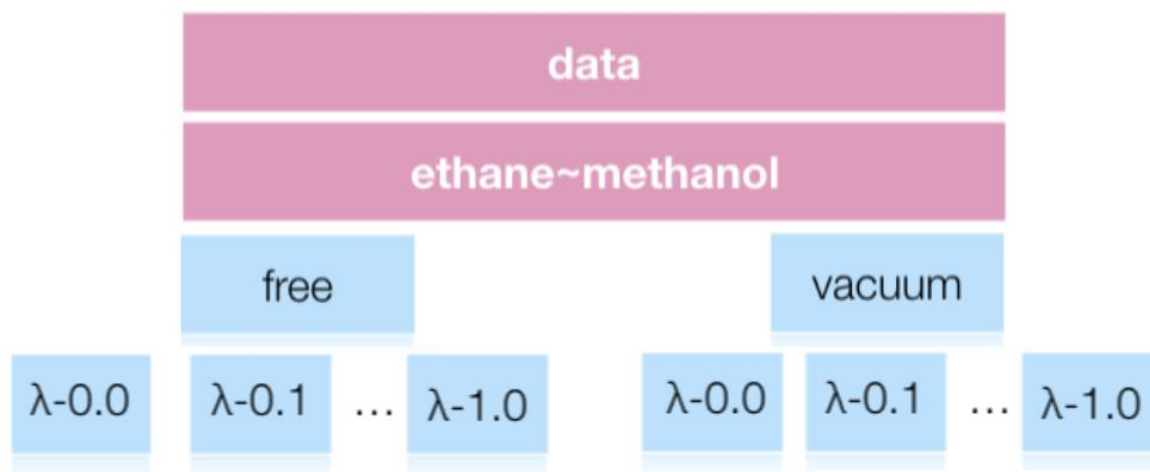
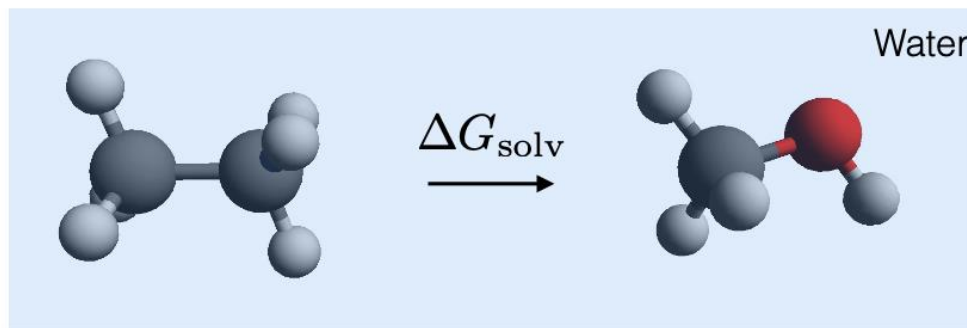
slide courtesy of Antonia Mey

BioSimSpace merged molecules



BioSimSpace holds a merged molecule and can write intermediates

BioSimSpace setups inputs for different simulation engines



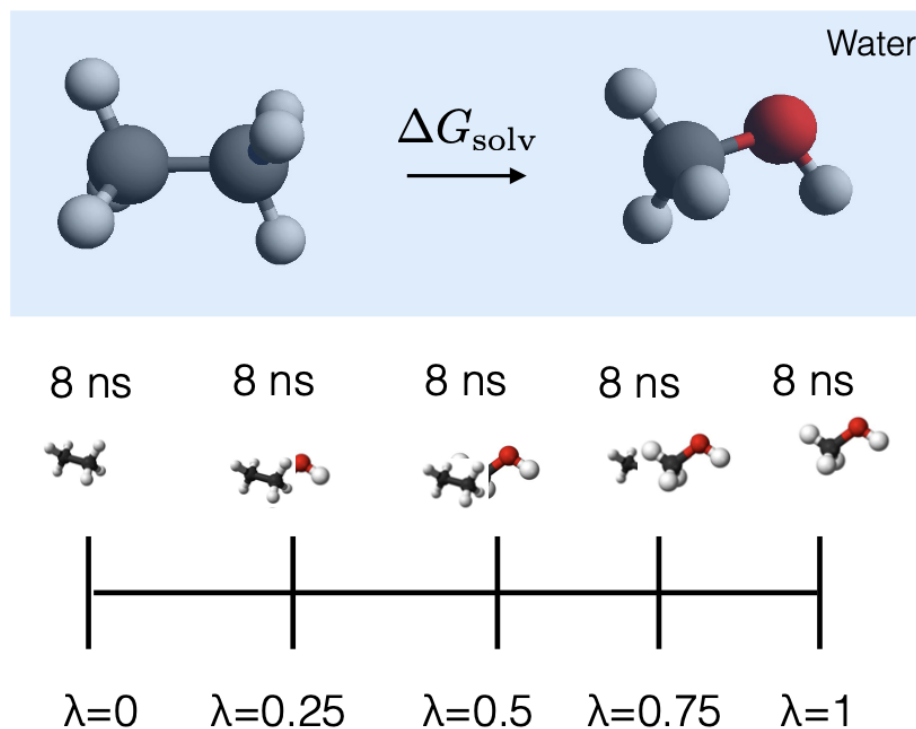
SOMD

AMBER MD

GROMACS
FAST. FLEXIBLE. FREE.



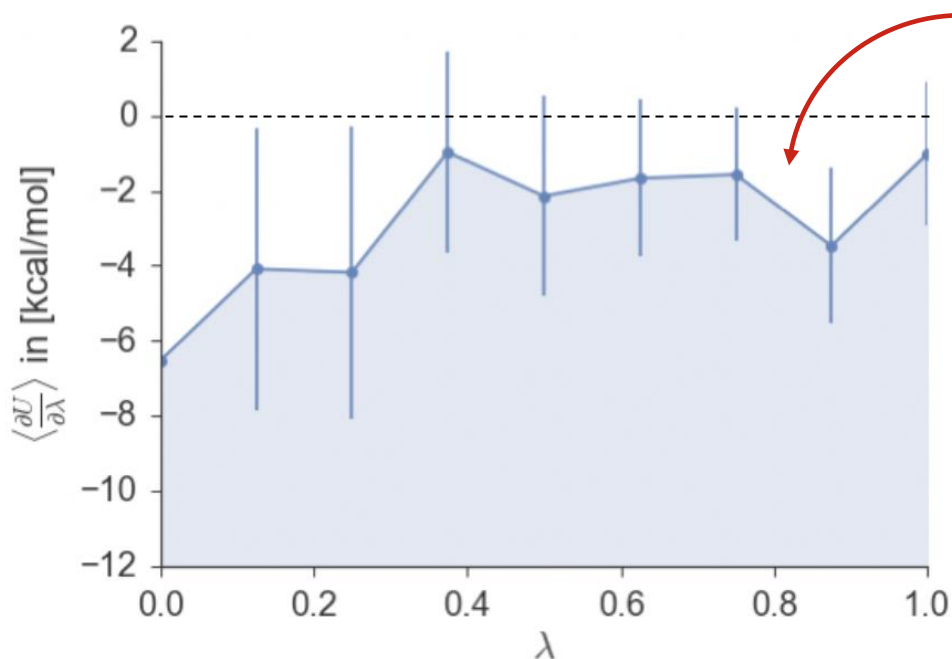
BioSimSpace analyses simulation outputs



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



White area

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

$$\Delta G = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle d\lambda$$

The integral represents the area under the curve.

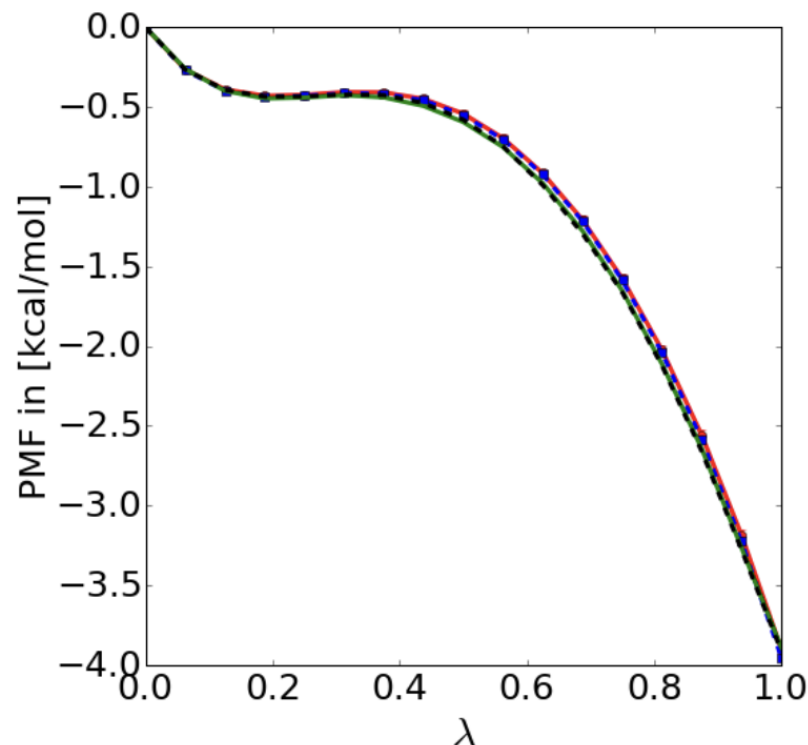
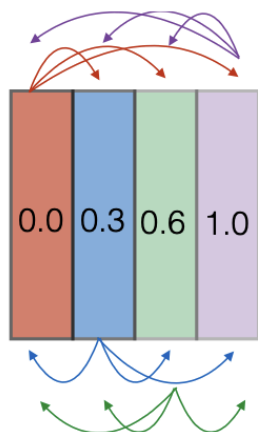
There are different ways in which one can numerically integrate.

Multistate Bennett Acceptance Ratio (MBAR)

$$e^{-f_i} = \sum_{n=1}^N \frac{e^{-u_i(\vec{x}_n)}}{\sum_k N_k e^{f_k - u_k(\vec{x}_n)}}$$

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

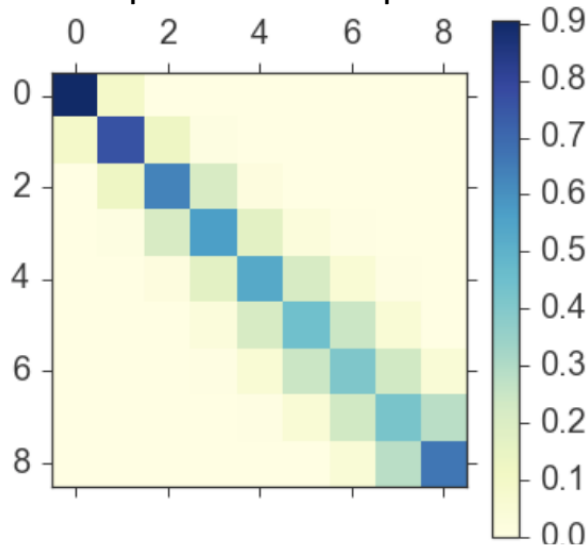
$$\Delta G_{AB} = G(\lambda_1) - G(\lambda_0)$$



slide courtesy of Antonia Mey

Overlap matrix

Overlap matrix estimates the phase space overlap



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

$$W_{n,i}(x_n) = \frac{e^{\beta G_i - \beta U_i(x_n)}}{\sum_{k=1}^K N_k e^{\beta G_k - \beta U_k(x_n)}}$$

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

workshop.biosimspace.org/user/6d63c272-748c-43bf-b6b6-7fdee14f9837/lab/tree/workshop/introduction_to_alchemistry/alchemical_introduction.ipynb

File Edit View Run Kernel Tabs Settings Help

Filter files by name

/ workshop / introduction_to_alchemi

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

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