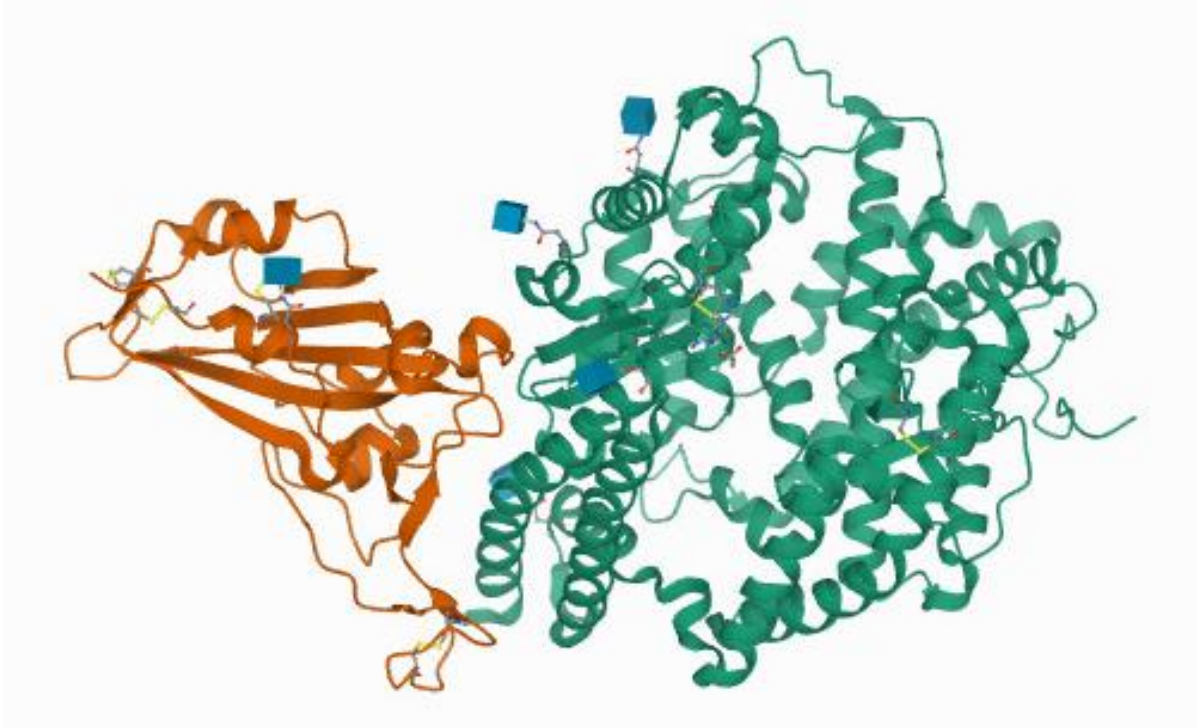
Energy analysis exercise

Analysis of a protein-protein interface

Biophysics 2021-22

Objective

- To evaluate the relative contribution of interface residues to the interaction energy in a protein-protein complex



Strategy

We will evaluate the contribution of individual amino acid residues through the following steps:

- Determine amino acid residues that form the interface between the complex components
- Determine the contribution to the stability of the complex by mimicking an Ala-scanning experiment, i.e. replacing each residue in turn by Ala and evaluating the changes in the inter-complex interaction energy.
- Use the system to evaluate SARS-Cov-2 spike variants on ACE2 binding (6m0j)

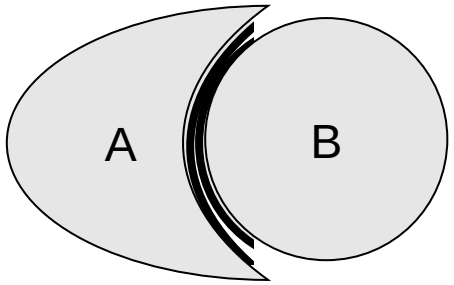
Methodology - Preparation

- Obtain the required structures from the PDB.
- Check at PDB which is the composition of a “Biological unit”. Remove all chains but those involved in the biological unit, if necessary
- Remove all heteroatoms
- Perform a quality checking on the structures, and add missing side-chains and hydrogen atoms

biobb_structure_checking

Methodology – Define the interface

- The interface between is defined by a list of residues on both chains that have at least one atom below a given distance.
- Using pymol inspect visually the structures and choose a suitable distance in the way that all contact residues are included. Add 1-2 Å to that distance so the adjacent residues are also considered.
- Prepare a python script to define the list of interface residues on each chain



Methodology- Energies

Interaction energy between chains corresponds to the difference between the total energy of each chain in the bound state (the complex) and the unbound state (the two chains isolated in solution). To simplify the calculation we will take the following approximations:

- We will assume that 3D structure does not change between bound and unbound states, hence bonded terms and non-bonded terms between atoms belonging to the same chain will not change and will not considered.
- We will consider solvation energies obtained from ASA values for all atom types (not only hydrophobic). Use a proper electrostatic solvation is left as optional task.

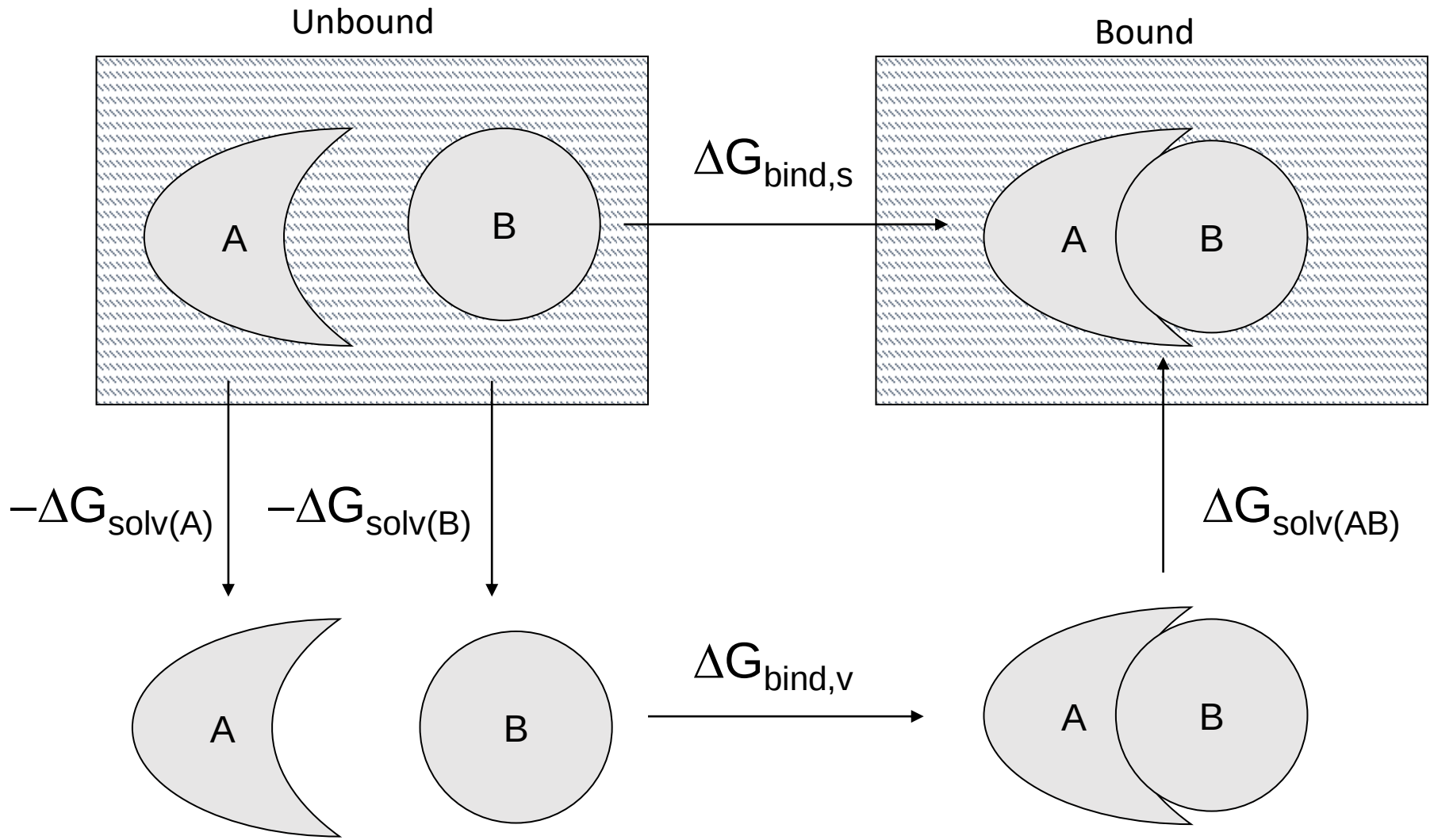
$$\Delta G^{A-B} = \Delta G_{elect}{}^{A-B} + \Delta G_{vdw}{}^{A-B} + \Delta G_{Solv}{}^{A-B} - \Delta G_{Solv}{}^{A} - \Delta G_{Solv}{}^{B}$$

- Prepare python script to evaluate the Interaction energy among chains will come from the following

- This can be done will all residues or only with the interface residues. Check that the interface from Step 1 represents most of the energy involved and modify the cut-off distance accordingly.

- *Optional:* Derive and implement an algorithm to define the interface from the interaction energy instead of distance based.

Thermodynamic cycle for binding



Methodology – Ala mutation

- Determine the effect of replacing each interface residue by Ala in the overall $\Delta G_{A\text{-}B}$, and make a plot of the results obtained, highlighting those residues that are more relevant for the stability of the interface.

- Structures do not change upon mutation!!!

Script rules

- Prepare reusable scripts (use meaningful command lines)
- Document the code
- One single script or several forming a pipeline (preferred)
- Outputs properly formatted
- Prepare re-usable functions

Report

- Complete report of the operations done
- Critical comparison of energies, types of interaction between the two cases.
- Scripts/Notebooks (ideally on github)
- Images of the interface, highlighting relevant residues / interactions