Analysis of Protein-Ligand Interactions Using Multiscale Cell Correlation

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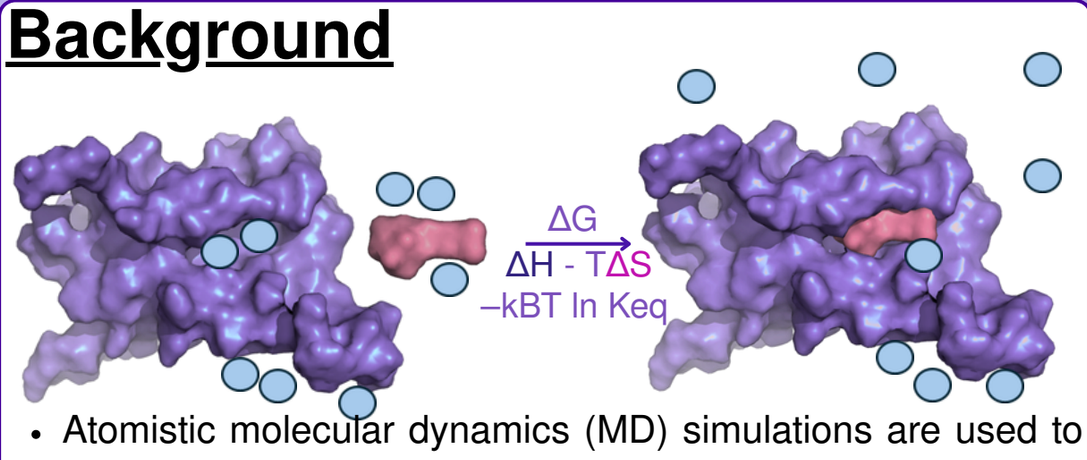
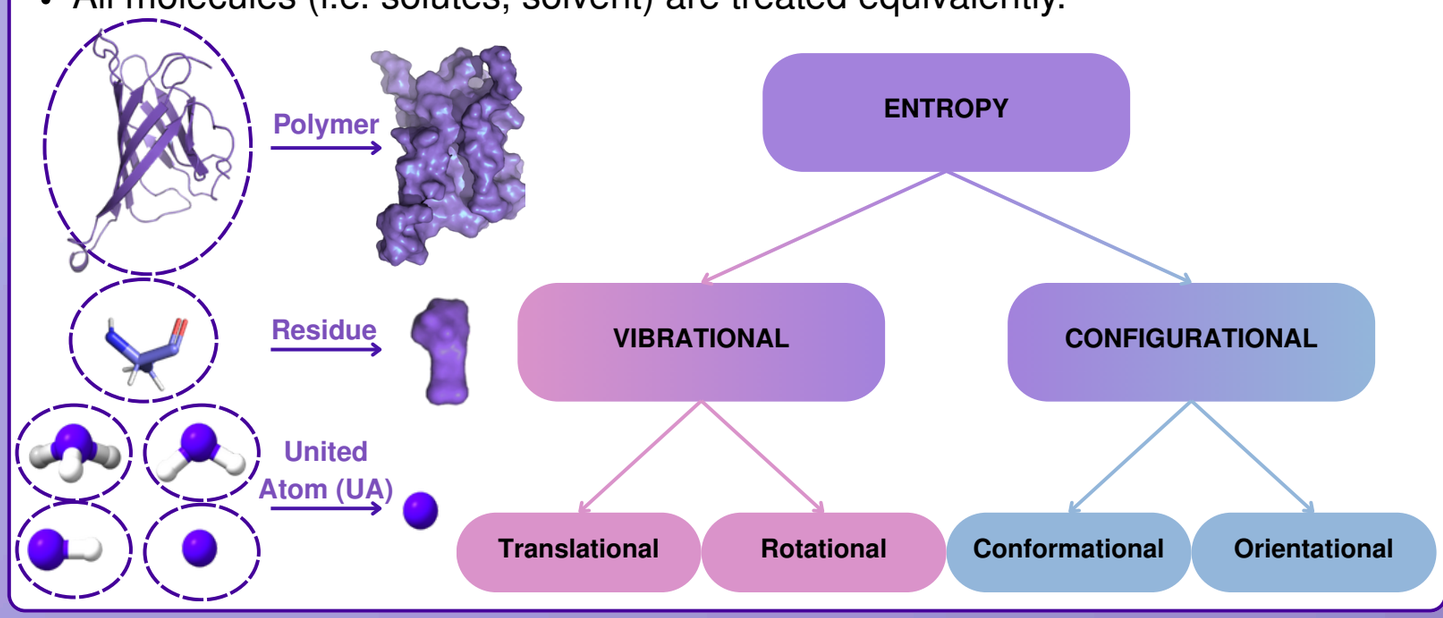
Background



- Atomistic molecular dynamics (MD) simulations are used to quantify *binding free energy* from *enthalpy* and *entropy*.
- *Enthalpy* quantifies the strength of non-covalent interactions.
- *Entropy* quantifies the flexibility and dynamics of molecules.
- Both solute and solvent entropy can play significant roles in determining the strength of binding.

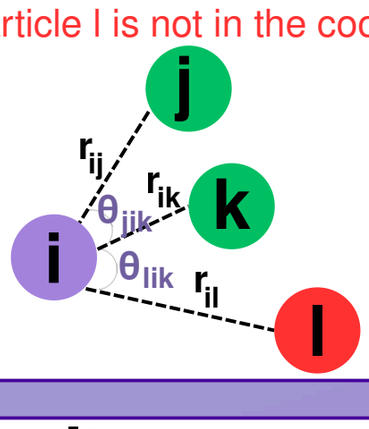
Multiscale Cell Correlation (MCC) [1-3]

- All terms are discretised into independent energy wells.
- All molecules (i.e. solutes, solvent) are treated equivalently.



Solvent Entropy

- The solvation shell of a particle is determined using the radial angular distance (RAD) algorithm: j is the shell of i if it is unblocked with respect to every closer k. [4,5]
- In a protein, the solvation shell of each residue is identified independently.
- Particles j and k are in the coordination shell of particle i.
- Particle l is not in the coordination shell of particle i.

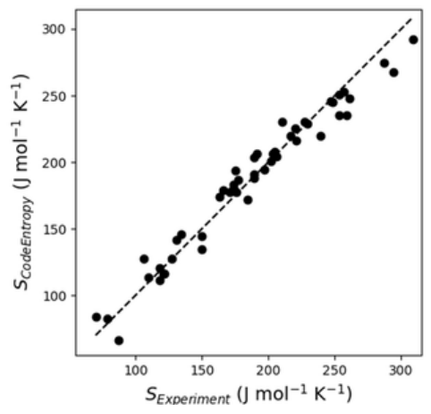


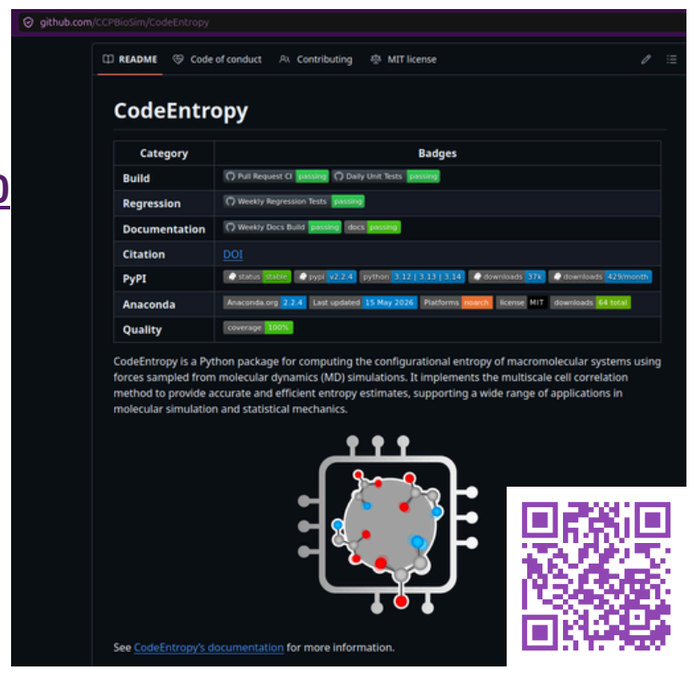
$$\frac{1}{r_{ij}^2} > \frac{1}{r_{ik}^2}\cos\theta_{jik}$$

CodeEntropy

- *CodeEntropy* is distributed under the MIT license and available through a public GitHub repository.

Comparison with experiment for 50 liquids [6]

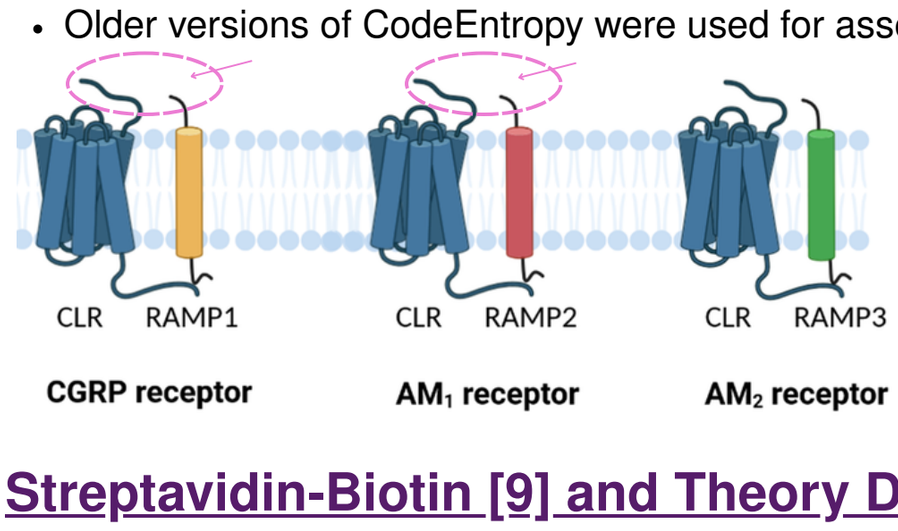


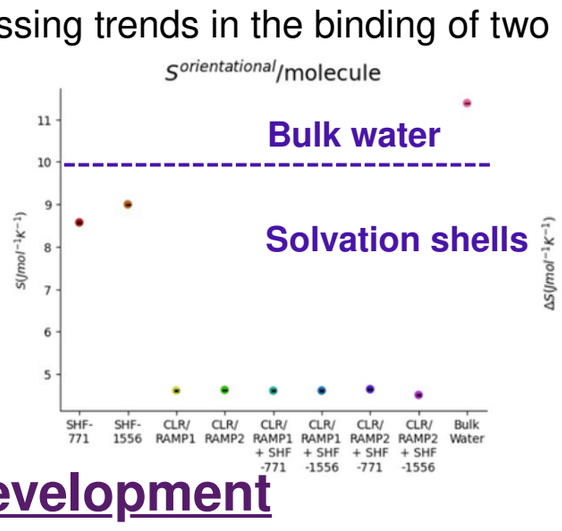


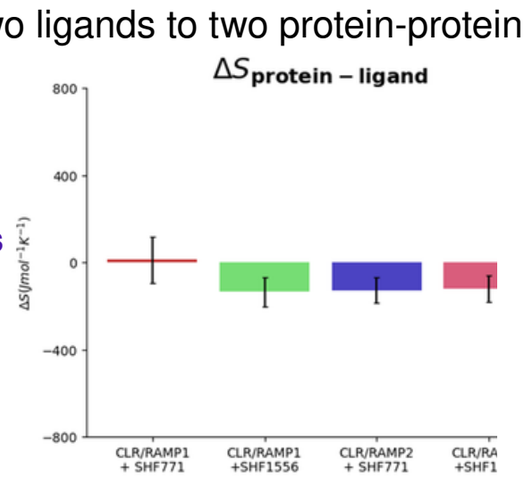
Results

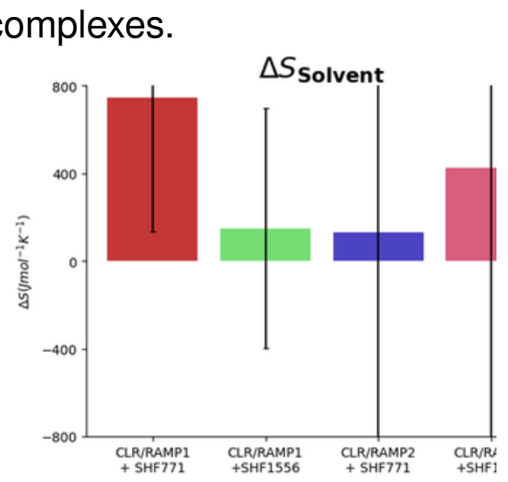
Extracellular Domain of GPCRs [7,8]

- Older versions of CodeEntropy were used for assessing trends in the binding of two ligands to two protein-protein complexes.



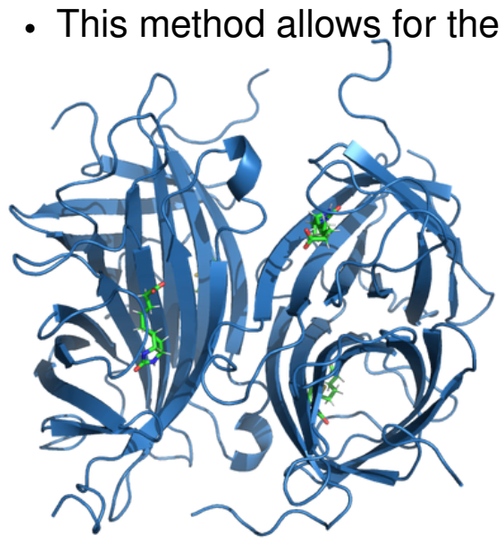


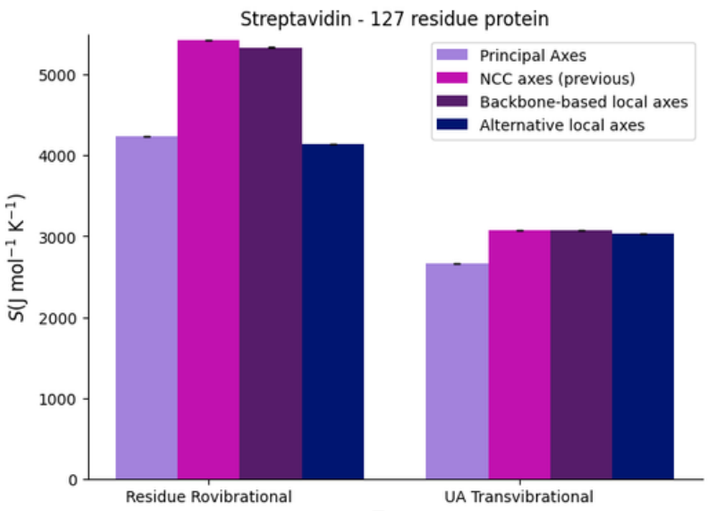


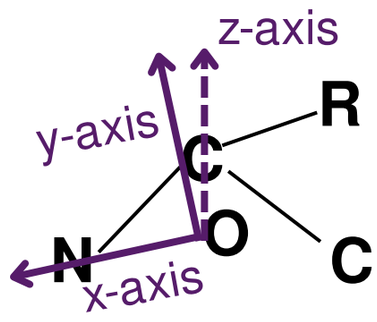


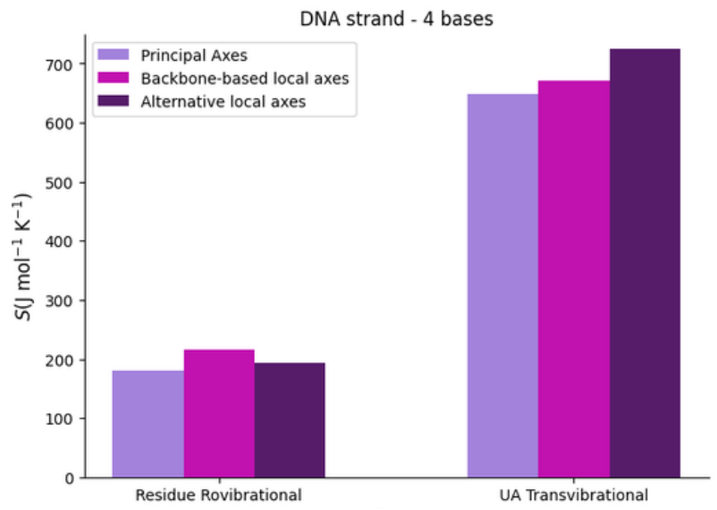
Streptavidin-Biotin [9] and Theory Development

- Residue level protein-specific axes from a previous implementation of MCC have been generalised.
- This method allows for the analysis of other polymers such as DNA or lipids.









Conclusions

- MCC has allowed for a detailed breakdown of entropy components.
- The most significant contribution to entropy change upon binding was found to arise from the solvent.
- The increase in entropy upon binding predominantly arises the increase in orientational entropy of water from solvation shells released back into the bulk water.

Future Work

- The accuracy of the solvent entropy calculations will be improved.
- The streptavidin-biotin system will be completely characterised and results will be compared quantitatively with experimental data.
- New polymer axes will be included in the main branch of CodeEntropy.
- More systems will be analysed to validate novel theory developments.

References