The Free Energy Effects of Harmonic Restraints on a Protein-ligand Complex

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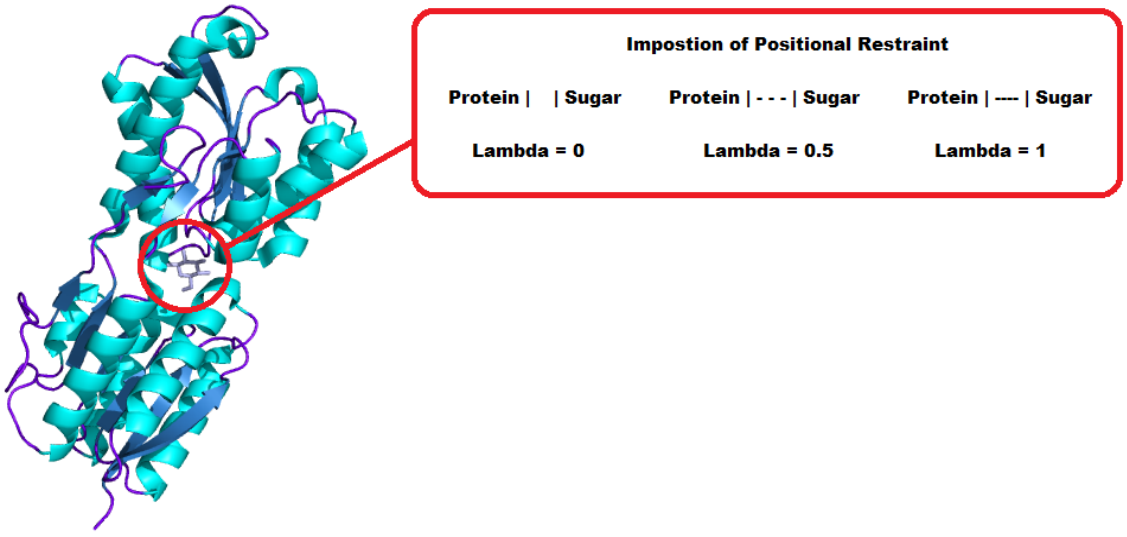
The use of umbrella sampling in molecular dynamics simulations to measure free energy changes is a widely known method in computational chemistry. When applying a harmonic potential to a ligand, in order to induce a pulling simulation, we are additionally applying a restraint to the system. Restraints can restrict the ligand from its full entropic potential and ultimately contribute to the calculated free energy of the system. This free energy penalty may or may not have a significant effect on the overall results obtained from umbrella sampling. The goal of this investigation is to quantify the difference in free energy when such a harmonic force is applied to and removed from a ligand in a protein-ligand complex. Our method involves using thermodynamic integration implemented with Gromacs (Version 4.6.5) to measure free energy values associated with the addition and removal of the harmonic restraining potential. This will be applied to a glucose-bound Glucose-Galactose Binding Protein (GGBP) system as part of a larger project that involves characterizing the binding site of the protein. The results of this study have the potential to improve previous and future results obtained through umbrella sampling in order to mirror results obtained experimentally. In addition, these results can be compared to the analytically calculated effect of imposing restraints as dictated by the Virtual Bond Algorithm, which allows the ligand even lesser degrees of freedom.



The figure above is a visual representation of the imposition of the harmonic restraint potential with respect to lambda states. Not all intermediate states are being represented for simplification.