Predicting the Effects of Base-Pair Mutations in DNA-Protein Complexes by Thermodynamic Integration

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Thermodynamically rigorous free-energy methods in principle allow the exact computation of binding free energies in biological systems. Here, we use thermodynamic integration together with molecular dynamics simulations of a DNA-protein complex to compute relative binding free energies of a series of mutants of a protein-binding DNA operator sequence. A guanine-cytosine base-pair that interacts strongly with the DNA-binding protein is mutated into adenine-thymine, cytosine-guanine and thymine-adenine. It is shown that base-pair mutations can be performed using a conservative protocol that gives error estimates of about 10% of the change in free energy of binding. Despite the high CPU-time requirements, this work opens the exciting opportunity of being able to perform base-pair scans to investigate protein-DNA binding specificity in great detail computationally. [1]

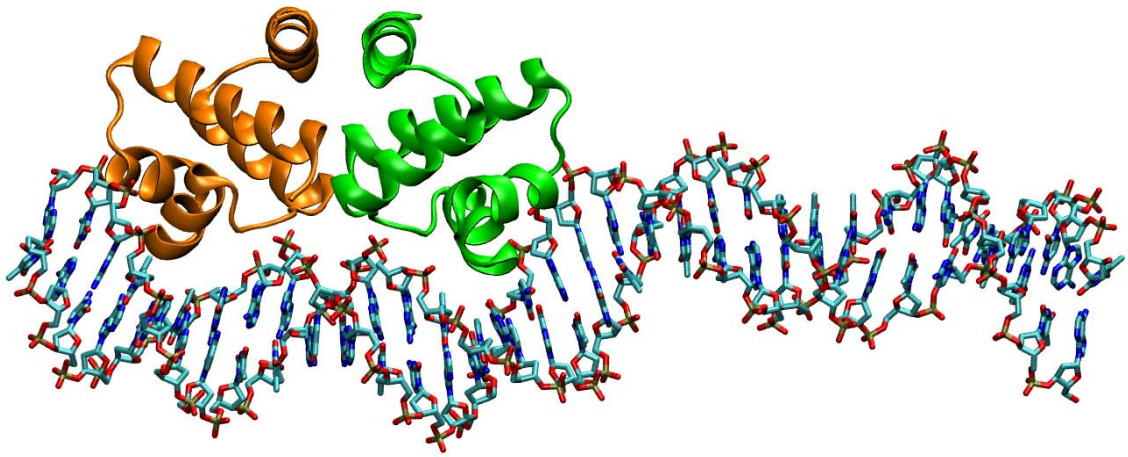

Figure 1. DNA-protein complex used in this study. Only the higher-affinity operator sequence (O_L) is bonded to a C-protein dimer (orange, green). The perturbation base-pair formed by DNA residues 3 and 68 is located on the left hand side of the 35 bp operator sequence. Hydrogen atoms, water molecules and counter-ions were omitted for clarity.

[1] F. R. Beierlein, G. G. Kneale, T. Clark, *Predicting the Effects of Basepair Mutations in DNA-Protein Complexes by Thermodynamic Integration, Biophys. J.* **2011**, *101*, 1130-1138.