Dynamic allostery in proteins

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Introduction

Allosteric proteins constitute a great puzzle. Classically it is believed that the communication between distant sites proceeds via a series of conformational changes. Recently allosteric proteins without substantial conformational change have been observed. This cannot be accounted for with the classical theory and therefore we have built a model that explains the long distance signaling in such cases. We believe that the signaling proceeds via a change in dynamic behavior of the protein and we illustrate the feasibility of such explanation on a few examples. Our most recent calculations involve allosteric signaling in Catabolite Activator Protein (CAP) and DNA.

Dynamical allostery of CAP

The CAP dimer displays a negative cooperativity without conformational change upon binding two CAMp ligands (one in each monomer). The binding is accompanied by dramatic changes in the protein dynamics as has been observed in detailed NMR experiments. Our coarse-grained model shows that the negative cooperativity can have a purely entropic origin. This is achieved by finely tuning the coupling between the monomers of the CAP dimmer. The allosteric free energy ($\Delta\Delta F$) landscape is shown in Figure 1. The plane $\Delta\Delta F = 0$ is shown to highlight the area of negative cooperativity area ($\Delta\Delta F > 0$).

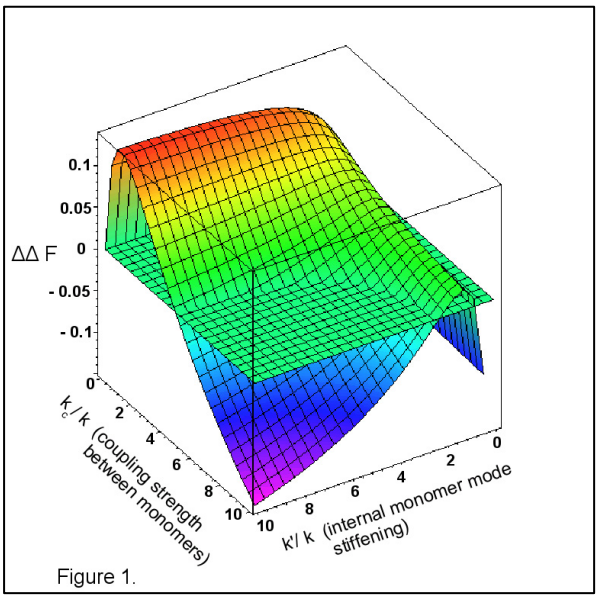

Figure 1.

Dynamical allostery in DNA

A second example constitutes a very popular DNA dye (HOECHST 33258) binding cooperatively to DNA (Fig. 2). Experiments (NMR and calorimetry) and computer simulations observe very strong positive cooperativity ($\Delta\Delta F \approx -10kT$). Many drugs and regulatory proteins bind cooperatively to DNA and therefore our model could serve as a paradigm for other drug-DNA and protein-DNA complexes. We coarse-grained the DNA as a rod with bending and twisting stiffness locally changing upon the dye binding. Our results give reasonable qualitative predictions, but fail to recover the cooperativity strength. This is probably due to excessive coarse-graining.

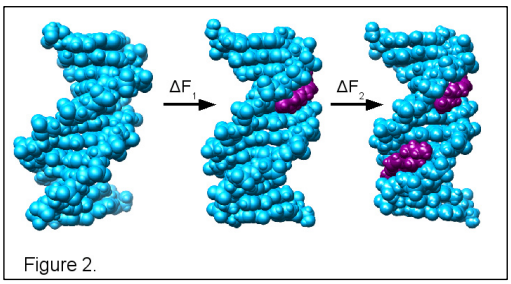

Figure 2.

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