

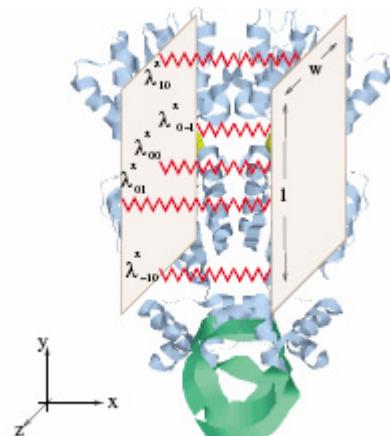
Brownian allosteric in proteins

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Introduction

Allosteric signalling is at the heart of protein networks: it is the effect by which the binding of a protein to a substrate molecule may be affected by the simultaneous binding of a second substrate, often at a site distant from the first. It permits a protein to act as a logical “gate”, but poses a puzzle: how do the two binding sites communicate with each other? The canonical explanation invokes binding-induced conformational change that affects the distant site, but increasing evidence suggests that in many cases the information is transmitted not structurally, but dynamically. In such a picture of “allostery without conformational change”, the Brownian motion of vibrational modes within the protein itself (some of them globally correlated over large distances) may be modified by the substrate binding. The binding free energy contains terms that arise from moderation of the amplitude of these fluctuations, so, although the motion itself is thermal and random, it may act as a channel for information flow across the protein.

We have applied these ideas to the DNA-binding *lac* repressor, using a coarse-grained model for the mutual vibrations of the dimeric protein. Harmonic potentials local to 5 patches on the dimer interface were themselves parameterised by a fully atomistic potential calculation (see Fig. 1). The full free-energy change on the three different binding states to DNA and co-repressor (lactose) could be calculated analytically within this model. We found that half of the allosteric free energy change can be attributed to the dynamic mechanism in the case of *lac*. Additionally, the model produces “design rules” for generating both co-operative and anti-cooperative binding that we are currently using to address other repressor systems.



More widely, this dynamic mechanism for allostery appears in many other systems, especially those involving coiled-coils. Current work is addressing the allosteric binding of the molecular motor dynein to microtubules, and the chemotaxis receptor cluster in *E. coli*. Both approaches work with models for the proteins that contain the long-wavelength modes (large scale), but not the local information, since small-scale dynamics is also generally unable to signal large distances. Initial results indicate that coiled-coils may transmit information along their length by bending, twisting and sliding motions of the two alpha-helices.

Publications

Hawkins, R.J. and McLeish, T.C.B. (2004) Coarse-grained model of entropic allostery, *Phys. Rev. Letts*, **93**, 098104.

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