The Noisy Physics of Protein Signalling: Global Low Frequency Protein Motions in Allosteric Binding

McLeish, Tom C.B.[1],

[1]Department of Physics and Biophysical Sciences Institute, University of York, Heslington, York, YO10 9DD, UK

We present a theory and predictive methdology for how protein allostery can recruit modulation of low frequency dynamics without a change in protein structure [1]. Elastic inhomogeneities allow entropic 'signalling at a distance'. Through multi-scale modelling of global normal modes we demonstrate negative co-operativity between the two cAMP ligands in CRP/FNR family allostery (fig. 1), without change to the mean structure. Crucially, the value of the co- operativity is itself controlled by the interactions around a set of third

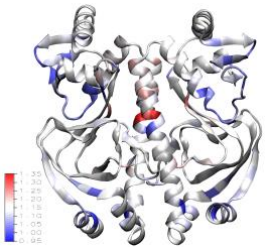

Figure 1 *CAP protein featuring fluctuation-allosteric control sites calculated in an ENM formalism*

allosteric 'control sites'. The theory makes key experimental predictions, validated by analysis of structure and isothermal calorimetry of variant proteins. Furthermore, we found that evolutionary selection pressure to conserve residues crucial for allosteric control [3]. The methodology establishes the means to engineer allosteric mechanisms that are driven by low frequency dynamics, and also suggests a programme of fundamental questions in thermally excited elastic matter [4], including control of biofilament self-assembly [5].

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