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Global Low Frequency Protein Motions in Long-Range Allosteric Signaling TOM MCLEISH, Durham University, THOMAS ROGERS, University of Manchester, PHILIP TOWNSEND, DAVID BURNELL, EHMKE POHL, MARK WILSON, MARTIN CANN, SHANE RICHARDS, MATTHEW JONES, Durham University — We present a foundational theory for how allostery can occur as a function of low frequency dynamics without a change in protein structure. Elastic inhomogeneities allow entropic "signalling at a distance." Remarkably, many globular proteins display just this class of elastic structure, in particular those that support allosteric binding of substrates (long-range co-operative effects between the binding sites of small molecules). Through multi-scale modelling of global normal modes we demonstrate negative co-operativity between the two cAMP ligands without change to the mean structure. Crucially, the value of the co-operativity is itself controlled by the interactions around a set of third allosteric "control sites." The theory makes key experimental predictions, validated by analysis of variant proteins by a combination of structural biology and isothermal calorimetry. A quantitative description of allostery as a free energy landscape revealed a protein "design space" that identified the key inter- and intramolecular regulatory parameters that frame CRP/FNR family allostery. Furthermore, by analyzing naturally occurring CAP variants from diverse species, we demonstrate an evolutionary selection pressure to conserve residues crucial for allosteric control. The methodology establishes the means to engineer allosteric mechanisms that are driven by low frequency dynamics.

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