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Title: MODULATION OF THE DYNAMICS OF PROTEINS and RELATED FUNCTIONS via pH CHANGES

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Proteins are complex systems made up of many conformational sub-states [1], mainly determined by the folded structure. These conformations are strongly influenced by environmental factors such as solvent type, temperature, pH and ionic strength. The dynamics and function of proteins were shown to be coupled to motions in bulk conformations of proteins [2]. In this work we focus on the protein calmodulin (CaM) to understand the effect of pH variation on the conformations it samples. CaM has a pivotal role as an intracellular Ca receptor involved in calcium signaling pathways in eukaryotic cells [3]. CaM can bind to a variety of proteins or small organic compounds, and can mediate different physiological processes by activating various enzymes [4,5]. Binding of Ca and proteins or small organic molecules to CaM induces large conformational changes that are distinct to each interacting partner [3,5,6]. We use molecular dynamics simulations, coupled to a recently developed technique, perturbation response scanning [7], to interpret the observed conformation distributions. Our findings are compared to FRET experiments results of other workers [8]. The joint interpretation of theory and FRET provide impetus for designing new experiments. REFERENCES [1] Frauenfelder H (2002) Proteins: Paradigms of complexity. Proc Natl Acad Sci USA 99: 2479-2480. [2] Servantie J, Atilgan C, Atilgan AR (2010) Depth dependent dynamics in the hydration shell of a protein. Journal of Chemical Physics 133. [3] Ikura M, Ames JB (2006) Genetic polymorphism and protein conformational plasticity in the calmodulin superfamily: Two ways to promote multifunctionality. Proceedings of the National Academy of Sciences of the United States of America 103: 1159-1164. [4] Fallon JL, Quiocho FA (2003) A closed compact structure of native Ca2+-calmodulin. Structure 11: 1303-U1307. [5] Vandonselaar M, Hickie RA, Quail JW, Delbaere LTJ (1994) Trifluoperazine-Induced Conformational Change in Ca2+-Calmodulin. Nature Structural Biology 1: 795-801. [6] Junker JP, Rief M (2009) Single-molecule force spectroscopy distinguishes target binding modes of calmodulin. Proceedings of the National Academy of Sciences of the United States of America 106: 14361-14366. [7] Atilgan C, Atilgan AR (2009) Perturbation-Response Scanning Reveals Ligand Entry-Exit Mechanisms of Ferric Binding Protein. PLoS Comput Biol 5(10): e1000544. doi:10.1371/journal.pcbi.1000544. [8] Slaughter BD, Allen MW, Unruh JR, Urbauer RJB, Johnson CK (2004) Single-molecule resonance energy transfer and fluorescence correlation spectroscopy of calmodulin in solution. Journal of Physical Chemistry B 108: 10388-10397.