MAR15-2014-020560

Abstract for an Invited Paper
for the MAR15 Meeting of
the American Physical Society

Dynamics of living matter: can we "see" collective motions in proteins?

DOEKE HEKSTRA, Green Center for Systems Biology, UT Southwestern Medical Center

Proteins are ideal model systems for quantitative study of the interplay of physical and evolutionary forces. Collective, anharmonic motions of amino acid residues within proteins are thought to be central to their function, and to explain, in large part, the complex dependence of protein function on its constituent parts. Currently, the experimental characterization of such motions poses a major stumbling block on the way to a physical understanding of protein function and evolution. We are addressing this problem in two ways. First, alternate conformations of protein residues can often be distinguished in the electron density estimated from room-temperature X-ray crystallography. The dense packing of residues in the folded protein requires that such conformational variations must propagate through networks of amino acids to preclude local steric clashes. Fraser and colleagues[1] showed that such steric conflicts can be used to extract contact networks of residues collectively switching conformation. We ask if these networks are conserved over homologous sequences and connected to the functional reaction coordinate, both of which would demonstrate their fundamental importance. I will describe initial results for the family of PDZ domains: small ligand-binding proteins for which a network of energetically and conformationally coupled residues controlling ligand affinity has been demonstrated previously by a range of methods. Second, the analysis of collective motions in proteins, by nearly any means, is indirect: nothing is seen moving. To directly induce and "see" motions on a range of time scales, we developed a new approach based on (a) electric field pulses to induce motions within a protein crystal and (b) time-resolved crystallography to observe these motions. Since proteins generically have a heterogeneous, modifiable charge distribution, this method could provide a powerful, general way of probing the collective motions, and excited states, of proteins in kinetic and atomic detail. I will present initial experiments showing the method is feasible. Taken together, these experiments begin to provide a basis for the development of a physical theory of proteins consistent with their function and adaptation – the source of their survival throughout the evolutionary process.

[1]Van den Bedem, H., Bhabha, G., Yang, K., Wright, P. E. & Fraser, J. S., *Nat. Methods* **10,** 896–902 (2013).