Functional Dynamics of Proteins: Learning from Experiments and Network Models

Ivet Bahar

Department of Computational & Systems Biology, School of Medicine, University of Pittsburgh, 3064 BST3, 3501 Fifth Avenue, Pittsburgh, PA 15213

Proteins are not static molecules. They undergo a variety of structural changes, ranging from local fluctuations to large scale collective domain movements. Many of them function as molecular machines, others transport substrate, or signal allosteric effects, and all these activities are achieved via suitable changes/fluctuations in the protein structure. With advances in structural genomics, we now have access to an increasingly number of alternative structures for well-studied proteins in different forms, in the presence of different substrates, which reveal the conformational flexibility and adaptability of proteins to optimize their interaction with substrates or undergo structural changes required to achieve their biological functions. The concept of 'unique native structure' is now being replaced by that of 'an ensemble of conformations near native state conditions' which is representative of the intrinsic ability of proteins to undergo structural changes. These ensembles are narrowly distributed, i.e., the core structure or the overall 'fold' is usually maintained, but particular regions (e.g., recognition loops) or relative positions of subunits vary depending on the particular experimental conditions under which these proteins have been crystallized. What is even more interesting is to see that the experimentally observed structural changes are in close agreement with changes in structure that are 'predicted' by simple structure-based computational models and methods such as elastic network models and normal mode analysis.[1,2] The fact that the motions predicted from these structure-based models correlate with the functional changes observed in experiments point to the intrinsic, structure-encoded ability of proteins to favor conformational changes that enable their function, and to the existence of evolutionary pressure for selecting those structures that lend themselves to functional dynamics.

1. Bakan, A.; Bahar, I. (2009) *Proc. Nat. Acad. Sci. U.S.A.* ***106*****,** 14349-14354.
2. Bahar I, Lezon TR, Yang LW, Eyal E. (2010) *Annu Rev Biophys.* **39**: 23-42.