Protein Dynamics and Stability: Universality vs. Specificity

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Two seemingly conflicting properties of native proteins, such as enzymes and antibodies, are known to coexist. While proteins need to keep their specific native fold structure thermally stable, the native fold displays the ability to perform large amplitude motions that allow proper function. This conflict cannot be bridged by compact objects which are characterized by small amplitude vibrations and by a Debye density of low frequency modes. Recently, however, it became clear that proteins can be described as fractals; namely, geometrical objects that possess self similarity. Adopting the fractal point of view to proteins makes it possible to describe within the same framework essential information regarding topology and dynamics using three parameters: the number of amino acids along the protein backbone N, the spectral dimension d_s and the fractal dimension d_f. The fractal character implies large amplitude vibrations of the protein that could have led to unfolding. We show that by selecting a thermodynamic state that is "close" to the edge of stability against unfolding, nature has solved the thermostability conflict. Starting off from a thermal marginal stability criterion we reach a universal equation describing the relation between the spectral and fractal dimensions of a protein and the number of amino acids. Using structural data from the protein data bank (PDB) and the Gaussian network model (GNM), we compute d_f and d_s for about 5,000 proteins (!) and demonstrate that the equation of state is well obeyed.

Proteins have been shown to exhibit anomalous dynamics. The anomalous behavior may, in principle, stem from various factors affecting the energy landscape under which a protein vibrates. Here we focus on the structure-dynamics interplay and show how the fractal-like properties of proteins lead to such anomalous dynamics. We use diffusion, a method sensitive to the structural features of the protein fold and them alone, in order to probe protein structure. Conducting a large scale study of diffusion on over 500 PDB structures we find it to be anomalous, an indication of a fractal-like structure. Taking advantage of known and newly derived relations between vibrational dynamics and diffusion, we demonstrate the equivalence of our findings to the existence of structurally originated anomalies in the vibrational dynamics of proteins. We conclude that these anomalies are a direct result of the fractal-like structure of proteins. The duality between diffusion and vibrational dynamics allows us to make, in a single molecule level, experimentally testable predictions. The time dependent vibrational mean square displacement of an amino acid is predicted

to be subdiffusive. The thermal variance in the instantaneous distance between amino acids is shown to grow as a power law of the equilibrium distance. The autocorrelation function in time of the instantaneous distance between amino acids is shown to decay anomalously. Our analysis offers a practical tool that may aid in the identification of amino acid pairs involved in large conformational changes.

More recently, we studied the effect of the hydrodynamic interaction between amino acids using a Zimm-type model. We computed the time-dependent mean square displacement of an amino acid and the time-dependent autocorrelation function of the distance between two amino acids, and showed that these dynamic quantities evolve anomalously, similar to the Rouse-type behavior, yet with modified dynamic exponents. Good agreement is found with recent neutron spin-echo studies of myoglobin and hemoglobin.

In addition, I will mention two other projects: (i) A new elastic network model that accounts for the tensorial aspects of protein elasticity and is a combination of stretch-compress springs and bond-bending energies. (ii) The unfolding of a protein under exertion of a large pulling force.