Vibrational normal-mode spectrum of globular proteins

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Slow vibrational modes of proteins (in the 5-psec range) have been the focus of numerous recent studies. Nevertheless, no attempt has yet been made to ascertain the general properties of these vibrational spectra. Comparing the spectra of several globular proteins, it is found that the density of states follows a characteristic, universal curve, which reflects the main structural similarities between proteins. The spectral (or fracton) dimension is $d_s=2$: for the slower modes, the density of states increases linearly with the frequency, as opposed to the regular increase with the square of the frequency, as in crystals. This is relevant to the kinetics of the mechanical transport of signals in proteins and to the function of proteins as catalysts.

Proteins play an important role in numerous biological systems. Their three-dimensional structure is of primary interest because it is mostly the structure that determines the specific function of a protein. In recent years, there has been an increasing interest in the dynamics of proteins. Dynamical studies have increased our appreciation of the importance of protein structure and have shed some light on the central problem of molecular biology of "protein folding".[1] To date, the vibrational spectra of several globular proteins have been analyzed. The focus is on the slowest normal modes because of their relatively larger level of activity. It is becoming apparent that the slow modes, and not only the structure, are important to the catalytic function of proteins.

Proteins are linear polymers assembled from about 20 amino acid monomers. The sequence of amino acids (primary structure) varies for different molecules. Indeed, the distribution of amino acids among proteins is nearly random. Sequences of amino acid residues fold into typical patterns (secondary structure), consisting mostly of helical and sheetlike patterns, such as α helices and β sheets. These secondary-structure elements bundle into a roughly globular shape[2] (tertiary structure) in a way that is unique to each protein.

Globular proteins are among the most densely packed organic molecules in nature, approaching the efficient packing of atoms in crystals. One may naively expect then, that their spectrum of vibrations would show the same characteristics as solids. Furthermore, because of the nearly random distribution of amino acids and of the uniformity of secondary structure elements, there is, statistically speaking, a large degree of homogeneity between different proteins. Thus, the vibrational spectrum ought to be essentially the same for all proteins.

The slow vibrations of proteins are chiefly studied through theoretical techniques. The most straightforward method is a classical normal modes analysis, based on a quadratic approximation of the potential energy of the molecule. Other approximations are usually involved, as, for example, assuming bond lengths to be frozen and allowing only for changes in rotational angles. The effect of these approximations has been explored. Generally, they do not seem to affect the slow edge of the vibrations spectrum. Indeed, one expects the slow, collective vibrations to be determined by average interactions within a mesoscopic length scale. Thus, microscopic details may be suppressed to some extent.

In Fig. 1, I have plotted $g(\omega)$, the density of vibrational modes (number of modes per frequency range, divided by the total number of modes) for crambin, BPTI, ribonuclease I, and lysozyme,[3] and for g actin.[4] The size of these proteins ranges from 39 amino acid residues (crambin) to 375 residues (g actin), spanning one order of magnitude. The data do seem to collapse into a universal curve. This scaling reflects the statistical similarities among different proteins (and, accordingly, deviations are largest for the smallest protein, crambin).

The spectra shown here were derived through a classical normal modes analysis. The spectrum of some of these proteins has been also derived independently by others, using completely different approximations.[1,5] As stated above, few differences are found, and these occur mainly at the farther edge of the spectrum. Thus, the curve of Fig. 1 is a good approximation for small ω. It is flawed for higher frequencies, where an analysis accurate at the microscopic level is crucial. However, since the

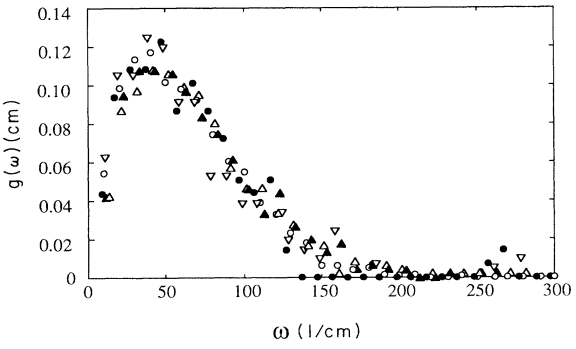

FIG. 1. Density of vibrational normal modes, $g(\omega)$, of g actin (○) lysozyme (△), ribonuclease I (▲), BPTI (▽), and crambin (●) as a function of frequency.

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scaling is due to the statistical similarities between proteins, I argue that data collapse would occur also for higher frequencies, though the curve's shape will differ from that in Fig. 1. In the following I shall concentrate on the slower modes, for which theory is more reliable.

To examine the small ω behavior, in Fig. 2 I plot $G(\omega)$, the fraction of the total number of modes up to frequency ω, versus ω, for the first (slowest) 70 modes of g actin. We see that $G(\omega)\sim\omega^2$. Since $g(\omega)=dG(\omega)/dw$, we have $g(\omega)\sim w$, a curious difference from Debye's theory. Assuming spherical symmetry, one derives[6] an anomalous dispersion relation: $w\sim k^{3/2}$. The group velocity of vibrations is then dependent on ω, $s\sim w^{1/3}$, and the oscillation period of the slowest modes is also anomalous, $T\sim\sqrt{N}$. (N is the number of residues.) This last result can also be derived without assuming spherical symmetry. It follows from the fact that for the slowest modes $G(\omega)$ is of order $1/N$ (since the total number of modes is proportional to the number of residues). On the other hand, $G(\omega)\sim\omega^2\sim 1/T^2$, so that $T\sim\sqrt{N}$.

The fact that for the slow modes $G(\omega)\sim\omega^2$ has no obvious explanation. Following the definition[7] of spectral, or fracton dimension, d_s,

$$g(\omega)\sim\omega^{d_s-1},$$

one concludes that $d_s=2$. Thus, as far as slow vibrations are concerned, globular proteins behave as two-dimensional objects. This is reminiscent of a different result,[8] that the fractal dimension of proteins is also $d_f=2$ for a significant range of length scales. Recall that[7]

$$d_s=\frac{2d_f}{d_\omega},$$

where d_w is the dimension of random walks in the object in question. The dimension d_w depends on the detailed web of interactions between atoms in the proteins. The equality $d_s=d_f$ requires $d_w=2$, suggesting that diffusion in this complex network is similar to diffusion in regular Euclidean space.

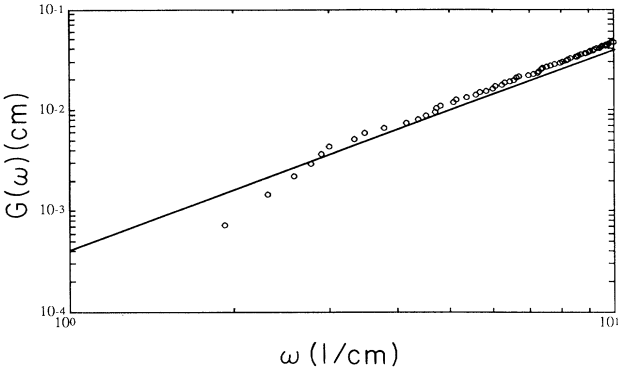

FIG. 2. Fraction of normal modes below frequency, ω, $G(\omega)$, as a function of ω as computed for the slowest 70 modes of g actin (○). The solid line, of slope 2, is shown for comparison.

The propagation of mechanical information across protein molecules depends strongly on the slow vibrational modes. The frequency-dependent group velocity would have a crucial effect on the kinetics of such process. It would also affect the kinetics of the catalytic function of enzymes, where slow vibrations are known to play an essential role.[9] Finally, the unusual energy dissipation rates, and other exotic behavior resulting from the anomalous spectrum of proteins could perhaps be exploited in biological nanotechnologies. The scaling of the spectra suggests that a general theory for proteins, analogous to Debye's theory for solids, may be developed, which will shed light on these fascinating issues.

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[1]For recent reviews of proteins, protein structure, and dynamics, see C. Branden and J. Tooze, *Introduction to Protein Structure* (Garland, New York, 1991); J. A. McCammon and S. C. Harvey, *Dynamics of Proteins and Nucleic Acids* (Cambridge University Press, Cambridge, England, 1987).

[2]Some proteins have more exotic tertiary structure, as for example silks, which form extended sheets. However, the vast majority of structurally determined proteins fold into globular shapes.

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