480. Title:Dielectric spectroscopy of proteins as a quantitative experimental test of computational models of their low-frequency harmonic motions

Authors:Vinh, N.Q. (1); Allen, S. James (1); Plaxco, Kevin W. (3)

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Abstract:Decades of molecular dynamics and normal mode calculations suggest that the largest-scale collective vibrational modes of proteins span the picosecond to nanosecond time scale. Experimental investigation of these harmonic, low-amplitude motions, however, has proven challenging. In response, we have developed a vector network analyzer-based spectrometer that supports the accurate measurement of both the absorbance and refractive index of solvated biomolecules over the corresponding gigahertz to terahertz frequency regime, thus providing experimental information regarding their largest-scale, lowest frequency harmonic motions. We have used this spectrometer to measure the complex dielectric response of lysozyme solutions over the range 65 to 700 GHz and an effective medium model to separate the dielectric response of the solvated protein from that of its buffer. In doing so, we find that each lysozyme is surrounded by a tightly bound layer of 165 ± 15 water molecules that, in terms of their picosecond dynamics, behave as if they are an integral part of the protein. We also find that existing computational descriptions of the protein's dynamics compare poorly with the results of our experiment. Specifically, published normal mode and molecular dynamics simulations do not explain the measured dielectric response unless we introduce a cutoff frequency of 250 GHz below which the density of vibrational modes drops to zero. This cutoff is physically plausible, given the known size of the protein and the known speed of sound in proteins, raising questions as to why it is not apparent in computational models of the protein's motions.