Intermolecular correlations are necessary to explain diffuse scattering from protein crystals

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Conformational changes drive protein function, including catalysis, allostery, and signaling. X-ray diffuse scattering from protein crystals has frequently been cited as a probe of these correlated motions, with significant potential to advance our understanding of biological dynamics. However, recent work challenged this prevailing view, suggesting that diffuse scattering instead originates from rigid body motions and thus could enable phase retrieval. To reconcile these opposing views about the physical origins – and thus potential applications – of diffuse scattering, we reconstructed the diffuse signal from three protein systems with distinct biological functions. A comprehensive comparison of competing models of disorder revealed that biologically-informed models could not explain the signal. By contrast, a model of long-range liquid-like motions correlated significantly with all three systems. This finding suggests that deconvolution of the intermolecular contribution to the signal will be required to employ diffuse scattering to extract biological information or aid structural inference.