Structure and its Variations from Random Low-Signal Snapshots

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ABSTRACT

At least in biology, it is well-known that structure determines function, and there is increasing evidence that structure is neither immutable, nor static. Conformational heterogeneity and dynamics have now been observed in ribosome particles and high-resolution studies of GroEL particles configurations revealed significant deviations from existing crystal structure analyses. Even in crystals, a new treatment of data has revealed statistically significant evidence for the presence of an ensemble of conformations. The study of such structural variability and dynamics thus represents a crucial, but difficult frontier in understanding biological processes down to the atomic level. In principle, "single-particle" approaches are ideally suited to study structural variability. Cryo-EM has been the single-particle technique of choice, yielding a host of valuable information. Emerging X-ray diffraction methods have used intense short pulses to obtain coherent diffraction snapshots of individual particles before the particle is destroyed. In Cryo-EM and X-ray diffraction, the relative orientations of the two-dimensional snapshots are unknown and can require $\sim 10^6$ snapshots from identical copies of a biological object to reconstruct its three-dimensional structure. Additionally radiation damage and/or weak scattering severely limit the signal in each snapshot. So even in the absence of structural variability, determining the structure is a key challenge, both, from conceptual and computational points of view.

We demonstrate how advanced manifold-embedding techniques can be used to determine the structure and dynamics of evolving objects from a collection of ultra-low-signal, two-dimensional snapshots emanating from unknown orientations and conformations.