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ID-8-O-2915 Validation of sorted subsets for single-particle reconstruction of heterogeneous macromolecular assemblies

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In single-particle reconstruction techniques, it is essential that heterogeneous populations due to conformational variability or differences in occupancy are properly accounted for in order to get the best possible representations of the underlying structures. This task is often difficult and there is a shortage of tools to detect or correct for heterogeneity in sorted data subdatasets. We developed a novel protocol to validate the homogeneity of sorted subdatasets and to correct for residual heterogeneity if present. Our approach is based on what we call the ‘inverted Einstein principle’ where the test imposes maximum bias away from the refined structure. The underlying idea is that heterogeneity in the sorted subdatasets will give rise to model dependence. We construct a test for heterogeneity by providing a starting model with maximum bias away from the main features of the reconstruction. Only if the reconstruction remains unchanged within predefined error bounds, the test is considered passed. Otherwise, sorting is repeated using specific rules defined within our procedure until convergence is achieved. The rules for constructing the new set of models for sorting and refinement, allow the models to drift away from features that are variable and to enhance features that are solid within the current sorted subdataset. We will present results for simulated data as well as for several experimental datasets that suffered from high degree of heterogeneity, showing that our procedure succeeds in each of these to generate robust sorted subdatasets that do not exhibit model bias.

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