Macromolecular flexibility and its study though the new Zernikes3D bases coupled with Molecular Dynamics

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We focus on analyzing macromolecular flexibility from cryo Electron Microscopy images without the constraint that images must come from a discrete set of conformations, which is a paradigm change in the way cryo EM data are currently handled in most cases (apart from recent approaches like manifold embedding, cryoDRGN and e3gmm). We do that by calculating the 3D deformation field and how every image contributes to it, obtaining information of the macromolecule conformational space. Our approach is unique in that it is based on expanding the deformation field in the new Zernikes3D bases in the context of a fully analytical approach, can be applied both to maps and to structural models, expressing them in the same space, and is able to handle projection uncertainties in a mathematically closed form. The deformation field we obtain is very rich, richer that what dicrete conformations traditional cryoEM software can describe, and it can be explored in a variate of ways, leading to a better understanding of macromolecular motion. Note that this experimental information on conformational landscapes can now be coupled to Molecular Dynamics analysis, trying to capture in this way a notion of time, eventually of “trajectory” and, also, higher resolution atomistic detail. Finally, and not with the goal of flexibility exploration but with the one of helping structural model tracing in difficult cases, we can partially “undo” the so obtained deformation field, increasing the resolution of “motion blurred” areas of the map