Macromolecular flexibility and the experimental determination of conformational landscapes in the context of 3DBioinformatics

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Abstract:

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. We do that by calculating the 3D deformation field and how every image contributes to it, obtaining information of the macromolecule conformational space. The deformation field we obtain is very rich, richer that what dicrete conformations traditional cryoEM software can be described, and it can be explored in a variate of ways, leading to a better understanding of macromolecular motion. We present in Figure 1, up, an exaple of the type of conformational information provided by Zernikes3D, where the bases space is non-linearly projected onto a 2-dimensional plot where each point is an experimental image. This data cloud can now be explored systematically, extracting the experimental conformational variability present in the data

Also, 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. This is presented in Figure 1, from bottom left to right, where the improuvement of map resolution between not applying any motion correction and applying it is evident. We have used our experimental data on SARS-Cov2 spike for the illustration

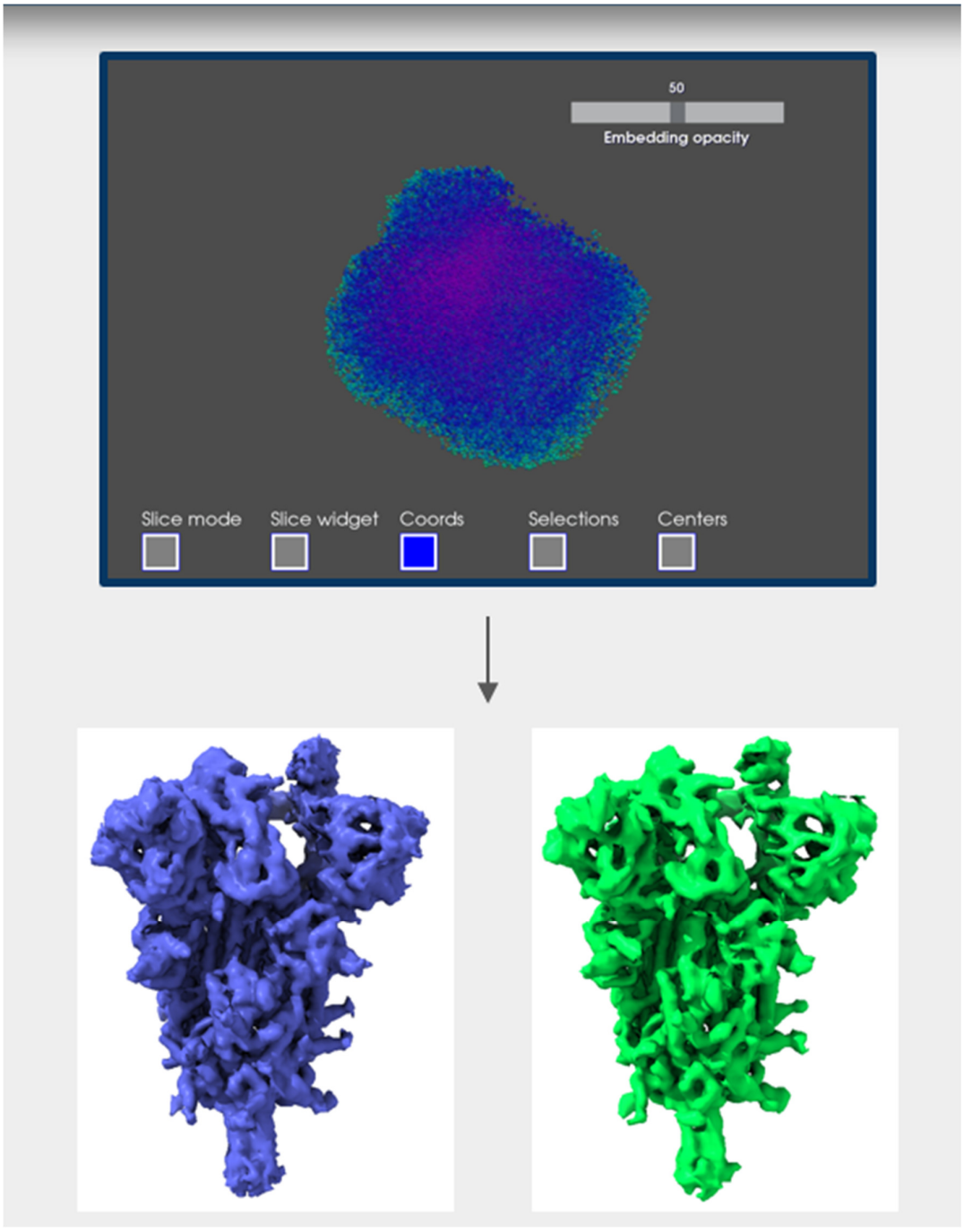
50
Embedding opacity
Slice mode
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Figure Legend: Top: Zernikes3D-based two-dimensional representation of the conformational landscap of SARS-CoV2 spike in its up position. Bottom: from left to right, the effect of explicitly considering conformational changes into the tree-dimensionsal reconstruction algorithm, helping model tracing.

Finally, we 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. It is currently one of the most porweful frameworks in which to integrate experimental information with computational capabilities.