StructMap: Method for mapping a set of electron-microscopy structures onto a space defined by their distances

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1. INTRODUCTION

Single-particle electron microscopy (EM) has been shown to be very powerful for studying conformational flexibility of macromolecular complexes. To further analyze flexibility and start understanding dynamics of a complex, its distinct conformations are usually computed by analyzing images of coexisting multiple conformations of the complex. The resulting structures are then analyzed to explain flexibility. However, a quantitative analysis of dissimilarities (distances) among structures, placing the entire set of structures into a common space of comparison, is often lacking. We have recently developed an approach that provides an overall view of distances among given structures. The approach is based on statistical analysis of distances among elastically aligned structures, and results in visualizing structures as points in a lower-dimensional distance space. The configuration of these points can be analyzed to explore potential pathways of conformational changes. The method was tested with several sets of synthetic and experimental structures at different resolutions. In this abstract, we show one example of use of the method. The method and other examples of its use will be presented at the meeting.

2. RESULTS

2.1 Experiment with EM structures of Pol α – B

In this experiment, we used three EM structures of Pol α – B published in [1]. They correspond to different states of bending of the flexible linker between two lobes of the complex. The EM volumes (volume size: 64 × 64 × 64 voxels; voxel size: 3.8 Å × 3.8 Å × 3.8 Å) have a resolution between 23 Å and 25 Å [1] and, here, the volumes will be referenced by their indexes (1, 2, and 3), as used in [1]. A pseudo-atomic structure and its 20 normal modes were first computed for each EM volume [2]. Then, each obtained pseudo-atomic structure was elastically aligned with all EM volumes [3], and the obtained 3-by-3 distance matrix was mapped onto a 1D space (**Fig. 1A**).

The 1D mapping results (**Fig. 1A**) show that structure 1 is almost equally distant from the two other structures (the two distances are 0.1 and 0.11), which could be interpreted as a movement around conformation 1, in the order 3-1-2 or 2-1-3 (**Fig. 1B**). Structures in the order 3-1-2 correspond to the unbending of the complex from the conformation 3 to the conformation 2 (from left to right in **Figure 1B)**. This interpretation is coherent with the one of Klinge *et al* 2009 (Fig. 6 in [1]). Moreover, it is based on a quantitative distance analysis, which was not the case in the previous study.

3. CONCLUSION

In this abstract, we presented an example of use of a methodology that is, to the best of our knowledge, the first one allowing a discrete set of EM structures, obtained by classical discrete (class-based) flexibility analysis, to be represented in a common and quantitative space defined by their mutual distances. Obtained results are fully consistent with previously published results and complement them with a graphical representation of dissimilarities among given structures.

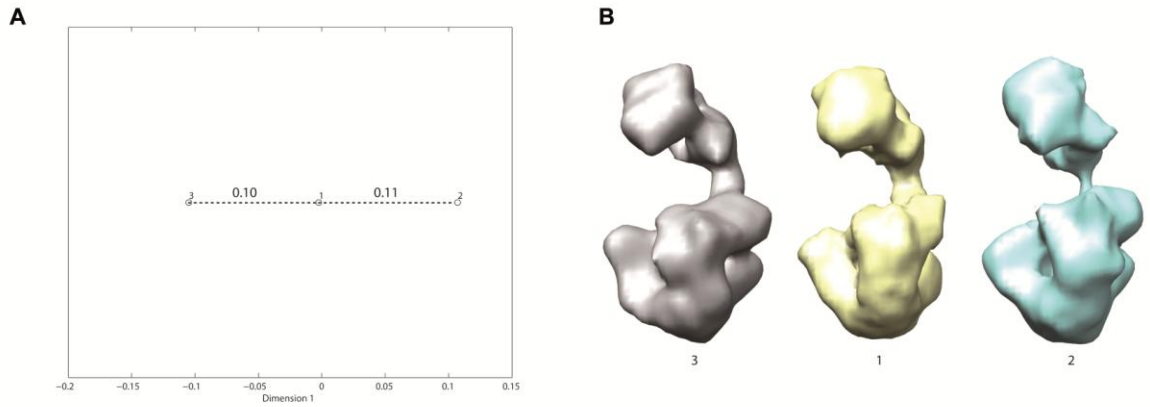

Figure 1. Mapping of three EM structures of DNA polymerase Pol α - B complex onto a 1D distance space and analysis of these structures based on their distances in the new space. (A) Mapping of structures onto a 1D distance space. (B) Ordered rigid-body aligned structures (3-1-2) according to their distances in the distance space shown in A. In A, the structures are marked with circles and the length of each dotted line segment (the distance between two structures) is shown above the segment (in arbitrary units).

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REFERENCES

[1] Klinge, S., Nunez-Ramirez, R., Llorca, O., and Pellegrini, L. (2009). 3D architecture of DNA Pol alpha reveals the functional core of multi-subunit replicative polymerases. Embo J *28*, 1978-1987.

[2] Nogales-Cadenas, R., Jonic, S., Tama, F., Arteni, A.A., Tabas-Madrid, D., Vazquez, M., Pascual-Montano, A., and Sorzano, C.O. (2013). 3DEM Loupe: Analysis of macromolecular dynamics using structures from electron microscopy. Nucleic Acids Res *41*, W363-367.

[3] Jin, Q., Sorzano, C. O., de la Rosa-Trevin, J. M., Bilbao-Castro, J. R., Nunez-Ramirez, R., Llorca, O., Tama, F., and Jonic, S. (2014). Iterative elastic 3D-to-2D alignment method using normal modes for studying structural dynamics of large macromolecular complexes. Structure *22*, 496-506.