StructMap: Elastic distance analysis of electron microscopy maps for studying conformational changes

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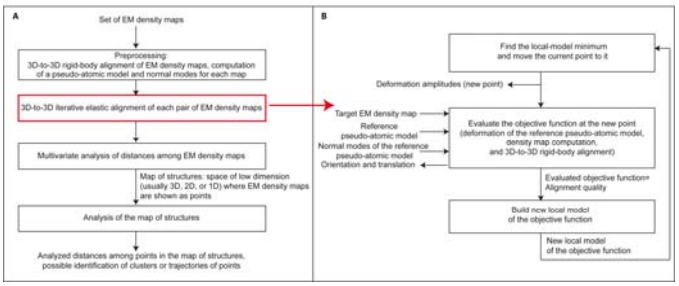
Abstract: Single-particle electron microscopy (EM) has been shown to be very powerful for studying structures and associated conformational changes of macromolecular complexes. In the context of analyzing conformational changes of complexes, distinct EM density maps obtained by image analysis and three-dimensional (3D) reconstruction are usually analyzed in 3D for the interpretation of structural differences. However, graph visualization of these differences based on a quantitative analysis of elastic transformations (deformations) among density maps has not been done yet due to the lack of appropriate methods. Here, we present an approach that allows such visualization. This approach is based on statistical analysis of distances among elastically aligned pairs of EM maps (a map is deformed to fit the other map), and results in visualizing EM maps as points in a lower-dimensional distance space [1]. The distances among points in the new space can be analyzed in terms of clusters or trajectories of points related to potential conformational changes. The results of the method are shown with synthetic and experimental EM maps at different resolutions.

1. Flowchart of StructMap

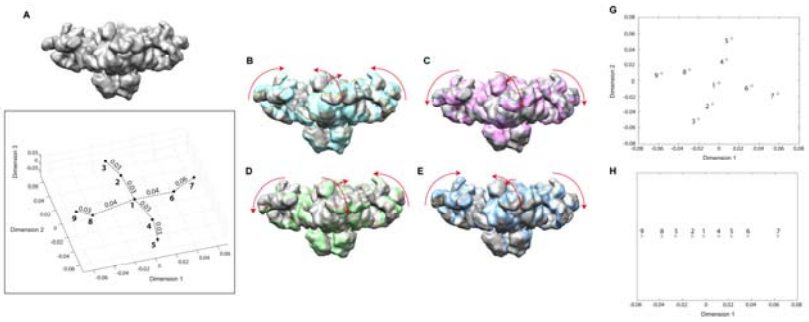


(A) Method [1].

(B) Iterative elastic 3D-to-3D alignment between two density maps (available in Xmipp and Scipion). It requires computing pseudo-atomic structures and their normal modes [2], and it uses objective-function optimization as in the iterative elastic 3D-to-2D alignment method of HEMNMA [3-4].

The measure of dissimilarity between two finally aligned EM density maps is taken as the distance between the two maps. The distances among all pairs of EM maps are used to construct a distance matrix that is then analyzed with a multivariate analysis method, so as to project all EM maps onto a common distance space (map of structures), in which each EM map is represented as a point. Points may then be analyzed in terms of their positions and mutual distances to potentially identify clusters or trajectories of points.

2. StructMap analysis of nine synthetic EM maps

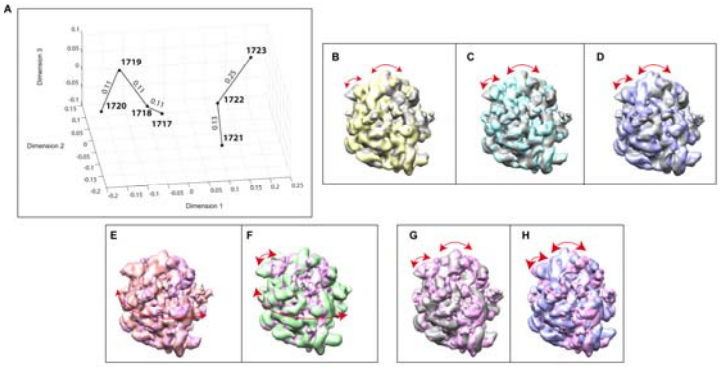


Procedure for obtaining synthetic EM density maps:
EM map of RyR1 from *Samso et al., PLoS Biol 2009* (EMDB:EMD-1606) was elastically deformed using normal modes to obtain nine ideal density maps corresponding to different RyR1 conformational states (fictional). These density maps were projected onto image planes (with noise and CTF) and nine density maps were then reconstructed from oriented images. These reconstructed maps were analyzed by StructMap.

(A) Map 1. (B) Overlapped maps 1 (grey), 2 (yellow), and 3 (emerald green). (C) Overlapped maps 1 (grey), 4 (violet), and 5 (magenta). (D) Overlapped maps 1 (grey), 6 (pink), and 7 (green). (E) Overlapped maps 1 (grey), 8 (brown), and 9 (blue). Arrows show main directions of deformation of map 1 when fitting the other two overlapped maps. Arrow scale shows the largest distance among these three maps after the deformation.

(F-H) Elastically aligned maps 1-9 projected onto 3D (F), 2D (G), and 1D (H) distance space, with distances among maps shown in arbitrary units above the corresponding line segments in (F).

3. StructMap analysis of seven experimental EM maps of *E. coli* 70S ribosome from *Fischer et al., Nature 2010*



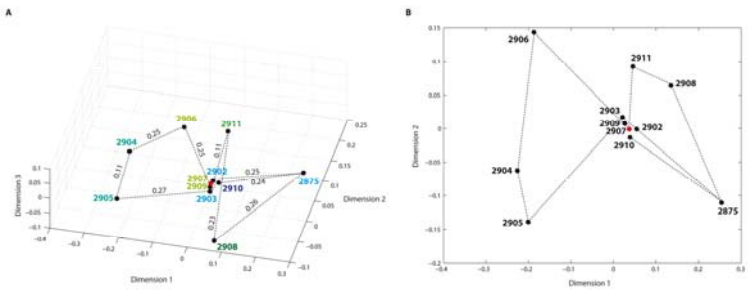
According to the original proposal: EMD-1717-EMD-1720: pre-translocational states pre2-pre5, respectively, EMD-1721-EMD-1723: post-translocational states post1-post3, respectively.

(A) Mapping of EM maps onto a 3D distance space, with distances among maps shown in arbitrary units above the corresponding line segments. Straight lines connect subsequent states according to the original proposal.

(B-H) Overlap of maps. (B) 1717 (gray) *vs* 1718. (C) 1717 (gray) *vs* 1719. (D) 1717 (gray) *vs* 1720. (E) 1721 (magenta) *vs* 1722. (F) 1721 (magenta) *vs* 1723. (G) 1721 (magenta) *vs* 1717. (H) 1721 (magenta) *vs* 1720.

Arrows show movements mainly contributing to elastic transformation between two maps, and the arrow scale shows the distance between these maps in the distance space i.e., dissimilarity between maps after the deformation (the amount of deformation is not represented by arrows but only the type of movement). Bi-directional arrows mean that elastic transformation between two maps is computed in both directions.

4. StructMap analysis of eleven experimental EM maps of human 80S ribosome from *Behrmann et al., Cell 2015*



States along the elongation cycle of 80S according to the original proposal:
classical iPRE state (EMD-2907), classical-1 PRE state (EMD-2909), PRE* state (EMD-2906), rotated-1 PRE state (EMD-2904), rotated-2 PRE state (EMD-2905), POST-i3 state (EMD-2903), POST-i2 state (EMD-2902), POST state (EMD-2875), pre-recycling state (EMD-2910), post-decoding/post-hydrolysis state (EMD-2908), post-decoding/post-dissociation state (EMD-2911). Translocation and decoding-sampling/-recognition states were not observed in the original work.

(A-B) Mapping of EM maps onto 3D (A) and 2D (B) distance space, with dotted lines connecting subsequent states according to the original proposal.

In (A), distances among maps are shown in arbitrary units above the corresponding line segments. The same colors are attributed to the maps with the same or similar composition, which resulted in using 6 different colors for the following 6 types of composition: 1) 2904-2905 (two tRNAs but slightly different, P/E, A/P in 2905 and P/E, A/A in 2904); 2) 2906-2909 (three tRNAs: E/E, P/P, A/A); 3) 2902-2903 and 2875 (two tRNAs: E/E, P/P); 4) 2911 (three tRNAs: E/E, P/P, A/T); 5) 2908 (eEF1A and three tRNAs: E/E, P/P, A/T), 6) 2910 (eRF1, ABCE1, and two tRNAs: E/E,P/P). The classical iPRE state (EMD-2907) is marked with a red point in A-B.

References

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