Ab initio structure determination using orthoaxial single particle projections

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In cryo-electron microscopy (cryo-EM), proteins sometimes appear on micrographs in highly preferred orientations. In such cases the protein will exhibit a predominant view; for example, only projections perpendicular to the long axis of the protein will be available. The associated reconstruction problem is known as single axis reconstruction. Because of the unique single axis, all views share precisely the same common line, so that the so called method of common lines cannot be used in determining the projection angles. Hereby, we propose a method that uses only the information (cross-correlation coefficient) contained in the pairwise comparison of images. We argue that the proposed method for assigning angular assignments *ab initio* is optimal in a sense that it uses the maximum amount of the information present in the data. The program that implements our method, we have called Sidewinder and has been employed to successfully aid in the structure determination of Hrs [1]. Sidewinder will appear in the new Sparx suite of single particle reconstruction tools, which will soon be publicly available.

References
[1] Pullan, L., Mullapudi, S., Huang, Z., Baldwin, P.R., Chin, C, Sun, W., Tsujimoto, Kolodziej, S.J., Stoops, J.K., Lee, J.C., Waxham, M.N., Bean, A.J., and Penczek, P.A. The endosome-associated protein Hrs is hexameric and controls cargo sorting as a "master molecule." Structure, in press.
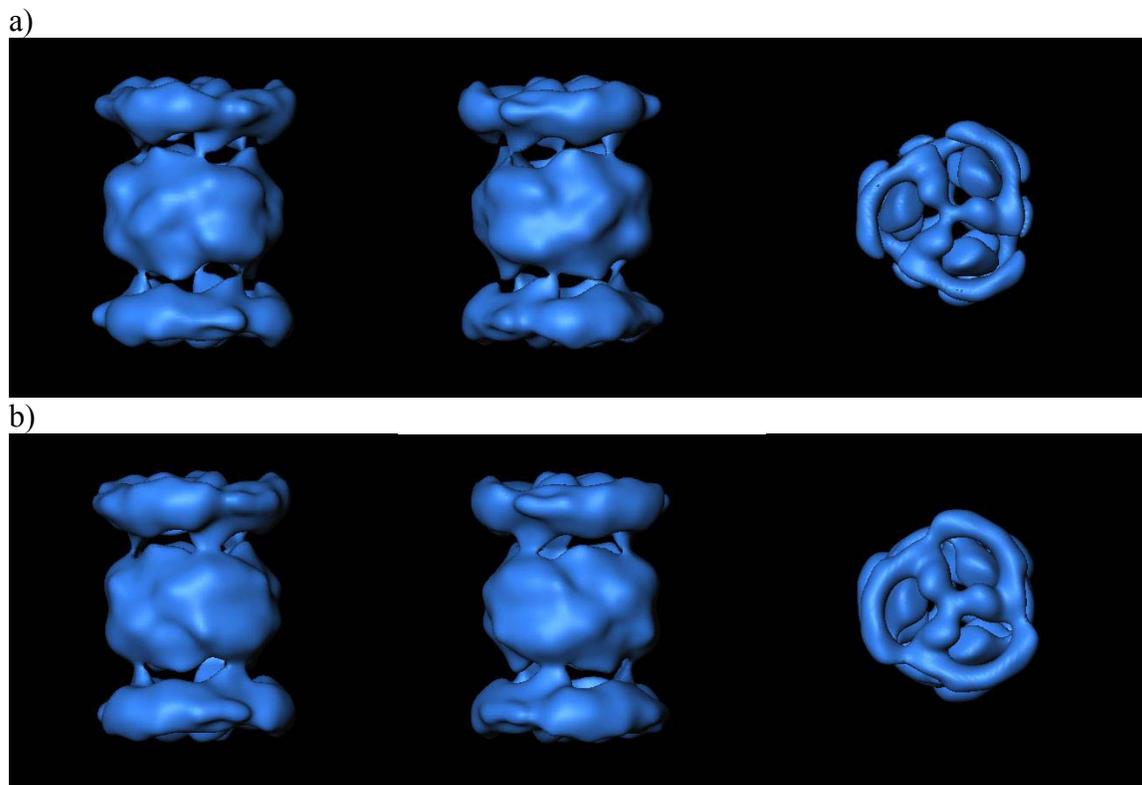
a)

b)

Fig. 1. 3D reconstruction methods for Hrs using a) random conical tilt, b) Sidewinder, our *ab initio* reconstruction tool. The structure in a) was refined from approximately 8500 side views of Hrs. The initial model in b) was built *ab initio* using Sidewinder from 100 aligned but otherwise reference free class sums. The symmetry of the molecule is D6. Note the close correspondence between reconstruction methods.