QUANTITATIVE COMPARISON OF 3D RECONSTRUCTION ALGORITHMS UNDER CONDITIONS OF UNEVEN ANGULAR DISTRIBUTION IN ELECTRON MICROSCOPY.

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Abstract

The full understanding of the way proteins and other macromolecules work in living beings is highly demanded in the design of selective drugs and development of illness treatments. In this way, the macromolecular structure determination is a key problem in biology in order to understand deeper the functionality of a given complex and the way it interacts with other particles. There are several methods of collecting such structural information. One among them is the 3D reconstruction from projections obtained by means of an electron microscope. Recently, several concerns in the field ([1]) have been raised about the 3D reconstruction algorithms performance when the angular distribution of the projections is highly uneven, which can be the case due to the differential macromolecular interactions with the supporting film that results in having more projections in some "preferred" directions. In this work a quantitative comparison among WBP (the standard reconstruction method in the field), SIRT and ART is done. At the end we will show that under this uneven distribution ART outperforms by far SIRT, and behaves better than WBP.

1. PROBLEM DEFINITION & EXPERIMENT DESIGN

The position of the macromolecular assembly on the supporting film, which holds it inside the electron microscope, is not random: there are preferential biochemical interactions resulting in preferential views of the complex. This is translated into a larger number of projections from one direction than from the rest, and consequently in an anisotropic distribution of information within the reconstructed volume. However, there are algorithms, like WBP (Weighted Back Projection, [2]) and SIRT (Simultaneous Iterative Reconstruction Technique, [3]), which seem to fail when dealing with these uneven angular distribution, creating an artefactual elongation along the direction which has been overloaded. In this work we will show that ART (Algebraic Recontruction Technique, [4]) does not suffer from this elongation. The ART and SIRT compared here are implemented using blobs on a BCC grid.

As a quantitative measure of performance is pursued, some figures of merit (FOM) have been defined to assess a numerical comparison. We will make use of a squared error measure (fFOM) for optimizing the algorithms' parameters and a vertical resolution FOM (vfFOM) to measure elongations. These FOMs are designed for the special case in which we have a phantom compound of a set of F pairs of cylinders, which are supposed to be embedded in a sphere where there's nothing else but background and the feature itself ([5]).

In the following formulas, range stands for the range of the phantom (this way the measure is independent from the signal power), F is the number of features (in this case pair of cylinders) present, P refers to the phantom, and R to the reconstruction.

Feature	$fFOM = 1 - \frac{1}{F}\sum_{f=1}^{F} e_f \,/\, range^2$	e_f is the mean squared error over the feature
Vertical Resolution	$vrFOM = \frac{\frac{m_{1R} + m_{2R} - 2m_{3R}}{\sqrt{v_{1R} + v_{2R} + v_{3R}}}}{\frac{m_{1P} + m_{2P} - 2m_{3P}}{\sqrt{v_{1P} + v_{2P} + v_{3P}}}}$	m_i refers to the mean and v_i to the variance within the plane i. Planes 1 and 2 are central to the couple of cylinders while 3 is in between them.

2. RESULTS

For a statistical comparison, phantoms with the same characteristics as in the training set have been reconstructed from 869 projections, 720 of them concentrated within 15º around the Z axis. The following table shows the vertical resolution FOMs for the three methods. Notice that ART is very significantly (0.005 level) better than WBP, and WBP is significantly (0.05 level) better than SIRT with respect to elongations along the preferred (Z) direction.

	ART	WBP	SIRT
vrFOM	0.645±0.107	0.38040±0.0601	0.2480±0.0491

In addition, we have investigated the algorithms for a phantom described at atomic level and composed by 12 spheres. Its projection images have been generated using a very realistic electron-atom interaction model. The results are shown in fig. 1

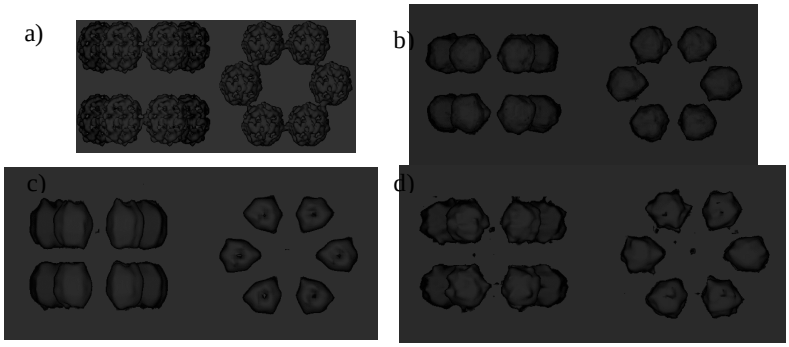

Fig. 1. a) Phantom constructed by pieces of actin at atomic resolution. b) ART reconstruction c) SIRT reconstruction d) WBP reconstruction

We conclude that when considering the case of an uneven distribution of projections, ART proves to be better than WPB, while the implementation of SIRT considered (as well as others used in the field of 3D electron microscopy, data not shown) performs much worse. Detailed mathematical explanation of the difference between the behavior of SIRT and ART remains to be found. At an intuitive level we can say that while SIRT and WBP give more importance to the information available in the projections near the preferred directions than to the rest, this is not the case for ART, since once a certain view in the volume is sufficiently matched, the volume is no longer updated with the same information time and time again.

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