Author's response to reviews

Title: Estimating view parameters from random projections for Tomography using spherical MDS

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Response to Reviewers

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Please note: In the revised manuscript, we highlight the new added content using red color. The grammar corrections are not highlighted in the revised manuscript.
General Answer to Reviewers’ Comments

We thank the second reviewer for providing valuable and constructive comments and suggestions. The major concerns arise from the two aspects:

1. The detailed description of the cryoEM application should be added in the introduction section.

2. How the proposed computational model be adapted to the cryoEM application.

We are sorry that we didn’t address those two parts clearly. We have added the corresponding description in the introduction section. We have explained how the proposed method can be adapted to the cryoEM application in the rebuttal letter. Please refer to the related explanations below.
Answers to Reviewer 2's Comments

(Notations: Ci: the ith comment; Ai: answer to the ith comment.)

C1: I am generally satisfied with authors' answers to my previous comments. Authors have removed claims about MR and 4DCT, and agreed that the method is only for spherical constraint motion, e.g. in cryo EM applications. But I see the presented results are not refined enough to support such adjustments.

A1: Thank you for your comments.

I am pleased that we have addressed your previous concerns about our work. Thanks for your interests on the spherical constrained tomography method and its cryoEM application.

The main contribution of our work in this paper is the proposed new tomography technique. At this stage, we do not constrain our method in a very specific research area. The motivation of this current work is towards proposing an algorithm that could be used in a spherical tomography case. We have to admit that we are not experts like the reviewer in CT and MR fields. The focus of our group in general is on the algorithm development. The general concerns for this round revision fall in the cryoEM applications by using our proposed methods. The cryoEM projects are one of collaboration projects which are on-going in our group. Basically, in cryoEM of biological molecules (viruses), the projection data at a single angle is taken for a large number of macromolecules at various random and unknown orientations. Assuming no overlapping for a single projection, so that individual particles can be distinguished, this is same as by having projection data at multiple but unknown angles [1]. We have used the latter approach as the basis for our computational model.

We have added a detailed description about cryoEM in our new revised form of manuscript. We hope the description addresses concerns from the reviewer. We are not going to talk more about the cryoEM application details as this work mainly serves as the prototype of our proposed method for the real problem. We were primarily interested in testing the correctness of our idea in this manuscript. We thank you again for your the key comments and continuous interests in our work. This paper is closed to the work in the [1, 2]. The difference between our method and that of [1,2] is the algorithm used in the orientation determination.

[1]. Yagle AE: A simple non-iterative algorithm for 2-D tomography with unknown view angles. (http://www.eecs.umich.edu/~aey/recent/angle.pdf) (note that if this doesn't work, please Google the paper and you will find the paper draft).

C2: Can authors add more details in section 1.1 about the targeted applications and the associated problems, about how cryoEM method is used to image virus. Please add some references.

A2: Thank you for your valuable suggestion.

We have added a detailed description about the cryoEM in of the revised manuscript. We hope the description addresses the concerns from the reviewer. The cryoEM projects are one of collaboration projects which are on going in our group. Basically, in cryoEM of biological molecules (viruses), the projection data at a single angle is taken for a large number of macromolecules at various random and unknown orientations. Assuming no overlapping for a single projection, so that individual particles can be distinguished, this is same as by having projection data at multiple but unknown angles [1]. We have used the latter approach as the basis for our computational model. Please refer to the Figure 1 below for the details about the real imaging system (Fig. 1(A)) and the equivalent computational model (Fig.1(B)).

[1]. Yagle AE: A simple non-iterative algorithm for 2-D tomography with unknown view angles. (http://www.eecs.umich.edu/~aey/recent/angle.pdf) (note that if this link doesn’t work, please Google the paper and you will find the paper draft).

C3: Is cryoEM method used to image single virus or a group of viruses? I guess it is difficult to image single virus. If a group of unknown number of viruses is imaged, the proposed method by this paper has to be upgraded to another level, to deal with multiple objects. Or at least, the problems of multiple objects need to be discussed.

A3: Thank you for pointing out the issue.

We have addressed the concerns in the revised manuscript. Please refer to Section 1.1 for added content (highlighted by red color). The cryoEM projects are one of collaboration projects which are on going in our group. Basically, in cryoEM of biological molecules (viruses), the projection data at a single angle is taken for a large number of macromolecules at various random and unknown orientations (Figure 1A). Assuming no overlapping for a single projection, so that individual particles can be distinguished, this is same as by having projection data at multiple but unknown angles [1] (Figure 1B). We have used the latter approach as the basis for our computational model (Figure 1B). The main assumption is that the macromolecules are homogeneous and identical copies which lead to the correctness of the equivalent computational model. Hence, our method does not address the problem in those situations where there is mixing of macromolecules (heterogeneity) or multiple
objects which is a research issue in itself and another research topic in our lab as well. Also, it is to be noted that, in our paper a macromolecule is perceived as a single entity and not as multiple objects.

Figure1. The model to simulate the cryoEM imaging system. (A) real imaging scenario (B) equivalent computational model

C4: Since the proposed method by this paper is (almost) nothing to do with MR and 4DCT images, why do authors still want to use the simulated 2D MR images in the
result section? The results are misleading the readers, and are not consistent along the claims and the final targeted applications of this paper. Can authors use (simulated) cryoEM images into the result section instead? Can authors finish the 3D implementation and add the results? Should 3D implementation be relatively straightforward?

A4: Thanks for your comments and questions about our paper.

Thank you for this important question. We totally understand the concerns from the reviewers. The experimental images are chosen in this manuscript is not from the application but for the test of the applicability of the proposed method. The images can be replaced by the phantom image at current stage like the authors in [1] to test their proposed methods. But the 2D MR image is closer to the real scenario compared to the 2D phantom image. This paper is our first paper for our spherical constrained MDS (SMDS) idea in the application of the cryoEM application. We start off the 2D case and try best to simulate as close as possible to the real scenario of cryoEM. The using of MR image is going to make our proposed model fit to a general case of tomography imaging application. The reason why we did not put our 3D case in the current version of our work is that we are still working on a good measurement of distance matrix among different 2D cryoEM images which is a big issue in this area. And the extension to 3D case is straightforward as long as we can propose a good distance metric among the different images. One of the reference [2] has proposed a good way to measure the distance among the different cryoEM but this paper is still not officially published (on the technical report form), which ,to the best of our knowledge, is because the proposed distance is not very robust to noise in 3D case. We are thinking of other ways to compute the distance between images captured at different angles, for example, the earth mover's distance (EMD) [3] might be better than Euclidean distance to capture the orientation difference. The work is still on going at this stage. So, 3D reconstruction is not straight forward at this moment and hence, we cannot include it in the current paper.


C5: Is beam divergence a problem? Is it worth to discuss? (Are the electron beams used in cryoEM cone beams, or fan beams, like the x-ray beams in CT scanners?) What are the conditions to approximate such beams into parallel beams?
A5: Thank you for the suggestion.

This comment reflects the reviewer having very solid background in the medical imaging research field. We appreciate that the reviewer gives us such good comment. The beam divergence is not a problem in cryoEM application and the electron beams are always considered as parallel beams. The proposed method is supposed to work for the Parallel-beam tomography. The electron beam is usually be treated as the parallel-beam and please refer to [1,2,3]. We quote the related statements in [1,2,3] below.

(1) Abstract in [1]: “Parallel-beam tomography in which the projection angles are unknown arises in MRI imaging, due to involuntary patient movement, and also electron microscopic imaging of biological macromolecules, due to random orientation of many identical macromolecules…”

(2) Abstract in [2]: “…The algorithm is shown to successfully reconstruct the Shepp - Logan phantom from its noisy projections. Such a reconstruction algorithm is desirable for the structuring of certain biological proteins using cryo-electron microscop…”

(3) Page 1, Para. 3, Line 1 in [2]: “… In this paper, we consider the reconstruction problem for the 2-D parallel-beam model with unknown acquisition angles…”

(4) Page 2, Para. 4 Line 1 in [3]: “Images obtained with the electron microscope are projections of the molecules along the direction of the electron beam…”


C6: I still like the paper as it is now. But I feel that the authors should try to move the method towards the actual applications.

A6: Thanks for your comment.

We greatly appreciate that the reviewer likes our work and give us so many constructive details about the improvements based on the current work. We really understand that the demands to move our method to the real applications. We are actually working on the real cryoEM applications now. However, before we published our real reconstruction result in the 3D cryoEM application, we want to first propose
our method, the initial computational model, and verify the correctness of our proposed method in the 2D case. The theoretical foundation for 2D and 3D application is the same and the only difference is that the way of defining the distance among different projections. In the 2D case, it is straightforward to define the distance based on the Euclidean distance between the high-dimensional projection vectors. In the 3D case, it is more difficult to define a reasonable distance among the 2D projection images which is one of the active areas of research. One of the reference [1] has proposed a good way to measure the distance among the different cryoEM but this paper is still not officially published (on the technical report form). We think that this is because the proposed distance is not very robust to noise in 3D case. We are thinking of other ways to compute the distance between images captured at different angles, for example, the earth mover's distance (EMD) [2] might be better than Euclidean distance to catch the orientation difference. The work is still on-going at this stage. So, 3D reconstruction is not straightforward at this moment and hence, we cannot include it in the current paper. We are working on another plan to release the code on our web server to provide the service to whole community for reconstruction of the 3D virus structure online. The core algorithm used in the web server is based on the work proposed in this work. We will release the server as soon as our work is finalized. Please visit the website which is provided along with this paper for the updated news if you are interested in our work. I really hope our work can be helpful in your research as well.
