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Peer Review

Review of: "CryoSAMU: Enhancing 3D Cryo-EM Density Maps of Protein Structures at Intermediate Resolution with Structure-Aware Multimodal U-Nets"

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I would review this preprint based on the practical use of a structural biologist rather than discussing the technical details of the paper.

So, the preprint discussed the enhancement of maps at intermediate resolution (4-7.9 Angstrom) and the speed improvement of CryoSAMU.

The speed improvement is real. CryoSAMU is very quick. It is very similar in speed to CryoTEN (https://github.com/jianlin-cheng/cryoten), a new enhancement program that seems to excel in speed and gives good performance. The speed is of great practicality as I don't hesitate to run the postprocess, and I can run it to compare with other methods. In addition, a lot of the time, we try to make a composite map before doing enhancement. The speed allows us to test quickly and tweak the composite map.

Then I tested CryoSAMU on different maps:
- A 4.6 Angstrom map: CryoSAMU did a good job for this map. In this case, EMReady did a better job with better connectivity in the map. I judged this based on my experience with cryo-EM reconstruction and modelling.
- A 5.8 Angstrom map: CryoSAMU didn't do a good job in this case. The map has a lot of details that should not be visible at 5.8 Angstrom. Comparatively, EMReady did a much better job here with

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appropriate detail.

- A 7.1 Angstrom map with low SNR: Similar to the 5.8 Å map, the CryoSAMU map output a lot of details that should not be visible at 7.1 Angstrom. At this resolution, DeepEmhancer output a good map, much better than the input map, but with a level of detail appropriate for the resolution. This takes really long with DeepEmhancer due to the lower pixel size.
- A 7.8 Angstrom map with good SNR: CryoSAMU and EMReady output quite equivalent maps. But this map is part of the training of CryoSAMU (emd_9949).
- An 8.1 Angstrom map with low SNR: CryoSAMU has a lot of details that are not real. DeepEmhancer output a good map like before. I didn't test with EMReady because it is outside the training resolution of EMReady.

So, I believe that the paper should be revised. Perhaps divide the comparison into resolution brackets (4-5, 5-6, 6-8), which probably reflects the performance better. Also, I believe that at the resolution of the 5-6 or 6-8 bracket, having the map with real examples (low and high SNR) is probably better than looking purely at CC criteria, as a lot of the time, the model fit quality is not great at this resolution for evaluation. That allows a better judgment for the practical usage of the software.

Declarations

Potential competing interests: No potential competing interests to declare.