

A membrane protein and detergent micelle *in silico* model for cryo-EM studies



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Single-particle Cryo-EM

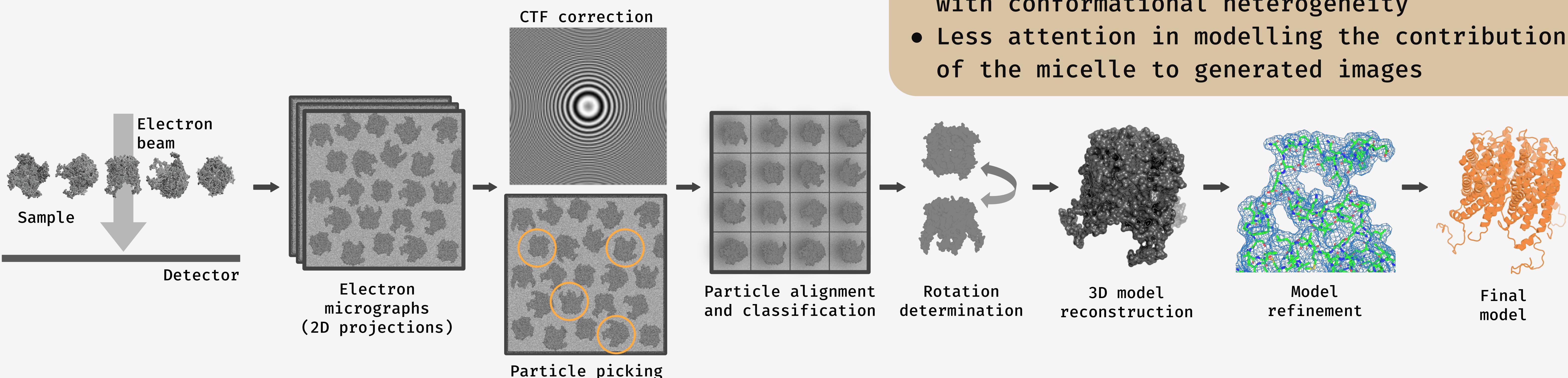


Fig1. Schematic of a single-particle cryo-EM experiment. The 2D projections of the sample are acquired using a transmission electron microscope. The Contrast Transfer Function (CTF) is estimated to correct the distortion of the image by the microscope. The images are processed by separating and classifying the individual particles and reconstructing the object from the various poses collected.

Membrane proteins

- Important pharmaceutical targets
- Hydrophobic transmembrane domains
- Challenging for experimental structural studies
- Stabilized by membrane-mimetic detergents

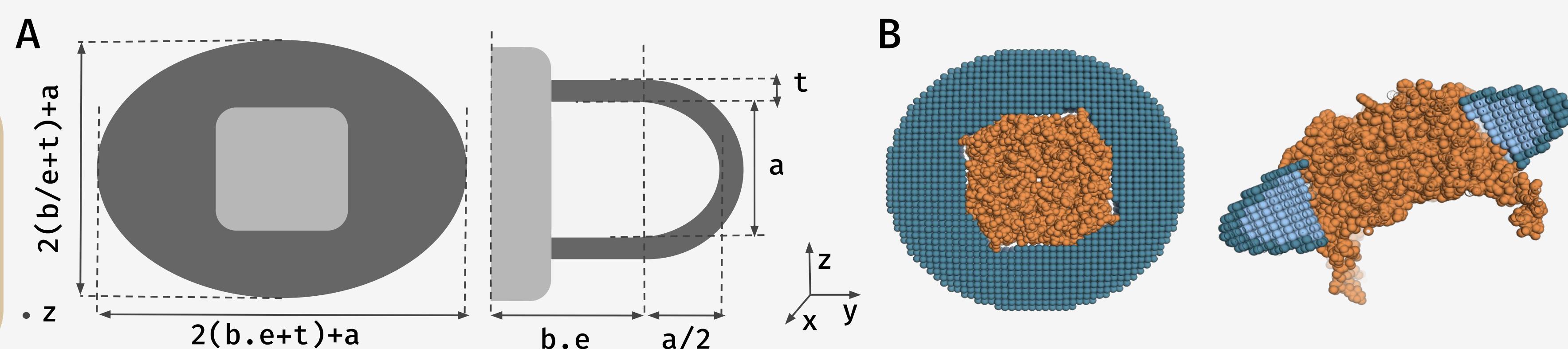


Fig2. A- Definition of the micelle parameters. The hydrophobic core of the detergent belt is modeled as an elliptical torus of minor and major semi axes b/e and be and height a (white), surrounded by a hydrophilic shell of thickness t (dark gray) around the protein (light gray). Modified from Berthaud et. al, 2012. B- Pymol visualization of a model of a detergent micelle and the membrane protein aquaporin (AQP0 PDB-2B6P) seen as a top view of the full model and frontal cut. The micelle hydrophobic core is represented in light blue, the hydrophilic shell in dark blue and the protein in orange.

Methodology

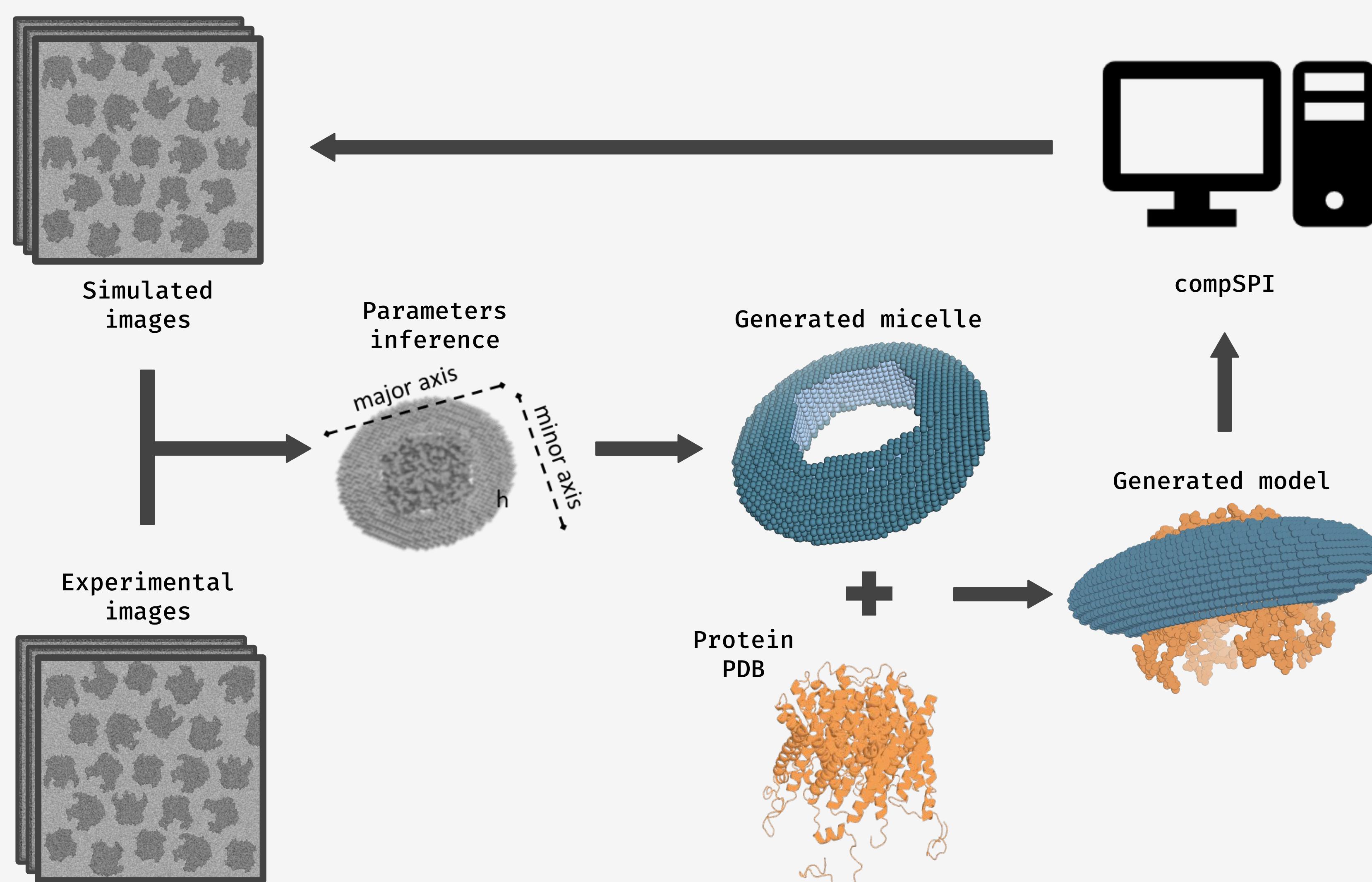


Fig3. Schematic of the pipeline for constructing the model. A coarse-grained model of a detergent micelle is generated around a protein of known structure using a script (Python) with the PDB of the model as input. Pseudo atoms represent a collection of detergent atoms of either the molecule's hydrophilic head or the hydrophobic tail, as inspired by Pérez & Koutsoubas, 2015. The github repository compSPI is used to simulate a cryo-EM experiment with the model. The experimental and simulated images are used to infer the approximate parameters of the micelle.

Preliminary results

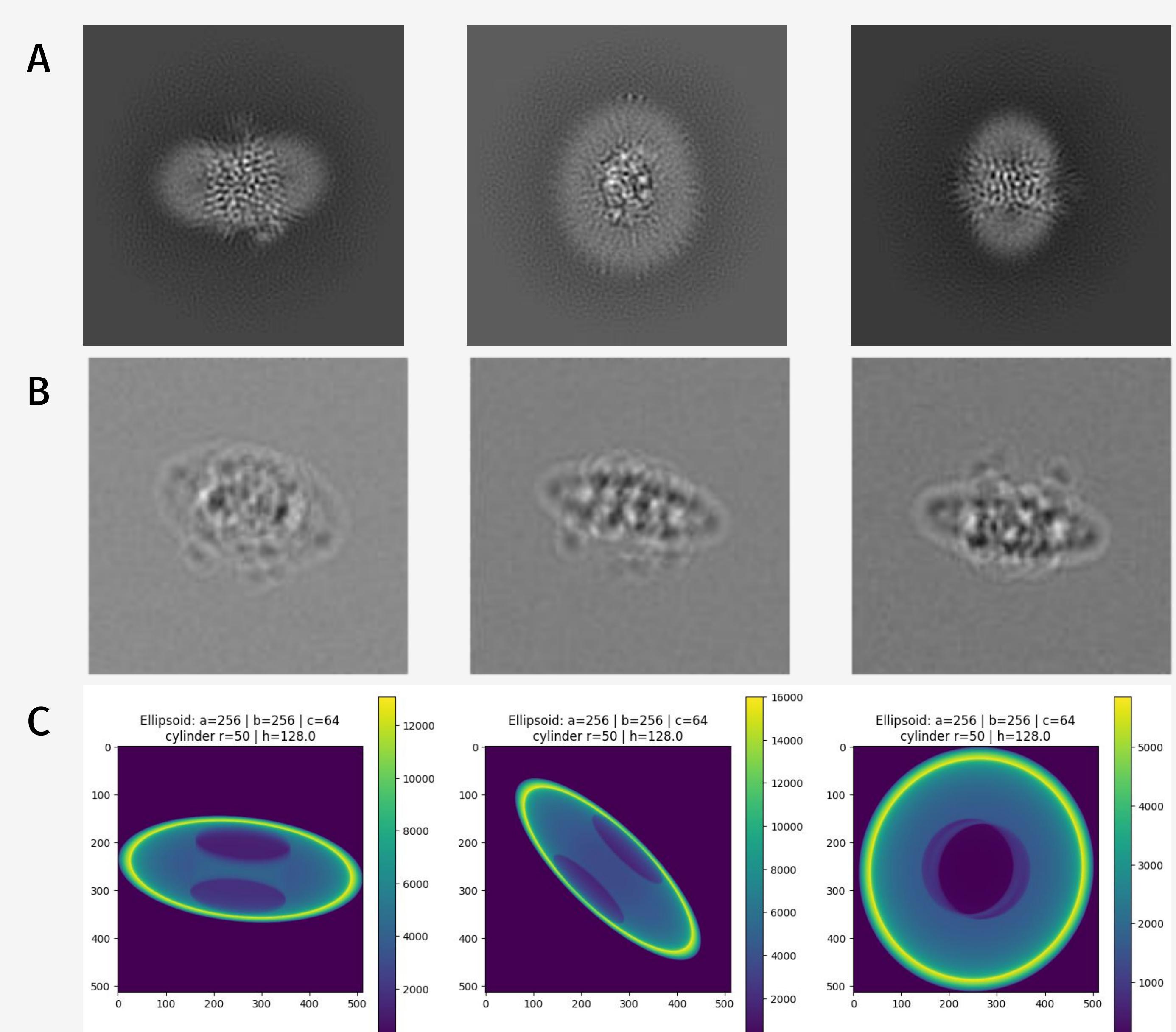


Fig4. Comparison of cryo-EM maps from three different techniques. A- Experimental orthogonal projection of the map of the human glucose transporter (GLUT4 EMD-32761). B- Simulation results of the model generated with the pipeline in Fig.3 for AQP0. C- Analytical description of the projected density of a micelle minus the density of a cylinder (a simplified representation of a protein transmembrane region).

Conclusion

The outcome of the work so far is a fast model for inference of micelle parameters in single-particle cryo-EM images. The next steps include the analysis of experimental data and further development of the pipeline.