Computer methods for cryo-Electron Tomography: current changes

AIRA Seminar

02/03/2023

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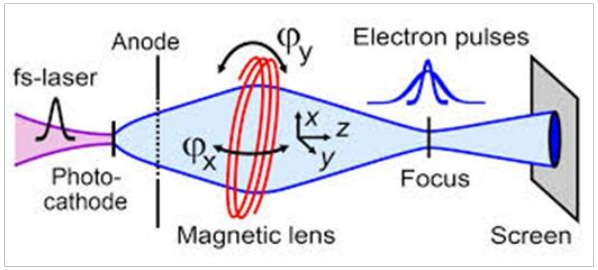
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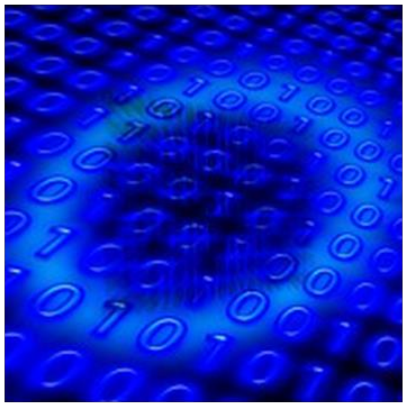
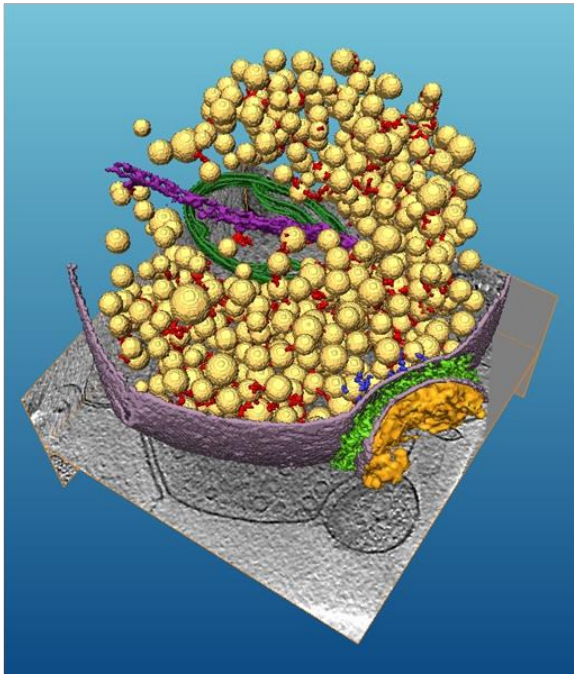
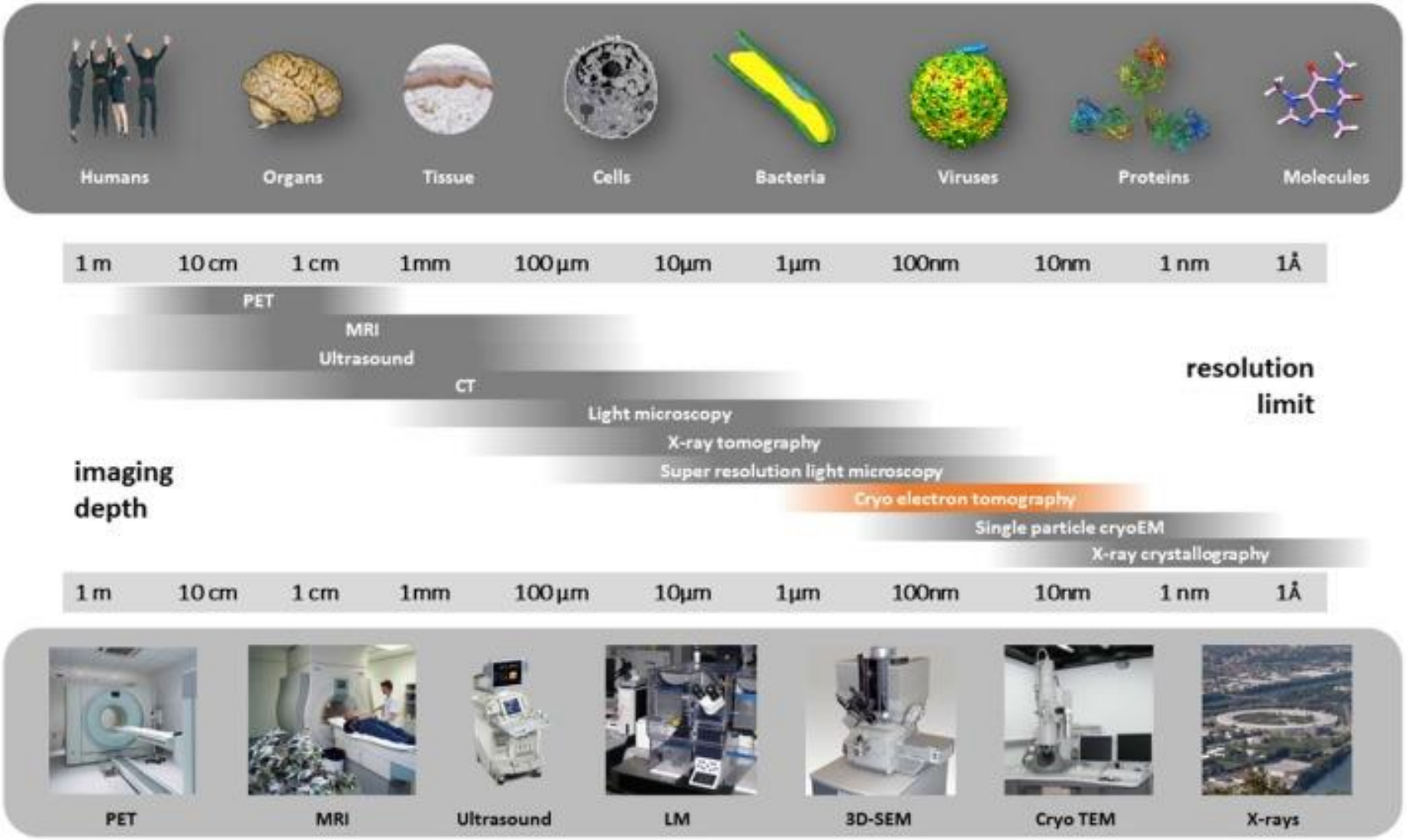
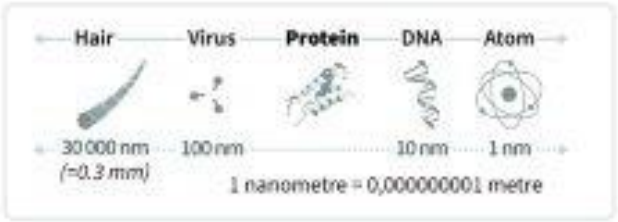




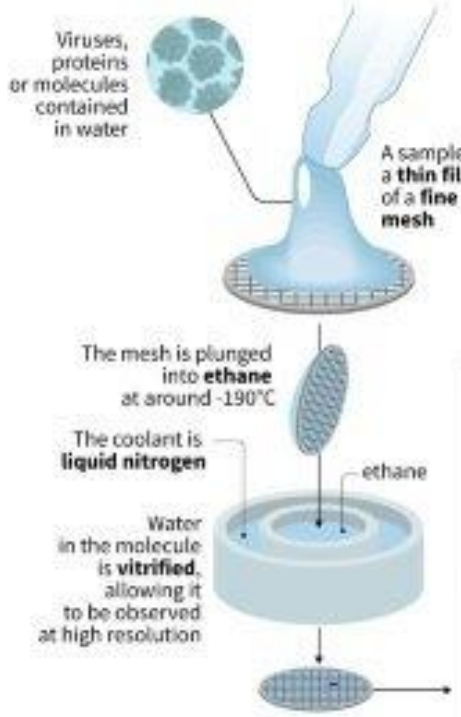


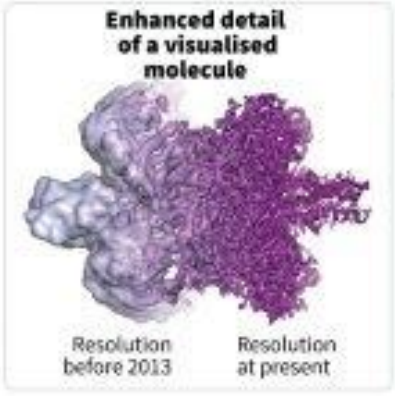
Koning et al. (2018) *Annals of Anatomy*

Cryo-electron microscopy (cryo-EM): vivid vitrified images



SAMPLE VITRIFICATION METHOD





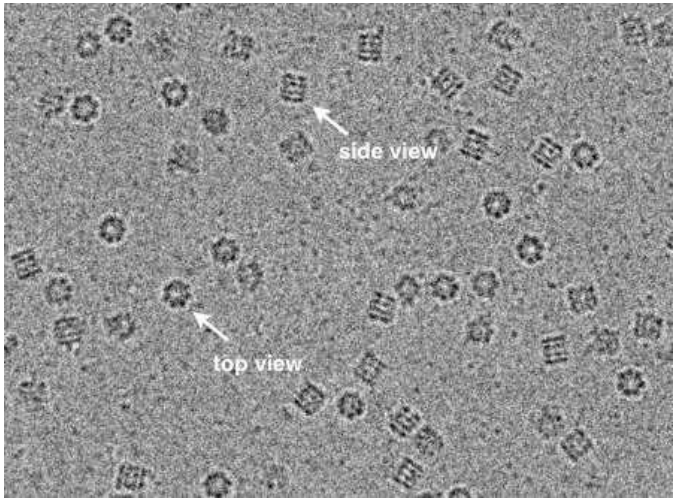
3D imaging technique

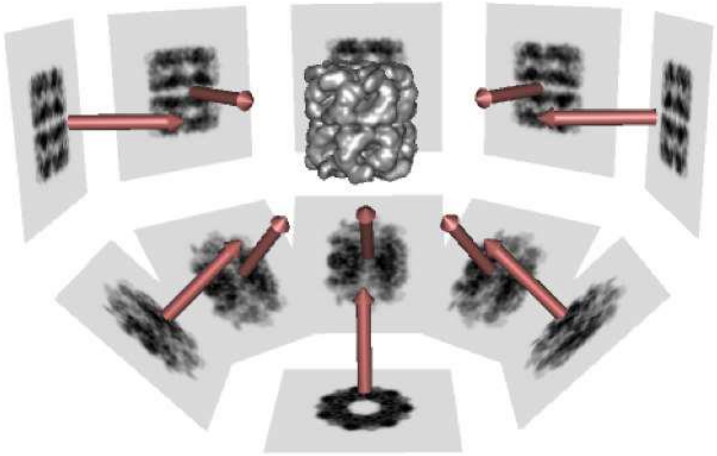
Modeling a molecule or protein in 3 dimensions

Source: The Royal Swedish Academy of Sciences/NobelPrize

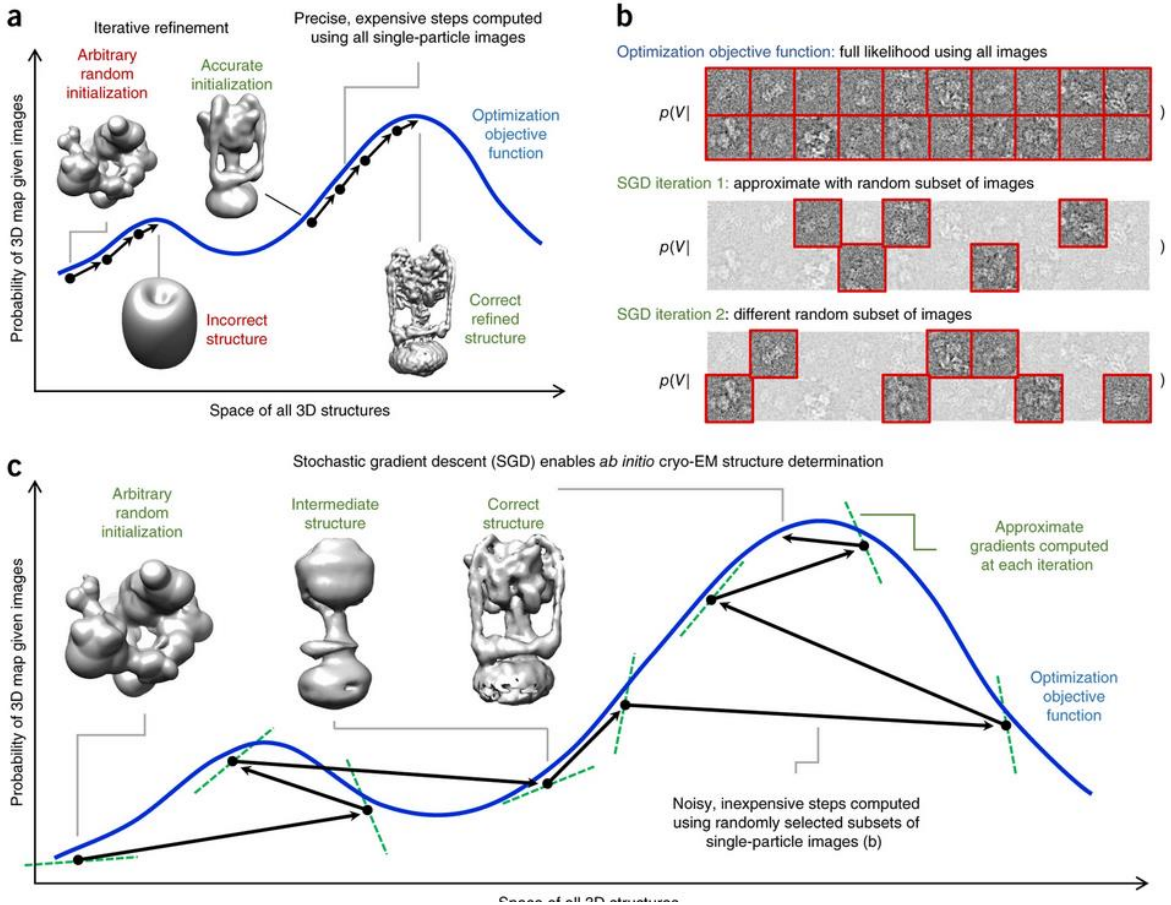
© AFP

3D Reconstruction: optimization problem





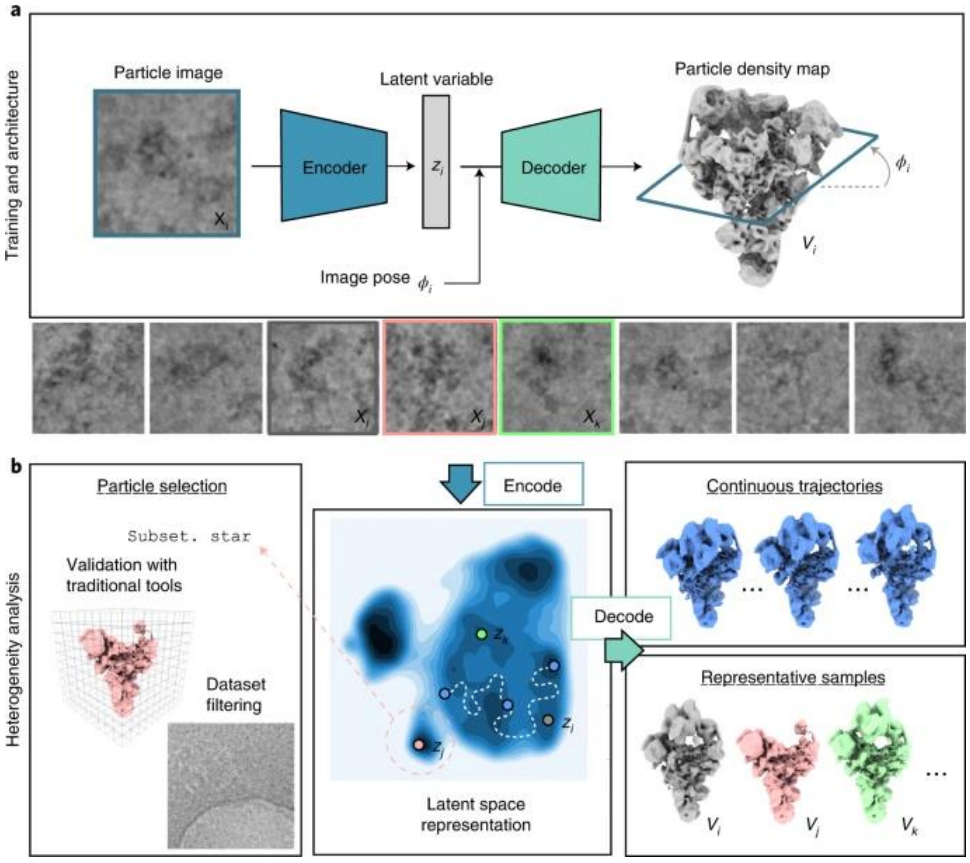
Punjani *et al.* (2021) *Nature Methods*

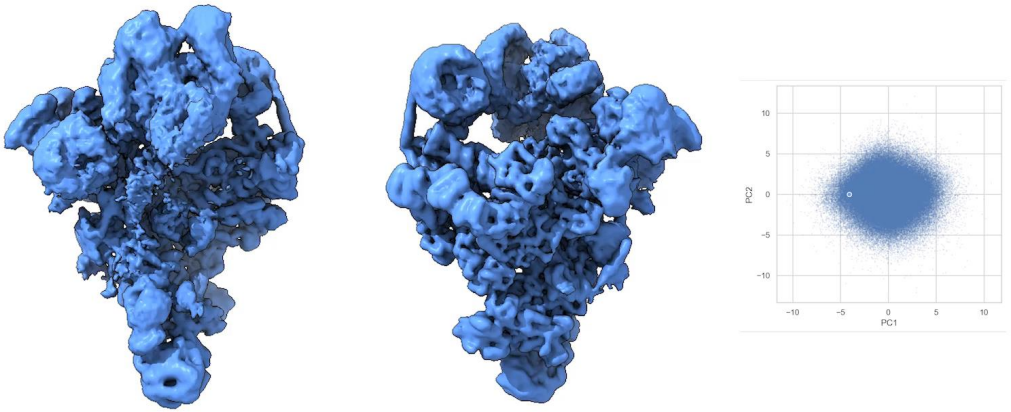


https://www.ifsc.usp.br/mx2018/presentations/Colin/Cryo-EM.pdf

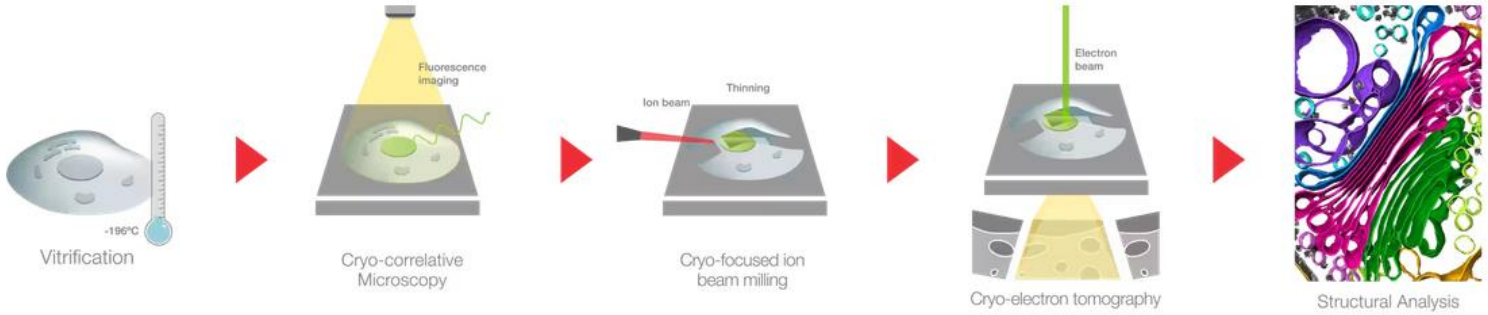
Macromolecular flexibility

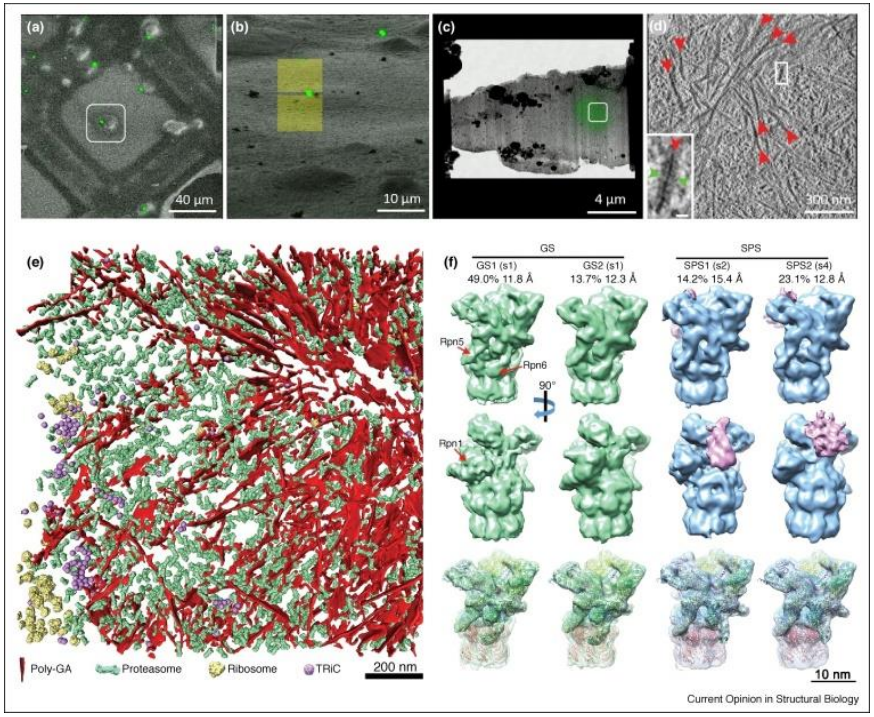
Zhong *et al.* (2021) *Nat Methods*





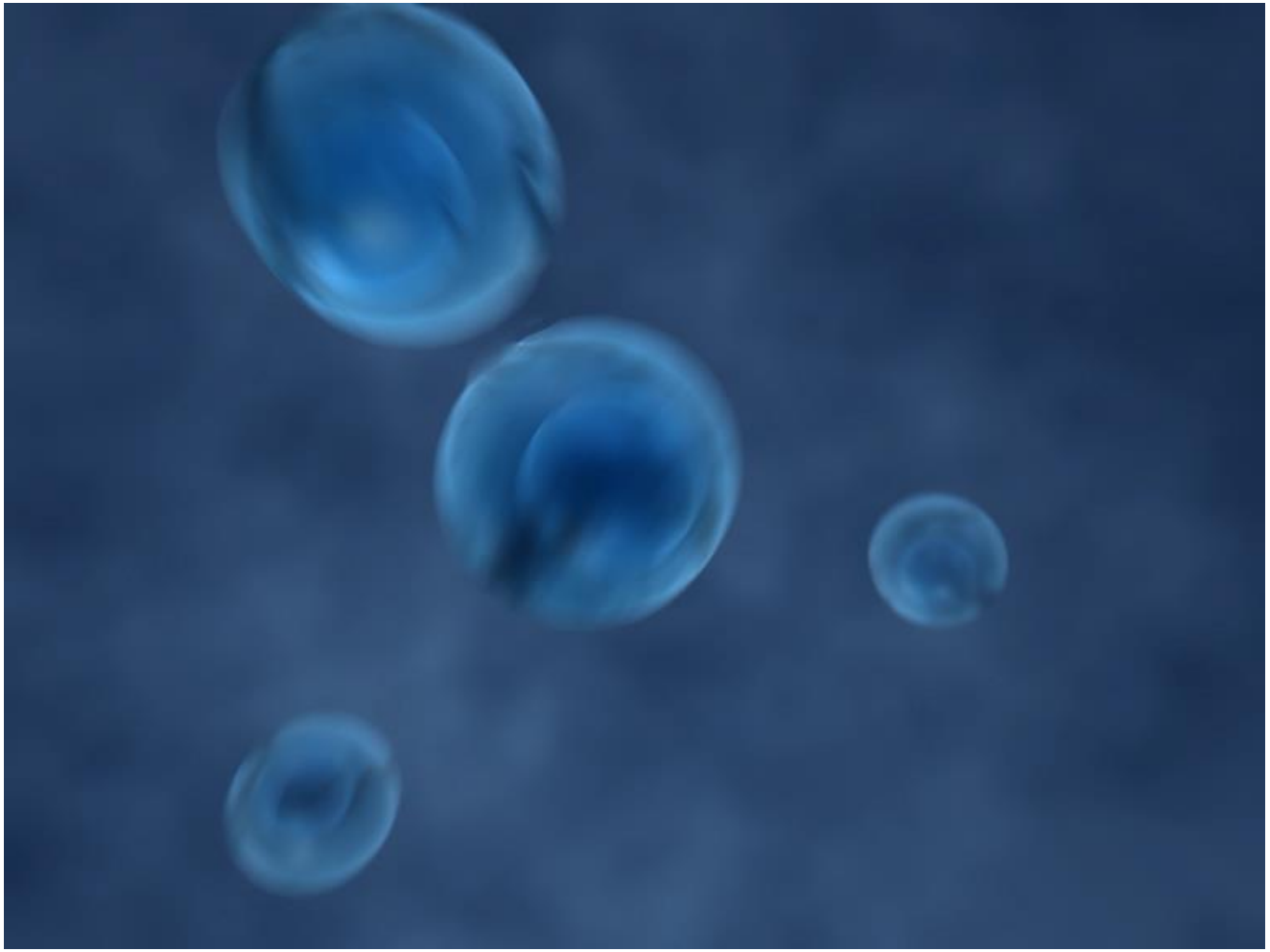
Cryo-Electron **Tomography**: cryo-ET (3D) / cryo-EM (2D)



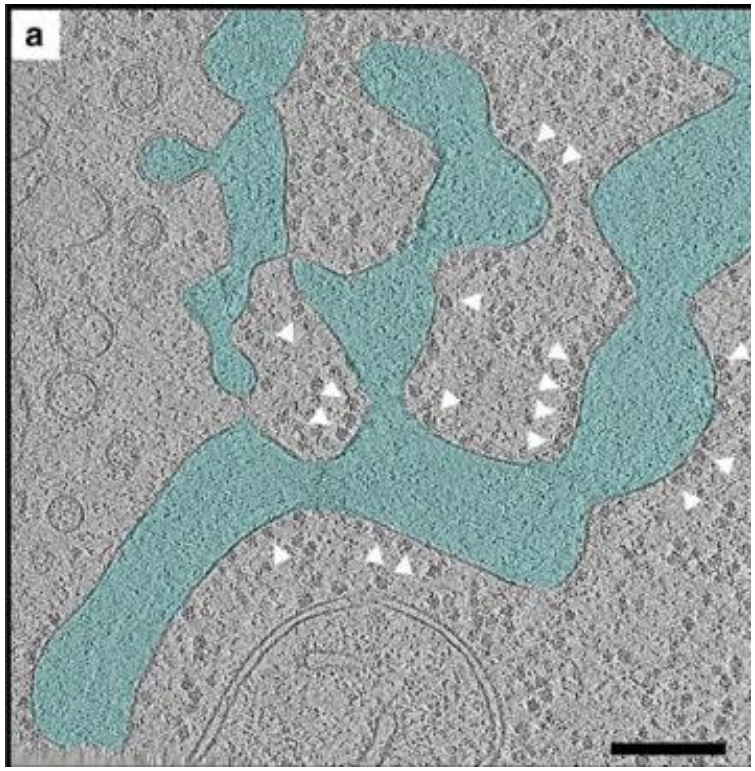


Guo, Q. et al (2018). *Cell*

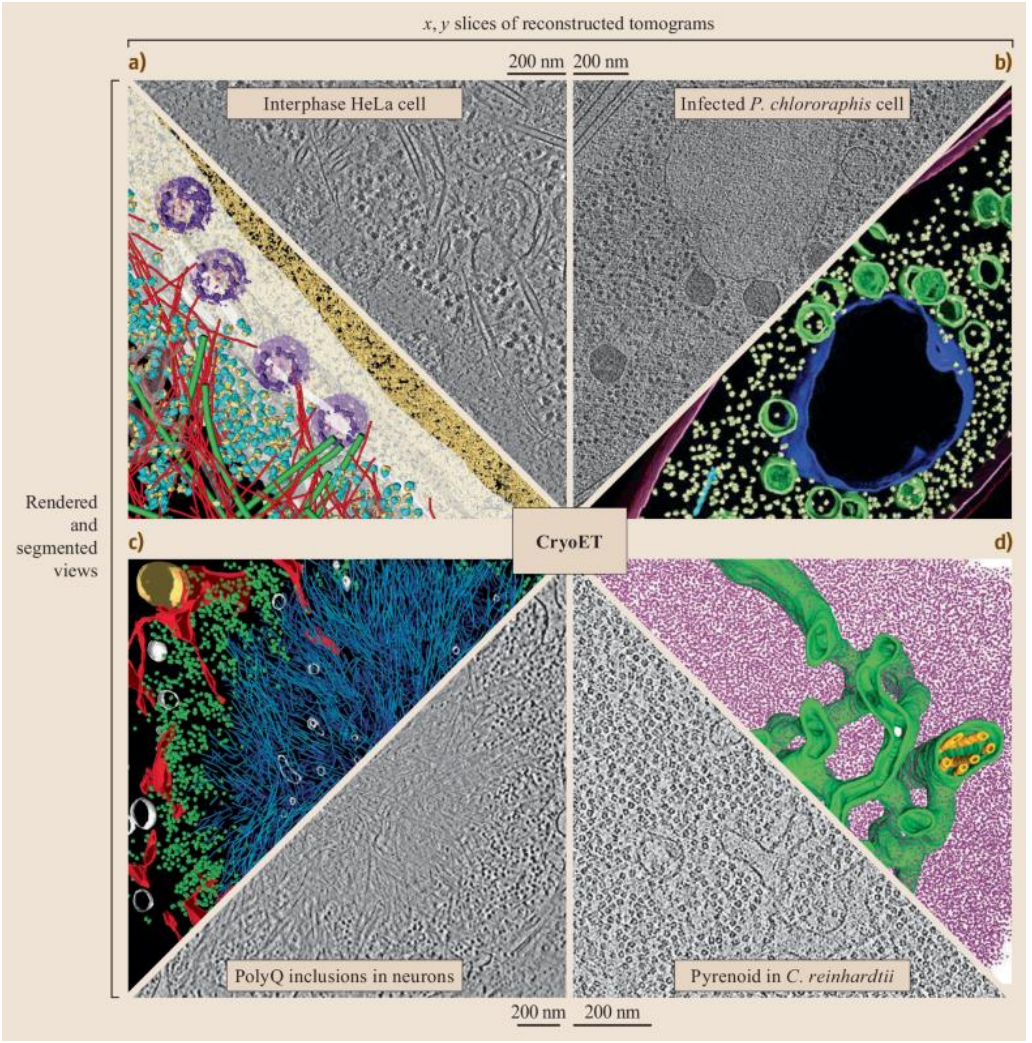
Cryo-ET workflow



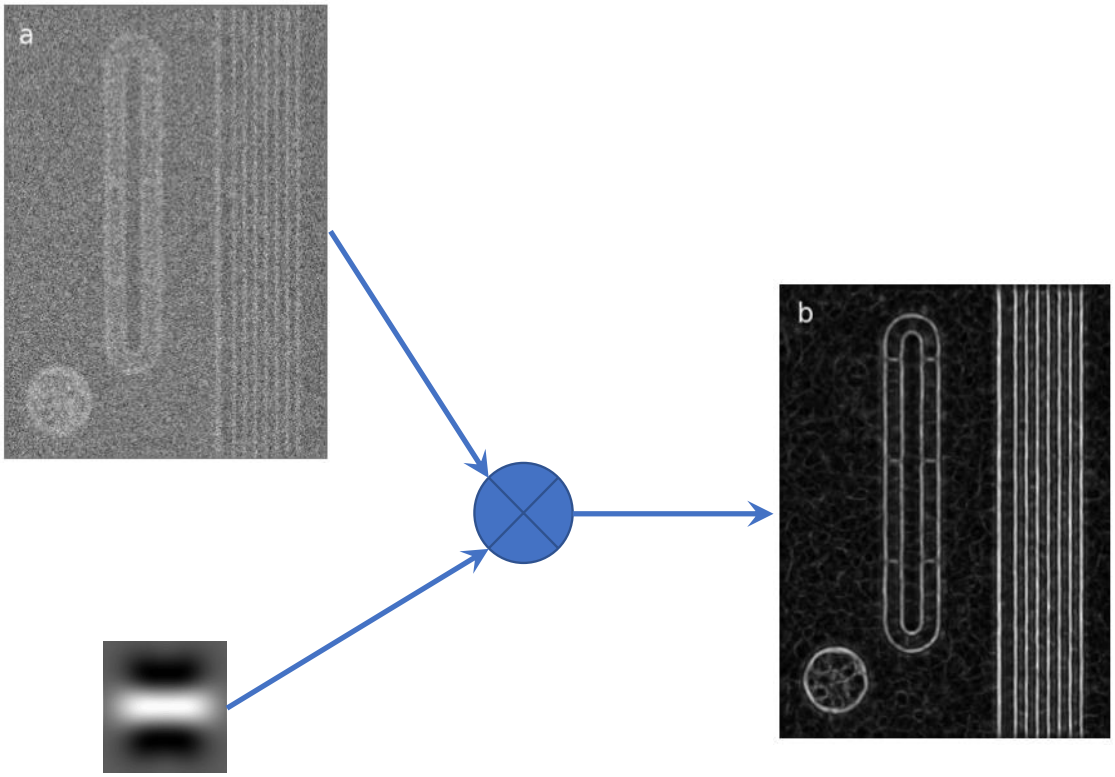
Membrane segmentation

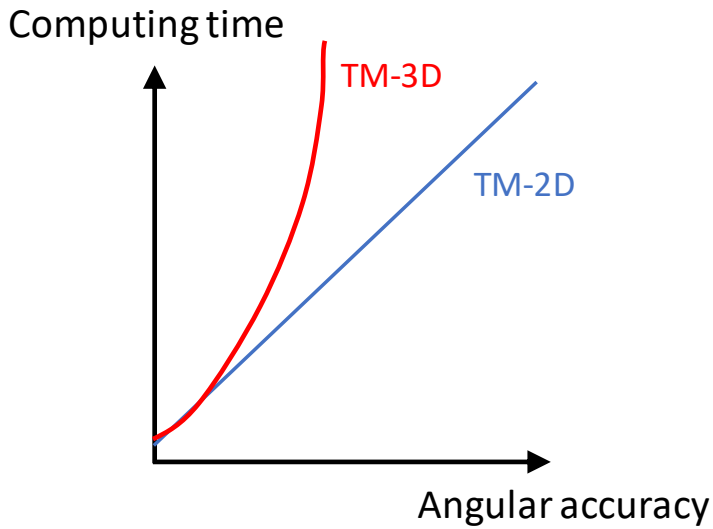


Pfeffer, S. et al (2017). *Nature Comms*

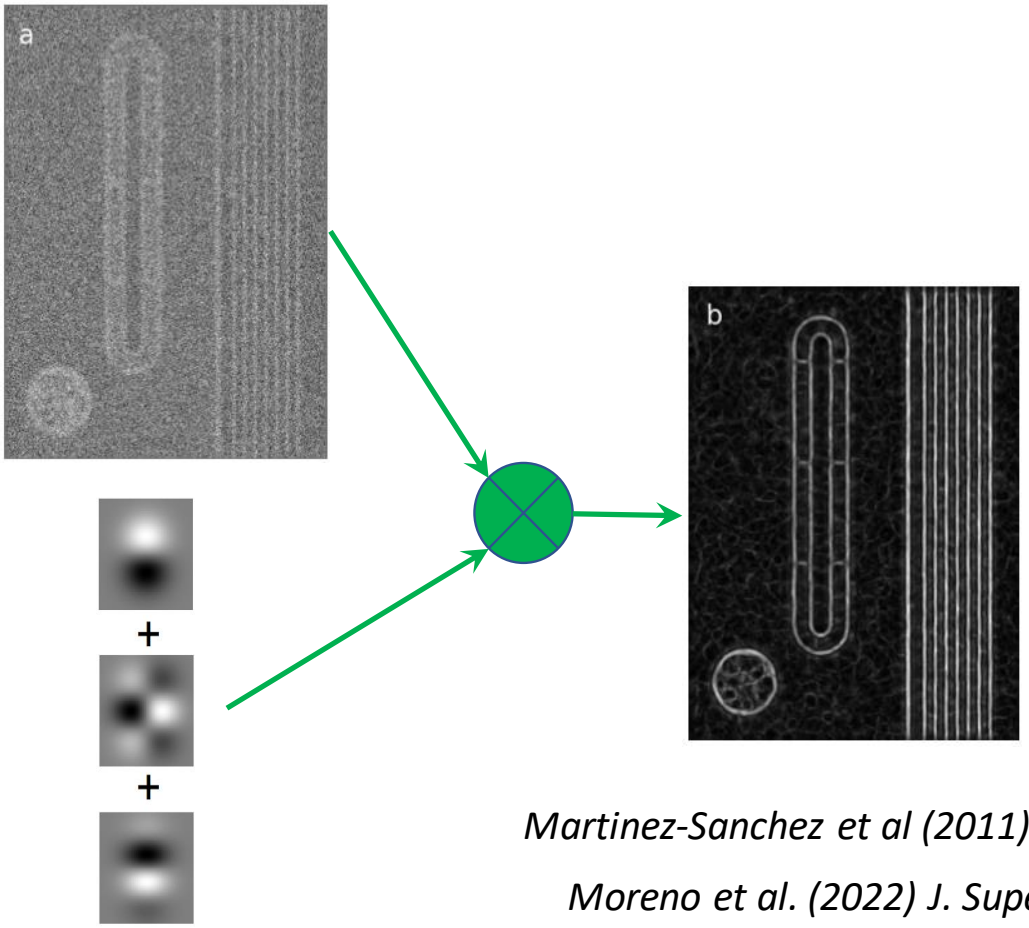


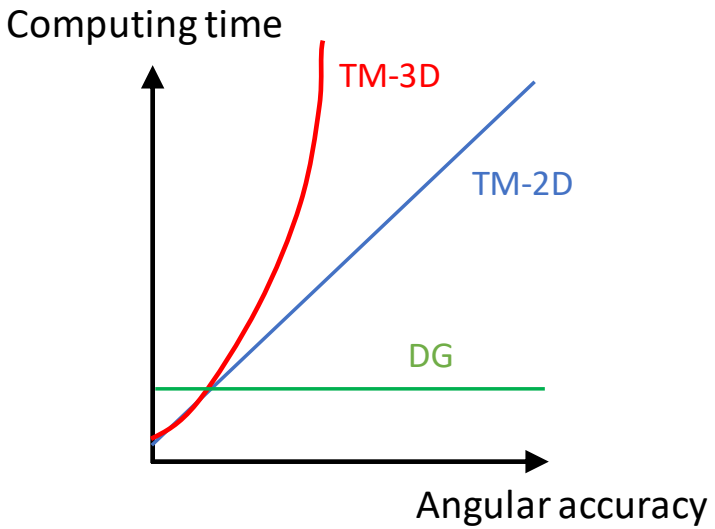
Membrane detection: Template Matching





Membrane detection: Differential Geometry



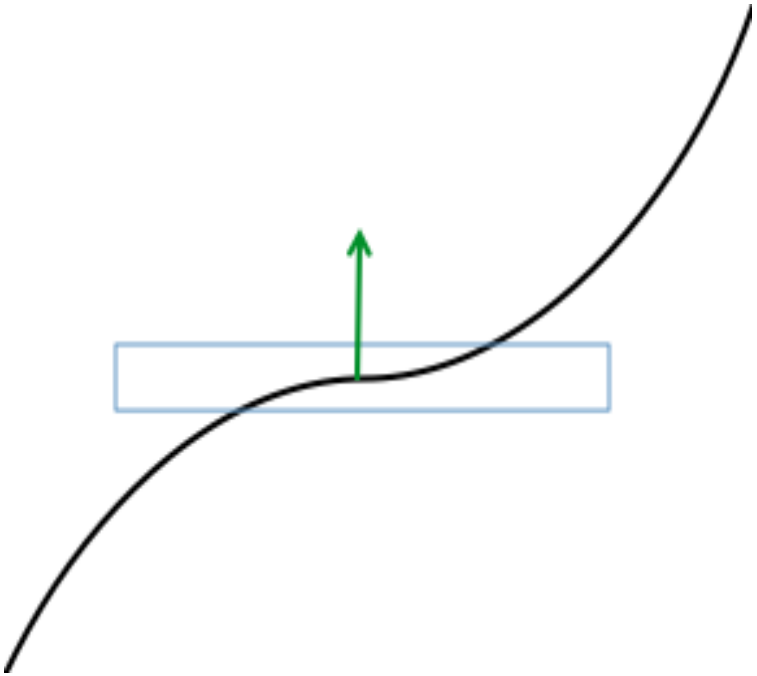


Martinez-Sanchez et al (2011) J. Struct. Biol.

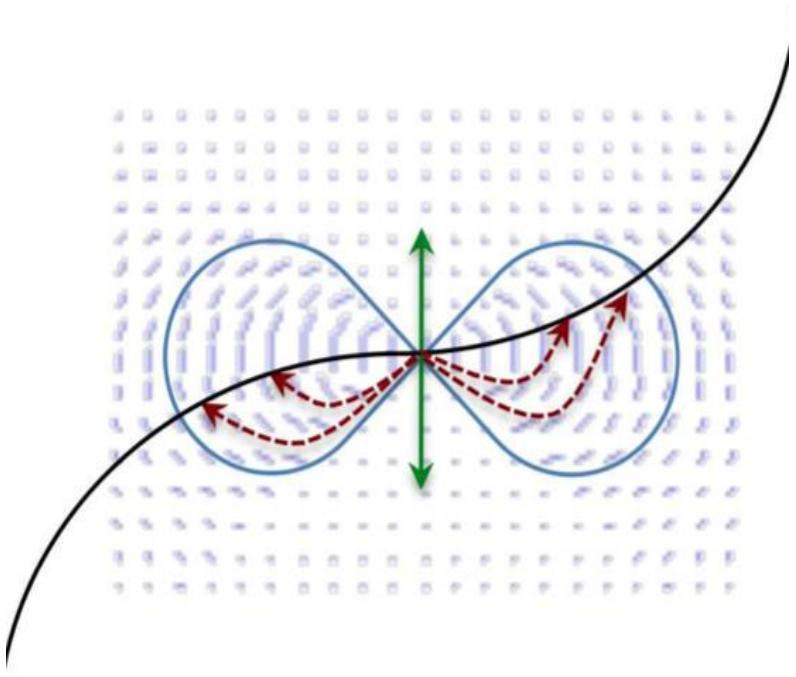
Moreno et al. (2022) J. Supercomput

Membrane detection: robustness by TV

TEMPLATE MATCHING



TENSOR VOTING

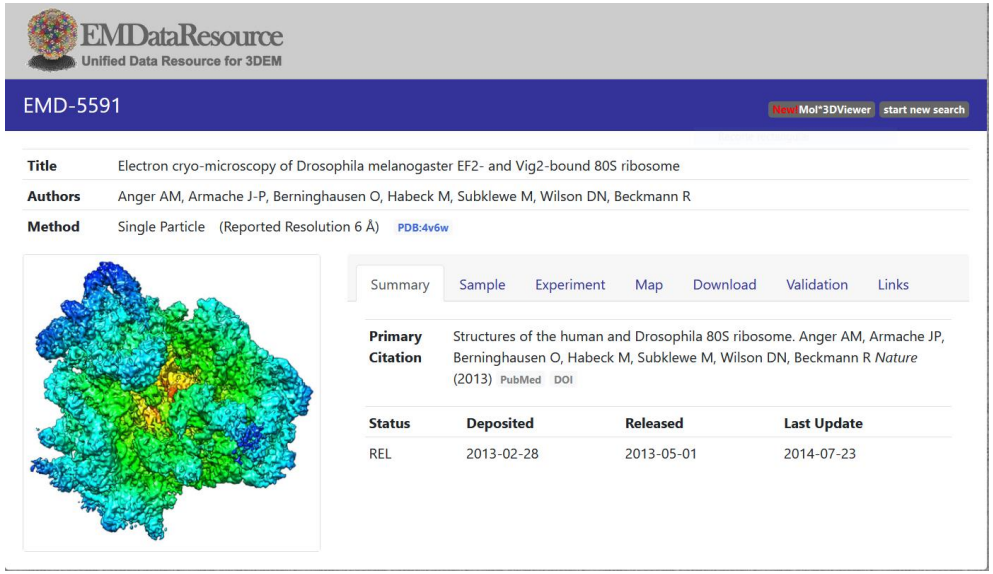


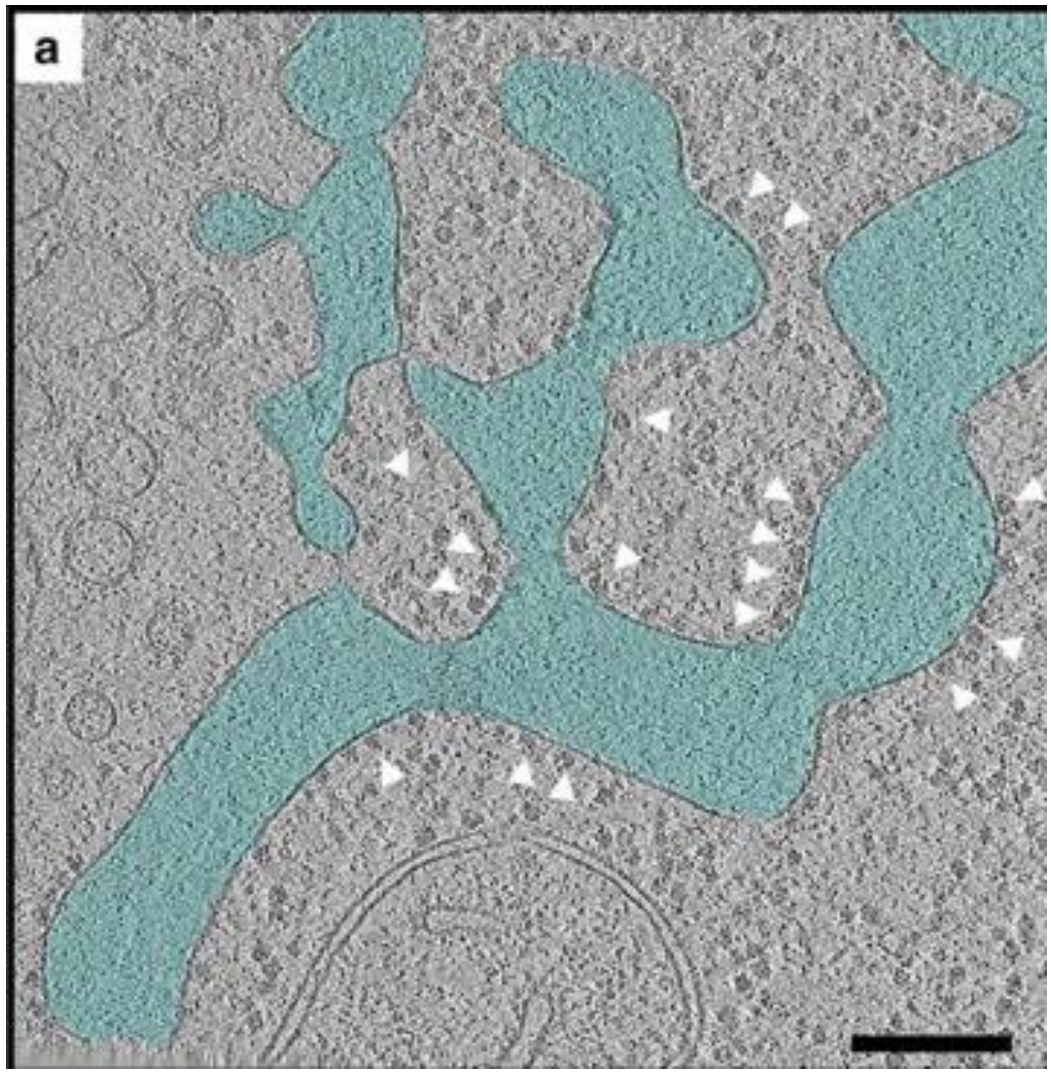
Martinez-Sanchez (2014) J. Struct. Biol.

Template-matching limitations

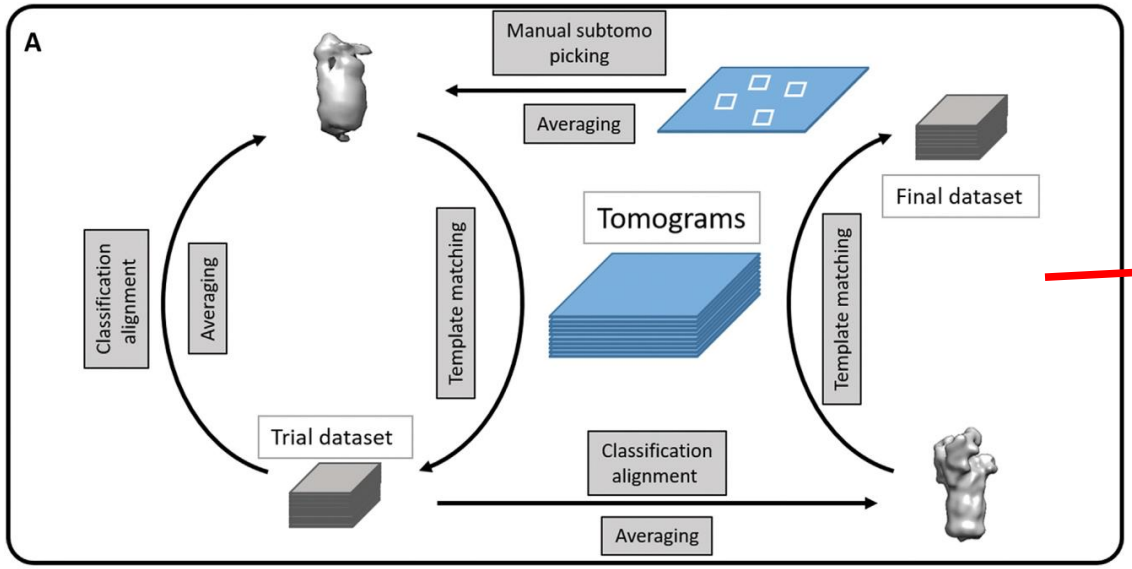
- Requires an initial model
- Limited performance: ribosomes or proteasomes on clean environments

Pfeffer, S. et al (2017). *Nature Comms*

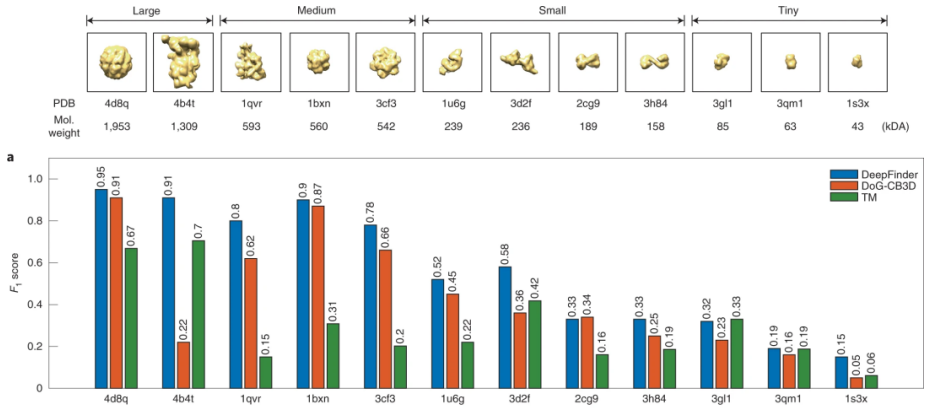


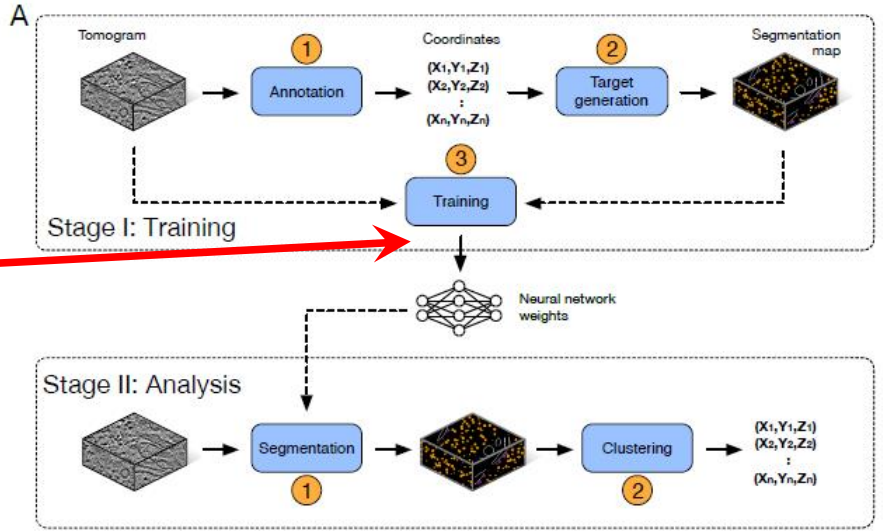


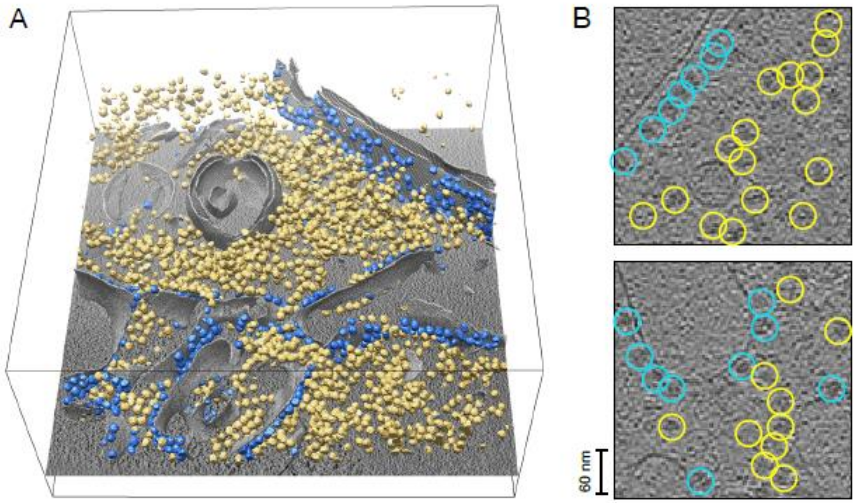
Deep Learning: no ground truth for experimental data in Cryo-ET



Guo et al. (2018). *Cell* 172(4):696-705



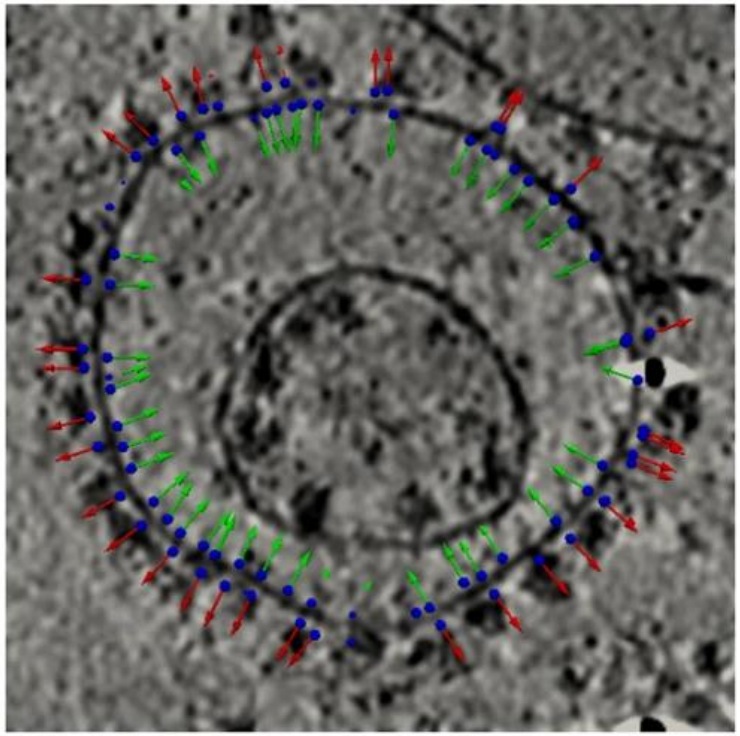




DeepFinder: Moebel et al. (2021) *Nature Methods* 18:1386-1394
1st ranked in SHREC'19 challenge

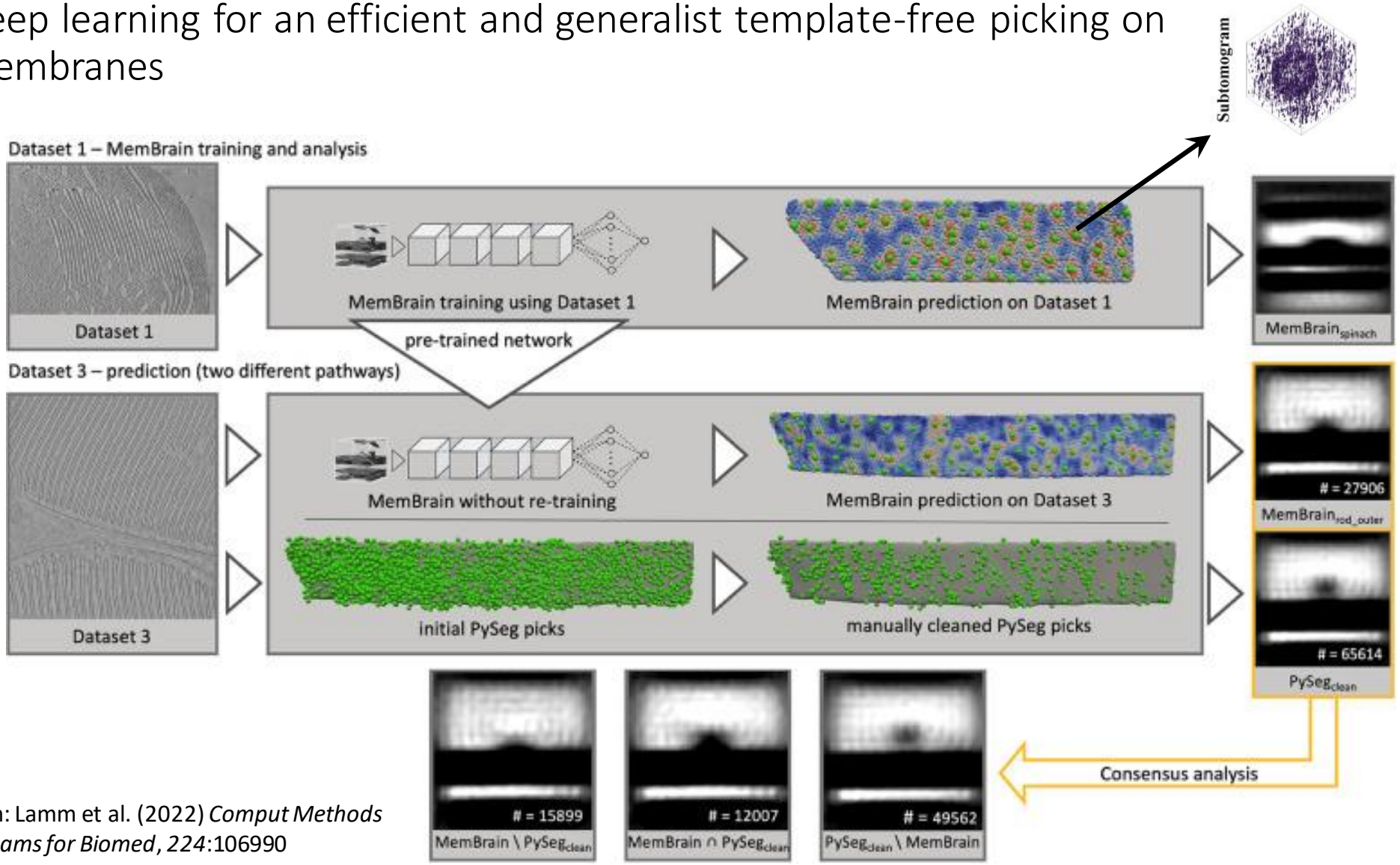
Template-free paradigm

- Membrane-bound proteins sparsely distributed
- Heterogenous set of complexes



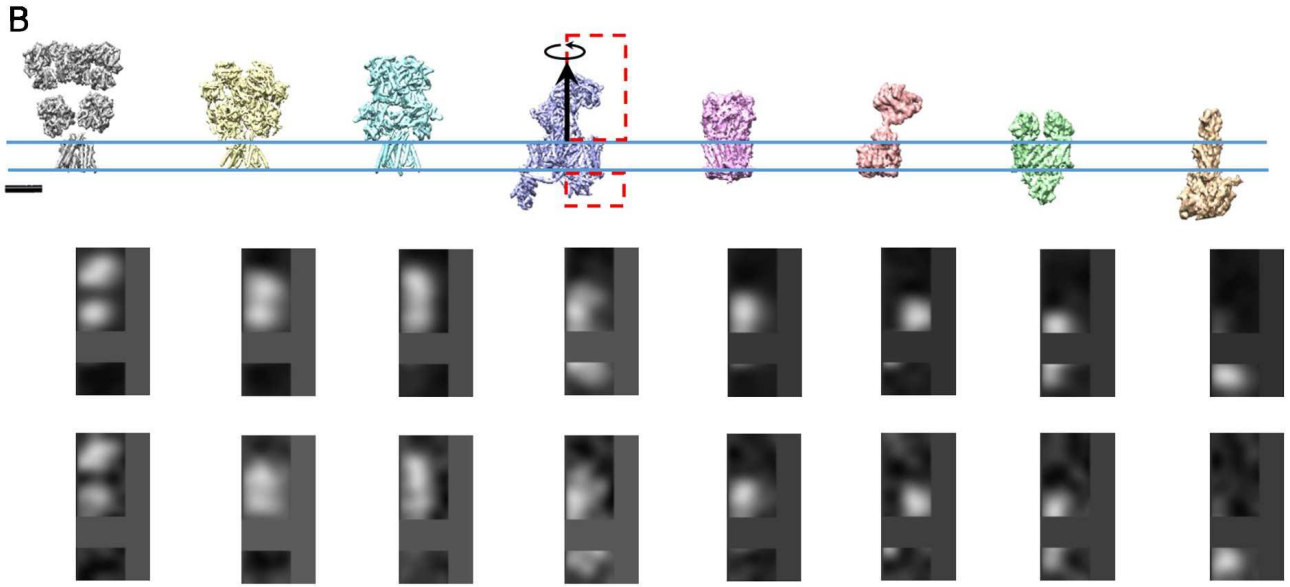
Martinez-Sanchez et al. (2020) Nature Methods 17:209–216

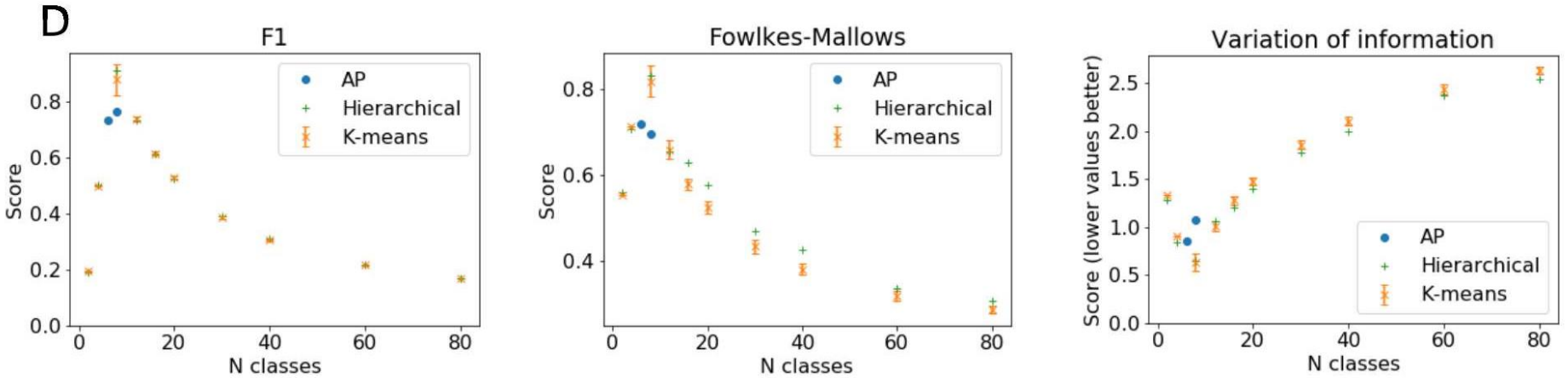
Deep learning for an efficient and generalist template-free picking on membranes



Membrain: Lamm et al. (2022) *Comput Methods and Programs for Biomed*, *224*:106990

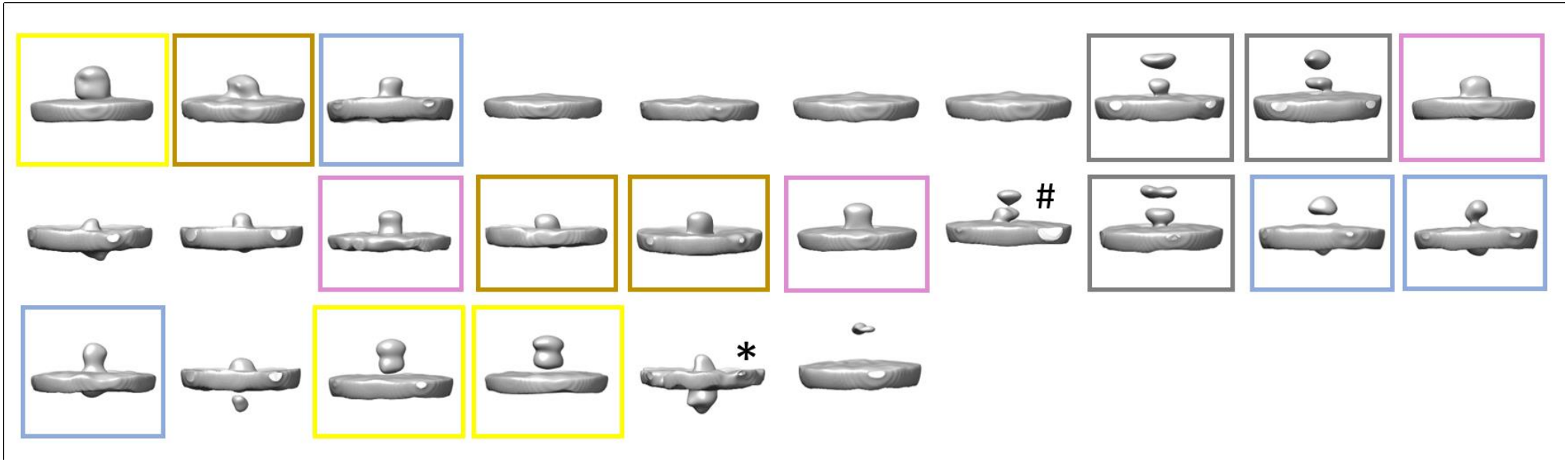
Unsupervised classification for membrane aligned particles



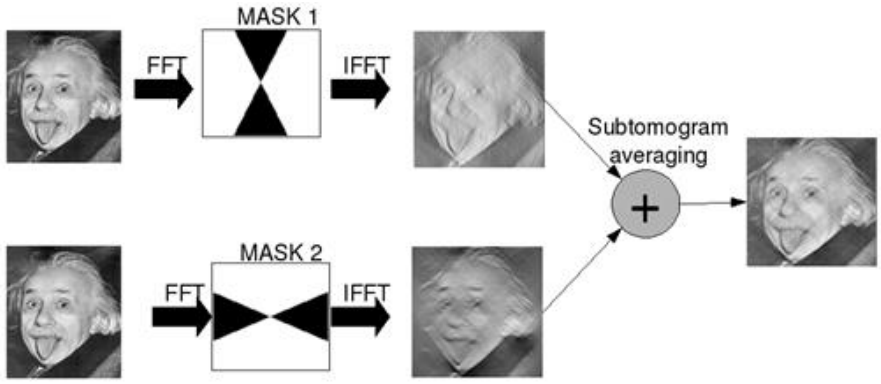


Direct 3D reconstruction

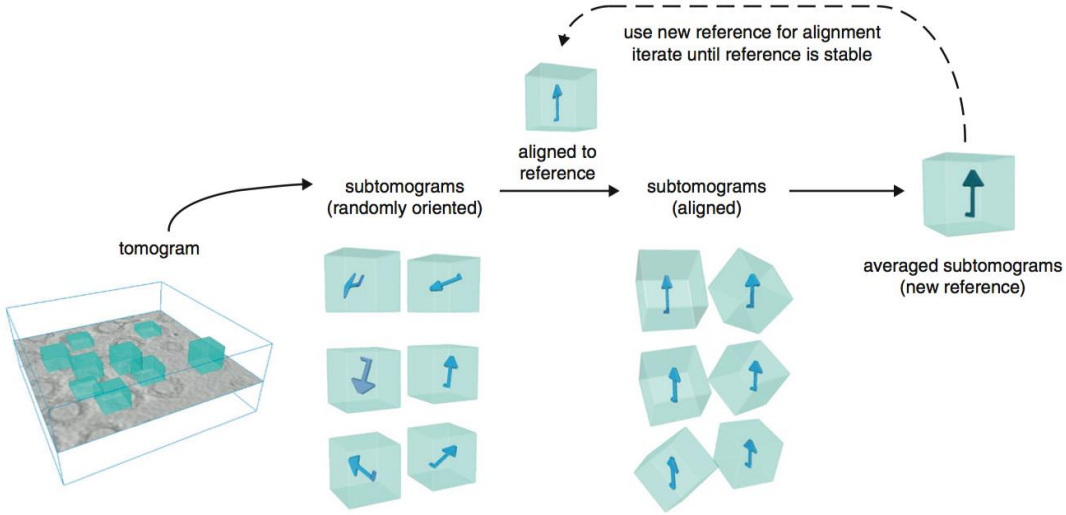
Wan & Briggs (2016) Methods Ezymol



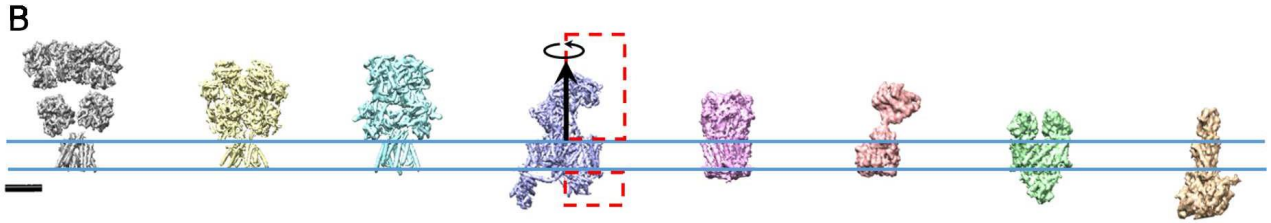
Subtomogram averaging



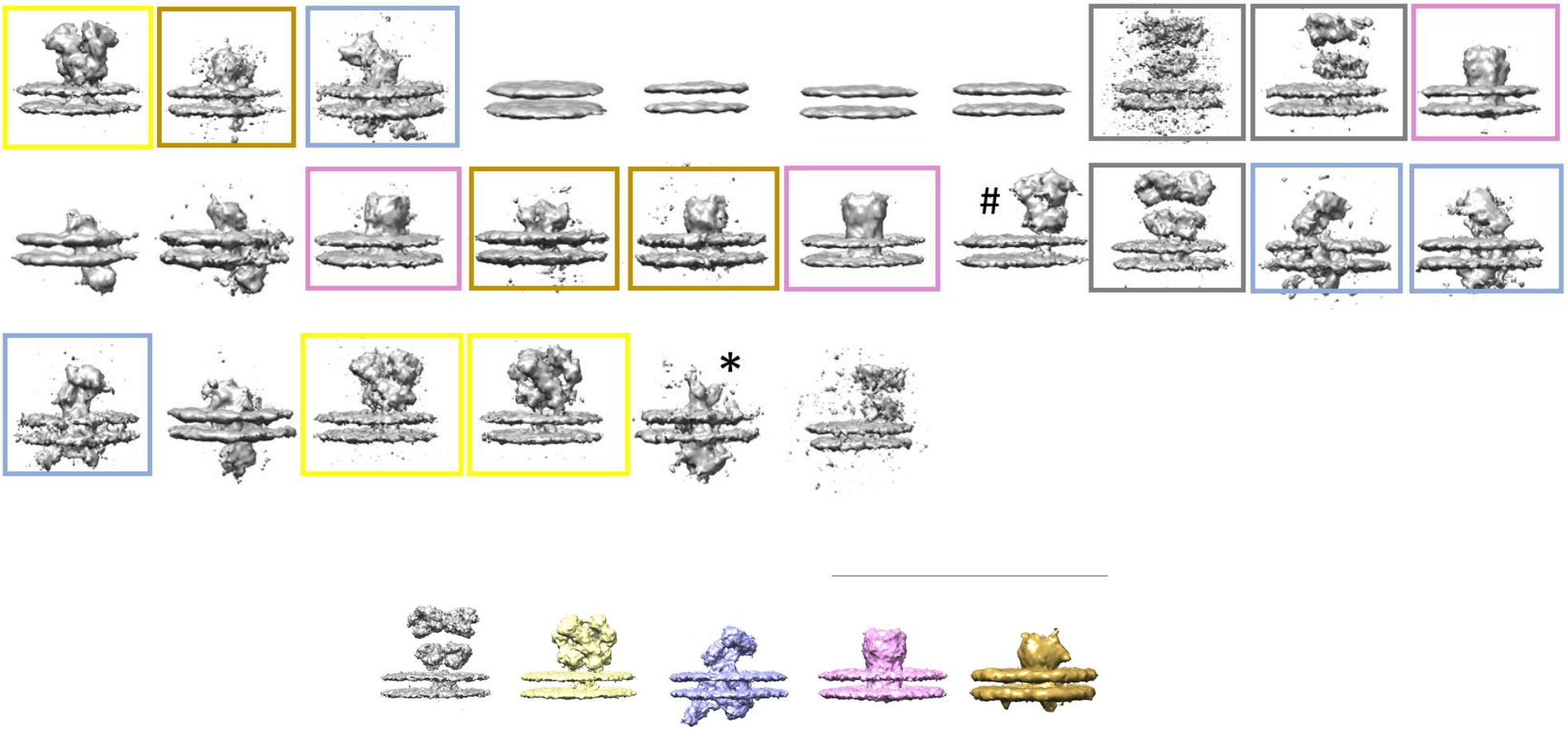
Wan & Briggs (2019) J. Struct. Biol.



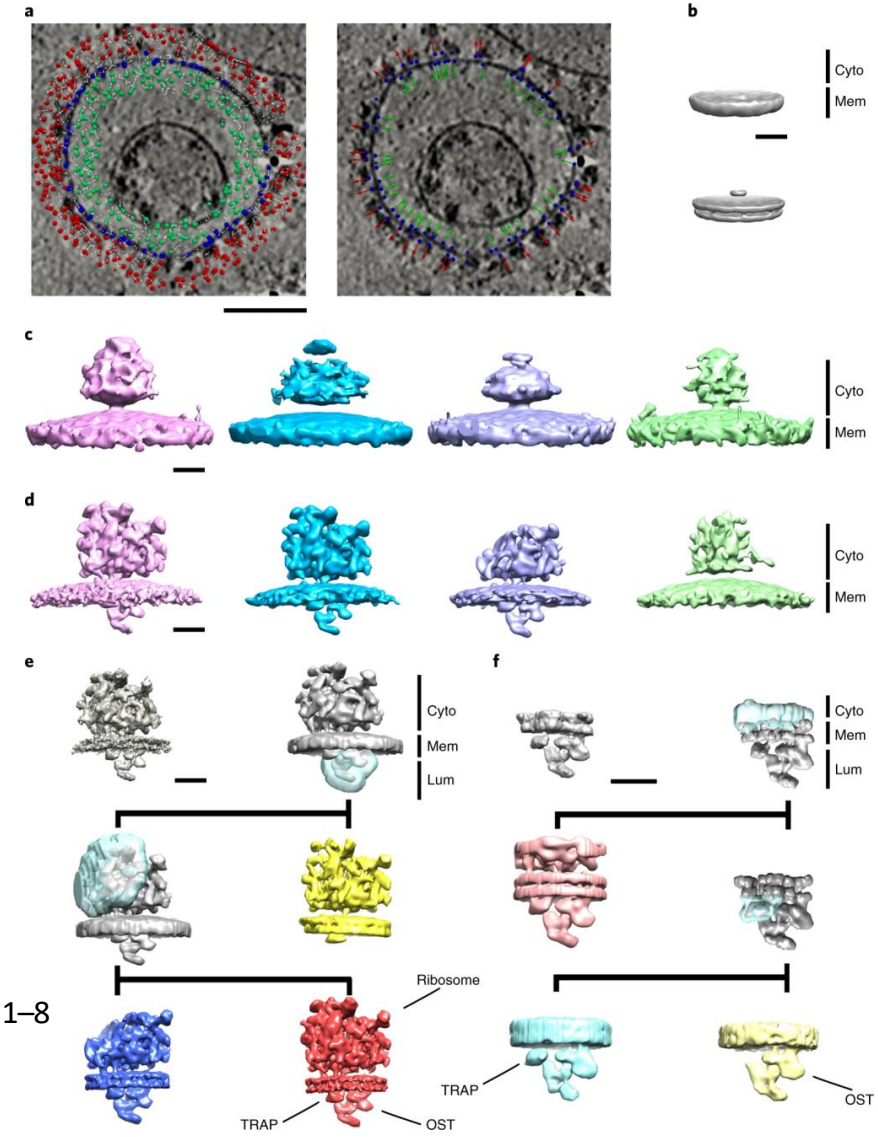
Martinez-Sanchez et al. (2020) *Nature Methods* 17:209–216



3D reconstruction with RELION



Results: native ER microsomes

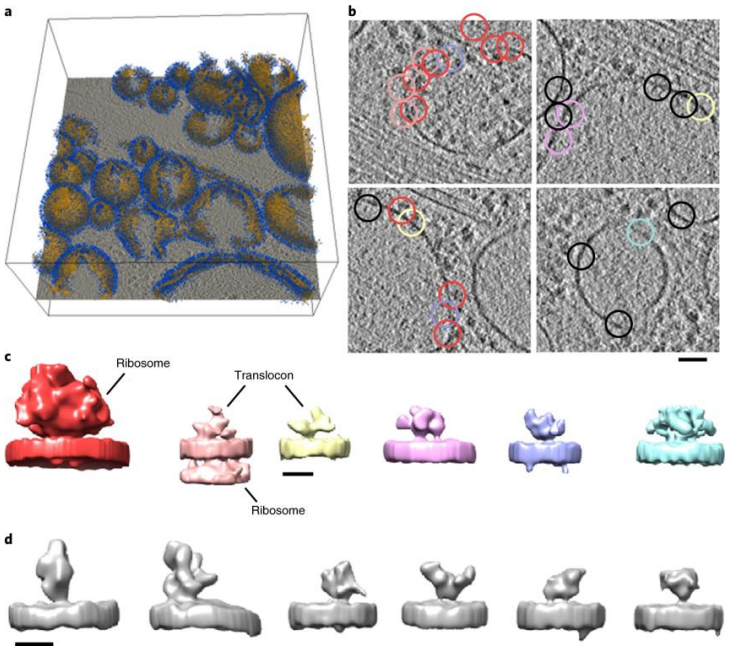


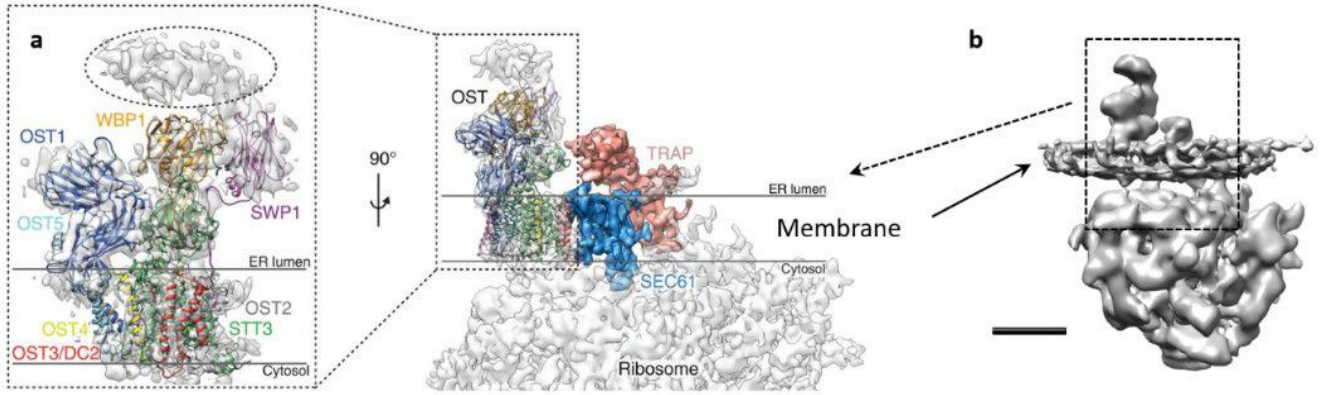
Pfeffer et al. (2014) *Nature Comms* 5(1):1–8

Martinez-Sanchez et al. (2020) *Nature Methods* 17:209–216

Massive data for nanometric resolution *in situ*

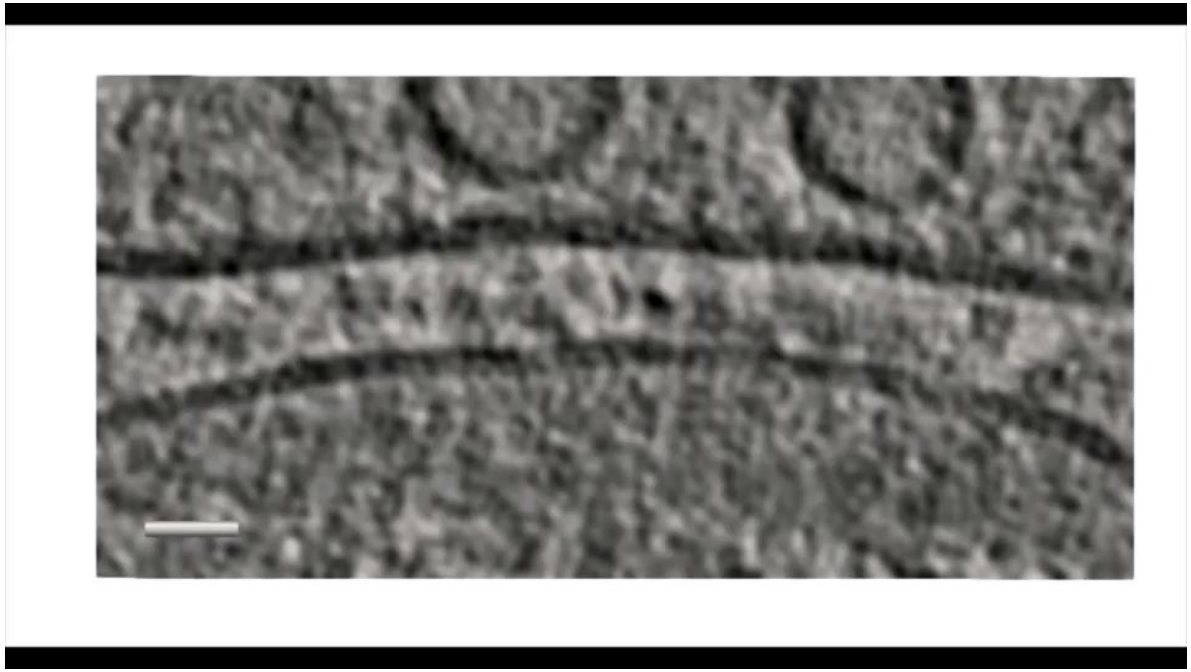
Martinez-Sanchez et al. (2020) *Nature Methods* 17:209–216

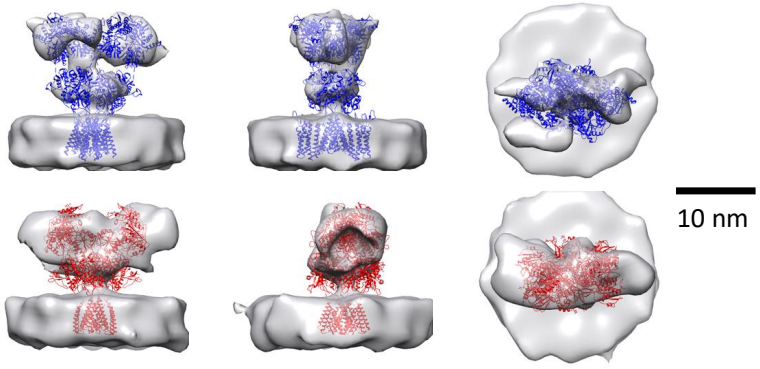


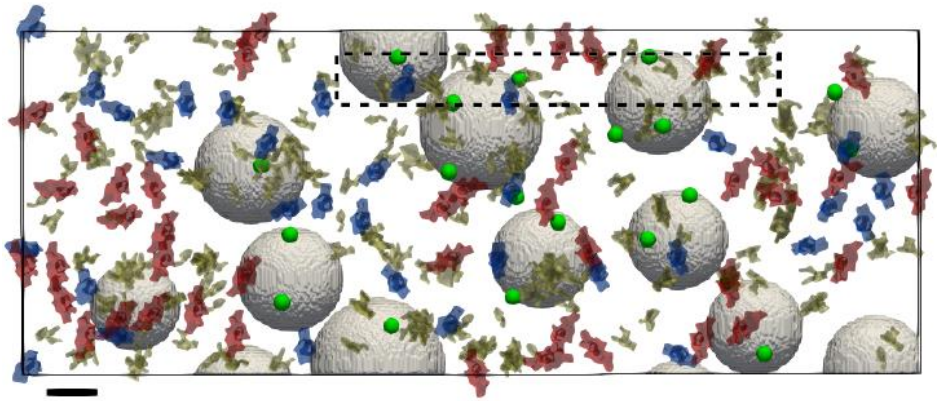


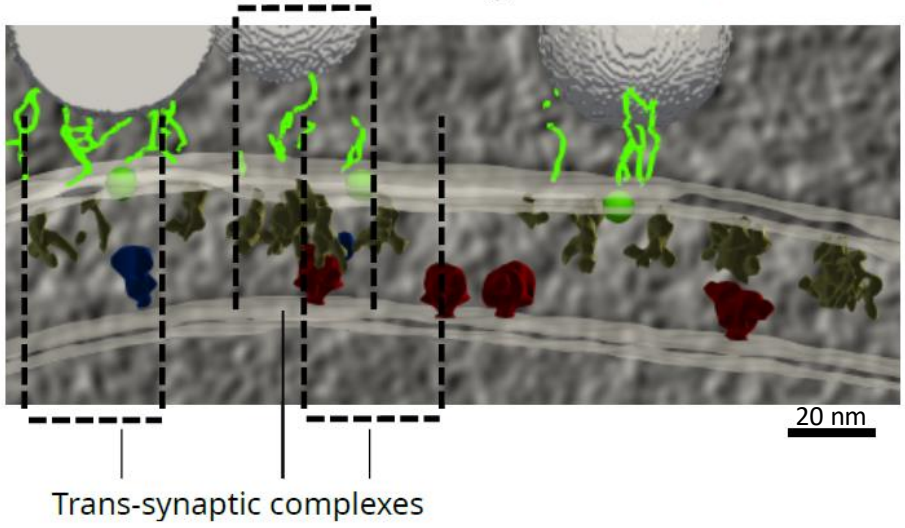
Organization of excitatory synapses

Martinez-Sanchez et al (2021) Science Adv. 7(10):eabe6204.

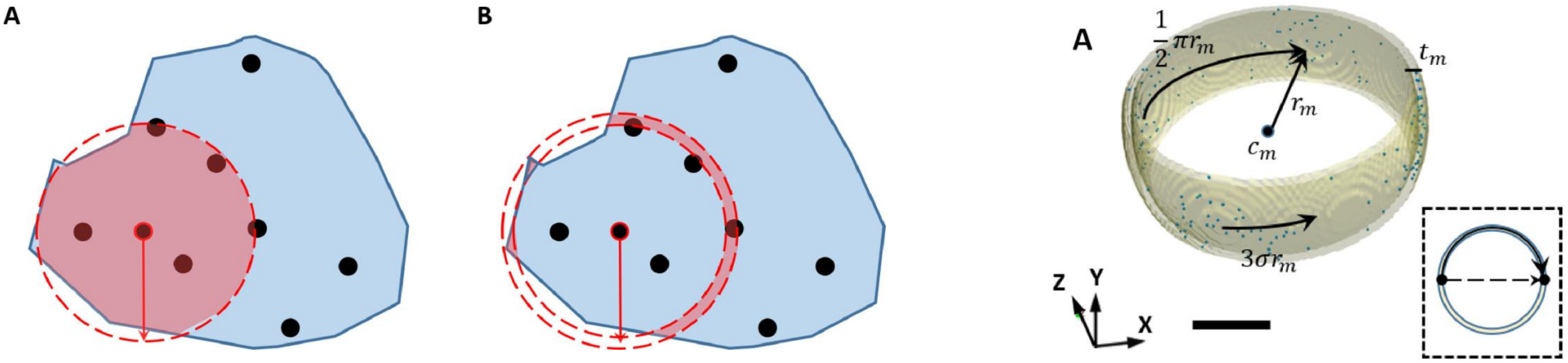




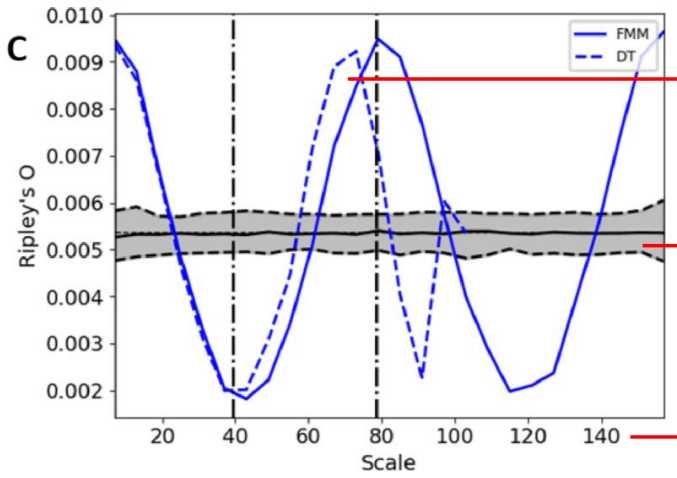




Statistical Spatial Analysis in Cryo-ET



Martinez-Sanchez et al (2022) Comput Meth and Programs in Biomed 218:106693



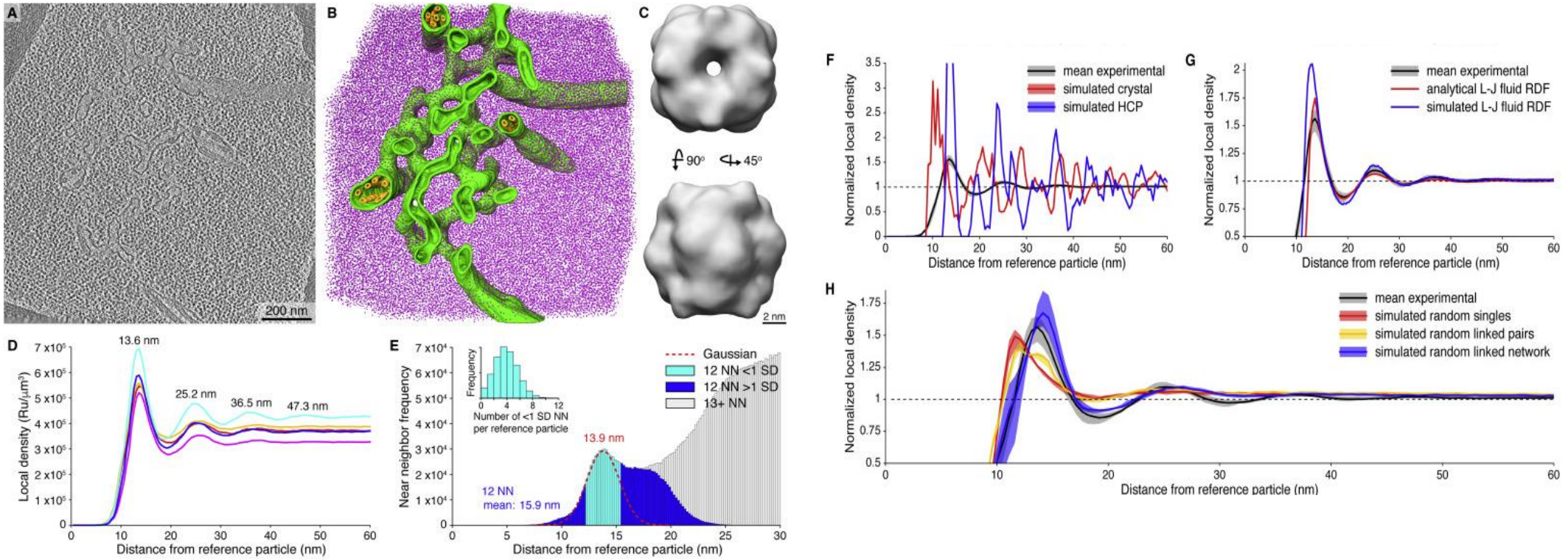
Geodesic distance metric is required (specially for membranes)

Synthetic models for null-model: set a reference, assign a statistical confidence to a hypothesis

2nd order analysis: organization depends on scales, compare tomograms with different global densities

Results: Actin waves and liquid-like Rubisco in pyrenoids

Rosenzweig et al. (2017) *Cell* 171(1):148-162



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