

# Deep Learning for Reconstructing in Situ Structural Landscapes From Cryo-Electron Tomography

Prof. Ellen D Zhong<sup>1</sup>

<sup>1</sup>*Princeton University*

*zhonge@princeton.edu*

Advances in cryo-electron tomography (cryo-ET) have produced new opportunities to visualize the structures of dynamic macromolecular complexes in their native contexts. However, image processing algorithms are currently a substantial bottleneck in cryo-ET and will only become more so as high throughput methods for sample preparation and imaging are developed. New deep learning methods have shown to be powerful tools for modeling heterogeneity in single particle cryo-EM datasets, and we hypothesize that these methods will be critical to processing large and complex data from cryo-ET to resolve structural states for in situ structural biology. Here, we describe the design choices and modifications to cryoDRGN, a state-of-the-art machine learning system for 3D reconstruction, to enable heterogeneous sub-tomogram averaging. We tackle high-resolution reconstruction in the presence of crowded cellular environments and recover dynamic states of biomolecular machinery within the cellular milieu. We benchmark on several published datasets and showcase the method in resolving the structural landscape of the eukaryotic ribosome from a dataset containing 120,000 particles.