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CryoDRGN2: Ab Initio Neural Reconstruction of Dynamic Protein Complexes

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Protein structure determination from cryo-EM data requires reconstructing a 3D volume (or distribution of volumes) from many noisy and randomly oriented 2D projection images. While the standard homogeneous reconstruction task aims to recover a single static structure, recently-proposed neural and non-neural methods can reconstruct distributions of structures, thereby enabling the study of protein complexes that possess intrinsic structural or conformational heterogeneity. These *heterogeneous reconstruction* methods, however, require fixed image poses, which are typically estimated from an upstream homogeneous reconstruction and are not guaranteed to be accurate under highly heterogeneous conditions.

In this work, originally presented at the 2021 International Conference on Computer Vision [1], we describe cryoDRGN2, an *ab initio* reconstruction algorithm that can jointly estimate image poses and learn a neural model of a distribution of 3D structures on real heterogeneous cryo-EM data. To achieve this, we adapt search algorithms from the traditional cryo-EM literature, and describe the optimizations and design choices required to make such a search procedure computationally tractable in the neural model setting. We show that cryoDRGN2 is robust to the high noise levels of real cryo-EM images, trains faster than earlier neural methods, and achieves state-of-the-art performance on real cryo-EM datasets.

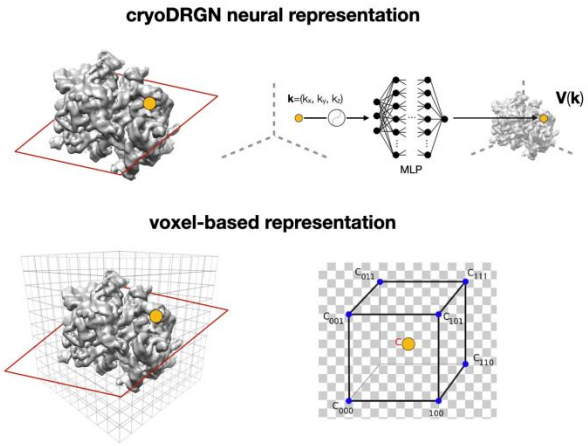

Figure 1. Evaluating a given image pixel under cryoDRGN's neural model involves a full pass through a multilayer perceptron (MLP), which is much more computationally expensive than evaluating traditional voxel-based representations.

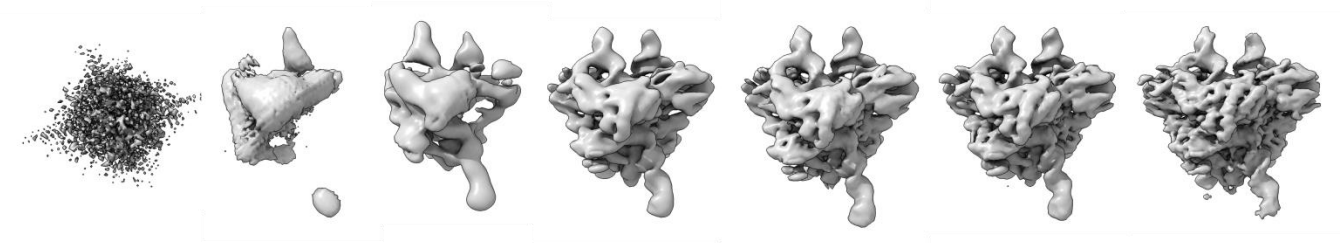

Figure 2. Training progression of cryoDRGN2 on the RAG1-RAG2 complex [EMPIAR-10049] [2].

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