

CryoDECO: Deconstructing Extreme Compositional and Conformational Heterogeneity in Cryo-EM via Foundation Model Priors

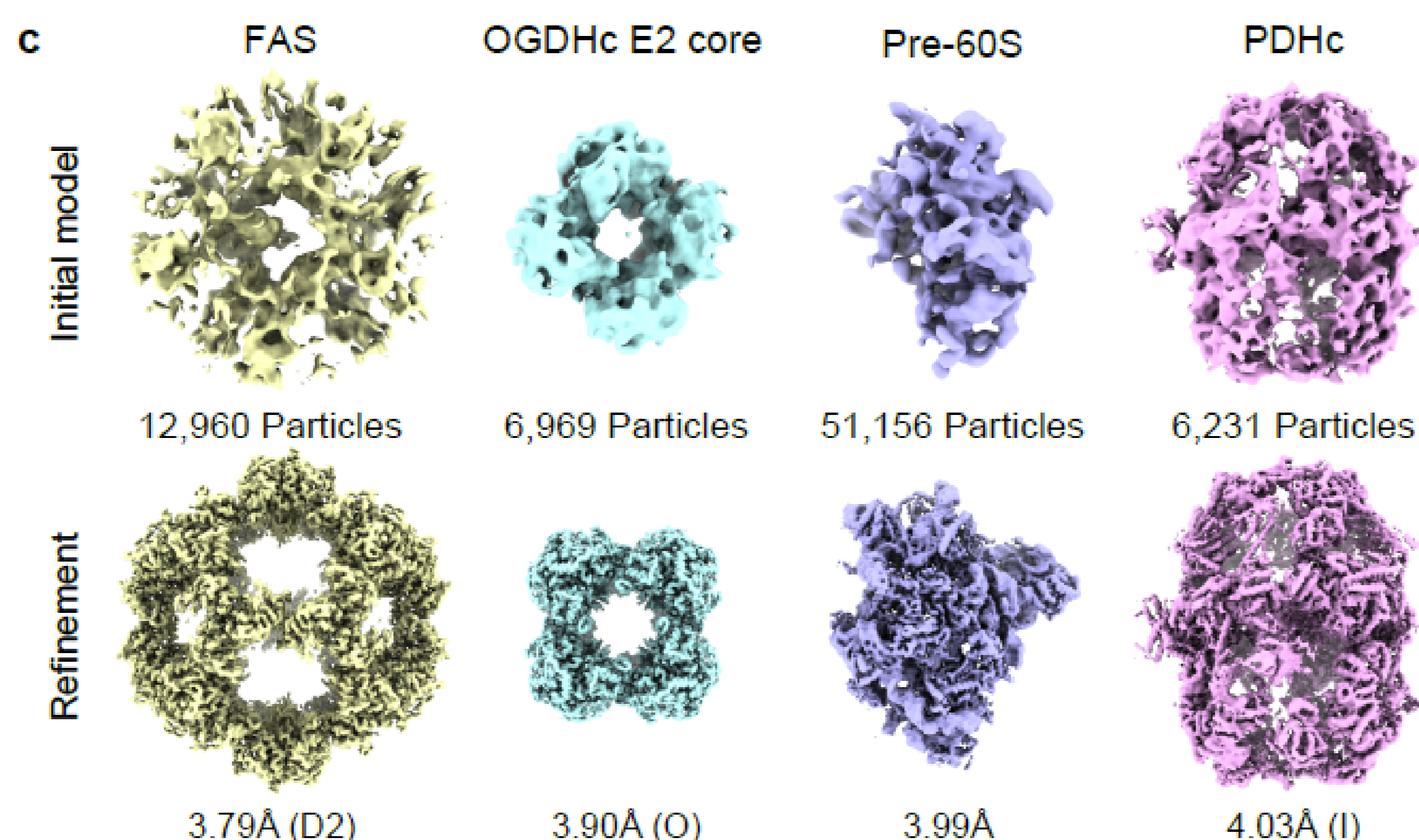
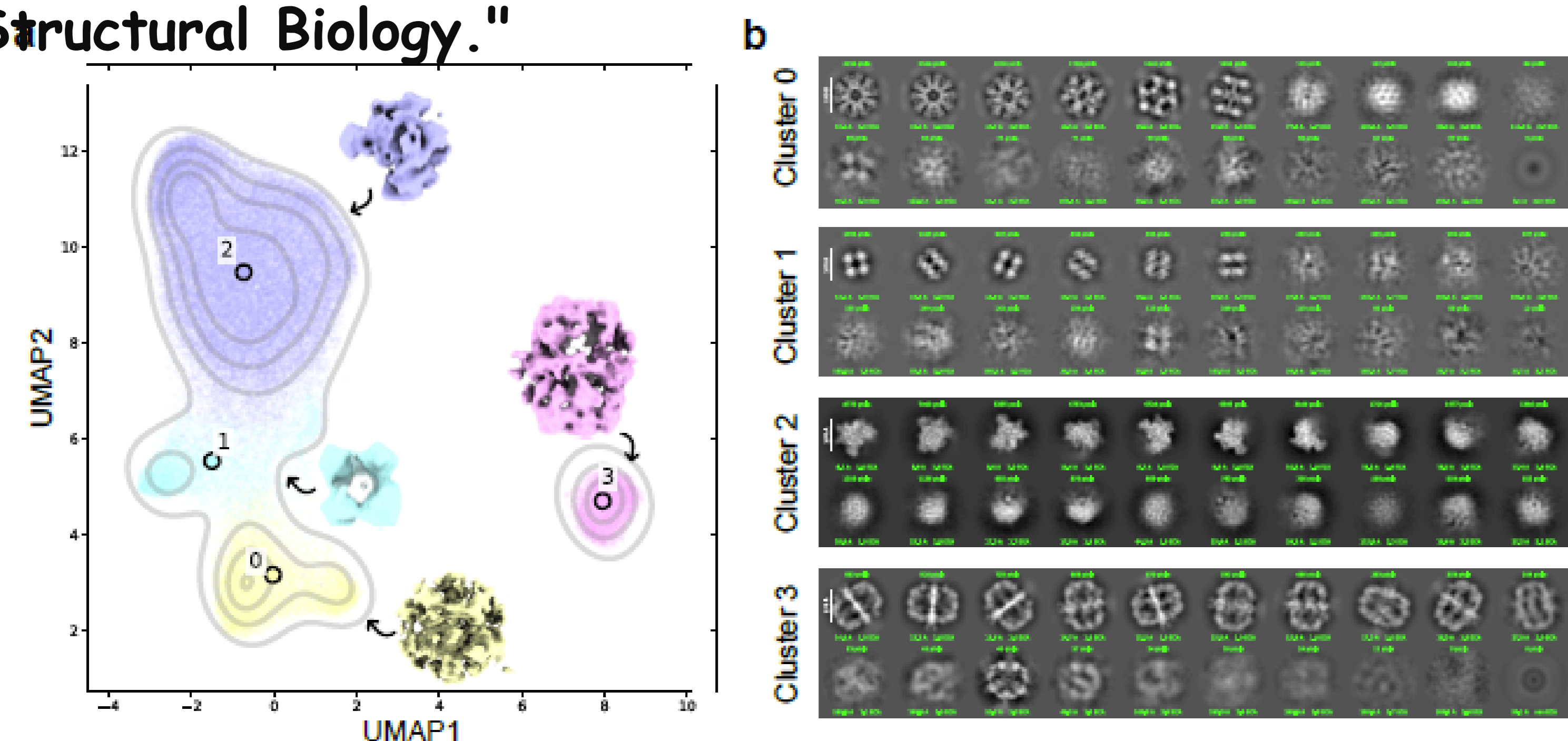
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Abstract

Resolving compositional and conformational heterogeneity remains the fundamental bottleneck in cryo-electron microscopy (cryo-EM). **This challenge involves a circular dependency: accurate particle classification requires reliable 3D structural templates, yet template reconstruction demands high-fidelity classification.** Current *ab initio* methods typically approach this as a joint optimization problem from a *tabula rasa* initialization, which frequently leads to optimization collapse when samples exhibit extreme complexity. **Here, we present CryoDECO, an autoencoder framework that breaks this deadlock.** By injecting robust representation priors from pretrained cryo-EM foundation models, CryoDECO projects particle images onto a semantically structured latent manifold—effectively disentangling classification from 3D reconstruction before optimization even begins.

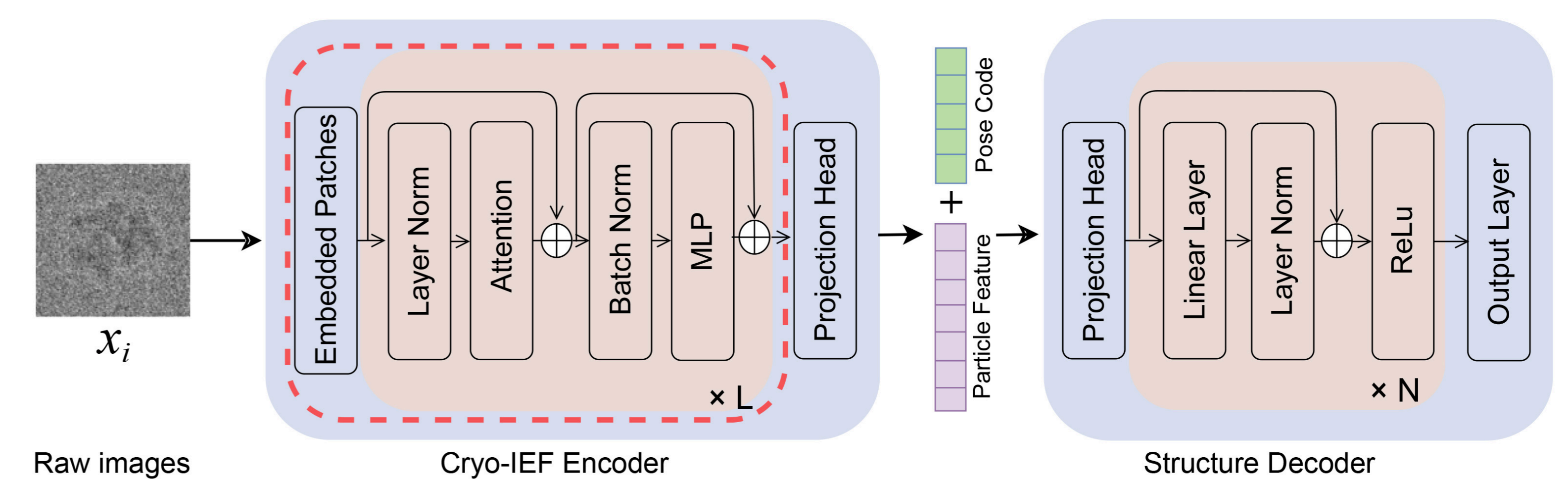
Enabling "Panoramic Structural Biology" in Native Extracts

Applied to an unpurified, native *Chaetomium thermophilum* lysate fraction, CryoDECO successfully deconvolved the crude mixture into four discrete macromolecular clusters, which demonstrates the viability of high-throughput "Panoramic Structural Biology."

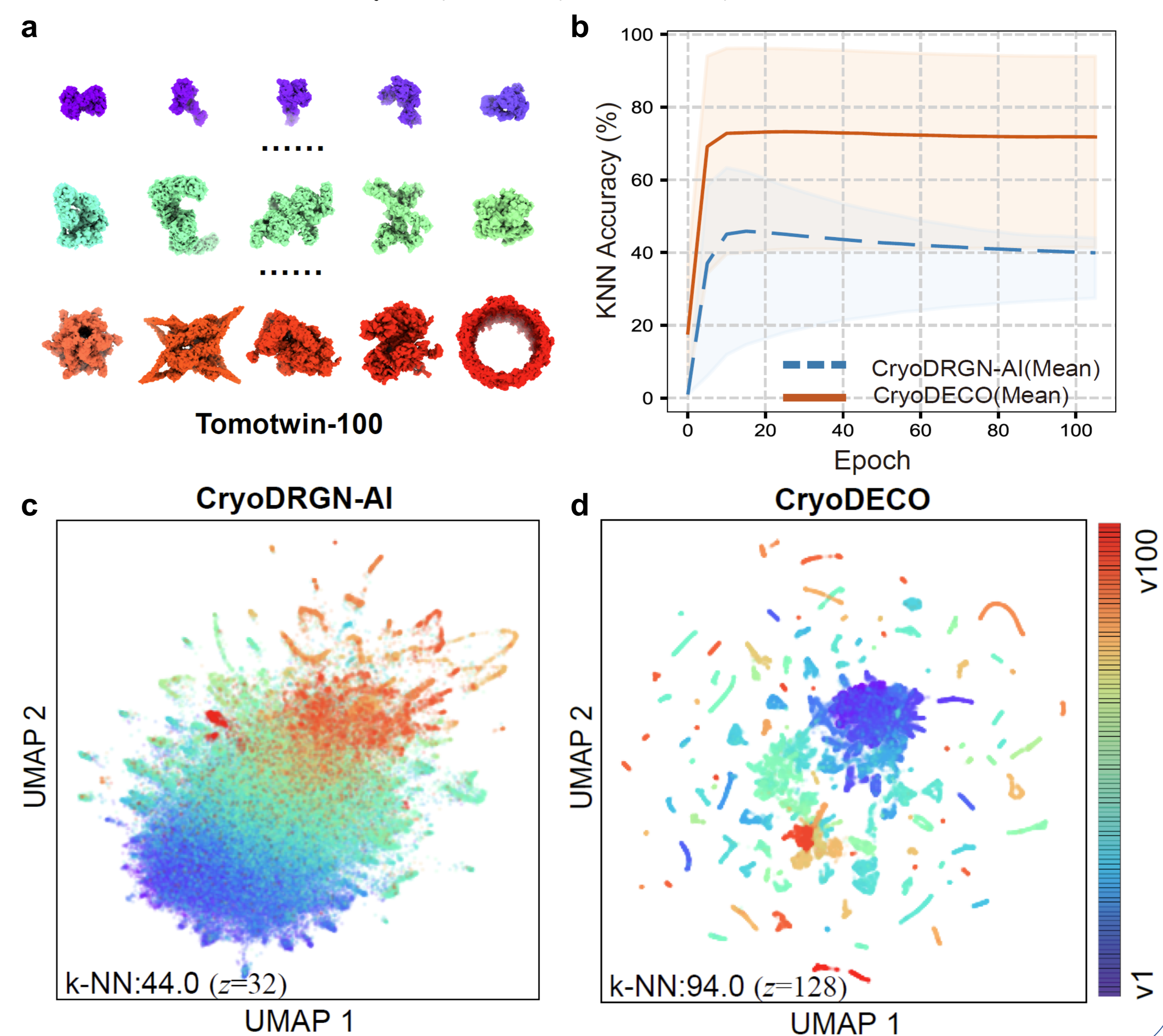


CryoDECO: Foundation Model Priors Break the Optimization Deadlock

By leveraging representation priors from a foundation model pretrained on ~134 million cryo-EM particles (cryo-IEF), CryoDECO injects a strong inductive bias to bypass the "blind" search phase.



This prior-informed strategy robustly resolves extreme compositional heterogeneity, successfully classifying 100 distinct structures from a simulated mixture.



Mapping Conformational Dynamics

Traversing the low-dimensional latent space of CryoDECO reveals smooth, biologically accurate transitions. For the tri-snRNP spliceosome complex, the model captured a continuous counter-clockwise rotation of the head region.

