

Integrative Structural Analysis of Human Nuclear Pore Complex

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Nuclear pore complexes (NPCs) mediate nucleocytoplasmic transport. Their intricate 120 MDa architecture remains incompletely understood. Here, we report a 70 MDa model of the human NPC scaffold with explicit membrane and in multiple conformational states. We combined AI-based structure prediction with in situ and in cellulo cryo-electron tomography and integrative modeling. We show that linker Nups spatially organize the scaffold within and across subcomplexes to establish the higher-order structure. Microsecond-long molecular dynamics simulations suggest that the scaffold is not required to stabilize the inner and outer nuclear membrane fusion, but rather widens the central pore. Our work exemplifies how AI-based modeling can be integrated with in situ structural biology to understand subcellular architecture across spatial organization levels.