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NeuralPLexer3: Accurate Biomolecular Complex Structure Prediction with Flow Models

Iambic

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Paper NPBench

NeuralPLexer3 is a physics-inspired flow model that predicts full biomolecular complex structures—proteins, nucleic acids, ligands, ions and PTMs—with higher accuracy and better physical realism than prior methods, while running in seconds.

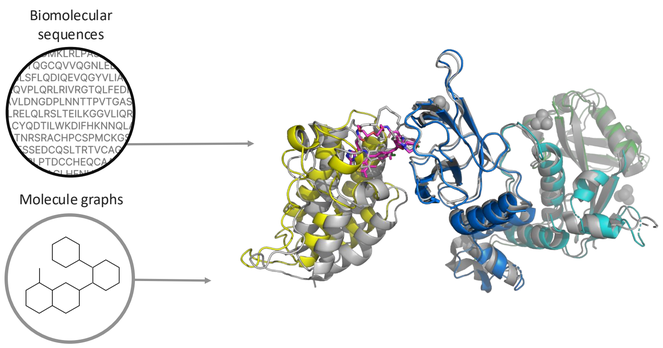
Motivation

Experimental structures are slow/expensive, but most drug discovery programs still depend on them.

AlphaFold2/3 revolutionized folding, but:

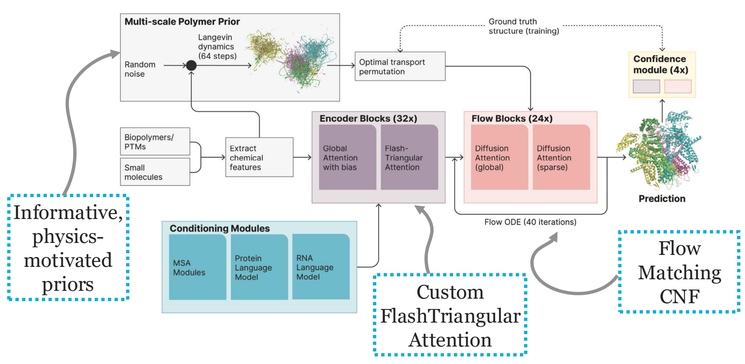
- can hallucinate unphysical ligands / geometries,
- are expensive to run at scale,
- and are not systematically evaluated on drug-discovery-relevant tasks.

Goal: accurate, physically valid, *fast* prediction of protein–ligand and other biomolecular complexes for real drug-discovery workflows.



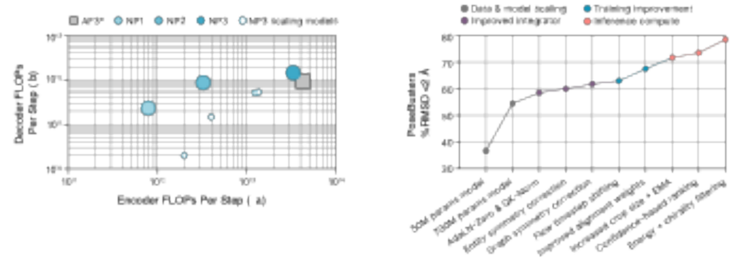
Model

NeuralPLexer3 is a conditional flow-matching model with a physics-informed polymer prior.

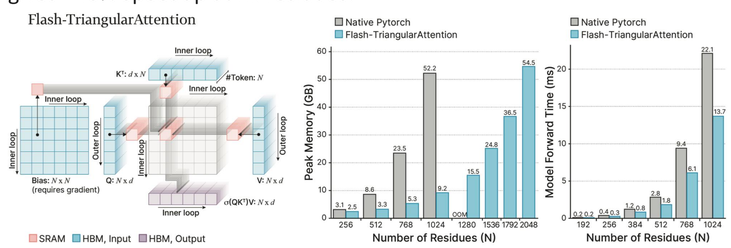


Training NeuralPLexer3

Compute optimal encoder-decoder scaling, and training and inference improvements led to NP3's high accuracy.

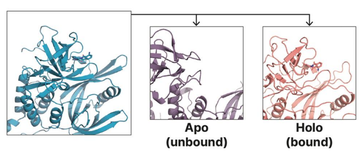


Our custom triangular attention kernel cuts peak memory by ~5× and gives ~40% speedup at 1k residues.

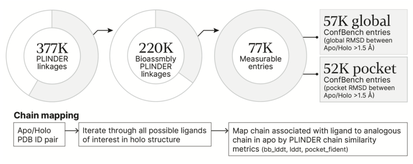


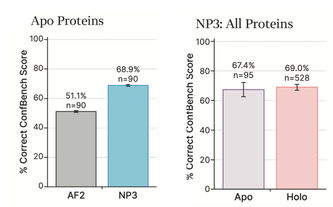
Results

ConfBench is a novel benchmark for ligand-induced conformational changes in structure prediction models. NeuralPLexer3 shows good ability to predict holo-like structures upon ligand binding.



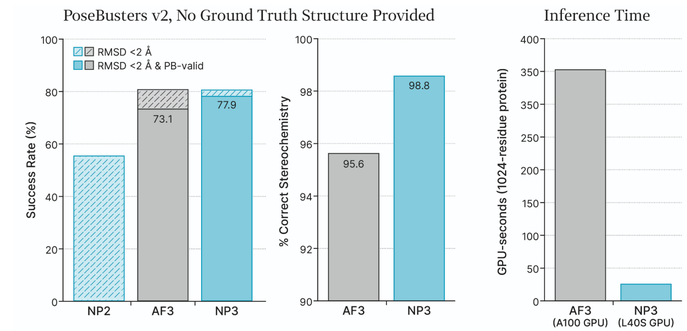
$$\text{Score}_{\text{ConfBench}} = \frac{\text{RMSD}_{\text{query_alt}} - \text{RMSD}_{\text{query_ref}}}{\sqrt{\left(\text{RMSD}^2_{\text{query_alt}} + \text{RMSD}^2_{\text{query_ref}} + \text{RMSD}^2_{\text{alt_ref}}\right) \times \frac{1}{2}}}$$



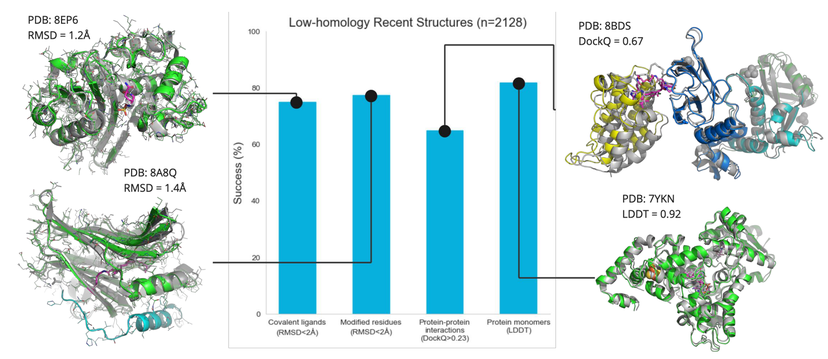
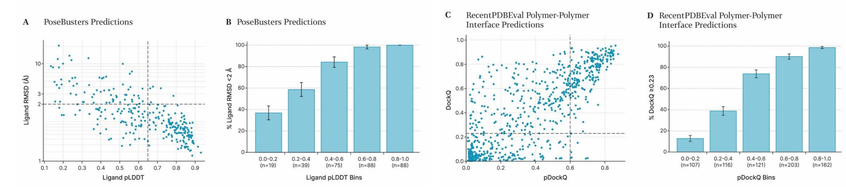


Results

PoseBusters is a benchmark for small-molecule structure-based drug design. NeuralPLexer3 gives more accurate structures, gives more rigorous stereochemistry, and is much faster than AlphaFold 3.



NeuralPLexer3 is accurate across diverse categories of biomolecular interactions. Test structures are low-homology, low-Tanimoto-similarity, recent PDB entries.



NeuralPLexer3 provides well callibraed confidence estimates for protein-ligand binding (ligand pLDDT) and protein-protein interfaces (pDockQ).