

Enzyme Design with RFdiffusionAA and LigandMPNN



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Rosetta Workshop July 2024

Enzyme Design

- Protein only versus Protein + Small Molecules

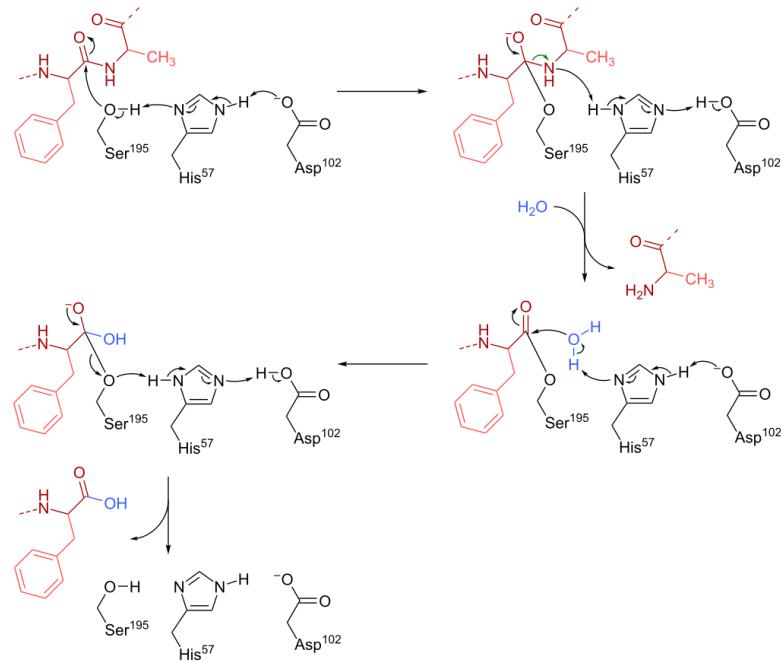
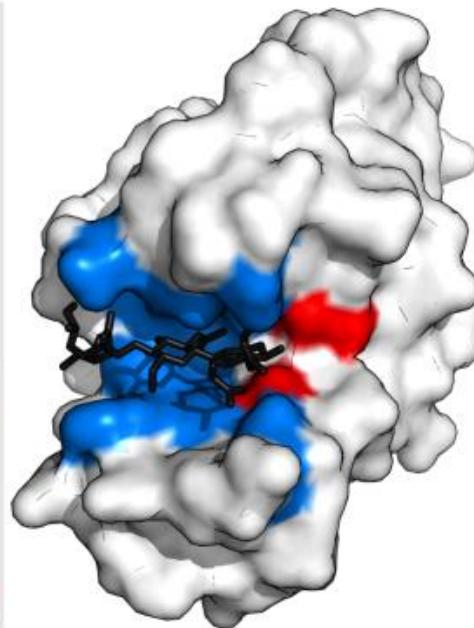
PROTEIN STRUCTURE

Scaffold to support and position active site

ACTIVE SITE

BINDING SITES
Bind and orient substrate(s)

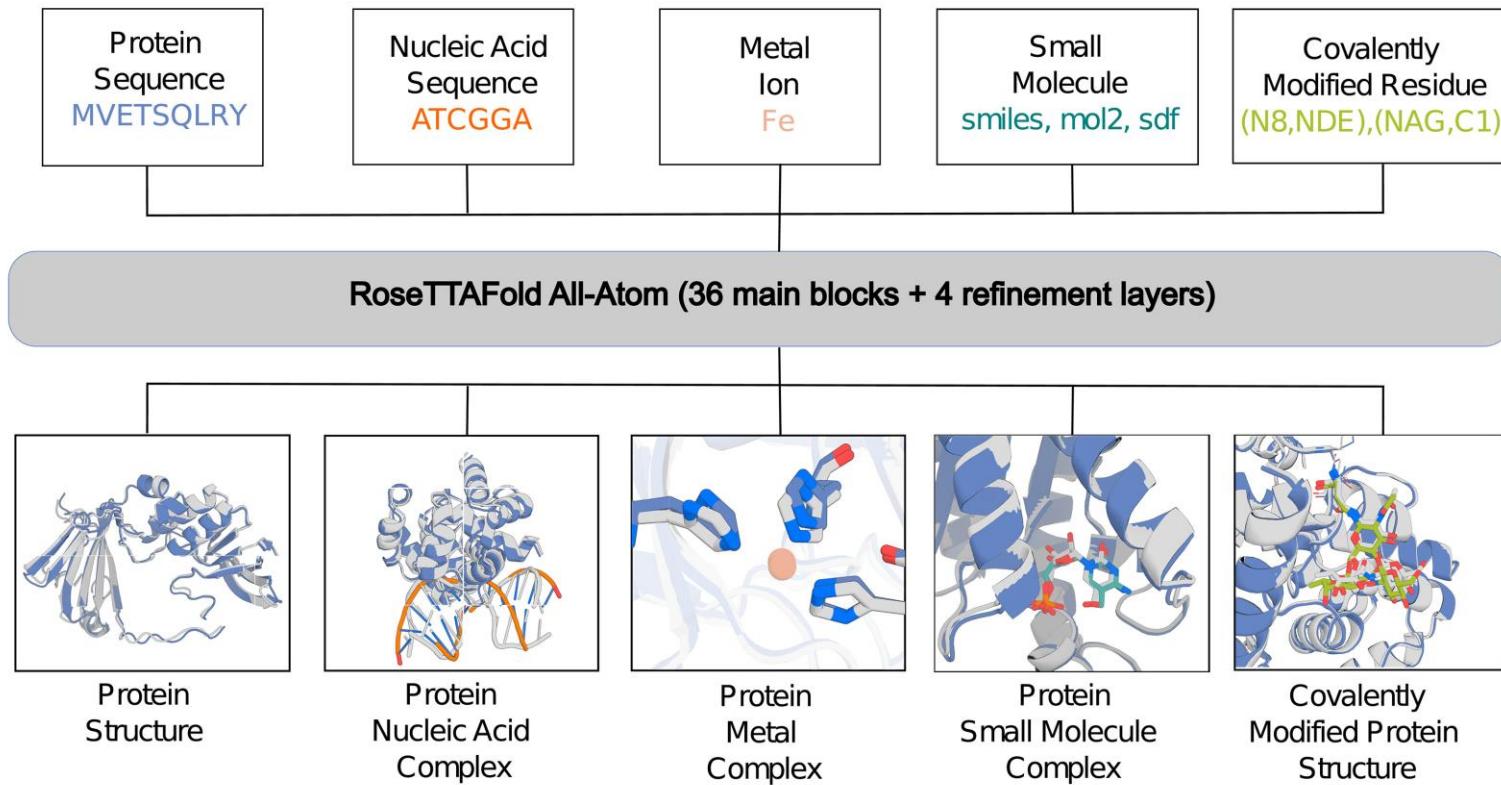
CATALYTIC SITE
Reduce chemical activation energy



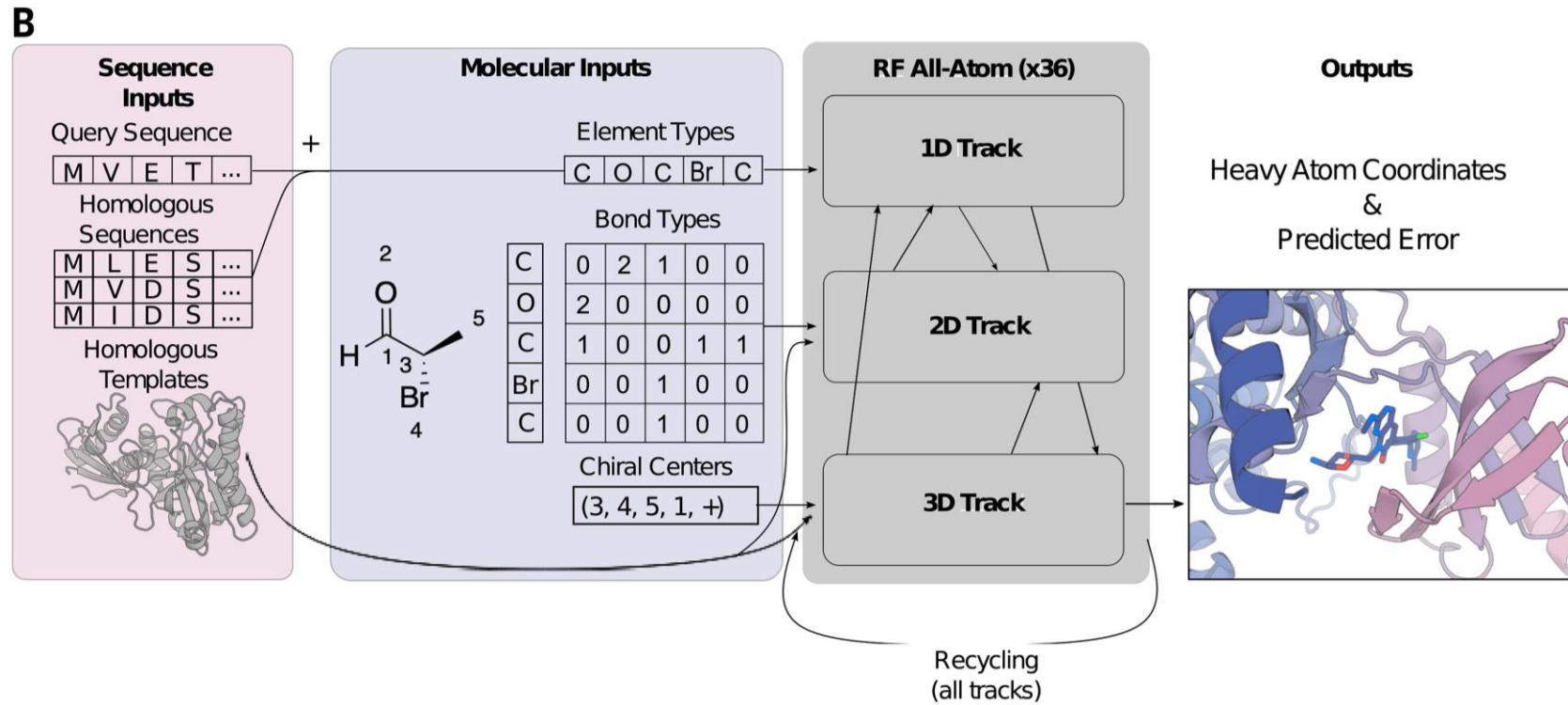
RoseTTAFold All Atom & AlphaFold 3

RoseTTAFold All Atom

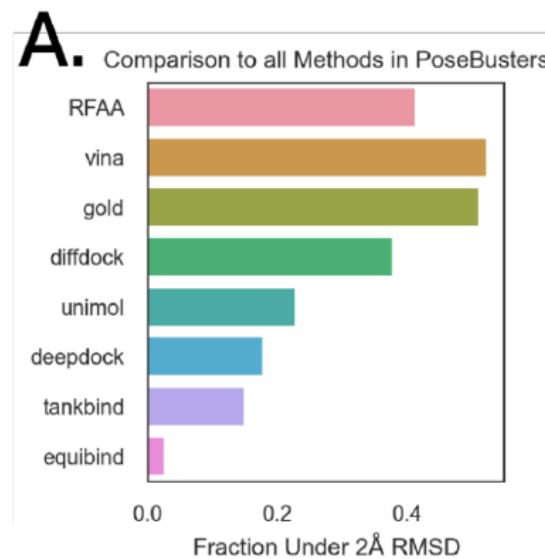
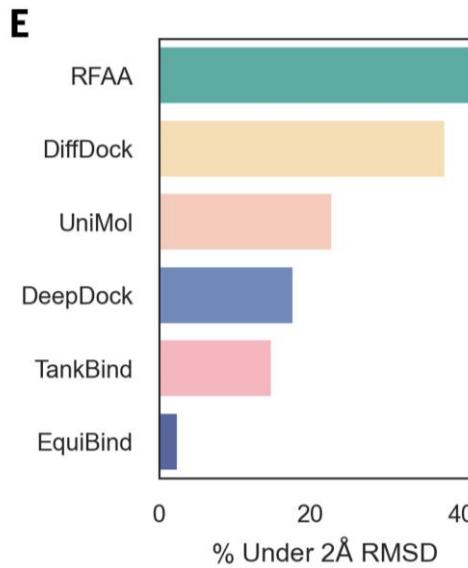
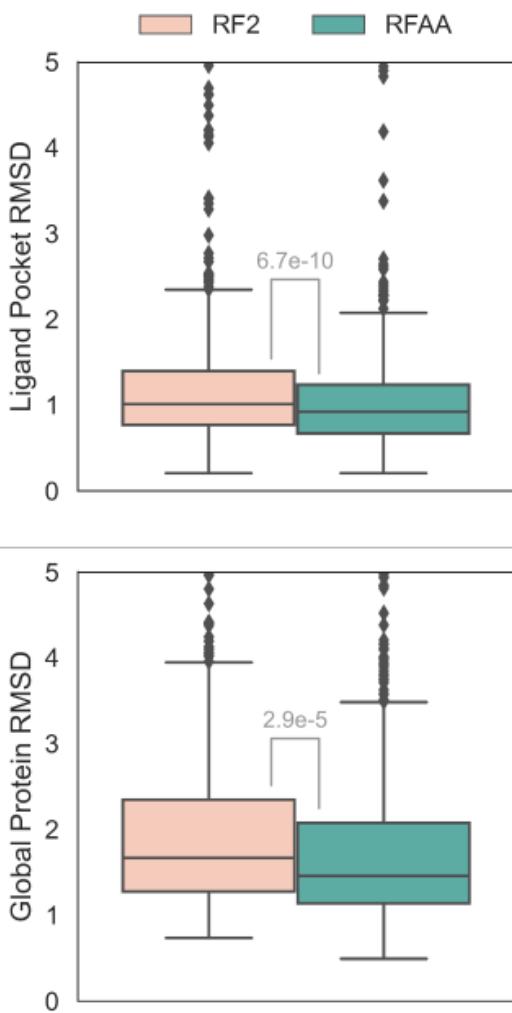
A



RoseTTAFold All Atom

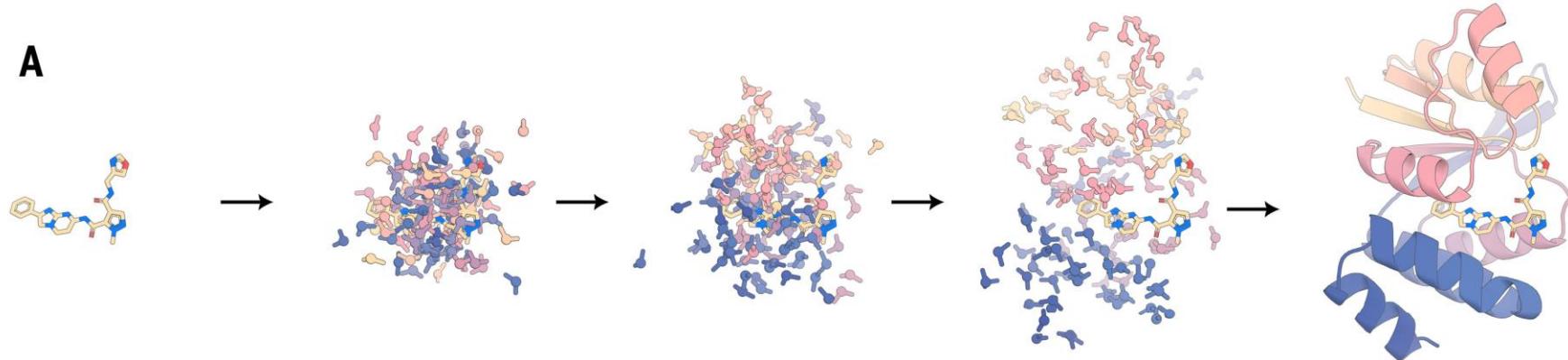


RoseTTAFold All Atom



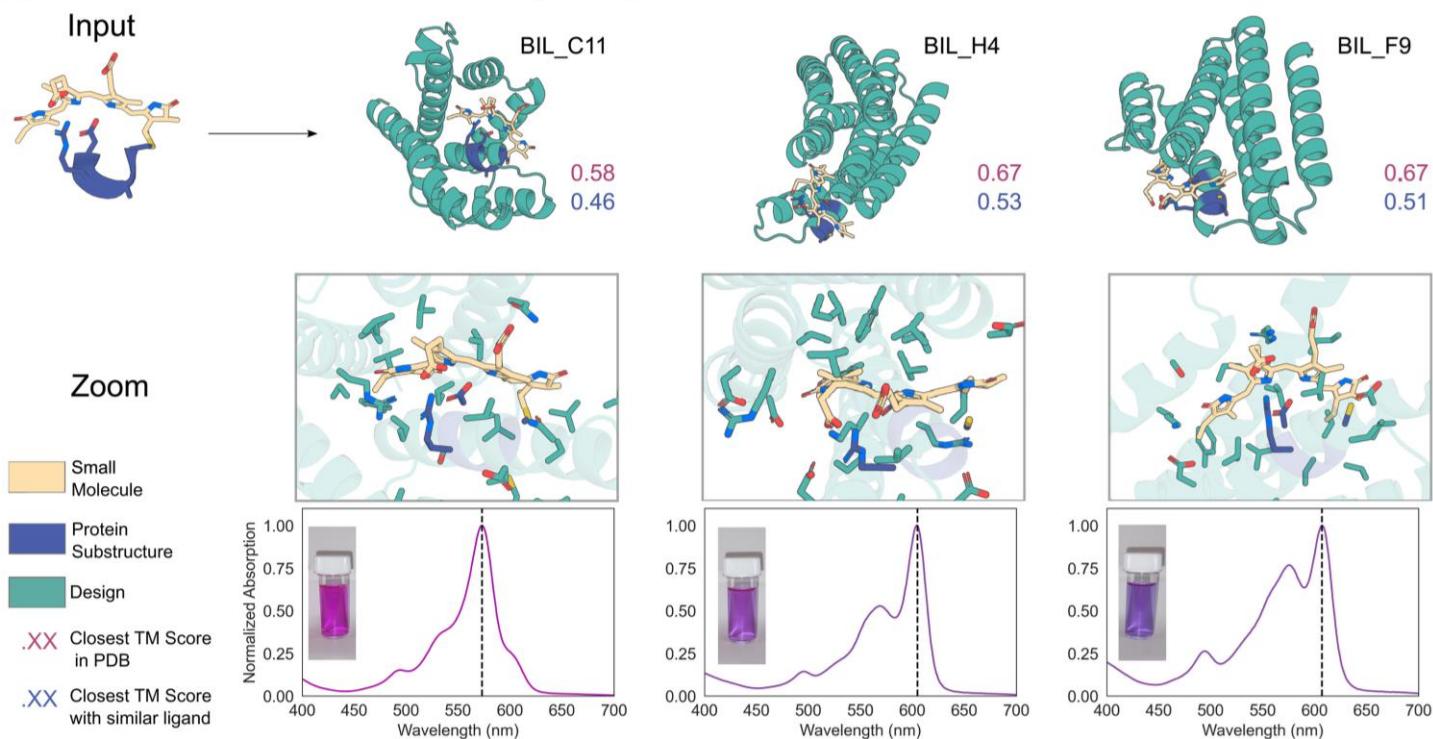
RFDiffusion All Atom

A



D

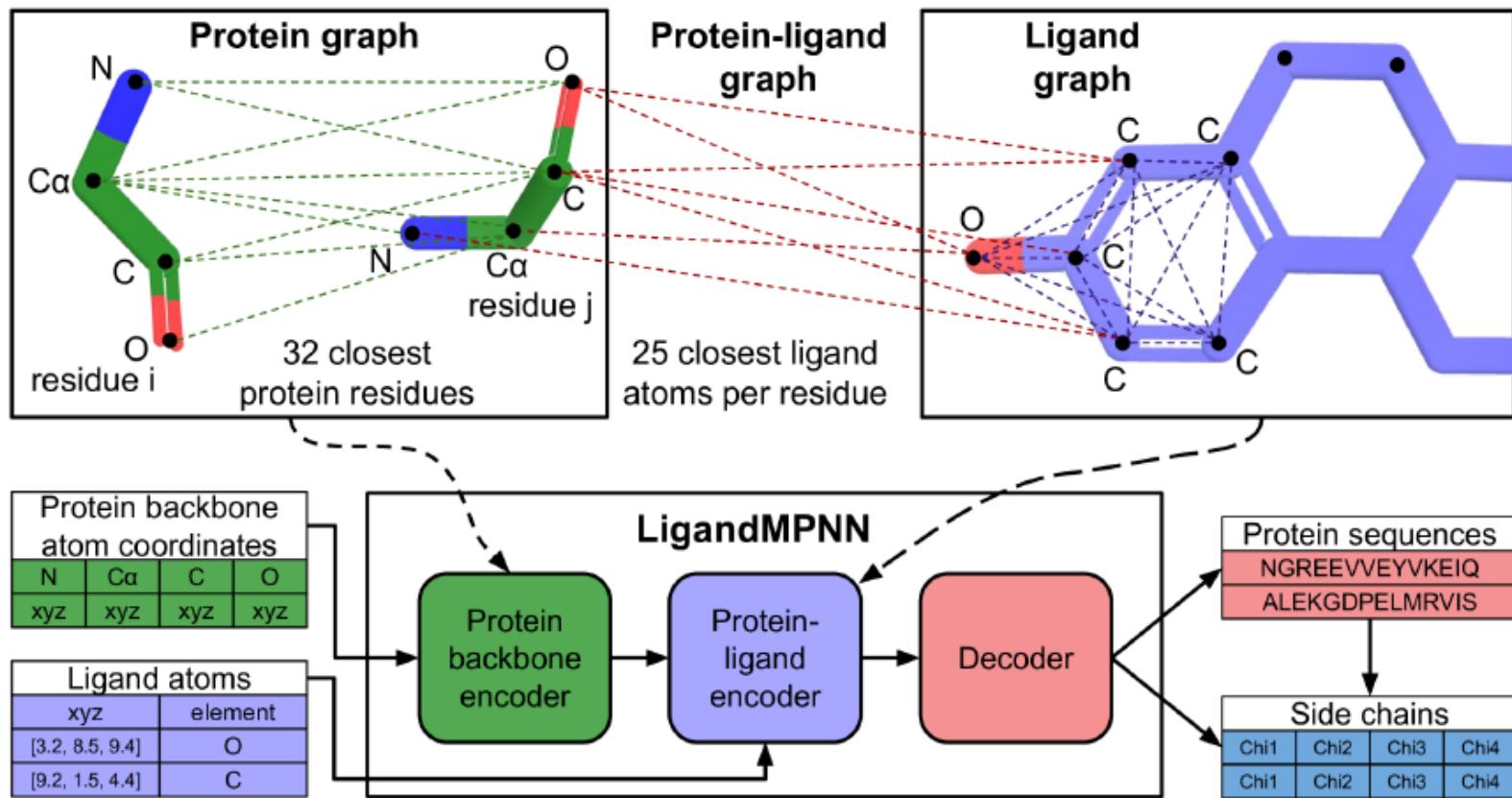
Optically Active Bilin Binders



Generalized biomolecular modeling and design with RoseTTAFold All-Atom <https://doi.org/10.1126/science.adl2528>

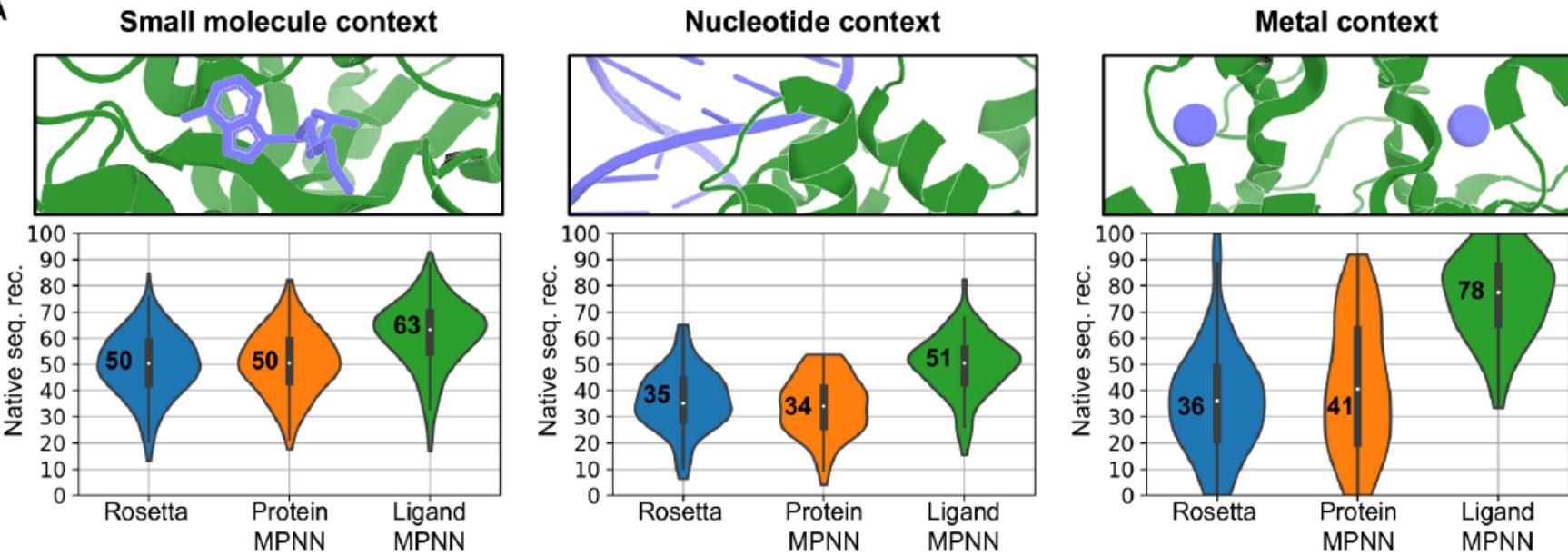
LigandMPNN

- ProteinMPNN ... but with Ligands



LigandMPNN

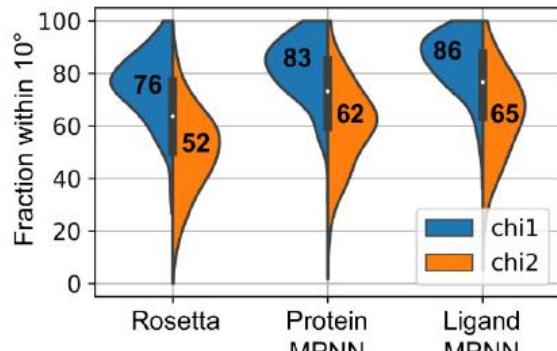
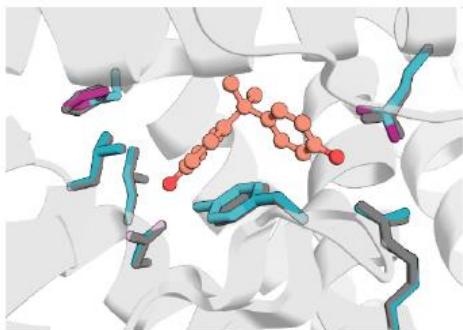
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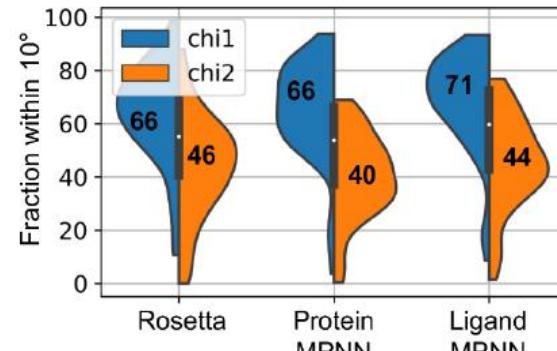
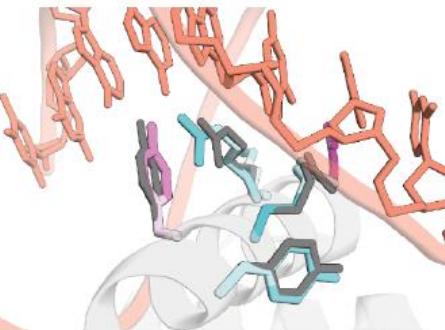
LigandMPNN can also pack sidechains

A

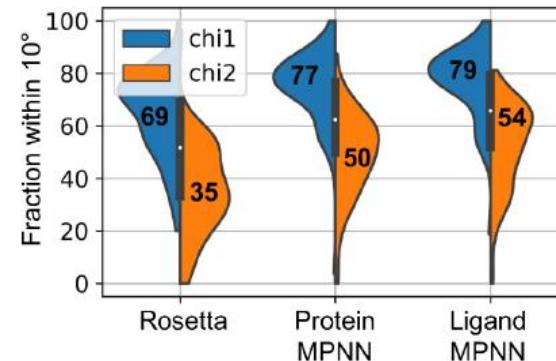
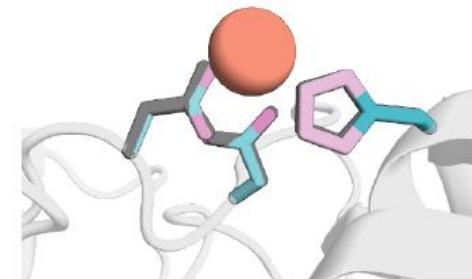
Small molecule context



Nucleotide context



Metal context

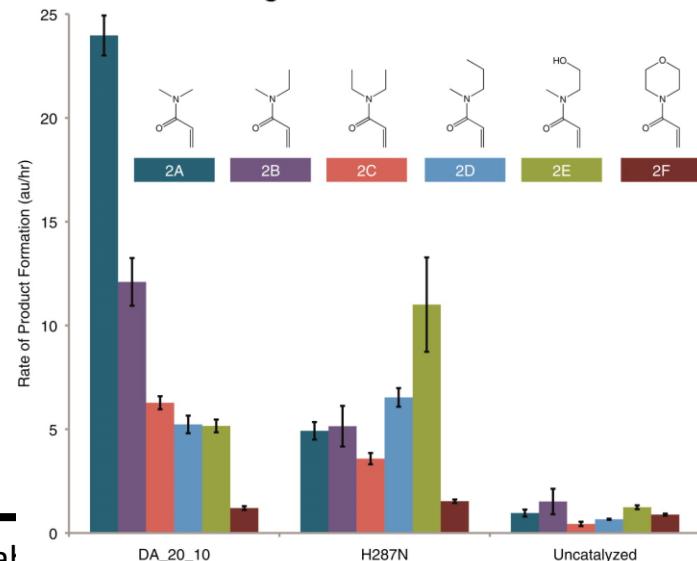
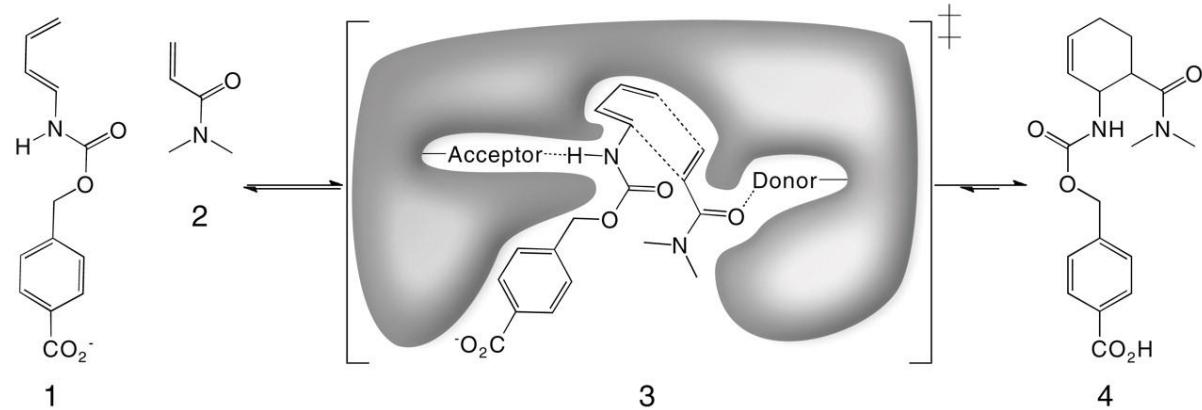


Tutorial Example:

Computational design of an enzyme catalyst for a stereoselective bimolecular Diels-Alder reaction. Siegel et al (2010) <https://doi.org/10.1126/science.1190239>

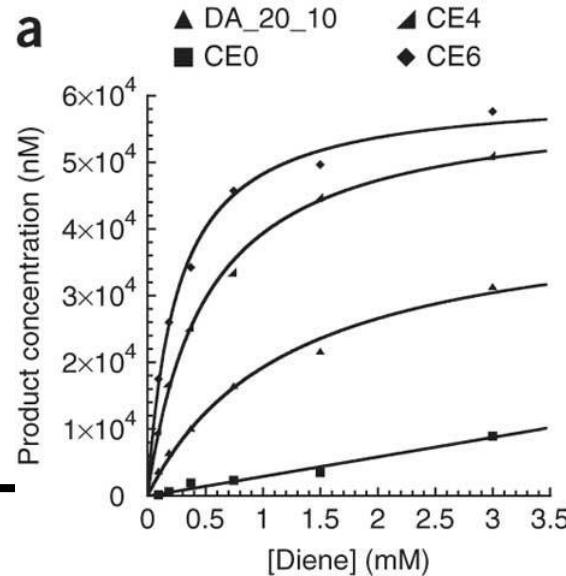
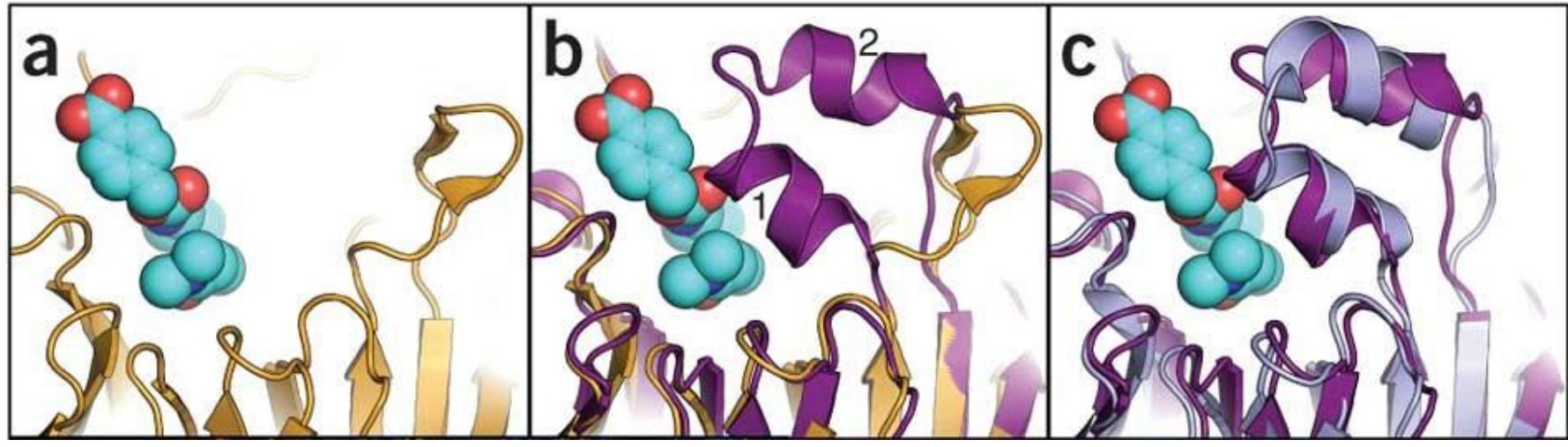
- “De novo” enzyme design.

- Theozyme:
 - QM
- Grafting
 - Rosetta Matcher
- Redesign
 - Rosetta



Tutorial Example:

Increased Diels-Alderase activity through backbone remodeling guided by Foldit players. Eiben et al (2012) <https://doi.org/10.1038/nbt.2109>



Broader Applicability

- Any protein-small molecule interaction
 - Enzymes
 - Receptors
 - Sensors
 - Binders
- Protein/Nucleic Acid interactions
 - DNA/RNA binding proteins
 - Transcription factors
- Protein Glycan interactions
 - Glycan binders
 - Proteins with glycans attached
- Proteins with modified residues
 - Post-translational modifications
 - Noncanonical amino acid containing proteins

