Enzyme Design with RFdiffusionAA and LigandMPNN

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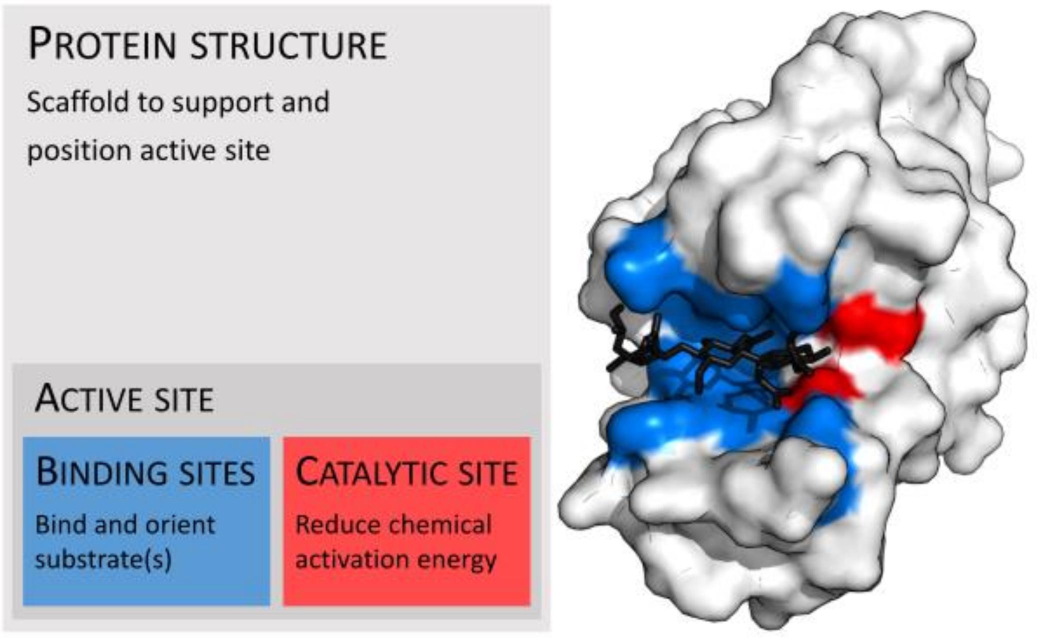
Enzyme Design

- Protein only versus Protein + Small Molecules



PROTEIN STRUCTURE

Scaffold to support and position active site

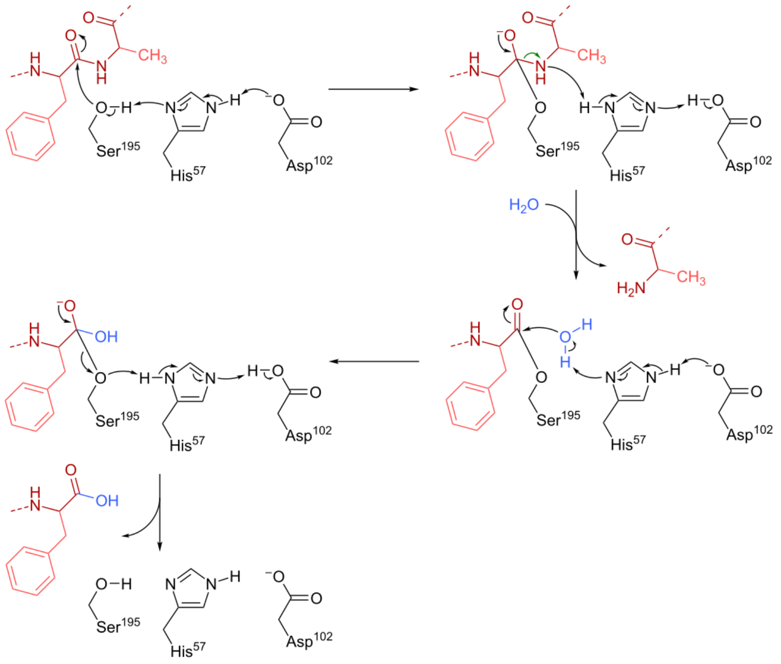
ACTIVE SITE

BINDING SITES

Bind and orient substrate(s)

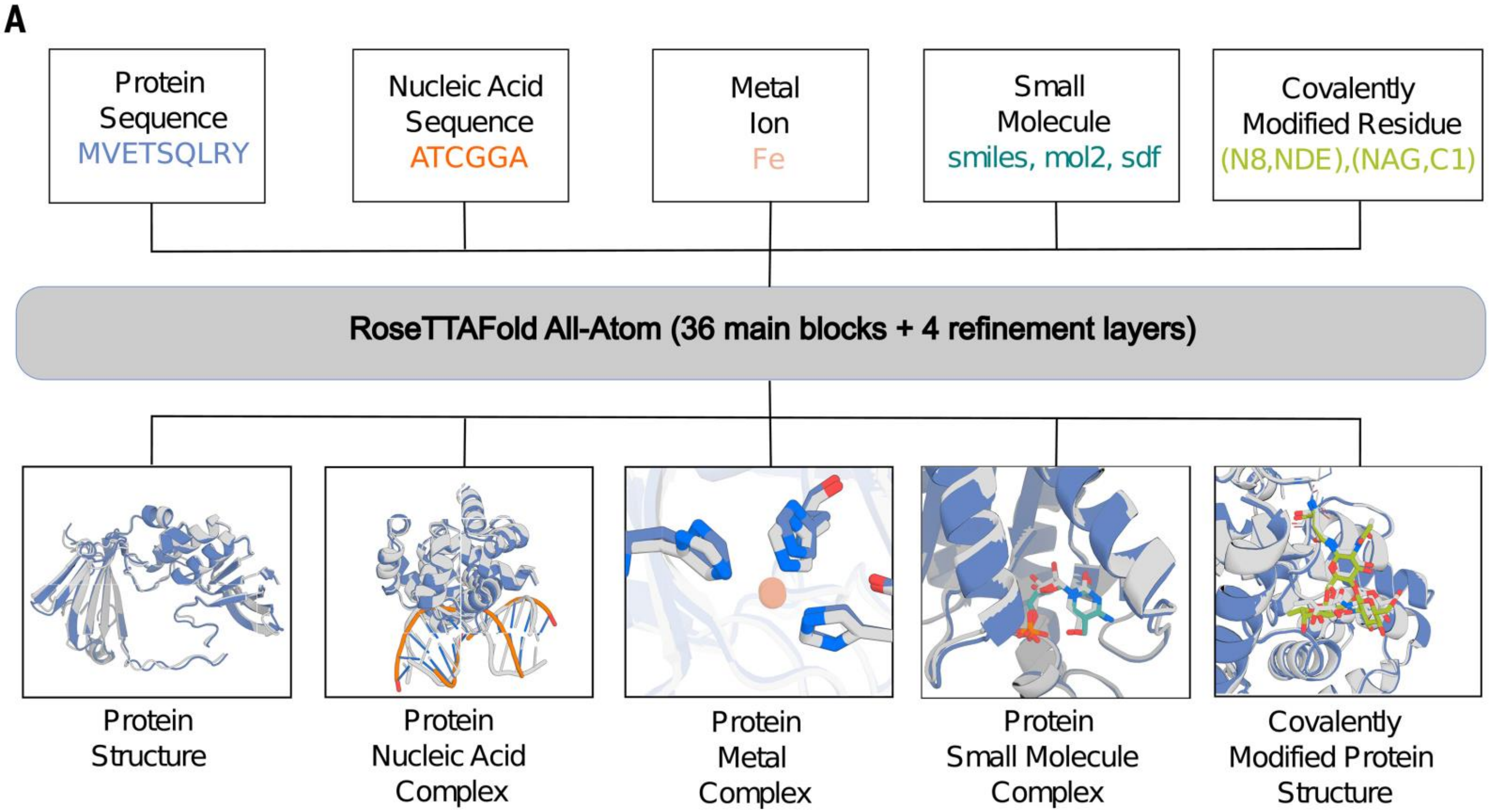
CATALYTIC SITE

Reduce chemical activation energy



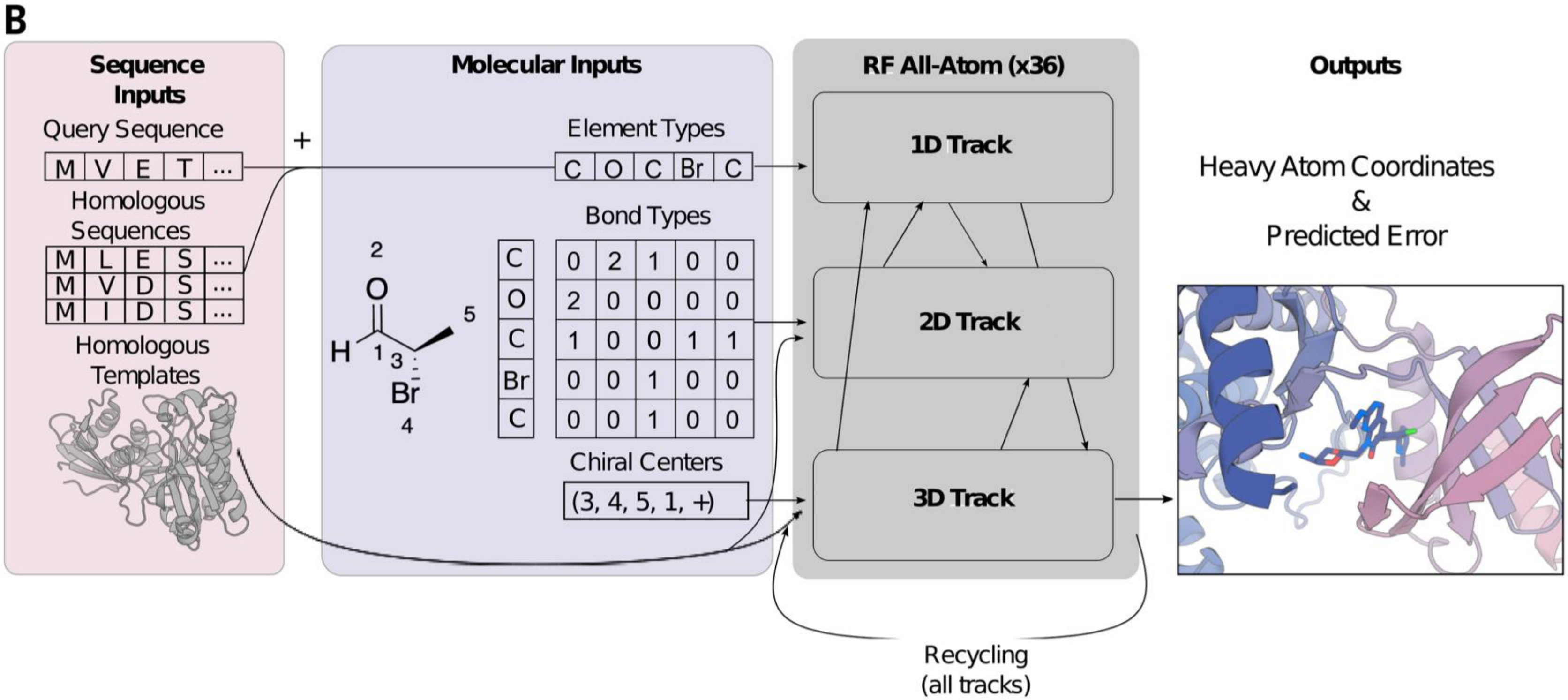
https://en.wikipedia.org/wiki/Active_site

RoseTTAFold All Atom



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

RoseTTAFold All Atom



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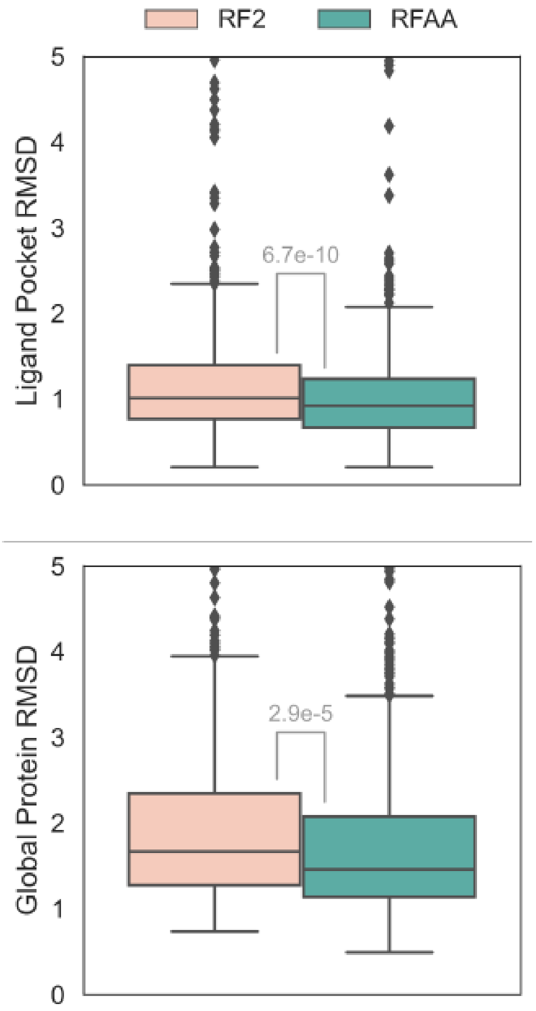
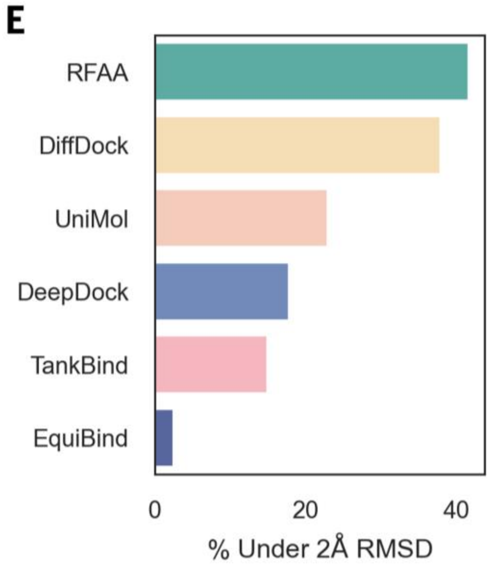
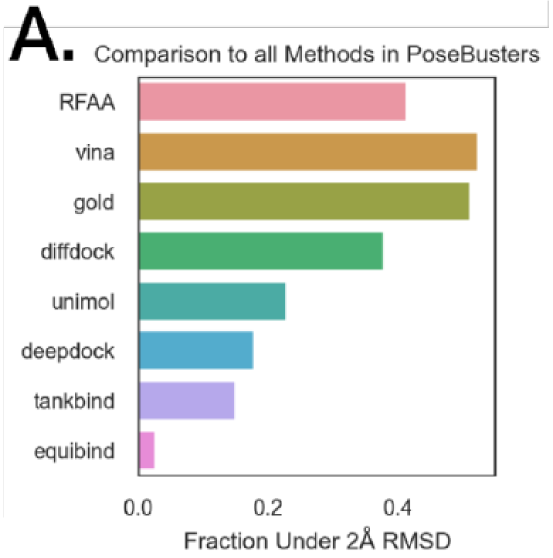
RoseTTAFold All Atom







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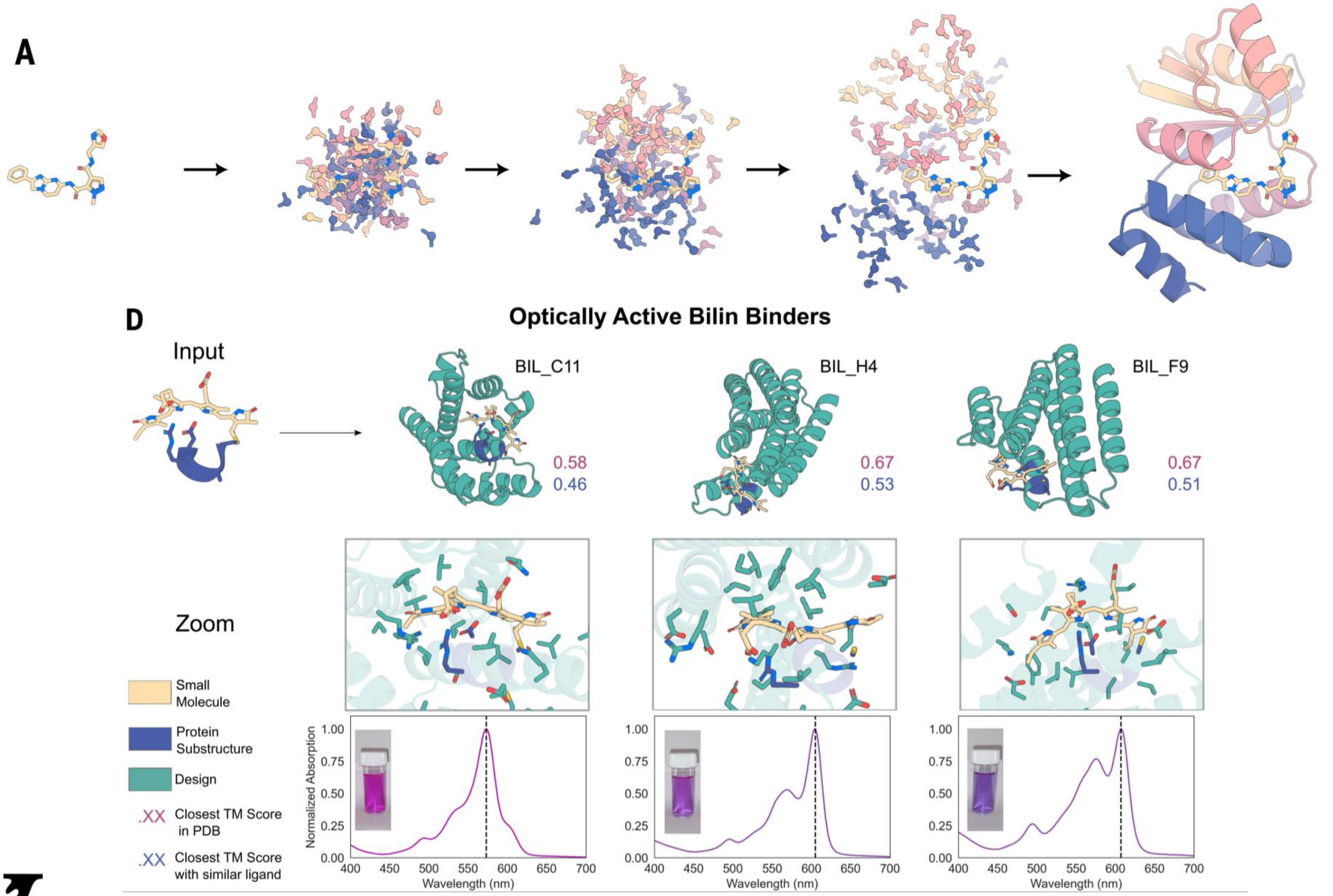
RFDiffusion All Atom



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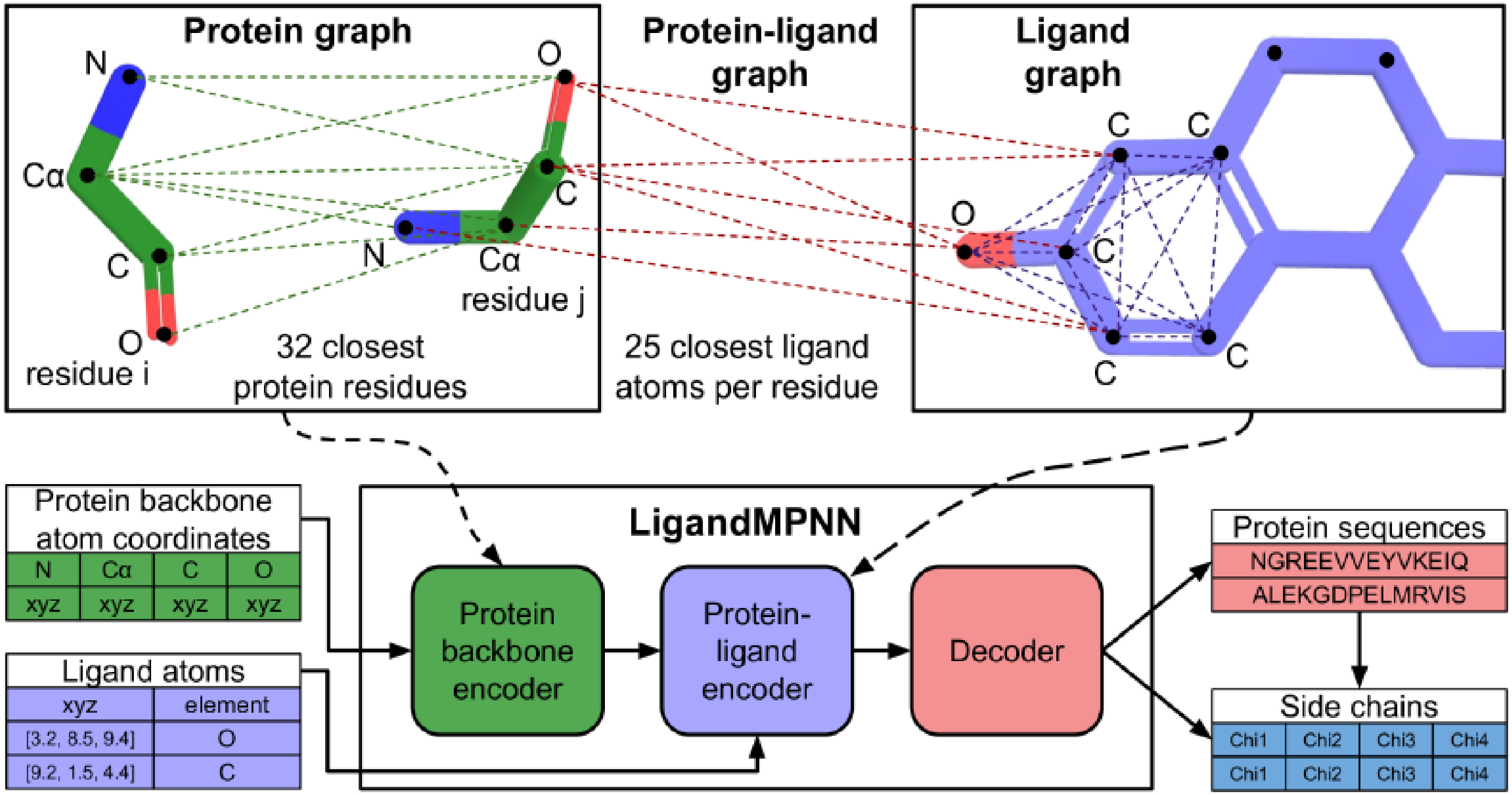
LigandMPNN

- ProteinMPNN … but with Ligands



Protein backbone atom coordinates

N	Cα	C	O
xyz	xyz	xyz	xyz

Ligand atoms

xyz	element
[3.2, 8.5, 9.4]	O
[9.2, 1.5, 4.4]	C

LigandMPNN

Protein backbone encoder

Protein-ligand encoder

Decoder

Protein sequences

NGREEVVEYVKEIQ

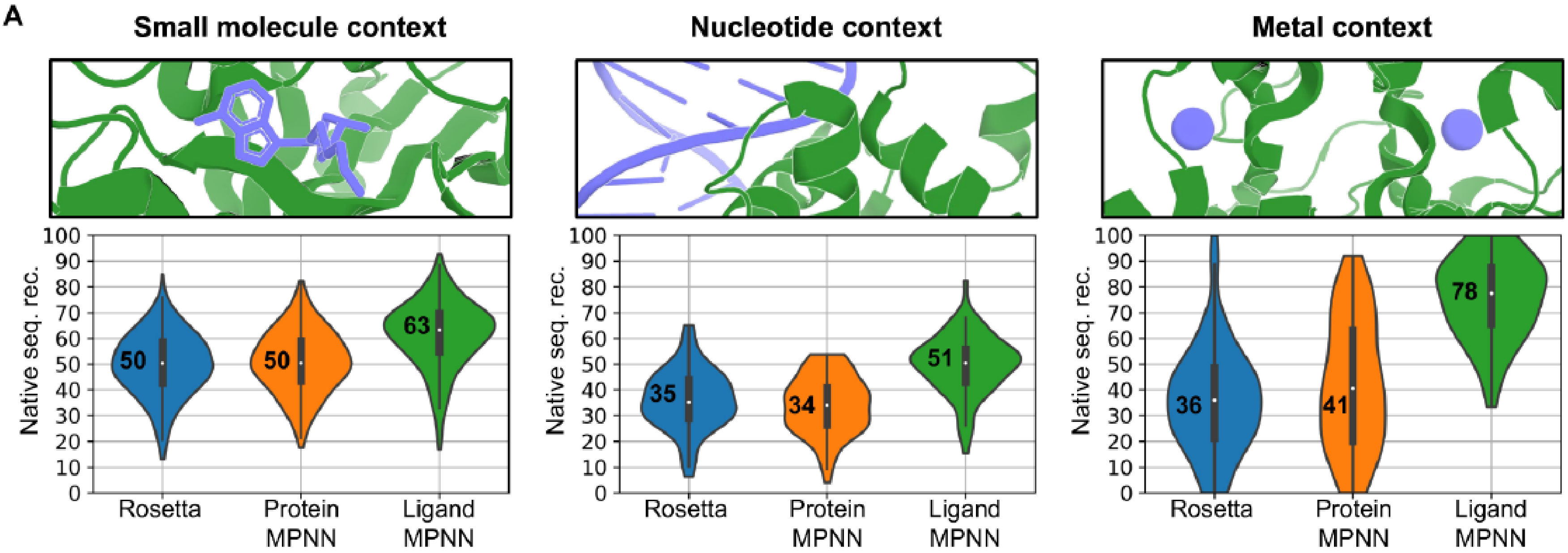
ALEKGDPELMRVIS

Side chains

Chi1	Chi2	Chi3	Chi4
Chi1	Chi2	Chi3	Chi4

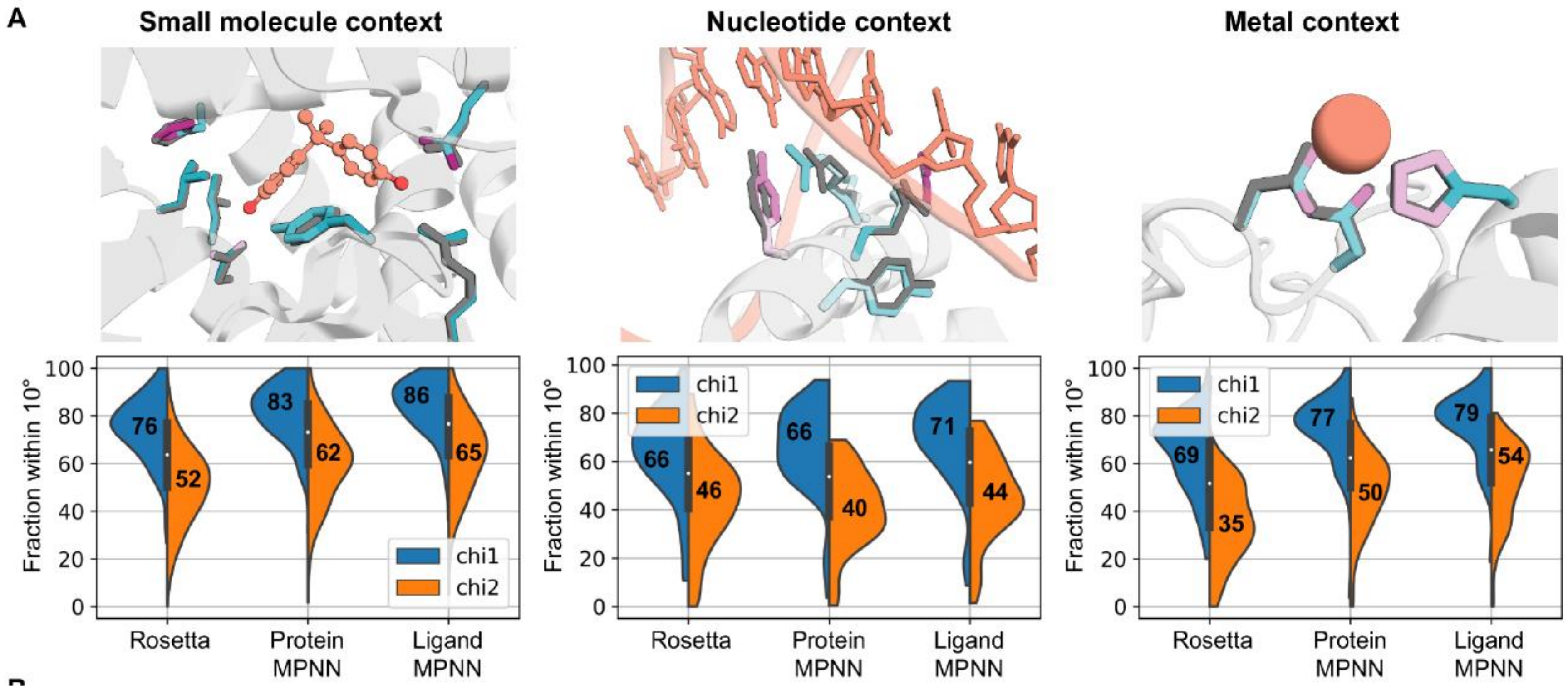
Atomic context-conditioned protein sequence design using LigandMPNN https://doi.org/10.1101/2023.12.22.573103

LigandMPNN



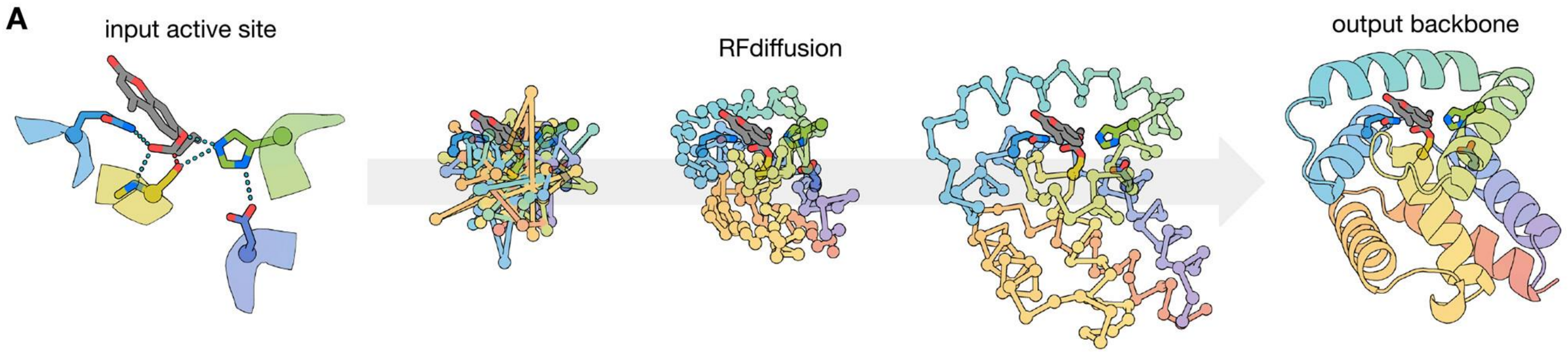
Atomic context-conditioned protein sequence design using LigandMPNN https://doi.org/10.1101/2023.12.22.573103

LigandMPNN can also pack sidechains

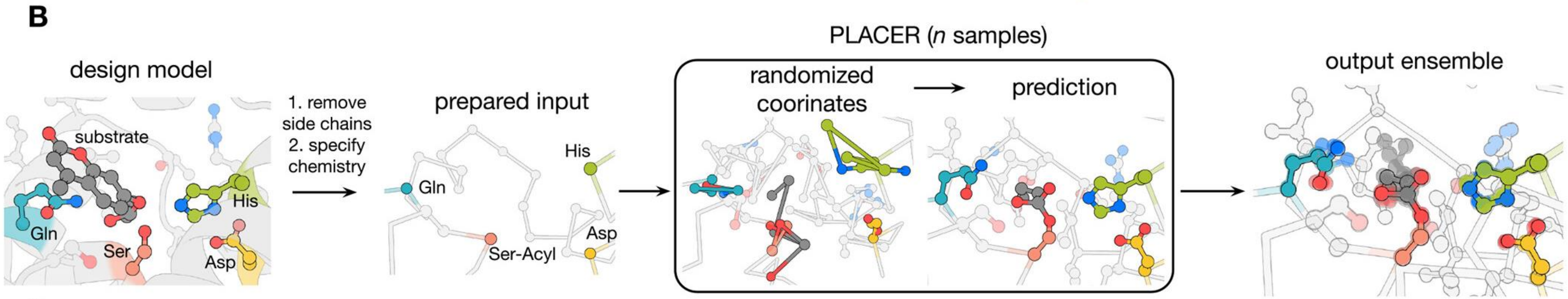


Atomic context-conditioned protein sequence design using LigandMPNN https://doi.org/10.1101/2023.12.22.573103

Computational design of serine hydrolases

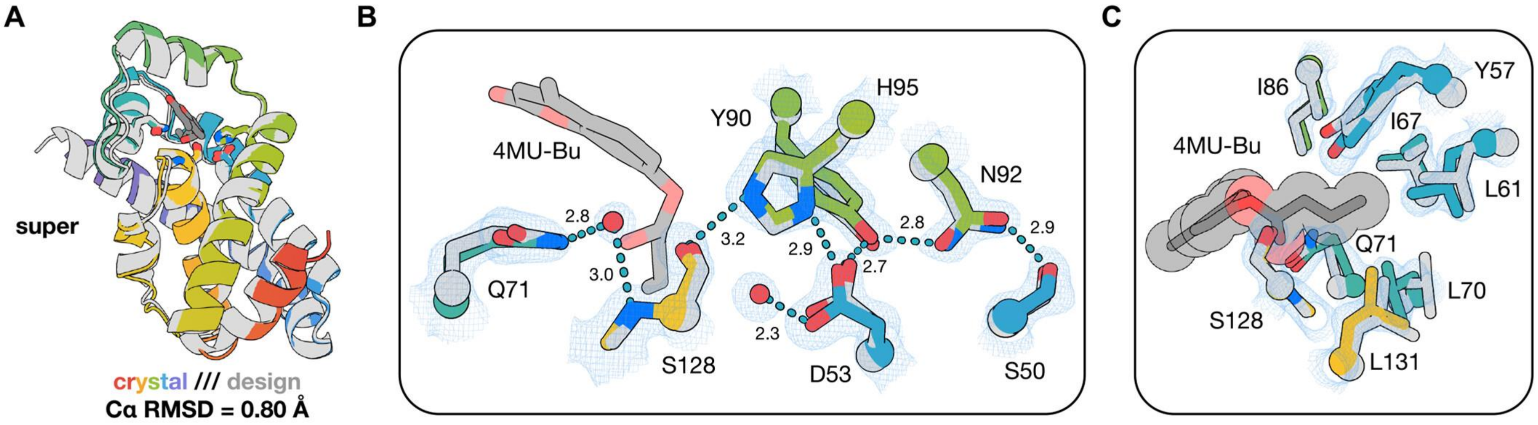


RFdiffusion ⟹ LigandMPNN ⟹ FastRelax ⟹ AlphaFold ⟹ PLACER



Computational design of serine hydrolases https://www.science.org/doi/10.1126/science.adu2454

Computational design of serine hydrolases



TM-score to known: 0.52

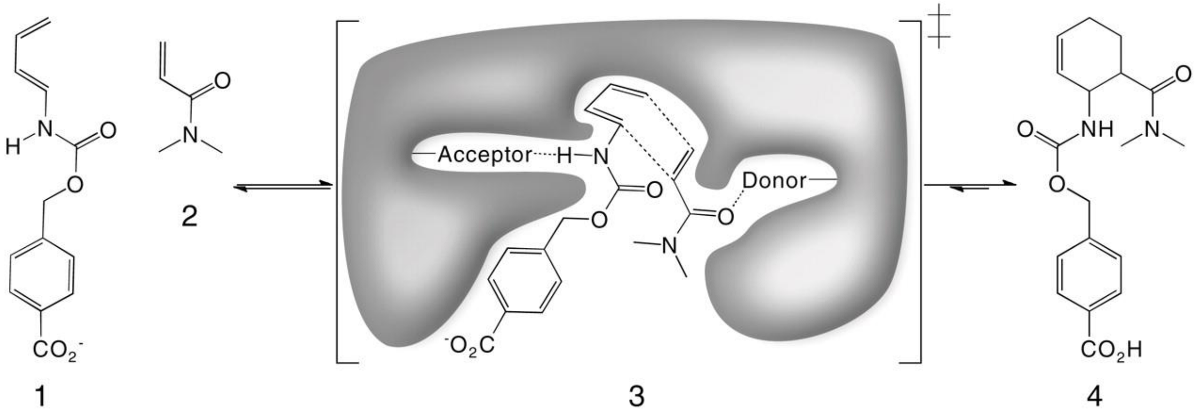
- Best k_{cat}/K_m: 2.2×10^5 M^{-1} s^{-1}
- Previously: 210 M^{-1} s^{-1} (3190 M^{-1} s^{-1} after directed evolution)

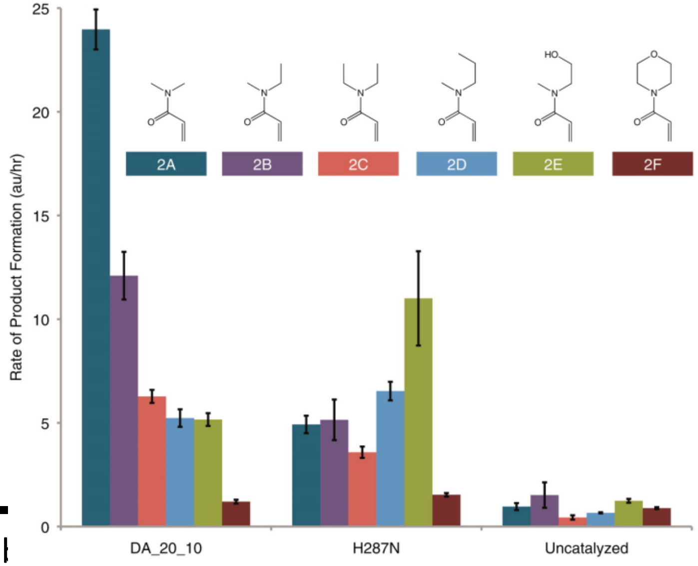
Computational design of serine hydrolases https://www.science.org/doi/10.1126/science.adu2454

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

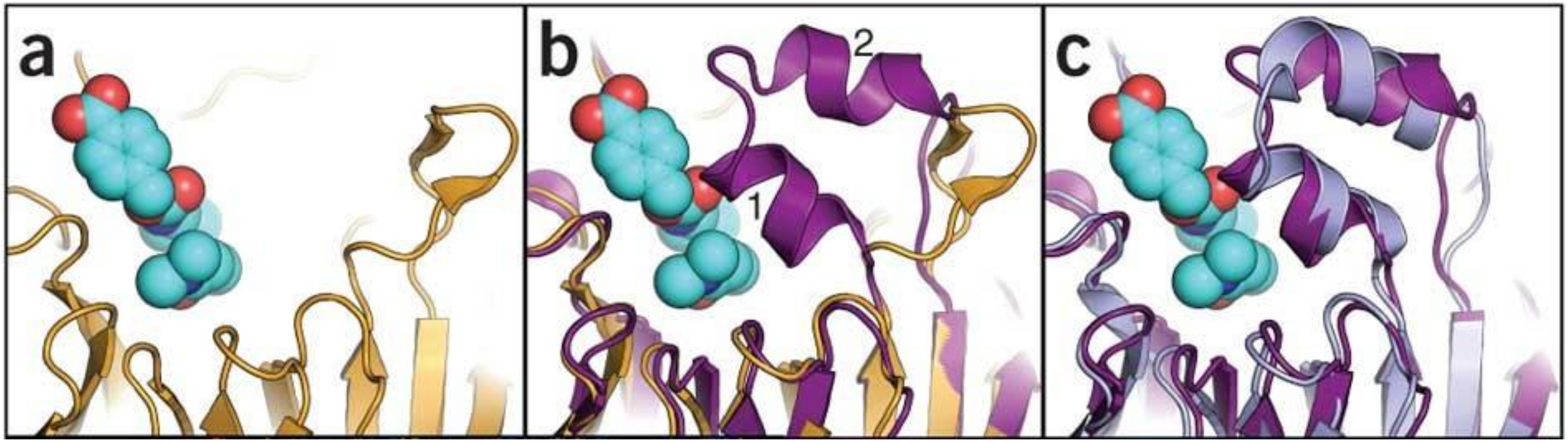
- "De novo" enzyme design.
    - Theozyme:
        - QM
    - Grafting
        - Rosetta Matcher
    - Redesign
        - Rosetta

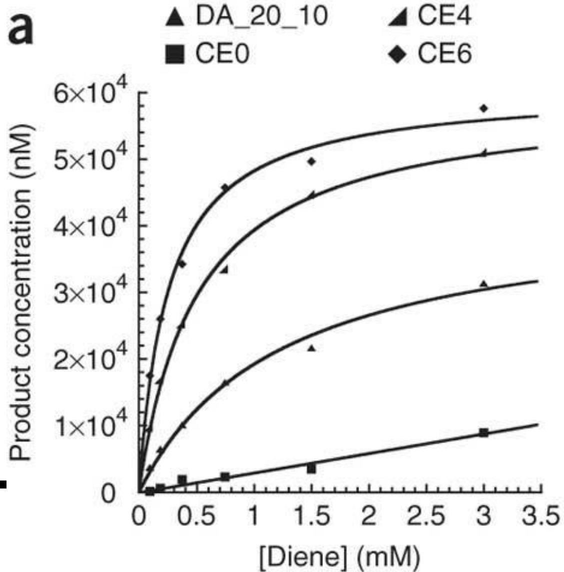




Tutorial Example:

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