GNN Applications: Graph for Protein Design

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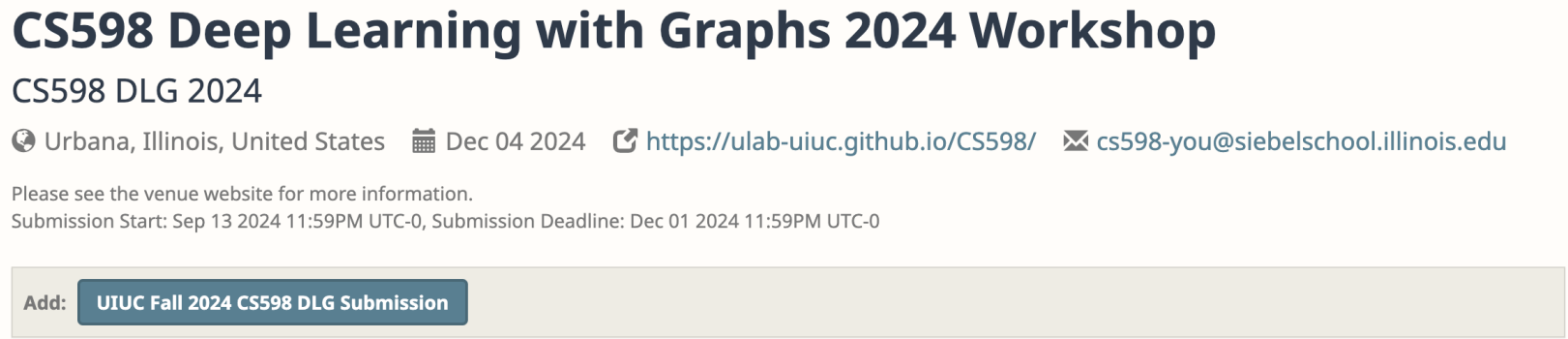
CS598: Deep Learning with Graphs, 2024 Fall

https://ulab-uiuc.github.io/CS598/

Logistics: Submission Task Due

- The deadline for the submission task is **Nov 21 (Thu), 11:59 PM CT**.
- We expect a minimum length of **6 pages** in **ICLR 2025 format** for the **draft submission**.
  - For the draft version, you are expected to include at least sections such as related work, methods, and **experiment settings**.
  - We will use the **OpenReview** to receive submissions: https://openreview.net/group?id=illinois.edu/UIUC/Fall_2024/CS598_DLG.

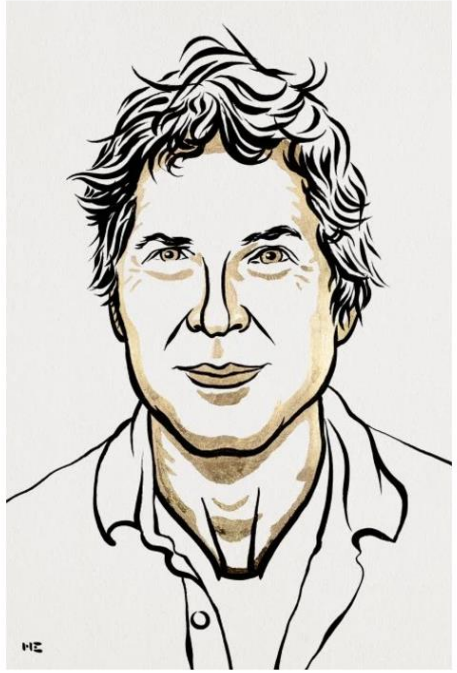


Logistics: Submission Task Due

- The submission task counts towards **15% (writing) + 15% (implementation) = 30%** of your final grade.
  - For the 15% of writing, **only 5%** is determined by the draft version (due on **Nov 21**) and **10%** is determined by the final version (due on **Dec 8**).
  - The 15% of implementation is determined by the code you provide for the final version (due on **Dec 8**).

GNN Applications: Graph for Protein Design

Basics of Protein Design



Ill. Niklas Elmehed © Nobel Prize Outreach

David Baker

Prize share: 1/2

Ill. Niklas Elmehed © Nobel Prize Outreach

Demis Hassabis

Prize share: 1/4

Ill. Niklas Elmehed © Nobel Prize Outreach

John Jumper

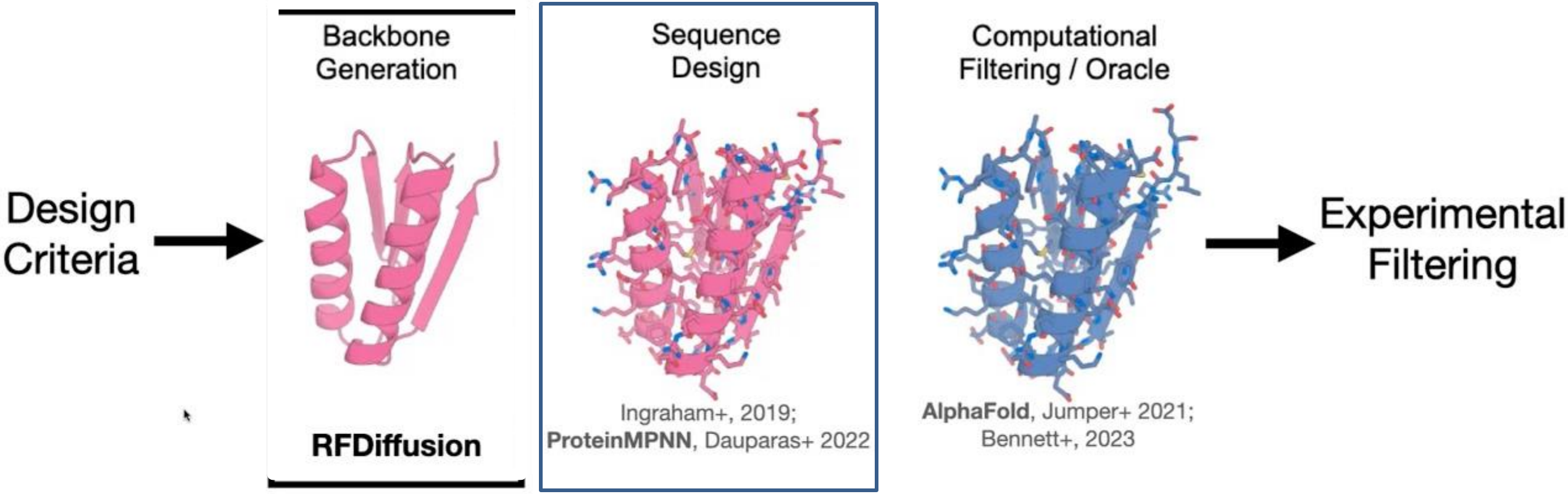
Prize share: 1/4

The Nobel Prize in Chemistry 2024 was divided, one half awarded to David Baker "for computational protein design", the other half jointly to Demis Hassabis and John Jumper "for protein structure prediction"

The Nobel Prize in Chemistry 2024

- The Nobel Prize in Chemistry 2024 is about **proteins, life's ingenious chemical tools**. David Baker has succeeded with the **almost impossible feat of building entirely new kinds of proteins**. Demis Hassabis and John Jumper have developed an AI model to solve a 50-year-old problem: **predicting proteins' complex structures**. These discoveries hold enormous potential. …
- Life could not exist without proteins. That we can now predict protein structures and design our own proteins confers the greatest beneft to humankind.

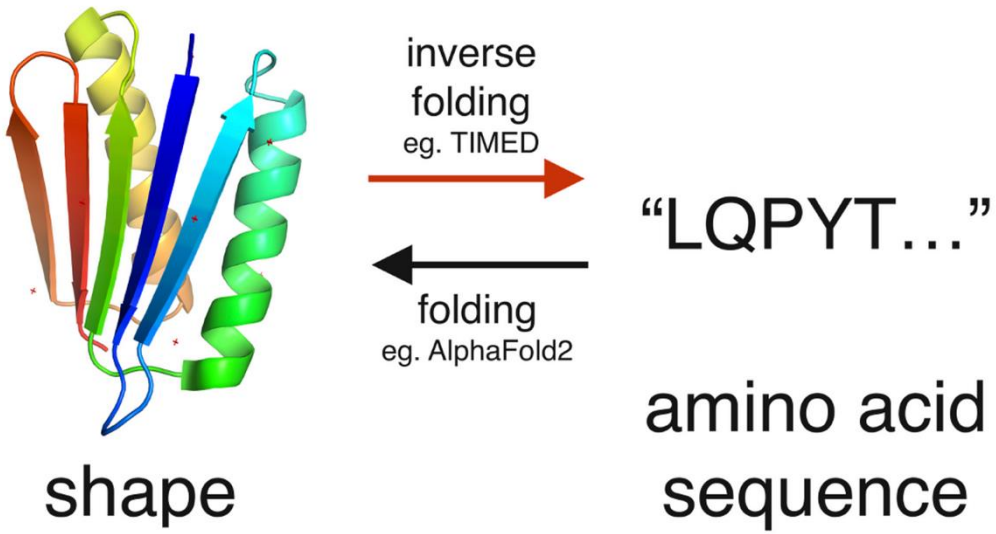
De Novo Protein Design Workflow

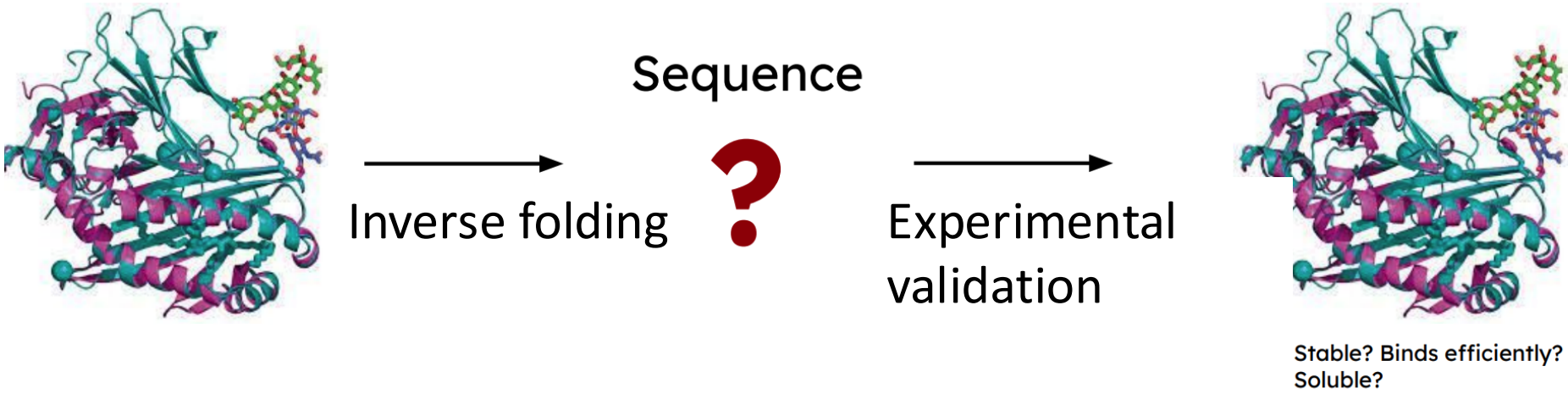


- Backbones must be (1) physically **realizable**, (2) **functional**, and (3) **diverse**

Protein Folding & Inverse Folding

- **Folding:** given amino acid sequence, predict protein structure
- **Inverse folding:** given desired protein structure, find amino acid sequence

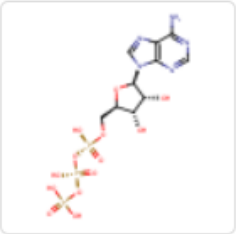
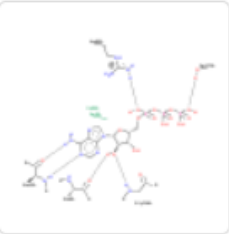
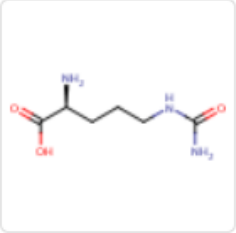
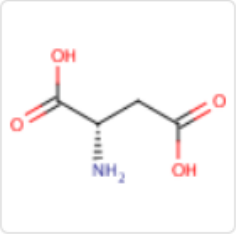
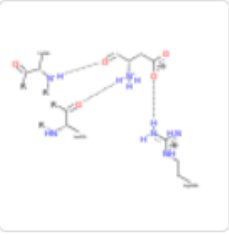




The Key Dataset: PDB

Small Molecules

Ligands 3 Unique

ID	Chains	Name / Formula / InChI Key	2D Diagram & Interactions	3D Interactions
ATP Query on ATP Download SDF File Download CCD File	A, B, C, D	**ADENOSINE-5'-TRIPHOSPHATE** $C_{10}H_{16}N_5O_{13}P_3$ ZKHQWZAMYRWXGA-KQYNXXCUSA-N	 	Ligand Explorer NGL Binding Pocket (JSmol) Electron Density (JSmol)
CIR Query on CIR Download SDF File Download CCD File	A, B, C, D	**CITRULLINE** $C_6H_{13}N_3O_3$ RHGKLRLOHDJJDR-BYPYZUCNSA-N	 	Ligand Explorer NGL Binding Pocket (JSmol) Electron Density (JSmol)
ASP Query on ASP Download SDF File Download CCD File	A	**ASPARTIC ACID** $C_4H_7NO_4$ CKLJMWTZIZZHCS-REOHCLBHSA-N	 	Ligand Explorer NGL Binding Pocket (JSmol) Electron Density (JSmol)

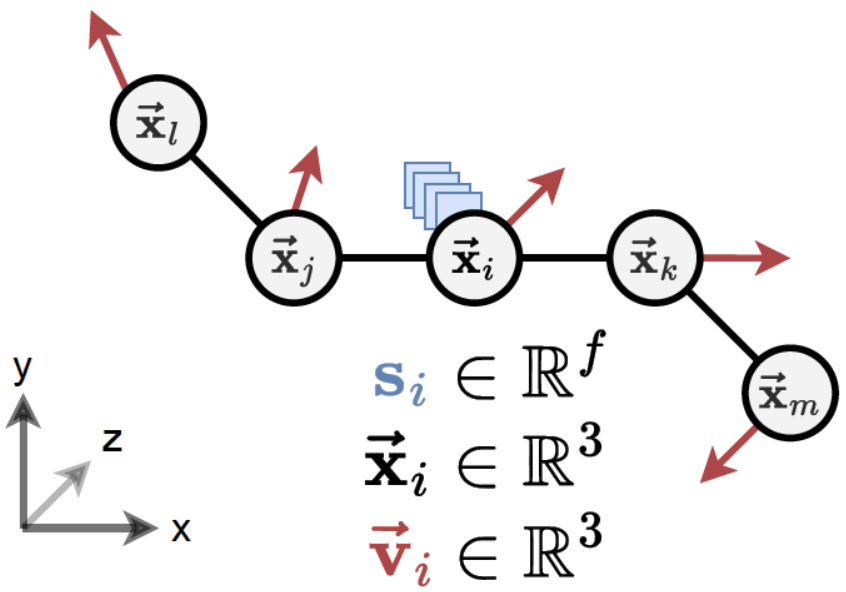
PDB Example

	id	type								x	y	z							
ATOM	1	N	N	.	VAL	A	1	1	?	6.204	16.869	4.854	1.00	49.05	?	1	VAL	A	N	1
ATOM	2	C	CA	.	VAL	A	1	1	?	6.913	17.759	4.607	1.00	43.14	?	1	VAL	A	CA	1
ATOM	3	C	C	.	VAL	A	1	1	?	8.504	17.378	4.797	1.00	24.80	?	1	VAL	A	C	1
ATOM	4	O	O	.	VAL	A	1	1	?	8.805	17.011	5.943	1.00	37.68	?	1	VAL	A	O	1
ATOM	5	C	CB	.	VAL	A	1	1	?	6.369	19.044	5.810	1.00	72.12	?	1	VAL	A	CB	1
ATOM	6	C	CG1	.	VAL	A	1	1	?	7.009	20.127	5.418	1.00	61.79	?	1	VAL	A	CG1	1
ATOM	7	C	CG2	.	VAL	A	1	1	?	5.246	18.533	5.681	1.00	80.12	?	1	VAL	A	CG2	1

Proteins as Geometric graphs

Each node is:

- **embedded in Euclidean space** *e.g.* atoms in 3D
- **decorated with geometric attributes** *s.a.* velocity



$$\mathcal{G} = (\boldsymbol{A}, \boldsymbol{S}, \vec{\boldsymbol{X}}, \vec{\boldsymbol{V}})$$

Adjacency $\in \mathbb{R}^{n \times n}$

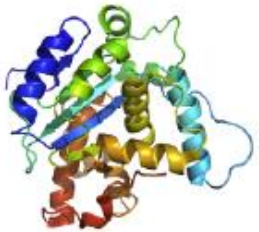
Scalar features $\in \mathbb{R}^{n \times a}$

Coordinates $\in \mathbb{R}^{n \times d}$

Geometric features* $\in \mathbb{R}^{n \times b \times d}$

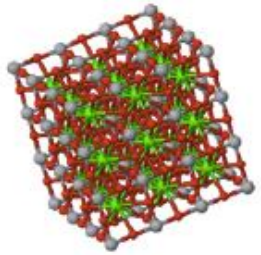
Real-world Geometric Graphs

Small Molecules

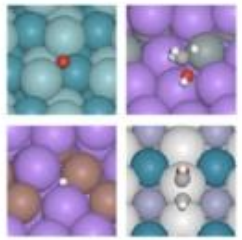


Proteins

DNA/RNA



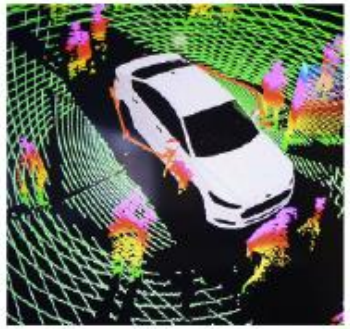
Inorganic Crystals



Catalysis Systems

Transportation & Logistics

Robotic Navigation



3D Computer Vision

GNN Applications: Graph for Protein Design

Inverse Protein Folding: ProteinMPNN

ProteinMPNN

RESEARCH

PROTEIN DESIGN

Robust deep learning–based protein sequence design using ProteinMPNN

J. Dauparas[1,2], I. Anishchenko[1,2], N. Bennett[1,2,3], H. Bai[1,2,4], R. J. Ragotte[1,2], L. F. Milles[1,2], B. I. M. Wicky[1,2], A. Courbet[1,2,4], R. J. de Haas[5], N. Bethel[1,2,4], P. J. Y. Leung[1,2,3], T. F. Huddy[1,2], S. Pellock[1,2], D. Tischer[1,2], F. Chan[1,2], B. Koepnick[1,2], H. Nguyen[1,2], A. Kang[1,2], B. Sankaran[6], A. K. Bera[1,2], N. P. King[1,2], D. Baker[1,2,4]*

- ProteinMPNN is to protein design what AlphaFold was to protein structure prediction – David Baker

ProteinMPNN's Empirical Verification

RESEARCH

PROTEIN DESIGN

Hallucinating symmetric protein assemblies

B. I. M. Wicky[1,2]†, L. F. Milles[1,2]†, A. Courbet[1,2,3]†, R. J. Ragotte[1,2], J. Dauparas[1,2], E. Kinfu[1,2], S. Tipps[1,2], R. D. Kibler[1,2], M. Baek[1,2], F. DiMaio[1,2], X. Li[1,2], L. Carter[1,2], A. Kang[1,2], H. Nguyen[1,2], A. K. Bera[1,2], D. Baker[1,2,3]*

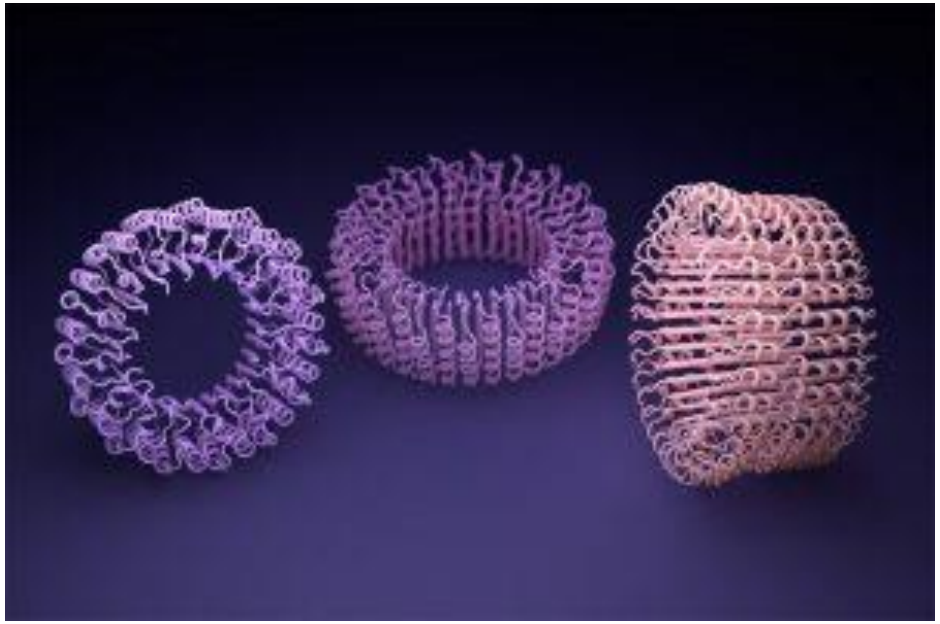
- ProteinMPNN together with the other new machine learning tools could reliably generate proteins that functioned in the laboratory

ProteinMPNN's Potential

NEWS | 15 September 2022 | Correction 21 September 2022

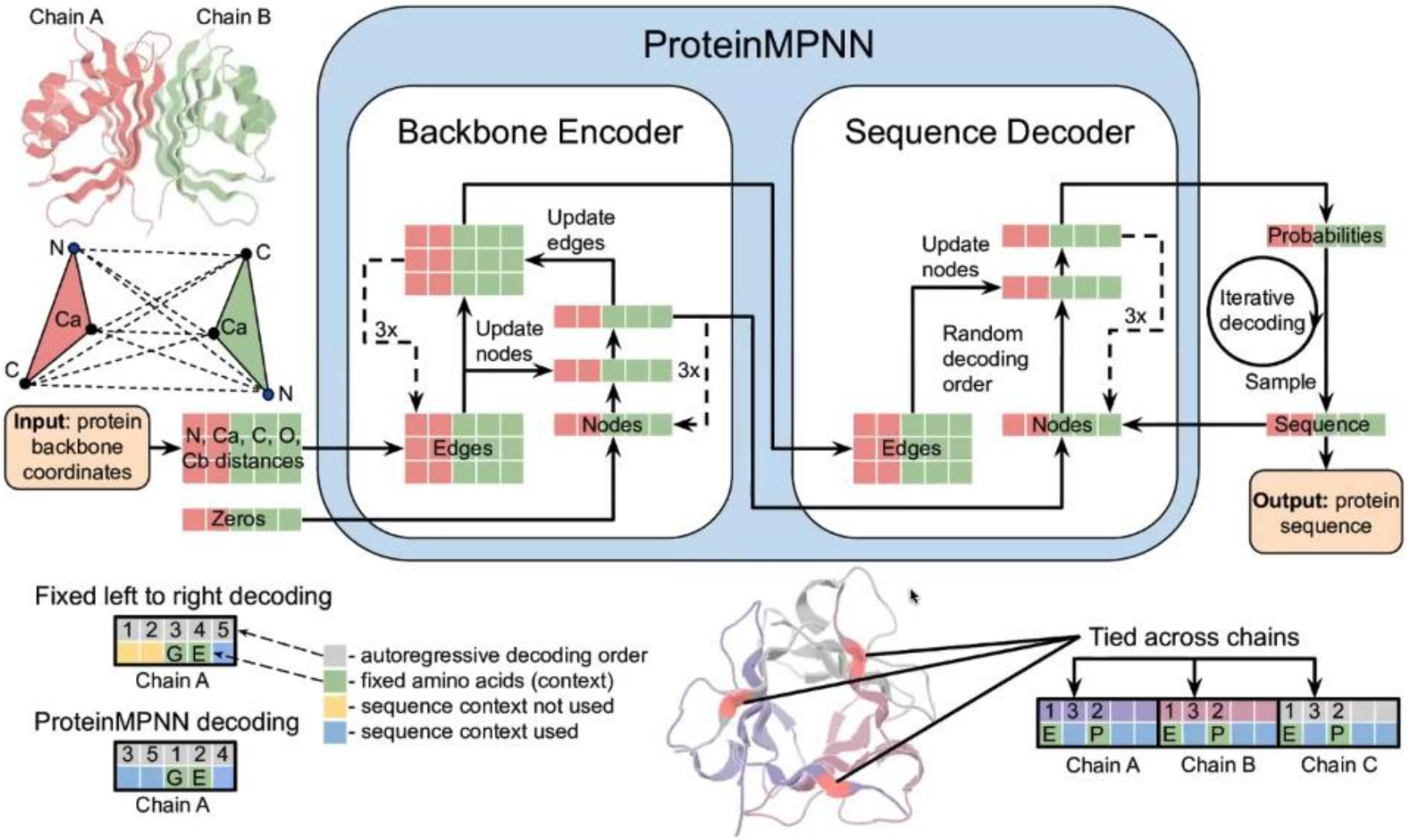
Scientists are using AI to dream up revolutionary new proteins

Huge advances in artificial intelligence mean researchers can design completely original molecules in seconds instead of months.



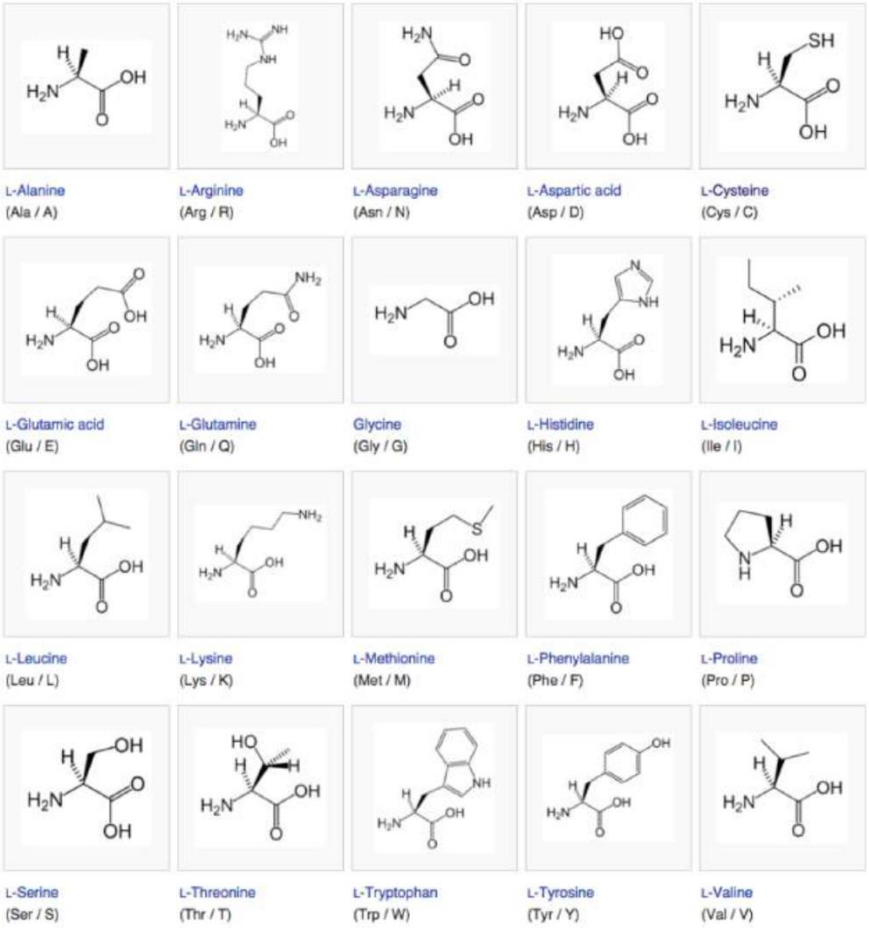
ProteinMPNN Framework

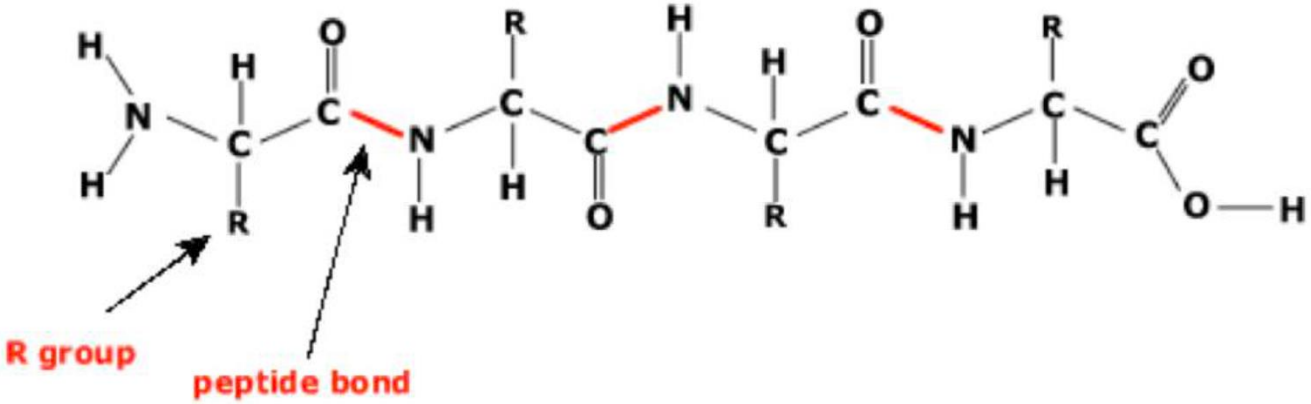
Structure



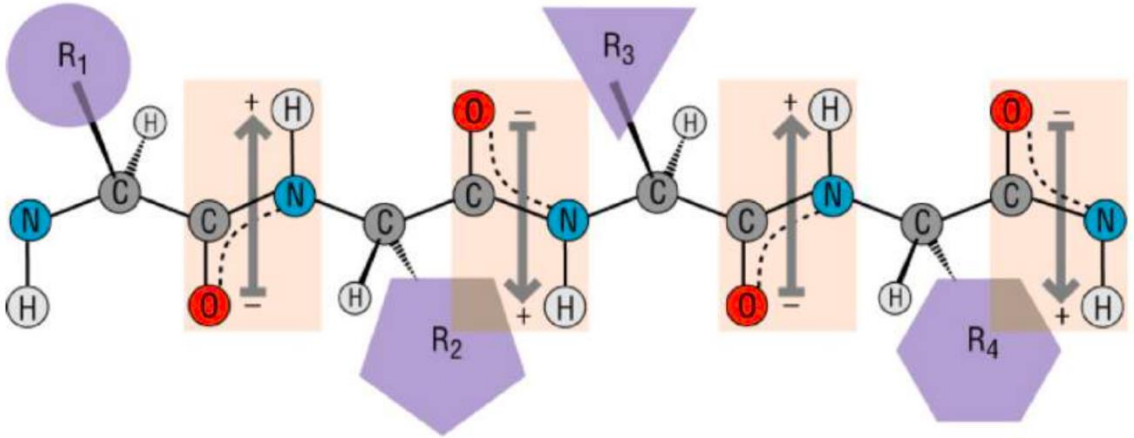
Sequence

Background: Protein Backbones

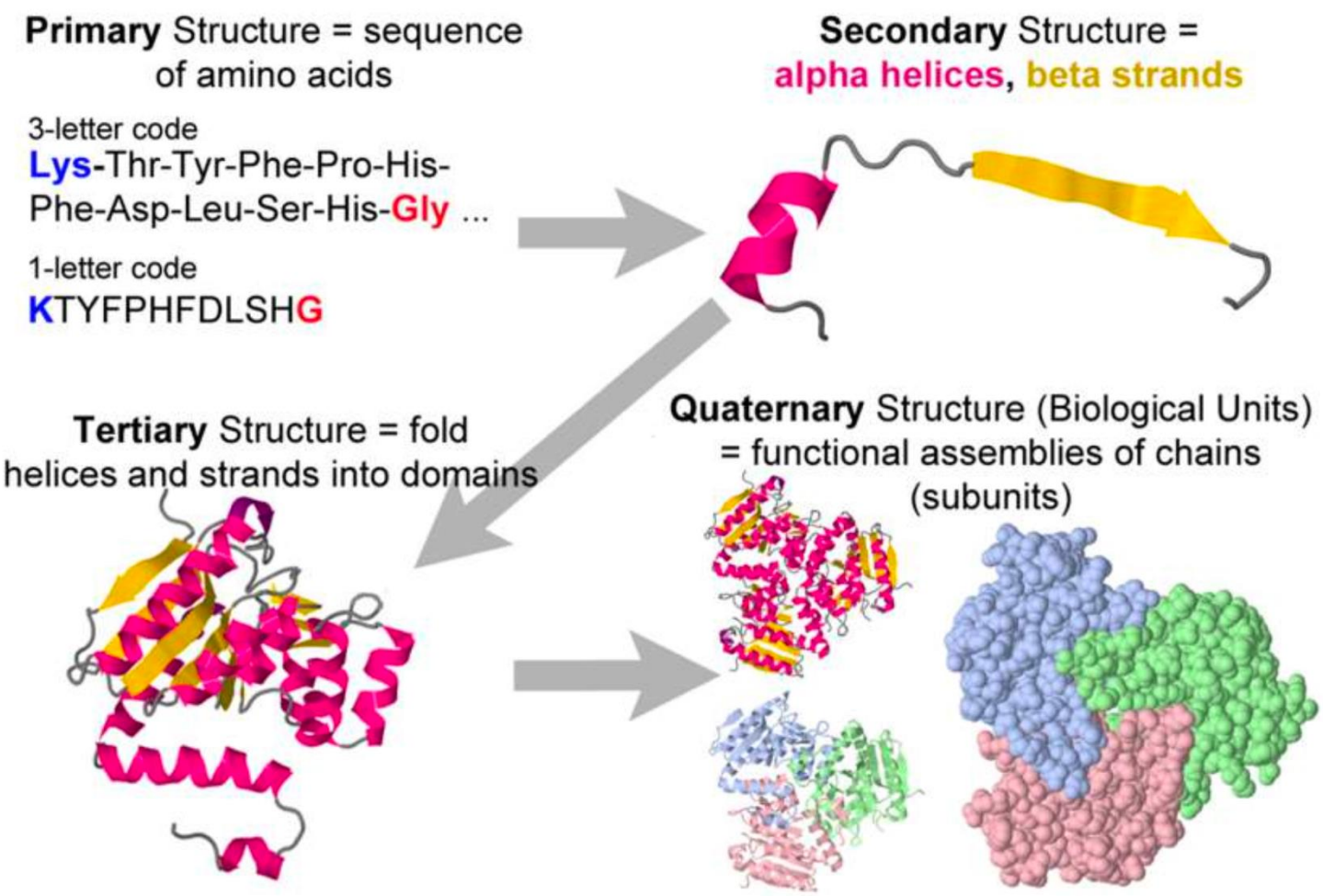




From Protein Structure and Function by Gregory A Petsko and Dagmar Ringe

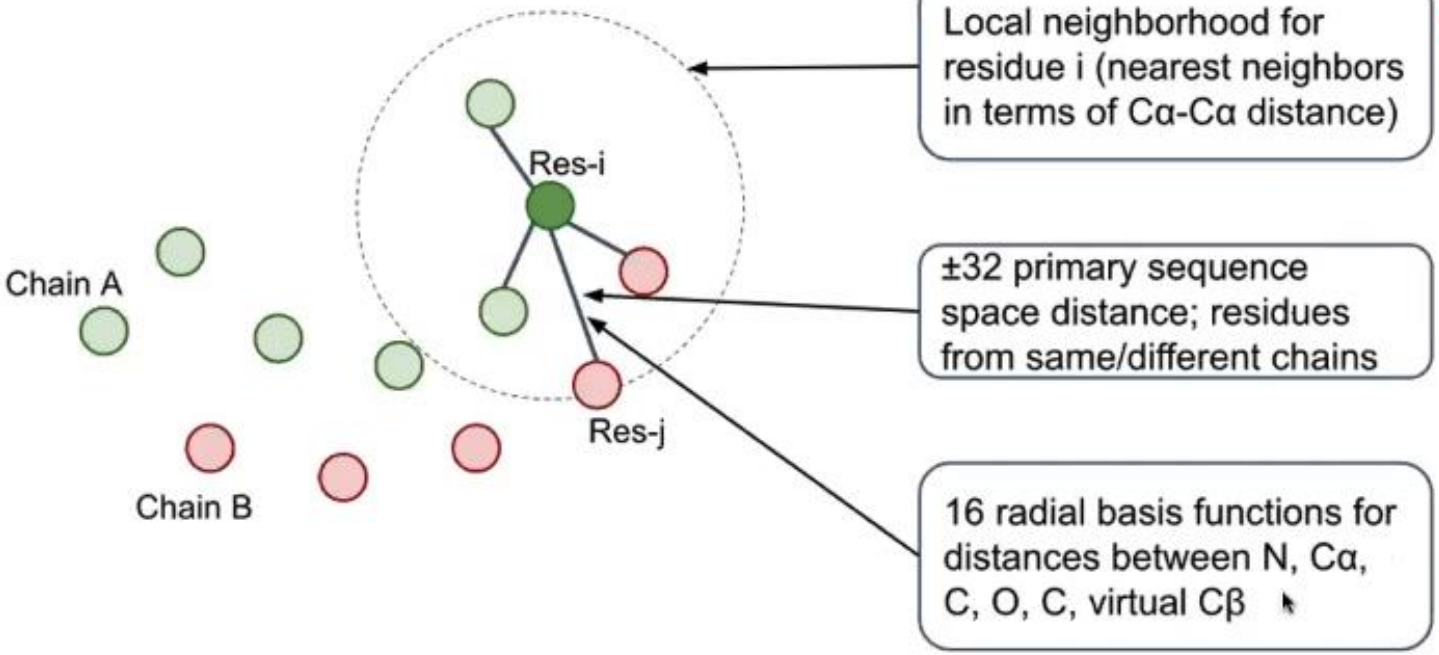


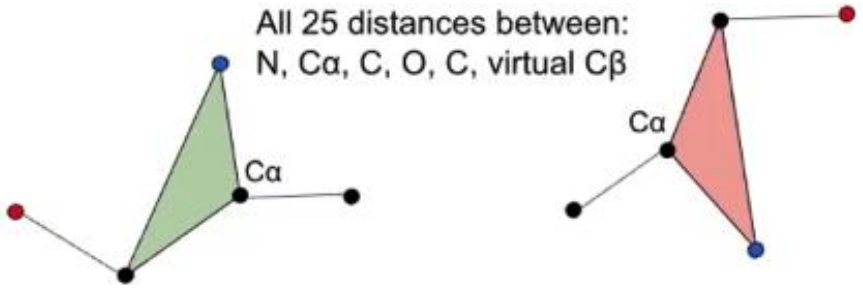
Background: Levels of Protein Structure

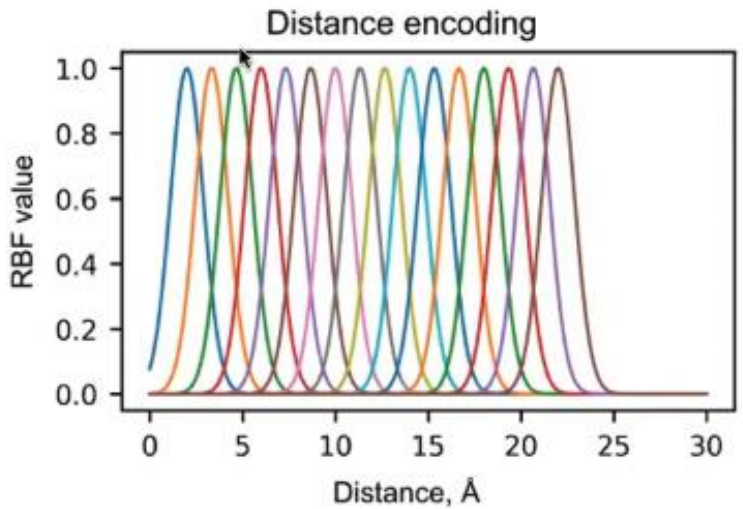


Input Featurization in ProteinMPNN

- Distance as edge features

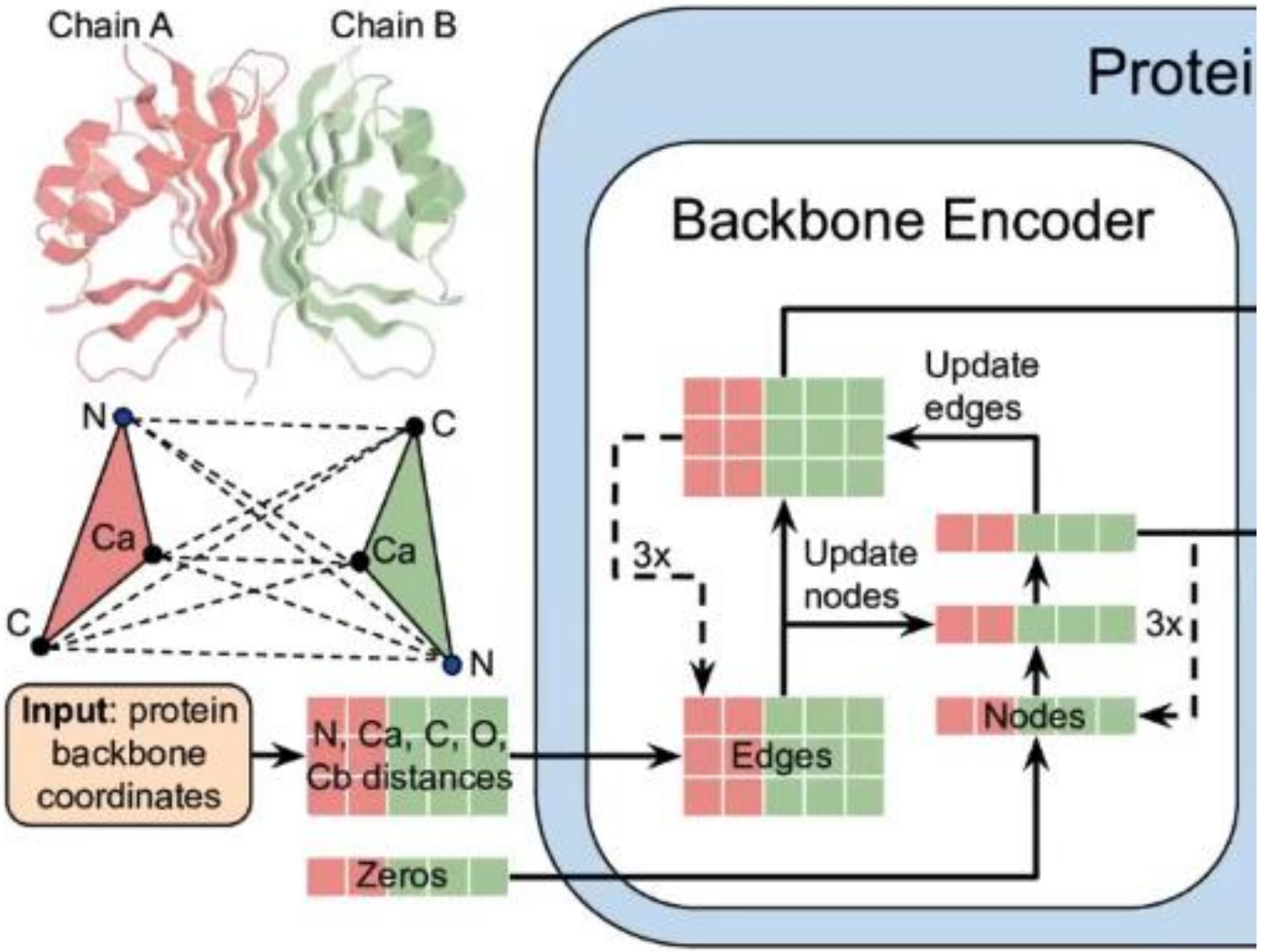






$$RBF(d; D_i) = \exp\left[-(d - D_i)^2/(2\sigma^2)\right]$$

Structure Encoder in ProteinMPNN



Pseudocode of ProteinMPNN **Encoder**

- 3-layer encoder -> 3-hop information

Pseudocode for the encoder layer (V - node features, E - edge features):

```
def encoder_layer_forward(V, E):
    M_ij = MLP[V_i, V_j, E_ij]
    dV_i = Sum_j [M_ij]
    V_i = LayerNorm[V_i + Dropout(dV_i)]
    dV_i = FeedForward[V_i]
    V_i = LayerNorm[V_i + Dropout(dV_i)]
    dE_ij = MLP[V_i, V_j, E_ij]
    E_ij = LayerNorm[E_ij + Dropout(dE_ij)]
    return V, E
```

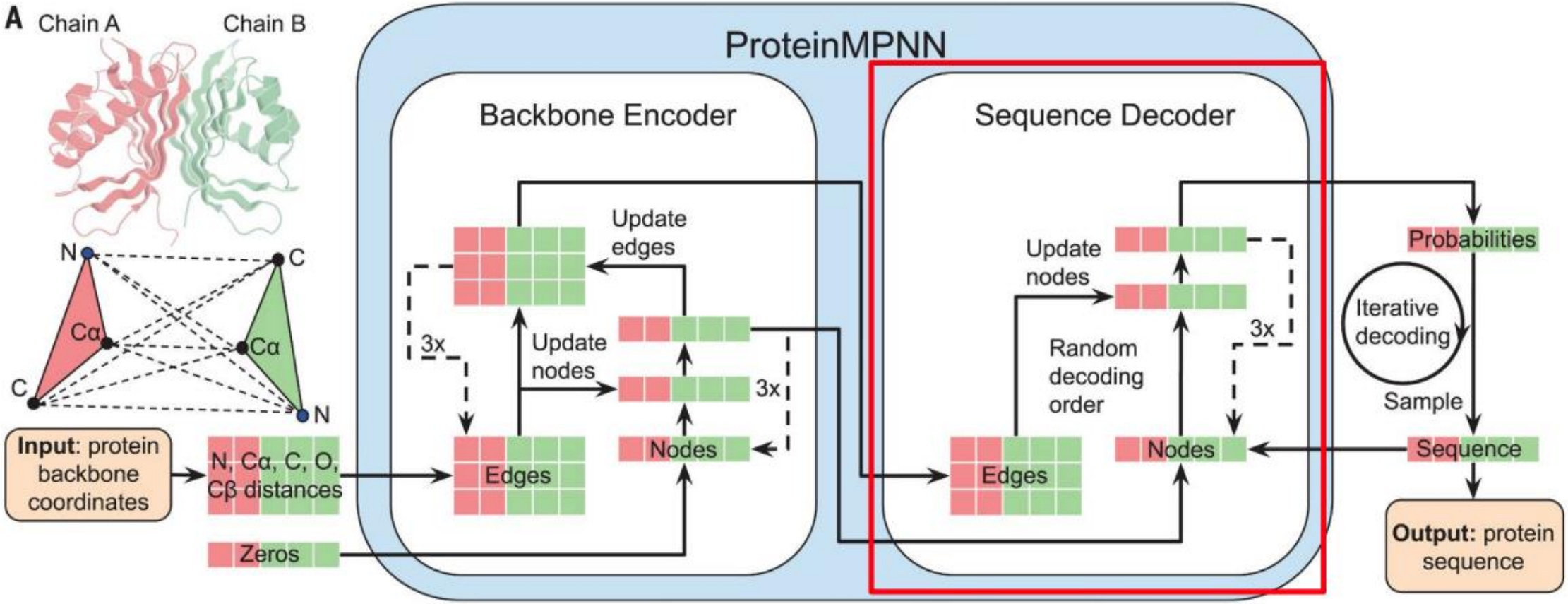
Get intermediate representation or “message” based on information of neighbors and edges for node i

Sum messages across all neighbors

Updates node representations

Updates edges representations based on new node representations

Autoregressive Decoder in ProteinMPNN



Pseudocode of ProteinMPNN **Decoder**

- 3-layer decoder -> additional 3-hop information

Pseudocode for the decoder layer (V - node features, E - edge features, S - sequence features, mask - autoregressive mask):

Use information about previous time step to predict at current step

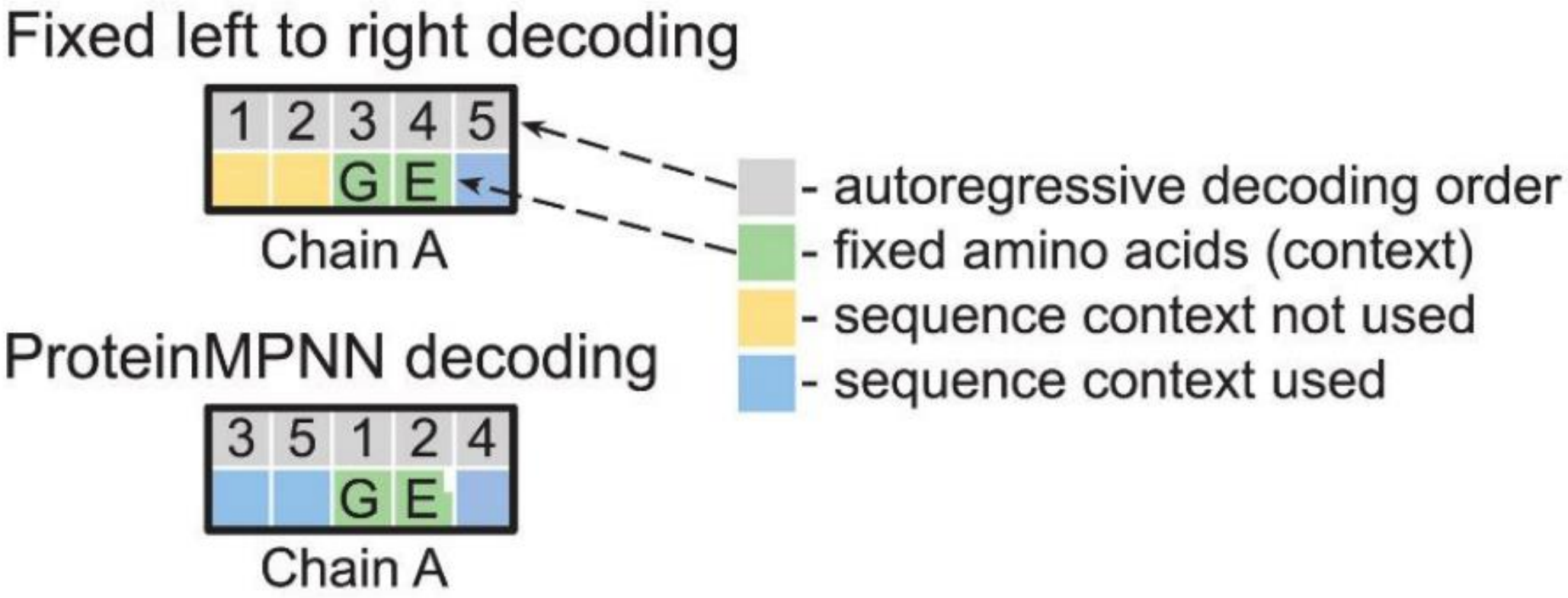
```
def decoder_layer_forward(V, E, S, mask):
    E_ij = Concat[E_ij, S_j] * mask_ij + Concat[E_ij, 0.0*S_j]  * (1-mask_ij)
    M_ij = MLP[V_i, V_j, E_ij]
    dV_i = Sum_j [M_ij]
    V_i = LayerNorm[V_i + Dropout(dV_i)]
    dV_i = FeedForward[V_i]
    V_i = LayerNorm[V_i + Dropout(dV_i)]
    return V
```

Add edge to sequence features together

Use encoded neighbor embeddings to update current embeddings

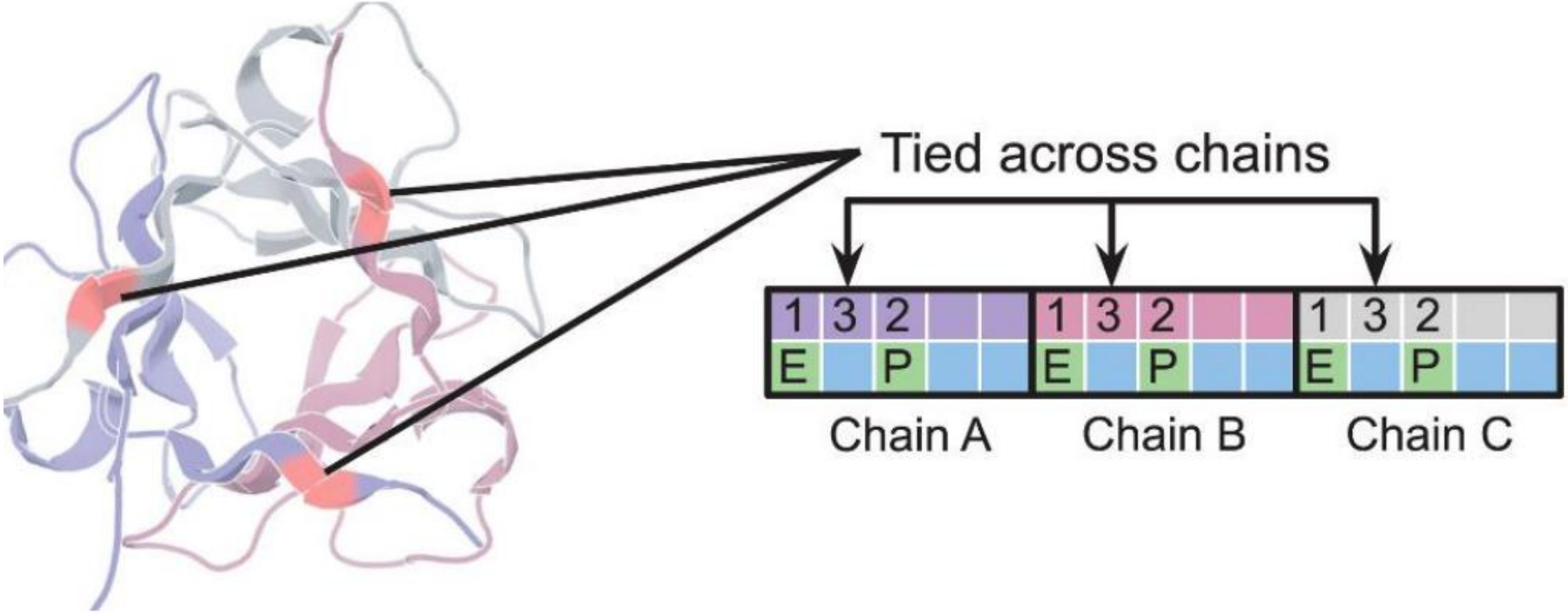
ProteinMPNN Uses Random Decoding Order

- Due to graph permutation equivariance
  - Recall in GraphRNN, BFS order could be better than random order

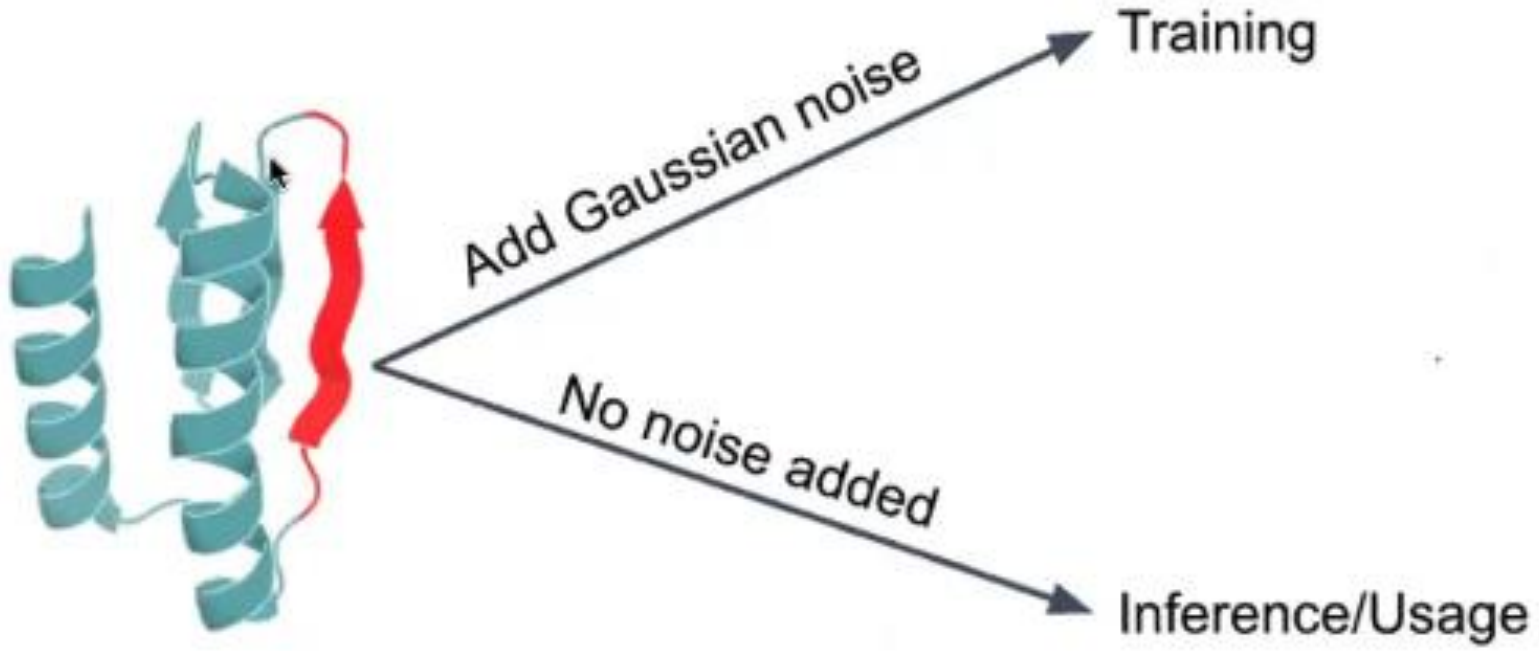


ProteinMPNN Uses Positional Coupling for Multichain Predictions

- Ensure certain residues have the same output



Add Noise to Backbone during Training



- Noise added to input edge features
  - Residue distances

How was ProteinMPNN Trained

- Data from PDB (X-ray or cryoEM)
- Random train/val/test split (23358/1464/1529)
  - Different chains from 1 protein must belong to the same split – no leakage
- Training
  - Pick a protein sequence
  - Given the sequence, pick a conformation (coordinates)
  - Loss: classification loss of the residual type
  - Metric: accuracy, runtime

ProteinMPNN Code

- **ProteinMPNN code**
- https://github.com/dauparas/ProteinMPNN/tree/main

- **Demo - Let's dive into the code!**
- https://github.com/dauparas/ProteinMPNN/blob/8907e6671bfbfc92303b5f79c4b5e6ce47cdef57/protein_mpnn_utils.py#L1019
- It's fun to learn that they implemented MPNN without PyG

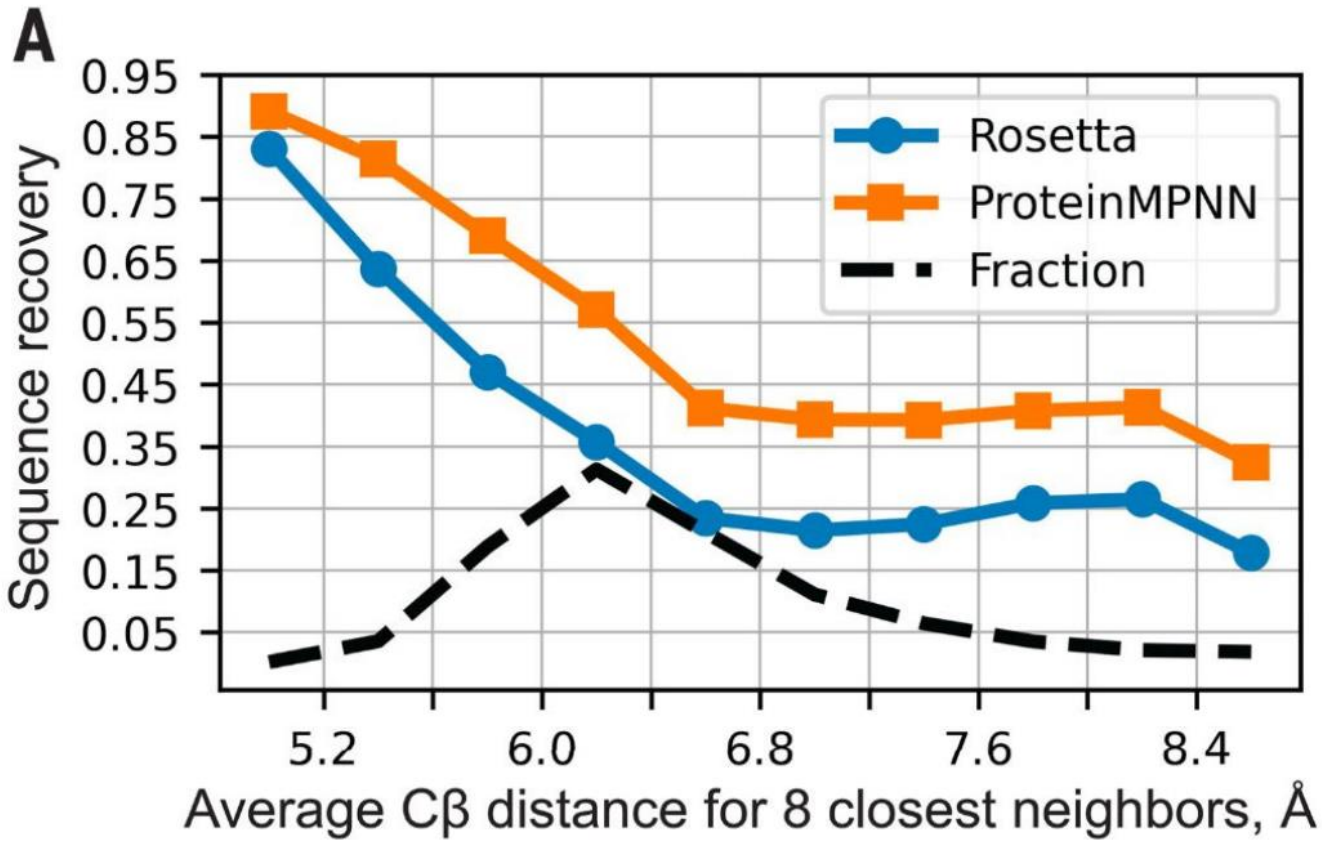
ProteinMPNN Results

- Adding distances as edge features are helpful

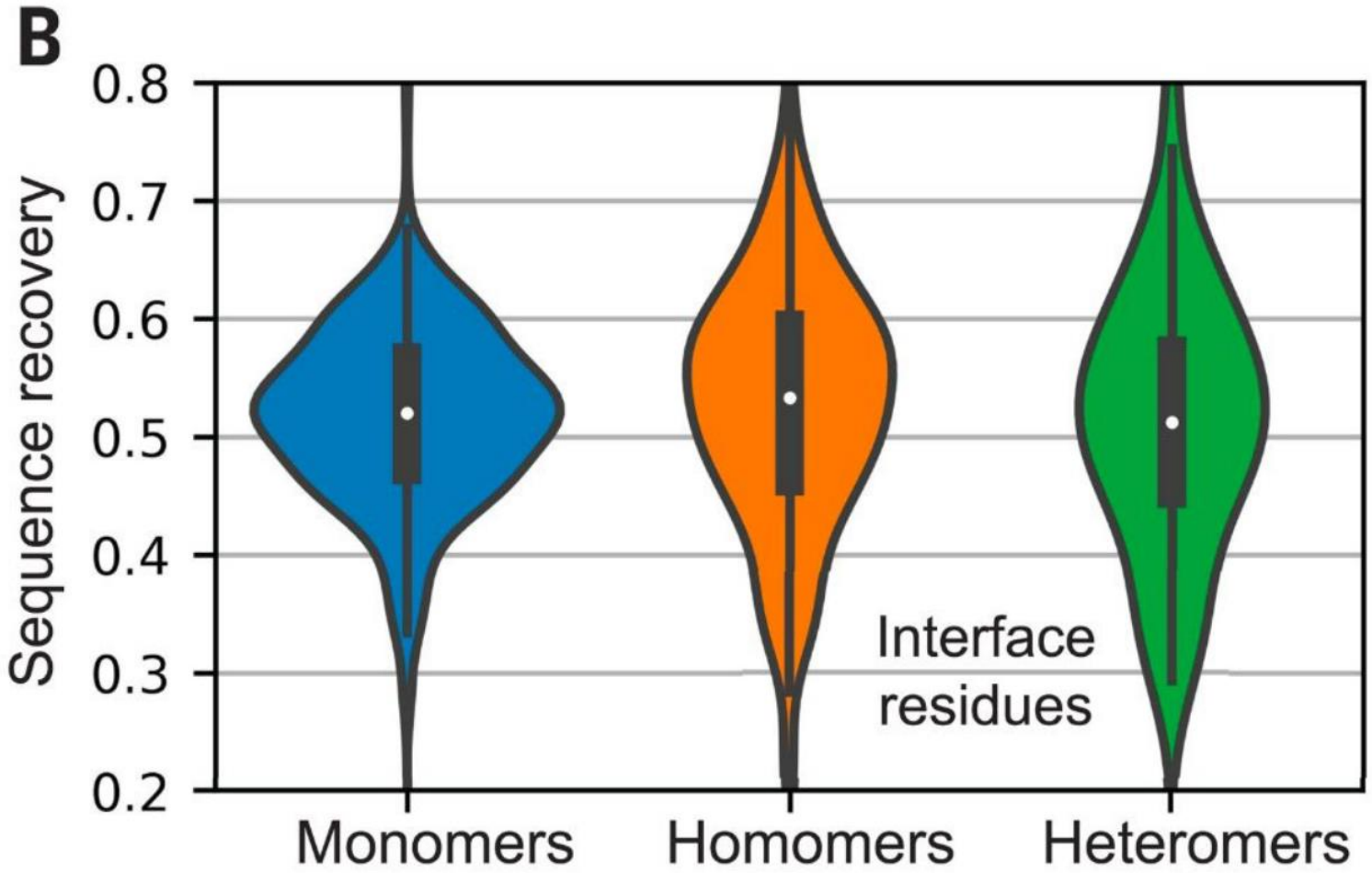
Ingraham et. al

Noise level when training: 0.00 Å/0.02 Å	Modification	Number of parameters in millions	PDB test accuracy (%)	PDB test perplexity	AlphaFold model accuracy (%)
Baseline model	None	1.381	41.2/40.1	6.51/6.77	41.4/41.4
Experiment 1	Add N, Cα, C, Cβ, O distances	1.430	49.0/46.1	5.03/5.54	45.7/47.4
Experiment 2	Update encoder edges	1.629	43.1/42.0	6.12/6.37	43.3/43.0
Experiment 3	Combine 1 and 2	1.678	50.5/47.3	4.82/5.36	46.3/47.9
Experiment 4	Experiment 3 with random decoding	1.678	50.8/47.9	4.74/5.25	46.9/48.5

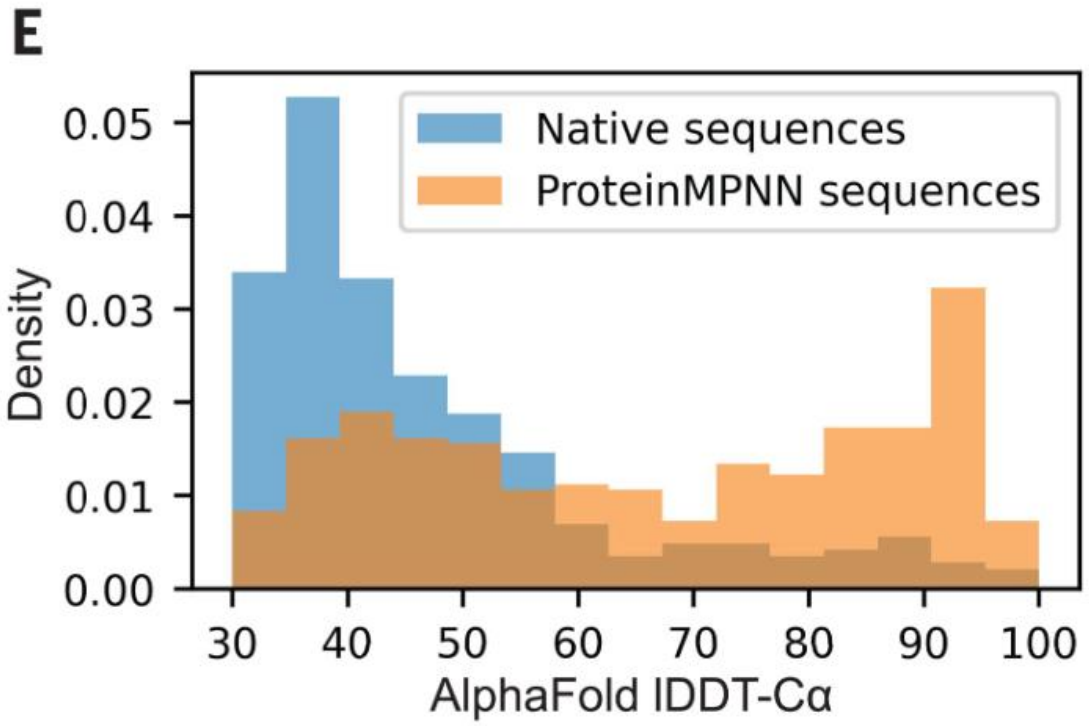
ProteinMPNN is Better than Classic Methods

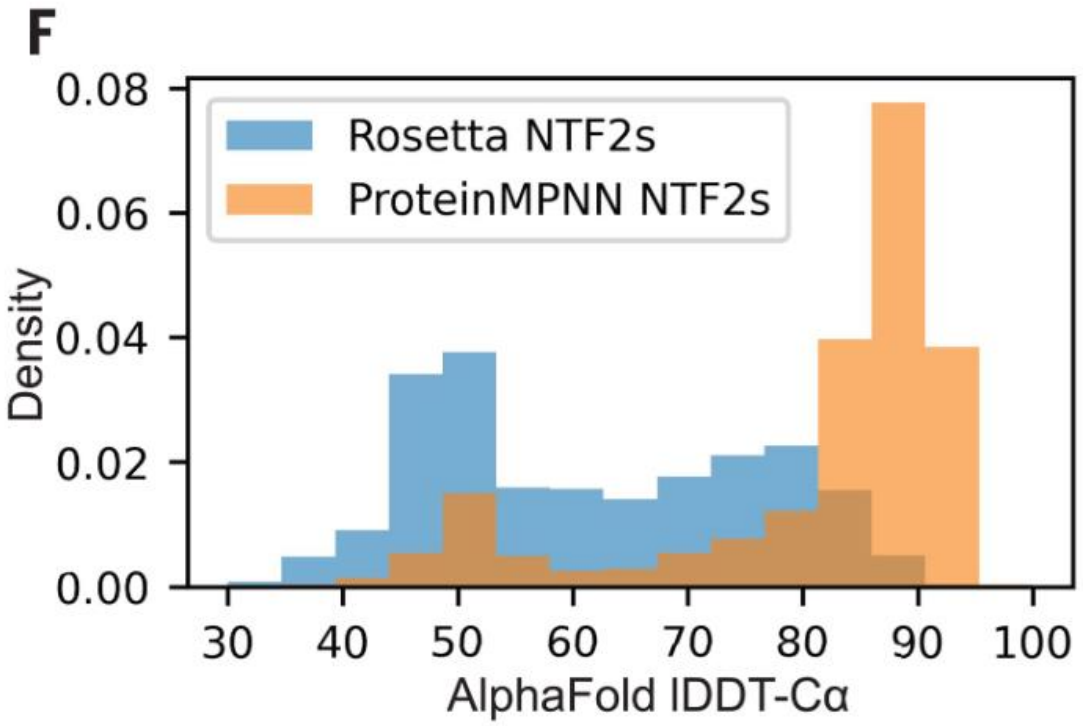


- **Sequence recovery**: 54.29% vs. 32.9%
- **Run time**: 1.2s vs. 258.8s (1 CPU for 100 residues)


B
Sequence recovery
0.8
0.7
0.6
0.5
0.4
0.3
0.2
Interface
residues
Monomers
Homomers
Heteromers

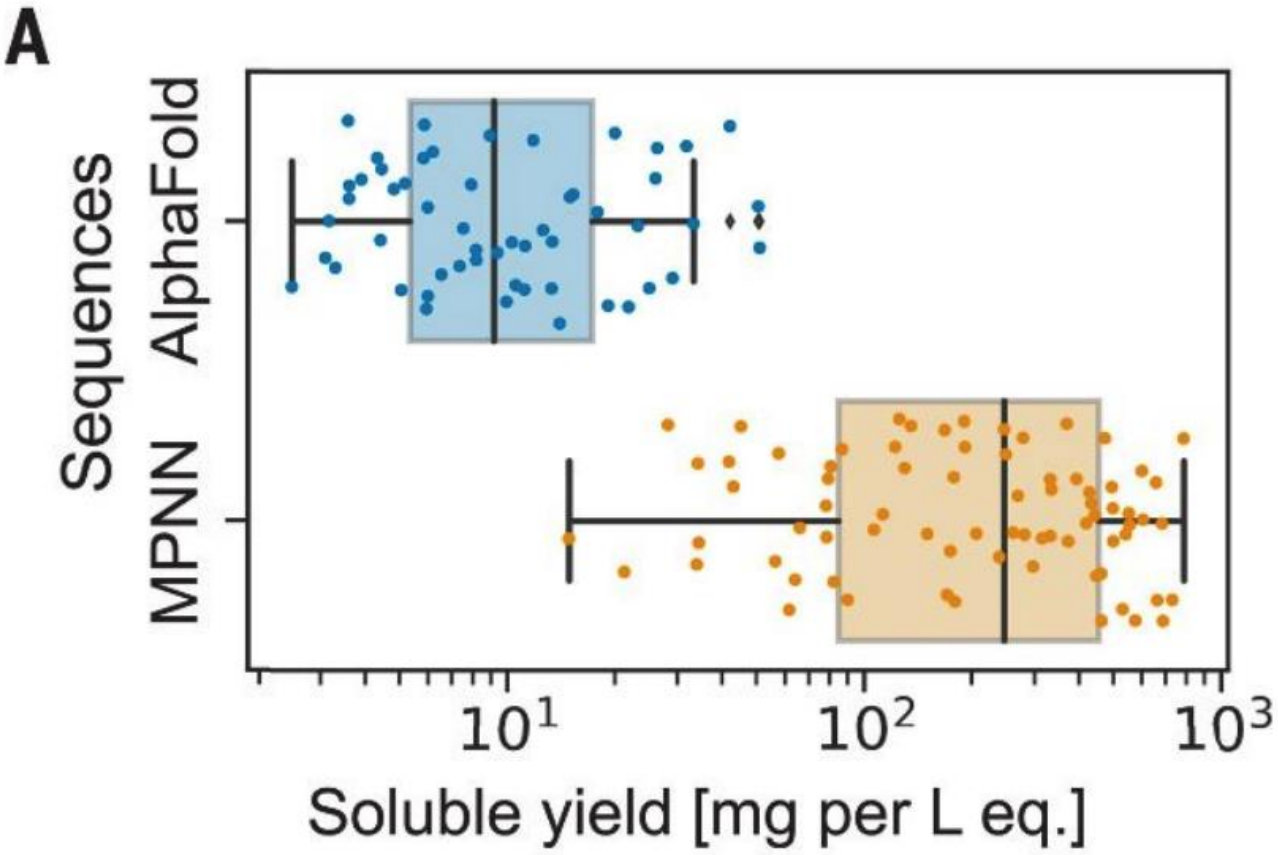
In Silico Evaluation of ProteinMPNN



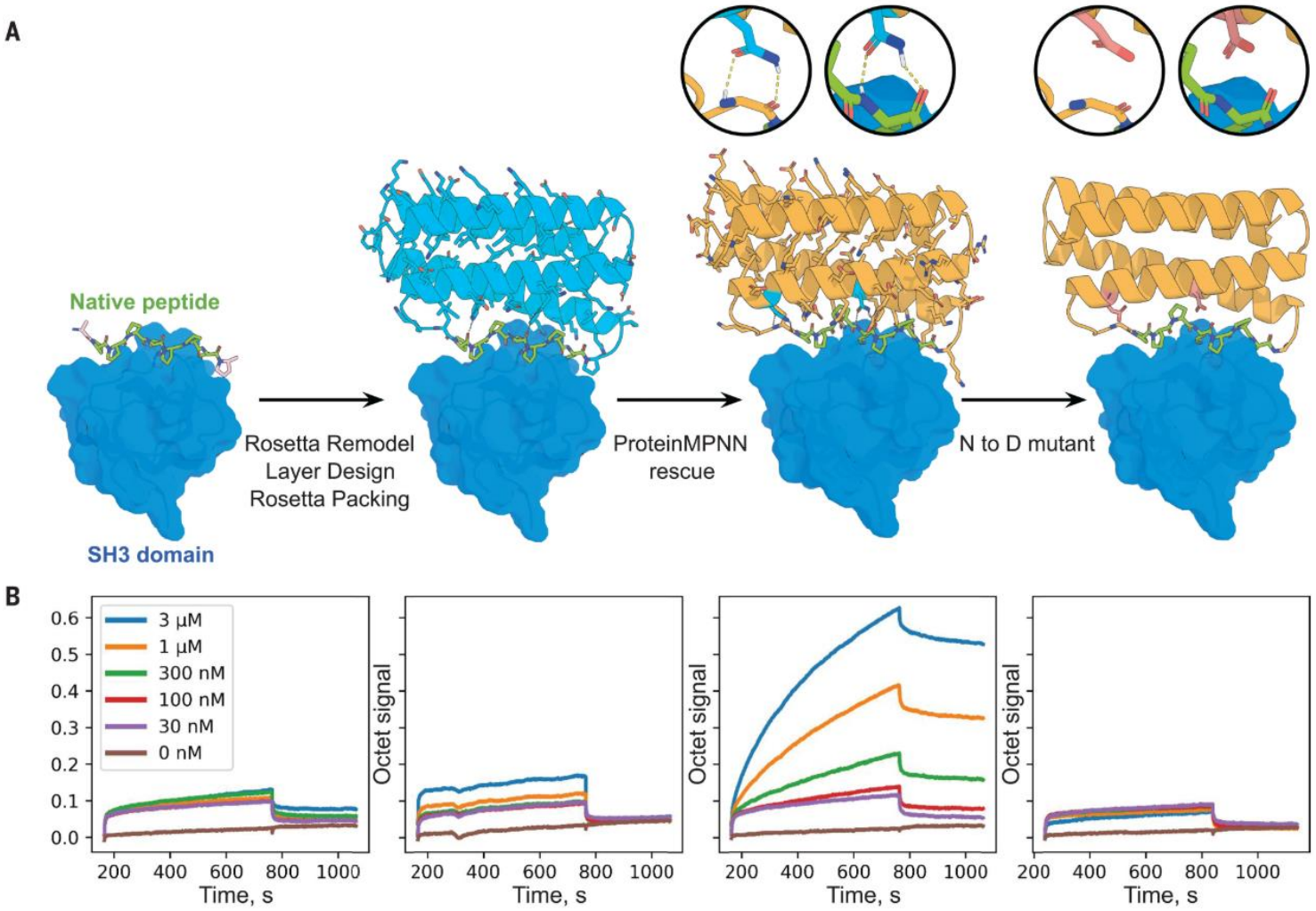


Experimental Validation of ProteinMPNN

1. Network hallucination by AlphaFold to produce backbone set
2. Monte Carlo to generate variety of AlphaFold sequences
3. ProteinMPNN to generate sequences
4. Express these proteins in E. coli



Rescure Failed Design with ProteinMPNN



Summary

- MPNN is effective in protein inverse folding task
  - Node distances as edge features
  - Node & edge embedding update after each layer
  - Encoder decoder design
- ProteinMPNN has yielded significant real-world impact
  - Used in combination with AlphaFold (folding) in protein design
  - Verified in real-world experiments
  - Dr. Baker & AlphaFold won Nobel Prize in Chemistry 2024 together