

# DualMPNN:

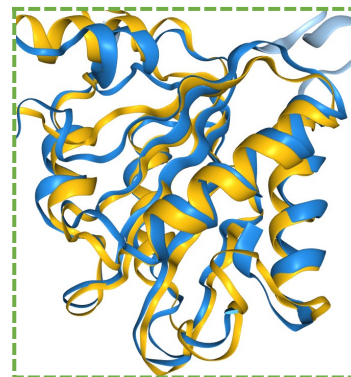
Harnessing Structural Alignments for High-Recovery Inverse Protein Folding

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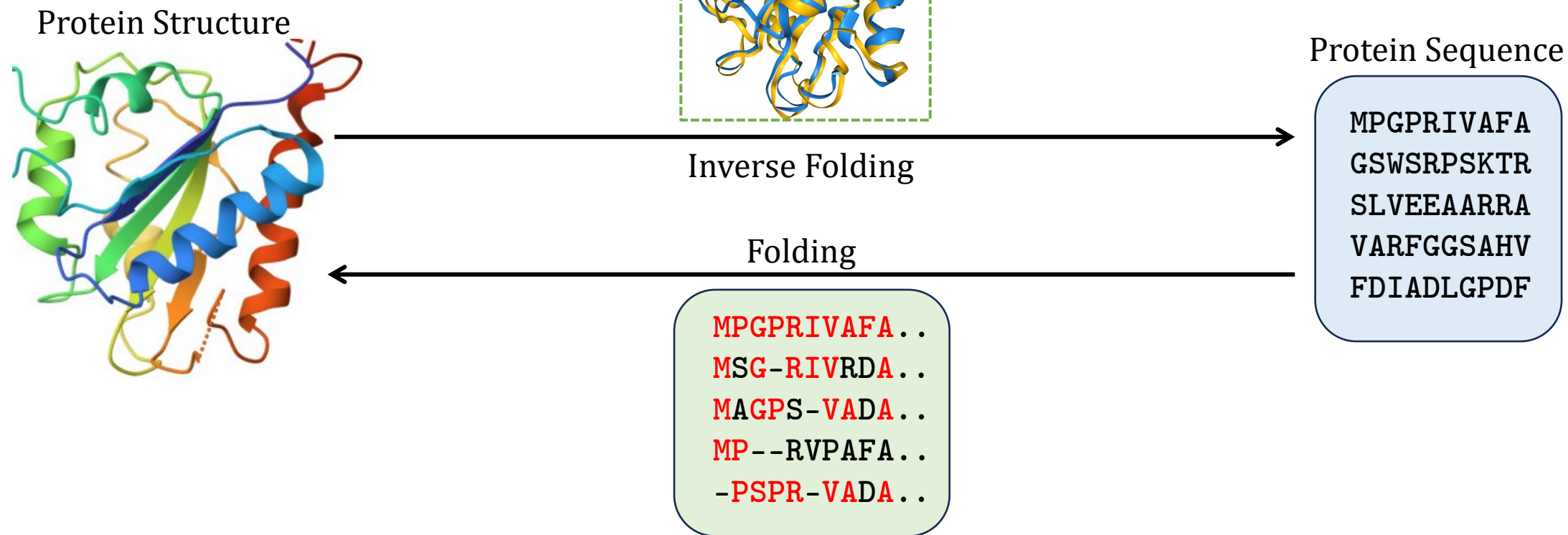
# Background Motivation:

Can we utilize **structure alignments** for inverse folding???

- ① The non-injective mapping
- ② The computational intractability
- ③ The plausibility of sequences



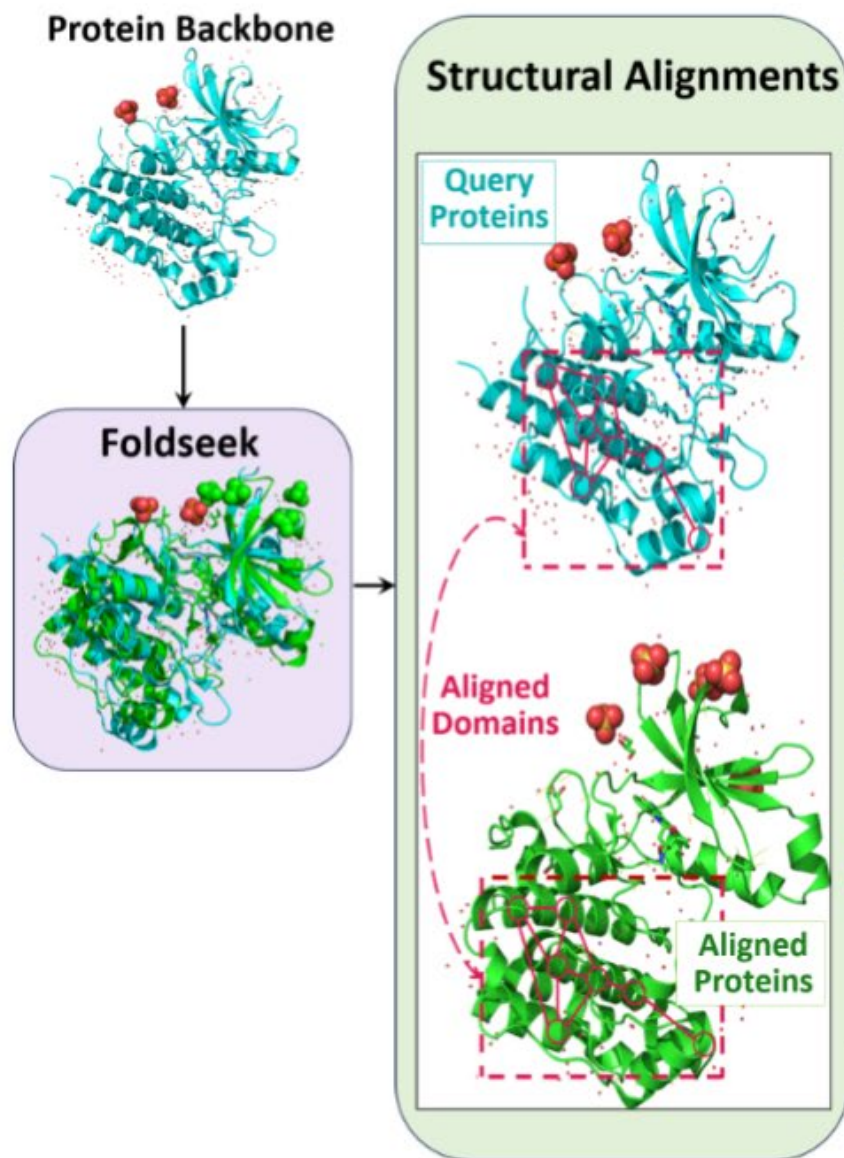
How to leverage  
structure alignments??



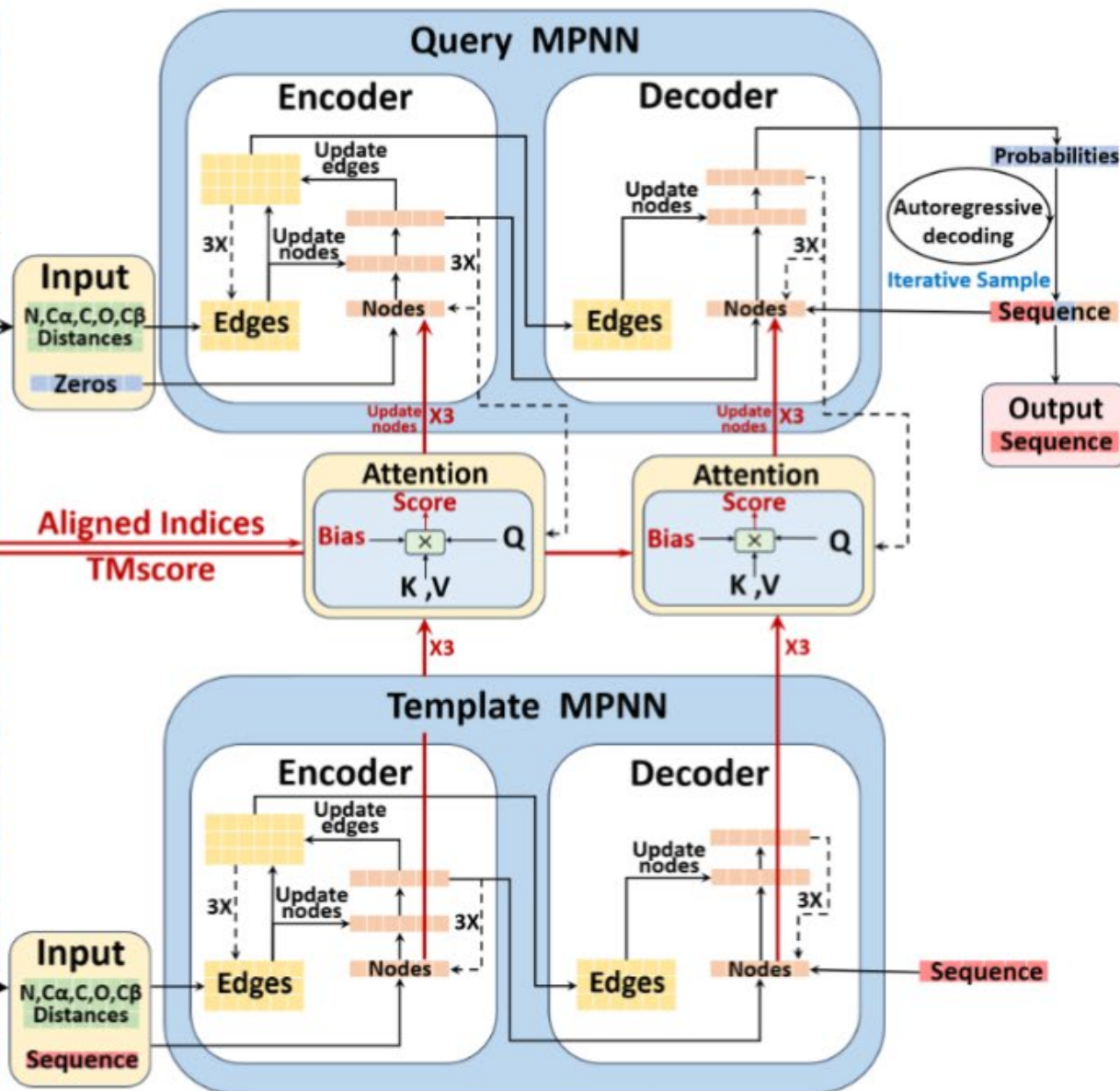
Utilize **sequence alignments** for protein folding  
(like AlphaFold and RosettaFold)

# Overview of DualMPNN

## A. Structure Alignments with Foldseek



## B. Dual-Stream Message Passing Neural Network



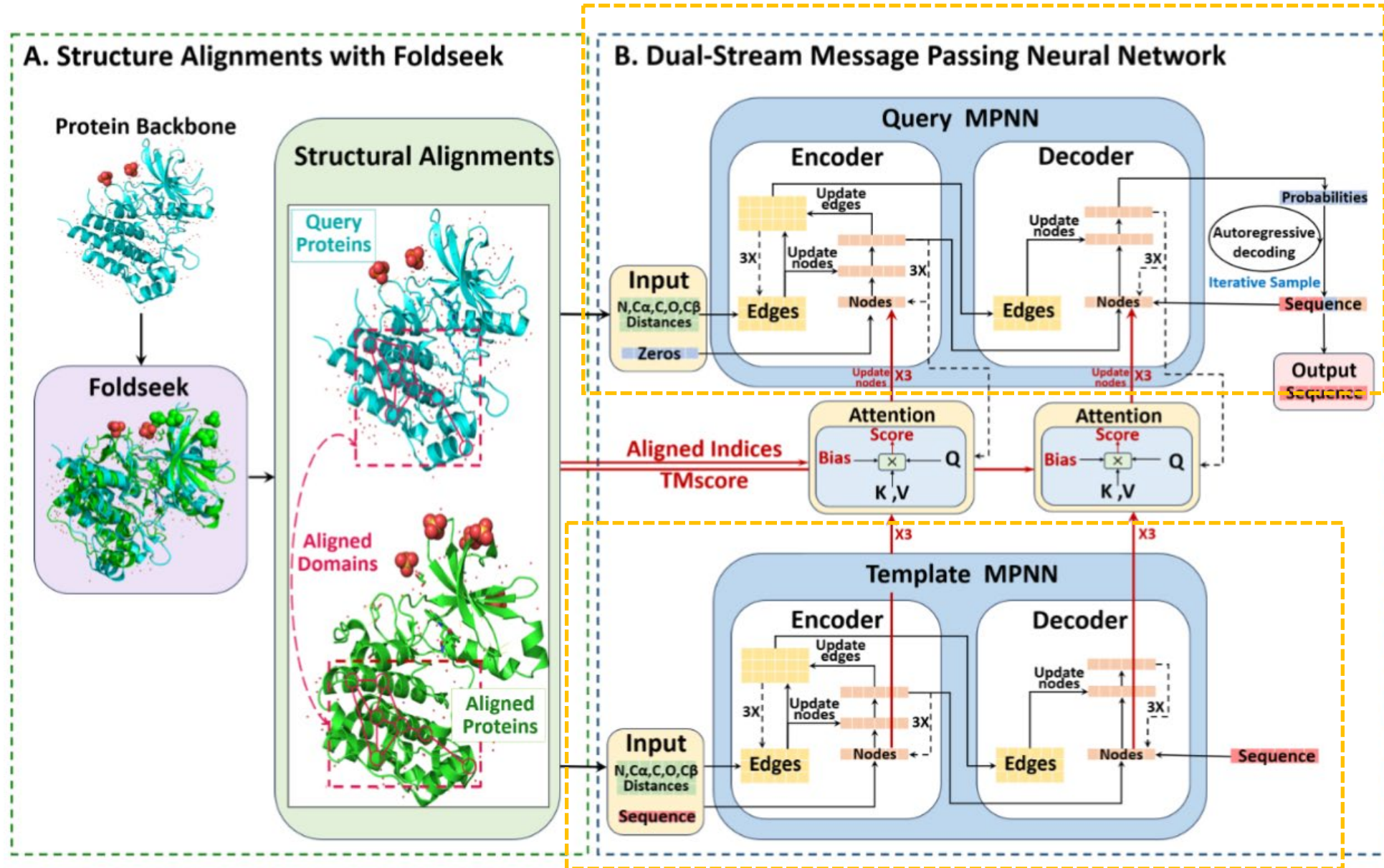




# Overview of DualMPNN

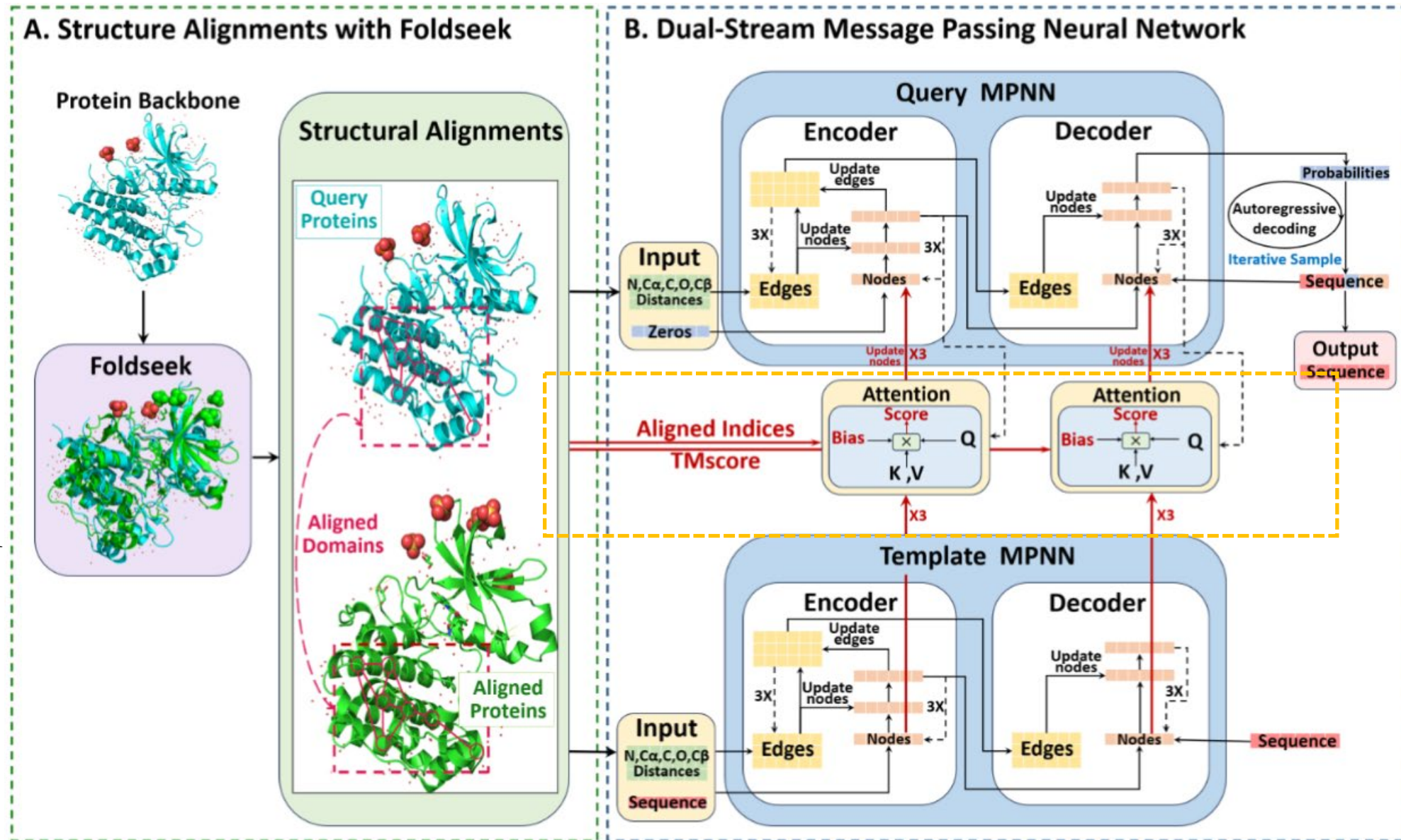
(1) **Query branch** processes geometric features from backbone atom coordinates to perform sequence recovery through inverse folding.

(2) **Template branch** leverages aligned template structures and sequences to guide the query branch's sequence recovery.



# Overview of DualMPNN

DualMPNN employs a cross-modal attention layer to enable information exchange between the query and template branches. The interaction leverages structural alignment-guided attention to fuse query and template features.





DualMPNN achieves state-of-the-art performance across all metrics, demonstrating superior sequence recovery capabilities and lower perplexity scores.

Table 1: Comparison of recovery rate and perplexity performance on **CATH**, **TS50**, and **T500**. Models marked with † use CATH v4.3, the rest use CATH v4.2. **PPL** denotes perplexity, **Rec.** denotes recovery rate.

Models	CATH						TS50		T500	
	PPL ↓			Rec. % ↑			PPL ↓	Rec.% ↑	PPL ↓	Rec.% ↑
	Short	Single	All	Short	Single	All				
STRUCTGNN [15]	8.29	8.74	6.40	29.44	28.26	35.91	5.40	43.89	4.98	45.69
GRAPHTRANS [15]	8.39	8.83	6.63	28.14	28.46	35.82	5.60	42.20	5.16	44.66
GCA [28]	7.09	7.49	6.05	32.62	31.10	37.64	5.09	47.02	4.72	47.74
GVP [17]	7.23	7.84	5.36	30.60	28.95	39.47	4.71	44.14	4.20	49.14
GVP-LARGE [11] †	7.68	6.12	6.17	32.60	39.40	39.20	—	—	—	—
ALPHADESIGN [29]	7.32	7.63	6.30	34.16	32.66	41.31	5.25	48.36	4.93	49.23
ESM-IF1 [11] †	8.18	6.33	6.44	31.30	38.50	38.30	—	—	—	—
PROTEINMPNN [9]	6.21	6.68	4.57	36.35	34.43	49.87	3.93	54.43	3.53	58.08
PIFOLD [30]	6.04	6.31	4.55	39.84	38.53	51.66	3.86	58.72	3.44	60.42
GRADE-IF [10]	5.49	6.21	4.35	45.27	42.77	52.21	3.71	56.32	3.23	61.22
<b>DualMPNN</b>	<b>4.42</b>	<b>5.04</b>	<b>3.18</b>	<b>55.97</b>	<b>52.41</b>	<b>65.51</b>	<b>2.76</b>	<b>70.99</b>	<b>2.71</b>	<b>70.37</b>

Template quality plays an important role in DualMPNN. When TM-score between query and template is higher than 0.5, DualMPNN gains more than 10% recovery improvement.

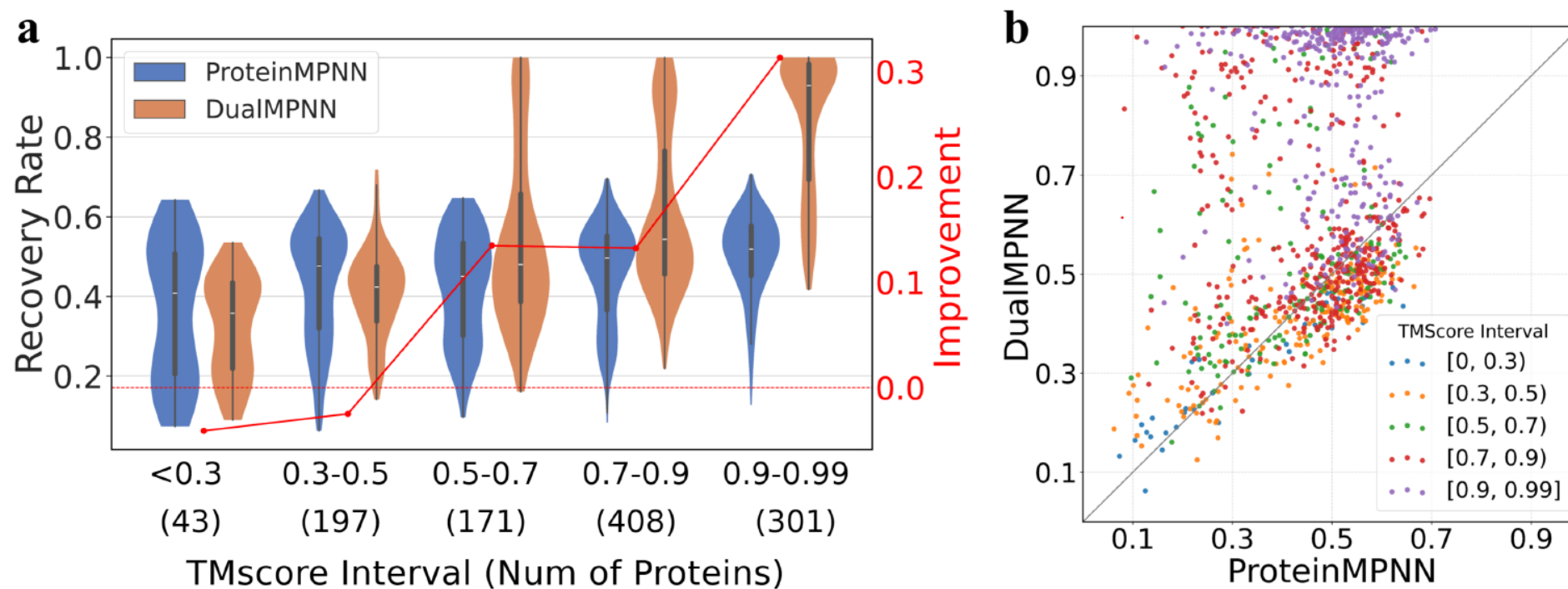


Figure 2: Impact of template quality on sequence recovery rate. (a) Violin plot comparing sequence recovery rates of DualMPNN and ProteinMPNN across distinct TM-score intervals on the CATH test set. (b) Scatter plot of per-protein recovery rates, colored by TM-score intervals. Points above the dashed parity line ( $y = x$ ) highlight instances where DualMPNN outperforms the baseline, particularly for high-quality templates (TM-score > 0.5).

## Ablation study

Configuration		PPL ↓			Rec. % ↑		
		Short	Single-chain	All	Short	Single-chain	All
<b>A</b>	Baseline Model	6.21	6.68	4.57	36.35	34.43	49.87
<b>B</b>	<b>A</b> + Node init by template	5.35	5.83	3.55	50.85	47.03	61.29
<b>C</b>	<b>B</b> + Dual-stream update	4.82	5.54	3.48	53.78	50.23	62.13
<b>D</b>	<b>C</b> + Interactive attention update	4.57	5.23	3.29	54.95	51.11	64.78
<b>E</b>	<b>D</b> + TM score bias	4.46	5.09	3.20	55.74	52.19	65.35
<b>F</b>	<b>E</b> + Sample 10 times	4.42	5.04	3.18	55.97	52.41	65.52



## Foldability

Table 4: Foldability comparison between generated structures and the native structures. The methods with † are generated by Alphafold3 and the rest using Alphafold2.

Method	Success $\uparrow$	TM score $\uparrow$	avg pLDDT $\uparrow$	avg RMSD $\downarrow$
PiFOLD	85	$0.80 \pm 0.22$	$0.84 \pm 0.15$	$1.67 \pm 0.99$
ProteinMPNN	94	$0.86 \pm 0.16$	$0.89 \pm 0.10$	<b><math>1.36 \pm 0.81</math></b>
GRaDe-IF	94	$0.86 \pm 0.17$	$0.86 \pm 0.08$	$1.47 \pm 0.82$
DualMPNN	94	$0.86 \pm 0.16$	$0.91 \pm 0.10$	$1.49 \pm 0.86$
ProteinMPNN †	94	$0.86 \pm 0.18$	$0.88 \pm 0.12$	$1.41 \pm 0.76$
DualMPNN †	<b>95</b>	<b><math>0.87 \pm 0.16</math></b>	<b><math>0.92 \pm 0.11</math></b>	$1.39 \pm 0.80$



The contributions of our work are summarized as:

- (1) **Dual-stream architecture for structural priors.** We proposed the first framework to explicitly integrate structural alignments-derived templates into inverse protein folding via dual-stream framework.
- (2) **Impact of template quality.** We systematically quantify how template selection impacts sequence recovery, establishing guidelines for optimal structural alignment utilization in protein design.
- (3) **State-of-the-art performance.** DualMPNN achieved state-of-the-art in sequence recovery rates, outperforming the base model ProteinMPNN by at least 12%.



# Thank you