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MSAGPT: Neural Prompting Protein Structure Prediction via MSA Generative Pre-Training

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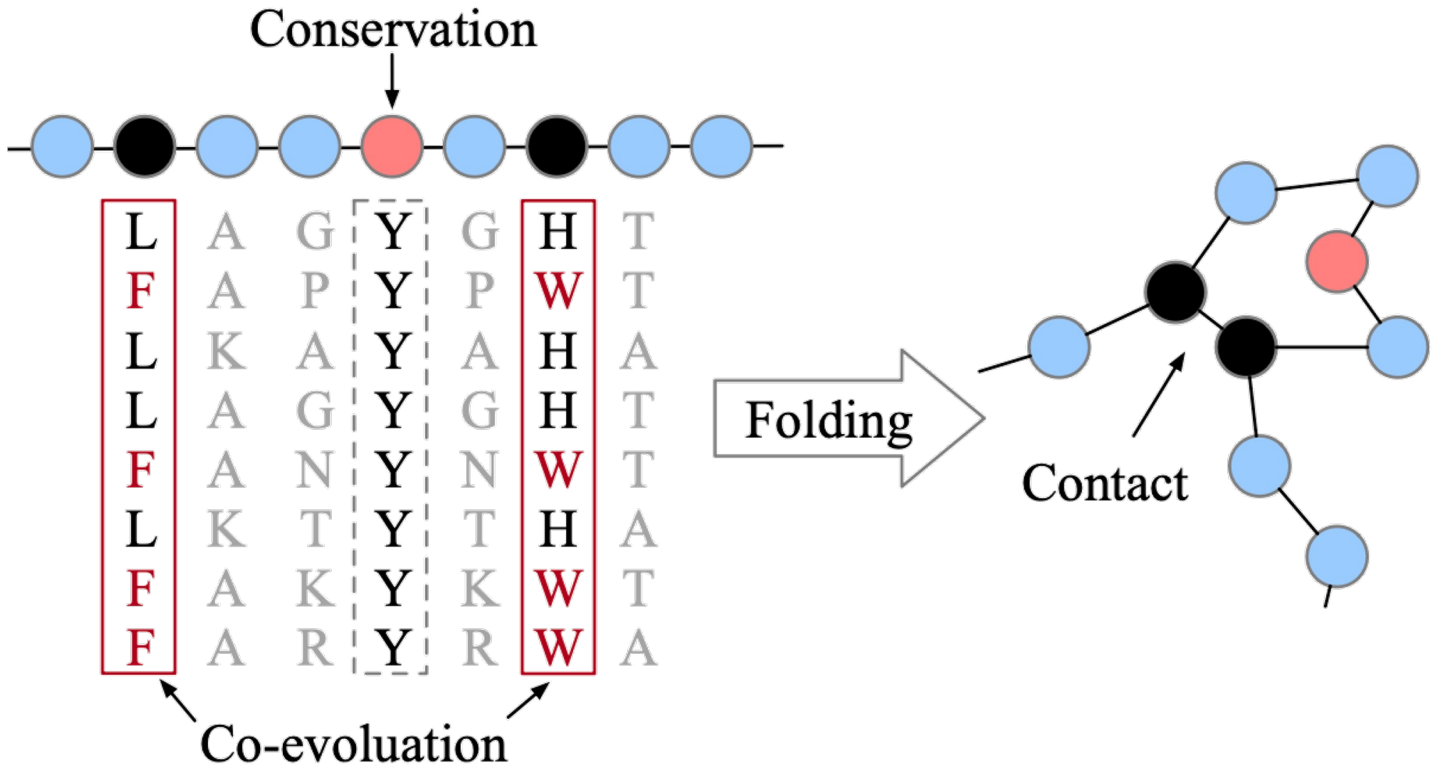
https://github.com/THUDM/MSAGPT

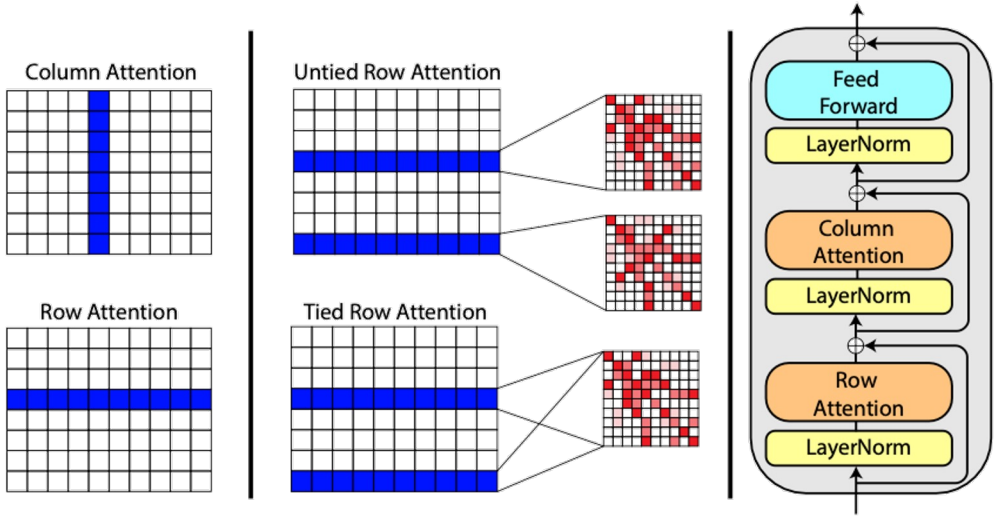
Multiple sequence alignment (MSA) facilitates protein structure prediction (PSP)

- Current PSP models **rely on MSA** for high accuracy
  - AlphaFold
  - RoseTTAFold
- "**Orphan**": 1/5 of all metagenomic proteins & 11% of eukaryotic proteins **lack sequence homologs**, compromising PSP accuracy

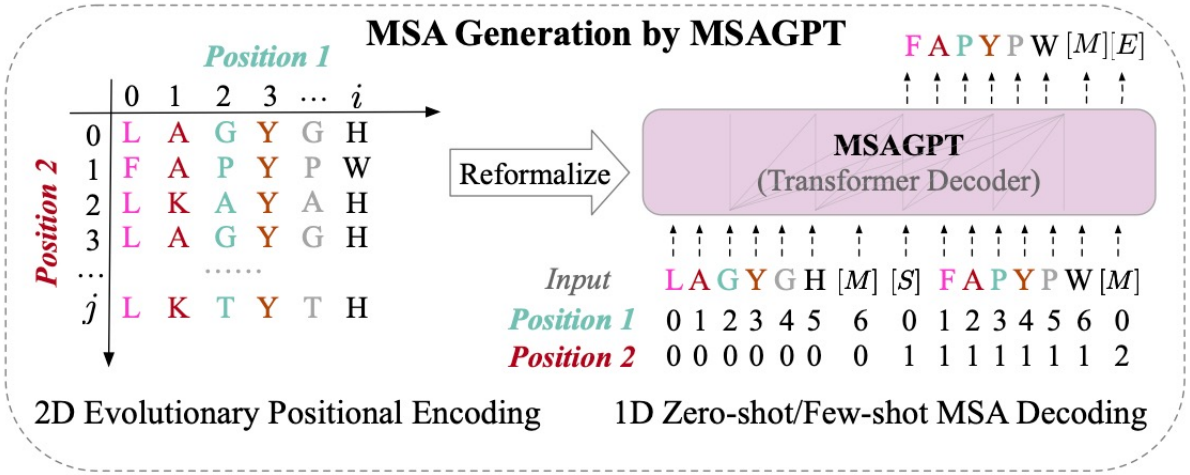


A simple yet effective decoding framework

- Previous MSA-based PLMs usually adopt **Axial Attention**
  - Constrained information fusion: Only allow row- or column-wise
  - Low Efficiency： Sequential attention in a transformer block
- We propose the **2D Evolutionary Position Encoding**
  - To relax the co-evolutionary information modeling from constrained attention flows to the 2D positional encoding
  - Re-formalizes MSA generation as a 1D sequence generation task, enables MSAGPT to conduct zero- or few-shot MSA generation under a flexible in-context learning framework



MSA Transformer (Axial Attention)



MSAGPT (Full Attention with 2D Evolutionary Positional Encoding)

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Generate virtual MSA to solve the problem

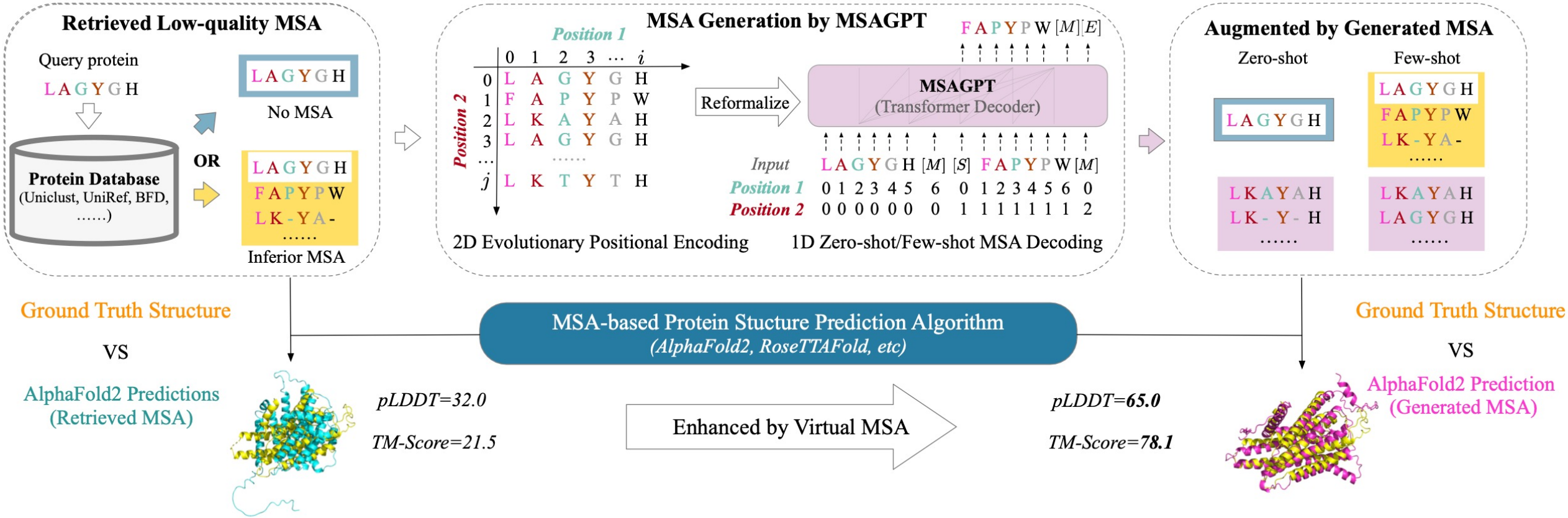
Low quality retrieved MSA
Low structural prediction accuracy

→

Enhanced by MSAGPT-generated virtual MSA

→

High quality augmented MSA
High structural prediction accuracy



Learning from AlphaFold2 feedback

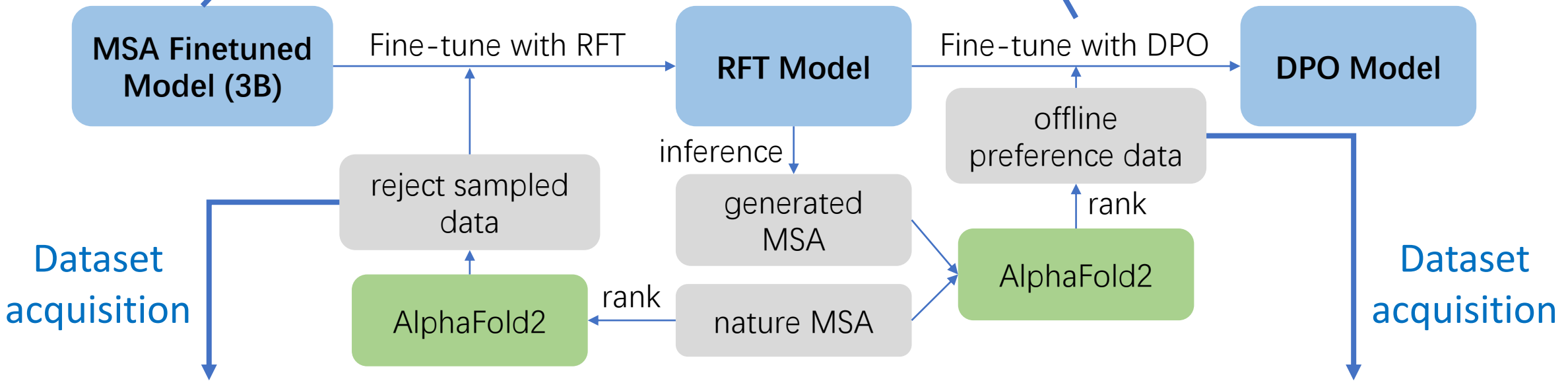
Post-training to alleviate the hallucination scene of MSA generation

- RFT stage: First fine-tune the model using high-quality natural MSA
- DPO stage: Then Use AlphaFold2 as a reward model and further fine-tune based on its feedback

$$L_{\text{ce}} = \mathbb{E}_{\mathbf{M}^f}\left[\sum_{i=0}^{N\times L} -\log p(\mathbf{M}_i^f|\mathbf{M}_{<i}^f,\theta)\right] \quad L_{\text{DPO}} = \mathbb{E}_{(Q,m_{\text{w}},m_{\text{l}})\in\mathcal{D}_{\text{DPO}}}\left[-\log\sigma\left(\beta\log\frac{\pi_\theta(m_{\text{w}}|Q)}{\pi_{\text{ref}}(m_{\text{w}}|Q)} - \beta\log\frac{\pi_\theta(m_{\text{l}}|Q)}{\pi_{\text{ref}}(m_{\text{l}}|Q)}\right)\right]$$

Loss calculation

Loss calculation



$$\mathcal{D}_{\text{RFT}} = \{(Q,m_i)|(\mathbb{I}_{acc}(Q,m_i)) > \theta_1 \cap (\mathbb{I}_{acc}(Q,m_i) - \mathbb{I}_{acc}(Q,-)) > \theta_2\} \quad \mathcal{D}_{\text{DPO}} = \{(Q,m_{\text{w}},m_{\text{l}})|\,(\mathbb{I}_{acc}(Q,m_{\text{w}}) - \mathbb{I}_{acc}(Q,m_{\text{l}})) > \theta_3\}$$

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Experimental Result

- Protein Structure Prediction in low-MSA cases
  - **Natural** MSA-scarce benchmark: low retrieved MSA (<20) from uniclust30
    - **Zero-shot**: only use the generated MSA
    - **Few-shot**: Retrieved low-quality MSA + generated MSA

	Model	CAMEO (avg. Depth = 8.5)				CASP (avg. Depth = 4.6)				PDB (avg. Depth = 2.6)			
		Zero-Shot		Few-Shot		Zero-Shot		Few-Shot		Zero-Shot		Few-Shot	
		pLDDT	TM	pLDDT	TM	pLDDT	TM	pLDDT	TM	pLDDT	TM	pLDDT	TM
	AF2 MSA	63.8	55.4	77.4	71.4	44.0	32.6	54.2	44.1	55.2	45.6	61.0	52.3
	MSA-Aug.	67.7	59.2	77.4	72.1	56.8	36.6	63.4	46.3	61.9	49.8	66.0	55.3
	EvoGen	66.1	60.3	78.6	75.3	48.2	38.4	55.1	48.5	57.6	49.5	62.8	55.4
w/ virtual MSA	MSAGPT	**70.8**	61.4	**80.8**	75.2	**59.0**	39.8	**65.4**	51.0	**68.6**	53.4	**71.3**	59.6
	+ **RFT**	68.0	60.5	79.8	76.4	56.8	40.2	64.0	53.6	66.8	53.4	70.3	**60.1**
	+ **DPO**	68.9	**62.7**	80.2	**76.7**	54.2	**43.7**	62.7	**57.0**	64.5	**53.6**	68.0	59.7
		(+3.1)	(+2.4)	(+2.2)	(+1.4)	(+2.2)	(+5.3)	(+2.0)	(+8.5)	(+6.7)	(+3.8)	(+5.3)	(+4.7)

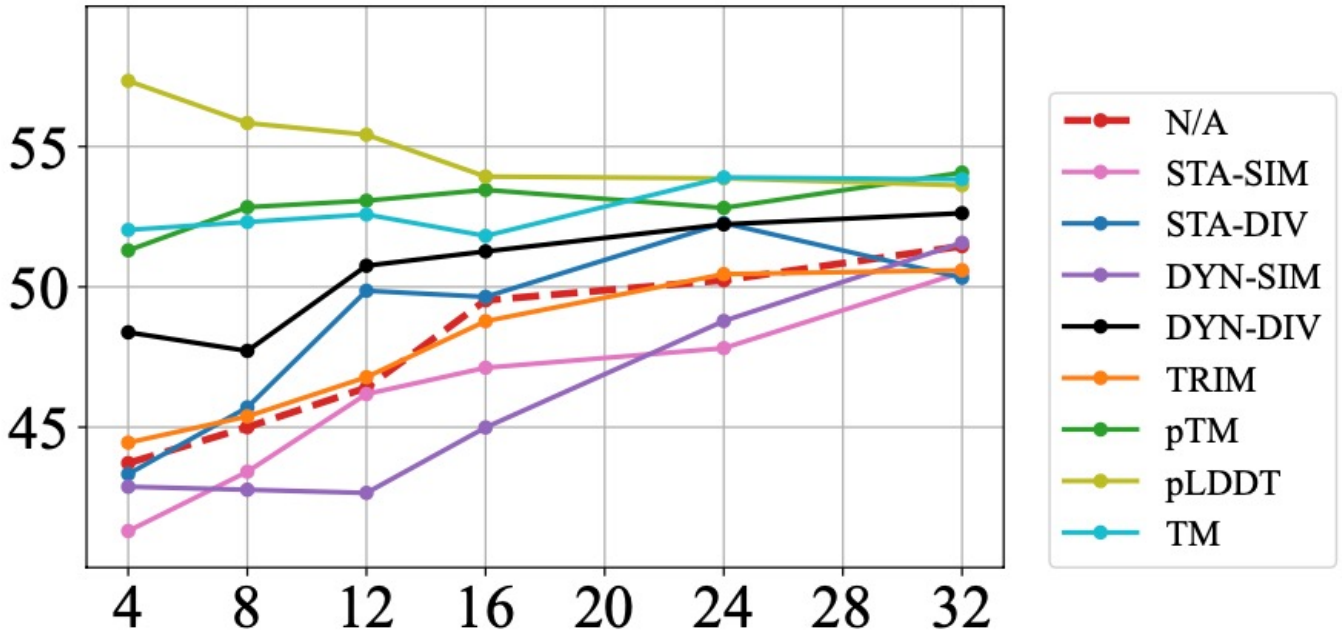
The post-training process significantly reduced hallucinations (Low Predictive metric) generated by the model and improved its performance (High Golden Metric).

Rethinking the MSA Selection Strategy

MSA Selection Criteria

- **1D Sequence** Diversity Measure
- **3D Structure** Validity Measure

Model	CAMEO	CASP	PDB
	TM	TM	TM
MSAGPT-DPO	76.7	57.0	59.7
+ **pLDDT Selection**	**77.5**	**57.6**	**60.5**



Sequence Diversity + Structure Validity → Informative MSA

Transfer Learning on Other Tasks

- Fine-tune MSA Transformer & task-specific head w/ or w/o virtual MSA generated by DPO model:

	Protein Structure		Protein Function	
Model	**CtP**	**SsP**	**LocP**	**MIB**
	ACC	ACC	ACC	ACC
w/o Virtual MSA	11.6	66.5	**58.3**	57.5
w/ Virtual MSA	**13.1**	**69.0**	56.4	**60.3**

Incorporating MSA from MSAGPT > Using single sequence only

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TL;DR:

Employing a 2D evolutionary positional encoding scheme
and learning from AlphaFold2 Feedback,
MSAGPT generates constructive virtual MSA
to enable accurate protein structure predictions
in situations where natural co-evolutionary information is scarce

Code Repo: https://github.com/THUDM/MSAGPT