Graph Denoising Diffusion for Inverse Protein Folding

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Outline

- Introduction
- Protein Graph Representation & Inverse Folding
- Graph Denoising Diffusion for Inverse Protein Folding (GraDe-IF)
- Experiment & Evaluation

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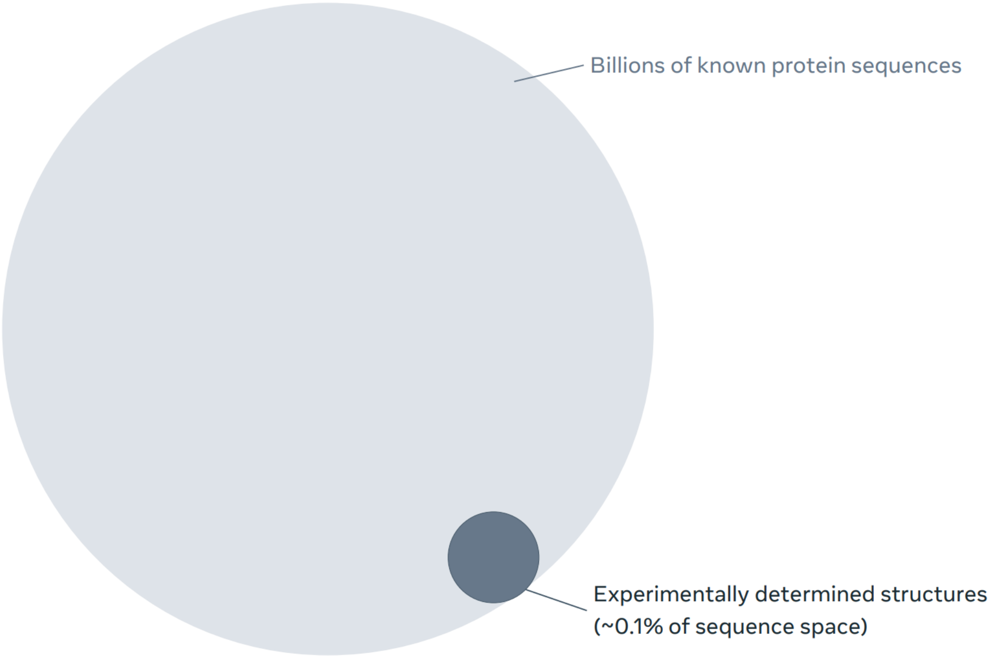
Introduction

www.nature.com/nmeth / January 2022 Vol.19 No. 1
nature methods
Method of the Year 2021:
Protein structure prediction

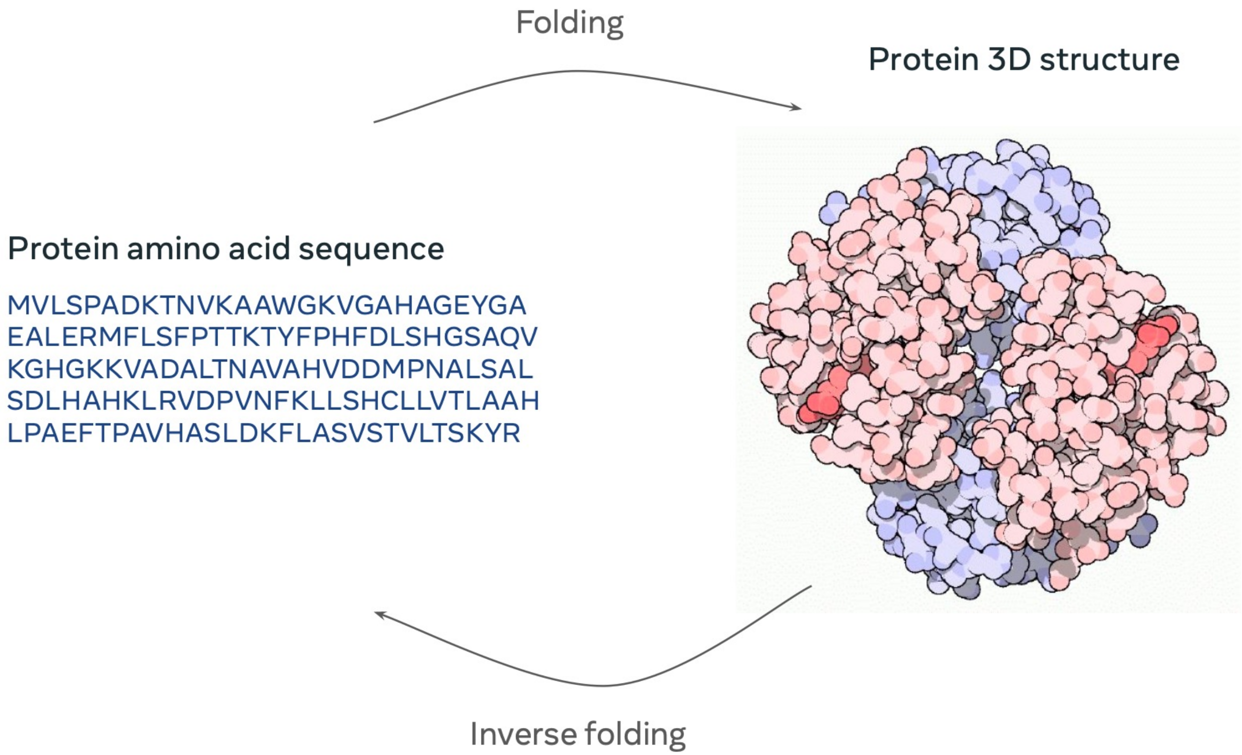
AlphaFold2 (2021)

SARS-CoV-2 is evolving fast. What will it do next? p. 844
Effects on surface water from hydraulic fracturing pp. 853 & 896
Baby bats babble like human babies p. 923
Science
$15
20 AUGUST 2021
sciencemag.org
AAAS
PREDICTING
STRUCTURES
Deep learning accurately folds proteins p. 871

RoseTTAFold (2021)


Billions of known protein sequences
Experimentally determined structures
(~0.1% of sequence space)

Introduction



Folding

Protein 3D structure

Protein amino acid sequence

MVLSPADKTNVKAAWGKVGAHAGEYGA
EALERMFLSFPTTKTYFPHFDLSHGSAQV
KGHGKKVADALTNAVAHVDDMPNALSAL
SDLHAHKLRVDPVNFKLLSHCLLVTLAAH
LPAEFTPAVHASLDKFLASVSTVLTSKYR

Inverse folding

- Structure determine function
- Many sequence can fold on one similar structure (524 different sequence fold into 1MBN)
- Diffusion model can generate diverse sample given the same input

Hsu, Chloe, et al. "Learning inverse folding from millions of predicted structures." . PMLR, 2022.

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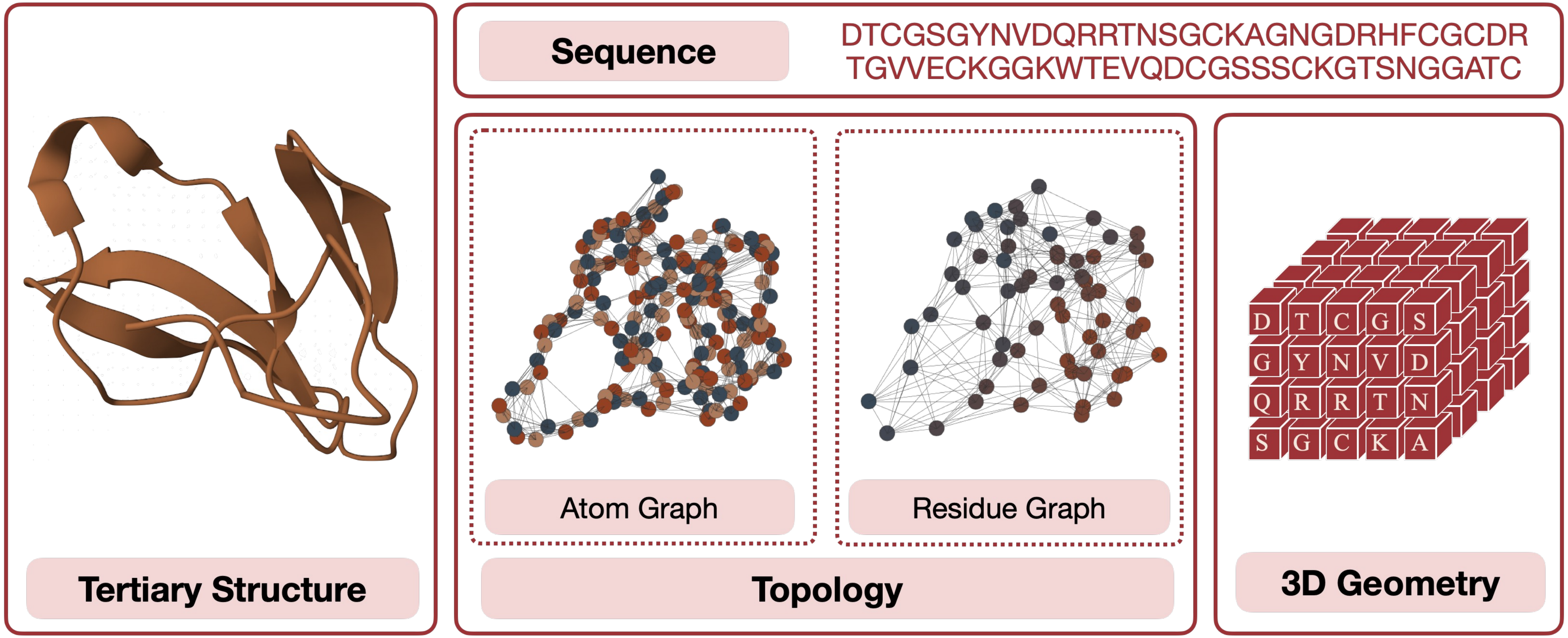
Protein Representation



Sequence

DTCGSGYNVDQRRTNSGCKAGNGDRHFCGCDR
TGVVECKGGKWTEVQDCGSSSCKGTSNGGATC

Atom Graph

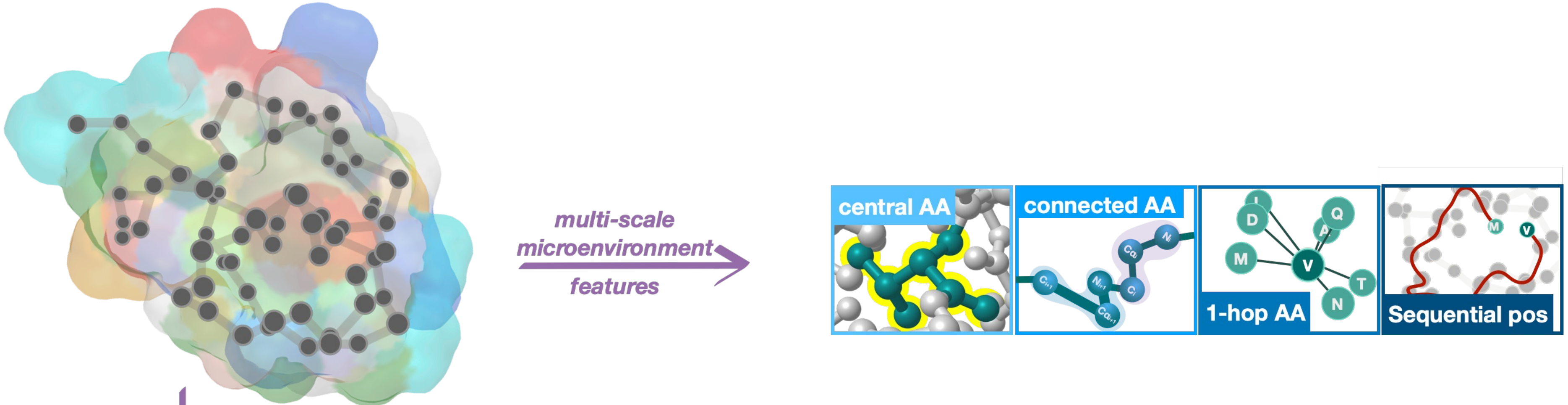
Residue Graph

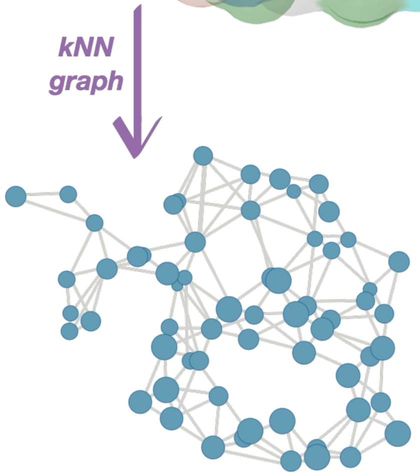
Tertiary Structure

Topology

3D Geometry

Protein Graph





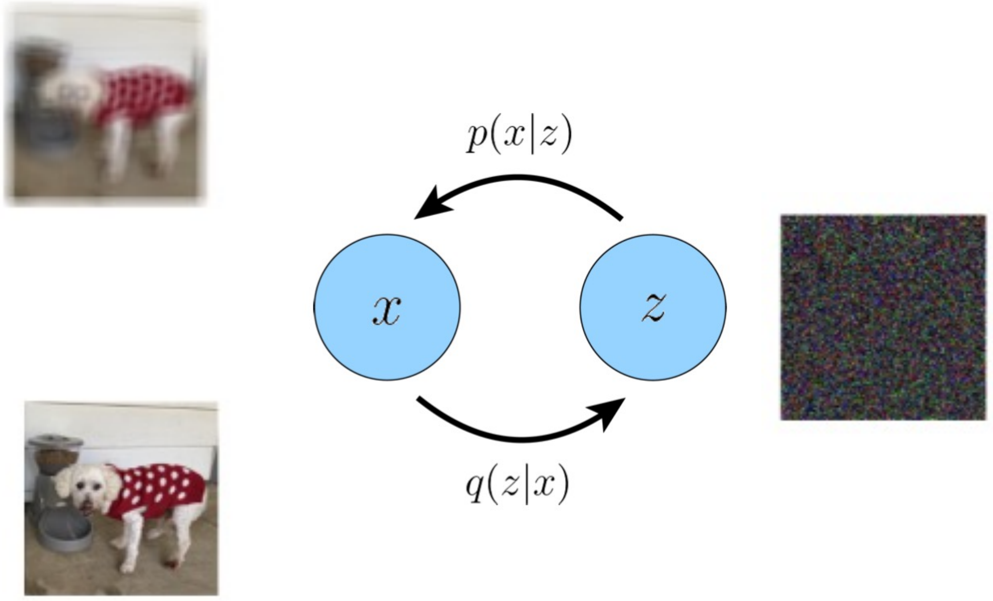
$$\mathcal{G} = \{X, A, E\}$$

Inverse Folding:

$$p(X^{aa} \mid X^{pos}) = p_\theta(X^{aa} \mid A, E) \quad \text{where} \quad X^{aa} \in \mathbb{R}^{N\times 20}$$

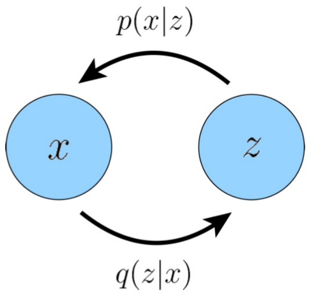
Diffusion Generative Model

$$
\begin{aligned}
\log p(\boldsymbol{x}) &= \log \int p(\boldsymbol{x}, \boldsymbol{z}) d\boldsymbol{z} \\
&= \log \int \frac{p(\boldsymbol{x}, \boldsymbol{z}) q_\phi(\boldsymbol{z} \mid \boldsymbol{x})}{q_\phi(\boldsymbol{z} \mid \boldsymbol{x})} d\boldsymbol{z} \\
&= \log \mathbb{E}_{q_\phi(\boldsymbol{z}|\boldsymbol{x})}\left[\frac{p(\boldsymbol{x}, \boldsymbol{z})}{q_\phi(\boldsymbol{z} \mid \boldsymbol{x})}\right] \\
&\geq \mathbb{E}_{q_\phi(\boldsymbol{z}|\boldsymbol{x})}\left[\log \frac{p(\boldsymbol{x}, \boldsymbol{z})}{q_\phi(\boldsymbol{z} \mid \boldsymbol{x})}\right] \\
&= \underbrace{\mathbb{E}_{q_\phi(\boldsymbol{z}|\boldsymbol{x})}[\log p_{\boldsymbol{\theta}}(\boldsymbol{x} \mid \boldsymbol{z})]}_{\text{reconstruction term}} - \underbrace{D_{KL}\left(q_\phi(\boldsymbol{z} \mid \boldsymbol{x}) \parallel p(\boldsymbol{z})\right)}_{\text{prior matching term}}
\end{aligned}
$$

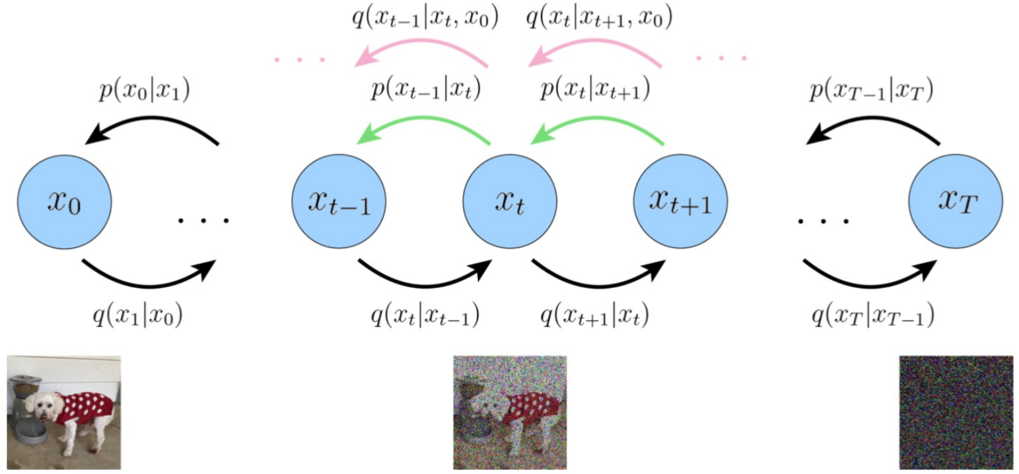


Diffusion Generative Model

$$\log p(\boldsymbol{x}) \quad \geq \mathbb{E}_{q_{\phi}(\boldsymbol{z}|\boldsymbol{x})}[\log p_{\boldsymbol{\theta}}(\boldsymbol{x} \mid \boldsymbol{z})] - D_{KL}\left(q_{\phi}(\boldsymbol{z} \mid \boldsymbol{x}) \parallel p(\boldsymbol{z})\right)$$



$$\begin{aligned}
\log\ p(\boldsymbol{x}) &= \log \int p(\boldsymbol{x}_{0:T}) d\boldsymbol{x}_{1:T} \\
&= \log \int \frac{p(\boldsymbol{x}_{0:T}) q(\boldsymbol{x}_{1:T} \mid \boldsymbol{x}_0)}{q(\boldsymbol{x}_{1:T} \mid \boldsymbol{x}_0)} d\boldsymbol{x}_{1:T} \\
&= \log\ \mathbb{E}_{q(\boldsymbol{x}_{1:T}|\boldsymbol{x}_0)}\left[\frac{p(\boldsymbol{x}_{0:T})}{q(\boldsymbol{x}_{1:T} \mid \boldsymbol{x}_0)}\right] \\
&\geq \mathbb{E}_{q(\boldsymbol{x}_{1:T}|\boldsymbol{x}_0)}\left[\log \frac{p(\boldsymbol{x}_{0:T})}{q(\boldsymbol{x}_{1:T} \mid \boldsymbol{x}_0)}\right] \\
&\dots \\
&= \mathbb{E}_{q(\boldsymbol{x}_1|\boldsymbol{x}_0)}[\log\ p_{\boldsymbol{\theta}}(\boldsymbol{x}_0 \mid \boldsymbol{x}_1)] - D_{\mathrm{KL}}\left(q(\boldsymbol{x}_T \mid \boldsymbol{x}_0) \parallel p(\boldsymbol{x}_T)\right) - \\
&\sum_{t=2}^{T} \mathbb{E}_{q(\boldsymbol{x}_t|\boldsymbol{x}_0)}\left[D_{\mathrm{KL}}\left(q(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t, \boldsymbol{x}_0) \parallel p_{\boldsymbol{\theta}}(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t)\right)\right]
\end{aligned}$$



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Define Diffusion Process in Discrete Space

$$\log p(\boldsymbol{x}) \geq \mathbb{E}_{q(\boldsymbol{x}_1 \mid \boldsymbol{x}_0)}[\log p_{\boldsymbol{\theta}}(\boldsymbol{x}_0 \mid \boldsymbol{x}_1)] - D_{\mathrm{KL}}\big(q(\boldsymbol{x}_T \mid \boldsymbol{x}_0) \parallel p(\boldsymbol{x}_T)\big)$$

$$- \sum_{t=2}^{T} \mathbb{E}_{q(\boldsymbol{x}_t \mid \boldsymbol{x}_0)}\big[D_{\mathrm{KL}}\big(q(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t, \boldsymbol{x}_0) \parallel p_{\boldsymbol{\theta}}(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t)\big)\big]$$

$$\arg \underset{\boldsymbol{\theta}}{min}\, \mathbb{E}_{t \sim U\{2,T\}}\Big[\mathbb{E}_{q(\boldsymbol{x}_t \mid \boldsymbol{x}_0)}\big[D_{\mathrm{KL}}\big(q(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t, \boldsymbol{x}_0) \parallel p_{\boldsymbol{\theta}}(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t)\big)\big]\Big]$$

- $q(\boldsymbol{x}_t \mid \boldsymbol{x}_0)$ requires a closed form

- $q(\boldsymbol{x}_T)$ should independent with x

- $q(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t\,,\ \boldsymbol{x}_0)$ should have closed form

Define Diffusion Process in Discrete Space

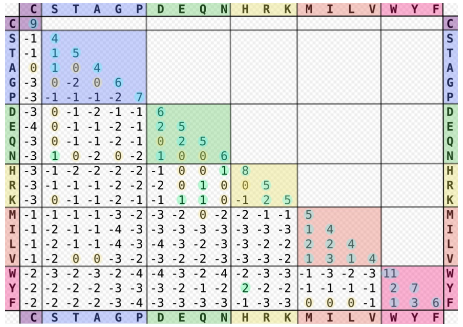
Diffusion Process:

$$q(\boldsymbol{x}_t \mid \boldsymbol{x}^{aa}) = \boldsymbol{x}^{aa}\overline{\boldsymbol{Q}}_t \qquad \overline{\boldsymbol{Q}}_t = \boldsymbol{Q}_1\boldsymbol{Q}_2 \dots \boldsymbol{Q}_t \qquad x^{aa} \in \mathbb{R}^{1\times 20}$$

Transition Matrix

$$\boldsymbol{Q}_t = \alpha_t \boldsymbol{I} + (1-\alpha_t)1_d\, 1_d^{\top}/d$$

(Uniform Diffusion Kernel)



	C	S	T	A	G	P	D	E	Q	N	H	R	K	M	I	L	V	W	Y	F	
C	9																				C
S	-1	4																			S
T	-1	1	5																		T
A	0	1	0	4																	A
G	-3	0	-2	0	6																G
P	-3	-1	-1	-1	-2	7															P
D	-3	0	-1	-2	-1	-1	6														D
E	-4	0	-1	-1	-2	-1	2	5													E
Q	-3	0	-1	-1	-2	-1	0	2	5												Q
N	-3	1	0	-2	0	-2	1	0	0	6											N
H	-3	-1	-2	-2	-2	-2	-1	0	0	1	8										H
R	-3	-1	-1	-1	-2	-2	-2	0	1	0	0	5									R
K	-3	0	-1	-1	-2	-1	-1	1	1	0	-1	2	5								K
M	-1	-1	-1	-1	-3	-2	-3	-2	0	-2	-2	-1	-1	5							M
I	-1	-2	-1	-1	-4	-3	-3	-3	-3	-3	-3	-3	-3	1	4						I
L	-1	-2	-1	-1	-4	-3	-4	-3	-2	-3	-3	-2	-2	2	2	4					L
V	-1	-2	0	0	-3	-2	-3	-2	-2	-3	-3	-3	-2	1	3	1	4				V
W	-2	-3	-2	-3	-2	-4	-4	-3	-2	-4	-2	-3	-3	-1	-3	-2	-3	11			W
Y	-2	-2	-2	-2	-3	-3	-3	-2	-1	-2	2	-2	-2	-1	-1	-1	-1	2	7		Y
F	-2	-2	-2	-2	-3	-4	-3	-3	-3	-3	-1	-3	-3	0	0	0	-1	1	3	6	F
	C	S	T	A	G	P	D	E	Q	N	H	R	K	M	I	L	V	W	Y	F	

(BLOSUM Matrix)

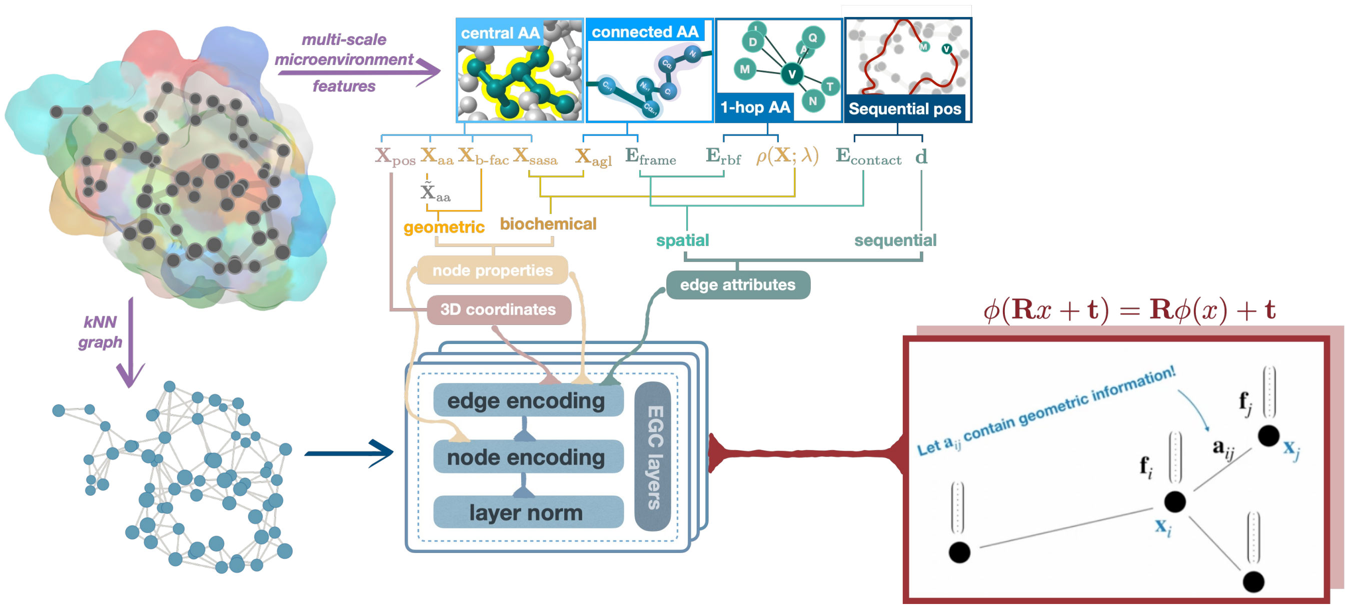
Posterior Distribution

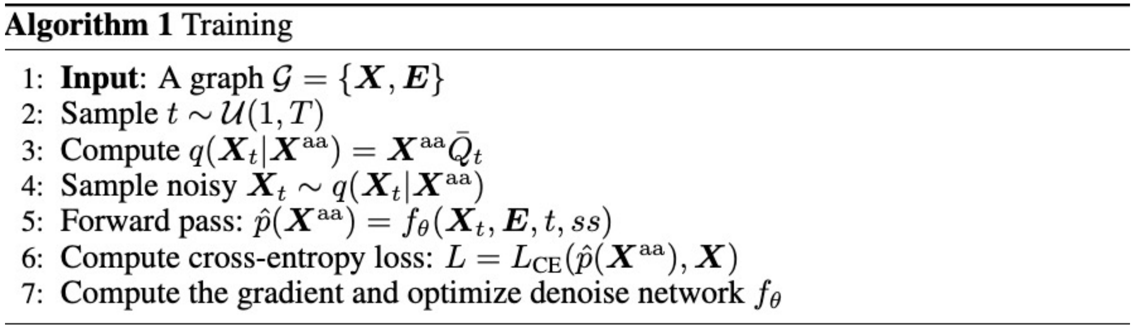
$$q(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t, \boldsymbol{x}^{aa}) = \frac{q(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{x}^{aa})\, q(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}^{aa})}{q(\boldsymbol{x}_t \mid \boldsymbol{x}^{aa})}$$

$$= \mathrm{Cat}\left(\boldsymbol{x}_{t-1} \mid \frac{\boldsymbol{x}_t Q_t^{\top} \odot \boldsymbol{x}^{aa}\bar{Q}_{t-1}}{\boldsymbol{x}^{aa}\bar{Q}_t \boldsymbol{x}_t^{\top}}\right)$$

Parameterized Generative Process : $p_\theta(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t) \propto \sum_{\hat{\boldsymbol{x}}^{\mathrm{aa}}} q(\boldsymbol{x}_{t-1} \mid \boldsymbol{x}_t, \boldsymbol{x}^{\mathrm{aa}})\hat{p}_\theta(\boldsymbol{x}^{\mathrm{aa}} \mid \boldsymbol{x}_t)$

Denoise Neural Network

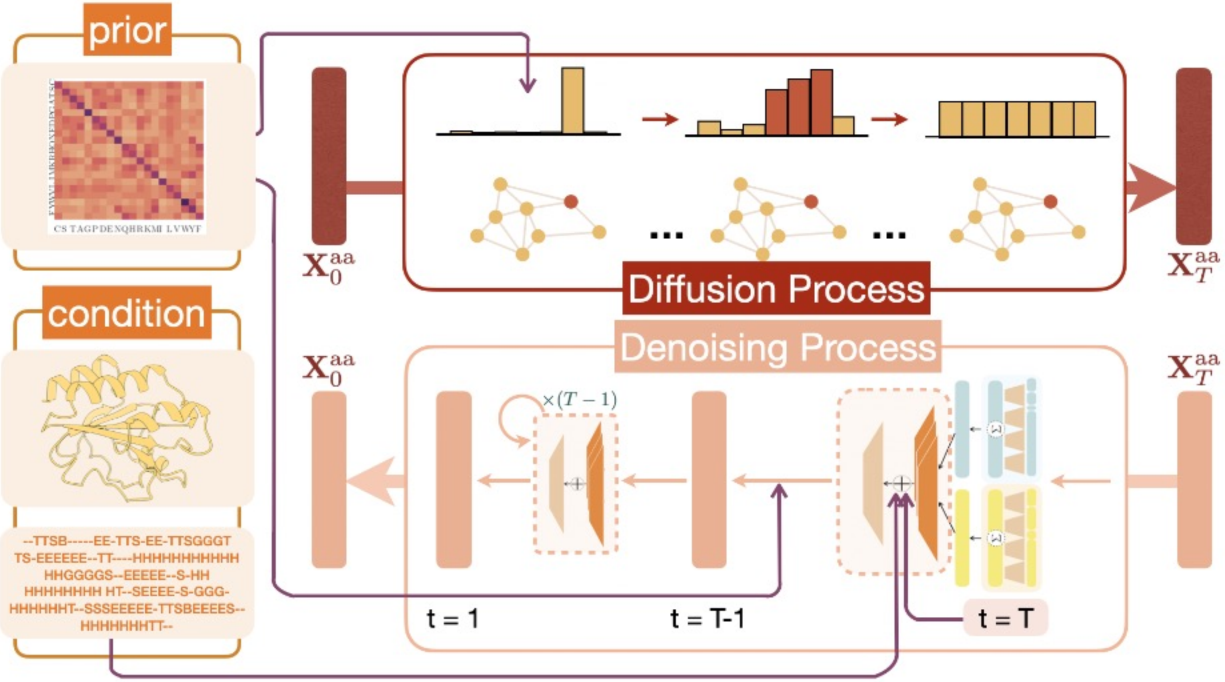

multi-scale microenvironment features
central AA
connected AA
1-hop AA
Sequential pos
$\mathbf{X}_{\text{pos}}$ $\mathbf{X}_{\text{aa}}$ $\mathbf{X}_{\text{b-fac}}$ $\mathbf{X}_{\text{sasa}}$ $\mathbf{X}_{\text{agl}}$ $\mathbf{E}_{\text{frame}}$ $\mathbf{E}_{\text{rbf}}$ $\rho(\mathbf{X};\lambda)$ $\mathbf{E}_{\text{contact}}$ $\mathbf{d}$
$\tilde{\mathbf{X}}_{\text{aa}}$
geometric
biochemical
spatial
sequential
node properties
edge attributes
3D coordinates
kNN graph
edge encoding
node encoding
layer norm
EGC layers
$\phi(\mathbf{R}x+\mathbf{t}) = \mathbf{R}\phi(x)+\mathbf{t}$
Let $\mathbf{a}_{ij}$ contain geometric information!
$\mathbf{f}_j$
$\mathbf{x}_j$
$\mathbf{a}_{ij}$
$\mathbf{f}_i$
$\mathbf{x}_i$

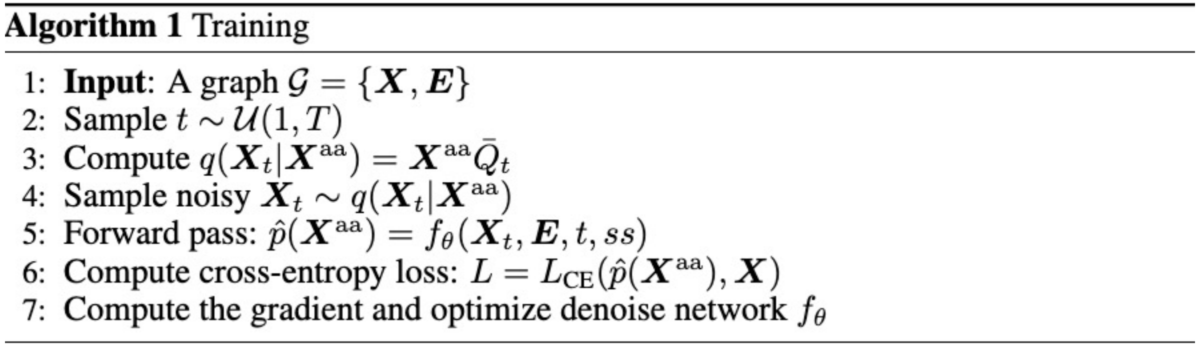


Algorithm 1 Training

```
1: Input: A graph $\mathcal{G} = \{\boldsymbol{X}, \boldsymbol{E}\}$
2: Sample $t \sim \mathcal{U}(1, T)$
3: Compute $q(\boldsymbol{X}_t|\boldsymbol{X}^{\text{aa}}) = \boldsymbol{X}^{\text{aa}}\bar{Q}_t$
4: Sample noisy $\boldsymbol{X}_t \sim q(\boldsymbol{X}_t|\boldsymbol{X}^{\text{aa}})$
5: Forward pass: $\hat{p}(\boldsymbol{X}^{\text{aa}}) = f_\theta(\boldsymbol{X}_t, \boldsymbol{E}, t, ss)$
6: Compute cross-entropy loss: $L = L_{\text{CE}}(\hat{p}(\boldsymbol{X}^{\text{aa}}), \boldsymbol{X})$
7: Compute the gradient and optimize denoise network $f_\theta$
```

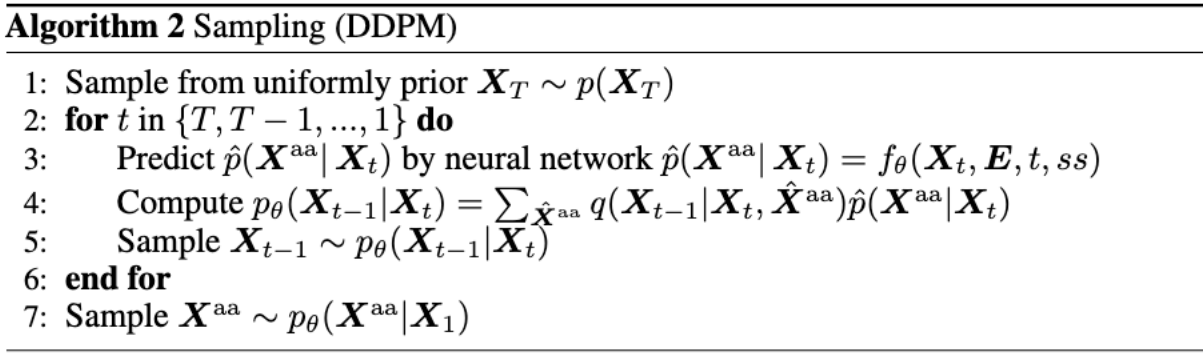
Graph Denoising Diffusion for Inverse Protein Folding





Algorithm 1 Training

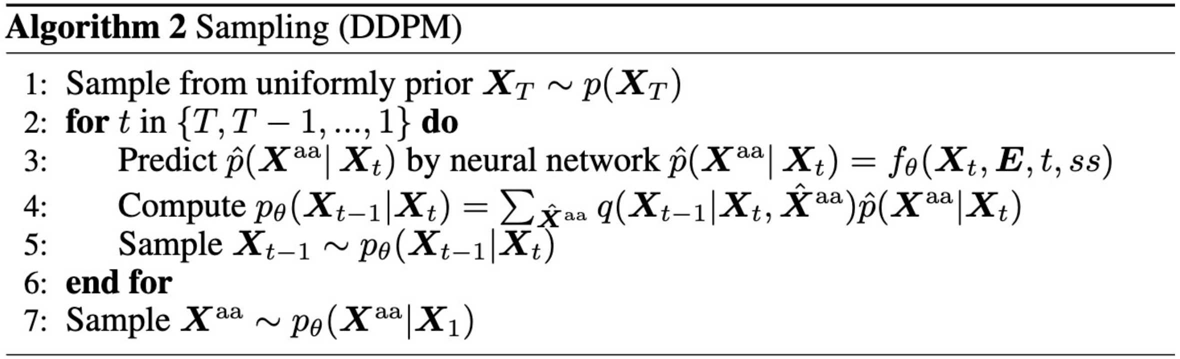
```
Input: A graph $\mathcal{G} = \{\boldsymbol{X}, \boldsymbol{E}\}$
Sample $t \sim \mathcal{U}(1, T)$
Compute $q(\boldsymbol{X}_t | \boldsymbol{X}^{\text{aa}}) = \boldsymbol{X}^{\text{aa}} \bar{Q}_t$
Sample noisy $\boldsymbol{X}_t \sim q(\boldsymbol{X}_t | \boldsymbol{X}^{\text{aa}})$
Forward pass: $\hat{p}(\boldsymbol{X}^{\text{aa}}) = f_\theta(\boldsymbol{X}_t, \boldsymbol{E}, t, ss)$
Compute cross-entropy loss: $L = L_{\text{CE}}(\hat{p}(\boldsymbol{X}^{\text{aa}}), \boldsymbol{X})$
Compute the gradient and optimize denoise network $f_\theta$
```



Algorithm 2 Sampling (DDPM)

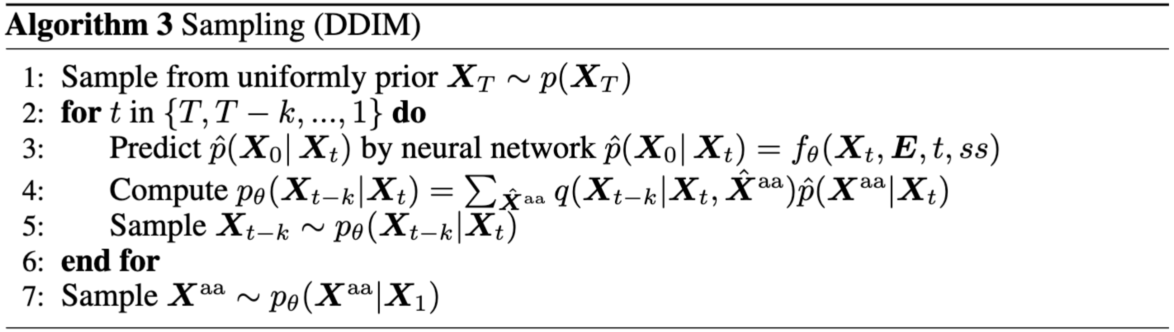
```
Sample from uniformly prior $\boldsymbol{X}_T \sim p(\boldsymbol{X}_T)$
for $t$ in $\{T, T-1, ..., 1\}$ do
    Predict $\hat{p}(\boldsymbol{X}^{\text{aa}} | \boldsymbol{X}_t)$ by neural network $\hat{p}(\boldsymbol{X}^{\text{aa}} | \boldsymbol{X}_t) = f_\theta(\boldsymbol{X}_t, \boldsymbol{E}, t, ss)$
    Compute $p_\theta(\boldsymbol{X}_{t-1} | \boldsymbol{X}_t) = \sum_{\hat{\boldsymbol{X}}^{\text{aa}}} q(\boldsymbol{X}_{t-1} | \boldsymbol{X}_t, \hat{\boldsymbol{X}}^{\text{aa}}) \hat{p}(\boldsymbol{X}^{\text{aa}} | \boldsymbol{X}_t)$
    Sample $\boldsymbol{X}_{t-1} \sim p_\theta(\boldsymbol{X}_{t-1} | \boldsymbol{X}_t)$
end for
Sample $\boldsymbol{X}^{\text{aa}} \sim p_\theta(\boldsymbol{X}^{\text{aa}} | \boldsymbol{X}_1)$
```

Generative Process



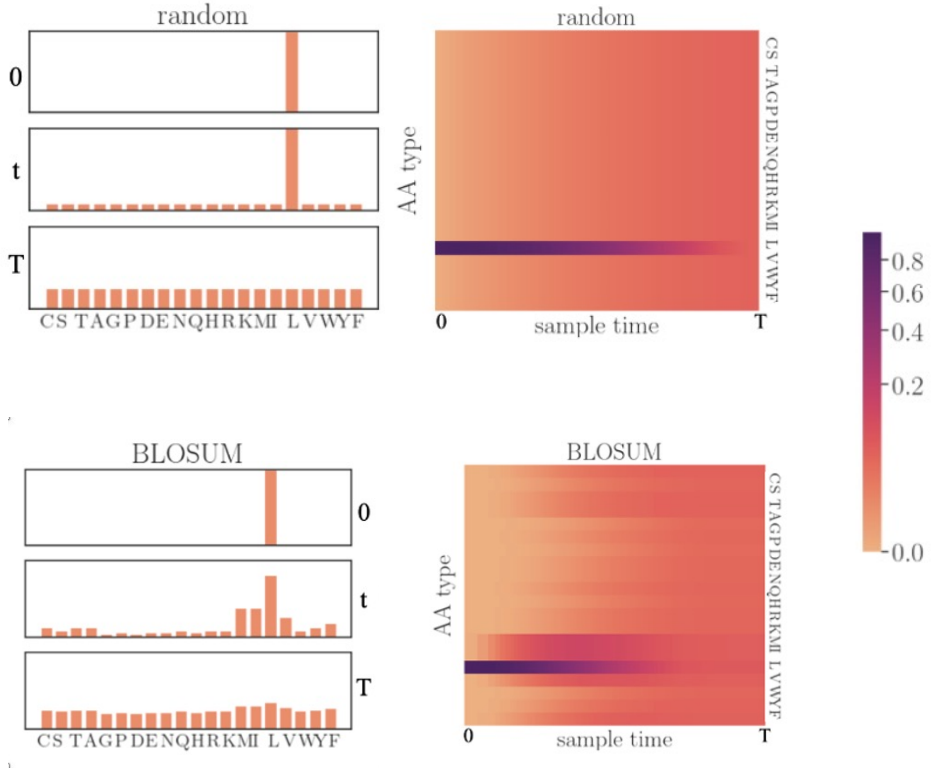
Algorithm 2 Sampling (DDPM)

```
Sample from uniformly prior $\boldsymbol{X}_T \sim p(\boldsymbol{X}_T)$
for $t$ in $\{T, T-1, ..., 1\}$ do
    Predict $\hat{p}(\boldsymbol{X}^{\text{aa}}|\, \boldsymbol{X}_t)$ by neural network $\hat{p}(\boldsymbol{X}^{\text{aa}}|\, \boldsymbol{X}_t) = f_\theta(\boldsymbol{X}_t, \boldsymbol{E}, t, ss)$
    Compute $p_\theta(\boldsymbol{X}_{t-1}|\boldsymbol{X}_t) = \sum_{\hat{\boldsymbol{X}}^{\text{aa}}} q(\boldsymbol{X}_{t-1}|\boldsymbol{X}_t, \hat{\boldsymbol{X}}^{\text{aa}})\hat{p}(\boldsymbol{X}^{\text{aa}}|\boldsymbol{X}_t)$
    Sample $\boldsymbol{X}_{t-1} \sim p_\theta(\boldsymbol{X}_{t-1}|\boldsymbol{X}_t)$
end for
Sample $\boldsymbol{X}^{\text{aa}} \sim p_\theta(\boldsymbol{X}^{\text{aa}}|\boldsymbol{X}_1)$
```



Algorithm 3 Sampling (DDIM)

```
Sample from uniformly prior $\boldsymbol{X}_T \sim p(\boldsymbol{X}_T)$
for $t$ in $\{T, T-k, ..., 1\}$ do
    Predict $\hat{p}(\boldsymbol{X}_0|\, \boldsymbol{X}_t)$ by neural network $\hat{p}(\boldsymbol{X}_0|\, \boldsymbol{X}_t) = f_\theta(\boldsymbol{X}_t, \boldsymbol{E}, t, ss)$
    Compute $p_\theta(\boldsymbol{X}_{t-k}|\boldsymbol{X}_t) = \sum_{\hat{\boldsymbol{X}}^{\text{aa}}} q(\boldsymbol{X}_{t-k}|\boldsymbol{X}_t, \hat{\boldsymbol{X}}^{\text{aa}})\hat{p}(\boldsymbol{X}^{\text{aa}}|\boldsymbol{X}_t)$
    Sample $\boldsymbol{X}_{t-k} \sim p_\theta(\boldsymbol{X}_{t-k}|\boldsymbol{X}_t)$
end for
Sample $\boldsymbol{X}^{\text{aa}} \sim p_\theta(\boldsymbol{X}^{\text{aa}}|\boldsymbol{X}_1)$
```



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Experiment & Evaluation

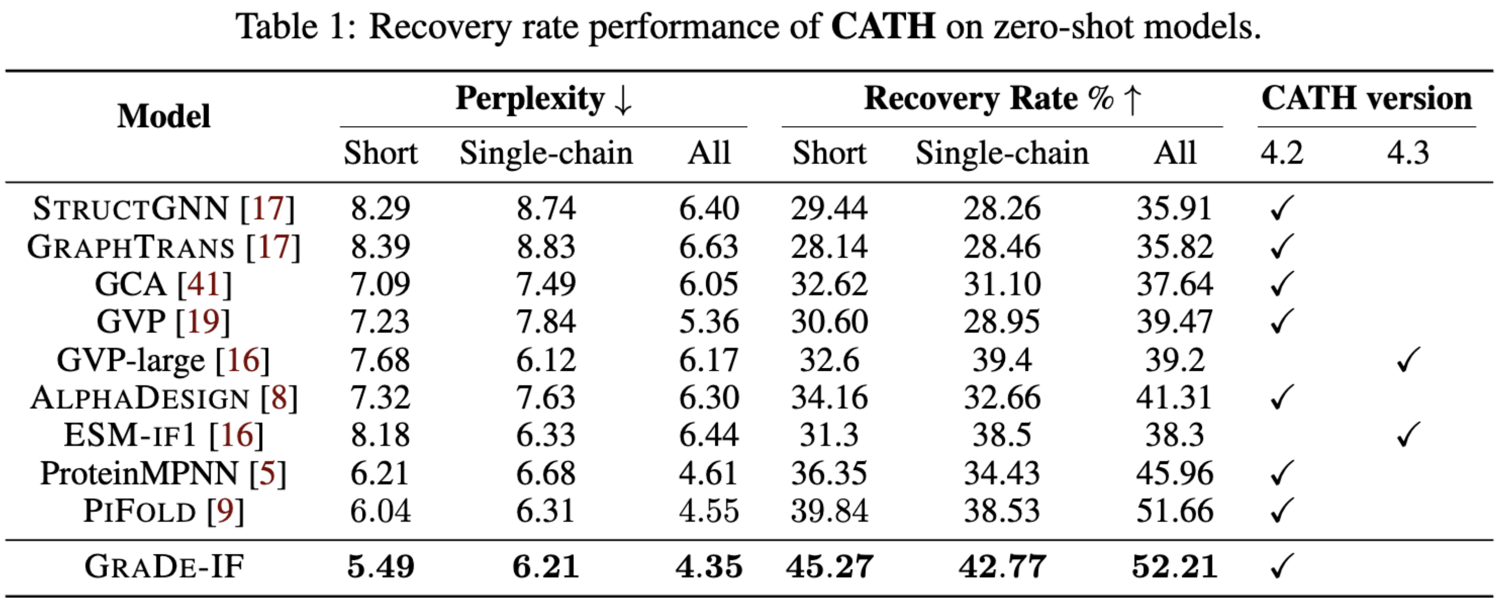


Table 1: Recovery rate performance of **CATH** on zero-shot models.

Model	**Perplexity ↓**			**Recovery Rate % ↑**			**CATH version**	
	Short	Single-chain	All	Short	Single-chain	All	4.2	4.3
STRUCTGNN [17]	8.29	8.74	6.40	29.44	28.26	35.91	✓	
GRAPHTRANS [17]	8.39	8.83	6.63	28.14	28.46	35.82	✓	
GCA [41]	7.09	7.49	6.05	32.62	31.10	37.64	✓	
GVP [19]	7.23	7.84	5.36	30.60	28.95	39.47	✓	
GVP-large [16]	7.68	6.12	6.17	32.6	39.4	39.2		✓
ALPHADESIGN [8]	7.32	7.63	6.30	34.16	32.66	41.31	✓	
ESM-IF1 [16]	8.18	6.33	6.44	31.3	38.5	38.3		✓
ProteinMPNN [5]	6.21	6.68	4.61	36.35	34.43	45.96	✓	
PIFOLD [9]	6.04	6.31	4.55	39.84	38.53	51.66	✓	
GRADE-IF	**5.49**	**6.21**	**4.35**	**45.27**	**42.77**	**52.21**	✓	

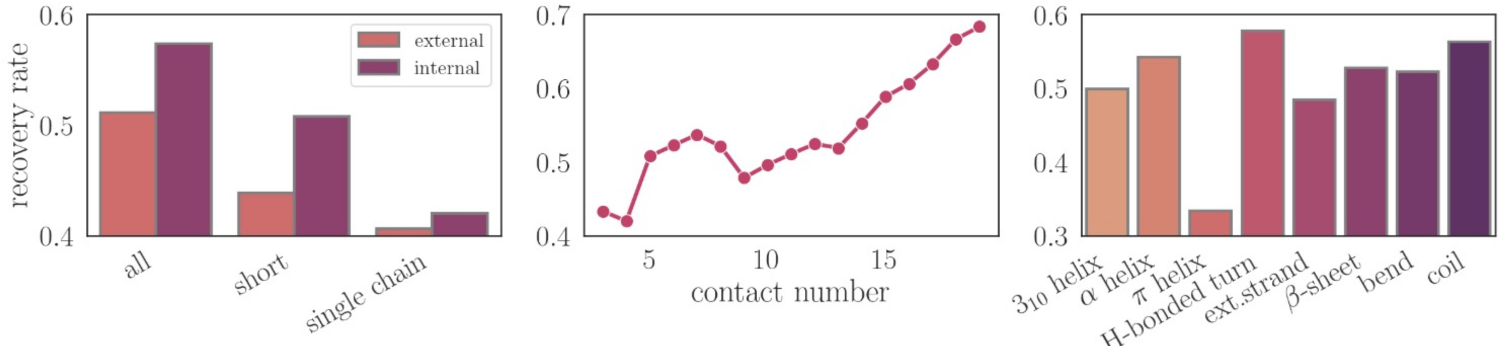
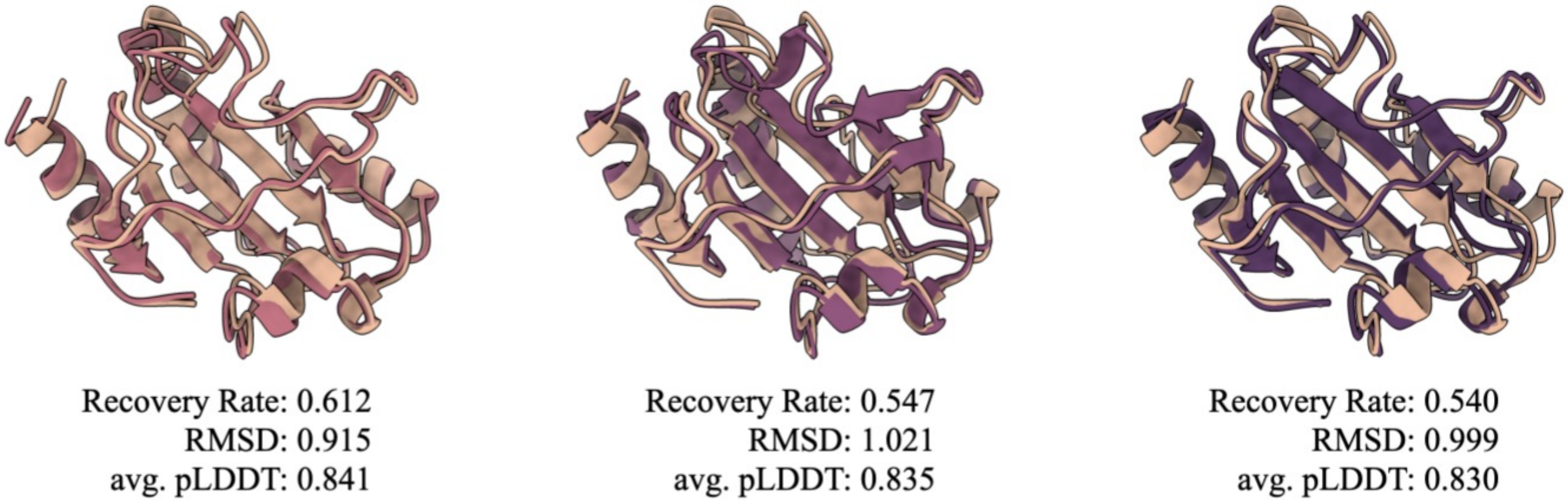


Figure 3: Recovery rate on core and surface residues and different secondary structure

Experiment & Evaluation



Recovery Rate: 0.612
RMSD: 0.915
avg. pLDDT: 0.841

Recovery Rate: 0.547
RMSD: 1.021
avg. pLDDT: 0.835

Recovery Rate: 0.540
RMSD: 0.999
avg. pLDDT: 0.830

Figure 6: Folding prediction of generated protein sequence by GraDe-IF with respect to the native protein (PDB ID: 3FKF, colored in nude).

Experiment & Evaluation

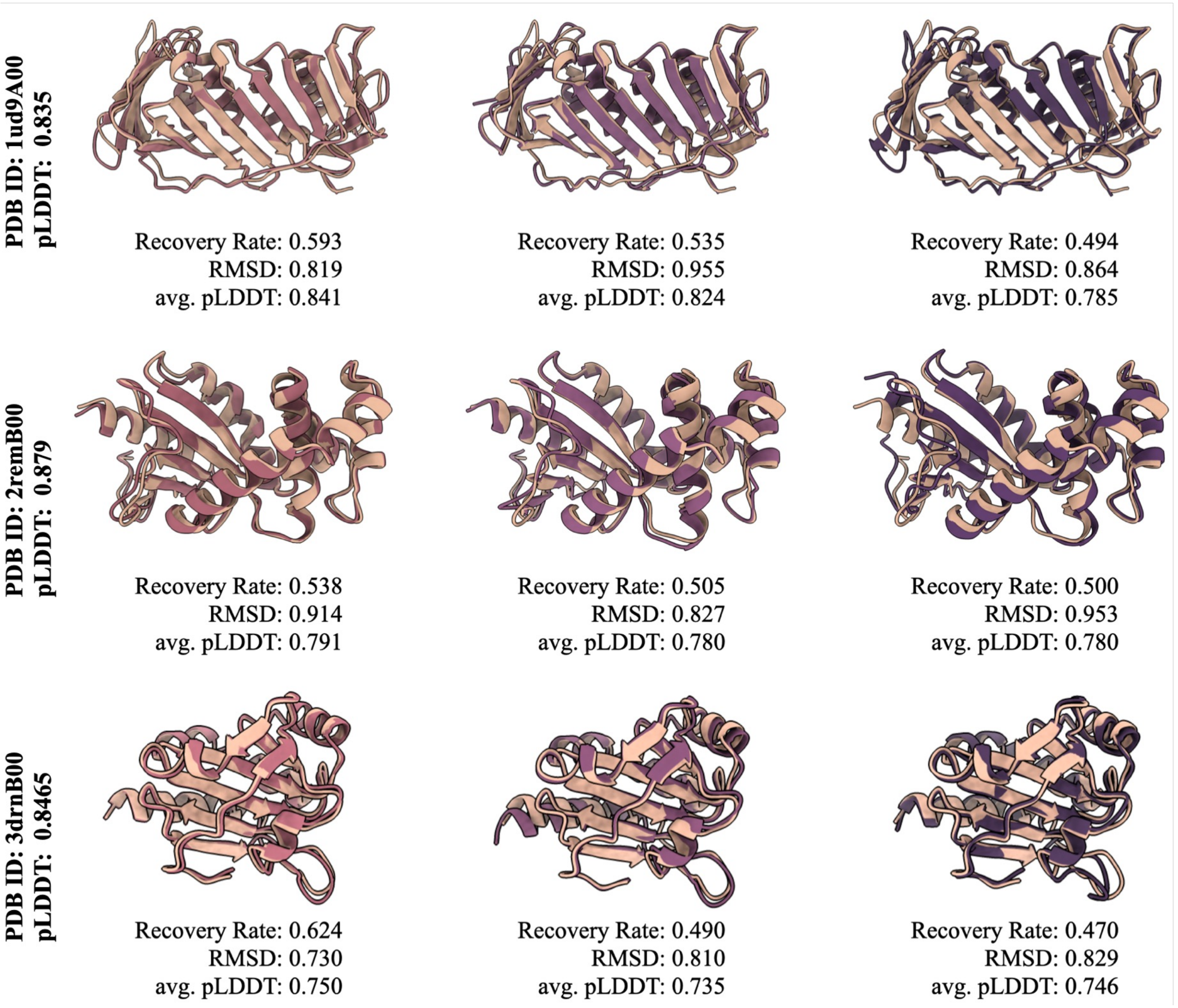


Table 2. Average RMSD and pLDDT across 42 protein structures (folded by AlphaFold2) with model-generated sequences.

Model	avg. pLDDT	avg RMSD
PiFold	0.847 ± 0.160	1.530 ± 0.928
ProteinMPNN	0.881 ± 0.084	1.499 ± 0.816
GraDe-IF	0.892 ± 0.106	1.284 ± 0.747

Table 4. TM score comparison. Each protein backbone generates 30 sequences.

Protein	GraDe-IF	ProteinMPNN	PiFold
1ud9.A	0.97 ± 0.01	0.95 ± 0.04	0.94 ± 0.04
2rem.B	0.96 ± 0.01	0.94 ± 0.01	0.93 ± 0.01
3drn.B	0.96 ± 0.01	0.95 ± 0.01	0.95 ± 0.01
3fkf.A	0.76 ± 0.03	0.67 ± 0.01	0.64 ± 0.02

Table 5. TM score comparison on 42 protein backbones, with each backbone generating 1 sample. A sequence is considered foldable if its TM score > 0.5.

Method	Success	TM score
PiFold	37	0.83 ± 0.21
ProteinMPNN	39	0.82 ± 0.16
GraDe-IF	39	0.87 ± 0.17

Reference

Yi, Kai, et al. "Graph Denoising Diffusion for Inverse Protein Folding." *arXiv preprint arXiv:2306.16819* (2023).

Hsu, Chloe, et al. "Learning inverse folding from millions of predicted structures." . PMLR, 2022.

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