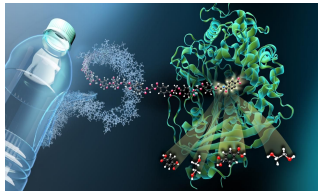
Repurposing Protein Folding Models for All-Atom Generation via Latent Space Compression

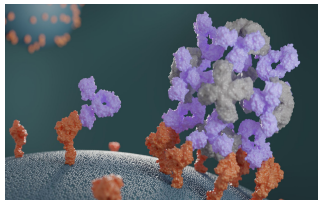
Amy X. Lu
PhD Student, UC Berkeley
March 3rd, 2025
Baker Lab Journal Club

Designing novel proteins with desired properties is useful



Plastic degrading enzymes

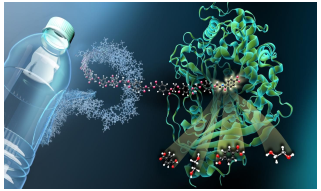
Vaccine development



Antibody therapeutics

and much more...

Designing novel proteins with desired properties is hard



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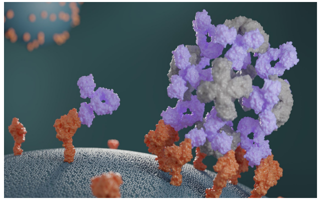
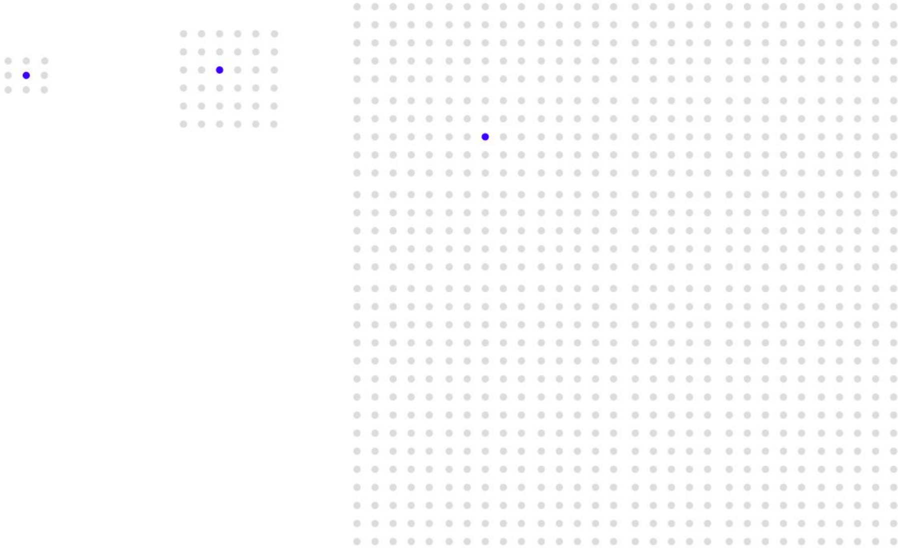


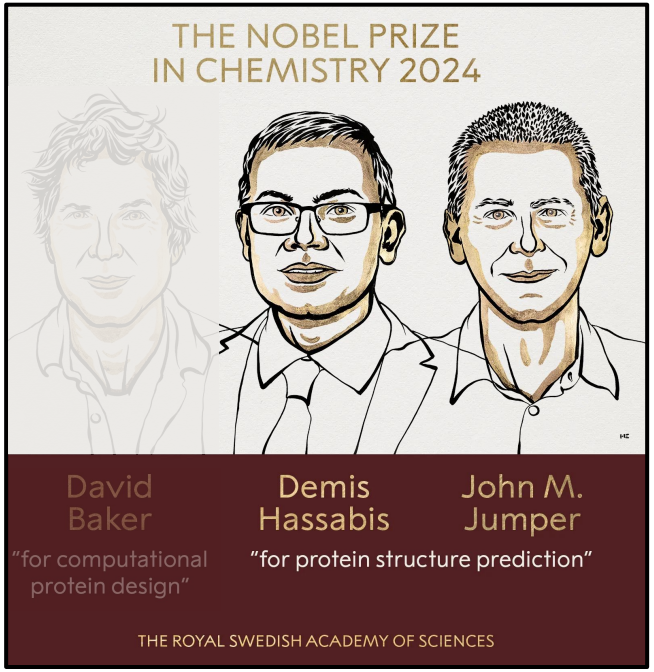
Antibody therapeutics

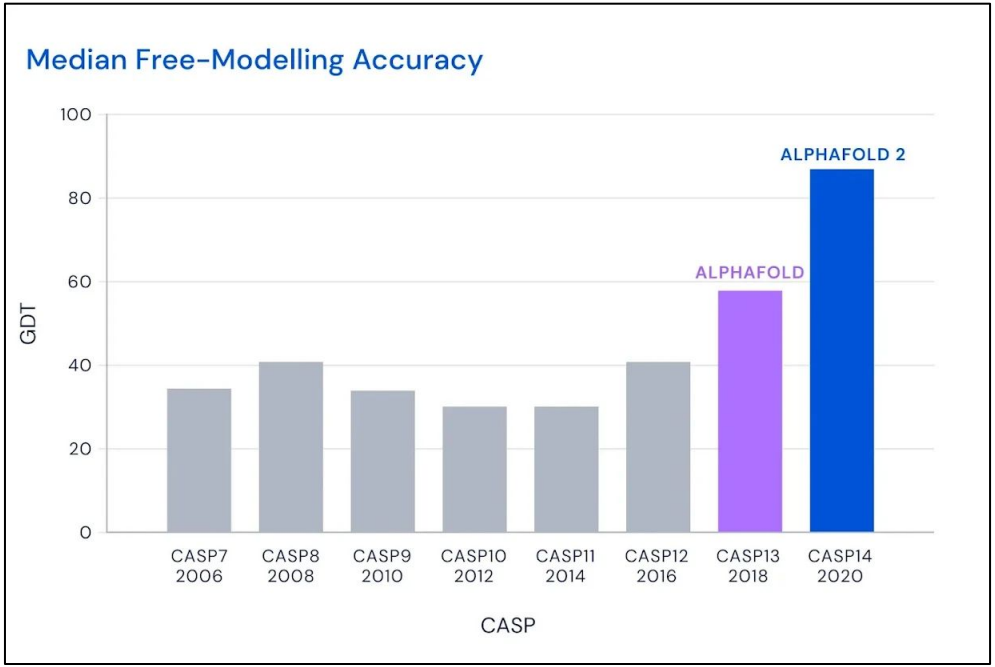
and much more...

HUMAN PROTEINS	UNIQUE PROTEINS ON EARTH	POSSIBLE PROTEINS
~20,000	~1,000,000,000,000,000,000	~10,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000

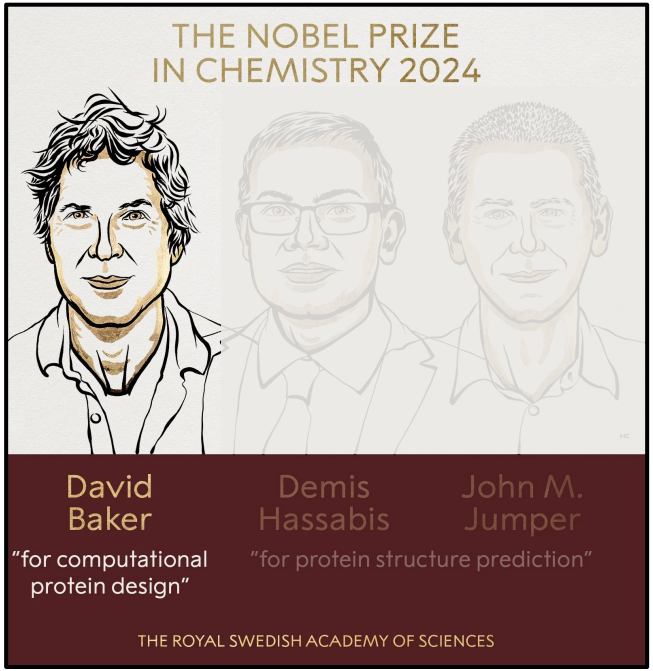


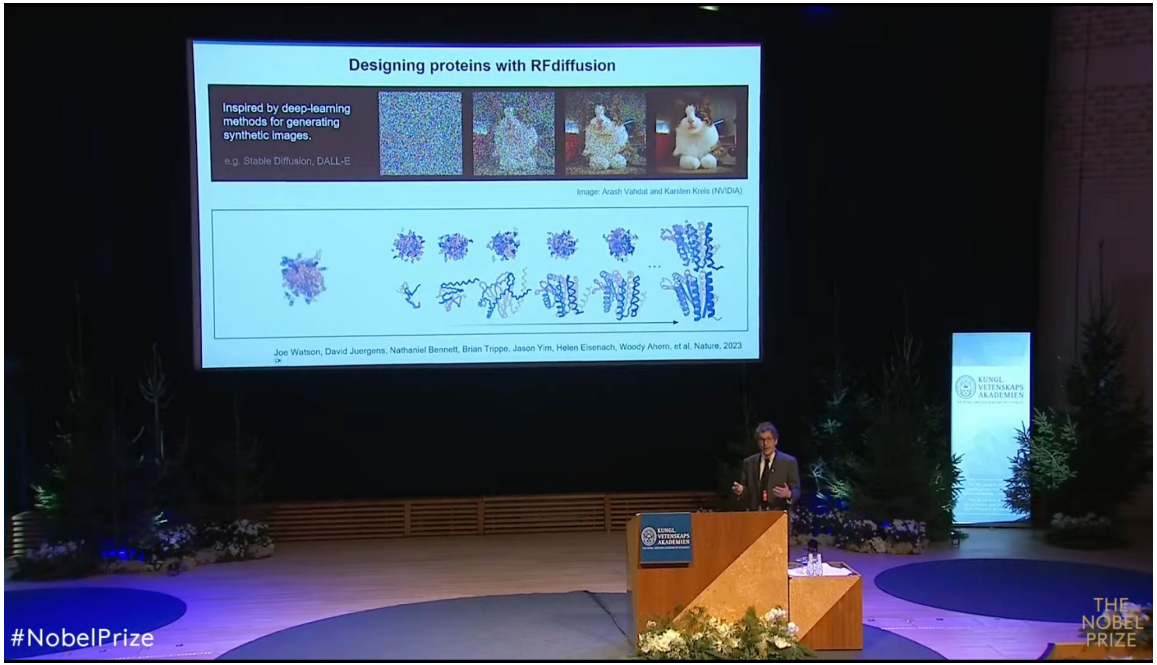
The potential of deep learning for protein structure prediction





The potential of deep learning for protein structure generation





But what else would we need for drug discovery?

this talk

Co-generation
→ can we simultaneously generate sequence and structure?

Control
→ how can we specify complex and multi-objective constraints?

Immunogenicity
→ can we achieve organism specificity?

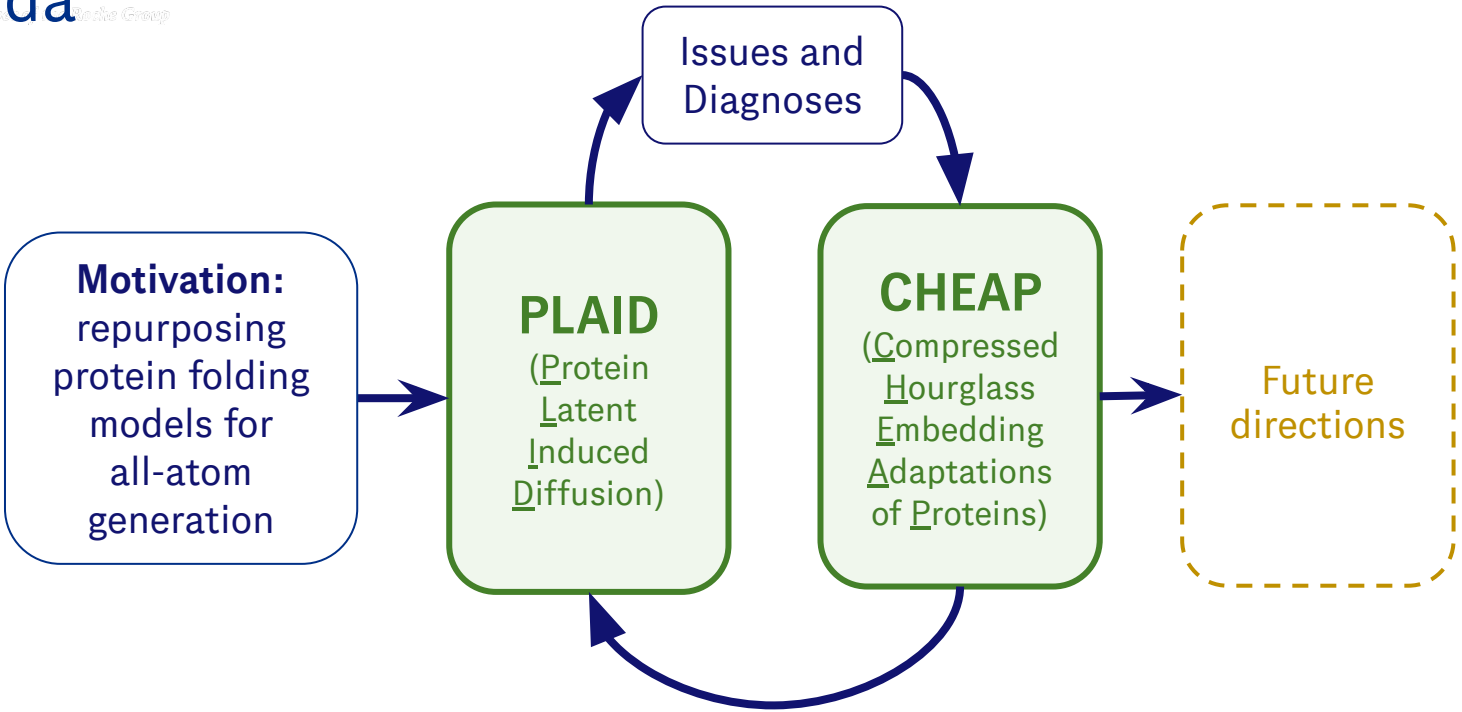
Deployment
→ can we speed up inference? what about ethics and biosafety concerns?

Task generalization
→ how can we generalize few-shot to new targets?

Modeling complexes
→ can we design small- & large-molecule binders?

other work / planned future work

Agenda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PLAID (Protein Latent Induced Diffusion)
CHEAP (Compressed Hourglass Embedding Adaptations of Proteins)
Future directions

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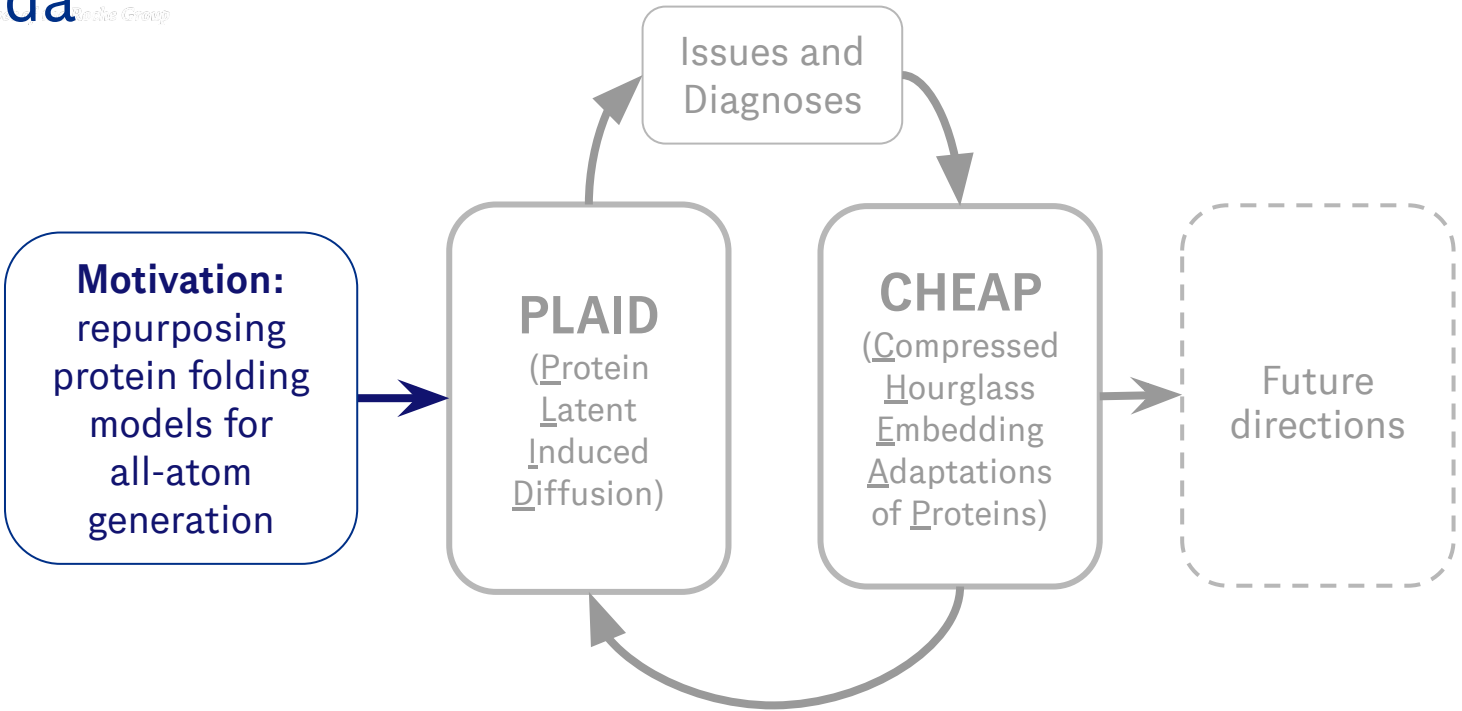
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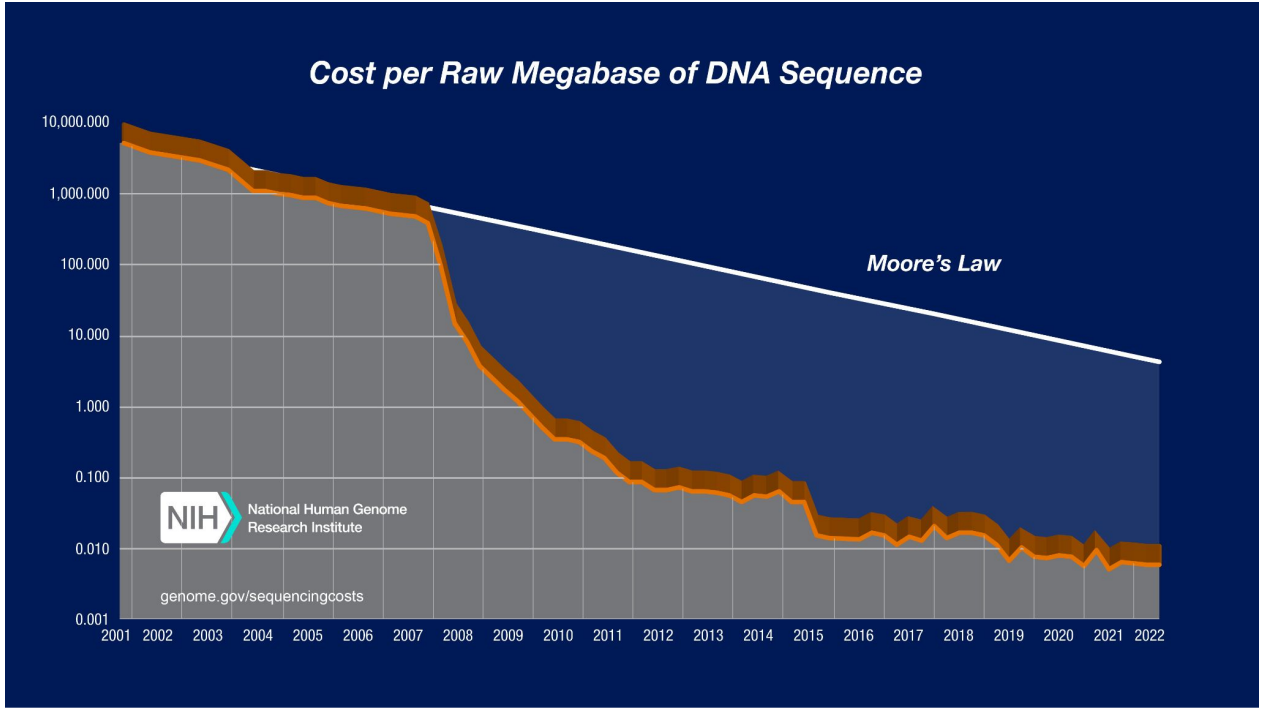
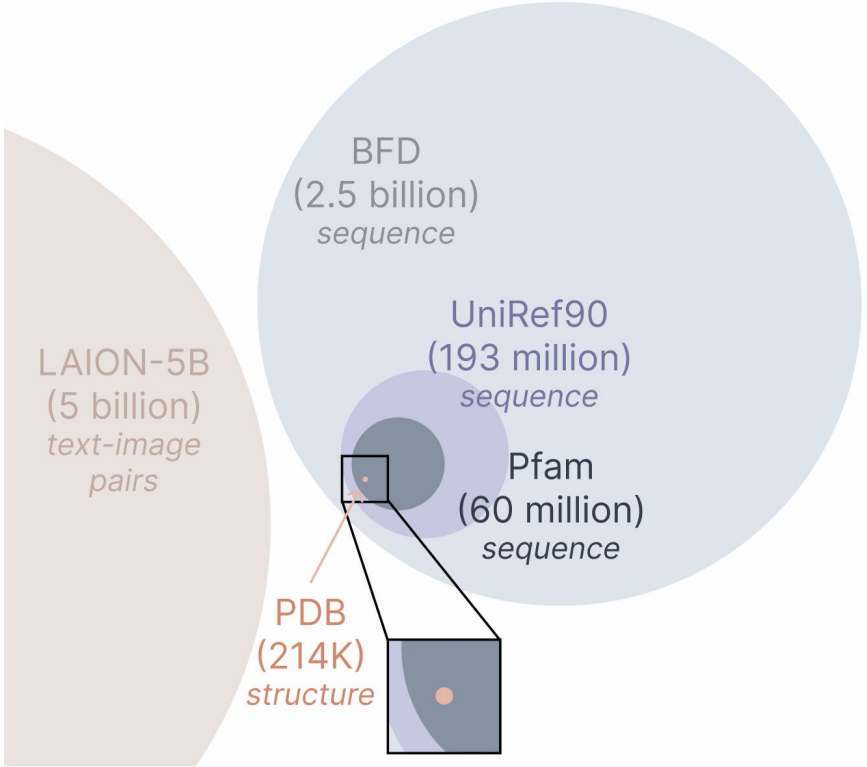
Sequence data is cheaper to collect than structure

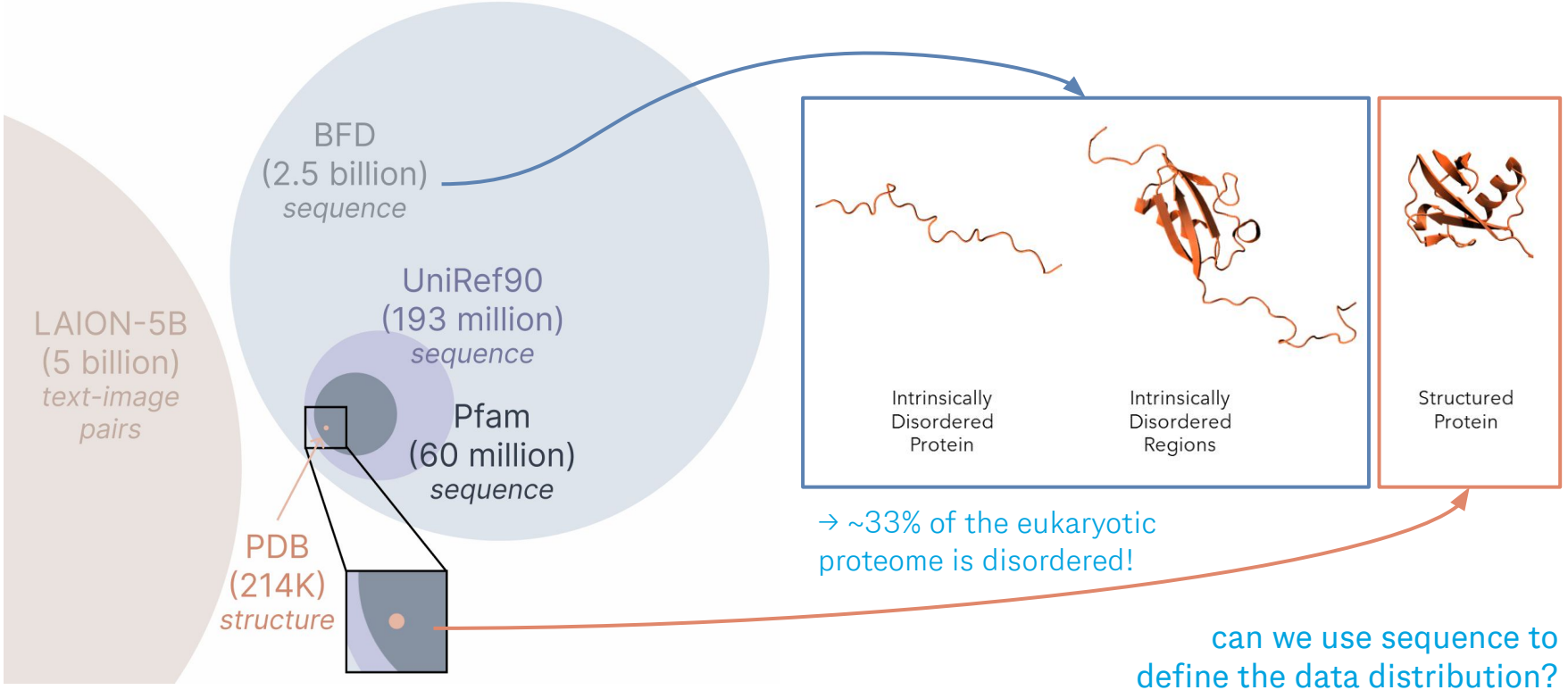


Source: https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

Sequence data is more abundant than structure



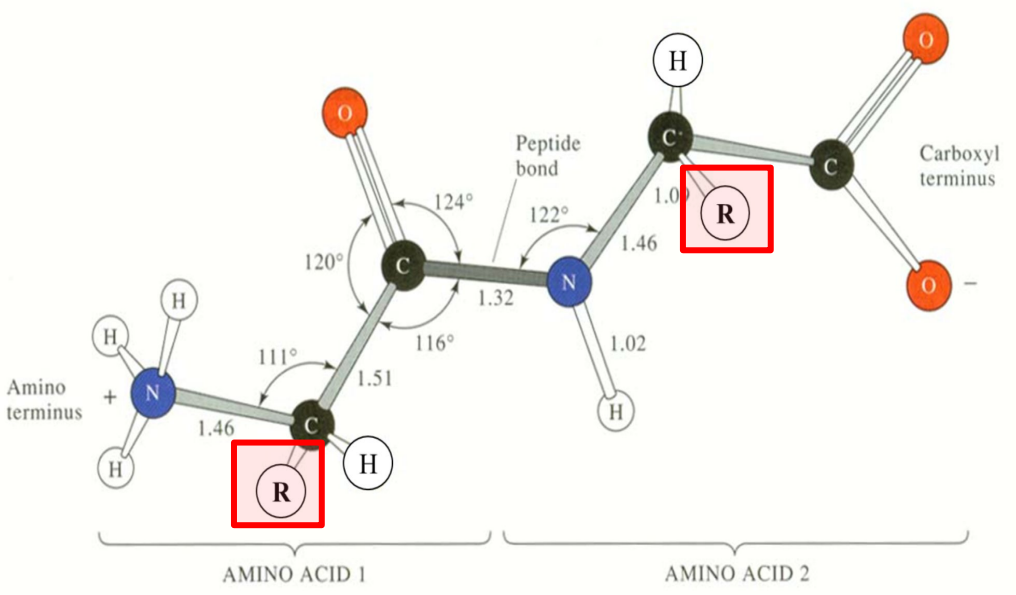
Sequence data has different coverage than structure



→ ~33% of the eukaryotic proteome is disordered!

can we use sequence to define the data distribution?

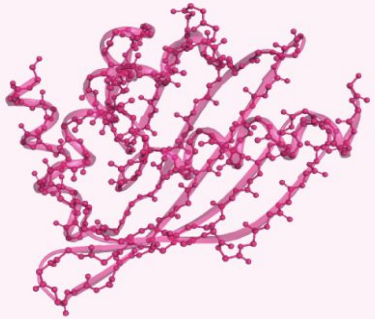
Backbone structure vs. all-atom structure



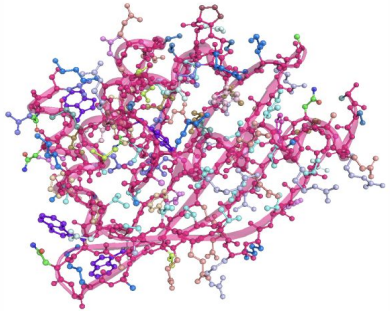
(order of t-shirts => protein sequence)

Sidechain atoms generation require knowing the sequence

BACKBONE ATOMS

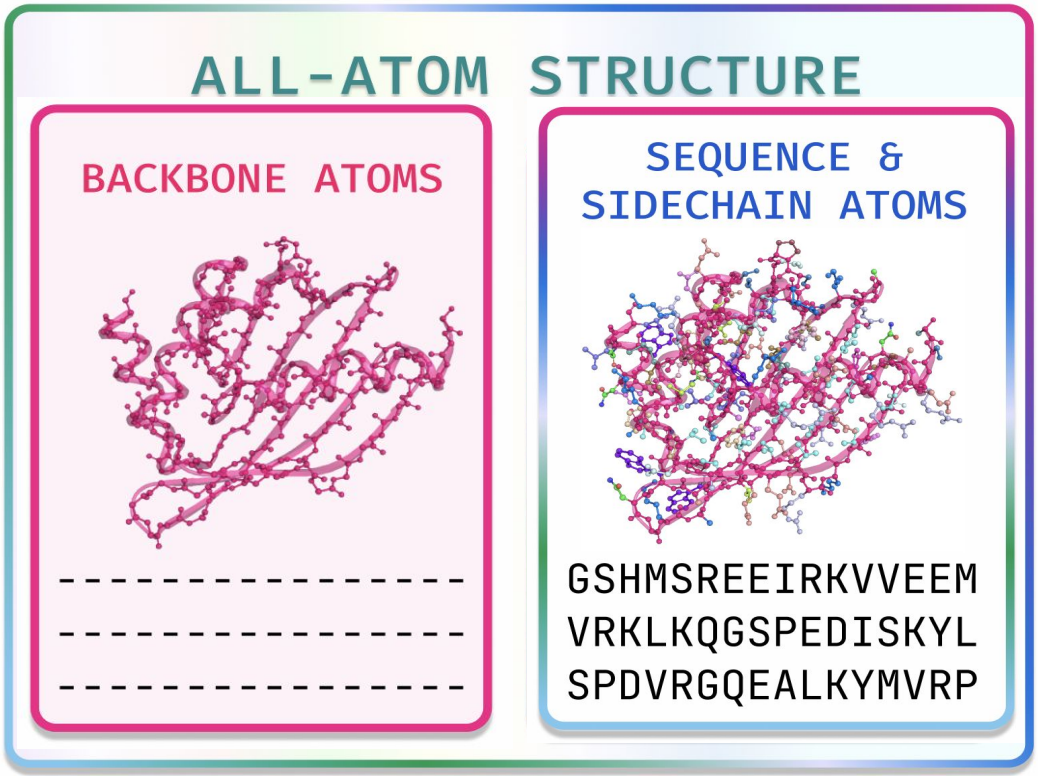


SEQUENCE & SIDECHAIN ATOMS

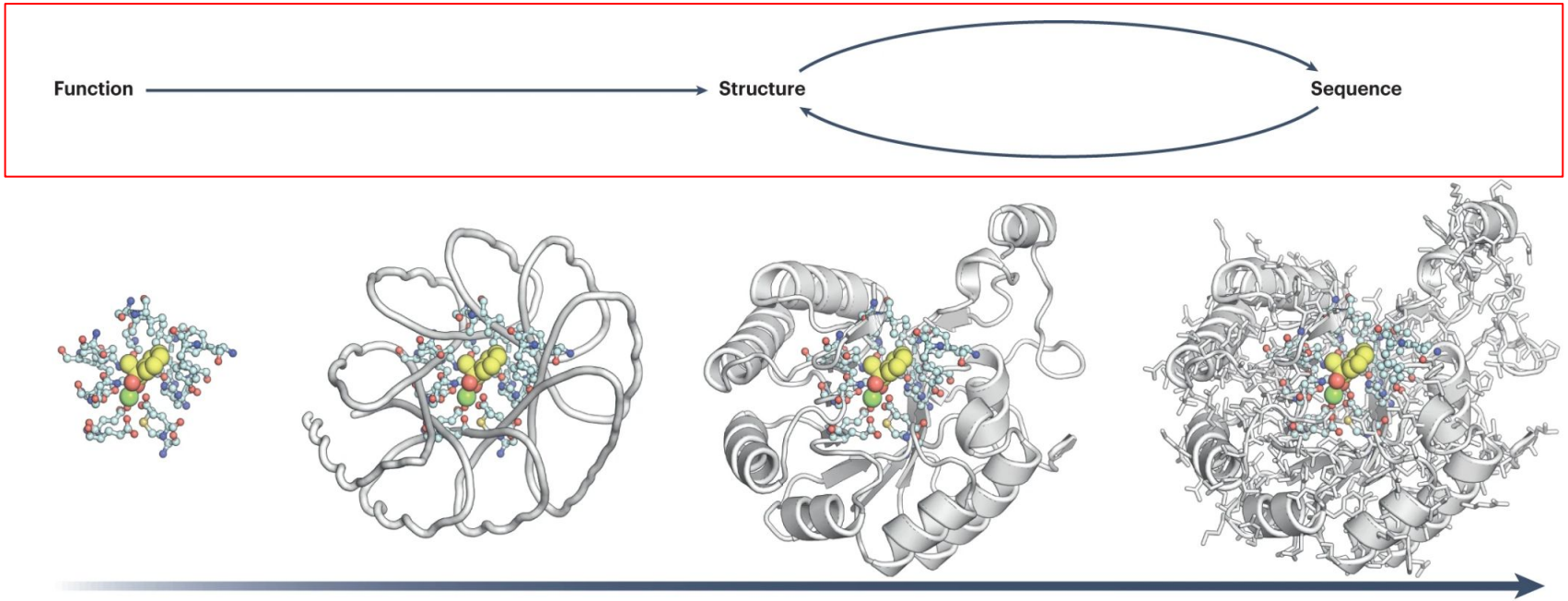


GSHMSREEIRKVVEEM
VRKLKQGSPEDISKYL
SPDVRGQEALKYMVRP

All-atom design as a multimodal generation problem



Problem: Current all-atom methods iterate between sequence and structure design



Chu, A.E., Lu, T. & Huang, PS. **Sparks of function by de novo protein design**. Nat Biotechnol 42, 203–215 (2024).

Motivation: Can we repurpose priors from pretrained models?

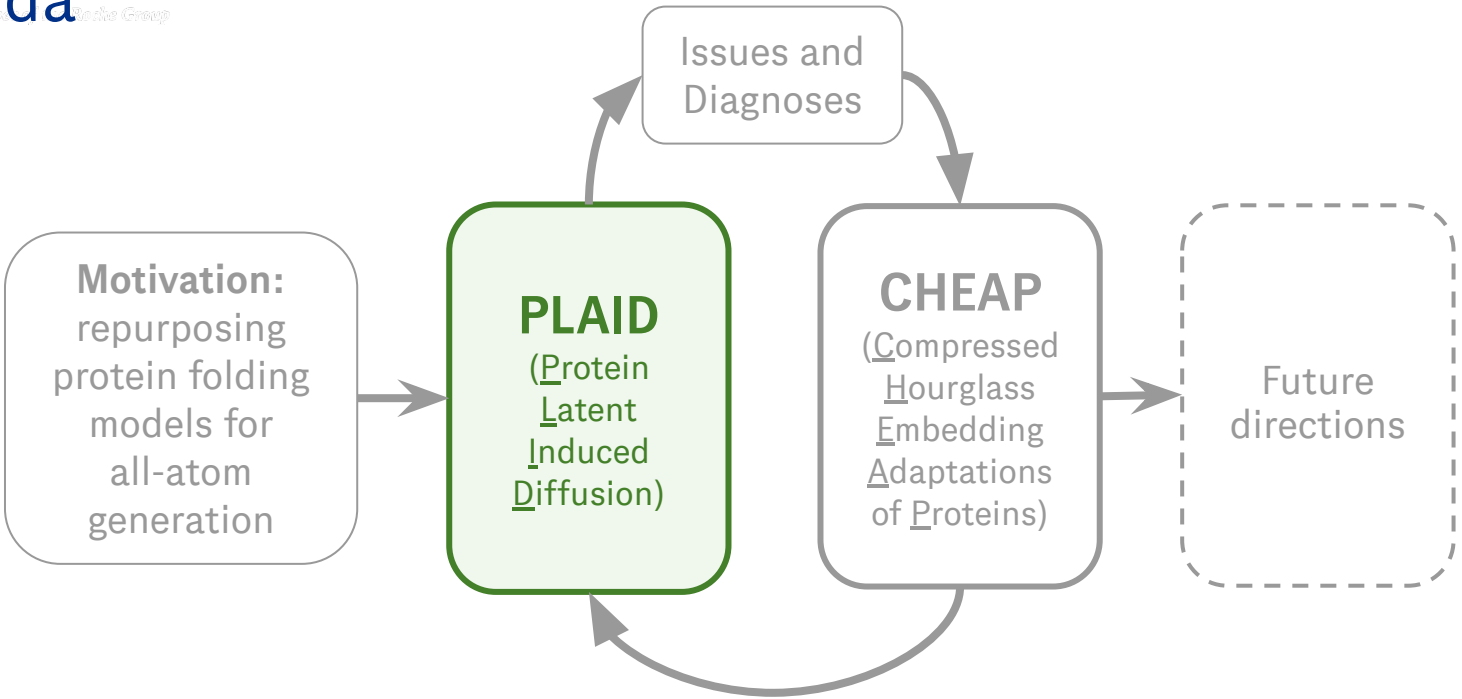
RT-2: Vision-Language-Action Models Transfer Web Knowledge to Robotic Control

Vision-language models trained on internet-scale datasets capture useful priors for robotic tasks.

How can we apply this to biology?

Can we sample all-atom structure from the joint distribution p(sequence, structure) and use priors from pretrained protein folding models?

Agenda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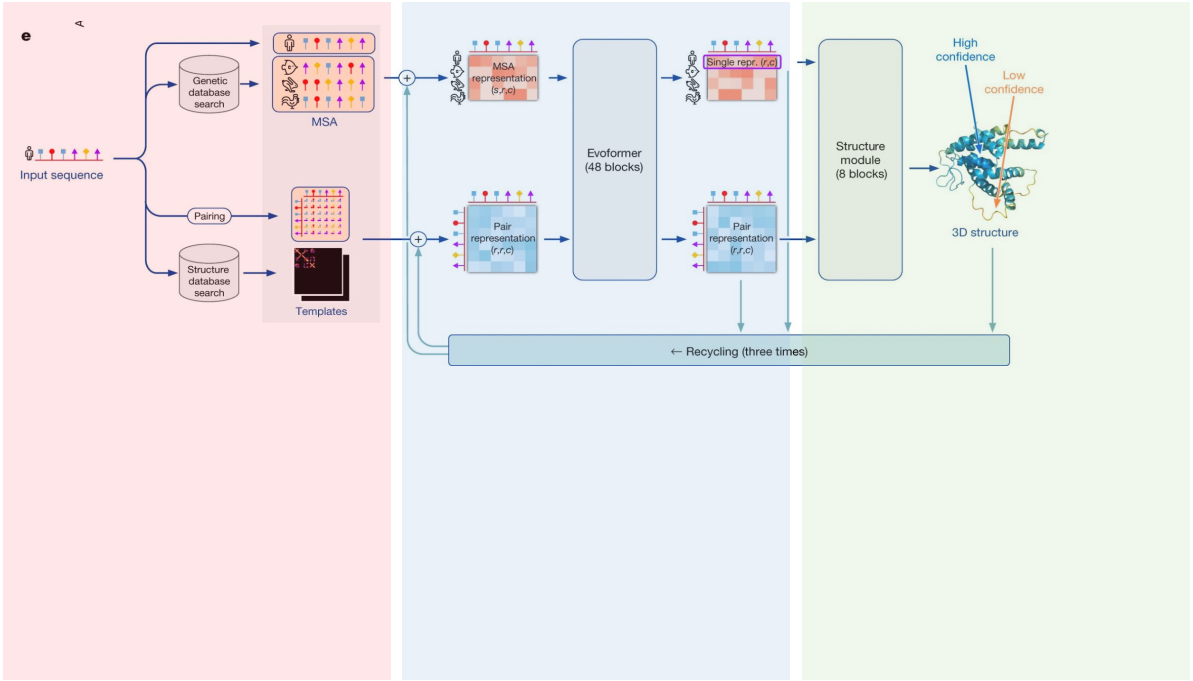
The base components: protein folding model architectures

AlphaFold2:

Uses an explicit retrieval step



harness additional sequence-based priors

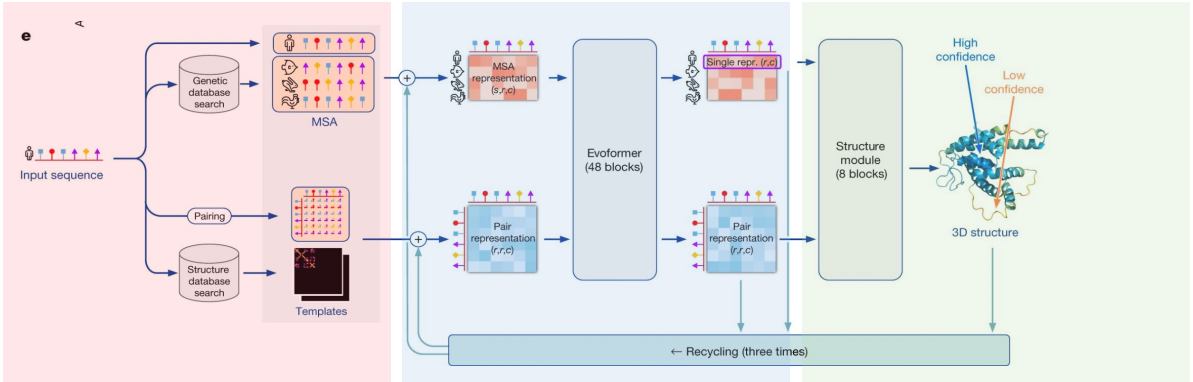
learn structural features from sequence latents

generate structures

The base components: protein folding model architectures

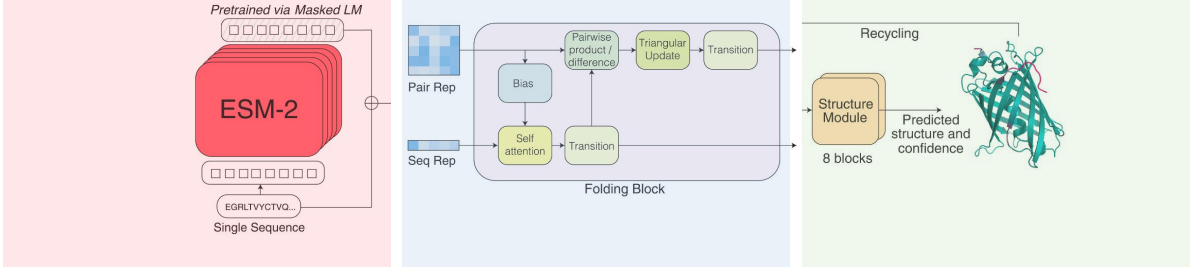
AlphaFold2:

Uses an explicit retrieval step



ESMFold:

Replaces retrieval step with a **language model**



harness additional sequence-based priors

learn structural features from sequence latents

generate structures

main esm / esm / esmfold / v1 / esmfold.py ↑ Top

Code Blame 364 lines (305 loc) · 13.6 KB Raw

```
152     def forward(
185         # === ESM ===
186         esmaa = self._af2_idx_to_esm_idx(aa, mask)
187
188         if masking_pattern is not None:
189             esmaa = self._mask_inputs_to_esm(esmaa, masking_pattern)
190
191         esm_s, esm_z = self._compute_language_model_representations(esmaa)
192
193         # Convert esm_s to the precision used by the trunk and
194         # the structure module. These tensors may be a lower precision if, for example,
195         # we're running the language model in fp16 precision.
196         esm_s = esm_s.to(self.esm_s_combine.dtype)
197         esm_s = esm_s.detach()
198
199         # === preprocessing ===
200         esm_s = (self.esm_s_combine.softmax(0).unsqueeze(0) @ esm_s).squeeze(2)
201
202         s_s_0 = self.esm_s_mlp(esm_s)
203         if self.cfg.use_esm_attn_map:
204             esm_z = esm_z.to(self.esm_s_combine.dtype)
205             esm_z = esm_z.detach()
206             s_z_0 = self.esm_z_mlp(esm_z)
207         else:
208             s_z_0 = s_s_0.new_zeros(B, L, L, self.cfg.trunk.pairwise_state_dim)
209
210         s_s_0 += self.embedding(aa)
211
212         structure: dict = self.trunk(
213             s_s_0, s_z_0, aa, residx, mask, no_recycles=num_recycles
214         )
```

Observation: at inference, the pairwise input is initialized as zeros…

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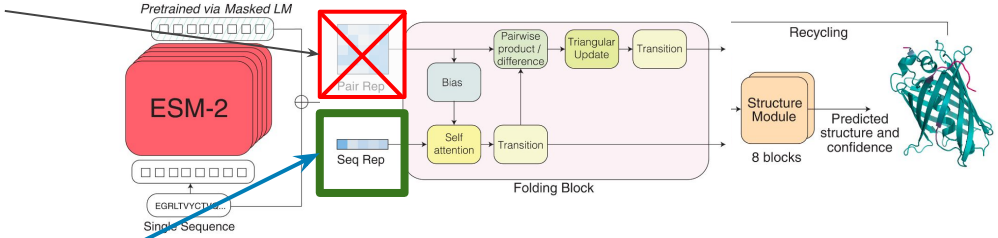
→ Sequence representation contains all information about the structure!



harness additional sequence-based priors

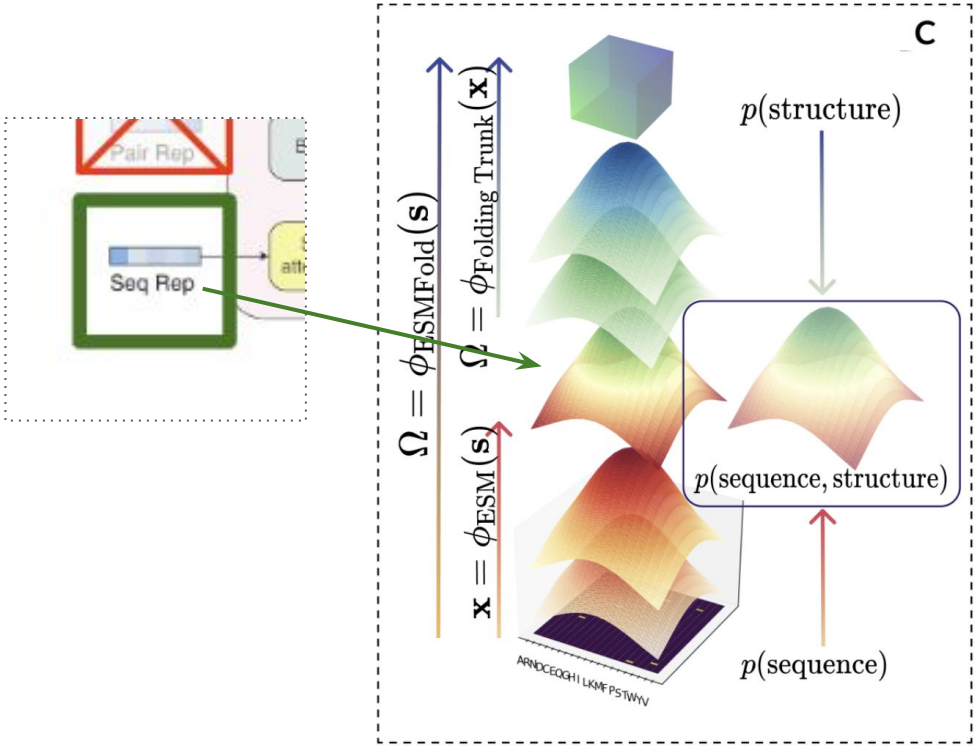
learn structural features from sequence latents

generate structures

Observation: at inference, the pairwise input is initialized as zeros...

→ Sequence representation contains all information about the structure!

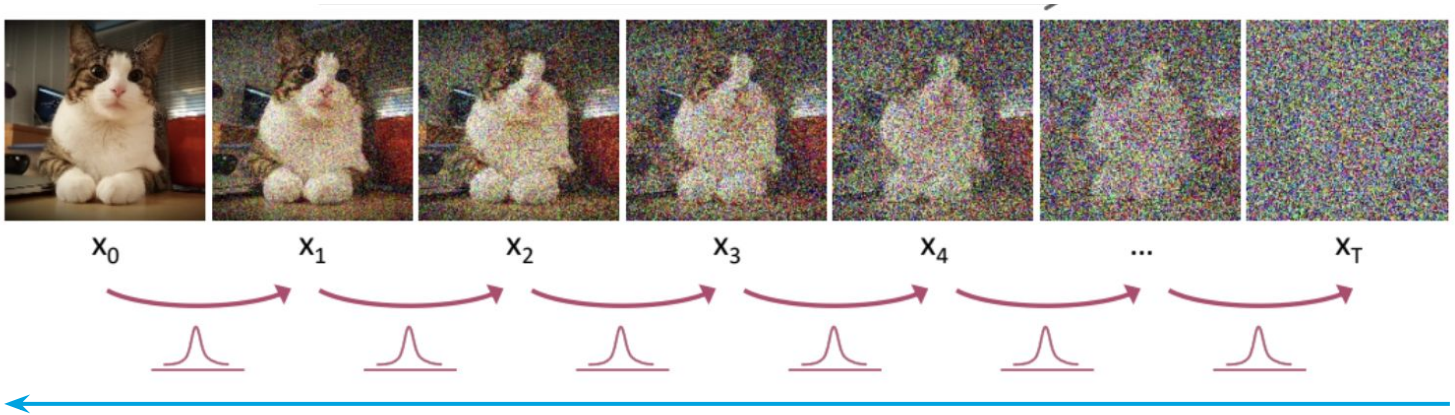
Generating this embedding would only require the sequence during training.



A 5 second primer on diffusion models

Training: add noise and predict denoised version

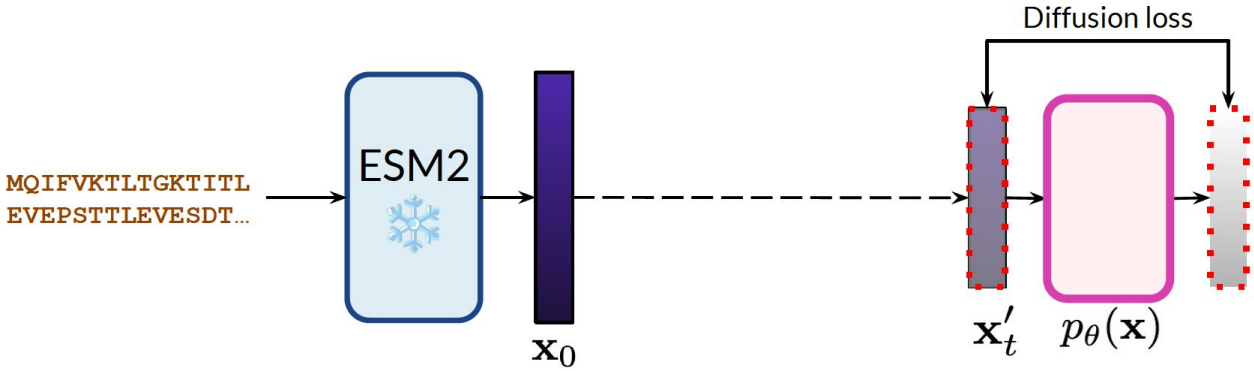
Data distribution



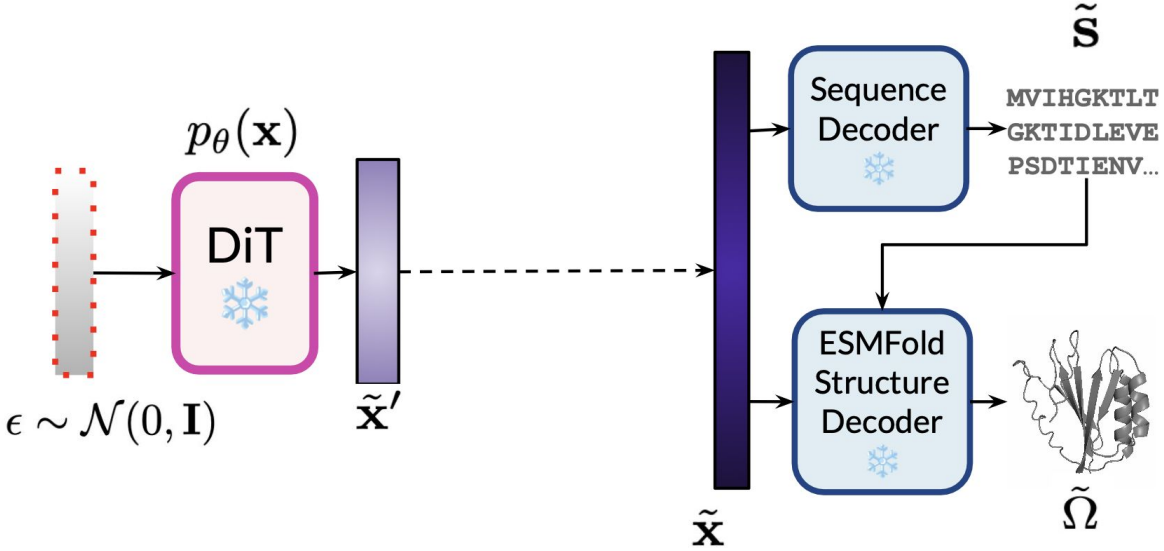
Inference: generate data from noise

Image source: Arash Vahdat and Karsten Kreis

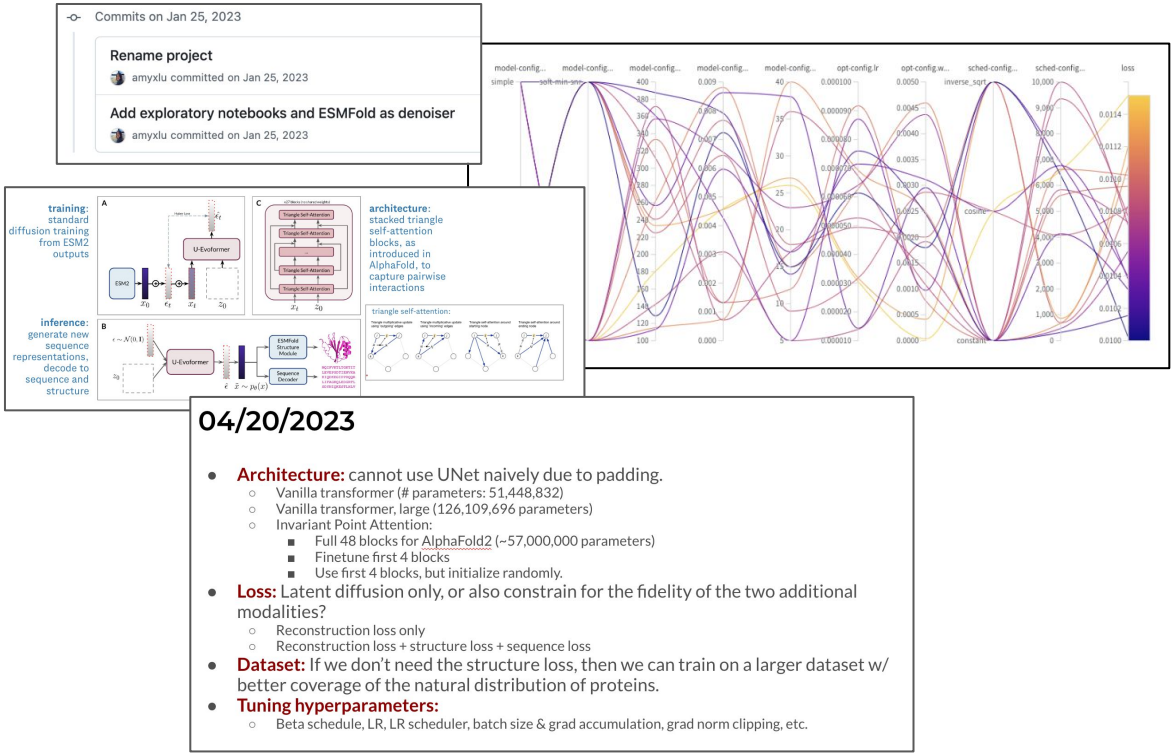
PLAID v0.5: Training a latent diffusion model



PLAID v0.5: Inference-time all-atom generation



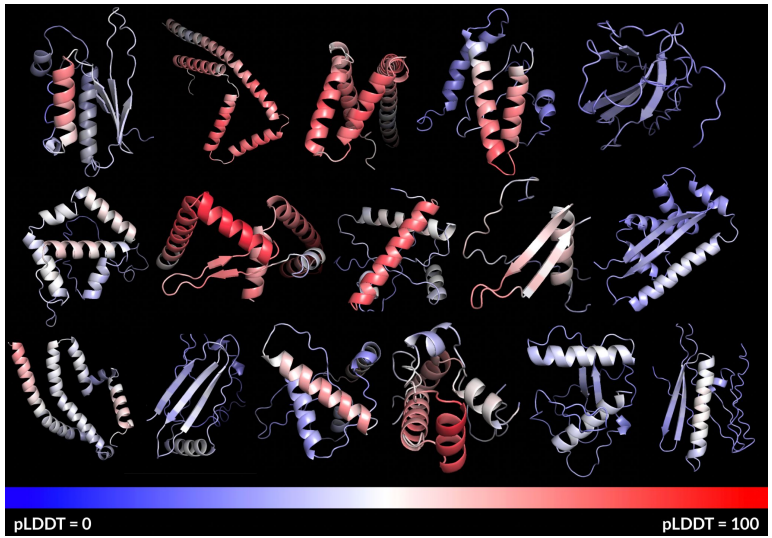
PLAID v0.5: Early attempts

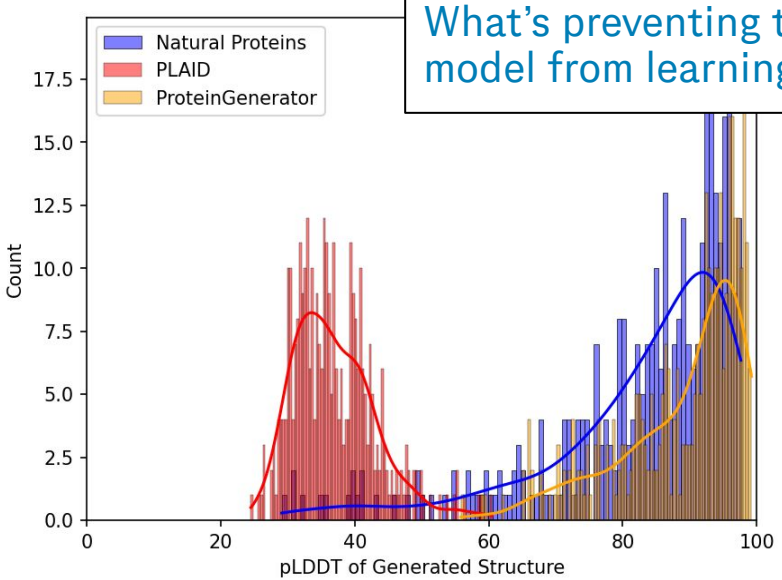


tried many things which did not work 😢

- adding a structure/sequence semantic reconstruction loss
- Finetuning ESMFold (à la RFDiffusion)
  - predict x_0 instead of noise?
- Huber vs. MSE loss
- Gradient-based guidance towards properties
- Triangle self-attention
- ...

PLAID v0.5: Early attempts

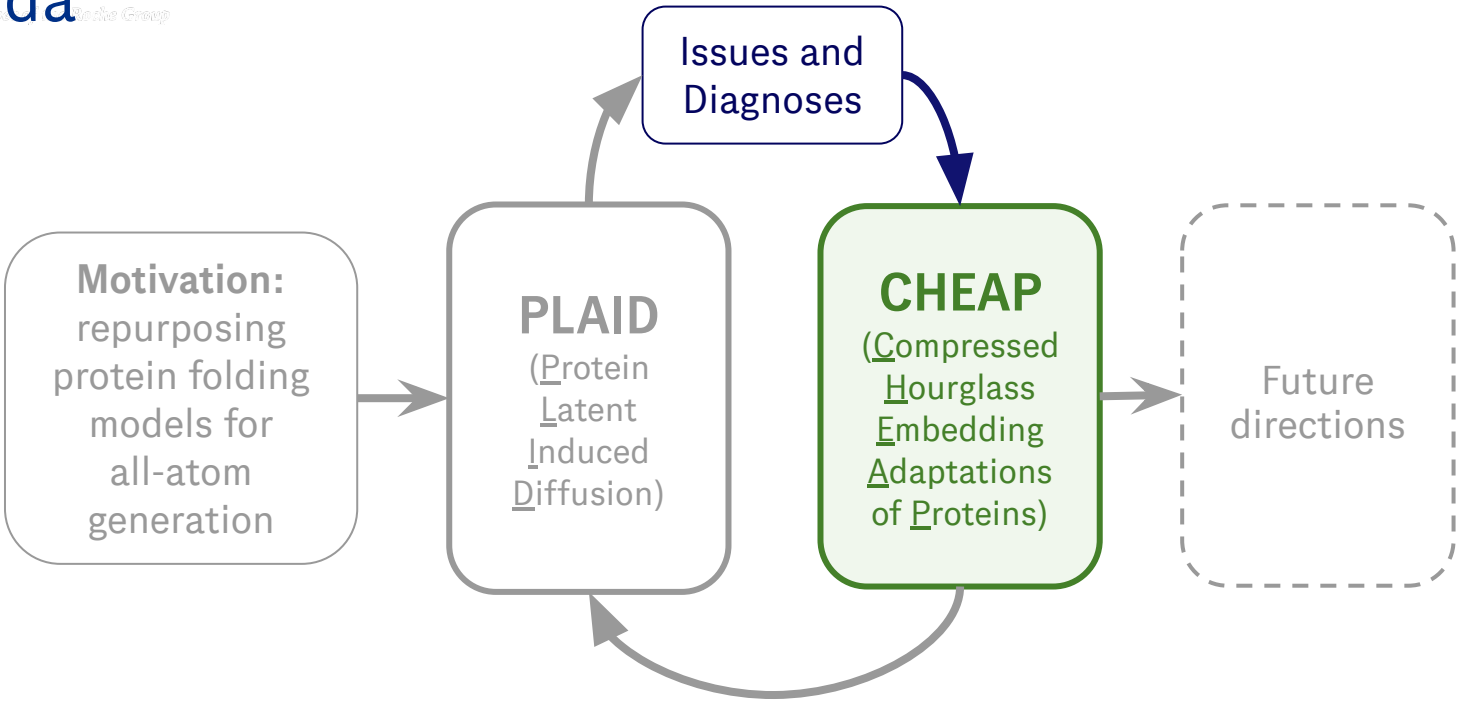




What's preventing the model from learning?

PLAID v0.5: Generating Protein Sequence and Structure Without Structural Training Data
Amy X. Lu, Kevin K. Yang, Pieter Abbeel
ICML 2024 Workshop on Machine Learning for Life and Material Sciences

Agenda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Issues and hypotheses

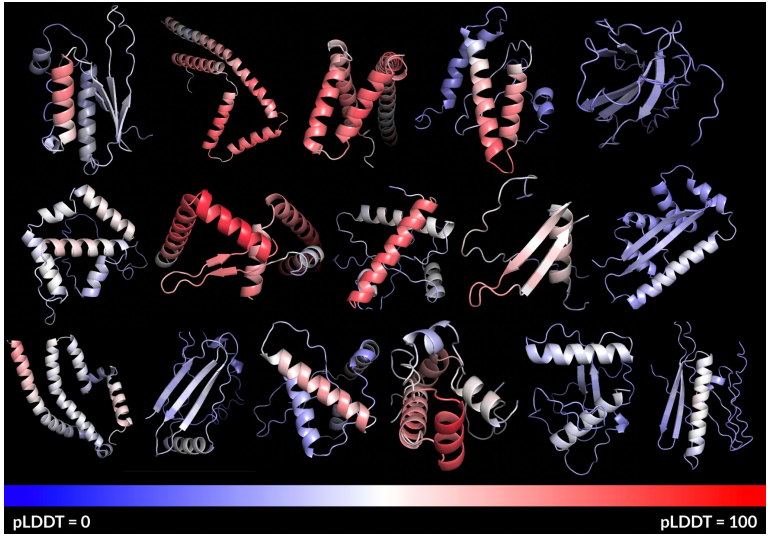
- Latent space requires regularization

> In order to avoid arbitrarily high-variance latent spaces, we experiment with two different kinds of regularizations. The first variant, *KL-reg.*, imposes a slight KL-penalty towards a standard normal on the learned latent, similar to a VAE [46, 69], whereas *VQ-reg.* uses a vector quantization layer [96] within the decoder. This model can be interpreted

Rombach et al. High-Resolution Image Synthesis with Latent Diffusion Models, CVPR 2022

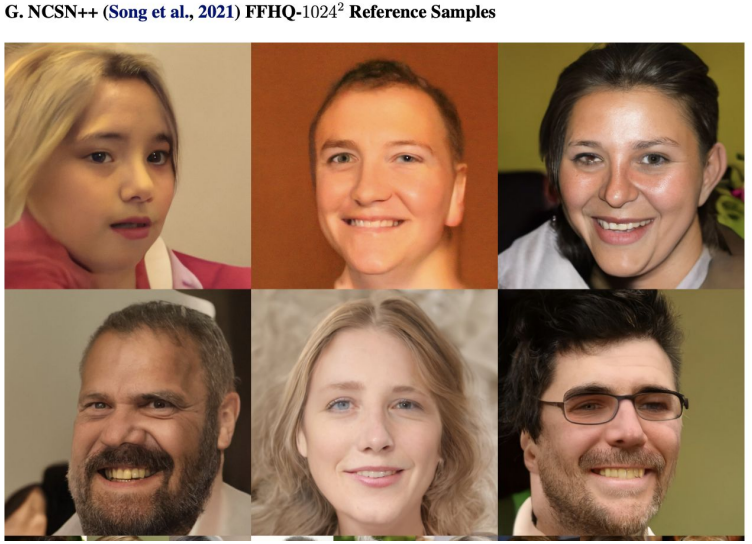
Issues and hypotheses

- Latent space requires regularization
- Overcome $O(L^2)$ memory constraints and increase protein length to 512



Issues and hypotheses

- Latent space requires regularization
- Overcome $O(L^2)$ memory constraints and increase protein length to 512
- Large latent space corresponds to **high-resolution** image generation
  - Rombach et al. latent space: HxWx4 = 64 x 64 x 4
  - Ours: Lx1024 = 512 x 1024



Addressing the hypotheses: latent space regularization

Issues and hypotheses -> CHEAP

- Latent space requires regularization

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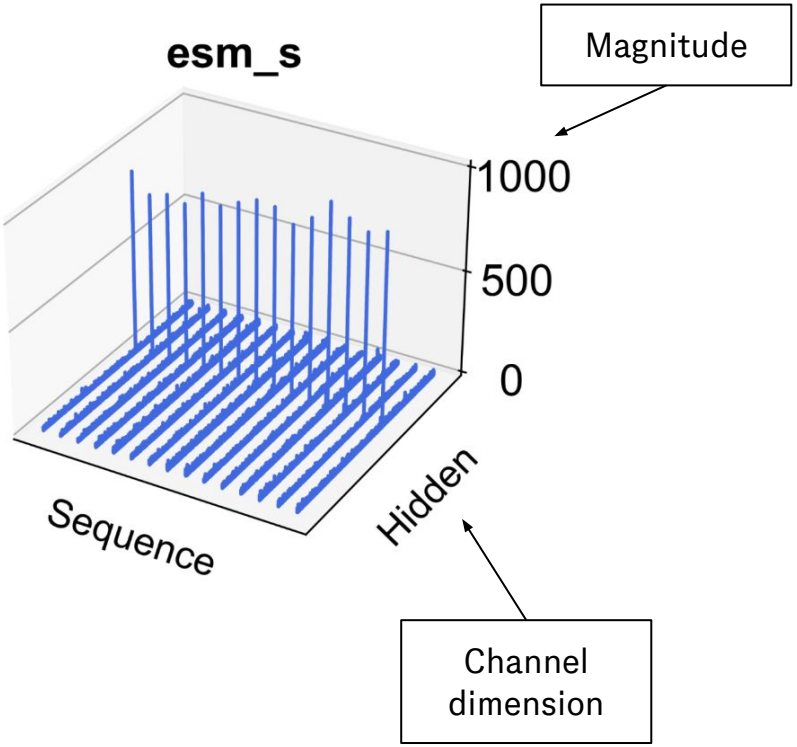
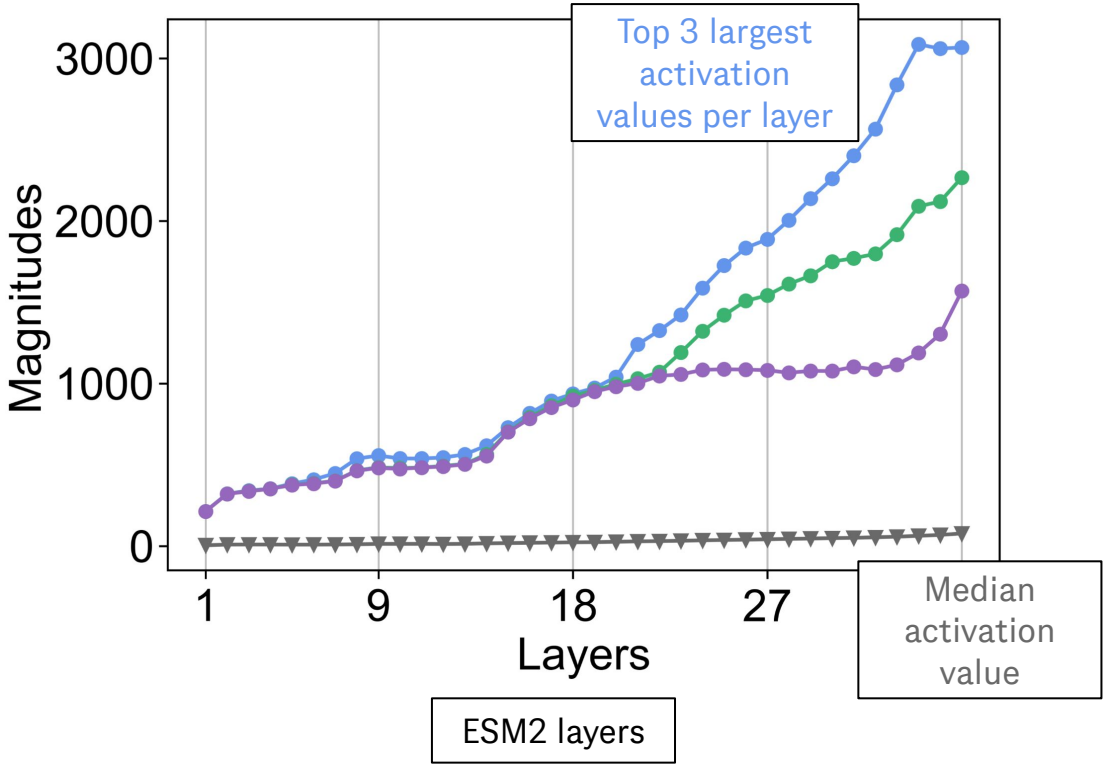
(1) Are the problems coming from the ESMFold latent space itself?

ESMFold latent space exhibits pathologically large values



Latent space will require regularization for diffusion to work.

~~ESMFold~~ ESM2 latent space exhibits pathologically large values



~~ESMFold~~ ~~ESM2~~ Large transformers latent space exhibits pathologically large values

→ a pervasive issue across LLMs, ViTs, etc.

[Submitted on 27 Feb 2024 (v1), last revised 14 Aug 2024 (this version, v2)]

Massive Activations in Large Language Models

Mingjie Sun, Xinlei Chen, J. Zico Kolter, Zhuang Liu

We observe an empirical phenomenon in Large Language Models (LLMs) -- very few activations exhibit significantly larger values than others (e.g., 100,000 times larger). We call them massive activations. First, we demonstrate the widespread existence of

LLM.int8(): 8-bit Matrix Multiplication for Transformers at Scale

Tim Dettmers[λ*] Mike Lewis[†] Younes Belkada[§∓] Luke Zettlemoyer[†λ]

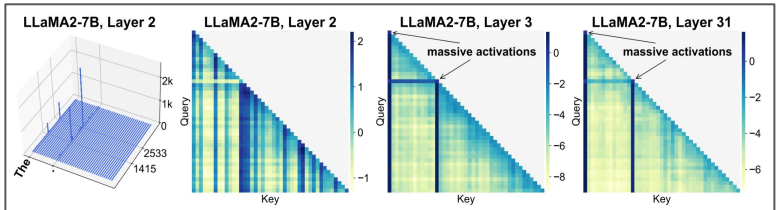
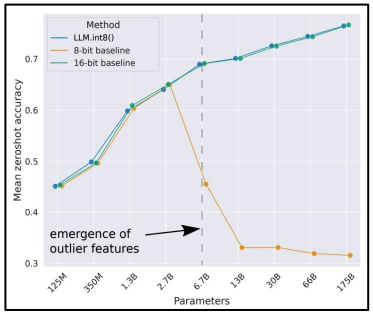
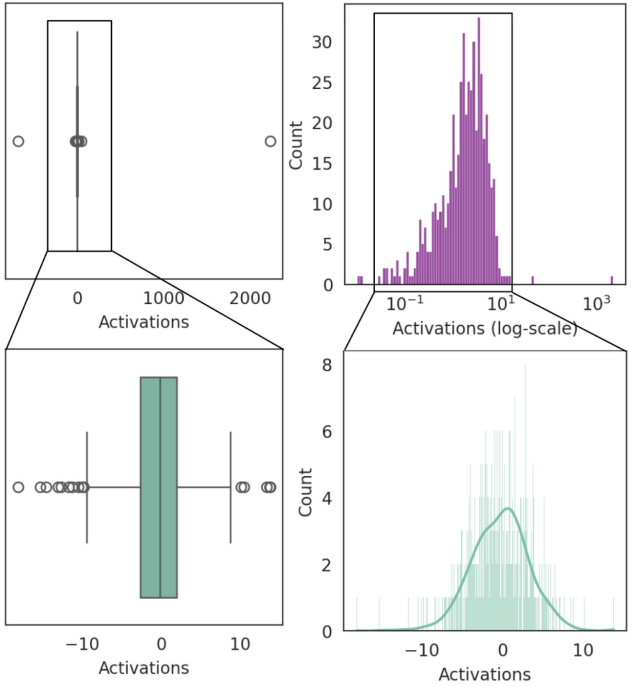


Figure 5: Attention patterns *before* and *after* massive activations appear in LLaMA2-7B. For each layer, we visualize average attention logits (unnormalized scores before softmax) over all heads, for an input sequence.



What if we just remove these wacky channels?



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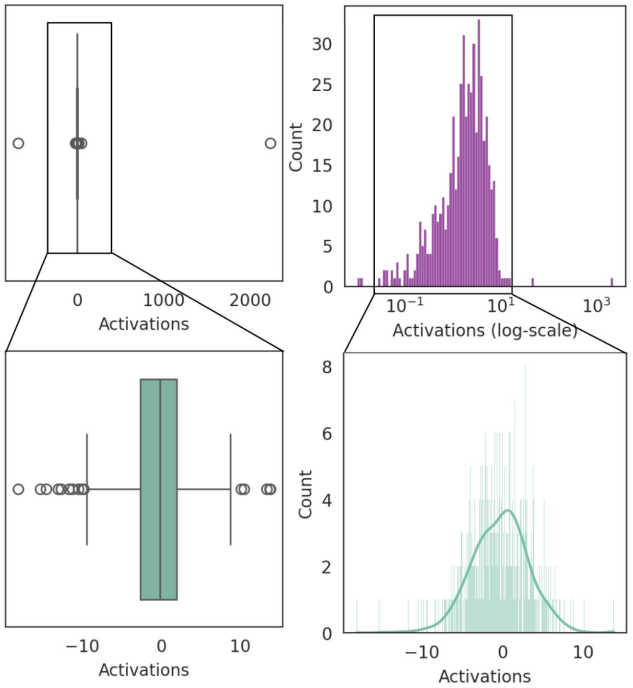
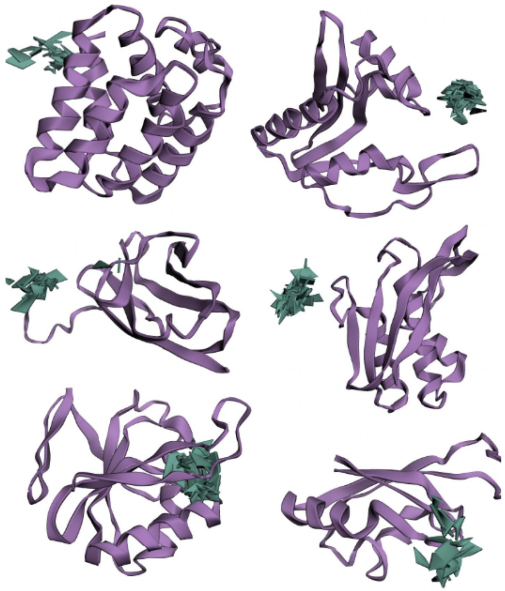
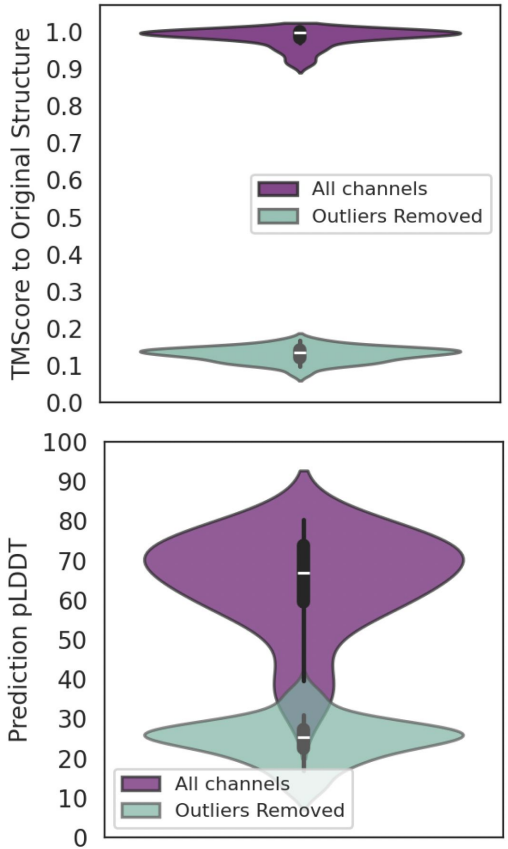
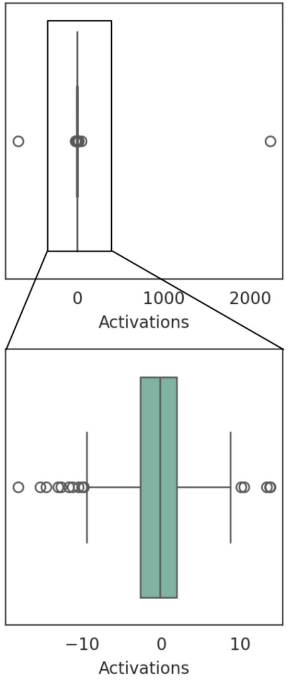
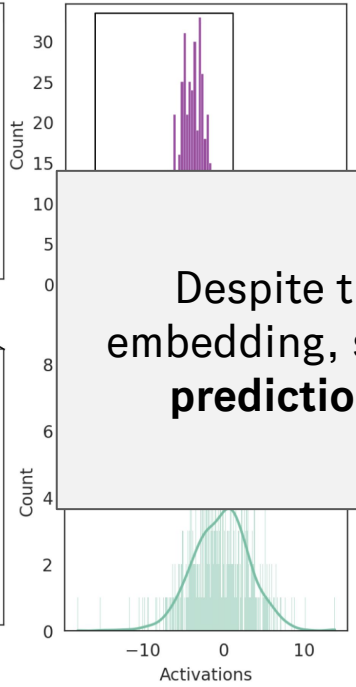




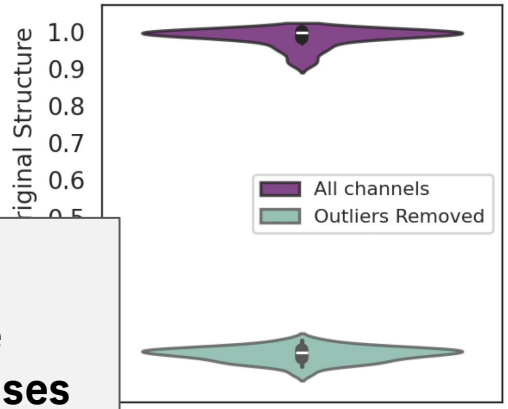


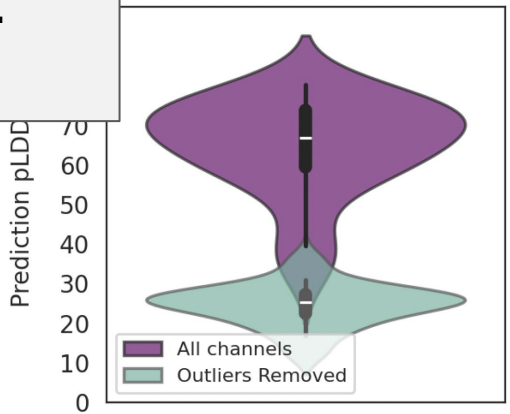
What if we just remove these wacky channels?





Despite there being **1024** channels in the embedding, simply **removing 3 channels causes prediction ability to entirely deteriorate.**

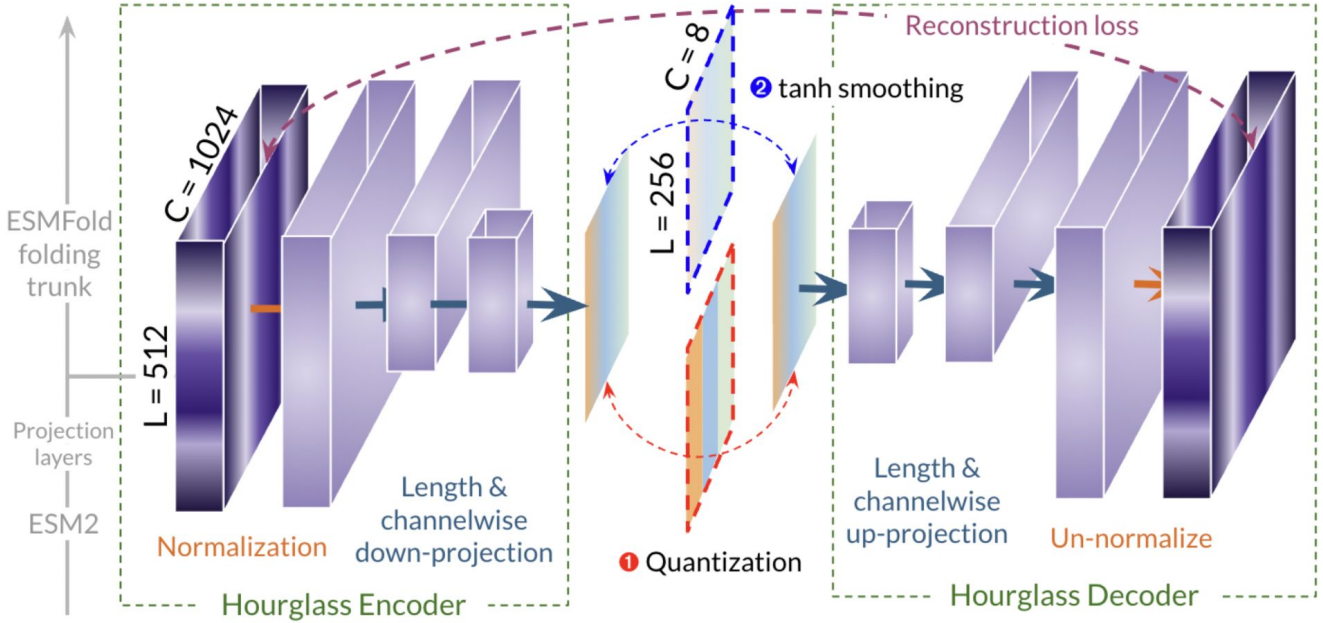




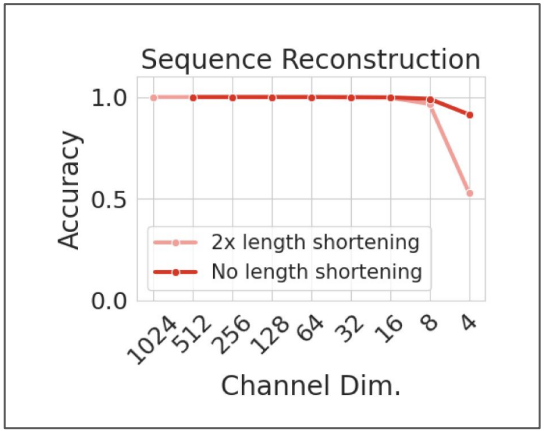
An autoencoder for protein embedding compression

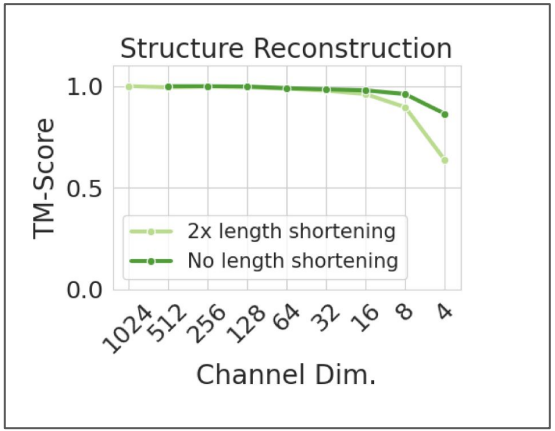
Simple fix for massive activations: standardize each channel independently.

$$\mathbf{x}' = \frac{\mathbf{x} - \mathbf{x}_{\min}}{\mathbf{x}_{\max} - \mathbf{x}_{\min}}$$



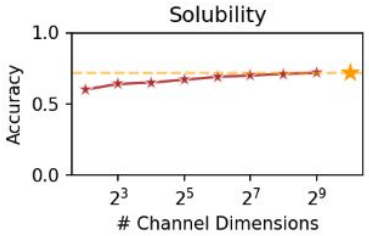
Turns out the latent space is highly compressible!

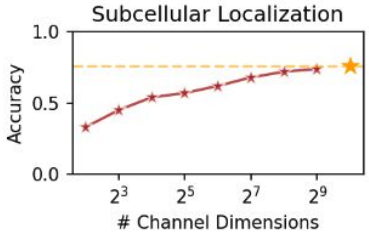




Sequence information is easier to retain than structure.

What about function information?

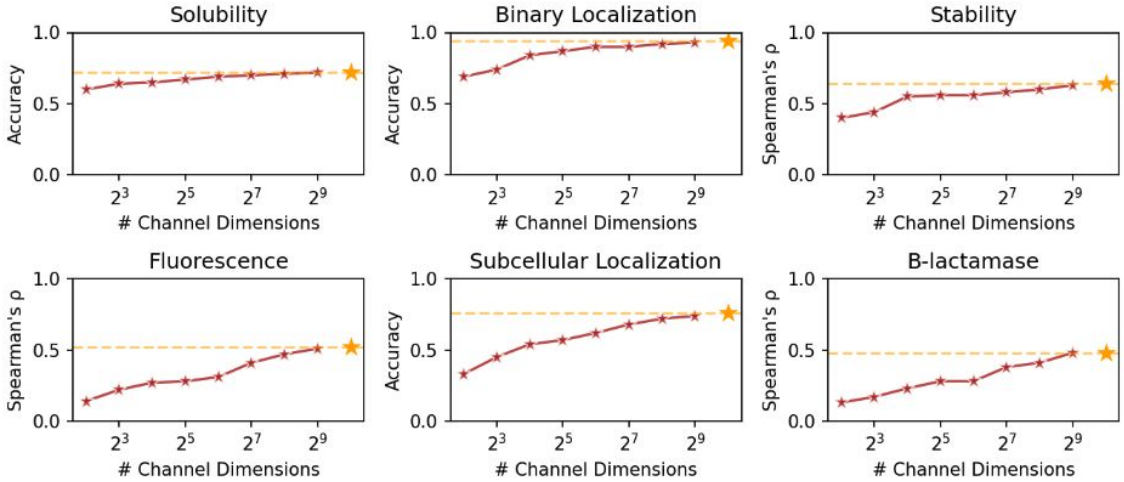




Performance degradation with compression is more gradual...

...for some functions.

What about function information?



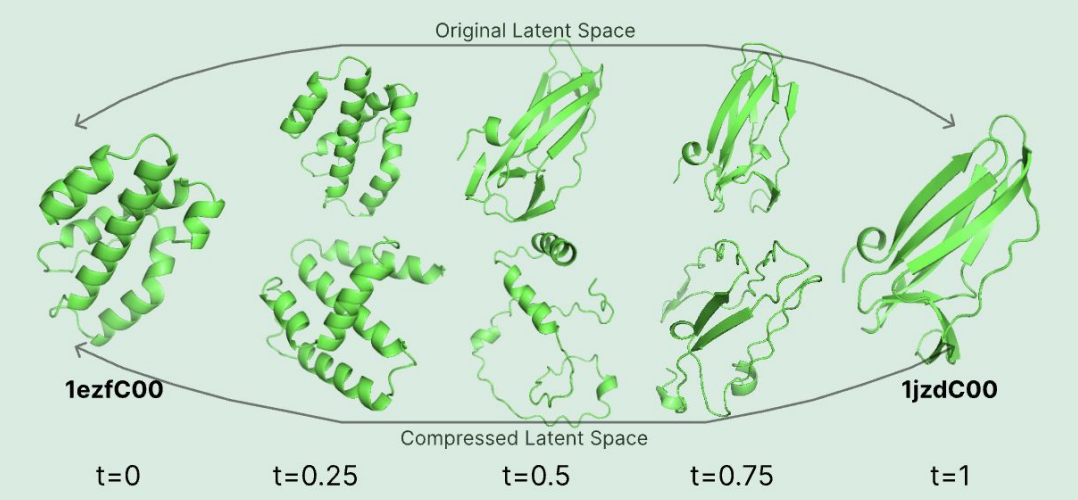
Performance degradation with compression is more gradual...

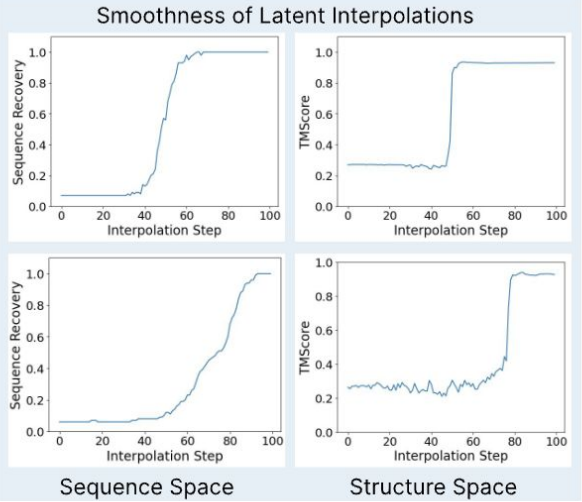
...for some functions.

Intuition: what is the speed of this motorcycle?

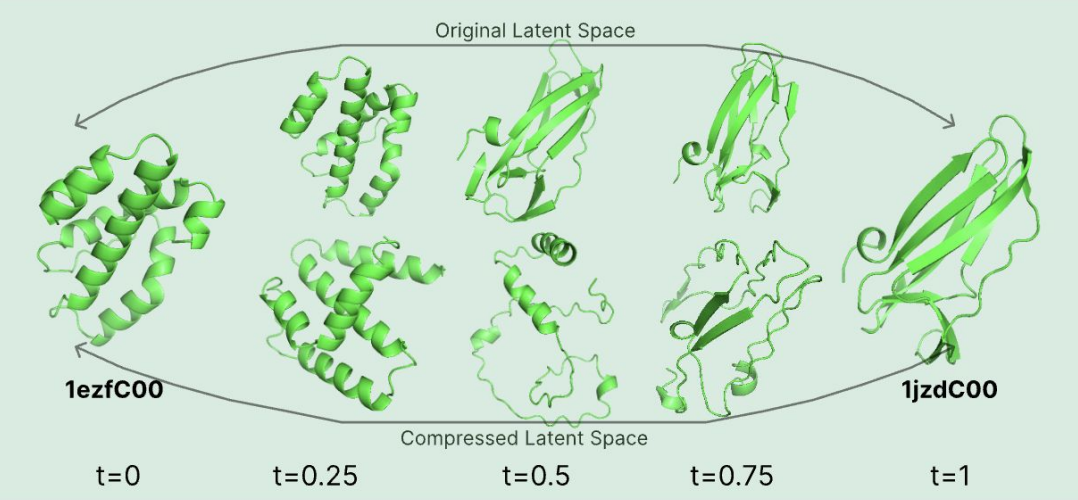
→ BMW S1000RR: 188 mph

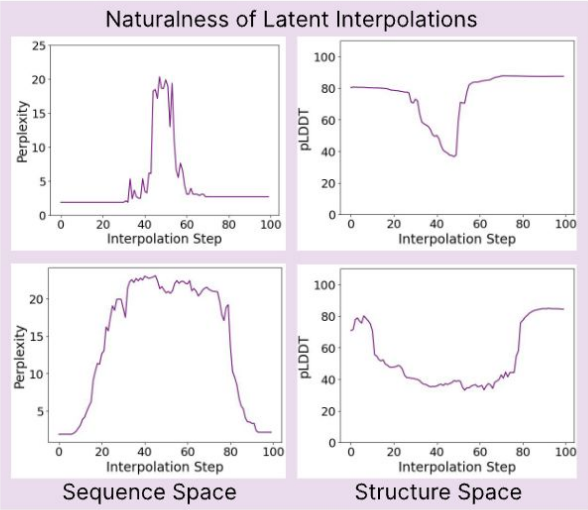
Linear interpolation in the latent space





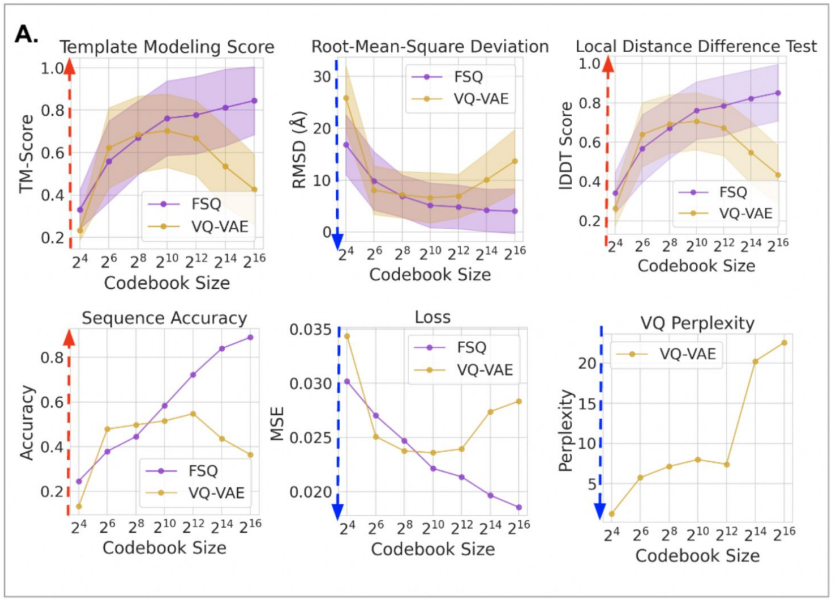
Linear interpolation in the latent space

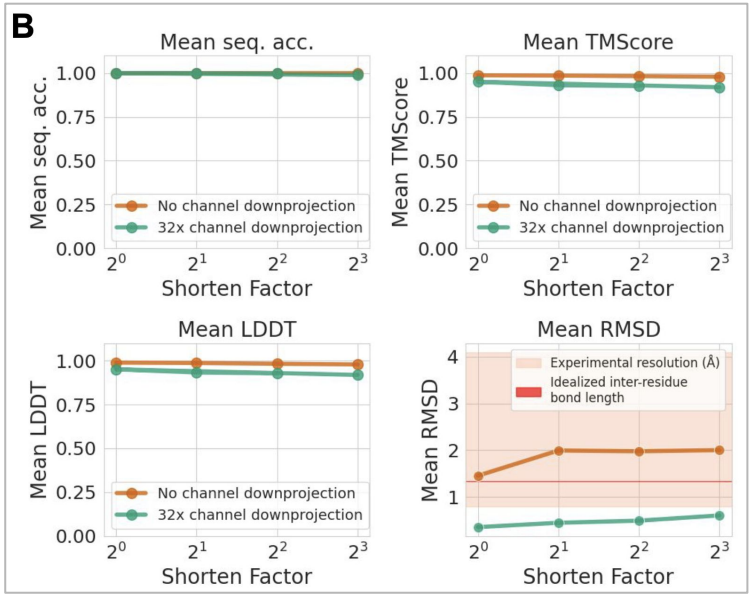




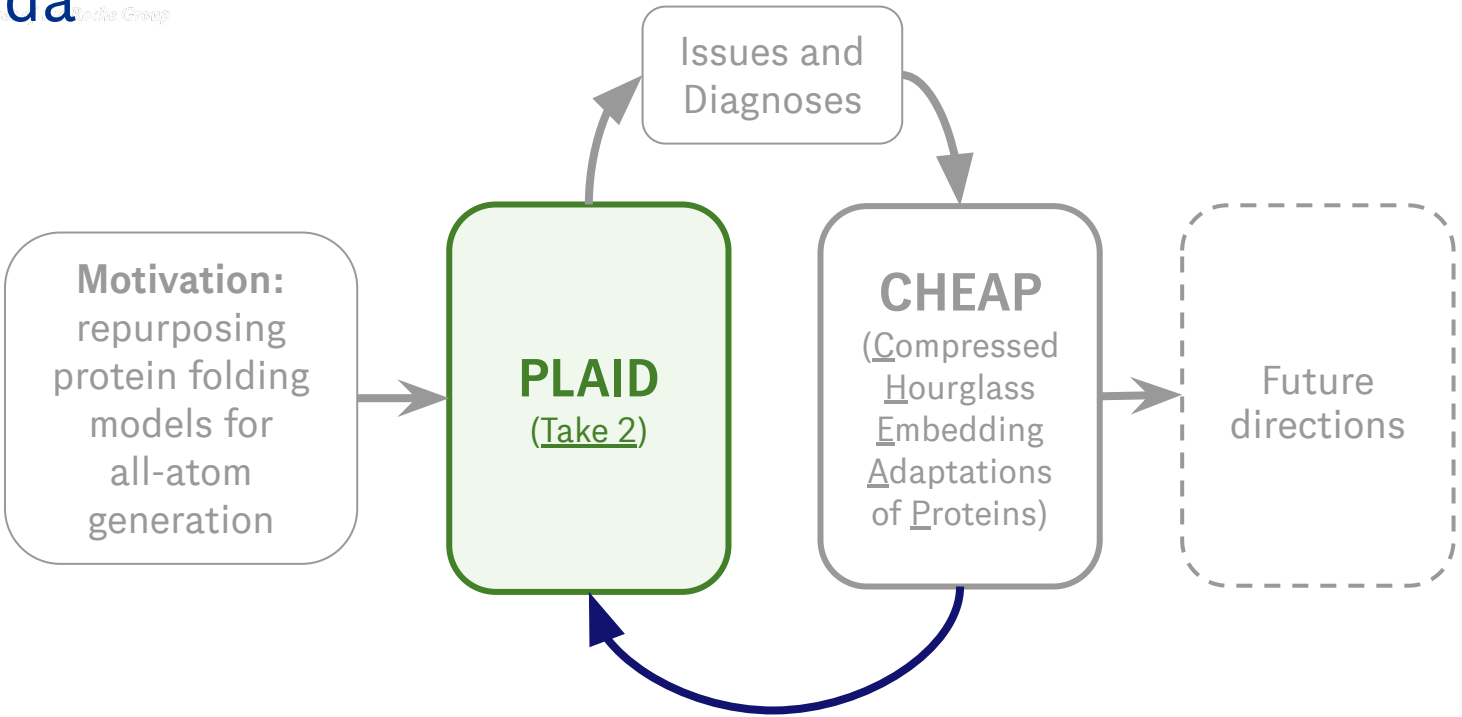
Protein language model latent spaces are less rugged than true fitness landscapes!

More results: bit.ly/cheap-proteins

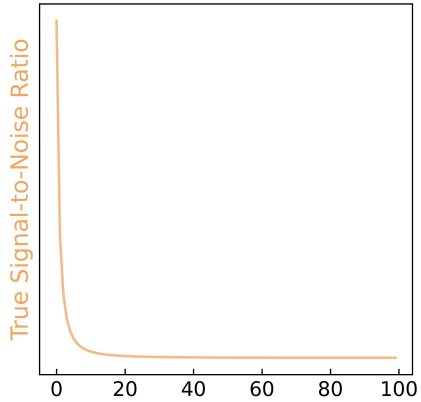


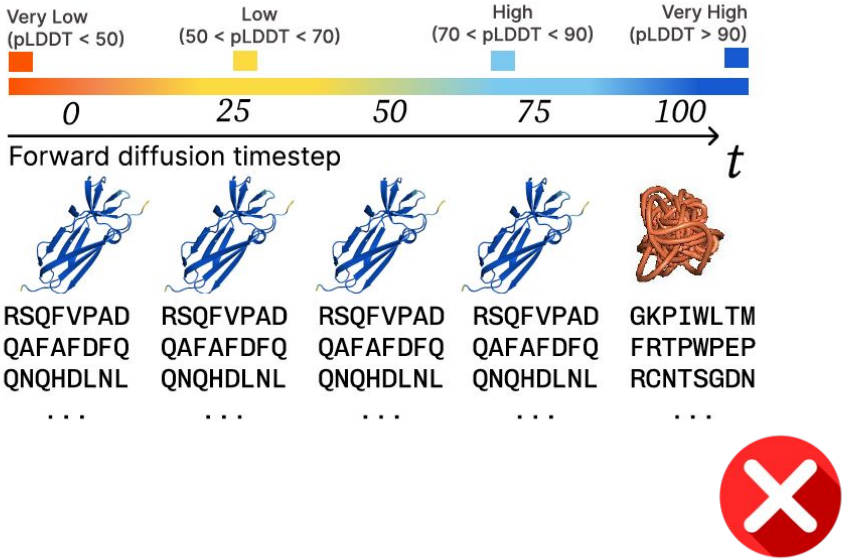


Agenda

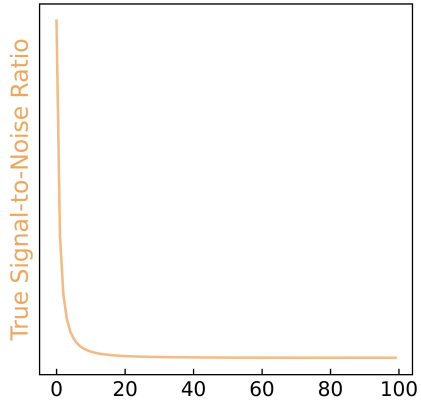

Issues and Diagnoses
Motivation: repurposing protein folding models for all-atom generation
PLAID (Take 2)
CHEAP (Compressed Hourglass Embedding Adaptations of Proteins)
Future directions

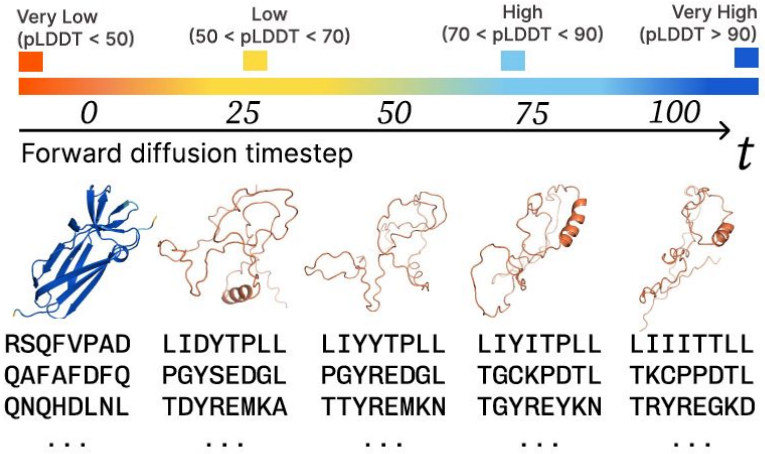
Noising the original latent space does not affect the structure...



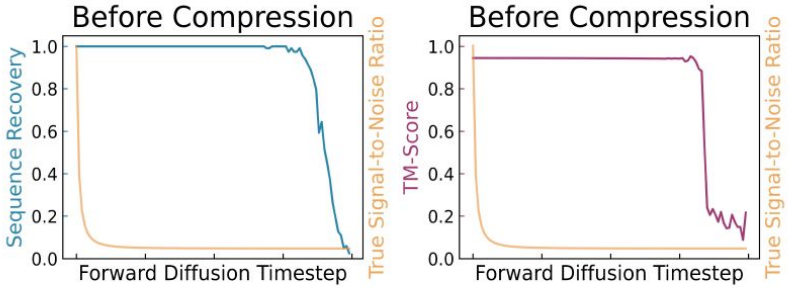


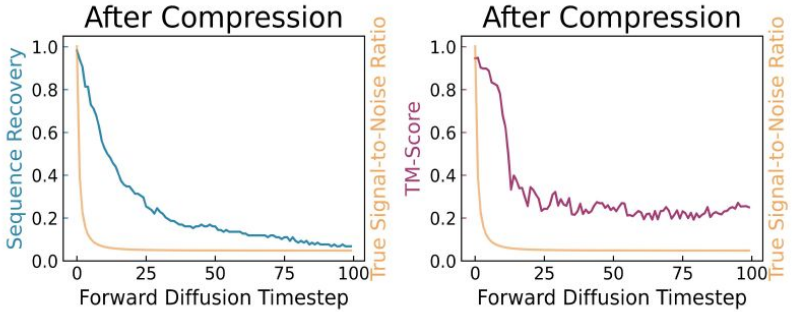
...noising the compressed latent space does map to corrupted structures



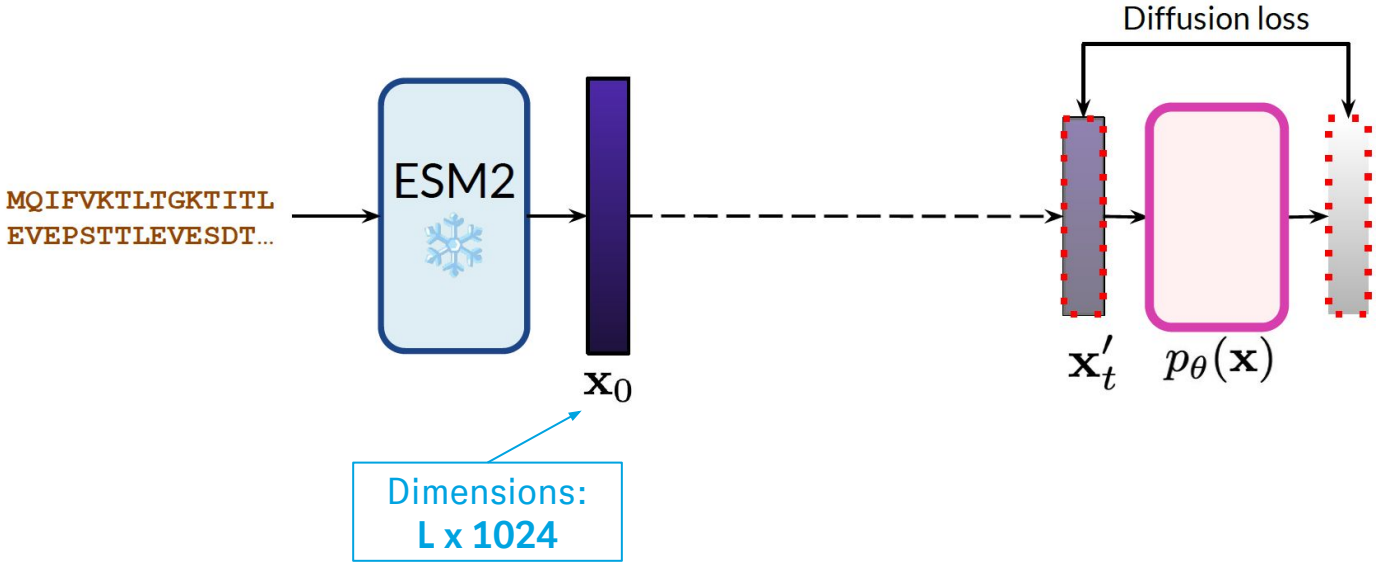


...noising the compressed latent space does map to corrupted structures

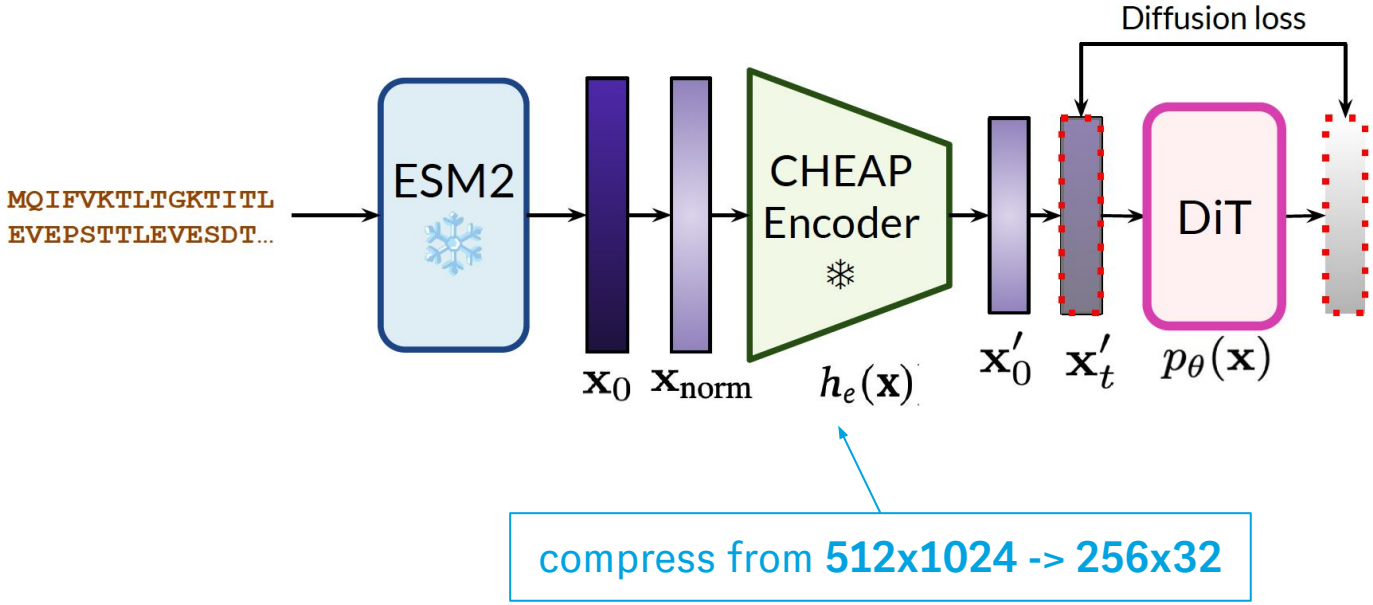




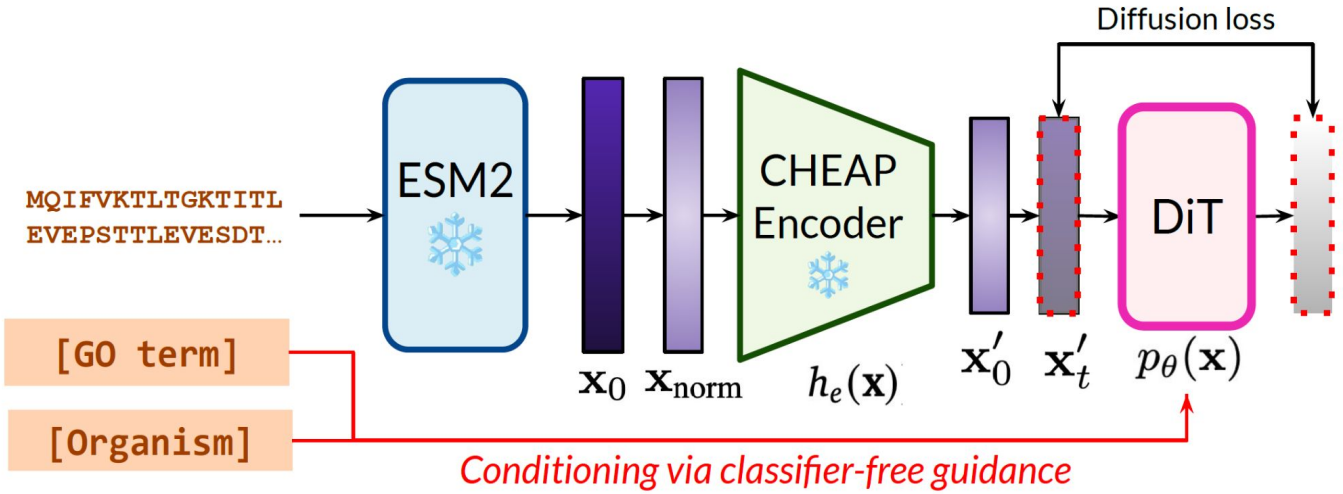
Training the PLAID latent diffusion model...



...but add embedding compression with CHEAP

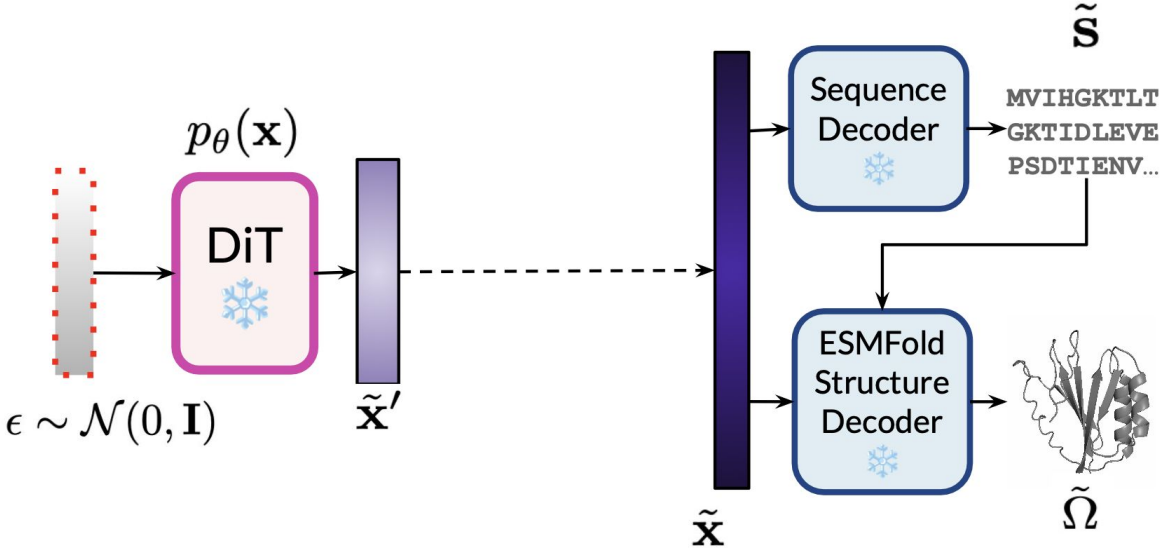


Adding compositional function + taxonomic conditioning

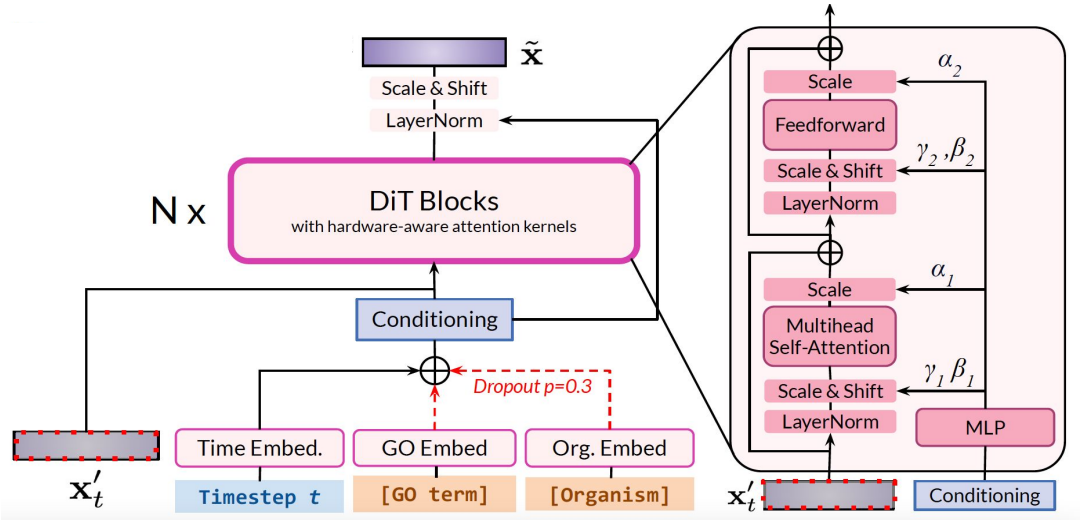


Sequence databases have more sample-annotation pairs!

PLAID Inference with CHEAP decoder

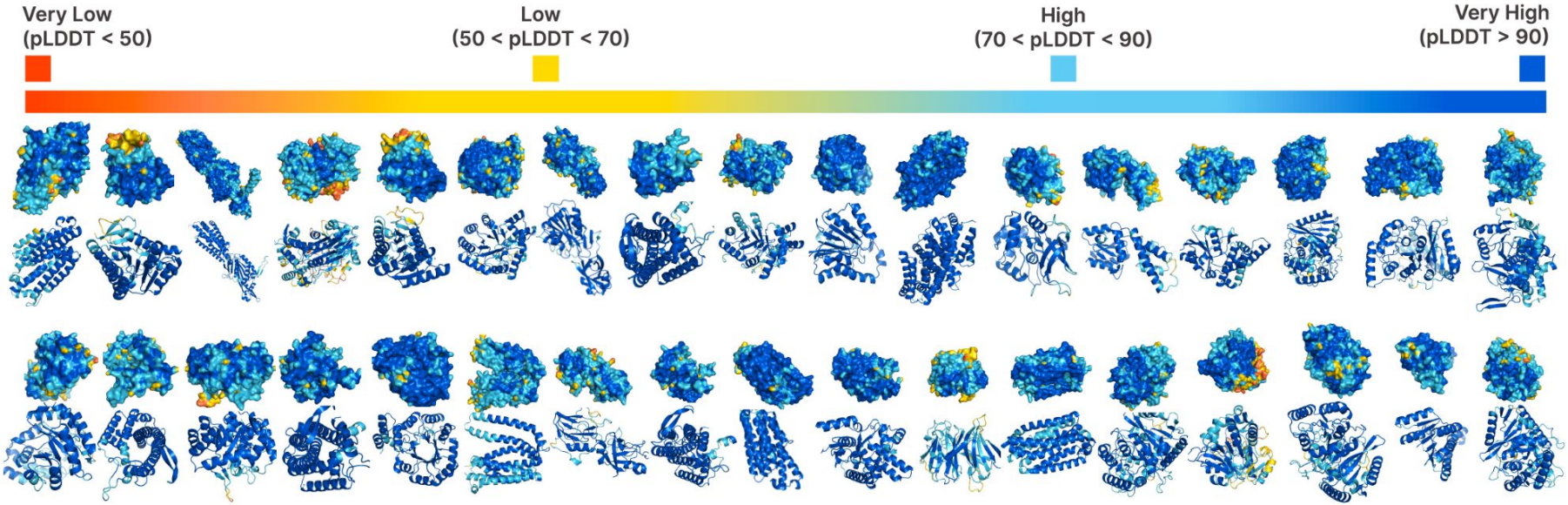


Scalable Architecture using Diffusion Transformers

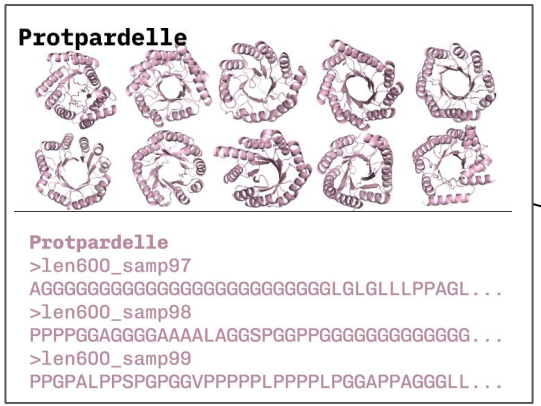


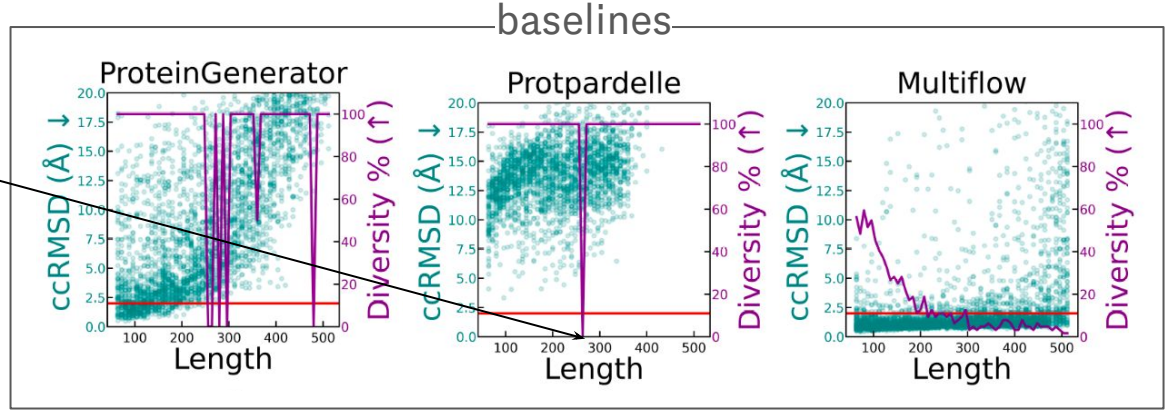
Latent diffusion allows for flexible architecture choice.

PLAID unconditionally generates diverse all-atom structures



PLAID unconditionally generates diverse, high-quality folds

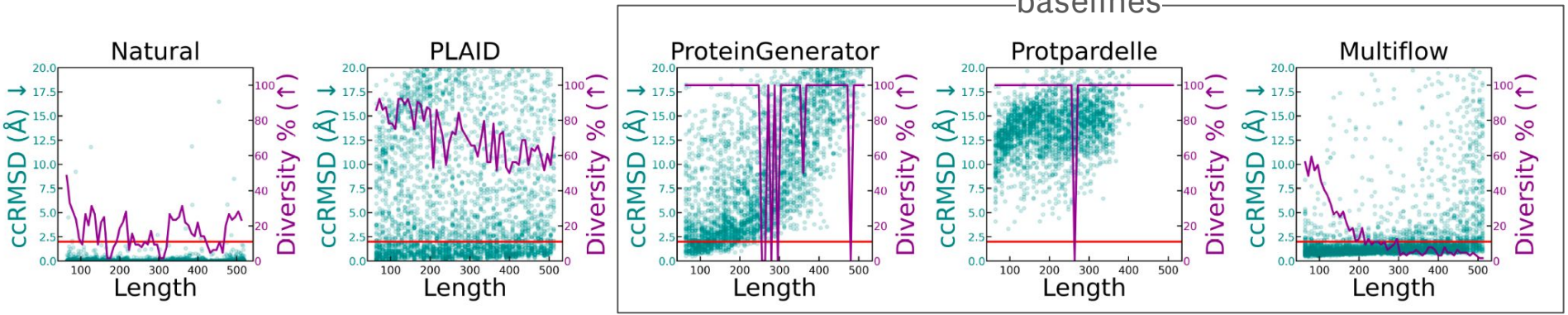




purple: diversity (↑)
(# of foldseek clusters / # of samples)

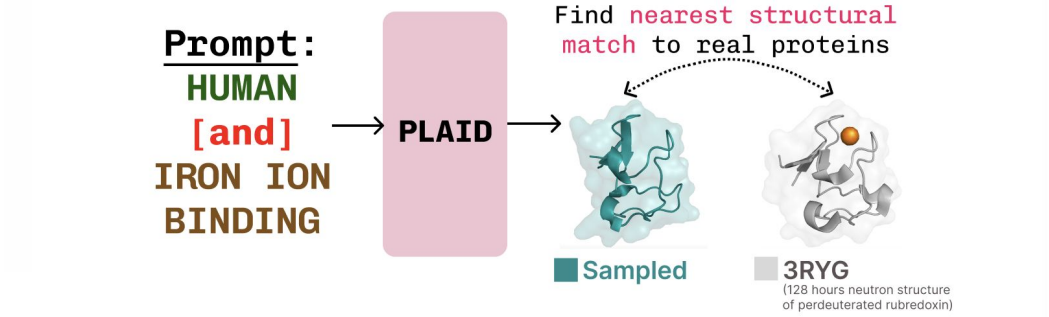
teal: quality (↓)
(ccRMSD between generated structure and predicted structure of generated sequence)

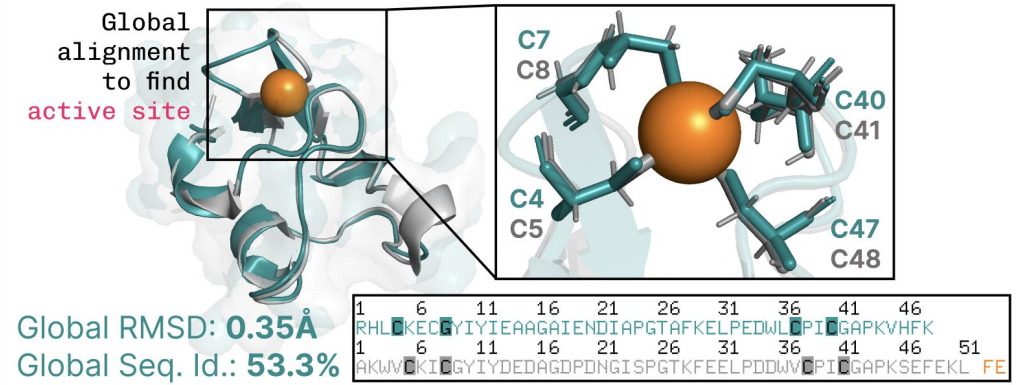
PLAID unconditionally generates diverse, high-quality folds



PLAID better balances diversity and quality, especially at longer sequence lengths.

Function-prompted generations learn active site sidechains

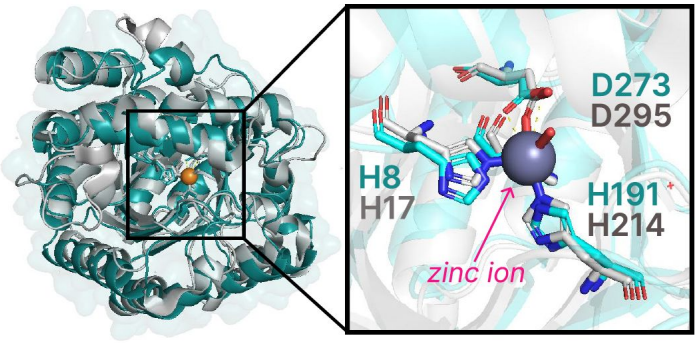




PLAID not only learns that cysteines coordinate the iron ion, but also the sidechain positioning...

Function-prompted generations learn active site sidechains

Prompt:
HUMAN [and] DEAMINASE ACTIVITY



RMSD: **2.25Å**
Seq. Id.: **24.3%**

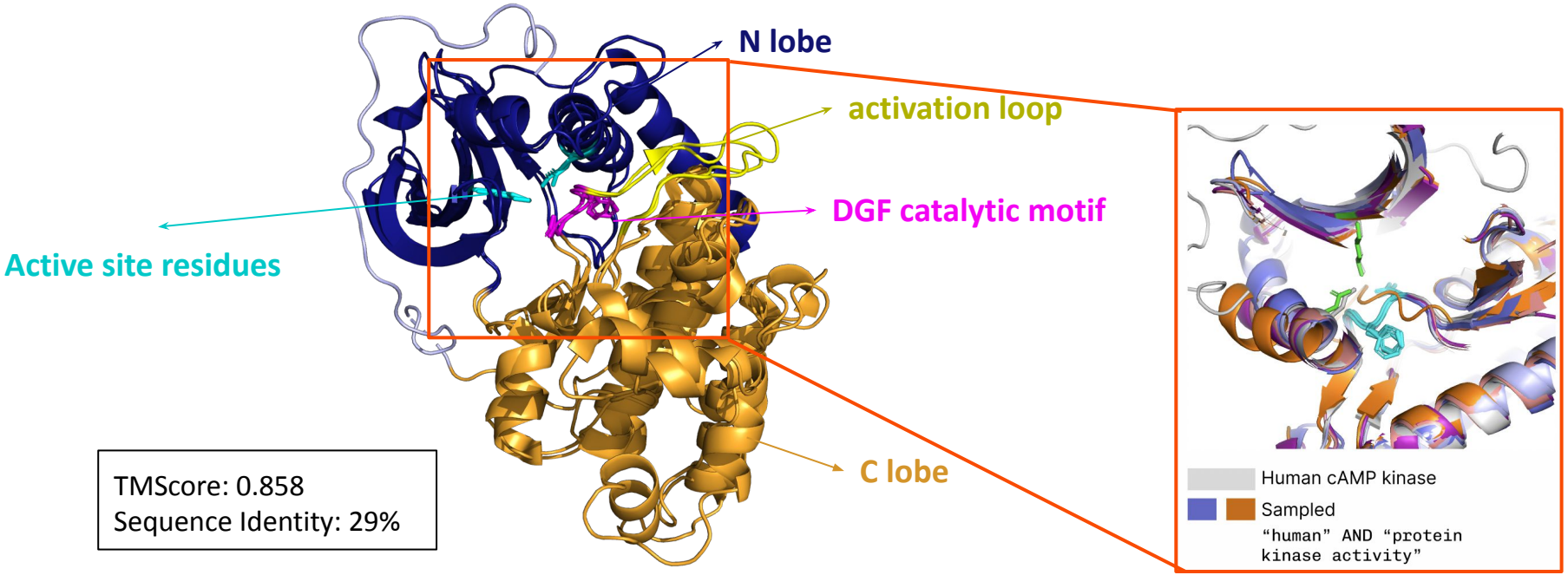
Sampled
7RTG (Crystal Structure of the Human Adenosine Deaminase 1)

...despite these key residues not being adjacent in the sequence.

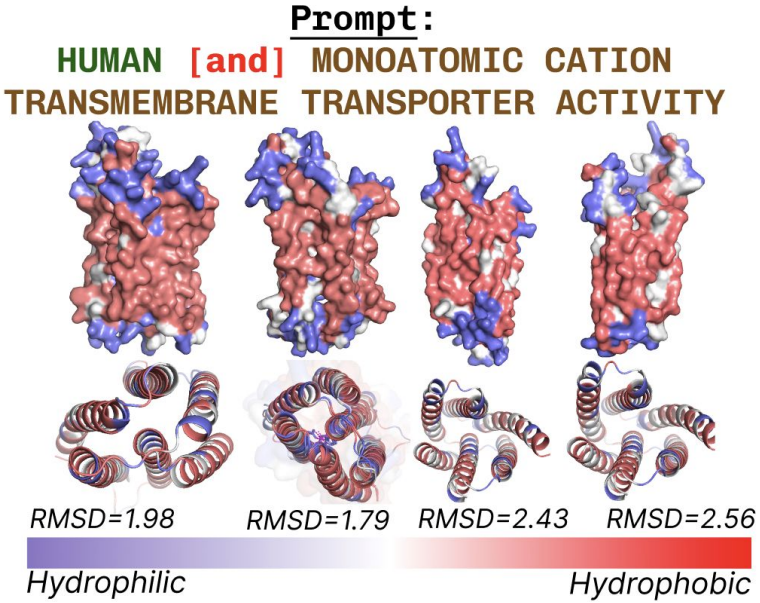
Examining active site conservation

prompt: **“human” AND “protein kinase activity”**

Closest Foldseek neighbor: **6cd6 (human calcium/calmodulin-dependent protein kinase kinase 1)**



Transmembrane proteins exhibit expected hydrophobicity patterns



Hydrophobic residues are found at the core, as expected.

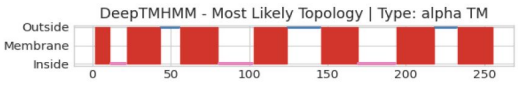
Transmembrane proteins exhibit expected numbers of helices

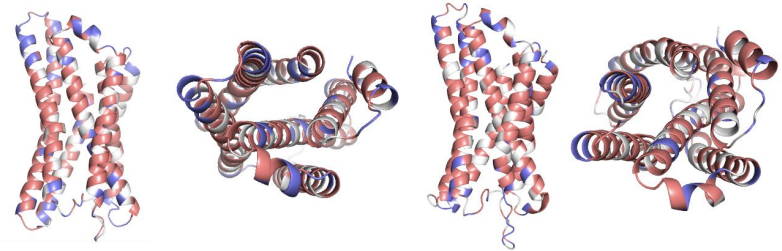
Prompt:

HUMAN [and]

G PROTEIN-COUPLED RECEPTOR ACTIVITY

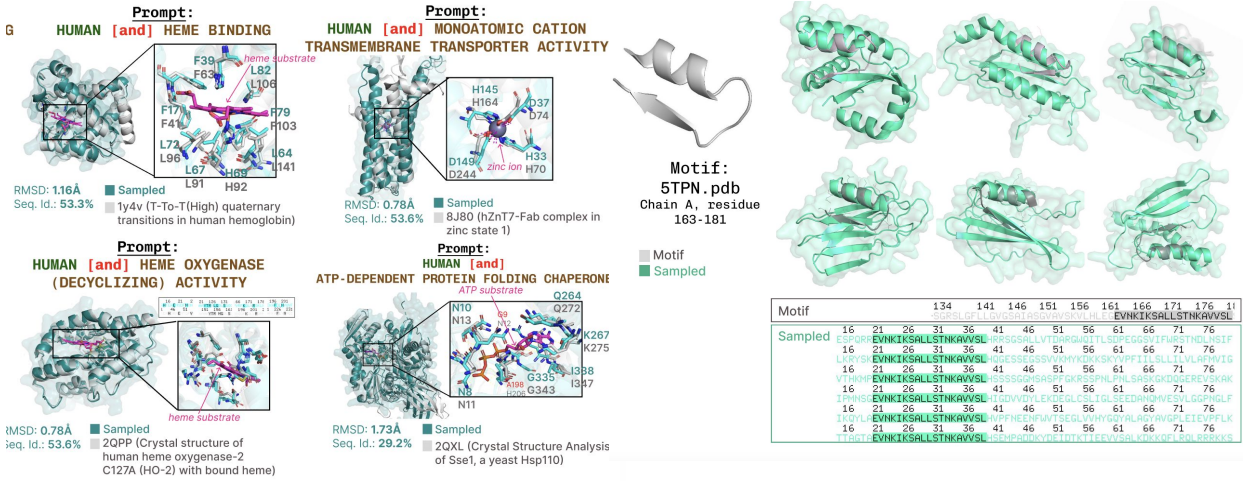
GNVLVLIMMILKQREVKSMPNV
WVFNLALSDLLFLLSTPLLVVK
MSDTSWNLGLSPCKITTFLLFL
NLYSSVFFLACLSLDRYLTVRQ
VRSN...

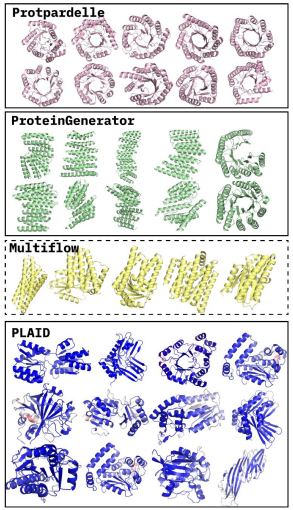




GPCRs have the expected 7-transmembrane topology, both when analyzing the sequence and structure.

More results: bit.ly/plaid-proteins





Protpardelle

```
>len600_samp97
AGGGGGGGGGGGGGGGGGGGGGGGGLGLGLLLPPAGL...
>len600_samp98
PPPPGGAGGGGAAAALAGGSPGGPPGGGGGGGGGGGG...
>len600_samp99
PPGPALPPSPGPGGVPPPPPLPPPPLPGGAPPAGGGLL...
```

ProteinGenerator

```
>len600_000097
GAAGLTAAAAVVGAAAAAGAAAAAALAAAAGAGAAAAA...
>len600_000098
AGAAGAAAAAAAAAAGAAAAGAGGGAGGAAAAAAAAAG...
>len600_000099
VAAAQAVQGAIAAAAALAATAALGLTAAGIAAPLLALV...
```

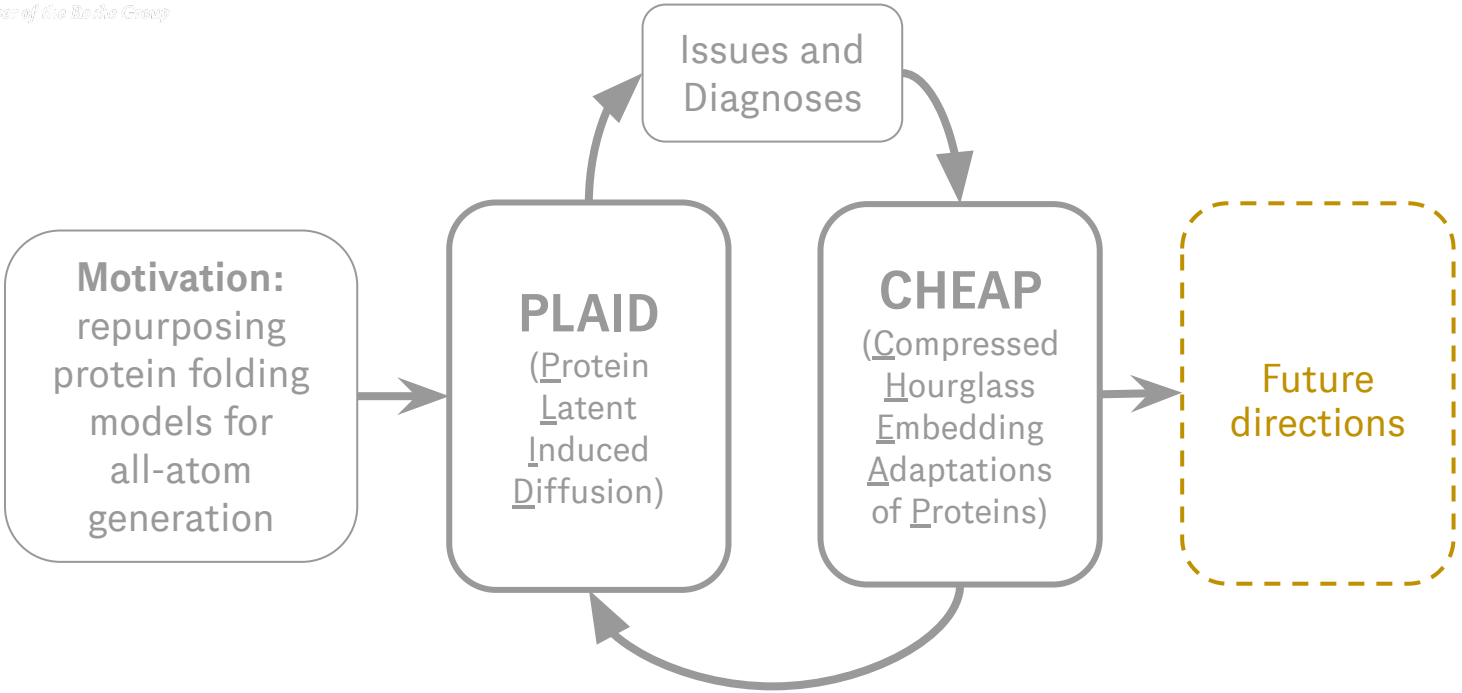
Multiflow

```
>len600_sample_97
LLGGLLGGLLGGAAGGAGAGAAAAGGGAVGVGVAGAVT...
>len600_sample_98
ADAATLTVGGGGTGGGGGAGGALGGAAAGGGGRVTLVV...
>len600_sample_99
AGGGAGLAGGAGGAGGAAAAAAAAAAAAAGAGGGAAAA...
```

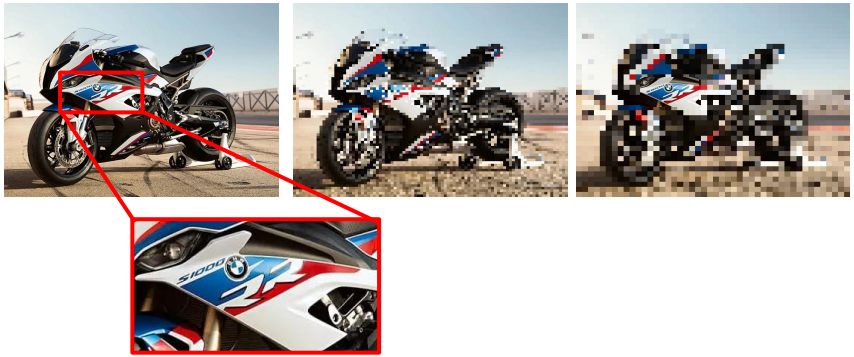
PLAID

```
>len600_sample97
PDMGTVLGLAHSVGHLDFKTPDLSVADLETNLALLAAH...
>len600_sample98
FEMFDDKGGDLWERAASSGQLLIDVAYLANNGLRDGAT...
>len600_sample99
GNGGQARGTDDPLTHALQTLFQSAALDQSLQGDPENAV...
```

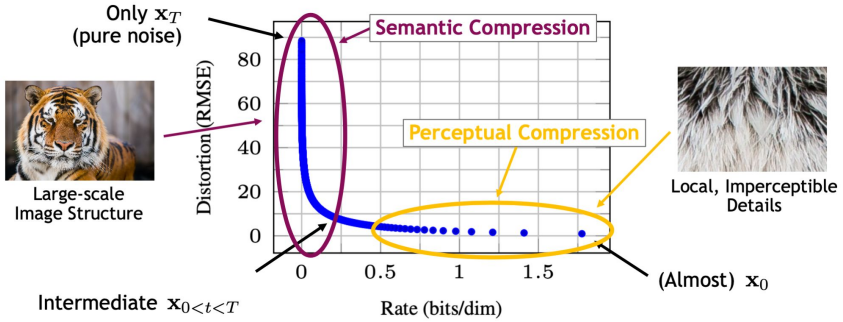
Agenda


Issues and Diagnoses
Motivation: repurposing protein folding models for all-atom generation
PLAID (Protein Latent Induced Diffusion)
CHEAP (Compressed Hourglass Embedding Adaptations of Proteins)
Future directions

Biological data selection from an information theoretic perspective



...what level of compression is optimal?



what constitutes semantic vs. perceptual compression for proteins? what level of detail do we need for drug discovery?

Connection between CHEAP, PLAID, and lossy compression

Figure 1.1: Compression as generative modeling. *Left:* A sample drawn from the probabilistic model underlying JPEG, which betrays an assumption of independence among neighboring 8 by 8 pixel blocks (except for the DC components within each row). *Right:* A sample generated by a recent neural compression model by Minnen *et al.* [132].

Representation learning => data compression => generative models!

Compression with Flows via Local Bits-Back Coding

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Denoising Diffusion Probabilistic Models

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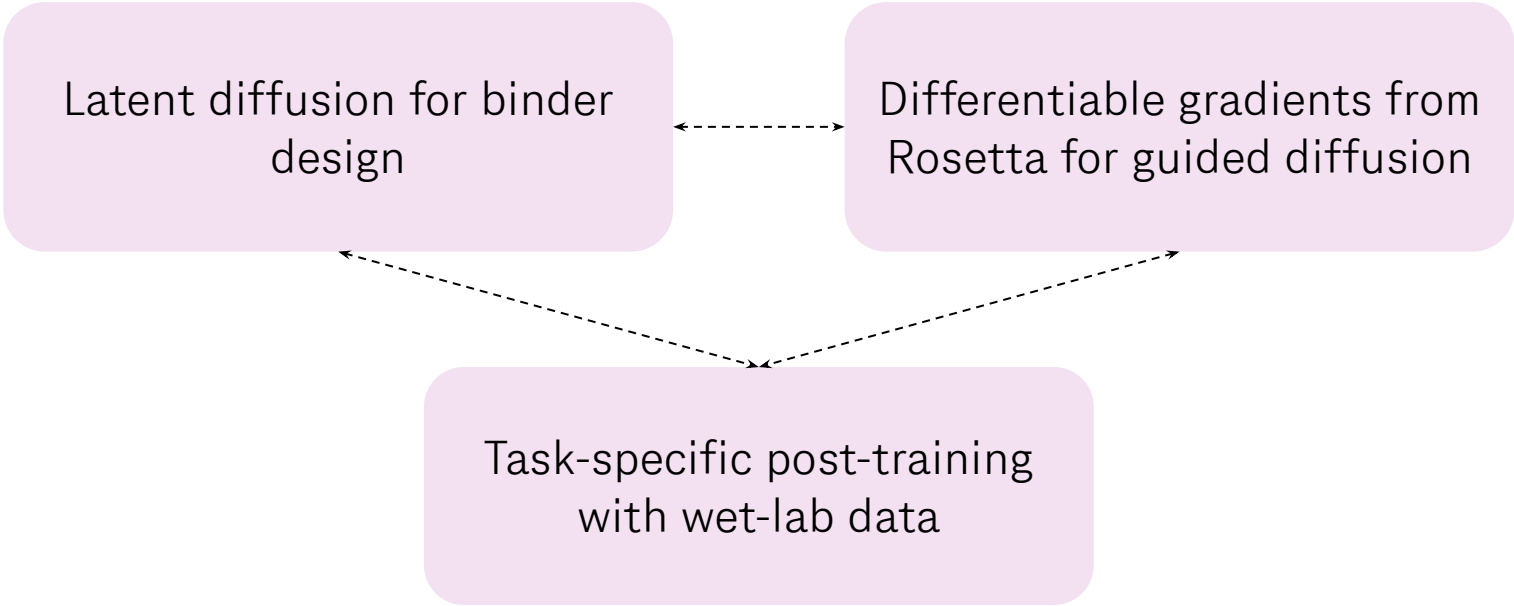
Future directions



Thanks!

Berkeley
Amy X. Lu
Wilson Yan
Pieter Abbeel

Microsoft Research
Kevin Yang

Prescient Design
Sai Pooja Mahajan
Sarah Robinson
Simon Kelow
Vladimir Gligorijevic
Kyunghyun Cho
Richard Bonneau
Nathan C. Frey

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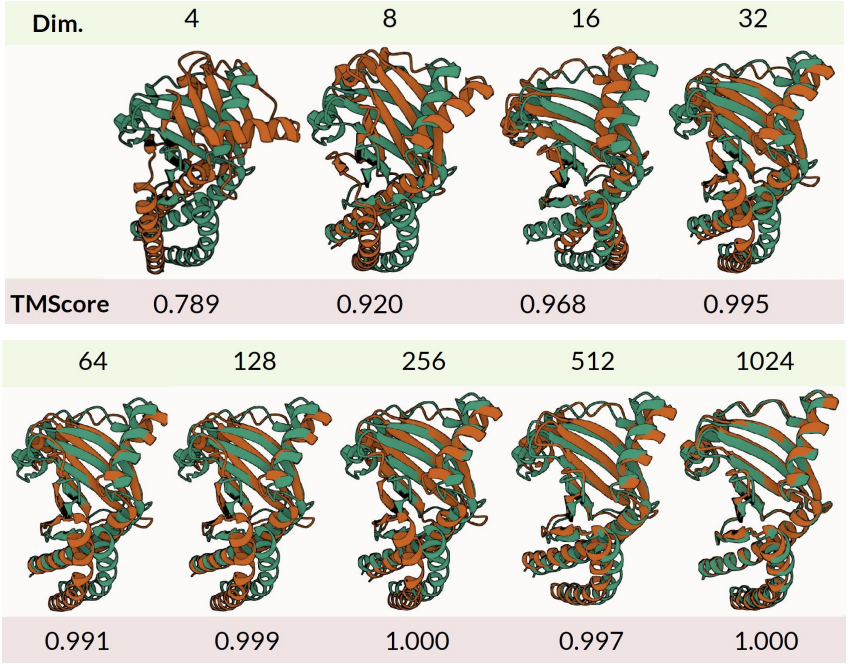
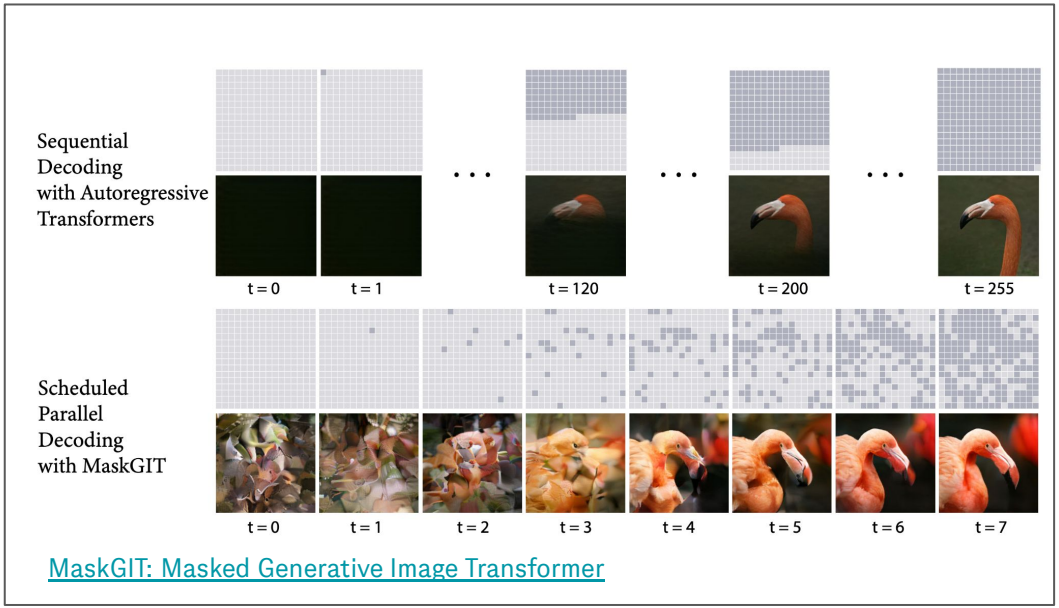
Appendix

Secondary structure is retained even at 256x compression

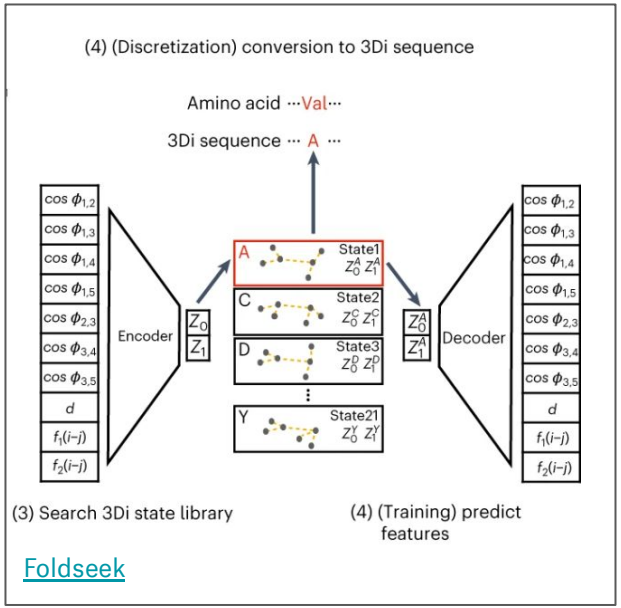


Side note: why tokenized representations?

Tokenized representations can be helpful for our downstream aims of generation and search:

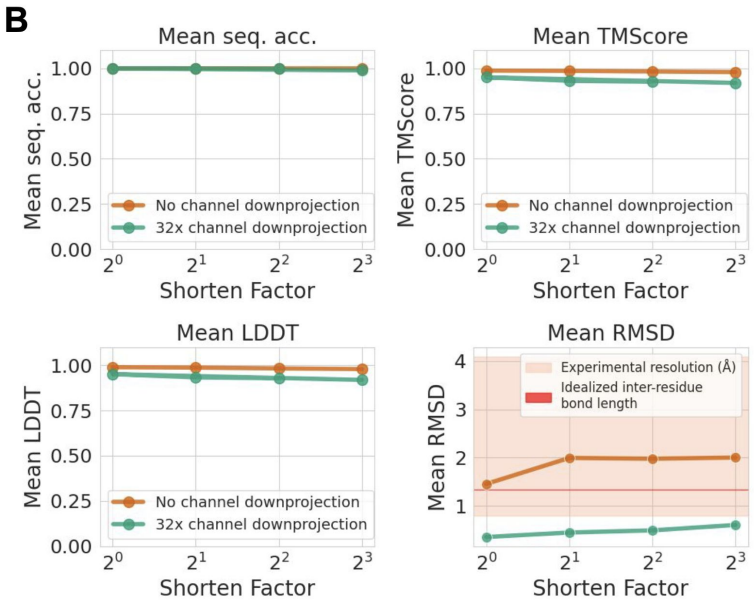


MaskGIT: Masked Generative Image Transformer



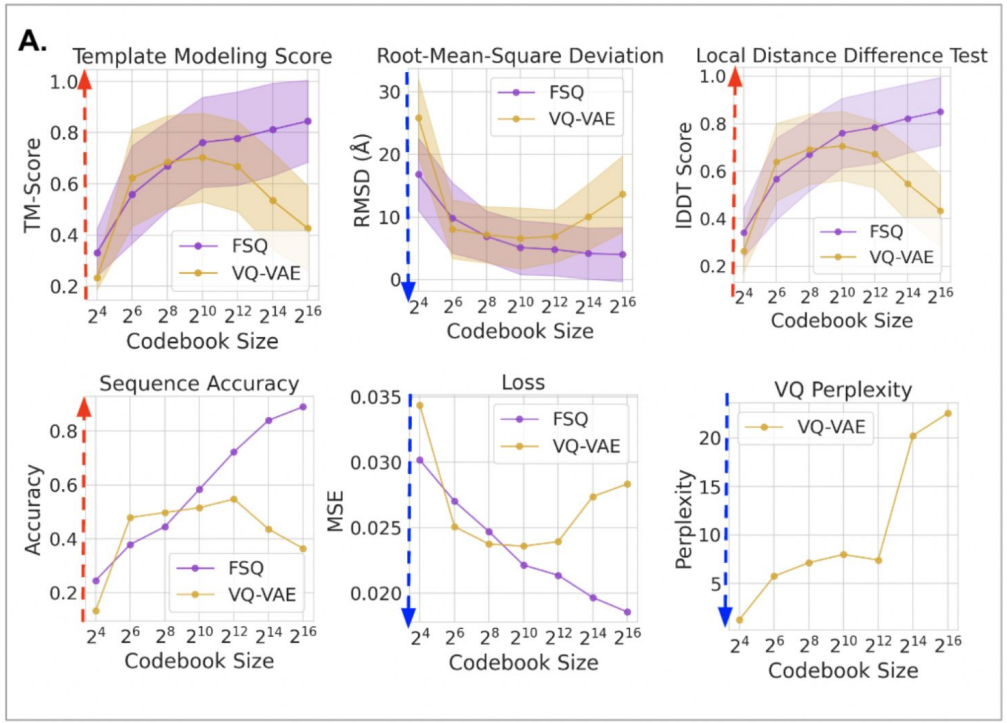
Foldseek

We can compress lengthwise and channelwise:

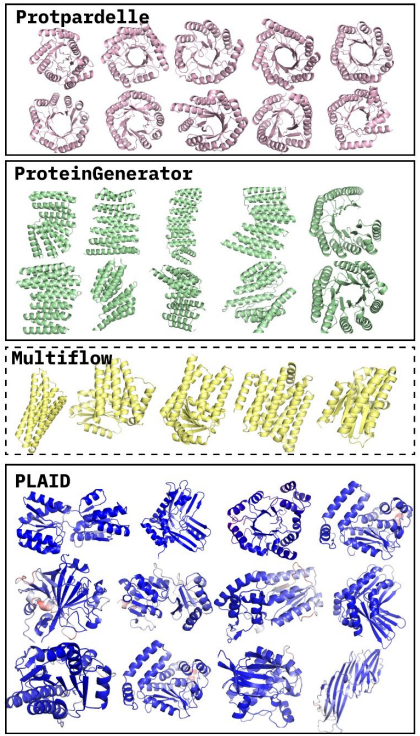


What does this mean for how structural information is shared across residue positions?

All-atom structural tokenizer, obtained from sequence alone



PLAID unconditionally generates diverse, high-quality folds



Protpardelle
>len600_samp97
AGGGGGGGGGGGGGGGGGGGGGGLGLGLLLPPAGL...
>len600_samp98
PPPPGGAGGGGAAAALAGGSPGGPPGGGGGGGGGGGGG...
>len600_samp99
PPGPALPPSPGPGGVPPPPPLPPPPLPGGAPPAGGGLL...

ProteinGenerator
>len600_000097
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>len600_000098
AGAAGAAAAAAAAAAGAAAAGAGGGAGGAAAAAAAAAG...
>len600_000099
VAAAQAVQGAIAAAAALAATAALGLTAAGIAAPLLALV...

Multiflow
>len600_sample_97
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>len600_sample_98
ADAATLTVGGGGTGGGGGAGGALGGAAAGGGGRVTLVV...
>len600_sample_99
AGGGAGLAGGAGGAGGAAAAAAAAAAAAAAGAGGGAAAA...

PLAID
>len600_sample97
PDMGTVLGLAHSVGHLDFKTPDLSVADLETNLALLAAH...
>len600_sample98
FEMFDDKGGDLWERAASSGQLLIDVAYLANNGLRDGAT...
>len600_sample99
GNGGQARGTDDPLTHALQTLFQSAALDQSLQGDPENAV...

Examining sampling hyperparameters