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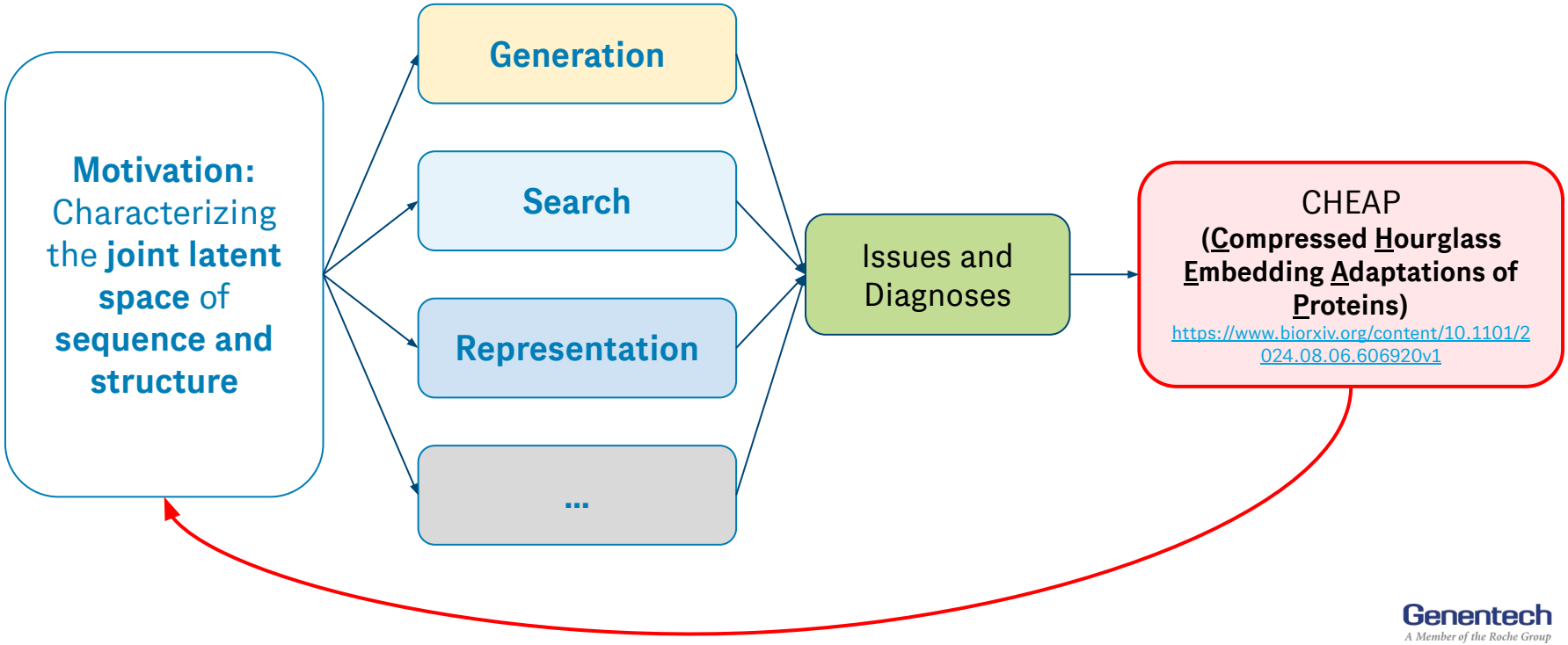
# *Tokenized and Continuous Embedding Compressions of Protein Sequence and Structure*

*October 22, 2024*
*Stanford AI + Biomedicine Seminar*

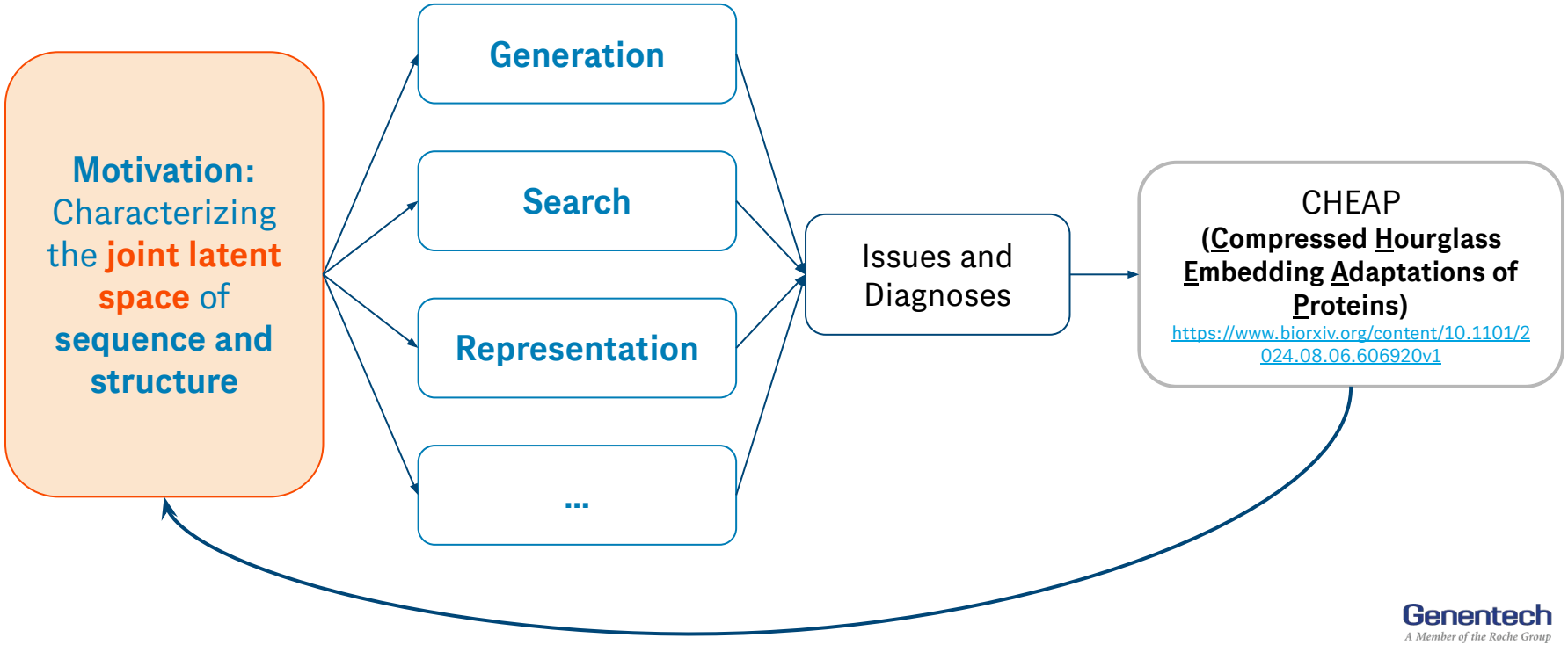
*Amy X. Lu*
*UC Berkeley / BAIR*
*Prescient Design / Genentech*

Paper: bit.ly/cheap-proteins
GitHub: github.com/amyxlu/cheap-proteins

# Agenda


Motivation: Characterizing the joint latent space of sequence and structure
Generation
Search
Representation
...
Issues and Diagnoses
CHEAP
(Compressed Hourglass Embedding Adaptations of Proteins)
https://www.biorxiv.org/content/10.1101/2024.08.06.606920v1

# Agenda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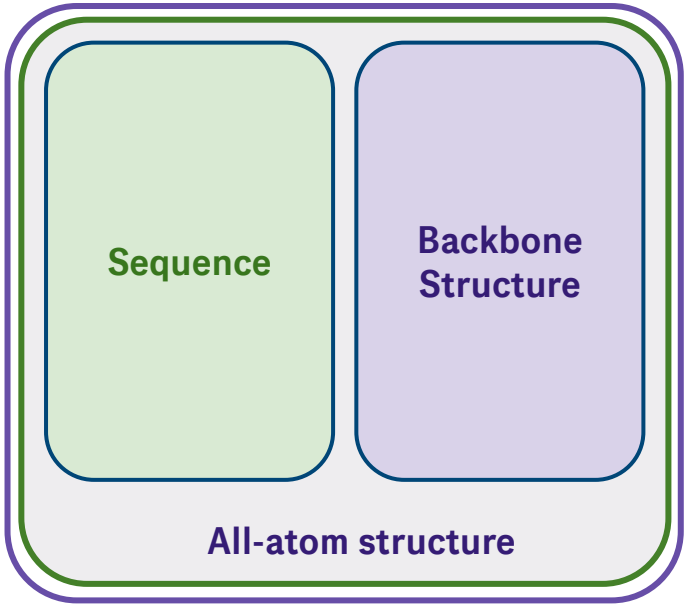
# Motivation: **Obtaining a joint embedding of structure & sequence from sequence alone**

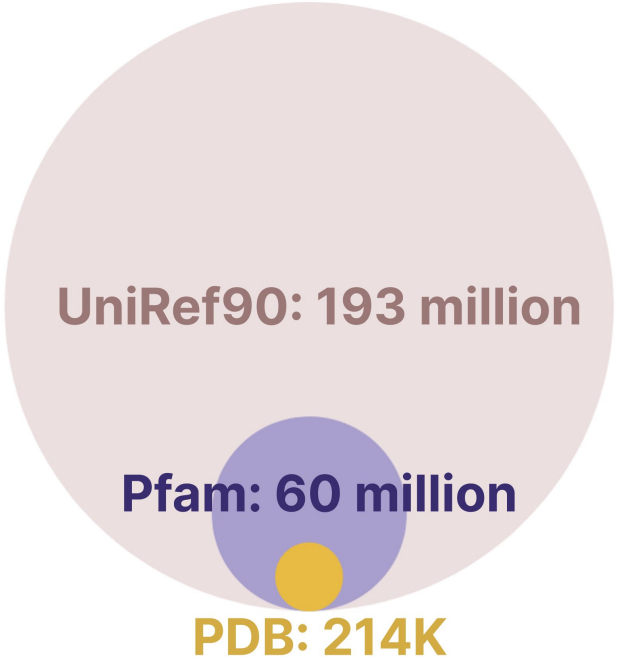
- Existing protein representation models often capture either p(sequence) or p(structure), limiting flexibility
- Desiderata:
  - Capture the joint embedding of sequence and structure
  - Can be explicitly decoded back to structure and sequence
  - Can be captured from sequence alone



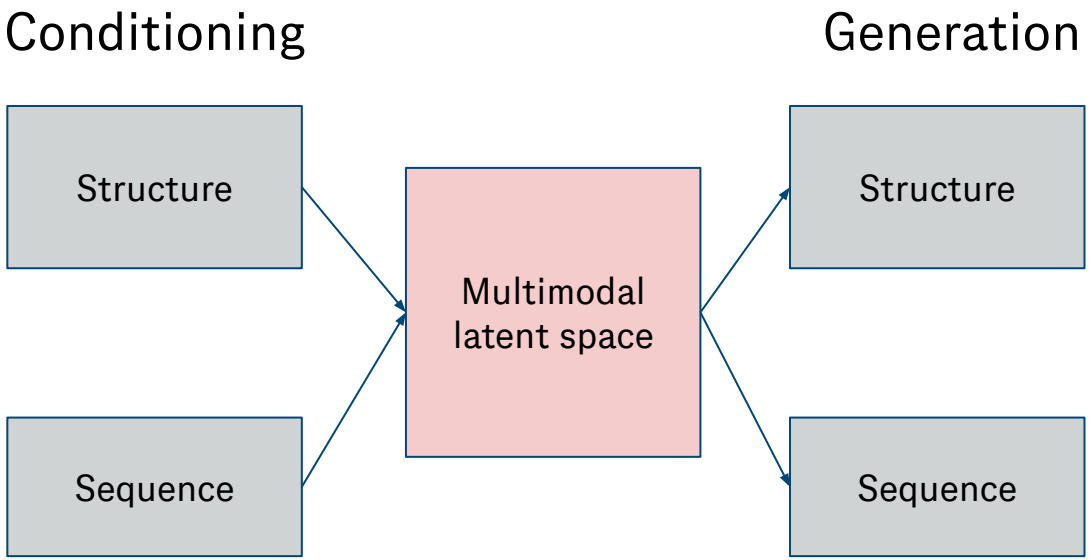

**All-atom structure is a superset of sequence information!**

# Motivation: **Sequence databases offer better data distribution coverage and function label abundance**

- Structure databases have strong priors which may not always be useful:
  - biased towards crystallizable proteins
  - sequence database sizes approaches internet-scale data, while structure databases are much smaller



# Motivation: **Directly capturing the joint distribution is flexible**




Being able to characterize a joint latent space allows flexibly conditioning by and generating either modality.

# Motivation: **Direct sampling from the joint distribution is natural**

## Structure generation + inverse folding

$p(\text{branches})$

Generate a picture of tree branches.

Here is the image of tree branches you requested. If you need any modifications or additional details, feel free to ask!

$p(\text{apples}|\text{branches})$

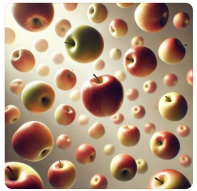
Add apples to this tree branch.

Here's the updated image with apples added to the tree branches. If you need any further adjustments, just let me know!

## Sequence generation + folding

$p(\text{apples})$

Generate a picture of apples in midair.



Here is the image of apples suspended in midair. I hope it captures the surreal effect you were looking for!

$p(\text{branches}|\text{apples})$

Add branches to these apples.

Here is the updated image with branches holding the apples in place. The branche touch while maintaining the surreal effect. I hope this meets your expectations!

## Co-generation

$p(\text{apples}, \text{branches})$

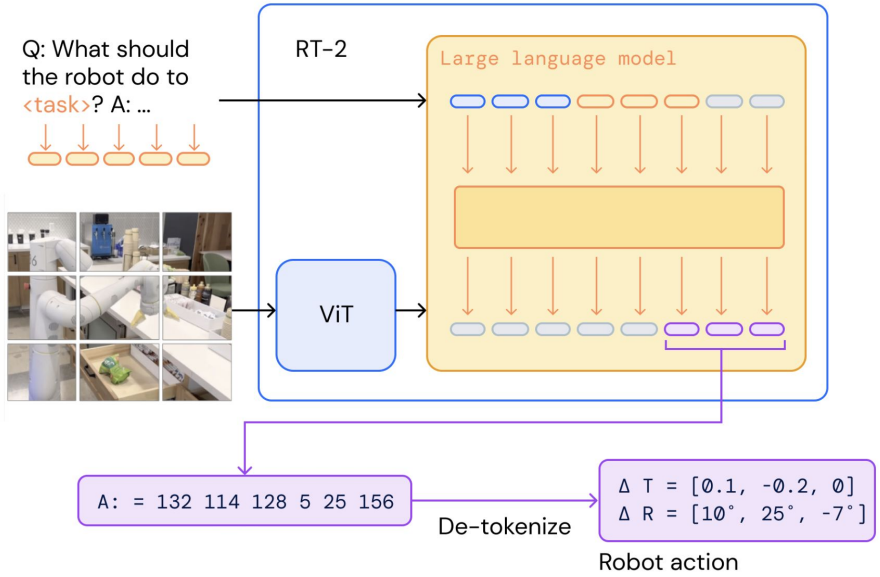
Generate a picture of an apple tree.

Here is the image of an apple tree you requested! Let me know if you need any adjustments or further assistance.

# Motivation: **Large pretrained models capture useful priors for decision making**

- Multimodal pretrained models offer useful priors
  - e.g. VLMs in robotics

→ can we use information captured by AlphaFold2, etc. as a “foundation model” for decision making in protein engineering?



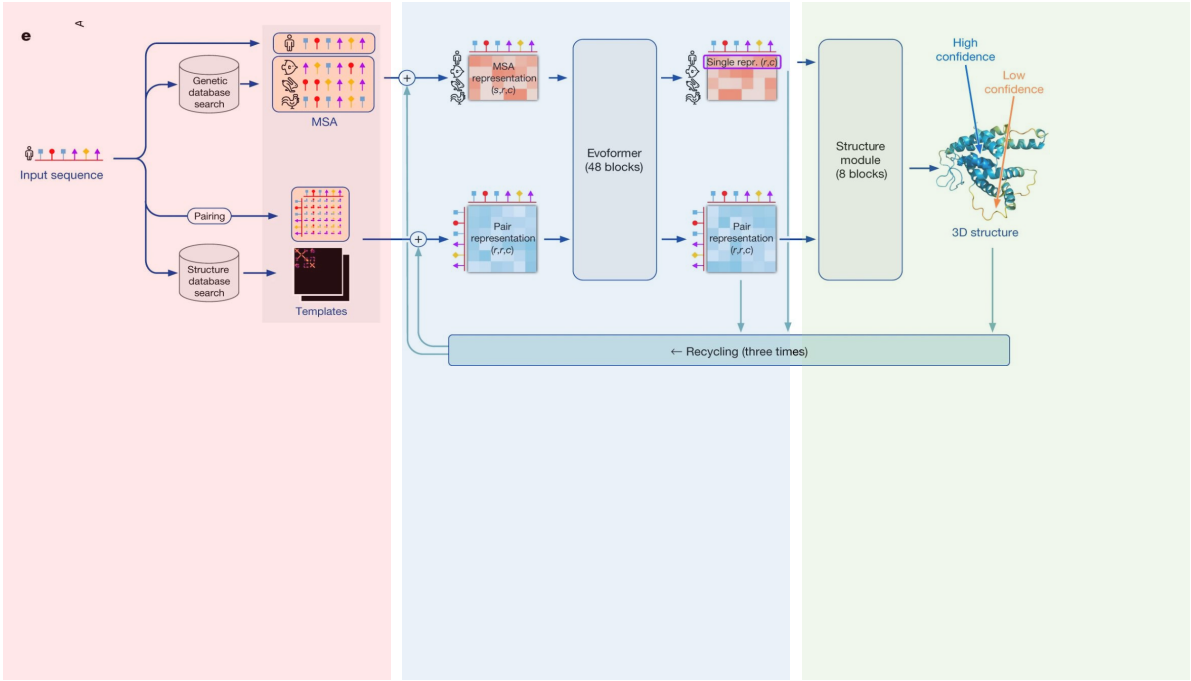

RT-2: Vision-Language-Action Models Transfer Web Knowledge to Robotic Control

# How can we repurpose the joint representation of p(sequence, structure) in protein folding models for downstream tasks?

# Refresher: ESMFold for sequence-to-structure prediction

**AlphaFold2:**

Uses an explicit retrieval step




harness additional sequence-based priors

learn structural features from sequence latents

generate structures

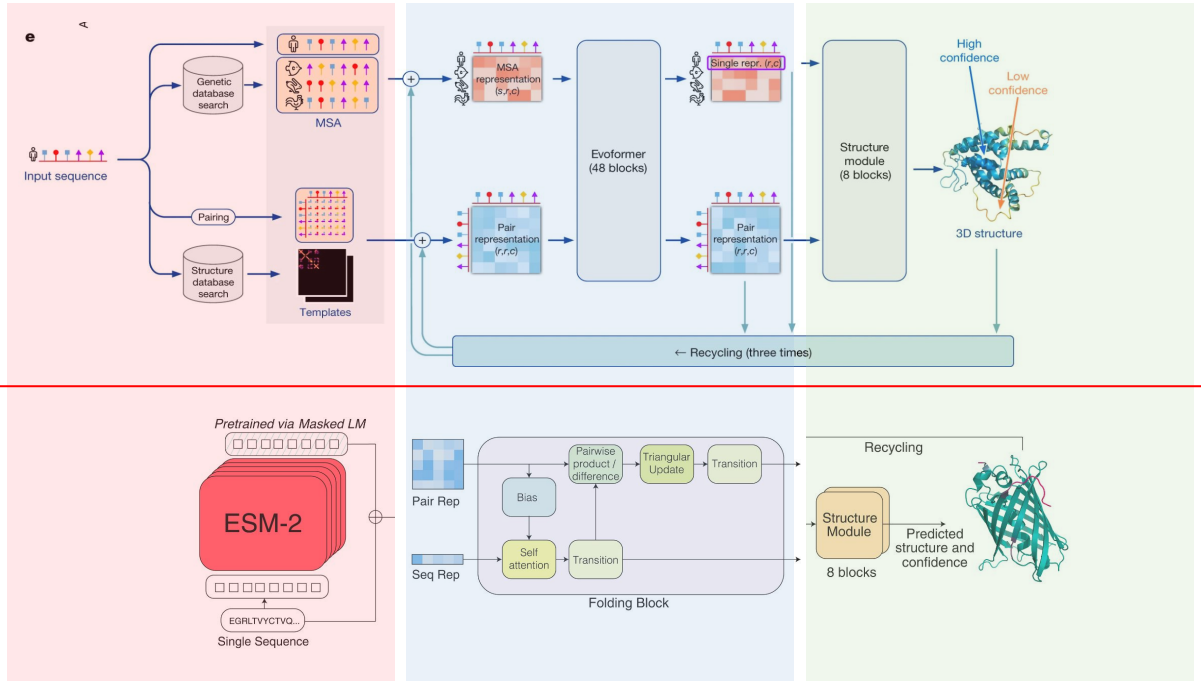
# Refresher: ESMFold for sequence-to-structure prediction

**AlphaFold2:**

Uses an explicit retrieval step

**ESMFold:**

Replaces retrieval step with a **language model**

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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 time, the pairwise input is initialized as zeros…

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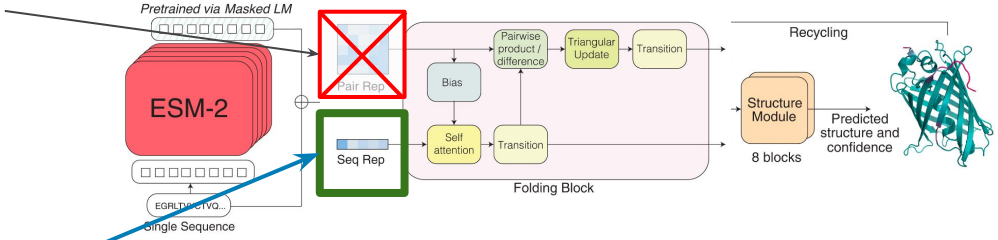
→ LM embedding captures sufficient inductive biases for structure, but requires **only sequence data** during training!

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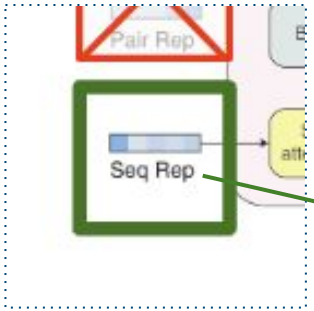
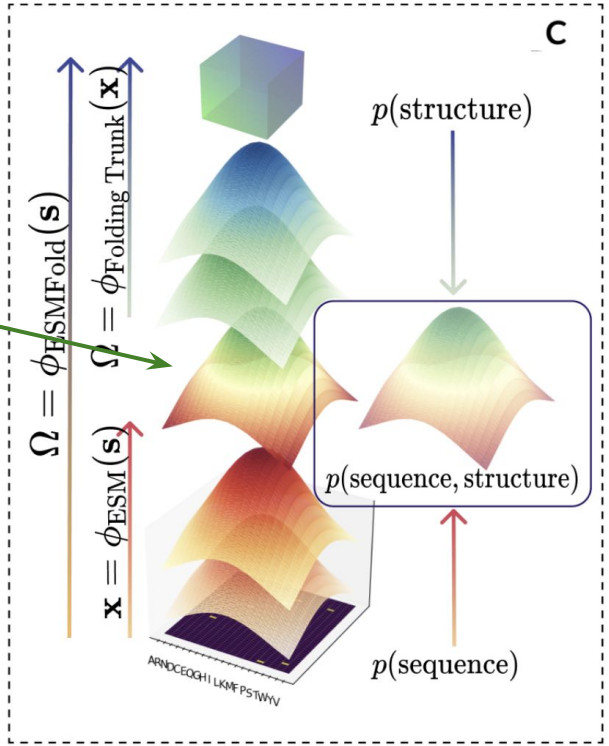
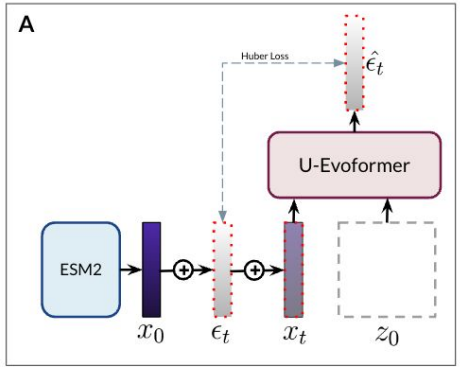


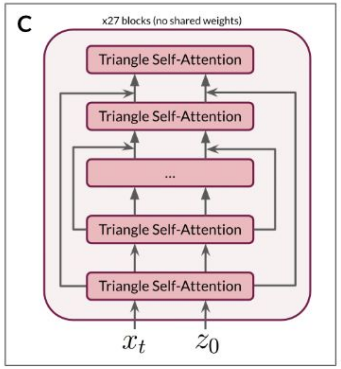




Consider this latent space as a **joint representation of protein sequence and structure that can be obtained from sequence only.**

# an early attempt at diffusing in this latent space…

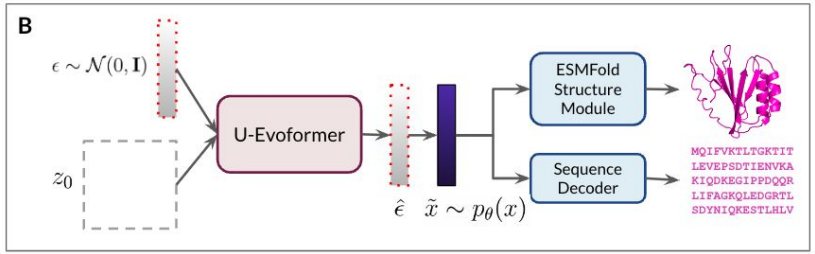
**training**: standard diffusion training from ESM2 outputs

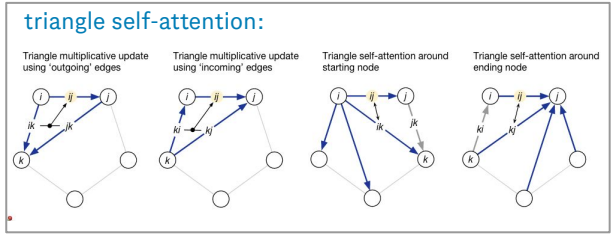



**architecture**: stacked triangle self-attention blocks, as introduced in AlphaFold, to capture pairwise interactions

**inference**: generate new sequence representations, decode to sequence and structure




**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*

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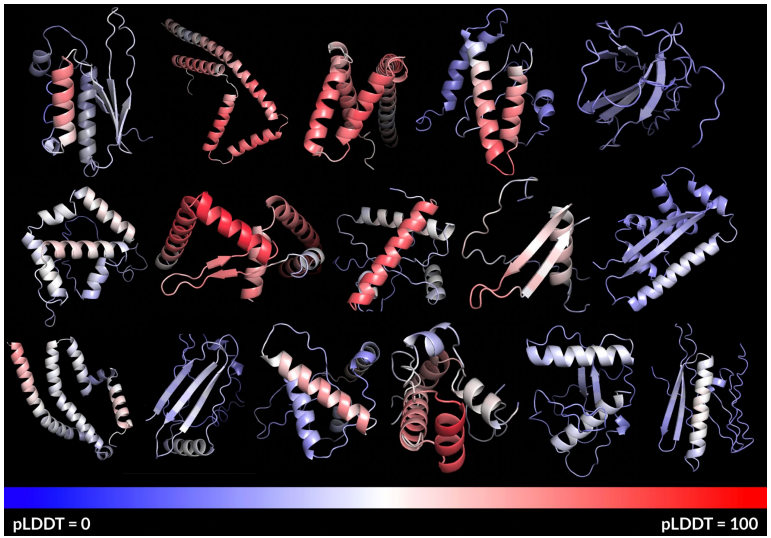
# an early attempt at diffusing in this latent space…




We are able to learn structural folds, despite using only sequence inputs!

Empirically considering this latent space as a joint distribution is a go ✅

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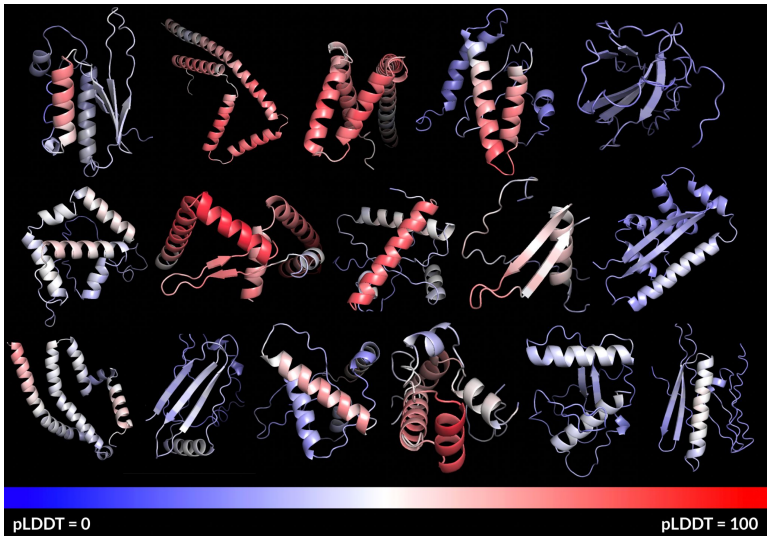


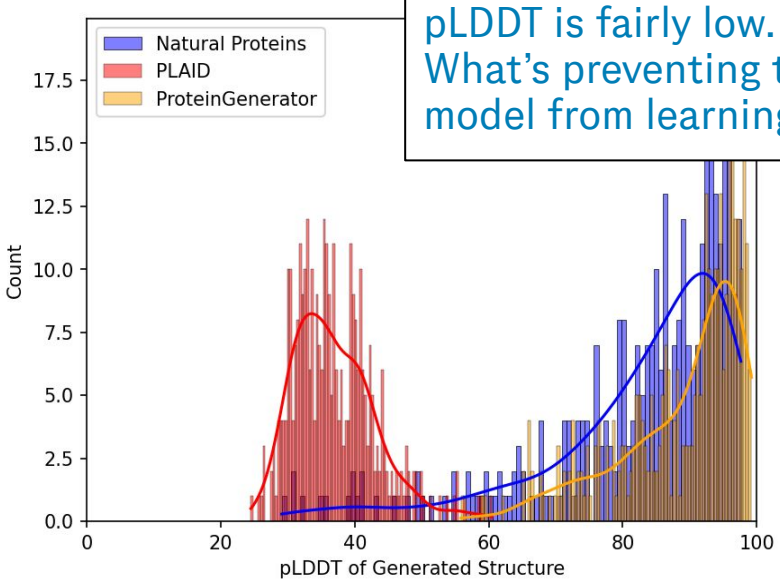


pLDDT is fairly low. What's preventing the model from learning?

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# Issues and hypotheses -> CHEAP

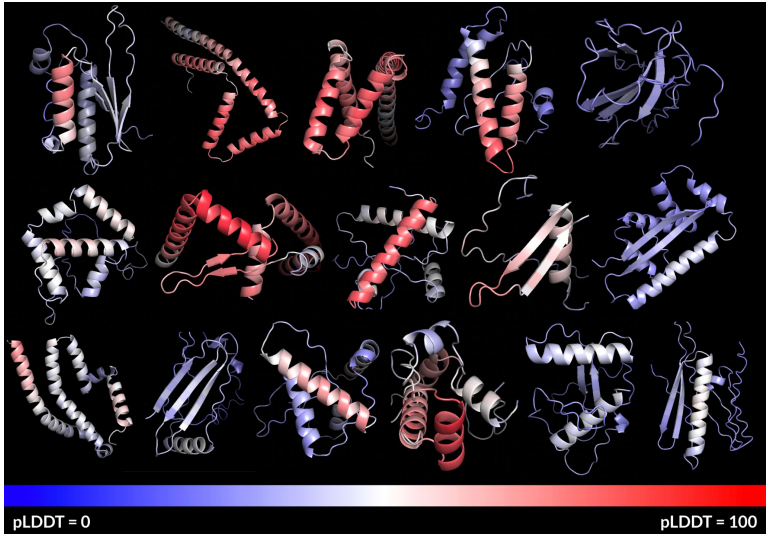
- Latent space requires regularization

> 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 as a VQGAN [23] but with the quantization layer absorbed by the decoder.

High-Resolution Image Synthesis with Latent Diffusion Models

# Issues and hypotheses -> CHEAP

- Latent space requires regularization
- Training data only allows for length of 128 due to memory constraints
  - Some samples show the curvatures of a beta barrel, but sequence length limits seeing a full beta barrel



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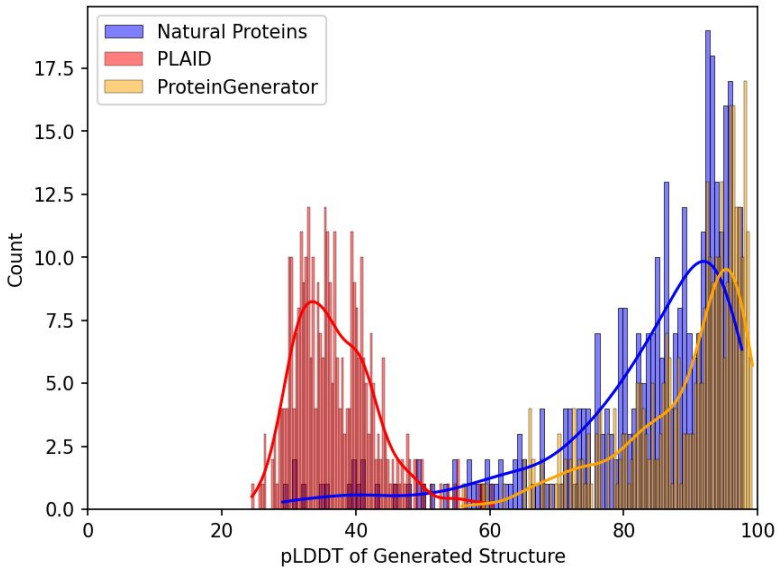
    - Need to shorten the protein?
- pLDDT is not designed to assess generation from evolutionary scale datasets
  - Biased towards generative models trained on the same data as AF2, i.e. PDB



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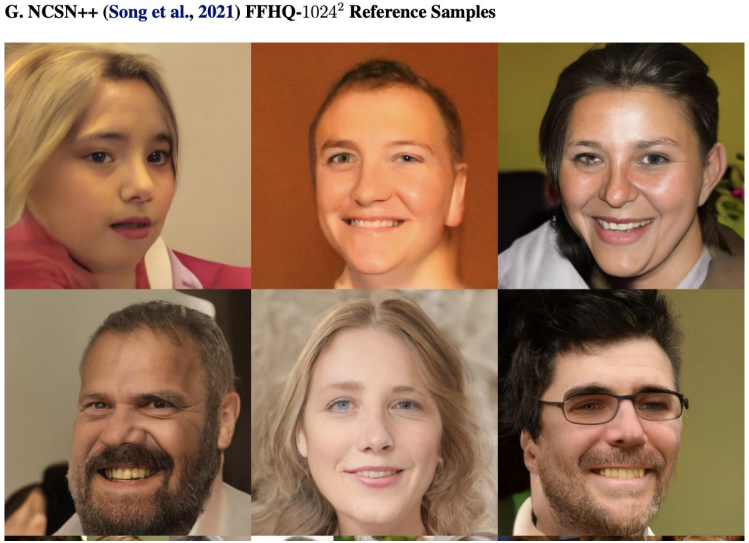
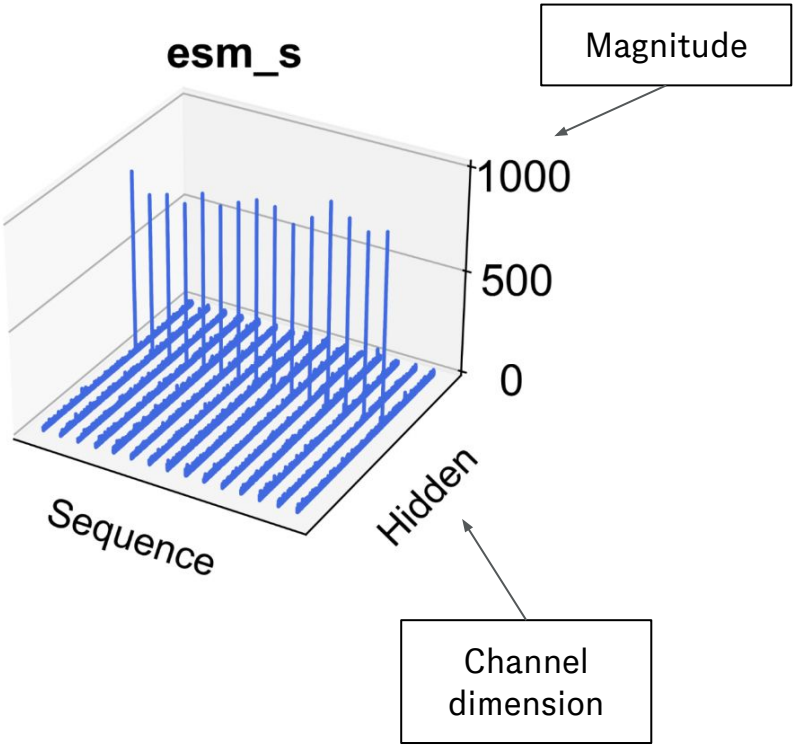
- Large latent space corresponds to high-resolution image generation
  - in LDMs, latent space is 64 x 4 x 4, as opposed to ours, which is 512 x 1024

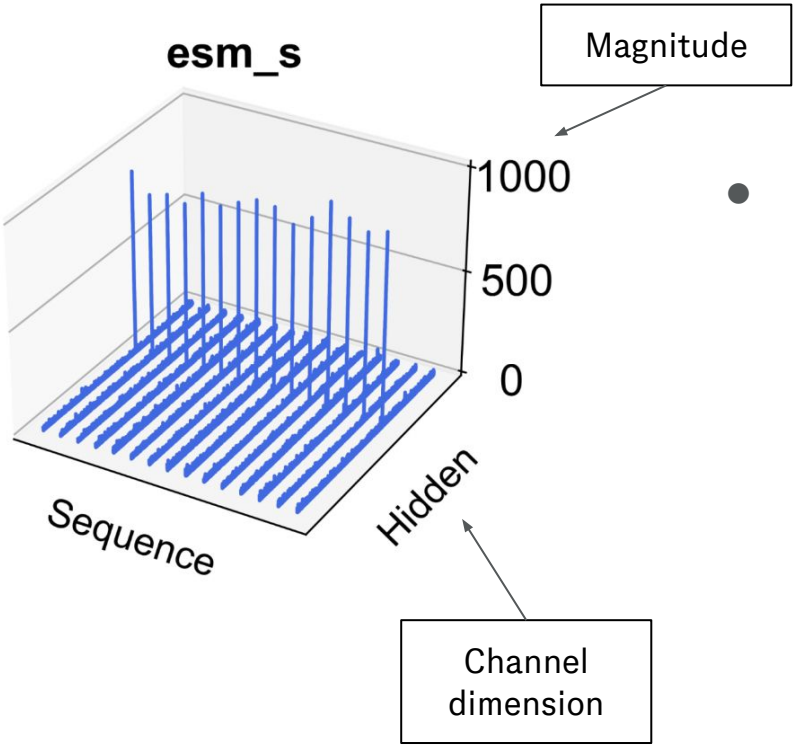



Diffusion models in their naive formulation often fail for 1024 x 1024 resolution generation.

# A closer look at the latent space of ESMFold…

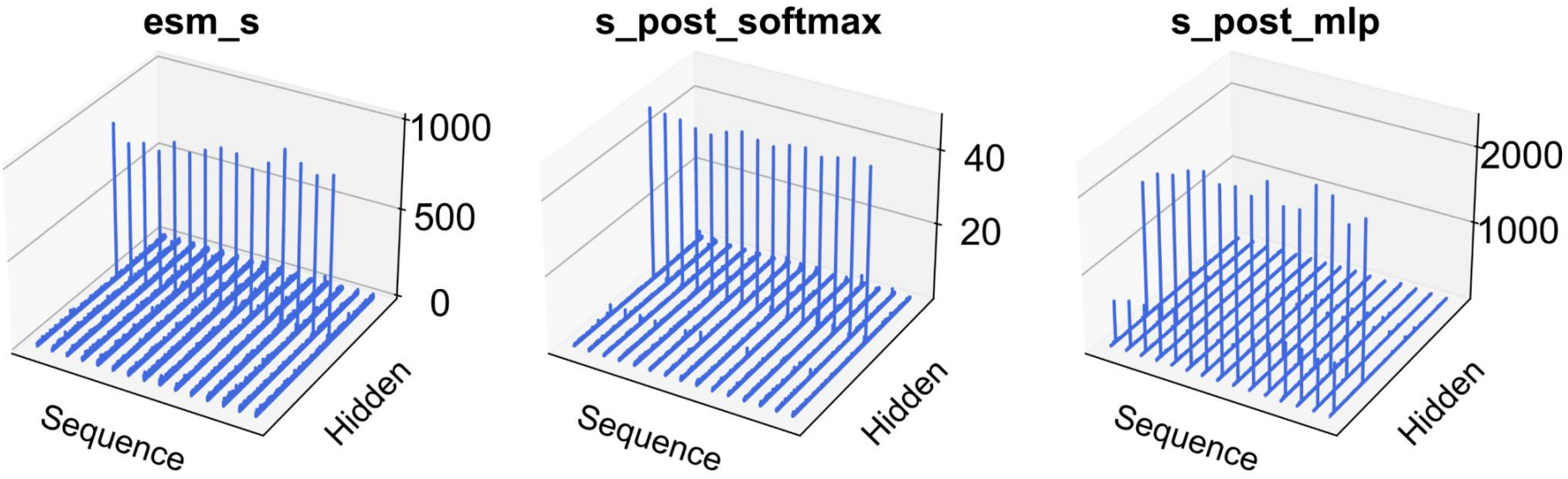


# …ESMFold latent space exhibits pathologically large values



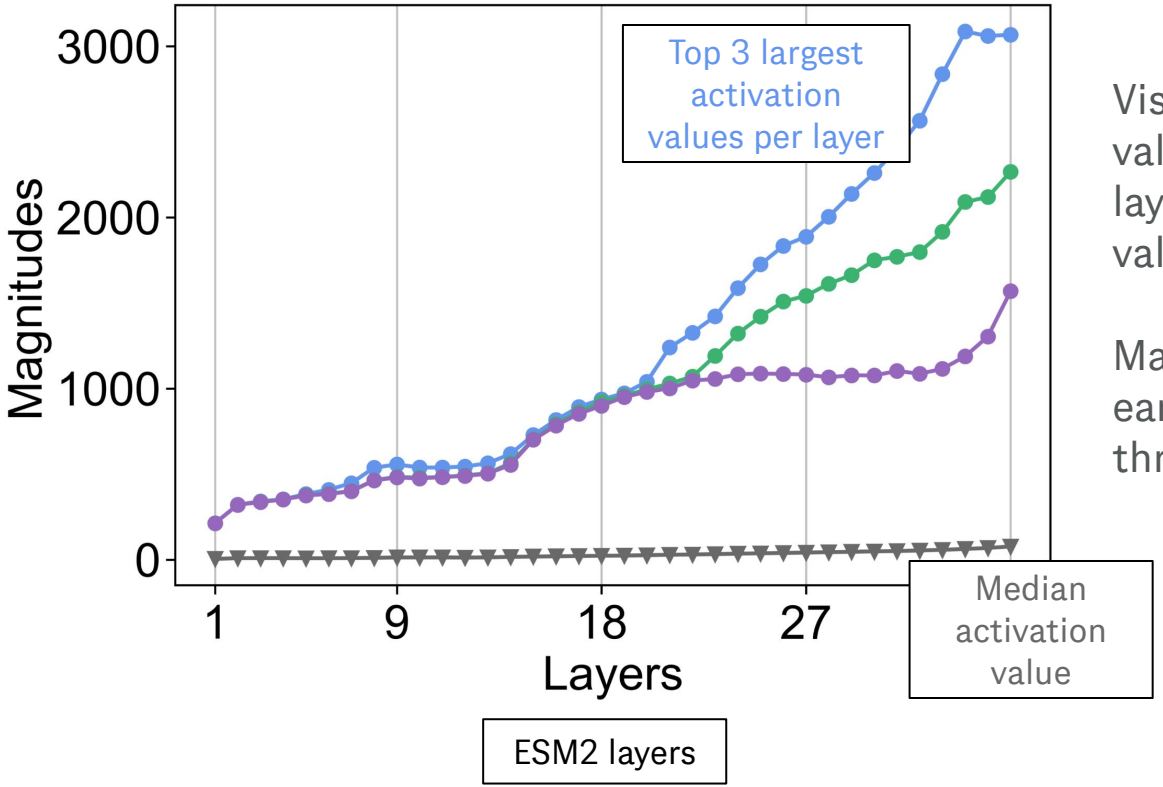

- Some channels exhibit very high mean values, regardless of the input.
  - Implications for generation: data distribution is no longer Gaussian distributed

# ...ESMFold latent space exhibits pathologically large values




Not just an issue for this particular layer...

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




Visualizing the top 3 highest values in intermediate ESM2 layers, against the median value.

Massive activations begin in early layers, and accumulate throughout the model.

# ~~ESMFold~~ Large transformer model latent spaces exhibits pathologically large values

A pervasive issue across large transformer models!

[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

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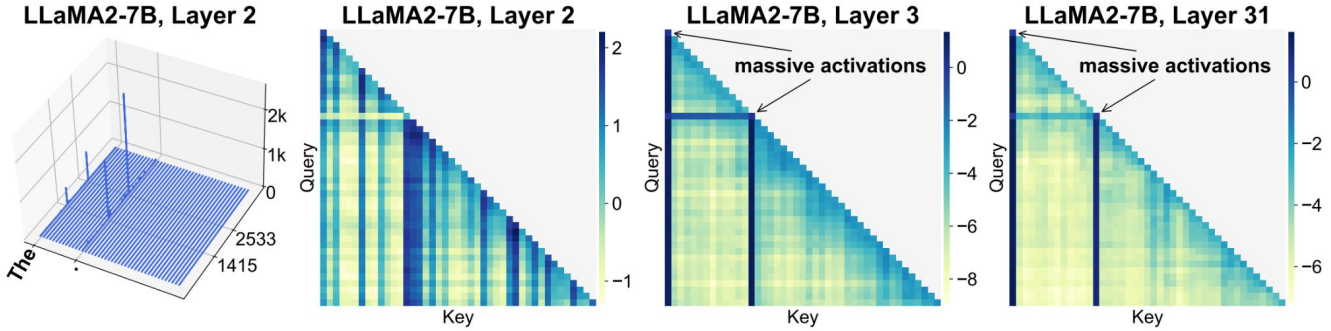
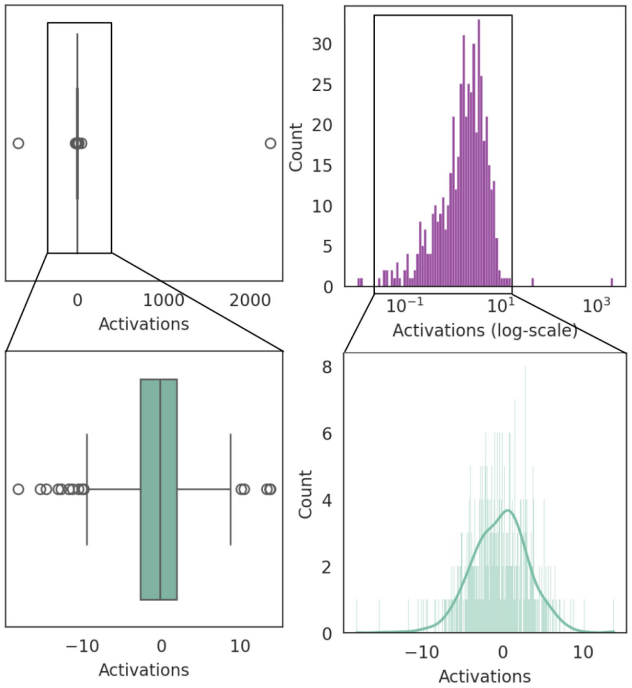



Figure 5: Attention patterns *before* and *after* massive activations appear in LLaMA2-7B. For each layer, we visualize average attention logits (unnormalized scores before softmax) over all heads, for an input sequence.

# What if we just remove these wacky channels?



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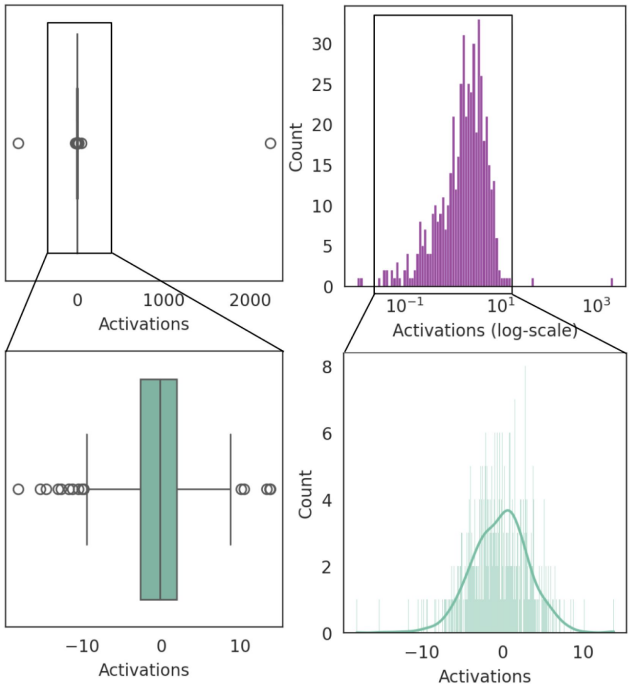


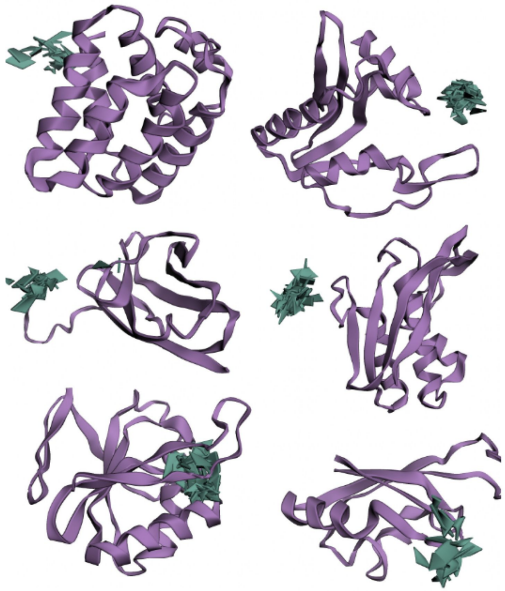

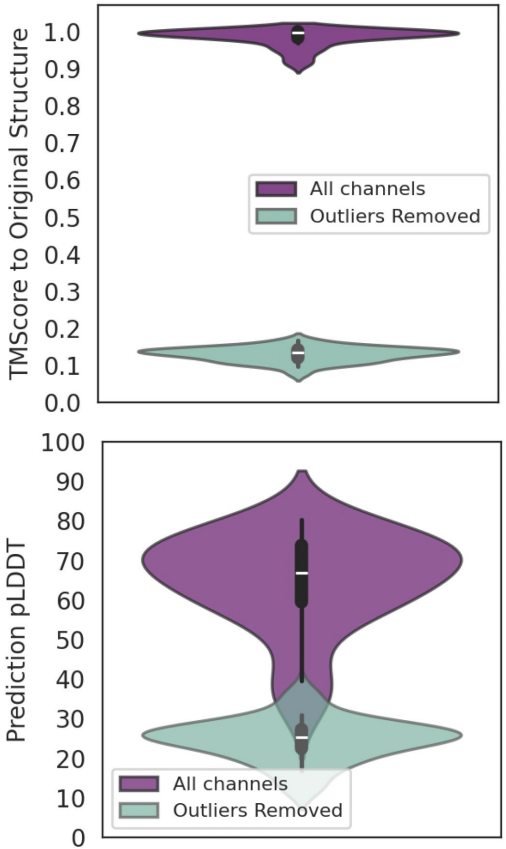

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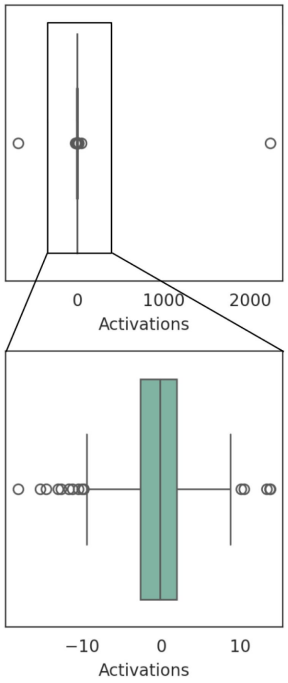
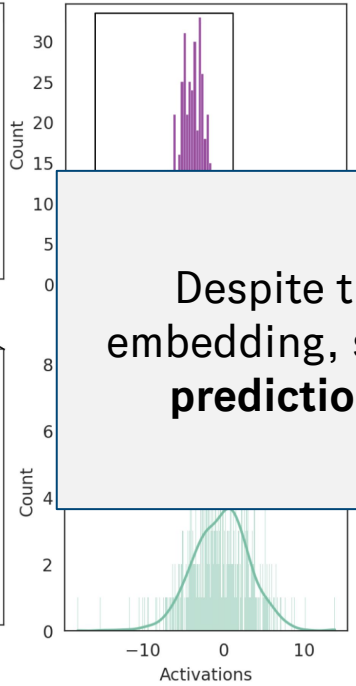
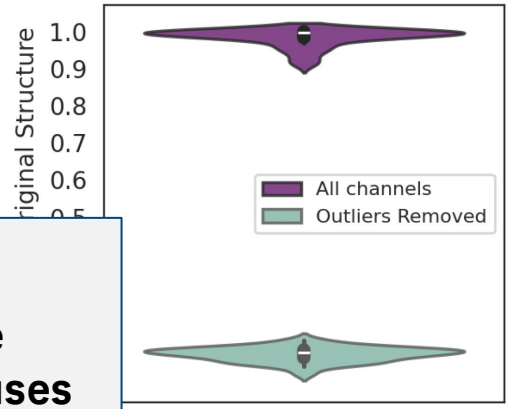
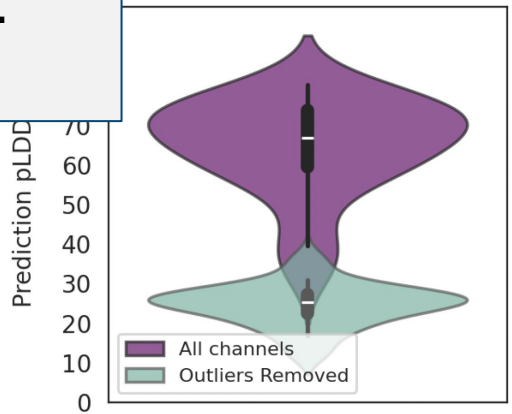


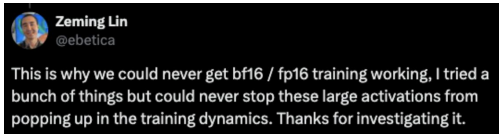

Despite there being **1024** channels in the embedding, simply **removing 3 channels causes prediction ability to entirely deteriorate.**



# Why should we care about these massive activations?

- Training stability
- Model compression and 8-bit quantization
- Model interpretability
- ...




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

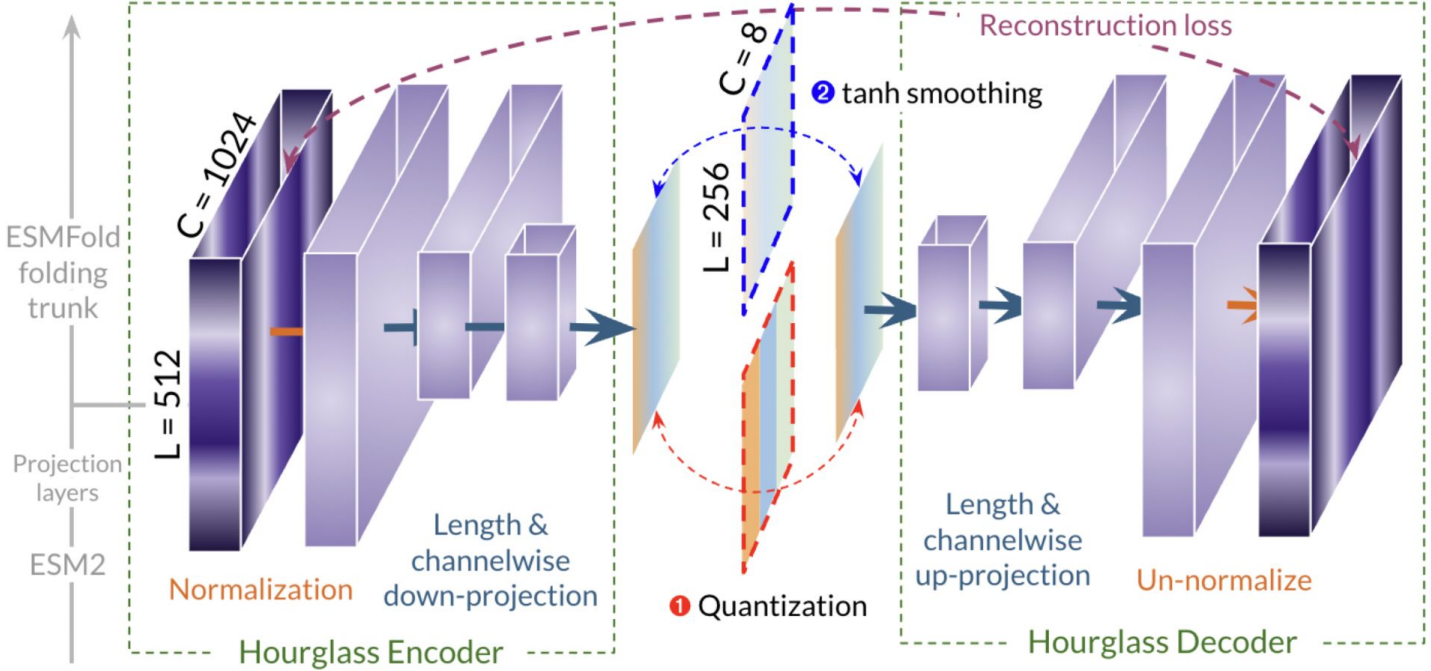
If removing 3 channels can remove performance, is the information evenly distributed through all the channels?

If not, can we **compress these channels?**

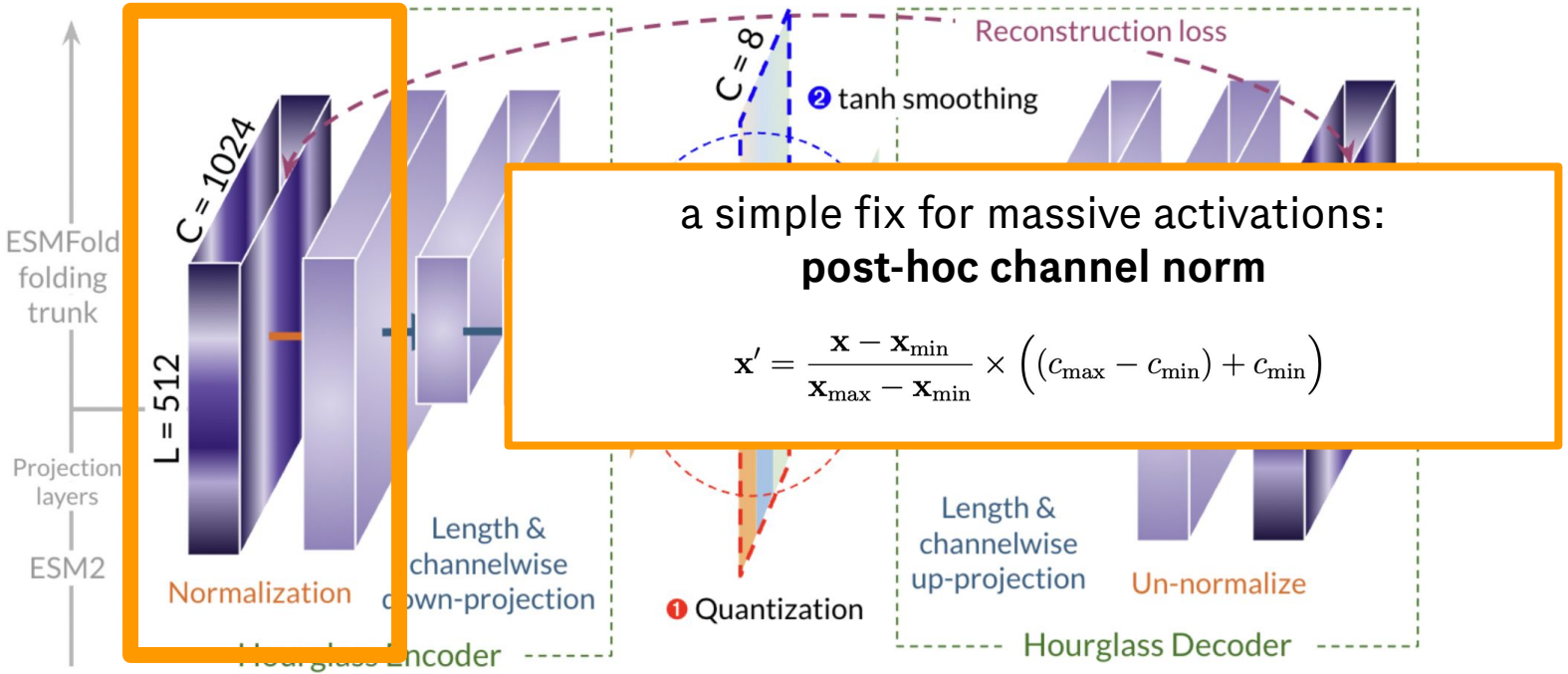
# Why compress?

- More portable representation
- Better understanding of protein folding internals
- Compressed data distributions are easier to learn during generative modeling

# An autoencoder for protein embedding compression



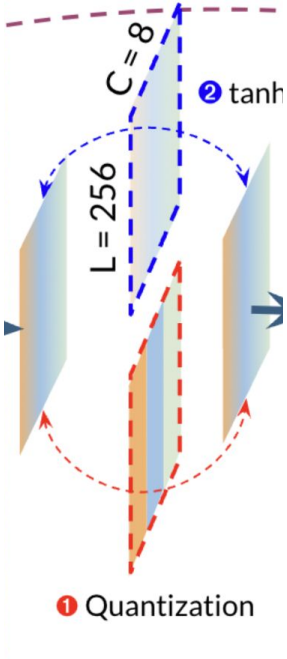
# An autoencoder for protein embedding compression



# Obtaining CHEAP embeddings

## 1. Tokenized

- Discretize embeddings using FSQ
  - ‘snaps’ continuous encoder values to discrete bins

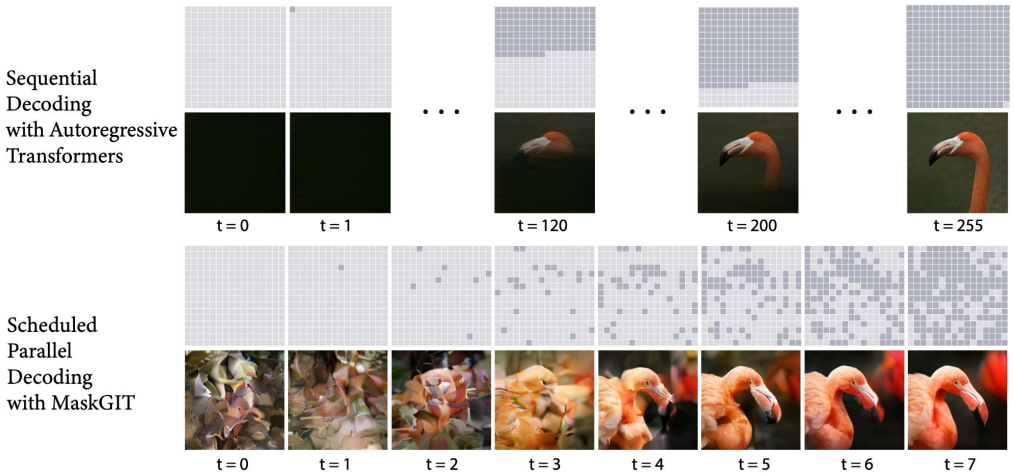



## 2. Continuous

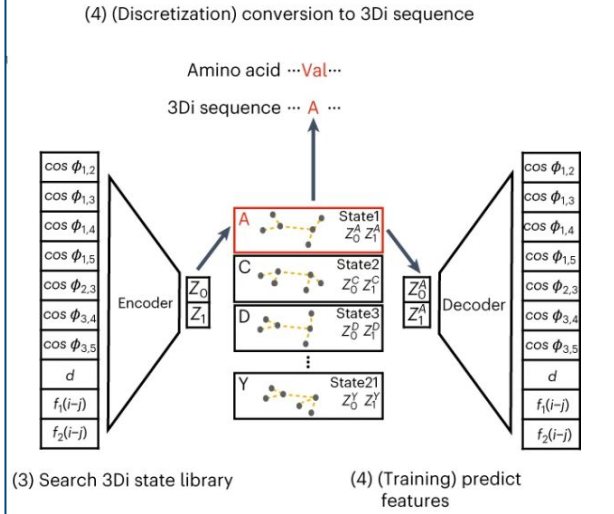
- Take the output of the downprojecting autoencoder
  - apply tanh to bound values between [-1, 1], to bound values during diffusion

# Side note: why tokenized representations?

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

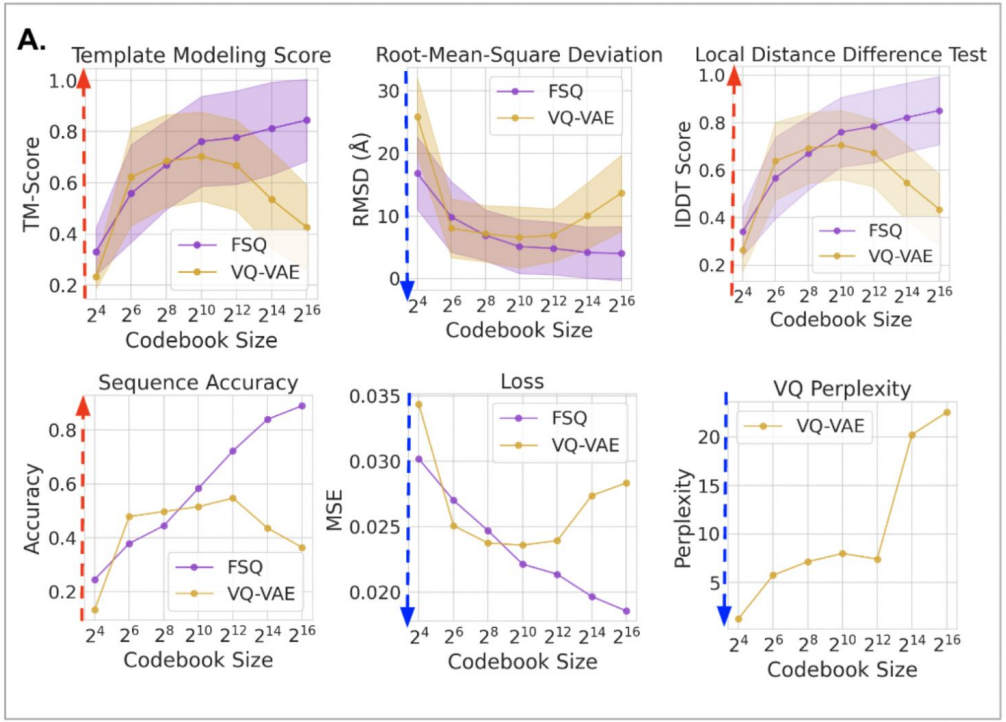



MaskGIT: Masked Generative Image Transformer

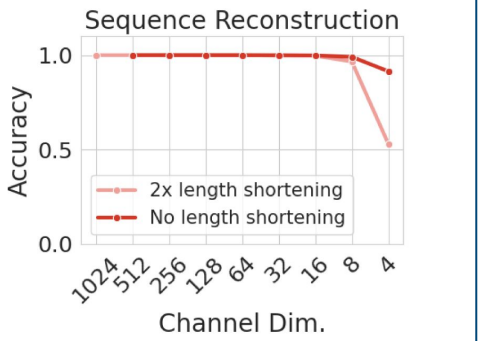



Foldseek

# All-atom structural tokenizer, obtained from sequence alone



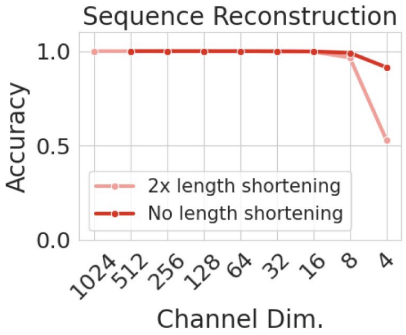
# ..yes, we *can* compress the embeddings:



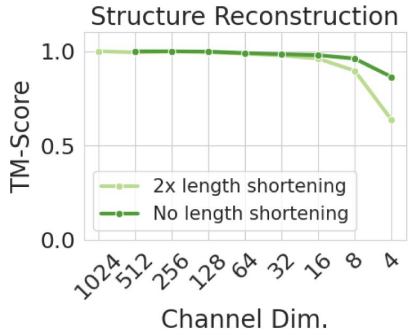

Compression performance with respect to sequence:

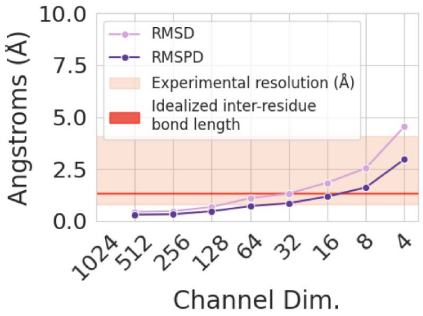
We can compress up to 8x, and sacrifice very little performance.

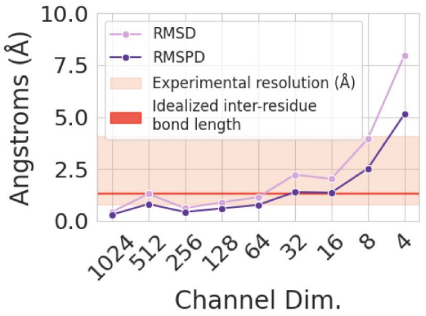
# ..yes, we *can* compress the embeddings:




Compression performance with respect to sequence:



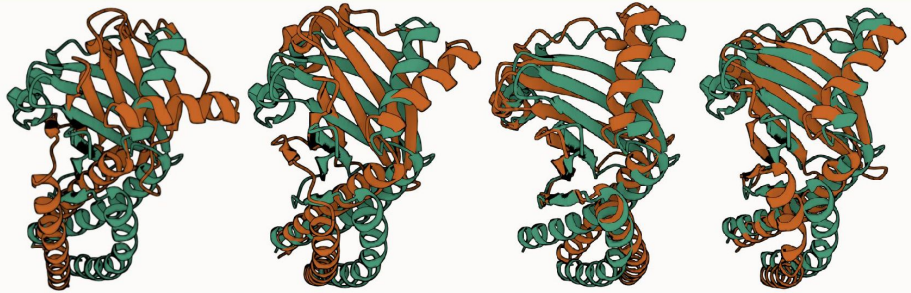



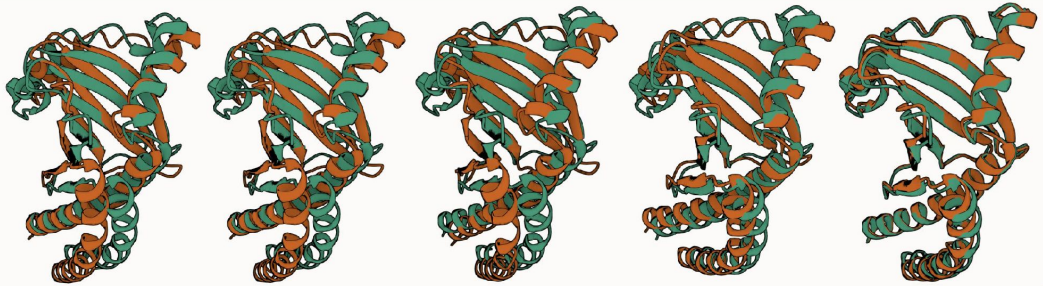




Compression performance with respect to structure:

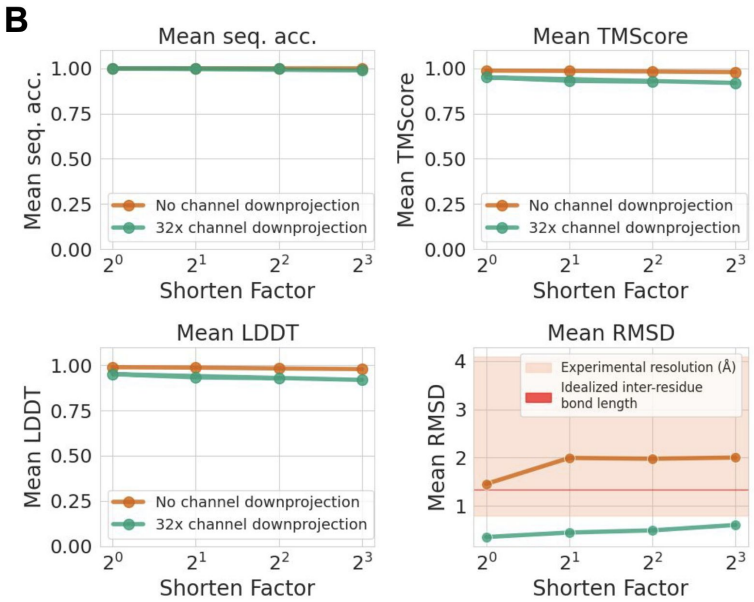
Sequence information is easier to retain than structure.

# ..yes, we *can* compress the embeddings:

| Dim. | 4 | 8 | 16 | 32 |
|---|---|---|---|---|
| |  | | | |
| TMScore | 0.789 | 0.920 | 0.968 | 0.995 |

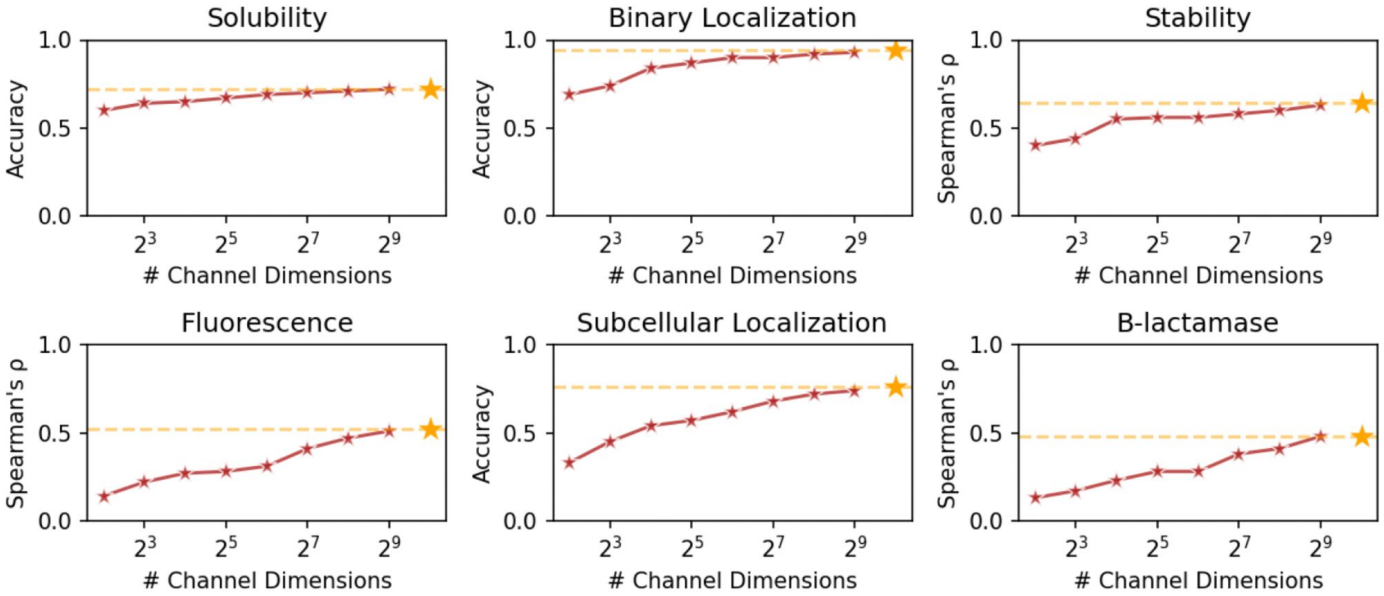
| 64 | 128 | 256 | 512 | 1024 |
|---|---|---|---|---|
|  | | | | |
| 0.991 | 0.999 | 1.000 | 0.997 | 1.000 |

# We can compress lengthwise and channelwise:




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

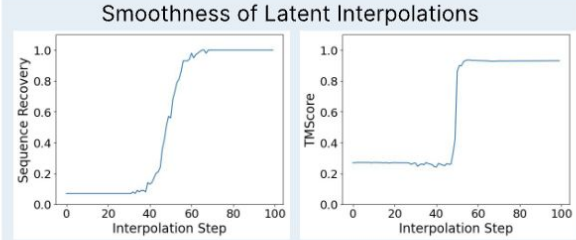
# What about function information?




Performance degradation with compression is much more gradual.
What does this imply about the information content captured in pLMs with respect to downstream tasks?

# Does the autoencoding scheme “fix” the irregular latent space?

Original

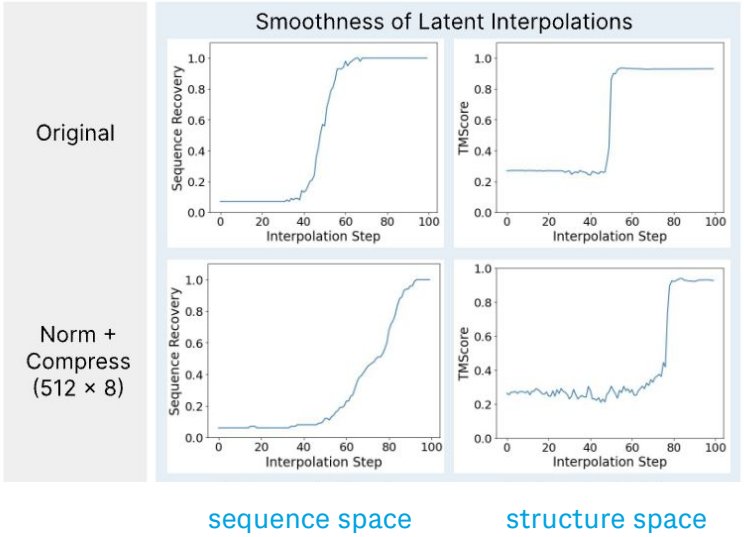



- Despite linearly interpolating in the latent space, the decoded sequence and structure changes very abruptly.

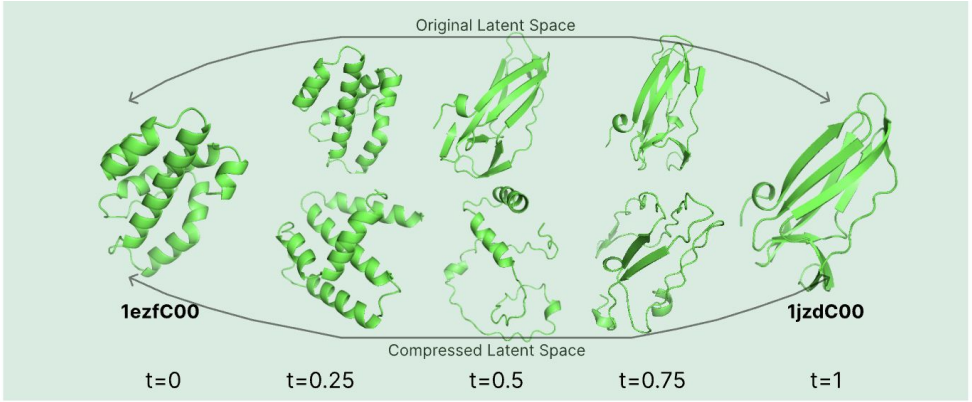
sequence space

structure space

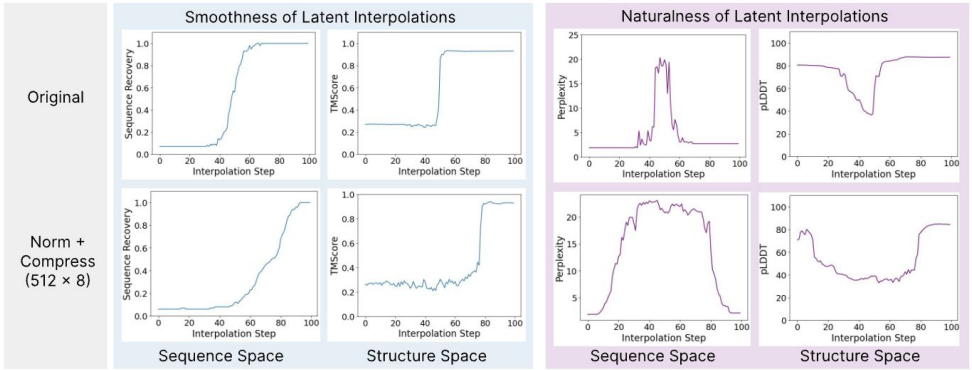
# Does the autoencoding scheme “fix” the irregular latent space?

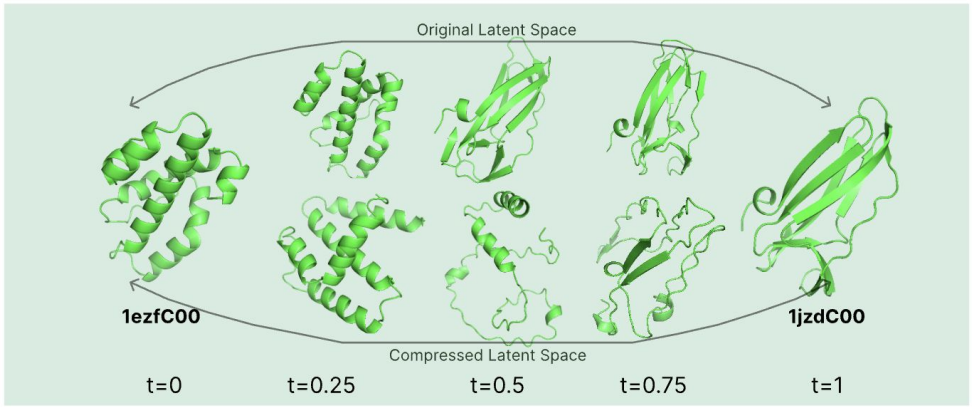



- Despite linearly interpolating in the latent space, the decoded sequence and structure changes very abruptly.
- After CHEAP regularization, the change is more gradual



# PLM latent manifolds might be less “rugged” than true protein fitness landscapes




What makes for a good latent space?

Should we want more of the latent space to map back to a “valid protein” for sampling purposes, or properly model the rugged protein landscape?

Do current PLM embeddings actually recapitulate protein fitness landscapes?

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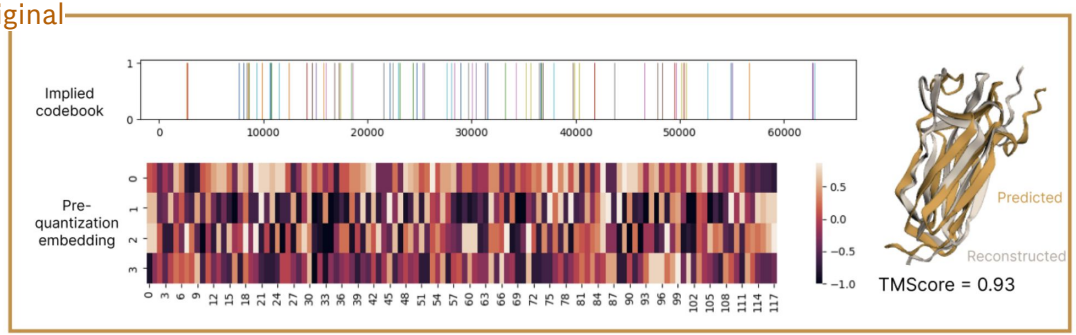
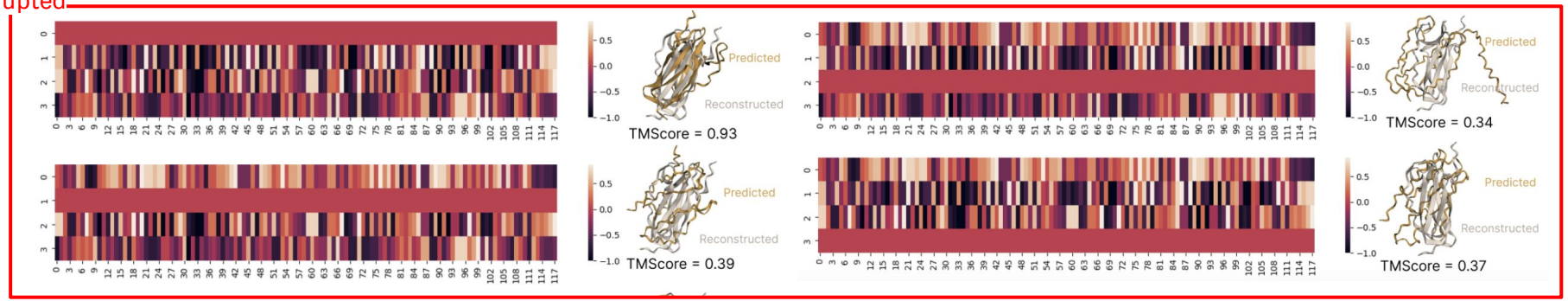
# “Disrupting” and reconstructing in the token space

original




corrupted

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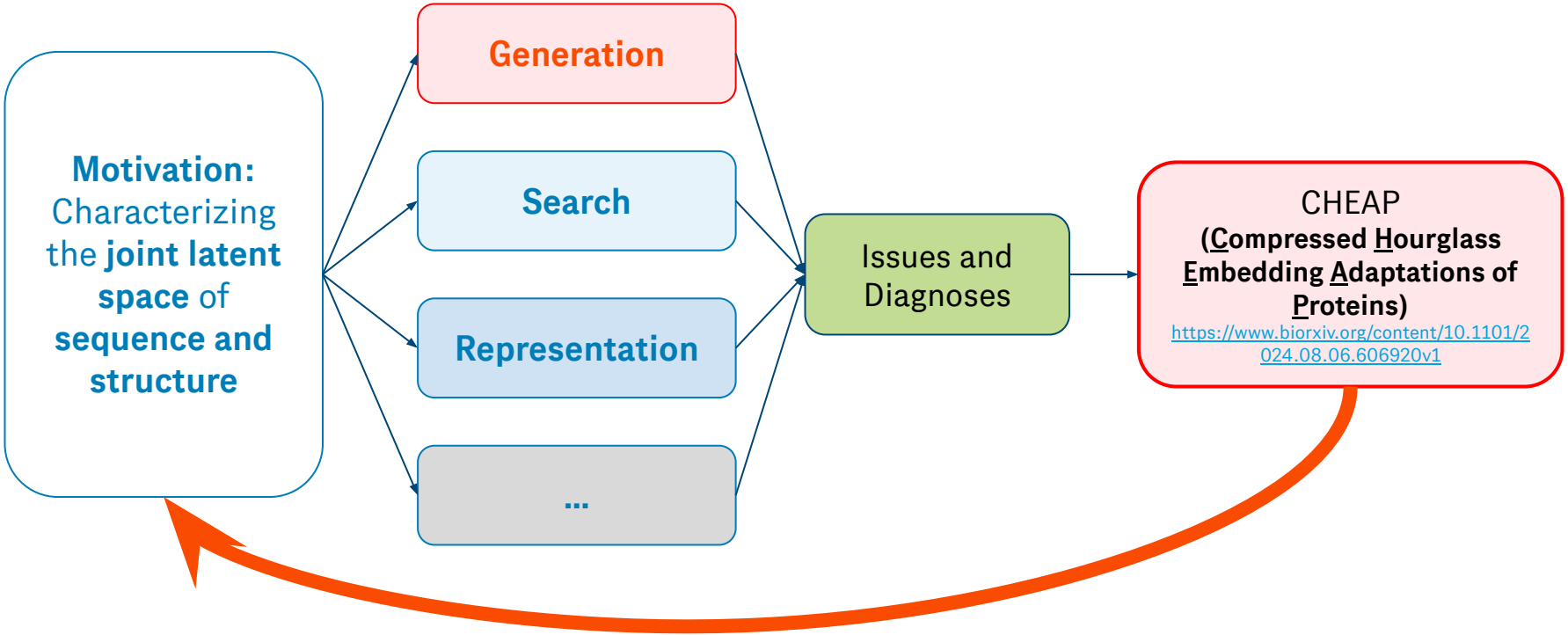
# Agenda

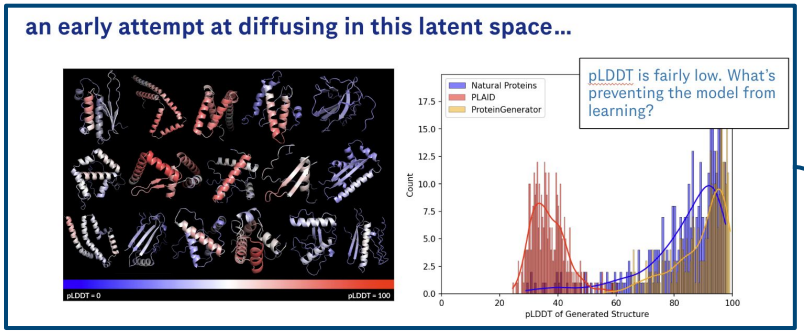

Motivation: Characterizing the joint latent space of sequence and structure
Generation
Search
Representation
...
Issues and Diagnoses
CHEAP
(Compressed Hourglass Embedding Adaptations of Proteins)
https://www.biorxiv.org/content/10.1101/2024.08.06.606920v1

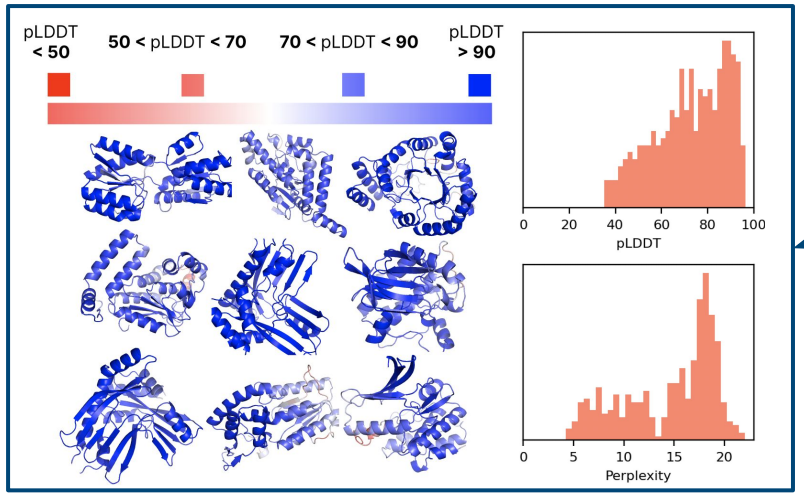
# PLAID (Protein LAtent Induced Diffusion)

*ongoing work!*

*tl;dr – now that we have a regularized & compressed embedding of p(sequence, structure), can we train a latent diffusion model for co-generation?*

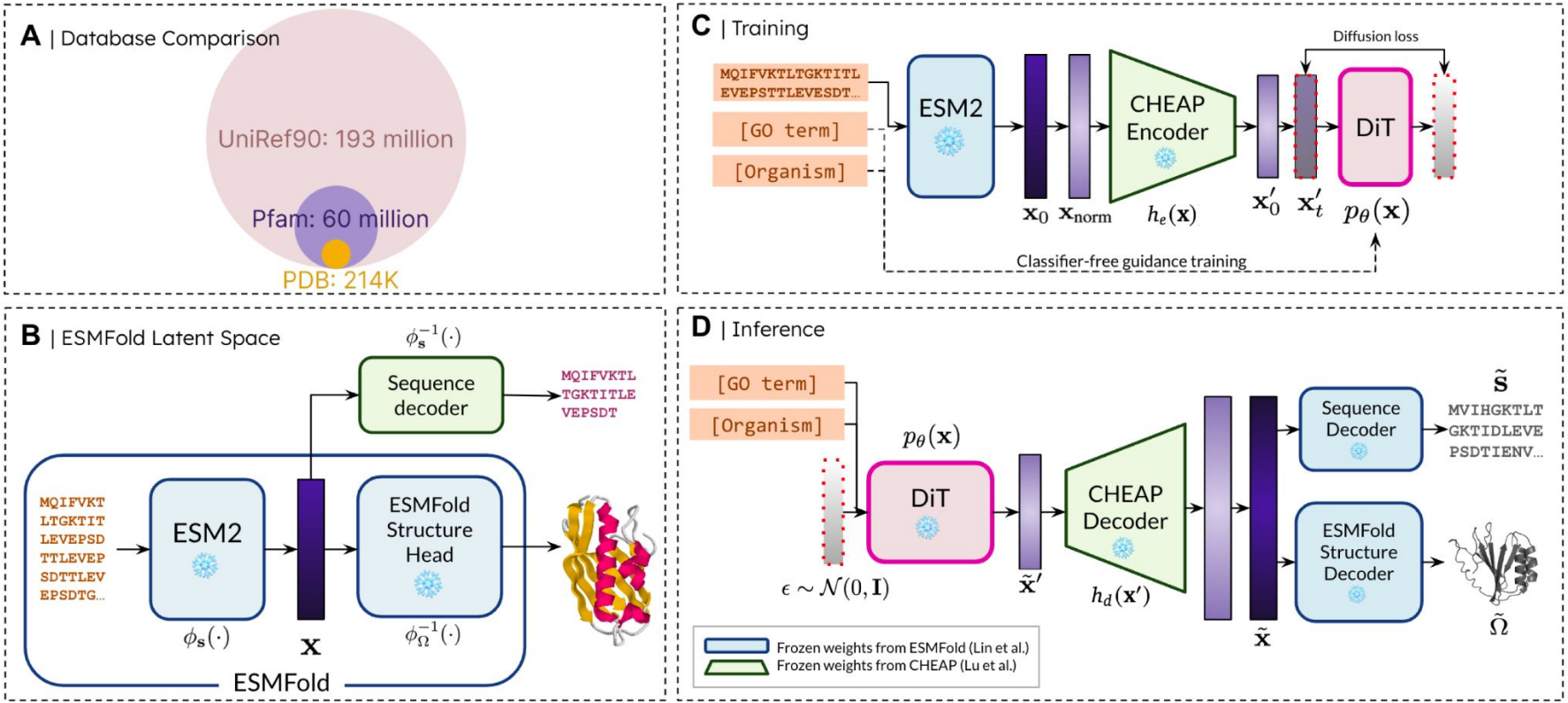
# PLAID, again



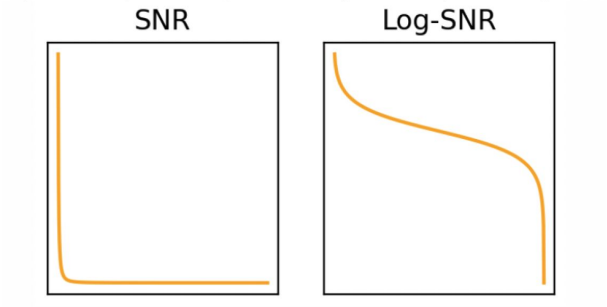



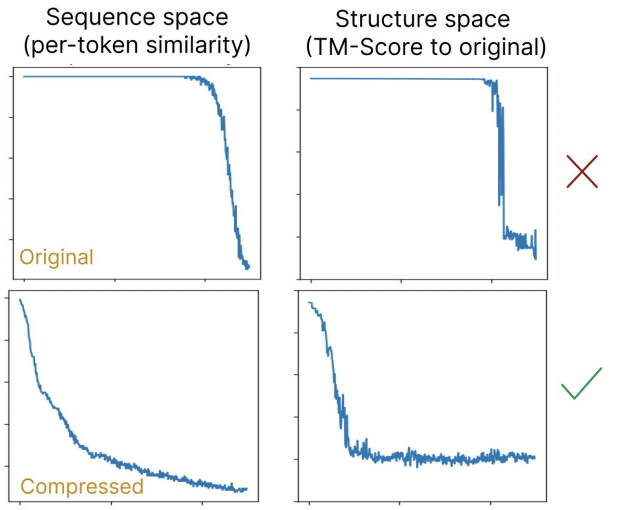

- Learn diffusion model in regularized and compressed latent space
  - mirrors the regularized autoencoder in LDM
- Can learn on longer sequences due to CHEAP shortening
- Use DiT instead of U-triangular self attention
  - allows for scaling up to higher parameter counts
- Scale up to 2B parameters with BS=2048

# PLAID, again


A | Database Comparison
UniRef90: 193 million
Pfam: 60 million
PDB: 214K
C | Training
MQIFVKTLTGKTITL
EVEPSTTLEVESDT...
[GO term]
[Organism]
ESM2
CHEAP Encoder
DiT
Diffusion loss
$\mathbf{x}_0$ $\mathbf{x}_{\text{norm}}$ $h_e(\mathbf{x})$ $\mathbf{x}'_0$ $\mathbf{x}'_t$ $p_\theta(\mathbf{x})$
Classifier-free guidance training
B | ESMFold Latent Space
$\phi_{\mathbf{s}}^{-1}(\cdot)$
Sequence decoder
MQIFVKTL
TGKTITLE
VEPSDT
MQIFVKT
LTGKTIT
LEVEPSD
TTLEVEP
SDTTLEV
EPSDTG...
ESM2
ESMFold Structure Head
$\phi_{\mathbf{s}}(\cdot)$
$\mathbf{x}$
$\phi_{\Omega}^{-1}(\cdot)$
ESMFold
D | Inference
[GO term]
[Organism]
$p_\theta(\mathbf{x})$
DiT
$\epsilon \sim \mathcal{N}(0, \mathbf{I})$
$\tilde{\mathbf{x}}'$
CHEAP Decoder
$h_d(\mathbf{x}')$
$\tilde{\mathbf{x}}$
Sequence Decoder
ESMFold Structure Decoder
$\tilde{\mathbf{s}}$
MVIHGKTLT
GKTIDLEVE
PSDTIENV...
$\tilde{\Omega}$
Frozen weights from ESMFold (Lin et al.)
Frozen weights from CHEAP (Lu et al.)

# Comparing noise schedules in original and compressed latent space:



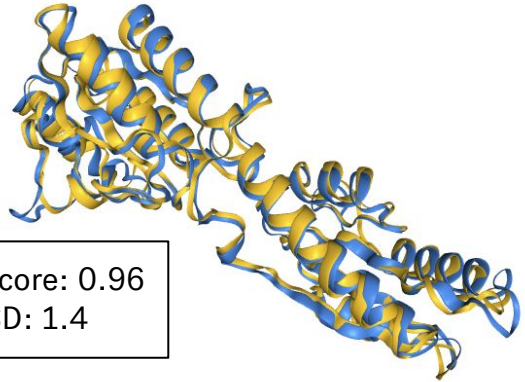




Noising in the CHEAP compressed space maps to noise in the sequence and structure space that is is closer to the true signal-to-noise ratio.

# Samples demonstrate sequence and structural conservation

prompt: **“yeast” AND “6-phosphofructokinase activity”**

Search against the **structure database (PDB100)** to see if our samples are sensible…



TMScore: 0.96
RMSD: 1.4

- closest match: 3o8o **[Structure of phosphofructokinase]**
- organism: **Saccharomyces cerevisiae** (i.e. yeast)
- Sequence identity: 47.9%

Search against the **sequence database (UniRef90)** to see if our samples are sensible…

| Score | Expect | Method | Identities | Positives | Gaps |
|---|---|---|---|---|---|
| 327 bits(838) | 3e-102 | Compositional matrix adjust. | 151/298(51%) | 219/298(73%) | 4/298(1%) |

```
Query  2    MAIVNVGAPASGLNSAVRSLVRHCLSQGHTALAVINGFNGLCK--NDSAMKII-ECKWEQ  58
            +AI++VGAPA G+NSA R+ V +CL++GHT +A+ NGF GLC+  +D  +  + E KW
Sbjct  409  IAIIHVGAPAGGMNSATRAAVAYCLTRGHTPIAIHNGFPGLCRHHDDKPLGAVREVKWLD  468

Query  59   VNLWFAKGGSQFGTARTIFNSNDLELIFDKFEANEINGLLIIGGFNSYNALTVLRHNRQQ  118
            V  W +KGGS+ GT R++  S D+E     FE  + +GL +IGGF ++ A+  LR  R+
Sbjct  469  VEGWISKGGSEIGTNRSL-PSEDMEQTAKCFEQYKFDGLFVIGGFEAFTAVGELRKARKD  527

Query  119  YPEFKIPMIIIPATISNNVPGTAYSLGSESSLNALCTCVDKIKQTASASKRRVFVVETLG  178
            YP F IP++I+PATISNNVPGT YS+GS++ LNAL +  D IKQ+ASA++RRVFVVET G
Sbjct  528  YPAFNIPIVILPATISNNVPGTEYSIGSDTCLNALVSYCDAIKQSASATRRRVFVVETQG  587

Query  179  GTSGYIATMAGVCCGARSIYLPEQGIDLHKLDKDCDFLKQAFDKDSPYNKSGRIIIKNEA  238
            G SGYIAT+AG+  GA ++Y PE+GID+  L +D + L+++F  D   N++G++I++NE
Sbjct  588  GRSGYIATIAGLSIGATAVYTPEEGIDIKMLSRDIEHLRESFANDKGQNRAGKLILRNEH  647

Query  239  ASKVYSTNIIAQLIRDESNGKFDTRTSIPGHQQKGGTPTSLDRVYATKMGAKAMHFIK  296
            ASK Y+T +IA +IR+ES G+F++R ++PGH Q+GGTP+ +DRV A ++  K M FI+
Sbjct  648  ASKTYTTELIANMIREESKGRFESRLAVPGHVQQGGTPSPMDRVRAVRLAVKCMQFIE  705
```

- closest match: PFK1 **[6-phosphofructokinase, alpha subunit]**
- organism: **Hypocenomyce scalaris** (also in the fungus kingdom)
- sequence identity: 50.67%

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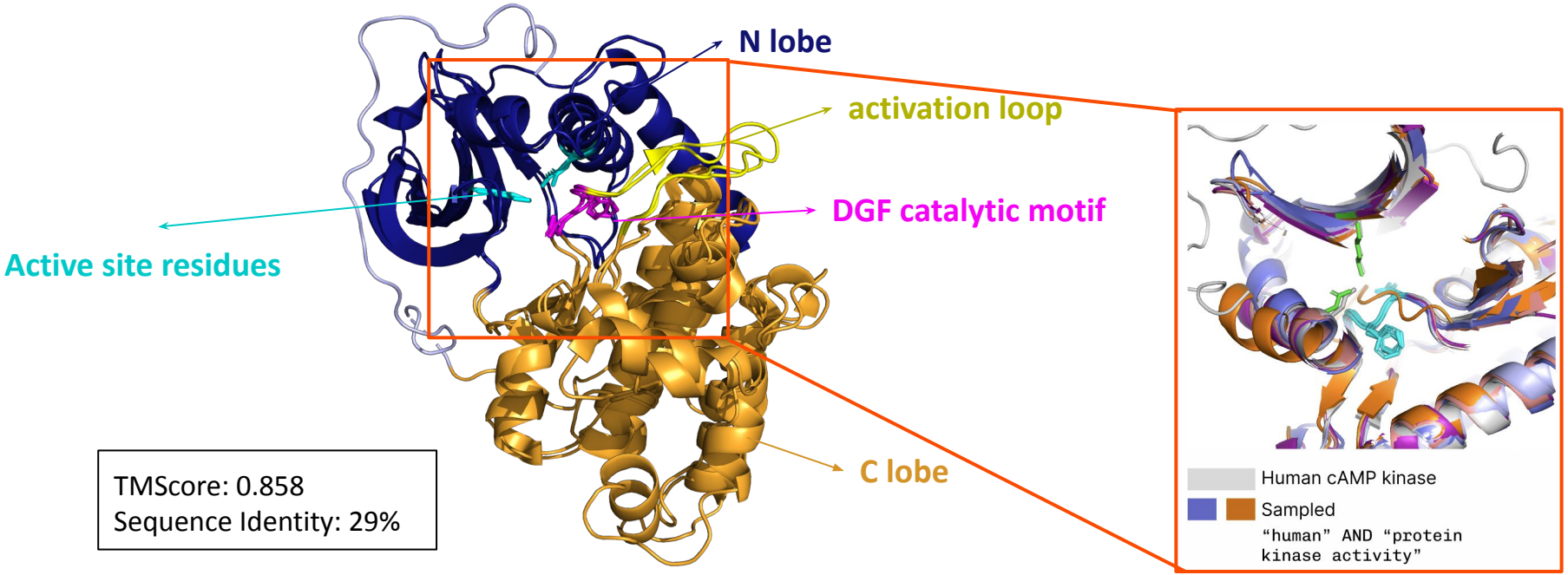
# Examining active site conservation

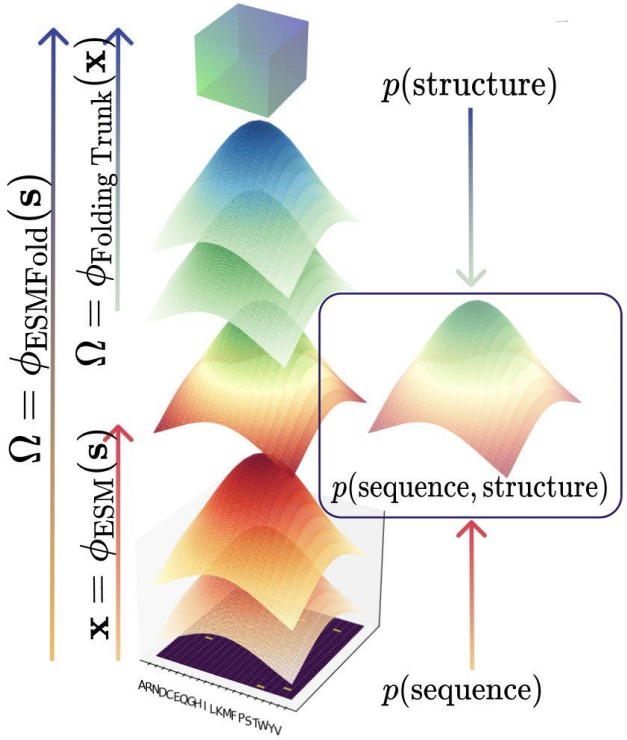
prompt: **“human” AND “protein kinase activity”**

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

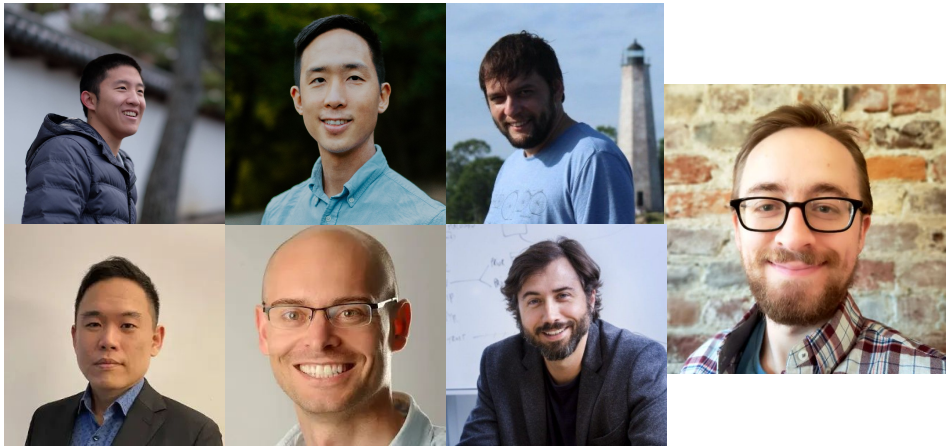


# Takeaways

- The latent space of ESMFold is disorganized with massive activations
- Compressing the latent space shows that *many* channels might be extraneous for structure prediction
- Information content relating to sequence, structure, and function is not symmetrical
- CHEAP regularization helps with latent diffusion model training, leading to **an all-atom co-generation model with sequence database scale coverage**



# Thanks!



**Berkeley**
Amy X. Lu
Wilson Yan
Pieter Abbeel

**Microsoft Research**
Kevin Yang

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

Paper: bit.ly/cheap-proteins

Code & weights: github.com/amyxlu/cheap-proteins

Paper

GitHub

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