Fast uncovering of protein sequence diversity from structure

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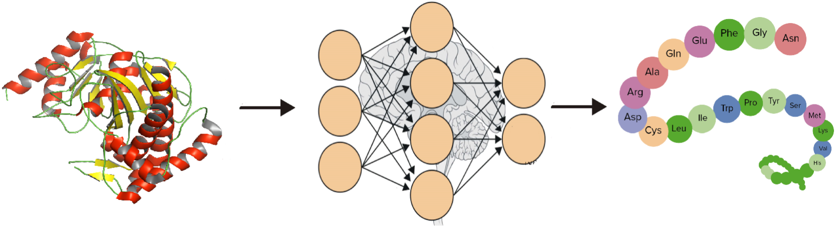
Protein inverse folding

Protein inverse folding: given a 3D structure X, find σ folding into X



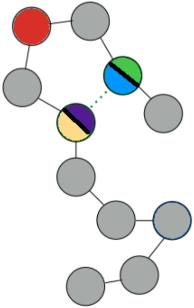
- Given the task's complexity, recently deep-learning methods emerged.
- Models such as ESM-IF1, Protein-MPNN though only map a $X \rightarrow \sigma_X$.

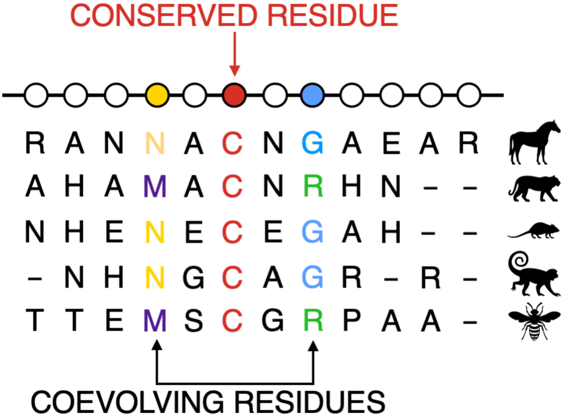
Sequence-structure data imbalance

- Determined sequences ~ 200 millions, determined structures $\sim 200k \implies 0.1\%$ of sequences have a determined structure.
- Mapping $X \to \sigma_X$ focuses on a very small part of sequences.
- Many proteins come from a common ancestor $\implies$ their sequences have some very conserved regions.
- We can cluster such sequences $\implies$ protein families.
- Such sequences evolve constrained by they function and hence structure.
- Crucial *many-to-one* nature of inverse folding

Protein Families

Function/structure conservation constraint evolution of **homologues** ⟹ statistical patterns in MSA.





CONSERVED RESIDUE

R A N N A C N G A E A R

A H A M A C N R H N – –

N H E N E C E G A H – –

– N H N G C A G R – R –

T T E M S C G R P A A –

COEVOLVING RESIDUES

Pairwise models

- MSA has long-range correlations $\Longrightarrow$ need a **global model**

- Probability of a sequence σ_i in a MSA is

$$p(\sigma_i|J,h) = \frac{1}{Z(J,h)} \exp\Big\{ -\Big[\sum_{i<j} J_{ij}(\sigma_i,\sigma_j) + \sum_i h_i(\sigma_i) \Big] \Big\}$$

- *Couplings* $J \in \mathbb{R}^{L\times q\times L\times q}$. $J_{i,j}(a,b)$ describe propensity of amino acids a, b to co-appear at position i, j.
- *Fields* $h \in \mathbb{R}^{L\times q}$. $h_i(a)$ describe the marginal propensity of an amino acid a to appear at position a.
- Potts models can replicate **first and second order** patterns of MSA

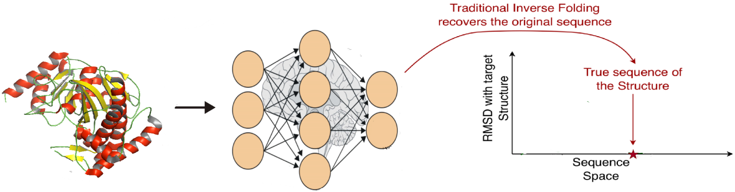
InvMSAFold architecture

- We propose a novel architecture, **InvMSAFold**, which forces the model to learn this variability

- **InvMSAFold** outputs the parameters of a light-weight low-rank approximation of the couplings J

  $$J_{i,j}[a,b] = \frac{1}{\sqrt{K}} V_i[a]^\top v_j[b],$$

  trained on the *augmented* dataset (X, M_X).



Traditional Inverse Folding recovers the original sequence
True sequence of the Structure
RMSD with target Structure
Sequence Space

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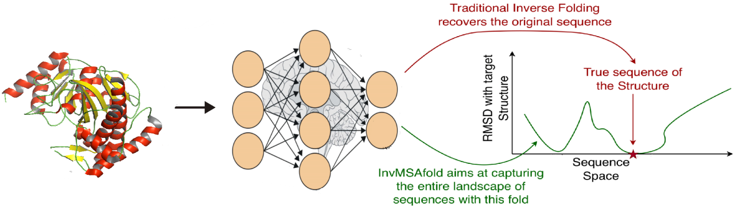

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True sequence of the Structure

InvMSAfold aims at capturing the entire landscape of sequences with this fold

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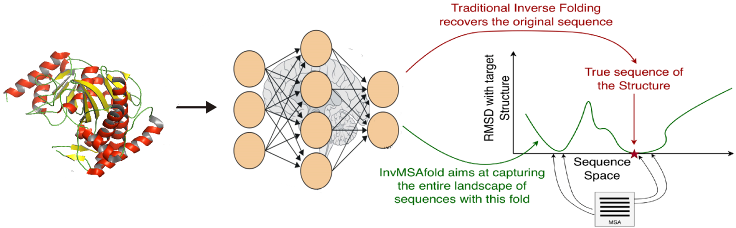
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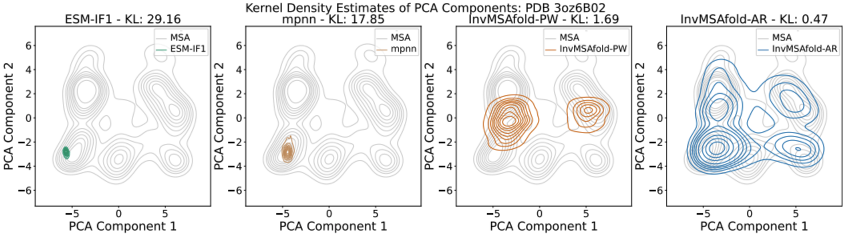
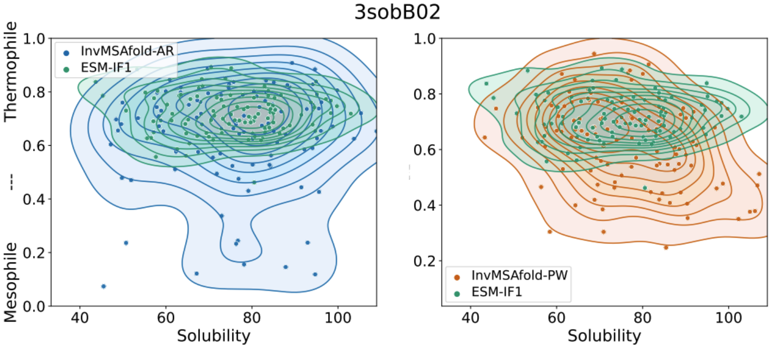
PCA plots


Kernel Density Estimates of PCA Components: PDB 3oz6B02
ESM-IF1 - KL: 29.16
mpnn - KL: 17.85
InvMSAfold-PW - KL: 1.69
InvMSAfold-AR - KL: 0.47
MSA
ESM-IF1
mpnn
InvMSAfold-PW
InvMSAfold-AR
PCA Component 1
PCA Component 2
−6
−4
−2
0
2
4
6
−5
0
5

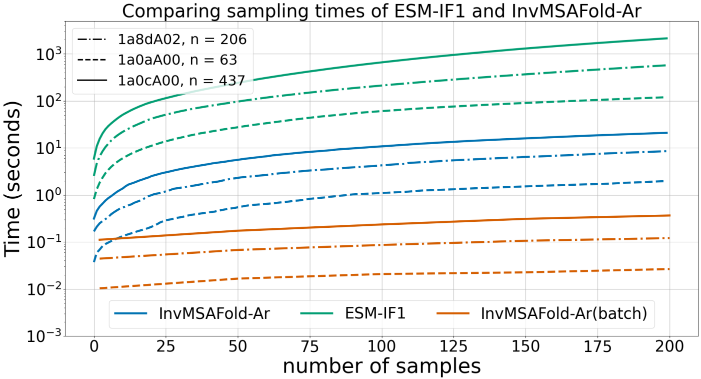
Protein property sampling



Sampling speed at generation

ESM-IF1, Protein-MPNN can be very expensive at inference

- Need $\Theta(L)$ passes through the transformer
- Inv-MSAFold-AR needs just **one**!



Thank you for you attention!

- Paper available at:
  `https://openreview.net/forum?id=1iuaxjssVp`
- Hope to see you all at the poster presentation:
  Fri 25 Apr 7 p.m. PDT 9:30 p.m. PDT!