UNI-FOLD MUSSE: DE NOVO PROTEIN COMPLEX PREDICTION WITH PROTEIN LANGUAGE MODELS

Jinhua Zhu [a,b,*], **Zhenyu He** [a,c,*], **Ziyao Li** [a,d], **Guolin Ke** [a,†] **and Linfeng Zhang** [a,e,†]

[a]DP Technology, China
[b]University of Science and Technology of China
[c]University of Electronic Science and Technology of China
[d]Center for Data Science, Peking University
[e]AI for Science Institute, China

teslazhu@mail.ustc.edu.cn, zhenyu.h@outlook.com,
{lizy01,kegl,zhanglf}@dp.tech

ABSTRACT

Accurately solving the structures of protein complexes is crucial for understanding and further modifying biological activities. Recent success of AlphaFold and its variants shows that deep learning models are capable of accurately predicting protein complex structures, yet with the painstaking effort of homology search and pairing. To bypass this need, we present Uni-Fold MuSSe (Multimer with Single Sequence inputs), which predicts protein complex structures from their primary sequences with the aid of pre-trained protein language models. Specifically, we built protein complex prediction models based on the protein sequence representations of ESM-2, a large protein language model with 3 billion parameters. In order to adapt the language model to inter-protein evolutionary patterns, we slightly modified and further pre-trained the language model on groups of protein sequences with known interactions. Our results highlight the potential of protein language models for complex prediction and suggest room for improvements.

1 INTRODUCTION

Proteins as well as their interactions substantiate a majority of biological activities. Therefore, accurately solving the structures of protein complexes provides key insights in understanding and further modifying these activities. A preliminary to protein complex prediction is to solve the structures of monomeric proteins. Thanks to the success of AlphaFold (Jumper et al., 2021) as well as its subsequent works (Mirdita et al., 2022; Li et al., 2022), *de novo* prediction of monomeric protein structures with atomic-level accuracy is now a regular tool in protein analysis. Based on AlphaFold, AlphaFold-Multimer (Evans et al., 2022) further showed that with inter-chain evolutionary information, retrained AlphaFold models are capable of accurately predicting protein complex structures.

Overall, these AlphaFold-based models rely on the evolutionary patterns embodied by the multiple sequence alignments (MSAs) to make accurate predictions. Specifically in AlphaFold-Multimer, a heuristic pairing strategy is introduced, which greedily matches the homologous sequences of target protein monomers by species similarity. However, obtaining these MSAs requires painstaking work of sequence searching in very large databases, which becomes the temporal bottleneck of the prediction pipeline. Also, the models cannot be well generalized to targets with few homologous sequences. To address these issues, an alternative approach was proposed, which replaced the MSAs with sequence representations from protein language models (PLM) (Rao et al., 2019; Elnaggar et al., 2020; Rives et al., 2021), in the hope of learning the evolutionary patterns directly from primary sequences (Lin et al., 2022; Wu et al., 2022). These PLMs were pre-trained to predict randomly masked tokens similarly to natural language models (Devlin et al., 2018), but on extensive protein sequence corpora with the vocabulary of amino acid types. In general, these models obtain

[*] These authors contributed equally to this work.

[†] Guolin Ke and Linfeng Zhang are corresponding authors of this work.

approaching or equivalent accuracies on monomer prediction tasks compared with AlphaFold, while bypassing the effort of homology searching.

Nevertheless, the use of PLMs in protein folding is so far limited to monomers. Although some tricks were proposed to predict complex structures with ESMFold (Lin et al., 2022), such as concatenating protein chains with gaps or soft linkers, the accuracies were much limited. A specific challenge of using PLMs for protein complex prediction is that all current PLMs were trained with individual protein chains, leaving it in doubt whether the sequence representations can capture inter-chain evolutionary patterns and further guide the complex prediction task. To answer this question, we i) trained a protein complex prediction model using the representations of input primary sequences from an existing PLM, ESM-2 (Rives et al., 2021) with 3 billion parameters; ii) enhanced the PLM with chain relative positional encoding, and further pre-trained it with the corpora of protein interactions; and iii) check if the further pre-training improves the folding accuracy.

To this end, we present Uni-Fold MuSSe (Multimer with Single Sequence inputs), an end-to-end model which *de novo* predicts protein complex structures from primary sequences only. We found that by retraining a multimeric folding model, the representations from ESM-2 were applicable to complex prediction with satisfying accuracy, largely outperforming existing PLM-based baselines, despite a gap to MSA-based models represented by AlphaFold-Multimer. By further pre-training the PLMs on protein interaction corpora, the retrained complex prediction model, Uni-Fold MuSSe+, displayed a better performance. Also, on several test cases that AlphaFold-Multimer failed to work, Uni-Fold MuSSe+ obtained correct predictions.

2 Related Work

Protein Structure Prediction. *In silico* protein structure prediction aims to predict protein structures from the amino acid sequences purely with computational methods. AlphaFold (Jumper et al., 2021) is the first deep learning model that claimed to achieve "atomic-level" accuracy, based on which AlphaFold-Multimer (Evans et al., 2022) achieved high accuracy on protein complex prediction. To facilitate the open-source community of deep protein folding models, Uni-Fold (Li et al., 2022) re-implemented both AlphaFold and AlphaFold-Multimer in PyTorch with equivalent accuracy, and released the training code in the repository. In this paper, we built the multimeric folding model following the implementation of Uni-Fold Multimer.

Protein Language Models. Inspired by the success of pre-trained language models (Devlin et al., 2018; Radford et al., 2018), encoding the amino sequences of proteins with large language models has been widely explored. Generally, protein language models (PLMs) are trained on large protein sequence corpora to predict randomly masked amino acids in the sequences, whose representations are leveraged in downstream tasks. Early works (Rives et al., 2021; Elnaggar et al., 2020) showed the effectiveness of using PLMs in secondary structure prediction and contact prediction. Later, these PLMs were improved with more curated architectures and larger parameters (Lin et al., 2022; Wu et al., 2022; Fang et al., 2022) and used on end-to-end monomeric folding tasks, achieving approaching or equivalent accuracies to AlphaFold-based models. In this paper, we used the ESM-2 (Rives et al., 2021) model with 3 billion parameters as the base PLM.

Further Pre-training. Based on existing explorations on PLMs, our work uses *further pre-training* to improve existing PLMs to capture inter-chain evolutionary patterns. Further pre-training is a widely used strategy in natural language processing for domain adaptation, where a pre-trained model is further trained to fit corpora in the target domain biased from the original one. Previous studies in Natural Language Processing (Lee et al., 2020; Beltagy et al., 2019; Sun et al., 2020) proved the effectiveness of further pre-training on domain transfer tasks, whereas the target domain generally has massive unlabeled data. In our case, notably, the known groups of interactive protein sequences are far sparser than monomeric ones.

3 Method

For an overall picture of our model, Figure 1 compares the workflows of protein complex prediction with i) MSA-based models such as AlphaFold-Multimer; ii) PLM-based (monomeric) models such as ESMFold and OmegaFold; and iii) our method Uni-Fold MuSSe+.

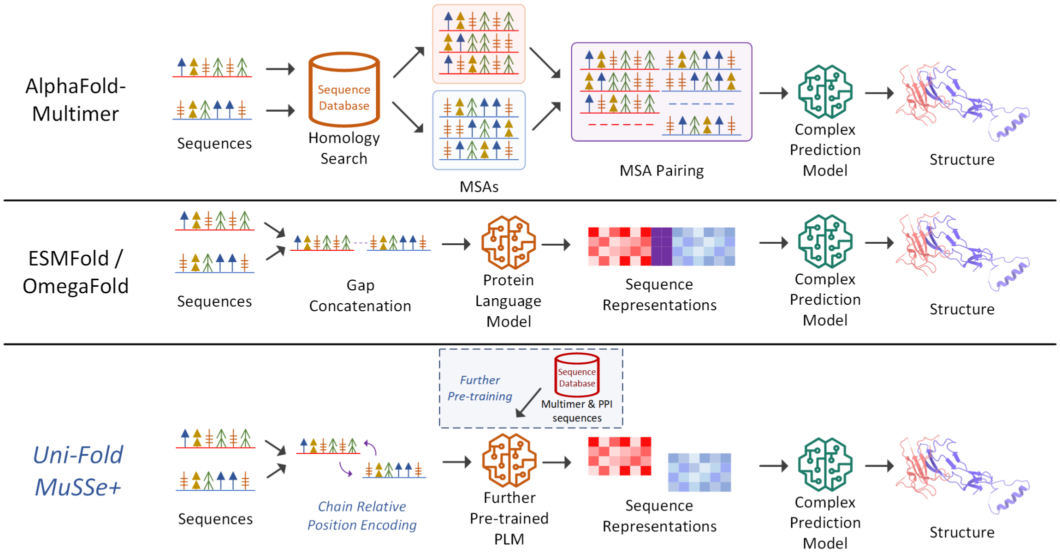


Figure 1: The workflows of MSA-based complex prediction methods, previous language model-based methods such as ESMFold and OmegaFold and our proposed method Uni-Fold MuSSe+.

3.1 Further Pre-training of Protein Language Model

In order to further pre-train ESM-2, we carefully modified the architecture to adapt the model to inputs of both single sequence and multiple interactive sequences, without damaging the effects of the pre-trained parameters. To summarize, we introduce chain-level relative positional embedding to properly distinguish different chains, a cropping strategy for large protein complexes, and a data augmentation strategy to relieve overfitting.

Chain Relative Positional Encoding. Based on the Rotary Position Embedding (RoPE) (Su et al., 2021) used in ESM-2 (Lin et al., 2022), we propose two modifications to correctly introduce relative chain information. The first is to fix the incorrect RoPE among different chains. RoPE multiplies query and key embeddings in the $\mathrm{attention}$ module with sinusoidal embeddings so that the relative positional information can be captured by the Query-Key dot-product. However, although RoPE works well for single-sequence, it produces incorrect relative positional signals for residues from different chains. To address this issue, we proposed a fix for RoPE as follows: 1) First, a pair-wise matrix $\boldsymbol{M}$ is used to check if a residue pair is from the same chain ($\boldsymbol{M}_{ij} = 1$) or not ($\boldsymbol{M}_{ij} = 0$); 2) Besides the Query-Key dot-product with RoPE embedding, denoted as $\boldsymbol{A}_{\text{RoPE}}$, we calculate an additional Query-Key dot-product without RoPE embedding, denoted as $\boldsymbol{A}_{\text{raw}}$. 3) To remove the wrong signals of RoPE for different chains, we use the following update for the Query-Key dot-product, $\boldsymbol{A} = \boldsymbol{A}_{\text{RoPE}} \cdot \boldsymbol{M} + (\boldsymbol{A}_{\text{raw}} + \mathrm{Mean}(\boldsymbol{A}_{\text{RoPE}} - \boldsymbol{A}_{\text{raw}})) \cdot (1 - \boldsymbol{M})$, where $\mathrm{Mean}(\cdot)$ is the mean pooling across the first two dimensions. This new update uses the RoPE-based $\mathrm{attention}$ for the residues on the same chain, and uses the non-RoPE $\mathrm{attention}$, with the background deltas (average of differences), for the residues on the different chains.

Algorithm 1 Self-attention with chain relative position embedding

```
Require: $\boldsymbol{M}$, $\boldsymbol{N}$, attention weights with RoPE $\boldsymbol{A}_{\text{RoPE}}$, attention weights without RoPE $\boldsymbol{A}_{\text{raw}}$, embedding matrices $\text{emb}^{\text{same\_chain}}$ and $\text{emb}^{\text{same\_entity}}$.
Fix the RoPE attention weights $\boldsymbol{A} = \boldsymbol{A}_{\text{RoPE}} \cdot \boldsymbol{M} + (\boldsymbol{A}_{\text{raw}} + \mathrm{Mean}(\boldsymbol{A}_{\text{RoPE}} - \boldsymbol{A}_{\text{raw}})) \cdot (1 - \boldsymbol{M})$
$\text{chain\_rel\_emb}_{ij} = \text{emb}^{\text{same\_entity}}(\boldsymbol{M}_{ij}) + \text{emb}^{\text{same\_chain}}(\boldsymbol{N}_{ij})$
Update attention weights $\{\boldsymbol{A}_{ij}\} \leftarrow \{\boldsymbol{A}_{ij}\} + \{\text{chain\_rel\_emb}_{ij}\}$
return $\{\boldsymbol{A}_{ij}\}$
```

The second is to introduce the chain-level information. Besides corrected RoPE, we introduce two chain-level relative positional encodings. 1) $\boldsymbol{M}$, in which $\boldsymbol{M}_{ij}$ encodes whether a residue pair is from the same chain or not. 2) $\boldsymbol{N}$, in which $\boldsymbol{N}_{ij}$ encodes whether a residue pair is from chains of identical sequences or not, i.e., the possible different chains, but with the same sequence content. The two positional encodings are used as the index for embedding lookup tables and then are added to the attention weights before $\mathrm{softmax}$ in the $\mathrm{attention}$ module. Note that the parameters of embedding lookup tables are shared across layers. The details can be found in Algorithm 1.

Multi-chain Proportionally Contiguous Cropping. The total number of residues can be very large in multimeric sequences, which is infeasible to be fitted into GPU memory and inefficient in training. We use a cropping method similar to $ContiguousCropping$ in AlphaFold-Multimer, with moderate changes, i.e., we crop chains proportionally according to their length. The details can be found in Algorithm 2.

Algorithm 2 Contiguous and Proportional Cropping

```
Require: Chain indices $\{f_i^{\text{chain\_id}}\}$, expected cropped length $N_{\text{res}}$
$\{f_{i\text{\_cropped}}^{\text{chain\_id}}\} \leftarrow$ random.choice($\{f_i^{\text{chain\_id}}\}, N_{\text{res}}$, replace=False)
$\{\text{crop\_size}_i\} \leftarrow$ Counter($\{f_{i_{\text{cropped}}}^{\text{chain\_id}}\}$)
for $i = 0$ to $N_{\text{chains}} - 1$ do
    $n_i = \text{len}(f_i^{\text{chain\_id}})$
    $\text{crop\_start} \leftarrow \text{uniform}(0, n_i - 1 - \text{crop\_size}_i)$
    $m_i \leftarrow 0$                                                # $m_i \in \{0,1\}^{n_i}$
    $\text{keep} \leftarrow [\text{crop\_start}, \cdots, \text{crop\_start} + \text{crop\_size}_i]$
    $m_{i\text{keep}} = 1$
end for
return $\{m_i\}$
```

Data Augmentation. Directly using multimeric sequences of solved complex crystal structures for further pre-training PLMs can easily cause over-fitting, due to limited available data. Hence, we leverage more protein sequences from other sources, i.e., the sequence pair from protein-protein interaction data and the monomeric sequence. As the sizes of these datasets vary different, we assign different sample probabilities for them during training. The details of these datasets and the sampling probabilities for them are presented in Sec. 4.1.

3.2 Complex Prediction Model

We followed the major implementation of Uni-Fold Multimer (Li et al., 2022) to build the complex prediction model. The model consists of an encoder block which encodes the PLM representations, and a structure module which predicts the complex structure. The encoder block is adapted from the Evoformer (Jumper et al., 2021), simply by removing Extra-MSA blocks, template-related blocks, and the `MSAColumnAttention` block. The structure module is implemented as-is. We enlarged the embedding sizes of both the encoder and structure module to match the input dimensionality of ESM-2.

Similar to ESMFold (Lin et al., 2022), we use the token representations in the ESM-2 as the initial hidden states for structure prediction, with no gradient propagated back to the PLM. Notably, instead of using the linear combination of representations from all 48 layers, we simply combine those from the first and the last layers as inputs with learnable parameters α, β:

$$\boldsymbol{s} = \text{MLP}(\tilde{\alpha}\boldsymbol{s}_{\text{first}}^{\text{PLM}} + \tilde{\beta}\boldsymbol{s}_{\text{last}}^{\text{PLM}}), \quad (\tilde{\alpha}, \tilde{\beta}) = \text{softmax}(\alpha, \beta) \tag{1}$$

This is based on the observation that the first and the last layers contribute up to 97.3% to the folding model in the learned parameters of ESMFold (see the results in Figure 2). By doing so, the computational and storage costs are dramatically reduced. We used the relative chain and position encoding as the initial pairwise states.

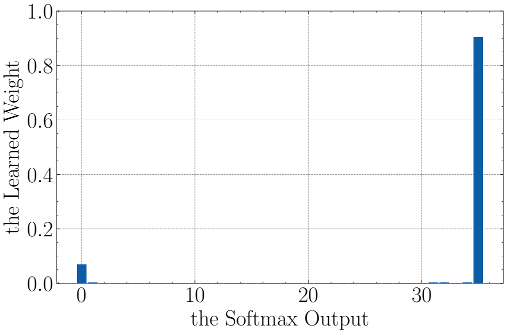


Figure 2: The probability distribution of learned weights for each layer output in ESMFold.

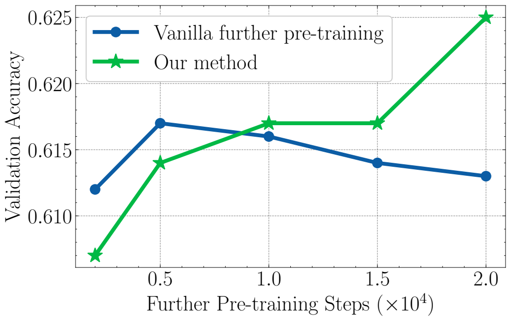


Figure 3: Mask token prediction accuracy on validation set during further pre-training.

4 Experiments

4.1 Further pre-training of ESM-2

Model, Data and Training. We conducted further pre-training on ESM-2 (Lin et al., 2022), one of the largest pre-trained protein language model pre-trained on vast protein sequence data via masked language modeling. The model with 3 billion parameters is chosen as the base model.

A combination of three datasets is used in the further pre-training: i) `UniRef50`: approximately 50 million monomeric sequences in UniRef50 (Mirdita et al., 2017); ii) `PDB`: a total of 133 thousand groups of sequences of solved protein multimers in the Protein Data Bank; and iii) `PPI`: 2.6 million pairs of protein sequences known to have potential interactions from existing databases. Specifically for `PPI`, raw and partially overlapping interaction protein pairs were combined from seven sources: HINT (Das & Yu, 2012), intACT (Orchard et al., 2014), HIPPIE (Alanis-Lobato et al., 2016), prePPI (Zhang et al., 2012), BioGRID (Oughtred et al., 2019), comPPI (Veres et al., 2015) and huMAP (Drew et al., 2017). For higher data quality, we filtered out duplicated interactions, protein sequences outside of the Swiss-Prot database, and interactions with confidence scores lower than 0.8 in intACT, comPPI and huMAP. A total of 2,619,684 interaction pairs between 61,643 proteins were finally acquired.

The further pre-training included a total of $100,000$ steps, each with a batch of 128 samples. Each sample contained one sequence in `UniRef50`, a group of multimeric sequences in `PDB`, or an interaction pair in `PPI`, with probability $2:4:4$. We used AdamW (Loshchilov & Hutter, 2017) as the optimizer with $\beta_1 = 0.9$, $\beta_2 = 0.98$, and L_2 weight decay of 0.01. The learning rate was linearly warmed up to $1e$-5 in the first 2,000 steps, and linearly decayed to $5e$-6 at the final step. This process was run on 32 NVIDIA A100 GPUs (80G) for approximately 30 hours.

Effectiveness of Further Pre-Training Strategies. We verified the effectiveness of the proposed method by the masked token prediction accuracy during further pre-training. In particular, we set up a baseline where the original ESM-2 model architecture was only with `PDB`. As is shown in Figure 3, the baseline was vulnerable to overfitting in further pre-training, whereas our method displayed better generalizabilty.

4.2 Single Sequence Protein Complex Prediction

Dataset. For the training dataset, we follow the processing steps described in (Jumper et al., 2021) and (Evans et al., 2022). First, we use all the PDB complexes released before 2022-05-01, and then filter out all chains of which the resolution is greater than $9\mathring{A}$ or there exists a residue whose occupancy frequency is greater than 0.8. For sequence clustering, we use MMseqs easy-cluster[1] with default parameters at 40% sequence identity and result in 37812 sequence clusters, 133954 unique sequences, 645947 chains, and 179854 PDB assemblies. When training complex predictor, each PDB assembly i is sampled with unnormalized probability $p_i = \sum_{c_j} \frac{1}{\text{cluster\_size}(c_j)}$, where c_j

[1] `https://github.com/soedinglab/MMseqs2`

Table 1: Performance on multimeric protein structure prediction. The second and third columns are the mean and median TM-score among all test samples, and the right two columns are the percentage of predictions with a TM score above a predetermined threshold.

	TM-Score			
	Mean	Median	% > 0.85	% > 0.95
AlphaFold-Multimer	**0.7106**	**0.9057**	**58.78**	**37.16**
AlphaFold-Multimer w/o MSA	0.3012	0.2001	8.11	1.35
OmegaFold (Wu et al., 2022)	0.3986	0.2439	16.89	6.08
ESMFold (Lin et al., 2022)	0.4357	0.2715	22.97	7.43
Uni-Fold MuSSe	**0.5871**	0.6038	39.86	20.27
Uni-Fold MuSSe+	0.5841	**0.6675**	**41.22**	**28.38**

is the j_{th} chain of assembly i, $\text{cluster\_size}(c_j)$ is the size of the corresponding cluster of c_j, and last the probability p_i is normalized over all PDB assemblies. We also construct a distillation dataset with 914800 structure predicted by AlphaFold2, of which the mean pLDDT$>$ 70. During training, we randomly sample distilled or PDB structures with probability 0.75 or 0.25, respectively. For inference data, we use all PDB complexes released after 2022-05-01, then filter out all multimeric data whose length-weighted sequence similarity is greater than 0.4 with any training sample, and randomly select one sample from each sequence cluster to constitute the last inference dataset.

Model and Training. We mainly followed the implementation of Uni-Fold Multimer (Li et al., 2022) to build the folding model. The hidden dimensions of Evoformer and the structure module were both extended to $1,024$ with 32 attention heads. We used Adam (Kingma & Ba, 2014) $\beta_1 = 0.9$, $\beta_2 = 0.999$ as the optimizer. The learning rate was warmed up in the first $1,000$ steps to a peak value of 0.001, and then decayed by 0.95 every $50,000$ steps in stair-case style. The model was trained on 64 NVIDIA A100 GPUs (80G) with $150,000$ steps and batch size 128 (by gradient accumulation) in about 15 days.

Baselines and Metric. We compared Uni-Fold MuSSe and MuSSe+ with i) AlphaFold-Multimer; ii) AlphaFold-Multimer with single sequence inputs, i.e. with MSAs and templates removed; iii) OmegaFold (Wu et al., 2022) and iv) ESMFold (Lin et al., 2022), in which we concatenated the sequences with 20-residue gaps embodied by the unknown symbol `X` (`[UNK]`). The only difference between MuSSe and MuSSe+ was that the latter used the further pre-trained PLM. Notably, both folding models in Uni-Fold MuSSe and MuSSe+ were trained from-scratch. Following Li et al. (2022), we used TM-score to evaluate the predicted complexes. Specifically, the optimal alignment between a prediction and the ground truth was calculated on the entire assembly structure. The scores were then calculated by averaging over all C_α atoms in all chains. Best scores across all possible permutation alignments was reported.

4.3 Results

The results of the experiment are presented in Table 1. As can be seen, (1) AlphaFold-Multimer without multiple sequence alignment (MSA) lags behind OmegaFold, ESMFold, Uni-Fold MuSSe and Uni-Fold MuSSe+ by a considerable margin, highlighting the crucial role of language model representation in the absence of MSA information. (2) Uni-Fold MuSSe and Uni-Fold MuSSe+ outperform OmegaFold and ESMFold, demonstrating that the incorporation of language model representations into the training process of protein complex prediction can further enhance performance. (3) Although Uni-Fold MuSSe and Uni-Fold MuSSe+ outperform OmegaFold and ESMFoLd, it still lags behind AlphaFold-Multimer with MSA input, indicating room for improvement in language model-based complex prediction methods. (4) Between the two variants of our method, although the average TM-Scores are similar, Uni-Fold MuSSe+ shows better performance in predicting high-quality complex structures, since it predicts more structures with TM-Score > 0.95 (and > 0.85). This is evident that Uni-Fold MuSSe+ is superior to the variant without further pre-training.

We also assessed the performance of our method and baseline methods using the TM-Score and RMSD metrics at the sample level and present the results in Figure 4. In agreement with our previous

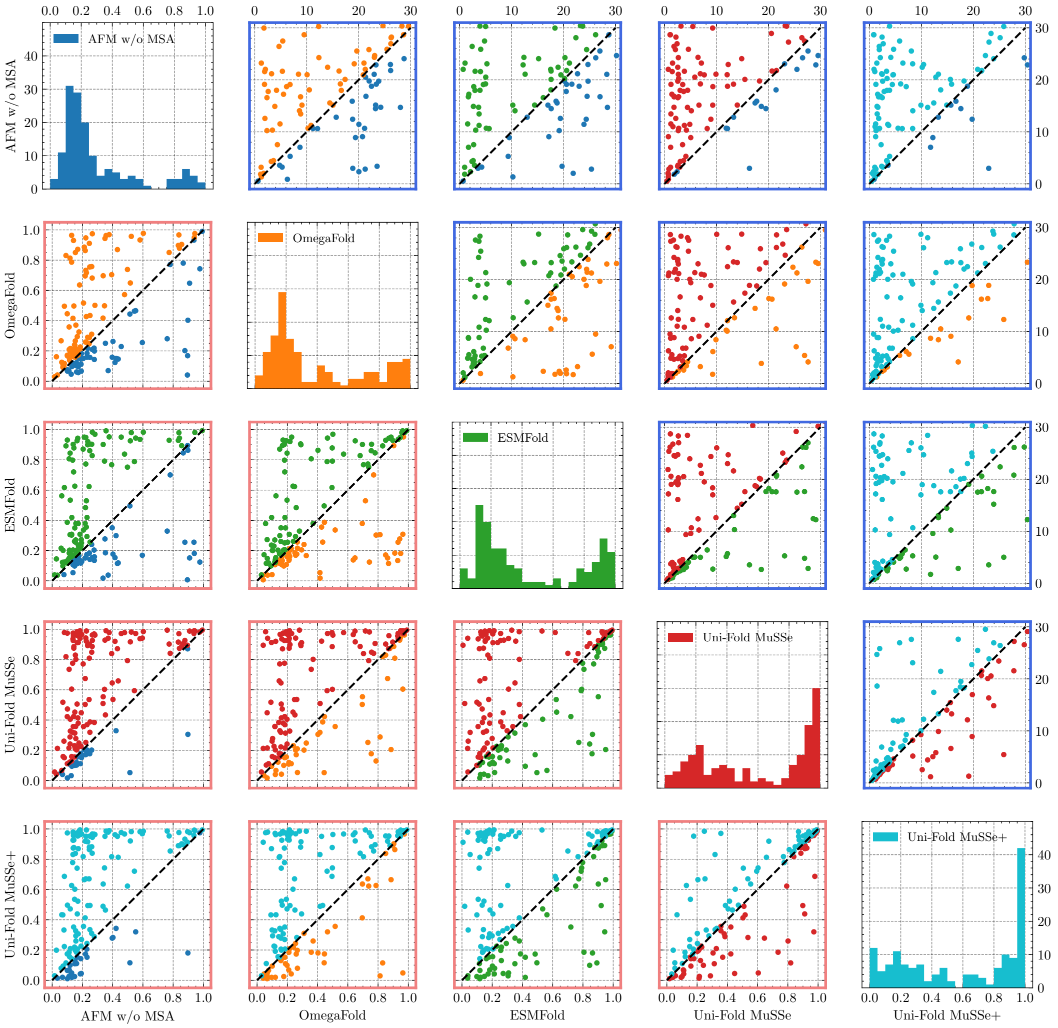
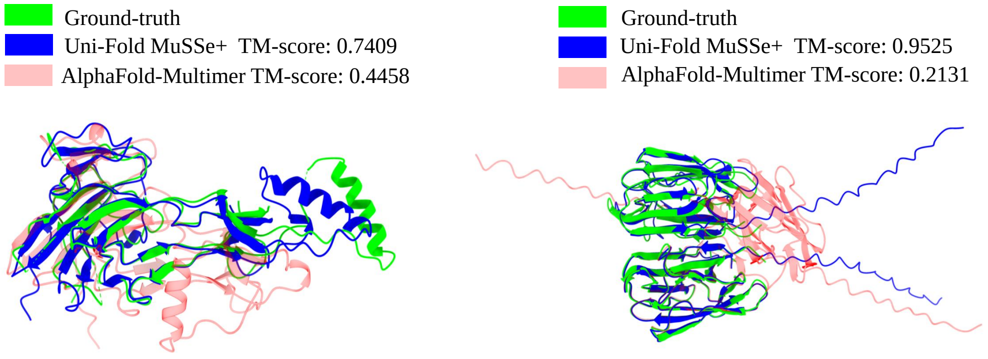


Figure 4: Scatter matrix of TM-score (bottom left, with red frames) and RMSD (top right, with blue frames) among our methods and baselines. Dots in different colors highlight that the corresponding method is better. The diagonal plots are histograms of TM-scores for each method.


Ground-truth
Uni-Fold MuSSe+ TM-score: 0.7409
AlphaFold-Multimer TM-score: 0.4458
Ground-truth
Uni-Fold MuSSe+ TM-score: 0.9525
AlphaFold-Multimer TM-score: 0.2131

(a) PDBid: 7U5O

(b) PDBid: 7YWG

Figure 5: Predicted structures of two cases. Experimentally solved structures are colored in green, AlphaFold-Multimer predictions in red, and Uni-Fold MuSSe+ predictions in blue.

conclusions, we also observed that Uni-Fold MuSSe+ produced a higher number of samples with TM scores close to 1.0 or 0.0, compared to Uni-Fold MuSSe without further pre-training. This observation offers valuable insights into how language models can be effectively utilized for protein structure prediction and serves as a basis for further improvement.

Our analysis also discovered some instances on which Uni-Fold MuSSe+ outperformed AlphaFold-Multimer, which relies on homology search and pairing. Two cases can be seen in the comparisons presented in Figure 5, where the predictions of Uni-Fold MuSSe+ were found to be better to those of AlphaFold-Multimer. The limited number of cross-chain multiple sequence alignments (MSA) pairings for these complexes may explain this outcome, as seen in the cases of 7U5O with 348 pairings. These results highlight the potential of language-model based complex predictors in scenarios where the number of cross-chain MSA pairings is limited.

5 Conclusions

In this work, we proposed Uni-Fold MuSSe+, a complex structure predictor with no need for homology search and pairing. The core idea of Uni-Fold MuSSe+ is to resort to pretrained protein language model representation for evolutionary patterns rather than from multiple sequence alignment. We verify the effectiveness of our method on protein complex prediction, and can improve the baseline methods significantly. For future works, first, we will dig deeper into why the average performance of further pretrained language model is similar to the one without further pretraining. Second, further improving protein language model based structure predictor to the performance of MSA based works is a valuable direction. Finally, how to pre-train a multimeric language model efficiently and effectively is also an interesting topic.

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References

Gregorio Alanis-Lobato, Miguel A Andrade-Navarro, and Martin H Schaefer. Hippie v2. 0: enhancing meaningfulness and reliability of protein–protein interaction networks. *Nucleic acids research*, pp. gkw985, 2016.

Iz Beltagy, Kyle Lo, and Arman Cohan. Scibert: A pretrained language model for scientific text. *arXiv preprint arXiv:1903.10676*, 2019.

Jishnu Das and Haiyuan Yu. Hint: High-quality protein interactomes and their applications in understanding human disease. *BMC systems biology*, 6(1):1–12, 2012.

Jacob Devlin, Ming-Wei Chang, Kenton Lee, and Kristina Toutanova. Bert: Pre-training of deep bidirectional transformers for language understanding. *arXiv preprint arXiv:1810.04805*, 2018.

Kevin Drew, Chanjae Lee, Ryan L Huizar, Fan Tu, Blake Borgeson, Claire D McWhite, Yun Ma, John B Wallingford, and Edward M Marcotte. Integration of over 9,000 mass spectrometry experiments builds a global map of human protein complexes. *Molecular systems biology*, 13(6): 932, 2017.

Ahmed Elnaggar, Michael Heinzinger, Christian Dallago, Ghalia Rihawi, Yu Wang, Llion Jones, Tom Gibbs, Tamas Feher, Christoph Angerer, Martin Steinegger, et al. Prottrans: towards cracking the language of life's code through self-supervised deep learning and high performance computing. *arXiv preprint arXiv:2007.06225*, 2020.

Richard Evans, Michael O'Neill, Alexander Pritzel, Natasha Antropova, Andrew Senior, Tim Green, Augustin Žídek, Russ Bates, Sam Blackwell, Jason Yim, et al. Protein complex prediction with alphafold-multimer. *BioRxiv*, pp. 2021–10, 2022.

Xiaomin Fang, Fan Wang, Lihang Liu, Jingzhou He, Dayong Lin, Yingfei Xiang, Xiaonan Zhang, Hua Wu, Hui Li, and Le Song. Helixfold-single: Msa-free protein structure prediction by using protein language model as an alternative. *arXiv preprint arXiv:2207.13921*, 2022.

John Jumper, Richard Evans, Alexander Pritzel, Tim Green, Michael Figurnov, Olaf Ronneberger, Kathryn Tunyasuvunakool, Russ Bates, Augustin Žídek, Anna Potapenko, et al. Highly accurate protein structure prediction with alphafold. *Nature*, 596(7873):583–589, 2021.

Diederik P Kingma and Jimmy Ba. Adam: A method for stochastic optimization. *arXiv preprint arXiv:1412.6980*, 2014.

Jinhyuk Lee, Wonjin Yoon, Sungdong Kim, Donghyeon Kim, Sunkyu Kim, Chan Ho So, and Jaewoo Kang. Biobert: a pre-trained biomedical language representation model for biomedical text mining. *Bioinformatics*, 36(4):1234–1240, 2020.

Ziyao Li, Xuyang Liu, Weijie Chen, Fan Shen, Hangrui Bi, Guolin Ke, and Linfeng Zhang. Unifold: An open-source platform for developing protein folding models beyond alphafold. *bioRxiv*, 2022.

Zeming Lin, Halil Akin, Roshan Rao, Brian Hie, Zhongkai Zhu, Wenting Lu, Nikita Smetanin, Allan dos Santos Costa, Maryam Fazel-Zarandi, Tom Sercu, Sal Candido, et al. Language models of protein sequences at the scale of evolution enable accurate structure prediction. *bioRxiv*, 2022.

Ilya Loshchilov and Frank Hutter. Decoupled weight decay regularization. *arXiv preprint arXiv:1711.05101*, 2017.

Milot Mirdita, Lars Von Den Driesch, Clovis Galiez, Maria J Martin, Johannes Söding, and Martin Steinegger. Uniclust databases of clustered and deeply annotated protein sequences and alignments. *Nucleic acids research*, 45(D1):D170–D176, 2017.

Milot Mirdita, Konstantin Schütze, Yoshitaka Moriwaki, Lim Heo, Sergey Ovchinnikov, and Martin Steinegger. Colabfold: making protein folding accessible to all. *Nature methods*, 19(6):679–682, 2022.

Sandra Orchard, Mais Ammari, Bruno Aranda, Lionel Breuza, Leonardo Briganti, Fiona Broackes-Carter, Nancy H Campbell, Gayatri Chavali, Carol Chen, Noemi Del-Toro, et al. The mintact project—intact as a common curation platform for 11 molecular interaction databases. *Nucleic acids research*, 42(D1):D358–D363, 2014.

Rose Oughtred, Chris Stark, Bobby-Joe Breitkreutz, Jennifer Rust, Lorrie Boucher, Christie Chang, Nadine Kolas, Lara O'Donnell, Genie Leung, Rochelle McAdam, et al. The biogrid interaction database: 2019 update. *Nucleic acids research*, 47(D1):D529–D541, 2019.

Alec Radford, Karthik Narasimhan, Tim Salimans, Ilya Sutskever, et al. Improving language understanding by generative pre-training. 2018.

Roshan Rao, Nicholas Bhattacharya, Neil Thomas, Yan Duan, Peter Chen, John Canny, Pieter Abbeel, and Yun Song. Evaluating protein transfer learning with tape. *Advances in neural information processing systems*, 32, 2019.

Alexander Rives, Joshua Meier, Tom Sercu, Siddharth Goyal, Zeming Lin, Jason Liu, Demi Guo, Myle Ott, C Lawrence Zitnick, Jerry Ma, et al. Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences. *Proceedings of the National Academy of Sciences*, 118(15):e2016239118, 2021.

Jianlin Su, Yu Lu, Shengfeng Pan, Ahmed Murtadha, Bo Wen, and Yunfeng Liu. Roformer: Enhanced transformer with rotary position embedding. *arXiv preprint arXiv:2104.09864*, 2021.

Yu Sun, Shuohuan Wang, Yukun Li, Shikun Feng, Hao Tian, Hua Wu, and Haifeng Wang. Ernie 2.0: A continual pre-training framework for language understanding. In *Proceedings of the AAAI conference on artificial intelligence*, volume 34, pp. 8968–8975, 2020.

Daniel V Veres, Dávid M Gyurkó, Benedek Thaler, Kristof Z Szalay, Dávid Fazekas, Tamás Korcsmáros, and Peter Csermely. Comppi: a cellular compartment-specific database for protein–protein interaction network analysis. *Nucleic acids research*, 43(D1):D485–D493, 2015.

Ruidong Wu, Fan Ding, Rui Wang, Rui Shen, Xiwen Zhang, Shitong Luo, Chenpeng Su, Zuofan Wu, Qi Xie, Bonnie Berger, et al. High-resolution de novo structure prediction from primary sequence. *BioRxiv*, 2022.

Qiangfeng Cliff Zhang, Donald Petrey, José Ignacio Garzón, Lei Deng, and Barry Honig. Preppi: a structure-informed database of protein–protein interactions. *Nucleic acids research*, 41(D1): D828–D833, 2012.