Prompt-Guided Injection of Conformation to Pre-trained Protein Model

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Abstract
Pre-trained protein models (PTPMs) represent a protein with one fixed embedding and thus are not capable for diverse tasks. For example, protein structures can shift, namely protein folding, between several conformations in various biological processes. To enable PTPMs to produce informative representations, we propose to learn interpretable, pluggable, and extensible protein prompts as a way of injecting task-related knowledge into PTPMs. In this regard, prior PTPM optimization with the masked language modeling task can be interpreted as learning a sequence prompt (Seq prompt) that enables PTPMs to capture the sequential dependency between amino acids. To incorporate conformational knowledge to PTPMs, we propose an interaction-conformation prompt (IC prompt) that is learned through back-propagation with the protein-protein interaction task. As an instantiation, we present a conformation-aware pre-trained protein model that learns both the sequence and interaction-conformation prompts in a multi-task setting. We conduct comprehensive experiments on nine protein datasets. Results show that using the Seq prompt does not hurt PTPMs’ performance on sequence-related tasks while incorporating the IC prompt significantly improves PTPMs’ performance on tasks where interaction conformational knowledge counts. Furthermore, the learned prompts can be combined and extended to deal with new protein tasks.

1. Introduction
Proteins play an essential role in biological activities. As proteins are composed of sequences of amino acids, the chemical properties of amino acids cause complex dynamic 3D structures and determine the protein functions as a whole (Epstein et al., 1963). One popular approach to deal with sequence data is pre-trained language models (PTLMs), which have achieved excellent performance in language understanding (Devlin et al., 2019) and translation (Raffel et al., 2020a) and dialogue systems (Zhang et al., 2019). Inspired by that, researchers have developed pre-trained protein models (PTPMs), such as TAPE Transformer (Rao et al., 2019), ProtBERT (Elaggar et al., 2021), and ESM-1b (Rao et al., 2021a), to predict protein structures and functions. PTPMs have achieved promising performance on various downstream tasks, such as secondary structure prediction (Berman et al., 2000), affinity prediction (Dunbar et al., 2013), and contact prediction (J et al., 2018).

However, proteins are complex biological structures and have unique characteristics. One important difference between sentences and amino acid sequences is that sentences have static structures and semantics while proteins composed of amino acids are dynamic and can be observed with various 3D structures, which are called conformations (Bu & Callaway, 2011). Figure 1 shows an example of different conformations and contact maps of the same protein. It has been reported that protein conformations are very sensitive and dynamic, significantly influenced by external factors and their specific function (RF et al., 2006). Therefore, it is inappropriate for existing PTPMs to use a single fixed embedding to represent a protein.

This paper sets out to inject task-related knowledge, e.g., conformational information, into PTPMs to produce more informative protein representations. Recently, prompts have been proposed to avoid fine-tuning PTLMs, which leads to improved performance. They are a sequence of discrete words designed by humans or continuous vectors learned through back-propagation. Prompt learning aims to close the gap between pre-training and downstream tasks by converting the latter into the former. In this regard, prompts are supposed to contain task-related knowledge so as to induce PTLMs to make correct predictions (Le Scao & Rush, 2021). Naturally, we are curious if we can leverage prompts to inject task-related knowledge into PTPMs. However, humans still cannot completely understand the life language, i.e., the amino acid sequence. It is thus infeasible to design prompts based on the amino acid vocabulary.
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Figure 1. The structure and contact map of protein CDK1 (pdbid: 4yc6). CDK1 is the only essential cell cycle CDK in human cells and is required for successful completion of M-phase. Here, we compare the native conformation and the interaction conformation with CSK1 protein (pdbid:2RSY). From the contact map, we can observe that there is a great difference between the two different conformations.

To solve this issue, we attempt to learn new prompts, which are out of the amino acid vocabulary, from the task of interest. The prompts can be plugged into PTPMs and optimized through back-propagation. During the optimization process, PTPMs can acquire task-related knowledge and produce enhanced protein representations. Taking conformational knowledge injection as an illustrative example, we develop a conformation-aware pre-trained protein model (ConfProtein). Specifically, ConfProtein has two learnable prompts for the properties of the protein itself and the interaction conformation in protein pairs respectively. As for the properties of the protein itself can be mined by the sequence of amino acids, we leverage the masked language modeling (MLM) task (Devlin et al., 2019) to learn this prompt, which is called the sequence prompt (Seq prompt). For conformations that exist in interaction pairs, an interaction conformation prompt (IC prompt) is learned with protein-protein interaction prediction (PPI) tasks. Two prompts can be learned in a multitask setting.

We train the ConfProtein on the physical-only protein interaction network that contains 12,106 species. The experimental results show that PTPMs with the Seq prompt can only acquire knowledge about amino acid sequences and relevant secondary structures, while those with the IC prompt can effectively acquire 3D structural knowledge. Notably, resulting PTPMs with appropriate learned prompts outperform state-of-the-art (SOTA) models while inappropriate prompts will degrade their performance. The main contributions of this paper are summarized as follows:

- We propose to learn pluggable, interpretable and extensible prompts to inject task-related knowledge into pre-trained protein models.
- As an instantiation, we design the ConfProtein model that injects sequential and conformational knowledge into pre-trained protein models in a multitask setting.
- We created a new dataset that contains interaction conformational information for contact prediction.
- A comprehensive evaluation on protein function and structure prediction tasks shows proper prompts significantly improve pre-trained models’ performance.

2. Related Works

Pre-trained Protein Models As PTLMs have been proved effective in natural language processing (NLP) (Devlin et al., 2019; Brown et al., 2020; Raffel et al., 2020b), some works try to extend such models to images (Dosovitskiy et al., 2021) and proteins. Rives et al. (2021) firstly explore whether the Transformer architecture can be used to deal with proteins and find that the features learned by PTPMs contribute to the structure prediction performance. Elnaggar et al. (2021) conduct comprehensive experiments to study the limits of up-scaling PTPMs and show that PTPMs with a single protein input can obtain comparable performance to the top prediction methods in computational biology based on multiple sequence alignment (MSA). To figure out why PTPMs work, Vig et al. (2021) focus on reconciling attention with known protein properties and identify that different layers can capture different structural information.

A growing body of works points out that general protein representations cannot meet the needs of describing specific properties in various biological processes. To incorporate co-evolutionary signals from MSAs, Rao et al. (2021b) develop the MSA Transformer and prove that homologous protein sequences can provide native conformational information and promote contact prediction performance. Moreover, MSAs inevitably contain non-homologous residues and gaps. Zhang et al. (2021a) introduce Co-evolution Transformer which considers the relationship between MSAs and the target protein and mitigates the influence of non-homologous information. Both models mine co-evolutionary information from homologous protein sequences which have similar amino acid sequences and achieve auspicious performance. However, using heterogeneous models to capture homologous protein patterns will greatly limit the application scenarios and it is hard to extend the models with other task-related knowledge.
The alternative structures of the same protein are referred to as different conformations, and transitions between them are called conformational changes. Since macromolecules are not rigid, protein structures can undergo reversible changes in response to various biological processes. The native conformation (NC) refers to the 3D structure into which a protein naturally folds, and the interaction conformation (IC) refers to the counterpart that a protein folds to interact with others when achieving its biological functions. Although great breakthroughs have been made in the study of protein native conformation (Jumper et al., 2021), other conformations of proteins remain to be explored. In this paper, we mainly focus on interaction conformation from which we can have a deeper understanding of PPI.

3.2. Prompt Learning

Given an input sequence \( S_{in} = \{s_{1}^{in}, s_{2}^{in}, \ldots, s_{n}^{in}\} \) where \( s_{i}^{in} \in \mathcal{V} \) is the \( i \)-th token in the sequence, \( n \) is the sequence length and \( \mathcal{V} \) is a vocabulary. With typical pre-trained models, an embedding operator is defined as

\[
E(\cdot) = E_{tok}(\cdot) + E_{seg}(\cdot) + E_{pos}(\cdot),
\]

which is the sum of the corresponding token, segment, and position embeddings. Thus we can have \( E(s_{i}^{in}) = x_{i}^{in} \) and \( E(S_{in}) = (x_{1}^{in}, x_{2}^{in}, \ldots, x_{n}^{in}) = X_{in} \). A pre-trained model \( M \) conducts a mapping \( f : \mathcal{X} \rightarrow \mathcal{H} \), where \( \mathcal{X} \) is the space of the input sequence embeddings and \( \mathcal{H} \) is the space of the returned representations \( h = f(X_{in}) \). It is \( h \) that represents the input sequence as a dense vector.

Prompt learning refers to those methods that utilize prompts to improve pre-trained models. Originating from the NLP area, prompts are designed to contain task-related information, and plugging prompts to pre-trained models can make them aware of the task of interest. Conventionally, a prompt is a sequence of tokens in a vocabulary \( \mathcal{V} \). Figure 2 shows an example of NLP prompts. The given task is to classify emotions of the input sequence This movie is so great! With the prompt (It is [MASK]), emotion classification is converted to the prediction of the masked word, i.e., good for the positive emotion class and bad for the negative emotion class. This is in line with the pre-training MLM objective. Thus the gap between the pre-training and the downstream classification task is closed and the pre-trained model is able to achieve better performance. The above example implements prompts as a task-oriented sequence with each discrete token from the vocabulary \( \mathcal{V} \). In contrast, the continuous prompt approach searches in a continuous embedding space \( \mathcal{X} \). Note that each token is not limited to vectors converted from tokens in the vocabulary \( \mathcal{V} \). As humans cannot completely understand amino acid sequences, it is infeasible to design discrete prompts based on the amino acid vocabulary while existing continuous prompts are task-oriented and suffer from low generalization.

Figure 2. The relationship between NLP Prompts and Protein Prompts. **Top** (NLP Prompts): Prompt engineering aims to search a task-oriented pattern string (a template which contains [MASK]) and a set of candidates in the embedding space. Given an input sentence, since [MASK] is a part of the pre-training MLM objective, its representation can be determined by the input and the template. **Bottom** (Protein Prompt): we aim to train a semantic token (such as [IC] which contains interaction conformational information). Given an amino acid sequence, the semantic token can be trained to provide protein representations with task-related information.

Prompts for Pre-trained Models Prompts are introduced in GPT-3 (Brown et al., 2020) and researchers have shown that prompts can be designed or learned to capture the task-related information (Liu et al., 2021a). Schick & Schütze (2021) introduce pattern-exploiting training (PET) and demonstrate that providing task descriptions to PTLMs can be comparable with standard supervised fine-tuning. To avoid the disturbance of human bias, Gao et al. (2021) propose LM-BFF which utilizes generative models to obtain prompt templates and label tokens. However, the above discrete prompt setting inherently requires the tokens in the vocabulary, which may limit the capability of prompt-based models. One solution is to find optimal prompt vectors in continuous spaces (Liu et al., 2021b; Li & Liang, 2021; Zhang et al., 2021b). Despite of promising performance (Li & Liang, 2021; Lester et al., 2021), these prompts are task-oriented, and thus suffers from low generality. Also, the learned continuous prompts are of low interpretability (Hambardzumyan et al., 2021).
4. Method

We propose to learn pluggable, interpretable, and extensible protein prompts that enable PTPMs to produce more informative representations. We will first introduce how to learn such prompts in Section 4.1, then instantiate a conformation-aware pre-trained protein model in Section 4.2. Figure 3 shows the overview of ConfProtein.

4.1. Protein Prompt Learning

We start this section by re-interpret the concept of prompts: A prompt is a symbolized pattern string that can be manually designed or automatically learned to inject task-related knowledge to pre-trained models so as to produce informative representations. With prompt learning, the model input consists of two parts – the original input sequence $S^\text{in}$ and the prompt $S^\text{pt}$. For the original input $S^\text{in}$, we use the embedding operator defined in Equation 1 to produce its embedding, i.e., $X^\text{in} = E(S^\text{in})$. As for $S^\text{pt}$, we assume the effects exerted by prompts on the input sequence $S^\text{in}$ is not disturbed by the positions of prompts, hence we do not add position and segment embeddings to prompt embeddings. That is, $X^\text{pt} = E_{\text{tok}}(S^\text{pt}) = \{E_{\text{tok}}(s^\text{pt}_1), \ldots, E_{\text{tok}}(s^\text{pt}_m)\}$. The whole model input can be denoted as:

$$X^\text{prompt} = X^\text{in} || X^\text{pt}, \quad (2)$$

where $||$ denotes the concatenation operation between two vectors. The length of the whole sequence thus is $n + m$.

With the self-attention mechanism in the Transformer architecture, each token in the whole sequence can attend to others at any position. However, prompts are supposed to provide task-related information to the representation of the original input sequence, so we only allow the one-way information flow from prompts to the original input, as illustrated in Figure 4. The information flow from the original token to the prompt tokens is thus forbidden. Also, to promote orthogonality and generalization, information flows between prompt tokens are forbidden. We design an attention mask matrix $M$ to fulfill this need. Let $M_{ij}$ denote the $(i,j)$-element of the mask matrix, and we define:

$$M_{ij} = \begin{cases} 0, & (1 \leq i \leq m \text{ and } m < j \leq m + n) \text{ or } (1 \leq i, j \leq m \text{ and } i \neq j) \\ 1, & \text{others} \end{cases} \quad (3)$$

then the output calculation is modified as:

$$h = g(\text{softmax}(\frac{QK^T}{\sqrt{d}}) \cdot M \cdot V), \quad (4)$$

where $Q$, $K$, and $V$ are the linear projection of the token embedding $x^\text{in}$ and $x^\text{pt}$, $d$ is the hidden dimension, and $g(\cdot)$ denotes the other operations on top of self-attention in the Transformer architecture, such as skip connections and feed-forward networks. After stacking multiple self-attention and other operations, the final representation, still can be denoted as $h$, can contain the information from both the original sequence and the prompts.

The loss function of protein prompt learning has two-folds: the knowledge conservation objective $L^\text{C}$ and knowledge injection objective $L^\text{P}$. The former tries to make pre-trained models preserve what has been learned from pre-training tasks while the latter aims to guide pre-trained models to acquire new knowledge.
Knowledge Conservation Objective In order to preserve the knowledge in the previously trained model, we calculate the previous task loss based on the returned representation:

$$\mathcal{L}_C = \mathcal{L}_{pr}(h),$$  \hspace{1cm} (5)

where $\mathcal{L}_{pr}$ is the loss function of the previous task, e.g., the MLM loss function during pre-training.

Knowledge Injection Objective As we expect the pre-trained model to grasp new knowledge by learning prompts, we calculate the loss on tasks where the knowledge of interest exists. We assume a specific type of knowledge, such as protein conformations, can be learned from multiple relevant tasks, such as protein-protein interaction and binding affinity prediction. Let $\mathcal{L}_r$ be the loss of the task $\tau$ from the relevant task collection $\mathcal{T}$, such as the PPI prediction loss. We denote this loss function as following:

$$\mathcal{L}_I = \sum_{\tau \in \mathcal{T}} \alpha_{\tau} \mathcal{L}_r(h)$$  \hspace{1cm} (6)

By optimizing $\mathcal{L}_I$, the pre-trained model can produce an informative representation based on the knowledge associated with the tasks in $\mathcal{T}$. Generally, we hope the pre-trained model not only preserves already learned knowledge but also grasps new skills, hence we have the following training object in a multitask setting:

$$\mathcal{L} = \mathcal{L}_C + \lambda \mathcal{L}_I$$  \hspace{1cm} (7)

where $\lambda$ is the hyper-parameter balancing the previous and new losses.

4.2. ConfProtein

We now instantiate the proposed prompt learning method by ConfProtein. We use the previous pre-training MLM task, which is to recover the replaced amino acids given the context, to optimize the PTPM and the Seq prompt $x_{Seq}$. Let $Y$ be the set of masked out tokens, the MLM loss can be formulated:

$$q(y|h) = \frac{\exp(p(y|h))}{\sum_{v \in Y} \exp(p(v|h))},$$  \hspace{1cm} (8)

$$\mathcal{L}_C = \sum_{y \in Y} - \log q(y|h).$$  \hspace{1cm} (9)

The resulting representation should capture the chemical properties between amino acids and contributes to the prediction of protein secondary structures. Further, we aim to inject protein conformational knowledge into the PTPM by learning the interaction-conformation prompt $x_{IC}$. Towards this end, we conduct the new task – predict whether the $p$-th and $q$-th proteins can interact with each other. The loss of the PPI task is as follows:

$$\mathcal{L}_I(h_p, h_q) = \text{BCE}(p(y_{p,q}|h_p, h_q))$$  \hspace{1cm} (10)

where BCE is the binary cross-entropy loss function.

5. Experiments

Pre-training Dataset We use the STRING dataset (Szklarczyk et al., 2019) that contains protein-protein interaction pairs for model pre-training. Some interactions in the STRING dataset do not form stable conformations. To remove unstable conformations, we choose the physical-only interaction subset from STRING. The subset contains 65 million protein sequences from 14,094 species and 2.7 billion protein-protein interaction pairs. A PPI network can be defined, in which a node represents a protein and an edge represents the two interacting proteins. The edge between protein pairs indicates that there is evidence of their binding or forming a physical complex. Similar to previous works, we reserve the Homo sapiens (a species contained in STRING) PPI pairs for downstream evaluation.

Downstream Datasets Researchers use the PPI data of the Homo sapiens to create downstream datasets. Chen et al.(2019) created the SHS27k and SHS148k datasets based on a random selection of the Homo sapiens PPI data, and Lv et al.(2021) uses them all, which we denote as STRING-HomoSapiens. We leverage the PPI prediction task to evaluate whether the IC prompt can inject conformational knowledge into PTPMs. Following Lv et al.(2021), we regard PPI prediction as a link prediction task in the protein network. Two methods, i.e., Breath-First Search (BFS) and Depth-First Search (DFS), are used to split training and evaluation datasets for SHS27k, SHS148k, and STRING-HomoSapiens, respectively. Note that during pre-training, models are optimized to predict whether two proteins can interact with each other. While for downstream tasks, besides interaction prediction, models are required to predict interaction types. We use the above three datasets for comparison with SOTA models in Section 6.1, the SAbDab (Dunbar et al., 2013) dataset for the ablation study in Section 6.2, and the TAPE (Rao et al., 2019) dataset to analyze our model in Section 6.3. The SAbDab (Dunbar et al., 2013) dataset is used for the prediction task of antibody-antigen binding affinity, which also requires protein conformational knowledge. TAPE is a benchmark designed to evaluate the generalization of protein models. There are three major aspects that the benchmark involves: structure prediction, detection of remote homologs, and protein engineering. With TAPE, we can analyze and discuss the learned protein prompts. Please see Appendix for the details of dataset statistics.

Pre-training We implement the proposed ConfProtein using Pytorch (Paszke et al., 2019) and Fairseq (Ott et al., 2019). ConfProtein has 650M parameters with 33 layers and 20 attention heads. The embedding size is 1280. The batch size is set to be 20 and the learning rate is $1 \times 10^{-5}$ without weight decay. We use a fixed learning rate schedule. Limited by memory, at each step we randomly sample a small set of proteins from one species and the maximum
Table 1. Results on Protein-Protein Interaction Prediction Tasks. There are two types of models that we compare with. The first four baselines are non pre-trained models including CNN, RCNN, LSTM, and GNN. The other baselines are pre-trained ones. For fair comparison, we only use pre-trained models to generate amino acid embeddings and feed these embeddings into GNN-PPI. Note that we do not modify the hyperparameters of GNN-PPI. The reported results are mean(std) micro-averaged F1 score.

| METHOD               | SHS27k BFS | SHS27k DFS | SHS148k BFS | SHS148k DFS | STRING-HomoSapiens BFS | STRING-HomoSapiens DFS |
|----------------------|------------|------------|-------------|-------------|-------------------------|------------------------|
| DPPI                 | 41.43(0.6) | 46.12(3.0) | 52.12(8.7)  | 52.03(1.2)  | 56.68(1.0)              | 66.82(0.3)             |
| DNN-PPI              | 48.09(7.2) | 54.34(1.3) | 57.40(9.1)  | 58.42(2.1)  | 53.05(0.8)              | 64.94(0.9)             |
| PIPR                 | 44.48(4.4) | 57.80(3.2) | 61.83(10.2) | 63.98(0.8)  | 55.65(1.6)              | 67.45(0.3)             |
| GNN-PPI              | 63.81(1.8) | 74.72(5.3) | 71.37(5.3)  | 82.67(0.9)  | 78.37(5.4)              | 91.07(0.6)             |
| ProtBERT             | 70.94      | 73.36      | 70.32       | 78.86       | 67.61                   | 87.44                  |
| OntoProtein          | 70.16      | 76.35      | 67.66       | 77.56       | 70.59                   | 81.94                  |
| ESM-1b               | 68.12(1.9) | 75.80(2.4) | 68.74(1.4)  | 75.16(2.8)  | 76.85(0.7)              | 86.66(0.1)             |
| ConfProtein-w/o-IC   | 68.49(4.1) | 75.64(3.7) | 68.90(2.7)  | 74.29(2.8)  | 77.17(0.9)              | 86.67(0.3)             |
| ConfProtein          | 71.24(3.5) | 77.62(2.6) | 72.23(3.4)  | 79.55(1.7)  | 78.26(0.2)              | 87.82(0.4)             |

6. Results and Discussion

6.1. Main Results

We present the evaluation results of the proposed ConfProtein and state-of-the-art baselines in Table 1. By comparing with non-pre-trained baselines, we find that our proposed ConfProtein is better than DPPI, DNN-PPI, and PIPR on all datasets, and outperforms GNN-PPI on the small SHS27k dataset, which indicates the learned IC prompt improves PTPMs for PPI prediction. On the largest STRING-HomoSapiens dataset, the performance of GNN-PPI surpasses all the PTPMs. This is that, due to memory limitation, we calculate the mean of amino acid embeddings in a sequence as the protein representation. It is not as capable as the convolutional network in GNN-PPI. For small datasets including SHS27k and SHS148k, we do not have the memory issue, hence we employ the same convolutional network in PTPMs and the performance is better than GNN-PPI.

OntoProtein tries to make use of all the information in a knowledge graph. Our model is better than OntoProtein on all datasets, indicating that not all information in knowledge graphs has a contributing effect on PPI tasks and sometimes incorporating inappropriate knowledge can be harmful. By comparing ESM-1b and ConfProtein-w/o-IC, we find that with the knowledge conservation objective, our model is still able to capture amino acid sequences information. Finally, the performance gap between the ConfProtein-w/o-IC and ConfProtein demonstrates that the IC prompt can indeed enhance the protein representations with interaction conformation knowledge.
Figure 6. Visualization of interaction conformational information. The two proteins are Transcription initiation factor TFIID subunit 4 (TAF4) and Transcription initiation factor TFIID subunit 5 (TAF5). (Humphreys et al., 2021). Left: Visualize the embedding of amino acids (TAF4) with and without conformational information by MDS. Middle: Visualize distances of corresponding amino acids with and without conformational information. Right: Visualize amino acids with distances greater than 100 (red).

6.2. Ablation Study

We conduct an ablation study on the SHS27k and SAbDab datasets to analyze the influence of the Seq and IC prompts. From Figure 5, we observe that the IC prompt can improve our model’s performance on the tasks of both PPI prediction and antibody-antigen binding affinity prediction, proving that prompts with explicit semantics can generalize to relevant tasks. We also notice that the performance of ConfProtein degrades when the Seq or IC prompt is absent, demonstrating that these two prompts can conjunctionally inject task-related knowledge to pre-trained protein models. Furthermore, we notice that the Seq prompt has more influence in the SAbDab dataset, while in the STRING-HomoSapiens dataset, the IC prompt is more influential. This is most likely because PPI is determined by protein conformations and ConfProtein can acquire conformational knowledge via the IC prompt. For the prediction of antibody-antigen binding affinity, the properties of amino acids play a key factor, which can be obtained by the Seq prompt. It also shows the learned prompts are extensible from PPI prediction to antibody-antigen binding affinity prediction.

6.3. Analysis of the Learned Prompts

How can we interpret the IC prompt? Since the IC prompt is trained to provide PTPMs with conformational knowledge, we analyze what exactly the amino acid representations have changed. As shown in Figure 6(a), we firstly visualize the embeddings of amino acids of the TAF4 protein with and without the IC prompt based on multi-dimensional scaling (MDS) (Kruskal, 1964). Then we calculate the distances between two embeddings of one amino acid and plot them in Figure 6(b). We mark the embedding pairs with distances larger than 100 in red in Figure 6(c). We observe that the marked embeddings are all amino acids on the protein surface, which is consistent with the fact that the amino acids related to PPI are almost located on the surface of the protein, not the core (Yan et al., 2008).

Table 2. Result on Contact Prediction Task

| METHOD                          | CASP12 (P@L/2) |
|---------------------------------|----------------|
| ProtBert                        | 0.35           |
| MSA TRANSFORMER                 | **0.49**       |
| ESM-1b                          | 0.42           |
| ConfProtein (w/o IC)            | 0.43           |
| ConfProtein                     | 0.41           |

Prompts can be negative to downstream tasks. The protein contact map represents the distance between all possible amino acid residue pairs. The task of contact prediction is to classify whether a pair of amino acids contact, and can be used to evaluate the ability of PTPMs to capture conformational information. In TAPE, the CASP12 (J et al., 2018) dataset is used to evaluate a model’s performance on contact prediction. The 3D coordinates of atoms in CASP12 are experimentally measured when the protein naturally folds, hence the contact map corresponds to the native conformation. To obtain the contact map corresponding to the interaction conformation, we build a protein structure dataset from Humphreys et al.(2021) that obtain through experiments the three-dimensional structures of proteins when they are interacting with others. The dataset, called ICProtein ², contains 1,106 protein complexes, thus there are 2,212 contact maps. Details are in Appendix.

We compare our model to two PTPMs (ProtBert and ESM-1b) which only leverage sequence information and the main differences between the two models are the number of parameters and their pre-training datasets. We also compare to the MSA Transformer which interleaves row and column attention across the input aligned sequences. We fit a linear classifier to predict whether two residues contact. We report the precision for the top L/2 contacts for medium- and long-range contacts, where L is the length of the protein.

In Table 2, there is a large gap between the MSA Trans-

²ICProtein is available at shorturl.at/sA345
Prompts can be knowledge probe for unknown downstream tasks. Since each prompt can be assigned specific semantics after learning, we utilize prompts as a knowledge probe to determine the information needed for each task. In this part, we will focus on two protein engineering tasks: fluorescence landscape prediction and stability landscape prediction. The green fluorescent protein exhibits bright green fluorescence when exposed to light (Prendergast FG, 1978). The fluorescence landscape prediction task aims to map proteins to a log-fluorescence intensity. The protein stability is measured by the free energy difference between the folded and unfolded protein states. The stability landscape prediction task aims to map a protein to the label indicating the most extreme circumstances in which the protein can maintain its fold. Performance on these two tasks is measured by spearman’s ρ on the test set.

From the result in Table 4, we can find that the performance of ConfProtein-w/o-IC is better than the performance of ConfProtein in the fluorescence task. From the analysis of the model on the CASP12 dataset in TAPE, we conclude that the information required for the log-fluorescence of proteins is incompatible with the IC prompt. This conclusion is consistent with the fluorescence mechanism that the process involves base-mediated cyclization followed by dehydration and oxidation (M et al., 1996). For the stability task, since the performance of ConfProtein-w/o-IC and ConfProtein is comparable, similar to the CB513 results, we believe that conformational knowledge has no effect on protein stability.

7. Conclusion
In this paper, we transfer the concept of prompts from NLP to protein representations. We present the conformation-aware pre-trained protein model with the sequence and interaction conformation prompts in a multi-task setting. People can leverage these prompts to achieve diverse protein representation. Experimental results on widespread protein tasks demonstrate that an appropriate prompt can provide task-related knowledge for protein representations.
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References

A. G. and J. S. Flexible algorithm for direct multiple alignment of protein structures and sequences. Computer applications in the biosciences: CABIOS, 10(6):587–596, 1994. URL https://doi.org/10.1093/bioinformatics/10.6.58.

Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weisssig, H., Shindyalov, I. N., and Bourne, P. E. The protein data bank. Nucleic acids research, 28(1): 235–242, 2000.

Brown, T., Mann, B., Ryder, N., Subbiah, M., Kaplan, J. D., et al. Language models are few-shot learners. In Larochelle, H., Ranzato, M., Hadsell, R., Balcan, M. F., and Lin, H. (eds.), Advances in Neural Information Processing Systems, volume 33, pp. 1877–1901. Curran Associates, Inc., 2020. URL https://proceedings.neurips.cc/paper/2020/file/1457c0d6bfc4967418bfb8ac142f64a-Paper.pdf.

Bu, Z. and Callaway, D. J. Proteins move! protein dynamics and long-range allosteric signaling in cell signaling. In Donev, R. (ed.), Protein Structure and Diseases, volume 83 of Advances in Protein Chemistry and Structural Biology, pp. 163–221. Academic Press, 2011. doi: https://doi.org/10.1016/B978-0-12-381262-9.00005-7.

Chen, M., Ju, C. J. T., Zhou, G., Chen, X., Zhang, T., Chang, K.-W., Zaniolo, C., and Wang, W. Multifaceted protein–protein interaction prediction based on Siamese residual RCNN. Bioinformatics, 35(14):i305–i314, 07 2019. ISSN 1367-4803. doi: 10.1093/bioinformatics/btz328.

Devlin, J., Chang, M.-W., Lee, K., and Toutanova, K. BERT: Pre-training of deep bidirectional transformers for language understanding. In Proceedings of the 2019 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies, Volume 1 (Long and Short Papers), pp. 4171–4186, Minneapolis, Minnesota, June 2019. Association for Computational Linguistics. doi: 10.18653/v1/N19-1423.

Dosovitskiy, A., Beyer, L., Kolesnikov, A., Weissenborn, D., Zhai, X., Unterthiner, T., Dehghani, M., Minderer, M., Heigold, G., Gelly, S., Uszkoreit, J., and Houlsby, N. An image is worth 16x16 words: Transformers for image recognition at scale. In International Conference on Learning Representations, 2021.

Dunbar, J., Krawczyk, K., Leem, J., Baker, T., Fuchs, A., Georges, G., Shi, J., and Deane, C. M. SAbDab: the structural antibody database. Nucleic Acids Research, 42 (D1):D1140–D1146, 11 2013. ISSN 0305-1048. doi: 10.1093/nar/gkt1043.

Elnaggar, A., Heinzinger, M., Dallago, C., Rihawi, G., Wang, Y., et al. Prottrans: Towards cracking the language of lifes code through self-supervised deep learning and high performance computing. IEEE Transactions on Pattern Analysis and Machine Intelligence, 2021. doi: 10.1109/TPAMI.2021.3095381.

Epstein, C. J., Goldberger, R. F., and Anfinsen, C. B. The genetic control of tertiary protein structure: Studies with model systems. Cold Spring Harbor Symposia on Quantitative Biology, 28:439–449, 1963.

Gao, T., Fisch, A., and Chen, D. Making pre-trained language models better few-shot learners. In Association for Computational Linguistics (ACL), 2021.

Hambardzumyan, K., Khachatrian, H., and May, J. WARP: Word-level Adversarial ReProgramming. In Proceedings of the 59th Annual Meeting of the Association for Computational Linguistics and the 11th International Joint Conference on Natural Language Processing (Volume 1: Long Papers), pp. 4921–4933, Online, August 2021. Association for Computational Linguistics. doi: 10.18653/v1/2021.acl-long.381.

Hashemifar, S., Neyshabur, B., Khan, A. A., and Xu, J. Predicting protein–protein interactions through sequence-based deep learning. Bioinformatics, 34(17):i802–i810, 09 2018. ISSN 1367-4803. doi: 10.1093/bioinformatics/bty573.

Humphreys, I. R., Pei, J., Baek, M., Krishnakumar, A., Anishechenko, I., Ovchinnikov, S., Zhang, J., Ness, T. J., Banjade, S., Bagde, S. R., et al. Computed structures of core eukaryotic protein complexes. Science, 374(6573): eabm4805, 2021.

Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasunuvakool, K., Bates, R., Židek, A., Potapenko, A., et al. Highly accurate protein structure prediction with alphafold. Nature, 596(7873):583–589, 2021. doi: 10.1038/s41586-021-03819-2. URL https://doi.org/10.1038/s41586-021-03819-2.
Prompt-Guided Injection of Conformation to Pre-trained Protein Model

Kruskal, J. Multidimensional scaling by optimizing goodness of fit to a nonmetric hypothesis. *Psychometrika*, 29(1):1–27, 1964. doi: 10.1007/BF02289565. URL https://doi.org/10.1007/BF02289565.

Le Scao, T. and Rush, A. How many data points is a prompt worth? In *Proceedings of the 2021 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies*, pp. 2627–2636, Online, June 2021. Association for Computational Linguistics. doi: 10.18653/v1/2021.naacl-main.208.

Lester, B., Al-Rfou, R., and Constant, N. The power of scale for parameter-efficient prompt tuning. In *Proceedings of the 2021 Conference on Empirical Methods in Natural Language Processing*, pp. 3045–3059, Online and Punta Cana, Dominican Republic, November 2021. Association for Computational Linguistics. doi: 10.18653/v1/2021.emnlp-main.243.

Li, X. L. and Liang, P. Prefix-tuning: Optimizing continuous prompts for generation. *CoRR*, abs/2101.00190, 2021. URL https://arxiv.org/abs/2101.00190.

Liu, P., Yuan, W., Fu, J., Jiang, Z., Hayashi, H., and Neubig, G. Pre-train, prompt, and predict: A systematic survey of prompting methods in natural language processing. *CoRR*, abs/2107.13586, 2021a.

Liu, X., Zheng, Y., Du, Z., Ding, M., Qian, Y., Yang, Z., and Tang, J. GPT understands, too. *CoRR*, abs/2103.10385, 2021b. URL https://arxiv.org/abs/2103.10385.

Lv, G., Hu, Z., Bi, Y., and Zhang, S. Learning unknown from correlations: Graph neural network for inter-novel-protein interaction prediction. In Zhong, Z.-H. (ed.), *Proceedings of the Thirtieth International Joint Conference on Artificial Intelligence, IJCAI-21*, pp. 3677–3683. International Joint Conferences on Artificial Intelligence Organization, 8 2021. doi: 10.24963/ijcai.2021/506. Main Track.

M., O., AB, C., K., K., LA, G., RY, T., and SJ, R. Crystal structure of the aquorea victoria green fluorescent protein. *Science*, 273(5280):1392–1395, 1996.

O’Boyle, N. M., Banck, M., James, C. A., Morley, C., Vandermeersch, T., and Hutchison, G. R. Open babel: An open chemical toolbox. *Journal of Cheminformatics*, 3(1):33, 2011. doi: 10.1186/1758-2946-3-33. URL https://doi.org/10.1186/1758-2946-3-33.

Ott, M., Edunov, S., Baevski, A., Fan, A., Gross, S., Ng, N., Grangier, D., and Auli, M. fairseq: A fast, extensible toolkit for sequence modeling. In *Proceedings of NAACL-HLT 2019: Demonstrations*, 2019.

Paszke, A., Gross, S., Massa, F., Lerer, A., Bradbury, J., et al. *PyTorch: An Imperative Style, High-Performance Deep Learning Library*. Curran Associates Inc., Red Hook, NY, USA, 2019.

Prendergast FG, M. K. Chemical and physical properties of aequorin and the green fluorescent protein isolated from aequorea forskålea. *Biochemistry*, 17:3448–3453, 1978.

Raffel, C., Shazeer, N., Roberts, A., Lee, K., Narang, S., Matena, M., Zhou, Y., Li, W., and Liu, P. J. Exploring the limits of transfer learning with a unified text-to-text transformer. *Journal of Machine Learning Research*, 21(140):1–67, 2020a. URL http://jmlr.org/papers/v21/20-074.html.

Raffel, C., Shazeer, N., Roberts, A., Lee, K., Narang, S., Matena, M., Zhou, Y., Li, W., and Liu, P. J. Exploring the limits of transfer learning with a unified text-to-text transformer. *Journal of Machine Learning Research*, 21:140:1–140:67, 2020b.

Rao, R., Bhattacharya, N., Thomas, N., Duan, Y., Chen, X., Canny, J., Abbeel, P., and Song, Y. S. Evaluating protein transfer learning with tape. In *Advances in Neural Information Processing Systems*, 2019.

Rao, R., Meier, J., Sercu, T., Ovchinnikov, S., and Rives, A. Transformer protein language models are unsupervised structure learners. 2021a.

Rao, R. M., Liu, J., Verkuil, R., Meier, J., Canny, J., Abbeel, P., Sercu, T., and Rives, A. Msa transformer. In Meila, M. and Zhang, T. (eds.), *Proceedings of the 38th International Conference on Machine Learning*, volume 139 of *Proceedings of Machine Learning Research*, pp. 8844–8856. PMLR, 18–24 Jul 2021b.

RF, M., HW, H., DK, G., PA, M., and VW, R. *Harper’s Illustrated Biochemistry*. 2006. ISBN 978-0-07-146197-9.

Rives, A., Meier, J., Sercu, T., Goyal, S., Lin, Z., Liu, J., Guo, D., Ott, M., Zitnick, C. L., Ma, J., and Fergus, R. Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences. *Proceedings of the National Academy of Sciences*, 118(15), 2021. ISSN 0027-8424. doi: 10.1073/pnas.2016239118.

Schick, T. and Schütze, H. Exploiting cloze-questions for few-shot text classification and natural language inference. In *Proceedings of the 16th Conference of the European Chapter of the Association for Computational Linguistics: Main Volume*, pp. 255–269, 2021.

Szklarzczyk, D., Gable, A. L., Lyon, D., Junge, A., Wyder1, S., et al. String v11: protein-protein association networks with increased coverage, supporting functional discovery
Prompt-Guided Injection of Conformation to Pre-trained Protein Model

in genome-wide experimental datasets. *Nucleic acids research*, 47(D1):D607–D613, 2019.

Vig, J., Madani, A., Varshney, L. R., Xiong, C., richard socher, and Rajani, N. *BERT*ology meets biology: Interpreting attention in protein language models. In *International Conference on Learning Representations*, 2021. URL https://openreview.net/forum?id=YWtLZvLmud7.

Yan, C., Wu, F., Jernigan, R. L., Dobbs, D., and Honavar, V. Characterization of protein-protein interfaces. *The protein journal*, 27(1), 2008.

Zhang, H., Lan, Y., Pang, L., Guo, J., and Cheng, X. Recosa: Detecting the relevant contexts with self-attention for multi-turn dialogue generation. In *Proceedings of the 57th Annual Meeting of the Association for Computational Linguistics*, pp. 3721–3730, 2019.

Zhang, H., Ju, F., Zhu, J., He, L., Shao, B., Zheng, N., and Liu, T.-Y. Co-evolution transformer for protein contact prediction. In Beygelzimer, A., Dauphin, Y., Liang, P., and Vaughan, J. W. (eds.), *Advances in Neural Information Processing Systems*, 2021a. URL https://openreview.net/forum?id=PcpExudEmDd.

Zhang, N., Li, L., Chen, X., Deng, S., Bi, Z., Tan, C., Huang, F., and Chen, H. Differentiable prompt makes pre-trained language models better few-shot learners. *CoRR*, abs/2108.13161, 2021b. URL https://arxiv.org/abs/2108.13161.
A. Construction of Pre-training Dataset

To inject interaction conformation knowledge into the Conf-Protein, we construct a PPI dataset – a large-scale physical-only interaction network. We use the latest STRING database with only the physical-only mode, which means edges between the protein pairs indicate evidence of their binding or forming a physical complex. The database contains in total 65 million protein sequences from 14,094 species and 2.7 billion protein-protein interaction pairs. Note that there is no edge between proteins that come from different species.

We observe that the PPI network has a problem of uneven distribution, as illustrated in Figure 8, the largest network contains 60,000 proteins and $3.5 \times 10^7$ edges. Such data distributions can lead models to over-focus on proteins from a single species. We pre-process our dataset by choosing the species networks with comparable sizes. Figure 9 illustrates the data distribution after being pre-processed.

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B. Datasets Statistics

The statistical results of the dataset are shown in Table 5. The number of proteins refers to the total number of occurrences in the training and test sets. An entry refers to a data point that contains input and output. Note that in some tasks (such as PPI prediction and antibody-antigen binding affinity prediction), an input contains more than one protein.

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C. ICProtein

To construct a contact map dataset based on 3D interaction conformation, we firstly obtain all the data of protein complex structures from Humphreys et al. (2021). Then we use obabel (O’Boyle et al., 2011) to convert the CIF file to the PDB file (A & J, 1994). By calculating the distance of residues, we obtain the contact map based on interaction conformation. Since each CIF file consists of two interacting proteins, we separate them and get 2,212 protein interaction contact maps.

In Figure 5, we illustrate the distance of corresponding amino acids with and without conformational information of TAF4 protein. Compared with the contact map (Figure 10), we find that our method successfully captures the binding sites of TAF4 and TAF5. This finding indicates that the IC prompt can enhance protein representations by changing the embedding of PPI-related amino acids.
Table 6. Hyper-parameter Search Space of Our Method

| DATASET          | BATCH_SIZE | MAX_SEQ_LENGTH | LEARNING_RATE | WEIGHT_DECAY | WARMUP_UPDATES |
|------------------|------------|----------------|---------------|---------------|----------------|
| SHS27K           | \{512, 1024, 2048\} | 2,000          | \{1E-5, 5E-5, 1E-4, 2E-4\} | \{0.0, 1E-4, 5E-4\} | -              |
| SHS148K          | \{512, 1024, 2048\} | 2,000          | \{1E-5, 5E-5, 1E-4, 2E-4\} | \{0.0, 1E-4, 5E-4\} | -              |
| STRING-HOMOSAPIENS | \{512, 1024, 2048\} | 2,000          | \{1E-5, 5E-5, 1E-4, 2E-4\} | \{0.0, 1E-4, 5E-4\} | -              |
| SAbDab           | 1          | 1.024          | \{1E-5, 3E-5, 1E-4, 2E-4\} | -              | \{0, 100, 10,000\} |
| CASP12           | 1          | 1.024          | \{1E-5, 3E-5, 1E-4, 2E-4\} | -              | \{0, 100, 10,000\} |
| ICPROTEIN        | 1          | 1.024          | \{1E-5, 3E-5, 1E-4, 2E-4\} | -              | \{0, 100, 10,000\} |
| CB513            | 2          | 1.024          | \{1E-5, 3E-5, 1E-4, 2E-4\} | -              | \{0, 100, 10,000\} |
| FLUORESCENCE     | 8          | 512            | \{1E-5, 3E-5, 1E-4, 2E-4\} | -              | \{0, 100, 10,000\} |
| STABILITY        | 2          | 1.024          | \{1E-5, 3E-5, 1E-4, 2E-4\} | -              | \{0, 100, 10,000\} |

D. Downstream Task Definition

Here, we define a list of downstream tasks and their inputs and outputs.

- **Protein-Protein Interaction Prediction** is a sequence-level classification task. Its input contains two amino acid sequences $S_i, S_j$, and since STRING divides PPI into 7 categories, we need to predict the interactions and types between these two proteins $y_{ij} \in \{0, 1\}^7$.

- **Antibody-Antigen Binding Affinity Prediction** is a sequence-level regression task. Its input contains three amino acid sequences $S_i, S_j, S_k$, and we need to predict the value of binding affinity $y_{ijk} \in \mathbb{R}$.

- **Contact Prediction** is a token-level classification task. Its input is an amino acid sequence $S = \{s_1, \cdots, s_n\}$, and we need to predict whether two residues are in contact $y \in \{0, 1\}^{n \times n}$.

- **Secondary Structure Prediction** is a token-level classification task. Its input is an amino acid sequence $S = \{s_1, \cdots, s_n\}$, and we need to predict the type of each amino acid $y \in \{\text{Helix}, \text{Strand}, \text{Other}\}^n$.

- **Fluorescence** is a sequence-level regression task. Its input is an amino acid sequence $S$, and we need to predict the log-florescence intensity $y \in \mathbb{R}$.

- **Stability** is a sequence level regression task. Its input is an amino acid sequence $S$, and we need to predict the most extreme circumstances in which $S$ maintains its activity $y \in \mathbb{R}$.

E. Experimental Details

We present our hyper-parameter search space in Table 6. The first three datasets are for the PPI prediction task. In this task, we freeze ConfProtein parameters and train the graph neural network predictor, so we only search the predictor parameters. The max sequence length $n$ denotes that the length of each input amino acid sequence will be padded by $[\text{PAD}]$ to make totally $n$ tokens.