

PFMBENCH: PROTEIN FOUNDATION MODEL BENCHMARK

Anonymous authors

Paper under double-blind review

ABSTRACT

This study investigates the current landscape and future directions of protein foundation model research. While recent advancements have transformed protein science and engineering, the field lacks a comprehensive benchmark for fair evaluation and in-depth understanding. Since ESM-1B, numerous protein foundation models have emerged, each with unique datasets and methodologies. However, evaluations often focus on limited tasks tailored to specific models, hindering insights into broader generalization and limitations. Specifically, researchers struggle to understand the relationships between tasks, assess how well current models perform across them, and determine the criteria in developing new foundation models. To fill this gap, we present PFMBench, a comprehensive benchmark evaluating protein foundation models across 38 tasks spanning 8 key areas of protein science. Through hundreds of experiments on 17 state-of-the-art models across 38 tasks, PFMBench reveals the inherent correlations between tasks, identifies top-performing models, and provides a streamlined evaluation protocol. Code will be released upon acceptance.

1 INTRODUCTION

Protein foundation models (PFMs) have garnered significant attention in recent years for their transformative potential in protein science and engineering. By training on large-scale protein datasets, these models capture intricate relationships between sequences, structures, and functions. Since the debut of ESM-1B Rives et al. (2021) in 2021, a diverse array of PFMs—spanning various architectures and training paradigms—has emerged Rives et al. (2021); Lin et al. (2023); Hayes et al. (2025); Elnaggar et al. (2021); Madani et al. (2023); Ferruz et al. (2022); Tan et al. (2025); Zhou et al. (2025); Elnaggar et al. (2023); Chen et al. (2024); Wang et al. (2024b); Su et al.; 2024); Xu et al. (2023); Bjerregaard et al. (2025); Guo et al. (2025); Li et al. (2024). Despite this rapid progress, prior models like ESM2 Lin et al. (2023) still dominate many bioengineering applications. This raises several pressing questions: Has the field reached a plateau and what is the next frontier for PFMs? Thus, a comprehensive and systematic benchmark is urgently needed.

Comparison of PFMBench with existing benchmarks. #PFM: number of PFMs (>500M), MM: multimodal PFMs, #Tasks: task count, Protocol: simplified evaluation protocol.

		#PFM	MM	#Tasks	Protocol
TAPE	NeurIPS 2019	0	X	4	X
PEER	NeurIPS 2022	1	X	14	X
CARE	NeurIPS 2024	0	X	2	X
Venus	Arxiv 2025	3	X	22	X
Our		14	✓	38	✓

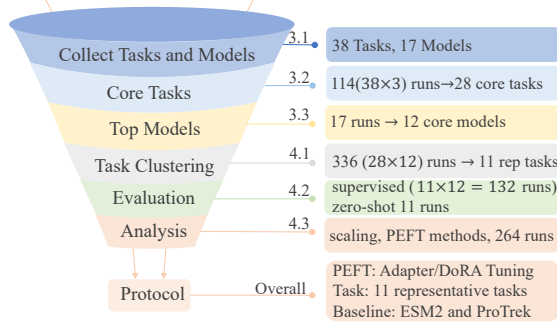


Figure 1: PFMBench: More tasks, multimodal PFMs, a simplified protocol, and hierarchical analysis.

Previous benchmarking efforts for protein models have either covered a limited set of tasks or were not explicitly designed for evaluating foundation models, as shown in Fig. 1. In the context of protein foundation models (PFMs)—typically defined as models with at least 500 million parameters—most existing benchmarks fall short of providing comprehensive evaluation. For example, TAPE Rao et al. (2019) assessed architectures such as Transformers Vaswani et al. (2017), LSTMs Hochreiter & Schmidhuber (1997), and ResNets He et al. (2016) across four tasks, but did not include any large-scale PFMs. PEER Xu et al. (2022) evaluated models on 14 tasks but was limited to sequence-based

architectures, with only ESM-1B Rives et al. (2021) exceeding the 500-million-parameter threshold. CARE Yang et al. (2024) focused narrowly on two enzyme-related tasks: classification and retrieval. More recently, VenusFactory Tan et al. (2025) introduced a unified benchmark spanning 22 tasks across five functional categories. However, it reported results for only three large sequence-based models, such as ESM2 Lin et al. (2023), Ankh Elnaggar et al. (2023), and ProtT5 Elnaggar et al. (2021), limiting its ability to capture the full spectrum of modern PFMs.

Multimodal PFMs are understudied in existing benchmarks, despite the field’s rapid shift toward models that integrate sequence, structure, and functional data. For example, ESM3 Hayes et al. (2025), GearNet Zhang et al. (b), and SaProt Su et al. have demonstrated strong performance on specialized tasks such as protein design and function prediction. However, their evaluations are often limited in scope, focusing on specific tasks or datasets, which impedes a systematic understanding of their limitations, generalizability, and cross-task performance. For instance, while ESM3 excels in protein design, its ability to generalize to other tasks remains largely unexplored. Similarly, GearNet and SaProt have shown promise in certain tasks, but their performance across broader protein function landscapes has yet to be thoroughly assessed. Consequently, it remains unclear under what conditions and how multimodal PFMs contribute to improved generalization capabilities.

A benchmark should not merely serve as a collection of tasks and models—it should also provide a streamlined protocol for model development. As both tasks and models become increasingly complex, exhaustively evaluating all models across all tasks becomes impractical and often fails to yield actionable insights. A more effective approach is to uncover the underlying relationships between tasks, identify a representative subset of tasks, and select a diverse yet informative set of models for focused evaluation. This strategy enables the benchmark to help researchers identify top-performing models for specific tasks and guide the development of new models—serving as a blueprint for future model evaluation, selection, and design.

To address this gap, we introduce PFMBench—a unified and comprehensive benchmark suite for protein foundation models. PFMBench spans 38 tasks across 8 categories, encompassing 19 sequence-based, sequence-structure, sequence-function, and multimodal PFMs. Both datasets and models are carefully curated to ensure robust, fair and meaningful comparisons. Through extensive evaluation, PFMBench offers detailed insights into the strengths and limitations of modern PFMs, and provide a simplified and useful protocol for future PFM development.

2 RELATED WORK

Protein Foundation Models. Protein foundation models (PFMs) have witnessed exponential growth in recent years, revolutionizing computational biology through self-supervised learning on vast protein sequence datasets. ESM-1b Rives et al. (2021) pioneered large-scale protein modeling with a 650M parameter transformer trained on 65 million protein sequences via masked language modeling. This trajectory continued with ESM-2 and ESMC models Lin et al. (2023), which demonstrated enhanced representation learning for protein structure and function through refined architecture and expanded training data. The ESM family evolved further with ESM3 Hayes et al. (2025), scaling to 98B parameters and incorporating structure-aware training to achieve state-of-the-art performance on zero-shot fitness prediction and structure modeling. ProtT5 Elnaggar et al. (2021) adapted the T5 architecture to proteins, scaling to 3B and 11B parameters with span-masking objectives, establishing strong baselines for protein sequence-to-sequence tasks. The generative approach was pioneered by ProGen Madani et al. (2023), a 1.2B parameter conditional generation model, and ProtGPT2 Ferruz et al. (2022), a 738M parameter GPT-2-based model for de novo protein sequence generation. VenusPLM Tan et al. (2025) employed transformer-based architectures with modular fine-tuning capabilities for enzyme engineering and protein function prediction. Multimodal approaches emerged with ProtCLIP Zhou et al. (2025), aligning protein sequences with biological text through function-informed pre-training. ANKH Elnaggar et al. (2023) built upon ProtT5’s architecture to optimize data efficiency through systematic ablation studies. xTrimopGLM Chen et al. (2024) adopt GLM’s training paradigm to protein sequences, expanding the model size to 100B. Other significant contributions include DPLM Wang et al. (2024b), leveraging deep learning for protein language modeling; SaProt Su et al., focusing on structure-aware protein representation learning; ProtRek Su et al. (2024), specialized in protein sequence retrieval and knowledge integration; and ProST Xu et al. (2023), which incorporates biomedical texts to guide protein function learning. Together, these

diverse foundation models have transformed protein research by enabling unprecedented advances in structure prediction, functional annotation, and protein design through their ability to learn complex evolutionary and structural patterns from sequence data.

Protein Benchmarks. Protein foundation model benchmarks have evolved significantly, transitioning from early efforts like TAPE Rao et al. (2019), which evaluated small models on a limited set of tasks, to more comprehensive frameworks. PEER Xu et al. (2022) expanded the scope by introducing a multi-task benchmark encompassing diverse protein understanding tasks, including function prediction and protein-protein interactions. BeProf Wang et al. (2024a) further contributed by evaluating deep learning-based protein function prediction models in different application scenarios. Recent benchmarks like VenusFactory Tan et al. (2025) have integrated a broader range of pre-trained models and datasets, yet they often lack consideration for multimodal approaches. Beyond predictive benchmarks, initiatives like ProteinGym Notin et al. (2023), ProteinInvBench Gao et al. (2023) and ProteinBench Ye et al. (2024) have introduced frameworks for evaluating protein mutation effects, inverse folding and protein design, respectively. These benchmarks have progressively incorporated more diverse tasks, models—including large pre-trained language models and multimodal approaches—and sophisticated evaluation metrics, thereby playing a crucial role in tracking progress, identifying state-of-the-art methods, and guiding future research. However, current benchmarks do not focus on protein foundation models, especially multimodal foundation models, also do not provide a streamlined evaluation protocol for these models.

Parameter-Efficient Fine-Tuning. Recent advances in parameter-efficient fine-tuning (PEFT) have enabled the adaptation of large pre-trained models by updating only a small subset of their parameters. Adapter-based methods insert trainable modules between frozen layers Houlsby et al. (2019); Pfeiffer et al. (2020), while Low-Rank Adaptation (LoRA) approximates weight updates using low-rank matrices Hu et al. (2022a). Prompt-based techniques—such as prefix tuning Li & Liang (2021) and prompt tuning Lester et al. (2021)—optimize soft prompts within the input embeddings, avoiding changes to the model weights. Other approaches, including BitFit (which updates only bias terms) Zaken et al. (2022), IA3 (which scales intermediate activations) Liu et al. (2022), and QLoRA (which enables quantized fine-tuning) Dettmers et al. (2023), further improve efficiency. Hybrid strategies that combine multiple techniques have also emerged He et al.. Recent innovations include AdaLoRA, which dynamically adjusts rank allocation during training Zhang et al. (2023); MoeLoRA, which integrates mixture-of-experts into LoRA for enhanced scalability Wu et al. (2024); DoRA, which decomposes weights into magnitude and direction for targeted adaptation Mao et al. (2024); and LoCA, which introduces location-aware cosine adaptation for more precise updates Du et al. (2025). Collectively, these developments continue to improve the efficiency, flexibility, and effectiveness of PEFT for large language models. This research select Adapter, LoRA, AdaLoRA, DoRA and IA3 as the representative methods for performance comparison.

3 METHOD

3.1 PFMBENCH FRAMEWORK

Framework. As shown in Figure 2, PFMBench comprises three main components: (1) a user-friendly interface, (2) a suite of downstream tasks, and (3) a comprehensive collection of foundation models. Designed with modularity in mind, the framework allows users to swap components and customize the evaluation process with ease. We employ Hydra to parse configuration files and PyTorch Lightning to manage model fine-tuning. To our knowledge, PFMBench is the largest and most comprehensive benchmark for protein foundation models, covering 38 tasks across 17 models.

Data Contribution. For each dataset, we retrieve protein structures from the AF2DB Varadi et al. (2022) when available; otherwise, we use ESMFold Lin et al. (2023) to generate the rank-1 protein structure. To standardize evaluation, we enforce a 30% sequence similarity cutoff when splitting data, resulting in an 8:1:1 ratio for training, validation, and test sets. Mutation datasets are exempt from this splitting due to their high similarity to wild-type sequences; thus, we retain their original train/validation/test partitions.

Protocol Contribution. Evaluating all models and tasks is impractical, especially when aiming to provide guidance for developing new foundation models. We believe that simplifying the selection of tasks and models is equally important, as it highlights the key insights. Through hundreds of experiments, we provide a hierarchical analysis that results in a streamlined protocol: (1) Baseline: select either the sequence-only ESM2 or the multimodal ProTrek; (2) Task: filter 11 representative tasks from the original 38 tasks; (3) PEFT: adopt either the transformer-adapter or the DoRA tuning.

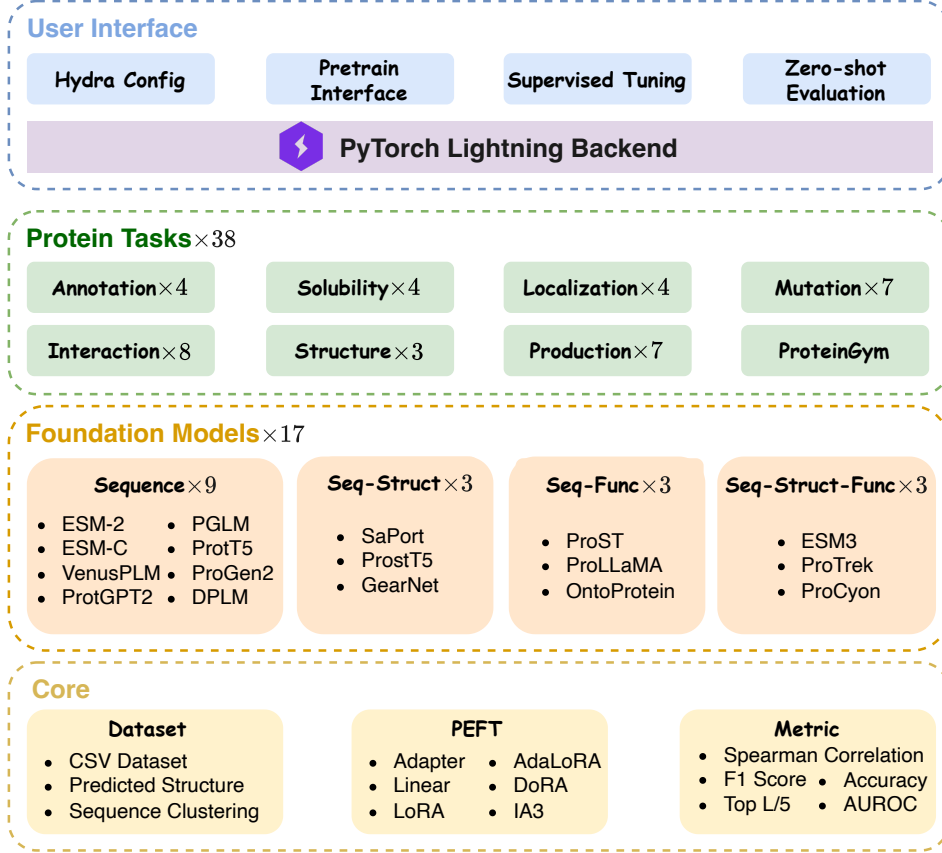


Figure 2: The Overall framework of PFMBench. The framework includes: (1) a user-friendly interface, (2) numerous downstream tasks, and (3) a comprehensive set of foundation models. Diverse datasets, parameter-efficient tuning methods, and evaluation metrics are integrated. The modular design allows users to easily swap components, customize models, tasks and metrics.

3.2 SUPPORTED TASKS

Core Tasks. PFMBench includes 38 tasks spanning diverse domains, covering both supervised and zero-shot learning. Supervised tasks are grouped into seven categories: Annotation, Solubility, Localization, Mutation, Interaction, Structure, and Production. Definitions, metrics, and impacts for each category are detailed in Appendix A.1. Datasets are split into training, validation, and test sets using an 8:1:1 ratio with a 30% sequence similarity threshold, except for mutation datasets. We evaluate ESM2-Adapter on all tasks, averaging results over three runs, with bias calculated as the absolute difference between the best and worst runs divided by the average performance (see Table 1). To ensure unbiased evaluation, we designate 28 tasks with a bias below 5% as core tasks.

3.3 SUPPORTED MODELS

Core Models. PFMBench supports a broad spectrum of protein foundation models, as summarized in Table 2. To ensure a fair comparison, we select models with parameter counts close to 1B when multiple versions are available. Based on input data modalities, the models are categorized into four

Table 1: PFMBench Tasks span eight categories, detailing training, validation, and test sample counts per task with references. Symbols $\triangle$ and $\star$ indicate datasets with sequence or sequence-structure pairs, as used in benchmarks like TAPE Rao et al. (2019), PEER Xu et al. (2022), Venus Tan et al. (2025), and our framework. ESM2-Adapter’s mean and bias performance are shown, with core tasks having bias below 5%.

Task	Metric	Train	Val	Test	TAPE	Peer	Venus	Our	Mean	Bias(%)	Core
Annotation											
Cellular Component Ashburner et al. (2000)	F1 Score	11196	1398	1400			$\star$	$\star$	0.6130	0.26%	✓
Molecular Function Ashburner et al. (2000)	F1 Score	22291	2785	2787			$\star$	$\star$	0.6488	0.38%	✓
Biological Process Ashburner et al. (2000)	F1 Score	21395	2662	2664			$\star$	$\star$	0.5412	0.79%	✓
Enzyme Commission Bairoch (2000)	F1 Score	13090	1465	1604			$\star$	$\star$	0.7379	0.09%	✓
Solubility											
DeepSol Khurana et al. (2018)	AUROC	55465	6932	6934		$\triangle$	$\star$	$\star$	0.8467	0.23%	✓
DeepSoluE Wang & Zou (2023)	AUROC	11627	1452	1454			$\star$	$\star$	0.7699	1.10%	✓
ProtSolM Tan et al. (2024b)	AUROC	57378	7171	7173			$\star$	$\star$	0.8572	0.93%	✓
eSOL Chen et al. (2021)	Spearman	2481	309	311			$\star$	$\star$	0.2761	38.3%	
Localization											
DeepLoc Multi Almagro Armenteros et al. (2017)	Accuracy	6992	749	751		$\triangle$	$\star$	$\star$	0.7666	1.27%	✓
DeepLoc2 Multi Thummuluri et al. (2022)	F1 Score	21949	2743	2744		$\triangle$	$\star$	$\star$	0.7505	0.16%	✓
DeepLoc Binary Almagro Armenteros et al. (2017)	AUROC	6887	846	848				$\star$	0.9338	0.42%	✓
Sorting Signal Thummuluri et al. (2022)	F1 Score	1484	185	186			$\triangle$	$\star$	0.8598	0.24%	✓
Mutation											
PETA.CHS.Sol Tan et al. (2024a)	Spearman	3872	484	484			$\triangle$	$\star$	0.2738	12.5%	
PETA.LGK.Sol Tan et al. (2024a)	Spearman	15308	1914	1914			$\triangle$	$\star$	0.1558	21.7%	
PETA.TEM.Sol Tan et al. (2024a)	Spearman	6444	808	808			$\triangle$	$\star$	0.1433	27.0%	
FLIP.AAV Dallago et al.	Spearman	66066	16517	16517			$\triangle$	$\star$	0.9412	0.13%	✓
FLIP.GB1 Dallago et al.	Spearman	6988	1745	1745			$\triangle$	$\star$	0.9517	0.13%	✓
TAPE.Stability Rao et al. (2019)	Spearman	55182	6897	6898	$\triangle$	$\triangle$	$\triangle$	$\star$	0.3211	4.01%	✓
TAPE.Fluorescence Rao et al. (2019)	Spearman	21446	5362	27217	$\triangle$	$\triangle$	$\triangle$	$\star$	0.6812	0.21%	✓
β -lactamase activity Gray et al. (2018)	Spearman	4158	520	520		$\triangle$		$\star$	0.5740	21.6%	
Interaction											
Human-PPI Pan et al. (2010)	AUROC	30133	270	195		$\triangle$		$\star$	0.4828	0.00%	✓
Yeast-PPI Guo et al. (2008)	AUROC	4157	83	335		$\triangle$		$\star$	0.5343	12.8%	
PPI affinity Moal & Fernández-Recio (2012)	Spearman	2421	203	326		$\triangle$		$\star$	-0.0047	114.3%	
PDBbind Liu et al. (2017)	Spearman	14687	1835	1836		$\triangle$		$\star$	0.1677	4.14%	✓
BindingDB Liu et al. (2007)	Spearman	9039	1115	1139		$\triangle$		$\star$	0.1922	3.02%	✓
Metal ion Binding Hu et al. (2022b)	Accuracy	5740	717	718			$\star$	$\star$	0.7066	2.43%	✓
Pept.HLA/MHC Aff. Wu et al. (2023)	AUROC	57357	7008	8406				$\star$	0.9631	0.00%	✓
TCR PMHC Affinity Koyama et al. (2023)	AUROC	19264	2265	2482				$\star$	0.9312	0.00%	✓
Structure											
Contact prediction Yang et al. (2020)	Top L/5	12005	1500	1501	$\triangle$	$\triangle$		$\star$	0.7199	0.40%	✓
Fold classification Lo Conte et al. (2000)	Accuracy	13034	1628	1630		$\triangle$		$\star$	0.7859	0.31%	✓
Secondary structure Klausen et al. (2019)	Accuracy	67007	8365	8262	$\triangle$	$\triangle$		$\star$	0.7601	0.00%	✓
Production											
Optimal PH Gado et al. (2023)	Spearman	7669	958	959				$\star$	0.0564	17.6%	
DeepET.Topt Li et al. (2022b)	Spearman	1479	184	185			$\star$	$\star$	0.2628	7.00%	
Cloning CLF Wang et al. (2014)	AUROC	22223	2777	2778				$\star$	0.8160	0.51%	✓
Material Production Wang et al. (2014)	Accuracy	22196	2773	2775				$\star$	0.7982	0.00%	✓
Enzyme Eff. Li et al. (2022a)	Spearman	10363	1298	1290				$\star$	0.2173	58.2%	
Antib. Res. Hu et al. (2022b)	Accuracy	2703	336	339				$\star$	0.6185	2.23%	✓
Thermostability Jarzab et al. (2020)	AUROC	33474	4184	4184			$\star$	$\star$	0.9553	1.27%	✓
Zero-shot											
ProteinGym Notin et al. (2023)	Spearman						$\star$	$\star$	0.4390	0%	✓

groups: (1) sequence-only models, (2) sequence-structure models, (3) sequence-function models, and (4) sequence-structure-function models. To establish a consistent evaluation baseline, we assess all models on the enzyme commission (EC) classification task under the adapter tuning setting. Models that achieve at least 85% of ESM2’s performance are selected as core models for further evaluation. For detailed reasons regarding the adoption of EC as a selective task, please refer to Appendix A.5.

3.4 SUPPORTED TUNING METHODS

PFMBench offers diverse parameter efficient fine-tuning (PEFT) methods: linear probing, adapter tuning, IA^3 , LoRA, AdaLoRA, and DoRA, with a unified interface for seamless switching.

Adapter Tuning & Linear Probing. We extract features using the pretrained model and employ a 6-layer transformer as a task-specific adapter with a hidden size of 480 and 20 attention heads. In Linear probing setting, we the transformer adapter is replaced with a linear layer. Without additional explanation, we report adapter tuning results in the main text.

Other Tuning Methods. LoRA decomposes attention and feedforward layer weight updates into the product of two low-rank matrices, which are the only trainable components during finetuning Hu et al. (2022a). IA^3 introduces trainable multiplicative scalars into the attention and MLP sublayers, modulating the flow of information through each component Liu et al. (2022). AdaLoRA dynamically

Table 2: Models in PFMBench. The table lists the models, architecture types, number of parameters, publication states, code sources. We report the Enzyme Commission (EC) results.

Model	Core	Architecture	# Params	Publication	EC	Code
Sequence						
ESM-2 Lin et al. (2023)	✓	Encoder	650M	Science 23	0.7358	HF
VenusPLM Tan et al. (2025)	✓	Encoder	300M	Arxiv 25	0.7519	HF
ESM-C	✓	Encoder	600M	Blog 25	0.7169	HF
ProtGPT2 Ferruz et al. (2022)	✓	Decoder	738M	Nat. Commun. 22	0.6969	HF
ProGen2 Nijkamp et al. (2023)		Decoder	764M	Cell Syst. 23	0.6198	GitHub
xTrimoPGLM Chen et al. (2024)	✓	Encoder-Decoder	1B	Nat. Methods 25	0.7466	HF
ProtT5 Elnaggar et al. (2021)	✓	Encoder-Decoder	3B	TPAMI 21	0.7620	HF
DPLM Wang et al. (2024b)	✓	Encoder+Diffusion	650M	ICLR 24	0.7552	GitHub
Sequence-Structure						
SaPort Su et al.	✓	Encoder	650M	ICLR 24	0.7514	HF
ProstT5 Heinzinger et al. (2024)	✓	Encoder-Decoder	3B	NAR Gen. Bio. 24	0.7683	GitHub
GearNet Zhang et al. (b)		GNN	20M	ICLR 23	0.5860	GitHub
Sequence-Function						
ProtST Xu et al. (2023)	✓	Encoder	750M	ICML 23	0.7176	GitHub
ProLLaMA Lv et al. (2025)		Decoder	6.7B	IEEE TAI 25	0.5475	GitHub
OntoProtein Zhang et al. (a)		Encoder	420M	ICLR 22	0.6287	GitHub
Sequence-Structure-Function						
ProCyon Queen et al. (2024)		Decoder	11B	Arxiv 24	0.1909	GitHub
ESM3 Hayes et al. (2025)	✓	Encoder	1.4B	Science 25	0.6483	GitHub
ProTrek Su et al. (2024)	✓	Encoder	650M	Arxiv 24	0.7641	GitHub

adjusts rank allocation during training Mao et al. (2024). **DoRA** decomposes weights into magnitude and direction for targeted adaptation Zhang et al. (2023). We implement these methods using the PEFT library Mangrulkar et al. (2022).

Hyper-parameters. All models are trained for up to 50 epochs using AdamW with a batch size of 64 and early stopping after 5 patience epochs. Optimal learning rate is selected from $\{1e-5, 1e-4\}$.

4 EXPERIMENTS

We conduct systematic experiments to answer the following questions:

- **Q1: Supervised Tuning.** How are different supervised downstream tasks correlated, and can a minimal, representative subset of tasks be identified to efficiently benchmark pre-trained models?
- **Q2: Zero-shot Evaluation.** Can zero-shot protocols reliably evaluate protein foundation models?
- **Q3: PEFT Strategies.** Which PEFT methods are more effective for protein tasks?
- **Q4: Scaling.** How does model performance improve with increased model size?

4.1 SUPERVISED TUNNING (Q1)

Task Correlations. We evaluate the adapter tuning performance of 12 core models across 28 core tasks, with the complete results provided in the appendix (Table 7) due to space constraints. We analyze task relationships using Spearman correlation and visualize the results in Figure 3, where p-values greater than 0.05 are marked with ✕. Finally, the 28 core tasks are grouped into 11 clusters based on their correlations, and the selected **representative tasks** (marked as ☆).

Core Model Performance on Representative Tasks. Table 3 summarizes the performance of 12 core models on 11 representative tasks. Poorly performing tasks are excluded due to the challenges adapter tuning faces in learning them. Upon analyzing the poorly performing datasets, we observe that the newly implemented 30% sequence identity split introduces significant challenges for model learning. While the stability performance under the original split aligns with SaProt Su et al., the new split proves to be more demanding. Interaction tasks, requiring paired sequence embeddings processed via transformer adapters, remain particularly challenging, underscoring the need for PLMs tailored for interaction prediction, as current models are trained solely on single sequences.

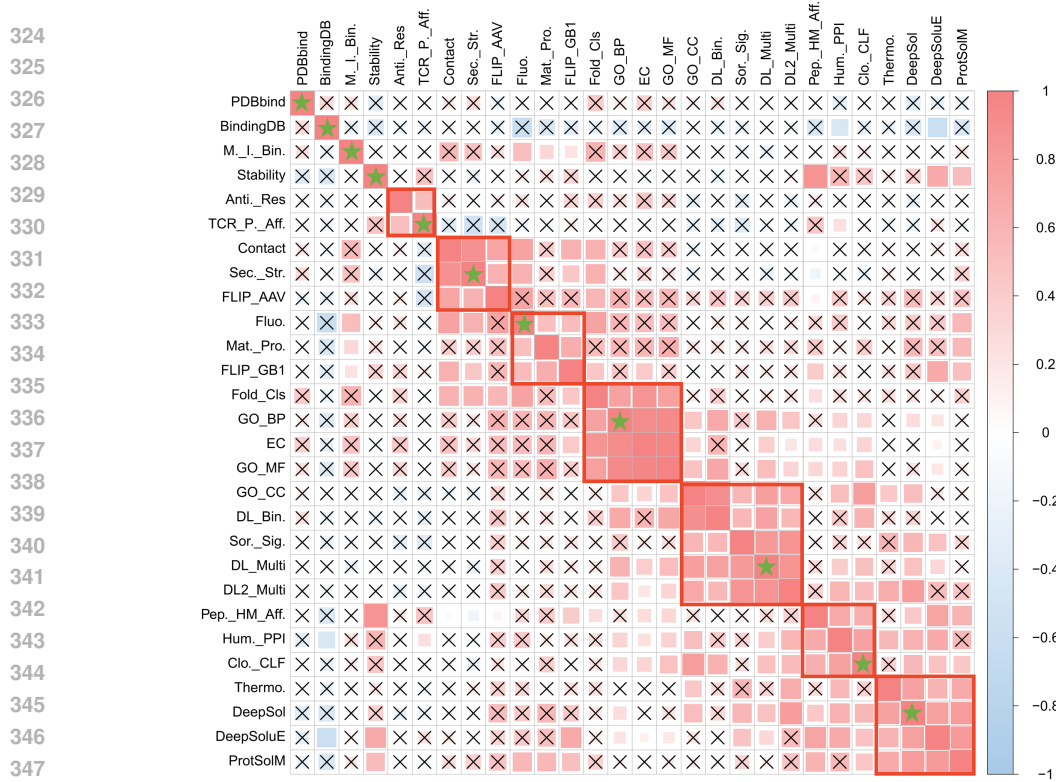


Figure 3: Task relations in supervised tuning.

Table 3: Core model results on representative tasks. **Best** and second-best ones are highlighted.

	PDBBind	Bind. DB	Stability	Anti.Res.	Mat.Pro.	EC	M. I. Bin.	Sec. Str.	DL2 M.	Clo. CLF	DeepSol	#Win
Sequence												
ESM-2 Lin et al. (2023)	0.14677	0.13692	0.32112	0.63422	0.81189	0.73578	0.71170	0.76375	0.76191	0.80586	0.84494	–
VenusPLM Tan et al. (2025)	0.16536	0.16834	0.33907	0.64602	0.82018	0.75194	0.70195	0.71637	0.73814	0.83172	0.82775	50%
ESM-C	0.14692	0.20716	0.29976	0.67257	0.81009	0.71694	0.70195	0.76777	0.75395	0.81033	0.84171	38%
ProtGPT2 Ferruz et al. (2022)	0.13503	0.17169	0.14803	0.68437	0.76757	0.69687	0.71170	0.49371	0.70341	0.77730	0.78883	13%
PGLM Chen et al. (2024)	0.16877	0.16884	0.33127	0.67257	0.79495	0.74659	0.74513	0.72842	0.74772	0.83638	0.82160	50%
ProT5 Elnaggar et al. (2021)	<u>0.20105</u>	0.19730	0.18638	0.68732	0.80072	0.76201	0.72145	0.77978	0.72624	0.78485	0.78741	50%
DPLM Wang et al. (2024b)	0.13659	0.17408	0.29440	0.68732	0.80144	0.75521	0.70056	0.75695	0.75759	0.81247	0.82841	38%
Sequence-Structure												
SaProt Su et al.	0.15549	0.16557	0.24804	0.65782	0.81081	0.75144	0.71031	0.82389	0.74006	0.81206	0.84364	50%
ProST5 Heinzinger et al. (2024)	0.18344	0.16642	0.13032	0.69027	<u>0.81622</u>	0.76829	0.72145	<u>0.81397</u>	0.73190	0.79853	0.81937	<u>63%</u>
Sequence-Function												
ProtST Xu et al. (2023)	<u>0.19514</u>	0.18886	0.06623	0.63422	0.69261	0.71761	0.51532	0.68468	0.74886	0.80714	0.81951	13%
Sequence-Structure-Function												
ESM3 Hayes et al. (2025)	0.15572	0.22519	0.15650	0.58407	0.77514	0.64830	0.70334	0.81264	0.65853	0.77391	0.78106	13%
ProTrek Su et al. (2024)	0.17322	0.19230	0.04924	0.59292	0.81477	<u>0.76408</u>	0.80362	0.77363	0.83944	0.82612	0.83427	75%

Do existing PLMs truly outperform ESM2? For the remaining 8 representative tasks, we compare each model against ESM2 and calculate the winning rate (#Win), which is defined as the proportion of tasks where a model outperforms ESM2. From the #Win metric, we observe that:

- **Sequence-based PLMs.** All sequence-based PLMs achieve no more than a 50% winning rate against ESM2, indicating that they could not outperform ESM2 on the representative tasks.
- **Decoder-only Model.** The decoder-only model ProtGPT2 performs the worst on these tasks, with a winning rate of only 13% on representative tasks. This suggests that the decoder-only architecture is currently unsuitable for protein understanding.
- **Multimodal PLMs.** Multimodal PLMs achieve the highest winning rates, with ProTrek attaining a 75% winning rate on representative tasks. This success is attributed to the effective semantic alignment of sequence and function information during the pre-training stage.
- **Challenges with Function Data.** ESM3 and ProtST show low winning rates (13%) due to noisy or insufficient function data, emphasizing the need for high-quality, large-scale datasets. For example, ProTrek excels when trained on such cleaned, large-scale annotations.

4.2 ZERO-SHOT EVALUATION (Q2)

While ProteinGym has established itself as a valuable zero-shot benchmark for protein function prediction, recent studies (Tsishyn et al., 2025; Gurev et al.; Zhou et al., 2024) have revealed limitations in its sensitivity to model size and performance differentiation. We greatly appreciate ProteinGym’s seminal role in standardizing zero-shot mutation evaluation and accelerating progress in protein ML. PFMBench complements ProteinGym by focusing on more supervised learning scenarios—including mutation tasks—that better align with real-world deployment needs, while introducing novel evaluation metrics (e.g., Mutual Information Difference) to assess functional sequence relationships. This complementary approach provides a more comprehensive evaluation framework for protein foundation models.

Complementary Evaluation Insights. Zero-shot mutation tests are a common practice, yet Table 4 shows that ProteinGym’s zero-shot performance has limited correlation with supervised tuning results, indicating the mutation tasks and predictive tasks probe different facets of model capability. This underscores PFMBench’s role as a complementary suite that include both mutation and predictive tasks, thereby providing signals that are orthogonal to mutation assessments. In addition, we introduce a new zero-shot evaluation metric (Mutual Information Difference) to better align the model’s ability with sequence-level mutual information.

Table 4: Zero-shot proteingym performance of core models.

	# Params	Architecture	Input	Loss	ProteinGym	Rank
SaProt Su et al.	650M	Encoder	Seq-Struct	MLM	0.45094	1
VenusPLM Tan et al. (2025)	300M	Encoder	Seq	MLM	0.43952	2
ESM-2 Lin et al. (2023)	650M	Encoder	Seq	MLM	0.43904	3
ESM-C	600M	Encoder	Seq	MLM	0.43422	4
DPLM Wang et al. (2024b)	650M	Encoder	Seq	MLM	0.42922	5
ESM3 Hayes et al. (2025)	1.4B	Encoder	Seq	MLM	0.41401	6
PGLM Chen et al. (2024)	1B	Encoder-Decoder	Seq	MLM	0.39750	7
ProTrek Su et al. (2024)	650M	Encoder	Seq	MLM+ Contrast	0.35919	8
ProtGPT2 Ferruz et al. (2022)	738M	Decoder	Seq	NTP	0.18962	9

UMAP Visualization. Figure 4 shows UMAP embeddings of ESM2, ProT5, and ProTrek on Deeploc2_Multi, colored by class labels. ESM2 and ProT5 exhibit overlapping clusters, while ProTrek, leveraging contrastive alignment, shows distinct boundaries. This highlights the importance of semantic alignment in pretraining for capturing functional relationships.

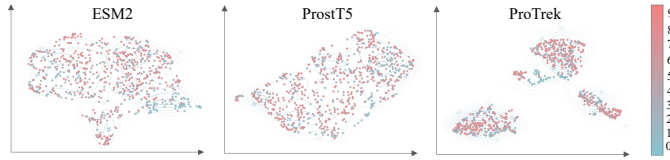


Figure 4: UMAP visualization of ESM2, ProT5, and ProTrek on Deeploc2_Multi.

MSA Mutual Information. We compute the Mutual Information Difference (MID) for sequence-only models relative to ESM2-35M across 100 MSA clusters (see Appendix A.4 for MID definition). MSA centers are randomly sampled from UniRef30 Suzek et al. (2015), with mmseq2 Steinegger & Söding (2017) used for top-10 MSA searches. Figure 5 shows that ProTrek and larger ESM models achieve higher MID, consistent with their downstream performance, suggesting that PLMs effectively clustering local MSA.

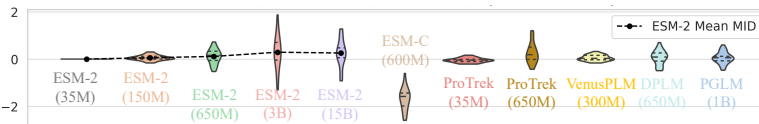


Figure 5: The MID distribution of sequence-only models relative to ESM2-35M.

4.3 OPTIMAL EFFICIENT FINE-TUNING AND SCALING (Q3 & Q4)

Table 5 presents the performance of the top-2 models alongside the ESM2 baseline on 11 representative tasks using various efficient fine-tuning methods, including Adapter, Linear Probing, LoRA, AdaLoRA, DoRA, and IA3. For each fine-tuning method, we calculate the winning rate (#WESM) against ESM2. Additionally, across different fine-tuning methods, we compute the winning rate (#WAdap) against the adapter tuning method for each model. We observe that:

- **Adapter Tuning is Sufficiently Effective.** The adapter tuning method consistently outperforms other fine-tuning methods across all models, except for DoRA.
- **ProTrek Consistently Outperforms ESM2.** ProTrek achieves the best performance across all fine-tuning methods, with a winning rate of 75% to 88% against ESM2.

Table 5: Results on 11 representative tasks using various efficient fine-tuning methods. PEFT methods that outperform the Adapter are marked in red; the others are marked in blue.

	PDBBind	BindingDB	Stability	Anti. Res.	Mat. Prod.	EC	M. I. Bin	Sec. Str.	DL2 Multi	Clo. CLF	DeepSol	#WESM	#WAdap
Adapter													
ESM-2	0.14677	0.13692	0.32112	0.63422	0.81189	0.73578	0.71170	0.76375	0.76191	0.80586	0.84494	–	–
ProstT5	0.18344	0.16642	0.13032	0.69027	0.81622	0.76829	0.72145	0.81397	0.73190	0.79853	0.81937	63%	–
ProTrek	0.17322	0.19230	0.04924	0.59292	0.81477	0.76408	0.80362	0.77363	0.83944	0.82612	0.83427	75%	–
Linear Probing													
ESM-2	0.21766	0.16427	0.04649	0.64307	0.81586	0.61163	0.71309	0.71846	0.74472	0.78807	0.79465	–	38%
ProstT5	0.24874	0.16144	0.05228	0.67552	0.80541	0.65167	0.66992	0.79928	0.70530	0.78722	0.77794	38%	0%
ProTrek	0.22595	0.25353	0.02332	0.63717	0.81766	0.64201	0.69777	0.73840	0.77847	0.80099	0.80312	75%	25%
LoRA													
ESM-2	0.18463	0.24559	0.32304	0.61652	0.80865	0.67146	0.69499	0.74305	0.76851	0.83616	0.86160	–	38%
ProstT5	0.19072	0.21411	0.28204	0.66077	0.81658	0.72779	0.64485	0.80878	0.77875	0.82997	0.84834	63%	0%
ProTrek	0.24707	0.19302	0.2776	0.67257	0.84324	0.71139	0.74373	0.76687	0.79566	0.83441	0.86326	88%	50%
AdaLoRA													
ESM-2	0.20398	0.23794	0.26715	0.60767	0.80829	0.68715	0.71448	0.7436	0.77209	0.84171	0.85077	–	50%
ProstT5	0.21487	0.07897	0.17776	0.68142	0.82883	0.71974	0.66156	0.80755	0.75642	0.82935	0.85272	63%	50%
ProTrek	0.24625	0.22491	0.15328	0.64307	0.83640	0.7384	0.68524	0.76651	0.80497	0.83713	0.86152	75%	50%
DoRA													
ESM-2	0.18497	0.20087	0.33022	0.63717	0.82739	0.68786	0.72006	0.74357	0.77774	0.84471	0.86346	–	75%
ProstT5	0.23039	0.10505	0.26731	0.69912	0.80000	0.70583	0.66574	0.80813	0.77520	0.83052	0.85343	38%	50%
ProTrek	0.23648	0.07242	0.25293	0.60177	0.83387	0.71772	0.72006	0.76710	0.80063	0.83988	0.86625	63%	75%
IA3													
ESM-2	0.18948	0.19144	0.09641	0.60177	0.79928	0.68549	0.63231	0.74286	0.76447	0.82562	0.83062	–	25%
ProstT5	0.24188	0.12700	0.04821	0.66962	0.82342	0.71467	0.71309	0.81016	0.74326	0.78942	0.80635	63%	25%
ProTrek	0.23836	0.10734	0.06299	0.59292	0.79676	0.70588	0.71031	0.76366	0.78881	0.82911	0.83146	75%	25%

Are Scaling PLMs Truly Worth It? In Table 6, we further examine whether increasing model size improves performance on the 11 representative tasks, focusing on the ESM2 series models. We calculate the winning rate (W150M) of each model against ESM2-150M and conclude the following:

- **Scaling Up Works but Comes at a Cost.** The scaling law is effective only when models are scaled up to 15B parameters; otherwise, none of the models outperform ESM2-150M. However, this increase in model size incurs significant costs in both pretraining and inference. Considering the marginal performance gains, the cost of scaling up may not be justified.
- **Pretraining Strategies Matter More.** Instead of scaling up to 15B, a more effective and efficient approach is to optimize the pretraining strategy. For instance, ProTrek-650M outperforms ESM2-15B on 6 out of 8 tasks and achieves a winning rate of 75% against ESM2-150M.

Table 6: Performance of ESM2 under the scaling law. Gray tasks are excluded from the winning rate analysis. Models that outperform the ESM2-150M are marked in red; the others are marked in blue.

	PDBBind	Bind. DB	Stability	Anti.Res.	Mat.Pro.	EC	M. I. Bin.	Sec. Str.	DL2 M.	Clo. CLF	DeepSol	#W150M
ESM2-35M	0.09985	0.14232	0.32337	0.67552	0.78595	0.71675	0.71866	0.69609	0.73219	0.79441	0.82486	13%
ESM2-150M	0.09371	0.13142	0.33728	0.65192	0.81946	0.73192	0.76462	0.73430	0.74744	0.81531	0.82825	–
ESM2-650M	0.14677	0.13692	0.32112	0.63422	0.81189	0.73578	0.71170	0.76375	0.76191	0.80586	0.84494	50%
ESM2-3B	0.10479	0.12724	0.31647	0.64012	0.80036	0.73878	0.73955	0.77111	0.77328	0.81031	0.83007	50%
ESM2-15B	0.08427	0.12559	0.03018	0.68142	0.81045	0.73259	0.77250	0.76714	0.80210	0.85155	63%	
ProTrek-650M	0.17322	0.19230	0.04924	0.59292	0.81477	0.76408	0.80362	0.77363	0.83944	0.82612	0.83427	75%

5 CONCLUSION

This work presents a comprehensive benchmark for evaluating protein foundation models (PFMs) across a diverse range of tasks, accompanied by a streamlined evaluation protocol. Starting with 38 tasks and 17 models, we identify 12 core models and 11 representative tasks to enable efficient and meaningful evaluation. Through extensive experiments, we reveal that current PFM research exhibits a high degree of homogeneity and provide in-depth analysis to guide future research directions.

REFERENCES

- José Juan Almagro Armenteros, Casper Kaae Sønderby, Søren Kaae Sønderby, Henrik Nielsen, and Ole Winther. Deeploc: prediction of protein subcellular localization using deep learning. *Bioinformatics*, 33(21):3387–3395, 2017.
- Michael Ashburner, Catherine A Ball, Judith A Blake, David Botstein, Heather Butler, J Michael Cherry, Allan P Davis, Kara Dolinski, Selina S Dwight, Janan T Eppig, et al. Gene ontology: tool for the unification of biology. *Nature genetics*, 25(1):25–29, 2000.
- Amos Bairoch. The enzyme database in 2000. *Nucleic acids research*, 28(1):304–305, 2000.
- Andreas Bjerregaard, Peter Mørch Groth, Søren Hauberg, Anders Krogh, and Wouter Boomsma. Foundation models of protein sequences: A brief overview. *Current Opinion in Structural Biology*, 91:103004, 2025.
- Bo Chen, Xingyi Cheng, Pan Li, Yangli-ao Geng, Jing Gong, Shen Li, Zhilei Bei, Xu Tan, Boyan Wang, Xin Zeng, et al. xtrimopglm: unified 100b-scale pre-trained transformer for deciphering the language of protein. *arXiv preprint arXiv:2401.06199*, 2024.
- Jianwen Chen, Shuangjia Zheng, Huiying Zhao, and Yuedong Yang. Structure-aware protein solubility prediction from sequence through graph convolutional network and predicted contact map. *Journal of cheminformatics*, 13:1–10, 2021.
- Christian Dallago, Jody Mou, Kadina E Johnston, Bruce Wittmann, Nick Bhattacharya, Samuel Goldman, Ali Madani, and Kevin K Yang. Flip: Benchmark tasks in fitness landscape inference for proteins. In *Thirty-fifth Conference on Neural Information Processing Systems Datasets and Benchmarks Track (Round 2)*.
- Tim Dettmers, Artidoro Pagnoni, Ari Holtzman, and Luke Zettlemoyer. Qlora: Efficient finetuning of quantized llms. *Advances in neural information processing systems*, 36:10088–10115, 2023.
- Zhekai Du, Yinjie Min, Jingjing Li, Ke Lu, Changliang Zou, Liuhua Peng, Tingjin Chu, and Mingming Gong. Loca: Location-aware cosine adaptation for parameter-efficient fine-tuning. *arXiv preprint arXiv:2502.06820*, 2025.
- Ahmed Elnaggar, Michael Heinzinger, Christian Dallago, Ghalia Rehawi, 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 learning. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 44:7112–7127, 2021.
- Ahmed Elnaggar, Hazem Essam, Wafaa Salah-Eldin, Walid Moustafa, Mohamed Elkerdawy, Charlotte Rochereau, and Burkhard Rost. Ankh: Optimized protein language model unlocks general-purpose modelling. *arXiv preprint arXiv:2301.06568*, 2023.
- Hehe Fan, Zhangyang Wang, Yi Yang, and Mohan Kankanhalli. Continuous-discrete convolution for geometry-sequence modeling in proteins. In *The Eleventh International Conference on Learning Representations*, 2022.
- Noelia Ferruz, Steffen Schmidt, and Birte Höcker. Protgpt2 is a deep unsupervised language model for protein design. *Nature communications*, 13(1):4348, 2022.
- Japheth E Gado, Matthew Knotts, Ada Y Shaw, Debora Marks, Nicholas P Gauthier, Chris Sander, and Gregg T Beckham. Deep learning prediction of enzyme optimum ph. *bioRxiv*, pp. 2023–06, 2023.
- Zhangyang Gao, Cheng Tan, Yijie Zhang, Xingran Chen, Lirong Wu, and Stan Z Li. Proteininvbench: Benchmarking protein inverse folding on diverse tasks, models, and metrics. *Advances in Neural Information Processing Systems*, 36:68207–68220, 2023.
- Vanessa E Gray, Ronald J Hause, Jens Luebeck, Jay Shendure, and Douglas M Fowler. Quantitative missense variant effect prediction using large-scale mutagenesis data. *Cell systems*, 6(1):116–124, 2018.

- Fei Guo, Renchu Guan, Yaohang Li, Qi Liu, Xiaowo Wang, Can Yang, and Jianxin Wang. Foundation models in bioinformatics. *National Science Review*, pp. nwaf028, 2025.
- Yanzhi Guo, Lezheng Yu, Zhining Wen, and Menglong Li. Using support vector machine combined with auto covariance to predict protein–protein interactions from protein sequences. *Nucleic acids research*, 36(9):3025–3030, 2008.
- Sarah Gurev, Noor Youssef, Navami Jain, and Debora Susan Marks. Sequence-based protein models for the prediction of mutations across priority viruses. In *ICLR 2025 Workshop on Generative and Experimental Perspectives for Biomolecular Design*.
- Thomas Hayes, Roshan Rao, Halil Akin, Nicholas J Sofroniew, Deniz Oktay, Zeming Lin, Robert Verkuil, Vincent Q Tran, Jonathan Deaton, Marius Wiggert, et al. Simulating 500 million years of evolution with a language model. *Science*, pp. eads0018, 2025.
- Junxian He, Chunting Zhou, Xuezhe Ma, Taylor Berg-Kirkpatrick, and Graham Neubig. Towards a unified view of parameter-efficient transfer learning. In *International Conference on Learning Representations*.
- Kaiming He, Xiangyu Zhang, Shaoqing Ren, and Jian Sun. Deep residual learning for image recognition. In *Proceedings of the IEEE conference on computer vision and pattern recognition*, pp. 770–778, 2016.
- Michael Heinzinger, Konstantin Weissenow, Joaquin Gomez Sanchez, Adrian Henkel, Milot Mirdita, Martin Steinegger, and Burkhard Rost. Bilingual language model for protein sequence and structure. *NAR Genomics and Bioinformatics*, 6(4):lqae150, 2024.
- Sepp Hochreiter and Jürgen Schmidhuber. Long short-term memory. *Neural computation*, 9(8): 1735–1780, 1997.
- Neil Houlsby, Andrei Giurgiu, Stanislaw Jastrzebski, Bruna Morrone, Quentin De Laroussilhe, Andrea Gesmundo, Mona Attariyan, and Sylvain Gelly. Parameter-efficient transfer learning for nlp. In *International conference on machine learning*, pp. 2790–2799. PMLR, 2019.
- Bozhen Hu, Cheng Tan, Lirong Wu, Jiangbin Zheng, Jun Xia, Zhangyang Gao, Zicheng Liu, Fandi Wu, Guijun Zhang, and Stan Z Li. Advances of deep learning in protein science: a comprehensive survey. *arXiv preprint arXiv:2403.05314*, 2024a.
- Bozhen Hu, Cheng Tan, Jun Xia, Yue Liu, Lirong Wu, Jiangbin Zheng, Yongjie Xu, Yufei Huang, and Stan Z Li. Learning complete protein representation by dynamically coupling of sequence and structure. *Advances in Neural Information Processing Systems*, 37:137673–137697, 2024b.
- Edward J Hu, Yelong Shen, Phillip Wallis, Zeyuan Allen-Zhu, Yuanzhi Li, Shean Wang, Lu Wang, Weizhu Chen, et al. Lora: Low-rank adaptation of large language models. *ICLR*, 1(2):3, 2022a.
- Mingyang Hu, Fajie Yuan, Kevin Yang, Fusong Ju, Jin Su, Hui Wang, Fei Yang, and Qiuyang Ding. Exploring evolution-aware &-free protein language models as protein function predictors. *Advances in Neural Information Processing Systems*, 35:38873–38884, 2022b.
- Chenqing Hua, Bozitao Zhong, Sitao Luan, Liang Hong, Guy Wolf, Doina Precup, and Shuangjia Zheng. Reactzyme: A benchmark for enzyme-reaction prediction. *Advances in Neural Information Processing Systems*, 37:26415–26442, 2024.
- Anna Jarzab, Nils Kurzawa, Thomas Hopf, Matthias Moerch, Jana Zecha, Niels Leijten, Yangyang Bian, Eva Musiol, Melanie Maschberger, Gabriele Stoehr, et al. Meltome atlas—thermal proteome stability across the tree of life. *Nature methods*, 17(5):495–503, 2020.
- Sameer Khurana, Reda Rawi, Khalid Kunji, Gwo-Yu Chuang, Halima Bensmail, and Raghvendra Mall. Deepsol: a deep learning framework for sequence-based protein solubility prediction. *Bioinformatics*, 34(15):2605–2613, 2018.

- Michael Schantz Klausen, Martin Closter Jespersen, Henrik Nielsen, Kamilla Kjaergaard Jensen, Vanessa Isabell Jurtz, Casper Kaae Soenderby, Morten Otto Alexander Sommer, Ole Winther, Morten Nielsen, Bent Petersen, et al. Netsurfp-2.0: Improved prediction of protein structural features by integrated deep learning. *Proteins: Structure, Function, and Bioinformatics*, 87(6): 520–527, 2019.
- Kyohei Koyama, Kosuke Hashimoto, Chioko Nagao, and Kenji Mizuguchi. Attention network for predicting t-cell receptor–peptide binding can associate attention with interpretable protein structural properties. *Frontiers in Bioinformatics*, 3:1274599, 2023.
- Brian Lester, Rami Al-Rfou, and Noah Constant. 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, 2021.
- Feiran Li, Le Yuan, Hongzhong Lu, Gang Li, Yu Chen, Martin KM Engqvist, Eduard J Kerkhoven, and Jens Nielsen. Deep learning-based k cat prediction enables improved enzyme-constrained model reconstruction. *Nature Catalysis*, 5(8):662–672, 2022a.
- Gang Li, Filip Buric, Jan Zrimec, Sandra Viknander, Jens Nielsen, Aleksej Zelezniak, and Martin KM Engqvist. Learning deep representations of enzyme thermal adaptation. *Protein Science*, 31(12): e4480, 2022b.
- Qing Li, Zhihang Hu, Yixuan Wang, Lei Li, Yimin Fan, Irwin King, Gengjie Jia, Sheng Wang, Le Song, and Yu Li. Progress and opportunities of foundation models in bioinformatics. *Briefings in Bioinformatics*, 25(6):bbae548, 2024.
- Xiang Lisa Li and Percy Liang. Prefix-tuning: Optimizing continuous prompts for generation. 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. 4582–4597, 2021.
- Zeming Lin, Halil Akin, Roshan Rao, Brian Hie, Zhongkai Zhu, Wenting Lu, Nikita Smetanin, Robert Verkuil, Ori Kabeli, Yaniv Shmueli, et al. Evolutionary-scale prediction of atomic-level protein structure with a language model. *Science*, 379(6637):1123–1130, 2023.
- Haokun Liu, Derek Tam, Mohammed Muqeeth, Jay Mohta, Tenghao Huang, Mohit Bansal, and Colin A Raffel. Few-shot parameter-efficient fine-tuning is better and cheaper than in-context learning. *Advances in Neural Information Processing Systems*, 35:1950–1965, 2022.
- Tiqing Liu, Yuhmei Lin, Xin Wen, Robert N Jorissen, and Michael K Gilson. Bindingdb: a web-accessible database of experimentally determined protein–ligand binding affinities. *Nucleic acids research*, 35(suppl.1):D198–D201, 2007.
- Zhihai Liu, Minyi Su, Li Han, Jie Liu, Qifan Yang, Yan Li, and Renxiao Wang. Forging the basis for developing protein–ligand interaction scoring functions. *Accounts of chemical research*, 50(2): 302–309, 2017.
- Loredana Lo Conte, Bart Ailey, Tim JP Hubbard, Steven E Brenner, Alexey G Murzin, and Cyrus Chothia. Scop: a structural classification of proteins database. *Nucleic acids research*, 28(1): 257–259, 2000.
- Liuzhenghao Lv, Zongying Lin, Hao Li, Yuyang Liu, Jiayi Cui, Calvin Yu-Chian Chen, Li Yuan, and Yonghong Tian. Prollama: A protein large language model for multi-task protein language processing. *IEEE Transactions on Artificial Intelligence*, 2025.
- Ali Madani, Ben Krause, Eric R Greene, Subu Subramanian, Benjamin P Mohr, James M Holton, Jose Luis Olmos Jr, Caiming Xiong, Zachary Z Sun, Richard Socher, et al. Large language models generate functional protein sequences across diverse families. *Nature biotechnology*, 41(8): 1099–1106, 2023.
- Sourab Mangrulkar, Sylvain Gugger, Lysandre Debut, Younes Belkada, Sayak Paul, and Benjamin Bossan. Peft: State-of-the-art parameter-efficient fine-tuning methods. <https://github.com/huggingface/peft>, 2022.

- Yulong Mao, Kaiyu Huang, Changhao Guan, Ganglin Bao, Fengran Mo, and Jinan Xu. Dora: Enhancing parameter-efficient fine-tuning with dynamic rank distribution. In *Proceedings of the 62nd Annual Meeting of the Association for Computational Linguistics (Volume 1: Long Papers)*, pp. 11662–11675, 2024.
- David McAllester and Karl Stratos. Formal limitations on the measurement of mutual information. In *International Conference on Artificial Intelligence and Statistics*, pp. 875–884. PMLR, 2020.
- Iain H Moal and Juan Fernández-Recio. Skempi: a structural kinetic and energetic database of mutant protein interactions and its use in empirical models. *Bioinformatics*, 28(20):2600–2607, 2012.
- Erik Nijkamp, Jeffrey A Ruffolo, Eli N Weinstein, Nikhil Naik, and Ali Madani. Progen2: exploring the boundaries of protein language models. *Cell systems*, 14(11):968–978, 2023.
- Pascal Notin, Aaron Kollasch, Daniel Ritter, Lood Van Niekerk, Steffanie Paul, Han Spinner, Nathan Rollins, Ada Shaw, Rose Orenbuch, Ruben Weitzman, et al. Proteingym: Large-scale benchmarks for protein fitness prediction and design. *Advances in Neural Information Processing Systems*, 36: 64331–64379, 2023.
- Xiao-Yong Pan, Ya-Nan Zhang, and Hong-Bin Shen. Large-scale prediction of human protein-protein interactions from amino acid sequence based on latent topic features. *Journal of proteome research*, 9(10):4992–5001, 2010.
- Jonas Pfeiffer, Aishwarya Kamath, Andreas Rücklé, Kyunghyun Cho, and Iryna Gurevych. Adapter-fusion: Non-destructive task composition for transfer learning. *arXiv preprint arXiv:2005.00247*, 2020.
- Ben Poole, Sherjil Ozair, Aaron Van Den Oord, Alex Alemi, and George Tucker. On variational bounds of mutual information. In *International conference on machine learning*, pp. 5171–5180. PMLR, 2019.
- Owen Queen, Yepeng Huang, Robert Calef, Valentina Giunchiglia, Tianlong Chen, George Dasoulas, LeAnn Tai, Yasha Ektefaie, Ayush Noori, Joseph Brown, et al. Procyon: A multimodal foundation model for protein phenotypes. *BioRxiv*, pp. 2024–12, 2024.
- 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.
- Martin Steinegger and Johannes Söding. Mmseqs2 enables sensitive protein sequence searching for the analysis of massive data sets. *Nature biotechnology*, 35(11):1026–1028, 2017.
- Jin Su, Chenchen Han, Yuyang Zhou, Junjie Shan, Xibin Zhou, and Fajie Yuan. Saprot: Protein language modeling with structure-aware vocabulary. In *The Twelfth International Conference on Learning Representations*.
- Jin Su, Xibin Zhou, Xuting Zhang, and Fajie Yuan. Protrek: Navigating the protein universe through tri-modal contrastive learning. *bioRxiv*, pp. 2024–05, 2024.
- Baris E Suzek, Yuqi Wang, Hongzhan Huang, Peter B McGarvey, Cathy H Wu, and UniProt Consortium. Uniref clusters: a comprehensive and scalable alternative for improving sequence similarity searches. *Bioinformatics*, 31(6):926–932, 2015.
- Yang Tan, Mingchen Li, Ziyi Zhou, Pan Tan, Huiqun Yu, Guisheng Fan, and Liang Hong. Peta: evaluating the impact of protein transfer learning with sub-word tokenization on downstream applications. *Journal of Cheminformatics*, 16(1):92, 2024a.

- Yang Tan, Jia Zheng, Liang Hong, and Bingxin Zhou. Protsolm: Protein solubility prediction with multi-modal features. In *2024 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, pp. 223–232. IEEE, 2024b.
- Yang Tan, Chen Liu, Jingyuan Gao, Banghao Wu, Mingchen Li, Ruilin Wang, Lingrong Zhang, Huiqun Yu, Guisheng Fan, Liang Hong, et al. Venusfactory: A unified platform for protein engineering data retrieval and language model fine-tuning. *arXiv preprint arXiv:2503.15438*, 2025.
- Vineet Thummuluri, José Juan Almagro Armenteros, Alexander Rosenberg Johansen, Henrik Nielsen, and Ole Winther. Deeploc 2.0: multi-label subcellular localization prediction using protein language models. *Nucleic acids research*, 50(W1):W228–W234, 2022.
- Michael Tschannen, Josip Djolonga, Paul K Rubenstein, Sylvain Gelly, and Mario Lucic. On mutual information maximization for representation learning. In *International Conference on Learning Representations*.
- Matsvei Tsishyn, Pauline Hermans, Marianne Rooman, and Fabrizio Pucci. Residue conservation and solvent accessibility are (almost) all you need for predicting mutational effects in proteins. *Bioinformatics*, 41(6):btaf322, 2025.
- Mihaly Varadi, Stephen Anyango, Mandar Deshpande, Sreenath Nair, Cindy Natassia, Galabina Yordanova, David Yuan, Oana Stroe, Gemma Wood, Agata Laydon, et al. Alphafold protein structure database: massively expanding the structural coverage of protein-sequence space with high-accuracy models. *Nucleic acids research*, 50(D1):D439–D444, 2022.
- Ashish Vaswani, Noam Shazeer, Niki Parmar, Jakob Uszkoreit, Llion Jones, Aidan N Gomez, Łukasz Kaiser, and Illia Polosukhin. Attention is all you need. *NeurIPS*, 30, 2017.
- Chao Wang and Quan Zou. Prediction of protein solubility based on sequence physicochemical patterns and distributed representation information with deepsolue. *BMC biology*, 21(1):12, 2023.
- Huilin Wang, Mingjun Wang, Hao Tan, Yuan Li, Ziding Zhang, and Jiangning Song. Predppcrys: accurate prediction of sequence cloning, protein production, purification and crystallization propensity from protein sequences using multi-step heterogeneous feature fusion and selection. *PloS one*, 9(8):e105902, 2014.
- Wenkang Wang, Yunyan Shuai, Qirong Yang, Fuhao Zhang, Min Zeng, and Min Li. A comprehensive computational benchmark for evaluating deep learning-based protein function prediction approaches. *Briefings in Bioinformatics*, 25(2):bbae050, 2024a.
- Xinyou Wang, Zaixiang Zheng, Fei Ye, Dongyu Xue, Shujian Huang, and Quanquan Gu. Diffusion language models are versatile protein learners. In *International Conference on Machine Learning*, pp. 52309–52333. PMLR, 2024b.
- Xun Wu, Shaohan Huang, and Furu Wei. Mixture of lora experts. *arXiv preprint arXiv:2404.13628*, 2024.
- Yejian Wu, Lujing Cao, Zhipeng Wu, Xinyi Wu, Xinqiao Wang, and Hongliang Duan. Ccbhla: pan-specific peptide–hla class i binding prediction via convolutional and bilstm features. *bioRxiv*, pp. 2023–04, 2023.
- Minghao Xu, Zuobai Zhang, Jiarui Lu, Zhaocheng Zhu, Yangtian Zhang, Ma Chang, Runcheng Liu, and Jian Tang. Peer: a comprehensive and multi-task benchmark for protein sequence understanding. *Advances in Neural Information Processing Systems*, 35:35156–35173, 2022.
- Minghao Xu, Xinyu Yuan, Santiago Miret, and Jian Tang. Protst: Multi-modality learning of protein sequences and biomedical texts. In *International Conference on Machine Learning*, pp. 38749–38767. PMLR, 2023.
- Jason Yang, Ariane Mora, Shengchao Liu, Bruce Wittmann, Animashree Anandkumar, Frances Arnold, and Yisong Yue. Care: a benchmark suite for the classification and retrieval of enzymes. *Advances in Neural Information Processing Systems*, 37:3094–3121, 2024.

- Jianyi Yang, Ivan Anishchenko, Hahnbeom Park, Zhenling Peng, Sergey Ovchinnikov, and David Baker. Improved protein structure prediction using predicted interresidue orientations. *Proceedings of the National Academy of Sciences*, 117(3):1496–1503, 2020.
- Fei Ye, Zaixiang Zheng, Dongyu Xue, Yuning Shen, Lihao Wang, Yiming Ma, Yan Wang, Xinyou Wang, Xiangxin Zhou, and Quanquan Gu. Proteinbench: A holistic evaluation of protein foundation models. *arXiv preprint arXiv:2409.06744*, 2024.
- Elad Ben Zaken, Yoav Goldberg, and Shauli Ravfogel. Bitfit: Simple parameter-efficient fine-tuning for transformer-based masked language-models. In *Proceedings of the 60th Annual Meeting of the Association for Computational Linguistics*, pp. 1–9, 2022.
- Ningyu Zhang, Zhen Bi, Xiaozhuan Liang, Siyuan Cheng, Haosen Hong, Shumin Deng, Qiang Zhang, Jiazhang Lian, and Huajun Chen. Ontoprotein: Protein pretraining with gene ontology embedding. In *International Conference on Learning Representations*, a.
- Qingru Zhang, Minshuo Chen, Alexander Bukharin, Nikos Karampatziakis, Pengcheng He, Yu Cheng, Weizhu Chen, and Tuo Zhao. Adalora: Adaptive budget allocation for parameter-efficient fine-tuning. *arXiv preprint arXiv:2303.10512*, 2023.
- Zuobai Zhang, Minghao Xu, Arian Rokkum Jamasb, Vijil Chenthamarakshan, Aurelie Lozano, Payel Das, and Jian Tang. Protein representation learning by geometric structure pretraining. In *The Eleventh International Conference on Learning Representations*, b.
- Hanjing Zhou, Mingze Yin, Wei Wu, Mingyang Li, Kun Fu, Jintai Chen, Jian Wu, and Zheng Wang. Protclip: Function-informed protein multi-modal learning. In *Proceedings of the AAAI Conference on Artificial Intelligence*, volume 39, pp. 22937–22945, 2025.
- Ziyi Zhou, Liang Zhang, Yuanxi Yu, Banghao Wu, Mingchen Li, Liang Hong, and Pan Tan. Enhancing efficiency of protein language models with minimal wet-lab data through few-shot learning. *Nature Communications*, 15(1):5566, 2024.