SaprotHub: Making Protein Modeling Accessible to All Biologists

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Abstract

Training and deploying deep learning models present challenges for users without Machine Learning (ML) expertise. SaprotHub offers a user-friendly platform for training, utilizing and sharing protein models, fostering collaboration within the biologist community - all with just a few clicks, regardless of ML background. At its core, Saprot or ColabSaprot serves as a near-universal protein language model, showcasing superior performance across various protein prediction tasks.

Proteins, the building blocks of life, are indispensable for a myriad of biological processes, serving as the linchpin in medical breakthroughs, pharmaceutical innovations, and genetic discoveries. Despite their significance, unraveling the intricate structure and function of proteins has remained a formidable puzzle within the scientific community. The triumph of AlphaFold2 [8] in CASP14 heralds a groundbreaking era in structural biology by achieving atom-level protein structure prediction. Concurrently, significant progress is being made in protein function prediction, driven by the emergence of large-scale protein language models.

Notably, several advancements have been made in this field, including the ESM models [18, 10, 35, 40], ProtTrans [3], UniRep [2], ProGen [11, 14], and ProtGPT2 [4],

This is the conference extended version of our Saprot paper [19]

each demonstrating remarkable efficacy in their respective tasks. However, training and deploying these machine learning (ML) models for proteins pose a significant challenge for researchers without ML expertise. These challenges encompass a spectrum of complexities, such as selecting suitable model architectures, managing the nuances of coding, preprocessing extensive datasets, training model parameters, and evaluating or interpreting outputs. Such inherent complexity often serves as a deterrent for non-ML researchers, hindering their active involvement in this domain, particularly in the era when large foundation AI models are increasingly complex.

Given these challenges, ColabFold [13] emerges as a pioneering initiative by deploying AlphaFold2 predictions on the Google Colaboratory, making protein folding accessible to researchers of all backgrounds. However, ColabFold merely emphasizes model inference, lacking support for researchers in the more complex tasks of training their own ML models. Furthermore, its focus is limited to protein structure tasks and does not encompass protein function prediction.

In response to this need, we present SaprotHub, an easy-to-use platform akin to ColabFold but tailored specifically for protein function prediction. SaprotHub empowers researchers by enabling them to create and train their own models without the need for advanced ML and coding expertise. Moreover, SaprotHub distinguishes itself by its commitment to supporting a broad range of protein function predictions, rather than being confined to specific functions.

Furthermore, we introduce the concept of the 'Open Protein Modeling Consortium (OPMC)' (see Supplementary), which aims to unify resources and efforts across the entire protein community. Within the framework of OPMC, researchers can easily share their individually trained models, facilitating the direct utilization of existing models and enabling continuous model learning and improvements through collaborative efforts. SaprotHub is designed to bring this vision to fruition, marking a significant stride towards the realization of OPMC.

SaprotHub consists of three parts: a universal protein language model called Saprot (Fig. 1a,b), ColabSaprot (Fig. 2a,b,c) for Saprot fine-tuning and inference by implementing adapter learning techniques [7] on the Colab platform, and an open community store (Fig. 2d) for the saving, sharing, retrieval, and collaboration of fine-tuned Saprot models. Through innovative integration of foundation protein models, Colab cloud computing technology, and adapter-based fine-tuning techniques, SaprotHub effectively overcomes several key challenges. These include the difficulty of model sharing and aggregation due to its large parameter scale, potential model catastrophic forgetting from continual learning, and the necessity to protect proprietary data owned by biologists.

Saprot is a large-scale protein foundation model that underpins SaprotHub. Its distinctive aspect lies in pioneering the introduction of a Structure-Aware (SA) protein representation method, departing from conventional amino acid sequences or 3D coordinate structural representations. Specifically, we introduce a SA vocabulary (SAV) for proteins, where $SAV = \{\mathcal{V}, \mathcal{F}\}$ represents the Cartesian product of $\mathcal{V}$ and $\mathcal{F}$, with $\mathcal{V}$ denoting the 20 Amino Acids (AA) and $\mathcal{F}$ denoting the 20-letter structural alphabet (a.k.a. 3Di) (Fig. 1a). The 3Di tokens are derived from encoding the 3D structures of proteins using Foldseek [21]. The SA token encompasses all combinations of AA and

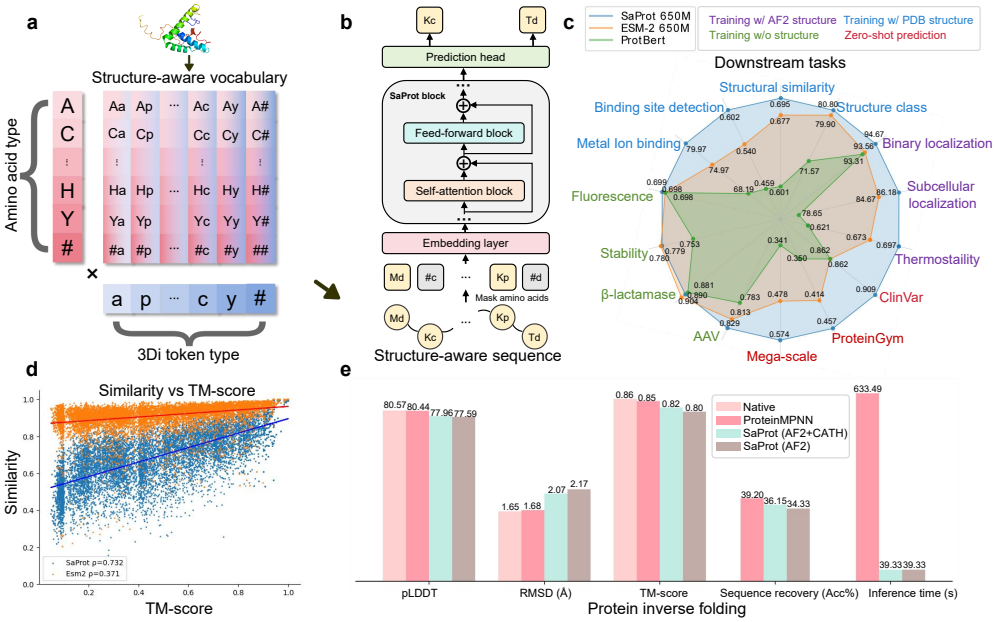

Fig. 1: **Illustration of Saprot. a,** The SA alphabet used in Saprot encodes both AA type and 3Di state. #a, #p,...,#y represent only the 3Di token being visible, while A#, C#,..., Y# represent the AA token being visible. **b,** neural architecture and pre-training strategy of Saprot. Saprot was pre-trained to predict the complete SA token based on the partially masked SA token and its surrounding context. **c,** Saprot shows state-of-the-art performance on over 10 diverse prediction tasks. **d,** comparison of Saprot and ESM-2 in structural representation ability. The y-axis represents the cosine similarity score of the last layer representation for every pair of proteins, while the x-axis represents the TM-score of the protein pairs. Saprot shows higher Pearson correlation coefficient (ρ) between x and y axes, indicating more accurate protein structure encoding. **e,** while not explicitly a generative model, Saprot matches ProteinMPNN's accuracy in inverse folding and has much faster inference speed due to parallel residue prediction at all positions. Saprot (AF2+CATH) indicates that it was pre-trained using AlphaFold2 predicted structures and fine-tuned with experimental structures from the CATH dataset. CATH is also used for training ProteinMPNN.

3Di types in SAV, such as $Aa, Ap, Ac, ..., Ya, Yp, Yy$, etc. With SAV, proteins can be represented as a string of these newly developed SA tokens, capturing both their primary and tertiary structure.

The neural network architecture of Saprot (Fig. 1b) adopts the popular bidirectional Transformer block, identical to ESM-2 [10]. During the pre-training process, Saprot takes SA sequences as input, partially masks a few randomly selected SA tokens, and predicts the complete form of these masked tokens (see Methods and Fig. 1b). With 650 million parameters, Saprot was trained from scratch on approximately 40 million protein SA sequences over a duration of three months, employing

64 NVIDIA 80G A100 GPUs, similar to the compute used for training ESM-2 (650M) and AlphaFold3 [1]. The protein structure used to represent the SA sequence during training is predicted using AlphaFold2 [8].

After training, Saprot becomes a nearly universal protein language model, adeptly addressing a wide array of prominent protein prediction tasks, including supervised prediction, zero-shot prediction, and protein inverse folding. In supervised prediction, Saprot tackles a spectrum of classification and regression tasks, spanning both protein-level (e.g., fluorescence, thermostability, structure, and folding class prediction) and residue-level challenges (e.g., binding site detection), while also facilitating prediction of protein-protein similarity and interaction. In zero-shot prediction scenarios, Saprot can be used in protein engineering, enabling predictions of enzyme activity and viral mutation fitness without requiring additional fine-tuning. Moreover, it excels in predicting disease variant effects and identifying driver mutations. While not explicitly designed as a generative model, Saprot can still show remarkable proficiency in protein inverse folding (Fig. 1e). This versatility allows a single model to support numerous tasks, much like a tree bearing diverse fruits, facilitating community collaboration and co-construction within this framework.

Fig. 1c illustrates Saprot's clear dominance across more than 10 critical tasks in comparison to ESM-2 [10] and ProtBert[3], two of the most prominent protein language models. Even in scenarios where it's not feasible to input available protein structures (either experimentally determined or predicted by AlphaFold2), Saprot remains competitive (tasks marked in green). Notably, Saprot substantially outperforms ESM-2 in three zero-shot mutational effect prediction tasks (Mega-scale [20]: 0.574 vs. 0.478, ProteinGym [15]: 0.457 vs. 0.414, ClinVar [9]: 0.909 vs. 0.862). Saprot also ranked first on the public blind ProteinGym leaderboard (Supplementary Fig. 1), surpassing over 60 well-known baselines, including ESM-2 (650M, 3B, 15B), EVE [28], ESM-1v [35], MSA Transformer [40], ESM-IF [6], DeepSequence [17], UniRep, etc. Supplementary Table 2, 3 provides more baseline comparisons, and Supplementary Fig. 3 provides a case study of the protein inverse folding task.

ColabSaprot integrates pre-trained Saprot as its core model and leverages Google Colab's robust infrastructure for seamless deployment and execution. This eliminates the need for environment setup and code debugging, enabling researchers to initiate training sessions effortlessly with just a few clicks (Fig. 2a). It also ensures scalability and resource availability, facilitating efficient model training without hardware constraints. Additionally, ColabSaprot exposes advanced settings, allowing researchers to customize training hyper-parameters, code, and data to suit their specific needs.

ColabSaprot supports all tasks within the Saprot framework, enabling direct utilization for tasks such as zero-shot mutational effect prediction and protein inverse folding. For supervised tasks, users are required to fine-tune ColabSaprot using their own data. We introduce a parameter-efficient fine-tuning technique by integrating lightweight adapter networks into the ColabSaprot model (Fig. 2b) (see Methods). During training, only the adapter parameters in ColabSaprot are updated, resulting

Note that the checkpoint of our Saprot model was released on Hugging Face in October 2023. Saprot remains in first place on the ProteinGym leaderboard until the end of May 2024.

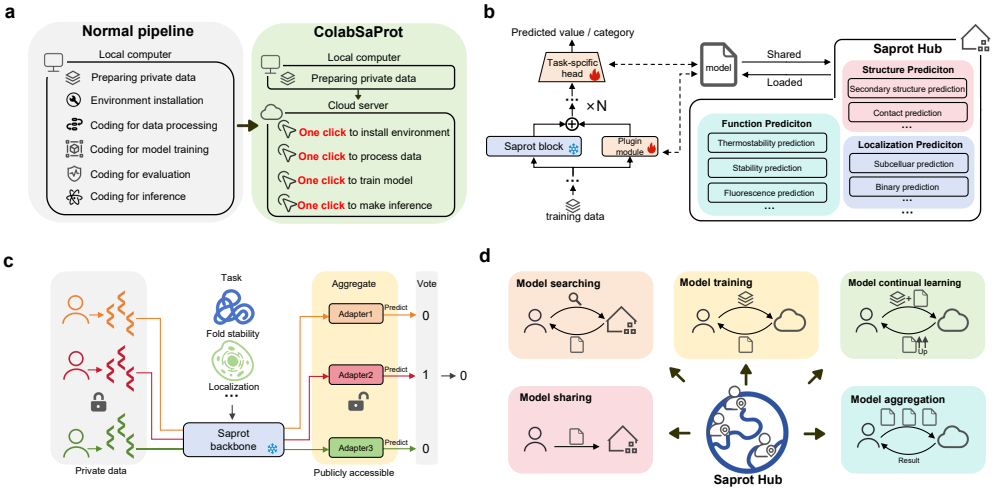

Fig. 2: **Schematic diagram of ColabSaprot and SaprotHub. a,** comparison of model training and inferring between normal pipeline and ColabSaprot. ColabSaprot streamlines the process, offering simplified procedures for model training and inference with just a few clicks. **b,** a lightweight plugin module (i.e., adapter) is inserted into Saprot for efficient training, sharing and co-construction. **c,** ColabSaprot predicts protein functions by aggregating existing models (or adapters) in SaprotHub. **d,** SaprotHub enables biologists to share, co-build and collaborate within the community.

in nearly identical accuracy compared to fine-tuning all Saprot parameters (Supplementary Fig. 5). This design not only enhances optimization efficiency [22, 43], but also, more significantly, as first proposed in this work, cultivates collaborative development of various Saprot models within the research community (Fig. 2c). Researchers can easily store and exchange their re-trained Saprot models on SaprotHub, accessing existing models by simply loading or uploading adapter networks (Fig. 2d). Given that adapter networks contain much fewer parameters, often around 1% of Saprot's, this method significantly reduces storage, communication, and management burdens on SaprotHub, making accessibility and co-construction possible for a broader scientific community.

SaprotHub also offers an open store for seamless sharing and co-construction of trained Saprot models within the biology community (Fig. 2d). Through the ColabSaprot interface, it enables advanced functionalities such as model saving, searching, sharing, continual learning and aggregation for better performance. This brings two primary benefits to SaprotHub: (1) allowing biologists to share models without compromising private data, thereby overcoming data sharing challenges, and (2) enabling biologists to continually train models based on shared models from peers. This is particularly valuable when data availability is limited as fine-tuning on a superior pre-trained model typically improves predictive accuracy. In the future, as more biologists join SaprotHub, multiple Saprot models will be submitted for the same protein function. For a new user, ColabSaprot can easily build upon existing Saprot models

through adapter aggregation (Fig. 2c,d), thereby enhancing predictive performance. (Supplementary Fig 2).

SaprotHub and ColabSaprot enable biology researchers to effortlessly train top-notch models. Additionally, they facilitate seamless model sharing within the scientific community, promoting collaboration and knowledge exchange. We have open-sourced the code for both Saprot and ColabSaprot, enabling other protein foundation models to adopt a similar approach or alternatively become part of SaprotHub.

Aligned with the OPMC vision, our goal is to inspire and foster the community-wide development of protein modeling through SaprotHub. We envision SaprotHub as the catalyst that initiates OPMC, driving innovation and collaboration in the field.

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Methods

Constructing SA Protein Sequence

The Structure-Aware (SA) vocabulary encompasses both residue and structure information, as illustrated in Fig. 1**a**. Given a protein P, its primary sequence can be denoted as $(s_1, s_2, ..., s_n)$, where $s_i \in \mathcal{V}$ represents the residue at the i_{th} site, and $\mathcal{V}$ represents residue alphabet. Drawing inspiration from the vector quantization learning technique [45], we can can encode protein tertiary structures into discrete residue-like structural tokens. Here, we use Foldseek [21], a purpose-built software. Through Foldseek, we have a structure alphabet $\mathcal{F}$, wherein P is expressed as the sequence $(f_1, f_2, ..., f_n)$, with $f_j \in \mathcal{F}$ representing the 3Di token for the j_{th} residue site. To maintain simplicity, we adhere to the default configuration of Foldseek, which sets the size m of $\mathcal{F}$ to 20. We then combine the residue and structure tokens per residue site, generating a new structure-aware protein sequence $P = (s_1f_1, s_2f_2, ..., s_nf_n)$, where $s_if_i \in \mathcal{V} \times \mathcal{F}$ is the so-called SA token naturally fusing both residue and geometric conformation information. The SA-token protein sequence can then be fed into a standard Transformer encoder as basic input. It's important to note that we also introduce a mask signal "#" to both residue and structure alphabet, which results in "s_i#" and "#f_i" that indicate only residue or structure information is available. The size of the SA vocabulary is $21 \times 21 = 441$.

Saprot architecture and pre-training

Saprot employs the same network architecture and parameter size as the 650M version of ESM-2 [10], which is inspired by the BERT [27] model in the Natural Language Processing (NLP) field. The main distinction lies in the expanded embedding layer, which encompasses 441 structure-aware tokens instead of the original 20 residue tokens. This nearly identical architecture enables straightforward comparison with the ESM model.

Saprot is pre-trained with the Masked Language Modeling (MLM) objective, similar to ESM-2 and BERT. Formally, for a protein sequence $P = (s_1f_1, s_2f_2, ..., s_nf_n)$, the input and output can be represented as: $input : (s_1f_1, ..., \#f_i, ..., s_nf_n) \rightarrow output : s_if_i$ (Fig. 1b). Given that the 3Di token may not always be accurate for certain regions in predicted structures by AlphaFold2, f_i in $\#f_i$ is made visible during training to reduce the emphasis the model places on its predictions.

It is worth noting that the structures predicted by AlphaFold2 (AF2) are accompanied by confidence scores, referred to as pLDDT, which provide an assessment of the precision of atom coordinates. Therefore, we have implemented special handling for regions with low pLDDT scores. During the pre-training process, when regions with pLDDT scores lower than 70 are chosen for MLM prediction, we predict the "s_i#" token. Here, the input SA sequence is masked with the "##" token. This approach forces the model to focus on predicting the types of residues in these regions based on their context. In cases where regions with lower pLDDT scores are not selected for MLM prediction, the input still use the "s_i#" token. This ensures that the model solely relies on residue context (instead of the structural context) in these regions to

assist in predicting other tokens. For downstream task prediction phases, we maintain consistency with the training data by handling regions with lower pLDDT scores (still with 70 as threshold). Specifically, tokens within these regions are represented as "$s_i\#$", with only residue tokens being visible.

Processing pre-training data

We followed the procedures outlined in ESM-2 [10] to generate filtered protein data. Subsequently, we acquired all AF2 structures via the AlphaFoldDB website (https://alphafold.ebi.ac.uk/), utilizing the UniProt IDs of protein sequences. Proteins without structures in AlphaFoldDB were omitted for pre-training. This process yielded a collection of approximately 40 million structures. Employing Foldseek, we encoded these structures into 3Di tokens. Subsequently, we formulated structure-aware sequences by combining residue and 3Di tokens, treating them as a single SA token at each position.

Pre-training hyper-parameters

Following ESM-2 and BERT, during training, 15% of the SA tokens in each batch are masked. We replace the SA token $s_i f_i$ with the $\# f_i$ token 80% of the time, while 10% of the tokens are replaced with randomly selected tokens, and the other 10% tokens remain unchanged. For the optimization of Saprot, we adopt similar hyper-parameters to those employed in the ESM-2 training phase. Specifically, we employ the AdamW optimizer [34], setting $\beta_1 = 0.9, \beta_2 = 0.98$ and we utilize L_2 weight decay of 0.01. We gradually increase the learning rate from 0 to 4e-4 over the first 2000 steps and linearly lower it to 5e-4 from 150K steps to 1.5M steps. The overall training phase lasts approximately 3M steps. Like the ESM model, we also truncate them to a maximum of 1024 tokens, and our batch size consists of 512 sequences. Additionally, we also employ mixed precision training to train Saprot.

Baseline models

We compared Saprot to several prominent protein language models (see Supplementary Table 2,3). For supervised learning tasks, we compared Saprot with ESM-2 (the 650M version) [10], ProtBert (the BFD version) [3], MIF-ST [48], and GearNet [50]. The first two models utilize residue sequences as input, while the latter two models incorporate both residue and 3D structures as input. ESM-2 (650M) stands out as the primary baseline for comparison, given its remarkably similar model architecture, size, and training approach when compared to Saprot. ESM-2 also offers a 15 billion (B) parameter version, which can be challenging to fine-tune even on GPUs with 80G memory. Therefore, we only conducted comparisons with ESM-2 (15B) for zero-shot mutational effect prediction tasks, which can be achieved without the need for fine-tuning.

For the zero-shot mutational effect prediction task, we compare with ESM-2, ProtBert, ESM-1v [35], Tranception L (without MSA retrieval) [36], MSA Transformer

[40], and EVE [28]. These models are also state-of-the-art according to the literature. For the protein inverse folding task, we compare with the well-known baseline ProteinMPNN [26] (see Fig. 1).

Zero-shot formula

Previous sequence-based protein language models like the ESM models predict mutational effects using the log odds ratio at the mutated position. The calculation can be formalized as follows:

$$\sum_{t \in T} [logP(x_t = s_t^{mt} | x_{\setminus T}) - logP(x_t = s_t^{wt} | x_{\setminus T})] \tag{1}$$

Here T represents all mutations and $s_t \in \mathcal{V}$ is the residue type for mutant and wild-type sequence. We slightly modify the formula above to adapt to the structure-aware vocabulary, where the probability assigned to each residue corresponds to the summation of tokens encompassing that specific residue type, as shown below:

$$\sum_{t \in T} [log \sum_{f \in \mathcal{F}} P(x_t = s_t^{mt} f | x_{\setminus T}) - log \sum_{f \in \mathcal{F}} P(x_t = s_t^{wt} f | x_{\setminus T})] \tag{2}$$

Here $f \in \mathcal{F}$ is the 3Di token generated by Foldseek and $s_t f \in \mathcal{V} \times \mathcal{F}$ is the SA token in our new vocabulary.

Zero-shot benchmarks

ProteinGym [15] is an extensive set of Deep Mutational Scanning (DMS) assays, enabling thorough comparison among zero-shot predictors. We assess all baselines on the substitution branch of the ProteinGym, utilizing its provided protein structures and following the standard evaluation pipeline from the original paper. For evaluation, We adopt Spearman's rank correlation as our metric.

ClinVar [9] serves as a freely accessible and publicly available repository containing information about human genetic variants and interpretations of their significance to disease. In our analysis, we harness the data sourced from EVE [28], and filter out proteins with length greater than 1024. To enhance the reliability of our data, we opt to consider proteins with labels 1 "Gold Stars" or higher, which indicate higher credibility. Following the methodology employed in EVE, we evaluate models' performance using the AUC metric.

Mega-scale [20] uses cDNA display proteolysis to measure the thermodynamic folding stability of protein domains. Its released dataset contains all single mutations and selected double mutants of natural and de novo designed proteins. We employ Spearman's rank correlation as our metric.

For each mutation dataset, we provide all variants with the wild-type structure, as AF2 cannot distinguish the structural changes induced by single mutations. The ClinVar dataset only provides UniProt IDs, so we manually downloaded all AF2 structures and eliminated proteins without structures in AlphaFoldDB. Both ProteinGym and

Mega-scale datasets provide protein structures, either predicted from AF2 or derived from de novo design.

Supervised fine-tuning benchmarks

Fine-tuning Saprot with AF2 structure. For benchmarks lacking PDB structures, we retrieve all AF2-predicted structures using UniProt IDs. These benchmarks encompass the Thermostability task from FLIP [25] and the Localization Prediction task from DeepLoc [23]. DeepLoc consists of two branches for subcellular localization prediction: one involving 10 location categories and the other involving binary localization prediction with 2 location categories. We assess the models' performance on both branches.

Fine-tuning Saprot with PDB structure. These tasks provide experimentally determined structures as training data. We evaluate Metal Ion Binding task [31] and a series of tasks from ProteinShake [33], including Structure Class Prediction, Structural Similarity Prediction and Binding Site Detection.

Fine-tuning Saprot without structure. Saprot is specifically developed to incorporate protein structures as valuable input. However, it can still work even in scenarios where structures are not provided. In such cases, the 3Di token is masked within the SA sequence. We evaluate the Fluorescence prediction and Stability prediction tasks from the TAPE [39] benchmark, the AAV dataset from the FLIP [25] benchmark and β-lactamase landscape prediction from the PEER [47] benchmark. For a given wild type protein, its variants do not offer additional structures.

Dataset splits

In previous literature, a common practice was to partition datasets based on sequence identity. However, a recent benchmark study, ProteinShake [33], mentioned that protein structures exhibit greater conservation than protein sequences. They argue that dissimilar sequences in training and test sets may share similar structures, leading to data leakage issues. Consequently, we adopt a more strict data splitting approach proposed by ProteinShake and split the data based on structure similarity. For all datasets with structures, we employ a 70% structure similarity threshold for splitting. For those without provided structures, we still follow the original data splits.

Supervised fine-tuning hyper-parameters

We employed the AdamW [34] optimizer during fine-tuning, setting $\beta_1 = 0.9, \beta_2 = 0.98$, along with L_2 weight decay of 0.01. We use a batch size of 64 for all datasets. We empirically found that the optimal learning rate for most baselines are in the range of 1e-5 to 5e-5. For **Training with AF2 structure** and **Training with PDB structure**, the optimal learning rate was set to 5e-5, whereas for **Training without structure**, it was set to 1e-5. We fine-tuned all model parameters until convergence and selected the best checkpoints based on their performance on the validation set.

Protein inverse folding

Given the 3D coordinates of a protein backbone, protein inverse folding aims to predict residue sequences that fold into this shape. This exhibits promising applications in protein de novo design. While not particularly targeted on this task, Saprot is endowed to predict reliable residue sequences from the backbone due to the large-scale pre-training tailored for predicting masked residues based on sequence and structure contexts. To utilize Saprot for inverse folding, we first encode protein backbone into 3Di tokens $(f_1, f_2, ..., f_n)$. Then we add masks to all residue parts of SA tokens, forming a SA sequence $(\#f_1, \#f_2, ..., \#f_n)$, which serves as input for Saprot to predict residue distributions at all positions. In contrast to ProteinMPNN [26] that generates residues in the auto-regressive manner, i.e. generating next token conditioned on all previous outputs, Saprot is able to simultaneously predict all residues with only one forward propagation. As shown in Fig. 1e, in CATH [37] test set, Saprot predicts 16 times faster than ProteinMPNN, while achieves comparable prediction accuracy, which demonstrates its huge potential in protein de novo design.

Embedding visualization

We employ t-SNE [46] to visualize the protein representations generated by Saprot and ESM-2 in three datasets (Supplementary Fig. 4). We use the non-redundant version ($PIDE < 40\%$) of the SCOPe [24] database, visualizing all alpha and beta proteins. We additionally visualize proteins in Subcellular Localization and Binary Localization datasets from DeepLoc [23]. To generate protein representations, we adopt the average pooling on the embeddings of the last layer for both Saprot and ESM-2.

Adapter learning

The adapter learning technique originated in the field of NLP [30, 29, 49] and has recently garnered attention in protein-related research. However, the existing preliminary literature primarily focused on its ability in model accuracy or efficient GPU memory consumption [43, 42, 44, 41]. Through the application of adapters, researchers have observed their ability to mitigate overfitting issues or integrate domain-specific knowledge into protein language models. In this paper, we innovatively integrate it with Google Colaboratory and endow it with deeper capabilities, namely, to promote model sharing and co-construction within the biologist community in the online SaprotHub. This represents a novel perspective on the application of adapter learning. In the broad AI community, there are various types of adapters exist in the broader field of deep learning, including the well-known adapters like Houlsby [30], Pfeiffer [38], Compacter [32], and LoRA [7]. We choose LoRA for its capacity to deliver comparable results with fewer parameters. By integrating learnable low-rank matrices into each Saprot block while freezing the backbone, LoRA enables parameter-efficient fine-tuning and model sharing for these downstream tasks.

Community-wide collaboration

As the SaprotHub community expands, an increasing number of Saprot models will become available for the same protein function. This paves the way for collaborative co-construction among biologists. To illustrate this advantage (Results are provided in Supplementary Fig 2), we employ intuitive approach. In regression tasks, the final prediction is obtained by calculating the mean value of outputs from all models. For classification tasks, we aggregate predicted categories from all models and select the category with the highest prediction as the final outcome. The lightweight adapter technique plays a vital role in model aggregation, addressing the impracticality of loading and sharing multiple large pre-trained models.

Furthermore, more advanced functionalities can be developed. For instance, by injecting multiple adapters into Saprot via SaprotHub, continual learning can be conducted to further enhance performance. Adapters eliminate the need to modify the weights of the original Saprot model, effectively mitigating the issue of catastrophic forgetting. This study introduces a pioneering concept of integrating community wisdom by utilizing shared adapters, thereby ensuring the privacy of biologists' proprietary data. This design enables the realization of the OPMC vision.

ColabSaprot notebooks

ColabSaprot comprises three key components. The first component focuses on training and inference, enabling researchers to swiftly set up the runtime environment, preprocess training data, and fine-tune Saprot with ease. We offer advanced hyperparameter settings, allowing researchers to customize their training strategy based on specific requirements, such as batch size, learning rate, and training steps. After completing the training process, researchers can share the model weights on the SaprotHub community store, benefiting other biologists.

Furthermore, researchers without their own training data can directly access a range of fine-tuned Saprot models from SaprotHub and perform inference for desired protein functions. These existing models also support continual training with additional data, leading to improved prediction accuracy.

The second component focuses on the zero-shot mutational effect prediction task, enabling users to leverage Saprot for predicting fitness changes resulting from residue mutations. We provide multiple options for users to predict single mutations, multi-site mutations, or saturation mutations on given proteins.

The final component of Saprot offers support for the protein inverse folding task based on the backbone structure. Saprot achieves an impressive 16 times faster inference speed than ProteinMPNN while maintaining competitive prediction performance. This capability empowers users to conduct precise protein designs on a large scale.

Data availability

The pre-training dataset for training Saprot is available at https://huggingface.co/datasets/westlake-repl/AF2_UniRef50. Downstream task datasets are all stored at https://huggingface.co/SaProtHub.

Code and Service availability

Saprot is an open-sourced model with MIT license. The code is available at https://github.com/westlake-repl/Saprot. The code implementation of Colab-Saprot notebook is available at https://github.com/westlake-repl/SaProtHub. ColabSaprot service is available at https://colab.research.google.com/drive/1nxYBed32rkAvoUpt8996Ge6D--Su4_oK. Fine-tuned models can be obtained through SaprotHub https://huggingface.co/SaProtHub.

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Be an OPMC member

The complete list of OPMC authors will be finalized in the last version of the paper. OPMC encompasses two membership categories: the steering committee and regular members.

Steering Committee: The steering committee comprises esteemed researchers with doctoral degrees who assume advisory roles within OPMC. Their primary responsibilities include:

- Providing constructive suggestions for OPMC and SaprotHub.
- Supporting academic activities such as organizing workshops, tutorials, and participating in peer review processes.
- Encouraging direct involvement of team members in the development of SaprotHub or OPMC.
- Participating in the review process for new members joining OPMC.
- Contributing high-quality open-source datasets and models to enhance OPMC's resources.
- Making other contributions or providing academic services that drive the progress of OPMC.

Regular Members: Regular members actively contribute to OPMC through practical means. This category includes independent researchers and professionals who:

- Participate in research, development, and collaborative efforts to advance OPMC's goals and objectives.
- Create innovative adapters for SaprotHub, trained on either private or publicly available data.
- Contributing more high-quality datasets to enrich the available resources.
- Aid in the development and administration of SaprotHub or ColabSaprot.

Membership Eligibility: We enthusiastically welcome individuals who make substantial contributions to OPMC and SaprotHub. The eligibility of regular members will be determined by the steering committee. Detailed requirements for joining will be provided at a later stage.

If you are interested in becoming a member of OPMC, please reach out to our corresponding author. Note that all OPMC members will be included as authors in the final version of this paper. The final list of members is expected to be finalized within the next 4 to 12 months.

Supplementary information

Dataset	Evaluation Metric	Train	Valid	Test
Training with AF2 structure				
Thermostability [25]	Spearman's ρ	5310	706	706
Subcellular localization [23]	Acc	10414	1368	1368
Binary localization [23]	Acc	6707	698	807
Training with PDB structure				
Structural similarity [33]	Spearman's ρ	300699	4559	4850
Structure class [33]	ACC	7990	955	1005
Metal ion binding [31]	ACC	5797	719	719
Binding site detection [33]	Mcc	2368	442	464
Training without structure				
Fluorescence [39]	Spearman's ρ	20963	5235	25517
Stability [39]	Spearman's ρ	53614	2512	12851
AAV [25]	Spearman's ρ	22246	2462	50432
β-lactamase [47]	Spearman's ρ	4158	520	520

Supplementary Table 1: Downstream dataset descriptions after all data preprocessing. All datasets that require structures as input are split based on structure similarity with 70 as threshold. For **Training with AF2 structure**, proteins with structures not available in AlphaFoldDB were excluded from both training and testing evaluations.

Model	ProteinGym	Mega-scale	ClinVar
	Spearman's ρ	Spearman's ρ	AUC
ESM-2 (650M) [10] (Science2023)	0.414	0.478	0.862
ESM-2 (15B) [10] (Science2023)	0.401	0.467	0.843
ProtBert [3] (TPAMI2021)	0.350	0.341	0.862
ESM-1v [35] (NeurIPS2021)	0.374	0.374	0.891
Tranception L [36] (ICML2022)	0.374	0.307	0.845
MSA Transformer [40] (ICML2021)	0.421	0.423	0.854
EVE [28] (Nature2021)	0.433	0.260	0.878
Saprot	**0.457**	**0.574**	**0.909**

Supplementary Table 2: More baseline results on zero-shot mutational effect prediction.

Task	Category	Metric	ESM-2	ProtBert	MIF-ST [48]	GearNet[50]	**Saprot**
Thermostability	Training w/ AF2 structure	Spearman's ρ	0.673	0.621	0.678	0.454	0.697
Subcellular localization		Acc%	84.67	78.65	82.46	75.73	86.18
Binary localization		Acc%	93.56	93.31	92.08	90.72	94.67
Structure class	Training w/ PDB structure	Acc%	79.90	71.57	71.63	74.52	80.80
Structural similarity		Spearman's ρ	0.677	0.601	0.555	0.101	0.695
Binding site detection		Mcc	0.540	0.459	0.504	0.415	0.602
Metal Ion binding		Acc%	74.97	68.19	69.58	67.61	79.97
Fluorescence	Training w/o structure	Spearman's ρ	0.698	0.698	-	-	0.699
Stability		Spearman's ρ	0.780	0.753	-	-	0.779
β-lactamase		Spearman's ρ	0.904	0.881	-	-	0.890
AAV		Spearman's ρ	0.813	0.783	-	-	0.829

Supplementary Table 3: More baseline results on supervised learning tasks. MIF-ST and GearNet are not applicable when protein structures are not available as input.

Task / Dataset	**Metric**	ProstT5	**Saprot**
ClinVar	AUC	0.620	**0.909**
Mega-scale	Spearman's ρ	0.194	**0.574**
Subcellular localization	Acc%	83.26	**86.18**
Binary localization	Acc%	94.11	**94.67**
Protein inverse folding	pLDDT	76.24	**77.96**
	RMSD	2.28	**2.07**
	TM-score	0.78	**0.82**
	Sequence recovery	33.72	**36.15**

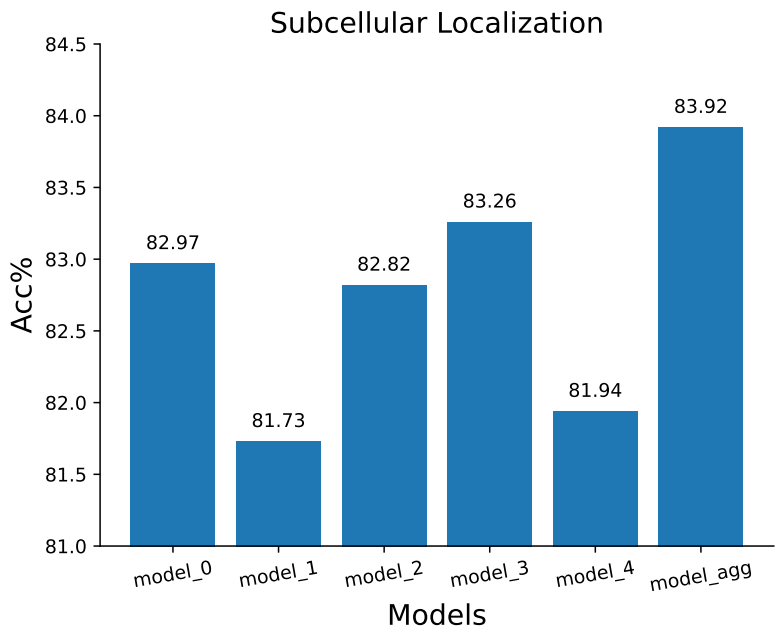
Supplementary Table 4: Comparison between ProstT5 and SaProt in several tasks. ProstT5 is a seq2seq T5 model where the input, if it is an amino acid sequence, corresponds to the output of the 3Di sequence, and vice versa. In general, Saprot is comparable to ProstT5 in the protein inverse folding task, but substantially outperform it on other tasks, e.g., zero-shot mutational effect prediction and supervised learning tasks.

Benchmark Scores

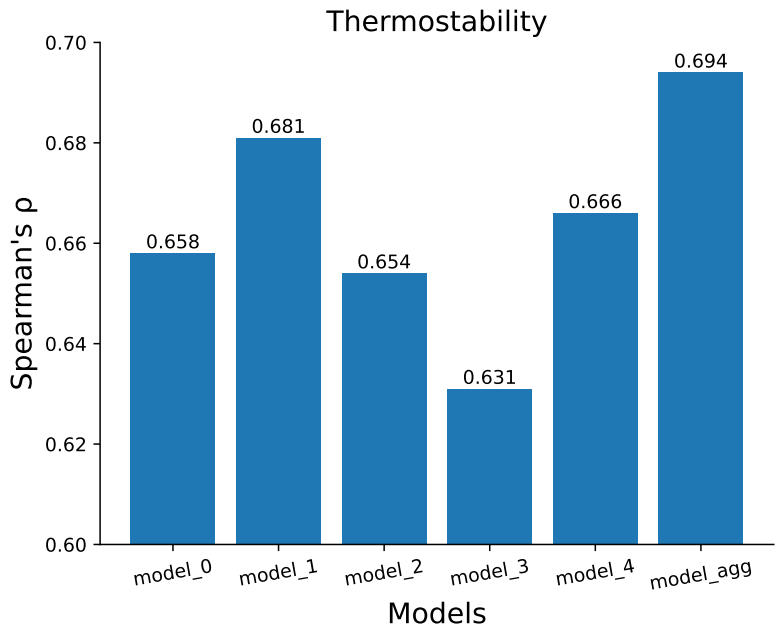
https://proteingym.org/benchmarks

Rank▲	Model name	Model type	Avg. Spearman
1	SaProt (650M)	Protein language model	0.457
2	TranceptEVE L	Hybrid - Alignment & PLM	0.456
3	TranceptEVE M	Hybrid - Alignment & PLM	0.455
4	GEMME	Alignment-based model	0.455
5	TranceptEVE S	Hybrid - Alignment & PLM	0.452
6	ProtSSN (ensemble)	Hybrid - Structure & PLM	0.449
7	ProtSSN (k=20 h=1280)	Hybrid - Structure & PLM	0.442
8	ProtSSN (k=20 h=512)	Hybrid - Structure & PLM	0.441
9	ProtSSN (k=20 h=768)	Hybrid - Structure & PLM	0.44
10	EVE (ensemble)	Alignment-based model	0.439
11	ProtSSN (k=30 h=512)	Hybrid - Structure & PLM	0.438
12	ProtSSN (k=30 h=768)	Hybrid - Structure & PLM	0.438
13	ProtSSN (k=30 h=1280)	Hybrid - Structure & PLM	0.438
14	VESPA	Protein language model	0.436
15	Tranception L	Hybrid - Alignment & PLM	0.434
16	MSA Transformer (ensemble)	Hybrid - Alignment & PLM	0.434
17	ProtSSN (k=10 h=1280)	Hybrid - Structure & PLM	0.433
18	EVE (single)	Alignment-based model	0.433
19	ProtSSN (k=10 h=512)	Hybrid - Structure & PLM	0.43
20	Tranception M	Hybrid - Alignment & PLM	0.427
21	ProtSSN (k=10 h=768)	Hybrid - Structure & PLM	0.423
22	ESM-IF1	Inverse folding model	0.422
23	MSA Transformer (single)	Hybrid - Alignment & PLM	0.421
24	DeepSequence (ensemble)	Alignment-based model	0.419
25	Tranception S	Hybrid - Alignment & PLM	0.418
26	ESM2 (650M)	Protein language model	0.414
27	DeepSequence (single)	Alignment-based model	0.407
28	ESM-1v (ensemble)	Protein language model	0.407
29	SaProt (35M)	Protein language model	0.406
30	ESM2 (3B)	Protein language model	0.406
31	ESM2 (15B)	Protein language model	0.401
32	MIF-ST	Hybrid - Structure & PLM	0.4
33	EVmutation	Alignment-based model	0.395
34	ESM-1b	Protein language model	0.394
35	VESPAI	Protein language model	0.394
36	Progen2 XL	Protein language model	0.391
37	ESM2 (150M)	Protein language model	0.387
38	MIF	Inverse folding model	0.383
39	Progen2 L	Protein language model	0.38
40	Progen2 M	Protein language model	0.379

Supplementary Fig. 1: Saprot (checkpoint: https://huggingface.co/westlake-repl/SaProt_650M_AF2) ranked first on the public ProteinGym leaderboard until May 2024, surpassing over 60 well-known baselines.

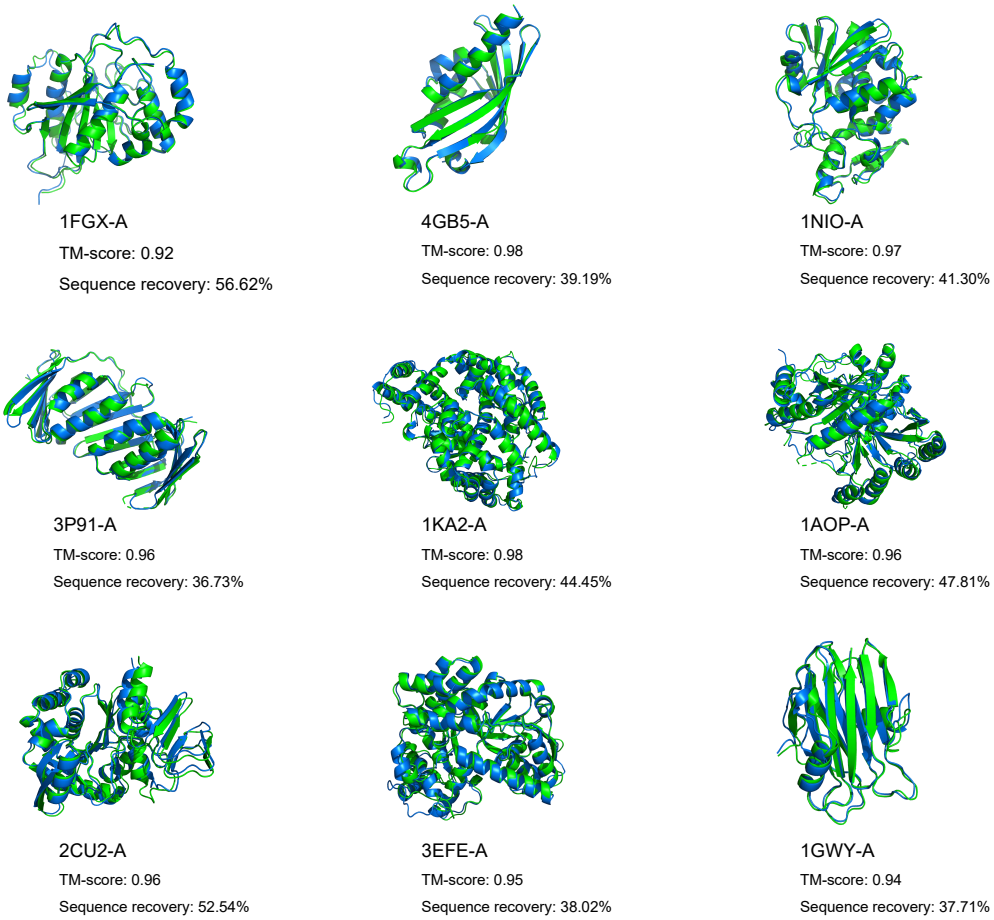


(a) Results for subcellular localization task.



(b) Results for thermostability task.

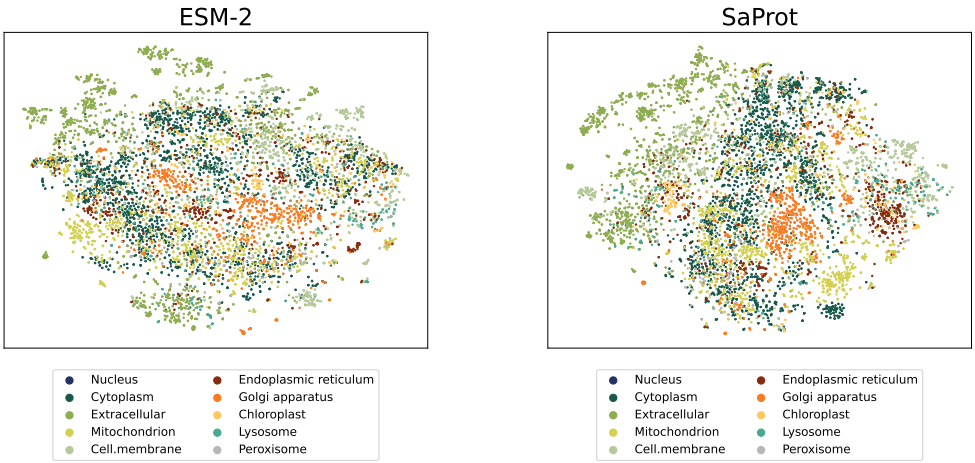
Supplementary Fig. 2: Individually trained models and the model (marked as model_agg) obtained by simply aggregating models trained by peers.



Supplementary Fig. 3: Case studies of protein inverse folding using Saprot. The blue-colored protein structures are predicted using ESMFold, with residue sequences generated by Saprot, and the green-colored structures are the experimentally determined structures. Given the backbone, Saprot is capable of predicting diverse sequences with few residue overlap while maintaining almost the same 3D structure.

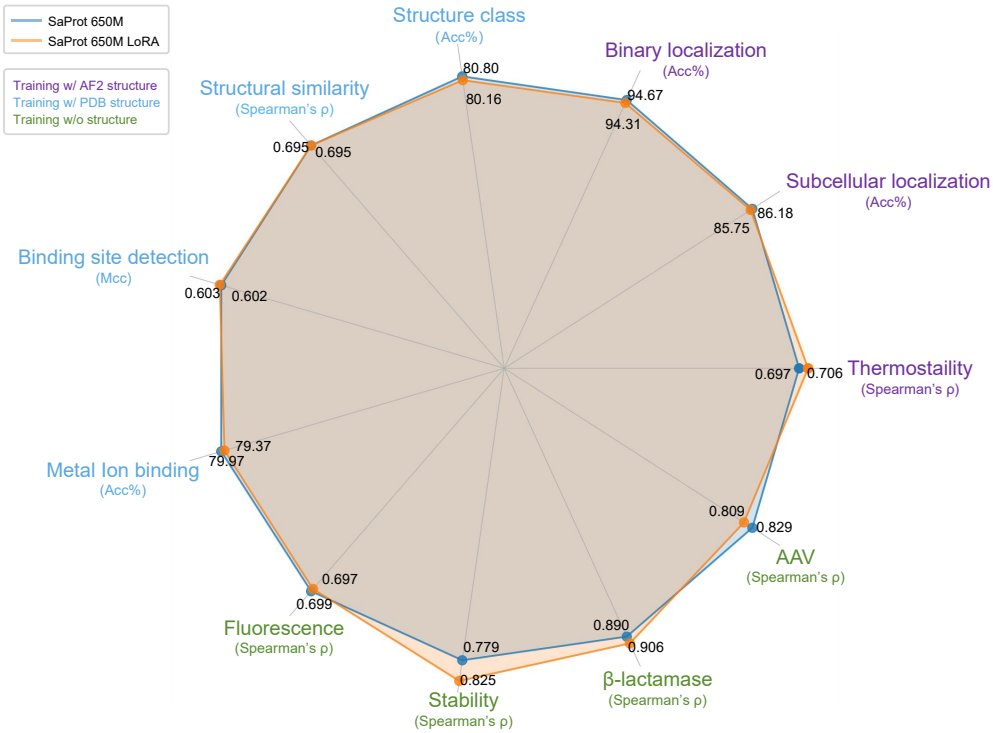
(a) Embedding visualizations of ESM-2 650M version and Saprot 650M version on SCOPe database. We use the non-redundant version ($PIDE < 40\%$) of the SCOPe database.

(b) Embedding visualizations of ESM-2 and SaProt on binary localization dataset.



(c) Embedding visualizations of ESM-2 and SaProt on subcellular localization dataset.

Supplementary Fig. 4: Embedding visualization



Supplementary Fig. 5: Comparison between full model fine-tuning and parameter efficient fine-tuning. While significantly reducing trainable parameters, fine-tuning Saprot using adapter module achieves competitive performance on all experimental settings, which demonstrates its applicability on various biological tasks.