

# Protein Large Language Models: A Comprehensive Survey

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<https://github.com/Yijia-Xiao/Protein-LLM-Survey>

## Abstract

Protein-specific large language models (Protein LLMs) are revolutionizing protein science by enabling more efficient protein structure prediction, function annotation, and design. While existing surveys focus on specific aspects or applications, this work provides the first comprehensive overview of Protein LLMs, covering their architectures, training datasets, evaluation metrics, and diverse applications. Through a systematic analysis of over 100 articles, we propose a structured taxonomy of state-of-the-art Protein LLMs, analyze how they leverage large-scale protein sequence data for improved accuracy, and explore their potential in advancing protein engineering and biomedical research. Additionally, we discuss key challenges and future directions, positioning Protein LLMs as essential tools for scientific discovery in protein science. Resources are maintained at <https://github.com/Yijia-Xiao/Protein-LLM-Survey>.

## 1 Introduction

*“Proteins are the machinery of life, and understanding their language unlocks the secrets of biology.”*

— David Baker (Nobel Prize laureate 2024)

Proteins are essential biological molecules, driving functions such as catalyzing biochemical reactions, maintaining cell structure, and enabling cellular communication. Understanding their sequence-structure-function relationships is central to biological research. However, traditional experimental methods, including X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy, are time-consuming and labor-intensive, posing bottlenecks for large-scale applications.

Recent advancements in language modeling have revolutionized computational biology, offering powerful tools for protein analysis. Protein

large language models (**Protein LLMs**) share several foundational similarities with LLMs: 1) *Training objectives and learning paradigms*, both LLMs and Protein LLMs are trained in a self-supervised manner on large-scale datasets using objectives such as masked language modeling (Devlin et al., 2019), auto-regressive modeling (Luo et al., 2022), or sentence permutation (Lewis et al., 2020; Yuan et al., 2022), learning to predict missing or next elements in sequences from the vocabulary. While LLMs predict missing words or phrases within textual data (Reimers and Gurevych, 2019; Liu et al., 2019; Touvron et al., 2023), Protein LLMs predict amino acids or subsequences within protein sequences. 2) *Pretraining data*. Protein LLMs adopt a data-driven paradigm to learn directly from large-scale protein datasets (Liu et al., 2024b; Jones et al., 2024). The datasets for training Protein LLMs consist of vast collections of protein sequences, analogous to the textual corpora used for LLMs. This eliminates the need for explicit feature engineering, allowing Protein LLMs to learn intricate patterns, such as structural motifs, evolutionary relationships, and functional insights, similar to how LLMs capture semantic and syntactic structures in language.

This paradigm shift has led to the emergence of highly effective models that can predict protein folding, annotate biological functions, and even design novel proteins with desired characteristics. Beyond their predictive capabilities, Protein LLMs also provide interactive interfaces that allow users to upload protein sequences or structural files (e.g., PDB format), pose questions, and interact with the model in a conversational manner (Liu et al., 2024c; Xiao et al., 2024b), proving deeper insights into protein structure, function, and design.

We present the first dedicated survey of Protein LLMs, analyzing their unique architectures, training methodologies, and practical applications in protein research. While previous studies have ex-

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plored the applications of various computational methods for protein research (Chen et al., 2024c; Wu et al., 2022) or discussed the role of language models in general scientific domains such as biomedicine (Wang et al., 2023a) and chemistry (Liao et al., 2024), this survey focuses specifically on Protein LLMs—a rapidly evolving area at the intersection of computational biology and NLP.

The key contributions are as follows:

- **Architectural Overview.** A structured taxonomy of state-of-the-art Protein LLMs (Figure 3) detailing their unique architectures for protein understanding (§2) and generation (§3), highlighting how these models surpass traditional experimental methods in both efficiency and accuracy (Appendix §A).
- **Data Insights.** A comprehensive summary of datasets for pretraining, fine-tuning, and benchmarking Protein LLMs, providing critical insights into data curation strategies and their impact on model performance (§4).
- **Evaluation Protocols.** A thorough discussion of methodologies for assessing the performance and impact of Protein LLMs, including comprehensive new benchmarking strategies (§5 and Appendix §B).
- **Applications.** A detailed exploration of practical applications in protein prediction, annotation, and design, remarkably highlighting recent innovative advancements and showcasing the transformative potential of Protein LLMs in advancing biomedical research.

## 2 LLM Methods for Protein Understanding and Prediction

### 2.1 Problem Definition

A protein, composed of amino acids (residues), can be represented as a sequence  $[x_1, \dots, x_L]$  in the residue token space  $\mathcal{P}$ , where  $L$  denotes its length. According to Anfinsen’s dogma, a protein’s primary sequence determines its structure and function. General problems in protein understanding and prediction are as follows:

*I. Sequence-to-Property Prediction:*  $f_\theta : \mathcal{P} \rightarrow \mathcal{R}^+$  mapping sequences to numerical properties, such as stability or fluorescence intensity.

*II. Sequence-to-Label Prediction:*  $f_\theta : \mathcal{P} \rightarrow \mathcal{L}$  mapping sequences to categorical labels, including secondary structure types, contact maps, or functional annotations.

*III. Sequence-to-Structure Prediction*  $f_\theta : \mathcal{P} \rightarrow \mathcal{S}$

mapping sequences to the 3D folding structures (i.e. tertiary structures).

*IV. Sequence-to-Text Understanding:*  $f_\theta : \mathcal{P} \rightarrow \mathcal{T}$ , where  $\mathcal{T}$  represents generated textual descriptions of protein sequences.

### 2.2 Protein Sequence Models

**Individual Protein Sequences Models.** Protein language models process amino acid sequences into meaningful representations for downstream tasks including structure and function prediction. Like NLP models, they are usually first pretrained on large sequence datasets with masked language modeling (MLM) objective; and then the protein sequences’ embeddings are adapted for downstream tasks. Initially, researchers leveraged long short-term memory (LSTM) architectures to learn representation of proteins (Alley et al., 2019; Bepler and Berger, 2019; Zhou et al., 2020). Following the breakthrough of transformer architectures (Vaswani et al., 2017) in NLP, transformer-based protein language models emerged as the new paradigm. Large-scale transformer models, scaling up to billions of parameters and trained on millions of protein sequences, have demonstrated remarkable effectiveness for protein understanding and prediction tasks (Rao et al., 2019; Elnaggar et al., 2021; Xiao et al., 2021; Hu et al., 2022), and 3D structure folding (Chowdhury et al., 2022; Fang et al., 2022; Chen et al., 2024a). The interpretability of these Protein LLMs has also been explored, with (Vig et al., 2021) analyzing learned representations through the lens of attention. Beyond general-purpose protein language models, several works have focused on domain-specific applications. For instance, Hie et al. (2021) applied BiLSTM to model viral escape patterns; TCR-BERT (Wu et al., 2024b) specialized in T-cell receptor (TCR) analysis for improved TCR-antigen binding prediction; PeptideBERT (Guntuboina et al., 2023) focused on predicting key properties of peptides; Kroll et al. (2023); Yu et al. (2023) adapted ESM-1b for enzymatic function prediction.

**Multiple Sequence Alignments (MSA) Models.** MSA aligns homologous proteins within sequence space by mapping their residues to the coordinate framework of a designated seed sequence. MSA reveals evolutionary relationships between proteins and thus serves as a cornerstone of computational biology, particularly for mutation effects prediction (Ram and Bepler, 2022; Hawkins-Hooker et al., 2021). The MSA Transformer (Rao et al., 2021)

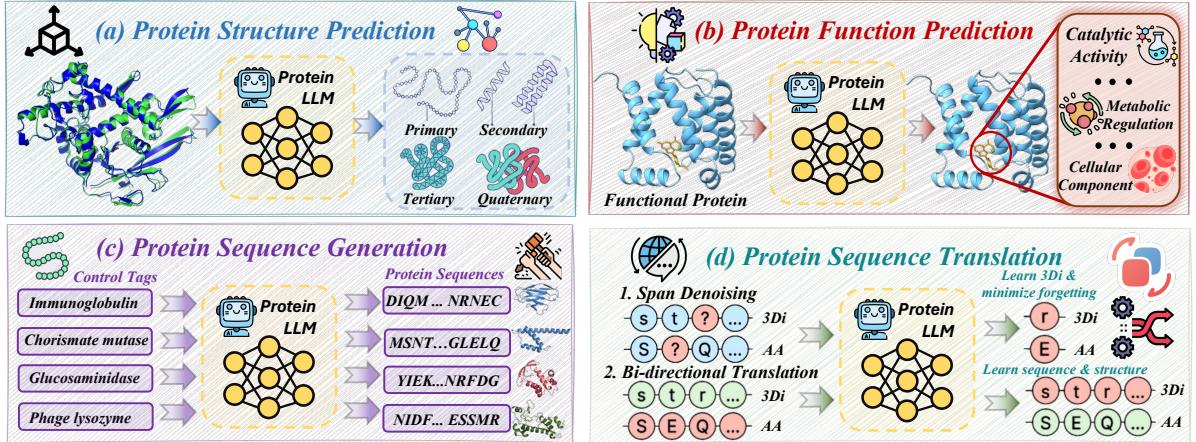


Figure 1: An Overview of Tasks in Protein Large Language Models.

processed MSAs instead of single sequences. It used a modified axial attention mechanism (Ho et al., 2019; Child et al., 2019) to model both intra- and inter-sequence relationships. In contrast, Tranception (Notin et al., 2022), was trained on individual non-aligned sequences but could leverage aligned sequences during inference. It extracted patterns from contiguous protein subsequences and improves fitness prediction by integrating MSAs retrieved at inference time. In specific subdomains, Lin et al. (2023a) developed a transfer learning framework that utilized ESM-MSA-1b for transmembrane protein complexes. Additionally, vCMMA (McWhite et al., 2023) and Poet (Truong Jr and Bepler, 2023) leveraged protein LLMs to identify MSAs or homologous sequences.

**Evolutionary Scale Modeling (ESM) Series.** ESM is a family of transformer models for protein modeling. ESM-1b (Rives et al., 2021), the first model in the series with up to 669.2 million parameters, was trained on 250 million protein sequences using a masked language modeling (MLM) objective and contains up to 669.2 million parameters. Building on this, ESM-1v (Meier et al., 2021) focused on predicting the effects of mutations in zero-shot setting, while incorporating the MSA Transformer (Rao et al., 2021) for few-shot mutation prediction. Thanks to the success of AlphaFold2 (Jumper et al., 2021), ESM-IF (Hsu et al., 2022) utilized predicted structures to train large models combining Geometric Vector Perceptron (Jing et al., 2021) with GNN or transformer on the inverse folding task that predicts protein strings from the 3D structures. The new general-purpose language protein model ESM-2 (Lin et al., 2023b) further scaled up the model size to 15 billion pa-

rameters and incorporated a folding head to create an end-to-end single-sequence structure prediction model ESMFold. The latest model ESM-3 (Hayes et al., 2025) is a multimodal generative model with 98 billion parameters that could reason over protein sequences, structures, and functions. Using a chain-of-thought approach, it successfully designed a novel fluorescent protein far from any known fluorescent proteins.

### 2.3 Structure-Integrated and Knowledge-Enhanced Models

Beyond residue sequences, many models integrate additional information, such as structure data or external knowledge, to enhance protein understanding and prediction ability.

**Structure-Integrated Models:** Structural information plays an important role in protein understanding, as a protein’s functions are determined by its structures. Therefore, many works have incorporated structural information to enhance protein modeling ability. Some works utilized structure information as additional inputs (Chen et al., 2024b; Tan et al., 2024). For instance, Zhang et al. (2023a) fused global structure information captured by structure encoder (GVP, GearNet (Zhang et al., 2023b), or CDCConv (Fan et al., 2022)) into representations of ESM-2; SaProt (Su et al., 2024) incorporated local structural information for each amino acid, derived from Foldseek (Van Kempen et al., 2024), to generate structure-aware tokens. Alternatively, other works injected the structure information only in the training stage by either additional training tasks Wang et al. (2022); Sun and Shen (2024); Zhang et al. (2024) or contrastive learning (Wang et al., 2025). Some studies have

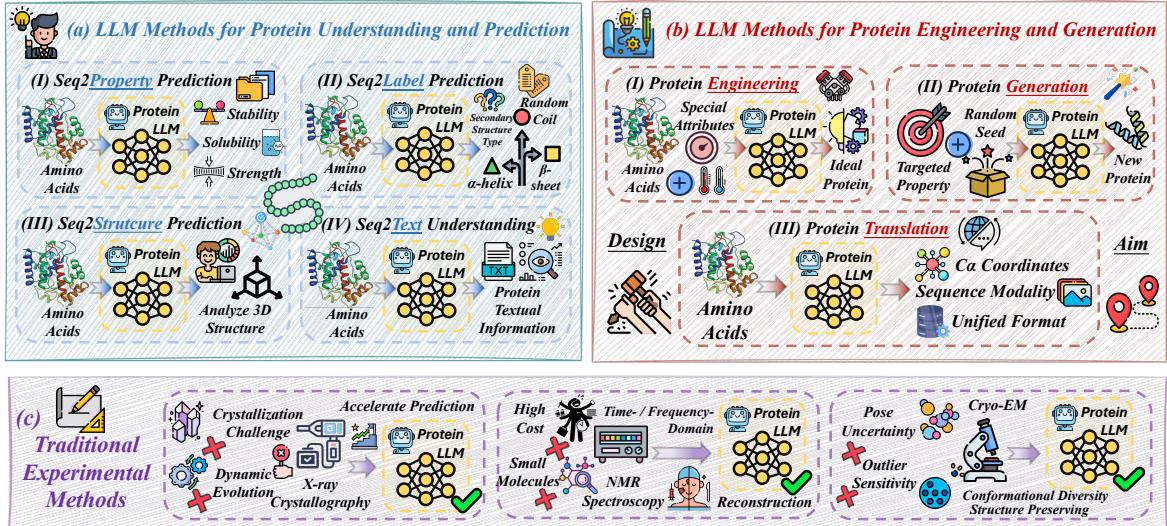


Figure 2: An Overview of Methods of Protein Large Language Models.

also leveraged pretrained protein language models to improve structure models (Wu et al., 2023; Zheng and Li, 2024).

**Knowledge-Enhanced Models:** Beyond large protein sequence datasets, information in other formats can further enhance a model’s understanding of proteins in the training stage. OntoProtein (Zhang et al., 2022) and KeAP (Zhou et al., 2023) incorporated knowledge graphs data during training by additional MLM objectives and/or contrastive learning to inject factual biological knowledge into the pre-trained Protein LLMs. ProteinBERT (Brandes et al., 2022) performed dual-task learning during pretraining to learn both protein sequence modeling and Gene Ontology (GO) annotation prediction. It utilized a specialized BERT architecture with parallel input pathways for sequences and annotations. To leverage the rich information in textual descriptions or other modalities, ProteinCLIP (Wu et al., 2024a) and MolBind (Xiao et al., 2024a) applied contrastive learning between protein sequences and textual descriptions and/or molecular to learn improved embeddings.

## 2.4 Protein Description and Annotation Models

The previously mentioned models have primarily focused on learning protein representations and utilizing them for classification, regression, or 3D structure folding tasks. To enhance expressiveness and understanding, more recent models have been trained on both protein sequences and textual data, allowing them to integrate NLP capabilities with protein representation learning (Wang et al., 2023b;

Liu et al., 2024c; Zhuo et al., 2024; Jin et al., 2024). Xu and Wang (2022) proposed ProTranslator, a bilingual translation framework between protein sequences and GO functions with textual descriptions. ProTranslator encoded and aligned the textual definitions of GO functions and protein sequences within the same low-dimensional space, facilitating the annotation of novel GO functions and the generation of textual descriptions for proteins. BioTranslator (Xu et al., 2023a) further improved ProTranslator by extending the bilingual framework to a multilingual translation framework, embedding text and multiple biomedical modalities into a shared space. ProtST (Xu et al., 2023b) was a framework designed to jointly learn from protein sequences and their associated biomedical text descriptions. It integrated protein language models (e.g., ESM or ProtBERT) with biomedical language models (e.g., PubMedBERT) to fuse sequence and text information through pre-training tasks. Prot2Text (Abidine et al., 2024) combined ESM-2 with a structure encoder (RGCN) and extended function prediction from categorical classification to free-text descriptions. BioT5 and BioT5+ (Pei et al., 2023, 2024) further unified molecular information within a more comprehensive training framework.

There have also been several interactive LLMs for protein understanding. These models enhanced pretrained LLMs with protein comprehension by integrating a protein processing module (Wu et al., 2024c; Wang et al., 2024a,b). For instance, ProteinChat (Guo et al., 2023) allowed users to input protein structures and query them using texts. Pro-

teinGPT (Xiao et al., 2024b) extended this capability by supporting both protein sequences and structures as inputs. In these models, protein data were processed through Protein LLMs to generate embeddings, which were then projected to the natural language embedding space. The backbone LLMs integrated these adapted embeddings with user’s queries to produce meaningful answers.

### 3 LLM Methods for Protein Engineering, Generation and Translation

Protein engineering and generation aims to design protein sequences with desired attributes (e.g. structures and properties). Given the desired attributes  $T$  and reference protein sequence  $\mathcal{S}$  (optional), the model is expected to output a protein sequence  $\mathcal{S}'$  with desired attributes. Key tasks include:

*I. Protein Engineering:*  $f_\theta : (\mathcal{S}, T) \rightarrow \mathcal{S}'$  modifies protein  $\mathcal{S}$  toward the desired attributes  $T$ , yielding the engineered protein  $\mathcal{S}'$ .

*II. Protein Generation:*  $f_\theta : (T, R) \rightarrow \mathcal{P}$  generates proteins with attributes  $T$  by sampling from the protein space using random seeds  $R$ .

*III. Protein Translation:*  $f_\theta : (\mathcal{P}, T) \rightarrow \mathcal{P}'$  translates a protein  $\mathcal{P}$  into an alternative representation  $\mathcal{P}'$  based on the target translation parameters  $T$ .

#### 3.1 Protein Engineering Models

ProteinDT (Liu et al., 2023) is a multimodal protein design framework that robustly integrates textual protein knowledge with sequence-based generative modeling. ProteinDT employs contrastive alignment and a facilitator module, enabling zero-shot text-to-protein generation and editing. Meanwhile, PLMeAE (Zhang et al., 2025) is a closed-loop protein engineering framework that integrates protein language models with an automated biofoundry within a Design-Build-Test-Learn cycle. Furthermore, Toursynbio (Shen et al., 2024b) introduces an agent that is capable of facilitating the modification and engineering of wet lab proteins.

#### 3.2 Protein Generation Models

Protein generation models are designed to create novel protein sequences for specific engineering applications, often leveraging large-scale datasets of existing proteins with known amino acid sequences and properties. These models typically employ decoder-based architectures to generate functional protein sequences conditioned on various biological annotations. For example, ProGen (Madani

et al., 2023) is a GPT-based generative protein engineering model that treats protein engineering as an unsupervised sequence generation process, and generates functional protein sequences conditioned on annotations like molecular function or taxonomy. The model is trained on diverse, non-redundant protein sequences from databases such as UniProt and Pfam, utilizing associated tags for conditional generation. ProtGPT2 (Ferruz et al., 2022) is another model that generates de novo protein sequences with natural amino acid compositions using autoregressive modeling. In particular, they noticed that the generated sequences could explore a few uncharted areas of the protein sequence space. ProGen2 (Nijkamp et al., 2023) is an extended version of ProGen, featuring a larger model size and a more extensive training dataset to enhance sequence diversity. Notably, ProGen2 can predict protein fitness without requiring additional fine-tuning. Recently, PROLLaMA (Lv et al., 2024) proposed a multi-task protein language model to handle both protein sequence generation and protein understanding tasks. Built on LLaMA2, ProLLaMA introduces a two-stage training framework: (1) continued pre-training on protein sequences, and (2) instruction tuning with a 13-million-sample dataset for multitasking capabilities.

Beyond conventional decoder-based approaches, Ankh (Elnaggar et al., 2023) employs an encoder-decoder architecture that optimizes efficiency by reducing parameters while maintaining high-quality protein generation. PAAG (Yuan et al., 2024) is another encoder-decoder architecture which focuses on the alignment between textual annotations and protein sequences at multiple levels before generating new sequences. Pinal (Dai et al., 2024) does not directly generate protein sequences from text. Instead, it first constrains the protein design space by generating structure tokens, then predicts sequences based on those constraints to improve foldability and function alignment.

While many of these models are designed for general protein generation, some focus on specialized applications such as antibody design. IgLM (Shuai et al., 2023) employs autoregressive sequence generation conditioned on an antibody’s sequence chain type and species of origin. As a further step, PALM-H3 (He et al., 2024) specifically targets SARS-CoV-2 antibody generation, highlighting how protein generation language models can be tailored for highly specific protein design tasks.

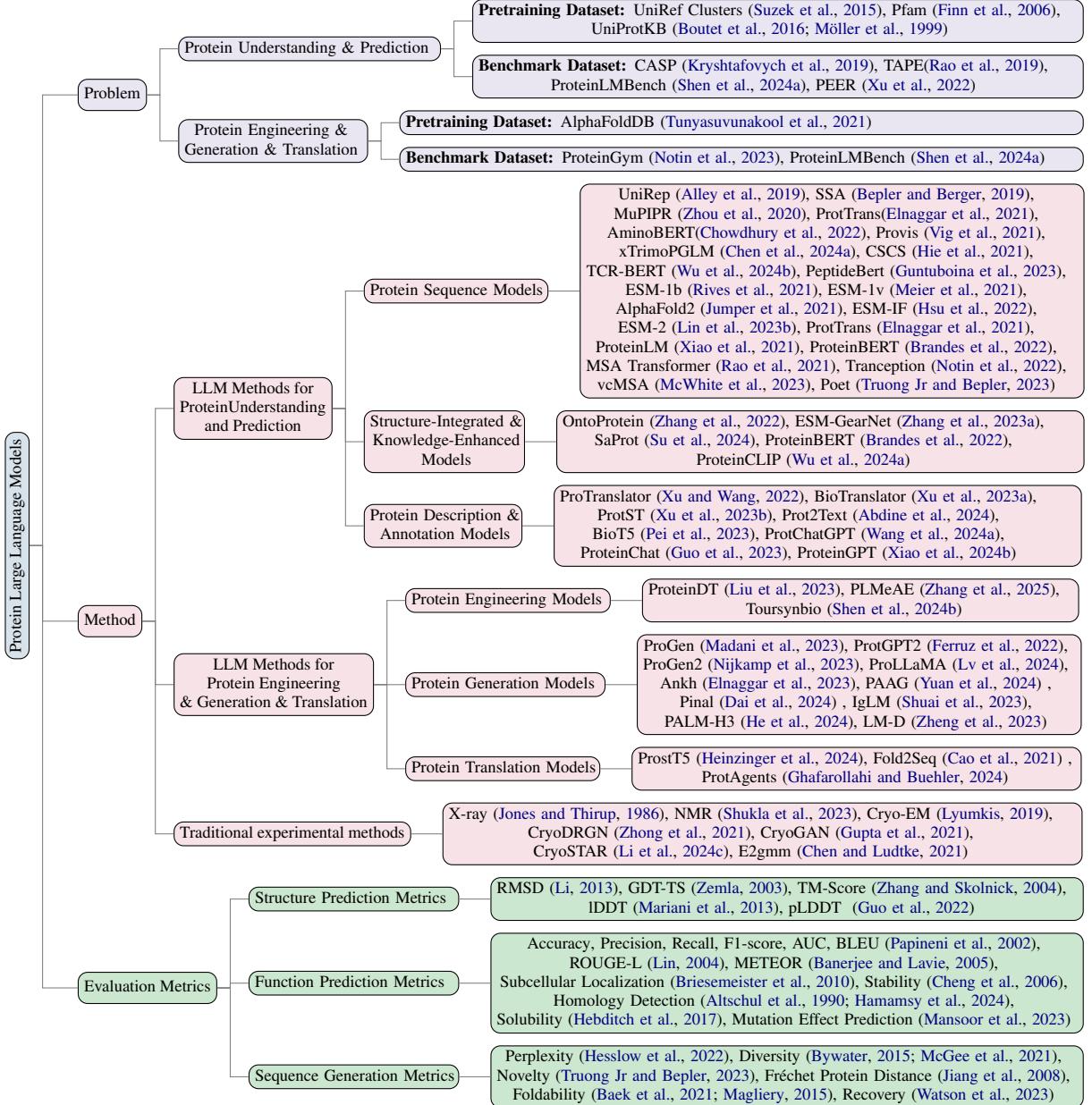


Figure 3: Taxonomy of Protein Large Language Models.

### 3.3 Protein Translation Models

Protein translation models are specifically developed to handle tasks that require translating between different protein representations, which could be helpful in protein design.

ProstT5 (Heinzinger et al., 2024) addresses the task of simultaneously modeling the dual nature of proteins — their linear one-dimensional (1D) sequences and three-dimensional (3D) structures — using a bilingual language model based on T5 (Rafefel et al., 2020) and ProtT5 (Pokharel et al., 2022). It extracts features and patterns from both the sequence and the structure data Fold2Seq (Cao et al., 2021) is another model that learns structure-

sequence relationships of proteins. The model could guide designs of protein sequences conditioned on desired structural folds. Recently, ProtAgents (Ghafarollahi and Buehler, 2024), a multiagent framework, has been proposed to handle 1D sequence generation and 3D fold generation simultaneously. LM-DESIGN (Zheng et al., 2023) is a method for reprogramming protein language models (pLMs) to design protein sequences for given structural folds.

## 4 Datasets

Datasets are crucial for training and evaluating Protein LLMs. They are categorized into pre-

training datasets, comprising unlabeled protein sequences for self-supervised learning, and benchmark datasets, which contain labeled sequences for supervised fine-tuning and evaluation on specific biological tasks.

#### 4.1 Pretraining Datasets

**UniProtKB**: A comprehensive protein sequence and annotation database composed of two main components: *Swiss-Prot* (Boutet et al., 2016), a manually curated, high-quality dataset with reliable annotations and *TrEMBL* (Möller et al., 1999), an automatically annotated dataset providing broader coverage.

**UniRef Clusters** (Suzek et al., 2015): A collection of clustered protein sequences designed to reduce data redundancy and improve computational efficiency. Provided by the UniProt database, UniRef is organized into three hierarchical levels: UniRef100, UniRef90, and UniRef50. UniRef100 contains a non-redundant set of all UniProt protein sequences where the latter two are created by clustering sequences with at least 90% and 50% sequence identity.

**Pfam** (Finn et al., 2006): A database of protein families and domains widely used for annotation and analysis of protein sequences. Each Pfam entry represents a group of related protein sequences defined by a multiple sequence alignment and a corresponding profile hidden Markov model (HMM). It provides insights into protein structure, function, and evolution, helping researchers identify conserved domains, predict functions, and classify proteins across organisms.

**PDB** (Bank, 1971): The Protein Data Bank is a repository for the 3D structural data of large biological molecules, such as proteins and nucleic acids. It provides valuable resources for understanding the structural aspects of proteins, which can be beneficial for training models that incorporate structural information.

**AlphaFoldDB** (Tunyasuvunakool et al., 2021): The AlphaFold Protein Structure Database offers predicted protein structures generated by the AlphaFold model containing over 200 million entries.

#### 4.2 Benchmark Datasets

**CASP** (Kryshtafovych et al., 2019): Critical Assessment of Structure Prediction is a biennial competition that evaluates methods for protein structure prediction. Participants predict 3D structures of

proteins from their sequences, compared against experimental results.

**ProteinGym** (Notin et al., 2023): A large-scale benchmark platform for protein design and fitness prediction. It includes over 250 Deep Mutational Scanning (DMS) assays, encompassing millions of mutated protein sequences, and curated clinical datasets with expert annotations. By integrating zero-shot and supervised evaluation frameworks, ProteinGym allows systematic comparison of over 70 machine learning models. It provides standardized metrics for tasks like mutation effect prediction and protein design, fostering innovation in computational biology and protein engineering.

**TAPE** (Rao et al., 2019): A benchmark designed to evaluate protein sequence embeddings in biologically relevant tasks using machine learning. It includes five tasks covering structure prediction, evolutionary understanding, and protein engineering. TAPE leverages self-supervised learning, enabling models to learn from unlabeled protein sequences, and offers standardized datasets and metrics for systematic comparisons. It aims to advance protein representation learning by addressing gaps in generalization and real-world applicability.

**PEER** (Xu et al., 2022): A comprehensive and multi-task benchmark designed to evaluate protein sequence understanding. It includes tasks such as protein function prediction, localization prediction, structure prediction, protein-protein interaction prediction, and protein-ligand interaction prediction.

**ProteinLMBench** (Shen et al., 2024a): A benchmark dataset comprising 944 manually verified multiple-choice questions aimed at assessing the protein understanding capabilities of LLMs. It incorporates protein-related details and sequences in multiple languages, setting a new standard for evaluating LLMs' abilities in protein comprehension.

### 5 Evaluation Metrics

Comprehensive evaluation is essential for applying Protein LLMs, which are assessed on tasks like structure prediction, function prediction, and sequence generation. Appendix 5 provides detailed descriptions of structure and function prediction metrics, as well as sequence generation metrics for generative Protein LLMs.

#### 5.1 Structure Prediction Metrics

Root Mean Square Deviation (RMSD) measures the distance between predicted and actual

atomic coordinates, with lower values indicating better accuracy (Li, 2013). Global Distance Test (GDT-TS) calculates the percentage of alpha-carbon atoms within 1, 2, 4, and 8 Å thresholds, reflecting structural similarity (Zemla, 2003). Template Modeling (TM) Score evaluates global structural similarity (scores between 0 and 1) via

$$TM = \max \left[ \frac{1}{L_{tgt}} \sum_i^{L_{com}} \frac{1}{1 + \left( \frac{d_i}{d_0(L_{tgt})} \right)^2} \right], \quad (1)$$

$$d_0(L_{tgt}) = 1.24 \sqrt[3]{L_{tgt} - 15} - 1.8. \quad (2)$$

Local Distance Difference Test (lDDT) quantifies local accuracy by comparing interatomic distances (Mariani et al., 2013), and Predicted Local Distance Difference Test (pLDDT) provides per-residue confidence scores (0–100) without a reference structure, as used in AlphaFold (Guo et al., 2022; Jumper et al., 2021).

## 5.2 Function Prediction Metrics

Protein function prediction determines biological roles, including biomolecular interactions (Radijovac et al., 2013). Machine learning metrics include classification measures (precision, recall, F-1 score, accuracy, AUC) and generative metrics such as BLEU (Papineni et al., 2002), ROUGE-L (Lin, 2004), and METEOR (Banerjee and Lavie, 2005). These evaluation methods offer quantitative benchmarks crucial for model validation and biological inference.

Subcellular Localization predicts proteins' cellular positions to infer functions (Briesemeister et al., 2010; Holm, 2020). Homology Detection identifies evolutionary relationships using sequence alignment methods like BLAST (Altschul et al., 1990) or deep learning approaches such as TM-vec (Hamamsy et al., 2024). Stability and Solubility assessments evaluate whether a protein can function effectively in its environment (Cheng et al., 2006; Hebditch et al., 2017), while Mutation Effect Prediction gauges the impact of amino acid changes on protein properties (Mansoor et al., 2023). These integrative metrics underpin the development of robust protein prediction systems and support advancements in drug design and molecular biology.

## 6 Conclusion and Future Work

This survey provides a comprehensive overview of Protein Large Language Models, highlighting their

architectures, datasets, evaluation, and applications. These works represent significant advancements in protein science and offer innovative approaches to protein analysis and design. In addition to these advancements, several challenges remain to be solved in the future.

**Protein Dynamics.** AlphaFold (Jumper et al., 2021) has been shown to provide accurate static 3D structures. However, proteins are naturally dynamic molecules with various conformations (Ohnuki and Okazaki, 2024). Although several works incorporate 3D structures into LLMs, the conformational dynamics of proteins have not yet been considered. Since conformational dynamics are highly related to the transporter functions of proteins, it would benefit the model to include protein dynamics.

**Combination with Single-cell Data.** Recently, single-cell proteomics sequencing technology (Li et al., 2024b; Liu et al., 2024a; Bennett et al., 2023) has attracted extensive attention in the field of biology, which can help us understand the pathways in specific cells. Since LLMs have shown effectiveness in understanding both proteins and single-cell data, they can be extended to learn from single-cell proteomics data in the future.

**Towards Biological Applications.** Although several biological applications have been studied in recent works, a range of detailed and complex problems remain unsolved, including protein-ligand interaction learning (Koh et al., 2024), cryptic pocket identification (Ge et al., 2024), and rational ligand generation (Li et al., 2024a). These applications require extensive and diverse domain knowledge of proteins and their related fields. We believe LLMs have the potential to incorporate and utilize more domain knowledge to solve these problems.

**Interpretability.** In addition to effectiveness, interpretability is also of strong significance for trustworthy models (Huang et al., 2024). Previous language models for proteins (Gu et al., 2023; Vecchietti et al., 2024) have provided extensive case studies, such as key residue analysis, which could be challenging for large-scale and closed-source models. To improve interpretability, InterPLM (Simon and Zou, 2024) employs sparse autoencoders to extract biologically meaningful features from Protein LLMs, revealing their alignment with known biological concepts. Inspired by this, we should design prompts to enhance the interpretability of Protein LLMs for reliable outputs.

## Limitations

This survey primarily focuses on Protein LLMs. We acknowledge that the study of protein interactions with other molecules (e.g., DNA, RNA) in the inter-molecular domain is a broad and valuable field worth reviewing. Given its vast scope, we do not extensively cover it in this survey, and instead focus on Protein LLMs centered on proteins themselves. In the future, we may either expand our review to include these areas or write a separate survey specifically dedicated to this domain, providing more comprehensive coverage for researchers.

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## A Experimental Methods in Proteomics and Their Limitations

Traditional experimental techniques such as X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and cryo-electron microscopy (cryo-EM) in protein science have laid the foundation for studying protein structure and functions. However, computational approaches and also embrace the progress of AI development. This section briefly covers methods, which are essential for determining protein structures and functions.

**X-ray Crystallography** is a widely utilized method for determining the 3D structures of proteins ([Jones and Thirup, 1986](#)). In this method, X-rays are directed at a crystallized sample, and the resulting diffraction patterns are analyzed to reveal the arrangement of atoms within the crystal. This process provides detailed insights into the protein's electron density and overall structure. However, crystallization can be challenging, especially for large, flexible, or membrane-associated proteins. The technique typically offers a static snapshot of the protein, which may not fully capture its dynamic nature in solution. Advancements in AI have led to the development of structure prediction tools like AlphaFold ([Jumper et al., 2021](#)) and RoseTTAFold ([Baek et al., 2021](#)). For instance, the crystal structure of the KINmd4 protein is predicted to consist of a single PIN domain ([Barbarin-Bocahu and Graille, 2021](#)). The study demonstrates that the high-quality models significantly accelerate the determination of KINmd4's structure, while existing models fail to achieve similar results.

**Nuclear Magnetic Resonance (NMR) Spectroscopy** is a non-destructive technique for determining the structure, dynamics, and interactions of molecules at the atomic level under near-physiological conditions ([Shukla et al., 2023](#)). It provides 3D structural data of proteins in solution and captures real-time dynamics, making it highly effective for studying protein flexibility and weak protein-ligand interactions. NMR exploits the magnetic properties of atomic nuclei (e.g., hydrogen nuclei in proteins) to provide detailed information about the local chemical environment.

With the development of AI, deep learning methods are more and more promising to advance the reconstruction of sparsely sampled data in NMR spectroscopy, particularly in the context of non-uniform sampling. The input data typically consists of sparsely sampled NMR spectra, while the output is

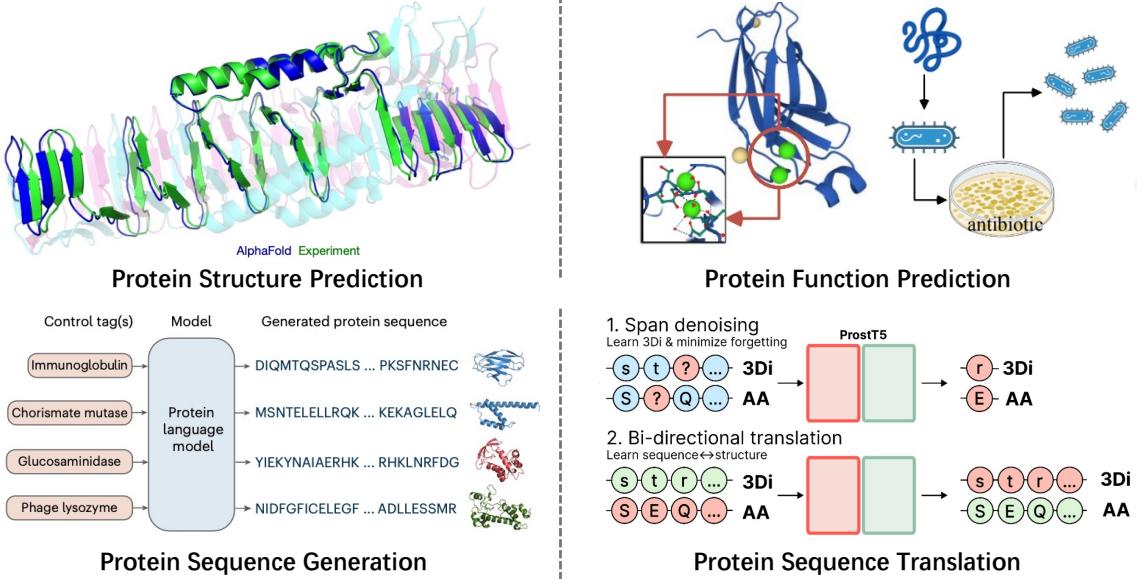


Figure 4: Illustrations on General Tasks of Protein Language Models.

the fully sampled spectrum, reconstructed either in the time (Hansen, 2019; Karunanthi and Hansen, 2021) or frequency domain (Qu et al., 2020; Luo et al., 2020). For time-domain reconstructions, neural networks effectively predict the missing data points. In frequency-domain reconstructions, they excel at removing artifacts caused by sparse and non-Nyquist sampling. Studies across various research groups have consistently demonstrated the high accuracy of DNN-based reconstructions, even under conditions of extremely sparse sampling, highlighting the potential of deep learning to enhance data acquisition and analysis in NMR.

However, NMR has limited size range: NMR is mostly suitable for proteins smaller than 30–50 kDa (larger proteins become challenging due to signal overlap). Protein sample preparation and data collection can also be expensive and take weeks to months.

**Cryo-EM** is a structural biology technique that enables the direct observation of conformational heterogeneity in individual dynamic macromolecules (Lyumkis, 2019). Researchers aim to reconstruct high-resolution 3D structural landscapes from numerous 2D observed projections, which may represent different conformational states. However, the cryo-EM reconstruction task is challenging because each particle’s pose is unknown during imaging. Recently, deep learning methods have demonstrated powerful capabilities in representing heterogeneity within datasets by mapping them onto nonlinear manifold embed-

dings. On the one hand, CryoDRGN (Zhong et al., 2021) is a pioneering work that captures this heterogeneity by employing variational autoencoders (VAEs) to map the data into a low-dimensional latent space. A generative decoder then reconstructs a 3D volume from a sampled point in this latent space. CryoGAN (Gupta et al., 2021) introduces an entirely new possibility to learn to reconstruct in a distributional sense with a generative adversarial framework. Because of its likelihood-free nature, CryoGAN does not require any additional processing steps such as pose estimation and can be directly applied to cryo-EM measurements. This greatly simplifies the reconstruction procedure. On the other hand, E2gmm (Chen and Ludtke, 2021) models the 3D structure using a set of Gaussians to automatically resolve the structural heterogeneity, whereas 3DFlex (Punjani and Fleet, 2023) employs a neural network to fit the 3D displacement field of each particle by concurrently exploring its deformation field and refining a canonical density. More recently, CryoSTAR (Li et al., 2024c) resolves continuous conformational heterogeneity by constructing reasonable coarse-grained models, meanwhile, density maps are also estimated for different conformations. It meticulously preserves local structures, minimizes erroneous solutions, and ultimately achieves enhanced, accelerated convergence. Overall, the current trend is to incorporate atomic information to better activate deep models, aiming for more precise 3D structures that better comply with natural laws.

Table 1: LLM Methods for Protein Understanding and Prediction: Protein Sequence Models

| Model  | Time | Base Model                                       | Dataset   | Keywords   |
|--|------|--|---|--|
| UniRep ( <a href="#">Alley et al., 2019</a> )        | 2019 | BiLSTM   | UniRef50  | Representation learning, Stability prediction, Functional effects of mutations     |
| Bepler and Berger ( <a href="#">2019</a> )           | 2019 | BiLSTM   | SCOPe ASTRAL, Pfam, PDB, TOPCONS, CASP12                | Structural property prediction, Soft symmetric alignment, Transmembrane            |
| MuPIPR ( <a href="#">Zhou et al., 2020</a> )         | 2020 | BiLSTM   | STRING, PDB, SKP1402m, SKP1102s                         | Protein–Protein Interactions (PPI), binding affinity, buried surface area          |
| CSCS ( <a href="#">Hie et al., 2021</a> )            | 2020 | BiLSTM   | IRD, LANL HIV database, ViPR, NCBI Virus, GISAID        | Viral escape patterns, Constrained Semantic Change Search                          |
| ProtTrans ( <a href="#">Elnaggar et al., 2021</a> )  | 2021 | Transformer-XL, XLNet, BERT, Albert, Electra, T5 | UniRef, BFD   | Protein secondary structure, sub-cellular localization, membrane vs. water-soluble |
| ESM-1b ( <a href="#">Rives et al., 2021</a> )        | 2021 | Transformer                                      | Uniparc   | Large-scale pretraining, protein structure, functional effects of mutations        |
| ESM-1v ( <a href="#">Meier et al., 2021</a> )        | 2021 | ESM-1b   | Uniref90  | Functional effects of mutations, zero-shot prediction                              |
| ESM-2, ESMFold ( <a href="#">Lin et al., 2023b</a> ) | 2023 | Transformer                                      | UniRef, PDB, CAMEO, CASP14, MGnify, trRosetta Dataset   | Atom-level resolution structure prediction   |
| AminoBERT ( <a href="#">Chowdhury et al., 2022</a> ) | 2022 | BERT   | ProteinNet12, SCOPe ASTRAL                              | Single-sequence protein structure prediction                                       |
| TCR-BERT ( <a href="#">Wu et al., 2024b</a> )        | 2021 | BERT   | VDJdb, PIRD, LCMV dataset                               | TCR–antigen binding  |
| MSA Transformer ( <a href="#">Rao et al., 2021</a> ) | 2021 | Transformer                                      | UniRef50, UniClust30, CASP13, CAMEO                     | Multiple sequence alignment, evolutionary relationships                            |
| Tranception ( <a href="#">Notin et al., 2022</a> )   | 2022 | Transformer                                      | UniRef  | Homologous sequences retrieval, fitness prediction                                 |
| XTrimopGLM ( <a href="#">Chen et al., 2024a</a> )    | 2024 | Transformer                                      | UniRef90, ColabFoldDB, UniProt, AlphaFold Database, PDB | 100B parameters, Unified Protein Language Model                                    |
| TurNuP ( <a href="#">Kroll et al., 2023</a> )        | 2022 | ESM-1b   | BRENDA, UniProt, Sabio-RK                               | Turnover number predictions, Differential Reaction Fingerprints                    |
| CLEAN ( <a href="#">Yu et al., 2023</a> )            | 2023 | ESM-1b   | UniProt, SwissProt                                      | Contrastive Learning, Enzymatic function prediction                                |
| DeepTMP ( <a href="#">Lin et al., 2023a</a> )        | 2023 | ESM-MSA-1b                                       | PDB, PDBTM, UniRef30, BFD                               | Transfer learning, Transmembrane protein complexes, Inter-chain Contact Prediction |
| vcMSA ( <a href="#">McWhite et al., 2023</a> )       | 2023 | ProtT5-XL-UniRef50                               | Quantest2, HOMSTRAD, UniRef50                           | MSA identification, Reciprocal Best Hits   |
| Poet ( <a href="#">Truong Jr and Bepler, 2023</a> )  | 2023 | Transformer                                      | UniRef50, UniRef100, ProteinGym                         | Homologous Sequences, Retrieval-augmented LM                                       |

Table 2: LLM Methods for Protein Understanding and Prediction: Structure-Integrated and Knowledge-Enhanced Models

| Model                              | Time      | Base Model  | Dataset   | Keywords   |
|------------------------------------|-----------|---|---|--|
| ProteinBERT (Brandas et al., 2022) | 2022      | BERT  | UniRef90, TAPE  | GO annotations, protein structures, post-translational modifications, biophysical properties |
| OntoProtein (Zhang et al., 2022)   | 2022      | ProtBert, Bert  | ProteinKG25, UniRef100, TAPE, STRING, SHS27k, SHS148k   | Knowledge graphs, gene ontology, PPI, structure prediction                                   |
| ProteinCLIP (Wu et al., 2024a)     | 2024      | ESM2, ProtT5, Text-Embedding-3-Large                                      | UniProt   | Contrastive learning, PPI, homology identification   |
| SaProt (Su et al., 2024)           | 2023      | ESM2  | AlphaFoldDB, UniProt, ProteinGym, ClinVar, thermostability, metal ion binding, DeepLoc, TAPE, PEER, FLIP, PDB | Structure-aware vocabulary, Foldseek   |
| ESM-GearNet (Zhang et al., 2023a)  | 2023      | GVP, GearNet, CDConv  | AlphaFold Database, GO (Gligorijević et al., 2021), Atom3D  | Structural encoders for protein modeling   |
| SES-Adapter(Tan et al., 2024)      | 2024      | ESM2, ProtBert, ProtT5, Ankh  | GO (Gligorijević et al., 2021)  | Parameter-Efficient Fine-Tuning, Structure Representation                                    |
| PromptProtein (Wang et al., 2022), | 2023      | Transformer   | UniRef50, PDB, STRING, GO (Gligorijević et al., 2021)   | Prompt Learning, Multi-level of structures   |
| SI-pLMs (Sun and Shen, 2024)       | 2024      | BERT  | Pfam, PDB, AlphaFold Database   | Variant Effect Prediction, Structural Information  |
| Zhang et al. (2024)                | 2024      | ESM-2   | SCOPe, GO and EC (Gligorijević et al., 2021), Swiss-Prot  | Remote Homology Detection, Structural Information  |
| S-plm (Wang et al., 2025)          | 2025      | ESM3, discrete diffusion  | BPTI, RMSD, Apo/holo, Fold-switch, ATLAS  | Contrastive Learning, Structural Information   |
| Wu et al. (2023)                   | 2023      | ESM-2, MSA-Transformer, GVP-GNN, EGNN, SE(3)-Transformer, Schnet, DimeNet | CASP, DB5.5, DIPS, PDBbind  | Geometric Deep Learning  |
| CCPL (Zheng and Li, 2024)          | 2023-2024 | GVP-GNN, ESM-2  | PDB, AlphaFoldDB, ProteinGym, trRosetta, CASP14, CATH, Ts 50&Ts500  | Contrastive Learning, Structure-Sequence Pairing   |
| KeAP (Zhou et al., 2023)           | 2023      | ProteinKG25   | ProteinNet, TAPE  | Knowledge Graph, Contrastive Learning  |
| MolBind (Xiao et al., 2024a)       | 2024      | SciBERT, GIN, Uni-Mol   | MolBind-M4, CASF-2016   | Contrastive Learning, Protein-text-molecule Alignment  |

Table 3: LLM Methods for Protein Understanding and Prediction: Protein Description and Annotation Models

| Model                             | Time | Base Model                               | Dataset  | Keywords  |
|-----------------------------------|------|--|--|---|
| ProtST (Xu et al., 2023b)         | 2023 | ProtBert, PubMedBERT, etc.               | ProtDescribe   | Multimodal learning, protein function annotation, zero-shot text-to-protein retrieval |
| ProtChatGPT (Wang et al., 2024a)  | 2024 | ESM-1b, Transformer                      | PDB-QA, ProteinKG25  | Protein Q&A, cross-modal protein retrieval, qualitative dialogs                       |
| ProteinChat (Guo et al., 2023)    | 2023 | ESM-IF1, Vicuna-13B                      | RCSB-PDB Protein Description   | Interactive protein inquiries, automated protein understanding                        |
| Prot2Text (Abdine et al., 2024)   | 2024 | RGCN, ESM2, GPT2                         | SwissProt  | Multimodality, textual function prediction  |
| ProTranslator (Xu and Wang, 2022) | 2022 | DeepGOCNN, Transformer                   | CAFA3, SwissProt, GOA, Reactome, KEGG, MSigDB  | Function annotation based on text description, text description generation            |
| BioTranslator (Xu et al., 2023a)  | 2023 | PubMedBERT                               | GOA, Swiss-Prot, CAFA3, STRING, GeneCards, Tabula Muris, Tabula Sapiens, Tabula Microcebus, GDSC, STITCH, Monarch Initiative, Reactome | Multimodality, text-to-bio-identity translation                                       |
| BioT5 (Pei et al., 2023)          | 2023 | T5                                       | ZINC20, UniRef, C4, PubMed articles, PubChem, ChEBI20, SwissProt, MoleculeNet, PEER, BindingDB, BioSNAP, HPRD, Yeast PPI dataset       | SELFIES-based molecular representation, wrapped text for bio-entities                 |
| BioT5+ (Pei et al., 2024)         | 2024 | T5                                       | MoleculeNet, ChEBI-20, PEER, BioSNAP, BindingDB  | Multi-task instruction tuning, Molecular  |
| ProLLaMA (Lv et al., 2024)        | 2024 | LLaMA2                                   | UniRef, InterPro   | Instruction understanding, protein understanding and generation                       |
| ProteinGPT (Xiao et al., 2024b)   | 2024 | ESM-2, ESM-IF1, Vicuna, LLaMA-2, LLaMA-3 | ProteinQA  | Multimodal, interactive protein Q&A   |
| ProLLM(Jin et al., 2024)          | 2024 | Flan-T5-large                            | Human, STRING, Mol-Instructions  | Chain-of-Thought, PPI   |

Table 4: LLM Methods for Protein Engineering, Generation and Translation

| Model                                       | Time | Base Model                         | Dataset   | Keywords   |
|---|------|------------------------------------|---|--|
| ProGen (Madani et al., 2023)                | 2020 | Transformer                        | UniParc, UniProtKB, Swiss-Prot, TrEMBL                                | Controllable protein generation, de novo protein design                    |
| ProGen2 (Nijkamp et al., 2023)              | 2022 | Autoregressive                     | UniRef50  | Protein generation, de novo protein design                                 |
| ProtGPT2 (Ferruz et al., 2022)              | 2022 | Autoregressive                     | UniRef50  | Autoregressive transformer, BPE tokenization, zero-shot protein generation |
| ProLLaMA (Lv et al., 2024)                  | 2024 | LLaMA2                             | UniRef50, InterPro  | Multi-task, instruction tuning   |
| IgLM (Shuai et al., 2023)                   | 2023 | GPT-style Transformer              | OAS Training Data, Thera-SAbDab                                       | Infilling, conditioned generation, controllable diversity                  |
| PALM-H3 (He et al., 2024)                   | 2024 | ESM2, RoFormer                     | Observed Antibody Space, CoV-AbDab, BioMap                            | Strong generalization to novel proteins, interpretability, antibody        |
| ProstT5 (Heinzinger et al., 2024)           | 2023 | T5, ProtT5                         | 3Di from AlphaFoldDB, CASP12/14, NetSurfP2.0                          | Bilingual LM, Foldseek, inverse folding                                    |
| Fold2Seq (Cao et al., 2021)                 | 2021 | Transformer                        | CATH 4.2  | Inverse protein design, fold-level representation                          |
| Ankh (Elnaggar et al., 2023)                | 2023 | T5                                 | UniRef50, CASP12/14, NetSurfP-2.0, DeepSF, etc                        | Contact prediction, secondary structure, fold classification, efficiency   |
| ProteinDT (Liu et al., 2023)                | 2023 | ProtBert, SciBERT, ProteinDiff, T5 | SwissProtCLAP   | Multimodal learning, text-to-protein generation, autoregressive            |
| PLMeAE (Zhang et al., 2025)                 | 2025 | ESM-2                              | GB1, UBC9 dataset, Ubiquitin  | Protein engineering, automatic biofoundry                                  |
| ESM-IF (Hsu et al., 2022)                   | 2022 | GVP, GNN, Transformer              | UniRef50, CATH  | Inverse folding, AlphaFold2 augmented dataset                              |
| ESM-3 (Hayes et al., 2025)                  | 2024 | Transformer                        | UniProt, PDB, AlphaFoldDB, Pfam, InterPro, MGnify, JGI, GO Consortium | Multimodal Learning, Evolutionary Simulation                               |
| PAAG (Yuan et al., 2024)                    | 2024 | ProtBERT, SciBERT                  | ProtAnnotation  | Text alignment, annotation   |
| Pinal (Dai et al., 2024)                    | 2024 | T2struct, SaProt-T                 | SwissProt, UniRef50-ProTrek   | Multi-step, functional labels  |
| ProtAgents (Ghafarollahi and Buehler, 2024) | 2024 | GPT-4, Chroma, OmegaFold           | GPTProteinPretrained  | Multi-agent, de novo protein design, protein folding                       |
| Toursynbio (Shen et al., 2024b)             | 2024 | InternLM2-7B                       | ProteinLMDataset  | Multi-modal, agent, interactive  |
| LM-DESIGN (Zheng et al., 2023)              | 2024 | ESM-1b, ESM-2, ProteinMPNN         | CATH 4.2, CATH 4.3, TS50, TS500                                       | De novo protein design, protein folding                                    |

Table 5: Summary of Datasets for Protein Language Model

|             | <b>Dataset</b>   | <b>Last Update</b> | <b>Scale</b> | <b>Keywords</b>   |
|-------------|--|--------------------|--------------|---|
| Pretraining | UniProtKB/Swiss-Prot ( <a href="#">Boutet et al., 2016</a> ) | 2025               | 573K         | Manually curated, high-quality annotations, reviewed                          |
|             | UniProtKB/TrEMBL ( <a href="#">Möller et al., 1999</a> )     | 2025               | 253M         | Computationally annotated, unreviewed, automated predictions                  |
|             | UniRef Clusters ( <a href="#">Suzek et al., 2015</a> )       | 2025               | >250M        | Clustered sequences, reduced redundancy, hierarchical organization            |
|             | Pfam ( <a href="#">Finn et al., 2006</a> )                   | 2024               | 22k          | Protein families, HMMs, functional domains                                    |
|             | PDB ( <a href="#">Bank, 1971</a> )                           | 2025               | 231K         | Protein structures, crystallography, molecular modeling                       |
|             | BFD ( <a href="#">Steinegger and Söding, 2018</a> )          | 2021               | 2.5B         | Massive protein database, sequence clustering, structure prediction           |
|             | UniParc ( <a href="#">Bairoch et al., 2005</a> )             | 2025               | >250M        | Non-redundant, protein sequence archive, database cross-referencing           |
|             | PIR ( <a href="#">Barker et al., 2001</a> )                  | 2025               | 513M         | Protein sequence database, functional annotation, evolutionary classification |
| Benchmark   | AlphaFoldDB ( <a href="#">Tunyasuvunakool et al., 2021</a> ) | 2025               | >200M        | Predicted protein structures, deep learning, proteome coverage                |
|             | CASP ( <a href="#">Kryshtafovych et al., 2019</a> )          | 2024               | N/A          | Protein structure prediction, modeling competitions                           |
|             | ProteinGym ( <a href="#">Notin et al., 2023</a> )            | 2024               | 2.7M         | Protein mutations, deep mutational scanning                                   |
|             | TAPE ( <a href="#">Rao et al., 2019</a> )                    | 2021               | ~120K        | Protein embeddings, sequence modeling   |
|             | CATH ( <a href="#">Orengo et al., 1997</a> )                 | 2024               | >150M        | Structure classification, evolutionary relationships, domain hierarchy        |
|             | PEER ( <a href="#">Xu et al., 2022</a> )                     | 2022               | >60K         | Protein understanding, multi-task benchmark, sequence evaluation              |
|             | ExplorEnz ( <a href="#">McDonald et al., 2009</a> )          | 2025               | 8K           | Enzyme classification, EC numbering, catalytic reactions                      |
| Evaluation  | HIPPIE ( <a href="#">Schaefer et al., 2012</a> )             | 2022               | 39K          | Human protein interactions, network analysis                                  |
|             | ProteinLMBench ( <a href="#">Shen et al., 2024a</a> )        | 2024               | 893K         | Protein language understanding, multiple-choice QA, model evaluation          |

## B Evaluation Metrics

Comprehensive and accurate evaluation is essential for understanding and applying Protein LLMs. Currently, these models are commonly assessed on tasks such as structure prediction, function prediction, and sequence generation.

### B.1 Structure Prediction Metrics

Structure prediction evaluates how accurately a model predicts a protein's three-dimensional structure from its sequence (Kuhlman and Bradley, 2019). Common metrics include:

**Root Mean Square Deviation (RMSD)** measures the distance between the predicted and actual atomic coordinates. Lower RMSD indicates higher structural accuracy (Li, 2013).

**Global Distance Test (GDT-TS)** calculates the percentage of alpha-carbon atoms within thresholds (1, 2, 4, and 8 Å) of the reference structure after iterative superimposition (Zemla, 2003).

GDT-TS usually uses thresholds of 1, 2, 4, and 8 Å. The higher the GDT-TS score, the closer the predicted structure is to the reference structure.

**Template Modeling (TM) Score** evaluates the global structural similarity of proteins with values ranging from 0 to 1 (Zhang and Skolnick, 2004).

$$TM = \max \left[ \frac{1}{L_{tgt}} \sum_i^{L_{com}} \frac{1}{1 + \left( \frac{d_i}{d_0(L_{tgt})} \right)^2} \right], \quad (3)$$

$$d_0(L_{tgt}) = 1.24 \sqrt[3]{L_{tgt} - 15} - 1.8. \quad (4)$$

Here,  $L_{tgt}$  is the length of the target protein amino acid sequence.  $L_{com}$  is the number of residues in the template and target structures.  $d_i$  represents the distance between the  $i$ -th residue pair in the template structure and the target structure. Higher scores indicate closer similarity.

**IDDT**, Local Distance Difference Test, evaluates the local accuracy of protein structure prediction by comparing distances between atom pairs in the predicted structures and those in the reference structures (Mariani et al., 2013).

A distance is considered preserved if it falls within a specified threshold. IDDT is calculated as the proportion of preserved distances, with higher values indicating better local accuracy.

**pLDDT**, Predicted Local Distance Difference Test, is a per-residue measure of local confidence (Guo et al., 2022). pLDDT evaluates the local quality of

the predicted structure without a reference structure. Its computation usually relies on models such as AlphaFold (Jumper et al., 2021), which learns patterns from large-scale protein data. Scores range from 0 to 100, with higher scores indicating greater confidence and more accurate predictions.

### B.2 Function Prediction Metrics

Protein function prediction aims to determine biological roles, including interactions with other biomolecules (Radivojac et al., 2013). The evaluation methods involve machine learning performance metrics and biomedical relevance validation.

Machine learning evaluation metrics can be categorized into classification task metrics and generative task metrics. For classification tasks, such as protein classification and interaction prediction, standard metrics can be adopted, such as precision, recall, F-1 scores, accuracy, and area under the curve (AUC). For generative tasks, such as question answering, evaluation is performed by measuring the alignment between the LLM's output and the ground truth using metrics such as BLEU (Papineni et al., 2002), ROUGE-L (Lin, 2004), and METEOR (Banerjee and Lavie, 2005).

In addition to machine learning metrics, there are also biometric-related evaluation metrics:

**Subcellular Localization** refers to the specific location of proteins within a cell (Briesemeister et al., 2010). The location of a protein is closely related to the function it performs, so by predicting the subcellular localization of a protein, it is possible to speculate on the biological function it may have (Holm, 2020).

**Homology Detection** aims to identify proteins that share an evolutionary relationship (homologous) with the target protein, usually reflected in similarities in sequences, structure, and functions. Traditional methods such as BLAST (Altschul et al., 1990) perform sequence alignment to identify homologs by comparing the query sequence against a database.

Recent deep learning approaches such as TMvec (Hamamsy et al., 2024) focus on structural similarity and generate vector representations of proteins.

**Stability** of the protein is critical for many applications, such as drug development. Predicting the stability of a protein can help determine whether the protein can perform its function efficiently in

the cellular environment (Cheng et al., 2006).

**Solubility** reflects the solubility characteristics of a protein in a particular solvent. Predictions of solubility can help to understand whether a protein can exist and function properly within a cell (Hebditch et al., 2017).

**Mutation Effect Prediction** of proteins refers to the assessment of the impact on various properties, structures, and functions of proteins when their amino acid sequences are changed (Mansoor et al., 2023). Commonly used methods include molecular dynamics-based methods, deep learning-based prediction models, and structural comparison methods.

### B.3 Sequence Generation Metrics

Protein sequence generation is the process of creating new protein sequences using specific methods, models, or algorithms (Anand and Achim, 2022). Common evaluation methods include:

**Perplexity (PPL)** can be used to measure how accurately a model predicts amino acids (Hesslow et al., 2022). The lower the perplexity, the more accurate the prediction.

**Novelty** refers to the degree of uniqueness of the generated protein sequence compared to a database of known protein sequences (Truong Jr and Bepler, 2023).

**Fréchet Protein Distance (FPD)** is used to measure the similarity between the distribution represented by the generated protein sequence and the distribution of the real protein sequence (Jiang et al., 2008), denoted as:

$$\delta_{\mathcal{F}}(f, g) = \inf_{\alpha, \beta} \max_{s \in [0, 1]} \text{dist}(f(\alpha(s)), g(\beta(s))) \quad (5)$$

where  $\alpha$  and  $\beta$  are continuous non-decreasing functions. The sequence distribution can be denoted by  $f$  and  $g$ .

**Diversity** is designed to evaluate the degree of difference between a range of protein sequences generated by a model. Rich diversity means that the model is capable of generating a variety of different sequences. Common methods include Shannon Entropy (Bywater, 2015) and Hamming Distance (McGee et al., 2021).

**Foldability** focuses on whether the generated protein sequence can be folded into a stable three-dimensional structure. Measuring foldability is usually performed with tools such as RoseTTAFold

(Baek et al., 2021) or computational methods based on physicochemical principles (Magliery, 2015) to predict the likelihood that the generated sequence will form a stable structure.

**Recovery** is focused on the ability of a model to predict the corresponding sequence for a given structure accurately (Watson et al., 2023). Evaluating recovery includes methods sequence comparison, structure comparison, functionality comparison, etc.