Prot2Text: Multimodal Protein's Function Generation with GNNs and Transformers

Hadi Abdine[1], **Michail Chatzianastasis**[1], **Costas Bouyioukos**[2, 3], **Michalis Vazirgiannis**[1]

[1]Laboratoire d'Informatique (LIX), École Polytechnique, Institut Polytechnique de Paris, Palaiseau, France
[2]Epigenetics and Cell Fate, CNRS UMR7216, Université Paris Cité, F-75013 Paris, France.
[3]Bioinformatics Research Laboratory, Department of Biological Sciences, University of Cyprus, Nicosia, Cyprus
{hadi.abdine, michail.chatzianastasis}@polytechnique.edu, costas.bouyioukos@u-paris.fr, mvazirg@lix.polytechnique.fr

Abstract

In recent years, significant progress has been made in the field of protein function prediction with the development of various machine-learning approaches. However, most existing methods formulate the task as a multi-classification problem, i.e. assigning predefined labels to proteins. In this work, we propose a novel approach, Prot2Text, which predicts a protein's function in a free text style, moving beyond the conventional binary or categorical classifications. By combining Graph Neural Networks(GNNs) and Large Language Models(LLMs), in an encoder-decoder framework, our model effectively integrates diverse data types including protein sequence, structure, and textual annotation and description. This multimodal approach allows for a holistic representation of proteins' functions, enabling the generation of detailed and accurate functional descriptions. To evaluate our model, we extracted a multimodal protein dataset from SwissProt, and demonstrate empirically the effectiveness of Prot2Text. These results highlight the transformative impact of multimodal models, specifically the fusion of GNNs and LLMs, empowering researchers with powerful tools for more accurate function prediction of existing as well as first-to-see proteins.

1 Introduction

Understanding proteins' function is a central problem in biological sciences, as proteins are the fundamental elements of almost all biological functions. Accurate prediction of proteins' function is essential for understanding biological systems as well as for various applications, such as drug discovery, enabling researchers to identify and target specific proteins that play critical roles in disease pathways (Ha et al. 2021). Traditionally, proteins' functions prediction has been approached through classification methods, assigning predefined labels to proteins based on their characteristics (Kulmanov and Hoehndorf 2019). However, this approach often oversimplifies the complexity of proteins' functionality, limiting the depth of our understanding. To overcome this limitation, we propose a novel view on proteins' functions prediction based on reformulating the task using free-text proteins' descriptions instead of relying on predefined labels. The rapid progress in transformer-based models has brought a massive revolution to the field of Natural Language Processing (NLP). These models have demonstrated impressive language generation capabilities, allowing them to perform a wide range of NLP tasks with remarkable performance, including text completion, translation, sentiment analysis and question-answering (Vaswani et al. 2017; Radford et al. 2019; Brown et al. 2020). On the other hand, Graph Neural Networks(GNNs) have emerged as a powerful tool for modeling graph-structured data, capturing the intricate relationships between different elements in a graph (Kipf and Welling 2017; Reiser et al. 2022). However, the integration of GNNs and transformers faces various challenges, such as effectively handling the heterogeneity of data representations, therefore the field is still in its early stages. Despite this, the potential benefits of leveraging both GNNs and transformers for graph-to-text applications, such as predicting the functional properties of proteins are substantial. To that end, we develop a novel multimodal framework, **Prot2Text**, that can generate detailed and accurate descriptions of proteins' functions in free text. We effectively integrate GNNs and Large Language Models (LLMs), to encompass both structural and sequential information of the protein's 3D structure and amino acid's sequence respectively. The encoder-decoder architecture forms the backbone of our model, with the encoder component employing a Relational Graph Convolution Network (RGCN) (Schlichtkrull et al. 2018) to process the proteins' graphs and the ESM protein language model (Lin et al. 2023a) to encode the proteins' sequences. The decoder component utilizes a pretrained GPT-2 model to generate detailed proteins' descriptions. To train our multimodal model, we compile a dataset of proteins extracted from SwissProt, a comprehensive collection of protein annotations obtained from the UniProt database (Consortium 2015). This dataset encompasses a vast number of proteins, each annotated with its corresponding function or description. In addition to the textual information, we obtain the 3D structure representation of the proteins from AlphaFold (Varadi et al. 2022). We further release this curated dataset to the public, allowing other researchers to use it for benchmarking and further advancements in the field. Code, data and models are publicly available[1]. Our main contributions can be summarized as follows:

[1]https://github.com/hadi-abdine/Prot2Text

- We introduce the **Prot2Text** framework, a novel multimodal approach for generating proteins' functions in free text. Our model combines both GNNs and ESM to encode the protein in a fused representation while a pretrained GPT-2 decodes the protein's text description.
- We propose various baselines for protein text generation and demonstrate that the integration of both graph and sequence protein information leads to better generation capabilities.
- We further release a comprehensive multimodal protein dataset, which includes $256,690$ protein structures, sequences, and textual function descriptions. Researchers can leverage this dataset to benchmark and compare their models, thereby driving advancements in the field and enabling for a more robust and standardized evaluation of proteins' functions prediction methods in free text format.

2 Related Work

Transformers. The transformer-based encoder-decoder model was first introduced by Vaswani et al. (2017). Since then, this model architecture has become the de-facto standard encoder-decoder architecture in Natural Language Processing (NLP). Despite significant research on different pretraining objectives for transformer-based encoder-decoder models such as T5 (Raffel et al. 2019) and Bart (Lewis et al. 2020), the model architecture has remained largely the same. Radford et al. took advantage of the transformer architecture, which is superior and conceptually simpler than Recurrent Neural Networks to introduce the OpenAI GPT model. Specifically, they pretrained a left-to-right transformer decoder as a general language model using the transformer architecture. Following, they fine-tuned the model on 12 different language understanding tasks by applying various transformations to the input. Later, GPT-2 (Radford et al. 2019), a more advanced version of GPT with more trainable parameters, was introduced. The authors showed that as long as general language models have very high capacities, they can reach reasonable performance on many specific natural language processing tasks. The use of the transformer architecture later expanded to include modalities other than natural language, such as images (Dosovitskiy et al. 2021), protein amino acid sequence (Rives et al. 2021; Lin et al. 2023a), and molecules SMILES string (Fabian et al. 2020; Chithrananda, Grand, and Ramsundar 2020).

Multimodal models. The success of the transformer's uni-modality tasks made this architecture broadly studied for multimodal representation learning. One example is The CLIP (Contrastive Language-Image Pre-training) model (Radford et al. 2021) which is a transformer model that facilitates cross-modal understanding between images and text. It combines a ViT vision encoder, with a transformer-based language encoder to learn joint representations of images and their associated textual descriptions. Another example is the MolT5 (Edwards et al. 2022) which is a self-supervised learning framework based on the T5 model for pretraining models on a vast amount of unlabeled natural language text and molecule SMILES strings. MolT5 is able to perform bidirectional translation between molecule representations and natural language allowing molecule captioning and generation providing text prompts. ProtST (Xu et al. 2023), enhances the protein language model classification and retrieval capabilities by co-training it with biomedical text. While ProteinDT (Liu et al. 2023) uses protein language models and pretrained language models to perform text-guided protein generation. Both of the aforementioned text-protein multimodal frameworks take only the protein sequence into consideration to encode the proteins.

Graph Neural Networks. Graph neural networks (GNNs) have emerged as a powerful framework for modeling and analyzing graph-structured data (Scarselli et al. 2009; Kipf and Welling 2017). By iteratively exchanging and integrating information among nodes, GNNs can propagate and refine features throughout the graph, ultimately encoding a comprehensive understanding of the graph's structure and semantics. This ability to capture complex relationships within graphs has contributed to the success of GNNs in various domains, including social network analysis, recommendation systems, and bioinformatics (Zitnik, Agrawal, and Leskovec 2018; Zhang et al. 2021; Chatzianastasis, Vazirgiannis, and Zhang 2023). Numerous studies have suggested various enhancements and expansions to the GNNs' models. Some notable contributions include the introduction of more expressive and adaptable aggregation functions, such as those proposed by Murphy et al. (2019), Seo, Loukas, and Perraudin (2019) and Chatzianastasis et al. (2023). Moreover, several schemes have been developed to incorporate different local structures or high-order neighborhoods, as explored by Morris, Rattan, and Mutzel (2020) and Nikolentzos, Dasoulas, and Vazirgiannis (2020). Furthermore, the domain of GNNs has expanded to encompass heterogeneous graphs, where nodes and edges can have different types and semantics, leading to the development of Heterogeneous Graph Neural Networks effectively handling such complex graph structures (Schlichtkrull et al. 2018; Zhang et al. 2019).

Protein Representation Learning. In the field of protein representation learning, various approaches have emerged over the years, aiming to capture meaningful information from proteins using different data modalities and computational techniques. One prominent avenue of research is focused on sequence-based representations, that extract features solely from the amino acid sequences of proteins. Drawing inspiration from the remarkable achievements of language models in Natural Language Processing (NLP), researchers have also developed pretrained language models tailored specifically for proteins (Brandes et al. 2022; Lin et al. 2023b). These models leverage large-scale protein datasets to learn powerful representations that can subsequently be utilized for various prediction tasks. In addition to sequence-based approaches, graph-based representations leverage the three-dimensional (3D) structure of proteins to capture their functional properties. Zhang et al. (2022) proposed a graph neural network model with a contrastive pertaining strategy for function prediction and fold classification tasks. Chen et al. (2023) proposed a 3D-equivariant graph neural network, specifically designed to estimate the accuracy of protein structural models. Wang et al. (2022) used a hierarchical graph network, which captures the hierarchical relations present in proteins and learns representations at different levels of granularity. Hybrid approaches integrate multiple modalities, including protein sequences, structures, and functional annotations, to create comprehensive representations. These methods combine the strengths of sequence-based and graph-based models to capture diverse aspects of protein function. Gligorijević et al. (2021) proposed DeepFRI which combines sequence features extracted from a protein language model with protein structures. Our work aims to leverage protein sequence and structure models to generate free text annotations of proteins.

3 Methodology

In this section, we present our proposed multimodal framework, **Prot2Text**, for generating protein function descriptions in free text. An illustration of the proposed architecture can be found in Figure 1.

Graph Construction. Upon obtaining the 3D proteins' structures using AlphaFold, we proceed to represent the proteins as a heterogeneous graph $G = (V, E, R)$, where $V = [N] := \{1, ..., N\}$ is the set of vertices representing the amino acids of the proteins, $E \subseteq V \times V$ is the set of edges representing various interactions between the nodes and R is a set of different edge interactions. Each node u is associated with a feature vector $\boldsymbol{x}_u \in \mathbb{R}^d$, encompassing relevant information such as local structural features, and physicochemical properties of the associated amino acids. This enables the graph to retain fine-grained information critical to the protein's structure and function. To model the diverse interactions and relationships between amino acids, we introduce different types of edges connecting the nodes. Therefore, each edge $i = (v, u)$ is associated with an edge type $\boldsymbol{e}_i \in R$. Sequential edges are employed to connect adjacent nodes in the protein sequence, effectively representing the sequential order of amino acids and capturing the linear arrangement of the protein's primary structure. This sequential information is crucial for understanding the folding patterns and functional motifs within the protein. Additionally, we utilize spatial edges to establish connections between nodes that are in close spatial proximity within the 3D structure of the protein. These edges play a pivotal role in encoding the protein's tertiary structure and folding patterns, enabling us to capture the intricate spatial arrangements of amino acids within the protein's core. We further extend the graph construction to include hydrogen bond interactions as an additional edge type. Hydrogen bonds are fundamental non-covalent interactions that are of paramount importance in stabilizing protein structures and enabling specific molecular recognition events. Through the integration of the different edge types, our comprehensive protein graph provides a more holistic and detailed depiction of the protein's structure while capturing both short and long-range interactions.

Graph Encoding. To encode the protein graph G into a vector $\boldsymbol{h}_G \in \mathbb{R}^{d_{out}}$, we employ a Relational Graph Convolutional Neural Network(RGCN) (Schlichtkrull et al. 2018), which effectively considers the various edge types present in the graph in the message-passing mechanism. We denote the neighborhood of type r of a vertex u by $\mathcal{N}_r(u)$ such that $\mathcal{N}_r(u) = \{v : (v, u) \in E_r\}$, where E_r is the set of edges with r edge type. In layer k of the GNN, we update the node representations as follows:

$$\boldsymbol{x}_i^k = \sigma\left(\boldsymbol{W}_{\text{root}}^k \cdot \boldsymbol{x}_i^{k-1} + \sum_{r \in \mathcal{R}} \sum_{j \in \mathcal{N}_r(i)} \frac{1}{|\mathcal{N}_r(i)|} \boldsymbol{W}_r^k \cdot \boldsymbol{x}_j^{k-1}\right), \tag{1}$$

where $\boldsymbol{W}_{\text{root}}^k$ represents the learnable weight matrix for the root transformation in layer k, $\boldsymbol{W}_r^k$ denotes the learnable weight matrix of layer k for relation r and $\sigma(\cdot)$ is an element-wise activation function such as ReLU. This formulation allows nodes to update their representations by incorporating information from neighboring nodes based on the specific edge types, capturing the structural and relational dependencies within the protein graph. To obtain the graph representation from the node representations of the last layer K of the GNN, we apply a mean-pooling layer as follows:

$$\boldsymbol{h}_G = \frac{1}{N} \sum_{i=1}^{N} \boldsymbol{x}_i^K \tag{2}$$

The resulting vector $\boldsymbol{h}_G$ serves as an informative encoded representation of the protein graph, capturing the essential structural and relational characteristics. This representation plays a crucial role in the subsequent text generation process, where it will be utilized to generate detailed and accurate protein functions.

Sequence Encoding. To encode the protein sequence P_S, we used ESM2-35M (Lin et al. 2023a) as our base model. ESM2 is a protein language model that uses a transformer-based architecture and an attention mechanism to learn the interaction patterns between pairs of amino acids in the input sequence. This allows the ESM model to capture amino acid sequence evolutionary information about proteins and their properties. In order to achieve uniform representation dimensions for all modalities within the spatial domain, a projection layer is applied after the last hidden layer of the ESM model. This layer functions as a projection layer that transforms the individual amino acid representations, derived from the ESM embedding dimension, into the graph embedding dimension d_{out}. As a result, a matrix $\boldsymbol{H}_S^0 \in \mathbb{R}^{N, d_{out}}$ is formed, containing the amino acid representations:

$$\boldsymbol{H}_S^0 = ESM(P_S)\boldsymbol{W}_p \tag{3}$$

where $\boldsymbol{W}_p$ is a trainable matrix.

Multimodal Fusion To obtain the final protein encoding, we utilize a fusion block that combines the representation of each amino acid inside the matrix $\boldsymbol{H}_S^0$ with the graph representation vector $\boldsymbol{h}_G$. The fusion process involves a simple element-wise addition of the two representations, followed by a projection layer. This fusion block enables the integration of information from both the sequence and the graph representations in a straightforward manner. Thus, allowing each amino acid to be contextually enriched with infor-

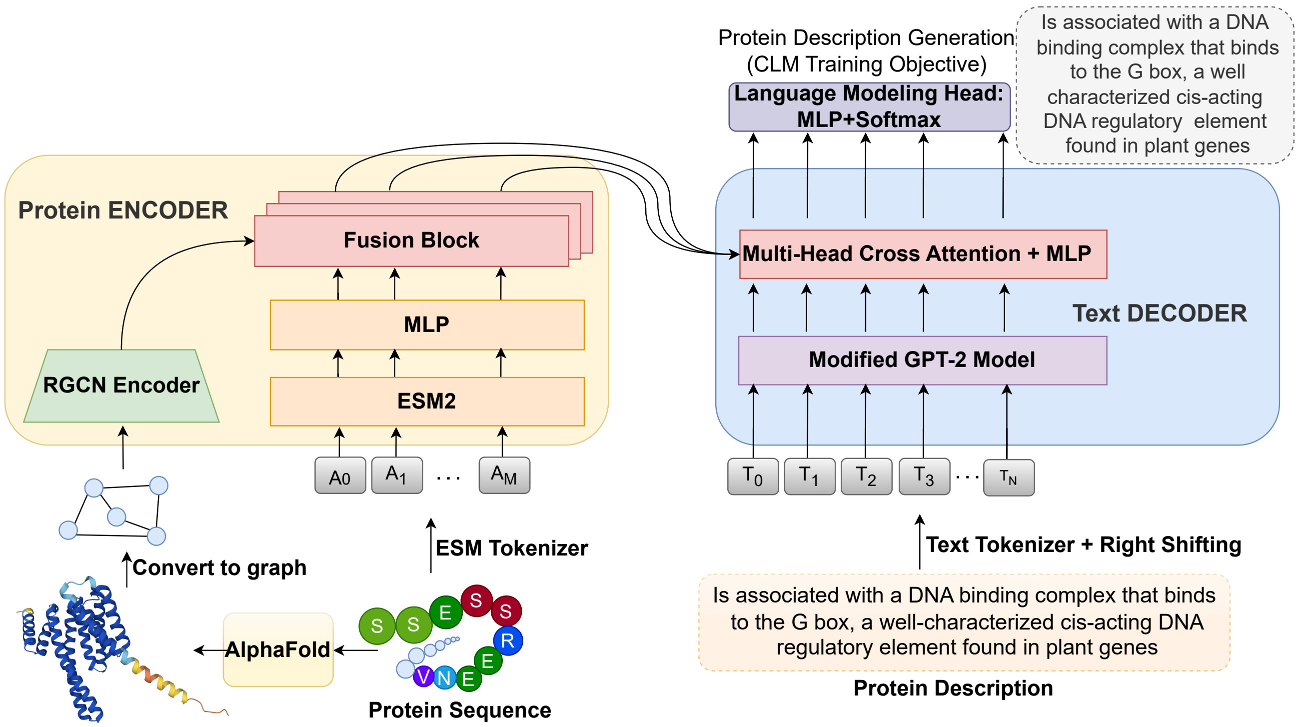


Figure 1: Architecture of the proposed Prot2Text framework for predicting protein function descriptions in free text. The model leverages a multimodal approach that integrates protein sequence, structure, and textual annotations. The encoder component utilizing an RGCN to process the protein graphs, and an ESM model to process the protein sequence. A fusion mechanism facilitates the exchange of relevant information between the graph-encoded and the sequence-encoded vectors, creating a fused representation synthesizing the structural and textual aspects. The decoder component employs a pretrained GPT-2 model, to generate detailed and accurate protein descriptions from the fused protein representation. By combining the power of GNNs and LLMs, Prot2Text enables a holistic representation of protein function, facilitating the generation of comprehensive descriptions.

mation from the graph representation. Additionally, a normalization layer is applied after each fusion block to maintain stable training and further enhance the learning process. Specifically, for each amino acid representation in $\boldsymbol{H}_S^k$, and the graph representation $\boldsymbol{h}_G$, the fusion block computes the combined representation $\boldsymbol{H}_S^{k+1}$ as follows:

$$\boldsymbol{H}_S^{k+1} = \left(\boldsymbol{H}_S^k + \mathbf{1}_n \boldsymbol{h}_G \boldsymbol{W}_V^k\right) \boldsymbol{W}_O^k, \tag{4}$$

where $\boldsymbol{W}_V^k$ and $\boldsymbol{W}_O^k$ are trainable matrices in fusion block k and $\mathbf{1}_n$ is a vector of ones of size n (length of the amino acid sequence).

By using this fusion block multiple times in the architecture (four times in this case), the model can capture complex interactions and dependencies between the sequence and graph representations, leading to an effective and contextually enriched encoding of the protein data. The fusion block could be seen as a special case of the transformers cross-attention block when the the input from the encoder represents only one token.

Text Generation We employed the transformer decoder architecture for generating protein descriptions. We initialized the main components of the decoder, namely the text embedding matrix, self-attention, and language modeling head, with the weights of GPT-2. By doing so, we leveraged the GPT-2 model's capacity to grasp the underlying textual semantics. We forward the protein representation obtained from the protein encoder as input to the multi-head cross-attention module within the transformer decoder. This interaction enabled the model to effectively incorporate context from the protein representation, contributing to the generation of coherent protein descriptions. We adopted the identical vocabulary and tokenizer from the GPT-2 model, with the introduction of two unique special tokens. These additional tokens serve as essential markers, enabling the model to discern the precise boundaries of each protein description within the input text. In the training phase, we employed Causal Language Modeling (CLM) as the training objective to optimize our model. Causal Language Modeling involves training the model to predict the next token in a sequence given the preceding tokens. This unidirectional prediction process ensures that the model generates text in a causal manner, without access to future tokens. The maximum length of each description is 256 tokens.

4 Experimental Results

Dataset To train the Prot2Text framework using proteins' structures, sequences and textual descriptions, we build a multimodal dataset with $256,690$ proteins. For each protein, we have three crucial information: the corresponding sequence, the AlphaFold accession ID and the textual description. To build this dataset, we used the SwissProt database (Bairoch and Apweiler 1996), the only curated proteins knowledge base with full proteins' textual description included in the UniProtKB (Consortium 2016) Release 2022_04. Initially, The SwissProt database in this release has $568,363$ proteins on which we perform the following: (1) Select the following properties: `name` that gives the full name of the protein, `sequence` that gives the amino acid sequence of the protein, `AlphaFoldDB` that gives the accession ID of the protein in AlphaFold database, `taxon` and `text` that gives the protein textual description. (2) Eliminate all samples that do not have all three crucial information. (3) Remove all samples with a duplicate amino acid sequence. (4) Remove all the samples where the textual description contains *"(By Similarity)"*. (5) Apply the CD-HIT clustering algorithm (Li and Godzik 2006) to create a train/-validation/test scheme with $248,315$, $4,172$ and $4,203$ proteins respectively. The maximum similarity threshold between the (train, validation test) sets used in the CD-HIT algorithm is 40%. (6) Preprocess the textual description to remove the *"PubMed"* information. The AlphaFoldDB accession is then used to download the protein structure in a ".PDB" file format using version 4 from AlphaFoldDB.

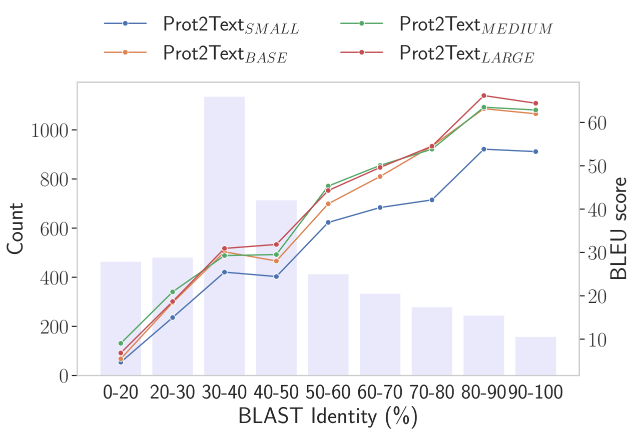


Figure 2: The test BLEU score for Prot2Text models as a function of the percentage identity using BLAST hit between the test and the train sets.

Baselines. In our experimental evaluation, we employed a comprehensive set of baselines to rigorously assess the text generation performance of the Prot2Text framework. Specifically, we compared our approach against unimodal encoders, namely RGCN, ESM, and a vanilla-Transformer trained from scratch. These encoders exclusively focus on either the protein graph or the protein sequence representation. Furthermore, we compared it with a multimodal baseline, RGCN+ESM, that concatenates the graph and sequence representations without fusing the representation of each amino acid and the structure representation. Finally, we compare with RGCN $\times$ vanilla-Transformer baseline, which has similar architecture as Prot2Text but instead uses a vanilla-Transformer model from scratch instead of the pretrained ESM2. In all ESM models, we use the last hidden state. The vanilla-Transformer baseline follows the same configuration and as the pretrained ESM2-35M.

Training Details. We implemented all the models using PyTorch and utilized 64 NVIDIA V100 GPUs for training. We used the AdamW optimizer (Loshchilov and Hutter 2019) with $\epsilon = 10^{-6}$, $\beta_1 = 0.9$, $\beta_2 = 0.999$, with a learning rate starting from 2.10^{-4} and decreasing to zero using a cosine scheduler. We used a warm-up of 6% of the total training steps. We fixed the batch size to four per GPU and we trained the models for 25 epochs. For the GNN encoder, we used 6 layers with a hidden size equal to GPT-2's hidden size (768 for the base model of GPT-2) in each layer. As for the amino acid sequence tokenization, We used the same tokenizer and configuration of ESM2. The training for each Base model lasted for approximately 12 hours. All experiments were carried out using the HuggingFace `transformers` library (Wolf et al. 2020). More details are available in the appendix of the preprint[2].

Metrics. In the experiments, we used several metrics to evaluate the performance of the model in the text generation task. Specifically, we used *BLEU Score* (Papineni et al. 2002) which is a widely used metric for evaluating the quality of machine-generated text. It measures the similarity between the generated text and the reference text based on n-grams. A higher BLEU score indicates better similarity between the generated and reference text. We further used *Rouge-1, Rouge-2* and *Rouge-L* scores (Lin 2004), which measure the overlap of unigrams, bigrams, and longest common subsequence between the generated text and the reference text, respectively. Finally, we used *BERT Score* (Zhang et al. 2020), which measures the similarity between the generated text and the reference text using contextualized word embeddings from a transformer-based model. In our experiments we choose to use BioBERT$_{\text{LARGE}}$-cased v1.1 (Lee et al. 2020) to compute the *BERT Score*.

Results. We report the results in Table 1, for different encoder models, including unimodal encoders like vanilla-Transformer, ESM2-35M, and RGCN, and multimodal encoders like RGCN $\times$ vanilla-Transformer and RGCN + ESM2-35. All models use a GPT-2 decoder. The unimodal vanilla-Transformer baseline, relying solely on the amino acid sequence of the protein, exhibits the lowest performance across all evaluation metrics. However, we observe a significant improvement in performance when using the unimodal graph encoder RGCN. The RGCN outperforms the vanilla-Transformer by over five absolute points in terms of BLEU score and three points in terms of BERT score. This performance disparity highlights the importance of incorporating structural information through the RGCN encoder for protein's function prediction. On the other hand, leveraging the pretrained protein language model ESM2-35M instead of initializing the vanilla-Transformer randomly, results in a remarkable improvement in performance. The

[2]https://arxiv.org/abs/2307.14367

Model	# Params	BLEU Score	Rouge-1	Rouge-2	Rouge-L	BERT Score
vanilla-Transformer	225M	15.75	27.80	19.44	26.07	75.58
ESM2-35M	225M	32.11	47.46	39.18	45.31	83.21
RGCN	220M	21.63	36.20	28.01	34.40	78.91
RGCN + ESM2-35M	255M	30.39	45.75	37.38	43.63	82.51
RGCN × vanilla-Transformer	283M	27.97	42.43	34.91	40.72	81.12
Prot2Text$_{\text{BASE}}$	283M	**35.11**	**50.59**	**42.71**	**48.49**	**84.30**

Table 1: Test set results for different encoder models. All models share the same GPT-2 decoder. Prot2Text$_{\text{BASE}}$ achieves the highest performance across all evaluation metrics, including BLEU score, Rouge scores, and BERT Score.

ESM2-35M encoder leads to a substantial increase of over 16 BLEU score points and 18 Rouge-L points compared to the standard vanilla-Transformer configuration. This notable enhancement can be attributed to the pretraining of ESM2-35M using masked protein modeling, which enables the encoder to capture intricate relationships and patterns within protein sequences. In the context of multimodal protein representation, the evaluation results demonstrate that Prot2Text$_{\text{BASE}}$ exhibits superior performance across all assessment metrics. Notably, it achieves the highest BLEU, Rouge-1, Rouge-2, Rouge-L, and BERT scores. These outcomes highlight the effectiveness of fusing protein structure and amino acid information in a multimodal manner. The incorporation of protein structure, facilitated by the Relational Graph Convolutional Network (RGCN) with the sequential representations of amino acids from ESM2-35, significantly enhances the overall performance across all evaluation metrics. This improvement is attributed to the enriched understanding of proteins achieved through the synergy of these two modalities. Furthermore, the efficacy of the multimodal fusion approach is corroborated by the results obtained from RGCN × vanilla-Transformer. Introducing structural information using RGCN to the randomly initialized vanilla-Transformer yields a substantial improvement of over 10 BLEU score points compared to using the vanilla-Transformer alone, and more than 6 BLEU score points improvement over using RGCN in isolation. Finally, to show the importance of the fusion block in the Prot2Text framework, we compare it against RGCN + ESM2-25, which concatenates the protein structure representation to the amino acids representations. In this case, the graph representation will simply be passed to the decoder alongside the ESM output. We notice that using this strategy leads to slightly worse results than using the ESM alone. This not only provides backing for the selection of the fusion block employed in Prot2Text, but also suggests that indiscriminately increasing the overall parameter count of the model could potentially lead to a degradation in its performance.

Ablation Study: Scaling to Larger Models. We conducted an ablation study to assess the performance of our Prot2Text framework as we varied the number of parameters. The primary objective of this experiment was to evaluate the benefits of employing larger models in terms of generating more accurate and detailed textual representations of protein's function. To conduct the ablation study, we systematically varied the size of the protein language model (ESM). Where Prot2Text$_{\text{SMALL}}$, Prot2Text$_{\text{BASE}}$, Prot2Text$_{\text{MEDIUM}}$ and Prot2Text$_{\text{LARGE}}$ use ESM2-8M, ESM2-35M, ESM2-150M and ESM2-650M respectively. We evaluated each configuration on the same test set of proteins and used the same evaluation metrics as described earlier. The results of the ablation study, presented in Table 2, show a trend of performance improvement as we scale up the model's architecture. Larger versions of ESM outperformed their smaller counterparts in most evaluation metrics. The increase in model size led to more accurate and relevant descriptions, indicating the benefit of leveraging larger language models in the Prot2Text framework. Yet, complementary analysis including corresponding computation time showed an increase in the inference cost following the use of larger models. Therefore, Prot2Text$_{\text{MEDIUM}}$ (398M parameters) is a good trade-off striking the balance between performance and computational cost. Furthermore, in Figure 2 we report the performance of all Prot2text models with respect to different similarity thresholds. Where the similarity represents the highest alignment score between the amino acid sequences of the test and train sets using BLAST identity. We observe that for test proteins with low similarity scores with the train set (between 20% and 30%) and for proteins with no counterpart in the train set, the Prot2Text$_{\text{MEDIUM}}$ is the dominant one while for higher similarity scores Prot2Text$_{\text{LARGE}}$ performs better.

Visualization of Generated Descriptions. To gain deeper insights into the quality of the generated proteins' functions by our *Prot2Text* framework, we provide in Figure 3 a textual comparison of the pre-defined labels and generated text outputs for a selected set of proteins from the test set. It illustrates a comparison between the ground truth and the corresponding descriptions generated by Prot2Text$_{\text{BASE}}$ for two different proteins using each protein's amino acid sequence and 3D structural representation. The results indicate a successful detailed reconstruction of the different proteins' functions including richer information than the known description. Following, Figure 3 showcases the model's ability to generate coherent and informative free-text descriptions that align closely with the ground truth annotations.

5 Conclusion

In conclusion, our paper introduces Prot2Text, a pioneering multimodal framework, for the accurate prediction of a protein's function in free text format, from graph and sequential input. By reformulating the task as text generation, we address the limitations of traditional classification-based methods, allowing for a more nuanced and in-depth under-

Model	# Params	BLEU Score	Rouge-1	Rouge-2	Rouge-L	BERT Score	Inference Time
Prot2Text$_{\text{SMALL}}$	256M	30.01	45.78	38.08	43.97	82.60	1,225
Prot2Text$_{\text{BASE}}$	283M	35.11	50.59	42.71	48.49	84.30	1,379
Prot2Text$_{\text{MEDIUM}}$	398M	**36.51**	52.13	44.17	50.04	84.83	1,334
Prot2Text$_{\text{LARGE}}$	898M	36.29	**53.68**	**45.60**	**51.40**	**85.20**	1,667

Table 2: Test set results for different size variations of Prot2Text. Larger models outperform their smaller counterparts across most evaluation metrics, indicating the benefits of employing larger language models in the Prot2Text framework. The Prot2Text$_{\text{MEDIUM}}$ model, strikes an optimal balance between performance and computational efficiency. The inference time is in seconds for text generation on the whole test set. The inference time is computed during text generation using two NVIDIA RTX 6000 with 48GB memory in parallel and batch size of four per device.

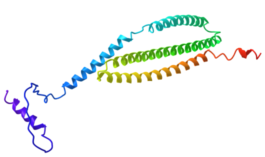
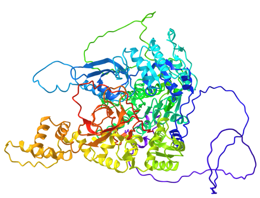
Protein	Labeled Text	Generated Text
 **P36108**	Required for the sorting and concentration of proteins resulting in the entry of these proteins into the invaginating vesicles of the multivesicular body (MVB). Acts a component of the ESCRT-III complex, which appears to be critical for late steps in MVB sorting, such as membrane invagination and final cargo sorting and recruitment of late-acting components of the sorting machinery. The MVB pathway requires the sequential function of ESCRT-O, -I,-II and -III complex assemblies. Can directly stimulate VPS4 ATPase activity. The DID4/VPS2-VPS24 subcomplex is required for the VPS4-dependent dissociation of ESCRT-III.	Probable peripherally associated component of the endosomal sorting required for transport complex III (ESCRT-III) which is involved in multivesicular bodies (MVBs) formation and sorting of endosome-derived cargo proteins into MVBs. MVBs contain intraluminal vesicles (ILVs) that are generated by invagination and scission from the limiting membrane of the cell and mostly are delivered to lysosomes enabling degradation of membrane proteins, such as stimulated growth factor receptors, lysogenic enzymes and lipids. The MVB pathway appears to require the sequential function of ESCRT-O, -I,-II and -III complexes. ESCRT proteins mostly dissociate from the invaginating membrane before the ILV is released. The ESCRT machinery also functions in topologically equivalent membrane fission events, such the terminal stages of cytokinesis and the budding of enveloped viruses (HIV-1 and other lentiviruses). ESCRT I, -II and III proteins mostly mediate the sorting of proteins into lysosphingolipids, primarily cytoplasmic membrane vesicle-derived proteins. ESCR-III proteins are believed to mediate a specialized role in the final stages
 **Q8NG08**	5'-3' DNA helicase involved in DNA damage response by acting as an inhibitor of DNA end resection. Recruitment to single-stranded DNA (ssDNA) following DNA damage leads to inhibit the nucleases catalyzing resection, such as EXO1, BLM and DNA2, possibly via the 5'-3' ssDNA translocase activity of HELB. As cells approach S phase, DNA end resection is promoted by the nuclear export of HELB following phosphorylation. Acts independently of TP53BP1. Unwinds duplex DNA with 5'-3' polarity. Has single-strand DNA-dependent ATPase and DNA helicase activities. Prefers ATP and dATP as substrates. During S phase, may facilitate cellular recovery from replication stress.	DNA-dependent ATPase and 5'-3' DNA helicase required for the maintenance of genome stability. Involved in various processes such as transcription-coupled nucleotide excision repair, mitotic spindle assembly, DNA damage response and DNA repair. During DNA double-strand break (DSB) repair, involved in limiting the number of single-stranded DSBs through DNA end resection by promoting the recruitment of RAD51 to sites of DNA damage. In addition to DNA end reannealing, also promotes the resumption of DNA synthesis from the new 3'-tail end of the existing DNA ends. Acts as a regulator of telomerase by inhibiting telomeric silencing: binds to telomeromyosin, and is required for telomeronucleolytic silencing of endogenous small interfering RNAs (endo-siRNAs) and their targeting to the telomere. Involves also DNA damage signaling via the 5'-5' helicase and DNA helicases activities, preventing disintegration of the DNA duplex and subsequent resection of the damaged DNA strand. In vitro able to unwind 5'-overhanging flap DNA and catalyzes ATP-dependent unwinding of 5'-DNA ends.

Figure 3: Ground-truth labeled text vs predicted text: A textual comparison of the labeled descriptions and generated text outputs for three different proteins from the test set.

standing of a protein's functionality. Leveraging the power of GNNs and LLMs, we integrate structural and textual protein information, resulting in highly detailed and coherent generated protein descriptions. The release of a comprehensive multimodal protein dataset further empowers the scientific community to benchmark and advance the field of protein function prediction in free text format. This innovative approach opens new horizons for research and applications in drug discovery, protein engineering, and various biological sciences, with the potential to revolutionize our understanding of proteins' functions.

6 Limitation and Future Work

One limitation of our proposed Prot2Text model is that the RGCN encoder is not pretrained. Unlike the ESM which benefits from pretraining on a large corpus, the RGCN encoder lacks this initial knowledge. As a result, the RGCN encoder might struggle to capture complex patterns, potentially leading to suboptimal performance. To address this limitation, we aim to explore pretraining techniques specifically tailored for graph neural networks. This could involve pretraining the RGCN encoder on auxiliary graph-related tasks, leveraging graph-level or node-level information to build a foundational understanding of protein structures.

Acknowledgements

This research was supported by the ANR chair AML/HELAS (ANR-CHIA-0020-01).

References

Bairoch, A.; and Apweiler, R. 1996. The SWISS-PROT Protein Sequence Data Bank and Its New Supplement TREMBL. *Nucleic Acids Research*, 24(1): 21–25.

Brandes, N.; Ofer, D.; Peleg, Y.; Rappoport, N.; and Linial, M. 2022. ProteinBERT: a universal deep-learning model of protein sequence and function. *Bioinformatics*, 38(8): 2102–2110.

Brown, T.; Mann, B.; Ryder, N.; Subbiah, M.; Kaplan, J. D.; Dhariwal, P.; Neelakantan, A.; Shyam, P.; Sastry, G.; Askell, A.; et al. 2020. Language models are few-shot learners. *Advances in neural information processing systems*, 33: 1877–1901.

Chatzianastasis, M.; Lutzeyer, J.; Dasoulas, G.; and Vazirgiannis, M. 2023. Graph ordering attention networks. In *Proceedings of the 37th AAAI Conference on Artificial Intelligence*, 7006–7014.

Chatzianastasis, M.; Vazirgiannis, M.; and Zhang, Z. 2023. Explainable Multilayer Graph Neural Network for Cancer Gene Prediction. *arXiv preprint arXiv:2301.08831*.

Chen, C.; Chen, X.; Morehead, A.; Wu, T.; and Cheng, J. 2023. 3D-equivariant graph neural networks for protein model quality assessment. *Bioinformatics*, 39(1): btad030.

Chithrananda, S.; Grand, G.; and Ramsundar, B. 2020. ChemBERTa: large-scale self-supervised pretraining for molecular property prediction. *arXiv preprint arXiv:2010.09885*.

Consortium, T. U. 2016. UniProt: the universal protein knowledgebase. *Nucleic Acids Research*, 45(D1): D158–D169.

Consortium, U. 2015. UniProt: a hub for protein information. *Nucleic acids research*, 43(D1): D204–D212.

Dosovitskiy, A.; Beyer, L.; Kolesnikov, A.; Weissenborn, D.; Zhai, X.; Unterthiner, T.; Dehghani, M.; Minderer, M.; Heigold, G.; Gelly, S.; Uszkoreit, J.; and Houlsby, N. 2021. An Image is Worth 16x16 Words: Transformers for Image Recognition at Scale. In *International Conference on Learning Representations*.

Edwards, C.; Lai, T.; Ros, K.; Honke, G.; Cho, K.; and Ji, H. 2022. Translation between Molecules and Natural Language. In *Proceedings of the 2022 Conference on Empirical Methods in Natural Language Processing*, 292–305.

Fabian, B.; Edlich, T.; Gaspar, H.; Segler, M.; Meyers, J.; Fiscato, M.; and Ahmed, M. 2020. Molecular representation learning with language models and domain-relevant auxiliary tasks. arXiv:2011.13230.

Gligorijević, V.; Renfrew, P. D.; Kosciolek, T.; Leman, J. K.; Berenberg, D.; Vatanen, T.; Chandler, C.; Taylor, B. C.; Fisk, I. M.; Vlamakis, H.; et al. 2021. Structure-based protein function prediction using graph convolutional networks. *Nature communications*, 12(1): 3168.

Ha, J.; Park, H.; Park, J.; and Park, S. B. 2021. Recent advances in identifying protein targets in drug discovery. *Cell Chemical Biology*, 28(3): 394–423.

Kipf, T. N.; and Welling, M. 2017. Semi-Supervised Classification with Graph Convolutional Networks. In *5th International Conference on Learning Representations*.

Kulmanov, M.; and Hoehndorf, R. 2019. DeepGOPlus: improved protein function prediction from sequence. *Bioinformatics*, 36(2): 422–429.

Lee, J.; Yoon, W.; Kim, S.; Kim, D.; Kim, S.; So, C. H.; and Kang, J. 2020. BioBERT: a pre-trained biomedical language representation model for biomedical text mining. *Bioinformatics*, 36(4): 1234–1240.

Lewis, M.; Liu, Y.; Goyal, N.; Ghazvininejad, M.; Mohamed, A.; Levy, O.; Stoyanov, V.; and Zettlemoyer, L. 2020. BART: Denoising Sequence-to-Sequence Pre-training for Natural Language Generation, Translation, and Comprehension. In *Proceedings of the 58th Annual Meeting of the Association for Computational Linguistics*, 7871–7880. Online: Association for Computational Linguistics.

Li, W.; and Godzik, A. 2006. Cd-hit: a fast program for clustering and comparing large sets of protein or nucleotide sequences. *Bioinformatics*, 22(13): 1658–1659.

Lin, C.-Y. 2004. Rouge: A package for automatic evaluation of summaries. In *Text summarization branches out*, 74–81.

Lin, Z.; Akin, H.; Rao, R.; Hie, B.; Zhu, Z.; Lu, W.; Smetanin, N.; Verkuil, R.; Kabeli, O.; Shmueli, Y.; dos Santos Costa, A.; Fazel-Zarandi, M.; Sercu, T.; Candido, S.; and Rives, A. 2023a. Evolutionary-scale prediction of atomic-level protein structure with a language model. *Science*, 379(6637): 1123–1130. Earlier versions as preprint: bioRxiv 2022.07.20.500902.

Lin, Z.; Akin, H.; Rao, R.; Hie, B.; Zhu, Z.; Lu, W.; Smetanin, N.; Verkuil, R.; Kabeli, O.; Shmueli, Y.; et al. 2023b. Evolutionary-scale prediction of atomic-level protein structure with a language model. *Science*, 379(6637): 1123–1130.

Liu, S.; Li, Y.; Li, Z.; Gitter, A.; Zhu, Y.; Lu, J.; Xu, Z.; Nie, W.; Ramanathan, A.; Xiao, C.; Tang, J.; Guo, H.; and Anandkumar, A. 2023. A Text-guided Protein Design Framework. *arXiv preprint arXiv:2302.04611*.

Loshchilov, I.; and Hutter, F. 2019. Decoupled Weight Decay Regularization. In *International Conference on Learning Representations*.

Morris, C.; Rattan, G.; and Mutzel, P. 2020. Weisfeiler and Leman go sparse: Towards scalable higher-order graph embeddings. In *Advances in Neural Information Processing Systems*, volume 34.

Murphy, R.; Srinivasan, B.; Rao, V.; and Ribeiro, B. 2019. Relational Pooling for Graph Representations. In *Proceedings of the 36th International Conference on Machine Learning*, 4663–4673.

Nikolentzos, G.; Dasoulas, G.; and Vazirgiannis, M. 2020. k-hop graph neural networks. *Neural Networks*, 130: 195–205.

Papineni, K.; Roukos, S.; Ward, T.; and Zhu, W.-J. 2002. Bleu: a method for automatic evaluation of machine translation. In *Proceedings of the 40th annual meeting of the Association for Computational Linguistics*, 311–318.

Radford, A.; Kim, J. W.; Hallacy, C.; Ramesh, A.; Goh, G.; Agarwal, S.; Sastry, G.; Askell, A.; Mishkin, P.; Clark, J.; and Krueger, G. 2021. CLIP: Learning Transferable Visual Models From Natural Language Supervision. In *International Conference on Learning Representations*.

Radford, A.; Narasimhan, K.; Salimans, T.; and Sutskever, I. 2018. Improving language understanding by generative pre-training.

Radford, A.; Wu, J.; Child, R.; Luan, D.; Amodei, D.; and Sutskever, I. 2019. Language Models are Unsupervised Multitask Learners.

Raffel, C.; Shazeer, N.; Roberts, A.; Lee, K.; Narang, S.; Matena, M.; Zhou, Y.; Li, W.; and Liu, P. J. 2019. Exploring the limits of transfer learning with a unified text-to-text transformer. *arXiv preprint arXiv:1910.10683*.

Reiser, P.; Neubert, M.; Eberhard, A.; Torresi, L.; Zhou, C.; Shao, C.; Metni, H.; van Hoesel, C.; Schopmans, H.; Sommer, T.; et al. 2022. Graph neural networks for materials science and chemistry. *Communications Materials*, 3(1): 93.

Rives, A.; Meier, J.; Sercu, T.; Goyal, S.; Lin, Z.; Liu, J.; Guo, D.; Ott, M.; Zitnick, C. L.; Ma, J.; et al. 2021. Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences. *Proceedings of the National Academy of Sciences*, 118(15): e2016239118. BioRxiv 10.1101/622803.

Scarselli, F.; Gori, M.; Tsoi, A. C.; Hagenbuchner, M.; and Monfardini, G. 2009. The Graph Neural Network Model. *IEEE Transactions on Neural Networks*, 20(1): 61–80.

Schlichtkrull, M.; Kipf, T. N.; Bloem, P.; Van Den Berg, R.; Titov, I.; and Welling, M. 2018. Modeling relational data with graph convolutional networks. In *The Semantic Web: 15th International Conference, ESWC 2018, Heraklion, Crete, Greece, June 3–7, 2018, Proceedings 15*, 593–607. Springer.

Seo, Y.; Loukas, A.; and Perraudin, N. 2019. Discriminative structural graph classification. *arXiv preprint arXiv:1905.13422*.

Varadi, M.; Anyango, S.; Deshpande, M.; Nair, S.; Natassia, C.; Yordanova, G.; Yuan, D.; Stroe, O.; Wood, G.; Laydon, A.; et al. 2022. AlphaFold Protein Structure Database: massively expanding the structural coverage of protein-sequence space with high-accuracy models. *Nucleic acids research*, 50(D1): D439–D444.

Vaswani, A.; Shazeer, N.; Parmar, N.; Uszkoreit, J.; Jones, L.; Gomez, A. N.; Kaiser, L. u.; and Polosukhin, I. 2017. Attention is All you Need. In Guyon, I.; Luxburg, U. V.; Bengio, S.; Wallach, H.; Fergus, R.; Vishwanathan, S.; and Garnett, R., eds., *Advances in Neural Information Processing Systems*, volume 30. Curran Associates, Inc.

Wang, L.; Liu, H.; Liu, Y.; Kurtin, J.; and Ji, S. 2022. Learning protein representations via complete 3d graph networks. *arXiv preprint arXiv:2207.12600*.

Wolf, T.; Debut, L.; Sanh, V.; Chaumond, J.; Delangue, C.; Moi, A.; Cistac, P.; Rault, T.; Louf, R.; Funtowicz, M.; Davison, J.; Shleifer, S.; von Platen, P.; Ma, C.; Jernite, Y.; Plu, J.; Xu, C.; Le Scao, T.; Gugger, S.; Drame, M.; Lhoest, Q.; and Rush, A. 2020. Transformers: State-of-the-Art Natural Language Processing. In *Proceedings of the 2020 Conference on Empirical Methods in Natural Language Processing: System Demonstrations*, 38–45. Online: Association for Computational Linguistics.

Xu, M.; Yuan, X.; Miret, S.; and Tang, J. 2023. ProtST: Multi-Modality Learning of Protein Sequences and Biomedical Texts. *arXiv preprint arXiv:2301.12040*.

Zhang, C.; Song, D.; Huang, C.; Swami, A.; and Chawla, N. V. 2019. Heterogeneous graph neural network. In *Proceedings of the 25th ACM SIGKDD international conference on knowledge discovery & data mining*, 793–803.

Zhang, T.; Kishore, V.; Wu, F.; Weinberger, K. Q.; and Artzi, Y. 2020. BERTScore: Evaluating Text Generation with BERT. In *International Conference on Learning Representations*.

Zhang, X.-M.; Liang, L.; Liu, L.; and Tang, M.-J. 2021. Graph neural networks and their current applications in bioinformatics. *Frontiers in genetics*, 12: 690049.

Zhang, Z.; Xu, M.; Jamasb, A.; Chenthamarakshan, V.; Lozano, A.; Das, P.; and Tang, J. 2022. Protein representation learning by geometric structure pretraining. *arXiv preprint arXiv:2203.06125*.

Zitnik, M.; Agrawal, M.; and Leskovec, J. 2018. Modeling polypharmacy side effects with graph convolutional networks. *Bioinformatics*, 34(13): i457–i466.