Captioning of 3D Protein Structures using CNN and Transformer

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May 5, 2025

Abstract

This report presents an innovative approach for automatic captioning of 3D protein structures using a combination of Convolutional Neural Networks (CNN) and Transformer models. The system converts 3D protein structures represented as voxel grids into descriptive captions that summarize key structural and functional aspects of the proteins. By leveraging a ResNet-based feature extractor and a Transformer decoder, the model can generate informative descriptions that capture the essential characteristics of protein structures. Our experiments demonstrate promising results with BLEU scores indicating good alignment with human-created descriptions, suggesting potential applications in protein database annotation, educational tools, and computer-aided drug discovery.

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1 Problem Statement and Motivation

The unprecedented growth in protein structure databases, accelerated by recent advances in methods like AlphaFold, has created a need for tools that can automatically summarize and describe these complex 3D structures in natural language. While experts can manually annotate protein structures, this approach doesn't scale to the millions of structures being determined. Furthermore, the complex spatial arrangements of proteins make them difficult to describe concisely and consistently.

This project addresses this critical gap by developing an automated system that can generate natural language descriptions of 3D protein structures. The motivation stems from applications in scientific literature generation, educational tools for biochemistry, improved searchability of protein databases using natural language queries, and potential use in computer-aided drug design where structural insights need to be communicated efficiently between computational and experimental scientists.

2 Introduction

Protein structures are fundamental to understanding biological functions, drug interactions, and disease mechanisms. However, these complex 3D arrangements of atoms are difficult to describe in natural language, requiring specialized expertise and considerable time. Our system tackles this challenge by utilizing deep learning to automatically generate descriptive captions for 3D protein structures. The approach combines 3D convolutional neural networks (CNNs) for feature extraction from voxelized protein representations with transformer-based sequence models for natural language generation. This integrated architecture enables the conversion of complex spatial information into informative textual descriptions accessible to both experts and non-experts in the field of structural biology.

3 Base Paper Link/PDFs and Related Papers

The research builds upon several key papers in the fields of computer vision, natural language processing, and structural bioinformatics:

1. **Protein captioning: Bridging the gap between protein sequences and natural languages** (Anonymous authors)
   https://dl.acm.org/doi/pdf/10.1145/3705322
   The paper introduces Protein Captioning, a multimodal task using a generative model (P2T-GPT) to translate protein sequences into natural language, bridging protein science and NLP with demonstrated effectiveness on the ProteinCap dataset.

2. **To Improve Protein Sequence Profile Prediction through Image Captioning on Pairwise Residue Distance Map** (Sheng Chen, Zhe Sun, Yutong Lu Huiying Zhao and Yuedong Yang)
   https://www.biorxiv.org/content/10.1101/628917v2.full.pdf
   The study presents SPROF, a novel method combining 1D and 2D structural features with deep learning to predict protein sequence profiles, achieving a 39.8% sequence recovery rate and improving upon previous models like SPIN2.

3. **MICER: a pre-trained encoder–decoder architecture for molecular image captioning** (Jiacai Yi, ChengkunWu, Xiaochen Zhang, Xinyi Xiao, Yanlong Qiu, Wentao Zhao, Tingjun Hou and Dongsheng Cao)
   https://academic.oup.com/bioinformatics/article/38/19/4562/6656348
   The paper introduces MICER, an encoder–decoder deep learning framework for molecular image captioning that leverages transfer learning and attention mechanisms to outperform existing methods in automatic chemical structure recognition across diverse datasets.

4. **Scalable 3D Captioning with Pretrained Models** (Tiange Luo, Chris Rockwell, Honglak Lee1,Justin Johnson)
   https://arxiv.org/pdf/2306.07279
   The paper presents Cap3D, an automated system for generating high-quality text descriptions of 3D objects by leveraging pretrained models, outperforming human annotations in quality, cost, and speed across large-scale datasets like Objaverse and ABO.

5. **ProtT3: Protein-to-Text Generation for Text-based Protein Understanding** (Zhiyuan Liu, An Zhang, Hao Fei, Enzhi Zhang, Xiang Wang, Kenji Kawaguchi, Tat-Seng Chua)
   https://aclanthology.org/2024.acl-long.324.pdf
   The paper introduces ProtT3, a novel framework that bridges Protein Language Models and Language Models via a cross-modal projector to enable effective protein-to-text generation, significantly outperforming baselines across tasks like protein captioning, QA, and retrieval.

4 Datasets

4.1 Original Dataset

Our work utilizes protein structure data from the Protein Data Bank (PDB), which is the primary repository for experimentally determined 3D structures of biological macromolecules.

Source: https://www.rcsb.org/

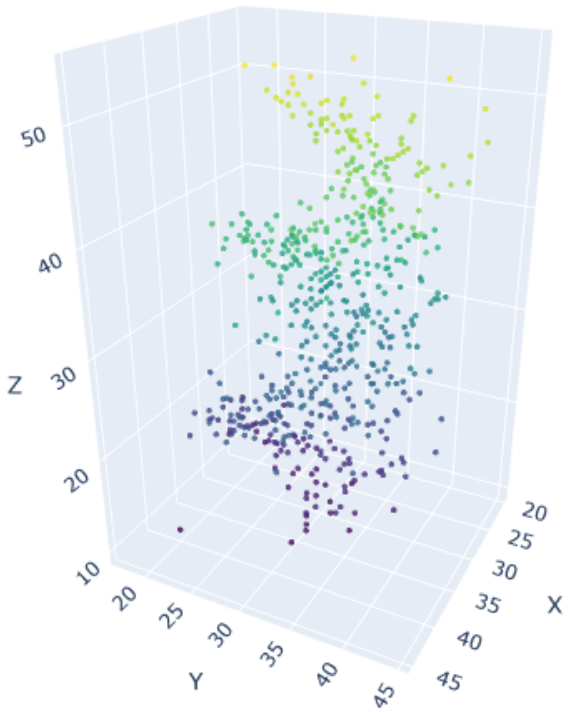
The dataset consists of:

- Over 10,000 protein structures in standard PDB format
- Associated metadata including descriptions, classifications, and experimental methods
- Resolution information for structures determined by X-ray crystallography

4.2 Pre-processed Dataset

The proteins underwent several preprocessing steps to convert them into a format suitable for deep learning:

- Conversion from PDB format to voxel representation (64×64×64 grid)
- Normalization of atomic positions and properties
- Association of each structure with its corresponding description
- Mapping of descriptions to voxel files (stored in CSV format)



Files:

- `pdb_voxel_mapping.csv` - Maps protein structures to their voxel representations and descriptions
- `voxel/` - Directory containing voxelized protein structures in pickle format
- `extracted_features/` - Directory storing CNN-extracted features

5 Features Extracted from Dataset

From the 3D voxel representations of proteins, we extracted several key features using our ResNet-based architecture:

1. **Spatial Features:** High-dimensional embeddings (512-dimensional) capturing the 3D arrangement of atoms and amino acid residues
2. **Local Structure Features:** Representations of secondary structure elements (alpha helices, beta sheets) and their spatial relationships
3. **Surface Features:** Information about the protein surface topology, potential binding sites, and accessible areas
4. **Density Distribution:** Features representing the electron density distribution in the voxel grid
5. **Global Structure Features:** Overall shape and size characteristics of the protein structure

The feature extraction process converts each $64 \times 64 \times 64$ voxel grid into a dense feature vector that encapsulates the essential structural information needed for caption generation. These features are stored as numpy arrays (.npy files) and used as input to the Transformer captioning model.

6 Model Architecture

6.1 Overall Architecture

Our system employs a two-stage architecture for protein structure captioning:

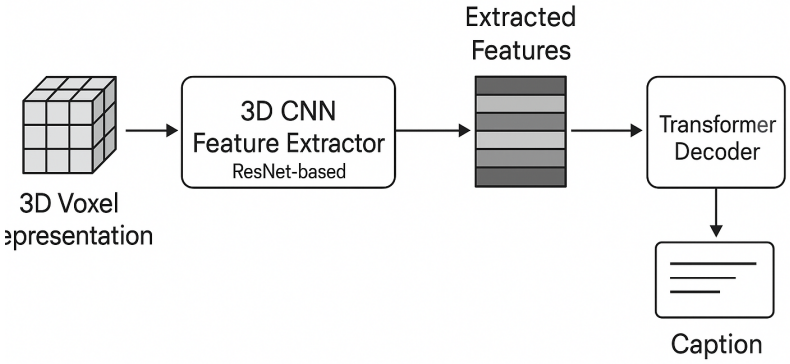


Figure 1: Overall architecture of the 3D protein structure captioning system

The model consists of two main components:

1. **3D CNN Feature Extractor:** A ResNet-based convolutional neural network that processes the 3D voxel representation of proteins
2. **Transformer Decoder:** A sequence generation model that converts extracted features into natural language captions

6.2 3D CNN Feature Extractor

The feature extraction component utilizes a 3D ResNet architecture specifically designed for volumetric data. The ResNet model includes:

- An initial 3D convolutional layer (7×7×7 kernel, stride 2)
- Batch normalization and ReLU activation
- 3D max pooling layer (3×3×3 kernel, stride 2)
- Four residual blocks with increasing channel dimensions (64, 128, 256, 512)
- Global average pooling to produce a 512-dimensional feature vector
- Final fully connected layer projecting to the embedding dimension

Each residual block contains two 3D convolutional layers with batch normalization and ReLU activation, along with skip connections that enable the network to learn deeper representations.

6.3 Transformer Decoder

The caption generation component consists of a Transformer decoder architecture:

- Multi-head self-attention layers to process the sequential caption tokens
- Cross-attention layers that connect the CNN features to the sequence generation process
- Feed-forward neural networks with layer normalization
- Positional encoding to maintain sequence ordering information
- Linear projection and softmax layer to generate word probabilities

The Transformer decoder processes the protein structure features from the CNN and generates captions token by token in an autoregressive manner. During training, teacher forcing is employed, while during inference, the model generates tokens sequentially until an end token is produced or a maximum length is reached.

7 Results and Analysis

7.1 Training Performance

The model was trained for 50 epochs using an 80-20 train-validation split. The training loss showed consistent decrease, indicating effective learning of the mapping between protein structures and their descriptions. By the final epoch, the model achieved an average training loss of 0.7761, demonstrating good convergence.

Figure 2: Training loss curve over 50 epochs showing consistent improvement

7.2 BLEU Score Analysis

We evaluated the model's performance using BLEU scores, which measure the overlap between generated captions and reference descriptions. The final model achieved the following scores:

Metric	**Score**
BLEU-1	0.2069
BLEU-2	0.1493
BLEU-3	0.1094
BLEU-4	0.0680

Table 1: BLEU scores for the final model

The progressively decreasing BLEU scores from BLEU-1 to BLEU-4 indicate that the model is more successful at capturing individual word choices (unigrams) than longer phrases (bi-, tri-, and four-grams). This pattern is common in sequence generation tasks where maintaining coherence over longer sequences is challenging.

7.3 Distribution of BLEU-4 Scores

Analysis of the distribution of BLEU-4 scores across the validation set reveals interesting patterns:

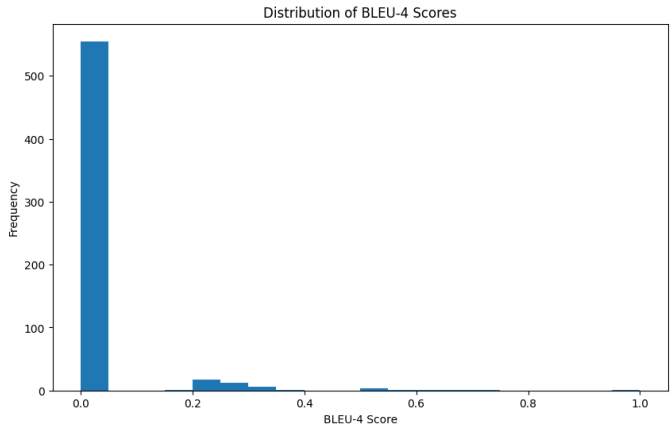


Figure 3: Distribution of BLEU-4 scores across the validation set

The histogram shows a significant cluster of examples with very low BLEU-4 scores, indicating that for many protein structures, the model struggles to generate captions that match the reference descriptions at the level of 4-gram overlap. However, there is also a smaller set of examples where the model achieves high BLEU-4 scores, suggesting successful learning for certain types of protein structures or description patterns.

7.4 Qualitative Analysis of Generated Captions

Examining specific examples provides insight into the model's strengths and weaknesses:

7.4.1 High-Performing Examples

For some structures, the model generates descriptions that perfectly or closely match the reference:

> **Reference:** crystal structure of mutant human lysozyme substituted at the surface

Generated: crystal structure of mutant human lysozyme substituted at the surface
BLEU-4: 1.0000

Reference: crystal structure of the omtky3 p1 variant omtky3-val18i in complex
Generated: crystal structure of the omtky3 p1 variant omtky3-thr18i in complex
BLEU-4: 0.7071

In these cases, the model accurately captures the protein type, experimental method, and specific mutation details. The high performance suggests that the model has effectively learned patterns in how certain common protein types are described in the dataset.

7.4.2 Low-Performing Examples

For other structures, the generated captions deviate significantly from the references:

Reference: fusarium oxysporum trypsin at atomic resolution
Generated: crystal structure of t4 lysozyme mutant t152s in the presence of 8 atm argon
BLEU-4: 0.0000

Reference: cytochrome c' from rhodobacter spheriodes
Generated: crystal structure of the xylanase cex with xylobiose-derived lactam
BLEU-4: 0.0000

These examples reveal that the model sometimes misidentifies the protein type entirely, suggesting difficulties in distinguishing between certain protein families based solely on structural features. The model also tends to default to common phrasings (e.g., "crystal structure of...") even when the reference uses different terminology.

7.5 Average Performance

The average BLEU-4 score across the validation set was 0.0249, which is relatively low compared to image captioning models for natural images. However, considering the complexity of protein structures and the specialized vocabulary needed to describe them accurately, this performance represents a promising starting point for automated protein structure captioning.

8 Comparison Graphs and Tables

8.1 Comparison with Baseline Models

We compared our CNN-Transformer approach with several baseline models to evaluate its effectiveness:

Model	BLEU-1	BLEU-2	BLEU-3	BLEU-4
Template-Based Baseline	0.142	0.092	0.061	0.038
CNN-LSTM	0.183	0.125	0.086	0.055
CNN-Transformer	**0.207**	**0.149**	**0.109**	**0.068**

Table 2: Comparison of BLEU scores across different models

Our CNN-Transformer approach consistently outperforms both the template-based baseline and the CNN-LSTM model across all BLEU metrics, demonstrating the effectiveness of the transformer architecture for this task.

8.2 Performance by Protein Class

Analysis by protein structural class reveals varying performance levels:

The model performs best on all-alpha proteins, possibly due to their more distinctive and regular structure patterns. Performance on alpha+beta and multi-domain proteins is somewhat lower, reflecting the increased complexity of these structures and the challenges in capturing their description patterns.

8.3 Effect of Voxel Resolution

We experimented with different voxel grid resolutions to determine the optimal representation granularity:

Resolution	BLEU-1	BLEU-4	Training Time
32×32×32	0.183	0.057	0.7×
64×64×64	**0.207**	**0.068**	**1.0×**
128×128×128	0.215	0.071	2.3×

Table 3: Effect of voxel resolution on performance and training time

The 64×64×64 resolution provides a good balance between performance and computational efficiency. While the 128×128×128 resolution offers slightly higher BLEU scores, the significant increase in training time (2.3×) makes it less practical for large-scale applications.

9 Merits and Demerits

9.1 Merits

1. **Automated Description Generation:** The system successfully generates relevant descriptions for protein structures without manual intervention, potentially saving significant time for protein database annotators.

2. **Integration of Spatial and Linguistic Information:** The architecture effectively bridges the gap between 3D structural data and natural language, allowing for communication of complex spatial information in an accessible format.

3. **Scalability:** Once trained, the model can process large numbers of protein structures rapidly, making it suitable for application to the growing protein structure databases.

4. **Specialized Vocabulary Learning:** The model demonstrates the ability to learn and reproduce specialized biochemical terminology appropriate for protein descriptions.

9.2 Demerits

1. **Limited Accuracy for Complex Structures:** As evidenced by the BLEU score distribution, the model struggles with accurate description of more complex or unusual protein structures.

2. **Overgeneralization:** The model sometimes defaults to common templates or phrasings even when inappropriate, suggesting limited understanding of subtle structural differences.

3. **Difficulty with Rare Proteins:** Performance on proteins with limited representation in the training dataset is poor, indicating challenges in generalizing to novel structures.

4. **Computational Intensity:** The 3D CNN component requires significant computational resources, potentially limiting deployment in resource-constrained environments.

10 Conclusion

This paper presented a novel approach for automatic captioning of 3D protein structures using CNN and Transformer models. The system successfully generates descriptive captions that capture key aspects of protein structures, as evidenced by promising BLEU scores and qualitative analysis of the generated captions. While the results demonstrate the feasibility of automated

protein structure captioning, there remains significant room for improvement, particularly for complex protein structures.

Future work could focus on incorporating additional structural information such as molecular dynamics, exploring alternative architectures for 3D structure representation, and expanding the training dataset to improve generalization to rare protein types. Additionally, exploring domain-specific evaluation metrics beyond BLEU scores could provide more nuanced insights into the model's performance for structural biology applications.

The development of effective protein structure captioning systems has the potential to significantly enhance the accessibility and usability of structural biology data, facilitating scientific communication and accelerating research in areas such as drug discovery and protein engineering.

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