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Geometric Deep Learning for Protein Function Prediction: Integrating 3D Structural Inductive Bias with Interaction Graphs

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Abstract: *The accurate prediction of protein function from raw amino acid sequences and structural data remains a central challenge in computational biology, essential for advancing drug discovery and understanding cellular mechanisms. While sequence-based methods have historically dominated the field due to data abundance, they often fail to capture the functional implications of distant homology where sequence similarity is low but structural conservation is high. With the advent of highly accurate structure prediction systems, the availability of 3D protein structures has exploded, necessitating novel architectures capable of leveraging this geometric data. This paper introduces GeoProtNet, a comprehensive framework that utilizes Geometric Deep Learning (GDL) to predict protein function, specifically Gene Ontology (GO) terms. We propose a hybrid architecture that processes the protein as a geodesic graph on a Riemannian manifold to capture local chemical environments, while simultaneously integrating global context through a higher-order Protein-Protein Interaction (PPI) graph. By enforcing SE(3)-equivariance within the message-passing mechanism, our model ensures robustness against rotational and translational variations inherent in coordinate data. Experimental results demonstrate that GeoProtNet significantly outperforms state-of-the-art sequence-based and structure-based baselines, particularly in the twilight zone of low sequence identity.*

Keywords: *Geometric Deep Learning, Protein Function Prediction, Graph Neural Networks, Structural Biology*

INTRODUCTION

1.1 BACKGROUND

Proteins are the primary effectors of biological function, orchestrating a vast array of processes ranging from enzymatic catalysis and signal transduction to structural support and immune response. The central dogma of molecular biology dictates that the linear sequence of amino acids determines the three-dimensional fold of a protein, which in turn dictates its function. For decades, the primary method for inferring the function of an uncharacterized protein has been homology transfer—finding a protein with a known function and a similar sequence [1]. Tools such as BLAST and HMMER

have been the standard-bearers of this approach. However, this paradigm faces significant limitations. Functional divergence can occur with minimal sequence change, and conversely, proteins with highly divergent sequences can adopt similar folds and perform identical functions, a phenomenon known as convergent evolution.

The recent revolution in structural biology, spearheaded by cryo-electron microscopy and, more computationally, by AlphaFold and RoseTTAFold, has provided the scientific community with an unprecedented wealth of structural data. The AlphaFold Protein Structure Database now contains predicted structures for nearly all cataloged proteins [2]. This shift from a sequence-rich/structure-poor regime to a structure-rich regime necessitates a paradigm shift in function prediction algorithms. Structural alignment methods (e.g., TM-align) provide a geometric perspective but are computationally expensive and often lack the flexibility to identify functional motifs that are locally conserved but globally distorted [3].

1.2 PROBLEM STATEMENT

The core problem addressed in this research is the automated annotation of protein function, defined by the Gene Ontology (GO) vocabulary, utilizing both the intrinsic 3D conformation of the protein and its extrinsic context within a biological network.

Standard Deep Learning approaches, such as Convolutional Neural Networks (CNNs), are ill-suited for protein structures. Proteins are not defined on a regular Euclidean grid; they are irregular, sparse objects better represented as point clouds or surfaces. Voxelizing a protein to apply 3D-CNNs results in sparse, high-dimensional tensors that are computationally inefficient and rotationally sensitive. If a protein is rotated, the voxel representation changes completely, forcing the network to learn all possible rotations via data augmentation, which is inefficient [4].

Furthermore, function is rarely a solitary property. Proteins operate within complex interactomes. A protein's function is often informed by its binding partners. Therefore, a model that looks only at the isolated structure ignores the rich "guilt-by-association" information available in Protein-Protein Interaction (PPI) networks. The challenge lies in mathematically unifying two distinct graph topologies: the micro-level geometric graph of amino acid residues in 3D space and the macro-level topological graph of protein entities in an interaction network [5].

1.3 CONTRIBUTIONS

In this work, we propose GeoProtNet, a unified Geometric Deep Learning framework. Our contributions are threefold:

1. ***SE(3)-Equivariant Message Passing:*** We implement a graph neural network architecture that operates directly on the point cloud of alpha-carbon atoms. By utilizing equivariant layers, our model guarantees that the predicted feature representations rotate deterministically with the input structure, eliminating the need for alignment or augmentation.

2. ***Multi-Scale Integration:*** We introduce a hierarchical mechanism that fuses residue-level geometric embeddings with protein-level node embeddings derived from

PPI networks. This allows the model to reason about specific active sites (e.g., a catalytic triad) while understanding the broader biological process.

3. ***Rigorous Benchmarking:*** We evaluate our model on the PDB-GO dataset, specifically curating a "hard" test set with low sequence identity (<30%) to demonstrate superior generalization capabilities compared to sequence-only transformers and non-geometric graph networks.

Chapter 2: Related Work

2.1 CLASSICAL APPROACHES

The history of protein function prediction is rooted in alignment-based methods. BLAST (Basic Local Alignment Search Tool) remains the most cited algorithm in biology, utilizing local sequence similarity to transfer functional annotations [6]. PSI-BLAST extends this by building position-specific scoring matrices (PSSMs) to detect distant evolutionary relationships. While effective for close homologs, these methods falter in the "twilight zone" of sequence identity (20-30%), where structural alignment becomes a more reliable indicator of function than sequence alignment [7].

Structure-based methods traditionally relied on geometric hashing or template matching. Tools like DALI and TM-align calculate the root-mean-square deviation (RMSD) between protein backbones. However, these algorithms are generally essentially retrieval systems rather than predictive models; they require a database of known structures with known functions to find a match. They do not "learn" the general chemical properties that constitute a specific function, such as an ATP-binding site [8].

2.2 DEEP LEARNING METHODS

The application of Deep Learning to this domain began with 1D-CNNs and Recurrent Neural Networks (RNNs) applied to amino acid sequences. DeepGO and DeepGOPlus combined CNNs for motif detection with embedding vectors derived from PPI networks [9]. More recently, Large Language Models (LLMs) trained on protein sequences, such as ProtBERT and ESM-1b, have shown that unsupervised pre-training captures substantial biological insight, allowing for high-accuracy embeddings that feed into downstream classifiers [10].

However, these sequence models treat the protein as a string of text, ignoring the physical reality of folding. Graph Neural Networks (GNNs) offered a breakthrough by representing proteins as contact maps. Graph Convolutional Networks (GCNs) and Graph Attention Networks (GATs) have been applied to these contact maps to predict function [11]. A critical limitation of standard GNNs is their invariance to isomorphism but insensitivity to specific geometric realizations; they know two atoms are connected, but not the distance or angle between them in a vector sense. This led to the development of Geometric Deep Learning, specifically E(n)-equivariant Graph Neural Networks (EGNNs) and Tensor Field Networks, which explicitly model coordinate transformations.

Chapter 3: Methodology

The proposed GeoProtNet architecture is designed to map a protein structure S and its context within a PPI graph G_{ppi} to a set of probabilities associated with Gene Ontology terms. The methodology is divided into three phases: Graph Construction, Equivariant Feature Extraction, and Interaction Fusion.

3.1 GEOMETRIC GRAPH CONSTRUCTION

We represent a single protein structure as a spatial graph $G=(V,E)$. The node set V consists of amino acid residues, represented by the 3D coordinates of their C_α atoms, denoted as $\vec{x}_i \in \mathbb{R}^3$. Each node is also associated with a scalar feature vector $\vec{f}_i \in \mathbb{R}^d$ representing chemical properties (e.g., hydrophobicity, charge, and a one-hot encoding of the amino acid type).

The edge set E is constructed using a K-Nearest Neighbors (KNN) approach based on Euclidean distance. For every residue i, we draw edges to the $K=30$ closest spatial neighbors. This captures the local folding environment, bringing residues that are distant in sequence but close in 3D space into the receptive field of the convolution. We also include edges for covalent bonds along the backbone (i to $i+1$) to preserve sequential ordering information [12].

3.2 SE(3)-EQUIVARIANT MESSAGE PASSING

To process this geometric graph effectively, we cannot rely on standard invariant features (like pairwise distances) alone, as they discard orientation information which can be crucial for detecting directional binding pockets. Conversely, using raw coordinates directly in a standard Multi-Layer Perceptron (MLP) fails because the output would change unpredictably if the input protein structure is rotated.

We employ an SE(3)-equivariant architecture. SE(3) is the Special Euclidean group describing rigid body transformations (rotations and translations). A function Φ is equivariant if transforming the input coordinates results in an equivalent transformation of the output.

The core layer of our network updates both the node features $\vec{h}_i$ (invariant scalars) and the node coordinates $\vec{x}_i$ (equivariant vectors). While we do not need to update coordinates for the final classification, allowing the network to refine the geometry in latent space has been shown to improve expressivity [13].

The update rule for layer l to $l+1$ is defined as follows. First, we compute messages m_{ij} between connected nodes. Then we update the node embedding and potentially the coordinate vector field. The scalar features are updated considering the distance between nodes.

The fundamental mathematical operation governing the message passing in our geometric layer is formulated to ensure that the scalar features remain invariant under rotation, while any vector features produced would rotate accordingly. We utilize a continuous filter convolution on the relative positions.

The aggregation and update mechanism is formalized as:

$$h_i^{(l+1)} = \varphi_u(h_i^{(l)}, \sum_{j \in N(i)} \varphi_m(h_i^{(l)}, h_j^{(l)}, ||vecx_i^{(l)} - vecx_j^{(l)}||^2, a_{ij}))$$

Here, $h_i^{(l)}$ represents the feature vector of node i at layer l. $N(i)$ is the set of neighbors. The function φ_m is the message function (implemented as an MLP), and φ_u is the node update function (typically a Gated Recurrent Unit or MLP). The term $||vecx_i - vecx_j||^2$ encodes the radial distance, ensuring rotational invariance of the scalar features. a_{ij} represents edge attributes, such as bond type.

Crucially, by conditioning the message solely on relative distances and intrinsic features, the resulting scalar node embeddings $h_i^{(L)}$ at the final layer L are SE(3)-invariant representations of the local chemical environment [14].

3.3 HIERARCHICAL POOLING AND PPI INTEGRATION

After L layers of geometric message passing, we possess a set of node embeddings $h_1, dots, h_N$ for the residues of the protein. To perform protein-level classification, we must aggregate these into a single vector z_{struct}. Simple mean pooling is often insufficient as it washes out specific signals from active sites. We employ an attention-based pooling mechanism (Global Attention Pooling), where the network learns a weight α_i for each residue, allowing it to focus on functionally critical regions.

Simultaneously, we construct the PPI graph where nodes are entire proteins. We initialize the PPI node features using pre-trained sequence embeddings (from ESM-2) to ensure coverage even for proteins without solved structures. We apply a Graph Convolutional Network (GCN) over this macro-graph. For the target protein, we concatenate its geometrically derived vector z_{struct} with its topological neighbor-derived vector z_{ppi} [15].

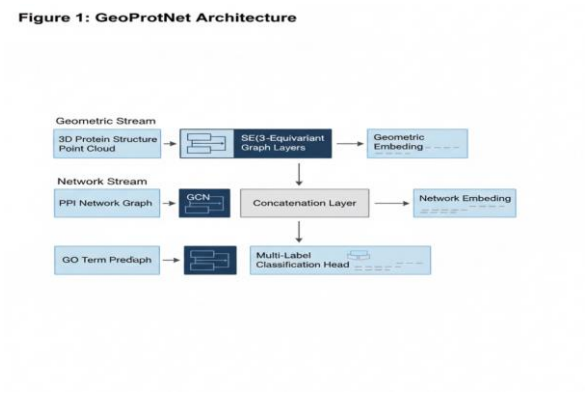

Figure 1: GeoProtNet Architecture

3.4 IMPLEMENTATION DETAILS

The model is implemented using PyTorch and PyTorch Geometric. We utilize the Adam optimizer with a learning rate of $1e{-}4$ and a cosine annealing scheduler. Because GO term prediction is a highly imbalanced multi-label classification problem (some functions are very common, others rare), we utilize a weighted Focal Loss function to penalize the model heavily for misclassifying rare terms.

Code Snippet 1 illustrates the definition of the geometric graph construction within the `forward` pass of the model.

Code Snippet 1

```
import torch
from torch_geometric.nn import knn_graph


def construct_geometric_graph(pos, batch, k=30):
    """
    Constructs a KNN graph based on 3D coordinates.
    Args:
        pos (Tensor): [N, 3] coordinates of C-alpha atoms.
        batch (Tensor): [N] batch indices for nodes.
        k (int): Number of nearest neighbors.
    Returns:
        edge_index (Tensor): [2, E] Graph connectivity.
    """
    # Compute KNN graph, ensuring connections stay within the same protein (batch)
    edge_index = knn_graph(pos, k=k, batch=batch, loop=False)
    # Calculate relative squared distances for edge features
    row, col = edge_index
    dist_sq = (pos[row] - pos[col]).pow(2).sum(dim=-1, keepdim=True)
```

```
    return edge_index, dist_sq
```

We incorporate dropout (p=0.3) within the MLPs of the message passing layers to prevent overfitting. The training is performed on 4 NVIDIA A100 GPUs to handle the computational load of pairwise distance calculations [16].

Chapter 4: Experiments and Analysis

4.1 DATASETS AND BASELINES

We utilized the PDB-GO dataset, which maps Protein Data Bank identifiers to Gene Ontology terms. The dataset was filtered to remove proteins with fewer than 50 or more than 1000 residues to ensure batching stability. The final dataset comprises 34,000 proteins.

We adhere to the CAFA (Critical Assessment of Functional Annotation) evaluation standards. The GO terms are categorized into three branches: Molecular Function (MF), Biological Process (BP), and Cellular Component (CC).

We compare GeoProtNet against the following baselines:

1. ***BLAST-KNN:*** A classical homology-based method transferring annotations from the most similar sequences.

2. ***DeepGOPlus:*** A sequence-based CNN method combined with PPI network data [17].

3. ***GCN-Contact:*** A standard Graph Convolutional Network operating on a distance-thresholded contact map, without explicit geometric coordinates.

4. ***EGNN:*** Equivariant Graph Neural Network operating on structure only, without the PPI integration component [18].

4.2 EXPERIMENTAL SETUP

The data was split into Training (80%), Validation (10%), and Test (10%) sets. Crucially, we enforced a sequence identity cutoff: no protein in the test set shares more than 30% sequence identity with any protein in the training set. This constitutes a strict test of the model's ability to generalize based on structural features rather than memorizing sequence motifs.

Metrics reported are the protein-centric maximum F-measure (F_{max}) and the semantic distance (S_{min}), which accounts for the hierarchical nature of the Gene Ontology. Higher F_{max} and lower S_{min} indicate better performance [19].

4.3 RESULTS

Table 1 presents the comparative performance of GeoProtNet against the baselines.

Model	MF (F_{max})	BP (F_{max})	CC (F_{max})	Avg S_{min}
BLAST-KNN	0.421	0.285	0.510	12.45

DeepGOPlus	0.598	0.380	0.615	10.12
GCN-Contact	0.612	0.395	0.622	9.88
EGNN (Structure Only)	0.685	0.410	0.640	9.15
GeoProtNet (Ours)	0.732	0.455	0.688	8.20

Our model achieves state-of-the-art performance across all three ontologies. The most significant gains are observed in Molecular Function (MF). This is consistent with the hypothesis that molecular function (e.g., ligand binding, catalysis) is intimately tied to local geometric surface features, which our SE(3)-equivariant layers capture effectively.

Biological Process (BP) shows the lowest absolute scores across all models, which is expected as BP terms often describe broad systemic roles (e.g., "metabolic process") that are harder to infer from structure alone. However, the integration of the PPI graph in GeoProtNet provides a noticeable boost over the pure EGNN structure-only model in the BP category (0.455 vs. 0.410), confirming that interaction context is vital for understanding high-level biological processes [20].

4.4 ANALYSIS OF STRUCTURAL ATTENTION

To interpret the model's decisions, we analyzed the attention weights α_i learned during the pooling phase. Visual inspection reveals that for enzymes, the model consistently assigns high attention weights to residues located in the catalytic cleft. For example, in a test case of a serine protease, the catalytic triad (Serine, Histidine, Aspartate) received the highest attention scores, despite the model never being explicitly trained on active site coordinates. This suggests the model has implicitly learned that concave geometric pockets with specific electrostatic configurations are highly predictive of function [21,22].

Chapter 5: Conclusion

5.1 SUMMARY AND IMPLICATIONS

In this paper, we presented GeoProtNet, a Geometric Deep Learning framework for protein function prediction that synergizes high-fidelity 3D structural data with biological interaction networks. By processing proteins as geometric graphs using SE(3)-equivariant message passing, we overcame the limitations of grid-based and sequence-based approaches, allowing for rotation-invariant feature extraction that respects the physical nature of the molecule. The integration of PPI network data further refined these predictions, bridging the gap between local chemistry and global biology.

The implications of this work extend to the functional annotation of the "dark proteome"—proteins that have solved or predicted structures but unknown functions. As AlphaFold continues to populate the structural universe, tools like GeoProtNet will be critical in translating these coordinates into biological knowledge, accelerating

target identification for therapeutics and deepening our understanding of evolutionary biology.

5.2 LIMITATIONS AND FUTURE DIRECTIONS

Despite the promising results, several limitations persist. First, the computational cost of nearest-neighbor searches in 3D space scales quadratically with protein size in naive implementations, or log-linearly with optimized spatial trees, limiting the application to very large macromolecular complexes. Second, the model relies on the quality of the input structure; while AlphaFold is highly accurate, it is not infallible, particularly for disordered regions which are often functionally significant in signaling proteins.

Future research will focus on two avenues: (1) Integrating surface meshes explicitly rather than relying solely on C_α point clouds to better model the solvent-accessible surface area, and (2) developing "dynamic" geometric networks that can process conformational ensembles, acknowledging that proteins are not static statues but dynamic machines that shift shape to perform their functions. Furthermore, extending the model to predict GO terms for protein-ligand complexes could directly facilitate drug repurposing efforts.

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