Designing Equivariant Graph Neural Network Models for Protein Structure Modeling

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Abstract

Equivariant Graph Neural Networks (EGNNs) have revolutionized molecular property prediction by encoding 3D structures while preserving physical symmetries. However, existing EGNNs struggle to capture fine-grained geometric features needed for tasks like protein binding site identification. Our proposed E(Q)AGNN-PPIS addresses this limitation, achieving state-of-the-art performance in binding site prediction by effectively leveraging detailed geometric information. Additionally, current SOTA methods fail to exploit rich information from diverse data modalities beyond 3-D coordinates and remains computationally expensive due to Clebsch–Gordan (CG) product in including higher order harmonics. In this context, my research focuses on learning more enriched and robust representations of 3-D molecules like proteins, which not only enhances the accuracy of property prediction but also mitigates the aforementioned limitations.

Keywords

Graph Neural Networks (GNNs), Geometric GNNs, Proteins, Equivariance, Molecular Modeling

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1 Introduction

The three-dimensional architecture of molecules from complex proteins to organic compounds—fundamentally determines their biological functions and is essential for drug discovery and molecular biology applications [5]. However, computationally capturing these geometric features from non-Euclidean molecular data remains a significant challenge for traditional machine learning approaches. Graph Neural Networks (GNNs) have emerged as a natural framework for molecular representation [18], with Equivariant GNNs (EGNNs) specifically designed to preserve rotational and translational symmetries critical for 3-D molecular systems [13, 17]. Foundational models like E(n)-GNN [14] and GVP-GNN [6] have demonstrated the effectiveness of this approach. Despite these advances, the pursuit of more expressive, efficient, and interpretable EGNN architectures continues. For instance, the role and necessity of mechanisms like attention in EGNNs, which has shown success in models like E(Q)AGNN-PPIS [1] in learning proteins representation more effectively. Nevertheless, current state-of-the-art models including Equiformer [8, 9], Geoformer [16], EQGAT [7], rely heavily on computationally intensive attention mechanisms and higher-order tensor operations through Clebsch-Gordan products, creating significant efficiency bottlenecks. Also, these architectures predominantly focus on 3-D geometric information while overlooking the multi-modal nature of data. Since molecular functions arise from the interplay of geometric, sequential, and physicochemical properties, integrating equivariant representations with complementary modalities such as evolutionary information from protein language models like ESM-2 [3], visual (image) data diffusion and domain specific features, presents a promising direction for more comprehensive molecular modeling frameworks.

2 Dissertation Plan

Accurate representation of molecular geometric features is essential for tasks including binding site identification, property prediction, and de-novo molecular design. In our work we present architectures that exploit 3-D structural information and integrate multi-modal data from textual and image sources. We outline the motivation and problem formulation for each proposed method.

2.1 Equivariant GNN model for Protein-Protein Interaction Site prediction (under second phase review) [1]

Accurate prediction of protein binding sites i.e. identifying the regions on the protein surface where interaction with other molecule occur, remains a fundamental challenge in structural biology. We address this through the following research question:

RQ1: ***Can geometric equivariance in graph neural networks improve protein-protein interaction site prediction accuracy and interpretability?***

Solution: ***E(Q)AGNN-PPIS:*** In our first work [1]we hypothesize that incorporating geometric features of the amino acids into model architecture will enhance performance of protein-protein interaction site prediction. To validate this, in this study, we proposed E(Q)AGNN-PPIS[1], a method which takes geometric features into consideration. Our approach leverages equivariant GNNs, specifically augmenting the GVP-GNN architecture [6] through the integration of an attention mechanism. Our method preserves rotational and translational equivariance while incorporating both scalar and vector features through attention-enhanced message passing. We

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Table 1: Comparative analysis of E(Q)AGNN-PPIS and other baseline methods on the test dataset.

Performance Metric	Machine Learning Based		Deep Learning Based			Graph Machine Learning Based			
	PSIVER [10]	ProNA2020 [12]	DeepPPISP [21]	SPPIDER [11]	MaSIF-site [4]	GraphPPIS [20]	AGAT-PPIS [23]	GHGPR-PPIS [22]	E(Q)AGNN-PPIS
Accuracy	0.56	0.74	0.66	0.75	0.78	0.78	0.86	0.86	**0.87**
Precision	0.19	0.28	0.24	0.33	0.37	0.37	0.54	0.55	**0.58**
Sensitivity (Recall)	0.53	0.40	0.54	0.56	0.56	0.58	0.60	0.62	**0.68**
F1-Score	0.28	0.33	0.34	0.42	0.45	0.45	0.57	0.58	**0.62**
MCC	0.07	0.18	0.17	0.29	0.33	0.33	0.48	0.50	**0.55**
AUPRC	0.19	N/A	0.28	0.37	0.44	0.43	0.57	0.60	**0.65**

Table 2: Performance Comparison on QM9 dataset. Scores are reported as mean absolute errors (MAE).

Task	α	$\Delta\varepsilon$ (GAP)	εHOMO	εLUMO	μ	Cv	G	H	R2	U	U0	ZPVE
Units	m-a0^3	m-eV	m-eV	m-eV	m-D	m-cal/(molK)	m-eV	m-eV	m-a0^2	m-eV	m-eV	m-eV
EQGAT [7]	53	32	20	16	11	24	23	24	382	25	25	2
TorchNet-MD(ET) [15]	59	36.1	20.3	17.5	11	26	7.62	6.16	33	6.38	6.15	1.84
Geoformer[16]	40	33.8	18.4	15.4	10	22	6.13	4.39	28	4.41	4.43	1.28
Equiformer[8]	46	30	15.4	14.7	12	23	7.63	6.63	251	6.74	6.59	1.26
EquiformerV2[9]	47	29	14.4	13.3	9.9	23	7.57	6.22	186	6.49	6.17	1.47
GotenNetS[2]	**34**	23.2	16.3	14.7	**7.5**	**20**	5.51	**3.86**	**27**	**3.76**	**3.82**	**1.15**
GDEGNN(Ours)	42	**22.8**	**10.6**	**12.7**	16	**20**	**5.05**	29	36	93	34	2.46

formally prove that attention integration maintains model equivariance. Empirical evaluation demonstrates state-of-the-art performance across all Additionally, our method demonstrates fast inference and robust generalization across proteins with varying sequence lengths, outperforming baseline methods as shown in our manuscript [1].

2.2 Do we really need attention in equivariant graph neural networks?

This work is currently in the exploration and experimentation phase. We investigate whether Gaussian-based mechanisms can replace conventional attention in equivariant GNNs while maintaining performance and improving computational efficiency. **Motivation:** While attention mechanisms have proven effective as we have shown in our earlier work [1] and in various other methods including Equiformer[8], EquiformerV2[9], EQGAT[7] and GotenNet[2], their computational overhead and interpretability challenges motivate exploring alternatives. We pose:

RQ2: ***Can learnable Gaussian receptive fields in equivariant GNNs match or exceed attention-based performance while offering superior computational efficiency and interpretability for molecular property prediction?***

Proposed Solution: We develop a method (GDEGNN) which utilizes learnable gaussian based weighting mechanism while message passing in equivariant graph neural network framework. We utilized EGNN [14] as base architecture to update the node features and 3-D coordinates. This framework is intended for tasks like molecular property prediction and 3-D molecular tasks in proteins, where adaptive spatial reasoning and equivariance are critical. We aim to demonstrate its efficacy without full reliance on conventional attention mechanisms.

Preliminary Results: We have conducted the experiments on QM9 dataset [19], a widely adapted benchmark dataset for molecular property prediction. Initial results are presented in the table 2.

2.3 Multi Model approach for accurate protein binding site identification

This work is in the planning phase and aims to build upon the insights and methods developed in the previous stages.

Method Motivation and Approach While we focus primarily on leveraging 3-D geometric information, protein binding site identification requires understanding beyond 3-D geometry evolutionary constraints, sequence-specific properties, and dynamic conformational states all contribute to binding specificity. In this work we intend to leverage recent advances in protein language models (pLMs) like ESM-2[3] and diffusion-based refinement to capture dynamic binding site conformations to address:

RQ3: ***Can multi-modal fusion of geometric features (GDEGNN), diffused with other data modalities can achieve superior binding site prediction accuracy and generalization compared to single-modality approaches?***

Proposed Solution: We plan to use the developed GDEGNN framework as a powerful backbone for extracting geometric and structural features from proteins. This will then be integrated with other relevant data modalities, including features generated from ESM-2[3], 3-D images, textual attributes etc. The core idea is to design a fusion mechanism that effectively combines the rich geometric insights from GDEGNN with complementary information from these other sources.

3 Next Steps

Moving forward, we will complete the GDEGNN implementation to address RQ2. Our immediate objectives include: (i) benchmarking Gaussian-based message passing across multiple equivariant architectures to establish generalizability, (ii) incorporating higher-order spherical harmonics to enhance geometric expressiveness. Subsequently, we plan to complete the architecture building for RQ3 and experiment with different data modalities.

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