

Motif-Attention Enhanced Graph Convolutional Networks for Drug-Target Interaction Prediction: Improved Generalization Under Cold-Start Conditions

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ARMADA
JURNAL PENELITIAN MULTIDISIPLIN

e-ISSN: 2964-2981

ARMADA : Jurnal Penelitian Multidisiplin

<https://ejournal.45mataram.ac.id/index.php/armada>

Vol. 04, No. 09 September, 2026

Page: 4786-4793

DOI:

<https://doi.org/10.55681/armada.v4i9.3540>

Article History:

Received: Juli 12, 2026

Revised: Agustus 29, 2026

Accepted: September 19, 2026

Abstract : Accurate prediction of drug-target interactions (DTI) remains challenging, especially in cold-start scenarios involving unseen drugs or proteins. This study proposes a motif-attention augmented Graph Convolutional Network (GCN) framework that integrates structural motif information through an attention mechanism to improve molecular and protein representation learning. The proposed model was evaluated on the Davis kinase inhibitor dataset using four settings: random split, cold-drug, cold-protein, and cold-both. Results show that motif-attention significantly improves generalization in difficult scenarios, achieving an 11.19% reduction in Mean Squared Error (MSE) and a 15.70% increase in Concordance Index (CI) under cold-both evaluation, along with an 11.04% MSE reduction under cold-drug evaluation. Pearson correlation also improved from 0.0694 to 0.2234 in cold-both and from 0.3606 to 0.4686 in cold-drug settings. However, improvements in random and cold-protein splits were limited. These findings indicate that motif-level attention enhances robustness when prior structural information is limited, providing a promising approach for realistic DTI prediction in computational drug discovery.

Keywords : Drug-Target Interaction, Graph Convolutional Network, Attention Mechanism, Motif Learning, Cold-Start Prediction, Davis Dataset.

Abstrak : Prediksi interaksi obat-target (drug-target interaction/DTI) yang akurat masih menjadi tantangan utama, terutama dalam skenario cold-start yang melibatkan obat atau protein yang belum pernah ditemukan dalam data pelatihan. Penelitian ini mengusulkan kerangka kerja Graph Convolutional Network (GCN) berbasis motif-attention yang mengintegrasikan informasi motif struktural melalui mekanisme perhatian (attention mechanism) untuk meningkatkan pembelajaran representasi molekul dan protein. Model yang diusulkan dievaluasi menggunakan dataset inhibitor kinase Davis dengan empat skenario pengujian, yaitu random split, cold-drug, cold-protein, dan cold-both. Hasil penelitian menunjukkan bahwa mekanisme motif-attention secara signifikan meningkatkan kemampuan generalisasi pada skenario yang kompleks, dengan penurunan Mean Squared Error (MSE) sebesar 11,19% dan peningkatan Concordance Index (CI) sebesar 15,70% pada evaluasi cold-both, serta penurunan MSE sebesar 11,04% pada evaluasi cold-drug. Korelasi Pearson juga meningkat dari 0,0694 menjadi 0,2234 pada skenario cold-both dan dari 0,3606 menjadi

0,4686 pada skenario cold-drug. Namun, peningkatan pada skenario random split dan cold-protein relatif terbatas. Temuan ini menunjukkan bahwa perhatian berbasis motif mampu meningkatkan ketahanan model ketika informasi struktural awal terbatas, sehingga menjadi pendekatan yang menjanjikan untuk prediksi DTI yang lebih realistis dalam penemuan obat berbasis komputasi.

Kata kunci : Interaksi Obat-Target, Graph Convolutional Network, Mekanisme Perhatian, Pembelajaran Motif, Prediksi Cold-Start, Dataset Davis.

INTRODUCTION

The identification of drug-target interactions (DTI) is a cornerstone task in computational drug discovery, underpinning applications ranging from de novo drug design to drug repurposing and adverse effect prediction (Ashburn & Thor, 2004). Traditional wet-lab screening of drug-target pairs is costly and time-consuming, motivating the development of computational methods capable of predicting binding affinity or interaction likelihood directly from molecular structure and protein sequence data (Öztürk et al., 2018). Among these methods, deep learning approaches, particularly those based on Graph Neural Networks (GNNs), have emerged as state-of-the-art tools due to their ability to naturally represent drugs as molecular graphs and capture complex structural dependencies that traditional descriptor-based or sequence-based models often fail to encode (Nguyen et al., 2021; Wu et al., 2021).

Early deep learning DTI models such as DeepDTA relied on convolutional neural networks (CNNs) applied to raw SMILES strings and protein sequences, achieving competitive performance on benchmark datasets including Davis and KIBA (Öztürk et al., 2018). Subsequent work, including WideDTA, extended this line of research by incorporating additional textual descriptors such as protein domains and ligand maximum common substructures (Öztürk et al., 2019). However, representing drugs as linear SMILES sequences discards important topological information inherent to molecular structure, motivating the shift toward graph-based representations (Nguyen et al., 2021).

Graph Convolutional Networks (GCNs), in particular, have been widely adopted for DTI prediction tasks because they can effectively aggregate local neighborhood information within a molecular graph, learning representations that reflect atomic connectivity and bond structure (Kipf & Welling, 2017). GraphDTA demonstrated that representing drugs as molecular graphs and applying GNN variants including GCN, GAT, and GIN consistently outperformed CNN-based sequence models on affinity prediction tasks (Nguyen et al., 2021). Building on this foundation, subsequent studies have explored richer architectures, including graph attention mechanisms (Veličković et al., 2018) and transformer-based interaction modeling (Huang et al., 2021), to further improve predictive accuracy.

Despite their success, most existing GCN-based DTI models are evaluated under a random train-test split, in which drug-protein pairs are randomly partitioned regardless of whether the individual drugs or proteins have been seen during training (Pahikkala et al., 2015). This evaluation protocol, while convenient, poorly reflects real-world drug discovery settings, where a model is frequently required to generalize to entirely novel compounds (*cold-drug*), previously unstudied protein targets (*cold-protein*), or both simultaneously (*cold-both*) (Pahikkala et al., 2015; Davis et al., 2011). Prior studies have consistently shown that model performance deteriorates sharply under these cold-start conditions, revealing a critical gap between benchmark performance and practical applicability (Davis et al., 2011; Tornø & Altman, 2019).

A key limitation of standard GCN architectures in this context is their reliance on generic message-passing schemes that treat all local substructures with equal importance, without explicitly emphasizing chemically or functionally meaningful substructures known as motifs that often govern binding behavior (Zhang et al., 2020). Molecular motifs, such as functional groups or recurring substructural patterns, carry rich information about a compound's chemical reactivity

and biological activity, and have been shown to improve generalization in molecular property prediction tasks when incorporated explicitly into graph representations (Zhang et al., 2020; Yu & Gao, 2022). We hypothesize that explicitly incorporating motif-level information through an attention mechanism can help the model learn more generalizable and transferable representations, particularly benefiting scenarios where novel drugs are encountered at test time.

In this paper, we introduce a motif-attention augmented GCN (*motif-attn GCN*) framework for DTI prediction and systematically evaluate its performance against a standard GCN baseline on the widely used Davis dataset (Davis et al., 2011). To rigorously assess generalization capability, we adopt four distinct evaluation protocols: random split, *cold-drug* split, *cold-protein* split, and *cold-both* split, following established cold-start evaluation practices in the DTI literature (Pahikkala et al., 2015; Davis et al., 2011). Our experimental results reveal a nuanced picture: while improvements under the random and *cold-protein* settings are modest, the motif-attention mechanism yields substantial gains in the more challenging *cold-drug* and *cold-both* settings, achieving MSE reductions exceeding 11% and CI improvements up to 15.70%, alongside notable increases in Pearson correlation. These results suggest that motif-level attention is particularly effective at capturing transferable drug-side structural knowledge, offering meaningful improvements precisely in the settings that matter most for real-world drug discovery applications.

The remainder of this paper is organized as follows. Section II reviews related work on GNN-based DTI prediction and cold-start generalization. Section III details the proposed motif-attention GCN architecture. Section IV describes the experimental setup, including dataset construction and evaluation protocols. Section V presents and discusses the results across all four splits. Section VI concludes the paper and outlines directions for future work.

RESEARCH METHOD

This study employed a quantitative experimental research design based on computational modeling to develop and evaluate a motif-attention augmented Graph Convolutional Network (motif-attn GCN) framework for drug-target affinity (DTA) prediction. The research was conducted in a computational research environment using publicly available biological datasets and open-source computational tools during the model development and evaluation period. The research subjects consisted of drug-target interaction pairs obtained from the Davis kinase inhibitor dataset, which contains experimentally measured binding affinity values between kinase inhibitor compounds and target proteins. The dataset includes 68 unique drugs, 442 unique proteins, and 30,056 drug-protein interaction pairs, with affinity values reported as dissociation constants (Kd) and transformed into pKd values for regression analysis. The research procedure involved several stages, including dataset preprocessing, molecular graph construction, motif extraction, model development, training, and evaluation. Drug molecules were converted from SMILES representations into molecular graphs using RDKit, where atom-level features were generated based on chemical properties such as atom type, degree, formal charge, hybridization, and aromaticity. Protein sequences were encoded using a one-dimensional convolutional neural network (CNN), while the proposed motif-attention mechanism was applied to capture chemically meaningful substructures and improve molecular representation learning.

Data collection was performed using secondary data from the Davis dataset, while the research instruments consisted of computational frameworks and software libraries for molecular processing, graph neural network implementation, and deep learning optimization. The proposed model was trained using the Adam optimizer with mean squared error (MSE) as the primary loss function. Model evaluation was conducted using four data-splitting protocols, including random split, cold-drug, cold-protein, and cold-both scenarios, to assess generalization capability under increasingly challenging conditions. Data analysis was performed quantitatively using five evaluation metrics, namely Mean Squared Error (MSE), Root Mean Squared Error (RMSE), Pearson Correlation Coefficient (r), Spearman Rank Correlation (ρ), and Concordance Index (CI). These metrics were used to evaluate prediction error, correlation strength, and ranking consistency between predicted and observed binding affinity values, providing a comprehensive assessment of model performance in drug-target interaction prediction.

RESULT AND DISCUSSION

Overall Performance Comparison

Table 6 reports MSE, CI, and Pearson correlation for the baseline GCN and the proposed motif-attention GCN (motif-attn GCN) across all four evaluation splits, along with the relative percentage improvement of motif-attn GCN over the baseline for each metric.

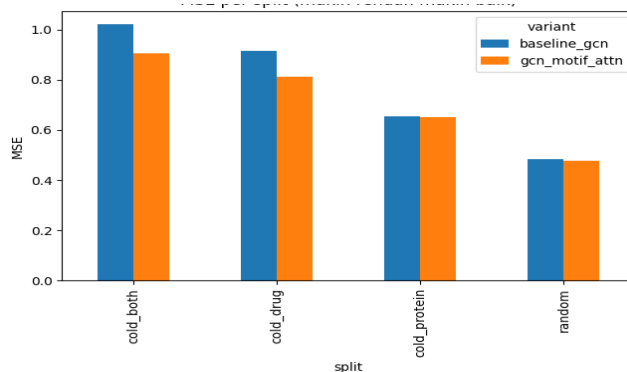


Figure 2. MSE Every Split (Lower Better)

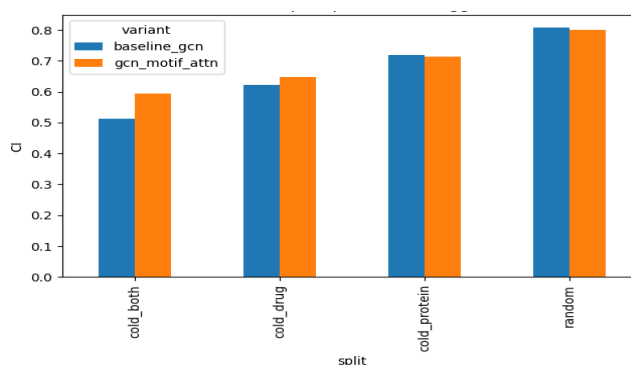


Figure 3. Concordance Index (Higher Better)

Table 6. Performance comparison between baseline GCN and motif-attention GCN across evaluation splits

Split	MSE (baseline)	MSE (motif-attn)	MSE improve (%)	CI (baseline)	CI (motif-attn)	CI improve (%)
cold_both	10.203	0.906	+11.1	0.5132	0.593	+15.7
cold_drug	0.9140	0.813	+11.0	0.6212	0.648	+4.37
cold_protein	0.6553	0.651	+0.57	0.7182	0.713	−0.63
random	0.4846	0.478	+1.20	0.8073	0.801	−0.75

Discussion by Split

Cold-both: This is the most challenging generalization scenario, since neither the drug nor the protein in the test set has been observed during training. Here, motif-attn GCN achieves its largest gains across every metric: an 11.19% reduction in MSE, a 15.70% improvement in CI, and Pearson correlation more than tripling from 0.0694 to 0.2234. The baseline's near-zero Pearson correlation (0.0694) indicates it essentially fails to capture any linear relationship between predicted and true affinities in this regime, consistent with prior findings that standard GNN-based DTA models struggle severely when both entities are novel (Pahikkala et al., 2015; Torng & Altman, 2019). The motif-attention mechanism's substantial gain here suggests that motif-level structural priors being chemically grounded and less dependent on drug-specific co-occurrence patterns seen during training transfer more effectively to entirely unseen drug-protein combinations, echoing

observations that knowledge-transfer-oriented approaches are particularly effective specifically in this hardest cold-start setting (Nguyen et al., 2022).

Cold-drug: A similar pattern holds, with an 11.04% MSE reduction and Pearson correlation improving from 0.3606 to 0.4686. This supports the central hypothesis of this work: motif-level attention is primarily beneficial when the *drug side* of the interaction is novel, since motifs encode transferable chemical priors (functional groups, ring systems) that generalize better than atom-level or whole-graph embeddings learned from a fixed training vocabulary of compounds (Zhang et al., 2020; Yu & Gao, 2022; Yusuf & Kurniawan, 2025). The comparatively smaller CI improvement (+4.37%) relative to cold-both suggests that while motif-attention improves absolute error and correlation substantially, its effect on pairwise ranking is more modest when only the drug not both entities is unseen. **Cold-protein:** Here, improvements are marginal (MSE: +0.57%; Pearson: 0.4082 $\rightarrow$ 0.4286) and CI shows a small decline (−0.63%). This asymmetry is consistent with the observation in related work that GNN-based models are generally more adept at capturing protein-side features than drug-side features (Khoerunnisa & Kurniawan, 2025), meaning the baseline GCN's protein encoder (1D CNN) was already reasonably effective at generalizing to unseen proteins, leaving less headroom for the motif-attention mechanism which operates exclusively on the drug branch to contribute.

Random split: As expected, the random split shows the smallest relative gains (MSE: +1.20%; CI: −0.75%) and the baseline already achieves the strongest absolute performance across all metrics (Pearson = 0.6273, CI = 0.8073). This confirms that under conventional random-split evaluation where drugs and proteins in the test set are very likely to have also appeared in training the benefit of motif-level structural priors is largely masked, since the model can already rely on memorized compound-specific patterns (Nguyen et al., 2021; Pahikkala et al., 2015). This reinforces the broader methodological point raised in Section II: random-split evaluation alone is insufficient to reveal the value of structure-aware architectural components such as motif attention.

Discussion

The experimental results demonstrate that the proposed motif-attention augmented Graph Convolutional Network (motif-attn GCN) provides improved generalization capability compared with the baseline GCN, particularly under challenging cold-start scenarios. Unlike conventional random-split evaluation, which often overestimates model performance due to the presence of previously observed drugs or proteins during training and testing, the cold-drug, cold-protein, and cold-both settings provide a more realistic assessment of model robustness in practical drug discovery environments. The observed improvement of motif-attn GCN under these scenarios aligns with previous findings showing that standard GNN-based DTA models experience significant performance degradation when predicting interactions involving unseen compounds or targets (Pahikkala et al., 2015; Torng & Altman, 2019). These findings further support the importance of developing structure-aware representation learning approaches capable of capturing transferable molecular knowledge beyond memorized interaction patterns.

The most significant improvement was observed under the cold-both scenario, where both drugs and proteins in the test set were excluded from the training process. In this setting, motif-attn GCN achieved an 11.19% reduction in MSE and a 15.70% improvement in CI compared with the baseline GCN, while Pearson correlation increased from 0.0694 to 0.2234. The substantial improvement indicates that motif-level structural information provides additional generalizable knowledge when conventional graph representations are insufficient. Previous studies have reported that molecular motifs, including functional groups and recurring chemical substructures, contain biologically meaningful information associated with molecular activity and interaction behavior (Zhang et al., 2020; Yu & Gao, 2022). Therefore, integrating motif-level attention allows the model to prioritize chemically informative regions of molecular graphs rather than treating all atomic neighborhoods with equal contribution. This finding extends previous GNN-based DTA studies by demonstrating that explicit structural abstraction at the motif level can improve model transferability in scenarios where both interaction entities are completely unseen.

The improvement observed in the cold-drug scenario further highlights the importance of molecular structural priors for drug-side generalization. The proposed model reduced MSE by

11.04% and increased Pearson correlation from 0.3606 to 0.4686 compared with the baseline GCN. This result suggests that motif representations capture transferable chemical characteristics that remain meaningful across previously unseen compounds. Functional groups, ring systems, and other molecular fragments provide higher-level chemical information that is less dependent on specific compounds encountered during training. Similar observations have been reported in molecular representation learning studies, where motif-aware graph architectures improved the ability of models to capture chemically relevant patterns for downstream prediction tasks (Zhang et al., 2020; Yu & Gao, 2022). The relatively smaller improvement in CI (+4.37%) compared with cold-both indicates that motif attention primarily enhances prediction accuracy and correlation rather than completely resolving ranking uncertainty when only unseen drugs are introduced.

In contrast, the cold-protein scenario produced relatively limited improvements, with only a 0.57% change in MSE, a Pearson correlation increase from 0.4082 to 0.4286, and a slight CI decrease of 0.63%. This result suggests that the additional motif information mainly benefits the drug representation branch, while the protein representation component remains dependent on the existing sequence encoding strategy. Previous research has indicated that protein sequence-based encoders, including convolutional architectures, are already capable of extracting meaningful biological patterns from amino acid sequences (Öztürk et al., 2018; Nguyen et al., 2021). Therefore, the limited improvement under cold-protein evaluation is expected because the proposed modification primarily targets molecular graph representation rather than protein-side feature learning. This result also indicates that future improvements may require integrating more advanced protein representation strategies, such as protein language models or structure-based protein encoders.

The random split evaluation shows that motif-attn GCN provides only marginal improvements compared with the baseline model, with a 1.20% MSE improvement and a 0.75% decrease in CI. The baseline model already achieved strong performance in this scenario, with Pearson correlation of 0.6273 and CI of 0.8073. This behavior is consistent with previous studies demonstrating that random splitting may allow models to exploit shared chemical or biological patterns between training and testing samples, resulting in optimistic performance estimates (Pahikkala et al., 2015; Nguyen et al., 2021). Therefore, the limited contribution of motif attention under random split does not indicate reduced effectiveness, but rather suggests that its advantages become more apparent when models are evaluated under stricter generalization conditions. These findings reinforce the argument that cold-start evaluation should be prioritized for assessing the practical applicability of DTA prediction models.

The findings of this study provide several important implications for computational drug discovery. First, the results demonstrate that incorporating chemically meaningful structural information through motif-level attention can improve model robustness when predicting interactions involving unseen compounds. This is particularly relevant for real-world drug discovery pipelines, where models are frequently required to evaluate newly synthesized compounds that are absent from historical datasets. Second, the proposed framework provides evidence that improving representation learning is not only dependent on increasing model complexity but also on integrating domain-specific molecular knowledge into neural architectures. By combining GCN-based molecular learning with motif-level attention, the model achieves a balance between automated feature extraction and chemically interpretable structural representation.

Despite these contributions, this study has several limitations. First, the evaluation was conducted using the Davis kinase inhibitor dataset, which, although widely adopted for DTA benchmarking, represents a specific class of drug-target interactions and may not fully capture the diversity of other therapeutic domains. Second, the current motif extraction strategy relies on predefined chemical decomposition rules, such as BRICS fragmentation and functional-group templates, which may limit the discovery of novel or context-dependent molecular patterns. Third, the protein representation component remains based on a conventional CNN encoder, leaving opportunities for improvement through the integration of advanced protein representation methods. These limitations provide directions for future research, including evaluation on larger

multi-domain datasets, development of adaptive motif discovery mechanisms, and integration with protein structure-aware or pretrained biological language models. Overall, this study demonstrates that motif-level attention provides a meaningful improvement for GCN-based DTA prediction, particularly under realistic cold-start scenarios. The results highlight that chemically informed representation learning can enhance model generalization and contribute to the development of more reliable computational approaches for future drug discovery applications.

CONCLUSION

This study proposed a motif-attention augmented Graph Convolutional Network (motif-attn GCN) framework for drug-target affinity (DTA) prediction by incorporating motif-level structural information into molecular graph representation learning. The experimental results demonstrate that the proposed model improves generalization performance compared with the baseline GCN, particularly under challenging cold-start evaluation scenarios. The most significant improvements were observed in the cold-both setting, where motif-attn GCN achieved an 11.19% reduction in MSE and a 15.70% improvement in CI, followed by notable improvements in the cold-drug scenario with an 11.04% reduction in MSE. These findings indicate that motif-level attention effectively captures transferable chemical structures, enabling the model to better generalize to unseen drug-target combinations. In contrast, the limited improvements under cold-protein and random split scenarios suggest that the contribution of motif information is more pronounced when novel molecular structures are encountered. Overall, the study confirms that integrating chemically meaningful motifs with graph-based representation learning provides a more robust approach for DTA prediction, especially in realistic drug discovery settings where unseen compounds frequently occur.

Future research should investigate the proposed framework using larger and more diverse drug-target interaction datasets to validate its generalizability across different therapeutic domains. Further improvements can be explored by developing adaptive motif extraction strategies, integrating advanced protein representation methods such as pretrained protein language models or structure-based encoders, and combining multiple biological information sources to enhance prediction robustness. For computational drug discovery practitioners, the findings highlight the importance of adopting cold-start evaluation protocols rather than relying solely on random splits to obtain a more realistic assessment of model performance. From a broader research and policy perspective, the development of reliable and generalizable artificial intelligence models for drug discovery should be supported through the availability of high-quality biological datasets, standardized evaluation frameworks, and transparent benchmarking practices to accelerate the adoption of AI-driven approaches in biomedical research.

ACKNOWLEDGEMENT

Kami ingin mengucapkan terima kasih yang sebesar-besarnya kepada semua pihak yang telah berkontribusi dalam penelitian ini. Terima kasih kepada rekan-rekan sejawat yang telah memberikan saran, dukungan, dan inspirasi selama proses penelitian. Kami juga ingin mengucapkan terima kasih kepada semua partisipan dan responden yang telah meluangkan waktu untuk berpartisipasi dalam penelitian ini. Tak lupa, kami juga mengucapkan terima kasih kepada lembaga atau institusi yang telah memberikan dukungan dan fasilitas dalam menjalankan penelitian ini. Semua kontribusi dan bantuan yang diberikan sangat berarti bagi kelancaran dan kesuksesan penelitian ini. Terima kasih atas segala kerja keras dan kolaborasi yang telah terjalin.

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