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Research Article

Multimodal Neural Network for Drug Activity Regression Model with Augmented Drug Graphs and Gene Expressions of Amyotrophic Lateral Sclerosis and Alzheimer's Diseases

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Abstract:

The proposed work aims for precise drug activity regression that is crucial in treating neurodegenerative diseases such as Amyotrophic Lateral Sclerosis and Alzheimer's. Two drug activity scores Half-Maximal Inhibitory Concentration and Half-Maximal Effective Concentration are used as regression targets in model building. To increase the performance of model equivariance is required which is made possible by extracting invariant features through data augmentation namely rotation and translation. The augmented data is passed to the permutation invariant architecture Graph Isomorphism Network and compared with the Graph Attention Network. The equivariant drug features obtained from the graph-based networks are combined with gene expression profiles using a multimodal neural network. The Multimodal Neural Network is trained with original, rotated, translated drug graphs and gene expression profiles. The trials use a carefully chosen dataset containing 665 graphs. Using proper hyperparameters tuning, the prediction results reveal that the GIN-Multimodal model performs exceptionally well, with an R2 Score of 0.94, a Mean Absolute Error of 0.16, and a Root Mean Square Error of 0.15.

1. Introduction

The current study demonstrates the need for Half-Maximal Inhibitory Concentration (IC50) and Half-Maximal Effective Concentration (EC50) in Alzheimer's (AD) [1] and Amyotrophic lateral Sclerosis (ALS) [2]. AD is characterized by memory impairment leading to ALS. The degeneration in ALS involves an array of cellular and molecular mechanisms. Genetic mutations in ALS cases have been characterized for C9orf72 [3], SOD1 [4], TARDBP [5], and FUS [6]. These mutations can lead to a toxic gain of function [7], protein misfolding, and impaired cellular processes [8]. In ALS, the pathogenesis includes protein misfolding [9] and aggregation due to proteins such as superoxide dismutase 1 (SOD1), TDP-43, and FUS. The process of axonal transportation gets weakened in ALS, thereby contributing to the accumulation of protein aggregates while minimizing the delivery of vital nutrients towards distal parts of the neuron. Within motor neurons and neighboring cells, these aggregates may build up and lead to dysfunction and cell damage. Proper transport of cellular components along the axons of neurons is crucial for neuronal health. Inflammatory processes within the central nervous system play a role in ALS progression [10]. Activated glial cells release inflammatory molecules that can contribute to neuronal damage and degeneration [11]. Thus, the degeneration of neurons can be treated with drugs where such drugs undergo drug optimization during drug discovery. Drug optimization [12] is achieved by predicting the IC50 and EC50 values of the drug.

IC50 represents the concentration of a drug needed to inhibit a specific biological or biochemical function by 50% whereas EC50 is used to induce growth. In drug discovery, both IC50 and EC50 is used to assess the potency of a compound in inhibiting and inducing the activity of enzymes, receptors, or other targets. IC50 and EC50 values [13] are normalized and referred to as pIC50 and

pEC50 respectively. Higher pIC50 and pEC50 values indicate higher potency, as it means that a lower concentration of the drug is needed to achieve the desired effect.

Predicting IC50 [14]and EC50 [15] values is vital in drug discovery because it helps in prioritizing compounds for further development. It provides insights into the mechanisms of action of drugs and compounds. Many Machine Learning (ML) algorithms are commonly used for building IC50 and EC50 prediction models [16]. They learn patterns from chemical structures and associated biological activities of compounds. Existing ML models often use molecular descriptors (e.g., physicochemical properties, structural features) as input features to predict IC50 and EC50 values. These descriptors capture important information about compound structure and properties that influence biological activity. Deep learning techniques, such as convolutional neural networks (CNNs) [17] and recurrent neural networks (RNNs) [18], are also increasingly being applied to drug activity prediction tasks [19, 20]. These methods serve as the foundation for the proposed work where equivariance is also included with different modalities. Equivariance is a property in graph-based networks that preserves the symmetries in graphs thereby increasing the accuracy [21]. Some of the existing works on Equivariance in Graph based networks are given below supporting the proposed work. Mallick et al. (2023) use the steppingstone method to solve the classic transportation problem in order to optimize drug delivery operations in pharmaceutical companies. The paper focuses on operational enhancement in pharmaceutical production but highlights that modeling and optimization enables better pipeline performance. The drug activity regression concept shares an identical goal of system and drug efficacy enhancement regardless of whether optimization efforts focus on delivery systems or biochemical reactions. The research paper contributes to the use of structured models to enhance pharmaceutical processes within wider pharmaceutical domains [22].

(Berrone et al., 2022) [23] presented a new architecture, Graph-Informed Neural Networks (GINNs), designed specifically for regression tasks on data structured as graphs. This architecture bypasses the limitations of traditional Graph Neural Networks (GNNs) that are not so appropriate for specific regression tasks. The authors conclude that GINNs are an interesting step forward in the generalized family of spatial-based graph convolutional networks, which show promise for improving regression tasks on data structured as graphs. The numerical experience shows that GINNs outperform MLPs and traditional GNNs, especially when the number of training observations increases. In their recent work, (Peng et al., 2020) [24] proposed Graph Isomorphism Network (MolGIN) for predicting ADMET properties (including IC50 regression). MolGIN outperformed baseline models significantly through bond features and neighborhood weights adjustment to improve molecular representation and prediction accuracy. MolGIN outperformed all baseline models for ADMET prediction. Achieves state-of-the-art results or better performance with similar or superior outcomes. The researchers from (Basheer et al., 2025) have introduced machine learning methods for industrial system denial of service attack detection. The paper implements a cybersecurity application but it follows similar methodologies to construct predictive models from complex data that mirroring drug activity predictions by neural networks. This paper demonstrates how machine learning effectively discovers patterns in dynamic data sources which matches the situation faced when attempting to model drug responses by processing molecular graphs and gene expressions [25].

(Satorras et al., 2021) described E(n)-Equivariant Graph Neural Networks (EGNNs), a variant of graph neural networks which is efficient and effective for handling a number of applications with graph data. Among the attributes for which this model appears to be important are those of transformation: rotation, translation, reflection, and permutation, all of which can be performed through direct computation rather than more complicated formulas associated with higher-order representations [26].

(Njanko & Rawat., 2022) concentrated on improving GNN performance using a multi-graph approach in recognizing isomorphic graphs as it means for many applications, including regression tasks. Successfully extracted isomorphism from small and simple graphs: A large graph proved to be very computationally demanding.

(Azizian & Lelarge., 2021) developed a general theoretical framework that permits to compare expression capacities and expressiveness of different GNN architectures. It thus instantaneously captures invariant GNNs, which produce values independent of permutations of the nodes, and equivariant GNNs, whose output are modified upon permutations. The study evidences that proposed algorithm, which utilize tensor operations enhanced with matrix multiplications, outperform traditional algorithms like spectral or semi-definite programming methods in solving the Quadratic Assignment problem (QAP), showcasing superior average performance.

The strategies of drug activity prediction models can be classified as omics-based [27] and structure-based [28] approaches. Machine learning (ML) and

deep learning (DL) models are then used to implement the above two approaches. Traditional studies have often adopted either gene expression, mutation profiles of cancer cell lines, or drug structures, as input or features, to predict the drug response [29]. However different combinations of data types have not been inspected thoroughly. Here, to address the limitation, comprehensive performance comparisons with various DL models that include transformations like rotation and translation of integrated drug SMILES and gene expression as input were performed. The application of generative AI technology to resolve secure coding issues by demonstrating how intelligent systems generate valuable results from multiple-dimensional inputs. The application of generative neural models demonstrates conceptual overlap with the drug activity regression system that uses multimodal neural networks although the research material does not use biomedical data. Your study adds credibility to the AI conceptual framework of your work because professionals show greater trust in AI systems for technical problem resolution and critical applications[30] .

Various existing surveys showed that models using Equivariant networks for graph and image data were built with numerous transformations for prediction tasks. Data was rotated and translated using various methodologies and procedures for accurate prediction in different contexts [31]. However, these types of networks were not applied in drug activity prediction and also the results of previous work with GCN trained with drug SMILES and gene expression [32] produced less generalizability and prediction rate where no data transformations were included. Hence to overcome the limitations it is proposed to build a robust drug activity prediction model with GAT-Multimodal and GIN-Multimodal Neural Networks that processes rotated and translated drug SMILES graphs with gene expression characteristics as training data to improve the prediction accuracy of the model.

2. Data preparation and Augmentation

Data preparation and Augmentation involves converting drug SMILES (Simplified Molecular Input Line Entry System) to graph format, creating augmented graphs with rotation and translation, and normalizing gene expression. The process of data preparation and augmentation is shown in Fig.1.

In this step, drug SMILES are converted to RDKit molecular objects. In the node creation step, each graph is initialized with nodes equal to a number of atoms. In the edge creation step, an edge list is used to create edges between nodes where there are two columns with the source having source nodes and the destination having ending nodes.

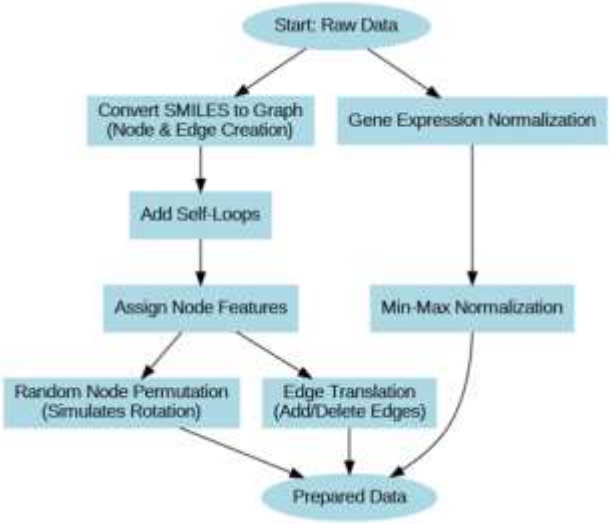

Figure 1*. The process of data preparation and Augmentation*

Edges with the same source and destination nodes are added as self-loops. In the node feature assignment phase ten molecular descriptors namely Molecular Weight, LogP, Hydrogen Bond Donors, Hydrogen Bond Acceptors, Topological Polar Surface Area, Rotatable Bond, Aromatic Ring Count, Molecular Refractivity, Atom Count, and Formal Charge.

Rotation is achieved with the help of Random Node Permutation having steps like Shuffling nodes, Mapping Indices, Recreating Edges, Adding Self-Loops, and Feature Reassignment. The shuffling nodes phase uses a random pattern to shuffle the indices in the graph. Mapping indices creates a record of old and new indices so that the graph can be recreated. Based on the new node indices edge list is updated in the Recreating edges step. Zero-degree edges are also added to retain the graph structure. Finally, the node features are assigned for rotated graphs in their corresponding nodes.

Graph shearing is used for Molecular graph translation. The molecular translation follows steps like Edge Deletion and Edge Addition such that it does not affect the existing graph topology ensuring edge integrity check and adding self-loops. Node features are added in the sheared graph for further analysis. The gene expression is normalized with Min-Max normalization so that it ranges between 0 to 1. Thus, the final data consists of original, rotated, translated graphs and normalized gene expression and few augmented graph samples are given in Fig.2a. Original graph, Fig.2b. Rotated graph, Fig.2c. Translated graph,

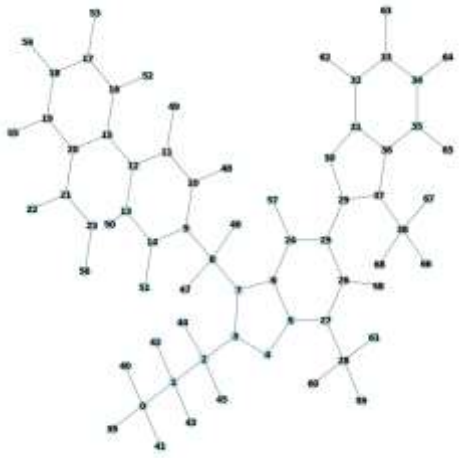

Figure 2a. *Original graph*

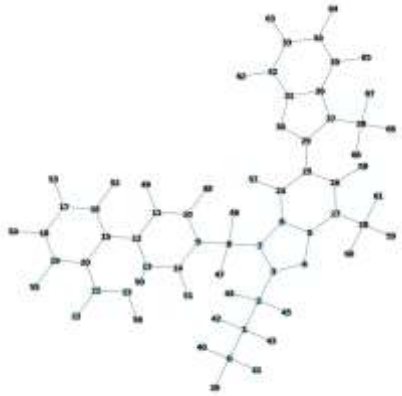

Figure 2b. *Rotated graph*

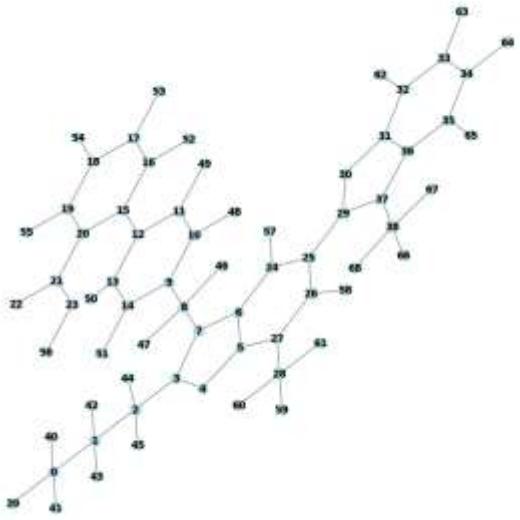

Figure 2c. *Translated graph*

The translation and rotation procedure are important in algorithms intended for handling spatial data, such as graphs, where permutation-invariant representations are needed. To achieve more efficient extraction of features and representation learning, architectures like Graph Isomorphism Networks and Graph Attention Networks are incorporated into the Multimodal networks. These architectures frequently include techniques for dynamically modifying filter parameters or feature networks based on the content of the input. A detailed explanation of the model architecture and hyperparameter setting is given in further sections.

3. Model Building

The drug activity regression model is built by leveraging multimodal neural networks [33], [34], [35],[36] trained with different graph representations, such as original, rotated, and translated, along with gene expression features. The model building is illustrated in Fig. 3, employing two graph network architectures namely Graph Isomorphism Networks (GIN) [37], [38],[39] and Graph Attention Networks (GAT) [40], [41], [42]. The entire model-building process is divided into five phases like Input Layer Design, Graph Convolutional layers, Gene Expression Feed Forward Neural Network Layer, Combined Linear layers and Output layer.

The input layer is designed with different components like original, translated and rotated graph objects along with gene expression features. The input layer accepts different forms of the same graph since the multimodal neural networks can process variable data representations. This unique property of multimodal neural networks increases the precision rate of the model and better feature extraction.

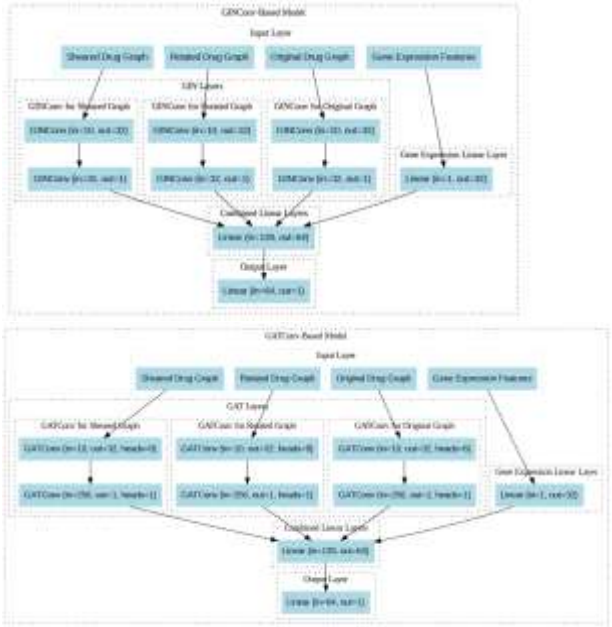

Figure 3. *Model Building process*

The Graph Convolutional layers included are GAT and GIN which differentiate the first GAT-Multimodal from GIN-Multimodal Regression models. The core functionality of GIN architecture is that it can isolate non-isomorphic graphs and extract only symmetrical features. The GIN-Conv-based model is designed with unique GINs for original, translated and rotated graphs. Each graph representation has 10 input features and passed to the GIN layer with 10 input units and 32 output units. The 32 output features are reduced to a single global feature by passing it to another GIN layer with 32 input units and 1 output unit. The same setting is repeated for the GAT-Conv-based model but instead of the GIN layer GAT layer is used. The GAT and GIN architecture is given in Fig 4.

The GINConv uses sum aggregation whereas GATConv uses attention-based aggregation. Feature transformation is performed in GIN with MLP layers while multi-head attention is used in GAT. GIN gives equal importance to its neighbors but GAT uses an attention mechanism.

GAT architecture has advantages like assigning dynamic weights to most important nodes based on the surrounding nodes. This helps in focusing on relevant nodes only. GAT is an advanced architecture compared to GCN since it uses fixed weights for message passing and follows uniform graph propagation. While GAT captures complex learned representations even in heterogeneous graphs with varying node sizes, node entities, degrees and feature sizes. The GAT architecture supports distributed computation and parallelization across graph entities, improving the computational power of the model in training graph data through lowering latency. Its ability to process sparse graphs with either more nodes or few nodes enable consistent learning. Multi-head attention allows extracting various types of features from graph data increasing the robustness of model. GAT has high generalizability capacity and adaptability to various graph tasks. Therefore, GAT architecture is employed in hybrid deep learning architecture due to its efficiency and performance in drug discovery.

GIN has a highly performing architecture in processing data with various permutations like rotation and translation. It extracts invariant features from permutated graphs thereby enhancing the performance of models better than other architectures like GCN and GAT. GIN excels in processing the same graph with varying topologies like cycles, trees and chains through extracting unique embeddings. MLP based aggregation distinguishes structurally similar compounds with different properties. It effectively captures structural information, distinguishing different graph topologies better than GCN and GAT. The model is particularly useful for training augmented graphs in for molecular property prediction, since smaller changes can have larger impact on model performance. The model is specifically applied in contexts where graph topology is important than connection between neighbouring nodes. Overall, GIN is chosen due to its capability to understand structural differences effectively and applied in structure based drug discovery methodologies like bioactivity regression.

The Gene Expression features with a single dimension are processed through the Feed Forward Neural Network layer. The FNN layer is defined with one input unit and 32 output units. After the above processing of drug graphs by graph convolutional layers and gene expression by FNN layers. The feature vectors extracted by these layers are passed to combined layers for feature concatenation. The combined linear layers are defined with 128 input units and 64 output units which are passed to the output layer with 64 input units and single output unit since it is a regression task.

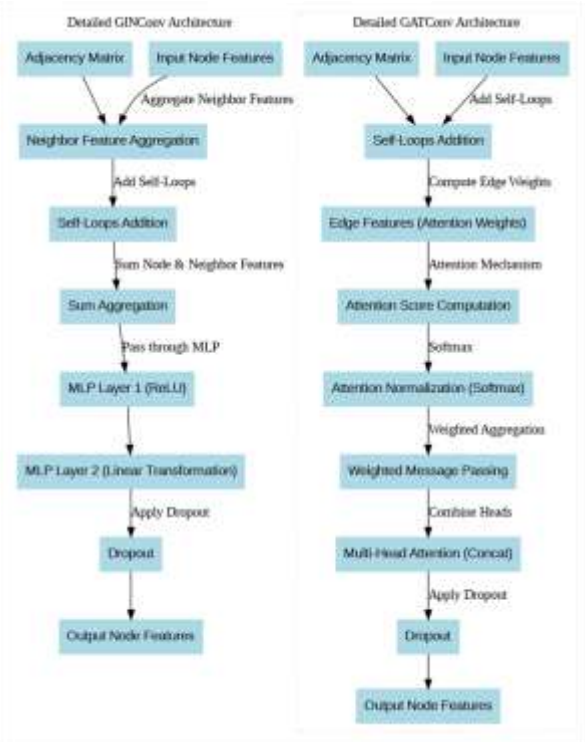

Figure 4*. GIN and GAT Architecture*

4. Experiments and Results

Deep Graph Library (DGL) [43] serves as a front-end framework while PyTorch [44-46] is the backend framework of DGL responsible for the data processing and implementation of the models. The

drug activity prediction model has been implemented by leveraging a Multimodal Neural Network using Python and training the original, translated, and rotated Drug graphs and gene expression. The experiments are carried out by setting proper hyperparameters as shown below in table 1. The output layer is assigned with one unit and there are two graph convolutional and combined layers. Adam optimizer is applied to
decrease the error rate and increase model efficiency.

Table 1. *Hyperparameters Setting for Multimodal Neural Network Model*

Hyperparameters	Values
Epoch	500
Graph Conv layers	2, hidden units=32
Dense layers	2, neuron size=64
Learning rate	0.001
Output size	1
Optimizer	Adam
k-fold	7

GIN-Multimodal network training starts from epoch 100 and converges at epoch 500 in fold 7.

The results are evaluated with metrics MAE, RMSE, and R2 Score after proper hyperparameter tuning. The precision rate with regard to R2 Score and error rate corresponding to MAE and RMSE gradually improve after each iteration. The minimum error rate is recorded as 0.16 and 0.15 respectively by MAE and RMSE. Similarly, the maximum accuracy produced by the R2 Score is 0.94 which signifies 94 percent accuracy. The Performance Results of the GIN-Multimodal Prediction Model using original, rotated and translated Drug SMILES and gene expression are shown in table 2 and depicted in Fig 5.

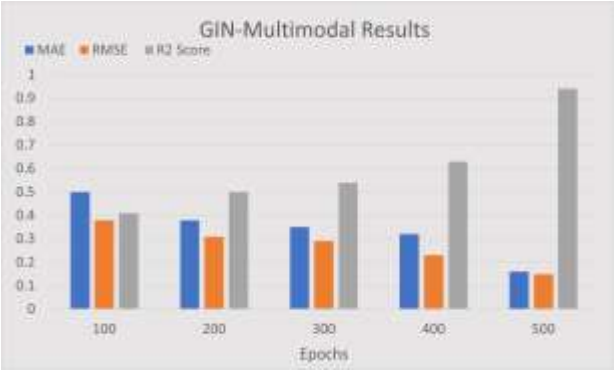

Figure 5. *GIN-Multimodal prediction model results*

The GAT-Multimodal Prediction model results are given in table 3 and shown in Fig 6. The highest accuracy is achieved at epoch 500. The GIN-Multimodal Prediction Model obtains an R2 score of 0.94, RMSE of 0.15, and MAE of 0.16 with better generalizability even when more data is added. The GAT-Multimodal Prediction Model
gets an R2 score of 0.92, RMSE of 0.16 and MAE of 0.18.

Table 2. *Performance Results of GIN-Multimodal Prediction Model*

Epoch	MAE	RMSE	R2 Score
100	0.50	0.38	0.41
200	0.38	0.31	0.50
300	0.35	0.29	0.54
400	0.32	0.23	0.63
500	0.16	0.15	0.94

Table 3. *Performance Results of GAT-Multimodal*

Epoch	MAE	RMSE	R2 Score
100	0.48	0.36	0.39
200	0.36	0.28	0.48
300	0.32	0.25	0.51
400	0.28	0.23	0.60
500	0.24	0.22	0.92

MPNN-IC50 Prediction Model achieves an R2 score of 0.85, RMSE of 0.28 and MAE of 0.26. GIN-IC50 Prediction Model attains an R2 score of

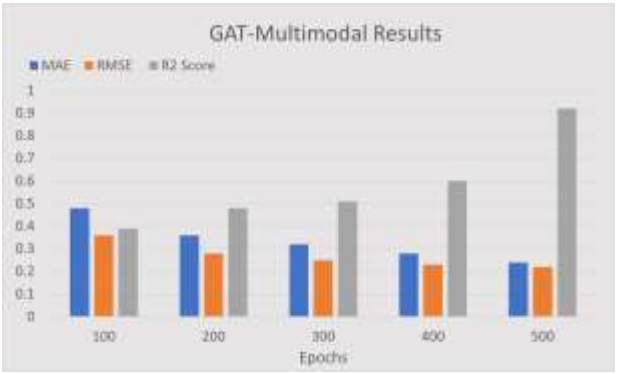

Figure 6. *GAT-Multimodal Results*

0.80, RMSE of 0.46 and MAE of 0.48. GCN-IC50 Prediction Model obtains 0.80 R2 score, RMSE of 0.48 and MAE of 0.50. The comparative results are also given in table 4 and Fig 7.

Table 4. *Comparative Results of Bioactivity Prediction Models*

Model	MAE	RMSE	R2 Score
GAT-Multimodal	0.16	0.15	0.94
GIN-Multimodal	0.24	0.22	0.92
GAT-IC50 Prediction Model	0.28	0.26	0.87

MPNN-IC50 Prediction Model	0.38	0.36	0.85
GIN-IC50 Prediction Model	0.48	0.46	0.80
GCN-IC50 Prediction Model	0.50	0.48	0.78

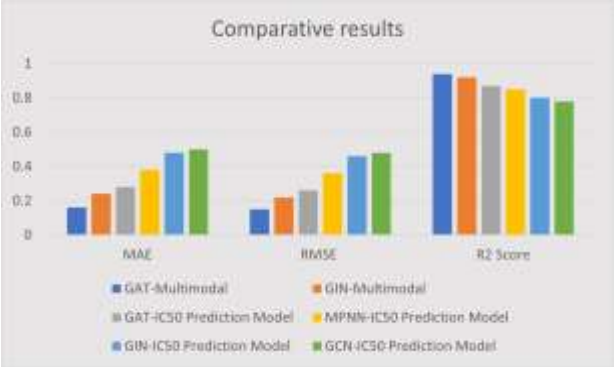

Figure 7. *Comparative results*

The study found that incorporating equivariance in graph-based algorithms significantly enhances drug activity prediction accuracy in neurodegenerative diseases like ALS and AD. Multimodal Neural networks effectively learn drug-gene interactions, leading to robust and invariant representations. Combining drug SMILES with gene expressions subjected to transformations such as rotation and translation improves model performance. The GIN-Multimodal Neural Network ensures consistent output despite variations in input data. Empirical studies on a carefully selected dataset of 665 graph instances reveal exceptional prediction results. In general, the research provides valuable insights in an attempt to increase the accuracy of drug activity prediction and understand drug-gene interactions in complex diseases. There are several other related studies [47-52] that contributed to different aspects of the disease.

5. Conclusions

The unavailability of equivariance prevents the appropriate exploiting of intrinsic symmetries embedded in the graph data and, subsequently, the deterioration of the performance of IC50 prediction tasks. The integration of drug SMILES with gene expressions under rotation and translation transformations of the input space is performed to address this issue. Networks built to be translation invariant or equivariant learn better from such transformed data for drug-gene interaction learning. Hyperparameter optimizations yield highly accurate predictive results with R2 value of 0.94, Mean Absolute Error of 0.16, and Root Mean Square Error of 0.15. The results, therefore, demonstrate the promises of Multimodal Neural networks toward developing invariant representations and superiority over traditionalizing neural networks in addressing transformed input.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
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- **Funding information:** The authors declare that there is no funding to be acknowledged.
- **Data availability statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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