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Original Article

Predicting the neurotoxic activity of diverse bio/chemical compounds on Acetylcholinesterase enzyme using deep learning-based QSAR model

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Abstract

A deep learning model that utilizes neural network architectures to predict bioactivity against Acetylcholinesterase (AChE) enzyme was applied. The model effectively captures complex relationships within high-dimensional data by integrating neural network architecture training and optimization techniques. The obtained results indicate that the deep learning model achieves high accuracy, sensitivity, and precision in the predictions. The enhanced performance with a low loss score can be attributed to the ability of the model to leverage the unique capabilities of deep learning computing, enabling it to explore a broader solution space. This work demonstrates that the use of computational modeling by means of deep learning provides a novel, rapid, accurate, and cost-effective method over traditional neurotoxic test alternatives in prediction, which can be used as a novel candidate for the neurotoxic effects of biochemical compounds on AChE, which is a potential biomarker used in neurotoxic research. This study highlights the potential of neural networks as a modeling approach for quantitative structure-activity relationship (QSAR) modeling, paving the way for advancements in drug discovery and toxicological research.

Keywords: QSAR; Acetylcholinesterase enzyme; neural networks; computational modeling, drug discovery; neurotoxicity.

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I. INTRODUCTION

Environmental chemistry plays a vital role in understanding neurotoxicity, particularly concerning how various environmental pollutants affect the nervous and the cholinergic systems. Neurotoxic agents, including heavy metals, pesticides, and industrial chemicals, can disrupt normal neurological functions, leading to both acute and chronic health (Caban-Holt et al., 2005; Costa et al., 2004). Exposure to neurotoxic substances can result in significant behavioral changes in wildlife, such as altered mating behaviors and impaired predator avoidance, which can cause different neuro-diseases and lead to population declines. Early life stages of organisms are particularly vulnerable to these toxicants, with potential long-term effects that may not be immediately apparent depending on exposure stage and the amount of to toxic induced. For example, neurotoxic exposure during critical developmental periods can trigger genetic and epigenetic changes, resulting in multi-generational impacts (Andersen et al., 2000). The complexity of neurotoxic effects is compounded by the vast number of chemicals present in the environment, many of which have unknown neurotoxic potential. In accordance to the American Conference of Governmental Industrial Hygienists (ACGIH), it is estimated that approximately 30% of commercially used chemicals may exhibit neurotoxic properties (Council, 1986). Current assessment methods primarily focus on human exposure, leaving a significant knowledge gap regarding the ecological impacts of these substances. To address these challenges, there is a pressing need for comprehensive research that evaluates the neurotoxic potential of environmental contaminants. This includes developing computational models to detect neurotoxic effects in various species and establishing standardized rapid detection methods to assess neurotoxicity of the toxic entities (Cronin et al., 2003). Due to the existence of many toxic chemical and biochemical agents from various industrial operations, there is a need for creating in vitro and in vivo models for measuring the toxic side effects on the biological entities and the nervous system (Kaufmann, 2003). However, the task of creating such models has increase in both difficulties and cost manners due to pollutants diversity. Therefore, the necessity of designing novel computational models for studying neurotoxic agents' effects on the nervous system is crucial to have rabid and accurate results for early detection of populates (Mager, 1982).

One of the most used computational models to assets and predicts neurotoxic effects on nervous system are quantitative structure-activity relationship (QSAR) models. QSAR models have gained a lot of attention in the past decades in neurotoxicity detection due to its rabid,

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accurate and cost effective properties. QSAR models suppose that the molecular activity effect can be estimated from physiochemical properties of the molecular structures (Mager, 1982). In QSAR models, the biological activity on the required biological target endpoint is typically estimated through structural and functional properties of the pollutant molecular structures (Devillers & Devillers, 2009; Mager, 1982). The biological target activity endpoint is proposed to have a functional dependency on the structural properties of the molecular compounds that exhibit molecular activity on the required target (Kruhlak et al., 2007; Lessigiarska et al., 2006). The QSAR models can be created using machine learning and deep learning methods for pattern and correlation prediction between the molecular and functional structures properties and the activity endpoints. QSAR models can be applied to predict the classification of compounds inhabitation effects based on PIC50 values thresholds to be active or inactive compounds.

The accuracy and rabid detection of QSAR models has encouraged researchers to develop novel models for predicting toxic effects of the required chemicals to be studied. For instance, Eldred DV and colleagues developed a QSAR model for predicting acute mammalian toxicity of organophosphorus pesticide compounds (Eldred & Jurs, 1999), demonstrating the applicability of QSAR models in predicting and classifying the toxic activity of these compounds. The developed QSAR models used various molecular descriptors, such as lipophilicity, molar refractivity, hydrogen-bonding acceptor ability (HBA), and hydrogen-bonding donor ability (HBD), to correlate the chemical structure with the acute toxicity. The models showed reasonable predictive accuracy in classifying organophosphorus pesticides based on their potential toxicity. Farther, Jurani.IO has developed QSAR models demonstrated reasonable predictive accuracy for classifying N-substituted fluoroacetamides based on their potential toxicity. The study specifically focused on predicting the acute toxicity, measured as the acute toxicity LD50 value, of these compounds in rats (Guo et al., 2006). Another study by Matthews et al. developed QSAR models for predicting hepatobiliary and urinary tract toxicities of various related pharmaceuticals based on their chemical molecular structures (Matthews et al., 2009), the toxic effects of these drugs used in the study were classified into categories cytotoxic injury, cholestasis, enzyme disorders and urinary tract injures. For predicting neurotoxic activity of organic compounds, Nikita Basanta and coworkers developed Probabilistic neural network (PNN) based qualitative and generalized regression neural network (GRNN) based quantitative structure toxic relationship (STR) models (Basant et al.,

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2016). The qualitative STR models have classification accuracies of 92.86% in the test data sets, whereas, the quantitative STRs yielded correlation (R2) of >0.93 between the measured and model predicted values. These models results suggest the applicability of developing machine learning and deep learning based QSAR models for predicting neurotoxic effects of some organic compounds on the nervous system. The previous QSAR based paper showed the potentiality of using machine learning models especially deep learning for QSAR models.

Acetyl cholinesterase (AChE) is a major enzyme that responsible for catalyzing the hydrolysis of acetylcholine (ACh) transmitter into choline and acetate in various cholinergic pathways which cause termination of the nerve impulse transmission in both central and peripheral neural systems (Colović et al., 2013). AChE activity aims to terminate synaptic transmission which stops nerve firing at the nerve end. Thus, AChE plays significant role to obtain the normal function in both central and peripheral nervous system (Lionetto et al., 2013). The AChE molecule is composed of two different protein domains as a catalytic domain of about 500 residues and small C-terminal domain of less than 50 amino-acid residues. AChE is a product of one gene expressed in different tissues with different splicing forms with a precise localization on the long arm of chromosome 7 (Getman et al., 1992). The synaptic AChE-s isoform, which is produced by splicing in the 3\ terminus of AChE pre-mRNA, considered the main multi-meric enzyme in brain and muscle (Taylor & Radić, 1994). There are two sub sites on the AChE active site, which are the anionic and esteratic sub sites. The anionic sub site binds to the positive quaternary amine of acetylcholine transmitter, while the esteratic sub site where the acetylcholine is hydrolyzed into acetate and choline. Hydrolyzing the carboxyl ester leads to formation of an acyl-enzyme and free choline. Then, the acyl-enzyme interact with a water molecule which synthesis acetic acid and regenerating the free enzyme (Hulka & Wilcosky, 1988). AChE enzyme is one of the most used biomarkers for studying neurotoxic effects on the nervous system. Biomarkers are known as “cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids” (Naylor, 2003). Biomarkers can also measure biological characteristics and used as an indicator of pharmacological responses to drugs for therapeutic intervention (Claus Henn et al., 2006). AChE e enzyme has been widely used as a biomarker for measuring neurotoxic effects of pollutants and drugs. AChE inhibition cause acetylcholine accumulation and thus lead to continuous nerve impulse, hyper stimulation of nicotinic and muscarinic receptors, and thus disrupt neurotransmission over synaptic ends.

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Several studies reported the use of AChE enzyme as a potential biomarker for studying neurotoxicity. For example, measuring AChE inhibition in human saliva as a neurotoxic biomarker for organophosphorus pesticide has been explored (Andersen et al., 2000; ELLMAN et al., 1961). Another study reported the effects of some metallic ions, such as Hg^{2+}, Cd^{2+}, Cu^{2+}, on humans and animals by using AChE enzyme as neurotoxic biomarker (Frasco et al., 2005). Ademuyiwa and coworkers (Ademuyiwa et al., 2007) studied the effect of lead on erythrocyte AChE activity during occupational exposure, suggesting that erythrocyte AChE activity could be used as a biomarker of lead-induced neurotoxicity. Chanin Nantasenamat et. al. (Malik et al., 2022) developed QSAR model for studying acetyl- and butyryl- cholinesterase inhibitors using random forest model which can be farther utilized for neurotoxic inhibitors initial prediction .

In the present work, we used AChE enzyme as potential biomarker for predicting neurotoxic inhibitors activity on it which eventually would affect the nervous system activity. However, a deep learning model for studying neurotoxic effects of some populates and drugs on AChE enzyme activity as potential biomarker in nervous system is developed. The deep learning based QSAR for predicting the neurotoxic effects of some molecular structures and visualizes the results of each other show that the deep learning model carries very good accuracy for neurotoxicity effects prediction.

This work is organized as follows: A detail description of the used materials and methods is given in Sec. II. Section III is devoted to the results and discussion. Finally, conclusions are reported in Sec. IV.

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II. Materials and Methods

II.1-Data collection:

The QSAR model consists of number of stages as shown in figure 1. Data set of 4695 molecule with bioactivity data points (IC50) against human AChE (Target ID: CHEMBL220) was collected from ChEMBL database. ChEMBL database is a large-scale bioactivity database that contains information about the biological activities of small molecules and widely used in drug discovery and chemo-informatics (Gaulton et al., 2012).

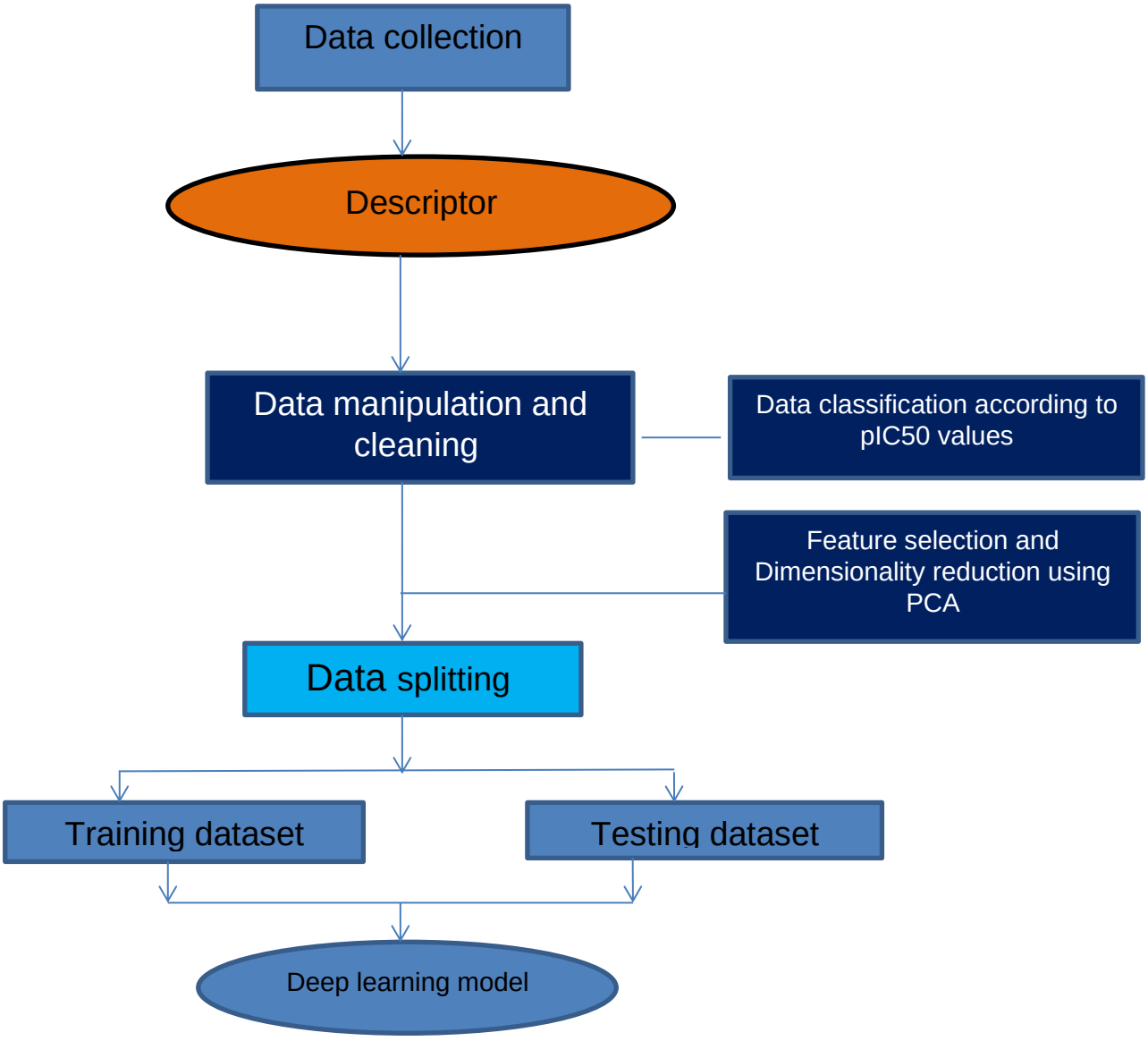

Fig. 1: Data processing and splitting for multivariate analysis.

II.2-Descriptor generation:

Descriptors are physiochemical properties of the molecular structures they are useful for model training and learning as features input for chemical structures (Consonni & Todeschini, 2010).

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The PaDEL Descriptor software (Yap, 2011) was used for calculating and generating 12 sets of molecular fingerprints that belong to nine different types as follows: E-state, KlekotaRoth, MACCS, PubChem, Substructure, AtomPairs 2D, CDK fingerprint, CDK extended and CDK graph only. There was 883 descriptor per every molecular structure of the dataset was generated.

The data was balanced using SMOT sampling to prevent model bias and improve model performance. Two sets of the curated and processed data of AChE inhibitors enzyme were collected with 1808 inactive compounds and 1848 active compounds.

II.3-Data manipulation and cleaning:

Pandas library was used to process and clean data (Mckinney, 2010) by removing all redundant, and duplicated data from the bioactivity dataset. Data set was first filtered against empty values in the rows, then all the duplicated data was removed to keep the dataset balanced for farther Multivariate analysis. Data was scaled by using standard scaling to standardizing features of the model input to have zero mean and unit variance to improve model stability and to have better generalization and better convergence during optimization. As the primary goal of this study is to develop deep learning model for binary classification of bioactivity data, we used two bioactivity data threshold for providing difference between active and inactive compounds.

The bioactivity endpoint is the effectiveness of a compound in inhibiting specific biological function, such as enzyme activity or affecting receptor binding. The IC50 is the half-maximal inhibitory concentration value which quantifies the concentration of substance required to inhibit a biological process by 50% as higher PIC50 value indicate greater potency of compound. The pIC50 is the logarithmic transformation of pIC50, which is used for normalizing data distributions for better statistical and predictive analysis.

The bioactivity of compound is considered to be active with pIC50 threshold greater than or equal to 6 and inactive when it equal or less than 5(corresponds to IC50 thresholds of < 1 and > 10 µM, respectively (Malik et al., 2020; Suvannang et al., 2018). All intermediate pIC50 values between 5 and 6(in the range of 1 and 10 µM in IC50) were removed and the data was classified to in accordance to the PIC50 values for farther analysis. The bioactivity data set of pIC50 was processed by applying one-hot encoding using Scikit-learn (Pedregosa et al., 2012) where inactive is 0 and active is 1.

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II.4-Feature selection and filtering:

In QSAR models, the redundant and unnecessary descriptors and fingerprints, which are used as input features, must be removed to remove inheritance bias and optimize model performance and learning. One of the most used techniques to handle high dimensional data set is principal component analysis (PCA). PCA aims to reduce the dimensionality of the dataset by transforming the original features into a smaller set of uncorrelated variables (principal components) that capture the most variance. Hence PCA remove noise and redundant features that cause poor performance and low accuracy by collecting necessary information of descriptors the original dataset. PCA aims to transform principal components which are linear combinations of the original features in the dataset. They are constructed in such a way that they capture the maximum variance in the data. Several QSAR models have applied PCA to remove noise data from the descriptors (Sahigara et al., 2012; Yoo & Shahlaei, 2018) that contain only the important data after dimensionality reduction. Principal Component Analysis (PCA) is applied using Sciket-learn to reduce the dimensionality of the dataset while preserving 95% of its variance, providing insight into number of components required to capturing the majority of the data's variance. Fig. 2 explains the number of components required for having sufficient cumulative variance 6 for dimensionality reduction application. The results of Fig. 2 indicate that 174 principal components capture and explain 95.07% of the total variance. Which mean the dimension of features after PCA would be 174 for every molecule in the data set.

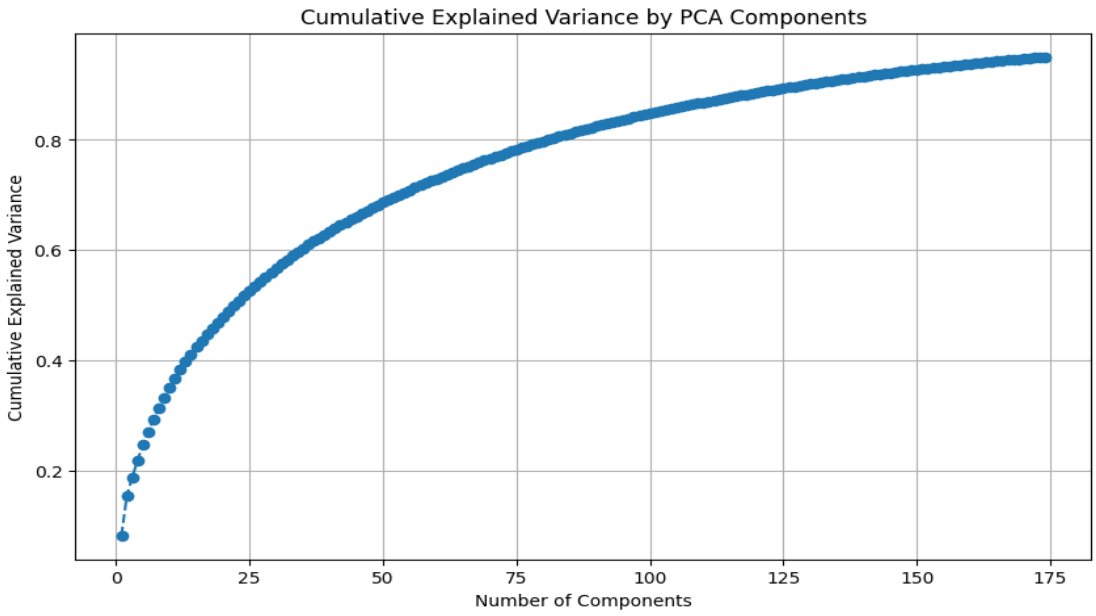

Fig. 2: Cumulative explained variance versus number of components.

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III. RESULTS AND DISCUSION

In the present study, a deep learning model is applied in order to predict the bioactivity classification of neurotoxic compounds. This model is a feed-forward neural network that consists of seven layers, with connections between them that are weighted and learned during the training process. The first layer is the input layer, which has a shape corresponding to the number of features in the dataset. The hidden layers are 5 layers that capture complex patterns and relationships within the data, while the output layer classifies the data into active and inactive compounds. The model's output is optimized with respect to the real binary data through back propagation. The activation function used for binary classification of the data was sigmoid function in the output layer. Dropout regularization was employed to enhance model performance by mitigating model bias (Srivastava et al., 2014). The loss function is binary cross-entropy function which is used in binary classification tasks. Early stopping was applied to save computational resources and prevent over fitting (Prechelt, 1998). Number of epochs is 500, batch size is 32, the optimizer is ADAM algorithm with learning rate set to be 0.001 and L2 regularization parameter is 0.001. The model was built using torch library (Paszke et al., 2019) and trained using Google CoLab platform.

III.1-Model loss:

The average Loss (cost) is a measure of how well the model's predictions match the actual outcomes (Wang et al., 2022). The loss plotted against the epochs in training and testing processes in Fig. 3. The loss is decreased during increasing number of epochs which reflect small difference between the actual and predicted outcome.

III.2-Model accuracy:

Accuracy is the percentage of correctly predicted instances to the total number of instances. It provides a measure of the overall correctness of the model's predictions. The accuracy plotted against number epochs in Fig. 4 on both training and testing phases with total average accuracy of testing set of 85.25%. The accuracy increase with increasing number of epochs during model learning and be stable at point whatever the epochs increased (Buduma et al., 2022).

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III.3-Model Sensitivity:

There are four types of predictions that the model can produce: True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN). Sensitivity metric (or recall) measures the model's ability to identify positive instances (active compounds). In bioactivity prediction, high sensitivity is crucial when missing a potential active compound (false negative) is costly or undesirable. Sensitivity is calculated using the equation:

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

As shown in Fig. 5, sensitivity starts to increase as the model improves its ability to correctly identify positive instances (true positives) with increasing number of epochs in the training phase (Buduma et al., 2022).

III.4- Matthews Correlation Coefficient (MCC):

Another important metric to asset model performance is the Matthews Correlation Coefficient (MCC). MCC is a measure used to assess the quality of binary classifications. MCC account true and false positives and negatives, providing a balanced metric that can be used even when the imbalanced classes data (Chicco et al., 2021).

$$MCC = \frac{TP \,.\, TN - FP \cdot FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}.$$

MCC is increasing with epochs, it suggests that your model is learning and improving its classification performance over time as shown in Fig. 6.

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III.5-The Receiver Operating Characteristic (ROC):

The Receiver Operating Characteristic (ROC) curve is a graphical representation used to evaluate the performance of our binary logistic regression model. It plots the True Positive Rate (TPR) against the False Positive Rate (FPR) at various threshold settings, provides insights into the trade-offs between sensitivity and specificity across different decision thresholds.as shown in Fig. 7.

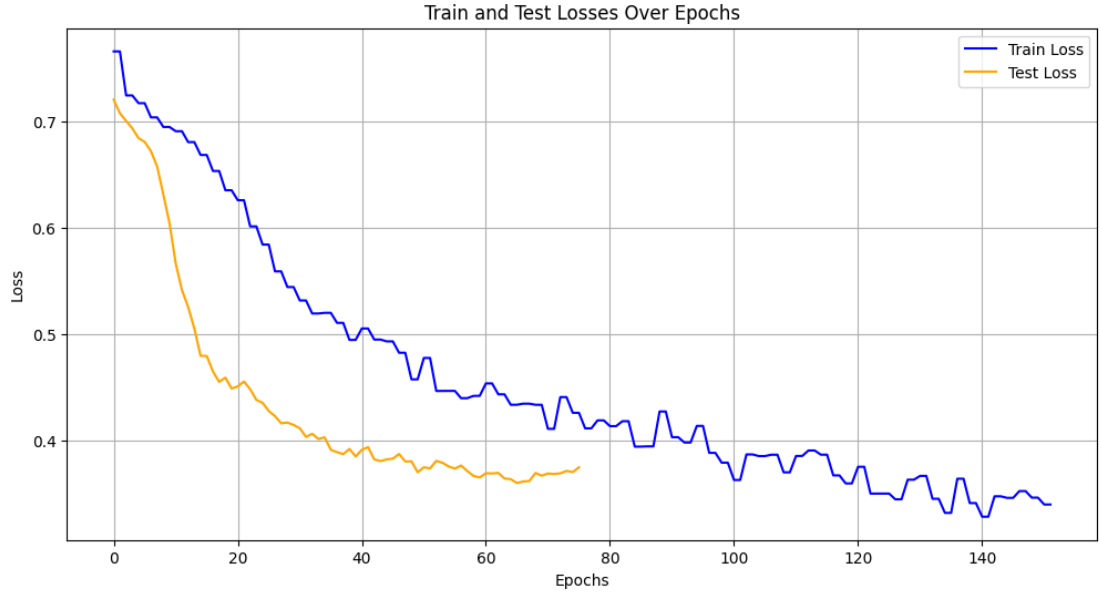

Fig. 3: Shows the loss metric decrease with number epochs during learning phases cross both training and testing data. Binary cross entropy loss function is dimensionless as it is based on logarithmic values.

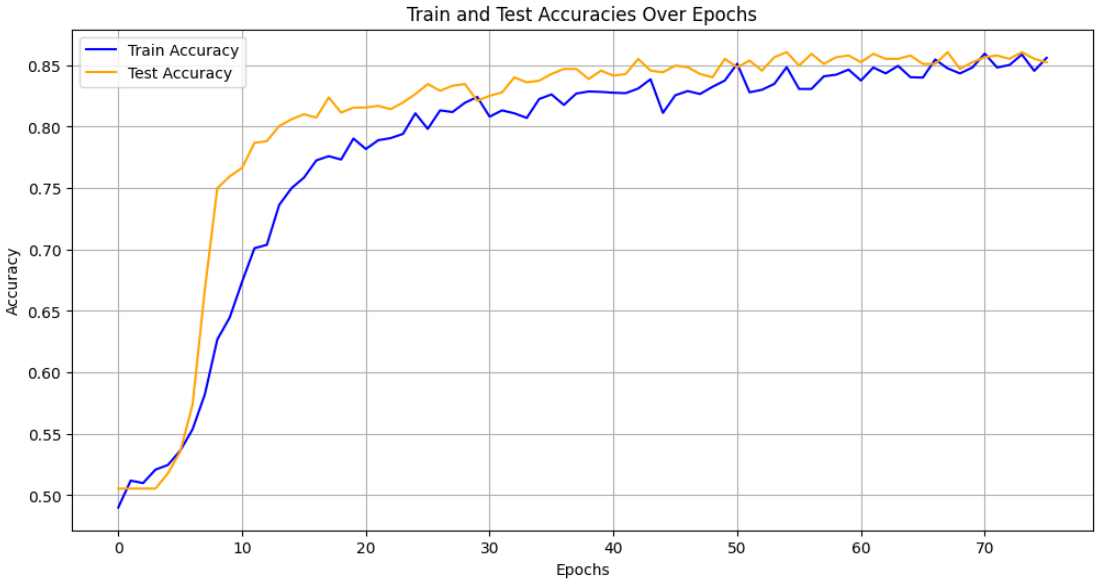

Fig. 4: Shows the accuracy increase with number of epochs in the model training and testing phases. Accuracy is unit-less; it is the ratio of correct predictions among the total predictions made by the model.

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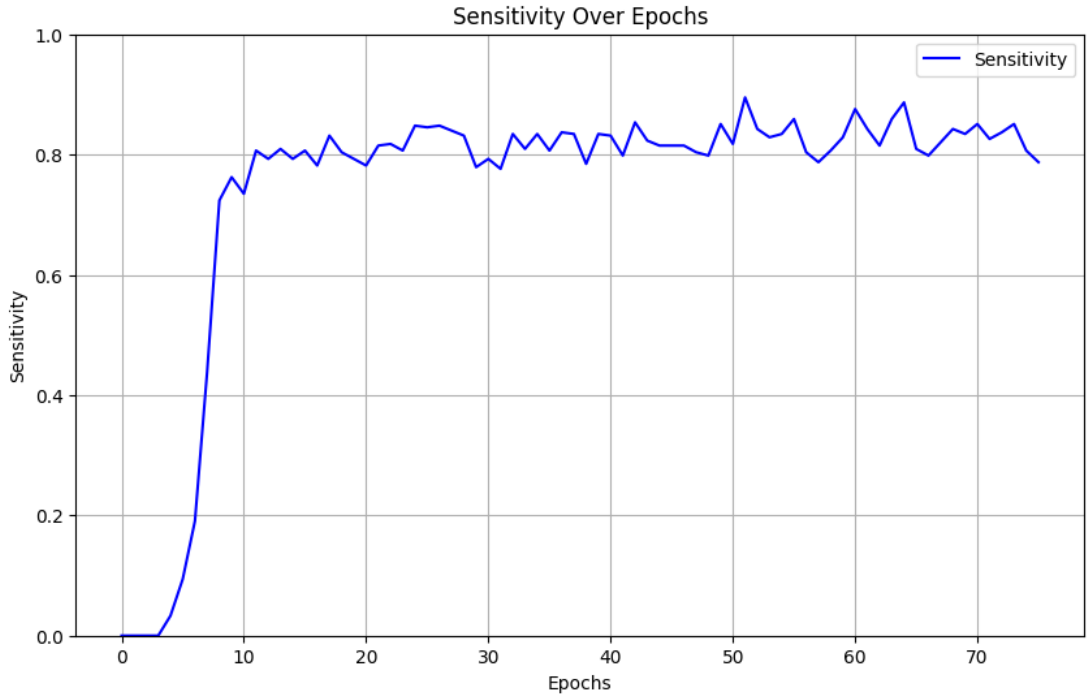

Fig. 5: Sensitivity metric ratio behavior against number of epochs during model learning.

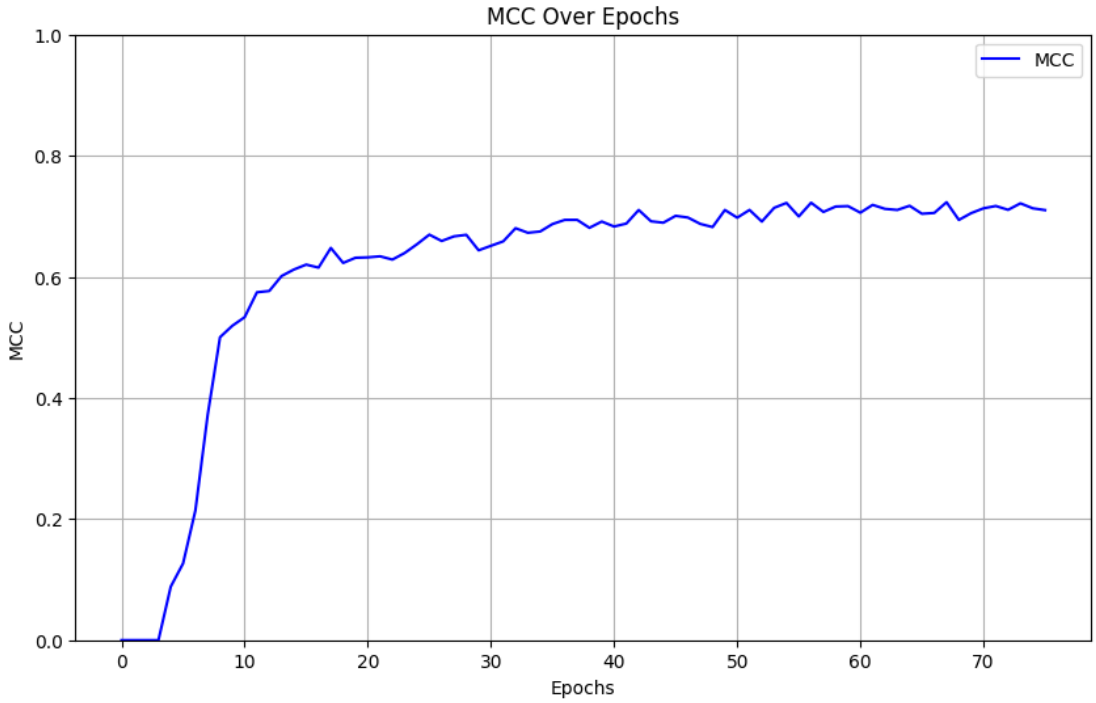

Fig. 6: MCC ratio increase with increasing number of epochs.

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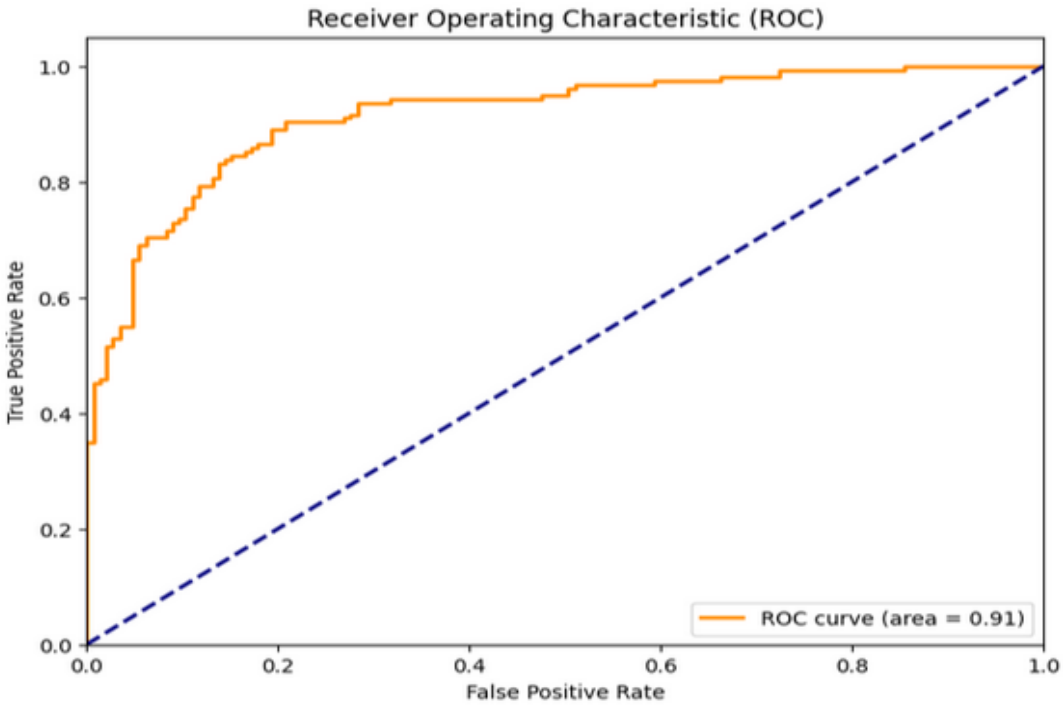

Fig. 7: ROC characteristics diagram.

IV. Conclusion

The results of the present study demonstrate that the deep learning model has a significant performance in predicting bioactivity against Acetylcholinesterase enzyme. This leads to an improvement in generalization and performance metrics, such as accuracy, sensitivity, and precision. Moreover, model's adaptability allows it to effectively handle diverse datasets, making it a promising alternative for quantitative structure-activity relationship (QSAR) modeling. As the field of artificial intelligence continues to grow, integrating QSAR modeling into deep learning frameworks could revolutionize predictive modeling in drug discovery and toxicology. Our findings suggest that deep learning represents a novel direction for future research in QSAR applications.

Conflict of Interest: *The authors declare that they have no conflict of interests.*

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Author Contributions: The authors, Moatamad, M. Saleh R. Hassan and Amal M. Hemmdan suggested the computational model, analyzed the data and verified the numerical results. Abdel-rahman Hamdy collected the data, carried out the calculations and contributed to the

interpretation of the results. All authors discussed the results and contributed to the final manuscript.

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