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Research article

Enhancing drug-target interaction predictions in context of neurodegenerative diseases using bidirectional long short-term memory in male Swiss albino mice pharmaco-EEG analysis

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ABSTRACT

Background and Objective: Emerging diseases like Parkinson or Alzheimer's, which are not curable, endanger human mental health and are challenging to research. Drug target interactions (DTI) are pivotal in the screening of candidate drugs and focus on a small pool of drug targets. Electroencephalogram shows the responses to psychotropic medicines in the brain bioelectric activity. Synaptic activity can be analyzed by using Local Field Potential recordings obtained from micro-electrodes implanted in the brain. The aim is to evaluate the effects of drug on brain bioelectric activity and increase the drug classification accuracy. The ultimate goal is to advance our understanding of how drugs affect synaptic activity and open the door to more focused treatment for neurodegenerative diseases.

Methods: In this study, Pharmaco-EEG recordings are processed using Advanced neural network models, particularly Convolutional Neural Networks, to assess the effects of medications. The five different medicines used in this study are Ephedrine, Fluoxetine, Kratom, Morphine, and Saline. The signals observed are local field potential signals. To overcome some limits of DTI prediction, we propose Bidirectional Long Short-Term Memory (LSTM) for the categorization of intracranial EEG (i-EEG) data, departing from standard approaches. Similar EEG patterns are presumably caused by drugs that work by homologous pharmacological pathways, producing similar psychotropic effects. To improve accuracy and reduce training loss, our study introduces a bidirectional LSTM model for classification along with Bayesian optimization

Results: High recall, precision, and F1-Scores, particularly a 95% F1-Score for morphine, ephedrine, fluoxetine, and saline, suggest good performance in predicting these drug classes. Kratom produces a somewhat lower recall of 94%, but a high F1-Score of 97% and perfect precision of 1.00. The weighted average F1-Score, macro average, and overall accuracy are all consistently high (around 97%), indicating that the model works well throughout the spectrum of drugs.

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Conclusions: Improved model performance was demonstrated by using a diversified dataset with five drug categories and bidirectional LSTM boosted with Bayesian optimization for hyperparameter tuning. From earlier limited-category models, it represents a substantial advancement.

1. Introduction

Numerous novel and established disorders that pose a significant threat to human mental health, including conditions such as Parkinson's and Alzheimer's disease, still lack definitive cures despite ongoing research efforts. It is imperative to speed up drug discovery with precision and efficiency to accelerate the development of therapies for these diseases. The pursuit of drug discovery typically involves a multi-phase approach, encompassing massive screening of candidate active ingredients, preclinical investigations, clinical trials, and the eventual attainment of marketing approval. Unfortunately, the success rate in drug discovery remains notably low, and is coupled with protracted duration and substantial financial investments required [6]. The conventional biomedical experimentation approach, while invaluable, falls short in addressing the formidable challenges posed by drug discovery, particularly when dealing with emerging and infectious diseases [28]. This limitation underscores the urgency of devising innovative strategies for drug development, especially in the context of addressing these pressing healthcare concerns.

Within the intricate realm of drug discovery, the exploration of drug-target interactions (DTI) holds paramount significance. Drug targets serve as the foundational cornerstone of the drug discovery and development process, with centuries of pharmaceutical progress relying heavily on the identification of numerous drug targets. The discernment of drug-target interactions marks the initial stride towards the inception of novel therapeutic agents and stands as a pivotal determinant in both drug screening and the synthesis of drug candidates. However, traditional methodologies for probing these interactions exhibit notable limitations.

1.1. Significance of the study

Leveraging high-throughput experiments, researchers are progressively gaining deeper insights into the expansive structural diversity of active compounds and the intricate epigenetic characteristics of target proteins. Nevertheless, our comprehension of the intricate interplay between these two domains remains constrained, primarily due to the laborious and time-intensive nature of experimental procedures involved [6]. This challenge underscores the pressing need for innovative computational approaches to bridge this knowledge gap effectively.

In the scope of this research, we have undertaken the recording of local field potential signals stemming from the administration of five distinct drug types: Ephedrine, Fluoxetine, Kratom, Morphine, and Saline. To overcome the constraints associated with conventional methodologies, we advocate for the application of Bidirectional Long Short-Term Memory (LSTM) networks in the classification of intracranial EEG (i-EEG) data. Additionally, we explore the utility of i-EEG data in predicting Drug-Target Interactions (DTI) through categorization.

1.2. Contribution (s)

The contribution is highlighted in following domain: **Model Development:** Sequential data problems like drug classification are a good fit for bidirectional LSTMs (it is well known to extract contextual information from past and future data) **Improvement Techniques:** Hyper-parameter optimization with Bayesian Optimization techniques is a noteworthy approach which seeks to improve accuracy and decrease training-related losses. **Expansion of Drug Categories:** It is innovative to utilize the diverse dataset containing five distinct drug classes. It provides a broader and more realist training scenario for model training. **Achievements:** The suggested model to get a noteworthy 97% accuracy, which shows how reliable and successful the model is for drug classification task.

2. Related work

2.1. Drug target interactions

In the domains of polypharmacology, drug repositioning and discovery, as well as the prediction of drug resistance, the role of Drug-Target Interaction (DTI) has assumed paramount significance [22,34,7,21,24,31]. Within this context, three prominent biological computational approaches have garnered recognition: the ligand-based approach, the target-based approach, and the chemogenomic approach, all of which serve as vital tools for forecasting DTI.

To confront the intricacies encountered by traditional methods, chemogenomic approaches have emerged as a pivotal strategy in the domain of drug discovery and repositioning, particularly on a large scale. Within the realm of Drug-Target Interaction (DTI) analysis, there are four essential viewpoints to consider: the protein, the disease, the gene, and potential side effects. These innovative methods seek to amalgamate the chemical landscape of compounds with the genomic landscape of target proteins, thus forging a unified domain known as the pharmacological space. This approach capitalizes on the wealth of biological data at our disposal, making it highly conducive to predictive modeling.

Nonetheless, these methods confront significant challenges, including a dearth of well-documented drug-protein interactions and the scarcity of validated negative DTI samples. Furthermore, these approaches can be broadly categorized into three main classes:

machine learning-based, network-based, and graph-based methods. Notably, machine learning-based approaches have garnered the most attention due to their capacity for delivering robust and reliable predictive outcomes [40]. These methodologies hold great promise in advancing our understanding of drug-protein interactions and facilitating more effective drug discovery processes.

2.2. Ligand-based approaches

It proves ineffective when an insufficient number of ligands is available for analysis [16]. Similarly, target-based techniques encounter impediments, especially when attempting to acquire the intricate structures of target proteins. These challenges stemming from structural complexity can render such methods impractical. Furthermore, the scarcity of well-characterized drug targets, ligands, and a comprehensive understanding of drug-protein interactions pose substantial hurdles for the chemogenomic approach to drug discovery. Addressing these limitations necessitates innovative strategies and technologies in the continuous pursuit of new therapeutic breakthroughs.

The ligand-based approach hinges on the comparison of both new and established ligands, wherein the chemical structures of these ligands are scrutinized. This method, akin to Quantitative Structure-Activity Relationship (QSAR), operates on the premise that similar molecules are prone to binding with similar proteins. However, it's worth noting that the efficacy of this approach can significantly deteriorate when the pool of known ligands is inadequate [16]. This caveat underscores the necessity for innovative approaches to address the limitations associated with ligand-based DTI predictions.

The target-based approach necessitates access to the three-dimensional (3D) structures of proteins for simulation purposes. However, it faces inherent limitations when a significant portion of proteins lacks accessible 3D structural information. Additionally, this method is not suitable for the examination of intricate protein structures, particularly membrane proteins like ion channels and G-Protein Coupled Receptors (GPCRs). Furthermore, it is essential to acknowledge that the target-based approach can be time-consuming and may exhibit inefficiencies in certain cases [28]. These considerations underscore the need for alternative strategies that can surmount these challenges and broaden the scope of drug discovery and interaction prediction.

2.3. Pharmaco EEG

The bioelectrical dynamics within the brain exhibit distinct alterations corresponding to the specific actions of psychotropic drugs. These molecules effectively modulate the electrical behavior of neurons, leading to discernible and drug-specific electroencephalogram (EEG) responses [4]. The field of pharmaco-EEG assumes a pivotal role in advancing our understanding of compounds that impact the central nervous system, offering insights into drug resistance, and shedding light on potential side effects [10], [13]. One valuable facet of this research involves the examination of local field potential, which provides a window into the electrical activity within discrete regions of the brain. This technique involves the recording of signals using microelectrodes that penetrate directly into the brain tissue. By doing so, it becomes possible to capture and interpret the synaptic activity occurring within the local population of neurons situated near the electrode. Such insights contribute significantly to our comprehension of neural processes at a microscale level.

The investigation of drug actions and their impacts on the brain encompasses a multitude of well-established methodologies [11]. These methods enable the exploration of changes in EEG frequencies as they relate to the modulation of various neurotransmitter systems, such as dopaminergic, serotonergic, noradrenergic, cholinergic, or opioidergic pathways. It's worth noting that identical EEG patterns can manifest in response to different drugs, highlighting the complexity of these neural responses. Furthermore, numerous EEG characteristics are believed to be distinct and specific to particular chemical agents, endowing them with a unique signature [20,17,1].

2.4. Machine learning for drug discovery

In the pursuit of unraveling the mechanisms underpinning the impact of drugs on the brain, researchers have at their disposal a range of methodologies. Notably, the frequency of EEG signals undergoes discernible alterations in response to the modulation of serotonergic, noradrenergic, dopaminergic, cholinergic, or opioidergic neurotransmission. To harness the wealth of information embedded within EEG signals, machine learning techniques have proven invaluable [10], [18]. Further, the application of ML techniques in system biology is discussed in a systematic literature review [27].

Within the realm of neuroscience, machine learning techniques serve as invaluable tools for processing EEG recordings, and one such method is the Convolutional Neural Network (CNN). This deep learning approach plays a pivotal role in quantifying the magnitude of pharmacological effects on EEG data. By harnessing the capabilities of CNNs, researchers can effectively assess and interpret the intricate patterns of neural activity induced by various pharmacological agents.

One of the pivotal strategies in this domain is the Convolutional Neural Network (CNN) [18], which stands as a prominent tool for a wide spectrum of EEG classification tasks. While these techniques have conventionally found applications across various EEG-related endeavors, they have recently empowered researchers in quantifying the pharmacological effects of specific medications through the analysis of brain signals. Additionally, EEG signals have been harnessed to quantitatively assess the depth of anesthesia administered to patients, marking a noteworthy development in clinical applications [33]. These multifaceted applications underscore the versatility and potential of EEG-based methodologies in advancing our understanding of brain-drug interactions and enhancing patient care.

Recently, EEG researchers have extended their endeavors to employ brain signals for predicting the specific type of drug administered to subjects. This novel application tackles the challenging Drug-Target Interaction (DTI) problem, which has been addressed through both supervised and unsupervised learning mechanisms. Furthermore, these techniques are leveraged to scrutinize the potential therapeutic effects of drugs, thereby enabling the prediction of whether a given drug interacts with its intended target or not. This innovative approach holds promise for advancing our capacity to discern and harness the intricate relationships between drugs and their biological targets.

In the endeavor to classify time-series EEG signals, researchers have employed the synergistic power of Recurrent Neural Networks (RNN) in conjunction with Convolutional Neural Networks (CNN) [39]. Additionally, Long Short-Term Memory (LSTM) networks have been integrated with CNN to effectively segment ictal EEG signals using spectral information [39]. Over the past few decades, numerous research articles have advocated for the adoption of LSTM or Bidirectional LSTM for time-series classification, and these algorithms have demonstrated remarkable performance across specific domains such as ECG, EEG, and MRI analysis [39]. The robust classification capabilities of the LSTM model have enabled significant advancements in solving complex multiclass classification problems [26] [15].

Taking a systematic approach rooted in Bayes' Theorem, Bayesian Optimization has emerged as a method for guiding an efficient and seamless exploration of global optimization strategies. It's worth noting that, to the best of our knowledge, the utilization of deep neural networks in tandem with Bidirectional LSTM has not been employed for drug classification, marking a novel and promising avenue for exploration in this research context.

3. Methods

3.1. Data collection: materials and methods

3.1.1. Data sets

In our research, we were fortunate to have access to a rich dataset of local field potential (LFP) recordings, which was provided by Asst. Prof. Dr. Dania Cheaha from the Biology Program, Division of Biological Science at Prince of Songkla University. This dataset comprises LFP recordings obtained from seven Swiss albino mice (Male) that were exposed to a wide range of psychoactive drugs (the administration of saline, kratom (10 mg/kg), morphine (15 mg/kg), ephedrine (10 mg/kg), and fluoxetine (10 mg/kg) through intraperitoneal injection), in accordance with prior investigations as documented in references [29,25,3,5]. This valuable dataset serves as the foundation for our study and allows us to delve into the intricate effects of these drugs on neural activity.

3.1.2. Animal surgery for intracranial electrode implantation

The procedure for implanting intracranial electrodes has been previously detailed in reference [30]. In a nutshell, the animals underwent intramuscular anesthesia with a combination of 16 mg/kg xylazine followed by 50 mg/kg of Zoletil® 100 (Virbac, Thailand Co. Ltd.). Subsequently, the animals' heads were securely mounted within a stereotaxic frame. To ensure local anesthesia, lidocaine (Locana, L.B.S. Laboratory Ltd., Part., Thailand) was applied to the exposed head tissue. An incision was then skillfully made along the midline to expose the cranial surface. This methodical procedure was employed to facilitate the subsequent implantation of intracranial electrodes.

In accordance with the mouse brain atlas [26], intracranial electrodes were positioned on the left hemisphere of the brain, specifically from bregma to the nucleus accumbens (NAc) (AP; +1.3 mm, ML; 1.0 mm; DV; 4.2 mm) and the dorsal hippocampus (HP) (AP; -2.5 mm, ML; 2.0 mm; DV; 1.5 mm). Additionally, reference and ground electrodes were skillfully implanted along the midline, directly overlying the cerebellum (AP; -6.0 mm, ML; 0.0 mm; DV; 1.5 mm). To ensure secure placement, stainless steel anchor screws were introduced through additional drilled holes. Dental acrylic (Unifast Trad, GC Dental Industrial Corp., Tokyo, Japan) was employed to firmly affix all electrodes to the skull. As a precautionary measure against infection, intramuscular administration of the antibiotic ampicillin (General Drug House Co., Ltd., Thailand) at a dosage of 100 mg/kg was carried out twice daily with a 12-hour interval, over a span of three days. Subsequently, the animals were allowed a recovery period of 7 to 10 days following electrode implantation. The experimental configuration is depicted in Fig. 1.

3.1.3. Local field potential signal recording

Once the animals had fully recuperated from the surgical procedure, a period of three days was allocated for acclimatization. This involved exposing the animals to the recording chamber for three hours each day, facilitating their adjustment to the novel experimental environment. The recording chamber, constructed from black laminate material and measuring 35 centimeters in diameter, was employed for this purpose. On the designated testing day, drug administration took place, and the subsequent LFP signals were recorded for a duration of 180 minutes as part of the post-treatment assessment, see Fig. 1. This procedure was implemented to ensure that the animals' responses were accurately captured under experimental conditions.

The signals derived from the electrodes implanted in the animals were subject to a rigorous processing pipeline. Firstly, these signals were amplified and then subjected to filtering, incorporating a low-pass filter set at 1 kHz and a high-pass filter at 0.3 Hz. Subsequently, digitization occurred at a rate of 2 kHz, utilizing the PowerLab 16/35 system (AD Instruments, Castle Hill, NSW, Australia) equipped with a 16-bit analog-to-digital converter. The recorded data were efficiently stored in a PC system using the LabChart 7 pro software. To mitigate the impact of power line artifacts and enhance signal quality, a notch filter at 50 Hz was applied, effectively eliminating noise originating from power line interference. This comprehensive signal processing procedure ensured the reliability and accuracy of the recorded data for subsequent analysis.

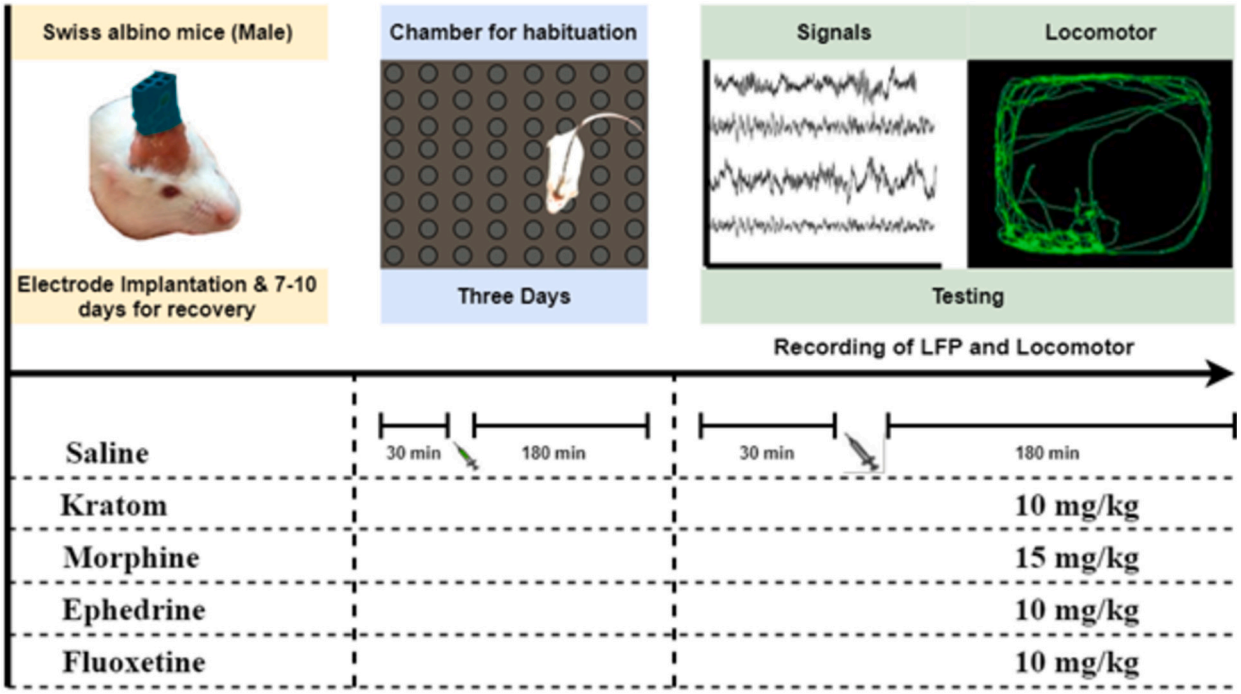

Fig. 1. Animal surgery for intracranial electrode implantation, Local Field Potential Signal Recording and Drug Administration.

3.2. Long-short-term memory neural network

3.2.1. Long-short-term memory neural network

Recurrent Neural Networks (RNNs) represent a specific category of feed-forward neural networks characterized by the presence of a recurring hidden element, which is activated at specific time steps and influenced by preceding states. This inherent architecture empowers RNNs to continuously capture contextual information and resolve dependencies of varying lengths within sequential data.

A notable advancement in the realm of RNN structures is the Long Short-Term Memory (LSTM) model, which has recently emerged as the gold standard for managing long-term dependencies within sequential data [38,36,12]. LSTM addresses the vanishing gradient problem that can impede traditional RNNs by introducing self-connected hidden layers of memory blocks. These memory blocks serve as specialized repositories for retaining and managing data in a purposeful manner, enabling the model to effectively detect and exploit long-range contextual information.

In essence, a single neuron within the LSTM framework comprises four key components, often referred to as gates in literature. Initially, the input gate regulates the incorporation of new information with the existing memory content. Furthermore, the forget gate plays a pivotal role in preserving a portion of the memory for subsequent sequences, while discarding the remainder of the data chunk [8,14]. This architecture equips LSTM networks with the capability to efficiently manage and process sequential data with extended temporal dependencies.

The third vital component in this architecture is referred to as the output gate, and its primary role is to regulate the release of information chunks. These individual neurons operate in parallel fashion, collectively contributing to the intricate process of retaining and discarding portions of information, thereby enabling the model to discern and learn classifiable patterns within time series datasets. This essential mechanism is graphically depicted and mathematically detailed in Fig. 2.

In the computational process, to calculate the current state represented as ht, both the input Xt and the previous state h_{t-1} are input into the LSTM cell unit. This collaborative operation underpins the LSTM's ability to effectively process and interpret sequential data with a focus on long-term dependencies, as illustrated Fig. 2 in the graphical and mathematical representations. Mathematically, the h_t can be calculated using following expression.

$$i_t = \sigma(W_x^i x_t + W_h^i h_{t-1} + b_i) \tag{1}$$

$$f_t = \sigma(W_x^f x_t + W_h^f h_{t-1} + b_f) \tag{2}$$

$$o_t = \sigma(W_x^o x_t + W_h^o h_{t-1} + b_o) \tag{3}$$

$$\tilde{c}_t = \tanh(W_x^c x_t + W_h^c h_{t-1} + b_c) \tag{4}$$

$$c_t = f_t \otimes c_{t-1} + i_t \otimes \tilde{c}_t \tag{5}$$

$$h_t = o_t \otimes \tanh(c_t) \tag{6}$$

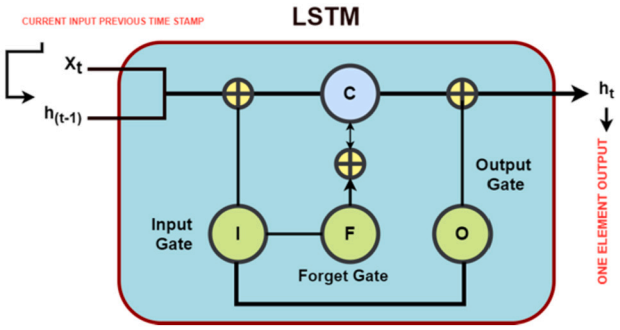

Fig. 2. Illustration of complete LSTM cell. Input gate and forget gate mutually decide which information to pass and filter for next computation.

Here i_t, f_t, o_t, and c_t in equation (1), (2), (3), (5) provide the values of i, f, o, and c at time step t. Moreover, the W, represent weights of hidden layer that are updated in back-propagation phase. Furthermore, the b_i in equations (1) through (4) represents the bias term and σ and tanh are sigmoid and hyperbolic-tangent activation functions which provide non-linearity to the model. It is also a common practice to set the values of gates within the range [0, 1]. In equations (5) and (6) the operator $\otimes$ is used to denote element-wise multiplication.

3.2.2. Bidirectional long-short-term memory neural network (bidirectional LSTM)

Leveraging the intrinsic capabilities of the deep neural network architecture, this research introduces an innovative drug classification method employing Bidirectional Long Short-Term Memory (BiLSTM), which has demonstrated exceptional performance in addressing multiclass classification challenges [15,35]. The comprehensive architecture of our proposed model is elucidated in Fig. 3.

Built upon time-series signal data, the model incorporates a single Bidirectional LSTM layer, strategically designed to capture and generalize long-term sequential patterns. This is achieved by integrating both a forward hidden layer and a backward hidden layer, a configuration illustrated in Fig. 3. The forward and backward passes across the unfolded network over time function much like conventional network forward and backward passes, albeit with the distinctive characteristic that BiLSTM extends these operations to encompass all time steps [40,38]. This innovative approach empowers our model to efficiently process temporal data and extract meaningful insights for drug classification tasks.

In the final module, as illustrated in Fig. 3, the architecture incorporates the LSTM network. Preceding this stage, the extracted features undergo a standardization process, after which they are input into the LSTM network. An intrinsic feature of the LSTM model is its capacity to learn and assess the significance of each feature during the final decision-making process. Consequently, there is no separate feature selection step preceding the classification phase.

To employ the capabilities of the Bidirectional LSTM model, we introduce a single layer of this specific model, featuring both forward and backward passes of sequence information. This Bidirectional LSTM layer, serving as a solitary bidirectional hidden layer, processes the sequence information bidirectionally, enhancing the model's ability to generalize effectively on time series data. This particular layer comprises 128 processing units, optimizing its capacity to process and interpret complex temporal patterns [41].

3.2.3. Bayesian optimization of bidirectional LSTM

Bayesian Optimization is a systematic strategy grounded in Bayes' Theorem, devised to streamline the exploration of global optimization endeavors. Its core methodology involves the creation of a surrogate function, essentially a probabilistic model representing the objective function. This surrogate function is subjected to an efficient search procedure utilizing an acquisition function, guiding the selection of candidate samples for evaluation against the actual objective function. In the context of this experiment, a total of three trials of Bayesian optimization were conducted to uncover the optimal parameters [9]. Each trial comprised three iterations.

Due to the inherently iterative and computationally intensive nature of the optimization process, a predefined range of hyperparameters was employed. These hyperparameters encompassed crucial aspects such as the learning rate, the number of neurons at each layer, the activation function, the number of layers, and the dropout rate, all essential in shaping the architecture for the intended application [32]. The objective function guiding this optimization process was categorical accuracy. The architecture learned through this rigorous optimization process is depicted in Fig. 4, encapsulating the culmination of these iterative endeavors.

Given the substantial time and computational resources demanded by the optimization process, a prudent approach was adopted, wherein a predetermined set of hyperparameters was employed [11,7]. The chosen hyperparameters remained consistent throughout the optimization process to expedite and stabilize the computations. Table 1 below illustrates the key parameters along with their respective predefined ranges, providing a clear overview of the parameter configuration employed in this optimization procedure.

3.3. Performance evaluation

3.3.1. Experiment setup

The experimentation was conducted on Intel Core i7 10th generation machines, each equipped with 24 GB of RAM and an NVIDIA GTX 1650Ti GPU. Notably, the proposed model's training phase demanded a substantial computational resource investment, requiring a total of 3 GPU days to complete a single training run. To enhance model accuracy, an initial batch size of 32 was utilized, yielding

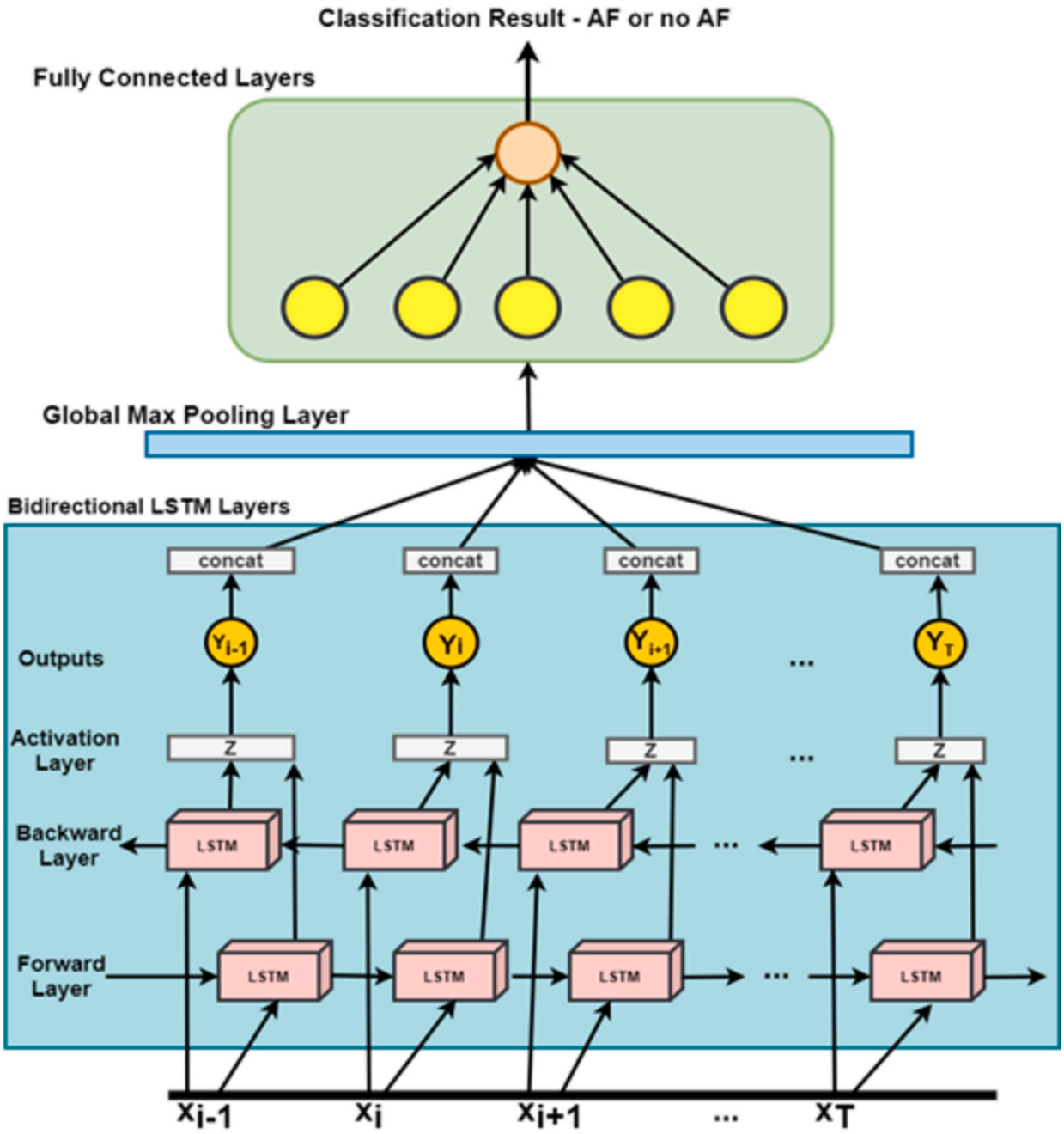

Fig. 3. A graphical illustration of Bidirectional LSTM model. The information is processed in both directions to improve the learning.

Table 1
Tunable hyperparameters for Bayesian optimization.

Sr#	Hyper-parameter	Range (Min – Max)
1	Number of neurons	[32 – 512]
2	Activation function	[Linear, ReLU, Sigmoid, Tanh]
3	Dropout Rate	[0.1 – 0.25]
4	Learning Rate	[0.00001 – 0.01]

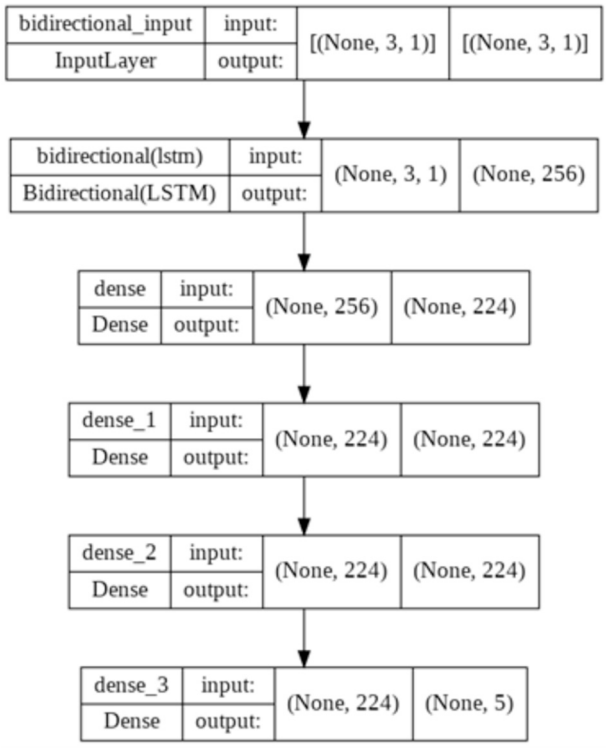

Fig. 4. Optimized architecture, learned by Bayesian Optimization. The first two layers are Bidirectional LSTM which are input layer and hidden layer with 3 neurons and 256 neurons, respectively. These are followed by 2 dense layers and the last layer is Softmax for probabilistic output.

a marked reduction in training time. Subsequently, to further optimize training efficiency and generalization capabilities, the batch size was increased to 256. Given the iterative nature of Bayesian optimization trials, the number of epochs was initially set at 5 and progressively refined with each subsequent run, allowing for a gradual improvement in performance. Additionally, to mitigate the risk of over-fitting, the number of iterations within each trial was incremented from one on-wards. The optimization yielded favorable outcomes in the first three trials, each consisting of three iterations [20]. These careful adjustments contributed to the model's enhanced performance and effectiveness.

3.3.2. Bidirectional LSTM architecture evaluation

Until now, the utilization of the Bidirectional LSTM model for drug classification via EEG signals has remained an uncharted territory within the literature. Moreover, there is no precedent in the literature concerning the application of Bidirectional LSTM in conjunction with Bayesian optimization [41]. Consequently, a series of preliminary internal architectural configurations were meticulously conducted to assess the performance of the drug dataset. As the complexity of the architecture progressively escalated, manual fine-tuning of the parameter set became infeasible [15,17].

To enhance the architectural performance, the architecture optimization process was pursued through a methodical and iterative approach, updating various parameters incrementally. In this research endeavor, the Bidirectional layers were initially configured with 32 memory units, gradually scaling up to 256 units. By employing diverse activation functions and integrating fully connected layers, the architecture's accuracy was substantially improved through the Bayesian optimization process. After evaluating various architectural configurations, Table 2 showcases the optimized architecture that notably achieved a categorical accuracy of up to 97.66%. This underscores the efficacy of the Bayesian optimization-driven approach in fine-tuning the architecture for outstanding performance.

4. Results

The proposed methodology was put to the test through a series of diverse experiments conducted on the dataset. These experiments encompassed various architectural configurations, including combinations of Convolutional Neural Networks (CNN) and Recurrent Neural Networks (RNN) tailored for time series datasets. It's important to note that several of these architectural variations did not yield satisfactory results. This outcome can be attributed to the considerable computational resources required and the complexity of the optimization process. To validate the performance of the obtained models, the two best-performing models were selected and subjected to further refinement with specific parameter settings. Both of these models exhibited impressive validation accuracies during the optimization trials, achieving 97.66% and 97.37% validation accuracies, respectively. However, the pinnacle of performance was reached with the model, that demonstrated exceptional results, boasting a validation accuracy of 98.18% and an associated loss

Table 2
Best evaluated architecture retrieved by Bayesian optimization.

Sr#	Layer (Type)	Output shape	Trainable Parameters
1	Bidirectional-LSTM	(None, 256)	133,120
2	Dense Layer 1	(None, 224)	575,668
3	Dense Layer 2	(None, 224)	50,400
4	Dense Layer 3	(None, 5)	1,125
	Total trainable parameters		292,613

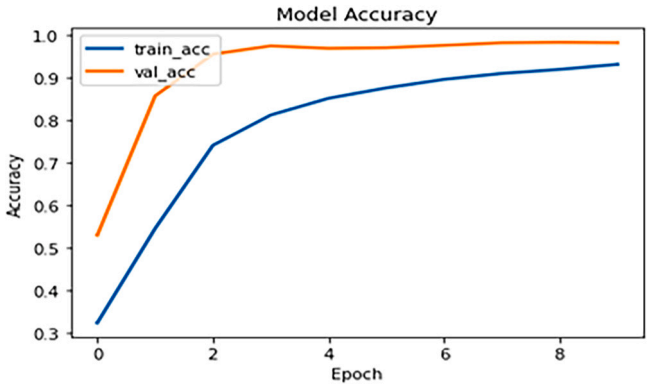

Fig. 5. The accuracy of model while training. Initially the accuracy starts improving from 0.3 and gradually improves up to 0.97 at the end of training. Validation accuracy also shows a gradual improvement.

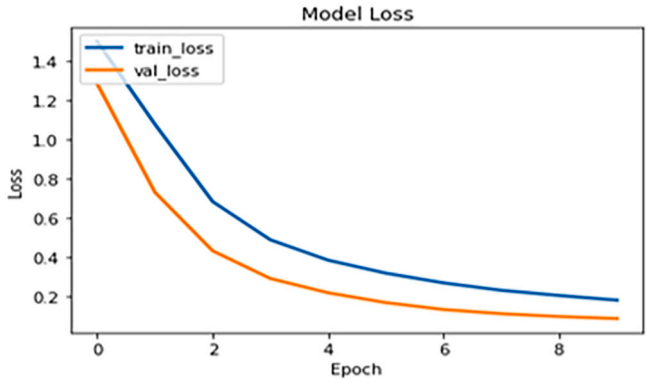

Fig. 6. The loss of model while training. Initially the loss starts improving from 1.5 and gradually decreases to 0.1 at the end of training. Validation loss curve also shows a gradual decrease to 0.09.

of just 0.23%. These findings underscore the efficacy and robustness of the proposed methodology in delivering outstanding results for the task at hand.

The obtained results are effectively visualized through straightforward accuracy and loss curves, which are separately presented for the training and validation datasets. Fig. 5 and Fig. 6, provide clear depictions of these curves. As the number of iterations increased, the model exhibited a discernible learning curve, ultimately achieving an impressive 98.18% validation accuracy and 93.50% training accuracy. The loss curve displayed in Fig. 6 further underscores this improvement, demonstrating a notable reduction in loss for both the training and validation datasets. These visualizations provide a tangible representation of the model's learning and performance enhancements over the course of the optimization process, reaffirming the significance of the results.

The loss curve is also thoughtfully presented for both the training and test datasets, providing insights into the model's performance. At the inception of the learning process, it was observed that both training and validation losses exceeded 100%. However, through the thorough tuning of hyperparameters, a substantial and gradual decrease in these losses was achieved.

Upon the conclusion of the training phase, the losses were substantially reduced to 15% for the training dataset and 9% for the test dataset. It's worth noting that, as discussed in the preceding section, attempts were made to further augment the model's performance by increasing the number of training epochs. However, these efforts did not yield the anticipated results; instead, the model exhibited

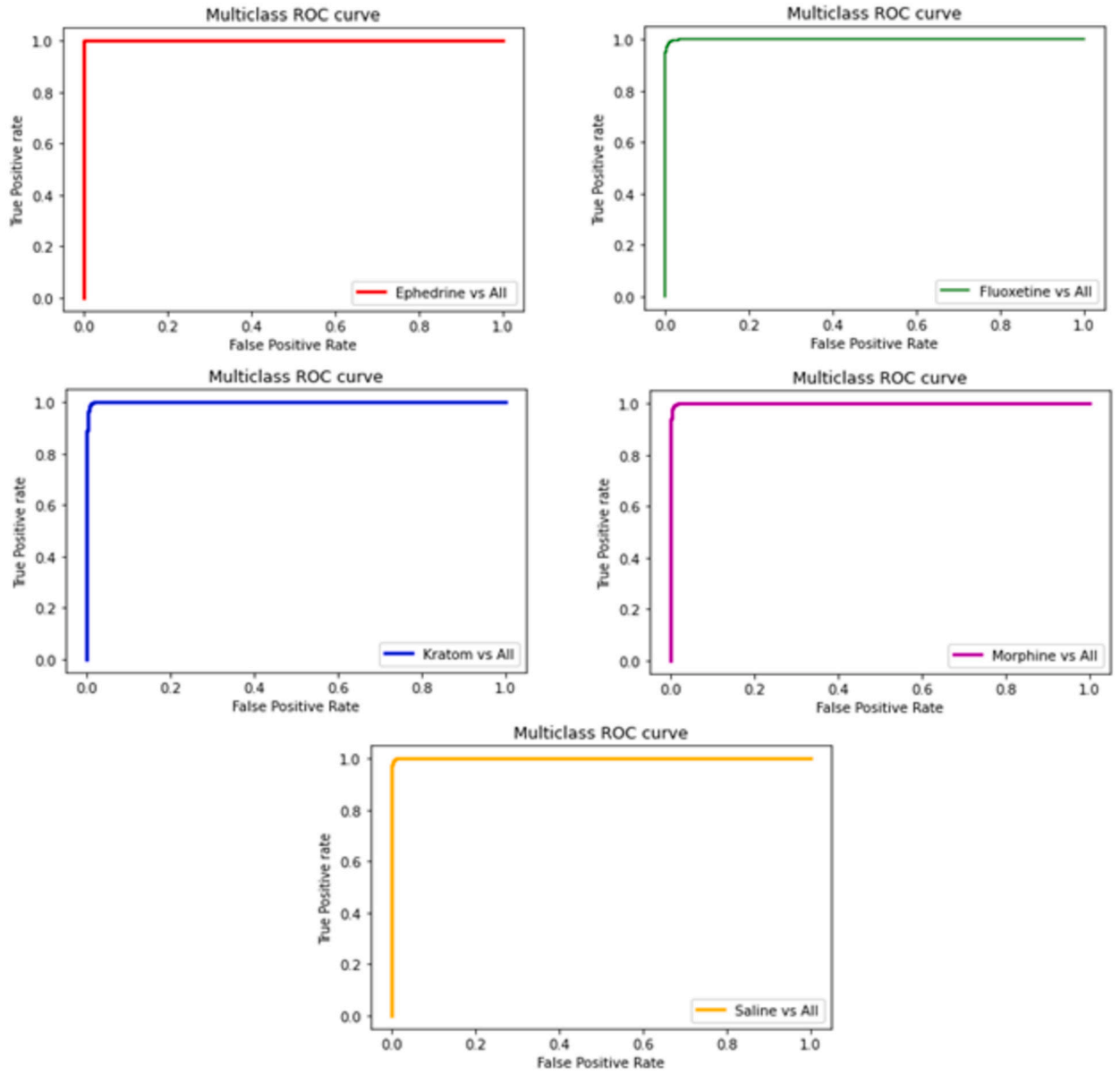

Fig. 7. Receiver Operating Characteristics (ROC) for multiclass classification. (a) The ROC curve for Ephedrine using one-vs-rest approach, (b) Fluoxetine ROC curve, (c) one-vs-rest ROC curve for Kratom, (d) ROC for Morphine drug, and (e) ROC curve for saline.

signs of over-fitting, exposing the generalization process. Consequently, the optimal outcomes were obtained within ten epochs, with a batch size of 256. This configuration proved to strike an effective balance between model complexity and generalization capacity.

To carefully validate the performance of our proposed classifier, an evaluation was carried out using Receiver Operating Characteristic (ROC) curves. These curves serve to illustrate the classifier's performance in terms of True Positives (TP), and False Positives (FP), for each individual class. Given the multi-class classification nature of the problem, we employed the one-vs-rest approach to depict the True Positive Rate (TPR) and False Positive Rate (FPR) for each drug class.

The ROC curves for each drug class are presented in Fig. 7. Notably, the dataset's temporal features substantially contribute to the classification performance, with the Ephedrine class achieving an exceptional accuracy of up to 99.97%, as evidenced in Fig. 7 (a). The model also exhibited a commendable classification performance of 97% for the Fluoxetine drug type, illustrated in Fig. 7 (b). Impressively, both the Kratom and Morphine classes demonstrated similar performances to Fluoxetine, each achieving 97% and 98%, respectively, as showcased in Fig. 7 (c) and (d). Furthermore, the model's performance for the Saline drug class exhibited an impressive 98% accuracy, as portrayed in Fig. 7 (e). These ROC curves collectively underscore the model's proficiency in accurately classifying various drug classes.

Table 3
Confusion Matrix with Actual and Called labels by instance counts.

Actual / Predicted	Class 1	Class 2	Class 3	Class 4	Class 5
Class 1	5978	0	0	0	0
Class 2	0	5984	2	0	0
Class 3	0	210	5630	0	142
Class 4	274	0	0	5786	0
Class 5	0	0	0	179	5815

Table 4
Precision, Recall, and F1-Score for each drug type.

Sr#	Drug Type	Precision	Recall	F1-Score
1	Ephedrine	0.96	1.00	0.98
2	Fluoxetine	0.97	1.00	0.98
3	Kratom	1.00	0.94	0.97
4	Morphine	0.97	0.95	0.96
5	Saline	0.98	0.97	0.97
	Accuracy			**0.97**
	Macro Avg.	**0.96**	**0.97**	**0.97**
	Weighted Avg.	**0.96**	**0.97**	**0.97**

The performance evaluation of the classifier includes a comprehensive analysis using a multiclass confusion matrix, as depicted in Table 3. This matrix provides a detailed breakdown of instances that were correctly classified as well as those that were misclassified for each respective class. The insights gained from the ROC curves for individual classes can be further validated through this confusion matrix.

For the Ephedrine class, the results are exemplary, with all instances correctly classified in accordance with their actual class labels. In the case of the Fluoxetine class, only two instances are misclassified, indicating that the trained model exhibited slight misclassification, mainly into the Kratom class. Furthermore, the Kratom drug type exhibits misclassification into two other classes, specifically Ephedrine and Saline, with 210 instances and 142 instances, respectively, for each of these classes. Similarly, the Saline drug class demonstrates a modest degree of miss-classification, involving 179 instances mistakenly classified as Morphine class. These insights provided by the confusion matrix offer a granular view of the model's performance and the areas where misclassification occurs.

In line with the provided evaluation metrics, various classification evaluation scores have been computed and are presented comprehensively in Table 4. The table includes precision, recall, and F1 score for each drug type. Notably, both Ephedrine and Fluoxetine achieved an impressive F1 score of 0.98, underscoring the exceptional performance of the model in these classes.

Furthermore, the overall accuracy of the model, as indicated in Table 4, stands at 0.97, reflecting the model's significant overall performance. These comprehensive evaluation scores provide a holistic assessment of the classifier's capabilities and underscore its efficacy in accurately classifying various drug types.

5. Discussion

To determine local DTIs using neighbor interaction profiles, a bipartite based local model is employed [23]. The purpose of the neighborhood regularized logistic matrix factorization approach is to identify DTI [19]. Gaussian interaction profiles and weighted closest neighbor profiles are combinned [37]. It is developed a framework for embedding heterogeneous networks [2].

This research endeavor was centered on the development of a classification-oriented Bidirectional Long Short-Term Memory (LSTM) model. In addition to this architectural improvement, we have exploited the power of Bayesian Optimization techniques to precisely fine-tune hyperparameters, thereby augmenting both accuracy and the reduction of training-related losses. Remarkably, our efforts have resulted in a notable achievement of 97% accuracy for our proposed model.

Furthermore, we have strengthened our study with the utilization of dataset, providing empirical validation for the robustness and efficacy of our proposed model. A significant distinction of our research lies in its comprehensive approach to drug classification. While prior literature mainly relied on a limited set of drug types for model training, we have expanded the scope by incorporating five distinct drug categories. This expansion has revealed the enhanced performance of our model, achieved through the strategic application of Bayesian Optimization techniques for fine-tuning hyperparameters.

5.1. Comparison with existing methods

Using a wide variety of five drugs (Ephedrine, Fluoxetine, Kratom, Morphine, and Saline), the current study offers a thorough assessment of the model's effectiveness across various drug types. This method improves the findings' robustness and generalizability. The existing studies referenced, on the other hand, concentrate on a smaller number of medications. Current study wider drug scope makes it possible to understand the model's performance across a variety of drug type more deeply.

Mumtaz et al. [24] achieved an accuracy of 87.5% in their classification of MDD (Major Depressive Disorder) patients treated with selective serotonin reuptake inhibitors (SSRIs) using logistic regression. Our proposed method, however, performs better than theirs, most likely because the bidirectional LSTM is better at capturing temporal relationships in EEG signals than logistic regression does. Moreover, our model performs better with hyperparameters optimized by Bayesian technique, obtaining a 97% accuracy rate.

By utilizing transformers on EEG data, the authors [31] were able to diagnose MDD patients with 97.14% accuracy and predict treatment response. Their model performed better than more conventional techniques like CNNs and LSTMs because transformers could capture temporal dependencies. In contrast, our work also achieved 97% accuracy utilizing bidirectional LSTM with Bayesian optimization. Saeedi's approach makes use of transformers, whereas ours benefits from LSTM's sequential learning and Bayesian hyperparameter tuning. In spite of this, both models perform similarly.

5.2. Limitations and future work

In this study, we have undertaken an optimization process focused on four specific parameters, while keeping the remaining hyperparameters constant. Our aim was to enhance the overall performance of our model.

As part of future work, we intend to expand our research by obtaining a larger dataset and increasing the number of drugs to be classified. Data from multiple sources to be incorporated in order to validate the models efficiency. This expansion has the potential to lead to further improvements in the proposed model's efficacy.

A rigorous comparative analysis will be conducted with existing models to clarify the strengths and weaknesses of our approach. To improve predictive power, additional types of biomedical data, e.g., MRI or CT scans will be included. A longitudinal study design will be implemented to track disease progression. By incorporating hyperparameter tuning and LSTM configurations, we will refine model technical aspects. Through joint efforts with neurologists and pharmacologists, we will investigate the usefulness of implementing our model in clinical settings. Through these efforts, we hope to improve the research's practical applicability and advance the development of more potent neurodegenerative disease treatment plans.

Additionally, we acknowledge that the Bayesian Optimization process exhibited slow convergence in our study. To address this issue and enhance the time complexity of our proposed model, we intend to explore the utilization of meta-heuristics in multi-objective optimization, a promising avenue for optimization. This approach holds the potential to expedite the convergence process and improve the overall efficiency of our model.

CRediT authorship contribution statement

Shahnawaz Qureshi: Methodology, Formal analysis, Conceptualization. **Syed Muhammad Zeeshan Iqbal:** Writing – original draft, Validation, Project administration, Investigation. **Asif Ameer:** Visualization, Validation, Software, Investigation, Data curation. **Seppo Karrila:** Writing – review & editing, Validation, Supervision. **Yazeed Yasin Ghadi:** Writing – review & editing, Supervision, Resources. **Syed Aziz Shah:** Writing – review & editing, Validation, Supervision.

Statements of ethical approval

The study followed the ethical principles (2004 of the International Committee on Laboratory Animal Science (ICLAS) and the European Science Foundation (ESF) (Use of Animals in Research, 2001). The Animal Ethical Committee of Prince of Songkla University's (MOE 0521.11/613) authorized and directed the experimental design.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT by OpenAI in order to improve language, refine content, provide suggestions, and enhance clarity. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Declaration of competing 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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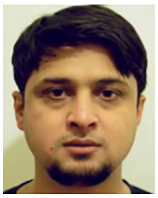

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