Multi-model transfer learning and Genotypic Analysis for Seizure Type Classification

Yue Yang[1], Kairui Guo[1], Zhen Fang[1], Hua Lin[2], Mark Grosser[2], and Jie Lu[1]

[1] Faculty of Engineering and IT University of Technology Sydney, Sydney, NSW, Australia
yue.yang-4@student.uts.edu.au (Kairui.guo, zhen.fang, Jie.Lu)@uts.edu.au
[2] 23Strands, Suite 107, 26-32 Pirrama Rd, Pyrmont NSW 2009 Sydney, Australia
(hua.lin, mark.grosser)@23strands.com

Abstract. The recent progress in phenotypic information and machine learning has led to a remarkable development in the accuracy of binary seizure detection. Yet the performance of classifying specific seizure types remains suboptimal due to the limited availability of annotated data with accurate seizure type labels. Transfer learning is promising to mitigate data scarcity to improve classification accuracy on smaller datasets. However, finding the best transferable model based on the specific training and testing dataset can be a complex and repetitive process, and a single-modelled approach may not fully capture the best feature representation of the input data. Moreover, genotypic data is often neglected in previous AI-based seizure detection studies, where analyses like Polygenic Risk Scores (PRS) could offer insights into genetic predispositions to seizures. To mitigate these challenges, we propose a seizure-type classification framework incorporating a multi-model weighting system designed to assign weights to different models, thus reducing computational complexity and processing time. In addition, we carry out a PRS analysis, aiming to bridge the gap between genotypic and phenotypic data, further enhancing the comprehensiveness and precision of seizure detection. Our model outperformed similar classifiers by more than 13 - 16% on the Temple University Hospital EEG Seizure Corpus dataset. This study represents a pioneering examination of the multi-source transfer learning framework in the field of type-specific seizure classification.

Keywords: Genomic · Transfer learning · Machine learning · Seizure genetic

1 Introduction

Seizure, a manifestation of abnormal brain activity, is one condition that demands immediate detection for effective management. Electroencephalogram (EEG), a form of phenotypic data, is commonly employed for this purpose.Since the 1970s, artificial intelligence (AI) has substantially explored the connection between biomedical traits and phenotypes, notably exemplified by the development of automated seizure detection (ASD). Despite the recent progress in

the detection accuracy of standard ASD, difficulties such as detecting the specific seizure type due to the limitation of data availability and the labelling issue remain to be solved [10]. To mitigate this, a variety of strategies such as Deep Learning and Riemann geometry have been introduced for the phenotypic study of seizure traits [16]. However, conventional methodologies presume that the training and testing datasets are derived from a uniform distribution, which might not hold true in real-world conditions. Furthermore, due to limitations in data collection and labelling processes like time, ethical considerations, and cost constraints, acquiring source data or target labels sufficient for deep learning algorithms often poses a challenge in seizure trait studies, leading to potential issues of overfitting and sampling bias.

To mitigate this problem, transfer learning can be a suitable solution. It involves leveraging knowledge and models obtained from a source domain to improve performance in a related but distinct target domain [8]. Several transfer learning methods, such as semi-supervised [5] and model-based transfer learning [9], have been investigated in phenotypic seizure classification to mitigate the data scarcity problem. However, in single-model-based seizure classification, due to the necessity of processing such massive labelled data, the computing complexity and time of finding the best transferable model may be tremendously high, and the process can be highly repetitive. Thus, using a multi-model network allows the system to capture multiple aspects of the input data and make more informed predictions. Therefore, researchers have focused on a practical problem known as multi-source domain adaptation [4]. This study explores the possibility of transferring knowledge from multiple source domains to a target domain. Based on this idea, we propose a framework wherein multiple pre-trained source models can be transferred and accessed simultaneously.

Moreover, the historical focus of AI research in seizures has predominantly utilized phenotypic data, with genotypic information often overlooked. This constraint can be attributed to the inherent complexity and interpretive challenges posed by genomic data. Yet, the recent advancements in genomic analysis tools have enabled a more profound exploration into the genetic aspects of seizures. One such genomic tool is the Polygenic Risk Score (PRS), which aggregates the effects of genetic variants to estimate an individual's genetic susceptibility to a particular trait or condition [2]. While phenotypic data like EEG recordings capture the manifestations of seizures, the integration of genotypic data and tools, such as PRS offers a genetically informed probability that may predispose an individual to these conditions. Consequently, integrating genotypic data and PRS into AI research on seizures could significantly augment predictive accuracy and enable the development of more personalized treatment strategies. As such, our study aims to fill this gap by proposing a novel framework that integrates AI models with PRS for enriched and more precise seizure detection,

In light of this, the present paper introduces a novel multi-model framework that employs ten pre-trained transferable models. Our approach aims to capture and integrate transferable knowledge from multiple sources, thereby enhancing the prediction accuracy in the target domain. To complement phenotypic data

with genotypic information, we incorporate a PRS analysis, designed to bridge the genotype-phenotype divide in seizure detection. To validate the performance of the proposed algorithm, we conduct extensive experiments on the largest publicly available dataset on seizure EEG, the Temple University Hospital EEG Corpus [12]. By combining AI and polygenic analysis, our study strives to push the boundaries of current seizure detection methods, offering a more integrated and precise approach to diagnosing this complex neurological condition.

The contributions of this paper are summarized as follows:

- A multi-model-based transfer learning approach was applied to capture transferable information to enhance the performance of the seizure classification performance. To our best knowledge, this study represents a pioneering examination of the multi-source domain adaptation in the field of type-specific seizure classification.
- A novel self-attention (SA) mechanism was designed to assign weight to each model, picking up the key information extracted from different models. The classifier developed using the combination of pre-trained networks outperformed other machine-learning-based classifiers.
- As an innovative approach to enriching phenotypic data with genotypic information, we incorporated PRS analysis into seizure detection, bridging the genotype-phenotype divide.

This manuscript is organized as follows. Section II reviewed the related work in automated seizure classification, transfer learning, and SA mechanism. Section III explained the feature extraction, multi-model system, and PRS methods. Next, section IV discribed the dataset, baseline model, and the results of our classifiers. The clinical applications and significance were also discussed in section V. Lastly, a conclusion of this work was drawn in section VI.

2 Related Work

The following areas need to be studied to establish the multi-model seizure classification system: automated seizure classification, transfer learning of convolutional neural networks, and SA mechanism.

2.1 Automated Seizure Classification

Generalized seizures include absence, myoclonic, tonic, clonic, tonic-clonic, and atonic. In clinical practice, trained individuals evaluate phenotypic and clinical information to identify seizure types. With the development of AI, the application of ASD in medical fields has had significant success. The majority of ASD applications focus on tonic-clonic seizures, and the classifiers' outputs are either binary (normal, ictal), or three-class (normal, interictal, ictal stages) [1]. Despite reaching 95% - 100% accuracy in these scenarios, several issues still need to be solved before clinical deployment. First, a specific type is needed after detecting seizures' start and end times. Knowing the seizure type is the first step

of personalized healthcare [10]. Second, the complexity, redundancy and significance of the phenotypic features need to be considered, especially in real-world applications. More importantly, the limited publicly available datasets with a relatively small number of participants pose the issue of poor performance for deep learning algorithms. Each step of the automated seizure type classification must be carefully designed to overcome these issues.

2.2 Transfer Learning of Convolutional Neural Network

Recently, Convolutional Neural Networks (CNN) have demonstrated remarkable outcomes in seizure classification. Several studies have applied transfer learning on CNN to mitigate the distribution difference between the source and target domains of the seizure phenotypic data [7]. Yang et al. [17] applied large-margin projection combined with Maximum Mean Discrepancy to identify essential knowledge between the source and target domains, resulting in better performance in seizure detection using EEG signals as the phenotypic data. Furthermore, Jiang et al. [5]adapted domain adaptation with the Takagi-Sugeno-Kang fuzzy system as the base classifier. The result showed higher classification accuracy. From the model-based transfer learning perspective, Raghu et al. [9] transferred 10 pre-trained CNN models separately with fine-tuning, among which GoogleNet yielded the highest classification accuracy of 82.85%. However, for such single-model-based studies, finding the best model can be highly complex and time-consuming. Using a multi-model network allows the system to capture multiple aspects of the input data and make more informed predictions. As this paper presents the first study using deep learning for the classification of multi-class seizure type, our framework was compared with this approach in the result section.

2.3 Self-attention Mechanism

The concept of SA was initially introduced in the research by [15] and applied in machine translation. It aimed to capture global input dependencies. In recent years, it has been applied to the field of seizure classification. Tao et al. [14] used SA to model long-range dependencies in the phenotypic information and to weigh the importance of each feature for classification, achieving improved performance compared to traditional CNNs. Choi et al. [3] combined SA with a bidirectional gated recurrent unit network for seizure classification. The authors found that the SA mechanism improved the ability of the model to identify important features in the input signals, leading to improved classification performance. These studies proved that the SA mechanism has the potential to capture the complex and dynamic patterns of EEG as the phenotypic data in deep learning models. Inspired by this, we applied the SA mechanism to look for critical information in multi-model transfer learning.

3 Proposed Methodology

In this section, we introduce the methodology employed in this study, which involves pre-processing and feature extraction of the phenotypic data, the implementation of a multi-model weighting system and the calculation of the PRS.

3.1 Phenotypic analysis: Pre-processing and Connectivity Analysis

Due to its exceptional ability to capture real-time brain activity, EEG signal is selected as the phenotypic data utilized for seizure-type classification in our proposed framework. The raw data from the Temple University Hospital EEG Seizure Corpus underwent a sequence of pre-processing stages, including band-pass filtering and segmentation of seizure and non-seizure events. We also reduced the number of channels to optimize the performance of our deep learning systems, employing both four (T3, F7), (C3, Cz), (O2, P4), (Fp2, F8) and eight-channel strategies (T3, T5), (F8, T4), (T4, T6), (P3, O1), following the findings by Shah [11]. As a key part of the data transformation, we implemented effective connectivity to generate image-based features for the classifiers. For this, we used Multivariate Auto-Regressive models and linear Kalman filtering method. The pre-processed recordings were treated as univariate time series, with consecutive measurements modeled as a weighted linear sum of their previous values. This approach was extended to multivariate time series in the Multivariate Auto-Regressive models. The model order, p, was determined using the Bayesian-Schwartz's criterion:

$$SC(p) = ln[det(V)] + \frac{ln(N) * p * n^2}{N} \tag{1}$$

where V is the noise covariance matrix, and N is the total number of the data. n indicates the number of channels. The normalized Directed Transfer Function (DTF) represents the ratio between the inflow from the source channel to the destination channel to the sum of all inflows to this channel. The value of the normalized DTF is from 0 to 1, where 0 means no influence and 1 means the maximum influence. The calculation is shown as follows:

$$\gamma_{ij}^2(\lambda) = \frac{(|H_{ij}^2(\lambda)|^2)}{\sum_{m=1}^{n}(|H_{im}^2(\lambda)|^2)} \tag{2}$$

where i is the destination channel and j is the source channel that is used to calculate the influences compared with the total influence from all channels for both direct and indirect flows. To distinguish between the direct and indirect transmissions, Partial Directed Coherence (PDC) is utilized to show the direct relations only in the frequency domain. It is defined as:

$$\pi_{ij}^2(\lambda) = \frac{(|A_{ij}^2(\lambda)|^2)}{\sum_{m=1}^{n}(|A_{im}^2(\lambda)|^2)} \tag{3}$$

This function describes the ratio between outflows from channel j to channel i to all the outflows from channel j. In this project, PDC and DTF were computed with the idea of a short-term 1-second window and 25% overlap to address the immediate direct dynamic frequency domain link between the various time series and expose the links from one time series to another regardless of the influence pathway.

3.2 Multi-model Weighting System

A multi-model weighting system is designed to investigate the contribution of the extracted feature from each model. We introduce it at the end of the output layer of the pre-trained models. It takes the model's feature embeddings em as input and outputs the weights W of all models based on the contribution of the extracted information. We utilize several paralleled SA mechanisms to capture the relationships between these embeddings from multiple aspects. A multi-attention mechanism is used to concatenate the multi- attention's weight. As the calculated weight ω now has the same dimension as em, a fully connected fc layer is introduced at the end to obtain the vector output W, which has 1 single value representing the weight of each model. The structure of the system is shown in Fig.1.

The SA mechanism is used in deep learning models that compute a set of attention scores to weigh the importance of different elements when making predictions [15]. Note that unlike the original SA algorithm proposed in [15], the Value Weight is not used in this paper as the main purpose of this system is not to update the original embedding vector, but instead computes and outputs the models' weights. The Query (Q) represents the current model that is being weighted and the Key (K) is the other model (including Q) that is being weighted against. Because multiple paralleled SA mechanisms are used, we introduce a multi-head attention algorithm, shown in Fig. 1 to concatenate the paralleled outputs into 1 linear vector W, which is the final output of the multi-model weighting system. Based on the previous experience from [15], the experiment set $h = 2$.

The dot product of Q and K is then calculated by Eq.(4).

$$S_{qk} = Q * K^T \tag{4}$$

where S_{qk} represents the similarity vector of the current model Q against model K.

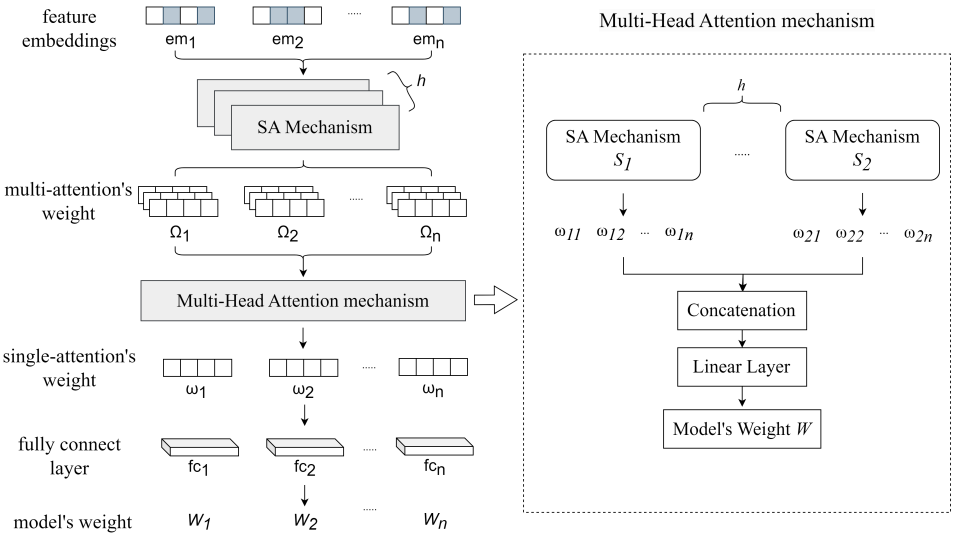

Fig. 1. The multi-model weighting system consists of multiple paralleled SA mechanisms, which compute the multi-attention weight and a multi-head mechanism that outputs the single-attention weight. The structure of the multi-head attention mechanism concatenates the paralleled outputs into one linear vector W is shown on the right. In this study, h was set as 2

The obtained score S is then normalized using SoftMax function:

$$\sigma(S_i) = \frac{e^{S_i}}{\sum_{j=1}^{n} e^{S_j}} \tag{5}$$

where $\sigma(S_i)$ represents the normalized score of the i_{th} model, n is the length of the feature embedding of Q_i. The final output of the SA mechanism ω is then computed by scaling $\sigma(S_i)$ as shown below:

$$\omega(S_i) = \frac{\sigma(S_i)}{\sqrt{d_k}} \tag{6}$$

where d_k is the dimension of the vector K. The final output ω is scaled by the square root of d_k to prevent the attention scores from becoming too large and overwhelming the other components of the model.

3.3 Genotypic Analysis: PRS Calulation

Our seizure-type classification framework integrates genotypic data through a PRS analysis. In this study, we focused on 29 Single Nucleotide Polymorphisms (SNPs) derived from the NHGRI-EBI GWAS Catalog [13]. Linkage disequilibrium metrics (0.4, 0.6, 0.8) and significance thresholds ($Pvalue$ = 0.5, 0.05,

5×10^{-4}) were employed to further refine this selection. The chosen SNPs were independently significant, presenting low collinearity (< 0.05) and maintaining a distance of more than 2000 kilobases apart. We estimated the squared correlation coefficient (r^2) among these SNPs, utilizing genotype data from the summary statistics to understand their genetic relationship and potential impact on seizure predispositions. These analyses were executed using the PLINK software package, version 1.9. Before proceeding to PRS analysis, we first conducted rigorous quality control checks on the genotype data. We checked for missing data and excluded SNPs with a high missingness rate. Additionally, we tested for deviations from Hardy-Weinberg equilibrium to identify and exclude potentially erroneous genotype calls. Subsequently, we constructed weighted PRS for each participant according to Eq.7, calculated as the weighted sum of risk alleles, each multiplied by its corresponding trait-specific weight. The PRS was normalized to a mean of 0 and a standard deviation of 1, enabling reporting of odds ratios per standard deviation increase in PRS.

$$PRS(k) = \sum_{j}^{N} \beta_j * dosage_{jk} \tag{7}$$

where k represents an individual sample, N is the total number of SNPs, β_j is the effect size of variant j and $dosage_{jk}$ indicates the number of copies of SNP j in the genotype of individual k.

4 Experiments

In this section, we introduce the phenotypic and genotypic data used in this study and list the parameter, baseline models and seizure classification results.

4.1 Phenotypic and Genotypic Dataset

The Temple University Hospital EEG Seizure Corpus version 2.0.0 [12] was used as the phenotypic data in this study. It contains EEG data with sampling frequency of 250 Hz, and the standard 10-20 system was used as the sensor placement guideline. Two annotation files were created for each data file to demonstrate the seizure types, channel indices, and the start/end time of seizure events. The seizure types are determined by certified professionals with both phenotypic and clinical information for absence, complex partial, simple partial, tonic-clonic, and tonic seizures, phenotype only for focal non-specific and generalized non-specific seizures. Due to the limited number of phenotypic information for atonic and myoclonic seizures, these two types are excluded from this work. It is worth noting that the clinical information is not provided in the public dataset. The issue of unmatched resources between the neurophysiologists who labelled the seizure events and the proposed framework is further addressed in the classifier design and the clinical significance of this framework.

The genotypic data used in this study was obtained from the Medical Genome Reference Bank [6]. It is a high-quality genomic database comprising sequence data from 4,011 healthy older individuals. This data, stored in the Variant Call Format, provides an industry-standard notation for storing gene sequence variations. Variant Call Format files are an efficient and compact way of storing and sharing genomic data, accommodating from SNPs to large structural variants, along with rich annotations. Additionally, the seizure summary statistics, which provides the association strengths and significances of different genetic variants to seizure incidents, was downloaded from the NHGRI-EBI GWAS Catalog [13].

4.2 Parameter Setup and Baseline Methods

Two classifiers were developed to verify the seizure type classification framework: the three-class (FN, GN and normal) and the six-class (AB, CP, SP, TC, TN and normal). The experiment was conducted using a LR decay with a staring LR of $1e-2$, the batch size was set to 32 and the epoch was set as 50. Based on the result from [9], we selected GooogleNet as the baseline model when running the single-model task. To compare the performance of the phenotypic features, short-time Fourier transform (STFT) [18] was used as the baseline as it is a common imaged-based feature in CNN-related EEG applications.

4.3 Seizure Classification Results

Table 1. three-class seizure type classification results using the single-model and multi-model system, key values are highlighted in bold for emphasis.

Seizure Type	Features	Precision		Recall		F1-score	
		Single model	Multi-model	Single model	Multi-model	Single model	Multi-model
FN	STFT	**0.6906**	0.7810	0.8298	0.8120	0.7562	0.7979
	8-Ch connectivity	0.7969	0.7803	0.8266	0.9510	0.8730	0.8435
	4-Ch connectivity	0.9293	**0.9862**	0.9730	0.9235	0.9177	**0.9561**
GN	STFT	**0.7827**	0.7931	0.6293	0.789	0.6922	0.7888
	8-Ch connectivity	0.8215	0.8893	0.7817	0.7563	0.7961	0.8149
	4-Ch connectivity	0.9385	**0.9282**	0.9293	0.9768	0.9288	**0.9567**
Normal	STFT	**1**	**1**	**1**	**1**	**1**	**1**
	8-Ch connectivity	**1**	**1**	**1**	**1**	**1**	**1**
	4-Ch connectivity	0.9797	0.9802	1	1	0.9843	0.9977

The results indicate that eight out of nine F1-Score pairs showed improved or maintained performance in three-class seizure classification using our multi-model system. It improved FN and GN seizure F1-scores by 3.84% and 2.79% respectively, using 4-channel features. Similarly, 15 out of 18 F1-scores were sustained or boosted in six seizure-type tasks. The optimal feature shown in this experiment is the four-channel connectivity images, presenting 98.62% and 92.82% precision with 0.956 F1-score in Table 1 for both focal and generalized seizures, demonstrating a balanced precision and sensitivity of the classifier. The

STFT's performance for tonic seizures in the six-type classifier shows imbalances due to fewer participant numbers, resulting in low sensitivity. Meanwhile, the multi-model approach with four-channel connectivity achieves 100% precision, recall, and F1-score, demonstrating stability even with smaller sample classes. Our method surpasses a similar classifier [9] where tonic seizures had the lowest accuracy. The multi-model approach enhances the F1 score substantially for both STFT and connectivity features. Using ten weighted pre-trained networks, we see an approximately 50% recall increase for STFT, 15% precision rise with eight channels, and around 45% F1-score improvement with four channels. This illustrates that our system effectively uses model-extracted key information, boosting detection performance and robustness.

Table 2. six-class seizure type classification results using the single-model and multi-model system, the key improvements and values are highlighted in bold for emphasis.

Seizure Type	Features	Precision		Recall		F1-score	
		Single model	Multi-model	Single model	Multi-model	Single model	Multi-model
AB	STFT	1	1	0.9910	0.9060	0.9582	0.9544
	8-Ch connectivity	0.8700	0.9139	1	1	0.9305	0.9584
	4-Ch connectivity	0.9514	1	1	1	0.9841	1
CP	STFT	0.8117	0.9720	0.9724	0.9474	0.8889	0.9681
	8-Ch connectivity	1	0.9340	0.9564	0.9581	0.9794	0.9307
	4-Ch connectivity	1	1	1	1	1	1
SP	STFT	1	0.7727	0.965	1	0.9596	0.8721
	8-Ch connectivity	0.9591	0.9518	0.9584	0.9583	0.9574	0.9595
	4-Ch connectivity	0.9538	1	0.9564	0.9594	0.9566	0.9790
TC	STFT	0.7543	0.8341	0.5810	0.8396	0.6160	0.8377
	8-Ch connectivity	1	1	0.9283	0.8394	0.9620	0.9104
	4-Ch connectivity	1	0.9234	0.9235	1	0.96270	0.9644
TN	STFT	1	1	**0.2568**	**0.7541**	**0.4110**	**0.8603**
	8-Ch connectivity	0.7158	0.8644	0.6283	0.7551	0.6720	0.8620
	4-Ch connectivity	0.8800	**1**	0.8804	**1**	0.8819	**1**

The three-class classifier using four-channel connectivity and ten pre-trained networks achieved the best performance with an average accuracy of 96.33%. With only four channels (eight electrodes), this classifier could be used in emergencies for efficient patient triage. Using the same configuration, the six-class classifier delivered 99.00% average accuracy, surpassing the highest accuracy from a similar work by over 13-16% [9].

5 Discussion

This result confirms that multi-model transfer learning is an excellent solution to the small dataset challenge often faced in clinical applications. Both classifiers exhibited exceptional precision and recall using the transfer learning approach, showing that transferring knowledge from large datasets to epileptic seizures can achieve excellence in detection tasks in clinical settings. Moreover, In the phenotypic dataset, seizure types were labelled using both EEG and clinical data, yet

our framework solely relied on phenotypic data. Despite a relatively small participant count, this finding suggests that with appropriate processing techniques and deep learning, an accurate differentiation of epileptic seizure types is possible with phenotypic data only. This could be particularly useful in situations where clinical data isn't readily available, such as telehealth in remote areas or rescue missions in challenging conditions. To capitalize on our classifier system in diagnosing various seizure types, we further expanded our research to target stroke epilepsy, a subtype posing complex diagnostic challenges. Stroke-induced seizures have complex mechanisms, making stroke epilepsy difficult to distinguish from other seizure types clinically, thereby complicating patient management. This underpins the necessity for better diagnostic tools to assist clinicians in accurately diagnosing stroke epilepsy. While age is a known risk factor for stroke and subsequent seizures, genetic factors introduce considerable risk variation among individuals of the same age group. Hence, a more comprehensive approach considering genetic predisposition is vital. To address this challenge, we conducted a PRS analysis, identifying 371 individuals presenting a heightened genetic risk for seizures. This approach of using genetic risk profiling serves as a proactive screening method for individuals at elevated risk for stroke epilepsy. When integrated with our high-performing machine learning model as a diagnostic tool, we provide a comprehensive solution promising enhanced diagnostic accuracy and improved patient outcomes, particularly for older individuals at risk of stroke-induced seizures. Given the precision of this approach, it has significant potential to aid in clinical decision-making and early intervention strategies.

6 Conclusion and Future Work

This study explores the potential of enhancing seizure classification by integrating multi-model transfer learning and genotypic data analysis. Our unique approach amalgamates multiple sources of transferable knowledge, effectively bridging the genotype-phenotype divide in seizure detection. Using four-channel EEG features with a ten-network model, we achieved 96.33% and 99.00% accuracy for the three-type and six-type classifiers with over 0.95 F1-score. This work improved the accuracy and robustness of the seizure-type classifiers compared with others' work. In the future, expanding the knowledge base by adding genetic data in this multi-source domain adaptation framework can potentially further enhance the performance.

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