Hindawi
Applied Computational Intelligence and Soft Computing
Volume 2022, Article ID 1419310, 8 pages
https://doi.org/10.1155/2022/1419310

Research Article

A Deep Longitudinal Model for Mild Cognitive Impairment to Alzheimer's Disease Conversion Prediction in Low-Income Countries

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Received 23 January 2022; Revised 25 August 2022; Accepted 10 September 2022; Published 18 October 2022

Academic Editor: Dimitrios A. Karras

Alzheimer's disease (AD) is a progressive and fatal disease, due to the nonavailability of any permanent cure. Some treatments are under experimentation that can slow down and possibly pause the progression of the disease only if the disease is diagnosed earlier. The onset of AD can only be detected at the mild cognitive impairment (MCI) stage in which slight memory loss is observed but daily routine functions are intact. A small fraction of the patient progresses from MCI to AD. In this research, we have designed a cascaded deep neural network model to identify those MCI subjects who will progress to AD in the following year. The analysis and experimentation have been performed using twenty longitudinal neuropsychological measures (NMs) provided by Alzheimer's Disease Neuroimaging Initiative (ADNI). After normalization and ranking of longitudinal data, the deep neural network regression model is trained and tuned to forecast the next in-sequence biomarker value using two previous follow-up readings for each marker. Then, the three time-domain window samples are fed into another deep neural network classifier model for the classification of MCI progressor (MCIp) and MCI stables (MCIs). Our model presented regression forecasting MAE of 0.13 and classification accuracy of 86.9% with AUC of 92.1% (Sensitivity: 67.7%, specificity: 92.3%) over 5-fold cross-validation. We conclude that time-domain measures of NM alone can deliver comparable MCI to AD conversion prediction performance without leveraging more expensive and invasive counterparts such as MR imaging, PET scans, and CSF measures. Middle and low-income countries will benefit from such cheap and effective solutions greatly.

1. Introduction

Alzheimer's disease (AD) is a major cause of dementia. It is an irreversible neurodegenerative disorder that usually occurs in middle or old age. It is a progressing disease, which means it gets worse along with time. Dr. Alois Alzheimer was the first to discover Alzheimer's disease (AD) in 1906 when he observed the strange brain condition of one of his patients who died due to an unusual mental disorder [1]. AD usually occurs after or from the age of 65. In extremely rare cases, it has also been observed in children and teenagers depending on their genetics and family history [2]. This condition initiates with the development of abnormal tau protein around the brain cells and then leads to gradual neuron deterioration. Hence, it is a multistage progressing disease. Along with the progression, a patient experiences mental deterioration, and resultantly the patient is unable to perform life's routine tasks. This disease is progressively becoming the leading cause of death commonly in low or middle-income and third-world countries [3] with a high population. Overall, 35.6 million people are affected worldwide, however, developing countries especially Pakistan, India, and Africa that do not have cutting-edge facilities to bear the higher cost of caregiving and management of the disease are now facing economical and psychological difficulties which will be increasing in the future [4]. Worldwide developing countries have to bear the burden of 60%. Studies have mentioned that in the coming years the increase in the AD will be from 2% to 6% in Pakistan alone [5]. Additionally, from 1.3% to 2.7% in Indonesia, Thailand, and Sri Lanka, and from 3.6% to 7.5% in India and South Asia. Prevalent people in Africa are 2.76 million of which the

majority live in SubSaharan. They are expected to increase with a rate from 0.9% to 1.6% by 2040 [6].

There are three stages of AD [7]. In its preclinical AD stage, the disease goes underdiagnosed due to no visible symptoms. Detection is only possible once the patient enters in MCI stage where very mild clinical and behavioral symptoms can be observed. However, it is of much important to identify which patients will convert to AD called mild cognitive impairment progressor (MCIp) and which of them will retain the MCI diagnosis also referred to as mild cognitive impairment stables (MCIs) in the future. For this task, a plethora of machine learning studies have been conducted while experimenting on feature sets, feature preprocessing, sophistication of the classification method, as well as the use of one timepoint or multiple timepoint data. We hypothesize that this slow-progressing disease will benefit from longitudinal feature values.

2. Related Work

A few studies employing longitudinal data for MCIp vs. MCIs classification are mentioned in Table 1. For early diagnosis of the disease in the MCI stage, there are many diagnostic tools e.g., early neuropsychological assessments (NAs), brain imaging, genetic sampling (GS), and erebrospinal fluid (CSF). Using these biomarkers several pieces of research have been proposed based on a single predictor model [8] as well as a multi-predictor model [9, 10]. Many of the research studies used a single diagnostic feature for the said task while others focused on combining heterogeneous, multimodal features [11, 12] used magnetic resonance imaging (MRI) and positron emission tomography (PET) for MCI to AD conversion prediction presenting the accuracy of 84.7% and 81% simultaneously. On the contrary, [13] used MRI features for 84.29% of accuracy alone whereas [14, 15] performed experiments on both unimodal and multimodal data using NMs and MRI-derived features and delivered 84% and 77.87% accuracy. Likewise, various other researchers have used other combinations of diagnostic biomarkers such as [16] which have used PET scans and cerebrospinal fluid (CSF). Machine (SVM) also accomplished the accuracy of 84.13% that was presented by [17]. Furthermore, the research conducted by [18] presented a novel ensemble-based machine learning algorithm to predict MCI to AD conversion using socio-demographic, clinical characteristics, and NMs. It presented a balanced accuracy of 84% along with an AUC of 88% [19] and has suggested the model using Mini-Mental State Examination (MMSE), NMs, MRI, PET, CSF, and genetic sampling to classify early MCI, late MCI, and normal control. This model used the Radial basis function (RBF) regression and SVM-RBF classification. A principle component analysis (PCA) based model anticipated by [14] claimed an accuracy of 84% for early diagnosis of AD. Within the past few years, neural networks (NNs) have made their place amongst traditional machine learning modules as they are more efficient, robust, and precise in learning, finding, and recognizing patterns within the data. However, as they are hungry for data so the more the data are provided, the more improved results are derived. As a compliment, NN-based models can also achieve better accuracy such as [20] which has reported an accuracy of 83% for the identification of MCIp and MCIs. Another model with promising accuracy of 80% along with the AUC of 84.6% presented by [21] used the combination of CSF and NMs biomarkers along with NN. Getting cutting-edge modeling techniques using deep neural networks (DNNs) [22] shows more encouraging accuracy results of 94% using MRI, GS, and NMs. An additional corresponding model is presented by [12] that has shown an accuracy of 81% using the longitudinal data of MRI, PET, CSF, and NMs. Moreover, an extreme learning-based grading method [11] that used MRI, PET, CSF, and GS claimed an accuracy of 84.7%. All of the above-mentioned single and multipredictor models for early AD detection and MCIp classification have shown encouraging accuracy results using various diagnostic biomarkers, combined as well as disjointedly. The diagnostic biomarkers are quite expensive and not reachable for everyone, especially for low or middle-income societies. Keeping this in view our research work is especially focused on low or middle-income societies of developing countries in which NMs are cheap and easily achievable. Obtaining NM data are simpler as compared to MRI and PET scans which require machine purchase, maintenance, and operational difficulties and costs. We have analyzed only the NM data and applied a deep learning approach by using DNNs to predict MCI to AD stage transition. An approach that is motivated to foresee the disease transition as early as possible in MCI.

Our model calculates and estimates the future biomarker value of the 3rd follow-up value in sequence using regression and later on, the DNN classifier is used to classify the MCI patients as MCIp or MCIs. In the following sections, details are provided about the proposed methodology, development of the related architecture model framework, data, training, and trends the same as the original. Furthermore, follow-up readings of all biomarkers are subjected to a stage transition.

3. Materials

In this paper, we aimed to design a pipeline that accepts two-timepoint readings of MCI patients, forecasts the next timepoint reading, and uses the three readings to predict whether the subject is MCIp or MCIs. The details of data acquisition and organization is described below.

3.1. Data. Few organizations are engaged in the research concerning AD. Amongst these organizations, Alzheimer's Disease Neuroimaging Initiative (ADNI) is the most successful longitudinal multicenter study organization [24]. ADNI was launched in 2003 under the leadership of Dr. Michael W. Weiner. The primary goals of ADNI were to measure the progression of the MCI and AD of the patients using brain imaging (MRI and PET), cognitive assessments (NM), blood tests (GS), and CSF. ADNI has recruited the subjects from about 50 sites across the USA and Canada. Updated information can be seen on http://www.adni-info.org. For our study, we have chosen longitudinal

Table 1: Studies using longitudinal data for early AD diagnosis.

Study	Algorithms	Demo	NM	MRI	PET	CSF	GS	Audio	Accuracy
[11]	Extreme learning machine			Y	Y	Y	Y		84.7
[12]	Multimodal deep learning		Y	Y	Y	Y			81
[13]	Auto regression		Y	Y					84.29
[14]	PCA and posterior probability		Y						84
[15]	LR, extrapolation, and SVM		Y						77.87
[18]	LR, NB, EN, KNN, KNN, GTB, and SVM	Y	Y						84
[20]	Deep sequential NN							Y	83
[21]	Rad-sig and SVM		Y	Y		Y			80
[22]	DNN	Y	Y	Y					63.30
[23]	CNN		Y	Y			Y		94
[24]	Regression and SVM		Y						71.16
[25]	WT and SVM			Y					84.13
[26]	ANN	Y	Y						66.67

neuropsychological measures (NMs) from the ADNI database repository. The data were downloaded on June 8th, 2021. Our gathered dataset for experimentation and technique validation consists of MCI subjects are those, were enrolled in ADNI-1, ADNI-Go, and ADNI-2. The subjects have at least three consecutive annual follow-up readings available. MCI stables (MCIs) are those subjects, who retain MCI stage at all the available annual follow-ups, while MCI progressor (MCIp) are those, who converted to AD at any annual follow-up visit before the last follow-up visit. As a result, our final dataset consisted of 96 MCIp and 150 MCIs subjects, each with three consecutive annual follow-up readings. Groupwise subject demographic for MCI patients converting to AD after 1 year are shown in Table 2. While class imbalance is inherent in medical problems, the average ages of MCIp and MCIs groups were almost equal. Male vs. female imbalance was clearly noted in the MCIs group, while the year of education for both groups was approximately similar.

Table 2: Subjects demographics.

		MCIp ($n = 96$)	MCIs ($n = 150$)
1 Year	Age	62.23 ± 8.7	62.68 ± 8.0
	Gender M/F	40/56	41/109
	Education	16.13 ± 2.5	14.7 ± 2.7

4. Methodology

This work aims at using the previous two marker values to predict the third in-line marker value and then classifying the marker trajectory into one of the two classes: MCIP vs. MCIs. For this purpose, we used cascaded deep learning models as shown in Figure 1. Briefly, after marker ranking and selection, normalization of data are performed. Heterogeneous DNN-based regression algorithms are employed to forecast future marker values. The three-point values of the markers are then used to classify an instance as MCIp or MCIs using a separate tuned DNN classifier. The prediction classification results are then recorded in a 5-fold cross-validation setup.

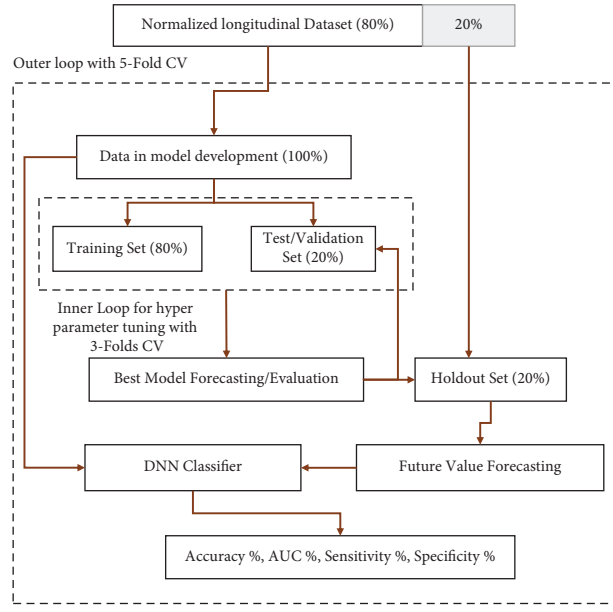


Figure 1: System overview.

4.1. Marker Selection and Normalization. Sperling et al.'s research [7] study demonstrates that cognitive performance is the most affected factor over time during MCI-to-AD. So in this work, we are focusing on neuropsychological measures (NMs) only. Pereira et al. [27] identified the top 30 NM features based on their effect to identify the disease effect on the brain during MCI-to-AD conversion. We selected 20 NM features from the top 30 due to the availability of the data. After running the T-test over the 20 NM features, they have been ranked based on the P-values mentioned in Table 3. The remaining 10 markers had a lot of missing values and could not satisfy the thresh hold set by the T-test.

To obtain a fair longitudinal model, the multiscale data are scaled to have values between 0 and 1. This removes the bias in the data as the data have bigger and smaller values. Each value of the individual feature is divided by the maximum recorded value of that feature in the time domain, hence scaling the data between 0 and 1 while preserving longitudinal trends the same as the original. Furthermore, follow-up readings of all biomarkers are subjected to a stage transition.

Table 3: Neuropsychological measures ranking based on P-values.

Rank	Features	MCIp: $M \pm$ SD	MCIs: $M \pm$ SD	P-values
1	COPYSCOR	4.22 ± 1.17	4.68 ± 0.61	$1.12E-200$
2	CLOCKSCOR	3.69 ± 1.52	4.48 ± 0.72	$1.54E-153$
3	ADAS_Cog_Q1	5.54 ± 1.54	4.16 ± 1.51	$4.96E-136$
4	AVDELTOT	7.54 ± 4.24	10.83 ± 3.3	$1.11E-115$
5	ADAS_Cog_Q4	7.98 ± 2.24	5.24 ± 2.65	$2.21E-107$
6	TOTAL13	24.30 ± 9.35	16.27 ± 7.54	$7.74E-107$
7	TRAASCOR	49.93 ± 29.19	41.01 ± 22.22	$8.45E-102$
8	TOTAL11	16.29 ± 6.7	10.17 ± 5.12	$4.62E-94$
9	AVTOTB	2.85 ± 1.7	3.79 ± 1.64	$6.32E-93$
10	LIMMTOTAL	5.92 ± 4.35	9.68 ± 4.49	$7.68E-85$
11	ADAS_Cog_Q8	6.13 ± 2.87	4.12 ± 2.81	$2.46E-63$
12	TRABSCOR	150.06 ± 104.9	110.12 ± 61.21	$1.74E-49$
13	LDELTOTAL	3.30 ± 4.64	7.52 ± 5.38	$3.58E-49$
14	AVTOT6	2.18 ± 2.55	5.2 ± 3.93	$1.24E-48$
15	FAQ	13.40 ± 6.31	3.26 ± 4.18	$1.60E-32$
16	AVDEL30MIN	1.07 ± 2.25	4.1 ± 4.13	$7.51E-29$
17	TRABERRCOM	1.34 ± 1.68	0.68 ± 0.99	$1.05E-09$
18	TRAAERRCOM	0.10 ± 0.33	0.07 ± 0.28	$2.05E-07$
19	TRAAERROM	0.33 ± 1.82	0.03 ± 0.33	$1.22E-06$
20	TRABERROM	1.82 ± 4.71	0.3 ± 1.54	0.805650742

4.2. Future Value Forecasting Using DNN Regressors. In this paper, a DNN-based model is proposed that utilizes longitudinal embeddings to classify the class of progression. It has two submodules (regressor and classifier). Regressor takes the two known consecutive values of a biomarker feature from the MCI subject and forecasts the third future value of that biomarker feature. Two regression models are trained: one for MCIp and another for MCIs. The hyperparameter tuning process is performed in an inner loop using 3-fold cross-validation. Regression estimates two possible future values,namely, (1) as MCIp and (2) as MCIs.

To choose the most suitable future value from the two possible values recorded, proximity measures are used. Let i be the sample having two known consecutive annual values whose next value, v_3 is to be forecasted.

$$i = v_1, v_2, v_3. \tag{1}$$

The two possible values for v_3 using MCIp and MCIs regressors can be f_p and f_s. Average values of third marker value from the training data of MCIp and MCIs are set as a benchmark i.e., $\mathrm{MCI}_p(\mathrm{avg})$ and $\mathrm{MCI}_s(\mathrm{avg})$. The final selection of v_3 is carried out by subtracting the respective forecasted measures from their group averages and selecting whichever is closest.

$$\begin{aligned} ff_s &= \mathrm{MCI}_s(\mathrm{avg}) - f_s, \\ ff_p &= \mathrm{MCI}_p(\mathrm{avg}) - f_p, \end{aligned} \quad \begin{aligned} &\text{if: } ff_s < ff_p, \quad v_3 = ff_s, \\ &\text{else,} \qquad\quad v_3 = ff_p. \end{aligned} \tag{2}$$

The chosen value is attached to the previously available two-year data that becomes a three-year time-domain trajectory window. Finally, it is ready to be served to the classifier for the final class predictions.

4.3. Classification of MCIp vs. MCIs Using DNN Classifier. Classification is the last phase of the model architecture to identify the class of the processed subject if it belongs to MCIp or MCIs. All the patients labeled as 1 by the classifier belong to the MCIp group, these are the patients who are expected to be progressing in the AD stage in the coming year. MCIs, on the other hand, are labeled as 0, and they are expected to be stable and will not progress to the AD stage in the coming year. It has also been substantiated that the classifier's performance has been optimized by applying hyperparameter tuning using 3-fold cross-validation. The best selected activation functions through hyperparameter tuning along with their equations are mentioned above in Table 4.

5. Results and Discussions

We evaluate our system in two categories: (1) accuracy of future value forecasting and (2) accuracy of MCip vs. MCIs classification. For accuracy of future value forecasting, we use the mean absolute error (MAE) value which is calculated as the mean absolute error between the actual predictor reading from the dataset and the value forecasted by our system. Whereas for classification performance evaluation, we employ accuracy, area under the ROC Curve (AUC), sensitivity, and specificity. We conducted these evaluations at both training and validation stages. Our data analysis is based on NMs biomarker's data taken from ADNI. Moreover, the performance measure is recorded by observing the results of ground truth (GT) values, and the results provided by our experiment using the "Future Value Forecasting" algorithm. GT is the provided benchmark data metrics by the ADNI in which they have classified the real-world data into MCIp vs. MCIs (used for training). The following sections consult and describe the observation recorded in the experiment.

Table 4: Best chosen activation functions and optimisers.

Activation function	Resulting equation
Selu	If $x > 0$: return (scale $*$ x), if $x < 0$: return (scale $*$ alpa $*$ $(\exp(x) - 1$ Where alpha = 1.67326324 and scale = 1.05070098
Elu	x if $x > 0$ and alpha $*$ $(\exp(x) - 1)$ if $x < 0$
ReLU	$y = ax$ where $x < 0$
Adam	$m_n = E[X^n]$
RMSProp	$\theta_{(t+1)} = \theta_t - \eta/(\sqrt{E[g^2] + \epsilon})g_t$
Sigmoid	$1/(1 + \exp(-x))$

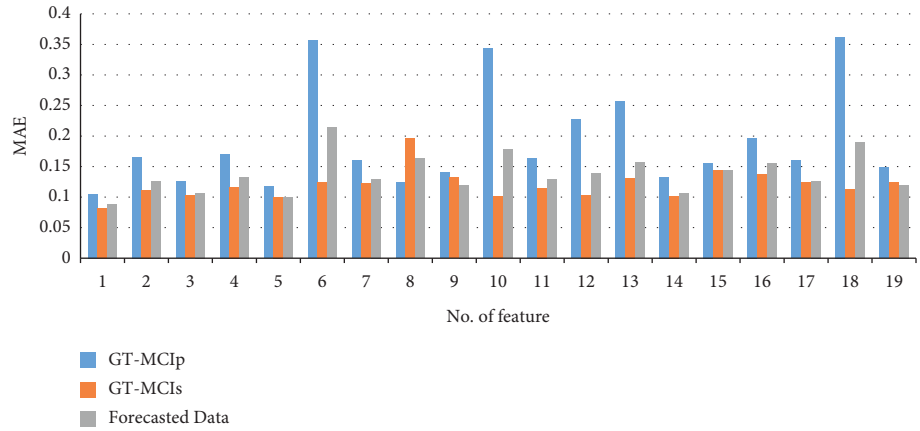


Figure 2: Mean absolute error (MAE) recorded for the best-performing regression model.

5.1. Biomarker Ranking Observations. While ranking the biomarkers we set 0.5 as the significant threshold value of the T-test. So we come up with 19 significant features out of 20 selected NM features. According to the p-value, the top of the ranked features is COPYSCOR with the p-value of $1.12E - 200$, and the last ranked feature is TRAAERROM with the p-value of $1.22E - 06$. The feature TRABERROM with a p-value of 0.8057 is ignored and has not been included for analysis as it does not satisfy the significance threshold of 0.5. Table 3 could be observed to see the ranking details.

5.2. Regression Performance Analysis for Future Value Forecasting. The regression module plays the primary role of precisely predicting the future values which is our primary objective. Our hypothesis says that the forecasted values are accurate enough to help predict the class of the subject at a future time point (one year ahead). The comparative results have been recorded as mean absolute error (MAE).

Figure 2 shows the regression performance at ground truth for MCIp (GT-MCIp) data, ground truth MCIs (GT-MCIs), and finally the forecasted data MAE. The comparison concludes that the MAE is quite abnormal for GT-MCIp, GT-MCIs, and also for the forecasted data. GT-MCIp comes up with more of the MAE because the subject quantity is less than the GT-MCIs. Whereas the model has shown balanced MAE results amongst GT-MCIp and GT-MCIs. Although, there are features for which the regression model has shown even lesser MAE but we have chosen a fully tuned model with 17 features based on the observation of the classification results. The observation shows that the model has generated results with the MAE of 0.16 for GT-MCIp, 0.12 for GT-MCIs, and 0.13 for the forecasted data, chosen through our closest value selection algorithm with 17 features.

5.3. Classification Performance Analysis. Classification performance can be perceived in Figure 3. The plots provide the comparative performance between the model accuracy on GT data, the data available as the ground truth, and the forecasted data which is gathered by applying the regression. We can observe that initially, the accuracy is quite low but adding the significant feature one by one shows the increase in the accuracy. The trend tends to increase till 17 features but after that, the accuracy began to come downwards. This behavior of the model accuracy is due to the addition of less significant features.

However, the classification performance power of our system is higher with 17 NM features which is 87%. Whereas our model has shown an accuracy of 87.4% on GT data which are not a big difference.

The proposed methodology delivers the maximum AUC of 90% for GT data. However, the AUC with the forecasted data selected through our forecasting selection algorithm is even better that is 92%. Comparative observation between GT-AUC and AUC on forecasted data can be seen in Figure 4(a). Finally, the sensitivity and specificity of our proposed model can be observed in Figure 4(b). The provided sensitivity and specificity results are plotted comparative to GT data and the forecasted data. These plots show that the classification model has shown a sensitivity of 68% and specificity of 92%. Here, we have less sensitivity because we had less data of MCIp. Figure 5 shows the average difference between the accuracy and accuracy, AUC,

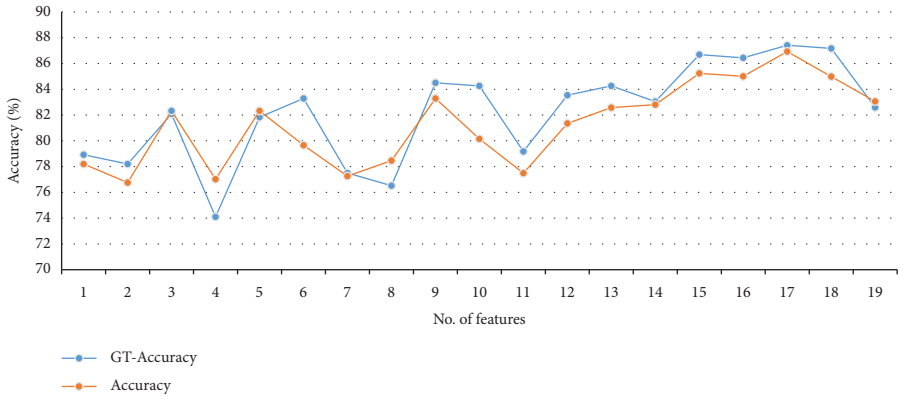
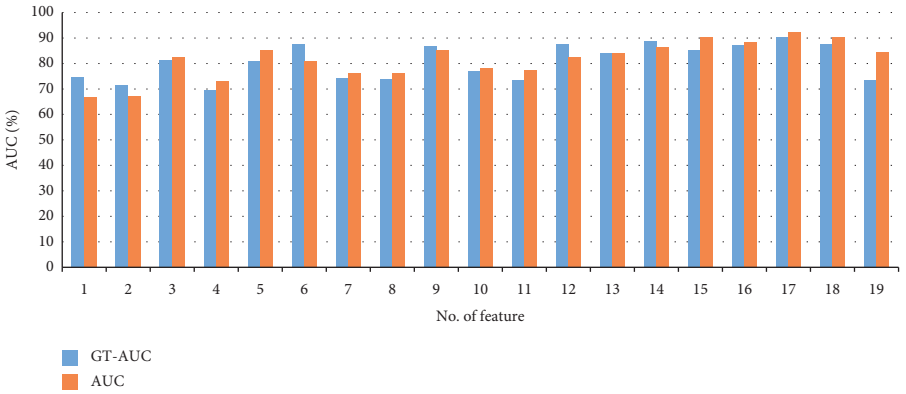
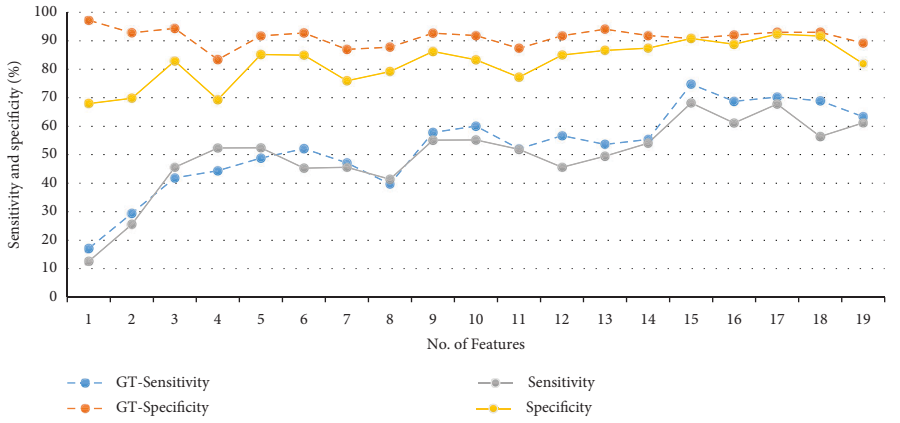


Figure 3: Classification accuracy recorded for GT data and forecasted data.



(a)



(b)

Figure 4: AUC, sensitivity, and specificity results. (a) AUC recorded for GT Data and Forecasted Data and (b) sensitivity and Specificity recorded on GT Data and Forecasted Data.

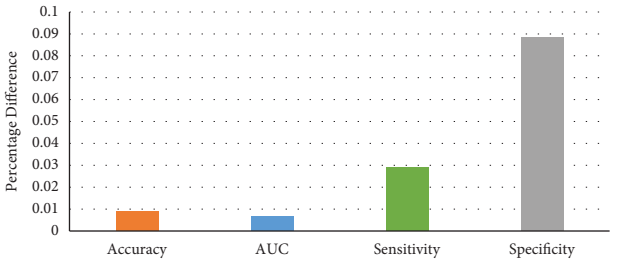


Figure 5: Percentage difference between accuracy, AUC, sensitivity, and specificity on GT data and forecasted data.

sensitivity, and specificity between GT data and forecasted data. These details show that the accuracy presented by the proposed system using NM is quite better than mentioned in the recent study [28] which is 84.7% using NMs.

6. Conclusion

The proposed research is especially focused on providing an effective, economical, and early diagnosis of Alzheimer's disease. Our proposed model uses NMs time series data to detect the disease at its MCI stage when mild physical and clinical symptoms are about to show up. This is a DNN-based model that has accomplished the MAE of 0.13 for the forecasted data. The classifier has predicted the stage of the patients for next year based on previously available NMs data of three years with an accuracy of 87% and AUC of 92%. These compiled up results are recorded with 17 NMs data features but the model could be expected to show improved performance by trying out the data features with various combinations for computation. This developed system can be used as a mild stone for future investigations and diagnostic tools for the hospitals and organizations that intend to work on the early detection of AD and giving care to patients accordingly. This detection can help physicians to plan the early treatment of the patients to slow down or perhaps block the AD progression. So the patients could spend a healthier and longer life than the expectation.

Data Availability

Data in preparation for this article and research were obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI, and/or provided data but did not participate in the analysis or writing of this article. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf Data collection and sharing for this project were funded by Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health under grant U01AG024904) and DOD ADNI (Department of Defense, under award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging and the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following companies: AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Araclon Biotech, BioClinica, Inc., Biogen, Bristol-Myers Squibb Company, CereSpir, Inc., Cogstate, Eisai Inc., Elan Pharmaceuticals, Inc., Eli Lilly and Company, EuroImmun, F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc., Fujirebio, GE Healthcare, IXICO Ltd., Janssen Alzheimer Immunotherapy Research and Development, LLC., Johnson and Johnson Pharmaceutical Research and Development LLC., Lumosity, Lundbeck, Merck & Co., Inc., Meso Scale Diagnostics, LLC., NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer Inc., Piramal Imaging, Servier, Takeda Pharmaceutical Company, and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private-sector contributions are facilitated by the Foundation for the National Institutes of Health (https://ida.loni.usc.edu/collaboration/access/www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see https://www.adni-info.org.

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