IEEE Access
Multidisciplinary | Rapid Review | Open Access Journal

Received 5 March 2024, accepted 18 March 2024, date of publication 28 March 2024, date of current version 9 April 2024.

Digital Object Identifier 10.1109/ACCESS.2024.3381956

SURVEY

Adversarial Network-Based Classification for Alzheimer's Disease Using Multimodal Brain Images: A Critical Analysis

MEENU GUPTA[1,2], (Senior Member, IEEE), RAKESH KUMAR[1,2], (Senior Member, IEEE), AND AJITH ABRAHAM[3,4], (Senior Member, IEEE)

[1]Department of Computer Science and Engineering, Chandigarh University, Ludhiana, Punjab 140413, India
[2]Machine Intelligence Research Labs, Auburn, WA 98071, USA
[3]School of Computer Science Engineering and Technology, Bennett University, Greater Noida, Uttar Pradesh 201310, India
[4]Center for Artificial Intelligence, Innopolis University, 420500 Innopolis, Russia

Corresponding authors: Meenu Gupta (gupta.meenu5@gmail.com) and Ajith Abraham (ajith.abraham@ieee.org)

This work was financially supported by The Analytical Center for the Government of the Russian Federation (Agreement No. 70-2021-00143 dd. 01.11.2021, IGK 000000D730324P540002).

ABSTRACT Alzheimer's disease (AD) is a progressive neurodegenerative disorder that represents a significant and growing public health challenge. This work concisely summarizes AD, encompassing its pathophysiology, risk factors, clinical manifestations, diagnosis, treatment, and ongoing research. The main goal of managing AD is to reduce symptoms while improving the lives of those impacted. This letter has conducted a systematic review to analyze the prediction of AD using the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) guidelines. The major scientific databases such as Scopus, Web of Science (WoS), and IEEE Xplorer are explored, where 2018-2023 publications are considered. The article selection process is based on keywords like ''Alzheimer's disease,'' ''Brain Images,'' ''Deep Learning (DL),'' etc. After rigorous analysis, 946 articles were extracted, and 42 were identified for final consideration. Further, several investigations based on the previous work are discussed along with its Proposed Solutions (PS). Finally, a case study on AD detection using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset and AD Detection Network (ADD-NET) implementation is presented.

INDEX TERMS Alzheimer, brain images, convolutional neural network, generative adversarial network, machine learning, magnetic resonance imaging, positron emission tomography, biomarkers, P-TAU, amyloid beta, systematic review, meta-analysis.

I. INTRODUCTION

Alzheimer's disease (AD) is a chronic and progressive neurological ailment that predominantly affects important brain processes such as thinking, memory, and behavior. This pattern is characterized by the slow loss of brain tissue along with the formation of aberrant protein deposits, resulting in a continuous decline of cognitive capacities over time [1]. Figure 1 shows that AD is primarily defined by an accumulation of abnormal tau proteins and amyloid plaques in the brain, which causes inflammation and oxidative damage. This process causes neuronal shrinkage, neurotransmitter abnormalities, and, eventually, widespread brain death, all of which contribute to AD development. It is estimated that 1 in 85 persons globally will have AD by the year 2050. Due to the growing aging population, AD is also substantially increasing not only in terms of influencing people but also impacting society with social and economic threats for the coming 30 to 40 years [2].

The alarming $800 billion in medical care expenses linked to AD each year highlight the need to investigate novel early detection techniques, especially for the identification of mild cognitive impairment (MCI) [3]. While, strong and complementary information is also obtained from multimodal

The associate editor coordinating the review of this manuscript and approving it for publication was Orazio Gambino.

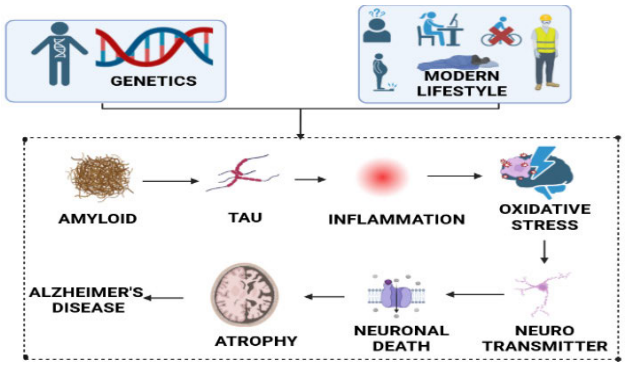

FIGURE 1. AD Nexus: Understanding the role of environmental and genetic factors.

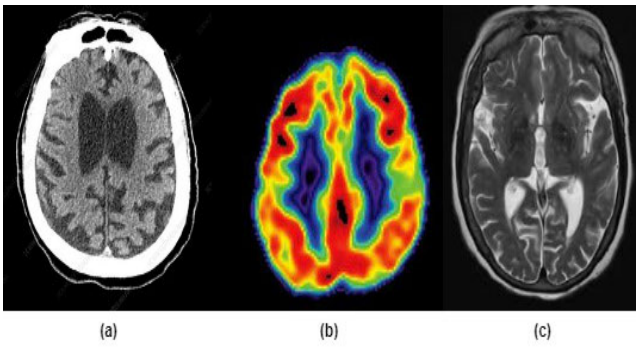

FIGURE 2. Samples of (a) CT, (b) PET, and (c) MRI scan of AD.

imaging for an earlier and more accurate diagnosis of brain disorders, including AD and Mild Cognitive Impairment (MCI) [4]. MCI is the prodromal stage of AD and is categorized into stable MCI (sMCI) and progressive MCI (pMCI). The person affected by MCI is not severe as compared to AD, but there is a chance of 10 to 15 % of having MCI to AD within a specified time frame of three years [5], [6], [7]. At present, proper medications (or treatments) are not available to stop AD progress. New research criteria were established by the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups [8] for diagnosing AD. The hypothesis behind this was that AD dementia develops gradually, starting with presymptomatic AD and progressing to symptomatic pre-dementia and then AD dementia. It is crucial to discover sensitive and specific biomarkers to monitor the early progression of AD and keep track of novel therapeutic developments. Due to the high psychological and financial costs associated with AD, it is critical to develop an automatic diagnosis method for possible early treatment [9]. Several ML techniques and pattern analyses are gradually used by the researcher to predict diseases associated with AD. Various neuroimaging modalities, such as MRI and PET, have been extensively used in AD as these can provide additional brain structure information to train the model for automatically predicting the disease [10], [11]. Implementing ML techniques in AD diagnosis has shown promising results and is currently a significant area of research. This is made possible by the availability of publicly available data from different repositories such as the AD Neuroimaging Initiative (ADNI), Australian Imaging, Bio-marker & Lifestyle Flagship Study of Ageing (AIBL), and Open Access Series of Imaging Studies (OASIS). On the other hand, DL techniques are quite effective since they automatically extract essential features from the input images. The anatomy and functional features of the human brain are documented by utilizing a range of imaging methods, including Computed Tomography (CT), Positron Emission Tomography (PET), and Magnetic Resonance Imaging (MRI) [12], [13], as illustrated in Figure 2.

This research shows that integrating information from multiple models produces better results than applying only one model. Further, this study explored proposed solutions for the extracted investigations based on previous work done by the researchers in this field.

Moreover, the following sections include the organization of this paper. Section II consists of the extracted articles based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards for predicting AD. Section III discusses investigations based on earlier work done by the researchers. Further, the critical review analysis is presented in Section IV. Section V includes proposed solutions for investigations addressed in section III. Finally, this work is concluded in section 6 with its future perspective.

II. LITERATURE REVIEW

This section performs a critical analysis of previous work done by different researchers to predict AD using DL techniques, along with the various proposed investigations based on the literature analysis as depicted in Table 1.

A. ANALYSIS OF AD

Alsadhan [14] proposed a CNN-based VGG16 and ResNet 50 model for AD detection. The proposed method extracted visual information from the image data using DL techniques, which accurately predicted the AD class value. They used a public dataset available at Kaggle that consisted of 5121 training and 1279 test images for the experimental work. Each image has a size of 244 * 244 pixels. They used accuracy, precision, sensitivity, and F1-score to evaluate the proposed model. As a result, they achieved 60% and 69% accuracy for the ResNet and VGG16, respectively. Balaji et al. [15] discussed the Hybridised DL method for early AD detection. The Convolutional Neural Network (CNN) and LSTM (Long-Short-Term Memory) model were used to train the model. In this work, two datasets were used (i.e., MRI and Munich), where MRI consisted of 512 images, and Munich consisted of 112 images for training. The accuracy was increased using Adam's optimization and the learning weights with the proposed methods. In the experimental analysis, they achieved a 98.5% accuracy level. Islam et al. [16] introduced ResNet 50 and a Support Vector Machine (SVM) classifier for diagnosing AD from MRI Scans. The authors

TABLE 1. Diverse findings from several studies and datasets combined cohesively.

Method/ Model	Dataset	Results/Outcomes
Densely connected CNN [31]	ADNI	Accuracy: 97.35% (AD vs. CN), 87.82% (MCI converters vs. non-converters), 78.79% (MCI converters vs. non-converters)
Ensemble ML [18]	NCA-F	Accuracy: 93.92%
SVM, ResNet 50 [16]	ADNI (2024 brain MR images)	Accuracy: 99.78% (training), 98.71% (testing), 99.52% (validation)
CNN [17]	MIRIAD	Accuracy: 89.0%, Precision: 89.0%, F1-Score: 77.0%, Sensitivity: 92.0%
Various DL Architectures [19]	ADNI	Accuracy: 99.79%
LSTM, CNN [15]	MRI, Munich	Accuracy: 98.5%
ML-based [21]	PET, CT	Precision: 83% (healthy), 81% (mild), 85% (severe AD)
DeepCurvMRI (CNN + CT) [22]	Alzheimer's MRI	Accuracy: 98.62%, Sensitivity: 99.05%, Specificity: 98.50%, F1-Score: 99.21%
RF, XGBoost, CNN [23]	ADNI	Accuracy: 97.57%, Sensitivity: 97.60%
ML techniques, logistic regression [2]	Antenna S-parameter data	Accuracy: 98.97%
CNN [25]	sMRI (ADNI)	Accuracy: 96.12%, Precision: 95.50%, F1-Score: 95.23%
GBM-centered instance-based TL [26]	ADNI, Mount Sinai	Improved classification accuracy
Hybrid classical-quantum network [27]	64000 labeled MRI scans	Training Accuracy: 99.1%, Classification Accuracy: 97.2%
Bidirectional LSTM, Stacked Deep Dense Neural Network [28]	DementiaBank clinical transcript dataset	Accuracy: 93.31%
Ensemble Learning [30]	ADNI (789 3D MRI images)	AUC: 91.28% (AD vs. MCI), 88.42% (MCI vs. CN)
Fusion-based Stacked Generalisation [31]	Spoken and Written Languages	Accuracy: 99.47% (written), 98.1% (spoken), F1-Score: 97% (written), 95% (spoken)
DA-MIDL (Dual Attention Multi-instance DL) [32]	AIBL, ADNI	Accuracy: 92.4%, Sensitivity: 91.0%
SVM model [33]	Blood plasma proteins	Sensitivity: >80%, Specificity: >70%
Deep transfer learning [34]	Synthetic images	Accuracy: 81.03%
Hierarchical FCNN [36]	Structural MRI	AUC: 95.01%, Sensitivity: 82.4%, Accuracy: 90.03%
TS-SVM (Temporally Structured SVM) [37]	MR image sequence	Accuracy: 81.75%
Data-Augmentation Framework [38]	OASIS	Accuracy: 95.11% (3D views), 98.41% (single view)
DL models, Resting State Brain Networks [39]	R-fMRI data	Prediction Accuracy: 31.21% (increased), Standard Deviation: 51.23% (lowered)
Efficient patch-based classifier [40]	GARD cohort dataset	Accuracy: 90.05%

used the ADNI dataset comprising 2024 brain MRI images. Further, the dataset consisted of CN (Cognitive Normal) and MCI classes of images. They concluded that the proposed model achieved 99.78%, 99.52%, and 98.71% accuracy during training, validation, and testing, respectively. de Silva and Kunz [17] suggested the CNN model for AD prediction from MRI. Medical images of the brain were used to train the CNN model. The proposed model differentiated between AD and non-AD patients with the help of a classification algorithm. The Minimal Interval Resonance Imaging in AD (MIRIAD) dataset was used to train the model and attained 89.0% accuracy, 89.0% F1-score, 92.0% Area Under the ROC Curve (AUC), and 77.0% MCC. Irfan et al. [18] proposed an innovative ensemble ML approach for early AD detection. The authors discussed a novel technique for identifying important cognitive traits from the dataset (called Neighbourhood Component Analysis and Correlation-based Filtration (NCA-F)). Next, the dataset was used to train various ML classifiers and select the best-performer classifier using the voting process. The results showed that the adaptive voting strategy

outperformed the traditional artificial neural network method for AD detection, with an accuracy of 93.92%. Kumar and Sasikala [19] proposed four methodologies to improve AD detection with different DL architectures. Methodology-I consisted of AlexNet, GoogLeNet, ResNet-18, ResNet-50, and ResNet-10, and Methodology-II includes four distinct ML classifiers and deep features taken from pre-trained networks. Methodology III concentrated on merging features from various pre-trained networks to improve system performance. Methodology IV also used principal component analysis (PCA) to reduce features to balance complexity and accuracy. The authors employed the ADNI dataset for the experimental study and achieved 99.79% accuracy. Yu et al. [20] introduced a new method for identifying AD. They applied CNN with surface-enhanced Raman Spectroscopy (SERS) fingerprints of human Cerebrospinal Fluid (CSF). The suggested method used CNN and SERS to find biomarkers in the CSF that indicate metabolic alterations associated with the condition. Based on clinical diagnosis, the results showed an overall diagnostic accuracy of 92%, with 100% accuracy for recognizing normal individuals and 88.9% for detecting AD individuals.

Ullah et al. [21] proposed an ML-based approach to categorize AD phases. Simulations were conducted to generate scattered signals using realistic numerical brain models. A novel data augmentation technique was also introduced to provide fake data for ML algorithms. The authors used CT and PET images to train the model. In the result analysis, the model achieved 83%, 81%, and 85% precision for healthy, mild, and severe AD. Chabib et al. [22] suggested a DeepCurvMRI model that combined a CNN and the Curvelet Transform (CT) to improve the accuracy of early-stage AD identification using MRI scans. After pre-processing the MRI images with CT, these modified images were used to train the CNN model. The authors trained DeepCurvMRI for multiclass and binary classification tasks using the AD MRI dataset. Using the Leave-One-Group-Out (LOGO) cross-validation approach, the model in the experiment attained an accuracy of 98.62% $\pm$ 0.10%, sensitivity of 99.05% $\pm$ 0.10%, specificity of 98.50% $\pm$ 0.03%, and an F1 score of 99.21 $\pm$ 0.08 respectively. Shukla et al. [23] discussed RF (Random Forest), XGBoost, and CNN for diagnosing and detecting AD. The authors introduced a set of innovative pre-processing techniques that significantly enhanced the classification performance of MRI images and reduced the training time for existing learning algorithms. For the model's training, the dataset was collected from the ADNI and converted from a 4D format to a 2D format. In the result analysis, the proposed model achieved 97.57% accuracy and a sensitivity of 97.60%. Fabietti et al. [24] introduced the Ensembled ML model with explainability (EXML). The author aimed to locate minute patterns in cortical and hippocampus Local Field Potential (LFP) signals that may predict AD in its early stages. The EXML model's total accuracy was 99.4% using a late fusion technique. Saied et al. [2] used ML techniques to track alterations in the brain linked with AD pathology non-invasively. S-parameter data gathered from six carefully positioned antennas around the head was employed for this. To acquire data, measurements were taken on nine different human models with different head sizes. The collected data was processed using many ML methods. Predictions and accuracy ratings were generated for each algorithm, and the outcomes were compared to determine which algorithm better classified the different stages of AD. The results demonstrated that the logistic regression model distinguished between the four stages of AD and attained the highest accuracy, at 98.97%. Faisal and Kwon [25] proposed a CNN model for the automatic detection of AD from brain MRI images. This research aimed to develop a DL technique to classify brain images into three categories: AD, MCI, and cognitively normal (CN). Relevant indicators associated with AD were identified using structural MRI (sMRI). The authors used modified CNN and trained the model with sMRI images collected from the ADNI datasets. Finally, the model achieved 96.12% accuracy, 95.50% precision, and 95.23% F1 score. Shojaie et al. [26] proposed a Gradient Boosting Machine (GBM)-centered instance-based TL system. The authors used the ADNI dataset for model training. According to experimental data, the suggested TrGB algorithm improved classification accuracy over conventional approaches by 1.5% for CN and 4.5% for multiclass classification.

Shahwar et al. [27] discussed a hybrid model that combined classical and quantum ML techniques to detect AD. Using the hybrid classical-quantum method, high-dimensional features from the images were extracted using classical neural networks, which integrated informative feature vectors into a quantum processor. A 512-feature vector was produced during the feature extraction process using Resnet34. The 512-feature vector is then processed by a quantum variational circuit (QVC) to produce a four-feature vector for precise decision-making bounds. Additionally, the authors employed 64000 labeled MRI scans with two different classes to train the model. With an optimum quantum depth of six layers spanning 20 epochs and a learning rate of 10^-4, the hybrid classical-quantum network achieved a training accuracy of 99.1% and a classification accuracy of 97.2%. Khan et al. [28] presented a Stacked Deep Dense Neural Network (SDDNN) based on text categorization and an AD prediction model. For the training of the model, the DementiaBank clinical transcript dataset was used which comprised clinical specialists' recorded interviews of AD patients. The proposed model showed an accuracy of 93.31%. Shanmugam et al. [29] presented three pre-trained networks for AD classification, AlexNet, ResNet-18, and GoogLeNet, which are trained and evaluated using the ADNI dataset. The overall detection accuracy for AD is 94.08%, 96.39%, and 97.51%, respectively. Gamal et al. [30] discussed the Ensemble Learning (EL) approach for diagnosing AD. The authors used the ADNI dataset consisting of 789 3D MRI images. The

suggested method produced AUC values of 91.28% and 88.42% between people with AD and MCI and between MCI and subjects with CN.

Zhang et al. [31] presented a densely connected CNN with a connection-wise attention mechanism to extract multi-level characteristics from brain MRI images for AD classification. The recommended method was 97.35% accurate in classifying AD. Zhu et al. [32] introduced a novel Dual Attention Multi-instance DL network called DA-MIDL to detect MCI, a prodromal AD stage. The authors used the baseline sMRI scans from 1689 images to evaluate the model. The images were collected from the two datasets, i.e., ADNI and AIBL. The proposed model achieved 92.4% accuracy and 91.0% sensitivity in the experimental analysis. Eke et al. [33] proposed an SVM model to identify the early stage of AD using blood plasma proteins. Using cutting-edge feature selection and evaluation techniques, the authors discovered five novel non-amyloid protein sets that may serve as early AD indicators. Additionally, the results showed that a vital biomarker profile for early-stage disease might include A2M, ApoE, BNP, Eot3, RAGE, and SGOT. These panels served as the basis for developing illness detection models that showed greater than 80% sensitivity, 70% specificity, and an area under the patient's operating curve (AUC) of at least 80%, particularly during the prodromal stage of the disease. Cilia et al. [34] suggested a Deep TL approach for detecting AD from synthetic images. This study aimed to investigate whether combining shape and dynamic data could enhance AD diagnosis by a decision support system. The authors used an offline synthetic color picture generator to create an offline version of a collection of online handwriting samples. Using the three RGB channels, the color of each elementary handwriting trait in these images encoded dynamic information related to that trait. In the experimental analysis, the proposed model achieved 81.03% accuracy. Alkenani et al. [35] introduced the Fusion-based Stacked Generalisation model to predict AD using Spoken and Written Languages. The author's objective was to create a range of heterogeneous stacked fusion models that improved AD diagnostic ML models' overall robustness and generalization by utilizing the advantages of different base learning techniques. The authors trained the stacking fusion models using two datasets, one based on spoken language and the other on written language. For the model evaluation, 99.47% AUC was achieved for the written dataset and 98.1% for the spoken dataset. After training, the proposed model obtained 95% accuracy and 97% F1 score. Lian et al. [36] discussed Hierarchical FCNN for localization and detection of AD using Structural MRI. Using whole-brain sMRI data, the suggested model automatically recognized discriminative local patches and regions. Multi-scale feature representations were concurrently learned and integrated based on these regions to build hierarchical classification models for AD diagnosis. The ADNI-1 and ADNI-2 datasets were used to train the model. The model obtained 95.01% AUC, 82.4% sensitivity, and 90.03% accuracy in the outcome analysis. Zhu et al. [37] presented a Temporally Structured SVM (TS-SVM) model that limits the detection score of the partial MR image sequence, allowing it to increase steadily as AD advances. The authors have suggested a combined feature selection and classification framework to determine the most pertinent morphological traits for enabling classifiers. Using only two follow-up MR scans, the experimental results achieved 81.75% accuracy.

Afzal et al. [38] introduced the Data-Augmentation Framework to address the issue of class imbalance in AD stage detection. The authors used the Open Access Series of Imaging Studies (OASIS) dataset consisting of 218 samples for the model's training. Each image has a size of $256 * 256$. The accuracy of the suggested model was 95.11% using 3D views of the brain MRI and 98.41% with a single view. Ju et al. [39] proposed DL models and Resting State Brain Networks for the early diagnosis of AD. Resting-state functional magnetic resonance imaging (R-fMRI) data was used to compute functional connectivity across different brain regions to construct the brain network. The clinical text data also includes the ApoE gene status, age, and gender of research participants. The proposed approach provided a classifier for AD detection and efficiently found discriminative characteristics in the brain network. The DL strategy lowers the standard deviation by 51.23% and increases prediction accuracy by about 31.21%. Ahmed et al. [40] discussed an efficient patch-based classifier for diagnosing AD. The authors suggested three goals with an emphasis on sMRI: a) increase accuracy to either meet or exceed ML techniques; b) tackle the problem of overfitting; and c) examine known brain landmarks that offer unique characteristics for the diagnosis of AD, with particular attention to the left and right hippocampal regions. Jha et al. [41] proposed a Dual-Tree Complex Wavelet Transform PCA and Feed-Forward Neural Network for Diagnosis of AD. PCA was used to reduce the feature vector's dimensionality. The reduced attributes were then sent into a FNN to categorize AD. This method produced accuracy rates of $90.06\% \pm 0.01\%$, sensitivity of $92.00\% \pm 0.04\%$, specificity of $87.78\% \pm 0.04\%$, and precision of $89.6\% \pm 0.03\%$ in classification accuracy using a 10-fold cross-validation process. Zhang et al. [42] suggested a multivariate method for detecting AD using stationary wavelet entropy and predator-prey particle swarm optimization. A novel method termed predator-prey particle swarm optimization was introduced to modify the classifier's weights and biases. The classification method's overall accuracy, sensitivity, and specificity were $92.73\% \pm 1.03\%$, $92.69\% \pm 1.29\%$, and $92.78\% \pm 1.51\%$, respectively. The model's performance was strong, with an area under the curve (AUC) of 0.95 ± 0.02. Ruiz et al. [43] discussed computer-aided diagnosis of AD and histogram-based analysis of regional MRI volumes for feature selection and classification. This study introduced a completely automated computer-aided diagnostic (CAD) system that employed supervised ML techniques to identify AD in its early stages. Rocca et al. [44] discussed a novel

TABLE 2. Search criteria.

Sources	IEEE Xplore, Scopus, WoS
Keywords	Alzheimer's Disease, Brain Images, Classification, GAN, DL, ML, Tau, PET
Query	"Alzheimer's Disease" AND "Brain Images" AND "Machine Learning" OR "Deep Learning" OR "GAN" OR "Biomarkers" OR "PET" OR "MRI" OR "P-TAU" OR "amyloid Beta" AND "Systematic Review" OR "Meta-Analysis"
Number of Articles	946

approach to studying brain connections that can identify early structural alterations in AD. The authors evaluated the white matter fibers that connect various anatomical brain regions by reconstructing probabilistic tractography using Diffusion Weighted Imaging (DWI) brain scans. The ADNI dataset, which comprised 222 publically accessible DWI scans, and brain connection graphs from 47 AD patients, 52 NC individuals, and 123 subjects with MCI, was examined by the authors.

III. RESEARCH METHODOLOGY USED

A. REVIEW PROCESS: PRISMA GUIDELINES

The critical review analysis for the detection of AD is discussed in this section. All the phases of this critical review analysis are shown in Figure 3. A total of 946 articles were collected from three popular databases such as IEEE, Scopus, and WoS using the keywords mentioned in Table 2. This process considered the articles published from 2018 to 2023, as shown in Figure 3. In the screening phase, all the collected manuscript (i.e., 946) records are checked manually, and 315 are excluded due to duplicate records. Further, the left records (946 – 315 = 631) are reviewed with their title and abstract, and 355 are excluded due to unrelated to the present study (631 – 355 = 276). Next, 234 articles are removed in the eligibility phase as they are out of scope. After completing the process, the left articles (276 - 234 = 42) are included in this study, as shown in Figure 4. This systematic review of AD used a broad search technique, including disease classification, technological applications, and global impact criteria. Emphasis was placed on the crucial void in the existing literature related to PET imaging, highlighting a critical gap in the existing literature. Table 3 lists several facts and findings associated with the papers.

IV. RESULT AND DISCUSSION

A. PROPOSED INVESTIGATION

This section includes the investigations with the proposed solution for AD detection leveraging ML and other techniques.

Investigation 1: Which ML models are most suitable for AD detection when employing neuroimaging data?

TABLE 3. Facts and figures.

S. No	Facts	Figures (Information)
1.	Year	All the finalized manuscripts are collected on and after 2018.
2.	Findings	Considered the research work that is focused on AD
3.	Relevant	Only those research papers detected AD.
4.	Techniques and Technology	DL-based manuscripts are finalized for the proposed work.
5.	Research Report	Experimental result-based analysis reports are included.
6.	Availability	Consider only those articles that are related to the subject and are available on the web.

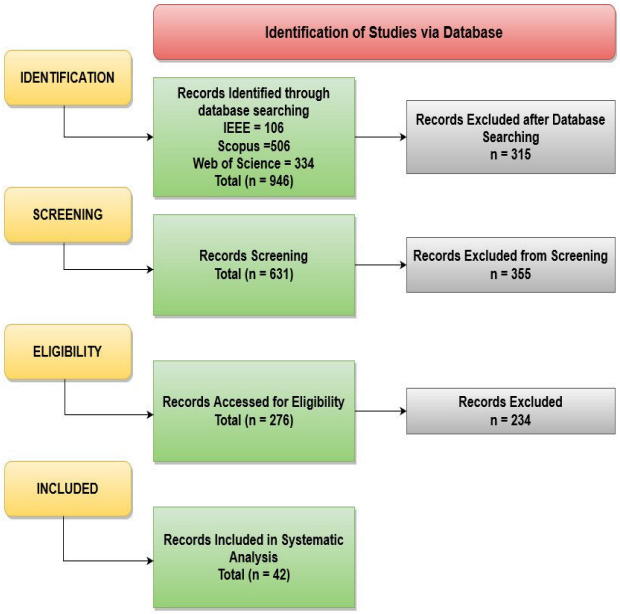

FIGURE 3. Systematic analysis of articles on AD using PRISMA.

PS: Based on published research, the ML models for AD identification exhibit various strengths and limitations, each accompanied by indicative numeric values. Support Vector Machines (SVM) are effective for small datasets, with an accuracy range of 70-80%, and provide interpretable results with noise robustness. Meanwhile, Random Forests excel at managing non-linear interactions and minimizing overfitting, although they are computationally costly for bigger datasets. With DL architectures, neural networks capture complicated associations with excellent accuracy of 85-90% but offer interpretability issues and are prone to overfitting with large datasets (5000 images). Figure 5 illustrates a brief overview of various AD detection techniques and models.

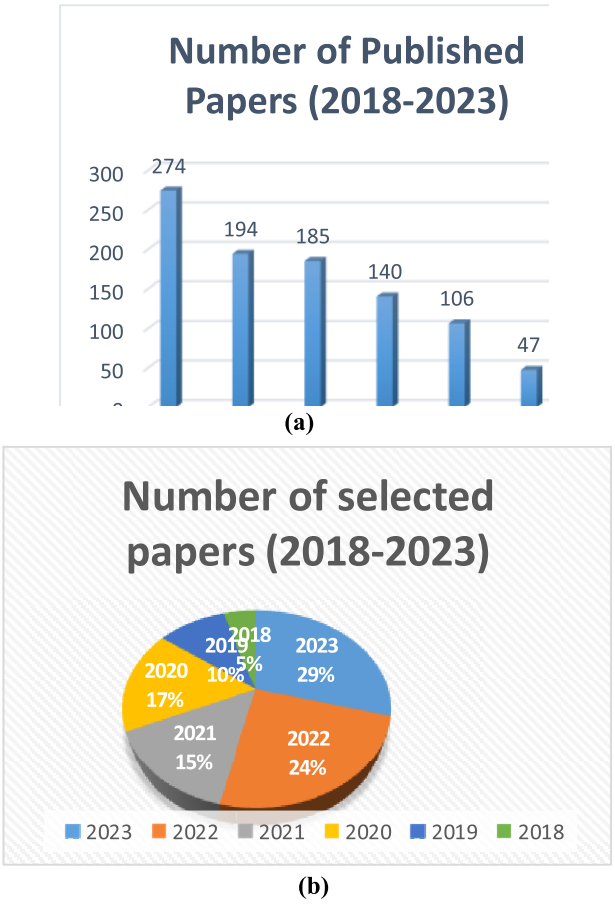

FIGURE 4. For the year (2018-2023) (a) Number of published papers, (b) Number of selected papers.

The suitability comparison highlights that SVM is best suited for smaller datasets, Random Forests for larger datasets along with scenarios requiring robustness to noise as well as non-linear relationships, and Neural Networks for high accuracy when computational resources and large datasets are available. Other considerations, such as combining different data modalities and employing good feature engineering, have a considerable impact on model performance across all three models. Beyond accuracy, evaluation parameters such as AUC, sensitivity, and specificity are critical for a thorough assessment of methods for AD detection. Furthermore, there is no universally superior model for AD detection, and the decision is influenced by a variety of contextual circumstances. It is proposed that distinct models be combined using ensemble learning to utilize their particular strengths and improve overall performance.

Investigation 2: What impact does integrating structural MRI, functional MRI, and genetic data have on the accuracy and robustness of AD detection models?

PS: The combination of structural MRI, genetic data and functional MRI improves the accuracy and robustness of AD detection. This technique takes advantage of the unique capabilities of each modality. Models provide increased accuracy, greater generalizability, and efficient feature selection by integrating various modalities, lowering the risk of overfitting fresh data. Fan et al. [45] used imaging along with genetic data to construct a prediction model for AD development, demonstrating the promise of multimodal techniques in improving diagnosis accuracy. In studies that combined structural and functional MRI, accuracy scores of up to 90%. Another example is the work of Zhang et al. [46], which used a multi-modal DL model for robust AD diagnosis. This model revealed the efficiency of combining multiple data sources for accurate and reliable AD detection, emphasizing the significance of a complete, multi-dimensional approach. Furthermore, the incorporation of genetic data is beneficial in identifying persons at risk for AD before symptoms occur, allowing for early intervention. Despite constraints like as data heterogeneity and computational complexity, this multidimensional technique has significant potential for AD diagnosis and care by offering a more comprehensive understanding of the disease.

Investigation 3: What prominent neuroimaging datasets are used to train and test GAN models specifically in the field of AD detection?

PS: Neuroimaging datasets are essential for training and testing GAN models for AD diagnosis since they create the groundwork for comprehending the complexities of brain pictures. Table 4 displays different datasets used for AD detection. Meanwhile, ADNI [1], [44], [46], and the Open Access Series of Imaging Studies (OASIS) [35], [36] stand out as significant contributors to advancing research in this domain.

Investigation 4: How does the strategic optimization of hyperparameters influence the convergence and generalization capabilities of DL models intended for AD-identifying biomarkers?

PS: The optimization of hyperparameters is vital in the construction of DL models for the discovery of AD biomarkers. Key Hyperparameters for Strategic Optimisation of DL Models for AD Detection are shown in Table 5.

Experimenting with different settings, including learning rates, regularisation terms, and batch sizes, is part of the strategic tuning of hyperparameters. The learning rate, in particular, determines the size of optimization steps and has a significant impact on how fast or slowly the model converges during training. An ideal learning rate is critical for preventing the model from converging too soon or too slowly, achieving a balance between rapid convergence and the capacity to capture complicated patterns in neuroimaging data. The proper hyperparameter setup is critical for effective learning from training data and reliable generalization to new, unknown data. Adequately fitting these hyperparameters improves the model's ability to adapt to the data distribution, resulting in a more accurate and reliable AD detection model. Figure 6 depicts the process of hyperparameter selection and model evaluation. Furthermore, regularisation terms, such as dropout rates, are critical in preventing overfitting, in which the model memorizes the training data rather than learning generalized patterns. Balancing these

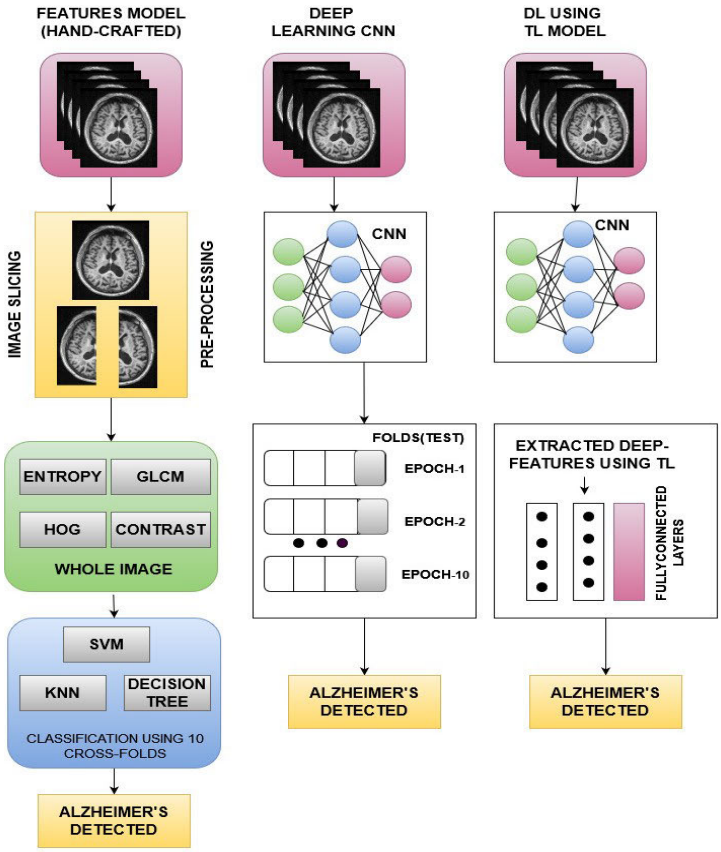

FIGURE 5. AD detection using various technique models.

TABLE 4. Datasets used in the detection of AD.

Dataset	Description	Modality	Datasets Used to Train the Model	Link
OASIS	MRI images of AD, diverse brain conditions	Structural MRI	[2], [18], [26], [31], [32], [35], [38]	OASIS
MRI	MRI images with a focus on brain tumor detection	Structural MRI	[5], [8], [14], [15], [17], [19], [21], [22], [24], [2], [35], [36], [37], [41], [42]	MRI
ADNI	Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset	Functional and Structural MRI, PET	[1], [4], [7], [16], [23], [27], [28], [29], [39], [40], [43], [44]	ADNI
GARD	Gwangju Alzheimer's and Related Dementia (GARD) dataset	Structural MRI	[6], [20], [25], [33], [34], [39]	GARD

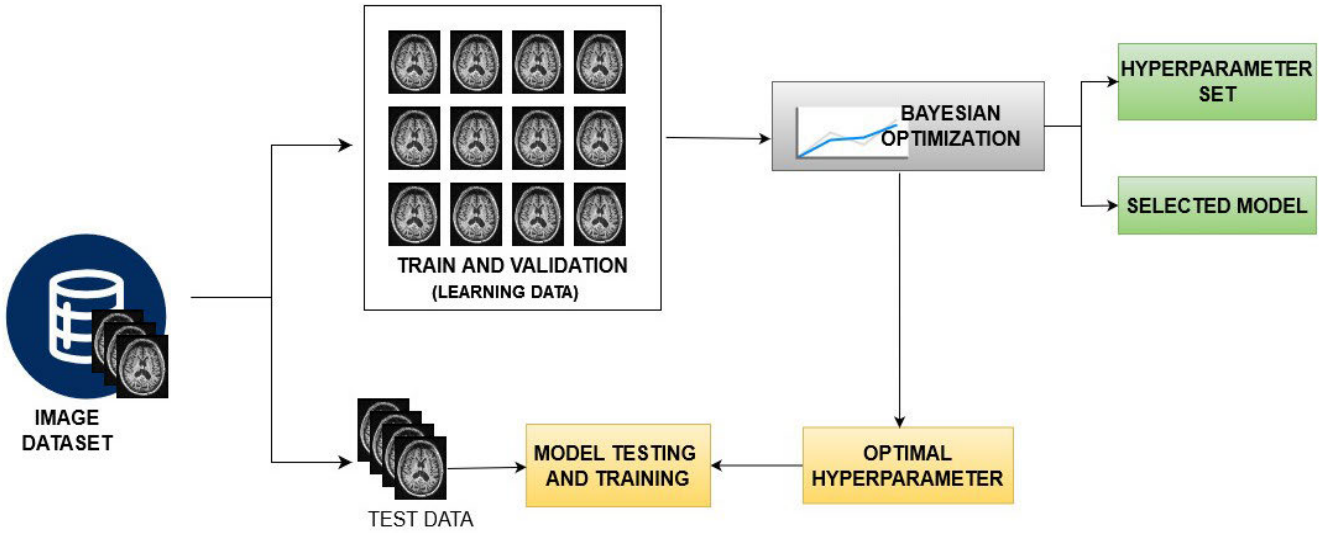

FIGURE 6. Hyperparameter selection along with the model evaluation process.

TABLE 5. Key Hyperparameters for strategic optimisation of DL models for AD detection.

Hyperparameter	Description	Impact
Batch Size	Number of samples propagated through the network per update	Larger batch size: faster but potentially worse generalization
Learning Rate	Controls size of update steps during training	Too small: slow convergence. Too large: unstable, miss optimum
Dropout Rate	Fraction of random units dropped during training	Higher: more regularization, prevents overfitting
Momentum	Acceleration of gradients in the right directions	Helps accelerate training and escape local minima
Early Stopping	Stop training when validation loss stops improving	Prevents overfitting, controls generalization
Weight Decay	The magnitude of L2 regularization on weights	Higher: increased regularization, prevents overfitting

regularisation terms ensures that the model stays strong and resilient, identifying significant biomarkers while being unaffected by noise or particular characteristics in the training data.

Investigation 5: What limitations are currently encountered by ML models in AD detection, and how can enhanced interpretability and standardized data elevate these challenges?

PS: Current ML models for AD identification have significant drawbacks that restrict their practical use. A significant problem stems from the black-box character of many models, particularly deep neural networks, which operate as opaque entities, making it difficult to understand the logic underlying their predictions. This lack of interpretability is a key barrier that jeopardizes confidence and complicates the smooth incorporation of these models into clinical decision-making procedures. Another major constraint is the potential of overfitting, which is especially dangerous in complicated models with high capacity. While these models have outstanding accuracy levels during training (ranging from 85-90%), their performance sometimes falters when applied to new patient groups, emphasizing real-world applicability issues. Furthermore, the availability of data heterogeneity in current datasets, resulting from differences in acquisition processes, picture quality, and preprocessing approaches, impedes model generalizability across varied populations and imaging centers. Additionally, the limited explainability of predictions, as well as the occurrence of errors in datasets, worsen the existing problems. Table 6. displays the conclusion for each investigation mentioned in this paper.

B. AD DETECTION USING ADD-NET: A CASE STUDY

Early identification of AD is crucial for advancing healthcare techniques. This section includes a case study on AD detection using the ADD-NET model.

This case study uses the ADNI-labeled dataset and 40 training epochs to demonstrate the ADD-Net model's efficiency in detecting AD from MRI images. Using stratified splitting, the dataset was divided into 65% for training, 15% for testing, and 20% for validation. The stratified division of the 2202 sample dataset divided the samples into 1431 training, 331 validation, and 440 testing samples. Class distribution across splits demonstrated consistent representation, which is essential for a reliable assessment of the model.

TABLE 6. List of mentioned investigations and the main conclusions to each of them.

Investigation	Research Question	Key Findings
1	Which ML models are most suitable for AD detection when employing neuroimaging data?	SVM, Random Forests, Neural Networks, and assembling distinct models are effective for small datasets, but computationally costly for larger ones, and overfitting can pose interpretability issues.
2	What impact does integrating structural MRI, functional MRI, and genetic data have on the accuracy and robustness of AD detection models?	The integration of structural, functional, and genetic MRI techniques enhances diagnosis accuracy and early intervention in Alzheimer's disease, with the potential for up to 90% accuracy.
3	What prominent neuroimaging datasets are used to train and test GAN models specifically in the field of AD detection?	The ADNI, OASIS, and GARD datasets are significant contributors to the training and testing of GAN models for AD diagnosis.
4	How does the strategic optimization of hyperparameters influence the convergence and generalization capabilities of DL models intended for AD-identifying biomarkers?	Key hyperparameters include batch size, learning rate, dropout rate, momentum, early stopping, and weight decay, which require strategic optimization for effective learning and reliable generalization to new data.
5	What limitations are currently encountered by ML models in AD detection, and how can enhanced interpretability and standardized data elevate these challenges?	Models, particularly deep neural networks, face issues like interpretability, overfitting, data heterogeneity, and limited explainability, affecting real-world applicability and exacerbated by existing problems.

Figure 7 depicts the design of the ADD-NET model, which uses a dataset separated into training, testing, and validation subsets created using SMOTETomek balancing. For model

TABLE 7. AD sample result analysis (65:15:20 approach) using the ADD-NET model.

METRIC	RESULT
Testing Accuracy	93.7%
Training Accuracy	94.8%
Validation Accuracy	92.9%
Precision	90.4%
Recall	90.3%
F1 score	91.2%

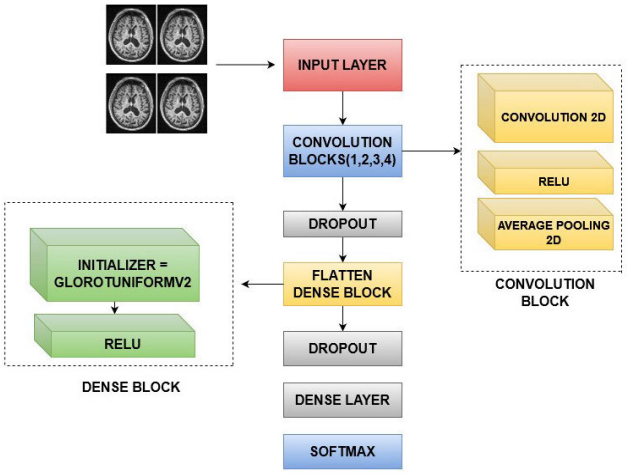

FIGURE 7. ADD-NET architecture for AD detection.

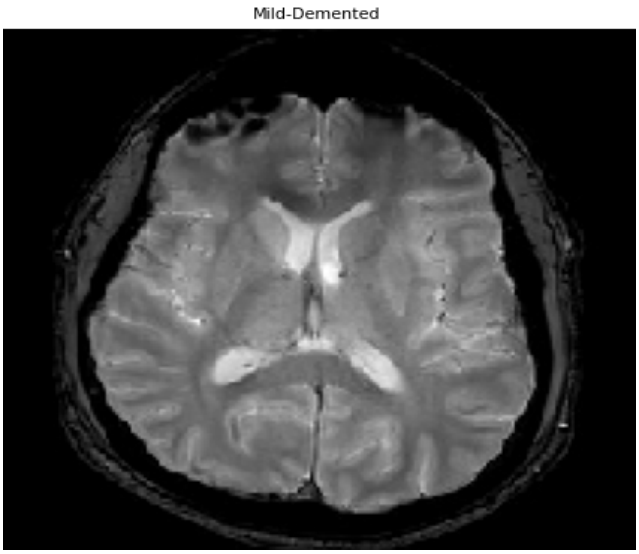

FIGURE 8. Predicted mild demented AD image using ADD-NET model.

analysis, images with dimensions of 1,000 × 800 pixels along with a learning rate of 0.01 were employed, with a batch size of 8 for each iteration. Its architecture includes a softmax output layer, dropout layers, average pooling, and convolutional layers using Rectified Linear Unit (ReLU) activations. Despite prioritizing efficiency, the model proved dependable, with a testing accuracy of 90.4%, 93.7% training accuracy, 92.9% validation accuracy, 90.4% Precision, 90.3% Recall,

TABLE 8. AD sample result analysis (cross-validation approach) using the ADD-NET model.

METRIC	RESULT
K-fold Cross-validation Accuracy Score (1-fold)	94.60%
K-fold Cross-validation Accuracy Score (2-fold)	93.58%
K-fold Cross-validation Accuracy Scores (3-fold)	93.58%
K-fold Cross-validation Accuracy Score (4-fold)	92.59%
K-fold Cross-validation Accuracy Score (5-fold)	94.33%
Average cross-validation Accuracy score	94.14%
Final test set accuracy	94.21%

TABLE 9. AD sample result analysis (cross-validation) using the ADD-NET model.

METRIC	RESULT
Accuracy	93.33%
Precision	91.32%
Recall	90.20%
F1 score	91.32%
Val Accuracy	93.85%
Val Precision	94.07%
Val Recall	90.6%
Val F1 score	91.69%

and 91.2% F1 score. Figure 8 depicts a sample anticipated outcome, while Table 7 presents full performance metrics.

The model's performance is further assessed using cross-validation, namely K-fold cross-validation concerning 5 folds, in addition to the traditional train-test split. This ensures robust assessment across various data partitions. The dataset is divided into five subsets using this procedure; each subset serves as a validation set, while the remaining folds are used for training. The validation set is rotated through each fold to fully assess the model's generalization ability. This method reduces biases and offers a thorough evaluation of the model's performance. Strong performance is demonstrated by the results, which show an average accuracy score of 94.14%. A final analysis of the test set results in a 94.21% test accuracy. Thorough performance metrics for distinct AD types provide useful insights into the model's capacity to discriminate between various disease stages, hence proving its dependability and efficacy in AD detection. Tables 8, 9, and 10 provide additional information into the model's performance metrics as well as its ability to diagnose AD from MRI images.

TABLE 10. Various AD types along with performance metrics (cross-validation) using the ADD-NET model.

AD Types	Precision	Recall	F1 Score
Mild-Demented	94.1%	92.2%	93.1%
Moderate Demented	90.3%	89.1%	91.4%
Non-Demented	92.1%	93.2%	94.3%
VeryMild-Demented	93.4%	90.1%	86.7%
Micro avg	92.2%	93.2%	91.3%
Macro avg	93.2%	92.2%	91.1%
Weighted avg	93.3%	93.3%	92.2%
Samples avg	93.2%	93.1%	93.2%

V. CONCLUSION AND FUTURE ASPECTS

Millions of individuals worldwide are impacted by AD which is the most common cause of dementia. It has a significant negative influence on people and their families, resulting in memory loss, cognitive decline, and a reduction in day-to-day functioning. The development of aberrant protein aggregates, such as tau tangles and beta-amyloid plaques, in the brain is a characteristic of AD. These pathogenic alterations result in memory loss and brain damage. The main goal of current AD treatments is to manage symptoms, and drugs like memantine and cholinesterase inhibitors are part of this arsenal. Important elements of treatment also include non-pharmacological measures including caregiver support and cognitive stimulation. This work first introduces the general overview of AD. Further, a systematic review has been conducted on AD, and PRISMA guidelines are followed for rigorous analysis. More than 946 articles were collected from this review process, and 42 were selected for the critical analysis. The synthesis of current knowledge highlights various methods and techniques of AD detection, and various investigations along with proposed solutions are discussed. One case study based on ADD-NET for AD detection is also included and achieved 93.7% training accuracy, 92.9% validation accuracy 93.7% testing accuracy, 90.4% Precision, 90.3% Recall, and 91.2% F1 score using 65:15:20 dataset split method. While 94.14% was the average accuracy score attained by employing the k-cross validation technique. The test set's final analysis yields a test accuracy of 94.21%. To improve early detection and patient care, AD diagnosis in the future is probably going to require a combination of personalized approaches, innovative technologies, and multidisciplinary efforts. To tackle the increasing global burden of AD, these advancements are necessary.

DATA AVAILABILITY

Source mentioned

FUNDING

This research received no external funding.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest regarding the present study.

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MEENU GUPTA (Senior Member, IEEE) received the Ph.D. degree in computer science and engineering with an emphasis on traffic accident severity problems from Ansal University, Gurgaon, India, in 2020. She has more than 15 years of teaching experience. She is currently an Associate Professor with the UIE-CSE Department, Chandigarh University, India. She has five edited and four authored books. She has also written over 20 book chapters and more than 150 papers in refereed international journals and conferences. She has five filled patents. Her research interests include computational techniques, intelligent systems, and data mining, with a specific interest in artificial intelligence, image processing and analysis, smart cities, data analysis, and human/brain machine interaction (BMI). She was awarded the Best Faculty of the Department and the Best Researcher Award, in 2021 and 2022, respectively. She chaired many conferences and was the Convener and the Organizer of IEEE and AIP conferences.

RAKESH KUMAR (Senior Member, IEEE) received the Ph.D. degree in computer science and engineering from Punjab Technical University, Jalandhar, in 2017. He has more than 18 years of teaching experience. He is currently a Professor with the UIE-CSE Department, Chandigarh University, India. He has published many authored books with the reputed publisher. He has authored or coauthored more than 100 publications in various national, international conferences, and international journals. His research interests include the IoT, machine learning, and natural language processing. He is a reviewer of several journals, including *Journal of Big Data*, *Computers, Materials and Continua*, *Scientific Reports*, and IEEE TRANSACTIONS ON SIGNAL PROCESSING. He chaired many conferences and was the Convener and the Organizer of IEEE and AIP conferences.

AJITH ABRAHAM (Senior Member, IEEE) received the B.Tech. degree in electrical and electronic engineering from the University of Calicut, in 1990, the M.Sc. degree from Nanyang Technological University, Singapore, in 1998, and the Ph.D. degree in computer science from Monash University, Melbourne, Australia, in 2001. He is currently the Pro-Vice Chancellor of Bennett University, New Delhi. Prior to this, he was the Dean of the Faculty of Computing and Mathematical Sciences, FLAME University, Pune, and the Founding Director of the Machine Intelligence Research Labs (MIR Labs), USA, a not-for-profit scientific network for innovation and research excellence connecting industry and academia. He also held two international university professorial appointments, such as, a Professor of artificial intelligence with Innopolis University, Russia, and the Yayasan Tun Ismail Mohamed Ali Professorial Chair of artificial intelligence With UCSI, Malaysia. He is involved in a multidisciplinary environment. He has authored/coauthored more than 1,400 research publications out of which there are more than 100 books covering various aspects of computer science. One of his books was translated into Japanese and a few other articles were translated into Russian and Chinese. He has more than 56,000 academic citations (H-Index of more than 111 as per Google Scholar). He has given more than 200 plenary lectures and conference tutorials (in more than 20 countries). He was the Chair of the IEEE Systems Man and Cybernetics Society Technical Committee on Soft Computing (which has over more than 200 members), from 2008 to 2021, and served as a Distinguished Lecturer for the IEEE Computer Society Representing Europe, from 2011 to 2013. He was the Editor-in-Chief of *Engineering Applications of Artificial Intelligence* (EAAI), from 2016 to 2021, and serves/served on the Editorial Board for over 15 international journals indexed by Thomson ISI.