Neural Computing and Applications (2020) 32:839–854
https://doi.org/10.1007/s00521-019-04069-0

INTELLIGENT BIOMEDICAL DATA ANALYSIS AND PROCESSING

Refining Parkinson's neurological disorder identification through deep transfer learning

Amina Naseer[1] · Monail Rani[1] · Saeeda Naz[1] · Muhammad Imran Razzak[2] · Muhammad Imran[3] · Guandong Xu[2]

Received: 12 November 2018 / Accepted: 28 January 2019 / Published online: 5 February 2019

Abstract
Parkinson's disease (PD), a multi-system neurodegenerative disorder which affects the brain slowly, is characterized by symptoms such as muscle stiffness, tremor in the limbs and impaired balance, all of which tend to worsen with the passage of time. Available treatments target its symptoms, aiming to improve the quality of life. However, automatic diagnosis at early stages is still a challenging medicine-related task to date, since a patient may have an identical behavior to that of a healthy individual at the very early stage of the disease. Parkinson's disease detection through handwriting data is a significant classification problem for identification of PD at the infancy stage. In this paper, a PD identification is realized with help of handwriting images that help as one of the earliest indicators for PD. For this purpose, we proposed a deep convolutional neural network classifier with transfer learning and data augmentation techniques to improve the identification. Two approaches like freeze and fine-tuning of transfer learning are investigated using ImageNet and MNIST dataset as source task independently. A trained network achieved 98.28% accuracy using fine-tuning-based approach using ImageNet and PaHaW dataset. Experimental results on benchmark dataset reveal that the proposed approach provides better detection of Parkinson's disease as compared to state-of-the-art work.

Keywords Parkinson disease · Handwriting analysis · Neurodegenerative disorder

1 Introduction

Walking into the bedroom, using technology gadgets, washing dishes, reading newspaper, writing or typing text, etc., all of these daily-based actions involve movement. We never noticed that how brain works, we never think twice about the certain action before performing it that goes into brain and makes the movement possible; however, some of us suffer this issue, i.e., movement disorder may be possible in case ones' process goes awry because something happens to brains deep parts basal ganglia and the substantia nigra and you lose control over the motor system. Deficiency results in change in speech and movement, depression and anxiety. Parkinson's disease is the best known movement disorder.

Worryingly the global prevalence of Parkinson's disease (PD) is increasing over time. Currently, about 1 million Americans and 10 million people worldwide suffer from Parkinson's, a progressive neurological disorder according to APDA (American Parkinson Disease Association) [1]. Famous patients-turned-advocates include Muhammad Ali, Michael J. Fox and Janet Reno. It is expected to double within the next 20 years (up to 2% and 6% in people over the age of 60 and 80 years, respectively). Currently, the cure for Parkinson disease is not available, and the therapies can only help to control motor symptoms by reversing the DA deficiency [2]. Furthermore, there is no single test for Parkinson's diagnosis, and moreover, there is no clear indication of what causes Parkinson, although physician

✉ Muhammad Imran Razzak
imran.razzak@ieee.org

Saeeda Naz
saeedanaz292@gmail.com

[1] Computer Science Department, Govt Girls Postgraduate College No.1, Abbottabad, Pakistan

[2] Advanced Analytics Institute, University of Technology, Sydney, NSW 2007, Australia

[3] Deanship of e-Transactions and Communication, King Saud University, Riyadh, Saudi Arabia

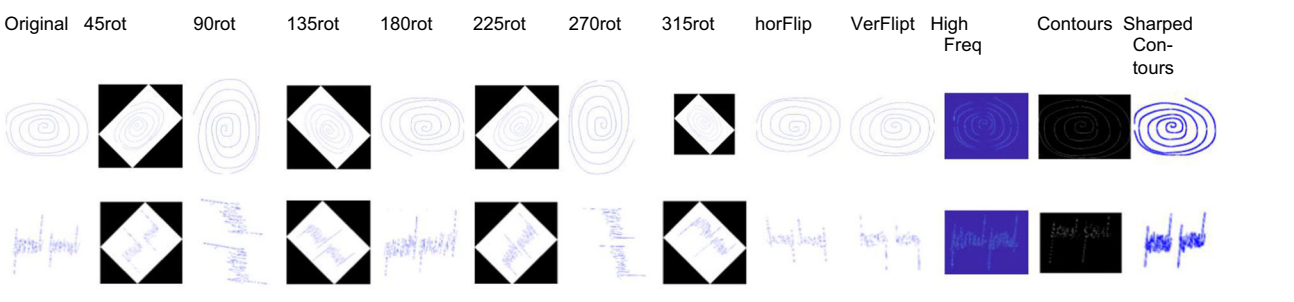
technically understand what happens with the patient. Unlike other disease diagnosis, genetic models even do not generate important cardinal features of PD [2, 3]. However, there are traditional approaches for diagnosis and investigation of PD which are invasive methods like computed tomography (CT) scan, MRI, X-rays, PET, SPECT ("single-photon emission computerized tomography")/DAT ("dopamine transporter") scan, ultrasound, etc., which are costly and can be effective when disease is spread over the brain. We require noninvasive and clinical screening test to diagnose PD at an early stage and assist the physician to cure and avoid the spreading of the Parkinson's disease in other cells of the brain (Tables 1, 2).

Recently, several machine-based systems have been proposed to identify the early symptoms of Parkinson's and similar neurological diseases, and different modes of input have been used such as voice, handwritten, speech patterns to observe subtle. Furthermore, muscular movements devices such as wearable sensors also have been used for PD identification. Among Parkinson's disease (PD) motor symptoms, freezing of gait (FOG) may be the most incapacitating. Aside from the primary motor symptoms, difficulties start to occur frequently in handwriting of patient, i.e., a major complaint of patients with PD is their inability to sign legibly. This phenomena is generally known as micrographia (abnormally small, cramped handwriting or the progression to progressively smaller handwriting) and considered as a biomarker for detection of Parkinson's disease, i.e., researches have revealed that about 63% of Parkinson's patients have suffered from micrographia [4]. It is the one the most commonly reported and easily detectable handwriting abnormality in patients with PD. However, micrographia is perhaps the tip of the iceberg representing the handwriting abnormalities in PD [5]. Studies have shown that there is a strong evidence of correlation between handwriting changes and problems in the nervous system [6–9]. The symptoms of handwriting impairment in Parkinson's patients are less handwriting speed, low pressure, velocity, less continuity as compared to healthy ones. Handwriting analysis is an efficient approach for detection of disease as compared to neurological testing and brain scanning as these methods are expensive and machinery dependent. There is no medication or cure available to stop the progression and spreading of Parkinson's disease. Though, it is possible to stop or decrease the PD at earlier or infancy stages. But at later stages, when the disease has gone to be worst, then an alternative solution is surgical treatment. However, for safety and curing the quality of patients brain cells, detection of Parkinson's disease at an earlier stage is necessary, but clinical diagnosis is expensive, leads to inaccurate results and inadequate services to patients.

Table 1 Summary of deep learning-based methods for Parkinson's disease prediction

Reference	Features	Method	Data description	Accuracy %
Pereira et al. [35, 36]	Pen-based features	CNN	Handwriting data	80.19
Pereira et al [35, 36]	Pen-based features	CNN	Handwriting data	90.38
Moetesum et al. [10]	Automated visual features	CNN	Handwriting data	83
Caliskan [27]	Automated	DNN	Voice data	93.79 and 68.05
Eskofier [32]	Automated	CNN	IMU Data	90.9
Choi [40]	Automated	CNN	SPECT images	90.7
Pereira [37]	Automated	CNN	Handwriting data (time series image)	93.50
Zhang [38]	Time frequency features	DNN with (KNN)	Speech dataset	90.53
Grover [39]	Voice features	DNN	Voice dataset	94.42 and 83.36%

Table 2 Augmentation



Over the period of time, a substantial number of studies based on handwriting have been presented and shown a product of perceptive, cognitive and fine motor skills that can also be employed as an effective tool for early diagnosis of PD [10–12]. Even though many clinical examinations as well as automatic diagnosis approaches PD have been proposed, it is still very important that we should exert more effort in automating its diagnosis efficiently. The paradigm-shifting results delivered by CNNs were in part accomplished with the help of extremely large training datasets, which are unrealistic Parkison's identification due to availability of small data size, and as a result, direct application of CNN could not be effective. In addition to the relatively small sample size, the other important limitation of most of the studies is focused on handcrafted features due to limitation of deep learning methods on small dataset; however, automatic extraction of features could help to increase the identification performance [13]. Deep learning methods have demonstrated tremendous success in a variety of applications in various fields [14–19]; however, it is data hungry approach and requires at least 10 times the degree of freedom that can often preclude the use of CNNs for applications where dataset can be challenging. In order to address the problem of limited training data, transfer learning could be used to tune the already grained storing knowledge on similar problem. To overcome these challenges, in this paper, we plan to investigate the extendability of the trained CNN classifier on ImageNet and MNIST via transfer learning on target dataset named as PaHaW dataset. The objective of this work is to perform an extensive experiment using convolutional neural network (CNN) and the concept of transfer learning due to limited and finite samples of PaHaW dataset collected from patients having PD and healthy persons, respectively. AlexNet is the relatively simple type of CNN architecture which has got great interest and success in different pattern recognition and classification tasks.

In the literature, AlexNet has been proven as an excellent deep leaner for various problems in different domains. Therefore, we explore the two common approaches of transfer leaning, i.e., freeze and fine-tuning. In each approach, we conduct two studies. The first study uses pre-trained AlexNet on ImageNet dataset (natural images) and second study implements AlexNet from scratch on MNIST dataset (handwriting digits) as a source task for extraction of features for transferring to the target task PaHaW dataset. Each study has series of experiments for investigation of ways of features extraction like AlexNet-freeze and AlexNet-fine-tune due to limited samples of PaHaW dataset in the next sections.

The key contributions of this study are:

- Development of early Parkinson's diagnosis using transfer learning and data augmentation techniques due to the limitation of handwritten data of Parkinson's patient.
- Find out the increase in the input raw samples using data augmentation and other prepossessing techniques which result in increasing the accuracy of deep CNN.
- Investigate how the visual patterns of natural images (ImageNet dataset) and handwritten digit images (MNIST dataset) can be beneficial in identification of PD.
- Explore how features learned from one large dataset using freeze features and fine-tuning approaches of transfer learning can improve the recognition in other domain.
- This study analyzes, evaluates and compares two different data sources for transfer learning for Parkinson's disease identification.

Rest of the paper is organized as follows. Section 2 presents the overview of related work regarding the deep and transferring-based approaches for PD's identification. Section 3 describes the proposed methodology for Parkinson's diagnosis. Section 4 details the experimental results in comparison with state-of-the-art work. Finally, conclusion and future directions are discussed in Sect. 5.

2 Related work

Ever since, difficulties in handwriting were first reported by James Parkinson in patients with the shaking palsy, described as "the hand failing to answer with exactness to the dictates of the will." Earliest identification was based on paper based handwritten text of selected patient with significant observable micrographia [20]. Since then, Parkinson's disease identification is an active area of research in the pattern recognition community for over 4 decades now. With the development of handheld devices and digitizing tablet, the collection of handwriting samples using digitizing tablets is easy, noninvasive and contains additional information (such as speed, pressure) that paper based does not.

Until now, machine learning-based approaches are considered as supportive and not substitutive of human in making the clinical decision. Unlike other machine learning applications, there are still some barriers to the complete translation in health industry. Recently, several attempts have been made to design decision support systems for differential diagnosis of PD in recent years. These include speech assessment [21–27], gait monitoring [28–32] or tremor assessment [33, 34]. There are several challenges involved in these methods, i.e., speech

assessment requires high-quality noise-free recording conditions; gait monitoring and tremor assessment require specialized equipment such as accelerometers or gyroscopes, whereas handwriting-based diagnosis of PD can be easily performed at clinic or even at patient's home and does not require any special equipment for data acquisition. Previous studies have proven that there is a significant difference between kinematics of PD patients and healthy controls. However, the extend to which any set of features could be useful in discriminating PD at early stage is still in progress.

Even though many automatic diagnosis approaches of PD have been proposed, it is still very important that we should exert more effort in automating its diagnosis efficiently. In order to overcome limitation of conventional models, the researchers moved toward deep learner in 2016. Pereira et al. [35] developed a handwriting dataset by capturing images during handwriting task and apply model on pen-based features like pressure, tilt and acceleration. Convolutional neural network (CNN) was applied with image resolution for classification and achieved overall test set accuracy of 80.19% using ImageNet while considering spiral data. In another work, Pereira et al. [36] applied CNN for identification of Parkinson's disease. Authors proposed metaheuristic-based techniques that is bat algorithm (BA), Firey algorithm (FA) and particle swarm optimization (PSO) in order to fine-tune CNN hyperparameters.

Handwriting dataset has been used for detection of Parkinson's disease. CNN gave the effective results on BA approach with overall accuracy of 90.38% for spiral data. Pereira et al. map signals extracted from handwriting dynamics into images. These time series images passed to convolutional neural network and achieved 93.50% accuracy using feature learned from CCN [37]. Zhang [38] applied stacked autoencoders and KNN classifier and employed the speech records and extract the time frequency features such as jitter, shimmer, voice pitch and obtained an accuracy 90.53%. Grover et al. [39] applied deep neural network using tensor flow library on voice dataset and yielded 83.36% accuracy on Motor UPDRS score and 94.42% accuracy on total UPDRS. Moetesum et al. [10] evaluated the visual attributes of handwriting for diagnosis of Parkinson's disease. Fusion techniques are applied in order to improve classification. For feature extraction applied, the convolutional neural network and extracted features are then classified by SVM. Proposed method effectively diagnosed the Parkinson's with 83% accuracy. Caliskan et al. [27] proposed deep neural network classifier for diagnosis of Parkinson's disease on two voice datasets, i.e., Oxford Parkinson's Disease Detection (OPD) and Parkinson Speech Dataset with Multiple Types of Sound Recordings (PSD). Authors compared results of deep and conventional models. DNN has the ability to extract hidden features so as to increase the classification performance. DNN classified the OPD and PSD datasets with effective accuracy of 93.79% and 68.05%, whereas SVM, decision tree and naive Bayes have accuracy of 85.780, 84.371, 69.64%. Eskofier et al. [32] performed the comparison of machine learning and deep learning techniques on IMU (inertial measurement unit sensor) data for detection of Parkinson's disease. CNN effectively classified data with accuracy of 90.0% as compared to AdaBoost.M1, PART and kNN with accuracy of 86.3, 67.1 and 85.6%, respectively. Choi et al. [40] developed an automatic deep learning-based FP CIT SPECT (I-fluoro propyl carbomethoxy iodophenyltropane single-photon emission computed tomography) interpretation system for diagnosis of Parkinson's disease through images. They applied deep CCN for classification, and the proposed method has effectively diagnosed the Parkinson's with accuracy of 90.7%. Afonso et al. [41] used the different CNN architecture (ImageNet, CIFAR-10, LeNet) for classifying the recurrence plot images evaluated from signals of menders and spiral data. By using recursive approach, they have achieved the recognition rate above to 90%. Gupta et al. [42] proposed an optimized cuttlefish algorithm (OCFA) for feature selection and evaluated it on Parkinson speech with multiple types of sound recordings and Parkinson Handwriting samples datasets. Decision tree and *k*-nearest neighbor classifier were used on OCFA-selected feature that diagnose the Parkinson's disease with an accuracy of 94% approximately. Pereira et al. applied OCSA (optimal crow search algorithm) for feature selection from handwriting dataset and proposed random forest, decision tree, *k*-nearest neighbor classifier which gave the 100% prediction rate on OCSA-selected features [43].

Not only handwritten text, but also Archimedean spiral drawing test and shape modifications have also been used for Parkinson's diagnosis [28, 44–47]. Deviations from original sample (like loop tightness and width variability, drawing speed and acceleration, frequency and amplitude of oscillations and spiral pressure, etc.) are considered as symptomatic indicators of a disorder. Drotar et al. presented a template consisting of seven different handwriting tasks in addition to conventional spiral drawing task and suggested that the choice of template has significant impact on the performance of the proposed features [48].

The current systems are able to achieve about 90% accuracy. However, the unavailability of Parkinson's patient handwriting datasets and complexity of designing features are the major impediments preventing the research community from mastering this task. On the other hand, recently deep learning approaches showed tremendous performance to deal such complex task by automatic learning of features as they learn features from raw data to

a representation that best describe the data. Deep learning is good to learn visual features from any type of huge data without knowing which feature is important. Deep learning-based techniques, however, do not perform well on small datasets. It is a greedy technique. ImageNet dataset is extensively used for the purpose of transfer learning for many image classification applications due to its large size. However, Parkinson's disease dataset consists of handwritten samples, and thus, MNIST could be the powerful source for transfer learning as compared to ImageNet. Therefore, in this paper, we are considering MNIST dataset as source dataset for features extraction and later compared with results achieved by networks using ImageNet dataset as a source.

3 Deep transfer learning-based Parkinson identification system

In this section, we demonstrate our proposed system using concepts of data augmentation, transfer learning and deep learning on handwriting sample images of Parkinson's patient. Even though, several automatic diagnosis methods for PD have been introduced, still it is very important to exert more effort in automating its diagnosis efficiently. The paradigm-shifting results delivered by CNNs were in part accomplished with the help of extremely large training datasets; however, we do not have enough data of Parkinson's patient. Thus, direct application of CNN could not be effective on hundreds of images gathered by patients. To cope with this challenge, one way is the data augmentation. Number of CNN-based networks is trained to investigate the potential of using the pre-trained CNN classifier on ImageNet and MNIST to learn features and then transfer the model on Parkinson's handwritten data. We have divided the proposed methodology into three steps, i.e., data preprocessing and data augmentation, CNN-based features extraction and identification.

Figure 1 shows the general overview of the proposed automated PD detection system using AlexNet with fine-tune architecture and freeze architecture for transfer learning.

3.1 Data preprocessing and data augmentation

Preprocessing is a key step in pattern recognition and machine learning. Different techniques like binarization, transformation, image enhancement, sampling, normalization, data augmentation or noise removal, etc., are the main techniques of preprocessing step that apply on raw data. As CNN directly works on raw data, it needs to be refined before training to reduce the variations and noisy pattern. We conducted studies using PaHaw dataset having handwritten text written by PD's patients and healthy person. The original dataset has number of online attributes like x, y coordinates, pen status (touching surface of paper or not), pressure, etc. We first plot the image using this information as shown in Fig. 2a. The handwritten text consists of several irrelevant information that could affect the accuracy of diagnosis, i.e., PaHaW data contain values of in-air as well as on surface movement. We have removed the in-air movement values from images. Figure 2b depicts the removal of in-air movement. We can observe from the data that the handwritten text consists of extensive amount of noise; thus, we have removed the noise from data first by applying filters such as median filter followed by transferring it into gray scale.

Deep neural networks need large number of instances of images for training the networks; however, in our case, we

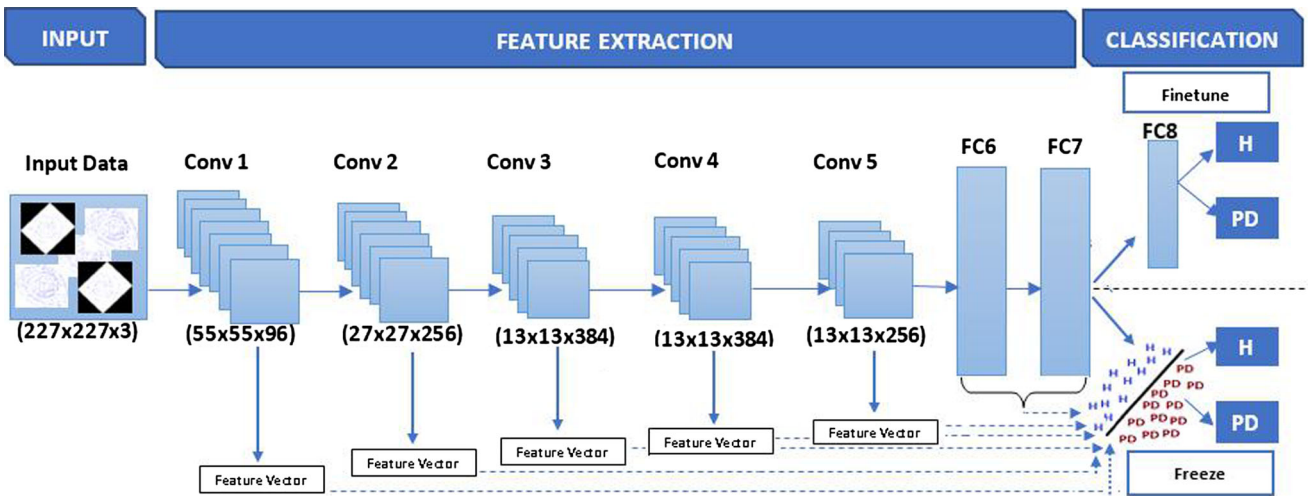


Fig. 1 Overview of proposed system for Parkinson's disease detection using AlexNet-fine-tune and AlexNet-freeze

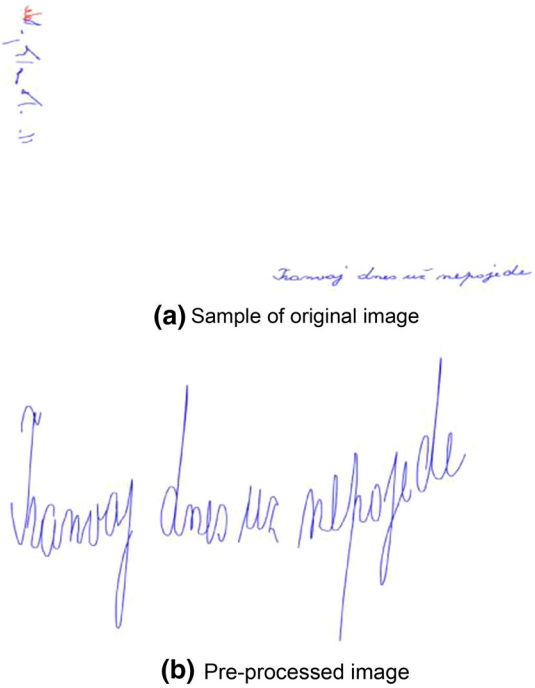


Fig. 2 Removal of irrelevant information and white region

do not have enough data of Parkinson's patient. Thus, direct application of CNN could not be effective on hundreds of collected images of Parkinson's patients. To cope with this challenge, one way is the data augmentation that can significantly improve the performance of deep neural networks. Therefore, we have applied several data augmentation techniques (rotations, flipping and contours) to increase the PaHaW training dataset for providing large input space to CNN. In order to reduce over-fitting and increase generalization of network, we deployed data augmentation to collect variety of visual patterns of input raw images as in our case we have small number of handwritten samples from Parkinson's patients. The basic data augmentation techniques applied in this study are rotation and flipping. The input images are rotated on various angles like angle of 45, 90, 135, 180, 225, 270, 315 and 360. Likewise, input images are horizontally and vertically flipped. As a result, we got ten variations of one original image using basic techniques of data augmentation. For useful and effective extraction of visual patterns, other techniques are also used for increasing the size. Besides basic data augmentation techniques, we also created contours, high frequency, sharpness of image for expanding the size of dataset. Contours are a single unit thickness of a pattern which helps in good features extraction. Contours are computed in the handwritten domains for the effective results. Thus, we computed the contour using $C(x, y) = 255$ Image(x, y).

High frequency is computed with the aid of discrete Fourier transform or DFT. The foundation of the product is the fast Fourier transform (FFT), a method for computing the DFT with reduced execution time. For the input sequence 'x' and its transformed version 'X' (the discrete-time Fourier transform at equally spaced frequencies around the unit circle), the two functions implement the relationships:

$$X(k+1) = \sum_{n=0}^{N-1} x(n+1) W_N^{kn} \tag{1}$$

and

$$x(n+1) = \sum_{k=0}^{N_1-1} NX(k+1) W_N^{kn} \tag{2}$$

At final step, we use unsharp masking in order to sharp the original image. The sharp image is generated by simply subtracting the image from blurred version of itself as $S_{\text{hp}}(x, y) = \text{Image}(x, y)\ \text{Image}_{\text{lp}}(x, y)$, where hp is the high-pass filter and lp is the low-pass filter. The size "N" of PaHaW dataset has increased to "13 × N" augmented dataset.

In order to train AlexNet on MNIST (base task) from scratch, we have performed other preprocessing approaches like resizing and channelization of digit images. As an image of MNIST dataset has 28 × 28 dimension we have to re-size it on 224 × 224 dimension according to AlexNet architecture and have to convert from 2D into 3D. It means that we converted gray scale (1 channel) images to RGB (3 channel image) for scratch training of AlexNet architecture and then we can use the visual patterns extracted from digits automatically by CNN and transfer to our augmented target task (PaHaW dataset) in classification and identification step.

In next section, the approaches of transfer learning like AlexNet-freeze and AlexNet-fine-tune are deployed for features extraction from source datasets, i.e., ImageNet and MNIST datasets.

3.2 CNN-based features extraction

The convolutional neural networks (CNN) are biologically inspired variants of multilayer perceptrons (MLPs) that perform machine learning tasks without requiring any handcrafted feature to be engineered and supplied by the user. Recently, they have gained considerable commercial interest due to the development of new variants of CNNs and showed promising performance by advocating the superiority over traditional machine learning algorithms. The main power of a CNN lies in its deep architecture, which allows for extracting a set of discriminating visual features at multiple levels of abstraction. They have

Table 3 Dimensions of features vectors

Conv1	Conv2	Conv3	Conv4	Conv5	fc6	fc7	fc6 + fc7
290,400	186,624	64,896	64,896	43,264	4096	4096	8192

different kinds of layers, and each layer works different than the other for extraction of visual features. However, one of the biggest limitations is the unavailability of larger and labeled good-quality data. The availability of large datasets is rare in the field of healthcare, as data in health industry are very sensitive, expensive confidential and very hard to collect.

Due to insufficient amount of training data, we have implemented pre-trained AlexNet architecture of CNN [49] for extraction of features. In the literature, this technique is known as transfer learning. The visual features are extracted in two ways, i.e., a pre-trained AlexNet with freeze or fixed approach and pre-trained AlexNet with fine-tune approach. Previous studies have clearly demonstrated that the selection of the source task has a great impact on the performance of CNN on the target task. Recently, ImageNet has been adopted as source for Parkinson's diagnosis [10]. However, MNIST dataset has not been explored for features extractions in transfer learning domain for PD identification in the literature. It can provide better performance due to its relevance to the data of PD dataset as both datasets have handwritten text samples.

We deployed the 25-layered deep convolutional neural Network for features extraction and then transfer these features to learn visual patterns from handwriting samples of PaHaW dataset for identification of PD using SVM classifier. AlexNet architecture consists of five convolution layers, max-pooling layers, dropout layers and three fully connected layers. The output of fully connected layer is pass to 1000-way which yields a distribution across 1000 class labels. First convolutional layer filters the $227 \times 227 \times 3$ input images with 96 kernels that have size $11 \times 11 \times 3$ with 4 pixels stride. Second convolutional layer takes the output of first layer (response-normalized and pooled) as an input and filters it with 256 kernels of $5 \times 5 \times 48$ size. Others convolutional layers are connected to each others without any intermediate pooling or normalization layers. Third layer has 384 kernels having $3 \times 3 \times 256$ connected to the normalized and pooled output of second layer, whereas fourth layer contains 384 kernels of size $3 \times 3 \times 192$ and fifth layer has 256 kernels of size $3 \times 3 \times 192$. Fully connected layers contain 4096 neurons each as shown in Table 3. The convolutional layers have more general weights and features which become more specific on fully connected layers. The details of AlexNet architecture deployed in our experiments are depicted in Table 4.

The network constructs a hierarchical representation of input images. Deeper layers include higher level features, constructed using the lower level features of earlier layers. Together, the convolutional and down-sampling layers serve as feature extractors, while the fully connected layers represent a trainable classier similar to a standard multi-layer neural network. In this paper, we conducted two studies having two different source datasets. One study explored the effect of visual patterns from ImageNet, and another study was carried out to investigate the impact of visual patterns extracted from MNIST dataset as the source tasks. The source tasks is that the ImageNet dataset consists of 1.2 million images (1000 different classes) in one study and MNIST consists of 0.6 million images (with 10 different classes) in another study for extraction of visual features. The target task is PaHaW dataset having 598 images (75 subject and 2 target classes) for identification of PD. These studies for AlexNet-based feature learning, i.e., reusing freeze or fixed features-based approach and fine-tuning the features-based approach, are demonstrated in the following subsections.

3.2.1 Reusing fixed or freeze features

We use the weights derived from training the network on the source task (ImageNet and MNIST datasets) and using the outputs from the intermediate hidden layer (like edges and blobs) as features for training a linear classifier on the data of target task (PaHaW dataset). This is called reusing freezing or fixed approach of transfer learning. We have convolutional (conv) and fully connected (fc) layers from which the features can be derived. The layers are named as conv1, conv2, conv3, conv4, conv5, fc6 and fc7 in AlexNet's architecture, respectively.

In this study, we performed series of experiments in order to select which layer extracts the best features for our target dataset using two different source datasets. The different layers of AlexNet are treated as fixed feature vectors extracted using ImageNet or MNIST database independently and then fed to another linear classifier for classification and identification of PD using PaHaW dataset. We conducted number of experiments to explore which layer outperforms in the extraction of features as compared to other. We employed transfer learning by extracting features from different layers like conv1–conv5, fc6, fc7 and fusion of fc6 + fc7 of the architecture of AlexNet and then fed these features to a dedicated linear classifier, i.e., SVM for classification as depicted in Fig. 1. The deeper we

go into the model, the more minute and smaller details of an image the weights represent. Thus, conv1–conv5 show higher level and generic representation of source dataset's images (like edge, blob, etc.), while outputs of fc7 represent a more detailed and specific features of the images of source dataset.

3.2.2 Fine-tuned features

This technique works by transferring the weights of the pre-trained model using two source datasets (ImageNet or MNIST) to a network using target dataset (PaHaW). The only exception is the replacement of last fully connected layer of the pre-trained network with new network's fully connected layer. The new last layer has the same number neuron as of the target classes of the target dataset or task. This is called fine-tuning approach of transfer learning.

By implementing these techniques, we conducted two studies. First, we have employed pre-trained AlexNet for feature extraction using ImageNet dataset (source task) and then replaced the last fully connected layer having 1000 neurons from ImageNet with fully connected layer consisting of two numbers of neurons from PaHaW dataset (target task).

In second study, experiment was carried out using MNIST dataset as a source task and PaHaW dataset as target task. As the last layers of pre-trained AlexNet are configured for 1000 classes of ImageNet dataset, we have to replace and fine-tune the last fully connected layer of AlexNet architecture to our new problem. We have set the fully connected layer to two classes in our new dataset, i.e., Parkinson's disease (PD) or healthy (H) for classification and identification purpose as shown in Fig. 1.

3.3 Classification and identification

Once the AlexNet is trained for Parkinson Disease (PD) learning and classification, then unseen PD and healthy (H) image(s) in the test set are fed to trained network for identification. The maximum number of epochs is 30. The training network takes 148 iterations per one epoch, and total iterations for whole training are 4440. The values of momentum, L2 regularization, initial learn rate and batch size are 0.9, 0.0005, 0.0001 and 7. Total elapsed time is taken up to 10 min and 34 s for training a network on fine-tuned-based features using ImageNet dataset for PD identification from PaHaW dataset.

The highest recognition rate (98.28%) achieved on spiral pattern using AlexNet-fine-tune-ImageNet approach of transfer learning as depicted in Fig. 3. In the subsequent section, a detailed experimental analysis for parameters, patterns and comparative analysis are given with the existing PD identification system in the literature.

4 Experimental design, analysis of results and discussion

This section aims at presenting the experimental designs and results analysis concerning the CNN-based approach for Parkinson's disease identification. We evaluate the different parameters for getting the best values of parameters for our experiment, evaluate the CNN networks on different patterns and different approaches (freeze and fine-tune) of transfer learning using ImageNet and MNIST datasets and compare our approach with other state-of-the-art methods [10, 35, 36].

4.1 Study subjects

We used PaHaW (Parkinson's disease handwriting) database to evaluate our proposed studies. It includes the handwriting samples of 37 Parkinson's patients and 38 healthy subjects collected by Droter [48] using digitized tablets. The mean UPDRS-Part V score for PD patients is 2.27 0.84. Each participants were asked to perform total eight handwriting tasks, but some participants did not complete their task according to given sample; hence, we have excluded their samples. After exclusion, we have 576 samples from 72 (36 PD and 36 control) subjects. The PaHaW is collected using digitizing tablet; thus it consists of various online attributes such as the (x, y) coordinates of the pen trajectory as well as the pen status (whether touching the writing surface or in air) rather than images. We have generated images of the drawing by plotting the normalized (x, y) coordinates corresponding to all positions where the pen is touching the writing surface.

The idea of capturing more information from different samples produced by the same subject was the prime incentive for using PaHaW, i.e., dataset consists of different tasks (task1–task8) performed by same subject. First task contains spiral drawings [50, 51] because it is a continuous handwriting sample and it is most suitable for evaluation of movement disorder. Another task includes the repeated cursive letter "l" and simple words and a complete sentence. An example of samples of dataset is shown in Fig. 4. Description and statistics of dataset are illustrated in Table 5. The PaHaW dataset is distributed in training and testing set for performance of our proposed methodology.

4.2 Experimental results

AlexNet is trained by varying the options of training parameters to get highest accuracy by training number of networks for our dataset using single graphics processor unit (GPU). We used the implementations provided by the

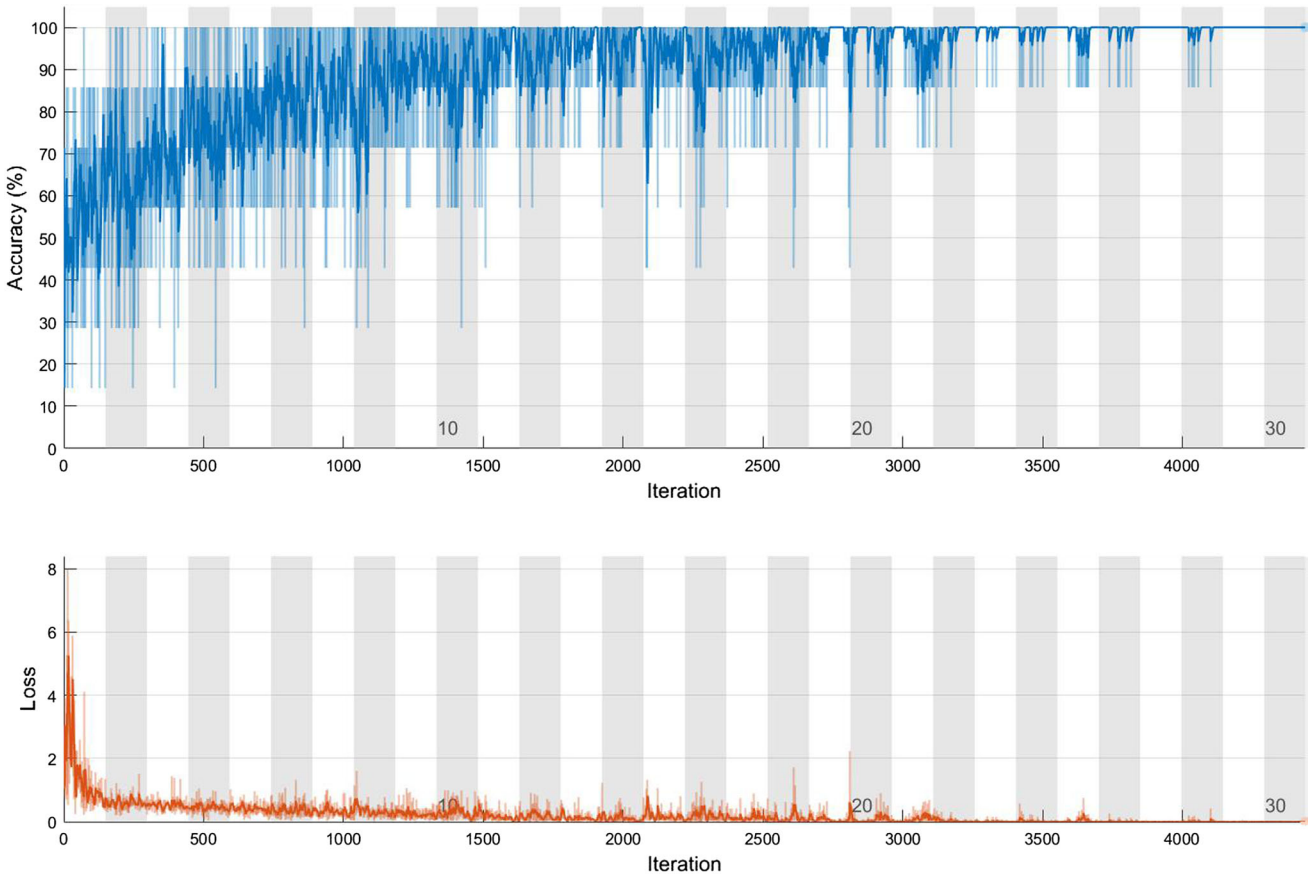


Fig. 3 Training progress and error rate of the proposed system for Parkinson's disease detection using AlexNet-fine-tune-ImageNet approach

Table 4 Detailed AlexNet architecture used in our experiments

Layer	Type	Input	Filter and Size	Stride	Output
Data	Input data	227 × 227 × 3	–	–	3 × 227 × 227
Conv1	Convolution	227 × 227 × 3	11 × 11 and 96	4	55 × 55 × 96
pool1	Max pooling	55 × 55 × 96	3 × 3	2	96 × 27 × 27
Conv2	Convolution	27 × 27 × 96	5 × 5 and 256	2	27 × 27 × 256
pool2	Max pooling	27 × 27 × 256	3 × 3	2	256 × 13 × 13
Conv3	Convolution	13 × 13 × 256	3 × 3 and 384	1	13 × 13 × 384
Conv4	Convolution	13 × 13 × 384	3 × 3 and 384	1	13 × 13 × 384
Conv5	Convolution	13 × 13 × 384	3 × 3 and 256	1	13 × 13 × 256
pool5	Max pooling	13 × 13 × 256	3 × 3	2	256 × 6 × 6
Fc6	Fully connected	6 × 6 × 256	6 × 6 and	–	4096 × 1
Fc7	Fully connected	4096 × 1	1 × 1 and	–	4096 × 1
Fc8	Fully connected	4096 × 1	1 × 1 and	–	2 × 1
Output	Fully connected	2 × 1	–	–	2 × 1

well-known Caffe library7, which is developed under a general-purpose computing on graphics processor units using single GPU having multiple processors of 2.80 GHz and 2.81 GHz. Default parameters are 0.9 momentum, 128 batch size, 0.0005 L2 regularization, 30 epochs, positive scalar for initial learning rate, 10 learn rate drop period and 0.1 learn rate drop factor. We have conducted number of experiments for evaluation of proposed CNN-based system's performance. We kept all default parameters and evaluate the performance of proposed fine-tuned features-based system by changing the values of the momentum, initial learn rate, L2 regularization and batch size. The best network achieved 0.9 momentum, 0.0005 L2 regularization, 0.0001 initial rate and 7 batch size and got best results

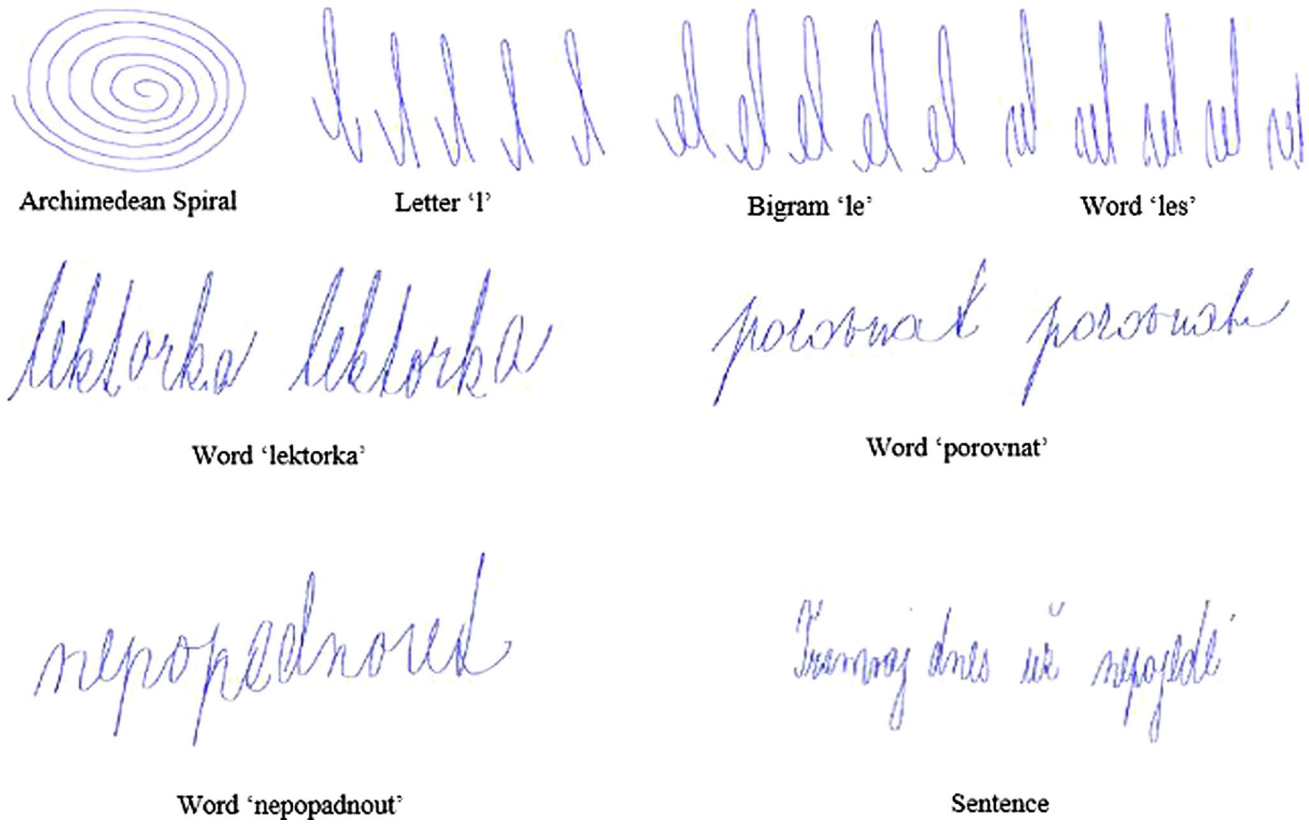


Fig. 4 An example of samples of PaHaW dataset

Table 5 PaHaW dataset description

Task	Samples	PD	Healthy	Instances
1	Archimedean Spiral	36	36	72
2	Letter ^{0}l^{0}	37	38	75
3	Bigram ^{0}le^{0}	37	38	75
4	Word ^{0}les^{0}	37	38	75
5	Word ^{0}lektorka^{0}	37	38	75
6	Word ^{0} porovnat^{0}	37	38	75
7	Word ^{0}nepopadnout^{0}	37	38	75
8	Sentence	37	38	75

up to 98.28%. The best parameter values in our study are shown in Table 6.

As discussed in earlier section, in this paper, two transfer learning techniques (freeze and fine-tuned) are carried out using augmented PaHaW dataset [35] consisting of eight handwritten patterns collected by Parkinson patients and healthy subjects. We have divided the dataset into training set that consists of 90% of samples and testing dataset that consists of 10% samples.

To explore the performance of freeze-based transfer learning, first we explore the performance of AlexNet on different patterns and combined data of PaHaW dataset. Series of eighteen experiments were conducted by fixing conv5 layer using AlexNet-freeze-ImageNet features and AlexNet-freeze-MNIST features, respectively. In the first nine experiments, we investigated and evaluated each and every pattern of PaHaW dataset independently using AlexNet-freeze by fixing the conv5 layer on ImageNet dataset and then other nine series of experiments were performed on AlexNet-freeze (conv5) using MNIST dataset. In Table 7, performance of each pattern of PaHaW dataset using fixed conv5 is further demonstrated and compared with both features. Results show that using AlexNet-freeze-ImageNet, the pattern of spiral drawing (pattern-1) has the highest recognition rate as compared to other patterns. Next higher identification rate is 89.29% on two short words (pattern-6) and 79.49% on two-letter word (pattern-3). Similarly, the results are 76.72%, 72.32%, 73.21% and 78.99% for patterns-2, patterns-5, patterns-4 and pattern-7, respectively. The proposed pre-trained AlexNet-freeze-ImageNet network gave 77.48% recognition rate on full sentence (pattern 8), whereas it provided 84.19% identification rate on combined patterns. The evaluation of each pattern using AlexNet-freeze-MNIST features is demonstrated in Table 7. Result shows that pattern of spiral drawing (pattern-1) provided the highest recognition rate of 94.97% as compared to other patterns

Table 6 Parameters values for fine-tune training the network by using features extracted by CNN

Parameters	Values													
Momentum	0.9	0.7	0.7	0.7	0.7	0.8	0.9	0.9	0.9	0.9	0.9	0.9	**0.9**	0.9
L2 Regularization	0.0005	0.00005	0.0005	0.0005	0.00005	0.005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	**0.0005**	0.0005
Initial Learn Rate	0.001	0.001	0.0001	0.0001	0.0001	0.1	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	**0.0001**	0.0001
Batch Size	128	128	128	7	128	100	255	200	128	100	64	32	**7**	1
Time (min:sec)	7:23	7:41	7:35	11:38	7:39	7:31	7:53	7:25	7:48	7:31	7:39	7:43	**10:54**	32.10
Accuracy (%)	51.72	65.52	73.28	79.31	53.45	46	92.24	92.24	95.60	95.69	93.10	93.10	**98.28**	50

Bold values show optimum result

and the next higher identification rate achieved on sentence (pattern-8) is 86.49% and 86.32% on two-letter word (pattern-3) and similarly 86.21%, 77.68%, 81.25% and 83.19% for patterns-2, patterns-4, patterns-5 and pattern-7, respectively. The proposed pre-trained AlexNet-freeze-MNIST network provided 68.75% recognition rate on two short words (pattern 6) and overall classification 77.28% on all patterns.

In the second technique (Fine-tuned) of transfer learning, we have also trained eighteen networks using AlexNet-fine-tune features for different patterns of PaHaW dataset. We conducted two studies to explore either which pattern or combined data show the best performance based on AlexNet-fine-tune features from sources, i.e., ImageNet, MNIST datasets or independently (in last two columns of Table 7). The networks showed promising accuracy for spiral drawing of pattern-1 using fine-tuned features from ImageNet (98.28%) and MNIST (80.17%) as compared to other patterns. The performance of networks is not satisfactory on combined data of all patterns as 84.10% was achieved by network-trained AlexNet-fine-tune-ImageNet features and 77.28% accuracy by network trained on MNIST dataset using fine-tuning approach.

We can conclude from the above discussion that accuracy differs for different patterns using AlexNet-freeze-ImageNet, AlexNet-freeze-MNIST, AlexNet-fine-tune-ImageNet and AlexNet-fine-tune-MNIST features. Notice that, all features provided promising result on spiral pattern as compared to others. Spiral images are informative in case of Parkinson's disease detection, so we conducted further experiments on spiral pattern. Table 8 depicts the average of ten runs for Parkinson's disease identification rate for the series of experiments having fixed features of conv1–conv5, fc6, fc7, fusion of fc6 and fc7 and fine-tuned features using ImageNet dataset as source task and spiral pattern of PaHaW dataset as target task. 93.10%, 93.97%, 94.83%, 96.69% and 98.28% accuracy was achieved using conv5, fc6, fc7, fc6 + fc7 and fine-tuned based features using ImageNet and PaHaW dataset (spiral), respectively. Table 9 also shows the precision, sensitivity and specificity as the evaluation matrices for these experiments.

In case of reusing fixed features case, it is concluded from series of experiments that highest accuracy 96.69% is achieved on learned features from fusion of fc6 and fc7 using ImageNet dataset. The results are less in other experiments having fixed features of fc7, fc6 and conv1–conv5, as shown in Tables 8 and 9. Similarly, AlexNet-freeze-based features achieved 94.97%, 91.38%, 90.52% and 92.24% accuracy on MNIST using conv5, fc6, fc7 and fc6 + fc7, respectively, as shown in Tables 8 and 10. The highest results up to 94.97% were achieved using AlexNet-freeze-MNIST at conv5 layer, while AlexNet-fine-tune-

Table 7 Results on each pattern using AlexNet-freeze-ImageNet features, AlexNet-freeze-MNIST, AlexNet-fine-tune-ImageNet and AlexNet-fine-tune-MNIST on augmented PaHaW dataset

Pattern	Samples	ImageNet conv5 fixed features-based accuracy (%)	MNIST conv5 fixed features-based accuracy (%)	Fine-tuned-ImageNet	Fine-tuned-MNIST
Pattern-1	Spiral	**93.10**	**94.97**	**98.28**	**80.17**
Pattern-2	Letter	76.72	86.21	91.38	70.69
Pattern-3	Two-letter word	79.49	86.32	96.58	71.79
Pattern-4	Three-letter word	73.21	77.68	75.89	63.39
Pattern-5	Short word	72.32	81.25	83.93	59.82
Pattern-6	Two short words	89.29	68.75	75.00	62.50
Pattern-7	Long words	78.99	83.19	83.19	68.91
Pattern-8	Sentence	77.48	86.49	54.95	50.45
All patterns	All samples	87.05	74.53	84.19	77.28

Bold values show optimum result

Table 8 Parkinson's disease identification (ImageNet-PaHaW and MNIST-PaHaW)) using different architecture of AlexNet: reusing freeze layers and fine-tune approaches of transfer learning on pattern-1

	Accuracy %	
Experiment	ImageNet	MNIST
conv1	49.14	50.00
conv2	45.69	74.14
conv3	54.31	93.62
conv4	62.07	92.76
conv5	93.10	**94.97**
fc6	93.97	91.38
fc7	94.83	90.52
fc6 + fc7	**96.69**	92.24
Fine-tuning	**98.28**	80.17

Bold values show optimum result

Table 9 Performance evaluation of Parkinson's disease identification using different fixed layers in freeze approach and fine-tuning approach of transfer learning using ImageNet and PaHaW datasets

Experiment	Precision	Sensitivity	Specificity
conv5	91.23	82.30	91.83
fc6	94.55	89.66	94.83
fc7	95.93	90.31	95.10
fc6 + fc7	97.21	91.55	98.16
Fine-tuning	85.98	67.57	76.37

based learning achieved the accuracy of 80.17% accuracy on MNIST dataset.

Fine-tune approach shows interesting results for both ImageNet and PaHaW datasets. AlexNet-fine-tune-ImageNet features yield outstanding result 98.28% due to large size of ImageNet dataset and 1000 classes. We assumed that MNIST dataset will perform well as compared to ImageNet dataset but AlexNet-fine-tune-MNIST network showed unsatisfactory performance and achieved 80.12% due to small size of data and 10 classes digits. Results showed that fine-tuning of the ConvNet is applicable in our case due to the over-fitting concerns on MNIST dataset. From the results, we notice that in case of small and different dataset like PaHaW, it is the best choice to train a linear classifier on extracted freeze features from source dataset.

Table 10 Performance evaluation of Parkinson's disease identification using different fixed layers in freeze approach and fine-tuning approach of transfer learning using MNIST and PaHaW datasets

Experiment	Precision	Sensitivity	Specificity
conv5	94.74	93.10	94.83
fc6	93.55	88.66	93.83
fc7	92.73	87.93	93.10
fc6 + fc7	88.89	96.55	87.93
Fine-tuning	61.62	54.91	61.98

4.3 Validation of dataset

Cross-validation is a statistical method that is applied for the performance evaluation of predictive model on an unknown dataset. We conducted the *k*-fold cross-validation on single task of dataset, i.e., spiral task only. The reason behind *k*-fold cross-validation is that, it guarantees that each sample eventually becomes the part of training as well as testing sets. The spiral sample contains 936 images. First, we divide the data into fourfold. We have conducted the experiment in such a way that 234 images are reserved for testing and remaining 702 images in three folders are used for training purpose. The learning model is then

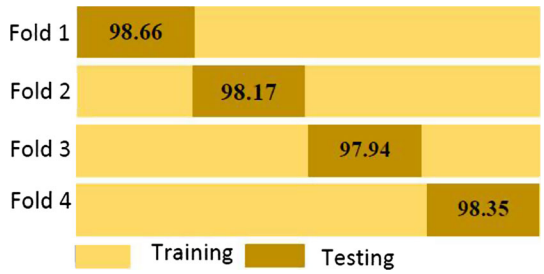


Fig. 5 Fourfold cross-validation

trained on three subsets (training set), and then, the model is tested on the remaining subsets (test or validation set).

The overall split of the dataset for fourfold cross-validation, and the results obtained by fourfold cross-validation are shown in Fig. 5. The average identification rate of fourfold cross-validation using fine-tuned features of ImageNet is computed as 98.28%, 0.38%.

4.4 Evaluation matrix

In order to evaluate the performance of proposed Parkinson's disease classification system, we have used sensitivity, specificity and precision as evaluation measures and performed fourfold evaluation. Each terminology is expressed by True Positives (t_p), False Positives (f_p), True Negatives (t_n) and False Negatives (f_n) rates.

Accuracy determines the overall ability of the system to correctly classify data (PD and healthy subjects)

$$\text{Accuracy} = \frac{t_p + f_n}{t_p + t_n + f_p + f_n}$$

Precision is the true positive-relevant measure and is calculated by

$$\text{Precision} = \frac{t_p}{t_p + f_p}$$

Sensitivity determines the ability of system to correctly classify the PD subjects and is defined as the proportion of True Positives in the diseased cases and calculated by

$$\text{Sensitivity} = \frac{t_p}{t_p + f_n}$$

Specificity determines the ability of the system to correctly classify the healthy subjects and is calculated by

$$\text{Specificity} = \frac{t_n}{t_n + f_p}$$

Tables 9 and 10 depict the precision, sensitivity and specificity of various layers of AlexNet-freeze-ImageNet and AlexNet-freeze-MNIST. These tables also depict precision, sensitivity and specificity of the proposed systems using fine-tune approach of transfer learning using ImageNet and MNIST.

4.5 Discussion

In this section, we analyzed and compare the performance of proposed system with existing state-of-the-art Parkinson's classification systems on PaHaW as target dataset using ImageNet and MNIST as source dataset. Table 11 describes the comparison of different Parkinson's disease classification.

A meaningful comparison of our system is possible with works of Pereira et al. [35, 36] and Moetesum et al. [10]. Pereira et al. [35] applied CNN on pen-based features by using three different techniques. We compare our system with his ImageNet technique out-performing their work by achieving 98.19% in comparison with 80.19% using ImageNet data on time series data. In another work, they have applied metaheuristic-based techniques that are bat algorithm (BA), Firey algorithm (FA) and particle swarm optimization (PSO) in order to fine-tune CNN hyper-parameters [36]. Handwriting dataset has been used for detection of Parkinson's disease and provided effective results on BA approach with overall accuracy of 90.38% for spiral data. In 2018, Pereira et al. [37] combined six representations (spirals, drawing of circles on the page and in air, meanders, left-wrist and right-wrist movements) and extracted features by deploying CNN using pen-based features (time series) from online images and reported

Table 11 Performance comparison of Parkinson's disease detection system

Study	Features	Classifier	Dataset	Accuracy (%)
Pereira et al. [35]	Pen-based features	CNN	HandPD	80.19
Pereira et al. [36]	Pen-based features	CNN	HandPD	90.38
Pereira et al. [37]	CNN-based features	CNN	HandPD	93.50
Moetesum et al. [10]	AlexNet-freeze-ImageNet features from fc7 layer	SVM	PaHaW	83
Proposed system	AlexNet-freeze-MNIST features from conv5 layer	SVM	PaHaW	94.97
Proposed system	AlexNet-freeze-ImageNet features from fc6 + fc7 layers	SVM	PaHaW	96.69
Proposed system	Fine-tuned-ImageNet features	AlexNet	PaHaW	98.28

about 93.50% accuracy. In both studies, time series data were used. In comparison with Pereira et al. [35–37], our system showed considerable gain in performance, i.e., 80.19% [35], 90.38% [36] and 93.50 [37] to 98.28%.

Moetesum applied pre-trained AlexNet-freeze-ImageNet for feature extraction using three representations of off-line images in input space and then applied SVM for classification using visual attributes that yielded 83% [10]. However, in this work, we have applied the same model, but further explored the performance of CNN model named as AlexNet architecture for different patterns of PaHaW dataset and investigated thoroughly the three common approaches, i.e., scratch, freeze or fixed features and fine-tune features. Results of [10] showed that basic approach showed poor performance. To improve the classification performance, we have used two different source datasets (ImageNet and MNIST) and their impact on PD identification. To increase the size of training dataset, we have used different techniques of data augmentation (rotation, flipping, contour, etc.) with raw images. In reusing freeze features of transfer learning, we thoroughly explored features at each layer and fusion of fc6 and fc7. The conv5 layer-based features showed highest identification rate in case of AlexNet-freeze-MNIST up to 94.97% (96.34% precision) and then passed the learned features to a linear SVM model for classification and identification of PD and H instance. The fine-tune-MNIST features-based networks showed less accuracy as compared to other networks. In proposed study, ImageNet fine-tune-based approach outperformed and achieved 98.28% accuracy as compared to the accuracy (96.69% accuracy (97.21% precision) based on the fusion of fc6 and fc7 using AlexNet-freeze-ImageNet features on spiral drawing patterns. Our proposed system showed the promising results on PaHaW (spiral data) using different approaches of deep transfer learning and of data augmentation-based techniques as compared to the existing studies in the literature.

5 Conclusion

Parkinson's disease (PD) is a hot neurological problem nowadays, and the diagnosis of PD at early stages can cure PD and save patient's life. In this study, we cope with the problem of Parkinson's disease identification through deep learner. For this purpose, we considered the noninvasive method using handwriting images for detection of PD. The AlexNet classifier with transfer learning technique is proposed for detection of handwriting impairments in Parkinson's patients so as to improve the diagnosis of PD. Basically, the idea is to model the handwriting features from AlexNet and transfer these features to our target data due to finite number of samples. So far, we have used the pre-trained AlexNet-ImageNet and AlexNet-MNIST. We explored the two common approaches (Freeze and fine-tuning) for transfer learning using two different source datasets (MNIST and ImageNet). The fine-tuned approach of transfer learning using ImageNet proved to be an efficient feature extraction approach and outperformed the state-of-the-art systems. Without extraction of traditional features, CNN system achieved accuracy of 98.28% on spiral pattern. The advantages of the proposed deep learner classifier are summarized as follows. The proposed classifier has the capacity to automatically extract hidden features, which extensively increases the performance of the classifier. Parkinson's disease can be diagnosed remotely and monitored using the proposed classifier. Therefore, patients rarely need to make visits to the clinic. The deep learner classifier can be used as a reliable classifier for the PD, and results show that the proposed classifier outperforms the conventional methods. From the proposed study, we concluded that spiral images for Parkinson's detection is more informative as compared to letters, words and sentences. As PaHaW dataset contains less spiral pattern that we increase by data augmentation, collection of huge amount of spiral dataset is more efficient for Parkinson's detection.

In regard to future work, we aim to extend our study to other deep learner models (Google-net, res-net and VGG) and compare their performance on PaHaW dataset, HandPD dataset or combination drawing of both. We also extend our work to other dataset of Parkinson's disease, i.e., voice and images dataset for effective diagnosis of Parkinson's.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

References

1. Lücking CB, Dürr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS et al (2000) Association between early-onset Parkinson's disease and mutations in the parkin gene. N Engl J Med 342(21):1560–1567
2. Grandi LC, Di Giovanni G, Galati S (2018) Animal models of early-stage Parkinsons disease and acute dopamine deficiency to study compensatory neurodegenerative mechanisms. J Neurosci Methods 308:205–218
3. Masliah E, Rockenstein E, Veinbergs I, Mal-lory M, Hashimoto M, Takeda A, Sagara Y, Sisk A, Mucke L (2000) Dopaminergic loss and inclusion body formation in *a*-synuclein mice: implications for neurodegenerative disorders. Science 287(5456):1265–1269

4. Letanneux A, Danna J, Velay J-L, Viallet F, Pinto S (2014) From micrographia to Parkinson's disease dysgraphia. Mov Disord 29(12):1467–1475
5. Thomas M, Lenka A, Kumar Pal P (2017) Hand-writing analysis in Parkinson's disease: current status and future directions. Mov Disord Clin Pract 4(6):806–818
6. Crespo Y, Soriano MF, Iglesias-Parro S, Aznarte JI, Ibáñez-Molina AJ (2018) Spatial analysis ofhandwritten texts as a marker of cognitive control. J Mot Behav 50(6):643–652
7. Collett J, Franssen M, Winward C, Izadi H, Meaney A, Mahmoud W, Bogdanovic M, Tims M, Wade D, Dawes H (2017) A long-term self-managed handwriting intervention for people with Parkinsons disease: results from the control group of a phase II randomized controlled trial. Clin Rehabilit 31(12):1636–1645
8. Nackaerts E, Broeder S, Pereira MP, Swinnen SP, Vandenberghe W, Nieuwboer A, Heremans E (2017) Handwriting training in Parkinsons disease: a trade-off between size, speed and fluency. PLoS ONE 12(12):e0190223
9. Vasquez-Correa JC, Orozco-Arroyave JR, Arora R, Nöth E, Dehak N, Christensen H, Rudzicz F, Bocklet T, Cernak M, Chinaei H et al (2017) Multi-view representation learning via gcca for multimodal analysis of Parkinson's disease. In: 2017 IEEE international conference on in acoustics, speech and signal processing (ICASSP). IEEE, pp 2966–2970
10. Moetesum M, Siddiqi I, Vincent N, Cloppet F (2018) Assessing visual attributes of handwriting for prediction of neurological disorders case study on Parkinsons disease. Pattern Recognit Lett. https://doi.org/10.1016/j.patrec.2018.04.008
11. di Biase L, Summa S, Tosi J, Taffoni F, Marano M, Cascio Rizzo A, Vecchio F, Formica D, Di Lazzaro V, Di Pino G et al (2018) Quantitative analysis of bradykinesia and rigidity in Parkinsons disease. Front Neurol 9:121
12. Werner P, Rosenblum S, Bar-On G, Heinik J, Korczyn A (2006) Handwriting process variables discriminating mild Alzheimer's disease and mild cognitive impairment. J Gerontol Ser B Psychol Sci Soc Sci 61(4):P228–P236
13. Razzak I, Imran M, Xu G (2018) Efficient brain tumor segmentation with multiscale two-pathway-group conventional neural networks. IEEE J Biomed Health Inform. https://doi.org/10.1109/JBHI.2018.2874033
14. Razzak MI, Naz S, Zaib A (2018) Deep learning for medical image processing: Overview, challenges and the future. In: Classification in bioapps. Springer, pp 323–350
15. Razzak MI, Naz S (2017) Microscopic blood smear segmentation and classification using deep contour aware cnn and extreme machine learning. In: 2017 IEEE conference on computer vision and pattern recognition workshops (CVPRW). IEEE, pp 801–807
16. Naz S, Umar AI, Ahmad R, Siddiqi I, Ahmed SB, Razzak MI, Shafiat F (2017) Urdu Nastaliq recognition using convolutional recursive deep learning. NeuroComputing 243:80–87
17. Naz S, Umar AI, Ahmad R, Ahmed SB, Shirazi SH, Razzak MI (2017) Urdu Nastaliq text recognition system based on multi-dimensional recurrent neural network and statistical features. Neural Comput Appl 28(2):219–231
18. Naz S, Umar AI, Ahmad R, Ahmed SB, Sid-diqi I, Razzak MI (2016) Offline cursive Nastaliq script recognition using multidimensional recurrent neural networks with statistical features. NeuroComputing 177:228–241
19. Rehman A, Naz S, Razzak MI, Hameed IA (2019) Automatic visual features for writer identification: a deep learning approach. Neural Comput Appl
20. McLennan J, Nakano K, Tyler H, Schwab R (1972) Micrographia in parkinson's disease. J Neurol Sci 15(2):141–152
21. Tsanas A, Little MA, McSharry PE, Spiel-man J, Ramig LO (2012) Novel speech signal processing algorithms for high-accuracy classification of Parkinson's disease. IEEE Trans Biomed Eng 59(5):1264–1271
22. Millian-Morell L, Lopez-Alburquerque T, Rodriguez-Rodriguez A, Gomez-Nieto R, Carro J, Meilan JJ, Martinez-Sanchez F, Sancho C, Lopez DE (2018) Relations between sensorimotor integration and speech disorders in Parkinson's disease. Curr Alzheimer Res 15(2):149–156
23. Hariharan M, Polat K, Sindhu R (2014) A new hybrid intelligent system for accurate detection of Parkinson's disease. Comput Methods Programs Biomed 113(3):904–913
24. Rusz J, Cmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E (2011) Acoustic assessment of voice and speech disorders in Parkinson's disease through quick vocal test. Mov Disord 26(10):1951–1952
25. Pettorino M, Pellegrino E, Busà MG (2016) Speech disorders and Parkinson's disease. Parkinsonism Relat Disord 22:e48
26. Aich S, Younga K, Hui KL, Al-Absi AA, Sain M (2018) A nonlinear decision tree based classification approach to predict the Parkinson's disease using different feature sets of voice data. In: 2018 20th international conference on advanced communication technology (ICACT). IEEE, pp 638–642
27. Caliskan A, Badem H, Basturk A, Yuksel ME (2017) Diagnosis of the Parkinson disease by using deep neural network classifier. Istanb Univ J Electr Electron Eng 17(2):3311–3319
28. Delrobaei M, Memar S, Pieterman M, Stratton TW, McIsaac K, Jog M (2018) Towards remote monitoring of Parkinsons disease tremor using wearable motion capture systems. J Neurol Sci 384:38–45
29. Cancela J, Pastorino M, Waldmeyer MTA (2018) Trends and new advances on wearable and mobile technologies for Parkinson's disease monitoring and assessment of motor symptoms: how new technologies can support Parkinson's disease. In: Biomedical engineering: concepts, methodologies, tools, and applications. IGI Global, pp 1180–1204
30. Xia Y, Yao Z, Lu Y, Zhang D, Cheng N (2018) A machine learning approach to detecting of freezing of gait in Parkinson's disease patients. J Med Imag Health Inform 8(4):647–654
31. Xu C, He J, Zhang X, Wang C, Duan S (2018) Template-matching-based detection of freezing of gait using wearable sensors. Procedia Comput Sci 129:21–27
32. Eskofier BM, Lee SI, Daneault J-F, Golabchi FN, Ferreira-Carvalho G, Vergara-Diaz G, Sapienza S, Costante G, Klucken J, Kautz T (2016) Recent machine learning advancements in sensor-based mobility analysis: deep learning for Parkinson's disease assessment. In: IEEE 38th annual international conference of the engineering in medicine and biology society (EMBC). IEEE, pp 655–658
33. Ruonala V, Pekkonen E, Airaksinen O, Kankaanpää M, Karjalainen PA, Rissanen SM (2018) Levodopa-induced changes in electromyographic patterns in patients with advanced Parkinsons disease. Front Neurol 9:35
34. Bond AE, Shah BB, Elias WJ (2018) Assessing tremor and adverse events in patients with tremor-dominant parkinson disease undergoing focused ultrasound thalamotomy reply. JAMA Neurol 75(5):633
35. Pereira CR, Weber SA, Hook C, Rosa GH, Papa JP (2016) Deep learning-aided Parkinson. In: 2016 29th SIBGRAPI conference on graphics, patterns and images (SIBGRAPI). IEEE, pp 340–346
36. Pereira CR, Pereira DR, Papa JP, Rosa GH, Yang X-S (2016) Convolutional neural networks applied for Parkinsons disease identification. In: Machine learning for health informatics. Springer, pp 377–390
37. Pereira CR, Pereira DR, Rosa GH, Al-buquerque VH, Weber SA, Hook C, Papa JP (2018) Handwritten dynamics assessment through convolutional neural networks: an application to Parkinson's disease identification. Artif Intell Med 87:67–77

38. Zhang Y (2017) Can a smartphone diagnose Parkinson disease? A deep neural network method and telediagnosis system implementation. Parkinsons Dis 2017:1–11
39. Grover S, Bhartia S, Yadav A, Seeja K et al (2018) Predicting severity of Parkinsons disease using deep learning. Procedia Comput Sci 132:1788–1794
40. Choi H, Ha S, Im HJ, Paek SH, Lee DS (2017) Refining diagnosis of Parkinson's disease with deep learning-based interpretation of dopamine transporter imaging. NeuroImage Clin 16:586–594
41. Afonso LCS, Rosa GH, Pereira CR, Weber SAT, Hook C, Albuquerque VHC, Papa JP (2019) A recurrence plot-based approach for Parkinson's disease identification. Future Gener Comput Syst 94:282–292. https://doi.org/10.1016/j.future.2018.11.054
42. Gupta D, Julka A, Jain S, Aggarwal T, Khanna A, Arunkumar N, de Albu-querque VHC (2018) Optimized cuttlefish algorithm for diagnosis of Parkinson's disease. Cognit Syst Res 52:36–48. https://doi.org/10.1016/j.cogsys.2018.06.006
43. Gupta D, Sundaram S, Khanna A, Has-sanien AE, de Albuquerque VHC (2018) Improved diagnosis of Parkinson's disease using optimized crow search algorithm. Comput Electr Eng 68:412–424
44. Ratliff J, Ortega RA, Ooi HY, Mirallave A, Glickman A, Yu Q, Raymond D, Bressman S, Pullman S, Saunders-Pullman R (2018) Digitized spiral analysis may be a potential biomarker for brachial dystonia. Parkinsonism Relat Disord 57:16–21
45. San Luciano M, Wang C, Ortega RA, Yu Q, Boschung S, Soto-Valencia J, Bressman SB, Lipton RB, Pullman S, Saunders-Pullman R (2016) Digitized spiral drawing: A possible biomarker for early Parkinsons disease. PLoS ONE 11(10):e0162799
46. Saunders-Pullman R, Derby C, Stanley K, Floyd A, Bressman S, Lipton RB, Deligtisch A, Severt L, Yu Q, Kurtis M et al (2008) Validity of spiral analysis in early Parkinson's disease. Mov Disord 23(4):531–537
47. Aly N, Playfer J, Smith S, Halliday D (2007) A novel computer-based technique for the assessment of tremor in Parkinson's disease. Age Ageing 36(4):395–399
48. Drotr P, Mekyska J, Rectorova I, Masarova L, Smekal Z, Faundez-Zanuy M (2014) Analysis of in-air movement in handwriting: a novel marker for parkinsons disease. Comput Methods Programs Biomed 117:405–411
49. Krizhevsky A, Sutskever I, Hinton GE (2012) Imagenet classification with deep convolutional neural networks. In: Advances in neural information processing systems, pp 1097–1105
50. Kraus PH, Hoffmann A (2010) Spiralometry: computerized assessment of tremor amplitude on the basis of spiral drawing. Mov Disord 25(13):2164–2170
51. Stanley K, Hagenah J, Brüggemann N, Reetz K, Severt L, Klein C, Yu Q, Derby C, Pullman S, Saunders-Pullman R (2010) Digitized spiral analysis is a promising early motor marker for Parkinson disease. Parkinsonism Relat Disord 16(3):233–234

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).
Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.
These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.
We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.
While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval , sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.
These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.
To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.
Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.
If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com