



**UNIVERSITY
OF TURKU**

This is a self-archived – parallel published version of an original article. This version may differ from the original in pagination and typographic details. When using please cite the original.

This is a post-peer-review, pre-copyedit version of an article published in

BOOK Enhanced Telemedicine and e-Health: Advanced IoT Enabled Soft Computing Framework

DOI The final authenticated version is available online at
https://doi.org/10.1007/978-3-030-70111-6_14

CITATION Subasi A. (2021) Disease Prediction Using Artificial Intelligence: A Case Study on Epileptic Seizure Prediction. In: Marques G., Kumar Bhoi A., de la Torre Díez I., Garcia-Zapirain B. (eds) Enhanced Telemedicine and e-Health. Studies in Fuzziness and Soft Computing, vol 410. Springer, Cham.

Metadata of the chapter that will be visualized in SpringerLink

Book Title	Enhanced Telemedicine and e-Health	
Series Title		
Chapter Title	Disease Prediction Using Artificial Intelligence: A Case Study on Epileptic Seizure Prediction	
Copyright Year	2021	
Copyright HolderName	The Author(s), under exclusive license to Springer Nature Switzerland AG	
Corresponding Author	Family Name	Subasi
	Particle	
	Given Name	Abdulhamit
	Prefix	
	Suffix	
	Role	
	Division	Faculty of Medicine, Institute of Biomedicine
	Organization	University of Turku
	Address	Turku, 20520, Finland
	Division	Department of Computer Science, College of Engineering
	Organization	Effat University
	Address	Jeddah, 21478, Saudi Arabia
	Email	abdulhamit.subasi@utu.fi absubasi@effatuniversity.edu.sa
Abstract	<p>Artificial Intelligence uses statistical theory to generate mathematical models from samples. After a model is generated, its depiction and algorithmic solution for understanding require being competent as well. Biomedical data related to different diseases are recorded from a body, which can be at the organ level, cell level or molecular level. Biomedical data is mainly utilized to predict, diagnose or identify particular physiological or pathological conditions. The goal of biomedical data analysis is exact modelling of data by employing feature extraction, feature selection and dimension reduction for the prediction and detection of upcoming pathological problems by utilizing artificial intelligence algorithms. This chapter explains the steps of biomedical data analysis and how artificial intelligence techniques are utilized in disease prediction. An automated epileptic seizure prediction and detection approach based on deep learning is also presented. Since Deep Learning can automatically extract and learn features, the electroencephalography (EEG) time series are fed into the deep learning model. Deep Learning has been utilized in the prediction and detection of epileptic seizures. Since EEG recordings are high dimensional data, a Convolutional Neural Network (CNN) is suitable for this use. The results show that CNN achieved a testing accuracy of 99.09% accuracy for the prediction of epileptic seizures from EEG signals.</p>	
Keywords (separated by '-')	Biomedical data analysis - Disease prediction - Artificial intelligence - Deep learning	

Disease Prediction Using Artificial Intelligence: A Case Study on Epileptic Seizure Prediction



Abdulhamit Subasi

1 **Abstract** Artificial Intelligence uses statistical theory to generate mathematical
2 models from samples. After a model is generated, its depiction and algorithmic
3 solution for understanding require being competent as well. Biomedical data related
4 to different diseases are recorded from a body, which can be at the organ level,
5 cell level or molecular level. Biomedical data is mainly utilized to predict, diag-
6 nose or identify particular physiological or pathological conditions. The goal of
7 biomedical data analysis is exact modelling of data by employing feature extrac-
8 tion, feature selection and dimension reduction for the prediction and detection of
9 upcoming pathological problems by utilizing artificial intelligence algorithms. This
10 chapter explains the steps of biomedical data analysis and how artificial intelligence
11 techniques are utilized in disease prediction. An automated epileptic seizure predic-
12 tion and detection approach based on deep learning is also presented. Since Deep
13 Learning can automatically extract and learn features, the electroencephalography
14 (EEG) time series are fed into the deep learning model. Deep Learning has been
15 utilized in the prediction and detection of epileptic seizures. Since EEG recordings
16 are high dimensional data, a Convolutional Neural Network (CNN) is suitable for
17 this use. The results show that CNN achieved a testing accuracy of 99.09% accuracy
18 for the prediction of epileptic seizures from EEG signals.

19 **Keywords** Biomedical data analysis · Disease prediction · Artificial intelligence ·
20 Deep learning

A. Subasi (✉)

Faculty of Medicine, Institute of Biomedicine, University of Turku, Turku 20520, Finland
e-mail: abdulhamit.subasi@utu.fi; absubasi@effatuniversity.edu.sa

Department of Computer Science, College of Engineering, Effat University, Jeddah 21478,
Saudi Arabia

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021
G. Marques et al. (eds.), *Enhanced Telemedicine and e-Health*, Studies in Fuzziness and
Soft Computing 410, https://doi.org/10.1007/978-3-030-70111-6_14

1

1 Introduction

Biomedical data is collected from a biological or medical source that might be at the organ, cell, or molecular levels. On the one hand, biomedical data is primarily collected in hospitals to identify certain clinical or pathological disorders and to evaluate the therapy and diagnose the disorder. On the other hand, biomedical data analysis is used to eliminate noise, construct reliable models and analyze their components, extract characteristics for vital component and predict possible functional or pathological events in the heart, brain, muscle and kidney [1]. Moreover, biomedical data includes information that is useful for understanding the complex mechanisms of pathophysiology and behavior of living systems. The analysis of biomedical data is usually required to improve the relevant knowledge and to define the pathology level for routine clinical diagnosis, recovery or therapy. Several biomedical data processing methods also referred to as preprocessing techniques, are available such as denoising, averaging, sampling, segmentation, spectral estimation and feature extraction [2].

Biomedical health data have been widely employed in recent years for research and clinical decision-making in the healthcare research field, such as diagnosis, treatment, and prediction of diseases. Clinical judgments have historically relied on the finding, expertise, and experience of physicians, with the aid of numerous clinical and diagnostic tests. This approach leads to unintended biases, mistakes and high costs, which has a negative effect on the quality of patient service [3]. Wu et al. [4] suggested combining clinical decision support with computer-based patient records that would eliminate medical errors and unintended changes in procedures and increase patient well-being. Computer-based decision support has become popular and started to combine with information management in healthcare. As a result, this has created a significant amount of biomedical data involving healthcare records, interactions between patient and doctor, medical history, referral details and insurance claim data. With the rapid evolution of methods and techniques for data processing, biomedical healthcare data are being used in an extensive range of healthcare research fields rather than simply for record-keeping, such as healthcare data analysis [5], chronic disease surveillance [6], the creation of disease risk forecasting models [6, 7] and the comparison of disease incidence and drug outcomes [8]. Besides, these data are an essential tool for chronic disease monitoring and observation [6]. Severe health problems such as heart failure and epilepsy are frequently identified with development at a later phase. If predictive models would detect these potential health risks before, patients could be treated better, which could alter the course of the disease or disorder. Because of the availability of massive biomedical healthcare data, prediction of diseases has become a significant research field [9]. Artificial intelligence techniques have had a substantial influence on the lifestyle of humans over the past two decades, by forecasting human activities and forthcoming developments. These techniques are well adapted to transforming collected data into useful knowledge to help decision making in the healthcare system to increase accuracy in diagnosis and speed up testing time [10].

64 Modern healthcare systems have improved human life expectancy through the
65 advent of medications, medical facilities, and the maintenance of health records for
66 patients. Nevertheless, healthcare support systems face substantial challenges with
67 modern developments in healthcare, such as lack of sufficient medical information,
68 misdiagnosis, inevitable errors, data risk, and delayed communication. Computerized
69 healthcare information management, such as the Electronic Health Record (EHR),
70 Disease Prediction Scheme (DPS), and Clinical Decision Support System (CDSS)
71 draw significant interest. To help the physician in the decision-making process,
72 early-stage monitoring of the healthcare data of patients became effective for the
73 correct diagnosis of the disease. Hence, CDSS gained unexpected prominence due
74 to technical advancement [11]. The advent of Internet of Things (IoT) and medical
75 sensors includes a significant amount of diverse devices, which continuously track
76 and acquire physiological signals from distant users such as heartbeat, brain signals,
77 motor characteristics, body temperature, and insulin [12]. In tracking the health
78 conditions of patients, valuable interpretations can only be extracted from the signals
79 of the medical sensors. Medical sensors have recently been equipped with emergency
80 warnings to inform the patient or his/her family members and emergency service once
81 the biomedical signal reaches the threshold. Finally, a large amount of medical data
82 for patients is obtained by healthcare service providers creating a valuable tool for
83 the support network for clinical decision making.

84 Cloud computing acts as a foundation for vast storage and data processing
85 because of the space limitation characteristics of IoT and minimal storage facilities.
86 The cloud-related healthcare framework monitors all cloud-based health information
87 while the patient is travelling for specific treatment from one hospital to
88 another. Nevertheless, as the medical data is kept on the cloud server to identify,
89 predict disorder, and maintain the healthcare records, it is suitable for medical data
90 being processed in real-time. Therefore, local processing of health information for
91 a patient and the sending of an instantaneous medical decision or a warning when
92 an emergency happens to allow healthcare services to save human lives [13]. The
93 main objective of this chapter is to present the disease prediction using artificial
94 intelligence.

95 Deep Learning algorithms are gaining a lot of attention because of their excellent
96 success in different machine learning applications. In the electroencephalography
97 (EEG) study, recurrent neural networks (RNN) were used to learn temporal patterns
98 for the detection of epileptic seizures [14]. Long Short-Term Memory (LSTM) is an
99 evolution of RNNs, which requires gates to deal with the issue of the disappearing
100 gradient. More recently, LSTM has been used to predict epileptic seizures using
101 EEG signals [15]. Noteworthy attention in the EEG signal analysis has also been
102 attracted by Convolutional Neural Networks (CNNs). CNNs are used to both raw
103 data [16] and wavelet space [17] to classify epileptic EEG signals and achieved
104 higher performance. The key benefit of CNNs is the ability to automatically learn
105 new features, producing better results while the amount of data is adequate to train
106 the CNNs [18]. This chapter presents the use of artificial intelligence techniques
107 for the prediction and detection of the epileptic seizure using feature extraction and
108 signal transformations to produce deep learning inputs.

109 The motivation for applying artificial intelligence to the problem of predicting
110 epileptic seizures is their effectiveness in the classification of biomedical signals.
111 Further exploratory studies are required to utilize EEG recordings for computerized
112 epileptic seizure detection. Moreover, this work is one of the studies used to tackle
113 the issue of seizure prediction using EEG and Deep Learning. Epileptic seizure
114 detection in advance will enable epileptic patients or their caregivers to take measures
115 until an epileptic seizure occurs, thus reducing complications and possible damage
116 associated with the case, where EEG is generally monitored [19]. By using CNN,
117 99.09% accuracy is achieved for the epileptic seizure prediction and detection.

118 This chapter is structured as follows: disease prediction is discussed in Sect. 2.
119 Section 3 includes artificial intelligence techniques for disease prediction, which
120 includes a description of the Deep Learning algorithm. Section 4 provides details of
121 the case study of epileptic seizure prediction, and Sect. 5 presents the discussion.
122 Finally, in Sect. 6, conclusions are given.

123 2 Disease Prediction

124 Disease prediction and detection is a technique of artificial intelligence that first
125 employs training data to create a model, and then the resulting model utilizes the
126 test data to obtain prediction results. Classification approaches based on artificial
127 intelligence for the chronic disease prediction and detection were applied on disease
128 datasets, and the findings are promising. An original classification strategy that can
129 accelerate and make simpler the process of chronic disease prediction and detection
130 is crucial [20].

131 Computer-aided decision support systems (CADSS) help the physician monitor
132 the symptom-based risks of disorder incidence in the subjects. A person cannot
133 easily detect signs of diseases such as diabetes and arrhythmia. Therefore, CADSS
134 is used for proper evaluation of the illness, assisted by artificial intelligence tech-
135 niques, medical sensors, and computing services. The use of artificial intelligence
136 techniques enables improved efficiency with ease of implementation for prediction
137 of complex disease. CADSS is a computerized decision-making system, which offers
138 a patient community with predictive disease and treatment recommendations, rather
139 than patient-centered recommendations. As CADSS does not find clear characteris-
140 tics of the patients for predicting illness, the recommendations given are unreliable.
141 The emergence of medical big data has driven customized CADSS production to
142 increase the efficiency of existing CADSS [13].

143 Disease prediction from healthcare data that demonstrate valuable knowledge
144 in large quantities relating to patients with specific diseases is a scientific domain
145 issue [21, 22]. Predicting the risk of the disease includes predicting the likelihood
146 of disease and implementing a preventive plan either to minimize the risk of disease
147 in a specific way or to avoid disease risk altogether. Prediction of illness has several
148 advantages, such as early-stage analysis and treatment of disease, disease drop, and
149 death prevention [23–25].

150 Artificial intelligence techniques are used extensively in medicine. Different clas-
151 sification algorithms for disease diagnosis have been developed to provide high
152 precision for disease prediction. After analyzing the various characteristics of the
153 disease, several artificial intelligence techniques are built for predicting different
154 types of disease at the early stages. These algorithms are commonly used in
155 breast cancer, kidney disease, thyroid disease, diabetes, other cancers, erythemato-
156 squamous diseases and much more. Different classification algorithms are applied
157 to obtain better prediction accuracy to build a CADSS [26].

158 3 Artificial Intelligence Techniques for Disease Prediction

159 Artificial intelligence is a term that uses a collection of data or some knowledge for
160 prediction and classification. The learning process is essentially the implementation
161 of optimization of the model parameter with the training dataset or previous experi-
162 ence. Models may either be predictive, to allow future predictions; descriptive, to
163 derive information from data input or both. Two essential tasks are carried out in
164 artificial intelligence: (1) analysing the volume of data and enhancing the model and
165 (2) testing the model and demonstrating the solution in an effective manner. In some
166 applications, the learning efficacy is as crucial as the precision of the classification.
167 Also, artificial intelligence helps the system to learn about and adapt to changes in
168 various environments. Artificial intelligence supports us in healthcare data, vision,
169 voice, face or other kinds of recognition [27].

170 In the study of medical data, literature presents numerous scientists who have
171 employed diverse artificial intelligence techniques for predicting chronic diseases to
172 obtain better diagnostic results and prediction performance. Several artificial intel-
173 ligence algorithms, such as Naïve Bayes, decision trees, artificial neural networks
174 (ANN), k-nearest neighbor, and support vector machines, have been introduced and
175 utilized recently for chronic disease prediction and detection. Intelligent automated
176 systems [28] are essential in other research and scientific applications for prediction
177 and detection of various diseases,. Nonetheless, most conventional methods are not
178 adaptive, that decreases the performance and increases the time for decision-making
179 on disease prediction. Because of these limitations of current traditional classification
180 methods, such as lower performance and longer decision-making time, an improved
181 classification precision is needed to predict diseases [20]. The general framework for
182 disease prediction using artificial intelligence techniques is shown in Fig. 1.

183 3.1 Artificial Neural Networks

184 ANN are a learner of greater interest in various fields of machine learning. ANN can
185 generate a high precision prediction for different sorts of problems. Furthermore,
186 ANN can mimic a human brain's role in making predictions, recognizing patterns or

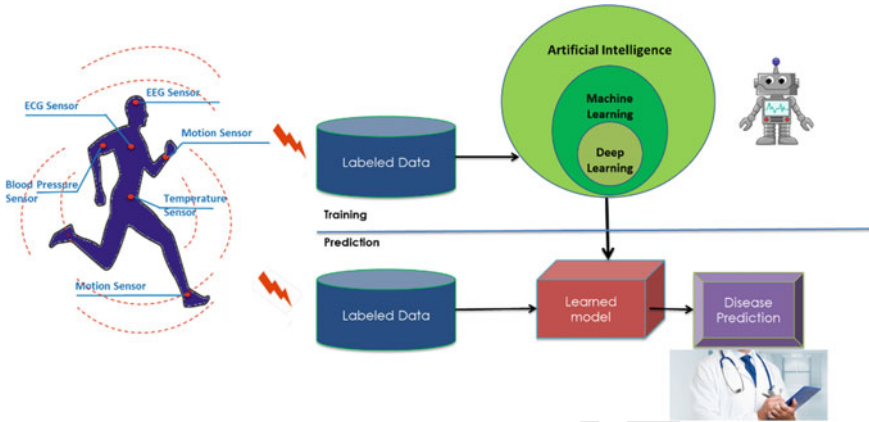


Fig. 1 General framework for disease prediction using artificial intelligence techniques

187 learning from past experiences. This procedure is expressed in a computer program
 188 that applies algorithms for machine learning and pattern recognition to construct an
 189 efficient predictive model. When building the ANN, the specialist will determine the
 190 number of nodes that are suitable for the problem, the most appropriate weight value
 191 for every connection, how the nodes should be connected, and how ANN should be
 192 trained. In ANN, input data is obtained through input nodes, the values of which are
 193 weighted by the values of the weights and preserved in the links.

194 In addition, in the hidden layer, a transfer function is utilized to generate the
 195 output. This output is transferred to the final node as a prediction. The nodes in ANN
 196 can be divided into input and output layers. Input layer contains a group of input
 197 values, while the output layer contains target values. Unit is of any input variable,
 198 which has its unit within neural networks. Each input layer is connected with the
 199 output layer by a minimum of one weight. The main drawback of the ANN is the
 200 complexity of the resulting model. The model is built as a “black-box”. As the model’s
 201 complexity increases, they may add additional hidden layers. This approach is among
 202 the most complicated of predictions to implement. Nevertheless, the advantage of
 203 neural networks is that all data forms can be processed without noticeable changes
 204 in input data and information of linearity and distribution [29].

205 ANN can be described as a combination of various models of predictions feeding
 206 into one another. There is a hidden layer between the input and output layer. This type
 207 of structure is called as multilayer architecture in neural networks. The model is built
 208 in propagating forward and backwards. In scientific studies, the back-propagation
 209 technique is the most popular. In reality, a finite amount of input variables can be
 210 interpreted by neural networks; otherwise, the time needed is high. The success of
 211 ANN depends on how the learning process evolves and what initial values are utilized
 212 in the training phase [29].

213 3.2 *Deep Learning*

214 For any learning process, if a linear model is not appropriate, new features, which
215 are nonlinear functions of the input are likely to be found, and then a linear model is
216 built in those features space. It requires to differentiate what roles of such a strong
217 basis are. The best approach in ANN is to extract these features in the hidden layer
218 since it has the advantage of extracting informative features and utilizing them to
219 predict the output in a supervised manner. An ANN with one hidden layer has poor
220 capability, whereas an ANN with numerous hidden layers can learn more complicated
221 functions. It is the philosophy behind deep neural networks, in which every hidden
222 layer, starting from simple network input, utilizes the preceding layer values and
223 learns more complex input features.

224 An additional characteristic of deep neural networks is that, up to the output
225 layer, succeeding hidden layers are connected to more complex structures where
226 these intangible definitions involve the outputs being studied. In deep learning, the
227 idea is to learn features with minimal human interference the characteristic levels of
228 that abstraction, since in some applications it is not known which assembly is present
229 in the input and any kind of dependences should be learned in an automated way
230 throughout the training [30].

231 One critical problem of training an ANN with several hidden layers is that subse-
232 quently multiplying the derivatives in all layers is crucial in order to back-propagate
233 the error to the preceding layer, and the gradient has vanished. This is also the
234 explanation for poor learning in recurrent, extended neural networks. For CNN, this
235 situation cannot occur since the fan-in, and fan-out of hidden units are, of course,
236 unimportant [31]. The entire deep neural network can be trained in a supervised
237 manner if there are enough labeled data and computing resources.

238 Deep learning methods are primarily popular, as they require less manual inter-
239 vention. It is intuitive to think of several layers of rising notion lying underneath
240 deep learning. In several applications, the abstraction layers can be understood as an
241 informative discovery of such an abstract illustration and a better understanding of
242 the problem [27, 32].

243 3.3 *Convolutional Neural Networks*

244 CNN are an improved version of deep neural networks. They consist of units named
245 neurons that take a weighted sum of inputs and generate an operating level of outputs.
246 The activity level is often a nonlinear input function, such as a rectified linear unit,
247 in which the operation is equal to the input for all positive inputs, and 0 for all non-
248 positive inputs. What is remarkable about CNN is how this architecture structures
249 the interactions between the neurons. Units are grouped into layers in a feedforward
250 neural network, and the units in a given layer only receive input from units in the layer

251 below. CNN are networks with feedforward features. Unlike regular vanilla feedfor-
252 ward networks, CNN has spatial structure units. In each layer, units are grouped into
253 2-D grids called feature maps. These maps of features are the product of a convo-
254 lution made on the layer below. This implies that the same convolutional filter (set
255 of weights) is used at each location in the layer below. Thus, a unit may only obtain
256 input from units in the layer below at a similar position with a specific location on
257 the 2-D grid. In addition, the weights attached to the inputs in a function map are the
258 same for each unit. CNN recognize images as volumes, i.e. three-dimensional objects
259 to be defined only by width and height, rather than flat canvases since digital color
260 images have a red-green-blue (RGB) encoding that perceives objects' color spec-
261 trum by mixing those three colors. These images are processed by a convolutional
262 neural network as three different layers of color piled one on top. A convolutional
263 neural network accepts a normal color image as a rectangular box, the height and
264 width of which is determined by the number of pixels in these dimensions with a
265 depth of three layers, one for every letter in RGB. Such layers of depth are called
266 channels. The intensity of R, G and B will be represented by a number for each
267 pixel of an image to form an element in one of the three stacked two-dimensional
268 matrices. These numbers are the original, sensory, raw, features that are served into
269 the convolutional neural network, and the aim of a CNN is to detect relevant signals,
270 which essentially benefit to better distinguish images [33].

271 4 Case Study of Epileptic Seizure Prediction

272 Epilepsy is a neurological disorder characterized by continuing inclination to produce
273 recurrent seizures and may disturb people of different age. Epilepsy results from
274 the progressive neurobiological mechanism of 'epileptogenesis' [34] that affects
275 the normal brain network to fire neurons in the cerebral cortex in a self-sustaining,
276 hyper-synchronized manner. Seventy million people worldwide suffer from epilepsy,
277 which is in the list of the most serious brain disorders after stroke, migraine, and
278 Alzheimer's disease [35]. Epileptic seizures are devastating and disrupting patients'
279 daily activities and are related to increased risk of early death. Epilepsy treatment is
280 further complicated by the shortage of neurologists in numerous countries, especially
281 in developing countries.

282 While in some literature epilepsy and seizures are often used synonymously, not all
283 seizures are epileptic, and seizures can also happen because of the desperate neuro-
284 logical problems without inevitably indicating a long-term inclination to repeated
285 epileptic seizures. The epileptic seizure is triggered by an abrupt irregular, self-
286 sustaining electrical discharge, which takes place in the cerebral networks and
287 typically persists less than a few minutes.

288 Epileptic seizure attacks are difficult to predict, and even the frequency and length
289 of the attack cannot be predicted. Hence, the prediction and detection of epilepsy
290 attacks in early stages are essential for preventing and counteracting their contrary

291 effects. The brain activity of epilepsy patients can be classified in diverse states: inter-
292 ictal (between seizures), pre-ictal (immediately preceding seizure), ictal (during a
293 seizure), and post-ictal (immediately after a seizure).

294 Epileptic seizure prediction is a problem of classification based on distinguishing
295 between pre-ictal and inter-ictal states. An epileptic seizure occurs in groups due
296 to the chronic nature of epilepsy and patients affected by seizure clusters may gain
297 benefit by predicting follow-up seizures [36]. Moreover, epileptic seizures, which
298 cause hardly long-lasting injuries or death, may lead to loss of perception or cause
299 only minor mental distress. Seizures have highly variable length of time and incidence
300 rate. Its length can vary from a few seconds to several minutes. There exist epileptic
301 patients who have only a few seizures in their lives, while others have multiple
302 seizures within a single day [37, 38].

303 EEG is a diagnostic technique especially useful for analyzing the brain anatomy
304 throughout an epileptic seizure attack. Epilepsy diagnosis and treatment has been
305 studied extensively by EEG. Furthermore, EEG signals are non-Gaussian, non-
306 stationary and utilized to identify the form of brain disorders by measuring the
307 electrical activity of the brain. EEG assessment research helps in the classification
308 between normal and abnormal brain activity. To accurately predict epilepsy, longer
309 duration EEG recordings need to be examined.

310 Expert neurologists analyze epilepsy by examining continuous EEG signals that
311 have been documented over multiple days, weeks, or even months, requiring signif-
312 icant human time and effort. Over the years, different studies have used predictive
313 methods based on Artificial Intelligence to tackle this problem. Deep learning is
314 an advanced machine learning technique, which can more effectively learn patterns
315 from large data sets by processing it via a multilayer hierarchical architecture. Since
316 deep learning can achieve very reliable results, researchers have inspired to eliminate
317 various real-world problems by using deep learning approaches. Moreover, different
318 scientists proposed deep learning-based techniques to the epileptic seizure prediction
319 [36]. The common structure for the epileptic seizure prediction is shown in Fig. 2.
320 This structure contains three key components: (i) signal preprocessing/denoising,
321 (ii) feature extraction/dimension reduction and (iii) classification. In this section, a
322 complete description of each component will be delivered.

323 Scientists have been working, since the last century, to overcome the challenges
324 associated with epilepsy diagnosis and prediction. Since EEG signals are a crucial
325 source for tracking brain activity before, during, and after an epileptic seizure,
326 epileptic seizure prediction centered first on EEG recording analysis. EEG signals
327 contain several contaminations such as eye-movements, blinks, heart impulses and
328 muscle noise. Various filtering and noise reduction methods are employed to reduce
329 the influence of these sources of noise and artifacts [39]. Substantial features are
330 required for creating an artificial intelligence model for identifying and classifying
331 inter ictal, pre-ictal and ictal phases after removal of noise [36].

332 EEG is the most popular way of investigating epilepsy and recording changes in
333 the behavior of the electrical brain that may announce an upcoming seizure. LSTM
334 networks are implemented using EEG signals in the prediction of an epileptic seizure.
335 To enhance the lives of patients with tonic seizures and drug-resistant epilepsy,

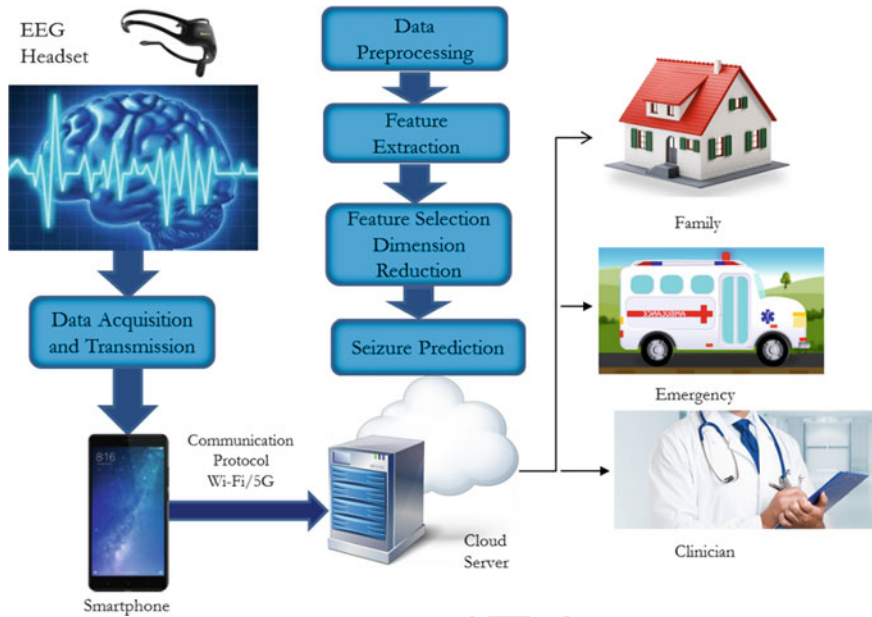


Fig. 2 General framework for epileptic seizure prediction using artificial intelligence techniques

seizure prediction has gained increasing attention as one of the most complicated predictive data analysis techniques. Several studies have achieved good results in delivering sensible alert systems or interactive regulation of neural stimulation over persistent seizures; some of them have accomplished high efficiency. Nevertheless, most of these works include handcraft feature extraction and/or tailor-made feature extraction that is implemented separately for every patient, to yield a low false prediction rate and high sensitivity.

Epilepsy is the second most prevalent brain disorder. Epilepsy makes living a normal life difficult for patients, as the occurrence of seizures cannot be predicted easily. Hence, if a fair amount of time before their occurrence could be predicted for seizures, patients with epilepsy might take precautions against them and enhance their health and life quality [40].

Truong et al. [41] applied CNN to various datasets of intracranial and scalp electroencephalogram and suggested a generalized retroactive and patient-specific technique for seizure prediction. They used the short-term Fourier transform to extract features in both the time domain and the frequency domain on 30-s EEG frames. The algorithm automatically produces optimized features to better recognize the pre-ictal and inter-ictal segments for each patient.

Chu et al. [40] studied a novel seizure prediction framework based on an interpretation of the attractor state. They investigated the transition phase from normal to attractor seizure state and examined the phenomenon realized before entering the attractor seizure state. Moreover, they have described a computed spectral measure

358 for seizure prediction in scalp EEG from the result of an experiment. Six EEG
359 frequency bands of Fourier coefficients are derived from scalp EEG recordings, and
360 the spectral measurement is determined on the basis of the coefficients for each half-
361 overlapped duration of 20 s. The computed spectral measure is implemented using
362 a low-complexity approach to predict seizures. They developed an early warning
363 system before the occurrence of the epileptic seizure from the scalp EEG. Using this
364 algorithm, a low-complexity seizure prediction framework was implemented using
365 scalp EEG.

366 Tsiouris et al. [15] used a two-layer LSTM network to test the efficiency of seizure
367 prediction employing four different pre-ictal window lengths, ranging from 15 min
368 to 2 h. The proposed LSTM network utilizes a broad range of features, containing
369 time and frequency domain features, the cross-correlation between EEG channels
370 and graph-theoretical features extracted before classification. The results showed that
371 the developed method is capable of predicting all 185 seizures, producing 0.11–0.02
372 false alarms per hour, based on the duration of the pre-ictal window, with high seizure
373 sensitivity levels and low false prediction levels (FPR).

374 A complex aspect of the treatment of epilepsy, the exact classification of various
375 epileptic disorders, is of specific concern and has been thoroughly studied. Gao et al.
376 [42] suggested a novel deep learning approach, called as the EEG epileptic signal
377 classification (EESC). First, this approach extracts power spectrum density energy
378 diagrams (PSDEDs) from the epileptic EEG signals, then extracted features from
379 the PSDED are utilized as an input of deep CNNs and transfer learning to classify
380 four types of epileptic states (inter-ictal, pre-ictal to 30 min, pre-ictal to 10 min, and
381 seizure). It outperforms the current methods of epileptic seizure prediction in terms
382 of accuracy and efficacy. The proposed model achieved an average classification
383 accuracy of over 90%.

384 Alickovic et al. [43] introduced a new model which is based on EEG measurements
385 for automatic seizure onset identification and seizure onset prediction. Two conven-
386 tional EEG databases, CHB-MIT (scalp EEG) and Freiburg (intracranial EEG), were
387 processed. The proposed model is characterized by four key components: (1) multi-
388 scale principal component analysis for EEG denoising, (2) EEG signal decomposition
389 utilizing time-frequency techniques, (3) statistical values of decomposed sub-bands,
390 and (4) machine learning techniques. In ictal versus inter-ictal EEG, the developed
391 scheme yielded an overall accuracy of 100% for both databases.

392 A seizure prediction model can detect seizures before they occur and enable
393 clinicians to treat patients with epilepsy on time. Studies on the prediction of seizures
394 have evolved from analysis of signal processing to machine learning. Since numerous
395 prediction techniques are hand-crafted and need high computational complexity, it
396 is difficult to make predictions in real-time.

397 Wei et al. [44] transformed the EEG time series into two-dimensional multichannel
398 fusion images. To create a deep spatiotemporal learning model for predicting epileptic
399 seizures, a long-term recurrent convolutional network (LRCN) was developed. The
400 CNN block was utilized for deep features extraction from the EEG data in an auto-
401 mated manner. In learning a time series to classify the pre-ictal segments, the LSTM
402 block was integrated into the learning. In the seizure prediction model, new network

403 set-up and a post-processing technique were suggested. The model of deep seizure
404 prediction achieved 93.40% accuracy, 91.88% sensitivity and 86.13% specificity in
405 segment-based evaluations. One hundred sixty-four seizures were predicted for the
406 tests based on the cases. The developed technique provides high sensitivity and a
407 low false prediction (FPR) rate of 0.04 FP/h.

408 Patients also consider the most troublesome aspect of epilepsy to be the unpre-
409 dictability of seizures. Hence Liu et al. [45] established an accurate indicator of
410 seizures to alert patients with epilepsy for the forthcoming seizures. They used time
411 and frequency domain features to deliver the same data source with two different
412 views utilizing a multi-view, CNN architecture to predict the occurrence of epileptic
413 seizures. The proposed deep learning model attained an average area of 0.82 and
414 0.89 area under the curve (AUCs) on two subjects of the CHB-MIT scalp EEG data
415 set.

416 An effective epileptic seizure prediction framework mitigates the issue and
417 reduces symptoms in a patient's life with epilepsy. Rukhsar et al. [46] developed a
418 model that can predict seizures well ahead of their occurrence. Multivariate statistical
419 process control was used in the long-term scalp EEG signal for seizure predictions.
420 Excessive neuronal activity in the pre-ictal seizure phase has been observed to shift
421 the electrical characteristics of the behavior from chaotic to rhythmic. Employing
422 multivariate statistical process control, commonly known as an anomaly monitoring
423 tool, eight temporal dependent features are utilized to predict the seizures. In total, 90
424 CHB-MIT EEG seizures of 10 patients are investigated. The findings of the suggested
425 approach showed that 80 out of 90 seizures were precisely predicted before the onset
426 of the seizure, resulting in a sensitivity of 88.89%. The false-positive rate is 0.39 per
427 hour.

428 **4.1 Biomedical Signal Denoising**

429 In raw biomedical signals, noise and artefact detection is a key issue. Filtering these
430 artifacts is required to reduce the impact on the feature extraction. Multiple filtering
431 techniques, such as band-pass filter, wavelet filter, finite impulse response filter, and
432 an adaptive filter, were employed. The analysis is often carried out to normalize the
433 data and to make it compatible with other patient records. Also, in the EEG recording
434 there are several data dropouts or corrupted data due to the limitations of implanted
435 electrodes that lead to lower algorithm performance. Moreover, some outliers can
436 exist in the data due to muscle artefacts and ambient noise. The existence of these
437 outliers affects the extracted features critically [36].

438 Biomedical signals include various forms of artifacts from internal or external
439 noise interference. These artifacts can be circumvented by using signal denoising
440 methods to filter out artifacts and noise [47]. Preprocessing/denoising is one of the
441 main steps of the analysis of biomedical signals. The key objective of the prepro-
442 cessing/denoising is to simplify successive processes without losing relevant infor-
443 mation by increasing the signal-to-noise ratio (SNR), and to improve the quality

444 of the signal. Researchers utilize these techniques to remove or decrease the unde-
445 sirable signal components by transforming the signals into another domain. Multi-
446 scale Principal Component Analysis (MSPCA) combines the ability of the Principal
447 Component Analysis (PCA) to minimize the relationship between variables with the
448 ability of the wavelet transform to eliminate the relationship between auto-correlated
449 measurements. On the one hand, MSPCA measures the PCA of the wavelet coeffi-
450 cients at each scale with the integration of the effects at appropriate scales. On the
451 other hand, MSPCA is effective, as it requires inputs of events that alter behaviors
452 over time and frequency [38, 48].

453 4.2 Feature Extraction

454 All methods for the prediction of seizure include reliable features which are well
455 associated with pre-ictal and inter-ictal levels. These characteristics can be classified
456 as univariate (measures taken separately across every EEG channel) and multivariate
457 (measures taken on two or more EEG channels) according to the number of EEG
458 channels. The categorization of each of these functions is as linear or nonlinear [36].

459 Feature extraction is one of the main steps in the evaluation of biomedical signals.
460 Thus, useful and informative features of the biomedical signals consisting of several
461 data points can be obtained employing various feature extraction techniques. Such
462 distinguishing and informative parameters define the signal waveform behavior that
463 defines a precise action. Frequencies and amplitudes may reflect the biomedical
464 signaling patterns. Features can be extracted utilizing various feature extraction tech-
465 niques that is the another signal processing step to simplify the subsequent classi-
466 fication step [49]. Time-frequency (TF) approaches can be utilized to decompose
467 biomedical signals to track changes in time and frequency. [47]. To achieve better
468 efficiency, a smaller number of values that define the informative characteristics of
469 the signals should be taken into consideration. In general, transformation of signals
470 into an informative feature vector is identified as feature extraction. A signal clas-
471 sification framework analyzes the characteristics of a signal, and based on those
472 characteristics, the signal class is determined [50]. Signals can be decomposed into
473 both time and frequency domain using time-frequency methods. In this study Dual
474 Tree Complex Wavelet Transform (DT-CWT) is utilized for features extraction [38].

475 4.3 Dimension Reduction

476 Dimension reduction is a technique to reduce the dimension of the original feature
477 vector while preserving the most distinguishing information and eliminating irrel-
478 evant information [51]. Numerous features extraction methods generate redundant
479 features. Some types of feature selection/reduction techniques that generate a novel
480 set of features must be implemented to enhance the classifier performance and yield

481 minimum classification error. Several methods used to reduce dimensions and choose
482 features to improve classification accuracy [38, 52].

483 To interpret the data, the dimensions of biomedical signals must be reduced to
484 obtain more precise results. Small number of parameters are utilized to decrease the
485 dimension of the biomedical signals by various means. In addition, to achieve greater
486 classification accuracy, the features or dimensions must be reduced. For example, the
487 DT-CWT generates wavelet coefficients to designate the signal energy distribution
488 in both time and frequency domains and describes the biomedical signals with a set
489 of wavelet coefficients. A dimension reduction approach must be employed to obtain
490 a smaller number of features from wavelet coefficients, since wavelet-based feature
491 extraction methods include the feature vector, which is too large in size to be used
492 as a classifier input.

493 Different techniques such as higher-order statistics, entropies and Lyapunov expo-
494 nents have been used recently for dimension reduction. First, second, third and fourth-
495 order statistics of wavelet decomposition sub-bands can be used for dimension reduc-
496 tion [38]. In this chapter, six statistical features are utilized namely mean absolute
497 values of the coefficients in every sub-band, standard deviation of the coefficients
498 in every sub-band, average power of the coefficients in every sub-band, skewness of
499 the signal coefficients in every sub-band, kurtosis of the signal coefficients in every
500 sub-band, ratio of the absolute mean values of coefficients of adjacent sub-bands.

501 **4.4 Prediction and Classification**

502 Biomedical signals can be decomposed into both time and frequency domain using
503 time-frequency methods such as Dual Tree Complex Wavelet Transform (DT-CWT).
504 Deep Learning methods are the result of advances in artificial intelligence research
505 and deliver a raw data processing capability. Moreover, Deep Learning includes
506 multiple layers of computational modules, which work together to process data and
507 yield the decisive outcome. These layers assist in isolating correct features for the
508 product result and their assessment or analysis.

509 The essence of Deep Learning algorithms is that they involve modular layers
510 designed to use universal algorithms to learn the data [53]. These layers form deep
511 neural networks (DNN) blocks. Widely known DNN structures are Convolutional
512 neural networks (CNN) and RNN [53].

513 CNN's architecture is similar to that of neuron communication patterns in the
514 brain. A CNN's convolution process is just like a weight filter that extracts the features
515 from multi-dimensional input data. While using the RNNs, logical sequences are
516 found in the input data. The output of the hidden layer passes through the next layer
517 and also feeds back to itself. The current performance is essentially a cumulative
518 knowledge of the present moment and of the past.

519 The main difference between the RNN and CNN architecture is that only the
520 current input is considered by CNNs, while the current input and the previous input
521 are considered by RNN, i.e. it includes memory logic. On data from the time series,

522 RNN performs marginally better, whereas CNN is good for tasks like classifying
523 images. Across several scientific fields, deep learning architectures have been used,
524 for example across disease prediction [17], clinical imaging [54], computational
525 biology [55] and genomics and proteomics [56].

526 Deep Learning algorithms are adequate to detect intricate patterns for the classifi-
527 cation of the high-dimensional data, particularly EEG data. CNN is a popular neural
528 network for EEG data training since CNN is very efficient in noise reduction [57].
529 Deep Learning solves problems in several fields. However, there is a powerful rela-
530 tionship between DNN and nervous system research. ANNs are used as a model for
531 computing brain function [58], whereas CNNs are employed for the processing of
532 visual information and hidden CNN layer activations, neuronal activity is considered
533 to be correlated with visual sensory motor processing in associated brain regions. In
534 neuroscience, deep networks have a valuable computational aspect as they are statisti-
535 cal time series models of brain neuronal activity [59]. The present period of progress
536 is driving the study of artificial intelligence techniques inspired by neuroscience
537 [36, 58].

538 Artificial intelligence techniques utilize feature vectors that are derived for training
539 from conventional methods of signal processing and provide good accuracy, but these
540 techniques cannot predict a generalized model. The existence of noise and artefacts
541 in data makes detection of features very difficult to manage. Hence, generalizing an
542 automated system with loyal output is a challenging issue, particularly when there are
543 limited samples of training available. At the other hand, in epileptic seizure prediction
544 [60], the ability of deep learning algorithms to automatically learn function opens
545 new ways of investigating. Features learned through Deep Learning techniques are
546 more efficient and robust than features created by hand [61]. Troung et al. [62]
547 developed a prediction method based on CNN by introducing a procedure, which
548 can be extended to all patients with limited preprocessing of EEG data [36]. Tsiouris
549 et al. [15] first used LSTM for an epileptic seizure prediction by comparing the
550 efficiency of different LSTM architectures for 5–30 s segment size of randomly
551 selected inputs. The performance of three LSTM architectures was evaluated using
552 EEG segment feature vectors as inputs to LSTM, in which the feature vector includes
553 specific time-domain features and frequency domain features, besides graph theory
554 local and global features [36].

555 In biomedical engineering, and especially in analyzing biomedical signals, artifi-
556 cial intelligence algorithms are used to solve problems. Researchers achieved real-
557 time prediction and detection. EEG research has considerably improved with the
558 widespread use of mathematical modelling and artificial intelligence techniques.
559 By classifying patterns within the EEG, artificial intelligence approaches have also
560 provided the opportunity to enhance the recognition, making EEG signals useful
561 for recognizing brain disorders and primary diseases. Various experiments have also
562 been carried out on the features of the EEG signals associated with neurological
563 disorders [38, 63].

564 An application software aimed to monitor seizures consists of two models [64]:
565 (i) an epileptic seizure prediction technique, which produces an alarm when it detects
566 a seizure coming up, (ii) a model, which monitor a seizure occurrence. In addition,

567 one simple seizure warning will provide for a patient to leave risky circumstances or
568 acts, such as playing sports or climbing stairs. The techniques of seizure prediction
569 are based on the EEG feature extraction, measured over a limited time span from a
570 few seconds to a few minutes [38].

571 **4.5 Experimental Data**

572 EEG data is downloaded from CHB-MIT Scalp EEG Database.¹ All EEG signals,
573 acquired at the Boston Children's Hospital, includes EEG signals of intractable
574 seizures of pediatric subjects. To classify their seizures and determine their candi-
575 dacy for surgery, subjects were tracked for up to several days following the removal
576 of anti-seizure medication. EEG signal recordings include 23 cases, which were
577 collected from 22 subjects (5 males, ages 3–22; and 17 females, ages 1.5–19). With
578 a resolution of 16 bits, all EEG recordings were sampled at 256 Hz. An International
579 10-20 EEG electrode positions and nomenclature were employed during the signal
580 acquisition [65, 66].

581 For the extraction of EEG segments from the EEG dataset of each subject, a
582 rectangular window with a length of 2048 samples (=8 s) was employed. Since
583 the time of onset of each seizure was known, a minimum number of rectangular
584 windows has been used to cover all seizure events. When removing ictal segments,
585 no overlapping was introduced. Since any seizure requires at least 5 min of pre-ictal
586 data, in order to generate 1000 pre-ictal segments, 8-second EEG segments were
587 extracted.

588 Finally, the experimental dataset containing 3000 8-s EEG segments containing
589 three different classes: inter-ictal, pre-ictal and ictal, which allow testing models of
590 seizure detection and prediction were created. As a result, 1000 inter-ictal, 1000 pre-
591 ictal and 1000 ictal seizures segments were produced. For the time between 30 and
592 15 min preceding to each seizure onset, 8-s long pre-ictal segments were produced.

593 **4.6 Performance Evaluation Measures**

594 The success of the training set is not a good performance measure on an independent
595 test set. A challenging issue is the predicting performance based on limited data. In
596 most realistic limited-data cases, repeated cross-validation method will be encoun-
597 tered. Another matter that is not as simple as it sounds is to compare the output of
598 various artificial intelligence approaches on a particular problem. It is normal for
599 classification problems to calculate the output of a classifier in terms of the error
600 rate. To predict a classifier's output on new data, it is essential to evaluate its error
601 rate on a dataset that has played no role in the prediction model creation. This distinct

¹<https://physionet.org/content/chbmit/1.0.0/>.

dataset is termed as test set. It is known that both the training data and the test data are characteristic samples of the essential question. The test data may be different in nature from the training data in certain instances. It is critical that the test information is not used to construct the classifier in any way. One or more learning schemes use the training data to come up with classifiers. The validation data is utilized to tune the classifier's parameters. Then the test data is utilized to assess the error rate of the tuned model. It is important to choose each of the three sets independently. To accomplish better performance in the parameter tuning, the validation set should be apart from the training set, and the test set should be apart from the training and validation set to achieve an accurate estimate of the true error rate [67].

When the volume of data for training and testing is small, it is common for one-third of the data to be kept for testing and the other two thirds to be used for training. To mitigate any bias induced, the unique sample chosen for holdout is utilized to repeat the whole procedure with various random training and testing samples several times. A certain amount of the data is chosen randomly for training in each iteration, likely with stratification, and the remainder is used for testing. A simple version, however, produces the base of an imperative statistical method known as cross-validation [67].

The typical method to estimate a learning technique's error rate given a single, fixed data sample is to employ 10-fold cross-validation. The data are randomly divided into 10 portions where each portion is defined roughly the same amounts as in the complete dataset. In turn, each part is kept out, and the learning system is trained on the remaining nine-tenths; then the holdout set measures its error rate. The learning process is therefore performed on separate training sets a total of 10 times. Finally, the 10 error estimates are averaged to produce an overall error estimate [67].

The right classifications are the true positives (TP) and true negatives (TN). If the answer is wrongly predicted as yes (or positive), a false positive (FP) is when it is actually no (negative). If the answer is wrongly predicted as negative, a false negative (FN) is when it is actually positive [67].

The most common approach to compare algorithms is the classification efficiency without concentrating on a class. Thus, the generally utilized empirical measure is the accuracy, which does not differentiate between the number of correct labels of different classes [68]:

$$Accuracy = \frac{TP + TN}{TP + FN + TN + FP} \times 100\% \quad (1)$$

On the contrary, two measures, which independently estimate the efficiency of a classifier for different classes are Sensitivity (2) and Specificity (3).

$$Sensitivity = \frac{TP}{TP + FN} \times 100\% \quad (2)$$

$$Specificity = \frac{TN}{TN + FP} \times 100\% \quad (3)$$

642 The positive class measured the indicators of preference [68]. Precision is the
643 relationship between true positives and false positives.

$$645 \quad \textit{Precision} = \frac{TP}{TP + FP} \quad (4)$$

646 A relationship between true positive instances, correctly classified and false-
647 negative instances, misclassified instances called as recall.

$$649 \quad \textit{Recall} = \frac{TP}{TP + FN} \quad (5)$$

650 The correct classification of labels within the various classes is distinguished by
651 all three measures. They focus on positive examples. Recall is a function of correctly
652 classified examples (true positives) and misclassified examples (false negatives).
653 Precision is a result of true positives and instances that are misclassified as positive
654 (false positives). The F-measure is a major indicator that supports algorithms with
655 higher sensitivity and challenges algorithms with higher specificity.

$$658 \quad \textit{F-measure} = 2 \times \frac{\textit{Precision} \times \textit{Recall}}{\textit{Precision} + \textit{Recall}} = \frac{2 \times TP}{2 \times TP + FP + FN} \quad (6)$$

658 This predicted percentage is taken into account by a measure termed the Kappa
659 statistic by deducting it from the successes of the predictor. The Kappa statistic is
660 employed to evaluate the agreement between the categorizations of a dataset predicted
661 and observed while correcting for a relationship, which happens by chance. However,
662 it does not take costs into account, as with the simple success rate [67]. The kappa
663 statistic was defined by Cohen [69] as an agreement index and defined as follows,

$$665 \quad K = \frac{P_0 - P_e}{1 - P_e} \quad (7)$$

666 where P_0 is observed agreement and P_e measures the agreement expected by chance
667 [70].

668 4.7 Experimental Results

669 The objective of this chapter is to establish a segment-based model for EEG signal
670 classification, which can be implemented using artificial intelligence in automatic
671 interval-based seizure prediction or onset detection systems. Shorter EEG segments
672 have also been extracted from the utilized database that can provide an opportunity to
673 build realistic and computationally efficient systems for seizure prediction. The goal
674 is to build a segment-based model for classifying EEG signals using the CHB-MIT
675 EEG database, which can be used to automatic interval-based seizure prediction.

676 Thus, the contribution of this chapter is to find a better model by comparing three
677 different commonly utilized artificial intelligence techniques, namely ANN, DNN,
678 CNN.

679 ANN is a learning algorithm that is stimulated by biological neuron networks to
680 solve different classification problems. The best accuracy is achieved with a hidden
681 layer of 128 neurons in the ANN implementation. ADAM is employed as an optimizer
682 and Rectified Linear Unit (ReLU) as an activation function. In addition, in the model,
683 batch normalization is employed.

684 A DNN is a particular form of ANN with more than 3 layers that implicitly fuses
685 the extraction and classification of features into a signal learning body and creates
686 a decision-making mechanism directly. In the complex field of machine learning,
687 these types of neural networks have achieved tremendous success in recent years.
688 By using the Tensor-Flow library in the Python programming language, DNN is
689 implemented. There is currently no specific technique for constructing an optimized
690 neural network with the correct number of layers and number of neurons for each
691 layer. Hence, by conducting a large range of trials, DNN is constructed empirically.
692 DNN parameters such as the activation function, the number of hidden layers, the
693 number of learning steps and the number of neurons in each layer are configured
694 manually in each trial. The classification performance of the testing set is assessed
695 for each manual configuration. The best classification accuracy is realized with a
696 DNN consists of 3 hidden layers, with 128, 64, and 32 neurons respectively, after
697 the tedious manual process. The ReLU activation function is utilized in all layers of
698 the DNN classifier. The Softmax function is employed in the output layer, and the
699 cross entropy is used as a cost function.

700 For the classification of EEG signals, a 7-layer deep convolutional neural network
701 was developed. The deep convolutional neural network model architecture includes
702 the classical CNN layers, but the 1D-CNN structure is prevalent. Feature maps,
703 which represent the EEG segments are exposed to convolution process with weights
704 of different sizes in 1D convolutional layers. 1D convolution is carried out in the
705 first layer of the model with 128 vectors on the input features. This layer's activation
706 outputs are normalized for each batch utilizing the batch normalization layer. New
707 feature maps are created in the 1D max pooling layer by taking the maximum values
708 in the region defined on the feature maps obtained from the previous layers. In the
709 next 1D convolution and 1D max pooling layers, these procedures are repeated.
710 The rectifier linear unit (ReLU) is employed as an activation function. The stride
711 2 is used for all inputs. The developed deep convolutional neural network has a
712 flattened layer on the 5th layer in order to obtain the feature maps from the 4th
713 layer with an appropriate size as an input to the subsequent layers of the network.
714 Multidimensional input feature vectors are transformed into one-dimensional output
715 data by this layer. A dense-connected neural network layer consisting of 64 units is
716 fed by the features taken from the flattened layer. There are 32 units for the last fully
717 connected layer (layer 7). The number of units is determined as 128 and 64 in layer 5
718 and layer 6 respectively. Layer 5 and 6 activation functions are still ReLU, while the
719 Softmax function is employed as the last layer activation function. The prediction of
720 the class to which the input data belongs is achieved through the use of the Softmax



Table 1 Classification accuracy of ANN, DNN and CNN for epileptic seizure prediction and detection

Performance	ANN	DNN	CNN
Training accuracy (%)	98.59	99.26	100.00
Validation accuracy (%)	99.40	98.95	99.70
Testing accuracy (%)	98.08	98.38	99.09
Inter-ictal (%)	98.00	98.00	98.18
Pre-ictal (%)	98.16	100.00	100.00
Ictal (%)	98.08	97.12	98.72
Precision	0.982	0.984	0.999
Recall	0.981	0.984	0.991
F-measure	0.981	0.984	0.991
Kappa	0.971	0.976	0.986

layer. The cross-entropy function is utilized for loss assessment during the network training. ADAM is employed for network training. Furthermore, in order to prevent overfitting during the learning process, layers 3, 4 and 5 have a dropout parameter. The probability of a dropout is equal to 0.8. The corresponding training set has been utilized for training the model for each scheme, and the test set was used for final performance assessment. 20% of the original training set was randomly taken as the validation set for tuning the hyperparameters while training the network. After finding the optimal parameters, the model was retrained with the learning rate of 0.01 and a momentum value of 0.90. The network was trained with a batch size of 200 and 25 epochs were used in the training process.

Table 1 presents the performance of three architectures in epileptic seizure prediction and detection, for various phases, inter-ictal, pre-ictal and ictal. Features have been extracted from raw EEG signals using dual tree complex wavelet transform.

With an average accuracy of 98.08%, the least effective approach was ANN. CNN classifier achieved a total classification accuracy of 99.09%, which is the best result obtained. DNN is the second-best among the classifiers and reached a total accuracy of 97.12%. Accordingly, all classifiers achieved good performance in F-measure and Kappa statistics. For pre-ictal state, DNN and CNN achieved 98.38% and 99.09% testing accuracy, respectively.

5 Discussion

In the success of the classification model, feature extraction plays an critical role. The Wavelet-based feature extraction technique, a DT-CWT-based approach, has advantages and drawbacks. The computational burden of examining DT-CWT with an increase in the number of potential levels is one of the difficulties of the DT-CWT-based methodology. Deep Learning has been proposed as a promising approach that can also be used to successfully predict and diagnose epileptic seizures. It should be

747 noted that while in some cases, seizure prediction has been difficult, Deep Learning
748 methods seem to work extremely better and excellent at classifying EEG signals [71].
749 Compared to the direct use of the raw EEG samples as input to the classifier, feature
750 extraction preceding the classification are mostly preferable. The benefit of feature
751 extraction is that it delivers a simpler and easier way to acquire secret information
752 about the frequency quality of the signal or brain areas.

753 In principle, if the size of the deep network was significantly increased by adding
754 more layers to compensate for the increased input size of the direct supply of the
755 EEG signals, better EEG signal representation would be learned. The computational
756 cost of training larger CNN models is, however, growing [15].

757 Instead of training the deep networks with the extracted feature vector, imple-
758 mented seizure prediction approach helps work in more controllable circumstances
759 by basically simulating the employment of a deep CNN. Deep Learning architectures
760 are assessed utilizing EEG data from the CHB-MIT database. In previous research,
761 the extracted features using DT-CWT have already been successfully used for the
762 prediction of epileptic seizures and according to the DT-CWT created a more infor-
763 mative feature space as a result of this research, provides a considerable gain in clas-
764 sification efficiency. These findings show the benefit of deep networks in EEG-based
765 seizure prediction using CNN and DNN [15].

766 Within a five-to-30 min' timeframe (pre-ictal segment), seizure prediction is effec-
767 tively accomplished, which happens right before seizure onset. Thus, before a seizure
768 happens, there is ample time to make clinical interventions. In convolutional layers,
769 the number of kernel coefficients and the number of coefficient weights are very large.
770 Seizures are detected before they occur, but steps cannot be taken until an epileptic
771 seizure happens. Three distinct groups are defined by one technique: inter-ictal,
772 pre-ictal and ictal.

773 This chapter explored the use of Deep Learning and EEG recordings to predict
774 epileptic seizures. It is proven that CNN's application to given the existence of EEG,
775 which can be modelled as two- or three-dimensional high-dimensionality [19]. Indi-
776 cation of the efficacy of the implemented method is achieved through the evaluation
777 of various performance indicators, such as 99.09% accuracy.

778 The high computational time during CNN training in a Python implementation is
779 a drawback of the application of CNNs to EEG recordings. Combining EEG signals
780 with the basic CNN algorithm is the most critical part of obtaining these results.
781 This research is one of the first investigations to discuss the issue of epileptic seizure
782 prediction based on EEG modality and deep learning.

783 The abilities of the artificial intelligence techniques have so far shown in different
784 practical classification problems. Deep Learning techniques improve the general-
785 ization accuracy on a wide variety of problems. Consequently, in this chapter, the
786 performance of popular artificial intelligence techniques is evaluated for epileptic
787 seizure prediction and detection. To evaluate the performance of studied artificial
788 intelligence techniques, a comparative study is realized by employing the publicly
789 available EEG data set containing inter-ictal, pre-ictal and ictal states.

790 The proposed technique, CNN seems to be suitable for epileptic seizure prediction
791 and detection. According to the presented results in the epileptic seizure prediction
792 and detection, we should emphasize the following:

- 793 • CNN, and DNN may be successfully applied in the epileptic seizure prediction
794 and detection due to their stable and high performance presented in Table 1.
- 795 • CNN is the best-applied method with an average accuracy above 99%.
- 796 • DNN has achieved the best result with an average accuracy of 98.38%.
- 797 • ANN has achieved the lowest performance, with an average accuracy of 98.08%.
- 798 • The drawback of deep learning models is a significant increase in computational
799 cost.

800 6 Conclusion

801 Artificial intelligence methods are becoming gradually efficient in epileptic seizure
802 prediction and detection. Several technical and practical solutions still needed to
803 solve their full potential. In this chapter, the use of artificial intelligence methods
804 in the epileptic seizure prediction and detection by employing only EEG signals
805 is presented. Moreover, CNN classification framework is presented to distinguish
806 different states related to epilepsy. This neurological disorder results in severe health-
807 related problems. The experimental validation was implemented with the widely
808 used epileptic EEG dataset. Regarding the comparison of deep learning classification
809 algorithms, CNN revealed better accuracy, while the DNN algorithm showed lower
810 performance.

811 In summary, different artificial intelligence techniques are compared to assist in
812 the early prediction and detection of the epileptic seizure using CHB-MIT Scalp EEG
813 Dataset. CNN method has achieved the best results in the prediction and detection of
814 the epileptic seizure. The proposed model for the automatic prediction and detection
815 of the epileptic seizure includes 4 steps: (1) denoising with MSPCA (2) feature
816 extraction with DT-CWT (3) Dimension reduction by using statistical values of each
817 sub-bands (4) classification with artificial intelligence techniques.

818 As the amount and complexity of EEG data increases, Deep Learning algorithms
819 are beginning to show their ability to manage the unpredictable existence of EEG
820 signals and open up new possibilities in demanding biomedical applications such as
821 prediction of epileptic seizures. Deep Learning was presented in seizure prediction
822 and proved to be an ideal instrument for the analysis of EEG pre-ictal and ictal
823 signals. In any pre-ictal period tested, the proposed technique was able to deliver
824 accurate seizure prediction that had not been achieved before.

825 The proposed approach needs to be thoroughly checked with more EEG data
826 in clinical practice, as the CHBMIT database includes mainly pediatric signals.
827 However, the findings of this chapter deliver clear signs of its effectiveness as an
828 important epilepsy prediction tool and its timely intervention for people. Moreover,
829 the presented approach can be used for any type of disease prediction as well.

830 The limitation of this study lies in the assessment process, as the small amount of
 831 pre-ictal EEG segments resulted in using segmented data to minimize the effect of
 832 overfitting and instead force the Deep Learning models to extract more generic pre-
 833 ictal information from the entire pre-ictal state period. This technique does not allow
 834 the average prediction time to be evaluated. A similar seizure prediction system that
 835 would separate timely pre-ictal trends in this direction and provide various warnings
 836 to decrease seizure onset could help predict seizures more precisely and minimize
 837 false predictions and is intended as future work. It applies additional hyperparameters
 838 to the model, such as weights, resulting in an improvement in model training time.

839 References

- 840 1. J. Muthuswamy, Biomedical signal analysis, in *Standard Handbook of Biomedical Engineering*
 841 *and Design*, vol. 14, ed. by M. Kutz (McGraw-Hill Education, New York, 2004), pp. 18
- 842 2. L.T. Mainardi, A.M. Bianchi, S. Cerutti, Digital biomedical signal acquisition and processing,
 843 in *Medical Devices and Systems* (CRC Press, 2006), pp. 49–72
- 844 3. S. Palaniappan, R. Awang, *Intelligent Heart Disease Prediction System Using Data Mining*
 845 *Techniques* (2008), pp. 108–115
- 846 4. R. Wu, W. Peters, M.W. Morgan, The next generation of clinical decision support: linking
 847 evidence to best practice. *J. Healthc. Inf. Manag. JHIM* **16**(4), 50 (2002)
- 848 5. S.D. Culler, M.L. Parchman, M. Przybylski, Factors related to potentially preventable
 849 hospitalizations among the elderly. *Med. Care*, 804–817 (1998)
- 850 6. N. Yiannakoulis, D. Schopflocher, L. Svenson, Using administrative data to understand the
 851 geography of case ascertainment. *Chronic Dis. Can.* **30**(1), 20–28 (2009)
- 852 7. T. McCormick, C. Rudin, D. Madigan, A hierarchical model for association rule mining of
 853 sequential events: an approach to automated medical symptom prediction (2011)
- 854 8. E.S. Fisher, D.J. Malenka, J.E. Wennberg, N.P. Roos, Technology assessment using insurance
 855 claims: example of prostatectomy. *Int. J. Technol. Assess. Health Care* **6**(2), 194–202 (1990)
- 856 9. M.E. Hossain, A. Khan, M.A. Moni, S. Uddin, Use of electronic health data for disease
 857 prediction: a comprehensive literature review. *IEEE/ACM Trans. Comput. Biol. Bioinform.*
 858 (2019)
- 859 10. C. Zhang, L. Zhu, C. Xu, R. Lu, PPDP: an efficient and privacy-preserving disease prediction
 860 scheme in cloud-based e-Healthcare system. *Future Gener. Comput. Syst.* **79**, 16–25 (2018)
- 861 11. H. Yin, N.K. Jha, A health decision support system for disease diagnosis based on wearable
 862 medical sensors and machine learning ensembles. *IEEE Trans. Multi-Scale Comput. Syst.* **3**(4),
 863 228–241 (2017)
- 864 12. G. Bieber, M. Haescher, M. Vahl, Sensor requirements for activity recognition on smart watches
 865 (2013), pp. 1–6
- 866 13. D. Malathi, R. Logesh, V. Subramaniaswamy, V. Vijayakumar, A.K. Sangaiah, Hybrid
 867 reasoning-based privacy-aware disease prediction support system. *Comput. Electr. Eng.* **73**,
 868 114–127 (2019)
- 869 14. A. Petrosian, D. Prokhorov, R. Homan, R. Dasheiff, D. Wunsch II, Recurrent neural network
 870 based prediction of epileptic seizures in intra-and extracranial EEG. *Neurocomputing* **30**(1–4),
 871 201–218 (2000)
- 872 15. K.M. Tsiouris, V.C. Pezoulas, M. Zervakis, S. Konitsiotis, D.D. Koutsouris, D.I. Fotiadis, A
 873 long short-term memory deep learning network for the prediction of epileptic seizures using
 874 EEG signals. *Comput. Biol. Med.* **99**, 24–37 (2018)
- 875 16. U.R. Acharya, S.L. Oh, Y. Hagiwara, J.H. Tan, H. Adeli, Deep convolutional neural network
 876 for the automated detection and diagnosis of seizure using EEG signals. *Comput. Biol. Med.*
 877 **100**, 270–278 (2018)

- 878 17. H. Khan, L. Marcuse, M. Fields, K. Swann, B. Yener, Focal onset seizure prediction using
879 convolutional networks. *IEEE Trans. Biomed. Eng.* **65**(9), 2109–2118 (2017)
- 880 18. R. San-Segundo, M. Gil-Martín, L.F. D'Haro-Enríquez, J.M. Pardo, Classification of epileptic
881 EEG recordings using signal transforms and convolutional neural networks. *Comput. Biol.
882 Med.* **109**, 148–158 (2019)
- 883 19. R. Rosas-Romero et al., Prediction of epileptic seizures with convolutional neural networks
884 and functional near-infrared spectroscopy signals. *Comput. Biol. Med.* **111**, 103355 (2019)
- 885 20. D. Jain, V. Singh, Feature selection and classification systems for chronic disease prediction:
886 a review. *Egypt. Inform. J.* **19**(3), 179–189 (2018)
- 887 21. S. Huda, J. Yearwood, H.F. Jelinek, M.M. Hassan, G. Fortino, M. Buckland, A hybrid feature
888 selection with ensemble classification for imbalanced healthcare data: A case study for brain
889 tumor diagnosis. *IEEE Access* **4**, 9145–9154 (2016)
- 890 22. M. Chen, J. Yang, X. Zhu, X. Wang, M. Liu, J. Song, Smart home 2.0: Innovative smart home
891 system powered by botanical IoT and emotion detection. *Mob. Netw. Appl.* **22**(6), 1159–1169
892 (2017)
- 893 23. M. Chen, Y. Zhang, M. Qiu, N. Guizani, Y. Hao, SPHA: smart personal health advisor based
894 on deep analytics. *IEEE Commun. Mag.* **56**(3), 164–169 (2018)
- 895 24. K. He, J. Chen, R. Du, Q. Wu, G. Xue, X. Zhang, Deypos: deduplicatable dynamic proof of
896 storage for multi-user environments. *IEEE Trans. Comput.* **65**(12), 3631–3645 (2016)
- 897 25. M. Usama, B. Ahmad, W. Xiao, M.S. Hossain, G. Muhammad, Self-attention based recurrent
898 convolutional neural network for disease prediction using healthcare data. *Comput. Methods
899 Programs Biomed.* **190**, 105191 (2020)
- 900 26. A.K. Verma, S. Pal, S. Kumar, Comparison of skin disease prediction by feature selection using
901 ensemble data mining techniques. *Inform. Med. Unlocked* **16**, 100202 (2019)
- 902 27. E. Alpaydin, *Introduction to Machine Learning* (MIT press, 2014)
- 903 28. N. Barakat, A.P. Bradley, M.N.H. Barakat, Intelligent support vector machines for diagnosis
904 of diabetes mellitus. *IEEE Trans. Inf. Technol. Biomed.* **14**(4), 1114–1120 (2010)
- 905 29. A. Ahlemeyer-Stubbe, S. Coleman, *A Practical Guide to Data Mining for Business and Industry*
906 (Wiley, 2014)
- 907 30. Y. Bengio, Learning deep architectures for AI. *Found. Trends® Mach. Learn.* **2**(1), 1–127
908 (2009)
- 909 31. G.E. Hinton, R.R. Salakhutdinov, Reducing the dimensionality of data with neural networks.
910 *Science* **313**(5786), 504–507 (2006)
- 911 32. A. Subasi, *Practical guide for biomedical signals analysis using machine learning techniques,
912 a MATLAB based approach* (Elsevier, First, 2019)
- 913 33. N. Fayyaz Khan, M. Kamil, A. Hussain, M. Sajjad, Detection and classification of vehicle-
914 type by using convolution neural network. Presented at the The 4th International Conference
915 on Next Generation Computing 2018 (2018)
- 916 34. S.N. Rakhade, F.E. Jensen, Epileptogenesis in the immature brain: emerging mechanisms. *Nat.
917 Rev. Neurol.* **5**(7), 380 (2009)
- 918 35. M.J. England, C.T. Liverman, A.M. Schultz, L.M. Strawbridge, Epilepsy across the spectrum:
919 promoting health and understanding.: a summary of the Institute of Medicine report. *Epilepsy
920 Behav.* **25**(2), 266–276 (2012)
- 921 36. K. Rasheed et al., Machine learning for predicting epileptic seizures using EEG signals: a
922 review. *IEEE Rev. Biomed. Eng.* (2020), pp. 1–1. <https://doi.org/10.1109/rbme.2020.3008792>
- 923 37. L. Sörnmo, P. Laguna, *Bioelectrical Signal Processing in Cardiac and Neurological Applica-
924 tions*, vol. 8 (Academic Press, San Diego, California, 2005)
- 925 38. A. Subasi, Biomedical signal analysis and its usage in healthcare, in *Biomedical Engineering
926 and its Applications in Healthcare* (Springer, 2019), pp. 423–452
- 927 39. M.M.N. Mannan, M.A. Kamran, M.Y. Jeong, Identification and removal of physiological
928 artifacts from electroencephalogram signals: A review. *IEEE Access* **6**, 30630–30652 (2018)
- 929 40. H. Chu, C.K. Chung, W. Jeong, K.-H. Cho, Predicting epileptic seizures from scalp EEG based
930 on attractor state analysis. *Comput. Methods Programs Biomed.* **143**, 75–87 (2017)

- 931 41. N.D. Truong et al., Convolutional neural networks for seizure prediction using intracranial and
932 scalp electroencephalogram. *Neural Netw.* **105**, 104–111 (2018)
- 933 42. Y. Gao, B. Gao, Q. Chen, J. Liu, Y. Zhang, Deep convolutional neural network-based epileptic
934 electroencephalogram (EEG) signal classification. *Front. Neurol.* **11**, 375 (2020). <https://doi.org/10.3389/fneur.2020.00375>
- 935
936 43. E. Alickovic, J. Kevric, A. Subasi, Performance evaluation of empirical mode decomposition,
937 discrete wavelet transform, and wavelet packed decomposition for automated epileptic seizure
938 detection and prediction. *Biomed. Signal Process. Control* **39**, 94–102 (2018)
- 939 44. X. Wei, L. Zhou, Z. Zhang, Z. Chen, Y. Zhou, Early prediction of epileptic seizures using a
940 long-term recurrent convolutional network. *J. Neurosci. Methods* **327**, 108395 (2019)
- 941 45. C.-L. Liu, B. Xiao, W.-H. Hsaio, V.S. Tseng, Epileptic Seizure prediction with multi-view
942 convolutional neural networks. *IEEE Access* **7**, 170352–170361 (2019)
- 943 46. S. Rukhsar, Y. Khan, O. Farooq, M. Sarfraz, A. Khan, Patient-specific epileptic seizure predic-
944 tion in long-term scalp eeg signal using multivariate statistical process control. *IRBM* **40**(6),
945 320–331 (2019)
- 946 47. S. Sanei, *Adaptive Processing of Brain Signals*. The Atrium, Southern Gate, Chichester, West
947 Sussex, PO19 8SQ, (John Wiley & Sons, UK, 2013)
- 948 48. B.R. Bakshi, Multiscale PCA with application to multivariate statistical process monitoring.
949 *AIChE J.* **44**(7), 1596–1610 (1998)
- 950 49. B. Graimann, B. Allison, G. Pfurtscheller, Brain–computer interfaces: a gentle introduction, in
951 *Brain-Computer Interfaces* (Springer, 2009), pp. 1–27
- 952 50. S. Siuly, Y. Li, Y. Zhang, *EEG Signal Analysis and Classification* (Springer, 2016)
- 953 51. A. Phinyomark, F. Quaine, S. Charbonnier, C. Serviere, F. Tarpin-Bernard, Y. Laurillau, EMG
954 feature evaluation for improving myoelectric pattern recognition robustness. *Expert Syst. Appl.*
955 **40**(12), 4832–4840 (2013)
- 956 52. A. Wolczowski, R. Zdunek, Electromyography and mechanomyography signal recognition:
957 Experimental analysis using multi-way array decomposition methods. *Biocybern. Biomed.*
958 *Eng.* **37**(1), 103–113 (2017). <https://doi.org/10.1016/j.bbe.2016.09.004>
- 959 53. Y. LeCun, Y. Bengio, G. Hinton, Deep learning. *Nature* **521**(7553), 436–444 (2015)
- 960 54. J.-G. Lee et al., Deep learning in medical imaging: general overview. *Korean J. Radiol.* **18**(4),
961 570–584 (2017)
- 962 55. C. Angermueller, T. Pärnamaa, L. Parts, O. Stegle, Deep learning for computational biology.
963 *Mol. Syst. Biol.* **12**(7), 878 (2016)
- 964 56. E. Asgari, M.R. Mofrad, Continuous distributed representation of biological sequences for
965 deep proteomics and genomics. *PLoS ONE* **10**(11), e0141287 (2015)
- 966 57. G. Li, C.H. Lee, J.J. Jung, Y.C. Youn, D. Camacho, Deep learning for EEG data analytics: a
967 survey. *Concurr. Comput. Pract. Exp.* e5199 (2019)
- 968 58. D. Hassabis, D. Kumaran, C. Summerfield, M. Botvinick, Neuroscience-inspired artificial
969 intelligence. *Neuron* **95**(2), 245–258 (2017)
- 970 59. V. Jain, H.S. Seung, S.C. Turaga, Machines that learn to segment images: a crucial technology
971 for connectomics. *Curr. Opin. Neurobiol.* **20**(5), 653–666 (2010)
- 972 60. I. Kiral-Kornek et al., Epileptic seizure prediction using big data and deep learning: toward a
973 mobile system. *EBioMedicine* **27**, 103–111 (2018)
- 974 61. A. Antoniadis, L. Spyrou, C.C. Took, S. Sanei, *Deep Learning for Epileptic Intracranial EEG*
975 *Data* (2016), pp. 1–6
- 976 62. N.D. Truong, A.D. Nguyen, L. Kuhlmann, M.R. Bonyadi, J. Yang, O. Kavehei, A gener-
977 alised seizure prediction with convolutional neural networks for intracranial and scalp
978 electroencephalogram data analysis. *ArXiv170701976* (2017)
- 979 63. R. Begg, D.T. Lai, M. Palaniswami, *Computational Intelligence in Biomedical Engineering*
980 (CRC Press, 2008)
- 981 64. M. Winterhalder, T. Maiwald, H. Voss, R. Aschenbrenner-Scheibe, J. Timmer, A. Schulze-
982 Bonhage, The seizure prediction characteristic: a general framework to assess and compare
983 seizure prediction methods. *Epilepsy Behav.* **4**(3), 318–325 (2003)

- 984 65. A.H. Shoeb, *Application of Machine Learning to Epileptic Seizure Onset Detection and*
985 *Treatment* (2009)
- 986 66. A.L. Goldberger et al., PhysioBank, PhysioToolkit, and PhysioNet: components of a new
987 research resource for complex physiologic signals. *Circulation*, **101**(23), Art. no. 23 (2000)
- 988 67. M. Hall, I. Witten, E. Frank, *Data mining: Practical machine learning tools and techniques*.
989 Kaufmann Burlingt. (2011)
- 990 68. M. Sokolova, N. Japkowicz, S. Szpakowicz, *Beyond Accuracy, F-score and ROC: A Family of*
991 *Discriminant Measures for Performance Evaluation* (2006), pp. 1015–1021
- 992 69. J. Cohen, A coefficient of agreement for nominal scales. *Educ. Psychol. Meas.* **20**(1), 37–46
993 (1960)
- 994 70. Z. Yang, M. Zhou, Kappa statistic for clustered physician–patients polytomous data. *Comput.*
995 *Stat. Data Anal.* **87**, 1–17 (2015)
- 996 71. N. LaPierre, C.J.-T. Ju, G. Zhou, W. Wang, MetaPheno: a critical evaluation of deep learning
997 and machine learning in metagenome-based disease prediction. *Methods* **166**, 74–82 (2019)

Author Queries

Chapter 14

Query Refs.	Details Required	Author's response
AQ1	Please check the edit made in the sentence 'Across several scientific fields ...', and correct if necessary.	

UNCORRECTED PROOF

MARKED PROOF

Please correct and return this set

Please use the proof correction marks shown below for all alterations and corrections. If you wish to return your proof by fax you should ensure that all amendments are written clearly in dark ink and are made well within the page margins.

<i>Instruction to printer</i>	<i>Textual mark</i>	<i>Marginal mark</i>
Leave unchanged	... under matter to remain	Ⓟ
Insert in text the matter indicated in the margin	∧	New matter followed by ∧ or ∧ [Ⓢ]
Delete	/ through single character, rule or underline or ┌───┐ through all characters to be deleted	Ⓞ or Ⓞ [Ⓢ]
Substitute character or substitute part of one or more word(s)	/ through letter or ┌───┐ through characters	new character / or new characters /
Change to italics	— under matter to be changed	↵
Change to capitals	≡ under matter to be changed	≡
Change to small capitals	≡ under matter to be changed	≡
Change to bold type	~ under matter to be changed	~
Change to bold italic	≈ under matter to be changed	≈
Change to lower case	Encircle matter to be changed	≡
Change italic to upright type	(As above)	⊕
Change bold to non-bold type	(As above)	⊖
Insert 'superior' character	/ through character or ∧ where required	Υ or Υ under character e.g. Υ or Υ
Insert 'inferior' character	(As above)	∧ over character e.g. ∧
Insert full stop	(As above)	⊙
Insert comma	(As above)	,
Insert single quotation marks	(As above)	ʹ or ʸ and/or ʹ or ʸ
Insert double quotation marks	(As above)	ʼ or ʻ and/or ʼ or ʻ
Insert hyphen	(As above)	⊞
Start new paragraph	┌	┌
No new paragraph	┐	┐
Transpose	└┐	└┐
Close up	linking ○ characters	Ⓞ
Insert or substitute space between characters or words	/ through character or ∧ where required	Υ
Reduce space between characters or words		↑