

Computational techniques for ECG analysis and interpretation in light of their contribution to medical advances

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Abstract:

Widely developed for clinical screenings, electrocardiogram (ECG) recordings capture the cardiac electrical activity from the body surface. ECG analysis can therefore be a crucial first step to help diagnose, understand and predict cardiovascular disorders responsible for 30% of deaths worldwide. Computational techniques, and more specifically machine learning techniques and computational modelling are powerful tools for classification, clustering and simulation, and they have recently been applied to address the analysis of medical data, especially ECG data. This review describes the computational methods in use for ECG analysis, with a focus on machine learning and 3D computer simulations, as well as their accuracy, clinical implications and contributions to medical advances. The first section focuses on heartbeat classification and the techniques developed to extract and classify abnormal from regular beats. The second section focuses on patient diagnosis from whole recordings, applied to different diseases. The third section presents real-time diagnosis and applications to wearable devices. The fourth section highlights the recent field of personalized ECG computer simulations and their interpretation. Finally, the discussion section outlines the challenges of ECG analysis and provides a critical assessment of the methods presented. The computational methods reported in this review are a strong asset for medical discoveries and their translation to the clinical world may lead to promising advances.

Keywords: machine learning, computer simulations, electrocardiogram, interpretation and analysis, classification

1. Introduction

Cardiovascular disorders are a major burden worldwide, causing 30% of the deaths in the world according to the World Health Organization (1). Therefore, an early detection of the patients at risk, and a better understanding of the disease mechanisms are crucial to improve diagnosis and treatment. Widely used by clinicians as a routine modality in hospitals, electrocardiogram (ECG) recordings capture the propagation of the electrical signal in the heart from the body surface. Therefore, many cardiac structural or electrophysiological abnormalities have a signature on the ECG and their identification can help diagnose cardiac disorders. ECG recordings include different formats: Holter ECGs record the electrical activity of the heart over longer period of time (several hours), whereas standard 12-lead ECGs provide information on cardiac activity from 12 different perspectives (leads) over several heart beats. Manually studying large amount of ECG data can be tedious and time consuming. Therefore, there is a need for powerful computational methods to maximise the information extracted from comprehensive ECG datasets (2). The variety of ECG formats and their clinical applications also call for a diversity of computational techniques to address this need.

In this review, we aim to describe the clinical applications and main machine learning methods currently used for ECG analysis to enable heartbeat and patient classification, and advanced computer simulation to explain cardiac ECG phenotypes. Whereas ECG signal processing techniques have been described before (3), here we review how machine learning methods have recently been used to automatically learn the dataset structure in order to make predictions. Learning can be supervised (training examples are given to the algorithm which learns the dataset relationships before testing them on unknown data), or unsupervised (the algorithm learns by itself the data structure). Classification of heartbeats (4) (5) (6) is

probably the most developed application of machine learning to the ECG. It focuses on the detection of abnormal, irregular beats that may occur at unpredicted times and help detect arrhythmias. Other studies focus on patient classification (7) (8) (9), based on the overall behaviour of the ECG, to diagnose specific diseases. In addition, with the development of wearable devices and the need for real-time diagnosis, other challenges such as speed or memory requirements have emerged, requiring the adaptation of these methods for quick classification (10) (11) (12). Analysing the ECG with machine learning methods is a promising approach but dealing with medical data for clinical applications raises some additional challenges, such as the lack of databases available for validation and the need to interpret ECG abnormalities at the organ and cellular level. 3D computer simulations are a powerful tool to address these issues. They allow personalized simulations of the ECG, allowing the interpretation of the ECG signals (13) (14) (15) as well as the generation of synthetic data for training and validation purposes.

2. Heartbeat classification

A heartbeat is defined as the sequence of electrical events happening in a whole cardiac cycle, from depolarization to repolarization. For a normal beat in sinus rhythm it includes the P wave, the QRS complex and the T wave. Heartbeat classification focuses on the automatic identification of beats of different nature, and can be useful for detecting ectopic beats or arrhythmic events. It is the most developed application of machine learning methods to ECG analysis, mostly because of the databases publically available for training and testing such as the MIT-BIH (16), composed of 48 half-hour excerpts of two-channel ambulatory ECG recordings and initially developed to evaluate arrhythmia detectors. Other databases are also available and widely used to develop these techniques such as those contained in Physionet's

Physiobank, INCART, or the American Heart Association database (17) (Table 1). The objective, performance and validation of the studies presented in the section below are summarized in Table 2.

2.1. Clinical objectives and ECG data

The MIT-BIH Arrhythmia database considers fifteen heartbeat classes, which have been also used in other studies (18). Due to this variety of heartbeats label sets, the classification objectives of the different studies may be different, making their performances harder to compare. Some studies focus on binary classification to distinguish between normal and abnormal beats (19) (20) , normal and premature ventricular beats (21) (22) or normal and diseased beats (23). Other works follow the classification recommendations of labelling rules such as the AAMI guidelines (normal, ventricular, supraventricular, fusion of normal and ventricular, and unknown beats (5)). However, most of these techniques report their classification performances in the same metrics, facilitating their comparison. Accuracy (%) measures the amount of correctly classified samples compared to the total number of samples classified. Sensitivity (resp. specificity) (%), or true positive (resp. negative) rate, measures the amount of positive (resp. negative) samples correctly classified.

Heartbeat classification can also be performed in recordings of different length, such as standard 12-lead ECGs, lasting for several seconds, or Holter ECGs, recorded for several hours. Longer recordings allow the analysis of the ECG over time and the identification of time-dependent abnormalities, such as changes in the beat morphologies with time or changes in heart rate. In addition to the length of the recording, the number of ECG leads may differ and various methods are proposed to handle multi-channel data. Some studies focus only on single lead data (24). Others combine features computed over several different leads in a

single feature vector (18). Another approach is to combine the output of classifiers when applied over the different leads following a voting approach. For example, in Zhang and Luo's (2014) work (25), the outputs of several support vector machine classifiers were merged based on the decision of each classifier.

2.2. Feature extraction and dimensionality reduction

Most machine learning classification techniques require the definition of a feature vector to describe the ECG beat and the training of a classifier. Each heartbeat is composed of multiple waves describing different events of the cardiac cycle (P-wave, QRS complex, T-wave) (Figure 1). Morphological features, such as slopes, peaks, amplitudes (26) (18), describe the shape of the ECG waveforms. They may be able to capture changes in the heart rhythm, such as sinus rhythm versus fibrillation, in which the complexes exhibit different morphologies. Some works focus on time interval features to characterize the dynamics of ECG phenomena such as QRS duration, QT interval or heart rate, defined as the number of beats per unit of time (27) (28) (20) (29) (30). Morphological features include the coefficients of the Hermite transform, the wavelet transform or the discrete cosine transform (21) (31) that aim at modelling the ECG beat instead of extracting features from the raw data. In most studies, a combination of these features is used to characterize the ECG signal. Other works such as Llamedo et al (2012) (32) combine the signal's multiple channels before performing feature extraction. They investigated several strategies such as combining features from the wavelet transform (a time-frequency representation of the signal by mathematical functions called wavelets) from all the leads, computing the wavelet transform from the vectocardiogram leads, or computing the features from the two first principal component of the ECG leads' principal component analysis.

One of the challenges is that the ratio between the amount of available training data and the number of extracted features is too small, which may lead to overfitting. The number of features must therefore be reduced for good generalization and performance and two main techniques are usually used: dimensionality reduction and feature selection. Dimensionality reduction aims at reducing the size of the space in which the data is represented by computing a reduced number of dimensions that contain most of the information of the dataset. As many features can be extracted from ECG signals, dimensionality reduction algorithms are often performed before running the classifier. Examples of dimensionality reduction techniques include principal component analysis (PCA) (linear or non-linear) (27) or linear discriminant analysis (18). Feature selection selects only a small subset of the most significant features in the classification. For this purpose, some studies include an optimization step testing different feature combinations (via optimisation algorithm such as genetic algorithm or particle swarm optimization, or statistical distribution analysis such as Gini's index) and retrieving only the relevant features for further analysis (33) (27) (34). For example, Mar et al (35) performed classification between normal, ventricular, premature ventricular and fusion beats based on the idea of Llamedo and Martínez (4) to use the sequential forward floating search (SFFS) feature selection procedure. This improved the classification accuracy of the multi-layer perceptron classifier from 79% using 71 features to 90% with only 9 features.

Feature quality and robustness is a challenge as poor quality features resulting from low quality delineators, filtering or approximations may lead to low performance and generalization properties despite powerful classification algorithms. Solutions to tackle this issue have been proposed such as in Llamedo and Martínez (2011) (4). In their study they

introduced the use of robust surrogates of typical features, using for example directly the wavelet transform signal instead of the QRS width to reduce the effect of delineation errors.

2.3. Machine learning methods for heartbeat classification

In terms of heartbeat classification accuracy, all the machine learning methods reported below present similar good performances (~95-99%). From the clinical viewpoint, two important benefits can be highlighted. Firstly, the outcomes of random forests and linear techniques, contrary to support vector machines or neural networks, are clinically interpretable, providing the opportunity to discover new biomarkers and enhance their importance in discriminating specific types of heartbeats. Secondly, neural network and Bayesian models may allow the analysis of the ECG without any preprocessing of the signal, which avoids the need of prior information on the biomarkers and may help discover new knowledge.

Linear and quadratic discriminant

De Chazal et al (2004) (18) implemented linear discriminants (LD) with weighted likelihood to classify 50,000 heartbeats in 5 classes (normal, ventricular ectopic, supraventricular ectopic, fusion of a normal and ventricular ectopic, or unknown beat type) from 22 recordings of the MIT-BIH arrhythmia database using QRS-based and time intervals features. The LD technique computes mean and covariance for the training data in order to maximise the likelihood. Posterior probabilities are then computed to output the final classification labelling. Their study reached a sensitivity of 75.9% (positive predictivity 38.5%, false positive rate 4.7%) for supraventricular ectopic beats, and a sensitivity of 77.7% (positive

predictivity 81.9%, false positive rate 1.2%) for ventricular ectopic beats. Similarly, another work by Llamedo and Martínez (2011) (4) used LD and quadratic discriminants to perform the classification of normal, ventricular and supraventricular beats. They extracted features from the RR interval and characterized the morphology of the ECG by discrete wavelet transform. A global accuracy of 93% (84% sensitivity and 75% positive predictivity) was achieved on the MIT-BIH arrhythmia database as well as on the MIT-BIH Supraventricular Arrhythmia and INCART databases. Similar work was conducted by Yeh et al (2009) (36), using LD for classification between normal and 5 different classes of abnormal beats for arrhythmia diagnosis. Evaluated on the recordings from the MIT-BIH database, their method reported correct detection between 84.68% and 98.97% for the five classes studied.

Some studies propose more elaborate ways of using these classifiers that may lead to patient-specific techniques and allow expert assistance. For example, de Chazal and Reilly (2006) (5) proposed a patient adaptable system in which a classifier is trained to annotate the first beats of a recording, then checked by a clinical expert. This patient specific adaptation was then added to a global classifier. This technique showed to increase the performance of the classifier by 10% (accuracy of 94%) for the classification of heartbeats according to the AAMI classes. Another work by Llamedo and Martínez (2012) (37) also combined a global classifier (linear discriminant analysis) and a patient specific step (an expectation-maximization clustering algorithm). This led to an automatic patient-adaptable technique which can also incorporate the input of a cardiologist (semi-automatic) when the clustering requires guidance from expert annotation because of interpatient variability.

Support Vector Machines

Support vector machines (SVM) are very popular class of machine learning algorithms because of their good classification and generalization properties. It is a supervised learning

method which learns the best separating hyperplane to maximize the margin between two classes in the feature space (Figure 2, Panel A). This decision boundary is then used to classify unknown testing data (38). SVM application to ECG beat classification and its optimization have been largely studied. For example, Ubeyli (2007) (6) applied SVM with error output correction code to classify heartbeats from 4 classes (normal, congestive heart failure, ventricular tachyarrhythmia and atrial fibrillation) from the Physionet database. Discrete wavelet transform was used to preprocess the data and extract features. They reached an accuracy of 98.61% (sensitivity of 98.89%) on a testing set of 360 beats. SVM optimization techniques have been investigated to improve the choice of features and parameters, reduce overfitting and speed-up the classification. For example, Melgani and Bazi (2008) (34) performed arrhythmia classification with SVM optimized by particle swarm optimization (PSO). PSO reduced the number of features from 303 to 46 and reached an overall accuracy of 89.72% in detecting 5 heartbeat classes (normal, atrial premature beat, ventricular premature beat, right bundle branch block, left bundle branch block and paced beat) from the MIT-BIH database. Another work by Asl et al (2008) (39) focused on the classification of heartbeats in 6 classes for arrhythmia detection (normal, premature ventricular contraction, atrial fibrillation, sick sinus syndrome, ventricular fibrillation and 2° heart block). They used 1367 ECG segments from the MIT-BIH database and designed feature vectors based on heart rate variability. They reached 99.16% of accuracy with discriminant analysis feature reduction (15 to 5 features). In another study, Nasiri et al (2009) (27) used principal component analysis (PCA) and genetic algorithm to determine the best parameters to tune the SVM algorithm and to perform feature reduction to remove the features that may lower the accuracy. They reached an accuracy of 93.46% for classifying between normal, right and left bundle branch block, and paced beat on the MIT-BIH arrhythmia database with genetic algorithm. Similar applications of SVM algorithms to ECG

beat classification were implemented by Li et al (40), Rabee and Barhumi (41), or Mehta and Lingayat (24)

Methods based on SVM and optimized SVM therefore reach high accuracies ranging from 90% to 99% in multi-class classification. A drawback of SVM classification for clinical applications is its lack of interpretability in order to evaluate each feature's influence and extract relevant discriminant biomarkers.

Random forests

The random forest method (42) is an ensemble learning technique combining the classification outputs of the decision trees that compose the forest (Figure 2, Panel B). A useful property of random forests is their ability to rank the variables according to their importance in the classification and therefore allow feature selection to avoid overfitting. Ganeshkumar and Kumaraswamy (2012) (29) investigated arrhythmia detection by identifying 6 heartbeat classes (normal, premature ventricular contraction, paced, atrial premature beat, and left and right bundle branch block) using random forest. They reached an accuracy of 92.16% on 150 beats extracted from the MIT-BIH database with 30 trees but their method was not validated over an independent testing set. In a recent work, Rahman et al (8) compared the heartbeats of 12-lead ECG from 1000 HCM patients to a group of ischemic and non ischemic cardiomyopathy patients. Their implementation used a random forest algorithm with 500 trees and 264 features (after feature selection) obtained from ECG waveforms morphology and duration. They reached an accuracy of 89% validated with 5-fold cross validation. Similar random forest classifiers for ECG classification were developed by Sathish and Vimal (43), or Emanet (44).

Bayesian networks

Bayesian networks are probabilistic graphical models representing variables and their probabilistic relationships. Following the successful application of Bayesian frameworks techniques to ECG segmentation (45) and denoising (46), de Oliveira et al (2010) (22) introduced the first approach of ECG beat classification using Bayesian networks. Their work focused on premature ventricular beat (PVC) detection by the implementation of a Bayesian network framework using channel fusion. They reached a sensitivity of 99.69% (positive predictivity 98.79%). Validation of their method was performed by splitting the labeled heart beats from the QT database into 75% as training set and 25% as test set. Similarly, Oster et al (2015) (47) developed a model-based filtering approach using switching Kalman filters to classify ventricular beats. In addition to the classification performance, their approach presented the ability to detect unknown beat morphologies. They reached an accuracy of 97.3% (positive predictivity 99.96%) for ventricular beats classification on the MIT-BIH and INCART databases.

A simple type of Bayesian networks are Hidden Markov models (HMM) which represent the system of study as a set of hidden states and transition probabilities where the sequence of hidden states is estimated from the observations (48) (Figure 2, Panel C). HMM do not require prior knowledge and the estimation of the parameters is automated. This technique is popular for sequence modelling and temporal pattern analysis. Hence, several studies focus on the application of HMM to ECG modelling and prediction. Early, Coast and al (1990) (49) investigated the use of HMM for classification and modelling of normal and ventricular ectopic beats (VEB) from the American Heart Association database (six 30-min ECG recordings). Each ECG waveform and duration was represented by a HMM state. Their method reached a sensitivity of 97.25% (specificity of 85.67% over 799 VEB beats). Similarly, Koski (1996) (19) performed ECG segmentation and classification between normal

and premature ventricular beats (PVB) signals using HMM. They estimated the ECG signal by broken line approximation. The classifier was composed of 20 to 30 states. They reported an accuracy of 100% on the very small testing set used (4 testing beats). Later, Andreao et al (2006) (50) performed modelling and classification of premature ventricular contraction (PVC) beats using 59 recordings from the QT database. They combined an HMM and a rule based system for beats identification (based on the beat prematurity and enlarged QRS morphology criteria). They reached a sensitivity of 99.79% (specificity of 99.96%) for PVB detection over the testing set. Most of these techniques based on HMM also integrate and estimate the parameters of the delineation of ECG waveforms in the model, avoiding the need for a separate segmentation step.

Neural networks

In the last fifteen years, neural networks (51) have been very popular in ECG classification. In this family of machine learning algorithms inspired by biological processes, the interconnected neurons of the system learn the structure of the data from training examples (Figure 2, Panel D). Neural networks are powerful for their ability to detect patterns and extract data structure without expert knowledge. An example of neural network application to ECG heartbeat classification was presented by Niwas et al (2005) (52). They implemented an artificial neural network (ANN) trained on feature vectors composed of heartbeat intervals and spectral entropy. They reached an accuracy of 99.02% in classification of testing heartbeats in 10 classes from the MIT-BIH database. Similarly, Inan et al (2006) (53) studied the detection of premature ventricular contractions (PVC) beats. They used morphological features derived from the wavelet transform and time intervals features as input to a feed-forward multi-layer perceptron (MLP) neural network with a single hidden layer. They

obtained 96.82% of accuracy for PVC beat classification on 22 ECG recordings from the MIT BIH database.

In another study, Ubeyli et al (2009) (54) used a more complex neural network architecture, recurrent neural networks (RNN), which differ from standard ANN by the presence of direct cycles in the neurons architecture. This allows the representation of dynamic temporal processes. They trained the RNN with Levenberg–Marquardt training algorithm and eigenvector based features. They tackled the classification of heartbeats in 4 classes on 720 heart beats from the Physionet database and reached an accuracy of 98.06%. Another work by Lagerholm and al (2000) (30) presented a clustering method for arrhythmia over 48 recordings of the MIT-BIH database. They preprocessed the signal with the Hermite transform which provided a better robustness to noise. The Hermite transform and the RR interval defined the feature vector. They implemented self organizing networks (SOM) to perform clustering in 25 groups and reach 1.5% of misclassification. SOM also conserves the neighbouring structure of the data, representing similar clusters physically close on the map, and therefore facilitating the interpretation of the results by the clinicians. Similarly, Linh et al (2003) (55) used the Hermite transform of QRS complexes coupled to a TSK fuzzy network, an association of neural network with logical rules, to classify 6 types of heart rhythms (premature ventricular ectopic, left bundle branch block, right bundle branch block, atrial premature beat, ventricular flutter wave, and ventricular escape beat) for arrhythmia. They reached 96% of accuracy in detecting these heartbeat classes, although no validation dataset is described in the paper. In addition, their method showed to be less sensitive to morphological variations of the ECG and handled heartbeat variability. Another method implementing fuzzy techniques was developed by Ozbay et al (2006) (56). Their fuzzy clustering neural network architecture achieved 99.9% of accuracy in arrhythmia detection (classifying normal beat, sinus bradycardia, ventricular tachycardia, sinus arrhythmia, atrial

premature contraction, paced beat, right and left bundle branch block, atrial fibrillation and atrial flutter) on 5342 segments from the MIT/BIH database. Similar works on neural networks were conducted by Jadhav et al (57), Meau et al (58), Dokur and Olmez (59) or Das et al (60).

3. ECG recording analysis for patient diagnosis, monitoring and stratification

Rather than classifying heartbeats, some studies focus on diagnosing patients based on their ECG (as summarized in Table 2). Patient classification and diagnosis requires analysing the ECG recordings as a whole (time changes, various beat morphologies) rather than analysing a single isolated beat. The machine learning methods described above can be adapted to this task. Clinical applications include risk stratification or disease monitoring, and these studies may be able to provide insight in the structure of diseased population thanks to clustering techniques, highlight which biomarkers are significant to distinguish between disorders, provide automatic diagnosis (or semi-automatic, taking into account expert input), and analyse ECG changes over time, which may be tedious to perform visually. The paragraphs below highlight some of the clinical areas that have benefited from the use of these machine learning methods to patient classification.

Pro-arrhythmic ventricular diseases

Several works approach patient diagnosis by identifying abnormal excerpts or events in the recordings. For example, ischemia is a disease condition normally manifested in ambulatory recordings by transient deviations of the ST segment voltage. Therefore, the automatic identification of ST deviations due to ischemia and due to non-ischemic events (such as or

axis shifts, and heart rate or conduction changes) has been widely investigated. In particular, Mincholé et al (2010) (61) automatically derived heart rate related depolarization and repolarization indices to discriminate between ST-segment changes due to ischemia and non-ischemic ST episodes due to heart rate. They reached an accuracy of 87.5% on the LTST database. They applied a multivariate discriminant analysis using the Wilk's Lambda minimization as the criteria for inclusion and removal of features.

On the same database, Faganeli and Jager (2010) (62) developed a decision-tree based classification to distinguish between ischemic and non-ischemic heart rate-related ST-segment episodes. They evaluated their performance by bootstrap method and reached a sensitivity of 98.1% and specificity of 85.2% with features from heart rate and Legendre orthonormal polynomial coefficients. Another work by Bailón et al (2003) (63) aimed at diagnosing coronary heart disease based on exercise ECG indexes. They developed an automated method to extract repolarization, depolarization and heart rate variability (HRV) indexes from noisy exercise recordings. A multivariate discriminant analysis then classified patients into two classes: ischemic and low risk patients based on independent set of indexes. HRV indexes provided the best results with a sensitivity of 94% and specificity of 92% to classify 65 ischemic and 40 low risk cases. Another disease condition investigated is Brugada syndrome, which leads to a high risk of sudden cardiac death because of episodes of ventricular fibrillation (VF) in patients with no structural heart disease (64). Kawazoe et al (65) investigated risk of VF in patients with Brugada syndrome thanks to a logistic regression model, cross-validated over a database of 143 patients (35 with VF, 108 without). Syncope episodes, R–J interval in lead V1, QRS duration in lead V6, and Tpeak–Tend dispersion were the best discriminating features identified by logistic regression. They led to a sensitivity of 97.1% and a specificity of 63.0% by leave-one-out cross validation.

The study by Rahman et al (2015) (8), mentioned earlier, presented a patient classifier to detect patients affected by hypertrophic cardiomyopathy (HCM) based on standard 12-lead ECG. They classified a patient as HCM if the majority of the beats show HCM beats morphology. Their dataset was composed of 221 HCM patients and 541 control (non HCM patients, but with implemented cardiac defibrillator). 264 standard ECG features, such as time intervals and waveforms amplitude, were extracted by feature selection (information gain criterion), and used to perform SVM and random forest classifications with 5-fold cross validation. They reached similar performance results with the two classifiers, with a precision of 0.84 (0.89 sensitivity, 0.93 specificity).

Acharya et al (2003) (66) were interested in diagnosing several groups of cardiac disorders based on ECG signals: ischemic or dilated cardiomyopathy, complete heart block, sick sinus syndrome, atrial fibrillation (AF) or ectopics, and normal beats. They developed an artificial neural network (ANN) coupled with a fuzzy equivalence relation and reached an accuracy of 85-95% using four heart rate variability features. In another work, Zheng et al (2014) (67) applied convolutional neural network (CNN) to time-series classification using a multi-channel technique. They aimed at classifying congestive heart failure from 2-lead ECG of 15 subjects by extracting sub-sequences of the signal. The model learned features from the ECG throughout the layers of the CNN and reached an accuracy of 94.7% for congestive heart failure detection on this dataset.

Atrial fibrillation

Atrial fibrillation (AF) is a condition investigated by many studies as its irregular and repetitive episodes can lead to heart failure, stroke and double the risk of mortality (68). In Pourbabaee and Lucas (2008) (7), time interval and morphological features were extracted from the three main ECG waveforms (P wave, QRS and T wave) of 25 patients with

paroxysmal AF episodes and 25 healthy subjects from the 2001 Computers in Cardiology Challenge database. The multi-layer perceptron implemented classified accurately 87% of the testing dataset, and suggested the importance of QRS-based features in the classification after testing the influence of each set of features. Similarly in (69), Colloca et al (2013) performed detection of atrial fibrillation episodes via support vector machines, evaluated on the MIT-BIH database with a specificity of 99.72% on the testing set. In another study by Asgari et al (2015) (70), stationary wavelet transform and support vector machine were designed to identify AF events with sensitivity and specificity of 97.0% and 97.1% respectively. More detailed techniques for AF management and detection can be found in (71).

Long term patient monitoring

ECG analysis can also be used for long term monitoring of patients in clinical care, to detect abnormal rhythmic events that may occur suddenly. For example in Kannathal et al (2003) (9), three degrees of disease severity (normal, abnormal, life threatening) were predicted from the ECG of patients in intensive care unit (ICU) using artificial neural networks (600 training patients, 200 testing patients). This reached an accuracy of 99% with RBF (radial basis function) networks. Similarly in Zhang et al (2016) (12), a combination of genetic algorithm and SVM was used to detect false critical arrhythmia alarms in ICUs with a true positive rate of 93% (true negative rate of 94%).

In this context, an example of successful integration of computational techniques in the clinical environment is the recent collaboration between Microsoft and the Cleveland Clinic (72), focused on the analysis of data from the ICU (clinical data, medical records, etc). They aimed at monitoring and identifying high-risk patients, using machine learning and advanced data analytics (Azure Machine Learning).

4. Real-time episodes' detection and wearable devices

The integration of classification techniques in clinical settings requires the detection of ECG abnormalities in real-time to be used in the hospital environment at bedside, or on wearable devices. This involves the development of classification algorithm with low complexity and low memory requirements, which add different challenges to these techniques (summarized in Table 2).

4.1. Real time diagnosis

Real-time analysis and classification of ECG signals find clinical applications in the detection of sudden abnormal heart rhythms (more than in the diagnosis of long term diseases), especially in intensive care units where the real-time monitoring of patients is crucial. In addition, future progress could see memory networks learn to predict severe events in real time, allowing clinicians to take action before fatal arrhythmias occur.

The standard machine learning methods presented earlier may perform real time classification if optimized to deal with a large influx of incoming data. However, most of them require the extraction of handcrafted features before classification. In addition to the already mentioned risk of poor feature quality due to inaccurate delineation of the ECG waves or an imprecise extraction of ECG features, these methods may struggle to run in real time. Recently, powerful tools have been developed in the field of deep learning, helping real time classification of very complex signals by the design of more complex and deep networks. Deep learning is a field of machine learning in which several hidden layers of computation are added to neural networks (learning algorithms inspired by biological brain networks) in order to model more complex behaviours and data structures. Popular applications of these techniques are image recognition and generation, and speech and time

series classification (73) (74). In Kiranyaz et al (2016) (10), a 1D convolutional neural network (CNN) merged feature extraction and classification in one step to develop a personalized patient classifier that can be used in real time, once trained, to classify longer recordings, on wearable devices for instance. They reached an accuracy of 98.6% (95% sensitivity, 98.1% specificity) on 24 test recordings of the MIT-BIH database in classifying ventricular and supraventricular ectopic beats. Presented earlier, Zheng et al (67) applied convolutional neural networks to the classification of time-series data using a multi-channel technique. One of their applications was the classification of congestive heart failure in 2-lead ECGs from 15 subjects by extracting sub-sequences of the signal. The model learnt directly the features from these time series throughout the layers of the CNN and reached an accuracy of 94.7% on this dataset. In Chauhan and Vig (2015) (75), a deep long short term memory (LSTM) network was implemented to tackle the classification of various types of ECG beats (premature ventricular contraction, atrial premature contraction, paced beats and ventricular couplet) from the MIT-BIH database. An advantage of LSTM networks is their ability to take a raw ECG signal as input without any preprocessing and automatically discover key features thanks to their ability to “remember” past events. In this study, the LSTM network ran in a short amount of time once trained (testing time of 0.5s for a 20-minute ECG signal on a 16 core CPU machine) making it suitable for time-constrained applications like real time classification.

4.2.Application to wearable devices

Wearable devices for ECG monitoring have a key impact on the recent effort to move the clinic to the home, especially in the case of elderly patients monitoring, or long-term diseases (Figure 3). Their development aims at reducing the costs for prevention and monitoring, by

freeing expert time and space in clinics. Current technologies are progressing towards this goal but challenges remain, such as portability (battery, computational costs), or reliability of the abnormality detection.

Additional challenges arise for classification methods, such as the need for rapid and real-time analysis of ECG signals to avoid the storage of large amount of data, and the ability to automatically handle noisy data, as wearable devices may generate data more affected by movement, noise or changes in heart rate than those generated in standard clinical equipment. Machine learning methods (presented in section 2) must tackle challenges of speed and memory requirements in order to be embedded on these portable devices. In (76), a portable device was designed to perform classification of normal beats, atrial fibrillation, and myocardial ischemia in real time and with a sensitivity of 95.1% and specificity of 95.9% using an SVM algorithm. Similarly, Leutheuser et al (2014) (77), compared several techniques for arrhythmia detection from ECG signals on Android mobile devices evaluated on the MIT-BIH databases and stressed the importance of balancing computational costs and memory demand in the design of such techniques. In 2010, Oresko et al (11) implemented a smartphone-based wearable platform to perform real-time ECG acquisition and beat classification for cardiovascular disorder detection. They based the classification step on the design of a feedforward multilayer perceptron (MLP) neural network and use the original QRS morphological beat as input to the classifier. This reduced the amount of preprocessing work and the method reaches a prediction accuracy greater than 90% to detect right bundle branch block, premature ventricular contraction, paced or normal beat.

An additional challenge for remote monitoring is the handling of unknown beat morphologies that the algorithm may encounter that could lead to false alarms. These should be reduced as much as possible on wearable devices when the patient is at home to avoid unnecessary alarming messages, or in the intensive care unit to optimise the nurses' time. Mentioned

earlier, Oster et al (2015) (47) tackled this issue by implementing switching Kalman filters with an additional X-factor mode to account for unseen beat morphologies. The analysis of the quality of these unknown beats confirmed that 639 out of 954 ($\sim 2/3$) of these beats were of poor or medium quality and should therefore be discarded for monitoring and diagnosis. Additional examples of such methods can be found in Supplementary Material. AliveCor (78) is a striking example of success in translating these computational methods to the clinic. The wearable technology is integrated in a smartphone application and records ECG and blood pressure data from patients. These measurements are then analysed with a machine learning algorithm to help detect atrial fibrillation. AliveCor received clearance from the Food and Drug administration (79). It is now widely used in the clinic for ECG monitoring. A further collaboration with the Mayo Clinic plans to develop the technology to discover hidden physiological signals from ECG data (80).

5. ECG computer simulations

One of the main challenges emerging from the summary of the classification studies presented earlier is the generalization to larger and different databases. Indeed, a limited number of databases and recordings are available for testing and validation, which may explain the limited number of heartbeat types and cardiac conditions investigated by these studies. Very few works actually explore the generalization performance of their techniques to other databases as in Llamedo and Martínez (2011) (4) who reported and tackled this issue by evaluating their method over three different databases to prove good generalization properties. The 3D computer simulations techniques presented in this section may be very helpful in addressing this problem given their ability to generate synthetic data that could

then be used as validation datasets for the classification studies. In addition, computer simulations using anatomically-based multiscale models of the electrical activity of the heart can help to interpret ECG findings from machine learning studies. Computer modelling studies can therefore find clinical applications in both the generation of synthetic ECG data and the interpretation of ECG abnormalities by linking structural or electrophysiological changes to ECG abnormalities. The drive towards personalized simulations also provides a unique opportunity for research, and clinical benefit is directly seen in therapy testing, and reduction of invasive techniques.

In 2013, Sovilj et al (81) presented simulations of the ECG using an ellipsoid 3D model of a heart embedded in a torso. They show the effect of simulated myocardial infarctions at various locations on ECG changes, specifically in the ST segment. Another work by Bacharova et al (2012) (82) used computer simulations to investigate the influence of LV mass on QRS, and specifically increased QRS amplitude, in the context of left ventricular (LV) hypertrophy. In a more recent work, Bacharova et al (2016) (83) investigated the effect of slow ventricular activation on the QRS complex and showed how alteration of electrical properties may mimic ECG morphologies associated with anatomical abnormalities. These approaches have the benefit of speed and low memory requirements, but they do not take into account a realistic anatomy of the heart.

Simulations using image-based anatomical models have also been used extensively to investigate the ionic and structural basis of ECG. (Figure 4). Substantial work by Potse and colleagues has used several approaches for investigations of the underlying basis of ECG changes in disease, from ST elevation in ischaemia to personalized models of heart failure patients (84) (85) (86). Furthermore, in (87), Chen et al (2011) used an MRI-based computer simulation model from patients with acute myocardial infarction to show that instabilities in

QT interval may predict ventricular tachycardia onset. Similarly, Wilhelms et al (2011) (88) applied realistic detailed 3D computer simulations to better understand the mechanisms underlying shifts in the ECG ST segment in acute cardiac ischaemia.

The simulation of the ECG through 3D computer simulations also finds applications in understanding the effect of drugs on the ECG (89) (15). Sebastian et al (2010) (90) investigated the effect of dofetilide, a drug affecting the IKr current on a patient-specific model simulating the pseudo-ECG. They observed a prolongation of the QT interval of 100ms with a total IKr block, in line with a prolongation of the APD90 in cardiac cells. Zemzemi et al (2013) (15) investigated the influence of drugs on the ECG signal using 3D computer simulations, allowing drug testing in silico rather than in vivo. They simulated channel conductance block for the hERG and fast sodium channels and observed QT prolongation for 50% hERG block (6%) as well as QRS and QT prolongation for 50% fast sodium current block (12% and 5% respectively).

Another work by Cardone-Noott et al (2016) (13) investigated the effect of changes in conductivities on the ECG morphology and how the variability in the activation sequence relates to changes in QRS biomarkers, by designing a 3D simulation pipeline with a human volumetric mesh and activation model based on the cellular O'Hara-Rudy model.

Phenomenological approaches to modelling and simulation of electrical propagation have also been proposed using fast algorithms based on graph based theory (91) (92). This may facilitate both simulations of the ECG as well as parameter inference from the ECG, from clinical datasets, by taking into account parameter uncertainty such as in Wallman et al (2014) (93) and Konukoglu et al (2011) (94).

In addition, abnormalities in human atrial electrophysiology and their consequences on ECG patterns have also been investigated building on substantial work on multiscale modelling of atrial dynamics. Geometrical atria models have been described and simple models represent

the shape of the atria as a two or three-dimensional folded sheet (95) (96). As in the case of ventricular models, these simple models are not derived from realistic imaging data but are based on a series of assumptions. The characteristics of the tissue can be easily modelled such as homogeneous tissue, anisotropy (96), etc, and these simple models allow the investigation of essential questions regarding atria behaviour such as the anatomy. Vigmond et al (2001) for example showed the importance of superior vena cava and pulmonary vein openings in rotors by using a model of the atria built with two spheres containing holes as anatomical elements. However, despite being very useful because of their simplicity, these models do not possess the anatomical details that would be obtained with imaging data.

As in ventricular models, another type of models therefore emerged, using imaging data (from MRI or CT scans) (97) (98) (99) , including realistic anatomical elements of the whole atria, such as sinoatrial node, left and right atrium appendage, Bachmann bundle, etc (100).

As in (101), these models allow the simulation of the body surface ECG in normal and arrhythmic cases to investigate P wave abnormalities in the ECG and their correlation with atrial fibrillation dynamics and propensity.

Computer simulation models of whole ventricles and atria therefore allow the modelling of the electrical propagation throughout the heart from ionic dynamics to the ECG. ECG computer simulations pipelines are powerful tools to provide a deeper understanding of the impact of cardiac diseases and treatments on the ECG. Furthermore, with advances in high performance computing and development of fast simulation methods, they can bring the generation of synthetic ECG data under various conditions, to improve training of machine learning classifiers and the development of new ECG features.

6. Discussion

The electrocardiogram is cheap, non-invasive and widely used in clinical practice. As a recording of the body surface electrical activity, it provides information about heart rhythm abnormalities and helps detect diseases. However, visual inspection of the ECG provides discrete clinically interpreted features which cannot objectively capture the diversity of ECG abnormalities and morphologies. This is why computational methods are required, as they can make sense of multivariate complex datasets and detect differences that might be challenging for the human eye. However, analysing ECG data presents many challenges. Indeed, most large clinical studies still record ECG in paper print-outs, requiring manual digitization before computational techniques can be applied. Digital ECG clinical acquisition is still to be implanted in many hospitals. In addition, many ECG databases are not publicly available, gather low numbers of patients, and require extensive signal preprocessing techniques to denoise the recordings for computational analysis. As a consequence, most studies in the literature and reviewed here focus on large, publicly available databases of ECG recordings. Some of these databases such as the widely used MIT-BIH were originally analog ECG recordings on tapes that were then digitized. Some frequency-domain artefacts were identified, although they should not pose problems for beat classification or wave delineation (102). Many methods are trained and tested on the same databases, despite ensuring separated training and testing sets, which may limit the generalization of these techniques to different clinical databases or other cardiac disorders. Availability of large clinical ECG datasets is therefore required for technical developments in machine learning application to ECG analysis and classification.

These challenges will also apply to other recording techniques such as body surface mapping (BSM) which samples multiple points around the chest to provide a more detailed mapping of the body surface electrical activity than the standard 12-lead ECG. It has been shown to be more accurate than the ECG in detecting transient episodes like myocardial ischaemia (103). It is a rich source of data but is, by far, less commonly used and accessible than standard ECG. Intracardiac recordings also present an alternative to measure the electrical activity in the heart, but they are invasive, and could therefore not be obtained for large numbers of patients, thus showing less interest for its analysis with machine learning techniques.

The clinical integration of these techniques also presents limitations. First, the gold standard for electrocardiographic abnormality detection remains the expert annotations, and there is no reference dataset to compare all these studies, limiting the analysis of their performances for clinical use. However, the use of these techniques provides automaticity and consistency in the analysis of large datasets, which are more and more needed when manual classification cannot be performed. More importantly, the benefit of computer techniques goes beyond these classification tasks where computational methods try to reproduce the expert judgement, and can help uncover new knowledge and discover new biomarkers by unravelling structures in the data that were unknown before.

The recent interest in computational ECG analysis is twofold. For the computational field, the challenge and diversity offered by ECG recordings provide a rich environment to develop new methods. From the clinical perspective, these methods provide a new horizon on how ECGs can be analysed, developing novel biomarkers to diagnose cardiac diseases. Progress in this field is recent, which explains why several studies investigate the behaviours of different machine learning methods on ECG data. The fact that the ECG signal can be analysed by so

many techniques actually provides a wide range of options depending on the goal and requirements of the study. These techniques were recently introduced in the clinical environment, and growing interest has been shown from the clinical field (2) (104). However, translating novel techniques to the clinic requires both technology developments and also addressing practical challenges such as regulation approval, and inclusion in clinical protocols, which require intersectorial collaborations (105). The novel approaches for ECG analysis reviewed here, in synergy with other modalities such as intracardiac electrical recordings or imaging techniques, have the potential to improve patient risk stratification and precision medicine.

7. Conclusions

This review shows that computational techniques have been widely developed to analyse ECG signals and are strong candidates to help clinical advances by providing a better understanding of medical challenges. Machine learning techniques provide accurate and automatic classifications of heartbeats to detect arrhythmias or unexpected changes in heart morphology. They also help in automatic disease diagnosis, monitoring and stratification by handling long ECG recordings for which visual and manual inspections can be tedious and time consuming. Their adaptability to real-time requirements and embedding on wearable devices ensures an efficient and reliable monitoring of the ECG activity in hospital settings or at home. Finally, 3D computer simulations are powerful tools to interpret the ECG and they may soon become of crucial help by generating large datasets of synthetic data for the training of machine learning classifiers. Despite the many challenges they face and the novelty of their introduction to clinical practice, these computational methods are becoming a

powerful tool for medical advances and their integration in clinical settings should help improve patient care.

Competing Interests

We have no competing interests.

Authors' contributions

AL designed and wrote the paper and carried out the literature review of the field. AM, JPM, PL, and BR provided advice on the shape of the review and input on the manuscript. All authors gave final approval for publication.

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Figure captions

Figure 1. Example of data available for the analysis of ECG signals. Panel A: ECG waveforms (P, QRS and T waves) and standard features extracted from an ECG beat. The RR interval is measured as the peak-to-peak interval between two consecutive QRS complexes, the PR interval is defined as the duration from the beginning of the P wave to the beginning of the QRS complex, the QRS duration (or width) is the duration between the start and the end of the QRS complex, the QRS amplitude is defined as the absolute value of the difference between the minimum and the maximum of the QRS complex, and the QT interval is measured as the time between the beginning of the Q wave and the end of the T wave. Panel B: examples of different ECG waveforms: normal ECG (106), ventricular ectopic beats (107), supraventricular ectopic beats (108) and second degree heart block arrhythmia (109).

Figure 2. Main machine learning methods used for ECG classification. Panel A: Support vector machine binary classification by maximization of the margin m . Panel B: Random forest classification using n decision trees. Panel C: Hidden Markov model with n states, transition matrix $(a_{i,j})$ and emission matrix $(b_{i,j})$. Panel D: Neural network with two hidden layers

Figure 3. Example of an ECG classification system on wearable device showing the methodology (panel A), and output (panel B). From Miao et al (2015) (110). Panel A details the ECG acquisition sensor implanted in the wearable device: the signal, recorded by electrodes, is amplified and filtered by the AFE module, converted to digital signal by the MCU module and recorded on the SD card, transmitted to the USB port or sent directly to the

phone via Bluetooth. Panel B describes the output panel provided to the user: a screenshot of the ECG excerpt (left), and a summary of the normal and abnormal beats recorded (right).

Figure 4. Computational pipeline for ECG simulation from magnetic resonance images through 3D meshes and cellular electrophysiological models (left, from Zacur et al 2017 (111)) and the obtained simulation of the cardiac electrical activity (right, from Cardone-Noott et al 2016 (13)). Personalized cardiac magnetic resonance images (1) are segmented and preprocessed (2). From this information, surface and volumetric meshes are generated (3) and an electrophysiological model defining the electrical activity in the cells is implemented (4). The obtained simulated electrical conduction (right panel) can then be investigated.

Tables

Table 1. Summary table of the major databases used for classification of ECG signals.

Database	Type of recordings	Number of recordings	Annotations
MIT-BIH Arrhythmia *	- 30-minute excerpts - 2-channel ambulatory ECG - 360 Hz	48	Beat-by-beat annotations for each beat in each recording (~110,000 annotations)
QT database *	- 15-minute excerpts - 2-channel ECG - 250 Hz	105	- reference beat annotations - segmentation of waveforms (for 30 to 100 normal beats per recording)
American Heart Association ventricular arrhythmia *	- 2-channel excerpts - analog ambulatory ECG - 250 Hz	80 for training – 75 for testing	- 8 classes of recordings (level of ventricular ectopy) - final 30min annotated beat-by-beat
INCART*	- 30-minute ECG - 12 leads - 275 Hz	75	- 175,000 beat annotations - 10 classes pathological diagnosis
UCI Machine Learning: Arrhythmia dataset	- 279 attributes (age, sex, height, waveforms description over 12 leads such as duration, amplitudes, areas)	452	16 arrhythmia classes labelled
Long-Term-ST*	- between 21 and 24 hours - 2 or 3 ECG signals - 250 Hz	86	- annotated ST episode - QRS annotations - ST level measures
* PhysioBank datasets (17) available at https://physionet.org/ : - gathers 60 databases (4TB) of physiological signals: cardiopulmonary, neural, other biomedical signals - freely available - healthy subjects and patients (sudden cardiac death, congestive heart failure, epilepsy, gait disorders, sleep apnea, aging)			

Table 2. Summary table of reviewed machine learning classification methods, along with their objective, dataset, performance and validation.

Study	Classes and focus	Method	Performance	Validation
Heartbeat classification				
Chazal et al (2004) (18)	Normal, ventricular ectopic beat (VEB), supraventricular ectopic beat (SVEB), fusion of normal and VEB, unknown	Linear discriminants (LD) with QRS-based and time intervals features	SVEB: 75.9% (sensitivity) VEB: 77.7% (sensitivity)	On 50,000 independent beats (MIT-BIH)
Llamedo and Martínez (2011) (4)	Normal, VEB and SVEB classification	LD (RR-intervals and wavelet transform features) with floating feature selection	93% global accuracy	On independent MIT-BIH beats and INCART
Yeh et al (2009) (36)	Normal, left bundle branch block (LBBB), right bundle branch block (RBBB), premature ventricular contraction (PVC), atrial premature contractions	Linear discriminants	96.23% (global accuracy)	On 14 30-min excerpts (MIT-BIH)
Ubeyli (2007) (6)	Normal, congestive heart failure, ventricular tachyarrhythmia, atrial fibrillation (AF)	Support Vector Machine (SVM) with error output correction code and discrete wavelet transform	98.61% accuracy	On 360 independent beats (Physionet)
Melgani and Bazi (2008) (34)	Normal, atrial premature beat, PVC, RBBB, LBBB, and paced beat	SVM optimized by particle swarm optimization	89.72% accuracy	On 40,438 independent beats (from 20 patient records of MIT-BIH)
Asl et al (2008) (39)	Normal, PVC, AF, sick sinus syndrome, ventricular fibrillation, 2° heart block	SVM with heart rate variability features and discriminant analysis feature reduction	99.16% accuracy	On 463 testing segments of MIT-BIH (average over 100 different runs)
Nasiri et al (2009) (27)	Normal, RBBB, LBBB, and paced beat	SVM with principal component analysis and genetic algorithm	93.46% accuracy	50% of MIT-BIH for testing
Ganeshkumar and Kumaraswamy (2012) (29)	Normal, PVC, paced, atrial premature beat, LBBB and RBBB	Random Forest (30 trees) on 150 beats from MIT-BIH	92.16% accuracy	Not validated on independent dataset
de Oliveira	PVC detection	Bayesian network	99.69%	On QT database

et al (2010) (22)		framework using channel fusion	sensitivity	(25% - 23,765 beats for testing)
Coast and al (1990) (49)	VEB detection (over American Heart association database)	Hidden Markov Model (HMM) with states corresponding to ECG waveforms or intervals	97.25% sensitivity	On 799 independent beats
Koski (1996) (19)	PVC detection	HMM and broken line approximation (30 states)	100% accuracy	On only 4 beats
Andreae et al (2006) (50)	PVC detection	HMM and rule based system	99.79% sensitivity	On 61,543 test beats from QT database
Niwas et al (2005) (52)	Normal, LBBB, RBBB, Atrial Premature beat , SVEB, PVC, AF, Ventricular Fibrillation, Sick Sinus Syndrome, Fusion of VEB and normal	Artificial neural network with heartbeat intervals and spectral entropy features	99.02% accuracy	On 180 (unspecified) independent datasets
Inan et al (2006) (53)	PVC detection	Feed-forward multi-layer perceptron with wavelet transform and time intervals features	96.82% accuracy	On 22 ECG recordings from MIT-BIH
Ubeyli (2009) (54)	Normal, congestive heart failure, ventricular tachyarrhythmia, AF	Recurrent neural network with Levenberg–Marquardt training algorithm and eigenvectors	98.06% accuracy	On 360 beats from Physionet
Lagerholm and al (2000) (30)	Normal, LBBB, RBBB, atrial premature, abberated atrial premature, nodal premature, SVEB, VEB, fusion normal and VEB, ventricular flutter, atrial escape, nodal escape, ventricular escape, unknown	Self organizing networks with Hermite transform and RR intervals features	1.5% of misclassification	Not validated on independent database
Linh et al (2003) (55)	Normal, LBBB, RBBB, atrial premature, VEB, ventricular flutter wave, ventricular escape	TSK fuzzy network with Hermite transform	96% accuracy	On 3,668 beats from MIT-BIH
Ozbay et al (2006) (56)	Normal, sinus bradycardia, ventricular tachycardia, sinus arrhythmia, atrial premature	Multi-layer perceptron with fuzzy clustering neural network architecture	99.9% accuracy	On 5342 segments from 92 patients (MIT-BIH)

	contraction, paced, RBBB, LBBB, AF and atrial flutter			
ECG recording analysis for patient diagnosis, monitoring and stratification				
Mincholé et al (2010) (61)	Ischemic and non-ischemic ST-segment changes	Multivariate discriminant analysis with Wilk’s Lambda minimization	87.5% accuracy	Cross-validated estimation on LTST database
Faganeli and Jager (2010) (62)	Patients with transient ischemia episodes	Decision trees with heart rate and Legendre polynomial coefficients features	98.1% sensitivity, 85.2% specificity	Bootstrap method
Rahman et al (2015) (8)	Hypertrophic cardiomyopathy detection on 12-lead ECG	SVM and random forest with 264 time intervals and waveforms amplitude features	precision of 0.84	5-fold cross validation over 10,930 beats
Bailón et al (2003) (63)	Diagnosis of coronary artery disease	Multivariate discriminant analysis with repolarization, depolarization and heart rate variability features	94% sensitivity, 92% specificity	Cross validated estimation (leave one out)
Kawazoe et al (65)	Risk of ventricular fibtillation in Brugada syndrome patients	Logistic regression with syncope, r–J interval, QRS duration, and Tpeak–Tend dispersion as features	97.1% sensitivity, 63.0% specificity	Leave-one-out cross validation over 143 patients
Pourbabae e and Lucas (2008) (7)	Paroxysmal AF episodes detection	Multi-layer perceptron with time interval and morphological waveform features	87.5% accuracy	Over 16 recordings from 2001 Computing in Cardiology challenge
Colloca et al (2013) (69)	AF episodes detection	SVM optimized with grid-search	85.45% accuracy with 100% sensitivity to AF	Series 200 of the MIT-BIH Arrhythmia (with 8 AF subjects)
Asgari et al (2015) (70)	AF episodes detection	SVM with stationary wavelet transform	97.0% sensitivity	2-fold stratified cross-validation on MIT-BIH
Acharya et al (2003) (66)	Ischemic/dilated cardiomyopathy, complete heart block, sick sinus syndrome, AF, ectopics, normal	Artificial neural network with fuzzy equivalence	85-95% accuracy	On 66 testing samples
Zheng et al (2014) (67)	Congestive heart failure (from 2-lead ECGs)	Convolutional neural network (CNN)	94.7% accuracy	10-fold cross validation over 15 subjects
Kannathal et al (2003) (9)	Normal, abnormal (PVC, RBBB, LBBB, paced), life threatening (sick sinus syndrome,	Artificial neural networks with radial basis function	99% accuracy	On 200 independent testing patients

	ischemic heart disease, ventricular fibrillation)			
Zhang et al (2016) (12)	Asystole, extreme bradycardia, extreme tachycardia, ventricular tachycardia or ventricular flutter/fibrillation arrhythmia	SVM with genetic algorithm	93% true positive rate	5-fold cross validation over 750 recordings (2015 Physionet Challenge)
Real-time episodes' detection and wearable devices				
Kiranyaz et al (2016) (10)	VEB and SVEB detection	1-D patient specific CNN	98.6% accuracy	On 41,766 testing beats from MIT-BIH
Chauhan and Vig (2015) (75)	PVC, atrial premature contraction, paced, ventricular couplet	Deep long short term memory (LSTM) network	0.975 precision, 0.9645 F-score	Testing set of unknown size
Jeon et al (2014) (76)	Normal beats, AF, myocardial ischemia classification	SVM on ARM processor	95.1% sensitivity	10-fold cross validation over MIT-BIH AF, 2001 and 2004 CinC challenge and STT database
Leutheuser et al (2014) (77)	Normal and abnormal (all MIT-BIH labels that are not normal), on Android devices	Decision tree classifier with heartbeat features	89.6% accuracy	Not validated on independent dataset
Oresko et al (2010) (11)	Normal, RBBB, PVC, paced or fusion of paced and normal beat detection on smartphone	Feedforward multilayer perceptron with QRS morphological beat pattern	99% accuracy for normal – 81% accuracy for fusion	3-fold cross validation over 5421 beats (MIT-BIH)
Oster et al (2015) (47)	Normal and SVEB, fusion and VEB, and unknown	Switching Kalman filters with X-factor mode	99.2% F1-score	Independent validation on INCART

1076
1077 AF Atrial Fibrillation
1078 ANN Artificial Neural Network
1079 CNN Convolutional Neural Network
1080 HMM Hidden Markov Model
1081 LBBB Left Bundle Branch Block
1082 LD Linear Discriminant
1083 LSTM Long Short Term Memory Network
1084 MLP MultiLayer Perceptron
1085 PVC Premature Ventricular Contraction
1086 RBBB Right Bundle Branch Block
1087 RNN Recurrent Neural Network
1088 SVEB Supra Ventricular Ectopic Beat
1089 SVM Support Vector Machine
1090 VEB Ventricular Ectopic Beat

Figure 1

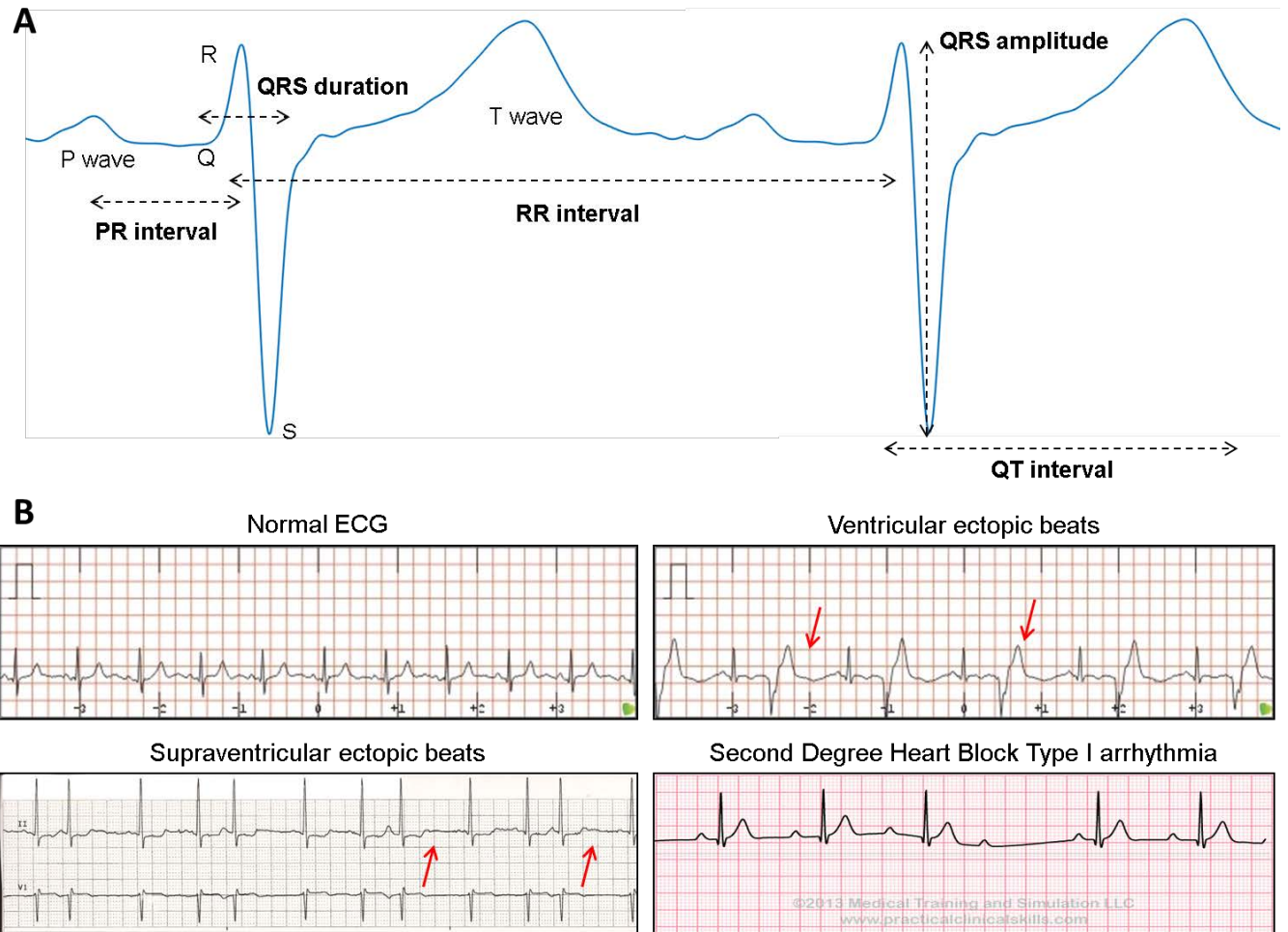


Figure 2

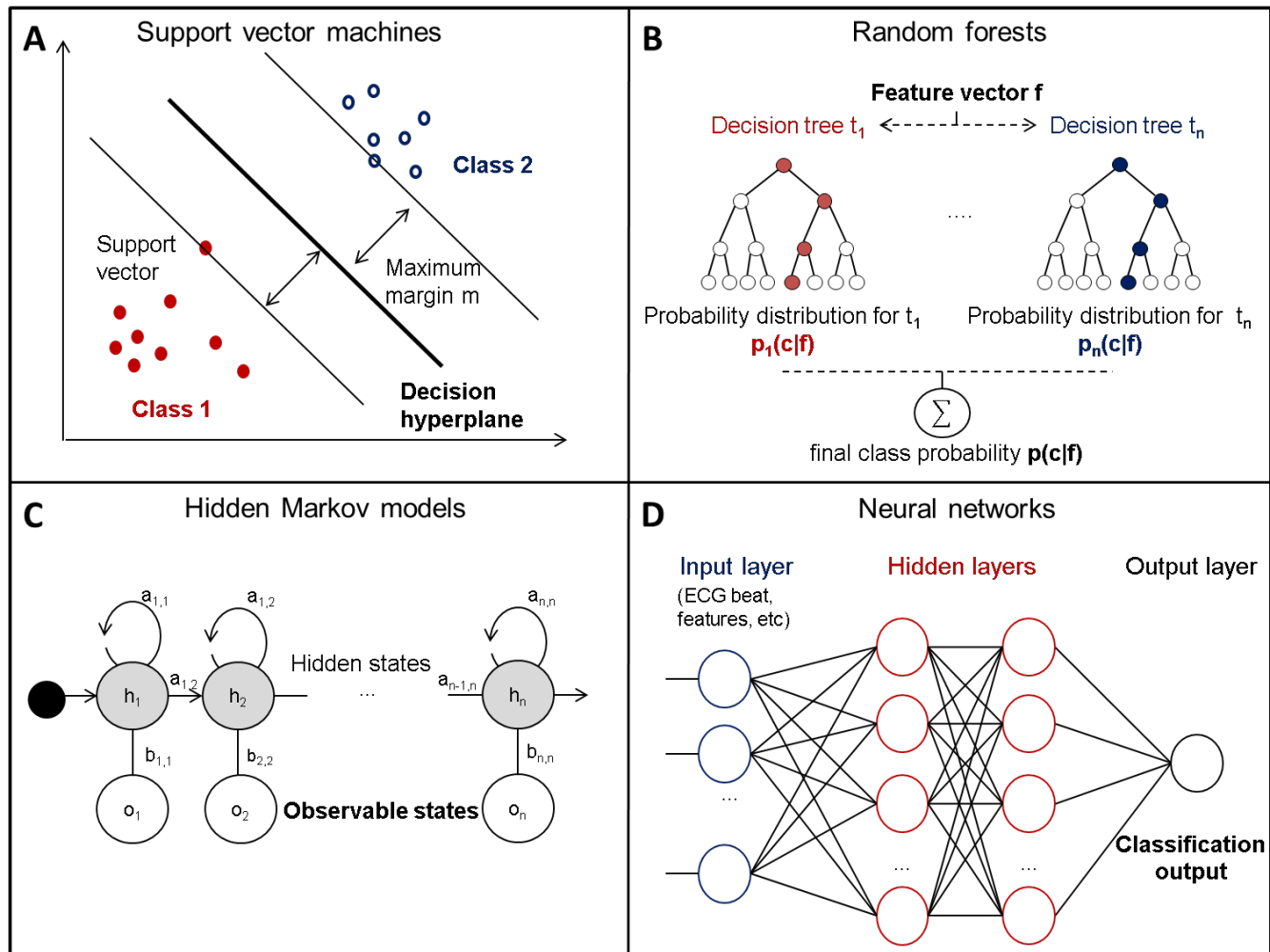
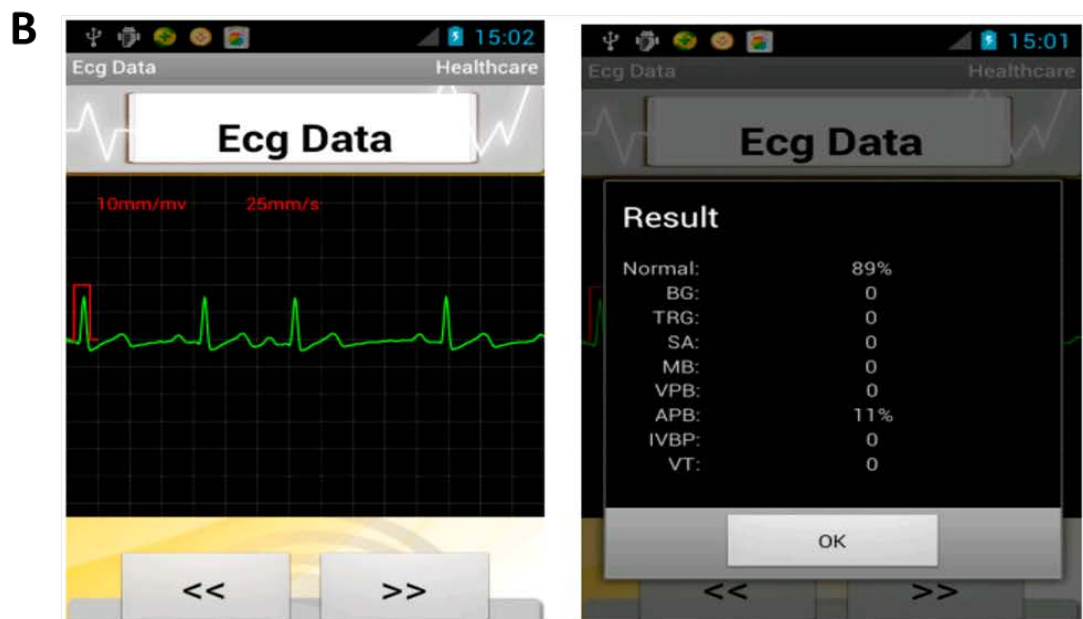
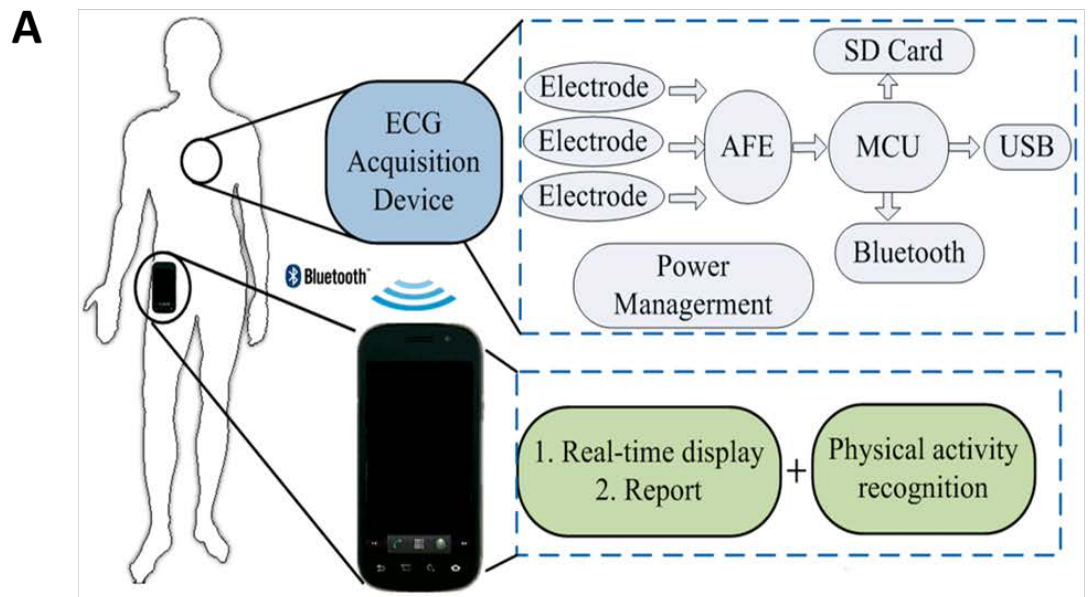


Figure 3



AFE:	Analog Front End	MB:	Missed Beat
MCU:	Module Control Unit	VPB:	Ventricular Premature
SD:	Secure Digital	Beat	
USB:	Universal Serial Bus	APB:	Atrial Premature Beat
BG:	Bigeminy	IVBP:	Interpolated Ventricular
TRG:	Trigeminy	Premature Beat	
SA:	Sinus Arrhythmia	VT:	Ventricular Tachycardia

Figure 4

