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Quality Control in ECG-based Atrial Fibrillation Screening

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LUND UNIVERSITY

Doctoral Dissertation

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Popular Summary

This thesis revolves around atrial fibrillation (AF), which is the most common cardiac arrhythmia encountered in clinical practice. Atrial fibrillation is manifested by an irregular heart rhythm, which may lead to formation of blood clots in the heart, and consequently, to stroke. The most common symptoms of AF are heart palpitation, fatigue, and chest pain, while it may as well be completely asymptomatic. Therefore, early identification of AF is of great importance, to enable timely initiation of anticoagulants and reduce the risk of stroke.

Screening the population at risk of AF provides the opportunity to find patients with AF at an early stage, and has led to numerous AF screening studies around the world. Such screening calls for specialized recording systems that are affordable, portable, safe, and easy to use, now available thanks to recent technological advances. Such systems include handheld ECG recorders, patches, and wearables, e.g., smartwatches.

Recording with these systems is often done outside the clinical environment to facilitate intermittent or continuous recordings over a longer period without the need for individuals to attend healthcare centers. However, this comes with the cost that the ECG signals recorded in the home environment often display a lower signal quality compared to conventional clinical ECG recordings. The lower signal quality disturbs the performance of automated ECG analysis and leads to false arrhythmia detections, which require expert review to be ruled out. Such expert review is a time-consuming and costly procedure.

With the aim to make AF screening more efficient, the main theme of the present thesis is on quality control in the ECG screening context from signal measurement to arrhythmia detection. The first part of the thesis addresses identification of transient noise and artifacts in ECGs recorded using a handheld device, using a convolutional neural network (CNN) applied before AF detection to reduce the number of false AF detections. The proposed CNN is able to identify false beat detections caused by transient noise, which leads to a reduced

number of false AF detections.

The second part investigates the signal quality produced by a novel electrode technology and its potential to reduce the number of false AF detections in comparison to a commercially available counterpart. The novel electrode technology is shown to produce ECGs with a better signal quality and is thus better suited for automated ECG analysis.

The usefulness of AF screening may be further enhanced by identifying individuals at risk of developing AF in the future. The third part of the thesis focuses on the detection of short-episode supraventricular tachycardias (sSVT) which have been shown to be associated with a higher risk for development of AF. In this work, the major challenge is to detect very brief episodes of arrhythmia, i.e., as short as 2.4 s, in data of lower signal quality, without causing large numbers of false detections. With the proposed method, the number of false detections of sSVT is considerably reduced.

Finally, the last part of the thesis presents a simulation model for ECG signals, capable of generating multiple types of rhythms, as well as noise and artifacts of various sources, in a time-varying manner. The availability of simulation models is of great importance for performance evaluation of arrhythmia detectors and quality control techniques where the availability of expert annotated data is limited, as well as when training machine learning models, which require large training databases.

Overall, the four parts of the thesis, in different ways, contribute to a more efficient AF screening.

Abstract

This thesis comprises an introductory chapter and four papers related to quality control in ECG-based atrial fibrillation (AF) screening. Atrial fibrillation is a cardiac arrhythmia characterized by an irregular rhythm and constitutes a major risk factor for stroke. Anticoagulation therapy significantly reduces this risk, and therefore, AF screening is motivated. Atrial fibrillation screening is often done using ECGs recorded outside the clinical environment. However, the higher susceptibility of such ECGs to noise and artifacts makes the identification of patients with AF challenging. The present thesis addresses these challenges at different levels in the data analysis chain.

Paper I presents a convolutional neural network (CNN)-based approach to identify transient noise and artifacts in the detected beat sequence before AF detection. The results show that by inserting a CNN, prior to the AF detector, the number of false AF detections is reduced by 22.5% without any loss in the sensitivity, suggesting that the number of recordings requiring expert review can be significantly reduced.

Paper II investigates the signal quality of a novel wet electrode technology, and how the improved signal quality translates to improved beat detection and AF detection performance. The novel electrode technology is designed for reduction of motion artifacts typically present in Holter ECG recordings. The novel electrode technology shows a better signal quality and detection performance when compared to a commercially available counterpart, especially when the subject becomes more active. Thus, it has the potential to reduce the review burden and costs associated with ambulatory monitoring.

Paper III introduces a detector for short-episode supraventricular tachycardia (sSVT) in AF screening recordings, which has been shown to be associated with an increased risk for future AF. Therefore, the identification of subjects with such episodes may increase the usefulness of AF screening. The proposed detector is based on the assumption that the beats in an sSVT episode display similar morphology, and that episodes including detections of deviating morphology should be excluded. The results show that the number of false sSVT detections can be significantly reduced (by a factor of 6) using the proposed detector.

Paper IV introduces a novel ECG simulation tool, which is capable of producing ECGs with various arrhythmia patterns and with several different types of noise and artifacts. Specifically, the ECG simulator includes models to generate noise observed in ambulatory recordings, and when recording using handheld recording devices. The usefulness of the simulator is illustrated in terms of AF detection performance when the CNN training in Paper I is performed using simulated data. The results show a very similar performance when training with simulated data compared to when training with real data. Thus, the proposed simulator is a valuable tool in the development and training of automated ECG processing algorithms.

Together, the four parts, in different ways, contribute to improved algorithmic efficiency in AF screening.

List of papers

Included

I. **Identification of Transient Noise to Reduce False Detections in Screening for Atrial Fibrillation.**
Hesam Halvaei, Emma Svennberg, Leif Sörnmo, Martin Stridh
Published in: Frontiers in Physiology, vol. 12, 672875, 2021

The author developed the method, designed and performed the experiments, and did most of the writing.

II. **Signal Quality Assessment of a Novel ECG Electrode for Motion Artifact Reduction.**
Hesam Halvaei, Leif Sörnmo, Martin Stridh
Published in: Sensors, vol. 21, no. 16, 5548, 2021.

The author designed and performed data collection and experiments, and did most of the writing.

III. **Detection of Short Supraventricular Tachycardias in Atrial Fibrillation Screening.**
Hesam Halvaei, Tove Hygrell, Emma Svennberg, Valentina D. A. Corino, Leif Sörnmo, Martin Stridh
Manuscript in preparation, ready for submission in September 2023

The author developed the method, designed and performed the experiments, and did most of the writing.

IV. ECG Modeling for Simulation of Arrhythmias in Time-Varying Conditions.
Lorenzo Bacchi, **Hesam Halvaei**, Cristina Pérez, Andrius Sološenko, Alba Martín-Yebra, Andrius Petrėnas, Linda Johnson, Vaidotas Marozas, Juan Pablo Martínez, Esther Pueyo, Martin Stridh, Pablo Laguna, Leif Sörnmo
Accepted for publication in IEEE Transactions on Biomedical Engineering, 2023.

The author developed the time-varying noise model, designed the approach for ECG model validation and performed validation of the simulation model.

Related

Different parts of the work have also been published in

I. False alarm reduction in atrial fibrillation screening
Hesam Halvaei, Emma Svennberg, Leif Sörnmo, Martin Stridh
Four-page paper presented at Computing in Cardiology, Rimini, Italy, 2020.

II. Detection of Short Supraventricular Tachycardias in Single-lead ECGs Recorded Using a Handheld Device
Hesam Halvaei, Tove Hygrell, Emma Svennberg, Valentina D. A. Corino, Leif Sörnmo, Martin Stridh
Four-page paper presented at Computing in Cardiology, Tampere, Finland, 2022.

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Thank you for everything Azin!

Hesam
Lund, September 2023

Contents

Part I

Introduction

Chapter 1

Background and Motivation

1.1 Thesis Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice with a prevalence of 3% and higher in the population above 60 years of age [1]. Atrial fibrillation constitutes a major risk factor for stroke [2], and recent estimates suggest that 13% of all patients with AF are undiagnosed [3]. Therefore, screening for AF has been suggested as a means to reduce the consequences of AF.

In recent years, home-based screening for AF has been facilitated by novel portable technologies for ECG measurement, and has reached a technological capacity to allow screening on a population level, also referred to as mass-screening [4–14]. One major challenge when performing ECG-based AF screening on a population level is the very large number of ECGs that are generated, which necessitates automated analysis for the detection of pathological ECG characteristics, ideally aiming at finding all patients with previously undetected AF to an as low false alarm rate as possible.

However, performing home-based screening for AF with such a requirement is challenging, mainly due to the higher susceptibility of home-based recording systems to noise and artifacts in comparison to standard resting ECGs. Another challenge that further complicates the detection of AF is the presence of a broad range of non-AF arrhythmias in the elderly population who are often the target of screening.

In the screening setting, ECG episodes with lower signal quality disturb the detection of important ECG characteristics such as the exact beat occurrence times, which in turn may lead to false arrhythmia detections. Such false arrhythmia detections will require manual review by clinical experts to be ruled out. Due to the size of screening databases and the aim to find all important cases, the required manual review may become a time-consuming and costly task. Thus, the inherent logic of ECG screening is that better ECG measurement quality translates to better arrhythmia detection performance, lower false alarm rates, and vice versa.

The work in the present thesis is closely related to the analysis chain from measurement via detection of ECG characteristics to clinical decision making, see Fig. 1.1. The common theme of the included papers is on signal quality and its relation to AF screening performance; how signal quality can be addressed in the arrhythmia detection stage, how a better signal quality achieved in the measurement stage translates to better detection of ECG characteristics, and how realistic noise and artifacts can be simulated for performance evaluation of arrhythmia detectors and for training of machine learning-based models.

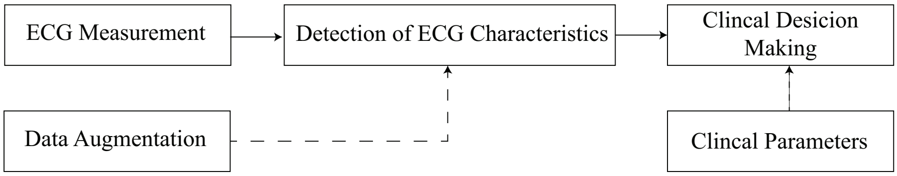

Figure 1.1: The AF screening analysis chain from ECG measurement, via detection of ECG characteristics to clinical uses cases, including AF detection and AF prediction. Data augmentation is important when training machine-learning-based models and for arrhythmia detection performance evaluation.

Specifically, in the context of ECG-based AF screening, this thesis consists of the following four parts:

- Paper I presents a novel approach to reduce the number of false AF detections by identification of transient noise which disturbs the beat detection.

- Paper II evaluates a novel electrode technology and investigates resulting improvements in signal quality and detection performance when compared to a commercially available electrode.

- Paper III presents a novel approach to the detection of short-episode supraventricular tachycardias, which are associated with a higher risk of development of AF, and therefore of importance in AF screening.

- Paper IV proposes a model for the simulation of motion artifacts in screening ECGs and assesses the performance of the method presented in Paper I when that machine learning model is trained using simulated ECGs instead of real ones.

The remainder of this introductory chapter gives an overview of AF, and associated treatment options, and summarizes the rationale for AF screening. An overview of different types of screening devices and electrodes is given in Chapter 2. Chapter 3 briefly introduces the machine learning approaches used in the present thesis and summarizes previous works related to data analysis involved in AF screening including beat detection, AF detection, signal quality assessment, and prediction of AF. Chapter 4 provides an overview of ECG and noise simulation models. Finally, a summary of the included papers is provided in Chapter 5.

1.2 What is Atrial Fibrillation?

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by abnormal electrical activity in the atria, which causes an irregular heart rhythm, and thereby inefficient contraction. The most common symptoms of atrial fibrillation are fatigue, shortness of breath, palpitations, and chest pain. However, many patients are asymptomatic, suggesting that the prevalence of AF may be underestimated.

The diagnosis of AF is based on the rhythm of beats in the ECG. The main components of a heartbeat in the ECG are the P wave, the QRS complex (consisting of the Q, R, and S waves), and the T wave, where the time between successive QRS complexes is called RR intervals. An ECG during AF is characterized by irregular RR intervals, and an irregularly oscillating baseline known as fibrillatory waves (f-waves) in place of the normal P waves, see Fig. 1.2.

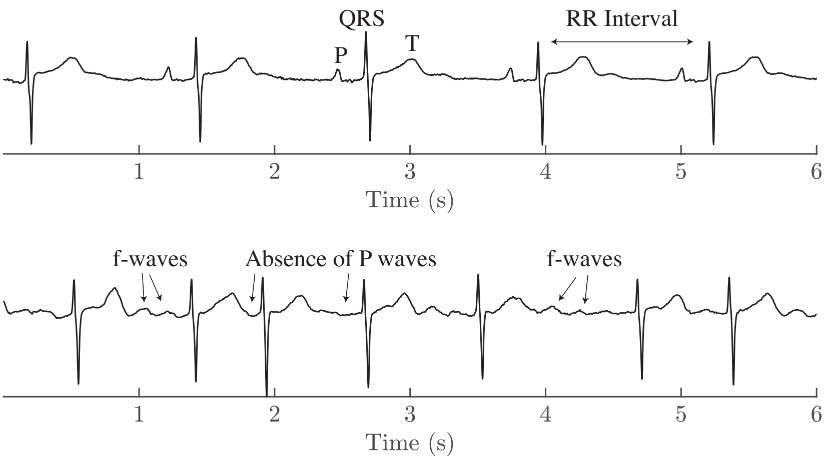

Figure 1.2: An example of an ECG during normal sinus rhythm (top panel), and an example of an ECG during AF (bottom panel), where the RR interval irregularity, presence of f-waves, and absence of P waves can be observed.

Based on the duration and recurrent nature of AF episodes, they are classified into different types, including paroxysmal AF, when recurrent self-terminating episodes last less than seven days, persistent AF, when self-termination fails within seven days, long-standing AF, i.e., when an episode is lasting for more than a year after starting a therapeutic intervention, and permanent AF, when the intervention has failed and AF has been manifested [15].

1.2.1 Treatment and management of AF

The main problem with atrial fibrillation is that irregular and less organized contraction of the atria may lead to formation of blood clots, which may be carried by the blood towards the brain, and which in turn, may cause a stroke. Therefore, anticoagulants are, according to guidelines [2], considered for all patients with AF to reduce the risk of stroke, and thereby, to reduce AF-related mortality.

Apart from stroke prevention, improving the quality of life in patients with AF is another fundamental objective in the management of AF, pursued using rate-controlling, or rhythm-controlling interventions. Atrial fibrillation episodes often display an abnormally high heart rate, which if left untreated, may lead to a deterioration of ventricular contractibility, and other complications. Rate-controlling interventions seek to reduce the heart rate by means of pharmaceuticals, or invasive catheter-based ablation therapy.

For most symptomatic patients, when rate-controlling interventions are unsatisfactory, or for patients in the early stages of AF progression, rhythm-controlling interventions may be applied. Such interventions aim at restoring normal sinus rhythm, and at preventing AF recurrence. Electrical cardioversion and antiarrhythmic drugs are rate-controlling interventions [16].

1.2.2 Rationale for AF Screening

Atrial fibrillation affects more than 30 million individuals worldwide. Only in Europe, it is estimated that the number of individuals with AF will more than double, reaching 18 million in 2060 [17], with 120,000-215,000 new cases per year [1]. The increase is mainly due to the aging population and to intensified efforts to find undiagnosed patients with AF [2].

Stroke is the first clinical manifestation in around 5-10% of individuals with AF [18, 19], and as described above, oral anticoagulation treatment has been shown to reduce the risk of stroke [2]. However, since AF may be paroxysmal and asymptomatic in many patients, they may remain undetected and are therefore not offered oral anticoagulants.

In combination, the factors mentioned above, namely the increasing prevalence of AF, and the availability of an accepted test and an efficient treatment option, are in line with the criteria for medical screening proposed by the World Health Organization [20] and have led to a Class I recommendation for AF screening by the European Society of Cardiology [2]. Ongoing clinical trials aim to answer questions related to the usefulness and cost-effectiveness of large-scale screening programs [7, 14, 21–23].

Chapter 2
ECG Electrodes and Recording Systems

Several different types of ECG systems are available, from the widely used standard 12-lead ECG used in clinical routine, over ambulatory/Holter ECG systems aimed at long-term monitoring during days or weeks, to simplified handheld ECG devices performing intermittent single-lead measurements [24]. There are also implantable cardiac loop recorders and different types of patches available for ECG measurements [25, 26].

Several of these types of devices may be used for AF screening either using long-term continuous monitoring or using intermittent short-term measurements recorded over a period of days or weeks. Obviously, a long-term continuous recording may find more arrhythmic events but at the cost of lower signal quality when the screened person is performing daily activities, which are well-known to cause large amounts of disturbances and thereby false alarms. Correspondingly, intermittent recordings have the advantages that no electrodes and wires are attached to the body, and that all recordings are performed at rest, but, on the other hand, may miss important events between the measurements.

The usefulness of each of the two techniques depends on the AF burden, i.e., the percentage of time in AF of the individual patient. The critical aspects for a system to be used in a screening setting are that the screening tools are capable of identifying patients with AF, safe to use, and cost-efficient. As described in Chapter 1, successful and efficient AF screening relies on ECG recordings of adequate quality. In this chapter, the measurement of the ECG is explained, first in terms of the electrode, i.e., the interface to the skin, and its susceptibility to various types of disturbances, and then, in terms of different recording systems.

2.1 ECG Electrodes and Related Disturbances

The electrical activity of the heart is recorded using a set of electrodes on the body surface, which serves as an interface between the body and the recording device. The difference in electrical potential measured between a pair of electrodes is referred to as a lead. The resulting recording, the ECG, is characterized by a series of waves with distinct morphology and timing reflecting the patient's heart rhythm, see Fig. 1.2. The heart rhythm contains significant diagnostic information reflecting whether the activation of the heart is normal or abnormal [27]. Often, a multi-lead configuration is used, combining unipolar and bipolar leads, so that the spatiotemporal variation in the cardiac electrical field in various directions is reflected. A unipolar lead measures its voltage in relation to a reference electrode positioned such that its potential remains almost constant during the cardiac cycle, while a bipolar lead is a measurement between any two electrodes.

In order to record a reliable, high-quality ECG signal, the electrode should provide stable contact with the body surface to ensure the minimal influence of so-called motion artifacts, see below. In addition, the electrode-skin impedance should be as low as possible to ensure that the measured ECG amplitude is large enough and thereby well reflects the cardiac activity.

When an ECG is recorded, it may be contaminated by various types of noise and artifacts, for example, when it is recorded in ambulatory conditions, or in the home environment without electrode attachment to the body. The most common types of noise and artifacts are powerline interference, baseline wander, motion artifacts, and muscle noise [27]. Powerline interference (50/60 Hz) is a narrowband interference caused by electrical currents induced in the wires to the electrodes, e.g., due to improper grounding or interference from nearby devices, whereas baseline wander is low-frequency artifact often caused by respiration, body movements, sweating, or poor electrode contact. Both these types of disturbances can be handled using linear and non-linear filtering approaches [27].

Motion artifacts are mainly caused by varying skin-electrode contact and a varying impedance level, especially problematic in ambulatory monitoring when ECG measurements are performed during daily activities. This type of artifact is also troublesome when recording using handheld recorders, since the skin-electrode contact may vary due to hand movements and varying pressure on the electrodes. Muscle noise is commonly seen in ECGs recorded during ambulatory monitoring, and during activities involving muscle contractions such as exercise. Motion artifacts and muscle noise, especially during physical activity, are more difficult to remove from ECG signals due to their overlapping spectral content when compared to normal cardiac activity. Instead, more sophisticated denoising strategies [28, 29] or signal quality assessment techniques are employed, to either suppress the noise and artifacts or to identify and exclude poor quality segments from further processing, see Sec. 3.4. Such approaches, however, carry the risk of distorting cardiac components of the ECG, and of missing important arrhythmic episodes occurring simultaneously with noise and artifacts.

The most direct way to address signal quality is by improvements in the ECG electrode technology and in that way increase the robustness to noise and artifacts. An important factor in electrode design is the skin-electrode impedance level. The electrode interface to the skin is illustrated in Fig. 2.1. The outermost layer of the epidermis called the stratum corneum (SC), has a high impedance. Hydrating this layer using gel creates an ionic pathway between the electrode and SC, thereby reducing the skin-electrode impedance. Hence, the wet/gel electrode is the most commonly used type of electrode in clinics today [30].

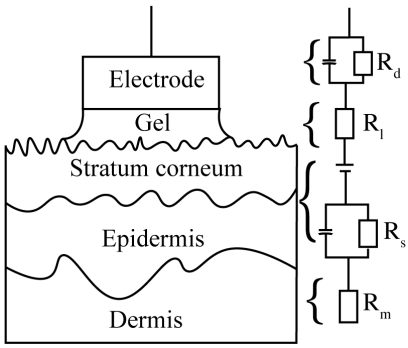

Figure 2.1: Equivalent circuit of the electrode-body interface.

The drawback of wet electrodes is that they dry out, which reduces the signal quality during long-term monitoring, and that they then may cause skin irritation and discomfort. Therefore, during recent years, there has been a large interest in the development of dry electrodes, often divided into contact and non-contact dry electrodes [31–39]. Comparisons between dry and wet electrodes have shown higher skin-impedance levels and more motion artifacts in wet electrodes [32–34]. The signal quality difference has, however, been shown to be less pronounced in recent studies [39]. Regardless of these efforts, wet electrodes remain the standard choice of electrodes in clinical routine, and work on improving their long-term properties is ongoing [38].

2.2 ECG Recording Systems

In this section, an overview of different types of ECG systems is provided. The following types of systems are considered (see Fig 2.2 for an illustration):

- The standard 12-lead ECG

- The ambulatory/Holter ECG and patches
- The handheld/single-lead ECG

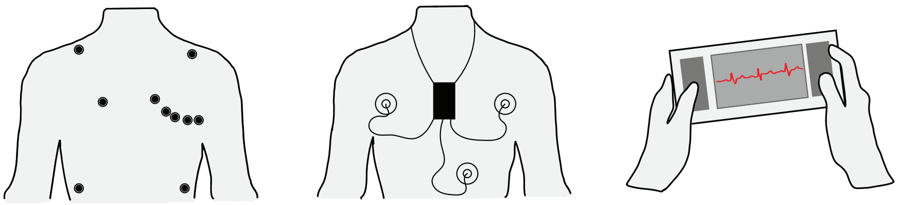

Figure 2.2: An illustration of three types of ECG recording systems: (left) Standard 12-lead ECG), (middle) Ambulatory/Holter ECG, and (right) Handheld recording system. Note that the exact position and the number of electrodes vary for specific devices. This illustration is only for presentation purposes.

The Standard 12-lead ECG

The standard 12-lead ECG is an inexpensive technology for the investigation of a patient's cardiac health. Numerous ECG handbooks are available describing the interpretation of various waves, amplitudes, and intervals; therefore, the standard 12-lead ECG is a globally accepted clinical tool. The recording duration varies from 10 seconds in many hospital databases up to several hours during different interventions. The standard 12-lead ECG is intended for diagnostics of ongoing abnormal activity but is less well-suited for long-term monitoring, where the main goal is to detect rare events. In AF screening, the main goal is to detect ongoing AF or more rare episodes of AF, and then a measurement method with fewer electrodes is sufficient.

The Ambulatory/Holter ECG and patches

Ambulatory monitoring devices, also known as Holter monitors, are widely accepted in many clinical applications, such as screening and follow-up after surgery, and are capable of recording ECGs with a duration of 1–30 days. Typically, a reduced lead system of 1-3 leads is used.

The main advantage of a Holter system is that the patient can wear the device for a longer period of time, allowing the detection of rare cardiac events. The main drawback is that the patient may be performing daily activities during the recording, often causing longer segments of poor quality and a lot of segments with moderate quality. See Fig. 2.3 for examples of signals recorded during daily activities. Since non-standard leads are used in Holter systems, the purpose of

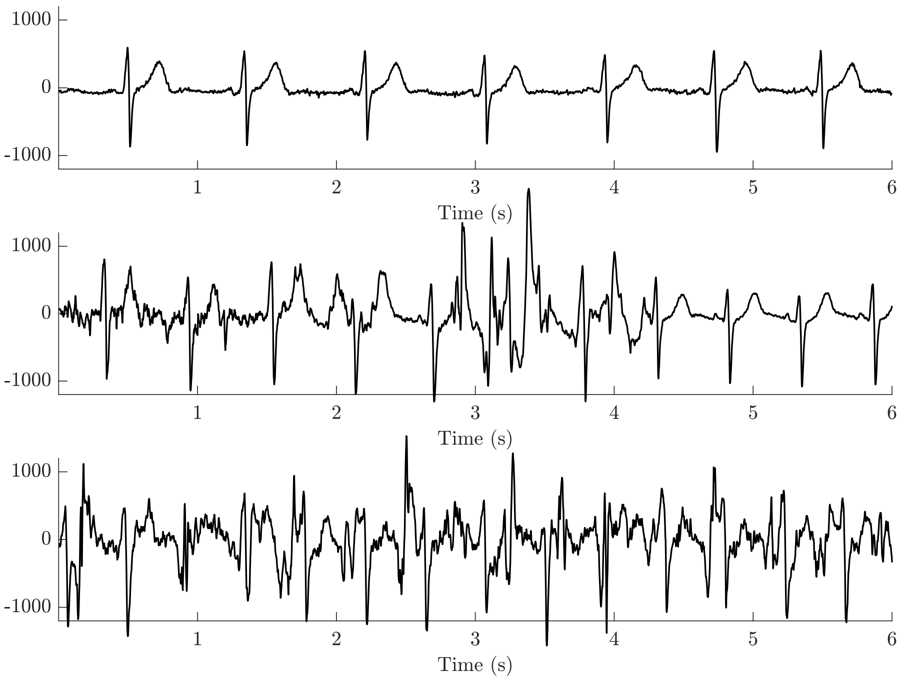

Figure 2.3: Examples of ECGs recorded with a Holter device when the subject is sitting at rest (top panel), is taking on clothes (middle panel), and is jogging (bottom panel).

such systems is mainly to detect rhythm-related pathologies and less to detect morphologic deviations.

Patches may be seen as a smaller and more integrated type of Holter system incorporating wearable technology that bypasses the need for wire attachments. The size of the patch limits the possibilities for tailoring specific bipolar leads, but the placement of the patch may be optimized with respect to a certain recording protocol so that the effects of noise and artifacts are minimized. Patches have been used in screening studies, which, due to the extended monitoring time, resulted in a higher yield of screening [22].

The Handheld/single-lead ECG

Handheld ECG recorders are inexpensive, portable, and easy-to-use devices that are gaining increasing attention as a reliable tool for AF screening. Handheld recorders produce an ECG similar to the standard lead I (between the arms) by placing thumbs, fingers, or palms on the two electrodes, often with a duration of 30 s to 1 minute. Handheld ECG recorders can be used in the home environment without expert supervision, producing signals with good/acceptable quality in a large majority of the recordings [40]. However, the quality of the recorded ECGs depends on whether the users have carefully followed the provided instructions for how to perform an ECG measurement. Figure 2.4 shows examples of ECGs recorded with a handheld device where the signal quality is affected, most likely due to hand movements or varying pressure on the electrodes.

Handheld devices may be provided with a built-in AF detection algorithm to produce an immediate response, or they can send the recording to a data center for analysis. The Zenicor ECG recorder [41], MyDiagnostick [42, 43], and Kardia by AliveCor [44] are examples of handheld recorders that have been used in screening studies.

The short duration limitation of handheld devices is compensated by instructing the users to record multiple ECGs per day for a period of time, e.g., two weeks or up to months. Such an approach has been shown to identify up to four times more patients with AF when compared to standard ambulatory monitoring during 24 h [45].

Interestingly, when comparing the two screening studies, LOOP [22], using implantable loop recorders, and StrokeStop I [21], using a handheld recording device, a higher reduction of stroke, systemic embolism, all-cause mortality, and major bleeding was shown in the StrokeStop I study [46]. The reason may be explained by the fact that many AF patients identified in the LOOP study displayed a lower AF burden, which has been shown to be associated with a more benign outcome [47], while in the StrokeStop I study, the identified AF patients may have possessed a higher AF burden since AF episodes were found in a limited screening time period.

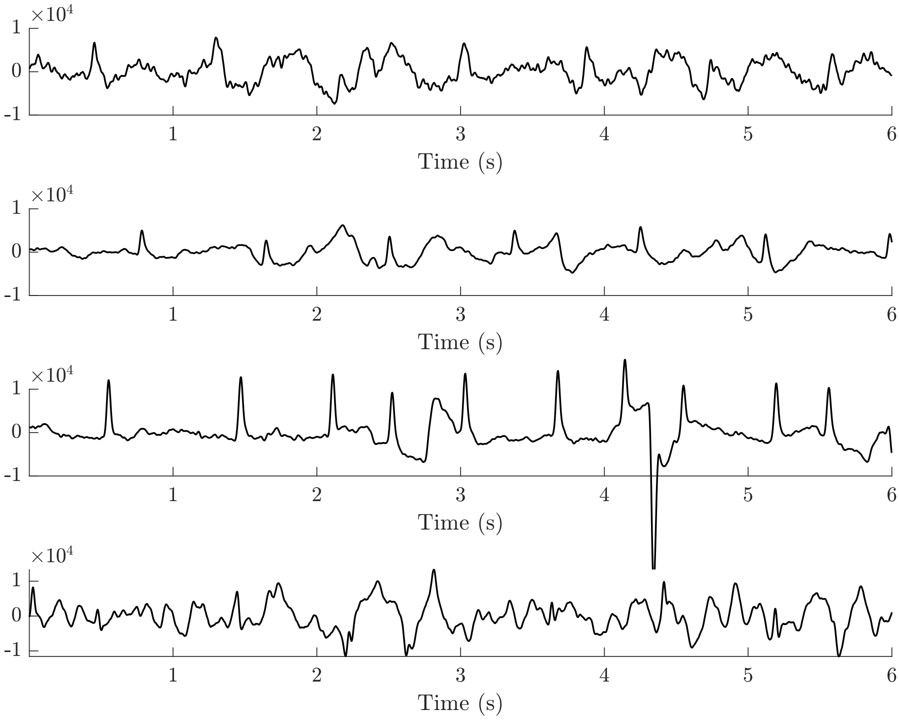

Figure 2.4: Examples of poor quality ECGs recorded using a handheld device, where the signal quality is affected by hand movements or varying pressure onto the electrodes.

Chapter 3

Detection of ECG Characteristics

The development of signal processing techniques for ECG analysis has been ongoing for several decades. And yet, advances in ECG device technology, availability of massive amounts of data, and new clinical studies generate new research questions and call for novel approaches to tackle the new challenges.

Examples of ECG signal processing needed in AF-related applications include preprocessing, beat detection and classification, rhythm analysis and arrhythmia detection, extraction and characterization of f-waves, characterization of AF episode patterns, assessment of drug responses, identification of individuals at risk of developing AF, and outcome prediction of various interventions. Some of these applications require more than one lead, long-term ECG recordings, or longitudinal data for a more reliable outcome, while rhythm analysis and AF detection are feasible with as short as 30-s single-lead recordings.

Signal quality assessment has emerged as a crucial processing step in ECG signal processing, mainly due to the growing interest in recording outside the clinical environment using portable devices as well as during normal daily activities. As described in previous chapters, poor-quality ECG segments deteriorate the performance of any subsequent ECG analysis.

Many applications in ECG signal processing involve parts where machine learning is a useful tool. Detection of ECG characteristics may include one or several thresholds applied to the extracted parameters (or features) that are selected for the task. Depending on the desired level of flexibility in terms of features and decision boundaries, more advanced machine learning approaches may be utilized. The present thesis is based on this view, where traditional signal processing and machine learning complement each other in order to solve practical problems. The description in the rest of the introduction is in line with this view and describes what has been done related to different applications without separating

ML-based approaches from other approaches.

In the first section of this chapter, a very brief summary of machine learning concepts and algorithms, relevant to this thesis, is provided. Then, in the remainder of this chapter, the focus is on the detection of ECG characteristics relevant to AF screening, signal quality assessment methods for ECG signals, and prediction of AF.

3.1 Machine Learning

Machine learning, in broad terms, is a field of study where algorithms learn to identify specific patterns within a dataset during a *training phase*. Two main types of learning can be distinguished as *supervised learning* and *unsupervised learning*[1]. In supervised learning, a model is exposed to a training dataset where ground truth (labels) related to the training dataset are provided, and this knowledge is used to optimize the performance of the model. In other words, the objective is to learn a function, which optimally maps the training data to the ground truth. Unsupervised learning, on the other hand, is the case where the ground truth is not provided, and the model learns the underlying structure of the training data by itself. In the present thesis, only supervised learning for classification purposes is used.

A multitude of algorithms and models exist for supervised learning. Traditional approaches include, e.g., k-nearest neighbors, linear discriminant analysis, decision trees, random forests, and support vector machines (SVM). In these approaches, the "raw input data" is transformed to a low-dimensional space, by means of *feature extraction*, which is typically based on prior knowledge related to the task at hand, and the performance becomes associated with the ability of the user to extract an optimal feature set. This step is bypassed in another class of models called artificial neural networks (ANN), which are composed of interconnected nodes and layers. The layered architecture of ANNs facilitates the mapping from raw data to the outputs.

In the following, two machine learning models relevant to the present thesis, the SVM and the convolutional neural network (CNN), are described in more detail. The objective of an SVM is to find the hyperplane, which separates the various classes in the training dataset by maximizing the distance between the hyperplane and the points closest to the decision boundary. While originally introduced for linearly separable data, SVMs were extended to non-separable cases by introducing a slack variable that penalizes data points that occur on the wrong side of the hyperplane, and to non-linear classification by the kernel trick,

[1] This is a rather traditional categorization; recent categorizations may include semi-supervised learning or reinforcement learning as well.

which maps the data into a higher-dimensional space, where the data can be linearly separated [48, 49].

A CNN is a specific type of feed-forward ANN. While a wide range of CNN architectures have been proposed in the literature, their building blocks are often very similar, namely convolutional, pooling, and fully connected layers [50]. The convolutional layer is the core of the CNN, which performs a convolution operation using a number of learnable filters/kernels. An element-wise nonlinear activation function is applied to the convolved results to generate feature maps. Common activation functions are tanh, ReLU, and sigmoid. Note the important property of the CNN, which is weight sharing, meaning that a kernel is shared by all locations (spatial) of the input. Pooling layers reduce the resolution of the generated feature maps model complexity and introduce a property called shift-invariance to the CNN. The most common pooling layers are average pooling, where the average of a local part of the feature map is selected, and max pooling, which as the name suggests, the maximum value is selected instead. After several convolutional and pooling layers, the generated feature maps are flattened, and connected to one or more fully-connected layers which perform the actual classification.

3.2 QRS Complex Detection

A crucial step for rhythm analysis and detection of AF is the correct detection of QRS complexes. An inadequate performance at this step propagates to the subsequent analysis and deteriorates the overall performance. Hence, the detection of QRS complexes has been widely studied over many decades.

Often, a QRS detector includes two main steps: a preprocessing step, which emphasizes the QRS complexes in relation to other ECG components, and a detection step, which utilizes a thresholding approach to identify the QRS complexes. The preprocessing step can be done by means of the first and/or second derivative of an ECG signal [51], Hilbert transform [52, 53], empirical mode decomposition [54, 55], or wavelet transform [56]. The detection step is done by means of zero-crossing, or fixed/adaptive thresholding of the transformed ECG signal [57].

The most common database used for performance evaluation of QRS complex detectors is the MIT-BIH Arrhythmia Database [58, 59], which contains ECG signals with a variety of QRS complex morphologies, ectopic beats, as well as noisy segments, where existing methods have reached sensitivities and positive predictive values above 99.5%.

However, in the presence of noise and artifacts displaying QRS-like waveforms, QRS detection is a complicated task. In fact, the topic has been revisited in recent years, now focusing on ECG signals recorded under ambulatory conditions using new recording systems such as wearables, where the signals present lower signal quality [60, 61].

3.3 Detection of AF

Detection of AF is a widely studied topic in the literature. As described previously, the main properties of an ECG signal during an AF episode are:

- the presence of an irregular rhythm,
- the presence of f-waves, and
- the absence of P waves.

An AF episode with a duration of ≥ 30 s has been considered the standard requirement for a clinically relevant AF diagnosis. However, AF episodes of duration < 30 s have received increasing attention in recent years since they may be an indicator of longer AF episodes outside the screening/monitoring period [46, 62, 63].

Quantification of rhythm irregularities is the most prominent attribute for the vast majority of the proposed AF detectors (referred to as rhythm-based AF detectors [64]), simply due to the dominant amplitude of R waves when compared to P and f-waves (cf. Fig. 1.2), which may be masked even in the presence of low-to-moderate levels of noise and artifacts.

An RR interval series is used as the input to rhythm-based AF detectors, computed by

$$d(k) = t(k) - t(k-1), \quad k = 1, \dots, K, \tag{3.1}$$

where K is the total number of detected QRS complexes and $t(k)$ is the occurrence time of the k:th R-wave. The most commonly used measures to quantify the irregularity of the RR interval series are statistical dispersion measures, turning points ratio, histogram-based parameters, entropy measures, symbolic dynamics, and Poincaré-based measures, see below for further details. An AF detector relies either only on one irregularity measure [65–68], or on a combination of several measures [69, 70].

As statistical dispersion measures, the *coefficient of variation*, defined by the ratio of the standard deviation to the mean of $d(k)$, and the *root mean square of successive differences* defined by

$$D_{RMSSD} = \sqrt{\frac{1}{K}\sum_{k=1}^{K} d(k)^2}, \tag{3.2}$$

are the most commonly used in rhythm-based AF detectors [65, 69].

The Poincaré plot is another technique used to characterize the dispersion of RR intervals as well as classify different types of cardiac rhythms, displaying successive pairs in an RR interval series, i.e., the current RR interval versus the previous one, see Fig. 3.1. During an AF episode, the constructed Poincaré plot is expected to be more scattered compared to during sinus rhythm, or in the presence of frequent ectopic beats. To translate the level of scattering into a detection feature, the density of points in different regions [66], or the geometrical characteristics of the points in the Poincaré plot [71], have been used.

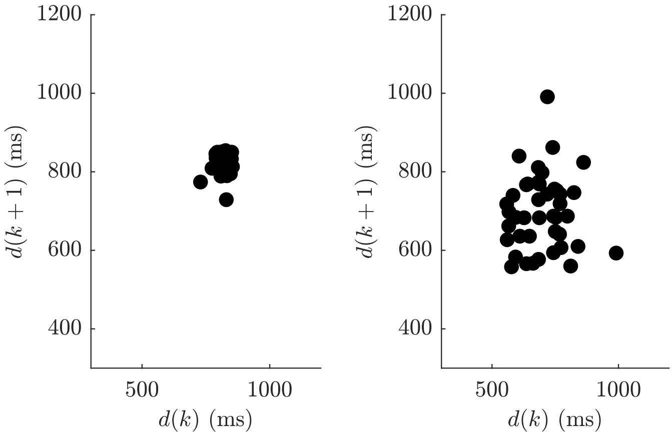

Figure 3.1: Poincaré plots obtained from the RR intervals of two 30 s ECGs; (left) during sinus rhythm, and (right) during AF.

Entropy-based measures, which quantify the predictability (or regularity) of a given series of observations, have also been used for AF detection. Given an RR interval series, entropy decreases when the series becomes more predictable (or less irregular) and increases when the series becomes less predictable (or more irregular). Several estimates of entropy have been used for AF detection, such as *Shannon entropy*, *approximate entropy*, and *sample entropy*. Shannon entropy is defined by

$$I_{\text{ShEn}} = -\sum_{i=1}^{B} p(x_i)\log_2(p(x_i)), \tag{3.3}$$

where x_i is an observation series, with B distinct values, and $p(x_i)$ is the probability of x_i to occur, which in practice is estimated using the histogram of the observation series. Here, the observation series is the RR intervals series, except that the shortest and longest RR are excluded to decrease the effect of outliers. This measure is, however, prone to produce a lower-than-expected entropy in higher heart rates, as the differences in the RR series are relatively smaller compared to those of a lower heart rate.

Sample entropy is defined as the logarithm of the conditional probability that if a series repeats itself for m samples within a tolerance r, it also repeats itself for $m+1$ samples,

$$I_{\text{SampEn}}(m,r) = \ln\left(\frac{B(m,r)}{B(m+1,r)}\right), \tag{3.4}$$

where $B(m,r)$ is the probability that a series, in this case $d(k)$, is repeating itself for m samples within a tolerance r. To estimate $B(m,r)$, the RR interval series $d(k)$, is divided into subsequences of length m. Then, $B(m,r)$ is computed as

$$B(m,r) = \frac{1}{(K-m)(K-m-1)} \sum_{i=0}^{K-m-1} \sum_{j=0, j\neq i}^{K-m-1} H(r - ||\mathbf{d}(i) - \mathbf{d}(j)||_{\infty}). \tag{3.5}$$

where $\mathbf{d}(i)$ is a vector of m consecutive RR intervals starting at interval i, and H is the Heaviside function. An increasing value of I_{SampEn} indicates a transition from normal sinus rhythm to AF.

A simplified approach to sample entropy based on $B(m=1,r)$ is used in [72], where the maximum norm in (3.5) is replaced by the probability of two RR intervals within a detection window is differing less than the threshold r. This simplified measure is estimated by

$$\hat{B}(m=1,r) = \frac{2}{(K-1)(K-2)} \sum_{i=0}^{K-2} \sum_{j=i+1}^{K-1} H(r - |d(i) - d(j)|. \tag{3.6}$$

To account for the higher heart rate during an AF episode, (3.6) is divided by the exponential average of the RR intervals, where RR intervals related to ectopic beats are excluded. Another possibility to include the heart rate information is to replace the tolerance r with a varying tolerance based on the estimated heart rate within the detection window.

Since morphological features of the beats are not considered in rhythm-based AF detectors, they are prone to generate false positives in the presence of frequent ectopic beats, other irregular arrhythmias, and poor-quality segments. Such problems with rhythm-based AF detectors have motivated the inclusion of information related to the atrial activity, i.e., the absence of P waves and presence of f-waves, in AF detectors, which may be challenging due to the much lower amplitude of such waves, especially in ECGs with low-to-moderate signal quality. The two approaches presented in [73,74] included P wave absence as a feature in the AF detection. Such detectors are also important since they can also be used in patients with pacemakers or in those taking rate-controlling drugs where beat irregularity has been suppressed.[2]

Detectors based on the above-described principles have reached a high performance, i.e., $\geq 97\%$ for both sensitivity and specificity, when tested on the MIT-BIH Atrial Fibrillation Database (AFDB) [59, 75], in part, since the mentioned challenges with irregular non-AF arrhythmias and poor quality signals are less significant in this database. Therefore, such performance cannot be translated to AF detection in a screening setting. Based on the AF screening guidelines and recommendations, the population included in screening studies is often older than 75 years (or older than 65 with additional risk factors). Therefore, the presence of arrhythmias other than AF is more likely compared to the case when a younger population is screened.

In addition to the described detectors, recent interest in deep learning has led to a new generation of AF detectors, exemplified by the studies [76–80]. Deep learning-based approaches enable the detection of AF without the need for "expert-crafted features" describing, e.g., irregularity. While showing promising results, comparison of performance between deep learning-based AF detectors and the "traditional" AF detectors has turned out to be complicated, even when using the same database, due to annotation conversion often required for deep learning-based AF detectors[3] (i.e., performance evaluation done on a beat-to-beat or episode-to-episode basis), exclusion of data to handle data imbalance or poor signal quality, as well as the presence of data from the same patients in training and test sets [81, 82].

Hence, it is reasonable to conclude that no AF detector is able to detect AF with high sensitivity and precision in the presence of complicating factors, such as non-AF rhythms with irregularities that resemble AF, and noise and artifacts. Such problems are by far more pronounced when dealing with screening ECGs either in the form of short-term intermittent recordings or in the form of continuous long-term ECGs recorded during daily activities. For intermittent recordings, the short duration makes the detection even more difficult as many irregularity parameters are developed for segments longer than 30 s, where the performance drops for increasingly shorter episodes.

[2] Interestingly, the inclusion of information on the atrial activity did not contribute to improving the performance of the AF detectors when tested on AFDB. This may be explained by the fact that no measure was included to address the signal quality, which makes reliable identification of P and f-waves difficult [64].

[3] Note that the annotation conversion is required for some of the "traditional" AF detectors as well.

3.4 Signal Quality Assessment

Automated ECG analysis requires reliable identification of ECG characteristics, which may be difficult when recording in ambulatory conditions, or when using handheld ECG devices where the electrodes are not attached to the body. Such recordings are prone to contain motion or muscle artifacts. In terms of arrhythmia detection, a lower signal quality translates to lower QRS and P wave detection performance, and consequently, poorer arrhythmia detection performance, often realized by very high false detection rates. Ruling out the false detections requires manual review by experts, which is a time-consuming and costly task, and ideally, should be limited to as small a subset of the recordings as possible.

As described in Sec. 2.1, noise and artifacts, including baseline wander and powerline interference can be suppressed using ECG denoising techniques. However, motion artifacts, often characterized by rapid baseline variations with QRS-like appearances, and muscle noise, especially during physical activity, remain problematic and deteriorate the QRS detection performance and any subsequent rhythm analysis. In such a case, a more feasible approach is to use *signal quality assessment* to exclude noisy ECG segments before further analysis takes place. A wide variety of approaches have been presented to address signal quality assessment, including the degree of agreement between two QRS detectors and statistical measures such as kurtosis and skewness of ECG segments [83–85], signal-to-noise ratio (SNR) estimation [86–88], heart rate-based criteria [89, 90], and correlation-based metrics either in time or in the time-frequency domain [91,92]. Such measures are either used in the form of a rule-based signal quality metric or fed to a machine learning model to classify an ECG segment into a relevant quality class.

Estimation of SNR requires an estimate of the noise-free ECG and an estimate of the noise. Estimation of a noise-free ECG was done in [87] by creating an ensemble average $y_{avg}(n)$, defined by

$$y_{avg}(n) = \frac{1}{K}\sum_{k=1}^{K} y_k(n) \tag{3.7}$$

where $y_k(n)$ is the k:th detected beat. Then, assuming that any deviation from this "noise-free ECG" is due to noise, the SNR of the k:th beat was computed by

$$SNR_k = 10\log_{10}\frac{\frac{1}{N}\sum_{n=1}^{N} y_{avg}(n)^2}{\frac{1}{N}\sum_{n=1}^{N}(y_k(n) - y_{avg}(n))^2}, \tag{3.8}$$

where N is the number of samples included in each beat. Alternatively, SNR estimation in [88] used wavelet Wiener filtering [93] to estimate a noise-free

ECG, which was subtracted from the original ECG to estimate the noise. The SNR was computed similarly to (3.8), except that the output was calculated on a sample-by-sample basis.

The intervals between successive detected QRS complexes (i.e., RR intervals) have also been used for signal quality assessment [89, 90], based on that erroneous QRS detections in a poor quality ECG affect the RR interval series. A heart rate variability (HRV)-based approach presented in [90] is based on that in poor quality ECGs, the estimated HRV signal displays a different energy distribution for various frequency bands compared to one derived from good quality ECGs, whereas in [89] measures including the mean RR interval, the RR intervals boundaries, and the ratio of the maximum RR interval to the minimum were used. These measures were then complemented with a template matching measure using the average of all crosscorrelation coefficients between an ensemble beat average and each detected beat.

Recently, deep learning approaches have been proposed for ECG signal quality assessment, exemplified by the studies [94, 95], alleviating the need for feature extraction. A deep belief network was employed to identify and exclude episodes of poor quality prior to AF detection in [94]. In another study [95], a two-dimensional convolutional neural network was employed to classify 5 s ECG segments, transformed into two-dimensional input using the continuous wavelet transform, into either good or poor quality. They reported an accuracy of 93%, while, misclassifying about 5% of the segments annotated as AF as poor quality.

Signal quality assessment is usually implemented as a binary classification, where an ECG recording/segment is classified into either poor quality, which should be rejected, or good quality, meaning that a reliable analysis is possible. A handful of studies have introduced a more detailed signal quality classification, e.g., in up to five levels, from clean (or minor noise) to extreme noise [88,96,97]. However, this more detailed classification may become problematic as ECG data used for training often are annotated by the majority vote of several experts.

While the purpose of signal quality assessment approaches is to identify noisy ECG segments, a number of studies have taken a step further and investigated the impact of such identification on arrhythmia detection performance [85, 94, 98, 99]. Obviously, when using a reliable ECG signal quality assessment technique, the number of false arrhythmia detections is expected to decrease. On the other hand, its impact on sensitivity in arrhythmia detection is of great importance and needs to be considered. Tuning a signal quality classifier between sensitivity and positive predictive value depends on the application. In AF screening, where high sensitivity is needed, the classifier may be tuned to exclude fewer segments to not miss important arrhythmic episodes.

3.5 Prediction of AF

While the main motive of AF screening is the early identification of patients with AF, the usefulness of screening may be enhanced by identifying individuals with a higher risk of developing AF in the future. Prediction of AF is closely related to AF incident risk assessment, where the aim can be to reduce the number of individuals that need to be screened or to indicate whether an individual may need extended screening.

Several approaches have been considered for the prediction of AF, including blood biomarkers [100–102], clinical risk scores [103–106], and ECG-based features [107–117].

The biomarker N-terminal B-type natriuretic peptide (NT-proBNP) has been investigated in two studies, showing that patients with AF had elevated NT-proBNP levels [101, 102]. The NT-proBNP was used in the StrokeStop II study to reduce the number of individuals that needed to be included in the screening program [14]. Several blood biomarkers related to the pathophysiological mechanisms of AF were also investigated in [100], where TIMP-4, NT-proANP, and NT-proBNP were the most associated with the presence of AF. However, measuring blood biomarkers is an invasive and costly procedure.

The two clinical risk scores, $\mathrm{CHADS_2}$ and $\mathrm{CHA_2DS_2-VASC}$ were originally introduced to assess the risk of stroke in patients with AF. The two scores summarize the risk factors of congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, and gender into a single metric. Given that the components of these scores are known to be risk factors for AF, their usefulness for the prediction of new-onset AF has also been investigated [118,119]. The CHARGE-AF score, another clinical risk score, specifically developed to assess the risk of future AF [104], was used in [106] and showed a better performance compared to $\mathrm{CHA_2DS_2-VASC}$ for AF prediction.

Several previous studies have investigated AF prediction using ECG-based features and characteristics. It has been reported that excessive supraventricular ectopic activity is associated with a higher risk of future AF [107–112], where excessive supraventricular activity was defined as ≥ 30 supraventricular ectopic complexes (SVEC) per hour or the presence of runs of ≥ 20 SVEC.

With the increasing interest in AF screening using short ECGs, the prognostic implications of short-episode supraventricular arrhythmias have also gained attention [114, 115]. It has been shown that patients with short-episode supraventricular tachycardias, had a higher risk for future development of AF [115].

Detection of SVECs has been addressed in the literature, often in beat classification studies, where the aim is to classify a single heartbeat into normal, ventricular, or supraventricular. Such beat classifiers are often based on two-lead ECGs, using a variety of features extracted from the RR intervals series, as well as from morphological features of the ECG waves [120–124].

Identification of patients with paroxysmal AF from sinus rhythm using ECG-based features has also been investigated. Such identification is of importance due to the paroxysmal nature of AF where the often limited ECG recording duration may cause AF episodes to otherwise be missed. Two studies [113, 117] addressed the identification of patients with a history of AF, based on ECGs recorded during normal sinus rhythm using deep convolutional neural networks with promising results. The ECG recordings during normal sinus rhythm were limited to 31 days before the first ECG in AF in [113] and to the screening period in [117].

The application of deep learning to 12-lead ECG signals to develop a five-year AF incidence risk metric has been addressed in [116], showing that the deep learning-based metric was correlated with the CHARGE-AF score, but the predictive performance was further enhanced when using both predictors. Saliency mapping of the deep learning-based approach showed that P wave information heavily influenced the predictive performance.

Chapter 4

ECG Simulation and Data Augmentation

The availability of numerous publicly available annotated ECG databases has facilitated the development of methodologies for the analysis of various ECG characteristics, such as beat detection and delineation, arrhythmia detection and classification, and ST-segment analysis. In practice, however, most public databases often include a limited number of subjects, a few leads, and mainly good-quality recordings, and the prevalence of arrhythmia may not reflect the realistic situation that may be encountered on a population level. This questions the generalization of such methodologies to a more complicated scenario compared to the case for which they have been validated.

One situation where a simulation model is useful is in the detection of brief AF episodes. There are only a limited number of brief AF episodes in the MIT-BIH Atrial Fibrillation Database, and therefore, the performance of AF detectors for brief AF episodes can not be accurately assessed. Similarly, ECG simulation models are of great importance for the development and validation of methodologies for the analysis of ECG characteristics in more complex conditions, e.g., for performance assessment in different leads, for different burdens of ectopies and other arrhythmias, and for different levels and burdens of noise and artifacts.

In the context of AF screening where large databases exist, these are highly imbalanced such that the number of recordings with sinus rhythm highly outnumbers the number of recordings with AF and other arrhythmias. Therefore, ECG simulation models with the capability to generate recordings with similar characteristics as the ones found in screening databases would pave the way for the training of more advanced machine learning-based models, as well as for the development and performance assessment of novel methodologies for the detection of ECG characteristics in the presence of complicating factors.

Two types of signal modeling may be considered: Either an electrophysiological model is used with the purpose of explaining and exemplifying mechanisms of arrhythmia and how they can lead to different ECG patterns, or a statistical model is considered which mainly focuses on producing ECG characteristics resembling those of real ones. Electrophysiological models may start at the cellular level with ion channel activity, and end with the spread of depolarization waves throughout the atria and ventricles, and their projection onto, e.g., the body surface. Such models may account for anatomical aspects of the heart, e.g., the position of the heart, atrial and ventricular volumes, and of the torso, and typically have very high levels of complexity [125].

Electrophysiological models are of great importance for the interpretation of ECG abnormalities by linking structural or electrophysiological changes to ECG features, e.g., investigating the origin of atrial and ventricular ectopic beats, the substrate and activation pattern behind atrial flutter which can guide ablation procedures, or the relationship between ion channel activity and drug-induced changes [126]. Several examples of the use of such models are available in the literature investigating the effect of simulated myocardial infarctions on ST and QT segments [127], the influence of left ventricular mass on QRS amplitude [128], and the effect of ventricular activation on QRS complex morphology [129]. For electrophysiological models, the most important question is the degree of reliability of such models, which is limited by the level of understanding of the underlying disease, as well as by the levels of electrophysiological and anatomical details introduced in the model. Electrophysiological models typically include numerous parameters which need to be set correctly to produce realistic signals.

The other approach to ECG modeling is to rely on mathematical and statistical models describing various ECG components, without taking underlying electrophysiological mechanisms into account. In a simple form [130], a single-lead ECG signal may be simulated in normal sinus rhythm, while such simulation may be extended to generate multi-lead ECG, to account for time-varying ECG characteristics (e.g., PQ and ST segments), as well as to include a spectrum of different arrhythmias. The following sections of this chapter describe various aspects of statistical ECG models.

4.1 Modeling of cardiac activity

Generally, the main components of an ECG signal may be described by the ventricular morphology, the ventricular rhythm, and the atrial morphology. A switch mechanism may be added to enable transitioning between different rhythms and arrhythmias, where the different components may be replaced by suitable alternatives in order to generate realistic ECGs [131].

A multi-lead model for simulation of PQRST complexes was presented in [132], which is the extended version of the single-lead PQRST complex model presented in [130] based on a dipole model of the heart. Inspired by [130, 132], the PQRST model in [131], for each lead l, is defined by a summation of K Gaussian functions

$$q_l(t) = \sum_{k=1}^{K} \alpha_{l,k} \exp\left[-\frac{(t-\mu_{l,k})^2}{2\sigma_{l,k}^2}\right], \; l \in \{\mathrm{X}, \mathrm{Y}, \mathrm{Z}\}, \tag{4.1}$$

where $\alpha_{l,k}$, $\sigma_{l,k}$, and $\mu_{l,k}$ determine the amplitude, width, and location of each Gaussian component. The model is able to generate a wide variety of PQRST complex morphologies and has been the basis for the ECG simulator presented in [131], except for the P waves, where a linear combination of three Hermite functions with mono-, bi-, and triphasic morphologies was used.

The PQRST morphology model was complemented by a ventricular rhythm model [130], accounting for high-frequency respiratory sinus arrhythmia and low-frequency baroreflex regulation, using a bimodal power spectrum, which consists of two Gaussian distributions, defined by

$$S(F) = \frac{P_1}{\sqrt{2\pi\sigma_{V,1}^2}} \exp\left[-\frac{(F-F_1)^2}{2\sigma_{V,1}^2}\right] + \frac{P_2}{\sqrt{2\pi\sigma_{V,2}^2}} \exp\left[-\frac{(F-F_2)^2}{2\sigma_{V,2}^2}\right] \tag{4.2}$$

where P_1 and P_2 are the power of the low-frequency and high-frequency components, respectively, and F_1, F_2, $\sigma_{V,1}^2$, and $\sigma_{V,2}^2$ are the mean frequency and width of the Gaussian for each of the low- and high-frequency components, respectively. The resulting RR interval series can be obtained using the inverse Fourier transform of $S(F)$, and an appropriate scaling in order to generate an RR series with a desired heart rate.

Introducing arrhythmia to a statistical simulation model adds complexity to the resulting signals, making such models suitable when assessing the performance of arrhythmia detectors under specific conditions. Paroxysmal AF modeling was introduced in [131], using a two-state continuous-time Markov chain, enabling switching between AF and normal sinus rhythm, where the duration d in each state (i.e., episode duration) was determined by an exponential probability density function (PDF),

$$p(d) = \lambda e^{-\lambda d} H(d), \tag{4.3}$$

where λ is the rate parameter of the exponential PDF, (i.e., the rate of episodes), and $H(d)$ is the Heaviside step function. The median duration of AF episodes is defined by

$$\bar{d}_{AF} = \frac{\ln 2}{\lambda_{AF}}, \tag{4.4}$$

where λ_{AF} denotes the rate of AF episodes. The median duration of normal sinus rhythm episodes is assumed to be

$$\bar{d}_{SR} = \frac{B}{1-B}\bar{d}_{AF} \tag{4.5}$$

where B $(0 \leq B \leq 1)$ is the burden of AF, i.e., the ratio of the total amount of time when AF is present to the duration of the ECG recording. When switching to AF, the ventricular rhythm and P wave models are replaced by the corresponding components during AF, i.e., a ventricular rhythm model representing AF irregularity, and an f-wave model representing the atrial activity, respectively [133, 134].

4.2 Modeling of noise and artifacts

The presence of noise and artifacts impacts any analysis of ECG signals. Hence, modeling of noise and artifacts is of great importance, since it allows assessment of the impact of noise and artifacts when estimating and detecting various types of ECG characteristics, or when assessing the performance of ECG denoising strategies [28, 87, 94, 135, 136].

The MIT-BIH Noise Stress Test Database (NSTDB) [59, 137], including 3 half-hour two-lead recordings of noise typical in ambulatory ECG (baseline wander, motion artifacts, and electrode movements), has been widely used for the purposes stated above. Meanwhile, this database is restricted both in the number of leads and with regard to signal duration, which limits its application in, e.g., ECG denoising performance evaluation. Still, this database has served as the starting point for noise modeling.

Given that noise and artifacts in ECG recordings often display a non-stationary behavior, a time-varying auto-regressive (AR) model was proposed in [132], and fitted to the NSTDB to model the noise, $x(n)$, as

$$x(n) = a_{1,n}x(n-1) + \cdots + a_{p,n}x(n-p) + w(n), \tag{4.6}$$

where p is the model order, $a_{i,n}(i = 1, \ldots, p)$ are the time-varying coefficients of the AR model, and $w(n)$ is white noise. To facilitate simulation of noise in multi-lead ECGs, given that NSTDB only includes two leads, reconstruction of a third lead has been proposed as a means to be able to further extend the noise to 12 leads using the inverse Dower matrix [138]. Such an approach has been proposed, where in [139], principal component analysis (PCA) was applied to the two available leads, and the first principal component was used as the third lead, while in [131], the square root of the sum of squares of the first two leads served as the third lead.

The appearance of noise and artifacts depends on the recording conditions. Hence, modeling and simulation of noise and artifacts in different conditions are warranted, exemplified by the studies [140, 141] aiming at such simulation for wearable sensors. For ECGs recorded using textile sensors, modeling of noise and artifacts was based on filtering of heavy-tailed non-Gaussian white noise using AR models [140]. Simulation of motion artifacts was investigated in [141] where three different approaches, including AR modeling, Markov chain modeling, and a recurrent neural network (RNN) were used. When modeling using a Markov chain, the input data (collected motion artifact) was min-max normalized and quantized, where each of the quantized values served as a discrete element in the Markov chain model. When using the RNN, a target sequence for each training window was created by shifting the data by one step. It was shown that the RNN was the best-performing approach in terms of morphological features, frequency characteristics, and distribution of motion artifacts, while both the Markov chain and AR modeling approaches had limitations when it came to imitating the frequency characteristics and morphology of motion artifacts.

Chapter 5

Summary of included papers

The four parts of the present thesis are all in different ways related to AF screening and how to improve the efficiency in the associated analysis chain from ECG measurement to clinical decision making. The connection of each paper in this analysis chain is illustrated the Fig. 5.1.

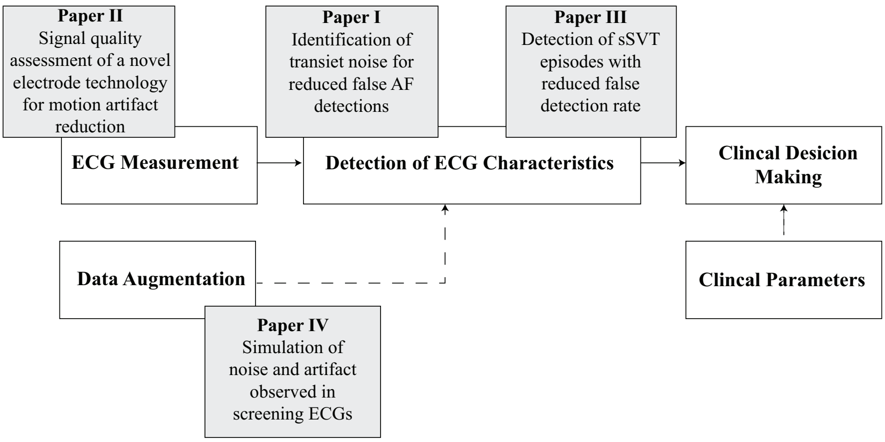

Figure 5.1: Connection of each of the four parts of the thesis to the AF screening analysis chain.

As described previously, the detection of ECG characteristics includes the detection of noise and disturbances, beats, AF, and other arrhythmias. Papers I and III deal with such detection and both use machine learning-based approaches. Paper II focuses on how better measurement quality leads to better detection performance, while paper IV proposes an improved ECG simulator with the capacity to produce realistic simulated ECG screening data for future studies.

Paper I: Identification of Transient Noise to Reduce False Detections in Screening for Atrial Fibrillation

Screening for AF using handheld ECG devices outside the clinical environment is gaining increasing attention. However, the very large size of screening databases in combination with the lower signal quality of signals recorded at home, typically caused by transient noise, becomes problematic and leads to large numbers of false AF detections. Since false AF detections require manual expert review to be ruled out, reduction of such false detections saves time and cost.

In this work, a CNN is proposed to identify transient noise in the sequence of beats before AF detection. The CNN classifies each detection produced by a QRS detector, into either a true or a false beat detection, and was trained using false beat detections compiled from poor-quality signals, and true beat detections compiled from good-quality signals. The performance of the CNN was evaluated using a subset of the AF screening database StrokeStop I, and resulted in sensitivity, specificity, and accuracy of 96.4%, 96.9%, and 96.9%, respectively. Despite being trained and validated on detections compiled from two different sets of signals, the classifier can be applied to any sequence of beat detections for separation into the two classes.

The RR interval series obtained after applying the CNN is fed to a low-complexity rhythm-based AF detector, which was optimized for 30 s ECG recordings. Another subset of StrokeStop I, which was labeled as ”irregular rhythm” using a commercial software, was selected for further performance evaluation and thus contains recordings that typically cause false AF detections and thereby require manual expert review.

By inserting the CNN before the AF detector, the number of false AF detections was reduced by 22.5% without any loss in sensitivity. Figure 5.2 shows two examples of ECGs contaminated with transient noise, which were excluded from manual review after inserting the CNN before the AF detector.

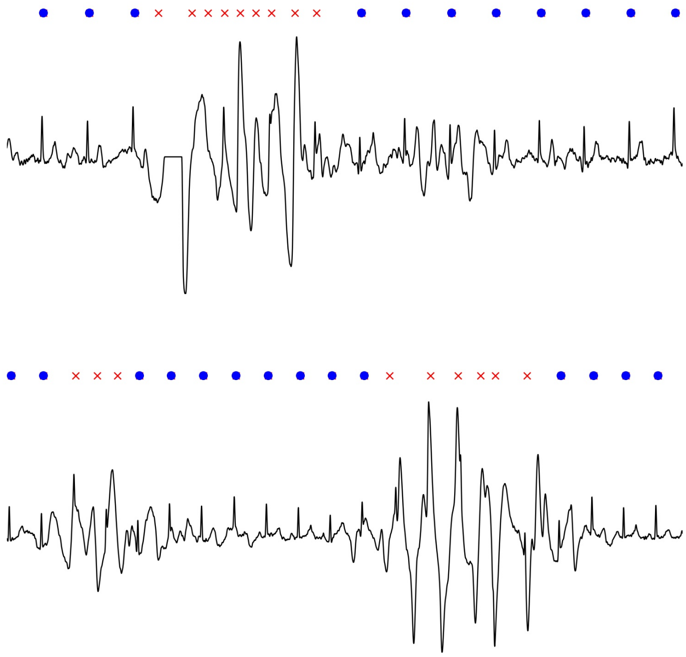

Figure 5.2: Two examples of ECGs contaminated with transient noise; without quality control, these two recordings are falsely detected as AF due to rhythm irregularities caused by transient noise. By identifying and excluding transients (red crosses) before AF detection, the two recordings are correctly detected as non-AF; true beat detections are indicated with blue dots.

Paper II: Signal Quality Assessment of a Novel ECG Electrode for Motion Artifact Reduction

The presence of noise and artifacts is a common problem when analyzing and interpreting ECGs, especially during ambulatory monitoring when the subjects are more active. The larger part of the signal that has an acceptable signal quality, the lower the risk that important arrhythmic episodes may be missed. Therefore, the development of novel electrode technologies robust to noise and artifacts has received a lot of attention in the research community.

This paper investigates a novel wet electrode technology (Piotrode) in terms of recorded signal quality when compared to a commercially available counterpart (Ambu). Two signal quality indices (ensemble standard deviation and time–frequency repeatability) were used for signal quality assessment. In addition, the resulting QRS and AF detection performance when the two types of electrodes are used, were investigated.

Electrocardiograms were collected from 20 healthy subjects during sitting at rest, sitting and crossing arms, walking, walking in stairs, running, and undressing and dressing. The two signal quality indices demonstrated similar trends: the signal quality improvement of the novel technology became increasingly larger as the subjects became increasingly more active, see Fig 5.3. Notably, during running, in 7 out of 20 ECGs recorded using the Ambu electrode, AF was falsely detected, with a false positive rate between 36% to 100%. On the other hand, no false AF detections were observed for ECGs recorded using the Piotrode electrode. The QRS detection performance using the Piotrode electrode was considerably better than that of the Ambu electrode, especially during running but also for lighter activities.

In conclusion, the novel wet ECG electrode produced signals with less motion artifacts, and therefore fewer false QRS and AF detections, thereby offering the potential to reduce the review burden and resulting cost, associated with ambulatory monitoring.

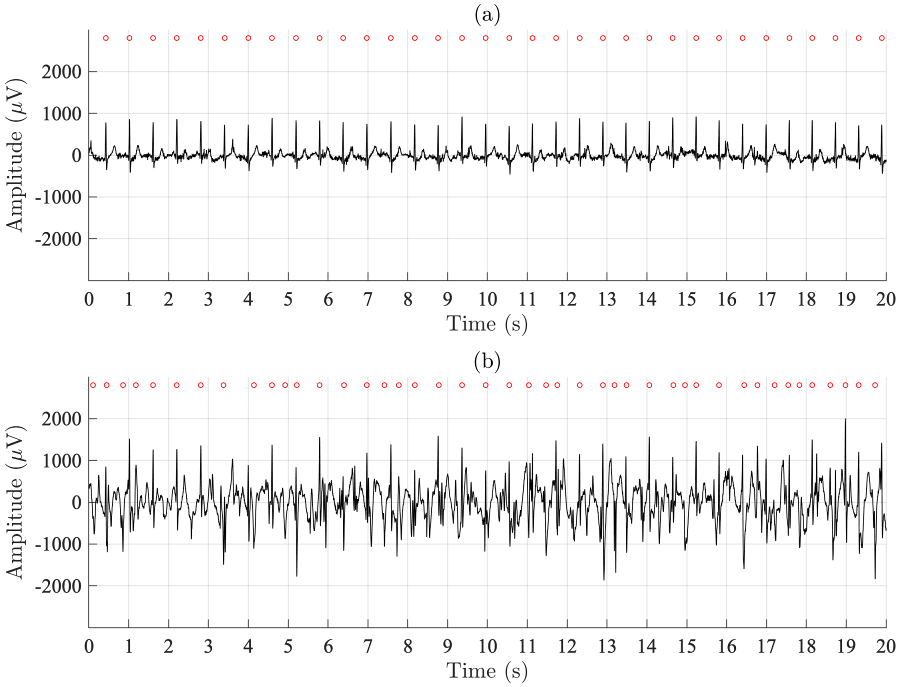

Figure 5.3: Examples of signal recorded simultaneously during running using (a) the Piotrode and (b) the Ambu electrodes. The red circles display the detected events by a QRS detector

Paper III: Detection of Short-Episode Supraventricular Tachycardias in Atrial Fibrillation Screening

This paper introduces a detector for short-episode supraventricular tachycardia (sSVT) in screening ECGs. The presence of sSVT has been shown to be associated with a higher risk of developing AF. Therefore, identification of individuals with such episodes may improve the usefulness of AF screening, where the identified cases may be subject to intensified screening to find the onset of AF.

Short-episode supraventricular tachycardias are defined as episodes of at least five consecutive supraventricular beats, with a heart rate of at least 100 beats per minute, and a duration shorter than 30 s. Detection of sSVT is challenged in ECGs recorded using a handheld device due to the lower signal quality, and the presence of ectopic beats which mimic rhythm characteristics of sSVT episodes, and lead to large amounts of false detections in screening databases.

The introduced sSVT detector assumes that supraventricular beats within an sSVT episode display similar morphology, meaning that a considerable deviation in morphology is either due to noise and artifacts, or to ectopic beats, and therefore such episodes need to be excluded. An SVM is trained using a simulated ECG database with recordings of varying signal-to-noise ratio, to classify a sequence of 5 beats into either a similar or a non-similar beat sequence. Examples of simulated signals with similar and non-similar beat sequences are displayed in Fig 5.4, where a template is selected from each sequence of 5 detections, and subtracted from the remaining detections within the sequence. Thus, the classification becomes independent of the patient's individual rhythm and beat morphology, and is rather focused on morphologic variation between the detected beats. The choice of 5 detections is motivated by the minimum number of supraventricular beats within an sSVT episode. Next, episodes with similar beats are subject to a set of rhythm criteria with regard to duration and heart rate.

The performance of the proposed detector is tested on the Swedish AF screening database StrokeStop II, which has been annotated with regard to the presence of sSVT episodes on a record basis, resulting in sensitivity, specificity, and positive predictive value of 84.6%, 99.4%, and 18.5%, respectively. In comparison to the performance of an sSVT detector in [115] the results show that a significant reduction in the expert review burden (by a factor of 6) can be achieved.

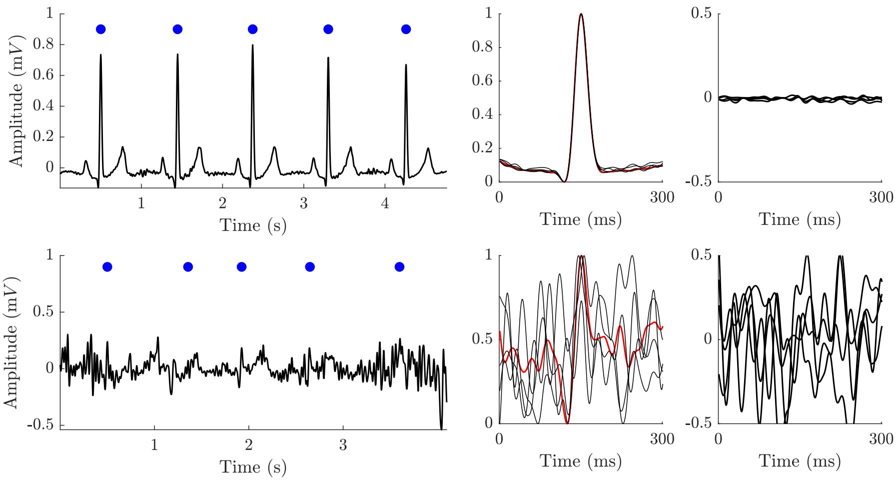

Figure 5.4: Example of a similar beat sequence (top) and non-similar beat sequence (bottom) episode. The left column shows an ECG episode and the detected events. The middle column shows the events and the template (in red), after min-max normalization. The template beat is taken as the beat yielding the lowest mean absolute value of the residuals when subtracted from each of the other four beats. The right column shows the residuals obtained by subtraction of the template from each event.

Paper IV: ECG Modeling for Simulation of Arrhythmias in Time-Varying Conditions

This paper introduces an ECG simulator capable of generating ECG signals intended for training and performance evaluation of novel ECG-related detection and classification algorithms. A major limitation today is the limited access to large annotated databases and to databases with varying levels of disturbances and rhythm complexity. The proposed simulator is able to produce ECG signals with varying beat morphologies, varying rhythm, multiple arrhythmic patterns, and several types of noise including noise typical in exercise stress tests, ambulatory recordings, and ECGs recorded using handheld devices.

The simulator is built around a discrete-time Markov chain model for the simulation of atrial and ventricular arrhythmias. Each state of the Markov chain is associated with statistical information on episode duration and heartbeat characteristics of the relevant rhythm. Modeling of muscle noise and motion artifacts increases the complexity of the simulated ECGs, making the simulator well suited for data augmentation in machine learning applications, as well as for performance evaluation of signal quality assessment and arrhythmia detection algorithms for signals contaminated with noise and artifacts. Here, the filtered white noise approach serves as the starting point but is altered in several aspects to account for prominent characteristics such as a time-varying level of muscle noise with a random occurrence pattern, and randomly changing QRS-like motion artifacts.

The realism of the simulated ECGs is assessed by three experienced doctors, where 79 out of 100 simulated ECGs were assessed as realistic, showing that simulated ECGs are difficult to distinguish from real ECGs (the corresponding number for the realistic signals was 84 out of 100). Examples of real and simulated ECGs are displayed in Fig 5.5. The usefulness of the simulator is illustrated in terms of AF detection performance where simulated and real ECGs, respectively, are used to train a CNN for signal quality control. The results show that both types of training lead to similar performance; using simulated ECGs, a slight decrease (0.5%) in the sensitivity resulted, while FPR increased by 3.9%.

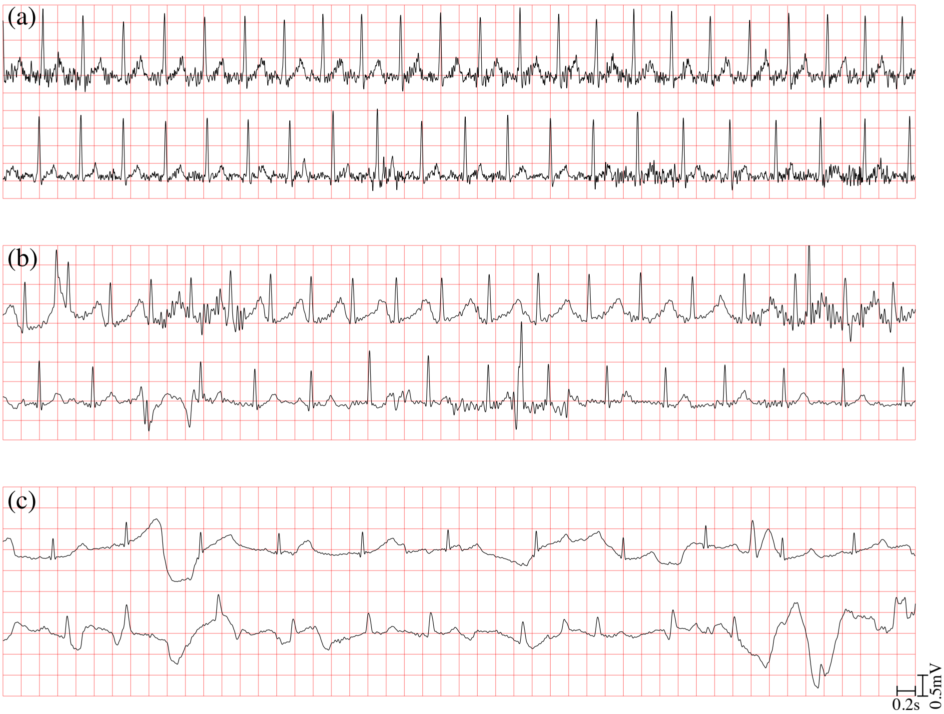

Figure 5.5: Single-lead, 10-s simulated ECGs (upper) and similar-looking real ECGs (lower) with (a) muscle noise, (b) motion artifacts, common in ambulatory monitoring and exercise stress testing, with muscle noise added, and (c) motion artifacts common in handheld AF screening.

References

[1] M. Zoni-Berisso, F. Lercari, T. Carazza, and S. Domenicucci, "Epidemiology of atrial fibrillation: European perspective," *Clin. Epidemiol.*, no. 6, pp. 213–20, 2014.

[2] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J. Bax, C. Blomström-Lundqvist, *et al.*, "2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC," *Eur. Heart. J.*, vol. 42, no. 5, pp. 373–498, 2021.

[3] M. P. Turakhia, J. Shafrin, K. Bognar, J. Trocio, Y. Abdulsattar, D. Wiederkehr, and D. P. Goldman, "Estimated prevalence of undiagnosed atrial fibrillation in the United States," *PLoS One*, vol. 13, pp. 1–11, 2018.

[4] J. Engdahl, L. Andersson, M. Mirskaya, and M. Rosenqvist, "Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention," *Circulation*, vol. 127, pp. 930–937, 2013.

[5] N. Lowres, L. Neubeck, G. Salkeld, *et al.*, "Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. the SEARCH-AF study," *Thromb. Haemost.*, vol. 111, no. 6, pp. 1167–1176, 2014.

[6] E. Svennberg, J. Engdahl, F. Al-Khalili, L. Friberg, V. Frykman, and M. Rosenqvist, "Mass screening for untreated atrial fibrillation the StrokeStop study," *Circulation*, vol. 131, no. 25, pp. 2176–2184, 2015.

[7] S. Uittenbogaart, N. V. van Gurp, P. Erkens, *et al.*, "Detecting and diagnosing atrial fibrillation (D2AF): study protocol for a cluster randomised

controlled trial," *Trials*, vol. 16, no. 1, p. 478, 2015.

[8] K. Haeusler, P. Kirchhof, P. Heuschmann, *et al.*, "Impact of standardized MONitoring for Detection of Atrial Fibrillation in Ischemic Stroke (MonDAFIS): Rationale and design of a prospective randomized multicenter study.," *Am. Heart J.*, vol. 172, pp. 19–25, 2016.

[9] J. Halcox, K. Wareham, A. Cardew, *et al.*, "Assessment of remote heart rhythm sampling using the alivecor heart monitor to screen for atrial fibrillation: The rehearse-af study," *Circulation*, vol. 136, no. 19, pp. 1784–1794, 2017.

[10] S. Diederichsen, K. Haugan, L. Køber, *et al.*, "Atrial fibrillation detected by continuous electrocardiographic monitoring using implantable loop recorder to prevent stroke in individuals at risk (the LOOP study): Rationale and design of a large randomized controlled trial," *Am. Heart J.*, vol. 187, pp. 122–132, 2017.

[11] S. Steinhubl, J. Waalen, A. Edwards, *et al.*, "Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: The mSToPS randomized clinical trial," *JAMA*, vol. 320, no. 2, pp. 146–155, 2018.

[12] E. L. Veale, A. J. Stewart, A. Mathie, S. K. Lall, M. Rees-Roberts, V. Savickas, S. K. Bhamra, and S. A. Corlett, "Pharmacists detecting atrial fibrillation (PDAF) in primary care during the influenza vaccination season: a multisite, cross-sectional screening protocol," *BMJ Open*, vol. 8, no. 3, 2018.

[13] J. Ashburner, S. Atlas, D. McManus, *et al.*, "Design and rationale of a pragmatic trial integrating routine screening for atrial fibrillation at primary care visits: The VITAL-AF trial," *Am. Heart. J.*, vol. 215, pp. 147–156, 2019.

[14] K. K. Gudmundsdottir, T. Fredriksson, E. Svennberg, F. Al-Khalili, L. Friberg, V. Frykman, Z. Hijazi, M. Rosenqvist, and J. Engdahl, "Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the StrokeStop II study.," *Europace*, vol. 22, no. 1, pp. 24–32, 2020.

[15] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, *et al.*, "2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS," *Eur. Heart. J.*, vol. 37, pp. 2893–2962, 2016.

[16] P. G. Platonov and V. D. A. Corino, "A clinical perspective on atrial fibrillation," in *Atrial Fibrillation from an Engineering Perspective* (L. Sörnmo,

ed.), Series in BioEngineering, pp. 1–24, Springer, 2018.

[17] B. Krijthe, A. Kunst, E. Benjamin, G. Lip, O. Franco, A. Hofman, J. Witteman, B. Stricker, and J. Heeringa, "Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060," *Eur. Heart J.*, vol. 34, no. 35, pp. 2746–51, 2013.

[18] A. Kishore, A. Vail, A. Majid, J. Dawson, K. Lees, P. Tyrrell, and C. Smith, "Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis," *Stroke*, vol. 45, no. 2, pp. 520–526, 2014.

[19] S. Lubitz, X. Yin, D. McManus, L. Weng, H. Aparicio, A. Walkey, J. R. Romero, C. Kase, P. Ellinor, P. Wolf, S. Seshadri, and E. Benjamin, "Stroke as the initial manifestation of atrial fibrillation: The Framingham Heart Study," *Stroke*, vol. 48, no. 2, pp. 490–492, 2017.

[20] J. M. G. Wilson and G. Jungner, "Principles and practice of screening for disease," 1968.

[21] E. Svennberg, L. Friberg, V. Frykman, F. Al-Khalili, J. Engdahl, and M. Rosenqvist, "Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial," *Lancet*, vol. 398, no. 10310, pp. 1498–1506, 2021.

[22] J. H. Svendsen, S. Z. Diederichsen, S. Højberg, D. W. Krieger, C. Graff, C. Kronborg, M. S. Olesen, J. B. Nielsen, A. G. Holst, A. Brandes, K. J. Haugan, and L. Køber, "Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP study): a randomised controlled trial," *Lancet*, vol. 398, pp. 1507–1516, 2021.

[23] K. Williams, R. N. Modi, A. Dymond, S. Hoare, A. Powell, J. Burt, *et al.*, "Cluster randomised controlled trial of screening for atrial fibrillation in people aged 70 years and over to reduce stroke: protocol for the pilot study for the SAFER trial.," *BMJ Open*, vol. 12, p. e065066, 2022.

[24] E. Ding, G. Marcus, and D. McManus, "Emerging technologies for identifying atrial fibrillation," *Circ. Res.*, vol. 127, no. 1, pp. 128–142, 2020.

[25] S. S. Lobodzinski, "ECG patch monitors for assessment of cardiac rhythm abnormalities," *Prog. Cardiovasc. Dis.*, vol. 56, no. 2, pp. 224–229, 2013.

[26] A. Bisignani, S. De Bonis, L. Mancuso, G. Ceravolo, and G. Bisignani, "Implantable loop recorder in clinical practice," *J. Arrhythm.*, vol. 35, no. 1, pp. 25–32, 2019.

[27] L. Sörnmo and P. Laguna, *Bioelectrical Signal Processing in Cardiac and Neurological Applications*. Amsterdam: Elsevier (Academic Press), 2005.

[28] R. Sameni, M. B. Shamsollahi, C. Jutten, and G. D. Clifford, "A nonlinear Bayesian filtering framework for ECG denoising," *IEEE Trans. Biomed. Eng.*, vol. 54, pp. 2172–2185, 2007.

[29] A. Kabir and C. Shahnaz, "Denoising of ECG signals based on noise reduction algorithms in EMD and wavelet domains," *Biomed. Signal Process. Control*, vol. 7, pp. 481–489, 2012.

[30] Y. M. Chi, T.-P. Jung, and G. Cauwenberghs, "Dry-contact and noncontact biopotential electrodes: Methodological review," *IEEE Rev. Biomed. Eng.*, vol. 3, pp. 106–119, 2010.

[31] J. Ottenbacher, M. Kirst, L. Jatobá, M. Huflejt, U. Großmann, and W. Stork, "Reliable motion artifact detection for ECG monitoring systems with dry electrodes," in *Int. Conf. IEEE Eng. Med. Biol. (EMBC)*, vol. 30, pp. 1695–1698, 2008.

[32] Y.-H. Chen, M. Op de Beeck, L. Vanderheyden, E. Carrette, V. Mihajlović, K. Vanstreels, B. Grundlehner, S. Gadeyne, P. Boon, and C. Van Hoof, "Soft, comfortable polymer dry electrodes for high quality ECG and EEG recording," *Sensors*, vol. 14, pp. 23758–23780, 2014.

[33] D. Pani, A. Dessi, J. Saenz-Cogollo, G. Barabino, B. Fraboni, and A. B. A., "Fully textile, PEDOT:PSS based electrodes for wearable ECG monitoring systems," *IEEE Trans. Biomed. Eng.*, vol. 63, no. 3, pp. 540–9, 2016.

[34] M. A. Yokus and J. S. Jur, "Fabric-based wearable dry electrodes for body surface biopotential recording," *IEEE Trans. Biomed. Eng.*, vol. 63, pp. 423–430, 2016.

[35] A. Pourahmad and A. Mahnam, "Evaluation of a low-cost and low-noise active dry electrode for long-term biopotential recording," *J. Med. Signals Sens.*, vol. 6, pp. 197–202, 2016.

[36] A. A. Chlaihawi, B. B. Narakathu, S. Emamian, B. J. Bazuin, and M. Z. Atashbar, "Development of printed and flexible dry ECG electrodes," *Sens. Bio-Sens. Res..*, vol. 20, pp. 9–15, 2018.

[37] T. Wang, H. Zhang, and S. F. Lin, "Influence of capacitive coupling on high-fidelity non-contact ECG measurement," *IEEE Sens. J.*, vol. 20, no. 16, pp. 9265–9273, 2020.

[38] Z. Saadatnia, S. G. Mosanenzadeh, M. M. Chin, H. E. Naguib, and M. R. Popovic, "Flexible, air dryable, and fiber modified aerogel-based wet electrode for electrophysiological monitoring," *IEEE Trans. Biomed. Eng.*, vol. 68, no. 6, pp. 1820–1827, 2021.

[39] S. Masihi, M. Panahi, D. Maddipatla, A. J. Hanson, S. Fenech, L. Bonek, N. Sapoznik, P. D. Fleming, B. J. Bazuin, and M. Z. Atashbar, "De-

velopment of a flexible wireless ECG monitoring device with dry fabric electrodes for wearable applications," *IEEE Sens. J.*, vol. 22, no. 12, pp. 11223–11232, 2022.

[40] E. Svennberg, M. Stridh, J. Engdahl, F. Al-Khalili, L. Friberg, V. Frykman, and M. Rosenqvist, "Safe automatic one-lead electrocardiogram analysis in screening for atrial fibrillation," *Europace*, vol. 19, no. 9, pp. 1449–1453, 2017.

[41] P. S. Doliwa, V. Frykman, and M. Rosenqvist, "Short-term ECG for out of hospital detection of silent atrial fibrillation episodes," *Scand. Cardiovasc. J.*, vol. 43, no. 3, pp. 163–168, 2009. PMID: 19096977.

[42] B. Vaes, S. Stalpaert, K. Tavernier, B. Thaels, D. Lapeire, W. Mullens, and J. Degryse, "The diagnostic accuracy of the MyDiagnostick to detect atrial fibrillation in primary care," *BMC Prim. Care*, vol. 15, no. 1, p. 113, 2014.

[43] R. Tieleman, Y. Plantinga, D. Rinkes, G. Bartels, J. Posma, R. Cator, C. Hofman, and R. Houben, "Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation," *Europace*, vol. 16, pp. 1291–1295, 2014.

[44] J. K. Lau, N. Lowres, L. Neubeck, D. B. Brieger, R. W. Sy, C. D. Galloway, D. E. Albert, and S. B. Freedman, "iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke," *Int. J. Cardiol.*, vol. 165, no. 1, pp. 193–194, 2013.

[45] T. Hendrikx, M. Rosenqvist, P. Wester, H. Sandström, and R. Hörnsten, "Intermittent short ECG recording is more effective than 24-hour holter ECG in detection of arrhythmias," *BMC Cardiovasc. Disord.*, vol. 14, no. 1, p. 41, 2014.

[46] B. F. Svennberg E, "Screening for atrial fibrillation: less is more?," *Eur. Heart J. Open*, vol. 1, no. 3, 2021.

[47] I. C. Van Gelder, J. S. Healey, H. J. G. M. Crijns, J. Wang, S. H. Hohnloser, M. R. Gold, A. Capucci, C.-P. Lau, C. A. Morillo, A. H. Hobbelt, M. Rienstra, and S. J. Connolly, "Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT," *Eur. Heart J.*, vol. 38, pp. 1339–1344, 2017.

[48] C. J. C. Bruges, "A tutorial on support vector machines for pattern recognition," *Data Min. Knowl. Discov.*, vol. 2, no. 2, pp. 121–167, 1998.

[49] C. M. Bishop, *Pattern recognition and machine learning*. New York: springer, 2006.

[50] J. Gu, Z. Wang, J. Kuen, L. Ma, A. Shahroudy, B. Shuai, T. Liu, X. Wang, G. Wang, J. Cai, and T. Chen, "Recent advances in convolutional neural networks," *Pattern Recognit.*, vol. 77, pp. 354–377, 2018.

[51] J. Pan and W. Tompkins, "A real-time qrs detection algorithm," *IEEE Trans. Biomed. Eng.*, vol. 32, no. 3, pp. 230–6, 1985.

[52] M. Nygårds and L. Sörnmo, "Delineation of the QRS complex using the envelope of the ECG," *Med. Biol. Eng. Comput*, vol. 21, pp. 538–547, 1983.

[53] D. S. Benitez, P. A. Gaydecki, A. Zaidi, and A. P. Fitzpatrick, "A new qrs detection algorithm based on the hilbert transform," in *Comput. Cardiol.*, vol. 27, pp. 379–382, 2000.

[54] Z.-E. Hadj Slimane and A. Naït-Ali, "QRS complex detection using empirical mode decomposition," *Digit. Signal Process.*, vol. 20, no. 4, pp. 1221–1228, 2010.

[55] B. Hossain, S. Bashar, A. Walkey, D. McManus, and K. Chon, "An accurate QRS complex and P wave detection in ecg signals using complete ensemble empirical mode decomposition approach," *IEEE Access*, vol. 7, pp. 128869–128880, 2019.

[56] J. P. Martínez, R. Almeida, S. Olmos, A. P. Rocha, and P. Laguna, "A wavelet-based ECG delineator: Evaluation on standard databases," *IEEE Trans. Biomed. Eng.*, vol. 51, pp. 570–581, 2004.

[57] S. Raj, K. C. Ray, and O. Shankar, "Development of robust, fast and efficient QRS complex detector: a methodological review," *Australas. Phys. Eng. Sci. Med.*, vol. 41, pp. 581–600, 2018.

[58] G. Moody and R. Mark, "The impact of the MIT-BIH Arrhythmia Database," *IEEE Eng. Med. Biol. Mag.*, vol. 20, no. 3, pp. 45–50, 2001.

[59] A. L. Goldberger, L. Amaral, L. Glass, J. Hausdorff, P. C. Ivanov, R. Mark, *et al.*, "Physiobank, physiotoolkit, and physionet: Components of a new research resource for complex physiologic signals," *Circulation*, vol. 101, no. 23, pp. 215–220, 2000.

[60] M. Zahid, S. Kiranyaz, T. Ince, O. Devecioglu, M. Chowdhury, A. Khandakar, A. Tahir, and M. Gabbouj, "Robust R-peak detection in low-quality Holter ecgs using 1d convolutional neural network," *IEEE Trans. Biomed. Eng.*, vol. 69, no. 1, pp. 119–128, 2022.

[61] E. D. Giovanni, T. Teijeiro, G. Millet, and D. Atienza, "Adaptive R-peak detection on wearable ECG sensors for high-intensity exercise," *IEEE Trans. Biomed. Eng.*, vol. 70, pp. 941–953, 2023.

[62] A. H. Tayal, M. Tian, K. M. Kelly, S. C. Jones, D. G. Wright, D. Singh, J. Jarouse, J. Brillman, S. Murali, and R. Gupta, "Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke," *Neurology*, vol. 71, pp. 1696–1701, 2008.

[63] A. A. Rabinstein, J. E. Fugate, J. Mandrekar, J. D. Burns, R. C. S. Seet, S. A. Dupont, T. J. Kauffman, S. J. Asirvatham, and P. A. Friedman, "Paroxysmal atrial fibrillation in cryptogenic stroke: a case-control study.," *J. Stroke Cerebrovasc. Dis.*, vol. 22, pp. 1405–1411, Nov 2013.

[64] L. Sörnmo, A. Petrėnas, and V. Marozas, "Detection of atrial fibrillation," in *Atrial Fibrillation from an Engineering Perspective* (L. Sörnmo, ed.), Series in BioEngineering, pp. 73–135, Springer, 2018.

[65] K. Tateno and L. Glass, "Automatic detection of atrial fibrillation using the coefficient of variation and density histograms of rr and deltarr intervals," *Med. Biol. Eng. Comput.*, vol. 39, no. 6, pp. 664–71, 2001.

[66] J. Lian, L. Wang, and D. Muessig, "A simple method to detect atrial fibrillation using RR intervals," *Am. J. Cardiol.*, vol. 107, no. 10, pp. 1494–1497, 2011.

[67] D. E. Lake and J. R. Moorman, "Accurate estimation of entropy in very short physiological time series: the problem of atrial fibrillation detection in implanted ventricular devices," *Amer. J. Physiol. Heart Circ. Physiol.*, vol. 300, no. 1, pp. H319–H325, 2011.

[68] X. Zhou, H. Ding, B. Ung, E. MacPherson, and Y. Zhang, "Automatic online detection of atrial fibrillation based on symbolic dynamics and shannon entropy," *BioMed. Eng. OnLine*, vol. 13, no. 18, 2014.

[69] S. Dash, K. H. Chon, S. Lu, and E. A. Raeder, "Automatic real time detection of atrial fibrillation," *Ann. Biomed. Eng.*, vol. 37, no. 9, pp. 1701–1709, 2009.

[70] C. Huang, S. Ye, H. Chen, D. Li, F. He, and Y. Tu, "A novel method for detection of the transition between atrial fibrillation and sinus rhythm," *IEEE Trans. Biomed. Eng.*, vol. 58, no. 4, pp. 1113–1119, 2011.

[71] J. Park, S. Lee, and M. Jeon, "Atrial fibrillation detection by heart rate variability in poincare plot," *Biomed. Eng. Online*, vol. 8, no. 38, 2009.

[72] A. Petrėnas, V. Marozas, and L. Sörnmo, "Low-complexity detection of atrial fibrillation in continuous long-term monitoring," *Comput. Biol. Med.*, vol. 65, pp. 184–191, 2015.

[73] S. Ladavich and B. Ghoraani, "Rate-independent detection of atrial fibrillation by statistical modeling of atrial activity," *Biomed. Signal Process. Control*, vol. 18, pp. 274–281, 2015.

[74] J. Ródenas, M. García, R. Alcaraz, and J. J. Rieta, "Wavelet entropy automatically detects episodes of atrial fibrillation from single-lead electrocardiograms," *Entropy*, vol. 17, pp. 6179–6199, 2015.

[75] G. Moody, "A new method for detecting atrial fibrillation using RR intervals," *Proc. Comput. Cardiol.*, vol. 10, pp. 227–230, 1983.

[76] Y. Xia, N. Wulan, K. Wang, and H. Zhang, "Detecting atrial fibrillation by deep convolutional neural networks," *Comput. Biol. Med.*, vol. 93, pp. 84–92, 2018.

[77] O. Faust, A. Shenfield, M. Kareem, T. R. San, H. Fujita, and U. R. Acharya, "Automated detection of atrial fibrillation using long short-term memory network with RR interval signals," *Comput. Biol. Med.*, vol. 102, pp. 327–335, 2018.

[78] H. Dang, M. Sun, G. Zhang, X. Qi, X. Zhou, and Q. Chang, "A novel deep arrhythmia-diagnosis network for atrial fibrillation classification using electrocardiogram signals," *IEEE Access*, vol. 7, pp. 75577–75590, 2019.

[79] R. S. Andersen, A. Peimankar, and S. Puthusserypady, "A deep learning approach for real-time detection of atrial fibrillation," *Expert Syst. Appl.*, vol. 115, pp. 465–473, 2019.

[80] S. Mousavi, F. Afghah, and U. R. Acharya, "HAN-ECG: An interpretable atrial fibrillation detection model using hierarchical attention networks," *Comput. Biol. Med.*, vol. 127, 2020.

[81] L. Sörnmo, A. Petrėnas, M. Henriksson, and V. Marozas, "Letter regarding the article "Detecting atrial fibrillation by deep convolutional neural networks" by Xia et al.," *Comput. Biol. Med.*, vol. 100, pp. 41–42, 2018.

[82] M. Butkuviene, A. Petrenas, A. Solosenko, A. Martin-Yebra, V. Marozas, and L. Sornmo, "Considerations on performance evaluation of atrial fibrillation detectors," *IEEE Trans. Biomed. Eng.*, vol. 68, pp. 3250–3260, 2021.

[83] Q. Li, R. G. Mark, and G. D. Clifford, "Robust heart rate estimation from multiple asynchronous noisy sources using signal quality indices and a kalman filter," *Physiol. Meas.*, vol. 29, pp. 15–32, 2008.

[84] G. D. Clifford, J. Behar, Q. Li, and I. Rezek, "Signal quality indices and data fusion for determining clinical acceptability of electrocardiograms," *Physiol. Meas.*, vol. 33, no. 9, pp. 1419–1433, 2012.

[85] J. Behar, J. Oster, Q. Li, and G. D. Clifford, "ECG signal quality during arrhythmia and its application to false alarm reduction," *IEEE Trans. Biomed. Eng.*, vol. 60, no. 6, pp. 1660–1666, 2013.

[86] D. Hayn, B. Jammerbund, and G. Schreier, "QRS detection based ECG quality assessment," *Physiol. Meas.*, vol. 33, pp. 1449–1461, 2012.

[87] M. Abdelazez, P. X. Quesnel, A. D. C. Chan, and H. Yang, "Signal quality analysis of ambulatory electrocardiograms to gate false myocardial ischemia alarms," *IEEE Trans. Biomed. Eng.*, vol. 64, no. 6, pp. 1318–1325, 2017.

[88] L. Smital, C. R. Haider, M. Vitek, P. Leinveber, P. Jurak, A. Nemcova, R. Smisek, L. Marsanova, I. Provaznik, C. L. Felton, B. K. Gilbert, and D. R. Holmes III, "Real-time quality assessment of long-term ECG signals recorded by wearables in free-living conditions," *IEEE Trans. Biomed. Eng.*, vol. 67, pp. 2721–2734, 2020.

[89] C. Orphanidou, T. Bonnici, P. Charlton, D. Clifton, D. Vallance, and L. Tarassenko, "Signal-quality indices for the electrocardiogram and photoplethysmogram: Derivation and applications to wireless monitoring," *IEEE J. Biomed. Health Inf.*, vol. 19, no. 3, pp. 832–838, 2015.

[90] C. Orphanidou and I. Drobnjak, "Quality assessment of ambulatory ECG using wavelet entropy of the HRV signal," *IEEE J. Biomed. Health Inf.*, vol. 21, no. 5, pp. 1216–1223, 2017.

[91] N. Yaghmaie, M. Maddah-Ali, H. Jelinek, and F. Marzbanrad, "Dynamic signal quality index for electrocardiograms," *Physiol. Meas.*, vol. 39, no. 10, 2018.

[92] J. Moeyersons, E. Smets, J. Morales, A. Villa, W. De Raedt, D. Testelmans, *et al.*, "Artefact detection and quality assessment of ambulatory ECG signals," *Comput. Methods Programs Biomed.*, vol. 182, 2019.

[93] L. Smital, M. Vítek, J. Kozumplík, and I. Provazník, "Adaptive wavelet wiener filtering of ECG signals," *IEEE Trans. Biomed. Eng.*, vol. 60, no. 2, pp. 437–445, 2013.

[94] B. Taji, A. D. C. Chan, and S. Shirmohammadi, "False alarm reduction in atrial fibrillation detection using deep belief networks," *IEEE Trans. Instrument. Meas.*, vol. 67, no. 5, pp. 1124–1131, 2018.

[95] Á. Huerta-Herraiz, A. Martínez-Rodrigo, V. Bertomeu-González, A. Quesada, J. J. Rieta, and R. Alcaraz, "A deep learning approach for featureless robust quality assessment of intermittent atrial fibrillation recordings from portable and wearable devices," *Entropy*, vol. 22, no. 7, 2020.

[96] Q. Li, C. Rajagopalan, and G. D. Clifford, "A machine learning approach to multi-level ECG signal quality classification," *Comput. Meth. Progr. Biomed.*, vol. 227, pp. 435–447, 2014.

[97] R. Holgado-Cuadrado, C. Plaza-Seco, L. Lovisolo, and M. Blanco-Velasco, "Characterization of noise in long-term ECG monitoring with machine learning based on clinical criteria," *Med. Biol. Eng. Comput.*, 2023.

[98] J. Oster and G. D. Clifford, "Impact of the presence of noise on RR interval-based atrial fibrillation detection," *J. Electrocardiol.*, vol. 48, no. 6, pp. 947–951, 2015.

[99] S. K. Bashar, E. Ding, A. J. Walkey, D. D. McManus, and K. H. Chon, "Noise detection in electrocardiogram signals for intensive care unit patients," *IEEE Access*, vol. 7, pp. 88357–88368, 2019.

[100] P. Wakula, B. Neumann, J. Kienemund, E. Thon-Gutschi, T. Stojakovic, M. Manninger, D. Scherr, H. Scharnagl, M. Kapl, B. Pieske, and F. R. Heinzel, "CHA2DS2-VASc score and blood biomarkers to identify patients with atrial high-rate episodes and paroxysmal atrial fibrillation," *Europace*, vol. 19, pp. 544–551, 05 2016.

[101] E. Svennberg, P. Henriksson, J. Engdahl, Z. Hijazi, F. Al-Khalili, L. Friberg, and V. Frykman, "N-terminal pro b-type natriuretic peptide in systematic screening for atrial fibrillation.," *Heart*, vol. 103, pp. 1271–1277, Aug 2017.

[102] F. Ghazal, H. Theobald, M. Rosenqvist, and F. Al-Khalili, "Assessment of N-terminal pro-B-type natriuretic peptide level in screening for atrial fibrillation in primary health care.," *PLoS One*, vol. 14, no. 2, p. e0212974, 2019.

[103] R. B. Schnabel, L. M. Sullivan, D. Levy, M. J. Pencina, J. M. Massaro, R. B. D'Agostino, *et al.*, "Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study," *Lancet*, vol. 373, no. 9665, pp. 739–745, 2009.

[104] A. Alonso, B. P. Krijthe, T. Aspelund, K. A. Stepas, M. J. Pencina, C. B. Moser, *et al.*, "Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium.," *J. Am. Heart Assoc.*, vol. 2, p. e000102, Mar 2013.

[105] B. M. Everett, N. R. Cook, D. Conen, D. I. Chasman, P. M. Ridker, and C. M. Albert, "Novel genetic markers improve measures of atrial fibrillation risk prediction.," *Eur. Heart. J.*, vol. 34, pp. 2243–2251, Aug 2013.

[106] I. E. Christophersen, X. Yin, M. G. Larson, S. A. Lubitz, J. W. Magnani, D. D. McManus, P. T. Ellinor, and E. J. Benjamin, "A comparison of the CHARGE-AF and the CHA2DS2-VASc risk scores for prediction of

atrial fibrillation in the Framingham Heart Study," *Am. Heart. J.*, vol. 178, pp. 45–54, 2016.

[107] Z. Binici, T. Intzilakis, O. W. Nielsen, L. Køber, and A. Sajadieh, "Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke," *Circulation*, vol. 121, pp. 1904–1911, 2010.

[108] S. Kochhäuser, D. G. Dechering, R. Dittrich, F. Reinke, M. A. Ritter, S. Ramtin, T. Duning, G. Frommeyer, and L. Eckardt, "Supraventricular premature beats and short atrial runs predict atrial fibrillation in continuously monitored patients with cryptogenic stroke," *Stroke*, vol. 45, pp. 884–886, 2014.

[109] N. Murakoshi, D. Xu, T. Sairenchi, M. Igarashi, F. Irie, T. Tomizawa, H. Tada, Y. Sekiguchi, K. Yamagishi, H. Iso, I. Yamaguchi, H. Ota, and K. Aonuma, "Prognostic impact of supraventricular premature complexes in community-based health checkups: the ibaraki prefectural health study.," *Eur. Heart J.*, vol. 36, pp. 170–178, Jan 2015.

[110] B. S. Larsen, P. Kumarathurai, J. Falkenberg, O. W. Nielsen, and A. Sajadieh, "Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation.," *J. Am. Coll. Cardiol.*, vol. 66, pp. 232–241, 2015.

[111] T. Acharya, S. Tringali, M. Bhullar, M. Nalbandyan, V. K. Ilineni, E. Carbajal, and P. Deedwania, "Frequent atrial premature complexes and their association with risk of atrial fibrillation," *Am. J. Cardiol.*, vol. 116, pp. 1852–1857, 2015.

[112] L. S. B. Johnson, A. P. Persson, P. Wollmer, S. Juul-Möller, T. Juhlin, and G. Engström, "Irregularity and lack of p waves in short tachycardia episodes predict atrial fibrillation and ischemic stroke," *Heart Rhythm*, vol. 15, pp. 805–811, 2018.

[113] Z. I. Attia, P. A. Noseworthy, F. Lopez-Jimenez, S. J. Asirvatham, A. J. Deshmukh, B. J. Gersh, R. E. Carter, X. Yao, A. A. Rabinstein, B. J. Erickson, S. Kapa, and P. A. Friedman, "An artificial intelligence-enabled ecg algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction," *Lancet*, vol. 394, no. 10201, pp. 861–867, 2019.

[114] T. Fredriksson, *Implications of Brief Episodes of Atrial Fibrillation (MicroAF)*. PhD thesis, Karolinska institutet, 2020.

[115] T. Hygrell, M. Stridh, L. Friberg, and E. Svennberg, "Prognostic implications of supraventricular arrhythmias.," *Am. J. Cardiol.*, vol. 151, pp. 57–63, 2021.

[116] S. Khurshid, S. Friedman, C. Reeder, P. Di Achille, N. Diamant, P. Singh, L. X. Harrington, X. Wang, M. A. Al-Alusi, G. Sarma, A. S. Foulkes, P. T. Ellinor, C. D. Anderson, J. E. Ho, A. A. Philippakis, P. Batra, and S. A. Lubitz, "ECG-based deep learning and clinical risk factors to predict atrial fibrillation," *Circulation*, vol. 145, pp. 122–133, 2022.

[117] T. Hygrell, F. Viberg, E. Dahlberg, P. H. Charlton, K. K. Gudmundsdottir, J. Mant, J. Lindman, Hörnlund, and E. Svennberg, "An artificial intelligence–based model for prediction of atrial fibrillation from single-lead sinus rhythm electrocardiograms facilitating screening," *Europace*, vol. 25, no. 4, pp. 1332–1338, 2023.

[118] M.-L. Zuo, S. Liu, K.-H. Chan, K.-K. Lau, B.-H. Chong, K.-F. Lam, Y.-H. Chan, Y.-F. Lau, G. Y. H. Lip, C.-P. Lau, H.-F. Tse, and C.-W. Siu, "The CHADS2 and CHA2DS2–VASc scores predict new occurrence of atrial fibrillation and ischemic stroke," *J. Interv. Card. Electrophysiol.*, vol. 37, no. 1, pp. 47–54, 2013.

[119] T.-F. Chao, C.-J. Liu, S.-J. Chen, K.-L. Wang, Y.-J. Lin, S.-L. Chang, L.-W. Lo, Y.-F. Hu, T.-C. Tuan, T.-J. Wu, T.-J. Chen, and S.-A. Chen, "CHADS2 score and risk of new-onset atrial fibrillation: a nationwide cohort study in Taiwan," *Int. J. Cardiol.*, vol. 168, pp. 1360–1363, 2013.

[120] P. de Chazal, M. O'Dwyer, and R. Reilly, "Automatic classification of heartbeats using ECG morphology and heartbeat interval features," *IEEE Trans. Biomed. Eng.*, vol. 51, no. 7, pp. 1196–1206, 2004.

[121] T. Mar, S. Zaunseder, J. P. Martínez, M. Llamedo, and R. Poll, "Optimization of ECG classification by means of feature selection," *IEEE. Trans. Biomed. Eng.*, vol. 58, no. 8, pp. 2168–2177, 2011.

[122] M. Llamedo and J. P. Martinez, "An automatic patient-adapted ECG heartbeat classifier allowing expert assistance," *IEEE Trans. Biomed. Eng.*, vol. 59, no. 8, 2012.

[123] E. Luz, W. Schwartz, G. Cámara-Chávez, and D. Menotti, "ECG-based heartbeat classification for arrhythmia detection: A survey," *Comput. Methods Programs Biomed.*, vol. 127, pp. 144–164, 2016.

[124] G. García-Isla, L. Mainardi, and V. D. A. Corino, "A detector for premature atrial and ventricular complexes," *Front. Physiol.*, vol. 16, no. 12, p. 678558, 2021.

[125] O. Dössel, G. Luongo, C. Nagel, and A. Loewe, "Computer modeling of the heart for ECG interpretation—a review," *Hearts*, vol. 2, no. 3, pp. 350–368, 2021.

[126] A. Lyon, A. Mincholé, J. P. Martínez, P. Laguna, and B. Rodriguez, "Computational techniques for ECG analysis and interpretation in light of their contribution to medical advances," *J. R. Soc. Interface*, vol. 15, 2018.

[127] S. Sovilj, R. Magjarević, N. H. Lovell, and S. Dokos, "A simplified 3D model of whole heart electrical activity and 12-lead ECG generation," *Comput. Math. Methods Med.*, vol. 2013, p. 134208, 2013.

[128] L. Bacharova, V. Szathmary, M. Potse, and A. Mateasik, "Computer simulation of ECG manifestations of left ventricular electrical remodeling," *J. Electrocardiol.*, vol. 45, pp. 630–634, 2012.

[129] L. Bacharova, V. Szathmary, J. Svehlikova, A. Mateasik, and M. Tysler, "QRS complex waveform indicators of ventricular activation slowing: Simulation studies," *J. Electrocardiol.*, vol. 49, no. 6, pp. 790–793, 2016.

[130] P. E. McSharry, G. D. Clifford, L. Tarassenko, and L. A. Smith, "A dynamical model for generating synthetic electrocardiogram signals," *IEEE Trans. Biomed. Eng.*, vol. 50, pp. 289–294, 2003.

[131] A. Petrenas, V. Marozas, A. Sološenko, R. Kubilius, J. Skibarkiene, J. Oster, and L. Sörnmo, "Electrocardiogram modeling during paroxysmal atrial fibrillation: application to the detection of brief episodes," *Physiol. Meas.*, vol. 38, p. 2058, 2017.

[132] R. Sameni, G. D. Clifford, C. Jutten, and M. B. Shamsollahi, "Multichannel ECG and noise modeling: Application to maternal and fetal ECG signals," *EURASIP J. Adv. Signal. Process.*, vol. 2007, no. 1, p. 043407, 2007.

[133] V. D. A. Corino, F. Sandberg, L. T. Mainardi, and L. Sörnmo, "An atrioventricular node model for analysis of the ventricular response during atrial fibrillation," *IEEE Trans. Biomed. Eng.*, vol. 58, pp. 3386–3395, 2011.

[134] M. Stridh and L. Sörnmo, "Spatiotemporal QRST cancellation techniques for analysis of atrial fibrillation," *IEEE Trans. Biomed. Eng.*, vol. 48, pp. 105–111, 2001.

[135] M. Blanco-Velasco, B. Weng, and K. E. Barner, "ECG signal denoising and baseline wander correction based on the empirical mode decomposition," *Comput. Biol. Med.*, vol. 38, no. 1, pp. 1–13, 2008.

[136] M.-B. Hossain, S. K. Bashar, J. Lazaro, N. Reljin, Y. Noh, and K. H. Chon, "A robust ECG denoising technique using variable frequency complex demodulation," *Comput. Methods Programs Biomed.*, vol. 200, p. 105856, 2021.

[137] G. B. Moody, W. Muldrow, and R. G. Mark, "A noise stress test for arrhythmia detectors," in *Comput. Cardiol.*, vol. 11, pp. 381–384, 1984.

[138] G. E. Dower, H. B. Machado, and J. Osborne, "On deriving the electrocardiogram from vectorcardiographic leads," *Clin. Cardiol.*, vol. 3, no. 2, pp. 87–95, 1980.

[139] J. Behar, F. Andreotti, S. Zaunseder, Q. Li, J. Oster, and G. D. Clifford, "An ECG simulator for generating maternal-foetal activity mixtures on abdominal ECG recordings," *Physiol. Meas.*, vol. 35, no. 8, pp. 1537–1550, 2014.

[140] Y. Tian, M. Kabir, M. Abdizadeh, B. Poursartip, A. Mahnam, P. Bhattachan, L. Eskandarian, M. Alizadeh-Meghrazi, I. Mellal, M. Popovic, and M. Lankarany, "Modeling and reproducing textile sensor noise: Implications for textile-compatible signal processing algorithms," *IEEE J. Biomed. Health Inform.*, vol. 26, pp. 243–253, 2022.

[141] E. Farago and A. D. Chan, "Motion artifact synthesis for research in biomedical signal quality analysis," *Biomed. Signal Process. Control*, vol. 68, p. 102611, 2021.