KAUNAS UNIVERSITY OF TECHNOLOGY

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**CARDIAC ARRHYTHMIA DETECTION IN PHOTOPLETHYSMOGRAM SIGNALS**

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Doctoral dissertation

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 Contents

## List of terms and abbreviations

Ac Accuracy

AC Alternating current

AF Atrial fibrillation

ANN Artificial neural network

AV Atrioventricular node

DC Direct current

ECG Electrocardiogram

LED Light emitting diode

Mcc Matthews correlation coefficient

NLMS Normalized least mean square algorithm

P Precision

PB Premature beats

PD Photodetector

PP Peak-to-peak interval

PPG Photoplethysmogram

PR Power ratio

PVC Premature ventricular contraction

QRS Wave corresponding to ventricular depolarization

ROC Receiver operating characteristic

RR Interval between two successive ventricular contractions

RMSE Root mean square error

Se Sensitivity

Sp Specificity

SA Sinoatrial node

SNR Signal-to-noise ratio

SR Sinus rhythm

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**Chapter**

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**Chapter 3**

# Introduction

## Relevance of the research

Premature ventricular contractions (PVCs) and atrial fibrillation (AF) are the most commonly encountered cardiac disorder in humans, affecting up to 4% and 2% of the general population, respectively Kostis1981, January2014.

PVCs are initiated by the secondary pacemakers – the ectopic foci, located in the ventricles, therefore causing them to contract prematurely. It is well known that PVCs may occur even in healthy hearts with no significant impact on overall well-being. Accordingly, early studies have suggested that PVCs could be considered as benign in the absence of structural heart disease Kennedy1985. However, more recent studies have denied the benignity of PVCs, linking them to various health abnormalities. For example, increased frequency of PVCs has been associated with heart failure and sudden death if a heart disease was suspected Ng2006, Ephrem2013, Ataklte2013. PVCs have also been found to be a trigger of other serious heart arrhythmias such as a ventricular fibrillation Santoro2014, and atrial fibrillation Watanabe2006, Agarwal2010.

Several studies have shown, e.g., Hirose2010, that PVCs have a potential to be used as a predictor of sudden cardiac death in men even without recognized heart disease. This particularly applies if frequent PVCs occur during physical exercise Jouven2000, Ng2006, and especially during the phase of recovery Frolkis2003, Ng2006. Since PVCs usually cause inefficiency in blood circulation, notably in cases of multiple frequent PVCs, i.e., bigeminy (every 2 beat is premature) and trigeminy (every 3 beat is premature), such condition may lead to a dizziness or a temporal loss of consciousness Zaret1992, Reed2006, Garcia-Touchard2007. In addition, PVCs are common in patients with chronic kidney disease Shamseddin2011, being a consequence of electrolyte shifts (e.g., low blood potassium and calcium), resulting in electrolyte imbalance during procedures such as hemodialysis.

AF has emerged as a world-wide cardiovascular epidemic, affecting nearly 3% of adults aged 20 years Haim2015. Considerably greater AF prevalence is found in older individuals and patients with serious health conditions such as hypertension, heart failure and coronary artery disease. Due to fast ageing of society, the prevalence is expected to increase up to 3-fold in the upcoming decades Colilla2013. AF is often asymptomatic, and cover from 55% to 80% of all AF cases Healey2012, Lowres2013, Lip2014, thus timely diagnosis of subclinical (silent) AF is crucial in order to prevent from severe outcomes such as stroke Kishore2014 and death Benjamin1998.

In most cases, PVCs and AF have a distinctive morphology, thus are relatively easy detectable in electrocardiogram (ECG). Hence, PVC and AF characterising properties, such as frequency and morphology, are usually evaluated using conventional Holter monitors. Although various technologies have been developed for arrhythmia detection, for many years, only ECG-based Holter monitors and event recorders are routinely used in clinical practice to detect PVCs and AF in high-risk patients. Since AF is often asymptomatic Lowres2013, Lip2014, patient-friendly screening technologies are highly desirable so that AF can be captured at an early stage. Advancements in medical technology have allowed to consider other strategies. For example, it has been shown that daily intermittent screening using handheld ECG recorders results in considerably higher arrhythmia detection rates compared to the standard 24 hour Holter monitoring Lowres2016, Kirchhof2017. Nevertheless such emerging hand-held ECG recorders are particularly easy to use, a 10-s ECG is not enough to detect paroxysmal AF. Moreover, the electrodes used to record ECG are attached to the patient’s chest, resulting in discomfort, limited freedom of movement, and increased feeling of unhealthiness, especially after wearing the device for several days Rosero2013. Therefore, it is essential to develop unobtrusive screening technologies capable of monitoring longer periods of time, i.e., days and weeks, resulting in a larger number of identified AF cases Charitos2012.

Currently, implantable devices are the only available technologies providing a convenient way for continuous AF monitoring. However, implantable devices are invasive and costly, therefore not suitable for mass AF screening. Recently, photoplethysmography has been considered as an alternative approach to detect AF Lee2013, McManus2016, Chan2016, Freedman2016. Smartphone camera-based application allows to acquire photoplehysmogram (PPG) waveform which reflects blood volume changes in a finger, thus pulse sequence can be used for finding AF caused irregular pulse. While smartphone camera-based AF detector offers a fast way to check for AF, such approach is inherently not suitable for continuous monitoring.

With an increasing number of commercially available wristwatch or bracelet-type devices capable of acquiring PPG, and thus pulse rate, opens the opportunity to screen for PVCs and AF for an unlimited period of time in cost effective an unobtrusive way. Although no guidelines exist on clinical interpretation of PPG signal, and an ECG should inevitably be recorded to confirm PVC and AF diagnosis, such PPG-based screening has potential to be valuable to select individuals from larger population for prolonged ECG monitoring.

## Scientific-technological problem

This doctoral thesis covers a scientific-technological problem of clinical relevance weather the most common cardiac arrhythmias, such as the premature ventricular contractions and atrial fibrillation, could be reliably detected by using solely the photoplethysmogram signals? To address the problem of unobtrusive and reliable arrhythmia monitoring and detection, the selection of alternative signals, features and noise-related issues, such as the problem of frequent false alarms, has to be solved.

## Working hypothesis

The hypothesis is formulated that both the premature ventricular contractions and atrial fibrillation could be reliably detected by analysing features, extracted from the alternative signals to electrocardiogram, e.g., photoplethysmogram signals, with an addition of automatic signal quality verification. The hypothesis is verified by the comparison of the obtained results with those provided in the scientific literature, using both clinical and simulated datasets.

## Research object

The research is based on the development and investigation of the algorithms for automatic detection of premature ventricular contractions and atrial fibrillation in photoplethysmogram signals.

## The aim of the research

The aim of this doctoral thesis is to develop and investigate photoplethysmogram signal modeling and processing methods for noninvasive long-term monitoring of cardiac arrhythmia.

## The objectives of the research

1. To critically analyse the available literature in the fields of heart arrhythmia and monitoring methods, on the genesis of photoplethysmogram signals and on the availability of biomedical signal databases recorded during arrhythmias.

2. To develop and investigate a photoplethysmogram model capable of simulating various arrhythmias including premature ventricular contractions and atrial fibrillation.

3. To develop and investigate a photoplethysmogram-based method for the detection of premature ventricular contractions.

4. To develop and investigate a photoplethysmogram-based method for the detection of atrial fibrillation.

## Scientific novelty

In this doctoral thesis, a phenomenological photoplethysmogram model, capable of simulating PPG signals during various cardiac events, starting from a normal sinus rhythm and ending with premature contractions and atrial fibrillation is proposed. PPG signals are generated by applying only RR interval series as an input to the model, obtained either from ECG signals or using RR interval simulators. The model also makes use of different PPG pulse types to account for age and vascular condition. The described qualities make this model one of a kind and, therefore, suitable for the development and the assessment of PPG-based arrhythmia detection algorithms.

High performance, real-time capable algorithms, one for PVC and the other for AF detection have been developed. Both algorithms rely on the features extracted solely from the PPG signals. Temporal, amplitude and frequency domain features are employed in order to distinguish arrhythmia of interest from other types of arrhythmias and noises. The algorithms have been developed for the application in wearable systems in mind. Currently there are no reliable solutions for a long-term PPG-based arrhythmia detection described in the scientific literature. Therefore, ambulatory application of the proposed algorithms would enable an unobtrusive, cost-effective and reliable solution for a long-term screening of PVCs and AF.

The PVC detection algorithm rely on three subsequent intervals describing a single beat, frequency domain features, and artifact detection. The classification of heart beats into premature and normal is accomplished by the artificial neural network. The extracted features are normalized according to the heart rate of a normal sinus rhythm, determined by employing a frequency domain-based estimator. Artifact-corrupted PPG segments are detected by the artifact detector and skipped before beat classification, thus reducing false alarms in a low signal to noise ratio environment.

The AF detection algorithm combines the analysis of the time intervals between successive heartbeats and PPG signal quality assessment. AF detection rely on the improved, modified and PPG-optimized low-complexity algorithm Petrenas2015. Approaches for minimizing the influence of other arrhythmia on the specificity of the algorithm, i.e., ectopic beats, bigeminy and sinus arrhythmia, were employed. The signal quality assessment is performed by comparing the extracted PPG pulses with a predefined template, which adapts to the morphology of a specific PPG signal. The output of the detector is modified according to the quality of the PPG signal, providing a reliable performance in terms of high AF detection accuracy in quality signals and high specificity even at low signal to noise ratios, i.e., during motion-induced artifacts, thus minimizing false alarms.

## Practical significance

1. The developed solutions for ambulatory monitoring of PVCs and AF can be used in the following clinical applications:

[label=()]

(a) Due to the high resemblance to the real photoplethysmogram signals, a developed photoplethysmogram model could be employed in the development and assessment of the PPG-based arrhythmia detection methods, in signal denoising.

(b) Potoplethysmogram-based detector of premature ventricular contractions can be used for a reliable and unobtrusive ambulatory long-term screening or applied in a real-time calculation of premature ventricular beats, e.g., during hemodialysis procedures.

(c) A method for detection of atrial fibrillation using photoplethysmogram signals has potential to be used for a reliable, cost-effective ambulatory long-term screening of AF in patients suspected of having brief and rare episodes of AF or in patients after myocardial infarctions or ischemic strokes.

2. The methods provided in this thesis have been developed and used in support of the following projects:

[label=()]

(a) "Intellectual wearable sensors system for human wellness monitoring – iMON" under the European Social Fund (No. VP1-3.1-SMM-10-V-02-004), 2013-2015.

(b) "Personalized patient empowerment and shared decision support for cardiorenal disease and comorbidities – CARRE" funded by the European Commission Framework Programme 7 (No. 611140), 2013-2016.

(c) "Automatic algorithms for atrial fibrillation risk prediction after acute myocardial infarction – AFAMI" supported by the Research Council of Lithuania (No. MIP088/15), 2015-2017.

## Approval of the results

The doctoral thesis resulted in two scientific papers, published in the international scientific journals referred to in the Thomson Reuters Web of Science database, while in total the results have been published in 11 scientific papers. The essential results have been presented in 6 conferences, including the worldwide recognized IEEE Biomedical Circuits and Systems Conference (BioCAS) 2014, and the 44th conference of Computing in Cardiology 2017 (CinC2017). The research has been positively assessed both internationally and domestically: BioCAS 2014 paper has been selected as one of the top 20 contributions to the conference and invited for publishing the extended version in the Special Issue of the IEEE Transactions on Biomedical Circuits and Systems journal, received the 1st place award for the presentation at the section of "Signals and Modeling" at the conference "Science for Health 2014" (Lithuanian University of Health Sciences), as well as a prize for the most attractive project for business (with coauthors) at the Young Scientists Exhibition "KTU Technorama 2015" (Kaunas University of Technology).

## The statements presented for defence

1. Photoplethysmogram model for simulating various arrhythmias, including premature contractions and atrial fibrillation can generate PPG signal by using the data extracted from ECG signals. Photoplethysmogram model can be used for the development and assessment of the PPG-based arrhythmia detection methods.

2. Premature ventricular contractions can be reliably detected by using rhythm and amplitude-based features, extracted from PPG signals, in combination with artifact detection and artificial neural network-based decision logic.

3. A combination of an ECG-derived and modified rhythm-based atrial fibrillation detector and PPG signal quality assessment provides a reliable approach for the detection of atrial fibrillation by relaying solely on PPG signal analysis both during screening and long-term monitoring.

## Structure of doctoral thesis

Thesis is organized as follows: chapters 2 and 3 are designated for the critical analysis of relevant scientific literature with respect to clinical significance and available technologies for the detection of cardiac arrhythmia, namely the premature ventricular contractions and atrial fibrillation. Chapter 4 presents the proposed methods for the modeling of photoplethysmogram, capable of simulating arrhythmia, PPG-based algorithm of the detection of PVCs, as well as PPG-based algorithm of the detection of AF. Section 5 describes the data used for the performance evaluation and presents the results obtained for each of the proposed methods. The doctoral thesis is finished with general conclusions in Chapter 6. The thesis consists of pages, figures, tables and 176 references.

**Chapter 4**

# Clinical significance of premature ventricular contractions and atrial fibrillation

## 4.1 Medical background

### 4.1.1 Introduction to premature ventricular contractions and atrial fibrillation

#### Anatomy and hemodynamics of the heart.

The heart is a muscular organ that pumps blood throughout the body via the circulatory system, supplying it with oxygen and nutritious material. Figure  shows the structure and main parts of the heart. The heart consists of four chambers, namely, the upper two chambers are the right and left atria, and the lower two chambers are the right and left ventricles. Blood returning to the heart from the body contain low levels of oxygen and high levels of carbon dioxide. This blood flows into the right atrium and then down into the adjacent right ventricle. After the right ventricle fills, contraction of the right atrium pumps additional blood into the right ventricle. The right ventricle then contracts and pumps the blood to the lungs where the blood takes up oxygen and gives off carbon dioxide. The blood then flows from the lungs trough the pulmonary veins to the left atrium, and then down into the adjacent left ventricle. Contraction of the left atrium pumps additional blood into the left ventricle. The left ventricle then contracts and pumps the blood to the aorta and then to rest of the body via the vascular system. The heartbeat (pulse) is caused by the contraction of the ventricles. The most important factor is the the heart rate. As the rate increases, more blood is pumped. The heart pumps more blood with each beat when the atria contract and fill the ventricles with additional blood just before the ventricles contract.

Figure 4.1: Structure of the heart.

#### Electrical system of the heart.

The electrical system of the heart controls the timing of each contraction. This system consists of the sinoatrial (SA) node, the atrioventruclar (AV) node, the bundle of His, Purkinje fibers and special tissues in the atria and the ventricles that conduct the current. The electrical discharge in the heart causes the muscle of the atria and then ventricles to contract and pump blood. During normal conditions, this system maintains a steady heart rate (the number of contractions per minute) in a range of 60–100 beats per minute at rest and increases hear rate to adapt oxygen delivery during physical activity, stress, or excitement, while lowering hear rate during low activity and sleep. In a healthy normal heart, the contraction rate of atria the same as that of ventricles. A normal synchronized contraction of atria and ventricles is defined as normal sinus rhythm. However, due to certain conditions or pathologies, either the atria and the ventricles or both may contract abnormally in an unsynchronized manner. Specialized heart cells in SA and AV nodes, His, Purkinje, and etc., may operate autonomously, therefore any suppression or enhancement of their activities may lead to abnormal contractions Mangoni2008. Normally, the SA node is the fastest in terms of initiating electrical impulses, while other nodes are slower, thus maintaining normal electrical operation of the heart. The rate at which the normal electrical impulses are initiated depends on the maximal diastolic potential, action potential threshold, and the rate of pacemaker potential. Changes in any of these factors may effect the rate of the electrical impulse initiation Issa2012. Therefore, the abnormal contractions are initiated by secondary pacemakers located in the atria and ventricles, defined as ectopic foci, which override the activity of SA node. Such abnormal heart contractions are defined as arrhythmias of which the most common are premature ventricular contractions and atrial fibrillation. Figure  demonstrates electrical activity of the heart during normal sinus rhythm, premature contractions and atrial fibrillations.

Figure 4.2: Heart and its electrical activity during: (a) normal sinus rhythm, (b) atrial and ventricular premature beats (PBs), and (c) atrial fibrillation.

#### Normal sinus rhythm.

During normal sinus rhythm (SR), the electrical impulse is discharged in a group of special conducting cells at the upper part of the heart, defined as the SA node. This impulse then propagates down through the heart, triggering first of two atria, the AV node and then both ventricles through the bundle of His. In a healthy heart, the impulse propagates through the heart rapidly, allowing all chambers to contract in a smooth, coordinated manner. The sequence of electrical and mechanical events during the normal cardiac cycle is as follows:

1. The SA node (primary pacemaker) initiates an electrical impulse.

2. The upper heart chambers (atria) contract.

3. The AV node transmits an impulse into the ventricles.

4. The lower heart chambers (ventricles) contract and pump blood.

5. The SA node transmits another signal to the atria to contract, starting cycle again.

#### Premature ventricular contractions.

Premature ventricular contractions (PVCs) are early contractions of the hearts’ ventricles, which may occur due to various conditions both in structurally normal and abnormal hearts. In contrast to normal sinus rhythm, during the PVCs, the electrical impulse is initiated the secondary pacemakers, located in the ventricles and are defined as the ectopic foci. PVCs occur before the impulses are initiated in the SA, thus overriding its operation and normal sinus rhythm contraction. Since electrical impulse occur in ventricles, the resulting QRS complex is of high voltage and of abnormal morphology. The sequence of electrical and mechanical events during the PVC is as follows:

1. The ectopic focus (secondary pacemaker) initiates an electrical impulse in the ventricles.

2. The lower heart chambers (ventricles) contract earlier than normal, while lower chambers (atria) do not, causing lower amount of blood to be pumped.

3. A pause is followed after the PVC, allowing ventricles to fill with more blood.

4. The following cycle might be initiated by the SA node.

PVCs maybe classified according the frequency of occurrence and their relationship to normal beats. Frequent PVCs are considered if occurrence is 10 PVCs per hour or 6 PVCs per minute. Relating to normal beats, PVCs may be classified to:

1. Bigeminy – every second beat is PVC.

2. Trigeminy – every third beat is PVC.

3. Quadrigeminy – PVC occur at every fourth beat.

4. Couplet – two consecutive PVCs.

5. Non-sustained ventricular tachycardia – 3 PVCs in a row.

#### 110Atrial fibrillation.

Atrial fibrillation (AF) is an abnormal rhythm during which the electrical impulses are generated chaotically throughout the upper atria of the heart, characterized by rapid and irregular contractions. It is a most common type of supraventricular tachycardia. During AF, the electrical impulses are not generated solely by the SA node, however, are initiated in other parts of the atria. These abnormal impulses occur more rapidly and irregularly and may exceed 350 bmp. Instead of producing an atrial beat, the muscles just fibrillate ineffectively, resulting in no p waves. The rapid and irregular impulses cause inefficient contractions of the atria, reducing the ability of the atria to pump blood into the ventricles. The ventricles are excited by the fast, irregularly spaced atrial impulses, however ventricles are partially protected by the AV node when pass through it. AV node dampens a number of those rapidly initiated atrial impulses before conducting some of the impulses to the ventricles. Still, the ventricular rate is usually much faster than normal, and irregular. The contractions of the ventricles may average 150 bpm, much slower than the rate in the atria, since ventricles are unable to contract at 350 bpm. Even at an average rate of 150 bpm, the ventricles may not have enough time to fully fill with blood before the following contraction, particularly without the normal contraction of the atria. Thus, AF decreases the amount of blood pumped by the ventricles because of their rapid rate of contraction and the absence of normal atrial contractions. The sequence of electrical and mechanical events during the AF is as follows:

1. Chaotic impulses occurring in the atrial tissue fibrillated atria.

2. Irregular pulses pass AV node and ventricles in an irregular fashion resulting in an inefficient pumping of blood.

3. The following cycle might be an irregular if AF episode is not over or AF is permanent or return to normal SR.

AF often it starts as brief periods of irregular rhythm which become longer and possibly constant over time, thus AF is classified into three major types ZoniBerisso2014:

1. Paroxysmal – when episodes of AF occur spontaneously and may stop on their own, without any treatment involved. The rhythm may return to SR within a week, usually in 24 hours. In some cases the duration of AF episodes may be 30 s.

2. Persistent – when rhythm of AF continues for more than a week. It may stop on its own, or it may still be restored to SR with treatment involved.

3. Permanent – type of AF when a normal heart rhythm cannot be restored with treatment.

### 4.1.2 Epidemiology and comorbidities

#### Premature ventricular contractions.

PVCs are one of the most common heart rhythm abnormalities and had been commonly referred to as being benign Kennedy1985, Gaita2001. It is estimated that PVCs are encountered in 1–4% of the general population Kennedy1985. The frequency of PVC occurrence in the adult population varies and depends on various factors such as medical condition, physical activity and etc. More than half (69%) of the population had at least 1 PVC event during the 24-hour monitoring period []. In a population of normal and healthy subjects, PVCs have been detected in 1% of subjects using a standard 12-lead electrocardiography and in 40–75% of subjects when performing 24–48-hour Holter monitoring Ng2006. Prevalence of PVCs is mostly age-dependent Messineo1989, ranging from <1% in children <11 years Southall1981, 69% in healthy adults aged 25–41 years Rotz2017, and 69% in subjects >75 years Camm1980. During physical exercise testing, PVCs were detected in 27% of subjects known cardiac disease and had a small, however statistically significant increased mortality hazards ratio of 1.71-1.86 MorshediMeibodi2004. However, subjects having heart disease have a higher incidence of complex or frequent PVCs Bikkina1992. Overall, PVCs appears to be a frequent finding with a small but statistically significant increase in risk of sudden cardiac death and mortality Abdalla1987. Since, PVCs are common on routine screening ECGs, a total of 1415 (5.8%) participants had at least 1 PVC at baseline, and 591 developed incident ischemic stroke during an average (SD) follow-up of 6.0 (2.0) years, resulting in a 38% increased risk of ischemic stroke Agarwal2015.

PVCs are thought to induce cardiomyopathy [], since pharmacological suppression of PVCs in patients with presumed idiopathic dilated cardiomyopathy subsequently improved left ventricular (LV) systolic dysfunction. Many of these patients often have no underlying structural heart disease and subsequently develop LV dysfunction and dilated cardiomyopathy; in cases of those with an already impaired LV function from underlying structural heart disease, worsening of LV function may occur Sarrazin2009, Singh1997. The exact prevalence of PVC-induced cardiomyopathy is not known; it is an underappreciated cause of LV dysfunction, and it is primarily observed in older patients Gaita2001. This observation could be due to the fact that the prevalence of PVCs increases with age or the possibility that PVC-induced cardiomyopathy develops in a time-dependent fashion Yarlagadda2005. In fact, [] demonstrated progressive worsening of LV function in patients with frequent PVCs (>1000 beats/day) as measured by the LV ejection fraction (LVEF) and LV end-diastolic dimension over a follow-up period of 4 to 8 years. On the other hand, PVCs in apparently healthy people were associated with a twofold increase in the risk of all-cause mortality, myocardial infarction and cardiac death Ng2006.

In meta-analysis of 11 studies, subjects with frequent PVC (1 time during a standard ECG recording or 30 times over a one-hour recording) had risk of cardiac death two-times higher than persons without frequent PVC. Although most studies made attempts to exclude high-risk subjects, such as those with histories of cardiovascular disease, they did not test participants for underlying structural heart disease Ataklte2013.

In a study of 239 patients having frequent PVCs (>1000 beats/day) without structural heart disease (i.e. in the presence of normal heart function), there were no serious cardiac events through 5.6 years on average, but there was a correlation between PVC prevalence and decrease of ejection fraction and increase of left ventricular diastolic dimension. In this study absence of heart of disease was excluded by echocardiography, cardiac magnetic resonance imaging in 63 persons and Holter monitoring Niwano2009.

In the ARIC study of 14,783 people followed for 15 to 17 years those with detected PVC during 2-minute ECG, and without hypertension or diabetes on the beginning, had risk of stroke increased by 109% Worthington2010. Hypertension or diabetes, both risk factors for stroke, did not change significantly risk of stroke for people with PVC Worthington2010. It is possible that PVCs identified those at risk of stroke with blood pressure and impaired glucose tolerance on a continuum of risk below conventional diagnostic thresholds for hypertension and diabetes Worthington2010. Subjects in ARIC study with any PVC had risk of heart failure increased by 63% Agarwal2012 and were >2 times as likely to die due to coronary heart disease. Furthermore, the risk was also higher for people with or without baseline oronary heart disease Massing2006.

In the Niigata study of 63,386 people with 10-year follow-up period those with PVC during a 10-second recording had risk of AF increased nearly 3 times independently from risk factors such as age, male sex, body mass index, hypertension, systolic and diastolic blood pressure, and diabetes Watanabe2006.

Ventricular ectopy is more prevalent in men than in women of the same age. Male sex alone increases the risk of identifying PVCs on routine screening, with an odds ratio for male sex of 1.39 compared with women. Furthermore, frequency and probability of PVC occurrence increases with age (see Fig. ), reflecting the increased prevalence of hypertension and cardiac disease in ageing populations Kostis1981.

Figure 4.3: Probability (%) of PVC occurrence during 24 hours in healthy subjects as a function of age Kostis1981.

PVCs have been examined as predictors of cardiovascular morbidity and mortality, especially with pre-existing heart disease Massing2006. Structural anomalies in the myocardium and/or pericardium were present in 85% of patients with exercise-induced PVCs. The majority of subjects with exercise-induced PVCs show evidence of myocardial disease consistent with acute or previous myocarditis or myopericarditis Jeserich2015.

PVCs in subjects with heart diseases, i.e., myocardial infarction, may be associated with a variety of underlying cardiac conditions such as cardiomyopathy and increased risks of developing ventricular tachycardia, a sustained run of rapid ventricular contractions Koplan2009. Prolonged ventricular tachycardia can result in a low cardiac output, low blood pressure, and fainting (syncope). Ventricular tachycardia is life-threatening, may occur suddenly with no prior warning, and frequently develops into ventricular fibrillation. It is a chaotic rhythm where the ventricles fibrillate rapidly and randomly. During ventricular fibrillation, heart is unable to pump blood into the brain and rest of the body effectively, thus if untreated, it can be fatal within minutes, killing 250,000 Americans annually due to incidence of sudden cardiac death Chugh2008.

Recent studies have shown that those subjects with frequent occurrence of PVCs, i.e., several thousand a day, are associated with left atrial enlargement in patients with normal left ventricular ejection fraction and can develop cardiomyopathy Park2014. In these cases, if the PVCs are reduced or removed, e.g., via ablation therapy, the cardiomyopathy usually regresses Shiraishi2002, Belhassen2005.

#### Atrial fibrillation.

Atrial fibrillation is the most common and ubiquitous type of cardiac arrhythmia Ball2013, Munger2014.

Epidemiological evidences, collected over the past few decades, suggest a rapidly increasing prevalence of AF, e.g., the analysis of current global epidemiological data has shown that the number of new AF cases had increased by about 5 million from 1990 to 2010 Chugh2013. AF resulted in 112,000 deaths in 2013, up from 29,000 in 1990 Naghavi2015.

Recent estimates suggest that 12.1 to 15.9 million patients will have AF in the United States by 2050 Miyasaka2006 and 17.9 million people in Europe by 2060 Chugh2013, Krijthe2013.

Estimated AF prevalence in the United States in 2010 was 2.7 to 6.1 million and is expected to rise to 5.6 and 12 million in 2050 Roger2011, Menezes2013. In Europe and North America, as of 2014, it affects about 2% to 3% of the population ZoniBerisso2014. This is an increase from 0.4 to 1% of the population around 2005 Fuster2007. According to the latest trends, AF prevalence will increase dramatically in the near future. Various studies expect a 2–3 fold increase in AF prevalence by the year of 2050 Go2001,Miyasaka2006

The estimated numbers of individuals to be affected by AF in upcoming decades varies quite a lot among different surveys, falling between 5.6 Go2001 to 15.9 million Miyasaka2006 in the United States alone. Similarly, the most recent data suggest AF prevalence in the US will rise from 5.2 million in 2010 to 12.1 million by 2030 Colilla2013. A discrepancy among the different studies is mainly caused by the incorrectly estimated baseline numbers of the population suffering from AF.

It has been estimated that 33 million people around the world are suffering from AF Chugh2013. Nevertheless, given that AF is usually asymptomatic, and undiagnosed for many patients, these numbers most likely represent an underestimate. Therefore, reasonably larger numbers of actual prevalence are expected, reaching up to 2% of the general population Camm2010.

The prevalence of AF increases substantially with age (see Fig. ) where 0.14% under 50 years old, 4% between 60 and 70 years old, and 14% over 80 years old being affected Marini2005, Barrios2012, ZoniBerisso2014. It is also higher in men than women with the odds of developing AF being twice as great for each advancing decade of age Benjamin1994, Marini2005, Heeringa2006, LloydJones2004. Consequently, more than 12% of adults aged >75 years have a diagnosis of AF Heeringa2006.

Figure 4.4: Prevalence (%) of AF as a function of age Barrios2012.

AF most commonly occurs secondary to cardiovascular pathologies as well as systemic disorders, where this relationship was first demonstrated in Benjamin1994, Menezes2013. It has significant effect on morbidity and mortality: it is estimated that AF increases the risk of stroke by fivefold and about 15% of all patients who have stroke have AF too Roger2011, Menezes2013. The percentage of strokes attributable to AF increases from 1.5% at 50-59 years of age to 23.5% at 80–89 years of age Roger2011.

The AF is associated with an increased risk of heart failure, dementia, and stroke Justin2013. The presence of AF at stroke onset and during the acute phase was confirmed by a standard electrocardiogram in 869 (24.6%) of 3530 patients with ischemic stroke. With respect to patients without the arrhythmia, those with AF were more frequently women, aged 80 years and older, with coronary heart disease and peripheral arterial disease. High prevalence of AF was found in patients with a first-ever ischemic stroke, especially among elderly women Marini2005.

AF, together with related complications (heart failure, stroke, dementia) Gross2013, produce a huge economic burden in many countries, reaching 1-2% of total health care expenditure Wolowacz2011. For instance, in the US, the annual AF-related cost was estimated to be in the range from 6.0 (exclusively AF-related costs) to 26.0 billion dollars Kim2011. A wide range of estimated costs was suggested in order not to underestimate the lower boundary, since it is not completely clear to what extent AF contributes to detrimental comorbidities that require special medical care. Comparable numbers of AF-related costs have been estimated in the countries of the European Union.

The Euro Heart Survey on AF  Ringborg2008 counted the combined annual cost of 6.2 billion euros in just five European countries (Greece, Italy, the Netherlands, Poland, and Spain). Approximately one-third of AF costs are due to hospitalizations, whereas outpatient medical and pharmacy expenditure accounts for the remaining two-thirds Kim2011. In addition, individuals with AF are hospitalized twice as many times as those without AF, while multiple cardiovascular hospitalizations are even 8 times more common. As a result, the total direct medical costs are considerably higher (around 70%) in patients with AF than in those without AF Kim2011. It has been speculated that at least a 2-fold reduction in AF prevalence could be achieved if other cardiovascular risk factors were maintained under the safe levels Huxley2011.

Several important factors are considered to be among the most influential on growing AF epidemic: ageing of population, globally increasing numbers of people affected by hypertension and obesity, and considerably improved survival from other cardiovascular diseases, such as heart failure and myocardial infarction. These conditions cause structural changes in myocardium, and therefore increase the risk for developing AF Chugh2013. On the other hand, emerging novel technologies for arrhythmia detection, i.e., implantable cardiac monitors, internal and external loop recorders, together with new strategies, contribute to increased numbers of newly diagnosed AF cases. As a result, an increased AF awareness and initiatives to improve detection of AF Fitzmaurice2007, Lowres2013, Lowres2014 have contributed to the greater incidence and reported prevalence of AF, in addition to an aging population and improved survival from other cardiovascular diseases.

### 4.1.3 Mechanism and pathophysiology

#### Premature ventricular contractions.

The underlying mechanism of PVC origin may vary depending on the clinical circumstances. Occurrence of PVCs is explained by three known physiological mechanisms, namely, the automaticity (enhanced normal and abnormal), reentry (anatomic and functional), and triggered activity (delayed and early afterdepolarization) Gaztanaga2012.

Enhanced cardiac automaticity refers to the accelerated initiation of an action potential by either normal pacemaker tissue (enhanced normal automaticity) or by abnormal ventricular tissue within the myocardium (abnormal automaticity). Enhanced automaticity suggests an ectopic focus of pacemaker cells in the ventricle that has a subthreshold potential for firing. The basic rhythm of the heart raises these cells to threshold, which precipitates an ectopic beat. This process is the underlying mechanism for arrhythmias due to excess certain organic compounds and some electrolyte deficiencies, particularly low blood potassium, known as hypokalemia. This ectopy of the ventricles when associated with a structurally normal heart most commonly occurs from the right ventricular outflow tract and the mechanism behind this is thought to be enhanced automaticity versus triggered activity. PVCs can be triggered when inhibitors such as caffeine lead to the increased intracellular concentration of calcium ions Huizar2011. The discharge rate of normal or abnormal pacemakers may be accelerated by drugs, various forms of cardiac disease, reduction in extracellular potassium, or alterations of autonomic nervous system tone. Enhanced normal automaticity accounts for the occurrence of sinus tachycardia, while abnormal automaticity may result in various atrial or ventricular arrhythmias. Potassium ion concentrations are a major determinant in the magnitude of the electrochemical potential of cells, and hypokalemia makes it more likely that cells will depolarize spontaneously. Hypercalcemia has a similar effect, although clinically it is of less concern. Magnesium ions affect the flow of calcium ions, and they affect the function necessary for maintaining potassium levels, therefore low blood magnesium may also make spontaneous depolarization.

Reentry usually occurs when slow conducting tissue, e.g., post-infarction myocardium, develops adjacent to normal tissue. Post-infarction PVCs, on the other hand, tend to occur in regions of scar and / or damaged myocardium and may be due to enhanced automaticity, triggered activity, or possibly reentry. It has been postulated that reentry may play a role in such cases, as post-infarction PVCs often exhibit characteristics similar to post-infarction ventricular tachycardia Hachiya2002. This condition is frequently seen in patients with underlying heart disease that creates areas of differential conduction and recovery due to myocardial scarring or ischemia. During ventricular activation, one bundle tract’s area of slow conduction activates the other tract’s bundle fibers post block after the rest of the ventricle has recovered, resulting in an extra beat. Reentry can produce single ectopic beats, or it can trigger paroxysmal tachycardia. Triggered beats are considered to be due to after-depolarizations triggered by the preceding action potential. These are often seen in patients with ventricular arrhythmias due to digoxin toxicity and reperfusion therapy after myocardial infarction. Existing damage to the myocardium can also provoke PVCs. The myocardial scarring that occurs in myocardial infarction and also in the surgical repair of congenital heart disease can disrupt the conduction system of the heart and may also irritate surrounding viable ventricular myocytes, make them more likely to depolarize spontaneously.

Triggered activity occurs due to the after-depolarizations, i.e, the oscillations of membrane potential before or after the completion of repolarization, which are triggered by the preceding action potential Zipes2003. When oscillations depolarize the cell to the level of threshold potential, they induce spontaneous action potentials (triggered activity) that are responsible for premature beats and tachycardias. After-depolarizations occur, only in the presence of a previous action potential (the trigger), and when they reach the threshold potential, a new action potential is generated. This may be the source of a new triggered response, leading to self-sustaining triggered activity. Afterdepolarization can occur either during (early) or after (delayed) completion of repolarization. Early afterdepolarizations are usually responsible for bradycardia associated PVCs as well as with ischemia and electrolyte disturbance.

#### Atrial fibrillation.

The pathophysiology and underlying mechanisms of AF are not yet fully understood. Nevertheless a number of theories and hypotheses tempting to explain the mechanism of atrial fibrillation has emerged (see Fig. ). Theories and hypotheses of mechanisms can be divided into two major groups, namely, single-focus (Fig.  (a)–(d)) and multiple-source (Fig.  (e)–(h)).

Figure 4.5: AF mechanisms: (a) single automatic focus, (b) mother wave, (c) fixed rotor, (d) moving rotor, (e) multiple foci, (f) unstable re-entry circuits, (g) multiple wavelets, (h) single focus together with multiple wavelets (partially based on []).

Single-focus hypotheses state that AF occur due to the increased automaticity or a single rapid macro re-entry circuit in the area of focal activity, with wavefronts emerging from the primary driver circuit (i.e., rotor) breaking against regions in the atria of the variable refractoriness, causing the arrhythmia Camm2005. The excitation impulses arising from different areas of focal activity, may result in the ectopic beats, which if rapid enough, may produce fibrillatory conduction and triggering of the AF.

According to the multiple sources hypotheses, electrical activation in AF proceeds as multiple re-entrant wavelets separated by lines of functional conduction block, generating irregular re-entrant activity, which occurs in a asynchronous fashion in different region of atrial (i.e., multiple circuit re-entry). These wavelets continuously initiate themselves (i.e., leading circle re-entry) or each other (i.e., random re-entry). The modelling by [] of multiple wavelet hypothesis showed that fibrillatory conduction during episodes of AF maybe be initiated and sustained by the propagation of of random wavelets in the heterogeneous arterial tissue. It was concluded that wavelets and subsequent "daughter wavelets" may result in from any triggering mechanisms. The AF is sustained as long as an adequate number of wavelets propagates simultaneously, in turn depending on the minimally sufficient atrial mass. Therefore, this hypothesis defines AF as a self-sustaining process independent either from a single source initiator, i.e., an ectopic focus, or the atrial structure needed to sustain a circular propagation. Later, the hypothesis was supported with the experiments by [], demonstrating that a minimum of 4–6 wavelets may be and adequate number to sustain the AF.

The evolution of AF from paroxysmal to persistent and then permanent is influenced by the atrial re-modeling caused by arrhythmia per se and/or progression of underlying heart disease Nattel2008.  [] suspected that the AF produce both electrophysiological and structural abnormalities, which may result in a permanent AF. It was revealed that the sources of focal triggering, located on the surface of pulmonary veins, are responsible for the initiation of AF []. In case of paroxysmal AF, electrophysiological remodeling and development of functional re-entry substrates, resulting in from altered expression and/or function of cardiac ion channels, can reverse-remodel when AF is terminated Allessie2002, Nattel2008. Ultimately, if AF frequently reoccurs and sustains for longer periods of time, a hazardous condition of atrial remodelling may start, which further leads to a very undesired and difficult to manage phenomenon when "AF begets AF" Wijffels1995. In other words, atrial cells start to remodel electrophysiologically during prolonged episodes of AF, therefore more abnormal atrial substrate is created, which promotes to sustain AF even longer. As atrial disease progresses to irreversible structural changes, AF becomes permanent Nattel2008. Propagation may be restricted but AF will not terminate during catheter ablation due to lack of a localized source. However, owing to the complex temporal interplay between AF driver and atrial substrate, electrical and structural re-modeling may allow AF to persist even after the driver is removed. As a result, depending on the amount of substrate in the atrial tissue, re-entry can originate in multiple circuits. During even more advanced stages of AF, i.e., chronic AF, multiple re-entry circuits may become highly unstable, engaging a rotor re-entry. Therefore, if AF is treated early, especially when AF episodes are rare and short, its progression can be halted.

### 4.1.4 Symptoms, risk factors, treatment and management

#### Symptoms and risk factors.

Mostly both PVC and episodes of AF are asymptomatic Bhandari1992, however symptoms, listed in Table  may be experienced during these arrhythmic events:

Table 4.1: List of symptoms experienced during arrhythmic events

[Sorry. Ignored \begin{tablenotes} ... \end{tablenotes}]

Many risk factors may be responsible for causing PVC and AF, therefore a number of risk factors and possible complication are presented in Table :

Table 4.2: List of arrhythmia-causing risk factors and complications

[Sorry. Ignored \begin{tablenotes} ... \end{tablenotes}]

#### Treatment and management of premature ventricular contractions.

Premature ventricular contractions (PVCs) are the most common type of irregular heartbeats. The reasons for treating PVCs are to relieve symptoms of palpitation or to treat conditions that cause PVCs, since many conditions that cause PVCs are potentially life threatening. Figure  shows the options used for the treatment and management of PVCs. In most cases PVC can be controlled with lifestyle changes such as reducing or eliminating caffeine, tobacco and alcohol intake and reducing stress and anxiety. A beta blocker medication may also be prescribed for patients with PVCs. Anti-arrhythmics and ablation is another treatment option for some patients with frequent or prolonged PVCs.

Figure 4.6: General approaches to treat and manage PVCs.

In the absence of heart disease and if PVCs are infrequent or reduce in frequency on exercise tolerance test, with no documented ventricular tachycardia, no further investigation and treatment is required, particularly if PVCs are relatively asymptomatic. Subjects with significant symptoms should have their blood pressure checked and investigated and treated if high. For relief of palpitations, some preventative measures to eliminate triggers might be considered, such as, stopping alcohol and caffeine intakes, stop using medications containing adrenaline, stopping drug abuse, and quit smoking. In healthy individuals, PVCs can often be resolved by restoring the balance of magnesium, calcium and potassium within the body.

Beta-blockers may be used to control symptoms in patients where PVCs arise from multiple sites. It should also be considered in patients with impaired ventricular systolic function and/or heart failure. There is no evidence to support the use of other anti-arrhythmic agents simply for the sake of suppressing PVCs, especially considering their pro-arrhythmic and other side effects Ng2006. A therapeutic medical trial or catheter ablation may be considered in patients with left ventricular dysfunction and frequent PVCs (a generally accepted range of 10,000–20,000 or >10% of total beats per 24 hours) if the clinical suspicion for PVC-induced cardiomyopathy is high Kanei2008, Niwano2009.

Anti-arrhythmia medications are used to control PVCs in order to prevent ventricular tachycardias, ventricular fibrillations, and sudden death. Unfortunately, there is little scientific evidence that suppressing PVCs with anti-arrhythmic medications prevent ventricular tachycardias, ventricular fibrillations, and sudden death. Some anti-arrhythmia medications can actually cause abnormal heart rhythms. Thus anti-arrhythmic medications are only prescribed cautiously in patients at high risk of developing ventricular tachycardia and ventricular fibrillation; and usually initially in the hospital setting. Although anti-arrhythmic medications could suppress PVCs, they increase the risk of death death risk Ng2006. This does not apply to beta-blockers, which are prescribed to many heart patients for many reasons, and not only do not accelerate arrhythmias, but usually decrease premature ventricular contractions. In many patients with PVCs and significant underlying cardiac disease, or with severe symptoms, electrophysiology testing may be recommended. This is a test performed with catheters to see if a patient is at risk of life-threatening ventricular arrhythmias, which are treated with either medications or sometimes implantable defibrillators.

Catheter ablation treatment is advised for subjects with ventricular dysfunction and frequent arrhythmias or very frequent PVC (>20% in 24 h) and normal ventricular function Niwano2009. This procedure destroys the area of the heart tissue that is causing the irregular contractions characteristic of PVCs using radio frequency energy. Reducing frequent PVC (>20%) by antiarrhythmic drugs or by catheter ablation significantly improves heart performance Belhassen2005, Ng2006.

Heart attacks can increase the likelihood of having PVCs. In severe cases, an implantable defibrillator may be used for patients with nonsustained ventricular tachycardia due to prior myocardial infarction, left ventricular ejection fraction less than or equal to 40%, and inducible ventricular fibrillation or sustained ventricular tachycardia at electrophysiological testing Ng2006, Ahn2013.

#### Treatment and management of atrial fibrillation.

The strategy for the atrial fibrillation treatment and management depends on the type of AF and its progression (i.e., paroxysmal, sustained or permanent), the severity of symptoms, the underlying cause of AF (e.g., thyroid disorder) and other problems with the heart. Generally, main goals of the AF treatment are to reset the rhythm or control the rate and to prevent blood clots. Figure  shows the available options for the treatment and management of AF.

Figure 4.7: General approaches for the treatment and management of AF.

Many people have episodes of AF and are not aware of them. Therefore lifelong anticoagulants such as either aspirin or anti-clotting medications such as warfarin or a novel oral anticoagulant may be recommended to minimize risk of stroke even after the rhythm has been restored to normal. Munger2014.

If there is possibility and no contraindications, AF is often treated with medications to slow the heart rate to a near normal range (known as rate control) or to convert the rhythm to normal sinus rhythm (known as rhythm control) Anumonwo2016. However, in some cases, a more invasive treatment, such as surgery or medical procedures using catheters may be required.

When the symptoms of AF are bothersome and AF is not permanent, the rhythm may be reset to normal sinus rhythm by applying cardioversion. Cardioversion can be conducted in two ways, by using electrical cardioversion or cardioversion with drugs.

Electrical cardioversion is used to convert AF to a normal sinus rhythm and is often used emergently when the subject is unstable Oishi2013. During electrical cardioversion, an electrical impulse is delivered to the heart through the electrodes on the chest which temporary pauses electrical activity of the heart. When electrical activity of the heart restarts, the heart may resume its normal rhythm. The procedure is performed during sedation, so there is no sensation of the electric impulse. As a preventative measure for future AF episodes, anti-arrhythmic medications maybe prescribed after the procedure.

Cardioversion with drugs uses medications called anti-arrhythmics to restore normal sinus rhythm. Depending on the heart condition, intravenous or oral medications doctor may be recommend. The treatment is often conducted during continuous monitoring of the heart rate. If the heart rhythm returns to normal, the same or a similar anti-arrhythmic medication may be prescribed to prevent recurrence of AF. Prior to cardioversion or in case of permanent AF, an anticoagulant medications (e.g., warfarin) may be given to reduce the risk of blood clots formation and stroke. Anticoagulant medication may also be taken to prevent a blood clots from forming even after the rhythm of heart is restored to normal. Although medications may help maintaining a normal heart rhythm, they can cause various adverse effects such as life-threatening ventricular arrhythmias, e.g., ventricular tachycardia and ventricular fibrillation, worsening of heart failure and low blood pressure, major bleeding Jun2015, Heidbuchel2015. However, sometimes even medications or cardioversion may not provide a significant effect and there is always a chance that AF will recur.

In such cases, a catheter ablation procedure used to eliminate the area of hearts’ tissue that is causing the erratic electrical signals and restore a normal heart rhythm may be applied. In catheter ablation, the catheters are inserted and guided through blood vessels to the heart. Electrodes at the catheter tips apply radiofrequency energy, extreme cold (e.g., cryotherapy) or heat to destroy and scar tissues causing erratic impulses. Since scar tissue does not carry electricity the rhythm could be normalized. Catheter ablation may correct the AF without the need for medications or implantable devices and prevent recurrence in some people Amerena2013. A surgical procedure to implant a pacemaker might be required to keep the ventricles beating properly.

Surgical procedures such as maze procedure is generally reserved for subjects not responding to other treatments or when it can be done during other necessary heart surgery, such as coronary artery bypass surgery or heart valve repair. The surgical maze procedure is conducted during an open-heart surgery, where a precise incisions in the upper chambers of the heart are made to create a pattern of scar tissue.

## 4.2 Diagnosis of premature ventricular contractions and atrial fibrillation

### 4.2.1 Diagnosis of the arrhythmia

A diagnosis is made by sensing the pulse and is confirmed using an electrocardiogram (ECG) Ferguson2014, i.e., a typical ECG during PVCs shows wide and abnormal QRS complex with a shorter preceding and longer succeeding intervals, while the ECG during AF shows no P waves and an irregular ventricular contractions Ferguson2014. Evolving technologies have provided a wide array of monitoring options for patients suspected of having cardiac arrhythmias, with each modality differing in duration of monitoring, quality of recording, convenience, and invasiveness.

There are three forms of ECG testing, which are used to assess the electrical activity of the heart under different circumstances: resting ECG, ECG stress test, and ambulatory ECG. Physicians also use electrophysiologic testing to diagnose arrhythmias. Electrophysiologic monitoring examines the electrical function of the heart within the heart itself inserting catheters, usually thin, flexible tubes into the coronary arteries. Resting ECG, ECG stress tests, and electrophysiologic testing are typically used for capturing arrhythmias that occur frequently, while ambulatory ECG is used for infrequent arrhythmias.

For frequent or constant arrhythmias, physicians perform a resting ECG or an ECG stress test in a physician’s office or a hospital, where 10–15 electrodes are placed on the subject’s chest, arms, and legs. For a resting ECG, the patient lies down during the test. For ECG stress test, patients walk on a treadmill for 5–15 minutes. For subjects who are unable to exercise, the effects of exercise on the heart can be simulated with drugs.

To monitor infrequent arrhythmias, the physician uses ambulatory ECG, or event recording. The patient wears portable ECG devices that record arrhythmic events while the patient is away from the physician’s office. Ambulatory monitoring devices include: Holter monitors and intermittent recorders.

### 4.2.2 Ambulatory arrhythmia monitoring and screening

Many heart problems are noticeable only during certain activities, including exercise, eating, sex, stress, bowel movements, and even sleeping, therefore an ambulatory ECG is more likely to find abnormal heartbeats that occur during these activities. Many people have irregular heartbeats (arrhythmias) from time to time. What this means depends on the type of pattern they produce, how often they occur, how long they last, and whether they occur at the same time the symptoms are felt. Because arrhythmias can come and go, it may be hard to record one while subject is visiting a physician. There are several different types of ambulatory monitors. The physician decides the type that works best for the subject and is most likely to help diagnose the heart problem Hoefman2010, Subbiah2013. An ambulatory ECG monitor records the electrical activity of the heart while subject performs usual daily activities. Ambulatory means that subject is able to walk during the test. This type of monitoring may also be called ambulatory ECG, Holter monitoring, 24-hour ECG, or cardiac event monitoring. A continuous recorder gives a 24–72 hour record of the electrical signals from the heart. A standard ECG monitor records only 40–50 heartbeats during the brief time when the subject is attached to the machine, while a continuous recorder monitors  100000 heartbeats in 24 hours, therefore it is more likely to capture any heart problems that happen with activity.

#### 110Holter monitors.

A Holter monitor is used to record ECG continuously during a period of at least 24–72 hours while subject performs normal daily tasks. Holter monitor is usually applied if a subject is suspected of having cardiac arrhythmia less frequent and is not detected by a conventional ECG recorder. This kind of monitoring is usually performed to ensure whether there is any dangerous cardiac arrhythmias that might require treatment. A relatively compact recorder (see Fig.  ) is worn and attached to the body by the straps for fastening the device itself and sticker electrodes similar to those applied during conventional ECG recordings.

Figure 4.8: Holter monitor Medilog® FD12 plus by Schiller AG.

Wires from the electrodes lead to a small battery-powered device that can be clipped onto a waistband or belt, or placed in a small carrying case and slung over a person’s shoulder. The electrode pads are then attached to the skin of the chest. Thin wires are connected to the electrodes and the monitor. To verify whether electrodes are attached correctly, subject may be briefly hooked up to a standard ECG recorder. A conventional ECG recorder employs 12 leads, which are useful when diagnosing, e.g., heart attack, however, usually not all leads are of interest. Additionally, it is very inconvenient for the subject to wear 10 electrodes for a longer period of time, therefore most portable Holter monitors are designed with 3–7 electrodes capable of recording 1, 2, 3, or 5 channels. A Holter recording is noninvasive and painless, however sometimes the sticker electrodes might irritate the skin during the recording time. Subjects are asked to keep a diary of events during the 24–72 hour period, which are helpful for knowing when the subject was active, sleeping or having any symptoms that might be caused by a cardiac arrhythmia. Subjects keep a diary of their activities, such as sleeping or eating, so that physicians can associate any arrhythmia with a specific activity. Once the recording has been completed, the recorder and sticker electrodes are disconnected, and the recorder is taken back to the physician for the ECG analysis and interpretation. A technician will process the information from the recorder for your cardiologist to review. Since a Holter recording is usually only worn for 24–72 hours, it is particularly helpful when symptoms occur at least once a day. If symptoms are happening less often, an intermittent event recorder may be recommended instead. During Holter monitor testing, patients should avoid taking showers or baths and limit the use of small electrical devices, such as electric toothbrushes or razors. Furthermore, the electrodes used to record ECG are attached to the patient’s chest, resulting in discomfort, limited freedom of movement, and increased feeling of unhealthiness, especially after wearing the device for several days Rosero2013. Study by [] showed that intermittent monitoring is more effective in detecting arrhythmic events than using Holter monitors.

#### Intermittent recorders.

Intermittent recorder is employed when symptoms of an irregular heart rhythm are rare. Compared to the Holter monitors, the intermittent recorder can be used for a longer period of time. The information collected by an intermittent recorder can often be sent over the phone to a physician for the analysis, interpretation, and further actions. The approach by which the intermittent recording is performed depends on the type of monitor used.

Figure 4.9: External loop recorder King of Hearts® by CardioComm Solutions Inc.

#### Loop recorder.

Loop recorder is used to perform a continuous recording of the ECG signal (see Fig. ). It records ECG when symptoms are present. Loop recorders also save a small amount of information about how the heart was beating when subject pressed the recording button. Continuous loop recorder captures only a few minutes worth of the ECG at a time on its memory. It continuously records new information and discards the oldest information, so that at any time it contains only the last few minutes of ECG in the memory. Since the loop recorder is continuously refreshing its memory, the loop recorder can be carried for long periods of time. This is called pre-symptom recording. This feature is especially useful for patients who faint when their heart problems occur and can press the button only after they wake up. Electrodes are attached to the chest in the same way as with a Holter monitor. When there are symptoms, subject presses a button on the monitor to start recording the heart rhythm. The recorder may start recording on its own when an irregular rhythm is detected. Or and additional hand-held device might be used to start the monitor when symptoms occur. The recorder can be worn for several weeks. This may be a good choice for subjects having symptoms that occur rarely, such as once every 6 months. Furthermore, loop recorders are optimal for capturing brief arrhythmia episodes when it takes too long to apply an event recorder or for capturing ECG recordings of episodes that are associated with incapacitating symptoms such as syncope. Subjects experiencing symptoms only few times a year may be recommended an implantable device which is inserted in the chest for up to 18 months.

Figure 4.10: Implantable loop recorder Reveal LINQTM by Medtronic plc.r (left) and AAA battery (right) for the size comparison.

#### Implantable loop recorders.

The implantable loop recorder (see Fig.) is a miniature, usually single-lead, subcutaneous loop recorder that are implanted between the chest skin and the rib cage, above the heart by means of surgery, sometimes using only a local anaesthesia. Same as the standard loop recorder, the implantable one can be programmed for automatic recording whether irregular rhythm is detected. Furthermore, the implantable loop recorder may be triggered externally from the remote control, e.g., attached to the wrist. Implantable loop recorders are particularly useful either when symptoms are infrequent and are not amenable to diagnosis using short-term external ECG recording techniques or when it is required to aggregate long-term data, e.g., burden of PVCs or AF. These kind of implantable devices may operate for up to 6 years and may even be recharged using wireless charging. The stored data is retrieved through the skin by using a wireless communication. There is no need to unplug the device, e.g., when taking a shower, and there is no discomfort in wearing it, as well as attaching and reattaching electrodes, since no external electrodes or power sources are required. Such characteristics are suitable for a long term continuous monitoring in high-risk subjects with recurrent episodes of palpitations or syncope and documented premature beats or AF, and for risk stratification in subjects who have sustained a myocardial infarction and those who have certain genetic disorders Krahn2004. However, the presence of an active infection or a bleeding diathesis may preclude implantation. Other factors include the need for a minor surgical procedure, the difficulty of always being able to differentiate supraventricular from ventricular arrhythmias, the presence of under- or over-sensing that may exhaust the memory of the implantable loop recorder, and the cost of the device. The implantable loop recorder has a high initial cost, however, it may actually be more cost-effective than a strategy incorporating multiple nondiagnostic investigations Davis2012.

#### Event monitor.

Event monitors are exploited when symptoms are presumed to be due to the rhythm disturbances, occurring less frequently than once during a 24–48 hour period. Like loop recorders, the event monitors tend to be smaller than Holter monitors due to the lesser information storage capacity, since the recording is only enabled when an incidence occurs as opposed to continual recording. Event monitors are capable of recording short episodes of ECG and may not be worn continuously. Although an event monitor could be detached from the body for the hygiene procedures, it should still be reattached after and worn for at least 24 hours. There are different types of event monitors, some of which require attaching electrode patches with wires to the chest area and linking the wires to a recording device. Others require no patches, however such devices are worn as a bracelet, wrist watch or used as a thumb ECG devices (see Fig. ). In these cases, the ECG is recorded by contacting second electrode with the opposite hand or touching both electrodes with thumbs. When symptoms are present, the monitor could be temporarily attached to the body. Depending on the design the back of the device might have small metal electrodes or if the device is of bracelet type, it usually have on electrode on the back and the second electrode on the top of the bracelet. The recording is usually activated by pressing the record button on the monitor attached to the chest or by touching the bracelet. The recording might last for up to a minute or slightly more. The recorded ECG might then be transmitted over the, e.g., smartphone via the internet connection to the physician for further analysis and interpretation. The event monitor might be issued for at least one month, allowing to capture suspicious cardiac events.

Figure 4.11: Event monitor Zenicor thumb-ECG by Zenicor Medical Systems AB.

#### Alternative screening approaches.

New, more convenient and cost-effective solutions, strategies and technological approaches for monitoring of the arrhythmia are emerging, i.e., using smartphone camera and dedicated App Freedman2016, Garabelli2017. Such approaches allow for the initial arrhythmia monitoring without attaching multiple electrocardiogram electrodes to the body. However, camera-based approaches are not intended for a long-term continuous arrhythmia screening. A long-term photoplethysmogram-based screening requires continuous recording and analysis of the photoplethysmogram signals which is associated with motion-induced artifacts and may dramatically increase the rate of false alarms. Therefore, approaches capable of distinguishing both normal and abnormal rhythm from the artifacts are needed. This would allow for a reliable, long-term continuous arrhythmia screening by using unobtrusive e.g., wrist-band type devices without using electrocardiogram signals.

## 4.3 Conclusions of the chapter

1. The prevalence and frequency of both premature ventricular contractions and atrial fibrillation is increasing because of the aging population.

2. Premature contractions may be both the symptom of the disease, e.g., myocardial infarction or the cause, e.g., cardiomyopathy. Frequent premature ventricular contractions, especially in subjects with heart disease and severe symptoms, are of interest and are considered for treatment.

3. Atrial fibrillation tends to progress without noticeable symptoms and may become incurable with serious comorbidities, e.g., stroke and myocardial infarction, therefore means for early detection and management are of interest.

4. Cardiac arrhythmias are usually detected and evaluated using electrocardiogram recordings, however, more convenient and cost-effective approaches are needed.

**Chapter 5**

# Overview of PPG-based methods for arrhythmia detection

## 5.1 Introduction to photoplethysmography

### 5.1.1 Principle of photoplethysmography

Photoplethysmography is a relatively simple, optical, non-invasive technique, primarily used for monitoring of local hemodynamical changes in the vascular system by illuminating tissues with the light of a certain wavelength. The principle of photoplethysmography utilizes the property of blood to absorb light more strongly compared to the surrounding tissues. The photoplethysmography sensor is composed of light emitting diode (LED) light source and photodetector (PD), usually a photodiode, to receive the unabsorbed light. The intensity of light received by PD, changes the output voltage signal which is proportional to the volume of blood in the blood vessels pumped during each cardiac cycle. This output voltage provides only a relative changed in blood volume and therefore, the exact amount of blood is not quantified.

Two main configurations of photoplethysmography sensors are employed for PPG acquisition, namely, the reflection and transmission modes, respectively. A detailed illustration of these configurations is demonstrated in Fig. :

Figure 5.1: Principle of reflection and transmission photoplethysmography as well as composition of the resulting PPG signal.

In a reflection sensor configuration, the light source and PD are positioned next to each other. In this configuration, the PD receives the light which is back-scattered or reflected from blood vessels, tissue, bone and etc. The reflection configuration has virtually no restrictions and problems, associated with the placement of the sensors and variety of measurement sites can be used.

In transmission configuration, the light source and PD are positioned on opposite sides of the tissue, e.g., earlobe, is located between the light source and PD. In this configuration, the light transmitted through the medium is received by a PD in opposite of the LED source. Clearly, in contrast to the sensors with reflection configuration, the application of a transmission sensor is limited by the measurement site. The earlobe and finger are the most common monitoring positions, used with transmission type sensor.

As seen in Fig. , a PPG signal is composed of several components, one being alternating (AC) and the other being constant (DC) offset. When light propagates through biological tissues it is absorbed by a pulsatile arterial blood, venous blood, bones, skin pigments and other surrounding tissues. Therefore, the AC component corresponds to variations in blood volume in synchronization with the heart beat. The DC component arises from the optical signals reflected or transmitted by the tissues and is determined by the tissue structure as well as venous and arterial blood volumes. The DC component shows minor changes with respiration. The basic frequency of the AC component varies with the heart rate and is superimposed on the DC baseline. The PPG signal consists mainly of these components:

1. Arterial blood volumetric changes that reflects cardiac activity. Absorption due to pulsatile arterial blood (AC).

2. Venous blood volume changes that is a slow signal having a modulatory effect on the PPG signal. Absorption due to nonpulsatile arterial blood and venous blood (DC).

3. A DC component due to the optical property of the biological tissue. Absorption due to skin, bone and tissue.

Originally, photoplethysmography employs two LEDs emitting light at different wavelengths, one being red (660 nm), the other being infrared (900–940 nm). These wavelengths are the most suitable for the use in the oxygen saturation (SpO2), since the oxygenated hemoglobin absorbs more infrared light and allows more red light to pass through. However, this works in the opposite for deoxyhemoglobin. Deoxyhemoglobin absorbs more red light and allows infrared light to pass through. As a result, the pulse oximeter needs to have both red and infrared light emitters to estimate the SpO2. However, red and, especially, infrared light penetrates deep into the tissue and for certain applications, such as heart rate measurement, this may result in addition sources of unwanted noise, since the deeper the light goes, the more tissue reflects and scatters it. Various studies showed that the green light penetrates deep enough to sense pulsatile blood variations, however not deep enough for the light to be affected by deeper tissues Lee2013, Matsumura2014. Figure  shows skin penetration depth by light at different wavelengths Bashkatov2005.

Figure 5.2: Optical penetration depth of skin as a function of the wavelength , ranging from 400 nm to 1000 nm Bashkatov2005.

To be effective, the photoplethysmography sensor must be located on the body at a site where the transmitted light can be readily detected. Table  shows PPG measurement sites:

Table 5.1: The list of sites suitable for the measurement of photoplethysmogram for reflection and transmission sensor configurations

[Sorry. Ignored \begin{tablenotes} ... \end{tablenotes}]

### 5.1.2 Waveform of the PPG

The morphology of the PPG waveform differs from subject to subject and depends on various factors starting from the location where and how the PPG sensor is attached and ending with the physiological peculiarities, such as vascular compliance. The pulsatile (AC) component of the PPG signal is comprised of individual pulses, associated with a single cardiac cycle. The formation of typical PPG pulse morphology is divided into two major phases: the anacrotic phase, associated with systole and the rising edge of the pulse and catacrotic phase, associated with diastole and the falling edge of the pulse. The principle of PPG pulse formation is illustrated in Fig. . During the anacrotic phase, the direct pulse wave () propagates from the ventricle along the aorta to the periphery, while during the catacrotic phase the pulse wave reflected from the periphery (), mainly in the lower body, returns back. The sum of and waves results in a PPG pulse with the gab between the two waves called the dicrotic notch. A dicrotic notch, shown in Fig. , is usually seen in young subjects with healthy arteries and is related to the compliance of the arteries.

Figure 5.3: Formation of a PPG pulse waveform (partially based on []).

Due to the advancing age and/or increasing arterial stiffness, the elasticity and damping function gradually degrades. Therefore, both the direct and reflected wave, and , respectively, propagate faster and tend to get closer. The decreasing delay of the returning wave results in an increasing overlap and reduce the gap between the two waves, finally declining the dicrotic notch. Figure  demonstrates the formation of the PPG pulse depending on the age and/or arterial stiffness.

Figure 5.4: Formation of the PPG pulse depending on the age and arterial stiffness: (a) direct and reflected waves, (b) resulting pulse.

Since the PPG waveform reflects the hemodynamics in the vascular system, various heart rhythm irregularities also change the morphology of the PPG signal. Figure  demonstrates the morphology of the PPG waveform during the normal sinus rhythm and various arrhythmias, namely, the premature beats and atrial fibrillation, together with the synchronously recorded ECG signals as the reference:

Figure 5.5: Segments of synchronously recorded ECG and PPG signals during sinus rhythm, premature beats and atrial fibrillation.

During a normal sinus rhythm, the ventricular filling time remains relatively constant as is the cardiac output. However, during arrhythmia (premature beats or atrial fibrillation), beat-to-beat intervals are irregular, resulting in the varying ventricular filling time. An early heart contraction cause ventricle to fill less, thus decreasing cardiac output, resulting in a decrease of the PPG amplitude. On the contrary, during a prolonged interval between the two cardiac cycles, e.g., in the case of compensatory pause, the ventricles are allowed to fill with more blood, thus producing an increase in PPG amplitude.

### 5.1.3 Artifacts in the PPG

It is widely renowned that acquisition of PPG is sensitive and susceptible to various noise sources which introduce signal corruptions, referred to as the artifacts. Artifacts limit the accuracy of the parameter extraction from the PPG signal or even make the extraction impossible, leading to misinterpretations or false alarms, e.g., due to the erroneously calculated heart rate. Figure  shows segments of both the synchronously recorded ECG and partially corrupted PPG signals. Generally, artifacts are induced by the motion of the sensor relative to the skin, altering and affecting paths of the propagating light due to the following reasons:

1. Deformation and movement of both external and inner tissue.

2. Blood movement, unrelated to the cardiac cycle.

3. Alternating distance between skin and sensor.

4. Varying contact pressure between skin and sensor.

5. Ambient light interference.

Figure 5.6: Synchronously recorded segments of: (a) ECG (b) PPG with artifacts.

Other types of artifacts may be induced by the sources other than the sensor movement, of which the most common ones are:

1. Respiratory artifacts, occurring due to the changes in thoracic volume during breathing.

2. Power line interference, i.e., 50/60 Hz depending on the country Elgendi2012.

3. Decrease or absence of PPG amplitude due to dirty or scratched sensor, sensor positioning, irregular heart contractions (ventricular fibrillation), low blood perfusion (caused by low ambient temperatures, hypotension, vascular occlusion, or other pathologies).

The effect of artifacts on the PPG is devastating, since artifacts overlap with the frequency band of the PPG signal. The baseline wandering, e.g., due to respiration is in the frequency range of 0.04-2 Hz, while the motion induced artifacts may occur in the frequency range of 0.1-10 Hz. Therefore, simple filtering techniques such as band-pass filtering can not significantly improve the quality of the corrupted PPG, since these techniques are only suitable for the removal of non-overlapping noises, e.g., baseline wandering (partially) and power line interferences.

Influence of artifacts can be reduced by suitably attaching the sensor to the skin in order to restrict excessive movement as well as positioning it perpendicularly to the skin. The PPG probe should be held securely in place to minimize probe-tissue movement artifacts. Other techniques used to improve the quality of PPG signals rely on digital signal processing. The application of adaptive filtering techniques showed promising results in the removal of the overlapping noises by using accelerometer signal as a motion reference Warren2016, Wijshoff2017. However, neither of previously stated artifact reduction means ensure the acquisition of a good quality PPG signal. Therefore, the automatic signal quality assessment and detection of motion artifacts, especially, their separation from the good quality recordings is highly desirable.

Figure 5.7: (a) Reference ECG signal together with its spectrum bellow, (b) PPG signal with marked temporal features (preceding and current intervals and , respectively) and amplitude features (rising and falling edges and , respectively) and spectral features bellow (here the largest peak correspond to the average heart rate in PPG segment).

### 5.1.4 Parameterization of the PPG

Despite different origins of ECG and PPG signals, one being electrical, the other being mechanical, respectively. Therefore, similar parameters could be derived and calculated solely from the PPG signal, e.g., the intervals between successive heart cycles, referred to as peak-to-peak (PP) intervals. PP intervals are equivalent to the ECG RR intervals, since R wave corresponds to the contraction of ventricles and PPG pulse maxima corresponds to the systole. Figure  shows a number of parameters that could be obtained from the PPG signal. Note that the PPG signal lags behind the ECG signal due to the time required for the pulse wave to propagate after electrical activation of ventricles. Furthermore, the the morphology of the PPG signal is less complex compared to that of ECG signals, which is clearly visible by comparing spectra of ECG and PPG signals. The advantage of a less complex signal morphology is that it allows sampling of the signal using lower sampling frequencies, thus reducing the amount of data and time for preprocessing and processing.

### 5.1.5 Devices and applications of photoplethysmography

Photoplethysmography due to its wearablity, non-invasiveness, low-cost and versatility, has been applied in many different clinical and non-clinical settings. Some possible applications of the photoplethysmography are listed in Table :

Table 5.2: Applications of photoplethysmography in clinical and non-clinical practice

## 5.2 Available PPG-based approaches and strategies for detection of premature ventricular contractions and atrial fibrillation

### 5.2.1 Background of arrhythmia detection using photoplethysmography

Photoplethysmography has been suggested for arrhythmia detection by []. On the contrary to Holter monitors, photoplethysmography–based devices offer a cheaper and a more convenient way for a daily life screening, since no electrodes are needed Allen2007. In contrast to ECG electrodes, the photoplethysmographic sensors are more patient–friendly since the sensor can be attached to a finger Suzuki2009, to be integrated into the ear-phones Wang2007, Tamura2014, implemented in a forehead band Tamura2014, Li2012 or used as a wrist sensor Li2012, Haahr2012, Tamura2014. Therefore, so far photoplethysmography has been considered for the detection of premature beats Suzuki2009, Gil2013, Drijkoningen2014, Polania2015 and the detection of AF using a smartphone’s camera Lewis2011, McManus2013, Lee2013, Chan2016, Freedman2016

### 5.2.2 Available databases of biomedical signals for testing and validation of arrhythmia detectors

Why simulate PPG signals when they can be easily recorded? An important advantage with simulated signals is that they can be annotated by design, thus avoiding the time-consuming manual process which is very costly when annotating day-long signals. In fact, simulated PPG signals can, at least to some extent, compensate for the current lack of annotated, public PPG databases. Such databases are urgently needed to facilitate the ongoing development and testing of PPG-specific AF detectors (due to the lack of guidelines for PPG-based arrhythmia diagnosis, the annotation of arrhythmias in the PPG today have to be based on a simultaneously acquired ECG). Another advantage is that simulated signals allow control of the signal-to-noise ratio, which acquired signals do not—an aspect which is critical to investigate in mHealth applications Steinhubl2016. To the best of our knowledge, only the Physionet MIMIC, MIMIC II and the University of Queensland Vital Signs Dataset (UQVSD) databases have synchronously recorded, but unannotated, PPG and ECG signals Moody1996, Goldberger2000, Saeed2011, Liu2012. Given that Physionet provides many ECG databases with annotated arrhythmias (i.e., MIT–BIH Arrhythmia, MIT–BIH Atrial Fibrillation, MIT–BIH Supraventricular Arrhythmia), these public databases may be employed to produce simulated PPG signals.

Several approaches have been proposed for modeling a single PPG pulse, most of them based on fitting multiple Gaussian waveforms Wang2013, Liu2014. Gaussians have also been combined with the gamma waveform to account for the skewed shape of PPG pulses Huang2014. Yet another approach relies entirely on the log-normal waveform Huotari2011.

While there have been attempts to concatenate individual PPG pulses into a sequence, none of them is intended for modeling arrhythmia. Clifford et al. Clifford2004 proposed a realistic model of blood pressure signals, intended for assessing noise performance of biomedical signal processing techniques. The model by [] is intended for a resource-efficient wireless PPG monitoring system where the received PPG signal is modeled according to the received PPG parameters. The model by [] was developed for tracking of physical activity, to obtain statistics of clinical parameters, and to recover corrupted or missing signal epochs. The modeling of hemodynamics by [] is aimed at investigating the impact of AF on the cardiovascular system.

### 5.2.3 Automatic detection of premature ventricular contractions using photoplethysmography

The study by [] is among the first attempts that have been published on the topic of automatic PPG-based premature beat detection. The algorithm makes use of the peak-to-peak (PP) intervals and pulse amplitude obtained from the PPG signal to distinguish between irregular rhythm resulted in from the arrhythmia and that by the artifact. The goal of this study was to detect the arrhythmic pulses, possessing the comparable detection accuracy to that of the ECG signals, recorded by using the Holter monitor. Wearable wristband type reflection photplethysmography sensor with sensor head worn on the finger was employed to record PPG signal. The integrated 3-axis accelerometer was used to record movement. Since ECG signal was used as a reference, the 2-lead ECG and the wearable photplethysmography sensor were synchronously measured during the night.

Authors analysed the correlation between synchronously measured ECG and PPG signals when the arrhythmic heartbeats occurred. PP intervals obtained from the PPG can be considered equivalent to RR interval obtained from ECG, provided that the physiological state is static. [] noticed that in the case of the irregular RR intervals caused by arrhythmia, the amplitude of PPG pulses also varies and it is important to consider the change of the pulse amplitude due to the irregular pulse when developing the irregular pulse detection algorithm. When the irregular interval is shorter than the normal interval, the amplitude of the irregular pulse is smaller than that of the normal pulse. This is because the duration of ventricular diastole is shorter owing to the shorter RR interval, causing blood volume in the ventricle to decrease, and consequently, decreasing the stroke volume. In contrast, when the irregular interval is longer than the normal interval, the amplitude of the irregular pulse is larger than that of the normal pulse. Irregularity in extracted PP interval series is detected by calculating the ratios of preceding and current PP intervals. Another features used to distinguish between the irregular rhythm and the artifact is defined as AIR (amplitude and interval ratio):

 (5.1)

where are amplitudes of the falling edge, are PP intervals.

In case of an irregular pulse, is almost a constant value. In contrast, during artifacts, vary, since artifacts have no regularity. Threshold values and were determined empirically, using data obtained from three subjects. Therefore, premature beats are detected by employing a condition-based beat classification:

 (5.2)

where = 1.1 and = 0.55 are the threshold values for the interval radio and , respectively.

The results show that the irregular heartbeat detection algorithm can discriminate between pulse wave of irregular heartbeat and pulse wave with an artifact, e.g., body movement. Most of the artifact cases were relate to rolling over during sleep. It was also noticed that the irregular pulse detected by the algorithm is coincident with the irregular heartbeats detected from ECG. However, the addressed limitation of the algorithm is related to irregular pulses with short intervals that could not be detected because their amplitude were too small to detect pulse trigger. Nevertheless, in other cases, the algorithm is claimed to have a sufficiently high specificity and the feasibility to detect irregular heart beats without false alarms due to the artifacts.

In order to test the performance of the algorithm and reveal unaddressed drawbacks, it was implemented and tested with three common cases, namely, the PPG signal with premature beats, the PPG signal with the rhythm of bigeminy, and PPG signal corrupted with artifacts. The case of successfully detected premature beats is demonstrated in Fig. :

Figure 5.8: Signals during premature beats: (a) ECG, (b) PPG, (c) Interval ratios, and (d) Amplitude and interval ratios ().

Figure  shows the synchronously recorded ECG and PPG signals during the transition from sinus rhythm to the rhythm of bigeminy, where every second beat is premature beat.

Figure 5.9: Signals during bigeminy episode: (a) ECG, (b) PPG, (c) Interval ratios, and (d) Amplitude and interval ratios ().

In the case of the ECG signal during bigeminy, both a short preceding and a longer succeeding intervals associated with the premature beat are available. However, in the PPG signal, due to the low cardiac output of the early contractions, the PPG pulse, associated with the premature beat, is absent and the resulting interval is two times as long as the interval between two normal beats. Therefore, the algorithm fails to detect bigeminy in the PPG. This is due to the interval ratios, which were used to detect changes in the intervals. Since the intervals between the adjacent beats in both sinus rhythm and rhythm of bigeminy are of similar length, the ratios does not show any changes, only the transition from sinus rhythm to bigeminy.

As described earlier, the PPG is more prone to artifacts induced by body movement than the ECG signals. [] claim that the algorithm reduces the influence of the body movement, therefore, for the testing purposes the algorithm was applied on the PPG signal, containing artifacts. Figure  shows the performance of the premature beat detector using the PPG signal partially contaminated with the artifacts and containing no premature beats, as seen in the synchronously recorded ECG:

Figure 5.10: Signals in case of artifacts: (a) ECG, (b) PPG, (c) Interval ratios, and (d) Amplitude and interval ratios ().

Another attempt to detect premature beats was performed by []. The study was not directly focused on the detection of premature beats but rather used the detected premature beats to determine whether the PPG-based detection could be used as an alternative to ECG-based detection of heart rate turbulence.

In contrast to [], [] concluded that the inclusion of pulse amplitude features did not improve classification performance significantly. The main reason is that the amplitude features are correlated with the temporal features, since the change in the pulse amplitude is due to the change in peak-to-peak interval, i.e., short interval leads to the reduction of amplitude, while longer interval – to the increase. The classification of PVCs was performed by applying a linear classifier.

The sensitivity/specificity of PVC classification was found to be 90.5/99.9%, with an accuracy of 99.3%, suggesting that classification of PVCs can be reliable performed from the PPG signals. The serious limitation of the algorithm, however, is that the PVCs which occurred within the 5 previous or 20 subsequent beats were excluded from further analysis. This suggests, that frequent PVCs, episodes of begeminy, trigeminy and etc. could not be detected by this approach.

### 5.2.4 Automatic detection of atrial fibrillation using photoplethysmography

To this day, very few photoplethysmogram-based atrial fibrillation detection methods have been developed. The first practical applications of PPG for the AF detection were proposed in McManus2013, Lee2013. These methods make use of the rhythm-based features, derived from the PPG signals. Irregularity of the rhythm is estimated by applying the same basic methodologies used for the ECG derived features, namely, root mean square of the successive difference (), Shannon entropy (), and sample entropy () Tateno2001, Dash2009. The normalized is defined as:

 (5.3)

where is the length of PP intervals and is the :th PP interval in the analysis window of the length , . Here was used for the best AF detection accuracy. The normalization of is performed to account for the various heart rates.

The Shannon entropy is defined as:

 (5.4)

where is the number of bins, and is the number of beats in the :th bin. The best accuracy was provided by using . The detection of AF is based on the simple logical conditions relaying on two statistical criterion, namely the fixed threshold values for and :

 (5.5)

where = 0.115 and = 0.55 are the threshold values for and , respectively, which correspond to the largest area under the ROC curves.

In this study, PPG signals were obtained using a smartphones’ camera on the subjects before (continuous AF) and after undergoing cardioversion (the rhythm is restored to a normal sinus rhythm). However, in order to test the described methodology for other potential use cases, it was implemented and applied to a few different and very common situations, i.e., the PPG signal during normal sinus rhythm, the PPG signal during AF, the PPG signals during ventricular bigeminy, and PPG corrupted with artifacts, which are presented in figures , , , and , respectively. Figure  demonstrates the output of the AF detector when only normal sinus rhythm is present in the PPG segment:

Figure 5.11: An example of AF detector performance on PPG segment during normal sinus rhythm: (a) ECG, (b) PPG, (c) Peak-to-peak intervals in seconds, (d) , (e) .

During the normal sinus rhythm, the intervals between successive beats are of relatively constant, no irregularity is detected and therefore the output of the AF detector remains bellow the detection threshold. However, notable differences between successive beats occur during arrhythmia, such as AF. Figure  shows the performance of the AF detector on the PPG segment during continuous AF:

Figure 5.12: An example of AF detector performance on PPG segment during AF: (a) ECG, (b) PPG, (c) Peak-to-peak intervals in seconds, (d) , (e) .

In this case, the AF was detected successfully. However, in addition to AF, other arrhythmia may also be present, therefore Fig.  shows the performance of the AF detector on PPG containing both sinus rhythm and episodes of the ventricular begiminy:

Figure 5.13: An example of AF detector performance on PPG segment with bigeminy episodes: (a) ECG, (b) PPG, (c) Peak-to-peak intervals in seconds, (d) , (e) .

The bigeminy introduces rhythm irregularity which force and values to raise above the threshold causing false alarms. However, the main source of false alarms when using PPG signals are the artifacts. Authors claim that the use of a smartphones’ camera to record the PPG signal partially bypasses the artifact problem, since during the recording, subjects were in lying positions, the breathing was assisted by the physician, and the recordings per se, were quite short. If subjects were prone to tremor, other potential recording sites were used instead of a finger, e.g., leg or forearm. However, there were no other measures taken to prevent false alarms in case of the artifacts, therefore the performance of the AF detector was also tested on a PPG segment corrupted with the artifacts (see Fig. ):

Figure 5.14: An example of AF detector performance on PPG segment with artifacts: (a) ECG, (b) PPG, (c) Peak-to-peak intervals in seconds, (d) , (e) .

[] claimed that the combination of and shows excellent sensitivity (), specificity (), and accuracy () using only the rhythm-derived features from the PPG signal. The reference for the comparison was the detection of the AF by using a standard 12-lead ECG. However, as the results with PPG signals containing other arrhythmia and arifacts show, the method is only applicable when PPG signals are of good quality and if only two rhythm types are present, namely, the AF and sinus rhythm. Another limitation of this study is due to the fact that and threshold values were obtained from the ECG RR intervals (Physionet MIT–BIH AF and MIT–BIH NSR databases) omitting the peculiarities because of a different origin of ECG and PPG signals. Thus, such approach could not be used for a long-term screening of the AF.

## 5.3 Conclusions of the chapter

1. Photoplethysmography is a low cost, simple and portable technology, found in a wide range of commercially available medical devices for measuring oxygen saturation, heart rate, assessing arterial compliance, and etc. The latest investigations demonstrate great potential for use of photoplethysmography in a detection of cardiac arrhythmias. However, the main challenges concerning the acquisition and analysis of photoplethysmogram signals are the motion-induced artifacts.

2. Currently available photoplethysmogram-based algorithms for the detection of premature beats and atrial fibrillation are not suitable for the ambulatory long-term screening due to the lack of measures taken to reduce the rate of false alarms during occurrence of other arrhythmia, such as bigeminy and especially, signals corruptions, such as artifacts.

3. Databases with synchronously recorded ECG and PPG signals are needed for testing and evaluation of PPG based arrhythmia detection algorithms.

**Chapter 6**

# Proposed methods for PPG modeling and PPG-based arrhythmia detection

## 6.1 Modeling of the PPG during cardiac arrhythmia

This chapter introduces a novel phenomenological model for simulating PPG signals during arrhythmia Solosenko2017. The model uses the RR interval series as input for generating a PPG signal. The model accounts for the presence of premature beats by introducing amplitude and time scale factors which modify pulse width and amplitude, thus making it possible to simulate ectopic beats and certain rhythms such as bigeminy known to cause false alarms in RR interval-based AF detection.

The RR interval series, obtained from an annotated ECG recording, serves as the input to the proposed simulation model, see Fig. . The model consists of two main parts, namely, modeling of a single PPG pulse and concatenation of pulses into a connected signal.

Figure 6.1: Block diagram of the proposed model for simulation of PPG signals.

### 6.1.1 Modeling of a single PPG pulse

A PPG pulse is modeled as a linear combination of three functions—one log-normal waveform and two Gaussians—together accounting for direct and reflected pulse waves Baruch2011. Here, the log-normal function is defined as

 (6.1)

where is time, is a scale parameter, and is a shape parameter. The Gaussian waveform is defined by

 (6.2)

where is a width parameter. Then, the PPG pulse is modeled as a linear combination of weighted, time-shifted, and time-scaled versions of , , and , i.e.,

 (6.3)

where denotes DC offset. For convenience, all model parameters are merged into the vector

 (6.4)

The parameters of the PPG pulse are estimated by nonlinear least squares fitting Coleman1996,

 (6.5)

 (6.6)

where is the vector minimizing the difference between the PPG pulse template and the model PPG pulse . Prior to minimization, each PPG template is normalized to unit amplitude.

Since pulse morphology varies considerably depending on factors such as age and medical condition, a set of template PPG pulses, displayed in Fig. , is employed.

Figure 6.2: Template PPG pulses according to Dawber et al. Dawber1973.

Figure 6.3: Steps required to model PPG signal. (a) ECG with detected R peaks and corresponding RR intervals, (b) modeled systolic and diastolic parts combined into a single pulse, and (c) the resulting, connected PPG signal. Note that the two pulses with lower amplitudes relate to premature beats. Arrows point to pulses associated with R peaks.

### 6.1.2 Contextualization of a single PPG pulse

A PPG pulse is composed of a systolic part and a diastolic part, where the width of each part depends on the adjacent RR intervals. For the :th pulse, two time scale factors are introduced, both inversely proportional to RR intervals,

 (6.7)

 (6.8)

where denotes the RR interval preceding the :th pulse. The threshold determines whether the current beat is premature.

Another factor is the PPG pulse amplitude related to ventricular filling time and, accordingly, to the length of the RR interval. For example, in sinus rhythm, the ventricular filling time does not change much from beat to beat, leading to negligible pulse amplitude variations. On the contrary, a premature beat causes diastole to be shorter, reducing the amplitude of the resulting pulse. The proposed model assumes that the amplitude of the premature pulse changes exponentially. Since a premature beat is followed by a compensatory pause, sufficiently long to fill the ventricles with extra blood, the subsequent pulse will have larger amplitude.

The amplitude of a PPG pulse is assumed to be proportional to , unless the beat is premature when the relationship between the length of the current RR interval and the diastolic period can be characterized by an exponential function Sarnari2009. The pulse amplitude is given by

 (6.9)

where the threshold determines whether the subsequent beat is premature, thus allowing the decrease in amplitude.

The :th PPG pulse, denoted , is put into context by scaling the amplitude of with and the width with either or :

 (6.10)

where is the time for the largest positive peak in . Finally, sampling of is performed by

 (6.11)

where denotes the length of the sampling interval.

Figure 6.4: A model PPG signal composed of Type 1 pulses (cf. Fig.) at SNRs equal to (a) 20 dB, (b) 15 dB, and (c) 10 dB.

### 6.1.3 Modeling of a connected PPG signal

Figure 6.5: Synchronously recorded ECG and PPG signals from the MIMIC database compared to the simulated PPG signals during atrial fibrillation, sinus rhythm with atrial premature beats, and sinus rhythm with ventricular bigeminy. The bottom row shows RR intervals and peak-to-peak (PP) intervals of the real and modeled PPG signals, respectively.

A connected, discrete-time model signal is generated by placing the contextualized PPG pulses at the heartbeat occurrence times , obtained from the RR interval series, and adding noise ,

 (6.12)

where denotes the number of pulses in the connected signal. The steps required to produce a simulated signal are demonstrated in Fig. .

The noise is generated by filtering white noise, where the filter is determined by the spectral properties of motion artifacts extracted from PPG signals in the MIMIC database. Using the above simulation model, a noise-free signal is generated from the RR intervals of the segment with the artifact. The artifact is extracted by cancelling the model signal from the observed signal using a normalized least-mean squares (NLMS) filter. Then, the extracted artifact serves as the desired input to the NLMS filter, whereas white noise is reference input. The filter output is a signal resembling the extracted artifact. The resulting impulse response of the NLMS filter is the used for producing . A connected model signal is displayed for different SNRs in Fig. .

Examples of model and real PPG signals during AF, premature atrial beats, and ventricular bigeminy are presented in Fig. . It is obvious that the model signals are similar to the real ones, also when rhythm disturbances occur. Furthermore, the difference between RR and corresponding peak-to-peak (PP) intervals is observed, especially during the rhythm with ventricular bigeminy, while retaining the similarity between PP intervals in real and model PPGs.

## 6.2 PPG-based detection of premature ventricular contractions

In this chapter, a method that involves PPG pulse power-derived features in addition to the temporal features for the detection of premature ventricular contractions is introduced. An important property of the proposed method is that the temporal features are normalized according to a preceding heart rate, estimated by combining temporal preprocessing and spectral analysis. Hence, differently from the previous studies, this solution allows to detect PVCs even during the episode of bigeminy. In addition, an artifact detector was implemented in order to reduce the number of false alarms.

It is well-known that the alternating part of the PPG is proportional to the peripheral blood volume changes Peper2007. Premature contractions result in a reduced ventricular filling, diminishing the peripheral pulse amplitude Zheng2008. Therefore, the PPG pulses during PVC may become hardly recognizable (Fig.  (a)), or may still have a sufficient amplitude for peak detection (Fig.  (b)). These two types of premature pulses in the PPG are denoted as  and , respectively.

Figure 6.6: Examples of PVC pulse types in PPG together with reference ECG: () PPG pulses during normal sinus rhythm (labelled as ) with a single PVC that is not followed by any observable pulse (labelled as ), () a single PVC characterized by a small pulse amplitude (labelled as ), (), consecutive type  pulses (bigeminy), () bigeminy with both PVC pulse types. In this particular example, ECGs and PPGs were preprocessed with zero-phase band-pass filters having cut-off frequencies of 0.05-150 Hz and 0.4-15 Hz, respectively.

The proposed method for PVC detection and classification exploits temporal (peak-to-peak intervals, PPs) and power-derived (the power ratios, PRs) features, obtained for each PPG pulse. The method is composed of 3 major parts: PPG preprocessing, feature extraction, and classification (see Fig. ).

Figure 6.7: Block diagram of the proposed method. Here is a normal heart rate, PP is a peak-to-peak interval, PR is a power ratio, ANN is an artificial neural network, is a preprocessed PPG, is a PPG with higher frequency components removed.

### 6.2.1 Preprocessing and feature extraction

To minimize high frequency noise and baseline wandering, PPGs are preprocessed by using low-pass and high-pass finite impulse response (FIR) filters with 5 Hz and 0.4 Hz cut-off frequencies, respectively, thus resulting in a signal (Fig.  block 1). These cut-off frequencies correspond to approximal maximal and minimal physiological heart rates. A 12 s sliding analysis window with 50% overlap is used for feature extraction (Fig.  block 2). Positive peaks of the preprocessed PPG are detected by using threshold crossing technique (Fig.  block 3). Then, series of operations are applied (Fig.  block 4) for estimation of a normal heart rate () (see Fig. ).

Figure 6.8: Block diagram of the normal heart rate estimator. Here is a 12 s segment of the preprocessed PPG.

When estimating , it is crucial to reduce the influence of impulse noise, i.e., noise of higher amplitude than PPG, which may be falsely associated to during spectral analysis. First, PPG is clipped in the empirically determined range of of the preprocessed PPG, and smoothed by applying a moving average filter. Then, the 1 derivative of the resulting PPG is calculated. The 1 derivative acts as a high pass filter that emphasizes higher frequency components of the PPG. In addition, the 1 derivative is particularly useful when PPG segments contain bigeminy episodes, which result in nearly 2 times lower PPG pulse rate compared to a normal rhythm (see Fig.  (c)). Next, is estimated by taking the frequency at the maximal amplitude of the power spectral density (PSD) function. Finally, outliers are removed by filtering the array of using a 3 order median filter.

Normally, heart rate is inversely related to PP intervals. However, for a specific PVC type (cf. Fig.  (a) and (c)), the length of PP can be approximately twice the length of the interval between the subsequent PPG pulses occurring during normal rhythm. Therefore, in order to make PPs heart rate independent, PP-related features are normalized before applying them to classifier. One way to normalize PP intervals is to calculate the ratio of the current and the mean values of the intervals Gil2013. However, the former normalization principle is sensitive to erroneously detected PP value, i.e., during bigeminy or artifacts. Hence, PP-related features are normalized (Fig.  block 5) with respect to :

 (6.13)

where is a PP number, is an array of index value of detected positive peaks, is a sampling frequency (Hz), and is a normal heart rate (Hz). Normalized PP intervals are close to 1 during normal heart rhythm, whereas take either lower or higher values during PVCs.

The second high-pass FIR filter is characterized by a variable cut-off frequency (Fig.  block 6), and is employed for the purpose to extract higher frequency components of PPG (from  to 5 Hz). The cut-off frequency is adjusted according to the current value of . Then, the resulting signal is used as a reference input to a pre-whitened recursive least squares (RLS) adaptive filter (Fig.  block 7) Douglas2000. The order and the forgetting factor of RLS filter were set to 10 and 0.999, respectively. Given that PPG pulses during PVCs are composed of lower frequency components compared to normal rhythm, subtraction of higher frequencies produce a signal , which consists solely of premature pulses. Therefore, the amplitude of PVCs is not affected, while the PPG pulses are suppressed considerably during a normal heart rate (see Fig.  (c)).

Figure 6.9: Example of detected PVCs in the PPG: () reference ECG, () preprocessed PPG with PVCs (), () output of the adaptive filter (), () normalized peak-to-peak intervals (PPs), and () power ratios (PRs). The vertical lines in () and () denote the ranges of the normalized PP and PR values, respectively.

The power ratios (PRs) are computed in segments between two adjacent PPG pulses by involving both preprocessed PPG and the signal :

 (6.14)

where is a segment number, is a segment length (total samples in PP interval), is a mean amplitude of samples in , and is a mean amplitude of samples in . Since PPG amplitude is markedly suppressed in normal beats, the power ratios PR take lower values than in PVCs.

### 6.2.2 Classification

Feed-forward artificial neural network (ANN) with either linear or non-linear outputs was investigated for classification of individual PPG pulses (see Fig. ).

Figure 6.10: Block diagram of the ANN-based PPG pulse classifier. Here stands for ANN inputs, are input and hidden layers connecting weights, are biases of hidden neurons, are hidden and output layers connecting weights, are biases of the neurons in the output layer, and are the outputs of the ANN (classes).

Since each individual PPG pulse is described by 3 intervals (preceding, current and subsequent), various interval combinations are feasible, therefore it is reasonable to distinguish many classes (i.e., 10, see Table ) in order to reduce a misclassification rate. These 10 classes (Fig.  block 9) are further grouped into 3 super-classes, denoted by , and , respectively (Fig.  block 10). The full list of classes and super-classes is presented in Table .

Table 6.1: PPG pulse classification into () 10 classes and () 3 super-classes

The number of neurons in a hidden layer of ANN was chosen empirically, and was set to 40. A back-propagation method was used for training Vogl1988. To cope with the overfitting, a small random noise was added to each of the input Piotrowski2013. Both ANN and back-propagation learning method were implemented in Mathworks inc. MATLABTM environment.

### 6.2.3 Artifact detection

Motion and tissue deformation induced artifacts is a crucial issue hindering the development of arrhythmia detectors that are based on the PPG. To reduce the number of false alarms due to falsely detected pulses, an artifact detector is implemented.

The process of artifact detection is illustrated in Fig. . In the analysis window, artifacts are flagged with respect to the ratio, obtained by dividing the clipped PPG by the preprocessed (Fig. (a)). Since the clipped PPG has lower amplitude, the ratio approaches to 0 when artifacts occur. PPG is flagged as an artifact whenever the empirically determined threshold exceeds 0.3. In addition, 4 pulses before and after the artifact are excluded from classification.

Figure 6.11: Example of artifact detection in the PPG: (a) the clipped PPG, (b) the preprocessed PPG, and (c) the ratio of the signals in (a) and (b). Vertical line denotes the ranges of ratio values.

### 6.2.4 Implementation of online premature ventricular contraction detector

The online version of the PVC detector was implemented as the application for the use in Android operating system. A configuration of the algorithm employing PP features, ANN with non-linear outputs, and the blocks 6, 7 and 8 in Fig.  excluded, was selected for the implementation. The PPG is transmitted to the smartphone via Bluetooth connection (see Fig.  in Appendix ). The same PPG signals from the MIMIC database are transmitted via PC by using a National Instruments LabVIEWTM application which reads .mat files and transmits PPG signals in a sample-by-sample fashion. PC and LabVIEWTM application simulates patient wearing a PPG sensor.

## 6.3 PPG-based detection of atrial fibrillation

In this chapter, a photoplethysmography-based method for continuous screening for silent AF is proposed. The proposed detector offers a number of solutions to reduce the false alarm rate, including the blocks of ectopic filtering, bigeminy suppression, sinus arrhythmia suppression, and signal quality evaluation. Moreover, the proposed solutions can be applied to any RR interval analysis based AF detector. The base for the AF detection part is an improved and modified algorithm [].

Block diagram of the PPG-based AF detector is presented in Fig. . The algorithm consists of four main parts, namely, preprocessing, feature extraction, artifact detection and AF detection which are described in detail below.

Figure 6.12: Block diagram of the proposed AF detector.

### 6.3.1 Preprocessing

PPG is mainly composed of lower frequency components, thus higher frequency noise is removed by using a low-pass finite impulse response filter with a cut-off frequency of 5 Hz. Baseline wander is removed with a first order least mean squares adaptive filter Laguna1992.

### 6.3.2 Peak detection

PPG peaks are detected using a peak detector with an adaptive threshold Aboy2005. Threshold is adapted by taking a :th percentile of the PPG samples contained in a 2-s sliding window so as to cover at least one hear cycle. The delay time for the next peak search is adapted by filtering extracted intervals with the third order median filter and multiplying the result with the experimentally determined multiplier . The resulting time series are further referred to as PP intervals.

### 6.3.3 Signal quality index

Artifacts and misdetected pulses are identified via the signal quality index (SQI). The SQI is based on the cross-correlation between the extracted PPG pulse and signal quality-dependant template. Normally, a previous PPG pulse, extracted from the analyzed signal, is used to evaluate the quality of a current PPG pulse. However, if the quality of a previous PPG pulse is low, then the hardcoded pulse template is used instead. The template is resampled to match the number of samples to that of the current pulse. Cross-correlation function is defined by

 (6.15)

where is a current pulse, is a template, is lag, and is a :th pulse. Both a current pulse and template are subject to normalization by subtracting the mean and dividing by standard deviation. The lag at maximal cross-correlation is determined by

 (6.16)

where is a :th lag value. The maximal cross-correlation is found by

 (6.17)

The template is updated by the previous pulse whenever the cross-correlation exceeds 95%, and the lag is within the range of 0.05 s. Template update is performed by

 (6.18)

where is a cross-correlation threshold, and are thresholds of correlation lags between the extracted pulse and template, is the hardcoded template.

Finally, the signal quality index is found by

 (6.19)

where approaches to 1 for a high quality pulse, whereas is much lower for pulses affected by motion artefacts. Figure  illustrates the main steps of signal quality assessment.

Figure 6.13: The steps of signal quality assessment: synchronously recorded (a) reference ECG and (b) PPG signals, (c) template matching, where the vertical lines denote the boundaries of the extracted PPG pulses, (d) cross-correlation between the extracted pulse and template, (e) cross-correlation lags, and (f) the resulting SQI.

### 6.3.4 Ectopic beat filtering

Premature heart contractions may result in irregular pulses or complete absence of the ectopic pulse, thus it is desirable to minimize false-positive rate due to ectopic activity-caused irregularity. We found that a 3-point median filter is useful for rejecting outlier PP intervals due to, e.g., irregular or missed pulses. Higher-order median filters are less beneficial since they smooth pulse series to such a degree that AF episodes with low PP irregularity remain undetected. Median filter is defined by

 (6.20)

where denotes the duration of the :th PP interval in seconds.

Normally AF is associated with increased heart rate, thus the mean RR interval can be employed as a feature in the AF detector, cf. [, ]. Here, the exponential averager is used to track the “trend” in the RR interval series. The exponential averager is defined by

 (6.21)

where () determines the degree of smoothing, and is a saturated linear transfer function, given by

 (6.22)

Limiting of low pulse rates using a saturated linear transfer function is useful for detecting AF episodes of very low pulse rate (60 bpm).

### 6.3.5 Sinus arrhythmia suppression

Regular, but highly variable pulse rates, for example, during sinus arrhythmia, may also cause false-positives []. Sinus arrhythmia is identified by finding a number of turning points in a detection window . For regular pulses takes values close to 0, whereas increases for irregular pulses.

### 6.3.6 PP interval irregularity

In a sliding detection window of length , located at time , the number of all pairwise PP interval combinations differing more than seconds is determined, and normalized with its maximum value , i.e.,

 (6.23)

where is the Heaviside step function. The division by is motivated by the wish to emphasize PP irregularity at higher heart rates. is close to 0 for regular rhythms since the difference between pairs of PP intervals is usually smaller than , whereas approaches 1 during AF.

### 6.3.7 Bigeminy suppression

The episodes of bigeminy might be incorrectly detected as AF when detection relies only on PP intervals. Since premature pulse usually merges with the preceding pulse, bigeminy in PPG signals might take different patterns than those observed in ECG. Therefore, the bigeminy suppression block, originally proposed in [], is modified to account for PPG properties. The bigeminy suppression measure is defined by

 (6.24)

where is an even-valued integer, and are median filtered ratios of successive PP intervals , and median filtered intervals , given by

 (6.25)

 (6.26)

The use of PP interval ratios is motivated by the observation that the original implementation of bigeminy filtering does not work properly due to constant PP interval length. Median filtering is for smoothing the resulting spikes during pulse transition from normal to bigeminy, and vice versa (see Fig. ). For bigeminy and regular pulse, the ratio in () is approximately 1 since and are similar, and thus is approximately 0, see Fig. .

Figure 6.14: The steps to obtain bigeminy suppression measure by processing PP intervals.

### 6.3.8 Signal fusion and detection

Simple signal fusion is employed to produce the decision function ,

 (6.27)

 is identical to , unless exceeds a fixed threshold . Otherwise is equal to .

Figure  illustrates outputs of both PPG-optimized and original AF detectors and together with corresponding intervals for the PPG signals with an AF episode surrounded by ectopic beats, sinus rhythm with the episodes of bigeminy and a segment with artifacts. It is obvious, that during the episode of AF, outputs of both the PPG-optimized and original algorithms exceeds threshold values and , respectively. However, unlike the original algorithm, the output of the PPG-optimized algorithm does not exceed threshold value during the PPG segment with episodes of bigeminy and artifacts, therefore, resulting in no false alarms. It is obvious that median filtering removes the PP intervals related to ectopic pulses so that the AF episode can be correctly detected and false alarms avoided.

Figure 6.15: Intervals and outputs of PPG-optimized () and original () AF detection algorithms together with corresponding detection thresholds and using PPG signals during: (a) atrial fibrillation, (b) bigeminy, and (c) artifacts.

### 6.3.9 110Implementation of online atrial fibrillation detector

The online version of the AF detector was implemented as the application for the use in the Android operating system. As in case with PVC detector, the PPG signal is transmitted to the smartphone via wirless Bluetooth connection (see Fig.  in Appendix ).

## 6.4 110Conclusion of the chapter

1. A phenomenological model for simulating PPG during sinus rhythm and arrhythmias has been developed. The model accepts RR interval series as input for generating simulated PPG signals. The model may be employed for development and assessment of a PPG-based arrhythmia detection algorithms.

2. A PPG-based algorithm for detection of PVCs has been developed. The proposed detector relies on temporal, frequency domain features and artificial neural network classifier for the detection of PVCs. The rate of false alarms is reduced by employing an artifact detector. The algorithm can be implemented for the online PVC detection.

3. A real-time PPG-based algorithm for the detection of AF, relying on an improved and modified low-complexity AF detection algorithm and signal quality assessment, has been proposed. The algorithm employs solutions to reduce the influence of false alarms sources, such as the ectopic beats, bigeminy, sinus arrhythmia and artifacts. The algorithm can be implemented for the online AF detection.

**Chapter 7**

# Performance evaluation of the developed

# methods

## 7.1 Modeling of the PPG during cardiac arrhythmia

### 7.1.1 Data

The proposed model is evaluated on PPG signals from the Physionet MIMIC Database, the University of Queens Vital Sign Database (UQVSD), and the MIT–BIH Atrial Fibrillation Database (AFDB).

ECG and PPG signals in the MIMIC database were originally sampled at 500 Hz and 125 Hz, respectively, both with 12-bit precision. The sampling rate of the PPG was then digitally increased to match that of the ECG. Records with both ECG and PPG signals and varying morphology (56 records in total, see Table  in Appendix) were selected and divided into 60-s segments. Only segments of the ECG and the PPG free of excessive noise and artifacts were included for further analysis. PPGs were preprocessed with a bandpass finite impulse response (FIR) filter with 0.5 and 15 Hz as cut-off frequencies, and scaled to have unit amplitude. Each segment was manually assigned to one of the following three rhythm types: sinus rhythm, sinus rhythm with premature beats, and AF, resulting in 510, 1198, and 377 segments, respectively. For single PPG pulse modeling, 56 pulses of distinctive morphologies, free from noise and artifacts were extracted from one of the 60-s segment and grouped according to pulse types shown in Fig. .

The University of Queensland Vital Signs Dataset contains data recorded during 32 surgical cases from patients who underwent anaesthesia at the Royal Adelaide Hospital (see Table  in Appendix). All signals in the UQVSD were recorded at 10 ms temporal resolution. Each case contains from 2 to 30 records of 10-min with a varying quality of both ECG and PPG signals. Only 60-s segments free of excessive noise in both the ECG and the PPG were selected: 341 segments with sinus rhythm, 78 segments of sinus rhythm with premature beats, and 33 segments with AF. For single PPG pulse modeling, 32 pulses of distinctive morphologies, free from noise and artifacts, were extracted and grouped according to the pulse types shown in Fig. . The ECG signals in AFDB were sampled at 250 Hz with 12-bit precision. The annotated RR interval series are used to generate model PPG signals.

### 7.1.2 AF detection

The significance of the proposed PPG model is studied in terms of AF detection performance. A low-complexity AF detector based on RR interval information is studied, designed to detect brief AF episodes ( 30 s); the detector is described in detail in Petrenas2015. Important features of the detector is the short sliding detection window (8 beats) and the low-power consumption thanks to few arithmetical operations, making the detector particularly well-suited for implementation in a wearable system. By controlling the cut-off frequency of the exponential trend filters, the detector can be tuned to detect AF episodes as short as 8 beats.

The model PPG signal subject to AF detection is further preprocessed using an FIR bandpass filter with cut-off frequencies at 0.5 and 5 Hz to remove noise components not overlapping with the spectrum of the PPG signal. Then, a real-time peak detector, based on Aboy2005, is applied to the preprocessed signal so that the intervals between successive pulses can be determined and used as input to the AF detector. In the peak detector, an adaptive threshold is used related to the 55:th percentile of the samples in a 2-s sliding window.

### 7.1.3 Performance evaluation

A number of parameter values need to be set in the simulation model. For a single PPG pulse, the initial values of the involved parameters are, prior to fitting, manually defined within reasonable ranges such that the direct wave of the pulse precedes the two reflection waves.

Therefore, the interval ratio thresholds and in ()-() are set to 0.8 and 1.4, respectively. Suitable threshold values are investigated in Results (see Fig. ).

The sampling interval in () is set to , where is the duration of a time interval used to obtain parameters for the model PPG pulses, and is the sampling rate, e.g., 500 Hz for MIMIC signals.

The adequacy of the proposed PPG model is evaluated by comparison to PPGs from the MIMIC and UQVSD databases. The root mean square error () between real and model signals is the primary measure to evaluate performance, defined by

 (7.1)

where is the total number of segments, is segment number, is total number of samples in a segment, is sample number, and is the real signal. Prior to computing , both real and modeled signals are normalized to unit amplitude. To avoid issues related to signal misalignment, crosscorrelation was used to align the two involved signals.

In order to test the AF detector, all 25 annotated RR interval series from AFDB database have been used. Since the morphology of PPG pulses depends on many factors, including age and medical condition, the evaluation is performed with PPGs modeled by utilizing the five PPG pulse types in Fig. ; thus, a total of 125 model PPGs are analyzed. The performance of the peak detector and the AF detector are evaluated separately in terms of precision (), sensitivity () and specificity (), respectively, at various SNRs ranging from 0 to 30 dB. Precision is defined as

 (7.2)

where is a number of correctly detected peaks and is a number of falsely detected peaks. Accuracy is given by

 (7.3)

where is a number of beats correctly identified as AF, is a number of beats that are falsely detected as AF.

 (7.4)

where is a number of beats correctly identified as non-AF, is a number of beats, falsely detected as non-AF.

To extract the artifact from the real PPG segment, the NLMS adaptation step size = 1e-3 and filter order 20 was used. The impulse response of an extracted artifact was determined by setting the values for the adaptation step size and filter order to 1e-7 and 200, respectively. This allows for slower adaptation and a larger number of coefficients for capturing the impulse response of the artifact.

### 7.1.4 Results

#### Modeling of single PPG pulses.

The proposed PPG pulse model was compared with the relative models based on gamma and two Gaussian waveforms Huang2014, three log-normal waveforms Huotari2011, and three Gaussian waveforms Wang2013, Liu2014 (see Fig. ). The initial set of pulse fitting parameters are provided in Table  (see Appendix ).

Figure 7.1: Examples of model PPG pulses. The top row shows PPG pulses obtained by combining log-normal and Gaussian waveforms, the second row shows PPG pulse obtained on the basis of gamma and Gaussian waveforms, the third row shows log-normal waveform-based approach and fourth row shows PPG pulses modeled by using Gaussian waveforms. The bottom row shows residuals between templates and model PPG pulses.

The top chart in Fig.  shows the average RMS errors that result from using different PPG pulse models, together with 56 PPG pulses from the MIMIC database (see table  in Appendix  for details), grouped into 3 PPG pulse types; types 2 and 3 bis pulses were not present in the database. The smallest error was obtained for the log-normal waveform combined with two Gaussians. The middle chart in Fig.  shows the average RMS errors that result from using different PPG pulse models, together with 32 PPG pulses from the UQVSD database (see table  in Appendix  for details), also grouped into 3 PPG pulse types; types 2 and 3 bis pulses were not present in the database. The largest error was obtained for the model with three Gaussians, while the smallest error for Type 3 and Type 4 pulses was obtained for the log-normal waveform combined with two Gaussians. The bottom chart in Fig.  shows the RMS errors obtained from the five different PPG pulse types shown in Fig. . A similar error was obtained for the log-normal waveform combined with two Gaussians and for the gamma waveform combined with two Gaussians, while the largest error was obtained for the model with three Gaussians.

Figure 7.2: From top to bottom. The RMS error for 56 normalized PPG pulses (3–Type 1, 40–Type 3, and 13–Type 4) from the MIMIC database, the RMS error for 32 normalized PPG pulses (3–Type 1, 20–Type 3, and 9–Type 4) from the UQVSD database, and the RMS error for 5 normalized single PPG pulse types (see Fig. ) using different modeling approaches: (a) log-normal and Gaussian, (b) gamma and Gaussian, (c) log-normal, (d) Gaussian.

#### Modeling of connected PPG signals.

Figure  shows RMS error between modeled and real PPG signals as a function of and thresholds, used in ()-(()). The results suggest that suitable values for and are 0.8 and 1.4, respectively. The increase in RMS error for 0.8 is due the rules in () and (), applying to beats associated with small interval variation but which are not premature. The threshold ensures that the ratio of a compensatory pause and premature is associated only with a premature beat when determining the pulse amplitude in () since, in cases when is a compensatory pause and is a normal interval, the ratio may also be below 0.8 and, accordingly, falsely associated with a premature pulse. Therefore, larger threshold than 1.4 leads to an increase in the RMS error due to that premature beats are associated with normal beats. As expected, and have no effect during sinus rhythm since the difference between successive intervals is insignificant.

Figure 7.3: The RMS error between 1-min connected model signals and real PPG signals as a function of the thresholds (a) , (b) in ()-(). Dashed horizontal lines show ratio thresholds for various rhythm types: atrial fibrillation (AF), sinus rhythm with premature beats (PB), and sinus rhythm (SR).

Figure  shows that the lowest RMS error is obtained for PPGs with sinus rhythm and sinus rhythm with premature beats, whereas increases to 0.1 for AF.

Figure 7.4: The RMS error for 1-min continuous PPG signals with (a) atrial fibrillation, (b) sinus rhythm with premature beats, and (c) sinus rhythm. PPG signals are simulated using log-normal and Gaussian pulse modeling approach.

Figure  presents the precision () of the peak detector and both sensitivity () and specificity () of the AF detector as a function of SNR for the five pulse types. It is obvious that detection performance of both peak and AF detectors drops rather quickly below a certain SNR which is strongly dependent on pulse type. Signals composed of Type 1 pulses cause the detection accuracy to drop at a higher SNR than do the other four types of pulses. The increase in at low SNRs is due to detection of extra random noise-induced peaks, resulting in the irregular intervals, causing the AF detector to produce false alarms.

Figure 7.5: (a) Precision of peak detection, (b) sensitivity of AF detection and (c) specificity of AF detection. The PPG signal, corresponding to the SNR at a precision of = 95%, is displayed above the corresponding curve. The sensitivity and specificity resulting from RR-based detection in AFDB (97.1% and 98.3%, respectively) are displayed as horizontal lines.

### 7.1.5 Discussion

The aim of this work is to develop a phenomenological model for simulating PPG signals with paroxysmal AF. With the emerging technologies, capable of acquiring PPG (wristbands with integrated PPG sensors, smartphone’s camera), there is still a lack of algorithms which could provide diagnostic information, i.e., detect arrhythmic episodes. The lack of annotated PPG databases with arrhythmic episodes is major limitation that hinders the development of such algorithms.

An important advantage of the proposed model for PPG signals is that annotated ECG databases with AF episodes, e.g., MIT–BIH Arrhythmia, MIT–BIH Atrial Fibrillation, Long Term AF database, or generators of RR interval series, e.g., McSharry2003, Lian2007, can be used for generating annotated PPG signals—a principle which makes it possible to compare the performance of a PPG-based detector to that of an ECG-based detector. Since the ECG and PPG signals have different origin, i.e., electrical and hemodynamic, their properties are quite different. For example, the PPG pulse related to a premature beat may not be observable, leading to that the peak-to-peak interval is approximately twice as long as is the corresponding RR interval (see Fig.). Therefore, it is desirable that PPG-based AF detectors are developed and evaluated on PPG signals, rather than on ECG signals Lee2013, so that PPG-specific changes in morphology are taken into account.

Various approaches to simulating hemodynamic signals have been proposed, however, none of them have been directly intended for simulation of arrhythmia Clifford2004, Nabar2011, Martin-Martinez2013, Scarsoglio2014. Therefore, an important aim of the present study was to develop a simulator accounting for PPG morphology during AF and premature beats, as well as transitions from sinus rhythm to AF, or vice versa.

This study proposes a combination of a log-normal and two Gaussian functions for modeling different types of PPG pulses. However, other approaches may be considered since negligible differences are observed in PPG sequences generated by different models, therefore making no significant impact on the morphology of the simulated signals, and no influence on the AF detection performance. While the Hermite functions, originally proposed for modeling QRS complexes Sornmo1981, are well-suited for simulating subtle changes in the PPG, i.e., dicrotic notch, they are less well-suited for modeling the reflected blood volume waves due to negative polarity; therefore, these functions were not further pursued.

Modeling of PPG pulse amplitude has received little, if any, attention in the literature. Since the amplitude depends on numerous factors such as age, arterial compliance, and permeability AllenMurray2003, we have, for the sake of simplicity, assumed that the pulse amplitude is inversely proportional to the length of the RR interval. Given that the simulator has been developed for modeling the PPG during AF, the model does not account for amplitude modulation induced by respiration, nor for modulation of pulse width. Therefore, the simulation model is not suitable for evaluating the performance of methods which derive the respiratory rate from PPG, e.g., the one in Lazaro2013.

The performance of the AF detector is heavily dependent on the accuracy of the PPG pulse detector since the series with peak-to-peak intervals serves as the input to the AF detector: the number of false positives increases considerably at lower SNRs due to incorrect peak detection. The results in Fig.  show that PPG signals composed of Type 1 pulses are particularly vulnerable to noise as the risk to falsely detect the dicrotic pulse as a systolic peak increases.

The PPG is much more prone to noise and artifacts than the ECG, therefore the synchronously recorded ECG is indispensable for high-precision annotation of the PPG. Therefore, the MIMIC Moody1996 and MIMIC II Saeed2011 databases are usually applied for developing and testing PPG-based algorithms. Nevertheless, MIMIC and MIMIC II databases are unannotated, and would require much time to manually annotate.

The idea to use an annotated ECG database as the basis for simulation of PPG signals may also be considered when other physiological signals are of interest to model, e.g., impedance plethysmography or continuous arterial blood pressure. The proposed simulator may also be explored for reconstructing noise-corrupted PPG signals when a synchronously recorded ECG is available or for other noise cleaning approaches such as Banerjee2015.

A limitation of the present study is that simulator performance was not investigated on other types of arrhythmias such as atrial flutter or supraventricular tachycardia since these are lacking in the MIMIC database. Although such arrhythmias may be present in the comprehensive MIMIC II database, signals are generally of lower quality: lower sampling rate, artifacts, and missing signals. The other limitation is that the model is not tested on a PPG-specific AF detector. The development of PPG-specific AF detectors is highly needed, hopefully prompted by the present model PPG signals.

## 7.2 PPG-based detection of premature ventricular contractions

### 7.2.1 Data

#### Clinical signals.

The algorithm was developed on 18 PPGs (training set), sampled at 125 Hz, which were taken from the PhysioNet MIMIC II database Goldberger2000, Saeed2011. Twenty-five 1-2 h PPGs, sampled at 250 Hz (the MIMIC database Moody1996), and 1 signal sampled at 250 Hz of 100 min (recorded in Kaunas Biomedical Engineering Institute, labelled as BMEI) were used for testing. To reduce the errors that may occur during feature extraction, all signals were resampled to 500 Hz.

PVCs in the PPG were annotated with respect to a synchronously recorded reference ECG. At first, PVCs in the ECG were detected by using an automated RR interval detection algorithm Benitez2001. Then, RR intervals were used for manual evaluation of ECG morphology to ensure that the particular beat is PVC. Finally, PVC-related PPG pulses were labelled as or according to the previously described procedure. The remaining PPG pulses were assigned to normal .

Since the signals in both databases (MIMIC and MIMIC II) contain severe signal corruptions or various pathologies, several of them were excluded from the study. The criteria for discarding the signals was the absence of usable information in either ECG or PPG, therefore resulting in difficulties to correctly annotate the signals. The list of the test signals is presented in Table .

Table 7.1: Test PPGs obtained from the MIMIC database (No. 1-25) and recorded in KTU BME institute (No. 26)

#### Simulated signals.

Simulated PPG signals are produced by applying the PPG model proposed in Solosenko2017. Since the PPG model accepts RR interval series as an input, the RR interval series generator is used to supply them McSharry2003. Generator of RR interval series is capable of simulating both the RR series during the normal sinus rhythm and during cardiac ectopy at various heart rates. Settings used for generating the RR interval series are presented in Table .

Table 7.2: Parameter settings used in RR interval generator

### 7.2.2 Performance evaluation

The performance of the method was evaluated in terms of sensitivity (), specificity () and accuracy (). Due to the a considerable difference in a number of normal pulses and PVCs, the Matthews correlation coefficient was employed as an additional performance measure () Gorodkin2004.

The method was tested by using ANN with either linear and non-linear outputs. The full feature set (3 PP and 3 PR) was applied for training the ANN. In addition, the performance was also tested with a reduced feature set, consisting of just 3 PP inputs. Since, the weights in the ANN are initialized randomly, the training process has been repeated 3 times, and then the averaged performance values were taken as the overall performance measure.

It should be noted that the initial testing was carried out without involving artifact detection. Then, both the best performing, and the most computationally efficient (with PP features, linear outputs, and the blocks 6, 7 and 8 excluded in Fig. ) configurations were used for a repeated testing but with the artifact detector involved.

### 7.2.3 Results

#### Clinical signals.

The results on clinical signals are presented in Tables –. Table  shows that the performance of ANN does not depend on the type of neurons in the output layer, although slightly better results are obtained when an ANN with the linear outputs is used. On the other hand, ANN that employs only PP feature set is associated with a higher accuracy when non-linear outputs are used (Table ).

Table 7.3: The classification results obtained using both PP and PR features as an input to ANN: () performance measures, () confusion matrices.

Table 7.4: The classification results obtained using solely PP-based features: () performance measures, () confusion matrices.

The ANN with non-linear outputs and full feature set was further reinvestigated but with the artifact detector included. The inclusion of the artifact detector allowed to reduce a number of false positives by approximately 60%. Thus, the for PVC types  and  increased from 99.6 / 99.8% to 99.9 / 99.9%, respectively. However, the inclusion of the artifact detector resulted in a slight decrease in from 94.2 / 93.1% to 93.2 / 92.4%, respectively (Table ). The decrease in sensitivity can be explained by the fact that some of premature pulses have similar morphology to artifacts, and therefore have been removed from further analysis.

Table 7.5: The classification results obtained using non-linear output ANN classifier, both PP and PR features and artifact detector: () performance measures, () confusion matrices.

Table 7.6: The classification results obtained using linear output ANN, PP features and artifact detector: () performance measures, () confusion matrices.

The most computationally efficient configuration is associated with a slightly worse performance compared to the best performing configuration (see Tables  and ). By combining this configuration with the artifact detector, a number of false positives decreased by approximately 63% compared to that without the artifact detector. Moreover, for the PVC type increased from 99.6% to 99.9%. In contrast, for PVC type remained unchanged. According to previous explanation, a slight decrease in is observed for both PVC pulse types, i.e., from 90.5 / 84.0% to 89.5 / 83.2% for and , respectively.

#### Online version with simulated signals.

Figure  presents PVC detection results obtained on simulated PPG signal database at various s ranging from 0 to 30 dB.

Figure 7.6: PVC detection sensitivity () and specificity () as a function of on simulated PPG signals with five PPG pulse types and at different heart rates: (a) 60 bpm, (b) 120 bpm, (c) 180 bpm, and (d) 240 bpm.

Here, algorithm configuration relaying on PP intervals and ANN with non-linear output was used as a compromise between detection sensitivity, specificity and algorithm complexity. The results show that in most cases, PVCs can be reliably detected up until 20 dB at 60 bpm with sensitivity and specificity as high as 94.43.1% and 99.980.01%, respectively. At higher heart rates, ranging 120-240 bpm, PVCs can be reliably detected at as low as 10 dB. In this case, mean sensitivity and specificity values for all pulse types are 96.60.9% and 99.060.6%, respectively. At 0 dB , a mean specificity of 91.91.6% is obtained. The performance drop at normal heart rate is explained by the fact that the spectrum of the noise applied is in lower frequency ranges and distorts fundamental components of the PPG signal more than in 180-240 bpm range.

### 7.2.4 Discussion

The goal of this work was to develop a method for detection of premature ventricular contractions by relying solely on photoplethysmography signal analysis. Our first attempt to detect premature contractions by using PPG was presented in an earlier study Solosenko2013. Besides that the pilot study was performed on the basis of just 9 PPG signals, the previous algorithm, in contrast to the proposed, had limited capabilities of detecting successive premature pulses such as bigeminy.

In contrast to ECG, the PPG can be acquired in a single spot of the body, let alone the fact that no adhesive electrodes are required. Considering these points, PPG-based arrhythmia detection is an attractive solution for both short-term screening and long-term arrhythmia monitoring when unobtrusiveness for the user is of special importance.

The proposed PVC detector, thanks to the blocks of adaptive feature extraction and artifact detection, allowed to achieve better performance than that obtained by []. Even though, [] excluded PVCs that had occurred within 5 previous or 20 subsequent beats, our method was more accurate (99.8 vs. 99.3%).

The study revealed that the main challenge is to distinguish PVCs from artifacts, since the distorted PPG pulse can be erroneously assigned to a class of premature beat. Thus is, high amplitude artifacts may usually distort a group of nearby pulses and introduce residual distortions in a shape of further pulses. Nevertheless, even the simplified configuration of the algorithm showed sufficient performance to detect PVCs in artifact-distorted PPGs (see Table  (a)). Therefore, the simplified (computationally efficient) configuration can be considered for the implementation in a mobile device.

Although the algorithm shows nearly perfect specificity (99.9%), the specificity can be further improved by computing PRs in several discrete ranges of each PP, rather than obtaining PRs in the entire PP interval. Additional improvement in specificity may be achieved by upgrading an artifact detector, since the current artifact detector is effective only in cases when artifacts have higher amplitude than a normal PPG pulse.

In this study, high-pass and low-pass FIR filters were used to pre-process the PPG. However, more advanced signal processing techniques can be employed either to eliminate PPG distortions, such as baseline wandering Laguna1992, Wang2014, or to assess PPG quality Patterson2011, Li2012a. Initial tests showed that a single-layer perceptron classifier does not converge during training, owing to the fact that the PPG features used in the present study are not linearly separable. Hence, a multi-layer perceptron (i.e., ANN) was chosen due to its universal characteristics and ability to approximate linear and non-linear functions. In addition, the performance of PPG pulse classification largely depends on an estimated normal heart rate (parameter ) which influences the normalization process.

The presented study has several limitations. Firstly, the signals have not been annotated by the medical experts. Secondly, the method has not been tested on the signals recorded during active motion, such as walking and jogging. Finally, for some rare PVC types (e.g., interpolated PVCs) Reilly1992, PVCs can not be detected by the algorithm because PPG is not enough sensitive to hemodynamic changes during such cardiac events.

## 7.3 PPG-based detection of atrial fibrillation

### 7.3.1 Dataset and performance evaluation

#### Simulated signals.

The algorithm was developed on the Long Term Atrial Fibrillation Database (LTAFDB) Petrutiu2007, Goldberger2000. LTAFDB is composed of 84 ECG recordings from patients with paroxysmal or persistent AF, most recordings with a 24-h duration. The entire database consists of nearly 9 million beats of which 59% occur during AF.

The MIT–BIH Atrial Fibrillation Database (AFDB) Moody1983, Goldberger2000, the MIT–BIH Arrhythmia Database (MITDB) Goldberger2000 and the MIT–BIH Normal Sinus Rhythm Database (NSRDB) Goldberger2000 were used for the performance evaluation. The AFDB database includes 25 AF recordings of approximately 10-h duration, and contains in total more than 1 million beats, of which 43% occur during AF. The MITDB consists of 48 half-hour ECG recordings with a total of approximately 109000 beats. The NSRDB contains 18 ECG recordings of approximately 24-h duration, with a total of almost 2 million beats. Since no significant arrhythmias are present, it is well-suited for evaluation of detector specificity.

Simulated PPG signals for the PPG-based AF detector evaluation were generated by applying the RR interval series with annotations from the LTAFDB and AFDB to the input of the PPG signal simulator proposed in Solosenko2017.

#### Clinical signals.

Clinical dataset was collected from signals recorded at Kulautuva Rehabilitation Hospital of Kaunas Clinics, Lithuania. Two groups of participants were involved at Kulautuva Rehabilitation Hospital of Kaunas Clinics, Lithuania. The first group consisted of 15 patients with AF, 72.9 8.9 years old, with body-mass index 28.3 5.9 kg/m, total monitoring time 316.2 hours (21 3.8 hours per patient). The second group consisted of 19 patients without AF, 67.5 10 years old, with body-mass index 28 5 kg/m, total monitoring time 411.1 hours (21.6 3.1 hours per patient). Signal recording was approved by Kaunas Region Biomedical Research Ethics Committee (No. BE-2-20).

#### Performance measures.

The performance was investigated in terms of sensitivity (), specificity (), accuracy () and Matthews correlation coefficient (). Sensitivity is defined by the number of correctly detected AF beats divided by the total number of AF beats, whereas specificity is defined by the number of correctly detected non-AF beats divided by the total number of non-AF beats. Accuracy is defined as a ratio of correctly detected both AF and non-AF beats with a total number of beats. All other types of rhythm, including atrial flutter, were labeled as non-AF.

### 7.3.2 Results

#### Parameter settings

Figure  displays the ROC curves of the original and PPG-optimized algorithms with LTAFDB. The detection threshold was changed from the original value of 0.725 to 0.630. As in the previous study, the threshold value was chosen at the point of the ROC curve where both sensitivity and specificity on the LTAFDB were equal, i.e., 95%.

Figure 7.7: ROC curves of both the original and PPG-optimized AF detectors.

Figure  shows AF detection performance as a function of peak detection threshold percentile. The highest AF detection accuracy is in the range between 55:th and 65:th percentiles.

Figure 7.8: AF detection accuracy on peak detection percentile with different PPG pulse types.

Figure  shows peak detection performance as a function of peak detection interval multiplier. The highest AF detection accuracy is obtained at = 0.45.

Figure 7.9: AF detection accuracy on peak detection interval multiplier with different PPG pulse types.

Figure  shows PPG-based AF detection algorithm performance on SQI threshold. Threshold was determined by using simulated PPG signal generated using RR intervals from LTAFDB. The AF detection does not change up until the correlation threshold value =0.7, when positive and negative correlation lags and are set to 0.35 ms, respectively.

Figure 7.10: AF detection accuracy () as a function of the SQI threshold and the type of the PPG pulse.

The remaining parameters were kept the same as in the original AF detector: , , , and .

#### Results with ECG RR intervals.

Table  presents the performance of the PPG-optimized AF detection part on the ECG RR interval series from various public databases. The results show that modifications and improvements does not degrade the performance of the detector on the RR interval series from AFDB ( = 97.1% and = 98.4%), however substantial improvement in specificity is noticed on MIDTB and NSRDB databases, 91.3% and 99.2%, respectively.

Table 7.7: Sensitivity (), specificity (), accuracy (), and Mathews correlation coefficient () of the PPG-optimized and original AF detectors, evaluated on RR interval series from the MIT–BIH Atrial Fibrillation (AFDB), MIT–BIH Arrhythmia (MITDB), and MIT–BIH Normal Sinus Rhythm (NSRDB) databases.

#### Detection on simulated database.

Figure  shows the results of both the proposed and original algorithms at various SNR levels, ranging from 0 to 30dB for five PPG pulse are shown. The proposed algorithm retains high specificity of nearly 100% even at SNR values in the range of 0–10dB, while the specificity of the original algorithm declines starting from the SNR value of 10dB.

Figure 7.11: Sensitivity (), specificity () of: (a) proposed and (b) original RR interval-based AF detection algorithms at various SNR values and for different PPG pulse types.

#### Detection on clinical database.

Figure  shows the performance of the algorithm using real PPG signals at different values of correlation threshold ranging from 0.4 to 0.8%. As in case with simulated PPG signals, the AF detection is based on triggering the AF detection part of the algorithm only when no artifacts are detected, e.g., and vice versa. Compared to the method based on the acceleration data, resulting in up to 65.4 5.7% of motion-free data, = 99.9%, and = 91.5%, the proposed method at threshold =0.7 results in the = 69.42%, and = 99.76%. The percentage of informative signal and can be considerably increased by lowering SQI threshold , however with the expense of reduced , which is undesirable in long-term monitoring applications due to a large number of false-positives (Fig.  c).

Figure 7.12: Detection performance on clinical PPG database for different SQI thresholds: (a) sensitivity on PPG signals with persistent AF, (b) specificity on PPG signals with no AF, and (c) the average number of false-positives per day.

### 7.3.3 Discussion

The proposed algorithm for AF screening is developed having high specificity at low SNRs in mind.

Various studies have stated that cardiac event recorders are prone to false alarms due to ectopic beats, since they share similar symptoms as AF. For example, a study of 48 participants (50% with AF) showed that using external loop recorder 3100 BT by Vitaphone (3100 BT, Vitaphone, Mannheim, Germany) each patient in sinus rhythm on average had more than 5 false-positive ECG recordings []. Comparable performance of this device was reported in another study, where 2923 ECG events were collected in 108 patients []. Roughly 1200 detected events were classified as AF by the automatic algorithm, however, only 56 were confirmed to be AF after manual revision.

For screening in the community or for personal use, a drop in sensitivity may be a necessary trade-off to achieve very high specificity. This is particularly important if large numbers of people are screened or when multiple recordings are requested in each person, as might be the case with a PPG app. In this situation even small reductions in specificity could lead to very large numbers of false-positive results, which would require verification with a separate ECG Freedman2016. Study by [] showed that even a commercial ECG-based AliveCor system composed of the ECG recording device and a mobile application has a relatively low sensitivity (55%) at a cost of high specificity. It was made intentionally in order to decrease the number of false alarms, especially when a large population is monitored. Moreover as opposed to ECG, no diagnosis could be made out of PPG signals, therefore high specificity in PPG-based AF detectors is of the utmost importance since even a small decrease in specificity may produce a large number of false alarms Freedman2016.

Currently used ECG-based screening devices are developed to have high sensitivity. This is due to short recording time and ability to confirm diagnosis in ECG recordings by physician. On the other hand, PPG-based continuous screening device would have a different purpose, because currently there are no clinical guidelines on how to interpret arrhythmias in PPG. Thus the device should have high specificity to reduce the number of false alarms as much as possible. If AF is detected by the PPG-based device then standard techniques should be prescribed, i.e., Holter monitoring. Such approach would allow to implement low-price mass-screening of target population.

When developing PPG-based AF detection algorithms peculiarities of PPG signals have to be taken into account. Other authors applied ECG-based AF detection methods on PPG signals without any specific modifications and adaptations and nevertheless they do work, there are differences between ECG and PPG derived features, particularly during arrhythmic events.

Nevertheless accelerometer can provide information on motion, there are certain activities which may not involve motion as such, e.g., curling fingers into the palm, which is sufficient to compromise the quality of PPG signal due to the movement of the internal tissues.

The modifications of the ECG RR interval-based AF detection algorithm not only accounts for differences between PPG and ECG derived features but also improved AF detection accuracy on ECG signals.

In order to improve sensitivity in a long-term PPG-based AF monitoring without compromising specificity, the quality of the recorded signal has to be improved.

## 7.4 Conclusions of the chapter

1. A phenomenological model for simulating PPG signals during AF, as well as other regular and irregular rhythms, is introduced. In quantitative terms, the simulated signals bear close resemblance to a wide range of signals taken from databases. The possibility to simulate connected PPG signals, composed of different types of PPG pulses at different SNRs, is valuable when developing and testing PPG-based AF detectors.

2. A photoplethysmography-based method for detection of premature ventricular contractions has been developed. Considering its high performance, the proposed PVC detector is expected to have both a non-clinical (e.g., sleep monitoring) and clinical (e.g., in hemodialysis procedures) relevance when moderate physical activity is involved.

3. The present study shows that the proposed PPG signal-based AF detection algorithm offers both good accuracy at moderate SNR levels and excellent specificity at low SNR levels.

**Chapter 8**

# Conclusions

1. The increase in arrhythmia prevalence is due to the aging population, usually associated with cardiovascular diseases, lifestyle and constantly improving ability to suspect and diagnose arrhythmia. Currently, there are various strategies and equipment available for the arrhythmia detection, however most of them are electrocardiogram-based, requiring not less then two electrodes attached to the body or held-held for either long-term or intermediate monitoring, respectively. New, more convenient and cost-effective approaches, employing alternative signals, e.g., photoplethysmogram, are being developed and investigated. However, to reduce the influence of motion induced artifacts on arrhythmia detection specificity, such approaches are only used for short recordings, e.g., by attaching finger to the smartphone camera. Therefore, signal processing methods and algorithms for a long-term arrhythmia screening in photoplethymogram signals are required.

2. There is a lack of annotated databases for testing of photoplethysmogram-based arrhythmia detection algorithms. Therefore, a photoplethysmogram model capable of simulating both normal rhythm and various types of arrhythmia, namely the premature contractions and atrial fibrillation has been developed. The model makes use of a rhythm-based information obtained either from annotated electrocardiogram signals or rhythm simulators to generate simulated photoplethysmogram signals. Results show that simulated signals visually resemble real photoplethysmogram signals with the root mean square error between both normalized simulated and real signals not exceeding 0.1. Currently this is the only photoplethysmogram model intended for the arrhythmia simulation so far. The model is well-suited for development and assessment of the photoplethysmogram-based arrhythmia detection algorithms.

3. The algorithm for detection of premature ventricular contractions relying solely on photoplethysmogram-based feature analysis has been developed. Characteristics of the proposed algorithm such as the normalization of extracted rhythm-based features according to an estimated normal sinus rhythm, false alarm suppression with artifact detection and the use of neural network classifier for beat classification into normal and premature allow detection of both single premature ventricular contractions and the rhythm of bigeminy. Compared to known algorithms, the proposed one shows substantial performance improvement, e.g., =94.43.1% and =99.980.01% with simulated signals and up to =92.8% and =99.9% on clinical signals, respectively, and could be used for a continuous ambulatory screening of premature ventricular contractions. The online version is implemented as an application for Android OS, making it is suitable for wearable systems such as PPG-capable smartwatches or smartphones.

4. The photoplethysmogram-based method combining heart rhythm analysis and signal quality assessment algorithms for a reliable atrial fibrillation detection has been developed. The detection part relies on a modified and improved low-complexity atrial fibrillation detector, adapted for the photoplethysmogram-based features. The photoplethysmogram quality assessment part employs correlation technique for distinguishing photoplethsmogram pulses from normal and noise-corrupted. The results show that atrial fibrillation detection supplemented by signal quality assessment allows achieving hight detection sensitivity, e.g., nearly 90%, till 20dB SNR with simulated signals composed of Type 1 pulses and up to 98.6% with clinical signals. An exceptionally high specificity is possible even at relatively low SNRs, e.g., nearly 100% at 0–10dB with simulated signals and up to 99.9% with clinical signals. The proposed algorithm has a potential to be applied for a continuous ambulatory screening of atrial fibrillation. The algorithm is suitable for the implementation in the wearable systems, e.g., smartwatches or smartphones, therefore online version is implemented as Android OS application.

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**Chapter**

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**Appendix** **A**

# Appendix: Databases and Signals

Tables  and  presents the signals included from the MIMIC and UQSVD databases, respectively, together with corresponding rhythm types.

Table 1.1: Signals from MIMIC database for model evaluation. Numbers correspond to record names in database. One pulse is extracted from each of the 56 records.

[Sorry. Ignored \begin{tablenotes} ... \end{tablenotes}]

Table 1.2: Signals from UQVSD database for model evaluation. One pulse is extracted from each of the 32 records.

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**Appendix** **B**

# Appendix: Initial PPG pulse fitting parameters

Table  provides the initial PPG pulse fitting parameters for various pulse modeling approaches.

Table 2.1: Initial sets of parameters used for PPG pulse modeling.

**Appendix** **C**

# Appendix: Implementations of developed algorithms in smart devices

Figure  shows a screenshot of the application running on the smartphone. PPG segment with correctly detected PVCs during the episode of bigeminy is shown in a chart on the top of the application window. The bottom chart shows the normalized peak-to-peak intervals. The sliding panel on the right side provides an important information about the number of detected PVCs and the PVC burden, determined by a percentage of PVC-related beats compared to a total number of beats.

Figure 3.1: Screenshot of the Android application with the implemented PVC detection algorithm. An application window shows detected PVCs during bigeminy episode, and other heart rhythm related parameters. Note that this particular signal is characterized by a very high heart rhythm (220 bpm) outside the episode of multiple PVCs.

Figure  shows a screenshot of the application running on the smartphone. PPG segment is shown in a chart on the top of the application window. The bottom chart shows the estimated SQI of the present segment. The sliding panel on the right side provides an important information about the number of detected AF beats and the AF burden, determined by a percentage of AF-related beats compared to a total number of beats.

Figure 3.2: Screenshot of the Android application with the implemented AF detection algorithm. An application window shows PPG signal during AF, together with the estimated SQI and other heart rhythm-related parameters.