Tampere University

Matias Kanniainen

RELATIONSHIP BETWEEN QT AND RR INTERVALS IN ELECTROCARDIOGRAM

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ABSTRACT

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The electrical activity of the heart can be monitored with electrocardiography. An electrocardiogram is a graph of voltage as a function of time presenting the electrical activity in the heart cells. From the electrocardiogram, it is possible to indentify the QT interval, which represents the de- and repolarization of the heart ventricles, and the RR interval, which represents the time between two subsequent heartbeats. It has been proved that between the two intervals there is a relationship. There are several heart conditions related to the QT interval, for example the long QT syndrome, which can even lead to death. The quantitative measurement of QT interval is important to be able to diagnose different QT-related conditions. Therefore the relationship between QT and RR needs to be understood in detail.

In this thesis, the relationship between QT and RR is examined. The purpose of the thesis is to prove the existence of the relationship, present the tools to remove the relationship and underline the importance of measuring the QT interval precisely. Also, the physiology of the heart and fundamentals of the electrocardiography are discussed. The most common methods to remove the relationship are Bazett's, Fridericia's, Hodges' and Framingham's QT correction methods. The methods are however shown to be inefficient and universally incompetent computational simplifications of a complex phenomenon. In the thesis, the methods are presented and they are analyzed and visualized. The main objective of the QT correction methods is to remove the relationship between the QT and RR, and the success of the objective is analyzed in the thesis.

In the experimental part of the thesis, the relationship between QT and RR is examined with several methods. Time series analysis is used to visually verify the relationship, and also the dynamical behaviour of the intervals is analyzed. Polynomial fitting is applied to point clouds, and the results are analyzed with respect to the relationship. Finally, the QT correction methods are analyzed with the help of density plots, with which the behaviour of the QT correction methods can be visualized clearly. The effects of the QT correction methods are shown on both healthy and long QT syndrome subjects.

This thesis shows, both qualitatively and quantitatively, that the QT and RR intervals are interdependent. The deficiencies of the different QT correction methods are demonstrated, and especially the Bazett's formula was shown to overcorrect QT values, often indicating abnormally long QT values for a healthy subject. Because of the unreliability of the conventional QT correction methods, a principle of a new QT correction method based on transfer entropy is presented as a promising novel tool.

Keywords: electrocardiogram, QT correction, time series analysis, computational cardiology, transfer entropy

TIIVISTELMÄ

Matias Kanniainen: QT- ja RR-intervallien välinen riippuvuus sydänsähkökäyrässä
Kandidaatintyö
Tampereen yliopisto
Teknis-luonnontieteellinen, TkK
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Sydämen sähköistä toimintaa voidaan seurata elektrokardiografian avulla. Sydänsähkökäyrä on sydänsolujen potentiaalin muutoksen kuvaaja ajan funktiona. Sydänsähkökäyrästä on mahdollista tunnistaa QT-intervalli, joka kuvaa sydämen kammioiden de- ja repolarisaatiota, sekä RR-intervalli, joka kuvaa peräkkäisten sydämenlyöntien välillä kulunutta aikaa. Näiden välillä on havaittu olevan riippuvuus, joka on osoitettu keskinäiseksi riippuvuudeksi. QT-intervalliin liittyy sydänsairauksia, esimerkiksi pitkä QT -oireyhtymä (eng. Long QT syndrome), joka aiheuttaa pahimmillaan kuoleman. QT-intervallin eksakti mittaaminen on tärkeää sydänsairauksien diagnosoimiseksi, joten QT-intervallin ja RR-intervallin välinen keskinäinen riippuvuus on poistettava laskennallisin keinoin.

Tässä työssä käsitellään QT- ja RR-intervallien välistä riippuvuutta. Työn tarkoituksena on todentaa riippuvuuden olemassaolo, esittää työkalut riippuvuuden poistoon ja korostaa QT-intervallin mittaamisen tärkeyttä. Sydämen fysiologiaa sekä elektrokardiografian perusteita käsitellään lisäksi pohjustuksena työlle. Yleisimmät menetelmät riippuvuuden poistoon, QT-korjaukseen, ovat Bazettin, Friderician, Hodgesin ja Framinghamin kaavat. Kaavojen on useiden tutkimusten perusteella kuitenkin osoitettu olevan epäluotettavia ja universaalisti pätemättömiä laskennallisia yksinkertaistuksia monimutkaisesta ilmiöstä. Työssä esitellään yllä mainitut kaavat ja niitä analysoidaan sekä visualisoidaan. QT-korjausmenetelmien ainoa tavoite on poistaa QT-intervallin ja RR-intervallin välinen riippuvuus, minkä onnistumista työssä analysoidaan.

Työn kokeellisessa osassa QT-intervallin ja RR-intervallin välistä riippuvuutta tarkastellaan useamman menetelmän avulla. Aikasarja-analyysin avulla riippuvuus todennetaan visuaalisesti, ja intervallien dynaamista käyttäytymistä analysoidaan. Myös pistepilviin sijoitettuja polynomisovitteita tarkastellaan, ja tuloksia analysoidaan. Lopuksi QT-korjausmenetelmiä mallinnetaan tiheyskartoilla, joiden avulla QT-korjausmenetelmien toimintaa voidaan visualisoida hyvin. QT-korjausmenetelmien vaikutusta havainnollistetaan sekä terveille että pitkä QT -syndroomaa sairastaville koehenkilöille.

Tässä työssä osoitettiin, kvantitatiivisesti ja kvalitatiivisesti, että QT- ja RR-intervallit ovat keskenään riippuvaisia. Erilaisten QT-korjausmenetelmien heikkoudet tulivat esiin, ja erityisesti Bazettin kaavan todettiin olevan hyvin epätarkka terveen koehenkilön diagnosoimisessa. Perinteisten QT-korjausmenetelmien epäluotettavuudesta johtuen uuden siirtoentropiaan perustuvan QT-korjausmenetelmän periaate esiteltiin ja tarpeellisuus todettiin.

Avainsanat: sydänsähkökäyrä, QT-korjaus, aikasarja-analyysi, laskennallinen kardiologia, siirtoentropia

CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS AND ABBREVIATIONS

A-V node	Atrioventricular node
arrhythmia	Change of normal heart rhythm
bpm	Beats per minute
DFA	Detrended fluctutation analysis
ECG	Electrocardiogram
HR	Heart rate
HRV	Heart rate variability
LQT1	Long QT syndrome subtype 1
LQT2	Long QT syndrome subtype 2
LQT3	Long QT syndrome subtype 3
LQTS	Long QT syndrome
QT	QT interval of the electrocardiogram
QTc	Corrected QT interval
QTc_{B}	Bazett's QT correction
QTc_{Fra}	Framingam's QT correction
QTc_{Fri}	Fridericia's QT correction
QTc_{H}	Hodges' QT correction
RR	RR interval of the electrocardiogram
SQTS	Short QT syndrome
TdP	Torsades de Pointes
TE	Transfer entropy
THEW	Telemetric and Holter ECG Warehouse

1 INTRODUCTION

Electrocardiography is a fundamental tool in modern cardiology. It is often used alongside other testing methods to diagnose and monitor different conditions of heart. An electrocardiogram (ECG) is a graph of voltage as a function of time presenting the electrical activity of the heart. It produces important clinical information about the heart rate and other mechanical and electrical activities present in different parts of the heart. Various clinical conditions, such as high blood pressure and acute heart attack can also be diagnosed from the electrocardiogram. [1]

It is clinically important to make quantitative measurements of the different components in the ECG. The ECG consists of five different waves and four different intervals that have particular physiological relevance. The RR interval (RR) is a reciprocal of the heart rate (HR), and it corresponds to the normal sinus rhythm of the heart. The QT interval (QT) of the ECG represents the electrical activity of the heart's ventricles, which play essential role in blood circulation. Many clinical conditions, such as severe abnormal heart rhythms (arrhythmias) are diagnosed based on the duration of the QT . [1] However, the length of the QT is dependent on the HR and accordingly on the length of the RR [2]. Therefore, to be able to make precise measurements of the QT independent of the HR, the dependency must be removed or at least reduced. Several formulas have been proposed to remove the dependency, but they are often criticised for their simplicity and lack of universal ability to present the relationship between QT and RR [3].

In this thesis, the relationship between QT and RR is examined. The different formulas to remove the dependency are presented and analyzed. The clinical importance of precise QT correction is emphasized, and different conditions involving QT abnormalities are presented. Also a principle of a new transfer entropy -based QT correction method is introduced as a possible solution to effectively remove the QT-RR relationship.

In Ch. 2 the heart physiology is presented, necessary physiological phenomena behind electrical activity of the heart are described and an ECG is analyzed in more detail. In Ch. 3 the practices of ECG measurements are described, and the different methods for removing QT-RR dependency are examined in more detail. Chapter 4 is the experimental part of the thesis, and the relations between QT and RR are examined. The different methods are visualized and analyzed, and the methods are compared. Finally, in Ch. 5 the results are discussed and the needs for new QT correction methods are highlighted.

2 HEART PHYSIOLOGY

The human heart is a muscular organ which has four chambers. The right side of the heart consists of the right atrium and ventricle, the right atrioventricular valve, and the pulmonary valve. Respectively, the left side of the heart consists of the left atrium and ventricle, the mitral valve, and the aortic valve. [4] The simplified anatomy of the heart is displayed in Fig 2.1.

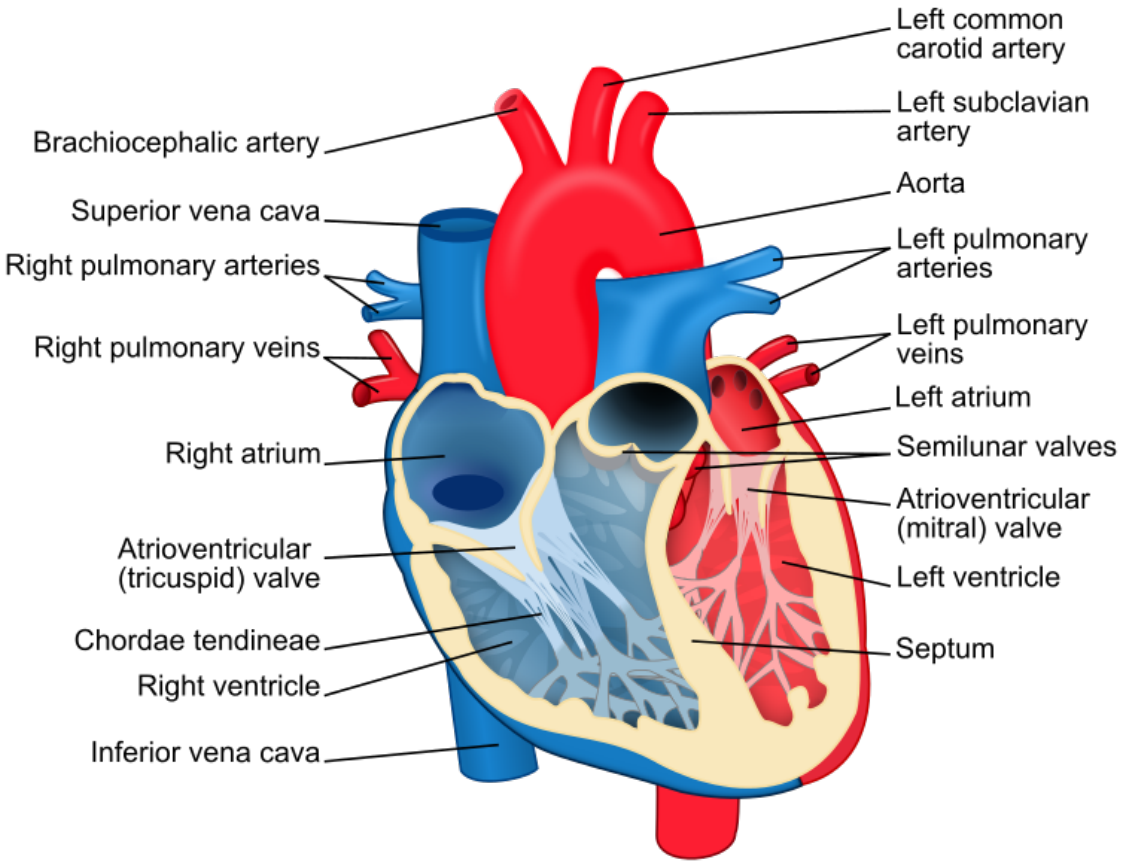

Figure 2.1. *Simplified anatomy of the heart [5].*

The heart is responsible of the blood circulation in the body. The right side of the heart pumps blood to the pulmonary circulation, while the left side pumps blood to the systemic circulation [4]. The pulmonary circulation takes care of the oxygenation of the blood, and the systemic circulation carries the oxygenated blood to the rest of the body. In addition, the systemic circulation is responsible for delivering hormones and nutrients to the tissues and transporting the waste products away from the tissues [6, pp. 113–126].

2.1 Electrical conduction system of the heart

The heart pumps blood by rhythmic contraction controlled by the electrical conduction system of the heart. The cardiac action potential causes the heart cells to contract, and blood is pumped rhythmically throughout the body. Also, the cells in the ventricles contract almost simultaneously, which generates the most effective pressure in the ventricular chambers, leading blood to effectively enter the circulatory system [7, pp. 141-172].

Most of the cells in the human body have electrically polarized membranes. There is a potential difference between the inside and the outside of the membrane, which is caused by electrically charged ions, such as Na^+, K^+, Ca^{2+}, and Cl^- [7, pp. 141–172]. Some cells, such as heart cells, can use the membrane potential for signaling purposes. Such signals in the cells are brief electrical impulses, which are called action potentials [6, pp. 127–133]. When an action potential occurs, the depolarization of the cell membrane takes place and the Na^+-ions flood inside the cell [7, pp. 141–172]. Respectively, a process called repolarization occurs as the ions are moved back to the cellular equilibrium.

The action potential required for electrical conduction is achieved through a specialized muscle tissue in the heart itself [7, pp. 141–172]. The electrical conduction system starts at the sinoatrial node, which is in the right atrium [4]. There a contraction signal is generated and the signal travels through the internodal pathways to the atrioventricular node (A–V node), while stimulating the right atrium to contract. [8, pp. 159–161] The left atrium contracts when the signal spreads through the Bachmann bundle. The A-V node delays the signal after the contraction of the atria and transmits the signal to the bundle of His. After leaving the bundle of His, the signal travels to both left and right side of the heart through the Purkinje fibres, and the ventricular depolarization spreads contracting the ventricles. [8, p. 161]

2.2 Electrocardiography

In electrocardiography, an ECG is produced by recording the electrical conduction of the heart. The ECG is determined by measuring the small electrical changes in the heart cells, since the electrical changes are a result of the de- and repolarization of the cardiac muscle [4]. The signals of de- and repolarization of the cardiac cells are collected in each heartbeat and they form the ECG as a voltage curve, i.e. voltage as a function of time. The ECG is often measured with 12 leads [9, p. 55]. The clinical measurement procedure is described in more detail in the Ch. 3. A normal pattern of an ECG is shown in Fig. 2.2.

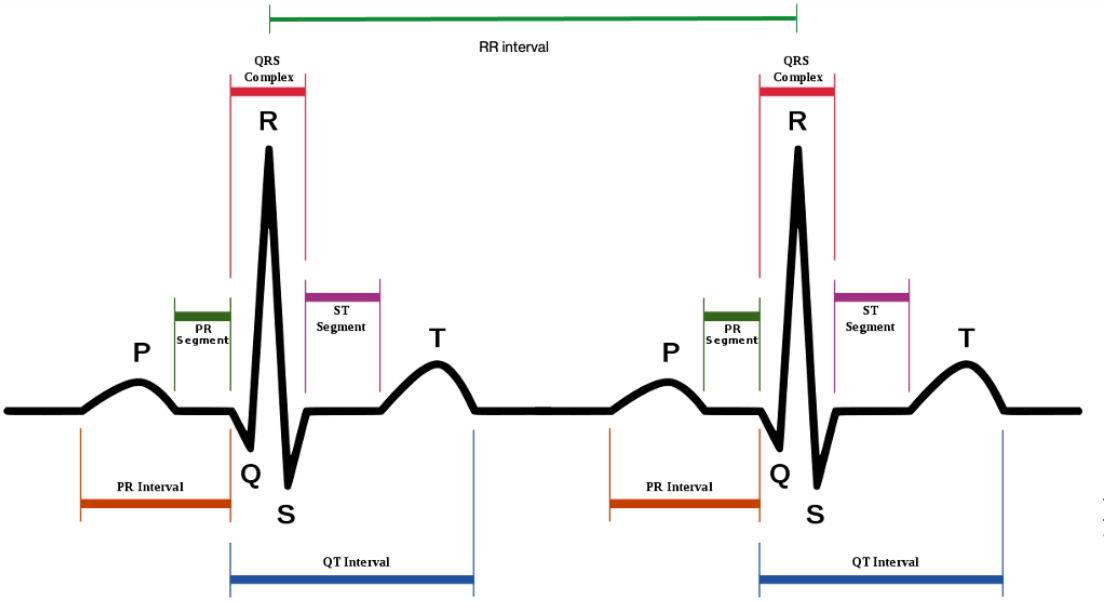

Figure 2.2. *Electrocardiogram representing the voltage of de- and repolarization in the heart cells as a function of time [10]. The same pattern repeats periodically over time.*

The ECG consists of three different main components: P wave, QRS complex and T wave. These components are described in more detail in Secs. 2.2.1 – 2.2.2.

2.2.1 P wave and T wave

The first part of the ECG is the P wave, which arises from the depolarization of the atria. The P wave is sometimes divided into two parts, where the first part expresses the depolarization of the right atrium, and the second part expresses the depolarization of the left atrium. The P wave is usually about 100 ms long, which is the normal time of atrial depolarization. [1]

The T wave is the final component of an ECG, and it represents the ventricular repolarization. The T wave follows the direction of the QRS complex, meaning that when the QRS complex is positive on the graph, the T wave is also positive [11, p. 40]. Sometimes an extra wave called the U wave, can follow the T wave. The origin of the U wave is still unknown [1]. Because the repolarization is a slower event compared to the depolarization, the duration of the T wave is longer than that of the P wave, around 160 ms. It is noteworthy, that the repolarization of the atria is not visible, since it is overwhelmed by the QRS complex [4].

2.2.2 QRS complex and RR interval

The QRS complex represents the depolarization of the ventricles. The depolarization occurs rapidly, and the duration of the complex is only 60 – 100 ms [1]. It can be divided

into three components: Q wave, R wave and S wave. The Q wave represents the depolarization of the wall between the vetricles. The R wave captures most of the ventricular depolarization, and finally the S wave represents the depolarization of the Purkinje fibres. [9, pp. 36–39]

Sometimes it is possible that not all of the waves of the QRS complex are visible on the ECG [11, pp. 12–13]. The QRS complex can vary considerably between different ECG graphs, for example, some of the waves could be significantly smaller than others. In that case, the waves are denoted with small characters q, r and s. [1] Often any combination of the three waves is registered as a QRS complex.

The R wave has a very high voltage because of the thickness of the ventricular muscular walls. Therefore, the R wave is also the most recognizable component of the ECG, and it is used in the heart rate detection. The interval between two adjacent R peaks is called an RR interval and its inverse corresponds to the heart rate (HR). [11, pp. 9–13] In other words, the HR is a reciprocal of the RR interval, and it is often presented as beats per minute (bpm). The HR varies throughout the day depending on the activity and stress, as the human circadian rhythm also affects the heart rate. The normal heart rhythm, called sinus rhythm, is between 60 – 100 bpm. [9, p. 27]

The heart rate variability (HRV) can be analyzed based on the properties of the RR interval time series. There are different time series analysis methods such as detrended fluctuation analysis (DFA) [12] and its variants [13, 14]). The RR time series can also be examined with other methods, such as time-domain methods, frequency-domain methods and geometrical methods [15]. The QT-RR relationship can be studied with, e.g., dynamical cross-correlation and transfer entropy [16] discussed above. [17, 18] The variations in the RR intervals have particular scaling properties that have been widely studied (see, e.g. Ref [19]). In essence, the RR variations for a healthy person resemble the so called pink noise, or flicker noise, which is often called as fractal. This long-range correlated behavior also corresponds to the 1/f noise in the frequency space. [12, p. 75] The detailed scaling properties of the RR variations can be determined by, e.g., DFA and its variants.

HRV can be used in determining various physiological conditions, such as sleep cycles, stress, and depression [20, pp. 185–189, 469–475]. HRV mirrors imbalances within the autonomous nerve system and can be thought of a parameter of complex interaction between the brain and the cardiovascular system. The HRV measurement is becoming a relevant tool for clinical purposes, even though its main applications are still in recreational consumer markets. [21]

2.3 QT Interval

The QT interval is a clinically important part of the ECG, and it is displayed in the bottom part of Fig. 2.2. The QT interval includes the de- and repolarization of the ventricles, and it starts from the beginning of the QRS complex and lasts up to the end of the T wave. The normal duration of the QT is 360 – 400 ms. Female subjects have often longer QT intervals than the male ones. Also, the QT interval length increases with the age. [22] The importance of the QT interval is fundamental in determining different clinical conditions. For example, severe arrhythmias and ventricular tachycardia are caused by abnormal QT interval prolongation, and they can lead to sudden death [23]. Besides the RR interval, the QT interval is also a well distinguishable component of the ECG. Therefore, a lot of important information can be determined in qualitatively measuring the QT interval.

The QT intervals are influenced by the RR intervals. Therefore the RR intervals must also be taken in account in the QT interval analysis. When the heart rate increases, the QT shortens, and respectively the other way around. It is often desirable to compare QT intervals regardless of the HR in the time of the measurement, so the QT-RR dependency must be corrected. When the QT correction methods are applied to the measured QT intervals, the dependency on the RR intervals is reduced. These QT values are regarded as the corrected QT intervals (QTc). The QTc values can be then analyzed regardless of the HR. [24] The uncorrected QT values are often referred as raw QT values.

Several QT correction methods have been introduced (see below). The methods are often criticized, because they are not universally able to present the corrected relationship between QT and RR, but instead overestimate the QTc in many cases [3]. The different QT correction methods are presented and described in more detail in Sec. 3.4.

2.3.1 QT interval abnormalities

In some cases, the QTc can be either too long or too short [1]. If the QTc is abnormally prolonged, the cause may be the long QT syndrome (LQTS), which is described in Sec. 2.3.2 in more detail. Respectively, if the QTc is too short, it may be due to the short QT syndrome (SQTS). Both diseases may lead to abnormal heart rhythms which may lead to death if untreated. A common type of arrhythmia caused by the prolongation of the QT is torsades de pointes (TdP), which is often lethal. [9] Regarding the prevalence of the QT interval abnormalities, Straus et al. conducted a study in 2006 investigating associations between the prolonged QTc and cardiovascular mortality [25]. The study shows that two-thirds of sudden cardiac deaths are related to abnormal QTc interval prolongation in patients aged 55 or older.

The SQTS is often diagnosed if QTc $\leq$ 320 ms. However, a unified diagnostic criteria is still to be formalized [26]. The diagnosis of SQTS is complicated, and the presence of

a short QT interval does not always indicate an increased arrhythmic risk [26]. Therefore, the short QTc values should not always lead to a diagnosis of the SQTS.

There are also several commonly prescribed drugs, which can cause prolongation of the corrected QT interval. Some antidepressants, such as imipramine and doxepin, as well as some antiarrhythmic agents such as quinidine are studied to prolong the QTc, and can lead to serious arrhythmia and even to death [27, 28]. Some antihistamines such as astemizole and terfenadin are withdrawn from the US market, because they induce TdP [23]. There are also some food ingredients which are shown to prolong the QT interval. For example, grapefruit is reported to cause prolongation of the QTc [23, 29].

In drug development, the QT interval analysis is in a fundamental role, and it is a part of the cardiotoxicology research in drug development protocols. As described previously, some drugs may cause temporary QTc interval prolongation, hence leading to possible death. It is therefore essential to address the effects of the drugs on the QT interval as early as possible, in order to modify the clinical development process in time. [30, 31]

2.3.2 Long QT syndrome

The long QT syndrome (LQTS) is a genetic condition, where the repolarization of the ventricles is delayed. The LQTS affects around 1 in 5000 people [32]. At worst, LQTS can lead to potentially lethal dysrhythmia and TdP, and hence to seizures or even to a sudden death, depending whether the heart rhythm either spontaneously reverts or is defibrillated to normal rhythm [33].

Genetically, the LQTS is thought to be a collection of different mutations in cardiac potassium- and sodium-channel genes [33]. The LQTS can be divided into subtypes depending on which gene causes the LQTS. Genes KVLQT1 (LQT1), HERG (LQT2) and SCN5A (LQT3) account for about 66% of the LQTS cases. In total, hundreds of mutations in the genes have been discovered, and LQTS can be caused by mutations in some other gene. [32] A study by Zareba et al. in 1998 [34], shows that the genotype of the LQTS patient also influences the probability and lethality of cardiac events independently of QTc. The results indicate that there is a significantly higher risk of cardiac event if the patient is in the LQT1 or LQT2 group. On the other hand, the patients of the LQT3 group are more likely to die from a cardiac event if it occurs. [34]

Sauer et al. have shown in a study from 2007 [35] that patients in the LQT1 group have the most significant risk of cardiac event compared to the other LQTS patients. The study also suggests that beta-blockers can effectively reduce the risk of a cardiac event in adult patients, whose LQTS is confirmed by mutation.

Schwartz et al. proposed a diagnostic criteria for the LQTS in 1993 [36]. The criteria still serve as the best available criteria of diagnosing the LQTS clinically. Schwartz et al. state

that a diagnosis of the LQTS based on values of QTc > 440 ms is untested for clinical purposes, and therefore a difficult way to diagnose patients. Instead, the new criteria are divided to three main categories, and the LQTS is diagnosed by combining the points of different categories. The categories are ECG findings, clinical history related to cardiological events and family history. [36] The diagnostic criteria are presented in Table 2.1.

Table 2.1. *LQTS diagnostic criteria as presented by Schwartz et al. [36].*

		Points
ECG findings [a]		
A.	QTc [b]	
	$\geq$ 480 ms	3
	460 - 470 ms	2
	450 ms	1
B.	Torsade de Pointes [c]	2
C.	T wave alternans	1
D.	Notched T wave in three leads	1
E.	Low heart rate for age [d]	0.5
Clinical history		
A.	Syncope [c]	
	With stress	2
	Without stress	1
B.	Congenital deafness	0.5
Family history [e]		
A.	Family members with definitive LQTS	1
B.	Unexplained sudden cardiac death below age 30 among immediate family members	0.5
Scoring:	Low probability of LQTS	$\leq$ 1
	Intermediate probability of LQTS	2-3
	High probability of LQTS	$\geq$ 4

[a] In the absence of medications or disorders known to affect ECG

[b] Calculated by Bazett's formula, $QTc = QT/\sqrt{RR}$

[c] Mutually exclusive

[d] Resting heart rate below the second percentile for age

[e] The same family member can not be counted in A and B

In the table, it is evident that even the modern LQTS diagnosis criteria are not particularly precise. Especially epilepsy and LQTS can be misdiagnosed as each other due to similar symptoms [37]. In fact, with a possible combination of family history and clinical history unrelated to the prolonged QTc, it is possible to get four points from the test and hence be diagnosed with the LQTS, even though the patient's QTc would be in normal limits, i.e. < 450 ms. In conclusion, the prevalent diagnostic criteria can possibly lead to rising misdiagnoses of the LQTS in fear of deadly cardiac events.

3 METHODS AND DATA

3.1 Measuring the electrocardiogram

A clinical electrocardiogram is commonly measured with 12 leads. A fewer number of electrodes is not sufficient to determine the ECG with a high precision due to the complex three-dimensional structure of the heart. Therefore, the electrical activity must also be understood in three dimensions. Each lead views the heart at a different and unique angle, and together they provide sufficient information of the electric activity. [9, pp. 55-56] The 12-lead placement is illustrated in Fig. 3.1.

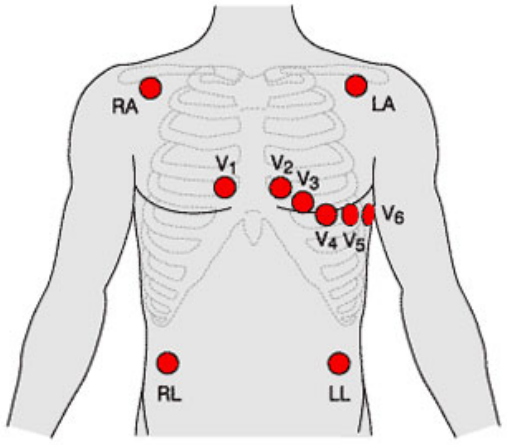

Figure 3.1. *Electrode placements for a 12-lead electrocardiogram [38].*

A 12-lead ECG is produced with 10 electrodes. Two electrodes are placed in both hands and legs (RA, LA, RL, LL in Fig. 3.1), and they comprise the so-called limb leads, which are denoted as I, II, III, avR, avF, avL. Additional six electrodes are placed across the chest, and they form the six precordial leads (V1-V6). [1] The precordial leads are arranged horizontally on the chest. Each precordial lead has its own line of sight, and each of them has the best view on the certain region of the heart. [9, p. 65]

The ECG can be measured for 24 hours with the Holter monitoring. In that case, a small box with the electrodes is carried by the patient on the belt. The patient can perform the daily activities even from sleeping to working out while the monitor records the ECG. The

complete recording of patient's heart activity can then be analyzed. [9, p. 132] Usually Holter recordings use two or three leads. The measurement can also be done with 12 leads, but since the purpose of Holter measurement is to track changes and patterns in the ECG activity, only a few leads are sufficient for the measurement. [1] The QT interval analysis can be effectively done with the Holter monitoring. The human heart beats approximately 100 000 times a day, so the Holter monitoring can give a comprehensive view of QT interval changes during the day. [1] The heart rate varies throughout the day depending on activity levels, so a number of sufficiently long segments of the QT intervals can be determined for further analysis.

3.2 Introduction of the data

The data used in this thesis is acquired from Telemetric and Holter ECG Warehouse (THEW) data administrated by the University of Rochester Medical Center [39]. The data can be accessed for free for non-profit organizations. In this thesis, the data have been aquired by the Computational Physics laboratory at Tampere University.

The THEW data is gathered from subjects under different clinical conditions and grouped accordingly. The information of the databases used in this thesis is displayed in Table 3.1.

Table 3.1. *THEW databases used in the thesis [39].*

Database	Leads	ECGs	Subjects
Healthy	3	202	202
Genotyped Long QT Syndrome	2-3	480	307

The ECGs in databases are 24h recordings. The subjects in Healthy database are selected with a strict criteria including: zero cardiovascular disease history, no disorders or strokes, no high blood pressure, no medication or chronic illness, no pregnancy, normal physical examination and exercise testing, normal ECGs [39, 40]. In the Genotyped LQTS set there are 171 subjects with 246 recordings of the LQT1 subtype, and 89 subjects with 145 recordings of the LQT2 subtype. Also 14 subjects with 35 recordings are of the LQT3 subtype, and 33 subjects with 54 recordings are of other LQTS types. The data is accumulated for over 25 years. The long QT syndrome in the database is confirmed with genetic tests. The database consists of a set of subjects between ages 1-88. In total, 168 subjects are females and 139 are males. Also, 132 subjects are treated with beta-blockers, while 175 subjects have either no treatment, or some other treatment. [39, 40]

In this thesis, the distributions of the QT and RR values for both Healthy and LQTS data sets are examined. Other than that, individual subjects are analyzed instead of the whole data set, because the further analysis based on the complete data sets goes be-

yond the topic of this thesis. The subjects in the data sets are classified, and the subject ID's can be found in the metadata of the THEW data set. The individual subjects from Healthy data set in this thesis are subjects 6021, 6088 and 6115, by ID. The individual subjects examined from LQTS data set are subjects 6, 196 and 350 by ID. The subjects are carefully selected typical examples of the respective data sets.

3.3 Data preprocessing

The THEW data set contains raw ECG data, which must be preprocessed in order to do further analysis regarding the QT and RR intervals. The preprocessing of the ECG data to extract the QT and RR intervals is a standard procedure on the field, but it is a non-trivial problem. There are also many companies that are specialized in QT-RR extraction from the ECG data.

The QT intervals have to be extracted from the raw data in parts, since the QT intervals consist of two separate components: the QRS complex and T wave. To compute the QRS complex, the QRS detection signals from each lead are computed and combined. The dominant QRS component is found, for which the succeeding and preceding peaks are located. Finally, the Q, R and S waves are computed based on the morphology of the peaks. From there, the RR intervals and QRS complexes can be determined. [41]

The T wave is also extracted in the procedure. The T waves are detected with the help of morphological filtering. Then a caricature of the T wave locations is built. The T wave peaks are detected from both the caricature and its morphological derivative difference. The detected peaks are organized, and the end of the T wave is computed from the peaks. [41] With these methods, the majority of the QT and RR intervals are well detected and extracted.

3.4 QT correction methods

Several methods have been proposed to remove the RR dependency from QT in the ECG. Most of the methods in use are computationally extremely simple (see below). The methods are not universally able to normalize the QT-RR relationship. Instead, they tend under- or overestimate QTc values with high or low HR. In addition, drug-induced QT prolongation is often under- or overcorrected [3, 42]. Even though they are criticized of their simplicity, the methods are still in clinical use [43].

3.4.1 Conventional methods

The most prominent method to reduce the QT-RR relationship is the formula of Bazett [44]. The formula was proposed by Henry Bazett in 1920, and it is still widely used in clinical practice, education and research [43]. Bazett deduced the model through simple

fitting procedures with various sets of data. Bazett's formula for the corrected QT interval $\mathrm{QTc_B}$ is presented as

$$\mathrm{QTc_B} = \frac{\mathrm{QT}}{\sqrt{\frac{\mathrm{RR}}{1\,000\ \mathrm{ms}}}}, \tag{3.1}$$

where $\mathrm{QTc_B}$ is returned in same units with QT, usually milliseconds. The reference RR interval is 1 000 milliseconds (or 60 bpm), where $\mathrm{QTc_B}$ = QT.
Generally, Bazett's formula is not considered as an accurate model to reduce the QT-RR relationship. The formula is known to overcorrect the QTc at high HR and undercorrect the QTc at low HR, respectively. [42] This can result in misdiagnosis of the LQTS [43].

Another frequently used formula is the one by L.S. Fridericia from 1920 [45]. Such as Bazett, Fridericia derived his relation by examining a set of patients and deducing a formula from the results. The $\mathrm{QTc_{Fri}}$ proposed by Fridericia is presented as

$$\mathrm{QTc_{Fri}} = \frac{\mathrm{QT}}{\sqrt[3]{\frac{\mathrm{RR}}{1\,000\ \mathrm{ms}}}}, \tag{3.2}$$

where the reference RR interval (where $\mathrm{QTc_{Fri}}$ = QT) is also 1 000 milliseconds. Fridericia's formula also faces the same kind of criticism for its extreme simplicity and for its inability to correct the QT precisely with all values of the HR [43].

A more recent clinically significant QT correction method was derived from the Framingham study in 1992 [46]. The QT intervals were measured from 5 108 subjects from the city of Framingham in Massachusetts. A linear regression model was developed from the results in order to correct the QT according to the RR cycle length. The linear regression model led to a form

$$\mathrm{QTc_{Fra}} = \mathrm{QT} + 0.154\left(1\,000 - \frac{\mathrm{RR}}{1\ \mathrm{ms}}\right), \tag{3.3}$$

where the reference RR interval is again 1 000 milliseconds. The Framingham equation improves the QT correction in comparison to Bazett. The linear model avoids the over- and under-correction with the high and low HR typical for Bazett. [46]

Another QT correction formula based on linear regression was introduced by Morrison Hodges in 1983 (see Ref. [12] in Ref. [47]). The formula is given by

$$\mathrm{QTc_H} = \mathrm{QT} + 1.75\left(\frac{60\,000\ \mathrm{ms}}{\mathrm{RR}} - 60\right), \tag{3.4}$$

where the reference RR interval is 1 000 ms. The formula was originally developed based

on the HR, but for a clear interpretation, it is presented here as an explicit function of QT and RR.

Bazett's method is the most used QT correction method, even though some approaches perform better. Vandenberk et al. conducted a vast study in 2016 on QT correction formulas in ECG monitoring [47]. The study confirmed the inferiority of Bazett's formula for the $\mathrm{QTc_B}$ compared to other clinical methods. Authors also state that the current use of the Bazett's formula in clinical practice should be questioned. The other QT correction methods perform better compared to $\mathrm{QTc_B}$, and therefore could replace it in hospital-based QT monitoring. [47]

Luo et al. also conducted a study in 2004 comparing different commonly used QT correction methods [43]. In the study, 10 303 ECG records were evaluated. The results showed that Hodges' formula for the $\mathrm{QTc_H}$ gives the best results. The study also shows that Bazett's formula suggests around 30% of the patients having abnormal QT interval if the normal limit is considered as QT < 440ms. In comparison, Hodges' and Fridericia's formulas suggest that < 2% of the patients have abnormal QT intervals. [43] There is alarming difference in the Bazett's method compared to other conventional methods, and it indicates that either the $\mathrm{QTc_B}$ overcorrects the QT values resulting in relatively large amount of false positive LQTS diagnoses, or that the $\mathrm{QTc_{Fri}}$ or $\mathrm{QTc_H}$ do not sufficiently correct the QT values resulting in false negative diagnoses. In any case, the conventional correction methods do not agree with each other in absence of a universal and unbiased QT correction method.

Both of these studies mentioned above show that $\mathrm{QTc_B}$ is clearly outdated, and it gives a considerate number of false-positive values. The other methods are better compared to $\mathrm{QTc_B}$, but most of them also tend to fail at high and low HR. All the methods only result from fitting procedures against studied data sets. A first-principles model for calculating the QTc has not yet been successfully developed. Instead, all the results have been derived from global trends. At present, the QT-RR dependency cannot be removed universally and precisely. Considering the huge investments in clinical practice, the waste of resources and time in erroneous QTc's is considerable.

3.4.2 Utilizing transfer entropy in QT correction

Potapov et al. have recently suggested an information theory approach to the QT correction [16]. The QT-RR relationship is studied with transfer entropy (TE) methods, and the information transfer affecting the QT values is calculated from the preceding k QT beats and n RR beats. The relation between the preceding samples and the next sample is calculated for the QT series, and the information transfer for both $\mathrm{QT} \rightarrow \mathrm{RR}$ and $\mathrm{RR} \rightarrow \mathrm{QT}$ is calculated. Importantly, the information theory provides a quantitative tool to evaluate the relationship between the QT and RR. The transfer entropy $\mathrm{TE}_{\mathrm{RR} \rightarrow \mathrm{QT}}$ for QT and RR

with histories n and k is presented as

$$\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}} = \sum_{\mathrm{i}} \mathrm{p}(\mathrm{QT_i}, \mathrm{QT}_{\mathrm{i-1}}^{(\mathrm{k})}, \mathrm{RR}_{\mathrm{i-1}}^{(\mathrm{n})}) \log_2 \frac{\mathrm{p}(\mathrm{QT_i}|\mathrm{QT}_{\mathrm{i-1}}^{(\mathrm{k})}, \mathrm{RR}_{\mathrm{i-1}}^{(\mathrm{n})})}{\mathrm{p}(\mathrm{QT_i}|\mathrm{QT}_{\mathrm{i-1}}^{(\mathrm{k})})}, \tag{3.5}$$

where $\mathrm{QT}_{\mathrm{i-1}}^{(\mathrm{k})})$ and $\mathrm{RR}_{\mathrm{i-1}}^{(\mathrm{n})}$ are the preceding values of k QT beats and n RR beats, $p(x)$ is a probability distribution and $p(x|y)$ is a conditional probability [48]. The QT history k and RR history n can be varied to get different results for $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$. The result units for TE are bits of information. [16]

The results [16] show that the information transfer from RR $\to$ QT is larger than the opposite QT $\to$ RR transfer. The inequality between RR $\to$ QT and QT $\to$ RR indicates that the subprocesses are asymmetric. Therefore, the results suggest that the RR history affects the upcoming QT values more than the QT history affects the upcoming RR values. When the history length was raised, $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR(n)}}$ was found to reach zero after 20 to 25 heartbeats. This means that there is no more influence of QT on RR with sufficiently long history. On the other hand, $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR(k)}}$ never reached zero with a history of over 50 heartbeats. [16] The results are important in showing quantitatively, with the help of information theory, that there is an dependency between the QT and RR. Also, the results show that the RR history influences on the QT values significantly more than vice versa.

As described, the fundamental purpose of the QT correction methods is to remove the dependency so that the QT values can be evaluated precisely and independently of the RR and HR. From the point of view of information theory, then the transfer entropy TE should then be equal to zero. However, the results show that using the conventional QT correction methods, the interdependency is not properly reduced. Instead, $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ and $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}$ get non-zero values when analyzing both RR history n and QT history k. [16] The results mean that the conventional QT correction methods can not reduce the interdependency of the QT and RR. Even though some methods like $\mathrm{QTc}_{\mathrm{Fri}}$ perform better than others such as $\mathrm{QTc}_{\mathrm{B}}$, none of the methods in clinical use are precise from the point of view of information theory.

The influence of RR to QT is correctly removed, when $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ = 0. Therefore, the QT correction can be approached in a new way based on the transfer entropy. Taking the QT and RR history in account and combining the time series of the QT and RR for each time point, it would be possible to find the QT values for which $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ = 0. These QT values should be considered as the QTc values. [16] This new approach can be very important considering the QT correction methods, as it completely removes the interdependency. Potapov et al. have patented a novel method in 2020 [49]. The purpose is to provide a new QT correction method based on transfer entropy. The method is a topic of further study.

4 RESULTS

4.1 Distributions of RR and QT intervals

The Healthy data set consists of 202 samples, and the LQTS data set consists of 480 samples. The QT and RR distributions of both the Healthy and LQTS data sets are presented in Fig. 4.1.

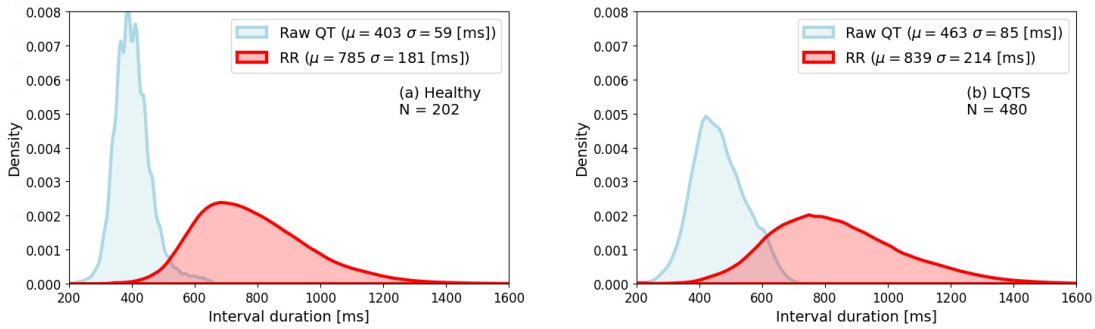

Figure 4.1. *QT and RR distributions for (a) Healthy (b) LQTS data set*

The mean value of QT intervals in the Healthy data set is about 403 ms, whereas the mean value of QT intervals in the LQTS data set is about 463 ms. The difference of the means with standard deviations of 59 and 85 ms is significant, but also expected considering the definition of the LQTS condition. Despite the differences of the QT interval distributions the RR distributions are relatively similar in both data sets. The mean values correspond to each other with a difference of below 54 ms. The standard deviations are 181 and 214 ms, so the difference in the mean values is relatively small. It is indeed expected that the RR distribution looks similar in both cases, since LQTS presumably affects only on the QT values. However, the possible effects of LQTS on the RR intervals deserve further studies.

It is noteworthy that the standard deviation has a significantly larger value in the RR distribution compared to the QT distribution. This is due to the fact that RR measures the distance between two full ECG cycles. This distance, i.e., the heart rhythm (or the pulse) varies significantly depending on the daily activities that vary between full rest and heavy exercise. The QT interval, on the other hand, measures a distance within a single ECG cycle, and therefore its variations are limited compared to those of the RR intervals.

There are several methods to analyze RR time series, as discussed in Sec. 2.2.2. However, in this thesis, we refrain from a detailed time series analysis with the methods mentioned above, since this goes beyond the scope of the work. Instead, we focus now on the qualitative nature of QT and RR intervals, respectively.

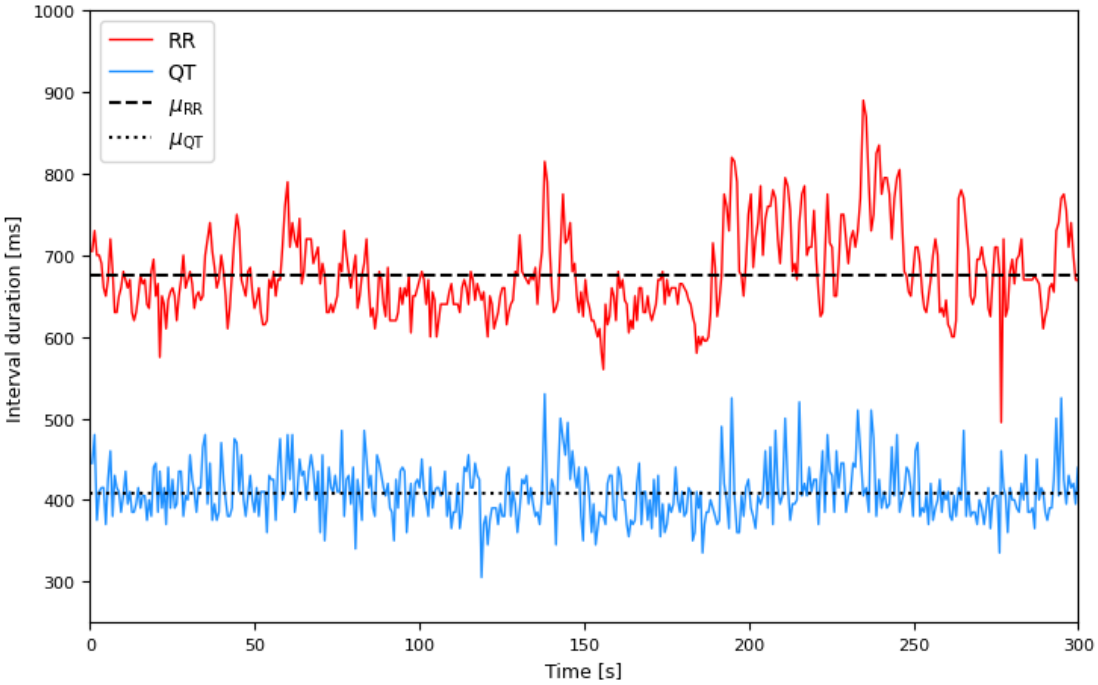

Figure 4.2. *Example of time series for QT and RR intervals over five minutes.*

Figure 4.2 shows five-minute excerpts of RR and QT time series of an LQTS subject (ID 6). There is quite a lot of variation in both QT and RR data, which is typical for physiological time series. Those variations appear on different scales, which indicates that the series may have fractal properties. A time series can be considered as a fractal, if it can be scaled in smaller and smaller parts while it qualitatively preserves its shape. The scaling properties of the ECG time intervals are beyond the scope of this thesis, but it is noteworthy, that a lot of research has been conducted regarding the topic (see Refs. [50, 51]). The quantitative analysis of the scaling properties or the fractal nature of the RR time series can serve as a great tool for diagnosing clinical conditions (see Refs. [52, 53]).

4.2 Relationship between RR and QT

Next we proceed on studying the explicit relationship between the RR and QT intervals. First, we take another look onto Fig. 4.2 to qualitatively assess the possible interdependencies. Despite of the apparent randomness of the QT and RR signals in Fig. 4.2, respectively, it is possible to observe clear correlations between them. A few distinguishable

sequences can be found in the series. At around 150 s the RR values get considerably high, and the corresponding QT values show similar behavior. Also, the RR values between 200 - 250 s reach considerably higher values compared to the RR mean value μ_{RR}. The corresponding QT sequence shifts also up as a result. It is easy to see that when the RR peaks are above the RR mean value μ_{RR}, also the QT peaks tend to be above the QT mean value μ_{QT}. The same effect occurs when the QT and RR peaks are below the mean value, respectively. Therefore, by examining the time series, a relationship can be visually verified. In other words, the QT and RR intervals seem to be clearly correlated.

The correlation can also be confirmed computationally by calculating the correlation coefficients, such as the Pearson correlation coefficient $\rho_{\mathrm{QT,RR}}$ and the cross-correlation CC. When the coefficient has a value of 0, there is no correlation. If the value is ± 1, the correlation is ideal either negatively or positively. The rest of the values fall between 0 and ± 1. The coefficient is calculated by dividing covariance of the QT and RR by the product of the standard deviations of the QT and RR.

In the QT-RR time series of Fig. 4.2, Pearson's correlation coefficient $\rho_{\mathrm{QT,RR}}$ = 0.32. The cross-correlation for the time series is also calculated. It measures the similarity between the two series, when the one is moved forward relative to the other. The normalized cross correlation coefficient NCC in Fig. 4.2 equals NCC = 0.99, which means that there is a strong cross-correlation between the series. These results confirm that there is a correlation between QT and RR, as discussed above.

The data can also be plotted in large point clouds. In a point cloud, an ECG recording is plotted to a diagram, where the x-axis is the duration of the RR interval between cardiac cycles n-1 and n, and the y-axis is the duration of the corresponding QT interval within cycle n. In this way, it is easy to capture the main trends of the QT-RR relationship. A polynomial function can be fitted in the data set to detect a general trend.

The point clouds are effective in examining the QT-RR distribution over a longer period of time. In the plots (see below), the data are complete recordings of 24h ECGs. Therefore, a large number of QT and RR intervals of different lengths are acquired, typically of order 100 000. Since the HR varies a great deal throughout the day, it is possible to combine a comprehensive visualization of the relation between the QT and RR.

Point clouds of a healthy male subject of age 29 and a male LQTS subject of age 7 are displayed in Figs. 4.3(a) and (b), respectively. A second-order polynomial is fitted to the point clouds, and a trend is observed by examining the slope of the polynomial.

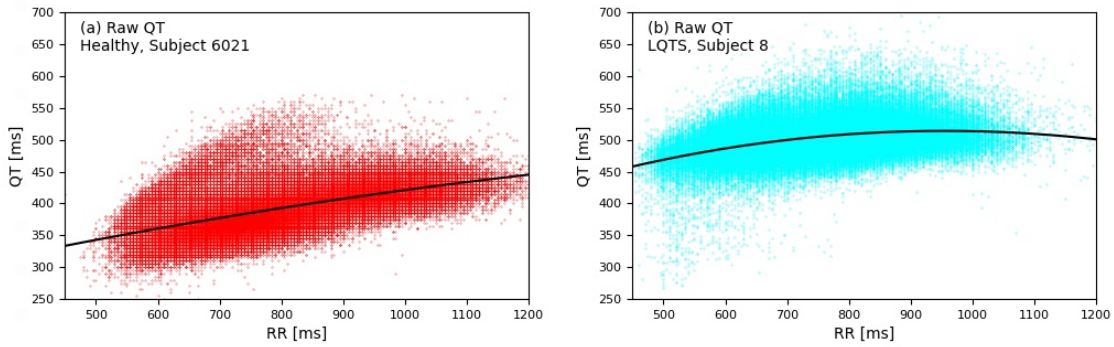

Figure 4.3. *Point clouds of corresponding RR and QT intervals with polynomial fits of second order for a (a) healthy subject and (b) LQTS subject.*

In both figures, the least squares polynomial fit has a non-zero slope, indicating dependence. The polynomial fit shows that the QT values become higher when the RR values become higher. This result confirms the previously known relationship between QT and RR. It can also be observed in Fig. 4.3 that the LQTS case consists of higher QT values compared to the healthy case. In Fig. 4.3(a) the highest QT values are around 550 ms, but in (b) the highest QT values are almost 650 ms. Even though the LQTS is diagnosed from the corrected QT values instead of the raw QT values seen in the figures, it is obvious that the LQTS yields higher QT values than the healthy case regardless of the possible QT correction. The results are well in line with the literature, where the QT-RR dependency is assessed (see Fig. 3 in Ref. [54])

4.3 Performance of QT correction methods

In this chapter, the QT correction methods presented in 3.4 are analyzed in more detail. The results of the Bazett's formula for the $\mathrm{QTc_B}$ [see. Eq. (3.1)] compared to the raw QT values of a 8-year-old male LQTS subject are shown in Fig. 4.4.

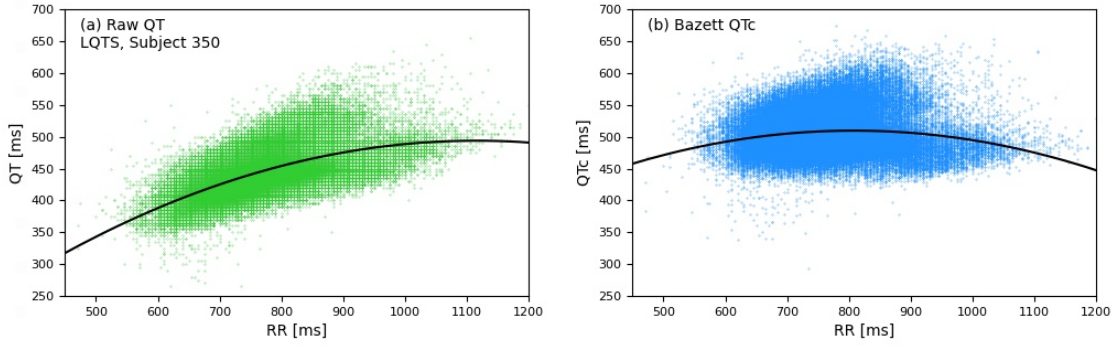

Figure 4.4. *Point clouds of corresponding RR and QT(c) intervals with polynomial fits of second order for an LQTS subject when using (a) uncorrected QT values (b) Bazett's QTc values.*

The data are from the same subject, so the performance of the Bazett's formula is easily

observable. In (b) the polynomial fit has still a non-zero slope, so the dependency is not completely removed, but it is clearly reduced. However, a fit with a single polynomial function does not provide considerable insight, since here the RR-QTc point cloud appears as two separate (sub)clouds: one horizontal cloud and one cloud with an almost linear slope. In fact, similar behavior but with two linear slopes can be seen in the uncorrected QT values in Fig. 4.4(a). There could be a physiological origin of this behaviour, but it is unknown at the time of this study. Nevertheless, the QT values corresponding to RR values at 600 - 700 ms differ considerably between Figs. 4.4(a) and (b). This is due to the fact that Bazett's formula tends to overcorrect the QT values at low RR (high HR), as noted above. The main purpose of the QT correction is to remove the relationship between the QT and RR. Based on the results above focused on individual subjects it is evident that the $\mathrm{QTc_B}$ has limited performance due to its extreme simplicity. Despite this deficiency the Bazett's method is still the most widely used QT correction method, as discussed above.

Density plots of the QT-RR distribution are useful to illustrate the concentration of the data points. The density estimation is calculated with Gaussian kernel density estimation in Python, and the pixels are stacked above each other based on the relative density of the points. The results for RR-QT relationship and the corresponding RR-QTc relationship with Bazett's formula for a 36-year-old healthy male subject and a LQTS subject are shown in Fig. 4.5.

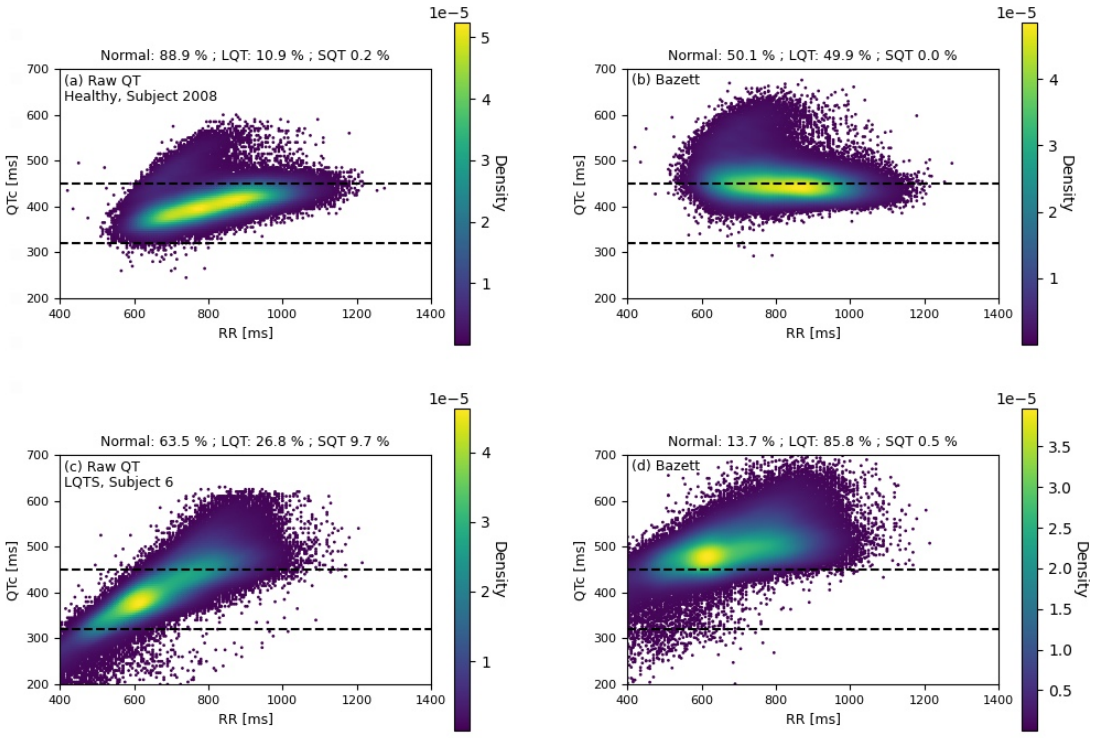

Figure 4.5. *Density plots of (a) Uncorrected QT values for a healthy subject, (b) Bazett's QTc values for the healthy subject, (c) Uncorrected QT values for an LQTS subject, (d) Bazett's QTc values for the LQTS subject*

In Fig. 4.5 the limits of the normal QTc values are drawn for reference. The minimum healthy QTc is considered to be at 320 ms and the maximum healthy QTc is considered to be at 450 ms. Points above and below these boundaries are indicated as LQT (long QT) and SQT (short QT), respectively, and their relative proportions are given in the figure. However, these lines are only plotted for visualization and they are not clinically valid for diagnosing the QT abnormalities. Also, applying the region of healthy QTc values is not valid for the raw QT values of plots (a) and (c). However, they serve as a good referential standpoint in comparing the shapes and values of two distributions.

In Fig. 4.5 it is clear that the $\mathrm{QTc_B}$ causes the distribution shift upwards in the QT axis. Almost 40$\%$ of the QT values are shifted up from the normal QTc region when applying the Bazett's formula for the healthy subject. However, most of the RR interval values are relatively low in Fig. 4.5(a) of the healthy subject, so the Bazett's formula tends to over-correct the values, as discussed before. In the case of an LQTS patient in Fig. 4.5(c-d), Bazett's formula seems to produce plausible results, since a large fraction (86$\%$) of the QTc values are located above the upper threshold. However, the problem here focuses on possible misdiagnosis of the healthy subject due to a large fraction (50$\%$) of "false positives" in the QTc values in Fig. 4.5(b).

Next in Fig 4.6 we examine the performance of four of the most widely used conventional methods presented in Sec. 3.4, i.e., Bazett, Fridericia, Framingham and Hodges. Here, we consider a 49-year-old female healthy subject as an example.

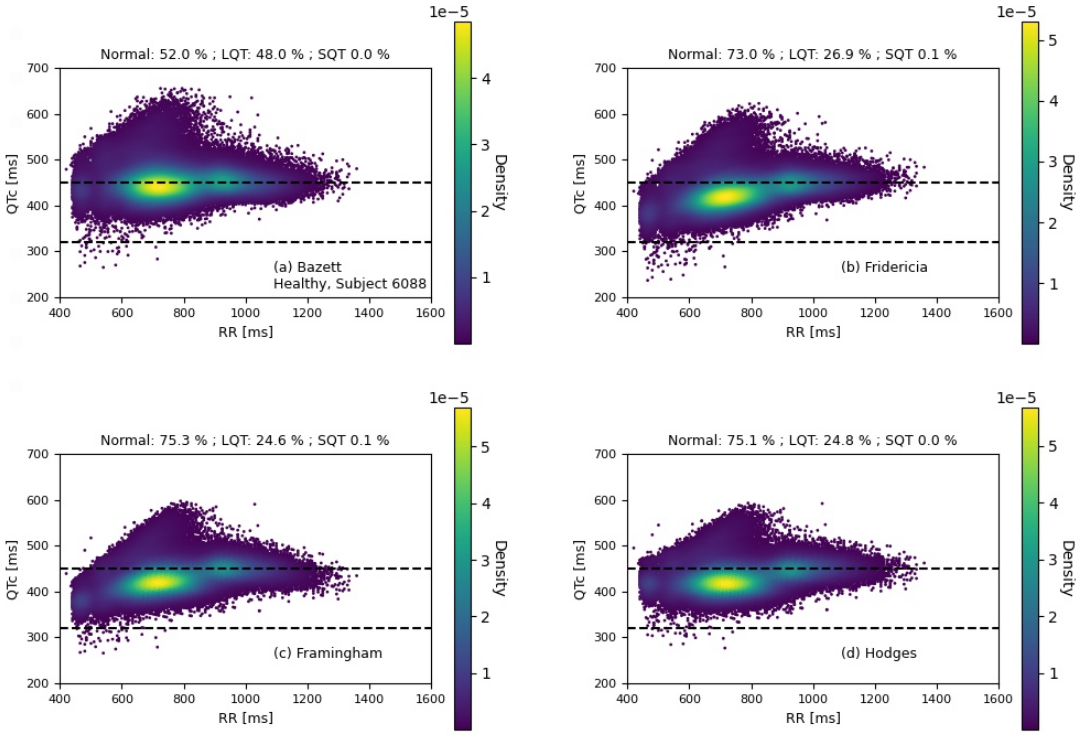

Figure 4.6. *Different QT correction methods for a healthy subject: a) Bazett, b) Fridericia, c) Framingham, d) Hodges*

It can be seen in 4.6(a) that Bazett's formula shows 48% of the QT values to be abnormally long, whereas the other methods in Figs. 4.6(b-d) show that about 25% of the QT values are abnormally long. This underlines the inferiority to Bazett's method compared to the other methods. As discussed before, this kind of behavior is also typical for the Bazett's method, and the rest of the methods are performing better in this regard. However, the fact that all the methods yield at least 25% of "false positives" for abnormally long QTc values is alarming in view of the wide use of the conventional methods.

Fig. 4.7 presents similar analysis for a 7-year-old male LQTS patient.

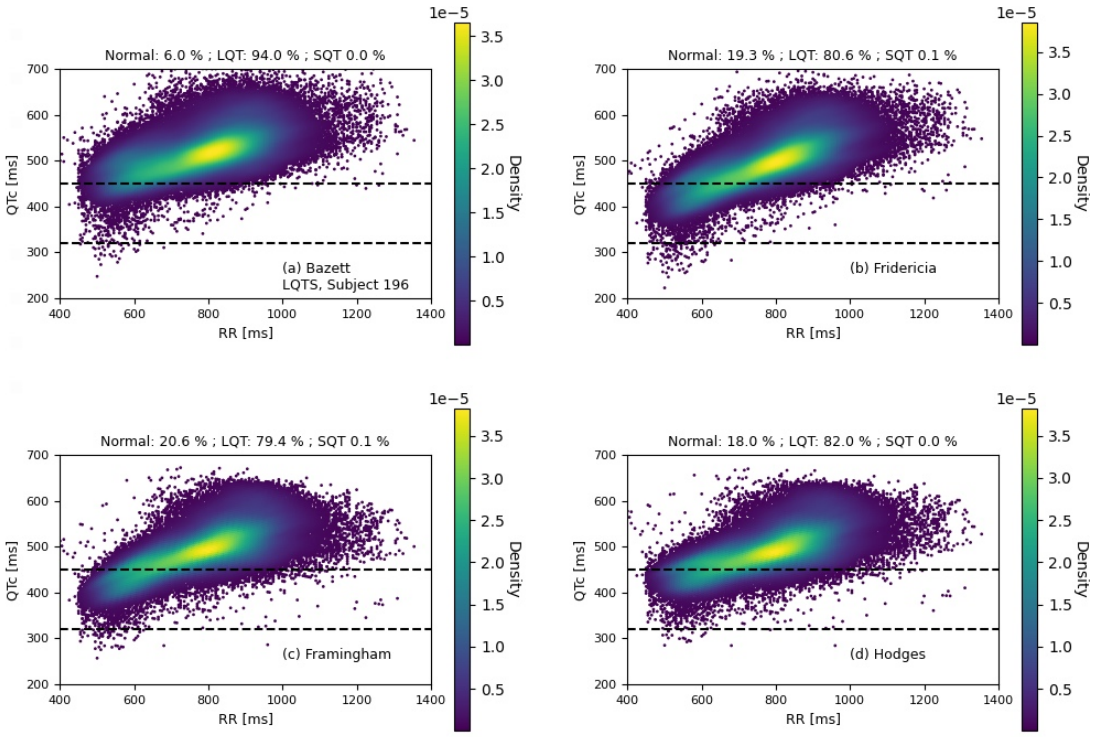

Figure 4.7. *Different QT correction methods for an LQTS subject: a) Bazett, b) Fridericia, c) Framingham, d) Hodges*

In Fig. 4.7(a) Bazett's formula shows clearly that most of the data points (94%) are in the LQT area. Actually, now Bazett's formula performs "better" in terms of "correct positives" compared to the other three methods, for which the proportion of LQT values vary between 79% and 82%. The behavior of Bazett's formula is plausible due to its obvious overcorrection of the QT intervals that affects both healthy and LQTS subjects. Nevertheless, the shapes of all the density concentrations indicate that the relationship between QT and RR is not reduced, since the densities follow a clear trend with a positive slope.

Finally we briefly examine the performance of the new QT correction [55] method based on transfer entropy in Eq. (3.5) We compare the method against Bazett's formula for a 72-year-old female subject.

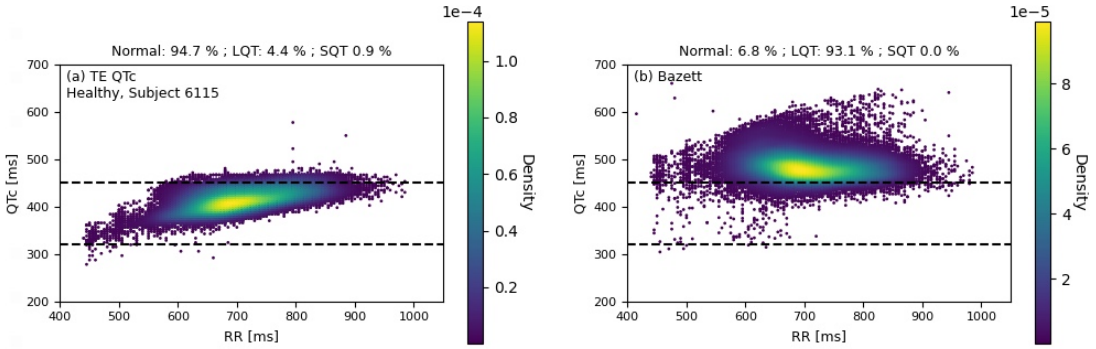

Figure 4.8. *RR-QTc relationship for a healthy subject with (a) transfer entropy -based QT correction method and (b) Bazett's correction method.*

In the Fig. 4.8 the superiority of the TE-based method over Bazett's method becomes obvious. Almost 95% of the QT values are in referential normal region after the TE-based correction, whereas Bazett's formula corrects over 93% of the QT values to be abnormally long. The difference is significant, and based on the Bazett's correction in Fig. 4.8(b) the misplaced suspicion of the LQTS is extremely likely. The RR distribution in the sample is relatively low compared to the reference RR value of 1 000 ms, so the already discussed overcorrection of Bazett's formula is pronounced. It is noteworthy, that the TE method does not overcorrect the QT values. On the other hand, the shape of the density is relatively horizontal. This shows that the new method has potential in significantly removing the RR influence on QT values, which is the principal objective of QT correction. However, this aspect still requires thorough validation with the full data set, which is currently ongoing.

It is noteworthy, that none of the figures above serve as a clinically significant method to diagnose the LQTS. Most commonly, the diagnosis is done by manually measuring a few QT intervals from the ECG recordings, applying a QT correction formula to measured intervals, and combining these results with the other indicators presented in Table 2.1. Hence, instead of trying to diagnose the conditions, the figures above show the general statistical patterns of both the QT-RR relationship, and overall performance of the QT correction methods. Most importantly, Figs. 4.5 – 4.7 demonstrate the weaknesses of Bazett's QT correction formula, as well as the deficiencies of the other conventional QT correction methods. Finally, in Fig. 4.8 exemplifies the high potential of the TE-based QT correction method compared to the clinically used Bazett's method in a case of a low RR distribution.

5 DISCUSSION AND CONCLUSIONS

In this thesis, the relationship between the QT and RR intervals in the electrocardiogram (ECG) was examined. The clinical and physiological importance of the QT interval measurement was underlined. The most common correction formulas to remove the relationship were presented and analyzed. Finally, a new approach to reduce the QT-RR relationship using the information theory and transfer entropy was presented.

The relationship between the QT and RR intervals was visualized and it became evident, that the intervals are interdependent. Longer or shorter RR intervals correspond to longer or shorter QT intervals, respectively. Physiologically, the results were as expected. When the heart rate is lower, the beats are more infrequent and therefore the intervals are longer. Then the heart pumps blood more slowly, so that the de- and repolarization of the ventricles last longer, leading to longer QT intervals. The same principle applies to short intervals as well. Summarizing, the mechanical and electrical behavior of the heart are interconnected in a natural way.

The QT interval is clinically a fundamental segment of the ECG, and many clinical conditions can be diagnosed with quantitatively measuring the QT interval. The QT correction methods to reduce the dependence on RR intervals are therefore essential in order to examine the normalized (or corrected) QT intervals independent of the heart rate during the measurement. However, the conventional QT correction methods were shown to be inefficient and imprecise in reducing the relationship.

The performance of different QT correction methods was visualized for long ECG recordings of both healthy subjects and for long QT syndrome (LQTS) subjects. It was shown that the widely used Bazett's QT correction formula is inefficient and can lead to wrong conclusions due to a large relative fraction of false positives for healthy subjects. In particular, it was shown that the Bazett's formula severely over- and undercorrects the QT intervals. Also the other QT correction methods of Fridericia, Framingham and Hodges were shown to be inefficient in reducing the RR dependency. Hence, these results underline that there are severe challenges in clinical cardiology to reliable utilize the corrected QT values. In essence, there is an strong need for better QT correction methods that minimize the RR dependence.

Importantly, not only the present QT correction methods are inefficient, but also the diag-

nostic criteria themselves may need substantial revision. This is due to the fact that the critical limits for corrected QT values have been composed based on the results procuded by the often erroneous conventional methods. Thus, the present criteria may be considered misleading.

Finally, a principle of a new QT correction method based on the transfer entropy was presented. It has been previously shown that the RR history has a considerable effect on the upcoming QT values. In other words, there is information transfer from RR to QT, and much less vice versa. In the new method, the properties of the transfer entropy are employed to significantly reduce the RR dependence. Therefore, the approach is viable in examining the QT intervals independent of the heart rate. As shown here, the results of the new method are very promising in comparison with the conventional QT correction. However, further demonstration and validation of the method are needed. This is a topic for a further study.

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