Model Based Approaches to Incorporate Recordings of Multiple Heartbeats into the Inverse Problem of Electrocardiography

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Abstract of the Dissertation

ModelBased Approaches to Incorporate Recordings of Multiple Heartbeats into the Inverse Problem of Electrocardiography

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Solutions to the inverse problem of electrocardiography, also known as Electrocardiographic Imaging (ECGI), non-invasively image the electrical activity of the heart to localize and quantify normal and abnormal cardiac electrophysiology, and have recently attracted considerable attention in the research community. These methods have great promise to aid planning of catheter ablation procedures as well as for screening and diagnosis. They solve a problem that uses electrocardiographic measurements on the body surface (ECGs) to characterize the unknown electrical activity of the heart, here described by the time series of distribution of electrical potential on the heart surface. To do so, they rely on the calculation of a “forward” model relating the potentials on the heart with the ECGs, typically known as “forward matrix”. However, ECGI has some limitations that impede its application to routine clinical practice. One of them is the ill-posedness of the forward model, which causes inverse solutions to be unreliable even with small levels of noise in the inputs and the model. One way of improving the resilience to this problem is to increase the Signal to Noise Ratio (SNR) of the signal by the incorporation of recordings from multiple heartbeats. During the course of this thesis we have addressed this approach in several applications: imaging the presence of T-wave alternans on the heart, localizing the site of earliest activation of pre-ventricular contractions (PVC) and the characterization of the errors introduced in the forward matrix.

T-wave alternans (TWA), defined as a beat-to-beat alternation of the T-wave in the ECG, have been advocated for the past two decades as a promising marker of susceptibility to sudden cardiac death (SCD). However current ECG tests for TWA have been reported to have high sensitivity but low specificity for SCD and thus there is still no consensus on their predictive value. The distinction between concordant alternans—for which the whole heart alternates at the same phase—and discordant alternans—for which different regions of the heart alternate in different magnitude and
phase—is of special interest as the latter have been observed preceding ventricular fibrillation in animal experiments and simulations. Thus, better characterization of the spatial behavior of discordant alternans could lead to improvements in the predictive value of TWA tests. Motivated by the desire to identify and localize discordant regions from body surface measurements, we present two studies related to TWA. In the first we introduce a theoretical characterization of how concordant and discordant alternans appear on the body surface. In the second study we present a method that directly estimates the location and phase of discordant TWA on the heart surface from body surface measurements by combining techniques from TWA detection with the methodology of ECGI.

The results obtained with both studies on TWA suggest considerable promise that these methods may help increase our ability to understanding TWA based on body surface recordings, and thereby more clearly study its link to SCD, by providing previously unavailable spatial information to researchers and clinicians.

Accurate detection of the site of first activation in a pre-ventricular contraction (PVC) can lead to substantial improvements in pre-procedure planning for ablation interventions and the subsequent reduction length and costs of these interventions. However, to be able to accurately localize these sites, it is necessary to obtain reliable inverse reconstructions of the activation wavefront that propagates throughout the heart during QRS. In this thesis, we present two approaches to increase the SNR through the incorporation of multiple recordings from the same underlying PVC activity. In the first one, we study deterministic averaging approaches to incorporate multiple heartbeats in an inverse solver. In the second one, we extend the previous averaging approaches into a statistically inspired model to characterize the beat-to-beat fluctuations observed on the ECG.

These studies showed some improvement over regular averaging techniques, but the beat-to-beat variability still present in the solutions suggested that there is need to better characterize the sources of noise, which led to the third contribution of this thesis.

Model mismatch in the forward matrix is a significant factor in inverse solution error. This is particularly problematic when incorporating multiple heartbeat recordings, as the heart moves within the thorax from beat to beat due to respiration. Therefore, the use of a single forward matrix necessarily introduces model errors in this setting. To overcome this limitation, we propose in this work to efficiently characterize the changes in the forward matrix due to movements of the heart and then adapt the forward matrix to each individual heartbeat. With that objective we developed a new method to characterize errors in the forward matrix that are produced by movement of the heart. This method approximates the changes in volume conductor geometry with a parameterized transform and then encapsulates the forward matrices that these changes would generate into a single mapping function that describes the whole sequence of computations. With this mapping, it is then possible to apply optimization methods that correct for the errors in the forward matrix, generating an approximate forward matrix corresponding to an estimated position and orientation of the heart and, if desired, also solve for the unknown cardiac electrical potentials in an iterative fashion.

We expect this work to impact ECGI research and beyond. In ECGI, we expect to improve results in animal models used for understanding mechanisms and validating inverse solutions and to reduce uncertainty of inverse solutions obtained in clinical applications, and to expand the range of potential clinical problems for which ECGI can be reasonably applied by reducing the need for extensive high resolution anatomical imaging. Beyond ECGI, the capacity to non-invasively track the position of the heart has the potential to impact a number of other clinical problems, for example,
improving catheter registration in ablation procedures.
Chapter 1

Introduction

Electrocardiography is a tool used in daily clinical practice to non-invasively image the electrical activity of the heart. It has multiple applications, ranging from diagnosis of heart diseases (e.g. conduction blocks, presence of arrhythmogenic substrate, re-entry pathways, etc.) to pre-procedure planning for catheterized ablation interventions \[64\]. However, clinical use of the electrocardiographic recordings (ECG) relies on the detection of features extracted from large population studies including many subjects and disease states \[36\].

Electrocardiographic Imaging (ECGI) is the technology that non-invasively images the electrical activity of the heart from body surface potentials to localize and quantify normal and abnormal cardiac electrophysiology. To do so, ECGI systems solve what is known as the inverse problem of electrocardiography, which relies on the “inversion” of a forward model that relates the electrical activity on the heart to the measurements on the body surface. The challenge of this method is that this relation is ill-posed and, thus, small errors in the measurements or the forward model can lead to wide variations in the solutions. It is thus necessary to regularize, that is to enforce prior knowledge about the desired solutions to stabilize them.

However, the imposition of prior knowledge has an inherent trade-off between the sensitivity of the solutions to random noise fluctuations—for small amount of regularization—and introduction of a strong bias towards a predetermined solution—for strong imposition of regularization. Hence, most regularization methods search for a trade-off point that provides stable solutions while preserving the useful information in the measurements. Typically, this point of equilibrium depends on the signal-to-noise ratio (SNR) of the available data and the quality of the model used. Thus, one approach to reduce the amount of regularization needed, is to increase the SNR of the signal by combining the information from multiple recordings of the same repeating phenomena. In the
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case of the ECG, we do so by taking advantage of the cyclical behavior of the cardiac activity and combine multiple heartbeats into a single inverse solver.

In the research presented in this thesis, we apply this approach of combining multiple heartbeats into an inverse solver. We model the beat to beat variations in the ECG for three electrocardiographic imaging problems: the spatial characterization of T-wave alternans (TWA), the detection of the site of first activation in pre-ventricular contractions and the correction of the errors in the forward model created due to changes in position of the heart.

In the following chapters, we provide a brief background description of the relevant electrophysiology and the ECGI systems. Then, we describe the work done on the aforementioned imaging problems in the three parts listed below:

**Part I: T-wave Alternans**

T-wave alternans (TWA) are characterized by a beat-to-beat alternation of the T-wave and are produced by abnormal alternating activity of the heart tissue. Improved characterization of the spatial behavior of these tissue abnormalities could lead to improvements in the predictive value of TWA tests to identify subjects at risk of sudden cardiac death (SCD). We explored this imaging problem from the perspective of the forward and inverse problems in:

- **chapter 3** the characterization of TWA from the perspective of the forward problem in electrocardiography. We present a generative model of how the abnormal alternating behavior of the TMPs appears on the body surface.
- **chapter 4** the creation of an inverse method that maps the alternating phenomena on the heart from non-invasive ECG measurements. In it, we leverage the characteristic behavior of TWA across heartbeats to stabilize the inverse solutions.

The publications related to this part are:

- J. Coll-Font, B. Erem and D.H. Brooks, “A Potential-Based Inverse Method to Non-Invasively Localize Discordant Distributions of Alternans on the Heart from the ECG”, *In preparation*
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Part II: Localization of First Site of Activation

Accurate detection of the site of first activation in a pre-ventricular contraction (PVC) can lead to substantial improvements in pre-procedure planning for ablation interventions and the subsequent reduction in length and costs of these interventions. Our working hypothesis was that, incorporating multiple heartbeats from recordings emanating from the same underlying PVC pattern could improve the stabilization of the inverse solutions. During the course of this thesis we have addressed this problems in:

- **chapter 5**: a study of deterministic averaging approaches to incorporate multiple heartbeats in an inverse solver.
- **chapter 6**: a study comparing the previous averaging methods to a statistically inspired model of the physiological noise in the ECG.

The relevant publications from this topic are:


Part III: Correction of the Heart Geometry

The geometric model errors created due to changes in position of the heart during respiration or postural changes introduce multiplicative noise to the recorded ECG and affect the accuracy of the inverse solutions. To overcome these errors, it is necessary to model the changes in the forward matrix due to movements of the heart and then compensate for those. In this thesis we:

- **chapter 7**: develop a method that first models the changes in the forward matrix due to changes in position of the heart and then uses it in an optimization solver to find for the position of the heart during each heartbeat.

The publications related to this contribution are:

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Other contributions during the course of this PhD that are not related to this thesis are:


- J. Coll-Font and B. Erem and P. Stovicek and D. H. Brooks and P. M. van Dam, “Quantitative comparison of two cardiac electrical imaging methods to localize pacing sites”, in Computing in Cardiology Conference (CinC), 2015


Chapter 2

Background

In this chapter, we provide some basic background about electrophysiology and technical concepts on electrocardiographic imaging that are relevant to this thesis.

2.1 Electrophysiology

The heart is an electromechanical pump which keeps the blood flowing within the circulatory system through repeated contractions of the myocardium. These contractions are driven by an ion flow across the membrane of the myocardial cells which, in turn, creates a potential difference known as the transmembrane potential (TMP) \(^{[75]}\). The TMPs serve, on the one hand, as the driver for contraction by means of a mechanism known as excitation contraction coupling \(^{[7]}\). At the same time, the extracellular currents generated by the TMPs flow into the heart and the surrounding volume conductor and provide a means of detecting cardiac electrical activity. Thus, the electrical activity of the heart provides some information about its correct or incorrect function that physicians can use for diagnosis. They do so through the indirect observation of the TMP with invasive measurements on the heart—the heart surface potentials (HSP)—or non-invasively on the torso surface—the body surface potentials (BSP).

The normal activity of the heart is characterized by the alternating contraction of the atrial and the ventricular chambers. The contraction movement of each chamber is in turn classified into two phases: systole, during which the heart contracts, and diastole, during which the heart relaxes. Electrically, these are preceded by a depolarization phase, characterized by a current wavefront that propagates throughout the myocardium, switching the TMP from a resting state of \(-90\text{mV}\) to \(10\text{mV}\), and a repolarization phase, when the potentials smoothly return to the \(-90\text{mV}\) baseline \(^{[30]}\).
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Figure 2.1: Illustrative example of a the transmembrane potentials throughout a full cardiac cycle. Above, the evolution of the spatial distribution of transmembrane potentials. Below, the temporal profile of the transmembrane potentials at a single node. Simulations generated with the ECGSIM software [51].

Figure 2.1 shows an example of the normal evolution of the TMP distribution on the ventricles during a full cardiac cycle.

The temporospatial pattern of propagation of the depolarization wavefront precedes and governs the contraction movement of the heart. Irregular behavior in this phase might lead to multiple pathologies characterized by inefficient blood pumping or none at all, as happens for ventricular fibrillation (VF) [65]. In turn, irregularities during repolarization are tied to abnormal tissue characteristics and offer putative mechanisms for the creation of turbulent depolarization wavefronts that can lead to VF [74].

The interest in ECGI lies in this connection between electrical activity and tissue or whole organ properties [5]. Typical ECG analysis techniques are capable of detecting instances of abnormal behavior, but offer very limited information about the specific spatial properties of those (e.g. depolarization wavefront patterns, localization of abnormal tissue properties, etc.). Improving the spatial resolution could bring better understanding of the pathologies observed and improve current diagnostic tools.
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2.2 Electrocardiographic Imaging (ECGI)

The field of ECGI has gained considerable recent attention both from industry and research, due to its potential impact to pre-procedure planning and risk stratification. The recent acquisition of CardioInsight by Medtronic has sparked the commercial interest of this technology. And in response, the research community has joined in an effort to share ideas and data by forming the Consortium of Electrocardiographic Imaging (CEI) (http://www.ecg-imaging.org/). This consortium seeks to foster interaction among researchers in ECGI and promote the exchange of methods and data through workgroups and the EDGAR data repository [4].

The ECGI research field is driven by two problems that need to be solved in order to image the electrical activity of the heart: the forward and the inverse problems in electrocardiography. The forward problem tries to predict the body surface potentials (BSP) from known electrical activity of the heart. In contrast, the inverse problem tries to solve the reverse problem, that is to estimate the electrical activity of the heart from the non-invasive BSP. In this section we provide a brief description of both problems and particular solutions that are relevant to this thesis. For more details we refer the interested readers to [37][59].

2.2.1 Forward Problem in Electrophysiology

A complete formulation of a forward problem needs to specify a model for the electrical sources on the heart and the conducting medium—the volume conductor—that contains them.

The source model provides a simplified description of the electrical activity of the heart. For this, it is necessary to find a balance between an accurate description of this electrical behavior and a computationally feasible model. For example, Einthoven modeled the electrical activity with a dipole that changes in amplitude and orientation during each heartbeat [37]. Due to its simplicity, this model is still used to interpret ECG measurements, although it provides limited accuracy in the representation of the heart. On the other extreme, there are now cardiac propagation models that describe the TMPs with highly accurate numerical models that characterize the flow of ion currents across the membrane [58]. These models provide realistic representations of the electrical behavior of the heart, but their computational demands and extensive number of parameters limit their applications.

In between, there are two source models that are often used to solve the inverse problem in electrocardiography: the equivalent double layer (EDL) and the surface potential representation—here denoted as heart surface potentials (HSP) [5][52]. Both methods represent the electrical activity
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of the heart with equivalent sources on a closed surface around it. The difference between them lies in how these sources are defined. On one hand, the EDL uses a double layer of dipoles representing the depolarization wavefront on a surface tightly enclosing both the epicardial and endocardial surfaces of the myocardial tissue. On the other, the HSP model uses a single layer of potentials on a closed surface around the heart, this surface can be tight as for the EDL or cover the pericardial surface around the heart. These methods offer a good balance between complexity and representation detail and will be used throughout the research presented in this thesis.

Whatever model is being used for the sources, to characterize the electric field generated within the torso it is necessary to also model the volume conductor that contains them. From electromagnetic theory, it is well known that the potential field within the torso depends only on its geometry and the conductivities inside, which can be described by Poisson’s equation (Equation 2.1).

$$\nabla \cdot (\sigma(x) \nabla \Phi(x)) = -i_v \forall x \in \tau \quad (2.1)$$

Where $\sigma$ determines the conductivities within the torso, $\Phi$ is the potential field in it and $i_v$ the current at the sources. Moreover, with the absence of other sources in the volume conductor, the previous equation can be expressed as Laplace’s equation (Equation 2.2)

$$\nabla \cdot (\sigma(x) \nabla \Phi(x)) = 0, \forall x \in \tau \quad (2.2)$$

In this case, the effects of the sources are introduced as a boundary condition, known as Dirichlet boundary condition. Finally, a complete characterization of the volume conductor often includes another boundary condition, known as Newmann boundary condition. This constraint imposes zero flux of current across the torso surface to account for the insulation effect of the air.

Each combination of source and volume conductor model, leads to a specific formulation of the forward problem. Throughout this thesis, we use the HSP as a source model and assume isotropic and piece-wise continuous conductivities in the volume conductor. Thus, solutions of the forward problem can be computed from discretized surface geometries of, at least, the heart and torso and the scalar conductivities defined inside of each surface. The solution is then obtained by solving Laplace’s equation with a boundary element method (BEM) solver [67], which returns a matrix known as the “forward matrix”. Finally, the multiplication of the forward matrix, here denoted as $A$, and the HSP, denoted as $\varphi$, computes the corresponding BSP, denoted as $\Phi$:

$$\Phi = A \cdot \varphi \quad (2.3)$$
Despite the fact that the equations to be solved are known and that there are freely available software implementations of PDE solvers, such as Boundary Element Method (BEM) or Finite Element Method (FEM) [2,67], some aspects of the forward problem remain open research questions in the ECGI community. There is still no consensus on the required level of detail of the geometric models [6,57,60,62,63], which are the appropriate conductivities of the tissues [24,33,73] nor the effects of segmentation errors [15,21].

Moreover, a source of error that has not received much attention is the one introduced due to the changes of position of the heart. When a subject changes position or during the respiration process, the heart moves within the torso, thus changing the volume conductor. Consequently, the measured BSP change in morphology even though the underlying electrical activity is the same.

There has been some work with human, animal and synthetic models to determine the impact of the heart position to the BSP. In humans, these studies showed that changes in position of the heart affect different parts of the PQRST sequence [1,41] and that these are subject specific [49]. More specifically, the variations observed in the BSP created due to respiration can be described as a continuous change in location of the maxima and minima in the spatial distribution of the BSP [3]. Synthetic and animal models have provided a more systematic understanding of the BSP variations due to the moving heart and showed the individual effects on these of each transformation of the geometry (e.g. translation or rotation of each axis) [38,70].

These variations in the BSP cannot be captured with the typical solutions of the forward problem since these rely on static geometries of the heart and torso. In Part III we address this issue and describe a forward model that accounts for those movements and corrects the solutions of the forward problem by leveraging the changes in the BSP across consecutive heartbeats.

### Inverse Problem in Electrophysiology

The objective of the inverse problem is to estimate the electrical activity of the heart from non-invasive BSP measurements. In order to solve this problem, it is first necessary to solve the forward problem and then reverse the mapping from sources on the heart to BSP. Thus, as in the forward problem, different definitions of the source model will lead to different formulations of the inverse solutions.

In all cases, an essential condition of the inverse problem is that it is ill-posed—*i.e.*, there is a loss of information from sources on the heart to the BSP. This condition is problematic since it makes the solutions of the inverse problem very sensitive to noise. Thus, it is necessary to introduce
prior knowledge about the desired solutions in the form of regularization \[59\]. The regularization imposed can be in the form of spatial or temporal characteristics of the electrical activity of the heart and it is tied to the specific source model used. Moreover, the strong restrictions of some source models act in themselves as a form of regularization. For example, the EDL source model results in a non-linear optimization problem whose initialization acts as an indirect form of regularization.

To simplify the following description, we restrict the source model formulation to the HSP, which is the model used to solve the inverse problems presented in this thesis. The most commonly used form of spatial regularization for this source model is Tikhonov regularization which solves

\[
\arg\min_\varphi \| \Phi - A \cdot \varphi \|_2^2 + \lambda \| R \cdot \varphi \|_2^2.
\]

Equation 2.4

where \( \Phi \) are the BSP, \( \varphi \) the unknown HSP and \( A \) is the forward matrix. The other two terms, \( \lambda \) and \( R \), respectively determine the amount and type of regularization being imposed. Typical options for \( R \) are the identity matrix (0\(^{th}\) order Tihonov), which constraints the amplitude of the solutions to be “small” or the Laplacian operator applied over the heart surface (2\(^{nd}\) order Tikhonov), which tends to favor solutions that are smooth in space.

Another common regularization technique is the Truncated Singular Value Decomposition (TSVD) \[27\], which computes the inverse matrix as the sum of outer products of its singular vectors \((u_l \text{ and } v_l)\), weighted by the inverse of its singular values \((\sigma_l)\).

\[
\hat{A}(p)^\dagger = \sum_{l=1}^{L} \frac{1}{\sigma_l} v_l u_l^T
\]

Equation 2.5

To regularize, this method restricts the computation to the first \( L \) singular values, which, in the case of the forward matrices, tends to restrict the solutions to the low frequency component in space.

One problem with most regularization methods is that these introduce bias to pre-specified solutions that, in the limit, is wrong. For example, solving the inverse problem with Tikhonov and setting \( \lambda \to \infty \) leads to HSP equal to 0. On the other hand, \( \lambda \to 0 \) is equivalent to no regularization and thus leads to unstable results. There are many methods that search for a “good” regularization parameter \[59\] that enforces as little regularization as possible without compromising the stability of the inverse solutions. These methods tend to be sensitive to the noise levels in measurements, thus one option to reduce the amount of regularization needed is to increase the signal to noise ratio (SNR). This is the approach taken throughout the work described in this thesis. In particular, we take advantage of the cyclical behavior of the cardiac activity and assemble multiple heartbeats (i.e. multiple observations of the repeating activation on the heart) into an inverse solver.
Part I

T-wave Alternans
Introduction

T-wave alternans (TWA), somewhat loosely defined as a beat-to-beat alternation of T-wave amplitude in the ECG, have been advocated for the past two decades as a promising marker of susceptibility to sudden cardiac death (SCD). However, current ECG tests for TWA have been reported to have high sensitivity but low specificity for SCD and thus there is still no consensus on their predictive value \[46, 72\].

More recently, investigators have reported that the TWA phenomenon may be more complex than originally thought, with a variety of distinctions between different methods to both conceptualize and analyze the alternans phenomenon \[72\]. Among these, one which has received considerable attention is alternans generated at a tissue level by an alternation in Action Potential Duration (APD) \[61, 74\], resulting in a beat-to-beat pattern in the transmembrane potential (TMP) length with the form short-long-short or with opposite phase, long-short-long. A number of studies using either cardiac propagation models or animal experiments have been carried out to understand the possible origins of APD alternation on the heart and the relationship to SCD \[35, 56, 74\]. These models have been taken as demonstrating putative causal mechanisms for the link between body-surface TWA and SDC. One important discovery from these myocardial propagation studies has been that there is an important distinction between “concordant” alternans, in which both ventricles alternate in phase—for example, if the alternation is between longer and shorter recovery intervals, the entire ventricular mass will have longer recovery on one cycle, shorter on the next, etc.—and “discordant alternans” \[46\]. In the latter, the alternans either are out of phase in different regions of the heart, \(i.e\). long-short-long in one region, short-long-short in the rest, or there may only be one region of the heart undergoing alternans while the rest is alternans-free. The concordant/discordant distinction is important since discordant alternans have been observed before ventricular fibrillation in animal experiments as well as computer simulations and are thought to be more arrhythmogenic than concordant alternans \[35, 56\]. A possible justification for this increased susceptibility of discordant alternans is the interaction between the spatial gradients these create during repolarization and the regular sinoatrial activation, which can lead to re-entrant circuits and degenerate into ventricular fibrillation and SCD. These findings suggest that the low specificity of current clinical TWA tests might be improved by taking this distinction into account and properly characterizing the discordant cases.

Motivated by the desire to identify and localize discordant regions from body surface measurements, we present two studies related to TWA. In the first we introduce a theoretical charac-
terization of how concordant and discordant alternans appear on the body surface. In the second study we present a method which directly estimates the location and phase of discordant TWA on the heart surface from body surface measurements by combining techniques from TWA detection with the methodology of ElectroCardioGraphic Imaging (ECGI).

To place our work in context, we first very briefly summarize some relevant reports in the literature. To aid in our description, we will denote TWA on the body surface, as seen in ECG signals, as body surface potential (BSP) TWA (BSP-TWA), TWA on the heart surface, as seen in electrograms, as heart surface potential (HSP) TWA (HSP-TWA), and the time course of TWA during the T-wave, as estimated from a sequence of heartbeats, as a "TWA signal". In the context of discordant alternans, studies have been published on methods to measure the spatial distribution of HSP-TWA, including optical imaging studies on animal hearts that searched for the link between discordant alternans and ventricular fibrillation (VF) \cite{orini2001} and the work of Orini et al. that studied whether different TWA detection algorithms applied to electrograms (EGMs) were capable of differentiating discordant from concordant alternans \cite{orini2001}. However BSP-TWA is typically detected in individual body surface ECG leads, separately, with single-channel signal processing methods designed to detect a repetitive beat-to-beat variation in amplitude \cite{mainardi2001}. While such methods may detect the presence of TWA, the physiological link to localization of activity in the heart is lost, and thus they cannot identify the spatial distribution of the underlying phenomena. Some work has been reported on methods to directly characterize discordance in HSP-TWA by signal processing applied directly to BSP-TWA. For example, some authors have used standard BSP-TWA detection methods across several ECG leads to extract a measure of heterogeneity that is linked to SCD \cite{mainardi2001,mainardi2002} and thus presumably to discordance.

A few groups have reported methods to take heart-torso spatial relationships into account \cite{mainardi2001,mainardi2002,mainardi2001,mainardi2001,mainardi2001,mainardi2001,mainardi2001}. Some have addressed this through the "forward problem", that is by attempting to reproduce alternans as seen in torso measurements by simulating different alternans distributions on the heart surface and then feeding them into a model relating heart surface to body surface potentials (a solution to the forward problem), with the assumption that the underlying cause of the observed BSP-TWA is an alternation of repolarization in the transmembrane potentials (TMP) \cite{mainardi2001,mainardi2001}. The authors concluded that discordant alternans introduce variations across leads on the BSP-TWA. Floré et al. confirmed with pig experiments that discordant and concordant alternans can be differentiated in the body surface TWA \cite{mainardi2001}. There have also been a few studies which, as with the work presented here, there was an attempt to non-invasively estimate the presence of discordant alternans on the heart from body surface ECG measurements. Mainardi and Sassi \cite{mainardi2001,mainardi2001}
reported on a method which calculates an index of repolarization heterogeneity on the heart directly from ECG measurements, based on the so-called dominant T-wave approximation [54]. More in the spirit of our work, Shvehlikova, Lenkova and Tysler developed an inverse method that detected isolated occurrences of TWA on the heart by modeling the TWA source as a set of candidate dipoles distributed on the heart surface and applying a dipole-based inverse solution to BSPs to identify the most appropriate locations among those candidates [69, 71].

The following two problems address TWA from the perspective of the forward and inverse problems in electrocardiology. In chapter 3, we characterize the effects of APD concordant and discordant alternans on the body surface. Then, in chapter 4, we switch to the inverse perspective and present a method that estimates the underlying distribution of discordant alternans on the heart from a series of BSP recordings.
Chapter 3

Mathematical model for APD alternans and corresponding ECG

3.1 Introduction

In this chapter we describe our mathematical model for the relationship between the concordant/ discordant distinction in terms of APDs on the heart surface and the consequent variations in the T-wave on the body surface ECG. To do so, we first introduce a model to distinguish concordant and discordant components of APD alternans on the heart, and then combine that model with a simple characterization of the relationship between body surface potentials and heart surface transmembrane potentials. This combination will allow us to elucidate some important aspects of how discordant and concordant alternans appear in body surface T-waves and derive potential implications to TWA testings.

In what follows of this chapter, we describe our mathematical model that we introduce. We show a few examples of how the model works in Section 3.3 and then discuss some of its implications in Section 3.4.

3.2 A simplified TMP model of concordant and discordant alternans

In this work we consider only alternans generated by action potential duration (APD) alternation. More specifically we ignore R-R variability, i.e. we assume constant heart rate. We further assume that the amplitude and depolarization time of the TMPs are constant, so that only the repolarization time changes from beat-to-beat. In other words in the model there is a direct relationship
between APD and diastolic interval (DI), such that their sum is constant on all beats. We also assume that the R-R interval remains longer than the APD, so that the DI is always positive. In summary, our generative model for alternans here is that the \textit{shape} of the TMP waveform does not change, and only the time of repolarization changes, so that in effect the plateau phase of the action potential alternately stretches and shrinks in length. We will discuss some of the implications of these assumptions later in the chapter.

Thus an appropriate TMP model for both types of alternans requires independent control over the repolarization time at each beat, and at any location on the heart; depolarization and repolarization are decoupled so that a change in repolarization time only causes a delay of the repolarization wave. Thus, if we describe the repolarization waveform at a location \(m\) on the heart for a particular heartbeat enumerated by an index \(b\), as \(\phi_{m,b}(t)\), we can write a model for APD alternans as:

\[
\phi_{m,b}(t) = \phi_{m}(t - bT - (1)^b \rho_{m}),
\]

\(\rho_{m} = \) the repolarization time variation between long/short APD.

\(T = \) inter-beat-interval. \hspace{1cm} (3.1)

Where \(\rho_{m}\) is the beat-to-beat change in repolarization time at each location on the heart surface. Thus, according to this model, in the general case of discordant alternans \(\rho_{m}\) varies in magnitude and phase (sign) across the heart, while in a purely concordant case all nodes undergo this APD variation with the same phase and magnitude, so that we can write \(\rho_{m} = \bar{\rho} \). \(\bar{\rho}\) Indeed, a general APD alternation can be decomposed into concordant and discordant parts; the TWA model becomes:

\[
\phi_{m,b}(t) = \phi_{m}(t - bT - (1)^b (\hat{\rho}_{m} + \bar{\rho})),
\]

\(\hat{\rho}_{m} = \) location specific repolarization delay.

\(\bar{\rho} = \) generalized constant repolarization delay. \hspace{1cm} (3.2)

\textbf{Figure 3.1} illustrates three different configurations of the distribution of APD alternans across the epicardial surface. In first panel we illustrate pure concordant alternans (\(\rho_{m} = \bar{\rho}\) and \(\hat{\rho}_{m} = 0\)).

\(^1\)Note that shifting \(b\) by 1 is equivalent to changing the sign of \(\rho_{m}\); thus there is an inherent ambiguity in the model. Here we assume that \(\rho_{m} \geq 0\) and that \(b\) has been adjusted accordingly. This implies that even indexed beats have longer APDs for \(\rho_{m} \geq 0\) and shorter for \(\rho_{m} \leq 0\).
CHAPTER 3. MATHEMATICAL MODEL FOR APD ALTERNANS AND CORRESPONDING ECG

The second panel shows pure discordant alternans ($\rho_m = \hat{\rho}_m$ and $\bar{\rho} = 0$). The third illustrates the case when alternans are present only in a single region. Simple addition shows that this case can be modeled as the sum of the first two cases, with appropriate choice of $\bar{\rho}$ and $\rho_m$.

![Figure 3.1: Example of the 3 distribution of alternans and their decomposition. The concordant case has $\rho_m = 5$ms throughout the heart, the discordant case has a region with $\rho_m = 5$ms and the rest of heart surface with $\rho_m = -5$ms and the single region case has two the same two regions with $\rho_m = 0$ms and $\rho_m = 10$ms respectively.](image)

3.2.1 Relating our repolarization waveform model to body surface potentials (the ECG)

It is well known that to a high degree of accuracy, the body surface potential differences due to cardiac electrical activity can be modeled as a weighted integral over (that is, a linear combination of) the transmembrane potentials (TMPs) in the heart wall [26, 37]. Additional well-accepted assumptions allow this dependence to be reduced to the TMPs on the endocardial and epicardial heart surface [53]. Ignoring any effects of heart motion, the linear weighting depends only on the geometry of the body and the tissue conductivity and represents the effect of the TMP at any given heart surface location on the body surface potential distribution at a particular measurement site. Under these conditions, if we discretize the heart surface, assume a common electrical reference for both heart and body surface, and represent the TMP distribution in terms of TMP waveforms at each of $M$ nodes (so that our location parameter $m$ above now is a discrete index, $m = 1, 2, \ldots, M$), we
CHAPTER 3. MATHEMATICAL MODEL FOR APD ALTERNANS AND CORRESPONDING ECG

get the linear relationship in \( \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \phi_{m,b}(t) \), \( \Phi_{l,b}(t) \) = T-wave in body surface potential

\( l = \) body surface location

\[ \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \phi_{m,b}(t), \quad \Phi_{l,b}(t) = T\text{-wave in body surface potential} \]

3.2.2 Effects of Concordant and Discordant Alternans on Body Surface Potentials

If we now combine the model in \( \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \phi_{m,b}(t) \) with the characterization of TWA in \( \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \phi_{m,b}(t) \), we can obtain a description of the effects of T-wave alternans as shown in \( \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \phi_{m,b}(t) \).

\[ \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \phi_{m,b}(t - bT - (-1)^b(\hat{\rho}_m + \bar{\rho})) \]

Since a delay \( \rho \) introduced to a signal can be mathematically described by a convolution —denoted with \( * \)— with an equivalent delayed delta function \( \delta(t - \rho) \), \( \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \phi_{m,b}(t - bT - (-1)^b(\hat{\rho}_m + \bar{\rho})) \) is equivalent to the double convolution in \( \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \phi_{m,b}(t - bT - (-1)^b(\hat{\rho}_m + \bar{\rho})) \).

\[ \Phi_{l,b}(t) = \sum_{m=1}^{M} a_{l,m} \left[ \phi_{m}(t - (-1)^b\hat{\rho}_m) * \delta(t - bT) * \delta(t - (-1)^b\bar{\rho}) \right], \quad \Phi_{l,b}(t) = \Phi_{l,b}(t) * \delta(t - bT) * \delta(t - (-1)^b\bar{\rho}) \]

Furthermore, since the convolution is linear it commutes with the linear forward operator as long as the convolved signal does not depend on the index of summation \( m \). Noticing this and that the concordant delay affects all TMPs equally by definition, we factor it out of the forward propagation and obtain a separate expression for the T-wave effect of the discordant alternans \( \Phi_{l,b}(t) = \Phi_{l,b}(t) * \delta(t - bT) * \delta(t - (-1)^b\bar{\rho}) \) as shown in \( \Phi_{l,b}(t) = \Phi_{l,b}(t) * \delta(t - bT) * \delta(t - (-1)^b\bar{\rho}) \):

\[ \Phi_{l,b}(t) = \Phi_{l,b}(t) * \delta(t - bT) * \delta(t - (-1)^b\bar{\rho}) = \Phi_{l,b}(t - bT - (-1)^b\bar{\rho}), \quad \Phi_{l,b}(t) = \Phi_{l,b}(t - bT - (-1)^b\bar{\rho}), \]

where we use \( \Phi_{l,b}(t) \) to represent the effect of repolarization TMP phase at body surface node \( l \), for beat \( b \), without the effect of any concordant APD alternation. In \( \Phi_{l,b}(t) = \Phi_{l,b}(t - bT - (-1)^b\bar{\rho}), \) we can see that the
effects of APD alternans on the body surface produced by concordant and discordant cases appear in different ways. Concordant alternans produce an alternating delay $\hat{\rho}$ of the T-waves, carried in the term $\delta(t - (-1)^b \hat{\rho})$, which is uniform across the body surface. On the other hand, discordant alternans modify the T-wave in a location-specific manner by, in general, modifying its shape. The representation of this change in shape is in the term $\hat{\Phi}_l(t) = \sum_{m=1}^{M} a_{l,m} \phi_m(t - (-1)^b \hat{\rho}_m)$. Indeed, as predicted by Sassi et al. in [66], in the case of small $|\hat{\rho}_m|$, this can be well approximated by simple alternation in amplitude of the T-waves.

Since the purely concordant alternans appear as an alternating delay of the T-wave, compensating for this delay by aligning T-waves across beats, as is typically done in standard TWA processing schemes, would eliminate the effect of any concordant alternans, reducing any effects on the body surface to be equivalent to a general case of purely discordant alternans. Note that, if multiple ECG leads are available, the delay applied must be uniform throughout all of them, since otherwise it would introduce a non-linearity that is inconsistent with the forward propagation of potentials.

In summary, in the case of pure concordant alternans, under our assumptions, the T-waves on the body surface will show a pure beat-to-beat shift in time whose magnitude is equal to that of the ADP change in the TMP. On the other hand, a case of pure discordant alternans will show no time shift, but rather a simple change in T-wave amplitude. A mixed case, such as when a subset of the heart is in alternans while the rest is not, will cause a mixture of both effects.

### 3.3 Computational Examples

In order to illustrate the different effects of concordant and discordant alternans on the ECG, we report on two sets of computational examples. The first set were designed as an illustration, simply to exemplify the effects of the concordant and discordant decomposition of TWA, using a parameterized TMP model built into the software program ECGSIM [51]. In ECGSIM, the TMP parameterization includes a selectively controllable repolarization timing parameter at each node on the heart surface model. Thus with ECGSIM we have a TMP model that can generate TWA fullfilling all the assumptions made in our mathematical model.

The second series of examples was designed to show the effects of different alignment techniques to the TWA measures on the ECG and how these can be leveraged to magnify or occlude the effect of concordant alternans. For these examples we use the previously generated dataset, as well as a non-idealized example that uses a complex whole-heart propagation simulation [16] to generate
TMPs that do not match our model assumptions. We manipulate this simulation to produce "more concordant" and "more discordant" alternans, and analyze the effects on predicted body surface potentials using our model.

3.3.1 Illustrative examples

The objective of this experiment was to illustrate how the decomposition described in Section 3.2 can be carried out and what are its effects on the body surface. To do so, we used the parametric TMP model in ECGSIM [51] to create 11 examples of APD alternans, a purely concordant case and 5 sets of examples composed of a purely discordant case and one with alternans concentrated in a single region. As noted above, this parametric model decouples the depolarization and repolarization stages of the TMP and has a single parameter that controls the repolarization time, hence fulfilling the assumptions of our mathematical model for TWA. For each example we fixed the shape of the TMP waveform and varied the repolarization time to create two consecutive beats (i.e. \(b = 0\) and \(b = 1\) in Equation 3.2). The spatial distributions of each example are shown in Figure 3.3 and the specific details for all examples are described here:

1. **Concordant**: equal variation of the repolarization time (\(\rho_m = 5ms\)).

2. **Discordant**: all nodes divided into two regions, one negative (\(\rho_m = -5ms\)) and another positive (\(\rho_m = 5ms\)).

3. **Single region**: all nodes divided into the same two regions, but this time one region had no alternation (\(\rho_m = 0ms\)) and the other had alternans with double the magnitude of the previous cases (\(\rho_m = 10ms\)).

The magnitude of the shifts, \(\Delta \text{APD}= 10ms\), was chosen to match our "small magnitude” assumption and thus to likely produce pure amplitude variations in discordant TWA. Once the transmembrane potentials were determined, we computed the corresponding body surface potential distribution using the forward matrix in ECGSIM and then subtracted the two consecutive T-waves to obtain the corresponding TWA signal on the body surface. The pipeline to interactively choose regions on the heart surface and then create these TWA examples uses the open source simulation software SCIRUN [67] and the software is freely available at https://github.com/jcollfont/TWAgeneration.git.

Three examples of APD distribution, concordant and the a matching discordant and single region, and their effects on the precordial lead V2 are summarized in Figure 3.2 Each row illustrates
one of the three distributions created— concordant, discordant and single region. The left column shows the beat-to-beat variation in repolarization time on the heart surface and the right column the V2 T-waves for the two consecutive beats and the corresponding TWA. The effects on the T-waves are as predicted by the mathematical model: the purely concordant case produces an delay equivalent to the APD difference, the purely discordant case produces a change in shape of the T-wave but no temporal shift consistent across all leads, and the single alternating region behaves as a mixture of the previous two. In this last case, the APD variation on the heart can be obtained by adding a baseline $\bar{\rho} = 5\text{ms}$ to the second case and thus can be understood as a purely discordant alternation on top of a concordant one. For this reason, this case produces a change of shape of the T-wave, equal to the purely discordant example, and a shift of $5\text{ms}$, corresponding to the concordant component.

To facilitate the visualization of this effect and to illustrate how this is independent from the underlying distribution APD alternans on the heart, we collected the T-waves of the second beat corresponding to the discordant and single region examples in Figure 3.3. In this figure, it is clear how the APD alternans from the discordant case and the single region produce T-waves with the same shape but displaced $5\text{ms}$ from one, which is exactly the concordant delay.

### 3.3.2 Effects of Alignment in TWA Testing

In this second set of examples we want to show how the choice of reference in an alignment method can preserve or attenuate the presence of concordant alternans and what are the interactions of discordant alternans and alignment methods applied in a lead-by-lead basis. To this objective we employed the ECGSIM single region examples generated in the previous illustration and an ionic model that is capable of, but not designed for, simulating TWA [16], and which does not match all the assumptions of our mathematical model. This example shows how even when these assumptions are not fully attained, the predictions provided by our mathematical model are still valid and that these have implications for TWA testing.

To generate the TMPs for the new model, we simulated the ionic model on a dense mesh modelling the heart of a rabbit. We set the initial ratio between diastolic interval (DI) and APD to produce alternation throughout the heart. Note that, as shown in Figure 3.4, these APD variations include shape deformations of the TMP and were not constrained to beat-to-beat repolarization changes that our mathematical model would assume. The APD variations generated with this model
Figure 3.2: Three cases of alternans shown as the distribution of beat-to-beat change in repolarization time $\rho_m$ on the heart surface (left) and the two consecutive T-waves observed and the corresponding TWA on lead V2. These correspond to a purely concordant case, a purely discordant case and case with a single region alternating. Note that the third case can be considered as the sum of the discordant case with a concordant baseline of $5\, ms$. 
Figure 3.3: At the left, the APD maps of each ECGSIM example and at the right odd T-waves of all the ECGSIM experiments plotted together. The vertical lines indicate position of the maximum T-wave. Magenta is the single region and green is the discordant.
are space varying, but since these are homogeneous in phase, the concordant alternans dominate over the discordant—\textit{i.e.} the beat-to-beat change in APD is not equal in magnitude throughout the heart, but has the same sign, and thus we will refer to this example as the concordant case. To generate a second example with dominantly discordant TWA, we placed an ectopic stimulus that altered the DI/APD ratio in some regions of the heart and thus reversed the phase of the alternans in those regions. To analyze the presence of TWA on the heart, we computed the change in APD length (in ms) between two consecutive beats and plotted the "iso-alternans" maps shown in Figure 3.5a and Figure 3.5b. These show how the concordant case undergoes beat-to-beat alternations of equal phase — homogeneous sign throughout the heart—, while the discordant case has two well defined out-of-phase regions — two distinct regions with opposite sign. The TMP sequences created from these two examples were then mapped to the geometry of a human heart surface, in particular one of the models that is distributed with ECGSIM, and then used with the corresponding ECGSIM forward solution to synthesize body surface potentials. To evaluate the sensitivity of the TWA estimation to the choice of alignment, we computed the TWA as the difference between consecutive T-waves segmented into $300\text{ms}$ windows whose reference timing point was determined by one of the following three alignment methods:

1. \textbf{Global QRS alignment:} the alignment was applied uniformly to all leads and was referenced to the QRS peak of the body surface RMS.

2. \textbf{Global T-wave alignment:} the alignment was applied uniformly in all leads and was extracted from the maximum cross-correlation between the body surface RMS of consecutive T-waves.

![Figure 3.4: Two consecutive TMPs from the Colin concordant case. The beat-to-beat difference is not restricted to a change in timing but there is also a change in slope of the plateau.](image)

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3. **Lead-by-lead T-wave alignment**: the alignment was applied separately on each lead and was extracted from the maximum cross-correlation between consecutive T-waves.

![Iso-alternans map for the concordant and discordant cases](image)

(a) Concordant  
(b) Discordant

Figure 3.5: Iso-alternans map for the concordant and discordant cases. Figures a and b show the APD difference between two consecutive beats of the concordant and discordant example respectively.

The resulting body surface TWA maps of the ECGSIM examples are shown in Figure 3.6 and the ionic model in Figure 3.7. The first observation is that each distribution of APD alternans on the heart produce distinct spatial distributions of TWA. Moreover, upon comparison between the QRS and T-wave global alignment methods, it is evident that these produce different TWA maps, whose magnitude and distribution depends on the underlying case of TWA. Thus, the presence of concordant alternans affects the TWA estimation in ways that are not predictable a priori without knowledge of the underlying distribution of APD alternans on the heart. Global alignment of the T-waves eliminates most of the concordant component and magnifies the effects of purely discordant alternans.

The change in alignment reference also affects the TWA estimation in the ionic experiments depending on the magnitude of the underlying concordant component. For example, while the discordant case does not show much difference between TWA maps using QRS or T-wave reference, for the concordant case not only does the TWA estimated using QRS alignment have double the magnitude, but also its sign is reversed. In a TWA case with a strong concordant component, the T-waves undergo a beat-to-beat shift in time; when the alignment method uses the QRS as a reference, it does not correct for this shift and the concordant alternans are fully “observed”. On the other hand, when the alignment uses the T-wave as a reference, the beat-to-beat shift is eliminated and the effect of the concordant component is attenuated. Thus the a case with strong concordant alternans, shows a great change in TWA estimation for different references, and a case with a small concordant component shows much less variation.
Figure 3.6: Difference between two consecutive beats across the torso during the peak of the T-wave. The columns indicate different alignment methods: alignment based on QRS, maximum cross-correlation of the RMS of the T-wave across space and maximum cross-correlation of two consecutive T-waves in a lead-by-lead basis.
With respect to lead-by-lead or global alignment methods, as can be observed in Figure 3.6 and Figure 3.7, the former produces a distortion of the TWA maps. In contrast to the variations due to choice of alignment reference (QRS or T-wave), the effects of lead-by-lead alignment are produced by the discordant component of TWA. The beat-to-beat changes on the body surface produced by discordant alternans can include space-varying delays of the T-waves on the body surface. Thus, when observing discordant alternans, lead-by-lead alignment methods referenced to the T-wave apply different temporal corrections in nearby electrodes that cannot be predicted a priori and appear in the form of distortion of the TWA maps.

### 3.4 Discussion

The idealized ECGSIM example, illustrates how, as predicted by our mathematical model, the effects of concordant and discordant alternans propagate to the body surface as a shift in time and a change of shape of the T-wave, respectively. In actual measurements the assumptions made by our model are not fully attained and the effects of the different characterizations of APD alternans are more similar to the examples shown using the ionic model. However, this assumption mismatch does not deem our mathematical model pointless. The concordant component still introduces a delay
to the T-waves, which for a mostly concordant cases dominates the TWA estimation on the body surface. In order to reduce the effects of concordant alternans, it is necessary to use an alignment method that uses the T-wave as a reference.

An important conclusion obtained from this mathematical model is that any alignment used in a TWA detection method should be applied globally — i.e. equal for all leads — to avoid distortion in the TWA estimation. As shown in [subsection 3.2.2] the discordant alternans create non-trivial spatial variations in the T-waves, which can appear in the form of delays of the T-wave that are inconsistent across electrodes. Lead-by-lead alignment methods detect those delays separately and thus, introduce a distortion that varies depending on the underlying discordant alternans. Moreover, since lead-by-lead alignment is mathematically inconsistent with the linear assumption of the forward propagation of potentials, it eliminates information in the body surface potentials about TWA distribution on the heart.

If global alignment methods are to be used, there are two additional characteristics that need to be considered in their design. First, they need of a joint spatial reference that is consistent for all electrodes. In this study we have only considered the RMS signal across electrodes, but other features such as using a specific lead of interest, the average in space or the sum of their absolute value, could also be used. Alignment methods also need a metric to determine the amount of temporal shift to be applied. For that purpose, here we have used the maximum of the correlation, but it is certainly possible to consider other references such as alignment based on the peak of the T-wave. It is for future work to study what is the best combination of spatial reference and temporal measure to be used in an alignment method for TWA estimation. And it also remains an open question whether correcting for the concordant component on the body surface can improve risk stratification.

As we have described here, the T-wave alignment step has a strong influence on the resulting TWA estimation. However typical descriptions of TWA studies explain little, if at all, about the alignment method applied. This unexplored variation across studies may explain some of the discrepancies between results in risk stratification studies, since these may attenuate the presence of the concordant component or may introduce distortion with a lead-by-lead alignment method. Better specification of the full pipeline in TWA detection algorithms should be reported in order to better understand what underlying phenomena is being observed and thus be able to determine the reliability of TWA testing in SCD prediction.
3.5 Conclusions

In this work we have introduced a TWA model that separates the effects of concordant and discordant APD alternans on the body surface potentials. The first corresponds to a delay of the T-waves while the latter introduces a change in their shape, thus elucidating the importance of alignment in TWA detection methods. The appropriate characterization of this pre-processing step potentially has important implications in research on TWA in that shows that it can change the APD alternans that are effectively being observed from the body surface. This may be a confounding factor that explains some of the differences among risk stratification studies.
Chapter 4

TWA characterization for inverse problems

4.1 Introduction

In this chapter, we present a method which directly estimates the location and phase of discordant TWA on the heart surface from body surface measurements by combining techniques from TWA detection with the methodology of ElectroCardioGraphic Imaging (ECGI). By specializing the inverse solution for TWA detection, we have developed a method which uses the temporal characteristics of the T-wave to obtain additional, TWA-specific, stabilization, or regularization, of the estimated TWA, while solving for localized TWA across many heartbeats in a single inverse solution, with associated gains in computational efficiency.

Our method involves an explicit TWA inverse solution, based on an inverse formulation of the spectral method, that assembles a series of consecutive heartbeats into an inverse solver, thus we denote it as the Inverse Spectral Method (ISM). In this chapter we describe our inverse spectral method (ISM) and report validation studies designed to evaluate its ability to distinguish discordant TWA distributions on the heart surface. We compare to TWA as measured by the standard test — the spectral method (SM). We apply both our method and the SM to two types of simulated body surface data. In one, we synthesize the HSP-TWA using models in the ECGSIM software package [51], while in the second we use canine heart surface potentials exhibiting discordant TWA that were experimentally recorded with a preparation designed to induce ischemia. Because we are interested in evaluating the potential to apply this method in a clinical setting, we evaluate how
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our results behave in the presence of different levels of additive noise, and we also compare results using a larger set of BSP measurement “electrodes” to results we obtain if we restrict ourselves to the leads corresponding to the standard clinical 12-lead montage.

In what follows, we first describe the SM and the ISM in Section 4.2. Section 4.3 describes the experiments we carried out to evaluate the method and Section 4.4 summarizes our results. Finally we discuss implications of our results in Section 4.5.

4.2 Methods

The fundamental assumption in BSP TWA estimation is that there is a periodic beat-to-beat alternation in the amplitude of the BSP during the T-wave in any lead under study that is the result of a corresponding beat-to-beat alternation in the underlying HSP. The spectral method (SM) translates that assumption into a Fourier-based approach by noting that if a sequence of beats is Fourier Transformed in the “beat direction” (that is, equivalent time instants across beat repetitions are taken as “beat signals” and the Fourier Transform is taken with respect to beats), a period two alternation will result in a significant magnitude response in the transform at the discrete frequency \( \frac{\pi}{2} \) radians/sample. Since calculating the Discrete Fourier Transform at the frequency \( \frac{\pi}{2} \) is identical to adding and subtracting consecutive samples, this calculation can also be accomplished by simply accumulating differences between samples at corresponding times in the T-wave across consecutive beats in and “add-subtract-add-subtract” fashion. The SM approach is taken by the most widely used TWA estimation algorithm, the spectral method (SM) [9]. Since BSP-TWA presumably reflect HSP-TWA, the SM can be applied to HSPs in the same way.

Thus, a straightforward approach to use ECGI to non-invasively measure the presence of TWA on the heart surface would be to record the BSP for a series of consecutive heartbeats, use an inverse method to estimate the source heart potentials, and then run the standard SM on those estimates. However due to the ill-posed nature of the inverse problem, uncorrelated noise, beat-to-beat variability, and model error, will all contribute to enhanced noisiness in the reconstructed HSPs, and the beat-to-beat differencing in the SM (or equivalently the extreme high-pass filtering in the Fourier approach) is highly likely to enhance that noise in the estimated HSP-TWA. Thus it is desirable to increase the effective SNR of the TWA signal before the inverse solution is applied, and then to apply it only once to calculate the HSP-TWA. (In addition doing so will provide a further advantage since we eliminate the computational load required to compute an inverse solution for every heartbeat.)
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The ISM method we describe here, then, was designed to directly estimate the HSP-TWA signal with a single inverse solution applied once to an appropriately pre-processed sequence of beats. The pre-processing, in effect, increases the effective SNR of the data before the inverse solution, where the SNR is meant in the sense of “TWA content”.

To do so, we take advantage of the linearity both of the inverse problem and SM-based estimation of TWA, along with the ability to separately regularize in space and time. By combining linearity with the fact that the inverse problem and TWA estimation act on space and time respectively we can specify a data formation model as matrix multiplications on the left — spatial operations — and right — temporal operations. Thus, leveraging associativity, we abstract the inverse problem to directly solve for HSP-TWA by applying the operations in reverse order: \( i.e. \) first applying SM and then solving the inverse problem.

In this section we will describe how these two problems are combined to design the ISM from the perspective of combining regularization constraints with TWA calculation in the inverse solution.

4.2.1 The Inverse Problem

Here we describe the specific formulations of the inverse problem in electrocardiography in the implementation of ISM. In what follows, we assume that we have time samples from a continuous sequence of \( B \) heartbeats, where \( B \) is assumed to be an even number. We assume that each beat consists of a T-wave with \( T \) time samples (for convenience we enforce that the T-wave segment of each beat has been identified and taken to have a constant duration during each beat over the sequence), separated by an inter-beat interval of \( IBI_i \) time samples for the \( i \)’th beat. We also assume that the first time sample in \( BSP \) is the first sample of the first T-wave, and the last sample is the end \( (T’ \)th sample) of the \( B’ \)th T-wave. Thus we have a total of \( L = B \cdot T + \sum_{i=1}^{B-1} IBI_i \) time samples. We further assume that we have \( M \) body surface electrode measurements and that we seek to estimate the HSP-TWA at \( N \) locations on the heart surface. With these assumptions the matrix \( BSP \) is \( M \times L \), \( A \) is \( M \times N \), and \( HSP \) is \( N \times L \).

An essential characteristic of the forward matrix \( (A) \), due to the physical properties of the problem, is that it is ill-conditioned, and thus its inverse operator \( (A^\dagger) \) is very sensitive to noise in the input and errors in the forward model [59]. To stabilize the inverse solutions, there are several approaches that can be used [59]. These introduce prior knowledge, or more realistically assumptions about the desired solution, in the form of spatial or temporal constraints. In ISM, to calculate
an inverse solution to estimate HSP-TWA, we apply one spatial and two temporal regularization schemes, whose assumptions come from the characterization of the TWA distributions on the heart and which are described in the sequel.

In space, to favor inverse solutions that are smooth and similar across the myocardium, we used Tikhonov regularization with a regularization matrix \( R \) that approximates the Laplace operator through the myocardium, in 3D space. This approximation of the 3D Laplacian, as in [20], was created by extending previous work that only considered the heart surface [17], where in [20] it was used to approximate the 3D spatial gradient and here we use it to calculate, as noted, the 3D Laplacian.

To regularize in time, we propose two characterizations of TWA behavior that can be described by linear projectors. First, the SM estimator itself can be formulated as two concatenated linear operations in time: extraction of the T-waves from a sequence of heartbeats followed by estimation of the accumulated beat-to-beat difference between ”equivalent” time instances within the T-waves. Our second temporal regularization scheme uses the fact that the TWA signal is slowly varying in time (again, within the T wave) by projecting the estimates onto a truncated basis of the temporal (not beat) Fourier space. A description of these two linear temporal regularizers is as follows:

### 4.2.1.1 The Inverse Spectral Method

We first note that, in practice, the SM is composed of two main steps: alignment and segmentation of the T-waves in each beat and selection of windows of time containing them, and the estimation of beat-to-beat alternation, which corresponds to a projection of the segmented T-waves onto high frequency Fourier space in the beat direction. We note again that since the SM is generally limited only to \( \pi \), the highest frequency in discrete frequency space, the latter operation can be carried out in the ”beat domain” by simply subtracting and adding T-waves from alternating beats.

These operations can be expressed as consecutive matrix multiplications (we denote the corresponding matrices by \( B_{\text{align}} \) and \( B_{\text{SM}} \)) on the right to the continuous ECG recording (\( BSP \)). Denoting the resultant BSP-TWA estimate as \( \widehat{BSP} - \widehat{TWA} \), we have

\[
\widehat{BSP} - \widehat{TWA} = BSP \cdot B_{\text{align}} \cdot B_{\text{SM}}.
\] (4.1)

The segmentation and alignment matrix, \( B_{\text{align}} \), is a block column selection matrix, where each block column has \( T \) individual columns. Each \( i \)’th block column is all zero except for a \( T \times T \)
identity matrix positioned so as to select all $M$ rows of the $i$’th T-wave. Thus after multiplication by $B_{align}$, we have a block row vector of size $M \times BT$ consisting of the $B$ concatenated T-waves for all measurements.

The matrix that estimates TWA, $B_{SM}$, is formed through the concatenation of identity matrices of size $T$ with alternating sign.

$$B_{SM} = \begin{bmatrix} I_T & -I_T & I_T & -I_T & \ldots \end{bmatrix}$$

Multiplying on the right it takes the concatenated T-waves and computes the accumulated beat-to-beat difference.

The multiplication of the measurement matrix $BSP$ by these two matrices, $B_{align}$ and $B_{SM}$, results in an SM-style estimate of BSP-TWA signals on the body surface at each of the $M$ measurement locations at each time instant within the $T$-sample duration of the T-wave. This estimation produces as $B \times T$ matrix that accumulates all TWA information in the BSP with an increased SNR due to the effective averaging across even and odd beats.

### 4.2.1.2 Low Frequency Constraint

The beat-to-beat difference of the T-waves preserves the smooth behavior in time of the T-waves. Thus, the physiologically meaningful components of the estimated BSP-TWA can be captured by its low-frequency components in Fourier space.

Calculating the low-frequency Fourier decomposition is equivalent to right hand multiplication of the ECG-TWA with a truncated ($k$-component) Discrete Fourier basis which we denote $B_{Fk}$. This operation reduces the dimensionality of the input of the inverse solver and filters out high frequency noise. Note that applying an inverse method to the Fourier transformed BSP-TWA results in the Fourier transformed HSP-TWA. In order to recover the temporal sequence of HSP-TWA, an inverse Fourier transform is then applied.
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Figure 4.1: Visual representation of the sequence of steps applied in the Inverse Spectral Method.

4.2.2 The Inverse Spectral Method

The complete inverse spectral method combines these previous three regularization techniques and solves the following optimization problem:

\[
\tilde{Y} = \text{BSP} \cdot B_{\text{align}} \cdot B_{\text{SM}} \cdot B_{Fk}
\]

\[
\tilde{X} = \arg\min_X \|\tilde{Y} - A \cdot X\|_2^2 + \lambda \|R \cdot X\|_2^2
\]

(4.3)

\[
\text{HSP-TWA} = X \cdot B_{Fk}^\dagger.
\]

(Note that \(B_{Fk}^\dagger\) in effect interpolates the reconstruction by assuming that \(\tilde{X}\) is zero outside \(k\) low frequency Fourier components.) In practice, this optimization is done sequentially in the following steps, which are also illustrated in Figure 4.1.

1. Segment T-waves in the BSP using QRS peak as a reference.

2. Estimate BSP-TWA.

3. Calculate the truncated Fourier Transform of the estimated BSP-TWA.
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4. Solve the inverse problem with Tikhonov regularization using the 3D Laplacian regularizer.

5. Reconstruct the temporal HSP-TWA by applying the inverse truncated Fourier Transform.

4.3 Experiments

We report on evaluations of the performance of the ISM on two types of synthesized body surface data, one starting from synthetic HSPs from ECGSIM and the other from experimental measurements from canine experiments. The corresponding heart surface models also differed. The first model included the epicardial and endocardial surfaces of a heart also supplied by ECGSIM [51], while the second model was created to represent only the epicardial surface of a canine heart. In particular, to create TWA in ECGSIM leveraged its ability to generate TMP with user-defined waveform parameters at each node of the heart surface model. The canine heart potentials were recorded during an open-chest experiment as described below in which extensive TWA was seen.

These distinct types of data allowed us to test different aspects of the ISM approach. With the synthetic TMPs generated with ECGSIM, we were able to validate the ability of ISM to localize the two out-of-phase regions in a relatively simple discordant alternans case but with full control over the alternans geometry and full knowledge of ground truth. With the epicardial canine recordings we tested the capacity of ISM to delineate complex discordant distributions on the heart during more realistic conditions when the alternans did not correspond to an idealized model of pure period 2 alternation of T-wave duration.

For each of these cases, we tested the sensitivity of the ISM results to additive white Gaussian noise (AWGN) in the measurements and also evaluated to what degree the results of ISM deteriorated when we only used data from a 12-lead configuration.

In the remainder of this section we describe in more detail how these data sets were obtained as well as the metrics we used to evaluate ISM results.

4.3.0.1 The ECGSIM dataset

This dataset was obtained by manipulating parameters of transmembrane potentials created using the model in ECGSIM [51]. In particular, ECGSIM allows users to modify the shape of the TMP at a set of locations on the heart through a parameterization of the TMP waveform that defines activation time, repolarization time, amplitudes, slopes, etc.. With this TMP model we created
Figure 4.2: Sequence of 927 heartbeats measured with a representative electrode on the canine epicardium. The figure shows the continuous evolution of the heartbeats during the ischemic intervention, as well as the disturbances produced by a sequence of VT and the ectopic beats. The timing of the 11 intervals used in the inverse solutions are indicated by the red lines below the signal. Note that the intervals overlapped by 50%.

alternans by modifying the repolarization time at selected nodes, adding a fixed time delay for even beats and subtracting the same interval for odd beats, thus creating a 64 beat sequence of HSPs with discordant TWA. Specifically, to create discordant alternans, two out-of-phase regions were defined, one with “positive” alternation, with nodes undergoing long-short-long variations, and one with “negative” alternation, with nodes undergoing short-long-short variations. To create a more realistic spatial transition from positive to negative alternans regions, a $-10 \text{ms}$ repolarization time change was applied at the centroid of the negative region and then the delay amount was varied smoothly with distance from this centroid so that a maximum repolarization change of $10 \text{ms}$ was reached over the rest of the heart surface. This procedure was designed so that the negative region was more-or-less circular and covered about a quarter of the heart.

By placing the centroid of the negative region at different locations on the heart, we created 10 different TWA distributions, as shown in Figure 4.3. Since the center of the negative region defined the TWA distribution, in what follows we use the area covered by this region to refer to each TWA distribution. Thus, we generated four lateral examples, three apical, three septal.

Using the forward model in ECGSIM, we synthesized corresponding BSPs at $M = 300$ body surface locations and then added Gaussian noise at various signal-to-noise (SNR) levels. Specifically this procedure was performed for 100 different pseudo-random noise realizations for each location at SNR levels of 15, 30 and 45 dB.

In order to avoid committing the inverse crime of computing the inverse solutions with the
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same forward matrix that was used to synthesize the data, we calculated a second forward matrix using the geometries provided in ECGSIM but the Boundary Element Method (BEM) software in the software package SCIRun \[67\], while also not including the presence of lungs in the model. (The lungs were included in the ECGSIM model used to synthesize the data.) We used this second forward solution in the inverse calculation.

The 12-lead tests simply selected the appropriate measurements from these larger BSP datasets and the corresponding forward model just used the corresponding rows of the forward matrix \[25\].

4.3.0.2 The canine dataset

This dataset was obtained with epicardial sock recordings during an open-chest canine ischemic experiment conducted at the CardioVascular Research and Training Institute (CVRTI) at the University of Utah, under the appropriate IACUC approval and generously provided to us by Dr. Robert Lux.

The sock had 64 electrodes and the recording consisted of a continuous sequence of 927 heartbeats which exhibited discordant TWA of varying spatial distribution and magnitude. The sequence ectopic beats and an interval of ventricular tachycardia (VT). To study the multiple stages of the evolution of TWA, we somewhat arbitrarily divided the recording into 11 overlapping intervals containing approximately 154 heartbeats each. A representative lead from these recordings is shown in Figure 4.2 with the windows corresponding to each interval superimposed. There is a continuous change of the HSP, even changing sign of the QRS complex after interval 5. The maximum peak of instability happens during intervals 8 and 9, with a sequence of VT and two ectopic beats that appear later within intervals 9 and 10. To better observe the spatial distribution of the TWA we show the HSP-TWA, in Figure 4.4a, estimated by applying SM directly to the HSP measurements and averaging over time. There are three clear groups during the sequence: the first two intervals with low amplitude TWA and erratic spatial distributions, intervals 3 through 5, where there is a region near the apex whose TWA start to dominate and all the remaining intervals, where this apical region clearly dominates over the rest of the heart. Note that there are changes in sign in intervals 3-4, 6-7-8 and 10-11. This effect is created when choosing the position of the segmenting window, which could reverse the phase of the estimated TWA.

We again generated synthetic BSPs using the SCIRun BEM forward model with an appropriate geometry obtained by manually translating and morphing the canine heart geometry within a model torso geometry with \(M = 354\) nodes to simulate the size and position of a human heart. As
in the ECGSIM dataset, we added 100 different realizations of AWGN at the same three SNR levels (15, 30 and 45 dB).

To again ensure error in the forward model used in the inverse solutions, we again computed a different forward matrix that was used to synthesize the data, this time using a less detailed version of the torso geometry [39,40]. And again as in the ECGSIM experiments, both the data and reduced geometric models used to test the ISM performance with a 12-lead electrode configuration was down-selected from the full data and model.

### 4.3.0.3 Quality measures

In all the experiments we computed the accuracy with which ISM detected the two out-of-phase regions on the heart. We counted the estimated TWA as positive at a given reconstruction location if the average amplitude of the T-waves in even beats was greater than that of the odd ones and as negative if even beats had smaller amplitude than the odd ones. The positive/negative TWA region classification was evaluated by comparing it to the TWA estimated using the SM applied directly to the potentials synthesized (case 1) or measured (case 2) on the heart. Note that in the case of the ECGSIM data this gave an accurate ground truth to compare against, while in the canine data it was itself an estimate of TWA but generally a reasonable surrogate for ground truth; we return to this last point in the discussion.

To quantify performance, we used two metrics. In the first, for each leadset and TWA location (case 1) or time segment (case 2) we computed the fraction of the 100 noise realizations for which each heart surface location was correctly classified as positive or negative, thus creating “accuracy maps” on the heart surface showing, in effect, the reliability of the ISM classification compared to the SM “ground truth” label. For visualization purposes we multiplied the resulting percentages for the “true negative” nodes by −1 so that the maps range from +100% to −100%. To provide a summary view, we then averaged the magnitude of these accuracy values across the heart surface to provide a single accuracy metric for each negative alternans site / data interval. We repeated these assessments at all 3 noise levels for both full and 12-lead datasets.
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Figure 4.3: True TWA distribution and reconstruction accuracy maps for ECGSIM generated data. Maps should posterior and superior views, with the latter allowing visualization of the endocardial surface as well. (a) The location and magnitude of repolarization change used to create the TWA distribution for all cases tested with ECGSIM, in ms. Note that negative means shorter T-waves on the odd beats. (b) The accuracy map for the results obtained using the full lead set. (c) The accuracy maps for the results obtained using the 12-lead configuration. As described in the text, accuracy maps were computed as the percentage of realizations where the phase of alternans in ISM reconstructions was the same as for SM applied to the true ECGSIM TMPs. Percentages for regions with negative alternans were multiplied by the -1 for better visualization.
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Figure 4.4: HSP-TWA distribution estimated directly from HSP and reconstruction accuracy maps for the canine experiments with $SNR = 15dB$. Panel (a) at the top shows the TWA estimated with the SM on the recorded heart potentials and averaged over time, taken as ground truth here. Panel (b) shows the accuracy maps for the results obtained using the full lead set, while panel (c) shows the maps for the results obtained using the standard 12-lead configuration. Note that the colormap for the SM “true” estimates are in millivolts of alternans change and differ from interval to interval, while panels (b) and (c) show percentage of correct classification over realizations as explained in the text.
4.4 Results

In this section we first give a brief description of the figures presenting our experimental results and then describe each in more detail. In the left column of Figure 4.3, we show the true repolarization alternans distribution for the ECGSIM experiments for all 10 chosen locations. The different locations of the ”out-of-phase” negative alternans region are clearly visible in these maps. The middle column shows the corresponding accuracy maps obtained with data from the full lead-set and the right-hand column with data from the 12-lead configuration. We then present corresponding results for the canine dataset in Figure 4.4. Here the comparisons are made to the TWA maps estimated directly from the sock data by the SM from each data interval and averaged over time, shown across the top row. Accuracy maps of the reconstruction using all leads are shown in the second row, and maps calculated using just the 12-lead configuration in the third row.

To summarize the results more succinctly, in Figure 4.5, we show the averaged results for all alternans positions across three different levels of SNR for both the full lead-set (top-left panel) and the 12-lead set (bottom-left panel). Corresponding figures for the canine data set are shown in the right panels on bottom and left respectively.

Examining first the accuracy maps from the experiments using all available leads shown in the second column of Figure 4.3, we observe that maps tend to have three distinct areas: two areas where the TWA are reconstructed accurately, shown in red for “positive” TWA and in blue for negative TWA, and a “transition” area between the two, shown in green and yellow, where the error is higher. The transition areas between those regions were not as reliably characterized, not surprising since the TWA were designed to have smaller beat-to-beat alternation as the ECGSIM parameter setting went through a gradual transition from one phase to the other. However, although the ECGSIM settings were essentially the same for all discordant TWA spatial arrangements, the width of the higher error transition regions varied with the location of the negative phase region. For example, ISM classified more tissue accurately when the negative region was placed in an anterior or apical positions than when it was placed in basal or septal positions. This observation suggests that the accuracy of ISM varies somewhat as a function of the geometry of the discordant regions.

This spatial dependency of the error is supported in the spatially averaged results in Figure 4.5a, where each column corresponds to the results of one location in Figure 4.3. Quantitatively, septal and basal locations were between 10% to 20% less accurate than other TWA distributions. Interestingly, this same spatial dependency also applies to the sensitivity of the solutions to decrease in SNR. We also note that results for most of the TWA distributions had very low standard deviation.
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— *i.e.* different noise realizations produce similar solutions — and that the standard deviation did
not increase much with decrease in SNR. However, again we note the same sensitivity to discordant
gometry, as septal and basal locations of the negative TWA showed higher standard deviation and
a more rapid decrease in accuracy as SNR dropped, compared to other locations.

The results for the standard 12-lead configuration were similar to the full lead set; in particular
the accuracy maps in Figure 4.3 show the same 3-region structure. Not surprisingly perhaps, the
lower accuracy transition region is wider for the standard 12 lead montage than when data from the
full lead set is used. The averaged results in Figure 4.5 show ~ 10% less accuracy than results with
the full lead set in most TWA distributions. However, surprisingly, the septal and basal locations,
which had worse accuracy than the other locations with the full lead set, are generally more accurate
with the 12 lead set than with all the leads. Thus with the 12-lead data, these average errors are more
uniform across TWA distributions. They also are somewhat less sensitive to decreased SNR than
the full lead results. Moreover with the 12-lead configuration the standard deviations are negligible.

Using the accuracy metric we have defined, the canine data set results were more accurate
overall than the ECGSIM results. The accuracy maps, with $SNR = 15dB$, for all data intervals,
in Figure 4.4 show well defined positive and negative regions with ~ 100% accuracy and a narrow
line of high error between them (much narrower than in the ECGSIM results). The intervals with
more complex distributions, such as numbers 2 and 10, have somewhat larger areas with higher er-
ror and do not reach 100% accuracy as uniformly as the other time intervals. The spatially averaged
results in Figure 4.5 confirm these observations. The average accuracy is around 90% for most of
the intervals, with the exceptions of the first two, where the amplitude of the TWA is considerably
smaller that it is later in the recordings, and in interval 10, where the discordant distribution more
spatially complex. However, we also observe that results with the canine data set were more sen-
sitive to decreased SNR compared to those obtained with the ECGSIM data, and that the standard
deviations were higher.

Using only the 12-lead measurements again results in similar accuracy maps to those obtained
with the full dataset. Only a few intervals (notably 5, 6, and 9) showed clear changes in the shapes
of the high accuracy positive and negative regions and about half (notably 4, 5, 7, 9, and 10) showed
wider "transition", higher-error, bands. These observations about the maps are consistent with the
average results in Figure 4.5. Similarly to the ECGSIM data set, using only the 12-lead montage
typically reduced accuracy by ~ 10%. Also similarly to the ECGSIM data, the 12 lead solutions
show a lower standard deviation across noise realizations and more similarity between results at
different SNR levels than when using the full dataset.

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CHAPTER 4. TWA CHARACTERIZATION FOR INVERSE PROBLEMS

Figure 4.5: Average accuracy of ISM across the heart surface in the ECGSIM data set. Each group of columns shows results for a single location, as in the text and Figure 4.3. The three columns in each grouping (in blue, green and red) correspond to results for different SNR levels of 15, 30, 40 dB respectively. The error bars indicate the standard deviation. Top panel shows results using full lead set, and bottom panel using 12-lead configuration.
4.5 Discussion

Our results suggest that ISM reliably detected the main areas covered by the two out-of-phase regions across all our tests. The fact that performance was comparable with the canine data as it was with the highly simplified and stylized ECGSIM TWA is also a positive indication. Clearly there was far more variability both between consecutive beats and across the TWA runs in the ischemia-provoked TWA in the dog hearts than is assumed in the putative “period two oscillation” model of TWA. Thus it is an indication of robustness of ISM that it reconstructed the spatial locations of the TWA regions with generally good accuracy in these data.

At face value, given the complexity of the canine data, it seems somewhat surprising that the accuracies achieved with those data were quantitatively higher, using our metrics, than with the ECGSIM data. However it is important to note that the ECGSIM experiments required reconstruction of potentials on the endocardial surface of the heart as well as on the epicardium, while the heart surface model for the canine data only included the epicardium since we only had epicardial measurements available from the experiment. Reconstructing endocardial potentials is always a challenge for Tikhonov-type ECGI methods and we speculate that this decreased the overall accuracy of the results.

In the canine data, as is clear from the SM results in the top row of Fig. 4.4, the TWA generally occurred in the same region, near the apex. (Note that the designation of “positive” or “negative” in these data is somewhat arbitrary, as it simply depends on where we start to count the beats in a given division of the data into intervals.) Thus we cannot make any observations with these data about sensitivity of ISM to location of discordant regions. However the ECGSIM experiments strongly support the idea that indeed there is such spatial sensitivity, and in particular that small discordant regions will be harder to locate if they are positioned on the septum or near the base. More generally this may be a factor of relative position and orientation of the heart with respect to the chest wall and thus the nearest electrodes. However despite this spatially-dependent increased in error, the centroids of the out-of-phase regions were reliably detected.

From the point of view of potential for use in screening, the fact that ISM results were only somewhat less accurate, and indeed also somewhat more robust to noise and spatial variability, when using only the 12-lead montage, is encouraging. Of course in this context it would be important to also in the future look at sensitivity to forward model error, as in a screening scenario individualized anatomical imaging is not likely to be available. We made some attempt to include such errors in the results here by using different forward models to synthesize the data compared to the ones used
in the inverse solution. However, how much model error can be tolerated, and conversely how accurate a model might be obtained by using methods such as atlases, morphing of standardized models, adoption of more easily obtained imaging from photographs or ultrasound, etc, remains to be explored.

As noted above, time intervals 9 and 10 of the canine recordings contain a number of ectopic beats as well as an episode of VT which spontaneously converted back to sinus rhythm. Clearly these beats violate the assumption underlying both SM and ISM, adversely affecting our ISM results as evaluated by our accuracy metrics. For example, an ectopic beat in the middle of a sequence of heartbeats in interval 10 reversed the phase of the beat-to-beat alternation mid-interval, and thus reduced the amplitude of the TWA estimation. In addition, the VT event in interval 9 impacted even the T-wave segmentation algorithm, which in itself caused loss of accuracy of the ISM calculations. This suggests that a smarter pre-processing algorithm which detected non-sinus rhythm beats and either discarded them or handled them separately would be a useful improvement for ISM estimation of TWA.

4.6 Conclusions

In this work we have described a new variant of ECGI, which we denote the inverse spectral method (ISM), to non-invasively localize TWA distributions on the heart. We evaluated it against TWA analysis of heart surface potentials (both simulated and invasively measured) using the standard SM spectral method, in synthetic scenarios. In our simulations ISM localized the discordant regions on the heart reliably, although we observed some limitations when in its ability to precisely define the boundaries of discordant regions. ISM maintained comparable performance even in experimental measurements despite the complex time-varying distributions of TWA which were induced in the experiment. However, in such realistic settings the method is sensitive to the presence of ectopic beats that do not match the assumption of continuous beat-to-beat alternation with similar electrogram waveform morphology. This suggests that such beats should be eliminated or handled separately via a pre-processing stage before applying ISM. We also found that when the number of ECG electrodes used was reduced to match a standard 12-lead configuration, ISM maintained a similar level of accuracy as was obtained with the full lead set. These results suggest considerable promise that this method may help increase our ability to understanding TWA based on body surface recordings, and thereby more clearly study its link to VF, by providing previously unavailable spatial information to researchers and clinicians.
Part II

Inclusion of Multiple Heartbeat Recordings for the Inverse Reconstruction of Repeating Electrical Activity on the Heart
Introduction

One application where ECGI has a great potential to impact clinical practice is in pre-procedure planning of ventricular ablation interventions. Patients that undergo those interventions have recurrent pre-ventricular contractions (PVC) that reduce their quality of life and are potentially life threatening. To eliminate them, the surgeon ablates the site of initiation of the PVC with a catheter enabled with a high intensity RF antenna in the tip.

The challenge during those operations is to localize the right point to ablate. To find it, the surgeons rely on the manual interpretation of the ECGs recorded during a PVC event and in-situ intracardiac mapping. These mapping procedures require to record the PVC directly on the heart from a series of point measurements taken with the catheter and can take hours or sometimes even fail to be completed. In this context, ECGI could provide a pre-procedure estimate of the position of the earliest activation of the PVC and help reduce the length of the ablation interventions.

In previous work exploring this problem we observed that the inverse reconstructions obtained from various BSP recordings, diffused from similar activations on the heart, produced widely different results in the estimation of the site of earliest activation of the PVC [20]. Based on those results, we decided to take advantage of the available BSP recordings from similar heart activity to estimate a joint inverse solution.

However, it is not obvious how to best take advantage of these multiple recordings. Standard approaches either pick the "best" single recordings to invert, reconstruct the hidden potentials using each epoch individually and then ensemble average the individual solutions, or ensemble average the recorded epochs and then apply the inverse method to the averaged recording. Because of the the sensitivity of reconstructions to the SNR of the "input" to the inverse procedure, and the need for regularization tailored to that SNR, these methods do not typically lead to equivalent results. More fundamentally, all these methods imply the assumption that the epochs are independent realizations of a stochastic process consisting of the same underlying signal contaminated by noise that is spatially and temporally uncorrelated. However in practice there are significantly correlated noise sources, in effect interference in the signal, stemming from uncontrolled "background" phenomena such as spatial effects of respiration and atrial electrical activity in recordings during arrhythmic heartbeats.

To address this problem, our group developed the two methods and their corresponding validation studies that we present here. The first method is a non-linear averaging approach for ECG that is more robust to this background noise [20,29], and second, a statistical model of the effects
of respiration and uncontrolled atrial activity on the BSP measurements.
Chapter 5

Averaging Study

5.1 Introduction

When there are multiple beats with the same initiation site available, it is possible to obtain an ensemble average beat with increased SNR. However, variability in the sampling time and intra-beat velocity can introduce correlated noise that instead decreases SNR and with it introduces more error in the inverse solutions \[19\]. To overcome this limitation we propose to average heartbeats with a spline-based method that only uses the geometric properties of the heart potential while disregarding the time stamps. This method was first studied as a denoising technique for BSPs in \[44\] and is a natural extension of the spline-inverse method.

In this study we will compare the differences in accuracy between traditional ensemble averaging of BSPs, our geometric averaging and ensemble average applied to the individual HSP solutions after applying the inverse procedure to each separate heartbeat in the ensemble. To do so, we will use the ventricle paced data previously used to validate the spline-inverse method \[20\] and the localization of the initial activation on the heart as reference to measure error.

5.2 Methods

5.2.1 Dataset

The dataset we used to compare the different averaging techniques consisted of BSP recordings from obtained during ventricular pacing on three volunteers with presumed healthy ventricles, performed, with appropriate human subject permission from Charles University Hospital in Prague,
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Czech Republic, in conjunction with standard atrial ablation procedures. Details of the experiment are in [20] but we summarize here.

During this intervention, the clinician paced the heart multiple times at several endocardial locations in both ventricles with a catheter-based device. The position of the pacing catheter was recorded using the CARTO XP system (Biosense Webster, Diamond Bar, CA, USA) electroanatomical mapping system while the BSP were recorded using an array of 120 ECG leads that also contained the standard 12 lead configuration as a subset. For the geometric model we fit generic torso and epicardial-endocardial ventricular heart surface geometries to limited axial X-Ray CT images of the volume containing the subjects heart. These geometries were then used to generate a mathematical forward model relating heart and body surface potentials. This dataset and geometry is freely available in the SCIRunData and EDGAR data repositories [4,12].

5.2.2 Inverse Problem

As mentioned above, to solve the inverse problem we used an algorithm that described in [20]; code is available on-line in the Forward/Inverse Toolkit of SCIRun [11]. Again we describe briefly and refer the reader to [20] for details.

Our algorithm imposes spatio-temporal regularization. The temporal assumption is that the BSPs and HSPs during a heartbeat each traverse a (distinct, but closely related) smooth curve in a high-dimensional space, in which the potential at each electrode represents a different dimension. With this assumption, the algorithm approximates this curve by fitting a high-dimensional spline to the measured BSPs. This fitting minimizes the average distance to the interpolated curve in the high dimensional space of all samples of the BSPs, disregarding the actual time stamps associated with each sample. The resulting spline is determined by its knot points — which are potential distributions themselves — and its time warp — the projection of each sample to the interpolated curve. The algorithm assumes, based on the fact that the BSPs and HSPs are related by a spatial PDE but with no temporal mixing, assumes the temporal position of the knot points is invariant on the heart and the body and thus calculates the inverse solution of each knot point using a Tikhonov inverse. Key to obtaining endocardial potentials is a regularization term that minimizes the volumetric (transmural) gradient in the heart. Finally, the HSPs are reconstructed creating a new spline with the inverse knot points and the time warp. More details on this inverse method can be found in [20].
5.2.3 Averaging Methods

In order to compare the distinct averaging methods, we averaged the recorded BSPs during QRS across multiple pacings at the same site and then fed the averaged BSPs as input to the inverse method. The averaging methods we compared were the ensemble average and a spline-based average. Also, with the objective of comparing with single beat inverses, we ensemble averaged the HSPs obtained after inverse solutions computed on all individual beats.

The standard method for averaging is the ensemble average which calculates the mean BSP for each time instance across all recordings. With the assumption of having at least partially uncorrelated additive noise, this method should always increase SNR. However, if other variability such as changes in intra-beat velocity are present, this method will introduce correlated noise that may strongly affect the inverse solutions.

A different approach to use a spline-based method, which is a natural extension of the spline-inverse method. In the inverse algorithm the curve in high-dimensional space is assumed to be the same for all heartbeats produced with the same activation pattern. Thus, in the spline-based averaging, the curve fitting was done by fitting across all available recordings from a single pacing site at once. This procedure is robust to variability in timing since the spline fitting is done independently of time stamps, while it also attenuates noise present in individual beats.

5.2.4 Validation

Validating results in inverse electrocardiography is not straightforward. Since the potentials of interest are usually inaccessible, there is no ground truth to compare the solutions to the inverse algorithms. However, this paced dataset provides a unique situation to test the validity of the reconstructed HSPs, by comparing initial activation sites extracted from the inversely-computed potentials to CARTO measurements of the pacing locations.

We used the algorithm described in [18] to estimate the node corresponding to the earliest activation site from the computed potential distribution and then calculated localization error as the distance (in mm) between that node and the CARTO-reported pacing location.

5.3 Results

To compare the overall error of the two BSP averaging methods, spline-based and ensemble, and the ensemble average of reconstructed HSPs, we show a histogram of the localization error in
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In it we observe that the distribution of the error is similar for all three averaging types. Most of the error centered around the mean at around 35mm although its distribution spreads to over 80mm for some pacing sites. In the case of inverse solutions using data restricted to the standard 12 lead measurements, the error distributions are similar but shifted to higher error, which was to be expected given the reduction in the number of leads.

To provide a clearer view of how the localization error of each pacing site changes when averaging HSPs or BSPs, we show in Figure 5.2 a histogram of the change of error between ensemble average in HSPs and the two other averaging techniques in BSPs. This change is shown as $\Delta Error_{spl} = Error_{spline} - Error_{HSP}$ and $\Delta Error_{ens} = Error_{ensemble} - Error_{HSP}$. Thus, negative independent variables in the histogram indicate improvement when using BSP averaging while positives values indicate a loss of performance. In these histograms it is clearer that, on average there is not much change between averaging BSPs or HSPs. It is possible that the inverse method is already smoothing out the solutions leaving most results unchanged and, although there are some pacing sites that do benefit from BSP averaging, other cases show an increase of error such that the overall mean gain is close to 0mm. An exception is subject 3, which shows an larger
improvement in localization error for several pacing sites when averaging BSPs and, as a result, a much better mean increase than in the other two subjects. Overall, the error improvement plots indicate that the spline-based averaging produces a slightly better improvement than ensemble averaging. However, even though the distribution of localization error improvement for both BSP averages are around the origin, the ensemble average shows a much tighter concentration at 0mm, indicating that its results do not differ much from the ensemble average at HSP. On the other hand, the error change produced with the spline-based average has more variance and some pacing sites shows a big improvement when this algorithm is applied.

Figure 5.3 shows the same error improvement histogram but this time for the inverses taken on the standard 12 lead configuration. In this case, the ensemble average on BSP shows much less change with respect to the HSP average, the distribution is highly concentrated in $\Delta Error_{ens} = 0$mm. A possible explanation is that the inverse solutions for datasets limited to the standard 12 lead
need more regularization to compensate for the missing information. Thus, the resulting HSPs are smoother and less sensitive to input noise. For the spline-based average, we observe that, as in the full leadset solutions, it shows a little better performance than the BSP ensemble average and the distribution of $\Delta Err_{spl}$ has longer tails, with a little bias towards negative values.

### 5.4 Conclusions

Our results indicate that averaging BSPs prior to calculating the inverse solutions lead to results that were similar or at times slightly better than the solutions obtained from ensemble averaging of the inverse solutions taken individually. When averaging BSPs, we did not see difference between ensemble average and spline-based average for most cases. Since our spline algorithm is non-linear, and the regularization is carried out independently for each inverse solution computed, it
CHAPTER 5. AVERAGING STUDY

is not obvious that this would be the case. Also, even considering the small improvement in the localization accuracy of averaging BSPs compared against HSPs, the gains in computation speed due the reduction of number of inverse solves needed make averaging a desirable step in when solving the inverse problem.

A clinically interesting feature are the inverse solutions taken on standard 12 lead recordings. For these cases we observed less of an effect of the averaging algorithm on the localization error. We speculate that this is related to the typically higher influence of the regularization term in inverses with reduced number of measurements.

More work is needed to determine under which specific situations these averaging methods perform better or worse and what metrics can be see to discern which one is better without advance knowledge of the correct location as we had here from the CARTO measurements.
Chapter 6

Statistical Study

In the study presented in chapter 5 we described a deterministic approach to aggregate multiple heartbeats before using them in an inverse method. From a statistical point of view, though, an optimal approach, if a statistical model of the interference is available, would be to directly use all the recordings jointly in the inverse estimate, accounting for the background noise and variability across epochs. A natural way of describing these type of problems is to use a probabilistic characterization of the signals of interest and the noise activity. Given this probabilistic model, it is possible to estimate the hidden potentials through Bayesian approaches or simply maximization of the posterior probability of the hidden potentials. In the simplest setting, under Gaussian noise assumptions, these methods are identical and are equivalent to Tikhonov regularization applied to the ensemble average of the input signal [34]. However when the interfering ”noise” has structure, as it does in both these settings, a more sophisticated statistical model may lead to a new regularized solution method. Here we present a statistical model of the interfering effects of respiration and uncontrolled atrial activity, developed in the context of electrocardiography body surface measurements during artificially-induced arrhythmic beats (using a intracardiac catheter device), and compare inverse results to those obtained both with ensemble averaging and our non-linear spline average, extending the work from chapter 5.

6.1 Methods

We start with the assumption that the forward problem describing the relationship between unknown sources and surface measurements has been solved, resulting in the relationship $y_t = Ax_t$, where $y_t$ and $x_t$ are the surface and hidden signals at time $t$ and $A$ encodes the forward solution.
CHAPTER 6. STATISTICAL STUDY

In this section we will discuss the two approaches to be compared: average first, then ”invert”, or reconstruct with all the data at once. To do so, we will first introduce the pipeline for the averaging techniques and then we will describe the combined approach.

6.1.1 Pre-Averaging methods

Averaging before applying inverse methods relies on the assumption that the pre-processing step will increase SNR and less regularization will be needed in the inverse to obtain equivalent stability. The standard approach, ensemble average the measured potentials across epochs, is optimal only in the case when the realizations are only contaminated with AWGN. Another approach to averaging is to fit a more complex model to the potentials; here we use a spline-based model. In previous work, Erem et al. observed that the measured potentials can be represented as a curve embedded in a high dimensional vector space defined by the potentials at each electrode [19]. However, biological noise, such as respiration, alters the trajectory of the potentials such that samples at equivalent time instances of different epochs appear at different positions along the curve. Thus, any denoising method that relies on time stamps of the signal to average will be affected by this variability. To overcome this problem, our group developed a spline averaging method, which fits a B-spline model that is defined over a pseudo-time parameter that is independent of the time stamps of the samples. This model represents the measured signal at epoch \( r \) and time \( t \) \((y_{r,t})\) as:

\[
y_{r,t} = \sum_{i=1}^{K} k_{y_i} b_i^T(\theta_{r,t}) + w
\]

\( k_{y_i} \) knot points.
\( K \) number of knot points.
\( b_i \) B-spline basis.
\( w \) AWGN.

The spline averaging optimizes over two sets of parameters, the knot points \( k_{y_i} \), which do not depend on the epoch and thus describe a ”spline average” curve, and the pseudo-time \( \theta_{r,t} \), by solving:

\[
\min_{k,\theta} \sum_{r=1}^{R} \|y_{r,t} - \sum_{i=1}^{K} k_{y_i} b_i^T(\theta_{r,t})\|^2_2
\]

(6.2)

More recent work (as yet unpublished) has indicated that this variability is predominately due to both respiration and atrial activity.
CHAPTER 6. STATISTICAL STUDY

by recursively solving for the knot points \( k \) and then updating the psuedo-time \( \theta \), similar to expectation maximization.

Similar to the inverse method applied to spline fits to recordings from individual beats in [20], since the knot points fully describe the curve and can be seen as potential distributions themsevles, we reconstruct only at the knot points and then obtain the whole temporal sequence of the solution using the pseudo-times obtained in the averaging step. With a Tikhonov regularization method we have:

\[
\min_{k_{x_i}} \| y_i - A x_i \|_2^2 + \lambda \| D x_i \|_2^2
\]

where the regularization term \( D x_i \) is an gradient estimator\( \lambda \) is determined using the L-curve method.

6.1.2 Probabilistic Inverse

Our general approach here is to develop a probabilistic model from observations of the data to characterize the biological noise in the measurements In the particular case of ECG, we observed that the spread of the samples around the ensemble average appeared to be approximately Laplacian distributed as shown in Figure 6.1 with a shape parameter that was consistent across all epochs but with a mean that shifted from one epoch to the next.

We posulate that this shift in the mean could be produced by differences in respiration and atrial activity across different epochs. Further observations showed that the time average at each
epoch had a non-trivial spatial distribution that could highly impact the inverse estimation if not taken into account. Thus we propose a probabilistic data model based on the Laplace distribution with mean given by the forward model of the potentials \((Ax)\) shared across epoch plus an unknown potential distribution \(b_r\) which is constant in time but varies for different epochs. Since the actual solutions cannot be observed we cannot develop a source signal model with the same approach. However due to the ill-posedness of the inverse problem we need a prior on the sources that is flexible but also regularizes to avoid overfitting. Here we used a prior distribution equivalent to the regularization term in the Tikhonov method applied for the spline average, a 0-mean Gaussian distribution with covariance matrix equal to the inverse volumetric derivative, thus favoring spatially smooth distributions. The resulting probability model is

\[
p(x_t) = \frac{1}{(2\pi)^{d/2}|D|^{1/2}} e^{-\frac{1}{2\sigma_l^2}(x_t^T D x_t)}
\]

\[
p(y_{r,t}|x_t) = \frac{1}{2\sigma_l} e^{-\frac{1}{2\sigma_l^2}(||x_t - Ax_t + b_r||_1)}
\]

Thus, the posterior probability of the heart potentials \(X\) given all the measurements \(Y\) is:

\[
p(X|Y) \propto \prod_{r=1}^{R} \prod_{t=1}^{T} p(y_{r,t}|x_t)p(x_t)
\]

We find the MAP estimate by minimizing the negative log posterior:

\[
\min_{x_t,b_r} L(x_t, b_r) = \sum_{r=1}^{R} \sum_{t=1}^{T} ||z_{r,t}||_1 + \lambda ||Dx_t||_2^2 + ct.
\]

To solve for the unknown parameters \(x_t\) and \(b_r\), we implemented a tailored alternative directions method of multipliers (ADMM) [10] algorithm. ADMM is an iterative optimization method that sequentially solves for each unknown parameter in the objective function while making use of the augmented Lagrangian to account for constraints. In particular, this MAP problem posed in the ADMM perspective can be written as:

\[
\min_{x_t,b_r} = \sum_{r=1}^{R} \sum_{t=1}^{T} ||z_{r,t}||_1 + \lambda ||Dx_t||_2^2
\]

\[st. \quad z_{r,t} = y_{r,t} - Ax_t + b_r\]

where the augmented Lagrangian is:

\[
\mathcal{L}(z_{r,t}, x_t, b_r, \mu) = \sum_{r=1}^{R} \sum_{t=1}^{T} ||z_{r,t}||_1 + \lambda ||Dx_t||_2^2
\]

\[+ \mu^T (z_{r,t} - y_{r,t} + Ax_t - b_r) + \frac{\rho}{2} ||z_{r,t} - y_{r,t} + Ax_t - b_r||_2^2\]
CHAPTER 6. STATISTICAL STUDY

This objective function is then optimized over \( x_t \) and \( b_r \). The proportion between variances given by \( \lambda \) can be computed with the L-curve method. Thus, the ADMM algorithm is:

Until convergence:

1. \( x_{t}^{k+1} = \arg\min_{x_t} L(z_{r,t}^{k}, x_t, b_r^{k}, \mu^k) \)
2. \( z_{r,t}^{k+1} = \arg\min_{z_{r,t}} L(z_{r,t}, x_t^{k+1}, b_r^{k}, \mu^k) \)
3. \( b_r^{k+1} = \arg\min_{b_r} L(z_{r,t}^{k+1}, x_t^{k+1}, b_r, \mu^k) \)
4. \( \mu^{k+1} = \mu^k + (z_{r,t}^{k} - y_{r,t}^{k} + Ax_t^{k} - b_r^{k}) \)

6.2 Experiments and results

6.2.1 Dataset and Experiments

As an initial comparison of the two distinct ways of approaching the problem we tested it using ECG data from a pacing experiment previously presented in [20]. The dataset were 120-electrode body surface ECG recordings obtained during ventricular pacing of three consenting volunteers with healthy ventricles in the Charles University Hospital of Prague in the Czech Republic in conjunction to clinical atrial ablations. The ventricles were paced multiple times at several locations using a catheter device whose position was recorded using the CARTO mapping system. The forward matrix was obtained based on X-Ray CT scans around the heart while the torso geometry was obtained by fitting a generic geometry. Details are in [20].

This data was then used to estimate the underlying heart potentials with 3 different variations of the inverse problem explained in Section 6.1: Ensemble average and spline averaging, both followed by an inverse solution, and the proposed probabilistic inverse using all epochs at once. We compared the estimated position earliest activated node in each solution to the CARTO-recorded pacing site coordinates as the Euclidean distance (in mm) between these two positions.

6.2.2 Results

Figure 6.2 shows the histogram of the error of each inverse method for all subjects and pacing locations. No clear systematic difference between the three methods is apparent; all peak around
32mm of error and have long tails to 80mm. In order to attempt to better observe the differences among the methods, in Figure 6.3 we show histograms of the error difference between the averaging methods (spline and ensemble) versus the probabilistic inverse, that is, $\Delta \text{Error}_{\text{spl}} = \text{Error}_{\text{spline}} - \text{Error}_{\text{prob}}$, and $\Delta \text{Error}_{\text{ens}} = \text{Error}_{\text{ensemble}} - \text{Error}_{\text{prob}}$. Thus negative values indicate worse performance of the probabilistic inverse with respect to the averaging based techniques, while positive values indicate improvement. Here we observe some differences across both methods and subjects. All subjects show a range of results, from more than 20mm improvement with the probabilistic method to equivalent loss in performance. However, for the first subject, the averaging methods tend to do better than the probabilistic model, while in the second this trend is reversed and in the third they do not show much difference. We also tried to segregate results according to the anatomical site of the pacing (left ventricular wall, right ventricular wall, and septum), to investigate if there was any systematic relationship, where the anatomical site of the pacing was categorized as in [20]. However while we did see some consistent differentiation within a given subject when results were categorized by pacing site location, again the results were inconsistent across subjects. For example, for the first subject the left ventricular wall pacings were less accurate with the probabilistic approach, while accuracy on the septal sites was generally the same, while for the second subject there was considerable improvement on the left ventricular wall while again results on the septum were similar.
CHAPTER 6. STATISTICAL STUDY

Figure 6.3: Histogram of the localization error variation of the probabilistic inverse with respect to spline average and ensemble average. The bar colors correspond to the comparison: Spline average - probabilistic (blue) and ensemble average - probabilistic (red). The vertical lines indicate the average variation w.r.t. spline (red) and ensemble (cyan). Each row represents a different subject.

6.3 Discussion

At this point, with data available from only three subjects, we cannot reach a definitive conclusion about which approach is preferred. It may well be that we can learn to differentiate among datasets where one or the other method is likely to achieve the best results. However, we point out that the initial probabilistic model designed for this inverse ECG experiments was relatively simple. We believe there is considerable room for better characterization of the noise. Finally the model presented here considers only spatial variation, and we are currently working to incorporate a temporal model similar to the spline approximation. For example, one may consider a linear approximation of the baseline drift at each epoch $b_r$ instead of the constant used here, as well as better characterizations of the prior that based on biophysical constraints. In addition, we are currently working on an analogous model for inter-ictal spike based source localization. In any case, we believe our attempt to carefully consider and model the question of how best to leverage the availability of repeated recordings will lead in the future to successful attempts to optimize their use.
Part III

Physiologically Informed Model for Correction of Forward Models in ElectroCardioGraphic Imaging (ECGI)


Introduction

A requirement in all ECGI methods is to pre-compute the forward relation between heart surface potentials (HSP) and the body surface potentials (BSP) [59]. However, the resulting forward matrix, which models this relation, is not a perfect representation of the diffusion of potentials within the torso and will introduce multiplicative noise.

In the work presented in [Part II] we modeled the error in the forward matrix with two data-driven approaches. These characterized the variations across measured heartbeats and created the models, one deterministic and one statistical, to account for those.

Here we propose to, instead, model the physiology processes that produce those variations. Specifically, we model the errors in the forward matrix that are created due to movements of the heart. We then use this model, in conjunction with a series of BSP recordings, to correct the position of the heart during each heartbeat.

There has been some previous work with human, animal and synthetic models to determine the impact of the heart position to the BSP. In humans, the studies showed that changes in position of the heart affect different parts of the PQRST sequence [1,41] and are subject specific [49]. More specifically, the variations observed in the BSP created due to respiration can be described as a continuous change in location of the maxima and minima in the spatial maps of the BSP [3]. On the other hand, the synthetic and animal models provided a more systematic understanding of the BSP variations and showed the individual effects on the BSP that each mode of geometry transformation (e.g. translation in each axis or rotation) produces [38,70].

However, in the spirit of correcting the errors in geometry, there has not been much work. García et.al. developed an algorithm that uses the ECG to detect changes in position of the subject [23]. Another approach, more similar to ours, was done by Shvelikova et al., who estimated the vertical position of the heart by tracking a single monopole representing the early electrical potentials on the heart [68]. Although this method is in its objective very similar to ours it is limited by its source model, which assumes a single first breakthrough activation on the heart. This assumption is limiting in that it blinds the reconstruction method to rotations around this monopole, but is also inconsistent with the regular activation of a healthy heart.

In this last section of this thesis, we describe this physiologically informed model to characterize the errors in the forward matrix and then discuss an approach to use it to find the position of the heart during each recorded heartbeat.
Chapter 7

Improving Forward Models through Correction of the Geometry

7.1 Introduction

In this section of the thesis we present our geometry correction method. We start by describing how to obtain the mapping between geometry correction parameters (i.e. translation and rotation) and forward matrices and then we describe the objective function that needs to be solved in order to obtain the “optimal” transformation parameters. We evaluate this approach with three experiments. In the first study we synthesize BSP on a torso surface by moving the heart to mimic movements due to respiration and then correct the position of the heart using both BSPs and HSPs. In the second study we explore a practical application where we try to explain the errors in forward model of a canine experiment through translations and rotations of the heart. We finally include a third experiment that serves as a proof of concept for the application of this method in a general scenario where the HSPs are not known. We end this chapter with a discussion on the results and implications of this method.

7.2 Methods

The geometry correction method is based on the assumption that, since small changes in position of the heart generate small variations in the forward matrix, these form a manifold in the space of matrices. Moreover, this manifold can be defined with a mapping from the space of geometry transformations $\mathbb{R}^d$ to the space of matrices $\mathbb{R}^{N \times M}$. Where $N$ is the number of BSP measurements
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and $M$ is the number of nodes on the discretized heart. Although this method could be extended to any continuous transformation of the geometry, in this work we restrict the geometry transformations to rigid translations and rotations of the heart. Hence, the relevant geometry transformation parameters have $d = 6$ dimensions, 3 for translation and 3 for rotation.

$$f : \mathbb{R}^6 \rightarrow \mathbb{R}^{NM}$$ (7.1)

Under this assumption, we set ourselves to find a function that efficiently approximates the manifold. We refer to this function as the Forward Matrix Manifold Approximation (FMMA) and is computed through the following blocks:

- A parametrization of the movements of the heart that allow to extract a set of sample forward matrices.
- A dimensionality reduction method that reduces the size needed to represent the forward matrices.
- An interpolation function that approximates the reduced coefficients in between the set of samples.

Figure 7.1 offers a visual representation of these blocks and the elements generated to build and later evaluate the FMMA.

### 7.2.1 Movement Parametrization

When breathing, the heart moves within the thorax driven by the diaphragm and the intercostal muscles. Although the position and movement of the heart is subject specific, there are general behaviors: the heart translates vertically and undergoes some rotation around a tethering point on the left atria [4, 13, 50]. A full characterization of the effects of respiration to forward matrices, should also incorporate shape deformation of the heart and even changes in conductivity [45]. However, in this work we will restrict the effects of respiration to rigid movements of the heart in the form of translation and rotation in 3D space.

The translations are defined with respect to the coordinate system described in the EDGAR database [4], where the vertical axis is the Z coordinate, the X coordinate crosses the torso from right to left and the Y coordinate from chest to back. Additionally, the rotation movements are defined with respect to two added references: an anchor point placed at the center of the atria and
Figure 7.1: Visual representation of the sequence of steps followed to generate the FMMA (left) and to evaluate it (right). The orange elements indicate data used or resulting from each process and green elements indicate the units of information generated during the FMMA estimation and necessary for its evaluation.

an axis that crosses the heart through the septum, from the atrial anchor point to the apex. Using these references, the rotation angles shown in Figure 7.2 correspond to:

- **Pitch** ($\theta$): the angle formed between the Z axis and the septal axis.
- **Yaw** ($\phi$): the angle that the septal axis projected on the X/Y plane forms with the X coordinate.
- **Roll** ($\rho$): the rotation of the heart around the septal axis.

Since we want the parametrization to be flexible, we allow for independent translation and rotation in all 3 axis and angles such that their parameters are bounded with the box constraint $\Xi$ (e.g. $\Xi = \{X = \pm10\,mm, \, Y = \pm10\,mm, \, Z = \pm20\,mm, \, \theta = \pm45^\circ, \, \phi = \pm45^\circ, \, \rho = \pm45^\circ\}$).

The parametrization of the geometry transformations allows to define the input space (i.e. the domain of the FMMA) and abstract the process of creation of a forward matrix, through the transformation of the geometry and the subsequent BEM calculation, to the evaluation of the function $A(x, y, z, \Theta, \Phi, \rho)$. The FMMA is an approximation of this function and is generated through the interpolation of samples obtained from strategic sampling of $A(x, y, z, \Theta, \Phi, \rho)$. Specifically, we sample the manifold by evaluating this function with a set of transformation parameters defined on
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Figure 7.2: Depiction of the rotation angles defined on the heart. Pitch ($\theta$): the angle formed between the $Z$ axis and the septal axis. Yaw ($\phi$): the angle that the septal axis projected on the $X/Y$ plane forms with the $X$ coordinate. Roll ($\rho$): the rotation of the heart around the septal axis.

an equally spaced grid with $K$ samples in each dimension. In practice, this is equivalent to moving the heart at the set of positions defined by the transformation parameters on this grid and then compute BEM on each geometry to obtain the sample forward matrices $\{A_k\}^K_{k=1}$.

7.2.2 Dimensionality Reduction

Without considering the inter-dependencies between entries in the forward matrix, in an experiment with $N$ BSP measurements on the body surface and $M$ nodes on the heart, it is necessary to generate and later evaluate $N \cdot M$ functions from $\mathbb{R}^6$ to $\mathbb{R}$. Such operation is inefficient and soon becomes computationally prohibitive. It is thus necessary to apply dimensionality reduction methods to minimize the number of functions needed to interpolate.

Here, we exploit the linear dependencies between the forward matrices that can be obtained from translations and rotations of the heart. In other words, we search for the subspace of dimension $Q \leq N \cdot M$ that contains most of the variance in the set possible forward matrices. To determine the desired subspace, we use Principal Component Analysis (PCA) to compute the $Q$th most relevant principal components and use them as the basis of the subspace [8]. Thus, we take the sample forward matrices $\{A_k\}^K_{k=1}$, subtract their average forward matrix $\bar{A}$ and vectorize them ($\text{vec}(A)$). Then we estimate their covariance matrix and compute its first $Q$ eigenvectors $\{\text{vec}(B_q)\}^Q_{q=1}$. After
reshaping back to matrix form, any new forward matrix can be approximated as a linear combination of these “basis matrices” (Equation 7.2).

\[
\tilde{A} = h(\beta) = \sum_{q=1}^{Q} \beta_q B_q + \tilde{A}
\]

\[
\beta_q = \text{vec}(A)^T \cdot \text{vec}(B_q)
\]

Where \(\beta_q\) are the projection of a vectorized forward matrix (\(\text{vec}(A)\)) onto the vectorized basis \(\text{vec}(B_q)\). This representation reduces the dimension needed to represent forward matrices from \(\mathbb{R}^{M \times N}\) to vectors in \(\mathbb{R}^Q\). Thus, the overall FMMA \((f(x, y, z, \Theta, \Phi, \rho) : \mathbb{R}^6 \rightarrow \mathbb{R}^{N \times M})\) is divided into two parts: a first non-linear function from transformation parameters to projected coefficients \((\hat{\beta}(x, y, z, \Theta, \Phi, \rho) : \mathbb{R}^6 \rightarrow \mathbb{R}^Q)\) and a linear combination of these to generate the final matrix \((h(\beta) : \mathbb{R}^Q \rightarrow \mathbb{R}^{N \times M})\).

### 7.2.3 Manifold Interpolation

The manifold interpolation block approximates the non-linear function \(\hat{\beta}(x, y, z, \Theta, \Phi, \rho)\) in the FMMA. To that purpose, we interpolate the \(Q\) functions from \(\mathbb{R}^6\) to \(\mathbb{R}\) with multidimensional splines.

A spline is a piecewise polynomial of order \(n\) defined as \(s_n(x) : \mathbb{R} \rightarrow \mathbb{R}\) with guaranteed smoothness \(C^{n-1}\) [14]. In the remaining of this work, we will only consider cubic splines (i.e. splines of order \(n = 3\)) and we will drop the sub-index \(n\) for simplicity.

One particular form of expressing spline functions is the basis spline, or B-spline, which express any spline \(s(x) : \mathbb{R} \rightarrow \mathbb{R}\) as the sum of the basis functions \(B_k(x) : \mathbb{R} \rightarrow \mathbb{R}\), weighted by the values at the knot points \(\Gamma_k\):

\[
s(x) = \sum_{k=1}^{K} \Gamma_k B_k(x)
\]

Thus, to find the B-spline function that best approximates a set of pairs \(\{(x_i, y_i)\}_{i=1}^{N}\), where \(x_i\) and \(y_i\) are the independent and dependent variables in a function, it is necessary to solve:

\[
\min_{\Gamma} \sum_{i=1}^{N} \|y_i - \sum_{k=1}^{K} \Gamma_k B_k(x_i)\|^2
\]

This minimization can be done with any available software package that includes splines representations and becomes especially efficient when the knot points and the samples provided are taken in an equally spaced grid in the interpolation domain.
The generalization of a spline function to multiple dimensions in its domain \( s(p) : \mathbb{R}^d \to \mathbb{R} \) is done through tensor products. For example, to generate a spline function defined in \( \mathbb{R}^2 \) \( s(x_1, x_2) : \mathbb{R}^2 \to \mathbb{R} \) it is necessary to evaluate the following equation:

\[
s(x_1, x_2) = \sum_{k_1} \sum_{k_2} \Gamma_{k_1, k_2} B_{k_1}(x_1) B_{k_2}(x_2)
\]

(7.5)

Where, in vector form, \( \Gamma \) is a matrix containing all knot points and \( B \) are the vectors with the evaluation of the basis splines in each dimension. Thus, for an arbitrary number of dimensions of the input domain \( d \) we have the spline approximation:

\[
s(p) = \sum_{k_1} \cdots \sum_{k_d} \Gamma_{k_1, \ldots, k_d} B_{k_1}(x_1) \cdot B_{k_2}(x_2) \cdots B_{k_d}(x_d)
\]

(7.6)

Where now \( \Gamma \) is a tensor of \( d \) dimensions containing all the \( K^d \) knot points and \( \circ \) indicates the Kronecker product of each basis vector \( B^i \), defined in the dimension \( i \).

In the particular case that we need to interpolate, the multidimensional spline functions \( \hat{\beta}_q(p) \) are defined from \( \mathbb{R}^6 \) to \( \mathbb{R} \) and the tensor \( \Gamma \) containing all the knot points has size \( K^6 \).

### 7.2.4 Forward Matrix Manifold Approximation and Evaluation

The complete procedure to interpolate the manifold, shown in Figure 7.1, is the following:

1. Define a parametrized geometry correction.

2. Generate sample \( K^6 \) forward matrices obtained from a heart geometry transformed according to the parameters sampled on an equally spaced grid \( \{A_k\}_{k=1}^{K^6} \).

3. Learn the truncated basis function of dimension \( Q \) \( \{B_q\}_{q=1}^{Q} \) using PCA.

4. Project sample matrices to the new basis and obtain projected coefficients \( \{\beta_k\}_{k=1}^{K^6} \).

5. Interpolate each dimension of the projected coefficients with a multidimensional spline \( \hat{\beta}(p) = \hat{\beta}(x, y, z, \Theta, \Phi, \rho) \).

With the previous operations we generate the elements necessary to fully describe the FMMA and compute an approximation of a forward matrix whose geometry has the heart displaced to \( (x, y, z, \Theta, \Phi, \rho) \). This evaluation concatenates the interpolation functions \( \hat{\beta}(x, y, z, \Theta, \Phi, \rho) \) and the linear function \( h(\beta) \) in the following procedure:
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1. Evaluate the function of projected coefficients $\hat{\beta}_q(x, y, z, \Theta, \Phi, \rho)$.

2. Generate an approximated forward matrix $\hat{A}(x, y, z, \Theta, \Phi, \rho)$ using $\hat{A} = \sum_{q=1}^{Q} \hat{\beta}_q B_q + \tilde{A}$.

As its name indicates, the FMMA is an approximation of a real forward matrix. Its approximation error can be reduced with increased number of knot points in each dimension $K$ and subspace dimension $Q$. However, the increase of these parameters comes at the cost of increased computational demands. In particular, for a number of knot points $K$, it is necessary to compute the eigenvalue decomposition of a squared covariance matrix of size $(K^6)^2$, which is a memory intensive calculation and soon becomes prohibitive. On the other hand, the increase in the subspace dimension $Q$ increases the computational time needed to evaluate the FMMA, thus limiting its use in optimization solvers. During the development of FMMA, we could not find a clear criteria for the selection of these parameters. We thus leave their selection to the particular computational resources available in each experiment.

7.2.5 Geometry Correction

With a computationally efficient function to approximate forward matrices $(\hat{A}(x, y, z, \Theta, \Phi, \rho))$ it is now possible to optimize over the geometry transformation parameters, which for simplification we denote as $p = (x, y, z, \Theta, \Phi, \rho)$, and find the parameters that best describe the relation between BSP and HSP. We pose this problem as a least squares optimization, bounded by the box constraint $\Xi$ (Equation 7.7).

$$\min_p \sum_t \|BSP(t) - \hat{A}(p)HSP(t)\|^2_2$$

$$st. p \in \Xi$$

(7.7)

This equation fits the synthesized $BSP = \hat{A}(p)HSP$ to the measured BSP. However, it has the inherent assumption that the HSP are known for every node on the heart. In practice there will only be partial measurements, if any, on the heart surface, rendering that assumption invalid. Blindly eliminating the columns of the forward matrix is equivalent to setting the potentials at those nodes to 0 mV, thus introducing errors in the BSP estimation [25]. To circumvent this limitation we modified the previous objective function so that the measure of error is only applied to the nodes on the heart with available measurements. (Equation 7.8).

$$\min_p \sum_t \|\hat{A}^t(p)BSP(t) - HSP(t)\|^2_2$$

$$st. p \in \Xi$$

(7.8)
This optimization function reverses the role of $\hat{A}$ and requires to compute its inverse. Unfortunately, as is the case for the forward matrix being approximated, $\hat{A}$ is ill-posed and needs regularization to compute a numerically stable inverse ($\hat{A}(p) \dagger \in \mathbb{R}^{M,N}$). To that objective we used the Truncated SVD method (TSVD) \(^\text{[27]}\), which computes the inverse matrix as the sum of outer products of the singular vectors ($u_l$ and $v_l$) of $\hat{A}(p)$ weighted by the inverse of their singular values ($\sigma_l$).

$$\hat{A}(p) \dagger = \sum_{l=1}^{L} \frac{1}{\sigma_l} v_l u_l^T$$

7.3 Experiments

To validate the FMMA optimization we designed three experiments. First, we created a synthetic dataset designed to test the algorithm in a controlled scenario where the heart is in a known position and moves in the same manner as respiration. In the second experiment, we tested it in a real scenario where the heart is suspended in an unknown position within a tank. And third, we evaluated if the previous results can be generalized to a scenario where the potentials on the heart are unknown. In the following, we will describe in more detail the three experiments with which we tested our geometry correction method.

7.3.1 Synthetic Experiment with Known HSP

We created this dataset to numerically evaluate the FMMA optimization. To that purpose, we took a heart and a homogeneous torso geometries and a real HSP recording. Then, we moved the heart at different locations within the torso and synthesized the corresponding body surface measurements. Once generated the BSPs, we used the heart and torso potentials to find the location of the heart for each heartbeat.
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Figure 7.3: Left: Illustration of the change of position of the heart throughout respiration. The lines superimposed on the heart, shown at maximum exhale ($\alpha = -1$), are the position of the septal axis for each respiratory phase: $\alpha = [-1, -0.75, -0.5, -0.25, 0]$, respectively in blue, cyan, green, orange and red.

Right: Example of sequence of respiration phases used in the synthetic experiment. The random walk process was generated with starting respiratory phase $\alpha_1 = -1$ and with variance 0.25. Sample phases outside the range $[-1, 1]$ were mapped back to the nearest bound.

7.3.1.1 Generation of Testing Data

To simulate a realistic movement of the heart, it was necessary to obtain a parametrized function that describes the movement of the heart. With that objective, we took a model of a respiration process obtained in previous work, where we tracked the movement of the heart from a series of MRI scans [13]. This model allowed us to parametrize the position of the heart with a multidimensional quadratic function that maps the phase in the breathing cycle ($\alpha \in [-1, 1]$) to translation and rotation parameters ($p$). We refer to this function as respiratory function ($r(\alpha)$) and the phase within the respiratory cycle as “respiratory phase”. The definition of the respiration function defines phase $\alpha = 0$ as maximum inhale position and $\alpha \rightarrow 1$ or $-1$ as approaching or moving away from maximum exhale. Figure 7.3 shows the change of position of the septal axis for different phases along the respiratory cycle to provide a visual reference of the changes in position of the heart.

In order to simulate an irregular breathing pattern, we generated $NB = 25$ respiration phases following a random walk process starting at $\alpha_1 = -1$ and with variance 0.25, constrained to remain within the range $[-1, 1]$. An example of a resulting sequence is shown in Figure 7.3.
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Figure 7.4: Illustration of the translation bounding box (purple grid) within the torso for the synthetic experiment (left) and torso-tank (right). In all plots, hearts plotted correspond to the heart at original position (grey), heart at maximum bound (green) and minimum bound (red).

Once obtained the respiration phases, we used the respiration function to move the heart at 25 different locations simulating a breathing pattern. For each one of them, we computed a forward matrix using the BEM software in SCIRun \[67\] and multiplied it with the HSP to synthesize the torso potentials per each beat. Finally, we added white Gaussian noise with sufficient power to create synthetic measurements with \( SNR = 30dB \).\[1\]

7.3.1.2 Geometry Correction

To find the appropriate position of the heart for each heartbeat, we used the procedure described in subsection 7.2.4: we first generated the FMMA and then used it with the HSP and the synthesized BSPs to solve for the transformation parameters.

More specifically, we first generated a set of forward matrices that we would use as a reference to interpolate. These were obtained by using a BEM software on the torso and heart geometries such that the heart had been moved according to the geometry transformation parameters sampled on an equally spaced grid. This sampling grid was defined such that the possible transformations of the heart (e.g. all the set of translation and rotation parameters) were contained within by a bounding box \( \Xi \). The bounds of this grid were chosen to enclose the movements of the heart due to respiration.

\[1\]Here SNR is computed as \( SNR(dB) = 20\log_{10}\left(\frac{V_{signal}}{V_{noise}}\right)\)
with some margin around it.

\[ \Xi = \{ X \in [-10, 10] \text{mm}, Y \in [-10, 10] \text{mm}, Z \in [-40, 10] \text{mm}, \theta \in [-95^\circ, 25^\circ], \phi \in [-45^\circ, 45^\circ], \rho \in [-45^\circ, 45^\circ] \} . \]  

(7.10)

See Figure 7.4 for an illustration of the limits established by this bounding box in relation to the torso. The number of samples on this grid is an important parameter of our algorithm, since it defines the number of knot points used during interpolation and thus the approximation accuracy of FMMA. In this experiment we used the maximum number of samples that our computational system allowed, resulting in \( K = 5 \) samples in each dimension (total of \( 5^6 \) samples).

Before applying the spline interpolation, we used PCA to extract the linear dependencies between the sampled forward matrices and thus reduce the dimensions needed to interpolate from \( N \cdot M \) to \( Q \). Similarly to the choice of samples, we truncated the subspace with a criteria based on computational limitations. In this case, we choose \( Q = 300 \) as it was the maximum number of dimensions for which the evaluation of FMMA was fast enough to be used in the optimization function.

Once generated the FMMA, we could use it in an optimization solver to obtain the “optimal” transformation parameters in each heartbeat. Thus, we took every pair of HSP and BSP, smoothed them with a moving average window of \( 20 \text{ms} \) (cut-off frequency of \( \sim 22.24 \text{Hz} \)), and included them into the optimization function:

\[
\min_p \sum_t \| \hat{A}^\dagger(p)BSP(t) - HSP(t) \|_2^2 \\
st. p \in \Xi
\]

(7.11)

For the estimation of \( \hat{A}^\dagger \) we used \( L = 25 \) in the TSVD truncation as it was the minimum dimension that yielded stable results.

7.3.2 Torso Tank

This dataset offers a unique opportunity to test our algorithm in a real scenario. In these experiments, the heart is suspended within a torso shaped tank filled with conductive medium while electrical recordings are being taken on both heart and tank surface. As will be described, at the end of the experiment the position of heart was registered within the tank to obtain a heart and torso geometry and then compute the forward matrix with a BEM software. However, it has been observed in the past that this forward matrix does not provide accurate synthetic BSPs. Our hypothesis is that
a considerable amount of this error can be explained by time varying rotations and translations of the heart within the tank.

To test our hypothesis we used the electrical measurements of both heart and torso in our geometry correction method to find the appropriate translation and rotation of the heart for each heartbeat. Then we evaluated the forward solutions by comparing the BSPs synthesized using the forward matrices obtained with the corrected geometries against the real BSP measurements.

7.3.2.1 Dataset Description

This dataset can be accessed online at the website of the Consortium of Electrocardiographic Imaging (CEI - [http://www.ecg-imaging.org/](http://www.ecg-imaging.org/)) within the EDGAR database [4] and was originally generated at the Cardiovascular Research and Training Institute (CVRTI) in Utah, under the appropriate IACUC approval. It was designed with a double objective: to study the effects of myocardial ischemia to the potentials on the heart and body surface and to generate test data for ECGI methods. The experimental procedure consisted on the placement of an excised canine heart within a torso shaped tank filled with conducting medium. In the meanwhile, electrical recording were taken on the surface of the tank (192 electrodes) and the heart ventricles (247 electrodes).

The experimental procedure was the following: after excision of the heart, its ventricles were surrounded with a sock containing 247 electrodes and then the heart was inserted inside of the tank. The rest of the experiment was divided into interventions consisting on: two interventions with atrial pacing to control the heart activity before and after the insertion of needles, a series of interventions with ventricular pacing and the interventions regarding the ischemic experiments. Thus, the first intervention consisted on a control recording with atrial pacing of the heart. Afterwards, the heart was extracted from the tank and needles were inserted within the myocardium with the double purpose of recording intramural potentials and pacing the ventricles. The heart was then introduced again into the tank and the second intervention, atrial pacing control, was recorded. The following 5 interventions consisted on recordings of heartbeats paced at different locations on the ventricles. After the ventricular pacing protocols the ischemic experiment began. These recordings were taken with atrial pacing and occlusion of the LAD artery to induce ischemia in alternating interventions. Thus, the ischemic protocol started with an intervention inducing ischemia, followed by a control intervention, another ischemic intervention and a final control. The full experiment included 3 more ischemic interventions. However the experimenters expressed some reservations about possible problems during the experimental procedure and thus, we excluded those interventions from this
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work. We report our results per each individual heartbeat, grouped by intervention and further classified by intervention type, *i.e.* interventions before the needle insertion, interventions with atrial pacing and interventions with ventricular pacing.

To register the heart geometry within the torso, the heart was vertically extracted from the tank at the end of the experiment and the position of each electrode and needle was digitized. We will refer to the heart geometry obtained through this procedure as the “original” geometry.

### 7.3.2.2 Geometry Correction

As in the previous synthetic experiment, we first evaluated the FMMA and then used it in the optimization function to solve for the transformation parameters. The choice of parameters was done based on the available computational resources and set again to $K = 5$ knot points and subspace truncation $Q = 300$ dimensions. This time, however, the bounding box for the transformation parameters was chosen to be wider, since it needed to account for greater variability in all directions:

$$
\Xi = \{ X \in [-30, 30] \text{mm}, Y \in [-30, 30] \text{mm}, Z \in [-20, 20] \text{mm}, \\
\theta \in [-95^\circ, 25^\circ], \phi \in [-60^\circ, 60^\circ], \rho \in [-60^\circ, 60^\circ] \}.
$$

(7.12)

See Figure 7.4 for an illustration of the limits established by this bounding box.

Finally, we smoothed each pair of measured BSP and HSP in time with a moving average filter of a width of 20ms. The optimization function solver was the same as in the synthetic experiments, but this time we choose to increase the regularization imposed by reducing the truncation point of the TSVD inverse to $L = 10$ in order to compensate the extra sources of noise present in real measurements.

### 7.3.3 Synthetic Experiment with Unknown HSP

The last experiment was designed to simulate a clinical application where the HSP are not known.

Hence, we took the synthetic dataset generated in the first experiments and used it in an optimization function that does not take the HSP as an input. Since the data generation is parallel to the first synthetic experiment, we refer to subsection 7.3.1 for details, here we will describe the necessary modifications in the optimization algorithm to estimate the unknown HSP.
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7.3.3.1 Estimating the Unknown HSP

When the HSP need to be estimated, the resulting optimization function becomes:

$$\min_{p,HSP(t)} \sum_t \|BSP(t) - \hat{A}(p)HSP(t)\|^2_2$$

(7.13)

$$st. p \in \Xi$$

As before, $\hat{A}(p)$ is the FMMA, $p$ are the transformation parameters but now the HSP are unknown and need to be estimated. To that purpose, we could use an ECGI method to iteratively solve for HSP and transformation parameters. However, there is an intrinsic ambiguity between potentials on the heart and transformation parameters. (i.e. for any fixed transformation parameter, there is a HSP distribution that can synthesize the measured BSP). To overcome this limitation we introduce prior knowledge on both the HSP and the transformation parameters.

On the HSP, we assume that all heartbeats in a series of BSP recordings are produced by the same underlying HSP. This constraint uses the beat to beat changes in morphology of the BSP to estimate the relative position of the heart across all heartbeats.

Since the beat to beat variations only resolve the relative position of the heart, there is still an unknown shift in the transformation parameters that remains elusive. To overcome this last ambiguity, it is necessary to enforce the position of one heartbeat with a known geometry transformation ($p_0$). To implement these priors, we concatenate all BSPs in a single matrix $X$ and the FMMA per each heartbeat in a matrix $\Sigma$ and solve (Equation 7.14).

$$\min_{p_0,HSP(t)} \sum_{b=1}^{NB} \sum_t \|BSP_b(t) - X(t)\|^2_2$$

$$HSP(t) = \Sigma^\dagger \cdot X$$

(7.14)

$$st. p \in \Xi, p_1 = p_0$$

$$\Sigma = \begin{bmatrix} \hat{A}(p_1) \cdots \hat{A}(p_b) \cdots \hat{A}(p_{NB}) \end{bmatrix}$$

$$X = \begin{bmatrix} BSP_1(t)^T \cdots BSP_b(t)^T \cdots BSP_{NB}(t)^T \end{bmatrix}^T$$

As in the previous optimization method, we use TSVD to compute the regularized inverse of the concatenated forward matrices $\hat{\Sigma}^\dagger$. 

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7.3.3.2 Geometry correction

The parameters used to estimate the FMMA were the same as in the first synthetic experiment: \( K = 5 \) knot points, \( Q = 300 \) dimensions and the transformation parameters bounding box:

\[
\Xi = \{ X \in [-10, 10] \text{ mm}, Y \in [-10, 10] \text{ mm}, Z \in [-40, 10] \text{ mm}, \\
\theta \in [-95^\circ, 25^\circ], \phi \in [-45^\circ, 45^\circ], \rho \in [-45^\circ, 45^\circ]\}.
\]

The BSP were smoothed out in time with a moving average filter with a window of \( 20 \text{ ms} \) and used them to solve the optimization problem described above. In order to preserve the similarity with the synthetic experiment where the HSP were known, we also used the truncation point of the TSVD as \( L = 25 \).

7.3.4 Evaluation Metrics

We evaluated the geometry correction algorithm with measures on two quantities: the heart geometry and the forward solutions.

In terms of evaluation of the geometry errors, we computed the root mean square distance (RMSD) between true and corrected geometry (Equation 7.16).

\[
RMSD = \sqrt{\frac{1}{M} \sum_{m=1}^{M} \| x_{true,m} - x_{rec,m} \|^2_2}
\]

\( x_m = 3D \) coordinates of node \( m \)

To evaluate the errors in the forward solutions, we synthesized the new BSPs and compared them with the true BSP. To synthesize the BSPs, we used the estimated transformation parameters \((\hat{p}_b)\) of each heartbeat \( b \) to move the heart and compute the forward matrix \((A(\hat{p}_b))\) with a BEM solver. Then we synthesized \( BSP_b \) by multiplying each HSP \( b \) with the corresponding forward matrix \((BSP_b = A(\hat{p}_b)HSP_b)\). To finally evaluate the errors in forward solutions, we measured the relative error between true/measured BSPs and the BSPs synthesized with the corrected forward matrices.

For comparison with the standard situation where no geometry correction is applied, we also computed the relative error of the synthesized \( BSP_b \) using a fixed geometry. As a fixed geometry we used the heart placed at maximum exhale position \((\alpha = -1)\), in the case of the synthetic experiments, and the “original” geometry registered during the experiments in the case of the torso-tank.
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7.4 Results

7.4.1 Synthetic Experiment with Known HSP

Since the fixed geometry model is taken with a static snapshot of the geometry at $\alpha = -1$ (full expiration), it is expected that every error metric will be small for respiration phases close to expiration and that it will increase as $|\alpha| \to 0$. Consequently, the objective of the geometry correction method is to adjust for the changes created due to respiration movement and decorrelate the error from the respiratory phase.

First, we refer to the errors in the geometry. We measure this error as the RMSD between the true and “corrected” geometries, plotted in Figure 7.5 and sorted by respiration phase. As expected, the RMSD between the fixed geometry and the true (in red) increases as $|\alpha| \to 0$ and reaches a maximum RMSD of 23mm at full inspiration (i.e. each node is, on average, displaced 23mm from its true position). Also, as desired from the geometries corrected with our method, the “corrected” RMSD is practically flat along the respiratory cycle. On average, the “corrected” heart is displaced 1.8mm with respect to the true geometry and the results achieve maximum and minimum RMSD of 3.6mm and 0.9mm. The average RMSD $\geq 0$ indicates that our solutions have some bias that the algorithm cannot resolve.

Equivalent results are observed in the forward solutions. The plot in Figure 7.6 showing the relative error between the true and “corrected” BSPs, is akin to the previous RMSD plot. As before, the error for the fixed geometry increases with inspiration, while the geometry correction is capable of flattening it, effectively decorrelating it from the respiration phase. Now, the average relative error is 0.049mV, which is almost the noise level introduced to the BSP. Reaching this level of SNR suggests that the algorithm finds a position of the heart that best synthesizes the true BSP and that the residual error observed in the RMSD (1.8mm) cannot be recovered from the noisy data. To complete the results, we show the BSP maps at time $t = 34ms$ (during R-wave) for the respiration phases $\alpha = \{-1, -0.83, -0.57, -0.4, -0.08\}$ plotted in rows for the true, “fixed” and “corrected” BSP maps in each column. Clearly, the fixed geometry is not capable of synthesizing the true BSP maps, having the heart fixed at $\alpha = -1$, these cannot track the BSP changes across beats at different respiration phases. On the other hand, the “corrected” maps do show the changes on BSP across respiration phase observed in the true BSP maps, although with somewhat smoother distributions.
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Figure 7.5: Synthetic Experiment: Relative Error of measured and synthesized tank surface potentials both with original geometry (in red) and rectified geometry (blue). Each column shows results for a type of intervention. Red line indicates point of equality and magenta dot indicates the mean per each intervention type.

Figure 7.6: Synthetic experiment: Relative Error of measured and synthesized tank surface potentials both with original geometry (in red) and rectified geometry (blue). Each column shows results for a type of intervention. Red line indicates point of equality and magenta dot indicates the mean per each intervention type.
Figure 7.7: Synthetic experiment potential map comparison at $t = 35\text{ms}$. Left column shows the recorded potentials on the tank, center column shows the synthesized potentials using the original position of the heart and the right column shows the synthesized potentials after rectifying the position of the heart.
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7.4.2 Torso-Tank

In the torso-tank experiments there is no equivalent to the respiratory phase nor a ground truth with which to validate the corrections in position of the heart. It is thus necessary to evaluate these results from the perspective of the hypothesis posed in their description, i.e. can rotation and translation of the heart account for the error in the forward solutions generated?. To evaluate it, we will discuss about the improvement in BSPs synthesized using the corrected geometry and consider the plausibility of the changes in position of the heart obtained.

We begin by showing a comparison of the BSP relative error between the “original” BSPs, obtained using the original geometry, and the “corrected” BSP, obtained after moving the heart according to our method. Figure 7.8 shows a scatter plot where each reconstructed beat is a dot and the horizontal and vertical axis represent the relative error of the “original” and “corrected” BSPs, respectively. Thus, beats along the diagonal line (in black) indicate perfect reconstruction, above it are beats where the relative error increased after correcting the geometry and below it are beats where the geometry correction improved the BSP fit. To distinguish between interventions, we further color the beats based on their intervention type: before needles (blue), atrial pacings (green) and ventricular pacings (yellow). The distribution of results along the horizontal line shows that,
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Initially, there is a considerable spread of error (between 0.38 and 1.45), which could be created by a myriad of possible causes. However, one of them could be the rotations and translations of the heart found, since the geometry correction does, on average, improve the BSP synthesized. Most of the beats in the scatter plot lie below the identity line and the improvement (measured as distance from the line) is around 20% for a great majority of the beats (median improvement is 14%) and up to 53.6% for a few cases. The exceptions are some beats with an “original” relative error around 0.5, which worsen somewhat with respect to the “original” BSP (∼10% with a maximum of 20% for an individual beat). For those beats the geometry reconstruction method probably failed to converge into a global minima. Looking at the differences across interventions, there is a clear distinction between atrial paced beats, which cluster together with relative error between 0.6 and 1 and show a fairly stable improvement of 20%, and the ventricular paced beats. The beats recorded during the latter interventions show an “original” relative error distributed all over the range [0.38, 1.45] and also appear to have much more sensitivity to the correction of the geometry. In some cases displacing the heart to the estiamted positions worsens the relative error, while in other it shows an improvement in relative error of 53.6%. This variability suggests that ventricular pacing beats might not remain as static as the atrial paced counterparts.

Direct observation of the BSP maps offers a more intuitive understanding than the plain relative error plots. Figure 7.9 shows the measured, “original” and “corrected” BSP maps (in columns) for a series of example beats (rows) that correspond to:

- Atrial pace before needles (“original” relative error 1.02 and “corrected 0.9).
- Atrial pace after needles (“original” relative error 1.14 and “corrected 0.99). 
- Ventricular pace, LV-base (“original” relative error 0.8 and “corrected 0.61). 
- Ventricular pace, LV-septum (“original” relative error 1.03 and “corrected 0.49).
- Ventricular pace, LV-wall (“original” relative error 0.67 and “corrected 0.83).

In all the examples shown, but the last one, the “corrected” BSP maps are better at reproducing the morphology observed on the measured. By subjective observation, the ordering of the results from worse to best are LV-wall, before needles, atrial pace after needles, LV-base and LV-septum, which matches the resulting relative errors. Comparing the “original” and “corrected” maps, it seems that the geometry correction method provides forward solutions that refine the “original” potential distributions on the torso to match the morphology of the measured BSP.

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Figure 7.9: Torso-Tank experiment potential map comparison. Left column shows the recorded potentials on the tank, center column shows the synthesized potentials using the original position of the heart and the right column shows the synthesized potentials after rectifying the position of the heart.
We complete our analysis of the torso-tank results with the analysis of the “corrected” positions of the heart. Since the interpretation of the transformation parameters and their relation to the intervention protocols is speculative, we delegate this discussion to Section 7.5. However, there are a few observations that need to be made. First, there is a considerable change in $\theta$ between the first intervention and the rest of about $45^\circ$. Another observation is that the intra-intervention variability of the transformation parameters is greater for interventions with ventricular pacings than otherwise. This increased variability is more apparent for translation in $X$, and the angles $\phi$ and $\rho$ and matches the wide distribution of the relative error in BSP observed in the forward solutions. To better quantify this observation, we computed the standard deviation within each intervention, averaged across intervention types, and plotted it in Figure 7.11. Indeed, there is an increased standard deviation in the ventricular paced interventions that mostly affects the angles $\phi$ and $\rho$. The last observation is that many transformation parameters lie on the edge of the bounding box where the FMMA is defined. For example, most of the ventricular paced beats show a translation along the $Y$ axis equal to $-30\,mm$. In Section 7.5 we will refer to these observations about the transformation parameters and put them in the context of the experiment to argue about possible explanations.

### 7.4.3 Synthetic Experiment with Unknown HSP

We expect the results of the geometry correction method with simultaneous estimation of HSP to be similar to the case with known HSP, only with a possible increase of error. Indeed, the results show this trend but, contrary to the prior belief, the joint estimation of HSP actually helps reduce the error in positioning the heart, both on average and standard deviation.

We first discuss the results of the RMSD, shown in Figure 7.13. As before, the “original” RMSD appears in red and the “corrected” in green and, again, the geometry correction method is capable of tracking the position of the heart across different respiration phases. The main difference appears on the values obtained. Now the average RMSD is $0.43\,mm$ and the standard deviation $0.19\,mm$, much smaller than when the HSP were known.

On the other hand, the relative error of the BSP, shown in Figure 7.14 are exactly the same results as in the previous experiment. The geometry correction method decorrelates the error in the forward solutions from the respiration phase and provides a relative error of $0.045$, again very
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Figure 7.10: Torso-Tank experiment: Scatter plot of all transformation parameters. On the left the translation parameters and on the right the rotation parameters. Colormap indicates the type of intervention: before needles (blue), after needles (green) and ventricular pacings (yellow).
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Figure 7.11: Standard deviation within an intervention averaged across intervention types. Blue, green and yellow columns correspond to atrial pacing before needles, after needles and ventricular pacings respectively. Each group of columns corresponds to a different geometry transformation parameter.

close to the experimental power of the additive noise, but not smaller than before. We omit plotting examples of the BSP maps obtained with this reconstruction as they are equivalent to the ones observed in Figure 7.7.

7.5 Discussion

The results presented in Section 7.4 show three major outcomes of the geometry reconstruction method.

We prove that it is capable of correcting most of the error introduced to the forward solutions due to changes in position of the heart, thus decorrelating it from the respiration process. Moreover, our model is capable of explaining a considerable amount of error in the torso-tank experiments and suggests that the geometry registration errors are higher than thought a priori.

The absolute positions of the heart estimated with our algorithm should be taken with care, as there is no direct validation for them. For example, we are aware of a probable error in the correction along the translation on the Y axis. Many corrected beats appear to be on the boundary of the constraint at $Y \geq -30\ mm$, which suggests that this bound should be extended to accommodate for further displacement. However, the obtained geometry corrections offer reasonable explanations when considered in the context of the interventions. The change in $\theta$ observed between the first
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Figure 7.12: Torso-Tank experiment: Examples of rectified geometries in two orthogonal views. In light grey, the heart at the original position within the tank, in green the heart at the rectified position.
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Figure 7.13: Synthetic Experiment with Unknown HSP: Scatter plot of RMSD versus respiratory phase. In red the results comparing the fixed geometry with the true and in green the results comparing the corrected geometry with the true.

Figure 7.14: Synthetic Experiment with Unknown HSP: Relative Error of measured and synthesized tank surface potentials both with original geometry (in red) and rectified geometry (blue). Each column shows results for a type of intervention. Red line indicates point of equality and magenta dot indicates the mean per each intervention type.
Figure 7.15: Torso-Tank experiment: Coronal and sagittal views of an example of the corrected heart (green) within the torso-tank geometry for a heartbeat before and after needles. Superimposed, the heart at the “original” registered position.

intervention (before needle insertion) and the following could be explained by the manipulation of the heart during the needle insertion. See Figure 7.15 for an illustrative example comparing the geometry corrections for two heartbeats, one before needles and another after. At the re-insertion of the heart in the tank, the cables connected to the needles might introduce some tension, which combined with pockets of air in the right ventricle, could create an effect buoyancy of the heart that lifts it. This tension might also be introducing an increased beat-to-beat variability in the position of the heart during the ventricular pacing experiments, which appears as increased intra-intervention variability of the transformation parameters obtained. The inhomogeneous contraction of the heart during those heartbeats might be creating an irregular tension with the cables and thus make the heart move erratically after each heartbeat.

The third outcome of these results is the proof that this method is capable of correcting for the position of the heart when no measurements are available on it. We have shown that, in this case, the forward solutions are comparable to the ones obtained in the previous experiments, but now the position of the heart is corrected with more accuracy. We hypothesize that this improvement is introduced by the two priors enforced in the inverse: aggregation of multiple BSP for a single
CHAPTER 7. IMPROVING FORWARD MODELS THROUGH CORRECTION OF THE GEOMETRY

inverse and imposition of the known position of a heartbeat. As observed in the first synthetic experiments, using a known HSP, the errors in geometry correction show beat-to-beat variability of about $4\text{mm}$ in RMSD. The two new constraints offer the advantage of first stabilizing the error variability, as the aggregation of BSP in an inverse effectively averages out the measurement noise, and second biasing the results towards the true solutions within the $4\text{mm}$ margin that the algorithm cannot resolve. The inclusion of these priors might seem limiting at first, however, the acquisition of multiple heartbeats only increases the recording time to a minute and the enforced known position could be taken as the position of the heart in the geometries segmented from the structural scans. Thus, the added experimental requisite would be to record one heart at the same breath hold position (e.g. full expiration) as the structural scans.

The results discussed encourage us to continue the development of this method with the objective of applying it in conjunction to other ECGI methods to clinical practice. Moreover, in the current implementation we are only considering geometry modifications caused by translation and rotation of the heart, nevertheless this work could be extended to any continuous transformation of the geometry. For example, it could include the contraction movements of the heart, thus allowing for accurate inverse solutions during the repolarization phase, or allow for more general deformations of the heart heart, possibly loosening the current need of structural scans obtained from CT or MRI.

7.6 Conclusions

In this work, we have introduced a new approach to correct for the position of the heart from electrocardiographic recordings. We have shown that this approach successfully improves the forward models in both synthetic experiments and showed that it can provide useful insight to current experimental procedures used to validate ECGI methods. Moreover, this algorithm is also capable of solving the joint problem of estimation of the potential distribution on the heart and its position within the torso.

This method also has implications beyond improving forward models in ECGI since, the capacity to non-invasively track the position of the heart has the potential to impact a number of other clinical problems, for example, improving catheter registration in ablation procedures.
Chapter 8

Conclusions

In this thesis we have described several methods with a common theme, the aggregation of multiple heartbeats in an inverse solver. In the development of all our methods we have also taken a model based approach; when faced with each individual problem (TWA, PVC localization or tracking of the heart), we first characterized the signal and the sources of noise and then designed our algorithms that model those.

In Part I, we applied these philosophies to imaging TWA. In chapter 3, we modeled the effects on the body surface of one putative source of TWA on the heart and characterized the effects of concordant and discordant alternans on the BSP. We also we used this approach in chapter 4, only this time to solve the inverse problem. In this case, we first took a global perspective of the TWA in the context of the forward and inverse problems in electrocardiography and then designed a specific inverse solver that uses the definition and characteristics of TWA to stabilize its solutions.

In Part II we considered the problem of PVC localization. In this case, the variability across heartbeats is generated by sources of noise and not part of the signal of interest. To reduce their presence, we studied two approaches: In chapter 5, we developed a data-driven method that generates a deterministic average, robust to the beat-to-beat variations observed in the BSP. In contrast, the approach in chapter 6 was to statistically characterize those sources of noise and then create a tailored measure of error for the optimization function.

Finally, in Part III we approached the problem with the specific characterization of one source of noise, the respiration process. In this work, described in chapter 7, we created a new method that corrects the position of the heart, leveraging the beat-to-beat differences in the measured BSP. This method is capable of, not only adapting the forward matrix to each individual beat, but also to track the position of the heart throughout the respiration cycle.
CHAPTER 8. CONCLUSIONS

The three contributions presented in this thesis do not stand on their own and improvements in each individual project can bring benefits to the others. For example, the correction in forward models from Part III will bring benefits to both TWA imaging and PVC localization. Moreover, the generalization of this method to other transformations of the geometry can correct for the contraction movement of the heart, thus alleviating the model errors present during imaging of TWA. Conversely, improvements in the inverse reconstruction of heart potentials, as done in Part II, would increase the accuracy of the geometry correction method.

The combination of the methods presented is in itself an important line of research. However, within each individual project there are several developments that should be done in the future. In particular, the future developments with regard to the T-wave alternans work are:

- Test the algorithm in real data from a Torso-tank experiment (geometry correction will be needed).
- Incorporate time varying forward matrices to account for contraction movements of the heart.
- Evaluate robustness of inverse algorithm to simplified geometries.

The geometry correction method is the extension of the algorithms described in Part II. Thus, the future developments related to these methods are tied to the geometry correction and are:

- Explore the sensitivity of the solutions to the parameters in the method: number of knots $K$, subspace dimension $Q$ and truncation point in the TSVD $L$.
- Evaluate the effects of different geometries to the method.
- Evaluate the effects of the geometry correction from the perspective of the inverse problem. Started doing analysis of the inverse solutions obtained after correction geometry.
- Test other respiration models.
- Test the algorithm with real data from animal or human models. Started tests with a pig model and X-ray validation.
- Include the estimation of the respiration function in the optimization. Started tests estimating the parameters of a quadratic function describing the respiration process.
- Integrate the geometry correction optimization with other ECGI methods (e.g. spline interpolation, inclusion of non-decreasing constraints, etc.).
CHAPTER 8. CONCLUSIONS

• Extend the geometry transformations to contractions of the heart to enable practical inverse reconstructions during repolarization.

• Extend the geometry transformations to general shape deformations and estimate the full heart geometry from minimal imaging.
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