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A Potential-Based Inverse Spectral Method to Non-Invasively Localize Discordant Distributions of Alternans on the Heart from the ECG

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Abstract

T-wave alternans (TWA), defined as the beat-to-beat alternation in amplitude of the T-waves, has been shown to be linked to ventricular fibrillation (VF). However, current TWA tests have high sensitivity but low specificity in determining who is at risk. To overcome this limitation, it might be helpful to determine the spatial distribution of any regions on the heart that alternate in opposite phase. Understanding these spatial distributions in relation to the regular activation of the heart could help explain the mechanism for the genesis of VF and thus disambiguate the low specificity of TWA.

Goal—Image the spatial distribution of TWA on the heart surface from ECG measurements.

Methods—We introduced the Inverse Spectral Method (ISM), a tailored inverse (or ElectroCardioGraphic Imaging) solution designed specifically to non-invasively image cases of TWA on the heart.

Results—We evaluate ISM on its capacity to reliably detect the spatial distributions of TWA compared against a standard TWA detection method applied directly to the electrograms on the heart surface. We report on results from both a series of synthetic simulations of TWA generated using the ECGSIM software and a set of continuous epicardial surface voltage recordings from a canine experiment. ISM detected TWA distributions that matched the phase of the true underlying out-of-phase regions over 64% and 80% of the heart surface respectively.

Conclusion—Our results suggest that ISM is capable of reliably detecting the different regions present in a TWA distribution across a wide variety of TWA locations on the heart in simulation and in the face of transients and non-idealities in the canine recordings.

Index Terms

T-wave alternans; inverse problems; electrocardiography; sudden cardiac death

I. 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) [1]. 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 [2].

The underlying mechanism for the link between body-surface TWA, the corresponding alternans phenomenon in the myocardium and SCD is not yet fully understood. A number of studies using either cardiac propagation models or animal experiments have been carried out to understand the possible manifestations of TWA on the heart and their relationship to SCD [3]–[5]. They indicated that an arrhythmogenic substrate, characterized by abnormal values of certain underlying myocardial parameters and the presence of premature stimuli, can lead to a variety of beat-to-beat (period two) alternations in transmembrane potential (TMP) waveforms during the repolarization phase. These models have been taken as demonstrating putative causal mechanisms for the link between body-surface TWA and SCD. One discovery from myocardial propagation studies that has received particular attention is the importance of the distinction between “concordant” alternans, in which the complete ventricular myocardium alternates 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” [2]. 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 [4], [5]. 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. In this context, not only classification of TWA into concordant and discordant cases, but also localization of discordant regions may carry clinically useful information.

In this work, motivated by the desire to identify and localize discordant regions from body surface measurements, 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, specifically the Spectral Method (SM) [6], with the methodology of ElectroCardioGraphic Imaging (ECGI), that is, inverse electrocardiography. 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, regularization of the estimated TWA, while solving for localized TWA across many heartbeats in a single inverse solution, with associated gains in computational efficiency.

To place our work in context, we first very briefly describe the SM and summarize some relevant reports in the literature on discordant alternans. To aid in our description, we will denote TWA on the body surface, as seen in ECG signals, as body surface potential TWA (BSP-TWA), TWA on the heart surface, as seen in electrograms, as heart surface potential TWA (HSP-TWA), and the time course of TWA during the T-wave, as estimated from a sequence of heartbeats, as a “TWA signal”.

The SM takes advantage of the fundamental assumption in BSP-TWA estimation: there is a periodic beat-to-beat alternation in the amplitude of the body surface potentials (BSP) during the T-wave that is the result of a corresponding beat-to-beat alternation in the underlying heart surface potentials (HSP). The 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 π (in radians/sample). This calculation is accomplished by simply accumulating differences between samples at corresponding times in the T-wave across consecutive beats in an “add-subtract-add-subtract” fashion. Since BSP-TWA presumably reflect HSP-TWA, the SM can also be applied to HSP in the same way.

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) [5] and the work of Orini *et al.* that studied whether different TWA detection algorithms applied to HSP were capable of differentiating discordant from concordant alternans [7]. 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 [8]. 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 [9]–[11] and thus presumably to discordance.

A few groups have reported methods to take heart-torso spatial relationships into account. 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) [12], [13]. 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 body surface TWA [14]. There have also been a few studies in 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 [15], [16] 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 [17]. 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 BSP to identify the most appropriate locations among those candidates [18], [19].

Our method does not employ a parameterized source, but instead involves an explicit TWA inverse solution, based on an inverse formulation of the spectral method, and thus we denote it as the Inverse Spectral Method (ISM). We presented a preliminary study on this approach in [20]. In this paper we describe our inverse spectral method (ISM) in more detail than in [20] and report more extensive 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 underlying HSP-TWA using models in the ECGSIM software package [21], while in the second we use experimentally recorded canine heart surface potentials exhibiting discordant TWA generated with a preparation designed to induce ischemia. Because we are interested in evaluating the potential to apply this method in a clinical setting, not only we evaluate how our results behave in the presence of different levels of additive noise, but 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 a standard clinical 12-lead montage.

In what follows, we first describe the ISM in Section II. Section III describes the experiments we carried out to evaluate the method and Section IV summarizes our results. Finally we discuss implications of our results in Section V.

II. Methods

A straightforward approach to use ECGI to non-invasively localize the presence of TWA on the heart surface would be to record the Body Surface Potentials (BSP) for a series of consecutive heartbeats, use an inverse method to estimate the source heart potentials for each beat, and then run the standard SM on those estimates. However due to the ill-posed nature of the inverse problem, uncorrelated noise, and model errors, will all contribute to increased 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 amplify that noise in the estimated HSP-TWA. Thus it is desirable to increase the effective Signal-to-Noise Ratio (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.

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, *i.e.* the estimated BSP-TWA have less noise than the measured BSP.

To do so, we take advantage of the linearity both of the standard inverse solutions [22] 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.

A. The Inverse Problem

The relevant formulation of the inverse problem in electrocardiography is to estimate the potentials on the heart surface from non-invasive torso measurements. The relation from sources to measurements is given by a forward mapping that must be known in order to solve the inverse problem. In the case of electrocardiography, it is found by modeling the electrical distribution of potentials in the body, a calculation known as solving the “forward problem” [23]. From electromagnetic theory we know that this mapping depends only on the geometry and that it is linear and static in time. Thus given appropriate imaging of the torso, obtained from MRI or CT, the forward problem provides a linear, biophysically accurate relationship between known heart potentials and the body surface potential measurements. Thus, with BSP measurements and unknown heart potentials, respectively, discretized in space (on each surface) and time, and sorted into two matrices Y and X — with rows representing spatial locations and columns representing time instances — the forward propagation of potentials reduces to the following matrix-matrix multiplication:

$$Y = A \cdot X, \quad (1)$$

where the matrix A identifies the forward solution. In what follows, we assume that we have L time samples comprising a continuous sequence of B heartbeats, where B is assumed to be an even number. We assume that each beat contains 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 Y is the first sample of the first T-wave, and the last sample is the end. 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 Y is $M \times L$, A is $M \times N$, and X 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 (denoted as $A^\dagger$) is very sensitive to noise in the input. To stabilize the inverse solutions, there are several approaches that can be used [22]. 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.

B. Spatial Regularization

The most commonly used form of spatial regularization is Tikhonov regularization which solves Equation 2.

$$X^* = \operatorname{argmin}_X \|Y - A \cdot X\|_F^2 + \lambda \|R \cdot X\|_F^2 \quad (2)$$

Tikhonov regularization balances minimizing the residual error between BSP measurements and inverse-derived estimates in the least-squares sense, on the one hand, with what amounts to a spatial “prior” through the second, regularization, term in Equation 2, on the other. Which prior is being enforced, and with what strength, is determined by the regularization matrix R and the parameter $\lambda > 0$ respectively. The latter is often found through the L-curve plot [24], while the former depends on the expected characteristics of the solution. Here, to favor inverse solutions that are smooth and similar across the myocardium, we used a regularization matrix (R) that approximates the Laplace operator through the myocardium, in 3D space. This approximation of the 3D Laplacian operator was computed using the same method as in [25]. This approach extends [26] but, instead of using the distance over the heart surface to estimate the gradient and hessian operators, it includes points on opposite sides of the myocardium in the neighborhoods used to define the derivative approximators, hence its 3D nature. This procedure returns the gradient and Hessian operators, and we then derive the Laplacian by adding the terms corresponding to the unmixed second partial derivatives in the Hessian operator.

C. Temporal Regularization

A classical approach to temporal regularization is to limit the solutions to a well-chosen low-dimensional linear subspace [27], [28] or to use a non-linear characterization of its temporal behavior [25]. Here we propose two characterizations of TWA behavior that can be described by linear projections. First, is the SM estimator itself, which 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:

1) The 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 π , 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 multiplications of the Y matrix (we denote the corresponding matrices by B_{align} and B_{SM}) on the right. Denoting the resultant BSP-TWA estimate as $\hat{Y}$, we have

$$\hat{Y} = Y \cdot B_{align} \cdot B_{SM}. \quad (3)$$

The segmentation and alignment matrix, B_{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.

$$B_{SM} = \begin{bmatrix} I_T \\ -I_T \\ I_T \\ -I_T \\ \dots \end{bmatrix} \quad (4)$$

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 a $M \times T$ matrix that accumulates all TWA information in the BSP with an increased SNR due to the effective averaging across even and odd beats.

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 HSP-TWA with a truncated (k -component) Discrete Fourier basis which we denote B_{Fk} . This operation acts as a low-pass filter and reduces the dimensionality of the input and the unknowns of the inverse solver, thus effectively regularizing the inverse solutions. Note that applying an inverse method to the Fourier transformed BSP-TWA ($\tilde{Y}$) results in the Fourier transformed HSP-TWA ($\tilde{X}$). In order to recover the temporal sequence of HSP-TWA, an inverse Fourier transform is then applied.

D. The Inverse Spectral Method

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

$$\begin{aligned}\tilde{Y} &= Y \cdot B_{align} \cdot B_{SM} \cdot B_{Fk} \\ \tilde{X}^* &= \operatorname{argmin}_{\tilde{X}} \|\tilde{Y} - A \cdot \tilde{X}\|_2^2 + \lambda \|R \cdot \tilde{X}\|_2^2 \quad (5) \\ \hat{X} &= \tilde{X}^* \cdot B_{Fk}^\dagger.\end{aligned}$$

(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 1.

1. Segment T-waves in the BSP using QRS peak as a reference.¹
2. Estimate BSP-TWA with SM.
3. Calculate the truncated Fourier Transform of the estimated BSP-TWA.
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.

III. 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 [21] 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, while the second model was created to represent only the epicardial surface of a canine heart. In particular, to create TWA in ECGSIM we 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.

¹Note that it is essential to use a QRS marker as the reference for alignment in order to preserve any T-wave alternations produced by alternations in action potential duration in the myocardium.

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.

1) The ECGSIM dataset

This dataset was obtained by manipulating parameters of transmembrane potentials created using the model in ECGSIM. 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 alternans by modifying the repolarization time at sets of selected nodes from ECGSIM's default heart model ($N = 257$), adding a fixed time delay for even beats and subtracting the same interval for odd beats, 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 10ms negative 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 10ms 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 the first column of Figure 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. We generated four lateral examples, three apical and three septal.

Using the forward model in ECGSIM, we synthesized corresponding BSPs at $M = 300$ body surface locations and then added zero mean Gaussian noise at various SNR levels. This procedure was performed for 100 different pseudorandom noise realizations for each location and with equal power across all electrodes, such that the average SNR levels was of 15, 30 and 40 dB.

In order to avoid committing the inverse crime of computing the inverse solutions with the 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 [29], while also omitting 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 [30].

2) The canine dataset

This dataset consisted of a continuous epicardial recording from an open-chest canine ischemic experiment conducted at the CardioVascular Research and Training Institute (CVRTI) at the University of Utah and generously provided to us by Dr. Robert Lux. The experiments were conducted with the appropriate approval of the IACUC committee of the University of Utah. The measurements were taken with 64 electrodes placed on a sock surrounding the ventricles and sampled at 1000 Hz, with bandpass filters between .03–150 Hz, for a 5 minutes duration. The left anterior descending artery was excised, clamped at the beginning of the recording and then released after 2 minutes of occlusion. During the recordings the heart was paced from the atria, recording 927 heartbeats which exhibited discordant TWA of varying spatial distribution and magnitude. The sequence also contains 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 2 with the windows corresponding to each interval superimposed. There is a continuous change of the HSP, even changing polarity 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 appearing later within intervals 9 and 10. To better observe the spatial distribution of the TWA we show the HSP-TWA, in Figure 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 positioning of the segmenting window, which could reverse the phase of the estimated TWA.

To synthesize the BSPs for the canine experiment, we followed a procedure similar to [31]. We defined the “canine heart” geometry, consisting of $N = 103$ nodes, with the 3D coordinates of the 64 sock electrodes and a set of extra added nodes covering the atria and closing the geometry. Then, we manually translated this heart into the geometry of a small torso formed of $M = 354$ nodes to simulate the size and position of a human heart within a torso. We finally solved the forward problem and, as in the ECGSIM dataset, we added 100 different realizations of zero mean AWGN with equal power level for all electrodes, such that the average SNR was of 15, 30 and 40 dB.

To again ensure mismatch in the forward model used in the inverse solutions, we computed a different forward matrix than the one used to synthesize the data, this time using a spatially smoothed torso geometry as done in [31], [32]. 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 down-selected from the full data and model.

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. Somewhat heuristically, we determined that areas with average amplitude of TWA smaller than 1% of the maximum observed on the heart did not have a meaningful presence of TWA and thus considered them alternans free. The positive/negative TWA region classification was evaluated by comparing it to the same procedure applied to TWA estimated using the SM applied directly to the potentials synthesized or measured 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 only an estimated 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 (synthetic experiments) or time segment (canine measurements) 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.

IV. 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 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. 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 5 we show the averaged results for all alternans positions for 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 top and bottom respectively.

Returning to the accuracy maps from the experiments using all available leads shown in the second column of Figure 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 5a, where each column corresponds to the results of one location in Figure 3. Quantitatively, septal and basal locations were 10% to 20% less accurate than other TWA distributions. This same spatial dependency appeared in the sensitivity of the solutions to a decrease in SNR. We also note that results for most of the TWA distributions had very low standard deviation — *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 geometry, 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 3c 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 5b show ~ 10% less accuracy than results with the full lead set in most TWA distributions. However, the septal and basal locations, which had worse accuracy than the other locations with the full lead set, were generally more accurate with the 12-lead set than with all the leads. Thus with the 12-lead data, these average errors were more uniform across TWA distributions. They also were somewhat less sensitive to decreased SNR than the full lead results. Moreover with the 12-lead configuration the standard deviations were 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 $SNR = 15\text{dB}$, for all data intervals, in Figure 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 error and do not reach 100% accuracy as uniformly as the other time intervals. The spatially averaged results in Figure 5c, confirm these observations. On average, the accuracy is around 90% for most of the intervals. Exceptions to this observation are the intervals 1, 2 and 10, which show characteristics that might be particularly susceptible to noise. In particular, intervals 1 and 2 have a considerably smaller TWA amplitude and interval 10 shows a spatially complex TWA distribution that is harder to estimate. However, we also observe that results with the canine data set were more sensitive

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

V. Discussion

Our results suggest that ISM detected position of the two out-of-phase regions, although it could not reliably delineate the affected area. The fact that performance was comparable for the canine data to 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 in Tikhonov-type ECGI methods is challenging due to the added ill-posedness of the resulting forward models. In our experiments, the ECGSIM dataset showed a conditioning number of the forward matrix 3 orders of magnitude lower than the canine dataset, which supports our hypothesis that the added complexity of the geometry reduced the overall accuracy of the results.

In the canine data, as is clear from the SM results in the top row of Figure 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 the extent of small discordant regions will be harder to determine 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 increase 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 were 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. The changes of phase or morphology of TWA caused by these events, suggests that a smarter pre-processing algorithm which detected non-sinus rhythm beats and either discarded them or restarted the BSP-TWA estimation after a delay of a few beats might be a useful improvement for ISM estimation of TWA.

VI. Conclusions

In this paper 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, in synthetic scenarios. In our simulations ISM localized the discordant regions on the heart reliably, although we observed some limitations in its ability to precisely define the boundaries of discordant regions. ISM maintained comparable performance even with 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. 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 to that obtained with the full lead set. These results suggest promise for this method to help increase our ability to understand 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.

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References

1. Verrier RL, Klingenhoben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH, Ikeda T, Martínez JP, Narayan SM, Nieminen T, Rosenbaum DS. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility—consensus guideline by International Society for Holter and Noninvasive Electrocardiology. *Journal of the American College of Cardiology*. Sep. 2011 58:1309–24. [PubMed: 21920259]
2. Merchant FM, Sayadi O, Moazzami K, Puppala D, Armoundas Aa. T-wave alternans as an arrhythmic risk stratifier: state of the art. *Current cardiology reports*. Sep.2013 15:398. [PubMed: 23881581]
3. Weiss JN, Karma A, Shiferaw Y, Chen PS, Garfinkel A, Qu Z. From pulsus to pulseless: the saga of cardiac alternans. *Circulation research*. May.2006 98:1244–53. [PubMed: 16728670]
4. Karma A. Electrical alternans and spiral wave breakup in cardiac tissue. *Chaos*. 1996; 4(3):461–472.
5. Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. *Circulation*. Mar.1999 99:1385–1394. [PubMed: 10077525]
6. Bloomfield DM, Hohnloser SH, Cohen RJ. Interpretation and Classification of Microvolt T Wave Alternans Tests. *Journal of cardiovascular electrophysiology*. 2002; 13(5):502–512. [PubMed: 12030535]
7. Orini M, Citi L, Hanson BM, Taggart P, Lambiase PD. Characterization of the Causal Interactions Between Depolarization and Repolarization Temporal Changes in Unipolar Electrograms. *Computers in Cardiology*. 2013; (v):719–722.
8. Martínez JP, Olmos S. Methodological principles of T wave alter-nans analysis: a unified framework. *IEEE Transactions on Biomedical Engineering*. Apr.2005 52:599–613. [PubMed: 15825862]
9. Nearing BD, Verrier RL. Tracking cardiac electrical instability by computing interlead heterogeneity of T-wave morphology. *Journal of applied physiology*. Dec.2003 95:2265–72. [PubMed: 12897035]
10. Monasterio V, Martinez JP. Multilead T-wave alternans quantification based on spatial filtering and the Laplacian likelihood ratio method. 2008 *Computers in Cardiology*. Sep.2008 :601–604.
11. Janusek D, Kania M, Zaczek R, Zavala-Fernandez H, Zbie A, Opolski G, Maniewski R. Application of Wavelet Based Denoising for T-Wave Alternans Analysis in High Resolution ECG Maps. *Measurement Science Review*. Jan.2011 11:181–184.
12. RSJ, Suszko AM, Anadaraja S, Sivananthan D, Hill A, Nanthakumar K, Chauhan VS. Body surface projection of action potential duration alternans: A combined clinical-modeling study with implications for improving T-wave alternans detection. *Heart Rhythm*. 2009; 6(8):1211–1219. [PubMed: 19632636]
13. Janusek D, Kania M, Kepski R, Maniewski R. Simulation of T-Wave Alternans and its Relation to the Duration of Ventricular Action Potentials Disturbance. *Therapy*. 2010:21–27.
14. Floré V, Claus P, Symons R, SMITH GL, Sipido KR, Willems RIK. Can Body Surface Microvolt T-Wave Alternans Distinguish Concordant and Discordant Intracardiac Alternans? *Pace Pacing And Clinical Electrophysiology (PACE)*. Aug.2013 36:1007–1016. [PubMed: 23614703]
15. Sassi R, Mainardi LT, Cerutti S. Amplitude of Dominant T – Wave Alternans assessment on ECGs obtained from a biophysical model. *EMBS*. 2011; (8):5872–5875.
16. Mainardi L, Sassi R. Some theoretical results on the observability of repolarization heterogeneity on surface ECG. *Journal of Electrocardiology*. May.2013 46:270–275. [PubMed: 23622343]

17. Oosterom AV. The Dominant T Wave and Its Significance. *Journal of Cardiovascular Electrophysiology*. Oct.2003 14:S180–S187. [PubMed: 14760922]
18. Svehlikova J, Lenkova J, Tysler M. Modified Inverse Solution to One Dipole for Location of Lesions with Changed Repolarization. *Computing in Cardiology*. 2012; 39:841–844.
19. Tysler M, Svehlikova J. Noninvasive finding of local repolarization changes in the heart using dipole models and simplified torso geometry. *Journal of Electrocardiology*. 2013; 46(4):284–288. [PubMed: 23628317]
20. Coll-Font, J., Erem, DBB., Karma, A. An Inverse Spectral Method to Localize Discordant Alternans Regions on the Heart from Body Surface Measurements. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013. p. 241–248.
21. Oostendorp TF, van Oosterom A. ECGSIM: an Interactive Tool for the Study of the Relation between the Electric Activity of the Heart and the QRST Waveforms at the Body Surface. *IEMBS*. 2004; 2:3559–3562.
22. Pullan, MNAGRMDBAJ., Cheng, LK. *Comprehensive Electrocardiology*. Springer; 2010. The inverse problem of electrocardiography.
23. MacLeod, R., Buist, M. *Comprehensive Electrocardiology*. Springer; 2010. The forward problem of electrocardiography.
24. Hansen PC. Regularization Tools A Matlab Package for Analysis and Solution of Discrete Ill-Posed Problems. Tech Rep. Mar.2008
25. Erem B, Coll-Font J, Martinez-Orellana R, Stovicek P, Brooks DH. Using Transmural Regularization and Dynamic Modeling for Non-Invasive Cardiac Potential Imaging of Endocardial Pacing with Imprecise Thoracic Geometry. *IEEE transactions on medical imaging*. 2013:1–13.
26. Erem B, Brooks DH. Differential Geometric Approximation of the Gradient and Hessian on a Triangulated Manifold. ISBI. 2011
27. Messnarz B, Tilg B, Modre R, Fischer G, Hanser F. A new spatiotemporal regularization approach for reconstruction of cardiac transmembrane potential patterns. *IEEE transactions on bio-medical engineering*. Feb.2004 51:273–81. [PubMed: 14765700]
28. Huiskamp G, Greensite F. A new method for myocardial activation imaging. *IEEE transactions on bio-medical engineering*. Jun.1997 44:433–46. [PubMed: 9151476]
29. SCI-Institute. SCIRun: A Scientific Computing Problem Solving Environment. Scientific Computing and Imaging Institute (SCI); 2014. Download from: <http://www.scirun.org>
30. Ghodrati A, Brooks DH, MacLeod RS. Methods of solving reduced lead systems for inverse electrocardiography. *j-BME*. Feb.2007 54:339–343.
31. MacLeod R, Miller R, Gardner M, Horá ek B. Application of an electrocardiographic inverse solution to localize myocardial ischemia during percutaneous transluminal coronary angioplasty. *j-JCE*. 1995; 6:2–18.
32. MacLeod, R., Taccardi, B., Lux, R. c-EMBS95. IEEE Press; 1995. Electrocardiographic mapping in a realistic torso tank preparation; p. 245–246.

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Fig. 1.

Visual representation of the sequence of steps applied in the Inverse Spectral Method.

Fig. 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%.

Fig. 3.

True TWA distribution and reconstruction accuracy maps for ECGSIM generated data. Maps show posterior and superior views, with the latter allowing visualization of the endocardial surface. (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 APDs on the odd beats. (b) The accuracy map for the results obtained using the full lead set at an $SNR = 15\text{dB}$. (c) The accuracy maps for the results obtained using the 12-lead configuration at the same SNR. 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.

Fig. 4.

HSP-TWA distribution estimated directly from HSP and reconstruction accuracy maps for the canine experiments with $SNR = 15\text{ dB}$. 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.

Fig. 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 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 show results using full lead set, and bottom panel using 12-lead configuration.