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Noninvasive Electrocardiographic Imaging (ECGI):

Application of the Generalized Minimal Residual (GMRes) Method

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Abstract

Electrocardiographic imaging (ECGI) is a developing imaging modality for cardiac electrophysiology and arrhythmias. It reconstructs epicardial potentials, electrograms, and isochrones from electrocardiographic body-surface potentials noninvasively. Current ECGI methodology employs Tikhonov regularization, which imposes constraints on the reconstructed potentials or their derivatives. This approach can sometimes reduce spatial resolution by smoothing the solution. Accuracy depends on *a priori* knowledge of solution characteristics and determination of an optimal regularization parameter. These properties led us to implement an independent, iterative approach for ECGI—the generalized minimal residual (GMRes) method—which does not apply constraints. GMRes was applied to experimental data during activation/repolarization of normal and infarcted hearts. GMRes reconstructions were compared to Tikhonov reconstructions and to measured “gold standards” in isolated hearts. Overall, the accuracy of GMRes solutions was similar to Tikhonov regularization. However, in certain cases GMRes recovered localized potential features (e.g., multiple potential minima), which were lost in the Tikhonov solution. Simultaneous use of these two complementary methods in clinical ECGI will ensure reliability and maximal extraction of diagnostic information in the absence of *a priori* information about a patient’s condition.

Keywords

Electrocardiographic inverse problem; Noninvasive arrhythmia diagnosis; Tikhonov regularization

INTRODUCTION

Despite the high prevalence of cardiac arrhythmias and associated mortality rate,¹³ a true noninvasive imaging modality for cardiac electrophysiology (EP) and for the diagnosis of cardiac rhythm disorders is not yet available for clinical application. Currently, noninvasive diagnosis is based on the standard 12-lead ECG, which measures electrical potentials (electrocardiograms) on the body surface, far away from the heart. Due to the limited number of leads and their distance from the heart’s surface, ECG is severely limited in resolution and lacks in sensitivity and specificity.²² In contrast, potentials and activation pattern (isochrones) from the epicardial surface of the heart provide detailed information on the underlying cardiac electrical activity.³⁰ Electrocardiographic imaging (ECGI) is a novel functional imaging modality under development in our laboratory, designed to noninvasively reconstruct

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epicardial potentials, electrograms, and isochrones from electrocardiographic body surface potentials.

Several studies^{2-4,9,21,24,25,28} from our laboratory have demonstrated the ability of ECGI to image normal and abnormal cardiac electrophysiological activity during activation and repolarization in canine experiments. Prior to the challenging and important step of systematic validation and evaluation in humans, we sought to address certain properties of the current ECGI methodology and to devise a complementary approach, based on independent methodology, that can provide cross-check and complementary information in the clinical application of ECGI. The basic ECGI methodology involves solving the electrocardiographic inverse problem, which can be defined as the computation of epicardial potentials from body surface potentials.^{29,31} This inverse problem is ill posed in the sense that small perturbations in the data (e.g., measurement noise or geometrical errors that are practically inevitable) can cause large unbounded errors in the solution.³³ Tikhonov regularization³³ is commonly used to overcome this property by imposing constraints on the magnitudes or derivatives of the computed epicardial potentials, and has been the method of choice in our laboratory. Applying constraints requires some *a priori* knowledge of the solutions' properties. It, typically, causes spatial smoothing of epicardial potentials, which in some cases could result in reduction of spatial resolution and loss of diagnostically meaningful information. The method also requires accurate determination of a regularization parameter, the value of which determines the level of constraint to be applied. Methods to determine the regularization parameter such as the composite residual and smoothing operator (CRESO),⁸ L-curve,¹¹ and zero crossing¹⁷ may not perform consistently and are also sensitive to the noise level in the data.¹⁷ In some cases, *a priori* information and manual adjustment may be required to choose the optimal regularization parameter. For example, *a priori* knowledge of the number of ectopic foci (sites from which excitation is initiated) may influence the level of regularization applied. In view of these properties, it is desirable to develop a complementary approach for ECGI that is not subject to the above requirements and does not have the characteristic effects of Tikhonov regularization.

In this study, we investigate the application of an iterative numerical method—the generalized minimal residual (GMRes) method,³² which has been quite successful in solving ill-posed problems in the field of image processing.⁶ The GMRes method is not based on imposing constraints and, therefore, does not require *a priori* information about the solution. Instead, we can obtain a regularized solution from the GMRes method by stopping the iterations prior to convergence. These properties make it quite different from the Tikhonov regularization approach and a suitable candidate as a complementary independent method for ECGI. In this study we evaluate the performance of GMRes in imaging normal and abnormal electrophysiological activity in canine hearts, and compare it to the Tikhonov regularization approach. We also demonstrate the ability of ECGI to image, noninvasively, various activation and repolarization patterns in several hearts, using the two independent approaches.

METHODS

Computational Methods

Body surface potentials (Φ_T) are related to epicardial potentials (Φ_E) through the linear system of equations;

$$\Phi_T = \mathbf{A} \Phi_E \quad (1)$$

where $\mathbf{A}$ is the geometry and conductivity transfer matrix reflecting the properties of the volume conductor between the epicardial surface and body surface.²⁸⁻³⁰ As mentioned in the introduction, the reconstruction of Φ_E from Φ_T is an ill-posed inverse problem. Therefore, the

solution needs to be regularized to attenuate the influence of noise/error components in the data. The Tikhonov regularization method³³ has been used to solve this inverse problem thus far in our laboratory. In this scheme, the regularized solution is given by $\min_{\Phi_E} [\|\mathbf{A}\Phi_E - \Phi_T\|^2 + t \|\mathbf{L}\Phi_E\|^2]$, where t is a regularization parameter, and $\mathbf{L}$ a regularization operator (unity, gradient, or Laplacian). Details can be found in previous publications.²⁹⁻³¹

Here, we introduce GMRes, an iterative method of computing Φ_E from Φ_T that does not require imposing constraints on the solution. The GMRes method belongs to the class of Krylov subspace iterative methods.³² Given Φ_T and the matrix $\mathbf{A}$, the n -dimensional Krylov subspace $K(n)$ is the set of all linear combinations of the vectors $\Phi_T, \mathbf{A}\Phi_T, \mathbf{A}^2\Phi_T, \dots, \mathbf{A}^{n-1}\Phi_T$. At the n th GMRes iteration, the inverse of matrix $\mathbf{A}$ is approximated by its projection onto $K(n)$, $p_n(\mathbf{A})$ and the n th approximate solution is computed from the solution of this projection, i.e., epicardial potentials Φ_E are approximated by $p_n(\mathbf{A})\Phi_T$. The GMRes method proceeds by constructing, at the n th step, an orthonormal basis for $K(n)$. Since the matrix $\mathbf{A}$ is accessed only via matrix-vector multiplications, it need not be explicitly stored in memory. Currently, the implementation of GMRes requires the matrix $\mathbf{A}$ to be square and in our problem the matrix $\mathbf{A}$ is nonsquare (number of torso electrodes is not equal to number of reconstruction points on the epicardium). Therefore, we multiply both sides of Eq. (1) by $\mathbf{A}^T$ and apply the GMRes method to the solution of the *normal* equation, $\mathbf{A}^T\mathbf{A}\Phi_E = \mathbf{A}^T\Phi_T$ ($\mathbf{A}^T\mathbf{A}$ is square). Although there are other implementations [e.g., minimal residual method (MINRES)] that take advantage of the symmetry of $\mathbf{A}^T\mathbf{A}$, we found that the GMRes method provides much more accurate results due to re-orthogonalization at each iteration step (this is also observed and discussed by Hansen¹²). As n increases, the Krylov subspace approaches the whole space and amplified noise components start being included in the solution. Therefore, a stable solution with minimal contamination from amplified noise components is achieved by stopping the iterations suitably early prior to convergence. Our Implementation of GMRes is based on the paper by Calvetti.⁵ The technical computing software MATLAB[®] also has an implementation of GMRes, which works just as well.

GMRes iterations converge to the desired solution and then, with continued iteration, diverge from it. The criterion for deciding when to stop the iterations is based on the following observation. At the n th GMRes iteration, the inverse of the matrix $\mathbf{A}$ is approximated by its projection $p_n(\mathbf{A})$ onto $K(n)$. This projection is an upper Hessenberg matrix, $\mathbf{H}(n)$.³² As n increases so does the condition number of $\mathbf{H}(n)$, while the 2 norm of the residual error decreases. At each step the GMRes method solves a linear system with the matrix $\mathbf{H}(n)$. A plot of the condition number of $\mathbf{H}(n)$ versus the base-10 logarithm of the 2-norm of the n th residual error (Fig. 1) illustrates the effect of each GMRes iteration on these two quantities. Typically, at first, as the iteration index increases, the increase of the condition number $\mathbf{H}(n)$ is accompanied by a sizable decrease in the 2-norm of the residual error. At some point, however, the 2-norm of the residual error remains stationary, while the condition number of the projected problem continues to increase. This causes the plot to take on the shape of the letter “L” and the iteration corresponding to the corner gives a solution which balances an acceptable residual and a reasonably well-conditioned projected problem. When the condition number of $\mathbf{H}(n)$ becomes too large, the corresponding approximate solution may be inaccurate. The use of this particular plot to terminate the GMRes iterations was proposed by Calvetti, Lewis, and Reichel⁷ who refer to it as the *condition L curve*. Figure 1 shows condition L curves and (traditional) L curves for GMRes and Tikhonov methods for data generated by single-site pacing (panel A) and dual-site pacing (panel B) protocols (The experimental protocols are described in the next section below.) Top row shows condition L curves for the GMRes method, the second row shows L curves for the GMRes method, and bottom row shows L curves for the Tikhonov method. The GMRes condition L curves show distinct corners. Note that the L curve criterion proposed by

Hansen¹¹ cannot be used since the L curve associated with GMRes may not exhibit a corner¹⁰ (second row of panels A and B). The L curve associated with Tikhonov exhibits a corner for the data of panel A but not for the data of panel B. Although we cannot predict that the GMRes condition L curve will always exhibit a corner, the condition L curves for all the GMRes-processed data sets (total of 21 data sets, of which six are presented here) display distinctly marked corners. The corner is automatically picked by a curvature detection algorithm similar to the algorithm developed for the L curve by Hansen (available for download¹⁴).

Experimental Methods and Protocols

We evaluated GMRes on 21 data sets pertaining to studies that were previously published.^{2,3,9,15,16,24,28} Here, we present selected results from six protocols that have implications to the clinical application of ECGI. GMRes performance was similar for the remaining 15 protocols. We also show examples where the Tikhonov method resulted in loss of some features due to smoothing and/or where *a priori* information aided in the choice of the regularization parameter or the type of constraint. The data were obtained from one of the experimental protocols listed below. All protocols included direct recording of potentials from the epicardium, thus permitting evaluation of reconstructed epicardial potentials through direct comparison with those directly measured.

Isolated Canine Hearts in a Human-Shaped Torso Tank (Experiments Conducted in Dr. Bruno Taccardi's Laboratory at the University of Utah)—This setup involved a Langendorff perfused dog heart suspended in the approximate anatomic position in a human-shaped torso tank.²⁴ This setup permitted simultaneous recording of body surface and epicardial potentials. Potentials were recorded for both single and dual site pacing from various sites.

Single-Site Pacing²⁴—In this data set,²⁴ both body surface and epicardial potentials were simultaneously recorded during pacing from a single anterior epicardial site. This data set simulated an arrhythmogenic ectopic focus and provided data for evaluating the accuracy of GMRes in localizing initiation sites of arrhythmic activity and other highly localized electrophysiological events. In the original publication,²⁴ the authors used Tikhonov zero-order regularization with the CRESO method used to find the regularization parameter.

Simultaneous Dual-Site Pacing²⁸—Epicardial potentials were recorded for simultaneous pacing from pacing sites located 2.5 cm apart. Body surface potentials were computed from the measured epicardial potentials using an accurate computer model of the human torso, containing the thoracic inhomogeneities of lungs, muscle, bone, and fluid layers.²⁷ The computed body surface potentials were then used to reconstruct epicardial potentials in a homogeneous torso of the same geometry. This protocol allowed us to evaluate the reconstruction accuracy of GMRes when a simplified homogeneous torso is assumed (an approximation that greatly simplifies the clinical application of ECGI,²⁸ eliminating the need to image thoracic organs such as the lungs). In addition, this data set also helped us evaluate the accuracy and spatial resolution of GMRes in localizing two closely spaced pacing sites. In the original publication,²⁸ the authors used Tikhonov zero-order regularization with the CRESO method used to find the regularization parameter.

Open Chest Canine Experiments—All data sets under this protocol involved measuring epicardial potentials directly from hearts of open chest dogs (exposed by sternotomy) using a multielectrode epicardial sock.^{2,3,9} These were then used to compute body surface potentials in a homogeneous or inhomogeneous computer model of the human torso. Measurement noise (50 μ V peak to peak, Gaussian) and geometrical errors (1 mm, Gaussian) were added to the

body surface potentials and electrode positions, respectively, to simulate experimental or clinical measurements. These “contaminated” body surface potentials were then used to reconstruct epicardial potentials using the ECGI methodology. Data sets obtained with this protocol are described below. (Infarct and ventricular-tachycardia data were obtained in Dr. Taccardi’s laboratory at the University of Utah; repolarization data were obtained in our laboratory at Case Western Reserve University.)

Infarct Substrate²—Epicardial potentials during right atrial (RA) pacing (simulating normal sinus rhythm) were recorded from a 490-electrode sock. A region of infarcted tissue was created in the left ventricle (LV) by the ligation of the left anterior descending coronary artery (LAD) and ethanol injection. Details of the experiment and protocol are provided in the original publication.² Through this data set we could evaluate the ability of GMRes to reconstruct abnormal electrophysiological properties of an infarct substrate. In the original publication,² the authors used Tikhonov zero-order regularization with the CRESO method used to find the regularization parameter.

Ventricular Tachycardia (VT)³—Infarction was produced in a canine heart through ligation of the LAD. After four days of infarct formation in a closed chest, the chest was opened again and a 490-electrode sock pulled over the heart to record potentials. Monomorphic VT due to double-loop epicardial reentry was induced through programed stimulation and recorded. Details can be found in the original publication.³ This data set was used to evaluate the ability of GMRes to reconstruct the reentry pathway and its various electrophysiological components. In the original publication,³ the authors used Tikhonov zero-order regularization with the CRESO method used to find the regularization parameter.

Dispersion of Repolarization⁹—Abnormal and heterogeneous repolarization is the underlying mechanism of many arrhythmias. In this experiment, localized epicardial cooling was applied to prolong action potential duration in a region of the LV, and consequently, increase dispersion of repolarization. Epicardial potentials were recorded during RA pacing and QRST integral maps were computed to reflect local repolarization properties.^{1,9,23,26} In the original publication,⁹ the authors used Tikhonov second-order regularization instead of zero order to better preserve reconstructed amplitudes of electrogram T waves. They used the L-curve method to find the regularization parameter.

Evaluation Protocols

For all the data sets presented in this study, epicardial potentials were reconstructed using the GMRes method and the results were validated by comparison directly to measured epicardial potentials, which served as the gold standard. A zero initial value was used as a starting point for the GMRes iterations. Next, the GMRes results were compared with corresponding Tikhonov reconstructions. A hybrid method (Tikhonov-GMRes method) was also developed and evaluated. In this method, GMRes solutions were computed with the Tikhonov solution (rather than zero) as the starting point for the iterative scheme.

Typically, three quantities were reconstructed: (1) Epicardial potential maps, which depict the spatial distributions of potentials on an epicardial envelope of the heart.²⁴ Each map depicts one instant of time; maps were computed at intervals of 1 ms during the entire cardiac cycle. (2) Electrograms, each depicting the variation of potential with respect to time at a single point on the epicardium; electrograms were computed at many points (typically, 200-500 sites) around the epicardial envelope. (3) Isochrone maps which depict the sequence of epicardial activation based on local activation time taken as the point of maximum negative derivative ($-dV/dt_{\max}$) of each electrogram. We evaluated our reconstruction results based on visual comparison to the directly measured epicardial potentials, electrograms, and isochrones, and

wherever possible, included statistical measures in the form of relative errors (RE) and correlation coefficients (CC) (defined in the Appendix).

RESULTS

Single-Site Pacing

Figure 2 shows epicardial potential maps for epicardial pacing from a single anterior ventricular site (indicated by the asterisk) at a time frame of 25 ms after the pacing stimulus. On the left are directly measured epicardial potentials, with the corresponding GMRes and Tikhonov reconstructions shown in the middle and right panels, respectively. The measured potentials display a central negative region (blue-green) containing a minimum at the pacing site (asterisk), flanked by two positive regions (red) containing local maxima (+). The inset is a cartoon adapted from Oster *et al.*,²⁴ which shows the equivalent dipole source and theoretical potential pattern associated with single-site pacing. The pacing site is surrounded by a negative region which contains two potential minima (-). Two corresponding potential maxima (+) are present in the flanking positive region. The entire pattern is oriented along the axis of myocardial fibers (background gray lines) in this region. The reconstructed maps (both, GMRes and Tikhonov) capture the two minima in the central negative region. Note that the measured map shows only one central minimum because of limited spatial resolution (insufficient density of measuring electrodes). The GMRes reconstruction is comparable in accuracy to the Tikhonov reconstruction; both locate the pacing site to within 3 mm of its actual position and reproduce correctly the progression of potential patterns during the entire paced beat (only 25 ms are shown here). Similar accuracy is obtained for potential maps generated by left-lateral and posterolateral pacing (not shown here).

Dual-Site Epicardial Pacing

Figure 3 shows epicardial potentials generated by simultaneous epicardial pacing from two closely spaced sites (2.5 cm apart, asterisks). The top panel shows potential maps during activation (25 ms, after the pacing stimulus). Body surface potential maps (BSPMs), shown on the left, were the input data for the noninvasive GMRes and Tikhonov reconstructions. The second column from the left shows measured epicardial potentials with two potential minima, one at each of the two pacing sites. Note that the corresponding BSPM shows only one minimum without any indication of dual-site pacing. From this smoothed BSPM, GMRes has reconstructed both pacing sites with reasonable localization accuracy; left minimum within 4 mm and right minimum within 6 mm of the corresponding pacing sites (Fig. 3, top panel, third column). The Tikhonov method has reconstructed only one elongated minimum (Fig. 3, top panel, right column) suggesting the presence of more than one pacing site but unsuccessful in capturing two distinct minima (due to the smoothing property of constrained regularization, there is loss of spatial resolution). The bottom panel shows potential maps during repolarization (90 ms, after pacing stimulus). The pattern during repolarization is similar to that of activation, except that the polarity is reversed (two maxima, indicated by +, replace the minima at the pacing site locations). Only one maximum is present in the BSPM. Here, also, GMRes has reconstructed both maxima (Fig. 3 bottom panel, third column), whereas Tikhonov has reconstructed only one elongated maximum (Fig. 3, bottom panel, right column). The insets (A, B top panel; C, D bottom panel) show that the inability of Tikhonov to resolve the two minima or maxima is not restricted to the displayed time frames, but is a property of adjacent time frames as well (the two minima/maxima are not resolved by Tikhonov in any time frame). The results demonstrate that in certain cases GMRes can resolve multiple electrophysiological events (e.g., sites of initial activation) with higher spatial resolution than the constraint-based Tikhonov approach.

Epicardial Electrograms and Potentials from Infarct Substrate

Figure 4 shows epicardial electrograms pre- and postinfarction. Panel E shows a cartoon of the heart on which the electrogram locations are marked; the infarct region is marked by the dashed line. The top row shows electrograms from site 1, located on the right ventricle, remote to the LV infarct location. Panel A shows electrograms from the control heart (preinfarction), including directly measured electrograms and the corresponding GMRes and Tikhonov reconstructions (from left to right). Electrograms from the infarcted heart from the same location are shown in B. The measured electrograms pre- and postinfarction show typical normal RS morphology with a sharp intrinsic deflection indicating local activation (electrograms at this location are not affected by the remote infarct and maintain their preinfarction morphology). Both GMRes and Tikhonov reconstructions show excellent similarity to the measured electrograms. The middle and bottom rows show electrograms from sites 2 and 3, both in the LV inside the infarct region. Panel C shows preinfarction electrograms, and panel D postinfarction electrograms. Preinfarction electrograms from sites 2 and 3 show typical RS morphology similar to site 1. However, the infarct produces a major change in their morphology from RS waves (panel C) to negative slow Q waves (panel D). The Q waves contain superimposed sharp small deflections that probably reflect local activation of islands of surviving myocardium within the infarct. Both GMRes reconstructions (middle column) and Tikhonov reconstructions (third column) show close similarity to the directly measured electrograms and capture the infarction-induced changes, including the small deflections generated by surviving myocardium.

Panel F shows epicardial potential maps for the preinfarction (top) and infarcted (bottom) hearts. Measured (left), GMRes reconstructed (middle), and Tikhonov reconstructed (right) epicardial potential maps are shown for a time frame of 48 ms after pacing. Note that both GMRes and Tikhonov show similar accuracy of reconstruction for the preinfarction and infarction potential maps. Importantly, negative potentials (white) are accurately reconstructed over the infarct region² by both methods. Although only one time frame is shown here, both reconstructions performed with similar accuracy for all time frames throughout the cardiac cycle. This is also evident in the similarity of reconstruction of the electrograms. However, it should be noted that Tikhonov electrograms are somewhat “jagged” in appearance due to the variation in regularization parameter from time frame to time frame. The corresponding GMRes electrograms are smoother, without sacrificing any detail that is contained in the measured electrograms. The average CC between reconstructed and measured electrograms over the entire epicardium are 0.93 for GMRes and 0.91 for Tikhonov. Note that although averaged values of correlation coefficients provide an overall quantitative measure of similarity, there may be localized regions with lower reconstruction accuracy. Therefore, visual assessment of pattern similarity between reconstructed and measured epicardial potential maps and electrograms should also be used in evaluating ECGI accuracy.

Monomorphic Ventricular Tachycardia (VT)

Figure 5 shows isochrone maps for two cycles of monomorphic ventricular tachycardia. The left column shows isochrones constructed from activation times determined from directly measured electrograms. The VT is caused by double-loop reentry (white arrows)—with a central common pathway in the infarct region between two lines of conduction block (black lines). The middle and right columns of Fig. 5 show corresponding GMRes and Tikhonov reconstructions, respectively. This demonstrates that the GMRes reconstruction, like its Tikhonov counterpart, can capture all the important features of the reentrant circuit, showing close correlation with the measured isochrones for the two displayed cycles.

Dispersion of Repolarization

Directly measured, GMRes reconstructed, and Tikhonov (second order) reconstructed epicardial QRST integral maps during local LV cooling are shown in the left, middle, and right panels of Fig. 6, respectively. Tikhonov second order (not zero order) was used because it better preserved the T-wave amplitude, which is included in the QRST integration.⁹ The cooling probe position is shown by the dotted rectangular region in the measured map. The measured QRST integral map shows lower QRST amplitudes in the region of cooling with a localized minimum directly under the cooling probe. Although both reconstructions show the cooling-induced reduction in QRST integral values (dark green) similar to the measured, only GMRes reconstructs the localized minimum (blue) under the cooling probe. The Tikhonov reconstruction is smoothed, resulting in loss of spatial resolution and under-representation of local repolarization heterogeneities. It should be mentioned that the average correlation coefficient of potential maps over the QRS portion of the electrogram is similar for GMRes and Tikhonov (0.82 and 0.79, respectively) whereas the CC over the T wave is much higher for GMRes (0.72 vs. 0.57 for Tikhonov). Since the QRST integral includes integration over the T wave, this explains why the GMRes QRST integral map exhibits much greater accuracy than Tikhonov for this data set.

Tikhonov-GMRes Hybrid Method

Figure 7 shows reconstructions using the Tikhonov-GMRes hybrid method applied to the simultaneous dualsite pacing data of Fig. 3. On the left is the measured potential map for a time frame of 25 ms after the pacing stimulus; the corresponding Tikhonov-GMRes reconstruction is shown on the right. Note that this hybrid reconstruction shows a much closer correlation with the pattern of the measured map and the pacing sites are located more accurately (within 1 mm) compared to the independent application of GMRes or Tikhonov methods in Fig. 3.

DISCUSSION

Prior to the methodology presented here, noninvasive imaging of epicardial potentials, electrograms, and isochrones was based on regularization methods that impose constraints on the solution (for a review, see Refs. 29-31). In our laboratory,^{2-4,9,21,24,25,28} we have used Tikhonov regularization of different orders and demonstrated its accuracy in animal studies. Constraint-based methods require incorporation of *a priori* information on properties of the solution (e.g., restricted magnitudes, gradients, or curvatures of the computed epicardial potential distribution in Tikhonov zero, first, and second order, respectively^{29,33}) and their accuracy depends on determination of an optimal regularization parameter.^{29,33} In addition, the imposed constraints often act to smooth the solution in space, sometimes with loss of localized patterns (e.g., highly localized minima, see Figs. 3 and 6), which may contain important electrophysiological and clinical information. These properties have suggested to us the potential usefulness of an independent, nonconstraint approach that can complement the Tikhonov method and overcome some of its limitations, especially in the clinical setting where *a priori* information may be very limited. In addition, reconstruction of ECGI images by two independent (constraint-based or iterative) methods increases the confidence level in the results. We have chosen the iterative GMRes method based on its successful application in processing images that contain highly localized spatial information (e.g., astronomy⁶). Although this method is not, typically, used for nonsparse matrices (the ECGI case), it has provided accurate results and robust determination of the choice iteration for all data sets we have tested (total of 21). Our earlier attempts to apply other methods, in particular, truncated singular value decomposition (tSVD) have met with little success and produced less accurate results than Tikhonov regularization.

We evaluated the performance of the GMRes method using extensive electrophysiological data from normal and abnormal canine hearts. In several situations, where the epicardial potential distributions were characterized by complex spatial details and highly localized features, GMRes recovered them more accurately than Tikhonov. To cite particular examples, GMRes reconstructed two distinct potential minima around two distinct pacing sites, while Tikhonov smoothing resulted in these minima merging into a single elongated minimum (Fig. 3). For the dispersion of repolarization data of Fig. 6, a highly localized epicardial QRST-integral minimum directly under the cooling probe was only reconstructed by GMRes but not by Tikhonov, which had a strong smoothing effect on the reconstructed epicardial QRST maps. The better capability of GMRes to resolve and locate electrophysiological events may be of important clinical significance. For example, the dual-site pacing protocol of Fig. 3 simulates two distinct ectopic foci of arrhythmogenic activity. Resolving the two sites may be crucial for correct diagnosis and guidance of intervention (ablation) in the clinical setting. Thus, GMRes can resolve spatial details that may be important determinants of the clinical course of action.

In general, the GMRes reconstructed electrograms for all data sets were smoother than those reconstructed by Tikhonov, where “jaggedness” was introduced by fluctuations of the regularization parameter between time frames [Fig. 4(D), arrow]. In addition, GMRes did not suppress electrogram T-wave amplitudes as much as Tikhonov zero order (which constrains magnitudes of epicardial potentials), a property of Tikhonov zero order that dictated the use of second-order regularization (constraint of Laplacian) in the original ECGI study of repolarization.⁹

We also tested GMRes for endocardial ECGI,^{15,16,18-20} a method which reconstructs endocardial potentials, electrograms, and isochrones from a noncontact, multielectrode intracavitary catheter (results not presented here but an example is included in the Electronic Supplement http://www.cwru.edu/med/CBRTC/gmres_esuppl.pdf). We compared its performance to Tikhonov reconstructions reported in our previous publications and observed similar properties to those described here for epicardial ECGI. In a particular example involving simultaneous pacing from two ventricular sites,¹⁵ GMRes reconstructed clearly the two distinct endocardial minima generated by dual-site pacing. In comparison, the corresponding Tikhonov solution reconstructed one distinct minimum but the second minimum was much smaller in amplitude and could not be distinguished on the same potential scale (electronic supplement, Fig. 10). By varying the Tikhonov regularization parameter over a large range of values, we identified a value that did reconstruct two distinct potential minima. This demonstrates the strong dependence of Tikhonov reconstructions on the regularization parameter and the need, in some cases, for *a priori* information for its optimal determination (in this example, knowledge of the existence of two pacing sites).

Conceptually, the choice of iteration number in the GMRes method is analogous to determination of the regularization parameter in Tikhonov regularization. The optimal GMRes iterate was chosen automatically using the condition-L-curve corner criterion. The choice of iteration was also obvious by observing the progression of solution characteristics through the iterations. As an example, potential maps over GMRes iterations for the dual-site pacing data of Fig. 3 are shown in Fig. 8. The solutions were generally smooth in the beginning few iterations (iterations <15), evolving into the best set of solutions (iterations 17-21) and then suddenly becoming noisy for higher iterations (iterations ≥22). This progression was observed for all data sets (Fig. 9 provides correlation coefficient curves with respect to number of iterations for all data sets). The condition L curves had distinct corners for all the different data sets of this study and the process of determining the optimal iterate was very robust. This supports the use of GMRes with the condition L curve criterion in the clinical application of ECGI. Theoretically, however, it cannot be guaranteed that the GMRes condition L curve will

always exhibit a corner. In general, GMRes computing times were longer than those for Tikhonov (Table 1 reports computing times for all data sets).

Instead of starting with a zero initial guess for GMRes, starting with the Tikhonov solution improved the patterns and localization accuracy of the reconstruction of two pacing sites (Fig. 7). For all the other data sets, slight improvement in accuracy was observed when using this hybrid method (error measures are given in Table 2). Further studies are required to investigate whether there are advantages of using the hybrid method for clinical data, as opposed to applying each method independently. This judgment will require a gold standard for evaluation, such as direct epicardial mapping during cardiac surgery. In addition, caution must be used not to erroneously “bias” the solution by providing an inaccurate Tikhonov first guess. However, it is understood that a better estimate of the initial solution may result in better GMRes reconstruction. Since we are obtaining very good results with zero initial vector and termination of iteration based on the condition-L curve, we conclude that *a priori* information is not essential, but when incorporated, may result in higher accuracy.

We also evaluated the sensitivity of the GMRes method to potential noise and geometric errors using the data set of Fig. 2. Various combinations of potential noise (either 50 or 100 μV , Gaussian) and geometrical errors in torso-electrode positions (1, 2, or 3 mm, Gaussian) were added to the input data. The quality of the solution was comparable to the solution obtained with the original data, without the added noise (see the Electronic Supplement http://www.cwru.edu/med/CBRTC/gmres_esuppl.pdf).

The results presented here suggest that the complementary application of the two independent methods in clinical ECGI will ensure reliability and maximal extraction of diagnostic information even in the absence of *a priori* information about a patient’s condition, making ECGI a powerful tool for arrhythmia detection and diagnosis.

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APPENDIX: MEASURES OF RECONSTRUCTION ACCURACY

Statistical measures in terms relative error and correlation coefficients (definitions below) were computed with respect to the measured data for each data set. RE gives an estimate of the amplitude differences and CC gives an estimate of the similarity of potential patterns or electrogram morphologies between the measured and computed data:

$$\text{RE} = \sqrt{\frac{\sum_{i=1}^n (V_i^C - V_i^M)^2}{\sum_{i=1}^n (V_i^M)^2}},$$

$$\text{CC} = \frac{\sum_{i=1}^n \left(V_i^M - \bar{V}^M \right) \left(V_i^C - \bar{V}^C \right)}{\sqrt{\sum_{i=1}^n \left(V_i^M - \bar{V}^M \right)^2} \sqrt{\sum_{i=1}^n \left(V_i^C - \bar{V}^C \right)^2}}.$$

where n is the number of nodes (points at which epicardial potentials are computed: vertices of the triangular elements that mesh the epicardial surface). For electrograms, n is the number of time frames. V_i^C is the computed potential for node i , V_i^M is the measured potential for

node i , $\bar{V}^M$ is the average measured potential, and $\bar{V}^C$ is the average computed potential. For isochrone maps, activation times replace potentials in the CC definition; for QRST integral maps, integral values replace potentials in the RE and CC definitions.

Pacing site localization errors [distance (in millimeters) between computed and measured locations] are also provided for the pacing data sets. The computed pacing site location was estimated by the center of an ellipse that best fits the quasielliptical negative potential region that develops around the pacing site (Fig. 2 in the paper). The earliest time frame after pacing, for which such pattern was visible, was used for this purpose.

Table 2 shows RE, CC, and/or localization errors for the data sets used in this study (wherever applicable).

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FIGURE 1.

Condition-L curves and L curves. Panel A: curves for single-site pacing data 25 ms (left) and 50 ms (right) after pacing. Top row: condition-L curve for GMRes. Second row: L curve for GMRes. Bottom row: L curve for Tikhonov regularization. Panel B: curves for dual-site pacing data. Same format as panel A. Note that the condition-L curves are in semilog scale and the L curves are log-log scale.

FIGURE 2.

Epicardial potential maps 25 ms after pacing from a single site (indicated by the asterisk). Measured potentials (left), GMRes reconstruction (middle), and Tikhonov reconstruction (right) are shown on an anterior view of the epicardial envelope. + and - indicate potential maxima and minima, respectively. Potential values (in microvolts) are displayed using a color scale. Inset shows a simplified (approximate) equivalent source configuration consisting of two opposing dipoles along the major axis of an elliptical wave front propagating from the pacing site. The major axis of the wave front is oriented along local fiber orientation (indicated by gray lines). This generates a potential pattern of a central negative region containing two minima and two flanking maxima oriented along the fiber direction, which is reconstructed by both GMRes and Tikhonov.

FIGURE 3.

Simultaneous dual-site pacing. Top row: potential maps during activation (25 ms after pacing). Left-most column shows the body surface potential map (BSPM). Second column shows directly measured epicardial potentials. Third column shows the GMRes reconstruction. Right-most column shows corresponding Tikhonov reconstruction. Insets A and B show Tikhonov reconstructions for time frames 23 and 27 ms, respectively. Asterisks in each epicardial potential map indicate the location of the pacing sites. Bottom row: potential maps during repolarization (90 ms after pacing). Bottom row follows the same format from left to right as the top row. Insets C and D show Tikhonov reconstructions for time frames 88 and 92 ms. + and - signs indicate potential maxima and minima, respectively. Lead II of the ECG is provided for timing purposes.

FIGURE 4.

Epicardial electrograms and potential maps pre- and postinfarction. The left column in panels A, B, and C shows the measured electrogram, the middle column the GMRes reconstruction, and the third column the Tikhonov reconstruction. Numbers in boxes indicated epicardial sites. Panels A and B: electrogram from site 1, located remote to the infarct. Panel A shows electrogram preinfarction. Panel B shows electrograms from the same site, postinfarction. Panels C and D, top row: electrograms from site 2, located inside the infarct region. Bottom row: electrograms from site 3, also located inside the infarct region. Panel C, preinfarction; panel D, postinfarction. CC: correlation coefficient relative to the measured electrogram. Panel E: diagram of the epicardial surface of the heart showing the infarct region (dashed line) and the locations of electrograms 1, 2, and 3. Panel F, top row: epicardial potential maps for the preinfarction heart (time frame of 48 ms after pacing). Measured (left), GMRes reconstruction (middle), and Tikhonov reconstruction (right). Bottom row: corresponding epicardial potential maps for the infarcted heart.

FIGURE 5.

Isochrone maps during monomorphic ventricular tachycardia (VT). Two consecutive cycles are shown. Top row: first cycle. On the left are directly measured isochrone maps. The GMRes and Tikhonov reconstructions are shown in the middle and right columns, respectively. White arrows indicate direction of wave front propagation. Black lines indicate conduction block. Blue region at the base is late activation from the previous cycle that occurs about the same time as the beginning of the present cycle at the entrance to the common pathway between the lines of block. Bottom row: second cycle. Same format as the top row.

FIGURE 6. Measured (left), GMRes reconstruction (middle), Tikhonov reconstruction (right) of epicardial QRST integral maps during enhanced regional dispersion of repolarization induced by localized cooling. Dotted rectangular box in the measured map shows the shape and location of the cooling probe.

FIGURE 7.

Tikhonov-GMRes hybrid method for the dual-site pacing data of Fig. 3. Tikhonov zero order provided the initial values for the GMRes iterative procedure. Measured epicardial potentials (left) and Tikhonov-GMRes reconstructed images (right).

FIGURE 8.

Potential maps for progressive numbers of GMRes iterations (dual-site pacing, 25 ms). Condition-L curve corner is at iteration 19 (dark box indicates chosen solution). Note moderate change in solution between 17 and 21 iterations and clear deterioration of solution for iteration ≥ 22 .

FIGURE 9.

CC of reconstructed potential maps as a function of number of GMRes iterations for all data sets. CC were calculated with respect to measured epicardial potentials and averaged over the entire cardiac cycle. The CC values are bell shaped, with a “plateau region” near the peak value. The iteration corresponding to the solution chosen by the condition-L-curve criterion is in this region and is indicated by the corresponding enlarged symbol shaded black.

TABLE 1

Computing times (total time for computing potential maps over the entire cardiac cycle). Note that computing time increases with the size of matrix A, which reflects the number of torso and epicardial nodes used in a given protocol.

Data	Computing time		Chosen iteration	
	Tikhonov	GMRes (time to compute 30 iterations)	Zero initial vector	Tikhonov initial vector
Single-site pacing (Fig. 2)	50 s	1 min 30 s	18	20
Dual-site pacing (Fig. 3)	50 s	1 min 28 s	18	20
Infarct data (Fig. 4)	2 min	3 min	22	25
VT (Fig. 5)	1 min 48 s	2 min 52 s	20	23
Repolarization (Fig. 6)	30 s	1 min	15	20

TABLE 2
RE and CC for all the data sets used in this study (wherever applicable) for Tikhonov, GMRes, and Tikhonov-GMRes hybrid methods.

Data set	Tikhonov	GMRes	Tik-GMRes
Single-site pacing (potential maps) Fig. 2			
RE	0.65	0.63	0.43
CC	0.84	0.88	0.91
Localization error	4 mm	4 mm	2 mm
Dual-site pacing (potential maps) Figs. 3 and 7			
RE	0.64	0.55	0.24
CC	0.78	0.84	0.96
Localization error (right minimum, left minimum)	Only one minimum	6 and 4 mm	1 and 1 mm
Infarct substrate (electrograms) Fig. 4			
Site 1: Preinfarction	0.93	0.96	0.97
Infarction	0.96	0.96	0.96
Site 2: Preinfarction	1.0	1.0	1.0
Infarction	0.99	0.97	1.0
Site 3: Preinfarction	0.98	1.0	1.0
Infarction	0.97	0.995	0.98
Dispersion of repolarization (QRST integral maps) Fig. 6			
CC	0.76	0.87	0.89