Recent Progress in Inverse Problems in Electrocardiology

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Short titles: Inverse Problems in Electrocardiology
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Introduction

The ultimate, if utopian, use of electrocardiography would be to describe the electrochemical activity of each cell in the heart based on body surface electrocardiograms (ECGs). Currently, in everyday practice, clinicians use the ECG to diagnose the health of a patient's heart based on a current dipole model of the cardiac electrical source. This diagnosis is typically qualitative rather than quantitative, and based more on empirical pattern recognition than on biophysical modeling. On the other hand, it is also performed in almost real time, and is amenable to the use of other clinical variables to constrain and confirm the resulting diagnosis. Both the utopian and the clinical use of the ECG require solutions to the inverse problem of electrocardiography, and they represent the two extremes among the many formulations of this problem. There are a number of useful formulations in between, more comprehensive and quantitative than current clinical practice; multichannel ECG measurements ("body surface potential maps") along with a mathematical model of cardiac bioelectric sources are used to describe macroscopic cardiac electrical activity by estimating the values of the modeled sources. The purpose of this paper is to review recent progress in such electrocardiographic inverse problems.

Solving the electrocardiographic inverse problem is made difficult by two characteristics it shares with many other scientific and engineering inverse problems. The first characteristic is the non-unique relationship between the true intra-cardiac sources and our remote observations—the same set of measurements could result from more than one source configuration. To accommodate this, we seek inverse problem formulations that have unique source models, and accept as a consequence the possible loss in generality, applicability, and ability to validate. The second troublesome characteristic is the ill-posedness of the inverse problem resulting from attenuation (due to dissipation) and smoothing (due to spatial superposition) of the electric fields in the medium between source and observation. Recovering the sources from the resulting remote measurements requires amplification and "unsmoothing". When applied to measurements contaminated with unavoidable noise, while

using models with unavoidable model error, the result can be large, nonlinear, even discontinuous errors in inverse solutions. In the discussion that follows, we outline several approaches to mitigate these difficulties.

The field of inverse electrocardiography was summarized comprehensively in 1988-89 in a series of reviews by Rudy and Messinger-Rapport [1, 2] and Gulrajani, *et al.* [3–6]. These papers describe methods that solved the basic problem, but produced results that were notoriously unreliable and their significance, in either research or clinical contexts, was not convincingly established. Research in the intervening years has focused on such topics as increasing robustness to discretization error and model assumptions, maximizing use of available *a priori* information, formulating the inverse problem in ways that reduce ambiguity and increase utility of the results, removing obstacles to clinical application, and carefully validating solution methods. More recent reviews and tutorials by Horáček [7], Greensite [8], and Rudy [9] have covered a few of the developments in the field. Here we emphasize a more comprehensive view of important recent results and the current state of the field. We apologize in advance for omissions due to space constraints and oversight.

Problem formulations

There are three requirements that govern formulations of an inverse problem in electrocardiology: 1) posing a problem that has a well-defined solution, 2) describing this problem in a form that facilitates the use of reasonable numerical techniques, and 3) defining source model and observation locations that permit measurements under physiological conditions. The two classes of formulations described in this section meet these conditions and, therefore, have emerged from a broad collection of alternatives as the most promising approaches. These two alternative formulations are based on different "equivalent representations" of the intra-cardiac sources. Each source representation then leads to a particular set of equations, solved by one or more numerical techniques. We omit any discussion of inverse problems based on discrete intra-cardiac dipole source models, as the coverage of this topic in [3] is still contemporary.

Solutions in terms of potential distributions

The more general of these formulations represents the actual intra-cardiac sources in terms of the distribution of electrical potential on a closed surface that completely separates the sources from the observations [10]. The field anywhere on the observation side of such a surface has, in principle, a one-to-one association with the potential distribution on the surface itself. Thus the potential distribution on this surface represents an equivalent source. For example, one such ideal surface is the epicardium, the outer surface of the heart, with the measurements made on the body surface. In addition to providing a theoretically unique solution, epicardial potentials can be—and, in fact, often are [11–13]—measured using invasive techniques. Thus they provide both a useful clinical description of cardiac electrical activity as well as a practical validation mechanism for inverse solutions.

The resulting mathematical formulation of the problem requires solving Laplace's equation for the region between the epicardial and torso surfaces, denoted as Γ_E and Γ_T respectively, *i.e.*,,

$$\nabla \cdot (\sigma \nabla \phi) = 0 \text{ in } \Omega, \tag{1}$$

with the appropriate Dirichlet

$$\phi = \phi_0 \text{ on } \Gamma_E \tag{2}$$

and Neumann

$$(\sigma \nabla \phi) \cdot \ \mathbf{n} \ = 0 \text{ on } \Gamma_T \tag{3}$$

boundary conditions, where ϕ is the potential anywhere in the volume Ω bounded by the surfaces Γ_E and Γ_T, σ is the conductivity, and $\mathbf{n}$ is the outward surface normal.

A second variant of the potential distribution formulation takes advantage of our ability to measure potentials measured with an intracavitary probe introduced surgically, or even percutaneously via catheter, into one of the heart's chambers [14, 15]. Here the bounding surface representing the source is the endocardium (the inner surface of the heart); the measurement probe provides

the Neumann boundary and the endocardial surface the Dirichlet boundary. This formulation is of great clinical interest because it offers the possibility of rapid and comprehensive endocardial mapping during ablation procedures.

Solutions in terms of activation wavefronts

During the spread of activation in the heart, the most significant bioelectric source is the large potential difference that exists across the moving wavefront that divides active (depolarized) from resting tissue. Thus investigators have developed source representations leading to tractable inverse problems that directly model this wavefront [16, 17]. One starts by assuming that the extracardiac field during activation can be approximated as the field produced by a uniform double layer of current dipoles (UDL) lying along the activation wavefront and oriented in the normal direction. This wavefront is accessible only to electrodes mounted within the heart tissue—thus we need a more convenient equivalent source. Because the external field from a UDL is a function of the solid angle swept out by the boundaries of the excited region, we can replace the actual activation wavefront by any UDL that has the same solid angle. The most convenient choice of equivalent UDL is the surface that lies on the boundary of the heart and encloses all currently excited tissue. The moving edge of this surface is defined by the time at which the underlying tissue becomes depolarized (the "activation time") and its full extent is the union of the epicardium and endocardium, made continuous by a small fictional adjoining segment near the base of the heart. The simplifying assumptions of the UDL—the constant voltage step across the wavefront and normal direction of the dipole moment—permit a further simplification of the extracardiac field:

$$\phi(y) = \int_{S_v} T(y,x) H(t - \tau(x)) dS_x, \tag{4}$$

where $\phi(y)$ is the potential at extracardiac site y, H is the Heaviside step function, $\tau(x)$ is the time at which each portion of the epi/endocardium (S_v) becomes depolarized (the activation time) and $T(y,x)$ is a transfer function that weights the contribution of each point of the cardiac surface x

to each point on the torso surface y [16, 17].

A pictorial summary of the three formulations described here is shown in Fig. 1.

Please place Figure 1 here

Discussion

One strength of the potential based formulations is that they are more general—they recover the potential anywhere on the surface or within the appropriate volume conductor at any point in the cardiac cycle. The UDL method, by contrast, only recovers the activation wavefronts (QRS complex) and gives no information about repolarization or recovery (ST segment and T wave). In addition, the UDL method requires the assumption of a *uniform* dipole layer, implying that the wavefront does not reflect the effects of anisotropic conduction. Many experimental studies have shown that such an assumption is incorrect [18–20], but the effect of this discrepancy on the inverse problem is a topic of current research [21, 22]. Thus the assumptions implicit in the potential based formulations are less restrictive, and the solutions may contain more information. However, potential formulations are over-parameterized to some extent—they do not take explicit advantage of the "wavefront" behavior (spatio-temporal coherence) which characterizes important aspects of cardiac electrical activity. As a result of its more parsimonious representation, the UDL formulation tends to be less ill-posed. Moreover, the activation wavefront trajectory has relatively clear physiological meaning and is an immediately useful result, while solutions in terms of potentials are more ambiguous and require further processing even to obtain activation wavefronts [23].

Modeling considerations

All the methods described above share certain common assumptions: quasi-static propagation, temporally constant geometry (questionable during recovery), a torso which is homogeneous or divided into piecewise homogeneous compartments with known relative conductivities, a linear medium, potentials that are recorded with respect to a common reference, and insignificant non-

cardiac electrical activity. Given these assumptions, Bayley, *et al.*, [24] and then later Rudy, *et al.*, [25–27] developed elegant analytical inverse solutions based on concentric and eccentric spheres and used them to investigate many aspects of the forward and inverse problems. Barr, *et al.*, [28, 29] and Colli-Franzone, *et al.*, [30, 31] incorporated realistic torso geometries into discrete forward/inverse solutions based on the epicardial potential formulation. Barr, *et al.*, applied a Green's theorem approach to the formulation in equations 1–3 and then used the boundary element method (BEM) to describe and solve the resulting integral equations. Colli-Franzone, *et al.*, and later Yamashita, *et al.* [32], on the other hand, employed a Galerkin formulation and the finite element method (FEM). The BEM and FEM remain the main numerical approaches and their relative merits have been well discussed in [2]. The UDL formulation of the inverse problem leads directly to surface integral equations and hence has been solved exclusively using the BEM, most notably by Huiskamp and van Oosterom [17].

The final result of all these approaches is a forward solution, a simple description of the relationship between sources and remote body-surface or probe-surface potentials. For the epicardial to body surface formulation, for example, we have

$$\phi_b(y) = Z(y, x)\phi_h(x), \tag{5}$$

where ϕ_b and ϕ_h are body surface and epicardial potentials, respectively and $Z(y, x)$ is a transfer function weighting the contribution of each epicardial site to the potential at each body surface site.

The geometric models required by both BEM and FEM for realistic inverse problems include a discrete set of points, linked to form a three-dimensional mesh and segmented into regions of locally constant conductivity. Notable landmarks in mesh generation research include the early results of van Oosterom on surface triangulation techniques based explicitly to the BEM method [33], and more recent progress by Johnson, MacLeod, Schmidt, and coworkers [34–37] on segmentation and tetrahedral mesh generation. The latest programs are capable of creating meshes with over one

million elements based on magnetic resonance imaging of human subjects. Early inverse solutions assumed homogeneous conditions throughout the volume conductor [28]. Many subsequent modeling studies have attempted to determine the influence of conductivity inhomogeneities on the inverse solution and Gulrajani has discussed their often contradictory conclusions [5]. The last ten years have seen relatively little resolution of this issue, although recent simulation studies with a three-dimensional forward solution using an elaborate geometrical model suggest that omission of subcutaneous fat, anisotropic skeletal muscle, and, to a lesser extent, the lungs cause the largest errors in forward solutions [38]. Experimental studies have revealed that variation in torso conductivity affects not only body surface potentials but also the potential distributions recorded on the epicardium [39–41].

Improvements in numerical techniques to solve forward/inverse problems have generally been restricted to *specific* problem formulations. For example, better numerical techniques have been applied to the integrations required for BEM solutions, moving from assumptions of constant potential over each element [28] to triangle subdivision schemes [42, 43], to linear variation over each element [2, 44]. Adaptive mesh refinement, a process by which selected elements of the mesh are subdivided or merged based on local error estimates, has been applied so far only to FEM models [45, 46]. A potentially powerful approach is to combine the strengths of both the BEM and FEM and apply them to different subdomains of the mesh [47]. One issue which has recently emerged is whether meshes which may be optimal for forward solutions are also optimal for inverse solutions: results indicate that in fact this may not be the case [48].

Solving the inverse problem

Given the ill-posed nature of the inverse problem, the ambiguities of various source models, the errors in any forward solution, and the presence of noise in measured data, the formulation of a useful inverse model does not follow directly from the source models and forward solutions described so far. One needs to find a way to select the best solution from the available information;

even the way that one chooses to define "best" can have a significant effect on the answer. The most straightforward way is to look for the solution that minimizes the difference between the torso measurements predicted by a candidate solution together with the forward model, on the one hand, and the actual measured data on the other hand. This difference, known as the residual error, is usually measured in terms of sum-squared error (or ℓ_2 norm). The effect of the ill-posedness of the inverse problem is that solutions which simply minimize this residual error will be unreliable and often unrealistic—consequently, a more sophisticated approach is required.

The standard response to this ill-posedness is known as regularization: a weighted sum of two terms is minimized. One term is the residual error and the other is a penalty term describing an undesirable property of the solution. The most common example of such penalty terms are the ℓ_2 norm of the solution, penalizing for excessive amplitude, or the ℓ_2 norm of its first or second (spatial) derivative, penalizing for lack of smoothness. The chosen undesirable property acts as a constraint on the solution, reducing the extreme sensitivity of the ill-posed minimum residual result. The constraint then becomes a way to incorporate into the inverse model *a priori* information about how a reasonable solution should behave. A weighting parameter, known as the "regularization parameter," is used to control the tradeoff between the two error terms. There is a rich literature about regularization, both generally in applied mathematics [49–52] as well as specifically in inverse electrocardiography, and these methods can be interpreted in terms of physics, linear algebra, complexity theory, information theory, statistics, image processing, and other fields. Moreover, ℓ_2 norm based regularization is not the *only* way to approach the problem. For instance, in earlier work by Brooks and collaborators, the inverse problem was posed in the power spectrum domain [53]; in this context other error measures, such as relative entropy, are available. Thus, solving the inverse problem is not merely a question of numerical implementation, but rather one of choosing the appropriate principle upon which an optimal or acceptable inverse solution will be judged, and one can use entirely different principles than constrained squared error,

i.e.,, regularization, to construct error functions to minimize.

The general result of the application of regularization methods to electrocardiography between the mid 1970's and the late 1980's was, as described above, only partially satisfactory. Two possible approaches to improving this result are to 1) reduce the various sources of error and 2) incorporate more *a priori* information. We will not discuss results from the considerable research utilizing the former approach (see, for example, [34, 46, 54, 21, 55]). We see recent work on the latter approach as generally having followed three main paths: 1) explicitly including more information by using novel constraints, or more than one constraint, 2) implicitly including more information by formulating the source model based on a characterization of the dynamics of cardiac electrical activity, thereby effectively restricting the solution domain, and 3) using the constraints in a "smarter," "tuned" manner. A number of methods cross the boundaries of these somewhat artificial categories, but we will use this scheme to delineate the major approaches we describe below.

Using novel and/or multiple constraints

There have been two general trends in this category: using other constraints besides the traditional amplitude and spatial derivative ℓ_2 norms, and using more than one constraint. Specific examples include orthogonality constraints [56], constraints on the normal component of current on the epicardial surface [57], and explicit constraints on the temporal behavior of solutions [58–63]. Much attention has been given to methods that incorporate more than one constraint, particularly temporal and spatial constraints. Oster and Rudy employed a two-step method to take advantage of presumed temporal continuity of solutions [58]; first spatially regularized solutions were calculated, then these solutions were "temporally regularized" to constrain nearby temporal samples at a particular epicardial location to be reasonably close to each other. Effectively this amounted to a temporal "post-filtering" operation on the spatial regularization. Brooks, *et al.*, incorporated a number of time instants into an "augmented" formulation of the problem, and then found a solution which jointly minimized a combination of three terms: the residual error, a spatial constraint error,

and a temporal constraint error. El-Jakl, *et al.*, [62] proposed a Kalman filter solution to essentially the same problem. Greensite [63] has recently introduced a method based on a doubly Truncated Singular Value Decomposition (TSVD) regularization which uses information about the interaction between "temporal" and "spatial" subspaces which depend on the temporal correlation of the data, and the inner product of the forward solution over the heart surface, respectively. Brooks, *et al.*, extended the time/space constraint approach to include first dual spatial constraints [64], and then later also a truncated conjugate gradient-type regularization [60]. Shahidi, *et al.*, combined two spatial constraints by means of a hybrid regularization term which merged a TSVD approach with an explicit constraint on the solution norm [65]. In general, combining constraints seems to produce results that are less sensitive to the choice of constraint and less sensitive to the choice of regularization parameters or truncation index. In addition, the incorporation of temporal information produces a much more realistic behavior of the reconstructed time signals (electrograms), without apparent loss of accuracy of spatial distributions.

Figure 2 shows a sample comparison of standard spatially regularized results to those achieved using the joint time/space regularization method described in [61]. The results are computed by first applying a forward solution to measured epicardial electrograms from an isolated heart to generate simulated torso surface ECGs, as described in the Validation section below. After adding noise to the simulated torso signals, we computed inverse solutions with a variety of regularization techniques and parameters. In the figure, sixty millisecond long segments of electrograms during QRS are shown for four different locations on the epicardium. The first and third rows show results using spatial regularization only, and the second and fourth rows using additional temporal regularization. Each plot shows the original measured electrogram as a solid line and reconstructions at various regularization parameters (or pairs of regularization parameters for the joint time/space method). Notable in the joint time/space results is the decreased sensitivity to variation of the regularization parameter values and significant decrease in unrealistic uncorrelated temporal behavior. In some

cases the price paid is an inability to follow accurately the sharp intrinsic deflection, but both methods suffer somewhat from this problem due to the smoothing implicit in any regularization.

Please place Figure 2 here

All of the methods above are based on the selection of at most two constraints and the calculation of a unique minimum of the ℓ_2 norm. In [66, 67] the authors suggest an approach which reflects a quite distinct inverse reconstruction principle: finding an admissible solution. They start with the assumption that there are a number of appropriate constraints on the solution available, based for instance on physical/physiological principles or empirical results obtained from experimental measurements. Examples include bounds on the residual error, spatial norms of the solution at each point in time, or temporal norms at each point in space, or norms of derivatives or gradients, as well as less standard constraints such as on the temporal frequency content of the solution. Each constraint generates its own subset of admissible solutions in the space of possible solutions. The intersection of these sets represents a region of acceptability for a solution—the set of all solutions which are *admissible*. The authors do not solve the inverse problem by seeking a unique optimal solution, but rather by using numerical optimization techniques that find an arbitrary member of this admissible set (subject to the restriction that all the constraints are convex).

Constrained source models

Inverse solutions framed in terms of activation wavefronts can be classified as constrained source models; the problem formulation parameterizes cardiac propagation in terms of activation time, and thus restricts the eventual solution domain. However, even this problem is considerably ill-posed—and it is also non-linear. In a recent series of papers, Greensite, Huiskamp, *et al.*, restrict the solution set even further by focusing only on breakthroughs onto the epi/endocardial surface [8, 68, 69]. Initially tied to the UDL hypothesis, their work uses concepts from differential topology to link these breakthroughs to jumps in the temporal derivative of the body surface potentials. In

the latter papers they attempt to remove the dependence on the UDL assumption. In another, related, approach, they use a subspace-based argument to detect timing of breakthroughs by means of the sudden appearance of an "independent source," causing a change in the distance between two subspaces, as they search both forward and backward in time through the QRS [70]. Once the breakthrough times have been located, they find the breakthrough locations and, finally, use these "high-quality" estimates of the breakthroughs and a regularization approach to find the rest of the isochronal distribution.

Tuned application of constraints

Another approach to improved accuracy and reliability in recent inverse problem research has been to use *a priori* information to apply constraints in a more effective manner. One such approach introduced by Johnson, *et al.*, factors an FEM forward solution into distinct matrices, each representing the relationship between two volume compartments in the model [54]. Some of these submatrices are considerably better conditioned than others, suggesting that the related "sub-inverse problems", as it were, are better posed. Thus the regularization can be tuned by only applying it to each submatrix as needed. A quite different approach introduced by Iakovidis and Gulrajani is based on the observation that over-regularization produces overly smooth solutions that are not very accurate around extrema but reasonably reliable where amplitudes are small[71]. In an analogous fashion, solutions with less regularization than optimal locate maxima and minima reasonably accurately, but produce very noisy reconstructions in other locations. Therefore, the authors constrained the inverse solution in small amplitude regions to agree with an overregularized solution, constrained the extremal locations according to an underregularized solution, and the remainder by the standard regularization criteria. This approach can be thought of as an attempt to adjust the amount of regularization to match the local Signal-to-Noise Ratio (SNR): where the SNR is high, only regularize a little, and where it is low, regularize a lot. Messinger-Rapport and Rudy, in [72], suggest an approach using constrained optimization techniques to impose constraints

such as a maximum value on the solution. Oster and Rudy describe a spatially varied regularization scheme [73] applied to concentric (and then eccentric) spheres, in which they use Legendre polynomials (and then the SVD) to delineate a sequence of orthogonally decomposed sub-reconstructions. Different regularization parameters are used to weight different terms in this decomposition; the idea is that the local SNR should guide the local degree of regularization. The admissible solutions work described above also included the use of spatially weighted constraints. Here the weighting of individual constraints varied spatially based on some *a priori* knowledge of the expected amplitude of constraint-specific properties. Thus, for example, where potential amplitudes are small an ℓ_2 norm constraint will be emphasized, while where they are large it will be downweighted, since this constraint by itself generally allows too much low-amplitude noise but smoothes the largest amplitudes. All these methods produce an increase in the accuracy and reliability of their inverse solutions over more straightforward regularization schemes.

Validation and Clinical Applications

In this section, we explicitly return to the theme of this special issue and discuss the link between the theory and numerics of the inverse problems and the techniques of multichannel data acquisition and processing. The input signals for any electrocardiographic inverse solution come from electrodes placed on the body surface or mounted in a probe that is inserted into the ventricle, with sufficient density and coverage to represent adequately the entire surface potential distribution. The practical interpretation of "sufficient density" is a point of considerable debate, reflected in the range of electrode numbers used in typical body surface potential mapping systems, between 32 and 200. (In fact, the theoretical claim made above of a unique one-to-one relationship between surface potential distributions is in fact only true if the *entire* distribution of potential on the surfaces is known.) Unlike the more common issue of temporal sampling, with spatial sampling it is difficult to apply Shannon sampling theory due to uncertainty about actual spatial frequency content, and there is no easy way to perform spatial anti-aliasing filtering. There have been a few theoretical

([74]) and practical ([75]) studies of spatial sampling, but there are no definitive conclusions. Thus the current practical solution is to try to ensure that coverage is dense enough to capture the significant features of the potential distribution on the body surface. For details on the technical requirements of obtaining these signals, see the article in this issue by Ershler and Lux.

The process of validating inverse solutions is not trivial. In fact the theoretical and practical difficulties of validating inverse solutions have, we believe, been significant obstacles to wider acceptance and application of inverse solutions. One source of complication is the fact that validation mechanisms must take into account both the specific source models employed and the practical measurement problems. Researchers have adopted a variety of validation mechanisms, ranging from analytically tractable models, to experimental tank models, to validation against clinical diagnoses.

The best known uses of analytically tractable models in electrocardiology are the concentric and eccentric spheres models proposed by Bayley and Berry [76], developed extensively by Rudy, *et al.*, [25–27], and still in use today [56, 73, 77–79]. Although such models can serve as initial testing scenarios, too little is certain about the influence of actual anatomical structures to be able to apply confidently conclusions drawn from such studies to physiologic situations.

Another general approach has been to begin with measured or simulated source data (dipole models, epicardial potentials or activation wavefronts), forward compute synthetic torso data, add noise, and then apply inverse solutions. (The simulated source data can, for example, be calculated from dipole models [80], taken from the literature [81], measured in open chest or torso tank experiments [65, 72], or calculated by an initial inverse solution from measured torso surface data (among many, see [82, 44, 61])). The justification for using noisy forward-computed signals as synthetic observations is that the ill-posedness of the inverse problem ensures that the inverse solution will always have more error than the associated forward solution. Hence it may be reasonable to treat the forward solution as a generator of "practically perfect" torso potentials. One weakness is that the same forward solution is used for both the forward and inverse computations; this neglects the

effects of model error. A hybrid approach uses dipole sources to calculate both epicardial and torso surface potentials from the dipole model, but takes an explicit epicardial/torso forward model for the inverse solution. Since the dipole source and the torso potentials are used as boundary conditions for the computed epicardial potentials, the forward model does not match exactly the relationship between epicardial and noise-free torso potentials, thus introducing a model mismatch [44, 61].

Yet another approach has been to use physical models for validation. The earliest such formulations used current dipoles and multipoles embedded in conductive paper or suspended in electrolytic tanks [83–86]. More modern approaches measure potentials from both heart and body surfaces, either simultaneously using animal preparations or at separate times [29, 87, 31, 88, 72, 58, 65, 56, 89]. The most important early use of an animal model was by the group at Duke, where epicardial electrodes were chronically implanted in dogs and then, after healing, signals were recorded from epicardial and body surfaces [29, 87]. Electrolytic tanks shaped like a human torso, in which isolated, perfused animal hearts are suspended, have been widely employed. Perhaps the best known are the tank models developed by Taccardi, *et al.*, which continue to provide data for validation studies by several groups [31, 72, 58, 56]. There has been a recent resurgence of studies with electrolytic tanks, due largely to the availability of acquisition systems capable of measuring from thousands of sites simultaneously [88, 15, 41, 90, 91, 89]. The isolated heart/torso tank approach allows for unequivocal validation by recording from both epicardial and torso tank surfaces without the cost and experimental and ethical difficulties of chronic animal preparations. It also offers great flexibility in modeling and experimental control of physiologic conditions. This, in turn, facilitates the study of specific sources of modeling error such as heart location, torso geometry, and inhomogeneities under a variety of conditions such as ischemia, varied pacing sequences, tachyarrhythmias, and altered repolarization [88, 41, 90, 91, 89]. The main weakness of this approach is that it lacks some physiologic conditions, such as mechanical load on the pumping heart, interaction with the

autonomic nervous system, and realistic torso inhomogeneities, the importance of which in forward/inverse solutions is not yet clear. In a variation of the isolated heart preparation, researchers have experimentally validated the endocardial inverse solution by recording ventricular potentials using an "olive" electrode inserted into the left ventricle together with endocardial source potentials measured using transmural needle electrodes [15].

The final method of validation we will discuss employs clinical diagnoses or other *a priori* clinical information. Obviously, the difficulty with clinical validation is that direct measurement of cardiac sources is usually impossible, especially under closed-chest conditions. In lieu of direct validation, inverse solutions can sometimes only be evaluated based on our general knowledge of what constitutes a *reasonable* description of, for example, the activation sequence [17, 81]. Controlled interventions may also offer a means of qualitative validation as, for instance, during coronary angioplasty [92], in which the angiographic localization of the catheter balloon within the coronary circulation permits an approximation of the regions of acute, transient ischemia that follows balloon inflation. MacLeod, *et al.*, computed epicardial potentials from patients during angioplasty and compared locations of ST-segment elevations with the locations of the balloon catheter [93], an example of which is shown in Fig. 3. This figure contains isopotential maps from corresponding instants from two beats, one recorded before inflation of the angioplasty balloon (upper panel) and the other during the latter phase of the inflation of the left circumflex artery (lower panel). The epicardial maps were computed from the measured torso potentials using a realistic torso model, a boundary element solution, and regularization with a single, Laplacian constraint [93]. During inflation, anterior torso potentials become more negative than at rest while the posterior torso shows a broad positive area suggestive of ischemia, but too diffuse for localization. The computed epicardial potentials, on the other hand, indicate a very local area of positive potentials on the postero-inferior aspect of the heart, suggestive of local acute ischemia. The estimated epicardial ischemia zone lies just distal to the site of the angioplasty balloon, within the approximate perfusion

area supplied by the distal circumflex artery. While this validation result is encouraging, it is still very qualitative in nature, and contains unexplained anomalies such as a second area of positive potential in the atrial region, visible in the posterior view of the epicardium (lower right view in the figure).

Another recent example of direct clinical application and validation is the use of an inverse solution to predict sites of pre-excitation in Wolff-Parkinson-White patients based on body surface potentials recorded before their ablation procedures [65, 94]. Inverse-computed epicardial maps from the first 30 ms of the delta waves showed distinct minima that indicated earliest pre-excitation, especially for sites on the free wall of the left ventricle. Shahidi, *et al.*, performed detailed comparison of not only the site of pre-excitation, but also epicardial distributions recorded during subsequent ablation surgery. They had limited success in predicting the measured potentials with relative errors in the range of 100% and correlation coefficients from 0.22–0.34 [65]. They attributed these discrepancies to errors in geometrical reconstruction of the epicardial surface and the sock electrodes on that surface, as well as the effect of air exposure of the epicardial electrodes during the open-chest measurements. They also found that errors paradoxically *increased* with improved model resolution and the inclusion of inhomogeneities. The proposed reasons for this finding was that more detail in the model increased the ill-conditioning of the forward solution matrix.

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Conclusions

The considerable progress achieved in the inverse problem of electrocardiography over the last decade has provided grounds for optimism about the possibility of approaching significant clinically-relevant applications in the next decade. However, there are a number of basic questions which still remain. In addressing these questions, we feel it is important to seek solutions that emphasize physiological rather than mathematical significance. This leads to twin requirements for useful

inverse solutions: accuracy, defined in a physiologically meaningful (and not just averaged and mathematical) sense, and reliability, not only to measurement noise but also to geometric modeling errors and other uncertainties which are inescapable in a practical application scenario. Studies using analytically tractable models may still be relevant, but it seems more important to find solutions to practical inverse problems that move the field towards wider acceptance and credibility.

From the discussion above we suggest the following three questions as critically important:

- What are the advantages and limitations of UDL or breakthrough-based methods compared to potential methods? For example, under physiologically reasonable conditions, what useful information, if any, can be reliably extracted from reconstructed potentials that is not present in the activation-based models? How much less reliable are activation wavefronts reconstructed from the potential-based solutions than those estimated from an activation-model formulation such as UDL?
- What are the effects of approximations such as discretization error, spatial sampling density, and the effects of inclusion/exclusion of various conductivity inhomogeneities? How do these errors affect the accuracy and reliability of inverse solutions?
- What are the advantages and limitations of various regularization methods? What is the best way to include *a priori* information? How can we decide which constraints are the most useful to include? To what extent do the increased computational efforts of more recent methods increase accuracy and reliability?

One basic question that affects our ability to answer these questions, using any of the formulations we have discussed, is how to compare results quantitatively. How different is one isochrone map or potential map sequence from another? How do we determine whether, and to what degree, new solution methods are converging *toward* the correct solution or *away* from it? Experienced electrophysiologists tend to use qualitative measures based on visual inspection to determine the accuracy and validity of a map result. Even here tradeoffs between, say, accuracy in location and

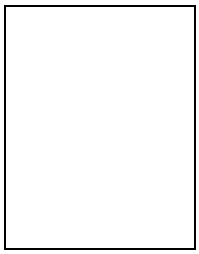
accuracy in amplitude of a wavefront or extremum are not well defined. At present, we have no corresponding, objective, quantitative metric to evaluate the difference between distributions, especially none that incorporates time and three-dimensional space in any physiologically justifiable manner. Most reports in the literature to date rely on cross-correlation or root-mean-square differences, which are clearly poor measures of the physiologically important features in a map or map sequence.

There are, however, notable examples of progress in developing useful inverse solutions, especially in the areas of improved regularization and the acquisition of realistic validation data. The very existence of such diversity of approaches in regularization—and the researchers pursuing them—can only improve the likelihood of one or more of them achieving the necessary breakthroughs. Every aspect of the process is under careful examination and whole new perspectives, influenced by fields such as signal processing, control theory, differential geometry, and optimization, have appeared in recent years. Of critical importance to evaluating these approaches is the availability of means of validation. The limited success of direct clinical validation, and the immense practical difficulty in obtaining and quantifying such results, suggest that this approach to validation of the inverse solution is somewhat premature if our goal is to answer the more basic questions raised above. Far more promising seem to be the validation techniques based on physical models of the torso in which realistic conditions can be sustained and at the same time offer simultaneous access to both source and remote potentials. Modern torso tanks are more realistically shaped than their predecessors, can be instrumented to a degree that was once impossible, and offer flexibility in volume conductivity, heart location and orientation, sampling density and arrangement, physiologic state of the heart, etc. The data from these experiments will soon be more easily available to inverse problems researchers and its widespread distribution could provide a consistent basis for direct comparisons among different modeling approaches. Validation based on clinical data will have to be very carefully controlled and evaluated, and compared to methods that employ body

surface map patterns directly [95, 96], to define limits of clinical utility.

The promise of the electrocardiographic inverse solution has been clear for a very long time; the amount of effort that has been invested in solving the inverse problem is a tribute to its desirability as well as its inherent difficulty. Existing solutions to the inverse problem do not yet deserve consideration as realistic clinical tools, but recent progress has been remarkable. Through synergistic efforts of modelers and experimentalists, further progress and eventual success seem assured.

Authors' bios



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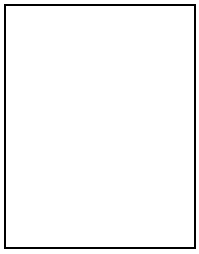

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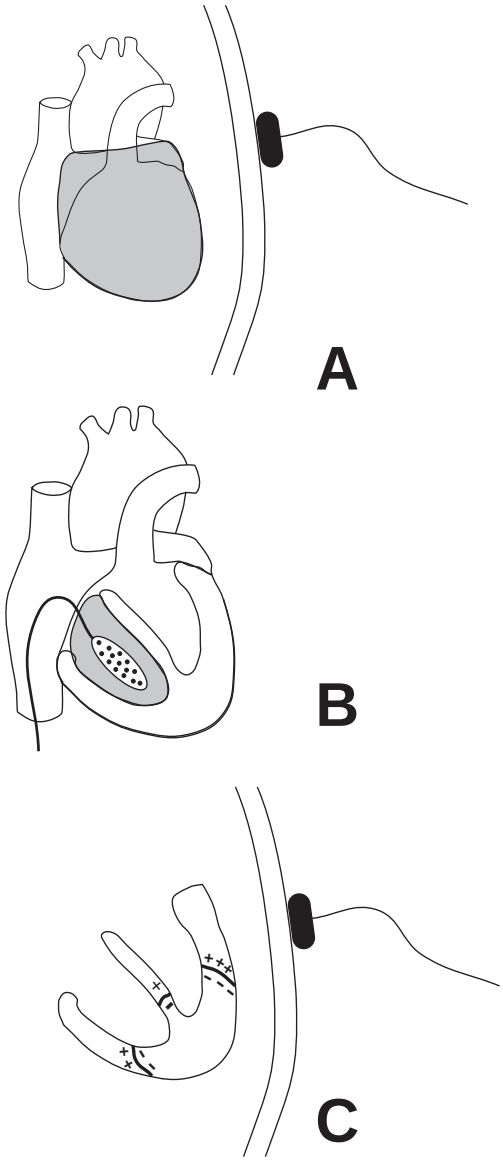

Fig. 1. Inverse problem formulations. Panel A shows the potential based formulation for epicardial potentials (shaded area) and measurement electrodes on the body surface. Panel B shows a potential based formulation where endocardial potentials are the source and measurement electrodes are mounted in a catheter probe. Panel C represents the UDL formulation, in which the activation wavefront serves as the source.

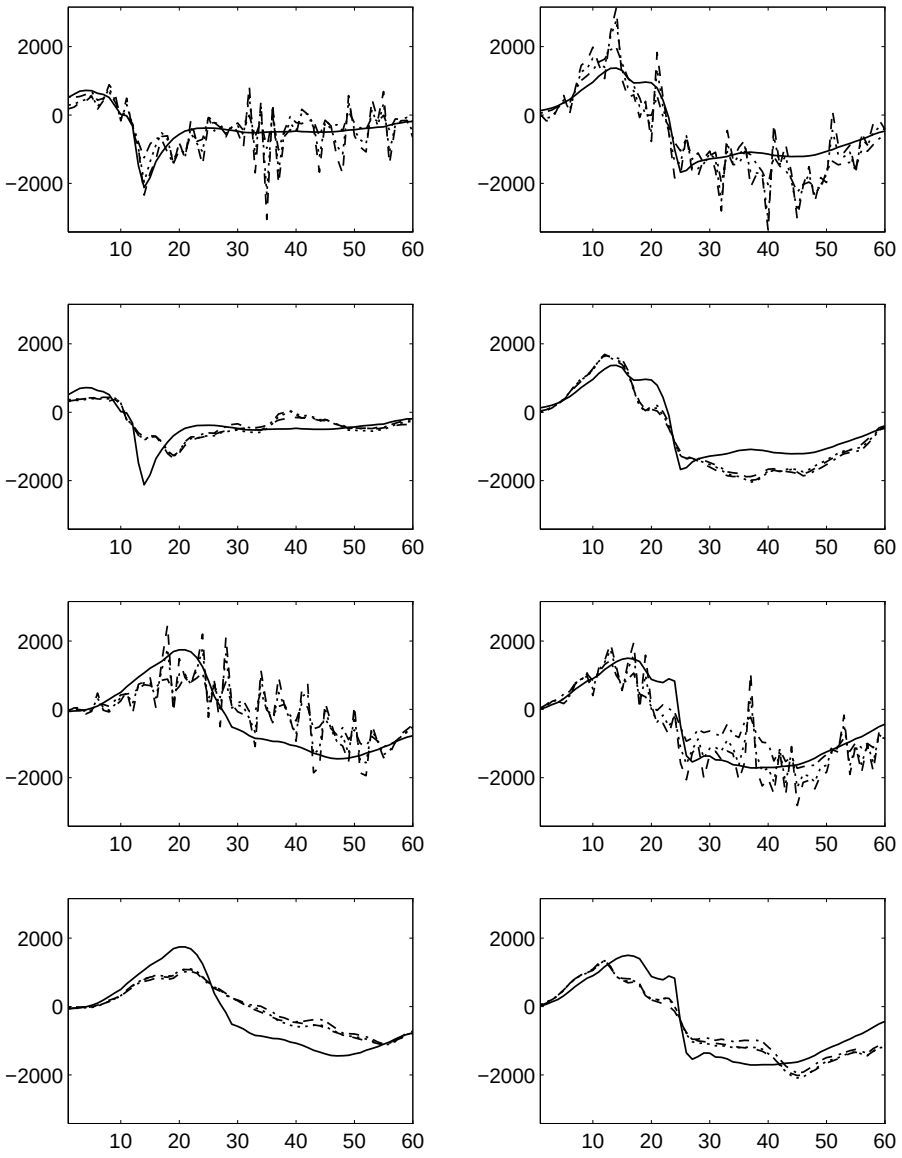

Fig. 2. Comparison of spatial to joint spatial and temporal regularization: Four epicardial electrograms are shown for 60 ms during QRS. The first and third rows contain results from spatial regularization, the other rows joint time/space regularization. In each panel the solid line is the original electrogram and the other lines correspond to various regularization parameters.

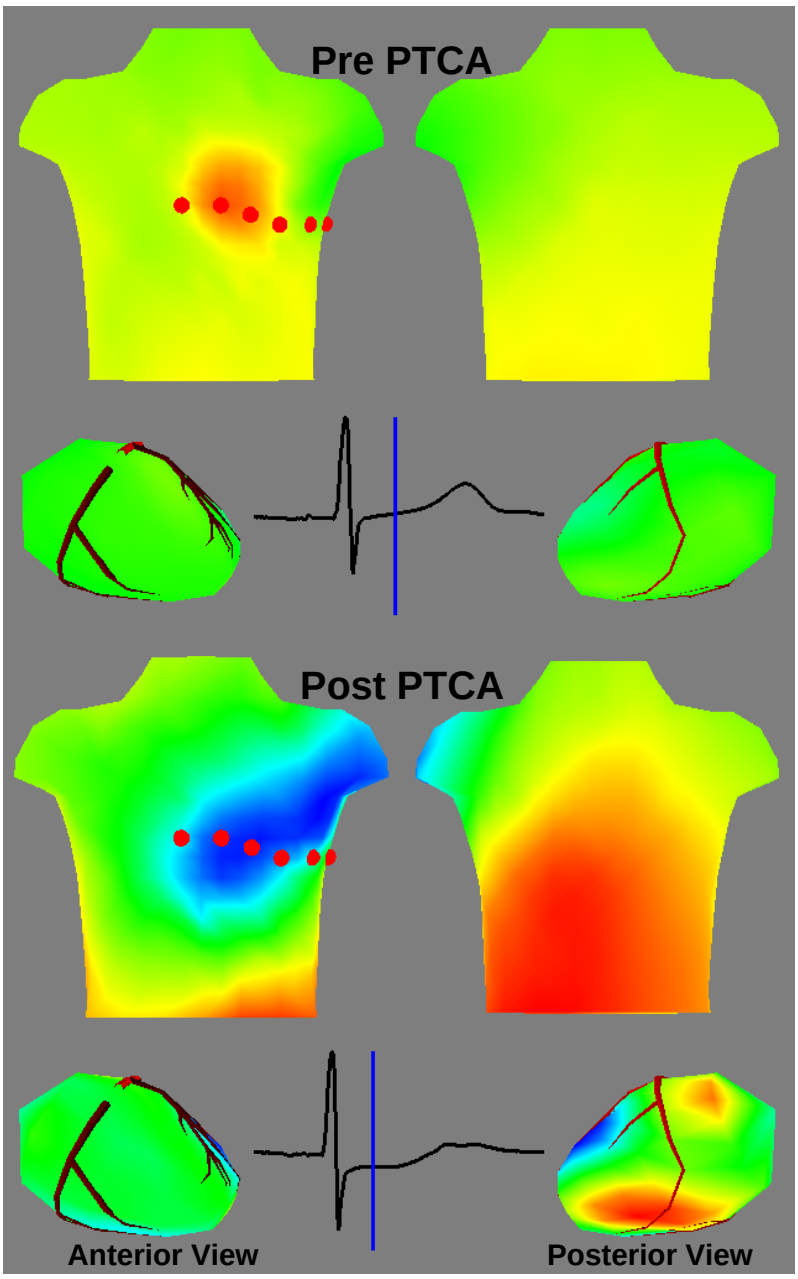

Fig. 3. Inverse solution validation using maps from angioplasty patients. The upper panel contains measured body-surface and inverse-computed epicardial potentials from a single instant (marked by the vertical line on the ECG) during a beat recorded before inflation of the angioplasty balloon. In the lower panel, corresponding maps from the peak phase of the angioplasty inflation show the effects of acute occlusion of the left circumflex coronary artery (balloon location marked by arrow). The left-hand column shows the anterior views of both torso and epicardium, while the right-hand column shows the posterior views. Circles in the anterior torso views indicate the locations of standard leads $V_1 - -V_6$. Color represents electric potential in a scale the goes from blue (most negative) through green, yellow, and red (most positive).