Validation approaches for electrocardiographic inverse problems

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Abstract

The topic of this chapter is the validation of electrocardiographic inverse problems. We describe three different approaches to validation: purely computational methods, physical and animal experiments, and validation from measurements on humans. Computation methods are typically the easiest to control and the most straightforward to implement and use, but they are limited in their fidelity to real conditions. Physical and experimental models have the richest history and provide somewhat more limited control but approach reality through the use of torso-shaped electrolytic tanks, animal hearts, and even completely instrumented whole-animal preparations. Validation based on human measurements are very difficult to control and present many measurement challenges. However, they represent the most realistic conditions and thus have great relevance. All three approaches are in common use and development today and have a role in rigorous validation schemes. We conclude with a description of some of the remaining challenges to validation as well as some recent developments that suggest imminent significant advances.

1 Introduction

In this chapter we address the topic of validating the performance of electrocardiographic inverse solutions. A well-defined and carefully implemented validation scheme is critical to the evaluation of any numerical method. The main goals of validation are typically to assess the accuracy, speed, reliability, and any other special characteristics of the method, as well as explore its utility in practical applications. The nature of the electrocardiography problem makes validation especially challenging. It is difficult to obtain ground truth measurements for comparison under conditions that faithfully replicate, or even approximate, useful application scenarios. At the same time, the complex nature of the source, the ill-posedness of the inverse problem, and the resulting numerical sensitivities and instabilities all add to the difficulties. Moreover, the very problem of defining what is a physiologically or medically relevant goal is a challenge in itself. Thus, from the perspective of validating an inverse solution that is applied to a patient, there is ambiguity in the interpretation of the results and thus difficulty in defining an appropriate error metric.

We begin with an outline of the necessary elements of a validation approach, a framework that we will apply repeatedly throughout the chapter. We then return to the topic of interpretation of inverse solution results and the resulting ambiguities that may arise.

Inverse solutions are based on a representation of the relevant geometry and a description of the sources one wishes to reconstruct. Examining a validation strategy, therefore, begins with an evaluation of these two main required elements of an inverse solution: a model of the geometry and a model of the relevant cardiac sources. Geometry information comes in two forms: simplified models, based on continuous functions such as spheres or cylinders, or more often discrete models from measured locations of electrode positions and points describing the anatomy of the thorax, heart, and, where appropriate, torso inhomogeneities. These points may lie only on the surface of the relevant organs or may span their interior. Obtaining geometry for validation often requires medical imaging techniques, segmentation of the tissue boundaries, and geometric model construction, with each step contributing some (hopefully known) error to the final result. Validation studies often include varying specific parameters such as resolution and accuracy of the geometric measurements, inclusion of inhomogeneous regions, and any anisotropy in the conductivity assigned to each region. The more control that is available over these parameters, both in the inverse problem formulation and the validation model, the more complete the testing that is possible. Validation can then expand beyond simply testing the accuracy of a particular inverse solution to general questions of what resolution, precision, or complexity is required of a geometric model to achieve a desired accuracy.

The second requirement for validation is a description of both the bioelectric source, in whatever form is dictated by the inverse solution formulation, and the remote signals, typically the body surface potentials, or catheter potentials for inverse solutions based on intracavitary potentials. It is the requirement for an accurate source description that generally poses the most difficult technical problem, because it often requires measurement of epicardial or endocardial potentials or cardiac activation times. Such measurements are often infeasible to make in humans and present considerable challenges even in animals. For example, opening the chest to access the heart will disrupt the torso and thus impair simultaneous cardiac and body surface measurements as well as create non-physiologic conduction conditions in the torso interior. As we shall see, the form of source information can be quantitative, based either on synthetic data or actual measurements, but also qualitative, often based on a particular electrophysiological feature available by means of other, non-electrical forms of measurement, invasive procedure, or prior medical history. Examples of these three source types are, respectively, echocardiograms from ultrasound, electrograms from cardiac catheterization, or knowledge of prior myocardial infarction from medical history. Combinations are obviously possible, too, such as medical history information based on previous invasive procedures.

A general consideration in obtaining both geometry and source descriptions for validation is the need to attach to each value an estimate of the accuracy with which it was obtained. For instance, if geometric

measurements are only accurate within an error of 5 mm, then it is unreasonable to expect an inverse solution based on that geometry to have a spatial error that is any lower than 5 mm. Similarly, if ground truth source measurements are only accurate to within a given noise figure, then this places a lower bound on the accuracy of any comparison with computed inverse solutions. More generally, the error assigned to each measurement determines by some means, not usually as direct as the examples above, the limit in accuracy that can be reasonably expected from any inverse solution based on those measurements. In the case where geometric and/or source data is synthesized rather than measured, it is necessary to add noise prior to inverse calculations to simulate some degree of realistic conditions. Moreover, a study of the way the solution accuracy changes with variable amounts of noise can become a valuable part of the validation procedure.

There is another aspect of validation for inverse solutions that leads to both ambiguity in the interpretation of results and additional approaches to the validation problem. One obvious gold standard of validation for electrocardiographic inverse solutions might be to reconstruct the source signals, for example, the epicardial potentials, over the entire heart, in a human subject, with near perfect fidelity. Practically, this is an impossible standard because such a detailed measurement of the source is not possible in humans. Even if it were technically and ethically possible, however, there would be another ambiguity with such a comparison. Common mathematical formulations of the error in inverse solutions may not have a clear relationship to the true criteria of interest, diagnostic accuracy and precision. Even qualitative accuracy measures, such as examination of isopotential map sequences or the excitation pattern of a premature excitation, have a certain clinical ambiguity; sufficient accuracy for a general diagnosis, for instance, may not be sufficient accuracy for a remediative procedure such as cardiac ablation. Hence, to validate an inverse solution requires a clear idea of the anticipated application and a set of associated requirements. There is no single gold standard, which is fortunate given that the obvious standard is not available.

A related practical challenge associated with validation of inverse problems is the immense range of different types of tests possible for a given formulation. One strategy with which to achieve a workable subset is to focus on the effects of specific parameters, for example, features of the geometric model such as resolution and accuracy. One can also select a specific type of source according to a particular application or related set of applications. It may be adequate to detect and localize a particular feature of the source that does not require an entire heart beat as, for example, when attempting to locate ischemic regions of the heart [1, 2] or sites of earliest epicardial activation for diagnosis of ectopic arrhythmias [3]. What is essential to note in any validation strategy is that results achieved in one configuration or for one instant in time do not necessarily extend to other conditions or times [4].

We continue our discussion with a review of a number of validation approaches that have been previously employed for electrocardiographic inverse problems. We organize these approaches in terms of physical models, purely computational techniques, and clinical experiments. The goal of the discussion is to make the reader aware of the specific requirements of validating electrocardiographic inverse solutions, and to suggest a range of feasible approaches that overcome at least some of the obvious obstacles to human validation.

We apologize at the outset to the authors whose work we have not cited. The literature on validation strategies for electrocardiography spans at least 60 years and we will inevitably have missed some of it.

2 Analytical and computational validation models

The traditional method of validating a simulation is to identify a problem that is simple enough that an analytical or closed form solution exists. Then one can compare a numerically computed solution with the analytically known true result. At a minimum, comparison of results from the analytical and numerical

solutions can be useful for identifying fundamental problems with either the concept or the implementation of the more general numerical approach. Because of their simplicity, however, analytical solutions may provide data that establish only a *useful* set of validation criteria, but clearly not a *sufficient* set. Any tenable numerical approach must mimic the analytical result, but this is not enough to ensure accuracy of the numerical approach under other, more realistic conditions. Computational cross validation may also be possible in cases in which two separate numerical or computational approaches can solve the same physical problem. Here, too, the range of applications of one of the computational approaches may be limited so that validation is incomplete. For example, one can implement a discrete source simulation to generate potentials on both heart and torso surfaces and use the results to cross validate a different inverse solution that computes heart potentials from torso potentials for *any* source. The surface-to-surface solution is then validated only for the dipole source and not for the broad range of applications for which it was conceived. We provide more examples of both these approaches in this section.

One significant advantage of most analytical or computational validation approaches in inverse problems is the relative ease with which one can control the essential factors such as geometric accuracy or level of detail and—sometimes to a more limited extent—the source configuration. In general, on the other hand, the geometry must remain simple in order for the analytic solution to exist. Even for simple shapes, it is sometimes possible to vary aspects of the geometry to at least begin to approach some aspects of realistic conditions and thus permit some general statements about the associated cardiac conditions. For example, one can use sets of nested spheres to represent external and internal boundaries in the volume conductor and then vary the conductivity assigned to each region. Rudy *et al.* have shown that one can also impose some eccentricity to the position of the spheres and thus suppress some of the complete symmetry that limits concentric sphere models [5,6]. The ease with which one can handle the second, more difficult requirement for validation—the availability of source values and remote measured potentials—is the main attraction of these methods; however, fidelity to biological conditions is often quite limited.

The best known analytically tractable models in electrocardiology are the concentric and eccentric spheres models proposed by Bayley and Berry, [7–9] developed extensively by Rudy *et al.*, [6,10,11] and still in use today [3,12–16]. Rudy *et al.* used these models for more than simply validating their numerical solution. By varying source types and locations and geometric model eccentricity, error, and conductivity, as well as regularization functionals used for the inverse solutions, they developed several more fundamental hypotheses about the relationships between each of these factors and inverse solution accuracy. Some of these ideas have subsequently been validated by physical models and human clinical studies. However, the basic limitation of analytical models based on simple geometries remains the uncertainty about the influence of real anatomical structures. This, in turn, restricts the application of conclusions drawn from such studies to realistic physiologic situations.

One validation approach that permits more realism in the geometric model is to begin with simulated or measured source data, and then place them in a realistic, discrete geometric model. These sources and a numerical forward solution then provide synthetic torso data to which one can (must) add noise, and then apply inverse solutions. Validation then consists of comparing the inverse solutions to the known sources. The simulated source data can, for example, be calculated from dipole models, [17,18] taken from the literature, [19] measured in open chest or torso tank experiments [20–25] (see next section), or calculated by an initial inverse solution from measured torso surface data [26–30].

The justification for this rather suspiciously circular validation strategy comes from the fact that electrocardiographic inverse solutions are much less accurate than the associated forward solutions. The main challenge of the inverse problem, in fact, is to succeed in restoring some portion of the accuracy of the associated forward solution, despite the fact that the inverse problem, unlike the forward problem, is ill-posed. Thus it is reasonable to validate an inverse solution with data that best matches the forward solution. Based on validation studies with analytic solutions, [11] it is probably safe to assume that the errors

that arise in constructing a geometric model derived from a patient or animal play a much larger role than those from the numerical methods used in the forward solution. Additional errors such as movement during mechanical systole simply compound the problem. By forward computing the torso potentials, one can reduce—or at least control—errors due to geometry because these errors are present in the forward solution. This strategy makes it possible to focus the validation studies on the errors that arise in the step of creating the inverse solution from the forward solution, which is the major challenge in electrocardiographic inverse problems.

One weakness of this approach is that it neglects the effects of any errors in the problem formulation, i.e., the equations used to describe the relationship between sources and remote potentials. This omission occurs because the same problem formulation is used in both the forward and inverse solutions. There is a hybrid approach that uses dipole sources to calculate both epicardial and torso surface potentials directly based on a realistic geometry, but uses an explicit epicardial to torso surface forward model, based on a different formulation, to generate separate surface-to-surface forward and inverse solutions. Because the two formulations are different, the dipole source forward model does not match exactly the surface-to-surface model. One can then compare the directly against the inversely computed epicardial potentials and perform cross validation [18,31]. This model mismatch can reduce at least some of the symmetry inherent in other computational approaches and potentially provide less biased validation conditions, but, of course, is limited to simple dipolar source models.

A more realistic hybrid approach is that described by Hren *et al.*, in which the source was not a dipole, but a cellular automata model of cardiac propagation [32–34]. Cellular automata models represent cardiac tissue as a regular mesh of "cells", each representing a region of approximately 1 mm^3 and use simplified cell-to-cell coupling and state transition rules to determine the activation sequence. Although not as detailed as the monodomain and bidomain models that are based on descriptions of membrane kinetics, cellular automata models have a long history in simulations of normal and abnormal cardiac activation [35–45]. In order to apply cellular automata models to validation of electrocardiographic inverse solutions, Hren *et al.* developed a method with which they assigned electrical source strength to the activation wavefront and were thus able to compute epicardial and torso potentials from the cellular automata model for realistic geometric models of the human torso [32,46]. They used this technique to both validate inverse solutions [33] and to examine the spatial resolution of body surface mapping [47,48].

An obvious, significant strength of the computational and analytical approaches is that they do not require the expense and extensive infrastructure of experimental studies, but can all be performed on a computer using methods that are well described in the literature. Moreover, as the examination of the results leads to new hypotheses to test, requiring new data, it is obviously easier to repeat a computational experiment after modifying the conditions or changing parameters than it is to have to modify and repeat experimental studies.

3 Physical and animal validation models

Long before it was technically possible to create computational validation methods, experimentalists developed physical and later animal models that provided insight into inverse problems and the entire field of electrocardiography. With the advent of modern data acquisition systems and computer storage and signal processing, these experimental approaches have become more detailed, more elaborate, and more similar to human-based validation. In this section, we provide an overview of the development of experimental models from the middle part of this century up to the present day and illustrate the strengths and weaknesses of this approach.

Experimental validation studies can involve animal preparations, completely synthetic physical mate-

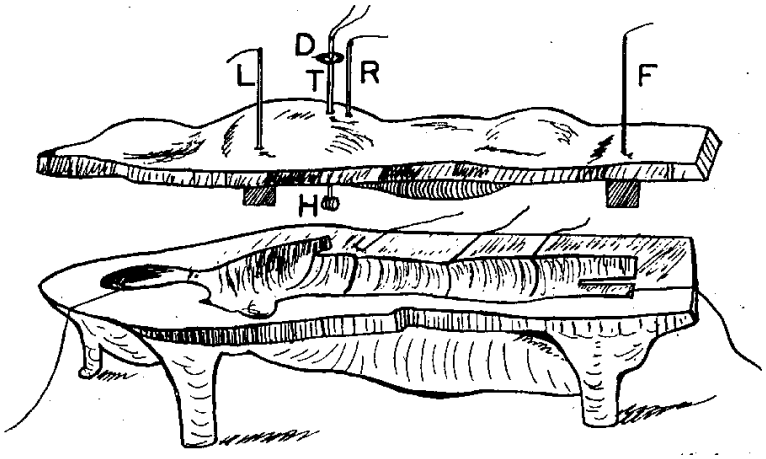

Figure 1: Electrolytic tank from Burger and van Milaan, (from *British Heart Journal*, **9**, 154–160, with permission)

rials, or even a combination of the two in order to simulate the ideal conditions of cardiac sources inside a human thorax. Given the technical challenges of measuring source parameters and geometry from animal models, it is no surprise that most of the earliest forms of validation in electrocardiographic inverse problems used synthetic electrical sources embedded in conducting media as a way to obtain controlled physical models of the heart and torso. Early implementations of these models used a current bipole to simulate the source because it is a direct equivalent of the single heart dipole vector that still serves as the basis of much of clinical electrocardiography. Later experimental validation models have made increasing use of biological tissues, either an intact animal with implanted instrumentation, or an isolated animal heart placed in a synthetic volume conductor that simulates a human thorax.

One of the earliest and certainly most thorough evaluations of a physical model based on a single bipolar source in a realistically shaped three-dimensional torso model was that of Burger and Van Milaan [49,50]. The physical model of the torso was an electrolytic tank made out of a michaplast shell molded on a statue of a supine human. The tank split horizontally to provide access to the interior, which was filled with copper sulfate and equipped with copper foil electrodes fixed to the inner surface (see Figure 1). Their heart source model was a set of copper disks oriented along one of the body axes and adjustable from outside the tank by means of a rod. The first model used only the electrolyte as the homogeneous volume conductor [49] but subsequent versions incorporated inhomogeneous regions constructed from cork and sand bags for spine and lungs, respectively [50].

The form of the inverse solution that Burger and van Milaan validated—derived, in fact—from their physical model differed from the more general formulations described elsewhere in this volume. They sought to describe the potentials measured from the limb leads on the body surface as the scalar product of the heart vector and a vector of weights (the "lead vector"), an early description of what later became known as "lead theory" (see e.g., Horáček [51] for a recent review). By fitting their measurements of limb lead potentials for known heart vector positions to a simple linear equation, they were able to derive both algebraic and geometric forms of this relationship for each of the standard limb leads. Validation also included repeating the derivation after including various inhomogeneities in the tank and observing the effect on weighting coefficients.

A pair of later studies of electrocardiographic lead fields using more simplified physical models was from Grayzel and Lizzi, who used conductive paper (Teledeltos) to create two-dimensional inhomogeneous models of the human thorax to which they attached current source/sink pairs (bipoles) to represent the heart

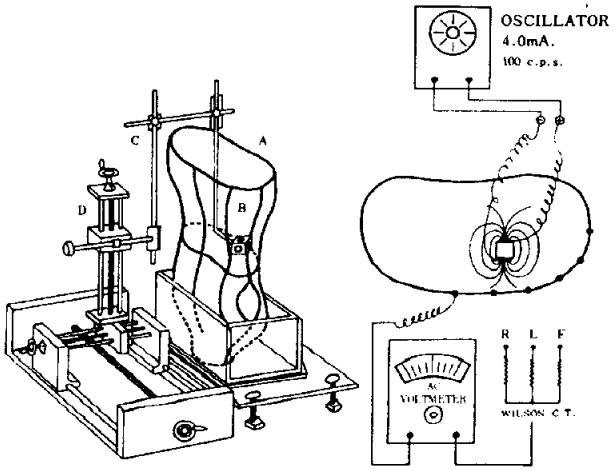

Figure 2: Electrolytic tank from Nagata (from *Japanese Heart Journal*, **11(2)**, 183–194, with permission)

[52,53]. The advantage of this approach was the ability to control the extent and value of inhomogeneities by means of perforations or silver spots applied to the conductive paper. Their results indicated that the relationship between source location and body surface, as expressed by the lead field, was more variable and complex in the inhomogeneous than the homogeneous torso. More importantly, these investigators showed a sharp deterioration in performance of several standard lead systems after adding inhomogeneities to their torso model.

Nagata later described several further refinements of artificial source/medium models and subsequently introduced the use of biological sources [54,55]. In a preliminary study, Nagata placed a bipolar source in 27 different locations and measured the torso tank surface potentials at electrode sites equivalent to eight different lead systems in common usage at that time [54]. Like Burger and van Milaan, Nagata used a torso geometry based on a three-dimensional human thorax (see Figure 2) and made measurements both in the homogeneously conducting tank as well as (in a subsequent study) with inflated dog lungs and agar gel models of human lungs inserted into the tank [55]. In this later study, Nagata made a significant step in validation studies by replacing the synthetic source with a perfused dog heart, thus achieving a much higher degree of realism than available with simple current bipoles. The goal of his work using the bipole source was to derive the lead vector—expressed here as the "impedance transform vector"—from measurements over a wide variety of bipole source locations and lead systems. A second goal was to evaluate the effects of torso boundaries and inhomogeneities on the shape of the lead vector field (for the bipole) and on the torso tank potentials (for the isolated heart). The limitations of this study lay in the lead field approach, which represents the heart as a single dipole, rather than a distributed source of bioelectric current. Nagata therefore had no means of describing the real heart quantitatively and did not measure cardiac potentials directly. Instead, his study focused on the relationship between ECG signal parameters such as R-wave amplitude and signal morphology and the presence or absence of torso inhomogeneities.

De Ambroggi and Taccardi described a two-dimensional form of the physical model approach in which they examined in great detail the electric field of two bipolar sources in a shallow circular bath [56]. Their aim was to establish whether it was possible to characterize sources composed of two eccentrically placed bipoles based on potentials measured at sites distributed throughout the bath. Hence it was not a validation of a quantitative inverse solution but more a qualitative evaluation of the relationship between cardiac sources and body surface potentials. A three-dimensional animal source study with similar aims was subsequently performed by Mirvis with rabbit hearts placed inside spherical electrolytic tanks [57].

Perhaps the first true validation of a computed inverse solution was by Ideker *et al.*, who created small epicardial burns in isolated rabbit hearts and then suspended each heart in a transparent, spherical electrolytic tank [58]. The goal of their inverse solution was to determine the location of the burns and also of discrete epicardial pacing sites by assuming that each represented a dipolar source that could be localized with an equivalent source model. To validate the accuracy of their computed locations, the investigators used visual measurements to determine burn location relative to the electrodes embedded in the clear epoxy surface of the sphere. The accuracy achieved with this approach was in the range of 3–4 mm differences between predicted and measured locations.

Mirvis *et al.* carried out a sequence of studies using a variety of discrete sources to represent not only the location of injury, but of the entire cardiac cycle [59, 60]. As the geometric model, they used a spherical electrolytic tank of 6.35 cm diameter with 32 embedded electrodes. The sources were isolated rabbit hearts suspended near the center of the sphere. They found that a single moving dipole was not an adequate representation of the heart's electrical activity but that any of three different higher order discrete sources they tested did virtually equally well at reproducing the potentials on the surface of the tank in which the hearts were suspended. The important result of this study was to demonstrate on an experimental model that the single heart dipole model of electrocardiography was incomplete. A new source description was necessary.

It was Barr *et al.* who provided the new source description when they proposed representing the heart in terms of the epicardial potential distribution [61, 62]. This also led to a new series of validation studies based on this formulation, the first of which Barr *et al.* carried out, not using an electrolytic tank, but instead a complete instrumented animal model to validate their inverse solution [63]. This preparation included surgical implantation of 75 epicardial electrodes, re-closure of the chest wall in order to restore the integrity of the thoracic volume conductor, and after a two-week recovery period, measurement of both epicardial and 150 body-surface potentials with a 24-channel acquisition system. To record geometric information, the thorax of the animal was later sliced and photographed to create a model consisting of the electrode locations on the epicardial and torso surfaces. This landmark study provided data that have been used by several other investigators to validate their inverse solutions [64, 65]. The major limitation of this validation model was that the spatial resolution of the geometric model was modest (the geometric model consisted of only the electrical measurement sites). Furthermore, because of the limited number of recording channels available (20), the potential measurements were performed in sequence and then time aligned, increasing the risk that changes occurring on a beat to beat basis or over the time of the measurements would be captured in only a subset of the recordings.

Only very recently has the complete, instrumented animal preparation been repeated in studies reported by Chengand and Pullan, in which they recorded simultaneous epicardial and torso surface potentials from an acutely instrumented pig [66]. Rather than measuring the geometry from each one of their animals, they have fitted a set of Hermite polynomial finite elements to the tomographic scans of a single animal and developed a scheme with which to fit this model to all subsequent subjects. Complete results of these validation studies have not yet been published.

Most of the experimental model validation studies performed since those of Barr *et al.* have been of the hybrid type pioneered by Nagata using an isolated heart either with an electrolytic tank [3, 21, 23–25, 67–79] or with endocardial and catheter measurements for the endocardial inverse solution [80–82]. The main advantages of this type of preparation over instrumented whole animal experiments are the relative ease of carrying out the experiments and the increased level of control they provide. The isolated heart is more directly accessible when suspended in an electrolytic tank, which permits manipulations of its position, pacing site, coronary flow, temperature, etc., as well as the injection of drugs. The simplified geometry of the (usually homogeneous) tank also makes constructing customized geometric models simpler and faster than when a complete medical imaging scan is required for a whole animal.

The experimental validation study which has had the greatest impact to date used an isolated heart preparation suspended in a cylindrically shaped electrolytic tank, a preparation developed by Taccardi to validate inverse solutions generated by Colli Franzone *et al.* [67–70]. The source potentials for this study were recorded from 122 electrodes mounted in a rigid cage in which the isolated heart was suspended, and the cage, in turn, placed inside the torso tank, which contained 156 electrodes. To provide some variety of sources, validation of the inverse solution was based on three different activation sequences (one atrial and two ventricular pacing sites). The data from this study have been used by other groups to validate their own inverse solutions [12,21]. One possible limitation of this study was the fact that potentials were measured up to several centimeters away from the heart surface, which resulted in smaller spatial gradients and thus an "easier" case against which to validate the inverse solution.

Soucy *et al.* conducted a similar study, but used an isolated dog heart from which they measured the potentials directly from the epicardial surface by means of a 128-electrode sock [71]. Another key element of their validation strategy, which we described in the previous section, is that they used the measured epicardial potentials to compute torso potentials with a forward solution and used these as the input signals for the inverse solution. This approach, with noise added to the resulting forward computed torso potentials before applying the inverse, has been used by many other investigators [12,23–25,75–77]. Soucy *et al.* found that forward computed and measured tank potentials were fairly similar (correlation coefficients of 0.95 and relative errors of 29%), but that inverse solutions computed from the measured potentials were dramatically worse than those computed from the forward computed signals.

A contemporary example of the isolated dog heart and human shaped electrolytic tank preparation is shown in Figure 3. This preparation uses a second dog to provide circulatory support for the isolated heart, which achieves very stable physiologic conditions over many hours. With the isolated heart it is also possible to cannulate individual arteries and then regulate the coronary flow rate, blood temperature, and the infusion of cardioactive drugs in order to examine the effects of physiologic change on forward and inverse solutions [74,78,83–85]. Rudy and a number of collaborators have used data from this preparation to validate their inverse solutions for the specific cases of locating sites of early activation [3] and reconstructing the effects of myocardial infarction [25]. A group including MacLeod, Brooks, and Ahmad has examined the behavior of the inverse solution under a variety of conditions including different pacing protocols, physiologic interventions, torso inhomogeneities, and geometrical arrangements with ever finer spatial measurement resolution, as well as developed novel inverse solution methods [23,74,78,85,86]. Oostendorp *et al.* have used this preparation to validate an inverse solution based on epicardial and endocardial activation times [87].

We conclude this section with a brief summary of the strengths and limitations of physical and animal models for validation of electrocardiographic inverse problems. We concentrate on the most popular and perhaps successful of these approaches, using animal, primarily canine, hearts as sources inside electrolytic torso-shaped tanks. The most significant utility of this approach is the ability to include a high level of realism and yet maintain adequate control over the relevant parameters. The tank or phantom can take on virtually any reasonable shape using modern rigid materials and can be instrumented with an almost unlimited number of recording electrodes located both on the surface and within the volume of the tank. The isolated animal heart provides a very realistic and versatile bioelectric source, which can be instrumented extensively and manipulated to mimic many pathologies. The physical component of the model permits variation in parameters such as conductivity or geometry of the volume conductor, both of which can be altered quickly during the experiment. This isolated animal heart preparation does require considerable experimental expertise and the multichannel acquisition systems represent a significant investment in electronic and computational resources, although the difficulty lies more in the lack of commercial systems than the overwhelming difficulties of the technology.

One specific technical challenge that can generate significant errors is the measurement of geometry.

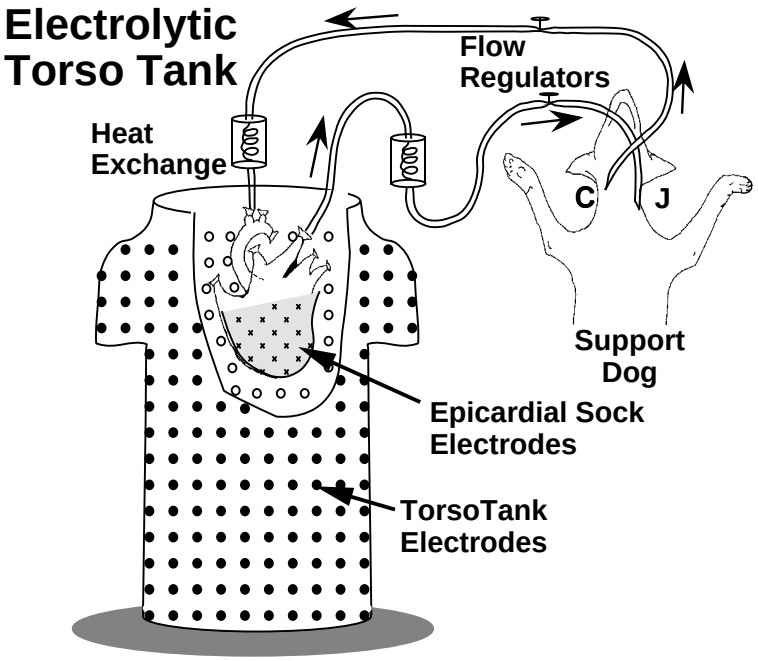

Figure 3: Torso tank apparatus originally devised by Taccardi with an isolated, perfused dog heart suspended in the electrolytic tank. Recording electrodes consist of 192–384 tank surface electrodes and a 64–490 lead epicardial sock array.

The coordinates of the electrolytic tank and the electrodes embedded in it are usually recorded carefully at the time of construction and are seldom altered. The heart, on the other hand, has a different shape, location, and electrode arrangement for each experiment, all of which must be measured in order to construct specific forward and inverse solutions. Acquisition of geometric information typically involves two components, the heart geometry and the location of the heart relative to the electrolytic tank. Only rarely do researchers have access to large scale tomographic imaging systems in the animal lab to acquire both components simultaneously so that, normally, they measure the heart location in the tank first, then remove the heart for detailed imaging or anatomical measurements.

One way to establish heart location in the tank is to take multiple distance measurements from landmarks on the heart to known sites on the tank and triangulate the heart locations or to take direct measurements of heart and tank with mechanical digitizers. One source of error in these measurements arises because the electrolyte must usually be drained from the tank before performing the measurements so that the heart takes on a different position in the tank. For measuring the detail of the heart itself, mechanical digitizers as well as medical imaging devices are commonly available. A final step is to align the detailed heart measurements with the torso tank geometry based on landmark locations measured in both reference frames, a process known as "registration". For this, there exist different linear and even non-linear algorithms, the best known of which is the Procrustes method [88, 89]. In Procrustes fitting one computes a rigid transformation (optionally with scaling) that is optimal in a least squares sense. This approach provides several error metrics (mean, maximum, and variance of the distances between landmarks after fitting) that can be used to guide the interpretation of subsequent validation errors. A persistent limitation of any measurement of the heart is that depending on the technique used, the heart may not be perfused as it is measured and so undergoes changes in shape and size. A further source of error is the fact that the heart, of course, changes its shape quite dramatically during each contraction.

And as with all findings based on animal models, great care is required in extending any validation

results from an animal model to the case of humans and clinical applications. The isolated heart contracts, but against no mechanical load. The mechanical behavior of the heart is further altered because it hangs freely in the electrolyte without pericardium or the constraining influences of other organs. There is also no autonomic nervous system present in the isolated heart so that many responses to external physiological influences may be either blunted or exacerbated, depending on the mechanisms involved. Likewise, the perfusion conditions of the heart are greatly altered because even when the isolated heart is not contracting fully (or at all), perfusion of the coronary arteries is maintained because it is driven by the support animal or external mechanical pumps. This external perfusion is especially relevant when one wishes to follow the response of the heart to acute myocardial ischemia, which in the intact animal will lead to a local reduction in contraction and a build up of metabolites and electrolytes [90]. This response will change in poorly defined ways under the conditions of the isolated, externally perfused heart. All these obstacles provide motivation for the human-based validation studies we discuss below. As with any experimental studies, because measurements are involved, there are also inevitable sources of error that cannot be completely controlled, a limitation not experienced in the computational validation approaches described in the previous section.

4 Clinical validation models

The final class of validation methods we will discuss manages to circumvent the limitations of human-based measurements by identifying clinical diagnoses or other *a priori* clinical information that can serve as (sometimes indirect) measures of electrocardiographic variables. The first requirement of validation in inverse electrocardiography, obtaining accurate geometric information, is possible through the use of modern medical imaging. Magnetic resonance (MR) and computed tomography (CT) are the two complementary techniques that provide the required spatial resolution as well as a means of identifying inhomogeneous regions (soft tissue from MR and bone from CT) from variation in image intensity. An important requirement of some medical imaging modalities for cardiac applications is the need to time the acquisition of data with the cardiac cycle. Temporal resolution of MR imaging, for example, is not yet adequate to sample the entire heart region within the diastolic interval of the heart so that multiple images gated to the ECG must be sampled and combined. A full gated MR tomography of the thorax can take many minutes to complete so that variations in cardiac shape can lead to errors in the resulting geometric models. Chest movement associated with breathing is another source of error in ECG-gated scans because the respiration cycle is independent of heart rhythm even as it couples via the diaphragm and lungs to alter heart position (see, for example, Pflugfelder [91]). The acquisition of accurate patient geometry remains a significant obstacle to application of inverse solutions to clinical settings. One consequence is the intense research interest in determining how dependent inverse solution results are on geometric accuracy, and how best to approximate that geometry with less time, effort, and cost [10, 28, 92–94].

Even with good quality tomographic images, the conversion to discrete geometric models is not a trivial undertaking. The first step is to identify contours that mark the boundaries between regions of interest, known as "segmentation", a subject which is the topic of ongoing research (see, for example, Hinshaw and Brinkley [95] or Calabi *et al.* [96]) and for which no reliable completely automatic scheme exists. From these contours, it is then possible to construct triangular surface meshes [97–100] or volume meshes from tetrahedra [101–105, 94] and hexahedra [106]. At present, construction of a detailed human geometric model still requires considerable technical expertise and time but is a feasible undertaking.

Obviously, the real difficulty with clinical validation lies in the second requirement—direct measurement of cardiac sources at an adequate spatial resolution is usually impossible, especially under closed-chest conditions. Some investigators have carried out inverse solutions and compared the signals at selected epicardial sites to measured electrograms from individual electrodes implanted chronically in patients [106, 107].

Budgett *et al.* recorded from six electrodes attached to the epicardium during coronary bypass surgery and compared the signals to those estimated over patches extracted from a finite difference calculation based on customized torso geometries [106]. They found reasonable agreement of signal morphology (but not amplitude) in four of the six sites, but had to time shift the signals by as much as 26 ms to achieve correlation levels in the range of 0.91–0.98. Two of the sites showed very little agreement between measurements and calculations.

Another approach to obtaining source data in patients is to apply epicardial sock electrodes during open chest surgery. Shahidi *et al.* performed a study in which they created patient specific geometric models and then recorded body surface potentials before the surgery [20]. They compared computed epicardial potential maps with those measured during surgery and found only approximate agreement. The main problem with the general approach of measuring body surface maps at one time and epicardial potentials during open chest surgery at a different time is that the effects of the resulting changes in patient state and the integrity of the volume conductor are poorly known. There is so much variability introduced by these disparate measurement conditions that it is virtually impossible to decide how to separate the resulting errors between the inverse solution and the measurements.

In lieu of direct validation, inverse solutions can sometimes be evaluated based on our general knowledge of what constitutes a *reasonable* description of, for example, the activation sequence. Huiskamp *et al.* performed inverse calculations of the epicardial and endocardial activation sequence [27, 28] and compared their results to the seminal publication by Durrer *et al.* on the measured activation sequence of an isolated, healthy human heart [19]. They also used another indirect validation measure by first estimating the activation time from the body surface potentials and then computing in a forward sense the body surface ECGs, against which they could compare original measurements [27, 28]. Budget *et al.* also compared their computed epicardial potentials against those described by Spach *et al.* for chimpanzee hearts [108, 109] as a means of validation [106].

Clinical conditions can facilitate validation of inverse solutions by providing non-electrocardiographic indicators of disease states that are also revealed by epicardial potentials. Kilpatrick and Walker described an early example of this approach in which they used computed epicardial potential distributions from the ST segment of the ECG to predict the vessel affected in cases of acute myocardial infarction [1]. To confirm the location of infarction, they performed angiography on each patient in the study and then quantified their results in terms of correct or incorrect prediction of the affected vessel. In a subsequent study Kilpatrick *et al.* used inverse solutions of epicardial potentials to differentiate the cardiac origins of ST-segment depressions visible in the body surface [110].

Another example of a clinical condition for validation is Wolff-Parkinson-White (WPW) syndrome, in which an accessory conductive pathway exists between the atria and the ventricles, which are normally electrically isolated [111]. The advantage of this condition from the perspective of the study of inverse solutions is that when the accessory path is active, there is a discrete deflection in the body surface ECG known as the "delta wave", which occurs just before the onset of the R wave. It is possible to apply inverse solutions to a few time instants during the delta wave and attempt to locate the accessory pathway. The very local extent of active tissue during the delta wave also justifies the use of dipole sources and thus inverse solutions based on epicardial surface potentials and activation times as well as discrete source models. Confirmation of the predicted accessory pathway site is then possible by means of either open chest cardiac mapping [112] or by catheter techniques in common use [113]. Shahidi *et al.* [20] and Penney *et al.* [114] in separate studies applied inverse solutions to WPW patients and compared the predicted accessory pathway with that found subsequently during ablation.

One limitation of all the clinical approaches described so far is the lack of control over the source potentials. Patients either have or do not have a particular clinical abnormality and it is often difficult or impossible to alter that state. Patients with WPW syndrome are one exception in that it is often

possible to elicit both normal sinus beats and beats with pre-excitation via the accessory pathway during the same electrophysiology study. There is, however, a palliative intervention that allows direct and continuous control over some aspects of the electrophysiologic state of the heart and thus lends itself to collateral use for validation of inverse solutions. During percutaneous transluminal coronary angioplasty (PTCA), a catheter balloon is inserted into a partially occluded coronary artery and inflated in order to mechanically disrupt the thickened and hardened linings of the artery [115]. During the inflation, which typically lasts from 20–200 s, blood flow in the affected artery is completely occluded and acute ischemia results. Electrophysiologic consequences of this ischemia are visible from the body surface ECG and resolve within seconds to minutes of the balloon deflating. The inflation/deflation cycle can be—and often is for clinical reasons—repeated many times in the same patient, both in the same and different segments of the coronary arteries.

PTCA has served as a human model of many aspects of cardiac physiology during acute ischemia [116] including ventricular contraction, [117] wall thickening, [118] coronary hemodynamics, [119] collateral flow, [120] left ventricular filling, [121] and the genesis of arrhythmias [122]. MacLeod *et al.* used PTCA to validate an electrocardiographic inverse solution [18, 2]. They computed epicardial potentials from body surface maps of patients during angioplasty and compared the predicted locations of epicardial ST-segment elevations with the locations of the balloon catheter documented via angiography. Working mostly with time-integrated potentials, they found patterns of torso potentials during inflation that were characteristic of the vessel under treatment. When used as inputs to inverse solutions, these torso potentials generated associated epicardial distributions that were similar to ST-segment potential changes seen in animal models of acute ischemia. Thus, in an optimistic interpretation, these inverse solutions may have succeeded in localizing focused areas of change in epicardial potential due to the induced ischemia from a diffuse change observed on the body surface. In fact, in many cases, elevations in ST-segment potentials on the epicardium corresponded to locations just distal to the site of the angioplasty balloon, within what could reasonably be assumed to be the approximate perfusion area supplied by the distal circumflex artery.

Figure 4 shows examples of body surface maps and computed inverse solution from angioplasty patients. The top row of images highlights a particularly powerful feature of the PTCA validation model, which is the ability to apply and measure the effects of controlled interventions. The leftmost body surface map shows the isointegral distribution of the ST segment during the last 30 s of an inflation lasting 150 s and the middle map shows the equivalent isointegral map recorded just prior to the onset of balloon inflation. The rightmost map is the difference between the other two (peak-inflation minus pre-inflation) and shows clearly the electrophysiologic influence of the transient occlusion on the body surface potentials. The light shaded (positive) area on the right anterior chest in the left and right maps is a typical characteristic of at least some of the patients undergoing angioplasty of the right coronary (RC) artery. The rightmost epicardial map in the bottom row of the figure contains the inverse computed isointegral distribution from the torso difference map directly above. The light area in this map lies over the terminal region of the RC artery and suggests that PTCA induced an elevation of ST-segment potentials during the balloon inflation, in agreement with the angiographic evidence for this patient. The left and middle epicardial maps in the lower row of the figure are inverse solutions computed from ST-segment isointegral difference maps from two other patients undergoing circumflex and left anterior descending artery PTCA, respectively. Here, too, the light shaded region indicates a positive potential change that lies over the region of expected underperfusion, again suggesting that one can detect locations of ischemic myocardium by means of an inverse solution.

While these validation results were encouraging, they were still very qualitative in nature, and contained unexplained anomalies such as secondary areas of positive potential in the atrial region or in parts of the ventricle where there was no angiographic evidence to indicate ischemia. The geometry used in this study was realistic but not anatomically accurate nor did it contain inhomogeneous regions. The heart was based

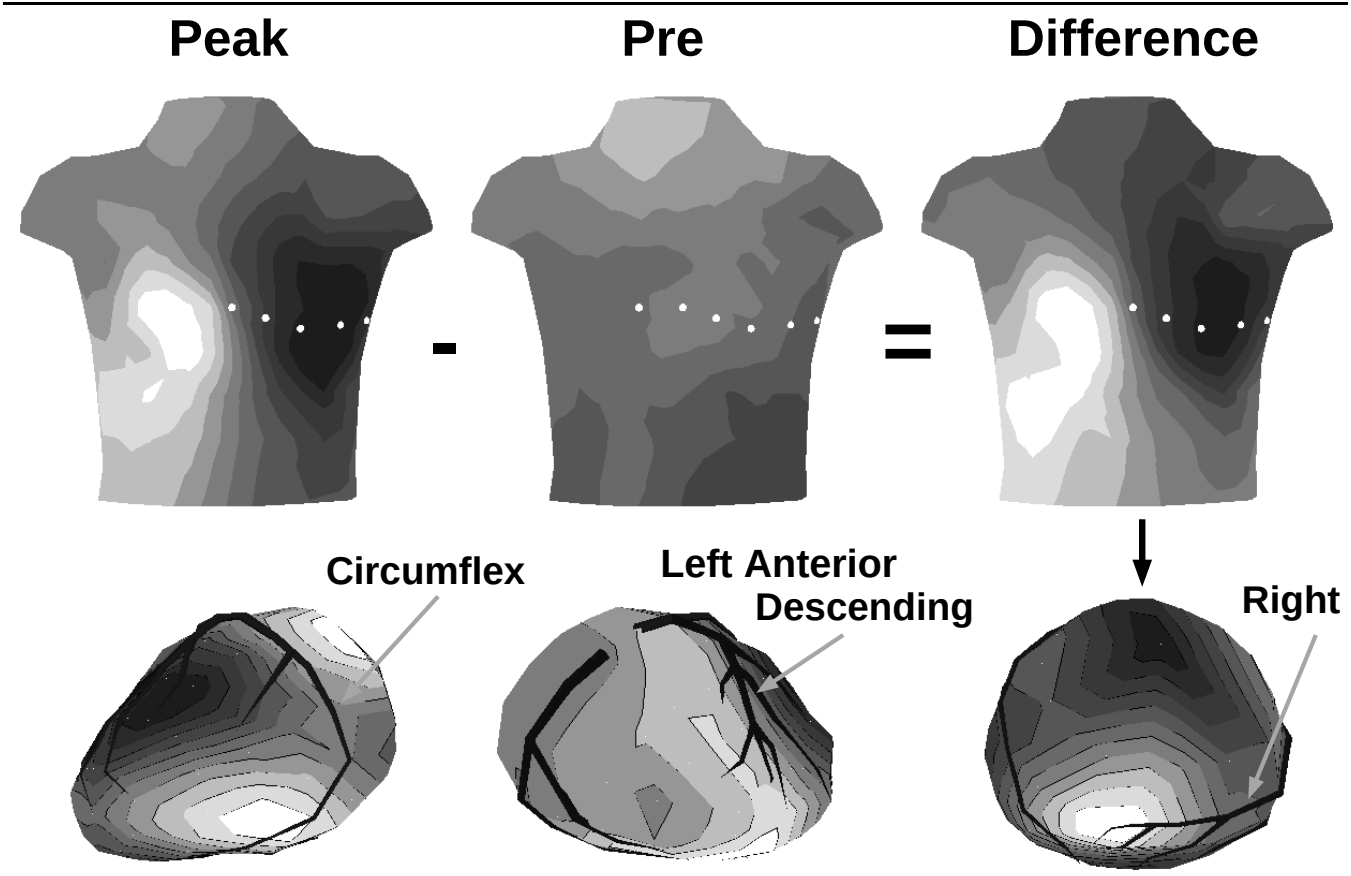

Figure 4: Example of body surface potential maps and computed inverse solution in an angioplasty patient. All maps are isointegral distributions from the ST segment and the level of gray shading indicates isointegral value, with black the minimum value and white the maximum. The upper row contains, from left to right, an anterior view of an isointegral map recorded at peak inflation of the PTCA balloon, a map recorded just prior to inflation, and the difference between the two. White dots on the torso maps show locations of precordial electrodes V_1–V_2. The lower row contains isointegral maps from computed inverse solutions. The rightmost map is the inverse solution of the torso map directly above and the left and middle maps are computed difference maps from other patients undergoing circumflex and left anterior descending artery angioplasty, respectively.

on a detailed model created from a human heart and used for cellular automata simulations of propagation [41, 123, 124] and it was placed in the torso model from a different subject created by mechanical measurements [2, 125, 126].

A recent report by Tilg *et al.* described a validation approach in humans that offers exceptional potential for testing at least one form of the inverse solution [127]. The breakthrough technology in this study was the use of a remote ranging system that measures activation time and location simultaneously from an endocardial catheter [128]. Tilg *et al.* recorded from a series of patients the endocardial activation times as well as simultaneous body surface potentials. They then performed MR imaging and a magnetocardiographic mapping, all within a day of the endocardial mapping. Using the geometry and the body surface potentials, they then created customized inverse solutions in terms of activation time, which they could validate against the direct measurements. Preliminary results suggest a reasonably good match between

predicted and measured values.

It is also possible to formulate an inverse solution in terms of reconstructing endocardial potentials from potentials measured in the interior of the cavities in the heart. Such an approach has been developed by Khoury *et al.* [80, 129] and Lui *et al.* [82]. Initial validation of this approach was by means of animal studies but recently this group has developed a combined probe that contains both a set of non-contact electrodes mounted on a cylinder, and a concentric basket catheter [130]. In this way, it is possible to record from both electrode arrays simultaneously and directly validate the computed endocardial potentials against measurements.

5 Discussion

In this section, we summarize some of the salient aspects of validating electrocardiographic inverse solutions and identify what we consider to be the most pressing requirements for continued progress.

A ubiquitous requirement of validation is to quantify the level of error between the estimated results and some ground truth or gold standard. For electrocardiographic inverse solutions, even assuming such a gold standard is available, however, there does not yet exist a suitable metric with which to express this error. Statistical parameters such as correlation, relative error, and root-mean-squared error are inadequate because they are measures with no link to the electrophysiology or pathophysiology that electrocardiographers seek to detect. For example, the presence of a small, isolated maximum or minimum in a measured isopotential map can suggest underlying abnormalities yet barely affect the overall statistical error when compared to a computed estimate that does not contain this feature. More generally, experienced human readers can detect the presence of specific features in distributions that one cannot capture in a robust automatic metric. As a result, any comparisons between estimated and measured results in an electrocardiographic validation study must be checked manually and often described qualitatively.

There is often a virtually unlimited number of different tests that are possible in a validation study. As a result, it is necessary to develop appropriate validation strategies, i.e., to extract from the infinite range of possible variations a reproducible subset of relevant features, parameters, and results. Such a strategy should include identification of the relevant parameters that are available for adjustment within the validation scheme. For example, in an experimental validation, a list of such parameters might include pacing sequence, heart rate, overall state of the heart, and choice of species. One must also decide how to impose shifts and random noise errors on the geometric model or conductivity values. At present, there exist no uniform guidelines for creating such a validation strategy. Defining such focused testing procedures will not only streamline execution and reporting, but also allow comparisons between methods proposed by different investigators.

A far greater hurdle to comparisons between investigators and laboratories is the lack of commonly available datasets. The measurements from the isolated heart and torso tank preparation first described by Taccardi, Colli-Franzone, *et al.* serve as the rare exceptions and have been used by several other groups around the world. If robust and comparable validation is to occur, it is necessary to collect many more such datasets and provide these to the research community in documented, electronic form. In recognition of this need, a goal of the recently established NIH/NCRR Center for Geometric Modeling, Simulation and Visualization for Bioelectric Field Problems at the University of Utah (`www.sci.utah.edu/ncrr`) is to provide such a service. Not only will isolated heart/torso tank data from within the Center be made available, but other investigators will have the opportunity to submit their data to the pool.

There are many reasons for optimism in the field of electrocardiographic inverse problems. The return to whole animal measurements by the Hunter group in Auckland and Oxford Universities, with the assistance of many new and powerful technologies for imaging and acquiring electrical data, offers new potential

for highly realistic validation studies in complex geometry. The recent clinical studies that Tilg and the groups at the Technical University of Graz and the University of California at San Francisco have recently conducted represent the first example of a true patient based validation. These studies were also made possible by improvements in technology, in this case catheters that measure simultaneously activation time and spatial location. This convergence of technology and collaboration among engineers, experimentalists, and physicians will certainly result in new discoveries in the near future based on improved validation.

A further encouraging development in inverse electrocardiography is the recent interest of industry in all aspects of mapping, both cardiac and body surface. The CARTO system for endocardial mapping, the implementation by Endocardial Solutions Inc. of a non-contact endocardial mapping by means of an inverse solution, and the appearance of a clinical body surface mapping system from Meridian Medical Technologies all indicate that industry recognizes the promise of inverse solutions in medicine.

With continued effort and careful validation using some of the methods described here, there can be little doubt that progress in inverse solution research and application will continue to accelerate.

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