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Journal of Cardiovascular Electrophysiology, Volume 12, No. 2, February 2001

The Forward and Inverse Problems: What Are They, Why Are They Important, and Where Do We Stand?

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Editorial Comment

The inverse problem is a general term for the process of inferring the distribution of an inaccessible variable from an accessible one. An example is the tomographic reconstruction of the opacity of tissue within the body from measured projections.[1] The forward problem is the computation of the measured variable from the source. The forward problem of electrocardiology is the calculation of electrical potentials generated by known sources at sites distant from those sources, typically through a volume conductor. The classic example is the computation of potentials at the body surface from a known set of sources, for example, an activation wavefront, in the heart. The companion and much more challenging problem is the ECG inverse problem. The task in the inverse problem is to use surface ECG recordings to compute the sources within the myocardium. The forward and inverse problems of ECG have been addressed with varying degrees of success for many decades.[2] The two problems are very closely related to each other mathematically and biophysically, but because of the potential practical uses of the inverse formulation, it has been more aggressively addressed.

The inverse problem is solved informally thousands of times per day, whenever a cardiologist makes an inference about the cardiovascular status of a patient by reading an ECG. However, the formal, technical solution is slow, approximate, and so far not useful in day-to-day practice. It is interesting to observe that clinical inverse solutions focus primarily on temporal sequences, often give special weight to cardiac repolarization, and use ECGs as a fast and inexpensive tool for gross evaluation. Conversely, formal inverse solutions have focused on spatial relationships, for example, the sequence of cardiac excitation, and have involved slow but elaborate analysis of detailed relationships among different regions of the heart. The latter has not been simply a matter of choice, because it is the spatial relationships that form the mechanistic basis of the origin of cardiac electrical signals. To date, formal solutions have contributed greatly to the understanding of the biophysical mechanisms by which electrical events within the heart lead to those observed on the body surface; however, this understanding so far has not led to improvements in most day-to-day measurements or evaluations of ECGs.

The crux of the problem solution is the computation of a transfer function, usually in the form of a two-dimensional matrix. The transfer function relates the torso potentials to the sources in the myocardium and can be established when both sets are known. This relationship is stated mathematically in Equation 1 in the second article by Ramanathan and Rudy in this issue of the *Journal*.[3] The function contains information about the transformation of the source potentials by the geometric and electrical characteristics of the volume conductor that result in body surface electrograms. The inverse problem is solved, then, by calculating the inverse of the transfer function. The inversion of the matrix is "ill-posed," meaning that there is too little information in the surface potentials to identify cardiac sources unambiguously and that small amounts of noise have a dramatic influence on the results. To avoid these problems, it is common to introduce constraints to the system, essentially using assumptions about the sources or other information to make the mathematics tractable. An early example is the determination of the characteristics of an equivalent electrical dipole from the recorded vectorcardiogram.[4] The mathematically precise definition of the components of the equivalent dipole was given by Geselowitz,[5,6] along with equations identifying the parts of the body surface signals that could not be accounted for by the dipole source. A variety of mathematical,[7] statistical,[8] and biophysical[9-11] constraints have been introduced and tested throughout the years.

Since the introduction of minimally invasive procedures for the treatment of cardiac rhythm disorders, there has been a resurgence of interest in the inverse problem. With improved capabilities to eliminate selectively bits of myocardium that support reentrant or automatic tachyarrhythmias comes an increasing need for a method to identify anatomically the offending region with a minimum of invasion. The inverse problem is one approach. A robust and accurate solution for estimating myocardial potentials from surface recordings would be an important extension in the diagnosis and treatment of arrhythmias.

There have been several limitations that have hin-

This work was supported in part by Research Grants HL-33637 and HL-50537 from The National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

J Cardiovasc Electrophysiol, Vol. 12, pp. 253-255, February 2001

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dered the routine use of the inverse problem in practical research and clinical applications. First is the complexity of the sensors and instrumentation required. The application of a large number of electrodes on the body surface in an accurately characterized geometric pattern and the high signal-to-noise ratio required in the ECGs are technically demanding. However, with increasing sophistication in body surface mapping, these challenges are being addressed effectively.[12]

A more fundamental problem is establishing adequate validation of the solutions in order to build confidence in the results. It is clearly quite difficult to make simultaneous measurements on endocardium, epicardium, or intramyocardium and on the body surface. In experimental animals, the need to open the chest in order to apply an adequate number and distribution of electrodes unavoidably disrupts the volume conductor and renders measurements from the body surface suspect. This problem is in addition to the changes resulting from simply introducing electrodes, often with metallic components, into the heart. Furthermore, even when measurements throughout the thickness of cardiac muscle are attempted, the number of measurement locations (hundreds) remains several orders of magnitude lower than the number of cells of the heart (billions), so that a great many details are known only approximately, if at all.

Another related challenge is the possibility that accurate solutions to the forward and inverse problems would require an unreasonably detailed specification of the anatomy and physiology of each patient or subject. Not only is the body habitus of each individual potentially important, but also the electrophysiologic characteristics of the various layers of the volume conductor (skeletal muscle, subcutaneous fat, lungs) might strongly influence the integrity of the computations. Thus, in addition to requiring detailed anatomic imaging with one of several widely available, but often costly, modalities, effective solutions might require precise measurements of conductivities in those intervening tissues.

These problems are partially addressed by two articles by Ramanathan and Rudy[3,13] in this issue of the *Journal.* The authors made very careful simultaneous measurements of epicardial and surface potentials using an isolated heart in a torso-shaped tank that has been established as a useful simulation of human anatomy.[7] These measurements, along with the realistic thoracic geometries available from the National Library of Medicine's Visual Human Project, allowed computation of transfer functions for homogeneous and inhomogeneous torsos and a torso with a stylized lung geometry. In the first article,[13] the known epicardial potentials and the various transfer functions were used to compute simulated torso potentials and compared with those that had been directly measured. In the second article,[3] the computed torso potentials then were used with the inverse formulation to compute epicardial potentials for the three thoracic models. Simulated electrograms, activation sequences, and potential maps were compared with their experimentally measured counterparts. In both articles, the influence of including thoracic inhomogeneities in the simulation was evaluated. It is encouraging that, in both cases, the use of the homogeneous, less realistic thoracic anatomy barely degraded the accuracy of the simulations. A good approximation with the simplified torso model was observed for different torso sizes, lung and skeletal muscle conductivities, and genders, even when noise and geometric error were introduced into the computations. Of interest is the ability of the technique to resolve two simultaneously paced epicardial sites approximately 6 cm apart, either with isochronal or isopotential maps, whereas only isochronal maps could distinguish between two sites with 2.5 cm spacing. These results lead to optimism that these techniques might become practical without exhaustive anatomic and electrophysiologic knowledge determined on a subject-to-subject basis. Combined with earlier work in computing intramural activation from epicardial potentials,[14] the technique could be very powerful for studying bioelectric phenomena in the heart in health and disease.

It is clear that the approach represented in these articles will continue to be a valuable tool in clinical and basic studies of cardiac excitation during normal conditions and arrhythmias. Inverse calculations will be able to provide a tool to address mechanisms with minimal invasiveness, and their application in carefully chosen circumstances will be invaluable. However, their role in the practical diagnosis and therapy of rhythm disorders is less clear. Current therapeutic approaches require at least insertion of catheters, so that the advantage of a completely noninvasive diagnostic capability is equivocal, at least presently, and there are several competing technologies from which to choose. Pace mapping[15] has been used for several years to identify areas responsible for the maintenance of arrhythmias. Rigid[16] and inflatable[17-19] probe arrays have been used effectively to implement a form of the inverse problem. In this approach, endocardial potentials are computed from electrograms measured by electrodes in the blood pool of the ventricles or atria. It is important to note that the mathematical and computer procedures for inverse problems remain the same for all remote-sensing electrodes, whether they be located on the body surface or within the heart, although the latter arrangement offers advantages because they are closer. Probes also have been designed to make direct contact with the endocardial wall after deployment in a cardiac cavity,[20] allowing direct measurement of potentials. An endocardial navigation and mapping system[21] provides both anatomic and electrophysiologic characterization of the endocardium, identifying locations that are candidates for ablation or other intervention.

The group from Case Western Reserve University that authored these two articles[3,13] is one of a few laboratories that are intensively pursuing improved methodologies for addressing the forward and inverse problems of electrocardiology. The work presented here is a further improvement and validation of the mathematical and electrophysiologic techniques that are necessary in this area. These investigators and others in the area have benefitted by certain major advances in the overall climate of inverse solutions that have occurred over the last decade.

These include enormously more powerful computer systems now widely available at low cost, the availability of imaging systems that can locate the position of the heart within the thorax, and the development of good mathematical models of the electrical behavior of the individual cell types (atrial, ventricular, and conduction system) that are present. Continued advances are taking a period of years to come to fruition, but promise to lead to more universal acceptance and use by the scientific community.

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