Modeling Cardiac Bioelectricity in Realistic Volumes: How Real is Real?

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Abstract

Electrocardiographic forward problems represent body surface potentials as a function of cardiac sources and thus encapsulate all knowledge of the bioelectric characteristics of the heart and torso. Since the time of Einthoven, scientists and physicians have created more and more detailed formulations of such problems with the goal of linking the ECG to normal and abnormal cardiac function. Einthoven created the first such model in the form of a triangle representing the lead vector of a dipole that captured the entire electrical activity of the heart. The most modern forward solutions now include detailed cardiac and thoracic anatomy based on medical images as well as dynamic simulation models of cardiac currents and anisotropic volume conductors. In this paper, we summarize this history and show some examples of contemporary forward solutions and the technical tools available to create them.

1 Introduction

Since before the time of Einthoven biophysicists and physicians have sought to understand the relationship between cardiac sources of bioelectricity and the resulting body surface potentials, a relationship expressed most generally as forward problems in electrocardiography. The sources of this fascination include the intellectual challenge of describing an apparently magical but completely tangible life force and the very pragmatic desire to connect a relatively simple measurement with the health of the heart. As a physician with a strong interest in physics, Einthoven tapped both sources of motivation to make first measuring and then understanding the ECG the centerpoint of his career.

The past century has seen remarkable progress and also great diversity in the approaches available to study and understand electrocardiographic forward problems. Models of the cardiac sources have evolved from the single dipoles of Einthoven's time to anatomically realistic, anisotropic bidomain models of the heart driven by dynamic cellular currents first described in the middle of the century by fellow Nobel Prize winners, Hodgkin and Huxley[1]. From the crude approximations of the body volume conductor as an infinite homogeneous region have evolved into high resolution, patient specific geometric models consisting of millions of points joined into surface or volume elements. To replace the qualitative descriptions of electric potentials generated by simple sources, there exist now highly quantitative approximations based on solutions of partial differential equations from Maxwell. And finally, to solve and display the measurements and predictions of the ECG, photographic images from string galvanometers have given way to modern computers, numerical mathematics, and scientific visualization.

The essential elements of a forward solution, however, have remained the same as in Einthoven's time, dictated as they are by the physics of the problem rather than the technology. One must first determine a suitable estimate of the electrical behavior of the heart that captures the important features and yet remains mathematically and computationally tractable. One must then place this source within a volume conductor that describes the passive electrical characteristics of the human body, again with as much detail as necessary but in a way that remains amenable to calculation. The third component of a forward solution are the physical equations that describe the relationships between electrical sources and volume potentials and currents, together with robust and accurate means of estimating them in the discrete geometric models of the body. Finally, one must have a means of capturing all this information in a framework that allows numerical solution of the equations and display and manipulation of the results, ideally coupled with measurements that server to validate the assumptions built into all stages of the solution.

Once developed and tested, an accurate solution to the electrocardiographic forward problem has a number of uses. It can serve as a means of testing the effect of variations of all components of the sources and geometric model on the resulting ECG. A typical goal would be to differentiate between pathological changes in the heart and a range of other variations that can effect body surface potentials. A forward solution can also serve as the bridge between a simulation model of cardiac activity (described elsewhere in this volume) and the resulting ECG and thus help determine whether the predictions of the source model are compatible with measured body surface signals. Forward solutions are also invariably a required element in any inverse problem formulation, *i.e.,* the problem of determining cardiac activity from (noninvasive) body-surface measurements, also described in this volume.

The exponential growth of computing—the hardware, software, and associated computational techniques–has facilitated substantial improvements in the quality and accuracy of quantitative forward solutions, culminating recently in preliminary studies that describe "complete" forward

solutions[2,3]. These models seek to include the entire simulation problem from action potential generation to the ECG within a single, multi-layered process. One advantages of this approach over one which consists of a sequence of solutions for each phase is that one can more directly link any and all features of the model to the ECG and to other features of the problem and thus study the entire problem with all possible interactions. The immense challenge of fully integrated modeling approaches is the enormous computational resources required.

The goal of this document is to describe briefly some of the more recent advances in the creation and application of electrocardiographic forward solutions. For more comprehensive reviews, see, for example, Gulrajani[4,5]. We will begin with an overview of the elements of a contemporary forward solution and the research findings that describe them. We will then highlight some of the integrated solutions formulations and the software available to compute them and then describe our own initial results using these tools to describe forward solution results in a novel and hopefully useful way. We conclude with what we feel is a novel approach to representing the forward solution and a few of the many intriguing questions left to resolve in the study of forward problems in electrocardiography.

2 Source Formulations

Every stage of a simulation model requires approximations of reality that reflect the goals, desired level of detail, and the imagination of its creator. In the electrocardiographic forward problem, it is arguably the formulation of the bioelectric source component that best characterizes the perspective of a particular model. Einthoven first described the electric behavior of the entire heart (and torso) as a single dipole that changes orientation and amplitude over the course of each heart beat[6] and this conceptual approach remains dominant in the teaching and clinical application of electrocardiography in medicine[7].

In subsequent years have followed a series of modification and refinements of the dipole source model, notable among them the experimental and modeling evaluation by Burger and van Milaan of the concept of a *lead field* to describe the relationship between dipolar sources and the resulting body surface potentials[8,9]. Further refinements of this basic concept include the use of moving dipole[10], multiple dipoles[11,12], multipole[13], and dipole layers[14]

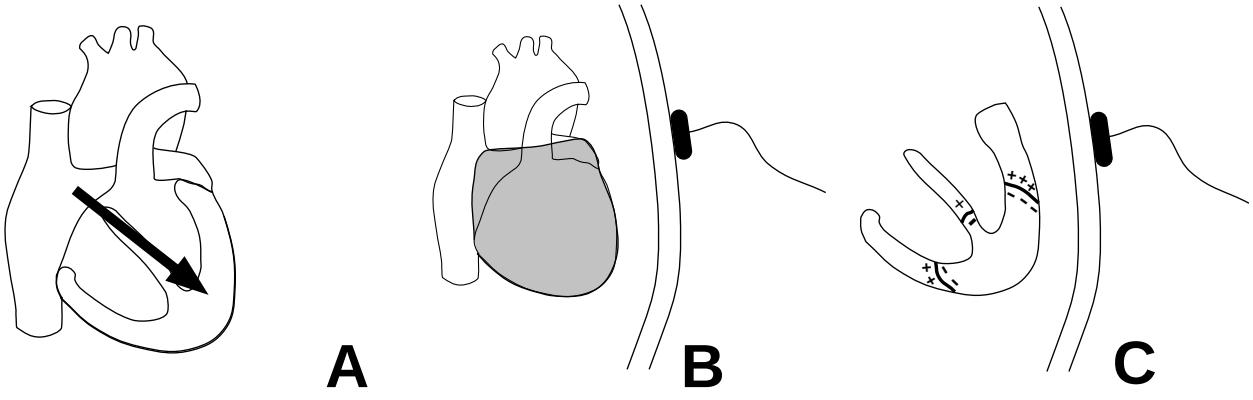

Figure 1: Source model configurations for electrocardiographic forward problems.

The inadequacies in the basic approximation of the heart as single dipole that arose fairly soon after its description[15] led not just to refinements of this basic idea but also to fundamentally different

source models of the heart, as summarized schematically in Figure 1. Crucial among them was the use of the epicardial potential distribution as an equivalent source of cardiac bioelectricity[16], an approach still in very common use today[17–21] (and illustrated in Panel B of Figure 1). Another source model that has gained considerable attention in recent years is based on a uniform dipole layer (UDL) representation of cardiac activation[22](illustrated in Panel C of Figure 1). Starting from this source and assuming the resulting electrocardiographic fields to be represented by the solid angle subtended by the UDL, one can describe the field from the entire activation sequence of the heart as that originating from the epicardial and endocardial surfaces[23]. Given some further assumption about the voltage source of the activation wavefront, it is then possible to formulate a quantitative expression for body surface potential as a function of activation time on the heart surface[23–27].

All of these formulations require in one form or another a description of the electrical activity of the heart. Measurements from cardiac mapping provide one source of this information, as we shall describe below. It is also possible, as reported elsewhere in this volume, to simulate the cardiac bioelectricity by means of a model of excitable cells and myocardial tissue. In the time since Einthoven there have been an impressive sequence of such models, starting most notably with the Nobel prize winning results of Hodgkin and Huxley on the dynamics of excitable membranes[1, 28]. This fundamental description of the time and voltage dependence of ionic currents provided the basic source for ever more complex models of myocytes, myocardium, and now entire hearts. Of special importance in the context of forward solutions have been models using networks of excitable cells[29, 30], cellular automata [31–35], and especially the bidomain approach[36–40].

3 Volume Conductor Models

Linking the cardiac sources with the body surface potentials is the thorax, an electrically passive volume conductor, geometric models of which have grown substantially in sophistication and detail since the time of Einthoven. Einthoven considered the volume conductor to be an infinite homogeneous region, and described the relationship between the heart dipole and limb lead potentials in terms of an equilateral triangle with the heart dipole in the center[6]. Burger and van Milaan investigated the effect of a finite homogeneous volume conductor on the ECG and especially the assumptions of the equilateral triangle. The proposed a skewed triangular shape and a set of ECG lead locations to compensate for the effects of the finite volume conductor on the lead field[9, 41].

Realistic geometric models of the human torso appeared in the latter part of the century and have formed the basis of forward problem volume conductors ever since. The model by Horáček included a body surface based on mechanical measurements of a human as well as lung and epicardial surfaces from X-ray images[42]. He and other investigators have subsequently used this same model for studies of electrocardiographic forward problems[12, 43, 18, 44]. We have developed the Utah torso, which was based on magnetic resonance imaging of a human subject and contains not only inhomogeneous but also anisotropic regions[45–49]. Computed tomography also provides images of very high spatial resolution, which have been the source of very detailed models of the thorax[50]. Many recent studies are based on the results of the Visible Human Project, which sought to create a set of medical image data at the highest possible resolution from the cadaver of one man and one woman[51]. Perhaps most contemporary are approaches that seek to customize a geometric model to the patient, either by fitting the measured data using basis functions[52, 53], or using supplementary imaging data to adjust a standard model[54].

A complete geometric model of the electrocardiographic volume conductor must contain not

only anatomical information but also a description of the electrical properties of the tissues. This requires that investigators assign estimates of local conductivity, typically based on values in the literature[55, 56] or, in rare cases, their own measurements[57]. The questions of just how accurately the values of conductivity must be known or even which inhomogeneous regions a model must include are still unresolved despite considerable study[58, 59, 55, 60–65, 49, 66]. Recent results suggest that *geometric* accuracy of the volume conductor may play a larger role than that of the conductivities assigned to the model[64, 67, 68]. Our own studies based on measurements using a human shaped torso tank revealed modest changes in potential amplitudes of both the epicardial and torso surface potentials in the presence of localized inhomogeneous regions within the tank. Figure 2 shows an example of such changes following insertion of two balloons to represent lungs in the torso tank. These results support earlier simulations using simplified concentric sphere geometries by Rudy *et al.*[61].

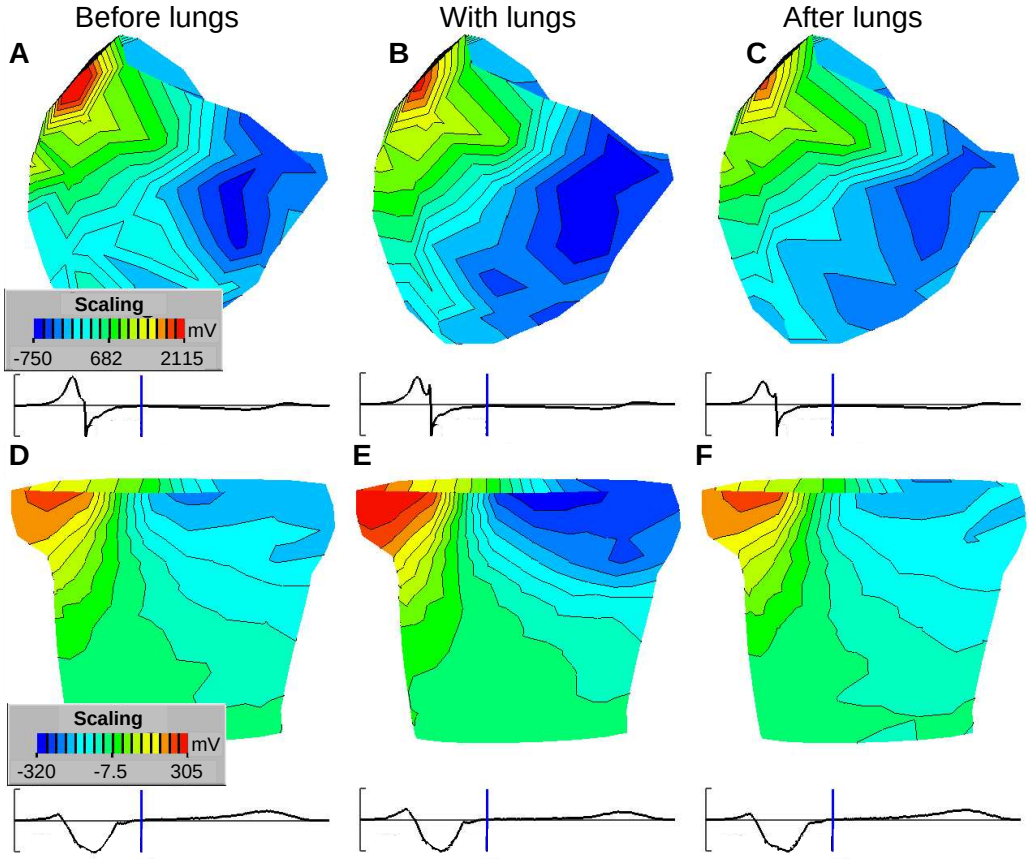

Figure 2: Effect of placing insulating balloon into the torso tank on epicardial potentials (top row) and torso tank potentials (bottom row) for equivalent instants in time during three separate beats. The maps of electric potential in left-hand column come from a beat before insertion of balloons, those in the middle column come from a beat with the balloons in place, and those in the right-hand column are from a beat after removing the balloons. The contours are linearly spaced with constant scaling across maps in each of the two surfaces, with contour values indicated by the scaling bars.

Perhaps the most important finding of these studies is that changing the characteristics of

the volume conductor results in changes not just in torso surface potentials but also those on the epicardial surface[65]. As a consequence, studies of conductivity effects based solely on simulation may not capture the true complexity of the response to changes in volume conductor characteristics. Moreover, it may be possible to carry out the definitive study of the role of the volume conductor only through a combination of simulation and experimental studies. To place these findings in a clinical context, the changes in potential than can arise from changes in torso geometry, as well as from physiologically reasonable changes in heart position, are large enough to exceed common thresholds for indicating pathological ECGs[65, 69].

4 Numerical Approximations

The ultimate biophysical basis of an electrocardiographic forward problem are Maxwell's equations, from which one can derive a wide variety of specific applications. The generalized quantitative implementation of Einthoven's heart vector approach is the lead field, which describes the relationship between heart vector and torso potentials by the equation

$$\phi_{Bi} = \vec{p} \cdot \vec{L_i}, \tag{1}$$

where ϕ_{Bi} is the body surface potential difference between a particular pair of electrodes (a lead), $\vec{p}$ is the dipole vector, and $\vec{L_i}$ is the lead field vector for that particular lead. The lead vector encapsulates all the geometric and conductivity information of the volume conductor for the specific lead. Using reciprocity, one can, in principle, measure the lead field for any set of leads, however, in the modern era, one typically approximates the lead field through a series of calculations for a discrete number of dipole locations and body-surface leads[70, 71].

Another approximation approach, which described the electrocardiographic source in terms of epicardial potentials, is by means of a Green's theorem applied to the potentials in the torso. First described by Barr *et al.*[16, 72], this method begins with an equation for the potential ϕ anywhere in the volume conductor as

$$\int_S (\frac{1}{r}\nabla\phi - \phi\nabla\frac{1}{r}) \cdot d\vec{A} = \int_V (\frac{1}{r}\nabla^2\phi - \phi\nabla^2\frac{1}{r})\, dV. \tag{2}$$

and then writes a pair of specific equations for the potential on the heart and body surfaces, making use of Laplace's equation, which governs the region of the volume conductor that contains no sources. The result is a set of integral equations for which one find numerical approximations by means of the boundary element method (BEM) and then, finally, a compact representation of the forward solution as

$$\Phi_B = Z_{BH}\Phi_H, \tag{3}$$

with Φ_H a vector of epicardial potentials, Φ_B, the associated body surface potentials, and Z_{BH} the forward coefficient transform matrix defined in terms of solutions to the various terms of the integral equation.

One can also formulate a solution based on a specific solution to Laplace's equation as

$$\nabla \cdot \sigma\nabla\Phi = 0 \tag{4}$$

anywhere in the volume conductor between the heart and body surfaces. Assuming we have known potentials on the heart surface, Φ_H and that the normal component of current at the body surface

is zero, one can then write a minimization equation that supplies the conditions for a finite element method solution of the problem[47, 73].

There exists another source formulation based on the activation time over the entire epicardial and endocardial surfaces, which also leads to an integral equation

$$\phi_B(y) = \int_{S_H} T(y,x)H(t-\tau(x))dS_x, \tag{5}$$

where $\Phi_B(y)$ is the potential on the body surface site y, H is the Heaviside step function, $\tau(x)$ is the time at which each portion of the epi/endocardium (S_H) 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[22, 23]. This equation also leads to a boundary element approached, based as it is on data limited to the heart and body surfaces.

5 Computational Implementation

According to the formulation of Einthoven, solving the forward problem required only simple manual computations using trigonometry and algebra. Solving a forward problem with realistic sources and geometry, in contrast, requires considerable computational expense and time. Here we outline just a few of the methodological aspects of solving realistic forward problems.

Some of the first descriptions of computational approaches to electrocardiographic forward problems came from Bernard *et al.* who described in very comprehensive terms the requirements of converting electromagnetic theory into equations and then computable solutions using dipole sources and the boundary element method[74, 75]. Researchers at Duke University, notably Martin, Pilkington, and Barr then developed a steady string of computational methods through the 1970's and 1980's [76, 77, 11, 78–81]. With the widespread availability of computers of the past two decades has come a dispersion of groups advancing the field of numerical and computational approaches in forward problems.

In the modern era, forward solution computations make use of either the BEM or FEM and, most recently, hybrid approaches that take advantages of the advantages of both[82]. BEM formulations require information only on the surfaces of the geometry and this leads to simpler geometric models, typically composed of hundreds to thousands of node points per surface connected to form triangles. FEM methods, by contrast, require a volume mesh of the entire solution domain, composed of thousands to millions of nodes connected to form tetrahedra or hexahedra. It is typically easier to create a surface mesh and especially easy to modify an existing one compared to volume meshes, which require more space and algorithmic complexity to create and to alter. The matrices resulting from the geometric models, the size of which depends on the number of nodes, are therefore much smaller for the BEM than those from the FEM. However, the nature of the matrix contents determines that BEM matrices are full, *i.e.,* they have few zero elements, while the FEM produces extremely sparse, positive definite, symmetric matrices. Because there are typically more numerical solution methods and programs available for solving such sparse systems, the FEM approach can often be easier to implement than the BEM. An additional advantage of the FEM method is that it is possible and quite straightforward to include any desired degree of anisotropy into the structure of the model. Achieving this with the BEM approach presents considerable challenges and additional computational cost. In summary, the choice of numerical method depends on the nature and size of the problem and most leading investigators have experience with both.

A critical aspect of solving realistic forward problems is having access to efficient software to solve the resulting numerical problems. In the past, this required individual laboratories to develop and maintain their own custom code, a task for which many scientists and engineers are poorly educated and prepared. In recent years, several software systems have appeared that are available to either purchase or received at no cost. For the FEM, commercial programs exist that with some adaptation are suitable for at least moderately sized electrocardiographic forward problems with simple geometries. Within academia, there are also programs developed by some of the leading labs that are available for free download. Notable examples include *CMISS* from the University of Auckland (`http://www.bioeng.auckland.ac.nz/cmiss/cmiss.php`), developed for a wide range of engineering problems using both FEM and BEM methods; *CardioWave* (http://www.ee.duke.edu/%7Ejpormann/simsys/CardioWave.html) from investigators at Duke University, which computes complex cardiac source models; and *BioPSE/SCIRun*, a package we have developed at the University of Utah[83, 84]. The driving vision for SCIRun is to create a highly integrated problem solving environment that includes all capabilities required to create geometric models, carry out simulation studies, and visualize the results interactively. The results in the next section are examples of SCIRun calculation and visualization using the BioPSE package, a set of modules created specifically for solving bioelectric field problems.

6 Forward solution in terms of currents

We present here an approach to manipulating and viewing the results of the forward solutions that seeks to reveal new features not previously directly accessible. The basic formulation of the forward problem is conventional, based on epicardial potentials located on the inner surface of a geometric model of the thorax. The novel aspect is that we solve the problem not just in terms of torso surface potentials, but first the potentials throughout the volume and then from them, the current density everywhere in the thorax. From this, we are able to integrate along the paths of current density and thus trace the pathways of current starting from seed points that we set interactively[21].

The specific example included here is from potentials measured in a human-shaped torso tank in which we suspended an isolated, perfused dog heart[85]. The tank also had electrodes located within the volume, which provided confirmation of the forward solution results at those locations—a subset of the full finite element model. The goal of the project was to understand more fully the patterns of torso potentials that result from the stimulation from one or more locations on the epicardial surface, ectopic beats as might arise in conjunction with ventricular tachycardia.

We used a range of software tools, including SCIRun/BioPSE, to create the geometric model and compute and then display the potentials and current density fields. Critical for this purpose was the ability to manually set seed point location and density in the volume and quickly visualize the resulting current lines, capabilities uniquely available within the SCIRun/BioPSE environment. We also used also a custom visualization program *map3d*[86, 87*] for visualizing sequences of surface potential distributions interactively.

Among the findings that emerged from this study was a clear picture of the flow of current between and among multiple sites of simulation. Close to the heart, each current source/sink connects to unique lines of current flow, sometimes slitting or merging close to the source to link to one or more sites of opposite polarity. Slightly further from the heart, however, the current lines from multiple sources and sinks tended to converge and lose their distinct patterns so that

*SCIRun/BioPSE and *map3d* are available for free download at `www.sci.utah.edu/software`

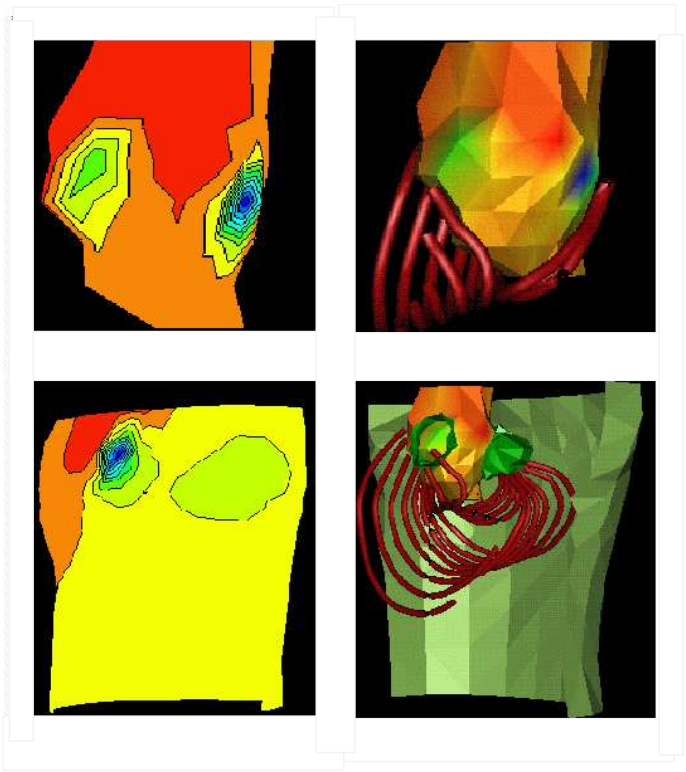

Figure 3: Electric fields at 16 ms after simultaneous pacing from two sites on the ventricular surface. All four panels have the same perspective view from the front of the body. Panel A: epicardial potentials; Panel B: current flow near the heart; Panel C: body surface potentials; and Panel D: torso volume currents and potentials. Streamlines depict current pathways, and the dark green surface within the volume is the iso-potential surface at 0 mV. The light green surface shows the posterior chest wall. Contour lines are equally spaced between -6.2 mV and 0.85 mV on the epicardial surface and between -1.6 mV and 0.38 mV on the tank surface. Values in mV marked on both epicardial and tank surfaces (Panel A and C) are maxima and minima or potential. The iso-potential surfaces in Panel C were at -0.5 mV.

individual sources or sinks were no longer separate, as reflected in the resulting potential maps on the torso tank surface. Thus is was possible to investigate in great detail the nature of the smoothing that occurs between cardiac sources and the resulting body surface potentials.

7 Discussion

Simulations of electrocardiographic forward problems serve many purposes; their greatest value is that they encapsulate the knowledge accumulated since the time of Einthoven in a form that permits examination, evaluation, and comparison with measured data. Each different implementation reflects a particular perspective and thus makes the required simplifications to answer one or more specific questions. As with any simulation, they cannot capture all possible detail or they become

intractable in their computational costs—just as no single scientist can grasp all that is published or known about electrocardiography. A review of the literature on simulations reveals that by almost any measure these models do a remarkable job at reproducing measured data with error rates in the range of 1–5% depending on the metric and specific conditions of the model.

The future holds great promise for simulation of forward problems. Along with the incremental refinements of the techniques come improvements in medical imaging that will provide better information on the structure of the volume conductor and with diffusion tensor magnetic resonance imaging even the fiber orientation of muscle. Ever increasing measurement capacities will provide more detailed source information and thus more sophisticated models of the spread of activation. Most important, however, will be the increase in computational capabilities so that it will soon be possible to create fully integrated models of realistic cardiac sources driven by bidomain models of activation located and properly coupled to fully inhomogeneous volume conductors that originate from single patients. With these new technological development will no doubt come new insights and hence a continuous growth in the quality of human ideas and abilities to make ever better predictions of the link between heart health and the simple ECG measurements that are more than 100 years old.

Einthoven's fame lay in his ability to develop new technology and then to make full use of its capabilities to improve our understanding of physiology. While he was uniquely able to perform both tasks with excellence, as a field, we have the collective ability to continue in his large footprints.

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