On the Correctness of the Transmembrane Potential Based Inverse Problem of ECG

Vitaly Kalinin[1], Alexander Kalinin[1], Walther HW Schulze[1], Danila Potyagaylo[1], Alexander Shlapunov[2]

[1] EP Solutions SA, Switzerland
[2] Institute of Mathematics and Computer Science Siberian Federal University, Russia

Abstract

Solving the inverse problem of electrocardiography in terms of transmembrane potentials (TMPs) is considered to be a promising approach in noninvasive imaging of cardiac electrical activity. However, the correctness of the statement of this problem (i.e. existence, uniqueness and stability of the solution) was not explored with sufficient mathematical rigor. In this work, we aim to eliminate this gap and provide some mathematical background for the facts that are well adopted in the engineering community.

We consider the inverse problem of TMP reconstruction from known body surface potentials using two models: First, a 'microscopic' model assuming knowledge of geometrical cellular contours. Furthermore, we analyze a conventional isotropic steady-state version of the bidomain model under the assumption that the body and myocardial domains are enclosed by an infinitely smooth boundary.

The extracellular potentials, TMP and the body potentials are supposed to be functions belonging to a wide class of Sobolev-Slobodetckij functional spaces. The main conclusions of this work can be formulated as follows: For the cellular model, TMPs can be uniquely found on the surface of the intracellular domain. For the more practical, bidomain model, the null-space of the inverse problem includes a constant TMP on the myocardial surface and an infinite set of TMP distributions in the myocardial domain. Therefore, the TMPs inside the myocardium are not uniquely defined, while the TMPs on the myocardial surface can be reconstructed up to an arbitrary additive constant. The obtained results can be used as a sound basis for creating numerical methods for noninvasive mapping of the heart.

1. Introduction

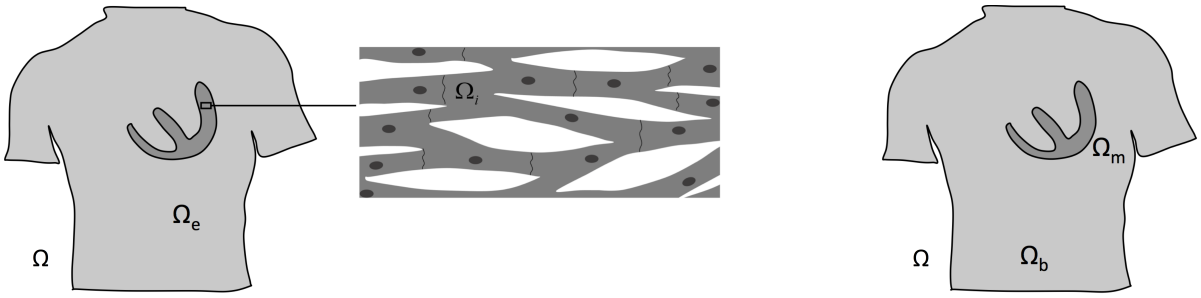
The inverse problem of electrocardiography, i.e. the problem of numerical reconstruction of cardiac electrical activity from EGC measurements on the body surface is of great value for diagnostics and treatment of cardiac arrhythmias. This raises an important question about a theoretical limit of our endeavours in this direction.

The inverse problem of electrocardiography can be approached in different ways. Its earliest and most studied version is the inverse problem in terms of electrical potentials on the cardiac surface: Some methods for noninvasive mapping of the heart have already found application in the clinical practice [1]. From a mathematical point of view, this problem is posed as a Cauchy problem for the Laplace equation and uniqueness of its solution was proved in [2]. Despite this fact, the solutions in terms of electrograms are often difficult to interpret: an electrogram signal at any heart point is composed of the near-field potential arising when the wavefront is passing through that point and the far-field component due to the passive properties of body tissues.

On the other hand, the electrical activity of the heart can be fully characterized by the spatio-temporal dynamics of the transmembrane potential (TMP) of cardiomyocytes. With this respect, the question raised may be put as follows: Can we uniquely reconstruct TMPs inside the myocardium using ECG signals recorded on the body surface? This issue is the subject to long-standing research [3–5] and, obviously, it can only be addressed within a chosen mathematical model of the cardiac cellular electrophysiology.

In this paper, we focus on uniqueness of the transmembrane potential based inverse problem of ECG. In particular, we investigate uniqueness of the solution in terms of TMP inside the myocardium. The analysis is performed for two models: a simplified cellular model and a simplified version of the bidomain model. A schematic representation of the treated domains is shown in Fig. 1.

 ISSN: 2325-887X DOI:10.22489/CinC.2017.077-438



Microscopic Cellular Model ***Macroscopic Bidomain Model***

Figure 1: In the cellular model, the intracellular domain is treated as a simply connected region and is separated from the extracellular one by an infinitely thin cell membrane. Thus, any point inside the domain Ω belongs either to the intracellular or extracellular space. In contrast to that, within a homogenized bidomain model presence of two intertwined spaces is assumed. Thereby, the values for intra- and extracellular potentials and conductivities are defined for each point inside the myocardium.

2. Model consideration and problem statement

2.1. Cellular model

Let us consider the myocardium surrounded by a homogeneous and isotropic volume conductor (the torso) which is, in turn, surrounded by a non-conductive medium (air). Let us assume that the myocardial tissue can be represented as a network of cells (cardiomyocytes) situated in the extracellular homogeneous and isotropic conductive medium. It is well known that the intracellular spaces of the cardiomyocytes are connected to each other with so called gap junctions characterized by a very low electrical resistance. Therefore, the intracellular space of the cardiomyocytes can be approximately considered as a single simply connected domain, which is separated from the extracellular media by the cellular membranes. Furthermore, we assume the conductivity of the intracellular and extracellular spaces to be homogeneous and isotropic and the cellular membrane to be infinitely thin.

Under these assumptions, the following holds:

$$\Delta u_i(x) = 0, \qquad x \in \Omega_i \quad (1)$$

$$\Delta u_e(x) = 0, \qquad x \in \Omega_e \quad (2)$$

$$u_i(x) - u_e(x) = v(x), \qquad x \in \partial\Omega_i \quad (3)$$

$$n_i \cdot (\sigma_i \nabla u_i) = -n_e \cdot (\sigma_e \nabla u_e), \qquad x \in \partial\Omega_i \quad (4)$$

$$n_e \cdot (\sigma_e \nabla u_e(x) = 0, \qquad x \in \partial\Omega \quad (5)$$

where Ω is the domain consisting of the torso, myocardial extracellular and intracellular subdomains, $\partial\Omega$ is its external boundary (i.e. the boundary between the torso and the air), $\in \partial\Omega_i$ is the boundary of Ω_i (i.e. the boundary between the intracellular and the extracellular domains), u_i is the intracellular electrical potential, u_e is the extracellular electrical potential, v is defined as their difference and called the transmembrane potential (TMP), σ_i and σ_e are the conductivity values of the intracellular and extracellular media respectively, n_i, n_e are the unit outward normal vectors.

For the specified system we consider the following problem:

Problem 1. Let u_e and u_i be governed by equations (1), (2) and satisfy the boundary conditions (3-5) and the values of electrical potentials on the boundary of the body domain be known:

$$u_e(x) = f(x), \qquad x \in \partial\Omega \quad (6)$$

where $f(x)$ is a known function. Under these conditions we seek for the transmembrane potential v on the boundary $\partial\Omega_i$.

Please note that the TMP is defined on the border between intracellular and extracellular domains. Thus, the problem of TMP reconstruction within the myocardium requires precise knowledge of 'microscopic' cellular geometry.

2.2. Bidomain model

Now let us consider the myocardial domain Ω_m being surrounded by a volume conductor $\Omega_b \supset \Omega_m$. The total domain, including the myocardium and the torso $\Omega = \Omega_b \cup \Omega_m$ is surrounded by a non-conductive medium (air).

Using a steady-state version of the bidomain model [6],

we can write:

$$\nabla \cdot (\sigma_i \nabla v(x)) + \nabla \cdot ((\sigma_e + \sigma_i)\nabla u_e(x)) = 0, \quad x \in \Omega_m \tag{7}$$

$$\nabla \cdot (\sigma_b \nabla u_b(x)) = 0, \quad x \in \Omega_b \tag{8}$$

$$u_e(x) = u_b(x), \quad x \in \partial\Omega_m \tag{9}$$

$$n_e \cdot (\sigma_e \nabla u_e(x)) = -n_i \cdot (\sigma_b \nabla u_b(x)), \quad x \in \partial\Omega_m \tag{10}$$

$$n_i \cdot (\sigma_i \nabla v(x)) + n_i \cdot (\sigma_i \nabla u_e(x)) = 0, \quad x \in \partial\Omega_m \tag{11}$$

$$n_e \cdot (\sigma_b \nabla u_b(x)) = 0, \quad x \in \partial\Omega \tag{12}$$

where u_i, u_e, u_b are intra-, extracellular and extracardiac potentials respectively, $v(x) = u_i(x) - u_e(x)$ for x in the closure of heart domain $\overline{\Omega}_m$, σ_i, σ_e, σ_b are the conductivity values in the intra-, extracellular and extracardiac spaces, n_i, n_e are the outward normal vectors to the surfaces of the heart and body volume (Ω_m and Ω_b) respectively. We assume intracellular, extracellular and extracardiac media to be homogeneous and isotropic.

For this system let us consider the following problem:

Problem 2. Let u_e and u_i be governed by equations (7), (8) and satisfy the boundary conditions (9-11) and the values of electrical potentials on the boundary of the body domain be known:

$$u_e(x) = f(x), \qquad x \in \partial\Omega \tag{13}$$

where $f(x)$ is a known function. Under these conditions we seek for the transmembrane potential v and extracellular potential u_e in the closure of the myocardial domain $\overline{\Omega}_m$.

It is worth noting that within the bidomain model the extracellular and intracellular spaces are homogenized over the whole myocardial domain, so that the values u_e, u_i and v are defined in the closure $\overline{\Omega}_m$.

2.3. Assumptions on smoothness for domain boundaries

For a strict mathematical statement of the problem, we need to specify classes of smoothness of the boundaries of considered domains and functional spaces for the functions. The simplest way is to consider classical solutions, such as solutions belonging to the $C^2(\overline{\Omega})$ class in the domain of interest Ω with a sufficiently smooth boundary $\partial\Omega$. However, TMP can have sharp variations at certain moments of a cardiac cycle (so called upstroke of an action potential), therefore, the model of twice differentiable function is not quite adequate. For this reason, we consider the boundaries of the domains in class C^∞, which gives us an opportunity to treat the function in the Hilbert space which is a completion of $C^\infty(\Omega)$ with respect to the following norm:

$$\|u\|_{H^s_\Delta(\Omega)} = \left(\|u\|_{H^s(\Omega)} + \|u\|_{H^{s-1/2}(\partial\Omega)} + \|\Delta u\|_{H^{s-2}(\partial\Omega)}\right)^{1/2}$$

This rather not trivial choice of the function space can be justified by the fact that the traces of such functions and its normal derivatives on $\partial\Omega$ belong to a wide class of Sobolev - Slobodetskij spaces: $H^{s-1/2}(\partial\Omega)$ with $s \geq 2$. In particular, this class includes the widely used $L_2(\partial\Omega)$ space, which is convenient for applications.

3. Results

As space precludes a detailed proof of the posed problems, we concentrate on the proposition statements and their interpretation for the inverse problem of ECG.

Proposition 1: If the solution of **Problem 1** exists, it is unique up to an arbitrary additive constant. Although we do not present a detailed proof of the theorem here, we can easily show the uniqueness of such a solution. First, using (2) and (13) we can find the potential u_e and its normal derivative on boundary $\partial\Omega_i$ by solving the Cauchy problem for the Laplace equation:

$$\Delta u_e = 0, \qquad x \in \Omega_e$$
$$u_e(x) = f(x), \qquad x \in \partial\Omega$$

This problem has a unique solution. Next, using (4) we obtain the normal derivative ϕ of u_i on $\partial\Omega_i$. Furthermore, we find u_i in Ω_i by solving the Neumann problem for the Laplace equation:

$$\Delta u_i = 0, \qquad x \in \Omega_i$$
$$n_i \cdot \nabla u_i(x) = \phi(x), \qquad x \in \partial\Omega_i$$

It is known that the Neumann problem has a unique solution up to an additive constant. Finally, we can calculate TMP by the formula: $v = u_i - u_e$.

Proposition 2: The null-space of **Problem 2** consists of all the pairs v, u_e satisfying the following conditions:

$$v = -\frac{u}{\sigma} + c$$
$$u_e = u$$

where c is an arbitrary constant and u is an arbitrary function in the heart domain Ω_m that has a zero trace on its boundary $\partial\Omega_m$.

Therefore, **Problem 2** does not have a unique solution in general. For our application, in particular, TMP cannot be reconstructed inside the myocardial domain. However, TMP on the myocardial surface can be found up to

an arbitrary additive constant. Below we outline the steps necessary for finding the TMP on the myocardial surface.

Let us introduce a new function $w(x)$ satisfying the following equation:

$$w(x) \equiv \frac{\sigma_i}{\sigma_i + \sigma_e} v(x) + u_e(x), \quad x \in \Omega_m$$

According to (7), this is a harmonic function in Ω_m with the normal derivative

$$\frac{\partial w(x)}{\partial n} = \frac{\sigma_b}{\sigma_i + \sigma_e} \frac{\partial u_b(x)}{\partial n}, \quad x \in \partial\Omega_m \qquad (14)$$

Thus, we can apply the same procedure as before for solving **Problem 1**: We find $u_b = u_e$ and $\frac{\partial u_b}{\partial n}$ on $\partial\Omega_m$ by solving the Cauchy problem for the Laplace equation in Ω_b. Next, we calculate $\frac{\partial w}{\partial n}$ on $\partial\Omega_m$ according to (14) and find $w(x)$ in $\overline{\Omega}_m$ as the solution of the Neumann problem for the Laplace equation up to an additive constant. Of course, we cannot isolate $v(x)$ from $w(x)$ inside the myocardial domain, but we can calculate $v(x)$ on the myocardial surface by the following formula:

$$v(x) = \frac{\sigma_i + \sigma_e}{\sigma_i} (w(x) - u_e(x)), \quad x \in \Omega_m \qquad (15)$$

4. Discussion and conclusions

In this study we demonstrated that the uniqueness of TMP reconstruction using body surface ECG measurements depends on the underlying mathematical model. Although application of the cellular model provides theoretical uniqueness of the solution, its practical use is restricted by heart imaging on cellular level on one hand and associated computational efforts on the other hand.

The transition to a well-established macroscopic bidomain model, where extra- and intracellular spaces are homogenized over the whole cardiac tissue, leads to the loss of solution uniqueness inside the myocardium: the nullspace of the solution contains all functions with zero trace on the heart surface. However, TMP can be uniquely reconstructed (up to an additive constant) on the myocardial surface. This fact opens a promising way for noninvasive cardiac mapping.

5. Acknowledgments

The work was supported by the grant of the Russian Federation Government for scientific research under the supervision of a leading scientist at the Siberian Federal University, contract N 14.Y26.31.0006, and by the Russian President's grant for the support of leading scientific schools NSH-9149.2016.1.

References

[1] Ramanathan C, Ghanem RN, Jia P, Ryu K, Rudy Y. Noninvasive electrocardiographic imaging for cardiac electrophysiology and arrhythmia. Nature medicine 2004;10(4):422.

[2] Yamashita Y. Theoretical studies on the inverse problem in electrocardiography and the uniqueness of the solution. IEEE Trans Biomed Eng 1982;(11):719–725.

[3] Dössel O, Schneider F. The nullspace of electrocardiography. Biomedizinische Technik 1997;42(Ergänzungsband 1):37–40.

[4] Messnarz B, Seger M, Modre R, Fischer G, Hanser F, Tilg B. A comparison of noninvasive reconstruction of epicardial versus transmembrane potentials in consideration of the null space. IEEE Trans Biomed Eng 2004;51(9):1609–1618.

[5] Burger M, Mardal KA, Nielsen BF. Stability analysis of the inverse transmembrane potential problem in electrocardiography. Inverse Problems 2010;26(10):105012.

[6] Geselowitz DB, Miller W. A bidomain model for anisotropic cardiac muscle. Ann Biomed Eng 1983;11(3-4):191–206.

Address for correspondence:

Vitaly Kalinin
EP Solutions, SA,
Avenue des Sciences 13, 1400 Yverdon-les-Bains, Switzerland
contact@ep-solutions.ch