Contributions to Simplifying Bidomain Simulations

by

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Introduction

1 Background

The theme of this thesis is the use of the bidomain equations for modeling the electrical activity in the human heart, and the pursuit of ways to use these equations for medical applications. The first paper investigates a simplification of the actual equations themselves which may contribute to speed up the necessary computing. The second looks at their use in inverse methods to identify ischemic heart disease from electrocardiograms (ECGs) recorded at the body surface. In Paper III they are simply used to give indications of where to take measurements of the body surface potential.

The bidomain equations form the conceptual basis of this work, and while the equations themselves are presented in each of the following papers, we will here go into further detail about this model and the electrical properties of the human heart in general.

1.1 Electrocardiography

In 1842 the great pioneer in the study of bioelectricity, Carlo Matteucci, announced that he had demonstrated that an electric current accompanies each heartbeat in a frog. This was very much a qualitative result, limited by the technology available at the time, (see Figure 1), but nevertheless marks the birth of electrocardiography.

After the discovery by Matteucci, many scientists worked on measuring the heart current with increasingly advanced measuring devices as the century wore on. All experiments at this time were done on animals, as the electrodes had to be attached directly to the heart surface. Then, in 1887 Augustus Desiré Waller had an important realization:

> *I studied the hearts of all sorts of animals ... and one fine day after leading off from the exposed heart of a decapitated cat to study the cardiogram by aid of a Lippman electrometer, it occurred to me that it ought to be possible to use the limbs as electrodes and thus lead off from the heart to the electrometer without exposing the heart, i.e. from the intact and normal organ. Obviously man was the most convenient animal to use so I dipped my right hand and*

Figure 1: Carlo Matteucci's illustration of one of his experiments for detecting "animal electricity". This preparation was known as a "rheoscopic frog"; the nerve of a frog's leg was used as the electrical sensor and the twitching of the attached muscle was the visual sign of electrical activity.

> *left foot into a couple of basins of salt solution, which were connected with the two poles of the electrometer and at once had the pleasure of seeing the mercury column pulsate with the pulsation of the heart.... This first demonstration was made in St Mary's laboratory in May 1887 and demonstrated there to many physiologists and among others, to my friend Professor Einthoven of Leiden...* [1]

The drastic improvement of no longer having to cut open the test subject paved the way for use in medicine. In the following decades Professor Einthoven developed the electrocardiogram (ECG) from concept to diagnostic tool, a work for which he received the Nobel Prize in Medicine in 1924. Einthoven identified the characteristic ECG pattern seen in Figure 2, improved the technology of measurements and recording, and identified electrocardiographic features of many heart diseases [2]. He standardized the three limb leads still in use today to measure the potential differences between the right arm and left arm, the right arm and left leg, and the left arm and left leg. Later the six chest electrodes were added. These are called unipolar leads, measuring the potentials between their own position and the *Wilson central terminal*, which is the average of the three limb measurements. Finally, in 1942 Goldberger [3] added the three augmented limb leads, comparing each of the limbs to a combination of the two others. This completed the 12-lead electrocardiogram in use today.

1.2 Cells

The source of the electrical activity in the heart lies at the cellular level. All living cells have a charge difference across the cell membrane, creating a *transmembrane potential*, typically in the range of -50 to -100 mV, with the zero set to be outside the cell. This is due to differing concentrations of positive and negative ions, which can not easily penetrate the cell membrane

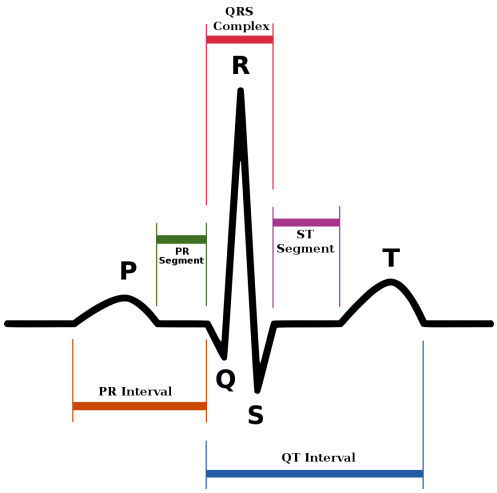

Figure 2: Schematic representation of normal ECG. Einthoven's arbitrary (but alphabetical) nomenclature for the various deflections is still in use today. The P wave is the result of depolarization in the atrias, the QRS complex comes from depolarization in the ventricles, and the T wave is from repolarization in the ventricles. Atrial repolarization happens during ventricular depolarization, and its signal is hidden by the much stronger QRS complex.

except through special ion channels or when carried by transport proteins. Certain types of cells have the ability to change their membrane potentials in response to stimuli, and are termed *excitable*. In neurons and cardiac muscle cells this ability is used to transmit a signal; when the transmembrane potential reaches a certain threshold, special ion channels are opened and ions move through to further raise the potential inside the cell. This *depolarization* is an all-or-nothing effect allowing the so-called *action potential* to travel along the cells without loss of strength. If the cells are electrically connected, such as the heart cells are by *gap junctions*, the signal can also propagate effectively through the tissue. In the heart this allows a depolarization wave to move in a coordinated manner, thus triggering heart contraction and pumping blood through the body.

We can now connect the cellular behavior to the ECG. The spreading depolarization wave is approximated as a surface of dipoles, with the positive poles in front of the wave and the negative pole behind, see [4] for a detailed explanation of why this is so. Einthoven's first lead measures the potential at the left arm, with zero set at the right arm. When the wave moves from the inside to the outside of the left wall of the left ventricle, this lead measures a significant positive signal, which is the R wave marked on Figure 2. The other deflections can be traced to specific movements of the depolarization wave in the same manner.

The standard model for the cell membrane describes it as an electrical circuit consisting of a capacitor in parallel with one ore more resistors. The current density across the membrane (J_m) is written as

$$J_m = C_m \frac{\partial v}{\partial t} + J_{ion}, \tag{1}$$

where C_m is the capacitance of the cell membrane per unit area, and v is the transmembrane potential. The ionic current density J_{ion} is a sum of different currents. In 1952 Hodgkin and Huxley [5] published the first quantitative description of I_{ion}, based on measurements of the giant squid axon, with terms for the sodium and potassium currents, as well as a *leakage current* lumping together all others. Since then numerous models have been developed, of different levels of complexity, and for different types of tissue.

1.3 The Cable Equation

In order to relate the behavior of ionic currents across the cell membrane, described in cell models, to the action potential itself, we need a model for the electrical behavior of the cells. The *Cable Equation* describes a 'leaky' cable and dates back to work done by Lord Kelvin in the 1850s to study the transatlantic telegraph cable.

Consider the cell as a long cylinder where the potential depends only on the length variable, and on time. Here, I_i is the current in the cell, and I_e is the current flowing along the cell in extracellular space. By Ohm's law

these currents are related to the respective potentials u_i and u_e through the equations

$$\frac{\partial u_i}{\partial x} = -I_i r_i, \tag{2}$$

$$\frac{\partial u_e}{\partial x} = -I_e r_e, \tag{3}$$

where r_i and r_e is the resistances per unit length in the intracellular and extracellular media, respectively.

Any current moving from one domain to the other must cross the membrane, and by Kirchhof's first law, which is basically just conservation of charge, the currents must balance. We denote the transmembrane current per unit length I_m, and pick the positive direction to point out of the cell wall resulting in the relationship

$$-\frac{\partial I_i}{\partial x} = \frac{\partial I_e}{\partial x} = I_m. \tag{4}$$

Combining this with equations (2) and (3) we find that

$$I_m = \frac{\partial}{\partial x}\left(\frac{1}{r_i}\frac{\partial}{\partial x}u_i\right), \tag{5}$$

and

$$I_m = -\frac{\partial}{\partial x}\left(\frac{1}{r_e}\frac{\partial}{\partial x}u_e\right). \tag{6}$$

The transmembrane potential is simply defined to be the difference between the potentials on either side of the cell membrane, written $v = u_i - u_e$. Assuming that r_i and r_e are constant along the cell, we find that

$$\begin{aligned} \frac{\partial^2 v}{\partial x^2} &= \frac{\partial^2}{\partial x^2}(u_i - u_e) \\ &= \frac{\partial^2 u_i}{\partial x^2} - \frac{\partial^2 u_e}{\partial x^2} \\ &= r_i I_m + r_e I_m \\ &= (r_i + r_e) I_m. \end{aligned} \tag{7}$$

We now recall from Section 1.2 that the transmembrane current is the combination of the capacitive and ionic currents. In order to relate I_m, which is the current passing through the membrane per unit length, to the transmembrane current per area from Equation (1), we merely need to multiply J_m with the circumference (c) of the cylinder; $I_m = cJ_m$. Consequently,

$$\begin{aligned} \frac{\partial^2 v}{\partial x^2} &= (r_i + r_e) I_m, \\ \frac{1}{r_i + r_e}\frac{\partial^2 v}{\partial x^2} &= c J_m, \\ \frac{1}{r_i + r_e}\frac{\partial^2 v}{\partial x^2} &= c\left(C_m \frac{\partial v}{\partial t} + J_{ion}\right). \end{aligned} \tag{8}$$

Equation (8) is the cable equation and one can insert a cell model of one's choice through the J_{ion} term. This equation can be used to model both the nerve axon and a muscle cell. Furthermore, strips of heart muscle show 'cable-like' properties when a signal moves along the muscle fibres [6].

1.4 The Bidomain Equations

Before taking on the bidomain model we should deal with the somewhat simpler issue of modeling the rest of the body. As accounting for every single cell is a Herculean task when dealing with anything but the smallest tissue samples we make use of continuum mechanics. Basically this means that when considering a physical parameter at any point in space, one substitutes the average value over a volume centered at this point. Thus one considers a material to be continuous, ignoring the fact that it consists of individual atoms, molecules, mineral grains or in our case cells. For this approach to be feasible there must be a volume for averaging that is large compared to the microstructure of the medium but small compared to the dimension of the problem studied.

As before we assume that the relationship between current density J and potential u is ohmic,

$$J = -M\nabla u, \tag{9}$$

where the negative sign is a convention. The conductivity (M) is a tensor to account for anisotropy in the material. For body tissue outside the heart we further assume that there are no current sources or sinks in the material, and no build up of charge. This can be written mathematically as $\nabla \cdot J = 0$, leading to the equation used to model the potential field in the torso in this work;

$$\nabla \cdot (M\nabla u) = 0. \tag{10}$$

The *Bidomain Model* is the extension of cable theory to three-dimensional space. As the welter of interconnected muscle cells cannot be properly described by a simple geometrical model, it also makes use of the concept of continuum mechanics. Any point in the heart tissue is either inside a cell, in the extracellular domain, or in the cell membrane. However, by using spatial averaging one can state that there exist averages at any point over

the nearby intracellular currents and potentials. The same applies for the extracellular and transmembrane properties. The concept of modeling cardiac tissue as interpenetrating domains was first proposed in 1969 [7], and the first works were published in 1978; two articles by Miller and Geselowitz [8, 9] and Tung's PhD thesis [10].

Both domains are assumed to be ohmic, and therefore Ohm's law must also hold for the spatial averages;

$$J_i = -M_i \nabla u_i, \tag{11}$$
$$J_e = -M_e \nabla u_e. \tag{12}$$

As in the derivation of the cable equation, any current that exits one domain must enter the other. This can be written as

$$\nabla \cdot J_i + \nabla \cdot J_e = 0. \tag{13}$$

Inserting (11) and (12) in (13) results in

$$\nabla \cdot (M_i \nabla u_i) + \nabla \cdot (M_e \nabla u_e) = 0, \tag{14}$$

which is the first of the bidomain equations, providing the relationship between the extracellular and intracellular potentials. For our purposes we prefer to work with the extracellular and transmembrane potentials, and so we insert $u_i = v + u_e$ in (14) and do some reshuffling, to end up with

$$\nabla \cdot (M_i \nabla v) + \nabla \cdot ((M_i + M_e) \nabla u_e) = 0. \tag{15}$$

The total current going form one domain to the other per unit volume is denoted i_m, and again we set the positive direction to be out of the intracellular domain, resulting in

$$i_m = -\nabla \cdot J_i = \nabla \cdot (M_i \nabla u_i), \tag{16}$$

which can be related to the transmembrane current per area from Equation (1) by introducing χ, the ratio of cell membrane area per unit volume. This leads to the second of the bidomain equations;

$$\nabla \cdot (M_i \nabla u_i) = \chi \left(C_m \frac{\partial v}{\partial t} + J_{ion} \right). \tag{17}$$

Again we prefer to deal with the extracellular and transmembrane potentials, and so the final equation becomes

$$\nabla \cdot (M_i \nabla v) + \nabla \cdot (M_i \nabla u_e) = \chi \left(C_m \frac{\partial v}{\partial t} + J_{ion} \right). \tag{18}$$

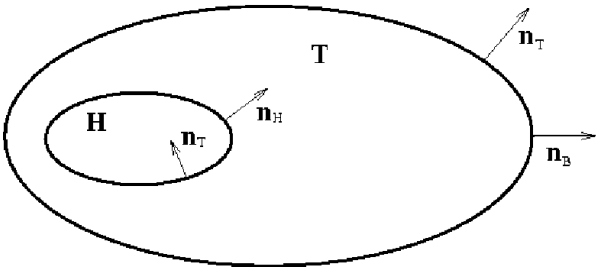

Figure 3: Schematic representation of the heart and torso domains.

1.5 Interface and Boundary Conditions

In order to use the bidomain equations (15) and (18) we also need a set of boundary conditions. We define the heart domain, denoted H, as the physical space containing both the extracellular and intracellular domains, and the torso domain, T, as the rest of the body. In an experimental setting, T could also describe, e.g., a liquid tank in which the heart is submerged. In the following the current,the conductivity and the potential in the torso domain are denoted J_o, M_o and u_o, respectively. The border between the torso and the heart is denoted ∂H, see Figure 3.

It is a feature of the bidomain model, as described by Tung [10], that there is no current going directly from the intracellular domain to the torso domain;

$$J_i \cdot \mathbf{n_H} = 0 \quad \text{on } \partial H, \tag{19}$$

where $\mathbf{n_H}$ is the unit length normal vector directed outwards from the heart surface. Inserting Equation (11) and replacing u_i with $v + u_e$, gives the commonly used form

$$(M_i \nabla v + M_i \nabla u_e) \cdot \mathbf{n_H} = 0 \quad \text{on } \partial H. \tag{20}$$

As for the interaction between the extracellular and torso domains, these are two connected volume conductors and so the potentials must match up at the interface, and any current leaving one domain must enter the other, i.e.;

$$u_e = u_o \quad \text{on } \partial H, \tag{21}$$

$$(M_e \nabla u_e) \cdot \mathbf{n_H} = -(M_o \nabla u_o) \cdot \mathbf{n_T} \quad \text{on } \partial H, \tag{22}$$

where $\mathbf{n_T}$ is the unit length normal vector directed *inwards* from the heart surface.

It is assumed that no current leaves the body surface (∂B). (Here, $B = \bar{H} \cup T$ is the body including the heart.) Thus the boundary condition on ∂B is

$$(M_o \nabla u_o) \cdot \mathbf{n_B} = 0 \quad \text{on } \partial B. \tag{23}$$

1.6 The Biodomain Model

We now have a system of coupled partial difference equations that constitute the core of the bidomain model:

$$\nabla \cdot (M_i \nabla v) + \nabla \cdot ((M_i + M_e) \nabla u_e) = 0 \quad \text{in } H, \tag{24}$$

$$\nabla \cdot (M_i \nabla v) + \nabla \cdot (M_i \nabla u_e) = \chi \left(C_m \frac{\partial v}{\partial t} + J_{ion} \right) \quad \text{in } H. \tag{25}$$

Together with the interface conditions (20) - (22), a cell model for J_{ion}, and equations(10) and (23) for the electric field in the torso, they provide a mathematical tool capable of connecting the electrophysiology at the cellular level to the body surface potential field. These equations will be the starting point for each of the papers in this thesis.

A more in-depth treatment of the subjects mentioned in this section can be found in, e.g., the books by Keener and Sneyd [11], Sundnes et al. [12] and Pullan et al. [13].

2 Summary of the Papers

The depolarization described above is a very quick phenomenon, meaning that the width of the depolarization is very small, estimated as being 0.32mm when propagating transverse to the fibre direction [14]. This leads to strict requirements for a finite element discretization of equations (24) and (25). It has been argued that a spatial resolution of 0.2mm is needed [15, 16]. Assuming a heart volume of 300cm^3, this means more than 37 million computational points. With a temporal resolution of, e.g., 0.1ms it consequently takes something like 5000 time steps to simulate a complete heartbeat. One must then solve a complex nonlinear fully coupled set of partial differential equations, connected to a cell model, which is often a large system of ordinary differential equations, to be solved at each grid node. Solving the bidomain model numerically is therefore a daunting task, both in terms of CPU-time and memory, only possible with extensive parallel computing or massive supercomputing facilities. In addition many conceivable applications of this model require that the system is solved many times. Clearly some improvements and (or) simplifications are needed.

Solving systems of ODEs, such as the different cell models, is an extensive research field. The reader is referred to, e.g., [17, 18]. For the more specific

issue of the bidomain model itself, various research groups are working on solution techniques like operator splitting, adaptivity, preconditioning, and parallelization, see e.g. [12, 13, 19, 20].

Another approach, often used in conjunction with improved solution techniques, is to simplify the model itself. One can use simpler cell models, perhaps just one equation in place of the more realistic systems of ODEs. Assumptions can be made on the variables in the equations. The required number of computations can be reduced directly by modeling small pieces of tissue, and/or brief spans of time. The grid can be made two-dimensional, and the geometry of the heart, the torso, or associated phenomena such as an ischemic region, can be simplified.

This thesis is an attempt to contribute to the understanding and use of some of these simplifications. Specifically, we will do the following:

- In Paper I we propose and analyze an optimalization process for monodomain approximations of the bidomain equations.
- In Paper II we propose a simplified approach for the inverse problem of identifying the characteristics of an ischemic region from measurements of the potential distribution on the body surface.
- In Paper III we consider where on the body surface recordings should be taken when using only a limited number of discrete measuring points, instead of assuming the entire BSPM is known.

2.1 Paper I: Optimal Monodomain Approximations of the Bidomain Equations

An obvious and well-known simplification of the bidomain equations is achieved by assuming that the conductivity tensors are proportional, i.e., $M_e = \lambda M_i$. One can then eliminate M_e from Equation (24) to end up with

$$\nabla \cdot (M_i \nabla v) + \nabla \cdot ((M_i + \lambda M_i) \nabla u_e) = 0. \tag{26}$$

Solving for $\nabla \cdot (M_i \nabla u_e)$ and inserting the result in Equation (25) leaves

$$\frac{\lambda}{1+\lambda} \nabla \cdot (M_i \nabla v) = \chi \left(C_m \frac{\partial v}{\partial t} + I_{ion} \right). \tag{27}$$

Thus it is possible to find the transmembrane potential by solving Equation (27) and then, if desirable, to solve (26) for the extracellular potential. It is simpler and faster than solving the coupled system (24) and (25). This is called the *Monodomain* model. The main disadvantage is of course that it is known from experiments that the conductivity tensors are not actually proportional. Also, certain aspects of the electrophysiology disappears when the model is simplified. As long as one keeps these weaknesses in mind the mondomain model is still useful in allowing quicker computation.

It is, however, difficult to find a suitable value for λ. As there is no "true" value one must instead look for something that will minimize the error caused by the initial assumption. One simple approach is to look for the value that minimizes the difference between M_e and λM_i, measured in a suitable norm. This provides a *feasible* value for λ, but not one that in general causes the least difference between the actual solutions of the bidomain and monodomain models.

In this paper we investigate a method for finding an optimal value for λ at each time step for a computation, resulting in a time-dependent coefficient $\lambda = \lambda(t)$. We show that it is possible to solve this problem without having to solve the bidomain model, by defining optimality in a suitable "energy" norm.

We test this method by running numerical experiments using a two-dimensional grid, modeling a slice of the heart, and not including the torso domain. The results of both the new method and the standard monodomain method are compared with a bidomain solution, and we find that the optimalization method gives superior results. This optimalization method adds only slightly to the CPU demand compared to the standard monodomain solver.

2.2 Paper II: A Computationally Efficient Method for Determining the Size and Location of Myocardial Ischemia

With the bidomain model it is possible to simulate the effect on the body surface potentials from conditions in the heart. By altering some of the constants in the model itself and/or the associated cell model one can simulate an ischemic region, and model the effects on an ECG measurement.

In this context the inverse problem is to look at the electrical potential on the body surface and calculate the potential distribution in the heart. This could possibly have applications in medical diagnostics.

In this paper we propose an algorithm for identifying the size and position of an ischemic region. We utilize a level set method, introduced in [21, 22], to make an initial estimate for the position. This is combined with a simpler minimization problem to determine the size. Due to the structure of the arteries supplying blood to the heart, an ischemia will start at the endocardial surface, and we use this knowledge to put constraints on the possible positions. We do not try to determine the shape but instead make the assumption that the ischemia is spherical. This allows for the size to be determined using just one variable, the radius.

In order to test this algorithm we run numerical experiments using a stationary model. We estimate the transmembrane potentials in the heart during the resting stage between heartbeats, and use Equation (24) together with the usual boundary conditions (20)-(23), and Equation (10) for the potential in the body. This model is employed on a two-dimensional grid with heart and torso domains. This allows for a reduction in computing time that makes an iterative method feasible. Ischemia is simulated by altering

the transmembrane potential and the conductivities in the ischemic region.

Based on our experiments, this method is a promising alternative to the straightforward level set approach.

2.3 Paper III: Body Surface ST shifts Generated by Ischemic Heart Disease; a Simulation Study

The previous paper used (synthetic) Body Surface Potential Maps (BSPMs) to gain information about ischemic regions, with the assumption that information from the entire body surface was available. In medical diagnostics a set of nine electrodes are placed on the body to measure an ECG. In real-world applications of simulation based diagnostics only values for the potential at specific points at the body surface of the patient would be available. However, the traditional ECG measuring points are not obviously sufficient or optimal for such an application.

In this paper we again use the stationary approximation of the complete bidomain model, this time to model the ST segment in the heartbeat. As in the previous paper, ischemic regions are defined as the intersection of the heart grid and a sphere centered at some point on the endocardial surface. We run simulations for 26 different cases of ischemia, varying the size and position. The resulting data is analyzed in terms of where measurements should be recorded for satisfactory coverage.

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