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Mathematical models and problems in electrocardiology (**)

dedicated to the memory of Giulio Di Cola

Introduction

Mathematical models and problems of various kind are encountered in cardiology. These problems are related to the flow of blood through the heart (fluid-dynamics), to the rhythmic contraction and dilatation of the heart (linear and nonlinear elasticity), to potential problems and the spreading of the excitation wavefront related to the bioelectric activity of the heart. We shall limit ourselves to problems in electrocardiology.

Most of the above problems in electrocardiology have been investigated by our group in cooperation with B. Taccardi who was for some years professor of physiology at Parma University, and is now with CVRTI (Cardiovascular Research and Training Institute) University of Utah, Salt Lake City, USA. Part of the researches have been carried out with physiologists of the Parma University and some mathematical problems in electrocardiology have been investigated at the Department of Mathematics of Parma University by a research unit under the direction of G. Di Cola.

These researches fit in the framework of a vast area of Applied Mathematics, i.e. Mathematical Physiology, see e.g. [**30**] and also for more detailed electro-physiological descriptions [**37**], [**24**], [**36**].

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1 - Bidomain model and reaction-diffusion systems

The bioelectric activity of the heart during an heartbeat is a fairly complex phenomenon of which we give only a brief description. The problems which we shall consider can be studied at the cellular or at the macroscopic level; we shall deal only with macroscopic models.

In the bidomain model [**24**], [**42**], [**48**], [**11**] the cardiac tissue is characterized by the intra (i) and the extracellular (e) media which we consider at a macroscopic level so that they are superposed continuous media with related potentials u_i, u_e. The two media are connected by the distributed cellular membrane and we consider also the transmembrane potential $v = u_i - u_e$.

The anisotropy of the (i) and (e) media depends on the fiber structure of the myocardium. At the macroscopic level the fibers are regular curves and we denote by $\boldsymbol{a} = \boldsymbol{a}(\boldsymbol{x})$ the unit vector tangent to the fiber at $\boldsymbol{x}$.

Starting from the sino-atrial node, which acts as a pacemaker, a front-like variation of the transmembrane potential v spreads first in the atria and then through the myocardium with a very fast transition from the resting v_r to the plateau value v_p. The values of v_r, v_p for the cardiac cell are about -90 mV and 10 mV. This phase constitutes the excitation or depolarization phase; it is followed by an interval of almost constant potential (refractory period) and a subsequent slower return to the initial state (repolarization). The time behavior of the transmembrane potential $v(\boldsymbol{x}, t)$, also called the action potential, may depend generally, on the position $\boldsymbol{x}$ and on the local state of the heart and the duration from depolarization to the return to the initial value v_r is about 300 ms in the human heart.

The fiber structure [**49**] strongly affects the excitation process and in particular is the main factor of the anisotropic conductivity in the cardiac tissue [**39**].

The whole process is quite complicate and is essentially due to a flow of sodium, potassium and calcium ions through the cellular membrane separating the (i) and (e) media. The process can be modeled by a set of ordinary differential equations of Hodgkin-Huxley type [**26**] or in qualitative studies by a simplified model of FitzHugh-Nagumo type [**20**].

Denoting by $\sigma_l^{i,e}$, $\sigma_t^{i,e}$ the conductivity coefficients along and across the fiber direction at a point $\boldsymbol{x}$ and always assuming axial simmetry for $\sigma_t^{i,e}$ we have in the media (i), (e) the conductivity tensors

$$M_{i,e} = \sigma_t^{i,e} I + (\sigma_l^{i,e} - \sigma_t^{i,e})\, \boldsymbol{a}\boldsymbol{a}^T.$$

Since the anisotropic conductivity is related to the fiber structure, the matrices

M_i, M_e have the same principal axes, one being the local fiber direction $\boldsymbol{a}$, the other two given by any orthogonal couple of unit vectors perpendicular to $\boldsymbol{a}$. The corresponding eigenvalues are $\sigma_l^{i,e}$ (simple) and $\sigma_t^{i,e}$ (double). The coefficients $\sigma_l^{i,e}$, $\sigma_t^{i,e}$ may depend in general on the position $\boldsymbol{x}$ and on the local state of the myocardial tissue; in our simulations we assume them constant.

To the potentials u_i, u_e are associated the current densities:

$$\boldsymbol{J}_i = -M_i \nabla u_i + \boldsymbol{J}_i' \qquad \boldsymbol{J}_e = -M_e \nabla u_e + \boldsymbol{J}_e'$$

in the myocardial volume Ω_H, where $\boldsymbol{J}_i'$, $\boldsymbol{J}_e'$ are applied currents. The heart is imbedded in an extracardiac medium Ω_0 (e.g. blood or physiological fluid) with conductivity $M_0 = \sigma_0 I$, current density $\boldsymbol{J}_0 = -M_0 \nabla u_0$ and potential u_0. Let

$$\overline{\Omega} = \overline{\Omega}_H \cup \overline{\Omega}_0, \qquad \Gamma = \partial\Omega, \qquad \Sigma = \partial\Omega_H$$

i.e. Ω, Γ and Σ represent the body volume, the body surface and the epi and endocardium, assumed entirely in contact with the extracardiac medium Ω_0. Moreover since the body is imbedded in the air, which is an insulating medium, Γ is an insulated boundary.

Since induction effects are negligible (see [**36**], [**38**]) the current field can be considered quasi-static. Therefore if there are no external applied sources, the field $\boldsymbol{J}_i + \boldsymbol{J}_e$ is solenoidal and the same holds for $\boldsymbol{J}_0$. We then have:

$$\begin{cases} \operatorname{div}(\boldsymbol{J}_i + \boldsymbol{J}_e) = 0 & \text{in } \Omega_H \\ \operatorname{div} \boldsymbol{J}_0 = 0 & \text{in } \Omega_0 \end{cases}$$

$u_e = u_0$ and $\boldsymbol{n}^T(\boldsymbol{J}_i + \boldsymbol{J}_e) = \boldsymbol{n}^T \boldsymbol{J}_0$, $\boldsymbol{n}^T \boldsymbol{J}_i = 0$ on the surface Σ and $\boldsymbol{n}^T \boldsymbol{J}_0 = 0$ on Γ; $\boldsymbol{n}$ is the normal to Σ or Γ.

In terms of u_i, u_e, u_0 the above differential system becomes:

$$\begin{cases} \operatorname{div}(M_i \nabla u_i + M_e \nabla u_e) = 0 & \text{in } \Omega_H \\ \operatorname{div} M_0 \nabla u_0 = 0 & \text{in } \Omega_0. \end{cases} \tag{1}$$

Using the relation $v = u_i - u_e$ the first equation becomes:

$$\operatorname{div} M \nabla u_e = -\operatorname{div} M_i \nabla v \qquad M = M_i + M_e \tag{2}$$

the condition on Σ:

$$u_0 = u_e, \qquad \boldsymbol{n}^T(M \nabla u_e + M_i \nabla v) = \boldsymbol{n}^T M_0 \nabla u_0 \tag{3}$$

and on the insulated boundary Γ we have

$$\boldsymbol{n}^T(M_0 \nabla u_0) = 0 \qquad on\ \Gamma. \tag{4}$$

This potential problem provides the framework for relating the torso potential to the transmembrane potential v; in fact, if $v(\boldsymbol{x}, t)$ is known, then the previous boundary value problem characterizes univocally, up to an additive constant, the extracellular and extracardiac potentials u_e, u_0.

The currents $\boldsymbol{J}_i$, $\boldsymbol{J}_e$ are related to the membrane current i_m by the conservation law $i_m = -\ \mathrm{div}\ M_e \nabla u_e = \mathrm{div}\ M_i \nabla u_i$; applying the nonlinear cable theory for the membrane current (see [**26**]) in terms of potentials we have the following reaction-diffusion (R-D) system:

$$\begin{cases} \mathrm{div}\ (M_i \nabla u_i) = i_m & \text{in } \Omega_H \\ \mathrm{div}\ (M_e \nabla u_e) = -\ i_m & \text{in } \Omega_H \\ i_m = \beta\ (C_m \partial_t v + I_{ion}), \quad v = u_i - u_e \end{cases} \tag{5}$$

where β is the membrane surface area per unit volume and C_m is the membrane capacitance. I_{ion} results from the combination of various ionic fluxes, i.e.

$$I_{ion} = \Sigma_s I_s \tag{6}$$

where

$$I_s = \bar{g}_s \prod_r y_r^{p_{rs}} (v - \bar{v}_s) \tag{7}$$

with p_{rs} non negative integer. The conductance variables y_r satisfy the ordinary differential equations:

$$\partial_t y_r = \alpha_r(v)(1 - y_r) - \beta_r(v)\, y_r. \tag{8}$$

Successive refinements of the I_{ion} model for cardiac cells and the parameters calibration appearing in (7, 8), by fitting new available experimental data, start from the Beeler-Reuter model in 1977, with $s = 4$, $r = 7$ [**3**], then Ebihara-Johnson in 1980 [**19**], Di Francesco-Noble 1985 [**18**], and Lou-Rudy 1991, 1995, with $s = 6$, $r = 9$ [**32**], [**33**]. The reaction diffusion system (R-D) represents a macroscopic description of the entire electric behavior of the cardiac tissue, i.e. depolarization and repolarization phases. To this end it was used for a few 2-D and 3-D simulations in a small piece of tissue [**6**], [**25**], [**41**], [**21**], [**22**], [**40**].

In problem (5) the transmembrane potential v exhibits a steep propagating layer spreading throughout the myocardium with an upstroke phase lasting about 1 ms during the depolarization process. The numerical solution of the problem re-

quires small space and time steps (of the order of 0.1 mm and 0.05 ms). For this reason the numerical simulations of only the excitation process were limited to a 3-D block with dimensions of few cm [**6**], [**25**].

For large scale simulations involving the whole ventricles the computer memory and time requirements become excessive and a less demanding approximation must be developed.

2 - Wavefront propagation and eikonal approximations

The main feature of the depolarization phase is the excitation wavefront configuration and motion. Hence we must investigate the internal layer of v which affects the spreading. To this end we can disregard the fine details associated to the ionic fluxes through the cellular membrane considering a simplified model of the membrane current called the FitzHugh-Nagumo approximation [**20**], [**11**]. For the excitation phase this model yields $I_{ion} = f(v)$ with $f(v)$ a cubic-like function of v; scaling appropriately the R-D system (see [**11**], [**13**]) we have the following singularly perturbed R-D system with $v = u_i - u_e$:

$$\text{(9)} \qquad \begin{cases} \partial_t v + \dfrac{1}{\varepsilon} f(v) - \varepsilon \ \mathrm{div}\,(M_i \nabla u_i) = 0 \\ -\partial_t v - \dfrac{1}{\varepsilon} f(v) - \varepsilon \ \mathrm{div}\,(M_e \nabla u_e) = 0 \end{cases} \qquad \text{in } \Omega_H .$$

This system must be closed by suitable boundary conditions which for an insulated heart are given by $\boldsymbol{n}^T M_{i,e} \nabla u_{i,e} = 0$ on $\partial\Omega_H$ and by the initial condition $v(\boldsymbol{x}, 0) = v_0(\boldsymbol{x})$.

We introduce the *activation time* $\varphi(\boldsymbol{x})$ which, for a given stimulation, is the time instant in which the v potential at $\boldsymbol{x}$ reaches the value $(v_r + v_p)/2$. The level surface $t = \varphi(\boldsymbol{x})$ represents then the excitation wavefront S_t at time t; actually it is the median surface of the thin layer where depolarization occurs. $\varphi(\boldsymbol{x})$ is a smooth function time-independent so that in the numerical simulations we can use a greater space step (about 1-2 mm) achieving a reduction by a factor of 4^3 in the number of grid nodes. We define:

$$\text{(10)} \qquad \Phi(\boldsymbol{x}, \boldsymbol{\xi}) = (q_i(\boldsymbol{x}, \boldsymbol{\xi})^{-1} + q_e(\boldsymbol{x}, \boldsymbol{\xi})^{-1})^{-1/2}$$

where

$$\text{(11)} \qquad q_{i,e}(\boldsymbol{x}, \boldsymbol{\xi}) = \boldsymbol{\xi}^T M_{i,e}(\boldsymbol{x})\, \boldsymbol{\xi} .$$

If $\boldsymbol{n}$ is a unit vector $q_{i,e}(\boldsymbol{x}, \boldsymbol{n})$ represents the conductivity coefficient at a point $\boldsymbol{x}$ in the intra and extra-cellular medium measured along the direction $\boldsymbol{n}$. The function Φ is the harmonic mean of the quadratic forms associated to the conductivity tensors $M_{i,e}$ [**11**].

Then using suitable perturbation analysis, see [**11**], [**13**], we obtain up to first order in ε, the equation:

$$c\ \Phi(\boldsymbol{x}, \nabla\varphi) - \varepsilon\ \mathrm{div}\ (\Phi_{\xi}(\boldsymbol{x}, \nabla\varphi)\ \Phi(\boldsymbol{x}, \nabla\varphi)) = 1 \qquad \text{in } \Omega_H \tag{12}$$

or, also up to terms of order $O(\varepsilon^2)$ (see [**4**], [**27**], [**29**], [**30**]) we have:

$$\Theta(\boldsymbol{n}) = \frac{1}{|\nabla\varphi|} = \Phi(\boldsymbol{x}, \boldsymbol{n})(c - \varepsilon\ \mathrm{div}\ \Phi_{\xi}(x, \boldsymbol{n})) \tag{13}$$

where $\boldsymbol{n} = \dfrac{\nabla\varphi}{|\nabla\varphi|}$ and $\Theta(\boldsymbol{n})$ are the normal to the front and the front velocity along $\boldsymbol{n}$; c is defined later by problem (15). The term of order ε is related to the influence of the wavefront curvature on the propagation in an anisotropic medium.

The transmembrane potential distribution in the eikonal approach is approximated by

$$v_{\varepsilon}(\boldsymbol{\xi}, t) = a\left(\frac{t - \varphi(\boldsymbol{\xi})}{\varepsilon}\right). \tag{14}$$

where (c, a) is the unique bounded solution of the eigenvalue problem:

$$\begin{cases} a'' + c\ a' + f(a) = 0 \\ a(\mp\infty) = v_r \text{ or } v_p, \qquad a(0) = (v_p + v_r)/2\ . \end{cases} \tag{15}$$

The condition $a(\mp\infty)$ corresponds to a stretching of the upstroke of the transmembrane potential near the wavefront.

The R-D model and the eikonal approximation have been tested on a small volume and the results have been found in very close agreement [**6**].

Therefore large scale simulations, concerning the depolarization process in the whole heart, can be performed by computing the activation time $\varphi(\boldsymbol{x})$ related to one of the two eikonal-curvature equations (12, 13) using a fairly large space resolution of the order of 1 mm since the activation time $\varphi(\boldsymbol{x})$ is a smooth function without internal or boundary layers. From the knowledge of the activation time we derive the transmembrane potential v_{ε} from equation (14). Then in the differential problem (2) the transmembrane potential v_{ε} acts as a source term while u_e and u_0 (if Ω_H is not insulated) are the quantities to be determined. This procedure

allows to perform an analysis of the potential pattern on the epi and endocardium and intramurally and also to study the morphology of the associated electrocardiograms. This last study can be more efficiently carried out by means of an integral representation of the potential.

We define:

$$\widehat{M} = \widehat{M}(\boldsymbol{x}) = \begin{cases} M(\boldsymbol{x}) & \boldsymbol{x} \in \Omega_H \\ M_0(\boldsymbol{x}) & \boldsymbol{x} \in \Omega_0 \end{cases}, \qquad u(\boldsymbol{x}, t) = \begin{cases} u_e(\boldsymbol{x}, t) & \boldsymbol{x} \in \Omega_H \\ u_0(\boldsymbol{x}, t) & \boldsymbol{x} \in \Omega_0 \end{cases}$$

with $M_0(\boldsymbol{x}) = \begin{cases} \sigma_f I & \boldsymbol{x} \in \Omega_f \\ \sigma_b I & \boldsymbol{x} \in \Omega_b \end{cases}$ the conductivity tensor in $\Omega_0 = \Omega_b \cup \Omega_f$ where Ω_b, Ω_f are the volumes occupied by the blood or by the fluid.

Moreover we set:

$$\boldsymbol{J}_{v_\varepsilon} = -M_i \nabla v_\varepsilon$$

then collecting equations (1, 3, 4) we have the following boundary value problem:

$$(16) \qquad \begin{cases} -\operatorname{div} \widehat{M} \nabla u = \begin{cases} \operatorname{div} \boldsymbol{J}_{v_\varepsilon} & \text{in } \Omega_H \\ 0 & \text{in } \Omega_0 \end{cases} \\ [\![u]\!]_\Sigma = 0, \quad [\![\boldsymbol{n}^T \widehat{M} \nabla u]\!]_\Sigma = \boldsymbol{n}^T \widehat{M} \nabla v_\varepsilon & \text{on } \Sigma \\ \boldsymbol{n}^T \widehat{M} \nabla u = 0 & \text{on } \Gamma \end{cases}$$

$[\![\phi]\!]_\Sigma$ denotes the jump of ϕ through Σ, i.e. $[\![\phi]\!]_\Sigma = \phi_{\Sigma^+} - \phi_{\Sigma^-}$ with $\phi_{\Sigma^\pm}$ the traces of ϕ taken on the positive and negative side of Σ with respect to the oriented normal.

For the solution of the bidomain model (16) in differential form the following integral representation holds:

$$(17) \qquad u(\boldsymbol{x}, t) - u(\boldsymbol{x}_0, t) = \int_{\Omega_H} \boldsymbol{J}_{v_\varepsilon}^T \nabla_\xi \psi \, \mathrm{d}\xi = -\int_{\Omega_H} (\nabla_\xi v_\varepsilon(\boldsymbol{\xi}, t))^T M_i(\boldsymbol{\xi}) \nabla_\xi \psi \, \mathrm{d}\xi$$

where, for the observation point $\boldsymbol{x}$, the Green function $\psi(\boldsymbol{\xi}, \boldsymbol{x})$, also called *lead field*, is the solution of the problem defined by:

$$(18) \qquad \begin{cases} -\operatorname{div}_\xi \widehat{M} \nabla_\xi \psi = \delta(\boldsymbol{\xi} - \boldsymbol{x}) - \delta(\boldsymbol{\xi} - \boldsymbol{x}_0) & \text{in } \Omega_0 \cup \Omega_H \\ \boldsymbol{n}^T \widehat{M} \nabla_\xi \psi = 0 & \text{on } \Gamma. \end{cases}$$

$\delta(\boldsymbol{\xi} - \boldsymbol{x})$, $\delta(\boldsymbol{\xi} - \boldsymbol{x}_0)$ are the Dirac measures in $\boldsymbol{x}$, $\boldsymbol{x}_0$ respectively.

The lead field ψ is the potential arising from the source and sink located at the observation and reference points $\boldsymbol{x}$ and $\boldsymbol{x}_0$ respectively in the body volume conductor.

We remark that in the case of media with equal anisotropy ratio $\varrho_i = \varrho_e$, where $\varrho_i = \sigma_l^i/\sigma_t^i$, $\varrho_e = \sigma_l^e/\sigma_t^e$, we have $M_e = \lambda M_i$ with $\lambda = \sigma_l^e/\sigma_l^i = \sigma_t^e/\sigma_t^i$ and $M = (1+\lambda)\, M_i$. Under this assumption and for λ constant we have:

$$u(\boldsymbol{x}, t) - u(\boldsymbol{x}_0, t) = -\frac{1}{1+\lambda} \int_{\Omega_H} \boldsymbol{J}_{v_\varepsilon}^T \nabla_\xi \psi \, \mathrm{d}\xi = -\int_{\Omega_H} \nabla_\xi v_\varepsilon^T M_i \nabla_\xi \psi \, \mathrm{d}\xi$$

and applying formally the Green formula, it follows

$$u(\boldsymbol{x}, t) - u(\boldsymbol{x}_0, t) = -\frac{1}{1+\lambda} \int_\Sigma v_\varepsilon \boldsymbol{n}^T M \nabla_\xi \psi \, \mathrm{d}\sigma_\xi +$$

$$+ \frac{1}{1+\lambda} \int_{\Omega_H} v_\varepsilon \operatorname{div} M \nabla_\xi \psi \, \mathrm{d}\xi \qquad \text{for } \boldsymbol{x} \in \Omega_H \cup \Omega_0.$$

Taking into account (18) this expression reduces to

$$u(\boldsymbol{x}, t) - u(\boldsymbol{x}_0, t) = -\frac{1}{1+\lambda} \int_\Sigma v_\varepsilon \boldsymbol{n}^T M \nabla_\xi \psi \, \mathrm{d}\sigma_\xi + \tag{19}$$

$$+ \frac{1}{1+\lambda} [\tilde{v}_\varepsilon(\boldsymbol{x}, t) - \tilde{v}_\varepsilon(\boldsymbol{x}_0, t)].$$

where $\tilde{v}_\varepsilon(\boldsymbol{x}, t) = \begin{cases} v_\varepsilon(\boldsymbol{x}, t) & \boldsymbol{x} \in \Omega_H \\ 0 & \boldsymbol{x} \in \Omega_0 \end{cases}$. Therefore in the case of equal anisotropy ratio the potential representation, apart an additive term proportional to the transmembrane potential, consists of an integral over the heart surface $\Sigma = \partial\Omega_H$. We refer to this model as the *heart surface source* (HSS), i.e. the potential is generated by a double layer on the heart surface Σ (see [**21**], [**48**], [**54**]).

3 - Models of the potential field: various degrees of approximation

The experimental results of Corbin and Scher in 1976 [**17**] indicated that the commonly accepted model of the uniform normal dipole layer is not a correct representation of the heart sources on the excitation wavefront.

In fact we may have negative potential values ahead of the front in the resting (not yet excited) tissue and in the case of a closed front the potential is not constant outside the front.

Corbin and Scher [**17**] attributed the discrepancies to the fiber structure of the heart and proposed an axial dipole layer model, i.e. with the dipole axis defined by the local fiber direction $\boldsymbol{a} = \boldsymbol{a}(\boldsymbol{x})$ and longitudinal dipole moment d_l. In this model it was also assumed that the axial dipole layer is imbedded in an isotropic and homogeneous medium. This model has been extended by considering the superposition to the axial layer of two mutually orthogonal dipole layers; these layers have dipole direction transverse to the fiber axis and the same dipolar moment d_t, see [**13**], [**14**], [**15**].

The corresponding potential can be expressed as the potential due to the superposition of a uniform normal double layer characterized by $d_t \boldsymbol{n}$ and an «axial» double layer characterized by $(d_l - d_t)(\boldsymbol{a}^T \boldsymbol{n})\, \boldsymbol{a}$, see [**14**]; hence the source is related to the dipolar tensor:

$$D = d_t I + (d_l - d_t)\, \boldsymbol{a}\boldsymbol{a}^T.$$

In an unbounded homogeneous and isotropic medium with conductivity σ_0 the potential generated by the Oblique Dipole Layer (ODL) on S_t is given by:

$$u(\boldsymbol{x}, t) = \frac{1}{4\pi\sigma_0} \int_{S_t} \boldsymbol{n}^T D \nabla r^{-1}\, \mathrm{d}S\,, \qquad r = |\boldsymbol{x} - \boldsymbol{\xi}|\,, \quad \boldsymbol{\xi} \in S_t. \tag{20}$$

For the jump potential relationships across S_t see e.g. [**14**]. Concerning the simulations with oblique dipole layers and some of their mathematical properties see [**15**], [**13**], [**7**]. If $d_l = d_t$ we recover the classical uniform normal dipole layer and in the case of an unbounded, homogeneous and isotropic medium we obtain the *solid angle theory*. A further simplification, widely used in electrocardiology, is given by the representation of the electric sources of the heart by a single or multiple dipoles with fixed or variable location and variable direction, see [**22**], [**23**], [**34**], [**35**].

In an unbounded, homogeneous and isotropic domain with conductivity σ_0 the potential due to a dipole located at $\boldsymbol{\xi}$ with moment d and direction $\boldsymbol{n}$ is given by $u(\boldsymbol{x}, t) = \dfrac{1}{4\pi\sigma_0}\, d\boldsymbol{n}^T \nabla r^{-1}$ with $r = |\boldsymbol{x} - \boldsymbol{\xi}|$.

The previous (ODL) model can be derived from the bidomain model considering successive simplifying assumptions.

If we want to simulate the potential field far away from the cardiac sources we can neglect the thickness of the layer displayed by v across the wave front surface S_t; this is achieved considering equation (14) with ε tending to zero. Therefore v_ε tends to $W = v_r + (v_p - v_r)\, \mathcal{H}(t - \varphi(\boldsymbol{x}))$, i.e. $W(\boldsymbol{x}, t) = \begin{cases} v_p, & \varphi(\boldsymbol{x}) < t \\ v_r, & \varphi(\boldsymbol{x}) > t \end{cases}$ with $\mathcal{H}$ the Heaviside function and, in the sense of distributions, ∇v_ε tends to $(v_p - v_r)\, \nabla_x \mathcal{H}(t - \varphi(\boldsymbol{x}))$

$= -(v_p - v_r)\, \boldsymbol{n}_{S_t} \delta_{S_t}$ where $\boldsymbol{n}_{S_t}(\boldsymbol{x})$ is the normal to the front $S_t = \{\boldsymbol{x}\colon \varphi(\boldsymbol{x}) = t\}$ oriented toward the resting region, which is characterized by $v = v_r$ and δ_{S_t} is the Dirac measure on the surface S_t.

Passing formally to the limit in (17) we obtain:

$$u(\boldsymbol{x}, t) - u(\boldsymbol{x}_0, t) = (v_p - v_r) \int_{S_t} \boldsymbol{n}^T M_i \nabla_\xi \psi \, \mathrm{d}\sigma_\xi, \qquad \text{for } \boldsymbol{x} \notin S_t \tag{21}$$

while in the case of equal anisotropy ratio we have, considering (19):

$$\begin{aligned} u(\boldsymbol{x}, t) - u(\boldsymbol{x}_0, t) &= \frac{v_p - v_r}{1+\lambda} \int_{\Sigma_t^a} \boldsymbol{n}^T M \nabla_\xi \psi \, \mathrm{d}\sigma_\xi + \\ &+ \frac{1}{1+\lambda} [\widetilde{W}(t - \varphi(\boldsymbol{x})) - \widetilde{W}(t - \varphi(\boldsymbol{x}))], \qquad \text{for } \boldsymbol{x} \notin \Sigma_t^a \end{aligned} \tag{22}$$

where $\widetilde{W} = \begin{cases} W(t - \varphi(\boldsymbol{x})), & \boldsymbol{x} \in \Omega_H \\ 0, & \boldsymbol{x} \in \Omega_0 \end{cases}$ and $\Sigma_t^a = \{\boldsymbol{x} \in \Sigma,\ \varphi(\boldsymbol{x}) \leqslant t\}$ i.e. the activated part of the heart surface Σ. We refer also to this model as the *activated heart surface source* (AHSS) model, i.e. the potential is generated by a double layer on the activated heart surface Σ_t^a (see [**21**]).

Formula (21) defines the potential generated by an oblique dipole layer on the wavefront surface S_t imbedded in a volume conductor with conductivity tensor $\widehat{M}(\boldsymbol{x})$ used in [**13**] for an anisotropic semispace with parallel fiber.

If $\Omega = R^3$ and $\widehat{M} = \sigma_0 I$ we have $\psi = \dfrac{1}{4\pi\sigma_0 r}$, with $r = |\boldsymbol{x} - \boldsymbol{\xi}|$ and the two previous models (ODL) and (AHSS) reduce to:

$$u(\boldsymbol{x}, t) = \frac{v_p - v_r}{4\pi\sigma_0} \begin{cases} \displaystyle\int_{S_t} \boldsymbol{n}^T M_i \nabla_\xi r^{-1} \, \mathrm{d}\sigma_\xi & \text{for } \boldsymbol{x} \notin S_t, \text{ when } \varrho_i \neq \varrho_e \\ \dfrac{1}{1+\lambda} \displaystyle\int_{\Sigma_t^a} \boldsymbol{n}^T M \nabla_\xi r^{-1} \, \mathrm{d}\sigma_\xi & \text{for } \boldsymbol{x} \notin \Sigma_t^a \text{ when } \varrho_i = \varrho_e. \end{cases}$$

Setting:

$$D = \frac{v_p - v_r}{\sigma_0} M_i$$

the first potential model yields the potential field due to cardiac generators represented by an oblique dipole layer on S_t imbedded into an infinite homogeneous

isotropic medium with conductivity σ_0, previously recalled in (20). The second model coincides with the classical uniform normal dipole layer on the activated epi- endocardial surface.

In order to use these models for simulating the electrocardiograms, i.e. the electrograms recorded on the body surface, we must consider the case of a domain Ω bounded and insulated; Ω represents the body volume imbedded in air and it is assumed to be an homogeneous, isotropic volume conductor. In this case the lead field is given by the solution of

$$\text{(23)} \qquad \begin{cases} -\sigma_0 \Delta_\xi \psi = \delta(\boldsymbol{\xi} - \boldsymbol{x}) - \delta(\boldsymbol{\xi} - \boldsymbol{x}_0) & \boldsymbol{\xi} \in \Omega \\ \boldsymbol{n}_\xi^T \nabla_\xi \psi = 0 & \boldsymbol{\xi} \in \partial\Omega \,. \end{cases}$$

Instead of solving this boundary value problem for any observation point $\boldsymbol{x}$, it is computationally more convenient to solve an integral equation on the body surface $\Gamma = \partial\Omega$. To derive this integral formulation we consider problem (1-4) for $v_\varepsilon = a\left(\dfrac{t - \varphi(\boldsymbol{\xi})}{\varepsilon}\right)$ and passing to the limit, problem (2, 3) becomes

$$\text{(24)} \qquad -\sigma_0 \Delta u = \begin{cases} \operatorname{div} M_i \nabla W & \text{in } \Omega_H \\ 0 & \text{in } \Omega_0, \end{cases} \qquad \boldsymbol{n}^T \nabla u = 0 \quad \text{on } \Gamma \,.$$

Using formally the second Green formula with u and $s(\boldsymbol{\xi}, \boldsymbol{x}) = \dfrac{1}{4\pi|\boldsymbol{x} - \boldsymbol{\xi}|}$ the fundamental solution of the Laplace operator we have:

$$-\sigma_0^{-1} \int_\Omega s \operatorname{div} M_i \nabla W \, \mathrm{d}\xi + u(\boldsymbol{x}, t) = -\int_\Gamma u \, \boldsymbol{n}^T \nabla s \, \mathrm{d}\sigma_\xi$$

but $\nabla W = -(v_p - v_r)\, \boldsymbol{n}_{S_t} \delta_{S_t}$ therefore:

$$\text{(25)} \qquad u(\boldsymbol{x}, t) = \frac{v_p - v_r}{\sigma_0} \int_{S_t} \boldsymbol{n}^T M_i \nabla s \, \mathrm{d}\sigma_\xi - \int_\Gamma u \, \boldsymbol{n}^T \nabla s \, \mathrm{d}\sigma_\xi, \qquad \text{for } \boldsymbol{x} \in \Omega - \overline{S}_t.$$

Moreover for $\boldsymbol{x} \in \Gamma$ we derive that the body surface potential u on Γ is the unique solution, apart from an additive constant, of the following integral equation on Γ:

$$u(\boldsymbol{x}, t) + \int_\Gamma u \, \boldsymbol{n}^T \nabla_\xi s \, \mathrm{d}\sigma_\xi = \frac{v_p - v_r}{\sigma_0} \int_{S_t} \boldsymbol{n}^T M_i \nabla_\xi s \, \mathrm{d}\sigma_\xi, \qquad \text{for } \boldsymbol{x} \in \Gamma \,.$$

Formula (25) yields the potential generated by the an oblique dipole layer on S_t in an isotropic conducting medium which is fully insulated and is obtained by adding

to the potential $u_\infty(\boldsymbol{x}, t)$ in the infinite medium, the correction

$$u(\boldsymbol{x}, t) = u_\infty(\boldsymbol{x}, t) - \int_\Gamma u\, \boldsymbol{n}^T \nabla s \, d\sigma_\xi$$

which is the potential due to a normal dipole layer on Γ with moment density u on Γ.

The same derivation can be applied to the case of equal anisotropy ratio.

Summarizing, the two models, one with anisotropic generators and the other with isotropic generators, are given by

$$u(\boldsymbol{x}, t) = u_\infty(\boldsymbol{x}, t) - \int_\Gamma u\, \boldsymbol{n}^T \nabla s \, d\sigma_\xi$$

with u on Γ solution of

$$u(\boldsymbol{x}, t) + \int_\Gamma u\, \boldsymbol{n}^T \nabla s \, d\sigma_\xi = u_\infty(\boldsymbol{x}, t), \qquad \text{for } \boldsymbol{x} \in \Gamma$$

and

$$u_\infty(\boldsymbol{x}, t) = \frac{v_p - v_r}{4\pi\sigma_0} \begin{cases} \displaystyle\int_{S_t} \boldsymbol{n}^T M_i \nabla_\xi r^{-1} \, d\sigma_\xi & \text{for } \boldsymbol{x} \notin S_t, \text{ when } \varrho_i \neq \varrho_e \\ \displaystyle\frac{1}{1+\lambda} \int_{\Sigma_t^a} \boldsymbol{n}^T M \nabla_\xi r^{-1} \, d\sigma_\xi & \text{for } \boldsymbol{x} \notin \Sigma_t^a \text{ when } \varrho_i = \varrho_e. \end{cases}$$

For convenience in the developments of Section 4 for a given wavefront surface S_t or activated heart surface Σ_t^a the potential generated by the (ODL) and (AHSS) source models will be denoted by $u_{S_t}(\boldsymbol{x}, t)$ and $u_{\Sigma_t^a}(\boldsymbol{x}, t)$.

Actually in the development of mathematical models in electrocardiology, the path from simpler to more complex models has been followed. Hence in the order the single dipole, the classical uniform dipole layer in an isotropic medium and the oblique dipole layer were applied.

4 - Direct and inverse problem in terms of potentials and sources

In a bounded and insulated volume Ω (e.g. the torso volume without sources) composed of parts Ω_j $j = 1, 2, \ldots, m$ each with constant conductivity σ_j (e.g.

lungs, bones, ...) we have the elliptic problem:

$$\Delta u_j = 0 \qquad \text{in } \Omega_j$$

$$\left.\begin{aligned} u_i &= u_j \\ \sigma_i \partial u_i/\partial n &= \sigma_j \partial u_j/\partial n \end{aligned}\right\} \qquad \text{on } S_{ij} = \partial\Omega_i \cap \partial\Omega_j \tag{26}$$

$$\partial u_i/\partial n = 0 \qquad \text{on } \Gamma_i = \partial\Omega \cap \partial\Omega_i$$

where S_{ij} is the surface separating the region Ω_i and Ω_j of different constant conductivity. The last condition characterizes the fact that Γ is insulated i.e. no current flows through it.

Consider the simple case of Ω isotropic and homogeneous defined by $\Omega_1 \subset \Omega_2$, $\Omega = \Omega_2 \setminus \Omega_1$, $S_1 = \partial\Omega_1$, $S_2 = \partial\Omega_2$.

The direct problem is defined by:

$$\begin{cases} \Delta u = 0 & \text{in } \Omega \\ u = f_1 & \text{on } S_1 \\ \partial u/\partial n = 0 & \text{on } S_2. \end{cases} \tag{27}$$

The case of interest is that of S_1 bounding the heart and close to it (the motion of the heart is neglected) and of S_2 the insulated torso surface. For t fixed and $u = u_1 = f_1(\boldsymbol{x}, t)$ on S_1, let $u = u_2$ be the trace on S_2 of the solution of the problem. We have a transfer operator A from u_1 to u_2. The problem is well posed.

The inverse problem is defined as:

$$\begin{cases} \Delta u = 0 & \text{in } \Omega \\ u = f_2 & \text{on } S^* \subset S_2 \\ \dfrac{\partial u}{\partial n} = 0 & \text{on } S_2 \end{cases} \tag{28}$$

where $S^* \subset S_2$ denotes the part of the torso surface where the potential $f_2 = f_2(\boldsymbol{x}, t)$ is measured. For t fixed we have a corresponding u_1 on S_1. The problem is known to be strongly ill-conditioned.

Discretizing the problem by FEM (Finite Element Method) or BEM (Boundary Element Method) the transfer operator A from S_1 to S_2 is approximated by a matrix in which the ratio between the greatest and smallest non zero singular values is of the order of 10^7 indicating strong ill-conditioning of the inverse problem, see [**1**], [**2**], [**5**], [**16**], [**43**], [**44**], [**45**].

The inverse problem has been applied to the torso volume Ω with S_1 contain-

ing the heart and close to it; for this reason S_1 is called «epicardial» surface. For a sequence of time instants f_2 represents the torso potential measured on a set of points and u_1 the corresponding potential on S_1. Since S_1 is close to the heart, the potential u_1 for a sequence of time instants, yields more detailed information than f_2 on the bioelectric activity of the heart. The inverse problem can be solved by means of regularization techniques (e.g. Tikhonov technique) see [**52**], [**31**] for details.

The inverse problem may be formulated also for Ω composed of different parts, with a piecewise constant conductivity.

We now consider the inverse problem in term of sources using the oblique dipole layer model. If $\mathcal{S}$ is the set of admissible wavefront surfaces S_t then the uniqueness of the inverse problem corresponds to:

$$u_{S_t'} = u_{S_t''} \quad \text{on } \Gamma = \partial\Omega \quad \text{implies } S_t' = S_t''.$$

In the case of equal anisotropy ratio the uniqueness problem is stated in terms of the activated epi-endocardial surface ($S_t = \Sigma_t^a$) at time t. In [**53**] the inverse problem is recast in terms of the activation time on the epi-endocardial surface (see eq. (20) and (21) in [**53**]).

For surveys on the direct and inverse problems see [**43**], [**44**], [**45**], [**53**]. The inverse problems can be formulated in terms of integral equations and this line has been followed for numerical simulations. However, in this approach, the conductivity anisotropy is neglected.

In the general case of the (ODL) model uniqueness results were achieved in [**7**] for various admissible classes $\mathcal{S}$ of wavefront surfaces.

For the *oblique dipole layer* model not much is known about the degree of ill-posedness of the problem. The eikonal-curvature equations could be considered as a constraint in order to define admissible physiological wavefront surfaces; hence the eikonal-curvature equation could be used for stabilizing the inverse problem.

5 - Numerical simulations

Large scale simulations of the eikonal model were mainly obtained by two groups of researchers [**28**], [**29**], [**6**], [**12**], [**9**], [**10**]. We now focus on the numerical simulations obtained by our group. The left ventricle has been modeled as a set of packed ellipsoidal surfaces truncated at the base and at the apex. We assumed rotational simmetry around the z-axis which coincides with the longitudinal axis of the ventricle. The volume Ω_H representing the ventricle was modeled using the system of curvilinear coordinates (φ, θ, r) as follows. Given $0 < a_1 < a_2$, $0 < c_1$

$< c_2$ the ellipsoidal surfaces describing Ω_H are defined by:

$$\begin{cases} x = a(r)\ \cos\theta\ \cos\varphi & \theta_1 \leqslant \theta \leqslant \theta_2 \\ y = a(r)\ \cos\theta\ \sin\varphi & 0 \leqslant \varphi \leqslant 2\pi \\ z = c(r)\ \sin\theta & 0 \leqslant r \leqslant 1 \end{cases}$$

with $a(r) = a_1 + r\,(a_2 - a_1)$ and $c(r) = c_1 + r\,(c_2 - c_1)$. The values $r = 0$ and $r = 1$ characterize the endo- and epicardium respectively, i.e. the inner and outer surfaces of the myocardium. Conducting media, e.g. blood or physiological fluid, were modeled by an interior or exterior ellipsoidal layer in contact with the endocardium or the epicardium. In our simulations the volume Ω_H was defined by $a_1 = 1.5$, $a_2 = 2.7$, $c_1 = 4.4$, $c_2 = 5$ (in cm), $\theta_1 = -3\pi/8$, $\theta_2 = \pi/8$ (see [**9**], [**10**]).

Our model included also the fiber rotation; more specifically fibers rotate counterclockwise moving from epicardium (-45^o) to endocardium (75^o). Moreover we incorporated the epi- endocardial obliqueness of the fibers through the so called «imbrication angle», i.e. fibers do not lie on the packed myocardial surfaces but intersect them at a small angle. For more details on the myocardial fiber architecture see Ref. [**9**]. We limited our simulations to the case of constant parameters since significant results can be obtained under this simplifying assumption. We used the constant calibration parameters of papers [**6**], [**9**].

The FEM has been used for the numerical computations concerning the spread of the excitation wavefront, the pattern of the potential u and the structure of the electrocardiograms. We considered a regular mesh $\mathcal{C}_h$ on $\Omega_0 \cup \Omega_H$ obtained by a uniform subdivision of φ, θ and r; the number of subdivisions were $n_\varphi = 90$, $n_\theta = 60$ and $n_r = 41$ respectively. We approximated the ellipsoidal volume Ω with hexahedral isoparametric elements of first order (see [**9**], [**10**], [8] for more details).

A suitable upwind technique has been used to solve the eikonal equation (12). More specifically the Hamiltonian term in (12), given by $c\ \Phi(\boldsymbol{x}, \nabla\varphi)^{1/2}$, required an upwind treatment similar to that investigated for propagating fronts with curvature dependent speed (see [**46**], [**47**], [**9**]). In this way large scale simulations of the potentials v and u for a sequence of time instants were obtained.

In the simulation of the potential distribution u away from the cardiac excitation wavefront, satisfactory results were obtained using a space resolution of about 1 mm (see [**10**]). This space resolution is not suitable for the simulation of EGs since numerical artifacts appear. Thus we developed a numerical procedure, based on an adaptive technique, which allowed large scale simulations of EGs maintaining a reasonable computational cost. Moreover, since EGs are usually recorded at a limited number of points, it is computationally more convenient to

use the integral formulation (17) instead of (16) since we can solve a number of problems, dependent on the parameter t, for the chosen observation points $\boldsymbol{x}$ [8], [**51**]. The accurate computation of integral (17) required a special treatment of the lead field ψ, due to the singularity in $\boldsymbol{x}$, and of the transmembrane potential $v(\boldsymbol{x}, t)$, characterized by a steep wavefront moving across the myocardium. The main steps of our numerical procedure were:

– a finer subdivision of the FEM mesh in proximity of the singular point $\boldsymbol{x}$

– a sub-element technique for the elements crossed by the wavefront

– a suitable decomposition of the potential $u(\boldsymbol{x}, t)$

(see [8] for more details).

The results of the numerical simulations have been compared with experimental measurements [**50**] in the case of fairly similar fiber structure and initial stimulation. These results have been found to agree very well, see ([**9**], [**10**]).

6 - Open problems

The models, previously outlined, allow to correctly capture the main features, at different levels of description and accuracy, of the spread of the excitation wavefronts and of the associated extracellular/extracardiac potentials.

A development of a family of models is not at present available for the description of the repolarization process with different levels of accuracy and therefore large scale simulations of an entire heart beat is an open problem.

Some problems, to be investigated by means of mathematical models and numerical simulations, concern the evolution of one or more complete heart beats (including repolarization) and the simulation of the excitation process when ischemic regions or arrhythmias or fibrillation are present in the heart.

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Abstract

Some mathematical models and problems, arising in electrocardiology, are reviewed. The excitation process, characterized by a front of the transmembrane potential spreading through the myocardium is examined. It is an evolution problem exhibiting considerable numerical difficulties for its solution and the eikonal approximation is introduced. Some aspects of these problems are described and we derive under subsequent assumptions different models for the far-field potential approximation yielding the model of the oblique dipole layer, imbedded into an anisotropic or in a uniform isotropic medium, and the classical model of a uniform normal double layer.

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