AN INVERSE MODEL FOR LOCALIZATION OF LOW-DIFFUSIVITY REGIONS IN THE HEART USING ECG/MCG SENSOR ARRAYS

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Abstract: Cardiac activation and consequently performance of the heart can be severely affected by certain electrophysiological anomalies such as irregular patterns in the activation of the heart. Since the wavefront propagation occurs through the diffusion of ions (Na^+, K^+, etc.) the reduced mobility of ions can be equivalently represented as a reduction of ionic diffusivity causing irregularities in heartbeats. In this paper we propose models for the cardiac activation using inhomogeneous reaction-diffusion equations in the presence of diffusivity disorders. We also derive corresponding statistical signal processing algorithms for estimating (localizing) parameters describing these anomalies. We illustrate applicability of our techniques and demonstrate the identifiability of the parameters through numerical examples using a realistic geometry.

1 INTRODUCTION

The phases of myocardial action potentials and processes of myocardial depolarization and repolarization are well studied and described in most handbooks of electrophysiology and electrocardiography (Gulrajani, Malmivuo). The underlying processes controlling the (re)polarization in the cardiac activation can be described, on a molecular level, as diffusion of ions through various channels (Na, K, etc.) giving a rise to ionic current which in turn creates electromagnetic field on the torso surface which can be externally measured.

Modeling the cardiac activation on a cellular level (Gulrajani) has been a subject of considerable research interest resulting in numerous models related to membrane potential (e.g. Hodgkin-Huxley model). However, these models are mainly suitable for forward modeling in which the cardiac activation is simulated using *a priori* knowledge of various parameters. Complimentary to this approach is inverse modeling in which information on cardiac activation (and some physiological parameters) is deduced from ECG/MCG measurements.

One of the most important parameters controlling the activation wavefront propagation is the diffusivity (i.e., mobility of ions). Namely, significant loss of ionic mobility can cause occurrence of irregular activation patterns and lead to various pathological conditions such as arrhythmia, early after-depolarization, etc. From a physiological point of view, these changes usually occur due to ion depletion from a particular region of the heart. As a result, the diffusivity in this region becomes very small preventing the propagation of the activation wavefront and causing the aforementioned irregular patterns. Therefore, any algorithm capable of detecting these anomalies can potentially be useful to predict the onset of these cardiac physiopathologies.

In this paper we propose a new activation model based on the diffusion equation. Although the FitzHugh-Nagumo model is based on the diffusion equation its applicability to inverse approach and real data is limited because of its isotropic and homogeneous nature. In Section 2 we develop cardiac activation model based on the reaction-diffusion equation with non-homogeneous and anisotropic diffusion tensor. Such a model can be used for detecting different physiological conditions such as conductivity anomalies, which can predate onset of various pathological conditions such as cardiac arrhythmia, early after-depolarization, etc. In Section 3 we derive the statistical and measurements model using Geselowitz equations corresponding to our diffusion based source. Using these models we derive the generalized least squares (GLS) estimator for localizing conductivity anomalies/disorders. In Section 5 we demonstrate the applicability of our results using numerical simulations and in Section 6 we present conclusions.

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2 PHYSICAL MODEL

During the spread of activation in the heart, the most significant bioelectric source is the large potential difference that exists across the moving wavefront that divides active (depolarized) from resting tissue. It has been proposed that the cardiac excitation can be modeled using reaction diffusion systems i.e., a set of nonlinear partial differential equations (Panfilov and Holden, 1997)

$$\frac{\partial u_i}{\partial t} = f_i(u) + \nabla \cdot (D_i \nabla u_i) \qquad i = 1, \dots n \quad (1)$$

where $u = [u_1, \dots u_n]^T$ is the state variable vector, f_i are excitations, and D_i diffusion tensors. Although the above models can be used to model the propagation even down to a cellular level, in order to develop an inverse model a simplified approach similar to (FitzHugh, 1961),(Rogers and McCulloch, 1994) is needed. Therefore, we propose a reaction diffusion model consisting of two state variables but with spatially dependent diffusivity tensor

$$\begin{aligned} \frac{\partial u_1(r,t)}{\partial t} &= \nabla \cdot (D(r) \nabla u_1(r,t)) + \\ &\quad + g^T(u(r,t)) A_1 g(u(r,t)) \\ \frac{\partial u_2(r,t)}{\partial t} &= u^T(r,t) A_2 u(r,t) \\ g(u(r,t)) &= [u_1^2(r,t), u_1(r,t), u_2(r,t), 1]^T \end{aligned}$$

where u_1 is the activation potential and u_2 is the resting potential.

The above model is the generalization of the existing models from at least two standpoints: a) by allowing the diffusivity matrix to be spatially dependent we can test for the presence of arbitrarily shaped anomalies, and b) by adding higher-order polynomial components we allow for wider range of dynamic behavior in the cardiac excitation. Note that in order to apply the above model to the realistic geometry we need to define boundary conditions. In our case we impose $\partial u_1 / \partial n$ on the epicardial surface of the heart. As for initial conditions, we define the active potential at time $t = 0$ as $u_1(r,0) = u_0 \delta(r - r_0)$ where $\delta()$ is a Dirac delta function and r_0 is the activation point in the myocardium. The initial condition for the inhibition (u_2) is set to zero.

To compute the electro-magnetic field on the torso surface we utilize the Geselowitz (Geselowtiz, 1970) equations that compute the potential $\phi(r,t)$ and magnetic field $B(r,t)$ at a location r on the torso surface at a time t from a given primary current distribution $J(r',t) = \nabla u_1(r,t)$ within the heart.We use a piecewise homogeneous torso model consisting of the following surfaces: the outer torso, the inner torso, and the heart. Therefore, we model the heart as a volume G of $M = 3$ homogeneous layers separated by closed surfaces $S_i, i = 1, \dots, M$. Let σ_i^- and σ_i^+ be the conductivities of the layers inside and outside S_i respectively. We will denote by G_i the regions of different conductivities, and by G_{M+1} the region outside the torso, which behaves as an insulator i.e, $\sigma_{M+1}^- = \sigma_M^+ = 0$.

It has been shown that in the case of a piecewise homogeneous torso model and using quasi-static assumption the magnetic field at a location r and time t is given by (Gulrajani, 1998) and (Malmivuo and Plonsey, 1995)

$$\begin{aligned} B(r,t) &= B_0(r,t) + \frac{\mu_0}{4\pi} \sum_{i=1}^{M} (\sigma_i^- - \sigma_i^+) \cdot \\ &\quad \cdot \int_{S_i} \phi(r',t) \frac{(r - r')}{\|r - r'\|^3} \times \mathrm{d}S(r') \\ B_0(r,t) &= \frac{\mu_0}{4\pi} \int_G \frac{J(r',t) \times (r - r')}{\|r - r'\|^3} \mathrm{d}^3 r', \quad (2) \end{aligned}$$

where μ_0 is the magnetic permeability of the vacuum. Similarly, the potential $\phi(r,t)$ is given by (Geselowitz)

$$\begin{aligned} \frac{\sigma_k^- + \sigma_k^+}{2} \phi(r,t) &= \phi_0(r)(\sigma_i^- - \sigma_i^+) + \\ &+ \frac{1}{4\pi} \sum_{i=1}^{M} (\sigma_i^- - \sigma_i^+) \int_{S_i} \phi(r',t) \frac{(r - r')}{\|r - r'\|^3} \cdot \mathrm{d}S(r'), \\ \phi_0(r,t) &= \frac{1}{4\pi} \int_G \frac{J(r',t) \cdot (r - r')}{\|r - r'\|^3} \mathrm{d}^3 r', \quad (3) \end{aligned}$$

where we k is chosen so that $r \in G_k$.

3 MEASUREMENT MODEL AND STATISTICAL MODEL

In this section we introduce our parametric description of the diffusion anomaly and measurement noise signals. To simplify the approach we assume that the anomaly region can be modeled with an ellipsoid i.e., the region $\mathcal{R}$ of anomaly is given by

$$\mathcal{R} = \{r : (r - r_a)^T F(a,b,c,\psi,\phi)^{-1} (r - r_a) \leq 1\}$$

where

$$F = T(\phi,\psi) \begin{bmatrix} a^2 & 0 & 0 \\ 0 & b^2 & 0 \\ 0 & 0 & c^2 \end{bmatrix} T^T(\phi,\psi)$$

where a, b, c are the axes of anomaly ellipsoid, r_a is the center, and ψ and ϕ are the orientation parameters (in 3D). The matrix $T(\phi,\psi)$ is the rotation matrix

given by

$$T(\phi,\psi)=\begin{bmatrix}\cos\phi & \sin\phi & 0\\ -\sin\phi & \cos\phi & 0\\ 0 & 0 & 1\end{bmatrix}\cdot\begin{bmatrix}\cos\psi & 0 & \sin\psi\\ 0 & 1 & 0\\ -\sin\psi & 0 & \cos\psi\end{bmatrix} \quad (4)$$

The diffusion tensor is then

$$D(r)=\begin{cases}0 & r\in\mathcal{R}\\ D & \text{otherwise.}\end{cases} \quad (5)$$

In the remainder of the myocardium tissue we assume homogeneous but possibly anisotropic diffusion tensor D.

Next, we assume that a bimodal array of n_{B} MCG and n_{E} ECG sensors is used for the measurements. Let $n=n_{\mathrm{B}}+n_{\mathrm{E}}$. We assume that the sensors are located at ρ_j, $j=1,\ldots,n$, and that time samples are taken at uniformly spaced time points $t_k, k=1,\ldots,n_{\mathrm{s}}$. In addition, we assume that data acquisition is repeated n_{c} times during several heart cycles in order to improve the signal-to-noise (SNR) ratio. Then, the n_{s}-dimensional measurement vector of this array obtained at time t_k in the lth cycle is

$$y_{lk}=f(\theta,t_k)+e_l(t_k), \quad (6)$$

where $y_{lk}=[y_{\mathrm{B}}^{\mathrm{T}}(t_k),y_{\mathrm{E}}^{\mathrm{T}}(t_k)]^{\mathrm{T}}$, θ is the collection of all the parameters $(a,b,c,r_0,\psi,\phi,u_0,D,A_1,A_2)$, $f(\theta,t_k)$ is the vector solution computed using finite elements, and $e_l(t_k)=[e_{\mathrm{B}}^{\mathrm{T}}(t_k),e_{\mathrm{E}}^{\mathrm{T}}(t_k)]^{\mathrm{T}}$ is additive noise. In the remainder of the paper we omit the subscript l whenever it is obvious that the samples belong to the same heart cycle. The subscripts B and E correspond to magnetic and electric components of the measurement vector (noise), respectively. We further assume that both magnetic and electric components of the noise are zero-mean Gaussian, uncorrelated in space and time with variances, σ_{B}^2 and σ_{E}^2, respectively.

4 PARAMETER ESTIMATION

We first start by splitting the unknown parameters θ into three groups: a) the unknown activation parameters $\theta_0=[u_0,r_a]^T$, and b) the unknown anomaly parameters $\theta_{\mathrm{a}}=[a,b,c,r_0,\phi,\psi]^T$. For simplicity in the remainder of the paper we assume that the heart parameters

$$\theta_{\mathrm{h}}=[\mathrm{vec}(D),\mathrm{vec}(A_1 1),\mathrm{vec}(A_2)]^T \quad (7)$$

where vec is the vector operator, are known. Note that some *in vitro* studies (Sachse, 2004) suggest that these parameters do not vary significantly between different subjects and thus can be easily estimated using data gathered from human subjects without any anomalies. Complicating the matter is the fact that the diffusion tensor in general is inhomogeneous. Namely, the ionic diffusion process is much larger along the myocardium fiber than across different fibers. Since the fiber orientations change in space the diffusion tensor should be spatially dependent. However, these changes are smooth in nature and can be easily modeled using a set of *a priori* known basis functions. Furthermore, information about fiber orientation can be easily obtained using cardiac diffusion MRI (et al., 2003).

To compute estimates $\hat{\theta}_0$ and $\hat{\theta}_a$ we use the generalized least squares (GLS) estimator which minimizes the following cost function (Vonesh and Chinchilli, 1997)

$$\begin{aligned}c(\theta_0,\theta_a,\hat{\sigma}_{\mathrm{E}}^2,\hat{\sigma}_{\mathrm{B}}^2) &= \sum_{k=1}^{n_{\mathrm{s}}}\sum_{l=1}^{q}\frac{1}{\hat{\sigma}_{\mathrm{E}}^2}\|y_{kl}^{\mathrm{E}}-f^{\mathrm{E}}(\theta_0,\theta_{\mathrm{a}},t_k)\|^2+\\ &\quad+\frac{1}{\hat{\sigma}_{\mathrm{B}}^2}\|y_{kl}^{\mathrm{B}}-f^{\mathrm{B}}(\theta_0,\theta_{\mathrm{a}},t_k)\|^2\\ \hat{\sigma}_{\mathrm{E}}^2 &= \frac{1}{n_{\mathrm{E}}n_{\mathrm{s}}q}\sum_{k=1}^{n_{\mathrm{s}}}\sum_{l=1}^{q}\|y_{kl}^{\mathrm{E}}-f^{\mathrm{E}}(\theta_0,\theta_{\mathrm{a}},t_k)\|^2\\ \hat{\sigma}_{\mathrm{B}}^2 &= \frac{1}{n_{\mathrm{B}}n_{\mathrm{s}}q}\sum_{k=1}^{n_{\mathrm{s}}}\sum_{l=1}^{q}\|y_{kl}^{\mathrm{B}}-f^{\mathrm{B}}(\theta_0,\theta_{\mathrm{a}},t_k)\|^2\end{aligned}$$

where we use superscripts E and B to denote electrical and magnetic, components of the measured field and solution vector.

The above GLS estimator is more efficient than the ordinary least squares estimator due to each contribution to the objective function is being normalized to the same unit variance (i.e., those measurements with less variation are given greater weight). The actual optimization can be done using any of the well known algorithms such as Davidson-Fletcher-Powell or Broyden-Fletcher-Goldfarb-Shanno. To further simplify the computational complexity, we propose to estimate θ_0 assuming that $a=b=c=0$ i.e. the diffusivity of the heart is homogeneous and using ordinary least squares. Then we can use this estimate as the initial guess for GLS estimation alghorithm.

5 NUMERICAL EXAMPLES

We now describe numerical study that demonstrates the applicability of the proposed algorithms. We used an anatomically correct mesh of the human torso that was kindly provided to us by Prof. McLeod, Utah University. In our model the Purkinje network was approximated by a set of nodes near the apex. To achieve higher precision we remeshed the original data into a new mesh (see Fig. 1). The volumetric

mesh was created using 15902 elements with 20830 degrees of freedom for the torso (electromagnetic) model and 1856 elements and 6190 degrees of freedom for the heart (diffusion) model. The computational model was developed using a general partial differential (PDE) toolbox in COMSOL software.
The torso conductivity was set to 5μS respectively as in (Malmivuo). To simplify the complexity of the numerical study we simulated the anomaly using $a = b = 2$cm , $c = 0.5$cm, and $\psi = \phi = 0$. The diffusion tensor was set to be isotropic with diagonal elements equal to 40cm^3/s. The diffusivity was chosen according to (Gulrajani) so that the activation wavefront propagates the whole heart in 0.2s. The control matrices A_1 and A_2 were chosen following the approach of (Rogers and Culloch). The heart rate was set to 72 beats per minute. We assume that the measurements are obtained using 64-channel ECG/MCG sensor array with sensors locations uniformly distributed on the chest. To evaluate the localization accuracy we use $\text{MSE}_{r_0} = \|r_0 - \hat{r_0}\|^2/\|r_0\|^2$, $\text{MSE}_a = \|a - \hat{a}\|^2/\|a\|^2$, and $\text{MSE}_c = \|c - \hat{c}\|^2/\|c\|^2$.

Figure 2 illustrates the activation wavefront in myocardium at approximately $t = 2T/3$ after the activation where T is the time length of the heart cycle. In Figure 3 we illustrate the body surface map of the electric field (voltage) on the torso surface. Similarly, Figure 4 illustrates the magnetic field map at the same time. In Figure 5 we illustrate the mean square error of the axis parameters with $c = a/10$ and $b = a$. The location of an anomaly was arbitrarily set to $r_0 = (0, 0.5, 0.75)$. As expected, due to the wavefront orientation as well as difference in size, the estimation accuracy of the cross-sectional axis parameters is much smaller. In Figure 6 we illustrate the localization accuracy i.e., MSE of r_0 as a function of noise. The SNR was defined as $SNR = 10\log(\sum \|y_{lk}\|^2/\sigma_{\text{E}}^2 + \sigma_{\text{B}}^2)$.

6 CONCLUSIONS

We addressed the problem of localizing the diffusivity disorder in the myocardium using ECG/MCG sensor arrays. To model the cardiac activation we considered an inhomogeneous reaction-diffusion model in a real human torso. To model a the loss we used a parametric model for an oblate spheroid and set its conductivity to zero. We assumed that the remainder of the myocardium tissue was homogeneous. The proposed algorithm can be easily extended to account for an arbitrary spatial variation in the diffusivity tensor using a set of *a priori* known basis functions. In addition the parametric shape of the anomaly can be extended to model an arbitrary region using a three-dimensional spatial Fourier transform. An effort should be made to examine the sensitivity of the proposed algorithms to the size of diffusivity difference between "regular" tissue and anomaly as well as the number of the unknown parameters needed to model arbitrary shapes.

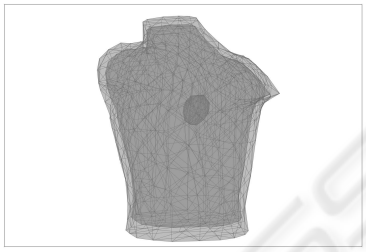

Figure 1: Mesh geometry used for numerical study.

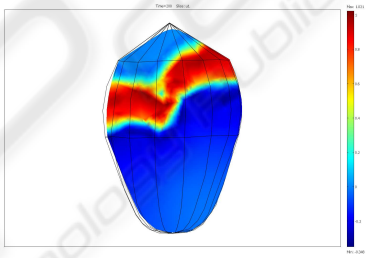

Figure 2: Activation wavefront, at $t = 2T/3$.

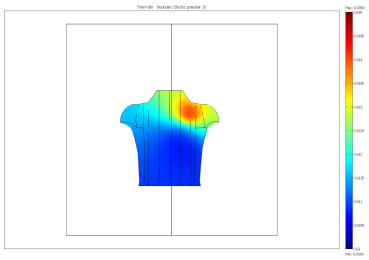

Figure 3: Body surface map of electric field at $t = 2T/3$.

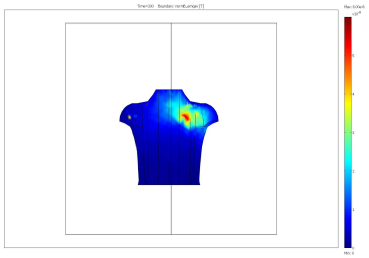

Figure 4: Body surface map of magnetic field at $t = 2T/3$.

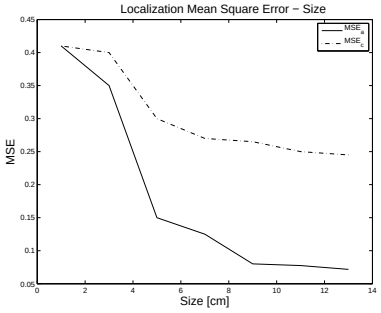

Figure 5: Mean square error for estimating the size of the anomaly.

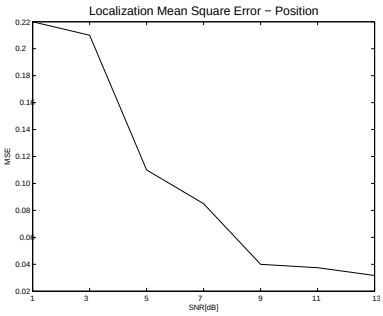

Figure 6: Mean square error for estimating the location of the anomaly.

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