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The Modified Bidomain Model with Periodic Diffusive Inclusions

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Abstract

Bidomain equations are the standard way to model the electric potential in cardiac tissue. They are based on the fact that active cardiomyocytes are present everywhere in the heart, while it is known that non-small regions exist where additional extracellular media take place. These regions, which play an important role in diseased hearts, are often taken into account through ad-hoc rough tuning of the tissue conductivities. In this work, we introduce a rigorous way to derive these conductivities from a microscopic description of the heterogeneities in the tissue.

We assume a periodic alternation of the healthy tissue and the fibrotic tissue. Such a microscopic model can be simulated directly, at the price of a very high computational cost. Instead we derive a homogenized model at the macroscopic scale, following a standard multiscale technique.

We recover a bidomain type model, but with modified conductivities, that depend on the volume fraction of the diffusive inclusions but also on their geometries. The numerical results confirm the convergence of the microscopic model to the homogenized equations. We observe the influence of the diffusive inclusions on the propagation of action potentials. With the final model we shall provide cheap modeling tools to account for tissue heterogeneities at intermediate scales. The diffusive volume ratio, that enters the model, might be available through functional imaging, which enlightens the practical interest of the method.

1. Introduction

The standard macroscopic model for the electrophysiology of the heart is the *bidomain model*. It is the anisotropic three-dimensional cable equation, that represents the averaged electric behaviour of the heart tissue. The first formal derivation of this model from the microscopic model using the homogenisation technique have been done by Krasowska - Neu (1993). In the bidomain model we have a different electrical conductivities for the intracellular and the extracellular spaces, and both of them are anisotropic, meaning that there is a different conductivity in the longitudinal and transversal direction with re-

spect to fibre direction. Even if it is widely accepted, this model still has several modelling limitations. The thorough review on the cardiac tissue electrophysiology can be found in [1].

The bidomain model assumes that active cardiomyocytes are present everywhere, organized into a network. It is not true in general although the model is well accepted for describing the propagation of the action potential in healthy tissues. But it is even more limited in many diseases, like fibrosis of the heart tissue. Another problem that we will try to address is the scar that stays in the tissue after the heart attack. It is known that the center of the scar is not active electrically, but the border of the scar is still not well understood. In this paper we start developing the model that can cover such situations.

In the proposed model of the electrical activity of the heart tissue we will assume the periodic alternations of the healthy tissue modelled with the standard bidomain model and the non-active regions, that we model with the simple diffusion equation. Further, we will use the two-scale homogenisation technique, developed by Allaire (1992) [2], to derive the macroscale model that we will then use in numerical simulations. Even though the theory that we develop, allows a use of any ionic model for the cardiac cells, in the numerical simulations we will use the Michael Schaefer ionic model.

2. Problem Setting

The main idea of the paper is to extend the standard bidomain model with the periodic diffusive inclusions and to study their effect on the macroscopic level.

We represent the heart tissue with some domain Ω , that is the bounded open set in \mathbb{R}^N , $N = 2, 3$ and we say $\Omega = \Omega_\varepsilon^B \cup \Omega_\varepsilon^D \cup \Sigma_\varepsilon$. Here Ω_ε^B represents the healthy heart tissue which can be modelled with standard bidomain equations, Ω_ε^D represents the collection of periodical diffusive inclusions and Σ_ε is the interface between these two subdomains. The domain Ω is a periodic medium, i.e. it is divided into the small cells identical to each other, that we call periodic cells and that are of order ε . This small cells are identical up to a translation and rescaling by ε to

the unit cell $Y = [0, 1]^N$. Furthermore, the unit cell is decomposed in two parts: Y_B represents the tissue that can be modelled by the standard bidomain model, Y_D is one diffusive inclusion, hence $Y = Y_B \cup Y_D \cup \Gamma$ where Γ is the interface.

In the standard bidomain model we have defined the intracellular electric potential $u_\varepsilon^i(t, x)$ and the extracellular one $u_\varepsilon^e(t, x)$. While the transmembrane potential is denoted as

$$v_\varepsilon = u_\varepsilon^i - u_\varepsilon^e.$$

The bidomain model assumes that the change in the transmembrane potential happens due to the ionic model and the diffusion of the electric potential. In the domain $(0, T) \times \Omega_\varepsilon^B$, we have

$$\partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) = \nabla \cdot (\sigma^i(x/\varepsilon) \nabla u_\varepsilon^i), \quad (1)$$

$$\partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) = -\nabla \cdot (\sigma^e(x/\varepsilon) \nabla u_\varepsilon^e), \quad (2)$$

$$\partial_t h_\varepsilon + g(v_\varepsilon, h_\varepsilon) = 0, \quad (3)$$

where $\sigma^i(y)$ and $\sigma^e(y)$ are the time-independent intracellular and extracellular conductivity tensors, whose coefficients are periodical functions of the period Y . The ODE in (3) represents the *ionic model* related to the behaviour of the myocardium cells membrane.

We couple this standard bidomain model with the simple diffusion equation on the periodic inclusions. So, in the domain $(0, T) \times \Omega_\varepsilon^D$, we have given

$$\nabla \cdot (\sigma^d(x/\varepsilon) \nabla u_\varepsilon^d) = 0. \quad (4)$$

It is assumed that we can neglect the membrane (capacitance) effect inside of these additional tissue patches. The standard transmission conditions for the bidomain model with the diffusive domain are given on the interface $(0, T) \times \Sigma_\varepsilon$, as follows

$$(\sigma^i(x/\varepsilon) \nabla u_\varepsilon^i) \cdot n_{\Omega_\varepsilon^B} = 0, \quad (5)$$

$$(\sigma^e(x/\varepsilon) \nabla u_\varepsilon^e) \cdot n_{\Omega_\varepsilon^B} = (\sigma^d(x/\varepsilon) \nabla u_\varepsilon^d) \cdot n_{\Omega_\varepsilon^B}, \quad (6)$$

$$u_\varepsilon^e(t, x) = u_\varepsilon^d(t, x), \quad (7)$$

where $n_{\Omega_\varepsilon^B}$ is the unit normal vector from Ω_ε^B to Ω_ε^D . These conditions have been previously studied on the heart - torso problem in [3]. On the outer boundary we have a homogeneous Neumann conditions on $\partial\Omega$. One can notice that the problem is defined up to the same constant for $u_\varepsilon^i, u_\varepsilon^e$ and u_ε^d . This can be fixed by enforcing the Gauge condition on u_ε^e ,

$$\forall t \in (0, T), \quad \int_\Omega u_\varepsilon^e(t, x) dx = 0. \quad (8)$$

We assume to be given the initial conditions on v_ε and h_ε in Ω_ε^B . The transmission conditions (6) and (7) provide

the continuity of the potential and the flux of extracellular potential in Ω_ε^B and the potential in Ω_ε^D . We can define a new function u_ε on the whole domain Ω that takes the values of u_ε^e in Ω_ε^B and values of u_ε^d in Ω_ε^D . We similarly define the conductivity tensor σ that takes values of σ^e in Y_B and values of σ^d in Y_D . In this way we can write the equations (2) and (4) as one, defined on the whole domain Ω and drop the transmission conditions (6) - (7). Redefine $v_\varepsilon = u_\varepsilon^i - u_\varepsilon|_{\Omega_\varepsilon^B}$ and finally, we can summarise the problem to be solved in the domain $(0, T) \times \Omega$, as follows,

$$\begin{aligned} \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) &= \nabla \cdot (\sigma^i(x/\varepsilon) \nabla u_\varepsilon^i), \quad \text{in } \Omega_\varepsilon^B, \\ \mathbb{1}_{Y_B}(\partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon)) &= -\nabla \cdot (\sigma(x/\varepsilon) \nabla u_\varepsilon), \quad \text{in } \Omega, \\ \partial_t h_\varepsilon + g(v_\varepsilon, h_\varepsilon) &= 0, \quad \text{in } \Omega_\varepsilon^B, \\ (\sigma^i(x/\varepsilon) \nabla u_\varepsilon^i) \cdot n_{\Omega_\varepsilon^B} &= 0, \quad \text{on } \Sigma_\varepsilon, \\ (\sigma^i(x/\varepsilon) \nabla u_\varepsilon^i) \cdot n &= 0, \quad \text{on } \partial\Omega, \\ (\sigma(x/\varepsilon) \nabla u_\varepsilon) \cdot n &= 0, \quad \text{on } \partial\Omega, \\ \int_{\Omega_\varepsilon^B} u_\varepsilon &= 0, \end{aligned}$$

The function $\mathbb{1}_{Y_B}(y)$ is the characteristic function of the domain Y_B , and we can choose a ionic model and functions I_{ion} and g .

Although stated in another context, we can use the proof from [3] for this problem. Additionally, under certain assumption one can prove the uniqueness of the solution. Furthermore, we can provide the uniform bounds on the solution, that enables us to use the two-scale homogenisation technique described in the following chapter.

3. Homogenisation

As usually, we do not want to deal numerically with the microscale problem, due to the high cost of the simulations that depend on ε , size of the periodic cell. Instead, we derive the corresponding macroscale problem that takes into account the structural heterogeneities. The solution of the macroscale (homogenised) problem is the asymptotic approximation of the solution for the microscale problem, when we assume that ε goes to 0, i.e. when we assume that the size of the whole domain is much larger than the size of the periodic cell. We have used the rigorous homogenisation technique, called the two-scale convergence and developed by Allaire in [2]. As we do not want to enter here into many technical details, and which will be given in the forthcoming work, we will just explain the heuristics of the formal asymptotic analysis and provide the form of the asymptotic macroscale solution, that we are interested in.

The main idea is to assume that the solution of the micro-

scopic problem $(u_\varepsilon^i, u_\varepsilon, h_\varepsilon)$ can be expanded into series as:

$$u_\varepsilon^i(t, x) = \sum_{k=0}^{\infty} \varepsilon^k u_k^i(t, x, \frac{x}{\varepsilon}), \quad u_\varepsilon(t, x) = \sum_{k=0}^{\infty} \varepsilon^k u_k(t, x, \frac{x}{\varepsilon}),$$

$$h_\varepsilon(t, x) = \sum_{k=0}^{\infty} \varepsilon^k h_k(t, x, \frac{x}{\varepsilon}),$$

where functions $u_k^i(t, x, y)$, $u_k(t, x, y)$, $h_k(t, x, y)$ for all $k \in \mathbb{N}$, are periodic in y with a period Y . Notice that,

$$\nabla u_\varepsilon = \frac{1}{\varepsilon} \nabla_y u_0 + \nabla_x u_0 + \nabla_y u_1 + \varepsilon (\nabla_x u_1 + \nabla_y u_2) + \dots,$$

and

$$\Delta u_\varepsilon = \frac{1}{\varepsilon^2} \Delta_{yy} u_0 + \frac{1}{\varepsilon} (\Delta_{yy} u_1 + \nabla_y \nabla_x u_0 + \nabla_x \nabla_y u_0) + \Delta_{yy} u_2 + \nabla_y \nabla_x u_1 + \nabla_x \nabla_y u_1 + \Delta_{xx} u_0 + \dots$$

Similarly we can derive formulae for ∇u_ε^i and Δu_ε^i . We, now, substitute these formulae in our equations and group together the terms with the same order of ε . We will obtain the cascade sequence of PDE systems. From the first PDE system, that is obtained from the terms that stand with the lowest order of ε , we conclude that u_0 and u_0^i do not depend on y . From the second PDE system, we can write u_1 and u_1^i as functions of u_0 and u_0^i as follows:

$$u_1^i(t, x, y) = \sum_{k=1}^N \frac{\partial u_0^i}{\partial x_k}(t, x) w_k^i(y),$$

$$u_1(t, x, y) = \sum_{k=1}^N \frac{\partial u_0}{\partial x_k}(t, x) w_k(y).$$

From this we will derive so-called cell problems for functions w_k^i, w_k for $k = \overline{1, N}$. These functions, as written above, depend only on the y variable, hence the cell problems, as the name says, has to be solved only once and only on the unit cell Y . The third PDE system we use to derive the final homogenised equations.

3.1. The homogenized bidomain with inclusions

We have obtained the homogenised problem defined in $(0, T) \times \Omega$,

$$\begin{aligned} \nabla_x \cdot (\sigma^{i*} \nabla_x u_0^i) &= (\partial_t v_0 + I(v_0, h_0)) |Y_B|, \\ \nabla_x \cdot (\sigma^* \nabla_x u_0) &= -(\partial_t v_0 + I(v_0, h_0)) |Y_B|, \\ \partial_t h_0 + g(v_0, h_0) &= 0, \end{aligned}$$

with the Neumann boundary conditions, and the corresponding initial conditions. As one can notice, the new

model is actually the bidomain model with changed conductivities σ^{i*} and σ^* . They are obtained by solving the cell problems

$$\begin{aligned} \nabla \cdot (\sigma_i \nabla w_k^i) &= 0, \text{ in } Y_B, \\ \sigma_i (\nabla w_k^i + e_k) \cdot n &= 0, \text{ on } \Gamma, \\ w_k^i &\text{ is } Y \text{ periodic,} \end{aligned}$$

and

$$\begin{aligned} \nabla \cdot (\sigma \nabla w_k) &= 0, \text{ in } Y, \\ [(\sigma \nabla w_k) \cdot n] &= -[(\sigma e_k) \cdot n], \text{ on } \Gamma, \\ w_k &\text{ is } Y \text{ periodic.} \end{aligned}$$

where $[\cdot]$ stands for a jump functions on the interface. The effective conductivities are then expressed as

$$\begin{aligned} \sigma_{kj}^{i*} &= \sigma_{kj}^i |Y_B| + \sigma_{k1}^i \int_{Y_B} \partial_{y_1} w_j^i dy + \\ &\sigma_{k2}^i \int_{Y_B} \partial_{y_2} w_j^i dy + \sigma_{k3}^i \int_{Y_B} \partial_{y_3} w_j^i dy, \end{aligned}$$

and

$$\begin{aligned} \sigma_{kj}^* &= \int_Y \sigma_{kj} dy + \int_Y \sigma_{k1} \partial_{y_1} w_j dy + \\ &\int_Y \sigma_{k2} \partial_{y_2} w_j dy + \int_Y \sigma_{k3} \partial_{y_3} w_j dy, \end{aligned}$$

First let us notice that we have to solve $2N$ cell problems (4 in 2D and 6 in 3D). Even though, now we have more problems to solve, we have to notice that none of them depend on ε , that resembles the typical size of the inclusions, i.e. we can take a coarse mesh in our simulations. If we were solving numerically the initial problem, we would have to take care that our mesh step is much smaller than ε which would take a lot of computational time. We should also notice, that even though we get rid of the fine computations, we still account for the structural heterogeneities through the computations of new conductivities. Let us emphasize that the variation of the conductivities depends on both the volume fraction of the inclusions, but also on their geometries. Hence, we can expect that with a different shapes of the periodic inclusions the anisotropy ratio of the conductivities can change significantly.

4. Numerical results

For the numerical simulation of our problem we have used the software *FreeFem++* and *gnuplot*. For the ionic model we concentrate on the regularised version of the Mitchell-Schaeffer (MS) model [3]. We used the second order semi-explicit backward differential formulae (SBDF2).

We have performed simulations with simple shapes of the diffusive inclusions such as circles and ellipses, ranging

the volume fractions from 20% to 75%. We have obtained the values for all parameters in the problem, including the values of tensors σ^i and σ^e from the literature. For the conductivity tensor σ^d we do not have any information in the literature so we performed experiments assuming it to be isotropic and we chose $\sigma^d = 3$, as it is of the same order as intracellular and extracellular conductivities of the standard bidomain model.

Firstly, we have confirmed the convergence of the microscopic problem to the derived homogenised equations. We have obtained the linear rate of convergence.

Table 1: The values of the new conductivities depending on the diffusive inclusions [10^{-1} S/m]. The first row: the values for the standard bidomain model, without inclusions. The first column describes the microstructure geometry, i.e. the shape of the diffusive inclusions.

geometry	vol frac	σ^d	σ_{i11}^*	σ_{i22}^*	σ_{e11}^*	σ_{e22}^*
-	-	-	1.74	0.19	3.9	1.97
circle	0.2	3	1.26	0.17	3.29	2.53
circle	0.4	3	1.07	0.15	3.42	3.53
circle	0.7	3	0.69	0.09	5.08	7.89
ellipse (1:1.5)	0.2	3	1.13	0.18	2.82	2.58
ellipse (1:1.5)	0.4	3	0.81	0.16	2.53	3.70
ellipse (1:2)	0.2	3	0.86	0.18	2.09	2.64
ellipse (1:4)	0.18	3	0.31	0.19	0.75	2.61
circle	0.18	3	1.29	0.18	3.28	2.45

Further, we have observed how conductivities change when we vary the volume fraction of the diffusive inclusions and their shape. See Table 1. We can observe that there is the strong influence on the conductivities if the volume fraction of the diffusive inclusions is large (70%, fourth row of the table). Also, if we look at the last two rows of the table, we can notice that for the same fraction circular and elliptical inclusions give significantly different results. While circular inclusions affect all values similarly, the elliptical inclusions strongly change the anisotropy ratio of the bidomain model. To visualise this effect, we have performed two simulations of the standard bidomain model with the "scar patch" where we modify conductivities as in the second last row of the Table 1. See Figure 1. The difference between these two simulation is the initially excited region. We can see that while the shape of the left-right signal propagation is very affected by the "scar patch", there is almost no change in bottom-up propagation.

5. Conclusions and Discussions

We have proposed a way to model the electrophysiology of the cardiac tissue, that extends the standard bidomain model with the periodic diffusive inclusions. We have a rigorous and practical way to link structural disease in the

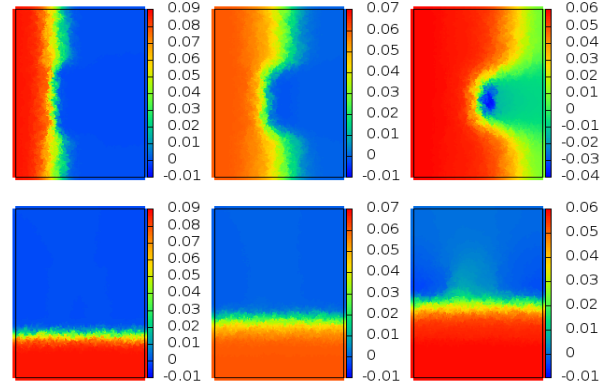


Figure 1: The standard bidomain with the "scar patch" evolution. Up and down the same tissue properties. Microstructure: elliptical inclusion, axes ratio 1:4, volume fraction 0.18. $\sigma^d = 3$. Times: 10s, 30s, 50s.

tissue to macroscopic electrical conductivity in a bidomain model. It can be used in many contexts, including simulation of fibrotic tissue in general and border zones of scars. From the more practical side, we plan to use high resolution imaging to experimentally obtain insight into the typical geometry/volume fractions in various types of fibrosis. There are several limitations of the proposed model. The inclusions that we address are purely diffusive, while we can expect to have different kind of cells in these non-excitable regions. Hence, we neglected the effect we might have from the ionic activity, due to the cells' membrane. Another difficulty that we need to address are transmission conditions given on the interface of the inclusions. We have used standard conditions, usually used in coupling torso and the heart, which might not be appropriate here. These are still open questions we plan to investigate in the future work.

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