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MODIFIED BIDOMAIN MODEL WITH PASSIVE PERIODIC HETEROGENEITIES

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Abstract. In this paper we study how mesoscopic heterogeneities affect electrical signal propagation in cardiac tissue. The standard model used in cardiac electrophysiology is a bidomain model - a system of degenerate parabolic PDEs, coupled with a set of ODEs, representing the ionic behviour of the cardiac cells. We assume that the heterogeneities in the tissue are periodically distributed diffusive regions, that are significantly larger than a cardiac cell. These regions represent the fibrotic tissue, collagen or fat, that is electrically passive. We give a mathematical setting of the model. Using semigroup theory we prove that such model has a uniformly bounded solution. Finally, we use two–scale convergence to find the limit problem that represents the average behviour of the electrical signal in this setting.

1. Introduction.

Heart contractions are coordinated by a complex electrical activation process which relies on millions of ion channels, pumps, and exchangers of various kinds embedded in the membrane of each cardiac cell. Their interactions result in periodic changes in transmembrane voltage, called *action potential*. Action potentials in the cardiac muscle propagate rapidly from cell to cell, synchronising the contraction of the entire muscle to achieve an efficient pump function. The

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spatio–temporal pattern of this propagation is related both to the function of the cellular membrane and to the structural organisation of the cells into tissues.

1.1. **The standard bidomain model.** Mathematical models of whole–heart physiology are based on the idea of a perfect cardiac muscle, made of uniformly distributed and interconnected cardiac cells and the extracellular matrix that surrounds them, approximated using homogenisation methods. The standard macroscopic electrophysiological model of the heart is the so–called *bidomain model*, which has been proposed in the late 70s and early 80s [25, 23, 15]. It is the anisotropic three–dimensional cable equation that represents the averaged electric behviour of the heart tissue. The bidomain model involves the electrical conductivities of the intracellular and the extracellular spaces. Both of them are anisotropic, meaning that there is a different conductivity in the longitudinal and the transversal direction with respect to fiber direction. Neu and Krassowska [26, 20] suggested the first mathematical approach in understanding the derivation of the bidomain model from the microscopic description of the tissue. Their derivation is based on an idealised representation of the syncytium as a network of interconnected cells, arranged periodically in space. From this microscopic model, a homogenisation process derives a macroscopic, volume–averaged model for intracellular, extracellular and transmembrane voltage and it's boundary conditions. This model adds a deeper understanding of the parameters and their connection to the cell scale processes to the already used bidomain model. Colli Franzone, Savaré and Pennacchio [14, 28] used the framework of the Γ–convergence theory and the same assumptions on the microstructure of the cardiac tissue to provide the rigorous mathematical derivation of the bidomain model, as a limit problem of the microscopic (cell scale) model.

Denoting by Ω the homogenised cardiac tissue, by σ_e and σ_i the respective homogenised conductivities of the extracellular medium and of the cell cytoplasm, and by C_m and I_{ion} the respective homogenised membrane capacitance and the homogenised ionic currents that flow through the membranes (see [20]), the bidomain model reads

$$\text{for almost all } (t,x) \in (0,+\infty) \times \Omega,$$

$$\nabla \cdot (\sigma_e \nabla u_e + \sigma_i \nabla u_i) = 0, \tag{1a}$$

$$C_m \partial_t v + I_{ion}(t, v) = \nabla \cdot (\sigma_e \nabla u_e), \quad \text{where } v = u_e - u_i, \tag{1b}$$

with initial and boundary conditions on (u_e, u_i) to close the system.

There are two main challenges to solving the model: the degeneracy of the parabolic system (1) and the derivation of the homogenised ionic model I_{ion} from the microstructure. The first rigorous proof of existence was given in [28], for the FitzHugh Nagumo ionic model. The following was the work of Bourgault, Coudière and Pierre [4], where the compactness technique is used and the proof of the existence was extended to the more complex ionic models, namely the Aliev–Panfilov and the MacCulloch models. In the same year Veneroni proved the existence and uniqueness for the Luo–Rudy ionic model [31]. Boulakia *et al.* [3] gave a proof for a coupled heart–torso problem and extended the proof to include the Mitchell–Schaeffer ionic model. The most recent extension of the proof for the FitzHugh Nagumo and Mitchell–Schaeffer ionic models was done by Collin and Imperiale in [8], using two–scale convergence theory.

While the bidomain model is widely accepted as a standard model for the cardiac electrophysiology, it has several limitations that come from the assumptions in its derivation. As pointed out in [7], some of the assumptions can have important implications, such as: the heart is treated as a static continuum, where parameter values are either uniformly distributed or vary smoothly in space; the cardiac tissue is comprised of myocytes and extracellular space only, while other types of cells and compartments are neglected. Similarly, the assumptions on the values of the model parameters can have important consequences on the propagation of the electric voltage, but many parameter values are difficult to obtain and verify.

1.2. **Limitations of the bidomain model.** The cardiac tissue is composed of many cell types, supported by the extracellular matrix and permeated by fluids. Myocytes are the most studied cells which occupy the largest volume of the cardiac tissue and they are electrically active and contractile cells. On the other hand, the most numerous cells in the heart are fibroblasts. They are much smaller than myocytes and they play an important role in maintenaning the extracellular matrix of the cardiac tissue as they produce interstitial collagen. They are involved in the development of fibrosis in the injured or aged heart. Pathological states are frequently associated with myocardial remodelling involving fibrosis. This is observed in ischemic and rheumatic heart disease, inflammation, hypertrophy and infarction [5]. The structural arrangement of the fibroblasts is still not well understood. Some work has been done to understand the role of the fibroblasts in electrophysiology [5, 18, 19, 22, 30], but it still remains to be studied.

The extracellular matrix is a complex network of fibrous proteins, mainly collagen and elastin. The arrangement of collagen differs throughout the heart. Collagen surrounds each myocyte cell, envelops groups of adjacent myocytes and provides the laminar structure of the myocardium. The thickness of collagen fibrils can increase in pathological cases from 40 nm up to 300 nm [7].

There are several open questions in modelling cardiac electrophysiology. They include the choice of the parameters, such as tissue conductivities, finding an efficient method to represent the detailed and heterogeneous tissue microstructure and the way to study pathological structure and function [7].

In the current modelling of such defects the standard models for the healthy tissues are usually used, and the model parameters are tuned ad hoc. We propose an explanatory model for more rigorous tuning of the parameters in such situations. It is a mesoscopic model, beyond the cell scale of the previously cited models.

1.3. **Accounting for the diffusive part of the heart.** In the proposed model of the electrical activity of the heart tissue we will assume periodic alternations of the healthy tissue, modelled with the standard bidomain model, and non–active regions, modelled with the electrostatic equation. We call it a mesoscale model and we prove the well–posedness of this model using the semigroup theory approach. Numerical simulation of such a problem is very demanding because the domain has to be discretised with the mesh whose step depends on the periodic cell of the domain. Instead, we are interested in finding the averaged macroscopic model over the whole domain. For this we use a homogenisation technique [2, 13]. More specifically, we use the two–scale convergence approach developed by Allaire in [1]. We obtain the homogenised macroscopic bidomain–like model, with modified conductivity tensors. As it turns out, the modified conductivity tensors depend on the size and shape of the diffusive inclusions. Hence, our approach bridges the standard modelling approach of the electrical activity in the heart with its structural heterogeneities.

This model has been firstly proposed in [9]. Here we give a rigorous proof for well posedness of the mesoscale model, and its two–scale convergence to the homogenised model, which has been presented in [10]. From an applied point of view, the homogenised model has been used in numerical studies in the rat heart in [11].

Remark 1. The bidomain model has been studied and almost validated in computational modelling since several decades. That is why we choose to use this model as a starting point and to study the influence of periodic diffusive inclusions on this model. This view point is justified by the fact that these diffusive inclusions are at the mescoscale, in between the cardiac cell scale and the heart tissue scale. We do believe that a three–scale expansion of the complete model would lead to similar limit problem, while it would have increased the technical complexity significantly. Indeed, we are mainly interested in the zeroth order term of the expansion, without accounting for the boundary layer terms that would appear in the next order expansion. These boundary layer terms would probably be different if we chose the three–scale expansion strategy.

1.4. **Outline of the paper.** In the next section, we present the mesoscopic bidomain model with periodic inclusions. In particular, we precise the partial differential equations and the model of nonlinear ionic current which is chosen here. In Section 3 we perform the formal two–scale expansion, which enables to identify the limit problem. Section 4 is devoted to the well–posedness of the limit problem, by defining the appropriate unbounded operators. In Section 5 the rigorous proof of the two–scale formal expansion of Section 3 is given. In particular we prove how the homogenised nonlinear electric current is linked to the mesoscale ionic current. We conclude the paper with numerical simulations, which illustrate the convergence results.

2. **Statement of the problem: The mesoscopic bidomain model with periodic diffusive inclusions.** We consider the bounded open set $\Omega \in \mathbb{R}^N$ (here $N = 3$), with Lipschitz boundary $\partial\Omega$, such that $\Omega = \Omega_\varepsilon^B \cup \Omega_\varepsilon^D \cup \Sigma_\varepsilon$. 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 small cells identical to each other. These 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 the diffusive inclusion, hence $Y = Y_B \cup Y_D \cup \Gamma$ where Γ is the interface. Let ε be a sequence of a strictly positive real numbers which tends to zero.

For the sake of simplicity, throughout the paper, we assume that Y_B and Y_D are smooth connected domains and that Ω_ε^B is also smooth and connected. We also assume that the boundary $\partial\Omega$ of Ω as well as Σ_ε are smooth. The domains Ω_ε^B, Ω_ε^D and Σ_ε read

$$\Omega_\varepsilon^B = \bigcup_{z\in Z^N} \varepsilon(z+Y_B)\cap\Omega,\ \Omega_\varepsilon^D = \bigcup_{z\in Z^N} \varepsilon(z+Y_D)\cap\Omega,\ \Sigma_\varepsilon = \bigcup_{z\in Z^N} \varepsilon(z+\Gamma)\cap\Omega,$$

as illustrated in Figure 1.

The idea is to extend the standard bidomain model on Ω_ε^B with the periodic diffusive inclusions on Ω_ε^D and to study their effect on the macroscopic level. Standard bidomain model involves the intracellular electric potential, $u_\varepsilon^i(t,x)$, and the extracellular one, $u_\varepsilon^e(t,x)$, while the transmembrane voltage is denoted as $v_\varepsilon = u_\varepsilon^i - u_\varepsilon^e$.

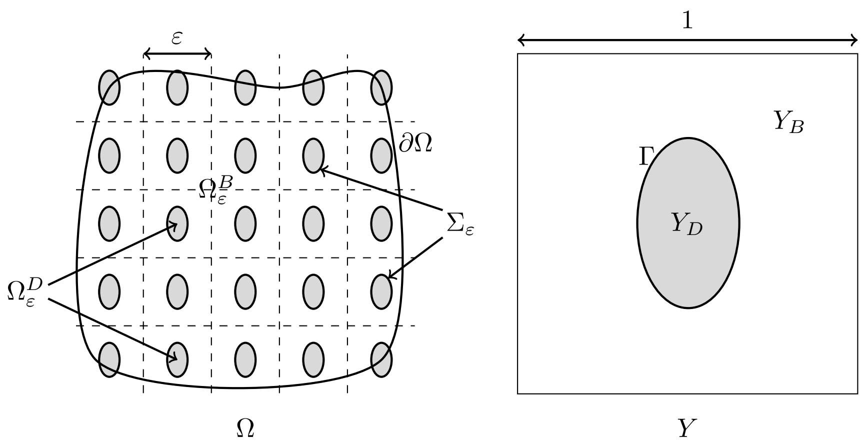

FIGURE 1. On the left: the idealised full 2D domain, Ω. On the right: the periodic cell, Y.

The bidomain model assumes that the change in the transmembrane voltage results from the ionic activity and the diffusion of the electric potential.

In $(0,T)\times\Omega_\varepsilon^B$ the bidomain model reads

$$\begin{aligned}
\partial_t h_\varepsilon(t,x)+g(v_\varepsilon(t,x),h_\varepsilon(t,x)) &= 0, && (2)\\
\partial_t v_\varepsilon(t,x)+I_{ion}(v_\varepsilon(t,x),h_\varepsilon(t,x))-\nabla\cdot\left(\sigma^i(x)\nabla u_\varepsilon^i(t,x)\right) &= 0, && (3)\\
\partial_t v_\varepsilon(t,x)+I_{ion}(v_\varepsilon(t,x),h_\varepsilon(t,x))+\nabla\cdot\left(\sigma^e(x)\nabla u_\varepsilon^e(t,x)\right) &= 0, && (4)
\end{aligned}$$

where σ^i and σ^e are the time–independent intracellular and extracellular conductivity tensors. They are assumed to be symmetric and positive definite matrices, whose coefficients are periodic functions of the period εY. Equation (2) and the function I_{ion} represent the *ionic model* related to the behviour of the myocardium cells' membrane, which depends on the transmembrane voltage, v_ε, and the state variables, h_ε. We will describe the ionic model later on.

We propose to extend the standard bidomain model by assuming passive diffusive inclusions Ω_ε^D, *i.e.* in $(0,T)\times\Omega_\varepsilon^D$,

$$\nabla\cdot\left(\sigma^d\nabla u_\varepsilon^d(t,x)\right)=0,$$

where σ^d is the conductivity tensor, and u^d is the electric potential in Ω_ε^D. Our modelling assumption is that the diffusive inclusions are "large" extensions of extracellular space of the standard bidomain model. We assume the continuity of potential and the flux between u_ε^e and u_ε^d. Additionally we assume no–flux on the intracellular potential u_ε^i. Hence, the standard transmission conditions are given on the interface $(0,T)\times\Sigma_\varepsilon$

$$\begin{aligned}
\left(\sigma^i\nabla u_\varepsilon^i(t,x)\right)\cdot n_{\Omega_\varepsilon^B} &= 0,\\
\left(\sigma^e\nabla u_\varepsilon^e(t,x)\right)\cdot n_{\Omega_\varepsilon^B} &= \left(\sigma^d\nabla u_\varepsilon^d(t,x)\right)\cdot n_{\Omega_\varepsilon^B},\\
u_\varepsilon^e(t,x) &= u_\varepsilon^d(t,x),
\end{aligned}$$

where $n_{\Omega_\varepsilon^B}$ is the unit normal vector from Ω_ε^B to Ω_ε^D. On the outer boundary homogeneous Neumann conditions are imposed, *i.e.* on $(0,T)\times\partial\Omega\cap\partial\Omega_\varepsilon^B$ holds $(\sigma^i\nabla u_\varepsilon^i(t,x))\cdot n=-(\sigma^e\nabla u_\varepsilon^e(t,x))\cdot n=0$, and on $(0,T)\times\partial\Omega\cap\partial\Omega_\varepsilon^D$ holds

$(\sigma^d \nabla u_\varepsilon^d(t,x)) \cdot n = 0$, where n is the outer unit normal vector on $\partial\Omega$. The following Gauge condition on u_ε^e is imposed to ensure the uniqueness,

$$\forall t \in (0,T), \ \int_{\Omega_\varepsilon^B} u_\varepsilon^e(t,x)dx + \int_{\Omega_\varepsilon^D} u_\varepsilon^d(t,x)dx = 0. \tag{5}$$

The Gauge condition is chosen to ensure the uniqueness of the solution, otherwise the electrical potentials would have been determined up to a constant. The choice of the Gauge condition is not so important since only the transmembrane voltage, v_ε, is physically relevant. A change in the Gauge condition would lead to the same transmembrane voltage. The initial conditions on v_ε and h_ε are $v_\varepsilon(0,x) = v_\varepsilon^0(x)$ in Ω_ε^B, and $h_\varepsilon(0,x) = h_\varepsilon^0(x)$ in Ω_ε^B.

Similar set of equations have been studied previously in [3] on the heart–torso problem, where the torso was represented by the diffusive part and the heart, i.e. the bidomain equations were embedded inside of the diffusive domain.

We summarise the full problem:

$$\partial_t h_\varepsilon + g(v_\varepsilon, h_\varepsilon) = 0, \qquad \text{in } (0,T)\times\Omega_\varepsilon^B, \tag{6a}$$

$$\partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) - \nabla\cdot\left(\sigma^i \nabla u_\varepsilon^i\right) = 0, \qquad \text{in } (0,T)\times\Omega_\varepsilon^B, \tag{6b}$$

$$\partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) + \nabla\cdot\left(\sigma^e \nabla u_\varepsilon^e\right) = 0, \qquad \text{in } (0,T)\times\Omega_\varepsilon^B, \tag{6c}$$

$$\nabla\cdot\left(\sigma^d \nabla u_\varepsilon^d\right) = 0, \qquad \text{in } (0,T)\times\Omega_\varepsilon^D, \tag{6d}$$

with the transmission and boundary conditions:

$$\left(\sigma^i \nabla u_\varepsilon^i\right)\cdot n_{\Omega_\varepsilon^B} = 0, \qquad \text{on } (0,T)\times\Sigma_\varepsilon, \tag{6e}$$

$$u_\varepsilon^e = u_\varepsilon^d, \qquad \text{on } (0,T)\times\Sigma_\varepsilon, \tag{6f}$$

$$\left(\sigma^e \nabla u_\varepsilon^e\right)\cdot n_{\Omega_\varepsilon^B} = \left(\sigma^d \nabla u_\varepsilon^d\right)\cdot n_{\Omega_\varepsilon^B}, \qquad \text{on } (0,T)\times\Sigma_\varepsilon, \tag{6g}$$

$$\left(\sigma^i \nabla u_\varepsilon^i\right)\cdot n = 0, \qquad \text{on } (0,T)\times\partial\Omega\cap\partial\Omega_\varepsilon^B, \tag{6h}$$

$$\left(\sigma^e \nabla u_\varepsilon^e\right)\cdot n = 0, \qquad \text{on } (0,T)\times\partial\Omega\cap\partial\Omega_\varepsilon^B, \tag{6i}$$

$$\left(\sigma^d \nabla u_\varepsilon^d\right)\cdot n = 0, \qquad \text{on } (0,T)\times\partial\Omega\cap\partial\Omega_\varepsilon^D, \tag{6j}$$

and with Gauge and the initial conditions:

$$\int_{\Omega_\varepsilon^B} u_\varepsilon^e + \int_{\Omega_\varepsilon^D} u_\varepsilon^d = 0, \qquad \text{in } (0,T), \tag{6k}$$

$$v_\varepsilon(0,x) = v_\varepsilon^0(x) \qquad \text{in } \Omega_\varepsilon^B, \tag{6l}$$

$$h_\varepsilon(0,x) = h_\varepsilon^0(x) \qquad \text{in } \Omega_\varepsilon^B. \tag{6m}$$

2.1. **Ionic model regularisation.** We focus on the use of the Mitchell–Schaeffer (MS) model [24]. This model has become the standard model in computational cardiac electrophysiology, because it has been well validated with biological experiments and its complexity is comparable to the FitzHugh–Nagumo model, which makes it useful in numerical simulations, especially in two or three spatial dimensions where numerical efficiency is so important. The ionic current I_{MS} of the Mitchell–Schaeffer model reads

$$I_{MS}(v,h) = \frac{1}{\tau_{in}} h v^2 (v-1) - \frac{v}{\tau_{out}}, \tag{7a}$$

where the gating variable h is defined as:

$$\partial_t h = \begin{cases} \dfrac{1-h}{\tau_{op}}, \text{if } v \le v_{gate}, \\ \\ -\dfrac{h}{\tau_{cl}}, \text{if } v > v_{gate}, \end{cases} \tag{7b}$$

where τ_{in}, τ_{out}, τ_{op}, τ_{cl} and v_{gate} are the constant model parameters. The former four parameters define the shape of cardiac action potential, while the latter one defines the threshold value of the transmembrane voltage for which an action potential is triggered.

The difficulties in analyzing the above model are two–fold. One difficulty lies in the step function involved in (7b), which prevents any regularity results, which is somehow needed in the homogenisation derivation. The second difficulty lies in the unboundedness of the ionic current I_{MS}, which is cubic in v. Since there is no maximum principles in bidomain model, such cubic behviour is a hard task to overcome when proving boundedness. Boulakia *et al.* in [3] proposed a regularised version of this model by regularising the step function of the right hand side of (7b). However, their ionic current remains unbounded since it grows cubically with respect to v. In order to use the two–scale convergence theory, as in Section 5, we need *a–priori* bounds on the solution of the mesoscopic problem. For this reason we need a better behaved ionic function.

Here we propose regularisation that accounts for the electroporation of the cell. It is well known that far from the physiological values of the transmembrane voltage electroporation of cell membranes occurs [17, 21, 32], which consists of a high increase of membrane conductance. Moreover the membrane conductance cannot be infinite since it is bounded by the medium conductivity. We thus propose the following modified version of the MS model: assuming v given, the ionic current I_{ion} is defined as

$$I_{ion}(v,h) = \frac{1}{\tau_{in}} h v^2 (v-1) e^{-(v/v_{th})^2} - \frac{v}{\tau_{out}}\left(1 + r_{max} e^{-(v_{th}/v)^2}\right), \tag{8}$$

where the gating variable h is given by

$$\partial_t h + g(v,h) = 0, \tag{9}$$

$$\text{with} \quad g(v,h) = \frac{h - h_\infty(v)}{\tau(v)}, \tag{10}$$

$$h|_{t=0} = h^0(v), \tag{11}$$

where the functions $h_\infty(v)$ and $\tau(v)$ are defined as

$$h_\infty(v) = 1 - e^{-(v_{gate}/v)^2}, \tag{12}$$

$$\frac{1}{\tau(v)} = \frac{1}{\tau_{cl}} + \frac{\tau_{cl} - \tau_{op}}{\tau_{cl}\tau_{op}} h_\infty(v), \tag{13}$$

and the parameters v_{th}, v_{gate}, and r_{max} are assumed to be given and constant and the initial datum $h^0(v)$ is a given function of v. The function g is a regularisation similar to the one given in [3], $v_{th} \gg v_{gate}$ is the membrane voltage above which electroporation occurs, and $r_{max} \gg 1$ stands for the maximal ratio of membrane conductance with membrane capacitance in a fully electroporated membrane. We refer to [17] for more details.

In the physiological range of membrane voltage, the current behaves similarly to the standard MS model, while for non–physiological values of v, when $v \gg v_{th}$, the current behaves as a passive conducting pore: $I_{ion} \sim (1 + r_{max})v/\tau_{out}$. The above model is interesting for two reasons: it provides a simple model for cardiac tissues submitted to electroporation and the ionic function has the Lipschitz property as we will see in the following proposition.

Proposition 1 (Lipschitz property of the modified MS)**.** *Let $M > 0$, and let $h^0(v)$ be a smooth function such that $0 < h^0(v) < 1$, and $\left|\partial_v h^0\right| \leq M$, for all $v \in \mathbb{R}$. Then, for all $v \in \mathbb{R}$, and all $t > 0$, we have $0 \leq h(t, v) \leq 1$. Moreover the current I_{ion} of the modified version of Mitchell–Schaeffer model (8) is globally Lipschitz with respect to v, i.e. that there exists $K > 0$ such that for all $t > 0$, and any $v_1, v_2 \in \mathbb{R}$, it holds $|I_{ion}(v_1, h(t, v_1)) - I_{ion}(v_2, h(t, v_2))| \leq K|v_1 - v_2|$.*

Proof. By hypothesis on h_0, it is easy to show that the function h stays between 0 and 1 for all $t > 0$ (see Lemma 4.2). Since g is a smooth function of v, h is globally Lipschitz with respect to v. Let us define function $H(t, v) := \partial_v h(t, v)$. Then the following ODE holds,

$$\begin{aligned} &\frac{\partial H}{\partial t} = \frac{1}{\tau(v)}\left(\left(h'_\infty(v) - \frac{\tau'(v)}{\tau(v)}(h_\infty(v) - h(v))\right) - H\right), \\ &H(0, v) = \partial_v h_0(v). \end{aligned}$$

Let $m = \max_{v\in\mathbb{R}}\left(h'_\infty(v) - \frac{\tau'(v)}{\tau(v)}(h_\infty(v) - h(v))\right)$. Then H is uniformly bounded on $\mathbb{R}^+$ by $\max(M, m)$ and there exists S_∞ such that the function $|\partial_v I_{ion}(t, v)| \leq S_\infty$, for all $t \geq 0$. Therefore by definition of I_{ion} one has the global Lipschitz property for any $t > 0$ and for all $v_1, v_2 \in \mathbb{R}$:

$$\begin{aligned} &|I_{ion}(v_2, h(t, v_2)) - I_{ion}(v_1, h(t, v_1))| \\ &\leq \left|\int_{v_1}^{v_2} \partial_v I_{ion}(\lambda, h(t, v_2))d\lambda\right| + \left|\int_{h(t,v_1)}^{h(t,v_2)} \partial_h I_{ion}(v_1, \mu)d\mu\right| \\ &\leq K|v_2 - v_1|. \end{aligned}$$

□

3. **Formal derivation of the macroscopic bidomain model with periodic diffusive inclusions.** We are interested in finding the averaged macroscopic model over the whole domain Ω. This is done by use of the homogenisation technique [2, 13]. The complexity of such a derivation is two–fold. Firstly, one has to tackle the coupling of the degenerate parabolic phase –the bidomain phase– and the elliptic phase, which corresponds to the diffusive inclusion. It is not clear whether or not this coupling problem is well–posed. Moreover, at the limit the two phases are tightly mixed and the resulting homogenised problem is not easy to figure out, even in the linear case. The second difficulty lies in the rigorous derivation of the homogenised nonlinearity. To address these two difficulties we first derive formally the limit problem thanks to a two–scale expansion strategy. Then we prove the well–posedness and uniform bounds on the mesoscopic coupled problem. The proof of the two–scale expansion is given in Section 5.

In this section the method of formal two–scale asymptotic expansions is performed in order to find the macroscopic homogenised problem for (6). This formal derivation is interesting from the modelling point of view, as it makes it possible to intuitively obtain the homogenised problem. We want to split mesoscopic ($\sim \varepsilon$)

and macroscopic (~ 1) scales contributions. The standard technique is to introduce a small scale variable y, such that $y = x/\varepsilon$. The assumption is that, due to the periodicity of space, the behviour of the solution can be split into the large scale behviour, given through dependence on x, and the small scale behviour of the same frequency ε, given through dependence on y. Then, the macroscopic behviour of the solution is extracted by taking $\varepsilon \to 0$.

Following the general idea, we assume that the solution $(u_\varepsilon^i, u_\varepsilon^e, u_\varepsilon^d, h_\varepsilon)$ can be written as formal series

$$h_\varepsilon(t,x) = \sum_{k\geq 0} \varepsilon^k h_k(t,x,x/\varepsilon), \quad u_\varepsilon^i(t,x) = \sum_{k\geq 0} \varepsilon^k u_k^i(t,x,x/\varepsilon), \tag{14}$$

$$u_\varepsilon^e(t,x) = \sum_{k\geq 0} \varepsilon^k u_k^e(t,x,x/\varepsilon), \quad u_\varepsilon^d(t,x) = \sum_{k\geq 0} \varepsilon^k u_k^d(t,x,x/\varepsilon), \tag{15}$$

with $u_k^{i,e,d}(t,x,y)$ and $h_k(t,x,y)$ as $Y-$periodic functions. Using the ansatz in (14) - (15), and substituting it into the system of equations (6) we obtain the cascade systems of equations with respect to the power of ε. We are interested in the first three terms, for $k = 0, 1$ and 2, that we will use to obtain the macroscopic problem. The following derivation rule is used $\nabla f\left(x, \frac{x}{\varepsilon}\right) = \left[\frac{1}{\varepsilon}\nabla_y f + \nabla_x f\right]\left(x, \frac{x}{\varepsilon}\right)$, where ∇_x and ∇_y denote the partial derivative with respect to the first and the second variable of $f(x,y)$. Identifying each power of ε as an individual equation yields a cascade of systems of equations.

Order 0: The ε^{-2} system of equations gives for u_0^i,

$$\begin{aligned} &\nabla_y \cdot \left(\sigma^i \nabla_y u_0^i\right) = 0, \text{ in } \Omega \times Y_B, \\ &\left(\sigma^i \nabla_y u_0^i\right) \cdot n_\Gamma = 0, \text{ on } \Sigma_\varepsilon \times \Gamma, \\ &\qquad + \text{ periodic boundary conditions on } \partial Y. \end{aligned} \tag{16}$$

Multiplying (16) by u_0^i and integrating over y, we deduce that u_0^i does not depend on variable y, *i.e.* $u_0^i = u_0^i(t,x)$.

And for u_0^e and u_0^d we get,

$$\begin{aligned} \nabla_y \cdot \left(\sigma^e \nabla_y u_0^e\right) &= 0, \text{ in } \Omega \times Y_B, \\ \nabla_y \cdot \left(\sigma^d \nabla_y u_0^d\right) &= 0, \text{ in } \Omega \times Y_D, \\ u_0^e &= u_0^d, \text{ on } \Sigma_\varepsilon \times \Gamma, \\ \left(\sigma^e \nabla_y u_0^e\right) \cdot n_\Gamma &= \left(\sigma^d \nabla_y u_0^d\right) \cdot n_\Gamma, \text{ on } \Sigma_\varepsilon \times \Gamma, \\ &+ \text{ periodic boundary conditions on } \partial Y. \end{aligned} \tag{17}$$

Due to the boundary conditions, *i.e.* continuity of potential and flux, we can define a new function $u_0(t,x,y)$ on the domain $\Omega \times Y$ such that $u_0 = u_0^e$ in $\Omega \times Y_B$, and $u_0 = u_0^d$ in $\Omega \times Y_D$. We also define the conductivity tensor σ as $\sigma = \sigma^e$ in $\Omega \times Y_B$, and $\sigma = \sigma^d$ in $\Omega \times Y_D$. Hence, the problem (17) simplifies to

$$\begin{aligned} &\nabla_y \cdot \left(\sigma \nabla_y u_0\right) = 0, \text{ in } \Omega \times Y, \\ &\qquad + \text{ periodic boundary conditions on } \partial Y. \end{aligned} \tag{18}$$

Similarly, we find that u_0 does not depend on y, *i.e.* $u_0 = u_0(t,x)$.

Order 1: The ε^{-1} system of equation then gives,

$$\begin{aligned} &\nabla_y \cdot (\sigma^i \nabla_y u_1^i) = 0, \text{ in } \Omega \times Y_B, \\ &\left(\sigma^i \nabla_y u_1^i\right) \cdot n_\Gamma = -\left(\sigma^i \nabla_x u_0^i\right) \cdot n_\Gamma, \text{ on } \Sigma_\varepsilon \times \Gamma, \\ &\qquad\qquad + \text{ periodic boundary conditions on } \partial Y, \end{aligned} \tag{19}$$

and,

$$\begin{aligned} \nabla_y \cdot (\sigma^e \nabla_y u_1^e) &= 0, \text{ in } \Omega \times Y_B, \\ \nabla_y \cdot (\sigma^d \nabla_y u_1^d) &= 0, \text{ in } \Omega \times Y_D, \\ \left(\sigma^e \nabla_y u_1^e - \sigma^d \nabla_y u_1^d\right) \cdot n_\Gamma &= -\left((\sigma^e - \sigma^d) \nabla_x u_0\right) \cdot n_\Gamma, \text{ on } \Sigma_\varepsilon \times \Gamma, \\ &\quad + \text{ periodic boundary conditions on } \partial Y. \end{aligned} \tag{20}$$

From (19) and (20) we see that the terms u_1^i, u_1^e and u_1^d can be expressed as functions of u_0^i and u_0, in a standard way as

$$u_1^i(t,x,y) = \sum_{j=1}^{3} w_j^i(y) \frac{\partial u_0^i}{\partial x_j}(t,x), \text{ on } \Omega \times Y_B, \tag{21}$$

$$u_1^e(t,x,y) = \sum_{j=1}^{3} w_j^e(y) \frac{\partial u_0}{\partial x_j}(t,x), \text{ on } \Omega \times Y_B, \tag{22}$$

$$u_1^d(t,x,y) = \sum_{j=1}^{3} w_j^d(y) \frac{\partial u_0}{\partial x_j}(t,x), \text{ on } \Omega \times Y_D. \tag{23}$$

By the substitution the problems for functions $w_j^i(y), w_j^e(y), w_j^d(y)$, for $j = 1, 2, 3$, read

$$\begin{aligned} \nabla_y \cdot (\sigma^i \nabla_y w_j^i) &= 0, \text{ in } Y_B, \\ \sigma^i \left(\nabla_y w_j^i + e_j\right) \cdot n_\Gamma &= 0, \text{ on } \Gamma, \\ w_j^i &\text{ is } Y \text{ periodic}, \end{aligned} \tag{24}$$

and

$$\begin{aligned} \nabla_y \cdot (\sigma^e \nabla_y w_j^e) &= 0, \text{ in } Y_B, \\ \nabla_y \cdot (\sigma^d \nabla_y w_j^d) &= 0, \text{ in } Y_D, \\ \left(\sigma^e \nabla_y w_j^e - \sigma^d \nabla_y w_j^d + (\sigma^e - \sigma^d) e_j\right) \cdot n_\Gamma &= 0, \text{ on } \Gamma, \\ w_j^e, w_j^d &\text{ are } Y \text{ periodic}. \end{aligned} \tag{25}$$

The problems (24) and (25) are called the cell problems.

Order 2: Finally, the ε^0 system of equation gives the equation for the term u_2^i in $\Omega \times Y_B$,

$$\begin{aligned} -\nabla_y \cdot (\sigma^i \nabla_y u_2^i) =& \nabla_y \cdot (\sigma^i \nabla_x u_1^i) \\ &+ \nabla_x \cdot (\sigma^i \nabla_x u_0^i) + \nabla_x \cdot (\sigma^i \nabla_y u_1^i) - \partial_t v_0 - I_{ion}(v_0, h_0), \end{aligned} \tag{26}$$

with the boundary condition,

$$\begin{aligned} &\left(\sigma^i \nabla_y u_2^i\right) \cdot n_\Gamma = \left(\sigma^i \nabla_x u_1^i\right) \cdot n_\Gamma, \text{ on } \Sigma_\varepsilon \times \Gamma \\ &\qquad + \text{periodic boundary condition on } \partial Y. \end{aligned}$$

Integrating (26) over Y_B, and using the boundary conditions we have on Ω

$$|Y_B|\left(\partial_t v_0 + I_{ion}(v_0,h_0)\right) = |Y_B|\nabla_x\cdot(\sigma^i\nabla_x u_0^i) + \int_{Y_B}\nabla_x\cdot(\sigma^i\nabla_y u_1^i)\,dy,$$

Then using (21), we obtain

$$|Y_B|\left(\partial_t v_0 + I_{ion}(v_0,h_0)\right) = \nabla_x\left(\sigma^{i*}\nabla_x u_0^i\right), \tag{27}$$

where

$$\sigma_{kj}^{i*} = |Y_B|\sigma_{kj}^i + \sigma_{k1}^i\int_{Y_B}\partial_{y_1}w_j^i\,dy + \sigma_{k2}^i\int_{Y_B}\partial_{y_2}w_j^i\,dy + \sigma_{k3}^i\int_{Y_B}\partial_{y_3}w_j^i\,dy. \tag{28}$$

For the term u_2^e, the system of equation gives on $\Omega\times Y_B$,

$$\begin{aligned}-\nabla_y\cdot(\sigma^e\nabla_y u_2^e) =& \nabla_y\cdot(\sigma^e\nabla_x u_1^e)\\ &+\nabla_x\cdot(\sigma^e\nabla_x u_0) + \nabla_x\cdot(\sigma^e\nabla_y u_1^e) - \partial_t v_0 - I_{ion}(v_0,h_0),\end{aligned} \tag{29}$$

and for the term u_2^d, the system of equation gives on $\Omega\times Y_D$,

$$-\nabla_y\cdot(\sigma^d\nabla_y u_2^d) = \nabla_y\cdot(\sigma^d\nabla_x u_1^d) + \nabla_x\cdot(\sigma^d\nabla_x u_0) + \nabla_x\cdot(\sigma^d\nabla_y u_1^d), \tag{30}$$

with the boundary conditions

$$\begin{aligned}(\sigma^e\nabla_y u_2^e)\cdot n_\Gamma &= (\sigma^e\nabla_x u_1^e)\cdot n_\Gamma, \text{ on } \Sigma_\varepsilon\times\Gamma,\\ \left(\sigma^d\nabla_y u_2^d\right)\cdot n_\Gamma &= \left(\sigma^d\nabla_x u_1^d\right)\cdot n_\Gamma, \text{ on } \Sigma_\varepsilon\times\Gamma,\\ &+ \text{periodic boundary conditions on } \partial Y.\end{aligned}$$

Once again, integrating (29) over Y_B, and (30) over Y_D, and using the boundary conditions, and summing them up, lead to the following equation on Ω

$$\begin{aligned}|Y_B|\left(\partial_t v_0 + I_{ion}(v_0,h_0)\right) =& \int_Y\nabla_x\cdot(\sigma\nabla_x u_0)\,dy\\ &+\int_{Y_B}\nabla_x\cdot(\sigma^e\nabla_y u_1^e)\,dy + \int_{Y_D}\nabla_x\cdot(\sigma^d\nabla_y u_1^d)\,dy.\end{aligned}$$

Using (22), we obtain

$$|Y_B|\left(\partial_t v_0 + I_{ion}(v_0,h_0)\right) = \nabla_x\left(\sigma^{e*}\nabla_x u_0\right), \tag{31}$$

where

$$\begin{aligned}\sigma_{kj}^{e*} = & |Y_B|\sigma_{kj}^e + \int_{Y_B}\sigma_{k1}^e\partial_{y_1}w_j^e\,dy + \int_{Y_B}\sigma_{k2}^e\partial_{y_2}w_j^e\,dy + \int_{Y_B}\sigma_{k3}^e\partial_{y_3}w_j^e\,dy\\ &+|Y_D|\sigma_{kj}^d + \int_{Y_D}\sigma_{k1}^d\partial_{y_1}w_j^d\,dy + \int_{Y_D}\sigma_{k2}^d\partial_{y_2}w_j^d\,dy + \int_{Y_D}\sigma_{k3}^d\partial_{y_3}w_j^d\,dy.\end{aligned} \tag{32}$$

Homogenised problem: Equations (27) and (31), together with

$$\partial_t h_0 + g(v_0,h_0) = 0, \tag{33}$$

represent the homogenised macroscopic problem, whose solution (h_0, u_0^i, u_0) is the limit of $(h_\varepsilon, u_\varepsilon^i, u_\varepsilon^e, u_\varepsilon^d)$ for $\varepsilon\to 0$, and does not depend on the small scale y. The small scale effects are accounted for through the conductivity tensors and parameter $|Y_B|$ that represents the volume fraction of the healthy tissue in the periodic cell. The constant tensors σ^{i*} and σ^{e*} describe the effective or homogenised properties of the heterogeneous tissue. They do not depend neither on time, nor on the choice of Ω. They depend on the initial conductivity tensors and on the shape and size of the diffusive inclusions.

Remark 2. The method of the two–scale expansion has yet to be rigorously proven. In other words, it leads heuristically to the homogenised system of equations, but it is not a sufficient proof for the homogenisation process. First issue is that we still did not prove the existence of the solution to the original ε-dependent mesoscopic problem. Secondly, we do not know if such mesoscopic problem has in fact a limit. And even if we assume it has, the ansatz (14)-(15) is not yet justified. Hence, we can not claim that (h_0, u_0^i, u_0) is actually a limit to $(h_\varepsilon, u_\varepsilon^i, u_\varepsilon^e, u_\varepsilon^d)$ when $\varepsilon \to 0$. And the last, but not least issue is that we have to deal with the nonlinearity and actually justify the assumption that $g(v_\varepsilon, h_\varepsilon) \to g(v_0, h_0)$, and $I_{ion}(v_\varepsilon, h_\varepsilon) \to I_{ion}(v_0, h_0)$. The rigorous proof is laid out in Section 4 and Section 5.

4. **Existence and bounds on the solutions of the mesoscopic problem.** We go back to our mesoscopic problem, where we want to prove the existence of the solution for (6), by use of the semigroup theory approach [6]. In this section we will use the parabolic–elliptic form of the problem.

$$\partial_t h_\varepsilon + g(v_\varepsilon, h_\varepsilon) = 0, \quad \text{in } \Omega_\varepsilon^B, \tag{34a}$$

$$\partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon(t, v_\varepsilon)) - \nabla \cdot (\sigma^i \nabla v_\varepsilon) = \nabla \cdot (\sigma^i \nabla u_\varepsilon), \quad \text{in } \Omega_\varepsilon^B, \tag{34b}$$

$$-\nabla \cdot ((\sigma^i + \sigma^e) \nabla u_\varepsilon) = \nabla \cdot (\sigma^i \nabla v_\varepsilon), \quad \text{in } \Omega_\varepsilon^B, \tag{34c}$$

$$-\nabla \cdot (\sigma^d \nabla u_\varepsilon) = 0, \quad \text{in } \Omega_\varepsilon^D, \tag{34d}$$

where u_ε is $H^1(\Omega)$. The boundary and transmission conditions are given as

$$(\sigma^i \nabla v_\varepsilon) \cdot n_{\Omega_\varepsilon^B} = -(\sigma^i \nabla u_\varepsilon) \cdot n_{\Omega_\varepsilon^B}, \quad \text{on } \Sigma_\varepsilon, \tag{34e}$$

$$(\sigma^e \nabla u_\varepsilon) \cdot n_{\Omega_\varepsilon^B} = -(\sigma^d \nabla u_\varepsilon) \cdot n_{\Omega_\varepsilon^D}, \quad \text{on } \Sigma_\varepsilon, \tag{34f}$$

$$(\sigma^i \nabla v_\varepsilon) \cdot n = 0, \quad \text{on } \partial\Omega \cap \partial\Omega_\varepsilon^B, \tag{34g}$$

$$\big((\sigma^i + \sigma^e) \nabla u_\varepsilon\big) \cdot n = 0, \quad \text{on } \partial\Omega \cap \partial\Omega_\varepsilon^B, \tag{34h}$$

$$(\sigma^d \nabla u_\varepsilon) \cdot n = 0, \quad \text{on } \partial\Omega, \tag{34i}$$

the initial conditions are

$$h_\varepsilon(0, v_\varepsilon) = h_\varepsilon^0(v_\varepsilon), \quad \text{in } \Omega_\varepsilon^B, \tag{34j}$$

$$v_\varepsilon(0, x) = v_\varepsilon^0(x), \quad \text{in } \Omega_\varepsilon^B, \tag{34k}$$

and the Gauge condition is

$$\int_\Omega u_\varepsilon dx = 0, \tag{34l}$$

where $n_{\Omega_\varepsilon^B}$ is the normal on Σ_ε outwards from Ω_ε^B, $n_{\Omega_\varepsilon^D}$ is the normal on Σ_ε outwards from Ω_ε^D, and n is the outwards normal on $\partial\Omega$.

Remark 3. Given the initial conditions for h_ε and v_ε, and assuming that there exists a unique solution to the above problem continuous in time, then $u_\varepsilon^0(x) := u_\varepsilon(0, x)$ is the solution to

$$\int_{\Omega_\varepsilon^B} (\sigma^i + \sigma^e) \nabla u_\varepsilon^0 \nabla \phi \, dx + \int_{\Omega_\varepsilon^D} \sigma^d \nabla u_\varepsilon^0 \nabla \phi \, dx = -\int_{\Omega_\varepsilon^B} \sigma^i \nabla v_\varepsilon^0 \nabla \phi \, dx, \tag{35}$$

for all $\phi \in H^1(\Omega)$, with the Gauge condition $\int_\Omega u_\varepsilon^0 \, dx = 0$.

In this section we prove the following well–posedness theorem.

Theorem 4.1 (Well–posedness of the mesoscopic model)**.** *Let $\varepsilon > 0$ be given. Let $h_\varepsilon^0 \in L^\infty(\Omega_\varepsilon^B)$, with $0 < h_\varepsilon^0(x) \le 1$ and let $v_\varepsilon^0 \in L^2(\Omega_\varepsilon^B)$. Then the problem (34) has a unique solution $(v_\varepsilon, u_\varepsilon, h_\varepsilon)$, such that*

$$\begin{aligned} v_\varepsilon &\in C([0,+\infty); H^1(\Omega_\varepsilon^B)) \cap C^1([0,+\infty); L^2(\Omega_\varepsilon^B)), \\ u_\varepsilon &\in C([0,+\infty); H^1(\Omega)), \\ h_\varepsilon &\in C([0,+\infty); L^\infty(\Omega_\varepsilon^B)) \cap C^1([0,+\infty); L^\infty(\Omega_\varepsilon^B)). \end{aligned}$$

Lemma 4.2 (A priori uniform estimates on h_ε)**.** *Let $h_\varepsilon^0 \in L^\infty(\Omega_\varepsilon^B)$, with $0 < h_\varepsilon^0 \le 1$, then we have $h_\varepsilon(t,\cdot) \in L^\infty(\Omega_\varepsilon^B)$ and $\partial_t h_\varepsilon(t,\cdot) \in L^\infty(\Omega_\varepsilon^B)$. Moreover,*

$$0 < h_\varepsilon(t,x) \le 1.$$

Proof. From the modified MS model we have

$$-\partial_t h_\varepsilon = (h_\infty(v_\varepsilon) - h_\varepsilon) \underbrace{\left(\frac{1}{\tau_{cl}} + \frac{\tau_{cl} - \tau_{op}}{\tau_{cl}\tau_{op}} h_\infty(v_\varepsilon)\right)}_{(*)}. \tag{36}$$

The term $(*)$ is positive, because $0 < \tau_{op} < \tau_{cl}$. From the definition of $h_\infty(v_\varepsilon)$, given in (12), we have that $0 \le h_\infty(v_\varepsilon) \le 1$, for all $v_\varepsilon \in \mathbb{R}$. Using this and applying the Gronwall lemma, we have the upper and lower bound on h_ε

$$h_\varepsilon(t,x) \ \ge \ h_\varepsilon^0(x) e^{-\int_0^T \left(\frac{1}{\tau_{cl}} + \frac{\tau_{cl}-\tau_{op}}{\tau_{cl}\tau_{op}} h_\infty(v_\varepsilon)\right) ds}, \tag{37}$$

$$h_\varepsilon(t,x) \ \le \ 1 - (1 - h_\varepsilon^0(x)) e^{-\int_0^T \left(\frac{1}{\tau_{cl}} + \frac{\tau_{cl}-\tau_{op}}{\tau_{cl}\tau_{op}} h_\infty(v_\varepsilon)\right) ds}. \tag{38}$$

The exponential part is bounded with,

$$1 \ge e^{-\int_0^T \left(\frac{1}{\tau_{cl}} + \frac{\tau_{cl}-\tau_{op}}{\tau_{cl}\tau_{op}} h_\infty(v_\varepsilon)\right) ds} \ge e^{-\int_0^T \left(\frac{1}{\tau_{cl}} + \frac{\tau_{cl}-\tau_{op}}{\tau_{cl}\tau_{op}}\right) ds} = e^{-\frac{T}{\tau_{op}}}. \tag{39}$$

Combining (37), (38) and (39), and using the assumption that the initial condition h_ε^0 is bounded, we obtain $\min\{h_\varepsilon^0(x)\} e^{-\frac{T}{\tau_{op}}} \le h_\varepsilon(t,x) \le 1$, in Ω_ε^B. Finally, from (36), we have $|\partial_t h_\varepsilon(t,x)| \le \frac{1}{\tau_{op}}$, in Ω_ε^B. ☐

Remark 4. Normally we work with constant conductivity tensors σ^i, σ^e and σ^d, but our proof will work in the following more general case. We suppose that the conductivity tensors $\sigma^e(x)$, $\sigma^i(x)$ and $\sigma^d(x)$ are symmetric definite positive matrix–functions, such that

$$\underline{\sigma}|\xi|^2 \le \xi^T \sigma^{e,i}(x) \xi \le \overline{\sigma}|\xi|^2, \qquad \forall x \in \Omega_\varepsilon^B, \tag{40}$$

and

$$\underline{\sigma}|\xi|^2 \le \xi^T \sigma^{d}(x) \xi \le \overline{\sigma}|\xi|^2, \qquad \forall x \in \Omega_\varepsilon^D. \tag{41}$$

We denote by $\sqrt{\sigma^i}$, $\sqrt{\sigma^e}$, and $\sqrt{\sigma^d}$ their respective symmetric definite positive square roots.

In this section, the parameter ε is fixed, so we will omit it as a subscript in the equations in the rest of the section. To build the proof we will use the semigroup approach, following the theory exposed in [6].

Definition 4.3. We define $\mathcal{B}$ as the operator from $H^1(\Omega_\varepsilon^B)$ to $H^1(\Omega)$, such that

$$\forall v \in H^1(\Omega_\varepsilon^B), \mathcal{B}(v) := u,$$

where u is the solution of the following variational problem

$$\begin{aligned}\int_{\Omega_\varepsilon^B}(\sigma^i+\sigma^e)\nabla u\nabla\phi\,dx+\int_{\Omega_\varepsilon^D}\sigma^d\nabla u\nabla\phi\,dx=-\int_{\Omega_\varepsilon^B}\sigma^i\nabla v\nabla\phi\,dx,\\ \forall\phi\in\left\{H^1(\Omega),\int_\Omega\phi=0\right\}.\end{aligned}\tag{42}$$

Additionally, we denote as $\mathcal{B}_{\Omega_\varepsilon^B}$ the restriction of the operator $\mathcal{B}$ to Ω_ε^B in the following sense:

$$\mathcal{B}_{\Omega_\varepsilon^B}(v):=u|_{\Omega_\varepsilon^B}.$$

Lemma 4.4. *For a constant $\beta>0$, the following inequality holds*

$$\|\nabla\mathcal{B}(v)\|_{L^2(\Omega_\varepsilon^B)}\leq\beta\|\nabla v\|_{L^2(\Omega_\varepsilon^B)}.\tag{43}$$

Proof. Taking $\phi=u$ in (42), we have

$$\int_{\Omega_\varepsilon^B}|\sqrt{\sigma^i}\nabla u|^2dx+\int_{\Omega_\varepsilon^B}|\sqrt{\sigma^e}\nabla u|^2dx+\int_{\Omega_\varepsilon^D}|\sqrt{\sigma^d}\nabla u|^2dx \quad=\quad -\int_{\Omega_\varepsilon^B}\sigma^i\nabla v\nabla u dx.$$

From the assumption on the boundedness of the conductivity tensors we have

$$\underline{\sigma}\,\|\nabla u\|^2_{L^2(\Omega_\varepsilon^B)}\quad\leq\quad\overline{\sigma}\,\|\nabla v\|_{L^2(\Omega_\varepsilon^B)}\,\|\nabla u\|_{L^2(\Omega_\varepsilon^B)}\,.$$

Taking $\beta=\overline{\sigma}/\underline{\sigma}$, we obtain the inequality (43). $\square$

Definition 4.5. Let $\mathcal{A}$ be the operator on $D(\mathcal{A})$, defined as

$$\forall v\in D(\mathcal{A}),\quad \mathcal{A}(v):=-\nabla\cdot\left(\sigma^i\nabla v\right)-\nabla\cdot\left(\sigma^i\nabla\mathcal{B}_{\Omega_\varepsilon^B}(v)\right),$$

with the domain $D(\mathcal{A})$,

$$D(\mathcal{A}):=\left\{v\in H^1(\Omega_\varepsilon^B):\,\mathcal{B}_{\Omega_\varepsilon^B}(v)\in L^2(\Omega_\varepsilon^B),\,\left(\sigma^i\nabla v+\sigma^i\nabla\mathcal{B}_{\Omega_\varepsilon^B}(v)\right)\cdot n_{\Omega_\varepsilon^B}=0\right\}.$$

Lemma 4.6. *The operator $(\mathcal{A},D(\mathcal{A}))$, is m-dissipative with dense domain in $L^2(\Omega_\varepsilon^B)$. Therefore the operator $\mathcal{A}$ generates a contraction semi–group, whose generator is denoted by $e^{-t\mathcal{A}}$.*

Proof. To prove that the operator $\mathcal{A}$ is m-dissipative, we need to prove that for any $\lambda>0$, and any $f\in L^2(\Omega_\varepsilon^B)$, there exists a unique solution $v\in D(\mathcal{A})$ to the equation

$$v-\lambda\mathcal{A}(v)=f,$$

or expanded,

$$v+\lambda\left(\nabla\cdot\left(\sigma^i\nabla v\right)+\nabla\cdot\left(\sigma^i\nabla\mathcal{B}_{\Omega_\varepsilon^B}(v)\right)\right)=f.$$

We define the bilinear form

$$a(v,\phi_B):=\int_{\Omega_\varepsilon^B}v\phi_B\,dx+\lambda\left(\int_{\Omega_\varepsilon^B}\sigma^i\nabla v\nabla\phi_B\,dx+\int_{\Omega_\varepsilon^B}\sigma^i\nabla\mathcal{B}_{\Omega_\varepsilon^B}(v)\nabla\phi_B\,dx\right).$$

Then the variational formulation for this problem reads,

$$a(v,\phi_B)=\int_{\Omega_\varepsilon^B}f\phi_B\,dx,\qquad\forall\phi_B\in H^1(\Omega_\varepsilon^B).\tag{44}$$

The boundedness of the bilinear form $a(v,\phi_B)$ is shown by using (43),

$$\begin{aligned}|a(v,\phi_B)|&\leq\|v\|_{L^2(\Omega_\varepsilon^B)}\,\|\phi_B\|_{L^2(\Omega_\varepsilon^B)}+\lambda\overline{\sigma}(1+\beta)\,\|\nabla v\|_{L^2(\Omega_\varepsilon^B)}\,\|\nabla\phi_B\|_{L^2(\Omega_\varepsilon^B)}\\&\leq\|v\|_{H^1(\Omega_\varepsilon^B)}\,\|\phi_B\|_{H^1(\Omega_\varepsilon^B)}\,.\end{aligned}$$

To prove coerciveness we use the definition (42) of the operator $\mathcal{B}(v)$, and express the bilinear form as follows,

$$a(v, \phi_B) = \int_{\Omega_\varepsilon^B} v\phi_B \, dx + \lambda \left(\int_{\Omega_\varepsilon^B} \sigma^i \nabla v \nabla \phi_B \, dx + \int_{\Omega_\varepsilon^B} \sigma^i \nabla u \nabla \phi_B \, dx \right.$$
$$\left. + \int_{\Omega_\varepsilon^B} (\sigma^i + \sigma^e) \nabla u \nabla \phi \, dx + \int_{\Omega_\varepsilon^B} \sigma^i \nabla v \nabla \phi \, dx + \int_{\Omega_\varepsilon^D} \sigma^d \nabla u \nabla \phi \, dx \right).$$

Then, for $\phi_B = v$, and $\phi = u$, and using the inequality: $0 \leq |a + \delta b|^2$, for all $a, b \in \mathbb{R}$, we have

$$a(v, v) \geq \int_{\Omega_\varepsilon^B} v^2 dx + \lambda \left(\int_{\Omega_\varepsilon^B} \left| \sqrt{\sigma^i} \nabla v \right|^2 dx \right.$$
$$- \delta \int_{\Omega_\varepsilon^B} \left| \sqrt{\sigma^i} \nabla v \right|^2 dx - \frac{1}{\delta} \int_{\Omega_\varepsilon^B} \left| \sqrt{\sigma^i} \nabla u \right|^2 dx$$
$$\left. + \int_{\Omega_\varepsilon^B} \left| \sqrt{\sigma^i} \nabla u \right|^2 dx + \int_{\Omega_\varepsilon^B} \left| \sqrt{\sigma^e} \nabla u \right|^2 dx + \int_{\Omega_\varepsilon^D} \left| \sqrt{\sigma^d} \nabla u \right|^2 dx \right) =: A.$$

Then using Remark 4 and choosing $\frac{1}{1+\underline{\sigma}/\overline{\sigma}} < \delta < 1$ we have

$$A \geq \int_{\Omega_\varepsilon^B} v^2 dx + \lambda \left(\int_{\Omega_\varepsilon^B} (1 - \delta) \underline{\sigma} \left| \nabla v \right|^2 dx \right.$$
$$\left. + \int_{\Omega_\varepsilon^B} \left(1 - \frac{1}{\delta} \right) \overline{\sigma} \left| \nabla u \right|^2 dx + \int_{\Omega_\varepsilon^B} \underline{\sigma} \left| \nabla u \right|^2 dx + \int_{\Omega_\varepsilon^D} \underline{\sigma} \left| \nabla u \right|^2 dx \right)$$
$$\geq \int_{\Omega_\varepsilon^B} v^2 dx + \lambda \underline{\sigma} \left(\int_{\Omega_\varepsilon^B} (1 - \delta) \left| \nabla v \right|^2 dx \right.$$
$$\left. + \int_{\Omega_\varepsilon^B} \left(1 + \left(1 - \frac{1}{\delta} \right) \frac{\overline{\sigma}}{\underline{\sigma}} \right) \left| \nabla u \right|^2 dx + \int_{\Omega_\varepsilon^D} \left| \nabla u \right|^2 dx \right).$$

Thanks to the choice of δ we have that every term in the rightmost side above is positive. Hence,

$$a(v, v) \geq c \left\| v \right\|_{H^1(\Omega_\varepsilon^B)}. \tag{45}$$

From Lax–Milgram theorem, the problem (44) has a unique solution. Hence, the operator $\mathcal{A}(v)$ is m-dissipative. Note that $D(\mathcal{A})$ is dense in $L^2(\Omega_\varepsilon^B)$ as it contains the set of infinitely smooth functions with compact support in Ω_ε^B, that is itself dense in $L^2(\Omega_\varepsilon^B)$. Hence, the operator $(\mathcal{A}, D(\mathcal{A}))$ generates the semigroup denoted by $e^{-t\mathcal{A}}$. □

Lemma 4.7. *The evolution problem* (34) *is equivalent to the problem*

$$\partial_t h_\varepsilon + g(v_\varepsilon, h_\varepsilon) = 0, \quad \text{in } \Omega_\varepsilon^B, \quad \forall t \in (0, T), \tag{46a}$$
$$\partial_t v_\varepsilon + \mathcal{A}(v_\varepsilon) + I_{ion}(v_\varepsilon, h_\varepsilon(t, v_\varepsilon)) = 0, \quad \text{in } \Omega_\varepsilon^B, \quad \forall t \in (0, T), \tag{46b}$$

with the initial conditions

$$h_\varepsilon(0, x) = h_\varepsilon^0(v_\varepsilon), \quad v_\varepsilon(0, x) = v_\varepsilon^0(x). \tag{46c}$$

Moreover, v_ε is also the solution of the following problem:

$$v_\varepsilon(t,x) = e^{-t\mathcal{A}}v_\varepsilon^0 - \int_0^t e^{-(t-s)\mathcal{A}} I_{ion}(s, h_\varepsilon(s, v_\varepsilon(s,x)))\, ds, \quad \forall t \in (0,T). \tag{47}$$

Proof. The equivalence of the two problems comes from the definition of the operators $\mathcal{A}$ and $\mathcal{B}$. The formula (47) is a straightforward use of the standard Duhamel's formula, see Lemma 4.1.1 in [6]. □

Proof of Theorem 4.1. The proof that v_ε exists and is unique, where

$$v_\varepsilon \in C([0,+\infty); H^1(\Omega_\varepsilon^B)) \cap C^1([0,+\infty); L^2(\Omega_\varepsilon^B))$$

is a straightforward consequence of the Hille–Yosida theorem, since $(\mathcal{A}, D(\mathcal{A}))$ is an m-dissipative operator with dense domain, and the Lipschitz property of the ionic function given in Proposition 1, see Section 4.3. in [6]. The regularity of h_ε comes directly from the assumption on the initial conditions and Lemma 4.2, and the regularity on u_ε from Definition 4.3 and the Poincare's inequality. □

Remark 5. For the function $u_\varepsilon^i := v_\varepsilon + u_\varepsilon \mathbb{1}_{\Omega_\varepsilon^B}$, we have

$$u_\varepsilon^i \in C([0,+\infty); H^1(\Omega_\varepsilon^B)).$$

5. **Two-scale convergence towards the macroscopic model.** In this section we provide a rigorous justification for the formal derivation of the homogenised problem given in Section 3. We will follow the idea of two–scale convergence as in [1]. For the sake of clarity, let us recall the definition–theorem of two–scale convergence (see [1, 27]).

Definition–Theorem 5.1. Let Ω be a bounded domain of $\mathbb{R}^N$, for $N \in \mathbb{N} \setminus \{0\}$. Let ϕ_ε be a bounded sequence in $L^2(\Omega)$. There exists a subsequence, still denoted by ϕ_ε, and a function $\phi_0(x,y) \in L^2(\Omega \times (\mathbb{R}/\mathbb{Z})^N)$ such that

$$\lim_{\varepsilon\to 0} \int_\Omega \phi_\varepsilon(x)\psi(x, x/\varepsilon)\, dx = \int_{\Omega\times Y} \phi_0(x,y)\psi(y)\, dy,$$

for any smooth function ψ defined on $\Omega \times (\mathbb{R}/\mathbb{Z})^N$ and $(\mathbb{R}/\mathbb{Z})^N$-periodic in y. Such a sequence ϕ_ε is said to two–scale converge to ϕ_0 and we denote it by

$$\phi_\varepsilon \xrightarrow{2-scale,\, L^2} \phi_0.$$

To apply the two–scale convergence to our case we need to address two problems: first to find uniform bounds, independent on ε, on the functions $v_\varepsilon, u_\varepsilon, h_\varepsilon, \nabla v_\varepsilon$, and ∇u_ε, and secondly to show the convergence of the nonlinear part of the problem.

Definition 5.2 (Trivial extension operator)**.** Denote with $\tilde{\cdot}$ the extension by zero in the domain Ω_ε^D, i.e. for any function $f_\varepsilon(x)$ defined in Ω_ε^B, its trivial extension is

$$\widetilde{f_\varepsilon}(x) = \begin{cases} f_\varepsilon(x), \text{if } x \in \Omega_\varepsilon^B, \\ 0, \text{if } x \in \Omega_\varepsilon^D. \end{cases}$$

Note that if $f_\varepsilon(x)$ has a uniform bound on Ω_ε^B, $\|f_\varepsilon\|_{L^2(\Omega_\varepsilon^B)} < C$, it's trivial extension is also uniformly bounded on Ω, $\|\tilde{f}_\varepsilon\|_{L^2(\Omega)} < C$.

5.1. **Hypotheses on the initial conditions.**

Hypothesis 5.3. The initial conditions v_ε^0 and h_ε^0 fulfill the following hypotheses: v_ε^0 and ∇v_ε^0 are uniformly bounded in $L^2(\Omega_\varepsilon^B)$, and h_ε^0 is uniformly bounded in $L^\infty(\Omega_\varepsilon^B)$, $0 \le h_\varepsilon^0(x) \le 1$ almost everywhere in Ω_ε^B.

- There exists $v_0^0 \in L^2(\Omega)$ and $v_1^0 \in L^2(\Omega; H^1(Y_B))$ such that the following two–scale convergences hold:
$$\widetilde{v_\varepsilon}^0(x) \xrightarrow{2-scale,\,L^2} \chi_{Y_B}(y)v_0^0(x),$$
$$\widetilde{\nabla v_\varepsilon^0}(x) \xrightarrow{2-scale,\,L^2} \chi_{Y_B}(y)\left(\nabla_x v_0^0(x) + \nabla_y v_1^0(x,y)\right).$$
- There exist $h_0^0 \in L^2(\Omega)$ such that
$$\widetilde{h_\varepsilon^0}(x) \xrightarrow{2-scale,\,L^\infty} \chi_{Y_B}(y)h_0^0(x).$$

Interestingly, no assumption are required on u^0, since from the above hypotheses the following proposition holds.

Proposition 2. *There exist $u_0^0 \in L^2(\Omega)$ and $u_1^0 \in L^2(\Omega; H^1(Y))$ such that u^0 defined by (35) satisfies*

$$u_\varepsilon^0(x) \xrightarrow{2-scale,\,L^2} u_0^0(x), \quad \nabla u_\varepsilon^0(x) \xrightarrow{2-scale,\,L^2} \nabla_x u_0^0(x) + \nabla_y u_1^0(x,y). \tag{48}$$

The functions (u_0^0, u_1^0) are the unique solution in $L^2(\Omega) \times L^2(\Omega; H^1(Y)|\mathbb{R})$ to the following problem:

$$-\nabla_x \cdot \int_{Y_B} (\sigma^i + \sigma^e)(\nabla_x u_0^0 + \nabla_y u_1^0)\,dy - \nabla_x \cdot \int_{Y_D} \sigma^d(\nabla_x u_0^0 + \nabla_y u_1^0)\,dy = \nabla_x \cdot \int_{Y_B} \sigma^i(\nabla_x v_0^0 + \nabla_y v_1^0)\,dy,$$

in Ω, with the Gauge condition $\int_\Omega u_0^0 dx = 0$, and the correction term is given as the solution to:

$$-\nabla_y \cdot \left((\chi_{Y_B}(\sigma^i + \sigma^e) + \chi_{Y_D}\sigma^d)(\nabla_x u_0^0 + \nabla_y u_1^0)\right) = \nabla_y \cdot \left(\chi_{Y_B}\sigma^i(\nabla_x v_0^0 + \nabla_y v_1^0)\right),$$

in $\Omega \times Y$, with the periodic boundary conditions for $y \to u_1^0(x,y)$ in Y, and the boundary condition:

$$\left((\sigma^i + \sigma^e - \sigma^d)(\nabla_x u_0^0 + \nabla_y u_1^0)\right) \cdot n_{Y_B} = -\left(\sigma^i(\nabla_x v_0^0 + \nabla_y v_1^0)\right) \cdot n_{Y_B},$$

on $\Omega \times \Gamma$.

Proof. From (35) taking $\phi = u_\varepsilon^0$, and Poincare's inequality, we have that the initial condition $u_\varepsilon^0(x)$ satisfies $\|u_\varepsilon^0\|_{L^2(\Omega)} \le C$, and $\|\nabla u_\varepsilon^0\|_{L^2(\Omega)} \le C$, so we have (48). The homogenised problem for (u_0^0, u_1^0) can be then derived, using the test function $\phi(x) + \varepsilon\phi_1(x, x/\varepsilon)$, such that $\phi(x) \in D(\Omega)$ and $\phi_1 \in D(\Omega, C_\#^\infty)$. We have,

$$\int_{\Omega_\varepsilon^B} (\sigma^i + \sigma^e)\nabla u_\varepsilon^0(\nabla_x\phi + \nabla_y\phi_1 + \varepsilon\nabla_x\phi_1)\,dx + \int_{\Omega_\varepsilon^D} \sigma^d\nabla u_\varepsilon^0(\nabla_x\phi + \nabla_y\phi_1 + \varepsilon\nabla_x\phi_1)\,dx = -\int_{\Omega_\varepsilon^B} \sigma^i\nabla v_\varepsilon^0(\nabla_x\phi + \nabla_y\phi_1 + \varepsilon\nabla_x\phi_1)\,dx.$$

Passing to the two–scale limit, and after the partial integration, we obtain the homogenised problem for u_0^0 and u_1^0. □

5.2. **Uniform bounds.** In order to find the uniform bound, we will introduce an energy functional $\mathcal{E}_{\lambda,\kappa}$. This is the key idea that is adapted from the work of Allaire [1], and used in a different context by Collin and Imperiale [8].

First, we multiply by $h_\varepsilon, v_\varepsilon, u_\varepsilon$ the first, second and third and fourth equations respectively and integrate by parts. Using the transmission conditions, we obtain

$$\frac{1}{2}\frac{d}{dt}\|h_\varepsilon\|^2_{L^2(\Omega^B_\varepsilon)} + \int_{\Omega^B_\varepsilon} g(v_\varepsilon, h_\varepsilon)h_\varepsilon\, dx = 0, \tag{49}$$

and

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|v_\varepsilon\|^2_{L^2(\Omega^B_\varepsilon)} + \int_{\Omega^B_\varepsilon} I_{ion}(v_\varepsilon, h_\varepsilon)v_\varepsilon\, dx + \left\|\sqrt{\sigma^i}\nabla(v_\varepsilon + u_\varepsilon)\right\|^2_{L^2(\Omega^B_\varepsilon)} \\ + \left\|\sqrt{\sigma}\nabla u_\varepsilon\right\|^2_{L^2(\Omega)} = 0,\end{aligned} \tag{50}$$

with σ as before, $\sigma = \sigma^e$, in Ω^B_ε, and $\sigma = \sigma^d$, in Ω^D_ε. Then we infer the following proposition.

Proposition 3. *For any λ, $\kappa \in \mathbb{R}$, let us define the energy functional*

$$\begin{aligned}\mathcal{E}_{\lambda,\kappa}(t, v, u, h) :=& \frac{1}{2}e^{-\lambda t}\left(\|v\|^2_{L^2(\Omega^B_\varepsilon)} + \kappa\,\|h\|^2_{L^2(\Omega^B_\varepsilon)}\right) \\ &+ \int_0^t e^{-\lambda s}\Bigg(\frac{\lambda}{2}\left(\|v\|^2_{L^2(\Omega^B_\varepsilon)} + \kappa\,\|h\|^2_{L^2(\Omega^B_\varepsilon)}\right) \\ &+ \left\|\sqrt{\sigma^i}\nabla(v+u)\right\|^2_{L^2(\Omega^B_\varepsilon)} + \left\|\sqrt{\sigma}\nabla u\right\|^2_{L^2(\Omega)}\Bigg)ds.\end{aligned}$$

Let $(v_\varepsilon, u_\varepsilon, h_\varepsilon)$ be the solution to problem (34). The energy functional $\mathcal{E}_{\lambda,\kappa}$ satisfies the following equality

$$\begin{aligned}\mathcal{E}_{\lambda,\kappa}(t, v_\varepsilon, u_\varepsilon, h_\varepsilon) + \int_0^t e^{-\lambda s}\int_{\Omega^B_\varepsilon}\Big(I_{ion}(v_\varepsilon, h_\varepsilon)v_\varepsilon + \kappa g(v_\varepsilon, h_\varepsilon)h_\varepsilon\Big)\, dx\, ds \\ = \frac{1}{2}\|v^0_\varepsilon\|^2_{L^2(\Omega^B_\varepsilon)} + \frac{\kappa}{2}\|h^0_\varepsilon\|^2_{L^2(\Omega^B_\varepsilon)} = \mathcal{E}_{\lambda,\kappa}(0, v^0_\varepsilon, u^0_\varepsilon, h^0_\varepsilon).\end{aligned} \tag{51}$$

Proof. By definition of $\mathcal{E}_{\lambda,\kappa}(t, v, u, h)$, using (49) (multiplied by $\kappa e^{-\lambda t}$) and (50) (multiplied by $e^{-\lambda t}$) one has

$$\partial_t\mathcal{E}_{\lambda,\kappa}(t, v_\varepsilon, u_\varepsilon, h_\varepsilon) + e^{-\lambda t}\int_{\Omega^B_\varepsilon}\left(I_{ion}(v_\varepsilon, h_\varepsilon)v_\varepsilon + \kappa g(v_\varepsilon, h_\varepsilon)h_\varepsilon\right)\, dx = 0.$$

□

Proposition 4. *The following inequalities hold:*

$$\left|\int_0^t e^{-\lambda s}\int_{\Omega^B_\varepsilon} I_{ion}(v_\varepsilon, h_\varepsilon)v_\varepsilon\, dx\, ds\right| \leq C\int_0^t e^{-\lambda s}\,\|v_\varepsilon\|^2_{L^2(\Omega^B_\varepsilon)}\, ds, \tag{52}$$

$$\|I_{ion}(v_\varepsilon, h_\varepsilon)\|_{L^2(\Omega^B_\varepsilon)} \leq C\,\|v_\varepsilon\|^2_{L^2(\Omega^B_\varepsilon)}\,. \tag{53}$$

Proof. From the definition of the ionic function we see that $I_{ion}(0, h(0)) = 0$. Then, using the Lipschitz property from Proposition 1, one can easily see that

$$|I_{ion}(v, h)| \leq |v|, \text{ for any } v \in \mathbb{R}.$$

Both inequalities fall directly from this. □

Proposition 5. *Assume that v_ε^0 and h_ε^0 satisfy Hypothesis 5.3. Then we have the uniform bounds:*

$$\begin{aligned}
&0 \le h_\varepsilon(t,x) \le 1, \quad |g(v_\varepsilon, h_\varepsilon)| \le C, \quad \forall t \in [0,T],\\
&\|v_\varepsilon(t,\cdot)\|_{L^2(\Omega_\varepsilon^B)} \le C, \qquad \|I_{ion}(v_\varepsilon, h_\varepsilon)\|_{L^2(\Omega_\varepsilon^B)} \le C, \quad \forall t \in [0,T],
\end{aligned}$$

and

$$\begin{aligned}
&\|\nabla v_\varepsilon(t,\cdot)\|_{L^2((0,T)\times\Omega_\varepsilon^B)} \le C,\\
&\|u_\varepsilon(t,\cdot)\|_{L^2((0,T)\times\Omega)} \le C, \quad \|\nabla u_\varepsilon(t)\|_{L^2((0,T)\times\Omega)} \le C.
\end{aligned}$$

Proof. The estimates on $h_\varepsilon(t,x)$ and $g(v_\varepsilon, h_\varepsilon)$ come directly from the assumption on the initial condition and Lemma 4.2. Then from Proposition 3 and Proposition 4, we have that

$$\begin{aligned}
\mathcal{E}_{\lambda,\kappa}(t, v_\varepsilon, u_\varepsilon, h_\varepsilon) &= \frac{1}{2}\left\|v_\varepsilon^0\right\|^2_{L^2(\Omega_\varepsilon^B)} + \frac{\kappa}{2}\left\|h_\varepsilon^0\right\|^2_{L^2(\Omega_\varepsilon^B)}\\
&\quad - \int_0^t e^{-\lambda s}\int_{\Omega_\varepsilon^B} \left(I_{ion}(v_\varepsilon, h_\varepsilon)v_\varepsilon + \kappa g(v_\varepsilon, h_\varepsilon)\right) dx\, ds\\
&\le \frac{1}{2}\left\|v_\varepsilon^0\right\|^2_{L^2(\Omega_\varepsilon^B)} + \frac{\kappa}{2}\left\|h_\varepsilon^0\right\|^2_{L^2(\Omega_\varepsilon^B)}\\
&\quad + \int_0^t e^{-\lambda s}\left(c_1\left\|v_\varepsilon\right\|^2_{L^2(\Omega_\varepsilon^B)} + \kappa c_2|\Omega_\varepsilon^B|\right) ds.
\end{aligned}$$

Note that the volume $|\Omega_\varepsilon^B| < |\Omega| < c_3$. Taking λ such that $\frac{\lambda}{2} > c_1$, and going back to the definition of $\mathcal{E}_{\lambda,\kappa}$, we obtain the uniform bound on $\|v_\varepsilon(t,\cdot)\|_{L^2(\Omega_\varepsilon^B)}$, and hence on $\|I_{ion}(v_\varepsilon, h_\varepsilon)\|_{L^2(\Omega_\varepsilon^B)}$. Now, going back to (50), and integrating over time, we obtain

$$\int_0^t \left\|\sqrt{\sigma^i}\nabla(v_\varepsilon + u_\varepsilon)\right\|^2_{L^2(\Omega_\varepsilon^B)} ds + \int_0^t \left\|\sqrt{\sigma}\nabla u_\varepsilon\right\|^2_{L^2(\Omega)} ds \le \left\|v_\varepsilon^0\right\|_{L^2(\Omega_\varepsilon^B)} \le C,$$

which, together with the bounds on conductivities provides the uniform bounds on the derivatives. From $\int_\Omega u_\varepsilon(t,x)dx = 0$ and the Poincare's inequality, we have the bound on $\|u_\varepsilon\|_{L^2((0,T)\times\Omega)}$. □

Remark 6 (Two–scale limits)**.** From the uniform bounds we obtained, by direct application of the theory developed in [1], we have the following convergences

- $\widetilde{h}_\varepsilon(t,x) \xrightarrow{2-scale,\, L^\infty} \chi_{Y_B}(y)h_0(t,x), \quad a.e.\, t \in (0,T),$
- $\widetilde{v}_\varepsilon(t,x) \xrightarrow{2-scale,\, L^2} \chi_{Y_B}(y)v_0(t,x), \quad a.e.\, t \in (0,T),$
- $\widetilde{\nabla v_\varepsilon}(t,x) \xrightarrow{2-scale,\, L^2} \chi_{Y_B}(y)(\nabla_x v_0(t,x) + \nabla_y v_1(t,x,y)),$
- $u_\varepsilon(t,x) \xrightarrow{2-scale,\, L^2} u_0(t,x),$
- $\nabla u_\varepsilon(t,x) \xrightarrow{2-scale,\, L^2} \nabla_x u_0(t,x) + \nabla_y u_1(t,x,y),$
- $\widetilde{I_{ion}}(v_\varepsilon, h_\varepsilon) \xrightarrow{2-scale,\, L^2} \chi_{Y_B}(y)I_0(t,x), \quad a.e.\, t \in (0,T),$
- $\widetilde{g}(v_\varepsilon, h_\varepsilon) \xrightarrow{2-scale,\, L^\infty} \chi_{Y_B}(y)g_0(t,x), \quad a.e.\, t \in (0,T),$

for some functions $h_0(t,\cdot), I_0(t,\cdot), g_0(t,\cdot) \in L^2(\Omega)$, $v_0(t,\cdot) \in H^1(\Omega)$, $v_1(t,\cdot,\cdot) \in L^2(\Omega; H^1(Y_B)/\mathbb{R})$, $u_0 \in L^2((0,T); H^1(\Omega))$, and $u_1 \in L^2((0,T)\times\Omega; H^1(Y)/\mathbb{R})$. These limit functions satisfy the homogenised problem given in Section 3, except the nonlinear functions from the ionic model which are still not identified.

5.3. **Nonlinear convergence.** We are now ready to prove that the functions I_0 and g_0 take the forms: $I_0 = I_{ion}(v_0,h_0)$, and $g_0 = g(v_0,h_0)$.

From the given two–scale limits on the functions we have that the equality (51) holds for a limit case in the form,

$$\begin{aligned}\mathcal{E}^0_{\lambda,\kappa}(t,(v_0,v_1),(u_0,u_1),h_0) :=& \frac{1}{2}e^{-\lambda t}\left(\|v_0\|^2_{L^2(\Omega\times Y_B)} + \kappa\,\|h_0\|^2_{L^2(\Omega\times Y_B)}\right)\\ &+\int_0^t e^{-\lambda s}\Big(\frac{\lambda}{2}\left(\|v_0\|^2_{L^2(\Omega\times Y_B)} + \kappa\,\|h_0\|^2_{L^2(\Omega\times Y_B)}\right)\\ &+\left\|\sqrt{\sigma^i}(\nabla(v_0+u_0)+\nabla_y(v_1+u_1))\right\|^2_{L^2(\Omega\times Y_B)}\\ &+\left\|\sqrt{\sigma}(\nabla_x u_0+\nabla_y u_1)\right\|^2_{L^2(\Omega\times Y)}\Big)ds,\end{aligned}$$

and

$$\begin{aligned}\mathcal{E}^0_{\lambda,\kappa}(t,(v_0,v_1),(u_0,u_1),h_0) + \int_0^t e^{-\lambda s}\int_\Omega\int_{Y_B}\Big(I_0v_0+\kappa g_0h_0\Big)\,dy\,dx\,ds&\\ = \frac{1}{2}\|v_0^0\|^2_{L^2(\Omega\times Y_B)} + \frac{\kappa}{2}\|h_0^0\|^2_{L^2(\Omega\times Y_B)}.&\end{aligned}\tag{54}$$

Using the above properties of the nonlinear terms, for appropriate choice of λ and κ, we get

$$\begin{aligned}&\mathcal{E}_{\lambda,\kappa}(t,v_\varepsilon-\mu_\varepsilon,u_\varepsilon-\rho_\varepsilon,h_\varepsilon-\eta_\varepsilon)\\ &+\int_0^t e^{-\lambda s}\int_{\Omega_\varepsilon^B}\Big((I_{ion}(v_\varepsilon,h_\varepsilon)-I_{ion}(\mu_\varepsilon,\eta_\varepsilon))(v_\varepsilon-\mu_\varepsilon)\\ &+\kappa(g(v_\varepsilon,h_\varepsilon)-g(\mu_\varepsilon,\eta_\varepsilon))(h_\varepsilon-\eta_\varepsilon)\Big)dx\,ds \geq 0,\end{aligned}$$

where $\mu_\varepsilon,\rho_\varepsilon,\eta_\varepsilon$ will be chosen later. We develop the above expression, as follows

$$\begin{aligned}&\mathcal{E}_{\lambda,\kappa}(t,v_\varepsilon-\mu_\varepsilon,u_\varepsilon-\rho_\varepsilon,h_\varepsilon-\eta_\varepsilon)\\ &+\int_0^t e^{-\lambda s}\int_{\Omega_\varepsilon^B}\Big(I_{ion}(v_\varepsilon,h_\varepsilon)v_\varepsilon - I_{ion}(v_\varepsilon,h_\varepsilon)\mu_\varepsilon - I_{ion}(\mu_\varepsilon,\eta_\varepsilon)v_\varepsilon + I_{ion}(\mu_\varepsilon,\eta_\varepsilon)\mu_\varepsilon\\ &+\kappa(g(v_\varepsilon,h_\varepsilon)h_\varepsilon - g(v_\varepsilon,h_\varepsilon)\eta_\varepsilon - g(\mu_\varepsilon,\eta_\varepsilon)h_\varepsilon + g(\mu_\varepsilon,\eta_\varepsilon)\eta_\varepsilon)\Big)\,dx\,ds \geq 0.\end{aligned}\tag{55}$$

Furthermore, for the energy functional we have,

$$\begin{aligned}\mathcal{E}_{\lambda,\kappa}(t,v_\varepsilon-\mu_\varepsilon,u_\varepsilon-\rho_\varepsilon,h_\varepsilon-\eta_\varepsilon) =& \frac{1}{2}e^{-\lambda t}\left(\|v_\varepsilon-\mu_\varepsilon\|^2_{L^2(\Omega_\varepsilon^B)} + \kappa\,\|h_\varepsilon-\eta_\varepsilon\|^2_{L^2(\Omega_\varepsilon^B)}\right)\\ &+\int_0^t e^{-\lambda s}\Big(\frac{\lambda}{2}\left(\|v_\varepsilon-\mu_\varepsilon\|^2_{L^2(\Omega_\varepsilon^B)} + \kappa\,\|h_\varepsilon-\eta_\varepsilon\|^2_{L^2(\Omega_\varepsilon^B)}\right)\\ &+\left\|\sqrt{\sigma^i}\nabla(v_\varepsilon-\mu_\varepsilon+u_\varepsilon-\rho_\varepsilon)\right\|^2_{L^2(\Omega_\varepsilon^B)} + \left\|\sqrt{\sigma}\nabla(u_\varepsilon-\rho_\varepsilon)\right\|^2_{L^2(\Omega)}\Big)ds.\end{aligned}$$

Hence,

$$\begin{aligned}\mathcal{E}_{\lambda,\kappa}(t,v_\varepsilon-\mu_\varepsilon,u_\varepsilon-\rho_\varepsilon,h_\varepsilon-\eta_\varepsilon) =& \mathcal{E}_{\lambda,\kappa}(t,v_\varepsilon,u_\varepsilon,h_\varepsilon)\\ &+\frac{e^{-\lambda t}}{2}\int_{\Omega_\varepsilon^B}(\mu_\varepsilon(-2v_\varepsilon+\mu_\varepsilon)+\kappa\eta_\varepsilon(-2h_\varepsilon+\eta_\varepsilon))\,dx\end{aligned}$$

$$
\begin{aligned}
&+\int_0^t e^{-\lambda s}\Big(\frac{\lambda}{2}\int_{\Omega_\varepsilon^B}(\mu_\varepsilon(-2v_\varepsilon+\mu_\varepsilon)+\kappa\eta_\varepsilon(-2h_\varepsilon+\eta_\varepsilon))\,dx\\
&+\int_{\Omega_\varepsilon^B}\sigma^i\nabla(\mu_\varepsilon+\rho_\varepsilon)(-2\nabla(v_\varepsilon+u_\varepsilon)+\nabla(\mu_\varepsilon+\rho_\varepsilon))\,dx\\
&+\int_\Omega \sigma\nabla\rho_\varepsilon(-2\nabla u_\varepsilon+\nabla\rho_\varepsilon)\,dx\Big)\,ds.
\end{aligned}
$$

Now, we use the fact that $(v_\varepsilon,u_\varepsilon,h_\varepsilon)$ is solution to the problem (34), so equality (51) holds. Hence, (55) becomes,

$$
\begin{aligned}
\frac{1}{2}\|v_\varepsilon^0\|^2_{L^2(\Omega_\varepsilon^B)}+\frac{\kappa}{2}\|h_\varepsilon^0\|^2_{L^2(\Omega_\varepsilon^B)}+\frac{e^{-\lambda t}}{2}&\int_{\Omega_\varepsilon^B}(\mu_\varepsilon(-2v_\varepsilon+\mu_\varepsilon)+\kappa\eta_\varepsilon(-2h_\varepsilon+\eta_\varepsilon))\,dx\\
&+\int_0^t e^{-\lambda s}\Big(\frac{\lambda}{2}\int_{\Omega_\varepsilon^B}(\mu_\varepsilon(-2v_\varepsilon+\mu_\varepsilon)+\kappa\eta_\varepsilon(-2h_\varepsilon+\eta_\varepsilon))\,dx\\
&+\int_{\Omega_\varepsilon^B}\sigma^i\nabla(\mu_\varepsilon+\rho_\varepsilon)(-2\nabla(v_\varepsilon+u_\varepsilon)+\nabla(\mu_\varepsilon+\rho_\varepsilon))\,dx\\
&+\int_\Omega \sigma\nabla\rho_\varepsilon(-2\nabla u_\varepsilon+\nabla\rho_\varepsilon)\,dx\Big)\,ds\\
+\int_0^t e^{-\lambda s}\int_{\Omega_\varepsilon^B}\Big(&-I_{ion}(v_\varepsilon,h_\varepsilon)\mu_\varepsilon-I_{ion}(\mu_\varepsilon,\eta_\varepsilon)v_\varepsilon+I_{ion}(\mu_\varepsilon,\eta_\varepsilon)\mu_\varepsilon\\
&+\kappa(-g(v_\varepsilon,h_\varepsilon)\eta_\varepsilon-g(\mu_\varepsilon,\eta_\varepsilon)h_\varepsilon+g(\mu_\varepsilon,\eta_\varepsilon)\eta_\varepsilon)\Big)\,dx\,ds\geq 0.
\end{aligned}
$$

Now let us choose, $\mu_\varepsilon,\rho_\varepsilon$ and η_ε as follows

$$
\begin{aligned}
\mu_\varepsilon(x) &= v_0(x)+\alpha\phi(x)+\varepsilon\phi_1(x,x/\varepsilon),\\
\rho_\varepsilon(x) &= u_0(x)+\varepsilon\psi_1(x,x/\varepsilon),\\
\eta_\varepsilon(x) &= h_0(x)+\alpha\theta(x),
\end{aligned}
$$

where $\phi_1(x,y)$ and $\psi_1(x,y)$ are smooth functions that we can choose as close as we need to $v^1(x,y)$ and $u^1(x,y)$, respectively. From the construction we have a strong convergences for $\mu_\varepsilon,\nabla\mu_\varepsilon,\ \rho_\varepsilon,\nabla\rho_\varepsilon$ and η_ε. Now, passing to the two–scale limit in the above inequality, we have,

$$
\begin{aligned}
&\frac{1}{2}\|v_0^0\|^2_{L^2(\Omega\times Y_B)}+\frac{\kappa}{2}\|h_0^0\|^2_{L^2(\Omega\times Y_B)}\\
&+\frac{e^{-\lambda t}}{2}\int_\Omega\int_{Y_B}\big((\alpha\phi)^2-v_0^2)+\kappa((\alpha\theta)^2-h_0^2)\big)\,dy\,dx\\
&+\int_0^t e^{-\lambda s}\Big(\frac{\lambda}{2}\int_\Omega\int_{Y_B}\big((\alpha\phi)^2-v_0^2)+\kappa((\alpha\theta)^2-h_0^2)\big)\,dy\,dx\\
&+\int_\Omega\int_{Y_B}\sigma^i\left((\alpha\nabla\phi)^2-(\nabla_x v_0+\nabla_y v_1+\nabla_x u_0+\nabla_y u_1)^2\right)\,dy\,dx\\
&-\int_\Omega\int_Y \sigma\nabla(\nabla_x u_0+\nabla_y u_1)\,dy\,dx\Big)ds\\
&+\int_0^t e^{-\lambda s}\int_\Omega\int_{Y_B}\Big(-I_0(v_0+\alpha\phi)+I_{ion}(v_0+\alpha\phi,h_0+\alpha\theta)\alpha\phi\\
&+\kappa(-g_0(h_0+\alpha\theta)+g(v_0+\alpha\phi,h_0+\alpha\theta)\alpha\theta\Big)\,dy\,dx\,ds\geq 0.
\end{aligned}
$$

Finally, we use the equality (54), and divide every term by $\alpha \neq 0$, to obtain

$$\alpha \int_\Omega \left[\frac{e^{-\lambda t}}{2} \left(\phi^2 + \kappa\theta^2\right) + \int_0^t e^{-\lambda s} \Big(\frac{\lambda}{2} \left(\phi^2 + \kappa\theta^2\right) + \sigma^i (\nabla\phi)^2 \Big) \, ds \right] dx$$
$$+ \int_0^t e^{-\lambda s} \int_\Omega (I_{ion}(v_0 + \alpha\phi, h_0 + \alpha\theta) - I_0)\phi \, dx \, ds$$
$$+ \int_0^t e^{-\lambda s} \int_\Omega \kappa(g(v_0 + \alpha\phi, h_0 + \alpha\theta) - g_0)\theta \, dx \, ds \geq 0.$$

Then letting α go to zero, we obtain for any functions $\theta(x), \phi(x)$

$$\int_0^t e^{-\lambda s} \int_\Omega \Big((I_{ion}(v_0, h_0) - I_0)\phi + \kappa(g(v_0, h_0) - g_0)\theta \Big) \, dx \, ds \geq 0.$$

Thus, we conclude $I_0 = I_{ion}(v_0, h_0)$ and $g_0 = g(v_0, h_0)$.

5.4. **Main theorem.**

Theorem 5.4. *For any time $t \in (0, T)$ let $(v_\varepsilon, u_\varepsilon, h_\varepsilon)$ be the sequence of solutions to the problem (34). Having the two–scale convergences given in Remark 6, then $(v_0, u_0, h_0, v_1, u_1)$ is the unique solution of the following two–scale homogenised system*

$$\partial_t h_0(t, x) + g(v_0, h_0) = 0,$$
$$|Y_B| \left(\partial_t v_0(t, x) + I_{ion}(v_0, h_0)\right)$$
$$- \nabla_x \cdot \left[\int_{Y_B} \sigma^i (\nabla v_0(t, x) + \nabla_y v_1(t, x, y)) dy \right]$$
$$- \nabla_x \cdot \left[\int_{Y_B} \sigma^i (\nabla u_0(t, x) + \nabla_y u_1(t, x, y)) dy \right] = 0,$$
$$- \nabla_x \cdot \left[\int_{Y_B} (\sigma^i + \sigma^e)(\nabla u_0(t, x) + \nabla_y u_1(t, x, y)) dy \right]$$
$$- \nabla_x \cdot \left[\int_{Y_D} \sigma^d (\nabla u_0(t, x) + \nabla_y u_1(t, x, y)) dy \right]$$
$$- \nabla_x \cdot \left[\int_{Y_B} \sigma^i (\nabla v_0(t, x) + \nabla_y v_1(t, x, y)) dy \right] = 0,$$

given in $(0, T) \times \Omega \times Y$, with the initial conditions on $h_0(t, x)$ and $v_0(t, x)$, given as

$$h_0(0, x) = h_0^0(x), \quad v_0(0, x) = v_0^0(x), \ \text{in } \Omega,$$

with the correction equations given on a unit cell Y as

$$-\nabla_y \cdot \left[\sigma^i (\nabla v_0(t, x) + \nabla_y v_1(t, x, y)) + \sigma^i (\nabla u_0(t, x) + \nabla_y u_1(t, x, y))\right] = 0, \qquad \text{in } Y_B,$$
$$-\nabla_y \cdot \left[\sigma^e (\nabla u_0(t, x) + \nabla_y u_1(t, x, y))\right] = 0, \qquad \text{in } Y_B,$$
$$-\nabla_y \cdot \left[\sigma^d (\nabla u_0(t, x) + \nabla_y u_1(t, x, y))\right] = 0, \qquad \text{in } Y_D,$$

and with the boundary and transmission conditions

$$\left(\sigma^i (\nabla v_0(t, x) + \nabla_y v_1(t, x, y)) + \sigma^i (\nabla u_0(t, x) + \nabla_y u_1(t, x, y))\right) \cdot n_{Y_B} = 0, \qquad \text{on } \Gamma,$$
$$\left((\sigma^e - \sigma^d)(\nabla u_0(t, x) + \nabla_y u_1(t, x, y))\right) \cdot n_{Y_B} = 0, \qquad \text{on } \Gamma,$$
$$y \to u_1(t, x, y) \ \text{and} \ y \to v_1(t, x, y) \ \text{are } Y\text{-periodic.}$$

Furthermore, we can recover the classical homogenised and cell equations if we use the relation

$$v_1(t,x,y) = \sum_{k=1}^{N} \frac{\partial v_0(t,x)}{\partial x_k} w_k^v(y),$$

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

Proof of Theorem 5.4. To find the homogenised equations we choose the test function $\phi(t,x)+\varepsilon\phi_1(x,x/\varepsilon)$, $\phi(t,x) \in D((0,T)\times\Omega)$ and $\phi_1(x,y) \in D(\Omega; C^\infty_\#(Y))$. Then by the partial integration and passing to the two–scale limits, using the assumptions on the nonlinear parts, we derive the homogenised system of equations. □

Remark 7. Note that the homogenised problem given in the main theorem is the parabolic–elliptic version of the homogenised problem we have derived formally in Section 3, for $u^i_\varepsilon := v_\varepsilon + u_\varepsilon|_{\Omega^B_\varepsilon}$, and then $u^i_0 = v_0 + u_0$, and $u^i_1 = v_1 + u_1$.

Remark 8. The existence and uniqueness of the solution of the homogenised (bidomain) model has been proved in [4]. It is not necessary from conductivity tensors to be symmetric definite positive, although in practice it is assumed.

6. **Numerical convergence.** In this section we want to observe numerically the convergence of the mesoscopic problem to the derived homogenised equations, and to find the rate of convergence. In order to do this we simulate the mesoscopic problem (6) for several values of ε, and the homogenised problem.

To be sure that we observe the change with respect to ε, we run all simulations with the same mesh and time steps. The parameters for the bidomain problem and for the Mitchell–Schaeffer model are set as in [29]. For all simulations we use the semi–implicit numerical time scheme with the finite element approach for the space discretisation. More precisely, we use the SBDF2 scheme as in [12]. The details of the algorithms for both cases are in the appendix.

We use a square–shaped domain Ω, with the side length of $30mm$. It is meshed with the mesh step $dx = 0.3mm$. For the time scheme we use $dt = 0.5ms$. We assume that the diffusive inclusions are circular and that they occupy 20% of the total volume, *i.e.* $|Y_B| = 0.8$.

We simulate the mesoscopic problems for several sizes of periodic cell. Namely, $\varepsilon \in \{1/10, 1/15, 1/20, 1/25, 1/30, 1/35, 1/40\}$. The solutions $(v_\varepsilon, h_\varepsilon)$ are obtained on domains Ω^B_ε and saved at the time $T = 10ms$.

The solution to the homogenised macroscopic problem (v, h) is given on the full domain Ω and is saved at the same time $T = 10ms$.

To find the rate of convergence we compute the L^2 errors of v_ε with respect to v, and of h_ε with respect to h, respectively defined as

$$\mathcal{E}_{L^2}(v_\varepsilon) = \frac{\|v_\varepsilon - v\|_{L^2(\Omega^B_\varepsilon)}}{\|v\|_{L^2(\Omega)}} \quad \text{and} \quad \mathcal{E}_{L^2}(h_\varepsilon) = \frac{\|h_\varepsilon - h\|_{L^2(\Omega^B_\varepsilon)}}{\|h\|_{L^2(\Omega)}}.$$

We use the log–log scale to fit the results with the linear functions. We have obtained approximately linear rates of the convergence. More precisely, we have the rate of convergence 1.39 for v_ε, and 0.63 for h_ε, as shown in Figure 2.

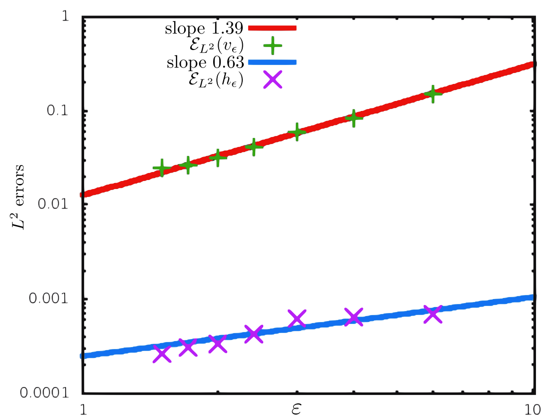

FIGURE 2. The convergence study for L^2 errors of v_ε and h_ε in log-log scale. Observed convergence rates are 1.39 for v_ε, and 0.63 for h_ε.

7. **Conclusions.** We proposed a model for the electrophysiology of the cardiac tissue that extends the standard bidomain model with periodic diffusive inclusions. In a rigorous and practical way it links structural disease of the cardiac tissue to macroscopic electrical conductivities of the bidomain model.

There are several limitations of the proposed model. The inclusions that we address are purely diffusive while we can expect to have different types 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 question that could be addressed is the choise of the transmission conditions on the interface of the inclusions. We used the same ones as in the heart–torso problem. While it is not clear if these are the appropriate transmission conditions for our case, the debate on which ones would be more suitable is open.

Finally, this study gives an additional insight to the electrical behaviour of the cardiac tissue in pathological states. It can be practiacally applied for numerical studyies of many structural diseases of the heart such as fibrosis, scars' border zones etc.

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Appendix A. Numerical algorithms.

A.1. **Mesoscale problem.** In order to simulate the mesoscopic problem we create a mesh of the domain with diffusive inclusions, as in Figure 1. The $u^i_\varepsilon, v_\varepsilon$ and h_ε are defined on Ω^B_ε, while u_ε is defined everywhere on Ω. For the convergence study we will mind only for the values of v_ε and h_ε. The full SBDF2 numerical scheme is given in Algorithm 1. The term $0 < \eta \ll 1$ is used to impose the Gauge condition on u^e_ε, given in (5). The software used for simulation is *FreeFem++* [16].

A.2. **Homogenised problem.** In order to simulate the macroscopic problem, we need to solve the cells problems first, on the unit cell $Y = Y_B \cup Y_D$, and to compute the modified conductivities. Then we use these to solve the modified bidomain model on the whole domain Ω, without distinguishing Ω_ε^B and Ω_ε^D, *i.e.* without including the boundary Γ_ε.

The cell problems (24) - (25) are static problems, that are solved in order to obtain the modified conductivities σ^{i*} and σ^{e*}, (28) and (32). The *FreeFem++* algorithm for the cell problems is given in Algorithm 2.

The *FreeFem++* algorithm, using SBDF2 numerical scheme (see [12]) for the homogenised problem (27), (31) and (33) is given in Algorithm 3. For simplicity, we omit the 0 subscripts in terms of $\varepsilon-$expansion.

Algorithm 1 The mesoscale problem.

Define meshes on Ω and Ω_ε^B. Define T and $N = \frac{T}{\Delta t}$.
Define var. form. spaces $H^1(\Omega), H^1(\Omega_\varepsilon^B)$ with P1 elements.
Declare $u^i_{\varepsilon n}, v_{\varepsilon n}, h_{\varepsilon n}, \phi_i, \phi \in H^1(\Omega_\varepsilon^B)$ and $u^e_{\varepsilon n}, \phi_e \in H^1(\Omega)$, for $n = 0, .., N$.
Define $v_{\varepsilon 0} := v^0, h_{\varepsilon 0} := h^0$.
Solve the coupled system to obtain $u^i_{\varepsilon 1}, u^e_{\varepsilon 1}$:

$$\int_{\Omega_\varepsilon^B} (u^i_{\varepsilon 1} - u^e_{\varepsilon 1})(\phi_i - \phi_e) + \int_\Omega \eta u^e_{\varepsilon 1}\phi_e$$
$$+\Delta t \left[\int_{\Omega_\varepsilon^B} \left(\sigma^i \nabla u^i_{\varepsilon 1}\right) \nabla \phi_i + \int_\Omega \left(\sigma \nabla u^e_{\varepsilon 1}\right) \nabla \phi_e\right] =$$
$$\int_{\Omega_\varepsilon^B} \left(v_{\varepsilon 0} - \Delta t I_{ion}(v_{\varepsilon 0}, h_{\varepsilon 0})\right)(\phi_i - \phi_e).$$

Solve the ODE to obtain $h_{\varepsilon 1}$: $\int_\Omega h_{\varepsilon 1}\phi = \int_\Omega \left(h_{\varepsilon 0} + \Delta t g(v_{\varepsilon 0}, h_{\varepsilon 0})\right)\phi$.
Define $v_{\varepsilon 1} := u^i_{\varepsilon 1} - u^e_{\varepsilon 1}|_{\Omega_\varepsilon^B}$.
for $n = 1$ to N **do**
    Solve the coupled system with SBDF2 to obtain $u^i_{\varepsilon n+1}, u^e_{\varepsilon n+1}$:

$$\int_{\Omega_\varepsilon^B} \frac{3}{2}\left(u^i_{\varepsilon n+1} - u^e_{\varepsilon n+1}\right)(\phi_i - \phi_e) + \int_\Omega \eta u^e_{\varepsilon n+1}\phi_e$$
$$+\Delta t \left[\int_{\Omega_\varepsilon^B} \left(\sigma^i \nabla u^i_{\varepsilon n+1}\right) \nabla \phi_i + \int_\Omega \left(\sigma \nabla u^e_{\varepsilon n+1}\right) \nabla \phi_e\right] =$$
$$\int_{\Omega_\varepsilon^B} \left((2v_{\varepsilon n} - \frac{1}{2}v_{\varepsilon n-1}) + \Delta t\left(2I_{ion}(v_{\varepsilon n}, h_{\varepsilon n}) - I_{ion}(v_{\varepsilon n-1}, h_{\varepsilon n-1})\right)\right)(\phi_i - \phi_e).$$

    Solve the ODE to obtain $h_{\varepsilon n+1}$:

$$\int_{\Omega_\varepsilon^B} \frac{3}{2} h_{\varepsilon n+1}\phi = \int_\Omega \left(2h_{\varepsilon n} - \frac{1}{2}h_{\varepsilon n-1} + \Delta t\left(2g(v_{\varepsilon n}, h_{\varepsilon n}) - g(v_{\varepsilon n-1}, h_{\varepsilon n-1})\right)\right)\phi.$$

    Define $v_{\varepsilon n+1} := u^i_{\varepsilon n+1} - u^e_{\varepsilon n+1}|_{\Omega_\varepsilon^B}$.

Algorithm 2 Static cell problems

Define meshes on Y, and Y_B.
Define periodic var. form. spaces $H^1(Y), H^1(Y_B)$ with P1 elements.
Declare $w_k^i, \phi_i \in H^1(Y_B)$ and $w_k^e, \phi_i \in H^1(Y)$, for $k = 1, 2$, or $k = 1, 2, 3$.
Solve for w_k^i: $\int_{Y_B}(\sigma^i \nabla w_k^i) \cdot \nabla \phi_i + \int_\Gamma (\sigma^i e_k) \cdot n_\Gamma \phi_i = 0$
Solve for w_k: $\int_{Y_B}(\sigma \nabla w_k) \cdot \nabla \phi + \int_\Gamma ((\sigma^e - \sigma^d) e_k) \cdot n_\Gamma \phi = 0$
Compute derivatives: ∂w_k^i and ∂w_k, and conductivities σ^{i*} and σ^{e*} using (28)-(32).

Algorithm 3 Homogenised problem

Define mesh on Ω, T and $N = \frac{T}{\Delta t}$.
Define var. form. space $H^1(\Omega)$ with P1 elements.
Declare $u_n^i, u_n, v_n, h_n, \phi_i, \phi_e, \phi \in H^1(\Omega)$, for $n = 0, .., N$.
Define $v_0 := v^0, h_0 := h^0$.
Solve the coupled system to obtain $u_{\varepsilon 1}^i, u_{\varepsilon 1}^e$:

$$|Y_B| \int_\Omega (u_1^i - u_1)(\phi_i - \phi_e) + \int_\Omega \eta u_1 \phi_e$$
$$+\Delta t \left[\int_\Omega \left(\sigma^{i*} \nabla {u^i}_1\right) \nabla \phi_i + \int_\Omega \left(\sigma^{e*} \nabla u_1\right) \nabla \phi_e \right] =$$
$$|Y_B| \int_\Omega \left(v_0 - \Delta t I_{ion}(v_0, h_0)\right)(\phi_i - \phi_e).$$

Solve the ODE to obtain h_1: $\int_\Omega h_1 \phi = \int_\Omega \left(h_0 + \Delta t g(v_0, v_0)\right) \phi$.
Define $v_1 := u_1^i - u_1$.
for $n = 1$ to N **do**
    Solve the coupled system with SBDF2 to obtain u_{n+1}^i, u_{n+1}:

$$|Y_B| \int_\Omega \frac{3}{2} \left(u_{n+1}^i - u_{n+1}\right)(\phi_i - \phi_e) + \int_\Omega \eta u_{n+1} \phi_e$$
$$+\Delta t \left[\int_\Omega \left(\sigma^{i*} \nabla u_{n+1}^i\right) \nabla \phi_i + \int_\Omega \left(\sigma^{e*} \nabla u_{n+1}\right) \nabla \phi_e \right] =$$
$$|Y_B| \left[\int_\Omega \left((2v_n - \frac{1}{2} v_{n-1}) + \Delta t \left(2 I_{ion}(v_n, h_n) - I_{ion}(v_{n-1}, h_{n-1})\right) \right) (\phi_i - \phi_e) \right].$$

    Solve the ODE to obtain $h_{\varepsilon n+1}$:

$$\int_\Omega \frac{3}{2} h_{n+1} \phi = \int_\Omega \left(2h_n - \frac{1}{2} h_{n-1} + \Delta t \left(2 g(v_n, h_n) - g(v_{n-1}, h_{n-1})\right) \right) \phi.$$

    Define $v_{n+1} := u_{n+1}^i - u_{n+1}$.

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