Microscopic tridomain model of electrical activity in the heart with dynamical gap junctions. Part 2 – Derivation of the macroscopic tridomain model by unfolding homogenization method

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MICROSCOPIC TRIDOMAIN MODEL OF ELECTRICAL ACTIVITY IN THE HEART WITH DYNAMICAL GAP JUNCTIONS. PART 2- DERIVATION OF THE MACROSCOPIC TRIDOMAIN MODEL BY UNFOLDING HOMOGENIZATION METHOD

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Abstract. We study the homogenization of a novel microscopic tridomain system, allowing for a more detailed analysis of the properties of cardiac conduction than the classical bidomain and monodomain models. In [5], we detail this model in which gap junctions are considered as the connections between adjacent cells in cardiac muscle and could serve as alternative or supporting pathways for cell-to-cell electrical signal propagation. Departing from this microscopic cellular model, we apply the periodic unfolding method to derive the macroscopic tridomain model. Several difficulties prevent the application of unfolding homogenization results, including the degenerate temporal structure of the tridomain equations and a nonlinear dynamic boundary condition on the cellular membrane. To prove the convergence of the nonlinear terms, especially those defined on the microscopic interface, we use the boundary unfolding operator and a Kolmogorov-Riesz compactness's result.

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1. Introduction

The conduction of electrical waves in cardiac tissue is key to human life, as the synchronized contraction of the cardiac muscle is controlled by electrical impulses that travel in a coordinated manner throughout the heart chambers. Under pathological conditions cardiac conduction can

2020 *Mathematics Subject Classification.* 65N55, 35A01, 35A02, 35B27, 35K57.
Key words and phrases. Tridomain model, reaction-diffusion system, homogenization theory, time-periodic unfolding method, gap junctions, cardiac electric field.
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be severely reduced, potentially leading to reentrant arrhythmias and ultimately death if normal propagation is not restored properly. At a sub-cellular level, electrical communication in cardiac tissue occurs by means of a rapid flow of ions moving through the cytoplasm of cardiac cells, and a slower inter-cellular flow mediated by gap junctions embedded in the intercalated discs (see Figure 1). Gap junctions are inter-cellular channels composed by hemichannels of specialized proteins, known as connexions, that control the passage of ions between neighboring cells.

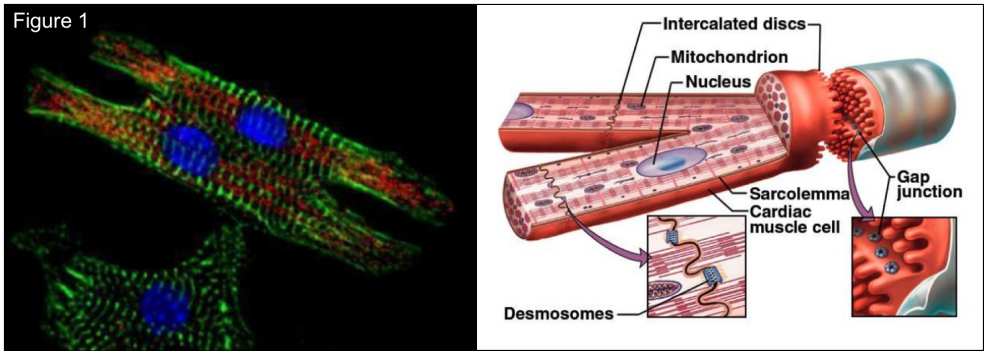

FIGURE 1. Representation of the cardiomyocyte structure
http://www.cardio-research.com/cardiomyocytes

Starting from a more accurate microscopic (cell-level) model of cardiac tissue, with the heterogeneity of the underlying cellular geometry represented in great detail, it is possible to derive the macroscopic tridomain model (tissue-level) using the homogenization method. The microscopic tridomain model consists of three quasi-static equations, two for the electrical potential in the intracellular medium and one for the extracellular medium, coupled by ordinary differential equations describing the dynamics of the ions channels at each membrane (the sarcolemma) and at gap junctions. These equations depend on scaling parameter ε whose is the ratio of the microscopic scale from the macroscopic one. The microscopic tridomain model was proposed three years ago [20, 15] in the case of just two coupled cells. Recently, we have extended in [5] this microscopic tridomain model to larger collections of cells. Further, we have established the well-posedness of this problem and proved the existence and uniqueness of their solutions based on Faedo-Galerkin method.

The macroscopic tridomain model is used as a quantitative description of the electric activity in cardiac tissue with dynamical gap junctions. The relevant unknowns are the two intracellular u_i^k for $k = 1, 2$ and extracellular u_e potentials, along with the so-called transmembrane potential $v^k := u_i^k - u_e$ for $k = 1, 2$ and the so-called gap potential $s := u_i^1 - u_i^2$. In this model, the intra- and extracellular spaces are considered at macro-scale as two separate homogeneous domains superimposed on the cardiac domain. Conduction of electrical signals in cardiac tissue relies on the flow of ions through cell membrane and gap junctions. Each intracellular domain and extracellular one are separated by the cell membrane while the two intracellular domains are connected by gap junctions (see Figure 2). The macroscopic tridomain model can be viewed as a PDE system consisting of three degenerate reaction-diffusion equations involving the unknowns (u_i^1, u_i^2, u_e). These equations are supplemented by a ODE system for the dynamics of the ion channels through the cell membrane (involving the gating variable w^k for $k = 1, 2$).

Regarding the classical bidomain model in the literature, there are formal and rigorous mathematical derivations of the macroscopic model from a microscopic description of heart tissue. From a mathematical point of view, Krassowska et al. [17] applied the two-scale method to formally obtain this macroscopic model (see also [1, 13] for different approaches). Furthermore, Pennachio et al.

[19] used the tools of the Γ-convergence method to obtain a rigorous mathematical form of this homogenized macroscopic model. Amar et al. [2] studied a hierarchy of electrical conduction problems in biological tissues via two-scale convergence. While, the authors in [6] proved the existence and uniqueness of solution of the microscopic bidomain model based on Faedo-Galerkin technique. Further, they used the periodic unfolding method at two scales to show that the solution of the microscopic biodmain model converges to the solution of the macroscopic one. Recently, we have developed the meso-microscopic bidomain model by taking account three different scales and derived a new approach of its macroscopic model using two different homogenization methods. The first method [3] is a formal and intuitive method based on a new three-scale asymptotic expansion method applied to the meso- and microscopic model. The second one [4] based on unfolding operators which not only derive the homogenized equation but also prove the convergence and rigorously justify the mathematical writing of the preceding asymptotic expansion method.

The main contribution of our paper is to provide a simple homogenization proof that can handle some relevant nonlinear membrane models (the FitzHugh-Nagumo model), relying only on unfolding operators. More precisely, we show that the solution constructed in the microscopic tridomain problem converge to the solution of the macroscopic (homogenized) tridomain model. So, we will derive the homogenized tridomain model of cardiac electro-physiology from the microscopic one using the periodic unfolding technique. The latter method not only makes it possible to derive the homogenized equation but also to prove the convergence and to rigorously justify the mathematical writing of the preceding formal method. The homogenization method that we propose allows us to investigate the effective properties of the cardiac tissue at each structural level, namely, micro-macro scales.

The paper is organized as follows: Section 2 is devoted to the geometrical setting and to the introduction of the microscopic tridomain problem. In Section 3, we state our main homogenization results. Next, some notations and properties on the domain and boundary unfolding operators are introduced in Section 4. Finally, Section 5 is devoted to homogenization procedure based on unfolding operators.

2. Tridomain modeling of the heart tissue

The aim of this section is to describe the geometry of the cardiac tissue and to present the microscopic tridomain model of the heart.

2.1. **Geometrical setting of heart tissue.** Let Ω be an open connected bounded subset of $\mathbb{R}^d$, $d \geq 3$. The typical periodic geometrical setting is displayed in Figure 2.

Let $\varepsilon \in (0,1)$ be a small positive parameter, related to the characteristic dimension of the microstructure and which takes values in a sequence of strictly positive numbers tending to zero. Under the one-level scaling, the characteristic length ℓ^{mic} is related to a given macroscopic length L (of the cardiac fibers), such that the scaling parameter ε introduced by:

$$\varepsilon = \frac{\ell^{\text{mic}}}{L}.$$

From the biological point of view, the cardiac cells are connected by many gap junctions. Therefore, geometrically, Ω represents the region occupied by the cardiac tissue and consists of two intracellular media $\Omega_{i,\varepsilon}^k$ for $k = 1, 2$, that are connected by gap junctions $\Gamma_\varepsilon^{1,2} = \partial\Omega_{i,\varepsilon}^1 \cap \partial\Omega_{i,\varepsilon}^2$ and extracellular medium $\Omega_{e,\varepsilon}$ (for more details see [20, 15]). Each intracellular medium $\Omega_{i,\varepsilon}^k$ and the extracellular one $\Omega_{e,\varepsilon}$ are separated by the surface membrane Γ_ε^k (the sarcolemma) which is expressed by:

$$\Gamma_\varepsilon^k = \partial\Omega_{i,\varepsilon}^k \cap \partial\Omega_{e,\varepsilon}, \text{ with } k = 1, 2,$$

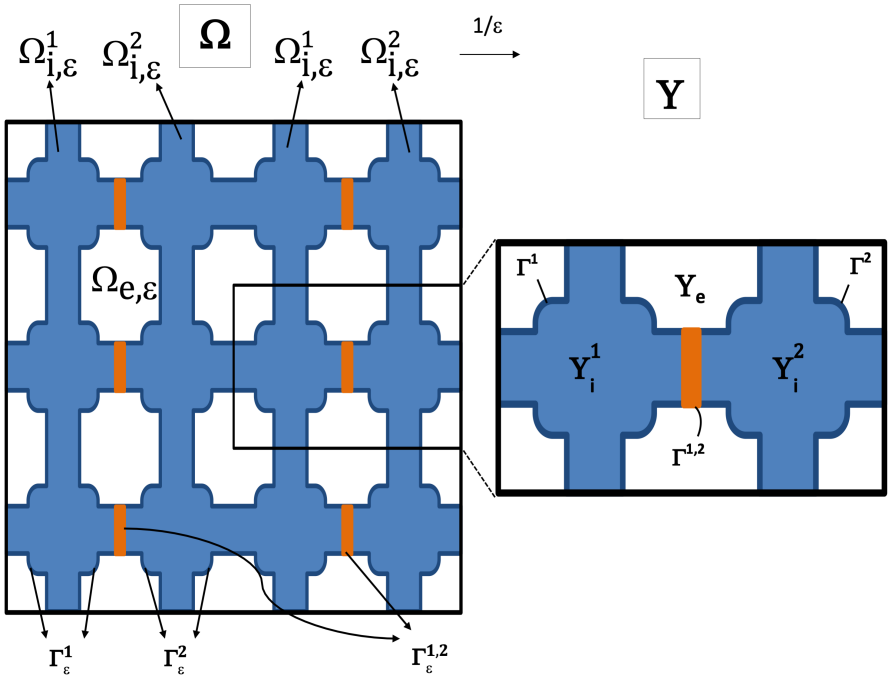

FIGURE 2. (Left) Periodic heterogeneous domain Ω. (Right) Reference cell Y at ε-structural level.

while the remaining (exterior) boundary is denoted by $\partial_{\text{ext}}\Omega$. We can consider that the intracellular zone as a perforated domain obtained from Ω by removing the holes which correspond to the extracellular domain $\Omega_{e,\varepsilon}$.

We can divide Ω into N_ε small elementary cells $Y_\varepsilon = \prod_{n=1}^{d}]0, \varepsilon\, \ell_n^{\text{mic}}[$, with $\ell_1^{\text{mic}}, \ldots, \ell_d^{\text{mic}}$ are positive numbers. These small cells are all equal, thanks to a translation and scaling by ε, to the same reference cell of periodicity called the reference cell $Y = \prod_{n=1}^{d}]0, \ell_n^{\text{mic}}[$. So, the ε-dilation of the reference cell Y is defined as the following shifted set $Y_{\varepsilon,h}$:

$$Y_{\varepsilon,h} := T_\varepsilon^h + \varepsilon Y = \{\varepsilon\xi : \xi \in h_\ell + Y\}, \tag{1}$$

where T_ε^h represents the translation of εh with $h = (h_1, \ldots, h_d) \in \mathbb{Z}^d$ and $h_\ell := (h_1 \ell_1^{\text{mic}}, \ldots, h_d \ell_d^{\text{mic}})$. Therefore, for each macroscopic variable x that belongs to Ω, we define the corresponding microscopic variable $y \approx \dfrac{x}{\varepsilon}$ that belongs to Y with a translation. Indeed, we have:

$$x \in \Omega \Rightarrow \exists h \in \mathbb{Z}^d \ \text{ such that } \ x \in Y_\varepsilon^h \Rightarrow x = \varepsilon(h_\ell + y) \Rightarrow y = \frac{x}{\varepsilon} - h_\ell \in Y.$$

Since we will study the behavior of the functions $u(x, y)$ which are $\mathbf{y}$-periodic, by periodicity we have $u\left(x, \dfrac{x}{\varepsilon} - h_\ell\right) = u\left(x, \dfrac{x}{\varepsilon}\right)$. By construction, we say that $y = \dfrac{x}{\varepsilon}$ belongs to Y.

We are assuming that the cells are periodically organized as a regular network of interconnected cylinders at the microscale. The microscopic reference cell Y is also divided into three disjoint connected parts: two intracellular parts Y_i^k for $k = 1, 2$, that are connected by an intercalated disc (gap junction) $\Gamma^{1,2}$ and extracellular part Y_e. Each intracellular parts Y_i^k and the extracellular one

are separated by a common boundary Γ^k for $k=1,2$. So, we have:

$$Y := \overline{Y}_i^1 \cup \overline{Y}_i^2 \cup \overline{Y}_e, \quad \Gamma^k := \partial Y_i^k \cap \partial Y_e, \quad \Gamma^{1,2} := \partial Y_i^1 \cap \partial Y_i^2,$$

with $k=1,2$. In a similar way, we can write the corresponding common periodic boundary as follows:

$$\Gamma_{\varepsilon,h} = T_\varepsilon^h + \varepsilon\Gamma = \{\varepsilon\xi : \xi \in h_\ell + \Gamma\}, \tag{2}$$

with T_ε^h denote the same previous translation, $\Gamma_{\varepsilon,h} := \Gamma_{\varepsilon,h}^k, \Gamma_{\varepsilon,h}^{1,2}$ and $\Gamma := \Gamma^k, \Gamma^{1,2}$ for $k=1,2$.

In summary, the intracellular and extracellular media can be described as follows:

$$\begin{aligned} \Omega_{i,\varepsilon}^k = \Omega \cap \bigcup_{h\in\mathbb{Z}^d} Y_{i,\varepsilon,h}^k, \quad \Omega_{e,\varepsilon} = \Omega \cap \bigcup_{h\in\mathbb{Z}^d} Y_{e,\varepsilon,h}, \\ \Gamma_\varepsilon^k = \Omega \cap \bigcup_{h\in\mathbb{Z}^d} \Gamma_{\varepsilon,h}^k \text{ and } \Gamma_\varepsilon^{1,2} = \Omega \cap \bigcup_{h\in\mathbb{Z}^d} \Gamma_{\varepsilon,h}^{1,2}, \end{aligned} \tag{3}$$

where $Y_{i,\varepsilon,h}^k$, $Y_{e,\varepsilon,h}$ and $\Gamma_\varepsilon^k, \Gamma_\varepsilon^{1,2}$ are respectively defined as (1)-(2) for $k=1,2$.

2.2. **Microscopic tridomain model.** The electric properties of the tissue at cellular level are described by the intracellular $u_{i,\varepsilon}^k$ for $k=1,2$ and extracellular $u_{e,\varepsilon}$, potentials respectively with the associated conductivities M_i^ε and M_e^ε. In [5], we presented and studied in details the non-dimensional tridomain model with respect the scaling parameter ε, as well as the models chosen for the membrane and gap junctions dynamics. More precisely, we consider the following microscopic tridomain model:

$$-\nabla\cdot\left(\mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k\right) = 0 \qquad \text{in } \Omega_{i,\varepsilon,T}^k := (0,T)\times\Omega_{i,\varepsilon}^k, \tag{4a}$$

$$-\nabla\cdot\left(\mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon}\right) = 0 \qquad \text{in } \Omega_{e,\varepsilon,T} := (0,T)\times\Omega_{e,\varepsilon}, \tag{4b}$$

$$u_{i,\varepsilon}^k - u_{e,\varepsilon} = v_\varepsilon^k \qquad \text{on } \Gamma_{\varepsilon,T}^k := (0,T)\times\Gamma_\varepsilon^k, \tag{4c}$$

$$-\mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k \cdot n_i^k = \mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon}\cdot n_e = \mathcal{I}_m^k \qquad \text{on } \Gamma_{\varepsilon,T}^k, \tag{4d}$$

$$\varepsilon\left(\partial_t v_\varepsilon^k + \mathcal{I}_{ion}\left(v_\varepsilon^k, w_\varepsilon^k\right) - \mathcal{I}_{app,\varepsilon}^k\right) = \mathcal{I}_m^k \qquad \text{on } \Gamma_{\varepsilon,T}^k, \tag{4e}$$

$$\partial_t w_\varepsilon^k - H\left(v_\varepsilon^k, w_\varepsilon^k\right) = 0 \qquad \text{on } \Gamma_{\varepsilon,T}^k, \tag{4f}$$

$$u_{i,\varepsilon}^1 - u_{i,\varepsilon}^2 = s_\varepsilon \qquad \text{on } \Gamma_{\varepsilon,T}^{1,2} := (0,T)\times\Gamma_\varepsilon^{1,2}, \tag{4g}$$

$$-\mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^1 \cdot n_i^1 = \mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^2 \cdot n_i^2 = \mathcal{I}_{1,2} \qquad \text{on } \Gamma_{\varepsilon,T}^{1,2}, \tag{4h}$$

$$\frac{\varepsilon}{2}\left(\partial_t s_\varepsilon + \mathcal{I}_{gap}\left(s_\varepsilon\right)\right) = \mathcal{I}_{1,2} \qquad \text{on } \Gamma_{\varepsilon,T}^{1,2}, \tag{4i}$$

with $k=1,2$ and each equation corresponds to the following sense: (4a) Intra quasi-stationary conduction, (4b) Extra quasi-stationary conduction, (4c) Transmembrane potential, (4d) Continuity equation at cell membrane, (4e) Reaction condition at the corresponding cell membrane, (4f) Dynamic coupling, (4g) Gap junction potential, (4h) Continuity equation at gap junction, (4e) Reaction condition at gap junction.

Observe that the tridomain equations (4a)-(4b) are invariant with respect to the scaling parameter ε. As usual in homogenization theory, the electrical potentials are assumed to have the following form

$$u_{i,\varepsilon}^k(t,x) := u_i^k\left(t,x,\frac{x}{\varepsilon}\right), \quad u_{e,\varepsilon}(t,x) := u_e\left(t,x,\frac{x}{\varepsilon}\right), \text{ for } k=1,2,$$

where each function depends on time $t\in(0,T)$, slow (macroscopic) variable x and the fast (microscopic) variable $y=x/\varepsilon$. Similarly, the transmembrane potential v_ε^k, the gap junction potential s_ε and the corresponding gating variable w_ε^k for $k=1,2$ have the same previous form. Furthermore, the

conductivity tensors are considered symmetric and dependent both on the slow and fast variables, i.e. for $j = i, e$, we have

$$\mathrm{M}_j^\varepsilon(x) := \mathrm{M}_j\left(x, \frac{x}{\varepsilon}\right), \tag{5}$$

satisfying the elliptic and periodicity conditions: there exist constants $\alpha, \beta \in \mathbb{R}$, such that $0 < \alpha < \beta$ and for all $\lambda \in \mathbb{R}^d$:

$$\mathrm{M}_j\lambda \cdot \lambda \geq \alpha \left|\lambda\right|^2, \tag{6a}$$

$$\left|\mathrm{M}_j\lambda\right| \leq \beta \left|\lambda\right|, \tag{6b}$$

$$\mathrm{M}_j \ \mathbf{y}\text{-periodic, for } j = i, e. \tag{6c}$$

We complete system (4) with no-flux boundary conditions on $\partial_{\text{ext}}\Omega$:

$$\left(\mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k\right) \cdot \mathbf{n} = \left(\mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon}\right) \cdot \mathbf{n} = 0 \quad \text{on} \quad (0,T) \times \partial_{\text{ext}}\Omega,$$

where $k = 1, 2$ and $\mathbf{n}$ is the outward reference normal to the exterior boundary of Ω. We impose initial conditions on transmembrane potential v_ε^k, gap junction potential s_ε and gating variable w_ε^k as follows:

$$\begin{aligned} &v_\varepsilon^k(0,x) = v_{0,\varepsilon}^k(x),\ w_\varepsilon^k(0,x) = w_{0,\varepsilon}^k(x) && \text{a.e. on } \Gamma_{\varepsilon,T}^k, \\ &\text{and } s_\varepsilon(0,x) = s_{0,\varepsilon}(x) && \text{a.e. on } \Gamma_{\varepsilon,T}^{1,2}, \end{aligned} \tag{7}$$

with $k = 1, 2$.

Next, we introduce some assumptions on the ionic functions, the source term and the initial data.
Assumptions on the ionic functions. The ionic current $\mathcal{I}_{ion}(v^k, w^k)$ at each cell membrane Γ^k can be decomposed into $\mathrm{I}_{a,ion}\left(v^k\right)$ and $\mathrm{I}_{b,ion}\left(w^k\right)$, where $\mathcal{I}_{ion}\left(v^k, w^k\right) = \mathrm{I}_{a,ion}\left(v^k\right) + \mathrm{I}_{b,ion}\left(w^k\right)$ with $k = 1, 2$. Furthermore, the nonlinear function $\mathrm{I}_{a,ion} : \mathbb{R} \to \mathbb{R}$ is considered as a C^1 function and the functions $\mathrm{I}_{b,ion} : \mathbb{R} \to \mathbb{R}$ and $H : \mathbb{R}^2 \to \mathbb{R}$ are considered as linear functions. Also, we assume that there exists $r \in (2, +\infty)$ and constants $\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, C > 0$ and $\beta_1 > 0, \beta_2 \geq 0$ such that:

$$\frac{1}{\alpha_1}\left|v\right|^{r-1} \leq \left|\mathrm{I}_{a,ion}\left(v\right)\right| \leq \alpha_1\left(\left|v\right|^{r-1} + 1\right),\ \left|\mathrm{I}_{b,ion}\left(w\right)\right| \leq \alpha_2(\left|w\right| + 1), \tag{8a}$$

$$\left|H(v,w)\right| \leq \alpha_3(\left|v\right| + \left|w\right| + 1), \text{ and } \mathrm{I}_{b,ion}\left(w\right) v - \alpha_4 H(v,w)w \geq \alpha_5 \left|w\right|^2, \tag{8b}$$

$$\tilde{\mathrm{I}}_{a,ion} : v \mapsto \mathrm{I}_{a,ion}(v) + \beta_1 v + \beta_2 \text{ is strictly increasing with } \lim_{v\to 0} \tilde{\mathrm{I}}_{a,ion}(v)/v = 0, \tag{8c}$$

$$\forall v, v' \in \mathbb{R},\ \left(\tilde{\mathrm{I}}_{a,ion}(v) - \tilde{\mathrm{I}}_{a,ion}(v')\right)(v - v') \geq \frac{1}{C}\left(1 + \left|v\right| + \left|v'\right|\right)^{r-2}\left|v - v'\right|^2, \tag{8d}$$

with $(v, w) := \left(v^k, w^k\right)$ for $k = 1, 2$.

Now, we represent the gap junction $\Gamma_\varepsilon^{1,2}$ between intra-neighboring cells by a passive membrane:

$$\mathcal{I}_{gap}(s) = G_{gap} \times s, \tag{9}$$

where $G_{gap} = \frac{1}{R_{gap}}$ is the conductance of the gap junctions. A discussion of the modeling of the gap junctions is given in [14].

Assumptions on the source term. There exists a constant C independent of ε such that the source term $\mathcal{I}_{app,\varepsilon}^k$ satisfies the following estimation for $k = 1, 2$:

$$\left\|\varepsilon^{1/2}\mathcal{I}_{app,\varepsilon}^k\right\|_{L^2(\Gamma_{\varepsilon,T}^k)} \leq C. \tag{10}$$

Assumptions on the initial data. The initial condition $v^k_{0,\varepsilon}$, $s_{0,\varepsilon}$ and $w^k_{0,\varepsilon}$ satisfy the following estimation:

$$\sum_{k=1,2}\left\|\varepsilon^{1/r}v^k_{0,\varepsilon}\right\|_{L^r(\Gamma^k_\varepsilon)}+\left\|\varepsilon^{1/2}s_{0,\varepsilon}\right\|_{L^2(\Gamma^{1,2}_\varepsilon)}+\sum_{k=1,2}\left\|\varepsilon^{1/2}w^k_{0,\varepsilon}\right\|_{L^2(\Gamma^k_\varepsilon)}\leq C, \tag{11}$$

for some constant C independent of ε. Moreover, $v^k_{0,\varepsilon}$, $s_{0,\varepsilon}$ and $w^k_{0,\varepsilon}$ are assumed to be traces of uniformly bounded sequences in $C^1(\overline{\Omega})$ with $k=1,2$.

Finally, we observe that the equations in (4) are invariant under the change of $u^k_{i,\varepsilon}$, $k=1,2$ and $u_{e,\varepsilon}$ into $u^k_{i,\varepsilon}+c$, $u_{e,\varepsilon}+c$, for any $c\in\mathbb{R}$. Therefore, we may impose the following normalization condition:

$$\int_{\Omega_{e,\varepsilon}} u_{e,\varepsilon}\,dx=0,\ \text{for a.e. } t\in(0,T). \tag{12}$$

3. Main results

In this part, we highlight the main results obtained in our paper. Based on the a priori estimates and unfolding homogenization method, we can pass to the limit in the microscopic equations and derive the following homogenized problem:

Theorem 1 (Macroscopic Tridomain Model)**.** *Assume that conditions (6)-(12) hold. Then, a sequence of solutions* $\left(u^1_{i,\varepsilon},u^2_{i,\varepsilon},u_{e,\varepsilon},w^1_\varepsilon,w^2_\varepsilon\right)_\varepsilon$ *of the microscopic tridomain model (4) converges as* $\varepsilon\to 0$ *to a weak solution* $\left(u^1_i,u^2_i,u_e,w^1,w^2\right)$ *satisfying the following conditions:*

(A) (Algebraic relation).

$$\begin{aligned} v^k&=u^k_i-u_e \qquad \text{for } k=1,2, \text{ a.e. in } \Omega_T,\\ s&=u^1_i-u^2_i \qquad\qquad\qquad \text{a.e. in } \Omega_T. \end{aligned}$$

(B) (Regularity).

$$\begin{aligned} &u^k_i,u_e\in L^2(0,T;H^1(\Omega)),\\ &\int_\Omega u_e(t,x)\,dx=0,\ \text{for a.e. } t\in(0,T),\\ &v^k\in L^2(0,T;H^1(\Omega))\cap L^r(\Omega_T),\ r\in(2,+\infty),\\ &s\in L^2(0,T;H^1(\Omega)),\\ &w^k\in C(0,T;L^2(\Omega)),\\ &\partial_t v^k\in L^2(0,T;(H^1(\Omega))')+L^{r/(r-1)}(\Omega_T),\\ &\partial_t s,\partial_t w^k\in L^2(\Omega_T),\ k=1,2. \end{aligned}$$

(C) (Initial conditions).

$$\begin{aligned} &v^k(0,x)=v^k_0(x),\ w^k(0,x)=w^k_0(x),\ k=1,2 \qquad \text{a.e. in } \Omega,\\ &\text{and } s(0,x)=s_0(x) \qquad\qquad\qquad\qquad\qquad\qquad \text{a.e. in } \Omega. \end{aligned}$$

(D) (Boundary conditions).

$$\left(\widetilde{\mathbf{M}}_e\nabla u_e\right)\cdot\mathbf{n}=\left(\widetilde{\mathbf{M}}_i\nabla u^k_i\right)\cdot\mathbf{n}=0\quad \text{on}\quad \Sigma_T:=(0,T)\times\partial_{ext}\Omega,$$

(E) (Differential equations).

$$
\begin{aligned}
\sum_{k=1,2} \mu_k \partial_t v^k + \nabla \cdot \left(\widetilde{\mathbf{M}}_e \nabla u_e \right) + \sum_{k=1,2} \mu_k \mathcal{I}_{ion}(v^k, w^k) &= \sum_{k=1,2} \mu_k \mathcal{I}^k_{app} && \text{in } \Omega_T, \\
\mu_1 \partial_t v^1 + \mu_g \partial_t s - \nabla \cdot \left(\widetilde{\mathbf{M}}_i \nabla u_i^1 \right) + \mu_1 \mathcal{I}_{ion}(v^1, w^1) + \mu_g \mathcal{I}_{gap}(s) &= \mu_1 \mathcal{I}^1_{app} && \text{in } \Omega_T, \\
\mu_2 \partial_t v^2 - \mu_g \partial_t s - \nabla \cdot \left(\widetilde{\mathbf{M}}_i \nabla u_i^2 \right) + \mu_2 \mathcal{I}_{ion}(v^2, w^2) - \mu_g \mathcal{I}_{gap}(s) &= \mu_2 \mathcal{I}^2_{app} && \text{in } \Omega_T, \\
\partial_t w^k - H(v^k, w^k) &= 0 && \text{in } \Omega_T,
\end{aligned} \tag{13}
$$

where $\mu_k = \left|\Gamma^k\right| / |Y|$, $k = 1, 2$, $\left(\text{resp. } \mu_g = \left|\Gamma^{1,2}\right| / 2\,|Y| \right)$ *is the ratio between the surface membrane (resp. the gap junction) and the volume of the reference cell. Furthermore,* $\mathbf{n}$ *represents the outward reference normal to the boundary of* Ω*. Herein, the homogenized conductivity matrices* $\widetilde{\mathbf{M}}_j = \left(\widetilde{\mathbf{m}}_j^{pq}\right)_{1 \le p,q \le d}$ *for* $j = i, e$ *are respectively defined by:*

$$
\widetilde{\mathbf{m}}_i^{pq} := \frac{1}{|Y|} \sum_{\ell=1}^{d} \int_{Y_i^k} \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell} \frac{\partial \chi_i^q}{\partial y_\ell} \right) dy, \tag{14a}
$$

$$
\widetilde{\mathbf{m}}_e^{pq} := \frac{1}{|Y|} \sum_{\ell=1}^{d} \int_{Y_e} \left(\mathrm{m}_e^{pq} + \mathrm{m}_e^{p\ell} \frac{\partial \chi_e^q}{\partial y_\ell} \right) dy, \tag{14b}
$$

where the components χ_j^q *of* χ_j *for* $j = i, e$ *are respectively the corrector functions, solutions of the* ε*-cell problems:*

$$
\begin{cases}
-\nabla_y \cdot (\mathrm{M}_e \nabla_y \chi_e^q) = \nabla_y \cdot (\mathrm{M}_e e_q) \ \text{ in } Y_e, \\
\chi_e^q \ y\text{-periodic}, \\
\mathrm{M}_e \nabla_y \chi_e^q \cdot n_e = -(\mathrm{M}_e e_q) \cdot n_e \ \text{ on } \Gamma^k, \ k = 1, 2
\end{cases} \tag{15a}
$$

$$
\begin{cases}
-\nabla_y \cdot (\mathrm{M}_i \nabla_y \chi_i^q) = \nabla_y \cdot (\mathrm{M}_i e_q) \ \text{ in } Y_i^k, \\
\chi_i^q \ y\text{-periodic}, \\
\mathrm{M}_i \nabla_y \chi_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \ \text{ on } \Gamma^k, \ k = 1, 2 \\
\mathrm{M}_i \nabla_y \chi_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \ \text{ on } \Gamma^{1,2},
\end{cases} \tag{15b}
$$

for e_q, $q = 1, \ldots, d$, *the standard canonical basis in* $\mathbb{R}^d$.

The proof of Theorem 1 is proved rigorously in Section 4.2 using unfolding homogenization method. The uniqueness of the solutions to the macroscopic model can be proved similar as that of the microscopic model with minor changes (see [5]). This implies that all the convergence results remain valid for the whole sequence. Furthermore, it is easy to verify that the macroscopic conductivity tensors of the intracellular and extracellular spaces are symmetric and positive definite (see Remark 14).

Remark 2. *The authors in* [6] *treated the microscopic bidomain problem where the gap junction is ignored. They considered that there are only two intra- and extracellular media separated by a single membrane (sarcolemma). Comparing to* [6]*, the microscopic tridomain model in our work consists of three elliptic equations coupled through three boundary conditions, two on each cell membrane and one on the gap junction which separates between two intracellular media. The macroscopic tridomain model is more general and complex than the classical monodomain and bidomain models. Using periodic unfolding homogenization method, we derive a new approach of the homogenized model* (13) *from the microscopic tridomain problem* (4).

Remark 3. *Regarding the classical bidomain model [9, 6], we can derive this model from our tridomain problem if we take* $u_i^1 = u_i^2$.

4. Time-depending unfolding operators

4.1. **Unfolding operator and some basic properties.** Under the notation (3), we begin with introducing the unfolding operator and describe some of its properties. For more properties and proofs, we refer to [7, 8]. First, we present the unfolding operators defined for perforated domains on the domain $(0,T)\times\Omega$. Then we define boundary unfolding operators one on the membrane $(0,T)\times\Gamma^k$, $k=1,2$ and the other on the gap junction $(0,T)\times\Gamma^{1,2}$.

In order to define an unfolding operator, we first introduce the following sets in $\mathbb{R}^d$ (see Figure 3)

- $\Xi_\varepsilon = \{h\in\mathbb{Z}^d,\ \varepsilon(h_\ell+Y)\subset\Omega\}$,
- $\widehat{\Omega}_\varepsilon = \text{interior}\ \{\bigcup_{h\in\Xi_\varepsilon}\varepsilon\left(h_\ell+\overline{Y}\right)\}$,
- $\widehat{\Omega}_{e,\varepsilon} = \text{interior}\ \{\bigcup_{h\in\Xi_\varepsilon}\varepsilon\left(h_\ell+\overline{Y_e}\right)\}$,
- $\widehat{\Omega}^k_{i,\varepsilon} = \text{interior}\ \{\bigcup_{h\in\Xi_\varepsilon}\varepsilon\left(h_\ell+\overline{Y_i^k}\right)\},\ k=1,2,$
- $\widehat{\Gamma}^k_\varepsilon = \{y\in\Gamma^k : y\in\widehat{\Omega}_\varepsilon\},\ k=1,2,$
- $\widehat{\Gamma}^{1,2}_\varepsilon = \{y\in\Gamma^{1,2} : y\in\widehat{\Omega}_\varepsilon\}$,
- $\Lambda^\varepsilon = \Omega\setminus\widehat{\Omega}^\varepsilon$,
- $\widehat{\Omega}_{\varepsilon,T} = (0,T)\times\widehat{\Omega}^\varepsilon$,
- $\widehat{\Omega}^k_{i,\varepsilon,T} = (0,T)\times\widehat{\Omega}^k_{i,\varepsilon},\ k=1,2, \qquad \widehat{\Omega}_{e,\varepsilon,T} = (0,T)\times\widehat{\Omega}_{e,\varepsilon}$,
- $\Lambda^\varepsilon_T = (0,T)\times\Lambda^\varepsilon$,

where $h_\ell := (h_1\ell_1^{\text{mic}},\dots,h_d\ell_d^{\text{mic}})$. For all $w\in\mathbb{R}^d$, let $[w]_Y$ be the unique integer combination of the periods such that $w-[w]_Y\in Y$. We may write $w=[w]_Y+\{w\}_Y$ for all $w\in\mathbb{R}^d$, so that for all $\varepsilon>0$, we get the unique decomposition:

$$x=\varepsilon\left(\left[\frac{x}{\varepsilon}\right]_Y+\left\{\frac{x}{\varepsilon}\right\}_Y\right),\ \text{for all } x\in\mathbb{R}^d.$$

Based on this decomposition, we define the unfolding operator in intra- and extracellular domains.

Definition 4 (Domain and boundary unfolding operator [7, 8])**.**

1. *For any function* ϕ *Lebesgue-measurable on the intracellular medium* $\Omega^k_{i,\varepsilon,T} := (0,T)\times\Omega^k_{i,\varepsilon}$ *for* $k=1,2$*, the unfolding operator* $\mathcal{T}^{i,k}_\varepsilon$ *is defined as follows:*

$$\mathcal{T}^{i,k}_\varepsilon(\phi)(t,x,y) = \begin{cases}\phi\left(t,\varepsilon\left[\frac{x}{\varepsilon}\right]_Y+\varepsilon y\right) & \text{a.e. for } (t,x,y)\in\widehat{\Omega}^\varepsilon_T\times Y_i^k,\\ 0 & \text{a.e. for } (t,x,y)\in\Lambda^\varepsilon_T\times Y_i^k,\end{cases} \tag{16}$$

where $[\cdot]$ *denotes the Gauβ-bracket. Similarly, we define the unfolding operator* $\mathcal{T}^e_\varepsilon$ *on the domain* $\Omega^\varepsilon_{e,T} := (0,T)\times\Omega^\varepsilon_e$*. We readily have that:*

$$\forall x\in\mathbb{R}^d,\ \mathcal{T}^{i,k}_\varepsilon(\phi)\left(t,x,\left\{\frac{x}{\varepsilon}\right\}_Y\right)=\phi(t,x),\ \text{with } k=1,2.$$

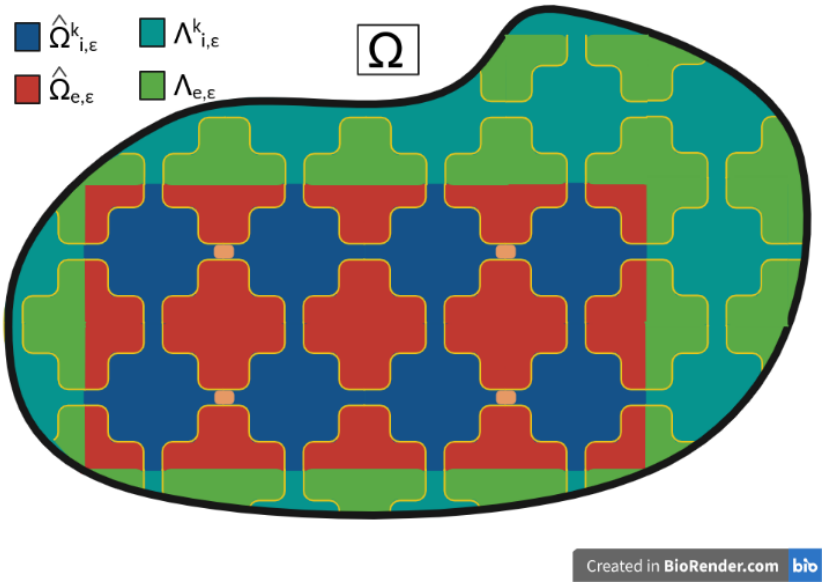

FIGURE 3. The sets $\widehat{\Omega}^k_{i,\varepsilon}$ for $k=1,2$ (in blue), $\widehat{\Omega}^\varepsilon_e$ (in red), $\Lambda^k_{i,\varepsilon}$ (in dark cyan) and $\Lambda_{e,\varepsilon}$ (in green).

2. *For any function φ Lebesgue-measurable on the membrane $\Gamma^k_\varepsilon := (0,T)\times\Gamma^k_\varepsilon$ for $k=1,2$, the boundary unfolding operator $\mathcal{T}^{b,k}_\varepsilon$ is defined as follows:*

$$\mathcal{T}^{b,k}_\varepsilon(\varphi)(t,x,y) = \begin{cases} \varphi\left(t, \varepsilon\left[\frac{x}{\varepsilon}\right]_Y + \varepsilon y\right) & \text{a.e. for } (t,x,y)\in \widehat{\Omega}^\varepsilon_T\times\Gamma^k, \\ 0 & \text{a.e. for } (t,x,y)\in \Lambda^\varepsilon_T\times\Gamma^k. \end{cases} \tag{17}$$

Similarly, we define the boundary unfolding operator $\mathcal{T}^{b,1,2}_\varepsilon$ on the gap junction $\Gamma^{1,2}_{\varepsilon,T} := (0,T)\times\Gamma^{1,2}_\varepsilon$.

4.1.1. ***Properties of the unfolding operator.*** In the following proposition, we state some basic properties of the unfolding operator which will be used frequently in the next sections.

Proposition 5 (Some properties of the unfolding operator [7, 8])**.**

(1) The operator $\mathcal{T}^{i,k}_\varepsilon : L^p\left(\Omega^k_{i,\varepsilon,T}\right) \longrightarrow L^p(\Omega_T\times Y^k_i)$ and $\mathcal{T}^{b,k}_\varepsilon : L^p(\Gamma^k_{\varepsilon,T}) \longrightarrow L^p(\Omega_T\times\Gamma^k)$ are linear and continuous for $p\in[1,+\infty)$ and $k=1,2$. Similarly, we have the same properties for the unfolding operator $\mathcal{T}^e_\varepsilon$ and for the boundary unfolding operator $\mathcal{T}^{b,1,2}_\varepsilon$.

(2) For $u,u'\in L^p\left(\Omega^k_{i,\varepsilon,T}\right)$ and $v,w\in L^p\left(\Gamma^k_{\varepsilon,T}\right)$, it holds that $\mathcal{T}^{i,k}_\varepsilon(uu') = \mathcal{T}^{i,k}_\varepsilon(u)\mathcal{T}^{i,k}_\varepsilon(u')$ and $\mathcal{T}^{b,k}_\varepsilon(vw) = \mathcal{T}^{b,k}_\varepsilon(v)\mathcal{T}^{b,k}_\varepsilon(w)$, with $p\in(1,+\infty)$ and $k=1,2$.

(3) For $u\in L^p\left(\Omega^k_{i,\varepsilon,T}\right), p\in[1,+\infty)$, we have

$$\left\|\mathcal{T}^{i,k}_\varepsilon(u)\right\|_{L^p(\Omega_T\times Y^k_i)} = |Y|^{1/p}\left\|u\mathbb{1}_{\widehat{\Omega}^k_{i,\varepsilon,T}}\right\|_{L^p\left(\Omega^k_{i,\varepsilon,T}\right)} \le |Y|^{1/p}\|u\|_{L^p\left(\Omega^k_{i,\varepsilon,T}\right)}.$$

(4) For $v\in L^p\left(\Gamma^k_{\varepsilon,T}\right)$, with $p\in[1,+\infty)$ and $k=1,2$. Then we have

$$\left\|\mathcal{T}^{b,k}_\varepsilon(v)\right\|_{L^p(\Omega_T\times\Gamma^k)} = \varepsilon^{1/p}|Y|^{1/p}\|v\|_{L^p(\widehat{\Gamma}^k_{\varepsilon,T})} \le \varepsilon^{1/p}|Y|^{1/p}\|v\|_{L^p(\Gamma^k_{\varepsilon,T})}.$$

(5) *Let* $\phi_\varepsilon \in L^p\left(0,T;W^{1,p}(\Omega)\right)$, *with* $p \in [1,+\infty)$ *and* $k = 1,2$. *If* $\phi_\varepsilon \to \phi$ *strongly in* $L^p(0,T;W^{1,p}(\Omega))$ *as* $\varepsilon \to 0$, *then*

$$\mathcal{T}_\varepsilon^{i,k}(\phi_\varepsilon) \to \phi \text{ strongly in } L^p(\Omega_T \times Y_i^k),$$
$$\mathcal{T}_\varepsilon^{b,k}(\phi_\varepsilon) \to \phi|_{\Gamma^k} \text{ strongly in } L^p(\Omega_T \times \Gamma^k) \text{ as } \varepsilon \to 0.$$

(6) *For* $u \in L^p\left(0,T;W\left(\Omega_{i,\varepsilon}^k\right)\right), p \in [1,+\infty)$, *it holds that* $\nabla_y \mathcal{T}_\varepsilon^{i,k}(u) = \varepsilon \mathcal{T}_\varepsilon^{i,k}(\nabla_x u)$ *with* $k = 1,2$.

Remark 6. *The unfolding operators* $\mathcal{T}_\varepsilon^{b,k}$ *and* $\mathcal{T}_\varepsilon^{i,k}$ *for* $k = 1,2$ *are related in the following sense:*

$$\mathcal{T}_\varepsilon^{b,k}(u|_{\Gamma_\varepsilon^k}) = \mathcal{T}_\varepsilon^{i,k}(u)|_{\Gamma^k}, \quad u \in L^p\left(0,T;W^{1,p}(\Omega_{i,\varepsilon}^k)\right), \quad k = 1,2,$$

for $p \in (1,+\infty)$ *and a.e.* $t \in (0,T)$. *In particular, by the standard trace theorem in* Y_i^k, *there is a constant* C *independent of* ε *and* t *such that*

$$\left\|\mathcal{T}_\varepsilon^{b,k}(u)\right\|_{L^p(\Omega_T\times\Gamma^k)}^p \le C\left(\left\|\mathcal{T}_\varepsilon^{i,k}(u)\right\|_{L^p\left(\Omega_T\times Y_i^k\right)}^p + \left\|\nabla_y \mathcal{T}_\varepsilon^{i,k}(u)\right\|_{L^p\left(\Omega_T\times Y_i^k\right)}^p\right).$$

From the properties of $\mathcal{T}_\varepsilon^{i,k}(\cdot)$ *in Proposition 5, it follows that*

$$\left\|\mathcal{T}_\varepsilon^{b,k}(u)\right\|_{L^p(\Omega_T\times\Gamma^k)}^p \le C\left(\|u\|_{L^p\left(\Omega_{i,\varepsilon,T}^k\right)}^p + \varepsilon^p \|\nabla u\|_{L^p\left(\Omega_{i,\varepsilon,T}^k\right)}^p\right).$$

Similarly, the trace theorem in Y_e *holds for* $u \in L^p\left(0,T;W^{1,p}(\Omega_{e,\varepsilon})\right)$ *(which can be found as Remark 4.2 in [8]).*

In the sequel, we will define $W_\#^{1,p}$ the periodic Sobolev space as follows:

Definition 7. *Let* $\mathcal{O}$ *be a reference cell and* $p \in [1,+\infty)$. *Then, we define*

$$W_\#^{1,p}(\mathcal{O}) = \{u \in W^{1,p}(\mathcal{O}) \text{ such that } u \text{ is periodic with } \mathcal{M}_\mathcal{O}(u) = 0\}, \tag{18}$$

where $\mathcal{M}_\mathcal{O}(u) = \dfrac{1}{|\mathcal{O}|}\displaystyle\int_\mathcal{O} u\, dy$. *Its duality bracket is defined by*

$$F(u) = (F,u)_{(W_\#^{1,p}(\mathcal{O}))',W_\#^{1,p}(\mathcal{O})} = (F,u)_{(W^{1,p}(\mathcal{O}))',W^{1,p}(\mathcal{O})}, \ \forall u \in W_\#^{1,p}(\mathcal{O}).$$

Furthermore, by the Poincaré-Wirtinger's inequality, the Banach space $W_\#^{1,p}$ *has the following norm:*

$$\|u\|_{W_\#^{1,p}(\mathcal{O})} = \|\nabla u\|_{L^p(\mathcal{O})}, \forall u \in W_\#^{1,p}(\mathcal{O}).$$

Notation*: We denote* $W_\#^{1,2}(\mathcal{O})$ *by* $H_\#^1(\mathcal{O})$ *for* $p = 2$.

4.2. **Microscopic tridomain model.** We start by stating the weak formulation of the microscopic tridomain model as given in the following definition.

Definition 8 (Weak formulation of microscopic system)**.** *A weak solution to problem (4)-(7) is a collection* $(u_{i,\varepsilon}^1, u_{i,\varepsilon}^2, u_{e,\varepsilon}, w_\varepsilon^1, w_\varepsilon^2)$ *of functions satisfying the following conditions:*

(A) (Algebraic relation).

$$v_\varepsilon^k = (u_{i,\varepsilon}^k - u_{e,\varepsilon})|_{\Gamma_{\varepsilon,T}^k} \quad \text{a.e. on } \Gamma_{\varepsilon,T}^k, \text{ for } k = 1,2,$$
$$s_\varepsilon = (u_{i,\varepsilon}^1 - u_{i,\varepsilon}^2)|_{\Gamma_{\varepsilon,T}^{1,2}} \quad \text{a.e. on } \Gamma_{\varepsilon,T}^{1,2}.$$

(B) (Regularity).

$$u_{i,\varepsilon}^k \in L^2\left(0,T;H^1\left(\Omega_{i,\varepsilon}^k\right)\right), \quad u_e^\varepsilon \in L^2\left(0,T;H^1(\Omega_{e,\varepsilon})\right),$$
$$\int_{\Omega_{e,\varepsilon}} u_{e,\varepsilon}(t,x)\ dx = 0, \ \textit{for a.e. } t \in (0,T),$$
$$v_\varepsilon^k \in L^2\left(0,T;H^{1/2}\left(\Gamma_\varepsilon^k\right)\right) \cap L^r\left(\Gamma_{\varepsilon,T}^k\right), \ r \in (2,+\infty)$$
$$s_\varepsilon \in L^2\left(\Gamma_{\varepsilon,T}^{1,2}\right), \quad w_\varepsilon^k \in L^2(\Gamma_{\varepsilon,T}^k), \ k=1,2,$$
$$\partial_t v_\varepsilon^k, \ \partial_t w_\varepsilon^k \in L^2(\Gamma_{\varepsilon,T}^k) \ \textit{for } k=1,2, \quad \partial_t s_\varepsilon \in L^2(\Gamma_{\varepsilon,T}^{1,2}).$$

(C) (Initial conditions).

$$v_\varepsilon^k(0,x) = v_{0,\varepsilon}^k(x), \ w_\varepsilon^k(0,x) = w_{0,\varepsilon}^k(x) \quad \textit{a.e. on } \Gamma_{\varepsilon,T}^k,$$
$$\textit{and } s_\varepsilon(0,x) = s_{0,\varepsilon}(x) \quad \textit{a.e. on } \Gamma_{\varepsilon,T}^{1,2}.$$

(D) (Variational equations).

$$\begin{aligned}
&\sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\partial_t v_\varepsilon^k \psi_i^k \ d\sigma_x dt + \iint_{\Gamma_{\varepsilon,T}^{1,2}} \frac{\varepsilon}{2}\partial_t s_\varepsilon \Psi \ d\sigma_x dt + \sum_{k=1,2}\int_{\Omega_{i,\varepsilon,T}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k \cdot \nabla\varphi_i^k \ dxdt \\
&+ \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\mathcal{I}_{ion}\left(v_\varepsilon^k, w_\varepsilon^k\right)\psi_i^k \ d\sigma_x dt + \frac{1}{2}\iint_{\Gamma_{\varepsilon,T}^{1,2}} \varepsilon\mathcal{I}_{gap}(s_\varepsilon)\Psi \ d\sigma_x dt \\
&= \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\mathcal{I}_{app,\varepsilon}^k \psi_i^k \ d\sigma_x dt
\end{aligned} \tag{19}$$

$$\begin{aligned}
&\sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\partial_t v_\varepsilon^k \psi_e^k \ d\sigma_x dt - \int_{\Omega_{e,\varepsilon,T}} \mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon} \cdot \nabla\varphi_e \ dxdt \\
&+ \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\mathcal{I}_{ion}\left(v_\varepsilon^k, w_\varepsilon^k\right)\psi_e^k \ d\sigma_x dt = \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\mathcal{I}_{app,\varepsilon}^k \psi_e^k \ d\sigma_x dt
\end{aligned} \tag{20}$$

$$\iint_{\Gamma_{\varepsilon,T}^k} \partial_t w_\varepsilon^k e^k \ d\sigma_x dt = \iint_{\Gamma_{\varepsilon,T}^k} H\left(v_\varepsilon^k, w_\varepsilon^k\right) e^k \ d\sigma_x dt \tag{21}$$

for all $\varphi_i^k \in L^2\left(0,T;H^1\left(\Omega_{i,\varepsilon}^k\right)\right)$, $\varphi_e \in L^2\left(0,T;H^1(\Omega_{e,\varepsilon})\right)$ *with*

- $\psi^k = \psi_i^k - \psi_e^k := \left(\varphi_i^k - \varphi_e\right)|_{\Gamma_{\varepsilon,T}^k} \in L^2\left(0,T;H^{1/2}\left(\Gamma_\varepsilon^k\right)\right) \cap L^r\left(\Gamma_{\varepsilon,T}^k\right)$ *for* $k=1,2$,
- $\Psi = \Psi_i^1 - \Psi_i^2 := \left(\varphi_i^1 - \varphi_i^2\right)|_{\Gamma_{\varepsilon,T}^{1,2}} \in L^2(\Gamma_{\varepsilon,T}^{1,2})$,
- $e^k \in L^2(\Gamma_{\varepsilon,T}^k)$ *for* $k=1,2$.

Then, the existence of the weak solution for the microscopic tridomain problem (4)-(7) is given in the following theorem whose proof is the main issue of the article [5], by using the Faedo-Galerkin method.

Theorem 9 (Microscopic Tridomain Model)**.** *Assume that the conditions* (6)-(11) *hold. Then, System* (4)-(7) *possesses a unique weak solution in the sense of Definition 8 for every fixed* $\varepsilon > 0$.

Furthermore, this solution verifies the following energy estimates: there exists constants C_1, C_2, C_3, C_4 *independent of* ε *such that:*

$$\sum_{k=1,2}\left\|\sqrt{\varepsilon}v_\varepsilon^k\right\|^2_{L^\infty(0,T;L^2(\Gamma_\varepsilon^k))} + \sum_{k=1,2}\left\|\sqrt{\varepsilon}w_\varepsilon^k\right\|^2_{L^\infty(0,T;L^2(\Gamma_\varepsilon^k))} + \left\|\sqrt{\varepsilon}s_\varepsilon\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^{1,2})\right)} \le C_1, \tag{22}$$

$$\sum_{k=1,2} \left\|u_{i,\varepsilon}^k\right\|_{L^2\left(0,T;H^1\left(\Omega_{i,\varepsilon}^k\right)\right)} + \left\|u_e^\varepsilon\right\|_{L^2(0,T;H^1(\Omega_{e,\varepsilon}))} \leq C_2, \tag{23}$$

$$\sum_{k=1,2} \left\|\varepsilon^{1/r} v_\varepsilon^k\right\|_{L^r(\Gamma_{\varepsilon,T}^k)} \leq C_3 \text{ and } \sum_{k=1,2} \left\|\varepsilon^{(r-1)/r} \mathrm{I}_{a,ion}(v_\varepsilon^k)\right\|_{L^{r/(r-1)}(\Gamma_{\varepsilon,T}^k)} \leq C_4. \tag{24}$$

Moreover, if $v_{\varepsilon,0}^k \in H^{1/2}(\Gamma_\varepsilon^k) \cap L^r(\Gamma_\varepsilon^k)$, $k = 1, 2$, *then there exists a constant* C_5 *independent of* ε *such that:*

$$\sum_{k=1,2} \left\|\sqrt{\varepsilon}\partial_t v_\varepsilon^k\right\|^2_{L^2(\Gamma_{\varepsilon,T}^k)} + \sum_{k=1,2} \left\|\sqrt{\varepsilon}\partial_t w_\varepsilon^k\right\|^2_{L^2(\Gamma_{\varepsilon,T}^k)} + \left\|\sqrt{\varepsilon}\partial_t s_\varepsilon\right\|^2_{L^2(\Gamma_{\varepsilon,T}^{1,2})} \leq C_5. \tag{25}$$

By summing the two first equations in (19)-(21) and since $\mathcal{I}_{ion}(v_\varepsilon^k, w_\varepsilon^k) = \mathrm{I}_{a,ion}(v_\varepsilon^k) + \mathrm{I}_{b,ion}(w_\varepsilon^k)$, we can rewrite the weak formulation as follows:

$$\begin{aligned}
&\sum_{k=1,2} \iint_{\Gamma_{\varepsilon,T}^k} \varepsilon \partial_t v_\varepsilon^k \psi^k \, d\sigma_x dt + \frac{1}{2} \iint_{\Gamma_{\varepsilon,T}^{1,2}} \varepsilon \partial_t s_\varepsilon \Psi \, d\sigma_x dt \\
&+ \sum_{k=1,2} \iint_{\Omega_{i,\varepsilon,T}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k \cdot \nabla \varphi_i^k \, dxdt + \iint_{\Omega_{e,\varepsilon,T}} \mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon} \cdot \nabla \varphi_e \, dxdt \\
&+ \sum_{k=1,2} \iint_{\Gamma_{\varepsilon,T}^k} \varepsilon \mathrm{I}_{a,ion}\left(v_\varepsilon^k\right) \psi^k \, d\sigma_x dt + \sum_{k=1,2} \iint_{\Gamma_{\varepsilon,T}^k} \varepsilon \mathrm{I}_{b,ion}\left(w_\varepsilon^k\right) \psi^k \, d\sigma_x dt \\
&+ \frac{1}{2} \iint_{\Gamma_{\varepsilon,T}^{1,2}} \varepsilon \mathcal{I}_{gap}\left(s_\varepsilon\right) \Psi \, d\sigma_x dt = \sum_{k=1,2} \iint_{\Gamma_{\varepsilon,T}^k} \varepsilon \mathcal{I}_{app,\varepsilon}^k \psi^k \, d\sigma_x dt,
\end{aligned} \tag{26}$$

$$\iint_{\Gamma_{\varepsilon,T}^k} \partial_t w_\varepsilon^k e^k \, d\sigma_x dt = \iint_{\Gamma_{\varepsilon,T}^k} H\left(v_\varepsilon^k, w_\varepsilon^k\right) e^k \, d\sigma_x dt. \tag{27}$$

5. Unfolding Homogenization Method

Our derivation of the tridomain model is based on a new approach describing not only the electrical activity but also the effect of the cell membrane and gap junctions in the heart tissue. Our goal in this section is to describe the asymptotic behavior, as $\varepsilon \to 0$, of the solution $(u_{i,\varepsilon}^1, u_{i,\varepsilon}^2, u_{e,\varepsilon}, w_\varepsilon^1, w_\varepsilon^2)$ given by System (4)-(7). We do this by following a three-steps procedure: In Step 5.1, the weak formulation of the microscopic tridomain model (4)-(7) is written by another one, called "unfolded" formulation, based on the unfolding operators stated in the previous part. As Step 5.2, we can pass to the limit as $\varepsilon \to 0$ in the unfolded formulation using some a priori estimates and compactness argument to get the corresponding homogenization equation. In Step 5.3, we take a special form of test functions to obtain finally the macroscopic tridomain model.

5.1. **Unfolded formulation of the microscopic tridomain model.** Based on the properties of the unfolding operators, we rewrite the weak formulation (26)-(27) in the "unfolded" form. First, we denote by E_i with $i = 1, \ldots, 5$ the terms of the equation (26) which is rewritten as follows (to respect the order):

$$E_1 + E_2 + E_3 + E_4 + E_5 + E_6 + E_7 = E_8.$$

Using property (4) of Proposition 5, then the first and second term of (26) is rewritten as follows:

$$\begin{aligned}
E_1 &= \sum_{k=1,2} \iint_{\widehat{\Gamma}^k_{\varepsilon,T}} \varepsilon \partial_t v^k_\varepsilon \psi^k \, d\sigma_x dt + \sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \partial_t v^k_\varepsilon \psi^k \, d\sigma_x dt \\
&= \frac{1}{|Y|} \sum_{k=1,2} \iiint_{\Omega_T\times\Gamma^k} \mathcal{T}^{b,k}_\varepsilon(\partial_t v^k_\varepsilon)\mathcal{T}^{b,k}_\varepsilon(\psi^k) \, dx d\sigma_y dt + \sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \partial_t v^k_\varepsilon \psi^k \, d\sigma_x dt \\
&:= J_1 + R_1.
\end{aligned}$$

$$\begin{aligned}
E_2 &= \frac{1}{2} \iint_{\widehat{\Gamma}^{1,2}_{\varepsilon,T}} \varepsilon \partial_t s_\varepsilon \Psi \, d\sigma_x dt + \frac{1}{2} \iint_{\Gamma^{1,2}_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \partial_t s_\varepsilon \Psi \, d\sigma_x dt \\
&= \frac{1}{2\,|Y|} \iiint_{\Omega_T\times\Gamma^{1,2}} \mathcal{T}^{b,1,2}_\varepsilon(\partial_t s_\varepsilon)\mathcal{T}^{b,1,2}_\varepsilon(\Psi) \, dx d\sigma_y dt + \frac{1}{2} \iint_{\Gamma^{1,2}_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \partial_t s_\varepsilon \Psi \, d\sigma_x dt \\
&:= J_2 + R_2.
\end{aligned}$$

Similarly, we rewrite the third and fourth term using the property (3) of Proposition 5:

$$\begin{aligned}
E_3 &= \frac{1}{|Y|} \sum_{k=1,2} \iiint_{\Omega_T\times Y^k_i} \mathcal{T}^{i,k}_\varepsilon(\mathrm{M}^\varepsilon_i)\mathcal{T}^{i,k}_\varepsilon(\nabla u^k_{i,\varepsilon})\mathcal{T}^{i,k}_\varepsilon(\nabla\varphi^k_i) \, dx dy dt \\
&\quad + \sum_{k=1,2} \iint_{\Lambda^k_{i,\varepsilon,T}} \mathrm{M}^\varepsilon_i \nabla u^k_{i,\varepsilon} \cdot \nabla\varphi^k_i \, dx dt \\
&:= J_3 + R_3 \\
E_4 &= \frac{1}{|Y|} \iiint_{\Omega_T\times Y_e} \mathcal{T}^e_\varepsilon(\mathrm{M}^\varepsilon_e)\mathcal{T}^e_\varepsilon(\nabla u_{e,\varepsilon})\mathcal{T}^e_\varepsilon(\nabla\varphi_e) \, dx dy dt \\
&\quad + \iint_{\Lambda_{e,\varepsilon,T}} \mathrm{M}^\varepsilon_e \nabla u_{e,\varepsilon} \cdot \nabla\varphi_e \, dx dt \\
&:= J_4 + R_4
\end{aligned}$$

Due to the form of $\mathrm{I}_{\ell,ion}$, we use the property (2)-(4) of Proposition 5 to obtain $\mathcal{T}^{b,k}_\varepsilon\left(\mathrm{I}_{\ell,ion}(\cdot)\right) = \mathrm{I}_{\ell,ion}\left(\mathcal{T}^{b,k}_\varepsilon(\cdot)\right)$ for $\ell = a, b$ and $k = 1, 2$. Thus, we arrive to:

$$\begin{aligned}
E_5 &= \frac{1}{|Y|} \sum_{k=1,2} \iiint_{\Omega_T\times\Gamma^k} \mathcal{T}^{b,k}_\varepsilon\left(\mathrm{I}_{a,ion}(v^k_\varepsilon)\right)\mathcal{T}^{b,k}_\varepsilon(\psi^k) \, dx d\sigma_y dt + \sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \mathrm{I}_{a,ion}(v^k_\varepsilon)\psi^k \, d\sigma_x dt \\
&= \frac{1}{|Y|} \sum_{k=1,2} \iiint_{\Omega_T\times\Gamma^k} \mathrm{I}_{a,ion}\left(\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right)\mathcal{T}^{b,k}_\varepsilon(\psi^k) \, dx d\sigma_y dt + \sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \mathrm{I}_{a,ion}(v^k_\varepsilon)\psi^k \, d\sigma_x dt \\
&:= J_5 + R_5 \\
E_6 &= \frac{1}{|Y|} \sum_{k=1,2} \iiint_{\Omega_T\times\Gamma^k} \mathcal{T}^{b,k}_\varepsilon(\mathrm{I}_{b,ion}(w^k_\varepsilon))\mathcal{T}^{b,k}_\varepsilon(\psi^k) \, dx d\sigma_y dt + \sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \mathrm{I}_{b,ion}(w^k_\varepsilon)\psi^k \, d\sigma_x dt \\
&= \frac{1}{|Y|} \sum_{k=1,2} \iiint_{\Omega_T\times\Gamma^k} \mathrm{I}_{b,ion}\left(\mathcal{T}^{b,k}_\varepsilon(w^k_\varepsilon)\right)\mathcal{T}^{b,k}_\varepsilon(\psi^k) \, dx d\sigma_y dt + \sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \mathrm{I}_{b,ion}(w^k_\varepsilon)\psi^k \, d\sigma_x dt \\
&:= J_6 + R_6
\end{aligned}$$

Similarly, we can rewrite the last two terms of (26) by taking account the form of $\mathcal{I}_{gap}$ as follows:

$$\begin{aligned}
E_7 &= \frac{1}{2\,|Y|} \iiint_{\Omega_T\times\Gamma^{1,2}} \mathcal{I}_{gap}\left(\mathcal{T}^{b,1,2}_\varepsilon(s_\varepsilon)\right)\mathcal{T}^{b,1,2}_\varepsilon(\Psi) \, dx d\sigma_y dt + \frac{1}{2} \iint_{\Gamma^{1,2}_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}} \varepsilon \mathcal{I}_{gap}(s_\varepsilon)\Psi \, d\sigma_x dt \\
&:= J_7 + R_7
\end{aligned}$$

$$E_8 = \frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\mathcal{I}_{app,\varepsilon}^k)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt + \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k\cap\Lambda_{\varepsilon,T}}\varepsilon\mathcal{I}_{app,\varepsilon}^k\psi^k\,d\sigma_x dt$$
$$:= J_8 + R_8$$

Collecting the previous estimates, we readily obtain from (26) the following "unfolded" formulation:

(28)
$$\begin{aligned}
&\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\partial_t v_\varepsilon^k)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt + \frac{1}{2|Y|}\iiint_{\Omega_T\times\Gamma^{1,2}}\mathcal{T}_\varepsilon^{b,1,2}(\partial_t s_\varepsilon)\mathcal{T}_\varepsilon^{b,1,2}(\Psi)\,dxd\sigma_y dt\\
&\quad+\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times Y_i^k}\mathcal{T}_\varepsilon^{i,k}(\mathrm{M}_i^\varepsilon)\mathcal{T}_\varepsilon^{i,k}(\nabla u_{i,\varepsilon}^k)\mathcal{T}_\varepsilon^{i,k}(\nabla\varphi_i^k)\,dxdydt\\
&\quad+\frac{1}{|Y|}\iiint_{\Omega_T\times Y_e}\mathcal{T}_\varepsilon^{e}(\mathrm{M}_e^\varepsilon)\mathcal{T}_\varepsilon^{e}(\nabla u_{e,\varepsilon})\mathcal{T}_\varepsilon^{e}(\nabla\varphi_e)\,dxdydt\\
&\quad+\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\mathrm{I}_{a,ion}\left(\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt\\
&\quad+\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\mathrm{I}_{b,ion}\left(\mathcal{T}_\varepsilon^{b,k}(w_\varepsilon^k)\right)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt\\
&\quad+\frac{1}{2|Y|}\iiint_{\Omega_T\times\Gamma^{1,2}}\mathcal{I}_{gap}\left(\mathcal{T}_\varepsilon^{b,1,2}(s_\varepsilon)\right)\mathcal{T}_\varepsilon^{b,1,2}(\Psi)\,dxd\sigma_y dt\\
&=\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\mathcal{I}_{app,\varepsilon}^k)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt\\
&\quad+R_8-R_7-R_6-R_5-R_4-R_3-R_2-R_1
\end{aligned}$$

Similarly, the "unfolded" formulation of (27) is given by:

(29)
$$\begin{aligned}
&\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\partial_t w_\varepsilon^k)\mathcal{T}_\varepsilon^{b,k}(e^k)\,dxd\sigma_y dt\\
&-\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^k}H(\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k),\mathcal{T}_\varepsilon^{b,k}(w_\varepsilon^k))\mathcal{T}_\varepsilon^{b,k}(e^k)\,dxd\sigma_y dt\\
&=-\varepsilon\iint_{\Gamma_{\varepsilon,T}^k\cap\Lambda_{\varepsilon,T}}\partial_t w_\varepsilon^k e^k\,d\sigma_x dt+\varepsilon\iint_{\Gamma_{\varepsilon,T}^k\cap\Lambda_{\varepsilon,T}}H(v_\varepsilon^k,w_\varepsilon^k)e^k\,d\sigma_x dt\\
&:=R_9+R_{10}
\end{aligned}$$

5.2. **Convergence of the unfolded formulation.** In this part, we pass to the limit in (28)-(29). First, we prove that:

$$R_1,\cdots,R_{10}\underset{\varepsilon\to0}{\longrightarrow}0,$$

by making use of estimates (22)-(25). So, we prove that $R_3\to0$ when $\varepsilon\to0$ and the proof for the other terms is similar. First, by Cauchy-Schwarz inequality, one has

$$R_3=\sum_{k=1,2}\iint_{\Lambda_{i,\varepsilon,T}^k}\mathrm{M}_i^\varepsilon\nabla u_{i,\varepsilon}^k\cdot\nabla\varphi_i^k\,dxdt\le\sum_{k=1,2}\left\|\mathrm{M}_i^\varepsilon\nabla u_{i,\varepsilon}^k\right\|_{L^2(\Omega_{i,\varepsilon,T}^k)}\left(\iint_{\Lambda_{i,\varepsilon,T}^k}\left|\nabla\varphi_i^k\right|^2\,dxdt\right)^{1/2}.$$

In addition, we observe that $\left|\Lambda_{i,\varepsilon}^k\right| \to 0$ and $\nabla\varphi_i^k \in L^2(\Omega_{i,\varepsilon}^k)$. Consequently, by Lebesgue dominated convergence theorem, one gets for $k = 1, 2$:

$$\iint_{\Lambda_{i,\varepsilon}^k} \left|\nabla\varphi_i^k\right|^2 \to 0, \text{ as } \varepsilon \to 0.$$

Finally, by using Hölder's inequality, the result follows by making use of estimate (23) and assumption (6) on M_i^ε.

Let us now elaborate the convergence results of $J_1, \cdots, J_8$. Using property (5) of Proposition 5 and due to the regularity of test functions, we know that the following strong convergence hold:

$$\begin{aligned}
&\mathcal{T}_\varepsilon^{b,k}(\psi^k) \to \psi^k \text{ and } \mathcal{T}_\varepsilon^{b,k}(e^k) \to e^k \text{ strongly in } L^2(\Omega_T \times \Gamma^k)\\
&\mathcal{T}_\varepsilon^{b,1,2}(\Psi) \to \Psi \text{ strongly in } L^2(\Omega_T \times \Gamma^{1,2})
\end{aligned}$$

and

$$\begin{aligned}
\mathcal{T}_\varepsilon^{i,k}(\varphi_i^k) \to \varphi_i^k \text{ strongly in } L^2(\Omega_T \times Y_i^k),\\
\mathcal{T}_\varepsilon^{e}(\varphi_e) \to \varphi_e \text{ strongly in } L^2(\Omega_T \times Y_e).
\end{aligned}$$

Next, we want to use the a priori estimates (22)-(25) to verify that the remaining terms of the equations in the unfolded formulation (28)-(29) are weakly convergent. Using estimation (23), we deduce that there exist $u_i^k, u_e \in L^2\left(0,T; H^1(\Omega)\right)$, $\widehat{u}_i^k \in L^2\left(0,T; L^2\left(\Omega, H^1_{\#}(Y_i^k)\right)\right)$ for $k = 1, 2$ and $\widehat{u}_e \in L^2\left(0,T; L^2\left(\Omega, H^1_{\#}(Y_e)\right)\right)$ such that, up to a subsequence (see for instance Theorem 3.12 in [8]), the following convergences hold as ε goes to zero:

$$\begin{aligned}
&\mathcal{T}_\varepsilon^{i,k}(u_{i,\varepsilon}^k) \rightharpoonup u_i^k \text{ weakly in } L^2\left(0,T; L^2\left(\Omega \times Y_i^k\right)\right),\\
&\mathcal{T}_\varepsilon^{i,k}(\nabla u_{i,\varepsilon}^k) \rightharpoonup \nabla u_i^k + \nabla_y \widehat{u}_i^k \text{ weakly in } L^2(\Omega_T \times Y_i^k),
\end{aligned}$$

and

$$\begin{aligned}
&\mathcal{T}_\varepsilon^{e}(u_{e,\varepsilon}) \rightharpoonup u_e \text{ weakly in } L^2\left(0,T; L^2\left(\Omega \times Y_e\right)\right),\\
&\mathcal{T}_\varepsilon^{e}(\nabla u_{e,\varepsilon}) \rightharpoonup \nabla u_e + \nabla_y \widehat{u}_e \text{ weakly in } L^2(\Omega_T \times Y_i^k),
\end{aligned}$$

with the space $H^1_{\#}$ given by (18). Thus, since $\mathcal{T}_\varepsilon^{i,k}\left(\mathrm{M}_i^\varepsilon\right) \to \mathrm{M}_i$ a.e. in $\Omega \times Y_i^k$ for $k = 1, 2$ and $\mathcal{T}_\varepsilon^{e}\left(\mathrm{M}_e^\varepsilon\right) \to \mathrm{M}_e$ a.e. in $\Omega \times Y_e$, one obtains:

$$\begin{aligned}
J_3 &\underset{\varepsilon\to 0}{\longrightarrow} \frac{1}{|Y|} \sum_{k=1,2} \iiint_{\Omega_T \times Y_i^k} \mathrm{M}_i \left[\nabla u_i^k + \nabla_y \widehat{u}_i^k\right] \nabla\varphi_i^k \, dxdydt,\\
J_4 &\underset{\varepsilon\to 0}{\longrightarrow} \frac{1}{|Y|} \iiint_{\Omega_T \times Y_e} \mathrm{M}_e \left[\nabla u_e + \nabla_y \widehat{u}_e\right] \nabla\varphi_e \, dxdydt.
\end{aligned}$$

Furthermore, we need to establish the weak convergence of the unfolded sequences that corresponds to $v_\varepsilon^k, w_\varepsilon^k, s_\varepsilon$ and $\mathcal{I}_{app,\varepsilon}^k$ for $k = 1, 2$. In order to establish the convergence of $\mathcal{T}_\varepsilon^{b,k}(\partial_t v_\varepsilon^k)$, we use estimation (25) to get for $k = 1, 2$

$$\left\|\mathcal{T}_\varepsilon^{b,k}(\partial_t v_\varepsilon^k)\right\|_{L^2(\Omega_T \times \Gamma^k)} \le \varepsilon^{1/2} |Y|^{1/2} \left\|\partial_t v_\varepsilon^k\right\|_{L^2(\Gamma_{\varepsilon,T}^k)} \le C.$$

So there exists $V^k \in L^2\left(\Omega_T\right)$ such that $\mathcal{T}_\varepsilon^{b,k}(\partial_t v_\varepsilon^k) \rightharpoonup V^k$ weakly in $L^2(\Omega_T \times \Gamma^k)$ with $k = 1, 2$. By a classical integration argument, one can show that $V^k = \partial_t v^k$. Therefore, we deduce that

$$\mathcal{T}_\varepsilon^{b,k}(\partial_t v_\varepsilon^k) \rightharpoonup \partial_t v^k \text{ weakly in } L^2(\Omega_T \times \Gamma^k).$$

Thus, we obtain

$$J_1 = \frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k} \mathcal{T}_\varepsilon^{b,k}(\partial_t v_\varepsilon^k)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\ dxd\sigma_y dt$$
$$\xrightarrow[\varepsilon\to 0]{} \frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k} \partial_t v^k\psi^k\ dxd\sigma_y dt.$$

By the same strategy for the convergence of J_1, there exits $S\in L^2(\Omega_T)$ such that $\mathcal{T}_\varepsilon^{b,1,2}(\partial_t s_\varepsilon)\rightharpoonup S$ weakly in $L^2(\Omega_T\times\Gamma^{1,2})$. Similarly, we get $S=\partial_t s$. Thus, one has

$$J_2 = \frac{1}{2|Y|}\iiint_{\Omega_T\times\Gamma^{1,2}} \mathcal{T}_\varepsilon^{b,1,2}(\partial_t s_\varepsilon)\mathcal{T}_\varepsilon^{b,1,2}(\Psi)\ dxd\sigma_y dt$$
$$\xrightarrow[\varepsilon\to 0]{} \frac{1}{2|Y|}\iiint_{\Omega_T\times\Gamma^{1,2}} \partial_t s\Psi\ dxd\sigma_y dt.$$

Now, making use of estimate (22) with property (4) of Proposition 5, one has

$$\left\|\mathcal{T}_\varepsilon^{b,k}(w_\varepsilon^k)\right\|_{L^2(\Omega_T\times\Gamma^k)} \le \varepsilon^{1/2}|Y|^{1/2}\left\|w_\varepsilon^k\right\|_{L^2(\Gamma_{\varepsilon,T}^k)} \le C,$$
$$\left\|\mathcal{T}_\varepsilon^{b,1,2}(s_\varepsilon)\right\|_{L^2(\Omega_T\times\Gamma^{1,2})} \le \varepsilon^{1/2}|Y|^{1/2}\left\|s_\varepsilon\right\|_{L^2(\Gamma_{\varepsilon,T}^{1,2})} \le C.$$

Then, up to a subsequences,

$$\mathcal{T}_\varepsilon^{b,k}(w_\varepsilon^k)\rightharpoonup w^k \text{ weakly in } L^2(\Omega_T\times\Gamma^k),$$
$$\mathcal{T}_\varepsilon^{b,1,2}(s_\varepsilon)\rightharpoonup s \text{ weakly in } L^2(\Omega_T\times\Gamma^{1,2}).$$

So, by linearity of $\mathrm{I}_{b,ion}$ and of $\mathcal{I}_{gap}$ we have respectively:

$$J_6 = \frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k} \mathrm{I}_{b,ion}\left(\mathcal{T}_\varepsilon^{b,k}(w_\varepsilon^k)\right)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\ dxd\sigma_y dt$$
$$\xrightarrow[\varepsilon\to 0]{} \frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k} \mathrm{I}_{b,ion}(w^k)\psi^k\ dxd\sigma_y dt,$$
$$J_7 = \frac{1}{2|Y|}\iiint_{\Omega_T\times\Gamma^{1,2}} \mathrm{I}_{gap}\left(\mathcal{T}_\varepsilon^{b,1,2}(s_\varepsilon)\right)\mathcal{T}_\varepsilon^{b,1,2}(\Psi)\ dxd\sigma_y dt$$
$$\xrightarrow[\varepsilon\to 0]{} \frac{1}{2|Y|}\iiint_{\Omega_T\times\Gamma^{1,2}} \mathcal{I}_{gap}(s)\Psi\ dxd\sigma_y dt.$$

Similarly, exploiting assumption (10) on $\mathcal{I}_{app,\varepsilon}^k$, we obtain the following convergence:

$$J_8 = \frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k} \mathcal{T}_\varepsilon^{b,k}(\mathcal{I}_{app,\varepsilon}^k)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\ dxd\sigma_y dt$$
$$\xrightarrow[\varepsilon\to 0]{} \frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k} \mathcal{I}_{app}^k\psi^k\ dxd\sigma_y dt.$$

Remark 10. *Proceeding exactly as in [4], we prove that the limits v^k and s coincide respectively with $u_i^k - u_e$ for $k=1,2$ and $u_i^1 - u_i^2$. Furthermore, since we have assumed that the initial data $v_{0,\varepsilon}^k, w_{0,\varepsilon}^k$ for $k=1,2$ and $s_{0,\varepsilon}$ introduced in (7), are also uniformly bounded in the adequate norm (see assumption (11)). Then, using the weak formulation (28)-(29), we prove similarly that $v^k(0,x)=v_0^k(x)$ a.e. on Ω, since, by construction, $v_\varepsilon^k(0,x)=v_{0,\varepsilon}^k(x)$ a.e. on Γ_ε^k for $k=1,2$. The same argument holds for the initial condition of w_ε^k for $k=1,2$ and of s_ε.*

It remains to obtain the limit of J_5 containing the ionic function $\mathrm{I}_{a,ion}$. By the regularity of ψ^k, it sufficient to show the weak convergence of $\mathrm{I}_{a,ion}\left(\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right)$ to $\mathrm{I}_{a,ion}(v^k)$ in $L^2(\Omega_T\times\Gamma^k)$. Due to the non-linearity of $\mathrm{I}_{a,ion}$, the weak convergence will not be enough. It is difficult to pass to the limit of this term on the microscopic membrane surface. Therefore, we need the strong convergence of $\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)$ to v^k in $L^2(\Omega_T\times\Gamma^k)$ for $k=1,2$ that we obtain by using Kolmogorov-Riesz type compactness criterion that can be found as Corollary 2.5 in [11]:

Proposition 11 (Kolmogorov-Riesz type compactness result)**.** *Let $\Omega\subset\mathbb{R}^d$ be an open and bounded set. Let $F\subset L^p(\Omega,B)$ for a Banach space B and $p\in[1;+\infty)$. For $f\in F$ and $\xi\in\mathbb{R}^d$, we define $\tau_\xi f(x):=f(x+\xi)$. Then F is relatively compact in $L^p(\Omega,B)$ if and only if*

(i) for every measurable set $A\subset\Omega$ the set $\{\int_A f dx\ :\ f\in F\}$ is relatively compact in B,

(ii) for all $\lambda>0$, $\xi\in\mathbb{R}^d$ and $\xi_i\geq 0$, $i=1,\dots,d$, there holds

$$\sup_{f\in F}\|\tau_\xi f-f\|_{L^p\left(\Omega_\lambda^\xi,B\right)}\to 0,\ \text{for } h\to 0,$$

where $\Omega_\lambda^\xi:=\{x\in\Omega_\lambda : x+\xi\in\Omega_\lambda\}$ and $\Omega_\lambda:=\{x\in\Omega : dist(x,\partial\Omega)>\lambda\}$,

(iii) for $\lambda>0$, there holds $\sup_{f\in F}\int_{\Omega\setminus\Omega_\lambda}|f(x)|^p\,dx\to 0$ for $\lambda\to 0$.

To cope with this, in the following lemma, we derive the convergence of the nonlinear term $\mathrm{I}_{a,ion}$:

Lemma 12. *The following convergence holds for $k=1,2$:*

$$\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\to v^k\ \text{strongly in } L^2(\Omega_T\times\Gamma^k),$$

as $\varepsilon\to 0$. Moreover, we have for $k=1,2$:

$$\mathrm{I}_{a,ion}\left(\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right)\to\mathrm{I}_{a,ion}(v^k)\ \text{strongly in } L^q(\Omega_T\times\Gamma^k),\ \forall q\in[1,r/(r-1)),$$

as $\varepsilon\to 0$.

Proof. We follow the same idea to the proof of Lemma 5.3 in [6]. The proof of the first convergence is based on the Kolmogorov compactness criterion 11. So, we want to verify that the sequence $\{\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\}_{\varepsilon>0}$ of unfolded membrane potentials satisfies the assumptions of Proposition 11 with $B=L^2\left(0,T;L^2(\Gamma^k)\right)$ for $k=1,2$ and $p=2$. It is carried out by proving three conditions:

(i) Let $A\subset\Omega$ a measurable set. We define the sequence $\{v_{A,\varepsilon}^k\}_{\varepsilon>0}$ as follows:

$$v_{A,\varepsilon}^k(t,y):=\int_A\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)(t,x,y)\,dx,\ \text{for a.e. } (t,y)\in(0,T)\times\Gamma^k\ (k=1,2).$$

It remains to show that the sequence $v_{A,\varepsilon}^k\in L^2\left(0,T;H^{1/2}(\Gamma^k)\right)$ is relatively compact in the space $L^2\left(0,T;L^2(\Gamma^k)\right)$ for $k=1,2$. Since the embedding $H^{1/2}(\Gamma^k)\hookrightarrow L^2(\Gamma^k)$ is compact, we have to show that the sequence $v_{A,\varepsilon}^k$ is bounded in $L^2\left(0,T;H^{1/2}(\Gamma^k)\right)\cap H^1\left(0,T;L^2(\Gamma^k)\right)$ with $k=1,2$. We first observe that for $k=1,2$

$$\begin{aligned}\left\|v_{A,\varepsilon}^k\right\|_{H^{1/2}(\Gamma^k)}^2&=\int_{\Gamma^k}\left|\int_A\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)(t,x,y)\,dx\right|^2 d\sigma_y\\&\quad+\iint_{\Gamma^k\times\Gamma^k}\int_A\frac{\left|\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)(t,x,y_1)-\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)(t,x,y_2)\right|^2}{|y_1-y_2|^{d+1}}\,dx d\sigma_{y_1}d\sigma_{y_2}\\&:=\left\|v_{A,\varepsilon}^k\right\|_{L^2(\Gamma^k)}^2+\left\|v_{A,\varepsilon}^k\right\|_{H_0^{1/2}(\Gamma^k)}^2.\end{aligned}$$

In view of Fubini theorem, Cauchy-Schwarz inequality and estimate (22), it follows that for $k=1,2$

$$\begin{aligned}\left\|v_{A,\varepsilon}^k\right\|^2_{L^2(\Gamma_T^k)} &\leq C\int_0^T\int_\Omega\int_{\Gamma^k}\left|\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)(t,x,y)\right|^2 d\sigma_y dxdt\\ &\leq C\left\|\sqrt{\varepsilon}v_\varepsilon^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})}\leq C.\end{aligned}$$

Next, we only need to bound the $H_0^{1/2}$ semi-norm and this is done as follows. Since $v_\varepsilon=(u_i^\varepsilon-u_e^\varepsilon)\,|\Gamma_\varepsilon^k$ for $k=1,2$, we use again Fubini theorem and Jensen inequality together with the trace inequality in Remark 6 to obtain

$$\begin{aligned}\left\|v_{A,\varepsilon}^k\right\|^2_{H_0^{1/2}(\Gamma^k)} &\leq C\left[\int_\Omega\left\|\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right\|^2_{H_0^{1/2}(\Gamma^y)}dxdt\right]\\ &\leq C\left[\left\|u_{i,\varepsilon}^k\right\|^2_{L^2(\Omega_{i,\varepsilon}^k)}+\varepsilon^2\left\|\nabla u_{i,\varepsilon}^k\right\|^2_{L^2(\Omega_{i,\varepsilon}^k)}+\left\|u_{e,\varepsilon}\right\|^2_{L^2(\Omega_{e,\varepsilon})}+\varepsilon^2\left\|\nabla u_{e,\varepsilon}\right\|^2_{L^2(\Omega_{e,\varepsilon})}\right].\end{aligned}$$

Hence, integrating over $(0,T)$ and using the a priori estimates (23), we have showed that the sequence $v_{A,\varepsilon}^k$ is bounded in $L^2\left(0,T;H^{1/2}(\Gamma^k)\right)$ for $k=1,2$.
By a similar argument and making use of the estimate (25) on $\varepsilon^{1/2}\partial_t v_\varepsilon^k$, we can also show that

$$\left\|\partial_t v_{A,\varepsilon}^k\right\|_{L^2(\Gamma_T^k)}\leq C,\ \text{with } k=1,2.$$

Finally, we deduce that the sequence $v_{A,\varepsilon}^k$ is bounded in $L^2\left(0,T;H^{1/2}(\Gamma^k)\right)\cap H^1\left(0,T;L^2(\Gamma^k)\right)$ and due to the Aubin-Lions Lemma the sequence is relatively compact in $L^2\left(0,T;L^2(\Gamma^k)\right)$ with $k=1,2$.

(ii) Due to the decomposition of the domain given in Subsection 4.1, Ω can always be represented by a union of scaled and translated reference cells. Fix $\varepsilon>0$ and let $k\in\Xi_\varepsilon$, be an index set such that

$$\widehat{\Omega}^\varepsilon=\bigcup_{h\in\Xi_\varepsilon}\varepsilon(h_\ell+Y),\ \text{with } h_\ell:=(h_1\ell_1^{\text{mes}},\ldots,h_d\ell_d^{\text{mes}}).$$

Note that $x\in\varepsilon(h_\ell+Y)\Leftrightarrow\left[\frac{x}{\varepsilon}\right]_Y=h_\ell$. For every fixed $h\in\Xi_\varepsilon$, we subdivide the cell $\varepsilon(h_\ell+Y)$ into subsets $\varepsilon\left(h_\ell+Y\right)^\sigma$ with $\sigma\in\{0,1\}^d$, defined as follows

$$\varepsilon(k_\ell+Y)^\sigma:=\left\{x\in\varepsilon(k_\ell+Y):\varepsilon\left[\frac{x+\varepsilon\left\{\frac{\xi}{\varepsilon}\right\}_Y}{\varepsilon}\right]_Y=\varepsilon(h_\ell+\sigma)\right\},$$

for a given $\xi\in\mathbb{R}^d$. It holds $\varepsilon(h_\ell+Y)=\bigcup\limits_{\sigma\in\{0,1\}^d}\varepsilon(h_\ell+Y)^\sigma$.
We use the same notation as in Proposition 11. Now, we compute for $k=1,2$ the following norm

$$\begin{aligned}\left\|\tau_\xi\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)-\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right\|^2_{L^2\left((0,T)\times\Omega_\lambda^\xi\times\Gamma^k\right)} &= \left\|\tau_\xi\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)-\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right\|^2_{L^2\left((0,T)\times(\Omega_\lambda^\xi\cap\widehat{\Omega}^\varepsilon)\times\Gamma^k\right)}\\ &\quad+\left\|\tau_h\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)-\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right\|^2_{L^2\left((0,T)\times(\Omega_\lambda^\xi\setminus\widehat{\Omega}^\varepsilon)\times\Gamma^k\right)}\\ &:=E_{a,\varepsilon}^\xi+E_{b,\varepsilon}^\xi.\end{aligned}$$

Proceeding in a similar way to [10, 18], we first estimate $E^{\xi}_{1,\varepsilon}$ using the above decomposition of the domain as follows:

$$\begin{aligned}
E^{\xi}_{a,\varepsilon} &= \sum_{h\in\Xi_\varepsilon}\int_0^T\int_{\varepsilon(h_\ell+Y)}\int_{\Gamma^k}\left|v^k_\varepsilon\left(t,\varepsilon\left[\frac{x+\xi}{\varepsilon}\right]_Y+\varepsilon y\right)-v^k_\varepsilon\left(t,\varepsilon\left[\frac{x}{\varepsilon}\right]_Y+\varepsilon y\right)\right|^2 d\sigma_y dxdt\\
&= \sum_{h\in\Xi_\varepsilon}\sum_{\sigma\in\{0,1\}^d}\int_0^T\int_{\varepsilon(h_\ell+Y)^\sigma}\int_{\Gamma^k}\left|v^k_\varepsilon\left(t,\varepsilon\left(h_\ell+\sigma+\left[\frac{\xi}{\varepsilon}\right]_Y\right)+\varepsilon y\right)-v^k_\varepsilon\left(t,\varepsilon h_\ell+\varepsilon y\right)\right|^2 d\sigma_y dxdt\\
&\le \sum_{h\in\Xi_\varepsilon}\sum_{\sigma\in\{0,1\}^d}\int_0^T\int_{\varepsilon(h_\ell+Y)}\int_{\Gamma^k}\left|v^k_\varepsilon\left(t,\varepsilon\left(h_\ell+\sigma+\left[\frac{\xi}{\varepsilon}\right]_Y\right)+\varepsilon y\right)-v^k_\varepsilon\left(t,\varepsilon h_\ell+\varepsilon y\right)\right|^2 d\sigma_y dxdt\\
&\le \sum_{\sigma\in\{0,1\}^d}\int_0^T\int_{\widehat{\Omega}^\varepsilon}\int_{\Gamma^k}\left|\mathcal{T}^{b,k}_\varepsilon v^k_\varepsilon\left(t,x+\varepsilon\left(\sigma+\left[\frac{\xi}{\varepsilon}\right]_Y\right),y\right)-\mathcal{T}^{b,k}_\varepsilon v^k_\varepsilon\left(t,x,y\right)\right|^2 d\sigma_y dxdt,
\end{aligned}$$

which by using the integration formula (4) (for $p=2$) of Proposition 5 is equal to

$$\sum_{\sigma\in\{0,1\}^d}\varepsilon|Y|\int_0^T\int_{\Gamma^k_\varepsilon}\left|v^k_\varepsilon\left(t,x+\varepsilon\left(\sigma+\left[\frac{\xi}{\varepsilon}\right]_Y\right)\right)-v^k_\varepsilon\left(t,x\right)\right|^2 d\sigma_y dt.$$

For a given small $\gamma>0$, we can choose an ε small enough such that $\left|\varepsilon\sigma+\varepsilon\left[\frac{\xi}{\varepsilon}\right]_Y\right|<\gamma$. This amounts to saying that in order to estimate $E^{\xi}_{a,\varepsilon}$, it is sufficient to obtain estimates for given $\ell\in\mathbb{Z}^d$, $|\varepsilon\ell|<\gamma$ of

$$\left\|v^k_\varepsilon\left(t,x+\varepsilon\ell\right)-v^k_\varepsilon\left(t,x\right)\right\|^2_{L^2\left((0,T)\times\Gamma^k_{\varepsilon,Q}\right)}, \tag{30}$$

where $\Gamma_{\varepsilon,Q}=\Gamma_\varepsilon\cap Q$ with $Q\subset\Omega$ an open set.

In order to estimate the norm (30), we test the variational equation the weak formulation (26) with $\varphi^k_i=\eta^2\left(\tau_{\varepsilon\ell}u^\varepsilon_{i,\varepsilon}-u^k_{i,\varepsilon}\right)$ for $k=1,2$ and $\varphi_e=\eta^2\left(\tau_{\varepsilon\ell}u_{e,\varepsilon}-u_{e,\varepsilon}\right)$, where $\eta\in D(Q)$ is a cut-off function with $0\le\eta\le1$, $\eta=1$ in Q and zero outside a small neighborhood Q' of Q. Proceeding exactly as Lemma 5.2 in [6], Gronwall's inequality and the assumptions on the initial data give the following result:

$$\varepsilon\left\|v_\varepsilon\left(t,x+\varepsilon\ell\right)-v_\varepsilon\left(t,x\right)\right\|^2_{L^2((0,T)\times\Gamma_{\varepsilon,Q})}\le C\varepsilon\left|\ell\right|,$$

where C is a positive constant. Then, we obtain by using the previous estimate

$$E^{\xi}_{a,\varepsilon}\le C\left(|\xi|+\varepsilon\right). \tag{31}$$

Hence, we can deduce that $E^h_{a,\varepsilon}\to0$ as $\xi\to0$ uniformly in ε, as in [12]. Indeed, to prove that

$$\forall\rho>0,\exists\mu>0 \text{ such that for every } \varepsilon \text{ tends to } 0^+,\ \forall\xi,\ |\xi|\le\mu\Rightarrow E^{\xi}_{a,\varepsilon}<\rho, \tag{32}$$

one identifies two cases:

(a) For $0<\varepsilon<\dfrac{\rho}{2C}$: take $\mu=\dfrac{\rho}{2C}$, then, from (31), we get that condition (32) holds for $|\xi|\le\mu$.

(b) For $\dfrac{\rho}{2C}<\varepsilon<1$: we remark that since ε tends to 0^+, there are only finitely many elements ε in the interval $(\frac{\rho}{2C},1)$, say $\{\varepsilon_n\}_{n=1}^N$ with $N\in\mathbb{N}$, $N<\infty$. Moreover, by the continuity of translations in the mean of L^2-functions, for every n, $\exists\mu_n=\mu(\varepsilon_n)$ such that $\forall\xi,\ |\xi|\le\mu_n$, condition (32) holds. Thus choosing $\mu=\min\{\frac{\rho}{2C},\mu_1,\dots,\mu_N\}$ together with the argument for the translation with respect to time, property (32) is proved.

It easy to check that

$$E^{\xi}_{b,\varepsilon} = \left\|\tau_\xi \mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right\|^2_{L^2\left((0,T)\times(\Omega^\xi_\lambda\setminus\widehat{\Omega}^\varepsilon)\times\Gamma^k\right)} \leq \left\|\tau_\xi \mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right\|^2_{L^2\left((0,T)\times(\Omega_\lambda\setminus\widehat{\Omega}^\varepsilon)\times\Gamma^k\right)}.$$

Hence, we can deduce that $E^{\xi}_{b,\varepsilon} \to 0$ as $\xi \to 0$ uniformly in ε. Indeed, to prove that

$$\forall \rho > 0, \exists \mu > 0 \text{ such that } \forall \varepsilon > 0,\ \forall \xi,\ |\xi| \leq \mu \Rightarrow E^{\xi}_{b,\varepsilon} < \rho, \tag{33}$$

one identifies two cases:

- (a) For ε small enough, say $\varepsilon < \varepsilon_0$, $\Omega_\lambda \subset \widehat{\Omega}^\varepsilon$, then $E^{\xi}_{b,\varepsilon} = 0$.
- (b) For $\varepsilon_0 < \varepsilon < 1$: we remark that since ε tends to 0^+, there are only finitely many elements ε in the interval $(\varepsilon_0, 1)$, say $\{\varepsilon_n\}_{n=1}^N$ with $N \in \mathbb{N}$, $N < \infty$. Moreover, by the continuity of translations in the mean of L^2-functions, for every n, $\exists \mu_n = \mu(\varepsilon_n)$ such that $\forall \xi,\ |\xi| \leq \mu_n$, condition (33) holds. Thus choosing $\mu = \min\{\frac{\rho}{2C}, \mu_1, \ldots, \mu_N\}$ together with the argument for the translation with respect to time, property (33) is proved.

This ends the proof of the condition (ii) in Proposition 11.

(iii) The last condition follows from the a priori estimate (24). Indeed, we have for $k = 1, 2$:

$$\int_0^T \int_{\Omega\setminus\Omega_\lambda} \left|\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right|^2 dxdt \leq |\Omega \setminus \Omega_\lambda|^{\frac{r-2}{r}} \left(\int_{\Omega_T} \left|\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right|^r dxdt\right)^{\frac{2}{r}} \leq C\,|\Omega \setminus \Omega_\lambda|^{\frac{r-2}{r}}.$$

The conditions (i)-(iii) imply that the Kolmogorov criterion for $\mathcal{T}^{b,k}_\varepsilon(v_\varepsilon)$ holds true in $L^2(\Omega_T \times \Gamma^k)$ for $k = 1, 2$. This concludes the proof of the first convergence in our Lemma.

It remains to prove the second convergence which will be done as follows. Note that from the structure of $\mathrm{I}_{a,ion}$ and using property (2) in Proposition 5, we have

$$\mathcal{T}^{b,k}_\varepsilon\left(\mathrm{I}_{a,ion}(v^k_\varepsilon)\right) = \mathrm{I}_{a,ion}\left(\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right), \text{ for } k = 1, 2.$$

Due to the strong convergence of $\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)$ in $L^2(\Omega_T \times \Gamma^y)$, we can extract a subsequence, such that $\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon) \to v^k$ a.e. in $\Omega_T \times \Gamma^k$ with $k = 1, 2$. Since $\mathrm{I}_{a,ion}$ is continuous, we have

$$\mathrm{I}_{a,ion}\left(\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right) \to \mathrm{I}_{1,ion}(v^k) \text{ a.e. in } \Omega_T \times \Gamma^y.$$

Further, we use estimate (24) with property (4) of Proposition 5 to obtain for $k = 1, 2$

$$\left\|\mathcal{T}^{b,k}_\varepsilon\left(\mathrm{I}_{a,ion}(v^k_\varepsilon)\right)\right\|_{L^{r/(r-1)}(\Omega_T\times\Gamma^y)} \leq |Y|^{(r-1)/r} \left\|\varepsilon^{(r-1)/r}\mathrm{I}_{a,ion}(v^k_\varepsilon)\right\|_{L^{r/(r-1)}(\Gamma_{\varepsilon,T})} \leq C.$$

Hence, using a classical result (see Lemma 1.3 in [16]):

$$\mathrm{I}_{a,ion}\left(\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right) \rightharpoonup \mathrm{I}_{a,ion}(v^k) \text{ weakly in } L^{r/(r-1)}(\Omega_T \times \Gamma^k) \text{ with } k = 1, 2.$$

Moreover, we obtain, using Vitali's Theorem, the strong convergence of $\mathrm{I}_{a,ion}\left(\mathcal{T}^{b,k}_\varepsilon(v^k_\varepsilon)\right)$ to $\mathrm{I}_{a,ion}(v^k)$ in $L^q(\Omega_T \times \Gamma^k)$, $\forall q \in [1, r/(r-1))$ and $k = 1, 2$. This finishes the proof of our Lemma. □

Finally, we pass to the limit when $\varepsilon \to 0$ in the unfolded formulation (28) to obtain the following limiting problem:

$$
\begin{aligned}
&\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\partial_t v^k\psi^k\ dxd\sigma_y dt+\frac{1}{2\,|Y|}\iiint_{\Omega_T\times\Gamma^{1,2}}\partial_t s\Psi\ dxd\sigma_y dt\\
&\quad+\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times Y_i^k}\mathrm{M}_i\left[\nabla u_i^k+\nabla_y\widehat{u}_i^k\right]\nabla\varphi_i^k\ dxdydt\\
&\quad+\frac{1}{|Y|}\iiint_{\Omega_T\times Y_e}\mathrm{M}_e\left[\nabla u_e+\nabla_y\widehat{u}_e\right]\nabla\varphi_e\ dxdydt\\
&\quad+\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\mathrm{I}_{a,ion}(v^k)\psi^k\ dxd\sigma_y dt+\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\mathrm{I}_{b,ion}(w^k)\psi^k\ dxd\sigma_y dt\\
&\quad+\frac{1}{2\,|Y|}\iint_{\Omega_T\times\Gamma^{1,2}}\mathcal{I}_{gap}(s)\Psi\ dxd\sigma_y dt\\
&=\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times\Gamma^k}\mathcal{I}_{app}^k\psi^k\ dxd\sigma_y dt,
\end{aligned}
\tag{34}
$$

Similarly, we can prove also that the limit of (29) for $k=1,2$ as ε tends to zero, is given by:

$$
\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^k}\partial_t w^k e^k\ dxd\sigma_y dt-\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^k}H(v^k,w^k)e^k\ dxd\sigma_y dt=0.
\tag{35}
$$

Remark 13. *Since the linear term H is not varying at the micro scale and since v^k does not depend on y, it can be proven, using Assumption (8b), that the solution w^k of*

$$
\begin{cases}\partial_t w^k=H(v^k,w^k) & \text{in } \Omega_T\times\Gamma^k,\\ w^k(0,x)=w_0^k(x) & \text{on } \Omega,\end{cases}
$$

is unique for all $y\in\Gamma^k$ for $k=1,2$ hence it is independent of the variable y.

5.3. **Derivation of the macroscopic tridomain model.** The convergence results of the previous part allow us to pass to the limit in the microscopic equations (19)-(21) and to obtain the homogenized model formulated in Theorem 1.

To this end, we choose a special form of test functions to capture the microscopic informations at each structural level. Then, we consider that the test functions have the following form:

$$
\begin{cases}\varphi_{e,\varepsilon}=\phi_e(t,x)+\varepsilon\theta_e(t,x)\Theta_{e,\varepsilon}(x),\\ \varphi_{i,\varepsilon}^k=\phi_i^k(t,x)+\varepsilon\theta_i^k(t,x)\Theta_{i,\varepsilon}^k(x),\end{cases}
\tag{36}
$$

with functions $\Theta_{e,\varepsilon}$ and $\Theta_{i,\varepsilon}^k$ for $k=1,2$ defined by:

$$
\Theta_{e,\varepsilon}(x)=\Theta_e\left(\frac{x}{\varepsilon}\right)\quad\text{and}\quad\Theta_{i,\varepsilon}^k(x)=\Theta_i^k\left(\frac{x}{\varepsilon}\right),\quad\text{for } k=1,2,
$$

where ϕ_e,ϕ_i^k,θ_e and θ_i^k are in $D(\Omega_T)$, Θ_e in $H^1_{\#}(Y_e)$ and Θ_i^k in $H^1_{\#}(Y_i^k)$ for $k=1,2$. Then, we have:

$$
\begin{cases}\nabla\varphi_{e,\varepsilon}=\nabla_x\phi_e+\varepsilon\nabla_x\theta_e\Theta_{e,\varepsilon}+\theta_e\nabla_y\Theta_{e,\varepsilon},\\ \nabla\varphi_{i,\varepsilon}^k=\nabla_x\phi_i^k+\varepsilon\nabla_x\theta_i^k\Theta_{i,\varepsilon}^k+\theta_i^k\nabla_y\Theta_{i,\varepsilon}^k.\end{cases}
$$

Due to the regularity of test functions and using property (5) of Proposition 5, there holds for $k=1,2$, when $\varepsilon \to 0$:

$$\begin{aligned}
&\mathcal{T}_\varepsilon^{i,k}(\varphi_{i,\varepsilon}^k) \to \phi_i^k \text{ strongly in } L^2\left(\Omega_T \times Y_i^k\right),\\
&\mathcal{T}_\varepsilon^{i,k}(\theta_i^k \Theta_{i,\varepsilon}^k) \to \theta_i^k(t,x)\Theta_i^k(y) \text{ strongly in } L^2\left(\Omega_T \times Y_i^k\right),\\
&\mathcal{T}_\varepsilon^{i,k}\left(\nabla\varphi_{i,\varepsilon}^k\right) \to \nabla_x\phi_i^k + \theta_i^k\nabla_y\Theta_{i,\varepsilon}^k \text{ strongly in } L^2\left(\Omega_T \times Y_i^k\right),\\
&\mathcal{T}_\varepsilon^{e}(\varphi_{e,\varepsilon}) \to \phi_e \text{ strongly in } L^2\left(\Omega_T \times Y_e\right),\\
&\mathcal{T}_\varepsilon^{e}(\theta_e \Theta_{e,\varepsilon}) \to \theta_e(t,x)\Theta_e(y) \text{ strongly in } L^2\left(\Omega_T \times Y_e\right),\\
&\mathcal{T}_\varepsilon^{e}\left(\nabla\varphi_{e,\varepsilon}\right) \to \nabla_x\phi_e + \theta_e\nabla_y\Theta_{e,\varepsilon} \text{ strongly in } L^2\left(\Omega_T \times Y_e\right).
\end{aligned}$$

Since $\psi_\varepsilon^k := \left(\varphi_{i,\varepsilon}^k - \varphi_{e,\varepsilon}\right)|_{\Gamma_{\varepsilon,T}^k}$ for $k=1,2$ and $\Psi_\varepsilon := \left(\varphi_{i,\varepsilon}^1 - \varphi_{i,\varepsilon}^2\right)|_{\Gamma_{\varepsilon,T}^{1,2}}$, then it holds also:

$$\begin{aligned}
&\mathcal{T}_\varepsilon^{b,k}(\psi_\varepsilon^k) \to \psi^k \text{ strongly in } L^2(\Omega_T \times \Gamma^k),\\
&\mathcal{T}_\varepsilon^{b,1,2}(\Psi_\varepsilon) \to \Psi \text{ strongly in } L^2(\Omega_T \times \Gamma^{1,2}),
\end{aligned}$$

where $\psi^k := \left(\phi_i^k - \phi_e\right)|_{\Omega_T\times\Gamma^k}$ for $k=1,2$ and $\Psi := \left(\phi_i^1 - \phi_i^2\right)|_{\Omega_T\times\Gamma^{1,2}}$.

Collecting all the convergence results of $J_1,\dots,J_8$ obtained in Section 4.2, we deduce the following limiting problem:

$$\begin{aligned}
&\sum_{k=1,2}\frac{|\Gamma^k|}{|Y|}\iint_{\Omega_T}\partial_t v^k\psi^k\,dxdt + \frac{|\Gamma^{1,2}|}{2\,|Y|}\iint_{\Omega_T}\partial_t s\Psi\,dxdt\\
&\quad+\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times Y_i^k}\mathrm{M}_i\left[\nabla u_i^k + \nabla_y\widehat{u}_i^k\right]\left[\nabla_x\phi_i^k + \theta_i^k\nabla_y\Theta_{i,\varepsilon}^k\right]\,dxdydt\\
&\quad+\frac{1}{|Y|}\iiint_{\Omega_T\times Y_e}\mathrm{M}_e\left[\nabla u_e + \nabla_y\widehat{u}_e\right]\left[\nabla_x\phi_e + \theta_e\nabla_y\Theta_{e,\varepsilon}\right]\,dxdydt\\
&\quad+\sum_{k=1,2}\frac{|\Gamma^k|}{|Y|}\iint_{\Omega_T}\mathrm{I}_{a,ion}(v^k)\psi^k\,dxdt + \sum_{k=1,2}\frac{|\Gamma^k|}{|Y|}\iint_{\Omega_T}\mathrm{I}_{b,ion}(w^k)\psi^k\,dxdt\\
&\quad+\frac{|\Gamma^{1,2}|}{2\,|Y|}\iint_{\Omega_T}\mathcal{I}_{gap}(s)\Psi\,dxdt\\
&=\sum_{k=1,2}\frac{|\Gamma^k|}{|Y|}\iint_{\Omega_T}\mathcal{I}_{app}^k\psi^k\,dxdt.
\end{aligned}\tag{37}$$

Similarly, we can prove also that the limit of the coupled dynamic equation for $k=1,2$ as ε tends to zero, which is given by:

$$\frac{|\Gamma^k|}{|Y|}\iint_{\Omega_T}\partial_t we^k\,dxdt - \frac{|\Gamma^k|}{|Y|}\iint_{\Omega_T}H(v^k,w^k)e^k\,dxdt = 0.\tag{38}$$

Now, we will find first the expression of $\widehat{u}_i^k$ in terms of the homogenized solution u_i^k for $k=1,2$. Then, we derive the cell problem from the homogenized equation (37). Finally, we obtain the weak formulation of the corresponding macroscopic equation.

We first take ϕ_e, θ_e and ϕ_i^k for $k=1,2$ are equal to zero, to get:

$$\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times Y_i^k}\mathrm{M}_i\left(\nabla u_i^k + \nabla_y\widehat{u}_i^k\right)\left(\theta_i^k\nabla_y\Theta_{i,\varepsilon}^k\right)\,dxdydt = 0.\tag{39}$$

Since $u_i^k, k=1,2$ is independent on the microscopic variable y then the formulation (39) corresponds to the following microscopic problem:

$$\begin{cases} -\nabla_y \cdot \left(\mathrm{M}_i \nabla_y \widehat{u}_i^k\right) = \sum\limits_{p,q=1}^{d} \dfrac{\partial \mathrm{m}_i^{pq}}{\partial y_p} \dfrac{\partial u_i^k}{\partial x_q} \text{ in } Y_i^k, \\ \widehat{u}_i^k \ y\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_y \widehat{u}_i^k + \mathrm{M}_i \nabla_x u_i^k\right) \cdot n_i^k = 0 \text{ on } \Gamma^k, \\ \left(\mathrm{M}_i \nabla_y \widehat{u}_i^k + \mathrm{M}_i \nabla_x u_i^k\right) \cdot n_i^k = 0 \text{ on } \Gamma^{1,2}. \end{cases} \tag{40}$$

Hence, by the y-periodcity of M_i and the compatibility condition, it is not difficult to establish the existence of a unique periodic solution up to an additive constant of the problem (40) (see [3] for more details).
Thus, the linearity of terms in the right-hand side of (40) suggests to look for $\widehat{u}_i^k$ under the following form in terms of u_i^k:

$$\widehat{u}_i^k(t,x,y,z) = \chi_i(y) \cdot \nabla_x u_i^k + \widehat{u}_{0,i}^k(t,x,y), \tag{41}$$

where $\widehat{u}_{0,i}^k, k=1,2$ is a constant with respect to y and each element χ_i^q of χ_i satisfies the following ε-cell problem:

$$\begin{cases} -\nabla_y \cdot (\mathrm{M}_i \nabla_y \chi_i^q) = \sum\limits_{p=1}^{d} \dfrac{\partial \mathrm{m}_i^{pq}}{\partial y_p} \text{ in } Y_i^k, \\ \chi_i^q \ y\text{-periodic}, \\ \mathrm{M}_i \nabla_y \chi_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \text{ on } \Gamma^k, \ k=1,2 \\ \mathrm{M}_i \nabla_y \chi_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \text{ on } \Gamma^{1,2}, \end{cases} \tag{42}$$

for $q=1,\dots,d$. Moreover, the compatibility condition is imposed to guarantee the existence and uniqueness of solution $\chi_i^q \in H^1_{\#}(Y_i^k)$ to problem (42) with $H^1_{\#}$ is given by (18).

Finally, inserting the form (41) of $\widehat{u}_i^k$ into (37) and setting $\theta_i^k, \theta_e \ \phi_e$ to zero, one obtains the weak formulation of the homogenized equation for the intracellular problem:

$$\begin{aligned} &\sum_{k=1,2} \mu_k \iint_{\Omega_T} \partial_t v^k \phi_i^k \ dxdt + \mu_g \iint_{\Omega_T} \partial_t s \phi_i^1 \ dxdt \\ &+ \frac{1}{|Y|} \sum_{k=1,2} \iiint_{\Omega_T \times Y_i^k} \widetilde{\mathbf{M}}_i \nabla u_i^k \cdot \nabla \phi_i^k \ dxdydt \\ &+ \sum_{k=1,2} \mu_k \iint_{\Omega_T} \mathrm{I}_{a,ion}(v^k) \phi_i^k \ dxdt + \sum_{k=1,2} \mu_k \iint_{\Omega_T} \mathrm{I}_{b,ion}(w^k) \phi_i^k \ dxdt \\ &+ \mu_g \iint_{\Omega_T} \mathcal{I}_{gap}(s) \phi_i^1 \ dxdt = \sum_{k=1,2} \mu_k \iint_{\Omega_T} \mathcal{I}_{app}^k \phi_i^k \ dxdt, \end{aligned} \tag{43}$$

with $\mu_k = \left|\Gamma^k\right| / |Y|, k=1,2, \mu_g = \left|\Gamma^{1,2}\right| / 2|Y|$ and the coefficients of the homogenized conductivity matrices $\widetilde{\mathbf{M}}_i = \left(\widetilde{\mathbf{m}}_i^{pq}\right)_{1 \le p,q \le d}$ defined by:

$$\widetilde{\mathbf{m}}_i^{pq} := \frac{1}{|Y|} \sum_{\ell=1}^{d} \int_{Y_i^k} \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell} \frac{\partial \chi_i^q}{\partial y_\ell} \right) \ dy. \tag{44}$$

Similarly, we can decouple the cell problem in the extracellular domain and define the homogenized matrix $\widetilde{\mathbf{M}}_e$. This completes the proof of Theorem 1 using periodic unfolding method.

Remark 14.

1. *Since the conductivity matrices* M_j *for* $j=i,e$ *are symmetric then the homogenized conductivity matrices* $\widetilde{\mathbf{M}}_j$ *defined by* (14a)-(14b) *are also symmetric for* $j=i,e$.
2. *We can rewrite the homogenized conductivity matrices* $\widetilde{\mathbf{M}}_i=(\widetilde{\mathbf{m}}_i^{pq})_{1\leq p,q\leq d}$ *as follows*

$$\widetilde{\mathbf{m}}_i^{pq}:=\frac{1}{|Y|}\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial\left(y_q+\chi_i^q\right)}{\partial y_{\ell'}}\frac{\partial\left(y_p+\chi_i^p\right)}{\partial y_\ell}\,dy. \tag{45}$$

Indeed, we recall that χ_i^q *is the solution of* (42). *Choosing* χ_i^p *as test function in* (42), *one has*

$$\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial\chi_i^q}{\partial y_{\ell'}}\frac{\partial\chi_i^p}{\partial y_\ell}\,dy=-\sum_{\ell=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell q}\frac{\partial\chi_i^p}{\partial y_\ell}\,dy=-\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial y_q}{\partial y_{\ell'}}\frac{\partial\chi_i^p}{\partial y_\ell}\,dy.$$

Hence, one obtains

$$\frac{1}{|Y|}\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial\left(y_q+\chi_i^q\right)}{\partial y_{\ell'}}\frac{\partial\chi_i^p}{\partial y_\ell}\,dy=0. \tag{46}$$

On the other hand, since

$$\int_{Y_i^k}\mathrm{m}_i^{pq}\,dy=\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial y_q}{\partial y_{\ell'}}\frac{\partial y_p}{\partial y_\ell}\,dy,$$

$$\sum_{\ell=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{p\ell}\frac{\partial\chi_i^q}{\partial y_\ell}\,dy=\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial\chi_i^q}{\partial y_{\ell'}}\frac{\partial y_p}{\partial y_\ell}\,dy,$$

formula (44) *can be written as follows:*

$$\widetilde{\mathbf{m}}_i^{pq}=\frac{1}{|Y|}\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial\left(y_q+\chi_i^q\right)}{\partial y_{\ell'}}\frac{\partial y_p}{\partial y_\ell}\,dy,\ \forall p,q=1,\dots,d. \tag{47}$$

Summing (46) *from* (47) *gives* (45). *Similarly, we can rewrite the other matrix* $\widetilde{\mathbf{M}}_e$ *in terms of the corresponding corrector function* χ_e.
3. *Since the conductivity matrices* M_j *for* $j=i,e$ *satisfy the elliptic conditions defined by* (6), *then the homogenized conductivity matrices* $\widetilde{\mathbf{M}}_j$, $j=i,e$ *verify the following elliptic conditions: there exits* $\alpha_0,\beta_0>0$ *such that*

$$\widetilde{\mathbf{M}}_j\lambda\cdot\lambda\geq\alpha_0\left|\lambda\right|^2, \tag{48a}$$

$$\left|\widetilde{\mathbf{M}}_j\lambda\right|\leq\beta_0\left|\lambda\right|,\quad \textit{for any } \lambda\in\mathbb{R}^d. \tag{48b}$$

Indeed, let $\lambda\in\mathbb{R}^d$ *and* $j=i$. *To prove* (48a), *then from* (45) *it follows that*

$$\sum_{p,q=1}^{d}\widetilde{\mathbf{m}}_i^{pq}\lambda_p\lambda_q=\frac{1}{|Y|}\sum_{p,q=1}^{d}\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\lambda_p\frac{\partial\left(y_p+\chi_i^p\right)}{\partial y_\ell}\lambda_q\frac{\partial\left(y_q+\chi_i^q\right)}{\partial y_{\ell'}}\,dy.$$

Setting $\zeta_i=\sum_{p=1}^{d}\lambda_p\left(y_p+\chi_i^p\right)$ *and using the ellipticity of* M_i *defined by* (6), *we get*

$$\sum_{p,q=1}^{d}\widetilde{\mathbf{m}}_i^{pq}\lambda_p\lambda_q\geq\frac{\alpha}{|Y|}\int_{Y_i^k}\left|\nabla\zeta_i\right|^2\,dy\geq 0,\ \textit{for any } \lambda\in\mathbb{R}^d. \tag{49}$$

Let us show that this inequality implies that

$$\sum_{p,q=1}^{d} \widetilde{\mathbf{m}}_i^{pq} \lambda_p \lambda_q > 0, \text{ for any } \lambda \in \mathbb{R}^d, \ \lambda \neq 0.$$

If this were not true. In view of (49)*, one would have some* $\lambda \neq 0$ *such that*

$$|\nabla \zeta_i| = 0.$$

This means that

$$\zeta_i = \sum_{p=1}^{d} \lambda_p \left(y_p + \chi_i^p\right) = constant.$$

Thus, one has

$$\sum_{p=1}^{d} \lambda_p y_p = -\sum_{p=1}^{d} \lambda_p \chi_i^p + C,$$

and this impossible since the right-hand side function is y-periodic by definition and $\lambda \neq 0$*. To end the proof of ellipticity, we know that the function* $\sum_{p,q=1}^{d} \widetilde{\mathbf{m}}_i^{pq} \xi_p \xi_q$ *is continuous on the unit sphere* $\mathbb{S}^{d-1}$ *which is a compact set of* $\mathbb{R}^d$*. Hence, this function achieves its minimum on* $\mathbb{S}^{d-1}$ *and, due to the previous result, this minimum is positive. So, there exists* $\alpha_0 > 0$ *such that*

$$\sum_{p,q=1}^{d} \widetilde{\mathbf{m}}_i^{pq} \xi_p \xi_q \geq \alpha_0, \ \forall \xi \in \mathbb{S}^{d-1}.$$

Consequently,

$$\sum_{p,q=1}^{d} \widetilde{\mathbf{m}}_i^{pq} \frac{\lambda_p}{|\lambda|} \frac{\lambda_q}{|\lambda|} \geq \alpha_0, \text{ for any } \lambda \in \mathbb{R}^d, \ \lambda \neq 0,$$

since the vector $\left(\frac{\lambda_1}{|\lambda|}, \ldots, \frac{\lambda_d}{|\lambda|}\right)$ *belongs to* $\mathbb{S}^{d-1}$*. This ends the proof of inequality* (48a) *and by the same way we obtain the second inequality.*

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