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« Multi-scale unfolding homogenization method applied to bidomain and tridomain electrocardiology models »

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Abstract

This thesis is mainly devoted to the modeling and multi-scale analysis of bidomain and tridomain electro-cardiology systems. Cardiac electro-physiology describes and models the chemical and electrical phenomena that occur in cardiac tissue.

At the microscopic level, cardiac tissue is very complex and it is therefore very difficult to understand and predict its behavior at the macroscopic (observable) scale. Thus, to each (bidomain or tridomain) system we associate a microscopic model (of elliptic type), coupled to a nonlinear ODE system and another macroscopic one (of reaction-diffusion type).

Based on Ohm's law of electrical conduction and conservation of electrical charge, we obtain the microscopic model that gives a detailed description of the electrical activity in the cells responsible for cardiac contraction. Then, using homogenization techniques, we obtain the macroscopic model which, in turn, allows us to describe the propagation of electrical waves in the entire heart.

This thesis is composed of two main parts. First, we give a formal and rigorous mathematical justification of the periodic homogenization process that leads to the macroscopic bidomain model. The formal method is a kind of asymptotic development at three scales that we apply to our meso- and microscopic bidomain model. Moreover, the rigorous method is based on unfolding operators which not only derive the homogenized equation but also prove the convergence of the solution sequence of the microscopic bidomain problem to the solution of the macroscopic problem. Because of nonlinear terms, the boundary unfolding operator and a Kolmogorov type argument for the phenomenological ionic models are used. Then, we work on the mathematical analysis of a new model that describes the electrical activity of cardiac cells in the presence of junctions. This model is the "tridomain" model. We show the existence and uniqueness of the weak solution of the tridomain microscopic model using the Faedo-Galerkin constructive technique and a compactness argument in L^2. Finally, while using the two previous homogenization methods, we develop the macroscopic tridomain model which corresponds to an approximation of our microscopic model.

Keywords: Bidomain, Tridomain, Homogenization, Three-scale asymptotic analysis, Periodic unfolding method, Gap junctions, Electro-cardiology.

Résumé

Cette thèse est principalement consacrée à la modélisation et à l'analyse multi-échelle de systèmes d'électrocardiologie bidomaine et tridomaine. L'électrophysiologie cardiaque décrit et modélise les phénomènes chimiques et électriques qui se produisent dans le tissu cardiaque.

Au niveau microscopique, le tissu cardiaque est très complexe et il est donc très difficile de comprendre et de prévoir son comportement à l'échelle macroscopique (observable). Ainsi, à chaque système (bidomaine ou tridomaine) on associe un modèle microscopique (de type elliptique), couplé à un système d'EDO non-linéaire et un autre macroscopique (de type réaction-diffusion).

En se basant sur la loi de la conduction électrique d'Ohm et la conservation de la charge électrique, on obtient le modèle microscopique qui donne une description détaillée de l'activité électrique dans les cellules responsables de la contraction cardiaque. Ensuite, en utilisant des techniques d'homogénéisation, on obtient le modèle macroscopique qui, à son tour, permet de décrire la propagation des ondes électriques dans le cœur entier.

Cette thèse est composée en deux grandes parties. D'abord, on donne une justification mathématique formelle et rigoureuse du processus d'homogénéisation périodique qui conduit au modèle macroscopique bidomaine. La méthode formelle est un développement asymptotique à trois échelles appliqué au modèle bidomaine méso- et microscopique. En outre, la justification mathématique rigoureuse est basée sur des opérateurs d'éclatement qui non seulement dérivent l'équation homogénéisée mais aussi prouvent la convergence de la suite de solutions du problème bidomaine microscopique vers la solution du problème macroscopique. Pour traiter les modèles ioniques non linéaires, l'opérateur d'éclatement sur la surface et un argument de type Kolmogorov sont utilisés pour assurer la compacité. Ensuite, on travaille sur l'analyse mathématique d'un nouveau modèle décrivant l'activité électrique des cellules cardiaques en présence de jonctions communicantes est proposé. Il s'agit notamment du modèle "tridomaine". On montre l'existence et l'unicité de la solution faible du modèle microscopique tridomaine en utilisant la méthode constructive de Faedo-Galerkin. Finalement, l'obtention du modèle tridomaine macroscopique (homogénéisé) est justifiée d'une part par la méthode de développement asymptotique et d'autre part par l'analyse de convergence du modèle microscopique en s'appuyant sur la méthode d'éclatement périodique.

Mots clés : Bidomaine, Tridomaine, Homogénéisation, Analyse asymptotique à trois échelles, Méthode d'éclatement périodique, Gap junctions, Électro-cardiologie.

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Introduction

Context of the thesis

The heart study started since more than two millennia back. This organ, about the size of its owner's clenched fist, contracts rhythmically to circulate blood throughout the body, while other organs like the brain and lungs, were thought to exist to cool the blood. Until this day the heart keeps the position of one of the most important and the most studied organs in the human body. Especially, cardiovascular disease (CVD) leading to heart attack, is the top cause of death in the worldwide as announced by the "World Health Organization" in 2019. Additionally, an estimated 8.9 million people died from CVDs in 2019, representing 16% of all global deaths. Most cardiovascular diseases can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity, and harmful use of alcohol using population-wide strategies. While the doctors are looking into the causes and correlations between CVDs and diet, physical activity and a lifestyle, we are on the quest to provide them with new and innovative techniques that can help them establish diagnostics (non-invasive, adapted specifically to patients, in real-time, ...) and plan the corresponding therapies (operations, treatments, ...).

The goal of this thesis is to develop powerful mathematical tools to improve the modeling of electrochemical phenomena occurring in the human heart.

Synopsis of the thesis

This thesis is mainly devoted to the modeling and multi-scale analysis of bidomain and tridomain electro-cardiology systems. Such cardiac models describes the chemical and electrical phenomena that occur in cardiac tissue. The thesis is structured in the following fashion:

Chapter 1

Chapter 1 has several parts. The first one is a brief review of the basic anatomy and functionality of the heart at the macroscopic and microscopic levels. The heart is a muscular organ, which is composed of two main pumps (see Figure 1): the left and right heart separated by a muscular wall (the septum). Each pump contains an atrium and a ventricle.

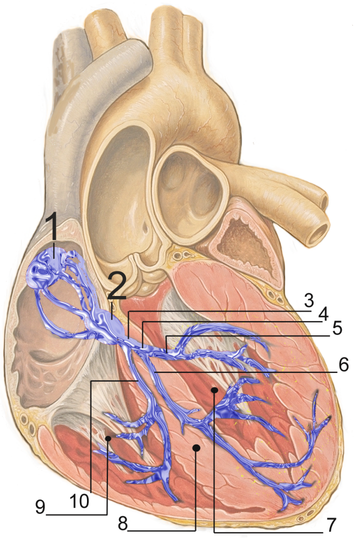

Figure 1 – Electrical conduction system of the heart: 1-Sinoatrial node, 2-Atrioventricular node, 3-Bundle of His, 4-Left bundle branch, 5-Left posterior fascicle, 6-Left anterior fascicle, 7-Left ventricle, 8-Ventricular septum, 9-Right ventricle, 10-Right bundle branch.
`https://commons.wikimedia.org/w/index.php?curid=1734607`

On the macroscopic level, the contraction of heart muscle is initiated by electrical impulses known as *action potentials* (AP). A propagation of the AP in the whole heart generates the rhythmical heart beat that follows the following schematic path (see Figure 1):

- initiation in the sinoatrial node (SA node),
- propagation in the atria,
- passing through the atrioventricular node (AV node),
- diverging and conducting through the left and right His bundle to the respective Purkinje fibers on each side of the heart,
- propagation in the ventricles.

On the microscopic level, the cardiac muscle cells or cardiomyocytes are the contracting cells that allow the heart to pump. These cells are surrounded by a lipid cell membrane called **sarcolemma**, which separates the intracellular part of the cells (the cytoplasm) from the extracellular environment (the fluid outside the cells). Typically, the sarcolemma connects the *basement membrane* which surrounds all connective tissues and allows the penetration of inorganic ions (sodium, potassium, calcium,...) and proteins. As shown in Figure 2, the cytoplasm contains :

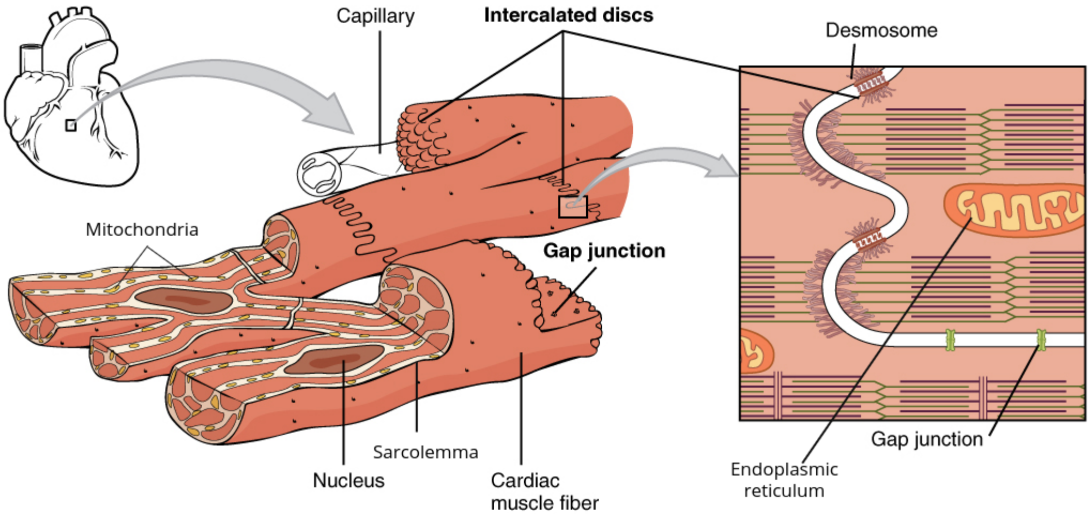

Figure 2 – Cardiac muscle at microscopic level.
`https://en.wikipedia.org/wiki/Cardiac_muscle#/media/File:1020_Cardiac_Muscle.jpg`

- one or more **nuclei**,
- **Mitochondria** store and supply the energy essential to the cell. They contain their own A.D.N,
- **the endoplasmic reticulum** play an important role in cellular metabolism, in protein synthesis and in calcium regulation,
- in addition to various organelles, allowing the cell to perform its functions.

Cardiomyocytes are attached to each other at plasma membrane junctions: the intercalated discs. At these junctions, we find :

- **Gap junctions** are essential for chemical and electrical coupling of neighboring cells,
- **Desmosomes** prevent cells from separating during muscle contraction.

Moreover, we are interested at cellular scale in the action potential which corresponds to the evolution in time of the transmembrane potential, that is the difference between the extracellular and intracellular potentials in the cell. A typical action potential for a ventricular muscle cell is divided in to five phases as outlined below, and depicted in Figure 3:

Phase 4 (resting potential) The value of the transmembrane potential in the resting state is around -90 mV in the human heart, which is closest to the reversal potential of potassium. It is polarized, excitable and responsive to stimuli.

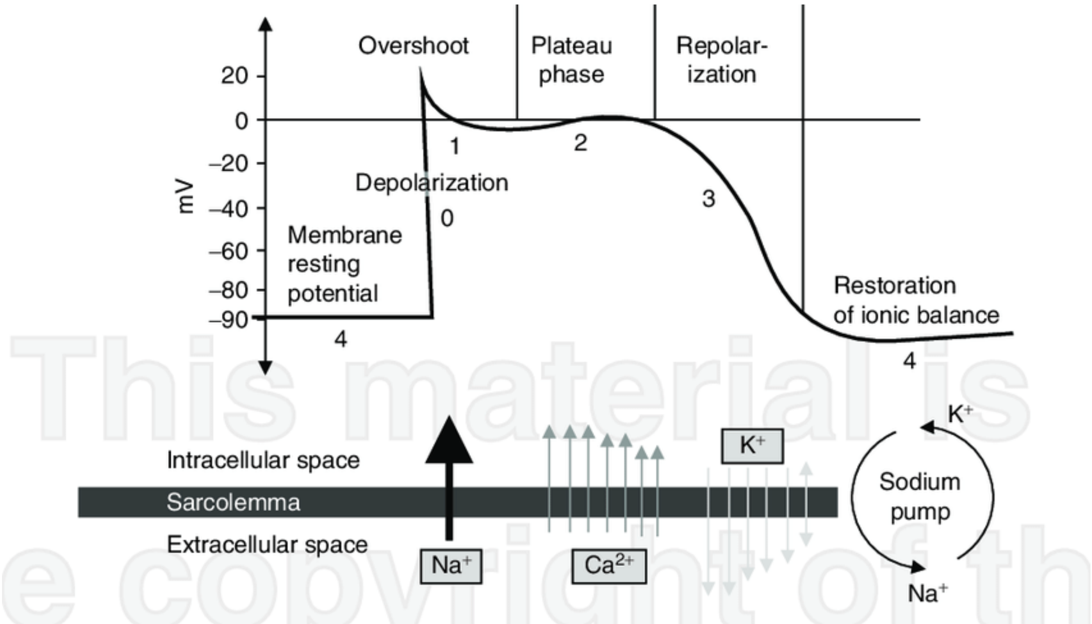

Figure 3 – Action potential of a ventricular muscle cell.
`https://www.researchgate.net/figure/Myocardial-action-potential-Shown-is-the-action-pot`
`fig3_40022512`

Phase 0 (depolarization) A small super-threshold electrical stimulus causes a deviation from the resting potential, and causes rapid opening of sodium (Na^+) channels. This permits a large influx of Na^+ ions, which depolarizes the cell.

Phase 1 (early repolarization) The inactivation of Na^+ channels, combined with the opening of the potassium (K^+) channel causing K^+ ions to flow out of the sarcolemma, begins the repolarization of the cell.

Phase 2 (plateau) The opening of L-type slow calcium (Ca^{2+}) channels (influx of Ca^{2+} ions) balances with the efflux of K^+ ions, which slows down the repolarization process and gives rise to a plateau phase at around 0 mV.

Phase 3 (repolarization) The closure of L-type Ca^{2+} channels disturbs the potential balance from the plateau phase, and creates a net outward current of the membrane which results in a drop in transmembrane potential. The K^+ channels close after the transmembrane potential is restored to resting state.

Knowing that the cardiac tissue contains a large number of cardiac cells, we find that these cells contain different organelles (mitochondria, ...) and are connected to neighboring cells by gap junctions. Such discrete modeling would be mathematically very challenging and numerically extremely expensive. Thus, the last part of this chapter aims to answer the following question

> Mathematically, how will we present the geometry of cardiac tissue via the microscopic and macroscopic scales?

In view of their complex structure, two different simplified geometries of cardiac tissue are presented using the literature:

(**G**.1) **Three-scale geometry of cardiac tissue due to the presence of a large number of mitochondria.**

We assume that the cardiac tissue Ω is open bounded set in $\mathbb{R}^d$ with a Lipschitz boundary $\partial\Omega$. Following the standard approach of the homogenization theory, their structure is featured by two parameters ℓ^{mes} and ℓ^{mic} characterizing, respectively, the mesoscopic and microscopic length of a cell in meso- or microscopic domain. Under the two-level scaling, the characteristic lengths ℓ^{mes} and ℓ^{mic} are related to a given macroscopic length L (of the cardiac fibers), such that the two scaling parameters are introduced by $\varepsilon = \frac{\ell^{\text{mes}}}{L}$ and $\delta = \frac{\ell^{\text{mic}}}{L}$ with $\ell^{\text{mic}} << \ell^{\text{mes}}$.

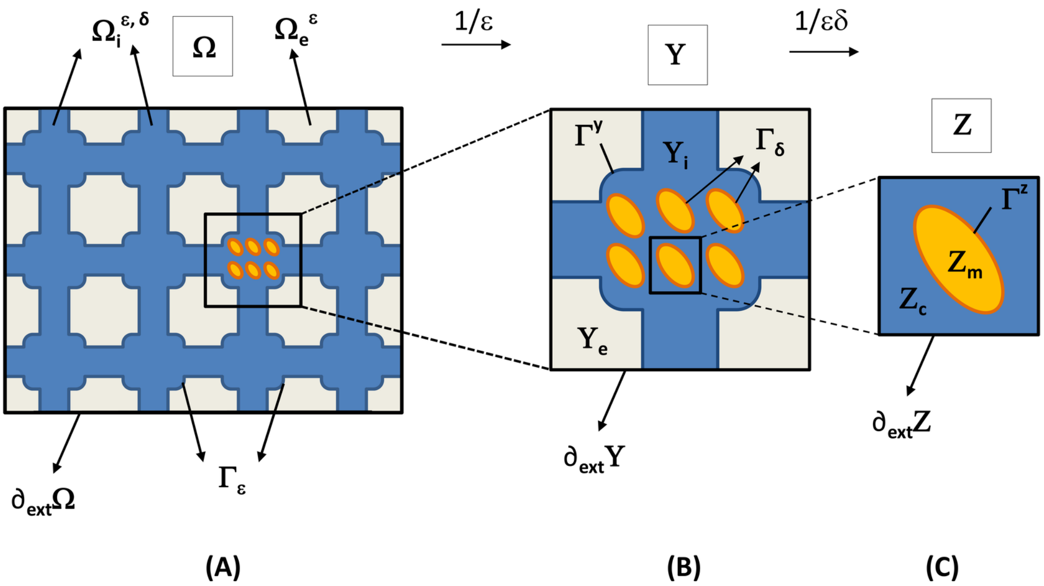

Figure 4 – (A) Periodic heterogeneous domain Ω, (B) Reference cell Y at ε-structural level and (B) Reference cell Z at δ-structural level.

- At mesoscale, the domain Ω is composed of two open connected regions, called intracellular $\Omega_i^{\varepsilon,\delta}$ and extracellular Ω_e^{ε} medium. These two regions are separated by the surface membrane $\Gamma_\varepsilon = \partial\Omega_i^{\varepsilon,\delta} \cap \partial\Omega_e^{\varepsilon}$ assuming that the membrane is regular.

  Let $Y := \prod_{n=1}^{d}]0, \ell_n^{\text{mes}}[$ be the mesoscopic reference cell, which is divided into two parts: intracellular Y_i and extracellular Y_e, separated by a common boundary $\Gamma^y = \partial Y_i \cap \partial Y_e$.

  At ε-structural level, the intracellular and extracellular domains are ε-dilations of reference lattice Y_j for $j = i, e$ extended periodically and defined by: for $k \in \mathbb{Z}^d$

$$Y_{j,\varepsilon}^k := T_\varepsilon^k + \varepsilon Y_j = \{\varepsilon\xi : \xi \in k_\ell + Y_j\},$$

  and their common boundary

$$\Gamma_\varepsilon^k := T_\varepsilon^k + \varepsilon\Gamma^y = \{\varepsilon\xi : \xi \in k_\ell + \Gamma^y\},$$

  with $T_\varepsilon^k := \varepsilon k_\ell$ and $k_\ell := (k_1\ell_1^{\text{mes}}, \ldots, k_d\ell_d^{\text{mes}})$.

  Hence, the intracellular and extracellular domains at mesoscale can be simply obtained by taking the intersection of Ω with $Y_{j,\varepsilon}^k$ for $j = i, e$ (see Figure 4)

$$\Omega_i^\varepsilon = \Omega \cap \bigcup_{k\in\mathbb{Z}^d} Y_{i,\varepsilon}^k, \quad \Omega_e^\varepsilon = \Omega \cap \bigcup_{k\in\mathbb{Z}^d} Y_{e,\varepsilon}^k, \quad \Gamma_\varepsilon = \Omega \cap \bigcup_{k\in\mathbb{Z}^d} \Gamma_\varepsilon^k.$$

  Similarly,

$$\Gamma_\varepsilon = \Omega \cap \bigcup_{k\in\mathbb{Z}^d} \Gamma_\varepsilon^k.$$

- At microscale, the cytoplasm contains far more mitochondria described as "the powerhouse of the myocardium" surrounded by another membrane Γ_δ. Similarly, we only assume that the intracellular medium $\Omega_i^{\varepsilon,\delta}$ can also be viewed as a periodic perforated domain.

  Let $Z := \prod_{n=1}^{d}]0, \ell_n^{\text{mic}}[$ be the microscopic reference cell, which is divided into two parts: mitochondria part Z_m and the complementary part $Z_c := Z \setminus Z_m$, separated by a common boundary $\Gamma^z = \partial Z_m \cap \partial Z_c$.

  At δ-structural level, we can write the intracellular domain at microscale $\Omega_i^{\varepsilon,\delta}$ as follows: for $k' \in \mathbb{Z}^d$

$$\Omega_i^{\varepsilon,\delta} = \Omega \cap \bigcup_{k \in \mathbb{Z}^d} \left(Y_{i,\varepsilon}^k \cap \bigcup_{k' \in \mathbb{Z}^d} Z_{c,\delta}^{k'} \right)$$

where $Z_{c,\delta}^{k'}$ is defined by:

$$Z_{c,\delta}^{k'} := T_\delta^{k'} + \delta Z_c = \{\delta\zeta : \zeta \in k'_{\ell'} + Z_c\}.$$

Similarly,

$$\Gamma_\delta = \Omega \cap \bigcup_{k' \in \mathbb{Z}^d} \Gamma_\delta^{k'},$$

where $\Gamma_\delta^{k'} := T_\delta^{k'} + \delta\Gamma^z = \{\delta\zeta : \zeta \in k'_{\ell'} + \Gamma^z\}$.

(**G**.2) **Two-scale geometry of cardiac tissue where the gap junctions are considered as connection between cardiomyocytes.**

We consider that the cardiac tissue $\Omega \subset \mathbb{R}^d$ is bounded open set with a Lipschitz boundary $\partial\Omega$. Their structure is featured by ℓ^{mic} characterizing the microscopic length of a cell. 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 introduced by $\varepsilon = \frac{\ell^{\text{mic}}}{L}$.

Physiologically, the cardiac cells are connected by many gap junctions. Therefore, geometrically, the domain Ω 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 $\Omega_{e,\varepsilon}$. Each intracellular medium $\Omega_{i,\varepsilon}^k$ and the extracellular one are separated by the surface membrane $\Gamma_\varepsilon^k = \partial\Omega_{i,\varepsilon}^k \cap \partial\Omega_{e,\varepsilon},$ with $k = 1, 2$, while the exterior boundary is denoted by $\partial_{\text{ext}}\Omega$ (see Figure 5).

The domain Ω is a periodic medium, i.e. it is divided into the small cells identical to each other. These small cells are identical up to a translation and rescaling by ε to the microscopic reference cell Y. Furthermore, this reference cell is decomposed into three disjoint connected parts: two intracellular parts Y_i^k for $k = 1, 2$, that are connected by gap junction $\Gamma^{1,2} = \partial Y_i^1 \cap \partial Y_i^2$ and extracellular part Y_e. Each intracellular parts Y_i^k and the extracellular one are separated by a common membrane $\Gamma^k = \partial Y_i^k \cap \partial Y_e$ for $k = 1, 2$.

The intracellular and extracellular domains are respectively ε-dilations of reference lattice Y_i^k for $k = 1, 2$ and Y_e extended periodically and defined by: for $h \in \mathbb{Z}^d$

$$Y_{i,\varepsilon,h}^k := T_\varepsilon^h + \varepsilon Y_i^k = \{\varepsilon\xi : \xi \in h_\ell + Y_i^k\}, Y_{e,\varepsilon,h} := T_\varepsilon^h + \varepsilon Y_e = \{\varepsilon\xi : \xi \in h_\ell + Y_e\},$$

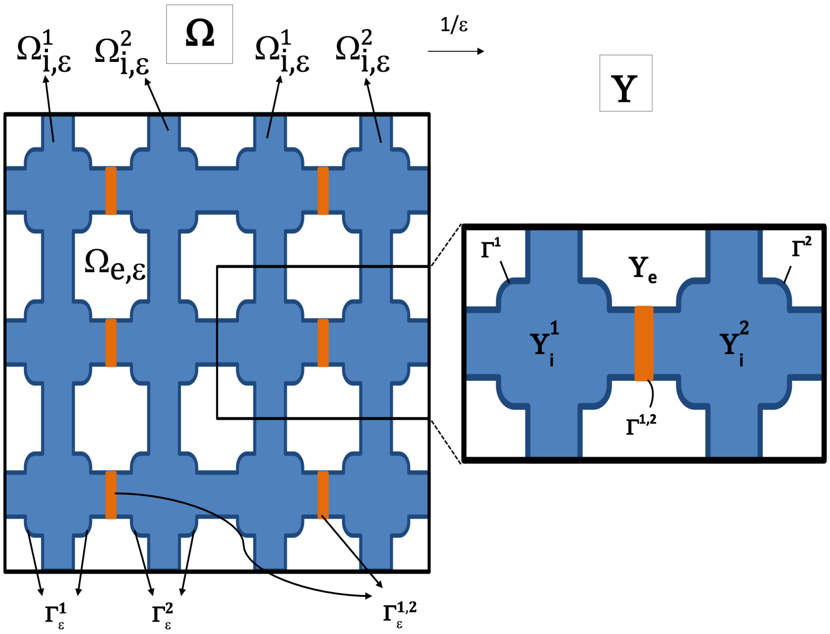

Figure 5 – (Left) Periodic heterogeneous domain Ω. (Right) Unit cell Y at ε-structural level.

and their corresponding boundaries

$$\Gamma_\varepsilon^k := T_\varepsilon^k + \varepsilon\Gamma^y = \{\varepsilon\xi : \xi \in k_\ell + \Gamma^y\},$$

with $h_\ell := (h_1\ell_1^{\text{mic}}, \ldots, h_d\ell_d^{\text{mic}})$ and $\Gamma := \Gamma^1, \Gamma^2, \Gamma^{1,2}$.

Hence, the intracellular and extracellular domains at microscale can be described as the intersection of Ω with $Y_{i,\varepsilon,h}^k$ for $k = 1, 2$, and $Y_{e,\varepsilon,h}$, respectively (see Figure 5)

$$\Omega_{i,\varepsilon}^k = \Omega \cap \bigcup_{h\in\mathbb{Z}^d} Y_{i,\varepsilon,h}^k, \quad \Omega_{e,\varepsilon} = \Omega \cap \bigcup_{h\in\mathbb{Z}^d} Y_{e,\varepsilon,h}.$$

Similarly, the corresponding boundaries are represented by

$$\Gamma_\varepsilon^k = \Omega \cap \bigcup_{h\in\mathbb{Z}^d} \Gamma_{\varepsilon,h}^k \text{ and } \Gamma_\varepsilon^{1,2} = \Omega \cap \bigcup_{h\in\mathbb{Z}^d} \Gamma_{\varepsilon,h}^{1,2}.$$

Many questions still remain in terms of modeling the electrical properties of the biological tissues and especially on the cardiac tissue. There are two modeling scales in cardiac electrophysiology: (a) the microscopic model aims at producing a detailed description of the origin of the electric wave in the cells and (b) the macroscopic one describes the propagation of the electrical wave in the heart. A homogenization procedure derives the macroscopic (homogenized) model, which is an approximation of the microscopic bidomain one and consists of equations formulated on the macroscopic scale.

We also are interested to present two mathematical model in cardiac electro-physiology:

- Microscopic and Macroscopic Bidomain Model.
- Microscopic and Macroscopic Tridomain Model.

The **bidomain** model is one of the most popular mathematical model in cardiac electrophysiology. It is based upon the assumption that the cardiac muscle is segmented into the intra- and extracellular domains and connected by the membrane (cf (**G**.1)), hence its name. While the **tridomain** model describes the electrical phenomena of myocytes cells in the presence of gap junctions. Comparing to the bidomain model, the cardiomycytes are not only electrically coupled by the cell membrane which are resistively connected to the extracellular space but are also connected to each other by many gap junctions (cf (**G**.2)). The tridomain model thus allows for a more detailed analysis of the properties of cardiac conduction than the classical bidomain model. Then, we present a detailed description of the bidomain and tridomain model at the microscopic and macroscopic level based on the literature. Furthermore, we illustrate with examples of both phenomenological and physiological ionic models in order to complete the microscopic models. In addition, we give a short explanation about the monodomain and eikonal models which are simplifications of the macroscopic bidomain model.

Chapter 2

Chapter 2 is mainly devoted to the modeling and multi-scale analysis of "*bidomain*" electrocardiology system coupled with the FitzHugh-Nagumo ionic model. The structure of cardiac tissue studied in this chapter, is characterized at three different scales defined in (**G**.1). We first perform a scaling of the microscopic bidomain equations given in Chapter 1. These equations therefore involve two small scaling parameters ε and δ which are respectively the ratio between the microscopic and mesoscopic scales and the macroscopic scale. The **microscopic** bidomain model is represented in the following form (see [Ben+19]):

$$
\begin{aligned}
-\nabla \cdot \left(\mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta}\right) &= 0 && \text{in } \Omega_{i,T}^{\varepsilon,\delta} := (0,T) \times \Omega_i^{\varepsilon,\delta}, && \text{(1a)}\\
-\nabla \cdot \left(\mathrm{M}_e^{\varepsilon} \nabla u_e^{\varepsilon}\right) &= 0 && \text{in } \Omega_{e,T}^{\varepsilon} := (0,T) \times \Omega_e^{\varepsilon}, && \text{(1b)}\\
\varepsilon \left(\partial_t v_\varepsilon + \mathcal{I}_{ion}(v_\varepsilon, w_\varepsilon) - \mathcal{I}_{app,\varepsilon}\right) &= \mathcal{I}_m && \text{on } \Gamma_{\varepsilon,T} := (0,T) \times \Gamma_\varepsilon, && \text{(1c)}\\
-\mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta} \cdot n_i = \mathrm{M}_e^{\varepsilon} \nabla u_e^{\varepsilon} \cdot n_e &= \mathcal{I}_m && \text{on } \Gamma_{\varepsilon,T}, && \text{(1d)}\\
\partial_t w_\varepsilon - H(v_\varepsilon, w_\varepsilon) &= 0 && \text{on } \Gamma_{\varepsilon,T}, && \text{(1e)}\\
\mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta} \cdot n_z &= 0 && \text{on } \Gamma_{\delta,T} := (0,T) \times \Gamma_\delta. && \text{(1f)}
\end{aligned}
$$

Note that each equation corresponds to the following sense: (1a) Intra quasi-stationary conduction, (1b) Extra quasi-stationary conduction, (1c) Reaction surface condition, (1d) Meso-continuity equation, (1e) Dynamic coupling, (1f) Micro-boundary condition.

Thus, the electrical properties of the cardiac tissue are described by the *intracellular* $u_i^{\varepsilon,\delta}$ and *extracellular* u_e^{ε} potentials respectively with the associated conductivities $\mathrm{M}_i^{\varepsilon,\delta}$ and $\mathrm{M}_e^{\varepsilon}$. Their difference, $v_\varepsilon := \left(u_i^{\varepsilon,\delta} - u_e^{\varepsilon}\right)|_{\Gamma_\varepsilon}$ is the *transmembrane* potential which satisfies the dynamic equation (1e) on Γ_ε involving the gating variable w_ε.

The system (1) is completed with no-flux boundary conditions:

$$
\left(\mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta}\right) \cdot \mathbf{n} = \left(\mathrm{M}_e^{\varepsilon} \nabla u_e^{\varepsilon}\right) \cdot \mathbf{n} = 0 \ \text{ on } \ (0,T) \times \partial_{\text{ext}}\Omega, \tag{2}
$$

where $\mathbf{n}$ is the outward unit normal to the exterior boundary of Ω, $n_i = -n_e$ to Γ_ε and n_z to Γ_δ. We also appropriate the initial Cauchy conditions for transmembrane potential v_ε and gating variable w_ε as follows:

$$
v_\varepsilon(0,x) = v_{0,\varepsilon}(x) \qquad \text{and} \qquad w_\varepsilon(0,x) = w_{0,\varepsilon}(x). \tag{3}
$$

Keeping in min the three-scale configuration of cardiac tissue (cf (**G**.1)), the assumptions about the system are given by:

(**A**.1) The conductivity of the tissue is represented by continuous tensors $\mathrm{M}_i^{\varepsilon,\delta}(x) := \mathrm{M}_i\left(x, x/\varepsilon, x/\varepsilon\delta\right)$ and $\mathrm{M}_e^{\varepsilon}(x) := \mathrm{M}_e\left(x, x/\varepsilon\right)$ satisfying the following elliptic and periodicity conditions: there exist constants $\alpha, \beta \in \mathbb{R}$, such that $0 < \alpha < \beta$ and for all $\lambda \in \mathbb{R}^d$:

$$\begin{aligned}
&\mathrm{M}_j\lambda \cdot \lambda \geq \alpha\,|\lambda|^2\,,\\
&|\mathrm{M}_j\lambda| \leq \beta\,|\lambda|\,,\ \text{for } j=i,e,\\
&\mathrm{M}_i\ \mathbf{y}\text{- and }\mathbf{z}\text{-periodic},\quad \mathrm{M}_e\ \mathbf{y}\text{-periodic}.
\end{aligned}$$

(**A**.2) The ionic current $\mathcal{I}_{ion}(v,w)$ can be decomposed into $\mathrm{I}_{1,ion}(v) : \mathbb{R} \to \mathbb{R}$ and $\mathrm{I}_{2,ion}(w) : \mathbb{R} \to \mathbb{R}$, where $\mathcal{I}_{ion}(v,w) = \mathrm{I}_{1,ion}(v) + \mathrm{I}_{2,ion}(w)$. Furthermore, $\mathrm{I}_{1,ion}$ is considered as a C^1 function, $\mathrm{I}_{2,ion}$ and $H : \mathbb{R}^2 \to \mathbb{R}$ are 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 $\beta_1,\beta_2 > 0$ such that:

$$\begin{aligned}
&\frac{1}{\alpha_1}\,|v|^{r-1} \leq |\mathrm{I}_{1,ion}(v)| \leq \alpha_1\left(|v|^{r-1}+1\right),\ |\mathrm{I}_{2,ion}(w)| \leq \alpha_2(|w|+1),\\
&|H(v,w)| \leq \alpha_3(|v|+|w|+1),\ \text{and } \mathrm{I}_{2,ion}(w)v - \alpha_4 H(v,w)w \geq \alpha_5\,|w|^2\,,\\
&\tilde{\mathrm{I}}_{1,ion} : z \mapsto \mathrm{I}_{1,ion}(z) + \beta_1 z + \beta_2 \text{ is strictly increasing with } \lim_{z\to 0} \tilde{\mathrm{I}}_{1,ion}(z)/z = 0,\\
&\forall z_1,z_2 \in \mathbb{R},\ \left(\tilde{\mathrm{I}}_{1,ion}(z_1) - \tilde{\mathrm{I}}_{1,ion}(z_2)\right)(z_1-z_2) \geq \frac{1}{C}\,(1+|z_1|+|z_2|)^{r-2}\,|z_1-z_2|^2\,.
\end{aligned}$$

(**A**.3) There exists a constant $C > 0$ independent of ε such that the source term $\mathcal{I}_{app,\varepsilon}$ satisfies the following estimation:

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

(**A**.4) The initial conditions $v_{0,\varepsilon}$ and $w_{0,\varepsilon}$ satisfy the following estimation:

$$\left\|\varepsilon^{1/r}v_{0,\varepsilon}\right\|_{L^r(\Gamma_\varepsilon)} + \left\|\varepsilon^{1/2}v_{0,\varepsilon}\right\|_{L^2(\Gamma_\varepsilon)} + \left\|\varepsilon^{1/2}w_{0,\varepsilon}\right\|_{L^2(\Gamma_\varepsilon)} \leq C,$$

for some constant C independent of ε. Moreover, $v_{0,\varepsilon}$ and $w_{0,\varepsilon}$ are assumed to be traces of uniformly bounded sequences in $C^1(\overline{\Omega})$.

(**A**.5) We end by imposing the following normalization condition:

$$\int_{\Omega_e^\varepsilon} u_e^\varepsilon(t,x)dx = 0,\ \text{for a.e. } t \in (0,T).$$

It is important to notice that the microscopic model is unusable for the whole heart. At the macroscopic scale, the heart appears as a continuous material with a fiber-based structure. At this scale, the intracellular and extracellular media are indistinguishable and we consider that the cardiac volume is "$\Omega \equiv \Omega_i^{\varepsilon,\delta} \equiv \Omega_e^{\varepsilon}$". Thus, this chapter aims to address the following question,

> How to connect information from the micro-scale to the macro-scale (e.g. via cell boundary, micro-macro conditions, ...) and how to derive the macroscopic behavior of cardiac tissues taking into account their complex structure?

The homogenization procedure has helped to answer this question to link the microscopic and macroscopic behaviors and leads to the equations of the **macroscopic** bidomain model presented in the following theorem:

Theorem 0.1 (Macroscopic Bidomain Model)**.** *Assume that the conditions (A.1)-(A.5) hold. A sequence of solutions* $\left((u_i^{\varepsilon,\delta})_{\varepsilon,\delta},(u_{e,\varepsilon})_\varepsilon,(w_\varepsilon)_\varepsilon\right)$ *of the microscopic bidomain model* (1)-(3) *converges (as* $\varepsilon,\delta\to 0$*) to a weak solution* (u_i,u_e,w) *with* $v=u_i-u_e$*,* $u_i,u_e\in L^2(0,T;H^1(\Omega))$*,* $v\in L^2(0,T;H^1(\Omega))\cap L^r(\Omega_T)$*,* $\partial_t v\in L^2(0,T;(H^1(\Omega))')\cap L^{r/(r-1)}(\Omega_T)$ *and* $w\in C(0,T;L^2(\Omega))$*, of the following reaction-diffusion system:*

$$\begin{aligned}
\mu_m\partial_t v+\nabla\cdot\left(\widetilde{\mathbf{M}}_e\nabla u_e\right)+\mu_m\mathcal{I}_{ion}(v,w)&=\mu_m\mathcal{I}_{app} \quad \text{in } \Omega_T,\\
\mu_m\partial_t v-\nabla\cdot\left(\widetilde{\widetilde{\mathbf{M}}}_i\nabla u_i\right)+\mu_m\mathcal{I}_{ion}(v,w)&=\mu_m\mathcal{I}_{app} \quad \text{in } \Omega_T,\\
\partial_t w-H(v,w)&=0 \qquad \text{on } \Omega_T,
\end{aligned} \tag{4}$$

completed with no-flux boundary conditions on u_i,u_e *on* $\partial_{ext}\Omega$:

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

and initial conditions for the transmembrane potential v *and the gating variable* w :

$$v(0,x)=v_0(x) \qquad \text{and} \qquad w(0,x)=w_0(x), \tag{5}$$

where $\mu_m=|\Gamma^y|\,/\,|Y|$ *is the ration between the surface membrane and the volume of the reference cell. Moreover,* $\mathbf{n}$ *is the outward unit normal to the exterior boundary of* Ω*. Herein, the first-level homogenized conductivity matrices* $\widetilde{\mathbf{M}}_j=\left(\widetilde{\mathbf{m}}_j^{pq}\right)_{1\le p,q\le d}$ *for* $j=i,e$ *and the second-level one* $\widetilde{\widetilde{\mathbf{M}}}_i=\left(\widetilde{\widetilde{\mathbf{m}}}_i^{pq}\right)_{1\le p,q\le d}$ *are respectively defined by:*

$$\widetilde{\mathbf{m}}_e^{pq}:=\frac{1}{|Y|}\sum_{k=1}^{d}\int_{Y_e}\left(\mathrm{m}_e^{pq}+\mathrm{m}_e^{pk}\frac{\partial\chi_e^q}{\partial y_k}\right)\,dy, \quad \widetilde{\mathbf{m}}_i^{pq}:=\frac{1}{|Z|}\sum_{\ell=1}^{d}\int_{Z}\left(\mathrm{m}_i^{pq}+\mathrm{m}_i^{p\ell}\frac{\partial\theta_i^q}{\partial z_\ell}\right)\,dz, \tag{6a}$$

$$\widetilde{\widetilde{\mathbf{m}}}_i^{pq} := \frac{1}{|Y|}\sum_{k=1}^{d}\int_{Y_i}\left(\widetilde{\mathbf{m}}_i^{pk}\frac{\partial \chi_i^q}{\partial y_k}(y) + \widetilde{\mathbf{m}}_i^{pq}\right) dy$$
$$= \frac{1}{|Y|}\frac{1}{|Z|}\sum_{k,\ell=1}^{d}\int_{Y_i}\int_{Z}\left[\left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{p\ell}\frac{\partial \theta_i^k}{\partial z_\ell}\right)\frac{\partial \chi_i^q}{\partial y_k}(y) + \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell}\frac{\partial \theta_i^q}{\partial z_\ell}\right)\right] dzdy. \tag{6b}$$

Herein, the components χ_e^q of χ_e and χ_i^q of χ_i are respectively the corrector functions, solutions of the ε-cell problems:

$$\begin{cases} -\nabla_y \cdot (\mathrm{M}_e \nabla_y \chi_e^q) = \nabla_y \cdot (\mathrm{M}_e e_q) \ \textit{in } Y_e, \\ \chi_e^q \ \textit{y-periodic}, \\ \mathrm{M}_e \nabla_y \chi_e^q \cdot n_e = -(\mathrm{M}_e e_q) \cdot n_e \ \textit{on } \Gamma^y, \end{cases} \tag{7a}$$

$$\begin{cases} -\nabla_y \cdot \left(\widetilde{\mathbf{M}}_i \nabla_y \chi_i^q\right) = \nabla_y \cdot \left(\widetilde{\mathbf{M}}_i e_q\right) \ \textit{in } Y_i, \\ \chi_i^q \ \textit{y-periodic}, \\ \widetilde{\mathbf{M}}_i \nabla_y \chi_i^q \cdot n_i = -\left(\widetilde{\mathbf{M}}_i e_q\right) \cdot n_i \ \textit{on } \Gamma^y, \end{cases} \tag{7b}$$

and the component θ_i^q of θ_i is the corrector function, solution of the δ-cell problem:

$$\begin{cases} \nabla_z \cdot (\mathrm{M}_i \nabla_z \theta_i^q) = \nabla_z \cdot (\mathrm{M}_i e_q) \ \textit{in } Z, \\ \theta_i^q \ \textit{y- and z-periodic}, \\ \mathrm{M}_i \nabla_z \theta_i^q \cdot n_z = -(\mathrm{M}_i e_q) \cdot n_z \ \textit{on } \Gamma^z, \end{cases} \tag{8}$$

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

Here, we propose two different homogenization methods that leads from the microscopic model (1) to the macroscopic bidomain model (4):

- Three-scale asymptotic expansion method.
- Three-scale unfolding method.

The first one is based on a power series expansion to formally obtain this macroscopic model. First, we use the two-scale asymptotic expansion to homogenize the extracellular problem. Next, we apply a new three-scale asymptotic expansion in the intracellular problem to obtain its homogenized equation at two levels. The first level upscaling of the intracellular structure yields the mesoscopic equation and the second one leads to the intracellular homogenized equation.

Finally, we obtain the macroscopic bidomain model independent on ε and δ describing the electrical behavior of the whole heart.

The second one is based on unfolding operators which not only derive the homogenized equations but also prove the convergence and rigorously justify the mathematical writing of the preceding formal method. Moreover, due to the nonlinear ionic terms on the membrane, we use the boundary unfolding operator and a Kolmogorov-type compactness argument.

Chapter 3

In Chapter 3, we are interested in "*tridomain*" system that is used for modeling the electrical activity of the heart in the presence of gap junctions. It is based upon the assumption that the cardiac tissue consists of two intracellular media that are connected by gap junctions and one extracellular medium (cf (**G**.2)), hence its name. Each intracellular medium and the extracellular one are separated by a cellular membrane (the sarcolemma). First, we formulate the tridomain equations at cellular level that are satisfied 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. More precisely, we consider the following **microscopic** tridomain model:

$$-\nabla \cdot \left(\mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k\right) = 0 \qquad \text{in } \Omega_{i,\varepsilon,T}^k := (0,T) \times \Omega_{i,\varepsilon}^k, \tag{9a}$$

$$-\nabla \cdot \left(\mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon}\right) = 0 \qquad \text{in } \Omega_{e,\varepsilon,T} := (0,T) \times \Omega_{e,\varepsilon}, \tag{9b}$$

$$u_{i,\varepsilon}^k - u_{e,\varepsilon} = v_\varepsilon^k \qquad \text{on } \Gamma_{\varepsilon,T}^k := (0,T) \times \Gamma_\varepsilon^k, \tag{9c}$$

$$-\mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k \cdot n_i^k = \mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon} \cdot n_e = \mathcal{I}_m^k \qquad \text{on } \Gamma_{\varepsilon,T}^k, \tag{9d}$$

$$\varepsilon \left(\partial_t v_\varepsilon^k + \mathcal{I}_{ion}\left(v_\varepsilon^k, w_\varepsilon^k\right) - \mathcal{I}_{app,\varepsilon}^k\right) = \mathcal{I}_m^k \qquad \text{on } \Gamma_{\varepsilon,T}^k, \tag{9e}$$

$$\partial_t w_\varepsilon^k - H\left(v_\varepsilon^k, w_\varepsilon^k\right) = 0 \qquad \text{on } \Gamma_{\varepsilon,T}^k, \tag{9f}$$

$$u_{i,\varepsilon}^1 - u_{i,\varepsilon}^2 = s_\varepsilon \qquad \text{on } \Gamma_{\varepsilon,T}^{1,2} := (0,T) \times \Gamma_\varepsilon^{1,2}, \tag{9g}$$

$$-\mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^1 \cdot n_i^1 = \mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^2 \cdot n_i^2 = \mathcal{I}_{1,2} \qquad \text{on } \Gamma_{\varepsilon,T}^{1,2}, \tag{9h}$$

$$\varepsilon \left(\partial_t s_\varepsilon + \mathcal{I}_{gap}\left(s_\varepsilon\right)\right) = \mathcal{I}_{1,2} \qquad \text{on } \Gamma_{\varepsilon,T}^{1,2}, \tag{9i}$$

with $k = 1, 2$ and each equation corresponds to the following sense: (9a) Intra quasi-stationary conduction, (9b) Extra quasi-stationary conduction, (9c) Transmembrane potential, (9d) Continuity equation at cell membrane, (9e) Reaction condition at the corresponding cell membrane, (9f) Dynamic coupling, (9g) Gap junction potential, (9h) Continuity equation at gap junction, (9e) Reaction condition at gap junction.

The system (9) is completed with no-flux boundary conditions on $\partial_{\text{ext}}\Omega$:

$$\left(\mathrm{M}_i^{\varepsilon}\nabla u_{i,\varepsilon}^k\right)\cdot\mathbf{n} = \left(\mathrm{M}_e^{\varepsilon}\nabla u_{e,\varepsilon}\right)\cdot\mathbf{n} = 0 \text{ on } (0,T)\times\partial_{\text{ext}}\Omega, \tag{10}$$

where $k=1,2$ and $\mathbf{n}$ is the outward unit normal to the exterior boundary of Ω. Also, we impose initial conditions on transmembrane potential v_{ε}^k, gap junction potential s_{ε} and gating variable w_{ε}^k as follows:

$$\begin{aligned} &v_{\varepsilon}^k(0,x) = v_{0,\varepsilon}^k(x),\ w_{\varepsilon}^k(0,x) = w_{0,\varepsilon}^k(x) && \text{a.e. on } \Gamma_{\varepsilon,T}^k,\\ &\text{and } s_{\varepsilon}(0,x) = s_{0,\varepsilon}(x) && \text{a.e. on } \Gamma_{\varepsilon,T}^{1,2}, \end{aligned} \tag{11}$$

with $k=1,2$.

Keeping in mind the two-scale geometry of cardiac tissue (cf (**G**.2)), the assumptions about the system are given by:

(**A**.1) The conductivity matrices are represented by continuous tensors $\mathrm{M}_j^{\varepsilon}(x) := \mathrm{M}_j\left(x,\frac{x}{\varepsilon}\right)$ for $j=i,e$, satisfying the following elliptic and periodicity conditions: there exist constants $\alpha,\beta\in\mathbb{R}$, such that $0<\alpha<\beta$ and for all $\lambda\in\mathbb{R}^d$:

$$\begin{aligned} &\mathrm{M}_j\lambda\cdot\lambda \geq \alpha\left|\lambda\right|^2,\\ &\left|\mathrm{M}_j\lambda\right| \leq \beta\left|\lambda\right|,\\ &\mathrm{M}_j\ \mathbf{y}\text{-periodic},\ \text{for } j=i,e. \end{aligned}$$

(**A**.2) 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 $\mathrm{I}_{b,ion}^k\left(w^k\right)$, 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:

$$\begin{aligned} &\frac{1}{\alpha_1}\left|v\right|^{r-1} \leq \left|\mathrm{I}_{a,ion}(v)\right| \leq \alpha_1\left(\left|v\right|^{r-1}+1\right),\ \left|\mathrm{I}_{b,ion}(w)\right| \leq \alpha_2(\left|w\right|+1),\\ &\left|H(v,w)\right| \leq \alpha_3(\left|v\right|+\left|w\right|+1),\ \text{and } \mathrm{I}_{b,ion}(w)\,v - \alpha_4 H(v,w)w \geq \alpha_5\left|w\right|^2,\\ &\tilde{\mathrm{I}}_{a,ion}: v\mapsto \mathrm{I}_{a,ion}(v)+\beta_1 v+\beta_2 \text{ is strictly increasing with } \lim_{v\to 0}\tilde{\mathrm{I}}_{a,ion}(v)/v = 0,\\ &\forall v,v'\in\mathbb{R},\ \left(\tilde{\mathrm{I}}_{a,ion}(v)-\tilde{\mathrm{I}}_{a,ion}(v')\right)(v-v') \geq \frac{1}{C}\left(1+\left|v\right|+\left|v'\right|\right)^{r-2}\left|v-v'\right|^2, \end{aligned}$$

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

(**A**.3) There exists a constant C independent of ε such that the source term $\mathcal{I}^k_{app,\varepsilon}$ satisfies the following estimation for $k = 1, 2$:

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

(**A**.4) The initial condition $v^k_{0,\varepsilon}$, $s_{0,\varepsilon}$ and $w^k_{0,\varepsilon}$ satisfy the following estimation:

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

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 $k = 1, 2$.

(**A**.5) We end by imposing the following normalization condition:

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

Then, we prove the existence and uniqueness of weak solutions of the problem (9) in the following sense

Definition 0.1 (Weak formulation of microscopic system)**.** *A weak solution to problem* (9)-(11) *is a collection* $(u^1_{i,\varepsilon}, u^2_{i,\varepsilon}, u_{e,\varepsilon}, w^1_\varepsilon, w^2_\varepsilon)$ *of functions satisfying the following conditions:*

(A) (Algebraic relation).

$$\begin{aligned} v^k_\varepsilon &:= (u^k_{i,\varepsilon} - u_{e,\varepsilon})|_{\Gamma^k_{\varepsilon,T}} && \textit{a.e. on } \Gamma^k_{\varepsilon,T}, \textit{ for } k = 1,2, \\ s_\varepsilon &:= (u^1_{i,\varepsilon} - u^2_{i,\varepsilon})|_{\Gamma^{1,2}_{\varepsilon,T}} && \textit{a.e. on } \Gamma^{1,2}_{\varepsilon,T}. \end{aligned}$$

(B) (Regularity).

$$\begin{aligned} & u^k_{i,\varepsilon} \in L^2\left(0,T; H^1\left(\Omega^k_{i,\varepsilon}\right)\right), \quad u^\varepsilon_e \in L^2\left(0,T; H^1(\Omega_{e,\varepsilon})\right), \\ & \int_{\Omega_{e,\varepsilon}} u_{e,\varepsilon}(t,x)\, dx = 0, \textit{ for a.e. } t \in (0,T), \\ & v^k_\varepsilon \in L^2\left(0,T; H^{1/2}\left(\Gamma^k_\varepsilon\right)\right) \cap L^r\left(\Gamma^k_{\varepsilon,T}\right), \\ & s_\varepsilon \in L^2\left(\Gamma^{1,2}_{\varepsilon,T}\right), \quad w^k_\varepsilon \in L^2(\Gamma^k_{\varepsilon,T}),\ k = 1,2, \\ & \partial_t v^k_\varepsilon,\ \partial_t w^k_\varepsilon \in L^2(\Gamma^k_{\varepsilon,T}) \textit{ for } k = 1,2, \quad \partial_t s_\varepsilon \in L^2(\Gamma^{1,2}_{\varepsilon,T}). \end{aligned}$$

(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).

$$\begin{aligned}&\sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\partial_t v_\varepsilon^k \psi_i^k \, d\sigma_x dt + \iint_{\Gamma_{\varepsilon,T}^{1,2}} \varepsilon\partial_t s_\varepsilon \Psi \, d\sigma_x dt + \sum_{k=1,2}\int_{\Omega_{i,\varepsilon,T}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k \cdot \nabla\varphi_i^k \, dx dt \\ &+ \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\mathcal{I}_{ion}\left(v_\varepsilon^k, w_\varepsilon^k\right)\psi_i^k \, d\sigma_x dt + \iint_{\Gamma_{\varepsilon,T}^{1,2}} \varepsilon\mathcal{I}_{gap}(s_\varepsilon)\Psi \, d\sigma_x dt \\ &= \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\mathcal{I}_{app,\varepsilon}^k \psi_i^k \, d\sigma_x dt\end{aligned} \tag{12}$$

$$\begin{aligned}&\sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\partial_t v_\varepsilon^k \psi_e^k \, d\sigma_x dt - \int_{\Omega_{e,\varepsilon,T}} \mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon} \cdot \nabla\varphi_e \, dx dt \\ &+ \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\mathcal{I}_{ion}\left(v_\varepsilon^k, w_\varepsilon^k\right)\psi_e^k \, d\sigma_x dt = \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k} \varepsilon\mathcal{I}_{app,\varepsilon}^k \psi_e^k \, d\sigma_x dt\end{aligned} \tag{13}$$

$$\iint_{\Gamma_{\varepsilon,T}^k} \partial_t w_\varepsilon^k e^k \, d\sigma_x dt = \iint_{\Gamma_{\varepsilon,T}^k} H\left(v_\varepsilon^k, w_\varepsilon^k\right) e^k \, d\sigma_x dt \tag{14}$$

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* $k = 1,2$,
- $\Psi = \Psi_i^1 - \Psi_i^2 := (\varphi_i^1 - \varphi_i^2)|_{\Gamma_{\varepsilon,T}^{1,2}} \in L^2(\Gamma_{\varepsilon,T}^{1,2})$,
- $e^k \in L^2(\Gamma_{\varepsilon,T}^k)$ *for* $k = 1,2$.

We also state the first theorem proved in this chapter

Theorem 0.2 (Microscopic Tridomain Model)**.** *Assume that the conditions (A.1)-(A.5) hold. Then, the microscopic tridomain problem* (9)-(11) *possesses a unique weak solution in the sense of Definition 0.1 for every fixed* $\varepsilon > 0$.

Notice that the proof of Theorem 0.2 is constructive, based on the Faedo-Galerkin technique on approximate systems followed by compactness in L^2. Thus, this chapter aims to address the following question, How to link information from the micro-scale to the macro-scale (e.g. via cell boundary, micro-macro conditions, ...) and how to derive the macroscopic behavior of cardiomyocytes that are connected by many gap junctions?

The homogenization procedure has helped to answer this question to connect the microscopic and macroscopic behaviors and leads to the equations of the **macroscopic** tridomain model presented in the following theorem:

Theorem 0.3 (Macroscopic Tridomain Model). *A sequence of solutions* $\left(u_{i,\varepsilon}^1, u_{i,\varepsilon}^2, u_{e,\varepsilon}, w_\varepsilon^1, w_\varepsilon^2\right)$ *of the microscopic tridomain model* (9)-(11) *(obtained in Theorem 0.2) converges as* $\varepsilon \to 0$ *to a weak solution* $\left(u_i^1, u_i^2, u_e, w^1, w^2\right)$ *such that* $u_i^k, u_e \in L^2(0,T;H^1(\Omega))$, $v^k = u_i^k - u_e \in L^2(0,T;H^1(\Omega)) \cap L^r(\Omega)$, $s = u_i^1 - u_i^2 \in L^2(0,T;H^1(\Omega))$, $\partial_t v^k \in L^2(0,T;(H^1(\Omega))') \cap L^{r/(r-1)}(\Omega_T)$, $w^k \in C(0,T;L^2(\Omega))$ *and* $\partial_t s \in L^2(\Omega_T)$ *satisfy the following reaction-diffusion system:*

$$\begin{aligned} \sum_{k=1,2} \mu_k \partial_t v^k + \nabla \cdot \left(\widetilde{\mathbf{M}}_e \nabla u_e\right) + \sum_{k=1,2} \mu_k \mathcal{I}_{ion}(v^k, w^k) &= \sum_{k=1,2} \mu_k \mathcal{I}_{app}^k && \text{in } \Omega_T, \\ \mu_1 \partial_t v^1 + \mu_g \partial_t s - \nabla \cdot \left(\widetilde{\mathbf{M}}_i \nabla u_i^1\right) + \mu_1 \mathcal{I}_{ion}(v^1, w^1) + \mu_g \mathcal{I}_{gap}(s) &= \mu_1 \mathcal{I}_{app}^1 && \text{in } \Omega_T, \\ \mu_2 \partial_t v^2 - \mu_g \partial_t s - \nabla \cdot \left(\widetilde{\mathbf{M}}_i \nabla u_i^2\right) + \mu_2 \mathcal{I}_{ion}(v^2, w^2) - \mu_g \mathcal{I}_{gap}(s) &= \mu_2 \mathcal{I}_{app}^2 && \text{in } \Omega_T, \\ \partial_t w^k - H(v^k, w^k) &= 0 && \text{on } \Omega_T, \end{aligned} \tag{15}$$

completed with no-flux boundary conditions on u_i, u_e *on* $\partial_{ext}\Omega$:

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

and initial conditions for the transmembrane potential v^k*, the gap potential* s *and the gating variable* w^k :

$$v^k(0,x) = v_0^k(x), \ s(0,x) = s_0(x) \text{ and } w^k(0,x) = w_0^k(x),$$

where $\mu_k = \left|\Gamma^k\right| / |Y|$, $k = 1,2$, *(resp.* $\mu_g = |\Gamma^{1,2}| / |Y|$*) is the ratio between the surface membrane (resp. the gap junction) and the volume of the reference cell. Furthermore,* $\mathbf{n}$ *represent the outward unit normal to the boundary of* Ω*. Herein, the homogenized conductivity matrices*

$\widetilde{\mathbf{M}}_j = \left(\widetilde{\mathbf{m}}_j^{pq}\right)_{1\leq p,q\leq d}$ *for* $j = i, e$ *are respectively defined by:*

$$\widetilde{\mathbf{m}}_i^{pq} := \frac{1}{|Y|}\sum_{\ell=1}^{d}\int_{Y_i^k}\left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell}\frac{\partial \chi_i^q}{\partial y_\ell}\right)\,dy, \tag{16a}$$

$$\widetilde{\mathbf{m}}_e^{pq} := \frac{1}{|Y|}\sum_{\ell=1}^{d}\int_{Y_e}\left(\mathrm{m}_e^{pq} + \mathrm{m}_e^{p\ell}\frac{\partial \chi_e^q}{\partial y_\ell}\right)\,dy, \tag{16b}$$

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

$$\begin{cases} -\nabla_y \cdot (\mathrm{M}_e \nabla_y \chi_e^q) = \nabla_y \cdot (\mathrm{M}_e e_q) \;\textit{ in } Y_e, \\ \chi_e^q \; y\textit{-periodic}, \\ \mathrm{M}_e \nabla_y \chi_e^q \cdot n_e = -(\mathrm{M}_e e_q)\cdot n_e \;\textit{on}\; \Gamma^k,\; k = 1,2 \end{cases} \tag{17a}$$

$$\begin{cases} -\nabla_y \cdot (\mathrm{M}_i \nabla_y \chi_i^q) = \nabla_y \cdot (\mathrm{M}_i e_q) \;\textit{ in } Y_i^k, \\ \chi_i^q \; y\textit{-periodic}, \\ \mathrm{M}_i \nabla_y \chi_i^q \cdot n_i^k = -(\mathrm{M}_i e_q)\cdot n_i^k \;\textit{on}\; \Gamma^k,\; k = 1,2 \\ \mathrm{M}_i \nabla_y \chi_i^q \cdot n_i^k = -(\mathrm{M}_i e_q)\cdot n_i^k \;\textit{on}\; \Gamma^{1,2}, \end{cases} \tag{17b}$$

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

The proof of Theorem 0.3 is proved using two different homogenization methods:

- two-scale asymptotic expansion.
- Unfolding homogenization method.

As explained before, the first method is a formal and intuitive method based on a two-scale asymptotic expansion method. While, the second one 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 formal method. Furthermore, the uniqueness of the solutions to the macroscopic model can be proved similar as that of the microscopic model with a small change. This implies that all the convergence results remain valid for the whole sequence.

List of Publications

To conclude this introduction, a review of the articles that illustrate the work produced in this thesis in their order of appearance is proposed.

- **Published article:**
  - ⋆ F. Bader, M. Bendahmane, M. Saad and R. Talhouk. Derivation of a new macroscopic bidomain model including three scales for the electrical activity of cardiac tissue, *Journal of Engineering Mathematics*, 131(1), pp. 1-30, Springer (2021).
    This paper presents the results obtained in the first part of Chapter 2.
  - ⋆ F. Bader, M. Bendahmane, M. Saad and R. Talhouk. Three scale unfolding homogenization method applied to the bidomain model, *Acta Applicandae Mathematicae*, 176(1), pp. 1-37, Springer (2021).
    This paper presents the results obtained in the second part of Chapter 2.
- **Submitted articles:**
  - ⋆ F. Bader, M. Bendahmane, M. Saad and R. Talhouk. Microscopic tridomain model of electrical activity in the heart with dynamical gap junctions. Part 1- Modeling and Well-posedness, Submitted.
    This paper presents the results obtained in the first part of Chapter 3.
  - ⋆ F. Bader, M. Bendahmane, M. Saad and R. Talhouk. Microscopic tridomain model of electrical activity in the heart with dynamical gap junctions. Part 2- Derivation of the macroscopic tridomain model by homogenization methods, Submitted.
    This paper presents the results obtained in the second part of Chapter 3.

1

Cardiac Electro-physiological Models

Before we dive into details about the mathematical modeling of the cardiac electro-physiology, let us give a motivation to study the heart into details. This chapter is organized as follows. In Section 1.1, we briefly review the basic physiology and the functionality of the heart. In Section 1.2, we present the macro- and microscopic description of the cardiac bioelectrical activity. In Section 1.3, we specify the multi-scale representation of the heart tissue we have in mind. Finally, Section 1.4 contains the mathematical models of the cardiac tissue.

1.1 Heart anatomy and electrocardiology

The heart is a hollow muscle whose role is to pump blood to the body's organ through blood vessels. It is located near the center of the thoracic cavity between the right and left lungs. It is a muscular organ can be viewed as double pump consisting of four chambers: upper left and right atria, separated by the inter-atrial septum and lower left and right ventricles, separated by the inter-ventricular septum. Atria and ventricles are separated by the atrioventricular valves, which contains the tricuspid valve in the right heart and the mitral valve in the left heart. The right ventricle is connected to the pulmonary artery via the pulmonary valve and the left one is connected to the aorta via the aortic valve, see Figure 1.1 for a schematic view and [Kat10] for more details.

The left ventricular wall is about three times thicker than the right one, while the atrial walls are considerably thinner. The right heart receives blood low in oxygen from the systemic circulation, which enters the right atrium from the superior and inferior vena cava and passes to the right ventricle. From here it is functioned as a pump driving blood through the pulmonary circulation, to the lungs where it receives oxygen and gives off carbon dioxide. Oxygenated blood then returns to the left atrium, passes through the left ventricle and the left heart functions as another pump driving this oxygenated blood through the systemic circulation, to every other part of the body. This is why the left ventricle is larger and more powerful than the right, as it has to pump blood over greater distances. This is also why left ventricular pressure is higher than right ventricular pressure.

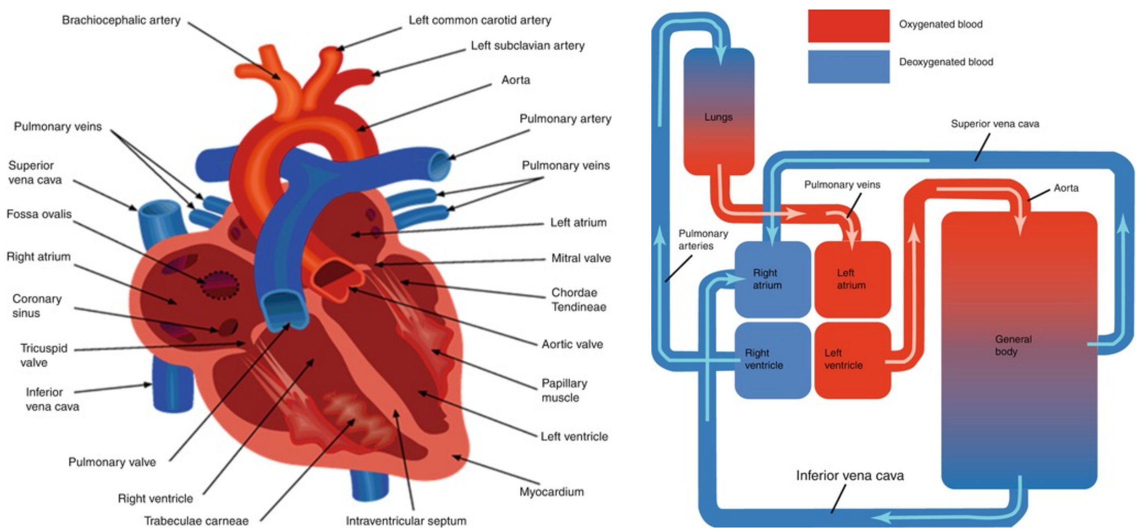

Figure 1.1 – Schematic diagram of the heart anatomy. `https://thoracickey.com/cardiac-anatomy-and-electrophysiology/`

1.2 Physiological background

In order to pump the blood, the atria and the ventricles contract at each cardiac cycle. An electrical signal is at the origin of the contraction. Indeed, at each cardiac beat, an electrical signal crosses the heart and depolarizes the cardiac cells thus triggering their contraction.

1.2.1 Macroscopic description

The heart is essentially a muscle that contracts and pumps blood. Its four cavities are surrounded by a cardiac tissue (myocardium) that is organized into muscle fibers (see Figure 1.2). These fibers consists of specialized muscle cells called "cardiac myocytes".

At the heart scale, the contraction of cardiomyocytes is initiated by electrical signals, known as *action potentials*, which are described by the following schematic path (see Figure 1.3):

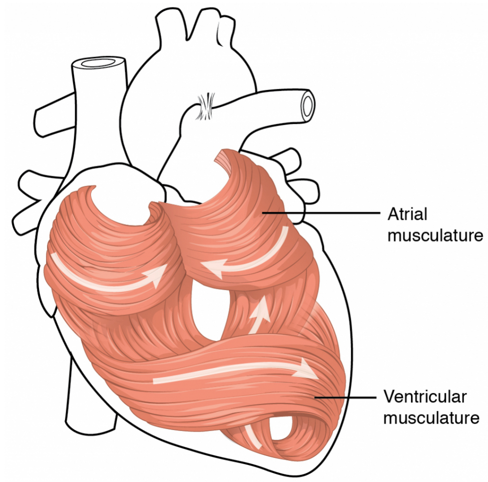

Figure 1.2 – Spiral arrangement of muscle cells.
http://ressources.unisciel.fr/physiologie/co/4a_1.html

1. These impulses start at the sinoatrial (SA) node, from a small group of myocytes called the "pacemaker" cells located on the top of the right atrium. Hence they constitute the cardiac conduction system and control the electrical activity of the entire heart in normal conditions. The pacemaker cells of SA node fire spontaneously, generating action potentials that propagates throughout the right atrium and through Bachmann's bundle to the left atrium in order to stimulate the muscle contraction of both atria.
2. The signal travels to the atrioventricular (AV) node located between the atria and the ventricles where the inter-atrial septum and inter-ventricular septum meet. In the AV node, impulses are slowed down for a very short period.
3. After passing through the AV node, the electrical signal then continue down the conduction pathway via a common bundle (bundle of His) into the ventricles. The bundle of His divides into right and left bundle branches and these branches are also subdivided into a complex network of Purkinje fibers, causing the right and left ventricles to contract. Each contraction of the ventricles represents one heartbeat.

1.2.2 Microscopic description

Cardiomyocytes, or myocardiocytes, are different from the other two main types of muscle cells, skeletal and smooth muscles in a number of ways. Unlike other muscle cells in the body, cardiomyocytes are highly resistant to fatigue and therefore always contracting and relaxing to

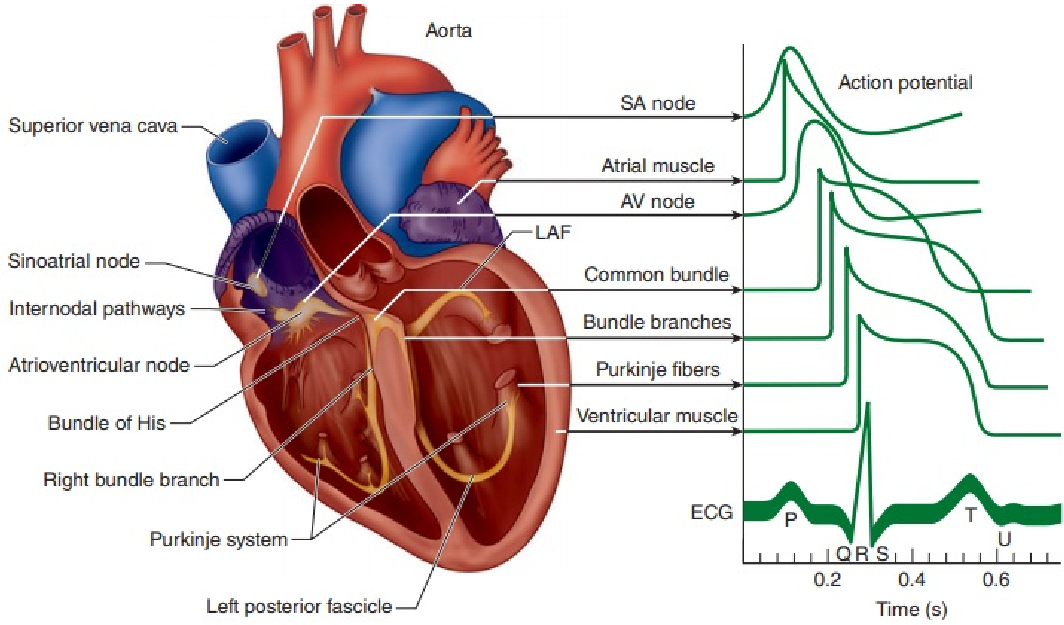

Figure 1.3 – Propagation of cardiac action potential and relative action profile for each part of the heart. `http://www.brainkart.com/article/Cardiac-Action-Potentials_26936/`

ensure proper circulation of blood around the body. However, in comparison with skeletal muscle cells, cardiomyocytes are narrower and much shorter, being about 50-150 μm long and 10-20 μm in diameter.

They are enclosed by a lipid cell membrane called the sarcolemma, are connected by junctions known as intercalated discs, and contain one or more nuclei, mitochondria in addition to various organelles filling the cytoplasm (the contents of the cardiomyocytes) whose functions are respectively described below:

The sarcolemma. The cell membrane consists of a phospholipid bilayer which provides protection for a cardiomyocyte. It acts as a semi-permeable barrier between the cytoplasm (the intracellular compartment) and the the fluid outside these cells (the extracellular compartment). It has two primary functions: it keeps toxic substances out of the cell; and contains channels, pumps and exchangers that allow the flow of specific ions (sodium Na^+, potassium K^+ and calcium Ca^{2+}) and some proteins, that maintains concentration differences of these ions involved in the action potential. The difference of concentrations across the sarcolemma creates a *transmembrane potential* v, which is the difference in potential between the intracellular and extracellular media. Hence, the cell membrane is modeled as a resistor-capacitor circuit (RC circuit) which is defined by using the current conservation law:

$$C_m \frac{dv}{dt} + \mathrm{I}_{ion} = \mathrm{I}_{app}, \tag{1.1}$$

where C_m is the membrane capacitance, I_{ion} and I_{app} are respectively the ionic and applied currents across the cell membrane. The structure of the total ionic current will be described by the specific ionic membrane model adopted. These circuit models have been formulated in Subsection 1.4.3 with several descriptions of ion channels.

Intercalated disks. They are part of the sarcolemma and contain two important structures in cardiac muscle contraction: gap junctions and desmosomes. Gap junctions allows the movement of not only inorganic ions but also organic ions such as sugars, amino acids and nucleotides between two adjacent cells. It provide the pathways for intracellular current flow, enabling coordinated action potential propagation. So, the difference of chemical through the gap junction produces a *gap potential* s, which is the difference in potential between these two intracellular media. So, the gap junction is also modeled as RC circuit which is given by:

$$C_{gap} \frac{ds}{dt} = -\mathrm{I}_{gap}, \tag{1.2}$$

where C_{gap} represents the capacity per unit area of the intercalated disc and I_{gap} represents the corresponding resistive current.

Unlike gap junctions, desmosomes serve to anchor ends of cardiac muscle fibers together. This prevents the cells of the cardiac muscles from pulling apart during contraction. Desmosomes are able to withstand mechanical stress which allows them to hold cells together.

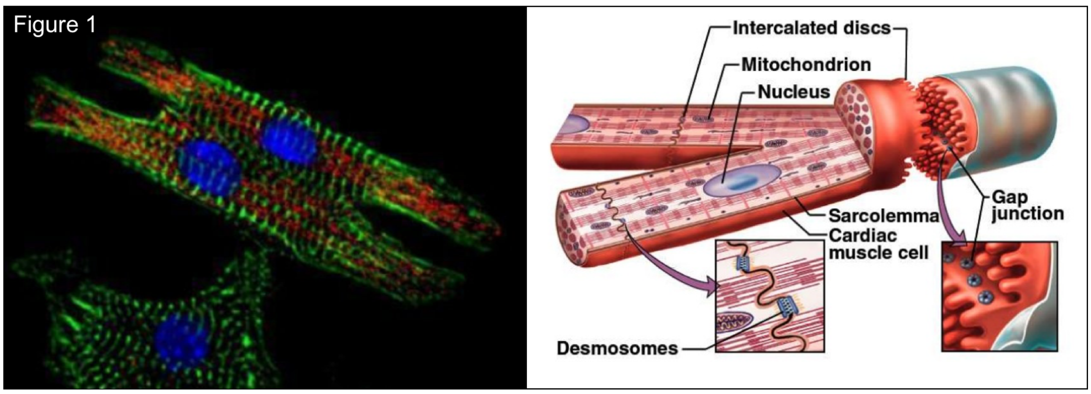

Figure 1.4 – Representation of the cardiomyocyte structure.
http://www.cardio-research.com/cardiomyocytes

Mitochondria. They play numerous roles in the body, including energy production, reactive oxygen species generation and signal transduction. Cardiac tissue contains far more mitochondria than any other type of muscles because the constantly-beating heart works harder than any other organ in the body. By comparison, the heart tissue has about 5,000 mitochondria per cell while the tissue of the biceps muscle has about 200 mitochondria per cell. Mitochondria play numerous roles in the body, including energy production, reactive oxygen species generation and signal transduction. Hence, they are often described as the "energy powerhouses" of cardiomyocytes.

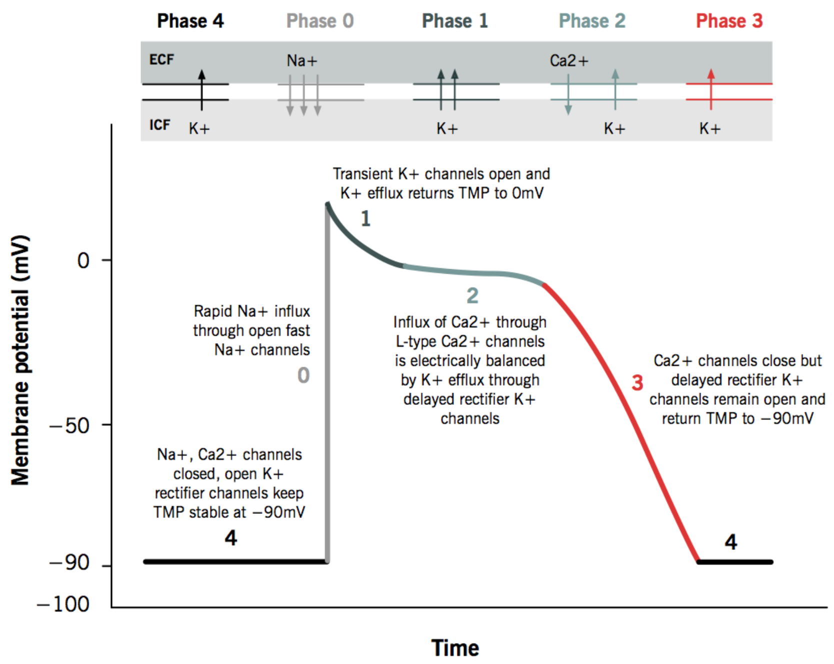

Figure 1.5 – Phases of the ventricular action potential.
http://www.pathophys.org/physiology-of-cardiac-conduction-and-contractility/

At the cellular scale, we are interested in the action potential which corresponds to the evolution in time of the transmembrane potential, that is the difference between the extracellular and intracellular potentials, in the cell. The action potential can pass through the entire heart within 220 ms after initiation in the SA node. The ventricular action potential in typical cardiomyocytes is composed of five phases $(0$-$4)$, beginning and ending with phase 4 (see Figure 1.5):

Phase 4 (resting potential)

- The resting potential in a cardiomyocyte is -90 mV due to a constant outward leak of K^+ through inward rectifier channels.

- Na^+ and Ca^{+2} channels are closed at resting potential.

Phase 0 (depolarization)

- An action potential triggered in a neighboring cardiomyocyte causes the transmembrane potential to rise above -90 mV.
- Fast Na^+ channels start to open one by one and Na+ leaks into the cell, further raising the transmembrane potential.
- The large Na^+ current rapidly depolarizes the transmembrane potential to 0 mV and slightly above 0 mV for a transient period of time called the overshoot; fast Na^+ channels close.
- L-type ("long-opening") Ca^{2+} channels open when the transmembrane potential is greater than -40 mV and cause a small but steady influx of Ca^{2+} down its concentration gradient.

Phase 1 (early repolarization)

- Transmembrane potential is now slightly positive.
- Some K^+ channels open briefly and an outward flow of K^+ returns the TMP to approximately 0 mV.

Phase 2 (plateau)

- L-type Ca^{2+} channels are still open and there is a small, constant inward current of Ca^{2+}. This becomes significant in the excitation-contraction coupling process.
- K^+ leaks out down its concentration gradient through delayed rectifier K^+ channels.
- These two counter-currents are electrically balanced, and the transmembrane potential is maintained at a plateau just below 0 mV throughout phase 2.

Phase 3 (repolarization)

- Ca^{2+} channels are gradually inactivated.
- Persistent outflow of K+, now exceeding Ca^{2+} inflow, brings transmembrane potential back towards resting potential of -90 mV to prepare the cell for a new cycle of depolarization.
- Normal ionic concentration gradients are restored by returning Na^+ and Ca^{2+} ions to the extracellular environment, and K^+ ions to the cell interior.

It may be noted that the cardiac action potential is different from the surface electrocardiogram (ECG) which represent the sum total of all electrical activity of the heart as recorded from the body surface (see Figure 1.4). We refer the reader to [Rus89] for more details about the cardio-vascular system.

1.3 Multi-scale representation of cardiac tissue

Myocytes volume and shape can be complex and variable, according to the tissue region, species, developmental stage and disease processes. Here, we consider two simplified micro-structure models that can be handled successfully: (i) Three-scale geometry of cardiac tissue, and (ii) Two-scale geometry of cardiac tissue with gap junction connections. Case (i) concerned the meso- and microscopic structure so that the heart tissue could be seen as a periodic double arrangement of unit cells. While in case (ii), we describe the cardiac tissue on a microscopic scale only as a periodic domain in the presence of connections (gap junctions) between the cardiomyocytes.

1.3.1 Three-scale geometry of cardiac tissue

The cardiac tissue $\Omega \subset \mathbb{R}^d$ is considered as a heterogeneous periodic domain with a Lipschitz boundary $\partial\Omega$. The structure of the tissue is periodic at meso- and microscopic scales related to two small parameters ε and δ, respectively, see Figure 1.6.

Following the standard approach of the homogenization theory, this structure is featured by two parameters ℓ^{mes} and ℓ^{mic} characterizing, respectively, the mesoscopic and microscopic length of a cell in meso- or microscopic domain. Under the two-level scaling, the characteristic lengths ℓ^{mes} and ℓ^{mic} are related to a given macroscopic length L (of the cardiac fibers), such that the two scaling parameters ε and δ are introduced by:

$$\varepsilon = \frac{\ell^{\text{mes}}}{L} \text{ and } \delta = \frac{\ell^{\text{mic}}}{L} \quad \text{with} \quad \ell^{\text{mic}} << \ell^{\text{mes}}.$$

The mesoscopic scale. The domain Ω is composed of two ohmic volumes, called intracellular $\Omega_i^{\varepsilon,\delta}$ and extracellular Ω_e^{ε} medium (for more details see [PSF05]). Geometrically, we find that $\Omega_i^{\varepsilon,\delta}$ and Ω_e^{ε} are two open connected regions such that:

$$\overline{\Omega} = \overline{\Omega}_i^{\varepsilon,\delta} \cup \overline{\Omega}_e^{\varepsilon}, \text{ with } \Omega_i^{\varepsilon,\delta} \cap \Omega_e^{\varepsilon} = \emptyset.$$

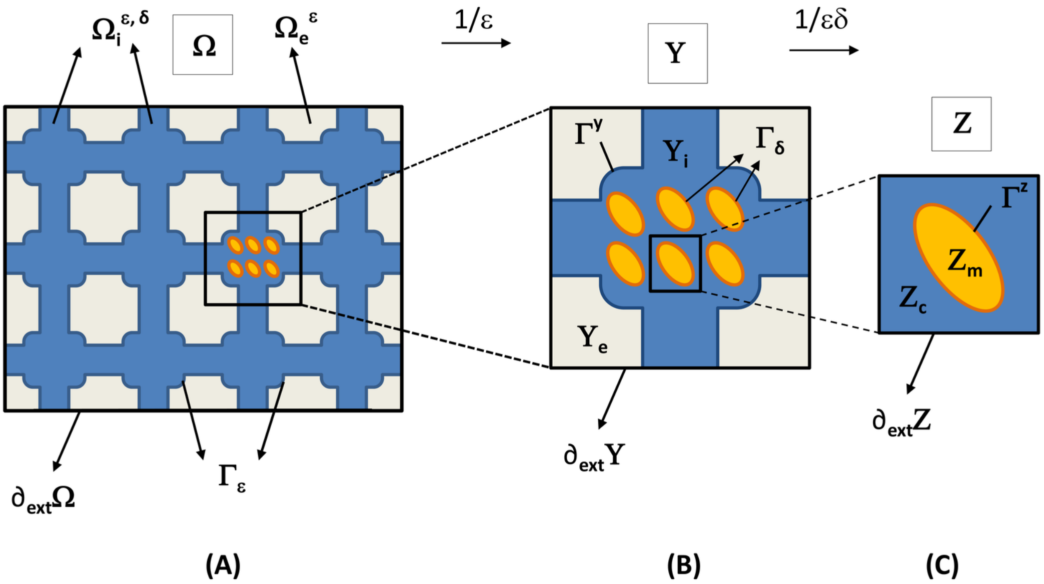

Figure 1.6 – (A) Periodic heterogeneous domain Ω, (B) Unit cell Y at ε-structural level and (B) Unit cell Z at δ-structural level.

These two regions are separated by the surface membrane Γ_ε which is expressed by:

$$\Gamma_\varepsilon = \partial\Omega_i^{\varepsilon,\delta} \cap \partial\Omega_e^{\varepsilon},$$

assuming that the membrane is regular. We can observe that the domain $\Omega_i^{\varepsilon,\delta}$ as a perforated domain obtained from Ω by removing the holes which correspond to the extracellular domain Ω_e^{ε}.

At this $\boldsymbol{\varepsilon}$-structural level, we can divide Ω into N_ε small elementary cells $Y_\varepsilon = \prod_{n=1}^{d}]0, \varepsilon\, \ell_n^{\text{mes}}[$, with $\ell_1^{\text{mes}}, \ldots, \ell_d^{\text{mes}}$ are positive numbers. These small cells are all equal, thanks to a translation and scaling by ε, to the same unit cell of periodicity called the reference cell $Y = \prod_{n=1}^{d}]0, \ell_n^{\text{mes}}[$. Next, we denote by T_ε^k a translation of εk with $k = (k_1, \ldots, k_d) \in \mathbb{Z}^d$. Note that if the cell considered Y_ε^k is located at the $k_n^{\text{ième}}$ position according to the direction n of space considered, we can write:

$$Y_\varepsilon^k := T_\varepsilon^k + \varepsilon Y = \{\varepsilon\xi : \xi \in k_\ell + Y\},$$

with $k_\ell := (k_1\ell_1^{\text{mes}}, \ldots, k_d\ell_d^{\text{mes}})$.
Therefore, for each macroscopic variable x that belongs to Ω, we define the corresponding meso-

scopic variable $y \approx \dfrac{x}{\varepsilon}$ that belongs to Y with a translation. Indeed, we have:

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

Since, we will study in the extracellular medium Ω_e^ε the behavior of the functions $u(x,y)$ which are **y**-periodic, so by periodicity we have $u\left(x, \dfrac{x}{\varepsilon} - k_\ell\right) = u\left(x, \dfrac{x}{\varepsilon}\right)$. By notation, 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 mesoscale. The mesoscopic unit cell Y is also divided into two parts: intracellular Y_i and extracellular Y_e. These two parts are separated by a common boundary Γ^y. So, we have:

$$Y = Y_i \cup Y_e \cup \Gamma^y, \quad \Gamma^y = \partial Y_i \cap \partial Y_e.$$

In a similar way, we can write the corresponding common periodic boundary as follows:

$$\Gamma_\varepsilon^k := T_\varepsilon^k + \varepsilon \Gamma^y = \{\varepsilon\xi : \xi \in k_\ell + \Gamma^y\},$$

with T_ε^k denote the same previous translation.

In summary, the intracellular and extracellular medium at mesoscale can be described as the intersection of the cardiac tissue Ω with the cell $Y_{j,\varepsilon}^k$ for $j = i, e$:

$$\Omega_i^\varepsilon = \Omega \cap \bigcup_{k \in \mathbb{Z}^d} Y_{i,\varepsilon}^k, \quad \Omega_e^\varepsilon = \Omega \cap \bigcup_{k \in \mathbb{Z}^d} Y_{e,\varepsilon}^k, \quad \Gamma_\varepsilon = \Omega \cap \bigcup_{k \in \mathbb{Z}^d} \Gamma_\varepsilon^k,$$

with each cell defined by $Y_{j,\varepsilon}^k = T_\varepsilon^k + \varepsilon Y_j$ for $j = i, e$.

The microscopic scale. The cytoplasm contains far more mitochondria described as "the powerhouse of the myocardium" surrounded by another membrane Γ_δ. Then, we only assume that the intracellular medium $\Omega_i^{\varepsilon,\delta}$ can also be viewed as a periodic perforated domain.

At this $\boldsymbol{\delta}$-structural level, we can divide this medium with the same strategy into small elementary cells $Z_\delta = \prod_{n=1}^{d}]0, \delta\, \ell_n^{\text{mic}}[$, with $\ell_1^{\text{mic}}, \ldots, \ell_d^{\text{mic}}$ are positive numbers. Using a similar translation (noted by $T_\delta^{k'}$), we return to the same unit cell noted by $Z = \prod_{n=1}^{d}]0, \ell_n^{\text{mic}}[$. Note that if the cell considered $Z_\delta^{k'}$ is located at the $k_n^{'\text{ième}}$ position according to the direction n of space considered, we can write:

$$Z_\delta^{k'} := T_\delta^{k'} + \delta Z = \{\delta\zeta : \zeta \in k'_{\ell'} + Z\},$$

with $k'_{\ell'} := (k'_1 \ell_1^{\text{mic}}, \ldots, k'_d \ell_d^{\text{mic}})$.
Therefore, for each macroscopic variable x that belongs to Ω, we also define the corresponding microscopic variable $z \approx \dfrac{y}{\delta} \approx \dfrac{x}{\varepsilon\delta}$ that belongs to Z with a translation $T_\delta^{k'}$.

The microscopic reference cell Z splits into two parts: mitochondria part Z_m and the complementary part $Z_c := Z \setminus Z_m$. These two parts are separated by a common boundary Γ^z. So, we have:

$$Z = Z_m \cup Z_c \cup \Gamma^z, \quad \Gamma^z = \partial Z_m.$$

By definition, we have $\partial Z_c = \partial_{\text{ext}} Z \cup \Gamma^z$.

More precisely, we can write the intracellular meso- and microscopic domain $\Omega_i^{\varepsilon,\delta}$ as follows:

$$\Omega_i^{\varepsilon,\delta} = \Omega \cap \bigcup_{k \in \mathbb{Z}^d} \left(Y_{i,\varepsilon}^k \cap \bigcup_{k' \in \mathbb{Z}^d} Z_{c,\delta}^{k'} \right)$$

with $Z_{c,\delta}^{k'}$ is defined by:

$$Z_{c,\delta}^{k'} := T_\delta^{k'} + \delta Z_c = \{\delta\zeta : \zeta \in k'_{\ell'} + Z_c\}.$$

In the intracellular medium $\Omega_i^{\varepsilon,\delta}$, we will study the behavior of the functions $u(x,y,z)$ which are **z**-periodic, so by periodicity we have $u\left(x, y, \dfrac{x}{\varepsilon\delta} - \dfrac{k_\ell}{\delta} - k'_{\ell'}\right) = u\left(x, y, \dfrac{x}{\varepsilon\delta}\right)$. By notation, we say that $z = \dfrac{x}{\varepsilon\delta}$ belongs to Z.

The microscopic unit cell Z considered as a reference perforated periodicity cell. Further, we denote by Γ^z the interface between the reference cell Z and the mitochondrion. By definition, we have $\partial Z = \partial_{\text{ext}} Z \cup \Gamma^z$. Similarly, we describe the common boundary at microscale as follows:

$$\Gamma_\delta = \Omega \cap \bigcup_{k' \in \mathbb{Z}^d} \Gamma_\delta^{k'},$$

where $\Gamma_\delta^{k'}$ given by:

$$\Gamma_\delta^{k'} := T_\delta^{k'} + \delta\Gamma^z = \{\delta\zeta : \zeta \in k'_{\ell'} + \Gamma^z\},$$

with $T_\delta^{k'}$ denote the same previous translation. Some other examples of periodic heart tissue approximations are studied at two scales e.g. in [HY09; PSF05; Ben+19] where the mitochondria are ignored.

1.3.2 Two-scale geometry of cardiac tissue with gap junction connections

The cardiac tissue $\Omega \subset \mathbb{R}^d$ $(d \geq 3)$ is considered as a heterogeneous periodic domain with a Lipschitz boundary $\partial\Omega$. The structure of the tissue is periodic at microscopic scale related to small parameter ε, see Figure 1.7.

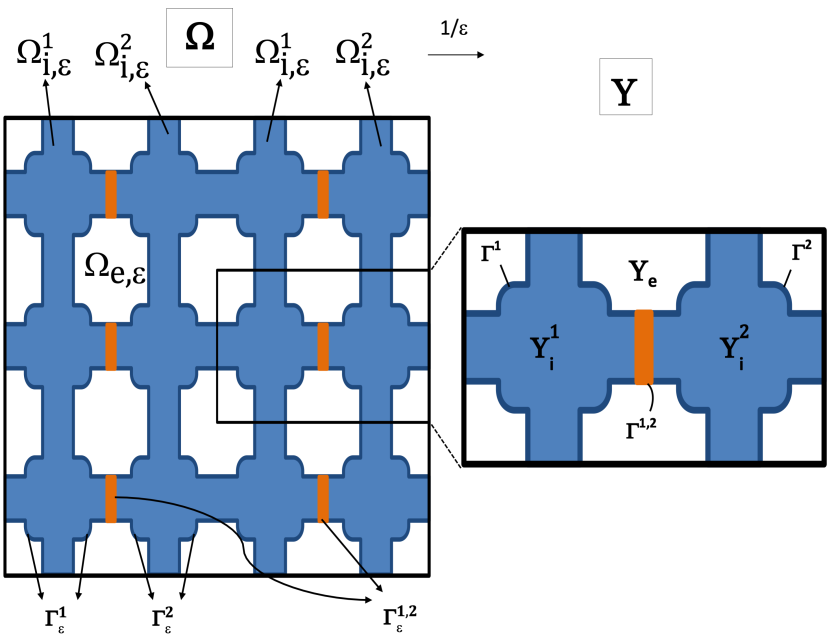

Figure 1.7 – (Left) Periodic heterogeneous domain Ω. (Right) Unit cell Y at ε-structural level.

Following the standard approach of the homogenization theory, this structure is featured by ℓ^{mic} characterizing the microscopic length of a cell. 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:

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

Physiologically, the cardiac cells are connected by many gap junctions. Therefore, geometrically, the domain Ω consists of two intracellular media $\Omega^k_{i,\varepsilon}$ for $k = 1, 2$, that are connected by gap junctions $\Gamma^{1,2}_\varepsilon = \partial\Omega^1_{i,\varepsilon} \cap \partial\Omega^2_{i,\varepsilon}$ and extracellular medium $\Omega_{e,\varepsilon}$ (for more details see [Tve+17; Jæg+19]). Each intracellular medium $\Omega^k_{i,\varepsilon}$ and the extracellular one $\Omega_{e,\varepsilon}$ are separated by the surface membrane Γ_ε^k (the sarcolemma) which is expressed by:

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

while the remaining (exterior) boundary is denoted by $\partial_{\text{ext}}\Omega$. We can observe that the intracellular domains 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 unit 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 $Y_{\varepsilon,h}$:

$$Y_{\varepsilon,h} := T_\varepsilon^h + \varepsilon Y = \{\varepsilon\xi : \xi \in h_\ell + Y\}, \tag{1.3}$$

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 **y**-periodic, so by periodicity we have $u\left(x, \dfrac{x}{\varepsilon} - h_\ell\right) = u\left(x, \dfrac{x}{\varepsilon}\right)$. By notation, 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 unit 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:

$$\Gamma_{\varepsilon,h} = T_\varepsilon^h + \varepsilon\Gamma = \{\varepsilon\xi : \xi \in h_\ell + \Gamma\}, \tag{1.4}$$

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:

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

where $Y_{i,\varepsilon,h}^k$, $Y_{e,\varepsilon,h}$ and $\Gamma_\varepsilon^k, \Gamma_\varepsilon^{1,2}$ are respectively defined as (1.3)-(1.4) for $k = 1, 2$.

Both sets $\Omega_{i,\varepsilon}^k$, $k = 1, 2$ and $\Omega_{e,\varepsilon}$ are assumed to be connected Lipschitz domains so that a Poincaré-Wirtinger inequality is satisfied in both domains. The boundaries Γ^k, $k = 1, 2$ and $\Gamma^{1,2}$ are smooth manifolds such that Γ_ε^k, $k = 1, 2$ and $\Gamma_\varepsilon^{1,2}$ are smooth and connected. Note however that it is impossible to have both $\Omega_{i,\varepsilon}^k$, $k = 1, 2$ and $\Omega_{e,\varepsilon}$ connected in a two-dimensional picture.

1.4 Mathematical Models of Cardiac Tissue

Cardiac electro-physiology models describes the electrical phenomena taking place in the heart tissue. In this chapter, we present two different models in cardiac electro-physiology. The microscopic model gives a detailed description of the electrical activity in the cells responsible for the heart contraction. While the macroscopic model is deduced from the microscopic one, using homogenization techniques, describes the propagation of this electrical wave in the heart. This kind of models appears in a multitude of real-world applications and are therefore of great importance mainly because they are able to connect the information from the micro-scale to the macro-scale (e.g. via the boundary of the cell, micro-macro conditions, ...). They are usually obtained in the homogenization limit as the scale of the inhomogeneity goes to zero. These models provide a way to represent a continuous distribution of cells within a global reference geometry.

One of the most commonly used approach for simulating cardiac activation is the so-called "bidomain model" because it includes an explicit representation of intra- and extracellular spaces. It was first proposed by Schmitt [Sch69] who formulated a macroscopic description of the cardiac tissue from two inter-penetrating domains which are the intracellular and extracellular domains at the microscopic scale, representing respectively the space inside the cardiac cells and the region between them. The first mathematical formulation of this model was constructed by Tung [Tun78] and it has been used in numerous studies [FS02; PSF05; CFPS12], [HY09] and others. This variant leads to two quasi-static whose unknowns are intra- and extracellular electric potentials coupled with non linear ordinary differential equations called ionic models at the membrane. They represent the transmembrane currents and other cellular ionic processes. Here, our bidomain model are studied at three different (macro-meso-micro) scales while others bidomain problems are treated only at micro-macro scales. Then, homogenization procedure allows for the deduction of the macroscopic behaviors from the microscopic ones and leads to the equations of the macroscopic bidomain model. Furthermore, we introduce other simplification of the macroscopic bidomain model for the electrical propagation in myocardial tissue, known as "monodomain" and "eikonal" models, where the bidomain model can be rewritten as a single parabolic reaction-diffusion equation for the transmembrane potential (still coupled with the same ODE system modeling cell membrane). The macroscopic bidomain model is quite popular for its physiological foundation and relevance whereas the monodomain and eikonal models are a heuristic approximation of the previous one, lacking this physiological foundation but providing computational facilities.

Another model describes the electrical activity of myocytes cells in the presence of gap junctions, known as "tridomain" model (see [Tve+17; Jæg+19] for more details). Comparing to the bidomain model, the cells are not only electrically coupled by the cell membrane which are resistively connected to the extracellular space but are also connected to each other by many gap junctions. The tridomain model thus allows for a more detailed analysis of the properties of cardiac conduction than the classical bidomain and monodomain models. From the mathematical viewpoint, 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 through a dynamic boundary equation at each cell membrane (the sarcolemma). Departing from this microscopic tridomain model, we apply the homogenization theory (see in the next chapter) to derive the macroscopic one.

We first consider the microscopic bidomain and tridomain models, respectively, in Section 1.4.1 and 1.4.2, coupled with various ionic membrane models. The first model is described at three scales by considering the presence of mitochondria in the cells while the second one described at two scales only taking into account that the cardiac cells are connected to each other by gap junctions. Having as departure point a microscopic model, we want to derive in the following chapters, by means of homogenization techniques, the corresponding macroscopic, monodomain and eikonal models of reaction-diffusion type used in electro-cardiology to simulate spreading of excitation potential waves in the myocardium, see Section 1.5 for more details. In the sequel, the space-time set $(0,T)\times O$ is denoted by O_T in order to simplify the notation.

1.4.1 The Meso-Microscopic Bidomain Model

The meso-microscopic bidomain equations modeling the propagation of cardiac action potentials at the cellular level. Note that the cardiac tissue at meso-scale can be viewed as composed by two ohmic volumes: the intracellular space Ω_i (inside the cells) and the extracellular space Ω_e (outside) separated by the active membrane Γ^y (see Subsection 1.3.1).

Thus, the membrane Γ^y is pierced by proteins whose role is to ensure ionic transport between the two media (intracellular and extracellular) through this membrane. So, this transport creates an electric current.

So by using Ohm's law, the intracellular and extracellular electrical potentials $u_j : \Omega_{j,T} \mapsto \mathbb{R}$ are related to the current volume densities $J_j : \Omega_{j,T} \mapsto \mathbb{R}^d$ for $j = i, e$:

$$J_j = \mathrm{M}_j \nabla u_j, \text{ in } \Omega_{j,T} := (0,T) \times \Omega_j,$$

with M_j represent the corresponding conductivities of the tissue (given in mS/cm^2).
In addition, the *transmembrane* potential v is known as the potential at the membrane Γ^y which is defined as follows:

$$v = (u_i - u_e)|_{\Gamma^y} : (0,T) \times \Gamma^y \mapsto \mathbb{R}.$$

Moreover, we assume the intracellular and extracellular spaces are source-free and thus the intracellular and extracellular potentials u_i and u_e are solutions to the elliptic equations:

$$-\operatorname{div} J_j = 0, \text{ in } \Omega_{j,T}. \tag{1.5}$$

According to the current conservation law, the surface current density $\mathcal{I}_m$ is now introduced:

$$\mathcal{I}_m = -J_i \cdot n_i = J_e \cdot n_e, \text{ on } \Gamma_T^y := (0,T) \times \Gamma^y, \tag{1.6}$$

with n_i denotes the unit exterior normal to the boundary Γ^y from intracellular to extracellular space and $n_e = -n_i$.

The membrane has both a capacitive property schematized by a capacitor and a resistive property schematized by a resistor (see Figure 1.8). On the one hand, the capacitive property depends on the formation of the membrane which can be represented by a capacitor of capacitance C_m (the capacity per unit area of the membrane is given in $\mu\mathrm{F/cm}^2$). We recall that the quantity of the charge of a capacitor is $q = C_m v$. Then, the capacitive current $\mathcal{I}_c$ is the amount of charge

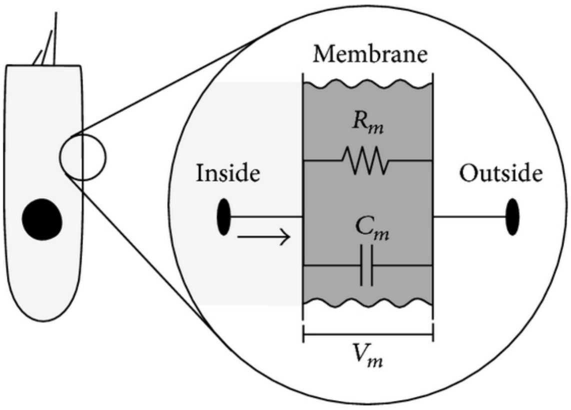

Figure 1.8 – Electrical circuit model of the cellular membrane.
https://www.researchgate.net/figure/Electrical-circuit-model-of-the-cell-membrane_fig1_281167544

that flows per unit of time:

$$\mathcal{I}_c = \partial_t q = C_m \partial_t v.$$

On the other hand, the resistive property depends on the ionic transport between the intracellular and extracellular media. Then, the resistive current $\mathcal{I}_r$ is defined by the ionic current $\mathcal{I}_{ion}$ measured from the intracellular to the extracellular medium which depends on the transmembrane potential v and the gating variable $w : \Gamma^y \mapsto \mathbb{R}$. Since the electric current can be blocked by the membrane or can be pass through the membrane with ionic current $\mathcal{I}_r - \mathcal{I}_{app}$. So, the charge conservation states that the total transmembrane current $\mathcal{I}_m$ (see [CFPS12]) is given as follows:

$$\mathcal{I}_m = \mathcal{I}_c + \mathcal{I}_r - \mathcal{I}_{app} \text{ on } \Gamma^y_T,$$

where $\mathcal{I}_{app}$ is the applied current per unit area of the membrane surface (given in μA/cm^2). Consequently, the transmembrane potential v satisfies the following dynamic condition on Γ^y involving the gating variable w:

$$\begin{aligned} \mathcal{I}_m = C_m \partial_t v + \mathcal{I}_{ion}(v, w) - \mathcal{I}_{app} \quad & \text{on } \Gamma^y_T, \\ \partial_t w - H(v, w) = 0 \quad & \text{on } \Gamma^y_T. \end{aligned} \tag{1.7}$$

Herein, the functions H and $\mathcal{I}_{ion}$ correspond to the ionic model of membrane dynamics.All surface current densities $\mathcal{I}_m$ and $\mathcal{I}_{ion}$ are given in μA/cm^2. Moreover, time is given in ms and length is given in cm.

In addition, the cytoplasm at micro-scale contain far more mitochondria described as "the powerhouse of the myocardium". So, we assume that the no-flux boundary condition at the interface Γ^z of mitochondria is given by:

$$\mathrm{M}_i \nabla u_i \cdot n_z = 0 \quad \text{on } \Gamma_T^z := (0,T) \times \Gamma^z, \tag{1.8}$$

with n_z denotes the unit exterior normal to the boundary Γ^z.

1.4.2 The Microscopic Tridomain Model

The basic tridomain equations modeling the propagation of cardiac action potentials at cellular level in the presence of gap junctions which can be formulated as follows. First, we know that the structure of the cardiac tissue can be viewed as composed by two intracellular spaces Ω_i^k for $k = 1, 2$, that are connected by gap junction $\Gamma^{1,2}$ and the extracellular space Ω_e. The membrane Γ^k is defined by the intersection between each intracellular domain Ω_i^k and the extracellular one with $k = 1, 2$ (see Subsection 1.3.2).

Thus, the cellular membrane acts as a barrier to the free flow of ions between the two media (intracellular and extracellular) and maintains concentration differences of these ions. So, this transport creates an electric current.
Using Ohm's law, the intracellular electrical potentials u_i^k and extracellular one u_e are respectively related to the current volume densities J_i^k and J_e for $k = 1, 2$:

$$J_i^k = \mathrm{M}_i \nabla u_i^k, \text{ in } \Omega_{i,T}^k := (0,T) \times \Omega_i^k, \tag{1.9a}$$

$$J_e = \mathrm{M}_e \nabla u_e, \text{ in } \Omega_{e,T} := (0,T) \times \Omega_e, \tag{1.9b}$$

where M_j represents the corresponding conductivities of the tissue for $j = i, e$ (given in mS/cm^2). In addition, the concentration gradients produce a potential difference across the membrane Γ^k, the *transmembrane* potential v^k which is defined as follows:

$$v^k = (u_i^k - u_e)|_{\Gamma^k} : (0,T) \times \Gamma^k \mapsto \mathbb{R} \text{ for } k = 1, 2.$$

Moreover, we assume the intracellular and extracellular spaces are source-free and thus the intracellular and extracellular potentials are solutions to the elliptic equations:

$$-\operatorname{div} J_i^k = 0, \text{ in } \Omega_{i,T}^k, \tag{1.10a}$$

$$-\operatorname{div} J_e = 0, \text{ in } \Omega_{e,T}, \tag{1.10b}$$

with $k = 1, 2$.

According to the current conservation law, the surface current density $\mathcal{I}_m^k$ is now introduced:

$$\mathcal{I}_m^k = -J_i^k \cdot n_i^k = J_e \cdot n_e, \text{ on } \Gamma_T^k := (0, T) \times \Gamma^k, \tag{1.11}$$

with n_i^k denotes is the (outward) normal pointing out from $\Omega_{i,\varepsilon}^k$ for $k = 1, 2$ and n_e is the normal pointing out from $\Omega_{e,\varepsilon}$.

Since the cell membrane separates charges that accumulate at its intra- and extracellular surfaces, it can be viewed as a capacitor. The capacitance C_m (given in μF/cm^2) is defined as the ratio between the charge q^k across the capacitor and the voltage potential drop v^k necessary to hold the charge

$$C_m = \frac{q^k}{v^k}, \text{ for } k = 1, 2.$$

Then, the capacitive current $\mathcal{I}_c^k$ for $k = 1, 2$ is the amount of charge that flows per unit of time:

$$\mathcal{I}_c^k = \partial_t q^k = C_m \partial_t v^k.$$

On the other hand, the resistive property depends on the ionic transport between the intracellular and extracellular media. Then, the resistive current $\mathcal{I}_r$ is defined by the ionic current $\mathcal{I}_{ion}^k$ measured from the intracellular to the extracellular medium which depends on the transmembrane potential v^k and the gating variable $w^k : \Gamma^k \mapsto \mathbb{R}$ with $k = 1, 2$. Moreover, the total transmembrane current $\mathcal{I}_m^k$ (see [CFPS12]) is given by:

$$\mathcal{I}_m^k = \mathcal{I}_c^k + \mathcal{I}_r^k - \mathcal{I}_{app}^k \text{ on } \Gamma_T^k,$$

with $\mathcal{I}_{app}^k$ is the applied current of the membrane surface for $k = 1, 2$ (given in μA/cm^2). Consequently, due to the dynamics of the ionic fluxes through the cell membrane, its electrical potential v^k satisfies the following dynamic condition on Γ^k involving the gating variable w^k:

$$\mathcal{I}_m^k = C_m \partial_t v^k + \mathcal{I}_{ion}\left(v^k, w^k\right) - \mathcal{I}_{app}^k \qquad \text{on } \Gamma_T^k, \tag{1.12a}$$

$$\partial_t w^k - H\left(v^k, w^k\right) = 0 \qquad \text{on } \Gamma_T^k. \tag{1.12b}$$

Furthermore, the functions H and $\mathcal{I}_{ion}$ correspond to the ionic model of membrane dynamics. All surface current densities $\mathcal{I}_m^k$ for $k = 1, 2$ and $\mathcal{I}_{ion}$ are given in μA/cm^2. Moreover, time is given in ms and length is given in cm.

In addition, we represent the gap junction between intra-neighboring cells by a passive model. This model includes several state variables in addition to the gap junction potential s which is defined as follows:

$$s = (u_i^1 - u_i^2)|_{\Gamma^{1,2}} : (0, T) \times \Gamma^{1,2} \mapsto \mathbb{R}.$$

The ionic current $\mathcal{I}_{1,2}$ through the gap junction $\Gamma^{1,2}$ defined by:

$$\mathcal{I}_{1,2} = -J_i^1 \cdot n_i^1 = J_i^2 \cdot n_i^2, \text{ on } \Gamma_T^{1,2} := (0, T) \times \Gamma^{1,2}. \tag{1.13}$$

Similarly, the ionic current $\mathcal{I}_{1,2}$ at a gap junction $\Gamma^{1,2}$ represents the sum of the capacitive and resistive currents. Consequently, regarding the dynamic structure of the gap junction, its electrical potential s satisfies the following dynamic condition on $\Gamma^{1,2}$:

$$\mathcal{I}_{1,2} = C_{1,2} \partial_t s + \mathcal{I}_{gap}(s) \quad \text{on } \Gamma_T^{1,2}, \tag{1.14}$$

where $C_{1,2}$ represents the capacity per unit area of the intercalated disc and $\mathcal{I}_{gap}$ represents the corresponding resistive current. In general, the value of $C_{1,2}$ is set to $C_m/2$ because the intercalated disc is assumed to be a membrane of thickness twice as large as the cell membrane, and the specific capacitance of a capacitor C_m formed by two parallel plates separated by an insulator may be assumed to be inversely proportional to the thickness of the insulator [Jæg+19].

1.4.3 Ionic Models

In order to complete the microscopic models, it is necessary to include the basic electrical circuit model of the cellular membrane, where the transmembrane current, modeled as the sum of the capacitive and ionic currents through the membrane, must balance the given applied current. We look to modeling the membrane ion transport of three different ions: the sodium Na^+, the potassium K^+ and the calcium Ca^{2+}. These ionic models are then described by using ion channel gating models, allowing us to build cardiac action potential models. We start with the physiological models, in particular the celebrated Hodgkin-Huxley (H-H) model and briefly review some of the historical ventricular models based on the H-H formalism, such as the Beeler-Reuter, Luo-Rudy I and II models. Phenomenological models, such as the minimal FitzHugh-Nagumo model are also presented.

Physiological models

Hodgkin-Huxley Model. The first mathematical model that describes the action potential waveform was proposed by Hodgkin and Huxley [HH52] and was developed specifically for nerve fibers. The celebrated Hodgkin-Huxley (H-H) model consists of the following system, coupling the circuit model with the equations of channel gating for three recovery variables m, h, n

$$\begin{cases} C_m \partial_t v + \mathcal{I}_{ion}(v, m, h, n) = \mathcal{I}_{app} \\ \dfrac{dm}{dt} = \dfrac{m_\infty(v) - m}{\tau_m(v)} \\ \dfrac{dh}{dt} = \dfrac{h_\infty(v) - h}{\tau_h(v)} \\ \dfrac{dn}{dt} = \dfrac{n_\infty(v) - n}{\tau_n(v)} \end{cases} \tag{1.15}$$

where the ionic current $\mathcal{I}_{ion}$ is sum of sodium, potassium and leakage currents

$$\mathcal{I}_{ion} = \mathrm{I}_{\mathrm{Na}} + \mathrm{I}_{\mathrm{K}} + \mathrm{I}_{\mathrm{L}}.$$

Each of these currents has a linear current-voltage structure, with three equal activation and one inactivation independent subunits for the sodium channel

$$\mathrm{I}_{\mathrm{Na}} = \overline{G}_{\mathrm{Na}} m^3 h (v - v_{\mathrm{Na}}),$$

four equal activation independent subunits for the potassium channel

$$\mathrm{I}_{\mathrm{K}} = \overline{G}_{\mathrm{K}} n^4 (v - v_{\mathrm{K}}),$$

and no units for the leakage current

$$\mathrm{I}_{\mathrm{L}} = \overline{G}_{\mathrm{L}} (v - v_{\mathrm{L}}).$$

Here, $\overline{G}_\ell$ and v_ℓ are the maximal conductances and the Nernst potentials of each channel type, respectively for $\ell := \text{Na}, \text{K}, \text{L}$. Furthermore, the coefficients of the recovery variables equations are given by for $w := m, h, n$

$$w_\infty = \frac{\alpha_w}{\alpha_w + \beta_w} \tag{1.16}$$

with

$$\begin{aligned}
\alpha_m &= \frac{0.1(25-v)}{\exp[0.1(25-v)]-1}, & \beta_m &= 4\exp\left(\frac{-v}{18}\right),\\
\alpha_h &= 0.07\exp\left(\frac{-v}{20}\right), & \beta_h &= \frac{1}{\exp[0.1(30-v)]+1},\\
\alpha_n &= \frac{0.01(10-v)}{\exp[0.1(10-v)]-1}, & \beta_n &= 0.125\exp\left(\frac{-v}{80}\right).
\end{aligned}$$

Beeler-Reuter Model

In 1977, the Beeler-Reuter model was proposed the first ventricular membrane model of mammalian cardiac myocytes (see [BR77]) based on Hodgkin-Huxley formalism. The ionic current $\mathcal{I}_{ion}$ is given by the sum of four currents (see Figure 1.9)

$$\mathcal{I}_{ion} = \mathrm{I}_{\mathrm{Na}} + \mathrm{I}_{\mathrm{s}} + \mathrm{I}_{\mathrm{K1}} + \mathrm{I}_{\mathrm{x1}}.$$

The so-called fast inward sodium current I_{Na} is the main current responsible for the depolarization of cardiac cells, while the other currents determine the configuration of the plateau and re-polarization phases. The slow inward current I_{s}, carried by calcium ions (Ca^{2+}), influences the duration of the action potential. Furthermore, the time-dependent and time-independent outward potassium currents I_{x1} and I_{K1} are instead responsible for the re-polarization phase.

Herein, the sodium current I_{Na} is expressed by

$$\mathrm{I}_{\mathrm{Na}} = \left(\overline{G}_{\mathrm{Na}} m^3 h j + \overline{G}_{\mathrm{NaC}}\right)(v - E_{\mathrm{Na}}),$$

where $\overline{G}_{\mathrm{Na}}$ is the maximal sodium conductance (0.04 mS/mm^2), $\overline{G}_{\mathrm{NaC}}$ is the constant background sodium conductance ($3 \cdot 10^{-5}$ mS/mm^2) and E_{Na} is the sodium equilibrium potential (50 mV). In addition to the activation gate m and the inactivation gate h of the Hodgkin-Huxley model, Beeler-Reuter added a slow inactivation gate j. All these recovery variables follow the dynamic equation defined by:

$$\partial_t w = H(v, w) = \alpha(v)(1-w) - \beta(v)w, \tag{1.17}$$

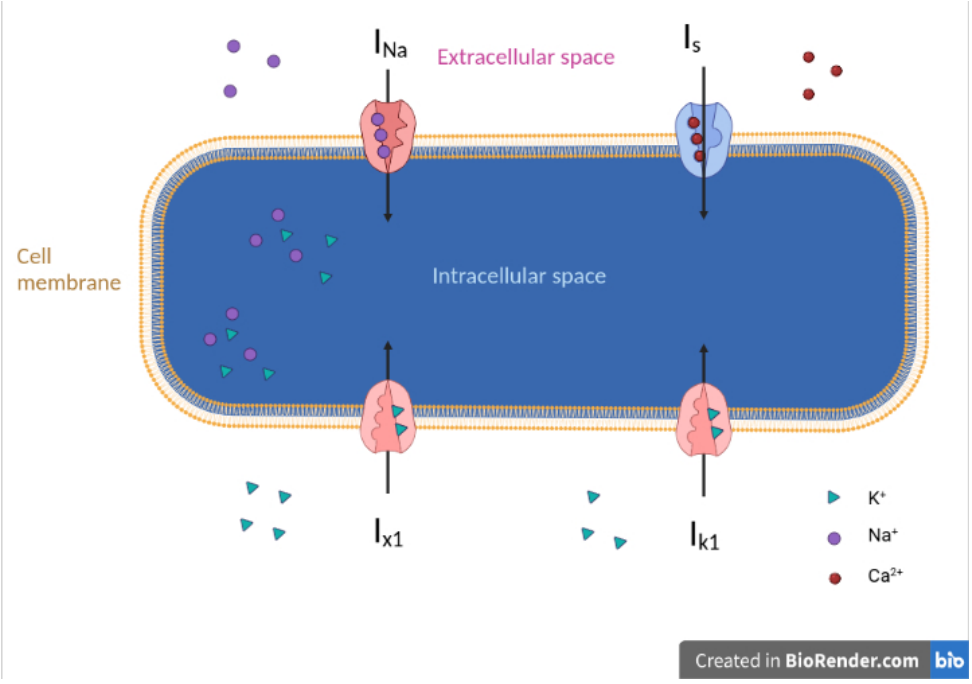

Figure 1.9 – The current flows across the cell membrane captured in the Beeler-Reuter model.

where $w := m, h, j$ and $\alpha, \beta > 0$.

The slow inward current $\mathrm{I_s}$ is controlled by an activation gate d and inactivation gate f, both following the dynamic equation (1.17). This current is given by

$$\mathrm{I_s} = \overline{G}_\mathrm{s} df \left(v - E_\mathrm{s}\right),$$

where $\overline{G}_\mathrm{s}$ is the maximal channel conductance ($9 \cdot 10^{-4}$ mS/mm^2) and E_s is the reversal potential depends on the intracellular calcium concentration $[\mathrm{Ca}^{2+}]_i$, precisely

$$E_\mathrm{s} = -82.3 - 13.0287 \log\left(0.001[\mathrm{Ca}^{2+}]_i\right). \tag{1.18}$$

The time-dependent outward potassium current $\mathrm{I_{x1}}$ is controlled, as in the Hodgkin-Huxley model, by a single gating variable x_1 satisfying (1.17). The expression of this current is

$$\mathrm{I_{x1}} = 8 \cdot 10^{-3} x_1 \left(\frac{\exp[0.04(77+v)] - 1}{\exp[0.04(35+v)]}\right).$$

Finally, the magnitude of the time-independent outward potassium current $\mathrm{I_{K1}}$ is given by

$$\begin{aligned}\mathrm{I_{K1}} = 0.0035 &\left(\frac{4\exp[0.04(85+v)]-1}{\exp[0.08(53+v)]+\exp[0.04(53+v)]}\right)\\ &+0.0035\left(\frac{0.2(23+v)}{1-\exp[-0.04(23+v)]}\right).\end{aligned}$$

Luo Rudy Model (LRI and LRII)

In 1991, Luo and Rudy [LR91] developed the Beeler-Reuter model of a mammalian ventricular muscle cell including additional potassium currents. The ionic current $\mathcal{I}_{ion}$ is given by the sum of six currents

$$\mathcal{I}_{ion} = \mathrm{I_{Na}} + \mathrm{I_s} + \mathrm{I_K} + \mathrm{I_{K1}} + \mathrm{I_{Kp}} + \mathrm{I_b},$$

two inwards ($\mathrm{I_{Na}}, \mathrm{I_s}$) and four outwards $\mathrm{I_K}, \mathrm{I_{K1}}, \mathrm{I_{Kp}}, \mathrm{I_b}$. The first three currents depend on six gating variables and one ion (intracellular calcium) concentration, while the last three are time-independent currents. For more details, we refer the reader to [LR91].

In 1994, Luo and Rudy [LR94a; LR94b] developed a new model for the mammalian ventricular action potential based mostly on the guinea pig ventricular cell. This second approach consists of producing "phenomenological" models which takes into account both the intracellular mechanisms of calcium regulation and the effect of the three buffers: the troponin (directly linked to muscle contraction), the calmodulin, and the sarcoplasmic reticulum (see Figure 1.10). In this case, the ionic current $\mathcal{I}_{ion}$ is expressed by the sum of eleven currents

$$\mathcal{I}_{ion} = \mathrm{I_{Na}} + \mathrm{I_{Ca(L)}} + \mathrm{I_K} + \mathrm{I_{K1}} + \mathrm{I_{Kp}} + \mathrm{I_{NaCa}} + \mathrm{I_{NaK}} + \mathrm{I_{nsCa}} + \mathrm{I_{pCa}} + \mathrm{I_{bCa}} + \mathrm{I_{bNa}}.$$

Phenomenological models

Other non-physiological ionic models have been introduced as approximations of ion current models. These models are unrealistic in that they cannot be interpreted in terms of biological quantities. These unknowns of these reduced models are a normalized transmembrane potential and a gating variable following the general kinetics where we neglect the applied current

$$\begin{cases}\dfrac{dv}{dt} = \mathcal{I}_{ion}(v,w)\\ \dfrac{dw}{dt} = H(v,w)\end{cases} \tag{1.19}$$

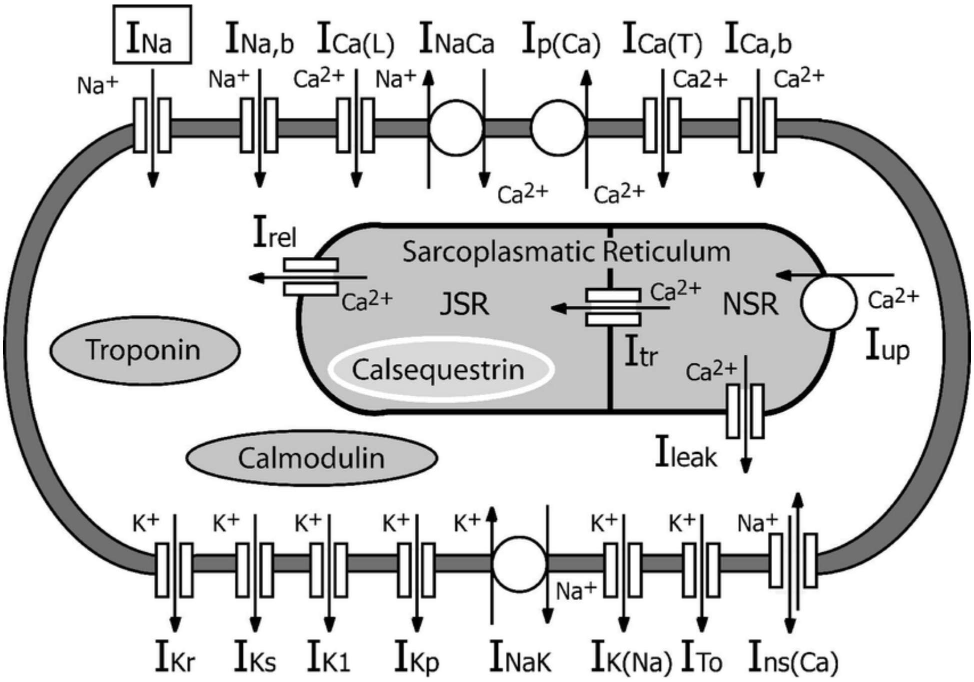

Figure 1.10 – The current flows across the cell membrane captured in the Luo-Rudy model.

- FitzHugh-Nagumo model [Fit61]:

$$\mathcal{I}_{ion}(v,w) = -kv(v-\alpha)(v-1) - w, \qquad H(v,w) = \beta(v - \gamma w);$$

- Roger-McCulloch model [RM94]:

$$\mathcal{I}_{ion}(v,w) = -kv(v-\alpha)(v-1) - vw, \qquad H(v,w) = \beta(v - \gamma w);$$

- Aliev-Panfilov model [AP96]:

$$\mathcal{I}_{ion}(v,w) = -kv(v-\alpha)(v-1) - vw, \qquad H(v,w) = \beta\left(\gamma v\left(v-1-a\right) + w\right);$$

- Mitchell-Schaeffer model [MS03]:

$$\mathcal{I}_{ion}(v,w) = -\frac{-w}{\tau_{in}} v^2(v-1) - \frac{v}{\tau_{out}}, \qquad H(v,w) = \begin{cases} \dfrac{1-w}{\tau_{open}} & \text{if } v \le v_{gate}, \\ \dfrac{-w}{\tau_{close}} & \text{if } v > v_{gate}. \end{cases};$$

Here, $0 < \alpha < 1$, $k,\ \beta,\ \Gamma$, $\tau_{in},\ \tau_{out}, \tau_{open},\ \tau_{close}$, $0 < v_{gate} < 1$ are given constants.

1.5 The Macroscopic (Homogenized) Models

The macroscopic bidomain and tridomain representations of the cardiac tissue has been derived respectively in Chapter 2 and 3 using two different homogenization techniques. Moreover, we also present in this part two simplifications of the macroscopic bidomain model: the monodomain and eikonal models. These heuristic approximations should be preferred to the bidomain model to simulate patterns of excitation in the cardiac tissue taking advantage of its lightest implementation and computational cost.

1.5.1 The Macroscopic Bidomain Model

At macroscopic level, the heart domain (denoted by Ω) coincides with the intracellular and extracellular ones, which are inter-penetrating and superimposed connected at each point by the cardiac cellular membrane. The macroscopic bidomain model describes the current flow through the myocardium in a volume averaged approach which is called the homogenized bidomain model (Reaction-Diffusion system):

$$\mu_m \partial_t v + \nabla \cdot (\mathbf{M}_e \nabla u_e) + \mu_m \mathcal{I}_{ion}(v, w) = \mu_m \mathcal{I}_{app} \qquad \text{in } \Omega_T := (0,T) \times \Omega, \qquad (1.20a)$$

$$\mu_m \partial_t v - \nabla \cdot (\mathbf{M}_i \nabla u_i) + \mu_m \mathcal{I}_{ion}(v, w) = \mu_m \mathcal{I}_{app} \qquad \text{in } \Omega_T, \qquad (1.20b)$$

$$\partial_t w - H(v, w) = 0 \qquad \text{on } \Omega_T, \qquad (1.20c)$$

completed with no-flux boundary conditions on u_i, u_e on $\partial_{\text{ext}}\Omega$:

$$(\mathbf{M}_e \nabla u_e) \cdot \mathbf{n} = (\mathbf{M}_i \nabla u_i) \cdot \mathbf{n} = 0 \ \text{ on } \ \Sigma_T := (0,T) \times \partial_{\text{ext}}\Omega, \qquad (1.21)$$

and initial conditions for the transmembrane potential v and the gating variable w :

$$v(0,x) = v_0(x) \qquad \text{and} \qquad w(0,x) = w_0(x), \qquad (1.22)$$

where $\mu_m = |\Gamma^y| \,/\, |Y|$ is the ration between the surface membrane and the volume of the reference cell. Moreover, $\mathbf{n}$ is the outward unit normal to the exterior boundary of Ω. Herein, we introduce the homogenized conductivity matrices $\mathbf{M}_j$ related to the macroscopic arrangement of the cardiac myocytes in the fiber structure which are described by:

$$\mathbf{M}_j = \sigma_j^\ell \mathbf{d}_\ell \otimes \mathbf{d}_\ell + \sigma_j^t \mathbf{d}_t \otimes \mathbf{d}_t + \sigma_j^n \mathbf{d}_n \otimes \mathbf{d}_n, \text{ for } j = i, e,$$

where $\sigma_j^k = \sigma_j^k(x)$, $k \in \{\ell, t, n\}$, are the intra- and extracellular conductivity coefficients measured along the longitudinal, transversal and normal to the fiber $x \in \Omega$.

Another formulation of the macroscopic bidomain equations is given by:

$$\mu_m \partial_t v + \nabla \cdot (\mathbf{M}_e \nabla u_e) + \mu_m \mathcal{I}_{ion}(v, w) = \mu_m \mathcal{I}_{app} \quad \text{in } \Omega_T, \tag{1.23a}$$

$$-\nabla \cdot ((\mathbf{M}_i + \mathbf{M}_e) \nabla u_e) = \nabla \cdot (\mathbf{M}_i \nabla v) \quad \text{in } \Omega_T, \tag{1.23b}$$

$$\partial_t w - H(v, w) = 0 \quad \text{on } \Omega_T, \tag{1.23c}$$

The two formulations (1.20)-(1.23) are equivalent. The second one can be obtained from the first one by replacing u_i by $v + u_e$ in (1.20a) and subtracting the resulting equation from (1.20b).

The Monodomain Model

In order to reduce the (theoretical and numerical) difficulties of the macroscopic bidomain model which are in the equation (1.23a) the differential operator $\nabla \cdot (\mathbf{M}_e \nabla u_e)$ is not given explicitly from v but only implicitly by the elliptic problem (1.23b). In the particular case where the intra- and extra-cellular media have the same anisotropy ratio, i.e. if there exits a constant $\lambda > 0$ such that

$$\forall x \in \Omega : \mathbf{M}_i(x) = \lambda \mathbf{M}_e(x),$$

this difficulty can be overcome and the bidomain model (1.20) can be rewritten as only one equation depending on v as follows:

$$\mu_m \partial_t v - \frac{1}{\lambda + 1} \nabla \cdot (\mathbf{M}_i \nabla v) + \mu_m \mathcal{I}_{ion}(v, w) = \mu_m \mathcal{I}_{app} \text{ in } \Omega_T, \tag{1.24}$$

This simplification of the bidomain model is called the "linear anisotropic monodomain model". This reduced formulation is adapted to the case where the heart is assumed to be electrically isolated. Consequently, on the boundary of the heart, one can impose the following homogeneous Neumann boundary condition:

$$(\mathbf{M}_i \nabla v) \cdot \mathbf{n} = 0 \text{ on } \Sigma_T := (0, T) \times \partial_{\text{ext}} \Omega. \tag{1.25}$$

We shall present another interesting approximation of the macroscopic bidomain model (see [FPT05a; FPT05b]) without assuming that the two tensors are proportional and we will always call it "monodomain model". This approximation consists of a single parabolic reaction-diffusion equation for the transmembrane potential v coupled with the same gating system:

$$\mu_m \partial_t v + \nabla \cdot (\mathbf{M} \nabla v) + \mu_m \mathcal{I}_{ion}(v, w) = \mu_m \mathcal{I}_{app} \qquad \text{in } \Omega_T, \tag{1.26a}$$

$$\partial_t w - H(v, w) = 0 \qquad \text{on } \Omega_T, \tag{1.26b}$$

$$\mathbf{M} \nabla v \cdot \mathbf{n} = 0 \qquad \text{on } \Sigma_T, \tag{1.26c}$$

with the conductivity tensor $\mathbf{M} = \mathbf{M}_e \left(\mathbf{M}_i + \mathbf{M}_e\right)^{-1} \mathbf{M}_i$.

From the knowledge of the distribution of $v(t, x)$ the extracellular potential distribution u_e is derived by solving the elliptic boundary value problem

$$-\nabla \cdot \left(\left(\mathbf{M}_i + \mathbf{M}_e\right) \nabla u_e\right) = \nabla \cdot \left(\mathbf{M}_i \nabla v\right) \qquad \text{in } \Omega_T, \tag{1.27a}$$

$$-\left(\mathbf{M}_i + \mathbf{M}_e\right) \nabla u_e \cdot \mathbf{n} = \mathbf{M}_i \nabla v \cdot \mathbf{n} \qquad \text{on } \Sigma_T. \tag{1.27b}$$

Observe that the first equation in (1.26) uniquely determines v, while the potential u_e is defined only up to an additive time-dependent constant related to the reference potential, chosen to be the average extracellular potential in the cardiac volume by imposing the normalization condition $\int_\Omega u_e dx = 0$.

Furthermore, we remark that the macroscopic bidomain model are described by a system of a parabolic equation coupled with an elliptic equation, but in the monodomain model the evolution equation is fully uncoupled with the elliptic one in the case of an insulated domain.

The Eikonal Model

Another route to avoid high computational costs is based on a heuristic approximation of the macroscopic bidomain model, known as "eikonal models," to describe the propagation of action potential wavefronts in the myocardium. With these models the simulation of the activation sequence in large volumes of cardiac tissue has become computationally practical but at the price of a loss of fine details concerning the thin layer where the upstroke of the action potential occurs. These numerical simulations are based on laws describing the macroscopic kinetic mechanism of the spreading of the excitation wavefronts, and do not require a fine spatial and temporal resolution.

The authors in [Kee91] proposed this model in order to study the effects of fiber orientation on propagation in the myocardial wall within the framework of the monodomain model. Furthermore, we find in [FGT90; FGR90; FG93] a more general version of this analysis within the framework of the bidomain model.

1.5.2 The Macroscopic Tridomain Model

At the macroscopic scale, the heart appears as a continuous material and the intracellular and extracellular media are indistinguishable. The macroscopic tridomain model attempts to describe the averaged electric potentials and current flows inside and outside the cardiac cells which is represented by the following Reaction-Diffusion system:

$$\begin{aligned}
\sum_{k=1,2} \mu_k \partial_t v^k + \nabla \cdot (\mathbf{M}_e \nabla u_e) + \sum_{k=1,2} \mu_k \mathcal{I}_{ion}(v^k, w^k) &= \sum_{k=1,2} \mu_k \mathcal{I}_{app}^k && \text{in } \Omega_T, \\
\mu_1 \partial_t v^1 + \mu_g \partial_t s - \nabla \cdot \left(\mathbf{M}_i \nabla u_i^1\right) + \mu_1 \mathcal{I}_{ion}(v^1, w^1) + \mu_g \mathcal{I}_{gap}(s) &= \mu_1 \mathcal{I}_{app}^1 && \text{in } \Omega_T, \\
\mu_2 \partial_t v^2 - \mu_g \partial_t s - \nabla \cdot \left(\mathbf{M}_i \nabla u_i^2\right) + \mu_2 \mathcal{I}_{ion}(v^2, w^2) - \mu_g \mathcal{I}_{gap}(s) &= \mu_2 \mathcal{I}_{app}^2 && \text{in } \Omega_T, \\
\partial_t w^k - H(v^k, w^k) &= 0 && \text{on } \Omega_T,
\end{aligned} \tag{1.28}$$

completed with no-flux boundary conditions on u_i, u_e on $\partial_{\text{ext}}\Omega$:

$$(\mathbf{M}_e \nabla u_e) \cdot \mathbf{n} = \left(\mathbf{M}_i \nabla u_i^k\right) \cdot \mathbf{n} = 0 \text{ on } \Sigma_T := (0,T) \times \partial_{\text{ext}}\Omega, \tag{1.29}$$

and initial conditions for the transmembrane potential v^k, the gap potential s and the gating variable w^k :

$$v^k(0,x) = v_0^k(x),\ s(0,x) = s_0(x) \text{ and } w^k(0,x) = w_0^k(x), \tag{1.30}$$

where $\mu_k = \left|\Gamma^k\right| / |Y|$, $k = 1,2$, (resp. $\mu_g = |\Gamma^{1,2}| / |Y|$) is the ratio between the surface membrane (resp. the gap junction) and the volume of the reference cell. As before, the conductivity tensors $\mathbf{M}_j$ can be expressed by:

$$\mathbf{M}_j = \sigma_j^\ell \mathbf{d}_\ell \otimes \mathbf{d}_\ell + \sigma_j^t \mathbf{d}_t \otimes \mathbf{d}_t + \sigma_j^n \mathbf{d}_n \otimes \mathbf{d}_n, \text{ for } j = i, e, \tag{1.31}$$

where $\sigma_j^k = \sigma_j^k(x)$, $k \in \{\ell, t, n\}$, are the intra- and extracellular conductivity coefficients measured along the longitudinal, transversal and normal to the fiber $x \in \Omega$.

2

Three-scale Homogenization Method Applied To Meso-Microscopic Bidomain Model

In this chapter, our attention is initially directed at the organization of cardiac muscle cells within the heart. The structure of cardiac tissue studied in this chapter is characterized at three different scales (see Figure 2.1). At mesoscopic scale, the cardiac tissue is divided into two media: one contains the contents of the cardiomyocytes, in particular the "cytoplasm" which is called the "intracellular" medium, and the other is called extracellular and consists of the fluid outside the cardiomyocytes cells. These two media are separated by a cellular membrane (the sarcolemma) allowing the penetration of proteins, some of which play a passive role and others play an active role powered by cellular metabolism. At microscopic scale, the cytoplasm comprises several organelles such as mitochondria. Mitochondria are often described as the "energy powerhouses" of cardiomyocytes and are surrounded by another membrane. In our study, we consider only that the intracellular medium can be viewed as a periodic structure composed of other connected cells. While at the macroscopic scale, this domain is well considered as a single domain (homogeneous). It should be noted that there is a difference between the chemical composition of the cytoplasm and that of the extracellular medium. This difference plays a very important role in cardiac activity. In particular, the concentration of anions (negative ions) in cardiomyocytes is higher than in the external environment. This difference of concentrations creates a transmembrane potential, which is the difference in potential between these two media. The model that describes the electrical activity of the heart, is called by "Bidomain model".

We start in this chapter from the meso-microscopic bidomain model given in Subsection 1.4.1, resolving the three-scale geometry of the domain, which consists of two quasi-static ap-

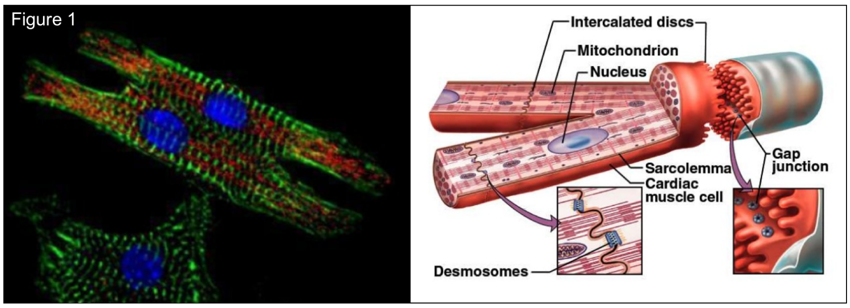

Figure 2.1 – Representation of the cardiomyocyte structure.
`http://www.cardio-research.com/cardiomyocytes`

proximation of elliptic equations, one for the electrical potential in the intracellular medium and one for the extracellular medium, coupled through a dynamical boundary equation at the interface of the two regions (the sarcolemma). Then we upscale our meso-microscopic model using two small scaling parameters ε and δ whose are respectively the ratio of the microscopic and mesoscopic scales from the macroscopic scale. Our goal in this chapter is to derive the macroscopic (homogenized) bidomain model from the meso-microscopic one via two different homogenization methods: the asymptotic expansion and unfolding methods. This macroscopic model of the cardiac tissue is an approximation of the microscopic bidomain one and consists of a system of reaction-diffusion equations with homogenized coefficients, approximating the microscopic solution on the two connected components of the domain.

In general, the homogenization theory is the analysis of macroscopic behavior as for instance of biological tissues by taking into account their complex microscopic structure. For an introduction to this theory, we cite [HP92], [CD99],[Tar09] and [BP12]. Applications of this technique can also be found in modeling solids, fluids, solid-fluid interation, porous media, composite materials, cells and cancer invasion. This technique also has an interest in the field of numerical analysis where various new computational techniques (finite difference, finite elements and finite volume methods) have been developed, we cite for instance [AE03],[BBH07]. Several methods are related to this theory. Classically, homogenization has been done by the multiple-scale method which was first introduced by A. Benssousan and al. [BLP11] and by Sanchez-Palencia [HP92] for linear and periodic operators. It is well adapted to the periodic structure and permits to obtain an explicit form of the homogenized model based on asymptotic expansion [OSY09]. There are now different mathematical homogenization methods: the Γ-convergence method introduced by De Giorgi [DG75], the G-convergence method introduced by Spagnolo [Spa76] and the H-convergence method introduced by L. Tartar [MT18] for non-periodic case. The two-scale convergence method was introduced by G. Nugesteng [Ngu89] and developped by G. Allaire and al. [All92]. In addition, G. Allaire and M. Briane [AB96], Trucu and al. [TCMC12] was introduced a further generalization of the previous method via a three-scale convergence approach for distinct problems. After that the first results in stochastic homogenization method are due to S. Kozlov [Koz79] and Papanicolaou and Varadhan [Pap79], essentially using compensated compactness. Based on the previous work, A. Gloria and F. Otto [GO11; GO12] recently give an optimal error estimate in stochastic homogenization of discrete elliptic equations. Recently, the periodic unfolding method was introduced by D. Cioranescu, A. Damlamian and G. Griso in [CDG02] for the study of classical periodic homogenization in the case of fixed domains and adapted to homogenization in domains with holes by D. Cioranescu and al. [CDZ06; Cio+12]. The unfolding reiterated homogenization method was studied first by N. Meunier and J. Van Schaftingen [MVS05] for nonlinear partial differential equations with oscillating coefficients and multiscales. The unfolding method is essentially based on two operators: the first represents the unfolding operator and the second operator consists to separate the microscopic and macroscopic scales. The idea of the unfolding operator was introduced firstly in [ADH90] under the name "dilation" operator. The name "unfolding operator" was then introduced in [CDG02] and deeply studied in [CDZ06; CDG08; Cio+12]. The interest of this method comes from the fact that we use standard weak or strong convergences in L^p spaces. On the other hand, the unfolding operator maps functions defined on oscillating domains into functions defined on fixed domains. Hence, the proof of homogenization results be comes quite simple.

Now, we mention some different homogenization methods that are applied to the microscopic bidomain model to obtain the macroscopic bidomain model. C. Henriquez and W. Ying applied the two-scale asymptoptic method to formally obtain this macroscopic model presented in [HY09]. Furthermore, M. Pennachio, G. Savaré and P. Franzone used the tools of the Γ-convergence method to obtain a rigorous mathematical form of this homogenized macroscopic model which presented in [PSF05]. The authors in [CI18; GK19] used the theory of two-scale convergence to derive the homogenized bidomain model where the cardiac domain was assumed to be cube in $\mathbb{R}^3$. Recently, the authors in [Ben+19] proved the existence and uniqueness of solution of the microscopic bidomain model based on Faedo-Galerkin method. Further, they used the unfolding homogenization method at two scales to show that the solution of the microscopic biodmain model converges to the solution of the macroscopic one.

However, in biological systems, it is very often the case that processes over three (or more) distinct scales. Obviously, by higher-order correctors and upscaling techniques, the microscale and mesoscale informations of electrical activity behaviors inside the cardiac tissue can be caught more effectively. In addition, the previous two-scale methods can be utilized to analyze the effective coefficients from smallest scale to largest scale step by step, but cannot be directly used to derive the homogenized model from the microscopic bidomain problem at three-scales. Then, our models can serve as tool for biophysicists to analyze the complex mechanisms involved in the cardiac tissue, justifying in a rigorous manner some biological points of view concerning such process.

In this chapter, the homogenization method is done at two levels on the intracellular medium. The first level homogenization of the microscopic intracellular structure yields the mesoscopic model describing the electrical properties in its cells. The second level homogenization is performed to obtain the intracellular homogenized equation. Together with the extracellular homogenized one, is called the macroscopic bidomain model. Moreover, the intracellular and extracellular media are identical at the macroscopic scale and the cardiac tissue is considered as single domain to be the superposition of these two media.

This chapter is organized as follows: In Section 2.1, we give a precise description of the geometry of cardiac tissue and introduce the meso-microscopic bidomain model in the non-dimensional form featured by two parameters, ε and δ, characterizing the meso- and microscopic scales. Furthermore, some assumptions used for homogenization and the existence of a unique weak solution for the microscopic problem are stated and a priori estimates for the microscopic solutions are derived. Section 2.2 contains the main result obtained by the previous homogenization methods. In Section 2.3, we apply three-scale asymptotic homogenization procedure for extracellular and intracellular problems. Section 2.4 is devoted to unfolding homogenization procedure. In Subsection 2.4.1, we recall the notion of the unfolding operator and the convergence results used for unfolding homogenization. The three-scale unfolding method applied in the intracellular problem is explained in Subsection 2.4.2. In Subsection 2.4.3, the homogenized equation for the extracellular problem is obtained at two scales only using the standard unfolding method. Finally, in Subsection in 2.4.4, the macroscopic bidomain model is recuperated from the limit equations obtained in Subsection 2.4.2 and 2.4.3 and the cell problems are decoupled.

2.1 Geometry. Meso-Microscopic Bidomain Model

This section contains a brief discussion of the geometry of cardiac tissue and presents the meso-microscopic bidomain equations posed in the heart.

2.1.1 Three-scale representation of cardiac tissue

We refer the reader to Subsection 1.3.1 where the concept of meso- and micro-structure has been introduced, also see Figure 2.2.

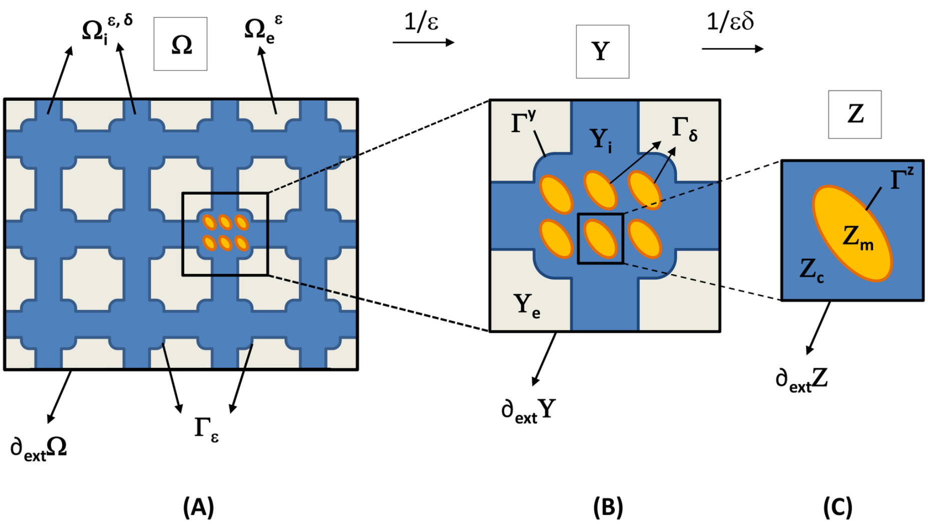

Figure 2.2 – (A) Periodic heterogeneous domain Ω, (B) Unit cell Y at ε-structural level and (C) Unit cell Z at δ-structural level.

2.1.2 Meso-Microscopic Bidomain Model

Before applying homogenization method, we introduce the basic equations of the meso-microscopic bidomain model given in Subsection 1.4.1 without using meso- and micro-scaling parameters denoted respectively by ε and δ. In the next section, a non-dimensionalization procedure, based on these scaling parameters, turns out to be an essential ingredient of the asymptotic analysis.

2.1.3 Non-dimensionalization procedure

In this part, we want to formulate the model equations given in Subsection 1.4.1 in dimensionless form in the hope of better understanding the meaning of meso-micro-macro scales. In the non-dimensionalization procedure, ε and δ will appear in these equations due to the scaling of the involved quantities.

Cardiac tissues have a number of important inhomogeneities, particularly those related to intercellular communications. The dimensionless analysis done correctly makes the problem simpler and clearer. In the literature, few works in that direction have been carried out, although we can cite [CFPS12; HY09; RB13] for the nondimensionalization procedure of the ionic current and [RC11; Whi20] for the non-dimensional analysis in the context of bidomain equations. So, this analysis follows three steps.

First, we can define the dimensionless scale parameter:

$$\varepsilon := \sqrt{\frac{\ell^{mes}}{R_m \lambda}},$$

where R_m denotes the surface specific resistivity of the membrane Γ^y and $\lambda := \lambda_i + \lambda_e$, with λ_j represents the average eigenvalues of the corresponding conductivity M_j for $j = i, e$, over the cells' arrangement. Now, we perform the following scaling of the space and time variables :

$$\widehat{x} = \frac{x}{L}, \quad \widehat{t} = \frac{t}{\tau},$$

with the macroscopic units of length $L = \ell^{mes}/\varepsilon = \ell^{mic}/\delta$ and the time constant τ associated with charging the membrane by the transmembrane current is given by:

$$\tau = R_m C_m,$$

where R_m is the surface specific resistivity of the membrane Γ^y.
We take $\widehat{x}$ to be the variable at the macroscale (slow variable),

$$y := \frac{\widehat{x}}{\varepsilon} \text{ and } z := \frac{\widehat{x}}{\varepsilon\delta}$$

to be respectively the mesoscopic and microscopic space variable (fast variables) in the corresponding unit cell.

Secondly, we scale all electrical potentials $u_j, \ v,$ currents and the gating variable w :

$$v = \Delta v \widehat{v}, \quad u_j = \Delta v \widehat{u}_j \text{ and } w = \Delta w \widehat{w}_e$$

where Δv and Δw are convenient units to measure electric potentials and gating variable, respectively, for $j = i, e$. By the chain rule, we obtain:

$$\frac{LC_m}{\tau} \partial_{\widehat{t}} \widehat{v} + \frac{L}{\Delta v} \left(\mathcal{I}_{ion} - \mathcal{I}_{app} \right) = -\mathrm{M}_i \nabla_{\widehat{x}} \widehat{u}_i \cdot n_i = \mathrm{M}_e \nabla_{\widehat{x}} \widehat{u}_e \cdot n_e.$$

Recalling that $\tau = R_m C_m$ and normalizing the conductivities M_j for $j = i, e$ using

$$\widehat{\mathrm{M}}_j = \frac{1}{\lambda}\mathrm{M}_j,$$

we get

$$\frac{L}{R_m\lambda}\partial_{\widehat{t}}\widehat{v} + \frac{L}{\Delta v\lambda}\left(\mathcal{I}_{ion} - \mathcal{I}_{app}\right) = -\widehat{\mathrm{M}}_i\nabla_{\widehat{x}}\widehat{u}_i \cdot n_i = \widehat{\mathrm{M}}_e\nabla_{\widehat{x}}\widehat{u}_e \cdot n_e.$$

Regarding the ionic functions $\mathcal{I}_{ion}$, H, and the applied current $\mathcal{I}_{app}$, we nondimensionalize them by using the following scales

$$\widehat{\mathcal{I}}_{ion}(\widehat{v},\widehat{w}) = \frac{R_m}{\Delta v}\widehat{\mathcal{I}}_{ion}(\widehat{v},\widehat{w}),\ \widehat{\mathcal{I}}_{app} = \frac{R_m}{\Delta v}\mathcal{I}_{app} \text{ and } \widehat{H}(\widehat{v},\widehat{w}) = \frac{\tau}{\Delta w}H(v,w).$$

Consequently, we have

$$\frac{L}{R_m\lambda}\left(\partial_{\widehat{t}}\widehat{v} + \widehat{\mathcal{I}}_{ion}(\widehat{v},\widehat{w}) - \widehat{\mathcal{I}}_{app}\right) = -\widehat{\mathrm{M}}_i\nabla_{\widehat{x}}\widehat{u}_i \cdot n_i = \widehat{\mathrm{M}}_e\nabla_{\widehat{x}}\widehat{u}_e \cdot n_e.$$

Remark 2.1. *Recalling that the dimensionless parameter ε, given by $\varepsilon := \sqrt{\dfrac{\ell^{mes}}{R_m\lambda}}$, is the ratio between the mesoscopic cell length ℓ^{mes} and the macroscopic length L, i.e. $\varepsilon = \ell^{mes}/L$ and solving for ε, we obtain*

$$\varepsilon = \frac{L}{R_m\lambda}.$$

Finally, we can convert the above microscopic bidomain system (1.5)-(1.8) to the following non-dimensional form:

$$-\nabla_{\widehat{x}} \cdot \left(\widehat{\mathrm{M}}_i^{\varepsilon,\delta}\nabla_{\widehat{x}}\widehat{u}_i^{\varepsilon,\delta}\right) = 0 \qquad \text{in } \Omega_{i,T}^{\varepsilon,\delta} := (0,T)\times\Omega_i^{\varepsilon,\delta}, \tag{2.1a}$$

$$-\nabla_{\widehat{x}} \cdot \left(\widehat{\mathrm{M}}_e^{\varepsilon}\nabla_{\widehat{x}}\widehat{u}_e^{\varepsilon}\right) = 0 \qquad \text{in } \Omega_{e,T}^{\varepsilon} := (0,T)\times\Omega_e^{\varepsilon}, \tag{2.1b}$$

$$\widehat{u}_i^{\varepsilon,\delta} - \widehat{u}_e^{\varepsilon} = \widehat{v}_\varepsilon \qquad \text{on } \Gamma_{\varepsilon,T} := (0,T)\times\Gamma_\varepsilon, \tag{2.1c}$$

$$\varepsilon\left(\partial_{\widehat{t}}\widehat{v}_\varepsilon + \widehat{\mathcal{I}}_{ion}(\widehat{v}_\varepsilon,\widehat{w}_\varepsilon) - \widehat{\mathcal{I}}_{app,\varepsilon}\right) = \widehat{\mathcal{I}}_m \qquad \text{on } \Gamma_{\varepsilon,T}, \tag{2.1d}$$

$$-\widehat{\mathrm{M}}_i^{\varepsilon,\delta}\nabla_{\widehat{x}}\widehat{u}_i^{\varepsilon,\delta} \cdot n_i = \widehat{\mathrm{M}}_e^{\varepsilon}\nabla_{\widehat{x}}\widehat{u}_e^{\varepsilon} \cdot n_e = \widehat{\mathcal{I}}_m \qquad \text{on } \Gamma_{\varepsilon,T}, \tag{2.1e}$$

$$\partial_{\widehat{t}}\widehat{w}_\varepsilon - \widehat{H}(\widehat{v}_\varepsilon,\widehat{w}_\varepsilon) = 0 \qquad \text{on } \Gamma_{\varepsilon,T}, \tag{2.1f}$$

$$\widehat{\mathrm{M}}_i^{\varepsilon,\delta}\nabla_{\widehat{x}}\widehat{u}_i^{\varepsilon,\delta} \cdot n_z = 0 \qquad \text{on } \Gamma_{\delta,T}, \tag{2.1g}$$

with each equation correspond to the following sense: (2.1a) Intra quasi-stationary conduction, (2.1b) Extra quasi-stationary conduction, (2.1c) Transmembrane potential, (2.1d) Reaction onface condition, (2.1e) Meso-continuity equation, (2.1f) Dynamic coupling, (2.1g) Micro-continuity equation.

For convenience, the superscript $\hat{\cdot}$ of the dimensionless variables is omitted. Note that the bidomain equations are invariant with respect to the scaling parameters ε and δ. Then, we define the rescaled electrical potential as follows:

$$u_i^{\varepsilon,\delta}(t,x) := u_i\left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta}\right), \quad u_e^{\varepsilon}(t,x) := u_e\left(t, x, \frac{x}{\varepsilon}\right).$$

Analogously, we obtain the rescaled transmembrane potential $v_\varepsilon = (u_i^{\varepsilon,\delta} - u_e^{\varepsilon})|_{\Gamma_{\varepsilon,T}}$ and gating variable w_ε. In general, the functions v_ε and w_ε does not depend on δ, we omit the index δ when non confusion arises. Next, we define also the following rescaled conductivity matrices:

$$\mathrm{M}_i^{\varepsilon,\delta}(x) := \mathrm{M}_i\left(x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta}\right) \text{ and } \mathrm{M}_e^{\varepsilon}(x) := \mathrm{M}_e\left(x, \frac{x}{\varepsilon}\right). \tag{2.2}$$

We complete system (2.1) with no-flux boundary conditions:

$$\left(\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\right)\cdot\mathbf{n} = \left(\mathrm{M}_e^{\varepsilon}\nabla u_e^{\varepsilon}\right)\cdot\mathbf{n} = 0 \text{ on } (0,T)\times\partial_{\text{ext}}\Omega,$$

where $\mathbf{n}$ is the outward unit normal to the exterior boundary of Ω. We impose initial conditions on the transmembrane potential and the gating variable:

$$v_\varepsilon(0,x) = v_{0,\varepsilon}(x) \quad \text{and} \quad w_\varepsilon(0,x) = w_{0,\varepsilon}(x) \quad \text{a.e. on } \Gamma_\varepsilon. \tag{2.3}$$

2.1.4 Assumptions on the Data

Keeping in mind the three-scale configuration of cardiac tissue (cf Subsection 1.3.1), we list some assumptions on the conductivity matrices, the ionic functions, the source term and the initial data:

Assumptions on the conductivity matrices. The rescaled intracellular and extracellular conductivity tensors $\mathrm{M}_i^{\varepsilon,\delta}(x) := \mathrm{M}_i\left(x, x/\varepsilon, x/\varepsilon\delta\right)$ and $\mathrm{M}_e^{\varepsilon}(x) := \mathrm{M}_e\left(x, x/\varepsilon\right)$ satisfying the elliptic and periodicity conditions: there exist constants $\alpha, \beta \in \mathbb{R}$, such that $0 < \alpha < \beta$ and for all

$\lambda \in \mathbb{R}^d$:

$$\mathrm{M}_j\lambda \cdot \lambda \geq \alpha \left|\lambda\right|^2, \tag{2.4a}$$
$$\left|\mathrm{M}_j\lambda\right| \leq \beta \left|\lambda\right|, \text{ for } j = i, e, \tag{2.4b}$$
$$\mathrm{M}_i \text{ } \mathbf{y}\text{- and } \mathbf{z}\text{-periodic}, \quad \mathrm{M}_e \text{ } \mathbf{y}\text{-periodic}. \tag{2.4c}$$

Assumptions on the ionic functions. The ionic current $\mathcal{I}_{ion}(v, w)$ can be decomposed into $\mathrm{I}_{1,ion}(v) : \mathbb{R} \to \mathbb{R}$ and $\mathrm{I}_{2,ion}(w); \mathbb{R} \to \mathbb{R}$, where $\mathcal{I}_{ion}(v, w) = \mathrm{I}_{1,ion}(v) + \mathrm{I}_{2,ion}(w)$. Furthermore, $\mathrm{I}_{1,ion}$ is considered as a C^1 function, $\mathrm{I}_{2,ion}$ and $H : \mathbb{R}^2 \to \mathbb{R}$ are 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 $\beta_1, \beta_2 > 0$ such that:

$$\frac{1}{\alpha_1}\left|v\right|^{r-1} \leq \left|\mathrm{I}_{1,ion}(v)\right| \leq \alpha_1\left(\left|v\right|^{r-1} + 1\right), \ \left|\mathrm{I}_{2,ion}(w)\right| \leq \alpha_2(\left|w\right| + 1), \tag{2.5a}$$
$$\left|H(v, w)\right| \leq \alpha_3(\left|v\right| + \left|w\right| + 1), \text{ and } \mathrm{I}_{2,ion}(w)v - \alpha_4 H(v, w)w \geq \alpha_5 \left|w\right|^2, \tag{2.5b}$$
$$\tilde{\mathrm{I}}_{1,ion} : z \mapsto \mathrm{I}_{1,ion}(z) + \beta_1 z + \beta_2 \text{ is strictly increasing with } \lim_{z\to 0} \tilde{\mathrm{I}}_{1,ion}(z)/z = 0, \tag{2.5c}$$
$$\forall z_1, z_2 \in \mathbb{R}, \ \left(\tilde{\mathrm{I}}_{1,ion}(z_1) - \tilde{\mathrm{I}}_{1,ion}(z_2)\right)(z_1 - z_2) \geq \frac{1}{C}\left(1 + \left|z_1\right| + \left|z_2\right|\right)^{r-2}\left|z_1 - z_2\right|^2. \tag{2.5d}$$

Remark 2.2. *One can easily show that* $\mathrm{I}_{1,ion}(0) = -\beta_2$, $\mathrm{I}'_{1,ion}(0) = -\beta_1$ *and* $\mathrm{I}_{1,ion}(z) \geq -\beta_1$ *for all* $z \in \mathbb{R}$.

Remark 2.3. *Physiological and phenomenological models to these functions are available in Section 1.4.3. Here, we take the Fitzhugh-Nagumo model [Fit61; NAY62] which is defined as follows*

$$H(v, w) = av - bw, \tag{2.6a}$$
$$\mathcal{I}_{ion}(v, w) = (\lambda v(1 - v)(v - \theta)) + (-\lambda w) := \mathrm{I}_{1,ion}(v) + \mathrm{I}_{2,ion}(w) \tag{2.6b}$$

where a, b, λ, θ *are given parameters with* $a, b \geq 0, \ \lambda < 0$ *and* $0 < \theta < 1$.

Assumptions on the source term. There exists a constant $C > 0$ independent of ε such that the source term $\mathcal{I}_{app,\varepsilon}$ satisfies the following estimation:

$$\left\|\varepsilon^{1/2}\mathcal{I}_{app,\varepsilon}\right\|_{L^2(\Gamma_{\varepsilon,T})} \leq C, \tag{2.7}$$

where $\Gamma_{\varepsilon,T} := (0,T)\times\Gamma_\varepsilon$. Furthermore, $\mathcal{I}_{app}$ denote the weak limit of the sequence.
Assumptions on the initial data. The initial conditions $v_{0,\varepsilon}$ and $w_{0,\varepsilon}$ satisfy the following estimation:

$$\left\|\varepsilon^{1/r}v_{0,\varepsilon}\right\|_{L^r(\Gamma_\varepsilon)} + \left\|\varepsilon^{1/2}v_{0,\varepsilon}\right\|_{L^2(\Gamma_\varepsilon)} + \left\|\varepsilon^{1/2}w_{0,\varepsilon}\right\|_{L^2(\Gamma_\varepsilon)} \leq C, \tag{2.8}$$

for some constant C independent of ε. Moreover, $v_{0,\varepsilon}$ and $w_{0,\varepsilon}$ are assumed to be traces of uniformly bounded sequences in $C^1(\overline{\Omega})$.

Clearly, the equations in (2.1) are invariant under the simultaneous change of $u_i^{\varepsilon,\delta}$ and u_e^ε into $u_i^{\varepsilon,\delta}+k$; $u_e^\varepsilon+k$, for any $k\in\mathbb{R}$. Hence, we may impose the following normalization condition:

$$\int_{\Omega_e^\varepsilon} u_e^\varepsilon(t,x)dx = 0 \text{ for a.e. } t\in(0,T). \tag{2.9}$$

Then, the weak formulation of the microscopic bidomain model can be written as follows.

Definition 2.1 (Weak formulation)**.** *A weak solution of problem* (2.1)-(2.3) *is a four tuple* $(u_i^{\varepsilon,\delta}, u_e^\varepsilon, w_\varepsilon)$ *such that* $u_i^{\varepsilon,\delta} \in L^2\left(0,T;H^1\left(\Omega_i^{\varepsilon,\delta}\right)\right)$, $u_e^\varepsilon \in L^2\left(0,T;H^1(\Omega_e^\varepsilon)\right)$, $v_\varepsilon = (u_i^{\varepsilon,\delta}-u_e^\varepsilon)|_{\Gamma_{\varepsilon,T}} \in L^2(0,T;H^{1/2}(\Gamma_\varepsilon)) \cap L^r(\Gamma_{\varepsilon,T})$, $r\in(2,+\infty)$, $w_\varepsilon\in L^2(\Gamma_{\varepsilon,T})$, $\partial_t v_\varepsilon \in L^2(0,T;H^{-1/2}(\Gamma_\varepsilon)) + L^{r/(r-1)}(\Gamma_{\varepsilon,T})$, $\partial_t w_\varepsilon\in L^2(\Gamma_{\varepsilon,T})$ *and satisfying the following weak formulation for a.e.* $t\in(0,T)$:

$$\begin{aligned}\iint_{\Gamma_{\varepsilon,T}} \varepsilon\partial_t v_\varepsilon\varphi\, d\sigma_x dt + \iint_{\Omega_{i,T}^{\varepsilon,\delta}} \mathrm{M}_i^{\varepsilon,\delta}(x)\nabla u_i^{\varepsilon,\delta}\cdot\nabla\varphi_i\, dxdt + \iint_{\Omega_{e,T}^\varepsilon} \mathrm{M}_e^\varepsilon(x)\nabla u_e^\varepsilon\cdot\nabla\varphi_e\, dxdt \\ + \iint_{\Gamma_{\varepsilon,T}} \varepsilon\mathcal{I}_{ion}(v_\varepsilon,w_\varepsilon)\varphi\, d\sigma_x dt = \iint_{\Gamma_{\varepsilon,T}} \varepsilon\mathcal{I}_{app,\varepsilon}\varphi\, d\sigma_x dt,\end{aligned} \tag{2.10}$$

$$\iint_{\Gamma_{\varepsilon,T}} \partial_t w_\varepsilon\phi\, d\sigma_x dt - \iint_{\Gamma_{\varepsilon,T}} H(v_\varepsilon,w_\varepsilon)\phi\, d\sigma_x dt = 0, \tag{2.11}$$

for all $\varphi_i\in L^2\left(0,T;H^1\left(\Omega_i^{\varepsilon,\delta}\right)\right)$, $\varphi_e\in L^2\left(0,T;H^1\left(\Omega_e^\varepsilon\right)\right)$ *with* $\varphi=(\varphi_i-\varphi_e)|_{\Gamma_{\varepsilon,T}}\in L^2\left(0,T;H^{1/2}(\Gamma_\varepsilon)\right)$ $\cap L^r(\Gamma_{\varepsilon,T})$ *and* $\phi\in L^2(\Gamma_{\varepsilon,T})$*. Moreover, the weak formulation makes sense in view of the following initial conditions:*

$$v_\varepsilon(0,x)=v_{0,\varepsilon}(x) \quad \textit{and} \quad w_\varepsilon(0,x)=w_{0,\varepsilon}(x) \quad \textit{a.e. on } \Gamma_\varepsilon. \tag{2.12}$$

The existence of the weak solution is given in the following theorem where the proof can be found in [Ben+19] where the mesoscopic domain is ignored .

Theorem 2.1 (Microscopic Bidomain Model)**.** *Assume that the conditions* (2.2)-(2.9) *hold. Then the microscopic bidomain problem* (2.1)-(2.3) *possesses a unique weak solution in the sense of Definition 2.1 for every fixed* ε, $\delta > 0$. *Moreover, there exists a constant* $C > 0$ *not depending on* ε *and* δ *such that:*

$$\left\|\sqrt{\varepsilon}v_\varepsilon\right\|_{L^\infty(0,T;L^2(\Gamma_\varepsilon))} + \left\|\sqrt{\varepsilon}w_\varepsilon\right\|_{L^\infty(0,T;L^2(\Gamma_\varepsilon))} \leq C, \tag{2.13}$$

$$\left\|u_i^{\varepsilon,\delta}\right\|_{L^2\left(0,T;H^1\left(\Omega_i^{\varepsilon,\delta}\right)\right)} \leq C, \quad \|u_e^\varepsilon\|_{L^2(0,T;H^1(\Omega_e^\varepsilon))} \leq C, \tag{2.14}$$

$$\left\|\varepsilon^{1/r}v_\varepsilon\right\|_{L^r(\Gamma_{\varepsilon,T})} \leq C \quad \textit{and} \quad \left\|\varepsilon^{(r-1)/r}\, \mathrm{I}_{1,ion}(v_\varepsilon)\right\|_{L^{r/(r-1)}(\Gamma_{\varepsilon,T})} \leq C. \tag{2.15}$$

Furthermore, if $v_{\varepsilon,0} \in H^{1/2}(\Gamma_\varepsilon) \cap L^r(\Gamma_\varepsilon)$, *there exists a constant* $C > 0$ *not depending on* ε *and* δ *such that:*

$$\left\|\sqrt{\varepsilon}\partial_t v_\varepsilon\right\|_{L^2(\Gamma_{\varepsilon,T})} + \left\|\sqrt{\varepsilon}\partial_t w_\varepsilon\right\|_{L^2(\Gamma_{\varepsilon,T})} \leq C. \tag{2.16}$$

The existence and uniqueness of weak solutions for the microscopic bidomain problem (2.1) for every fixed ε, $\delta > 0$ is standard, e.g., by using the Faedo-Galerkin method based on a priori estimates (2.13)-(2.16). We notice that we get the same energy estimates as in [Ben+19], this comes from the consideration of homogeneous Neumann type conditions on the microscopic scale.

2.2 Main results

In this section, we highlight the main results obtained in our first work. Based on three-scale asymptotic expansion in Subsection 2.3 and unfolding homogenization method in Subsection 2.4, we can pass to the limit in the microscopic equations and derive the following macroscopic problem:

Theorem 2.2 (Macroscopic Bidomain Model)**.** *A sequence of solutions* $\left((u_i^{\varepsilon,\delta})_{\varepsilon,\delta}, (u_{e,\varepsilon})_\varepsilon, (w_\varepsilon)_\varepsilon\right)$ *of the microscopic bidomain model* (2.1)-(2.3) *(obtained in Theorem 2.1) converges (as* $\varepsilon, \delta \to 0$*)*

to a weak solution (u_i, u_e, w) *with* $u_i, u_e \in L^2(0,T;H^1(\Omega))$, $v = u_i - u_e \in L^2(0,T;H^1(\Omega)) \cap L^r(\Omega_T)$, $\partial_t v \in L^2(0,T;H^{-1}(\Omega)) + L^{r/(r-1)}(\Omega_T)$ *and* $w \in C(0,T;L^2(\Omega))$, *of the macroscopic problem (Reaction-Diffusion system)*

$$\begin{aligned} \mu_m \partial_t v + \nabla \cdot \left(\widetilde{\mathbf{M}}_e \nabla u_e \right) + \mu_m \mathcal{I}_{ion}(v,w) &= \mu_m \mathcal{I}_{app} \quad \text{in } \Omega_T, \\ \mu_m \partial_t v - \nabla \cdot \left(\widetilde{\widetilde{\mathbf{M}}}_i \nabla u_i \right) + \mu_m \mathcal{I}_{ion}(v,w) &= \mu_m \mathcal{I}_{app} \quad \text{in } \Omega_T, \\ \partial_t w - H(v,w) &= 0 \qquad \text{on } \Omega_T, \end{aligned} \tag{2.17}$$

completed with no-flux boundary conditions on u_i, u_e *on* $\partial_{ext}\Omega$:

$$\left(\widetilde{\mathbf{M}}_e \nabla u_e \right) \cdot \mathbf{n} = \left(\widetilde{\widetilde{\mathbf{M}}}_i \nabla u_i \right) \cdot \mathbf{n} = 0 \ \text{ on } \ \Sigma_T := (0,T) \times \partial_{ext}\Omega, \tag{2.18}$$

and initial conditions for the transmembrane potential v *and the gating variable* w :

$$v(0,x) = v_0(x) \qquad \text{and} \qquad w(0,x) = w_0(x) \text{ a.e. on } \Omega, \tag{2.19}$$

where $v_0, w_0 \in L^2(\Omega)$. *Here,* $\mu_m = |\Gamma^y| \, / \, |Y|$ *is the ration between the surface membrane and the volume of the reference cell. Moreover,* $\mathbf{n}$ *is the outward unit normal to the exterior boundary of* Ω. *Herein, the first-level homogenized conductivity matrices* $\widetilde{\mathbf{M}}_j = \left(\widetilde{\mathbf{m}}_j^{pq} \right)_{1 \le p,q \le d}$ *for* $j = i, e$ *and the second-level one* $\widetilde{\widetilde{\mathbf{M}}}_i = \left(\widetilde{\widetilde{\mathbf{m}}}_i^{pq} \right)_{1 \le p,q \le d}$ *are respectively defined by:*

$$\widetilde{\mathbf{m}}_e^{pq} := \frac{1}{|Y|} \sum_{k=1}^{d} \int_{Y_e} \left(\mathrm{m}_e^{pq} + \mathrm{m}_e^{pk} \frac{\partial \chi_e^q}{\partial y_k} \right) \, dy, \quad \widetilde{\mathbf{m}}_i^{pq} := \frac{1}{|Z|} \sum_{\ell=1}^{d} \int_{Z} \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell} \frac{\partial \theta_i^q}{\partial z_\ell} \right) \, dz, \tag{2.20a}$$

$$\begin{aligned} \widetilde{\widetilde{\mathbf{m}}}_i^{pq} &:= \frac{1}{|Y|} \sum_{k=1}^{d} \int_{Y_i} \left(\widetilde{\mathbf{m}}_i^{pk} \frac{\partial \chi_i^q}{\partial y_k}(y) + \widetilde{\mathbf{m}}_i^{pq} \right) dy \\ &= \frac{1}{|Y|} \frac{1}{|Z|} \sum_{k,\ell=1}^{d} \int_{Y_i} \int_{Z} \left[\left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{p\ell} \frac{\partial \theta_i^k}{\partial z_\ell} \right) \frac{\partial \chi_i^q}{\partial y_k}(y) + \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell} \frac{\partial \theta_i^q}{\partial z_\ell} \right) \right] \, dz dy. \end{aligned} \tag{2.20b}$$

Herein, the components χ_e^q *of* χ_e *and* χ_i^q *of* χ_i *are respectively the corrector functions, solutions* *of the ε-cell problems:*

$$\begin{cases} -\nabla_y \cdot (\mathrm{M}_e \nabla_y \chi_e^q) = \nabla_y \cdot (\mathrm{M}_e e_q) \ \textit{in } Y_e, \\ \chi_e^q \ y\textit{-periodic}, \\ \mathrm{M}_e \nabla_y \chi_e^q \cdot n_e = -(\mathrm{M}_e e_q) \cdot n_e \ \textit{on } \Gamma^y, \end{cases} \tag{2.21a}$$

$$\begin{cases} -\nabla_y \cdot \left(\widetilde{\mathbf{M}}_i \nabla_y \chi_i^q\right) = \nabla_y \cdot \left(\widetilde{\mathbf{M}}_i e_q\right) \ \textit{in } Y_i, \\ \chi_i^q \ y\textit{-periodic}, \\ \widetilde{\mathbf{M}}_i \nabla_y \chi_i^q \cdot n_i = -\left(\widetilde{\mathbf{M}}_i e_q\right) \cdot n_i \ \textit{on } \Gamma^y, \end{cases} \tag{2.21b}$$

and the component θ_i^q of θ_i is the corrector function, solution of the δ-cell problem:

$$\begin{cases} \nabla_z \cdot (\mathrm{M}_i \nabla_z \theta_i^q) = \nabla_z \cdot (\mathrm{M}_i e_q) \ \textit{in } Z, \\ \theta_i^q \ y\textit{- and } z\textit{-periodic}, \\ \mathrm{M}_i \nabla_z \theta_i^q \cdot n_z = -(\mathrm{M}_i e_q) \cdot n_z \ \textit{on } \Gamma^z, \end{cases} \tag{2.22}$$

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

Theorem 2.2 is proved using two different methods: the first one given in Section 2.3 and the other one in Section 2.4. The uniqueness of the solutions to the macroscopic model can be proved by standard methods. This implies that all the convergence results remain valid for the whole sequence. It is easy to verify that the macroscopic conductivity tensors of the intracellular $\widetilde{\widetilde{\mathbf{M}}}_i$ and extracellular $\widetilde{\mathbf{M}}_e$ spaces are symmetric and positive definite.

2.3 Three-scale Asymptotic Homogenization Method

In this section, we will introduce a homogenization method based on asymptotic expansion using multi-scale variables (i.e. slow and fast variables). The aim is to show how to obtain a mathematical writing of the macroscopic model from the microscopic model. This method, among others, is a formal and intuitive method for predicting the mathematical writing of a homogenized solution that can eventually approach the solution of the initial problem (2.1).

For that, we start to treat the problem in the extracellular medium then we will solve the other one in the intracellular medium using this method.

2.3.1 Extracellular problem

The authors in [HY09] have applied and developed the two-scale asymptotic expansion method established by Benssousan and Papanicolaou [BLP11] on the bidomain model (for the case of Laplace equations) defined at two scales to obtain the homogenized model. In our approach, we investigate the same two-scale technique used in [HY09] for the extracellular problem. Whereas for the intracellular domain, we develop a new three-scale approach applied to the intracellular problem to handle with the two structural levels of this domain (see Figure 2.2). We recall the following initial extracellular problem:

$$\begin{aligned} \mathcal{A}_\varepsilon u_e^\varepsilon &= 0 && \text{in } \Omega_{e,T}^\varepsilon, \\ \mathrm{M}_e^\varepsilon \nabla u_e^\varepsilon \cdot n_e = \varepsilon \left(\partial_t v_\varepsilon + \mathcal{I}_{ion}(v_\varepsilon, w_\varepsilon) - \mathcal{I}_{app,\varepsilon} \right) &= \mathcal{I}_m && \text{on } \Gamma_{\varepsilon,T}, \end{aligned} \tag{2.23}$$

with $\mathcal{A}_\varepsilon = -\nabla \cdot (\mathrm{M}_e^\varepsilon \nabla)$, where the extracellular conductivity matrices M_e^ε defined by:

$$\mathrm{M}_e^\varepsilon(x) = \mathrm{M}_e \left(\frac{x}{\varepsilon} \right), \ a.e. \text{ on } \mathbb{R}^d,$$

satisfying the following elliptic and periodic conditions given by (2.4).

The two-scale asymptotic expansion is assumed for the electrical potential u_e^ε as follows:

$$u_e^\varepsilon(t,x) := u_e\left(t,x,\frac{x}{\varepsilon}\right) = u_{e,0}\left(t,x,\frac{x}{\varepsilon}\right) + \varepsilon u_{e,1}\left(t,x,\frac{x}{\varepsilon}\right) + \varepsilon^2 u_{e,2}\left(t,x,\frac{x}{\varepsilon}\right) + \cdots \tag{2.24}$$

with each $u_j(\cdot, y)$ is y-periodic function dependent on time $t \in (0,T)$, slow (macroscopic) variable x and the fast (mesoscopic) variable y. The slow and fast variables correspond respectively to the global and local structure of the field. Similarly, the applied current $\mathcal{I}_{app,\varepsilon}$ has the same two-scale asymptotic expansion.
So, the derivation with respect to x is defined as:

$$\frac{\partial u_e^\varepsilon}{\partial x_q}(t,x) = \frac{\partial u_e}{\partial x_q}\left(t,x,\frac{x}{\varepsilon}\right) + \frac{1}{\varepsilon}\frac{\partial u_e}{\partial y_q}\left(t,x,\frac{x}{\varepsilon}\right).$$

Consequently, the full operator $\mathcal{A}_\varepsilon$ in the initial problem (2.23) is represented as:

$$\mathcal{A}_\varepsilon u_e^\varepsilon(t,x) = \left[(\varepsilon^{-2}\mathcal{A}_{yy} + \varepsilon^{-1}\mathcal{A}_{xy} + \varepsilon^0 \mathcal{A}_{xx}) u_e \right] \left(t,x,\frac{x}{\varepsilon}\right) \tag{2.25}$$

with each operator is defined by:

$$\begin{cases} \mathcal{A}_{yy} = -\sum\limits_{p,q=1}^{d} \dfrac{\partial}{\partial y_p}\left(\mathrm{m}_e^{pq}(y)\dfrac{\partial}{\partial y_q}\right), \\ \mathcal{A}_{xy} = -\sum\limits_{p,q=1}^{d} \dfrac{\partial}{\partial y_p}\left(\mathrm{m}_e^{pq}(y)\dfrac{\partial}{\partial x_q}\right) - \sum\limits_{p,q=1}^{d} \dfrac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\dfrac{\partial}{\partial y_q}\right), \\ \mathcal{A}_{xx} = -\sum\limits_{p,q=1}^{d} \dfrac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\dfrac{\partial}{\partial x_q}\right). \end{cases}$$

Indeed, we have :

$$\begin{aligned} \mathcal{A}_\varepsilon u_e^\varepsilon(t,x) &= -\left[\nabla\cdot(\mathrm{M}_e^\varepsilon \nabla u_e^\varepsilon)\right](t,x) \\ &= -\left[\sum_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\left(\frac{\partial u_e}{\partial x_q} + \frac{1}{\varepsilon}\frac{\partial u_e}{\partial y_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon}\right) \\ &\quad -\frac{1}{\varepsilon}\left[\sum_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_e^{pq}(y)\left(\frac{\partial u_e}{\partial x_q} + \frac{1}{\varepsilon}\frac{\partial u_e}{\partial y_q}\right)\right)\right]\left(x,\frac{x}{\varepsilon}\right) \\ &= \varepsilon^{-2}\left[-\sum_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_e^{pq}(y)\frac{\partial u_e}{\partial y_q}\right)\right]\left(t,x,\frac{x}{\varepsilon}\right) \\ &\quad + \varepsilon^{-1}\left[-\sum_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_e^{pq}(y)\frac{\partial u_e}{\partial x_q}\right) - \sum_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\frac{\partial u_e}{\partial y_q}\right)\right]\left(t,x,\frac{x}{\varepsilon}\right) \\ &\quad + \varepsilon^{0}\left[-\sum_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\frac{\partial u_e}{\partial x_q}\right)\right]\left(t,x,\frac{x}{\varepsilon}\right) \\ &= \left[(\varepsilon^{-2}\mathcal{A}_{yy} + \varepsilon^{-1}\mathcal{A}_{xy} + \varepsilon^{0}\mathcal{A}_{xx})u_e\right]\left(t,x,\frac{x}{\varepsilon}\right). \end{aligned}$$

Now, we substitute the asymptotic expansion (2.24) of u_e^ε in the developed operator (2.25) to obtain

$$\begin{aligned} \mathcal{A}_\varepsilon u_e^\varepsilon(x) &= \left[\varepsilon^{-2}\mathcal{A}_{yy}u_{e,0} + \varepsilon^{-1}\mathcal{A}_{yy}u_{e,1} + \varepsilon^{0}\mathcal{A}_{yy}u_{e,2} + \cdots\right]\left(t,x,\frac{x}{\varepsilon}\right) \\ &\quad + \left[\varepsilon^{-1}\mathcal{A}_{xy}u_{e,0} + \varepsilon^{0}\mathcal{A}_{xy}u_{e,1} + \cdots\right]\left(t,x,\frac{x}{\varepsilon}\right) \\ &\quad + \left[\varepsilon^{0}\mathcal{A}_{xx}u_{e,0} + \cdots\right]\left(t,x,\frac{x}{\varepsilon}\right) \\ &= \left[\varepsilon^{-2}\mathcal{A}_{yy}u_{e,0} + \varepsilon^{-1}\left(\mathcal{A}_{yy}u_{e,1} + \mathcal{A}_{xy}u_{e,0}\right)\right. \\ &\quad \left. + \varepsilon^{0}\left(\mathcal{A}_{yy}u_{e,2} + \mathcal{A}_{xy}u_{e,1} + \mathcal{A}_{xx}u_{e,0}\right)\right]\left(t,x,\frac{x}{\varepsilon}\right) + \cdots. \end{aligned}$$

Similarly, we substitute the asymptotic expansion (2.24) of u_e^ε into the boundary condition equation (2.23) on Γ^y. Consequently, by equating the powers-like terms of ε^ℓ to zero ($\ell = -2, -1, 0$), we have to solve the following system of equations for the functions $u_{e,k}(t,x,y),\ k = 0, 1, 2$:

$$\begin{cases} \mathcal{A}_{yy} u_{e,0} = 0 \text{ in } Y_e, \\ u_{e,0}\ y\text{-periodic}, \\ \mathrm{M}_e \nabla_y u_{e,0} \cdot n_e = 0 \text{ on } \Gamma^y, \end{cases} \tag{2.26}$$

$$\begin{cases} \mathcal{A}_{yy} u_{e,1} = -\mathcal{A}_{xy} u_{e,0} \text{ in } Y_e, \\ u_{e,1}\ y\text{-periodic}, \\ (\mathrm{M}_e \nabla_y u_{e,1} + \mathrm{M}_e \nabla_x u_{e,0}) \cdot n_e = 0 \text{ on } \Gamma^y, \end{cases} \tag{2.27}$$

$$\begin{cases} \mathcal{A}_{yy} u_{e,2} = -\mathcal{A}_{xy} u_{e,1} - \mathcal{A}_{xx} u_{e,0} \text{ in } Y_e, \\ u_{e,2}\ y\text{-periodic}, \\ (\mathrm{M}_e \nabla_y u_{e,2} + \mathrm{M}_e \nabla_x u_{e,1}) \cdot n_e = \partial_t v_0 + \mathcal{I}_{ion}(v_0, w_0) - \mathcal{I}_{app,0} \text{ on } \Gamma^y, \end{cases} \tag{2.28}$$

The authors in [BLP11]-[CD99] have successively solved the three systems into Dirrichlet boundary conditions (2.26)-(2.28). Herein, the functions $u_{e,0}, u_{e,1}$ and $u_{e,2}$ in the asymptotic expansion (2.24) for the extracellular potential u_e^ε satisfy the Neumann boundary value problems (2.26)-(2.28) in the local portion Y_e of a unit cell Y (see [FS02; HY09] for the case of Laplace equations).

The resolution is described as follows:

- **First step** We begin with the first boundary value problem (2.26) whose variational formulation:

$$\begin{cases} \text{Find } \dot{u}_{e,0} \in \mathcal{W}_{per}(Y_e) \text{ such that} \\ \dot{a}_{Y_e}(\dot{u}_{e,0}, \dot{v}) = \displaystyle\int_{\partial Y_e} (\mathrm{M}_e \nabla_y u_{e,0} \cdot n_e) v \, d\sigma_y, \ \forall \dot{v} \in \mathcal{W}_{per}(Y_e), \end{cases} \tag{2.29}$$

with $\dot{a}_{Y_e}(\dot{u}, \dot{v})$ is given by:

$$\dot{a}_{Y_e}(\dot{u}, \dot{v}) = \int_{Y_e} \mathrm{M}_e \nabla_y u \nabla_y v dy, \ \forall u \in \dot{u}, \ \forall v \in \dot{v}, \ \forall \dot{u}, \ \forall \dot{v} \in \mathcal{W}_{per}(Y_e) \tag{2.30}$$

and $\mathcal{W}_{per}(Y_e)$ is given by Definition A.4.

We want to clarify the right-hand side of the variational formulation (2.29). By the definition of $\partial Y_e := (\partial_{\text{ext}} Y \cap \partial Y_e) \cup \Gamma^y$, we use Proposition A.1 and the y-periodicity of M_i by taking account the boundary condition on Γ^y to say that :

$$\begin{aligned}\int_{\partial Y_e} (\mathrm{M}_e \nabla_y u_{e,0} \cdot n_e) v \, d\sigma_y \\ = \int_{\partial_{\text{ext}} Y \cap \partial Y_e} (\mathrm{M}_e \nabla_y u_{e,0} \cdot n_e) v \, d\sigma_y + \int_{\Gamma^y} (\mathrm{M}_e \nabla_y u_{e,0} \cdot n_e) v \, d\sigma_y = 0.\end{aligned}$$

Using Theorem A.2, we can prove the existence and uniqueness of the solution $\dot{u}_{e,0}$. Then, problem (2.26) has a unique solution $u_{e,0}$ independent of y, so we deduce that:

$$u_{e,0}(t, x, y) = u_{e,0}(t, x).$$

In the next section, we show that $u_{i,0}$ does not depend on y (by the same strategy). Since $v_0 = (u_{i,0} - u_{e,0}))|_{\Gamma^y}$ then we also deduce that v_0 and w_0 not depend on the mesoscopic variable y.

Remark 2.4. *In the asymptotic expansion (2.24), each element $u_{e,k}$ is a priori an oscillating function, since it depends on the fast variable x/ε. Actually, $u_{e,0}$ depends only on the slow (macroscopic) variable x, so it does not oscillate "rapidly" with x/ε. This is why we now expect $u_{e,0}$ to be the "solution homogenized". It remains to find if there is an equation on Ω satisfied by $u_{e,0}$, in which case we would have found "homogenized equation" too.*

- **Second step** We now turn to the second boundary value problem (2.27). Since $u_{e,0}$ is independent of y, this equation can be rewritten as:

$$\begin{cases} \mathcal{A}_{yy} u_{e,1} = \sum_{p,q=1}^{d} \dfrac{\partial \mathrm{m}_e^{pq}}{\partial y_p} \dfrac{\partial u_{e,0}}{\partial x_q} \text{ in } Y_e, \\ u_{e,1} \; y\text{-periodic}, \\ (\mathrm{M}_e \nabla u_{e,1} + \mathrm{M}_e \nabla u_{e,0}) \cdot n_e = 0 \text{ on } \Gamma^y, \end{cases} \tag{2.31}$$

Its variational formulation is:

$$\begin{cases} \text{Find } \dot{u}_{e,1} \in \mathcal{W}_{per}(Y_e) \text{ such that} \\ \dot{a}_{Y_e}(\dot{u}_{e,1}, \dot{v}) = (F_1, \dot{v})_{(\mathcal{W}_{per}(Y_e))', \mathcal{W}_{per}(Y_e)} \; \forall \dot{v} \in \mathcal{W}_{per}(Y_e), \end{cases} \tag{2.32}$$

with $\dot{a}_{Y_e}$ is given by (2.30) and F_1 is defined by:

$$(F_1, \dot{v})_{(\mathcal{W}_{per}(Y_e))', \mathcal{W}_{per}(Y_e)} = \sum_{p,q=1}^{d} \frac{\partial u_{e,0}}{\partial x_q} \int_{Y_e} \mathrm{m}_e^{pq}(y) \frac{\partial v}{\partial y_p} dy, \ \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{per}(Y_e). \tag{2.33}$$

Using Theorem A.2, we obtain that the second system (2.31)-(2.33) has a unique weak solution $\dot{u}_{e,1} \in \mathcal{W}_{per}(Y_e)$ (defined by [BLP11] and [OSY09]). Thus, the linearity of terms in the right hand side of equation (2.31) suggests to look for $\dot{u}_{e,1}$ under the following form:

$$\dot{u}_{e,1}(t,x,y) = \sum_{q=1}^{d} \dot{\chi}_e^q(y) \frac{\partial \dot{u}_{e,0}}{\partial x_q}(t,x) \text{ in } \mathcal{W}_{per}(Y_e), \tag{2.34}$$

with the corrector function $\dot{\chi}_e^q$ satisfies the following ε-cell problem:

$$\begin{cases} \mathcal{A}_{yy} \dot{\chi}_e^q = \sum_{p=1}^{d} \dfrac{\partial \mathrm{m}_e^{pq}}{\partial y_p} \text{ in } Y_e, \\ \dot{\chi}_e^q \ y\text{-periodic}, \\ \mathrm{M}_e \nabla_y \dot{\chi}_e^q \cdot n_e = -(\mathrm{M}_e e_q) \cdot n_e \text{ on } \Gamma^y, \end{cases} \tag{2.35}$$

for e_q, $q = 1, \ldots, d$, the standard canonical basis in $\mathbb{R}^d$. Moreover, we can choose a representative element χ_e^q of the class $\dot{\chi}_e^q$ satisfying the following variational formulation:

$$\begin{cases} \text{Find } \chi_e^q \in W_\#(Y_e) \text{ such that} \\ \\ a_{Y_e}(\chi_e^q, v) = (F, v)_{(W_\#(Y_e))', W_\#(Y_e)}, \quad \forall v \in W_\#(Y_e), \end{cases} \tag{2.36}$$

with a_{Y_e} is given by (2.30) and F is defined by:

$$(F, v)_{(W_\#(Y_e))', W_\#(Y_e)} = \sum_{p=1}^{d} \int_{Y_e} \mathrm{m}_e^{pq}(y) \frac{\partial v}{\partial y_p} dy,$$

where the space $W_\#(Y_e)$ is given by the expression (A.3). Since F belongs to $(W_\#(Y_e))'$ then the condition of Theorem A.2 is imposed in order to guarantee existence and uniqueness of the solution.

Thus, by the form of $\dot{u}_{e,1}$ given by (2.34), the solution $u_{e,1}$ of the second system (2.27) can be represented by the following ansatz:

$$u_{e,1}(t,x,y) = \chi_e(y) \cdot \nabla_x u_{e,0}(t,x) + \tilde{u}_{e,1}(t,x) \text{ with } u_{e,1} \in \dot{u}_{e,1}, \tag{2.37}$$

where $\tilde{u}_{e,1}$ is a constant with respect to y (i.e $\tilde{u}_{e,1} \in \dot{0}$ in $\mathcal{W}_{per}(Y)$).

• **Last step** We now pass to the last boundary value problem (2.28). Taking into account the form of $u_{e,0}$ and $u_{e,1}$, we obtain

$$\begin{aligned} &-\mathcal{A}_{xy}u_{e,1} - \mathcal{A}_{xx}u_{e,0} \\ &\quad = \sum_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_e^{pq}(y)\frac{\partial u_{e,1}}{\partial x_q}\right) + \sum_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\left(\frac{\partial u_{e,1}}{\partial y_q} + \frac{\partial u_{e,0}}{\partial x_q}\right)\right). \end{aligned}$$

Consequently, this system (2.28) have the following variational formulation:

$$\begin{cases} \text{Find } \dot{u}_{e,2} \in \mathcal{W}_{per}(Y_e) \text{ such that} \\ \dot{a}_{Y_e}(\dot{u}_{e,2}, \dot{v}) = (F_2, \dot{v})_{(\mathcal{W}_{per}(Y_e))', \mathcal{W}_{per}(Y_e)} \ \forall \dot{v} \in \mathcal{W}_{per}(Y_e), \end{cases} \tag{2.38}$$

with $\dot{a}_{Y_e}$ is given by (2.30) and F_2 is defined by:

$$\begin{aligned} &(F_2, \dot{v})_{(\mathcal{W}_{per}(Y_e))', \mathcal{W}_{per}(Y_e)} \\ &= \int_{\Gamma^y} (\mathrm{M}_e \nabla_y u_{e,2} + \mathrm{M}_e \nabla_x u_{e,1}) \cdot n_e \, v \, d\sigma_y - \sum_{p,q=1}^{d} \int_{Y_e} \mathrm{m}_e^{pq}(y) \frac{\partial u_{e,1}}{\partial x_q}\frac{\partial v}{\partial y_p} dy \\ &+ \sum_{p,q=1}^{d} \int_{Y_e} \frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\left(\frac{\partial u_{e,1}}{\partial y_q} + \frac{\partial u_{e,0}}{\partial x_q}\right)\right) v dy, \ \ \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{per}(y). \end{aligned} \tag{2.39}$$

The problem (2.38)-(2.39) is well-posed according to Theorem A.2 under the compatibility condition:

$$(F_2, 1)_{(\mathcal{W}_{per}(Y_e))', \mathcal{W}_{per}(Y_e)} = 0.$$

which equivalent to:

$$-\sum_{p,q=1}^{d} \int_{Y_e} \frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\left(\frac{\partial u_{e,1}}{\partial y_q} + \frac{\partial u_{e,0}}{\partial x_q}\right)\right) dy = |\Gamma^y| \left(\partial_t v_0 + \mathcal{I}_{ion}(v_0, w_0) - \mathcal{I}_{app}\right).$$

In addition, we replace $u_{e,1}$ by its form (2.37) in the above condition to obtain:

$$\begin{aligned} -\sum_{p,q=1}^{d} \int_{Y_e} \frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\left(\sum_{k=1}^{d} \frac{\partial \chi_e^k}{\partial y_q}\frac{\partial u_{e,0}}{\partial x_k} + \frac{\partial u_{e,0}}{\partial x_q}\right)\right) dy \\ = |\Gamma^y| \left(\partial_t v_0 + \mathcal{I}_{ion}(v_0, w_0) - \mathcal{I}_{app}\right). \end{aligned}$$

By expanding the sum and permuting the index, we obtain

$$-\sum_{p,q=1}^{d}\sum_{k=1}^{d}\int_{Y_e}\frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\frac{\partial \chi_e^k}{\partial y_q}\frac{\partial u_{e,0}}{\partial x_k}\right)dy-\sum_{p,k=1}^{d}\int_{Y_e}\frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pk}(y)\frac{\partial u_{e,0}}{\partial x_k}\right)dy$$
$$=|\Gamma^y|\left(\partial_t v_0+\mathcal{I}_{ion}(v_0,w_0)-\mathcal{I}_{app}\right)$$

which equivalent to find $u_{e,0}$ satisfying the following problem:

$$-\sum_{p,k=1}^{d}\left[\frac{1}{|Y|}\sum_{q=1}^{d}\int_{Y_e}\left(\mathrm{m}_e^{pk}(y)+\mathrm{m}_e^{pq}(y)\frac{\partial \chi_e^k}{\partial y_q}\right)dy\right]\frac{\partial^2 u_{e,0}}{\partial x_p\partial x_k}$$
$$=\frac{|\Gamma^y|}{|Y|}\left(\partial_t v_0+\mathcal{I}_{ion}(v_0,w_0)-\mathcal{I}_{app}\right),$$

where $\mathcal{I}_{app}(t,x)=\dfrac{1}{|\Gamma^y|}\displaystyle\int_{\Gamma^y}\mathcal{I}_{app,0}(\cdot,y)\,d\sigma_y$.

Consequently, we see that's exactly the **homogenized** equation satisfied by $u_{e,0}$ of the extracellular problem can be rewritten as:

$$\mathcal{B}_{xx}u_{e,0}=\mu_m\left(\partial_t v_0+\mathcal{I}_{ion}(v_0,w_0)-\mathcal{I}_{app}\right)\ \text{ on } \Omega_T, \tag{2.40}$$

where $\mu_m=|\Gamma^y|\,/\,|Y|$. Herein, the homogenized operator $\mathcal{B}_{xx}$ is defined by :

$$\mathcal{B}_{xx}=-\nabla_x\cdot\left(\widetilde{\mathbf{M}}_e\nabla_x\right)=-\sum_{p,k=1}^{d}\frac{\partial}{\partial x_p}\left(\widetilde{\mathbf{m}}_e^{pq}\frac{\partial}{\partial x_k}\right) \tag{2.41}$$

with the coefficients of the homogenized conductivity matrices $\widetilde{\mathbf{M}}_e=\left(\widetilde{\mathbf{m}}_e^{pk}\right)_{1\le p,k\le d}$ defined by:

$$\widetilde{\mathbf{m}}_e^{pk}:=\frac{1}{|Y|}\sum_{q=1}^{d}\int_{Y_e}\left(\mathrm{m}_e^{pk}+\mathrm{m}_e^{pq}\frac{\partial \chi_e^k}{\partial y_q}\right)\,dy. \tag{2.42}$$

2.3.2 Intracellular problem

Using the two-scale asymptotic expansion method, the extracellular problem is treated on two scales. Our derivation bidomain model is based on a new three-scale approach. We apply three-scale asymptotic expansion in the intracellular problem to obtain its homogenized equation.

Recall that $u_i^{\varepsilon,\delta}$ the solution of the following initial intracellular problem:

$$\begin{aligned} \mathcal{A}_{\varepsilon,\delta} u_i^{\varepsilon,\delta} &= 0 && \text{in } \Omega_{i,T}^{\varepsilon,\delta}, \\ -\mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta} \cdot n_i = \varepsilon \left(\partial_t v_\varepsilon + \mathcal{I}_{ion}(v_\varepsilon, w_\varepsilon) - \mathcal{I}_{app,\varepsilon} \right) &= \mathcal{I}_m && \text{on } \Gamma_{\varepsilon,T}, \\ -\mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta} \cdot n_z &= 0 && \text{on } \Gamma_{\delta,T}, \end{aligned} \tag{2.43}$$

with $\mathcal{A}_{\varepsilon,\delta} = -\nabla \cdot \left(\mathrm{M}_i^{\varepsilon,\delta} \nabla \right)$, where the intracellular conductivity matrices $\mathrm{M}_i^{\varepsilon,\delta}$ defined by:

$$\mathrm{M}_i^{\varepsilon,\delta}(x) = \mathrm{M}_i \left(\frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right),$$

satisfying the following elliptic and periodicity conditions given by (2.4).

In the intracellular problem, we consider three different scales: the slow variable x describes the macroscopic one, the fast variables $\frac{x}{\varepsilon}$ describes the mesoscopic one while $\frac{x}{\varepsilon\delta}$ describes the microscopic one.

To proceed with multi-scale formulation of the microscopic bidomain problem, a three-scale asymptotic expansion is assumed for the intracellular potential $u_i^{\varepsilon,\delta}$ as follows:

$$\begin{aligned} u_i^{\varepsilon,\delta}(t,x) := u_i \left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right) &= u_{i,0} \left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right) + \varepsilon u_{i,1} \left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right) + \varepsilon\delta u_{i,2} \left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right) \\ &+ \varepsilon^2 u_{i,3} \left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right) + \varepsilon^2 \delta u_{i,4} \left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right) \\ &+ \varepsilon^2 \delta^2 \, u_{i,5} \left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right) + \cdots \end{aligned} \tag{2.44}$$

with each $u_{i,q}(\cdot, y, z)$ is y- and z-periodic function dependent on time $t \in (0,T)$, the macroscopic variable x, the mesoscopic variable y, and the microscopic variable z.
Next, we use the chain rule to derive with respect to x

$$\frac{\partial u_i^{\varepsilon,\delta}}{\partial x_q}(t,x) = \left[\frac{\partial u_i}{\partial x_q} + \frac{1}{\varepsilon} \frac{\partial u_i}{\partial y_q} + \frac{1}{\varepsilon\delta} \frac{\partial u_i}{\partial z_q} \right] \left(t, x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta} \right).$$

Remark 2.5. *The authors in [RT+18] used the iterated three-scale homogenization methods to study macroscopic performance of hierarchical composites in the context of mechanics where the microscale and mesoscale are very well-separated, i.e.*

$$u^{\varepsilon,\delta}(x,y,z) = u_0(x,y,z) + \sum_{k=1}^{\infty} \varepsilon^k u_k(x,y,z) + \sum_{k=1}^{\infty} \delta^k u_k'(x,y,z),$$

with $y = x/\varepsilon$ and $z = x/\delta$ ($\delta << \varepsilon$). The approach proposed in the present work is exploited the effective properties of cardiac tissue with multiple small-scale configurations. We note that our present technique recovers the classical reiterated homogenization [BLP11] where $\delta = \varepsilon$.

Consequently, we can write the full operator $\mathcal{A}_{\varepsilon,\delta}$ in the initial problem (2.43) as follows:

$$\begin{aligned}
\mathcal{A}_{\varepsilon,\delta} u_i^{\varepsilon,\delta}(t,x) &= -\left[\nabla \cdot \left(\mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta}\right)\right](t,x) \\
&= -\left[\sum_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q} + \frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q} + \frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) \\
&\quad - \frac{1}{\varepsilon}\left[\sum_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q} + \frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q} + \frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) \\
&\quad - \frac{1}{\varepsilon\delta}\left[\sum_{p,q=1}^{d} \frac{\partial}{\partial z_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q} + \frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q} + \frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) \\
&= [(\varepsilon^{-2}\delta^{-2}\mathcal{A}_{zz} + \varepsilon^{-2}\delta^{-1}\mathcal{A}_{yz} + \varepsilon^{-1}\delta^{-1}\mathcal{A}_{xz} \\
&\quad + \varepsilon^{-2}\mathcal{A}_{yy} + \varepsilon^{-1}\mathcal{A}_{xy} + \varepsilon^{0}\delta^{0}\mathcal{A}_{xx})u_i]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)
\end{aligned} \tag{2.45}$$

with each operator is defined by:

$$\begin{cases}
\mathcal{A}_{ss} = -\sum\limits_{p,q=1}^{d} \dfrac{\partial}{\partial s_p}\left(\mathrm{m}_i^{pq}(y,z)\dfrac{\partial}{\partial s_q}\right), \\
\mathcal{A}_{sh} = -\sum\limits_{p,q=1}^{d} \dfrac{\partial}{\partial s_p}\left(\mathrm{m}_i^{pq}(y,z)\dfrac{\partial}{\partial h_q}\right) - \sum\limits_{p,q=1}^{d} \dfrac{\partial}{\partial h_q}\left(\mathrm{m}_i^{pq}(y,z)\dfrac{\partial}{\partial s_p}\right) & \text{if } s \neq h,
\end{cases}$$

for $s, h := x, y, z$.

Indeed, we have:

$$\begin{aligned}
\mathcal{A}_{\varepsilon,\delta} u_i^{\varepsilon,\delta}(t,x) &= -\left[\nabla \cdot \left(\mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta}\right)\right](t,x) \\
&= -\left[\sum_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q} + \frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q} + \frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) \\
&\quad - \frac{1}{\varepsilon}\left[\sum_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q} + \frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q} + \frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) \\
&\quad - \frac{1}{\varepsilon\delta}\left[\sum_{p,q=1}^{d} \frac{\partial}{\partial z_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q} + \frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q} + \frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)
\end{aligned}$$

$$
\begin{aligned}
&= \varepsilon^{-2}\delta^{-2}\left[-\sum_{p,q=1}^{d}\frac{\partial}{\partial z_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial z_q}\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&\quad + \varepsilon^{-2}\delta^{-1}\left[-\sum_{p,q=1}^{d}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial z_q}\right) - \sum_{p,q=1}^{d}\frac{\partial}{\partial z_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial y_q}\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&\quad + \varepsilon^{-1}\delta^{-1}\left[-\sum_{p,q=1}^{d}\frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial z_q}\right) - \sum_{p,q=1}^{d}\frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial z_q}\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&\quad + \varepsilon^{-2}\left[-\sum_{p,q=1}^{d}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial y_q}\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&\quad + \varepsilon^{-1}\left[-\sum_{p,q=1}^{d}\frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial y_q}\right) - \sum_{p,q=1}^{d}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial x_q}\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&\quad + \varepsilon^{0}\delta^{0}\left[-\sum_{p,q=1}^{d}\frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_i}{\partial x_q}\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&= [(\varepsilon^{-2}\delta^{-2}\mathcal{A}_{zz} + \varepsilon^{-2}\delta^{-1}\mathcal{A}_{yz} + \varepsilon^{-1}\delta^{-1}\mathcal{A}_{xz}\\
&\quad + \varepsilon^{-2}\mathcal{A}_{yy} + \varepsilon^{-1}\mathcal{A}_{xy} + \varepsilon^{0}\delta^{0}\mathcal{A}_{xx})u_i]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right).
\end{aligned}
$$

Now, we substitute the asymptotic expansion (2.44) of $u_i^{\varepsilon,\delta}$ into the operator developed (2.45) to obtain :

$$
\begin{aligned}
&\mathcal{A}_{\varepsilon,\delta}u^{\varepsilon,\delta}(t,x)\\
&= [\varepsilon^{-2}\delta^{-2}\mathcal{A}_{zz}u_{i,0} + \varepsilon^{-2}\delta^{-1}\mathcal{A}_{yz}u_{i,0} + \varepsilon^{-2}\mathcal{A}_{yy}u_{i,0} + \varepsilon^{-1}\delta^{-2}\mathcal{A}_{zz}u_{i,1} + \delta^{-2}\mathcal{A}_{zz}u_{i,3}\\
&+ \varepsilon^{-1}\delta^{-1}\left(\mathcal{A}_{zz}u_{i,2} + \mathcal{A}_{yz}u_{i,1} + \mathcal{A}_{xz}u_{i,0}\right) + \delta^{-1}\left(\mathcal{A}_{zz}u_{i,4} + \mathcal{A}_{yz}u_{i,3} + \mathcal{A}_{xz}u_{i,1}\right)\\
&+ \varepsilon^{-1}\left(\mathcal{A}_{yz}u_{i,2} + \mathcal{A}_{yy}u_{i,1} + \mathcal{A}_{xz}u_{i,0}\right)\\
&+ \varepsilon^{0}\delta^{0}\left(\mathcal{A}_{zz}u_{i,5} + \mathcal{A}_{yz}u_{i,4} + \mathcal{A}_{yy}u_{i,3} + \mathcal{A}_{xz}u_{i,2} + \mathcal{A}_{xy}u_{i,1} + \mathcal{A}_{xx}u_{i,0}\right)]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) + \cdots .
\end{aligned}
$$

Similarly, we have the boundary condition:

$$
\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\cdot n = \left[\mathrm{M}_i^{\varepsilon,\delta}\nabla_x u_i + \varepsilon^{-1}\mathrm{M}_i^{\varepsilon,\delta}\nabla_y u_i + \varepsilon^{-1}\delta^{-1}\mathrm{M}_i^{\varepsilon,\delta}\nabla_z u_i\right]\cdot n, \tag{2.46}
$$

for $n := n_i, n_z$.

Thus, we also substitute the asymptotic expansion (2.44) of $u_i^{\varepsilon,\delta}$ into the boundary condition equation (2.43) on Γ^y and on Γ^z :

$$\begin{aligned}
\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\cdot n &= [\varepsilon^0\delta^0(\mathrm{M}_i\nabla_x u_{i,0})\cdot n + \varepsilon(\mathrm{M}_i\nabla_x u_{i,1})\cdot n + \varepsilon\delta(\mathrm{M}_i\nabla_x u_{i,2})\cdot n + \cdots]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&+ [\varepsilon^{-1}(\mathrm{M}_i\nabla_y u_{i,0})\cdot n + \varepsilon^0\delta^0(\mathrm{M}_i\nabla_y u_{i,1})\cdot n + \delta(\mathrm{M}_i\nabla_y u_{i,2})\cdot n\\
&\quad + \varepsilon(\mathrm{M}_i\nabla_y u_{i,3})\cdot n + \varepsilon\delta(\mathrm{M}_i\nabla_y u_{i,4})\cdot n + \cdots]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&+ [\varepsilon^{-1}\delta^{-1}(\mathrm{M}_i\nabla_z u_{i,0})\cdot n + \delta^{-1}(\mathrm{M}_i\nabla_z u_{i,1})\cdot n + \varepsilon^0\delta^0(\mathrm{M}_i\nabla_z u_{i,2})\cdot n\\
&\quad + \varepsilon\delta^{-1}(\mathrm{M}_i\nabla_z u_{i,3})\cdot n + \varepsilon(\mathrm{M}_i\nabla_z u_{i,4})\cdot n + \varepsilon\delta(\mathrm{M}_i\nabla_z u_{i,5})\cdot n + \cdots]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&= [\varepsilon^{-1}\delta^{-1}(\mathrm{M}_i\nabla_z u_{i,0})\cdot n + \varepsilon^{-1}(\mathrm{M}_i\nabla_y u_{i,0})\cdot n + \delta^{-1}(\mathrm{M}_i\nabla_z u_{i,1})\cdot n\\
&+ \varepsilon^0\delta^0\left(\mathrm{M}_i\nabla_z u_{i,2} + \mathrm{M}_i\nabla_y u_{i,1} + \mathrm{M}_i\nabla_x u_{i,0}\right)\cdot n + \varepsilon^{-1}\delta^{-1}\left(\mathrm{M}_i\nabla_z u_{i,3}\right)\cdot n\\
&+ \varepsilon\left(\mathrm{M}_i\nabla_z u_{i,4} + \mathrm{M}_i\nabla_y u_{i,3} + \mathrm{M}_i\nabla_x u_{i,1}\right)\cdot n + \delta(\mathrm{M}_i\nabla_y u_{i,2})\cdot n\\
&+ \varepsilon\delta\left(\mathrm{M}_i\nabla_z u_{i,5} + \mathrm{M}_i\nabla_y u_{i,4} + \mathrm{M}_i\nabla_x u_{i,2}\right)\cdot n]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) + \cdots.
\end{aligned}$$

where n represents the outward unit normal on Γ^y or on Γ^z $(n := n_i, n_z)$. Consequently, by equating the terms of the powers coefficients $\varepsilon^\ell\delta^m$ for the elliptic equations and of the powers coefficients $\varepsilon^{\ell+1}\delta^{m+1}$ for the boundary conditions ($\ell, m = -2, -1, 0$), we obtain the following systems:

$$\begin{cases}\mathcal{A}_{zz}u_{i,0} = 0 \text{ in } Z_c,\\ u_{i,0}\ z\text{-periodic},\\ \mathrm{M}_i\nabla_z u_{i,0}\cdot n_z = 0 \text{ on } \Gamma^z,\end{cases} \tag{2.47}$$

$$\begin{cases}\mathcal{A}_{yy}u_{i,0} = 0 \text{ in } Y_i,\\ u_{i,0}\ y\text{-periodic},\\ \mathrm{M}_i\nabla_y u_{i,0}\cdot n_i = 0 \text{ on } \Gamma^y,\end{cases} \tag{2.48}$$

$$\begin{cases}\mathcal{A}_{yz}u_{i,0} = 0 \text{ in } Z_c,\\ u_{i,0}\ y\text{- and } z\text{-periodic},\\ \mathrm{M}_i\nabla_y u_{i,0}\cdot n_i = 0 \text{ on } \Gamma^y,\\ \mathrm{M}_i\nabla_z u_{i,0}\cdot n_z = 0 \text{ on } \Gamma^z,\end{cases} \tag{2.49}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,1} = 0 \text{ in } Z_c, \\ u_{i,1} \ z\text{-periodic}, \\ \mathrm{M}_i \nabla_z u_{i,1} \cdot n_z = 0 \text{ on } \Gamma^z, \end{cases} \tag{2.50}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,2} = -\mathcal{A}_{yz} u_{i,1} - \mathcal{A}_{xz} u_{i,0} \text{ in } Z_c, \\ u_{i,2} \ z\text{-periodic}, \\ (\mathrm{M}_i \nabla_z u_{i,2} + \mathrm{M}_i \nabla_y u_{i,1} + \mathrm{M}_i \nabla_x u_{i,0}) \cdot n_z = 0 \text{ on } \Gamma^z, \end{cases} \tag{2.51}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,3} = 0 \text{ in } Z_c, \\ u_{i,3} \ z\text{-periodic}, \\ (\mathrm{M}_i \nabla_z u_{i,3}) \cdot n_z = 0 \text{ on } \Gamma^z, \end{cases} \tag{2.52}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,4} = -\mathcal{A}_{yz} u_{i,3} - \mathcal{A}_{xz} u_{i,1} \text{ in } Z_c, \\ u_{i,4} \ y\text{- and } z\text{-periodic}, \\ (\mathrm{M}_i \nabla_z u_{i,4} + \mathrm{M}_i \nabla_y u_{i,3} + \mathrm{M}_i \nabla_x u_{i,1}) \cdot n_i = -\left(\partial_t v_0 + \mathcal{I}_{ion}(v_0, w_0) - \mathcal{I}_{app}\right) \text{ on } \Gamma^y, \\ (\mathrm{M}_i \nabla_z u_{i,4} + \mathrm{M}_i \nabla_y u_{i,3} + \mathrm{M}_i \nabla_x u_{i,1}) \cdot n_z = 0 \text{ on } \Gamma^z, \end{cases} \tag{2.53}$$

$$\begin{cases} \mathcal{A}_{yz} u_{i,2} = -\mathcal{A}_{yy} u_{i,1} - \mathcal{A}_{xy} u_{i,0} \text{ in } Z_c, \\ u_{i,2} \ y\text{- and } z\text{-periodic}, \\ (\mathrm{M}_i \nabla_z u_{i,2} + \mathrm{M}_i \nabla_y u_{i,1} + \mathrm{M}_i \nabla_x u_{i,0}) \cdot n_i = 0 \text{ on } \Gamma^y, \\ \mathrm{M}_i \nabla_y u_{i,2} \cdot n_z = 0 \text{ on } \Gamma^z, \end{cases} \tag{2.54}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,5} = -\mathcal{A}_{yz} u_{i,4} - \mathcal{A}_{yy} u_{i,3} - \mathcal{A}_{xz} u_{i,2} - \mathcal{A}_{xy} u_{i,1} - \mathcal{A}_{xx} u_{i,0} \text{ in } Z_c, \\ u_{i,5} \ z\text{-periodic}, \\ (\mathrm{M}_i \nabla_z u_{i,5} + \mathrm{M}_i \nabla_y u_{i,4} + \mathrm{M}_i \nabla_x u_{i,2}) \cdot n_z = 0 \text{ on } \Gamma^z. \end{cases} \tag{2.55}$$

These systems (2.47)-(2.55) have a particular structure in the sense that their unknowns will be found iteratively.

We will solve these nine problems (2.47)-(2.55) successively to determine the homogenized problem (based on the work [CD99] and [BLP11]). The resolution is described as follows:

- **Step 1** We begin with the first problem (2.47) whose the following variational formulation:

$$\begin{cases} \text{Find } \dot{u}_{i,0} \in \mathcal{W}_{per}(Z_c) \text{ such that} \\ \dot{a}_{Z_c}(\dot{u}_{i,0}, \dot{v}) = \displaystyle\int_{\partial Z_c} (\mathrm{M}_i \nabla_z u_{i,0} \cdot n_z)\, v \, d\sigma(z), \ \forall \dot{v} \in \mathcal{W}_{per}(Z_c), \end{cases} \tag{2.56}$$

with $\dot{a}_{Z_c}$ given by:

$$\dot{a}_{Z_c}(\dot{u}, \dot{v}) = \int_{Z_c} \mathrm{M}_i \nabla_z u \nabla_z v \, dz, \ \forall u \in \dot{u}, \ \forall v \in \dot{v}, \ \forall \dot{u}, \ \forall \dot{v} \in \mathcal{W}_{per}(Z_c) \tag{2.57}$$

and

$$\mathcal{W}_{per}(Z_c) = H^1_{per}(Z_c)/\mathbb{R}$$

is given by Definition A.4. Similarly, we want to clarify the right hand side of the variational formulation (2.56). By the definition of $\partial Z_c := \partial_{\text{ext}} Z \cup \Gamma^z$, we use Proposition A.1 and the z-periodicity of M_i by taking account the boundary condition on Γ^z to say that :

$$\int_{\partial Z_c} (\mathrm{M}_i \nabla_z u_{i,0} \cdot n_z)\, v \, d\sigma(z) \\ = \int_{\partial_{\text{ext}} Z} (\mathrm{M}_i \nabla_z u_{i,0} \cdot n_z)\, v \, d\sigma + \int_{\Gamma^z} (\mathrm{M}_i \nabla_z u_{i,0} \cdot n_z)\, v \, d\sigma = 0.$$

Using Theorem A.2, we obtain the existence and the uniqueness of solution $\dot{u}_{i,0}$ to the problem (2.56). In addition, we have:

$$\|\dot{u}_{i,0}\|_{\mathcal{W}_{per}(Z_c)} = 0.$$

So, $u_{i,0}$ is independent of the microscopic variable z. Thus, we deduce that:

$$u_{i,0}(t, x, y, z) = u_{i,0}(t, x, y), \ \forall u_{i,0} \in \dot{u}_{i,0}.$$

- **Step 2** We now solve the second boundary value problem (2.48) that is defined in Y_i. Its variational formulation is:

$$\begin{cases} \text{Find } \dot{u}_{i,0} \in \mathcal{W}_{per}(Y_i) \text{ such that} \\ \\ \dot{a}_{Y_i}(\dot{u}_{i,0}, \dot{v}) = \displaystyle\int_{\partial Y_i} \mathrm{M}_i \nabla_y u_{i,0} \cdot n_i \, v \, d\sigma(y) \ \forall \dot{v} \in \mathcal{W}_{per}(Y_i), \end{cases} \tag{2.58}$$

with $\dot{a}_{Y_i}$ given by:

$$\dot{a}_{Y_i}(\dot{u}, \dot{v}) = \int_{Y_i} \mathrm{M}_i \nabla_y u \nabla_y v dy, \ \forall u \in \dot{u}, \ \forall v \in \dot{v}, \ \forall \dot{u}, \ \forall \dot{v} \in \mathcal{W}_{per}(Y_i) \tag{2.59}$$

and $\mathcal{W}_{per}(Y_i)$ given by Definition A.4.

Similarly, we want to clarify first the right hand side in the variational formulation (2.58). By the definition of $\partial Y_i := (\partial_{\text{ext}} Y \cap \partial Y_i) \cup \Gamma^y$, wwe use Proposition A.1 and the y-periodicity of M_i by taking account the boundary condition on Γ^y to say that:

$$\begin{aligned}
&\int_{\partial Y_i} \mathrm{M}_i \nabla_y u_{i,0} \cdot n_i(y) v \, d\sigma(y) \\
&\qquad = \int_{\partial_{\text{ext}} Y \cap \partial Y_i} \mathrm{M}_i \nabla_y u_{i,0} \cdot n_i(y) v \, d\sigma(y) + \int_{\Gamma^y} \mathrm{M}_i \nabla_y u_{i,0} \cdot n_i(y) \, d\sigma(y) = 0.
\end{aligned}$$

Therefore, we can apply Theorem A.2 to prove the existence and uniqueness of solution $\dot{u}_{i,0}$. In addition, we have:

$$\|\dot{u}_{i,0}\|_{\mathcal{W}_{per}(Y_i)} = 0.$$

Thus, we deduce that $u_{i,0}$ is also independent of the mesoscopic variable y. Consequently, the third boundary value problem (2.49) is satisfied automatically.
Next, we solve the fourth problem (2.50) by the same process of the first step. So, we deduce that $u_{i,1}$ is independent of z. Finally, we have:

$$u_{i,0}(t, x, y, z) = u_{i,0}(t, x) \text{ and } u_{i,1}(t, x, y, z) = u_{i,1}(t, x, y).$$

Remark 2.6. *Since $u_{i,0}$ is independent of y and z then it does not oscillate "rapidly". This is why now expect $u_{i,0}$ to be the "homogenized solution". To find the homogenized equation, it is sufficient to find an equation in Ω satisfied by $u_{i,0}$ independent on y and z.*

- **Step 3** We solve the fifth problem (2.51). Taking into account the form of $u_{i,0}$ and $u_{i,1}$, system (2.51) can be rewritten as:

$$\begin{cases}
\mathcal{A}_{zz} u_{i,2} = \sum_{p,q=1}^{d} \dfrac{\partial \mathrm{m}_i^{pq}}{\partial z_p} \left(\dfrac{\partial u_{i,1}}{\partial y_q} + \dfrac{\partial u_{i,0}}{\partial x_q} \right) \text{ in } Z_c, \\
u_{i,2} \ z\text{-periodic}, \\
(\mathrm{M}_i \nabla_z u_{i,2} + \mathrm{M}_i \nabla_y u_{i,1} + \mathrm{M}_i \nabla_x u_{i,0}) \cdot n_z = 0 \text{ on } \Gamma^z,
\end{cases} \tag{2.60}$$

Its variational formulation is:

$$\begin{cases} \text{Find } \dot{u}_{i,2} \in \mathcal{W}_{per}(Z_c) \text{ such that} \\ \dot{a}_{Z_c}(\dot{u}_{i,2}, \dot{v}) = (F_2, \dot{v})_{(\mathcal{W}_{per}(Z_c))', \mathcal{W}_{per}(Z_c)} \ \forall \dot{v} \in \mathcal{W}_{per}(Z_c), \end{cases} \tag{2.61}$$

with $\dot{a}_{Z_c}$ given by (2.57) and F_2 defined by:

$$(F_2, \dot{v})_{(\mathcal{W}_{per}(Z_c))', \mathcal{W}_{per}(Z_c)} = -\sum_{p,q=1}^{d} \left(\frac{\partial u_{i,1}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q} \right) \int_{Z_c} \mathrm{m}_i^{pq}(t,y,z) \frac{\partial v}{\partial z_p} dz, \tag{2.62}$$

for all $v \in \dot{v}$ and $\dot{v} \in \mathcal{W}_{per}(Z_c)$.

Note that F_2 belongs to $(\mathcal{W}_{per}(Z_c))'$. Then, Theorem A.2 gives a unique solution $\dot{u}_{i,2} \in \mathcal{W}_{per}(Z_c)$ of the problem (2.60)-(2.62).
Thus, the linearity of terms in the right of equation (2.60) suggests to look for $\dot{u}_{i,2}$ under the following form:

$$\dot{u}_{i,2} = \dot{\theta}_i(z) \cdot (\nabla_y \dot{u}_{i,1} + \nabla_x \dot{u}_{i,0}) \ \text{ in } \mathcal{W}_{per}(Z_c), \tag{2.63}$$

with the corrector function $\dot{\theta}_i^q$ (i.e the components of the function $\dot{\theta}_i$) satisfies the δ-cell problem:

$$\begin{cases} \mathcal{A}_{zz}\dot{\theta}_i^q = \sum_{p=1}^{d} \frac{\partial \mathrm{m}_i^{pq}}{\partial z_p}(y,z) \text{ in } Z_c, \\ \dot{\theta}_i^q \ y\text{- and } z\text{-periodic}, \\ \mathrm{M}_i \nabla_z \dot{\theta}_i^q \cdot n_z = -(\mathrm{M}_i e_q) \cdot n_z \text{ on } \Gamma^z, \end{cases} \tag{2.64}$$

for e_q, $q = 1, \dots, d$, the standard canonical basis in $\mathbb{R}^d$. Moreover, we can choose a representative element θ_i^q of the class $\dot{\theta}_i^q$ which satisfy the following variational formulation:

$$\begin{cases} \text{Find } \theta_i^q \in W_\#(Z_c) \text{ such that} \\ \\ a_{Z_c}(\theta_i^q, v) = -\sum_{p=1}^{d} \int_{Z_c} \mathrm{m}_i^{pq}(t,y,z) \frac{\partial v}{\partial z_p} \, dz, \ \forall v \in W_\#(Z_c), \end{cases} \tag{2.65}$$

with $W_\#(Z_c)$ given by the expression (2.91). The condition of Theorem A.2 is imposed to guarantee the existence and uniqueness of the solution of the problem (2.64)-(2.65). Thus, by the form $\dot{u}_{i,2}$ given by the expression (2.63), the solution $u_{i,2}$ can be represented by the following ansatz:

$$u_{i,2}(t,x,y,z) = \theta_i(z) \cdot (\nabla_y u_{i,1}(t,x,y) + \nabla_x u_{i,0}(t,x)) + \tilde{u}_{i,2}(t,x,y) \text{ with } u_{i,2} \in \dot{u}_{i,2}, \tag{2.66}$$

and $\tilde{u}_{i,2}$ is a constant with respect to z (i.e $\tilde{u}_{i,2} \in \dot{0}$ in $\mathcal{W}_\#(Z_c)$).

Next, we pass to the sixth problem (2.52) by the same strategy of the first step. We obtain that $u_{i,3}$ is independent of z and we have:

$$u_{i,3}(t,x,y,z) = u_{i,3}(t,x,y).$$

- **Step 4** We now solve the seventh boundary value problem (2.53). Taking into account the form of $u_{i,3}$ and $u_{i,1}$, we can rewrite this problem as follows:

$$\begin{cases} \mathcal{A}_{zz} u_{i,4} = \sum\limits_{p,q=1}^{d} \dfrac{\partial \mathrm{m}_i^{pq}}{\partial z_p} \left(\dfrac{\partial u_{i,3}}{\partial y_q} + \dfrac{\partial u_{i,1}}{\partial x_q} \right) \text{ in } Z_c, \\ u_{i,4} \; y\text{- and } z\text{-periodic}, \\ (\mathrm{M}_i \nabla_z u_{i,4} + \mathrm{M}_i \nabla_y u_{i,3} + \mathrm{M}_i \nabla_x u_{i,1}) \cdot n_z = 0 \text{ on } \Gamma^z. \end{cases} \tag{2.67}$$

Its variational formulation is:

$$\begin{cases} \text{Find } \dot{u}_{i,4} \in \mathcal{W}_{per}(Z_c) \text{ such that} \\ \dot{a}_{Z_c}(\dot{u}_{i,4}, \dot{v}) = (F_4, \dot{v})_{(\mathcal{W}_{per}(Z_c))', \mathcal{W}_{per}(Z_c)} \; \forall \dot{v} \in \mathcal{W}_{per}(Z_c), \end{cases} \tag{2.68}$$

with $\dot{a}_{Z_c}$ given by (2.57) and F_4 defined by:

$$(F_4, \dot{v})_{(\mathcal{W}_{per}(Z_c))', \mathcal{W}_{per}(Z_c)} = -\sum_{p,q=1}^{d} \left(\frac{\partial u_{i,3}}{\partial y_q} + \frac{\partial u_{i,1}}{\partial x_q} \right) \int_{Z_c} \mathrm{m}_i^{pq}(t,y,z) \frac{\partial v}{\partial z_p} dz, \tag{2.69}$$

for all $v \in \dot{v}$ and $\dot{v} \in \mathcal{W}_{per}(Z_c)$.
The problem (2.67)-(2.69) is well-posed according to Theorem A.2 under the compatibility condition:

$$(F_4, 1)_{(\mathcal{W}_{per}(Z_c))', \mathcal{W}_{per}(Z_c)} = 0.$$

This implies that problem (2.53) has a unique periodic solution up to a constant. Thus, the linearity of terms in the right hand side of equation (2.67) suggests to look for $u_{i,4}$ under the following form:

$$u_{i,4}(t,x,y,z) = \theta_i(z)\cdot(\nabla_y u_{i,3}(t,x,y) + \nabla_x u_{i,1}(x)) + \tilde{u}_{i,4}(t,x,y) \text{ with } u_{i,4}\in \dot{u}_{i,4}, \tag{2.70}$$

where $\tilde{u}_{i,4}$ is a constant with respect to z and θ_i satisfies problem (2.64).

- **Step 5** We consider the eighth problem (2.54):

$$\begin{cases} \mathcal{A}_{yz}u_{i,2} = -\mathcal{A}_{yy}u_{i,1} - \mathcal{A}_{xy}u_{i,0} \text{ in } Z_c,\\ u_{i,2} \ z\text{-periodic},\\ (\mathrm{M}_i\nabla_z u_{i,2} + \mathrm{M}_i\nabla_y u_{i,1} + \mathrm{M}_i\nabla_x u_{i,0})\cdot n_i = 0 \text{ on } \Gamma^y,\\ \mathrm{M}_i\nabla_y u_{i,2}\cdot n_z = 0 \text{ on } \Gamma^z. \end{cases}$$

Taking into account the form of $u_{i,0}$ and $u_{i,1}$, we can rewrite the first equation as follows:

$$\mathcal{A}_{yz}u_{i,2} = \sum_{p,q=1}^{d}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_{i,1}}{\partial y_q}\right) + \sum_{p,q=1}^{d}\frac{\partial \mathrm{m}_i^{pq}}{\partial y_p}(y,z)\frac{\partial u_{i,0}}{\partial x_q}.$$

To find the explicit form of $u_{i,1}$, we will follow the following steps: First, we integrate over Z_c the above equation as follows:

$$\begin{aligned} -\sum_{p,q=1}^{d}\int_{Z_c}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_{i,2}}{\partial z_q}\right)\,dz - \sum_{p,q=1}^{d}\int_{Z_c}\frac{\partial}{\partial z_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_{i,2}}{\partial y_q}\right)\,dz\\ = \sum_{p,q=1}^{d}\int_{Z_c}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_{i,1}}{\partial y_q}\right) + \sum_{p,q=1}^{d}\int_{Z_c}\frac{\partial \mathrm{m}_i^{pq}}{\partial y_p}(y,z)\frac{\partial u_{i,0}}{\partial x_q}\,dz. \end{aligned} \tag{2.71}$$

We denote by E_i with $i = 1,\ldots,4$ the terms of the previous equation which is rewritten as follows (to respect the order):

$$E_1 + E_2 = E_3 + E_4.$$

Next, we use the divergence formula for the second term E_2 together with Proposition A.1 and the boundary condition on Γ^z to obtain:

$$\begin{aligned} E_2 &= -\int_{\partial Z_c}\mathrm{M}_i\nabla_y u_{i,2}\cdot n_z\,d\sigma(z)\\ &= -\int_{\partial_{\text{ext}}Z}\mathrm{M}_i\nabla_y u_{i,2}\cdot n_z\,d\sigma(z) - \int_{\Gamma^z}\mathrm{M}_i\nabla_y u_{i,2}\cdot n_z\,d\sigma(z) = 0. \end{aligned}$$

Now, we replace $u_{i,2}$ by its expression (2.66) in the first term E_1 to obtain the following:

$$E_1 = -\sum_{p,q=1}^{d} \int_{Z_c} \frac{\partial}{\partial y_p} \left(\mathrm{m}_i^{pq}(y,z) \left(\sum_{k=1}^{d} \frac{\partial \theta_i^k}{\partial z_q} \left(\frac{\partial u_{i,1}}{\partial y_k} + \frac{\partial u_{i,0}}{\partial x_k} \right) \right) \right) \, dz.$$

By permuting the index in the right hand side of the equation (2.71), we obtain:

$$\begin{aligned} E_3 &= \sum_{p,k=1}^{d} \int_{Z_c} \frac{\partial}{\partial y_p} \left(\mathrm{m}_i^{pk}(y,z) \frac{\partial u_{i,1}}{\partial y_k} \right), \\ E_4 &= \sum_{p,k=1}^{d} \int_{Z_c} \frac{\partial \mathrm{m}_i^{pk}}{\partial y_p}(y,z) \frac{\partial u_{i,0}}{\partial x_k} \, dz. \end{aligned}$$

Finally, we obtain an equation for the mesoscopic scale (independent of z) satisfied by $u_{i,1}$:

$$\begin{aligned} &- \sum_{p,k=1}^{d} \frac{\partial}{\partial y_p} \left(\frac{1}{|Z|} \sum_{q=1}^{d} \left[\int_{Z_c} \left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{pq} \frac{\partial \theta_i^k}{\partial z_q} \right) \, dz \right] \frac{\partial u_{i,1}}{\partial y_k} \right) \\ &\qquad = \sum_{p,k=1}^{d} \frac{\partial}{\partial y_p} \left(\frac{1}{|Z|} \sum_{q=1}^{d} \left[\int_{Z_c} \left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{pq} \frac{\partial \theta_i^k}{\partial z_q} \right) \, dz \right] \right) \frac{\partial u_{i,0}}{\partial x_k}. \end{aligned}$$

Similarly, we replace $u_{i,2}$ by its form (2.66) in the boundary condition on Γ^y then we integrate over Z_c to obtain another condition satisfied by $u_{i,1}$. Then, we obtain a mesoscopic problem defined on the unit cell portion Y_i and satisfied by $u_{i,1}$ as follows:

$$\begin{cases} \mathcal{B}_{yy} u_{i,1} = \sum\limits_{p,k=1}^{d} \dfrac{\partial \widetilde{\mathbf{m}}_i^{pk}}{\partial y_p} \dfrac{\partial u_{i,0}}{\partial x_k} \text{ in } Y_i, \\ \\ \left(\widetilde{\mathbf{M}}_i \nabla_y u_{i,1} + \widetilde{\mathbf{M}}_i \nabla_x u_{i,0} \right) \cdot n_i = 0 \text{ on } \Gamma^y, \end{cases} \tag{2.72}$$

with the operator $\mathcal{B}_{yy}$ (homogenized operator with respect to z) defined by:

$$\mathcal{B}_{yy} = -\sum_{p,k=1}^{d} \frac{\partial}{\partial y_p} \left(\widetilde{\mathbf{m}}_i^{pk}(y) \frac{\partial}{\partial y_k} \right), \tag{2.73}$$

where with the coefficients of the (homogenized with respect to z) conductivity matrices

$\widetilde{\mathbf{M}}_i = (\widetilde{\mathbf{m}}_i^{pk})_{1 \leq p,k \leq d}$ defined by:

$$\widetilde{\mathbf{m}}_i^{pk}(y) = \frac{1}{|Z|} \sum_{q=1}^{d} \int_{Z_c} \left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{pq} \frac{\partial \theta_i^k}{\partial z_q} \right) dz, \; \forall p,k = 1,\ldots,d. \tag{2.74}$$

Note that the y-periodicity of function $\widetilde{\mathbf{m}}_i^{pk}$ comes from the fact that the coefficients of conductivity matrix M_i and of the function θ_i are y-periodic.

Remark 2.7. *The operator $\mathcal{B}_{yy}$ has the same properties of the* ***homogenized*** *operator* (2.41) *for the extracellular problem. At this point, we deduce that this method is used to homogenize the problem with respect to z and then with respect to y. We remark also that allows to obtain the effective properties at δ-structural level and which become the input values in order to find the effective behavior of the cardiac tissue.*

Now, we prove the existence and uniqueness of solution of the problem (2.72) defined in Y_i. Consider the variational formulation of problem (2.72):

$$\begin{cases} \text{Find } \dot{u}_{i,1} \in \mathcal{W}_{per}(Y_i) \text{ such that} \\ \dot{b}_{Y_i}(\dot{u}_{i,1}, \dot{v}) = (F_1, \dot{v})_{(\mathcal{W}_{per}(Y_i))', \mathcal{W}_{per}(Y_i)} \; \forall \dot{v} \in \mathcal{W}_{per}(Y_i), \end{cases} \tag{2.75}$$

with $\dot{b}_Y$ given by:

$$\dot{b}_{Y_i}(\dot{u}, \dot{v}) = \int_{Y_i} \widetilde{\mathbf{M}}_i \nabla_y u \nabla_y v dy, \; \forall u \in \dot{u}, \; \forall v \in \dot{v}, \; \forall \dot{u}, \; \forall \dot{v} \in \mathcal{W}_{per}(Y_i) \tag{2.76}$$

and F_1 defined by:

$$(F_1, \dot{v})_{(\mathcal{W}_{per}(Y_i))', \mathcal{W}_{per}(Y_i)} = -\sum_{p,k=1}^{d} \frac{\partial u_{i,0}}{\partial x_k} \int_{Y_i} \widetilde{\mathbf{m}}_i^{pk}(y) \frac{\partial v}{\partial y_p} dy, \; \forall v \in \dot{v}, \; \forall \dot{v} \in \mathcal{W}_{per}(Y_i). \tag{2.77}$$

The linear form F_1 belongs to $(\mathcal{W}_{per}(Y_i))'$. Thus, there exists a unique solution $\dot{u}_{i,1} \in \mathcal{W}_{per}(Y_i)$ of problem (2.75)-(2.77).
Finally, the linearity of terms in the right of the equation (2.72) suggests to look for $\dot{u}_{i,2}$ under the following form:

$$\dot{u}_{i,1} = \dot{\chi}(y) \cdot \nabla_x \dot{u}_{i,0} \text{ in } \mathcal{W}_{per}(Y_i), \tag{2.78}$$

with each element of the corrector function $\dot{\chi}_i = \left(\dot{\chi}_i^k \right)_{k=1,\ldots,d}$ satisfies the following ε-cell problem:

$$\begin{cases} \mathcal{B}_{yy}\dot{\chi}_i^k = \sum\limits_{p=1}^{d} \dfrac{\partial \widetilde{\mathbf{m}}_i^{pk}}{\partial y_p} \text{ in } Y_i, \\ \\ \widetilde{\mathbf{M}}_i \nabla_y \dot{\chi}_i^k \cdot n_i = -\left(\widetilde{\mathbf{M}}_i e_k\right) \cdot n_i \text{ on } \Gamma^y, \end{cases} \tag{2.79}$$

for e_k, $k = 1, \ldots, d$, the standard canonical basis in $\mathbb{R}^d$. Moreover, we can choose a representative element χ_i^k of the class $\dot{\chi}_i^k$ which satisfy the following variational formulation:

$$\begin{cases} \text{Find } \chi_i^k \in W_{\#}(Y_i) \text{ such that} \\ \\ \dot{b}_{Y_i}(\chi_i^k, \dot{v}) = -\sum\limits_{p=1}^{d} \displaystyle\int_{Y_i} \widetilde{\mathbf{m}}_i^{pk}(y) \frac{\partial w}{\partial y_p} dy, \ \forall w \in W_{\#}(Y_i), \end{cases} \tag{2.80}$$

with $\dot{b}_{Y_i}$ given by (2.76). Thus, we prove the existence and uniqueness of the solution χ_i^k of the problem (2.79) using Theorem A.2.

So, by the form of $\dot{u}_{i,1}$ given by (2.78), the solution $u_{i,1}$ of the problem (2.72) can be represented by the following ansatz:

$$u_{i,1}(t,x,y) = \chi_i(y) \cdot \nabla_x u_{i,0}(t,x) + \tilde{u}_{i,1}(t,x) \text{ avec } u_{i,1} \in \dot{u}_{i,1}, \tag{2.81}$$

where $\tilde{u}_{i,1}$ is a constant with respect to y, (i.e $\tilde{u}_{i,1} \in \dot{0}$ in $\mathcal{W}_{per}(Y_i)$).

- **Last step** Our interest is the last boundary value problem (2.55). We have

$$\begin{aligned} -\mathcal{A}_{yz}u_{i,4} - \mathcal{A}_{yy}u_{i,3} - \mathcal{A}_{xz}u_{i,2} - \mathcal{A}_{xy}u_{i,1} - \mathcal{A}_{xx}u_{i,0} \\ = \sum_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_{i,4}}{\partial z_q} + \frac{\partial u_{i,3}}{\partial y_q} + \frac{\partial u_{i,1}}{\partial x_q}\right)\right) \\ + \sum_{p,q=1}^{d} \frac{\partial}{\partial z_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_{i,4}}{\partial y_q} + \frac{\partial u_{i,2}}{\partial x_q}\right)\right) \\ + \sum_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_{i,2}}{\partial z_q} + \frac{\partial u_{i,1}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q}\right)\right). \end{aligned}$$

Note that, the variational formulation of system (2.55) can be written as follows:

$$\begin{cases} \text{Find } \dot{u}_{i,5} \in \mathcal{W}_{per}(Z_c) \text{ such that} \\ \dot{a}_{Z_c}(\dot{u}_{i,5}, \dot{v}) = (F_5, \dot{v})_{(\mathcal{W}_{per}(Z_c))', \mathcal{W}_{per}(Z_c)} \ \forall \dot{v} \in \mathcal{W}_{per}(Z_c), \end{cases} \tag{2.82}$$

with $\dot{a}_{Z_c}$ given by (2.57) and F_5 defined by

$$
\begin{aligned}
&(F_5, \dot{v})_{(\mathcal{W}_{per}(Z_c))', \mathcal{W}_{per}(Z_c)} \\
&\quad = \int_{\Gamma^z} [(\mathrm{M}_i \nabla_z u_{i,5} + \mathrm{M}_i \nabla_y u_{i,4} + \mathrm{M}_i \nabla_x u_{i,2}) \cdot n_z]\, v \, d\sigma(z) \\
&\quad + \sum_{p,q=1}^{d} \int_{Z_c} \frac{\partial}{\partial y_p} \left(\mathrm{m}_i^{pq}(y,z) \left(\frac{\partial u_{i,4}}{\partial z_q} + \frac{\partial u_{i,3}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q} \right) \right) v dz \\
&\quad - \sum_{p,q=1}^{d} \int_{Z_c} \mathrm{m}_i^{pq}(y,z) \left(\frac{\partial u_{i,4}}{\partial y_q} + \frac{\partial u_{i,2}}{\partial x_q} \right) \frac{\partial v}{\partial z_p} dz \\
&\quad + \sum_{p,q=1}^{d} \int_{Z_c} \frac{\partial}{\partial x_p} \left(\mathrm{m}_i^{pq}(y,z) \left(\frac{\partial u_{i,2}}{\partial z_q} + \frac{\partial u_{i,1}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q} \right) \right) v dz, \ \ \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{per}(Z_c).
\end{aligned}
\tag{2.83}
$$

The aim is to find the homogenized equation in Ω. Firstly, we will homogenize the problem (2.55) with respect to z. Next, we homogenize the last one with respect to y using the explicit forms of previous solutions. Finally, we obtain the corresponding homogenized model.

Firstly, the problem (2.82)-(2.83) defined in Z_c is well-posed if and only if F_5 belongs to $(\mathcal{W}_{per}(Z_c))'$, i.e,

$$(F_5, 1)_{(\mathcal{W}_{per}(Z_c))', \mathcal{W}_{per}(Z_c)} = 0$$

which equivalent to:

$$
\begin{aligned}
&- \frac{1}{|Z|} \sum_{p,q=1}^{d} \int_{Z_c} \frac{\partial}{\partial y_p} \left(\mathrm{m}_i^{pq}(y,z) \left(\frac{\partial u_{i,4}}{\partial z_q} + \frac{\partial u_{i,3}}{\partial y_q} + \frac{\partial u_{i,1}}{\partial x_q} \right) \right) dz \\
&= \frac{1}{|Z|} \sum_{p,q=1}^{d} \int_{Z_c} \frac{\partial}{\partial x_p} \left(\mathrm{m}_i^{pq}(y,z) \left(\frac{\partial u_{i,2}}{\partial z_q} + \frac{\partial u_{i,1}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q} \right) \right) dz.
\end{aligned}
$$

In addition, we replace $u_{i,4}$ by its expression (2.70) into the above condition and into the boundary condition equation on Γ^y satisfied by $u_{i,4}$. Then, we obtain that $u_{i,3}$ satisfies the following problem defined in Y_i

$$
\begin{cases}
\mathcal{B}_{yy} u_{i,3} = -\mathcal{B}_{xy} u_{i,1} - \mathcal{B}_{xx} u_{i,0} \text{ in } Y_i, \\
\\
\left(\widetilde{\mathbf{M}}_i \nabla_y u_{i,3} + \widetilde{\mathbf{M}}_i \nabla_x u_{i,1} \right) \cdot n_i = - \left(\partial_t v_0 + \mathcal{I}_{ion}(v_0, w_0) - \mathcal{I}_{app} \right) \text{ on } \Gamma^y,
\end{cases}
\tag{2.84}
$$

with $\mathcal{B}_{xy} := -\nabla_x \cdot \left(\widetilde{\mathbf{M}}_i \nabla_y \right) - \nabla_y \cdot \left(\widetilde{\mathbf{M}}_i \nabla_x \right)$.

Consequently, system (2.84) have the following variational formulation:

$$\begin{cases} \text{Find } u_{i,3} \in \mathcal{W}_{per}(Y_i) \text{ such that} \\ \dot{b}_{Y_i}(u_{i,3}, \dot{w}) = (F_3, \dot{w})_{(\mathcal{W}_{per}(Y_i))', \mathcal{W}_{per}(Y_i)} \ \forall \dot{w} \in \mathcal{W}_{per}(Y_i), \end{cases} \tag{2.85}$$

with $\dot{b}_{Y_i}$ given by (2.76) and F_3 defined by:

$$\begin{aligned} &(F_3, \dot{w})_{(\mathcal{W}_{per}(Y_i))', \mathcal{W}_{per}(Y_i)} \\ &= \int_{\Gamma^y} \left(\widetilde{\mathbf{M}}_i \nabla_y u_{i,3} + \widetilde{\mathbf{M}}_i \nabla_x u_{i,1} \right) \cdot n_i w \, d\sigma(y) - \sum_{p,k=1}^{d} \int_{Y_i} \widetilde{\mathbf{m}}_i^{pk} \frac{\partial u_{i,1}}{\partial x_k} \frac{\partial w}{\partial y_p} dy \\ &+ \sum_{p,k=1}^{d} \int_{Y_i} \frac{\partial}{\partial x_p} \left(\widetilde{\mathbf{m}}_i^{pk} \left(\frac{\partial u_{i,1}}{\partial y_k} + \frac{\partial u_{i,0}}{\partial x_k} \right) \right) w dy, \end{aligned} \tag{2.86}$$

for all $w \in \dot{w}, \ \dot{w} \in \mathcal{W}_{per}(Y_i)$.

Observe that problem (2.84)-(2.86) is well-posed if and only if F_3 belongs to $(\mathcal{W}_{per} Y))'$, which means

$$(F_3, 1)_{(\mathcal{W}_{per}(Y_i))', \mathcal{W}_{per}(Y_i)} = 0$$

which gives:

$$-\sum_{p,k=1}^{d} \int_{Y_i} \frac{\partial}{\partial x_p} \left(\widetilde{\mathbf{m}}_i^{pk} \left(\frac{\partial u_{i,1}}{\partial y_k} + \frac{\partial u_{i,0}}{\partial x_k} \right) \right) dy = -\left| \Gamma^y \right| \left(\partial_t v_0 + \mathcal{I}_{ion}(v_0, w_0) - \mathcal{I}_{app} \right).$$

Next, we replace $u_{i,1}$ by its form (2.81) in the above condition. Then, we obtain:

$$\begin{aligned} -\sum_{p,k=1}^{d} \int_{Y_i} \frac{\partial}{\partial x_p} \left(\widetilde{\mathbf{m}}_i^{pk} \left(\sum_{q=1}^{d} \frac{\partial \chi_i^q}{\partial y_k}(y) \frac{\partial u_{i,0}}{\partial x_q} + \frac{\partial u_{i,0}}{\partial x_k} \right) \right) dy \\ = -\left| \Gamma^y \right| \left(\partial_t v_0 + \mathcal{I}_{ion}(v_0, w_0) - \mathcal{I}_{app} \right) \end{aligned}$$

By expanding the sum and permuting the index, we obtain

$$\begin{aligned} -\sum_{p,q=1}^{d} \int_{Y_i} \frac{\partial}{\partial x_p} \left[\left(\sum_{k=1}^{d} \widetilde{\mathbf{m}}_i^{pk} \frac{\partial \chi_i^q}{\partial y_k}(y) + \widetilde{\mathbf{m}}_i^{pq} \right) \frac{\partial u_{i,0}}{\partial x_q} \right] dy \\ = -\left| \Gamma^y \right| \left(\partial_t v_0 + \mathcal{I}_{ion}(v_0, w_0) - \mathcal{I}_{app} \right). \end{aligned}$$

Then, the function $u_{i,0}$ satisfies the following problem:

$$-\sum_{p,q=1}^{d}\left[\frac{1}{|Y|}\sum_{k=1}^{d}\int_{Y_i}\left(\widetilde{\mathbf{m}}_i^{pk}\frac{\partial \chi_i^q}{\partial y_k}(y)+\widetilde{\mathbf{m}}_i^{pq}\right)dy\right]\frac{\partial^2 u_{i,0}}{\partial x_p \partial x_q}$$
$$=-\frac{|\Gamma^y|}{|Y|}\left(\partial_t v_0+\mathcal{I}_{ion}(v_0,w_0)-\mathcal{I}_{app}\right)$$

Finally, we deduce the **homogenized** equation satisfied by $u_{i,0}$ for the intracellular problem:

$$\mathcal{B}_{xx}u_{i,0}=-\mu_m\left(\partial_t v_0+\mathcal{I}_{ion}(v_0,w_0)-\mathcal{I}_{app}\right) \text{ on } \Omega_T, \tag{2.87}$$

where $\mu_m=|\Gamma^y|\,/\,|Y|$. Here, the homogenized operator $\mathcal{B}_{xx}$ (with respect to y and z) is defined by:

$$\mathcal{B}_{xx}=-\nabla_x\cdot\left(\widetilde{\widetilde{\mathbf{M}}}_i\nabla_x\right)=-\sum_{p,q=1}^{d}\frac{\partial}{\partial x_p}\left(\widetilde{\widetilde{\mathbf{m}}}_i^{pq}\frac{\partial}{\partial x_q}\right)$$

with the coefficients of the homogenized conductivity matrix $\widetilde{\widetilde{\mathbf{M}}}_i=\left(\widetilde{\widetilde{\mathbf{m}}}_i^{pq}\right)_{1\leq p,q\leq d}$ defined by:

$$\begin{aligned}\widetilde{\widetilde{\mathbf{m}}}_i^{pq}&:=\frac{1}{|Y|}\sum_{k=1}^{d}\int_{Y_i}\left(\widetilde{\mathbf{m}}_i^{pk}\frac{\partial \chi_i^q}{\partial y_k}(y)+\widetilde{\mathbf{m}}_i^{pq}\right)dy\\&=\frac{1}{|Y|}\frac{1}{|Z|}\sum_{k,\ell=1}^{d}\int_{Y_i}\int_{Z_c}\left[\left(\mathrm{m}_i^{pk}+\mathrm{m}_i^{p\ell}\frac{\partial \theta_i^k}{\partial z_\ell}\right)\frac{\partial \chi_i^q}{\partial y_k}(y)+\left(\mathrm{m}_i^{pq}+\mathrm{m}_i^{p\ell}\frac{\partial \theta_i^q}{\partial z_\ell}\right)\right]dzdy\end{aligned} \tag{2.88}$$

with the coefficients of the conductivity matrix $\widetilde{\mathbf{M}}_i=\left(\widetilde{\mathbf{m}}_i^{pk}\right)_{1\leq p,k\leq d}$ defined by (2.74).

Remark 2.8. *The authors in [HY09] treated the initial problem with the coefficients m_j^{pq} depending only on the variable y for $j=i,e$. Using the same two-scale technique, we found three systems to solve and then obtained its homogenized model with respect to y which is well defined in Section 2.3.1. But in the intracellular problem, the coefficients m_i^{pq} depend on two variables y and z. Using a new three-scale expansion method, we obtain nine systems to solve in order to find the homogenized model (2.87) of the initial problem (2.43). Obtaining this homogenized problem is described in six steps. First, the first five steps help to find the explicit forms of the associated solutions. Second, the last step describes the two-level homogenization whose the coefficients $\widetilde{\widetilde{\mathbf{m}}}_i^{pq}$ of the homogenized conductivity matrix $\widetilde{\widetilde{\mathbf{M}}}_i$ are integrated with respect to z and then with respect to y. Finally, we obtain the homogenized model defined on Ω.*

2.4 Three-scale Unfolding Homogenization Method

In this section, we will introduce a rigorous homogenization method based on the unfolding operator for extra- and intracellular domains and on the boundary unfolding operator defined in Subsection 2.4.1. The aim is to show how to obtain the macroscopic model from the meso-microscopic bidomain model. First, the weak formulation of the meso-microscopic problem is written by another one, called "unfolded" formulation in Subsection 2.4.2 and 2.4.3, based on unfolding operators. Then, we can pass to the limit as $\varepsilon \to 0$ in the unfolded formulation using some a priori estimates and compactness argument to obtain finally the macroscopic bidomain model (see Subsection 2.4.4).

2.4.1 Unfolding operator and some basic properties

In this part, we give the definitions for the concepts of unfolding operator defined on the domain $\Omega_T := (0,T) \times \Omega$ and on the membrane $\Gamma^y_T := (0,T) \times \Gamma^y$. Further, we recall some properties and results related to these concepts used in our paper. For the reader's convenience, we recall the notion of the unfolding operator. The following results can be found in [CDZ07; CDG18].

In order to define an unfolding operator, we first introduce the following sets in $\mathbb{R}^d$ (see Figure 2.3)

- $\Xi_\varepsilon = \{k \in \mathbb{Z}^d,\ \varepsilon(k_\ell + Y) \subset \Omega\}$, where $k_\ell := (k_1\ell_1^{\text{mes}}, \dots, k_d\ell_d^{\text{mes}})$,

- $\Xi_\delta = \{k' \in \mathbb{Z}^d,\ \delta(k'_{\ell'} + Z) \subset \Omega\}$, where $k'_{\ell'} = (k'_1\ell_1^{\text{mic}}, \dots, k'_d\ell_d^{\text{mic}})$,

- $\widehat{\Omega}^\varepsilon = \text{interior}\,\{\bigcup_{\xi\in\Xi_\varepsilon} \varepsilon(\xi + \overline{Y})\}$,

- $\widehat{\Omega}^\varepsilon_j = \text{interior}\,\{\bigcup_{\xi\in\Xi_\varepsilon} \varepsilon(\xi + \overline{Y_j})\}$, $j = i, e$,

- $\widehat{\Omega}^{\varepsilon,\delta}_i = \text{interior}\,\{\bigcup_{\xi\in\Xi_\varepsilon} \varepsilon(\xi + \overline{Y_i^\delta})\}$, $\qquad \overline{Y_i^\delta} = \text{interior}\,\{\bigcup_{\zeta\in\Xi_\delta} \delta(\zeta + \overline{Z})\}$,

- $\widehat{\Gamma}_\varepsilon = \{y \in \Gamma^y : y \in \widehat{\Omega}^\varepsilon\}$,

- $\Lambda^\varepsilon = \Omega \setminus \widehat{\Omega}^\varepsilon$,

- $\widehat{\Omega}^{\varepsilon}_{T} = (0, T) \times \widehat{\Omega}^{\varepsilon}$,
- $\widehat{\Omega}^{\varepsilon,\delta}_{i,T} = (0, T) \times \widehat{\Omega}^{\varepsilon,\delta}_{i}$, $\quad \widehat{\Omega}^{\varepsilon}_{e,T} = (0, T) \times \widehat{\Omega}^{\varepsilon}_{e}$,
- $\Lambda^{\varepsilon}_{T} = (0, T) \times \Lambda^{\varepsilon}$.

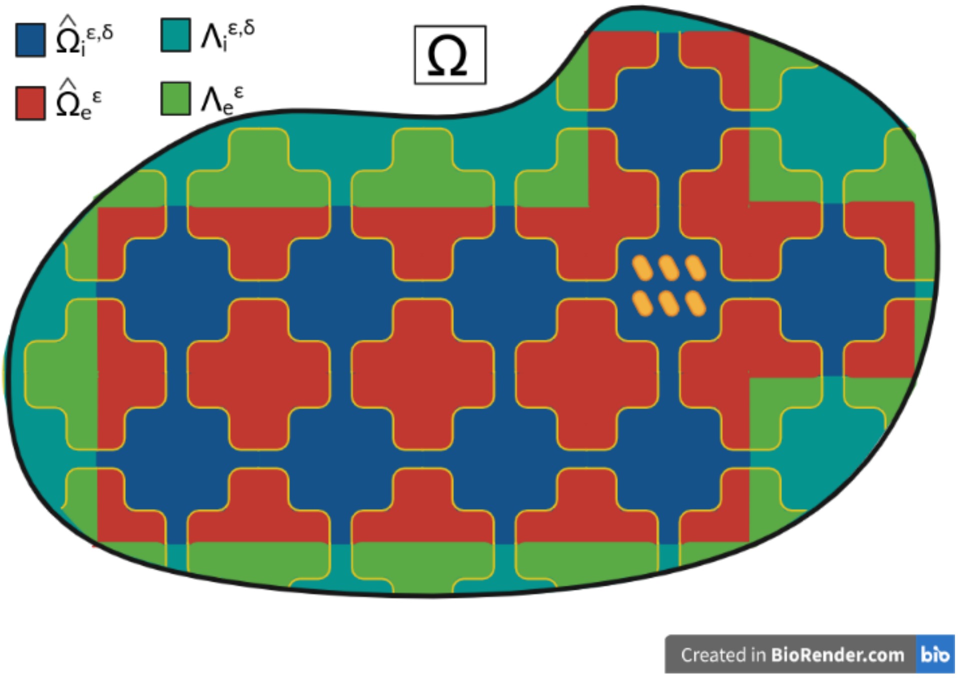

Figure 2.3 – The sets $\widehat{\Omega}^{\varepsilon,\delta}_{i}$, $\widehat{\Omega}^{\varepsilon}_{e}$, $\Lambda^{\varepsilon,\delta}_{i}$ and $\Lambda^{\varepsilon}_{e}$.

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 extra- and intracellular domains. Note that the meso-microscopic bidomain model contains a dynamical boundary system at the interface of these two regions. We need also to define the unfolding operator on the boundary Γ_ε, which has been developed in [CDZ06; Cio+12]. To do that, we suppose that Γ^y has a Lipschitz boundary.

Definition 2.2 (Domain and boundary unfolding operator)**.**

1. *For any function ϕ Lebesgue-measurable on $\Omega^\varepsilon_{i,T} := (0,T)\times\Omega^\varepsilon_i$ (the intracellular medium at mesoscale), the unfolding operator $\mathcal{T}^i_\varepsilon$ is defined as follows:*

$$\mathcal{T}^i_\varepsilon(\phi)(t,x,y) = \begin{cases} \phi\left(t, \varepsilon\left[\dfrac{x}{\varepsilon}\right]_Y + \varepsilon y\right) & \text{a.e. for } (t,x,y) \in \widehat{\Omega}^\varepsilon_T \times Y_i, \\ 0 & \text{a.e. for } (t,x,y) \in \Lambda^\varepsilon_T \times Y_i, \end{cases} \tag{2.89}$$

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:

$$\forall x \in \mathbb{R}^d,\ \mathcal{T}^i_\varepsilon(\phi)\left(t, x, \left\{\frac{x}{\varepsilon}\right\}_Y\right) = \phi(t,x).$$

2. *For any function φ Lebesgue-measurable on $\Gamma_{\varepsilon,T} := (0,T)\times\Gamma_\varepsilon$, the boundary unfolding operator $\mathcal{T}^b_\varepsilon$ is defined as follows:*

$$\mathcal{T}^b_\varepsilon(\varphi)(t,x,y) = \begin{cases} \varphi\left(t, \varepsilon\left[\dfrac{x}{\varepsilon}\right]_Y + \varepsilon y\right) & \text{a.e. for } (t,x,y) \in \widehat{\Omega}^\varepsilon_T \times \Gamma^y, \\ 0 & \text{a.e. for } (t,x,y) \in \Lambda^\varepsilon_T \times \Gamma^y. \end{cases} \tag{2.90}$$

The following results summarizes some basic properties of the unfolding operator and we refer the reader to [CDZ06; Cio+12] for more details.

Proposition 2.1 (Some properties of the unfolding operator)**.**

1. *The operators $\mathcal{T}^j_\varepsilon : L^p\left(\Omega^\varepsilon_{j,T}\right) \longrightarrow L^p(\Omega_T\times Y_j)$ and $\mathcal{T}^b_\varepsilon : L^p(\Gamma_{\varepsilon,T}) \longrightarrow L^p(\Omega_T\times\Gamma^y)$ are linear and continuous for $p\in[1,+\infty)$ and $j=i,e$.*

2. *For every $u, u' \in L^p\left(\Omega^\varepsilon_{j,T}\right)$ and $v, w \in L^p\left(\Gamma_{\varepsilon,T}\right)$ it holds that*

$$\mathcal{T}^j_\varepsilon(uu') = \mathcal{T}^j_\varepsilon(u)\mathcal{T}^j_\varepsilon(u') \text{ and } \mathcal{T}^b_\varepsilon(vw) = \mathcal{T}^b_\varepsilon(v)\mathcal{T}^b_\varepsilon(w),$$

with $p\in(1,+\infty)$ and $j=i,e$.

3. *For every $u \in L^1\left(\Omega^\varepsilon_{j,T}\right)$, the following integration formula holds for $j=i,e$*

$$\frac{1}{|Y|}\iint_{\Omega\times Y_j} \mathcal{T}^j_\varepsilon(u)(t,x,y)\,dxdy = \iint_{\widehat{\Omega}^\varepsilon_{j,T}} u(t,x)\,dx = \int_{\Omega^\varepsilon_j} u(t,x)\,dx - \int_{\Lambda^\varepsilon_j} u(t,x)\,dx.$$

4. *For every* $u \in L^p\left(\Omega^\varepsilon_{j,T}\right)$, $p \in [1,+\infty)$, *we have for* $j = i, e$

$$\left\|\mathcal{T}^j_\varepsilon(u)\right\|_{L^p(\Omega\times Y_j)} = |Y|^{1/p}\left\|u\mathbb{1}_{\widehat{\Omega}^\varepsilon_j}\right\|_{L^p\left(\Omega^\varepsilon_j\right)} \le |Y|^{1/p}\|u\|_{L^p\left(\Omega^\varepsilon_j\right)}.$$

5. *For every* $v \in L^1(\Gamma_{\varepsilon,T})$, *we have the following integration formula:*

$$\frac{1}{\varepsilon|Y|}\iint_{\Omega\times\Gamma^y}\mathcal{T}^b_\varepsilon(v)(t,x,y)\,dxd\sigma_y = \int_{\widehat{\Gamma}_\varepsilon} v(t,x)\,d\sigma_x.$$

6. *For every* $v \in L^p(\Gamma_{\varepsilon,T})$ *with* $p \in (1,+\infty)$, *one has:*

$$\left\|\mathcal{T}^b_\varepsilon(v)\right\|_{L^p(\Omega\times\Gamma^y)} = \varepsilon^{1/p}|Y|^{1/p}\|v\|_{L^p(\widehat{\Gamma}_\varepsilon)} \le \varepsilon^{1/p}|Y|^{1/p}\|v\|_{L^p(\Gamma_\varepsilon)}.$$

7. *For* $u \in L^p\left(0,T;W^{1,p}\left(\Omega^\varepsilon_j\right)\right)$, *with* $p \in [1,+\infty)$, *it holds that*

$$\nabla_y\mathcal{T}^j_\varepsilon(u)(t,x,y) = \varepsilon\mathcal{T}^j_\varepsilon(\nabla_x u)(t,x,y)$$

   with $j = i, e$.

8. *Let* $\phi^\varepsilon \in L^p(0,T;W^{1,p}(\Omega))$ *with* $p \in [1,+\infty)$ *and* $j = i, e$. *If* $\phi^\varepsilon \to \phi$ *strongly in* $L^p(0,T;W^{1,p}(\Omega))$ *as* ε *tends to zero. Then, one has*

$$\mathcal{T}^j_\varepsilon(\phi^\varepsilon) \underset{\varepsilon\to 0}{\longrightarrow} \phi \text{ strongly in } L^p(\Omega_T\times Y_j),$$
$$\mathcal{T}^b_\varepsilon(\phi^\varepsilon) \underset{\varepsilon\to 0}{\longrightarrow} \phi|_{\Gamma^y} \text{ strongly in } L^p(\Omega_T\times\Gamma^y).$$

9. *For every* $\varphi \in D(\Omega_T\times\Gamma^y)$ *and* $\psi \in W^{1,1}(0,T;L^1(\Gamma_\varepsilon))$, *the following integration by parts holds:*

$$\int_0^T\iint_{\Omega\times\Gamma^y}\mathcal{T}^b_\varepsilon(\partial_t\psi)\mathcal{T}^b_\varepsilon(\varphi)\,dxd\sigma_y dt = -\int_0^T\iint_{\Omega\times\Gamma^y}\mathcal{T}^b_\varepsilon(\psi)\mathcal{T}^b_\varepsilon(\partial_t\varphi)\,dxd\sigma_y dt.$$

Remark 2.9. *Note that the last property (which is not listed in [CDZ06; Cio+12]) is a direct consequence of the integration by parts formula and the integration formula in property (5) of Proposition 2.1.*

Remark 2.10. *If* $u_j \in L^p\left(0,T;W^{1,p}(\Omega^\varepsilon_j)\right)$ *for* $p \in (1,+\infty)$, $\mathcal{T}^b_\varepsilon(u_j)$ *is the trace on* Γ^y *of* $\mathcal{T}^j_\varepsilon(u_j)$

with $j = i, e$. In particular, by the standard trace theorem in Y_j, there is a constant C such that

$$\left\|\mathcal{T}_\varepsilon^b(u_j)\right\|^p_{L^p(\Omega_T\times\Gamma^y)} \leq C\left(\left\|\mathcal{T}_\varepsilon^j(u_j)\right\|^p_{L^p(\Omega_T\times Y_j)} + \left\|\nabla_y\mathcal{T}_\varepsilon^j(u_j)\right\|^p_{L^p(\Omega_T\times Y_j)}\right).$$

From the properties of $\mathcal{T}_\varepsilon^j(\cdot)$ in Proposition 2.1, it follows that

$$\left\|\mathcal{T}_\varepsilon^b(u_j)\right\|^p_{L^p(\Omega_T\times\Gamma^y)} \leq C\left(\|u_j\|^p_{L^p\left(\Omega^\varepsilon_{j,T}\right)} + \varepsilon^p\|\nabla u_j\|^p_{L^p\left(\Omega^\varepsilon_{j,T}\right)}\right).$$

This inequality can be found as Remark 4.2 in [Cio+12].

Remark 2.11. *Fix $j \in \{i, e\}$. Suppose that $u_j^\varepsilon \in L^2\left(0, T; H^1\left(\Omega_j^\varepsilon\right)\right)$ satisfies $\left\|u_j^\varepsilon\right\|_{L^p\left(0,T;H^1\left(\Omega_j^\varepsilon\right)\right)} \leq C$. Let*

$$g_j^\varepsilon := u_j^\varepsilon|_{\Gamma_\varepsilon} \in L^2(\Gamma_{\varepsilon,T}),$$

be the trace of u_j^ε on Γ_ε. Then, there exists $u_j \in L^2\left(0, T; H^1(\Omega)\right)$ (cf. Theorem 2.3) such that, up to a subsequence, the following hold when $\varepsilon \to 0$:

$$\mathcal{T}_\varepsilon^b(g_j^\varepsilon) \rightharpoonup u_j \text{ weakly in } L^2\left(\Omega_T \times \Gamma^y\right).$$

We can prove this remark by following Remark 2.13-(a).

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

Definition 2.3. *Let $\mathcal{O}$ be a reference cell and $p \in [1, +\infty)$. Then, we define*

$$W^{1,p}_\#(\mathcal{O}) = \{u \in W^{1,p}(\mathcal{O}) \text{ such that } u \text{ periodic with } \mathcal{M}_\mathcal{O}(u) = 0\}, \tag{2.91}$$

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 $p = 2$.*

Now we state two important results which are needed to get the convergence for the corresponding unfolding operator, see for e.g Proposition 2.8 and Theorem 3.12 in [Cio+12].

Theorem 2.3. *Let $p \in (1, +\infty)$ and $j = i, e$.*

1. *Suppose that $u_j^\varepsilon \in L^p\left(0, T; W^{1,p}\left(\Omega_j^\varepsilon\right)\right)$ satisfies*

$$\left\|u_j^\varepsilon\right\|_{L^p\left(0,T;W^{1,p}\left(\Omega_j^\varepsilon\right)\right)} \leq C.$$

   Then, there exists $u_j \in L^p\left(0, T; W^{1,p}(\Omega)\right)$ and $\widehat{u}_j \in L^p\left(0, T; L^p\left(\Omega, W_\#^{1,p}(Y_i)\right)\right)$, such that, up to a subsequence, the following hold when $\varepsilon \to 0$:

$$\begin{aligned}&\mathcal{T}_\varepsilon^j(u_j^\varepsilon) \rightharpoonup u_j \text{ weakly in } L^p\left(0, T; L^p\left(\Omega, W^{1,p}(Y_j)\right)\right),\\&\mathcal{T}_\varepsilon^j(\nabla u_j^\varepsilon) \rightharpoonup \nabla u_j + \nabla_y \widehat{u}_j \text{ weakly in } L^p(\Omega_T \times Y_j),\end{aligned}$$

   with the space $W_\#^{1,p}$ defined by (2.91).

2. *Suppose that $v_\varepsilon \in L^p(\Gamma_{\varepsilon,T})$ satisfies*

$$\varepsilon^{1/p} \left\|v_\varepsilon\right\|_{L^p(\Gamma_{\varepsilon,T})} \leq C.$$

Then, there exist $v \in L^p\left(\Omega_T \times \Gamma^y\right)$ such that, up to a subsequence, the following convergence hold when $\varepsilon \to 0$:

$$\mathcal{T}_\varepsilon^b(v_\varepsilon) \rightharpoonup v \text{ weakly in } L^p\left(\Omega_T \times \Gamma^y\right).$$

Composition of unfolding operators

In the intracellular problem, since the electrical potential $u_i^{\varepsilon,\delta}$ depends on the mesoscopic variable y and the microscopic one z so we will define a composition of two unfolding operators. In this section, we compose unfolding operators with the following convention:
Any unfolding operator acts on the two last variables of a function. Herein, we will state the result for a composition of two unfolding operators (see [MVS05]). Let Y and Z be two reference cells (see Figure 2.2). For $\varepsilon, \delta > 0$, with $\delta \leq \varepsilon$, the unfolding operators $\mathcal{T}_\varepsilon^i$ and $\mathcal{T}_\delta$ are respectively associated to Y_i and Z_c. The unfolding operator $\mathcal{T}_\delta$ is defined on $\Omega_T^\varepsilon \times Y_i$ as follows:

$$\mathcal{T}_\delta(\psi)(t, x, y, z) = \begin{cases}\psi\left(t, x, \delta\left[\dfrac{y}{\delta}\right]_Z + \delta z\right) & \text{a.e. for } (t, x, y, z) \in \widehat{\Omega}_T^\varepsilon \times Y_i \times Z_c,\\ 0 & \text{a.e. for } (t, x, y, z) \in \Lambda_T^\varepsilon \times Y_i \times Z_c,\end{cases} \tag{2.92}$$

for any function ψ Lebesgue-measurable on $(0,T)\times\Omega_i^{\varepsilon,\delta}\times Y_i$.

First, we define the composition of the unfolding operators associated to Y_i and Z_c as follows:

$$\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\phi)\right)(t,x,y,z)=\begin{cases}\phi\left(t,\varepsilon\left[\dfrac{x}{\varepsilon}\right]_Y+\varepsilon\delta\left[\dfrac{y}{\delta}\right]_Z+\varepsilon\delta z\right) & \text{a.e. for } (t,x,y,z)\in\widehat{\Omega}_T^\varepsilon\times Y_i\times Z_c,\\ 0 & \text{a.e. for } (t,x,y,z)\in\Lambda_T^\varepsilon\times Y_i\times Z_c,\end{cases}\tag{2.93}$$

for any function ϕ Lebesgue-measurable on $(0,T)\times\Omega_i^{\varepsilon,\delta}$.

We see immediately that for all $x\in\Omega$ and for any ϕ Lebesgue-measurable on $(0,T)\times\Omega_i^{\varepsilon,\delta}$, we have:

$$\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\phi)\right)\left(t,x,\left\{\frac{x}{\varepsilon}\right\}_Y,\left\{\frac{\left\{\frac{x}{\varepsilon}\right\}}{\delta}\right\}_Z\right)=\phi(t,x).$$

Next, we also have some properties for this composition of unfolding operators (see [MVS05] for more details).

Proposition 2.2. *For $p\in[1,+\infty)$, the operator $\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\cdot)\right)$ is linear and continuous from $L^p\left(\Omega_{i,T}^{\varepsilon,\delta}\right)$ to $L^p(\Omega_T\times Y_i\times Z)$. Moreover, the following formula holds:*

1. *For every $u,u'\in L^p\left(\Omega_{i,T}^{\varepsilon,\delta}\right)$, it holds that $\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(uu')\right)=\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(u)\right)\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(u')\right)$ with $p\in(1,+\infty)$.*

2. *For every $\phi\in L^1\left(\Omega_{i,T}^{\varepsilon,\delta}\right)$, the following integration formula holds*

$$\frac{1}{|Y|}\frac{1}{|Z|}\iiint_{\Omega\times Y_i\times Z_c}\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\phi)\right)(t,x,y,z)\,dxdydz=\int_{\widehat{\Omega}_i^{\varepsilon,\delta}}\phi(t,x)\,dx$$

3. *For every $u\in L^p\left(\Omega_{i,T}^{\varepsilon,\delta}\right)$, we have*

$$\left\|\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(u)\right)\right\|_{L^p(\Omega\times Y_i\times Z_c)}=|Y|^{1/p}|Z|^{1/p}\left\|u\mathbb{1}_{\widehat{\Omega}_i^{\varepsilon,\delta}}\right\|_{L^p\left(\Omega_i^{\varepsilon,\delta}\right)}\leq|Y|^{1/p}|Z|^{1/p}\|u\|_{L^p\left(\Omega_i^{\varepsilon,\delta}\right)}.$$

4. *For $u\in L^p\left(0,T;W^{1,p}\left(\Omega_i^{\varepsilon,\delta}\right)\right)$ with $p\in[1,+\infty)$, it holds that*

$$\nabla_z\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(u)\right)=\delta\mathcal{T}_\delta\left(\nabla_y\mathcal{T}_\varepsilon^i(u)\right)=\varepsilon\delta\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\nabla_x u)\right).$$

5. *Let* $\varphi^{\varepsilon,\delta} \in L^p(\Omega_T)$ *with* $p \in [1,+\infty)$. *If* $\varphi^{\varepsilon,\delta} \underset{\varepsilon\to 0}{\longrightarrow} \varphi$ *strongly in* $L^p(\Omega_T)$, *then* $\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\varphi^{\varepsilon,\delta})\right) \underset{\varepsilon\to 0}{\longrightarrow} \varphi$ *strongly in* $L^p(\Omega_T \times Y_i \times Z_c)$.

Finally, we end by stating the main convergence result which proved as Theorem 4.1 and Theorem 6.1 in [MVS05] (see also Theorem 5.17 in [Cio+12]):

Theorem 2.4. *Let* $\{u_i^{\varepsilon,\delta}\}$ *be sequence in* $L^p\left(0,T;W^{1,p}\left(\Omega_i^{\varepsilon,\delta}\right)\right)$ *for* $p \in (1,+\infty)$, *satisfies*

$$\left\|u_i^{\varepsilon,\delta}\right\|_{L^p\left(0,T;W^{1,p}\left(\Omega_i^{\varepsilon,\delta}\right)\right)} \leq C.$$

Then, there exist $u_i \in L^p(0,T;W^{1,p}(\Omega))$, $\widehat{u}_i \in L^p\left(0,T;L^p\left(\Omega,W_\#^{1,p}(Y_i)\right)\right)$ *and* $\widetilde{u}_i \in L^p\left(0,T;L^p\left(\Omega\times Y_i,W_\#^{1,p}(Z_c)\right)\right)$, *such that, up to a subsequence, the following convergences hold as* ε *goes to zero:*

1. $\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(u_i^{\varepsilon,\delta})\right) \rightharpoonup u_i$ *weakly in* $L^p(0,T;L^p(\Omega\times Y_i\times Z_c))$,
2. $\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\nabla u_i^{\varepsilon,\delta})\right) \rightharpoonup \nabla u_i + \nabla_y \widehat{u}_i + \nabla_z \widetilde{u}_i$ *weakly in* $L^p(\Omega_T\times Y_i\times Z_c)$,

with the space $W_\#^{1,p}$ *is given by the expression* (2.91).

2.4.2 Intracellular problem

Our derivation bidomain model is based on a new three-scale approach. We apply the composition of unfolding operator $\mathcal{T}_\delta(\mathcal{T}_\varepsilon^i(\cdot))$ in the intracellular problem to obtain its homogenized equation. Recall that $u_i^{\varepsilon,\delta}$ the solution of the following initial intracellular problem:

$$\begin{aligned} -\nabla\cdot(\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}) &= 0 && \text{in } \Omega_{i,T}^{\varepsilon,\delta}, \\ -\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\cdot n_i = \varepsilon\left(\partial_t v_\varepsilon + \mathcal{I}_{ion}(v_\varepsilon,w_\varepsilon) - \mathcal{I}_{app,\varepsilon}\right) &= \mathcal{I}_m && \text{on } \Gamma_{\varepsilon,T}, \\ \partial_t w_\varepsilon - H(v_\varepsilon,w_\varepsilon) &= 0 && \text{on } \Gamma_{\varepsilon,T}, \\ -\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\cdot n_z &= 0 && \text{on } \Gamma_{\delta,T}, \end{aligned} \tag{2.94}$$

where the intracellular conductivity matrices $\mathrm{M}_i^{\varepsilon,\delta} = (\mathrm{m}_i^{pq})_{1\leq p,q\leq d}$ defined by:

$$\mathrm{M}_i^{\varepsilon,\delta}(x) = \mathrm{M}_i\left(\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right),\ a.e. \text{ on } \mathbb{R}^d,$$

satisfying the elliptic and periodic conditions (2.4).

The problem (2.94) satisfies the weak formulation (2.10). Since $\mathcal{I}_{ion}(v_\varepsilon, w_\varepsilon) = \mathrm{I}_{1,ion}(v_\varepsilon) + \mathrm{I}_{2,ion}(w_\varepsilon)$, we can rewrite the formulation (2.10) as follows:

$$\begin{aligned}\iint_{\Gamma_{\varepsilon,T}} \varepsilon \partial_t v_\varepsilon \varphi_i \, d\sigma_x dt + \iint_{\Omega_{i,T}^{\varepsilon,\delta}} \mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta} \cdot \nabla \varphi_i \, dx dt \\ + \iint_{\Gamma_{\varepsilon,T}} \varepsilon \mathrm{I}_{1,ion}(v_\varepsilon) \varphi_i \, d\sigma_x dt + \iint_{\Gamma_{\varepsilon,T}} \varepsilon \mathrm{I}_{2,ion}(w_\varepsilon) \varphi_i \, d\sigma_x dt \\ = \iint_{\Gamma_{\varepsilon,T}} \varepsilon \mathcal{I}_{app,\varepsilon} \varphi_i \, d\sigma_x dt.\end{aligned} \tag{2.95}$$

We denote by E_i with $i = 1, \ldots, 5$ the terms of the previous equation which is rewritten as follows (to respect the order):

$$E_1 + E_2 + E_3 + E_4 = E_5.$$

"Unfolded" formulation of the intracellular problem

The unfolding operator is used below to unfold the oscillating functions such that they are expressed in terms of global and local variables describing positions at the upper and lower heterogeneity scales, respectively. Using the properties of the unfolding operator, we rewrite the weak formulation (2.95) in the "unfolded" form.
Using the property (5) of Proposition 2.1, then the first term is rewritten as follows:

$$\begin{aligned} E_1 &= \iint_{\widehat{\Gamma}_{\varepsilon,T}} \varepsilon \partial_t v_\varepsilon \varphi_i \, d\sigma_x dt + \iint_{\Gamma_{\varepsilon,T} \cap \Lambda_T^\varepsilon} \varepsilon \partial_t v_\varepsilon \varphi_i \, d\sigma_x dt \\ &= \frac{1}{|Y|} \iiint_{\Omega_T \times \Gamma^y} \mathcal{T}_\varepsilon^b(\partial_t v_\varepsilon) \mathcal{T}_\varepsilon^b(\varphi_i) \, dx d\sigma_y dt + \iint_{\Gamma_{\varepsilon,T} \cap \Lambda_T^\varepsilon} \varepsilon \partial_t v_\varepsilon \varphi_i \, d\sigma_x dt \\ &:= J_1 + R_1. \end{aligned}$$

Similarly, we rewrite the second term using the property (2) of Proposition 2.2:

$$\begin{aligned} E_2 = &\frac{1}{|Y|} \frac{1}{|Z|} \iiiint_{\Omega_T \times Y_i \times Z_c} \mathcal{T}_\delta(\mathcal{T}_\varepsilon^i(\mathrm{M}_i^{\varepsilon,\delta})) \mathcal{T}_\delta(\mathcal{T}_\varepsilon^i(\nabla u_i^{\varepsilon,\delta})) \mathcal{T}_\delta(\mathcal{T}_\varepsilon^i(\nabla \varphi_i)) \, dx dy dz dt \\ &+ \iint_{\Lambda_{i,T}^{\varepsilon,\delta}} \mathrm{M}_i^{\varepsilon,\delta} \nabla u_i^{\varepsilon,\delta} \cdot \nabla \varphi_i \, dx dt \\ := &J_2 + R_2 \end{aligned}$$

Due to the form of $\mathrm{I}_{k,ion}$, we use the properties (2) and (5) of Proposition 2.1 to obtain

$\mathcal{T}_\varepsilon^b\left(\mathrm{I}_{k,ion}(\cdot)\right) = \mathrm{I}_{k,ion}\left(\mathcal{T}_\varepsilon^b(\cdot)\right)$ for $k = 1, 2$ and we arrive to:

$$\begin{aligned} E_3 &= \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathcal{T}_\varepsilon^b\left(\mathrm{I}_{1,ion}(v_\varepsilon)\right)\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt + \iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon} \varepsilon \mathrm{I}_{1,ion}(v_\varepsilon)\varphi_i\,d\sigma_x dt \\ &= \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathrm{I}_{1,ion}\left(\mathcal{T}_\varepsilon^b(v_\varepsilon)\right)\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt + \iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon} \varepsilon \mathrm{I}_{1,ion}(v_\varepsilon)\varphi_i\,d\sigma_x dt \\ &:= J_3 + R_3 \end{aligned}$$

$$\begin{aligned} E_4 &= \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathcal{T}_\varepsilon^b(\mathrm{I}_{2,ion}(w_\varepsilon))\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt + \iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon} \varepsilon \mathrm{I}_{2,ion}(w_\varepsilon)\varphi_i\,d\sigma_x dt \\ &= \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathrm{I}_{2,ion}\left(\mathcal{T}_\varepsilon^b(w_\varepsilon)\right)\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt + \iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon} \varepsilon \mathrm{I}_{2,ion}(w_\varepsilon)\varphi_i\,d\sigma_x dt \\ &:= J_4 + R_4 \end{aligned}$$

$$\begin{aligned} E_5 &= \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathcal{T}_\varepsilon^b(\mathcal{I}_{app,\varepsilon})\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt + \iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon} \varepsilon \mathcal{I}_{app,\varepsilon}\varphi_i\,d\sigma_x dt \\ &:= J_5 + R_5 \end{aligned}$$

Collecting the previous estimates, we readily obtain from (2.95) the following "unfolded" formulation:

$$\begin{aligned} &\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathcal{T}_\varepsilon^b(\partial_t v_\varepsilon)\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt \\ &+ \frac{1}{|Y|}\frac{1}{|Z|}\iiiint_{\Omega_T\times Y_i\times Z_c} \mathcal{T}_\delta(\mathcal{T}_\varepsilon^i(\mathrm{M}_i^{\varepsilon,\delta}))\mathcal{T}_\delta(\mathcal{T}_\varepsilon^i(\nabla u_i^{\varepsilon,\delta}))\mathcal{T}_\delta(\mathcal{T}_\varepsilon^i(\nabla\varphi_i))\,dxdydzdt \\ &+ \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathrm{I}_{1,ion}\left(\mathcal{T}_\varepsilon^b(v_\varepsilon)\right)\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt \\ &+ \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathrm{I}_{2,ion}\left(\mathcal{T}_\varepsilon^b(w_\varepsilon)\right)\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt \\ &= \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathcal{T}_\varepsilon^b(\mathcal{I}_{app,\varepsilon})\mathcal{T}_\varepsilon^b(\varphi_i)\,dxd\sigma_y dt + R_5 - R_4 - R_3 - R_2 - R_1 \end{aligned} \tag{2.96}$$

Similarly, the "unfolded" formulation of (2.11) is given by:

$$\begin{aligned}
&\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}\mathcal{T}_\varepsilon^b(\partial_t w_\varepsilon)\mathcal{T}_\varepsilon^b(\phi)\,dx d\sigma_y dt\\
&-\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}H(\mathcal{T}_\varepsilon^b(v_\varepsilon),\mathcal{T}_\varepsilon^b(w_\varepsilon))\mathcal{T}_\varepsilon^b(\phi)\,dx d\sigma_y dt\\
&=-\varepsilon\iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon}\partial_t w_\varepsilon\phi\,d\sigma_x dt+\varepsilon\iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon}H(v_\varepsilon,w_\varepsilon)\phi\,d\sigma_x dt\\
&:=R_6+R_7
\end{aligned}\tag{2.97}$$

The intracellular homogenized model has been derived using the unfolding homogenization method at two-levels. The first level homogenization concerns the asymptotic analysis $\delta\to 0$ related to the electrical activity behavior in the micro-porous structure situated in $\Omega_i^{\varepsilon,\delta}$. At the second level homogenization, the asymptotic analysis $\varepsilon\to 0$ is related to the electrical activity behavior in the mesoscopic structure situated in $\Omega_i^{\varepsilon,\delta}$. Since $\delta\leq\varepsilon$, we pass to the limit directly in the unfolded formulation when $\varepsilon\to 0$.

Convergence of the "Unfolded" formulation

In this part, we establish the passage to the limit in (2.96)-(2.97). First, we prove that:

$$R_1,\cdots,R_7\underset{\varepsilon\to 0}{\longrightarrow}0,$$

by making use of estimates (2.13)-(2.16). So, we prove that $R_2\to 0$ when $\varepsilon\to 0$ and the proof for the other terms is similar. First, by Cauchy-Schwarz inequality, one has

$$R_2=\iint_{\Lambda_{i,T}^{\varepsilon,\delta}}\mathrm{M}_i^{\varepsilon,\delta}(x)\nabla u_i^{\varepsilon,\delta}\cdot\nabla\varphi_i\,dxdt\leq\left\|\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\right\|_{L^2(\Omega_{i,T}^{\varepsilon,\delta})}\left(\iint_{\Lambda_{i,T}^{\varepsilon,\delta}}|\nabla\varphi_i|^2\,dxdt\right)^{1/2}.$$

In addition, we observe that $\left|\Lambda_i^{\varepsilon,\delta}\right|\to 0$ and $\nabla\varphi_i\in L^2(\Omega_i^{\varepsilon,\delta})$. Consequently, by Lebesgue dominated convergence theorem, one gets

$$\iint_{\Lambda_i^{\varepsilon,\delta}}|\nabla\varphi_i|^2\to 0,\ \text{as}\ \varepsilon\to 0.$$

Finally, by using Holder inequality, the result follows by using estimate (2.14) and assumption (2.4).

Let us now elaborate the convergence results of $J_1,\cdots,J_5$. First, we choose a special form of test functions to capture the mesoscopic and microscopic informations at each structural level. Then, we consider that the test functions have the following form:

$$\varphi_i^{\varepsilon,\delta} = \Psi_i(t,x) + \varepsilon\Psi_1(t,x)\Phi_1^\varepsilon(x) + \varepsilon\delta\Psi_2(t,x)\Phi_2^\varepsilon(x)\Theta^{\varepsilon,\delta}(x), \tag{2.98}$$

with functions Φ_k^ε and $\Theta^{\varepsilon,\delta}$ defined by:

$$\Phi_k^\varepsilon(x) = \Phi_k\left(\frac{x}{\varepsilon}\right), \quad \text{for } k = 1,2 \text{ and } \Theta^{\varepsilon,\delta}(x) = \Theta\left(\frac{x}{\varepsilon\delta}\right),$$

where Ψ_i, Ψ_k, are in $D(\Omega_T)$, Φ_k in $H^1_\#(Y_i)$ for $k = 1,2$ and Θ in $H^1_\#(Z_c)$. We have:

$$\nabla\varphi_i^{\varepsilon,\delta} = \nabla_x\Psi_i + \Psi_1\nabla_y\Phi_1^\varepsilon + \Psi_2\Phi_2^\varepsilon\nabla_z\Theta^{\varepsilon,\delta} + \varepsilon\nabla_x\Psi_1\Phi_1^\varepsilon + \varepsilon\delta\nabla_x\Psi_2\Phi_2^\varepsilon\Theta^{\varepsilon,\delta} + \delta\Psi_2\nabla_y\Phi_2^\varepsilon\Theta^{\varepsilon,\delta}.$$

Due to the regularity of test functions together with property (8) of Proposition 2.1 and property (5) of Proposition 2.2, there holds:

$$\begin{aligned}
&\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\varphi_i^{\varepsilon,\delta})\right) \to \Psi_i \text{ strongly in } L^2\left(\Omega_T \times Y_i \times Z_c\right),\\
&\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\Psi_1\Phi_1^\varepsilon)\right) \to \Psi_1(t,x)\Phi_1(y) \text{ strongly in } L^2\left(\Omega_T \times Y_i \times Z_c\right),\\
&\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i(\Psi_2\Phi_2^\varepsilon\Theta^{\varepsilon,\delta})\right) \to \Psi_2(t,x)\Phi_2(y)\Theta(z) \text{ strongly in } L^2\left(\Omega_T \times Y_i \times Z_c\right),\\
&\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i\left(\nabla\varphi_i^{\varepsilon,\delta}\right)\right) \to \nabla_x\Psi_i + \Psi_1\nabla_y\Phi_1 + \Psi_2\Phi_2\nabla_z\Theta \text{ strongly in } L^2\left(\Omega_T \times Y_i \times Z_c\right),\\
&\mathcal{T}_\varepsilon^b(\varphi_i^{\varepsilon,\delta}) \to \Psi_i \text{ strongly in } L^2(\Omega_T \times \Gamma^y).
\end{aligned}$$

Next, we want to use the a priori estimates (2.13)-(2.16) to verify that the remaining terms of the equations are weakly convergent in the unfolded formulation (2.96)-(2.97). Using estimation (2.14), we deduce from Theorem 2.4 that there exist $u_i \in L^2\left(0,T;H^1(\Omega)\right)$, $\widehat{u}_i \in L^2\left(0,T;L^2\left(\Omega,H^1_\#(Y_i)\right)\right)$ and $\widetilde{u}_i \in L^2\left(0,T;L^2\left(\Omega\times Y_i,H^1_\#(Z_c)\right)\right)$ such that, up to a subsequence, the following convergences hold as ε goes to zero:

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

with the space $H^1_\#$ is given by (2.91). Thus, since $\mathcal{T}_\delta\left(\mathcal{T}_\varepsilon^i\left(\mathrm{M}_i^{\varepsilon,\delta}\right)\right) \to \mathrm{M}_i$ a.e in $\Omega\times Y_i\times Z_c$, one obtains:

$$J_2 \to \frac{1}{|Y|}\frac{1}{|Z|}\iiiint_{\Omega_T\times Y_i\times Z_c} \mathrm{M}_i\left[\nabla u_i + \nabla_y \widehat{u}_i + \nabla_z \widetilde{u}_i\right]\left[\nabla_x \Psi_i + \Psi_1\nabla_y\Phi_1 + \Psi_2\Phi_2\nabla_z\Theta\right] dxdydzdt.$$

Remark 2.12. *Since u_i is independent of y and z then it does not oscillate "rapidly". This is why now expect u_i to be the "homogenized solution". To find the homogenized equation, it is sufficient to find an equation in Ω satisfied by u_i independent on y and z.*

Furthermore, we need to establish the weak convergence of the unfolded sequences that corresponds to $v_\varepsilon, w_\varepsilon$ and $\mathcal{I}_{app,\varepsilon}$. In order to establish the convergence of $\mathcal{T}_\varepsilon^b(\partial_t v_\varepsilon)$, we use estimation (2.16) to get

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

So there exists $V \in L^2(\Omega_T\times\Gamma^y)$ such that $\mathcal{T}_\varepsilon^b(\partial_t v_\varepsilon) \rightharpoonup V$ weakly in $L^2(\Omega_T\times\Gamma^y)$. By a classical integration argument, one can show that $V = \partial_t v$. Therefore, we deduce from Theorem 2.3 that

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

Thus, we obtain

$$J_1 = \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}\mathcal{T}_\varepsilon^b(\partial_t v_\varepsilon)\mathcal{T}_\varepsilon^b(\varphi_i)\, dxd\sigma_y dt \to \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}\partial_t v\Psi_i\, dxd\sigma_y dt.$$

Remark 2.13. *(a) We observe that the limit v coincides with $u_i - u_e$. Indeed, it follows that, by using property* (5) *of Proposition 2.1,*

$$\begin{aligned}\varepsilon\iint_{\Gamma_{\varepsilon,T}} v_\varepsilon\varphi\, d\sigma_x dt &= \varepsilon\iint_{\widehat{\Gamma}_{\varepsilon,T}} v_\varepsilon\varphi\, d\sigma_x dt + \varepsilon\iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon} v_\varepsilon\varphi\, d\sigma_x dt\\ &= \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}\mathcal{T}_\varepsilon^b(v_\varepsilon)\mathcal{T}_\varepsilon^b(\varphi)\, dxd\sigma_y dt + \iint_{\Gamma_{\varepsilon,T}\cap\Lambda_T^\varepsilon}\varepsilon v_\varepsilon\varphi\, d\sigma_x dt\\ &:= J_\varepsilon + R_\varepsilon,\end{aligned}$$

for all $\varphi \in C^\infty(\Omega_T)$. We can similarly prove that $R_\varepsilon \to 0$ as in the proof for the terms $R_1,\ldots,R_7$ when ε goes to zero. Then, it sufficient to prove the convergence results of J_ε when $\varepsilon \to 0$. On the one hand, to establish the convergence of $\mathcal{T}_\varepsilon^b(v_\varepsilon)$, we use estimation (2.15) *to get*

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

So, we deduce from Theorem 2.3 that there exists $v \in L^2(\Omega_T \times \Gamma^y)$ *such that*

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

Therefore, we obtain

$$J_\varepsilon = \frac{1}{|Y|} \iiint_{\Omega_T \times \Gamma^y} \mathcal{T}_\varepsilon^b(v_\varepsilon) \mathcal{T}_\varepsilon^b(\varphi) \, dx d\sigma_y dt \to \frac{1}{|Y|} \iiint_{\Omega_T \times \Gamma^y} v\varphi \, dx d\sigma_y dt.$$

On the other hand, since $v_\varepsilon = (u_i^\varepsilon - u_e^\varepsilon)\,|_{\Gamma_{\varepsilon,T}}$ *and due to the fact that* $\mathcal{T}_\varepsilon^b(u_j^\varepsilon)$ *is the trace on* Γ^y *of* $\mathcal{T}_\varepsilon^j(u_j^\varepsilon)$ *for* $j = i, e$ (*consult Remark 2.10*)*, we can rewrite* J_ε *as follows*

$$\begin{aligned} J_\varepsilon &= \frac{1}{|Y|} \iiint_{\Omega_T \times \Gamma^y} \mathcal{T}_\varepsilon^b(v_\varepsilon) \mathcal{T}_\varepsilon^b(\varphi) \, dx d\sigma_y dt \\ &= \frac{1}{|Y|} \iiint_{\Omega_T \times \Gamma^y} \mathcal{T}_\varepsilon^b\left((u_i^\varepsilon - u_e^\varepsilon)\,|_{\Gamma_{\varepsilon,T}} \right) \mathcal{T}_\varepsilon^b(\varphi) \, dx d\sigma_y dt \\ &= \frac{1}{|Y|} \iiint_{\Omega_T \times \Gamma^y} \left(\mathcal{T}_\varepsilon^i(u_i^\varepsilon) - \mathcal{T}_\varepsilon^e(u_e^\varepsilon) \right) |_{\Omega_T \times \Gamma^y} \mathcal{T}_\varepsilon^b(\varphi) \, dx d\sigma_y dt. \end{aligned}$$

Now, by using Theorem 2.3, there exist $u_j \in L^2(0,T;H^1(\Omega))$ *such that* $\mathcal{T}_\varepsilon^j(u_j^\varepsilon) \rightharpoonup u_j$ *weakly in* $L^2(0,T;L^2(\Omega, H^1(Y_j)))$ *, for* $j = i, e$*. Thus, we deduce*

$$J_\varepsilon \to \frac{1}{|Y|} \iiint_{\Omega_T \times \Gamma^y} (u_i - u_e)\,|_{\Omega_T \times \Gamma^y} \varphi \, dx d\sigma_y dt.$$

Herein, we used the integration formula of the operator $\mathcal{T}_\varepsilon^b$ *in the first step and exploited that* v *is independent of* y *and* v *coincides with* $u_i - u_e$ *in the last step. This prove Remark 2.11 for* $v_\varepsilon = (u_i^\varepsilon - u_e^\varepsilon)|_{\Gamma_\varepsilon}$.

(b) *Moreover, since we have assumed that the initial data* $v_{0,\varepsilon}, w_{0,\varepsilon}$ *in* (2.3)*, are also uniformly bounded in the adequate norm* (*see assumption* (2.8))*. Therefore, in the same way as the previous proof (a), using again the integration formula* (3) *of the operator* $\mathcal{T}_\varepsilon^b$*, we know that there exist* $v_0', w_0' \in L^2(\Omega_T \times \Gamma^y)$ *such that, up to a subsequence,*

$$\begin{aligned} \varepsilon \iint_{\Gamma_\varepsilon} v_{0,\varepsilon} \phi \, d\sigma_x &\to \frac{|\Gamma^y|}{|Y|} \int_\Omega v_0 \phi \, dx, \\ \varepsilon \iint_{\Gamma_\varepsilon} w_{0,\varepsilon} \phi \, d\sigma_x &\to \frac{|\Gamma^y|}{|Y|} \int_\Omega w_0 \phi \, dx, \end{aligned}$$

for all $\phi \in C^\infty(\Omega)$, *where* $v_0 = \frac{1}{|\Gamma^y|}\int_{\Gamma^y} v_0' \, d\sigma_y$ *and* $w_0 = \frac{1}{|\Gamma^y|}\int_{\Gamma^y} w_0' \, d\sigma_y$.

(c) Finally, one can pass to the limit in the normalization condition defined by (2.9) *to recover a condition on the average of* u_e *(the limit of* $\mathcal{T}_\varepsilon^e(u_e^\varepsilon)$*) and we get the following equation, for all* $\varphi \in C^0([0,T])$,

$$0 = \int_0^T \left(\int_{\Omega_e^\varepsilon} u_e^\varepsilon dx\right)\varphi \, dt = \frac{1}{|Y|}\int_0^T \left(\iint_{\Omega\times Y_e} \mathcal{T}_\varepsilon^e(u_e^\varepsilon) dx dy\right)\varphi \, dt + \int_0^T \left(\int_{\Lambda_e^\varepsilon} u_e^\varepsilon dx\right)\varphi \, dt$$
$$\to 0 = \frac{|Y_e|}{|Y|}\int_0^T \left(\int_\Omega u_e dx\right)\varphi \, dt,$$

where the second term in the previous equality goes to zero as the proof for the terms $R_1, \ldots, R_7$ *when* $\varepsilon \to 0$. *This implies that we have, for almost all* $t \in [0,T]$,

$$\int_\Omega u_e(t,x) dx = 0.$$

Now, making use of estimate (2.13) with property (6) of Proposition 2.1, one has

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

Then, up to a subsequence,

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

So, by linearity of $\mathrm{I}_{2,ion}$, we have:

$$J_4 = \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathrm{I}_{2,ion}\left(\mathcal{T}_\varepsilon^b(w_\varepsilon)\right)\mathcal{T}_\varepsilon^b(\varphi_i)\, dx d\sigma_y dt \to \frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y} \mathrm{I}_{2,ion}(w)\Psi_i \, dx d\sigma_y dt.$$

Similarly, we can prove the convergence of $\mathcal{T}_\varepsilon^b(\mathcal{I}_{app,\varepsilon})$, by using assumption (2.7), to get

$$\left\|\mathcal{T}_\varepsilon^b(\mathcal{I}_{app,\varepsilon})\right\|_{L^2(\Omega_T\times\Gamma^y)} \leq \varepsilon^{1/2}|Y|^{1/2}\|\mathcal{I}_{app,\varepsilon}\|_{L^2(\Gamma_{\varepsilon,T})} \leq C.$$

So we can conclude from Theorem 2.3 that there exists $\mathcal{I}_{app,0} \in L^2(\Omega_T \times \Gamma^y)$ such that

$$\mathcal{T}_\varepsilon^b(\mathcal{I}_{app,\varepsilon}) \rightharpoonup \mathcal{I}_{app,0} \text{ weakly in } L^2(\Omega_T \times \Gamma^y).$$

Thus, we obtain the following convergence:

$$J_5 = \frac{1}{|Y|} \iiint_{\Omega_T \times \Gamma^y} \mathcal{T}_\varepsilon^b(\mathcal{I}_{app,\varepsilon}) \mathcal{T}_\varepsilon^b(\varphi_i) \, dx d\sigma_y dt \to \frac{|\Gamma^y|}{|Y|} \iint_{\Omega_T} \mathcal{I}_{app} \Psi_i \, dx dt,$$

where $\mathcal{I}_{app} = \frac{1}{|\Gamma^y|} \int_{\Gamma^y} \mathcal{I}_{app,0} \, d\sigma_y.$

It remains to obtain the limit of J_3 containing the ionic function $\mathrm{I}_{1,ion}$. By the regularity of φ_i, it sufficient to show the weak convergence of $\mathrm{I}_{1,ion}\left(\mathcal{T}_\varepsilon^b(v_\varepsilon)\right)$ to $\mathrm{I}_{1,ion}(v)$ in $L^2(\Omega_T \times \Gamma^y)$. Due to the non-linearity of $\mathrm{I}_{1,ion}$, the weak convergence will not be enough. Therefore, we need also the strong convergence of $\mathcal{T}_\varepsilon^b(v_\varepsilon)$ to v in $L^2(\Omega_T \times \Gamma^y)$ by using Kolmogorov-Riesz type compactness criterion B.1. Next, we prove by Vitali's Theorem the strong convergence of $\mathrm{I}_{1,ion}\left(\mathcal{T}_\varepsilon^b(v_\varepsilon)\right)$ to $\mathrm{I}_{1,ion}(v)$ in $L^q(\Omega_T \times \Gamma^y)$, $\forall q \in [1, r/(r-1))$ with $r \in (2, +\infty)$.
To cope with this, we derive the convergence of the nonlinear term $\mathrm{I}_{1,ion}$, in the following theorem:

Theorem 2.5. *The following convergence holds:*

$$\mathcal{T}_\varepsilon^b(v_\varepsilon) \to v \text{ strongly in } L^2(\Omega_T \times \Gamma^y), \tag{2.99}$$

as $\varepsilon \to 0$. *Moreover, we have:*

$$\mathrm{I}_{1,ion}\left(\mathcal{T}_\varepsilon^b(v_\varepsilon)\right) \to \mathrm{I}_{1,ion}(v) \text{ strongly in } L^q(\Omega_T \times \Gamma^y), \ \forall q \in [1, r/(r-1)), \tag{2.100}$$

as $\varepsilon \to 0$.

Proof. In the case of elliptic problems where no time variable is involved, this compactness result will be closely related to Theorem 5.2 in [CD12] in which the nonlinear function $\mathrm{I}_{1,ion}$ satisfies the same conditions of the nonlinear term h (see also Theorem 6.1 in [CDZ07]). In our case (when the time variable is present), we follow the same idea to the proof of Lemma 5.3 in [Ben+19]. The proof of first convergence (2.99) is based on the Kolmogorov compactness criterion, which is recalled for the convenience of the reader in Proposition B.1. It is carried out in three conditions:

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

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

It remains to show that the sequence $v_A^\varepsilon \in L^2\left(0, T; H^{1/2}(\Gamma^y)\right)$ is relatively compact in the space

$L^2\left(0,T;L^2(\Gamma^y)\right)$. Since the embedding $H^{1/2}(\Gamma^y)\hookrightarrow L^2(\Gamma^y)$ is compact, we have to show first that the sequence v_A^ε is bounded in $L^2\left(0,T;H^{1/2}(\Gamma^y)\right)\bigcap H^1\left(0,T;L^2(\Gamma^y)\right)$.

We first observe that

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

With Fubini and Cauchy-Schwarz inequality and the a priori estimate (2.13), one has

$$\begin{aligned}\|v_A^\varepsilon\|^2_{L^2(\Gamma^y_T)} &\le C\int_0^T\int_\Omega\int_{\Gamma^y}\left|\mathcal{T}^b_\varepsilon(v_\varepsilon)(t,x,y)\right|^2 d\sigma_y dxdt\\ &\le C\left\|\sqrt{\varepsilon}v_\varepsilon\right\|^2_{L^2(\Gamma_{\varepsilon,T})}\le C.\end{aligned}$$

Next, we need now to bound the $H_0^{1/2}$ semi-norm. Since $v_\varepsilon=(u_i^\varepsilon-u_e^\varepsilon)\,|\Gamma_\varepsilon$, we use again Fubini and Jensen inequality together with the trace inequality in Remark 2.10 to obtain

$$\begin{aligned}\|v_A^\varepsilon\|^2_{H_0^{1/2}(\Gamma^y)} &\le C\left[\int_\Omega\left\|\mathcal{T}^b_\varepsilon(v_\varepsilon)\right\|^2_{H_0^{1/2}(\Gamma^y)}dxdt\right]\\ &\le C\left[\left\|u_i^{\varepsilon,\delta}\right\|^2_{L^2(\Omega_i^{\varepsilon,\delta})}+\varepsilon^2\left\|\nabla u_i^{\varepsilon,\delta}\right\|^2_{L^2(\Omega_i^{\varepsilon,\delta})}+\|u_e^\varepsilon\|^2_{L^2(\Omega_e^\varepsilon)}+\varepsilon^2\|\nabla u_e^\varepsilon\|^2_{L^2(\Omega_e^\varepsilon)}\right].\end{aligned}$$

Hence, integrating over $(0,T)$ and using the a priori estimates (2.14), we have showed that the sequence v_A^ε is bounded in $L^2\left(0,T;H^{1/2}(\Gamma^y)\right)$.

By a similar argument and making use of the estimate (2.16) on $\varepsilon^{1/2}\partial_t v_\varepsilon$, we can also show that

$$\|\partial_t v_A^\varepsilon\|_{L^2(\Gamma^y_T)}\le C.$$

Finally, we deduce that the sequence v_A^ε is bounded in $L^2\left(0,T;H^{1/2}(\Gamma^y)\right)\bigcap H^1\left(0,T;L^2(\Gamma^y)\right)$ and due to the Aubin-Lions Lemma the sequence is relatively compact in $L^2\left(0,T;L^2(\Gamma^y)\right)$.

(ii) Due to the decomposition of the domain (defined in Subsection 2.4.1), 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

$$\widehat{\Omega}^\varepsilon=\bigcup_{k\in\Xi_\varepsilon}\varepsilon(k_\ell+Y),\ \text{with } k_\ell:=(k_1\ell_1^{\text{mes}},\ldots,k_d\ell_d^{\text{mes}}).$$

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

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

for a given $h \in \mathbb{R}^d$. It holds $\varepsilon(k_\ell + Y) = \bigcup_{\sigma \in \{0,1\}^d} \varepsilon(k_\ell + Y)^\sigma$.

We use the same notation as in Proposition B.1. Now, we compute

$$\begin{aligned}\left\|\tau_h \mathcal{T}_\varepsilon^b(v_\varepsilon) - \mathcal{T}_\varepsilon^b(v_\varepsilon)\right\|^2_{L^2\left((0,T)\times\Omega_\lambda^h\times\Gamma^y\right)} &= \left\|\tau_h \mathcal{T}_\varepsilon^b(v_\varepsilon) - \mathcal{T}_\varepsilon^b(v_\varepsilon)\right\|^2_{L^2\left((0,T)\times(\Omega_\lambda^h\cap\widehat{\Omega}^\varepsilon)\times\Gamma^y\right)} \\ &\quad + \left\|\tau_h \mathcal{T}_\varepsilon^b(v_\varepsilon) - \mathcal{T}_\varepsilon^b(v_\varepsilon)\right\|^2_{L^2\left((0,T)\times(\Omega_\lambda^h\setminus\widehat{\Omega}^\varepsilon)\times\Gamma^y\right)} \\ &:= E^h_{1,\varepsilon} + E^h_{2,\varepsilon}.\end{aligned}$$

Proceeding in a similar way to [Dob15; NRJ07], we first estimate $E^h_{1,\varepsilon}$ using the above decomposition of the domain as follows:

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

which by using the integration formula (6) (for $p = 2$) of Proposition 2.1 is equal to

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

For a given small $\gamma > 0$, we can choose an ε small enough such that $\left|\varepsilon\sigma + \varepsilon\left[\frac{h}{\varepsilon}\right]_Y\right| < \gamma$.

This amounts to saying that in order to estimate $E^h_{1,\varepsilon}$, it is sufficient to obtain estimates for given $\ell \in \mathbb{Z}^d$, $|\varepsilon\ell| < \gamma$ of

$$\|v_\varepsilon(t, x + \varepsilon\ell) - v_\varepsilon(t, x)\|^2_{L^2((0,T)\times\Gamma_{\varepsilon,K})}, \tag{2.101}$$

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

In order to estimate the norm (2.101), we test the variational equation (2.10) for $\tau_{\varepsilon\ell}u^\varepsilon_e - u^\varepsilon_e$ with $\varphi_i = \eta^2 \left(\tau_{\varepsilon\ell}u^{\varepsilon,\delta}_i - u^{\varepsilon,\delta}_i\right)$ and $\varphi_e = \eta^2 \left(\tau_{\varepsilon\ell}u^\varepsilon_e - u^\varepsilon_e\right)$, where $\eta \in D(K)$ is a cut-off function with $0 \le \eta \le 1$, $\eta = 1$ in K and zero outside a small neighborhood K' of K. Proceeding exactly as Lemma 5.2 in [Ben+19], Gronwall's inequality and the assumptions on the initial data give the following result:

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

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

$$E^h_{1,\varepsilon} \le C(|h| + \varepsilon). \tag{2.102}$$

Hence, we can deduce that $E^h_{1,\varepsilon} \to 0$ as $h \to 0$ uniformly in ε, as in [GNRK16]. Indeed, to prove that

$$\forall \rho > 0, \exists \mu > 0 \text{ such that } \forall \varepsilon > 0,\ \forall h,\ |h| \le \mu \Rightarrow E^h_{1,\varepsilon} < \rho, \tag{2.103}$$

one identifies two cases:

(a) For $0 < \varepsilon < \dfrac{\rho}{2C}$: take $\mu = \dfrac{\rho}{2C}$, then, from (2.102), we get that condition (2.103) holds for $|h| \le \mu$.

(b) For $\dfrac{\rho}{2C} < \varepsilon < 1$: we consider sequences ε of the form $\varepsilon_k = \dfrac{1}{k}$, $k \in \mathbb{N}$, there are finitely many elements ε_k in the interval $(\frac{\rho}{2C}, 1)$ and for each ε_k, $\exists \mu_k = \mu(\varepsilon_k)$ such that $\forall h,\ |h| \le \mu_k$, condition (2.103) holds, due to the continuity of translations in the mean of L^2-functions. Thus choosing $\mu = \min\{\frac{\rho}{2C}, \mu_k\}$, property (2.103) is proved.

It easy to check that

$$E^h_{2,\varepsilon} = \left\|\tau_h \mathcal{T}^b_\varepsilon(v_\varepsilon)\right\|^2_{L^2((0,T)\times(\Omega^h_\lambda\setminus\widehat{\Omega}^\varepsilon)\times\Gamma^y)} \le \left\|\tau_h \mathcal{T}^b_\varepsilon(v_\varepsilon)\right\|^2_{L^2((0,T)\times(\Omega_\lambda\setminus\widehat{\Omega}^\varepsilon)\times\Gamma^y)}.$$

Hence, we can deduce that $E^h_{2,\varepsilon} \to 0$ as $h \to 0$ uniformly in ε. Indeed, to prove that

$$\forall \rho > 0, \exists \mu > 0 \text{ such that } \forall \varepsilon > 0,\ \forall h,\ |h| \le \mu \Rightarrow E^h_{2,\varepsilon} < \rho, \tag{2.104}$$

one identifies two cases:

(a) For ε small enough, say $\varepsilon < \varepsilon_0$, $\Omega_\lambda \subset \widehat{\Omega}^\varepsilon$, then $E^h_{2,\varepsilon} = 0$.

(b) For $\varepsilon_0 < \varepsilon < 1$: we consider sequences ε of the form $\varepsilon_k = \dfrac{1}{k}$, $k \in \mathbb{N}$, there are finitely many elements ε_k in the interval $(\varepsilon_0, 1)$ and for each ε_k, $\exists \mu_k = \mu(\varepsilon_k)$ such that $\forall h,\ |h| \leq \mu_k$, condition (2.104) holds, due to the continuity of translations in the mean of L^2-functions. Thus choosing $\mu = \min\{\mu_k\}$, property (2.104) is proved.

This ends the proof of the condition (ii) in Proposition B.1.

(iii) The last condition follows from the a priori estimate (2.15). Indeed, we have:

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

The conditions (i)-(iii) imply that the Kolmogorov criterion for $\mathcal{T}^b_\varepsilon(v_\varepsilon)$ holds true in $L^2(\Omega_T \times \Gamma^y)$. This gives (2.99).

Next, we want to prove the second convergence. Note that from the structure of $\mathrm{I}_{1,ion}$ given by (2.6) and using property (2) of Proposition 2.1, we have

$$\mathcal{T}^b_\varepsilon\left(\mathrm{I}_{1,ion}(v_\varepsilon)\right) = \mathrm{I}_{1,ion}\left(\mathcal{T}^b_\varepsilon(v_\varepsilon)\right)$$

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

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

Further, we use estimate (2.15) with property (6) of Proposition (2.1) to obtain

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

Hence, using a classical result (see Lemma 1.3 in [Lio69]):

$$\mathrm{I}_{1,ion}\left(\mathcal{T}^b_\varepsilon(v_\varepsilon)\right) \rightharpoonup \mathrm{I}_{1,ion}(v) \text{ weakly in } L^{r/(r-1)}(\Omega_T \times \Gamma^y).$$

Moreover, we use Vitali's Theorem to obtain the strong convergence of $\mathrm{I}_{1,ion}\left(\mathcal{T}^b_\varepsilon(v_\varepsilon)\right)$ to $\mathrm{I}_{1,ion}(v)$ in $L^q(\Omega_T \times \Gamma^y)$, $\forall q \in [1, r/(r-1))$. □

Finally, collecting all the convergence results of $J_1, \ldots, J_5$ obtained above, we pass to the limit when $\varepsilon \to 0$ in the unfolded formulation (2.96) to obtain the following limiting problem:

$$\begin{aligned}
&\frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T} \partial_t v \Psi_i \, dxdt \\
&+ \frac{1}{|Y|}\frac{1}{|Z|}\iiiint_{\Omega_T\times Y_i\times Z_c} \mathrm{M}_i \left[\nabla u_i + \nabla_y \widehat{u}_i + \nabla_z \widetilde{u}_i\right]\left[\nabla_x \Psi_i + \Psi_1 \nabla_y \Phi_1 + \Psi_2 \Phi_2 \nabla_z \Theta\right] \, dxdydzdt \\
&+ \frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T} \mathrm{I}_{1,ion}(v)\Psi_i \, dxdt + \frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T} \mathrm{I}_{2,ion}\left(w\right)\Psi_i \, dxdt \\
&= \frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T} \mathcal{I}_{app}\Psi_i \, dxdt
\end{aligned} \tag{2.105}$$

Similarly, we can prove also that the limit of (2.97) as ε tends to zero, is given by:

$$\frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T} \partial_t w \phi \, dxdt - \frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T} H(v,w)\phi \, dxdt = 0. \tag{2.106}$$

2.4.3 Extracellular problem

The authors in [Ben+19] have applied and developed the two-scale unfolding method established by Cioranescu et al. [CDZ06] on a problem defined at two scales to obtain the homogenized model (see also [CDG08; Cio+12]). Whereas for the intracellular domain, we develop a three-scale approach applied to the intracellular problem to handle with the two structural levels of this domain (see Subsection 2.4.2). We recall the following initial extracellular problem:

$$\begin{aligned}
\mathcal{A}_\varepsilon u_e^\varepsilon &= 0 && \text{in } \Omega^\varepsilon_{e,T}, \\
\mathrm{M}_e^\varepsilon \nabla u_e^\varepsilon \cdot n_e = \varepsilon\left(\partial_t v_\varepsilon + \mathcal{I}_{ion}(v_\varepsilon, w_\varepsilon) - \mathcal{I}_{app,\varepsilon}\right) &= \mathcal{I}_m && \text{on } \Gamma_{\varepsilon,T},
\end{aligned} \tag{2.107}$$

with $\mathcal{A}_\varepsilon = -\nabla\cdot\left(\mathrm{M}_e^\varepsilon \nabla\right)$, where the extracellular conductivity matrices $\mathrm{M}_e^\varepsilon = (\mathrm{m}_e^{pq})_{1\le p,q\le d}$ defined by:

$$\mathrm{M}_e^\varepsilon(x) = \mathrm{M}_e\left(\frac{x}{\varepsilon}\right), \ a.e. \text{ on } \mathbb{R}^d,$$

satisfying the elliptic and periodic conditions (2.4).

In our approach, we investigate the same technique used in [Ben+19] for problem (2.107). So, we unfold the weak formulation (2.10) of the extracellular problem using only the unfolding operators $\mathcal{T}_\varepsilon^e$ and $\mathcal{T}_\varepsilon^b$ to obtain:

$$\begin{aligned}
&\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}\mathcal{T}_\varepsilon^b(\partial_t v_\varepsilon)\mathcal{T}_\varepsilon^b(\varphi_e)\,dxd\sigma_y dt\\
&+\frac{1}{|Y|}\iint_{\Omega_T\times Y_e}\mathcal{T}_\varepsilon^e\left(\mathrm{M}_e^\varepsilon\right)\mathcal{T}_\varepsilon^e\left(\nabla u_e^\varepsilon\right)\mathcal{T}_\varepsilon^e\left(\nabla\varphi_e\right)\,dxdydt\\
&+\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}\mathrm{I}_{1,ion}\left(\mathcal{T}_\varepsilon^b(v_\varepsilon)\right)\mathcal{T}_\varepsilon^b(\varphi_e)\,dxd\sigma_y dt\\
&+\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}\mathrm{I}_{2,ion}\left(\mathcal{T}_\varepsilon^b(w_\varepsilon)\right)\mathcal{T}_\varepsilon^b(\varphi_e)\,dxd\sigma_y dt\\
&=\frac{1}{|Y|}\iiint_{\Omega_T\times\Gamma^y}\mathcal{T}_\varepsilon^b(\mathcal{I}_{app,\varepsilon})\mathcal{T}_\varepsilon^b(\varphi_e)\,dxd\sigma_y dt+R_5'-R_4'-R_3'-R_2'-R_1'
\end{aligned} \tag{2.108}$$

with $R_1',\dots,R_5'$ are similarly defined as $R_1,\dots,R_5$ in the previous section.

Proceeding similarly for the extracellular problem by taking into account that the test functions have the following form:

$$\varphi_e^\varepsilon=\Psi_e(t,x)+\varepsilon\Psi_1(t,x)\Phi_1^\varepsilon(x), \tag{2.109}$$

with function Φ_1^ε defined by:

$$\Phi_1^\varepsilon(x)=\Phi_1\left(\frac{x}{\varepsilon}\right),$$

where Ψ_e,Ψ_1 are in $D(\Omega_T)$ and Φ_1 in $H^1_\#(Y_e)$. Then, we can prove that the limit of (2.108), as ε tends zero, is given by:

$$\begin{aligned}
&\frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T}\partial_t v\Psi_e\,dxdt+\frac{1}{|Y|}\iiint_{\Omega_T\times Y_e}\mathrm{M}_e\left[\nabla u_e+\nabla_y\widehat{u}_e\right]\left[\nabla\Psi_e+\Psi_1\nabla_y\Phi_1\right]\,dxdydt\\
&+\frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T}\mathrm{I}_{2,ion}\left(w\right)\Psi_e\,dxdt+\frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T}\mathrm{I}_{1,ion}(v)\Psi_e\,dxdt\\
&=\frac{|\Gamma^y|}{|Y|}\iint_{\Omega_T}\mathcal{I}_{app}\Psi_e\,dxdt.
\end{aligned} \tag{2.110}$$

2.4.4 Derivation of the macroscopic bidomain model

The convergence results of the previous section allow us to pass to the limit in the microscopic equations (2.10)-(2.11) and to obtain the homogenized model formulated in Theorem 2.2.

We first derive the macroscopic (homogenized) equation for the intracellular problem. To this end, we will find the expression of $\widehat{u}_i$ and $\widetilde{u}_i$ in terms of the homogenized solution u_i. Then, we derive the cell problem from the homogenized equation (2.105). Finally, we obtain the weak formulation of the corresponding macroscopic equation.

We first take Ψ_i equal to zero, to get:

$$\frac{1}{|Y|}\frac{1}{|Z|}\iiiint_{\Omega_T\times Y_i\times Z_c} \mathrm{M}_i\left[\nabla u_i + \nabla_y \widehat{u}_i + \nabla_z \widetilde{u}_i\right]\left[\Psi_1\nabla_y\Phi_1 + \Psi_2\Phi_2\nabla_z\Theta\right]\, dxdydzdt = 0. \tag{2.111}$$

Next, to determine the explicit form of $\widetilde{u}_i$ so we take Ψ_1 equal to zero. Since u_i and $\widehat{u}_i$ are independent of the microscopic variable z, then the formulation (2.111) corresponds to the following microscopic problem:

$$\begin{cases} -\nabla_z\cdot(\mathrm{M}_i\nabla_z\widetilde{u}_i) = \sum\limits_{p,q=1}^{d}\dfrac{\partial \mathrm{m}_i^{pq}}{\partial z_p}\left(\dfrac{\partial\widehat{u}_i}{\partial y_q}+\dfrac{\partial u_i}{\partial x_q}\right) \text{ in } Z_c,\\ (\mathrm{M}_i\nabla_z\widetilde{u}_i + \mathrm{M}_i\nabla_y\widehat{u}_i + \mathrm{M}_i\nabla_x u_i)\cdot n_z = 0 \text{ on } \Gamma^z,\\ \widetilde{u}_i\ z\text{-periodic.}\end{cases} \tag{2.112}$$

Hence, by the z-periodicity of M_i and the comptability condition, it is not difficult to establish the existence of a unique periodic solution up to an additive constant of the problem (2.112) (see for instance the work of [Bad+21a]).
Thus, the linearity of terms in the right of the equation (2.112) suggests to look for $\widetilde{u}_i$ under the following form in terms of u_i and $\widehat{u}_i$:

$$\widetilde{u}_i(t,x,y,z) = \theta_i(z)\cdot(\nabla_y\widehat{u}_i + \nabla_x u_i) + \tilde{u}_{0,i}(t,x,y), \tag{2.113}$$

where $\tilde{u}_{0,i}$ is a constant with respect to z and each element θ_i^q of θ_i satisfies the δ-cell problem:

$$\begin{cases} -\nabla_z\cdot(\mathrm{M}_i\nabla_z\theta_i^q) = \sum\limits_{p=1}^{d}\dfrac{\partial \mathrm{m}_i^{pq}}{\partial z_p}(y,z) \text{ in } Z_c,\\ \theta_i^q\ y\text{- and } z\text{-periodic,}\\ \mathrm{M}_i\nabla_z\theta_i^q\cdot n_z = -(\mathrm{M}_i e_q)\cdot n_z \text{ on } \Gamma^z,\end{cases} \tag{2.114}$$

for $q = 1,\dots,d$. Moreover, the existence and uniqueness of solution $\theta_i^q \in H^1_\#(Z_c)$ to problem (2.114) are automatically satisfied with $H^1_\#(Z_c)$ is given by (2.91).

Furthermore, we take Ψ_2 equal to zero to find the form of $\widehat{u}_i$ (note that ψ_1 is now chosen different from zero). So, we replace $\widetilde{u}_i$ by its form (2.113) on the formulation (2.111). Then, we obtain a mesoscopic problem defined on the unit cell portion Y_i and satisfied by $\widehat{u}_i$ as follows:

$$\begin{cases} -\nabla_y \cdot \left(\widetilde{\mathbf{M}}_i \nabla_y \widehat{u}_i\right) = \sum_{p,k=1}^{d} \dfrac{\partial \widetilde{\mathbf{m}}_i^{pk}}{\partial y_p} \dfrac{\partial u_i}{\partial x_k} \text{ in } Y_i, \\ \\ \left(\widetilde{\mathbf{M}}_i \nabla_y \widehat{u}_i + \widetilde{\mathbf{M}}_i \nabla_x u_i\right) \cdot n_i = 0 \text{ on } \Gamma^y, \end{cases} \tag{2.115}$$

where the coefficients of the **first-level** homogenized conductivity matrix $\widetilde{\mathbf{M}}_i = (\widetilde{\mathbf{m}}_i^{pk})_{1 \le p,k \le d}$ defined by:

$$\widetilde{\mathbf{m}}_i^{pk}(y) = \frac{1}{|Z|} \sum_{q=1}^{d} \int_{Z_c} \left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{pq} \frac{\partial \theta_i^k}{\partial z_q} \right) dz. \tag{2.116}$$

Remark 2.14. *Note that the y-periodicity of $\widetilde{\mathbf{M}}_i$ comes from the fact that the coefficients of conductivity matrix M_i and of the function θ_i are y-periodic. Following [BLP11; CD99], it is easy to verify that the homogenized conductivity tensors of the intracellular $\widetilde{\mathbf{M}}_i$ and extracellular $\widetilde{\mathbf{M}}_e$ spaces are symmetric and positive definite.*

Thus, we prove the existence and uniqueness by using same arguments from Lax-Milgram theorem (see [Bad+21a] for more details).
Hence, the linearity of terms in the right of the equation (2.115) suggests to look for $\widehat{u}_i$ under the following form in terms of u_i:

$$\widehat{u}_i(t,x,y) = \chi_i(y) \cdot \nabla_x u_i + \widehat{u}_{0,i}(t,x), \tag{2.117}$$

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

$$\begin{cases} -\nabla_y \cdot \left(\widetilde{\mathbf{M}}_i \nabla_y \chi_i^k\right) = \sum_{p=1}^{d} \dfrac{\partial \widetilde{\mathbf{m}}_i^{pk}}{\partial y_p} \text{ in } Y_i, \\ \\ \widetilde{\mathbf{M}}_i \nabla_y \chi_i^k \cdot n_i = -\left(\widetilde{\mathbf{M}}_i e_k\right) \cdot n_i \text{ on } \Gamma^y, \end{cases} \tag{2.118}$$

for $e_k, k = 1, \ldots, d$, the standard canonical basis in $\mathbb{R}^d$. Since the matrix $\widetilde{\mathbf{M}}_i$ is positive definite, so we can prove the existence and uniqueness of the solution $\chi_i^k \in H^1_\#(Y_i)$ to problem (2.118).

Finally, inserting the form (2.113)-(2.117) of $\widetilde{u}_i$ and $\widehat{u}_i$ into (2.105) and setting Ψ_1, Ψ_2 equals to zero, one obtains the weak formulation of the homogenized equation for the intracellular problem:

$$\begin{aligned}&\mu_m \iint_{\Omega_T} \partial_t v \Psi_i \, dxdt + \iint_{\Omega_T} \widetilde{\widetilde{\mathbf{M}}}_i \nabla u_i \cdot \nabla \Psi_i \, dxdt + \mu_m \iint_{\Omega_T} \mathrm{I}_{1,ion}(v) \, \Psi_i \, dxdt \\ &+ \mu_m \iint_{\Omega_T} \mathrm{I}_{2,ion}(w) \Psi_i \, dxdt = \mu_m \iint_{\Omega_T} \mathcal{I}_{app} \Psi_i \, dxdt\end{aligned} \tag{2.119}$$

with $\mu_m = |\Gamma^y| / |Y|$ and the coefficients of the **second-level** homogenized conductivity matrix $\widetilde{\widetilde{\mathbf{M}}}_i = \left(\widetilde{\widetilde{\mathbf{m}}}_i^{pq}\right)_{1 \le p,q \le d}$ defined by:

$$\begin{aligned}\widetilde{\widetilde{\mathbf{m}}}_i^{pq} &:= \frac{1}{|Y|} \sum_{k=1}^{d} \int_{Y_i} \left(\widetilde{\mathbf{m}}_i^{pk} \frac{\partial \chi_i^q}{\partial y_k}(y) + \widetilde{\mathbf{m}}_i^{pq} \right) dy \\ &= \frac{1}{|Y|} \frac{1}{|Z|} \sum_{k,\ell=1}^{d} \int_{Y_i} \int_{Z_c} \left[\left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{p\ell} \frac{\partial \theta_i^k}{\partial z_\ell} \right) \frac{\partial \chi_i^q}{\partial y_k}(y) + \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell} \frac{\partial \theta_i^q}{\partial z_\ell} \right) \right] dzdy\end{aligned} \tag{2.120}$$

with the coefficients of the conductivity matrix $\widetilde{\mathbf{M}}_i = \left(\widetilde{\mathbf{m}}_i^{pk}\right)_{1 \le p,k \le d}$ defined by (2.116).

Remark 2.15. *At this point, we deduce that this method is used to homogenize the problem with respect to z and then with respect to y. We remark also that allows to obtain the effective properties at δ-structural level and which become the input values in order to find the effective behavior of the cardiac tissue.*

Similarly, we obtain the second homogenized equation for the extracellular problem:

$$\begin{aligned}&\mu_m \iint_{\Omega_T} \partial_t v \Psi_e \, dxdt + \iint_{\Omega_T} \widetilde{\mathbf{M}}_e \nabla u_e \cdot \nabla \Psi_e \, dxdt + \mu_m \iint_{\Omega_T} \mathrm{I}_{2,ion}(w) \, \Psi_e \, dxdt \\ &+ \mu_m \iint_{\Omega_T} \mathrm{I}_{1,ion}(v) \Psi_e \, dxdt = \mu_m \iint_{\Omega_T} \mathcal{I}_{app} \Psi_e \, dxdt\end{aligned} \tag{2.121}$$

with $\mu_m = |\Gamma^y| / |Y|$ and the coefficients of the homogenized conductivity matrices $\widetilde{\mathbf{M}}_e = \left(\widetilde{\mathbf{m}}_e^{pk}\right)_{1 \le p,k \le d}$ defined by:

$$\widetilde{\mathbf{m}}_e^{pk} := \frac{1}{|Y|} \sum_{q=1}^{d} \int_{Y_e} \left(\mathrm{m}_e^{pk} + \mathrm{m}_e^{pq} \frac{\partial \chi_e^k}{\partial y_q} \right) dy. \tag{2.122}$$

each element $\chi_e^k \in H^1_\#(Y_e)$ of χ_e satisfies the following ε-cell problem:

$$\begin{cases} -\nabla_y \cdot \left(\mathbf{M}_e \nabla_y \chi_e^k\right) = \sum\limits_{p=1}^{d} \dfrac{\partial \mathbf{m}_e^{pk}}{\partial y_p} \text{ in } Y_e, \\ \\ \mathbf{M}_e \nabla_y \chi_e^k \cdot n_e = -\left(\mathbf{M}_e e_k\right) \cdot n_e \text{ on } \Gamma^y, \end{cases} \tag{2.123}$$

for $e_k, k = 1, \ldots, d$, the standard canonical basis in $\mathbb{R}^d$.

Remark 2.16. *The authors in [Ben+19] treated the initial problem with the coefficients m_j^{pq} depending only on the variable y for $j = i, e$. Comparing to [Ben+19], in our work the microscopic conductivity matrix M_i of the intracellular space depends on two variables y and z. Using a three-scale unfolding method, we derive a new approach of the homogenized model (2.17) from the microscopic problem (2.1). Our homogenized problem is described in three steps. First, we unfold the weak formulation of the initial problem and prove the convergence results of the corresponding terms using the properties of the unfolding operators. Next, we pass to the limit in the unfolded formulation and we find the explicit forms of the associated solutions. Finally, the last step describes the two-level homogenization whose the homogenized (macroscopic) conductivity matrix $\widetilde{\widetilde{\mathbf{M}}}_i$ of the intracellular space are integrated with respect to z and then with respect to y.*

3

Homogenization Method Applied To Microscopic Tridomain Model

The structure of cardiac tissue (myocarde) studied in this chapter is characterized at two different scales (see Figure 3.1). At microscopic scale, the cardiac tissue consists of two intracellular media which contains the contents of the cardiomyocytes (the cytoplasm) that are connected by gap junctions and the other is called extracellular and consists of the fluid outside the cardiomyocytes cells. Each intracellular medium and the extracellular one are separated by a cellular membrane (the sarcolemma). While at the macroscopic scale, this domain is well considered as a single domain (homogeneous).

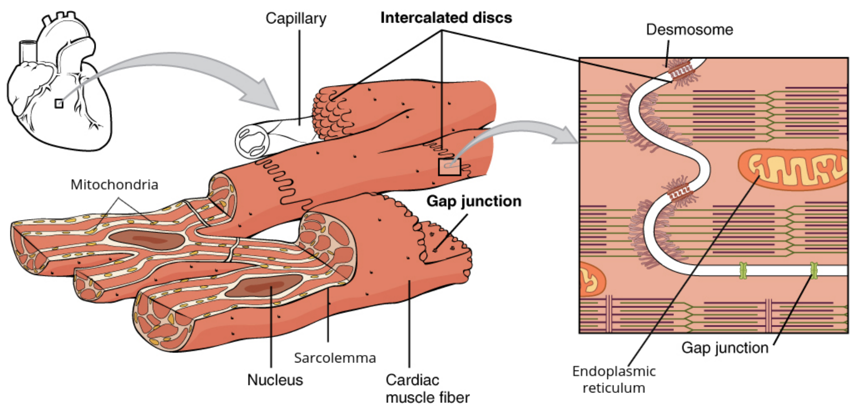

Figure 3.1 – Cardiac muscle at microscopic level.
https://en.wikipedia.org/wiki/Cardiac_muscle#/media/File:1020_Cardiac_Muscle.jpg

It should be noted that there is a difference between the chemical composition of the cytoplasm and that of the extracellular medium. This difference plays a very important role in cardiac activity. On the one hand, the sarcolemma allows the penetration of inorganic ions (sodium, potassium, calcium,...) and proteins, some of which play a passive role and others play an active role powered by cellular metabolism. In particular, the concentration of anions (negative ions) in cardiomyocytes is higher than in the external environment. This difference of concentrations creates a transmembrane potential, which is the difference in potential at the sarcolemma between each intracellular medium and the extracellular one. On the other hand, gap junctions allows the movement of not only inorganic ions but also organic ions such as sugars, amino acids and nucleotides between two adjacent cells. It provide the pathways for intracellular current flow, enabling coordinated action potential propagation. So, the difference of chemical through the gap junction creates a gap potential, which is the difference in potential between these two intracellular media. This model that describes the electrical activity of the heart, is called by "tridomain model". 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 through a dynamic boundary equation at each membrane (the sarcolemma). These equations depend on scaling parameter ε whose is the ratio of the microscopic scale from the macroscopic one. The tridomain model was proposed three years ago [Tve+17; Jæg+19].

The goal of the present chapter is to investigate existence and uniqueness of solutions of the triidomain equations, commonly used for modeling the electrical activity of the heart at a cellular level. Furthermore, we will derive, using a formal and unfolding homogenization method, the macroscopic (homogenized) tridomain model of the cardiac tissue from the microscopic tridomain problem.

We mention some different homogenization methods that are applied on the microscopic bidomain model where the gap junction is ignored. First, M. Pennachio and al. [PSF05] used the tools of the Γ-convergence method to obtain a rigorous mathematical form of its homogenized model. Furthermore, C. Henriquez and W. Ying applied the two-scale asymptoptic method to formally obtain the macroscopic model which presented in [HY09]. In [CI18; GK19], the authors used the theory of two-scale convergence method to derive the homogenized bidomain model. Moreover, the authors in [Ben+19] proved the existence and uniqueness of solution of the microscopic bidomain model by using the Faedo-Galerkin method and they applied the unfolding homogenization method at two scales. Recently, we are developed the 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 [Bad+21a] is a formal and intuitive method based on a new three-scale asymptotic expansion method applied to our meso- and microscopic model. The second one [Bad+21b] 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 formal method.

The main of contribution of the present chapter: The cardiac tissue structure studied at micro-macro scales. We start by proving the well-posedness of the microscopic tridomain problem by using Faedo-Galerkin method and L^2-compactness argument on the membrane surface. Further, we will derive the homogenized tridomain model of cardiac electro-physiology from the microscopic one using two different methods. We will apply first a formal approach on the microscopic tridomain model to obtain its homogenized model based on asymptotic expansion method. Next, we will derive, using unfolding method, the macroscopic tridomain model from the microscopic one. The latter method not only makes it possible to develop the homogenized equation but also to prove the convergence and to rigorously justify the mathematical writing of the preceding formal method. The homogenization method proposed to investigate the effective properties of the cardiac tissue at each structural level, namely, micro-macro scales. Moreover, to treat the tridomain problem in this work, the multi-scale technique is needed to be established in time domain directly.

This chapter is organized as follows: In Section 3.1, we give a precise description of the geometry of cardiac tissue and introduce the microscopic tridomain model in the non-dimensional form featured by scaling parameter ε characterizing the microscopic scale. Furthermore, some assumptions used for homogenization and the existence of a unique weak solution for the microscopic problem are stated and a priori estimates for the microscopic solutions are derived. Section 3.2 contains the main result obtained by the previous homogenization methods. In Section 3.4, we apply three-scale asymptotic homogenization procedure for extracellular and intracellular problems. Section 3.5 is devoted to unfolding homogenization procedure. In Section 3.5.1, we recall the notion of the unfolding operator and the convergence results used for unfolding homogenization. The unfolding method applied in the microscopic tridomain problem is explained in Subsection 3.5.2. Finally, in Subsection 3.5.3, the macroscopic tridomain model is recuperated from the limit equations obtained in Subsection 3.5.2 and the cell problems are decoupled.

3.1 Geometry. Microscopic Tridomain Model

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

3.1.1 Two-scale geometry of cardiac tissue with gap junction connections

We refer the reader to Subsection 1.3.2 where the concept of micro-structure and gap junction connections has been introduced, also see Figure 3.2.

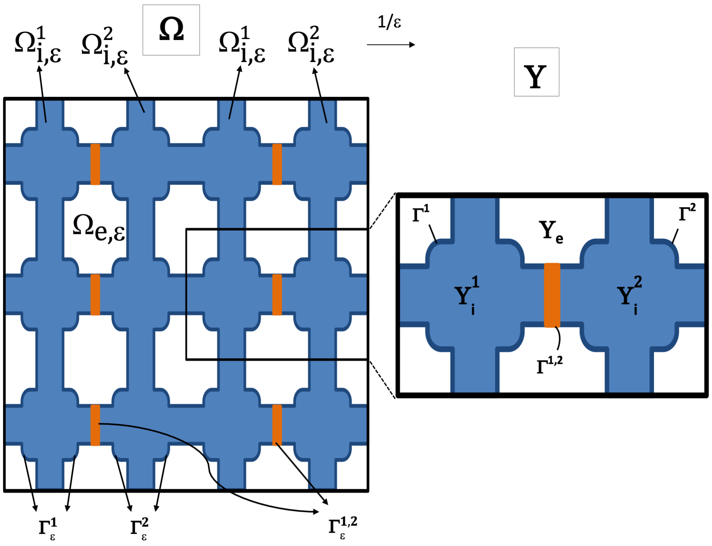

Figure 3.2 – (Left) Periodic heterogeneous domain Ω. (Right) Unit cell Y at ε-structural level.

3.1.2 Microscopic Tridomain Model

Before applying homogenization method, we introduce the basic equations of the microscopic tridomain model given in Subsection 1.4.2 without using micro-scaling parameter denoted by ε. In the next section, a non-dimensionalization analysis, based on this scaling parameter, turns out to be an essential ingredient of the asymptotic analysis. In the non-dimensionalization procedure, ε will appear also in each boundary condition due to the scaling of the involved quantities (see [HY09; CFPS12] for the bidomain case).

3.1.3 Non-dimensionalization procedure

As a natural assumption for homogenization, we want to formulate the tridomain equations (cf. Subsection 1.4.2) in dimensionless form with the hope to get more insight in the meaning of the parameter ε. We define the dimensionless parameter ε as the ratio between the microscopic length ℓ^{mic} and the macroscopic length L, i.e.

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

Using all fundamental material constants, several additional time and length constants can be formulated. For convenience, the macroscopic length is defined as $L = \sqrt{R_m \lambda \ell^{mic}}$, the membrane time constant τ_m is given by:

$$\tau_m = R_m C_m,$$

where R_m is the resistance of the passive membrane and λ is a normalization of the conductivity matrix M_j for $j = i, e$.
After that, we can convert the microscopic tridomain problem into a non-dimensional form by scaling space and time with the constants, such as,

$$x = L\widehat{x} \text{ and } t = \tau_m \widehat{t}.$$

We take $\widehat{x}$ to be the variable at the macroscale (slow variable), $y := \dfrac{\widehat{x}}{\varepsilon}$ to be the microscopic space variable (fast variable) in the unit cell Y. We also scale the electric potentials for $k = 1, 2$:

$$\begin{aligned} u_i^k = \delta v \ \widehat{u}_i^k, \ u_e = \delta v \ \widehat{u}_e, \\ \text{and } w^k = \delta w \ \widehat{w}^k \end{aligned}$$

where δv, δw are respectively the convenient units to measure the electric potentials and the gating variable. Furthermore, we normalize the conductivities matrices as follows

$$\widehat{\mathrm{M}}_j = \frac{1}{\lambda} \mathrm{M}_j, \text{ for } j = i, e,$$

and we nondimensionalize the ionic functions $\mathcal{I}_{ion}$, H, the applied current $\mathcal{I}_{app}^k$, $k = 1, 2$, and the gap current $\mathcal{I}_{gap}$ by using the following scales:

$$\begin{aligned} &\widehat{\mathcal{I}}_{ion}\left(\widehat{v}^k, \widehat{w}^k\right) = \frac{R_m}{\delta v} \mathcal{I}_{ion}\left(v^k, w^k\right), \quad \widehat{H}\left(\widehat{v}^k, \widehat{w}^k\right) = \frac{\tau_m}{\delta w} H\left(v^k, w^k\right), \\ &\widehat{\mathcal{I}}_{app}^k = \frac{R_m}{\delta v} \mathcal{I}_{app}^k, \text{ and } \widehat{\mathcal{I}}_{gap}\left(\widehat{s}\right) = \frac{R_m C_m}{\delta v C_{1,2}} \mathcal{I}_{gap}\left(s\right), \end{aligned}$$

where $\widehat{v}^k = \widehat{u}_i^k - \widehat{u}_e$ for $k = 1, 2$ and $\widehat{s} = \widehat{u}_i^1 - \widehat{u}_i^2$.

Remark 3.1. *Recalling that the dimensionless parameter ε, given by $\varepsilon := \sqrt{\dfrac{\ell^{mic}}{R_m\lambda}}$, is the ratio between the microscopic cell length ℓ^{mic} and the macroscopic length L, i.e. $\varepsilon = \ell^{mic}/L$ and solving for ε, we obtain $\varepsilon = \dfrac{L}{R_m\lambda}$.*

Remark 3.2. *Using all scaling parameters, we obtain the dimensionless of gap boundary condition (1.14) as follows*

$$\varepsilon\frac{C_{1,2}}{C_m}\left(\partial_{\hat{t}}\widehat{s}+\widehat{\mathcal{I}}_{gap}\left(\widehat{s}\right)\right)=\widehat{\mathcal{I}}_{1,2}\ \text{ on }\ \Gamma^{1,2}_{\varepsilon,T}.$$

As previously stated, we can consider $C_{1,2} = C_m/2$ so we rewrite the above equation as follows

$$\frac{\varepsilon}{2}\left(\partial_{\hat{t}}\widehat{s}+\widehat{\mathcal{I}}_{gap}\left(\widehat{s}\right)\right)=\widehat{\mathcal{I}}_{1,2}\ \text{ on }\ \Gamma^{1,2}_{\varepsilon,T}.$$

Cardiac tissue exhibits a number of significant inhomogeneities in particular those related to cell-to-cell communications. Rescaling the equations (1.10)-(1.14) in the intracellular and extracellular media and omitting the superscript $\widehat{\cdot}$ of the dimensionless variables, we obtain the following non-dimensional form:

$$-\nabla\cdot\left(\mathrm{M}_i^\varepsilon\nabla u_{i,\varepsilon}^k\right)=0 \qquad \text{in } \Omega^k_{i,\varepsilon,T}:=(0,T)\times\Omega^k_{i,\varepsilon}, \tag{3.1a}$$

$$-\nabla\cdot\left(\mathrm{M}_e^\varepsilon\nabla u_{e,\varepsilon}\right)=0 \qquad \text{in } \Omega_{e,\varepsilon,T}:=(0,T)\times\Omega_{e,\varepsilon}, \tag{3.1b}$$

$$u_{i,\varepsilon}^k-u_{e,\varepsilon}=v_\varepsilon^k \qquad \text{on } \Gamma^k_{\varepsilon,T}:=(0,T)\times\Gamma^k_{\varepsilon}, \tag{3.1c}$$

$$-\mathrm{M}_i^\varepsilon\nabla u_{i,\varepsilon}^k\cdot n_i^k=\mathrm{M}_e^\varepsilon\nabla u_{e,\varepsilon}\cdot n_e=\mathcal{I}_m^k \qquad \text{on } \Gamma^k_{\varepsilon,T}, \tag{3.1d}$$

$$\varepsilon\left(\partial_t v_\varepsilon^k+\mathcal{I}_{ion}\left(v_\varepsilon^k,w_\varepsilon^k\right)-\mathcal{I}^k_{app,\varepsilon}\right)=\mathcal{I}_m^k \qquad \text{on } \Gamma^k_{\varepsilon,T}, \tag{3.1e}$$

$$\partial_t w_\varepsilon^k-H\left(v_\varepsilon^k,w_\varepsilon^k\right)=0 \qquad \text{on } \Gamma^k_{\varepsilon,T}, \tag{3.1f}$$

$$u_{i,\varepsilon}^1-u_{i,\varepsilon}^2=s_\varepsilon \qquad \text{on } \Gamma^{1,2}_{\varepsilon,T}:=(0,T)\times\Gamma^{1,2}_{\varepsilon}, \tag{3.1g}$$

$$-\mathrm{M}_i^\varepsilon\nabla u_{i,\varepsilon}^1\cdot n_i^1=\mathrm{M}_i^\varepsilon\nabla u_{i,\varepsilon}^2\cdot n_i^2=\mathcal{I}_{1,2} \qquad \text{on } \Gamma^{1,2}_{\varepsilon,T}, \tag{3.1h}$$

$$\frac{\varepsilon}{2}\left(\partial_t s_\varepsilon+\mathcal{I}_{gap}\left(s_\varepsilon\right)\right)=\mathcal{I}_{1,2} \qquad \text{on } \Gamma^{1,2}_{\varepsilon,T}, \tag{3.1i}$$

with $k = 1, 2$ and each equation corresponds to the following sense: (3.1a) Intra quasi-stationary conduction, (3.1b) Extra quasi-stationary conduction, (3.1c) Transmembrane potential, (3.1d) Continuity equation at cell membrane, (3.1e) Reaction condition at the corresponding cell membrane, (3.1f) Dynamic coupling, (3.1g) Gap junction potential, (3.1h) Continuity equation at gap junction, (3.1e) Reaction condition at gap junction.

Observe that the tridomain equations (3.1a)-(3.1b) are invariant with respect to the above scaling. We define now the rescaled electrical potential as follows:

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

Analogously, we obtain the rescaled transmembrane potential v_ε^k, the rescaled gap junction potential s_ε and the corresponding gating variable w_ε^k for $k = 1, 2$. Furthermore, the conductivity tensors are considered dependent both on the slow and fast variables, i.e. for $j = i, e$, we have

$$\mathrm{M}_j^\varepsilon(x) := \mathrm{M}_j\left(x, \frac{x}{\varepsilon}\right), \tag{3.2}$$

satisfying the elliptic and periodicity conditions defined by (3.4). We complete system (3.1) with no-flux boundary conditions on $\partial_{\text{ext}}\Omega$:

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

where $k = 1, 2$ and $\mathbf{n}$ is the outward unit 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:

$$\begin{aligned} &v_\varepsilon^k(0,x) = v_{0,\varepsilon}^k(x),\ w_\varepsilon^k(0,x) = w_{0,\varepsilon}^k(x) && \text{a.e. on } \Gamma_{\varepsilon,T}^k, \\ &\text{and } s_\varepsilon(0,x) = s_{0,\varepsilon}(x) && \text{a.e. on } \Gamma_{\varepsilon,T}^{1,2}, \end{aligned} \tag{3.3}$$

with $k = 1, 2$.

3.1.4 Assumptions on the Data

Keeping in mind the two-scale geometry of cardiac tissue (cf Subsection 1.3.2), we list some assumptions on the conductivity matrices, the ionic functions, the source term and the initial data:

Assumptions on the conductivity matrices. The rescaled conductivity tensors $\mathrm{M}_j^\varepsilon(x) := \mathrm{M}_j\left(x, x/\varepsilon\right)$ satisfying the following elliptic and periodicity conditions: there exist constants $\alpha, \beta \in \mathbb{R}$, such that $0 < \alpha < \beta$ and for all $\lambda \in \mathbb{R}^d$:

$$\mathrm{M}_j\lambda \cdot \lambda \geq \alpha \left|\lambda\right|^2, \tag{3.4a}$$

$$\left|\mathrm{M}_j\lambda\right| \leq \beta \left|\lambda\right|, \tag{3.4b}$$

$$\mathrm{M}_j \ \mathbf{y}\text{-periodic}, \text{ for } j = i, e. \tag{3.4c}$$

Remark 3.3. *Finally, we assume that each* M_j *is symmetric:* $\mathrm{M}_j^T = \mathrm{M}_j$.

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 $\mathrm{I}^k_{b,ion}\left(w^k\right)$, 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:

$$\frac{1}{\alpha_1} |v|^{r-1} \leq |\mathrm{I}_{a,ion}(v)| \leq \alpha_1 \left(|v|^{r-1} + 1\right), \ |\mathrm{I}_{b,ion}(w)| \leq \alpha_2(|w| + 1), \tag{3.5a}$$

$$|H(v, w)| \leq \alpha_3(|v| + |w| + 1), \text{ and } \mathrm{I}_{b,ion}(w)\, v - \alpha_4 H(v, w) w \geq \alpha_5 |w|^2, \tag{3.5b}$$

$$\tilde{\mathrm{I}}_{a,ion} : v \mapsto \mathrm{I}_{a,ion}(v) + \beta_1 v + \beta_2 \text{ is strictly increasing with } \lim_{v \to 0} \tilde{\mathrm{I}}_{a,ion}(v)/v = 0, \tag{3.5c}$$

$$\forall v, v' \in \mathbb{R}, \ \left(\tilde{\mathrm{I}}_{a,ion}(v) - \tilde{\mathrm{I}}_{a,ion}(v')\right)(v - v') \geq \frac{1}{C}(1 + |v| + |v'|)^{r-2} |v - v'|^2, \tag{3.5d}$$

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

Remark 3.4. *One can easily show that* $\mathrm{I}_{a,ion}(0) = -\beta_2$, $\mathrm{I}'_{a,ion}(0) = -\beta_1$ *and* $\mathrm{I}_{a,ion}(v) \geq -\beta_1$ *for all* $v \in \mathbb{R}$.

Remark 3.5. *Physiological and phenomenological ionic models are available in Subsection 1.4.3. Here, we take the FitzHugh-Nagumo model [Fit61; NAY62] that satisfies assumptions* (3.5) *which reads as*

$$H(v, w) = a_1 v - b_1 w, \tag{3.6a}$$

$$\mathcal{I}_{ion}(v, w) = [\rho v(1 - v)(v - \theta)] - \rho w := \mathrm{I}_{a,ion}(v) + \mathrm{I}_{b,ion}(w) \tag{3.6b}$$

where a_1, b_1, ρ, θ *are given parameters with* $a_1, b_1 > 0,\ \rho < 0$ *and* $\theta \in (0, 1)$. *According to this model, the functions* $\mathcal{I}_{ion}$ *and* H *are continuous and the non-linearity* $\mathrm{I}_{a,ion}$ *is of cubic growth at infinity then the most appropriate value is* $r = 4$. *Using Young's inequality, we have*

$$|v|^2 \leq \frac{2|v|^3}{3} + \frac{1}{3}, \quad |v| \leq \frac{|v|^3}{3} + \frac{2}{3}, \quad |v| \leq \frac{|v|^2}{2} + \frac{1}{2} \tag{3.7}$$

and then assumption (3.5a) *holds for* $r = 4$:

$$\begin{aligned}
&|\mathrm{I}_{a,ion}(v)| = |\rho v(1-v)(v-\theta)| \le \left(\frac{2}{3}\theta + \frac{1}{3}(1+\theta)\right)|\rho| + \left(\frac{1}{3}\theta + \frac{2}{3}(1+\theta)+1\right)|\rho|\,|v|^3,\\
&|\mathrm{I}_{b,ion}(w)| = |\rho|\,|w|,\\
&|H(v,w)| = |a_1 v - b_1 w| \le a_1|v| + b_1|w|.
\end{aligned}$$

Now, we compute the function $E(u,v) := \mathrm{I}_{b,ion}(w)\,v - \alpha_4 H(v,w)w$ *defined in* $\mathbb{R}^2$*. So, the second assumption* (3.5b) *holds with* $\alpha_4 = -\dfrac{\rho}{a_1}$:

$$E(u,v) = \frac{\rho}{a_1}w^2. \tag{3.8}$$

Moreover, the conditions (3.5c)-(3.5d) *are automatically satisfied by any cubic polynomial* $\mathcal{I}_{ion}$ *with positive leading coefficient. We end this remark by mentioning other reduced ionic models: the Roger-McCulloch model [RM94] and the Aliev-Panfilov model [AP96], may consider more general that the previous model but still rise some mathematical difficulties. Furthermore, the Mitchell-Schaeffer model [MS03] has been studied in [Bou+08; KM13] and its regularized version have a very specific structure. In particular, no proof of uniqueness of solutions for these models exists in the literature.*

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

$$\mathcal{I}_{gap}(s) = G_{gap}s, \tag{3.9}$$

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 [HLR92].

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

$$\left\|\varepsilon^{1/2}\mathcal{I}^k_{app,\varepsilon}\right\|_{L^2(\Gamma^k_{\varepsilon,T})} \le C. \tag{3.10}$$

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

$$\sum_{k=1,2}\left\|\varepsilon^{1/r}v^k_{0,\varepsilon}\right\|_{L^r(\Gamma^k_\varepsilon)} + \left\|\varepsilon^{1/2}s_{0,\varepsilon}\right\|_{L^2(\Gamma^{1,2}_\varepsilon)} + \sum_{k=1,2}\left\|\varepsilon^{1/2}w^k_{0,\varepsilon}\right\|_{L^2(\Gamma^k_\varepsilon)} \le C, \tag{3.11}$$

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

Finally, one can observe that Equations in (3.1) are invariant under the change of $u_{i,\varepsilon}^k$, $k = 1, 2$ and $u_{e,\varepsilon}$ into $u_{i,\varepsilon}^k + c$, $u_{e,\varepsilon} + c$, for any $c \in \mathbb{R}$. Therefore, we may impose the following normalization condition:

$$\int_{\Omega_{e,\varepsilon}} u_{e,\varepsilon}\, dx = 0, \text{ for a.e. } t \in (0,T). \tag{3.12}$$

3.2 Main results

In this part, we highlight our main results obtained in our paper. First, we define the weak solutions of the microscopic tridomain model. Next, we find a priori estimates and we supply our existence and uniqueness results by using Faedo-Galerkin method, compactness argument and monotonicity.

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

Definition 3.1 (Weak formulation of microscopic system)**.** *A weak solution to problem* (3.1)-(3.3) *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).

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

(B) (Regularity).

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

(C) (Initial conditions).

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

(D) (Variational equations).

$$
\begin{aligned}
&\sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k}\varepsilon\partial_t v_\varepsilon^k\psi^k\,d\sigma_x dt+\frac{1}{2}\iint_{\Gamma_{\varepsilon,T}^{1,2}}\varepsilon\partial_t s_\varepsilon\Psi\,d\sigma_x dt\\
&\quad+\sum_{k=1,2}\int_{\Omega_{i,\varepsilon,T}^k}\mathrm{M}_i^\varepsilon\nabla u_{i,\varepsilon}^k\cdot\nabla\varphi_i^k\,dxdt+\int_{\Omega_{e,\varepsilon,T}}\mathrm{M}_e^\varepsilon\nabla u_{e,\varepsilon}\cdot\nabla\varphi_e\,dxdt\\
&\quad+\sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k}\varepsilon\mathcal{I}_{ion}\left(v_\varepsilon^k,w_\varepsilon^k\right)\psi^k\,d\sigma_x dt+\frac{1}{2}\iint_{\Gamma_{\varepsilon,T}^{1,2}}\varepsilon\mathcal{I}_{gap}(s_\varepsilon)\Psi\,d\sigma_x dt\\
&=\sum_{k=1,2}\iint_{\Gamma_{\varepsilon,T}^k}\varepsilon\mathcal{I}_{app,\varepsilon}^k\psi^k\,d\sigma_x dt
\end{aligned}
\tag{3.13}
$$

$$
\iint_{\Gamma_{\varepsilon,T}^k}\partial_t w_\varepsilon^k e^k\,d\sigma_x dt=\iint_{\Gamma_{\varepsilon,T}^k}H\left(v_\varepsilon^k,w_\varepsilon^k\right)e^k\,d\sigma_x dt \tag{3.14}
$$

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* $k=1,2$,
- $\Psi=\Psi_i^1-\Psi_i^2:=(\varphi_i^1-\varphi_i^2)\,|_{\Gamma_{\varepsilon,T}^{1,2}}\in L^2(\Gamma_{\varepsilon,T}^{1,2})$,
- $e^k\in L^2(\Gamma_{\varepsilon,T}^k)$ *for* $k=1,2$.

Remark 3.6. *Due to Lions-Magenes theorem* (*see [BF12] p. 101*), *the following injection*

$$
\mathcal{V}:=\left\{u\in L^2\left(0,T;H^{1/2}\left(\Gamma_\varepsilon^k\right)\right)\cap L^r\left(\Gamma_{\varepsilon,T}^k\right)\ \text{and}\ \partial_t u\in L^2\left(0,T;H^{-1/2}\left(\Gamma_\varepsilon^k\right)\right)+L^{r/(r-1)}\left(\Gamma_{\varepsilon,T}^k\right)\right\}
$$
$$
\subset C^0\left([0,T];L^2(\Gamma_\varepsilon)\right),\ \text{for } k=1,2
$$

is continuous with $r\in(2,+\infty)$. *Then,* $v_\varepsilon^k\in C^0\left([0,T];L^2(\Gamma_\varepsilon^k)\right)$ *for* $k=1,2$. *Therefore, the initial data of* v_ε^k *for* $k=1,2$ *in Definition 3.1 is well defined. In the same manner, the initial condition on* s_ε *and on* w_ε^k *for* $k=1,2$ *makes sense.*

Theorem 3.1 (Microscopic Tridomain Model)**.** *Assume that the conditions* (3.4)-(3.11) *hold. Then, System* (3.1)-(3.3) *possesses a unique weak solution in the sense of Definition 3.1 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:

$$\sum_{k=1,2} \left\|\sqrt{\varepsilon} v_\varepsilon^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^k)\right)} + \sum_{k=1,2} \left\|\sqrt{\varepsilon} w_\varepsilon^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^k)\right)} + \left\|\sqrt{\varepsilon} s_\varepsilon\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^{1,2})\right)} \leq C_1 \quad (3.15)$$

$$\sum_{k=1,2} \left\|u_{i,\varepsilon}^k\right\|_{L^2\left(0,T;H^1\left(\Omega_{i,\varepsilon}^k\right)\right)} + \|u_e^\varepsilon\|_{L^2(0,T;H^1(\Omega_{e,\varepsilon}))} \leq C_2, \quad (3.16)$$

$$\sum_{k=1,2} \left\|\varepsilon^{1/r} v_\varepsilon^k\right\|_{L^r(\Gamma_{\varepsilon,T}^k)} \leq C_3 \text{ and } \sum_{k=1,2} \left\|\varepsilon^{(r-1)/r} \mathrm{I}_{a,ion}(v_\varepsilon^k)\right\|_{L^{r/(r-1)}(\Gamma_{\varepsilon,T}^k)} \leq C_4. \quad (3.17)$$

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:

$$\sum_{k=1,2} \left\|\sqrt{\varepsilon} \partial_t v_e^k\right\|^2_{L^2(\Gamma_{\varepsilon,T}^k)} + \sum_{k=1,2} \left\|\sqrt{\varepsilon} \partial_t w_\varepsilon^k\right\|^2_{L^2(\Gamma_{\varepsilon,T}^k)} + \left\|\sqrt{\varepsilon} \partial_t s_\varepsilon\right\|^2_{L^2(\Gamma_{\varepsilon,T}^{1,2})} \leq C_5. \quad (3.18)$$

The proof of Theorem 3.1 is treated in Section 3.3.

Finally, based on homogenization methods, we can derive the following homogenized problem:

Theorem 3.2 (Macroscopic Tridomain Model)**.** *A sequence of solutions $\left(u_{i,\varepsilon}^1, u_{i,\varepsilon}^2, u_{e,\varepsilon}, w_\varepsilon^1, w_\varepsilon^2\right)$ of the microscopic tridomain model (3.1)-(3.3) (obtained in Theorem 3.1) converges as $\varepsilon \to 0$ to a weak solution $\left(u_i^1, u_i^2, u_e, w^1, w^2\right)$ such that $u_i^k, u_e \in L^2(0,T;H^1(\Omega))$, $v^k = u_i^k - u_e \in L^2(0,T;H^1(\Omega)) \cap L^r(\Omega)$, $s = u_i^1 - u_i^2 \in L^2(0,T;H^1(\Omega))$, $\partial_t v^k \in L^2(0,T;(H^1(\Omega))') \cap L^{r/(r-1)}(\Omega_T)$, $w^k \in C(0,T;L^2(\Omega))$ and $\partial_t s \in L^2(\Omega_T)$ satisfy the macroscopic problem (Reaction-Diffusion system):*

$$\begin{aligned}
\sum_{k=1,2} \mu_k \partial_t v^k + \nabla \cdot \left(\widetilde{\mathbf{M}}_e \nabla u_e\right) + \sum_{k=1,2} \mu_k \mathcal{I}_{ion}(v^k, w^k) &= \sum_{k=1,2} \mu_k \mathcal{I}_{app}^k && \text{in } \Omega_T, \\
\mu_1 \partial_t v^1 + \mu_g \partial_t s - \nabla \cdot \left(\widetilde{\mathbf{M}}_i \nabla u_i^1\right) + \mu_1 \mathcal{I}_{ion}(v^1, w^1) + \mu_g \mathcal{I}_{gap}(s) &= \mu_1 \mathcal{I}_{app}^1 && \text{in } \Omega_T, \\
\mu_2 \partial_t v^2 - \mu_g \partial_t s - \nabla \cdot \left(\widetilde{\mathbf{M}}_i \nabla u_i^2\right) + \mu_2 \mathcal{I}_{ion}(v^2, w^2) - \mu_g \mathcal{I}_{gap}(s) &= \mu_2 \mathcal{I}_{app}^2 && \text{in } \Omega_T, \\
\partial_t w^k - H(v^k, w^k) &= 0 && \text{on } \Omega_T,
\end{aligned} \quad (3.19)$$

completed with no-flux boundary conditions on u_i, u_e on $\partial_{ext}\Omega$:

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

and initial conditions for the transmembrane potential v^k, the gap potential s and the gating variable w^k :

$$v^k(0,x) = v_0^k(x), \ s(0,x) = s_0(x) \text{ and } w^k(0,x) = w_0^k(x),$$

where $\mu_k = \left|\Gamma^k\right| / |Y|$, $k = 1, 2$, (resp. $\mu_g = |\Gamma^{1,2}| / |Y|$) is the ratio between the surface membrane (resp. the gap junction) and the volume of the reference cell. Furthermore, $\mathbf{n}$ represent the outward unit 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:

$$\widetilde{\mathbf{m}}_i^{pq} := \frac{1}{|Y|} \sum_{\ell=1}^{d} \int_{Y_i^k} \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell} \frac{\partial \chi_i^q}{\partial y_\ell} \right) \, dy, \tag{3.20a}$$

$$\widetilde{\mathbf{m}}_e^{pq} := \frac{1}{|Y|} \sum_{\ell=1}^{d} \int_{Y_e} \left(\mathrm{m}_e^{pq} + \mathrm{m}_e^{p\ell} \frac{\partial \chi_e^q}{\partial y_\ell} \right) \, dy, \tag{3.20b}$$

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

$$\begin{cases} -\nabla_y \cdot (\mathrm{M}_e \nabla_y \chi_e^q) = \nabla_y \cdot (\mathrm{M}_e e_q) \ \text{ in } Y_e, \\ \chi_e^q \ y\text{-periodic}, \\ \mathrm{M}_e \nabla_y \chi_e^q \cdot n_e = -(\mathrm{M}_e e_q) \cdot n_e \text{ on } \Gamma^k, \ k = 1, 2 \end{cases} \tag{3.21a}$$

$$\begin{cases} -\nabla_y \cdot (\mathrm{M}_i \nabla_y \chi_i^q) = \nabla_y \cdot (\mathrm{M}_i e_q) \ \text{ in } Y_i^k, \\ \chi_i^q \ y\text{-periodic}, \\ \mathrm{M}_i \nabla_y \chi_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \text{ on } \Gamma^k, \ k = 1, 2 \\ \mathrm{M}_i \nabla_y \chi_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \text{ on } \Gamma^{1,2}, \end{cases} \tag{3.21b}$$

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

3.3 Existence and Uniqueness of solutions for the microscopic tridomain model

This section is devoted to proving existence and uniqueness of solutions to the heterogeneous microscopic tridomain model presented in Section 3.1 for fixed $\varepsilon > 0$. The proof of Theorem 3.1 is based on the Faedo-Galerkin method and carried out in several steps:

- Construction of the basis on the intra- and extracellular domains.
- Construction and local existence of approximate solutions.
- Find some a priori estimates of the approximate solutions.
- Existence and uniqueness of solution to the microscopic tridomain model.

We refer the reader to the well-posedness results for weak solutions of the microscopic bidomain model, established in [BCP09; Ben+19] by using a Faedo-Galerkin technique. See also [BK06; Bou+08] for a similar approach, based on a parabolic regularization technique.

In this proof, we will remove the ε-dependence in the solution $\left(u^1_{i,\varepsilon}, u^2_{i,\varepsilon}, u_{e,\varepsilon}, v^1_\varepsilon, v^2_\varepsilon, s_\varepsilon, w^1_\varepsilon, w^2_\varepsilon\right)$ for simplification of notation. The demonstration is described as follows:

Step 1: Construction of the basis

We first consider functions ϕ, $\tilde{\phi} \in C^0(\overline{\Omega}^k_{i,\varepsilon})$ and we let $\mathbb{V}^k_{0,i}$ denote the completion of $C^0(\overline{\Omega}^k_{i,\varepsilon})$ under the norm induced by the inner product $\langle \cdot, \cdot \rangle_{\mathbb{V}^k_{0,i}}$ which defined by

$$\langle \Theta, \tilde{\Theta} \rangle_{\mathbb{V}^k_{0,i}} := \int_{\Omega^k_{i,\varepsilon}} \phi\tilde{\phi}\, dx + \int_{\Gamma^k_\varepsilon} \phi|_{\Gamma^k_\varepsilon}\tilde{\phi}|_{\Gamma^k_\varepsilon} d\sigma + \int_{\Gamma^{1,2}_\varepsilon} \phi|_{\Gamma^{1,2}_\varepsilon}\tilde{\phi}|_{\Gamma^{1,2}_\varepsilon} d\sigma, \text{ for } k = 1, 2,$$

where $\Theta = {}^t\left(\phi \quad \phi|_{\Gamma^k_\varepsilon} \quad \phi|_{\Gamma^{1,2}_\varepsilon}\right)$, $\tilde{\Theta} = {}^t\left(\tilde{\phi} \quad \tilde{\phi}|_{\Gamma^k_\varepsilon} \quad \tilde{\phi}|_{\Gamma^{1,2}_\varepsilon}\right)$.

Similarly, for functions ϕ, $\tilde{\phi} \in C^1(\overline{\Omega}^k_{i,\varepsilon})$ and we let $\mathbb{V}^k_{1,i}$ denote the completion of $C^1(\overline{\Omega}^k_{i,\varepsilon})$ under the norm induced by the inner product $\langle \cdot, \cdot \rangle_{\mathbb{V}^k_{1,i}}$ which defined by

$$\begin{aligned}\langle \Theta, \tilde{\Theta} \rangle_{\mathbb{V}^k_{1,i}} := &\int_{\Omega^k_{i,\varepsilon}} \mathrm{M}^\varepsilon_i \nabla\phi \cdot \nabla\tilde{\phi}\, dx + \int_{\Gamma^k_\varepsilon} \phi|_{\Gamma^k_\varepsilon}\tilde{\phi}|_{\Gamma^k_\varepsilon}\, d\sigma + \int_{\Gamma^k_\varepsilon} \nabla_{\Gamma^k_\varepsilon}\phi \cdot \nabla_{\Gamma^k_\varepsilon}\tilde{\phi}\, d\sigma \\ &+ \int_{\Gamma^{1,2}_\varepsilon} \phi|_{\Gamma^{1,2}_\varepsilon}\tilde{\phi}|_{\Gamma^{1,2}_\varepsilon}\, d\sigma + \int_{\Gamma^{1,2}_\varepsilon} \nabla_{\Gamma^{1,2}_\varepsilon}\phi \cdot \nabla_{\Gamma^{1,2}_\varepsilon}\tilde{\phi}\, d\sigma, \text{ for } k = 1, 2\end{aligned}$$

where ∇_Γ denotes the tangential gradient operator on Γ ($\Gamma := \Gamma^k_\varepsilon, \Gamma^{1,2}_\varepsilon$). We note that the following injections hold:

$$\mathbb{V}^k_{0,i} \subset L^2(\Omega^k_{i,\varepsilon}), \text{ and } \mathbb{V}^k_{1,i} \subset H^1(\Omega^k_{i,\varepsilon}).$$

Moreover, the injection from $\mathbb{V}^k_{1,i}$ to $\mathbb{V}^k_{0,i}$ is continuous and compact for $k = 1, 2$. We refer the reader to [Gal08; RZ+03] for similar approaches. It follows from a well-known result (see e.g. [Tem12] p. 54) that the bilinear form $a(\Theta, \tilde{\Theta}) := \langle \Theta, \tilde{\Theta} \rangle_{\mathbb{V}^k_{1,i}}$ defines a strictly positive self adjoint unbounded operator $\mathcal{B}^k_i : D(\mathcal{B}^k_i) = \{\Theta \in \mathbb{V}^k_{1,i} : \mathcal{B}^k_i \Theta \in \mathbb{V}^k_{1,i}\} \to \mathbb{V}^k_{0,i}$ such that, for any $\tilde{\Theta} \in \mathbb{V}^k_{1,i}$, we have $\langle \mathcal{B}^k_i \Theta, \tilde{\Theta} \rangle_{\mathbb{V}^k_{0,i}} = a(\Theta, \tilde{\Theta})$. Thus, for $n \in \mathbb{N}$, we take a complete system of eigenfunctions $\{\Theta^k_{i,n} = {}^t \begin{pmatrix} \phi^k_{i,n} & \psi^k_{i,n} & \Psi^k_{i,n} \end{pmatrix}\}_n$ of the problem

$$\mathcal{B}^k_i \Theta^k_{i,n} = \lambda_n \Theta^k_{i,n}, \text{ in } \mathbb{V}^k_{0,i}, \text{ for } k = 1, 2,$$

with $\{\lambda_n\}_n$ be a sequence such that $0 < \lambda_1 \leq \lambda_2, \dots, \lambda_n \to \infty$ as $n \to \infty$,
and $\Theta^k_{i,n} \in D(\mathcal{B}^k_i)$, $\psi^k_{i,n} := \phi^k_{i,n}|_{\Gamma^k_\varepsilon}$ and $\Psi^k_{i,n} := \phi^k_{i,n}|_{\Gamma^{1,2}_\varepsilon}$ where $\phi^k_{i,n}$, $\psi^k_{i,n}$ and $\Psi^k_{i,n}$ are regular enough for $k = 1, 2$.
Moreover, the eigenvectors $\{\Theta^k_{i,n}\}_n$ turn out to form an orthogonal basis in $\mathbb{V}^k_{1,i}$ and $\mathbb{V}^k_{0,i}$, and they may be assumed to be normalized in the norm of $\mathbb{V}^k_{0,i}$ for $k = 1, 2$. Since $C^1(\overline{\Omega}^k_{i,\varepsilon}) \subset \mathbb{V}^k_{1,i} \subset H^1(\Omega^k_{i,\varepsilon})$ and $C^1(\overline{\Omega}^k_{i,\varepsilon})$ is dense in $H^1(\Omega^k_{i,\varepsilon})$ then $\mathbb{V}^k_{1,i}$ is dense in $H^1(\Omega^k_{i,\varepsilon})$ for the H^1-norm. Therefore, $\{\Theta^k_{i,n}\}_n$ is a basis in $H^1(\Omega^k_{i,\varepsilon})$ for the H^1-norm.

On the other hand, we consider a basis $\{\zeta^k_n\}_n, n \in \mathbb{N}$ that is orthonormal in $L^2(\Gamma^k_\varepsilon)$ and orthogonal in $H^1(\Gamma^k_\varepsilon)$ and we set the spaces

$$\mathcal{P}^k_{i,\ell} = \text{span}\{\Theta^k_{i,1}, \dots, \Theta^k_{i,\ell}\}, \quad \mathcal{P}^k_{i,\infty} = \bigcup_{\ell=1}^{\infty} \mathcal{P}^k_{i,\ell},$$
$$\mathcal{K}^k_{i,\ell} = \text{span}\{\zeta^k_1, \dots, \zeta^k_\ell\}, \quad \mathcal{K}^k_{i,\infty} = \bigcup_{\ell=1}^{\infty} \mathcal{K}^k_{i,\ell},$$

where $\mathcal{P}^k_{i,\infty}$ and $\mathcal{K}^k_{i,\infty}$ are respectively dense subspaces of $\mathbb{V}^k_{1,i}$ and $H^1(\Gamma^k_\varepsilon)$ for $k = 1, 2$.

Remark 3.7. *Analogously, we construct a basis on the extracellular domain. We let $\mathbb{V}_{p,e}$ denote the completion of $C^p(\overline{\Omega}_{e,\varepsilon})$ under the norm induced by the inner product $\langle \cdot, \cdot \rangle_{\mathbb{V}_{p,e}}$ for ϕ, $\tilde{\phi} \in C^p(\overline{\Omega}_{e,\varepsilon})$, $p = 0, 1$ which respectively defined by*

$$\langle \Theta', \tilde{\Theta}' \rangle_{\mathbb{V}_{0,e}} := \int_{\Omega_{e,\varepsilon}} \phi \tilde{\phi} \, dx + \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \phi|_{\Gamma^k_\varepsilon} \tilde{\phi}|_{\Gamma^k_\varepsilon} d\sigma,$$
$$\textit{and } \langle \Theta', \tilde{\Theta}' \rangle_{\mathbb{V}_{1,e}} := \int_{\Omega_{e,\varepsilon}} \mathrm{M}^\varepsilon_e \nabla \phi \cdot \nabla \tilde{\phi} \, dx + \sum_{k=1,2} \left[\int_{\Gamma^k_\varepsilon} \phi|_{\Gamma^k_\varepsilon} \tilde{\phi}|_{\Gamma^k_\varepsilon} \, d\sigma + \int_{\Gamma^k_\varepsilon} \nabla_{\Gamma^k_\varepsilon} \phi \cdot \nabla_{\Gamma^k_\varepsilon} \tilde{\phi} \, d\sigma \right],$$

where $\Theta' = {}^t \begin{pmatrix} \phi & \phi|_{\Gamma^1_\varepsilon} & \phi|_{\Gamma^2_\varepsilon} \end{pmatrix}$, $\tilde{\Theta}' = {}^t \begin{pmatrix} \tilde{\phi} & \tilde{\phi}|_{\Gamma^1_\varepsilon} & \tilde{\phi}|_{\Gamma^2_\varepsilon} \end{pmatrix}$. Similarly, we take a complete basis *which is orthogonal in* $\mathbb{V}_{1,e}$ *and orthonormal in* $\mathbb{V}_{0,e}$ *and we set the spaces*

$$\mathcal{P}_{e,\ell} = span\{\Theta_{e,1}, \dots, \Theta_{e,\ell}\}, \quad \mathcal{P}_{e,\infty} = \bigcup_{\ell=1}^{\infty} \mathcal{P}_{e,\ell},$$

where $\mathcal{P}_{e,\infty}$ *is a dense subspace of* $\mathbb{V}_{1,e}$.

Step 2: Construction and local existence of approximate solutions

Supplied with the basis introduced in the first step, we look for the approximate solutions as sequences $\{u_{i,n}^k\}_{n>1}$, $\{u_{e,n}\}_{n>1}$ and $\{w_n^k\}_{n>1}$, $k = 1, 2$ defined for $t > 0$ and $x \in \Omega$ by:

$$U_i^k = \begin{pmatrix} u_{i,n}^k \\ \\ \overline{u}_{i,n}^k \\ \\ \overline{\overline{u}}_{i,n}^k \end{pmatrix} := \sum_{\ell=1}^{n} d_{i,\ell}^k(t) \begin{pmatrix} \phi_{i,\ell}^k \\ \\ \psi_{i,\ell}^k \\ \\ \Psi_{i,\ell}^k \end{pmatrix}, \quad U_e = \begin{pmatrix} u_{e,n} \\ \\ \overline{u}_{e,n}^1 \\ \\ \overline{u}_{e,n}^2 \end{pmatrix} := \sum_{\ell=1}^{n} d_{e,\ell}(t) \begin{pmatrix} \phi_{e,\ell} \\ \\ \psi_{e,\ell}^1 \\ \\ \psi_{e,\ell}^2 \end{pmatrix} \tag{3.22}$$
$$\text{and } w_n^k := \sum_{\ell=1}^{n} c_\ell^k(t) \zeta_\ell^k(x),$$

with $\phi_{i,\ell}^k|_{\Gamma_\varepsilon^k} = \psi_{i,\ell}^k$, $\phi_{i,\ell}^k|_{\Gamma_\varepsilon^{1,2}} = \Psi_{i,\ell}^k$ and $\phi_{e,\ell}|_{\Gamma_\varepsilon^k} = \psi_{e,\ell}^k$ for $k = 1, 2$. To apply the Faedo-Galerkin scheme, we first regularize the microscopic tridomain system (3.1)-(3.3) using specific approximation as follows (recall that our system is degenerate)

$$\begin{aligned} &(\varepsilon + \delta_n) \int_{\Gamma_\varepsilon^1} \partial_t \overline{u}_{i,n}^1 \psi_i^1 \, d\sigma_x - \varepsilon \int_{\Gamma_\varepsilon^1} \partial_t \overline{u}_{e,n}^1 \psi_i^1 \, d\sigma_x + \delta_n \int_{\Omega_{i,\varepsilon}^1} \partial_t u_{i,n}^1 \phi_i^1 \, dx \\ &\quad + (\frac{\varepsilon}{2} + \delta_n) \int_{\Gamma_\varepsilon^{1,2}} \partial_t \overline{\overline{u}}_{i,n}^1 \Psi_i^1 \, d\sigma_x - \frac{\varepsilon}{2} \int_{\Gamma_\varepsilon^{1,2}} \partial_t \overline{\overline{u}}_{i,n}^2 \Psi_i^1 \, d\sigma_x \\ &= \int_{\Gamma_\varepsilon^1} \varepsilon \left(-\mathcal{I}_{ion}(v_n^1, w_n^1) + \mathcal{I}_{app,\varepsilon}^1 \right) \psi_i^1 \, d\sigma_x \\ &\quad - \frac{1}{2} \int_{\Gamma_\varepsilon^{1,2}} \varepsilon \mathcal{I}_{gap}(s_n) \Psi_i^1 \, d\sigma_x - \int_{\Omega_{i,\varepsilon}^1} \mathrm{M}_i^\varepsilon \nabla u_{i,n}^1 \cdot \nabla \phi_i^1 \, dx \end{aligned} \tag{3.23}$$

$$
\begin{aligned}
&(\varepsilon+\delta_n)\int_{\Gamma^2_\varepsilon}\partial_t\overline{u}^2_{i,n}\psi^2_i\,d\sigma_x-\varepsilon\int_{\Gamma^2_\varepsilon}\partial_t\overline{u}^2_{e,n}\psi^2_i\,d\sigma_x+\delta_n\int_{\Omega^2_{i,\varepsilon}}\partial_t u^2_{i,n}\phi^2_i\,dx\\
&\quad-\frac{\varepsilon}{2}\int_{\Gamma^{1,2}_\varepsilon}\partial_t\overline{\overline{u}}^1_{i,n}\Psi^2_i\,d\sigma_x+(\frac{\varepsilon}{2}+\delta_n)\int_{\Gamma^{1,2}_\varepsilon}\partial_t\overline{\overline{u}}^2_{i,n}\Psi^2_i\,d\sigma_x\\
&=\int_{\Gamma^2_\varepsilon}\varepsilon\left(-\mathcal{I}_{ion}(v^2_n,w^2_n)+\mathcal{I}^2_{app,\varepsilon}\right)\psi^2_i\,d\sigma_x\\
&\quad+\frac{1}{2}\int_{\Gamma^{1,2}_\varepsilon}\varepsilon\mathcal{I}_{gap}(s_n)\Psi^2_i\,d\sigma_x-\int_{\Omega^2_{i,\varepsilon}}\mathrm{M}^\varepsilon_i\nabla u^2_{i,n}\cdot\nabla\phi^2_i\,dx
\end{aligned}
\tag{3.24}
$$

$$
\begin{aligned}
&-\varepsilon\sum_{k=1,2}\int_{\Gamma^k_\varepsilon}\partial_t\overline{u}^k_{i,n}\psi^k_e\,d\sigma_x+(\varepsilon+\delta_n)\sum_{k=1,2}\int_{\Gamma^k_\varepsilon}\partial_t\overline{u}^k_{e,n}\psi^k_e\,d\sigma_x+\delta_n\int_{\Omega_{e,\varepsilon}}\partial_t u_{e,n}\phi_e\,dx\\
&=\sum_{k=1,2}\int_{\Gamma^k_\varepsilon}\varepsilon\left(\mathcal{I}_{ion}(v^k_n,w^k_n)-\mathcal{I}^k_{app,\varepsilon}\right)\psi^k_e\,d\sigma_x-\int_{\Omega_{e,\varepsilon}}\mathrm{M}^\varepsilon_e\nabla u_{e,n}\cdot\nabla\phi_e\,dx
\end{aligned}
\tag{3.25}
$$

$$
\int_{\Gamma^k_\varepsilon}\partial_t w^k_n\zeta^k\,d\sigma_x=\int_{\Gamma^k_\varepsilon}H\left(v^k_n,w^k_n\right)\zeta^k\,d\sigma_x,
\tag{3.26}
$$

where the regularization parameter $\delta_n=\dfrac{1}{n}$, $\Theta^k_i={}^t\left(\phi^k_i\;\;\psi^k_i\;\;\Psi^k_i\right)\in\mathcal{P}^k_{i,n}$, $\zeta^k\in\mathcal{K}^k_n$ for $k=1,2$, and $\Theta_e={}^t\left(\phi_e\;\;\psi^1_e\;\;\psi^2_e\right)\in\mathcal{P}_{e,n}$. The regularization terms multiplied by δ_n have been added to overcome degeneracy in (3.13). Moreover, the resulting regularized problem is supplemented with initial conditions:

$$
\begin{aligned}
&u^k_{i,n}(0,x)=u^k_{0,i,n}(x):=\sum_{\ell=1}^n d^k_{i,\ell}(0)\phi^k_{i,\ell}(x),\\
&\overline{u}^k_{i,n}(0,x)=\overline{u}^k_{0,i,n}(x):=\sum_{\ell=1}^n d^k_{i,\ell}(0)\psi^k_{i,\ell}(x),\\
&\overline{\overline{u}}^k_{i,n}(0,x)=\overline{\overline{u}}^k_{0,i,n}(x):=\sum_{\ell=1}^n d^k_{i,\ell}(0)\Psi^k_{i,\ell}(x),\quad d^k_{i,\ell}(0):=\langle U^k_{0,i},\Theta^k_{i,\ell}\rangle_{\mathbb{V}^k_{0,i}},\\
&u_{e,n}(0,x)=u_{0,e,n}(x):=\sum_{\ell=1}^n d_{e,\ell}(0)\phi_{e,\ell},\\
&\overline{u}^k_{e,n}(0,x)=\overline{u}_{0,e,n}(x):=\sum_{\ell=1}^n d_{e,\ell}(0)\psi^k_{e,\ell}(x),\quad d_{e,\ell}(0):=\langle U_{0,e},\Theta_{e,\ell}\rangle_{\mathbb{V}_{0,e}},\\
&w^k_n(0,x)=w^k_{0,n}:=\sum_{\ell=1}^n c^k_\ell(0)\zeta^k_\ell(x),\quad c^k_\ell(0):=\langle w^k_0,\zeta^k_\ell\rangle_{L^2(\Gamma^k_\varepsilon)},
\end{aligned}
\tag{3.27}
$$

where $U^k_{0,i}:=U^k_i(0,x)$, for $k=1,2$ and $U_{0,e}:=U_e(0,x)$.

Next, we prove in the following lemma the local existence of solutions for the previous regularized problem:

Lemma 3.1 (Local existence of solutions for the regularized problems)**.** *Assume that the conditions* (3.4)-(3.11) *hold. Then, there exits a positive time* $0 < t_0 \leq T$ *such that System* (3.23)-(3.27) *admit a unique solution over the time interval* $[0, t_0]$.

Proof. The goal is to determine the coefficients $\mathbf{d}_i^k = \{d_{i,\ell}^k\}_{\ell=1}^n$, $\mathbf{d}_e = \{d_{e,\ell}\}_{\ell=1}^n$ and $\mathbf{c}^k = \{c_\ell^k\}_{\ell=1}^n$ for $k = 1, 2$. For this purpose, if n fixed, we choose $\Theta_i^k = \Theta_{i,m}^k$, $\Theta_e = \Theta_{e,m}$ and $\zeta^k = \zeta_m^k$ for $1 \leq m \leq n$ and substitute the approximate solutions (3.22) into (3.23)-(3.26). Then, the problem (3.23)-(3.26) is equivalent to the system of ordinary differential equations (ODE) in the following compact form:

$$\begin{aligned}
(\varepsilon + \delta_n)\overline{\mathbb{A}}_{ii}^1(\mathbf{d}_i^1)' - \varepsilon\overline{\mathbb{A}}_{ie}^1\mathbf{d}_e' + \delta_n\mathbb{A}_{ii}^1(\mathbf{d}_i^1)' + (\frac{\varepsilon}{2} + \delta_n)\overline{\overline{\mathbb{A}}}_{ii}^1(\mathbf{d}_i^1)' - \frac{\varepsilon}{2}\overline{\overline{\mathbb{A}}}_{ii}^{1,2}(\mathbf{d}_i^2)' &= \mathbb{F}_i^1(t, \mathbf{d}_i^1, \mathbf{d}_i^2, \mathbf{d}_e, \mathbf{c}^1, \mathbf{c}^2) \\
(\varepsilon + \delta_n)\overline{\mathbb{A}}_{ii}^2(\mathbf{d}_i^2)' - \varepsilon\overline{\mathbb{A}}_{ie}^2\mathbf{d}_e' + \delta_n\mathbb{A}_{ii}^2(\mathbf{d}_i^2)' - \frac{\varepsilon}{2}\overline{\overline{\mathbb{A}}}_{ii}^{1,2}(\mathbf{d}_i^1)' + (\frac{\varepsilon}{2} + \delta_n)\overline{\overline{\mathbb{A}}}_{ii}^2(\mathbf{d}_i^2)' &= \mathbb{F}_i^2(t, \mathbf{d}_i^1, \mathbf{d}_i^2, \mathbf{d}_e, \mathbf{c}^1, \mathbf{c}^2) \\
\sum_{k=1,2}\left[-\varepsilon\overline{\mathbb{A}}_{ie}^k(\mathbf{d}_i^k)' + (\varepsilon + \delta_n)\overline{\mathbb{A}}_{ee}^k\mathbf{d}_e'\right] + \delta_n\mathbb{A}_{ee}\mathbf{d}_e' &= \mathbb{F}_e(t, \mathbf{d}_i^1, \mathbf{d}_i^2, \mathbf{d}_e, \mathbf{c}^1, \mathbf{c}^2) \\
\mathbb{G}^k(\mathbf{c}^k)' &= \mathbb{H}^k(t, \mathbf{d}_i^1, \mathbf{d}_i^2, \mathbf{d}_e, \mathbf{c}^1, \mathbf{c}^2)
\end{aligned} \tag{3.28}$$

with the (ℓ, m) entry of matrix:

- $\mathbb{A}_{ii}^k$ is $\langle\phi_{i,\ell}^k, \phi_{i,m}^k\rangle_{L^2(\Omega_{i,\varepsilon}^k)}$ $\Big($resp. of $\mathbb{A}_{ee}$ is $\langle\phi_{e,\ell}, \phi_{e,m}\rangle_{L^2(\Omega_{e,\varepsilon})}\Big)$,
- $\overline{\mathbb{A}}_{ii}^k$ is $\langle\psi_{i,\ell}^k, \psi_{i,m}^k\rangle_{L^2(\Gamma_\varepsilon^k)}$ $\Big($resp. of $\overline{\mathbb{A}}_{ee}^k$ is $\langle\psi_{e,\ell}^k, \psi_{e,m}^k\rangle_{L^2(\Gamma_\varepsilon^k)}\Big)$,
- $\overline{\mathbb{A}}_{ie}^k$ is $\langle\psi_{i,\ell}^k, \psi_{e,m}^k\rangle_{L^2(\Gamma_\varepsilon^k)}$,
- $\overline{\overline{\mathbb{A}}}_{ii}^k$ is $\langle\Psi_{i,\ell}^k, \Psi_{i,m}^k\rangle_{L^2(\Gamma_\varepsilon^k)}$ $\Big($resp. of $\overline{\overline{\mathbb{A}}}_{ii}^{1,2}$ is $\langle\Psi_{i,\ell}^1, \Psi_{i,m}^2\rangle_{L^2(\Gamma_\varepsilon^{1,2})}\Big)$,
- $\mathbb{G}^k$ is $\langle\zeta_\ell^k, \zeta_m^k\rangle_{L^2(\Gamma_\varepsilon^k)}$,

for $1 \leq \ell, m \leq n$ and $k = 1, 2$. Herein, the vectors $\mathbb{F}_i^k$, $\mathbb{F}_e$ and $\mathbb{H}^k$ for $k = 1, 2$ correspond to the right hand sides of the equations given in (3.23)-(3.26).

Furthermore, the first three equations in ODE system (3.28) can be written as follows:

$$\mathbb{M}\begin{bmatrix}(\mathbf{d}_i^1)' \\ (\mathbf{d}_i^2)' \\ \mathbf{d}_e' \\ (\mathbf{c}^1)' \\ (\mathbf{c}^2)'\end{bmatrix} = \begin{bmatrix}\mathbb{F}_i^1 \\ \mathbb{F}_i^2 \\ \mathbb{F}_e \\ \mathbb{H}^1 \\ \mathbb{H}^2\end{bmatrix}, \tag{3.29}$$

with $\mathbb{M} := \mathbb{M}_1 + \varepsilon\mathbb{M}_2$ and each matrix defined by:

$$\mathbb{M}_1 = \begin{bmatrix} \delta_n\left(\overline{\mathbb{A}}_{ii}^1 + \mathbb{A}_{ii}^1 + \overline{\overline{\mathbb{A}}}_{ii}^1\right) & 0 & 0 & 0 & 0 \\ 0 & \delta_n\left(\overline{\mathbb{A}}_{ii}^2 + \mathbb{A}_{ii}^2 + \overline{\overline{\mathbb{A}}}_{ii}^2\right) & 0 & 0 & 0 \\ 0 & 0 & \delta_n\left(\overline{\mathbb{A}}_{ee}^1 + \overline{\mathbb{A}}_{ee}^2 + \mathbb{A}_{ee}\right) & 0 & 0 \\ 0 & 0 & 0 & \mathbb{G}^1 & 0 \\ 0 & 0 & 0 & 0 & \mathbb{G}^2 \end{bmatrix} \tag{3.30}$$

and

$$\mathbb{M}_2 = \begin{bmatrix} \overline{\mathbb{A}}_{ii}^1 + \frac{1}{2}\overline{\overline{\mathbb{A}}}_{ii}^1 & -\frac{1}{2}\overline{\overline{\mathbb{A}}}_{ii}^{1,2} & -\overline{\mathbb{A}}_{ie}^1 & 0 & 0 \\ -\frac{1}{2}{}^t\overline{\overline{\mathbb{A}}}_{ii}^{1,2} & \overline{\mathbb{A}}_{ii}^2 + \frac{1}{2}\overline{\overline{\mathbb{A}}}_{ii}^2 & -\overline{\mathbb{A}}_{ie}^2 & 0 & 0 \\ -{}^t\overline{\mathbb{A}}_{ie}^1 & -{}^t\overline{\mathbb{A}}_{ie}^2 & \overline{\mathbb{A}}_{ee}^1 + \overline{\mathbb{A}}_{ee}^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}. \tag{3.31}$$

In order to write

$$\begin{bmatrix} (\mathbf{d}_i^1)' \\ (\mathbf{d}_i^2)' \\ \mathbf{d}_e' \\ (\mathbf{c}^1)' \\ (\mathbf{c}^2)' \end{bmatrix} = \mathbb{M}^{-1} \begin{bmatrix} \mathbb{F}_i^1 \\ \mathbb{F}_i^2 \\ \mathbb{F}_e \\ \mathbb{H}^1 \\ \mathbb{H}^2 \end{bmatrix},$$

one needs to prove that the matrix $\mathbb{M}$ is invertible. According to Lemma 3.2, given below, the matrix $\mathbb{M}$ is symmetric positive definite, hence invertible. Consequently, we can write the ODE system (3.28) in the form $z'(t) = F(t, z(t))$. Finally, we prove the existence of a local solution $[0, t_0)$ to this ODE system with $t_0 \in (0, T)$ (independent of the initial data). To this end, we show that th entries of $\mathbb{F}_i^k, \mathbb{F}_e$ and $\mathbb{H}^k$ for $k = 1, 2$ are Caratheodory functions bounded by L^1 functions using the assumptions (3.4)-(3.11) by following the same strategy in [BK06]. □

Lemma 3.2. *For all $n \in \mathbb{N}^*$, the matrix $\mathbb{M}$ is positive definite.*

Proof. Since we have $\mathbb{M} = \mathbb{M}_1 + \varepsilon\mathbb{M}_2$ with $\mathbb{M}_1$ and $\mathbb{M}_2$ defined respectively by (3.30)-(3.31). Note that by the orthonormality of the basis, the matrices $\overline{\mathbb{A}}_{ii}^k$, $\mathbb{A}_{ii}^k$, $\overline{\overline{\mathbb{A}}}_{ii}^k$, $\overline{\mathbb{A}}_{ee}^k$, $\mathbb{A}_{ee}$ and $\mathbb{G}^k$ are equal to the identity matrix $\mathbb{I}_{n\times n}$ for $k = 1, 2$. So, the matrix

$$\mathbb{M}_1 = \begin{bmatrix} 3\delta_n \mathbb{I}_{n\times n} & 0 & 0 & 0 & 0 \\ 0 & 3\delta_n \mathbb{I}_{n\times n} & 0 & 0 & \\ 0 & 0 & 3\delta_n \mathbb{I}_{n\times n} & 0 & 0 \\ 0 & 0 & 0 & \mathbb{I}_{n\times n} & 0 \\ 0 & 0 & 0 & 0 & \mathbb{I}_{n\times n} \end{bmatrix}$$

It suffices to show that the matrix $\mathbb{M}_2$ is positive semi-definite. Let $\mathbf{d} = {}^t\left(\mathbf{d}_i^1 \;\; \mathbf{d}_i^2 \;\; \mathbf{d}_e \;\; \mathbf{c}^1 \;\; \mathbf{c}^2\right)$ where $\mathbf{d}_i^k = {}^t\left(\mathbf{d}_{i,1}^k, \ldots, \mathbf{d}_{i,n}^k\right) \in \mathbb{R}^n$, $\mathbf{d}_e = {}^t\left(\mathbf{d}_{e,1}, \ldots, \mathbf{d}_{e,n}\right) \in \mathbb{R}^n$ and $\mathbf{c}^k = {}^t\left(\mathbf{c}_1^k, \ldots, \mathbf{c}_n^k\right) \in \mathbb{R}^n$ for $k = 1, 2$, we prove that ${}^t\mathbf{d}\mathbb{M}_2\mathbf{d} \geq 0$.
Indeed, we have:

$$\begin{aligned} {}^t\mathbf{d}\mathbb{M}_2\mathbf{d} &= {}^t\mathbf{d}_i^1\left(\overline{\mathbb{A}}_{ii}^1 + \frac{1}{2}\overline{\overline{\mathbb{A}}}_{ii}^1\right)\mathbf{d}_i^1 + {}^t\mathbf{d}_i^2\left(\overline{\mathbb{A}}_{ii}^2 + \frac{1}{2}\overline{\overline{\mathbb{A}}}_{ii}^2\right)\mathbf{d}_i^2 + {}^t\mathbf{d}_e\left(\overline{\mathbb{A}}_{ee}^1 + \overline{\mathbb{A}}_{ee}^2\right)\mathbf{d}_e \\ &\quad - {}^t\mathbf{d}_i^1\overline{\overline{\mathbb{A}}}_{ii}^{1,2}\mathbf{d}_i^2 - 2\,{}^t\mathbf{d}_i^1\overline{\mathbb{A}}_{ie}^1\mathbf{d}_e - 2\,{}^t\mathbf{d}_i^2\overline{\mathbb{A}}_{ie}^2\mathbf{d}_e \\ &= {}^t\mathbf{d}_i^1\overline{\mathbb{A}}_{ii}^1\mathbf{d}_i^1 - 2\,{}^t\mathbf{d}_i^1\overline{\mathbb{A}}_{ie}^1\mathbf{d}_e + {}^t\mathbf{d}_e\overline{\mathbb{A}}_{ee}^1\mathbf{d}_e \\ &\quad + {}^t\mathbf{d}_i^2\overline{\mathbb{A}}_{ii}^2\mathbf{d}_i^2 - 2\,{}^t\mathbf{d}_i^2\overline{\mathbb{A}}_{ie}^2\mathbf{d}_e + {}^t\mathbf{d}_e\overline{\mathbb{A}}_{ee}^2\mathbf{d}_e \\ &\quad + \frac{1}{2}{}^t\mathbf{d}_i^1\overline{\overline{\mathbb{A}}}_{ii}^1\mathbf{d}_i^1 - {}^t\mathbf{d}_i^1\overline{\overline{\mathbb{A}}}_{ii}^{1,2}\mathbf{d}_i^2 + \frac{1}{2}{}^t\mathbf{d}_i^2\overline{\overline{\mathbb{A}}}_{ii}^2\mathbf{d}_i^2 \\ &:= \mathbb{E}_1 + \mathbb{E}_2 + \mathbb{E}_3 \end{aligned}$$

We complete by showing that $\mathbb{E}_1 \geq 0$ and the proof of the other terms $\mathbb{E}_2, \mathbb{E}_3$ is similar. Due the form of matrices and the orthonormality of basis, we obtain:

$$\begin{aligned} \mathbb{E}_1 &= {}^t\mathbf{d}_i^1\overline{\mathbb{A}}_{ii}^1\mathbf{d}_i^1 - 2\,{}^t\mathbf{d}_i^1\overline{\mathbb{A}}_{ie}^1\mathbf{d}_e + {}^t\mathbf{d}_e\overline{\mathbb{A}}_{ee}^1\mathbf{d}_e \\ &= \sum_{\ell,m=1}^{n}\left[\mathbf{d}_{i,\ell}^1\mathbf{d}_{i,m}^1\int_{\Gamma_\varepsilon^1}\psi_{i,\ell}^1\psi_{i,m}^1 - 2\mathbf{d}_{i,\ell}^1\mathbf{d}_{e,m}\int_{\Gamma_\varepsilon^1}\psi_{i,\ell}^1\psi_{e,m}^1 + \mathbf{d}_{e,\ell}\mathbf{d}_{e,m}\int_{\Gamma_\varepsilon^1}\psi_{e,\ell}^1\psi_{e,m}^1\right] d\sigma_x \\ &= \int_{\Gamma_\varepsilon^1}\left[\sum_{\ell}^{n}\mathbf{d}_{i,\ell}^1\psi_{i,\ell}^1 - \mathbf{d}_{e,\ell}\psi_{e,\ell}^1\right]^2 d\sigma_x \;\geq 0. \end{aligned}$$

□

Remark 3.8. *The above proof of the matrix* $\mathbb{M}$ *points out the role of the regularization term* $\mathbb{M}_1$*. It allows to obtain a matrix* $\mathbb{M}$ *in* (3.29) *which is nonsingular, so that the resulting system of ODE is non-degenerate.*

To prove global existence of the Faedo-Galerkin solutions on $[0, T)$, we derive a priori estimates, independent of the regularization parameter n, bounding $u_{i,n}^k, u_{e,n}, v_n^k, w_n^k$ for $k = 1, 2$ and s_n in the next step.

Step 3: Energy estimates

The Faedo-Galerkin solutions satisfy the following weak formulations:

$$\begin{aligned}
&(\varepsilon+\delta_n)\int_{\Gamma_\varepsilon^1}\partial_t\overline{u}_{i,n}^1\psi_{i,n}^1\,d\sigma_x-\varepsilon\int_{\Gamma_\varepsilon^1}\partial_t\overline{u}_{e,n}\psi_{i,n}^1\,d\sigma_x+\delta_n\int_{\Omega_{i,\varepsilon}^1}\partial_t u_{i,n}^1\varphi_{i,n}^1\,dx\\
&\quad+(\frac{\varepsilon}{2}+\delta_n)\int_{\Gamma_\varepsilon^{1,2}}\partial_t\overline{\overline{u}}_{i,n}^1\Psi_{i,n}^1\,d\sigma_x-\frac{\varepsilon}{2}\int_{\Gamma_\varepsilon^{1,2}}\partial_t\overline{\overline{u}}_{i,n}^2\Psi_{i,n}^1\,d\sigma_x\\
&=\int_{\Gamma_\varepsilon^1}\varepsilon\left(-\mathcal{I}_{ion}(v_n^1,w_n^1)+\mathcal{I}_{app,\varepsilon}^1\right)\psi_{i,n}^1\,d\sigma_x\\
&\quad-\frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}}\varepsilon\mathcal{I}_{gap}(s_n)\Psi_{i,n}^1\,d\sigma_x-\int_{\Omega_{i,\varepsilon}^1}\mathrm{M}_i^\varepsilon\nabla u_{i,n}^1\cdot\nabla\varphi_{i,n}^1\,dx
\end{aligned}\tag{3.32}$$

$$\begin{aligned}
&(\varepsilon+\delta_n)\int_{\Gamma_\varepsilon^2}\partial_t\overline{u}_{i,n}^2\psi_{i,n}^2\,d\sigma_x-\varepsilon\int_{\Gamma_\varepsilon^2}\partial_t\overline{u}_{e,n}\psi_{i,n}^2\,d\sigma_x+\delta_n\int_{\Omega_{i,\varepsilon}^2}\partial_t u_{i,n}^2\varphi_{i,n}^2\,dx\\
&\quad-\frac{\varepsilon}{2}\int_{\Gamma_\varepsilon^{1,2}}\partial_t\overline{\overline{u}}_{i,n}^1\Psi_{i,n}^2\,d\sigma_x+(\frac{\varepsilon}{2}+\delta_n)\int_{\Gamma_\varepsilon^{1,2}}\partial_t\overline{\overline{u}}_{i,n}^2\Psi_{i,n}^2\,d\sigma_x\\
&=\int_{\Gamma_\varepsilon^2}\varepsilon\left(-\mathcal{I}_{ion}(v_n^2,w_n^2)+\mathcal{I}_{app,\varepsilon}^2\right)\psi_{i,n}^2\,d\sigma_x\\
&\quad+\frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}}\varepsilon\mathcal{I}_{gap}(s_n)\Psi_{i,n}^2\,d\sigma_x-\int_{\Omega_{i,\varepsilon}^2}\mathrm{M}_i^\varepsilon\nabla u_{i,n}^2\cdot\nabla\varphi_{i,n}^2\,dx
\end{aligned}\tag{3.33}$$

$$\begin{aligned}
&-\varepsilon\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\partial_t\overline{u}_{i,n}^k\psi_{e,n}^k\,d\sigma_x+(\varepsilon+\delta_n)\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\partial_t\overline{u}_{e,n}^k\psi_{e,n}^k\,d\sigma_x+\delta_n\int_{\Omega_{e,\varepsilon}}\partial_t u_{e,n}\varphi_{e,n}\,dx\\
&=\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\varepsilon\left(\mathcal{I}_{ion}(v_n^k,w_n^k)-\mathcal{I}_{app,\varepsilon}^k\right)\psi_{e,n}^k\,d\sigma_x-\int_{\Omega_{e,\varepsilon}}\mathrm{M}_e^\varepsilon\nabla u_{e,n}\cdot\nabla\varphi_{e,n}\,dx
\end{aligned}\tag{3.34}$$

$$\int_{\Gamma_\varepsilon^k}\partial_t w_n^k e_n^k\,d\sigma_x=\int_{\Gamma_\varepsilon^k}H\left(v_n^k,w_n^k\right)e_n^k\,d\sigma_x,\tag{3.35}$$

where

$$\varphi_{i,n}^k(t,x):=\sum_{\ell=1}^n a_{i,\ell}^k(t)\phi_{i,\ell}^k(x),\ \varphi_{e,n}(t,x):=\sum_{\ell=1}^n a_{e,\ell}(t)\phi_{e,\ell}(x),\ e_n^k(t,x):=\sum_{\ell=1}^n b_\ell(t)\xi_\ell^k(x),$$

for some given (absolutely continuous) coefficients $a^k_{i,\ell}(t), a_{e,\ell}(t), b^k_\ell(t)$ with $\ell = 1, \dots, n$ and $k = 1, 2$. Moreover, we recall that $\psi^k_{i,n}$ (resp. $\psi^k_{e,n}$) is the trace of $\varphi^k_{i,n}$ (resp. of $\varphi_{e,n}$) on Γ^k_ε and $\Psi^k_{i,n}$ is the trace of $\varphi^k_{i,n}$ on $\Gamma^{1,2}_\varepsilon$ for $k = 1, 2$.

We find now the a priori estimates of the solution of approximate problem (3.32)-(3.35). First, we sum the three equations (3.32)-(3.34) to obtain the following weak formulation:

$$
\begin{aligned}
&\sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \varepsilon \partial_t v^k_n \psi^k_n \, d\sigma_x + \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \delta_n \partial_t \overline{u}^k_{i,n} \psi^k_{i,n} \, d\sigma_x + \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \delta_n \partial_t \overline{u}^k_{e,n} \psi^k_{e,n} \, d\sigma_x \\
&\quad + \frac{1}{2} \int_{\Gamma^{1,2}_\varepsilon} \varepsilon \partial_t s_n \Psi_n \, d\sigma_x + \sum_{k=1,2} \int_{\Gamma^{1,2}_\varepsilon} \delta_n \partial_t \overline{\overline{u}}^k_{i,n} \Psi^k_{i,n} \, d\sigma_x \\
&\quad + \sum_{k=1,2} \int_{\Omega^k_{i,\varepsilon}} \delta_n \partial_t u^k_{i,n} \varphi^k_{i,n} \, dx + \int_{\Omega_{e,\varepsilon}} \delta_n \partial_t u_{e,n} \varphi_{e,n} \, dx \\
&\quad + \sum_{k=1,2} \int_{\Omega^k_{i,\varepsilon}} \mathrm{M}^\varepsilon_i \nabla u^k_{i,n} \cdot \nabla \varphi^k_{i,n} \, dx + \int_{\Omega_{e,\varepsilon}} \mathrm{M}^\varepsilon_e \nabla u_{e,n} \cdot \nabla \varphi_{e,n} \, dx \\
&\quad + \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \varepsilon \mathcal{I}_{ion} \left(v^k_n, w^k_n \right) \psi^k_n \, d\sigma_x + \frac{1}{2} \int_{\Gamma^{1,2}_\varepsilon} \varepsilon \mathcal{I}_{gap} \left(s_n \right) \Psi_n \, d\sigma_x \\
&= \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \varepsilon \mathcal{I}^k_{app,\varepsilon} \psi^k_n \, d\sigma_x,
\end{aligned}
\tag{3.36}
$$

$$
\int_{\Gamma^k_\varepsilon} \partial_t w^k_n e^k_n \, d\sigma_x = \int_{\Gamma^k_\varepsilon} H \left(v^k_n, w^k_n \right) e^k_n \, d\sigma_x, \tag{3.37}
$$

where $\psi^k_n = \psi^k_{i,n} - \psi^k_{e,n}$ for $k = 1, 2$ and $\Psi_n = \Psi^1_{i,n} - \Psi^2_{i,n}$.

Next, we substitute $\varphi^k_{i,n} = u^k_{i,n}$, $\varphi_{e,n} = u_{e,n}$ and $e^k_n = \varepsilon \alpha_4 w^k_n$, respectively, in (3.36)-(3.37) to get the following equality:

$$
\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\Bigg[\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\left|\sqrt{\varepsilon}v_n^k\right|^2\,d\sigma_x+\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\left|\sqrt{\delta_n}\overline{u}_{i,n}^k\right|^2\,d\sigma_x+\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\left|\sqrt{\delta_n}\overline{u}_{e,n}^k\right|^2\,d\sigma_x\\
&\quad+\frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}}\left|\sqrt{\varepsilon}s_n\right|^2\,d\sigma_x+\sum_{k=1,2}\int_{\Gamma_\varepsilon^{1,2}}\left|\sqrt{\delta_n}\overline{\overline{u}}_{i,n}^k\right|^2\,d\sigma_x\\
&\quad+\sum_{k=1,2}\int_{\Omega_{i,\varepsilon}^k}\left|\sqrt{\delta_n}u_{i,n}^k\right|^2\,dx+\int_{\Omega_{e,\varepsilon}}\left|\sqrt{\delta_n}u_{e,n}\right|^2\,dx\Bigg]\\
&\quad+\sum_{k=1,2}\int_{\Omega_{i,\varepsilon}^k}\mathrm{M}_i^\varepsilon\nabla u_{i,n}^k\cdot\nabla u_{i,n}^k\,dx+\int_{\Omega_{e,\varepsilon}}\mathrm{M}_e^\varepsilon\nabla u_{e,n}\cdot\nabla u_{e,n}\,dx\\
&\quad+\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\varepsilon\mathcal{I}_{ion}\left(v_n^k,w_n^k\right)v_n^k\,d\sigma_x+\frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}}\varepsilon\mathcal{I}_{gap}\left(s_n\right)s_n\,d\sigma_x\\
&=\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\varepsilon\mathcal{I}_{app,\varepsilon}^k v_n^k\,d\sigma_x,
\end{aligned}
\tag{3.38}
$$

$$
\frac{\alpha_4}{2}\frac{d}{dt}\int_{\Gamma_\varepsilon^k}\left|\sqrt{\varepsilon}w_n^k\right|^2\,d\sigma_x=\int_{\Gamma_\varepsilon^k}\varepsilon\alpha_4 H\left(v_n^k,w_n^k\right)w_n^k\,d\sigma_x,\ \text{for } k=1,2. \tag{3.39}
$$

Integrating (3.38)-(3.39) over $(0,t)$ for $t\in(0,t_0]$ in each equation and then summing the resulting equations, we procure the following equality using the assumption (3.5) on $\mathcal{I}_{ion}$:

$$
\begin{aligned}
&\frac{1}{2}\Bigg[\sum_{k=1,2}\left\|\sqrt{\varepsilon}v_n^k\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\alpha_4\sum_{k=1,2}\left\|\sqrt{\varepsilon}w_n^k\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\frac{1}{2}\left\|\sqrt{\varepsilon}s_n\right\|^2_{L^2(\Gamma_\varepsilon^{1,2})}\\
&\quad+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{u}_{i,n}^k\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{u}_{e,n}^k\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{\overline{u}}_{i,n}^k\right\|^2_{L^2(\Gamma_\varepsilon^{1,2})}\\
&\quad+\sum_{k=1,2}\left\|\sqrt{\delta_n}u_{i,n}^k\right\|^2_{L^2(\Omega_{i,\varepsilon}^k)}+\left\|\sqrt{\delta_n}u_{e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon})}\Bigg]\\
&\quad+\sum_{k=1,2}\int_0^t\int_{\Omega_{i,\varepsilon}^k}\mathrm{M}_i^\varepsilon\nabla u_{i,n}^k\cdot\nabla u_{i,n}^k\,dxd\tau+\int_0^t\int_{\Omega_{e,\varepsilon}}\mathrm{M}_e^\varepsilon\nabla u_{e,n}\cdot\nabla u_{e,n}\,dxd\tau\\
&\quad+\sum_{k=1,2}\int_0^t\int_{\Gamma_\varepsilon^k}\varepsilon\tilde{\mathrm{I}}_{a,ion}\left(v_n^k\right)v_n^k\,d\sigma_xd\tau\\
&=\frac{1}{2}\Bigg[\sum_{k=1,2}\left\|\sqrt{\varepsilon}v_{0,n}^k\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\alpha_4\sum_{k=1,2}\left\|\sqrt{\varepsilon}w_{0,n}^k\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\frac{1}{2}\left\|\sqrt{\varepsilon}s_{0,n}\right\|^2_{L^2(\Gamma_\varepsilon^{1,2})}\\
&\quad+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{u}_{0,i,n}^k\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{u}_{0,e,n}^k\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{\overline{u}}_{0,i,n}^k\right\|^2_{L^2(\Gamma_\varepsilon^{1,2})}\\
&\quad+\sum_{k=1,2}\left\|\sqrt{\delta_n}u_{0,i,n}^k\right\|^2_{L^2(\Omega_{i,\varepsilon}^k)}+\left\|\sqrt{\delta_n}u_{0,e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon})}\Bigg]\\
&\quad-\frac{1}{2}\int_0^t\int_{\Gamma_\varepsilon^{1,2}}\varepsilon\mathcal{I}_{gap}\left(s_n\right)s_n\,d\sigma_xd\tau+\sum_{k=1,2}\int_0^t\int_{\Gamma_\varepsilon^k}\varepsilon\left(-\mathrm{I}_{b,ion}\left(w_n^k\right)v_n^k+\alpha_4H\left(v_n^k,w_n^k\right)w_n^k\right)\,d\sigma_xd\tau\\
&\quad+\sum_{k=1,2}\int_0^t\int_{\Gamma_\varepsilon^k}\varepsilon\left(\beta_1v_n^k+\beta_2\right)v_n^k\,d\sigma_xd\tau+\sum_{k=1,2}\int_0^t\int_{\Gamma_\varepsilon^k}\varepsilon\mathcal{I}_{app,\varepsilon}^kv_n^k\,d\sigma_xd\tau.
\end{aligned}
\tag{3.40}
$$

We denote by E_ℓ with $\ell=1,\dots,9$ the terms of the previous equation which is rewritten as follows (to respect the order):

$$E_1+E_2+E_3+E_4=E_5+E_6+E_7+E_8+E_9.$$

Now, we estimate E_ℓ for $\ell=2,\dots,9$ as follows:

- Due the uniform ellipticity (3.4) of M_j^ε for $j=i,e$, we have

$$E_2+E_3\geq\alpha\left(\sum_{k=1,2}\int_0^t\left\|\nabla u_{i,n}^k\right\|^2_{L^2(\Omega_{i,\varepsilon}^k)}\,d\tau+\int_0^t\left\|\nabla u_{e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon})}\,d\tau\right)\geq 0.$$

- Using the assumption (3.5d) on $\tilde{\mathrm{I}}_{a,ion}$, we deduce that $E_4\geq 0$.

- By the assumptions (3.11) on the initial data, we have $E_5 \leq C$ for some constant independent of n and ε.

- By the structure form of $\mathcal{I}_{gap}$ defined in (3.9), we obtain

$$E_6 \leq G_{gap} \int_0^t \left\| \sqrt{\varepsilon} s_n \right\|^2_{L^2(\Gamma_\varepsilon^{1,2})} \, d\tau.$$

- Using the assumption on $\mathrm{I}_{b,ion}$ and H defined as (3.5b), then we obtain

$$E_7 \leq \alpha_5 \sum_{k=1,2} \int_0^t \left\| \sqrt{\varepsilon} w_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} \, d\tau.$$

- It easy to estimate E_8 as follows

$$E_8 \leq C \sum_{k=1,2} \int_0^t \left\| \sqrt{\varepsilon} v_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} \, d\tau,$$

  with C is constant independent of n and ε.

- By Young's inequality with the uniform L^2 boundedness (3.10) of $\mathcal{I}^k_{app,\varepsilon}$, there exist constants $C_1, C_2 > 0$ independent of n and ε such that

$$E_9 \leq C_1 + C_2 \sum_{k=1,2} \int_0^t \left\| \sqrt{\varepsilon} v_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} \, d\tau.$$

Collecting all the estimates stated above, one obtains from (3.40) the following inequality for all $t \leq t_0$,

$$\begin{aligned} &\sum_{k=1,2} \left\| \sqrt{\varepsilon} v_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} + \sum_{k=1,2} \left\| \sqrt{\varepsilon} w_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} + \left\| \sqrt{\varepsilon} s_n \right\|^2_{L^2(\Gamma_\varepsilon^{1,2})} \\ &\leq C \left(1 + \sum_{k=1,2} \int_0^{t_0} \left\| \sqrt{\varepsilon} v_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} \, d\tau + \sum_{k=1,2} \int_0^{t_0} \left\| \sqrt{\varepsilon} w_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} \, d\tau + \int_0^{t_0} \left\| \sqrt{\varepsilon} s_n \right\|^2_{L^2(\Gamma_\varepsilon^{1,2})} \, d\tau \right). \end{aligned} \tag{3.41}$$

By an application of Gronwall's lemma in the last inequality, one gets

$$\sum_{k=1,2} \left\| \sqrt{\varepsilon} v_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} + \sum_{k=1,2} \left\| \sqrt{\varepsilon} w_n^k \right\|^2_{L^2(\Gamma_\varepsilon^k)} + \left\| \sqrt{\varepsilon} s_n \right\|^2_{L^2(\Gamma_\varepsilon^{1,2})} \leq C.$$

Hence, we conclude that

$$\sum_{k=1,2}\left\|\sqrt{\varepsilon}v_n^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^k)\right)}+\sum_{k=1,2}\left\|\sqrt{\varepsilon}w_n^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^k)\right)}+\left\|\sqrt{\varepsilon}s_n\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^{1,2})\right)}\leq C.$$

Then, we can deduce from this inequality that our approximate weak solution of the microscopic tridomain problem is global on $(0,T)$.

Moreover, one can obtain by exploiting this last inequality along with (3.40) the following a priori estimates for some constant $C>0$ not depending on n and ε:

$$\begin{aligned}\sum_{k=1,2}\left\|\sqrt{\varepsilon}v_n^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^k)\right)}&+\sum_{k=1,2}\left\|\sqrt{\varepsilon}w_n^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^k)\right)}+\left\|\sqrt{\varepsilon}s_n\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^{1,2})\right)}\\&+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{u}_{i,n}^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^{1,2})\right)}+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{u}_{e,n}^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^k)\right)}\\&\quad+\sum_{k=1,2}\left\|\sqrt{\delta_n}\overline{\overline{u}}_{i,n}^k\right\|^2_{L^\infty\left(0,T;L^2(\Gamma_\varepsilon^k)\right)}\leq C,\end{aligned}\tag{3.42}$$

$$\sum_{k=1,2}\left\|\nabla u_{i,n}^k\right\|^2_{L^2(\Omega_{i,\varepsilon,T}^k)}+\left\|\nabla u_{e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon,T})}\leq C,\tag{3.43}$$

$$\sum_{k=1,2}\left\|\varepsilon\tilde{\mathrm{I}}_{a,ion}\left(v_n^k\right)v_n^k\right\|_{L^1(\Gamma_{\varepsilon,T}^k)}\leq C.\tag{3.44}$$

$$\sum_{k=1,2}\left\|\sqrt{\varepsilon}v_n^k\right\|^2_{L^2(\Gamma_{\varepsilon,T}^k)}+\sum_{k=1,2}\left\|\sqrt{\varepsilon}w_n^k\right\|^2_{L^2(\Gamma_{\varepsilon,T}^k)}+\left\|\sqrt{\varepsilon}s_n\right\|^2_{L^2(\Gamma_{\varepsilon,T}^{1,2})}\leq C,\tag{3.45}$$

for some constant $C>0$ not depending on n and ε.

Furthermore, we deduce from (3.44) together with assumption (3.5d) on $\tilde{\mathrm{I}}_{a,ion}$ the following estimation:

$$\sum_{k=1,2}\left\|\varepsilon^{1/r}v_n^k\right\|^r_{L^r(\Gamma_{\varepsilon,T}^k)}\leq C,\tag{3.46}$$

for some constant $C>0$ not depending on n and ε. The second estimate (3.17) in Theorem 3.1 is a direct consequence of (3.46) and assumption (3.5a) on $\mathrm{I}_{a,ion}$.

It remains to estimate on the L^2 norms of the intracellular and extracellular potentials which are need to complete the proof of Estimate (3.16) on H^1. To do this end, we will use the next lemma, which is a consequence of the uniform Poincaré-Wirtinger's inequality and the trace theorem for ε-periodic surfaces.

Lemma 3.3. *Let* $u_i^k\in H^1\left(\Omega_{i,\varepsilon}^k\right)$ *for* $k=1,2$ *and* $u_e\in H^1\left(\Omega_{e,\varepsilon}\right)$. *Set* $v^k:=\left(u_i^k-u_e\right)|_{\Gamma_\varepsilon^k}$

for $k = 1, 2$. Assume that the condition (3.12) holds, then there exists a positive constants C, independent of ε, such that

$$\left\|u_i^k\right\|^2_{L^2(\Omega^k_{i,\varepsilon})} \leq C\left(\left\|\sqrt{\varepsilon}v^k\right\|^2_{L^2(\Gamma^k_\varepsilon)} + \left\|\nabla u_i^k\right\|^2_{L^2(\Omega^k_{i,\varepsilon})} + \left\|\nabla u_e\right\|^2_{L^2(\Omega_{e,\varepsilon})}\right), \text{ with } k = 1, 2. \tag{3.47}$$

Proof. We follow the same idea to the proof of Lemma 3.7 in [GK19]. Due the normalization condition (3.12), Poincaré-Wirtinger's inequality implies that

$$\left\|u_{e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon})} \leq C\left\|\nabla u_{e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon})}, \tag{3.48}$$

for some constant C independent on n and ε. Note that in the sequel C is a generic constant whose value can change from one line to another.
To estimate on the L^2 norms of $u^k_{i,n}$ for $k = 1, 2$, we write

$$u^k_{i,n} = \widehat{u}^k_{i,n} + \widetilde{u}^k_{i,n},$$

where $\widetilde{u}^k_{i,n} := \dfrac{1}{\left|\Omega^k_{i,\varepsilon}\right|}\displaystyle\int_{\Omega^k_{i,\varepsilon}} u^k_{i,n}dx$ is constant in $\Omega^k_{i,\varepsilon}$ and $\widehat{u}^k_{i,n} := u^k_{i,n} - \widetilde{u}^k_{i,n}$ has zero mean in $\Omega^k_{i,\varepsilon}$.
Clearly, we see that for $k = 1, 2$

$$\left\|u^k_{i,n}\right\|^2_{L^2\left(\Omega^k_{i,\varepsilon}\right)} = \left\|\widehat{u}^k_{i,n}\right\|^2_{L^2\left(\Omega^k_{i,\varepsilon}\right)} + \left\|\widetilde{u}^k_{i,n}\right\|^2_{L^2\left(\Omega^k_{i,\varepsilon}\right)}.$$

In view of Poincaré-Wirtinger's inequality, one has

$$\left\|\widehat{u}^k_{i,n}\right\|^2_{L^2\left(\Omega^k_{i,\varepsilon}\right)} \leq C\left\|\nabla\widehat{u}^k_{i,n}\right\|^2_{L^2\left(\Omega^k_{i,\varepsilon}\right)} = C\left\|\nabla u^k_{i,n}\right\|^2_{L^2\left(\Omega^k_{i,\varepsilon}\right)} \text{ for } k = 1, 2. \tag{3.49}$$

Let us bound now $\left\|\widetilde{u}^k_{i,n}\right\|^2_{L^2\left(\Omega^k_{i,\varepsilon}\right)} = \dfrac{\left|\Omega^k_{i,\varepsilon}\right|}{\left|\Gamma^k_\varepsilon\right|}\left\|\widetilde{u}^k_{i,n}\right\|^2_{L^2\left(\Gamma^k_\varepsilon\right)}$ for $k = 1, 2$. Since $\left|\Gamma^k_\varepsilon\right| = \varepsilon^{-1}\left|\Gamma^k\right|$ and $\left|\Omega^k_{i,\varepsilon}\right| \leq |\Omega|$, we deduce that

$$\left\|\widetilde{u}^k_{i,n}\right\|^2_{L^2\left(\Omega^k_{i,\varepsilon}\right)} \leq C\varepsilon\left\|\widetilde{u}^k_{i,n}\right\|^2_{L^2\left(\Gamma^k_\varepsilon\right)}, \text{ for } k = 1, 2.$$

It easy to check that

$$\left|\widetilde{u}^k_{i,n}\right|^2 \leq C\left(\left|u^k_{i,n} - u_{e,n}\right|^2 + \left|\widehat{u}^k_{i,n}\right|^2 + \left|u_{e,n}\right|^2\right).$$

Finally, we obtain for $k = 1, 2$

$$\begin{aligned}
\left\| \widetilde{u}_{i,n}^k \right\|^2_{L^2\left(\Omega_{i,\varepsilon}^k\right)} &\leq C \left(\varepsilon \left\| v_n^k \right\|^2_{L^2\left(\Gamma_\varepsilon^k\right)} + \varepsilon \left\| \widehat{u}_{i,n}^k \right\|^2_{L^2\left(\Gamma_\varepsilon^k\right)} + \varepsilon \left\| u_{e,n} \right\|^2_{L^2\left(\Gamma_\varepsilon^k\right)} \right) \\
&\leq C\varepsilon \left\| v_n^k \right\|^2_{L^2\left(\Gamma_\varepsilon^k\right)} \\
&\quad + C \left(\left\| \widehat{u}_{i,n}^k \right\|^2_{L^2\left(\Omega_{i,\varepsilon}^k\right)} + \varepsilon^2 \left\| \nabla \widehat{u}_{i,n}^k \right\|^2_{L^2\left(\Omega_{i,\varepsilon}^k\right)} \right) \\
&\quad + C \left(\left\| u_{e,n} \right\|^2_{L^2(\Omega_{e,\varepsilon})} + \varepsilon^2 \left\| \nabla u_{e,n} \right\|^2_{L^2(\Omega_{e,\varepsilon})} \right) \\
&\leq C \left(\left\| \sqrt{\varepsilon} v_n^k \right\|^2_{L^2\left(\Gamma_\varepsilon^k\right)} + \left\| \nabla u_{i,n}^k \right\|^2_{L^2\left(\Omega_{i,\varepsilon}^k\right)} + \left\| \nabla u_{e,n} \right\|^2_{L^2(\Omega_{e,\varepsilon})} \right),
\end{aligned}$$

where the second inequality is a direct consequence of the trace theorem and the final one is a result of (3.48) and (3.49). This completes the proof of this lemma. □

Now, Estimate (3.43) and (3.47) imply that

$$\left\| u_{e,n} \right\|_{L^2(0,T;H^1(\Omega_{e,\varepsilon}))} \leq C, \tag{3.50}$$

for some constant C independent on n and ε. Furthermore, we have $\left\| \sqrt{\varepsilon} v_n^k \right\|^2_{L^2(\Gamma_{\varepsilon,T}^k)} \leq C$ for $k = 1, 2$. Then Estimates (3.47), (3.43) and (3.50) ensure that for $k = 1, 2$,

$$\left\| u_{i,n}^k \right\|_{L^2\left(0,T;H^1(\Omega_{i,\varepsilon}^k)\right)} \leq C. \tag{3.51}$$

This completes the proof of (3.15)-(3.17) in Theorem 3.1.

Now we turn to find some uniform estimates on the time derivatives by following [BK06] which will be useful for the passage to the limit. We notice first for $k = 1, 2$ that,

$$\begin{aligned}
&\iint_{\Omega_{i,\varepsilon,T}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,n}^k \cdot \nabla \left(\partial_t u_{i,n}^k \right) \, dx = \frac{1}{2} \int_0^T \partial_t \left(\int_{\Omega_{i,\varepsilon}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,n}^k \cdot \nabla u_{i,n}^k \, dx \right) dt \\
&= \frac{1}{2} \left[\int_{\Omega_{i,\varepsilon}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,n}^k(T,\cdot) \cdot \nabla u_{i,n}^k(T,\cdot) \, dx - \int_{\Omega_{i,\varepsilon}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,n}^k(0,\cdot) \cdot \nabla u_{i,n}^k(0,\cdot) \, dx \right],
\end{aligned}$$

and

$$\iint_{\Gamma^k_{\varepsilon,T}} \mathrm{I}_{a,ion}\left(v_n^k\right)\partial_t v_n^k \, d\sigma_x dt = \int_0^T \partial_t \left(\int_{\Gamma^k_\varepsilon}\int_0^{v_n^k} \mathrm{I}_{a,ion}\left(\tilde{v}_n^k\right)\, d\tilde{v}_n^k d\sigma_x\right) dt$$
$$= \int_{\Gamma^k_\varepsilon}\int_0^{v_n^k(T,\cdot)} \mathrm{I}_{a,ion}\left(v_n^k\right)\, dv_n^k d\sigma_x - \int_{\Gamma^k_\varepsilon}\int_0^{v_n^k(0,\cdot)} \mathrm{I}_{a,ion}\left(v_n^k\right)\, dv_n^k d\sigma_x.$$

Next, we substitute $\varphi^k_{i,n} = \partial_t u^k_{i,n}$, $\varphi_{e,n} = \partial_t u_{e,n}$ and $e^k_n = \varepsilon\alpha_4\partial_t w^k_n$, respectively, in (3.36)-(3.37) then integrate in time to deduce using the previous equalities:

$$\begin{aligned}
&\sum_{k=1,2}\left\|\sqrt{\varepsilon}\partial_t v_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \alpha_4\sum_{k=1,2}\left\|\sqrt{\varepsilon}\partial_t w_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \frac{1}{2}\left\|\sqrt{\varepsilon}\partial_t s_n\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})}\\
&\quad + \sum_{k=1,2}\left\|\sqrt{\delta_n}\partial_t \overline{u}^k_{i,n}\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \sum_{k=1,2}\left\|\sqrt{\delta_n}\partial_t \overline{u}^k_{e,n}\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \sum_{k=1,2}\left\|\sqrt{\delta_n}\partial_t \overline{\overline{u}}^k_{i,n}\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})}\\
&\quad + \sum_{k=1,2}\left\|\sqrt{\delta_n}\partial_t u^k_{i,n}\right\|^2_{L^2(\Omega^k_{i,\varepsilon,T})} + \left\|\sqrt{\delta_n}\partial_t u_{e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon,T})}\\
&\quad + \frac{1}{2}\Bigg[\sum_{k=1,2}\int_{\Omega^k_{i,\varepsilon}} \mathrm{M}^\varepsilon_i\nabla u^k_{i,n}\cdot\nabla u^k_{i,n}(T,\cdot)\,dx + \int_{\Omega_{e,\varepsilon}} \mathrm{M}^\varepsilon_e\nabla u_{e,n}(T,\cdot)\cdot\nabla u_{e,n}(T,\cdot)\,dx\\
&\quad + \sum_{k=1,2}\int_{\Gamma^k_\varepsilon}\int_0^{v_n^k(T,\cdot)} \varepsilon\tilde{\mathrm{I}}_{a,ion}\left(v_n^k\right)\, dv_n^k d\sigma_x\Bigg]\\
&= \frac{1}{2}\Bigg[\sum_{k=1,2}\int_{\Omega^k_{i,\varepsilon}} \mathrm{M}^\varepsilon_i\nabla u^k_{i,n}(0,\cdot)\cdot\nabla u^k_{i,n}(0,\cdot)\,dx + \int_{\Omega_{e,\varepsilon}} \mathrm{M}^\varepsilon_e\nabla u_{e,n}(0,\cdot)\cdot\nabla u_{e,n}(0,\cdot)\,dx\\
&\quad + \sum_{k=1,2}\int_{\Gamma^k_\varepsilon}\int_0^{v_n^k(0,\cdot)} \varepsilon\mathrm{I}_{a,ion}\left(v_n^k\right)\, dv_n^k d\sigma_x + \sum_{k=1,2}\int_{\Gamma^k_\varepsilon}\int_0^{v_n^k(T,\cdot)} \varepsilon\left(\beta_1 v_n^k + \beta_2\right)\, dv_n^k d\sigma_x\Bigg]\\
&\quad - \frac{1}{2}\iint_{\Gamma^{1,2}_{\varepsilon,T}} \varepsilon\mathcal{I}_{gap}\left(s_n\right)\partial_t s_n\, d\sigma_x d\tau + \sum_{k=1,2}\int_{\Gamma^k_{\varepsilon,T}} \varepsilon\left(-\mathrm{I}_{b,ion}\left(w_n^k\right)\partial_t v_n^k + \alpha_4 H\left(v_n^k, w_n^k\right)\partial_t w_n^k\right)\, d\sigma_x d\tau\\
&\quad + \sum_{k=1,2}\int_{\Gamma^k_{\varepsilon,T}} \varepsilon\mathcal{I}^k_{app,\varepsilon}\partial_t v_n^k\, d\sigma_x d\tau.
\end{aligned} \tag{3.52}$$

We denote by E'_ℓ with $\ell = 1,\ldots,6$ the terms of the previous equation which is rewritten as follows (to respect the order):

$$E'_1 + E'_2 = E'_3 + E'_4 + E'_5 + E'_6,$$

where

$$E'_1 := \sum_{k=1,2} \left\|\sqrt{\varepsilon}\partial_t v_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \alpha_4 \sum_{k=1,2} \left\|\sqrt{\varepsilon}\partial_t w_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \frac{1}{2}\left\|\sqrt{\varepsilon}\partial_t s_n\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})}$$
$$+ \sum_{k=1,2} \left\|\sqrt{\delta_n}\partial_t \overline{u}^k_{i,n}\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \sum_{k=1,2} \left\|\sqrt{\delta_n}\partial_t \overline{u}^k_{e,n}\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \sum_{k=1,2} \left\|\sqrt{\delta_n}\partial_t \overline{\overline{u}}^k_{i,n}\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})}$$
$$+ \sum_{k=1,2} \left\|\sqrt{\delta_n}\partial_t u^k_{i,n}\right\|^2_{L^2(\Omega^k_{i,\varepsilon,T})} + \left\|\sqrt{\delta_n}\partial_t u_{e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon,T})}.$$

Now, we estimate E'_ℓ for $\ell = 2, \dots, 6$ as follows:

- Due the uniform ellipticity (3.4) of M^ε_j for $j = i, e$, with the monotonicity (3.5d) on $\tilde{\mathrm{I}}_{a,ion}$, then we have

$$E'_2 \geq \alpha \left(\sum_{k=1,2} \left\|\nabla u^k_{i,n}(T,\cdot)\right\|^2_{L^2(\Omega^k_{i,\varepsilon})} + \|\nabla u_{e,n}(T,\cdot)\|^2_{L^2(\Omega_{e,\varepsilon})} \right)$$
$$+ \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \int_0^{v^k_n(T,\cdot)} \varepsilon \tilde{\mathrm{I}}_{a,ion}\left(v^k_n(T,\cdot)\right) \, d\sigma_x dv^k_n \geq 0.$$

- Furthermore, using the a priori estimate (3.42) with the assumption on $\mathrm{I}_{a,ion}$ and on the initial data, one gets

$$E'_3 \leq \beta \left(\sum_{k=1,2} \left\|\nabla u^k_{i,n}(0,\cdot)\right\|^2_{L^2(\Omega^k_{i,\varepsilon})} + \|\nabla u_{e,n}(0,\cdot)\|^2_{L^2(\Omega_{e,\varepsilon})} \right)$$
$$+ \alpha_1 \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \varepsilon \left(\left|v^k_n(0,\cdot)\right|^r + \left|v^k_n(0,\cdot)\right| \right) d\sigma_x$$
$$+ \frac{\beta_1}{2} \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \varepsilon \left|v^k_n(T,\cdot)\right|^2 d\sigma_x + \beta_2 \sum_{k=1,2} \int_{\Gamma^k_\varepsilon} \varepsilon \left|v^k_n(T,\cdot)\right| d\sigma_x \leq C_3$$

  for some constant C_3 independent of n and ε.

- By the structure form of $\mathcal{I}_{gap}$ defined in (3.9), we obtain using Young's inequality with estimate (3.45)

$$E'_4 \leq \frac{G_{gap}}{2} \left\|\sqrt{\varepsilon} s_n\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})} + \frac{1}{4}\left\|\sqrt{\varepsilon}\partial_t s_n\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})}.$$
$$\leq C_4 + \frac{1}{4}\left\|\sqrt{\varepsilon}\partial_t s_n\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})}$$

  with C_4 independent of n and ε.

- Similarly, using the assumption on $\mathrm{I}_{b,ion}$ and H defined as (3.5a)-(3.5b), then we obtain using Young's inequality with the estimate (3.45)

$$E_5' \leq C_5 + \frac{1}{2}\sum_{k=1,2}\left(\left\|\sqrt{\varepsilon}\partial_t v_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \left\|\sqrt{\varepsilon}\partial_t w_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon})}\right)$$

  with C_5 independent of n and ε.

- By Young's inequality with the uniform L^2 boundedness (3.10) of $\mathcal{I}^k_{app,\varepsilon}$, there exist constants $C_1, C_2 > 0$ independent of n and ε such that

$$E_6' \leq C_6 + \frac{1}{2}\sum_{k=1,2}\left\|\sqrt{\varepsilon}\partial_t v_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})},$$

  with C_6 independent of n and ε.

Exploiting all this estimates along with (3.52), one obtains

$$\begin{aligned}
&\sum_{k=1,2}\left\|\sqrt{\varepsilon}\partial_t v_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \alpha_4\sum_{k=1,2}\left\|\sqrt{\varepsilon}\partial_t w_n^k\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \left\|\sqrt{\varepsilon}\partial_t s_n\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})}\\
&\quad + \sum_{k=1,2}\left\|\sqrt{\delta_n}\partial_t \overline{u}^k_{i,n}\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \sum_{k=1,2}\left\|\sqrt{\delta_n}\partial_t \overline{u}^k_{e,n}\right\|^2_{L^2(\Gamma^k_{\varepsilon,T})} + \sum_{k=1,2}\left\|\sqrt{\delta_n}\partial_t \overline{\overline{u}}^k_{i,n}\right\|^2_{L^2(\Gamma^{1,2}_{\varepsilon,T})} \\
&\quad + \sum_{k=1,2}\left\|\sqrt{\delta_n}\partial_t u^k_{i,n}\right\|^2_{L^2(\Omega^k_{i,\varepsilon,T})} + \left\|\sqrt{\delta_n}\partial_t u_{e,n}\right\|^2_{L^2(\Omega_{e,\varepsilon,T})} \leq C
\end{aligned} \tag{3.53}$$

for some constant $C > 0$ not depending on n and ε.

The next steps is devoted to completing the proof of Theorem 3.1 and to passing to the limit when n goes to infinity. Further, it treat the uniqueness of the weak solutions to System (3.1)-(3.3)

Step 4: Passage to the limit and global existence of solutions

In view of (3.50)-(3.51), we can see that v_n^k, $\overline{u}^k_{j,n}$ are bounded in $L^2\left(0,T;H^{1/2}(\Gamma^k_{\varepsilon})\right)$ for $j = i,e$ and $k = 1,2$ using the standard trace lemma. Similarly, it easy to check that s_n and $\overline{\overline{u}}^k_{i,n}$ are bounded in $L^2\left(0,T;H^{1/2}(\Gamma^{1,2}_{\varepsilon})\right)$ for $k = 1,2$. Furthermore, we deduce from (3.53) the uniform bound on $\partial_t v_n^k$ in $L^2(\Gamma^k_{\varepsilon,T})$ for $k = 1,2$ and the uniform bound on $\partial_t s_n$ in $L^2(\Gamma^{1,2}_{\varepsilon,T})$.

Recall that by the Aubin-Lions compactness criterion, the following injection

$$\mathcal{W} := \left\{ u \in L^2 \left(0, T; H^{1/2}(\Gamma_\varepsilon)\right) \text{ and } \partial_t u \in L^2 \left(0, T; H^{-1/2}(\Gamma_\varepsilon)\right)\right\} \subset L^2(\Gamma_{\varepsilon,T})$$

is compact with $\Gamma_\varepsilon := \Gamma_\varepsilon^k, \Gamma_\varepsilon^{1,2}$ for $k = 1, 2$. Hence, we can assume there exist limit functions $u_{i,\varepsilon}^1$, $u_{i,\varepsilon}^2$, $u_{e,\varepsilon}$, v_ε^1, v_ε^2, s_ε, w_ε with $v_\varepsilon^k = \overline{u}_{i,\varepsilon}^k - \overline{u}_{e,\varepsilon}^k$ on $\Gamma_{\varepsilon,T}^k$ for $k = 1, 2$ and $s_\varepsilon = \overline{\overline{u}}_{i,\varepsilon}^1 - \overline{\overline{u}}_{i,\varepsilon}^2$ on $\Gamma_{\varepsilon,T}^{1,2}$, such that as $n \to \infty$ (for fixed ε and up to an unlabeled subsequence)

$$\begin{cases} v_n^k \to v_\varepsilon^k \text{ a.e. in } \Gamma_\varepsilon^k, \text{ strongly in } L^2(\Gamma_{\varepsilon,T}^k), \\ \text{ and weakly } L^2 \left(0, T; H^{1/2}(\Gamma_\varepsilon^k)\right) \text{ for } k = 1, 2, \\ s_n \to s_\varepsilon \text{ a.e. in } \Gamma_\varepsilon^{1,2}, \text{ strongly in } L^2(\Gamma_{\varepsilon,T}^{1,2}), \\ \text{ and weakly } L^2 \left(0, T; H^{1/2}(\Gamma_\varepsilon^{1,2})\right), \\ w_n^k \rightharpoonup w_\varepsilon^k \text{ weakly in } L^2(\Gamma_{\varepsilon,T}^k), \\ u_{i,n}^k \rightharpoonup u_{i,\varepsilon}^k \text{ weakly in } L^2 \left(0, T; H^1(\Omega_{i,\varepsilon}^k)\right) \text{ for } k = 1, 2, \\ u_{e,n} \rightharpoonup u_{e,\varepsilon} \text{ weakly in } L^2 \left(0, T; H^1(\Omega_{e,\varepsilon})\right), \\ \mathrm{I}_{a,ion} \left(v_n^k\right) \to \mathrm{I}_{a,ion} \left(v_\varepsilon^k\right) \text{ a.e. in } \Gamma_\varepsilon^k, \text{ weakly in } L^{r/(r-1)}(\Gamma_{\varepsilon,T}^k), \end{cases} \tag{3.54}$$

and

$$\begin{cases} \partial_t v_n^k \rightharpoonup \partial_t v_\varepsilon^k \text{ weakly in } L^2(\Gamma_{\varepsilon,T}^k), \\ \partial_t w_n^k \rightharpoonup \partial_t w_\varepsilon^k \text{ weakly in } L^2(\Gamma_{\varepsilon,T}^k) \text{ for } k = 1, 2, \\ \partial_t s_n \rightharpoonup \partial_t s_\varepsilon \text{ weakly in } L^2(\Gamma_{\varepsilon,T}^{1,2}). \end{cases} \tag{3.55}$$

Moreover, using again estimate (3.53), we get for $j = i, e$ and $k = 1, 2$,

$$\begin{cases} \sqrt{\delta_n} \partial_t \overline{u}_{j,\varepsilon}^k \rightharpoonup 0 \text{ in } D' \left(0, T; L^2(\Gamma_\varepsilon^k)\right) \text{ for } j = i, e, \\ \\ \sqrt{\delta_n} \partial_t \overline{\overline{u}}_{i,\varepsilon}^k \rightharpoonup 0 \text{ in } D' \left(0, T; L^2(\Gamma_\varepsilon^{1,2})\right), \ \sqrt{\delta_n} \partial_t u_{i,\varepsilon}^k \rightharpoonup 0 \text{ in } D' \left(0, T; L^2(\Omega_{i,\varepsilon}^k)\right), \\ \\ \text{and } \sqrt{\delta_n} \partial_t u_{e,\varepsilon} \rightharpoonup 0 \text{ in } D' \left(0, T; L^2(\Omega_{e,\varepsilon})\right). \end{cases} \tag{3.56}$$

The last difficulty is to prove that the nonlinear term $\mathrm{I}_{a,ion} \left(v_n^k\right)$ converges weakly to the term $\mathrm{I}_{a,ion} \left(v_\varepsilon^k\right)$ for $k = 1, 2$. Since v_n^k converges strongly to v_ε^k in $L^2(\Gamma_{\varepsilon,T}^k)$, we can extract a subsequence, such that v_n^k converges almost everywhere to v_ε^k in Γ_ε^k for $k = 1, 2$. Moreover, since $\mathrm{I}_{a,ion}$ is continuous, we have

$$\mathrm{I}_{a,ion}\left(v_n^k\right) \to \mathrm{I}_{a,ion}\left(v_\varepsilon^k\right) \text{ a.e. in } \Gamma_\varepsilon^k \text{ for } k=1,2. \tag{3.57}$$

However, using a classical result (see Lemma 1.3 in [Lio69]):

$$\mathrm{I}_{a,ion}\left(v_n^k\right) \rightharpoonup \mathrm{I}_{a,ion}\left(v_\varepsilon^k\right), \text{ weakly in } L^{r/(r-1)}(\Gamma_{\varepsilon,T}^k) \text{ for } k=1,2. \tag{3.58}$$

Remark 3.9. *By our choice of basis, it is clear that $\overline{u}_{j,n}^k(0,x) \to \overline{u}_{0,j,\varepsilon}^k$ in $L^2(\Gamma_\varepsilon^k)$ for $k=1,2$ and $j=i,e$. Furthermore, we have $\overline{\overline{u}}_{i,n}^k(0,x) \to \overline{\overline{u}}_{0,i,\varepsilon}^k$ in $L^2(\Gamma_\varepsilon^k)$ for $k=1,2$.*

Keeping in mind (3.54)-(3.58), we obtain by letting $n\to\infty$ in the weak formulation (3.36)-(3.37)

$$\begin{aligned}
&\sum_{k=1,2}\int_{\Gamma_\varepsilon^k} \varepsilon\partial_t v_\varepsilon^k \psi^k \, d\sigma_x + \frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}} \varepsilon\partial_t s_\varepsilon \Psi \, d\sigma_x \\
&\quad + \sum_{k=1,2}\int_{\Omega_{i,\varepsilon}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k \cdot \nabla\varphi_i^k \, dx + \int_{\Omega_{e,\varepsilon}} \mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon} \cdot \nabla\varphi_e \, dx \\
&\quad + \sum_{k=1,2}\int_{\Gamma_\varepsilon^k} \varepsilon\mathcal{I}_{ion}\left(v_\varepsilon^k, w_\varepsilon^k\right)\psi^k \, d\sigma_x + \frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}} \varepsilon\mathcal{I}_{gap}\left(s_\varepsilon\right)\Psi \, d\sigma_x \\
&= \sum_{k=1,2}\int_{\Gamma_\varepsilon^k} \varepsilon\mathcal{I}_{app,\varepsilon}^k \psi^k \, d\sigma_x,
\end{aligned} \tag{3.59}$$

$$\int_{\Gamma_\varepsilon^k} \partial_t w_\varepsilon^k e^k \, d\sigma_x = \int_{\Gamma_\varepsilon^k} H\left(v_\varepsilon^k, w_\varepsilon^k\right) e^k \, d\sigma_x, \tag{3.60}$$

for all $\varphi_i^k \in H^1(\Omega_{i,\varepsilon}^k)$, $\varphi_e \in H^1(\Omega_{e,\varepsilon})$ with $\psi^k = \psi_i^k - \psi_e^k \in H^{1/2}(\Gamma_\varepsilon^k) \cap L^r(\Gamma_\varepsilon^k)$ for $k=1,2$, $\Psi = \Psi_i^1 - \Psi_i^2 \in L^2(\Gamma_\varepsilon^{1,2})$ and $e^k \in L^2(\Gamma_\varepsilon^k)$ for $k=1,2$. Finally, it only remains to be proved that v_ε^k, w_ε^k for $k=1,2$ and s_ε satisfy the initial conditions stated in Definition 3.1. Using the weak formulation (3.32)-(3.34), we see that $v_\varepsilon^k(0,x) = v_{0,\varepsilon}^k(x)$ a.e. on $\Gamma_{\varepsilon,T}^k$, since, by construction, $\overline{u}_{j,n}^k(0,x) \to \overline{u}_{0,j,\varepsilon}^k$ in $L^2(\Gamma_\varepsilon^k)$ for $k=1,2$ and $j=i,e$. The same argument holds for w_ε^k for $k=1,2$ and s_ε.

Step 5: Uniqueness of solutions

This step prove that there there exists at most one weak solution of (3.59)-(3.60). We assume that $u^\ell = \left(u_{i,\varepsilon}^{1,\ell}, u_{i,\varepsilon}^{2,\ell}, u_{e,\varepsilon}^\ell, w_\varepsilon^{1,\ell}, w_\varepsilon^{2,\ell}\right)$, $\ell \in \{\ell', \ell''\}$ are two weak solutions in the sense of Definition 3.1 with same initial data. Thus, this weak formulations hold respectively for $u_{i,\varepsilon}^{k,\ell'} - u_{i,\varepsilon}^{k,\ell''}$ and $w_\varepsilon^{k,\ell'} - w_\varepsilon^{k,\ell''}$ for $k=1,2$.

Firstly, we substitute $\varphi_i^k = u_{i,\varepsilon}^{k,\ell'} - u_{i,\varepsilon}^{k,\ell''}$, $\varphi_e = u_{e,\varepsilon}^{\ell'} - u_{e,\varepsilon}^{\ell''}$, and $e^k = \varepsilon\left(w_\varepsilon^{k,\ell'} - w_\varepsilon^{k,\ell''}\right)$, $k = 1, 2$, respectively in (3.59)-(3.60). Then, we add the resulting equations and integrate over $(0, t)$ for $0 < t \leq T$ to get

$$\begin{aligned}
&\frac{1}{2}\left[\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\left(\varepsilon\left|\left(v_\varepsilon^{k,\ell'} - v_\varepsilon^{k,\ell''}\right)(t,\cdot)\right|^2 + \varepsilon\left|\left(w_\varepsilon^{k,\ell'} - w_\varepsilon^{k,\ell''}\right)(t,\cdot)\right|^2\right)\, d\sigma_x\right.\\
&\quad\left. + \frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}} \varepsilon\left|\left(s_\varepsilon^{\ell'} - s_\varepsilon^{\ell''}\right)(t,\cdot)\right|^2\, d\sigma_x\right]\\
&\quad + \sum_{k=1,2}\iint_{\Omega_{i,\varepsilon,t}^k} \mathrm{M}_i^\varepsilon \nabla\left(u_{i,\varepsilon}^{k,\ell'} - u_{i,\varepsilon}^{k,\ell''}\right)\cdot\nabla\left(u_{i,\varepsilon}^{k,\ell'} - u_{i,\varepsilon}^{k,\ell''}\right)\, dx d\tau\\
&\quad + \iint_{\Omega_{e,\varepsilon,t}} \mathrm{M}_e^\varepsilon \nabla\left(u_{e,\varepsilon}^{\ell'} - u_{e,\varepsilon}^{\ell''}\right)\cdot\nabla\left(u_{e,\varepsilon}^{\ell'} - u_{e,\varepsilon}^{\ell''}\right)\, dx d\tau\\
&\quad + \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,t}^k} \varepsilon\left(\tilde{\mathrm{I}}_{a,ion}\left(v_\varepsilon^{k,\ell'}\right) - \tilde{\mathrm{I}}_{a,ion}\left(v_\varepsilon^{k,\ell''}\right)\right)\left(v_\varepsilon^{k,\ell'} - v_\varepsilon^{k,\ell''}\right)\, d\sigma_x d\tau\\
&= \frac{1}{2}\left[\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\left(\varepsilon\left|\left(v_{0,\varepsilon}^{k,\ell'} - v_{0,\varepsilon}^{k,\ell''}\right)\right|^2 + \varepsilon\left|\left(w_{0,\varepsilon}^{k,\ell'} - w_{0,\varepsilon}^{k,\ell''}\right)\right|^2\right)\, d\sigma_x\right.\\
&\quad\left. + \frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}} \varepsilon\left|\left(s_{0,\varepsilon}^{\ell'} - s_{0,\varepsilon}^{\ell''}\right)\right|^2\, d\sigma_x\right]\\
&\quad + \beta_1\sum_{k=1,2}\iint_{\Gamma_{\varepsilon,t}^k} \varepsilon\left(v_\varepsilon^{k,\ell'} - v_\varepsilon^{k,\ell''}\right)^2\, d\sigma_x d\tau\\
&\quad - \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,t}^k} \varepsilon \mathrm{I}_{b,ion}\left(w_\varepsilon^{k,\ell'} - w_\varepsilon^{k,\ell''}\right)\left(v_\varepsilon^{k,\ell'} - v_\varepsilon^{k,\ell''}\right)\, d\sigma_x d\tau\\
&\quad - \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,t}^k} \varepsilon\left(H\left(v_\varepsilon^{k,\ell'}, w_\varepsilon^{k,\ell'}\right) - H\left(v_\varepsilon^{k,\ell''}, w_\varepsilon^{k,\ell''}\right)\right)\left(w_\varepsilon^{k,\ell'} - w_\varepsilon^{k,\ell''}\right)\, d\sigma_x d\tau\\
&\quad - \frac{1}{2}\iint_{\Gamma_{\varepsilon,t}^{1,2}} \varepsilon\mathcal{I}_{gap}\left(s_\varepsilon^{\ell'} - s_\varepsilon^{\ell''}\right)\left(s_\varepsilon^{\ell'} - s_\varepsilon^{\ell''}\right)\, d\sigma_x d\tau\\
&\quad + \sum_{k=1,2}\iint_{\Gamma_{\varepsilon,t}^k} \varepsilon\mathcal{I}_{app,\varepsilon}^k\left(v_\varepsilon^{k,\ell'} - v_\varepsilon^{k,\ell''}\right)\, d\sigma_x d\tau.
\end{aligned}$$

Due the uniform ellipticity (3.4) of $\mathrm{M}_j^{\varepsilon}$ for $j = i, e$, we have

$$\begin{aligned}
&\sum_{k=1,2} \iint_{\Omega^k_{i,\varepsilon,t}} \mathrm{M}_i^{\varepsilon} \nabla \left(u^{k,\ell'}_{i,\varepsilon} - u^{k,\ell''}_{i,\varepsilon}\right) \cdot \nabla \left(u^{k,\ell'}_{i,\varepsilon} - u^{k,\ell''}_{i,\varepsilon}\right) \, dx d\tau \\
&\quad + \iint_{\Omega_{e,\varepsilon,t}} \mathrm{M}_e^{\varepsilon} \nabla \left(u^{\ell'}_{e,\varepsilon} - u^{\ell''}_{e,\varepsilon}\right) \cdot \nabla \left(u^{\ell'}_{e,\varepsilon} - u^{\ell''}_{e,\varepsilon}\right) \, dx d\tau \\
&\geq \alpha \left(\sum_{k=1,2} \left\| \nabla \left(u^{k,\ell'}_{i,\varepsilon} - u^{k,\ell''}_{i,\varepsilon}\right) \right\|^2_{L^2(\Omega^k_{i,\varepsilon,t})} + \left\| \nabla \left(u^{\ell'}_{e,\varepsilon} - u^{\ell''}_{e,\varepsilon}\right) \right\|^2_{L^2(\Omega_{e,\varepsilon,t})} \right) \geq 0.
\end{aligned}$$

Furthermore, thanks to the monotonicity assumption (3.5d) on $\tilde{\mathrm{I}}_{a,ion}$, we deduce that

$$\sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,t}} \varepsilon \left(\tilde{\mathrm{I}}_{a,ion}\left(v^{k,\ell'}_{\varepsilon}\right) - \tilde{\mathrm{I}}_{a,ion}\left(v^{k,\ell''}_{\varepsilon}\right) \right) \left(v^{k,\ell'}_{\varepsilon} - v^{k,\ell''}_{\varepsilon}\right) \, d\sigma_x d\tau \geq 0.$$

Moreover, by the linearity of $\mathrm{I}_{b,ion}$, H and $\mathcal{I}_{gap}$, we can deduce using Young's inequality the following estimation

$$\begin{aligned}
&\frac{1}{2} \Bigg[\sum_{k=1,2} \int_{\Gamma^k_{\varepsilon}} \left(\varepsilon \left| \left(v^{k,\ell'}_{\varepsilon} - v^{k,\ell''}_{\varepsilon}\right)(t,\cdot) \right|^2 + \varepsilon \left| \left(w^{k,\ell'}_{\varepsilon} - w^{k,\ell''}_{\varepsilon}\right)(t,\cdot) \right|^2 \right) d\sigma_x + \\
&\quad + \frac{1}{2} \int_{\Gamma^{1,2}_{\varepsilon}} \varepsilon \left| \left(s^{\ell'}_{\varepsilon} - s^{\ell''}_{\varepsilon}\right)(t,\cdot) \right|^2 \, d\sigma_x \Bigg] \\
&\quad + \alpha \left(\sum_{k=1,2} \left\| \nabla \left(u^{k,\ell'}_{i,\varepsilon} - u^{k,\ell''}_{i,\varepsilon}\right) \right\|^2_{L^2(\Omega^k_{i,\varepsilon,t})} + \left\| \nabla \left(u^{\ell'}_{e,\varepsilon} - u^{\ell''}_{e,\varepsilon}\right) \right\|^2_{L^2(\Omega_{e,\varepsilon,t})} \right) \\
&\leq \frac{1}{2} \Bigg[\sum_{k=1,2} \int_{\Gamma^k_{\varepsilon}} \left(\varepsilon \left| \left(v^{k,\ell'}_{0,\varepsilon} - v^{k,\ell''}_{0,\varepsilon}\right) \right|^2 + \varepsilon \left| \left(w^{k,\ell'}_{0,\varepsilon} - w^{k,\ell''}_{0,\varepsilon}\right) \right|^2 \right) d\sigma_x \\
&\qquad\qquad + \frac{1}{2} \int_{\Gamma^{1,2}_{\varepsilon}} \varepsilon \left| \left(s^{\ell'}_{0,\varepsilon} - s^{\ell''}_{0,\varepsilon}\right) \right|^2 \, d\sigma_x \Bigg] \\
&\qquad + C \Bigg[\sum_{k=1,2} \int_0^t \int_{\Gamma^k_{\varepsilon}} \left(\varepsilon \left| \left(v^{k,\ell'}_{\varepsilon} - v^{k,\ell''}_{\varepsilon}\right) \right|^2 + \varepsilon \left| \left(w^{k,\ell'}_{\varepsilon} - w^{k,\ell''}_{\varepsilon}\right) \right|^2 \right) d\sigma_x \\
&\qquad\qquad + \frac{1}{2} \int_{\Gamma^{1,2}_{\varepsilon}} \varepsilon \left| \left(s^{\ell'}_{\varepsilon} - s^{\ell''}_{\varepsilon}\right) \right|^2 \, d\sigma_x d\tau \Bigg]
\end{aligned} \tag{3.61}$$

where $C > 0$ is a constant independent of ε. Thus, we obtain by applying Gronwall's inequality

$$\frac{1}{2}\left[\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\left(\varepsilon\left|\left(v_\varepsilon^{k,\ell'}-v_\varepsilon^{k,\ell''}\right)(t,\cdot)\right|^2+\varepsilon\left|\left(w_\varepsilon^{k,\ell'}-w_\varepsilon^{k,\ell''}\right)(t,\cdot)\right|^2\right)\,d\sigma_x\right.$$
$$\left.+\frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}}\varepsilon\left|\left(s_\varepsilon^{\ell'}-s_\varepsilon^{\ell''}\right)(t,\cdot)\right|^2\,d\sigma_x\right]$$
$$\leq C\left[\sum_{k=1,2}\int_{\Gamma_\varepsilon^k}\left(\varepsilon\left|\left(v_{0,\varepsilon}^{k,\ell'}-v_{0,\varepsilon}^{k,\ell''}\right)\right|^2+\varepsilon\left|\left(w_{0,\varepsilon}^{k,\ell'}-w_{0,\varepsilon}^{k,\ell''}\right)\right|^2\right)\,d\sigma_x\right.$$
$$\left.+\frac{1}{2}\int_{\Gamma_\varepsilon^{1,2}}\varepsilon\left|\left(s_{0,\varepsilon}^{\ell'}-s_{0,\varepsilon}^{\ell''}\right)\right|^2\,d\sigma_x\right]$$

for some constant $C > 0$. Hence, we deduce that $v_\varepsilon^{k,\ell'} = v_\varepsilon^{k,\ell''}$, $w_\varepsilon^{k,\ell'} = w_\varepsilon^{k,\ell''}$ for $k = 1, 2$ and $s_\varepsilon^{\ell'} = s_\varepsilon^{\ell''}$. Moreover, using Estimation (3.61), we conclude that

$$\nabla\left(u_{e,\varepsilon}^{\ell'}-u_{e,\varepsilon}^{\ell''}\right)=0 \qquad \text{a.e. on } \Omega_{e,\varepsilon,t},$$
$$\nabla\left(u_{i,\varepsilon}^{k,\ell'}-u_{i,\varepsilon}^{k,\ell''}\right)=0 \qquad \text{a.e. on } \Omega_{i,\varepsilon,t}^k,$$

which means that $u_{e,\varepsilon}^{\ell'} = u_{e,\varepsilon}^{\ell''} + c$ and $u_{i,\varepsilon}^{k,\ell'} = u_{i,\varepsilon}^{k,\ell''} + c$ for $k = 1, 2$. On the one hand, due to the normalization condition (3.12), $c = 0$ and $u_{e,\varepsilon}^{\ell'} = u_{e,\varepsilon}^{\ell''}$. On the other hand, the estimation (3.47) holds for $u_{i,\varepsilon}^{k,\ell'} - u_{i,\varepsilon}^{k,\ell''}$ which gives

$$\left\|u_{i,\varepsilon}^{k,\ell'}-u_{i,\varepsilon}^{k,\ell''}\right\|^2_{L^2(\Omega_{i,\varepsilon}^k)}\leq C\left(\left\|\sqrt{\varepsilon}\left(v_\varepsilon^{k,\ell'}-v_\varepsilon^{k,\ell''}\right)\right\|^2_{L^2(\Gamma_\varepsilon^k)}+\left\|\nabla\left(u_{i,\varepsilon}^{k,\ell'}-u_{i,\varepsilon}^{k,\ell''}\right)\right\|^2_{L^2(\Omega_{i,\varepsilon}^k)}\right.$$
$$\left.+\left\|\nabla\left(u_{e,\varepsilon}^{\ell'}-u_{e,\varepsilon}^{\ell''}\right)\right\|^2_{L^2(\Omega_{e,\varepsilon})}\right),\ \text{with } k=1,2.$$

In addition, we have $v_\varepsilon^{k,\ell'} = v_\varepsilon^{k,\ell''}$ so we obtain finally $u_{i,\varepsilon}^{k,\ell'} = u_{i,\varepsilon}^{k,\ell''}$ for $k = 1, 2$. This gives the uniqueness proof of weak solutions.

3.4 Two-scale Asymptotic Homogenization Method

The key idea of this method is to guess the solution of the microscopic model using the asymptotic expansion (3.62) involving the time t, the macroscopic (slow) variable x and the microscopic (fast) variable $y = x/\varepsilon$. In this section, we study the asymptotic behavior of the solutions to the microscopic tridomain model (3.1). This method, among others, is a formal and intuitive method for predicting the mathematical writing of a homogenized solution that can eventually approach the solution of the initial problem (3.1).

For that, we start to treat the problem in the intracellular medium then we can solve in similar way the other one in the extracellular medium using this method.

The authors in [HY09] are applied the two-scale asymptotic expansion method on the microscopic bidomain model. In our approach, we investigate the same two-scale technique but herein we have three different domains separated by two boundaries (membrane cellular and gap junction, see Figure 3.2).

The two-scale asymptotic expansion is assumed for the intracellular electrical potential $u^k_{i,\varepsilon}$ for $k = 1, 2$ as follows:

$$u^k_{i,\varepsilon}(t,x) := u^k_i\left(t, x, \frac{x}{\varepsilon}\right) = u^k_{i,0}\left(t, x, \frac{x}{\varepsilon}\right) + \varepsilon u^k_{1,1}\left(t, x, \frac{x}{\varepsilon}\right) + \varepsilon^2 u^k_{i,2}\left(t, x, \frac{x}{\varepsilon}\right) + \cdots \tag{3.62}$$

with each function $u^k_{i,m}(\cdot, y), m = 1, 2, \ldots,$ is y-periodic function dependent on time $t \in (0, T)$, slow (macroscopic) variable x and the fast (microscopic) variable y. The slow and fast variables correspond respectively to the global and local structure of the field. Similarly, the extracellular electrical potential $u_{e,\varepsilon}$, the gating variable w^k_ε and the applied current $\mathcal{I}^k_{app,\varepsilon}$ have the same two-scale asymptotic expansion for $k = 1, 2$.

We investigate the asymptotic behavior of the solution to the following problem posed in the intracellular domain $\Omega^k_{i,\varepsilon}$ for $k = 1, 2$

$$\begin{aligned}
\mathcal{A}_\varepsilon u^k_{i,\varepsilon} &= 0 && \text{in } \Omega^k_{i,\varepsilon,T} := (0,T) \times \Omega^k_{i,\varepsilon}, \\
-\mathrm{M}^\varepsilon_i \nabla u^k_{i,\varepsilon} \cdot n^k_i = \varepsilon \left(\partial_t v^k_\varepsilon + \mathcal{I}_{ion}(v^k_\varepsilon, w^k_\varepsilon) - \mathcal{I}^k_{app,\varepsilon}\right) &= \mathcal{I}^k_m && \text{on } \Gamma^k_{\varepsilon,T} := (0,T) \times \Gamma^k_\varepsilon, \\
u^k_{i,\varepsilon} - u_{e,\varepsilon} &= v^k_\varepsilon && \text{on } \Gamma^k_{\varepsilon,T}, \\
-\mathrm{M}^\varepsilon_i \nabla u^1_{i,\varepsilon} \cdot n^1_i = \mathrm{M}^\varepsilon_i \nabla u^2_{i,\varepsilon} \cdot n^2_i = \varepsilon \left(\partial_t s_\varepsilon + \mathcal{I}_{gap}(s_\varepsilon)\right) &= \mathcal{I}_{1,2} && \text{on } \Gamma^{1,2}_{\varepsilon,T} := (0,T) \times \Gamma^{1,2}_\varepsilon, \\
u^1_{i,\varepsilon} - u^2_{i,\varepsilon} &= s_\varepsilon && \text{on } \Gamma^{1,2}_{\varepsilon,T},
\end{aligned} \tag{3.63}$$

with $\mathcal{A}_\varepsilon = -\nabla \cdot (\mathrm{M}^\varepsilon_i \nabla)$, where the intracellular conductivity matrices M^ε_i defined by:

$$\mathrm{M}^\varepsilon_i(x) = \mathrm{M}_i\left(\frac{x}{\varepsilon}\right),$$

satisfying the elliptic and periodicity conditions (3.4).

So, the derivation with respect to x for $k = 1, 2$ is defined as:

$$\frac{\partial u_{i,\varepsilon}^k}{\partial x_q}(t,x) = \frac{\partial u_i^k}{\partial x_q}\left(t, x, \frac{x}{\varepsilon}\right) + \frac{1}{\varepsilon}\frac{\partial u_i^k}{\partial y_q}\left(t, x, \frac{x}{\varepsilon}\right).$$

Consequently, the full operator $\mathcal{A}_\varepsilon$ in the initial problem (3.63) is represented as:

$$\mathcal{A}_\varepsilon u_{i,\varepsilon}^k(t,x) = [(\varepsilon^{-2}\mathcal{A}_{yy} + \varepsilon^{-1}\mathcal{A}_{xy} + \varepsilon^0\mathcal{A}_{xx})u_i^k]\left(t, x, \frac{x}{\varepsilon}\right), \text{ for } k = 1, 2 \tag{3.64}$$

with each operator is defined by:

$$\begin{cases} \mathcal{A}_{yy} = -\sum\limits_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y)\frac{\partial}{\partial y_q}\right), \\ \mathcal{A}_{xy} = -\sum\limits_{p,q=1}^{d} \frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y)\frac{\partial}{\partial x_q}\right) - \sum\limits_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y)\frac{\partial}{\partial y_q}\right), \\ \mathcal{A}_{xx} = -\sum\limits_{p,q=1}^{d} \frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y)\frac{\partial}{\partial x_q}\right). \end{cases}$$

Now, we substitute the asymptotic expansion (3.62) of $u_{i,\varepsilon}^k$, $k = 1, 2$ in the developed operator (3.64) to obtain

$$\begin{aligned} \mathcal{A}_\varepsilon u_{i,\varepsilon}^k(x) &= \left[\varepsilon^{-2}\mathcal{A}_{yy}u_{i,0}^k + \varepsilon^{-1}\mathcal{A}_{yy}u_{i,1}^k + \varepsilon^0\mathcal{A}_{yy}u_{i,2}^k + \cdots\right]\left(t, x, \frac{x}{\varepsilon}\right) \\ &\quad + \left[\varepsilon^{-1}\mathcal{A}_{xy}u_{i,0}^k + \varepsilon^0\mathcal{A}_{xy}u_{i,1}^k + \cdots\right]\left(t, x, \frac{x}{\varepsilon}\right) \\ &\quad + \left[\varepsilon^0\mathcal{A}_{xx}u_{i,0}^k + \cdots\right]\left(t, x, \frac{x}{\varepsilon}\right) \\ &= \left[\varepsilon^{-2}\mathcal{A}_{yy}u_{i,0}^k + \varepsilon^{-1}\left(\mathcal{A}_{yy}u_{i,1}^k + \mathcal{A}_{xy}u_{i,0}^k\right)\right. \\ &\quad \left. + \varepsilon^0\left(\mathcal{A}_{yy}u_{i,2}^k + \mathcal{A}_{xy}u_{i,1}^k + \mathcal{A}_{xx}u_{i,0}^k\right)\right]\left(t, x, \frac{x}{\varepsilon}\right) + \cdots. \end{aligned}$$

Thus, we also substitute the asymptotic expansion (3.62) of $u_i^{\varepsilon,\delta}$ into the two boundary condition equations (3.63) on $\Gamma^k, k = 1, 2$ and on $\Gamma^{1,2}$:

$$\begin{aligned} \mathrm{M}_i^{\varepsilon} \nabla u_{i,\varepsilon}^k \cdot n_i^k &= \left[\varepsilon^0 (\mathrm{M}_i \nabla_x u_{i,0}^k) \cdot n_i^k + \varepsilon (\mathrm{M}_i \nabla_x u_{i,1}^k) \cdot n_i^k + \cdots \right] \left(t, x, \frac{x}{\varepsilon}\right) \\ &+ \left[\varepsilon^{-1} (\mathrm{M}_i \nabla_y u_{i,0}^k) \cdot n_i^k + \varepsilon^0 (\mathrm{M}_i \nabla_y u_{i,1}^k) \cdot n_i^k + \varepsilon (\mathrm{M}_i \nabla_y u_{i,2}^k) \cdot n_i^k + \cdots \right] \left(t, x, \frac{x}{\varepsilon}\right) \\ &= \left[\varepsilon^{-1} (\mathrm{M}_i \nabla_y u_{i,0}^k) \cdot n_i^k + \varepsilon^0 \left(\mathrm{M}_i \nabla_y u_{i,1}^k + \mathrm{M}_i \nabla_x u_{i,0}^k\right) \cdot n_i^k \right. \\ &+ \left. \varepsilon \left(\mathrm{M}_i \nabla_y u_{i,2}^k + \mathrm{M}_i \nabla_x u_{i,1}^k\right) \cdot n_i^k \right] \left(t, x, \frac{x}{\varepsilon}\right) + \cdots . \end{aligned}$$

where n_i^k, $k = 1, 2$ represents the (outward) normal pointing out from $\Omega_{i,\varepsilon}^k$ for $k = 1, 2$ and n_e is the normal pointing out from $\Omega_{e,\varepsilon}$.

Hence, by equating the powers-like terms of ε to zero, we have to solve the following system of equations for the functions $u_{i,m}^k(t, x, y),\ m = 0, 1, 2,$:

$$\begin{cases} \mathcal{A}_{yy} u_{i,0}^k = 0 \text{ in } Y_i^k, \\ u_{i,0}^k \ y\text{-periodic}, \\ \mathrm{M}_i \nabla_y u_{i,0}^k \cdot n_i^k = 0 \text{ on } \Gamma^k, \\ \mathrm{M}_i \nabla_y u_{i,0}^k \cdot n_i^k = 0 \text{ on } \Gamma^{1,2}, \end{cases} \tag{3.65}$$

$$\begin{cases} \mathcal{A}_{yy} u_{i,1}^k = -\mathcal{A}_{xy} u_{i,0}^k \text{ in } Y_i^k, \\ u_{i,1}^k \ y\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_y u_{i,1}^k + \mathrm{M}_i \nabla_x u_{i,0}^k\right) \cdot n_i^k = 0 \text{ on } \Gamma^k, \\ \left(\mathrm{M}_i \nabla_y u_{i,1}^k + \mathrm{M}_i \nabla_x u_{i,0}^k\right) \cdot n_i^k = 0 \text{ on } \Gamma^{1,2}, \end{cases} \tag{3.66}$$

$$\begin{cases} \mathcal{A}_{yy} u_{i,2}^k = -\mathcal{A}_{xy} u_{i,1}^k - \mathcal{A}_{xx} u_{i,0}^k \text{ in } Y_i^k, \\ u_{i,2}^k \ y\text{-periodic}, \\ -\left(\mathrm{M}_i \nabla_y u_{i,2}^k + \mathrm{M}_i \nabla_x u_{i,1}^k\right) \cdot n_i^k = \partial_t v_0^k + \mathcal{I}_{ion}\left(v_0^k, w_0^k\right) - \mathcal{I}_{app,0}^k \text{ on } \Gamma^k, \\ -\left(\mathrm{M}_i \nabla_y u_{i,2}^1 + \mathrm{M}_i \nabla_x u_{i,1}^1\right) \cdot n_i^1 = \left(\mathrm{M}_i \nabla_y u_{i,2}^2 + \mathrm{M}_i \nabla_x u_{i,1}^2\right) \cdot n_i^2 = \partial_t s_0 + \mathcal{I}_{gap}(s_0) \text{ on } \Gamma^{1,2}, \end{cases} \tag{3.67}$$

The authors in [BLP11]-[CD99] have successively solved the three systems into Dirrichlet boundary conditions (3.65)-(3.67). Herein, the functions $u_{i,0}^k$, $u_{i,1}^k$ and $u_{i,2}^k$ in the asymptotic expansion (3.62) for the intracellular potential $u_{i,\varepsilon}^k$, $k = 1, 2$ satisfy the Neumann boundary value problems (3.65)-(3.67) in the local portion Y_i^k of a unit cell Y (see [FS02; HY09] for the case of Laplace equations).

The resolution is described as follows:

- **First step** We begin with the first boundary value problem (3.65) whose variational formulation:

$$\begin{cases} \text{Find } \dot{u}_{i,0}^k \in \mathcal{W}_{per}(Y_i^k) \text{ such that} \\ \dot{a}_{Y_i^k}(\dot{u}_{i,0}^k, \dot{v}) = \int_{\partial Y_i^k} (\mathrm{M}_i \nabla_y u_{i,0}^k \cdot n_i^k) v \, d\sigma_y, \ \forall \dot{v} \in \mathcal{W}_{per}(Y_i^k), \end{cases} \tag{3.68}$$

with $\dot{a}_{Y_i^k}(\dot{u}, \dot{v})$ is given by:

$$\dot{a}_{Y_i^k}(\dot{u}, \dot{v}) = \int_{Y_i^k} \mathrm{M}_i \nabla_y u \nabla_y v dy, \ \forall u \in \dot{u}, \ \forall v \in \dot{v}, \ \forall \dot{u}, \ \forall \dot{v} \in \mathcal{W}_{per}(Y_i^k) \tag{3.69}$$

and $\mathcal{W}_{per}(Y_i^k)$ is given by Definition A.4.

We want to clarify the right hand side of the variational formulation (3.68). By the definition of $\partial Y_i^k := \Gamma^k \cup \Gamma^{1,2}$, by taking account the boundary condition on Γ^k, $k = 1, 2$ and on $\Gamma^{1,2}$ to say that :

$$\int_{\partial Y_i^k} (\mathrm{M}_i \nabla_y u_{i,0}^k \cdot n_i^k) v \, d\sigma_y \\ = \int_{\Gamma^k} (\mathrm{M}_i \nabla_y u_{i,0}^k \cdot n_i^k) v \, d\sigma + \int_{\Gamma^{1,2}} (\mathrm{M}_i \nabla_y u_{i,0}^k \cdot n_i^k) v \, d\sigma = 0.$$

Using Theorem A.2, we can prove the existence and uniqueness of the solution $\dot{u}_{i,0}^k$. Then, the problem (3.65) has a unique solution $u_{i,0}^k$ independent of y, so we deduce that:

$$u_{i,0}^k(t, x, y) = u_{i,0}^k(t, x), \text{ for } k = 1, 2.$$

Similarly, we show that $u_{e,0}$ does not depend on y (by the same strategy). Since $v_0^k = (u_{i,0}^k - u_{e,0}))|_{\Gamma^k}$ with $k = 1, 2$. Then we also deduce that s_0 and w_0^k, $k = 1, 2$ not depend on the microscopic variable y.

Remark 3.10. *In the asymptotic expansion (3.62), each element $u_{i,m}^k$ is a priori an oscillating function, since it depends on the fast variable x/ε. Actually, $u_{i,0}^k$, $k = 1, 2$ and $u_{e,0}$ depends only on the slow (macroscopic) variable x, so it does not oscillate "rapidly" with x/ε. This is why we now expect $u_{i,0}^k$ and $u_{e,0}$ to be the "solution homogenized". It remains to find if there is three equations on Ω satisfied by $u_{i,0}^k$, $k = 1, 2$ and $u_{e,0}$, in which case we would have found "homogenized equation" too.*

- **Second step** We now turn to the second boundary value problem (3.66). Since $u_{i,0}^k$ is independent of y, this equation can be rewritten as:

$$\begin{cases} \mathcal{A}_{yy} u_{i,1}^k = \sum_{p,q=1}^{d} \dfrac{\partial \mathrm{m}_i^{pq}}{\partial y_p} \dfrac{\partial u_{i,0}^k}{\partial x_q} \text{ in } Y_i^k, \\ u_{i,1}^k \ y\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_y u_{i,1}^k + \mathrm{M}_i \nabla_x u_{i,0}^k\right) \cdot n_i^k = 0 \text{ on } \Gamma^k, \\ \left(\mathrm{M}_i \nabla_y u_{i,1}^k + \mathrm{M}_i \nabla_x u_{i,0}^k\right) \cdot n_i^k = 0 \text{ on } \Gamma^{1,2}, \end{cases} \tag{3.70}$$

Its variational formulation is:

$$\begin{cases} \text{Find } \dot{u}_{i,1}^k \in \mathcal{W}_{per}(Y_i^k) \text{ such that} \\ \dot{a}_{Y_i^k}(\dot{u}_{i,1}^k, \dot{v}) = (F_1, \dot{v})_{(\mathcal{W}_{per}(Y_i^k))', \mathcal{W}_{per}(Y_i^k)} \ \forall \dot{v} \in \mathcal{W}_{per}(Y_i^k), \end{cases} \tag{3.71}$$

with $\dot{a}_{Y_i^k}$ is given by (3.69) and F_1 is defined by:

$$(F_1, \dot{v})_{(\mathcal{W}_{per}(Y_i^k))', \mathcal{W}_{per}(Y_i^k)} = \sum_{p,q=1}^{d} \frac{\partial u_{i,0}^k}{\partial x_q} \int_{Y_i^k} \mathrm{m}_i^{pq}(y) \frac{\partial v}{\partial y_p} dy, \ \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{per}(Y_i^k). \tag{3.72}$$

Using Theorem A.2, we obtain that the second system (3.70)-(3.72) has a unique weak solution $\dot{u}_{i,1}^k \in \mathcal{W}_{per}(Y_i^k)$ (defined by [BLP11] and [OSY09]). Thus, the linearity of terms in the right hand side of equation (3.70) suggests to look for $\dot{u}_{i,1}^k$ under the following form:

$$\dot{u}_{i,1}^k(t,x,y) = \sum_{q=1}^{d} \dot{\chi}_i^q(y) \frac{\partial \dot{u}_{i,0}^k}{\partial x_q}(t,x) \text{ in } \mathcal{W}_{per}(Y_i^k), \tag{3.73}$$

with the corrector function $\dot{\chi}_i^q$ satisfies the following ε-cell problem:

$$\begin{cases} \mathcal{A}_{yy} \dot{\chi}_i^q = \sum_{p=1}^{d} \dfrac{\partial \mathrm{m}_i^{pq}}{\partial y_p} \text{ in } Y_i^k, \\ \dot{\chi}_i^q \ y\text{-periodic}, \\ \mathrm{M}_i \nabla_y \dot{\chi}_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \text{ on } \Gamma^k, \ k = 1,2 \\ \mathrm{M}_i \nabla_y \dot{\chi}_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \text{ on } \Gamma^{1,2}, \end{cases} \tag{3.74}$$

for e_q, $q = 1, \ldots, d$, the standard canonical basis in $\mathbb{R}^d$. Moreover, we can choose a representative element χ_i^q of the class $\dot{\chi}_i^q$ satisfying the following variational formulation:

$$\begin{cases} \text{Find } \chi_i^q \in W_\#(Y_i^k) \text{ such that} \\ \\ a_{Y_i^k}(\chi_i^q, v) = (F, v)_{(W_\#(Y_i^k))', W_\#(Y_i^k)}, \quad \forall v \in W_\#(Y_i^k), \end{cases} \tag{3.75}$$

with $a_{Y_i^k}$ is given by (3.69) and F is defined by:

$$(F, v)_{(W_\#(Y_i^k))', W_\#(Y_i^k)} = \sum_{p=1}^{d} \int_{Y_i^k} \mathrm{m}_i^{pq}(y) \frac{\partial v}{\partial y_p} dy,$$

where the space $W_\#(Y_i^k)$ is given by the expression (2.91) for $k = 1, 2$. Since F belongs to $(W_\#(Y_i^k))'$ then the condition of Theorem A.2 is imposed in order to guarantee existence and uniqueness of the solution.
Thus, by the form of $\dot{u}_{i,1}^k$ given by (3.73), the solution $u_{i,1}^k$, $k = 1, 2$ of the second system (3.70) can be represented by the following ansatz:

$$u_{i,1}^k(t, x, y) = \chi_i(y) \cdot \nabla_x u_{i,0}^k(t, x) + \tilde{u}_{i,1}^k(t, x) \text{ with } u_{i,1}^k \in \dot{u}_{i,1}^k, \tag{3.76}$$

where $\tilde{u}_{i,1}^k$ is a constant with respect to y (i.e $\tilde{u}_{i,1}^k \in \dot{0}$ in $\mathcal{W}_{per}(Y_i^k)$).

- **Last step** We now pass to the last boundary value problem (3.67). Taking into account the form of $u_{i,0}^k$ and $u_{i,1}^k$ for $k = 1, 2$, we obtain

$$\begin{aligned} &- \mathcal{A}_{xy} u_{i,1}^k - \mathcal{A}_{xx} u_{i,0}^k \\ &\quad = \sum_{p,q=1}^{d} \frac{\partial}{\partial y_p} \left(\mathrm{m}_i^{pq}(y) \frac{\partial u_{i,1}^k}{\partial x_q} \right) + \sum_{p,q=1}^{d} \frac{\partial}{\partial x_p} \left(\mathrm{m}_i^{pq}(y) \left(\frac{\partial u_{i,1}^k}{\partial y_q} + \frac{\partial u_{i,0}^k}{\partial x_q} \right) \right). \end{aligned}$$

Consequently, this system (3.67) have the following variational formulation:

$$\begin{cases} \text{Find } \dot{u}_{i,2}^k \in \mathcal{W}_{per}(Y_i^k) \text{ such that} \\ \dot{a}_{Y_i^k}(\dot{u}_{i,2}^k, \dot{v}) = (F_2, \dot{v})_{(\mathcal{W}_{per}(Y_i^k))', \mathcal{W}_{per}(Y_i^k)} \ \forall \dot{v} \in \mathcal{W}_{per}(Y_i^k), \end{cases} \tag{3.77}$$

with $\dot{a}_{Y_i^k}$ is given by (3.69) and F_2 is defined by:

$$\begin{aligned}
&(F_2, \dot{v})_{(\mathcal{W}_{per}(Y_i^k))', \mathcal{W}_{per}(Y_i^k)} \\
&\quad = \int_{\Gamma^k} \left(\mathrm{M}_i \nabla_y u_{i,2}^k + \mathrm{M}_i \nabla_x u_{i,1}^k \right) \cdot n_i^k \, v \, d\sigma_y \\
&\quad + \int_{\Gamma^{1,2}} \left(\mathrm{M}_i \nabla_y u_{i,2}^k + \mathrm{M}_i \nabla_x u_{i,1}^k \right) \cdot n_i^k \, v \, d\sigma_y \\
&\quad - \sum_{p,q=1}^{d} \int_{Y_i^k} \mathrm{m}_i^{pq}(y) \frac{\partial u_{i,1}^k}{\partial x_q} \frac{\partial v}{\partial y_p} dy \\
&\quad + \sum_{p,q=1}^{d} \int_{Y_i^k} \frac{\partial}{\partial x_p} \left(\mathrm{m}_i^{pq}(y) \left(\frac{\partial u_{i,1}^k}{\partial y_q} + \frac{\partial u_{i,0}^k}{\partial x_q} \right) \right) v dy, \quad \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{per}(y).
\end{aligned} \tag{3.78}$$

The problem (3.77)-(3.78) is well-posed according to Theorem A.2 under the compatibility condition for $k = 1, 2$:

$$(F_2, 1)_{(\mathcal{W}_{per}(Y_i^k))', \mathcal{W}_{per}(Y_i^k)} = 0.$$

which equivalent to:

$$\begin{aligned}
&- \sum_{p,q=1}^{d} \int_{Y_i^k} \frac{\partial}{\partial x_p} \left(\mathrm{m}_i^{pq}(y) \left(\frac{\partial u_{i,1}^k}{\partial y_q} + \frac{\partial u_{i,0}^k}{\partial x_q} \right) \right) dy \\
&\quad = - \left| \Gamma^k \right| \left(\partial_t v_0^k + \mathcal{I}_{ion} \left(v_0^k, w_0^k \right) - \mathcal{I}_{app}^k \right) \\
&\quad\quad + (-1)^k \left| \Gamma^{1,2} \right| \left(\partial_t s_0 + \mathcal{I}_{gap}(s_0) \right),
\end{aligned}$$

where $\mathcal{I}_{app}^k(t, x) = \dfrac{1}{|\Gamma^k|} \displaystyle\int_{\Gamma^k} \mathcal{I}_{app,0}^k(\cdot, y) \, d\sigma_y$ for $k = 1, 2$.

In addition, we replace $u_{i,1}^k$ by its form (3.76) for $k = 1, 2$ in the above condition to obtain:

$$\begin{aligned}
&- \sum_{p,q=1}^{d} \int_{Y_i^k} \frac{\partial}{\partial x_p} \left(\mathrm{m}_i^{pq}(y) \left(\sum_{\ell=1}^{d} \frac{\partial \chi_i^\ell}{\partial y_q} \frac{\partial u_{i,0}^k}{\partial x_\ell} + \frac{\partial u_{i,0}^k}{\partial x_q} \right) \right) dy \\
&\quad = - \left| \Gamma^k \right| \left(\partial_t v_0^k + \mathcal{I}_{ion} \left(v_0^k, w_0^k \right) - \mathcal{I}_{app}^k \right) \\
&\quad\quad + (-1)^k \left| \Gamma^{1,2} \right| \left(\partial_t s_0 + \mathcal{I}_{gap}(s_0) \right).
\end{aligned}$$

By expanding the sum and permuting the index, we obtain for $k = 1, 2$

$$-\sum_{p,q=1}^{d}\sum_{\ell=1}^{d}\int_{Y_i^k}\frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y)\frac{\partial \chi_i^\ell}{\partial y_q}\frac{\partial u_{i,0}^k}{\partial x_\ell}\right)dy-\sum_{p,\ell=1}^{d}\int_{Y_i^k}\frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{p\ell}(y)\frac{\partial u_{i,0}^k}{\partial x_k}\right)dy$$
$$=-\left|\Gamma^k\right|\left(\partial_t v_0^k+\mathcal{I}_{ion}\left(v_0^k,w_0^k\right)-\mathcal{I}_{app}^k\right)+(-1)^k\left|\Gamma^{1,2}\right|\left(\partial_t s_0+\mathcal{I}_{gap}(s_0)\right),$$

which equivalent to find $u_{i,0}^k$ for $k = 1, 2$ satisfying the following problem:

$$-\sum_{p,\ell=1}^{d}\left[\frac{1}{|Y|}\sum_{q=1}^{d}\int_{Y_i^k}\left(\mathrm{m}_i^{p\ell}(y)+\mathrm{m}_i^{pq}(y)\frac{\partial \chi_i^\ell}{\partial y_q}\right)dy\right]\frac{\partial^2 u_{i,0}^k}{\partial x_p\partial x_\ell}$$
$$=-\frac{\left|\Gamma^k\right|}{|Y|}\left(\partial_t v_0^k+\mathcal{I}_{ion}\left(v_0^k,w_0^k\right)-\mathcal{I}_{app}^k\right)$$
$$+(-1)^k\frac{\left|\Gamma^{1,2}\right|}{|Y|}\left(\partial_t s_0+\mathcal{I}_{gap}(s_0)\right).$$

Consequently, we see that's exactly the **homogenized** equation satisfied by $u_{i,0}^k$ for $k = 1, 2$ of the intracellular problem can be rewritten as:

$$\mathcal{B}_{xx}^i u_{i,0}^k=-\mu_k\left(\partial_t v_0^k+\mathcal{I}_{ion}\left(v_0^k,w_0^k\right)-\mathcal{I}_{app}^k\right)+(-1)^k\mu_g\left(\partial_t s_0+\mathcal{I}_{gap}(s_0)\right)\text{ on }\Omega_T, \tag{3.79}$$

where $\mu_k = \left|\Gamma^k\right| / |Y|$, $k = 1, 2$ and $\mu_g = |\Gamma^{1,2}| / |Y|$. Herein, the homogenized operator $\mathcal{B}_{xx}^i$ is defined by :

$$\mathcal{B}_{xx}^i=-\nabla_x\cdot\left(\widetilde{\mathbf{M}}_i\nabla_x\right)=-\sum_{p,\ell=1}^{d}\frac{\partial}{\partial x_p}\left(\widetilde{\mathbf{m}}_i^{p\ell}\frac{\partial}{\partial x_\ell}\right) \tag{3.80}$$

with the coefficients of the homogenized conductivity matrices $\widetilde{\mathbf{M}}_i=\left(\widetilde{\mathbf{m}}_i^{p\ell}\right)_{1\le p,\ell\le d}$ defined by:

$$\widetilde{\mathbf{m}}_i^{p\ell}:=\frac{1}{|Y|}\sum_{q=1}^{d}\int_{Y_i^k}\left(\mathrm{m}_i^{p\ell}+\mathrm{m}_i^{pq}\frac{\partial \chi_i^\ell}{\partial y_q}\right)dy. \tag{3.81}$$

Similarly, we can obtain the dimensionless averaged equations for the extracellular problem

$$\mathcal{B}_{xx}^e u_{e,0}=\sum_{k=1,2}\mu_k\left(\partial_t v_0^k+\mathcal{I}_{ion}\left(v_0^k,w_0^k\right)-\mathcal{I}_{app}^k\right)\text{ on }\Omega_T, \tag{3.82}$$

where $\mu_k = \left|\Gamma^k\right| / |Y|$, $k = 1, 2$ and the homogenized operator $\mathcal{B}^e_{xx}$ is defined by :

$$\mathcal{B}^e_{xx} = -\nabla_x \cdot \left(\widetilde{\mathbf{M}}_e \nabla_x\right) = -\sum_{p,\ell=1}^{d} \frac{\partial}{\partial x_p}\left(\widetilde{\mathbf{m}}_e^{p\ell} \frac{\partial}{\partial x_\ell}\right) \tag{3.83}$$

with the coefficients of the homogenized conductivity matrices $\widetilde{\mathbf{M}}_e = \left(\widetilde{\mathbf{m}}_e^{p\ell}\right)_{1\leq p,\ell\leq d}$ defined by:

$$\widetilde{\mathbf{m}}_e^{p\ell} := \frac{1}{|Y|}\sum_{q=1}^{d} \int_{Y_e} \left(\mathrm{m}_e^{p\ell} + \mathrm{m}_e^{pq} \frac{\partial \chi_e^\ell}{\partial y_q}\right) dy. \tag{3.84}$$

Herein, the corrector function χ_e^ℓ satisfies the following ε-cell problem:

$$\begin{cases} \mathcal{A}_{yy}\chi_e^\ell = \sum\limits_{p=1}^{d} \dfrac{\partial \mathrm{m}_e^{p\ell}}{\partial y_p} \text{ in } Y_e, \\ \chi_e^\ell \ y\text{-periodic}, \\ \mathrm{M}_e \nabla_y \chi_e^\ell \cdot n_e = -(\mathrm{M}_i e_\ell) \cdot n_e \text{ on } \Gamma^k,\ k = 1, 2 \end{cases} \tag{3.85}$$

for e_ℓ, $q = 1, \ldots, \ell$, the standard canonical basis in $\mathbb{R}^d$. This completes the proof of Theorem 3.2 using formal asymptotic homogenization method.

3.5 Two-scale Unfolding Homogenization Method

We begin with introducing the unfolding operator and describe some of its properties. For more properties and proofs, we refer to [Cio+12; CDG18]. 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 $(0, T) \times \Gamma^{1,2}$.

3.5.1 Unfolding operator and some basic properties

In order to define an unfolding operator, we first introduce the following sets in $\mathbb{R}^d$ (see Figure 3.3)

- $\Xi_\varepsilon = \{\xi \in \mathbb{Z}^d,\ \varepsilon(\xi + Y) \subset \Omega\}$,
- $\widehat{\Omega}_\varepsilon = \text{interior}\ \{\bigcup_{\xi\in\Xi_\varepsilon} \varepsilon\left(\xi + \overline{Y}\right)\}$,

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

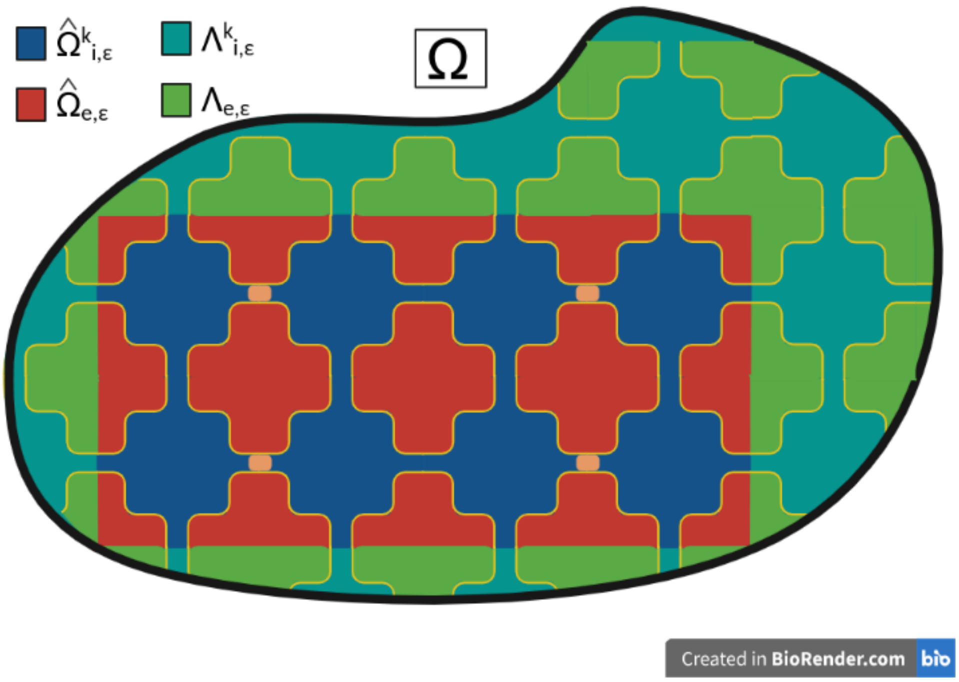

Figure 3.3 – The sets $\widehat{\Omega}^k_{i,\varepsilon}$ for $k=1,2$ (in blue), $\widehat{\Omega}^\varepsilon_e$ (in red), $\Lambda^k_{i,\varepsilon}$ (in dark cyan) and $\Lambda_{e,\varepsilon}$ (in green).

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 3.2 (Domain and boundary unfolding operator)**.**

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:*

$$\mathcal{T}^{i,k}_\varepsilon(\phi)(t,x,y) = \begin{cases} \phi\left(t, \varepsilon\left[\frac{x}{\varepsilon}\right]_Y + \varepsilon y\right) & \text{a.e. for } (t,x,y) \in \widehat{\Omega}^\varepsilon_T \times Y^k_i, \\ 0 & \text{a.e. for } (t,x,y) \in \Lambda^\varepsilon_T \times Y^k_i, \end{cases} \tag{3.86}$$

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:

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

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:*

$$\mathcal{T}^{b,k}_\varepsilon(\varphi)(t,x,y) = \begin{cases} \varphi\left(t, \varepsilon\left[\frac{x}{\varepsilon}\right]_Y + \varepsilon y\right) & \text{a.e. for } (t,x,y) \in \widehat{\Omega}^\varepsilon_T \times \Gamma^k, \\ 0 & \text{a.e. for } (t,x,y) \in \Lambda^\varepsilon_T \times \Gamma^k. \end{cases} \tag{3.87}$$

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

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 3.1 (Some properties of the unfolding operator)**.**

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

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

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

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

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

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

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 3.11. *If* $u \in L^p\left(0,T;W^{1,p}(\Omega_{i,\varepsilon}^k)\right)$ *for* $p \in (1,+\infty)$, $\mathcal{T}_\varepsilon^{b,k}(u)$ *is just the trace on* Γ^k *of* $\mathcal{T}_\varepsilon^{i,k}(u)$. *In particular, by the standard trace theorem in* Y_i^k, *there is a constant* C *such that*

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

From the properties of $\mathcal{T}_\varepsilon^{i,k}(\cdot)$ *in Proposition 3.1, it follows that*

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

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 [Cio+12]).

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

Definition 3.3. *Let $\mathcal{O}$ be a reference cell and $p \in [1, +\infty)$. Then, we define*

$$W^{1,p}_{\#}(\mathcal{O}) = \{u \in W^{1,p}(\mathcal{O}) \text{ such that } u \text{ periodic with } \mathcal{M}_{\mathcal{O}}(u) = 0\}, \tag{3.88}$$

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

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

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 $p = 2$.*

Now we state two important results which are needed to get the convergence for the corresponding unfolding operator, see for e.g. Theorem 3.12 in [Cio+12].

Theorem 3.3. *Let $p \in (1, +\infty)$ and $k = 1, 2$.*

1. *For any $u_\varepsilon \in L^p\left(0, T; W^{1,p}\left(\Omega^k_{i,\varepsilon}\right)\right)$ that satisfies $\|u_\varepsilon\|_{L^p\left(0,T;W^{1,p}\left(\Omega^k_{i,\varepsilon}\right)\right)} \leq C$. Then, there exist $u \in L^p\left(0, T; W^{1,p}(\Omega)\right)$ and $\widehat{u} \in L^p\left(0, T; L^p\left(\Omega, W^{1,p}_{\#}(Y^k_i)\right)\right)$, such that, up to a subsequence (still denoted u_ε), the following hold when $\varepsilon \to 0$:*

$$\mathcal{T}^{i,k}_\varepsilon(u^\varepsilon) \rightharpoonup u \text{ weakly in } L^p\left(0, T; L^p\left(\Omega, W^{1,p}(Y^k_i)\right)\right),$$
$$\mathcal{T}^{i,k}_\varepsilon(\nabla u^\varepsilon) \rightharpoonup \nabla u + \nabla_y \widehat{u} \text{ weakly in } L^p(\Omega_T \times Y^k_i).$$

   with the space $W^{1,p}_{\#}$ is defined by (3.88) and $k = 1, 2$.

2. *For any $v_\varepsilon \in L^p(\Gamma^k_{\varepsilon,T})$ that satisfies $\varepsilon^{1/p}\|v_\varepsilon\|_{L^p(\Gamma^k_{\varepsilon,T})} \leq C$. Then, there exist a subsequence of v_ε and $v \in L^p(\Omega_T)$ such that*

$$\mathcal{T}^{b,k}_\varepsilon(v_\varepsilon) \rightharpoonup v \text{ weakly in } L^p\left(\Omega_T \times \Gamma^k\right), \ k = 1, 2.$$

3.5.2 Microscopic tridomain model

Our novel derivation 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. We intend to pass to the unfolding homogenization limit. We do this by following a three-steps procedure: In Step 1, the weak formulation of the microscopic tridomain model (3.1) is written by another one, called "unfolded" formulation, based on the unfolding operators stated in the previous part. As step 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 3, we take a special form of test functions to obtain finally the macroscopic tridomain model.

The problem (3.1) satisfies the weak formulation given by (3.13)-(3.14). By summing the two first equations 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:

$$\begin{aligned}
&\sum_{k=1,2} \int_{\Gamma_{\varepsilon,T}^k} \varepsilon \partial_t v_\varepsilon^k \psi^k \, d\sigma_x dt + \int_{\Gamma_{\varepsilon,T}^{1,2}} \varepsilon \partial_t s_\varepsilon \Psi \, d\sigma_x dt \\
&+ \sum_{k=1,2} \int_{\Omega_{i,\varepsilon,T}^k} \mathrm{M}_i^\varepsilon \nabla u_{i,\varepsilon}^k \cdot \nabla \varphi_i^k \, dx dt + \int_{\Omega_{e,\varepsilon,T}} \mathrm{M}_e^\varepsilon \nabla u_{e,\varepsilon} \cdot \nabla \varphi_e \, dx dt \\
&+ \sum_{k=1,2} \int_{\Gamma_{\varepsilon,T}^k} \varepsilon \mathrm{I}_{a,ion} \left(v_\varepsilon^k\right) \psi^k \, d\sigma_x dt + \sum_{k=1,2} \int_{\Gamma_{\varepsilon,T}^k} \varepsilon \mathrm{I}_{b,ion} \left(w_\varepsilon^k\right) \psi^k \, d\sigma_x dt \\
&+ \int_{\Gamma_{\varepsilon,T}^{1,2}} \varepsilon \mathcal{I}_{gap} \left(s_\varepsilon\right) \Psi \, d\sigma_x dt = \sum_{k=1,2} \int_{\Gamma_{\varepsilon,T}^k} \varepsilon \mathcal{I}_{app,\varepsilon}^k \psi^k \, d\sigma_x dt,
\end{aligned} \tag{3.89}$$

$$\int_{\Gamma_{\varepsilon,T}^k} \partial_t w_\varepsilon^k e^k \, d\sigma_x dt = \int_{\Gamma_{\varepsilon,T}^k} H\left(v_\varepsilon^k, w_\varepsilon^k\right) e^k \, d\sigma_x dt. \tag{3.90}$$

We denote by E_i with $i = 1, \ldots, 5$ the terms of the equation (3.89) which is rewritten as follows (to respect the order):

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

"Unfolded" formulation of the microscopic tridomain model

The unfolding operator is defined which is employed below to unfold the oscillating functions such that they are expressed in terms of global and local variables describing positions at the upper and lower heterogeneity scales, respectively. Using the properties of the unfolding operator, we rewrite the weak formulation (3.89)-(3.90) in the "unfolded" form.

Using the property (3.1) of Proposition 3.1, then the first and second term of (3.89) is rewritten as follows:

$$\begin{aligned}
E_1 &= \sum_{k=1,2} \iint_{\widehat{\Gamma}^k_{\varepsilon,T}} \varepsilon \partial_t v^k_\varepsilon \psi^k \, d\sigma_x dt + \sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,T} \cap \Lambda_{\varepsilon,T}} \varepsilon \partial_t v^k_\varepsilon \psi^k \, d\sigma_x dt \\
&= \frac{1}{|Y|} \sum_{k=1,2} \iint_{\Omega_T \times \Gamma^k} \mathcal{T}^{b,k}_\varepsilon(\partial_t v^k_\varepsilon) \mathcal{T}^{b,k}_\varepsilon(\psi^k) \, dx d\sigma_y dt + \sum_{k=1,2} \iint_{\Gamma^k_{\varepsilon,T} \cap \Lambda_{\varepsilon,T}} \varepsilon \partial_t v^k_\varepsilon \psi^k \, d\sigma_x dt \\
&:= J_1 + R_1. \\
E_2 &= \iint_{\widehat{\Gamma}^{1,2}_{\varepsilon,T}} \varepsilon \partial_t s_\varepsilon \Psi \, d\sigma_x dt + \iint_{\Gamma^{1,2}_{\varepsilon,T} \cap \Lambda_{\varepsilon,T}} \varepsilon \partial_t s_\varepsilon \Psi \, d\sigma_x dt \\
&= \frac{1}{|Y|} \iint_{\Omega_T \times \Gamma^{1,2}} \mathcal{T}^{b,1,2}_\varepsilon(\partial_t s_\varepsilon) \mathcal{T}^{b,1,2}_\varepsilon(\Psi) \, dx d\sigma_y dt + \iint_{\Gamma^{1,2}_{\varepsilon,T} \cap \Lambda_{\varepsilon,T}} \varepsilon \partial_t s_\varepsilon \Psi \, d\sigma_x dt \\
&:= J_2 + R_2.
\end{aligned}$$

Similarly, we rewrite the third and fourth term using the property (3.1) of Proposition 3.1:

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

Due to the form of $\mathrm{I}_{\ell,ion}$, we use the property (3.1)-(3.1) of Proposition 3.1 to obtain $\mathcal{T}^{b,k}_\varepsilon \left(\mathrm{I}_{\ell,ion}(\cdot)\right) =$

$\mathrm{I}_{\ell,ion}\left(\mathcal{T}_\varepsilon^{b,k}(\cdot)\right)$ for $\ell = a, b$ and $k = 1, 2$. Thus, we arrive to:

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

Similarly, we can rewrite the last two terms of (3.89) by taking account the form of $\mathcal{I}_{gap}$ as follows:

$$\begin{aligned}
E_7 &= \frac{1}{|Y|}\iint_{\Omega_T\times\Gamma^{1,2}}\mathcal{I}_{gap}\left(\mathcal{T}_\varepsilon^{b,1,2}(s_\varepsilon)\right)\mathcal{T}_\varepsilon^{b,1,2}(\Psi)\,dxd\sigma_y dt + \iint_{\Gamma^{1,2}_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}}\varepsilon\mathcal{I}_{gap}(s_\varepsilon)\Psi\,d\sigma_x dt\\
&:= J_7 + R_7\\
E_8 &= \frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\mathcal{I}^k_{app,\varepsilon})\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt + \sum_{k=1,2}\iint_{\Gamma^k_{\varepsilon,T}\cap\Lambda_{\varepsilon,T}}\varepsilon\mathcal{I}^k_{app,\varepsilon}\psi^k\,d\sigma_x dt\\
&:= J_8 + R_8
\end{aligned}$$

Collecting the previous estimates, we readily obtain from (3.89) the following "unfolded" formulation:

$$\begin{aligned}
&\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\partial_t v_\varepsilon^k)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt+\frac{1}{|Y|}\iint_{\Omega_T\times\Gamma^{1,2}}\mathcal{T}_\varepsilon^{b,1,2}(\partial_t s_\varepsilon)\mathcal{T}_\varepsilon^{b,1,2}(\Psi)\,dxd\sigma_y dt\\
&\frac{1}{|Y|}\sum_{k=1,2}\iiint_{\Omega_T\times Y_i^k}\mathcal{T}_\varepsilon^{i,k}(\mathrm{M}_i^\varepsilon)\mathcal{T}_\varepsilon^{i,k}(\nabla u_{i,\varepsilon}^k)\mathcal{T}_\varepsilon^{i,k}(\nabla\varphi_i^k)\,dxdydt\\
&+\frac{1}{|Y|}\iiint_{\Omega_T\times Y_e}\mathcal{T}_\varepsilon^{e}(\mathrm{M}_e^\varepsilon)\mathcal{T}_\varepsilon^{e}(\nabla u_{e,\varepsilon})\mathcal{T}_\varepsilon^{e}(\nabla\varphi_e)\,dxdydt\\
&+\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathrm{I}_{a,ion}\left(\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt\\
&+\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathrm{I}_{b,ion}\left(\mathcal{T}_\varepsilon^{b,k}(w_\varepsilon^k)\right)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt\\
&+\frac{1}{|Y|}\iint_{\Omega_T\times\Gamma^{1,2}}\mathcal{I}_{gap}\left(\mathcal{T}_\varepsilon^{b,1,2}(s_\varepsilon)\right)\mathcal{T}_\varepsilon^{b,1,2}(\Psi)\,dxd\sigma_y dt\\
&=\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\mathcal{I}_{app,\varepsilon}^k)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_y dt+R_8-R_7-R_6-R_5-R_4-R_3-R_2-R_1
\end{aligned}\tag{3.91}$$

Similarly, the "unfolded" formulation of (3.90) is given by:

$$\begin{aligned}
&\frac{1}{|Y|}\iint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\partial_t w_\varepsilon^k)\mathcal{T}_\varepsilon^{b,k}(e^k)\,dxd\sigma_y dt\\
&-\frac{1}{|Y|}\iint_{\Omega_T\times\Gamma^k}H(\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k),\mathcal{T}_\varepsilon^{b,k}(w_\varepsilon^k))\mathcal{T}_\varepsilon^{b,k}(e^k)\,dxd\sigma_y dt\\
&=-\varepsilon\iint_{\Gamma_{\varepsilon,T}^k\cap\Lambda_{\varepsilon,T}}\partial_t w_\varepsilon^k e^k\,d\sigma_x dt+\varepsilon\iint_{\Gamma_{\varepsilon,T}^k\cap\Lambda_{\varepsilon,T}}H(v_\varepsilon^k,w_\varepsilon^k)e^k\,d\sigma_x dt\\
&:=R_9+R_{10}
\end{aligned}\tag{3.92}$$

Convergence of the "Unfolded" formulation

In this part, we establish the passage to the limit in (3.91)-(3.92). First, we prove that:

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

by making use of estimates (3.15)-(3.18). So, we prove that $R_3\to 0$ when $\varepsilon\to 0$ and the proof for the other terms is similar. First, by Cauchy-Schwarz inequality, one has

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

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 Holder inequality, the result follows by making use of estimate (3.16) and assumption (3.4) on M_i^ε.

Let us now elaborate the convergence results of $J_1, \cdots, J_8$. Using property (3.1) of Proposition 3.1 and due to the regularity of test functions, we know that the following strong convergence:

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

and

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

Next, we want to use the a priori estimates (3.15)-(3.18) to verify that the remaining terms of the equations are weakly convergent in the unfolded formulation (3.91)-(3.92). Using estimation (3.16), we deduce from Theorem 3.3 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, the following convergences hold as ε goes to zero:

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

and

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

with the space $H_\#^1$ is given by (3.88). 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:

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

Remark 3.12. *Since u_i^k and u_e are independent of y then it does not oscillate "rapidly". This is why now expect u_i^k and u_e to be the "homogenized solutions". To find the homogenized equations, it is sufficient to find an equation in Ω satisfied by u_i^k and the other one satisfied by u_e both independent on y.*

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 (3.18) to get for $k = 1, 2$

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

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 from Theorem 3.3 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

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

By the same strategy for the convergence of J_1, there exits $\partial_t s \in L^2\left(\Omega_T\right)$ such that

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

Thus, one has

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

Now, making use of estimate (3.15) with property (3.1) of Proposition 3.1, one has

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

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:

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

Similarly, using assumption (3.10) on $\mathcal{I}_{app,\varepsilon}^k$, we obtain the following convergence:

$$J_8 = \frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathcal{T}_\varepsilon^{b,k}(\mathcal{I}_{app,\varepsilon}^k)\mathcal{T}_\varepsilon^{b,k}(\psi^k)\,dxd\sigma_ydt \to \frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathcal{I}_{app}^k\psi^k\,dxd\sigma_ydt.$$

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 $k=1,2$ by using Kolmogorov-Riesz type compactness criterion B.1 that can be found as Corollary 2.5 in [GNR16]. Next, we prove by Vitali's Theorem the strong convergence of $\mathrm{I}_{a,ion}\left(\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right)$ to $\mathrm{I}_{a,ion}(v^k)$ in $L^q(\Omega_T\times\Gamma^k)$, $\forall q \in [1, r/(r-1))$ with $r\in(2,+\infty)$.
To cope with this, in the following theorem, we derive the convergence of the nonlinear term $\mathrm{I}_{a,ion}$:

Theorem 3.4. *The following convergence holds for $k=1,2$:*

$$\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k) \to v^k \textit{ strongly in } L^2(\Omega_T\times\Gamma^k), \tag{3.93}$$

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

$$\mathrm{I}_{a,ion}\left(\mathcal{T}_\varepsilon^{b,k}(v_\varepsilon^k)\right) \to \mathrm{I}_{a,ion}(v^k) \textit{ strongly in } L^q(\Omega_T \times \Gamma^k),\ \forall q \in [1, r/(r-1)), \tag{3.94}$$

as $\varepsilon \to 0$.

Proof. We follow the same idea to the proof of Lemma 5.3 in [Ben+19] for first convergence (3.93) which is based on the Kolmogorov compactness criterion (cf. Theorem B.1).

Next, we want to prove second convergence (3.94). Note that from the structure of $\mathrm{I}_{a,ion}$ given by (3.6) and using property (3.1) in Proposition 3.1, we have

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

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

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

Further, we use estimate (3.17) with property (3.1) of Proposition 3.1 to obtain for $k = 1, 2$

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

Hence, using a classical result (see Lemma 1.3 in [Lio69]):

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

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

Finally, we pass to the limit when $\varepsilon \to 0$ in the unfolded formulation (3.91) to obtain the following limiting problem:

$$
\begin{aligned}
&\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\partial_t v^k\psi^k\,dxd\sigma_y dt+\frac{1}{|Y|}\int_{\Omega_T\times\Gamma^{1,2}}\partial_t s\Psi\,dxd\sigma_y dt\\
&+\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times Y_i^k}\mathrm{M}_i\left[\nabla u_i^k+\nabla_y\widehat{u}_i^k\right]\nabla\varphi_i^k\,dxdydt\\
&+\frac{1}{|Y|}\iiint_{\Omega_T\times Y_e}\mathrm{M}_e\left[\nabla u_e+\nabla_y\widehat{u}_e\right]\nabla\varphi_e\,dxdydt\\
&+\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathrm{I}_{a,ion}(v^k)\psi^k\,dxd\sigma_y dt+\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathrm{I}_{b,ion}(w^k)\psi^k\,dxd\sigma_y dt\\
&+\frac{1}{|Y|}\iint_{\Omega_T\times\Gamma^{1,2}}\mathcal{I}_{gap}(s)\Psi\,dxd\sigma_y dt\\
&=\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times\Gamma^k}\mathcal{I}_{app}^k\psi^k\,dxd\sigma_y dt,
\end{aligned}
\tag{3.95}
$$

Similarly, we can prove also that the limit of (3.92) for $k=1,2$ as ε tends to zero, is given by:

$$
\frac{1}{|Y|}\iint_{\Omega_T\times\Gamma^k}\partial_t we^k\,dxd\sigma_y dt-\frac{1}{|Y|}\iint_{\Omega_T\times\Gamma^k}H(v^k,w^k)e^k\,dxd\sigma_y dt=0. \tag{3.96}
$$

3.5.3 Derivation of the macroscopic tridomain model

The convergence results of the previous section allow us to pass to the limit in the microscopic equations (3.13)-(3.14) and to obtain the homogenized model formulated in Theorem 3.2.

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:

$$
\begin{cases}
\varphi_{e,\varepsilon}=\phi_e(t,x)+\varepsilon\theta_e(t,x)\Theta_{e,\varepsilon}(x),\\
\varphi_{i,\varepsilon}^k=\phi_i^k(t,x)+\varepsilon\theta_i^k(t,x)\Theta_{i,\varepsilon}^k(x),
\end{cases}
\tag{3.97}
$$

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

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

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 (3.1) of Proposition 3.1, there holds for $k = 1, 2$:

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

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 $\Psi := (\phi_i^1 - \phi_i^2)|_{\Omega_T \times \Gamma^{1,2}}$.

Collecting all the convergence results of $J_1, \ldots, J_8$ obtained in Section 3.5.2, we deduce the following limiting problem:

$$\begin{aligned}
&\sum_{k=1,2} \frac{\left|\Gamma^k\right|}{|Y|} \iint_{\Omega_T} \partial_t v^k \psi^k \, dxdt + \frac{|\Gamma^{1,2}|}{|Y|} \int_{\Omega_T} \partial_t s \Psi \, dxdt\\
&+ \frac{1}{|Y|} \sum_{k=1,2} \iint_{\Omega_T \times Y_i^k} \mathrm{M}_i \left[\nabla u_i^k + \nabla_y \widehat{u}_i^k\right]\left[\nabla_x \phi_i^k + \theta_i^k \nabla_y \Theta_{i,\varepsilon}^k\right] \, dxdydt\\
&+ \frac{1}{|Y|} \iiint_{\Omega_T \times Y_e} \mathrm{M}_e \left[\nabla u_e + \nabla_y \widehat{u}_e\right]\left[\nabla_x \phi_e + \theta_e \nabla_y \Theta_{e,\varepsilon}\right] \, dxdydt\\
&+ \sum_{k=1,2} \frac{\left|\Gamma^k\right|}{|Y|} \iint_{\Omega_T} \mathrm{I}_{a,ion}(v^k)\psi^k \, dxdt + \sum_{k=1,2} \frac{\left|\Gamma^k\right|}{|Y|} \iint_{\Omega_T} \mathrm{I}_{b,ion}(w^k)\psi^k \, dxdt\\
&+ \frac{|\Gamma^{1,2}|}{|Y|} \iint_{\Omega_T} \mathcal{I}_{gap}(s)\Psi \, dxdt\\
&= \sum_{k=1,2} \frac{\left|\Gamma^k\right|}{|Y|} \iint_{\Omega_T} \mathcal{I}_{app}^k \psi^k \, dxdt.
\end{aligned} \tag{3.98}$$

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

$$\frac{\left|\Gamma^k\right|}{|Y|}\iint_{\Omega_T} \partial_t w e^k \, dxdt - \frac{\left|\Gamma^k\right|}{|Y|}\iint_{\Omega_T} H(v^k, w^k) e^k \, dxdt = 0. \tag{3.99}$$

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 (3.98). 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:

$$\frac{1}{|Y|}\sum_{k=1,2}\iint_{\Omega_T\times Y_i^k} \mathrm{M}_i \left[\nabla u_i^k + \nabla_y \widehat{u}_i^k\right]\left[\theta_i^k \nabla_y \Theta_{i,\varepsilon}^k\right] \, dxdydt = 0. \tag{3.100}$$

Since $u_i^k, k = 1, 2$ is independent on the microscopic variable y then the formulation (3.100) corresponds to the following microscopic problem:

$$\begin{cases} -\nabla_y \cdot \left(\mathrm{M}_i \nabla_y \widehat{u}_i^k\right) = \sum_{p,q=1}^{d} \dfrac{\partial \mathrm{m}_i^{pq}}{\partial y_p}\dfrac{\partial u_i^k}{\partial x_q} \text{ in } Y_i^k, \\ \widehat{u}_i^k \ y\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_y \widehat{u}_i^k + \mathrm{M}_i \nabla_x u_i^k\right) \cdot n_i^k = 0 \text{ on } \Gamma^k, \\ \left(\mathrm{M}_i \nabla_y \widehat{u}_i^k + \mathrm{M}_i \nabla_x u_i^k\right) \cdot n_i^k = 0 \text{ on } \Gamma^{1,2}. \end{cases} \tag{3.101}$$

Hence, by the y-periodcity of M_i and the comptability condition, it is not difficult to establish the existence of a unique periodic solution up to an additive constant of the problem (3.101) (see Section 3.4).

Thus, the linearity of terms in the right of the equation (3.101) suggests to look for $\widehat{u}_i^k$ under the following form in terms of u_i^k:

$$\widehat{u}_i^k(t, x, y, z) = \chi_i(y) \cdot \nabla_x u_i^k + \widehat{u}_{0,i}^k(t, x, y), \tag{3.102}$$

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:

$$\begin{cases} -\nabla_y \cdot (\mathrm{M}_i \nabla_y \chi_i^q) = \sum_{p=1}^{d} \dfrac{\partial \mathrm{m}_i^{pq}}{\partial y_p} \text{ in } Y_i^k, \\ \dot{\chi}_i^q \; y\text{-periodic}, \\ \mathrm{M}_i \nabla_y \dot{\chi}_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \text{ on } \Gamma^k, \; k = 1,2 \\ \mathrm{M}_i \nabla_y \dot{\chi}_i^q \cdot n_i^k = -(\mathrm{M}_i e_q) \cdot n_i^k \text{ on } \Gamma^{1,2}, \end{cases} \tag{3.103}$$

for $q = 1, \ldots, d$. Moreover, the comptability condition is imposed to guarantee the existence and uniqueness of solution $\chi_i^q \in H^1_{\#}(Y_i^k)$ to problem (3.103) with $H^1_{\#}$ is given by (3.88).

Finally, inserting the form (3.102) of $\widehat{u}_i^k$ into (3.98) and setting $\theta_i^k, \theta_e \; \phi_e$ to zero, one obtains the weak formulation of the homogenized equation for the intracellular problem:

$$\begin{aligned} &\sum_{k=1,2} \mu_k \iint_{\Omega_T} \partial_t v^k \phi_i^k \, dxdt + \mu_g \int_{\Omega_T} \partial_t s \phi_i^1 \, dxdt \\ &+ \frac{1}{|Y|} \sum_{k=1,2} \iint_{\Omega_T \times Y_i^k} \widetilde{\mathbf{M}}_i \nabla u_i^k \cdot \nabla \phi_i^k \, dxdydt \\ &+ \sum_{k=1,2} \mu_k \iint_{\Omega_T} \mathrm{I}_{a,ion}(v^k) \phi_i^k \, dxdt + \sum_{k=1,2} \mu_k \iint_{\Omega_T} \mathrm{I}_{b,ion}(w^k) \phi_i^k \, dxdt \\ &+ \mu_g \iint_{\Omega_T} \mathcal{I}_{gap}(s) \phi_i^1 \, dxdt = \sum_{k=1,2} \mu_k \iint_{\Omega_T} \mathcal{I}_{app}^k \phi_i^k \, dxdt, \end{aligned} \tag{3.104}$$

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

$$\widetilde{\mathbf{m}}_i^{pq} := \frac{1}{|Y|} \sum_{\ell=1}^{d} \int_{Y_i^k} \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell} \frac{\partial \chi_i^q}{\partial y_\ell} \right) dy. \tag{3.105}$$

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 3.2 using unfolding homogenization method.

Remark 3.13.

1. *Since the conductivity matrices* M_j *for* $j = i, e$ *are symmetric then the homogenized conductivity matrices* $\widetilde{\mathbf{M}}_j$ *defined by* (3.20a)-(3.20b) *are also symmetric for* $j = i, e$.

2. *We can rewrite the homogenized conductivity matrices* $\widetilde{\mathbf{M}}_i = (\widetilde{\mathbf{m}}_i^{pq})_{1\le p,q\le d}$ *as follows*

$$\widetilde{\mathbf{m}}_i^{pq} := \frac{1}{|Y|}\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k} \mathrm{m}_i^{\ell\ell'}\frac{\partial\left(y_q+\chi_i^q\right)}{\partial y_{\ell'}}\frac{\partial\left(y_p+\chi_i^p\right)}{\partial y_\ell}\,dy. \tag{3.106}$$

Indeed, we recall that χ_i^q *is the solution of* (3.103)*. Choosing* χ_i^p *as test function in* (3.103)*, 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,

$$\frac{1}{|Y|}\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial\left(y_q+\chi_i^q\right)}{\partial y_{\ell'}}\frac{\partial\chi_i^p}{\partial y_\ell}\,dy = 0. \tag{3.107}$$

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 (3.105) *can be written as follows:*

$$\widetilde{\mathbf{m}}_i^{pq} = \frac{1}{|Y|}\sum_{\ell,\ell'=1}^{d}\int_{Y_i^k}\mathrm{m}_i^{\ell\ell'}\frac{\partial\left(y_q+\chi_i^q\right)}{\partial y_{\ell'}}\frac{\partial y_p}{\partial y_\ell}\,dy,\ \forall p,q=1,\ldots,d. \tag{3.108}$$

Summing (3.107) *from* (3.108) *gives* (3.106)*. 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 ellipticity conditions defined by* (3.4)*. Then there exits* $\alpha_0>0$ *such that*

$$\widetilde{\mathbf{M}}_j\lambda\cdot\lambda \ge \alpha_0\left|\lambda\right|^2, \tag{3.109a}$$
$$\left|\widetilde{\mathbf{M}}_j\lambda\right| \le \beta_0\left|\lambda\right|,\ \textit{for any } \lambda\in\mathbb{R}^d. \tag{3.109b}$$

Indeed, let $\lambda \in \mathbb{R}^d$ *and* $j = i$. *To prove* (3.109a)*, then from* (3.106) *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 $\zeta_i = \sum_{p=1}^{d} \lambda_p \frac{\partial \left(y_p + \chi_i^p\right)}{\partial y_\ell}$ *and using the ellipticity of* M_i *defined by* (3.4)*, we get*

$$\sum_{p,q=1}^{d} \widetilde{\mathbf{m}}_i^{pq} \lambda_p \lambda_q \geq \frac{\alpha}{|Y|} \int_{Y_i^k} \left|\nabla \zeta_i\right|^2 \, dy \geq 0, \text{ for any } \lambda \in \mathbb{R}^d. \tag{3.110}$$

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 (3.110)*, one would have some* $\lambda \neq 0$ *such that*

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

This means that

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

Thus, one has

$$\sum_{p=1}^{d} \lambda_p \frac{\partial y_p}{\partial y_\ell} = \sum_{p=1}^{d} \lambda_p \frac{\partial \chi_i^p}{\partial y_\ell} + C,$$

and this impossible since the right-hand side function is y*-periodic by definition and* $\lambda \neq 0$. *To end the proof of ellipticity, let* $\widetilde{\mathbf{M}}$ *be the following function:*

$$\widetilde{\mathbf{M}}(\xi, \xi) = \sum_{p,q=1}^{d} \widetilde{\mathbf{m}}_i^{pq} \xi_p \xi_q.$$

This function is continuous on the unit sphere $\mathbb{S}^{d-1}$ *which is a compact set of* $\mathbb{R}^d$. *Hence,* $\widetilde{\mathbf{M}}$ *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*

$$\widetilde{\mathbf{M}}(\xi, \xi) \geq \alpha_0, \ \forall \xi \in \mathbb{S}^{d-1}.$$

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* (3.109a) *and by the same way we obtain the second inequality.*

Conclusion and Outlook

Many cardiovascular pathologies are due to electro-physiological disorders that disturb the cardiac rhythm. The mathematical problems that arise on this subject are diverse, which explains why the literature is so abundant. In this thesis, we are concerned with the analysis of a *bidomain* and, respectively, of a *tridomain* model describing the chemical and the electrical activity of the complex structured cardiac tissue. We have proposed suitable homogenization methods, both formal and rigorous, allowing the improvement of the existing models for analyzing the electrochemical phenomena arising in the human heart. The main lessons and conclusions we have drawn from this work are given in this last chapter. The innovative tools developed in this thesis lead to new questions, and perspectives will be proposed. will be proposed. We start with a list of conclusions and perspectives by chapter. The equations that are referenced refer to those given in the introduction.

Chapter 2

- ⋆ **Conclusions:** In Chapter 2, we have proposed a model that extends the standard microscopic bidomain model with the periodic inclusions. These inclusions represent non-excitable regions in the intracellular medium, such as mitochondria, the powerhouse of the myocardium. The scale of such inclusions is significantly smaller than the scale of the extracellular and intracellular spaces, and then much smaller compared to the scale of the tissue. In the first part of this chapter, we proposed a detailed study that consists in providing a non-dimensionalization to make appear three different scales (macro-meso-micro) in microscopic equations, based on the literature.

  From a computational point of view this microscopic model is very costly, as we need to create very detailed meshes of the tissue with the sub-domains, and the mesh step would depend directly on the size of the sub-domains and the periodic cell. To avoid this problem, we have presented a complete mathematical analysis of the homogenization procedure that leads to the macroscopic bidomain model based on two different methods: the asymptotic and unfolding approaches. The macroscopic (homogenized) model is in fact the bidomain model, where the effects of the micro-structure are observed within the modified intracellular and extracellular conductivity tensors. In the derivation of the modified conductivity tensors, we see that both volume and shape of the inclusions play a role.

- ⋆ **Perspectives:** To quantify these effects, we could perform numerical tests in 2D or 3D. We could observe that the modified conductivity tensors, for different shapes, will express a different dependence on volume fractions. In addition, we could observe changes in the anisotropy ratios for intracellular and extracellular conductivities. Tests on wave propagation could show that the inclusions modify the velocity as well as the shape of the wavefront.
  In a second perspective, one could numerically confirm the convergence of the meso-microscopic problem to the derived homogenized equations.

Chapter 3

- ⋆ **Conclusions:** The gap junctions that electrically connect the cardiac cells together, play an important role for signal propagation in cardiac tissue. They have a dynamical behavior that is neglected in the current mathematical models such as the bidomain model. In Chapter 3, we were interested in the construction of a novel model describing the electrical activity in cardiac tissue with dynamical gap junctions. First, we established the global existence and uniqueness of the weak solutions to our microscopic tridomain model. The global existence of solution, which constitutes the main result of this paper, is proved by means of an approximate non-degenerate system, the Faedo-Galerkin method, and an appropriate compactness argument. Then, using the asymptotic and unfolding methods in homogenization, we showed that the sequence of solutions constructed in this microscopic model converges to the solution of the macroscopic tridomain model. Because of the nonlinear ionic function, the proof is based on the surface unfolding method and Kolmogorov compactness argument.
- ⋆ **Perspectives:** A first perspective would be to see if it is possible to add the other organelles (mitochondria, endoplasmic reticulim, ...) inside cardiac cells in the tridomain model. We would need a new analysis taking into account three different scales as described in the previous chapter.
  A second perspective of this work is the consideration of the monodomain model, which will be a simplification of the tridomain model obtained in the particular case where the intra- and extracellular domains have equal anisotropy ratios. Then we could numerically illustrate the diffusion term of this problem.

Finally, for the sake of mathematical "simplicity" we have assumed in our work the periodic structure of the tissue. This is not very realistic, and one might explore the non-periodic structures and non-periodic homogenization techniques.

A

Appendix A

A.1 Periodic Sobolev space

In this section, we give the properties which play an important role in the theory of homogenization (see [CD99]). For more details on functional analysis, the reader is referred to the following references: [Rud73], [AF75], [Edw95], [BCL99], [Zei13]. We denote by $\mathcal{O}$ the interval in $\mathbb{R}^d$ defined by :

$$\mathcal{O} =]0, \ell_1[\times \cdots \times]0, \ell_d[\,, \tag{A.1}$$

where $\ell_1, \ldots, \ell_d$ are given positive numbers. We will refer to $\mathcal{O}$ as the reference cell.

We define now the periodicity for functions which are defined almost everywhere.

Definition A.1. *Let $\mathcal{O}$ the reference cell defined by (A.1) and f a function defined a.e on $\mathbb{R}^d$. The function f is called* **y***-periodic, if and only if,*

$$f(y + k\ell_i e_i) = f(y) \text{ p.p. on } \mathbb{R}^d,\ \forall k \in \mathbb{Z},\ \forall i \in \{1, \ldots, d\},$$

where $\{e_1, \ldots, e_d\}$ is the canonical basis of $\mathbb{R}^d$.

Definition A.2. *Let $\alpha, \beta \in \mathbb{R}$, such that $0 < \alpha < \beta$. We denote by $M(\alpha, \beta, \mathcal{O})$ the set of the $d \times d$ matrices $\mathrm{M} = (\mathrm{m}^{pq})_{1 \le p,q \le d} \in L^\infty(\mathcal{O})^{d \times d}$ such that :*

$$\begin{cases} (\mathrm{M}(x)\lambda, \lambda) \ge \alpha\, |\lambda|^2\,, \\ |\mathrm{M}(x)\lambda| \le \beta\, |\lambda|\,, \end{cases} \tag{A.2}$$

for any $\lambda \in \mathbb{R}^d$ and almost everywhere on $\mathcal{O}$.

In this part, we introduce a notion of periodicity for functions in the Sobolev space H^1. In the sequel, we take $\mathcal{O}$ an open bounded set in $\mathbb{R}^d$.

Definition A.3. *Let $C^\infty_{per}(\mathcal{O})$ be the subset of $C^\infty(\mathbb{R}^d)$ of periodic functions. We denote by $H^1_{per}(\mathcal{O})$ the closure of $C^\infty_{per}(\mathcal{O})$ for the H^1-norm, namely,*

$$H^1_{per}(\mathcal{O}) = \overline{C^\infty_{per}(\mathcal{O})}^{H^1(\mathcal{O})}.$$

Proposition A.1. *Let $u \in H^1_{per}(\mathcal{O})$. Then u has the same trace on the opposite faces of $\mathcal{O}$.*

In the sequel, we will define the quotient space $H^1_{per}(\mathcal{O})/\mathbb{R}$ and introduce some properties on this space.

Definition A.4. *The quotient space $\mathcal{W}_{per}(\mathcal{O})$ is defined by:*

$$\mathcal{W}_{per}(\mathcal{O}) = H^1_{per}(\mathcal{O})/\mathbb{R}.$$

It is defined as the space of equivalence classes with respect to the following relation:

$$u \simeq v \Leftrightarrow u - v \text{ is a constant, } \forall u, v \in H^1_{per}(\mathcal{O}).$$

We denote by $\dot{u}$ the equivalence class represented by u.

Proposition A.2. *The following quantity:*

$$\|\dot{u}\|_{\mathcal{W}_{per}(\mathcal{O})} = \|\nabla u\|_{L^2(\mathcal{O})}, \forall u \in \dot{u}, \dot{u} \in \mathcal{W}_{per}(\mathcal{O})$$

defines a norm on $\mathcal{W}_{per}(\mathcal{O})$.
Moreover, the dual space $(\mathcal{W}_{per}(\mathcal{O}))'$ can be identified with the set:

$$(\mathcal{W}_{per}(\mathcal{O}))' = \{F \in (H^1_{per}(\mathcal{O}))' \text{ tel que } F(c) = 0,\ \forall c \in \mathbb{R}\},$$

with

$$F(u) = (F, \dot{u})_{(\mathcal{W}_{per}(\mathcal{O}))', \mathcal{W}_{per}(\mathcal{O})} = (F, u)_{(H^1_{per}(\mathcal{O}))', H^1_{per}(\mathcal{O})},\ \forall u \in \dot{u}, \dot{u} \in \mathcal{W}_{per}(\mathcal{O}).$$

Remark A.1. *In particular, we can choose a representative element u of the equivalence class $\dot{u}$ by fixing the constant. Then, we define a particular space of periodic functions with a null mean* *value as follows:*

$$W_{per}(\mathcal{O}) = \{u \in H^1_{per}(\mathcal{O}) \text{ such that } \mathcal{M}_{\mathcal{O}}(u) = 0\}. \tag{A.3}$$

with $\mathcal{M}_{\mathcal{O}}(u) = \dfrac{1}{|\mathcal{O}|}\displaystyle\int_{\mathcal{O}} u\, dx$. *Its dual coincides with the dual space* $(\mathcal{W}_{per}(\mathcal{O}))'$ *and the duality bracket is defined by:*

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

Furthermore, by the Poincaré-Wirtinger's inequality, the Banach space $W_\#(\mathcal{O})$ *has the following norm:*

$$\|u\|_{W_\#(\mathcal{O})} = \|\nabla u\|_{L^2(\mathcal{O})}, \forall u \in W_\#(\mathcal{O}).$$

In the sequel, we will introduce some elliptic partial differential equations with different boundary conditions: Neumann and periodic conditions. In these cases, to prove existence and uniqueness, the Lax-Milgram theorem will be applied. Few works are available in the literature about boundary value problems, we cite for instance [LM68], [Lio69]. In this part, we will treat the following partial equation:

$$\mathcal{A}u = f \text{ in } \mathcal{O},$$

with the operator $\mathcal{A}$ is defined by:

$$\mathcal{A} = -\nabla \cdot (\mathrm{M}\nabla) \tag{A.4}$$

where the matrix $\mathrm{M} = (\mathrm{m}^{pq})_{1 \le p,q \le d} \in M(\alpha, \beta, \mathcal{O})$ is given by Definition A.2 but with different boundary conditions:

- **Nonhomogenous Neumann condition:**

$$\mathrm{M}\nabla u \cdot n = g \text{ on } \partial\mathcal{O}.$$

- **Periodic-Neumann condition:** Let $\mathcal{O}_j$ a portion of a reference cell $\mathcal{O}$ given by (A.1), with a boundary Γ separate the two regions $\mathcal{O}_j$ and $\mathcal{O} \setminus \mathcal{O}_j$. So, we have :

$$\partial\mathcal{O}_j = (\partial\mathcal{O} \cap \partial\mathcal{O}_j) \cup \Gamma.$$

The boundary condition which plays an essential role in the homogenization of perforated periodic media, namely,

$$\begin{cases} u \ \textbf{y}\text{-periodic}, \\ \mathrm{M}\nabla u \cdot n = g \text{ on } \Gamma. \end{cases}$$

Theorem A.1. (*Nonhomogenous Neumann condition*)
We consider the following problem:

$$\begin{cases} \mathcal{A}u = f \textit{ in } \mathcal{O}, \\ \mathrm{M}\nabla u \cdot n = g \textit{ on } \partial\mathcal{O}. \end{cases} \tag{A.5}$$

with the operator $\mathcal{A}$ is defined by (A.4)*. Its variational formulation is:*

$$\begin{cases} \textit{Find } u \in H^1(\mathcal{O}) \textit{ such that} \\ a_{\mathcal{O}}(u,v) = (f,v)_{H^{-1}(\mathcal{O}),H^1(\mathcal{O})} + (g,v)_{H^{-\frac{1}{2}}(\partial\mathcal{O}),H^{\frac{1}{2}}(\partial\mathcal{O})} \ \forall v \in H^1(\mathcal{O}), \end{cases} \tag{A.6}$$

with $a_{\mathcal{O}}$ is defined by:

$$a_{\mathcal{O}}(u,v) = \int_{\mathcal{O}} \mathrm{M}\nabla u \nabla v dx, \ \forall u,v \in H^1(\mathcal{O}).$$

We take $V = H^1(\mathcal{O})$. Suppose that $f \in L^2(\mathcal{O})$ and $g \in H^{\frac{1}{2}}(\partial\mathcal{O})$ satisfy the following compatibility condition:

$$(f,1)_{H^{-1}(\mathcal{O}),H^1(\mathcal{O})} + (g,1)_{H^{-\frac{1}{2}}(\partial\mathcal{O}),H^{\frac{1}{2}}(\partial\mathcal{O})} = 0. \tag{A.7}$$

Then, the problem (A.5)-(A.6) *has a unique solution $u \in H^1(\mathcal{O})$. Moreover,*

$$\|u\|_{H^1(\mathcal{O})} \leq \frac{1}{\alpha_0}\left(\|f\|_{L^2(\mathcal{O})} + C_\gamma \|g\|_{H^{-\frac{1}{2}}(\partial\mathcal{O})}\right),$$

where $\alpha_0 = \min(1,\alpha)$ and C_γ is the trace constant.

Theorem A.2. (*Periodic-Newmann condition*)
Let $\mathcal{O}_j$ a portion of a unit cell $\mathcal{O}$ given by (A.1)*, with Lipschitz continuous boundary Γ separate*

the two regions $\mathcal{O}_j$ and $\mathcal{O} \setminus \mathcal{O}_j$. Consider the following problem:

$$\begin{cases} \mathcal{A}u = f \text{ in } \mathcal{O}_j, \\ u \ y\text{-periodic}, \\ \mathrm{M}\nabla u \cdot n = g \text{ on } \Gamma. \end{cases} \tag{A.8}$$

We take $V = \mathcal{W}_{per}(\mathcal{O}_j)$. Then, for any $f \in (\mathcal{W}_{per}(\mathcal{O}_j))'$ and for any $g \in H^{\frac{1}{2}}(\Gamma)$, the variational formulation of the problem (A.8) is:

$$\begin{cases} \text{Find } \dot{u} \in \mathcal{W}_{per}(\mathcal{O}_j) \text{ such that} \\ \dot{a}_{\mathcal{O}_j}(\dot{u}, \dot{v}) = (F, \dot{v})_{(\mathcal{W}_{per}(\mathcal{O}_j))', \mathcal{W}_{per}(\mathcal{O}_j)} \ \forall \dot{v} \in \mathcal{W}_{per}(\mathcal{O}_j), \end{cases} \tag{A.9}$$

with $a_{\mathcal{O}_j}$ is given by:

$$\dot{a}_{\mathcal{O}_j}(\dot{u}, \dot{v}) = \int_{\mathcal{O}_j} \mathrm{M}\nabla u \nabla v dy, \ \forall u \in \dot{u}, \ \forall v \in \dot{v},$$

and F is defined by:

$$(F, \dot{v})_{(\mathcal{W}_{per}(\mathcal{O}_j))', \mathcal{W}_{per}(\mathcal{O}_j)} = \int_{\Gamma} \mathrm{M}_i \nabla u \cdot nv \, d\sigma(y) + \int_{\mathcal{O}_j} fv \, dy, \ \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{per}(\mathcal{O}_j),$$

where n denotes the unit outward normal to Γ.

Assume that M belongs to $M(\alpha, \beta, \mathcal{O})$ with y-periodic coefficients. Suppose that F belongs to $(\mathcal{W}_{per}(\mathcal{O}_j))'$ which equivalent to

$$(F, 1)_{(\mathcal{W}_{per}(\mathcal{O}_j))', \mathcal{W}_{per}(\mathcal{O}_j)} = 0.$$

Then problem (A.9) has a unique weak solution. Moreover, we have the following estimation:

$$\|\dot{u}\|_{\mathcal{W}_{per}(\mathcal{O}_j)} \leq \frac{1}{\alpha_0} \left(\|f\|_{L^2(\mathcal{O}_j)} + C_\gamma \|g\|_{H^{-\frac{1}{2}}(\Gamma)} \right).$$

where $\alpha_0 = \min(1, \alpha)$ and C_γ is the trace constant.

By the definition of $\mathcal{W}_{per}$, the previous theorem shows that the problem (A.8) admits a solution in H^1_{per}, defined up to an additive constant. If we take the particular case $V = W_\#(\mathcal{O})$ defined by (2.91), we obtain the same result.

B

Appendix B

B.1 Compactness result for the space $L^p(\Omega, B)$

In this part, we give a characterization of relatively compact sets F in $L^p(\Omega, B)$ for $p \in [1; +\infty)$, $\Omega \subset \mathbb{R}^d$ open and bounded set and B a Banach space.

Proposition B.1 (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 $h \in \mathbb{R}^d$, we define $\tau_h f(x) := f(x+h)$. Then F is relatively compact in $L^p(\Omega, B)$ if and only if*

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

(ii) *for all $\lambda > 0$, $h \in \mathbb{R}^d$ and $h_i \geq 0$, $i = 1, \ldots, d$, there holds*

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

where $\Omega_\lambda^h := \{x \in \Omega_\lambda : x + h \in \Omega_\lambda\}$ 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 $\lambda \to 0$.*

Proof. The proof of the proposition can be found as Corollary 2.5 in [GNR16]. □

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UNIVERSITE BRETAGNE LOIRE / MATHSTIC

Lebanese University

Doctoral School
Science & Technology

CENTRALE NANTES

Titre : Méthode d'homogénéisation d'éclatement multi-échelle appliquée aux modèles d'électrocardiologie bidomaine et tridomaine.

Mot clés : Bidomaine, Tridomaine, Méthode d'homogénéisation asymptotique à trois échelles, Méthode d'éclatement périodique, Gap junctions, Électro-cardiologie.

Résumé : Cette thèse est principalement consacrée à la modélisation et à l'analyse multi-échelle de systèmes d'électrocardiologie bidomaine et tridomaine. L'électrophysiologie cardiaque décrit et modélise les phénomènes chimiques et électriques qui se produisent dans le tissu cardiaque.

Au niveau microscopique, le tissu cardiaque est très complexe et il est donc très difficile de comprendre et de prévoir son comportement à l'échelle macroscopique (observable). Ainsi, à chaque système (bidomaine ou tridomaine) on associe un modèle microscopique (de type elliptique), couplé à un système d'EDO non-linéaire et un autre macroscopique (de type réaction-diffusion).

En se basant sur la loi de la conduction électrique d'Ohm et la conservation de la charge électrique, on obtient le modèle microscopique qui donne une description détaillée de l'activité électrique dans les cellules responsables de la contraction cardiaque. Ensuite, en utilisant des techniques d'homogénéisation, on obtient le modèle macroscopique qui, à son tour, permet de décrire la propagation des ondes électriques dans le cœur entier.

Cette thèse est composée en deux grandes parties. D'abord, on donne une justification mathématique formelle et rigoureuse du processus d'homogénéisation périodique qui conduit au modèle macroscopique bidomaine. La méthode formelle est un développement asymptotique à trois échelles appliqué au modèle bidomaine méso- et microscopique. En outre, la justification mathématique rigoureuse est basée sur des opérateurs d'éclatement qui non seulement dérivent l'équation homogénéisée mais aussi prouvent la convergence de la suite de solutions du problème bidomaine microscopique vers la solution du problème macroscopique. Pour traiter les modèles ioniques non linéaires, l'opérateur d'éclatement sur la surface et un argument de type Kolmogorov sont utilisés pour assurer la compacité.

Ensuite, on travaille sur l'analyse mathématique d'un nouveau modèle décrivant l'activité électrique des cellules cardiaques en présence de jonctions communicantes est proposé. Il s'agit notamment du modèle "tridomaine". On montre l'existence et l'unicité de la solution faible du modèle microscopique tridomaine en utilisant la méthode constructive de Faedo-Galerkin. Finalement, l'obtention du modèle tridomaine macroscopique (homogénéisé) est justifiée d'une part par la méthode de développement asymptotique et d'autre part par l'analyse de convergence du modèle microscopique en s'appuyant sur la méthode d'éclatement périodique.

Title: Multi-scale unfolding homogenization method applied to bidomain and tridomain electrocardiology models.

Keywords: Bidomain, Tridomain, Three-scale asymptotic homogenization method, Periodic unfolding method, Gap junctions, Electro-cardiology.

Abstract: This thesis is mainly devoted to the modeling and multi-scale analysis of bidomain and tridomain electrocardiology systems. Cardiac electro-physiology describes and models the chemical and electrical phenomena that occur in cardiac tissue.

At the microscopic level, cardiac tissue is very complex and it is therefore very difficult to understand and predict its behavior at the macroscopic (observable) scale. Thus, to each (bidomain or tridomain) system we associate a microscopic model (of elliptical type), coupled to a nonlinear ODE system and another macroscopic one (of reaction-diffusion type).

Based on Ohm's law of electrical conduction and conservation of electrical charge, we obtain the microscopic model that gives a detailed description of the electrical activity in the cells responsible for cardiac contraction. Then, using homogenization techniques, we obtain the macroscopic model which, in turn, allows us to describe the propagation of electrical waves in the entire heart.

This thesis is composed of two main parts. First, we give a formal and rigorous mathematical justification of the periodic homogenization process that leads to the macroscopic bidomain model. The formal method is a kind of asymptotic development at three scales that we apply to our meso- and microscopic bidomain model. Moreover, the rigorous method is based on unfolding operators which not only derive the homogenized equation but also prove the convergence of the solution sequence of the microscopic bidomain problem to the solution of the macroscopic problem. Because of nonlinear terms, the boundary unfolding operator and a Kolmogorov type argument for the phenomenological ionic models are used.

Then, we work on the mathematical analysis of a new model that describes the electrical activity of cardiac cells in the presence of junctions. This model is the "tridomain" model. We show the existence and uniqueness of the weak solution of the tridomain microscopic model using the Faedo-Galerkin constructive technique and a compactness argument in L^2. Finally, while using the two previous homogenization methods, we develop the macroscopic tridomain model which corresponds to an approximation of our microscopic model.