J Eng Math (2021) 131:3
https://doi.org/10.1007/s10665-021-10174-8

Derivation of a new macroscopic bidomain model including three scales for the electrical activity of cardiac tissue

Fakhrielddine Bader · Mostafa Bendahmane · Mazen Saad · Raafat Talhouk

Received: 12 December 2020 / Accepted: 30 August 2021 / Published online: 11 October 2021
© The Author(s), under exclusive licence to Springer Nature B.V. 2021

Abstract In the present paper, a new three-scale asymptotic homogenization method is proposed to study the electrical behavior of the cardiac tissue structure with multiple heterogeneities at two different levels. The first level is associated with the mesoscopic structure such that the cardiac tissue is composed of extracellular and intracellular domains. The second level is associated with the microscopic structure in such a way the intracellular medium can only be viewed as a periodical layout of unit cells (mitochondria). Then, we define two kinds of local cells that are obtained by upscaling methods. The homogenization method is based on a power series expansion which allows determining the macroscopic (homogenized) bidomain model from the microscopic bidomain problem at each structural level. First, we use the two-scale asymptotic expansion to homogenize the extracellular problem. Then, we apply a three-scale asymptotic expansion in the intracellular problem to obtain its homogenized equation at two levels. The first upscaling level of the intracellular structure yields the mesoscopic equation and the second step of the homogenization leads to obtain the intracellular homogenized equation. Both the mesoscopic and microscopic information are obtained by homogenization to capture local characteristics inside the cardiac tissue structure. Finally, we obtain the macroscopic bidomain model and the heart domain coincides with the intracellular medium and extracellular one, which are two inter-penetrating and superimposed continua connected at each point by the cardiac cellular membrane. The interest of the proposed method comes from the fact that it combines microscopic and mesoscopic characteristics to obtain a macroscopic description of the electrical behavior of the heart.

Keywords Bidomain model · Double-periodic media · Homogenization theory · Reaction–diffusion system · Three-scale method

F. Bader (✉) · R. Talhouk
Mathematics Laboratory, Doctoral School of Sciences and Technologies, Lebanese University, Hadat Beirut, Lebanon
e-mail: fakhrielddine.bader@ec-nantes.fr; fakhri.bader.fb@gmail.com

F. Bader · M. Saad
Ecole Centrale de Nantes, Laboratoire de mathématiques Jean Leray, UMR 6629 CNRS, 1 rue de Noë, 44321 Nantes, France

M. Bendahmane
Institut de Mathématiques de Bordeaux and INRIA-Carmen Bordeaux Sud-Ouest, Université de Bordeaux, Bordeaux, France

1 Introduction

The heart is an organ that ensures life for all living beings. Indeed, its great importance comes from its organic function which allows the circulation of blood throughout the body. It is a muscular organ composed of four cavities: the left atrium and ventricle which represent the left heart, the right atrium and ventricle which form the right heart. These four cavities are surrounded by a cardiac tissue that is organized into muscle fibers. These fibers form a network of cardiac muscle cells called "cardiomyocyte" connected end-to-end by junctions. For more details about the physiological background, we refer to [1] and about the electrical activity of the heart we refer to [2].

The structure of cardiac tissue (myocarde) studied in this paper is characterized at three different scales (see Fig. 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. Then, we consider only that the intracellular medium can be viewed as a periodic perforated structure composed of other connected cells. While at the macroscopic scale, this domain coincides with the intracellular medium and extracellular one, which are two inter-penetrating and superimposed continua connected at each point by the cardiac cellular membrane.

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." The first mathematical formulation of this model was constructed by Tung [3]. The authors in [4] established the well-posedness of this microscopic bidomain model under different conditions and proved the existence and uniqueness of their solutions (see other work [5]).

The microscopic bidomain model [6,7] consists of two quasi-static equations, one for the electrical potential in the intracellular medium and one for the extracellular medium, coupled through a dynamic boundary equation at the interface of the two regions (the membrane Γ^y). In our study, these equations depend on two small scaling parameters ε and δ whose are, respectively, the ratio of the microscopic and mesoscopic scales from the macroscopic scale.

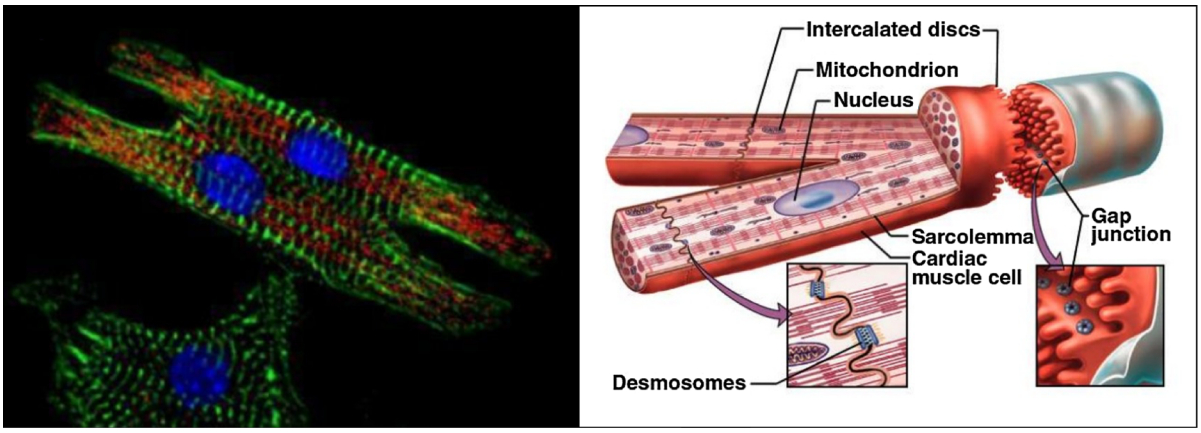

Fig. 1 Representation of the cardiomyocyte structure http://www.cardio-research.com/cardiomyocytes

Our goal in this paper is to derive, using a homogenization method, the macroscopic (homogenized) bidomain model of the cardiac tissue from the microscopic bidomain model. In general, the homogenization theory is the analysis of the macroscopic behavior of biological tissues by taking into account their complex microscopic structure. For an introduction to this theory, we cite [8–11]. Applications of this technique can be found in modeling solids, fluids, solid–fluid interaction, porous media, composite materials, cells, and cancer invasion. Several methods are related to this theory. First, the multiple-scale method established by Benssousan et al. [12] and used in mechanics and physics for problems containing several small scaling parameters.

The two-scale convergence method was introduced by Nugesteng [13] and developed by Allaire et al. [14]. In addition, Allaire et al. [15], Trucu et al. [16] introduced a further generalization of the previous method via a three-scale convergence approach for distinct problems. Here, we are not dealing with a rigorous multi-scale convergence setting, as our main motivation lies in the direct application of asymptotic homogenization by following a formal approach and accounting for a novel series expansion in terms of two distinct scaling parameters ε and δ. Recently, the periodic unfolding method was introduced by Cioranescu et al. for the fixed domains in [17] and for the perforated domains in [18]. This 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 (see also [19,20]).

There are some of these methods that are applied on the microscopic bidomain model to obtain the homogenized macroscopic model. First, Krassowska and Neu [21] applied the two-scale asymptotic method to formally obtain this macroscopic model (see also [6,22] for different approaches). Furthermore, Pennachio et al. [7] used the tools of the Γ-convergence method to obtain a rigorous mathematical form of this homogenized macroscopic model. In [23,24], the authors used the theory of two-scale convergence method to derive the homogenized bidomain model. Recently, the authors in [4] proved the existence and uniqueness of solution of the microscopic bidomain model by using the Faedo–Galerkin method. Further, they applied the unfolding homogenization method at two scales. Some recent works are available on the numerical implementation of bidomain models in the context of pure electro-physiology in [25] and of cardiac electromechanics in [26,27].

The main of contribution of the present paper. The cardiac tissue structure is viewed at micro–macro scales and studied at the three different scales where the intracellular medium is a periodic composed of connected cells. The aim is to derive the two levels of homogenized bidomain model of cardiac electro-physiology from the microscopic bidomain model. This paper presents a formal mathematical writing for the results obtained in a recent work [28] based on a three-scale unfolding homogenization method. In [28], we used unfolding operators to converge our meso–microscopic bidomain problem as $\varepsilon, \delta \to 0$ and then to obtain the same macroscopic bidomain system. While in the present work, we will apply the two-scale asymptotic expansion method on the extracellular medium (similar derivation may be found in [6]). Further, we will derive a formal approach, by accounting for a three-scale asymptotic expansion, in terms of two distinct scaling parameters ε and δ on the intracellular medium based on the work of Benssousan et al. [12]. The asymptotic expansion is proposed to investigate the effective properties of the cardiac tissue at each structural level, namely, micro–meso–macro scales. Moreover, to treat the bidomain problem in this work, the multi-scale technique is needed to be established in time domain directly.

The outline of the paper is as follows. In Sect. 2, we introduce the microscopic bidomain model in the cardiac tissue structure featured by two parameters, ε and δ, characterizing the microscopic and mesoscopic scales. Section 3 is devoted to homogenization procedure. The two-scale asymptotic expansion method applied in the extracellular problem is explained in Sect. 3.1. The homogenized equation for the extracellular problem is obtained in terms of the coefficients of conductivity matrices and cell problems. In Sect. 3.2, the homogenized equation for the intracellular problem is obtained similarly at two levels but using a three-scale asymptotic expansion which depends on ε and δ. The first level of homogenization yields the mesoscopic problem and then we complete the second level to obtain the corresponding homogenized equation. Finally, the main result is presented in Sect. 3.3 and the macroscopic bidomain equations are recuperated from the extracellular and intracellular homogenized equations. In Appendix A, we report some notations and special functional spaces used for the homogenization. More properties and theorems including these spaces are also postponed in the Appendix A.

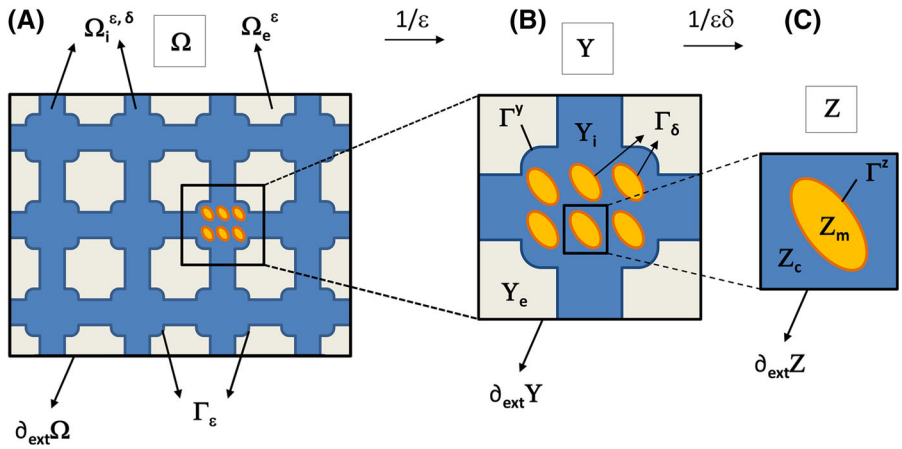

Fig. 2 **A** Periodic heterogeneous domain Ω, **B** Unit cell Y at ε-structural level, and **C** Unit cell Z at δ-structural level

2 Bidomain modeling of the heart tissue

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

2.1 Geometric idealization of the myocardium microstructure

The cardiac tissue $\Omega \subset \mathbb{R}^d$ is considered as a heterogeneous double periodic domain with a Lipschitz boundary $\partial\Omega$. The structure of the tissue is periodic at mesoscopic and microscopic scales related to two small parameters ε and δ, respectively, see Fig. 2.

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. 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

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

2.1.1 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 [7]). Geometrically, we find that $\Omega_i^{\varepsilon,\delta}$ and Ω_e^{ε} are two open connected regions such that

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

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 $Y = \prod_{n=1}^{d}]0, \ell_n^{\text{mes}}[$. Indeed, if we denote by T_ε^k a

translation of εk with $k = (k_1, \ldots, k_d) \in \mathbb{Z}^d$. In addition, if the cell considered Y_ε^k is located at the $k_i^{\text{iéme}}$ position according to the direction i 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 mesoscopic variable $y \approx x/\varepsilon$ 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

$$u\left(x, \frac{x}{\varepsilon} - k_\ell\right) = u\left(x, \frac{x}{\varepsilon}\right).$$

By notation, we say that $y = x/\varepsilon$ 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 denoting the same previous translation.

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

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

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

2.1.2 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 reference 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 $k_n^{'\text{iéme}}$ 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 $z \approx y/\delta \approx x/(\varepsilon\delta)$ that belongs to Z with the translation $T_\delta^{k'}$.

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

$$Z = Z_{\text{m}} \cup Z_{\text{c}} \cup \Gamma^z, \quad \Gamma^z = \partial Z_{\text{m}}.$$

By definition, we have $\partial Z_{\mathrm{c}} = \partial_{\mathrm{ext}} Z \cup \Gamma^z$.

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

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

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

$$u\left(x, y, \frac{x}{\varepsilon\delta} - \frac{k_\ell}{\delta} - k'_{\ell'}\right) = u\left(x, y, \frac{x}{\varepsilon\delta}\right).$$

By notation, we say that $z = x/(\varepsilon\delta)$ belongs to 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 $\Gamma_\delta^{k'}$ is given by

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

with $T_\delta^{k'}$ denoting the same previous translation.

2.2 Microscopic bidomain model

A vast literature exists on the bidomain modeling of the heart, we refer to [2,6,7,29,30] for more details.

2.2.1 Basic equations

The basic equations modeling the electrical activity of the heart can be obtained as follows. First, we know that the structure of the cardiac tissue can be viewed as composed by two volumes: the intracellular space Ω_i (inside the cells) and the extracellular space Ω_e (outside) separated by the active membrane Γ^y.

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 representing the corresponding conductivities of the tissue (which are assumed to be isotropic at the microscale) and are 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 that 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:

$$-\operatorname{div} J_j = 0 \text{ in } \Omega_{j,T}. \tag{1}$$

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

$$\mathcal{I}_{\mathrm{m}} = -J_i \cdot n_i = J_e \cdot n_e \quad \text{on } \Gamma_T^y := (0, T) \times \Gamma^y \tag{2}$$

with n_i denoting 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. 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 $q = C_{\mathrm{m}} v$. Then, the capacitive current $\mathcal{I}_{\mathrm{c}}$ is the amount of charge that flows per unit of time:

$$\mathcal{I}_{\mathrm{c}} = \partial_{\mathrm{t}} q = C_{\mathrm{m}} \partial_{\mathrm{t}} v.$$

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 $\mathcal{I}_{\mathrm{ion}}$ measured from the intracellular to the extracellular medium which depends on the transmembrane potential v and the gating variable $w : \Gamma^y \mapsto \mathbb{R}$. The electric current can be blocked by the membrane or can be passed through the membrane with ionic current $\mathcal{I}_{\mathrm{r}} - \mathcal{I}_{\mathrm{app}}$. So, the charge conservation states that the total transmembrane current $\mathcal{I}_{\mathrm{m}}$ (see [29]) is given as follows:

$$\mathcal{I}_{\mathrm{m}} = \mathcal{I}_{\mathrm{c}} + \mathcal{I}_{\mathrm{r}} - \mathcal{I}_{\mathrm{app}} \quad \text{on } \Gamma_T^y,$$

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

$$\begin{aligned} &\mathcal{I}_{\mathrm{m}} = C_{\mathrm{m}} \partial_{\mathrm{m}} v + \mathcal{I}_{\mathrm{ion}}(v, w) - \mathcal{I}_{\mathrm{app}} && \text{on } \Gamma_T^y, \\ &\partial_{\mathrm{t}} w - H(v, w) = 0 && \text{on } \Gamma_T^y. \end{aligned} \tag{3}$$

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

Mitochondria are a subcompartment of the cell bound by a double membrane. Although some mitochondria probably do look like the traditional cigar-shaped structures, it is more accurate to think of them as a budding and fusing network similar to the endoplasmic reticulum. Mitochondria are intimately involved in cellular homeostasis. Among other functions they play a part in intracellular signaling and apoptosis, intermediary metabolism, and in the metabolism of amino acids, lipids, cholesterol, steroids, and nucleotides. Perhaps most importantly, mitochondria have a fundamental role in cellular energy metabolism. This includes fatty acid oxidation, the urea cycle, and the final common pathway for ATP production—the respiratory chain (see [31] for more details). For this, we assume that the mitochondria are electrically insulated from the remainder of the intracellular space. Thus, we suppose that the no-flux boundary condition at the interface Γ^z is given by

$$\mathrm{M}_i \nabla u_i \cdot n_z = 0 \quad \text{on } \Gamma_T^z := (0, T) \times \Gamma^z, \tag{4}$$

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

2.2.2 Non-dimensional analysis

Cardiac tissues have a number of important inhomogeneities, particularly those related to inter-cellular 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 [6,29,32] for the non-dimensionalization procedure of the ionic current and [22,33] 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:

$$\varepsilon := \sqrt{\frac{\ell^{\mathrm{mes}}}{R_{\mathrm{m}} \lambda}},$$

where R_{m} denotes the surface specific resistivity of the membrane Γ^y and $\lambda := \lambda_i + \lambda_e$, with λ_j representing 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 $L = \ell^{\mathrm{mes}}/\varepsilon = \ell^{\mathrm{mic}}/\delta$ and the time constant τ associated with charging the membrane by the transmembrane current is given by

$$\tau = R_{\mathrm{m}} C_{\mathrm{m}}.$$

We take $\widehat{x}$ to be the variable at the macroscale (slow variable)

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

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

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

Recalling that $\tau = R_{\mathrm{m}} C_{\mathrm{m}}$ and normalizing the conductivities M_j for $j = i, e$ using

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

we get

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

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

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

Consequently, we have

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

Remark 1 Recalling that the dimensionless parameter ε, given by $\varepsilon := \sqrt{\ell^{\mathrm{mes}}/R_{\mathrm{m}}\lambda}$, is the ratio between the mesoscopic cell length ℓ^{mes} and the macroscopic length L, i.e., $\varepsilon = \ell^{\mathrm{mes}}/L$ and solving for ε, we obtain

$$\varepsilon = \frac{L}{R_{\mathrm{m}}\lambda}.$$

Finally, we can convert the above microscopic bidomain system (1)–(4) to the following non-dimensional form:

$$-\nabla_{\widehat{x}} \cdot \left(\widehat{\mathrm{M}}_i^{\varepsilon,\delta}\nabla_{\widehat{x}}\widehat{u}_i^{\varepsilon,\delta}\right) = 0 \qquad \text{in } \Omega_{i,T}^{\varepsilon,\delta} := (0, T) \times \Omega_i^{\varepsilon,\delta}, \tag{5a}$$

$$-\nabla_{\widehat{x}} \cdot \left(\widehat{\mathrm{M}}_e^{\varepsilon}\nabla_{\widehat{x}}\widehat{u}_e^{\varepsilon}\right) = 0 \qquad \text{in } \Omega_{e,T}^{\varepsilon} := (0, T) \times \Omega_e^{\varepsilon}, \tag{5b}$$

$$\varepsilon\left(\partial_{\widehat{t}}\widehat{v}_\varepsilon + \widehat{\mathcal{I}}_{\mathrm{ion}}(\widehat{v}_\varepsilon, \widehat{w}_\varepsilon) - \widehat{\mathcal{I}}_{app,\varepsilon}\right) = \widehat{\mathcal{I}}_m \qquad \text{on } \Gamma_{\varepsilon,T} := (0, T) \times \Gamma_\varepsilon, \tag{5c}$$

$$-\widehat{\mathrm{M}}_i^{\varepsilon,\delta}\nabla_{\widehat{x}}\widehat{u}_i^{\varepsilon,\delta}\cdot n_i = \widehat{\mathrm{M}}_e^{\varepsilon}\nabla_{\widehat{x}}\widehat{u}_e^{\varepsilon}\cdot n_e = \widehat{\mathcal{I}}_m \quad \text{on } \Gamma_{\varepsilon,T}, \tag{5d}$$

$$\partial_{\widehat{t}}\widehat{w}_\varepsilon - \widehat{H}(\widehat{v}_\varepsilon, \widehat{w}_\varepsilon) = 0 \quad \text{on } \Gamma_{\varepsilon,T}, \tag{5e}$$

$$\widehat{\mathrm{M}}_i^{\varepsilon,\delta}\nabla_{\widehat{x}}\widehat{u}_i^{\varepsilon,\delta}\cdot n_z = 0 \quad \text{on } \Gamma_{\delta,T}, \tag{5f}$$

with each equation corresponding to the following sense: (5a) Intra quasi-stationary conduction, (5b) Extra quasi-stationary conduction, (5c) Reaction on face condition, (5d) Meso-continuity equation, (5e) Dynamic coupling, and (5f) Micro-boundary condition.

For convenience, the superscript $\widehat{\cdot}$ 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. Thus, we define also the following rescaled conductivity matrices:

$$\mathrm{M}_i^{\varepsilon,\delta}(x) := \mathrm{M}_i\left(x, \frac{x}{\varepsilon}, \frac{x}{\varepsilon\delta}\right) \quad \text{and} \quad \mathrm{M}_e^{\varepsilon}(x) := \mathrm{M}_e\left(x, \frac{x}{\varepsilon}\right), \tag{6}$$

satisfying the elliptic and periodicity conditions (11)–(29).

Finally, the ionic current $\mathcal{I}_{\text{ion}}(v,w)$ can be decomposed into $\mathrm{I}_{1,\text{ion}}(v) : \mathbb{R} \to \mathbb{R}$ and $\mathrm{I}_{2,\text{ion}}(w); \mathbb{R} \to \mathbb{R}$, where $\mathcal{I}_{\text{ion}}(v,w) = \mathrm{I}_{1,\text{ion}}(v) + \mathrm{I}_{2,\text{ion}}(w)$. Furthermore, $\mathrm{I}_{1,\text{ion}}$ is considered as a C^1 function, $\mathrm{I}_{2,\text{ion}}$ 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

$$\frac{1}{\alpha_1}|v|^{r-1} \le \left|\mathrm{I}_{1,\text{ion}}(v)\right| \le \alpha_1\left(|v|^{r-1}+1\right), \quad \left|\mathrm{I}_{2,\text{ion}}(w)\right| \le \alpha_2(|w|+1), \tag{7a}$$

$$|H(v,w)| \le \alpha_3(|v|+|w|+1), \quad \text{and} \quad \mathrm{I}_{2,\text{ion}}(w)v - \alpha_4 H(v,w)w \ge \alpha_5|w|^2, \tag{7b}$$

$$\tilde{\mathrm{I}}_{1,\text{ion}} : z \mapsto \mathrm{I}_{1,\text{ion}}(z) + \beta_1 z + \beta_2 \text{ is strictly increasing with } \lim_{z\to 0}\tilde{\mathrm{I}}_{1,\text{ion}}(z)/z = 0, \tag{7c}$$

$$\forall z_1, z_2 \in \mathbb{R}, \ \left(\tilde{\mathrm{I}}_{1,\text{ion}}(z_1) - \tilde{\mathrm{I}}_{1,\text{ion}}(z_2)\right)(z_1 - z_2) \ge \frac{1}{C}(1+|z_1|+|z_2|)^{r-2}|z_1-z_2|^2. \tag{7d}$$

Remark 2 In the mathematical analysis of bidomain equations, several paths have been followed in the literature according to the definition of the ionic currents. We summarize below the encountered various cases:

1. **Physiological models**
   These types of models attempt to describe specific actions within the cell membrane. Such exact models are derived either by fitting the parameters of an equation to match experimental data or by defining equations that were confirmed by later experiments. Moreover, they are based on the cell membrane formulation developed by Hodgkin and Huxley for nerve fibers [34] (see [35] for more details). To go further in the physiological description, some models consider the concentrations as variables of the system, see for example, the Beeler–Reuter model [36] and the Luo–Rudy model [37–39]. In [5,40], such models are considered.
2. **Phenomenological models**
   Other non-physiological models have been introduced as approximations of ion current models. They can be used in large problems because they are typically small and fast to solve, although they are less flexible in their response to variations in cellular properties such as concentrations or cell size. We take in this paper the FitzHugh–Nagumo model [41,42] that satisfies assumptions (7) which reads as

$$H(v,w) = av - bw, \tag{8a}$$

$$\mathcal{I}_{\text{ion}}(v,w) = (\lambda v(1-v)(v-\theta)) + (-\lambda w) := \mathrm{I}_{1,\text{ion}}(v) + \mathrm{I}_{2,\text{ion}}(w), \tag{8b}$$

where a, b, λ, θ are given parameters with $a, b \geq 0$, $\lambda < 0$, and $0 < \theta < 1$. According to this model, the functions $\mathcal{I}_{\text{ion}}$ and H are continuous and the non-linearity $\mathrm{I}_{\text{a,ion}}$ is of cubic growth at infinity then the most appropriate value is $r = 4$. We end this remark by mentioning other reduced ionic models: the Roger–McCulloch model [43] and the Aliev–Panfilov model [44] may be considered more general than the previous model but still rise some mathematical difficulties.

We complete system (5) with no-flux boundary conditions:

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

and appropriate the initial Cauchy conditions for transmembrane potential v and gating variable w. Herein, $\mathbf{n}$ is the outward unit normal to the exterior boundary of Ω.

Clearly, the equations in (5) 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:

$$\int_{\Omega_e^{\varepsilon}} u_e^{\varepsilon}(t,x)\mathrm{d}x = 0 \quad \text{for a.e. } t \in (0,T). \tag{9}$$

3 Asymptotic expansion homogenization

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 (5).

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.

3.1 Extracellular problem

In the literature, Cioranescu and Donato [9] are applied and developed the two-scale asymptotic expansion method established by Benssousan and Papanicolaou [12] on a problem defined at two scales to obtain the homogenized model (see also [8,10,45]). Further, the authors in [46] have used this method to derive the macroscopic linear behavior of a porous elastic solid saturated with a compressible viscous fluid. Its derivation is based on the linear elasticity equations in the solid, the linearized Navier–Stokes equations in the fluid, and the appropriate conditions at the solid–fluid boundary.

In our approach, we investigate the same two-scale technique for the extracellular problem. 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 Fig. 2). We recall the following initial extracellular problem:

$$\begin{aligned} \mathcal{A}_\varepsilon u_e^{\varepsilon} &= 0 && \text{in } \Omega_{e,T}^{\varepsilon},\\ \mathrm{M}_e^{\varepsilon}\nabla u_e^{\varepsilon}\cdot n_e = \varepsilon\left(\partial_t v_\varepsilon + \mathcal{I}_{ion}(v_\varepsilon, w_\varepsilon) - \mathcal{I}_{app,\varepsilon}\right) &= \mathcal{I}_m && \text{on } \Gamma_{\varepsilon,T}, \end{aligned} \tag{10}$$

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

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

satisfying the following elliptic and periodic conditions:

$$\begin{cases} \mathrm{M}_e(y) \in M(\alpha,\beta,Y),\\ \mathrm{M}_e = (\mathrm{m}_e^{pq})_{1\leq p,q\leq d} \quad \text{with } \mathrm{m}_e^{pq}\ y\text{-periodic},\ \forall p,q = 1,\ldots,d, \end{cases} \tag{11}$$

with $\alpha, \beta \in \mathbb{R}$, such that $0 < \alpha < \beta$ and $M(\alpha, \beta, Y)$ given by Definition 10.

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

$$u_e^\varepsilon(t,x) := u_e\left(t,x,\frac{x}{\varepsilon}\right) = u_{e,0}\left(t,x,\frac{x}{\varepsilon}\right) + \varepsilon u_{e,1}\left(t,x,\frac{x}{\varepsilon}\right) + \varepsilon^2 u_{e,2}\left(t,x,\frac{x}{\varepsilon}\right) + \cdots, \tag{12}$$

where 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.

Consequently, the full operator $\mathcal{A}_\varepsilon$ in the initial problem (10) is represented as

$$\mathcal{A}_\varepsilon u_e^\varepsilon(t,x) = [(\varepsilon^{-2}\mathcal{A}_{yy} + \varepsilon^{-1}\mathcal{A}_{xy} + \varepsilon^0\mathcal{A}_{xx})u_e]\left(t,x,\frac{x}{\varepsilon}\right), \tag{13}$$

with each operator defined by

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

Now, we substitute the asymptotic expansion (12) of u_e^ε in the developed operator (13) to obtain

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

Similarly, we substitute the asymptotic expansion (12) of u_e^ε into the boundary condition Eq. (10) 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 $u_{e,k}(t,x,y)$, $k = 0, 1, 2$:

$$\begin{cases} \mathcal{A}_{yy}u_{e,0} = 0 \quad \text{in } Y_e, \\ u_{e,0}\ y\text{-periodic}, \\ \mathrm{M}_e\nabla_y u_{e,0}\cdot n_e = 0 \quad \text{on } \Gamma^y, \end{cases} \tag{14}$$

$$\begin{cases} \mathcal{A}_{yy}u_{e,1} = -\mathcal{A}_{xy}u_{e,0} \quad \text{in } Y_e, \\ u_{e,1}\ y\text{-periodic}, \\ \left(\mathrm{M}_e\nabla_y u_{e,1} + \mathrm{M}_e\nabla_x u_{e,0}\right)\cdot n_e = 0 \quad \text{on } \Gamma^y, \end{cases} \tag{15}$$

$$\begin{cases} \mathcal{A}_{yy}u_{e,2} = -\mathcal{A}_{xy}u_{e,1} - \mathcal{A}_{xx}u_{e,0} \quad \text{in } Y_e, \\ u_{e,2}\ y\text{-periodic}, \\ \left(\mathrm{M}_e\nabla_y u_{e,2} + \mathrm{M}_e\nabla_x u_{e,1}\right)\cdot n_e = \partial_t v_0 + \mathcal{I}_{\text{ion}}(v_0, w_0) - \mathcal{I}_{app,0} \quad \text{on } \Gamma^y. \end{cases} \tag{16}$$

The authors in [9,12,17,19,20,26,31,46,47] have successively solved the three systems into Dirichlet boundary conditions (14)–(16). Herein, the functions $u_{e,0}$, $u_{e,1}$, and $u_{e,2}$ in the asymptotic expansion (12) for the extracellular potential u_e^ε satisfy the Neumann boundary value problems (14)–(16) in the local portion Y_e of a unit cell Y (see [6,30] for the case of Laplace equations).
The resolution is described as follows:

- **First step** We begin with the first boundary value problem (14) whose variational formulation is as follows:

$$\begin{cases} \text{Find } \dot{u}_{e,0} \in \mathcal{W}_{\text{per}}(Y_e) \text{ such that} \\ \dot{a}_{Y_e}(\dot{u}_{e,0}, \dot{v}) = \displaystyle\int_{\partial Y_e} (\mathrm{M}_e \nabla_y u_{e,0} \cdot n_e) v \, \mathrm{d}\sigma_y, \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Y_e), \end{cases} \tag{17}$$

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

$$\dot{a}_{Y_e}(\dot{u}, \dot{v}) = \int_{Y_e} \mathrm{M}_e \nabla_y u \nabla_y v \mathrm{d}y, \ \forall u \in \dot{u}, \ \forall v \in \dot{v}, \ \forall \dot{u}, \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Y_e) \tag{18}$$

and $\mathcal{W}_{\text{per}}(Y_e)$ is given by Definition 13.
We want to clarify the right-hand side of the variational formulation (17). By the definition of $\partial Y_e := (\partial_{\text{ext}} Y \cap \partial Y_e) \cup \Gamma^y$, we use Proposition 12 and the y-periodicity of M_i by taking into account the boundary condition on Γ^y to say that

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

Using Theorem 17, we can prove the existence and uniqueness of the solution $\dot{u}_{e,0}$. Then, the problem (14) 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 and z (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 do not depend on the mesoscopic variable y.

- **Second step** We now turn to the second boundary value problem (15).
Using Theorem 17, we obtain that the second system (15) has a unique weak solution $\dot{u}_{e,1} \in \mathcal{W}_{\text{per}}(Y_e)$ (defined by [12,45]).
Thus, the linearity of terms in the right-hand side of Eq. (15) suggests to look for $\dot{u}_{e,1}$ under the following form:

$$\dot{u}_{e,1}(t, x, y) = \sum_{q=1}^{d} \dot{\chi}_e^q(y) \frac{\partial \dot{u}_{e,0}}{\partial x_q}(t, x) \quad \text{in } \mathcal{W}_{\text{per}}(Y_e), \tag{19}$$

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

$$\begin{cases} \mathcal{A}_{yy} \dot{\chi}_e^q = \displaystyle\sum_{p=1}^{d} \frac{\partial \mathrm{m}_e^{pq}}{\partial y_p} \quad \text{in } Y_e, \\ \dot{\chi}_e^q \ y\text{-periodic}, \\ \mathrm{M}_e \nabla_y \dot{\chi}_e^q \cdot n_e = -(\mathrm{M}_e e_q) \cdot n_e \quad \text{on } \Gamma^y, \end{cases} \tag{20}$$

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:

$$\begin{cases} \text{Find } \chi_e^q \in W_\#(Y_e) \text{ such that} \\ a_{Y_e}(\chi_e^q, v) = (F, v)_{(W_\#(Y_e))', W_\#(Y_e)}, \ \forall v \in W_\#(Y_e), \end{cases} \tag{21}$$

with a_{Y_e} given by (18) and F defined by

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

where the space $W_\#(Y_e)$ is given by the expression (79). Since F belongs to $(W_\#(Y_e))'$ then the condition of Theorem 17 is imposed in order to guarantee existence and uniqueness of the solution.

Thus, by the form of $\dot{u}_{e,1}$ given by (19), the solution $u_{e,1}$ of the second system (15) can be represented by the following ansatz:

$$u_{e,1}(t,x,y) = \chi_e(y)\cdot\nabla_x u_0(t,x) + \tilde{u}_{e,1}(t,x) \quad \text{with } u_{e,1} \in \dot{u}_{e,1}, \tag{22}$$

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

- **Last step** We now pass to the last boundary value problem (16). Taking into account the form of $u_{e,0}$ and $u_{e,1}$, we obtain

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

Consequently, this system (16) has the following variational formulation:

$$\begin{cases}\text{Find } \dot{u}_{e,2} \in \mathcal{W}_{\text{per}}(Y_e) \text{ such that}\\ \dot{a}_{Y_e}(\dot{u}_{e,2},\dot{v}) = (F_2,\dot{v})_{(\mathcal{W}_{\text{per}}(Y_e))',\mathcal{W}_{\text{per}}(Y_e)}\ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Y_e),\end{cases} \tag{23}$$

with $\dot{a}_{Y_e}$ given by (18) and F_2 defined by

$$\begin{aligned}&(F_2,\dot{v})_{(\mathcal{W}_{\text{per}}(Y_e))',\mathcal{W}_{\text{per}}(Y_e)}\\ &\quad= \int_{\Gamma^y}\left(\mathrm{M}_e\nabla_y u_{e,2} + \mathrm{M}_e\nabla_x u_{e,1}\right)\cdot n_e\, v\,\mathrm{d}\sigma_y - \sum_{p,q=1}^{d}\int_{Y_e}\mathrm{m}_e^{pq}(y)\frac{\partial u_{e,1}}{\partial x_q}\frac{\partial v}{\partial y_p}\mathrm{d}y\\ &\qquad+ \sum_{p,q=1}^{d}\int_{Y_e}\frac{\partial}{\partial x_p}\left(\mathrm{m}_e^{pq}(y)\left(\frac{\partial u_{e,1}}{\partial y_q} + \frac{\partial u_{e,0}}{\partial x_q}\right)\right)v\mathrm{d}y,\quad \forall v \in \dot{v},\ \forall \dot{v} \in \mathcal{W}_{\text{per}}(y).\end{aligned} \tag{24}$$

The problem (23)–(24) is well posed according to Theorem 17 under the compatibility condition

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

which is equivalent to

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

In addition, we replace $u_{e,1}$ by its form (22) in the above condition to obtain

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

By expanding the sum and permuting the index, we obtain

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

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

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

$$= \frac{|\Gamma^y|}{|Y|}\left(\partial_t v_0 + \mathcal{I}_{\text{ion}}(v_0, w_0) - \mathcal{I}_{\text{app}}\right),$$

where

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

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

$$\mathcal{B}_{xx} u_{e,0} = \mu_m \left(\partial_t v_0 + \mathcal{I}_{\text{ion}}(v_0, w_0) - \mathcal{I}_{\text{app}}\right) \text{ on } \Omega_T, \tag{25}$$

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

$$\mathcal{B}_{xx} = -\nabla_x \cdot \left(\widetilde{\mathbf{M}}_e \nabla_x\right) = -\sum_{p,k=1}^{d} \frac{\partial}{\partial x_p}\left(\widetilde{\mathbf{m}}_e^{pq} \frac{\partial}{\partial x_k}\right), \tag{26}$$

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

$$\widetilde{\mathbf{m}}_e^{pk} := \frac{1}{|Y|}\sum_{q=1}^{d}\int_{Y_e}\left(\mathrm{m}_e^{pk} + \mathrm{m}_e^{pq}\frac{\partial \chi_e^k}{\partial y_q}\right)\mathrm{d}y. \tag{27}$$

Remark 3 (*Comparison with other papers*) The technique we use in the extracellular problem is closely related to that of Krassowska and Neu [21], with some clarifications, although the resulting model differs in important ways (described in Sect. 3.2). Keener and Panfilov [48] consider a network of myocytes, and transform to a local curvilinear coordinate system in which one coordinate is aligned with the fiber orientation. They make a transformation to the reference frame and then obtain the bidomain model analogous to that performed by Krassowska and Neu [21] on a regular lattice of myocytes. As such, this model provides insight into the mechanism of direct stimulation and defibrillation of cardiac tissue after injection of large currents. Further, Richardson and Chapman [22] have applied the two-scale asymptotic expansion to bidomain problems which have an almost periodic microstructure not in Cartesian coordinates but in a general curvilinear coordinate system. They used this method to derive a version of the bidomain equations describing the macroscopic electrical activity of cardiac tissue. The treatment systematically took into account the non-uniform orientation of the cells in the tissue and the deformation of the tissue due to the heart beat. Recently, Whiteley [33] used the homogenization technique for an almost periodic microstructure described by Richardson and Chapman [22], to derive the tissue level bidomain equations. They also presented some observations on the entries of the conductivity tensors, as well as some observations arising from the computation of the numerical solution of ε-cell problems.

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 a three-scale asymptotic expansion in the intracellular problem to obtain its homogenized equation. Recall that $u_i^{\varepsilon,\delta}$ is the solution of the following initial intracellular problem:

$$\begin{aligned} \mathcal{A}_{\varepsilon,\delta} u_i^{\varepsilon,\delta} &= 0 && \text{in } \Omega_{i,T}^{\varepsilon,\delta}, \\ -\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\cdot n_i = \varepsilon\left(\partial_t v_\varepsilon + \mathcal{I}_{\text{ion}}(v_\varepsilon, w_\varepsilon) - \mathcal{I}_{\text{app},\varepsilon}\right) &= \mathcal{I}_{\text{m}} && \text{on } \Gamma_{\varepsilon,T}, \\ -\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\cdot n_z &= 0 && \text{on } \Gamma_{\delta,T}, \end{aligned} \tag{28}$$

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

$$\begin{cases} \mathrm{M}_i(y,\cdot) \in M(\alpha,\beta,Y), \ \mathrm{M}_i(\cdot,z) \in M(\alpha,\beta,Z), \\ \mathrm{M}_i = \left(\mathrm{m}_i^{pq}\right)_{1\le p,q\le d} \quad \text{with } \mathrm{m}_i^{pq} \ y\text{- and } z\text{-periodic}, \ \forall p,q = 1,\dots,d, \end{cases} \tag{29}$$

with $\alpha, \beta \in \mathbb{R}$, such that $0 < \alpha < \beta$ and $M(\alpha,\beta,\mathcal{O})$ given by Definition 10.

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:

$$\begin{aligned} u_i^{\varepsilon,\delta}(t,x) := u_i\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) &= u_{i,0}\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) + \varepsilon u_{i,1}\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) + \varepsilon\delta u_{i,2}\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) \\ &\quad + \varepsilon^2 u_{i,3}\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) + \varepsilon^2\delta u_{i,4}\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) \\ &\quad + \varepsilon^2\delta^2\, u_{i,5}\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right) + \cdots, \end{aligned} \tag{30}$$

where each $u_{i,q}(\cdot,y,z)$ is y- and z-periodic functions 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 4 The authors in [49] 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 exploited the effective properties of cardiac tissue with multiple small-scale configurations. We note that our present technique recovers the classical reiterated homogenization [12] where $\delta = \varepsilon$.

Consequently, we can write the full operator $\mathcal{A}_{\varepsilon,\delta}$ in the initial problem (28) as follows:

$$\begin{aligned}
\mathcal{A}_{\varepsilon,\delta}u_i^{\varepsilon,\delta}(t,x) &= -\left[\nabla\cdot\left(\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\right)\right](t,x)\\
&= -\left[\sum_{p,q=1}^{d}\frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q}+\frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q}+\frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&\quad -\frac{1}{\varepsilon}\left[\sum_{p,q=1}^{d}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q}+\frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q}+\frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&\quad -\frac{1}{\varepsilon\delta}\left[\sum_{p,q=1}^{d}\frac{\partial}{\partial z_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_i}{\partial x_q}+\frac{1}{\varepsilon}\frac{\partial u_i}{\partial y_q}+\frac{1}{\varepsilon\delta}\frac{\partial u_i}{\partial z_q}\right)\right)\right]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right)\\
&= [(\varepsilon^{-2}\delta^{-2}\mathcal{A}_{zz}+\varepsilon^{-2}\delta^{-1}\mathcal{A}_{yz}+\varepsilon^{-1}\delta^{-1}\mathcal{A}_{xz}\\
&\quad +\varepsilon^{-2}\mathcal{A}_{yy}+\varepsilon^{-1}\mathcal{A}_{xy}+\varepsilon^{0}\delta^{0}\mathcal{A}_{xx})u_i]\left(t,x,\frac{x}{\varepsilon},\frac{x}{\varepsilon\delta}\right),
\end{aligned}\tag{31}$$

with each operator defined by

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

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

Now, we substitute the asymptotic expansion (30) of $u_i^{\varepsilon,\delta}$ into the operator developed (31) to obtain

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

Similarly, we have the boundary condition

$$\mathrm{M}_i^{\varepsilon,\delta}\nabla u_i^{\varepsilon,\delta}\cdot n = \left[\mathrm{M}_i^{\varepsilon,\delta}\nabla_x u_i+\varepsilon^{-1}\mathrm{M}_i^{\varepsilon,\delta}\nabla_y u_i+\varepsilon^{-1}\delta^{-1}\mathrm{M}_i^{\varepsilon,\delta}\nabla_z u_i\right]\cdot n,\tag{32}$$

for $n := n_i, n_z$. Thus, we also substitute the asymptotic expansion (30) of $u_i^{\varepsilon,\delta}$ into the boundary condition Eq. (28) on Γ^y and on Γ^z :

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

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:

$$\begin{cases} \mathcal{A}_{zz} u_{i,0} = 0 \quad \text{in } Z_c, \\ u_{i,0} \ z\text{-periodic}, \\ \mathrm{M}_i \nabla_z u_{i,0} \cdot n_z = 0 \quad \text{on } \Gamma^z, \end{cases} \tag{33}$$

$$\begin{cases} \mathcal{A}_{yy} u_{i,0} = 0 \quad \text{in } Y_i, \\ u_{i,0} \ y\text{-periodic}, \\ \mathrm{M}_i \nabla_y u_{i,0} \cdot n_i = 0 \quad \text{on } \Gamma^y, \end{cases} \tag{34}$$

$$\begin{cases} \mathcal{A}_{yz} u_{i,0} = 0 \quad \text{in } Z_c, \\ u_{i,0} \ y\text{- and } z\text{-periodic}, \\ \mathrm{M}_i \nabla_y u_{i,0} \cdot n_i = 0 \quad \text{on } \Gamma^y, \\ \mathrm{M}_i \nabla_z u_{i,0} \cdot n_z = 0 \quad \text{on } \Gamma^z, \end{cases} \tag{35}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,1} = 0 \quad \text{in } Z_c, \\ u_{i,1} \ z\text{-periodic}, \\ \mathrm{M}_i \nabla_z u_{i,1} \cdot n_z = 0 \quad \text{on } \Gamma^z, \end{cases} \tag{36}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,2} = -\mathcal{A}_{yz} u_{i,1} - \mathcal{A}_{xz} u_{i,0} \quad \text{in } Z_c, \\ u_{i,2} \ z\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_z u_{i,2} + \mathrm{M}_i \nabla_y u_{i,1} + \mathrm{M}_i \nabla_x u_{i,0}\right) \cdot n_z = 0 \quad \text{on } \Gamma^z, \end{cases} \tag{37}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,3} = 0 \quad \text{in } Z_c, \\ u_{i,3} \ z\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_z u_{i,3}\right) \cdot n_z = 0 \quad \text{on } \Gamma^z, \end{cases} \tag{38}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,4} = -\mathcal{A}_{yz} u_{i,3} - \mathcal{A}_{xz} u_{i,1} \quad \text{in } Z_c, \\ u_{i,4} \ y\text{- and } z\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_z u_{i,4} + \mathrm{M}_i \nabla_y u_{i,3} + \mathrm{M}_i \nabla_x u_{i,1}\right) \cdot n_i = -\left(\partial_t v_0 + \mathcal{I}_{\text{ion}}(v_0, w_0) - \mathcal{I}_{\text{app}}\right) \quad \text{on } \Gamma^y, \\ \left(\mathrm{M}_i \nabla_z u_{i,4} + \mathrm{M}_i \nabla_y u_{i,3} + \mathrm{M}_i \nabla_x u_{i,1}\right) \cdot n_z = 0 \quad \text{on } \Gamma^z, \end{cases} \tag{39}$$

$$\begin{cases} \mathcal{A}_{yz} u_{i,2} = -\mathcal{A}_{yy} u_{i,1} - \mathcal{A}_{xy} u_{i,0} \quad \text{in } Z_c, \\ u_{i,2} \ y\text{- and } z\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_z u_{i,2} + \mathrm{M}_i \nabla_y u_{i,1} + \mathrm{M}_i \nabla_x u_{i,0}\right) \cdot n_i = 0 \quad \text{on } \Gamma^y, \\ \mathrm{M}_i \nabla_y u_{i,2} \cdot n_z = 0 \quad \text{on } \Gamma^z, \end{cases} \tag{40}$$

$$\begin{cases} \mathcal{A}_{zz} u_{i,5} = -\mathcal{A}_{yz} u_{i,4} - \mathcal{A}_{yy} u_{i,3} - \mathcal{A}_{xz} u_{i,2} - \mathcal{A}_{xy} u_{i,1} - \mathcal{A}_{xx} u_{i,0} \quad \text{in } Z_c, \\ u_{i,5} \ z\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_z u_{i,5} + \mathrm{M}_i \nabla_y u_{i,4} + \mathrm{M}_i \nabla_x u_{i,2}\right) \cdot n_z = 0 \quad \text{on } \Gamma^z. \end{cases} \tag{41}$$

These systems (33)–(41) have a particular structure in the sense that their unknowns will be found iteratively.

We will solve these nine problems (33)–(41) successively to determine the homogenized problem (based on the work [9,12]). The resolution is described as follows:

- **Step 1** We begin with the first problem (33) whose variational formulation is as follows:

$$\begin{cases} \text{Find } \dot{u}_{i,0} \in \mathcal{W}_{\text{per}}(Z_{\text{c}}) \text{ such that} \\ \dot{a}_{Z_{\text{c}}}(\dot{u}_{i,0}, \dot{v}) = \displaystyle\int_{\partial Z_{\text{c}}} \left(\mathrm{M}_i \nabla_z u_{i,0} \cdot n_z\right) v \, \mathrm{d}\sigma_z, \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Z_{\text{c}}), \end{cases} \tag{42}$$

with $\dot{a}_{Z_{\text{c}}}$ given by

$$\dot{a}_{Z_{\text{c}}}(\dot{u}, \dot{v}) = \int_{Z_{\text{c}}} \mathrm{M}_i \nabla_z u \nabla_z v \, \mathrm{d}z, \ \forall u \in \dot{u}, \ \forall v \in \dot{v}, \ \forall \dot{u}, \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Z_{\text{c}}), \tag{43}$$

and

$$\mathcal{W}_{\text{per}}(Z_{\text{c}}) = H^1_{\text{per}}(Z_{\text{c}})/\mathbb{R},$$

is given by Definition 13. Similarly, we want to clarify the right-hand side of the variational formulation (42). By the definition of $\partial Z_{\text{c}} := \partial_{\text{ext}} Z \cup \Gamma^z$, we use Proposition 12 and the z-periodicity of M_i by taking into account the boundary condition on Γ^z to say that

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

Using Theorem 17, we obtain the existence and the uniqueness of solution $\dot{u}_{i,0}$ to the problem (42). In addition, we have

$$\left\|\dot{u}_{i,0}\right\|_{\mathcal{W}_{\text{per}}(Z_{\text{c}})} = 0.$$

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 (34) that is defined in Y_i. Its variational formulation is as follows:

$$\begin{cases} \text{Find } \dot{u}_{i,0} \in \mathcal{W}_{\text{per}}(Y_i) \text{ such that} \\ \dot{a}_{Y_i}(\dot{u}_{i,0}, \dot{v}) = \displaystyle\int_{\partial Y_i} \mathrm{M}_i \nabla_y u_{i,0} \cdot n_i \ v \, \mathrm{d}\sigma_y \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Y_i), \end{cases} \tag{44}$$

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

$$\dot{a}_{Y_i}(\dot{u}, \dot{v}) = \int_{Y_i} \mathrm{M}_i \nabla_y u \nabla_y v \mathrm{d}y, \ \forall u \in \dot{u}, \ \forall v \in \dot{v}, \ \forall \dot{u}, \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Y_i) \tag{45}$$

and $\mathcal{W}_{\text{per}}(Y_i)$ given by Definition 13.

Similarly, we want to clarify first the right-hand side in the variational formulation (44). By the definition of $\partial Y_i := (\partial_{\text{ext}} Y \cap \partial Y_i) \cup \Gamma^y$, we use Proposition 12 and the y-periodicity of M_i by taking into account the boundary condition on Γ^y to say that

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

Therefore, we can apply Theorem 17 to prove the existence and uniqueness of solution $\dot{u}_{i,0}$. In addition, we have

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

Thus, we deduce that $u_{i,0}$ is also independent of the mesoscopic variable y. Consequently, the third boundary value problem (35) is satisfied automatically.

Next, we solve the fourth problem (36) by the same process of the first step. So, we deduce that $u_{i,1}$ is independent of z. Finally, we have

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

Remark 5 Since $u_{i,0}$ is independent of y and z then it does not oscillate "rapidly." This is why now we 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 (37). Taking into account the form of $u_{i,0}$ and $u_{i,1}$, system (37) can be rewritten as

$$\begin{cases} \mathcal{A}_{zz} u_{i,2} = \sum_{p,q=1}^{d} \frac{\partial \mathrm{m}_i^{pq}}{\partial z_p} \left(\frac{\partial u_{i,1}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q} \right) \quad \text{in } Z_\mathrm{c}, \\ u_{i,2} \ z\text{-periodic}, \\ \left(\mathrm{M}_i \nabla_z u_{i,2} + \mathrm{M}_i \nabla_y u_{i,1} + \mathrm{M}_i \nabla_x u_{i,0} \right) \cdot n_z = 0 \quad \text{on } \Gamma^z, \end{cases} \tag{46}$$

Its variational formulation is

$$\begin{cases} \text{Find } \dot{u}_{i,2} \in \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}) \text{ such that} \\ \dot{a}_{Z_\mathrm{c}}(\dot{u}_{i,2}, \dot{v}) = (F_2, \dot{v})_{(\mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}))', \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c})} \quad \forall \dot{v} \in \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}), \end{cases} \tag{47}$$

with $\dot{a}_{Z_\mathrm{c}}$ given by (43) and F_2 defined by

$$(F_2, \dot{v})_{(\mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}))', \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c})} = - \sum_{p,q=1}^{d} \left(\frac{\partial u_{i,1}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q} \right) \int_{Z_\mathrm{c}} \mathrm{m}_i^{pq}(t, y, z) \frac{\partial v}{\partial z_p} \mathrm{d}z, \tag{48}$$

for all $v \in \dot{v}$ and $\dot{v} \in \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c})$.
Note that F_2 belongs to $(\mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}))'$. Then, Theorem 17 gives a unique solution $\dot{u}_{i,2} \in \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c})$ of the problem (46)–(48).
Thus, the linearity of terms in the right of equation (46) suggests to look for $\dot{u}_{i,2}$ under the following form:

$$\dot{u}_{i,2} = \dot{\theta}_i(z) \cdot \left(\nabla_y \dot{u}_{i,1} + \nabla_x \dot{u}_{i,0} \right) \text{ in } \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}), \tag{49}$$

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

$$\begin{cases} \mathcal{A}_{zz} \dot{\theta}_i^q = \sum_{p=1}^{d} \frac{\partial \mathrm{m}_i^{pq}}{\partial z_p}(y, z) \quad \text{in } Z_\mathrm{c}, \\ \dot{\theta}_i^q \ y\text{- and } z\text{-periodic}, \\ \mathrm{M}_i \nabla_z \dot{\theta}_i^q \cdot n_z = -(\mathrm{M}_i e_q) \cdot n_z \quad \text{on } \Gamma^z, \end{cases} \tag{50}$$

for e_q, $q = 1, \ldots, d$, 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:

$$\begin{cases} \text{Find } \theta_i^q \in W_\#(Z_\mathrm{c}) \text{ such that} \\ a_{Z_\mathrm{c}}(\theta_i^q, v) = - \sum_{p=1}^{d} \int_{Z_\mathrm{c}} \mathrm{m}_i^{pq}(t, y, z) \frac{\partial v}{\partial z_p} \, \mathrm{d}z, \ \forall v \in W_\#(Z_\mathrm{c}), \end{cases} \tag{51}$$

with $W_\#(Z_\mathrm{c})$ given by the expression (79). The condition of Theorem 17 is imposed to guarantee the existence and uniqueness of the solution of the problem (50)–(51). Thus, by the form $\dot{u}_{i,2}$ given by the expression (49), the solution $u_{i,2}$ can be represented by the following ansatz:

$$u_{i,2}(t, x, y, z) = \theta_i(z) \cdot \left(\nabla_y u_{i,1}(t, x, y) + \nabla_x u_{i,0}(t, x) \right) + \tilde{u}_{i,2}(t, x, y) \quad \text{with } u_{i,2} \in \dot{u}_{i,2}, \tag{52}$$

and $\tilde{u}_{i,2}$ is a constant with respect to z (i.e., $\tilde{u}_{i,2} \in \dot{0}$ in $\mathcal{W}_\#(Z_\mathrm{c})$).
Next, we pass to the sixth problem (38) 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 (39). Taking into account the form of $u_{i,3}$ and $u_{i,1}$, we can rewrite this problem as follows:

$$\begin{cases} \mathcal{A}_{zz}u_{i,4} = \sum_{p,q=1}^{d} \frac{\partial \mathrm{m}_i^{pq}}{\partial z_p}\left(\frac{\partial u_{i,3}}{\partial y_q} + \frac{\partial u_{i,1}}{\partial x_q}\right) \quad \text{in } Z_\mathrm{c}, \\ u_{i,4}\ y\text{- and } z\text{-periodic}, \\ \left(\mathrm{M}_i\nabla_z u_{i,4} + \mathrm{M}_i\nabla_y u_{i,3} + \mathrm{M}_i\nabla_x u_{i,1}\right)\cdot n_z = 0 \quad \text{on } \Gamma^z. \end{cases} \tag{53}$$

Its variational formulation is as follows:

$$\begin{cases} \text{Find } \dot{u}_{i,4} \in \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}) \text{ such that} \\ \dot{a}_{Z_\mathrm{c}}(\dot{u}_{i,4}, \dot{v}) = (F_4, \dot{v})_{(\mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}))', \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c})}\ \forall \dot{v} \in \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}), \end{cases} \tag{54}$$

with $\dot{a}_{Z_\mathrm{c}}$ given by (43) and F_4 defined by

$$(F_4, \dot{v})_{(\mathcal{W}_{\mathrm{per}}(Z_\mathrm{c}))', \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c})} = -\sum_{p,q=1}^{d}\left(\frac{\partial u_{i,3}}{\partial y_q} + \frac{\partial u_{i,1}}{\partial x_q}\right)\int_{Z_\mathrm{c}} \mathrm{m}_i^{pq}(t,y,z)\frac{\partial v}{\partial z_p}\mathrm{d}z, \tag{55}$$

for all $v \in \dot{v}$ and $\dot{v} \in \mathcal{W}_{\mathrm{per}}(Z_\mathrm{c})$.
The problem (53)–(55) is well posed according to Theorem 17 under the compatibility condition:

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

This implies that problem (39) has a unique periodic solution up to a constant. Thus, the linearity of terms in the right-hand side of Eq. (53) suggests to look for $u_{i,4}$ under the following form:

$$u_{i,4}(t,x,y,z) = \theta_i(z)\cdot\left(\nabla_y u_{i,3}(t,x,y) + \nabla_x u_{i,1}(x)\right) + \tilde{u}_{i,4}(t,x,y) \quad \text{with } u_{i,4} \in \dot{u}_{i,4}, \tag{56}$$

where $\tilde{u}_{i,4}$ is a constant with respect to z and θ_i satisfies problem (50).

- **Step 5** We consider the eighth problem (40):

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

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:

$$\begin{aligned} &-\sum_{p,q=1}^{d}\int_{Z_c}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_{i,2}}{\partial z_q}\right)\mathrm{d}z - \sum_{p,q=1}^{d}\int_{Z_c}\frac{\partial}{\partial z_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_{i,2}}{\partial y_q}\right)\mathrm{d}z \\ &\quad = \sum_{p,q=1}^{d}\int_{Z_c}\frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\frac{\partial u_{i,1}}{\partial y_q}\right) + \sum_{p,q=1}^{d}\int_{Z_c}\frac{\partial \mathrm{m}_i^{pq}}{\partial y_p}(y,z)\frac{\partial u_{i,0}}{\partial x_q}\,\mathrm{d}z. \end{aligned} \tag{57}$$

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 12 and the boundary condition on Γ^z to obtain

$$E_2 = -\int_{\partial Z_c} \mathrm{M}_i \nabla_y u_{i,2} \cdot n_z \, \mathrm{d}\sigma_z - \int_{\partial_{\mathrm{ext}} Z} \mathrm{M}_i \nabla_y u_{i,2} \cdot n_z \, \mathrm{d}\sigma_z - \int_{\Gamma^z} \mathrm{M}_i \nabla_y u_{i,2} \cdot n_z \, \mathrm{d}\sigma_z = 0.$$

Now, we replace $u_{i,2}$ by its expression (52) in the first term E_1 to obtain the following:

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

By permuting the index in the right-hand side of Eq. (57), we obtain

$$E_3 = \sum_{p,k=1}^{d} \int_{Z_c} \frac{\partial}{\partial y_p} \left(\mathrm{m}_i^{pk}(y,z) \frac{\partial u_{i,1}}{\partial y_k} \right),$$

$$E_4 = \sum_{p,k=1}^{d} \int_{Z_c} \frac{\partial \mathrm{m}_i^{pk}}{\partial y_p}(y,z) \frac{\partial u_{i,0}}{\partial x_k} \, \mathrm{d}z.$$

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

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

Similarly, we replace $u_{i,2}$ by its form (52) 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:

$$\begin{cases} \mathcal{B}_{yy} u_{i,1} = \displaystyle\sum_{p,k=1}^{d} \frac{\partial \widetilde{\mathbf{m}}_i^{pk}}{\partial y_p} \frac{\partial u_{i,0}}{\partial x_k} \quad \text{in } Y_i, \\ \left(\widetilde{\mathbf{M}}_i \nabla_y u_{i,1} + \widetilde{\mathbf{M}}_i \nabla_x u_{i,0} \right) \cdot n_i = 0 \ \text{ on } \ \Gamma^y, \end{cases} \tag{58}$$

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

$$\mathcal{B}_{yy} = -\sum_{p,k=1}^{d} \frac{\partial}{\partial y_p} \left(\widetilde{\mathbf{m}}_i^{pk}(y) \frac{\partial}{\partial y_k} \right), \tag{59}$$

where with the coefficients of the (homogenized with respect to z) conductivity matrices $\widetilde{\mathbf{M}}_i = (\widetilde{\mathbf{m}}_i^{pk})_{1 \le p,k \le d}$ defined by

$$\widetilde{\mathbf{m}}_i^{pk}(y) = \frac{1}{|Z|} \sum_{q=1}^{d} \int_{Z_c} \left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{pq} \frac{\partial \theta_i^k}{\partial z_q} \right) \mathrm{d}z, \quad \forall p, k = 1, \ldots, d. \tag{60}$$

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 6 The operator $\mathcal{B}_{yy}$ has the same properties of the **homogenized** operator (26) 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 (58) defined in Y_i. Consider the variational formulation of problem (58)

$$\begin{cases} \text{Find } \dot{u}_{i,1} \in \mathcal{W}_{\text{per}}(Y_i) \text{ such that} \\ \dot{b}_{Y_i}(\dot{u}_{i,1}, \dot{v}) = (F_1, \dot{v})_{(\mathcal{W}_{\text{per}}(Y_i))', \mathcal{W}_{\text{per}}(Y_i)} \quad \forall \dot{v} \in \mathcal{W}_{\text{per}}(Y_i), \end{cases} \tag{61}$$

with $\dot{b}_Y$ given by

$$\dot{b}_{Y_i}(\dot{u}, \dot{v}) = \int_{Y_i} \widetilde{\mathbf{M}}_i \nabla_y u \nabla_y v \mathrm{d}y, \ \forall u \in \dot{u}, \ \forall v \in \dot{v}, \ \forall \dot{u}, \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Y_i), \tag{62}$$

and F_1 defined by

$$(F_1, \dot{v})_{(\mathcal{W}_{\text{per}}(Y_i))', \mathcal{W}_{\text{per}}(Y_i)} = -\sum_{p,k=1}^{d} \frac{\partial u_{i,0}}{\partial x_k} \int_{Y_i} \widetilde{\mathbf{m}}_i^{pk}(y) \frac{\partial v}{\partial y_p} \mathrm{d}y, \ \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(Y_i). \tag{63}$$

The linear form F_1 belongs to $(\mathcal{W}_{\text{per}}(Y_i))'$. Thus, there exists a unique solution $\dot{u}_{i,1} \in \mathcal{W}_{\text{per}}(Y_i)$ of problem (61)–(63).
Finally, the linearity of terms in the right-hand side of equation (58) suggests to look for $\dot{u}_{i,2}$ under the following form:

$$\dot{u}_{i,1} = \dot{\chi}(y) \cdot \nabla_x \dot{u}_{i,0} \text{ in } \mathcal{W}_{\text{per}}(Y_i), \tag{64}$$

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

$$\begin{cases} \mathcal{B}_{yy} \dot{\chi}_i^k = \sum_{p=1}^{d} \frac{\partial \widetilde{\mathbf{m}}_i^{pk}}{\partial y_p} \text{ in } Y_i, \\ \widetilde{\mathbf{M}}_i \nabla_y \dot{\chi}_i^k \cdot n_i = -\left(\widetilde{\mathbf{M}}_i e_k\right) \cdot n_i \text{ on } \Gamma^y, \end{cases} \tag{65}$$

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 satisfies the following variational formulation:

$$\begin{cases} \text{Find } \chi_i^k \in W_{\#}(Y_i) \text{ such that} \\ \dot{b}_{Y_i}(\chi_i^k, \dot{v}) = -\sum_{p=1}^{d} \int_{Y_i} \widetilde{\mathbf{m}}_i^{pk}(y) \frac{\partial w}{\partial y_p} \mathrm{d}y, \ \forall w \in W_{\#}(Y_i), \end{cases} \tag{66}$$

with $\dot{b}_{Y_i}$ given by (62). Thus, we prove the existence and uniqueness of the solution χ_i^k of the problem (65) using Theorem 17.

So, by the form of $\dot{u}_{i,1}$ given by (64), the solution $u_{i,1}$ of the problem (58) can be represented by the following ansatz:

$$u_{i,1}(t, x, y) = \chi_i(y) \cdot \nabla_x u_{i,0}(t, x) + \tilde{u}_{i,1}(t, x) \text{ avec } u_{i,1} \in \dot{u}_{i,1}, \tag{67}$$

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

- **Last step** Our interest is the last boundary value problem (41). We have

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

Note that, the variational formulation of system (41) can be written as follows:

$$
\begin{cases}
\text{Find } \dot{u}_{i,5} \in \mathcal{W}_{\mathrm{per}}(Z_{\mathrm{c}}) \text{ such that} \\
\dot{a}_{Z_{\mathrm{c}}}(\dot{u}_{i,5}, \dot{v}) = (F_5, \dot{v})_{(\mathcal{W}_{\mathrm{per}}(Z_{\mathrm{c}}))', \mathcal{W}_{\mathrm{per}}(Z_{\mathrm{c}})} \ \forall \dot{v} \in \mathcal{W}_{\mathrm{per}}(Z_{\mathrm{c}}),
\end{cases}
\tag{68}
$$

with $\dot{a}_{Z_{\mathrm{c}}}$ given by (43) and F_5 defined by

$$
\begin{aligned}
&(F_5, \dot{v})_{(\mathcal{W}_{\mathrm{per}}(Z_{\mathrm{c}}))', \mathcal{W}_{\mathrm{per}}(Z_{\mathrm{c}})} \\
&= \int_{\Gamma^z} \left[\left(\mathrm{M}_i \nabla_z u_{i,5} + \mathrm{M}_i \nabla_y u_{i,4} + \mathrm{M}_i \nabla_x u_{i,2}\right) \cdot n_z\right] v \, \mathrm{d}\sigma_z \\
&\quad + \sum_{p,q=1}^{d} \int_{Z_{\mathrm{c}}} \frac{\partial}{\partial y_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_{i,4}}{\partial z_q} + \frac{\partial u_{i,3}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q}\right)\right) v \mathrm{d}z \\
&\quad - \sum_{p,q=1}^{d} \int_{Z_{\mathrm{c}}} \mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_{i,4}}{\partial y_q} + \frac{\partial u_{i,2}}{\partial x_q}\right) \frac{\partial v}{\partial z_p} \mathrm{d}z \\
&\quad + \sum_{p,q=1}^{d} \int_{Z_{\mathrm{c}}} \frac{\partial}{\partial x_p}\left(\mathrm{m}_i^{pq}(y,z)\left(\frac{\partial u_{i,2}}{\partial z_q} + \frac{\partial u_{i,1}}{\partial y_q} + \frac{\partial u_{i,0}}{\partial x_q}\right)\right) v \mathrm{d}z, \quad \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{\mathrm{per}}(Z_{\mathrm{c}}).
\end{aligned}
\tag{69}
$$

The aim is to find the homogenized equation in Ω. Firstly, we will homogenize the problem (41) 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 (68)–(69) defined in Z_{c} is well posed if and only if F_5 belongs to $(\mathcal{W}_{\mathrm{per}}(Z_{\mathrm{c}}))'$, i.e.,

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

which equivalent to

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

In addition, we replace $u_{i,4}$ by its expression (56) 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

$$
\begin{cases}
\mathcal{B}_{yy} u_{i,3} = -\mathcal{B}_{xy} u_{i,1} - \mathcal{B}_{xx} u_{i,0} \text{ in } Y_i, \\
\left(\widetilde{\mathbf{M}}_i \nabla_y u_{i,3} + \widetilde{\mathbf{M}}_i \nabla_x u_{i,1}\right) \cdot n_i = -\left(\partial_t v_0 + \mathcal{I}_{\mathrm{ion}}(v_0, w_0) - \mathcal{I}_{\mathrm{app}}\right) \text{ on } \Gamma^y,
\end{cases}
\tag{70}
$$

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 (70) has the following variational formulation:

$$\begin{cases} \text{Find } u_{i,3} \in \mathcal{W}_{\text{per}}(Y_i) \text{ such that} \\ \dot{b}_{Y_i}(u_{i,3}, \dot{w}) = (F_3, \dot{w})_{(\mathcal{W}_{\text{per}}(Y_i))', \mathcal{W}_{\text{per}}(Y_i)} \ \forall \dot{w} \in \mathcal{W}_{\text{per}}(Y_i), \end{cases} \tag{71}$$

with $\dot{b}_{Y_i}$ given by (62) and F_3 defined by

$$\begin{aligned} &(F_3, \dot{w})_{(\mathcal{W}_{\text{per}}(Y_i))', \mathcal{W}_{\text{per}}(Y_i)} \\ &\quad = \int_{\Gamma^y} \left(\widetilde{\mathbf{M}}_i \nabla_y u_{i,3} + \widetilde{\mathbf{M}}_i \nabla_x u_{i,1}\right) \cdot n_i w \, \mathrm{d}\sigma_y - \sum_{p,k=1}^{d} \int_{Y_i} \widetilde{\mathbf{m}}_i^{pk} \frac{\partial u_{i,1}}{\partial x_k} \frac{\partial w}{\partial y_p} \mathrm{d}y \\ &\qquad + \sum_{p,k=1}^{d} \int_{Y_i} \frac{\partial}{\partial x_p} \left(\widetilde{\mathbf{m}}_i^{pk} \left(\frac{\partial u_{i,1}}{\partial y_k} + \frac{\partial u_{i,0}}{\partial x_k} \right) \right) w \, \mathrm{d}y, \end{aligned} \tag{72}$$

for all $w \in \dot{w}$, $\dot{w} \in \mathcal{W}_{\text{per}}(Y_i)$.
Observe that problem (70)–(72) is well posed if and only if F_3 belongs to $(\mathcal{W}_{\text{per}} Y))'$, which means

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

which gives

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

Next, we replace $u_{i,1}$ by its form (67) in the above condition. Then, we obtain

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

By expanding the sum and permuting the index, we obtain

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

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

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

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

$$\mathcal{B}_{xx} u_{i,0} = -\mu_m \left(\partial_t v_0 + \mathcal{I}_{\text{ion}}(v_0, w_0) - \mathcal{I}_{\text{app}}\right) \text{ on } \Omega_T, \tag{73}$$

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 $\widetilde{\widetilde{\mathbf{M}}}_i = \left(\widetilde{\widetilde{\mathbf{m}}}_i^{pq}\right)_{1\le p,q\le d}$ defined by

$$\begin{aligned}\widetilde{\widetilde{\mathbf{m}}}_i^{pq} &:= \frac{1}{|Y|}\sum_{k=1}^{d}\int_{Y_i}\left(\widetilde{\mathbf{m}}_i^{pk}\frac{\partial \chi_i^q}{\partial y_k}(y) + \widetilde{\mathbf{m}}_i^{pq}\right)\mathrm{d}y \\ &= \frac{1}{|Y|}\frac{1}{|Z|}\sum_{k,\ell=1}^{d}\int_{Y_i}\int_{Z_c}\left[\left(\mathrm{m}_i^{pk} + \mathrm{m}_i^{p\ell}\frac{\partial \theta_i^k}{\partial z_\ell}\right)\frac{\partial \chi_i^q}{\partial y_k}(y) + \left(\mathrm{m}_i^{pq} + \mathrm{m}_i^{p\ell}\frac{\partial \theta_i^q}{\partial z_\ell}\right)\right]\mathrm{d}z\,\mathrm{d}y,\end{aligned} \tag{74}$$

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 (60).

Remark 7 The authors in [6] 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 Sect. 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 (73) of the initial problem (28). 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 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.

3.3 Macroscopic bidomain model

At macroscopic level, the heart domain coincides with the intracellular and extracellular ones, which are interpenetrating and superimposed connected at each point by the cardiac cellular membrane. The homogenized model of the microscopic bidomain model is recuperated from the extracellular and intracellular homogenized Eqs. (25)–(73), which is called the macroscopic bidomain model (Reaction–Diffusion system):

$$\begin{aligned}\mu_m \partial_t v + \nabla\cdot\left(\widetilde{\mathbf{M}}_e \nabla u_e\right) + \mu_m \mathcal{I}_{\text{ion}}(v,w) &= \mu_m \mathcal{I}_{\text{app}} && \text{in } \Omega_T,\\ \mu_m \partial_t v - \nabla\cdot\left(\widetilde{\widetilde{\mathbf{M}}}_i \nabla u_i\right) + \mu_m \mathcal{I}_{\text{ion}}(v,w) &= \mu_m \mathcal{I}_{\text{app}} && \text{in } \Omega_T,\\ \partial_t w - H(v,w) &= 0 && \text{on } \Omega_T,\end{aligned} \tag{75}$$

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

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

where $\mathbf{n}$ is the outward unit normal to the boundary of Ω, and by assigning the initial Cauchy condition for the transmembrane potential v and the gating variable w we have:

$$v(0,x) = v_0(x) \quad \text{and} \quad w(0,x) = w_0(x), \ \text{a.e. on } \Omega. \tag{76}$$

Herein, the conductivity matrices $\widetilde{\mathbf{M}}_e$ and $\widetilde{\widetilde{\mathbf{M}}}_i$ are defined, respectively, in (27)–(74). System (75)–(76) corresponds to the sought macroscopic equations. Finally, note that we close the problem by the normalization condition on the extracellular potential for almost all $t \in [0, T]$,

$$\int_\Omega u_e(t,x)\mathrm{d}x = 0.$$

Remark 8 Following [9,12], it is easy to verify that these homogenized conductivity tensors are symmetric, positive definite. Moreover, the functions $\mathcal{I}_{\text{ion}}$ and $H(v,w)$ preserve the same form of Fitzhugh–Nagumo model defined in (8).

4 Conclusion

Many biological and physical phenomena arise in highly heterogeneous media, the properties of which vary on three (or more) length scales. In this paper, a new three-scale asymptotic homogenization technique have been established for predicting the bioelectrical behaviors of the cardiac tissue with multiple small-scale configurations. Furthermore, we have presented the main mathematical models to describe the bioelectrical activity of the heart, from the microscopic activity of ion channels of the cellular membrane to the macroscopic properties in the whole heart. We have described how reaction–diffusion systems can be derived from microscopic models of cellular aggregates by homogenization method and a new three-scale asymptotic expansion.

The present study has some limitations and is open to several improvements. For example, analytical formulas have been found for an ideal particular geometry at the mesoscale and microscale. Nevertheless, the natural next step is to consider more realistic geometries by solving the appropriate cellular problems analytically and numerically.

A key assumption underlying the whole method is periodicity of the microstructure at both structural levels. This assumption can be considered realistic for specific types of microstructures only. However, our framework is extended to more complex geometries by taking into account two parameters of scaling dependent on the cell geometry on the macroscale. A special attention to the boundary conditions for the unit cell to ensure periodicity.

The homogenization process described in this work is also suitable for regions far enough from the boundary so that its effect is not felt (for example composite material). To account properly the homogenization process on bounded domains, the so-called boundary-layer technique established by Benssousan et al. [12] could be used (see also the work of Panasenko [50]). We know the results from reiterated and two-scale asymptotic homogenization techniques as particular cases of the proposed method.

Funding This research was supported by IEA-CNRS in the context of HIPHOP project.

Appendix: Periodic Sobolev space

In this section, we give the properties which play an important role in the theory of homogenization (see [9]). For more details on functional analysis, the reader is referred to the following references: [47,51–54]. We denote by $\mathcal{O}$ the interval in $\mathbb{R}^d$ defined by

$$\mathcal{O} =]0, \ell_1[\times \cdots \times]0, \ell_d[\,, \tag{77}$$

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 9 Let $\mathcal{O}$ the reference cell defined by (77) 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 10 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

$$\begin{cases} (\mathrm{M}(x)\lambda, \lambda) \ge \alpha\, |\lambda|^2\,, \\ |\mathrm{M}(x)\lambda| \le \beta\, |\lambda|\,, \end{cases} \tag{78}$$

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 11 Let $C^{\infty}_{\text{per}}(\mathcal{O})$ be the subset of $C^{\infty}(\mathbb{R}^d)$ of periodic functions. We denote by $H^1_{\text{per}}(\mathcal{O})$ the closure of $C^{\infty}_{\text{per}}(\mathcal{O})$ for the H^1-norm, namely,

$$H^1_{\text{per}}(\mathcal{O}) = \overline{C^{\infty}_{\text{per}}(\mathcal{O})}^{H^1(\mathcal{O})}.$$

Proposition 12 *Let $u \in H^1_{\text{per}}(\mathcal{O})$. Then u has the same trace on the opposite faces of $\mathcal{O}$.*

In the sequel, we will define the quotient space $H^1_{\text{per}}(\mathcal{O})/\mathbb{R}$ and introduce some properties on this space.

Definition 13 The quotient space $\mathcal{W}_{\text{per}}(\mathcal{O})$ is defined by

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

It is defined as the space of equivalence classes with respect to the following relation:

$$u \simeq v \Leftrightarrow u - v \text{ is a constant}, \forall u, v \in H^1_{\text{per}}(\mathcal{O}).$$

We denote by $\dot{u}$ the equivalence class represented by u.

Proposition 14 *The following quantity*

$$\|\dot{u}\|_{\mathcal{W}_{\text{per}}(\mathcal{O})} = \|\nabla u\|_{L^2(\mathcal{O})}, \quad \forall u \in \dot{u}, \quad \dot{u} \in \mathcal{W}_{\text{per}}(\mathcal{O})$$

defines a norm on $\mathcal{W}_{\text{per}}(\mathcal{O})$.

Moreover, the dual space $(\mathcal{W}_{\text{per}}(\mathcal{O}))'$ can be identified with the set

$$(\mathcal{W}_{\text{per}}(\mathcal{O}))' = \{F \in (H^1_{\text{per}}(\mathcal{O}))' \textit{ tel que } F(c) = 0, \ \forall c \in \mathbb{R}\},$$

with

$$F(u) = (F, \dot{u})_{(\mathcal{W}_{\text{per}}(\mathcal{O}))', \mathcal{W}_{\text{per}}(\mathcal{O})} = (F, u)_{(H^1_{\text{per}}(\mathcal{O}))', H^1_{\text{per}}(\mathcal{O})}, \ \forall u \in \dot{u}, \dot{u} \in \mathcal{W}_{\text{per}}(\mathcal{O}).$$

Remark 15 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:

$$W_{\text{per}}(\mathcal{O}) = \{u \in H^1_{\text{per}}(\mathcal{O}) \text{ such that } \mathcal{M}_{\mathcal{O}}(u) = 0\}. \tag{79}$$

with

$$\mathcal{M}_{\mathcal{O}}(u) = \frac{1}{|\mathcal{O}|} \int_{\mathcal{O}} u \, \mathrm{d}x. \tag{80}$$

Its dual nature coincides with the dual space $(\mathcal{W}_{\text{per}}(\mathcal{O}))'$ and the duality bracket is defined by

$$F(v) = (F, v)_{(W_{\#}(\mathcal{O}))', W_{\#}(\mathcal{O})} = (F, u)_{(H^1_{\text{per}}(\mathcal{O}))', H^1_{\text{per}}(\mathcal{O})}, \quad \forall u \in W_{\#}(\mathcal{O}).$$

Furthermore, by the Poincaré–Wirtinger's inequality, the Banach space $W_{\#}(\mathcal{O})$ has the following norm:

$$\|u\|_{W_{\#}(\mathcal{O})} = \|\nabla u\|_{L^2(\mathcal{O})}, \quad \forall u \in W_{\#}(\mathcal{O}).$$

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 [55,56]. In this part, we will treat the following partial equation:

$$\mathcal{A}u = f \text{ in } \mathcal{O},$$

with the operator $\mathcal{A}$ defined by

$$\mathcal{A} = -\nabla \cdot (\mathrm{M}\nabla) \tag{81}$$

where the matrix $\mathrm{M} = (\mathrm{m}^{pq})_{1 \le p,q \le d} \in M(\alpha, \beta, \mathcal{O})$ is given by Definition 10 but with different boundary conditions:

- **Non-homogenous Neumann condition:**

  $\mathrm{M}\nabla u \cdot n = g$ on $\partial\mathcal{O}$.

- **Periodic–Neumann condition:** Let $\mathcal{O}_j$ a portion of a reference cell $\mathcal{O}$ given by (77), 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,

  $$\begin{cases} u \ \ \mathbf{y}\text{-periodic}, \\ \mathrm{M}\nabla u \cdot n = g \text{ on } \Gamma. \end{cases}$$

Theorem 16 (Non-homogenous Neumann condition) *We consider the following problem:*

$$\begin{cases} \mathcal{A}u = f \quad \text{in } \mathcal{O}, \\ \mathrm{M}\nabla u \cdot n = g \quad \text{on } \partial\mathcal{O}. \end{cases} \tag{82}$$

with the operator $\mathcal{A}$ defined by (81). Its variational formulation is:

$$\begin{cases} \text{Find } u \in H^1(\mathcal{O}) \text{ such that} \\ a_{\mathcal{O}}(u, v) = (f, v)_{H^{-1}(\mathcal{O}), H^1(\mathcal{O})} + (g, v)_{H^{-\frac{1}{2}}(\partial\mathcal{O}), H^{\frac{1}{2}}(\partial\mathcal{O})} \quad \forall v \in H^1(\mathcal{O}), \end{cases} \tag{83}$$

with $a_{\mathcal{O}}$ defined by

$$a_{\mathcal{O}}(u, v) = \int_{\mathcal{O}} \mathrm{M}\nabla u \nabla v \mathrm{d}x, \ \forall u, v \in H^1(\mathcal{O}).$$

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:

$$(f, 1)_{H^{-1}(\mathcal{O}), H^1(\mathcal{O})} + (g, 1)_{H^{-\frac{1}{2}}(\partial\mathcal{O}), H^{\frac{1}{2}}(\partial\mathcal{O})} = 0. \tag{84}$$

Then, the problem (82)–(83) 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 17 (Periodic–Neumann condition) *Let $\mathcal{O}_j$ a portion of a unit cell $\mathcal{O}$ is given by (77), with Lipschitz continuous boundary Γ separating the two regions $\mathcal{O}_j$ and $\mathcal{O} \setminus \mathcal{O}_j$. Consider the following problem:*

$$\begin{cases} \mathcal{A}u = f \quad \text{in } \mathcal{O}_j, \\ u \ y\text{-periodic}, \\ \mathrm{M}\nabla u \cdot n = g \quad \text{on } \Gamma. \end{cases} \tag{85}$$

We take $V = \mathcal{W}_{\mathrm{per}}(\mathcal{O}_j)$. Then, for any $f \in (\mathcal{W}_{\mathrm{per}}(\mathcal{O}_j))'$ and for any $g \in H^{\frac{1}{2}}(\Gamma)$, the variational formulation of the problem (85) is

$$\begin{cases} \text{Find } \dot{u} \in \mathcal{W}_{\mathrm{per}}(\mathcal{O}_j) \text{ such that} \\ \dot{a}_{\mathcal{O}_j}(\dot{u}, \dot{v}) = (F, \dot{v})_{(\mathcal{W}_{\mathrm{per}}(\mathcal{O}_j))', \mathcal{W}_{\mathrm{per}}(\mathcal{O}_j)} \ \forall \dot{v} \in \mathcal{W}_{\mathrm{per}}(\mathcal{O}_j), \end{cases} \tag{86}$$

with $a_{\mathcal{O}_j}$ is given by

$$\dot{a}_{\mathcal{O}_j}(\dot{u}, \dot{v}) = \int_{\mathcal{O}_j} \mathrm{M}\nabla u \nabla v y, \ \forall u \in \dot{u}, \ \forall v \in \dot{v},$$

and F is defined by

$$(F, \dot{v})_{(\mathcal{W}_{\text{per}}(\mathcal{O}_j))', \mathcal{W}_{\text{per}}(\mathcal{O}_j)} = \int_{\Gamma} \mathrm{M}_i \nabla u \cdot n v \, \mathrm{d}\sigma_y + \int_{\mathcal{O}_j} f v \, \mathrm{d}y, \ \forall v \in \dot{v}, \ \forall \dot{v} \in \mathcal{W}_{\text{per}}(\mathcal{O}_j),$$

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 $(\mathcal{W}_{\text{per}}(\mathcal{O}_j))'$ which equivalent to

$$(F, 1)_{(\mathcal{W}_{\text{per}}(\mathcal{O}_j))', \mathcal{W}_{\text{per}}(\mathcal{O}_j)} = 0.$$

Then problem (86) has a unique weak solution. Moreover, we have the following estimation:

$$\|\dot{u}\|_{\mathcal{W}_{\text{per}}(\mathcal{O}_j)} \leq \frac{1}{\alpha_0} \left(\|f\|_{L^2(\mathcal{O}_j)} + C_\gamma \, \|g\|_{H^{-\frac{1}{2}}(\Gamma)} \right).$$

where $\alpha_0 = \min(1, \alpha)$ and C_γ is the trace constant.

By the definition of $\mathcal{W}_{\text{per}}$, the previous theorem shows that the problem (85) 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 (79), we obtain the same result.

References

1. Keener JP, Sneyd J (1998) Mathematical physiology, vol 1. Springer, New York
2. Pierre C (2005) Modélisation et simulation de l'activité électrique du coeur dans le thorax, analyse numérique et méthodes de volumes finis. Ph.D. thesis, Université de Nantes
3. Tung L (1978) A bi-domain model for describing ischemic myocardial DC potentials. Ph.D. thesis, Massachusetts Institute of Technology
4. Bendahmane M, Mroue F, Saad M, Talhouk R (2019) Unfolding homogenization method applied to physiological and phenomenological bidomain models in electrocardiology. Nonlinear Anal 50:413–447
5. Veneroni M (2009) Reaction–diffusion systems for the macroscopic bidomain model of the cardiac electric field. Nonlinear Anal 10(2):849–868
6. Henriquez CS, Ying W (2009) The bidomain model of cardiac tissue: from microscale to macroscale. In: Efimov IR et al (eds) Cardiac bioelectric therapy. Springer, New York, pp 401–421
7. Pennacchio M, Savaré G, Franzone PC (2005) Multiscale modeling for the bioelectric activity of the heart. SIAM J Math Anal 37(4):1333–1370
8. Bakhvalov NS, Panasenko G (2012) Homogenisation: averaging processes in periodic media: mathematical problems in the mechanics of composite materials, vol 36. Springer, New York
9. Cioranescu D, Donato P (1999) An introduction to homogenization, vol 17. Oxford University Press, Oxford
10. Hubert JS, Palencia ES (1992) Introduction aux méthodes asymptotiques et à l'homogénéisation: application à la mécanique des milieux continus. Masson
11. Tartar L (2009) The general theory of homogenization: a personalized introduction, vol 7. Springer, New York
12. Bensoussan A, Lions JL, Papanicolaou G (2011) Asymptotic analysis for periodic structures, vol 374. American Mathematical Society, Providence
13. Nguetseng G (1989) A general convergence result for a functional related to the theory of homogenization. SIAM J Math Anal 20(3):608–623
14. Allaire G (1992) Homogenization and two-scale convergence. SIAM J Math Anal 23(6):1482–1518
15. Allaire G, Briane M (1996) Multiscale convergence and reiterated homogenisation. Proc R Soc Edinb Sect A 126(2):297–342
16. Trucu D, Chaplain M, Marciniak-Czochra A (2012) Three-scale convergence for processes in heterogeneous media. Appl Anal 91(7):1351–1373
17. Cioranescu D, Damlamian A, Griso G (2002) Periodic unfolding and homogenization. Comptes Rendus Math 335(1):99–104
18. Cioranescu D, Donato P, Zaki R (2006) The periodic unfolding method in perforated domains. Portugaliae Math 63(4):467
19. Cioranescu D, Damlamian A, Donato P, Griso G, Zaki R (2012) The periodic unfolding method in domains with holes. SIAM J Math Anal 44(2):718–760
20. Cioranescu D, Damlamian A, Griso G (2008) The periodic unfolding method in homogenization. SIAM J Math Anal 40(4):1585–1620
21. Neu J, Krassowska W (1993) Homogenization of syncytial tissues. Crit Rev Biomed Eng 21(2):137–199
22. Richardson G, Chapman SJ (2011) Derivation of the bidomain equations for a beating heart with a general microstructure. SIAM J Appl Math 71(3):657–675

23. Collin A, Imperiale S (2018) Mathematical analysis and 2-scale convergence of a heterogeneous microscopic bidomain model. Math Models Methods Appl Sci 28(05):979–1035
24. Grandelius E, Karlsen KH (2019) The cardiac bidomain model and homogenization. Netw Heterog Media 14:173–204
25. Dal H, Göktepe S, Kaliske M, Kuhl E (2012) A fully implicit finite element method for bidomain models of cardiac electrophysiology. Comput Methods Biomech Biomed Eng 15(6):645–656
26. Cansız B, Dal H, Kaliske M (2018) Computational cardiology: the bidomain based modified hill model incorporating viscous effects for cardiac defibrillation. Comput Mech 62(3):253–271
27. Dal H, Göktepe S, Kaliske M, Kuhl E (2013) A fully implicit finite element method for bidomain models of cardiac electromechanics. Comput Methods Appl Mech Eng 253:323–336
28. Bader F, Bendahmane M, Saad M, Talhouk R Three scale unfolding homogenization method applied to cardiac bidomain model (Preprint 2020)
29. Colli-Franzone P, Pavarino LF, Scacchi S (2012) Mathematical and numerical methods for reaction–diffusion models in electrocardiology. In: Modeling of physiological flows, pp 107–141. Springer
30. Franzone PC, Savaré G (2002) Degenerate evolution systems modeling the cardiac electric field at micro-and macroscopic level. In: Evolution equations, semigroups and functional analysis, pp. 49–78. Springer
31. Chinnery PF, Schon EA (2003) Mitochondria. J Neurol Neurosurg Psychiatry 74(9):1188–1199
32. Rioux M, Bourgault Y (2013) A predictive method allowing the use of a single ionic model in numerical cardiac electrophysiology. ESAIM 47(4):987–1016
33. Whiteley JP (2020) An evaluation of some assumptions underpinning the bidomain equations of electrophysiology. Math Med Biol 37(2):262–302
34. Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol 117(4):500–544
35. Noble D, Garny A, Noble PJ (2012) How the Hodgkin–Huxley equations inspired the cardiac physiome project. J Physiol 590(11):2613–2628
36. Beeler GW, Reuter H (1977) Reconstruction of the action potential of ventricular myocardial fibres. J Physiol 268(1):177–210
37. Luo Ch, Rudy Y (1991) A model of the ventricular cardiac action potential: depolarization, repolarization, and their interaction. Circ Res 68(6):1501–1526
38. Luo Ch, Rudy Y (1994) A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes. Circ Res 74(6):1071–1096
39. Luo CH, Rudy Y (1994) A dynamic model of the cardiac ventricular action potential. II. After depolarizations, triggered activity, and potentiation. Circ Res 74(6):1097–1113
40. Veneroni M (2006) Reaction–diffusion systems for the microscopic cellular model of the cardiac electric field. Math Methods Appl Sci 29(14):1631–1661
41. FitzHugh R (1961) Impulses and physiological states in theoretical models of nerve membrane. Biophys J 1(6):445–466
42. Nagumo J, Arimoto S, Yoshizawa S (1962) An active pulse transmission line simulating nerve axon. Proc IRE 50(10):2061–2070
43. Rogers JM, McCulloch AD (1994) A collocation-Galerkin finite element model of cardiac action potential propagation. IEEE Trans Biomed Eng 41(8):743–757
44. Aliev RR, Panfilov AV (1996) A simple two-variable model of cardiac excitation. Chaos Solitons Fractals 7(3):293–301
45. Oleinik OA, Shamaev A, Yosifian G (2009) Mathematical problems in elasticity and homogenization, vol 2. Elsevier, Amsterdam
46. Burridge R, Keller JB (1981) Poroelasticity equations derived from microstructure. J Acoust Soc Am 70(4):1140–1146
47. Brezis H, Ciarlet PG, Lions JL (1999) Analyse fonctionnelle: théorie et applications, vol 91. Dunod, Dunod
48. Keener JP, Panfilov A (1996) A biophysical model for defibrillation of cardiac tissue. Biophys J 71(3):1335–1345
49. Ramírez-Torres A, Penta R, Rodríguez–Ramos R, Merodio J, Sabina FJ, Bravo-Castillero J, Guinovart-Díaz R, Preziosi L, Grillo A (2018) Three scales asymptotic homogenization and its application to layered hierarchical hard tissues. Int J Solids Struct 130:190–198
50. Panasenko GP (2005) Multi-scale modelling for structures and composites, vol 615. Springer, New York
51. Adams R, Fournier J (1975) Sobolev spaces. Acad Press, New York
52. Edwards RE (1995) Functional analysis: theory and applications. Courier Corporation, Chelmsford
53. Rudin W (1973) Functional analysis. Higher mathematics. McGraw-Hill, Inc, New York
54. Zeidler E (2013) Nonlinear functional analysis and its applications, vol 4. Applications to mathematical physics. Springer, New York
55. Lions JL (1969) Quelques méthodes de résolution des problemes aux limites non linéaires
56. Lions JL, Magenes E (1968) Problemes aux limites non homogenes et applications

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.