# DEGENERATE EVOLUTION SYSTEMS MODELING THE CARDIAC ELECTRIC FIELD AT MICRO AND MACROSCOPIC LEVEL

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*Dedicated to the memory of Brunello Terreni.*

ABSTRACT. We study the reaction-diffusion systems of FitzHugh-Nagumo type related to the behaviour of the electrical conduction of cardiac muscle at micro- and macroscopic level. We introduce a variational formulation for both models and we identify a unifying structure. In this framework, adapting the tools of (degenerate) abstract evolution equations in Hilbert spaces, we derive existence, uniqueness and some regularity results. Finally we also deduce convergence and error estimates of a semidiscrete approximation scheme.

## 1. INTRODUCTION

The aim of this paper is to study the reaction-diffusion systems arising from the mathematical models of the cardiac electric activity at the micro- and macroscopic level.

Recent theoretical and computational advanced studies in electrocardiology investigating the electrical behavior of the anisotropic cardiac tissue are based on the so called "bidomain" model as a representation of the macroscopic tissue properties [41, 16, 23]. This approach conceives the cardiac muscle, despite its discrete structure, as the coupling of two anisotropic continuous superimposed domains. We refer to [24] for an extensive review on the use of the bidomain approach for simulating the electrical behavior of the cardiac tissue. Recently in [37, 30] it was presented a first formal derivation of the bidomain continuous representation of the cardiac tissue from a discrete model consisting of a periodic network of interconnected cells.

A distinctive feature of the mathematical description of both models, i.e. the macroscopic bidomain and the microscopic cellular models, lies in the structure of the coupling between the intra- and extra-cellular media. Both models are reaction-diffusion systems (see e.g. [50, 12]) but of degenerate parabolic type.

***The microscopic model of the cardiac tissue.*** At a microscopic level the cardiac cellular structure of the tissue can be viewed as composed by two volumes: the intra-cellular space (inside the cells) and the extra-cellular space (outside) separated by the active membrane.

More specifically at the microscopic level the cardiac structure is composed of a collection of elongated cardiac cells, connected end–to–end and/or side–to–side by

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*Key words and phrases.* Degenerate evolution equations, reaction-diffusion systems of FitzHugh-Nagumo type, cardiac electric field, bidomain model.

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junctions, surrounded by the extra-cellular fluid. The end–to–end contacts forms the long fibers structure of the cardiac muscle whereas the presence of lateral junctions establishes a connection between the elongated fibers. Since the interconnection between cells has junction resistance comparable to that of the intra-cellular volume, we can consider the cardiac tissue as a single isotropic intramural connected domain $\Omega_i$ separated from the extra-cellular fluid $\Omega_e$ by a membrane surface $\Gamma_m$.

*The geometry and the main physical quantities.* Therefore

$$(\mu_1)\qquad \begin{gathered}\Omega := \Omega_i \cup \Omega_e \cup \Gamma_m \subset \mathbb{R}^3 \text{ is the physical region occupied by the heart,}\\ \Omega_{i,e} \text{ are the \textit{disjoint intra- and extra-cellular domains},}\\ \text{their interface } \overline{\Gamma}_m = \partial\Omega_i \cap \partial\Omega_e \text{ is the \textit{active membrane}.}\end{gathered}$$

We denote by $u_i$, $u_e$

$$(\mu_2)\qquad \begin{gathered}\text{the \textit{intra- and extra-cellular electric potentials}}\quad u_{i,e} : \overline{\Omega_{i,e}} \to \mathbb{R},\\ \text{whose difference is the \textit{transmembrane potential}}\quad v := u_i - u_e : \Gamma_m \to \mathbb{R},\end{gathered}$$

and by $\sigma_i$, $\sigma_e$

$$(\mu_3)\quad \text{the \textit{intra- and extra-cellular conductivities}}\quad \sigma_{i,e} : \overline{\Omega_{i,e}} \to \mathbb{R},\quad \inf_{\Omega_{i,e}} \sigma^{i,e} > 0.$$

*Basic equations.* Due to the current conservation law, the normal current flux through the membrane is continuous: if $\nu_i, \nu_e$ denote the unit exterior normals to the boundary of $\Omega_i$ and $\Omega_e$ respectively, satisfying $\nu_i = -\nu_e$ on $\Gamma_m$, we have

$$\sigma_i \nabla u_i \cdot \nu_i + \sigma_e \nabla u_e \cdot \nu_e = 0, \quad \text{on } \Gamma_m.$$

On the other hand, since the only active source elements lie on the membrane $\Gamma_m$, each flux equals the membrane current per unit area $I_m$, which consists of a capacitive and a ionic term (see [27]):

$$(\mu_4)\quad \sigma_i \nabla u_i \cdot \nu_i + I_m = -\sigma_e \nabla u_e \cdot \nu_e + I_m = 0, \quad I_m := \mathsf{C}_m \partial_t v + I_{ion}, \quad \text{on } \Gamma_m,$$

where $\mathsf{C}_m$ is the surface capacitance of the membrane; in particular, $\Gamma_m$ is a discontinuity surface for the potential.

Moreover, denoting by $I_i^s, I_e^s$ the (given) stimulation currents applied to the intra- and extra-cellular space, we have

$$(\mu_5)\qquad -\operatorname{div}(\sigma_i \nabla u_i) = I_i^s, \quad \text{in } \Omega_i, \qquad -\operatorname{div}(\sigma_e \nabla u_e) = I_e^s, \quad \text{in } \Omega_e.$$

If suitable (lateral and initial) boundary conditions are provided, to complete the system ($\mu_4$-$\mu_5$) a further constitutive description of the ionic current $I_{ion}$ is needed.

*The ionic current: Hodgkin-Huxley model.* Dynamics structure of the ionic models have been developed extending the Hodgkin-Huxley formalism [25] to the ionic current source density of the cardiac membrane (see e.g. [20, 34, 18]) and are of the type

$$I_{ion} = I_{ion}(v, w_1, \ldots, w_k) = \sum_n I_n(v, w_1, \ldots, w_k), \tag{1.1}$$

where $w_1, \ldots, w_k$ are additional *gating variables* taking their values between 0 and 1 and each $I_n$ is a polynomial function of the form

$$I_n(v, w_1, \ldots, w_k) := \mathsf{G}_n \, \Pi_{j=1}^k \, w_j^{p_{j,n}} \big(v - \mathsf{v}_n\big).$$

Here $p_{k,n}$ are integers (some of which may be zero), $\mathsf{G}_n$ is the conductance and the equilibrium potential $\mathsf{v}_n$ depends on the intra- and extra-cellular concentration of the ionic species $n$.

Relation (1.1) should be coupled with the system of first order differential equations linking each gating variable to the transmembrane potential $v$: it has the form

$$\partial_t w_j = r_j(v, w_j) := \alpha_j(v)\ (1 - w_j)\ - \beta_j(v)\ w_j, \quad j = 1, \ldots, k, \tag{1.2}$$

where $\alpha_j$ and $\beta_j$ are in general *positive* rational functions of exponentials in $v$.

*The FitzHugh-Nagumo simplification and the recovery variable.* Simplified models are often used for simulating the propagation of excitation wavefronts in large myocardial domains. In this work we first focus on a excitable model of the FitzHugh-Nagumo type, which was first introduced as a simplified membrane kinetic of the Hodgkin-Huxley equations in the description of the transmission of nervous electric impulses (see e.g. [14, 36]). It requires only one additional

$$\textit{recovery variable} \quad w : \Gamma_m \to \mathbb{R}, \tag{$\mu_6$}$$

and (1.1), (1.2) reduce to

$$\begin{gathered} \begin{cases} I_{ion} = I_{ion}(v, w) := F(v) + \Theta w, \\ \partial_t w = r(v, w) := \eta v - \gamma w, \end{cases} \quad \text{on } \Gamma_m, \\ \text{where } \Theta, \eta, \gamma \geq 0 \text{ are given constants and} \\ F \in C^1(\mathbb{R}) \text{ is a cubic-like function with } \inf_{\mathbb{R}} F' > -\infty. \end{gathered} \tag{$\mu_7$}$$

We refer to ($\mu_1$,. . . ,$\mu_7$) as the *microscopic model*, together with Neumann boundary conditions imposed on $u_i, u_e$ on the remaining part of the boundaries $\Gamma_{i,e} := \partial\Omega_{i,e} \setminus \Gamma_m$ respectively

$$\sigma_i \nabla u_i \cdot \nu_i = G_i \quad \text{on } \Gamma_i, \quad \sigma_e \nabla u_e \cdot \nu_e = G_e \quad \text{on } \Gamma_e, \tag{$\mu_8$}$$

and with the (degenerate) initial Cauchy condition

$$v(x, 0) = v^0(x), \quad w(x, 0) = w^0(x), \quad \text{on } \Gamma_m. \tag{$\mu_9$}$$

Thus our problem consists of two adjoining open domains with their boundaries partly intersecting, of a Poisson equation in each of them, and, on the common boundary, of two conditions connecting the fluxes and the potentials. In contrast to classical problems for the Poisson equation with a jump discontinuity across some surface, here the boundary conditions for the potentials is a dynamic boundary condition involving the assistant variable $w$.

***The macroscopic "bidomain" model.*** At a macroscopic level, in spite of the discrete cellular structure, the cardiac tissue can be represented by a continuous model, called *bidomain model* (see e.g. [24, 17, 41] and also [30]), which attempts to describe the averaged electric potentials and current flows inside (intra-) and outside (extra-cellular space) the cardiac cells. The equations should result from an homogenization process as shown formally in [37] working on a scaled version of the cellular model on a periodic cardiac structure. For completeness we will present another formal derivation of the average model by using the standard two-scaled method in the Appendix A and we defer to a forthcoming paper the rigorous mathematical justification of the model by the tools of Γ-convergence theory.

In this homogenized representation the heart domain coincides with the intra- ($i$) and extra-cellular ($e$) ones, which are two interpenetrating and superimposed continua connected at each point by the cardiac cellular membrane, i.e.

$$(M_1) \qquad \Omega \equiv \Omega_i \equiv \Omega_e \subset \mathbb{R}^3 \text{ is the physical region occupied by the heart}$$

$$(M_2) \qquad \begin{array}{rl} u_i, u_e : \Omega \to \mathbb{R} & \text{are the intra- } (i) \text{ and extra-cellular } (e) \text{ electric potentials} \\ v := u_i - u_e : \Omega \to \mathbb{R} & \text{is the transmembrane potential.} \end{array}$$

The anisotropy of the ($i$)–($e$) media depends on the fiber structure of the myocardium. At the macroscopic level the fibers are regular curves, whose unit tangent vector at the point $x$ is denoted by $\vec{a} = \vec{a}(x)$. Denoting by $\sigma^l_{i,e}(x)$, $\sigma^t_{i,e}(x)$ the conductivity coefficients along and across the fiber direction at a point $x$ and always assuming axial simmetry for $\sigma^t_{i,e}$, the conductivity tensors $M_{i,e}$ in the media ($i$), ($e$), can be expressed by

$$M_{i,e}(x) = \sigma^t_{i,e} I + (\sigma^l_{i,e} - \sigma^t_{i,e}) \vec{a} \otimes \vec{a},$$

and they are

$$(M_3) \qquad \textit{symmetric, positive definite, continuous} \text{ tensors } M_{i,e} : \overline{\Omega} \to \mathbb{M}^{3\times 3}.$$

To the potentials $u_i, u_e$ are associated the current densities $\vec{I}_{i,e} := -M_{i,e} \nabla u_{i,e}$; since induction effects are negligible, the current field can be considered quasi–static and they are related to the membrane current per unit volume $i_m$ and to the injected stimulating currents $i^s_{i,e}$ by the conservation laws

$$(M_4) \qquad -\operatorname{div}(M_i \nabla u_i) = -i_m + i^s_i, \quad -\operatorname{div}(M_e \nabla u_e) = i_m + i^s_e, \quad \text{in } \Omega.$$

On the other hand the membrane current per unit volume $i_m$ is the sum of a capacitance and a ionic term

$$(M_5) \qquad i_m = \mathsf{c}_m \partial_t v + i_{ion} \quad \text{in } \Omega.$$

Again the FitzHugh-Nagumo model supply the form of the ionic current $i_{ion}$ by means of a

$$(M_6) \qquad \textit{recovery variable} \quad w : \Omega \to \mathbb{R},$$

and of

$$(M_7) \qquad \begin{array}{c} \begin{cases} i_{ion} = i_{ion}(v, w) = f(v) + \theta w, \\ \partial_t w = r(v, w) = \eta v - \gamma w \end{cases} \text{on } \Omega \\ \text{where } \theta, \eta, \gamma \geq 0 \text{ are given constants and} \\ f \in C^1(\mathbb{R}) \text{ is a cubic-like function with } \inf_{\mathbb{R}} f' > -\infty. \end{array}$$

In fact, $\mathsf{c}_m$ and the forms of $f, i_{ion}$ are related to the corresponding microscopic quantities by the relation

$$\mathsf{c}_m = \beta \mathsf{C}_m, \quad f(v) = \beta F(v), \quad \theta = \beta \Theta, \quad i_{ion}(v, w) = \beta I_{ion}(v, w),$$

where $\beta$ is the ratio of membrane area per unit of tissue volume.

We complete the Reaction-Diffusion system ($M_1$,…,$M_7$) by imposing Neumann boundary conditions on $u_i, u_e$ on $\partial\Omega$ respectively

$$(M_8) \qquad M_i \nabla u_i \cdot \nu = g_i, \quad M_e \nabla u_e \cdot \nu = g_e,$$

and by assigning the (degenerate) initial Cauchy condition

$$(M_9) \qquad v(x,0) = v^0(x), \quad w(x,0) = w^0(x), \quad \text{on } \Omega.$$

When $M_i = \lambda M_e$, with $\lambda$ constant, the macroscopic system $(M_1 - M_9)$ in the variables $(u_i, u_e, w)$ is equivalent to a parabolic reaction-diffusion equation in $v = u_i - u_e$ coupled with the dynamics of the recovery variable $w$. This case is called in literature *equal anisotropic ratio* and this assumption is often used in modeling cardiac tissue. Experimental evidence indicates that this simplifying hypothesis is definitely not applicable to cardiac muscle. The degenerate structure of the mathematical model is primarily the result of differences in the intra- and extra-cellular anisotropy of the cardiac tissue. Morover unequal anisotropic ratio makes possible more complex phenomena [52, 51] and can play an important role for the re-entrant excitation [53, 42].

***Plan of the paper.*** In the two following sections we will propose a variational formulation of both the microscopic problem $(\mu_1, \ldots, \mu_9)$ and the macroscopic one $(M_1, \ldots, M_9)$. We will show that they have a common structure which fits into the abstract framework of (degenerate) evolution variational inequalities in Hilbert spaces; therefore, we will focus on the basic structural features of both the models, and we will state our main results about existence, uniqueness, and regularity of their solutions.

In § 4, we will present the abstract version of the evolution problems shared by the micro- and macroscopic models, we will discuss the links with the results available in the literature, and we will introduce an approach which allows us to eliminate the time degeneration; in this way it is possible to apply finer results which give a better insight into the properties of the solutions: in particular, general stability and approximation results could also be applied for the time discretization of both the systems.

The effort to enucleate a similar variational structure in the problems not only allows to reduce the length and the difficulty of the proofs, but also suggests a possible way to deduce the macroscopic setting from the microscopic one. However, the classical theory for convex evolution problems (see e.g. [1]) cannot be directly applied, due to the degeneracy and to the different kind of domains where the microscopic ($\Gamma_m$) and the macroscopic ($\Omega$) quantities live. Nevertheless, we will show in a forthcoming work a possible way to overcome this difficulty; in the Appendix of the present paper, by developing formal asymptotic expansions using the two–scales method and neglecting the presence of stimulation currents, we will show how to convert the microscopic model of the cellular media into the averaged continuum "bidomain" representation of the cardiac tissue.

## 2. Variational formulation of the microscopic problem

In this section we will deal with the system $(\mu_1, \ldots, \mu_9)$ presented in the Introduction and we will rewrite it in a suitable variational form.

*Fixing technical assumptions and notation.* Besides $(\mu_1, \ldots, \mu_9)$, we are also assuming that

$$(\mu_1') \qquad \begin{aligned} \Omega_i, \Omega_e \quad &\text{are Lipschitz domains and at least one of them is connected,} \\ \Gamma_m \quad &\text{is a (non empty) Lipschitz hypersurface.} \end{aligned}$$

From the mathematical point of view, it is not always necessary to restrict the dimension of the ambient space, which we will denote by $d$. The regularity assumptions on $F$ could be relaxed: so $F:\mathbb{R}\to\mathbb{R}$ could be a continuous function such that

$$(\mu_7') \quad F(0)=0; \quad \exists\,\lambda_F\ge 0: \quad \frac{F(x)-F(y)}{x-y}\ge -\lambda_F, \quad \forall\, x,y\in\mathbb{R}, \quad \text{with } x\ne y.$$

More general existence results in dimension $d=3$ (see Proposition 2.4) will also require that $F$ has a cubic growth at infinity, i.e.

$$(\mu_7'') \qquad 0<\liminf_{|s|\to+\infty}\frac{F(s)}{s^3}\le\limsup_{|s|\to+\infty}\frac{F(s)}{s^3}<+\infty.$$

$]0,T[$ is the evolution time interval, and we define the associated space-time domains following the usual notation of [32]

$$Q_{i,e}:=\Omega_{i,e}\times\,]0,T[,\qquad \Sigma_{i,e,m}:=\Gamma_{i,e,m}\times\,]0,T[\,. \tag{2.1}$$

The formal statement of $(\mu_1-\mu_9)$ is then:

**Problem $(\boldsymbol{\mu})$.** Given

$$I^s_{i,e}:Q_{i,e}\to\mathbb{R},\quad G_{i,e}:\Sigma_{i,e}\to\mathbb{R},\quad\text{and}\quad v^0,w^0:\Gamma_m\to\mathbb{R}, \tag{2.2}$$

we seek

$$u_{i,e}:Q_{i,e}\to\mathbb{R},\quad w:\Sigma_m\to\mathbb{R},\quad v:=u_i-u_e:\Sigma_m\to\mathbb{R},$$

satisfying the equations on $Q_{i,e}$ and $\Sigma_{i,e}$

$$\begin{cases}-\operatorname{div}\big(\sigma_{i,e}\nabla u_{i,e}\big)=I^s_{i,e}, & \text{in } Q_{i,e},\\ \sigma_{i,e}\nabla u_{i,e}\cdot\nu_{i,e}=G_{i,e} & \text{on } \Sigma_{i,e},\end{cases} \tag{2.3}$$

the evolution system on the surface $\Sigma_m$

$$\begin{cases}\mathsf{C}_m\partial_t v+F(v)+\Theta w=-\sigma_i\nabla u_i\cdot\nu_i=\sigma_e\nabla u_e\cdot\nu_e & \text{on } \Sigma_m,\\ \partial_t w+\gamma w-\eta v=0 & \text{on } \Sigma_m,\\ v(x,0)=v^0(x),\quad w(x,0)=w^0(x) & \text{on } \Gamma_m.\end{cases} \tag{2.4}$$

***Variational formulation.*** In order to write the variational formulation of Problem $(\boldsymbol{\mu})$, let us assume at first that for a.e. $t\in\,]0,T[$

$$I^s_{i,e}(\cdot,t)\in L^2(\Omega_{i,e}),\quad G_{i,e}(\cdot,t)\in H^{-1/2}(\Gamma_{i,e}), \tag{2.5}$$

$$u_{i,e}(\cdot,t),\,\partial_t u_{i,e}(\cdot,t)\in H^1(\Omega_{i,e}),\quad w(\cdot,t),\,\partial_t w(\cdot,t)\in L^2(\Gamma_m), \tag{2.6}$$

so that the trace operator $u_{i,e}\mapsto u_{i,e}|_{\Gamma_m}$ is well defined and maps continuously $H^1(\Omega_{i,e})$ onto $H^{1/2}(\Gamma_m)$ (cf. [32]). By using the simplified notation $v:=u_i-u_e$ instead of $u_i|_{\Gamma_m}-u_e|_{\Gamma_m}$, we also suppose that

$$F(v(\cdot,t))\in L^1(\Gamma_m)\cap H^{-1/2}(\Gamma_m). \tag{2.7}$$

We choose the test functions

$$\hat u_{i,e}\in H^1(\Omega_{i,e}),\quad \hat w\in L^2(\Gamma_m),\quad\text{with}\quad \hat v:=\hat u_i-\hat u_e\in H^{1/2}(\Gamma_m), \tag{2.8}$$

and we multiply the two equations of the first row of (2.4) by the trace of $\hat u_i$ and $-\hat u_e$ respectively, and the next equation by $\rho\hat w$, $\rho$ being the ratio $\Theta/\eta$. Summing up them after an integration on $\Gamma_m$ (we denote by $\mathscr{H}^{d-1}$ the usual $(d-1)$-dimensional Hausdorff measure) we get

$$
\begin{aligned}
&\int_{\Gamma_m} \big(\mathsf{C}_m\, \partial_t v\, \hat v + \rho\, \partial_t w\, \hat w\big)\, d\mathscr{H}^{d-1} \\
&\qquad + {}_{H^{-1/2}(\Gamma_m)}\langle F(v), \hat v\rangle_{H^{1/2}(\Gamma_m)} + \rho\gamma \int_{\Gamma_m} w\, \hat w\, d\mathscr{H}^{d-1} \\
&\qquad\qquad + \sum_{i,e} \int_{\Omega_{i,e}} \sigma_{i,e} \nabla u_{i,e} \cdot \nabla \hat u_{i,e}\, dx + \Theta \int_{\Gamma_m} \big(w\hat v - v\hat w\big)\, d\mathscr{H}^{d-1} = \\
&= \sum_{i,e} \int_{\Omega_{i,e}} I^s_{i,e}\, \hat u_{i,e}\, dx + \sum_{i,e} {}_{H^{-1/2}(\Gamma_{i,e})}\langle G_{i,e}, \hat u_{i,e}\rangle_{H^{1/2}(\Gamma_{i,e})},
\end{aligned}
\tag{2.9}
$$

where we used (2.3) and the Green formulae

$$
\begin{aligned}
&{}_{H^{-1/2}(\Gamma_m)}\langle \sigma_{i,e} \nabla u_{i,e} \cdot \nu_{i,e}\, \hat u_{i,e}\rangle_{H^{1/2}(\Gamma_m)} = \\
&\quad = \int_{\Omega_{i,e}} \Big(\sigma_{i,e}\nabla u_{i,e} \cdot \nabla \hat u_{i,e} + \operatorname{div}(\sigma_{i,e}\nabla u_{i,e})\, \hat u_{i,e}\Big)\, dx \\
&\qquad\qquad - {}_{H^{-1/2}(\Gamma_{i,e})}\langle \sigma_{i,e}\nabla u_{i,e} \cdot \nu_{i,e}, \hat u_{i,e}\rangle_{H^{1/2}(\Gamma_{i,e})} = \\
&\quad = \int_{\Omega_{i,e}} \sigma_{i,e}\nabla u_{i,e} \cdot \nabla \hat u_{i,e}\, dx - \int_{\Omega_{i,e}} I^s_{i,e}\, \hat u_{i,e}\, dx - {}_{H^{-1/2}(\Gamma_{i,e})}\langle G_{i,e}, \hat u_{i,e}\rangle_{H^{1/2}(\Gamma_{i,e})}.
\end{aligned}
$$

which are justified by the usual arguments of [32]. Let us point out the particular structure of (2.9), which is common to more general situations.

*"Vector" functional spaces.* Denoting by boldface letters $\boldsymbol{u}, \hat{\boldsymbol{u}}, \dots$ the triple of functions $(u_i, u_e, w)$, $(\hat u_i, \hat u_e, \hat w), \dots$, we introduce the product space

$$
\boldsymbol{X} := H^1(\Omega_i) \times H^1(\Omega_e) \times L^2(\Gamma_m), \tag{2.10}
$$

and the bilinear forms

$$
b(\boldsymbol{u}, \hat{\boldsymbol{u}}) := \int_{\Gamma_m} \big[\mathsf{C}_m (u_i - u_e)(\hat u_i - \hat u_e) + \rho\, w \hat w\big]\, d\mathscr{H}^{d-1}, \tag{2.11}
$$

$$
\begin{aligned}
a(\boldsymbol{u}, \hat{\boldsymbol{u}}) := &\sum_{i,e} \int_{\Omega_{i,e}} \sigma_{i,e}\nabla u_{i,e} \cdot \nabla \hat u_{i,e}\, dx + \rho\gamma \int_{\Gamma_m} w\, \hat w\, d\mathscr{H}^{d-1} + \\
&+\Theta \int_{\Gamma_m} \Big[w(\hat u_i - \hat u_e) - (u_i - u_e)\hat w\Big]\, d\mathscr{H}^{d-1},
\end{aligned}
\tag{2.12}
$$

which are defined for every $\boldsymbol{u}, \hat{\boldsymbol{u}} \in \boldsymbol{X}$.

If (2.5) holds and $v^0, w^0$ belong to $L^2(\Gamma_m)$, then we can also associate to the right hand member of (2.9) and to the initial data the time-depending family of linear functionals $\boldsymbol{L}(t) \in \boldsymbol{X}'$ and the linear functional $\boldsymbol{\ell}^0 \in \boldsymbol{X}'$ respectively, which act on a generic elements $\hat{\boldsymbol{u}} \in X$ in the following way

$$
\begin{cases}
\langle \boldsymbol{L}(t), \hat{\boldsymbol{u}}\rangle := \displaystyle\sum_{i,e} \int_{\Omega_{i,e}} I^s_{i,e}\, \hat u_{i,e}\, dx + \sum_{i,e} {}_{H^{-1/2}(\Gamma_{i,e})}\langle G_{i,e}, \hat u_{i,e}\rangle_{H^{1/2}(\Gamma_{i,e})}, \\
\langle \boldsymbol{\ell}^0, \hat{\boldsymbol{u}}\rangle := \displaystyle\int_{\Gamma_m} \Big(\mathsf{C}_m\, v^0\, (\hat u_i - \hat u_e) + \rho\, w^0\, \hat w\Big)\, dx.
\end{cases}
\tag{2.13}
$$

The remaining (non-linear term) $\mathfrak{F} : D(\mathfrak{F}) \subset \boldsymbol{X} \to \boldsymbol{X}'$ is defined by

$$\langle \mathfrak{F}\boldsymbol{u}, \hat{\boldsymbol{u}} \rangle := {}_{H^{-1/2}(\Gamma_m)}\langle F(u_i - u_e), \hat{u}_i - \hat{u}_e \rangle_{H^{1/2}(\Gamma_m)}, \tag{2.14}$$

for every $\boldsymbol{u} \in D(\mathfrak{F})$, $\hat{\boldsymbol{u}} \in \boldsymbol{X}$, with

$$D(\mathfrak{F}) := \big\{ \boldsymbol{u} \in \boldsymbol{X} : F(u_i - u_e) \in L^1(\Gamma_m) \cap H^{-1/2}(\Gamma_m) \big\}. \tag{2.15}$$

We collect all these calculations in the following standard lemma.

**Lemma 2.1.** *Let $\boldsymbol{X}, b(\cdot,\cdot), a(\cdot,\cdot), \boldsymbol{L}, \mathfrak{F}$ be defined by* (2.10),...,(2.15) *respectively, and let us suppose that*

$$I^s_{i,e} \in L^2(Q) = L^2(0,T; L^2(\Omega_{i,e})), \quad G_{i,e} \in L^2(0,T; H^{-1/2}(\Gamma_{i,e})). \tag{2.16}$$

*Then $u_i, u_e, w$ satisfy* (2.6), (2.7) *and solve Problem ($\boldsymbol{\mu}$) if and only if the function*

$$\boldsymbol{u}(t) := \big(u_i(\cdot,t), u_e(\cdot,t), w(\cdot,t)\big), \quad \textit{belongs to } W^{1,1}(0,T;\boldsymbol{X}), \tag{2.17}$$

*and solves the abstract evolution equation*

$$\begin{cases} b(\boldsymbol{u}', \hat{\boldsymbol{u}}) + a(\boldsymbol{u}, \hat{\boldsymbol{u}}) + \big\langle \mathfrak{F}\boldsymbol{u}, \hat{\boldsymbol{u}} \big\rangle = \langle \boldsymbol{L}(t), \hat{\boldsymbol{u}} \rangle, \quad \forall\, \hat{\boldsymbol{u}} \in \boldsymbol{X}, \quad \textit{a.e. in } ]0,T[\,, \\ b(\boldsymbol{u}(0), \hat{\boldsymbol{u}}) = \langle \boldsymbol{\ell}^0, \hat{\boldsymbol{u}} \rangle, \quad \forall\, \hat{\boldsymbol{u}} \in X. \end{cases} \tag{2.18}$$

*Remark* 2.2. Different types of (variational) boundary conditions could also be considered in Problem ($\boldsymbol{\mu}$), by simply modifying $\boldsymbol{X}$ and $\boldsymbol{L}$. E.g., if we want to impose the homogeneous Dirichlet condition

$$u_e = 0, \quad \text{on } \Gamma_e, \tag{2.19}$$

instead of the corresponding Neumann one, we can replace $H^1(\Omega_e)$ by its closed subspace

$$H^1_{\Gamma_e}(\Omega_e) := \Big\{ u \in H^1(\Omega_e) : u_{|_{\Gamma_e}} = 0, \ \text{ in the sense of traces} \Big\}$$

in the definition (2.10) of $\boldsymbol{X}$.

*Remark* 2.3. We point out that (2.11), (2.12), and (2.14) are not modified by adding to $\boldsymbol{u}, \hat{\boldsymbol{u}}$ a constant vector $\mathbf{c}$ of the type

$$\mathbf{c} := (c, c, 0), \quad \forall\, c \in \mathbb{R}. \tag{2.20}$$

Analogously, the solutions $u_i, u_e, w$ of Problem ($\boldsymbol{\mu}$) can be determined at every time $t$ up to this kind of additive constants. Therefore, it is natural to replace $\boldsymbol{X}$ by its quotient

$$\boldsymbol{V} := \Big( H^1(\Omega_i) \times H^1(\Omega_e) \times L^2(\Gamma_m) \Big) / \Big\{ (c,c,0) : c \in \mathbb{R} \Big\} \tag{2.21}$$

and to look for $\boldsymbol{u}$ with values in $\boldsymbol{V}$; to simplify our notation, we still denote by $(u_i, u_e, w)$ the corresponding equivalence class and take for granted to check the independence of the particular representative.

As usual, we can identify the dual $\boldsymbol{V}'$ of $\boldsymbol{V}$ with the closed subspace of $\boldsymbol{X}'$ whose elements $\boldsymbol{L}$ verify

$$\big\langle \boldsymbol{L}, \mathbf{c} \big\rangle = 0, \quad \text{for every } \mathbf{c} \text{ given by (2.20).} \tag{2.22}$$

It follows that we have to impose the compatibility condition

$$\sum_{i,e} \int_{\Omega_{i,e}} I^s_{i,e}\, dx + \sum_{i,e} {}_{H^{-1/2}(\Gamma_{i,e})}\langle G_{i,e}, 1 \rangle_{H^{1/2}(\Gamma_{i,e})} = 0, \quad \text{a.e. in } ]0,T[, \tag{2.23}$$

in order to have $\boldsymbol{L}(t) \in \boldsymbol{V}'$ in the case of (2.13). Finally, we note that $\mathfrak{F}$ maps $D(\mathfrak{F})$ into $\boldsymbol{V}'$ without any further restriction.

*Where to choose initial data.* In order to avoid extra regularity assumptions on the solution and to understand how to choose the correct functional framework for the initial data, we introduce the linear continuous operators $A, B : \boldsymbol{V} \to \boldsymbol{V}'$ associated to $a, b$ respectively, i.e.

$$\big\langle A\boldsymbol{u}, \hat{\boldsymbol{u}}\big\rangle := a(\boldsymbol{u}, \hat{\boldsymbol{u}}), \quad \big\langle B\boldsymbol{u}, \hat{\boldsymbol{u}}\big\rangle := b(\boldsymbol{u}, \hat{\boldsymbol{u}}), \quad \forall\, \boldsymbol{u}, \hat{\boldsymbol{u}} \in \boldsymbol{V}. \tag{2.24}$$

Then we can rewrite (2.18) in the operator form

$$\big(B\boldsymbol{u}(t)\big)' + A\boldsymbol{u}(t) + \mathfrak{F}\boldsymbol{u}(t) = \boldsymbol{L}(t) \quad \text{in } \boldsymbol{V}', \quad \text{for a.e. } t \in ]0, T[, \tag{2.25}$$

which suggests that (2.17) can be weakened by asking

$$\boldsymbol{u} \in L^2(0, T; \boldsymbol{V}), \quad B\boldsymbol{u} \in W^{1,1}_{loc}(0, T; \boldsymbol{V}') \cap C^0([0, T]; \boldsymbol{V}'), \tag{2.26}$$

so that we can give a meaning in $\boldsymbol{V}'$ to the initial value of $B\boldsymbol{u}$. Let us introduce the distribution spaces $\tilde{V}_b \subset \tilde{V}_b'$ on $\Gamma_m$

$$\tilde{V}_b := H^{1/2}(\Gamma_m) \times L^2(\Gamma_m), \quad \tilde{V}_b' := H^{-1/2}(\Gamma_m) \times L^2(\Gamma_m),$$

and let us observe that the operator $B : \boldsymbol{V} \to \boldsymbol{V}'$ admits the decomposition

$$B = \tilde{B}^* J_b \tilde{B}, \quad b(\boldsymbol{u}, \hat{\boldsymbol{u}}) = {}_{\boldsymbol{V}'}\langle B\boldsymbol{u}, \hat{\boldsymbol{u}}\rangle_{\boldsymbol{V}} = {}_{\tilde{V}_b'}\langle J_b \tilde{B}\boldsymbol{u}, \tilde{B}\hat{\boldsymbol{u}}\rangle_{\tilde{V}_b} \tag{2.27}$$

where $J_b : \tilde{V}_b \to \tilde{V}_b'$ is the inclusion map, $\tilde{B}$ is the linear surjection

$$\tilde{B} : \boldsymbol{V} \to \tilde{V}_b, \quad \tilde{B}\boldsymbol{u} := \Big(\sqrt{\mathsf{C}_m}\,(u_i - u_e), \sqrt{\rho}\, w\Big) \tag{2.28}$$

and $\tilde{B}^* : \tilde{V}_b' \to \boldsymbol{V}'$ is the transposed linear isomorphism

$$\begin{aligned} \big\langle \tilde{B}^*(v, w), \hat{\boldsymbol{u}}\big\rangle := {}& {}_{H^{-1/2}(\Gamma_m)}\langle \sqrt{\mathsf{C}_m}\, v, \hat{v}\rangle_{H^{1/2}(\Gamma_m)} + \\ & + \int_{\Gamma_m} \sqrt{\rho}\, w\, \hat{w}\, d\mathscr{H}^{d-1}, \quad \forall\, \hat{\boldsymbol{u}} \in \boldsymbol{V}. \end{aligned} \tag{2.29}$$

We observe that (2.26) entails

$$(u_i - u_e, w) \in C^0([0, T]; \tilde{V}_b')$$

so that we have to require $(v^0, w^0) \in \tilde{V}_b'$ at least.

On the other hand, if $\mathfrak{F}$ would be linear, we could read from the equation that $\tilde{B}\boldsymbol{u}$ belongs also to $H^1(0, T; \tilde{V}_b') \cap L^2(0, T; \tilde{V}_b)$, and we could deduce by standard interpolation results (cf. [32]), the mapping

$$t \mapsto \big(v(t), w(t)\big) \quad \text{is uniformly continuous in} \quad \tilde{H}_b := L^2(\Gamma_m) \times L^2(\Gamma_m). \tag{2.30}$$

Even if $B\boldsymbol{u}$ does not belong to $H^1(0, T; \boldsymbol{V}')$ in the general nonlinear case, however (2.30) still holds, and we shall require

$$(v^0, w^0) \in L^2(\Gamma_m) \times L^2(\Gamma_m), \quad \boldsymbol{\ell}^0 \in H_b := \tilde{B}^*(\tilde{H}_b) \tag{2.31}$$

writing the initial condition as

$$\big(B\boldsymbol{u}\big)(0) = \boldsymbol{\ell}^0 \in H_b. \tag{2.32}$$

***Main result.*** We have now all the elements to reformulate Problem ($\boldsymbol{\mu}$) in an abstract variational form and to state our main result about it.

**Problem ($\boldsymbol{A\mu}$).** Let us assume that (2.16), (2.23), and (2.31) hold. Then, if $\boldsymbol{V}, b, a, L, \mathfrak{F}$ are defined by (2.21), (2.11),...,(2.14) respectively, we look for

$$\boldsymbol{u} \in L^2(0,T;\boldsymbol{V}), \quad \text{with} \quad B\boldsymbol{u} \in W^{1,1}_{loc}(0,T;\boldsymbol{V}') \cap C^0([0,T];\boldsymbol{V}') \tag{2.33}$$

satisfying the abstract Cauchy problem (2.25), (2.32).

**Theorem 1.** *In the framework of* $(\mu_1,\ldots,\mu_9)$, $(\mu_1',\mu_7')$, *let us assume that*

$$I^s_{i,e} \in W^{1,1}(0,T;L^2(\Omega_{i,e})), \quad G_{i,e} \in W^{1,1}(0,T;H^{-1/2}(\Gamma_{i,e})), \tag{2.34}$$

*and* (2.23), (2.31) *are satisfied. Then there exists a unique solution* $\boldsymbol{u}$ *of Problem* ($\boldsymbol{A\mu}$)*; in particular there exist a couple*

$$u_i, u_e \in L^2(0,T;H^1(\Omega_{i,e})) \cap C^0(]0,T];H^1(\Omega_{i,e}))$$

*uniquely determined up to a family of additive constants* $c(t)$ *and a unique couple* $(v,w)$ *with*

$$v \in C^0([0,T];L^2(\Gamma_m)) \cap L^2(0,T;H^{1/2}(\Gamma_m)), \quad \partial_t v \in L^1_{loc}(0,T;H^{-1/2}(\Gamma_m)), \tag{2.35}$$

$$w, \partial_t w \in C^0([0,T];L^2(\Gamma_m)) \cap L^2(0,T;H^{1/2}(\Gamma_m)), \tag{2.36}$$

*which solve the microscopic model* $(\mu_1,\ldots,\mu_9)$*, as formulated by Problem* ($\boldsymbol{\mu}$)*, in the standard distribution sense. Moreover, if*

$$v^0 \in H^{1/2}(\Gamma_m), \quad v^0\, F(v^0) \in L^1(\Gamma_m), \tag{2.37}$$

*then*

$$u_{i,e} \in C^0([0,T];H^1(\Omega_{i,e})), \quad \partial_t v \in L^2(\Sigma_m), \quad w \in C^0([0,T];H^{1/2}(\Gamma_m)). \tag{2.38}$$

***Structural properties.*** The *proof* of this theorem follows from a direct application of Theorem 4 of § 4; now we limit ourselves to point out some distinctive properties of $a, b, \mathfrak{F}, \boldsymbol{L}$ which will guide us in the choice and the application of the abstract framework and which are common to different situations, as the macroscopic model. These properties will conclude the proof of theorem 1.

**P1.** $b$ is *symmetric* and the associated quadratic form (which we will denote by $b$ again) is *nonnegative* but its kernel has infinite dimension, so that (2.18) is a *degenerate evolution equation.* However, by $(\mu_3)$ and Poincaré inequality, the sum of the quadratic forms associated to $a$ and $b$ is coercive on $\boldsymbol{V}$, i.e.

$$\exists\,\alpha > 0: \quad a(\boldsymbol{u},\boldsymbol{u}) + b(\boldsymbol{u},\boldsymbol{u}) \geq \alpha \|\boldsymbol{u}\|^2_{\boldsymbol{V}}, \quad \forall\,\boldsymbol{u} \in \boldsymbol{V}, \tag{2.39}$$

and $a$ verifies

$$\begin{aligned} |a(\boldsymbol{u},\hat{\boldsymbol{u}}) - a(\hat{\boldsymbol{u}},\boldsymbol{u})|^2 &= 4\Theta^2 \left| \int_{\Gamma_m} \big(v\hat{w} - \hat{v}\,w\big)\, d\mathscr{H}^{d-1} \right|^2 \\ &\leq \frac{4\Theta^2}{\rho\mathsf{C}_m} \int_{\Gamma_m} \big(\mathsf{C}_m v^2 + \rho w^2\big)\, d\mathscr{H}^{d-1} \int_{\Gamma_m} \big(\mathsf{C}_m \hat{v}^2 + \rho \hat{w}^2\big)\, d\mathscr{H}^{d-1} \\ &\leq \frac{4\Theta^2}{\rho\mathsf{C}_m} b(\boldsymbol{u},\boldsymbol{u})\; b(\hat{\boldsymbol{u}},\hat{\boldsymbol{u}}). \end{aligned} \tag{2.40}$$

**P2.** The nonlinear operator $\mathfrak{F} : D(\mathfrak{F}) \subset \boldsymbol{V} \to \boldsymbol{V}'$ is a linear perturbation of a subdifferential one; in order to show this fact, let us set for $\lambda \in \mathbb{R}$

$$F_\lambda(v) := F(v) + \lambda v, \quad \phi_\lambda(v) := \int_0^v F_\lambda(s)\, ds = \frac{\lambda \mathsf{C}_m}{2} v^2 + \int_0^v F(s)\, ds. \tag{2.41}$$

In this way, if $\lambda \geq \lambda_F/\mathsf{C}_m$, $F_\lambda$ is an increasing function whose primitive $\phi_\lambda$ is convex. We introduce the convex l.s.c. functional on $\boldsymbol{V}$

$$\Phi(\boldsymbol{u}) := \begin{cases} \int_{\Gamma_m} \Big(\phi_\lambda(u_i - u_e) + \frac{\lambda}{2}\rho w^2\Big)\, d\mathscr{H}^{d-1}, & \text{if } \phi(u_i - u_e) \in L^1(\Gamma_m) \\ +\infty & \text{otherwise,} \end{cases} \tag{2.42}$$

and, adapting the results of [9], we know that a functional $\boldsymbol{\ell} \in \boldsymbol{V}'$ belongs to the subdifferential $\partial\Phi(\boldsymbol{u})$ if and only if

$$\begin{cases} F_\lambda(u_i - u_e) \in L^1(\Gamma_m) \cap H^{-1/2}(\Gamma_m), \quad \text{i.e. } \boldsymbol{u} \in D(\mathfrak{F}), \text{ and} \\ \langle \boldsymbol{\ell}, \hat{\boldsymbol{u}} \rangle = {}_{H^{-1/2}(\Gamma_m)}\langle F_\lambda(u_i - u_e), \hat{u}_i - \hat{u}_e \rangle_{H^{1/2}(\Gamma_m)} + \lambda\rho \int_{\Gamma_m} w\hat{w}\, d\mathscr{H}^{d-1}. \end{cases} \tag{2.43}$$

This formula shows that $\boldsymbol{\ell} \in \partial\Phi(\boldsymbol{u})$ is equivalent to

$$\begin{aligned} \langle \boldsymbol{\ell}, \hat{\boldsymbol{u}} \rangle =& \langle \mathcal{F}\boldsymbol{u}, \hat{\boldsymbol{u}} \rangle + \lambda \int_{\Gamma_m} \Big(\mathsf{C}_m (u_i - u_e)\,(\hat{u}_i - \hat{u}_e) + \rho w \hat{w}\Big)\, d\mathscr{H}^{d-1} = \\ =& \langle \mathfrak{F}\boldsymbol{u}, \boldsymbol{u} \rangle + \lambda b(\boldsymbol{u}, \hat{\boldsymbol{u}}), \end{aligned}$$

i.e.

$$\mathfrak{F} = \partial\Phi - \lambda B. \tag{2.44}$$

Let us remark that if $v \in L^2(\Gamma_m)$, the property $\phi(v) \in L^1(\Gamma_m)$ is equivalent to ask $vF(v) \in L^1(\Gamma_m)$, by the monotonicity of $F_\lambda$ and (2.41).

**P3.** Let us denote by $\boldsymbol{K}_b \subset \boldsymbol{V}$ the kernel of $B$ and $b(\cdot,\cdot)$, i.e.

$$\boldsymbol{K}_b := \{\boldsymbol{u} \in \boldsymbol{V} : u_i|_{\Gamma_m} \equiv u_e|_{\Gamma_m},\ w \equiv 0\} = \{\boldsymbol{u} \in \boldsymbol{V} : b(\boldsymbol{u}, \boldsymbol{u}) = 0\}. \tag{2.45}$$

The functional $\Phi$ is invariant with respect to the translation of $\boldsymbol{K}_b$, or equivalently, it admits the obvious decomposition

$$\Phi := \tilde{\phi}_b \circ \tilde{B}, \quad \text{where} \quad \tilde{\phi}_b : \tilde{V}_b \to [0, +\infty] \tag{2.46}$$

can be formally obtained from (2.42) by replacing $u_i - u_e$ with $v$. Analogously, $\mathfrak{F}$ can be written as

$$\mathfrak{F} = \tilde{B}^* \circ \tilde{\phi}_b \circ \tilde{B}, \quad \text{with} \quad \tilde{\phi}_b : D(\tilde{\phi}_b) \subset \tilde{V}_b \to \tilde{V}_b'. \tag{2.47}$$

We observe that, with respect to the duality between $\tilde{V}_b$ and $\tilde{V}_b'$, $\tilde{\Phi}$ and $\tilde{\mathfrak{F}}$ have the same properties of $\Phi, \mathcal{F}$ with respect to $\boldsymbol{V}, \boldsymbol{V}'$.

**P4.** We can characterize the image $V_b' := \tilde{B}^*(\tilde{V}_b')$ as the closed subspace of $\boldsymbol{V}'$

$$V_b' := \big\{\boldsymbol{\ell} \in \boldsymbol{V}' : \langle \boldsymbol{\ell}, \boldsymbol{u} \rangle = 0, \quad \forall\, \boldsymbol{u} \in \boldsymbol{K}_b\big\} \tag{2.48}$$

Setting $V_b := \tilde{B}^* J_b(\tilde{V}_b) = B(\boldsymbol{V}) \subset V_b'$, endowed with the induced norm, $\tilde{B}^*$ establishes an isomorphism between the Hilbert triple $V_b, \tilde{H}_b, \tilde{V}_b'$ and $V_b, H_b, V_b'$, where $H_b$ is the intermediate interpolation space $H_b := (V_b, V_b')_{1/2,2}$. It is easy to translate all the properties holding in one of these triples (as in the next Theorem 4) into the corresponding ones in the other setting.

***Extra regularity.*** In the case of a single parabolic equation of second order, further regularity properties can often be deduced by the usual maximum principle arguments (see [50]); since we are dealing with a parabolic system, this technique can not be applied.

In any case, we are mostly interested to point out the abstract variational structure of the micro- and macroscopic problems, which is preserved by the asymptotic (formal) limit and which will play a crucial role in a rigorous asymptotic analysis. Postponing to a forthcoming paper this study, here we do not exploit further regularity properties, which are also influenced by the particular choice of $F$ and by the singular character of the boundary conditions at the junction points of $\Gamma_i, \Gamma_e$, and $\Gamma_m$. Let us only mention another existence result under slightly weaker assumptions, which is important for the specific cardiac model we are referring to, and which is an immediate consequence of the abstract theory.

**Proposition 2.4.** *Suppose that (the space dimension) $d = 3$, $\Gamma_m$ has a finite measure, and $F$ has a cubic growth at infinity as in ($\mu_7''$). Then* (2.35) *and* (2.36) *hold even if we assume* (2.16) *instead of the stronger* (2.34).

*Proof.* By the Sobolev Imbedding Theorem, we know that $H^{1/2}(\Gamma_m)$ is continuously imbedded into $L^4(\Gamma_m)$, and consequently

$$L^2(\Gamma_m) \subset L^{4/3}(\Gamma_m) \subset H^{-1/2}(\Gamma_m).$$

We deduce that, for $\lambda \geq \lambda_F$ and suitable constants $C_i$ dependent only on $\Gamma_m$

$$\begin{aligned}\|F(v)\|^{4/3}_{H^{-1/2}(\Gamma_m)} &\leq C_1 \|F(v)\|^{4/3}_{L^{4/3}(\Gamma_m)} \leq C_2\Big(1 + \int_{\Gamma_m} v^4 \, d\mathscr{H}^2\Big) \\ &\leq C_3\Big(1 + \int_{\Gamma_m} \phi_\lambda(v)\, d\mathscr{H}^2\Big) \leq C_3\big(1 + \Phi(\boldsymbol{u})\big);\end{aligned} \tag{2.49}$$

thus we can apply the next Proposition 4.3. □

## 3. Variational formulation of the macroscopic problem.

We now consider the variational formulation of the macroscopic bidomain model $(M_1, \ldots, M_9)$. Because of the analogy with the procedure of the previous section, we will proceed on more quickly.

*Preliminaries.* As we did before, we slightly reinforce $(M_1, M_3, M_7)$ by requiring that

($M_1'$) $\Omega$ is a Lipschitz domain of $\mathbb{R}^d$, $\Gamma = \partial\Omega$, $\nu$ :=unitary exterior normal to $\Gamma$,

As usual we set $Q := \Omega \times ]0, T[$, $\Sigma := \Gamma \times ]0, T[$.

We also suppose that $M_i(x), M_e(x)$, are measurable and satisfy the uniform ellipticity condition

$$(M_3') \qquad \exists\, \alpha, m > 0: \quad \alpha|\xi|^2 \leq M_{i,e}(x)\xi\cdot\xi \leq m|\xi|^2, \quad \forall\, \xi \in \mathbb{R}^d,\ x \in \Omega.$$

Finally, $f$ is a continuous function with

$$(M_7') \qquad f(0) = 0; \quad \exists\, \lambda_f \geq 0: \quad \frac{f(x) - f(y)}{x - y} \geq -\lambda_f, \quad \forall\, x, y \in \mathbb{R}, \quad \text{with } x \neq y;$$

sometimes we will also require that $f$ has a cubic growth at infinity, i.e.

$$(M_7'') \qquad 0 < \liminf_{|s|\to+\infty} \frac{f(s)}{s^3} \leq \limsup_{|s|\to+\infty} \frac{f(s)}{s^3} < +\infty.$$

The following problem collects the discussion presented in the Introduction:

**Problem ($\boldsymbol{M}$).** Given

$$i^s_{i,e} : Q \to \mathbb{R}, \quad g_{i,e} : \Sigma \to \mathbb{R}, \quad \text{and} \quad v^0, w^0 : \Omega \to \mathbb{R}, \tag{3.1}$$

we seek

$$u_i, u_e, w : Q \to \mathbb{R}, \quad \text{with} \quad v := u_i - u_e,$$

which solve

$$\begin{cases} \mathsf{c}_m \partial_t v + f(v) + \theta w = \operatorname{div}\big(M_i \nabla u_i\big) + i^s_i & \text{in } Q, \\ \mathsf{c}_m \partial_t v + f(v) + \theta w = -\operatorname{div}\big(M_e \nabla u_e\big) - i^s_e & \text{in } Q, \\ \partial_t w + \gamma w - \eta v = 0 & \text{in } Q, \\ v(x,0) = v^0(x), \quad w(x,0) = w^0(x) & \text{in } \Omega, \\ M_{i,e} \nabla u_{i,e} \cdot \nu = g_{i,e} & \text{on } \Sigma. \end{cases} \tag{3.2}$$

Arguing as in the previous section, we introduce the Hilbert spaces

$$\boldsymbol{X} := H^1(\Omega) \times H^1(\Omega) \times L^2(\Omega), \quad \boldsymbol{V} := X / \big\{(c,c,0) : c \in \mathbb{R}\big\}, \tag{3.3}$$

(whose generic elements $(u_i, u_e, w)$ we denote by $\boldsymbol{u}$ again), the bilinear forms on $\boldsymbol{V} \times \boldsymbol{V}$ (here $\rho := \theta/\eta$)

$$b(\boldsymbol{u}, \hat{\boldsymbol{u}}) := \int_\Omega \big[\mathsf{c}_m (u_i - u_e)(\hat{u}_i - \hat{u}_e) + \rho\, w \hat{w}\big]\, dx, \tag{3.4}$$

$$a(\boldsymbol{u}, \hat{\boldsymbol{u}}) := \sum_{i,e} \int_\Omega M_{i,e} \nabla u_{i,e} \cdot \nabla \hat{u}_{i,e}\, dx + \theta \int_\Omega \Big[w(\hat{u}_i - \hat{u}_e) - (u_i - u_e)\hat{w}\Big]\, dx, \tag{3.5}$$

the functionals on $X$

$$\begin{cases} \langle \boldsymbol{L}(t), \hat{\boldsymbol{u}} \rangle := \displaystyle\sum_{i,e} \int_\Omega i^s_{i,e}\, \hat{u}_{i,e}\, dx + \sum_{i,e} {}_{H^{-1/2}(\Gamma)}\langle g_{i,e}, \hat{u}_{i,e} \rangle_{H^{1/2}(\Gamma)}, \\ \langle \boldsymbol{\ell}^0, \hat{\boldsymbol{u}} \rangle := \displaystyle\int_\Omega \Big(\mathsf{C}_m\, v^0\, \hat{v} + \rho\, w^0\, \hat{w}\Big)\, dx, \end{cases} \tag{3.6}$$

and the operator $\mathfrak{F} : D(\mathfrak{F}) \subset \boldsymbol{V} \to \boldsymbol{V}'$

$$\langle \mathfrak{F}\boldsymbol{u}, \hat{\boldsymbol{u}} \rangle := \int_\Omega \Big[f(u_i - u_e)(\hat{u}_i - \hat{u}_e)\Big]\, dx, \tag{3.7}$$

with domain

$$D(\mathfrak{F}) := \big\{\boldsymbol{u} \in \boldsymbol{V} : f(u_i - u_e) \in L^1(\Omega) \cap (H^1(\Omega))'\big\}; \tag{3.8}$$

this means that for every $\boldsymbol{u} \in D(\mathfrak{F})$ there exists a constant $C > 0$ such that

$$\int_\Omega f(u_i - u_e)\, \zeta\, dx \le C \|\zeta\|_{H^1(\Omega)}, \quad \forall\, \zeta \in H^1(\Omega) \cap L^\infty(\Omega). \tag{3.9}$$

Again we observe that all these definitions are compatible with the quotient space $\boldsymbol{V}$, provided that

$$\int_\Omega \big(i^s_i + i^s_e\big)\, dx + {}_{H^{-1/2}(\Gamma)}\langle g_i + g_e, 1 \rangle_{H^{1/2}(\Gamma)} = 0, \qquad \text{for a.e. } t \in ]0, T[. \tag{3.10}$$

Here is the precise statement of Problem ($\boldsymbol{M}$) in a variational abstract form.

**Problem $(\boldsymbol{AM})$.** Let us assume that

$$i^s_{i,e} \in L^2(Q), \quad g_{i,e} \in L^2(0,T;H^{-1/2}(\Gamma)), \quad v^0, w^0 \in L^2(\Omega), \tag{3.11}$$

and (3.10) is satisfied. Then, if $\boldsymbol{V}, b, a, L, \boldsymbol{\ell}^0, \mathfrak{F}$ are defined by (3.3),. . .,(3.7) respectively, and $A, B$ are defined as in (2.24), we seek $\boldsymbol{u}(t) := \big(u_i(\cdot,t), u_e(\cdot,t), w(\cdot,t)\big)$, with

$$\boldsymbol{u} \in L^2(0,T;\boldsymbol{V}), \quad B\boldsymbol{u} \in W^{1,1}_{loc}(0,T;\boldsymbol{V}') \cap C^0([0,T];\boldsymbol{V}'), \tag{3.12}$$

satisfying for

$$\big(B\boldsymbol{u}\big)' + A\boldsymbol{u} + \mathfrak{F}\boldsymbol{u} = \boldsymbol{L}, \quad \text{in } \boldsymbol{V}', \quad \text{a.e. in } ]0,T[, \tag{3.13}$$

together to the initial condition

$$\big(B\boldsymbol{u}\big)(0) = \boldsymbol{\ell}^0. \tag{3.14}$$

Also for this problem we could repeat the same structural remarks **P1,. . . ,4** of the previous section, the basic properties of $\boldsymbol{V}, b, a, \mathfrak{F}, \boldsymbol{L}$ being the same. We deduce the following statement.

**Theorem 2.** *In the framework of the macroscopic model* $(M_1, \dots, M_9)$, $(M_1', M_3', M_7')$, *let us assume that* (3.11) *and* (3.10) *are satisfied, together with*

$$i^s_i + i^s_e \in W^{1,1}(0,T;L^2(\Omega)), \quad g_{i,e} \in W^{1,1}(0,T;H^{-1/2}(\Gamma)). \tag{3.15}$$

*Then Problem* $(\boldsymbol{AM})$ *admits a unique solution* $\boldsymbol{u}$. *In particular there exist a couple*

$$u_i, u_e \in L^2(0,T;H^1(\Omega)),$$

*uniquely determined up to a family of additive constants* $c(t)$, *and a unique couple* $(v,w)$ *with*

$$v \in C^0([0,T];L^2(\Omega)) \cap L^2(0,T;H^1(\Omega)), \quad \partial_t v \in L^2_{loc}(0,T;L^2(\Omega)), \tag{3.16}$$

$$w, \partial_t w \in C^0([0,T];L^2(\Omega)),$$

*which solve the macroscopic model* $(M_1, \dots, M_9)$ *in the sense of Problem* $(\boldsymbol{M})$. *Moreover, if*

$$v^0 \in H^1(\Omega), \quad v^0 f(v^0) \in L^1(\Omega), \tag{3.17}$$

*then*

$$u_{i,e} \in C^0([0,T];H^1(\Omega)), \quad \partial_t v \in L^2(Q), \quad w \in C^0([0,T];H^1(\Omega)). \tag{3.18}$$

*Proof.* We argue as before by invoking Theorem 4 of the next session; in this case we can establish an isomorphism of the "abstract Hilbert triple" $V_b, H_b, V_b'$ introduced there with the "concrete"

$$\tilde V_b := H^1(\Omega) \times L^2(\Omega), \quad \tilde H_b := L^2(\Omega) \times L^2(\Omega), \quad \tilde V_b' := \big(H^1(\Omega)\big)' \times L^2(\Omega)$$

via the transpose of the operator $\tilde B\boldsymbol{u} := (u_i - u_e, w)$. The first condition of (3.15) follows from the simple splitting

$$\int_\Omega (i^s_i\, u_i + i^s_e\, u_e)\, dx = \frac12 \int_\Omega (i^s_i - i^s_e)(u_i - u_e)\, dx + \frac12 \int_\Omega (i^s_i + i^s_e)(u_i + u_e)\, dx$$

□

***Further results.*** We conclude this section by extending Theorem 2 in two different directions.

**Proposition 3.1.** *Suppose that* $d = 3$, *and* $(M_7'')$ *holds; then, if* (3.11) *holds, Problem* ($\boldsymbol{M}$) *admits a unique strong solution* $\boldsymbol{u}$. *Moreover, if* (3.15) *and* (3.17) *hold, then*

$$-\operatorname{div}\big(M_{i,e}\nabla u_{i,e}\big) \in L^2(Q). \tag{3.19}$$

*Proof.* It follows from Propositions 4.3 and 4.4 by the same arguments of Proposition 2.4. □

*Remark* 3.2. If

$$\Omega \text{ is of class } C^{1,1}, \quad M_{i,e} \text{ are Lipschitz in } \Omega, \tag{3.20}$$

and

$$g_{i,e} \in L^2(0,T;H^{1/2}(\Gamma)), \tag{3.21}$$

then (3.19) and standard regularity estimates for elliptic problems yield

$$u_{i,e} \in L^2(0,T;H^2(\Omega)). \tag{3.22}$$

**Proposition 3.3.** *Suppose that* (3.20) *holds and* $M_i\nu$ *and* $M_e\nu$ *have the same direction on* $\Gamma$. *If*

$$\partial_t i^s_{i,e} \in L^2(Q), \quad \partial_t g_{i,e} \in L^2(0,T;H^{-1/2}(\Gamma)) \tag{3.23}$$

*and*

$$v^0 \in H^2(\Omega), \quad f(v^0) \in L^2(\Omega), \quad g_{i,e}(0) \in H^{1/2}(\Gamma) \tag{3.24}$$

*then, for every* $\varepsilon > 0$,

$$v \in W^{1,\infty}(0,T;L^2(\Omega)) \cap H^{3/2-\varepsilon}(0,T;L^2(\Omega)), \quad u_{i,e} \in H^1(0,T;H^1(\Omega)). \tag{3.25}$$

*Proof.* It follows from the third implication of Theorem 4.

## 4. The abstract theory.

Let $\boldsymbol{V}$ be a (separable) Hilbert space with dual $\boldsymbol{V}'$, $\langle\cdot,\cdot\rangle$ denoting the duality pairing between them,

$$\text{let } a(\cdot,\cdot), \quad b(\cdot,\cdot): \ \boldsymbol{V}\times\boldsymbol{V}\to\mathbb{R} \quad \text{be continuous bilinear forms,} \tag{$A_1$}$$

with the associated linear continuous operators

$$A, B : \boldsymbol{V} \to \boldsymbol{V}'; \quad \langle A\boldsymbol{u},\boldsymbol{w}\rangle = a(\boldsymbol{u},\boldsymbol{w}), \quad \langle B\boldsymbol{u},\boldsymbol{w}\rangle = b(\boldsymbol{u},\boldsymbol{w}), \quad \forall\, \boldsymbol{u},\boldsymbol{w}\in\boldsymbol{V}, \tag{$A_2$}$$

$$\text{let } \mathfrak{F} : D(\mathfrak{F}) \subset \boldsymbol{V} \to \boldsymbol{V}' \quad \text{be a (nonlinear) operator.} \tag{$A_3$}$$

We are interested to the following abstract Cauchy problem.

**Problem** ($\boldsymbol{A}$)**.** Given $\boldsymbol{L} \in L^2(0,T;\boldsymbol{V}')$ and $\boldsymbol{\ell}^0 \in \boldsymbol{V}'$, find

$$\boldsymbol{u} \in L^2(0,T;\boldsymbol{V}), \quad \text{with} \quad B\boldsymbol{u} \in W^{1,1}_{loc}(0,T;\boldsymbol{V}') \cap C^0([0,T];\boldsymbol{V}')$$

such that

$$\begin{cases} \big(B\boldsymbol{u}\big)' + A\boldsymbol{u} + \mathfrak{F}\boldsymbol{u} = \boldsymbol{L}, & \text{a.e. in } ]0,T[\,, \\ \big(B\boldsymbol{u}\big)(0) = \boldsymbol{\ell}^0. \end{cases} \tag{4.1}$$

Degenerate parabolic equations of this kind have been studied by many authors (see [11, 8, 19, 15], and [13, 49, 21] for an extensive bibliography) in a very general context: e.g. $\boldsymbol{V}$ could be a reflexive Banach space and $A$ a (pseudo)monotone bounded operator; under suitable compatibility assumptions [19] also $B$ could be nonlinear. In particular, adapting a result of [13] via the techniques developed in [7], an existence and uniqueness result could be given for a weak formulation of (4.1). Another possible way is to use a regularizing method as in [19], replacing the (possibly) degenerate bilinear form $b$ with a coercive one $b_\varepsilon$ and proving uniform estimates with respect to $\varepsilon \to 0^+$ in an appropriate functional setting. A natural choice in this approach is

$$b_\varepsilon(u, w) := b(u, w) + \varepsilon(u, w)_{\boldsymbol{V}}.$$

***Main assumptions.*** In this paper, inspired by the structural properties **P1-4** we detailed in § 2, we follow a more direct way, exploiting the particular compatibility of the nonlinear operator $\mathfrak{F}$ with respect to the degeneration of $b$.

More precisely, we assume that $b$ is symmetric and positive, but possibly degenerate on the closed subspace $\boldsymbol{K}_b$:

$$(A_4)\quad b(\boldsymbol{u},\boldsymbol{w}) = b(\boldsymbol{w},\boldsymbol{u}),\quad b(\boldsymbol{u},\boldsymbol{u}) \ge 0;\quad b(\boldsymbol{u},\boldsymbol{u}) = 0 \;\Leftrightarrow\; \boldsymbol{u} \in \boldsymbol{K}_b \quad \forall\, \boldsymbol{u},\boldsymbol{w} \in \boldsymbol{V},$$

$a$ is weakly coercive on $\boldsymbol{V}$ and "almost" symmetric:

$$(A_5)\quad \exists\, \alpha, c > 0 : \quad \begin{cases} a(\boldsymbol{u},\boldsymbol{u}) + b(\boldsymbol{u},\boldsymbol{u}) \ge \alpha \|\boldsymbol{u}\|^2_{\boldsymbol{V}}, \\ |a(\boldsymbol{u},\boldsymbol{w}) - a(\boldsymbol{w},\boldsymbol{u})|^2 \le c\, b(\boldsymbol{u},\boldsymbol{u})\, b(\boldsymbol{w},\boldsymbol{w}), \end{cases} \qquad \forall\, \boldsymbol{u},\boldsymbol{w} \in \boldsymbol{V}.$$

We will suppose that $\mathfrak{F} = \partial\Phi - \lambda B$, $\lambda \ge 0$, is a linear perturbation of the subdifferential of

$$(A_6)\quad \begin{gathered} \Phi : \boldsymbol{V} \to [0, +\infty] \quad \text{proper, convex, l.s.c. function,} \\ \boldsymbol{\ell} = \mathfrak{F}\boldsymbol{u} \quad \Leftrightarrow \quad \langle \boldsymbol{\ell}, \boldsymbol{w} - \boldsymbol{u}\rangle + \lambda b(\boldsymbol{u}, \boldsymbol{w} - \boldsymbol{u}) + \Phi(\boldsymbol{w}) \le \Phi(\boldsymbol{u}), \quad \forall\, \boldsymbol{w} \in \boldsymbol{V}. \end{gathered}$$

Finally, we shall assume that $\Phi$ is invariant with respect to the translation of $\boldsymbol{K}_b$:

$$(A_7)\quad \begin{gathered} \Phi(\boldsymbol{u} + \boldsymbol{k}) = \Phi(\boldsymbol{u}) \quad \forall\, \boldsymbol{u} \in \boldsymbol{V},\ \boldsymbol{k} \in \boldsymbol{K}_b, \quad \text{or, equivalently,} \\ \langle \mathfrak{F}\boldsymbol{u}, \boldsymbol{k}\rangle = 0, \quad \mathfrak{F}(\boldsymbol{u} + \boldsymbol{k}) = \mathfrak{F}(\boldsymbol{u}), \quad \forall\, \boldsymbol{u} \in D(\mathfrak{F}),\ \forall\, \boldsymbol{k} \in \boldsymbol{K}_b. \end{gathered}$$

***A reduction technique.*** We shall show that Problem ($\boldsymbol{A}$) can be reduced, by the "change of variable $v := B\boldsymbol{u}$", to a usual (non degenerate) evolution variational inequality of the type

$$(4.2)\quad v(0) = \boldsymbol{\ell}^0, \quad \big(v' + (A_b - \lambda)v - L_b, v - w\big)_b + \Phi_b(v) \le \Phi_b(w), \qquad \forall\, w \in V_b$$

in a suitable Hilbert triple $V_b \subset H_b \subset V_b'$, with $A_b, L_b, \Phi_b$ related in a explicit way to $A, L, \Phi$.

In this formulation, regularity and approximation results are easier and deeply studied (see [33, 10, 7, 31, 22, 2, 48]) and they give corresponding information about the original problem A. In particular the study of the time discretization by the backward Euler method and of some further regularity properties of (4.1) are developed by [2, 43, 47, 48, 38]. In order to state our results, we introduce the Hilbert spaces

$$(4.3)\qquad V_b = B(\boldsymbol{V}), \quad \text{with the norm} \quad \|v\|_b = \inf\big\{\|\boldsymbol{u}\|_{\boldsymbol{V}} :\ \boldsymbol{u} \in \boldsymbol{V},\, B\boldsymbol{u} = v\big\},$$

and

$$(4.4)\qquad V_b' = \Big\{L \in \boldsymbol{V}' :\ \langle L, \boldsymbol{k}\rangle = 0, \quad \forall\, \boldsymbol{k} \in \boldsymbol{K}_b\Big\}.$$

It is easy to see that $V_b$ is included in $V_b'$ and it is isomorphic to the quotient space $\boldsymbol{V}/\boldsymbol{K}_b$, whereas $V_b'$ is isomorphic to its dual, so that our notation is correct. We denote by $\boldsymbol{J} : V_b \to \boldsymbol{V}$ a right inverse of $B$, defined by

$$\boldsymbol{J}v = \boldsymbol{u} \quad \Leftrightarrow \quad B\boldsymbol{u} = v, \quad \text{and} \quad a(\boldsymbol{u}, \boldsymbol{k}) = 0, \quad \forall\, \boldsymbol{k} \in \boldsymbol{K}_b. \tag{4.5}$$

By $(A_5)$ $a(\cdot,\cdot)$ is coercive on $\boldsymbol{K}_b$; Lax-Milgram lemma ensures that $\boldsymbol{J}$ is a linear isomorphism. Observe that, when $a$ is symmetric, (4.5) is equivalent to the minimization problem

$$B\boldsymbol{u} = v, \quad a(\boldsymbol{u}, \boldsymbol{u}) = \min\big\{a(\boldsymbol{w}, \boldsymbol{w}) : B\boldsymbol{w} = v\big\}. \tag{4.6}$$

Each element $\boldsymbol{u} \in \boldsymbol{V}$ admits the linear decomposition

$$\boldsymbol{u} = \boldsymbol{J}v + \boldsymbol{k} : \quad v = B\boldsymbol{u}, \quad \boldsymbol{k} = \boldsymbol{u} - \boldsymbol{J}B\boldsymbol{u} \in \boldsymbol{K}_b. \tag{4.7}$$

We define the duality pairing between $V_b'$ and $V_b$ as

$$\big(\ell, v\big)_b := {}_{\boldsymbol{V}'}\langle \ell, \boldsymbol{J}v\rangle_{\boldsymbol{V}} = {}_{\boldsymbol{V}'}\langle \ell, \boldsymbol{u}\rangle_{\boldsymbol{V}}, \quad \forall\, \ell \in V_b',\, v \in V_b,\, \boldsymbol{u} \in B^{-1}v. \tag{4.8}$$

It is easy to see that $(\cdot,\cdot)_b$ restricted to $V_b \times V_b$ is a scalar product, associated to the intermediate norm

$$|v|_b^2 := (v, v)_b = b(\boldsymbol{J}v, \boldsymbol{J}v). \tag{4.9}$$

By the standard duality theory, we can identify the completion $H_b$ of $V_b$ with respect to this norm with the space

$$H_b' = \Big\{\ell \in V_b' : \sup_{w \in \boldsymbol{V}\setminus \boldsymbol{K}_b} \frac{\langle \ell, w\rangle}{\sqrt{b(w,w)}} = \sup_{v \in V_b \setminus\{0\}} \frac{(\ell, v)_b}{|v|_b} < +\infty\Big\}. \tag{4.10}$$

In this way $V_b$, $H_b \equiv H_b'$, $V_b'$ becomes a standard Hilbert triple and defining

$$\Phi_b(v) := \Phi(\boldsymbol{J}v), \qquad a_b(v, w) := a(\boldsymbol{J}v, \boldsymbol{J}w), \tag{4.11}$$

we can consider the following evolution variational inequality:

**Problem $(\boldsymbol{A}_b)$.** Given $L_b \in L^2(0,T; V_b')$ and $\boldsymbol{\ell}^0 \in V_b'$, find

$$v \in L^2(0,T; V_b) \cap W^{1,1}_{loc}(0,T; V_b') \cap C^0([0,T]; V_b')$$

such that:

$$\begin{cases} \big(v' + (A_b - \lambda)v - L_b, v - w\big)_b + \Phi_b(v) \le \Phi_b(w), \quad \forall w \in V_b, \text{ a.e. in } ]0,T[\,, \\ v(0) = \boldsymbol{\ell}^0. \end{cases} \tag{4.12}$$

The link with problem $(\boldsymbol{A})$ is given by the following result.

**Theorem 3.** *The function $u$ is a strong solution of problem $(\boldsymbol{A})$ if and only if it admits the decomposition*

$$\boldsymbol{u} = u_{\boldsymbol{L}} + \boldsymbol{J}v, \tag{4.13}$$

*where $u_{\boldsymbol{L}}$ solves*

$$u_{\boldsymbol{L}}(t) \in \boldsymbol{K}_b, \quad a(u_{\boldsymbol{L}}(t), \boldsymbol{k}) = \langle \boldsymbol{L}(t), \boldsymbol{k}\rangle, \quad \forall\, \boldsymbol{k} \in \boldsymbol{K}_b, \text{ a.e. in } ]0,T[, \tag{4.14}$$

*and $v$ is a solution of problem $(\boldsymbol{A}_b)$ with respect to*

$$L_b(t) := \boldsymbol{L}(t) - Au_{\boldsymbol{L}}(t). \tag{4.15}$$

*Proof.* Observe that $L_b(t) \in V_b'$ for a.e. $t \in ]0,T[$ so that (4.12) makes sense. Let $\boldsymbol{u}$ be a strong solution of Problem $(\boldsymbol{A})$ and $v := B\boldsymbol{u}$; by $(A_7)$ we have $\mathfrak{F}\boldsymbol{u} \in V_b'$ so that, taking the duality of each member of equation (4.1) by a generic element $\boldsymbol{k} \in \boldsymbol{K}_b$ we get

$$a(\boldsymbol{u}(t), \boldsymbol{k}) = \langle \boldsymbol{L}(t), \boldsymbol{k}\rangle, \quad \forall\, \boldsymbol{k} \in \boldsymbol{K}_b, \quad \text{for a.e. } t \in ]0,T[. \tag{4.16}$$

This implies that

$$a(\boldsymbol{u}(t) - u_{\boldsymbol{L}}(t), \boldsymbol{k}) = 0, \quad B(\boldsymbol{u}(t) - u_{\boldsymbol{L}}(t)) = v(t), \quad \forall\, \boldsymbol{k} \in \boldsymbol{K}_b, \text{ for a.e. } t \in ]0,T[,$$

i.e. $\boldsymbol{u} - u_{\boldsymbol{L}} = \boldsymbol{J}v$ by definition (4.5).

Coming back to equation (4.1), since $\mathfrak{F}$ is invariant by $\boldsymbol{K}_b$-translations, we read that

$$v' + A(\boldsymbol{J}v) + \mathfrak{F}(\boldsymbol{J}v) = (B\boldsymbol{u})' + A(\boldsymbol{u} - u_{\boldsymbol{L}}) + \mathfrak{F}(\boldsymbol{u} - u_{\boldsymbol{L}}) = \boldsymbol{L} - Au_{\boldsymbol{L}} = L_b. \tag{4.17}$$

Taking the duality of (4.17) with $\boldsymbol{J}(v-w)$, $w \in V_b$, and recalling (4.11), we get

$$\begin{aligned}(v', v-w)_b + a_b(v, v-w) - (L_b, v-w)_b = \langle \mathcal{F}(\boldsymbol{J}v), w - v\rangle \le \\ \le \Phi(\boldsymbol{J}w) - \Phi(\boldsymbol{J}v) - \lambda b(\boldsymbol{J}v, \boldsymbol{J}(w-v)) = \Phi_b(w) - \Phi_b(v) - \lambda(v, w-v)_b\end{aligned}$$

by $(A_6)$, (4.5), (4.8), and (4.11); therefore, $v$ solves (4.12).

Let now $v$ be a solution of (4.12), $u_{\boldsymbol{L}}$ be given by (4.14), and $\boldsymbol{u} := u_{\boldsymbol{L}} + \boldsymbol{J}v$. By (4.11) and (4.15) we deduce

$$\langle B(\boldsymbol{J}v)' + A(\boldsymbol{J}v) - L_b, \boldsymbol{J}(v-w)\rangle \le \Phi(\boldsymbol{J}w) - \Phi(\boldsymbol{J}v) - \lambda\langle B\boldsymbol{J}v, \boldsymbol{J}(w-v)\rangle, \quad \forall\, w \in V_b.$$

By (4.14), (4.5), and $(A_7)$ we have

$$\begin{aligned}&\langle B\boldsymbol{J}v' + A(\boldsymbol{J}v) - (\boldsymbol{L} - Au_{\boldsymbol{L}}), \boldsymbol{J}v + u_{\boldsymbol{L}} - (\boldsymbol{J}w + \boldsymbol{k})\rangle \le \\ &\Phi(\boldsymbol{J}w + \boldsymbol{k}) - \Phi(\boldsymbol{J}v + u_{\boldsymbol{L}}) - \lambda\langle B\boldsymbol{J}v, \boldsymbol{J}w + \boldsymbol{k} - (\boldsymbol{J}v + u_{\boldsymbol{L}})\rangle, \quad \forall\, w \in V_b,\ \forall\, \boldsymbol{k} \in \boldsymbol{K}_b.\end{aligned}$$

Since $Bu_{\boldsymbol{L}} \equiv 0$, (4.15) yields

$$\langle (B\boldsymbol{u})' + A\boldsymbol{u} - \boldsymbol{L}, \boldsymbol{u} - (\boldsymbol{J}w + \boldsymbol{k})\rangle \le \Phi(\boldsymbol{J}w + \boldsymbol{k}) - \Phi(\boldsymbol{u}) - \lambda\langle B\boldsymbol{u}, \boldsymbol{J}w + \boldsymbol{k} - \boldsymbol{u}\rangle,$$

for every choice of $w \in V_b$, $\boldsymbol{k} \in \boldsymbol{K}_b$. Since $\boldsymbol{V} = \boldsymbol{J}(V_b) + \boldsymbol{K}_b$ thanks to (4.7), by $(A_6)$ we deduce that

$$(B\boldsymbol{u})' + A\boldsymbol{u} - \boldsymbol{L} = -\mathfrak{F}\boldsymbol{u}$$

i.e. (4.1). □

***Main result.*** We have now all the elements to state our main result.

**Theorem 4.** *Let us assume that*

$$\boldsymbol{\ell}^0 \in \overline{D(\Phi_b)}^{H_b}, \quad \boldsymbol{L} \in W^{1,1}(0,T;\boldsymbol{V}') + L^2(0,T;H_b'). \tag{4.18}$$

*Then there exists a unique strong solution $\boldsymbol{u}$ of problem $(\boldsymbol{A})$ with*

$$v := B\boldsymbol{u} \in H^1_{loc}(0,T;H_b) \cap C^0([0,T];H_b), \quad \boldsymbol{u} \in C^0(]0,T];V). \tag{4.19}$$

*If*

$$\boldsymbol{\ell}^0 \in V_b, \quad \textit{and} \quad \exists\, \boldsymbol{u}^0 \in D(\Phi) :\ B\boldsymbol{u}^0 = \boldsymbol{\ell}^0, \tag{4.20}$$

*then*

$$v := B\boldsymbol{u} \in H^1(0,T;H_b), \quad \boldsymbol{u} \in C^0([0,T];V). \tag{4.21}$$

*Finally, if*

$$\boldsymbol{L} \in H^1(0,T;\boldsymbol{V}'), \quad \boldsymbol{\ell}^0 \in V_b,\ \boldsymbol{J}\boldsymbol{\ell}^0 \in D(\mathfrak{F}), \quad A(\boldsymbol{J}\boldsymbol{\ell}^0) + \mathfrak{F}(\boldsymbol{J}\boldsymbol{\ell}^0) \in H_b' \tag{4.22}$$

*then*

$$\text{(4.23)} \qquad \boldsymbol{u} \in H^1(0,T;\boldsymbol{V}) \quad \textit{and} \quad v = B\boldsymbol{u} \in W^{1,\infty}(0,T;H_b) \cap H^{3/2-\varepsilon}(0,T;H_b),$$

*for every* $\varepsilon > 0$.

*Proof.* Let us observe that $(A_4,\dots,A_7)$ imply that

$$\text{(4.24)} \qquad a_b(\cdot,\cdot) - \lambda(\cdot,\cdot)_b \text{ is weakly coercive on } V_b, \quad \Phi_b \text{ is l.s.c. and convex on } V_b.$$

By the general theory of evolution variational inequalities (see e.g. [6], prop. II.2 and [48], thm. 3), if (4.22) holds then problem $(\boldsymbol{A}_b)$ admits a unique strong solution

$$\text{(4.25)} \qquad v \in H^1(0,T;V_b) \cap W^{1,\infty}(0,T;H_b) \cap H^{3/2-\varepsilon}(0,T;H_b),$$

and Theorem 3 gives (4.23). Moreover, the mapping $(L_b,\boldsymbol{\ell}^0) \mapsto v$ is Lipschitz with respect to the norm (cf. [48, 4.12]) of

$$\Big(L^2(0,T;V_b') + L^1(0,T;H_b')\Big) \times H_b$$

with values in $L^\infty(0,T;H_b) \cap L^2(0,T;V_b)$. This regular dependence of the solution from the data and a standard density argument allow us to prove the other two results (which are already known, in a slightly different form, when $a(\cdot,\cdot)$ is symmetric; cf. [6, cor. II.2] by simply showing the corresponding a priori estimates. To get (4.21), we write (4.12) as a differential equation governed by the subdifferential of $\Phi_b$ in $H_b$ and multiply it by $v'$, obtaining

$$\begin{aligned} |v'|_b^2 + \frac{d}{dt}\Big[\frac{1}{2}a_b(v,v) + \Phi_b(v)\Big] &= (L_b,v')_b - \frac{1}{2}\big[a_b(v,v') - a_b(v',v)\big] + \lambda(v,v')_b \\ &\le (L_b,v')_b + (c+\lambda)|v|_b\,|v'|_b, \end{aligned}$$

thanks to $(A_5)$. By integrating in time and applying Gronwall lemma, we get the estimate

$$\begin{aligned} &\int_0^T |v'|_b^2\,dt + \sup_{t\in[0,T]} \Big[a_b(v,v) + \Phi_b(v)\Big] \\ &\qquad \le C\Big[\|\boldsymbol{\ell}^0\|_{V_b}^2 + \Phi_b(\boldsymbol{\ell}^0) + \|L_b\|_{W^{1,1}(0,T;V_b') + L^2(0,T;H_b)}\Big] \end{aligned}$$

with $C$ independent of the data. Since $\Phi_b(\boldsymbol{\ell}^0) = \Phi(u^0)$, (4.21) follows by (4.20).

The first implication follows by the same technique, multiplying the equation by $tv'$ (cf. [6]). □

*Remark* 4.1. Analogous results hold if $\mathfrak{F}$ is a multivalued (subdifferential) operator; we considered the single-valued case, in order to simplify our exposition.

*Remark* 4.2. We could give an existence and uniqueness result for a suitable weak formulation of problems $(\boldsymbol{A})$, $(\boldsymbol{A}_b)$ (see [6, rem. II.5], and [48, rem. 1.1]), which requires

$$\text{(4.26)} \qquad \boldsymbol{L} \in L^2(0,T;\boldsymbol{V}') + L^1(0,T;H_b), \quad \boldsymbol{\ell}^0 \in \overline{D(\Phi_b)}^{H_b}$$

and gives $\boldsymbol{u} \in L^2(0,T;\boldsymbol{V})$ with $B\boldsymbol{u} \in C^0([0,T];H_b) \cap H^{1/2-\varepsilon}(0,T;H_b)$, for every $\varepsilon > 0$, together to the a priori estimate (cf. [48, 3.1 and thm. 3])

$$\text{(4.27)} \quad \sup_{[0,T]} b(\boldsymbol{u},\boldsymbol{u}) + \int_0^T \Big[\|\boldsymbol{u}\|_{\boldsymbol{V}}^2 + \Phi(\boldsymbol{u})\Big]\,dt \le C\Big[\|L_b\|^2_{L^2(0,T;\boldsymbol{V}')+L^1(0,T;H_b)} + |\boldsymbol{\ell}^0|_b^2\Big].$$

We give two other simple regularity results, under some additional assumptions on $\mathfrak{F}$.

**Proposition 4.3.** *Assume that* $D(\mathfrak{F}) \equiv D(\Phi)$ *and that there exists* $C > 0$, $p \in ]1, 2]$ *such that*

$$\|\mathfrak{F}\boldsymbol{w}\|^p_{\boldsymbol{V}'} \le C(1 + \|\boldsymbol{w}\|^2_{\boldsymbol{V}} + \Phi(\boldsymbol{w})), \quad \forall\, \boldsymbol{w} \in D(\Phi). \tag{4.28}$$

*If* (4.26) *holds (instead of the stronger* (4.18)*), then Problem* ($\boldsymbol{A}$) *admits a unique strong solution.*

*Proof.* Starting from the strongest result of Theorem 4 and the a priori estimate (4.27), we deduce

$$\begin{aligned} \|v'\|^p_{L^p(0,T;\boldsymbol{V}')} + \|\mathfrak{F}\boldsymbol{u}\|^p_{L^p(0,T;\boldsymbol{V}')} &\le C\Big[T + \int_0^T \Big(\|\boldsymbol{u}\|^2_{\boldsymbol{V}} + \Phi(\boldsymbol{u})\Big)\,dt\Big] \\ &\le C\Big[1 + \|\boldsymbol{L}\|^2_{L^2(0,T;\boldsymbol{V}')+L^1(0,T;H_b)} + |\boldsymbol{\ell}^0|^2_b\Big] \end{aligned} \tag{4.29}$$

with $C$ independent of the data. By the usual density arguments, this is sufficient to obtain a strong solution of the problems ($\boldsymbol{A}$),($\boldsymbol{A}_b$) under (4.26). □

**Proposition 4.4.** *Assume that* $D(\mathfrak{F}) \equiv \boldsymbol{V}$, $\mathfrak{F}(\boldsymbol{V}) \subset H_b$ *and there exists* $C > 0$, $p \ge 1$ *such that*

$$\|\mathfrak{F}\boldsymbol{w}\|_{H_b} \le C(1 + \|\boldsymbol{w}\|^p_{\boldsymbol{V}}) \quad \forall\, \boldsymbol{w} \in \boldsymbol{V}. \tag{4.30}$$

*If* (4.20) *holds, we get*

$$A\boldsymbol{u} - \boldsymbol{L} \in L^2(0, T; H_b) \tag{4.31}$$

*Proof.* It is an immediate consequence of (4.21) and the equation (4.1). □

***Approximation results.*** We conclude this section with an *example* of the possible approximation results, which follow by applying the theory developed in [48, 38] to the abstract formulation ($\boldsymbol{A}_b$): other *a priori* and *a posteriori* estimates are available and it should not be difficult to translate them in the framework of the micro- and macroscopic problems ($\boldsymbol{\mu}$,$\boldsymbol{M}$); this is also the starting point for a complete space-time discretization, as studied in [46] (for other approximation results in the context of reaction-diffusion problems, see e.g. [26, 28, 35]; a different abstract approach has been developed in [4].)

We choose a partition $\mathcal{P}$ of the time interval $[0, T]$ into $N$ subintervals

$$\mathcal{P} := \{0 = t_0 < t_1 < \ldots < t_{N-1} < t_N = T\}, \tag{4.32}$$

with variable step $\tau_n := t_n - t_{n-1}$, and we consider the sequence $\{U_n\}_{n=0}^N$ whose first term is given and satisfies $BU^0 = \boldsymbol{\ell}^0$ and the other ones are recursively defined for $1 \le n \le N$ by

$$\frac{1}{\tau_n} B(U^n - U^{n-1}) + A(U^n) + \mathfrak{F}U^n = L^n, \quad \text{for } n = 1, \ldots, N,$$

where $L^n$ is a suitable approximation of $\boldsymbol{L}$ in the time interval $(t_{n-1}, t_n]$, e.g. $L^n := \boldsymbol{L}(t_n)$.

Hereafter, $\boldsymbol{U}$ is the piecewise linear interpolant of the values $\{U_n\}_{n=0}^N$ on the grid $\mathcal{P}$ and $|\tau| := \max_{1\le n\le N} \tau_n$ denotes the maximum of the time-step sizes. Combining Theorems 8 and 9 of [38] (see also [48, Thm. 3] in the case of a uniform mesh) we get

**Theorem 5.** *Assume that* (4.22) *holds. Then we have the estimate*

$$\|\boldsymbol{u}-\boldsymbol{U}\|_{L^2(0,T;\boldsymbol{V})}+\max_{t\in[0,T]} b(\boldsymbol{u}-\boldsymbol{U},\boldsymbol{u}-\boldsymbol{U})\le C|\tau|, \tag{4.33}$$

*with $C$ independent of the partition $\mathcal{P}$.*

## Appendix A. The derivation of the "bidomain" model

For completeness in this appendix, using the two–scales method, we develop formal asymptotic expansions and we convert a microscopic model of the cellular media into an averaged continuum representation of the cardiac tissue, when the presence of stimulation currents are neglected and $\sigma_{i,e}$ do not depend on the position $x$. With respect to the procedure followed in [37], based on current balances expressed by means of integral identities, the formal derivation here presented is shorter and more standard. For the electric potentials $u_i$, $u_e$ we can consider two characteristic length scales, the microscopic one related to a typical dimension $\mathsf{d}_c$ of the cells (e.g. the cell diameter is of order $10^{-3}cm$) and the other macroscopic one determined by a suitable length constant of the tissue. Following [37] we consider the dimensionless parameter

$$\varepsilon^2=\mathsf{d}_c/(\mathsf{R}_m\sigma_i) \quad \text{with} \quad \mathsf{R}_m^{-1}=\partial_v I_{ion}(0,0)$$

assuming that $v=0$, $w=0$ is the equilibrium point for the problem $(\boldsymbol{\mu})$.

We convert the cellular problem into a non-dimensional form, by scaling space and time with the macroscopic units of length $\mathsf{L}=\mathsf{d}_c/\varepsilon$ and with respect to the membrane constant $\mathsf{T}=\mathsf{R}_m\ \mathsf{C}_m$ i.e.

$$\widehat{x}=x/\mathsf{L}, \quad \widehat{t}=t/\mathsf{T}$$

the microscopic space variable measured in unit cell is defined by

$$\xi:=\widehat{x}/\varepsilon=x/\mathsf{d}_c.$$

Disregarding the presence of applied current terms, rescaling the equations $(\mu_4)$, $(\mu_5)$ in the intra- and extra-cellular potentials we obtain:

$$\begin{cases} -\Delta u_{i,e}=0 & \text{in } \Omega^\varepsilon_{i,e},\\ \varepsilon\ (\partial_t v+I(v,w)=-\nabla u_i\cdot\nu_i=\alpha\ \nabla u_e\cdot\nu_e & \text{on } \Gamma^\varepsilon_m,\\ \partial_t w=r(v,w) & \text{on } \Gamma^\varepsilon_m, \end{cases} \tag{A.1}$$

where $\alpha:=\sigma_e/\sigma_i$, $I=\mathsf{R}_m\, I_{ion}$, and for convenience, the superscripts $\widehat{\ }$ of the dimensionless variables are omitted.

In order to establish a formal relationship between a cellular model and the macroscopic bidomain structure we consider an ideal geometry and interconnection model of the cardiac cells assuming a periodic organization of the cellular tissue i.e. a periodic network of interconnected cells similar to a regular lattice of interconnected cylinders.

More precisely $\Omega^\varepsilon_i$ and $\Omega^\varepsilon_e$ are two open, disjoint, connected, periodic domains covering the entire space i.e. $\overline{\Omega}^\varepsilon_i\cup\overline{\Omega}^\varepsilon_i=\mathbb{R}^3$ with their common boundary $\partial\Omega^\varepsilon_i\cap\partial\Omega^\varepsilon_e=\Gamma^\varepsilon_m$ locally Lipschitz.

For $\alpha>0$, we set

$$Y^\varepsilon=[0,\varepsilon]^2\times[0,\alpha\,\varepsilon], \quad Y^\varepsilon_{i,e}=\Omega^\varepsilon_{i,e}\cap Y^\varepsilon, \quad \partial Y^\varepsilon_i\cap\partial Y^\varepsilon_e=S^\varepsilon$$

which defines the elementary unit $\varepsilon$–sized box with its intra- and extra-cellular parts, whose periodic repetition cover the whole space $\mathbb{R}^3$, while

$$Y, \quad Y_i, \quad Y_e, \quad S$$

denote the corresponding transformed sets expressed in the microscopic variable $\xi = x/\varepsilon$. When the reference parallelepiped $Y^\varepsilon$ represents a volume box including a cardiac cell unit, then $\alpha$ can be interpreted as the ratio between the length and the diameter of the elongated cardiac cells.

To investigate solutions of (A.1) we use the two-scales method (see [3, 5, 45, 44, 29, 40, 29]) and we seek a solution $u_i$ and $u_e$ having the following asymptotic form in powers of $\varepsilon$ of the type (the indexes $i$ and $e$ are omitted):

$$u = u_0(x, \xi, t) + \varepsilon u_1(x, \xi, t) + \varepsilon^2 u_2(x, \xi, t) + \cdot \tag{A.2}$$

where $x$ denotes the slow macroscopic variable and $\xi = x/\varepsilon$ the fast microscopic one. The slow and fast variables correspond respectively to the global and local structure of the field and the coefficients $u_k$ are 1–periodic function of $\xi$.

Considering the full derivative operators,

$$\nabla u = \varepsilon^{-1}\nabla_\xi u + \nabla_x u,$$

$$\Delta u = \varepsilon^{-2}\Delta_{\xi\xi} u + \varepsilon^{-1}\operatorname{div}_\xi \nabla_x u + \varepsilon^{-1}\operatorname{div}_x \nabla_\xi u + \Delta_{xx} u,$$

substituting the asymptotic form for $u = u_i$ into the original equation (A.1) and equating the coefficients of the powers $-1$, 0, 1, of $\varepsilon$ to zero, we obtain the following equations for the functions $u_k(x, \xi, t)$, $k = 0, 1, 2$:

$$\begin{cases} \Delta_{\xi\xi} u_0 = 0 & \text{in } Y_i, \\ \nabla_\xi \cdot \nu_\xi u_0 = 0 & \text{on } S, \end{cases} \tag{A.3}$$

$$\begin{cases} \Delta_{\xi\xi} u_1 = -2\operatorname{div}_x \nabla_\xi u_0 & \text{in } Y_i, \\ \nabla_\xi u_1 \cdot \nu_\xi + \nabla_x u_0 \cdot \nu_\xi = 0 & \text{on } S, \end{cases} \tag{A.4}$$

$$\begin{cases} \Delta_{\xi\xi} u_2 = -\operatorname{div}_x \nabla_\xi u_1 - \operatorname{div}_\xi \nabla_x u_1 - \Delta_{xx} u_0 & \text{in } Y_i, \\ \nabla_\xi u_2 \cdot \nu_\xi + \nabla_x u_1 \cdot \nu_\xi = -(\partial_t v_0 + I(v_0, w_0)) & \text{on } S, \\ v_0 = u_{i,0} - u_{e,0}, \qquad \partial_t w_0 = r(v_0, w_0). \end{cases} \tag{A.5}$$

In the previous problems $x$ appears as a parameter and we seek 1–periodic solutions in $\xi$ on the reference cell $Y_i$. We recall the following well known result [39, 3].

**Lemma A.1.** *Let $\Omega$ be a bounded domain with Lipschitz boundary and $S$ be a subset of $\partial\Omega$. If $f_k(\xi)$, $k = 0, 1, 2, 3$ e $g(\xi)$ are 1-periodic bounded, measurable functions in $\xi$ then the problem*

$$\begin{cases} \textit{Find } u \in H^1(\Omega) \textit{ periodic such that:} & \\ -\Delta u = f_0 - \operatorname{div} \boldsymbol{f} & \textit{in } \Omega, \\ \nabla u \cdot \nu = \nu_\xi \cdot \boldsymbol{f} + g & \textit{on } S, \end{cases}$$

*admits a unique solution apart from an additive constant if and only if*

$$\int_\Omega f_0 - \int_S g = 0.$$

Applying this lemma to problem (A.3) we obtain that the 1–periodic solution $u_0$ is independent of $\xi$; since $u_0$ depends only on the macroscopic variable $x$ then it represents a potential average over $Y_i$.

Problem (A.4) becomes:

$$\Delta_{\xi\xi} u_1 = 0 \quad \text{in } Y_i, \qquad \nabla_\xi u_1 \cdot \nu_\xi = -\nabla_x u_0 \cdot \nu_\xi \quad \text{on } S, \tag{A.6}$$

and lemma A.1 guarantees its solvability. An easy check shows that the solution of (A.4) can be represented as:

$$u_1(x,\xi,t) = -\boldsymbol{w}(\xi)\cdot\nabla_x u_0 + \tilde{u}_1(x,t), \tag{A.7}$$

where $\boldsymbol{w} = (w^1(\xi), w^2(\xi), w^3(\xi))^T$ satisfies:

$$\Delta_{\xi\xi} w^k = 0, \quad \text{in } Y_i, \qquad \nabla_\xi w^k \cdot \nu_\xi = n_{\xi_k} \quad \text{on } S, \quad k = 1,2,3. \tag{A.8}$$

These problems are solvable by lemma A.1 apart an additive constant, which can be fixed e.g. by the condition $\int_S w^k = 0$.

Problem (A.5) becomes:

$$\begin{cases} \Delta_{\xi\xi} u_2 = \operatorname{div}_\xi \nabla_x (\nabla_x u_0 \cdot \boldsymbol{w}) + \operatorname{div}_x \nabla_\xi (\nabla_x u_0 \cdot \boldsymbol{w}) - \Delta_{xx} u_0 & \text{in } Y_i, \\ \nabla_\xi u_2 \cdot \nu = \nabla_\xi (\nabla_x u_0 \cdot \boldsymbol{w}) \cdot \nu - (\partial_t v_0 + I(v_0,w_0)) & \text{on } S. \end{cases} \tag{A.9}$$

Applying always lemma A.1 for the solvability of problem (A.9) for the class of 1–periodic functions we obtain:

$$-\int_{Y_i} \operatorname{div}_x \nabla_\xi (\nabla_x u_0 \cdot \boldsymbol{w})\, d\xi - \int_{Y_i} \Delta_{xx} u_0 \, d\xi + \int_S (v_{0,t} + I(v_0,w_0))\, d\sigma_\xi = 0.$$

Considering that $u_0$ is independent of $\xi$ and substituting in (A.7) it follows:

$$\operatorname{div}_x \left[ \int_{Y_i} \nabla_\xi \boldsymbol{w}\, d\xi - |Y_i| I \right] \cdot \nabla_x u_0 + |S|(\partial_t v_0 + I(v_0,w_0)) = 0, \tag{A.10}$$

where $\nabla_\xi \boldsymbol{w} = [\nabla_\xi w^1, \nabla_\xi w^2, \nabla_\xi w^3]$ and $|Y_i|$, $|S|$ denote the volume and the area of $Y_i$ and $S$ respectively.

Let $\widehat{\beta} = |S|/|Y|$ be the ratio between the surface membrane and the volume of the unit cell; then we have:

$$\operatorname{div}_x \left[ \frac{1}{|Y|} \left( \int_{Y_i} \nabla_\xi \boldsymbol{w}\, d\xi - |Y_i| I \right) \nabla_x u_0 \right] + \widehat{\beta}(\partial_t v_0 + I(v_0,w_0)) = 0,$$

with reference to medium $(i)$ $\boldsymbol{w}_i = \boldsymbol{w}$ and we set

$$D_i = \frac{1}{|Y|} \left\{ |Y_i| I - \int_{Y_i} \nabla_\xi \boldsymbol{w}_i \; d\xi \right\}. \tag{A.11}$$

Applying the Green formula and taking into account the periodicity of $\boldsymbol{w}_i$ we have the following expression for the macroscopic tensor of intra-cellular conductivity:

$$D_i = \frac{1}{|Y|} \left\{ |Y_i| I - \int_S \nu_i \otimes \boldsymbol{w}_i \, d\sigma_\xi \right\}.$$

Hence we obtain the following *"averaged equation"* for the intra-cellular potential:

$$\operatorname{div} D_i \nabla_x u_{i,0} = \widehat{\beta} \left( \partial_t v_0 + I(v_0,w_0) \right)).$$

Proceeding similarly for $u = u_e$ we obtain the following averaged equation for the extra-cellular potential:

$$\operatorname{div} D_e \nabla_x u_{e,0} = -\widehat{\beta} \left( \partial_t v_0 + I(v_0,w_0) \right)),$$

where

$$
\begin{aligned}
D_e =&\frac{\alpha_e}{|Y|}\left\{|Y_e|I - \int_{Y_e} \nabla_\xi \boldsymbol{w}_e d\xi\right\} \\
=&\frac{\alpha_e}{|Y|}\left\{|Y_e|I - \int_{S} \nu_e \otimes \boldsymbol{w}_e\, d\sigma_\xi,\right\}, \qquad \alpha_e = \sigma_e/\sigma_i,
\end{aligned}
\tag{A.12}
$$

and $w_e^k,\ k = 1, 2, 3$, are solutions of:

$$\Delta_{\xi\xi} w_e^k = 0, \quad \text{in } Y_e, \qquad \nabla_\xi w_e^k \cdot \nu_e = \nu_e^k \quad \text{on } S, \quad k = 1, 2, 3.$$

Finally we rescale the previous dimensionless equations using $x = \widehat{x}\cdot \mathsf{L}$ and $t = \widehat{t}\cdot \mathsf{T}$, and we denote by $Y^d$, $Y_i^d$, $Y_e^d$, $S^d$ the dimensional sets in the variable $x = \xi \cdot \mathsf{d}_c$ corresponding to $Y$, $Y_i$, $Y_e$, $S$, respectively; moreover we set $\beta = |S^d|/|Y^d| = \widehat{\beta}/\mathsf{d}_c$.

Summarizing, for a periodic network of interconnected cells the governing dimensional equations, at the zero order in $\varepsilon$, of the macroscopic intra- and extra-cellular potentials are given by:

$$
\begin{cases}
\operatorname{div} M_i \nabla_x u_i = \beta\left(\partial_t v + I_{ion}(v, w)\right), \\
\operatorname{div} M_e \nabla_x u_e = -\beta\left(\partial_t v + I_{ion}(v, w)\right), \\
v = u_i - u_e, \quad \partial_t w = r(v, w),
\end{cases}
\tag{A.13}
$$

where the effective conductivity tensors are given by:

$$M_{i,e} = \frac{\sigma_{i,e}}{|Y^d|}\left\{|Y_{i,e}^d|I - \int_{S^d} \nu_{i,e} \otimes \boldsymbol{w}_{i,e}\, d\sigma_\xi\right\},$$

with $\nu_{i,e}$ unit normal to $S^d$ pointing outside $Y_{i,e}^d$ and $w_i^k$ and $w_e^k$ solutions of the cellular problems:

$$
\begin{aligned}
\Delta \boldsymbol{w}_i = 0 \quad \text{in } Y_i^d, \qquad \nabla_\xi \boldsymbol{w}_i \cdot \nu_i = \nu_i \quad \text{on } S^d, \\
\Delta \boldsymbol{w}_e = 0 \quad \text{in } Y_e^d, \qquad \nabla_\xi \boldsymbol{w}_e \cdot \nu_e = \nu_e \quad \text{on } S^d.
\end{aligned}
$$

*Remark* A.2. Following [5], it is easy to verify that the macroscopic conductivity tensors of the intra-cellular $M_i$ and extra-cellular $M_e$ spaces are symmetric and positive definite.

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