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Mathematical models for the cardiac electric field

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Contents

Chapter 1

Introduction

The aim of this thesis is to study the reaction-diffusion systems arising from the mathematical models of the electric activity of cardiac ventricular cells, at microscopic and macroscopic level. The models we analyze are widely used in medical and bioengineering studies, in numerical simulations, and they constitute the bases for present research and more and more accurate and complex modelizations. Moreover, computational studies and numerical simulations play an important role in electrocardiology and many experimental studies are coupled with numerical investigations, due to the difficulty of direct measurements. From the *microscopic cellular model* of the cardiac electric potential it is possible to derive the *macroscopic Bidomain model*, which is the most complete model used in numerical simulations of the bioelectric activity of the heart, see Colli Franzone et al. [15, 17, 18, 20, 19], Roth [60], Hooke et al. [36], Henriquez et al. [33, 34], Muzikant et al. [52]. Modeling the bioelectric cardiac sources and the conducting media in order to derive the potential field constitutes the so-called *forward problem of electrocardiology* (also the *inverse problems* are of considerable interest for applications (see e.g. [32, 63]). The study of the forward problem and the formulation of models at both cellular and tissue levels provides essential tools for integrating the increasing knowledge of bioelectrochemical phenomena occurring through cardiac cellular membranes.

Up to now, a rigorous mathematical analysis regarding the well posedness of the most advanced models is still lacking. In this thesis we prove existence for a solution of the microscopic cellular model, and existence and uniqueness for the solution of the macroscopic bidomain model (these results are essentially contained respectively in [70] and [69]). Each of the models is made up of the constitutive equations, which characterize the microscopic or the macroscopic setting, coupled with the equations describing the flow of ionic currents through the cellular membrane, which are the same for both models. While the constitutive equations of the micro- and macroscopic models are universally accepted, the description of the ionic currents is undergoing a continuous development and at present there exists a great variety of reliable models. Our results hold for a wide class of models of ionic currents, including the classical Hodgkin-Huxley model [35], the first membrane model for ionic currents in an axon (and, as will be detailed later on, the common denominator of *all* the following models), and the Phase-I Luo-Rudy (LR1) model [50], which is one of the most widely used models in two-dimensional and three-dimensional simulations of the cardiac action potential propagation, and laid the basis for many subsequent *dynamical* models (see e.g. [49, 55, 37]).

In the last few years many different problems of mathematical analysis related to the modelization of the cardiac electric field have been studied: variational methods in Hilbert triples are used in [21], in order to prove the well posedness for the micro and macroscopic model, endowed with FitzHugh-Nagumo simplification for the description of the ionic currents; [56] deals with the homogenization of the microscopic model by means of Γ-convergence and uniform error estimates for a suitable time discretization and obtains a rigorous derivation of the macroscopic model from the microscopic one; [6] investigates, in the framework of Γ-convergence, the asymptotic behaviour of vectorial integral functionals arising from the study of the macroscopic Bidomain model; in [8] is proved existence and uniqueness for a general class of degenerate reaction-diffusion systems, including the macroscopic bidomain equations (endowed with a particular simplification for the ionic currents). See [19] for a survey which collects the aspects related to the formulation of mathematical models, the problems of well posedness and homogenization, the numerical discretization of these models and their computer simulations.

The electric activity of the heart

Let us now describe the physiological phenomenon that we intend to modelize: the propagation of the electric signal which originates the heartbeat.

The contraction of the heart muscle is initiated by the action potential: an electric signal starting in the sinoatrial node, see e.g. [42, ch. 11], [43]. It spreads from here to the muscle of the atria causing its contraction. The atria and ventricles are separated by a ring of fibrous tissue and the excitation can only be transmitted from the atria to the ventricles by passing through the atrioventricular node. Then it passes to the left and right bundles of His, which are made up of Purkinje fibres. The Purkinje fibres rapidly transmit the action potential to all regions of the two ventricles which, finally, contract. When the muscle cells are stimulated electrically, they rapidly depolarize, *i.e.,* the electrical potential inside the cell is changed. The depolarization causes the contraction of the cells and the electrical signal is also passed on to the neighbouring cells. This reaction causes an electric field to be created in the heart and the body.

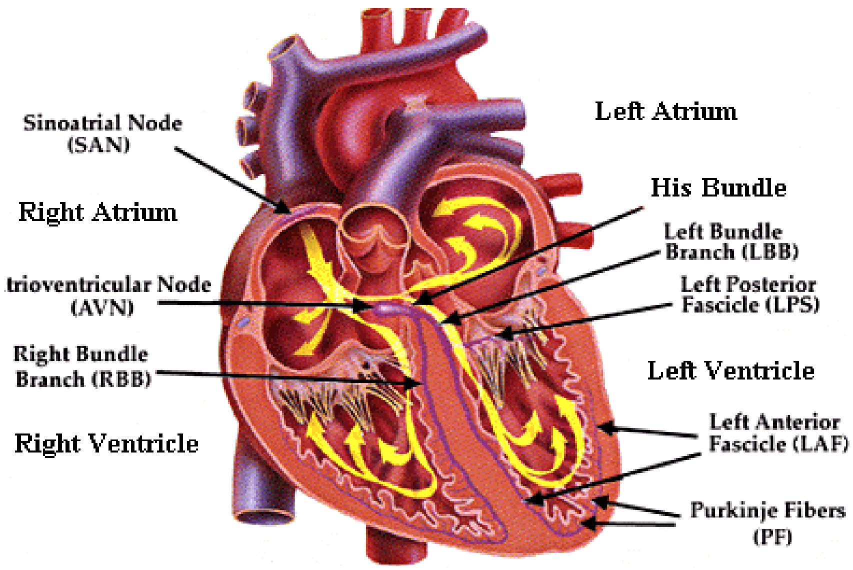

Figure 1: The propagation of the action potential

The measurement of this field on the body surface is called the electrocardiogram (ECG). Since the electrode location of the ECG is centimetres away from the heart surface and the current conduction from heart to thorax results in strong signal attenuation and smoothing, the information content of ECGs is limited and it is a difficult task to extract from this signals detailed information on pathological heart states associated with ischemia or sudden death. Moreover in many cases it is not easy to infer the origin of a pathology from the results of the ECG alone. The conduction in the body tissue and, more generally, in biological systems, is a vast field of present research, see e.g. [42], [29], [39], [1, 2, 4, 3].

The dynamics inside the heart are much complex, mainly, due to the different anisotropy of the intracellular and the extracellular tissue, to the excitability of the heart muscle cells and to the great variety of different cell and ionic channels types. The electric behaviour of the membrane of excitable cells has been widely investigated in the last fifty years, and the modeling of the ionic currents in the ventricular myocardium, in particular, has undergone a continuous development from the paper by Beeler and Reuter [7], in 1977, to nowadays: [50, 49, 28], for example, study guinea pigs, [72, 30, 37] focus on canine cells, [66, 58] concentrate on the human myocardium, while [55] is a review of the development of cardiac ventricular models (we cite only a few examples, but we remark that the literature concerning the modelization of the cardiac action potential, in different species and with different pathologies, is impressively rich).

In the following section we will describe the microscopic model of the cardiac electric potential, its structure and the constitutive equations, detailing in particular the complex role of the cellular membrane and the historical development of its modelization (at this point, the eager reader may jump to Problem (**m**) in Subsection 1.1.2, for a quick summary of the equations involved). In Section 1.2 we will present the Macroscopic Bidomain model, while we defer a plan of the whole thesis to end of this chapter.

1.1 The microscopic model of the cardiac electric potential

The microscopic structure of the cardiac tissue

At a microscopic level the cardiac structure is composed of a collection of elongated cells, endowed with special electric (mainly end-to-end) connections, named *gap junctions*, embedded in the extra-cellular fluid. The *gap junctions* form the long fiber structure of the cardiac muscle, whereas the presence of lateral junctions establishes a connection between the elongated fibers.

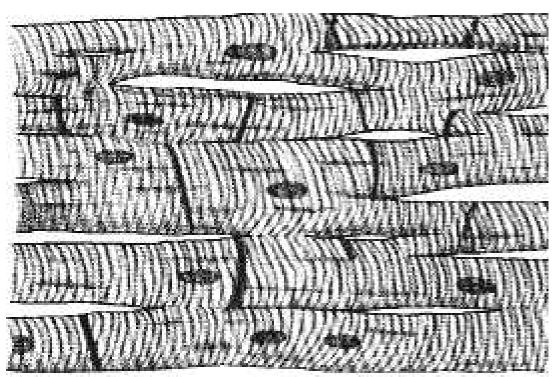

Figure 2: The microscopic structure of the cardiac cells

Since the interconnection between cells has resistance comparable to that of the intra-cellular volume, we can consider the cardiac tissue as a single isotropic *connected* domain Ω_i, separated from the (connected) extra-cellular fluid Ω_e by a membrane surface Γ.

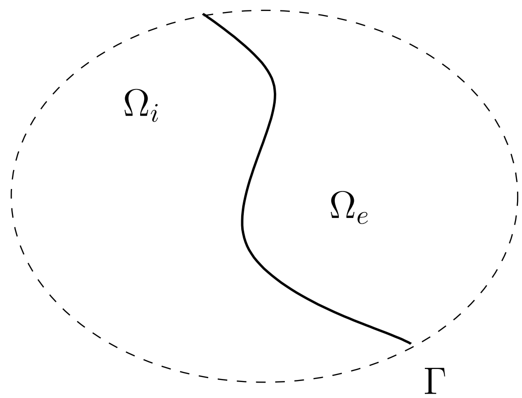

Figure 3: A scheme of the abstract representation

The geometry and the main physical quantities and variables

We call

Ω_i the intra-cellular domain,
Ω_e the extra-cellular domain,
$\overline{\Gamma} = \partial\Omega_i \cap \partial\Omega_e$ the cellular membrane,
$\Omega := \Omega_i \cup \Omega_e \cup \Gamma \in \mathbb{R}^3$ the physical region occupied by the heart.

We denote by

$u_{i,e} : \overline{\Omega}_{i,e} \to \mathbb{R}$, the intra- and extra-cellular electric potentials,
$v := u_i - u_e : \Gamma \to \mathbb{R}$, the transmembrane potential,
$\mathbf{w} : \Gamma \to \mathbb{R}^k$, the vector of the gating variables,
$\mathbf{z} : \Gamma \to \mathbb{R}^m$, the vector of the intracellular ionic concentrations,
$\sigma_{i,e} : \overline{\Omega}_{i,e} \to \mathbb{M}^{3\times 3}$, the intra- and extra-cellular conductivities,
which are *symmetric, positive definite, continuous* tensors, and satisfy the uniform ellipticity condition:

$$\exists\, \underline{\sigma}, \overline{\sigma} > 0 : \quad \underline{\sigma}|\xi|^2 \le \sigma_{i,e}(x)\xi\cdot\xi \le \overline{\sigma}|\xi|^2, \quad \forall\, \xi \in \mathbb{R}^3,\ \forall\, x \in \Omega_{i,e}. \tag{1.1}$$

Basic equations

(See e.g. [42, ch. 11.3], [40, 41]) Let $-\sigma_{i,e}\nabla u_{i,e}$ be the current densities related to the electric potentials $u_{i,e}$. Let ν_i, ν_e denote the unit exterior normals to the boundary of Ω_i and Ω_e respectively, satisfying $\nu_i = -\nu_e$ on Γ. Under quasi-stationary conditions (see [57]), due to the current conservation law, the normal current flux through the membrane is continuous:

$$\sigma_i \nabla u_i \cdot \nu_i + \sigma_e \nabla u_e \cdot \nu_e = 0, \qquad \text{on } \Gamma. \tag{1.2}$$

Denoting by i_i^s, i_e^s the (given) stimulation currents applied to the intra- and extracellular space, we have

$$-\text{div}(\sigma_i \nabla u_i) = i_i^s, \quad \text{in } \Omega_i, \qquad -\text{div}(\sigma_e \nabla u_e) = i_e^s, \quad \text{in } \Omega_e. \tag{1.3}$$

On the other hand, since the only active source elements lie on the membrane Γ, each flux equals the membrane current per unit area I_m

$$\sigma_e \nabla u_e \cdot \nu_e + I_m = -\sigma_i \nabla u_i \cdot \nu_i + I_m = 0. \tag{1.4}$$

In order to find an expression for the membrane current I_m, we have to consider the structure of the membrane (see [42, ch. 2],[38]). The cellular membrane is constituted by a lipid bilayer in which are immersed some proteins. The membrane behaves as an insulator, while some of the proteins behave as channels, with relatively low resistance, which permit the flow of electrically charged ions. Assuming that these channels are uniformly distributed into the membrane, it is possible to describe the cellular membrane as an RC circuit, that is, as a capacitor (whose plates represents the lipid bilayer) connected in parallel with several resistances, acting for the ionic channels. If a difference of potential is applied to the sides of the membrane, the circuit is crossed by a current I_m, which may be expressed as the sum of a capacitive and a ionic term:

$$\boxed{I_m := C_m \partial_t v + I_{ion}(v,t),} \qquad \text{on } \Gamma, \tag{1.5}$$

where C_m is the surface capacitance of the membrane and I_{ion} is the ionic current.

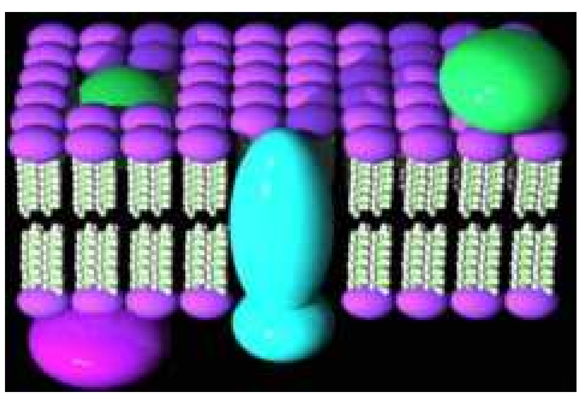

Figure 4: The lipid bilayer

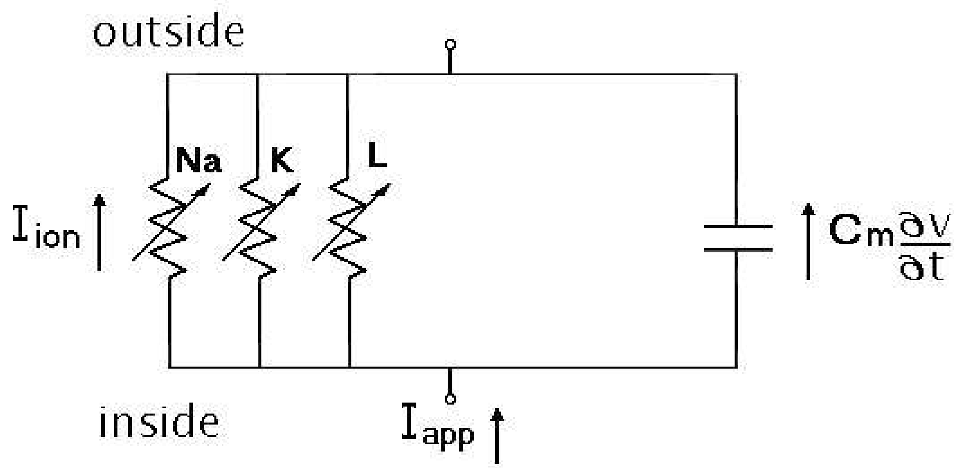

Figure 5: The RC circuit

In order to complete the model, we need a description of the ionic current I_{ion} which appears in (1.5).

1.1.1 Membrane models and ionic currents

We shall now give a description of the structure of the ionic currents, referring in particular to the celebrated work of Hodgkin and Huxley on the currents in the squid's giant axon. In order to justify our assumptions, we also establish a comparison between the equations which appear in the cited physiological models and the mathematical hypothesis on the ionic currents (1.17a)–(1.15) and on the dynamics of the concentration variables (1.19), (1.20).

The first membrane model for ionic currents was given in the work on nerve action potential by Alan Hodgkin and Andrew Huxley [35], work that earned them the Nobel prize in Medicine in 1963. Models of Hodgkin-Huxley type have been later developed for the cardiac action potential. In these models, (see, for example, [54, 7, 50, 49, 72, 66]) the ionic current through channels of the membrane depends on

- the transmembrane potential v;
- k gating variables (introduced by Hodgkin and Huxley), $(w_1, \dots, w_k) =: \mathbf{w}$;
- m intracellular ionic concentrations, $(z_1, \dots, z_m) =: \mathbf{z}$.

Ionic currents - a first description. In general, I_{ion} may be expressed as the sum of several contributions by the different ionic species (e.g. Sodium, Potassium, Calcium...). The flow of an ionic species through the cell membrane via a channel depends on the concentration (or chemical gradient) for that ion, i.e. the difference in the concentration of the ion on either side of the membrane. An ion will tend to flow from the side at which its concentration its higher to the side at which its concentration its lower. Because a ion is charged, the flow of the ion will also depend on the potential across the membrane (i.e. the electrical gradient). The net force acting on an ionic species (S) is determined by both the electrical and chemical gradients and is referred to as the "electrochemical gradient", or "driving force": it is the difference between the membrane potential (v) and the equilibrium potential of the ion (E_S), i.e. $v - E_S$. The equilibrium (or Nernst) potential E_S is the potential at which an ion S is at equilibrium, that is, at which the chemical and electrical gradients are equal and opposite, and is given by the Nernst equation, which describes how a difference in ionic concentration between two phases can result in a potential difference:

$$E_S = \frac{RT}{\zeta_S F} \log \frac{[S]_e}{[S]_i}, \tag{1.6}$$

where R is the gas constant, T is the absolute temperature, F is the Faraday number, ζ_S is the valence on the ion S and $[S]_{i,e}$ are the intracellular and extracellular concentrations for the ion S (see [9, 42]). The simplest expression for the ionic current that satisfies the Nernst principle (see e.g. [42, ch. 2.6]), is then a linear model, giving the current as

$$I_{ion} = \sum_S I_S, \qquad \text{(total current as sum of ionic contributions)}$$

$$I_S = I_S(v) = \bar{G}_S(v - E_S), \quad \text{(Ohm law, taking into account Nernst potential)}$$

where $S = Na^+, K^+, Ca^{2+}, \ldots$ are the different ionic species, $\bar{G}_S$ is the constant membrane conductivity of the specific channel, v is the difference of potential across the membrane and E_S is the Nernst potential for the ion S, as given in (1.6). This linear model, however, is not sufficient to explain the dynamics we are interested in. In fact, the electrical behaviour of cardiac cells exhibits a highly nonlinear dependence on the difference of potential. For a better understanding, we will give a brief overview of the dynamics of nerve conduction in general, of the successful description by Hodgkin-Huxley and of the modelization of ionic currents in cardiac fibers in particular.

Nerve conduction and the Hodgkin-Huxley model. The conduction through the membrane of excitable cells is a far more complex phenomenon (excitable cells are those cells whose electrical properties change during their normal functioning, and they can be found in nerve fiber, striated muscle fiber, and various types of cardiac fibers, whence our interest in this topic). The behaviour of a stimulated cell is not linear, in fact, it is possible to experimentally observe various phenomena (see e.g. [22] for a more detailed analysis of these dynamics). Suppose that a stimulus in the form of a brief current pulse is applied to the cell (e.g. an axon): *a)* if the stimulus is very weak, there is a temporary change in the membrane potential that is proportional to the amplitude of the stimulus, which dies away very rapidly and affects only a very small area nearby; *b)* if the amplitude of the stimulus is large enough so that the membrane potential is raised above a critical value called the *threshold*, then the membrane potential increases abruptly to form a roughly triangular solitary wave, called an *action potential*. Although it arises locally, it splits immediately into two separate waves that travel away in opposite directions. The action potential can be recorded along the nerve fiber as it passes, but there is no way to deduce from the record alone where it originated nor the amplitude of the stimulus that produced it. The fact that only the presence or absence of the travelling wave can be recorded is called the *all-or-nothing law*, and it is an efficient way of avoiding interference and disturbance. *c)* Following such a stimulus there is a time interval called *absolute refractory period*, during which no stimulus, however strong, can produce an action potential.

The purpose of the work of Hodgkin and Huxley was to obtain a physical explanation of the processes that produce these (and other, more subtle) observed phenomena. Following a series of experiments on the squid's axon, they understood that the permeability of the membrane to Na and K ions is dependent on the potential difference across the membrane. Denoting the permeabilities by g_{Na}, g_K, experimental work suggested that the equations might take the form

$$\begin{cases} C_m \dfrac{dv}{dt} &= I_m - g_{Na}(v - E_{N_a}) - g_K(v - E_K) - g_l(v - E_l), \\ \dfrac{dg_{Na}}{dt} &= G(t, v, g_{Na}, g_K), \\ \dfrac{dg_K}{dt} &= H(t, v, g_{Na}, g_K), \end{cases}$$

where g_l, E_l are the (constant) conductivity and equilibrium potential for the remaining *leakage* current. (Remember that owing to the model of the membrane as a circuit with capacitor and resistances connected in parallel, the total current through the membrane is linked to the difference of potential by:

$$I_m = C_m \frac{dv}{dt} + I_{ion},$$

and the expected expression for the ionic current is

$$I_{ion} = g_{Na}(v - E_{N_a}) + g_K(v - E_K) + g_l(v - E_l).$$

Instead of determining directly the functions H and G, Hodgkin and Huxley decided to introduce other variables w_j and to express g_{Na} and g_K as functions of w_j. As J. Cronin points out in [22], “the choice of this variables cannot be entirely explained on a logical basis”, but indeed the mathematical formulation given by this choice was so successful that it has remained essentially unchanged in the fifty years of work that followed. We therefore introduce the *gating variables*

$$\mathbf{w} := (w_1, \dots, w_k).$$

In Hodgkin-Huxley model each contribution to the total ionic current I_{ion} takes the form

$$I_S^{(1)} = I_S^{(1)}(v, \mathbf{w}) = G_S(\mathbf{w})(v - E_S),$$
$$G_S(\mathbf{w}) := \bar{G}_S \prod_{j=1}^{k} w_j^{p_{j,S}}$$

where $\bar{G}_S$ is the (constant) maximum membrane conductivity, $S = Na^+, K^+, L$ (L is a non-specified leakage current) and the exponents $p_{j,S}$ are nonnegative integers. Each w_j is related to the difference of potential v by an ordinary differential equation of the type

$$\frac{dw_j}{dt} = \alpha_j(v)(1 - w_j) - \beta_j(v)w_j,$$

where the functions α_j, β_j are chosen in such a way as to fit the tabulated values gathered in the experiments (H-H chose to fit the experimental values with exponential functions and, as we will point out later, precisely this seemingly harmless choice leads to serious problems when it comes to the variational formulation of the problem).

Cardiac models. In recent models of the cardiac fibers, the variation of $[Ca^{2+}]_i$ is considered [7, 50], while other more recent descriptions consider the variation of the internal concentration of all the ionic species [49, 72, 66], so that $[S]_i$ becomes an unknown in the model, which we denote by z_S, and its dynamics are described by the system of ordinary differential equations:

$$\frac{d}{dt} z_S = -\gamma_S \sum_j I_{S_j}, \tag{1.7}$$

where γ_S is a constant (depending on the geometry of the cell, temperature and valence of S) and I_{S_j} are the currents which carry the ion S (for example, in [49], the current of Sodium ions $I^{tot}_{Na^+}$ is constituted by six different independent subcurrents $I_{Na}, I_{NaCa}, I_{NaK}, I_{nsNa}, I_{bNa}, I_{CaNa}$, each with its proper role and function in the cell exchange economy). Equation (1.7) states that the variation in the internal concentration of S can be evaluated by counting the S ions carried in (and out) by each current. In these models, the contribution by the ion S to the $\mathbf{w}$-gated, time-dependent current, becomes

$$I_S^{(2)} = I_S^{(2)}(v, \mathbf{w}, z_S) = G_S(\mathbf{w})(v - E_S(z_S)),$$

where E_S is given by (1.6). To be precise, there are also currents like the Ca^{2+} and Na^+ background currents [49, 72, 66], or the ATP-sensitive K^+ current [64], which are not gated by $\mathbf{w}$, so that a general expression may become

$$I_S^{(3)} = I_S^{(3)}(v, \mathbf{w}, z_S) = G_S(\mathbf{w})(v - E_S(z_S)) + \underline{G}_S(v - E_S(z_S)), \tag{1.8}$$

$\underline{G}_S$ constant.

Remark 1.1. The presence of these background currents, which may not be quantitatively relevant in itself, prevents the term I_S from disappearing when $\mathbf{w}$ becomes zero, and henceforward protects equation (1.7) from the flaw of degeneracy (see Section 2.2 for a better insight).

Remark 1.2. In the particular case of the phase–I Luo–Rudy model [50], there is a single background current I_b, which does not take into account the variation in the internal Calcium concentration, i.e. it is not correctly described by (1.8). We remark that any of the subsequent models involving Calcium dynamics does include a Calcium background current with the needed shape ($I_{bCa}(v, z) = \underline{G}\,(v - E_{Ca}(z))$), and that the LR1 model, with this addition, satisfies all our assumptions.

In some currents, instead of the time-dependent gating $G_S(\mathbf{w})$, there is a gating function K_S depending directly on the membrane potential v:

$$I_S^{(3bis)} = I_S^{(3bis)}(v, z_S) = K_S(v)(v - E_S(z_S)). \tag{1.9}$$

In the LR1 model, where the concentrations $[K^+]_i$ and $[Na^+]_i$ are constant, the time-dependent Potassium current has the particular form

$$I_K = I_K(v, \mathbf{w}) = X(\mathbf{w})X_i(v)(v - \bar{E}), \tag{1.10}$$

where X is a continuous function of $\mathbf{w}$, $X_i(v)v$ is a Lipschitz function and $\bar{E} = E_K$ is a constant.

The sense of all this listing is to gather the main typologies of currents, in order to epitomize a great variety of functions into one general expression. Owing to (1.8), (1.9) and (1.10) we will consider a current with the form

$$I_S^{(4)} = I_S^{(4)}(v, \mathbf{w}, z_S) = \left(G_S(\mathbf{w}) + \underline{G}_S + K_S(v)\right)(v - E_S(z_S)) + X(\mathbf{w})X_i(v)(v - \bar{E}). \tag{1.11}$$

But in order to have also a manageable function and to provide the reader with some intelligible hypothesis, in the following mathematical analysis, we describe $I_S^{(4)}$ by means of a general C^1 function $J_S = J_S(v, \mathbf{w}, \log z_S)$. We preferred to explicit the logarithmic dependence on z_S, which is unavoidable and comes out from Nernst potential (1.6). The definitive assumptions (1.14b,1.14c) on J_S reflect

- the monotonicity of $I_S^{(4)}(v, \mathbf{w}, \log z_S)$, with respect to $\log z_S$,
- the linear growth of $I_S^{(4)}(v, \mathbf{w}, \log z_S)$ with respect to v,
- the ubiquitous and unrestricted presence of $\mathbf{w}$.

About the linear growth w.r.t. v, we remark that if K_S, X_i are continuously differentiable, bounded, and their derivatives decrease fast enough as $|v| \to +\infty$, then $K_S(v)v, X_i(v)v$ are Lipschitz functions. This is, for example, the case of the K^+ Plateau function in [49, 72, 66] and of all the Potassium currents in [50].

Moreover, any model for the cardiac action potential takes into account (more or less explicitly) the ionic exchanges due to other non–Hodgkin–Huxley–type dynamics, such as: Ca^{2+} current through the L-type channel, Na^+-Ca^{2+} exchanger, Na^+-K^+ pump, currents through the sarcolemma, and other. We assume that the remaining part of the ionic current carrying the ion S may be approximated by a Lipschitz function $H_S := H_S(v, \mathbf{w}, \mathbf{z})$, so that the structure of (1.11) becomes

$$I_S^{(5)}(v, \mathbf{w}, z_S) = J_S(v, \mathbf{w}, \log z_S) + H_S(v, \mathbf{w}, \mathbf{z}), \tag{1.12}$$

(this assumption is satisfied, in general, by the Na^+-K^+ pump and by the nonspecific Ca-activated currents, but not by the Na^+-Ca^{2+} exchanger, see e.g. [49]). The variation of $z_S = [S]_i$ is then completely described by (1.12). Finally we observe (though it is just a modelistic attention, mathematically uninfluential) that not all the currents which compose H_S are part of the final I_{ion}, because some of these subcurrents flow inside the cell (through the sarcolemma, a sort of storehouse of Calcium ions) instead of between the intra- and extracellular medium [49, 66], and therefore they account for the variation in the intracellular concentration, but not for the total ionic current through the cellular membrane;

$$H_S = \underbrace{\tilde{H}_S}_{\text{intra-extracell. exchange}} + \underbrace{h_S.}_{\text{internal flow}}$$

In order to take into account this difference, we shall call $\tilde{H}_S$ the non-Hodgkin-Huxley-type current in I_{ion} and we shall suppose that $\tilde{H}_S$ shares the same structural properties of H_S.

The ionic currents.

Enlightened by the above considerations, we assume that the ionic current

$$\begin{aligned} I_{ion} : \mathbb{R} \times \mathbb{R}^k \times (0, +\infty)^m &\to \mathbb{R}, \\ (v, \mathbf{w}, \mathbf{z}) &\to I_{ion}(v, \mathbf{w}, \mathbf{z}) \end{aligned}$$

has the general form:

$$I_{ion}(v, \mathbf{w}, \mathbf{z}) := \sum_{i=1}^{m} \left(J_i(v, \mathbf{w}, \log z_i)\right) + \tilde{H}(v, \mathbf{w}, \mathbf{z}), \tag{1.13}$$

where, $\forall\, i = 1, \ldots, m$,

$$J_i \in C^1\left(\mathbb{R} \times \mathbb{R}^k \times \mathbb{R}\right), \tag{1.14a}$$

$$0 < \underline{G}(\mathbf{w}) \leq \frac{\partial}{\partial \zeta} J_i(v, \mathbf{w}, \zeta) \leq \overline{G}(\mathbf{w}), \tag{1.14b}$$

$$\left| \frac{\partial}{\partial v} J_i(v, \mathbf{w}, 0) \right| \leq L_v(\mathbf{w}), \tag{1.14c}$$

$\underline{G}, \overline{G}, L_v$ belong to $C^0(\mathbb{R}^k, \mathbb{R}_+)$, and

$$\tilde{H} \in C^0(\mathbb{R} \times \mathbb{R}^k \times (0, +\infty)^m) \cap \text{ Lip}(\mathbb{R} \times [0,1]^k \times (0, +\infty)^m). \tag{1.15}$$

The dynamics of the gating variables.

We have the system of ODE's

$$\frac{\partial w_j}{\partial t} = F_j(v, w_j), \qquad j = 1, \ldots, k. \tag{1.16}$$

We assume that

$$F_j : \mathbb{R}^2 \to \mathbb{R} \text{ is locally Lipschitz continuous;} \tag{1.17a}$$

$$F_j(v, 0) \geq 0, \quad \forall\, v \in \mathbb{R}; \tag{1.17b}$$

$$F_j(v, 1) \leq 0, \quad \forall\, v \in \mathbb{R}, \tag{1.17c}$$

$\forall\ j = 1, \ldots, k.$

In the models considered F_j has the particular form

$$F_j(v, w_j) := \alpha_j(v)(1 - w_j) - \beta_j(v) w_j, \qquad j = 1, \ldots, k,$$

where α_j and β_j are positive rational functions of exponentials in v. A general expression for both α_j and β_j is given by

$$\frac{C_1 e^{\frac{v - v_n}{C_2}} + C_3(v - v_n)}{1 + C_4 e^{\frac{v - v_n}{C_5}}}, \tag{1.18}$$

where C_1, C_3, C_4, v_n are non-negative constants and C_2, C_5 are positive constants.

The dynamics of the ionic concentrations.

We have the system of ODE's

$$\frac{\partial z_i}{\partial t} = G_i(v, \mathbf{w}, \mathbf{z}) := -J_i(v, \mathbf{w}, \log z_i) + H_i(v, \mathbf{w}, \mathbf{z}), \qquad i = 1, \ldots, m, \tag{1.19}$$

where J_i is the function described in (1.14a, 1.14b, 1.14c) and

$$H_i \in C^0(\mathbb{R} \times \mathbb{R}^k \times (0, +\infty)^m) \cap \operatorname{Lip}(\mathbb{R} \times [0, 1]^k \times (0, +\infty)^m), \qquad i = 1, \ldots, m. \tag{1.20}$$

The simplified model of Fitzhugh-Nagumo.

Simplified models are often used for the simulation of the propagation of excitation wavefronts in large myocardial domains. In this thesis we shall often refer to a particular simplified model, called the Fitzhugh-Nagumo simplification, 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. [13], [51]). It requires only one additional

$$\textit{recovery variable} \quad w : \Gamma \to \mathbb{R},$$

and the Ionic current is described by

$$\begin{cases} I_{ion} = I_{ion}(v, w) := F(v) + \Theta w \\ \partial_t w = r(v, w) := \eta v - \gamma w \end{cases} \tag{1.21}$$

where $\Theta, \eta, \gamma \geq 0$ are given constants and
$F \in C^1(\mathbb{R})$ is a cubic-like function with $\inf_{x \in \mathbb{R}} F'(x) > -\infty$.

1.1.2 The complete formulation.

We refer to (1.2)-(1.13), (1.16), (1.19) as the equations of the *microscopic model*, together with Neumann boundary conditions imposed on u_i, u_e on the remaining part of the boundaries $\Gamma_{i,e} := \partial\Omega_{i,e} \backslash \Gamma$

$$\sigma_i \nabla u_i \cdot \nu_i = g_i, \quad \text{on } \Gamma_i, \qquad \sigma_e \nabla u_e \cdot \nu_e = g_e, \quad \text{on } \Gamma_e,$$

or with homogeneous Dirichlet boundary conditions

$$u_i = 0 \quad \text{on } \ \Gamma_i, \qquad u_e = 0 \quad \text{on } \ \Gamma_e,$$

and with the (degenerate with respect to v) initial Cauchy condition

$$v(x,0) = v_0(x), \qquad \mathbf{w}(x,0) = \mathbf{w}_0(x), \qquad \mathbf{z}(x,0) = \mathbf{z}_0(x), \qquad \text{on } \ \Gamma.$$

In order to give a complete formulation of the problem, let us suppose that $\Omega_{i,e}$ are bounded, Lipschitz domains, that Ω_i is connected (since we are going to put Neumann boundary conditions on Ω_i), that Γ is a Lipschitz surface and that σ_i, σ_e are measurable. We fix $]0,T[$ as the evolution time interval, and we define the associated space-time domains following the usual notation of [47]

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

We denote the vectors by boldface letters (i.e. $\mathbf{F} = (F_1, \ldots, F_k)$, $\mathbf{G} = (G_1, \ldots, G_m)$, and so on). Moreover, for sake of simplicity, we choose Neumann boundary conditions on Γ_i and homogeneous Dirichlet boundary conditions on Γ_e. We also define the space

$$H^1_{\Gamma_e^0}(\Omega_e) := \left\{ u \in H^1(\Omega_e) : u(x)_{|\Gamma_e} = 0, \ \text{a.e.} \right\}.$$

Remark 1.3. The result stated in Theorem 4.1 would be identical if we made the widely used choice of Neumann conditions on both boundaries Γ_i and Γ_e. In this case, we should ask for both domains to be connected and the potentials u_i, u_e would result defined up to an additive constant.

The formal statement of the microscopic model is then:

Problem (m). Given

$$\begin{aligned} i^s_{i,e} : Q_{i,e} \to \mathbb{R}, \qquad & g_i : \Sigma_i \to \mathbb{R}, \\ v_0 : \Gamma \to \mathbb{R}, \qquad & \mathbf{w}_0 : \Gamma \to \mathbb{R}^k, \qquad \mathbf{z}_0 : \Gamma \to (0, +\infty)^m, \end{aligned}$$

we seek

$$u_{i,e} : Q_{i,e} \to \mathbb{R}, \qquad \mathbf{w} = (w_1, \ldots, w_k) : \Sigma \to \mathbb{R}^k,$$

$$v := u_i - u_e : \Sigma \to \mathbb{R}, \qquad \mathbf{z} = (z_1, \dots, z_m) : \Sigma \to (0, +\infty)^m,$$

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

$$\begin{aligned} -\mathrm{div}(\sigma_{i,e}\nabla u_{i,e}) &= i^s_{i,e} && \text{on } Q_{i,e}, \\ \sigma_i \nabla u_i \cdot \nu_i &= g_i && \text{on } \Sigma_i, \\ u_e &= 0 && \text{on } \Sigma_e, \end{aligned} \tag{1.22}$$

and the evolution system on the surface Σ

$$C_m \partial_t v + I_{ion}(v, \mathbf{w}, \mathbf{z}) = -\sigma_i \nabla u_i \cdot \nu_i \qquad \text{on } \Sigma, \tag{1.23a}$$

$$C_m \partial_t v + I_{ion}(v, \mathbf{w}, \mathbf{z}) = \sigma_e \nabla u_e \cdot \nu_e \qquad \text{on } \Sigma, \tag{1.23b}$$

$$\partial_t \mathbf{w} = \mathbf{F}(v, \mathbf{w}) \qquad \text{on } \Sigma, \tag{1.23c}$$

$$\partial_t \mathbf{z} = \mathbf{G}(v, \mathbf{w}, \mathbf{z}) \qquad \text{on } \Sigma, \tag{1.23d}$$

with initial data

$$v(x, 0) = v_0(x) \qquad \text{on } \Gamma, \tag{1.24a}$$

$$\mathbf{w}(x, 0) = \mathbf{w}_0(x) \qquad \text{on } \Gamma, \tag{1.24b}$$

$$\mathbf{z}(x, 0) = \mathbf{z}_0(x) \qquad \text{on } \Gamma. \tag{1.24c}$$

Our problem is made up of two adjoining open domains with their boundaries partly intersecting, of a Poisson equation in each of them and, on the common boundary, of a system of equations connecting the fluxes and the difference of potentials. In contrast to classical problems for the Poisson equation with a jump discontinuity for normal derivatives across some surface, here Γ is a discontinuity surface for the potential and the related conditions are dynamic and involve the assistant variables w_j, z_i in a nonlinear way.

We will state the result of existence for Problem **(m)** in Chapter 4. By now we point out that the main difficulties in the equations (5.4a) and (5.4b) reside in their degenerate structure (as will be described in Section 3.1), which reflects the differences in the anisotropy of the intra- and extra-cellular tissues, and in the lack of a maximum principle. The latter, in addition, forbids a distributional formulation for the gating variables ODEs, because v appears as argument for exponential functions in F_j (equation (1.23c)) and since $v \notin L^\infty$, we do not know if $F_j(v) \in L^1_{loc}$ and the equation cannot be taken in the sense of distributions. Moreover, the concentration variables z_i appear as argument of a logarithm, both in the dynamics of the concentrations and in the ionic currents, and therefore it is necessary to bound $\mathbf{z}$ far from zero. Again, the task of finding an estimate for $log(z)$ in L^∞, is complicated by the absence of an estimate for v in L^∞, due to the lack of a maximum principle for the parabolic equations.

1.2 The Macroscopic Bidomain model

The macroscopic model of the cardiac tissue. 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. [33, 17, 61] and also [42]), which attempts to describe the averaged electric potentials and current flows inside and outside the cardiac cells. It is possible to derive a macroscopic model from the microscopic one, for a periodic assembling, by a homogenization process; a first formal derivation, based on current balances and expressed by averages of integral identities was obtained in [53]. By standard multiscale arguments of homogenization the same formal derivation can be found also in the Appendix of [21] or in [41, 40], while a rigorous derivation, directly from the microscopic properties of the tissue, was obtained only recently in [56], using the tools of Γ-convergence theory and uniform error estimates for a semi-implicit time discretization of the microscopic problem.

The resulting macroscopic Bidomain model is constituted by a reaction-diffusion system of degenerate parabolic type and it represents the cardiac tissue as the superimposition of two anisotropic continuous media: the intra- and extra-cellular media, coexisting at every point of the tissue and connected by a distributed continuous cellular membrane, i.e.

$\Omega \equiv \Omega_i \equiv \Omega_e \equiv \Gamma \subset \mathbb{R}^3$ is the physical region occupied by the heart,
$u_i, u_e : \Omega \to \mathbb{R}$ are the intra- and extra-cellular electric potentials and
$v := u_i - u_e : \Omega \to \mathbb{R}$ is the transmembrane potential.

Basic equations.

The anisotropy of the two 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 point x and always assuming axial symmetry for $\sigma^t_{i,e}(x)$, the conductivity tensors $M_{i,e}$ in the two media can be expressed by

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

and they are *symmetric, positive definite, continuous* tensors $M_{i,e} : \overline{\Omega} \to \mathbb{M}^{3\times3}$. To the potentials u_i, u_e are associated the current densities $-M_{i,e}\nabla u_{i,e}$; since induction effects are negligible, the current field can be considered quasi-static. The current densities 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

$$-\mathrm{div}(M_i \nabla u_i) = -I_m + I_i^s, \qquad -\mathrm{div}(M_e \nabla u_e) = I_m + I_e^s, \qquad \text{in } \Omega. \tag{1.25}$$

On the other hand the membrane current per unit volume I_m, as in (1.5), is the sum of a capacitance and ionic term

$$I_m = \chi(C_m \partial_t v + I_{ion}), \qquad \text{in } \Omega, \tag{1.26}$$

where χ is the ratio of membrane area per unit of tissue volume (for simplicity, from now on we shall suppose $\chi = 1,\ C_m = 1$).

In order to complete the model, we adopt the expression of the ionic currents (and of the related gating and concentration dynamics) described in the previous section. In the following, we assume that the cardiac tissue is insulated, therefore homogeneous Neumann boundary conditions are assigned on $\partial\Omega \times (0, T)$

$$M_i \nabla u_i \cdot \nu = 0, \qquad M_e \nabla u_e \cdot \nu = 0. \tag{1.27}$$

We refer to (1.25)-(1.27) and (1.13), (1.16), (1.19) as the equations of the *macroscopic bidomain model*. We complete this reaction diffusion system by assigning the (degenerate with respect to v) initial Cauchy condition

$$v(x,0) = V_0(x), \qquad \mathbf{w}(x,0) = \mathbf{w}_0(x), \qquad \mathbf{z}(x,0) = \mathbf{z}_0(x), \quad \text{in } \Omega.$$

Observe that adding the two equations (1.25) we have $-\mathrm{div}(M_i \nabla u_i) - \mathrm{div}(M_e \nabla u_e) = I_i^s + I_e^s$. Integrating on Ω and applying the divergence theorem and the Neumann boundary conditions, we have the following compatibility condition for the system to be solvable:

$$\int_\Omega (I_i^s + I_e^s)\, dx = 0. \tag{1.28}$$

We recall that electric potentials in bounded domains are defined up to an additive constant; in our case u_i and u_e are determined up to the same additive time-dependent constant, while v is uniquely determined. This common constant is related to the choice of a reference potential. A usual choice consists in selecting this constant so that u_e has zero average on Ω, i.e.

$$\int_\Omega u_e\, dx = 0. \tag{1.29}$$

Remark 1.4. When $M_i = \lambda M_e$, with λ constant, the macroscopic system in the variables $(u_i, u_e, \mathbf{w}, \mathbf{z})$ is equivalent to a parabolic reaction-diffusion equation in $v = u_i - u_e$ coupled with the dynamics of the assistant variables $\mathbf{w}, \mathbf{z}$. This case is called in literature *equal anisotropic ratio* and this assumption is often used in modeling cardiac tissue, see e.g. [59], [31]. Nevertheless, it is not an adequate cardiac model since it is unable to reproduce some patterns and morphology of the experimentally observed extracellular potential maps and electrograms, see [16], [34] and [52]. Moreover *un*equal anisotropic ratio makes possible more complex phenomena (see [71], [67]) and can play an important role for the re-entrant excitation (see [73], [62]).

The complete formulation.
In order to give the formal statement of the problem, we shall suppose that $\Omega \subset \mathbb{R}^3$ is a Lipschitz bounded domain, ν is the unitary exterior normal to $\partial\Omega$. We define the related space-time domain $Q := \Omega\times]0,T[$. We also suppose that $M_i(x), M_e(x)$, are measurable and satisfy the uniform ellipticity condition

$$\exists\ \alpha, m > 0: \quad \alpha|\xi|^2 \le M_{i,e}(x)\xi\cdot\xi \le m|\xi|^2, \quad \forall\ \xi \in \mathbb{R}^3,\ x \in \Omega. \tag{1.30}$$

We denote the vectors by boldface letters (so that $\mathbf{F} = (F_1, ..., F_k)$, $\mathbf{G} = (G_1, ..., G_m)$, and so on). The formal statement of the macroscopic model is then:

Problem (M). Given

$$\begin{aligned} &I_i^s : Q \to \mathbb{R}, \qquad I_e^s : Q \to \mathbb{R},\\ &V_0 : \Omega \to \mathbb{R}, \qquad \mathbf{w}_0 : \Omega \to \mathbb{R}^k, \qquad \mathbf{z}_0 : \Omega \to (0, +\infty)^m, \end{aligned}$$

we seek

$$\begin{aligned} &u_{i,e} : Q \to \mathbb{R}, \qquad \mathbf{w} = (w_1, ..., w_k) : Q \to \mathbb{R}^k,\\ &v := u_i - u_e : Q \to \mathbb{R}, \qquad \mathbf{z} = (z_1, ..., z_m) : Q \to (0, +\infty)^m, \end{aligned}$$

satisfying the reaction-diffusion system

$$\partial_t v + I_{ion}(v, \mathbf{w}, \mathbf{z}) = \operatorname{div}(M_i\nabla u_i) + I_i^s \quad \text{on } Q, \tag{1.31a}$$
$$\partial_t v + I_{ion}(v, \mathbf{w}, \mathbf{z}) = -\operatorname{div}(M_e\nabla u_e) - I_e^s \quad \text{on } Q, \tag{1.31b}$$
$$M_i\nabla u_i \cdot \nu = 0 \quad \text{on } \partial\Omega \times (0, T), \tag{1.31c}$$
$$M_e\nabla u_e \cdot \nu = 0 \quad \text{on } \partial\Omega \times (0, T), \tag{1.31d}$$
$$v(x, 0) = V_0(x) \quad \text{on } \Omega, \tag{1.31e}$$

and the ODE system

$$\partial_t \mathbf{w} = \mathbf{F}(v, \mathbf{w}) \quad \text{on } Q, \tag{1.32a}$$
$$\partial_t \mathbf{z} = \mathbf{G}(v, \mathbf{w}, \mathbf{z}) \quad \text{on } Q, \tag{1.32b}$$
$$\mathbf{w}(x, 0) = \mathbf{w}_0(x) \quad \text{on } \Omega, \tag{1.32c}$$
$$\mathbf{z}(x, 0) = \mathbf{z}_0(x) \quad \text{on } \Omega. \tag{1.32d}$$

1.3 Plan of the thesis and open problems

In this thesis we prove existence for a solution of the microscopic Problem (**m**), and existence and uniqueness for the solution of the macroscopic Problem (**M**). In both cases our choice was to divide the problem into two independent subproblems to be solved separately, and then to make use of a fixed point technique in order to obtain a solution of the whole problem.

In other papers on the same subject (e.g. [21], [8]), the well posedness is obtained by means of a unique variational formulation for the entire set of equations; we decided to follow a different path according to the following reason. In [21] the set of gating and concentrations equations is reduced to a linear equation, in [8] it is completely neglected[1], instead, following Hodgkin-Huxley model, we need to solve a system of equations where the difference of potential v appears as argument of exponential functions in F_j (1.16–1.18). Since we do not expect to estimate v in L^∞, we cannot suppose that $F_j(v) \in L^1_{loc}$, and this part of the problem evades any attempt of weak or distributional formulation. On the other hand, if we suppose v to be continuous in time, we can regard the gating and concentrations equations as Ordinary Differential Equations, depending on a parameter $x \in \Gamma$ (or $x \in \Omega$). The remaining evolution system, if we suppose the ionic current to be a known function, can be easily solved making use of the techniques developed in [21] and finally we can use a fixed point scheme in order to obtain the well posedness.

Plan of the thesis.

More precisely, in Chapter 2 we consider v as an assigned function and we solve the ODE system of the gating variables (1.16) and the ODE system of the concentration variables (1.19), obtaining suitable a priori estimates and qualitative properties of the solutions $\mathbf{w}$ and $\mathbf{z}$. In this chapter it is possible to develop a completely unified treatment for the ordinary differential equations belonging to the microscopic problem and the correspondent ones in the macroscopic problem.

In Chapter 3 we study the remaining part of the models (i.e. equations (1.22), (1.23a), (1.23b) in Problem (**m**) and (1.31a),. . . ,(1.31e) in Problem (**M**)). In this part we consider I_{ion} as a fixed function. For both of the problems we give a variational formulation, showing that they share the same structural properties and they can be collocated in the framework of reaction-diffusion equations of degenerate parabolic type. Then we apply an abstract theorem of [21] which relies on a general

[1] the simplification adopted in these two papers in fact leads to other difficulties, which our approach avoids. In this case, the study of slightly different biological models entails heavily different mathematical problems.

reduction technique for degenerate problems in classical Hilbert triples. Thus we obtain existence, uniqueness and suitable a priori estimates.

In Chapter 4 we state the precise existence Theorem related to the microscopic Problem (**m**) and we prove it using Schauder Fixed Point Theorem. Denote by $\mathcal{F}_1$ the operator which maps v into the solutions of the ODE systems, and by $\mathcal{F}_2$ the operator which maps $I_{ion}(v, \mathbf{w}, \mathbf{z})$ into the solution of the microscopic *passive* model. The continuity of $\mathcal{F}_1$ is obtained by means of a classical interpolation inequality, combined with an infinite dimensional version of a theorem on the continuity of Nemitski operators and with the a priori estimates derived in Chapter 2. The continuity of $\mathcal{F}_2$ relies on the a priori estimates derived in Chapter 3 combined with the previous theorem on Nemitski operators.

In Chapter 5 we state and prove the existence and uniqueness Theorem about the macroscopic Problem (**M**). In Section 5.1 we apply the reduction technique described in Section 3.3.2, then we combine a maximal regularity result for generators of analytic semigroups in L^p with classical interpolation methods, in order to obtain the crucial bound for v in L^∞. Then, in Section 5.2, by choosing the correct functional spaces for $v, \mathbf{w}$ and $\mathbf{z}$, it is possible to find existence and uniqueness for a solution $(v, \mathbf{w}, \mathbf{z})$ of Problem (**M**), using Banach Fixed Point Theorem and the previously obtained estimates.

Open problems.

The homogenization problem. A rigorous derivation of the macroscopic bidomain problem from the microscopic model has been recently obtained in [56]. In this paper the ionic currents through the membrane are described by means of Fitzhugh-Nagumo simplification (1.21), a variational formulation is given and then, using the tool of Γ-convergence theory and a priori error estimates for a suitable time discretization. At present, we can prove an equivalent result for the passive model studied in Chapter 3 (in fact, this easily follows from [56]) and we verified that, under strong hypothesis on the difference of potential, the solutions of the (ε-rescaled) microscopic gating ODE converge (as $\varepsilon \to 0$) to the solution of the correspondent macroscopic equations (and this is not trivial at all), but we couldn't combine these two partial results in order to show a homogenization result for the whole model.

The interface conditions problem. In order to establish a connection between a potential measurement on the body surface and the bioelectric cardiac source, we must couple the macroscopic bidomain model of the cardiac tissue with a description of the current conduction in the extracardiac medium, i.e. we need a model describing the electrical conduction in the system *heart + body.* The modelization of the body itself is straightforward, from this point of view, while a problem arise in the choice of the *interface conditions* that must be imposed in order to fully define the reaction-diffusion system in the two media. At present, it is still missing a rigorous derivation of homogenized interface conditions at the cardiac tissue boundary in contact with a conducting medium.

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Chapter 2

The ODE systems

In this chapter we will treat the ODE systems of the gating and concentration variables for both the microscopic and the macroscopic models. We observe that, with respect to systems (1.23c), (1.23d) and (1.32a), (1.32b), the only difference resides in the spatial domain, which is Γ, the cellular membrane, for the microscopic systems, and Ω, the whole region occupied by the heart, for the macroscopic model. In order to develop the treatment in a unified way, let Λ be a bounded subset of $\mathbb{R}^3$, let $\mathscr{M}$ be a $\sigma-$algebra of Λ, and let λ be a measure on $\mathscr{M}$. We shall consider the general measure space $(\Lambda, \mathscr{M}, \lambda)$, and the related Lebesgue space $L^2(\Lambda) := L^2(\Lambda, \lambda)$. The results thus obtained will be applied, in the following Chapters, either to Γ, endowed with the Hausdorff bidimensional measure, or to Ω, endowed with the usual Lebesgue tridimensional measure. For simplicity, in this Chapter, we shall always write '*for a.e. x in* Λ', instead of the more precise '*for λ-a.e. x in* Λ'.

2.1 The gating variables

Our first step will be to show that, for every $v \in H^1(0,T;L^2(\Lambda))$, there exists a unique $\mathbf{w} = (w_1, \dots, w_k)$, measurable, which solves equations (1.23c), (1.24b)

$$\begin{cases} \dfrac{\partial \mathbf{w}}{\partial t} = \mathbf{F}(v, \mathbf{w}), & \text{on } \Lambda \times (0,T), \\ \mathbf{w}(x,0) = \mathbf{w}_0(x), & \text{on } \Lambda. \end{cases} \tag{2.1}$$

in a sense which we will make precise, moreover we will also show the universal bounds

$$\boxed{0 \le w_j \le 1, \quad \text{a.e. in } \Lambda \times (0,T), \quad \forall\, j = 1, \dots, k.}$$

Remark 2.1. In Section 3.1 we will show that in the microscopic setting the difference of potential satisfies $v \in H^1(0,T;L^2(\Gamma)) \cap L^2(0,T;H^{1/2}(\Gamma))$; since the dimension of

Γ is 2, we cannot deduce from this regularity and standard Sobolev embeddings that $v \in L^\infty(\Gamma \times (0,T))$, moreover, no maximum principle seems to apply to equations (1.22),(1.23a),(1.23b). So, we do not know if $F_j(v) \in L^1_{loc}(\Gamma \times (0,T))$ and therefore system (2.1) cannot be taken in the sense of distributions. In the macroscopic setting, instead, we are able to deduce $v \in C^0(\Omega \times (0,T))$ (Section 5.1), but in order to apply Banach's Fixed Point theorem in Section 5.2, we have to assume, at this point of the proof, only $v \in H^1(0,T;L^2(\Omega))$.

Proposition 2.1. *Let $v \in H^1(0,T;L^2(\Lambda))$, $\mathbf{w}_0(x) : \Lambda \to [0,1]^k$, measurable. Then $\exists!\ \mathbf{w} : \Lambda \times [0,T] \to [0,1]^k$, measurable, such that for a.e. $x \in \Lambda$, $\mathbf{w}(x,\cdot) \in (C^1(0,T))^k$, and*

$$\begin{cases} \dfrac{\partial \mathbf{w}}{\partial t}(x,t) = \mathbf{F}(v(x,t),\mathbf{w}(x,t)), & \text{for a.e. } x \in \Lambda,\ \forall\, t \in (0,T], \\ \mathbf{w}(x,0) = \mathbf{w}_0(x), & \text{for a.e. } x \in \Lambda. \end{cases} \tag{2.2}$$

If we consider $v \in C^0([0,T])$, and therefore we drop the dependence on $x \in \Lambda$, then we can prove the continuous dependence on v, precisely:

Lemma 2.1. *The operator which maps a function $v \in C^0([0,T])$ into the solution $\mathbf{w}$ of the ODE system*

$$\begin{cases} \dfrac{d}{dt}\mathbf{w}(t) = \mathbf{F}(v(t),\mathbf{w}(t)), & \forall\, t \in (0,T], \\ \mathbf{w}(0) = \mathbf{w}_0 \in [0,1]^k, \end{cases} \tag{2.3}$$

is continuous.

Proof of Proposition 2.1. We will make use of the following standard lemma:

Lemma 2.2. *Let $v \in L^2(\Lambda \times (0,T))$; the map $t \mapsto v_t(\cdot) = v(\cdot,t)$ belongs to $H^1(0,T,L^2(\Lambda))$ if and only if for a.e. $x \in \Lambda$*

$$t \mapsto v_t(x) \in H^1(0,T) \quad \textit{and} \quad \int_\Lambda \|v_t(x)\|^2_{H^1(0,T)} d\lambda(x) \ < +\infty.$$

Therefore, for a.e. $x \in \Lambda$, the map $t \mapsto v_t(\cdot) = v(\cdot,t)$ admits a unique representative in $C^0([0,T])$, and then, by continuity of F_j (1.17a), the map $t \mapsto F_j(v_t(x),w)$ admits a representative in $C^0([0,T])$, for a.e. $x \in \Lambda$, $\forall\, w \in \mathbb{R}$. Owing to (1.17a), (1.17b), (1.17c) and standard results for ordinary differential equations, for a.e.

$x \in \Lambda$ there exists a unique classical solution $\mathbf{w}_t(x) = \mathbf{w}(x,t)$ of the Cauchy problem (2.2) and

$$0 \le w_j(x,t) \le 1, \quad \text{for a.e. } (x,t) \in \Lambda \times (0,T), \quad \forall\, j = 1,\dots,k. \tag{2.4}$$

Moreover, $\mathbf{w}$ is measurable. In fact, the map

$$\begin{array}{rccc} \mathbf{F} \circ v : & \Lambda \times [0,T] \times [0,1]^k & \to & \mathbb{R}^k, \\ & (x,t,\mathbf{w}) & \mapsto & \mathbf{F}(v(x,t),\mathbf{w}), \end{array}$$

is a Carathéodory function (it is measurable in x and continuous in t and $\mathbf{w}$), therefore, by Scorza–Dragoni theorem (see e.g. [26]), $\forall\,\varepsilon > 0$ there exists a compact set $K_\varepsilon \subset \Lambda$, such that $\lambda(\Lambda \backslash K_\varepsilon) \le \varepsilon$, and

$$(\mathbf{F} \circ v)_{|K_\varepsilon \times [0,T] \times [0,1]^k} \quad \text{is continuous.}$$

Thus, we have that

$$\mathbf{w}_{|K_\varepsilon \times [0,T]} \quad \text{is continuous,}$$

and therefore measurable. Since this is true $\forall\,\varepsilon > 0$, we conclude that $\mathbf{w}$ is measurable on $\Lambda \times [0,T]$. □

Proof of Lemma 2.1. For sake of simplicity we shall suppress index j from calculations, and we carry on this part of the proof for the generic w, F, instead of w_j, F_j.

Let $v, v_n \in C^0([0,T])$, $w_0 \in [0,1]$. The correspondent solutions w, w_n of system (2.3) satisfy

$$w(t) = w_0 + \int_0^t F(v(s), w(s))ds,$$
$$w_n(t) = w_0 + \int_0^t F(v_n(s), w_n(s))ds.$$

We make the difference and we sum and subtract $F(v(s), w_n(s))$

$$|w_n(t) - w(t)| = \Bigg| \int_0^t [F(v_n(s), w_n(s)) - F(v(s), w_n(s))]ds + \\ + \int_0^t [F(v(s), w_n(s)) - F(v(s), w(s))]ds \Bigg|.$$

Owing to the local Lipschitz continuity of F (hypothesis (1.17a)), there exists a nonnegative function $\mu \in C^0(\mathbb{R}^2)$ such that

$$|F(\nu_1,\omega_1) - F(\nu_2,\omega_2)| \le \mu(\nu_1,\nu_2)(|\nu_1 - \nu_2| + |\omega_1 - \omega_2|), \quad \forall \nu_1,\nu_2 \in \mathbb{R},\ \forall \omega_1,\omega_2 \in [0,1].$$

Then, the map $s \mapsto \mu(v(s), v_n(s))$ is continuous in $[0,T]$, and we have that

$$\left|\int_0^T F(v_n(t), w_n(t)) - F(v(t), w_n(t))\,dt\right| \le \int_0^T \mu(v_n(t), v(t))|v_n(t) - v(t)|\,dt =: M_n, \tag{2.5}$$

and

$$\left|\int_0^t F(v(s), w_n(s)) - F(v(s), w(s))\,ds\right| \le \int_0^t \mu(v(s), v(s))|w_n(s) - w(s)|\,ds.$$

We define

$$L := \max_{s\in[0,T]} \mu(v(s), v(s)) < +\infty, \tag{2.6}$$

so that

$$|w_n(t) - w(t)| \le M_n + L\int_0^t |w_n(s) - w(s)|\,ds,$$

and owing to Gronwall Lemma, we conclude that

$$|w_n(t) - w(t)| \le M_n e^{LT}, \quad \forall\, t \in [0,T]. \tag{2.7}$$

Now let $\{v_n\}_{n\in\mathbb{N}}$, v be such that $v_n \to v$ in $C^0([0,T])$. Then, there exists a compact set $K \subset \mathbb{R}^2$ such that

$$(v_n(t), v(t)) \in K, \quad \forall\, t \in [0,T], \quad \forall\, n \in \mathbb{N},$$

and by estimates (2.5), (2.6) and (2.7) we have

$$|w_n(t) - w(t)| \le e^{LT}\int_0^T \mu(v_n(s), v(s))\,|v_n(s) - v(s)|\,ds, \quad \forall\, t \in [0,T], \quad \forall\, n \in \mathbb{N}.$$

Let $\bar\mu := \max\{\mu(\nu_1, \nu_2) : (\nu_1, \nu_2) \in K\} < +\infty$. Hence

$$\max_{t\in[0,T]} |w_n(t) - w(t)| \le e^{LT}\bar\mu\int_0^T |v_n(s) - v(s)|\,ds, \quad \forall\, n \in \mathbb{N},$$

and

$$w_n \to w, \quad \text{strongly in } C^0([0,T]). \tag{2.8}$$

□

2.2 The concentration variables

Now we turn to the system of ODEs (1.23d), with initial data (1.24c), which describes the dynamics of the m concentration variables. We follow the same idea as for the gating variables, that is, we show that for every $v \in H^1(0,T;L^2(\Lambda))$ and for every vector function $\mathbf{w}$ given by Proposition 2.1, we can solve an ordinary Cauchy Problem in time, for a.e. $x \in \Lambda$. The difficulty, now, lies in the lack of a priori conditions such as (1.17b) and (1.17c), which, in (2.1) guaranteed the boundedness for $\mathbf{w}$. We use instead the monotonicity of J_i in the variable z_i, combined with the linear growth of H_i. Moreover, functions J_i contain a logarithmic term, so we also need to bound $\mathbf{z}$ far from zero.

Proposition 2.2. *Let $v \in H^1(0,T;L^2(\Lambda))$, $\mathbf{w}$ as in Proposition 2.1, and $\mathbf{z}_0 : \Lambda \to (0,+\infty)^m$, such that*

$$\mathbf{z}_0 \in (L^2(\Lambda))^m, \qquad \mathbf{log}\, \mathbf{z}_0 \in (L^2(\Lambda))^m.$$

Then $\exists!\ \mathbf{z} : \Lambda \times [0,T] \to (0,+\infty)^m$, measurable, such that for a.e. $x \in \Lambda$: $\mathbf{z}(x,\cdot) \in (C^1(0,T))^k$, and

$$\begin{cases} \dfrac{\partial \mathbf{z}}{\partial t}(x,t) = \mathbf{G}(v(x,t),\mathbf{w}(x,t),\mathbf{z}(x,t)), & \textit{for a.e. } x \in \Lambda,\ \forall\ t \in (0,T], \\ \mathbf{z}(x,0) = \mathbf{z}_0(x), & \textit{for a.e. } x \in \Lambda. \end{cases} \tag{2.9}$$

Moreover, $\mathbf{z}$, $\mathbf{log}\,\mathbf{z}$, $\partial \mathbf{z}/\partial t$ belong to $(L^2(\Lambda \times (0,T)))^m$ and there exists a constant $C > 0$, independent of $v, \mathbf{w}, \mathbf{z}_0$, such that

$$|\mathbf{z}(x,t)| \le C\left(1 + |\mathbf{z}_0(x)| + \|v(x)\|_{L^2(0,t)}\right), \tag{2.10}$$

$$|\mathbf{log}\,\mathbf{z}(x,t)| + \left|\frac{\partial \mathbf{z}}{\partial t}(x,t)\right| \le C\left(1 + |\mathbf{z}_0(x)| + \|v(x)\|_{C^0(0,t)}\right), \tag{2.11}$$

$$\int_0^t |\mathbf{log}\,\mathbf{z}(x,s)|^2 + \left|\frac{\partial \mathbf{z}}{\partial s}(x,s)\right|^2 ds \le C\left(1 + |\mathbf{z}_0(x)\,\mathbf{log}\,\mathbf{z}_0(x)| + |\mathbf{z}_0(x)|^2 + \|v(x)\|^2_{L^2(0,t)}\right), \tag{2.12}$$

$\forall\ t \in [0,T]$, for a.e. $x \in \Lambda$.

Like in Lemma 2.1, we let $v \in C^0([0,T])$, that is, we suppress the dependence on $x \in \Lambda$, and we state the continuous dependence on $v, \mathbf{w}$ of the correspondent solution.

Lemma 2.3. *The operator which maps the functions* $(v, \mathbf{w}) \in C^0([0,T]) \times C^0([0,T])^k$ *into the solution* $\mathbf{z}$ *of the ODE system*

$$\begin{cases} \dfrac{d}{dt}\mathbf{z}(t) = \mathbf{G}(v(t), \mathbf{w}(t), \mathbf{z}(t)), & \forall\, t \in (0,T], \\ \mathbf{z}(0) = \mathbf{z}_0 \in (0,+\infty)^m, \end{cases} \tag{2.13}$$

is continuous.

Proof of Proposition 2.2. We note that, for $i = 1, \dots, m$, we can write

$$J_i(v, \mathbf{w}, \log z_i) = J_i(v, \mathbf{w}, 0) + \frac{J_i(v, \mathbf{w}, \log z_i) - J(v, \mathbf{w}, 0)}{\log z_i} \log z_i. \tag{2.14}$$

Owing to (1.14c), there exists a constant $\bar{L} > 0$, depending on L_v, such that $\forall\,(v, \mathbf{w}) \in \mathbb{R} \times [0,1]^k$

$$\begin{aligned} |J_i(v, \mathbf{w}, 0)| &\leq \left| \frac{J_i(v, \mathbf{w}, 0) - J_i(0, \mathbf{w}, 0)}{v} v \right| + |J_i(0, \mathbf{w}, 0)| \\ &\leq \bar{L}(1 + |v|), \end{aligned} \tag{2.15}$$

by (1.14b) there exist constants $\underline{G}, \overline{G} > 0$ such that

$$\underline{G} \leq \frac{J_i(v, \mathbf{w}, \log z_i) - J(v, \mathbf{w}, 0)}{\log z_i} \leq \overline{G}, \quad \forall\, (v, \mathbf{w}, z_i) \in \mathbb{R} \times [0,1]^k \times (0, +\infty), \tag{2.16}$$

and by hypothesis (1.20) there exists a constant $\Lambda > 0$ such that

$$|\mathbf{H}(v, \mathbf{w}, \mathbf{z})| \leq \Lambda(1 + |v| + |\mathbf{z}|), \quad \forall\, (v, \mathbf{w}, \mathbf{z}) \in \mathbb{R} \times [0,1]^k \times (0, +\infty)^m. \tag{2.17}$$

By Lemma 2.2, there exists $\mathcal{N} \subset \Lambda$ such that $\lambda(\mathcal{N}) = 0$, and $\forall\, x \in \Lambda \backslash \mathcal{N}$, $v(x, \cdot)$, $\mathbf{w}(x, \cdot)$ have a representative in $C^0([0,T])$. Thus, we can simplify the following calculations, considering x fixed in $\Lambda \backslash \mathcal{N}$. Our estimates will then hold only for a.e. $x \in \Lambda$. Since $\mathbf{G}$ is locally Lipschitz continuous in $(0, +\infty)$, local existence and uniqueness for the maximal solution are straightforward. In order to get existence and uniqueness on the whole interval $[0,T]$, we must find an estimate for $\log z_i$ in $L^\infty(0,T)$ (estimate II). The measurability of $\mathbf{z}$ follows from the Carathéodory property of $\mathbf{G}$, like in the previous subsection. The proof of Proposition 2.2 relies on four estimates.

Estimate I. We now prove:

$$|\mathbf{z}(t)| \leq C \left(1 + |\mathbf{z}_0| + \|v\|_{L^2(0,t)} \right).$$

We get a first a priori estimate by multiplying equation (2.9) (scalarly in $\mathbb{R}^m$) by $\mathbf{z}(t)$:

$$\frac{d\mathbf{z}}{dt}(t)\cdot\mathbf{z}(t) = -\mathbf{J}(v,\mathbf{w},\ \mathbf{log\,z})(t)\cdot\mathbf{z}(t) + \mathbf{H}(v,\mathbf{w},\mathbf{z})(t)\cdot\mathbf{z}(t),$$

and using (2.17), we get

$$\frac{1}{2}\frac{d}{dt}|\mathbf{z}(t)|^2 \le -\sum_{i=1}^{m} J_i(v(t),\mathbf{w}(t),\log z_i(t))z_i(t) + \Lambda(1+|v(t)|+|\mathbf{z}(t)|)|\mathbf{z}(t)|,$$

using decomposition (2.14) and the following estimates (2.15), (2.16), (2.17), we find

$$\frac{1}{2}\frac{d}{dt}|\mathbf{z}(t)|^2 \le \sum_{i=1}^{m}\left(\bar{L}(1+|v(t)|)|z_i(t)| + \overline{G}[\log z_i(t)z_i(t)]^-\right) + \Lambda(1+|v(t)|+|\mathbf{z}(t)|)|\mathbf{z}(t)|,$$

Since $z\log z \ge -e^{-1},\ \forall\ z>0$, by Cauchy's inequality we get

$$\frac{1}{2}\frac{d}{dt}|\mathbf{z}(t)|^2 \le \frac{m\overline{G}}{e} + \frac{1}{2}\bar{L}^2(1+|v(t)|)^2 + \frac{1}{2}|\mathbf{z}(t)|^2 +$$

$$+\frac{\Lambda^2}{2}(1+|v(t)|)^2 + \frac{1}{2}|\mathbf{z}(t)|^2 + \Lambda|\mathbf{z}(t)|^2.$$

By Gronwall's Lemma we obtain

$$|\mathbf{z}(t)|^2 \le e^{C_1 t}\left[|\mathbf{z}(0)|^2 + C_2\int_0^t (1+|v(s)|)^2 ds\right], \quad \forall\ t\in[0,T],$$

where $C_1 := 2(\Lambda+1)$, and C_2 depends on $m, \bar{L}, \overline{G}, \Lambda$. We conclude that there exists a constant $C_3>0$, dependent on $m, \bar{L}, \overline{G}, \Lambda$, and T such that

$$|\mathbf{z}(t)| \le C_3\left(1+|\mathbf{z}_0| + \|v\|_{L^2(0,t)}\right), \quad \forall\ t\in[0,T]. \tag{2.18}$$

Estimate II. Now we can show that each z_i is far from zero, or, more precisely, that

$$z(t) \ge \exp\left[-C(1+|\mathbf{z}_0| + \|v\|_{C^0(0,t)})\right] > 0, \quad \forall\ t\in[0,T]. \tag{2.19}$$

For sake of simplicity we shall suppress index i from calculations and carry on this part of the proof for the generic z instead of z_i, moreover, since we now want to show (2.19) and $\exp[-C(1+|\mathbf{z}_0|+\|v\|_{C^0(0,t)})] < 1$, we can limit the study to $z<1$.

We consider the equation

$$\frac{dz}{dt} = -J(v,\mathbf{w},\log z) + H(v,\mathbf{w},\mathbf{z}),$$

Again, by (2.14, ..., 2.17) we find

$$\frac{dz}{dt} \geq -\bar{L}(1+|v|) - \underline{G}\log z - \Lambda(1+|v|+|\mathbf{z}|). \tag{2.20}$$

Owing to estimate (2.18), if

$$\underline{G}\log z(t) \leq -\bar{L}\left(1+\|v\|_{C^0(0,t)}\right) - \Lambda\left(1+\|v\|_{C^0(0,t)} + C_3(1+|\mathbf{z}_0|+\|v\|_{L^2(0,t)})\right)$$

then

$$\frac{dz}{dt}(t) \geq 0.$$

Since

$$\|v\|_{L^2(0,t)} \leq \sqrt{T}\|v\|_{C^0(0,t)}, \quad \forall\, t \in [0,T]$$

there exist a constant $C_4 > 0$, depending on $m, \bar{L}, \underline{G}, \overline{G}, \Lambda, T$ such that

$$z(t) \geq \exp\left[-C_4\left(1+|\mathbf{z}_0|+\|v\|_{C^0(0,t)}\right)\right] > 0, \quad \forall\, t \in [0,T].$$

We need two more estimates.

Estimate III. We are going to show that

$$\left\|\frac{dz}{dt}\right\|_{L^2(0,t)} \leq C\left(1+C(z_0)+\|v\|_{L^2(0,t)}\right), \quad \forall\, t \in [0,T].$$

We multiply the i-th equation of (2.9) by dz_i/dt, (and we suppress index i), obtaining

$$\left(\frac{dz}{dt}(t)\right)^2 = -J(v(t),\mathbf{w}(t),\log z(t))\frac{dz}{dt}(t) + H(v(t),\mathbf{w}(t),\mathbf{z}(t))\frac{dz}{dt}(t) =$$

$$= -\left[\frac{J(v(t),\mathbf{w}(t),\log z(t)) - J(v(t),\mathbf{w}(t),0)}{\log z(t)}\right]\log z(t)\frac{dz}{dt}(t) +$$

$$+[J(v(t),\mathbf{w}(t),0) + H(v(t),\mathbf{w}(t),\mathbf{z}(t))]\frac{dz}{dt}(t). \tag{2.21}$$

Let

$$\Phi(t) := \left[\frac{J(v(t),\mathbf{w}(t),\log z(t)) - J(v(t),\mathbf{w}(t),0)}{\log z(t)}\right],$$

by (2.16), we have that

$$\underline{G} \leq \Phi(t) \leq \overline{G}, \qquad \forall\, t \in [0,T]. \tag{2.22}$$

We note that
$$\frac{d}{dt}[z(t)\log z(t) - z(t)] = \frac{dz}{dt}(t)\log z(t).$$
We divide equation (2.21) by $\Phi(t)$ and we integrate between 0 and t
$$\int_0^t \frac{1}{\Phi(s)}\left(\frac{dz}{ds}(s)\right)^2 ds = -[z(t)\log z(t) - z(t) - z(0)\log z(0) + z(0)] +$$
$$+\int_0^t \left(\frac{J(v(s),\mathbf{w}(s),0) + H(v(s),\mathbf{w}(s),\mathbf{z}(s))}{\Phi(s)}\right)\frac{dz}{ds}(s)\, ds.$$
Since $z\log z - z \geq -1,\ \forall\, z > 0$, using (2.22), we get
$$\frac{1}{\overline{\overline{G}}}\int_0^t \left(\frac{dz}{ds}(s)\right)^2 ds \leq z(0)\log z(0) - z(0) + 1 +$$
$$+\int_0^t \underline{G}^{-1}(|J(v(s),\mathbf{w}(s),0)| + |H(v(s),\mathbf{w}(s),\mathbf{z}(s))|)\left|\frac{dz}{ds}(s)\right| ds.$$
By (2.15) and (2.17) we get
$$\frac{1}{\overline{\overline{G}}}\int_0^t \left(\frac{dz}{ds}(s)\right)^2 ds \leq z(0)\log z(0) - z(0) + 1 + \frac{\bar{L}+\Lambda}{\underline{G}}\int_0^t (1 + |v(s)| + |\mathbf{z}(s)|)\left|\frac{dz}{ds}(s)\right| ds,$$
and by Cauchy inequality and estimate I (2.18) we find
$$\int_0^t \left(\frac{dz}{ds}(s)\right)^2 ds \leq C_5\Bigg(1 + z(0)\log z(0) - z(0) +$$
$$+\int_0^t \left(1 + |v(s)| + |\mathbf{z}_0| + \|v\|_{L^2(0,t)}\right)^2 ds,\Bigg)$$
and we conclude that there exists $C_6 > 0$ such that
$$\int_0^t \left(\frac{dz}{ds}(s)\right)^2 ds \leq C_6\left(1 + |z(0)\log z(0) - z(0)| + |\mathbf{z}_0|^2 + \|v\|^2_{L^2(0,t)}\right), \quad \forall\, t \in [0,T]. \tag{2.23}$$
This estimate can be immediately used to get an equivalent estimate for $\log z(t)$.

Estimate IV.
We have
$$J(v,\mathbf{w},\log z) = H(v,\mathbf{w},\mathbf{z}) - \frac{dz}{dt},$$
$$\left(\frac{J(v,\mathbf{w},\log z) - J(v,\mathbf{w},0)}{\log z}\right)\log z = H(v,\mathbf{w},\mathbf{z}) - \frac{dz}{dt} - J(v,\mathbf{w},0),$$

$$\left(\frac{J(v,\mathbf{w},\log z)-J(v,\mathbf{w},0)}{\log z}\right)^2(\log z)^2\leq 3\left(H^2(v,\mathbf{w},\mathbf{z})+\left(\frac{dz}{dt}\right)^2+J(v,\mathbf{w},0)^2\right),$$

$$\underline{G}^2(\log z)^2\leq 3\left(H^2(v,\mathbf{w},\mathbf{z})+\left(\frac{dz}{dt}\right)^2+J(v,\mathbf{w},0)^2\right),$$

$$\int_0^t\underline{G}^2(\log z)^2\ ds\leq 3\int_0^t\left(H^2(v,\mathbf{w},\mathbf{z})+\left(\frac{dz}{dt}\right)^2+J(v,\mathbf{w},0)^2\right)\ ds,$$

therefore, by (2.17) and (2.18), (2.23), (2.15), we find

$$\int_0^t(\log z(s))^2\ ds\leq C\left(1+|z(0)\log z(0)-z(0)|+|\mathbf{z}_0|^2+\|v\|^2_{L^2(0,t)}\right).$$

□

Proof of Lemma 2.3. Let $v,v_n\in C^0([0,T])$, $\mathbf{w},\mathbf{w}_n\in C^0([0,T])^k$. We denote by z,z_n the corresponding solutions of system (2.13). We take the difference between the two equations

$$\frac{dz_n}{dt}-\frac{dz}{dt}=-[J(v_n,\mathbf{w}_n,\log z_n)-J(v,\mathbf{w},\log z)]+H(v_n,\mathbf{w}_n,\mathbf{z}_n)-H(v,\mathbf{w},\mathbf{z}),$$

we sum and subtract $J(v_n,\mathbf{w}_n,\log z)$

$$\begin{aligned}\frac{dz_n}{dt}-\frac{dz}{dt}\ =\ & -[J(v_n,\mathbf{w}_n,\log z_n)-J(v_n,\mathbf{w}_n,\log z)]+ && (2.24a)\\ & -[J(v_n,\mathbf{w}_n,\log z)-J(v,\mathbf{w},\log z)]+ && (2.24b)\\ & +H(v_n,\mathbf{w}_n,\mathbf{z}_n)-H(v,\mathbf{w},\mathbf{z}), && (2.24c)\end{aligned}$$

we multiply by z_n-z and, since *log* is monotone increasing and the incremental quotient is positive by (1.14b), for the term (2.24a) we have

$$\frac{J(v_n,\mathbf{w}_n,\log z_n)-J(v_n,\mathbf{w}_n,\log z)}{\log z_n-\log z}(\log z_n-\log z)(z_n-z)\geq 0. \tag{2.25}$$

In order to deal with (2.24b), we remark that since J is locally Lipschitz continuous (1.14a), there exists a nonnegative function
$\eta\in C^0(\mathbb{R}^2\times(0,+\infty))$ such that

$$|J(\nu_2,\boldsymbol{\omega}_2,\zeta)-J(\nu_1,\boldsymbol{\omega}_1,\zeta)|\leq\eta(\nu_1,\nu_2,\zeta)(|\nu_2-\nu_1|+|\boldsymbol{\omega}_2-\boldsymbol{\omega}_1|),$$

$\forall\,\nu_1,\nu_2\in\mathbb{R}$, $\forall\,\boldsymbol{\omega}_1,\boldsymbol{\omega}_2\in[0,1]^k$, $\forall\,\zeta\in\mathbb{R}$. Hence, using (2.25) and (2.17), we obtain

$$\frac{1}{2}\frac{d}{dt}|z_n-z|^2\leq\eta(v,v_n,\log z)(|v_n-v|+|\mathbf{w}_n-\mathbf{w}|)|z_n-z|+$$

$$+\Lambda\Big(|v_n - v| + |\mathbf{w}_n - \mathbf{w}| + |\mathbf{z}_n - \mathbf{z}|\Big)|z_n - z|.$$

Summing up the contributions of the m components of $\mathbf{z}$ and integrating between 0 and t we obtain

$$\frac{1}{2}|\mathbf{z}_n(t) - \mathbf{z}(t)|^2 \leq \int_0^t |\eta(v, v_n,\, \mathbf{log\, z})|(|v_n - v| + |\mathbf{w}_n - \mathbf{w}|)|\mathbf{z}_n - \mathbf{z}|\; ds +$$

$$+\sqrt{m}\Lambda \int_0^t \Big(|v_n - v| + |\mathbf{w}_n - \mathbf{w}| + |\mathbf{z}_n - \mathbf{z}|\Big)|\mathbf{z}_n - \mathbf{z}|\; ds,$$

where $\eta(v, v_n,\, \mathbf{log\, z})$ denotes the vector of components $\eta_i(v, v_n, \log z_i)$, and by Cauchy's inequality

$$|\mathbf{z}_n(t) - \mathbf{z}(t)|^2 \leq M + L \int_0^t |\mathbf{z}_n(s) - \mathbf{z}(s)|^2\; ds, \tag{2.26}$$

where

$$M := \int_0^T \Big(|\eta(v, v_n,\, \mathbf{log\, z})|^2 + m\Lambda^2\Big)\, (|v_n - v| + |\mathbf{w}_n - \mathbf{w}|)^2 ds, \tag{2.27}$$

and $L = 2(\sqrt{m}\Lambda + 1)$.

Therefore, applying Gronwall Lemma to equation (2.26), we get

$$|\mathbf{z}_n(t) - \mathbf{z}(t)|^2 \leq M e^{LT}, \quad \forall\, t \in [0, T]. \tag{2.28}$$

Now let $\{v_n\}_{n\in\mathbb{N}}$, v, $\{\mathbf{w}_n\}_{n\in\mathbb{N}}$, $\mathbf{w}$, be such that

$$v_n \to v \quad \text{in } C^0([0,T]), \qquad \mathbf{w}_n \to \mathbf{w} \quad \text{in } C^0([0,T])^m.$$

We remark that $\mathbf{z}$ is continuous by Proposition 2.2, and $\mathbf{log}(\mathbf{z})$ is continuous and bounded owing to estimate (2.11), moreover, since $v_n \to v$ in $C^0([0,T])$, there exists a compact set $K \subset \mathbb{R}^{2+m}$ such that

$$(v(t), v_n(t),\, \mathbf{log\, z}(t)) \in K, \quad \forall\, t \in [0,T],\ \forall\, n \in \mathbb{N}.$$

Let

$$\bar{\eta} := \max_{(\nu_1,\nu_2,\zeta)\in K} |\eta(\nu_1, \nu_2, \zeta)|^2 < +\infty.$$

By estimates (2.27), (2.28), we obtain

$$\max_{t\in[0,T]} |\mathbf{z}_n(t) - \mathbf{z}(t)|^2 \leq (\bar{\eta} + m\Lambda^2) \int_0^T (|v_n(s) - v(s)| + |\mathbf{w}_n(s) - \mathbf{w}(s)|)^2 ds, \quad \forall\, n \in \mathbb{N},$$

and therefore

$$\mathbf{z}_n \to \mathbf{z} \quad \text{in } C^0([0,T])^m.$$

□

Chapter 3

The passive model

In this chapter we study the microscopic and the macroscopic problems endowed with a *passive* model for the description of the ionic currents, i.e. we simply consider I_{ion} as a known function, instead of a function of $v, \mathbf{w}, \mathbf{z}$, and consequently we drop the ODE systems for $\mathbf{w}$ and $\mathbf{z}$. This approach allows us to conduct a compact study of both models, showing a common variational structure, proving existence and uniqueness of solutions. The second step of the fixed point scheme is thus made up of these results, which combined with the estimates obtained in Chapter 2 will yield existence (and uniqueness in the macroscopic case) for a solution of the complete models endowed with the *dynamic* ionic currents. For sake of simplicity, we also choose Neumann homogeneous boundary conditions for both models, but we remark that also Dirichlet or Neumann nonhomogeneous conditions constitute a possible choice. We recall the notation for the space-time domains:

$$\begin{array}{ll} Q_{i,e} := \Omega_{i,e} \times (0,T) & Q := \Omega \times (0,T), \\ \Sigma_{i,e} := \Gamma_{i,e} \times (0,T) & \Sigma := \Gamma \times (0,T). \end{array}$$

This is the *passive* microscopic problem:

Problem *(m-passive)*. Given

$$i^s_{i,e} : Q_{i,e} \to \mathbb{R}, \qquad v_0 : \Gamma \to \mathbb{R},$$
$$I_{ion} \in L^2(0,T; L^2(\Gamma)),$$

we seek

$$u_{i,e} : Q_{i,e} \to \mathbb{R}, \qquad v := u_i - u_e : \Sigma \to \mathbb{R},$$

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

$$\begin{array}{rcll} -\mathrm{div}(\sigma_{i,e} \nabla u_{i,e}) & = & i^s_{i,e} & \text{on } Q_{i,e}, \\ \sigma_i \nabla u_i \cdot \nu_i & = & 0 & \text{on } \Sigma_i, \\ \sigma_e \nabla u_e \cdot \nu_e & = & 0 & \text{on } \Sigma_e, \end{array} \tag{3.1}$$

the evolution system on the surface Σ and the initial datum

$$
\begin{aligned}
C_m \partial_t v + I_{ion} &= -\sigma_i \nabla u_i \cdot \nu_i \qquad \text{on } \Sigma, && (3.2a)\\
C_m \partial_t v + I_{ion} &= \sigma_e \nabla u_e \cdot \nu_e \qquad \text{on } \Sigma, && (3.2b)\\
v(x,0) &= v_0(x) \qquad \text{on } \Gamma. && (3.2c)
\end{aligned}
$$

And this is the *passive* macroscopic bidomain problem:
Problem *(M-passive)*. Given

$$I^s_{i,e} : Q \to \mathbb{R}, \qquad V_0 : \Omega \to \mathbb{R},$$

$$I_{ion} \in L^2(0,T;L^2(\Omega)),$$

we seek

$$u_{i,e} : Q \to \mathbb{R}, \qquad v := u_i - u_e : Q \to \mathbb{R},$$

satisfying the reaction-diffusion system

$$
\begin{aligned}
\partial_t v + I_{ion} &= \operatorname{div}(M_i \nabla u_i) + I^s_i \qquad \text{on } Q, && (3.3a)\\
\partial_t v + I_{ion} &= -\operatorname{div}(M_e \nabla u_e) - I^s_e \qquad \text{on } Q, && (3.3b)\\
M_i \nabla u_i \cdot \nu &= 0 \qquad \text{on } \partial\Omega \times (0,T), && (3.3c)\\
M_e \nabla u_e \cdot \nu &= 0 \qquad \text{on } \partial\Omega \times (0,T), && (3.3d)\\
v(x,0) &= V_0(x) \qquad \text{on } \Omega. && (3.3e)
\end{aligned}
$$

We observe that if (u_i, u_e) is a solution, then the couple $(u_i + c(t), u_e + c(t))$ is still a solution for every time-depending function c, therefore we determine a reference value for the potential u_e by imposing

$$\int_{\Omega_e} u_e(x)\, dx = 0 \qquad \text{and} \qquad \int_{\Omega} u_e(x)\, dx = 0, \tag{3.4}$$

respectively, in the micro and macroscopic setting.

The variational formulation of the passive models and the well posedness for the resulting problems follow directly from [21], where the ionic current I_{ion} is described using Fitzhugh-Nagumo simplification (1.21). This choice leads to the presence of a nonlinear operator, precisely to a linear perturbation of the subdifferential of a proper, convex, lower semicontinuous function. The *passive* models can be viewed as a particular case, and all the results and estimates directly apply. In the following section we recall the variational formulation and the results obtained in [21], giving an adaptation of the proof.

3.1 Variational formulation for the microscopic model

Our next step will be to write a variational formulation for system (3.1) and equations (3.2a), (3.2b), (3.2c). We need to choose the functional spaces in which we will set the equations and seek a solution. Let us assume that for a.e. $t \in]0, T[$

$$i^s_{i,e}(\cdot,t) \in L^2(\Omega_{i,e}), \qquad I_{ion}(\cdot,t) \in L^2(\Gamma), \tag{3.5}$$

$$u_e(\cdot,t),\, \partial_t u_e(\cdot,t) \in H^1(\Omega_e), \qquad u_i(\cdot,t),\, \partial_t u_i(\cdot,t) \in H^1(\Omega_i),$$

so that the trace operator $u_{i,e} \mapsto u_{i,e|\Gamma}$ is well defined and continuous from $H^1(\Omega_{i,e})$ in $H^{1/2}(\Gamma)$ (see e.g. [47]). From now on we shall use the simplified notation $v := u_i - u_e$ instead of $u_{i|\Gamma} - u_{e|\Gamma}$. We choose the test functions

$$\hat{u}_e \in H^1(\Omega_e), \quad \hat{u}_i \in H^1(\Omega_i), \quad \text{denote} \quad \hat{v} := \hat{u}_i - \hat{u}_e \in H^{1/2}(\Gamma),$$

and multiply equations (3.2a), (3.2b) by the trace of $\hat{u}_i$ and $-\hat{u}_e$ respectively. We denote by $\mathscr{H}^2$ the usual bidimensional Haussdorff measure. Integrating on Γ and adding the two equations we get

$$\int_\Gamma (\partial_t v)\hat{v}\, d\mathscr{H}^2 + \int_\Gamma (\sigma_i \nabla u_i \cdot \nu_i)\hat{u}_i\, d\mathscr{H}^2 + \int_\Gamma (\sigma_e \nabla u_e \cdot \nu_e)\hat{u}_e\, d\mathscr{H}^2 + \int_\Gamma I_{ion}\hat{v}\, d\mathscr{H}^2 = 0. \tag{3.6}$$

The second integral can be written as

$$\int_\Gamma (\sigma_i \nabla u_i \cdot \nu_i)\hat{u}_i\, d\mathscr{H}^2 = {}_{H^{-1/2}(\Gamma)}\langle \sigma_i \nabla u_i \cdot \nu_i \,,\, \hat{u}_i \rangle_{H^{1/2}(\Gamma)} .$$

Using the Green formula we get

$$\int_\Gamma (\sigma_i \nabla u_i \cdot \nu_i)\hat{u}_i\, d\mathscr{H}^2 = \int_{\Omega_i} (\sigma_i \nabla u_i \cdot \nabla \hat{u}_i + \operatorname{div}(\sigma_i \nabla u_i)\hat{u}_i)\, dx$$

and, in the same way, we can write the third integral of (3.6) as

$$\int_\Gamma (\sigma_e \nabla u_e \cdot \nu_e)\hat{u}_e\, d\mathscr{H}^2 = \int_{\Omega_e} (\sigma_e \nabla u_e \cdot \nabla \hat{u}_e + \operatorname{div}(\sigma_e \nabla u_e)\hat{u}_e)\, dx,$$

which are justified by the usual arguments of [47]. We now write (3.6) using the previous calculations and (3.1)

$$\int_\Gamma (\partial_t v)\hat{v}\, d\mathscr{H}^2 + \sum_{i,e} \int_{\Omega_{i,e}} \sigma_{i,e} \nabla u_{i,e} \cdot \nabla \hat{u}_{i,e}\, dx + \int_\Gamma I_{ion}\hat{v}\, d\mathscr{H}^2 = \sum_{i,e} \int_{\Omega_{i,e}} i^s_{i,e} \hat{u}_{i,e}\, dx. \tag{3.7}$$

Let us analyze the particular structure of equation (3.7).
We denote by boldface letters $\mathbf{u}$ and $\hat{\mathbf{u}}$ the couples of functions (u_i, u_e), $(\hat{u}_i, \hat{u}_e)$ and we introduce the Hilbert space

$$\mathbf{V} := H^1(\Omega_i) \times H^1_*(\Omega_e), \qquad H^1_*(\Omega_e) := \left\{ u \in H^1(\Omega_e) \ : \ \int_{\Omega_e} u(x)\ dx = 0 \right\},$$

endowed with the norm

$$\|\mathbf{u}\|_{\mathbf{V}} = (\|u_i\|^2_{H^1(\Omega_i)} + \|u_e\|^2_{H^1(\Omega_e)})^{\frac{1}{2}},$$

and the bilinear forms

$$b(\mathbf{u}, \hat{\mathbf{u}}) := \int_\Gamma (u_i - u_e)(\hat{u}_i - \hat{u}_e)\ d\mathscr{H}^2,$$

$$a(\mathbf{u}, \hat{\mathbf{u}}) := \sum_{i,e} \int_{\Omega_{i,e}} \sigma_{i,e} \nabla u_{i,e} \cdot \nabla \hat{u}_{i,e}\ dx,$$

defined $\forall\ \mathbf{u}, \hat{\mathbf{u}} \in \mathbf{V}$. Denoting by $\mathbf{V}'$ the dual space of $\mathbf{V}$, and by $\langle \cdot, \cdot \rangle$ the pairing between $\mathbf{V}'$ and $\mathbf{V}$, we can associate to the bilinear forms a, b the linear continuous operators $A, B : \mathbf{V} \to \mathbf{V}'$ defined by

$$\langle A\mathbf{u}, \hat{\mathbf{u}} \rangle := a(\mathbf{u}, \hat{\mathbf{u}}), \qquad \langle B\mathbf{u}, \hat{\mathbf{u}} \rangle := b(\mathbf{u}, \hat{\mathbf{u}}), \qquad \forall\ \mathbf{u}, \hat{\mathbf{u}} \in \mathbf{V}. \tag{3.8}$$

We introduce the family of linear functionals $\{\mathcal{I}_{ion}(t)\}_{t \in]0,T[} \in \mathbf{V}'$

$$\langle \mathcal{I}_{ion}(t), \hat{\mathbf{u}} \rangle := \int_\Gamma I_{ion}(x,t)(\hat{u}_i(x) - \hat{u}_e(x))\ d\mathscr{H}^2, \tag{3.9}$$

Assuming (3.5) and $v_0 \in L^2(\Gamma)$ we can associate to the remaining part of the right side member in (3.7) the family of linear functionals $\{\mathbf{L}(t)\}_{t \in]0,T[} \in \mathbf{V}'$, and to the initial data the linear functional $\ell^0 \in \mathbf{V}'$ defined by

$$\langle \mathbf{L}(t), \hat{\mathbf{u}} \rangle \ := \ \sum_{i,e} \int_{\Omega_{i,e}} i^s_{i,e} \hat{u}_{i,e}\, dx, \tag{3.10}$$

$$\langle \ell^0, \hat{\mathbf{u}} \rangle \ := \ \int_\Gamma v_0(\hat{u}_i - \hat{u}_e)\ d\mathscr{H}^2. \tag{3.11}$$

Now we have all the elements to give a precise statement of the problem.

Problem (m2). Given

$$i^s_{i,e} \in L^2(0,T; L^2(\Omega_{i,e})), \qquad I_{ion} \in L^2(0,T; L^2(\Gamma)),$$

$A, B, \mathcal{I}_{ion}(t), \mathbf{L}(t), \ell^0$, defined in (3.8),...,(3.11), we look for

$$\mathbf{u} \in L^2(0,T;\mathbf{V}), \text{ with } B\mathbf{u} \in H^1(0,T;\mathbf{V}'),$$

which solves the evolution system

$$\begin{cases} (B\mathbf{u}(t))' + A\mathbf{u}(t) + \mathcal{I}_{ion}(t) = \mathbf{L}(t), & \text{in } \mathbf{V}' \quad \text{a.e. in }]0,T[, \\ B\mathbf{u}(0) = \ell^0 & \text{in } \mathbf{V}'. \end{cases} \tag{3.12}$$

We can now state the result concerning this section

Proposition 3.1. *If*

$$i^s_{i,e} \in H^1(0,T;L^2(\Omega_{i,e})), \qquad I_{ion} \in L^2(0,T;L^2(\Gamma)), \qquad v_0 \in H^{1/2}(\Gamma),$$

there exists a unique solution $\mathbf{u}$ *of* ***Problem (m2)***,

$$\begin{aligned} &\mathbf{u} \in C^0([0,T];\mathbf{V}), \\ &B\mathbf{u} = v \in H^1(0,T;L^2(\Gamma)) \cap C^0([0,T];H^{1/2}(\Gamma)), \end{aligned}$$

we have the a priori estimates

$$\|\mathbf{u}\|_{L^2(0,T;\mathbf{V})} \leq C\Big(\|v_0\|_{L^2(\Gamma)} + \|I_{ion}\|_{L^2(\Sigma)} + \|i^s_{i,e}\|_{L^2(Q_{i,e})}\Big), \tag{3.13}$$

$$\max_{t\in[0,T]} \|v(t)\|_{L^2(\Gamma)} \leq C\Big(\|v_0\|_{L^2(\Gamma)} + \|I_{ion}\|_{L^2(\Sigma)} + \|i^s_{i,e}\|_{L^2(Q_{i,e})}\Big), \tag{3.14}$$

$$\max_{t\in[0,T]} \|\mathbf{u}(t)\|_{\mathbf{V}} \leq C\Big(\|v_0\|_{H^{1/2}(\Gamma)} + \|I_{ion}\|_{L^2(\Sigma)} + \|i^s_{i,e}\|_{H^1(0,T;L^2(\Omega_{i,e}))}\Big) \tag{3.15}$$

$$\|\partial_t v\|_{L^2(0,T;L^2(\Gamma))} \leq C\Big(\|v_0\|_{H^{1/2}(\Gamma)} + \|I_{ion}\|_{L^2(\Sigma)} + \|i^s_{i,e}\|_{H^1(0,T;L^2(\Omega_{i,e}))}\Big) \tag{3.16}$$

and, if $v^{(1)}, v^{(2)}$ *are the solutions corresponding to data* $I^{(1)}_{ion}, I^{(2)}_{ion}$, *it holds:*

$$\|v^{(1)}(t) - v^{(2)}(t)\|^2_{L^2(\Gamma)} \leq C\|I^{(1)}_{ion} - I^{(2)}_{ion}\|^2_{L^2(0,t;L^2(\Gamma))}, \quad \forall\, t \in [0,T]. \tag{3.17}$$

3.2 Variational formulation for the macroscopic bidomain model

Arguing as in the previous Section, let be given

$$I_{ion}, I^s_i, I^s_e \in L^2(Q), \tag{3.18}$$

we choose the test functions

$$\hat{u}_e \in H^1(\Omega), \quad \hat{u}_i \in H^1(\Omega), \quad \text{denote} \quad \hat{v} := \hat{u}_i - \hat{u}_e \in H^1(\Omega),$$

and multiply equations (3.3a), (3.3b) by $\hat{u}_i$ and $-\hat{u}_e$ respectively. Integrating on Ω, using the boundary conditions after integration by parts and adding the two equations we get

$$\int_\Omega (\partial_t v)\hat{v}\ dx + \sum_{i,e} \int_\Omega M_{i,e} \nabla u_{i,e} \cdot \nabla \hat{u}_{i,e}\, dx + \int_\Omega I_{ion} \hat{v}\, dx = \sum_{i,e} \int_\Omega I^s_{i,e} \hat{u}_{i,e}\, dx. \quad (3.19)$$

we introduce the Hilbert space

$$\mathbf{V} := H^1(\Omega) \times H^1_*(\Omega), \qquad H^1_*(\Omega) := \left\{ u \in H^1(\Omega)\ :\ \int_\Omega u(x)\ dx = 0 \right\},$$

endowed with the norm

$$\|\mathbf{u}\|_{\mathbf{V}} = (\|u_i\|^2_{H^1(\Omega)} + \|u_e\|^2_{H^1(\Omega)})^{\frac{1}{2}},$$

and the bilinear forms

$$b(\mathbf{u}, \hat{\mathbf{u}}) := \int_\Omega (u_i - u_e)(\hat{u}_i - \hat{u}_e)\, dx,$$

$$a(\mathbf{u}, \hat{\mathbf{u}}) := \sum_{i,e} \int_\Omega M_{i,e} \nabla u_{i,e} \cdot \nabla \hat{u}_{i,e}\ dx,$$

defined $\forall\ \mathbf{u}, \hat{\mathbf{u}} \in \mathbf{V}$. Denoting by $\mathbf{V}'$ the dual space of $\mathbf{V}$, and by $\langle \cdot, \cdot \rangle$ the pairing between $\mathbf{V}'$ and $\mathbf{V}$, we can associate to the bilinear forms a, b the linear continuous operators $A, B : \mathbf{V} \to \mathbf{V}'$ defined by

$$\langle A\mathbf{u}, \hat{\mathbf{u}} \rangle := a(\mathbf{u}, \hat{\mathbf{u}}), \qquad \langle B\mathbf{u}, \hat{\mathbf{u}} \rangle := b(\mathbf{u}, \hat{\mathbf{u}}), \qquad \forall\ \mathbf{u}, \hat{\mathbf{u}} \in \mathbf{V}. \quad (3.20)$$

We introduce the family of linear functionals $\{\mathcal{I}_{ion}(t)\}_{t \in]0,T[} \in \mathbf{V}'$

$$\langle \mathcal{I}_{ion}(t), \hat{\mathbf{u}} \rangle := \int_\Omega I_{ion}(x,t)(\hat{u}_i(x) - \hat{u}_e(x))\, dx, \quad (3.21)$$

Assuming (3.18) and $V_0 \in L^2(\Omega)$, we can associate to the right side member in (3.19) the family of linear functionals $\{\mathbf{L}(t)\}_{t \in]0,T[} \in \mathbf{V}'$, and to the initial data the linear functional $\ell^0 \in \mathbf{V}'$ defined by

$$\langle \mathbf{L}(t), \hat{\mathbf{u}} \rangle \ := \ \sum_{i,e} \int_\Omega I^s_{i,e} \hat{u}_{i,e}\, dx, \quad (3.22)$$

$$\langle \ell^0, \hat{\mathbf{u}} \rangle \ := \ \int_\Omega V_0 (\hat{u}_i - \hat{u}_e)\, dx. \quad (3.23)$$

In perfect analogy with the variational formulation of the microscopic problem *m-passive*, we can now give the precise variational formulation of system (3.3a,...,3.4).

Problem (M-var). Given

$$I^s_{i,e}, I_{ion} \in L^2(Q), \qquad V_0 \in L^2(\Omega),$$

$A, B, \mathcal{I}_{ion}(t), \mathbf{L}(t), \ell^0$, defined in (3.20),…,(3.23), we look for

$$\mathbf{u} \in L^2(0,T;\mathbf{V}), \text{ with } B\mathbf{u} \in H^1(0,T;\mathbf{V}'),$$

which solves the evolution system

$$\begin{cases} (B\mathbf{u}(t))' + A\mathbf{u}(t) + \mathcal{I}_{ion}(t) = \mathbf{L}(t), & \text{in } \mathbf{V}' \quad \text{a.e. in }]0,T[, \\ B\mathbf{u}(0) = \ell^0 & \text{in } \mathbf{V}'. \end{cases} \tag{3.24}$$

Proposition 3.2. *If*

$$I^s_{i,e} \in H^1(0,T;L^2(\Omega)), \qquad I_{ion} \in L^2(Q), \qquad V_0 \in H^1(\Omega),$$

there exists a unique solution $\mathbf{u}$ *of Problem (**M-var**),*

$$\begin{aligned} &\mathbf{u} \in C^0([0,T];\mathbf{V}), \\ &B\mathbf{u} = v \in H^1(0,T;L^2(\Omega)) \cap C^0([0,T];H^1(\Omega)), \end{aligned}$$

we have the a priori estimates

$$\|\mathbf{u}\|_{L^2(0,T;\mathbf{V})} \le C\left(\|V_0\|_{L^2(\Omega)} + \|I_{ion}\|_{L^2(Q)} + \|I^s_{i,e}\|_{L^2(Q)}\right),$$

$$\max_{t\in[0,T]} \|v(t)\|_{L^2(\Omega)} \le C\left(\|V_0\|_{L^2(\Omega)} + \|I_{ion}\|_{L^2(Q)} + \|I^s_{i,e}\|_{L^2(Q)}\right),$$

$$\max_{t\in[0,T]} \|\mathbf{u}(t)\|_{\mathbf{V}} \le C\left(\|V_0\|_{H^1(\Omega)} + \|I_{ion}\|_{L^2(Q)} + \|I^s_{i,e}\|_{H^1(0,T;L^2(\Omega))}\right)$$

$$\|\partial_t v\|_{L^2(0,T;L^2(\Omega))} \le C\left(\|V_0\|_{H^1(\Omega)} + \|I_{ion}\|_{L^2(Q)} + \|I^s_{i,e}\|_{H^1(0,T;L^2(\Omega))}\right)$$

and, if $v^{(1)}, v^{(2)}$ *are the solutions corresponding to data* $I^{(1)}_{ion}, I^{(2)}_{ion}$*, it holds:*

$$\|v^{(1)}(t) - v^{(2)}(t)\|^2_{L^2(\Omega)} \le C\|I^{(1)}_{ion} - I^{(2)}_{ion}\|^2_{L^2(0,t;L^2(\Omega))}, \quad \forall\, t \in [0,T].$$

3.3 Proof

In this section we point out some distinctive properties of $a, b, \mathcal{I}_{ion}, \mathbf{L}$, which are common to the microscopic and the macroscopic variational formulation, and which define the structure of the abstract setting we are going to adopt. Then, we state the related abstract problem and we use a reduction technique in order to split the degenerate evolution equation into an elliptic problem and a parabolic (nondegenerate) equation. Finally we state and prove the abstract result, the direct application of which yields Propositions 3.1 and 3.2. This theorem is a simplified version of Theorem 4 in [21].

3.3.1 Structural properties

$\mathcal{P}1$) The bilinear form $b(\cdot,\cdot) : \mathbf{V} \times \mathbf{V} \to \mathbb{R}$ is symmetric and continuous, and the associated quadratic form is nonnegative, but its kernel, that is

$$\mathbf{K}_b := \{\mathbf{u} \in \mathbf{V} \ : \ b(\mathbf{u}, \mathbf{u}) = 0\},$$

has infinite dimension, so that equations (3.12) and (3.24) are *degenerate evolution equations.*

$\mathcal{P}2$) The bilinear form $a(\cdot,\cdot) : \mathbf{V} \times \mathbf{V} \to \mathbb{R}$ is symmetric and continuous, owing to (1.1) and (1.30) and the associated quadratic form is nonnegative.

$\mathcal{P}3$) The sum of the quadratic forms associated to a and b is coercive on $\mathbf{V}$, that is

$$\exists\, \alpha > 0 : \quad a(\mathbf{u}, \mathbf{u}) + b(\mathbf{u}, \mathbf{u}) \geq \alpha \|\mathbf{u}\|^2_{\mathbf{V}}, \quad \forall\, \mathbf{u} \in \mathbf{V}. \tag{3.25}$$

$\mathcal{P}4$) The family of linear and continuous functionals $\mathcal{I}_{ion} : \mathbf{V}' \to \mathbb{R}$ is invariant with respect to the translation of $\mathbf{K}_b$, that is

$$\mathcal{I}_{ion} \in V_b' := \{\mathbf{f} \in \mathbf{V}' \ : \ \langle \mathbf{f}, \mathbf{u} \rangle = 0, \quad \forall\, \mathbf{u} \in \mathbf{K}_b\}.$$

Remark 3.1. We will give a more precise (and useful) characterization of $\mathcal{I}_{ion}$ later on, using the notation established in subsection 3.3.2. In the formulation of the abstract problem ($\mathbf{A}$) we will collect $\mathcal{I}_{ion}$ and $\mathbf{L}$ in a unique term $\mathcal{L}$.

We will now give the proof of property $\mathcal{P}3$), in the microscopic setting. The correspondent proof for the macroscopic operators follows in the same way.

Proof. Recall that by definition

$$\|\mathbf{u}\|^2_{\mathbf{V}} := \int_{\Omega_i} |u_i(x)|^2 + |\nabla u_i(x)|^2 dx + \int_{\Omega_e} |u_e(x)|^2 + |\nabla u_e(x)|^2 dx.$$

By hypothesis (1.1), we have that

$$\exists\, \underline{\sigma} > 0, \quad \underline{\sigma}|\xi|^2 \leq \sigma_{i,e}(x)\xi \cdot \xi, \quad \forall\, \xi \in \mathbb{R}^3,\ \forall\, x \in \Omega_{i,e}.$$

Therefore

$$a(\mathbf{u},\mathbf{u}) = \int_{\Omega_i} \sigma_i(x)\nabla u_i(x) \cdot \nabla u_i(x) dx + \int_{\Omega_e} \sigma_e(x)\nabla u_e(x) \cdot \nabla u_e(x)\, dx \geq$$

$$\geq \underline{\sigma}\left(\int_{\Omega_i} |\nabla u_i(x)|^2 dx + \int_{\Omega_e} |\nabla u_e(x)|^2 dx\right). \tag{3.26}$$

Denote by $\gamma_{i,e} : H^1(\Omega_{i,e}) \to H^{1/2}(\partial\Omega_{i,e})$ the trace operator. Then, by Poincaré-Wirtinger inequality, there exists $c_e > 0$ such that

$$\int_{\Omega_e} |u_e(x)|^2 dx = \left(\int_{\Omega_e} |u_e(x) - \frac{1}{|\Omega_e|}\int_{\Omega_e} u_e(\xi)\, d\xi|^2 dx\right) \leq c_e \int_{\Omega_e} |\nabla u_e(x)|^2 dx, \tag{3.27}$$

and by Poincaré's Lemma there exists $c_i > 0$ such that

$$\int_{\Omega_i} |u_i(x)|^2 dx \leq c_i \left(\int_{\Omega_i} |\nabla u_i(x)|^2 dx + \int_{\Gamma} |\gamma_i(u_i)(x)|^2 d\mathscr{H}^2\right), \tag{3.28}$$

we can estimate the last integral with $b(\cdot,\cdot)$

$$\begin{aligned} \int_{\Gamma} |\gamma(u_i)(x)|^2 d\mathscr{H}^2 &\leq 2\int_{\Gamma} (|\gamma_i(u_i)(x) - \gamma_e(u_e)(x)|^2 + |\gamma_e(u_e)(x)|^2) d\mathscr{H}^2 \\ &\leq 2b(\mathbf{u},\mathbf{u}) + 2\int_{\Gamma} |\gamma_e(u_e)(x)|^2 d\mathscr{H}^2 \end{aligned} \tag{3.29}$$

and by continuity of the trace operator and (3.27), there exists $c > 0$ such that

$$\int_{\Gamma} |\gamma_e(u_e)(x)|^2 d\mathscr{H}^2 \leq c \int_{\Omega_e} |\nabla u_e(x)|^2 dx. \tag{3.30}$$

Therefore, by (3.28), (3.29), (3.30) and (3.27), we have that

$$\int_{\Omega_i} |u_i(x)|^2 dx \leq c_i \left(\int_{\Omega_i} |\nabla u_i(x)|^2 dx + 2b(\mathbf{u},\mathbf{u}) + 2\,c \int_{\Omega_e} |\nabla u_e(x)|^2 dx\right). \tag{3.31}$$

Summing up (3.26), (3.27) and (3.31) we obtain the thesis.

□

3.3.2 A reduction technique

First of all, since owing to $\mathcal{P}1) - \mathcal{P}3)$, the variational formulations of Problem (**m-var**) and Problem (**M-var**) fit into a common abstract framework, we consider the following abstract problem:

Problem (A) Let $\mathbf{V}$ be a separable Hilbert space with dual $\mathbf{V}'$, given

$$\mathcal{L} \in L^2(0,T;\mathbf{V}'), \qquad \ell^0 \in \mathbf{V}',$$

and a, b defined as in Properties $\mathcal{P}1) - \mathcal{P}3)$, we look for

$$\mathbf{u} \in L^2(0,T;\mathbf{V}), \text{ with } B\mathbf{u} \in H^1(0,T;\mathbf{V}'),$$

which solves the evolution system

$$\begin{cases} (B\mathbf{u}(t))' + A\mathbf{u}(t) = \mathcal{L}(t), & \text{in } \mathbf{V}' \quad \text{a.e. in }]0,T[, \\ B\mathbf{u}(0) = \ell^0 & \text{in } \mathbf{V}'. \end{cases} \tag{3.32}$$

Degenerate parabolic equations of this kind have been studied by many authors (see e.g. [21, 25, 12, 65, 14]) in a very general contest: for example $\mathbf{V}$ could be a reflexive Banach space, A could be a (pseudo)monotone bounded operator, A and B could be time-dependent and under suitable assumptions, also B could be nonlinear. Following the argument of [21], we will use a reduction technique which allows us to derive the optimal a priori estimates on $u_i - u_e$ and, in Chapter 5, enables the application of a maximal regularity result about generators of analytic semigroups.

Now we will show that Problem (**A**) can be reduced, by the "change of variable $v = B\mathbf{u}$", to a usual, nondegenerate, parabolic equation coupled with an elliptic time-dependent problem. The parabolic equation is of the type

$$v(0) = v_0, \qquad v'(t) + A_b v(t) = L_b(t),$$

in an abstract Hilbert triple V_b, H_b, V_b', with A_b, L_b related in an explicit way to A and $\mathcal{L}$. We recall just the basic definitions, referring to the bibliography for details. Let us denote by $\mathbf{K}_b \subset \mathbf{V}$ the kernel of the bilinear form $b(\cdot,\cdot)$, that is

$$\mathbf{K}_b := \{\mathbf{u} \in \mathbf{V} \ : \ b(\mathbf{u},\mathbf{u}) = 0\},$$

and by $\mathbf{K}_a \subset \mathbf{V}$ the subspace of $\mathbf{V}$ which is a-orthogonal to $\mathbf{K}_b$:

$$\mathbf{K}_a := \{\mathbf{u} \in \mathbf{V} : a(\mathbf{u},\mathbf{k}) = 0, \ \forall \mathbf{k} \in \mathbf{K}_b\}.$$

We introduce the Hilbert spaces

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

and

$$V_b' = \{L \in \mathbf{V}' : \langle L, \mathbf{k}\rangle = 0,\ \forall\, \mathbf{k} \in \mathbf{K}_b\}.$$

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

$$\mathbf{R}v = \mathbf{u} \quad \Leftrightarrow \quad B\mathbf{u} = v, \quad \text{and} \quad \mathbf{u} \in \mathbf{K}_a, \tag{3.33}$$

Moreover, observe that since $a(\cdot,\cdot)$ is symmetric, (3.33) is equivalent to the minimization problem

$$B\mathbf{u} = v, \quad \text{and} \quad a(\mathbf{u},\mathbf{u}) = \min\{a(\mathbf{y},\mathbf{y}) : \mathbf{y} \in \mathbf{V},\ B\mathbf{y} = v\}. \tag{3.34}$$

By Property $\mathcal{P}3$), we have that $A + B$ is coercive on $\mathbf{V}$, and therefore $a(\cdot,\cdot)$ is coercive on $\mathbf{K}_b$. Then, Riesz Fréchet Theorem ensures that $\mathbf{R} : V_b \to \mathbf{K}_a \subset \mathbf{V}$ is a linear isomorphism. Observe that $\mathbf{V} \cong \mathbf{K}_a \oplus \mathbf{K}_b$ and each $\mathbf{u} \in \mathbf{V}$ admits the linear decomposition

$$\mathbf{u} = \mathbf{R}v + \mathbf{u}_b : \quad v = B\mathbf{u}, \quad \mathbf{R}v \in \mathbf{K}_a, \quad \mathbf{u}_b \in \mathbf{K}_b. \tag{3.35}$$

We define the duality pairing between V_b' and V_b as

$$(\ell, v)_b := {}_{\mathbf{V}'}\langle \ell, \mathbf{R}v\rangle_{\mathbf{V}} = {}_{\mathbf{V}'}\langle \ell, \mathbf{u}\rangle_{\mathbf{V}}\,, \qquad \forall\, \ell \in V_b',\ \forall\, v \in V_b,\ \forall\, \mathbf{u} \in B^{-1}v.$$

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

$$|v|_b^2 := (v, v)_b = b(\mathbf{R}v, \mathbf{R}v).$$

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

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

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

By the light of these definitions we see that:

$\mathcal{P}4)_b$ The family of linear and continuous functionals $\mathcal{I}_{ion}(t) : \mathbf{V}' \to \mathbb{R}$ defined in (3.9) and (3.21) satisfies

$$\mathcal{I}_{ion} \in L^2(0, T; H_b'),$$

Therefore, in order to treat terms like $\mathbf{L} + \mathcal{I}_{ion}$, in the hypothesis of Theorem 3.1, we will assume that $\mathcal{L} \in H^1(0, T; \mathbf{V}') + L^2(0, T; H_b')$.

Lemma 3.1. *The function* $\mathbf{u}$ *is a solution of* Problem $(\mathbf{A})$ *if and only if it admits the decomposition*

$$\mathbf{u} = \mathbf{R}v + \mathbf{u}_b,$$

where $\mathbf{u}_b$ *solves*

$$\mathbf{u}_b(t) \in \mathbf{K}_b, \quad a(\mathbf{u}_b(t), \mathbf{k}) = \langle \mathcal{L}(t), \mathbf{k} \rangle, \quad \forall\, \mathbf{k} \in \mathbf{K}_b, \ \textit{a.e. in }]0,T[,$$

and $v \in L^2(0,T;V_b) \cap H^1(0,T;V_b')$ *solves the evolution system*

$$\begin{cases} \dfrac{d}{dt}v(t) + A_R v(t) = L_R(t), & \textit{in } V_b' \quad \textit{a.e.} \ \in]0,T[, \\ v(0) = v_0, \end{cases} \tag{3.36}$$

where,

$$L_R(t) := \mathcal{L}(t) - A\mathbf{u}_b(t),$$

and

$$\langle A_R v, \hat{v} \rangle = a_R(v, \hat{v}) := a(\mathbf{R}v, \mathbf{R}\hat{v}), \quad \forall\, v, \hat{v} \in V_b.$$

Proof. Let $\mathbf{u}$ be a solution of Problem $(\mathbf{A})$, then $\mathbf{u}$ admits the decomposition (3.35), and therefore there exist $v \in V_b$ and $\mathbf{u}_b \in \mathbf{K}_b$, such that

$$\begin{cases} \dfrac{d}{dt}B(\mathbf{R}v(t) + \mathbf{u}_b(t)) + A(\mathbf{R}v(t) + \mathbf{u}_b(t)) = \mathcal{L}(t), & \text{in } \mathbf{V}' \quad \text{a.e. in }]0,T[, \\ B(\mathbf{R}v(0) + \mathbf{u}_b(0)) = \ell^0 & \text{in } \mathbf{V}'. \end{cases}$$

We first test the equation against $\mathbf{k} \in \mathbf{K}_b$. Exploiting the definition of $\mathbf{K}_a$, $\mathbf{K}_b$ we obtain

$$\langle B(\mathbf{R}v(t) + \mathbf{u}_b(t)), \mathbf{k} \rangle = \langle A\mathbf{R}v(t), \mathbf{k} \rangle = 0,$$

and therefore

$$\langle A\mathbf{u}_b(t), \mathbf{k} \rangle = \langle \mathcal{L}(t), \mathbf{k} \rangle, \quad \forall\, \mathbf{k} \in \mathbf{K}_b, \ \text{a.e. in }]0,T[.$$

Now, let $\hat{v} \in V_b$, if we test the equation against $\mathbf{R}\hat{v} \in \mathbf{K}_a$ we find

$$\frac{d}{dt}\langle B\mathbf{R}v(t), \mathbf{R}\hat{v} \rangle + \langle A\mathbf{R}v(t), \mathbf{R}\hat{v} \rangle = \langle \mathcal{L}(t) - A\mathbf{u}_b(t), \mathbf{R}\hat{v} \rangle \quad \text{a.e. in }]0,T[.$$

Observe that, by definition (of $\mathbf{R}$ and $(\cdot,\cdot)_b$) we have

$$\begin{aligned} \langle B\mathbf{R}v(t), \mathbf{R}\hat{v} \rangle &= (v(t), \hat{v})_b, \\ \langle A\mathbf{R}v(t), \mathbf{R}\hat{v} \rangle &= a_R(v, \hat{v}), \\ \langle \mathcal{L}(t) - A\mathbf{u}_b(t), \mathbf{R}\hat{v} \rangle &= (L_R(t), \hat{v})_b, \end{aligned}$$

thus we obtain

$$\begin{cases} \dfrac{d}{dt}v(t) + A_R v(t) = L_R(t), \quad \text{in } V_b' \quad \text{a.e. } \in]0,T[, \\ v(0) = \ell^0, \end{cases}$$

The converse implication follows since $\mathbf{V} \cong \mathbf{K}_a \oplus \mathbf{K}_b$, and therefore testing the equation separately against $\mathbf{K}_a$ and $\mathbf{K}_b$ is equivalent to testing against $\mathbf{V}$.

□

3.3.3 The abstract result

We now have all the element to state the abstract Theorem which gives an answer to Problem (**A**).

Theorem 3.1. *Let us assume that*

$$\ell^0 \in V_b, \quad \mathcal{L} \in H^1(0,T;\mathbf{V}') + L^2(0,T;H_b'). \tag{3.37}$$

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

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

and there exists $C > 0$ *such that*

$$\int_0^T (a(\mathbf{u}(t),\mathbf{u}(t)) + b(\mathbf{u}(t),\mathbf{u}(t)))\,dt \le C\left(|\ell^0|_b^2 + \|\mathcal{L}\|^2_{L^2(0,T;\mathbf{V}')+L^2(0,T;H_b')}\right),$$

$$\sup_{t\in[0,T]} (a(\mathbf{u}(t),\mathbf{u}(t)) + b(\mathbf{u}(t),\mathbf{u}(t))) \le C\left(\|\ell^0\|_{V_b}^2 + \|\mathcal{L}\|^2_{H^1(0,T;\mathbf{V}')+L^2(0,T;H_b')}\right).$$

Proof. Observe that $\mathcal{P}1) - \mathcal{P}3)$ imply that $a_R(\cdot,\cdot)$ is weakly coercive on V_b, that is

$$\exists\,\alpha > 0 \ : \ a_R(v,v) + (v,v)_b \ge \alpha\|v\|_b^2, \quad \forall\, v \in V_b.$$

By the general theory of parabolic evolution equations (see e.g. [65]), if (3.37) holds, then the reduced equation (3.36) admits a unique strong solution

$$v \in H^1(0,T;H_b) \cap C^0([0,T];V_b). \tag{3.38}$$

On the other side, by standard regularity estimates for elliptic problems depending on the time parameter t (see e.g. [27]), there exists a unique $\mathbf{u}_b$ which solves

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

and we have

$$\mathbf{u}_b \in H^1(0,T;\mathbf{V}). \tag{3.39}$$

Observe that (3.38) and (3.39) entail

$$\mathbf{u} = \mathbf{R}v + \mathbf{u}_b \in C^0([0,T];\mathbf{V}).$$

Now we briefly show a formal derivation of the basic *a priori* estimates for the reduced parabolic equation (3.36). These computations can be made rigorous, e.g. by passing to the limit in the analogous stability estimates for a suitably discretized or regularized system.

A priori estimates for $\mathbf{u}$, $\boldsymbol{v}$. We derive these estimates by means of standard techniques for monotone, coercive operators (see e.g. [46], [21, 56]). We also split the datum $\mathcal{L}$ into a term $\mathbf{L}$ belonging to $H^1(0,T;\mathbf{V}')$ and a term $-I_{ion} \in L^2(0,T;H_b)$.

By means of exponential shift (put $v(t) := w(t)e^{-\lambda t}$, $\lambda \in \mathbb{R}$) the following are equivalent

$$i) \quad \begin{cases} w \in L^2(0,T;V_b), \\ w'(t) + A_R w(t) = -I_{ion}(t) + L_R(t), \qquad \text{in } V_b', \end{cases}$$

$$ii) \quad \begin{cases} v \in L^2(0,T;V_b), \\ v'(t) + (\lambda + A)v(t) = e^{-\lambda t}(-I_{ion}(t) + L_R(t)), \quad \text{in } V_b'. \end{cases}$$

For a.e. t in $]0,T[$ we consider the shifted equation:

$$v'(t) + (\lambda + A_R)v(t) = e^{-\lambda t}(-I_{ion}(t) + L_R(t)) \qquad \text{in } V_b'. \tag{3.40}$$

We test equation (3.40) against $v(t)$

$$(v'(t), v(t))_b + ((\lambda + A_R)v(t), v(t))_b = (e^{-\lambda t}(-I_{ion}(t) + L_R(t)), v(t))_b$$

Each of the above terms may be treated in the following way

- $(v'(t), v(t))_b \;=\; \frac{1}{2}\frac{d}{dt}(v(t), v(t))_b,$
- $((\lambda + A_R)v(t), v(t))_b \;\geq\; \alpha \|v(t)\|^2_{V_b},$
- $\left|\left(e^{-\lambda t} I_{ion}(t), v(t)\right)_b\right| \;\leq\; |I_{ion}(t)|_b |v(t)|_b,$
- $\left|\left(e^{-\lambda t} L_R(t), v(t)\right)_b\right| \;\leq\; \|L_R(t)\|_{V_b'} \|v(t)\|_{V_b}.$

Using Cauchy-Schwartz inequality and integrating in time we get, for a.e. $t \in (0,T)$:

$$|v(t)|_b^2 + \|v\|^2_{L^2(0,t;V_b)} \leq C_1 \left(|\ell^0|_b^2 + \|L_R\|^2_{L^2(0,t;V_b')} + \|I_{ion}\|^2_{L^2(0,t;H_b)} \right), \tag{3.41}$$

A priori estimate for $\mathbf{v}'$. We now consider equation

$$v'(t) + A_R v(t) + I_{ion}(t) = L_R(t), \quad \text{in } V_b',$$

and we multiply it by $v'(t)$, obtaining

$$|v'(t)|_b^2 + \frac{1}{2}\frac{d}{dt} a(\mathbf{R}v(t), \mathbf{R}v(t)) + (I_{ion}(t), v'(t))_b = (L_R(t), v'(t))_b.$$

Integrating in time we get the estimate

$$\int_0^T |v'(t)|_b^2 \, dt + \sup_{t \in [0,T]} a(\mathbf{R}v(t), \mathbf{R}v(t)) \leq$$

$$\leq C \left(\|\ell^0\|_{V_b}^2 + \|I_{ion}\|_{L^2(0,T;H_b)}^2 + \|L_R\|_{H^1(0,T;V_b')}^2 \right).$$

By definition of L_R and standard estimates for elliptic problems we have

$$\|L_R\|_{H^1(0,T;V_b')} \leq C_1 \left(\|\mathbf{L}\|_{H^1(0,T;\mathbf{V}')} + \|\mathbf{u}_b\|_{H^1(0,T;\mathbf{V})} \right) \leq C_2 \|\mathbf{L}\|_{H^1(0,T;\mathbf{V}')}.$$

□

Chapter 4

The Microscopic model - Proofs

We recall the complete formulation of the microscopic model for the cardiac electric potential:
Problem (m). Given

$$i^s_{i,e} : Q_{i,e} \to \mathbb{R}, \qquad g_i : \Sigma_i \to \mathbb{R},$$
$$v_0 : \Gamma \to \mathbb{R}, \qquad \mathbf{w}_0 : \Gamma \to \mathbb{R}^k, \qquad \mathbf{z}_0 : \Gamma \to (0, +\infty)^m,$$

we seek

$$u_{i,e} : Q_{i,e} \to \mathbb{R}, \qquad \mathbf{w} = (w_1, \dots, w_k) : \Sigma \to \mathbb{R}^k,$$
$$v := u_i - u_e : \Sigma \to \mathbb{R}, \qquad \mathbf{z} = (z_1, \dots, z_m) : \Sigma \to (0, +\infty)^m,$$

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

$$\begin{aligned} -\text{div}(\sigma_{i,e} \nabla u_{i,e}) &= i^s_{i,e} && \text{on } Q_{i,e}, \\ \sigma_i \nabla u_i \cdot \nu_i &= g_i && \text{on } \Sigma_i, \\ u_e &= 0 && \text{on } \Sigma_e, \end{aligned} \tag{4.1}$$

and the evolution system on the surface Σ

$$C_m \partial_t v + I_{ion}(v, \mathbf{w}, \mathbf{z}) = -\sigma_i \nabla u_i \cdot \nu_i \qquad \text{on } \Sigma, \tag{4.2a}$$
$$C_m \partial_t v + I_{ion}(v, \mathbf{w}, \mathbf{z}) = \sigma_e \nabla u_e \cdot \nu_e \qquad \text{on } \Sigma, \tag{4.2b}$$
$$\partial_t \mathbf{w} = \mathbf{F}(v, \mathbf{w}) \qquad \text{on } \Sigma, \tag{4.2c}$$
$$\partial_t \mathbf{z} = \mathbf{G}(v, \mathbf{w}, \mathbf{z}) \qquad \text{on } \Sigma, \tag{4.2d}$$

with initial data

$$v(x, 0) = v_0(x) \qquad \text{on } \Gamma, \tag{4.3a}$$
$$\mathbf{w}(x, 0) = \mathbf{w}_0(x) \qquad \text{on } \Gamma, \tag{4.3b}$$
$$\mathbf{z}(x, 0) = \mathbf{z}_0(x) \qquad \text{on } \Gamma. \tag{4.3c}$$

In the following part, the expression ' $\log \mathbf{z}$' stands for the vector $(\log z_1, ..., \log z_m)$ and '$\mathbf{z} \log \mathbf{z}$' is not a scalar product, but represents the vector $(z_1 \log z_1, ..., z_m \log z_m)$. We can now state our main result concerning the existence of a variational solution of Problem **m**.

Theorem 4.1. *Let be given the data*

$$v_0 \in H^{1/2}(\Gamma), \qquad \mathbf{w}_0 : \Gamma \to [0,1]^k \quad \textit{measurable},$$
$$\mathbf{z}_0 \in (L^2(\Gamma))^m, \quad \textit{with} \quad \log \mathbf{z}_0 \in (L^2(\Gamma))^m,$$
$$i^s_{i,e} \in H^1(0,T; L^2(\Omega_{i,e})), \qquad g_i \in H^1(0,T; H^{-1/2}(\Gamma_i)),$$

the ionic currents $I_{ion}(v, \mathbf{w}, \mathbf{z})$, satisfying (1.13–1.15), the dynamics of the gating variables $\mathbf{F}(v, \mathbf{w})$, satisfying (1.16–1.17c), the dynamics of the ionic concentrations $\mathbf{G}(v, \mathbf{w}, \mathbf{z})$, satisfying (1.19), (1.20).

Then, there exist $k + m + 2$ functions $w_1, \dots, w_k,\ z_1, \dots, z_m,\ u_i,\ u_e$,

$$u_i \in C^0([0,T]; H^1(\Omega_i)), \qquad u_e \in C^0([0,T]; H^1_{\Gamma_e^0}(\Omega_e)),$$

$$v := u_{i|\Gamma} - u_{e|\Gamma} \ \in H^1(0,T; L^2(\Gamma)) \cap C^0([0,T]; H^{1/2}(\Gamma)),$$

$$\mathbf{w} : \Sigma \to [0,1]^k \ \textit{measurable}, \quad \mathbf{z} : \Sigma \to (0, +\infty)^m \ \textit{measurable},$$
$$w_j(x, \cdot) \in C^1(0,T) \cap C^0([0,T]) \ \ \textit{for a.e. } x \in \Gamma, \quad j = 1, \dots, k,$$
$$z_i(x, \cdot) \in C^1(0,T) \cap C^0([0,T]) \ \ \textit{for a.e. } x \in \Gamma, \quad i = 1, \dots, m,$$
$$\mathbf{w} \in L^2(\Gamma; C^0([0,T]))^k, \quad \mathbf{z} \in H^1(0,T; L^2(\Gamma))^m, \quad \log(\mathbf{z}) \in L^2(\Gamma; C^0([0,T])^m,$$

which solve Problem **m**.

As we anticipated, the proof of the existence is divided into three parts. In a first step we considered v as an assigned function on Σ and we solved the ODE system of the gating variables (1.23c) and the ODE system of the concentration variables (1.23d), obtaining suitable a priori estimates and qualitative properties of the solution (Chapter 2).

In the second step we wrote a variational formulation for the remaining part of the model, which lead to a reaction-diffusion equation of degenerate parabolic type in a classical Hilbert triple, and we solved the parabolic equation considering $I_{ion}(v, \mathbf{w}, \mathbf{z})$ as a known function (Section 3.1).

Now, by choosing the correct functional spaces for $\mathbf{w}, \mathbf{z}$ and v, it is possible to combine the results of the previous chapters, in order to find existence for a solution $(v, \mathbf{w}, \mathbf{z})$ using Schauder Fixed Point Theorem (Section 4.1). Continuity of the fixed point operator is obtained by means of a classical interpolation inequality combined with an infinite dimensional version of a theorem on the continuity of Nemitski operators.

Back to the dynamic model. In Chapter 3 we considered the ionic current as a known function (we assumed $I_{ion} \in L^2(0,T;L^2(\Gamma))$), now we turn back to the dynamic model described in Chapter 1, where the ionic current depends on $v, \mathbf{w}, \mathbf{z}$, and we look at the results on the ODE systems obtained in Chapter 2, in order to correctly estimate this dependence. Let $\mathbf{w}$, $\mathbf{z}$, be known functions, satisfying the thesis of Propositions 2.1 and 2.2, let $\bar{v} \in H^1(0,T;L^2(\Gamma))$ be given, and set

$$\bar{I}_{ion}(x,t) := I_{ion}(\bar{v}(x,t), \mathbf{w}(x,t), \mathbf{z}(x,t)). \tag{4.4}$$

Then, by the definition of I_{ion} (1.13), using estimates (1.14b), (1.14c) and (2.4) we obtain

$$|J(v, \mathbf{w}, \log z)| \leq |J(0, \mathbf{w}, 0)| + L_v|v| + \overline{G}|\log z| \leq C(1 + |v| + |\log z|),$$

and thus, owing to (2.12), we have that $\bar{I}_{ion} \in L^2(\Sigma)$, and

$$\|\bar{I}_{ion}\|^2_{L^2(0,t;L^2(\Gamma))} \leq C\left(1 + \|\bar{v}\|^2_{L^2(0,t;L^2(\Gamma))}\right), \qquad \forall\, t \in [0,T]. \tag{4.5}$$

On the other hand, using estimate (2.11), we get

$$\left|\bar{I}_{ion}(x,t)\right| \leq C\left(1 + \|\bar{v}(x)\|_{H^1(0,T)}\right), \qquad \text{a.e. in } Q.$$

Then, $\forall\, p \in (1, +\infty)$ we have $\bar{I}_{ion} \in L^p(0,T;L^2(\Omega))$:

$$\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} \leq C\left(1 + \|\bar{v}\|_{L^2(\Omega,H^1(0,T))}\right), \tag{4.6}$$

where C is a constant, independent of $\bar{v}, \mathbf{w}, \mathbf{z}$.

In Proposition 3.1 we estimated v and $\partial_t v$ through the ionic current I_{ion}, now denoted $\bar{I}_{ion}$ and dependent upon the choice of $\bar{v} \in H^1(0,T;L^2(\Gamma))$. Now we will choose a subspace $\mathcal{K} \subset H^1(0,T;L^2(\Gamma))$ such that, if $\bar{v} \in \mathcal{K}$, then the solution v of the microscopic *passive* model with ionic current given by $\bar{I}_{ion}$ belongs to $\mathcal{K}$. In order to find such an invariant set it will be useful to define an equivalent norm on $L^2(0,T;L^2(\Gamma))$.

The norm $|||v|||_{\lambda,H}$**.** Let H be a Hilbert space, for every $\lambda > 0$, we can define a new norm on $L^2(0,T;H)$ as

$$|||v|||_{\lambda,H} := \left(\int_0^T e^{-\lambda t}\|v(t)\|^2_H \, dt\right)^{1/2}, \tag{4.7}$$

and we have that $|||\cdot|||_{\lambda,H}$ and $\|\cdot\|$ are equivalent norms on $L^2(0,T;H)$.

Corollary 4.1. *Let $\bar{v} \in H^1(0,T;L^2(\Gamma))$, let $\mathbf{w}, \mathbf{z}$ be the unique solutions of systems (2.2) and (2.9), given as in Propositions 2.1 and 2.2, and let $\bar{I}_{ion}$ be given as in (4.4), thus satisfying (4.5). Then there exists $\lambda > 0$ such that the solution v of Problem (**m2**) satisfies*

$$|||v|||^2_{\lambda,L^2(\Gamma)} \leq \max\left\{1, |||\bar{v}|||^2_{\lambda,L^2(\Gamma)}\right\}, \quad \forall\, \bar{v} \in H^1(0,T;L^2(\Gamma)).$$

Proof. By estimate (3.14) we have

$$\|v(t)\|^2_{L^2(\Gamma)} \leq C_2\Big(\|v_0\|^2_{L^2(\Gamma)} + \|i^s_{i,e}\|^2_{L^2(Q_{i,e})} + \|g_i\|^2_{L^2(0,T;H^{-1/2}(\Gamma_i))} + \|\bar{I}_{ion}\|^2_{L^2(0,t;L^2(\Gamma))}\Big). \tag{4.8}$$

Let $\varphi(t) := \|v(t)\|^2_{L^2(\Gamma)}$, and $\bar{\varphi}(t) := \|\bar{v}(t)\|^2_{L^2(\Gamma)}$; owing to estimates (4.5) and (4.8) we find

$$\varphi(t) \leq C_3 + C_4 \int_0^t \bar{\varphi}(s)\ ds, \tag{4.9}$$

where C_3 may depend on T, $\|v_0\|^2_{L^2(\Gamma)}$, $\|i^s_{i,e}\|_{L^2(Q_{i,e})}$, $\|g_i\|_{L^2(0,T;H^{-1/2}(\Gamma_i))}$, $\|\mathbf{z}_0\|^2_{L^2(\Gamma)}$, $\|\mathbf{z}_0 \log \mathbf{z}_0\|_{L^2(\Gamma)}$, $\mathscr{H}^2(\Gamma)$, and

$$C_4 = C_4\left(T,\ \mathscr{H}^2(\Gamma)\right).$$

Now we multiply (4.9) by $e^{-\lambda t}$, $(\lambda > 0)$, and we integrate between 0 and T:

$$\int_0^T e^{-\lambda t}\varphi(t)\ dt \leq C_3 \int_0^T e^{-\lambda t}\ dt + C_4 \int_0^T e^{-\lambda t}\left(\int_0^t \bar{\varphi}(s)\ ds\right) dt,$$

and integrating by parts

$$\begin{aligned}\int_0^T e^{-\lambda t}\varphi(t)\ dt &\leq \frac{1}{\lambda}\left[C_3\left(1 - e^{-\lambda T}\right) + C_4 \int_0^T e^{-\lambda t}\bar{\varphi}(t)\ dt - C_4 e^{-\lambda T}\int_0^T \bar{\varphi}(t)\ dt\right] \\ &\leq \frac{1}{\lambda}\left[C_3 + C_4 \int_0^T e^{-\lambda t}\bar{\varphi}(t)\ dt\right].\end{aligned}$$

If $\displaystyle\int_0^T e^{-\lambda t}\bar{\varphi}(t)\ dt \geq 1$, we have that

$$\int_0^T e^{-\lambda t}\varphi(t)\ dt \leq \frac{C_3 + C_4}{\lambda}\int_0^T e^{-\lambda t}\bar{\varphi}(t)\ dt.$$

Hence, if $\lambda \geq C_3 + C_4$, then

$$|||v|||^2_{\lambda,L^2(\Gamma)} = \int_0^T e^{-\lambda t}\varphi(t)\ dt \leq \max\left\{1, \int_0^T e^{-\lambda t}\bar{\varphi}(t)\ dt\right\} = \max\left\{1, |||\bar{v}|||^2_{\lambda,L^2(\Gamma)}\right\}.$$

$\square$

Using estimates (3.13) and (3.16), Corollary 4.1 and the continuity of the trace operator, we easily obtain:

Corollary 4.2. *Let $M_0 \geq 1$, let $\bar{v}, \mathbf{w}, \mathbf{z}$, be as in the statement of Corollary 4.1, such that*

$$|||\bar{v}|||_{\lambda, L^2(\Gamma)} \leq M_0,$$

then there exist $M_1 > 0$, depending only on M_0 and the data of the problem, such that

$$|||\mathbf{u}|||_{\lambda, \mathbf{V}} \leq M_1,$$

$$|||v|||_{\lambda, H^{1/2}(\Gamma)} \leq M_1,$$

$$|||\partial_t v|||_{\lambda, L^2(\Gamma)} \leq M_1.$$

4.1 The fixed point argument

Let us recall Schauder's fixed point theorem, (see e.g. [74, p. 56]).

Schauder's Theorem *Let M be a nonempty, compact, convex subset of a Banach space X. Let $\mathcal{T} : M \to M$ be a continuous operator. Then $\mathcal{T}$ has a fixed point.*

We denote by $\mathcal{K}_\lambda$, $\mathcal{W}$ and $\mathcal{Z}$ the following sets

$$\mathcal{K}_\lambda := \Big\{ \ v \in H^1(0,T; L^2(\Gamma)) \cap L^2(0,T; H^{1/2}(\Gamma)), \text{ s.t. } \quad |||v|||_{\lambda, L^2(\Gamma)} \leq M_0,$$
$$|||\partial_t v|||_{\lambda, L^2(\Gamma)}, |||v|||_{\lambda, H^{1/2}(\Gamma)} \leq M_1, \text{ and } v(x,0) = v_0(x) \text{ a.e } \Big\},$$

endowed with the topology of $(L^2(0,T; L^2(\Gamma)), ||| \cdot |||_{\lambda, L^2(\Gamma)})$, (the norm $||| \cdot |||_{\lambda, H}$ was defined in (4.7));

$$\mathcal{W} := \Big\{ \ \mathbf{w} \in \big(L^2(\Sigma)\big)^k \text{ s.t. } \quad \mathbf{w}(x,t) \in [0,1]^k, \quad \text{ for a.e. } (x,t) \in \Sigma \Big\},$$

endowed with the topology of $(L^2(\Sigma))^k$;

$$\mathcal{Z} := \Big\{ \ \mathbf{z} \in \big(L^2(\Sigma)\big)^m \text{ s.t. } \quad \mathbf{z}(x,t) \in (0, +\infty)^k, \quad \text{ for a.e. } (x,t) \in \Sigma,$$
$$\log(\mathbf{z}) \in \big(L^2(\Sigma)\big)^m \text{ and } \ \|\mathbf{z}\|_{(L^2(\Sigma))^m} + \|\log(\mathbf{z})\|_{(L^2(\Sigma))^m} \leq \overline{Z} \ \Big\},$$

endowed with the topology induced by the metric

$$d_{\mathcal{Z}}(\mathbf{z}_1, \mathbf{z}_2) := \|\mathbf{z}_1 - \mathbf{z}_2\|_{(L^2(\Sigma))^m} + \|\log(\mathbf{z}_1) - \log(\mathbf{z}_2)\|_{(L^2(\Sigma))^m},$$

where the constants M_0, M_1 were established in Section 3.1-Corollary 4.2, and the constant $\overline{Z}$ derives from estimates (2.10), (2.12) and M_0.
We define operators $\mathcal{F}_1,\ \mathcal{F}_2,\ \mathcal{T}$

$$\begin{array}{rccc} \mathcal{F}_1: & \mathcal{K}_\lambda & \longrightarrow & \mathcal{K}_\lambda \times \mathcal{W} \times \mathcal{Z} \\ & \bar{v} & \longmapsto & \bar{v}, \mathbf{w}, \mathbf{z} \end{array} \tag{4.10}$$

where $\mathbf{w}$ is the solution of (2.1), as in Proposition 2.1, and $\mathbf{z}$ is the solution of (2.9), as in Proposition 2.2, and

$$\begin{array}{rccc} \mathcal{F}_2: & \mathcal{K}_\lambda \times \mathcal{W} \times \mathcal{Z} & \longrightarrow & \mathcal{K}_\lambda \\ & \bar{v}, \mathbf{w}, \mathbf{z} & \longmapsto & v, \end{array}$$

where v is the solution of Problem (**m2**), as in Proposition 3.1, and

$$\mathcal{T} := \mathcal{F}_2 \circ \mathcal{F}_1 : \ \mathcal{K}_\lambda \ \longrightarrow \ \mathcal{K}_\lambda.$$

In order to apply Schauder's Theorem to $\mathcal{K}_\lambda$ and $\mathcal{T}$, (being $\mathcal{K}_\lambda$ convex and non-empty), we need to check the compactness of $\mathcal{K}_\lambda$ and the continuity of $\mathcal{T}$ with respect to the strong topology of $(L^2(0,T;L^2(\Gamma)), |||\cdot|||_{\lambda,L^2(\Gamma)})$.

Compactness for $\mathcal{K}_\lambda$.
In order to obtain compactness for $\mathcal{K}_\lambda$ we apply Lions-Aubin Theorem (see e.g. [65, p. 106]).

Lions–Aubin Theorem *Let B_0, B, B_1 be Banach spaces with $B_0 \subset B \subset B_1$; assume $B_0 \hookrightarrow B$ is compact and $B \hookrightarrow B_1$ is continuous. Let $1 < p < \infty,\ 1 < q < \infty$, let B_0 and B_1 be reflexive, and define*

$$W \equiv \{u \in L^p(0,T;B_0) : u' \in L^q(0,T;B_1)\}.$$

Then the inclusion $W \hookrightarrow L^p(0,T;B)$ is compact.

We choose $B_0 = H^{1/2}(\Gamma),\ B = B_1 = L^2(\Gamma),\ p = q = 2$. Owing to Rellich Theorem the inclusion $H^{1/2}(\Gamma) \hookrightarrow L^2(\Gamma)$ is compact. Then, by Lions-Aubin theorem we obtain that the inclusion

$$L^2(0,T;H^{1/2}(\Gamma)) \cap H^1\left(0,T;L^2(\Gamma)\right) \hookrightarrow L^2\left(0,T;L^2(\Gamma)\right)$$

is compact; since the norms $\|\cdot\|$ and $|||\cdot|||_\lambda$ are equivalent, in particular we have that

$$\mathcal{K}_\lambda \text{ is compact in } \left(L^2\left(0,T;L^2(\Gamma)\right), |||\cdot|||_{\lambda,L^2(\Gamma)}\right).$$

Continuity of operator $\mathcal{T} = \mathcal{F}_2 \circ \mathcal{F}_1$

Theorem 4.2. *The operator $\mathcal{T}$ is continuous with the topology of*

$$\Big(L^2(0,T;L^2(\Gamma)), |||\cdot|||_{\lambda,L^2(\Gamma)}\Big).$$

Remark 4.1. Since the norms $\|\cdot\|$ and $|||\cdot|||_\lambda$ are equivalent, in order to simplify the notation, we shall check instead the continuity of $\mathcal{T}$ in

$$\mathcal{K} := \Big\{ v \in H^1(0,T;L^2(\Gamma)) \cap L^2(0,T;H^{1/2}(\Gamma)), \text{ s.t. } \quad \|v\|_{L^2(0,T;L^2(\Gamma))} \leq M_0, \\ \|\partial_t v\|_{L^2(0,T;L^2(\Gamma))}, \|v\|_{L^2(0,T;H^{1/2}(\Gamma))} \leq M_1, \text{ and } v(x,0) = v_0(x) \text{ a.e} \Big\}, \quad (4.11)$$

endowed with the topology of $\big(L^2(0,T;L^2(\Gamma)), \|\cdot\|\big)$.

The proof is divided into two steps: 1) the continuity of operator $\mathcal{F}_1$, which is divided into Propositions 4.1 and 4.2, and: 2) the continuity of operator $\mathcal{F}_2$.

4.1.1 Continuity of operator $\mathcal{F}_1$

The proof is based on:

- the estimates on the ODE systems established in Propositions 2.1 and 2.2,
- Theorem 4.3, on the continuity of infinite dimensional Nemitski operators,
- a classical interpolation inequality (Lemma 4.1 and Lemma 4.2).

Let us recall the necessary tools.

Theorem 4.3. *Let X be a measure space, let B, C be separable Banach spaces and $\mathcal{A} : B \to C$ be a (nonlinear) continuous operator satisfying*

$$\|\mathcal{A}u\|_C \leq c_1 + c_2\|u\|_B, \quad \forall\, u \in B. \quad (4.12)$$

Let $p \in [1, +\infty)$, then the operator

$$\tilde{\mathcal{A}} : L^p(X;B) \to L^p(X;C),$$

$$(\tilde{\mathcal{A}}u)(x) := \mathcal{A}u(x), \quad \forall\, x \in X,$$

is continuous.

See [5] for a finite dimensional proof, which is almost identical in the case of continuous operators between Banach spaces.

We will make use of the following interpolation inequalities (see e.g. [47, 44]).

Lemma 4.1. *There exists $c > 0$ such that*

$$\|v\|_{C^0(0,T)} \le c\|v\|^{1/2}_{H^1(0,T)}\|v\|^{1/2}_{L^2(0,T)}, \quad \forall\, v \in H^1(0,T).$$

Lemma 4.2. *Let X be a measure space, A, B, C Banach spaces such that*

(i) $A \subset B \subset C$, *with continuous inclusions;*
(ii) $\|v\|_B \le c\|v\|_A^{1/2}\|v\|_C^{1/2}, \quad \forall\ v \in A.$

Then

$$\|v\|_{L^2(X,B)} \le c\|v\|^{1/2}_{L^2(X,A)}\|v\|^{1/2}_{L^2(X,C)}.$$

In particular, let $M > 0$, $\{u_n\}_{n\in\mathbb{N}} \in L^2(X, A)$ such that $u_n \to u$ in $L^2(X, C)$ and $\|u_n\|_{L^2(X,A)} \le M$. Then $u_n \to u$ in $L^2(X, B)$.

The following Propositions 4.1 and 4.2 are based on the same idea. We shall detail 4.1, while 4.2 follows likewise.

Proposition 4.1. *Let $\{v_n\} \in \mathcal{K}$, v such that $v_n \to v$ in $L^2(0,T; L^2(\Gamma))$ ($\mathcal{K}$ is compact, so $v \in \mathcal{K}$). We denote by $\mathbf{w}_n, \mathbf{w}$ the solutions (for a.e. x, $\forall\ t$) of the Cauchy problems*

$$\begin{cases} \mathbf{w}_n' = \mathbf{F}(v_n, \mathbf{w}_n), & on\ \ \Sigma, \\ \mathbf{w}_n(0) = \mathbf{w}_0, & on\ \ \Gamma, \end{cases}$$

$$\begin{cases} \mathbf{w}' = \mathbf{F}(v, \mathbf{w}), & on\ \ \Sigma, \\ \mathbf{w}(0) = \mathbf{w}_0, & on\ \ \Gamma. \end{cases}$$

Then

$$\mathbf{w}_n \to \mathbf{w} \quad in\ \ L^2(\Gamma; C^0([0,T])^k. \tag{4.13}$$

Proof. By Lemma 2.1 we know that the operator

$$\begin{array}{rccc} \mathcal{A}: & C^0([0,T]) & \to & C^0([0,T])^k, \\ & v & \mapsto & \mathbf{w}, \end{array}$$

which maps $v \in C^0([0,T])$ into the solution $\mathbf{w}$ of the system of ODE (2.3), is continuous. Moreover, estimate (2.4) ensures that $\mathcal{A}$ satisfies condition (4.12):

$$\|\mathcal{A}v\|_{C^0([0,T])^k} = \|\mathbf{w}\|_{C^0([0,T])^k} \le c_1.$$

Therefore we can apply Theorem 4.3 with $B = C = C^0([0,T])$, $X = \Gamma$, and we find that the operator

$$\tilde{\mathcal{A}} : L^2(\Gamma; C^0([0,T])) \to L^2(\Gamma; C^0([0,T])),$$

$$(\tilde{\mathcal{A}}v)(x) := \mathcal{A}v(x) = \mathbf{w}(x),$$

is continuous.

Now, let $\{v_n\}_{n\in\mathbb{N}}$ and v belong to $\mathcal{K}$, thus satisfying

$$\|v_n\|_{L^2(\Gamma;H^1(0,T))},\ \|v\|_{L^2(\Gamma;H^1(0,T))} \leq \sqrt{M_0^2 + 4M_1^2},$$

(see the definition of $\mathcal{K}$ (4.11) and Lemma 2.2), and suppose that

$$v_n \to v, \qquad \text{in } L^2(0,T;L^2(\Gamma)) \cong L^2(\Gamma;L^2(0,T)).$$

Then, by Lemma 4.2,

$$v_n \to v \qquad \text{in } \ L^2(\Gamma;C^0([0,T])), \tag{4.14}$$

and finally, by continuity of $\tilde{\mathcal{A}}$, we obtain

$$\mathbf{w}_n \to \mathbf{w} \quad \text{in } \ L^2(\Gamma;C^0([0,T]))^k. \tag{4.15}$$

□

Proposition 4.2. *Let $\{v_n\}, v \in \mathcal{K}$, $\{\mathbf{w}_n\}, \mathbf{w} \in \mathcal{W}$, satisfy (4.14) and (4.15), that is*

$$\begin{array}{lll} i) & v_n \to v, & \textit{in } L^2(\Gamma;C^0([0,T])), \\ ii) & \mathbf{w}_n, \to \mathbf{w} & \textit{in } L^2(\Gamma,C^0([0,T]))^k, \end{array}$$

We denote by $\mathbf{z}_n, \mathbf{z}$ the solutions of the Cauchy problems

$$\begin{cases} \mathbf{z}_n' = -\mathbf{J}(v_n, \mathbf{w}_n,\ \mathbf{log}\,(\mathbf{z}_n)) + \mathbf{H}(v_n,\mathbf{w}_n,\mathbf{z}_n), & \textit{on } \Sigma, \\ \mathbf{z}_n(0) = \mathbf{z}_0, & \textit{on } \Gamma, \end{cases}$$

$$\begin{cases} \mathbf{z}' = -\mathbf{J}(v, \mathbf{w},\ \mathbf{log}\,(\mathbf{z})) + \mathbf{H}(v,\mathbf{w},\mathbf{z}), & \textit{on } \Sigma, \\ \mathbf{z}(0) = \mathbf{z}_0, & \textit{on } \Gamma. \end{cases}$$

Then

$$\mathbf{z}_n \to \mathbf{z}, \quad \mathbf{log}(\mathbf{z}_n) \to \mathbf{log}(\mathbf{z}), \quad \textit{in } L^2(\Gamma;C^0([0,T]))^m.$$

Proof. Now we consider the operator

$$\begin{array}{rccc} \mathcal{A}: & C^0([0,T]) \times C^0([0,T])^k & \to & (C^0([0,T]))^m \times (C^0([0,T]))^m, \\ & (v,\mathbf{w}) & \mapsto & (\mathbf{z},\ \mathbf{log}(\mathbf{z})), \end{array}$$

where $\mathbf{z}$ is the solution of (2.9). Hence, let $\{v_n\}_{n\in\mathbb{N}}$, v, $\{\mathbf{w}_n\}_{n\in\mathbb{N}}$, $\mathbf{w}$ be as in the hypothesis of Proposition 4.2. Then, by Lemma 2.3

$$\mathcal{A}(v_n,\mathbf{w}_n) = \mathbf{z}_n \to \mathbf{z} = \mathcal{A}(v,\mathbf{w}) \quad \text{in } C^0([0,T])^m. \tag{4.16}$$

Moreover, convergence (4.16) and estimate (2.11) imply that there exists a compact set $K_2 \subset (0, +\infty)^m$ such that $\mathbf{z}_n(t) \in K$, $\forall\, t \in [0, T]$, $\forall\, n \in \mathbb{N}$, and therefore we obtain

$$\mathbf{log}(\mathbf{z}_n) \to \mathbf{log}(\mathbf{z}) \quad \text{in } C^0([0, T])^m, \tag{4.17}$$

so that $\mathcal{A}$ is continuous. Moreover, operator $\mathcal{A}$ satisfies condition (4.12), in fact, owing to estimate (2.10), there exist c_1, c_2 such that

$$\|\mathbf{z}\|_{C^0([0,T])^m} \le c_1 + c_2 \|v\|_{L^2(0,T)}, \quad \forall\, v \in C^0([0, T]),\ \mathbf{w} \in C^0([0, T]; [0, 1])^k,$$

and estimate (2.11) guarantees that

$$\| \mathbf{log}(\mathbf{z})\|_{C^0([0,T])^m} \le c_1 + c_2 \|v\|_{C^0([0,T])}, \quad \forall\, v \in C^0([0, T]),\ \mathbf{w} \in C^0([0, T]; [0, 1])^k.$$

Hence, by Theorem 4.3, the operator

$$\tilde{\mathcal{A}} : L^2(\Gamma; C^0([0, T])) \times L^2(\Gamma; C^0([0, T]))^k \to L^2(\Gamma; C^0([0, T]))^m \times L^2(\Gamma; C^0([0, T]))^m,$$

$$(\tilde{\mathcal{A}}(v, \mathbf{w}))(x) := \mathcal{A}(v(x), \mathbf{w}(x)) = (\mathbf{z}(x),\ \mathbf{log}\, \mathbf{z}(x))$$

is continuous.

Arguing as in the proof of Proposition 4.1, we conclude that if $\{v_n\}_{n\in\mathbb{N}}$ belong to $\mathcal{K}$ and $v_n \to v$ in $L^2(0, T; L^2(\Gamma))$, then

$$\mathbf{z}_n \to \mathbf{z}, \quad \mathbf{log}(\mathbf{z}_n) \to \mathbf{log}(\mathbf{z}) \quad \text{in } L^2(\Gamma; C^0([0, T]))^m. \tag{4.18}$$

□

4.1.2 Continuity of operator $\mathcal{F}_2$

Now we are going to use the convergences (4.14), (4.15) and (4.18) in order to obtain continuity for $\mathcal{F}_2$.

Remark 4.2. Since $L^2(0, T; L^2(\Gamma)) \cong L^2(\Gamma; L^2(0, T))$, we remark that if

$$\{f_n\}, f \in L^2(\Gamma; C^0([0, T])), \quad f_n \to f \quad \text{in } \ L^2(\Gamma; C^0([0, T])),$$

then

$$f_n \to f \quad \text{in } \ L^2(0, T; L^2(\Gamma)).$$

Proposition 4.3. *Let* $\{\bar{v}_n\},\ \bar{v} \in \mathcal{K}$*, such that*

$$\bar{v}_n \to \bar{v} \quad \text{in } L^2(0, T; L^2(\Gamma)).$$

Let $\{\mathbf{w}_n\},\ \mathbf{w}\in\mathcal{W}$, *such that*

$$\mathbf{w}_n \to \mathbf{w} \quad in\ L^2(0,T;L^2(\Gamma))^k.$$

Let $\{\mathbf{z}_n\},\ \mathbf{z}\in\mathcal{Z}$, *such that*

$$\mathbf{z}_n \to \mathbf{z}, \quad \mathbf{log}(\mathbf{z}_n) \to \mathbf{log}(\mathbf{z}) \quad in\ L^2(0,T;L^2(\Gamma))^m.$$

We denote by $\mathbf{u}, \mathbf{u}_n$ *the solutions of the systems*

$$\begin{cases} (B\mathbf{u}(t))' + A\mathbf{u}(t) = -\mathcal{I}_{ion}(t) + \mathbf{L}(t), & in\ \mathbf{V}' \quad for\ a.e.\ t\in]0,T[, \\ B\mathbf{u}(0) = \ell^0 & in\ \mathbf{V}', \end{cases}$$

$$\begin{cases} (B\mathbf{u}_n(t))' + A\mathbf{u}_n(t) = -\mathcal{I}^n_{ion}(t) + \mathbf{L}(t), & in\ \mathbf{V}' \quad for\ a.e.\ t\in]0,T[, \\ B\mathbf{u}_n(0) = \ell^0 & in\ \mathbf{V}', \end{cases}$$

where $\mathcal{I}_{ion} = \mathcal{I}_{ion}(\bar v, \mathbf{w}, \mathbf{z}),\ \mathcal{I}^n_{ion} = \mathcal{I}_{ion}(\bar v_n, \mathbf{w}_n, \mathbf{z}_n),\ \mathbf{u} = (u_i, u_e),\ \mathbf{u}_n = (u_{i,n}, u_{e,n})$, $v = u_i - u_e,\ v_n = u_{i,n} - u_{e,n}$.
Then

$$v_n \to v \quad in\ \ L^2(0,T;L^2(\Gamma)).$$

Proof. By estimate 3.17 we have that

$$\|v_n(t) - v(t)\|^2_{L^2(\Gamma)} \le C\int_0^t \|\bar I^n_{ion}(s) - \bar I_{ion}(s)\|^2_{L^2(\Gamma)}\ ds. \tag{4.19}$$

By definition (1.13), the right hand side is

$$\|\bar I^n_{ion} - \bar I_{ion}\|^2_{L^2(\Sigma)} = \int_0^T\int_\Gamma \left(\sum_{i=1}^m [J_i(\bar v_n, \mathbf{w}_n, \log z_{i,n}) - J_i(\bar v, \mathbf{w}, \log z_i)] + \right.$$

$$\left. + \tilde H(\bar v_n, \mathbf{w}_n, \mathbf{z}_n) - \tilde H(\bar v, \mathbf{w}, \mathbf{z})\right)^2 d\mathscr{H}^2 dt,$$

so we need to show that

$$i) \quad J_i(\bar v_n, \mathbf{w}_n, \log z_{i,n}) \to J_i(\bar v, \mathbf{w}, \log z_i), \quad \text{in } L^2(\Sigma),$$

and

$$ii) \quad \tilde H(\bar v_n, \mathbf{w}_n, \mathbf{z}_n)) \to \tilde H(v, \mathbf{w}, \mathbf{z}), \quad \text{in } L^2(\Sigma),$$

$\forall\ i = 1, ..., m$. We see that $ii)$ comes immediately from the Lipschitz continuity of $\tilde H$ (see (1.15)), and the hypothesis on $\bar v_n$, $\mathbf{w}_n$ and $\mathbf{z}_n$. In order to prove $i)$ we make use of the finite–dimensional version of Theorem 4.3, with $X = \Sigma,\ B = \mathbb{R}\times\mathbb{R}^k\times\mathbb{R}^m,\ C = \mathbb{R}$.

For every $i = 1, \ldots, m$, we can decompose J_i into

$$J_i(v, \mathbf{w}, \log z_i) = J_i(v, \mathbf{w}, 0) + \frac{J_i(v, \mathbf{w}, \log z_i) - J_i(v, \mathbf{w}, 0)}{\log z_i} \log z_i =$$

$$= J_i(v, \mathbf{w}, 0) - J_i(0, \mathbf{w}, 0) + J_i(0, \mathbf{w}, 0) + \frac{J_i(v, \mathbf{w}, \log z_i) - J_i(v, \mathbf{w}, 0)}{\log z_i} \log z_i.$$

By hypothesis (1.14b) and (1.14c), since $\mathbf{w} \in [0,1]^k$ we obtain

$$|J_i(v, \mathbf{w}, \log z_i)| \leq J_i(0, \mathbf{w}, 0) + L_v|v| + \overline{G}|\log z_i| \leq C(1 + |v| + |\log z_i|).$$

Therefore, owing to Theorem 4.3 we conclude that

$$J_i(\bar{v}_n, \mathbf{w}_n, \log z_{i,n}) \to J_i(\bar{v}, \mathbf{w}, \log z_i) \quad \text{in} \quad L^2(0, T; L^2(\Gamma)), \quad \forall\, i = 1, \ldots, m.$$

$\square$

Chapter 5

The Macroscopic model - Proofs

We recall the formulation of the macroscopic bidomain model stated in Section 1.2
Problem (M). Given

$$\begin{aligned} &I_i^s : Q \to \mathbb{R}, && I_e^s : Q \to \mathbb{R}, && \\ &V_0 : \Omega \to \mathbb{R}, && \mathbf{w}_0 : \Omega \to \mathbb{R}^k, && \mathbf{z}_0 : \Omega \to (0, +\infty)^m, \end{aligned}$$

we seek

$$\begin{aligned} &u_{i,e} : Q \to \mathbb{R}, && \mathbf{w} = (w_1, ..., w_k) : Q \to \mathbb{R}^k, \\ &v := u_i - u_e : Q \to \mathbb{R}, && \mathbf{z} = (z_1, ..., z_m) : Q \to (0, +\infty)^m, \end{aligned}$$

satisfying the reaction-diffusion system

$$\partial_t v + I_{ion}(v, \mathbf{w}, \mathbf{z}) = \mathrm{div}(M_i \nabla u_i) + I_i^s \quad \text{on } Q, \tag{5.1a}$$

$$\partial_t v + I_{ion}(v, \mathbf{w}, \mathbf{z}) = -\mathrm{div}(M_e \nabla u_e) - I_e^s \quad \text{on } Q, \tag{5.1b}$$

$$M_i \nabla u_i \cdot \nu = 0 \quad \text{on } \partial\Omega \times (0, T), \tag{5.1c}$$

$$M_e \nabla u_e \cdot \nu = 0 \quad \text{on } \partial\Omega \times (0, T), \tag{5.1d}$$

$$v(x, 0) = V_0(x) \quad \text{on } \Omega, \tag{5.1e}$$

and the ODE system

$$\partial_t \mathbf{w} = \mathbf{F}(v, \mathbf{w}) \quad \text{on } Q, \tag{5.2a}$$

$$\partial_t \mathbf{z} = \mathbf{G}(v, \mathbf{w}, \mathbf{z}) \quad \text{on } Q, \tag{5.2b}$$

$$\mathbf{w}(x, 0) = \mathbf{w}_0(x) \quad \text{on } \Omega, \tag{5.2c}$$

$$\mathbf{z}(x, 0) = \mathbf{z}_0(x) \quad \text{on } \Omega. \tag{5.2d}$$

The condition on the initial datum.

In view of the result of continuity for the solution v of the macroscopic model, we must ask for the initial datum V_0 to be compatible, in a sense that we shall make precise, with the Neumann homogeneous conditions (5.1c) and (5.1d). Intuitively, if $V_0 = u_i^0 - u_e^0$, then we should have

$$M_i \nabla u_i^0 \cdot \nu = 0 = M_e \nabla u_e^0 \cdot \nu, \quad \text{on } \partial\Omega,$$

but fixing both $u_i(x,0)$ and $u_e(x,0)$, as initial data, may render the problem unsolvable, since the time derivative involves only the difference $u_i - u_e$. The correct assumption may seem abstract at present, but will be clarified in Section 5.1: let $v \in H^1(\Omega)$ be given, then the following minimization problem has a unique solution:

$$\min \left\{ \sum_{i,e} \int_\Omega M_{i,e} \nabla \bar{u}_{i,e} \cdot \nabla \bar{u}_{i,e} \, dx \ : \ \bar{u}_{i,e} \in H^1(\Omega), \quad \int_\Omega \bar{u}_e \, dx = 0, \quad \bar{u}_i - \bar{u}_e = v \right\}. \tag{5.3}$$

Now, if $I_i^s(0) + I_e^s(0) \in L^2(\Omega)$, then the following elliptic problem has a unique solution $u_b^0 \in H^2(\Omega)$:

$$\begin{cases} -\operatorname{div}((M_i + M_e)\nabla u_b^0) = I_i^s(0) + I_e^s(0) & \text{on } \Omega, \\ ((M_i + M_e)\nabla u_b^0) \cdot \nu = 0 & \text{on } \partial\Omega, \\ \displaystyle\int_\Omega u_b^0 \, dx = 0. \end{cases} \tag{5.4}$$

Finally, we say that an initial datum V_0 satisfies the *admissibility property* if

$$\begin{cases} \textit{the couple } (\bar{u}_i, \bar{u}_e) \textit{ solution of } (5.3) \textit{ w.r.t. } V_0, \textit{ satisfies} \\ M_i(\nabla \bar{u}_i + u_b^0) \cdot \nu = M_e \nabla(\bar{u}_e + u_b^0) \cdot \nu = 0 \quad \text{on } \partial\Omega. \end{cases} \tag{5.5}$$

Remark 5.1. From the modelistic point of view, it is not restrictive to suppose that the myocardial fibers are tangent to $\partial\Omega$, i.e. that

$$M_i \nu \textit{ and } M_e \nu \textit{ have the same direction on } \partial\Omega.$$

In this case, the *admissibility property* (5.5) has a considerably simpler formulation, since it is equivalent to

$$M_i \nabla V_0 \cdot \nu = 0, \quad (\text{or } M_e \nabla V_0 \cdot \nu = 0,) \quad \text{on } \partial\Omega. \tag{5.6}$$

For sake of generality, we shall state the main result and carry on the proofs only with the choice (5.5).

We can now state our main result concerning the existence of a variational solution for Problem ($\mathbf{M}$).

Theorem 5.1. *Assume that*

$$\Omega \textit{ is of class } C^{1,1}, \qquad M_{i,e} \textit{ are Lipschitz in } \Omega.$$

Let be given the data

$$V_0 \in H^2(\Omega), \textit{ satisfying the admissibility property (5.5),}$$

$$\mathbf{w}_0 : \Omega \to [0,1]^k, \quad \textit{measurable},$$
$$\mathbf{z}_0 \in (L^2(\Omega))^m, \quad \textit{with } \mathbf{log}\, \mathbf{z}_0 \in (L^2(\Omega))^m,$$
$$I^s_{i,e} \in L^p(0,T;L^2(\Omega)), \quad \textit{for } p > 4, \textit{ satisfying (1.28) and}$$
$$I^s_i + I^s_e \in H^1(0,T;L^2(\Omega)).$$

Let be given the ionic currents satisfying (1.13–1.15), the dynamics of the gating variables $\mathbf{F}(v,\mathbf{w})$*, satisfying (1.16–1.17c), the dynamics of the ionic concentrations* $\mathbf{G}(v,\mathbf{w},\mathbf{z})$*, satisfying (1.19), (1.20).*

*Then, there exists a unique solution of Problem (**M**), given by $k+m+2$ functions* $w_1, ..., w_k,\ z_1, ..., z_m,\ u_i,\ u_e$*, satisfying*

$$u_{i,e} \in L^p(0,T;H^2(\Omega)) \cap C^0([0,T];H^1(\Omega)),$$

$$v := u_i - u_e \ \in W^{1,p}(0,T;L^2(\Omega)) \cap L^p(0,T;H^2(\Omega)) \cap C^0([0,T];C^0(\Omega)),$$
$$\mathbf{w} : Q \to [0,1]^k \textit{ measurable}, \quad \mathbf{z} : Q \to (0,+\infty)^m \textit{ measurable},$$
$$w_j(x,\cdot) \in C^1(0,T) \cap C^0([0,T]) \textit{ for a.e. } x \in \Omega, \quad j = 1,...,k,$$
$$z_i(x,\cdot) \in C^1(0,T) \cap C^0([0,T]) \textit{ for a.e. } x \in \Omega, \quad i = 1,...,m,$$
$$\mathbf{z} \in H^1(0,T;L^2(\Omega))^m \cap L^\infty(Q)^m, \quad \mathbf{log}\,\mathbf{z} \in L^\infty(Q)^m.$$

Remark 5.2. If we assume that $M_i\nu$ and $M_e\nu$ have the same direction on $\partial\Omega$, as in Remark 5.1, the hypothesis on the initial datum $V_0 \in H^2(\Omega)$ can be weakened, assuming that V_0 belongs to the real interpolation space:

$$(L^2(\Omega), H^2(\Omega))_{\theta,p} = B^{2\theta}_{2,p}(\Omega), \quad \theta = 1 - 1/p, \quad p > 4,$$

and that V_0 satisfies hypothesis (5.6). For instance, it is sufficient that $V_0 \in H^{3/2+\varepsilon}(\Omega)$, for some $\varepsilon > 0$ (and (5.6) holds).

Steps of the proof. The proof of Theorem 5.1 is divided into three parts. In a first step we fixed v and solved the ODE systems of the gating (5.2a, 5.2c) and concentration (5.2b, 5.2d) variables, obtaining suitable a priori estimates and qualitative properties of the solution. This part is common for the microscopic and the macroscopic models and is described in Chapter 2.

In the second step we will apply the abstract reduction technique exposed in Section 3.3 to system (5.1a)–(5.1e), in order to divide it into an elliptic equation coupled with a non degenerate parabolic equation in $L^2(\Omega)$, governed by the generator of an analytic semigroup. Considering $I_{ion}(v, \mathbf{w}, \mathbf{z})$ as a known function, we apply a result of maximal regularity in L^p, obtaining existence, uniqueness and estimates for $v = u_i - u_e$ in $L^p(0,T; H^2(\Omega)) \cap W^{1,p}(0,T; L^2(\Omega))$ (Section 5.1). Proposition 5.1, in particular, is a refinement of Proposition 3.2. This improvement has been possible due to the simpler geometrical situation with respect to the microscopic setting (for instance, the difference of potential v is not defined only the surface Γ, but it has the same domain Ω as u_i and u_e, and we can obtain the regularity we need on v up to the boundary of Ω. These details translate in the possibility to obtain a better regularity for the solutions of the macroscopic problem, and finally to obtain uniqueness for the solution).

The estimates thus obtained, owing to classical interpolation techniques, provide a crucial bound for v in $L^\infty(Q)$. Then, by choosing the correct functional spaces for $\mathbf{w}, \mathbf{z}$ and v, it is possible to find existence and uniqueness for a solution $(v, \mathbf{w}, \mathbf{z})$ of Problem (**M**), using Banach's Fixed Point Theorem (Section 5.2).

5.1 The Parabolic equation

Our next step will be to solve system (5.1a–5.1e), considering the ionic current I_{ion} as a known function, as we did in Chapter 3. As before, let $\mathbf{w}$, $\mathbf{z}$, be known functions, satisfying the thesis of Propositions 2.1 and 2.2, let $\bar{v} \in H^1(0,T; L^2(\Omega))$ be given, and set

$$\bar{I}_{ion}(x,t) := I_{ion}(\bar{v}(x,t), \mathbf{w}(x,t), \mathbf{z}(x,t)). \tag{5.1}$$

We recall the estimates on $\bar{I}_{ion}$:

$$\|\bar{I}_{ion}\|^2_{L^2(0,t;L^2(\Omega))} \leq C \left(1 + \|\bar{v}\|^2_{L^2(0,t;L^2(\Omega))}\right), \qquad \forall\, t \in [0,T], \tag{5.2}$$

and

$$\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} \leq C \left(1 + \|\bar{v}\|_{L^2(\Omega, H^1(0,T))}\right), \tag{5.3}$$

where C is a constant, independent of $\bar{v}, \mathbf{w}, \mathbf{z}$.

We state the main result of this section.

Proposition 5.1. *Assume that*

$$\Omega \text{ is of class } C^{1,1}, \qquad M_{i,e} \text{ are Lipschitz in } \Omega.$$

Let $p \in (4, +\infty)$. *Given* V_0*, satisfying the admissibility property (5.5), with*

$$V_0 \in H^2(\Omega), \quad \bar{I}_{ion} \in L^p(0,T;L^2(\Omega)),$$

$$I^s_{i,e} \in L^p(0,T;L^2(\Omega)): \quad I^s_i + I^s_e \in H^1(0,T;L^2(\Omega)),$$

satisfying the compatibility condition

$$\int_\Omega I^s_i + I^s_e \; dx = 0, \quad \forall\, t \in [0,T].$$

There exists a unique couple (u_i, u_e)*,* $(v = u_i - u_e)$ *with* $\int_\Omega u_e \; dx = 0$*,*

$$u_{i,e} \in L^p(0,T;H^2(\Omega)) \cap C^0([0,T];H^1(\Omega)),$$

$$v \in W^{1,p}(0,T;L^2(\Omega)) \cap L^p(0,T;H^2(\Omega)),$$

which satisfies

$$\begin{aligned}
\partial_t v + \bar{I}_{ion} - \operatorname{div}(M_i \nabla u_i) - I^s_i &= 0 && \text{on } Q, && (5.4a)\\
\partial_t v + \bar{I}_{ion} + \operatorname{div}(M_e \nabla u_e) + I^s_e &= 0 && \text{on } Q, && (5.4b)\\
M_e \nabla u_e \cdot \nu &= 0 && \text{on } \partial\Omega \times (0,T), && (5.4c)\\
M_i \nabla u_i \cdot \nu &= 0 && \text{on } \partial\Omega \times (0,T), && (5.4d)\\
v(x,0) &= V_0(x) && \text{on } \Omega. && (5.4e)
\end{aligned}$$

We have the a priori estimates

$$\begin{aligned}
&\|u_{i,e}\|_{L^p(0,T;H^2(\Omega))} + \|v\|_{W^{1,p}(0,T;L^2(\Omega))} \le C\big(\|V_0\|_{H^2(\Omega)} + \\
&\quad + \|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} + \|I^s_{i,e}\|_{L^p(0,T;L^2(\Omega))} + \|I^s_i + I^s_e\|_{H^1(0,T;L^2(\Omega))}\big),
\end{aligned} \tag{5.5}$$

and, if $v^{(1)}, v^{(2)}$ *are the solutions corresponding to data* $\bar{I}^{(1)}_{ion}, \bar{I}^{(2)}_{ion}$*, it holds:*

$$\|v^{(2)}(t) - v^{(1)}(t)\|^2_{L^2(\Omega)} \le C\|\bar{I}^{(1)}_{ion} - \bar{I}^{(2)}_{ion}\|^2_{L^2(0,t;L^2(\Omega))}, \quad \forall\, t \in [0,T]. \tag{5.6}$$

In system (5.4a)–(5.4e) the time derivative involves only the difference of the potentials u_i, u_e (it is a parabolic degenerate evolution system). Owing to the unequal anisotropy ratio of the diffusion tensors M_i, M_e, we cannot reduce the system directly to a single equation in v, see Remark 1.4. We will use the special *reduction* *technique*, exhibited in Section 3.1, in order to separate the system into an elliptic equation and a parabolic (nondegenerate) equation.

Subtracting equation (5.4b) from (5.4a) and summing Neumann conditions (5.4c) and (5.4d) we find

$$\begin{cases} -\operatorname{div}(M_i \nabla u_i) - \operatorname{div}(M_e \nabla u_e) = I_i^s + I_e^s & \text{on } \ Q, \\ (M_i \nabla u_i + M_e \nabla u_e) \cdot \nu = 0 & \text{on } \ \Sigma. \end{cases} \tag{5.7}$$

Summing equations (5.4a) and (5.4b) and subtracting equation (5.4c) from (5.4d), we have

$$\begin{cases} \partial_t v + \bar{I}_{ion} - \dfrac{\operatorname{div}(M_i \nabla u_i) - \operatorname{div}(M_e \nabla u_e)}{2} = \dfrac{I_i^s - I_e^s}{2} & \text{on } \ Q, \\ (M_i \nabla u_i - M_e \nabla u_e) \cdot \nu = 0 & \text{on } \ \Sigma, \\ v(x,0) = V_0(x) & \text{on } \ \Omega. \end{cases} \tag{5.8}$$

The reduction technique. We can now use the reduction technique (Section 3.1) in order to exploit the particular form of systems (5.7) and (5.8). We recall the basic definitions, making the necessary adjustments. We denote by boldface letters $\mathbf{u}$ and $\hat{\mathbf{u}}$ the couples of functions (u_i, u_e), $(\hat{u}_i, \hat{u}_e)$ and we recall the Hilbert spaces

$$\mathbf{V} := H^1(\Omega) \times H^1_*(\Omega), \qquad H^1_*(\Omega) := \left\{ u \in H^1(\Omega) \ : \ \int_\Omega u(x)\ dx = 0 \right\},$$

the *symmetric, nonnegative* bilinear forms

$$b(\mathbf{u}, \hat{\mathbf{u}}) := \int_\Omega (u_i - u_e)(\hat{u}_i - \hat{u}_e)\ dx,$$

$$a(\mathbf{u}, \hat{\mathbf{u}}) := \int_\Omega (M_i \nabla u_i) \cdot \nabla \hat{u}_i + (M_e \nabla u_e) \cdot \nabla \hat{u}_e\ dx,$$

and the linear continuous operators $A, B : \mathbf{V} \to \mathbf{V}'$ defined by

$$\langle A\mathbf{u}, \hat{\mathbf{u}} \rangle := a\,(\mathbf{u}, \hat{\mathbf{u}}), \qquad \langle B\mathbf{u}, \hat{\mathbf{u}} \rangle := b\,(\mathbf{u}, \hat{\mathbf{u}}),$$

$\forall\ \mathbf{u}, \hat{\mathbf{u}} \in \mathbf{V}$. We remark that the kernel of b has infinite dimension, and that by Property $\mathcal{P}3$), using (1.30) and Poincaré inequality, the sum of the quadratic forms associated to a and b is coercive on $\mathbf{V}$, i.e.

$$\exists\, \alpha > 0 : \quad a(\mathbf{u}, \mathbf{u}) + b(\mathbf{u}, \mathbf{u}) \geq \alpha \|\mathbf{u}\|^2_{\mathbf{V}}, \quad \forall\, \mathbf{u} \in \mathbf{V}. \tag{5.9}$$

Then we associate to the bilinear forms a, b the Let us denote by $\mathbf{K}_b \subset \mathbf{V}$ the kernel of $b(\cdot,\cdot)$, which is now given by

$$\mathbf{K}_b := \{\mathbf{u} \in \mathbf{V} : u_i \equiv u_e, \text{ a.e. in } \Omega\} = \{\mathbf{u} \in \mathbf{V} : b(\mathbf{u}, \mathbf{u}) = 0\},$$

and by $\mathbf{K}_a \subset \mathbf{V}$ the subspace of $\mathbf{V}$ which is a-orthogonal to $\mathbf{K}_b$:

$$\mathbf{K}_a := \{\mathbf{u} \in \mathbf{V} : a(\mathbf{u}, \mathbf{k}) = 0, \ \forall \mathbf{k} \in \mathbf{K}_b\}.$$

Remark 5.3. If $\mathbf{u} \in \mathbf{K}_a$, and $u_i, u_e \in H^2(\Omega)$, then (u_i, u_e) is a solution of

$$\begin{cases} \operatorname{div}(M_i \nabla u_i + M_e \nabla u_e) = 0, & \text{on } \Omega, \\ (M_i \nabla u_i + M_e \nabla u_e) \cdot \nu = 0, & \text{on } \partial\Omega. \end{cases}$$

We denote by $\mathbf{R} : H^1(\Omega) \to \mathbf{V}$ a right inverse of B, defined by

$$\mathbf{R}v = \mathbf{u} \quad \Leftrightarrow \quad B\mathbf{u} = v, \quad \text{and} \quad \mathbf{u} \in \mathbf{K}_a. \tag{5.10}$$

By (5.9) we have that $a(\cdot,\cdot)$ is coercive on $\mathbf{K}_b$, then Riesz Fréchet Theorem ensures that $\mathbf{R} : H^1(\Omega) \to \mathbf{K}_a \subset \mathbf{V}$ is a linear isomorphism. Observe that $\mathbf{V} \simeq \mathbf{K}_a \oplus \mathbf{K}_b$ and each $\mathbf{u} \in \mathbf{V}$ admits the linear decomposition

$$\mathbf{u} = \mathbf{R}v + \mathbf{u}_b : \quad v = B\mathbf{u}, \quad \mathbf{R}v \in \mathbf{K}_a, \quad \mathbf{u}_b \in \mathbf{K}_b. \tag{5.11}$$

The reduced equations. If we denote $(R_i v, R_e v) = \mathbf{R}v$, and $(u_b, u_b) = \mathbf{u}_b$, owing to decomposition (5.11) and to Remark 5.3, we can rewrite system (5.7) as

$$\begin{cases} -\operatorname{div}((M_i + M_e)\nabla u_b) = I_i^s + I_e^s & \text{on } Q, \\ ((M_i + M_e)\nabla u_b) \cdot \nu = 0 & \text{on } \Sigma, \end{cases} \tag{5.12}$$

and system (5.8) as

$$\begin{cases} \partial_t v + \bar{I}_{ion} - \operatorname{div} \beta (\mathbf{R}v + \mathbf{u}_b) = \dfrac{I_i^s - I_e^s}{2} & \text{on } Q, \\ \beta(\mathbf{R}v + \mathbf{u}_b) \cdot \nu = 0 & \text{on } \Sigma, \\ v(x, 0) = V_0(x) & \text{on } \Omega, \end{cases} \tag{5.13}$$

where $\beta : H^1(\Omega) \times H^1(\Omega) \to L^2(\Omega)^3$, is the linear continuous operator defined by

$$\beta\mathbf{u} := \frac{M_i \nabla u_i - M_e \nabla u_e}{2}, \quad \forall \mathbf{u} = (u_i, u_e) \in H^1(\Omega) \times H^1(\Omega). \tag{5.14}$$

In order to univocally solve (5.12), we impose the condition

$$\int_\Omega u_b \, dx = 0,$$

which is the analogous of the usual condition (1.29) in Section 1.2.

Proof of Proposition 5.1.
The proof is structured as follows: first we solve the elliptic equation (depending from the time parameter) (5.12), which is independent of v, and we derive the estimates on u_b (Lemma 5.1). Then, considering u_b as a known function, we give a variational formulation of (5.13) in the classical Hilbert triple $(H^1(\Omega), L^2(\Omega), H^1(\Omega)')$. In order to obtain the best regularity for the solution of equation (5.13), we separate in two different equations the term $\bar{I}_{ion} + (I_i^s - I_e^s)/2$ (Lemma 5.2) and the term $-\text{div}\beta(\mathbf{u}_b)$ (Lemma 5.3).

Lemma 5.1. *Assume that*

$$\Omega \textit{ is of class } C^{1,1}, \qquad M_{i,e} \textit{ are Lipschitz in } \Omega. \tag{5.15}$$

Given

$$I_{i,e}^s \in L^2(0,T;L^2(\Omega)) : \quad I_i^s + I_e^s \in H^1(0,T;L^2(\Omega)), \tag{5.16}$$

satisfying the compatibility condition

$$\int_\Omega I_i^s + I_e^s \, dx = 0, \quad \forall\, t \in [0,T],$$

there exists a unique

$$u_b \in H^1(0,T;H^2(\Omega)) \tag{5.17}$$

which solves

$$\begin{cases} -\text{div}((M_i + M_e)\nabla u_b) = I_i^s + I_e^s & \textit{on } \; Q, \\ ((M_i + M_e)\nabla u_b) \cdot \nu = 0 & \textit{on } \; \Sigma, \\ \displaystyle\int_\Omega u_b \, dx = 0 & \forall\, t \in [0,T], \end{cases} \tag{5.18}$$

and

$$\|u_b\|_{H^1(0,T;H^2(\Omega))} \leq C\|I_i^s + I_e^s\|_{H^1(0,T;L^2(\Omega))}. \tag{5.19}$$

Proof. By hypothesis (1.30), $M_i + M_e$ is uniformly elliptic, therefore, owing to (5.15), (5.16), the result of Lemma 5.1 follows directly by standard regularity estimates for elliptic problems depending on the time parameter t (see e.g. [27]).

Our next step will be to write a variational formulation for system (5.13), in the classical Hilbert triple $(H^1(\Omega), L^2(\Omega), H^1(\Omega)')$, considering $\mathbf{u}_b$ as a known function. We denote by $\langle \cdot, \cdot \rangle$ the duality between $H^1(\Omega)'$ and $H^1(\Omega)$.

We choose a test function $\varphi \in H^1(\Omega)$, multiply the first equation in (5.13) by φ, integrate on Ω and use Green formula and the boundary condition in (5.13), thus obtaining:

$$\int_\Omega \partial_t v(t)\varphi \, dx + \int_\Omega \beta(\mathbf{R}v(t) + \mathbf{u}_b(t))\nabla\varphi \, dx = \int_\Omega \left(\frac{I_i^s(t) - I_e^s(t)}{2} - \bar{I}_{ion}(t) \right) \varphi \, dx. \tag{5.20}$$

We denote by $\mathbf{R}^*a : H^1(\Omega) \times H^1(\Omega) \to \mathbb{R}$ the pullback form of a through $\mathbf{R}$:

$$(\mathbf{R}^*a)(v, w) = a(\mathbf{R}v, \mathbf{R}w) = \int_\Omega M_i \nabla(R_i v)\nabla(R_i w) + M_e \nabla(R_e v)\nabla(R_e w) \, dx, \tag{5.21}$$

for every $v, w \in H^1(\Omega)$. Since $\mathbf{R}$ is a linear isomorphism, $\mathbf{R}^*a$ is a continuous, symmetric bilinear form, and it is weakly elliptic, that is

$$\exists\, \alpha > 0 : \; \mathbf{R}^*a(v, v) + (v, v)_{L^2(\Omega)} \geq \alpha \|v\|_{H^1(\Omega)}, \quad \forall\, v \in H^1(\Omega).$$

By definition of $\mathbf{R}$, we have that $\mathbf{R}v \in \mathbf{K}_a$, and therefore we can write $\mathbf{R}^*a$ as

$$(\mathbf{R}^*a)(v, w) = \frac{1}{2}\int_\Omega (M_i \nabla R_i v - M_e \nabla R_e v)(\nabla R_i w - \nabla R_e w) \, dx = \int_\Omega \beta(\mathbf{R}v)\nabla w \, dx, \tag{5.22}$$

moreover, we can associate to the bilinear form $\mathbf{R}^*a$ the linear continuous operator $A_R : H^1(\Omega) \to H^1(\Omega)'$

$$\langle A_R v, \varphi \rangle := \mathbf{R}^*a(v, \varphi), \quad \forall\, \varphi \in H^1(\Omega). \tag{5.23}$$

We shall also consider the realization of A_R on the domain

$$\begin{aligned} D_{L^2(\Omega)}(A_R) \; &:= \{ v \in H^1(\Omega) \; : \; A_R v \in L^2(\Omega) \} \\ &= \{ v \in H^2(\Omega) \; : \; \beta(\mathbf{R}v) \cdot \nu = 0, \text{ on } \partial\Omega \}. \end{aligned} \tag{5.24}$$

We define the function

$$L_1(t) := \frac{I_i^s(t) - I_e^s(t)}{2} - \bar{I}_{ion}(t), \tag{5.25}$$

and the family of linear operators $\{L_2(t)\}_{t \in [0,t]} : H^1(\Omega) \to H^1(\Omega)'$

$$\langle L_2(t), \varphi \rangle := -\int_\Omega \beta(\mathbf{u}_b(t))\nabla\varphi \, dx, \quad \forall\, \varphi \in H^1(\Omega). \tag{5.26}$$

Owing to definitions (5.22)–(5.26), and linearity of $\mathbf{R}^*a$, in order to study equation (5.20), we can examine the separate problems

$$\begin{cases} \dfrac{d}{dt}v_1(t) + A_R v_1(t) = L_1(t), \quad \text{in } L^2(\Omega), \text{ for a.e. } t \in (0,T), \\ v_1(0) = 0, \end{cases}$$

with boundary conditions included in the definition of the domain $D_{L^2(\Omega)}(A_R)$, and

$$\begin{cases} \dfrac{d}{dt}v_2(t) + A_R v_2(t) = L_2(t), \quad \text{in } H^1(\Omega)', \text{ for a.e. } t \in (0,T), \\ v_2(0) = V_0. \end{cases}$$

Lemma 5.2. *Assume that (5.15) holds, let $p \in (4, +\infty)$. Given $\mathbf{R}$, β, A_R, $D_{L^2(\Omega)}(A_R)$, L_1 defined in (5.10), (5.14), (5.23), (5.24), (5.25).*

$$\begin{aligned} &\bar{I}_{ion} \in L^p(0,T;L^2(\Omega)), \\ &I_i^s, I_e^s \in L^p(0,T;L^2(\Omega)). \end{aligned} \tag{5.27}$$

There exists a unique

$$v_1 \in W^{1,p}(0,T;L^2(\Omega)) \cap L^p(0,T;H^2(\Omega)),$$

which solves $v_1(0) = 0$, $v_1(t) \in D_{L^2(\Omega)}(A_R)$, a.e. in $(0,T)$,

$$\frac{d}{dt}v_1(t) + A_R v_1(t) = L_1(t), \quad \textit{in } L^2(\Omega), \textit{ for a.e. } t \in (0,T), \tag{5.28}$$

and we have the a priori estimates

$$\|v_1\|_{W^{1,p}(0,T;L^2(\Omega))} \le C\left(\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} + \|I_{i,e}^s\|_{L^p(0,T;L^2(\Omega))}\right), \tag{5.29}$$

$$\|v_1\|_{L^p(0,T;H^2(\Omega))} \le C\left(\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} + \|I_{i,e}^s\|_{L^p(0,T;L^2(\Omega))}\right). \tag{5.30}$$

Lemma 5.3. *Assume that (5.15) holds. Let be given*

$$V_0 \in H^2(\Omega), \quad \textit{satisfying } (5.5), \tag{5.31}$$

$$I_{i,e}^s \in L^2(0,T;L^2(\Omega)): \quad I_i^s + I_e^s \in H^1(0,T;L^2(\Omega)), \tag{5.32}$$

u_b as in Lemma 5.1, thus satisfying $u_b \in H^1(0,T;H^2(\Omega))$, and $\mathbf{R}$, β, A_R, L_2 as defined in (5.10), (5.14), (5.23), (5.26). There exists a unique function

$$v_2 \in W^{1,\infty}(0,T;L^2(\Omega)) \cap H^1(0,T;H^1(\Omega)) \cap L^\infty(0,T;H^2(\Omega))$$

which solves $v_2(0) = V_0$,

$$\frac{d}{dt} v_2(t) + A_R v_2(t) = L_2(t), \quad \text{in } H^1(\Omega)', \text{ for a.e. } t \in (0,T), \tag{5.33}$$

and we have the a priori estimates

$$\|v_2\|_{W^{1,\infty}(0,T;L^2(\Omega))} \leq C\left(\|V_0\|_{H^2(\Omega)} + \|I_i^s + I_e^s\|_{H^1(0,T;L^2(\Omega))}\right),$$

$$\|v_2\|_{H^1(0,T;H^1(\Omega))} \leq C\left(\|V_0\|_{H^2(\Omega)} + \|I_i^s + I_e^s\|_{H^1(0,T;L^2(\Omega))}\right),$$

$$\|v_2\|_{L^\infty(0,T;H^2(\Omega))} \leq C\left(\|V_0\|_{H^2(\Omega)} + \|I_i^s + I_e^s\|_{H^1(0,T;L^2(\Omega))}\right).$$

Proof of Lemma 5.2. We recall a result by L. de Simon on maximal regularity in L^p (see [24])

Theorem 5.1. *Let* H *be a Hilbert space,* $p \in (1, +\infty)$,
$\mathcal{A} : D(\mathcal{A}) \to H$ *be the generator of an analytic semigroup on* H,
$f \in L^p(0,T;H)$.
Then, there exists a unique

$$u \in L^p(0,T;D(\mathcal{A})) \cap W^{1,p}(0,T;H),$$

satisfying the system

$$\begin{cases} u'(t) + \mathcal{A}u(t) = f(t), & \text{in } H, \text{ for a.e. } t \in]0,T[, \\ u(0) = 0. \end{cases}$$

and there exist $C > 0$ *such that*

$$\|u'\|_{L^p(0,T;H)} + \|u\|_{L^p(0,T;D(\mathcal{A}))} \leq C\|f\|_{L^p(0,T;H)}.$$

Remark 5.4. De Simon's result can be generalized, since, for every $p \in (1, +\infty)$, it holds

$$(H, D(\mathcal{A}))_{1-\frac{1}{p},p} = \left\{x = u(0) : \ u \in L^p(0,+\infty;D(\mathcal{A})) \cap W^{1,p}(0,+\infty;H)\right\},$$

then it is possible to choose $u(0) \in (H, D(\mathcal{A}))_{1-\frac{1}{p},p}$, moreover, under suitable assumptions, the space H can be a Banach space (see e.g. [44], [10], [11]).

By standard results about the generation of analytic semigroups, (see [23], [48]), the operator

$$A_R : D_{L^2(\Omega)}(A_R) \to L^2(\Omega)$$

is sectorial. This can be easily verified, owing to the properties of the associated bilinear form $\mathbf{R}^*a$ (5.21). It may also be observed that A_R is symmetric self-adjoint on a Hilbert space ([23]). See, in particular, [48, Theorem 3.1.2–*(iii)*] for the resolvent estimates in the case of second order elliptic operators with first order boundary conditions.

Estimate (5.3) and hypothesis (5.27) yield $L_1 \in L^p(0,T;L^2(\Omega))$. Then, we can apply Theorem 5.1, which provides existence, uniqueness and estimates (5.29) and (5.30) for v_1, solution of (5.13). Moreover (as will be better explained in the next Section) $v_1 \in W^{1,p}(0,T;L^2(\Omega)) \cap L^p(0,T;H^2(\Omega))$, for $p \geq 2$ implies

$$v_1 \in C^0([0,T];H^1(\Omega)).$$

Since by Lemma 5.3 we will also have $v_2 \in C^0([0,T];H^1(\Omega))$, by continuity of $\mathbf{R}$ we obtain

$$\mathbf{R}(v_1 + v_2) \in C^0([0,T];\mathbf{V}),$$

which combined with (5.17) yields $\mathbf{u} \in C^0([0,T];\mathbf{V})$.

□

Proof of Lemma 5.3. We recall a classical result by J. L. Lions for linear parabolic partial differential equations in a Hilbert triple (V,H,V') [46, 45]. Let $A \in \mathcal{L}(V,V')$ be a weakly elliptic operator, let be given $u_0 \in H$, $f \in L^2(0,T;V')$, there exists a unique function u which satisfies

$$u \in L^2(0,T;V), \quad u' \in L^2(0,T;V'), \tag{5.34a}$$

$$u'(t) + Au(t) = f(t) \text{ in } V', \quad u(0) = u_0, \tag{5.34b}$$

$$\|u\|_{L^2(0,T;V)} + \|u'\|_{L^2(0,T;V')} \leq C_1(\|u_0\|_H + \|f\|_{L^2(0,T;V')}). \tag{5.34c}$$

Moreover, if

$$df/dt \in L^2(0,T;V') \quad \text{and} \quad Au_0 - f(0) \in H, \tag{5.35}$$

owing to the linearity of equation (5.34b), it can be seen that

$$u \in H^1(0,T;V) \cap W^{1,\infty}(0,T;H),$$

$$Au(t) - f(t) \in L^\infty(0,T;H), \tag{5.36}$$

$$\|u\|_{H^1(0,T;V)} + \|u\|_{W^{1,\infty}(0,T;H)} \leq C_2(\|u_0\|_H + \|Au_0 - f(0)\|_H + \|f\|_{H^1(0,T;V')}),$$

$$\|Au(t) - f(t)\|_{L^\infty(0,T;H)} \le C_2(\|u_0\|_H + \|Au_0 - f(0)\|_H + \|f\|_{H^1(0,T;V')}).$$

By hypothesis (5.32) we have $L_2 \in H^1(0,T;H^1(\Omega)')$, then, in order to meet condition (5.35) we have to ask that

$$A_R v_2(0) - L_2(0) \in L^2(\Omega).$$

For every $v,\varphi \in H^1(\Omega)$, $\forall\, t \in [0,T]$ we have that

$$\langle A_R v - L_2(t), \varphi \rangle = \int_\Omega \beta(\mathbf{R}v + \mathbf{u}_b(t))\nabla\varphi \; dx.$$

Therefore $A_R v - L_2(t) \in L^2(\Omega)$ if and only if

$$\int_\Omega \beta(\mathbf{R}v + \mathbf{u}_b(t))\nabla\varphi \; dx = -\int_\Omega \text{div } \beta(\mathbf{R}v + \mathbf{u}_b(t))\varphi \; dx.$$

Since, by Lemma 5.1, $\mathbf{u}_b(t) \in H^2(\Omega)$ $\forall\, t \in [0,T]$, $A_R v - L_2(t) \in L^2(\Omega)$ if and only if

$$-\text{div } \beta(\mathbf{R}v) = -\text{div } \frac{M_i \nabla R_i v - M_e \nabla R_e v}{2} \in L^2(\Omega),$$

and $\beta(\mathbf{R}v + \mathbf{u}_b(t)) \cdot \nu = 0$ on $\partial\Omega$, that is

$$(M_i \nabla R_i v - M_e \nabla R_e v) \cdot \nu = -(M_i - M_e)\nabla u_b(t) \cdot \nu, \quad \text{on } \partial\Omega. \tag{5.37}$$

Since, by (5.18) and Remark 5.3

$$((M_i + M_e)\nabla u_b(t)) \cdot \nu = (M_i \nabla R_i v + M_e \nabla R_e v) \cdot \nu = 0 \qquad \text{on } \ \partial\Omega,$$

then (5.37) is equivalent to

$$M_i \nabla(R_i v + u_b(t) \cdot \nu = M_e \nabla(R_e v + u_b(t) \cdot \nu = 0, \qquad \text{on } \ \partial\Omega. \tag{5.38}$$

Then, since V_0 satisfies (5.5) by hypothesis (and therefore (5.38)), we have that

$$\beta(\mathbf{R}V_0 + \mathbf{u}_b(0)) \cdot \nu = 0, \quad \text{on } \partial\Omega,$$

and (5.36) and Lemma 5.1 imply

$$\begin{cases} -\text{div } \beta(\mathbf{R}v_2) \in L^\infty(0,T;L^2(\Omega)), \\ \beta(\mathbf{R}v_2 + \mathbf{u}_b) \cdot \nu = 0, \quad \text{on } \partial\Omega \times [0,T], \end{cases}$$

then standard regularity estimates for elliptic problems yield

$$v_2 \in L^\infty(0,T;H^2(\Omega)),$$

$$\begin{aligned} \|v_2\|_{L^\infty(0,T;H^2(\Omega))} &\le C_2 \left(\|V_0\|_{H^2(\Omega)} + \|u_b\|_{H^1(0,T;H^2(\Omega))} \right) \\ &\le C_3 \left(\|V_0\|_{H^2(\Omega)} + \|I_i^s + I_e^s\|_{H^1(0,T;L^2(\Omega))} \right). \end{aligned}$$

□

In order to conclude the proof of Proposition 5.1, let $V_0 \in H^2(\Omega)$, satisfying (5.5) as in the hypothesis of Proposition 5.1, let u_b, v_1, v_2 be the solutions of equations (5.18), (5.28), (5.33) as in Lemma 5.1, 5.2, 5.3 and define

$$\begin{aligned} u_i &:= R_i(v_1+v_2) + u_b - \frac{1}{|\Omega|}\int_\Omega R_e(v_1+v_2) + u_b \, dx \\ u_e &:= R_e(v_1+v_2) + u_b - \frac{1}{|\Omega|}\int_\Omega R_e(v_1+v_2) + u_b \, dx \\ v &:= v_1 + v_2 \end{aligned}$$

Then $v = u_i - u_e$, the triple (v, u_i, u_e) is the unique solution of system (5.4a)–(5.4e), and u_e satisfies $\int_\Omega u_e \, dx = 0, \ \forall\, t \in [0,T]$.

At last, the stability estimate (5.6) follows from the linearity of equation (5.28) and estimate (5.29), $p = 2$.

□

5.2 Existence and uniqueness

Let us denote by $\mathcal{T}$ the operator that maps a function $\bar{v}$ into the solution of (5.4a)–(5.4e). We shall now introduce a suitable closed subset K of $L^2(Q)$ satisfying the following two properties:

P1) $\mathcal{T}(K) \subset (K)$

P2) $\mathcal{T}$ is a contraction with respect to a norm inducing the $L^2(Q)$ topology

Thus, Banach's Fixed Point Theorem provides existence and uniqueness for $(v, \mathbf{w}, \mathbf{z})$, solution of Problem (**M**).

Notation: If H is a Hilbert space and $\lambda \in \mathbb{R}$, denote by $|||\cdot|||_{\lambda,H}$ the norm on $L^2(0,T;H)$:

$$|||v|||_{\lambda,H} := \left(\int_0^T e^{-\lambda t}\|v(t)\|_H^2 \, dt\right)^{1/2}.$$

It is immediate to check that $|||\cdot|||_{\lambda,H}$ and $\|\cdot\|$ are equivalent norms on $L^2(0,T;H)$.

Proposition 5.2. *Let $V_0 \in H^2(\Omega)$, satisfying (5.5), $I^s_{i,e} \in L^p(0,T;L^2(\Omega))$, for $p > 4$. There exist $M_0, M_1, M_\infty, \lambda > 0$ such that the set*

$$K := \{v \in L^2(0,T;H^2(\Omega)) \cap H^1(0,T;L^2(\Omega)) \cap L^\infty((0,T)\times\Omega) : v(x,0) = V_0,$$
$$|||v|||_{\lambda,L^2(\Omega)} \le M_0,\ |||v'|||_{\lambda,L^2(\Omega)} \le M_1,\ |||v|||_{\lambda,H^2(\Omega)} \le M_1,\ \|v\|_{L^\infty(Q))} \le M_\infty\Big\},$$

satisfies the previous conditions (P1)-(P2) with respect to the norm $|||\cdot|||_{\lambda,L^2(\Omega)}$.

Our first step will be to show that $\mathcal{T}(K) \subseteq K$. This forces the solution $(v, \mathbf{w}, \mathbf{z})$ into a compact set of $\mathbb{R}^{1+k+m}$. In a second step, owing to the local Lipschitz continuity of the functions $\mathbf{F}, \mathbf{G}, I_{ion}$, we can prove a contraction estimate for operator $\mathcal{T}$.

P1) $\mathcal{T}(\mathbf{K}) \subseteq \mathbf{K}$.

Lemma 5.4. *Let* $\bar{v} \in H^1(0,T;L^2(\Omega))$*, let* $\mathbf{w}, \mathbf{z}$ *be the unique solutions of systems (2.2) and (2.9), given as in Propositions 2.1 and 2.2, and let* $\bar{I}_{ion}$ *be given as in (5.1), thus satisfying (5.2) and (5.3). Then there exists* $\lambda > 0$ *such that the solution* v *of system (5.4a)–(5.4e) satisfies*

$$|||v|||^2_{\lambda,L^2(\Omega)} \leq \max\left\{1, |||\bar{v}|||^2_{\lambda,L^2(\Omega)}\right\}, \quad \forall\, \bar{v} \in H^1(0,T;L^2(\Omega)).$$

Proof. Since

$$\|v\|_{L^\infty(0,T;L^2(\Omega))} \leq C_1 \|v\|_{H^1(0,T;L^2(\Omega))},$$

by estimate (5.5) ($p = 2$) we have

$$\|v(t)\|^2_{L^2(\Omega)} \leq C_2 \left(\|V_0\|^2_{H^1(\Omega)} + \|I_i^s\|^2_{L^2(Q)} + \|I_e^s\|^2_{L^2(Q)} + \|\bar{I}_{ion}\|^2_{L^2(0,t;L^2(\Omega))}\right). \quad (5.39)$$

Let $\varphi(t) := \|v(t)\|^2_{L^2(\Omega)}$, and $\bar{\varphi}(t) := \|\bar{v}(t)\|^2_{L^2(\Omega)}$; owing to estimates (5.2) and (5.39) we find

$$\varphi(t) \leq C_3 + C_4 \int_0^t \bar{\varphi}(s)\, ds, \quad (5.40)$$

where C_3 may depend on T, $\|V_0\|^2_{H^1(\Omega)}$, $\|I^s_{i,e}\|_{L^2(Q)}$, $\|\mathbf{z}_0\|^2_{L^2(\Omega)}$, $\|\mathbf{z}_0 \log \mathbf{z}_0\|_{L^2(\Omega)}$, $|\Omega|$, and

$$C_4 = C_4\,(T, \,|\,\Omega\,|)\,.$$

Now we multiply (5.40) by $e^{-\lambda t}$, ($\lambda > 0$), and we integrate between 0 and T:

$$\int_0^T e^{-\lambda t} \varphi(t)\, dt \leq C_3 \int_0^T e^{-\lambda t}\, dt + C_4 \int_0^T e^{-\lambda t} \left(\int_0^t \bar{\varphi}(s)\, ds\right) dt,$$

and integrating by parts

$$\int_0^T e^{-\lambda t} \varphi(t)\, dt \leq \frac{1}{\lambda}\left[C_3\left(1 - e^{-\lambda T}\right) + C_4 \int_0^T e^{-\lambda t} \bar{\varphi}(t)\, dt - C_4 e^{-\lambda T} \int_0^T \bar{\varphi}(t)\, dt\right]$$

$$\leq \frac{1}{\lambda}\left[C_3 + C_4 \int_0^T e^{-\lambda t} \bar{\varphi}(t)\, dt\right].$$

If $\displaystyle\int_0^T e^{-\lambda t}\bar\varphi(t)\,dt \geq 1$, we have that

$$\int_0^T e^{-\lambda t}\varphi(t)\,dt \leq \frac{C_3+C_4}{\lambda}\int_0^T e^{-\lambda t}\bar\varphi(t)\,dt.$$

Hence, if $\lambda \geq C_3 + C_4$, then

$$|||v|||^2_{\lambda,L^2(\Omega)} = \int_0^T e^{-\lambda t}\varphi(t)\,dt \leq \max\left\{1, \int_0^T e^{-\lambda t}\bar\varphi(t)\,dt\right\} = \max\left\{1, |||\bar v|||^2_{\lambda,L^2(\Omega)}\right\}.$$

□

Owing to estimates (5.5), $p = 2$ and (5.2), we immediately obtain

Corollary 5.3. *Let $M_0 \geq 1$, let $\bar v, \mathbf{w}, \mathbf{z}$, be as in the statement of Lemma 5.4, such that*

$$|||\bar v|||_{\lambda,L^2(\Omega)} \leq M_0,$$

then there exist $M_1 > 0$, depending only on M_0 and the data of the problem, such that

$$|||v|||_{\lambda,H^2(\Omega)} \leq M_1, \tag{5.41}$$

$$|||\partial_t v|||_{\lambda,L^2(\Omega)} \leq M_1. \tag{5.42}$$

Lemma 5.5. *Let M_0, M_1, be as in Corollary 5.3, $\bar I_{ion}$ be given as in (5.1), and $\bar v \in H^1(0,T;L^2(\Omega))$ such that*

$$|||\bar v|||_{\lambda,L^2(\Omega)} \leq M_0, \quad |||\partial_t \bar v|||_{\lambda,L^2(\Omega)} \leq M_1.$$

Let $p = 4 + \varepsilon > 4$, $I^s_{i,e} \in L^p(0,T;L^2(\Omega))$ and $V_0 \in H^2(\Omega)$, satisfying (5.5). There exists $M_\infty > 0$, depending only on M_1, p and the data of the problem, such that:

$$\sup\{|v(x,t)| : (x,t) \in Q\} \leq M_\infty.$$

We recall some classical results on real interpolation (see [68], [10], [44]). Let (X,Y) be a real interpolation couple of Banach spaces. From now on, by $Y \subset X$ we mean that Y is *continuously* embedded in X.

i) Let $p \in [1,+\infty]$, if $u \in L^p(0,T;X)$ and $\frac{du}{dt} \in L^p(0,T;Y)$, then there exists a continuous extension

$$u \in C^0\left([0,T];(X,Y)_{1-1/p,p}\right),$$

and

$$\|u(t)\|_{(X,Y)_{1-1/p,p}} \leq \|u\|_{L^p(0,T;X)} + \left\|\frac{du}{dt}\right\|_{L^p(0,T;Y)}, \quad \forall\, t \in [0,T].$$

ii) For $0 < \theta < 1$, $1 \leq p, q < +\infty$, $m \in \mathbb{N}$,

$$(L^p(\Omega), W^{m,p}(\Omega))_{\theta,q} = B^{m\theta}_{p,q}(\Omega).$$

By classical inclusions we have:
iii) If $1 \leq p < \infty$, $\Omega \subset \mathbb{R}^3$ is bounded, then

$$B^{2-2/p}_{2,p}(\Omega) \subset C^0(\Omega) \quad \text{if} \quad 2 - 2/p > 3/2.$$

Proof of Lemma 5.5. By property *ii)* we have

$$V_p := (L^2(\Omega), H^2(\Omega))_{1-1/p,p} = B^{2-2/p}_{2,p}(\Omega).$$

By (5.5) and *i)* we have that

$$v \in C^0\left([0,T]; V_p\right), \quad \forall\, p \geq 1,$$

and

$$\|u(t)\|_{V_p} \leq 2C\Big(\|V_0\|_{V_p} + \|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} + \|I^s_{i,e}\|_{L^p(0,T;L^2(\Omega))} + \|I^s_i + I^s_e\|_{H^1(0,T;L^2(\Omega))}\Big). \tag{5.43}$$

By estimate (5.3) there exists $C_5 > 0$ such that, $\forall\, p \in (1, +\infty)$

$$\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} \leq C_5\left(1 + \|\bar{v}\|_{L^2(\Omega,H^1(0,T))}\right) \leq C_6(1 + M_1). \tag{5.44}$$

By *ii)* and *iii)*, if $2 - 2/p > 3/2$, (i.e. $p > 4$) then

$$V_p \subset C^0(\Omega),$$

and therefore (v admits a continuous representative)

$$v \in C^0([0,T]; C^0(\Omega)),$$

and by estimates (5.43) and (5.44) there exists $M_\infty > 0$, depending only on M_1, p and the data of the problem, such that

$$\sup\left\{|v(x,t)|,\ (x,t) \in Q\right\} \leq M_\infty. \tag{5.45}$$

□

P2) $\mathcal{T}$ ***is a contraction.*** Now we want to show that $\mathcal{T} : K \to K$ is a contraction in $L^2(0,T;L^2(\Omega))$, endowed with the norm $|||\cdot|||_{\lambda,L^2(\Omega)}$.

Let $p > 4$, $V_0 \in H^2(\Omega)$, $\mathbf{w}_0(x) : \Omega \to [0,1]^k$, measurable, and $\mathbf{z}_0 : \Omega \to (0,+\infty)^m$, such that

$$\mathbf{z}_0 \in (L^2(\Omega))^m, \qquad \mathbf{log}\, \mathbf{z}_0 \in (L^2(\Omega))^m.$$

Let $\bar{v}_i \in K$, $i = 1, 2$. Let $\mathbf{w}_i$ be the solutions of system (2.1), as in the thesis of Proposition 2.1, corresponding to $\bar{v}_i$:

$$\begin{cases} \dfrac{\partial \mathbf{w}_i}{\partial t} = \mathbf{F}(\bar{v}_i, \mathbf{w}_i), & \text{on } Q, \\ \mathbf{w}_i(x,0) = \mathbf{w}_0(x), & \text{on } \Omega, \end{cases}$$

and let $\mathbf{z}_i$, as in the thesis of Proposition 2.2, be the corresponding solutions of system (2.9)

$$\begin{cases} \dfrac{\partial \mathbf{z}_i}{\partial t} = \mathbf{G}(\bar{v}_i, \mathbf{w}_i, \mathbf{z}_i), & \text{on } Q, \\ \mathbf{z}_i(x,0) = \mathbf{z}_0(x), & \text{on } \Omega. \end{cases}$$

By estimates (2.4), (2.11), (5.45), there exists a compact set $\tilde{\mathcal{C}} = \tilde{\mathcal{C}}(T) \subseteq \mathbb{R} \times \mathbb{R}^k \times \mathbb{R}^m$ such that

$$(\bar{v}_i(x,t), \mathbf{w}_i(x,t), \mathbf{log}\, \mathbf{z}_i(x,t)) \in \tilde{\mathcal{C}}, \quad \forall (x,t) \in Q, \; i = 1, 2,$$

and therefore, there exists a compact set $\mathcal{C} = \mathcal{C}(T) \subseteq \mathbb{R} \times \mathbb{R}^k \times (0,+\infty)^m$ such that

$$(\bar{v}_i(x,t), \mathbf{w}_i(x,t), \mathbf{z}_i(x,t)) \in \mathcal{C}, \quad \forall (x,t) \in Q, \; i = 1, 2.$$

By hypothesis (1.17a), $\mathbf{F}$ is locally Lipschitz continuous, therefore, there exists $L_1 > 0$, depending on $\mathcal{C}$ such that

$$|\mathbf{w}_1(x,t) - \mathbf{w}_2(x,t)| \le L_1 \int_0^t |\bar{v}_1(x,s) - \bar{v}_2(x,s)| + |\mathbf{w}_1(x,s) - \mathbf{w}_2(x,s)| \, ds, \quad \forall (x,t) \in Q.$$

Thus, by Jensen inequality, integrating on Ω we obtain

$$\|\mathbf{w}_1(t) - \mathbf{w}_2(t)\|^2_{L^2(\Omega)} \le 2L_1 \int_0^t \|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)} + \|\mathbf{w}_1(s) - \mathbf{w}_2(s)\|^2_{L^2(\Omega)} ds,$$

for every $t \in (0,T)$, and by Gronwall's Lemma

$$\|\mathbf{w}_1(t) - \mathbf{w}_2(t)\|^2_{L^2(\Omega)} \le 2L_1 e^{2L_1 T} \int_0^t \|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)} ds, \; \forall\, t \in (0,T). \tag{5.46}$$

By hypothesis (1.14a) we have $J_i \in C^1\left(\mathbb{R} \times \mathbb{R}^k \times \mathbb{R}\right)$, thus

$$J_i(\cdot, \cdot, \log(\cdot)) \in C^1\left(\mathbb{R} \times \mathbb{R}^k \times (0,+\infty)\right),$$

so $\mathbf{G} = \mathbf{J} + \mathbf{H}$ is locally Lipschitz continuous on $(\mathbb{R} \times \mathbb{R}^k \times (0, +\infty)^m)$, and therefore there exists $L_2 > 0$, depending on $\mathcal{C}$ such that $\forall\,(x,t) \in Q$ we have

$$|\mathbf{z}_1(x,t) - \mathbf{z}_2(x,t)| \leq L_2 \int_0^t |\bar{v}_1(x,s) - \bar{v}_2(x,s)| ds +$$

$$+ \int_0^t |\mathbf{w}_1(x,s) - \mathbf{w}_2(x,s)| + |\mathbf{z}_1(x,s) - \mathbf{z}_2(x,s)|\, ds,$$

and, as above, using Jensen's inequality, Gronwall's Lemma and (5.46), we find a constant $L_3 = L_3(L_1, L_2, T)$ such that

$$\|\mathbf{z}_1(t) - \mathbf{z}_2(t)\|^2_{L^2(\Omega)} \leq L_3 \int_0^t \|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)}, \quad \forall\, t \in (0,T) \tag{5.47}$$

We recall system (5.4a)–(5.4e) and estimate (5.6)

$$\begin{aligned}
\partial_t v + \bar{I}_{ion} - \operatorname{div}(M_i \nabla u_i) - I_i^s = 0 \qquad & \text{on } \; Q, \\
\partial_t v + \bar{I}_{ion} + \operatorname{div}(M_e \nabla u_e) + I_e^s = 0 \qquad & \text{on } \; Q, \\
M_{i,e} \nabla u_{i,e} \cdot \nu = 0 \qquad & \text{on } \; \Sigma, \\
v(x,0) = V_0(x) \qquad & \text{on } \; \Omega.
\end{aligned}$$

$$\|v_1(t) - v_2(t)\|^2_{L^2(\Omega)} \leq C \|\bar{I}_{ion,1} - \bar{I}_{ion,2}\|^2_{L^2(0,t;L^2(\Omega))}.$$

Since $\bar{I}_{ion}$ is locally Lipschitz continuous, we can find $L_4 > 0$, depending on $\mathcal{C}$ such that $\forall\, t \in (0,T)$ it holds

$$\|v_1(t) - v_2(t)\|^2_{L^2(\Omega)} \leq L_4 \int_0^t \Big(\|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)} + \|\mathbf{w}_1(s) - \mathbf{w}_2(s)\|^2_{L^2(\Omega)} +$$

$$+ \|\mathbf{z}_1(s) - \mathbf{z}_2(s)\|^2_{L^2(\Omega)} \Big)\, ds, \tag{5.48}$$

and using (5.46), (5.47), we find a constant $L = L(L_1, L_2, L_3, L_4, T)$ such that

$$\|v_1(t) - v_2(t)\|^2_{L^2(\Omega)} \leq L \int_0^t \|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)} ds. \tag{5.49}$$

Now we define

$$\varphi(t) := \|v_1(t) - v_2(t)\|^2_{L^2(\Omega)},$$
$$\bar{\varphi}(t) := \|\bar{v}_1(t) - \bar{v}_2(t)\|^2_{L^2(\Omega)}.$$

By (5.49) we have

$$0 \leq \varphi(t) \leq L \int_0^t \bar{\varphi}(s)\, ds, \quad \forall\, t \in (0,T). \tag{5.50}$$

Now we multiply (5.50) by $e^{-\lambda t}$, $(\lambda > 0)$, and we integrate between 0 and T:

$$\int_0^T e^{-\lambda t}\varphi(t)\ dt \leq L\int_0^T e^{-\lambda t}\left(\int_0^t \bar{\varphi}(s)\ ds\right) dt,$$

and integrating by parts

$$\int_0^T e^{-\lambda t}\varphi(t)\ dt \leq \frac{L}{\lambda}\left[\int_0^T e^{-\lambda t}\bar{\varphi}(t)\ dt - C_4 e^{-\lambda T}\int_0^T \bar{\varphi}(t)\ dt\right] \leq \frac{L}{\lambda}\int_0^T e^{-\lambda t}\bar{\varphi}(t)\ dt.$$

We conclude that

$$|||\mathcal{T}\bar{v}_1 - \mathcal{T}\bar{v}_2|||_{\lambda,L^2(\Omega)} \leq \frac{L}{\lambda}|||\bar{v}_1 - \bar{v}_2|||_{\lambda,L^2(\Omega)},$$

and thus, if $\lambda > L$, then $\mathcal{T}$ is a contraction and we have proved existence and uniqueness for a solution of Problem (**M**).

□

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