Reaction-Diffusion systems for the macroscopic Bidomain model of the cardiac electric field*

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Abstract. The paper deals with a mathematical model for the electric activity of the heart at macroscopic level. The membrane model used to describe the ionic currents is a generalization of the phase-I Luo-Rudy, a model widely used in 2-D and 3-D simulations of the action potential propagation. From the mathematical viewpoint the model is made up of a degenerate parabolic reaction diffusion system coupled with an ODE system. We derive existence, uniqueness and some regularity results.

1 Introduction and main result

The aim of this paper is to study the reaction-diffusion systems arising from the mathematical models of the electric activity of cardiac ventricular cells, at 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 have played an important role in electrocardiology and many experimental studies have been coupled with numerical investigations, due to the difficulty of direct measurements. The anisotropic Bidomain model is the most complete model used in numerical simulations of the bioelectric activity of the heart, see Colli Franzone et al. [9, 11, 12, 13], Roth [44], Hooke et al. [25], Henriquez et al. [22, 23], Muzikant et al. [37].

In this paper we prove existence and uniqueness for a solution of a wide class of models, including the classical Hodgkin-Huxley model [24], the first membrane model for ionic currents in an axon, and the Phase-I Luo-Rudy (LR1) model [36], 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 the modern dynamical models. We remark that the well posedness for the Bidomain model with FitzHugh-Nagumo simplification for the ionic currents, was exhaustively studied by Colli Franzone

*This work was partially supported by the IMATI (CNR Pavia, Italy).

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and Savaré [14], while the existence of a solution for a microscopic cellular model with LR1-type currents was studied in [53].

The contraction of the heart muscle is initiated by an electric signal starting in the sinoatrial node, see e.g. [28, ch. 11], [29]. The electrical signal then travels along a special type of cells known as Purkinje fibres, through the atria and the ventricula. 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. The measurement of this field on the body surface is called the electrocardiogram (ECG). In order to achieve realistic simulations of these measurements, it is important to study how the electric signal is created in the heart and how it is conducted through the heart and body tissue. The conduction in the body tissue and, more generally, in biological systems, is a vast field of present research, see e.g. [28], [19], [27], [2, 3, 5, 4].

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 modelling of the ionic currents in the ventricular myocardium, in particular, has undergone a continuous development from the paper by Beeler and Reuter [6], in 1977, to nowadays: [36, 35, 18], for example, study guinea pigs, [55, 20, 26] focus on canine cells, [50, 42] concentrate on the human myocardium, while [40] is a review of the development of cardiac ventricular models (we cite only a few examples, but we remark that the literature concerning the modellization of the cardiac action potential, in different species and with different pathologies, is impressively rich).

From the mathematical viewpoint, the problem consists of a system of two degenerate parabolic reaction-diffusion equations, coupled with a system of ODEs. We remark that standard techniques and results on reaction diffusion systems (see e.g. [49, 1]), cannot be directly exploited in the case of microscopic models of the cardiac electric field, due to their degenerate structure and to the lack of a maximum principle. We will give more details about the mathematical difficulties after the description of the model.

The macroscopic model of the cardiac tissue. At a microscopic level the cardiac structure is composed of a collection of elongated cardiac cells, endowed with special electric (mainly end-to-end) connections, named *gap junctions*, embedded in the extracellular 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. 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 intramural connected domain Ω_i separated from the extra-cellular fluid Ω_e by a membrane surface Γ.

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. [22, 11, 45] and also [28]), 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 (see [38, 41] for a formal and a rigorous derivation and modelling details). The resulting macroscopic Bidomain model describes the averaged intra- and extra-cellular electric potentials and currents 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.

$\Omega \equiv \Omega_i \equiv \Omega_e \equiv \Gamma_m \subset \mathbb{R}^3$ 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 $M_{i,e} : \overline{\Omega} \to \mathbf{M}^{3\times 3}$. To the potentials u_i, u_e are associated the current densities $J_{i,e} := -M_{i,e}\nabla u_{i,e}$; 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

$$-\mathrm{div}(M_i \nabla u_i) = -I_m + I^s_i, \qquad -\mathrm{div}(M_e \nabla u_e) = I_m + I^s_e, \qquad \text{in } \Omega. \tag{1.1}$$

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

$$I_m = \chi(C_m \partial_t v + I_{ion}), \qquad \text{in } \Omega, \tag{1.2}$$

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 the following, we assume that the cardiac tissue is insulated, therefore homogeneous Neumann boundary conditions are assigned on $\partial\Omega \times (0, T)$

$$M_i \nabla u_i \cdot \nu = 0, \qquad M_e \nabla u_e \cdot \nu = 0. \tag{1.3}$$

In order to complete the model, we need a description of the ionic current I_{ion} which appears in (1.2).

The ionic current. In this work 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:

$$I_{ion}(v, \mathbf{w}, \mathbf{z}) := \sum_{i=1}^{m} \left(J_i(v, \mathbf{w}, \log z_i) \right) + \tilde{H}(v, \mathbf{w}, \mathbf{z}), \tag{1.4}$$

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

$$J_i \in C^1 \left(\mathbb{R} \times \mathbb{R}^k \times \mathbb{R} \right), \tag{1.5a}$$

$$0 < \underline{G}(\mathbf{w}) \leq \frac{\partial}{\partial \zeta} J_i(v, \mathbf{w}, \zeta) \leq \overline{G}(\mathbf{w}), \tag{1.5b}$$

$$\left| \frac{\partial}{\partial v} J_i(v, \mathbf{w}, 0) \right| \leq L_v(\mathbf{w}), \tag{1.5c}$$

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

$$\tilde{H} \in C^0(\mathbb{R} \times \mathbb{R}^k \times (0, +\infty)^m) \cap \text{ Lip}(\mathbb{R} \times [0,1]^k \times (0, +\infty)^m). \tag{1.6}$$

The dynamics of the gating variables are described by the system of ODE's

$$\frac{\partial w_j}{\partial t} = F_j(v, w_j), \qquad j = 1, ..., k. \tag{1.7}$$

We assume that

$$F_j : \mathbb{R}^2 \to \mathbb{R} \text{ is locally Lipschitz continuous;} \tag{1.8a}$$

$$F_j(v, 0) \geq 0, \quad \forall\, v \in \mathbb{R}; \tag{1.8b}$$

$$F_j(v, 1) \leq 0, \quad \forall\, v \in \mathbb{R}, \tag{1.8c}$$

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

In the models considered F_j has the particular form

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

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

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

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 are described by the system of ODE's

$$\frac{\partial z_i}{\partial t} = G_i(v, \mathbf{w}, \mathbf{z}) := -J_i(v, \mathbf{w}, z_i) + H_i(v, \mathbf{w}, \mathbf{z}) \qquad i = 1, ..., m, \tag{1.9}$$

where J_i is the function described in (1.5a, 1.5b, 1.5c) and

$$H_i \in C^0(\mathbb{R} \times \mathbb{R}^k \times (0, +\infty)^m) \cap \text{ Lip}(\mathbb{R} \times [0, 1]^k \times (0, +\infty)^m), \qquad i = 1, \dots, m. \tag{1.10}$$

We refer to (1.1)-(1.4), (1.7), (1.9) 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

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

Adding the two equations (1.1) 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:

$$\int_\Omega (I_i^s + I_e^s)\, dx = 0. \tag{1.11}$$

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.

$$\int_\Omega u_e\, dx = 0. \tag{1.12}$$

Remark 1. 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 modelling cardiac tissue, see e.g. [43], [21]. 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 [10], [23] and [37]. Moreover *un*equal anisotropic ratio makes possible more complex phenomena (see [54], [51]) and can play an important role for the re-entrant excitation (see [56], [46]).

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, $\Gamma := \partial\Omega$, ν is the unitary exterior normal to Γ. We define the related space-time domains following the usual notation of [33]

$$Q := \Omega\times]0,T[, \qquad \Sigma := \Gamma\times]0,T[.$$

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

$$\exists\ \alpha, m > 0: \qquad \alpha|\xi|^2 \leq M_{i,e}(x)\xi\cdot\xi \leq m|\xi|^2, \qquad \forall\ \xi\in\mathbb{R}^3,\ x\in\Omega. \tag{1.13}$$

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

$$\begin{array}{lll} I_i^s : Q \to \mathbb{R}, & I_e^s : Q \to \mathbb{R}, & \\ v_0 : \Omega \to \mathbb{R}, & \mathbf{w}_0 : \Omega \to \mathbb{R}^k, & \mathbf{z}_0 : \Omega \to (0,+\infty)^m, \end{array}$$

we seek

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

satisfying the reaction-diffusion system

$$\partial_t v + I_{ion}(v,\mathbf{w},\mathbf{z}) = \mathrm{div}(M_i\nabla u_i) + I_i^s \quad \text{on} \quad Q, \tag{1.14a}$$

$$\partial_t v + I_{ion}(v,\mathbf{w},\mathbf{z}) = -\mathrm{div}(M_e\nabla u_e) - I_e^s \quad \text{on} \quad Q, \tag{1.14b}$$

$$M_i\nabla u_i\cdot\nu = 0 \quad \text{on} \quad \Sigma, \tag{1.14c}$$

$$M_e\nabla u_e\cdot\nu = 0 \quad \text{on} \quad \Sigma, \tag{1.14d}$$

$$v(x,0) = v_0(x) \quad \text{on} \quad \Omega, \tag{1.14e}$$

and the ODE system

$$\partial_t\mathbf{w} = \mathbf{F}(v,\mathbf{w}) \quad \text{on} \quad Q, \tag{1.15a}$$

$$\partial_t\mathbf{z} = \mathbf{G}(v,\mathbf{w},\mathbf{z}) \quad \text{on} \quad Q, \tag{1.15b}$$

$$\mathbf{w}(x,0) = \mathbf{w}_0(x) \quad \text{on} \quad \Omega, \tag{1.15c}$$

$$\mathbf{z}(x,0) = \mathbf{z}_0(x) \quad \text{on} \quad \Omega. \tag{1.15d}$$

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 (1.14c) and (1.14d). 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 3: let $v \in H^1(\Omega)$ be given, then the following minimization problem has a unique solution:

$$\min \left\{ \sum_{i,e} \int_\Omega M_{i,e} \nabla \bar{u}_{i,e} \cdot \nabla \bar{u}_{i,e} \, dx \; : \; \bar{u}_{i,e} \in H^1(\Omega), \quad \int_\Omega \bar{u}_e \, dx = 0, \quad \bar{u}_i - \bar{u}_e = v \right\}. \tag{1.16}$$

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

$$\begin{cases} -\mathrm{div}((M_i + M_e)\nabla u_b^0) = I_i^s(0) + I_e^s(0) & \text{on } \Omega, \\ ((M_i + M_e)\nabla u_b^0) \cdot \nu = 0 & \text{on } \partial\Omega, \\ \displaystyle\int_\Omega u_b^0 \, dx = 0. \end{cases} \tag{1.17}$$

Finally, we say that an initial datum v_0 satisfies the *admissibility property* if

$$\begin{cases} \textit{the couple } (\bar{u}_i, \bar{u}_e) \textit{ solution of } (1.16) \textit{ w.r.t. } v_0, \textit{ satisfies} \\ M_i(\nabla \bar{u}_i + u_b^0) \cdot \nu = M_e \nabla(\bar{u}_e + u_b^0) \cdot \nu = 0 \quad \text{on } \partial\Omega. \end{cases} \tag{1.18}$$

Remark 2. From the modellistic 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* (1.18) has a considerably simpler formulation, since it is equivalent to

$$M_i \nabla v_0 \cdot \nu = 0, \quad (\text{or } M_e \nabla v_0 \cdot \nu = 0,) \quad \text{on } \partial\Omega. \tag{1.19}$$

For sake of generality, we shall state the main result and carry on the proofs only with the choice (1.18).

In the following part, the expression '$\mathbf{log\,z}$' stands for the vector $(\log z_1, ..., \log z_m)$ and '$\mathbf{z\,log\,z}$' 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 for Problem (M).

Theorem 1.1. *Assume that*

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

Let be given the data

$$v_0 \in H^2(\Omega), \text{ satisfying the admissibility property (1.18),}$$

$$\mathbf{w}_0 : \Omega \to [0,1]^k, \quad \text{measurable,}$$

$$\mathbf{z}_0 \in (L^2(\Omega))^m, \qquad \text{with } \mathbf{log}\, \mathbf{z}_0 \in (L^2(\Omega))^m,$$

$$I^s_{i,e} \in L^p(0,T;L^2(\Omega)), \quad \text{for } p > 4, \text{ satisfying (1.11) and}$$

$$I^s_i + I^s_e \in H^1(0,T;L^2(\Omega)).$$

Let be given the ionic currents satisfying (1.4–1.6), the dynamics of the gating variables $\mathbf{F}(v,\mathbf{w})$*, satisfying (1.7–1.8c), the dynamics of the ionic concentrations* $\mathbf{G}(v,\mathbf{w},\mathbf{z})$*, satisfying (1.9), (1.10).*

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*

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

$$v := u_i - u_e \ \in W^{1,p}(0,T;L^2(\Omega)) \cap L^p(0,T;H^2(\Omega)) \cap C^0([0,T];C^0(\Omega)),$$

$$\mathbf{w} : Q \to [0,1]^k \text{ measurable,} \qquad \mathbf{z} : Q \to (0,+\infty)^m \text{ measurable,}$$

$$w_j(x,\cdot) \in C^1(0,T) \cap C^0([0,T]) \ \text{ for a.e. } x \in \Omega, \qquad j = 1,...,k,$$

$$z_i(x,\cdot) \in C^1(0,T) \cap C^0([0,T]) \ \text{ for a.e. } x \in \Omega, \qquad i = 1,...,m,$$

$$\mathbf{z} \in H^1(0,T;L^2(\Omega))^m \cap L^\infty(Q)^m, \qquad \mathbf{log}\,\mathbf{z} \in L^\infty(Q)^m.$$

Steps of the proof and plan of the paper. The proof of Theorem 1.1 is divided into three parts. In a first step we fix v and solve the ODE systems of the gating (1.15a, 1.15c) and concentration (1.15b, 1.15d) variables, obtaining suitable a priori estimates and qualitative properties of the solution (Section 2).

In the second step we use a reduction technique in order to split the degenerate parabolic system (1.14a)-(1.14e) 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 the potentials u_i, u_e (and thus for $v = u_i - u_e$) in $L^p(0,T;H^2(\Omega)) \cap W^{1,p}(0,T;L^2(\Omega))$. (Section 3).

These estimates, 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 4).

The main difficulties in the parabolic equation reside in its degenerate structure, which reflects the differences in the anisotropy of the intra- and extra-cellular tissues, and in the lack of a maximum principle. 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.

For a description of the structure of the ionic currents and of the relation between the mathematical hypothesis in this work and the explicit equations in the considered models, we refer to [53], where the same membrane models are studied in the context of a microscopic cellular model for the propagation of the cardiac electric potential.

Acknowledgments. I would like to thank Piero Colli Franzone and Giuseppe Savaré, the advisor of my Ph.D. thesis, for having proposed me the problem and for the inspiring conversations.

2 The ODE systems

We recall here some results proved in [53] for the ODE systems of the gating and concentration variables.

2.1 The gating variables

Our first step will be to show that, for every $v \in H^1(0,T;L^2(\Omega))$, there exists a unique $\mathbf{w} = (w_1, \dots, w_k)$, measurable, which solves the gating variables equations in system (1.15a, 1.15c)

$$\begin{cases} \dfrac{\partial \mathbf{w}}{\partial t} = \mathbf{F}(v, \mathbf{w}), & \text{on } \; Q, \\ \mathbf{w}(x,0) = \mathbf{w}_0(x), & \text{on } \; \Omega, \end{cases} \tag{2.1}$$

in a sense which we will make precise; moreover we will also obtain the universal bounds

$$\boxed{0 \le w_j \le 1, \qquad \text{a.e. in } \Sigma, \quad \forall\, j = 1, \dots, k.} \tag{2.2}$$

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

$$\begin{cases} \dfrac{\partial \mathbf{w}}{\partial t}(x,t) = \mathbf{F}(v(x,t), \mathbf{w}(x,t)), & \text{for a.e. } x \in \Omega, \ \forall\, t \in (0,T], \\ \mathbf{w}(x,0) = \mathbf{w}_0(x), & \text{for a.e. } x \in \Omega. \end{cases} \tag{2.3}$$

2.2 The concentration variables

Now we turn to the system of ODEs of the concentration variables in (1.15b, 1.15d). We follow the same idea as for the gating variables, that is, we show that for every $v \in H^1(0,T;L^2(\Omega))$ and for every vector function $\mathbf{w}$ given by Proposition 2.1, we can solve an ordinary Cauchy Problem in time, for a.e. $x \in \Omega$.

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

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

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

$$\begin{cases} \dfrac{\partial \mathbf{z}}{\partial t}(x,t) = \mathbf{G}(v(x,t),\mathbf{w}(x,t),\mathbf{z}(x,t)), & \text{for a.e. } x \in \Omega,\ \forall\, t \in (0,T], \\ \mathbf{z}(x,0) = \mathbf{z}_0(x), & \text{for a.e. } x \in \Omega. \end{cases} \tag{2.4}$$

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

$$|\mathbf{z}(x,t)| \le C\left(1 + |\mathbf{z}_0(x)| + \|v(x)\|_{L^2(0,t)}\right), \tag{2.5}$$

$$|\mathbf{log\,z}(x,t)| + \left|\frac{\partial \mathbf{z}}{\partial t}(x,t)\right| \le C\left(1 + |\mathbf{z}_0(x)| + \|v(x)\|_{C^0(0,t)}\right), \tag{2.6}$$

$$\int_0^t |\mathbf{log\,z}(x,s)|^2 + \left|\frac{\partial \mathbf{z}}{\partial s}(x,s)\right|^2 ds \le C\left(1 + |\mathbf{z}_0(x)\,\mathbf{log\,z}_0(x)| + |\mathbf{z}_0(x)|^2 + \|v(x)\|^2_{L^2(0,t)}\right), \tag{2.7}$$

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

The difficulty, in this case, lies in the lack of a priori conditions such as (1.8b) and (1.8c), which, in (2.1) guaranteed the boundedness for $\mathbf{w}$. We used 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.

3 The Parabolic equation

Our next step will be to solve system (1.14a–1.14e), considering the ionic current I_{ion} as a known function. In order to choose the correct assumptions on I_{ion}, we look at the estimates just stated: let $\mathbf{w}$, $\mathbf{z}$ be known functions, satisfying the thesis of Propositions 2.1 and 2.2, with $\bar{v} \in H^1(0,T;L^2(\Omega))$ given, and set

$$\bar{I}_{ion}(x,t) := I_{ion}(\bar{v}(x,t), \mathbf{w}(x,t), \mathbf{z}(x,t)). \tag{3.1}$$

Then, by the definition of I_{ion} (1.4), using estimates (1.5b), (1.5c) and (2.2) 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 (2.7), we have that $\bar{I}_{ion} \in L^2(Q)$, and

$$\|\bar{I}_{ion}\|^2_{L^2(0,t;L^2(\Omega))} \leq C\left(1 + \|\bar{v}\|^2_{L^2(0,t;L^2(\Omega))}\right), \qquad \forall\, t \in [0,T]. \tag{3.2}$$

On the other hand, by using estimate (2.6), 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 $\bar{I}_{ion} \in L^p(0,T;L^2(\Omega))$:

$$\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} \leq C\left(1 + \|\bar{v}\|_{L^2(\Omega, H^1(0,T))}\right), \tag{3.3}$$

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

We state the main result of this section

Proposition 3.1. *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 (1.18), 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 $\int_\Omega u_e \; dx = 0$,

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

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

which satisfies

$$\partial_t v + \bar{I}_{ion} - \operatorname{div}(M_i \nabla u_i) - I_i^s = 0 \qquad on \ \ Q, \tag{3.4a}$$
$$\partial_t v + \bar{I}_{ion} + \operatorname{div}(M_e \nabla u_e) + I_e^s = 0 \qquad on \ \ Q, \tag{3.4b}$$
$$M_e \nabla u_e \cdot \nu = 0 \qquad on \ \ \Sigma, \tag{3.4c}$$
$$M_i \nabla u_i \cdot \nu = 0 \qquad on \ \ \Sigma, \tag{3.4d}$$
$$v(x,0) = v_0(x) \qquad on \ \ \Omega. \tag{3.4e}$$

We have the a priori estimates

$$\begin{aligned} \|u_{i,e}\|_{L^p(0,T;H^2(\Omega))} + \|v\|_{W^{1,p}(0,T;L^2(\Omega))} \le C \big(\|v_0\|_{H^2(\Omega)} + \\ + \|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} + \|I_{i,e}^s\|_{L^p(0,T;L^2(\Omega))} + \|I_i^s + I_e^s\|_{H^1(0,T;L^2(\Omega))} \big), \end{aligned} \tag{3.5}$$

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

$$\|v^{(2)}(t) - v^{(1)}(t)\|^2_{L^2(\Omega)} \le C \|\bar{I}_{ion}^{(1)} - \bar{I}_{ion}^{(2)}\|^2_{L^2(0,t;L^2(\Omega))}, \quad \forall\, t \in [0,T]. \tag{3.6}$$

In system (3.4a)–(3.4e) 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. We will use a particular reduction technique, in order to separate the system into an elliptic equation and a parabolic (nondegenerate) equation.

Subtracting equation (3.4b) from (3.4a) and summing Neumann conditions (3.4c) and (3.4d) we find

$$\begin{cases} -\operatorname{div}(M_i \nabla u_i) - \operatorname{div}(M_e \nabla u_e) = I_i^s + I_e^s & \text{on } \ Q, \\ (M_i \nabla u_i + M_e \nabla u_e) \cdot \nu = 0 & \text{on } \ \Sigma. \end{cases} \tag{3.7}$$

Summing equations (3.4a) and (3.4b) and subtracting equation (3.4c) from (3.4d), we have

$$\begin{cases} \partial_t v + \bar{I}_{ion} - \dfrac{\operatorname{div}(M_i \nabla u_i) - \operatorname{div}(M_e \nabla u_e)}{2} = \dfrac{I_i^s - I_e^s}{2} & \text{on } \ Q, \\ (M_i \nabla u_i - M_e \nabla u_e) \cdot \nu = 0 & \text{on } \ \Sigma, \\ v(x,0) = v_0(x) & \text{on } \ \Omega. \end{cases} \tag{3.8}$$

The reduction technique. We can now use a reduction technique (see e.g. [48, 14]) in order to exploit the particular form of systems (3.7) and (3.8). We recall just the basic definitions, referring to the bibliography for details. 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 spaces

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

and the *symmetric, nonnegative* bilinear forms

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

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

defined $\forall\ \mathbf{u}, \hat{\mathbf{u}} \in \mathbf{V}$. We remark that the kernel of b has infinite dimension, however, by (1.13) and Poincaré inequality, the sum of the quadratic forms associated to a and b is coercive on $\mathbf{V}$, i.e.

$$\exists\, \alpha > 0: \quad a(\mathbf{u}, \mathbf{u}) + b(\mathbf{u}, \mathbf{u}) \geq \alpha \|\mathbf{u}\|^2_{\mathbf{V}}, \quad \forall\, \mathbf{u} \in \mathbf{V}. \tag{3.9}$$

Denoting by $\mathbf{V}'$ the dual space of $\mathbf{V}$, we can associate to the bilinear forms a, b the linear continuous operators $A, B : \mathbf{V} \to \mathbf{V}'$ defined by

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

Let us denote by $\mathbf{K}_b \subset \mathbf{V}$ the kernel of $b(\cdot, \cdot)$, which is 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 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

$$\mathbf{R}v = \mathbf{u} \quad \Leftrightarrow \quad B\mathbf{u} = v, \quad \text{and} \quad \mathbf{u} \in \mathbf{K}_a. \tag{3.10}$$

Moreover, observe that since $a(\cdot, \cdot)$ is symmetric, (3.10) is equivalent to the minimization problem

$$B\mathbf{u} = v, \quad \text{and} \quad a(\mathbf{u}, \mathbf{u}) = \min\{a(\mathbf{y}, \mathbf{y}) : \mathbf{y} \in \mathbf{V},\ B\mathbf{y} = v\}. \tag{3.11}$$

By (3.9) 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

$$\mathbf{u} = \mathbf{R}v + \mathbf{u}_b : \qquad v = B\mathbf{u}, \qquad \mathbf{R}v \in \mathbf{K}_a, \qquad \mathbf{u}_b \in \mathbf{K}_b. \tag{3.12}$$

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 (3.12) and to Remark 3, we can rewrite system (3.7) as

$$\begin{cases} -\mathrm{div}((M_i + M_e)\nabla u_b) = I_i^s + I_e^s & \text{on } Q, \\ ((M_i + M_e)\nabla u_b) \cdot \nu = 0 & \text{on } \Sigma, \end{cases} \tag{3.13}$$

and system (3.8) as

$$\begin{cases} \partial_t v + \bar{I}_{ion} - \mathrm{div}\,\beta\,(\mathbf{R}v + \mathbf{u}_b) = \dfrac{I_i^s - I_e^s}{2} & \text{on } Q, \\ \beta(\mathbf{R}v + \mathbf{u}_b) \cdot \nu = 0 & \text{on } \Sigma, \\ v(x,0) = v_0(x) & \text{on } \Omega, \end{cases} \tag{3.14}$$

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

$$\beta\mathbf{u} := \frac{M_i \nabla u_i - M_e \nabla u_e}{2}, \quad \forall\, \mathbf{u} = (u_i, u_e) \in H^1(\Omega) \times H^1(\Omega). \tag{3.15}$$

In order to univocally solve (3.13), we impose the condition

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

which is the analogous of the usual condition (1.12) in Section 1.

Proof of Proposition 3.1. The proof is structured as follows: first we solve the elliptic equation (depending from the time parameter) (3.13), which is independent of v, and we derive the estimates on u_b (Lemma 3.1). Then, considering u_b as a known function, we give a variational formulation of (3.14) 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 (3.14), we separate in two different equations the term $\bar{I}_{ion} + (I_i^s - I_e^s)/2$ (Lemma 3.2) and the term $-\mathrm{div}\beta(\mathbf{u}_b)$ (Lemma 3.3).

Lemma 3.1. *Assume that*

$$\Omega \textit{ is of class } C^{1,1}, \qquad M_{i,e} \textit{ are Lipschitz in } \Omega. \tag{3.16}$$

Given

$$I_{i,e}^s \in L^2(0,T;L^2(\Omega)) : \quad I_i^s + I_e^s \in H^1(0,T;L^2(\Omega)), \tag{3.17}$$

satisfying the compatibility condition

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

there exists a unique $u_b \in H^1(0,T;H^2(\Omega))$ *which solves*

$$\begin{cases} -\mathrm{div}((M_i+M_e)\nabla u_b) = I_i^s + I_e^s & on \;\; Q, \\ ((M_i+M_e)\nabla u_b)\cdot \nu = 0 & on \;\; \Sigma, \\ \displaystyle\int_\Omega u_b \, dx = 0 & \forall\, t\in[0,T], \end{cases} \tag{3.18}$$

and

$$\|u_b\|_{H^1(0,T;H^2(\Omega))} \leq C\|I_i^s + I_e^s\|_{H^1(0,T;L^2(\Omega))}. \tag{3.19}$$

Proof. By hypothesis (1.13), $M_i + M_e$ is uniformly elliptic, therefore, owing to (3.16), (3.17), the result of Lemma 3.1 follows directly by standard regularity estimates for elliptic problems depending on the time parameter t (see e.g. [17]).

Our next step will be to write a variational formulation for system (3.14), 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 (3.14) by φ, integrate on Ω and use Green formula and the boundary condition in (3.14), thus obtaining:

$$\int_\Omega \partial_t v(t)\varphi \, dx + \int_\Omega \beta(\mathbf{R}v(t) + \mathbf{u}_b(t))\nabla\varphi \, dx = \int_\Omega \left(\frac{I_i^s(t) - I_e^s(t)}{2} - \bar{I}_{ion}(t)\right)\varphi \, dx. \tag{3.20}$$

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

$$(\mathbf{R}^*a)(v,w) = a(\mathbf{R}v,\mathbf{R}w) = \int_\Omega M_i\nabla(R_iv)\nabla(R_iw) + M_e\nabla(R_ev)\nabla(R_ew)\, dx, \tag{3.21}$$

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

$$(\mathbf{R}^*a)(v,w) = \frac{1}{2}\int_\Omega (M_i\nabla R_iv - M_e\nabla R_ev)(\nabla R_iw - \nabla R_ew)\, dx = \int_\Omega \beta(\mathbf{R}v)\nabla w\, dx, \tag{3.22}$$

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

$$\langle A_R v, \varphi \rangle := \mathbf{R}^* a(v, \varphi), \quad \forall\, \varphi \in H^1(\Omega). \tag{3.23}$$

We shall also consider the realization of A_R on the domain

$$\begin{aligned} D_{L^2(\Omega)}(A_R) \quad &:= \left\{ v \in H^1(\Omega) \;:\; A_R v \in L^2(\Omega) \right\} \\ &= \left\{ v \in H^2(\Omega) \;:\; \beta(\mathbf{R}v) \cdot \nu = 0, \text{ on } \partial\Omega \right\}. \end{aligned} \tag{3.24}$$

We define the function

$$L_1(t) := \frac{I_i^s(t) - I_e^s(t)}{2} - \bar{I}_{ion}(t), \tag{3.25}$$

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

$$\langle L_2(t), \varphi \rangle := - \int_\Omega \beta(\mathbf{u}_b(t)) \nabla \varphi \, dx, \quad \forall\, \varphi \in H^1(\Omega). \tag{3.26}$$

Owing to definitions (3.22)–(3.26), and linearity of $\mathbf{R}^* a$, in order to study equation (3.20), 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 3.2. *Assume that (3.16) holds, let $p \in (4, +\infty)$. Given $\mathbf{R}$, β, A_R, $D_{L^2(\Omega)}(A_R)$, L_1 defined in (3.10), (3.15), (3.23), (3.24), (3.25).*

$$\begin{aligned} &\bar{I}_{ion} \in L^p(0, T; L^2(\Omega)), \\ &I_i^s, I_e^s \in L^p(0, T; L^2(\Omega)). \end{aligned} \tag{3.27}$$

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 $(0, T)$,

$$\frac{d}{dt} v_1(t) + A_R v_1(t) = L_1(t), \quad \textit{in } L^2(\Omega), \textit{ for a.e. } t \in (0, T), \tag{3.28}$$

and we have the a priori estimates

$$\|v_1\|_{W^{1,p}(0,T;L^2(\Omega))} \le C\left(\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} + \|I^s_{i,e}\|_{L^p(0,T;L^2(\Omega))}\right), \tag{3.29}$$

$$\|v_1\|_{L^p(0,T;H^2(\Omega))} \le C\left(\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} + \|I^s_{i,e}\|_{L^p(0,T;L^2(\Omega))}\right). \tag{3.30}$$

Lemma 3.3. *Assume that (3.16) holds. Let be given*

$$v_0 \in H^2(\Omega), \quad \textit{satisfying } (1.18), \tag{3.31}$$

$$I^s_{i,e} \in L^2(0,T;L^2(\Omega)) : \quad I^s_i + I^s_e \in H^1(0,T;L^2(\Omega)), \tag{3.32}$$

u_b as in Lemma 3.1, thus satisfying $u_b \in H^1(0,T;H^2(\Omega))$, and $\mathbf{R}$, β, A_R, L_2 as defined in (3.10), (3.15), (3.23), (3.26). 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 $v_2(0) = v_0$,

$$\frac{d}{dt}v_2(t) + A_R v_2(t) = L_2(t), \quad \textit{in } H^1(\Omega)',\ \textit{for a.e. } t \in (0,T), \tag{3.33}$$

and we have the a priori estimates

$$\|v_2\|_{W^{1,\infty}(0,T;L^2(\Omega))} \le C\left(\|v_0\|_{H^2(\Omega)} + \|I^s_i + I^s_e\|_{H^1(0,T;L^2(\Omega))}\right),$$

$$\|v_2\|_{H^1(0,T;H^1(\Omega))} \le C\left(\|v_0\|_{H^2(\Omega)} + \|I^s_i + I^s_e\|_{H^1(0,T;L^2(\Omega))}\right),$$

$$\|v_2\|_{L^\infty(0,T;H^2(\Omega))} \le C\left(\|v_0\|_{H^2(\Omega)} + \|I^s_i + I^s_e\|_{H^1(0,T;L^2(\Omega))}\right).$$

Proof of Lemma 3.2. We recall a result by L. de Simon on maximal regularity in L^p (see [16])

Theorem 3.1. *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

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

and there exist $C > 0$ such that

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

Remark 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. [30], [7], [8]).

By standard results about the generation of analytic semigroups, (see [15], [34]), 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 $\mathbf{R}^*a$ (3.21). It may also be observed that A_R is symmetric self-adjoint on a Hilbert space ([15]). See, in particular, [34, Theorem 3.1.2–*(iii)*] for the resolvent estimates in the case of second order elliptic operators with first order boundary conditions.

Estimate (3.3) and hypothesis (3.27) yield $L_1 \in L^p(0, T; L^2(\Omega))$. Then, we can then apply Theorem 3.1, which provides existence, uniqueness and estimates (3.29) and (3.30) for v_1, solution of (3.14).

□

Proof of Lemma 3.3. We recall a classical result by J. L. Lions for linear parabolic partial differential equations in a Hilbert triple (V, H, V') [32, 31]. 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

$$u \in L^2(0, T; V), \quad u' \in L^2(0, T; V'), \tag{3.34a}$$

$$u'(t) + Au(t) = f(t) \text{ in } V', \quad u(0) = u_0, \tag{3.34b}$$

$$\|u\|_{L^2(0,T;V)} + \|u'\|_{L^2(0,T;V')} \leq C_1(\|u_0\|_H + \|f\|_{L^2(0,T;V')}). \tag{3.34c}$$

Moreover, if

$$df/dt \in L^2(0, T; V') \quad \text{and} \quad Au_0 - f(0) \in H, \tag{3.35}$$

owing to the linearity of equation (3.34b), it can be seen that

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

$$Au(t) - f(t) \in L^\infty(0, T; H), \tag{3.36}$$

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

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

By hypothesis (3.32) we have $L_2 \in H^1(0, T; H^1(\Omega)')$, then, in order to meet condition (3.35) 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

$$\int_\Omega \beta(\mathbf{R}v + \mathbf{u}_b(t))\nabla\varphi\ dx = -\int_\Omega \mathrm{div}\ \beta(\mathbf{R}v + \mathbf{u}_b(t))\varphi\ dx.$$

Since, by Lemma 3.1, $\mathbf{u}_b(t) \in H^2(\Omega)\ \forall\, t \in [0,T]$, $A_R v - L_2(t) \in L^2(\Omega)$ if and only if

$$-\mathrm{div}\ \beta(\mathbf{R}v) = -\mathrm{div}\ \frac{M_i\nabla R_i v - M_e\nabla R_e v}{2} \in L^2(\Omega),$$

and $\beta(\mathbf{R}v + \mathbf{u}_b(t)) \cdot \nu = 0$ on $\partial\Omega$, that is

$$(M_i\nabla R_i v - M_e\nabla R_e v)\cdot\nu = -(M_i - M_e)\nabla u_b(t)\cdot\nu, \quad \text{on } \partial\Omega. \tag{3.37}$$

Since, by (3.18) and Remark 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 (3.37) is equivalent to

$$M_i\nabla(R_i v + u_b(t)\cdot\nu = M_e\nabla(R_e v + u_b(t)\cdot\nu = 0, \qquad \text{on } \partial\Omega. \tag{3.38}$$

Then, since v_0 satisfies (1.18) by hypothesis (and therefore (3.38)), we have that

$$\beta(\mathbf{R}v_0 + \mathbf{u}_b(0))\cdot\nu = 0, \quad \text{on } \partial\Omega,$$

and (3.36) and Lemma 3.1 imply

$$\begin{cases} -\mathrm{div}\ \beta(\mathbf{R}v_2) \in L^\infty(0,T;L^2(\Omega)), \\ \beta(\mathbf{R}v_2 + \mathbf{u}_b)\cdot\nu = 0, \quad \text{on } \partial\Omega\times[0,T], \end{cases}$$

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 3.1, let $v_0 \in H^2(\Omega)$, satisfying (1.18) as in the hypothesis of Proposition 3.1, let u_b, v_1, v_2 be the solutions of equations (3.18), (3.28), (3.33) as in Lemma 3.1, 3.2, 3.3 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 (3.4a)–(3.4e), and u_e satisfies $\int_\Omega u_e \; dx = 0, \; \forall\, t \in [0,T]$. At last, the stability estimate (3.6) follows from the linearity of equation (3.28), and estimate (3.29), $p = 2$. $\square$

4 Existence and uniqueness

Let us denote by $\mathcal{T}$ the operator that maps a function $\bar{v}$ into the solution of (3.4a)–(3.4e). 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 4.1. *Let $v_0 \in H^2(\Omega)$, satisfying (1.18), $I^s_{i,e} \in L^p(0,T;L^2(\Omega))$, for $p > 4$. There exist $M_0, M_1, M_\infty, \lambda > 0$ such that the set*

$$\begin{aligned} K := \big\{ & v \in L^2(0,T;H^2(\Omega)) \cap H^1(0,T;L^2(\Omega)) \cap L^\infty((0,T)\times\Omega) : v(x,0) = v_0, \\ & |||v|||_{\lambda,L^2(\Omega)} \le M_0, \; |||v'|||_{\lambda,L^2(\Omega)} \le M_1, \; |||v|||_{\lambda,H^2(\Omega)} \le M_1, \; \|v\|_{L^\infty(Q))} \le M_\infty \Big\}, \end{aligned}$$

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 4.1. *Let $\bar{v} \in H^1(0,T;L^2(\Omega))$, let $\mathbf{w}, \mathbf{z}$ be the unique solutions of systems (2.3) and (2.4), given as in Propositions 2.1 and 2.2, and let $\bar{I}_{ion}$ be given as in (3.1), thus satisfying (3.2) and (3.3). Then there exists $\lambda > 0$ such that the solution v of system (3.4a)–(3.4e) 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 (3.5) ($p = 2$) we have

$$\|v(t)\|^2_{L^2(\Omega)} \leq C_2 \left(\|v_0\|^2_{H^1(\Omega)} + \|I_i^s\|^2_{L^2(Q)} + \|I_e^s\|^2_{L^2(Q)} + \|\bar{I}_{ion}\|^2_{L^2(0,t;L^2(\Omega))}\right). \tag{4.1}$$

Let $\varphi(t) := \|v(t)\|^2_{L^2(\Omega)}$, and $\bar{\varphi}(t) := \|\bar{v}(t)\|^2_{L^2(\Omega)}$; owing to estimates (3.2) and (4.1) we find

$$\varphi(t) \leq C_3 + C_4 \int_0^t \bar{\varphi}(s)\, ds, \tag{4.2}$$

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 (4.2) 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

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

$\square$

Owing to estimates (3.5), $p=2$ and (3.2), we immediately obtain

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

$$|||v|||_{\lambda, H^2(\Omega)} \leq M_1, \tag{4.3}$$

$$|||\partial_t v|||_{\lambda, L^2(\Omega)} \leq M_1. \tag{4.4}$$

Lemma 4.2. *Let M_0, M_1, be as in Corollary 4.1, $\bar{I}_{ion}$ be given as in (3.1), 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 (1.18). There exists $M_\infty > 0$, depending only on M_1, p and the data of the problem, such that:

$$\sup\left\{|v(x,t)| : (x,t) \in Q\right\} \leq M_\infty.$$

We recall some classical results on real interpolation (see [52], [7], [30]). 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 4.2. 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 (3.5) and *i)* we have that

$$v \in C^0\left([0,T]; V_p\right), \quad \forall\, p \geq 1,$$

and

$$\|u(t)\|_{V_p} \leq 2C\left(\|v_0\|_{V_p} + \|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} + \|I^s_{i,e}\|_{L^p(0,T;L^2(\Omega))} + \|I^s_i + I^s_e\|_{H^1(0,T;L^2(\Omega))}\right). \tag{4.5}$$

By estimate (3.3) there exists $C_5 > 0$ such that, $\forall\, p \in (1, +\infty)$

$$\|\bar{I}_{ion}\|_{L^p(0,T;L^2(\Omega))} \leq C_5\left(1 + \|\bar{v}\|_{L^2(\Omega,H^1(0,T))}\right) \leq C_6(1 + M_1). \tag{4.6}$$

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 (4.5) and (4.6) there exists $M_\infty > 0$, depending only on M_1, p and the data of the problem, such that

$$\sup\{|v(x,t)|,\ (x,t) \in Q\} \leq M_\infty. \tag{4.7}$$

$\square$

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 (2.4)

$$\begin{cases} \dfrac{\partial \mathbf{z}_i}{\partial t} = \mathbf{G}(\bar{v}_i, \mathbf{w}_i, \mathbf{z}_i), & \text{on } Q, \\ \mathbf{z}_i(x,0) = \mathbf{z}_0(x), & \text{on } \Omega. \end{cases}$$

By estimates (2.2), (2.6), (4.7), 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 (1.8a), $\mathbf{F}$ 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

$$\|\mathbf{w}_1(t) - \mathbf{w}_2(t)\|^2_{L^2(\Omega)} \le 2L_1 \int_0^t \|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)} + \|\mathbf{w}_1(s) - \mathbf{w}_2(s)\|^2_{L^2(\Omega)} ds,\ \forall t \in (0,T),$$

and by Gronwall's Lemma

$$\|\mathbf{w}_1(t) - \mathbf{w}_2(t)\|^2_{L^2(\Omega)} \le 2L_1 e^{2L_1 T} \int_0^t \|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)} ds,\ \forall\, t \in (0,T). \tag{4.8}$$

By hypothesis (1.5a) 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

$$|\mathbf{z}_1(x,t) - \mathbf{z}_2(x,t)| \le L_2 \int_0^t |\bar{v}_1(x,s) - \bar{v}_2(x,s)| + |\mathbf{w}_1(x,s) - \mathbf{w}_2(x,s)| + |\mathbf{z}_1(x,s) - \mathbf{z}_2(x,s)|\, ds,$$

and, as above, using Jensen's inequality, Gronwall's Lemma and (4.8), we find a constant $L_3 = L_3(L_1, L_2, T)$ such that

$$\|\mathbf{z}_1(t) - \mathbf{z}_2(t)\|^2_{L^2(\Omega)} \le L_3 \int_0^t \|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)}, \quad \forall\, t \in (0,T) \tag{4.9}$$

We recall system (3.4a)–(3.4e) and estimate (3.6)

$$\begin{aligned}
\partial_t v + \bar{I}_{ion} - \operatorname{div}(M_i \nabla u_i) - I_i^s &= 0 && \text{on } Q,\\
\partial_t v + \bar{I}_{ion} + \operatorname{div}(M_e \nabla u_e) + I_e^s &= 0 && \text{on } Q,\\
M_{i,e} \nabla u_{i,e} \cdot \nu &= 0 && \text{on } \Sigma,\\
v(x,0) &= v_0(x) && \text{on } \Omega.
\end{aligned}$$

$$\|v_1(t) - v_2(t)\|^2_{L^2(\Omega)} \le C \|\bar{I}_{ion,1} - \bar{I}_{ion,2}\|^2_{L^2(0,t;L^2(\Omega))}.$$

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

$$\|v_1(t) - v_2(t)\|^2_{L^2(\Omega)} \le L_4 \int_0^t \Big(\|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)} + \|\mathbf{w}_1(s) - \mathbf{w}_2(s)\|^2_{L^2(\Omega)} + \\ + \|\mathbf{z}_1(s) - \mathbf{z}_2(s)\|^2_{L^2(\Omega)}\Big)\, ds, \tag{4.10}$$

and using (4.8), (4.9), we find a constant $L = L(L_1, L_2, L_3, L_4, T)$ such that

$$\|v_1(t) - v_2(t)\|^2_{L^2(\Omega)} \le L \int_0^t \|\bar{v}_1(s) - \bar{v}_2(s)\|^2_{L^2(\Omega)} ds. \tag{4.11}$$

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 (4.11) we have

$$0 \le \varphi(t) \le L \int_0^t \bar{\varphi}(s)\, ds, \quad \forall\, t \in (0,T). \tag{4.12}$$

Now we multiply (4.12) by $e^{-\lambda t}$, $(\lambda > 0)$, and we integrate between 0 and T:

$$\int_0^T e^{-\lambda t} \varphi(t)\, dt \le L \int_0^T e^{-\lambda t} \left(\int_0^t \bar{\varphi}(s)\, ds \right) dt,$$

and integrating by parts

$$\int_0^T e^{-\lambda t}\varphi(t)\, dt \le \frac{L}{\lambda} \left[\int_0^T e^{-\lambda t} \bar{\varphi}(t)\, dt - C_4 e^{-\lambda T} \int_0^T \bar{\varphi}(t)\, dt \right] \le \frac{L}{\lambda} \int_0^T e^{-\lambda t} \bar{\varphi}(t)\, dt.$$

We conclude that

$$|||\mathcal{T}\bar{v}_1 - \mathcal{T}\bar{v}_2|||_{\lambda, L^2(\Omega)} \le \frac{L}{\lambda} |||\bar{v}_1 - \bar{v}_2|||_{\lambda, L^2(\Omega)},$$

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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