

DERIVATION OF CABLE EQUATION BY MULTISCALE ANALYSIS FOR A MODEL OF MYELINATED AXONS

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ABSTRACT. We derive a one-dimensional cable model for the electric potential propagation along an axon. Since the typical thickness of an axon is much smaller than its length, and the myelin sheath is distributed periodically along the neuron, we simplify the problem geometry to a thin cylinder with alternating myelinated and unmyelinated parts. Both the microstructure period and the cylinder thickness are assumed to be of order ε , a small positive parameter. Assuming a nonzero conductivity of the myelin sheath, we find a critical scaling with respect to ε which leads to the appearance of an additional potential in the homogenized nonlinear cable equation. This potential contains information about the geometry of the myelin sheath in the original three-dimensional model.

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1. **Introduction.** As population aging and obesity prevalence increase, ensuing neurological disorders [39, 31] have become the target of an evergrowing biomedical community aiming at treating such conditions. Thanks to these efforts, functional loss in patients can now be partially treated through therapies such as peripheral nerve or spinal cord stimulation [10, 35, 9], gene transfection [28, 11], membrane electro-permeabilization [40] or myelin growth [20]. Thus, improving our understanding of the complex bioelectrical processes involved in neural signal transmission is key. In particular, more accurate and rigorous mathematical depictions can lead to individual patient care, a trend known as medicine *in silico* [13].

The Hodgkin-Huxley (HH) axon model [16] stands out as being the first phenomenological description able to reproduce neuron electrical activity. As is now well understood, excitability of nerve cells follows a non-linear dynamic relation between electric currents and potential differences across the axon membrane. These differences are created by the membrane's own capacitance, resistivity and ion-selective pumps and channels [36, 17]. Voltage differences between intra- and extra-cellular domains satisfy Laplace equations in each subdomain as a quasi-static regime can be assumed. Hence, one typically couples a dynamic model taking place on the cellular membrane with a static volumic one on either side. Along the longitudinal direction, peripheral nerve cellular membranes alternate unmyelinated and myelinated layers –called Ranvier nodes and internodes, respectively–, which correspondingly allow or deter current flow. Such structures affect nerve pulse propagation speed and account for morphological differences in motor and sensorial fibers. Thus, describing the complete macroscopic response of an electrically stimulated axon can be a daunting effort.

Homogenization models present an alternative to simplify the above coupling [4, 3, 5, 6] by reducing the heterogenous domain into an homogenous or *effective medium* possibly diminishing dimensionality. For this, it is required large numbers of either cells or alternating myelin periods –as in our case–, with respect to the physical scales of the quantities of interest studied. There are many results where homogenization is applied to cardiac tissue [29, 33, 12, 2]. However, cardiac muscle is fundamentally different from nerve tissue as the intracellular space of each cardiac cell is coupled to its neighbor's through channels. Thus, electric current can flow from one cell to another without crossing a cell membrane in opposition to the neural case.

Peripheral nerve pulse propagation has been classically modeled via cable equations. These are usually derived by considering dendrites and axons as cylinders composed of segments with capacitances and resistivities combined in parallel [37, 38, 8, 26]. The coefficients in such dimensionally reduced equations depend on membrane parameters over Ranvier nodes and internodes (myelinated parts) as well as on their lengths. Several works present formal two-scale expansions applied to a one-dimensional model in order to show that a myelinated neuron can be approximated by a homogeneous cable equation [8, 27]. Yet, these results do not justify the formal approximation nor do they take into account either the fibers' microstructure or myelin sheath geometry. In [25] the authors present a computer-based model for myelinated axons reproducing a wide range of experimental data. The models developed in this study use an explicit representation of the nodes of Ranvier, paranodal, and internodal sections of the axon (21 nodes of Ranvier separated by 20 internodes) as well as a finite impedance myelin sheath. The result is the accurate adjustment of the Hodgkin-Huxley model to the experimental data.

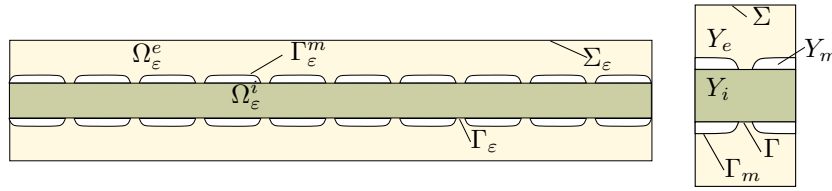


FIGURE 1. Simplified cross-section of a cylindrical myelinated axon (left) and the periodicity cell Y (right).

The present work presents a rigorous derivation of a nonlinear cable equation depicting signal propagation along a myelinated neuron. We assume that the conductivity of the myelin sheath is small compared to that of extra- and intracellular domains, but not equal to zero. We find a critical scaling for the myelin conductivity which leads to the appearance of an additional potential in the homogenized equation due to energy concentration in the neighborhoods of contact points between Ranvier nodes and myelin sheaths, which we describe in detail in Section 4. This effect is similar to the appearance of strange terms in homogenization of elliptic operators in domains with fine-grained boundary. The pioneering work [22] showed that Dirichlet boundary conditions on fine-grained boundaries can lead to a homogenized equation with an effective potential.

Different nontrivial effects arise in homogenization of elliptic operators which do not satisfy uniform ellipticity and/or boundedness condition. In such cases the homogenized equation can be vectorial or contain nonlocal terms [18] or exhibit memory effects as in the celebrated double porosity model [7].

The technical difficulties in the present work come from the combination of a thin structure, which leads to the dimension reduction, and the presence of alternating boundary conditions: continuity of fluxes through the myelin sheath and nonlinear HH dynamics on the Ranvier nodes. The original thin three-dimensional structure shrinks to a segment, as the microstructure period goes to zero, and since the energy concentrates in the neighborhoods of Ranvier nodes, we obtain a one-dimensional nonlinear parabolic problem. The limit equation has a strong resemblance to the well-known Kolmogorov-Petrovsky-Piskunov (KPP) equation allowing traveling wave and traveling pulses solutions [19].

The paper is organized as follows. In Section 2 we formulate the problem and present the main result in Theorem 2.1. The rest of the paper is devoted to the proof of Theorem 2.1. Section 3 presents a priori estimates for the potential u_ε and its jump across the Ranvier nodes. In Section 4 we construct an auxiliary test function which is used when passing to the limit in Section 5.

2. Problem setup.

2.1. Geometry. Let us consider a myelinated axon sparsely suspended in an extracellular medium. We assume that the axon has a periodic structure, containing myelinated and unmyelinated parts (Ranvier nodes) as illustrated on Figure 1. We will consider a model geometry with radially symmetric intra- and extracellular domains.

In order to describe the periodic microstructure, we first introduce a periodicity cell $Y = (-\frac{1}{2}, \frac{1}{2}) \times D_{R_0}$, where D_{R_0} is the disk in \mathbb{R}^2 with finite radius R_0 centered

at zero. The periodicity of Y assumes that it is translated by integers in the y_1 -direction. As shown in Figure 1, the cell Y is decomposed into the following disjoint bounded domains: (i) an intracellular part $Y_i = (-\frac{1}{2}, \frac{1}{2}) \times D_{r_0}$, for a radius $0 < r_0 < R_0$; (ii) an extracellular medium Y_e ; and, (iii) a myelin sheath Y_m . We denote by Γ_{mi} (resp. Γ_{me}) the interface between Y_m and Y_i (resp. Y_e) and write $\Gamma_m = \Gamma_{mi} \cup \Gamma_{me}$ for the myelinated part of the interface that we assume Lipschitz continuous. The unmyelinated interface corresponding to the surface of a Ranvier node is denoted by Γ . The lateral boundary of Y is denoted by Σ .

Thanks to radial symmetry, the domains Y_i, Y_m, Y_e are volumes of revolution generated by 2D domains Y'_i, Y'_m and Y'_e , correspondingly (see Figure 2). After identifying the opposite faces of Y in the y_1 -direction (due to the periodicity), Y'_m becomes a simply connected domain whose boundary is naturally divided into two parts $\Gamma'_{mi} = \partial Y'_m \cap \partial Y'_i$ and $\Gamma'_{me} = \partial Y'_m \cap \partial Y'_e$. Let $A = (a, r_0)$ and $B = (b, r_0)$ denote the points where myelin meets the Ranvier node. Then, Γ'_{me} is a smooth curve which never intersects or touches Y'_i except at the endpoints A and B , and locally near these points it is given by $r = r_A(x_1)$ and $r = r_B(x_1)$. Moreover, we assume that r_A and r_B are C^2 -functions whose derivatives do not vanish at points A and B .

The periodicity cell is then scaled by a small parameter $\varepsilon > 0$ and periodically translated along the x_1 -axis to form a thin cylinder $\Omega_\varepsilon = (0, L) \times \varepsilon D_{R_0}$ with periodic microstructure and a fixed length L . Let $\Omega_\varepsilon^i = (0, L) \times (\varepsilon D_{r_0})$ denote the intracellular domain, Ω_ε^e the extracellular domain and Ω_ε^m the myelin part. The unmyelinated part of the boundary of Ω_ε^i is denoted by Γ_ε , while Γ_ε^m represents the boundary of the myelin Ω_ε^m . For simplicity we assume that Ω_ε is formed by an integer number of periodicity cells. The whole domain Ω_ε is the union of the extracellular, intracellular and myelin domains, and interfaces between them: $\Omega_\varepsilon = \Omega_\varepsilon^i \cup \Omega_\varepsilon^e \cup \Omega_\varepsilon^m \cup \Gamma_\varepsilon^m \cup \Gamma_\varepsilon$. The bases of the cylinder Ω_ε are the disks $S_{\varepsilon,0} = \{0\} \times \varepsilon D_{R_0}$ and $S_{\varepsilon,L} = \{L\} \times \varepsilon D_{R_0}$, while the lateral boundary is denoted by Σ_ε .

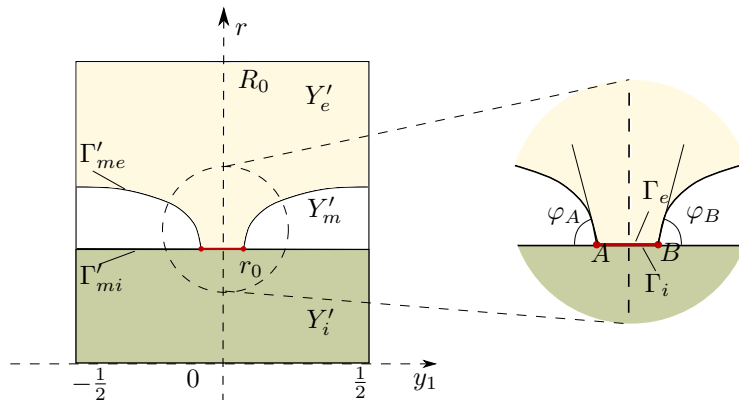


FIGURE 2. 2D surface generating by revolution the periodicity cell in the neighborhood of a Ranvier node.

2.2. Mathematical model. Let u_ε be the electric potential whose restrictions to intracellular, extracellular and myelin domains are denoted by u_ε^i , u_ε^e , and u_ε^m , respectively. The electric potential satisfies Laplace equations in the intracellular domain Ω_ε^i , extracellular domain Ω_ε^e and in the myelin Ω_ε^m , and we prescribe homogeneous Neumann boundary condition on the lateral boundary Σ_ε and homogeneous Dirichlet boundary condition on the bases $S_{\varepsilon,0}$ and $S_{\varepsilon,L}$. The jump of the potential through the axon’s membrane, called the transmembrane potential, is denoted by

$$[u_\varepsilon] = u_\varepsilon^i - u_\varepsilon^e \quad \text{on } \Gamma_\varepsilon.$$

We assume that the conductivity $\sigma_\varepsilon \in L^\infty(\Omega_\varepsilon)$ is a piecewise-constant function given by

$$\sigma_\varepsilon = \begin{cases} \sigma_e & \text{in } \Omega_\varepsilon^e, \\ \sigma_i & \text{in } \Omega_\varepsilon^i, \\ \varepsilon^4 & \text{in } \Omega_\varepsilon^m, \end{cases}$$

where σ_e, σ_i are positive constants independent of ε . We consider the critical scaling ε^4 in the myelin sheath though this dependence could be different. In fact, the technique developed in this work can also be applied in the case when the conductivity in Ω_ε^m is of order ε^n , with $n \geq 4$. However, our choice ensures that an extra potential will appear in the limit equation (cf. $\bar{\Lambda}$ in Theorem 2.1).

On the Ranvier nodes Γ_ε we assume current continuity and HH dynamics for the transmembrane potential (see (3)–(5) below). Following the HH model [16], the applied current through the membrane is a sum of a capacitive current $c_m \partial_t [u_\varepsilon]$, where c_m is the membrane capacitance per unit area, and an ionic current $I_{ion}([u_\varepsilon], g_\varepsilon)$ through ionic channels. Various ionic fluxes are regulated by the vector of gating variables g_ε with $m \in \mathbb{N}$ nonnegative components $0 \leq (g_\varepsilon)_j \leq 1$, satisfying an ordinary differential equation $\partial_t g_\varepsilon = HH([u_\varepsilon], g_\varepsilon)$. The ionic current is given by

$$I_{ion}(v_\varepsilon, g_\varepsilon) = \sum_{j=1}^m H_j((g_\varepsilon)_j)(v_\varepsilon - v_{r,j}), \tag{1}$$

where $(g_\varepsilon)_j$ is the j -th component of the gating variable vector g_ε , $v_{r,j}$ are given constants (components of the resting potential), and H_j are positive bounded functions. In the HH model [16], the authors consider three ionic channels: sodium (Na), potassium (K) and leakage (L), and the explicit form of functions H and HH is presented. In this work we use the following properties of these functions:

- (H1) The functions H_j are positive, bounded and Lipschitz continuous.
- (H2) The vector function HH is given by $HH(v, g) = F(v) - \alpha(v)g$, where F is a vector function with positive components and α is a diagonal $m \times m$ matrix with positive Lipschitz continuous entries.
- (H3) G_0 is a vector function, continuous in $(0, L)$ with components taking values in the interval $[0, 1]$.

We denote by ν the unit normal exterior to Ω_ε^e on Σ_ε and to the interface between the myelin and the extracellular domain, and exterior to Ω_ε^i on Γ_ε and on the interface between the myelin Ω_ε^m and Ω_ε^i . Note that ν on Γ_ε is orthogonal to the x_1 -axes, that is its first component is zero.

The full system describing the dynamics of the electric potential u_ε and the gating variables vector g_ε is as follows

$$-\operatorname{div}(\sigma_\varepsilon \nabla u_\varepsilon) = 0, \quad (t, x) \in (0, T) \times \Omega_\varepsilon \setminus \Gamma_\varepsilon, \quad (2)$$

$$\sigma_\varepsilon \nabla u_\varepsilon^e \cdot \nu = \sigma_i \nabla u_\varepsilon^i \cdot \nu, \quad (t, x) \in (0, T) \times \Gamma_\varepsilon, \quad (3)$$

$$u_\varepsilon^e = u_\varepsilon^i, \quad (t, x) \in (0, T) \times \Gamma_\varepsilon^m, \quad (4)$$

$$\varepsilon(c_m \partial_t [u_\varepsilon] + I_{ion}([u_\varepsilon], g_\varepsilon)) = -\sigma_i \nabla u_\varepsilon^i \cdot \nu, \quad (t, x) \in (0, T) \times \Gamma_\varepsilon, \quad (5)$$

$$\partial_t g_\varepsilon = HH([u_\varepsilon], g_\varepsilon), \quad (t, x) \in (0, T) \times \Gamma_\varepsilon, \quad (6)$$

$$[u_\varepsilon](0, x) = 0, \quad g_\varepsilon(0, x) = G_0(x_1), \quad x \in \Gamma_\varepsilon, \quad (7)$$

$$\nabla u_\varepsilon^e \cdot \nu = 0, \quad (t, x) \in (0, T) \times \Sigma_\varepsilon, \quad (8)$$

$$u_\varepsilon = 0, \quad (t, x) \in (0, T) \times (S_{\varepsilon,0} \cup S_{\varepsilon,L}). \quad (9)$$

Remark 1. When measuring neural response to external stimulation, one seeks to exclude the appearance of an action potential in the absence of the external stimulation. To this end, one can control the initial state of the ionic channels (initial conditions for the gating variables) in order to guarantee zero potential at the initial moment. This has motivated the choice of zero initial condition for the transmembrane potential (7).

In order to define a weak solution of problem (2)–(9), we will use test functions

$$\phi \in L^\infty(0, T; H^1(\Omega_\varepsilon \setminus \Gamma_\varepsilon)) \quad \text{such that} \quad \partial_t \phi \in L^2(0, T; L^2(\Gamma_\varepsilon))$$

with $\phi = 0$ on $S_{\varepsilon,0}$ and $S_{\varepsilon,L}$. The jump of ϕ across Ranvier nodes is denoted by $[\phi] = (\phi^i - \phi^e)|_{\Gamma_\varepsilon}$. With these, the weak formulation of (2)–(9) reads:

Find $g_\varepsilon \in [C(0, T; L^2(\Gamma_\varepsilon))]^m$ and $u_\varepsilon \in L^\infty(0, T; H^1(\Omega_\varepsilon \setminus \Gamma_\varepsilon))$ satisfying boundary conditions $u_\varepsilon = 0$ for $x_1 = \{0, L\}$ and the initial condition $[u_\varepsilon](0, x) = 0$, with

$$\partial_t [u_\varepsilon] \in L^2(0, T; L^2(\Gamma_\varepsilon)),$$

such that, for any test function $\phi \in L^\infty(0, T; H^1(\Omega_\varepsilon \setminus \Gamma_\varepsilon))$, $\phi = 0$ for $x_1 = 0$ and $x_1 = L$, and for almost all $t \in (0, T)$, it holds

$$\varepsilon \int_{\Gamma_\varepsilon} c_m \partial_t [u_\varepsilon][\phi] ds + \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \nabla \phi dx + \varepsilon \int_{\Gamma_\varepsilon} I_{ion}([u_\varepsilon], g_\varepsilon)[\phi] ds = 0. \quad (10)$$

The vector of gating variables $g_\varepsilon \in [L^\infty(0, T; L^2(\Gamma_\varepsilon))]^m$ solves the following ordinary differential equation

$$\partial_t g_\varepsilon = HH([u_\varepsilon], g_\varepsilon), \quad g_\varepsilon(0, x) = G_0(x_1).$$

Since HH is linear with respect to g_ε , we can solve the last ODE and obtain g_ε as a function (integral functional) of the jump $v_\varepsilon = [u_\varepsilon]$:

$$\langle g_\varepsilon, v_\varepsilon \rangle = e^{-\int_0^t \alpha(v_\varepsilon(\zeta, x)) d\zeta} \left(G_0(x) + \int_0^t e^{\int_0^\tau \alpha(v_\varepsilon(\zeta, x)) d\zeta} F(v_\varepsilon(\tau, x)) d\tau \right). \quad (11)$$

Substituting this expression into (10), we obtain the weak formulation of problem (2)–(9) in terms of the potential u_ε and its jump $v_\varepsilon = [u_\varepsilon]$ across Γ_ε :

$$\varepsilon \int_{\Gamma_\varepsilon} c_m \partial_t v_\varepsilon [\phi] ds + \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \nabla \phi dx + \varepsilon \int_{\Gamma_\varepsilon} I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle)[\phi] ds = 0. \quad (12)$$

The main result of the paper is Theorem 2.1 which describes the convergence, as $\varepsilon \rightarrow 0$, of the electric potential u_ε and the vector of gating variables g_ε to the unique solution (v_0, g_0) of the following one-dimensional problem:

$$\begin{aligned} c_m \partial_t v_0 + I_{ion}(v_0, g_0) + \bar{\Lambda} v_0 &= a^{\text{eff}} \partial_{x_1 x_1}^2 v_0, & (t, x_1) \in (0, T) \times (0, L), \\ \partial_t g_0 &= HH(v_0, g_0), & (t, x_1) \in (0, T) \times (0, L), \\ v_0(t, 0) = v_0(t, L) &= 0, & t \in (0, T), \\ v_0(0, x_1) = 0, g_0(0, x_1) &= G_0(x_1), & x_1 \in (0, L). \end{aligned} \tag{13}$$

The effective coefficient a^{eff} is given by

$$a^{\text{eff}} = \frac{1}{|\Gamma|} \left((\sigma_e \int_{Y_e} (\partial_{y_1} N + 1) dy)^{-1} + (\sigma_i |Y_i|)^{-1} \right)^{-1}, \tag{14}$$

where the 1-periodic in y_1 function N solves an auxiliary 3D cell problem:

$$\begin{aligned} -\Delta N(y) &= 0, & y \in Y_e, \\ \nabla N \cdot \nu &= -\nu_1, & y \in \Gamma_m, \\ \nabla N \cdot \nu &= 0, & y \in \Gamma \cup \Sigma, \\ N(y_1, y') &\text{ is periodic in } y_1. \end{aligned} \tag{15}$$

The constant $\bar{\Lambda}$ depends on the geometry of the myelin sheath described in detail in Section 4 (see Figure 2) and the conductivities σ_e, σ_i , and is given by

$$\bar{\Lambda} = \frac{1}{b-a} \left(\left(\frac{\varphi_A}{\sigma_e(\pi - \varphi_A)} + \frac{\varphi_A}{\sigma_i \pi} \right)^{-1/2} + \left(\frac{\varphi_B}{\sigma_e(\pi - \varphi_B)} + \frac{\varphi_B}{\sigma_i \pi} \right)^{-1/2} \right). \tag{16}$$

Theorem 2.1. *The solutions $[u_\varepsilon]$ and g_ε of problem (2)–(9) converge to the solutions v_0 and g_0 of (13) in the following sense:*

$$\begin{aligned} \sup_{t \in (0, T)} \varepsilon^{-1} \int_{\Gamma_\varepsilon} |[u_\varepsilon] - v_0|^2 ds &\rightarrow 0, \\ \sup_{t \in (0, T)} \varepsilon^{-1} \int_{\Gamma_\varepsilon} |g_\varepsilon - g_0|^2 ds &\rightarrow 0, \quad \varepsilon \rightarrow 0. \end{aligned}$$

Remark 2. The effective coefficient a^{eff} can be interpreted as the conductivity of the bulk medium corresponding to the conductivity of the intra- and extracellular domains connected in series. Indeed, the second derivative term in (13) provides an approximation to the influence of electrical stimulation or neuromodulation firing cells in classic cable models [38].

Remark 3. Similarly to g_ε , one can resolve the equation for g_0 to get

$$\langle g_0, v_0 \rangle = e^{-\int_0^t \alpha(v_0(\zeta, x)) d\zeta} \left(G_0(x) + \int_0^t e^{\int_0^\tau \alpha(v_0(\zeta, x)) d\zeta} F(v_0) d\tau \right). \tag{17}$$

Due to the hypotheses (H1), (H2), the mapping $v \mapsto I_{ion}(v, \langle g, v \rangle)$ is Lipschitz continuous in $L^2((0, T) \times \Gamma_\varepsilon)$. In this way, the effective problem is written as one nonlinear diffusion equation:

$$\begin{aligned} c_m \partial_t v_0 + I_{ion}(v_0, \langle g_0, v_0 \rangle) + \bar{\Lambda} v_0 &= a^{\text{eff}} \partial_{x_1 x_1}^2 v_0, & (t, x_1) \in (0, T) \times (0, L), \\ v_0(t, 0) = v_0(t, L) &= 0, & t \in (0, T), \\ v_0(0, x_1) = 0, & & x_1 \in (0, L). \end{aligned} \tag{18}$$

The proof of Theorem 2.1 is carried out through Sections 3–5. First, we derive *a priori* estimates in Section 3 (Lemma 3.2). Then, we prove the two-scale convergence of u_ε and its gradient (Lemma 3.5) and the convergence of the transmembrane potential $[u_\varepsilon]$ in appropriate spaces (Lemma 3.6). Finally, in Section 5 we pass to the limit in the weak formulation and derive the limit problem (13). Section 4 is devoted to the construction of an auxiliary function, the main ingredient of the test function used when passing to the limit in the weak formulation.

3. A priori estimates.

Lemma 3.1. *There exists a unique solution u_ε of problem (2)–(9) such that*

$$u_\varepsilon \in L^\infty(0, T; H^1(\Omega_\varepsilon \setminus \Gamma_\varepsilon)), \quad \text{with} \quad \partial_t v_\varepsilon = \partial_t [u_\varepsilon] \in L^2(0, T; L^2(\Gamma_\varepsilon)).$$

Proof. The existence of a mild solution follows from the classical semigroup theory (see, for example, [32]). Its regularity is addressed in [23, 15, 14]. For the sake of completeness we present a sketch of the proof.

Let us rewrite (2)–(9) in the form:

$$\varepsilon(c_m \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle)) = A_\varepsilon v_\varepsilon, \quad (t, x) \in (0, T) \times \Gamma_\varepsilon, \tag{19}$$

$$v_\varepsilon(0, x) = 0, \quad x \in \Gamma_\varepsilon, \tag{20}$$

introducing the operator $A_\varepsilon : D(A_\varepsilon) \subset L^2(\Gamma_\varepsilon) \rightarrow L^2(\Gamma_\varepsilon)$ on the jump across the nodes $v_\varepsilon = [u_\varepsilon]$ as follows. For a given v_ε , we solve the stationary problem (2)–(4), (8)–(9) in $\Omega_\varepsilon \setminus \Gamma_\varepsilon$. Then, by means of weak solutions, we define $A_\varepsilon v_\varepsilon := \sigma_\varepsilon \nabla u_\varepsilon \cdot \nu$ on Γ_ε . To describe the domain of A_ε we prescribe $f = -\sigma_\varepsilon \nabla u_\varepsilon \cdot \nu \in L^2(\Gamma_\varepsilon)$ and find the solution $u_\varepsilon \in H^1(\Omega_\varepsilon \setminus \Gamma_\varepsilon)$ of (2)–(4), (8)–(9), which gives us the value of $v_\varepsilon = u_\varepsilon^i - u_\varepsilon^e$. Taking arbitrary $f \in L^2(\Gamma_\varepsilon)$ we obtain $D(A_\varepsilon)$. Problem (2)–(4), (8)–(9) has a unique solution by the Lax-Milgram theorem. Alternatively, the operator A_ε is nothing but the operator associated with the quadratic form

$$(A_\varepsilon v_\varepsilon, v_\varepsilon)_{L^2(\Gamma_\varepsilon)} = - \min_u \int_{\Omega_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \nabla u_\varepsilon \, dx,$$

where the minimum is taken over $u_\varepsilon \in H^1(\Omega_\varepsilon \setminus \Gamma_\varepsilon)$ such that $[u_\varepsilon] = v_\varepsilon$ on Γ_ε and $u_\varepsilon = 0$ for $x_1 = \{0, L\}$. This form is closed and densely defined in $L^2(\Gamma_\varepsilon)$. Moreover, due to the Poincaré inequality, this form is negative definite

$$(A_\varepsilon v_\varepsilon, v_\varepsilon)_{L^2(\Gamma_\varepsilon)} = - \int_{\Omega_\varepsilon} \sigma_\varepsilon |\nabla u_\varepsilon|^2 \, dx \leq -C_\varepsilon \|v_\varepsilon\|_{L^2(\Gamma_\varepsilon)}^2 < 0,$$

with $C_\varepsilon > 0$, and thus, the resolvent set of A_ε contains \mathbb{R}_+ . Therefore A_ε is an infinitesimal generator of a strongly continuous semigroup of contractions (see Theorem 3.1 in [32]). Since $I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle)$ is Lipschitz continuous with respect to v_ε , following the lines of Theorem 1.2, Ch. 6 in [32], one can prove that there exists a unique mild solution $v_\varepsilon \in C([0, T]; L^2(\Gamma_\varepsilon))$ of (19). It is left to show that $u_\varepsilon \in L^\infty(0, T; H^1(\Omega_\varepsilon \setminus \Gamma_\varepsilon))$ in the bulk domain and $\partial_t v_\varepsilon \in L^2(0, T; L^2(\Gamma_\varepsilon))$. This is done by deriving *a priori* estimates as in Lemma 3.2 below. \square

Note that due to the regularity of the initial condition, v_ε is also a strict solution of (19), that is $v_\varepsilon \in C^1([0, T], L^2(\Gamma_\varepsilon))$ (see Proposition 7.1.10 in [21]).

Lemma 3.2 (*A priori estimates*). *Let $(u_\varepsilon, g_\varepsilon)$ be a solution of problem (2)–(9). Denote again the transmembrane potential $v_\varepsilon = [u_\varepsilon]$. Then, for $t \in [0, T]$, the following estimates hold:*

- (i) $\varepsilon^{-1} \int_{\Gamma_\varepsilon} |v_\varepsilon|^2 ds \leq C,$
- (ii) $\varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} |\partial_\tau v_\varepsilon|^2 ds d\tau \leq C,$
- (iii) $\varepsilon^{-2} \int_{\Omega_\varepsilon^i \cup \Omega_\varepsilon^e} (|u_\varepsilon|^2 + |\nabla u_\varepsilon|^2) dx \leq C,$
- (iv) $\int_{\Omega_\varepsilon^m} |u_\varepsilon|^2 dx + \varepsilon^2 \int_{\Omega_\varepsilon^m} |\nabla u_\varepsilon|^2 dx \leq C,$

for a generic constant C independent of ε .

Proof. Let us multiply (2) by u_ε , integrate by parts over $\Omega_\varepsilon \setminus \Gamma_\varepsilon$:

$$\frac{\varepsilon}{2} \frac{d}{dt} \int_{\Gamma_\varepsilon} c_m v_\varepsilon^2 ds + \varepsilon \int_{\Gamma_\varepsilon} I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle) v_\varepsilon ds + \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon |\nabla u_\varepsilon|^2 dx = 0.$$

Integrating the last equality with respect to t we get

$$\frac{\varepsilon}{2} \int_{\Gamma_\varepsilon} c_m v_\varepsilon^2 ds + \varepsilon \int_0^t \int_{\Gamma_\varepsilon} I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle) v_\varepsilon ds d\tau + \int_0^t \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon |\nabla u_\varepsilon|^2 dx d\tau = 0, \tag{21}$$

where we have used (7). By dividing the resulting identity by ε^2 (the scaling factor of the order $|\Omega_\varepsilon|$), recalling the definition (1) of I_{ion} and the positivity of H we get

$$\begin{aligned} \frac{\varepsilon^{-1}}{2} \int_{\Gamma_\varepsilon} c_m v_\varepsilon^2 ds + \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} \sum_j H(\langle g_\varepsilon, v_\varepsilon \rangle_j) (v_\varepsilon - v_{r,j}) v_\varepsilon ds d\tau &\leq 0, \\ \frac{\varepsilon^{-1}}{2} \int_{\Gamma_\varepsilon} c_m v_\varepsilon^2 ds &\leq \frac{\varepsilon^{-1}}{2} \int_0^t \int_{\Gamma_\varepsilon} \sum_j H(\langle g_\varepsilon, v_\varepsilon \rangle_j) (v_{r,j})^2 ds d\tau \leq C. \end{aligned}$$

Estimate (i) is proved. Now, from (21) and (i) we derive an integral estimate for ∇u_ε :

$$\varepsilon^{-2} \int_0^t \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon |\nabla u_\varepsilon|^2 dx d\tau \leq C.$$

Let us now multiply (2) by $\partial_t u_\varepsilon$ and integrate by parts over $\Omega_\varepsilon \setminus \Gamma_\varepsilon$:

$$\begin{aligned} \varepsilon^{-1} \int_{\Gamma_\varepsilon} c_m |\partial_t v_\varepsilon|^2 ds + \varepsilon^{-1} \int_{\Gamma_\varepsilon} I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle) \partial_t v_\varepsilon ds \\ + \frac{\varepsilon^{-2}}{2} \frac{d}{dt} \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon |\nabla u_\varepsilon|^2 dx = 0. \end{aligned}$$

Integrating with respect to t gives

$$\begin{aligned} \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} c_m |\partial_\tau v_\varepsilon|^2 ds d\tau + \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle) \partial_\tau v_\varepsilon ds d\tau \\ + \frac{\varepsilon^{-2}}{2} \int_{\Omega_\varepsilon} \sigma_\varepsilon |\nabla u_\varepsilon|^2 dx = \frac{\varepsilon^{-2}}{2} \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon |\nabla u_\varepsilon|^2 \Big|_{t=0} dx. \end{aligned} \tag{22}$$

Since v_ε is a strict solution, we can use (10) pointwise, choose $\phi = u_\varepsilon$ and set $t = 0$. Then we have $\nabla u_\varepsilon|_{t=0} = 0$. Using the definition (1) of I_{ion} , the boundedness of H and the estimate (i) proved above we get

$$\begin{aligned} \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} c_m |\partial_\tau v_\varepsilon|^2 ds d\tau + \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} \sum_j H(\langle g_\varepsilon, v_\varepsilon \rangle_j) (v_\varepsilon - v_{r,j}) \partial_\tau v_\varepsilon ds d\tau &\leq 0, \\ \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} c_m |\partial_\tau v_\varepsilon|^2 ds d\tau &\leq C \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} (v_\varepsilon - v_{r,j}) \partial_\tau v_\varepsilon ds d\tau, \\ \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} |\partial_\tau v_\varepsilon|^2 ds d\tau &\leq C \varepsilon^{-1} \int_0^t \int_{\Gamma_\varepsilon} (v_\varepsilon - v_{r,j})^2 ds d\tau \leq C. \end{aligned}$$

Estimate (ii) is proved. Estimates (22) and (ii) imply that

$$\varepsilon^{-2} \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon |\nabla u_\varepsilon|^2 dx \leq C, \quad t \in (0, T). \tag{23}$$

Since u_ε satisfies the homogeneous Dirichlet boundary condition for $x_1 = 0$, the Friedrichs inequality is valid for u_ε in Ω_ε^i and Ω_ε^e leading to (iii).

In order to obtain an L^2 -bound for u_ε in Ω_ε^m we use the Poincaré inequality in each myelin part $\varepsilon Y_{m,k}$, $k = 1, \dots, N_\varepsilon$, and then sum them up to obtain an estimate in $\bigcup_{k=1}^L \varepsilon Y_{m,k} = \Omega_\varepsilon^m$. We denote by $\bar{u}_{\varepsilon,k}^m$ and $\bar{u}_{\varepsilon,k}^i$ the mean values of u_ε^m and u_ε^i over $\varepsilon \Gamma_{mi,k}$, the k -th interface between the intracellular domain and the myelin sheath:

$$\begin{aligned} \bar{u}_{\varepsilon,k}^m &= \frac{1}{|\varepsilon \Gamma_{mi}|} \int_{\varepsilon \Gamma_{mi,k}} u_\varepsilon^m ds, \\ \bar{u}_{\varepsilon,k}^i &= \frac{1}{|\varepsilon \Gamma_{mi}|} \int_{\varepsilon \Gamma_{mi,k}} u_\varepsilon^i ds. \end{aligned}$$

With the help of the Poincaré inequality, we derive the next estimate:

$$\begin{aligned} \int_{\varepsilon Y_{m,k}} |u_\varepsilon^m - \bar{u}_{\varepsilon,k}^m|^2 dx &\leq C \varepsilon^2 \|\nabla u_\varepsilon^m\|_{L^2(\varepsilon Y_{m,k})}^2 \\ \int_{\varepsilon Y_{m,k}} |u_\varepsilon^m|^2 dx &\leq C \left(\varepsilon^2 \int_{\varepsilon Y_{m,k}} |\nabla u_\varepsilon^m|^2 dx + \int_{\varepsilon Y_{m,k}} |\bar{u}_{\varepsilon,k}^m|^2 dx \right). \end{aligned} \tag{24}$$

Due to the continuity of traces of u_ε ,

$$\int_{\varepsilon Y_{m,k}} |\bar{u}_{\varepsilon,k}^m|^2 dx = \int_{\varepsilon Y_{m,k}} |\bar{u}_{\varepsilon,k}^i|^2 dx \leq C \varepsilon \|u_\varepsilon^i\|_{L^2(\varepsilon \Gamma_{mi})}^2, \tag{25}$$

$$\varepsilon \|u_\varepsilon^i\|_{L^2(\varepsilon \Gamma_{mi})}^2 \leq C \left(\|u_\varepsilon^i\|_{L^2(\varepsilon Y_{i,k})}^2 + \varepsilon^2 \|\nabla u_\varepsilon^i\|_{L^2(\varepsilon Y_{i,k})}^2 \right). \tag{26}$$

Combining (24)–(26) we obtain

$$\int_{\varepsilon Y_{m,k}} |u_\varepsilon^m|^2 dx \leq C \left(\varepsilon^2 \int_{\varepsilon Y_{m,k}} |\nabla u_\varepsilon^m|^2 dx + \int_{\varepsilon Y_{i,k}} |u_\varepsilon^i|^2 dx + \varepsilon^2 \int_{\varepsilon Y_{i,k}} |\nabla u_\varepsilon^i|^2 dx \right).$$

Adding up $\varepsilon Y_{m,k}$ and taking into account (23) yields the estimate for the L^2 -norm for u_ε^m

$$\int_{\Omega_\varepsilon^m} |u_\varepsilon^m|^2 dx \leq C \left(\varepsilon^2 \int_{\Omega_\varepsilon^m} |\nabla u_\varepsilon^m|^2 dx + \int_{\Omega_\varepsilon^i} |u_\varepsilon^i|^2 dx + \varepsilon^2 \int_{\Omega_\varepsilon^i} |\nabla u_\varepsilon^i|^2 dx \right) \leq C,$$

which yields (iv) completing the proof. □

Let us recall the notion of the two-scale convergence that will be used when passing to the limit (see [1] and [30] for two-scale convergence on periodic surfaces, [41] and [34] for two-scale convergence in thin structures and dimension reduction).

Definition 3.3. We say that $u_\varepsilon(t, x)$ converges weakly two-scale to $u_0(t, x_1, y)$ in $L^2(0, T; L^2(\Omega_\varepsilon^l))$, $l = i, e$, if

- (i) $\varepsilon^{-2} \int_0^T \int_{\Omega_\varepsilon^l} |u_\varepsilon|^2 dx dt < \infty$.
- (ii) For any $\phi(t, x_1) \in C(0, T; L^2(0, L))$, $\psi(y) \in L^2(Y_l)$ which is 1-periodic in y_1 we have

$$\begin{aligned} & \lim_{\varepsilon \rightarrow 0} \varepsilon^{-2} \int_0^T \int_{\Omega_\varepsilon^l} u_\varepsilon(x) \phi(t, x_1) \psi\left(\frac{x}{\varepsilon}\right) dx dt \\ &= \int_0^T \int_0^L \int_{Y_l} u_0(t, x_1, y) \phi(t, x_1) \psi(y) dy dx_1 dt, \end{aligned}$$

for some function $u_0 \in L^2(0, T; L^2((0, L) \times Y))$, 1-periodic in y_1 .

Definition 3.4. We say that $v_\varepsilon(t, x)$ converges weakly two-scale to $v_0(t, x_1, y)$ in $L^2(0, T; L^2(\Gamma_\varepsilon))$ if

- (i) $\varepsilon^{-1} \int_0^T \int_{\Gamma_\varepsilon} v_\varepsilon^2 ds dt < \infty$.
- (ii) For any $\phi(t, x_1) \in L^\infty(0, T; L^2(0, L))$, $\psi(y) \in L^2(\Gamma)$ which is 1-periodic in y_1 we have

$$\begin{aligned} & \lim_{\varepsilon \rightarrow 0} \varepsilon^{-1} \int_0^T \int_{\Gamma_\varepsilon} v_\varepsilon(x) \phi(t, x_1) \psi\left(\frac{x}{\varepsilon}\right) ds_x dt \\ &= \int_0^T \int_0^L \int_\Gamma v_0(t, x_1, y) \phi(t, x_1) \psi(y) ds_y dx_1 dt \end{aligned}$$

for some function $v_0 \in L^2(0, T; L^2((0, L) \times \Gamma))$, 1-periodic in y_1 .

Lemma 3.5. Let u_ε be a solution of (2)–(9). Denote by $\mathbf{I}_{\Omega_\varepsilon^l}$ the characteristic functions of Ω_ε^l , $l = i, e$. Then, up to a subsequence, it holds

- (i) $[u_\varepsilon]$ converges two-scale to $v_0(t, x_1, y)$ in $L^2(0, T; L^2(\Gamma_\varepsilon))$.
- (ii) $\partial_t [u_\varepsilon]$ converges two-scale to $\partial_t v_0(t, x_1, y)$ in $L^2(0, T; L^2(\Gamma_\varepsilon))$.
- (iii) $\mathbf{I}_{\Omega_\varepsilon^l} u_\varepsilon$ converges two-scale to $u_0^l(t, x_1)$ in $L^2(0, T; L^2(\Omega_\varepsilon^l))$.
- (iv) $\mathbf{I}_{\Omega_\varepsilon^l} \nabla u_\varepsilon$ converges two-scale to $(\partial_{x_1} u_0^l(t, x_1) \mathbf{e}_1 + \nabla_y w^l(t, x_1, y))$ in $(L^2(0, T; L^2(\Omega_\varepsilon^l)))$. Here $\mathbf{e}_1 = (1, 0, 0) \in \mathbb{R}^3$, and $w^l \in L^2(0, T; L^2(0, L) \times H^1(Y))$ is 1-periodic in y_1 .

Proof. The proof follows the lines of classical compactness results for two-scale convergence and therefore is omitted. We refer to [1] for two-scale convergence on periodic surfaces (on Γ_ε), to [41] and [34] for two-scale convergence in thin structures and dimension reduction. □

Lemma 3.6 (Properties of $[u_\varepsilon]$). Let u_ε be a solution of problem (2)–(9). Then, there exists a function

$$\tilde{v}_\varepsilon(t, x_1) \in L^\infty(0, T; H^1(0, L)) \cap H^1(0, T; L^2(0, L))$$

such that

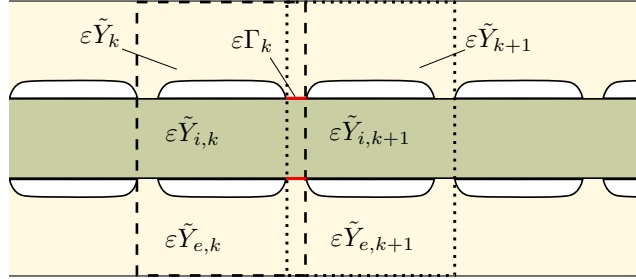


FIGURE 3. Overlapping cells \tilde{Y}_k covering Ω_ε .

(i) For $t \in (0, T)$, the function \tilde{v}_ε approximates $[u_\varepsilon]$:

$$\int_{\Gamma_\varepsilon} |\tilde{v}_\varepsilon - [u_\varepsilon]|^2 ds \leq C\varepsilon \int_{\Omega_\varepsilon^i \cup \Omega_\varepsilon^e} |\nabla u_\varepsilon|^2 dx.$$

(ii) There exists $v_0(t, x_1) \in L^\infty(0, T; L^2(0, L))$ such that along a subsequence \tilde{v}_ε converges to $v_0(t, x_1)$ uniformly on $[0, T]$, as $\varepsilon \rightarrow 0$.

Proof. Let us cover Ω_ε by a union of overlapping cells $\varepsilon \tilde{Y}_k$ as depicted in Figure 3. Each cell contains two Ranvier nodes – compared to one in the original periodicity cell εY . The Ranvier node which belongs to the intersection $\varepsilon \tilde{Y}_k \cap \varepsilon \tilde{Y}_{k+1}$ is denoted by $\varepsilon \Gamma_k$. The intra- and extracellular parts of \tilde{Y}_k are referred to as $\tilde{Y}_{i,k}$ and $\tilde{Y}_{e,k}$, respectively. We start by estimating the difference between the mean values of $[u_\varepsilon]$ over $\varepsilon \Gamma_k$ and $\varepsilon \Gamma_{k+1}$. Let

$$\bar{u}_{\varepsilon,k}^l := \frac{1}{|\varepsilon \Gamma|} \int_{\varepsilon \Gamma_k} u_\varepsilon^l ds, \quad l = i, e.$$

For each $\varepsilon \tilde{Y}_{l,k}$, $l = i, e$, owing to the Poincaré inequality, we have

$$\int_{\varepsilon \tilde{Y}_{l,k}} |u_\varepsilon^l - \bar{u}_{\varepsilon,k}^l|^2 dx \leq C\varepsilon^2 \int_{\varepsilon \tilde{Y}_{l,k}} |\nabla u_\varepsilon^l|^2 dx,$$

with C independent of ε . Considering traces on Γ_k , by a simple scaling argument one has

$$\begin{aligned} \int_{\varepsilon \Gamma_k} |u_\varepsilon^l - \bar{u}_{\varepsilon,k}^l|^2 ds &\leq C\varepsilon^{-1} \left(\int_{\varepsilon \tilde{Y}_{l,k}} |u_\varepsilon^l - \bar{u}_{\varepsilon,k}^l|^2 dx + \varepsilon^2 \int_{\varepsilon \tilde{Y}_{l,k}} |\nabla u_\varepsilon^l|^2 dx \right) \\ &\leq C\varepsilon \int_{\varepsilon \tilde{Y}_{l,k}} |\nabla u_\varepsilon^l|^2 dx, \quad l = i, e. \end{aligned} \tag{27}$$

Then, the difference between two averages $\bar{u}_{\varepsilon,k}$ and $\bar{u}_{\varepsilon,k+1}$ is estimated as follows

$$\begin{aligned} |\bar{u}_{\varepsilon,k}^l - \bar{u}_{\varepsilon,k+1}^l|^2 &\leq \frac{2}{|\varepsilon \tilde{Y}_{l,k} \cap \varepsilon \tilde{Y}_{l,k+1}|} \int_{\varepsilon \tilde{Y}_{l,k} \cap \varepsilon \tilde{Y}_{l,k+1}} (|u_\varepsilon^l - \bar{u}_{\varepsilon,k}^l|^2 + |u_\varepsilon^l - \bar{u}_{\varepsilon,k+1}^l|^2) dx \\ &\leq C\varepsilon^{-1} \int_{\varepsilon \tilde{Y}_{l,k} \cup \varepsilon \tilde{Y}_{l,k+1}} |\nabla u_\varepsilon^l|^2 dx. \end{aligned}$$

Adding up in k the above estimates, we obtain an estimate in Ω_ε^l :

$$\sum_k |\bar{u}_{\varepsilon,k}^l - \bar{u}_{\varepsilon,k+1}^l|^2 \leq C\varepsilon^{-1} \int_{\Omega_\varepsilon^l} |\nabla u_\varepsilon^l|^2 dx. \quad (28)$$

Introduce the following notation

$$\bar{v}_{\varepsilon,k} := \bar{u}_{\varepsilon,k}^i - \bar{u}_{\varepsilon,k}^e = \frac{1}{|\varepsilon\Gamma|} \int_{\varepsilon\Gamma_k} [u_\varepsilon] ds.$$

Then (27) and (28) yield

$$\begin{aligned} \int_{\varepsilon\Gamma_k} |[u_\varepsilon] - \bar{v}_{\varepsilon,k}|^2 ds &\leq C\varepsilon \int_{\varepsilon\tilde{Y}_{i,k} \cup \varepsilon\tilde{Y}_{e,k}} |\nabla u_\varepsilon|^2 dx, \\ \sum_k |\bar{v}_{\varepsilon,k} - \bar{v}_{\varepsilon,k+1}|^2 &\leq C\varepsilon^{-1} \int_{\Omega_\varepsilon^i \cup \Omega_\varepsilon^e} |\nabla u_\varepsilon|^2 dx. \end{aligned} \quad (29)$$

Bounds (29) show that $[u_\varepsilon]$ in each cell $\varepsilon\tilde{Y}_k$ is close to a constant $\bar{v}_{\varepsilon,k}$, and the difference between $\bar{v}_{\varepsilon,k}$ and $\bar{v}_{\varepsilon,k+1}$ is small due to (iii) in Lemma 3.2.

Now, we construct a piecewise linear function $\tilde{v}_\varepsilon(t, x_1)$ interpolating values $\bar{v}_{\varepsilon,k}$ linearly and show that

$$\int_0^L |\tilde{v}_\varepsilon|^2 dx_1 \leq C, \quad t \in (0, T), \quad (30)$$

$$\int_0^L |\partial_{x_1} \tilde{v}_\varepsilon|^2 dx_1 \leq C, \quad t \in (0, T), \quad (31)$$

$$\int_0^T \int_0^L |\partial_t \tilde{v}_\varepsilon|^2 dx_1 dt \leq C. \quad (32)$$

Indeed, (30) and (31) follow directly from (29) and (i), (ii) in Lemma 3.2:

$$\begin{aligned} \int_0^L |\tilde{v}_\varepsilon|^2 dx_1 &= \sum_k \int_{-\varepsilon/2}^{\varepsilon/2} \left| \frac{\bar{v}_{\varepsilon,k} + \bar{v}_{\varepsilon,k+1}}{2} + x_1 \frac{\bar{v}_{\varepsilon,k+1} - \bar{v}_{\varepsilon,k}}{\varepsilon} \right|^2 dx_1 \\ &\leq C \sum_k \varepsilon (|\bar{v}_{\varepsilon,k}|^2 + |\bar{v}_{\varepsilon,k+1}|^2) \leq C \frac{1}{|\varepsilon\Gamma|} \int_{\Gamma_\varepsilon} [u_\varepsilon]^2 ds \leq C. \end{aligned} \quad (33)$$

Estimate (31) is proved in a similar way using (29):

$$\begin{aligned} \int_0^L |\partial_{x_1} \tilde{v}_\varepsilon|^2 dx_1 &\leq C \sum_k \int_{-\varepsilon/2}^{\varepsilon/2} \left| \frac{\bar{v}_{\varepsilon,k} - \bar{v}_{\varepsilon,k+1}}{\varepsilon} \right|^2 dx_1 \\ &\leq C\varepsilon^{-1} \sum_k |\bar{v}_{\varepsilon,k} - \bar{v}_{\varepsilon,k+1}|^2 \\ &\leq C\varepsilon^{-2} \int_{\Omega_\varepsilon^i \cup \Omega_\varepsilon^e} |\nabla u_\varepsilon|^2 dx \leq C. \end{aligned}$$

Let us prove (32). Differentiating $\bar{v}_{\varepsilon,k}$ with respect to t , using the Cauchy-Schwarz inequality yields

$$|\partial_t \bar{v}_{\varepsilon,k}|^2 = \left| \frac{1}{|\varepsilon\Gamma_k|} \int_{\varepsilon\Gamma_k} \partial_t [u_\varepsilon] ds \right|^2 \leq \frac{1}{|\varepsilon\Gamma_k|} \int_{\varepsilon\Gamma_k} (\partial_t [u_\varepsilon])^2 ds.$$

Similarly to (33), estimate (32) follows from the last bound and (ii) in Lemma 3.2. Estimate (i) in the current lemma follows from (29).

The uniform convergence on $(0, T)$ of the constructed piecewise linear approximation is given by the Arzelà-Ascoli theorem, which we now recall. Let (X, d) be a compact metric space and E a normed space. A set $\mathcal{F} \subset C^0(X; E)$ is precompact¹ provided that

1. $\mathcal{F}(x)$ in precompact in E , for each $x \in X$.
2. \mathcal{F} is equicontinuous at each $x \in X$, *i.e.* for all $\gamma > 0$ there exists $\delta = \delta(\gamma, x_0) > 0$, so that, $\forall x \in X$,

$$d(x, x_0) < \delta \quad \Rightarrow \quad \|f(x) - f(x_0)\|_E < \gamma \quad \forall f \in \mathcal{F}.$$

In our case, condition (1) is guaranteed for \tilde{v}_ε due to (30) and (31), while the equicontinuity property follows from (32). Indeed, since

$$\tilde{v}_\varepsilon(t + \Delta t) - \tilde{v}_\varepsilon(t) = \int_t^{t+\Delta t} \partial_\tau \tilde{v}_\varepsilon(\tau) d\tau,$$

we obtain

$$\begin{aligned} \varepsilon^{-1} \int_0^L |\tilde{v}_\varepsilon(t + \Delta t) - \tilde{v}_\varepsilon(t)|^2 dx &\leq \int_0^L \left(\int_t^{t+\Delta t} \partial_\tau \tilde{v}_\varepsilon(\tau) d\tau \right)^2 dx_1 \\ &\leq \Delta t \int_0^L \int_t^{t+\Delta t} |\partial_\tau \tilde{v}_\varepsilon(\tau)|^2 d\tau dx_1 \leq \Delta t. \end{aligned}$$

The proof is completed by applying the Arzelà-Ascoli theorem. □

4. Auxiliary minimization problem. In the present section we construct an auxiliary function θ_δ as a solution of a minimization problem on the periodicity cell Y . This function will be used when passing to the limit in the weak formulation (10). The periodicity cell geometry is as described in Section 2.1. It is convenient to introduce a new small parameter $\delta = \varepsilon^2$.

Let σ_δ be given by

$$\sigma_\delta = \begin{cases} \sigma_i & \text{in } Y_i, \\ \delta^2 & \text{in } Y_m, \\ \sigma_e & \text{in } Y_e. \end{cases}$$

Introduce the subspace $H^1_{\text{per}}(Y \setminus \Gamma)$ of $H^1(Y \setminus \Gamma)$ which consists of 1-periodic in y_1 functions, and consider the minimization problem:

$$\lambda_\delta = \inf_{\theta \in H^1_{\text{per}}(Y \setminus \Gamma)} \frac{\int_Y \sigma_\delta |\nabla \theta|^2 dy}{\int_\Gamma [\theta]^2 ds}, \tag{34}$$

where the infimum is taken over $H^1_{\text{per}}(Y \setminus \Gamma)$, $[\theta]$ denotes the jump of θ across Γ , $[\theta] = \theta_i - \theta_e$, θ_i and θ_e being limit values (traces) of θ on Γ from Y_i and Y_e , correspondingly. It is easy to see that the infimum in (34) is attained by a function θ_δ , up to a multiplicative and an additive constant, satisfying

$$\begin{aligned} \operatorname{div}(\sigma_\delta \nabla \theta_\delta) &= 0 \quad \text{in } Y \setminus \Gamma, \\ \sigma_i \nabla \theta_\delta^i \cdot \nu &= \sigma_e \nabla \theta_\delta^e \cdot \nu = \lambda_\delta [\theta_\delta] \quad \text{on } \Gamma, \\ \sigma_e \nabla \theta_\delta^e \cdot \nu &= 0 \quad \text{when } |y| = R_0. \end{aligned} \tag{35}$$

¹Any sequence has a converging subsequence converging uniformly in X to $f \in C_0(0, T; E)$, not necessarily in \mathcal{F} .

By radial symmetry, we can employ cylindrical coordinates (y_1, r) and write $\theta_\delta = \theta_\delta(y_1, r)$ so that

$$\lambda_\delta = \frac{\int_{Y'} \sigma_\delta |\nabla_{y_1, r} \theta_\delta|^2 r dr dy_1}{\int_{\{r_0\} \times (a, b)} [\theta_\delta]^2 r_0 dy_1}. \tag{36}$$

In what follows, we will also make use of polar coordinates in the cross section Y' , which are centered at the end points A and B of the cut $\Gamma' = [a, b] \times \{r_0\}$ (see the red segment on Figure 2).

Lemma 4.1. *The following statements hold:*

(i) *The infimum in (34) admits the bound*

$$\lambda_\delta \leq \Lambda \delta, \tag{37}$$

with $\Lambda > 0$ independent of δ .

(ii) *Let θ_δ be normalized by*

$$\int_\Gamma [\theta_\delta]^2 ds = |\Gamma|, \quad \int_{Y_e} \theta_\delta dy = 0 \quad \text{and} \quad \int_{Y_i} \theta_\delta dy \geq 0. \tag{38}$$

Then,

$$\theta_\delta \rightharpoonup 1 \quad \text{weakly in } H^1(Y_i), \quad \theta_\delta \rightharpoonup 0 \quad \text{weakly in } H^1(Y_e), \quad \text{as } \delta \rightarrow 0, \tag{39}$$

and the following uniform in $\delta > 0$ bound holds:

$$\|\theta_\delta\|_{L^\infty(Y)} \leq C. \tag{40}$$

Proof. (i) We begin by constructing an approximation of θ_δ away from points $A = (a, r_0)$ and $B = (b, r_0)$ (cf. Figure 2). There exists a function $\Theta \in C_{\text{loc}}^2(Y' \setminus \Gamma')$ such that

$$0 \leq \Theta \leq 1, \quad \text{and} \quad \Theta = 1 \text{ in } Y'_i, \quad \Theta = 0 \text{ in } Y'_e.$$

Also

$$|\nabla \Theta(y')| \leq \frac{C}{\text{dist}(y', \{A\} \cup \{B\})}, \quad \|\nabla^2 \Theta(x')\| \leq \frac{C}{\text{dist}^2(y', \{A\} \cup \{B\})},$$

where $\|\nabla^2 \Theta\|$ denotes the norm of the Hessian of Θ . Since $|\nabla \Theta|$ blows up at points A and B with the rate $1/\text{dist}(y', \{A\})$ and $1/\text{dist}(y', \{B\})$, any such a function Θ does not belong to $H^1(Y \setminus \Gamma)$, hence it is to be corrected near the endpoints A and B of Γ' . For simplicity, we assume that in a neighborhood of A and B the boundary of the domain Y'_m is formed by two rays with angles φ_A and φ_B (cf. Figure 2).

Consider the δ -neighborhood $D_\delta(B)$ of the point B and employ polar coordinates (ρ, φ) centered at B . Assume that δ is sufficiently small so that the set $Y'_m \cap D_\delta(B)$ is a circular sector given by $0 < \varphi < \varphi_B$ and $0 < \rho < \delta$. We set

$$\theta_\delta^B = \frac{1}{1 - V_\delta} \begin{cases} \rho^{\alpha_\delta \delta} \frac{\cos(\alpha_\delta \delta (\varphi + \pi))}{\cos(\alpha_\delta \delta \pi)} - V_\delta, & -\pi < \varphi \leq 0, \\ \rho^{\alpha_\delta \delta} \left(1 - \frac{\alpha_\delta \sigma_i}{\delta} \tan(\alpha_\delta \delta \pi) \varphi \right) - V_\delta, & 0 < \varphi \leq \varphi_B, \\ V_\delta \left(\rho^{\alpha_\delta \delta} \frac{\cos(\alpha_\delta \delta (\varphi - \pi))}{\cos(\alpha_\delta \delta (\varphi_B - \pi))} - 1 \right), & \varphi_B < \varphi < \pi, \end{cases} \tag{41}$$

with

$$V_\delta := 1 - \frac{\alpha_\delta \sigma_i}{\delta} \tan(\alpha_\delta \delta \pi) \varphi_B \tag{42}$$

and α_δ solving the transcendental equation:

$$\alpha_\delta \sigma_i \tan(\alpha_\delta \delta \pi) = \alpha_\delta \sigma_e \tan(\alpha_\delta \delta (\varphi_B - \pi)) \left(1 - \frac{\alpha_\delta \sigma_i}{\delta} \tan(\alpha_\delta \delta \pi) \varphi_B \right). \quad (43)$$

Rewriting this equation as $\alpha_\delta \sigma_i \sigma_e \varphi_B = \delta \sigma_e / \tan(\alpha_\delta \delta \pi) + \delta \sigma_i / \tan(\alpha_\delta \delta (\pi - \varphi_B))$ one readily sees that there is a unique solution α_δ of (43) on $(0, 1/(2\delta))$. Moreover, it is asymptotically given by

$$\alpha_\delta = \frac{1}{\sqrt{\varphi_B}} \sqrt{\frac{1}{\sigma_i \pi} + \frac{1}{\sigma_e (\pi - \varphi_B)}} + O(\delta^2), \quad \delta \rightarrow 0.$$

Note that θ_δ^B is continuous on $\mathbb{R}^2 \setminus \mathbb{R}_-$ and

$$\begin{aligned} \lim_{\varphi \rightarrow \pm\pi} \frac{\partial \theta_\delta^B}{\partial \varphi} &= 0, \\ \lim_{\varphi \rightarrow -0} r \sigma_\delta \frac{\partial \theta_\delta^B}{\partial \varphi} &= \lim_{\varphi \rightarrow +0} r \sigma_\delta \frac{\partial \theta_\delta^B}{\partial \varphi}, \\ \lim_{\varphi \rightarrow \varphi_B - 0} r \sigma_\delta \frac{\partial \theta_\delta^B}{\partial \varphi} &= \lim_{\varphi \rightarrow \varphi_B + 0} r \sigma_\delta \frac{\partial \theta_\delta^B}{\partial \varphi}. \end{aligned}$$

Now, consider the δ -neighborhood of the point A and define the function θ_δ^A by replacing φ with $\pi - \varphi$ and φ_B with φ_A in (41)–(43), redefining α_δ and V_δ accordingly. To glue Θ , θ_δ^A and θ_δ^B together, let us introduce a cut-off function $\chi \in C^\infty(\mathbb{R})$ such that $\chi(\rho) = 0$ for $\rho \geq 1$ and $\chi(\rho) = 1$ for $\rho \leq 1/2$. Set

$$\tilde{\theta}_\delta := (1 - \chi(|y' - A|/\delta) - \chi(|y' - B|/\delta)) \Theta + \chi(|y' - A|/\delta) \theta_\delta^A + \chi(|y' - B|/\delta) \theta_\delta^B,$$

and use $\tilde{\theta}_\delta$ as a test function in (34). Direct computations yield the bound (37). Indeed, by the properties of Θ , it holds

$$\begin{aligned} \int_{Y'} \sigma_\delta |\nabla_{y_1, r} \tilde{\theta}_\delta|^2 r dy_1 dr &= O(\delta^2 \log(1/\delta)) + \int_{D_\delta(A)} \sigma_\delta |\nabla_{y_1, r} \tilde{\theta}_\delta|^2 r dy_1 dr \\ &\quad + \int_{D_\delta(B)} \sigma_\delta |\nabla_{y_1, r} \tilde{\theta}_\delta|^2 r dy_1 dr. \end{aligned}$$

The last two integrals are similar and we consider only the second one, performing calculations in polar coordinates (ρ, φ) :

$$\begin{aligned} \int_{D_\delta(B)} \sigma_\delta |\nabla_{y_1, r} \tilde{\theta}_\delta|^2 r dy_1 dr &= (r_0 + O(\delta)) \int_{-\pi}^\pi d\varphi \int_0^\delta \sigma_\delta \left(|\partial_\rho \tilde{\theta}_\delta|^2 + \frac{1}{\rho^2} |\partial_\varphi \tilde{\theta}_\delta|^2 \right) \rho d\rho \\ &= \frac{\sigma_i \pi (r_0 + O(\delta))}{(1 - V_\delta)^2} \int_0^\delta (\chi'(\rho/\delta) (\rho^{\alpha_\delta \delta} - 1)/\delta + \alpha_\delta \delta \chi(\rho/\delta) \rho^{\alpha_\delta \delta - 1})^2 \rho d\rho \\ &\quad + \frac{\sigma_e V_\delta^2 (\pi - \varphi_B) (r_0 + O(\delta))}{(1 - V_\delta)^2} \int_0^\delta (\chi'(\rho/\delta) (\rho^{\alpha_\delta \delta} - 1)/\delta + \alpha_\delta \delta \chi(\rho/\delta) \rho^{\alpha_\delta \delta - 1})^2 \rho d\rho \\ &\quad + \frac{\delta^2 (r_0 + O(\delta))}{\varphi_B} \int_0^\delta \chi^2(\rho/\delta) \rho^{2\alpha_\delta \delta - 1} d\rho + O(\delta^2) \\ &= r_0 \delta^2 \left(\frac{1}{\varphi_B} + \alpha_\delta^2 \frac{\sigma_i \pi + \sigma_e V_\delta^2 (\pi - \varphi_B)}{(1 - V_\delta)^2} \right) \int_0^{\delta/2} \rho^{2\alpha_\delta \delta - 1} d\rho + O(\delta^2 \log^2(1/\delta)) \\ &= r_0 (\varphi_B / (\sigma_e (\pi - \varphi_B)) + \varphi_B / (\sigma_i \pi))^{-1/2} \delta + O(\delta^2 \log^2(1/\delta)). \end{aligned}$$

Also,

$$\int_{\Gamma'} [\tilde{\theta}_\delta]^2 dy_1 = (b - a) + O(\delta),$$

and thus

$$\lambda_\delta \leq \bar{\Lambda} \delta + O(\delta^2 \log^2(1/\delta)), \tag{44}$$

where $\bar{\Lambda}$ is given by

$$\bar{\Lambda} := \frac{1}{b - a} \left(\left(\frac{\varphi_A}{\sigma_e(\pi - \varphi_A)} + \frac{\varphi_A}{\sigma_i \pi} \right)^{-1/2} + \left(\frac{\varphi_B}{\sigma_e(\pi - \varphi_B)} + \frac{\varphi_B}{\sigma_i \pi} \right)^{-1/2} \right). \tag{45}$$

(ii) Convergences in (39) easily follow from the bound (37) and by the normalization (38) via Poincaré’s inequality. To prove (40), we multiply the equation in (35) by $\theta_\delta |\theta_\delta|^{p-2}$, $p \geq 2$, and integrate over $Y \setminus \Gamma$ to find, after integrating by parts,

$$(p - 1) \int_Y \sigma_\delta |\nabla \theta_\delta|^2 |\theta_\delta|^{p-2} dy = \lambda_\delta \int_\Gamma [\theta_\delta] [\theta_\delta |\theta_\delta|^{p-2}] ds.$$

Therefore, we have

$$(p - 1) \int_Y \sigma_\delta |\nabla \theta_\delta|^2 |\theta_\delta|^{p-2} dy \leq 2\lambda_\delta \int_{\Gamma_i \cup \Gamma_e} |\theta_\delta|^p ds,$$

where Γ_i and Γ_e denote opposite sides of the surface Γ . Thus, for $p \geq 2$, it holds

$$\frac{p - 1}{p^2} \left(\int_Y \sigma_\delta |\nabla |\theta_\delta|^{p/2}|^2 dy + \int_{\Gamma_i \cup \Gamma_e} |\theta_\delta|^p dy \right) \leq C \int_{\Gamma_i \cup \Gamma_e} |\theta_\delta|^p dy,$$

with C independent of δ and $p \geq 2$. This yields H^1 -bounds for $|\theta_\delta|^{p/2}$ in Y_i and Y_e , that in turn lead to bounds for traces of $|\theta_\delta|^{p/2}$ on Γ_i and Γ_e :

$$\| |\theta_\delta|^{p/2} \|_{H^{1/2}(\Gamma_i \cup \Gamma_e)}^2 \leq C_1 p \| \theta_\delta \|_{L^p(\Gamma_i \cup \Gamma_e)}^p.$$

Since $H^{1/2}(\Gamma)$ is continuously embedded in $L^{2q}(\Gamma)$ for some $q > 1$ ($q = 2$ is maximal in the tree-dimensional case [24]), we have

$$\| |\theta_\delta|^{p/2} \|_{L^{2q}(\Gamma_i \cup \Gamma_e)}^2 \leq C_2 p \| \theta_\delta \|_{L^p(\Gamma_i \cup \Gamma_e)}^p$$

or

$$\| \theta_\delta \|_{L^{pq}(\Gamma_i \cup \Gamma_e)} \leq (C_2 p)^{1/p} \| \theta_\delta \|_{L^p(\Gamma_i \cup \Gamma_e)}. \tag{46}$$

It follows from (37) and (38) that

$$\| \theta_\delta \|_{L^2(\Gamma_i \cup \Gamma_e)} \leq C_3.$$

Then, iterative use of (46) yields

$$\| \theta_\delta \|_{L^{2q^{k+1}}(\Gamma_i \cup \Gamma_e)} \leq C_3 \exp \left(\frac{1}{2} \sum_0^k \log(2C_2 q^j) / q^j \right)$$

for every integer $k \geq 0$. The series $\sum_1^\infty \log(C_2 q^j) / q^j$ converges, and hence $\| \theta_\delta \|_{L^\infty(\Gamma_i \cup \Gamma_e)} \leq C$. Finally, by the maximum principle θ_δ satisfies the same L^∞ -bound on $Y \setminus \Gamma$. □

Next, we show that the bound (37) for λ_δ is in fact precise to the leading order.

Lemma 4.2. *The following asymptotic result holds:*

$$\lambda_\delta = \bar{\Lambda} \delta + O \left(\delta^{3/2} \log^2(1/\delta) \right), \tag{47}$$

where $\bar{\Lambda}$ is given by (45).

Proof. In view of (44), it suffices to show that $\lambda_\delta \geq \bar{\Lambda}\delta + O(\delta^{3/2} \log^2(1/\delta))$. We use the test function $\tilde{\theta}_\delta$ constructed in the proof of Lemma 4.1. Since normal derivatives of $\tilde{\theta}_\delta$ vanish on both sides of Γ' and fluxes $r\sigma_\delta \frac{\partial \tilde{\theta}_\delta}{\partial \nu}$ are continuous across $\partial Y'_m$ we have

$$0 = \int_{Y' \setminus \Gamma'} \operatorname{div}(r\sigma_\delta \nabla \theta_\delta) \tilde{\theta}_\delta dr dy_1 \tag{48}$$

$$= \lambda_\delta r_0 \int_{\Gamma'} [\theta_\delta] [\tilde{\theta}_\delta] dy_1 + \int_{Y' \setminus \Gamma'} \operatorname{div}(r\sigma_\delta \nabla \tilde{\theta}_\delta) \theta_\delta dr dy_1. \tag{49}$$

It follows from the construction of $\tilde{\theta}_\delta$, the pointwise bound (40) and the normalization condition (38) that

$$\int_{\Gamma'} [\theta_\delta] [\tilde{\theta}_\delta] dy_1 = \int_{\Gamma'} [\theta_\delta] dy_1 + \int_{\Gamma'} [\theta_\delta] ([\tilde{\theta}_\delta] - 1) dy_1 \tag{50}$$

$$= \int_{\Gamma'} [\theta_\delta] dy_1 + O(\delta) \leq (b - a) + O(\delta). \tag{51}$$

Next, we perform asymptotic calculations for the second term in the right hand side of (48). Split the domain Y' into $Z_\delta := Y' \setminus (D_\delta(A) \cup D_\delta(B))$ and two disks $D_\delta(A), D_\delta(B)$. Since $\tilde{\theta}_\delta = \Theta$ in Z_δ , using properties of Θ and the L^∞ -bound (40) for θ_δ we get

$$\int_{Z_\delta \setminus \Gamma'} \operatorname{div}(r\sigma_\delta \nabla \tilde{\theta}_\delta) \theta_\delta dr dy_1 = O(\delta^2 \log(1/\delta)). \tag{52}$$

In what follows we show that

$$\begin{aligned} & - \int_{D_\delta(A) \setminus \Gamma'} \operatorname{div}(r\sigma_\delta \nabla \tilde{\theta}_\delta) \theta_\delta dr dy_1 - \int_{D_\delta(B) \setminus \Gamma'} \operatorname{div}(r\sigma_\delta \nabla \tilde{\theta}_\delta) \theta_\delta dr dy_1 \\ &= r_0 \delta (\varphi_A / (\sigma_e(\pi - \varphi_A)) + \varphi_A / (\sigma_i \pi))^{-1/2} \\ &+ r_0 \delta (\varphi_B / (\sigma_e(\pi - \varphi_B)) + \varphi_B / (\sigma_i \pi))^{-1/2} + O(\delta^{3/2} \log^2(1/\delta)). \end{aligned}$$

It is sufficient to consider only the integral over $D_\delta(B) \setminus \Gamma'$. We pass to polar coordinates (ρ, φ) with the center at B and split the domain $D_\delta(B) \setminus \Gamma'$ into the six subdomains:

$$S_1^i = \{(\rho, \varphi) : -\pi < \varphi < 0, \delta/2 \leq \rho < \delta\}, \quad S_2^i = \{(\rho, \varphi) : -\pi < \varphi < 0, \rho < \delta/2\},$$

$$S_1^e = \{(\rho, \varphi) : \varphi_B < \varphi < \pi, \delta/2 \leq \rho < \delta\}, \quad S_2^e = \{(\rho, \varphi) : \varphi_B < \varphi < \pi, \rho < \delta/2\},$$

and

$$S_1^m = \{(\rho, \varphi) : 0 < \varphi < \varphi_B, \delta/2 \leq \rho < \delta\}, \quad S_2^m = \{(\rho, \varphi) : 0 < \varphi < \varphi_B, \rho < \delta/2\}.$$

The following pointwise bounds hold in these domains:

$$|\operatorname{div}(r\sigma_\delta \nabla \tilde{\theta}_\delta)| = \begin{cases} O(\delta^{-1} \log(1/\delta)) & \text{in } S_1^i \text{ and } S_1^e, \\ O(\delta \rho^{\alpha_\delta \delta^{-1}}) & \text{in } S_2^i \text{ and } S_2^e, \\ O(1) & \text{in } S_1^m, \\ O(\delta^3 \rho^{\alpha_\delta \delta^{-2}}) & \text{in } S_2^m. \end{cases}$$

Indeed, in each of these domains, the following pointwise inequalities can be verified by direct calculations:

$$|\operatorname{div}(r\sigma_\delta\nabla\tilde{\theta}_\delta)| = \frac{\sigma_\delta}{\rho} \left| \frac{\partial}{\partial\rho} \left(r\rho \frac{\partial\tilde{\theta}_\delta}{\partial\rho} \right) + \frac{\partial}{\partial\varphi} \left(\frac{r}{\rho} \frac{\partial\tilde{\theta}_\delta}{\partial\varphi} \right) \right| \leq \frac{\sigma_\delta r}{\rho^2} \left| \rho \frac{\partial}{\partial\rho} \left(\rho \frac{\partial\tilde{\theta}_\delta}{\partial\rho} \right) + \frac{\partial^2\tilde{\theta}_\delta}{\partial\varphi^2} \right| + \sigma_\delta |\partial_\rho\tilde{\theta}_\delta| + \frac{\sigma_\delta}{\rho} |\partial_\varphi\tilde{\theta}_\delta|$$

where $r = r_0 + \rho \sin \varphi$. Thus,

$$\int_{D_\delta(B)\setminus\Gamma'} \operatorname{div}(r\sigma_\delta\nabla\tilde{\theta}_\delta)\theta_\delta drdy_1 = \int_{S_1^i \cup S_1^e} \operatorname{div}(r\sigma_\delta\nabla\tilde{\theta}_\delta)\theta_\delta drdy_1 + O(\delta^2).$$

Observe that θ_δ on S_1^i and S_1^e is sufficiently close to its mean values over Y_i and Y_e ,

$$\tau_i := \frac{1}{|Y_i|} \int_{Y_i} \theta_\delta dy = 1 + O(\delta^{1/2}) \quad \text{and} \quad \tau_e = \frac{1}{|Y_e|} \int_{Y_e} \theta_\delta dy = 0,$$

correspondingly. Namely, Hardy’s inequality (see, e.g., [24]) combined with the Poincaré inequality yield

$$\int_{Y'_k} |\theta_\delta - \tau_k|^2 / (\rho(1 + |\log \rho|))^2 r drdy_1 \leq C \int_{Y_k} |\nabla\theta_\delta|^2 dy,$$

where k is either i or e , and implying that

$$\int_{S_1^i} |\theta_\delta - \tau_i|^2 drdy_1 \leq C\delta^2 \log^2(1/\delta) \int_{Y_i} |\nabla\theta_\delta|^2 dy \leq C_1\delta^3 \log^2(1/\delta).$$

Hence,

$$\int_{S_1^e} |\theta_\delta|^2 drdy_1 \leq C_2\delta^3 \log^2(1/\delta)$$

and

$$\int_{D_\delta(B)\setminus\Gamma'} \operatorname{div}(r\sigma_\delta\nabla\tilde{\theta}_\delta)\theta_\delta drdy_1 = \tau_i \int_{S_1^i} \operatorname{div}(r\sigma_\delta\nabla\tilde{\theta}_\delta) drdy_1 + O\left(\delta^{3/2} \log^2(1/\delta)\right).$$

It remains to compute the integral on the right-hand side: by integrating by parts, we derive

$$\begin{aligned} \int_{S_1^i} \operatorname{div}(r\sigma_\delta\nabla\tilde{\theta}_\delta) drdy_1 &= -\frac{\alpha_\delta\delta\sigma_i}{1-V_\delta} \int_{-\pi}^0 (\delta/2)^{\alpha_\delta} r \frac{\cos(\alpha_\delta\delta(\varphi+\pi))}{\cos(\alpha_\delta\delta\pi)} d\varphi \\ &\quad + \frac{\alpha_\delta\delta\sigma_i r_0}{1-V_\delta} \int_{\delta/2}^\delta \tan(\alpha_\delta\delta\pi) \chi(\rho/\delta) \frac{\rho^{\alpha_\delta\delta}}{\rho} d\rho \\ &= -\frac{\alpha_\delta\delta\sigma_i}{1-V_\delta} (\delta/2)^{\alpha_\delta} r_0 \pi + O(\delta^2) \\ &= -r_0\delta \left(\frac{\varphi_B}{\sigma_e(\pi-\varphi_B)} + \frac{\varphi_B}{\sigma_i\pi} \right)^{-1/2} + O(\delta^2 \log(1/\delta)). \end{aligned}$$

This completes the proof of the Lemma. □

Next we show that, θ_δ being normalized by (38), one has

$$\frac{1}{\sqrt{\delta}} \sigma_\delta \nabla \theta_\delta \rightharpoonup 0 \quad \text{weakly in } L^2(Y). \tag{53}$$

To this end we use the test function $\tilde{\theta}_\delta$ constructed in the proof of Lemma 4.1 to write

$$\int_Y \sigma_\delta |\nabla \tilde{\theta}_\delta|^2 dy - \int_Y \sigma_\delta |\nabla \theta_\delta|^2 dy \leq C\delta^{3/2} \log^2(1/\delta), \tag{54}$$

where we have used Lemma 4.2 together with the fact that θ_δ minimizes (34), and calculations from the proof of Lemma 4.1. Representing $\tilde{\theta}_\delta$ as $\tilde{\theta}_\delta = (\tilde{\theta}_\delta - \theta_\delta) + \theta_\delta$ and expanding the left-hand side of (54) we get

$$\begin{aligned} \int_Y \sigma_\delta |\nabla \tilde{\theta}_\delta - \nabla \theta_\delta|^2 dy &\leq C\delta^{3/2} \log^2(1/\delta) - 2 \int_Y \sigma_\delta \nabla \theta_\delta \cdot \nabla (\tilde{\theta}_\delta - \theta_\delta) dy \\ &= C\delta^{3/2} \log^2(1/\delta) - 2\lambda_\delta \int_\Gamma [\theta_\delta] [\tilde{\theta}_\delta - \theta_\delta] ds = o(\delta), \end{aligned} \tag{55}$$

by (37) and (39). Straightforward calculations show that $\frac{1}{\sqrt{\delta}}\sigma_\delta \nabla \tilde{\theta}_\delta \rightharpoonup 0$, which in conjunction with (55) yields (53).

Lemma 4.3. *The rescaled function $\theta_{\varepsilon^2}(\frac{x}{\varepsilon})$ has the following properties:*

(i) $\theta_{\varepsilon^2}(\frac{x}{\varepsilon})$ converges to one strongly in $L^2(\Omega_\varepsilon^i)$ and to zero strongly in $L^2(\Omega_\varepsilon^e)$, as $\varepsilon \rightarrow 0$:

$$\begin{aligned} \varepsilon^{-2} \int_{\Omega_\varepsilon^i} \left| \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) - 1 \right|^2 dx &\rightarrow 0, \\ \varepsilon^{-2} \int_{\Omega_\varepsilon^e} \left| \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) \right|^2 dx &\rightarrow 0. \end{aligned}$$

(ii) $\theta_{\varepsilon^2}(\frac{x}{\varepsilon})$ converges strongly in $L^2(\Gamma_\varepsilon)$ to 1, as $\varepsilon \rightarrow 0$:

$$\varepsilon^{-1} \int_{\Gamma_\varepsilon} \left| \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) - 1 \right|^2 ds \rightarrow 0.$$

(iii) $\varepsilon^{-1} \sigma_\varepsilon \nabla_y \theta_{\varepsilon^2}(\frac{x}{\varepsilon})$ converges, as $\varepsilon \rightarrow 0$, weakly two-scale in $L^2(\Omega_\varepsilon^i \cup \Omega_\varepsilon^e)$ to 0.

(iv) $\|\nabla_y \theta_{\varepsilon^2}(\frac{x}{\varepsilon})\|_{L^2(\Omega_\varepsilon^m)} \leq C$.

Proof. (i) Let us prove the convergence in Ω_ε^i . Writing Ω_ε^i as the union of scaled periodicity cells $\bigcup_{k=1}^{N_\varepsilon} (\varepsilon Y_k)$, rescaling and applying (ii) in Lemma 4.1 we have

$$\begin{aligned} \varepsilon^{-2} \int_{\Omega_\varepsilon^i} \left| \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) - 1 \right|^2 dx &= \varepsilon^{-2} \sum_k \int_{\varepsilon Y_{i,k}} \left| \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) - 1 \right|^2 dx \\ &= \varepsilon^{-2} \sum_k \varepsilon^3 \int_{Y_{i,k}} |\theta_\delta - 1|^2 dy = o(1), \quad \varepsilon \rightarrow 0. \end{aligned}$$

The convergence in Ω_ε^e is proved in the same way.

(ii) Similar arguments as above yield

$$\begin{aligned} \varepsilon^{-1} \int_{\Gamma_\varepsilon} \left| \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) - 1 \right|^2 dx &= \varepsilon^{-1} \sum_k \int_{\varepsilon \Gamma_k} \left| \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) - 1 \right|^2 dx \\ &= \varepsilon^{-1} \sum_k \varepsilon^2 \int_{\Gamma_k} |\theta_\delta - 1|^2 dy = o(1), \quad \varepsilon \rightarrow 0. \end{aligned}$$

(iii) The convergence to zero follows directly from (53).

(iv) Combining (34) and (37) one can see that

$$\int_{Y_m} |\nabla\theta_\delta|^2 dy \leq C\delta^{-1}.$$

Writing Ω_ε^m as a union $\cup_k(\varepsilon Y_m)$, rescaling and setting $\delta = \varepsilon^2$ we obtain

$$\begin{aligned} \int_{\Omega_\varepsilon^m} \left| \nabla_y \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) \right|^2 dx &= \sum_k \int_{\varepsilon Y_{m,k}} \left| \nabla_y \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) \right|^2 dx \\ &= \sum_k \varepsilon^3 \int_{Y_{m,k}} |\nabla\theta_\delta(y)|^2 dy \leq C. \end{aligned}$$

ending the proof. □

5. Derivation of the macroscopic model. To conclude, we prove Theorem 2.1. As before, $v_\varepsilon = [u_\varepsilon]$ denotes the jump of u_ε through Γ_ε . Lemmas 3.5 and 3.6 guarantees the convergence of v_ε and g_ε . Indeed, using (i) in Lemma 3.6 and the estimate (iii) in Lemma 3.2 we conclude that $(v_\varepsilon - \tilde{v}_\varepsilon)$ converges strongly in $L^2(\Gamma_\varepsilon)$ to zero. Then, (ii) in Lemma 3.6 yields the strong convergence of $v_\varepsilon(t, x)$ to $v_0(t, x_1)$ in $L^2(\Gamma_\varepsilon)$. Thanks to assumptions (H1)–(H3), we can pass to the limit in the representation (11) for g_ε , as $\varepsilon \rightarrow 0$, and obtain (17), which is equivalent to the equation $\partial_t g_0 = HH(v_0, g_0)$ with initial condition $g_0(0, x_1) = G_0(x_1)$. Thus, in order to prove Theorem 2.1 it remains to derive the macroscopic equations (13).

Using Lemmas 3.5, 3.6 and 4.3, we pass to the limit in the weak formulation (10):

$$\frac{1}{\varepsilon} \int_0^T \int_{\Gamma_\varepsilon} (c_m \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle)) [\phi] ds dt + \frac{1}{\varepsilon^2} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \nabla \phi dx dt = 0, \tag{56}$$

where $\phi \in L^\infty(0, T; H^1(\Omega_\varepsilon \setminus \Gamma_\varepsilon))$ such that $\phi = 0$ for $x_1 \in \{0, L\}$.

For $U_i(t, x_1), U_e(t, x_1) \in C(0, T; H^1(0, L))$ and $U_1(t, x_1, y) \in C(0, T; H^1((0, L) \times Y))$, we construct the following test function:

$$\phi_\varepsilon(t, x) = U_i(t, x_1) \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) + \left(1 - \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) \right) \left(U_e(t, x_1) + \varepsilon U_1 \left(t, x_1, \frac{x}{\varepsilon} \right) \right),$$

where $\theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right)$ is the auxiliary function introduced in Section 4.

Note that due to the strong convergence of the jump of $\theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right)$ (see (ii) Lemma 4.3), the jump of ϕ_ε on Γ_ε converges strongly in $L^2(\Gamma_\varepsilon)$ to $U_i(t, x_1) - U_e(t, x_1)$. Substituting ϕ_ε into (56) we get

$$\varepsilon^{-1} \int_0^T \int_{\Gamma_\varepsilon} (c_m \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle)) [\phi_\varepsilon] ds dt \tag{57}$$

$$+ \varepsilon^{-2} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \left(\theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) \mathbf{e}_1 \partial_{x_1} U_i + \varepsilon^{-1} U_i \nabla_y \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) \right) dx dt \tag{58}$$

$$+ \varepsilon^{-2} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \left(1 - \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) \right) \left(\mathbf{e}_1 \partial_{x_1} U_e + \nabla U_1 \left(x_1, \frac{x}{\varepsilon} \right) \right) dx dt \tag{59}$$

$$\begin{aligned} - \varepsilon^{-2} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \varepsilon^{-1} \nabla_y \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon} \right) \left(U_e + \varepsilon U_1 \left(x_1, \frac{x}{\varepsilon} \right) \right) dx dt \\ = I_{1\varepsilon} + I_{2\varepsilon} + I_{3\varepsilon} + I_{4\varepsilon} = 0, \end{aligned} \tag{60}$$

We now take the limit $\varepsilon \rightarrow 0$ for each integral $I_{k\varepsilon}$, $k = 1, 2, 3, 4$ given by (57)-(60). Since $[\phi_\varepsilon]$ on Γ_ε converges strongly in $L^2(\Gamma_\varepsilon)$ to $U_i(t, x_1) - U_e(t, x_1)$ and $\partial_t v_\varepsilon$ converges two-scale (weakly) in $L^2(0, T; L^2(\Gamma_\varepsilon))$ and uniformly on $(0, T)$ to $v_0(t, x_1)$, we can pass to the limit in (57) and obtain

$$\begin{aligned} I_{1\varepsilon} &= \varepsilon^{-1} \int_0^T \int_{\Gamma_\varepsilon} (c_m \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, \langle g_\varepsilon, v_\varepsilon \rangle)) [\phi_\varepsilon] ds dt \\ &\xrightarrow{\varepsilon \rightarrow 0} |\Gamma| \int_0^T \int_0^L (c_m \partial_t v_0 + I_{ion}(v_0, \langle g_0, v_0 \rangle)) (U_i - U_e) dx_1 dt. \end{aligned}$$

Integrating by parts the second integral in (58) containing $\nabla_y \theta_{\varepsilon^2}(\frac{x}{\varepsilon})$ and using (35) and Lemma 4.2, we have

$$\begin{aligned} I_{2\varepsilon} &= \varepsilon^{-2} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \partial_{x_1} u_\varepsilon \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon}\right) \partial_{x_1} U_i dx dt \\ &\quad - \varepsilon^{-3} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon u_\varepsilon \partial_{y_1} \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon}\right) \partial_{x_1 x_1}^2 U_i dx dt \\ &\quad + \varepsilon^{-3} \int_0^T \int_{\Gamma_\varepsilon} \lambda_{\varepsilon^2} [\theta_{\varepsilon^2} \left(\frac{x}{\varepsilon}\right)] v_\varepsilon U_i ds dt \\ &\xrightarrow{\varepsilon \rightarrow 0} |Y_i| \int_0^T \int_0^L \sigma_i \partial_{x_1} u_0^i \partial_{x_1} U_i dx_1 dt + |\Gamma| \int_0^T \int_0^L \bar{\Lambda} v_0 U_i dx_1 dt. \end{aligned}$$

To take the two-scale limit in (59) we use (iv) in Lemma 3.5 and (i) in Lemma 4.3 and derive

$$\begin{aligned} I_{3\varepsilon} &= \frac{1}{\varepsilon^2} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \left(1 - \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon}\right)\right) \left(\mathbf{e}_1 \partial_{x_1} U_e + \nabla_y U_1 \left(x_1, \frac{x}{\varepsilon}\right) + \varepsilon \partial_{x_1} U_1 \left(x_1, \frac{x}{\varepsilon}\right)\right) dx dt \\ &\xrightarrow{\varepsilon \rightarrow 0} \int_0^T \int_0^L \int_{Y_e} \sigma_e (\mathbf{e}_1 \partial_{x_1} u_0^e + \nabla_y w^e) \cdot (\mathbf{e}_1 \partial_{x_1} U_e(t, x_1) + \nabla_y U_1(t, x_1, y)) dy dx_1 dt. \end{aligned}$$

By integrating by parts (60), using Lemma 4.3 (iii), the interface conditions for $\theta_{\varepsilon^2}(\frac{x}{\varepsilon})$ on Γ_ε , and Lemma 4.2, one can obtain

$$\begin{aligned} I_{4\varepsilon} &= -\varepsilon^{-2} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} \sigma_\varepsilon \nabla u_\varepsilon \cdot \varepsilon^{-1} \nabla_y \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon}\right) \left(U_e + \varepsilon U_1 \left(x_1, \frac{x}{\varepsilon}\right)\right) dx dt \\ &= \varepsilon^{-3} \int_0^T \int_{\Omega_\varepsilon \setminus \Gamma_\varepsilon} u_\varepsilon \sigma_\varepsilon \nabla_y \theta_{\varepsilon^2} \left(\frac{x}{\varepsilon}\right) \cdot \nabla \left(U_e + \varepsilon U_1 \left(x_1, \frac{x}{\varepsilon}\right)\right) dx dt \\ &\quad - \varepsilon^{-3} \int_0^T \int_{\Gamma_\varepsilon} \lambda_{\varepsilon^2} [\theta_{\varepsilon^2} \left(\frac{x}{\varepsilon}\right)] v_\varepsilon \left(U_e + \varepsilon U_1 \left(x_1, \frac{x}{\varepsilon}\right)\right) ds dt \\ &\xrightarrow{\varepsilon \rightarrow 0} -|\Gamma| \int_0^T \int_0^L \bar{\Lambda} v_0 U_e dx_1 dt. \end{aligned}$$

In this way we obtain a weak formulation of the effective problem:

$$\begin{aligned} & |\Gamma| \int_0^T \int_0^L (c_m \partial_t v_0 + I_{ion}(v_0, \langle g_0, v_0 \rangle)) (U_i - U_e) dx_1 dt \\ & + |\Gamma| \int_0^T \int_0^L \bar{\Lambda} v_0 (U_i - U_e) dx_1 dt \\ & + |Y_i| \int_0^T \int_0^L \sigma_i \partial_{x_1} u_0^i \partial_{x_1} U_i dx_1 dt \\ & + \int_0^T \int_0^L \int_{Y_e} \sigma_e (\mathbf{e}_1 \partial_{x_1} u_0^e + \nabla_y w^e) \cdot (\mathbf{e}_1 \partial_{x_1} U_e(t, x_1) + \nabla_y U_1(t, x_1, y)) dy dx_1 dt = 0. \end{aligned}$$

Computing consequently the variation of the left-hand side of the last equality with respect to U_1, U_i and U_e gives the representation $U_1(t, x_1, y) = N(y) \partial_{x_1} U_e(t, x_1)$, the cell problem (15) and the two one-dimensional equations

$$|\Gamma| (c_m \partial_t v_0 + I_{ion}(v_0, \langle g_0, v_0 \rangle) + \bar{\Lambda} v_0) = |Y_i| \sigma_i \partial_{x_1 x_1}^2 u_0^i, \quad (61)$$

$$|\Gamma| (c_m \partial_t v_0 + I_{ion}(v_0, \langle g_0, v_0 \rangle) + \bar{\Lambda} v_0) = - \int_{Y_e} \sigma_e |\mathbf{e}_1 + \nabla_y N|^2 \partial_{x_1 x_1}^2 u_0^e dy. \quad (62)$$

Introducing (14) and adding up (62) and (61) yield (18). The proof of Theorem 2.1 is complete.

REFERENCES

- [1] G. Allaire, *Commissariat 'a L'energie Atomique, Alain Damlamian, and Ulrich Hornung*, Two-scale convergence on periodic surfaces and applications, *Mathematical Modelling of Flow through Porous Media*, 1995.
- [2] M. Amar, D. Andreucci, P. Bisegna and R. Gianni, [On a hierarchy of models for electrical conduction in biological tissues](#), *Mathematical Methods in the Applied Sciences*, **29** (2006), 767–787.
- [3] M. Amar, D. Andreucci, P. Bisegna and R. Gianni, et al., A hierarchy of models for the electrical conduction in biological tissues via two-scale convergence: the nonlinear case, *Differential and Integral Equations*, **26** (2013), 885–912.
- [4] M. Amar, D. Andreucci and R. Gianni, [Asymptotic decay under nonlinear and noncoercive dissipative effects for electrical conduction in biological tissues](#), *Nonlinear Differ. Equ. Appl.*, **23** (2016), Art. 48, 24 pp.
- [5] H. Ammari, L. Giovangigli, H. Kwon, J. K. Seo and T. Wintz, [Spectroscopic conductivity imaging of a cell culture](#), *Asymptotic Analysis*, **100** (2016), 87–109.
- [6] H. Ammari, T. Widlak and W. Zhang, [Towards monitoring critical microscopic parameters for electroporation](#), *Quart. Appl. Math.*, **75** (2017), 1–17.
- [7] T. Arbogast, J. Douglas, Jr, and U. Hornung, [Derivation of the double porosity model of single phase flow via homogenization theory](#), *SIAM Journal on Mathematical Analysis*, **21** (1990), 823–836.
- [8] P. J. Basser, [Cable equation for a myelinated axon derived from its microstructure](#), *Medical & Biological Engineering & Computing*, **31** (1993), S87–S92.
- [9] P. J. Basser and B. J. Roth, [New currents in electrical stimulation of excitable tissues](#), *Annu. Rev. Biomed. Eng.*, **2** (2000), 377–397.
- [10] C. Bollini and F. Cacheiro, [Peripheral nerve stimulation](#), *Tech. Reg. Anesth. Pain Manag.*, **10** (2006), 79–88.
- [11] S. O. Choi, Y. C. Kim, J. W. Lee, J. H. Park, M. R. Prausnitz and M. G. Allen, [Intracellular protein delivery and gene transfection by electroporation using a microneedle electrode array](#), *Small*, **10** (2012), 1081–1091.
- [12] P. Colli-Franzone, L. F. Pavarino and S. Scacchi, Mathematical and numerical methods for reaction-diffusion models in electrocardiology, In Davide Ambrosi, Alfio Quarteroni, and Gianluigi Rozza, editors, *Modeling of Physiological Flows*, Springer Milan, Milano, 2012, 107–141.

- [13] S. Doi, J. Inoue, Z. Pan and K. Tsumoto, *Computational Electrophysiology*, volume 2. Tokyo, Japan: Springer Series, A First Course in On Silico Medicine, 2010.
- [14] F. Henríquez and C. Jerez-Hanckes, [Multiple traces formulation and semi-implicit scheme for modelling biological cells under electrical stimulation](#), *ESAIM: M2AN*, **52** (2018), 659–703.
- [15] F. Henríquez, C. Jerez-Hanckes and F. Altermatt, [Boundary integral formulation and semi-implicit scheme coupling for modeling cells under electrical stimulation](#), *Numer. Math.*, **136** (2016), 101–145.
- [16] A. L. Hodgkin and A. F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve, *The Journal of Physiology*, **117** (1952), 500.
- [17] J. Keener and J. Sneyd, *Mathematical Physiology I: Cellular Physiology*, Springer-Verlag, New York, 1998.
- [18] E. Y. Khruslov, Homogenized models of strongly inhomogeneous media, In *Proceedings of the International Congress of Mathematicians*, Springer, 1995, 1270–1278.
- [19] A. N. Kolmogorov, I. G. Petrovsky and N. S. Piskunov, Investigation of the equation of diffusion combined with increasing of the substance and its application to a biology problem, *Bull. Moscow State Univ. Ser. A: Math. Mech*, **1** (1937), 1–25.
- [20] D. C. Li and Q. Li, [Electrical stimulation of cortical neurons promotes oligodendrocyte development and remyelination in the injured spinal](#), *Neural Regeneration Research*, **12** (2017), 1613–1615.
- [21] A. Lunardi, *Analytic Semigroups and Optimal Regularity in Parabolic Problems*, Birkhäuser/Springer Basel AG, Basel, 1995.
- [22] V. A. Marchenko and E. Y. Khruslov, Boundary-value problems with fine-grained boundary, *Matematicheskii Sbornik*, **65** (1964), 458–472.
- [23] H. Matano and Y. Mori, [Global existence and uniqueness of a three-dimensional model of cellular electrophysiology](#), *Discrete Contin. Dyn. Syst*, **29** (2011), 1573–1636.
- [24] V. G. Maz’ya, *Sobolev Spaces*, Springer-Verlag, 1985.
- [25] C. C. McIntyre, A. G. Richardson and W. M. Grill, [Modeling the excitability of mammalian nerve fibers: Influence of afterpotentials on the recovery cycle](#), *Journal of Neurophysiology*, **87** (2002), 995–1006.
- [26] H. Meffin, B. Tahayori, E. N. Sergeev, I. M. Y. Mareels, D. B. Grayden and A. N. Burkitt, [Modelling extracellular electrical stimulation: III. derivation and interpretation of neural tissue equations](#), *Journal of Neural Engineering*, **11** (2014), 065004.
- [27] C. Meunier and B. Lamotte d’Incamps, [Extending cable theory to heterogeneous dendrites](#), *Neural Computation*, **20** (2008), 1732–1775.
- [28] L. M. Mir, M. F. Bureau, J. Gehl, R. Rangara, D. Rouy, J. M. Caillaud, P. Delaere, D. Branellec, B. Schwartz and D. Scherman, [High-efficiency gene transfer into skeletal muscle mediated by electric pulses](#), *Proc. Nat. Acad. Sci. USA.*, **96** (1999), 4262–4267.
- [29] J. C. Neu and W. Krassowska, Homogenization of syncytial tissues, *Critical Reviews in Biomedical Engineering*, **21** (1993), 137–199.
- [30] M. Neuss-Radu, Some extensions of two-scale convergence, *Comptes Rendus de l’Académie des Sciences. Série 1, Mathématique*, **322** (1996), 899–904.
- [31] P. D. O’Brien, L. M. Hinder, B. C. Callaghan and E. L. Feldman, [Neurological consequences of obesity](#), *The Lancet Neurology*, **16** (2017), 465–477.
- [32] A. Pazy, *Semigroups of Linear Operators and Applications to Partial Differential Equations*, Applied Mathematical Sciences, 44. Springer-Verlag, New York, 1983.
- [33] M. Pennacchio, G. Savaré and P. C. Franzone, [Multiscale modeling for the bioelectric activity of the heart](#), *SIAM Journal on Mathematical Analysis*, **37** (2005), 1333–1370.
- [34] I. Pettersson, [Two-scale convergence in thin domains with locally periodic rapidly oscillating boundary](#), *Differential Equations & Applications*, **9** (2017), 393–412.
- [35] C. Pham-Dang, O. Kick, T. Collet, F. Gouin and M. Pinaud, Continuous peripheral nerve blocks with stimulating catheters, *Reg. Anesth. Pain Med.*, **28** (2003), 83–88.
- [36] R. Plonsey and R. C. Barr, *Bioelectricity: A Quantitative Approach*, Springer, Boston, MA, 2007.
- [37] W. Rall, [Time constants and electrotonic length of membrane cylinders and neurons](#), *Biophysical Journal*, **9** (1969), 1483–1508.
- [38] F. Rattay, *Electrical Nerve Stimulation. Theory, Experiments and Applications*, Vienna, Austria: Springer-Verlag, 1990.
- [39] J. E. Riggs, [The aging population](#), *Neurologic Clinics*, **16** (1998), 555–560.

- [40] J. Teissié, N. Eynard, B. Gabriel and M. P. Rols, Electropermeabilization of cell membranes, *Adv. Drug. Del. Rev.*, **35** (1999), 3–19.
- [41] V. Zhikov, [On an extension and an application of the two-scale convergence method](#), *Mat. Sb.*, **191** (2000), 31–72; translation in *Sb. Math.*, **191** (2000), 973–1014.

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