Discrete and Continuous Dynamical Systems - Series B

doi:10.3934/dcdsb.2023072

HOMOGENIZATION THEORY OF ION TRANSPORTATION IN MULTICELLULAR TISSUE

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(Communicated by Pingbing Ming)

Abstract. The transport of ions in biological tissues plays a crucial role in studying many biological and pathological problems. Certain multi-cellular structures, such as smooth muscles on vessel walls, can be considered as periodic bi-domain structures consisting of intracellular and extracellular spaces separated by semipermeable membranes. To model these structures, macroscale models are proposed based on an electro-neutral (EN) microscale model with nonlinear interface conditions, using an unfolding operator. The membranes are treated as combinations of capacitors and resistors, while also taking into account the connectivity of the intracellular space. If the intracellular space is fully connected and forms a syncytium, the macroscale model is a bidomain nonlinear coupled partial differential equations system. Otherwise, if the intracellular cells are not connected, the macroscale model for the intracellular space is an ordinary differential system with source/sink terms from the connected extracellular space. The first-order error estimates for these models are achieved with proper regularity assumptions.

2020 *Mathematics Subject Classification.* Primary: 35Q92, 92C37; Secondary: 92C05.
Key words and phrases. Ion transport, Unfolding operator, Bi-domain model, Connectivity.
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1. **Introduction.** Ions in human body play vital roles in many aspects such as helping the transport of nerve impulses, maintaining the proper functions of muscles, activating various enzymes, helping blood coagulation and so on. Studying ion transport in biological tissues can help us understand the mechanisms of many physiological phenomenon and gain some insight about how to treat certain diseases. The Poisson-Nernst-Planck (PNP) system is one of the most popular mathematical models that describe the ion transport under the influence of both ionic concentration gradient and electric field. PNP system has extensive and successful applications in biological systems, particularly in ion channels on cell membrane [8, 10, 16, 25, 29, 37]. Due to the capacitance of membranes, there are thin boundary layers (BLs) near the interfaces formed by excessive charges accumulation. BLs requires extra computation cost during numerical simulations in order to resolve the fast change behaviors of solution inside the layers and attain certain accuracy[6, 44]. A lot of efforts are put in order to get rid of this constrain, like Mori[35]. By using asymptotic analysis, Song et al. proposed effective interface conditions by introducing a time dependent capacitance on the membrane[43, 42]. In this paper, we take the linearization of the effective boundary conditions and propose a microscale electro-neutral (EN) PNP system with interface conditions describing the membrane fluxes and capacitor effect.

Due to the existence of pumps on membranes, ion concentrations across the membrane are discontinuous, for example potassium is $140 \sim 150$ mM in the intracelluar space and $3 \sim 5$ mM in the extracellular space. However, the flux across the membrane is continuous and determined by conductance and the difference between membrane potential and Nernst Potential. When studying biological tissues, there are thousands of cells in the system and the solution is highly oscillatory. The obtained mircoscale model requires significant computational resources to solve numerically. In order to simulate ion transport in biological tissues more efficiently, an effective macroscale model is demanded. One of the most popular ways to derive the macroscale models is through homogenization by deriving an "average" or "effective" homogenized system, which extracts macro information from micro structures. Specific methods of homogenization include oscillating test function method[45], asymptotic expansion method[5], two-scale method [36, 1] and unfolding method [15, 11]. Unfolding method is easy to use and can be extended to other periodic problems with small parameters. For example, it can be applied to Neumann sieve models[13]. The homogenization theory for system with jump solution is first developed by Monsurro and Donato to a linear elliptic model for heat conductors problem by using extension operators[33, 34, 21, 17]. Results for linear parabolic and hyperbolic equations can be found in [30, 19, 48, 47, 18, 20]. Another factor for bi-domain homogenization is whether two sub-domains are all connected domain, respectively. The linear problems mentioned above only considered the case when one sub-domain is embedded in the other sub-domain and disconnected. In [7], a linear diffusion problem in a bi-domain with flux jump at the interface is discussed. The authors considered both when one sub-domain is connected and disconnected, and explained the reasons for the difference in the resulting homogenization systems for the two cases, which is mainly due to the different spaces of the test functions. For nonlinear bi-domain homogenization problems, the main difficulty is the strong convergence requirement both in domain and on the interface. By two-scale convergence and unfolding operator, Gahn et al.[26, 23]. proposed homogenization results for a nonlinear problem in a bi-domain for calcium dynamics (connected sub-domains) and diffusion-reaction system (one disconnected sub-domain).

For the homogenization theory of PNP system, which is a nonlinear coupled system, asymptotic expansion method [32] is first used to derive the homogenized system for the linearized Navier-Stokes-PNP model in porous media in [38]. Later, a rigorous derivation by using two-scale method is proposed by Alliare et al.[3]. Similar method is extended to study ion transport through deformable porous media[2]. Homogenization of a full nonlinear PNP model in porous media is discussed in [46, 41] by using unfolding method and two-scale method, where nonflux boundary condition is used on the interface for ion concentraion. Most of the homogenization research for PNP model and ion transport model are established in porous media without considering the electric-diffusion of ions in the intracellular region, and sometimes linearization technique is used to simplify the process. In this paper, by using unfolding operator and two-scale convergence, we develop the homogenization theory for the fully nonlinear EN bi-domain model in the whole domain with nonlinear interface flux boundary conditions which depends on the jumps of ion concentrations, electric potential, and the time derivative of potential jump. Two different scenarios, connected and disconnected intracellular regions, are both taken into consideration and lead to different macroscopic models.

The remainder of this paper is organized as follows: The microscale EN ion transport model is given in Section 2; Section 3 is devoted to proving the a priori estimates; Then convergence results and homogenization process are presented in Section 4 according to different connectivity conditions of intracellular region; Error estimates are given in Section 5; We draw conclusions in the last Section.

2. **Setting of the mathematical model.** In this section, the micro-scale bi-domain ion transport model in multi-cellular tissues is introduced. Consider a domain $\Omega = (0,1)^d$ which consists of two components: Ω_I^ε and Ω_E^ε (see Figure 1). Let $Y = (0,1)^d$ and Y_I, Y_E are two disjoint subsets of Y, such that

$$\overline{Y} = \overline{Y_E} \cup \overline{Y_I}.$$

And $\Gamma = \partial Y_I \bigcap \partial Y_E$ is smooth. Let $\vec{n}_1$ be the normal direction of Γ, pointing from Y_I to Y_E. Let $\beta_s, s = I, E$ be the characteristic function on $Y_s, s = I, E$, which extend periodically to $\mathbb{R}^d$. For any $k \in \mathbb{Z}^d$, let

$$Y^k = k + Y, \ \Gamma^k = k + \Gamma, \ Y_s^k = k + Y_s,$$

where $k = (k_1, \cdots, k_d)$, $s = I, E$. For any $\varepsilon > 0$ and $1/\varepsilon \in \mathbb{N}^+$, let $K_\varepsilon = \left\{k \in \mathbb{Z}^d | \varepsilon Y_s^k \cap \Omega \neq \emptyset, s = I, E\right\}$. Denote the two disjoint subsets of Ω and the interface between them as:

$$\Omega_I^\varepsilon = \bigcup_{k \in K_\varepsilon} \varepsilon Y_I^k, \quad \Omega_E^\varepsilon = \Omega \backslash \overline{\Omega_I^\varepsilon}, \quad \Gamma_\varepsilon = \bigcup_{k \in K_\varepsilon} \varepsilon \Gamma^k.$$

So $\Omega = \Omega_I^\varepsilon \bigcup \Omega_E^\varepsilon \bigcup \Gamma_\varepsilon$ and Ω is a union of εY-periodic sets. Assume both Ω_E^ε and Ω_I^ε have Lipschitz boundaries, especially Γ_ε is a Lipschitz boundary. When Ω_I^ε is connected, we call this case "connected-connected" case. In this case both Y_I and Y_E reach ∂Y, thus both Ω_I^ε and Ω_E^ε reach $\partial\Omega$. When Ω_I^ε is not connected, we call this case "connected-disconnected" case (see Figure 1). In this case, $\overline{Y_I} \subset Y$ and Ω_I^ε is a disconnected union of εY-periodic sets of size εY_I.

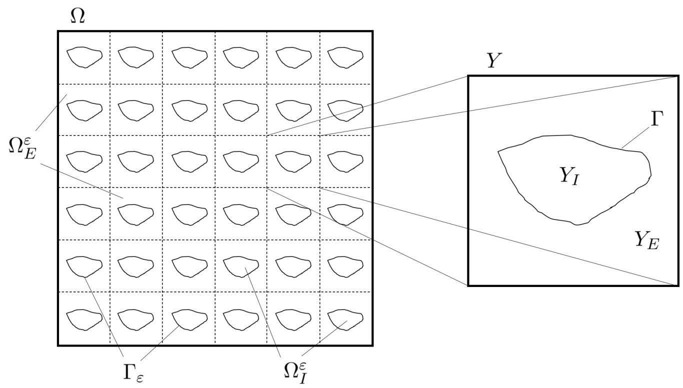

FIGURE 1. Schematic of the "connected-disconnected" domain Ω.

Remark 2.1. For the reference cell $Y = (0,1)^d$, due to topological restriction, for "connected-disconnected" case, the dimension is $d \geq 2$, and for "connected-connected" case, the dimension is $d = 3$.

Let $C_{i,s}^\varepsilon > 0, i = 1,2,3$ denote the concentrations of ions $\mathrm{Na}^+, \mathrm{K}^+, \mathrm{Cl}^-$ and ϕ_s^ϵ be the electric potential in $\Omega_s, s = I, E$, respectively. $z_1 = 1, z_2 = 1, z_3 = -1$ are the corresponding valences of ions.

The linearized EN model proposed in [42, 43] based on an asymptotic analysis of the PNP system in the cellular scale is adopted as the micro-scale model.

$$\sum_{i=1}^{3} z_i C_{i,s}^\varepsilon(t,x) = 0 \ in \ (0,T) \times \Omega_s^\varepsilon, \tag{1a}$$

$$\partial_t C_{i,s}^\varepsilon = -\nabla \cdot J_{i,s} = \nabla \cdot [D(\nabla C_{i,s}^\varepsilon + z_i C_{i,s}^\varepsilon \nabla \phi_s^\varepsilon)] \ in \ (0,T) \times \Omega_s^\varepsilon, \tag{1b}$$

$$z_i J_{i,s} \cdot \vec{n} = \varepsilon G_i \big([\![\phi^\varepsilon]\!] + \frac{1}{z_i} [\![\ln C_i^\varepsilon]\!] \big) + \varepsilon P_i^\varepsilon + \varepsilon \lambda_i P_m \partial_t [\![\phi^\varepsilon]\!] \ on \ (0,T) \times \Gamma_\varepsilon, \tag{1c}$$

$$J_{i,E} \cdot \vec{\nu} = 0 \ on \ (0,T) \times \partial\Omega, \tag{1d}$$

$$C_{i,s}^\varepsilon|_{t=0} = C_{i,s}^0 \ in \ \Omega_s^\varepsilon, \tag{1e}$$

where $\vec{n}$ is the normal direction of Γ_ε, pointing from Ω_I^ε to Ω_E^ε and $\vec{\nu}$ is the outer normal direction of Ω and $[\![f]\!] = f_I - f_E$ is the jump across the interface. Here the first equation is the local electroneutrality, i.e., at each point, the total number of cations is always equal to the number of anions, and the second equation is the law of conservation for each ion, $i = 1,2,3, s = I, E$.

By multiplying z_i with the second equation and using EN condition (1a), system (1) could be written as follows

$$\partial_t C_{i,s}^\varepsilon = -\nabla \cdot J_{i,s} = \nabla \cdot [D(\nabla C_{i,s}^\varepsilon + z_i C_{i,s}^\varepsilon \nabla \phi_s^\varepsilon)] \ in \ (0,T) \times \Omega_s^\varepsilon, \tag{2a}$$

$$-\nabla \cdot (D\sigma_s^\varepsilon \nabla \phi_s^\varepsilon) = 0 \ in \ (0,T) \times \Omega_s^\varepsilon, \tag{2b}$$

$$z_i J_{i,s} \cdot \vec{n} = \varepsilon G_i \big([\![\phi^\varepsilon]\!] + \frac{1}{z_i} [\![\ln C_i^\varepsilon]\!] \big) + \varepsilon P_i^\varepsilon + \varepsilon \lambda_i P_m \partial_t [\![\phi^\varepsilon]\!] \ on \ (0,T) \times \Gamma_\varepsilon, \tag{2c}$$

$$-D\sigma_s^\varepsilon \nabla \phi_s^\varepsilon \cdot \vec{n} = \sum_{i=1}^{3} \varepsilon G_i [\![\phi^\varepsilon]\!] + \sum_{i=1}^{3} \varepsilon G_i \frac{1}{z_i} [\![\ln C_i^\varepsilon]\!] + \varepsilon I_P^\varepsilon + \varepsilon P_m \partial_t [\![\phi^\varepsilon]\!] \ on \ (0,T) \times \Gamma_\varepsilon, \tag{2d}$$

$$J_{i,l} \cdot \vec{\nu} = 0 \ on \ (0,T) \times \partial\Omega, \tag{2e}$$

$$-D\sigma_l^\varepsilon \nabla \phi_l^\varepsilon \cdot \vec{\nu} = 0 \ on \ (0,T) \times \partial\Omega, \tag{2f}$$

$$C_{i,s}^\varepsilon|_{t=0} = C_{i,s}^0 \ in \ \Omega_s^\varepsilon, \tag{2g}$$

$$[\![\phi^\varepsilon]\!]|_{t=0} = \phi^0 \ on \ \Gamma_\varepsilon, \tag{2h}$$

where σ_s^ε is the effective conductance

$$\sigma_s^\varepsilon = \sum_{i=1}^{3} z_i^2 C_{i,s}^\varepsilon, \ \ s = I, E. \tag{3}$$

l in (2e), (2f) is I or E for "connected-connected" case, and $l = E$ for "connected-disconnected" case.

Note that if the potentials ϕ_I and ϕ_E are the solutions, then for any constant C, $\phi_I + C$ and $\phi_E + C$ are still the solutions. To ensure the uniqueness, average free condition is applied here

$$\int_{\Omega_E^\varepsilon} \phi_E^\varepsilon \, dx = 0. \tag{4}$$

In the EN model (2), the thin boundary (Debye) layers near the interface in traditional PNP model are modelled by effective boundary conditions (2c). It is much easier to be dealt with numerically compared with the original PNP system. However, we need to cope with the nonlinear effective boundary conditions when deriving macroscopic models.

There are three parts in the trans-membrane flux (2c):

- The current induced by passive ion channel which is modeled by Ohm's Law. Here G_i is the conductance of the i_{th} ion on the membrane, $[\![\phi^\varepsilon]\!] = \phi_I - \phi_E$ is the membrane potential and $E_i \triangleq -\frac{1}{z_i}[\![\ln C_i^\varepsilon]\!] = \frac{1}{z_i}(\ln C_{i,E}^\varepsilon - \ln C_{i,I}^\varepsilon)$ is the Nernst potential.
- The current induced by the active pumps on the membrane. Here we only consider the Na^+/K^+ pumps[50].

$$P_1^\varepsilon = 3I_p^\varepsilon, \ P_2^\varepsilon = -2I_p^\varepsilon, \ P_3^\varepsilon = 0,$$

with

$$\begin{aligned} I_p^\varepsilon &= I_{\max 1} \left(\frac{C_{1,I}^\varepsilon}{C_{1,I}^\varepsilon + K_{Na1}} \right)^3 \left(\frac{C_{2,E}^\varepsilon}{C_{2,E}^\varepsilon + K_{K1}} \right)^2 \\ &+ I_{\max 2} \left(\frac{C_{1,I}^\varepsilon}{C_{1,I}^\varepsilon + K_{Na2}} \right)^3 \left(\frac{C_{2,E}^\varepsilon}{C_{2,E}^\varepsilon + K_{K2}} \right)^2 , \end{aligned} \tag{5}$$

where I_{max1}, I_{max2} are maximum Na^+/K^+ pump current density and K_{K1}, K_{K2}, K_{Na1}, K_{Na2} are positive threshold constants for I_p^ε. It is a common formula proposed in [24] by fitting the experimental data.

- The current induced by the capacitor effect of membrane with capacitance P_m . λ_i reflects the effect of capacitor on the i_{th} ion species and $\sum_{i=1}^{3} \lambda_i = 1$. Here we take λ_i as constant[35] which is simplification and linearization version of models in [43, 42].

In order to derive the homogenization theory of EN model (2), the following assumption (H0) are needed:

$$
(H0)\quad \begin{cases}
\bullet\ \text{Connectivity: } \Omega_E^\varepsilon \text{ is always connected and } \Omega_I^\varepsilon \text{ can be connected or not.} \\
\bullet\ \text{Boundness on the interface :} \\
0 < C_d \le C_{i,s}^\varepsilon \le C_u \text{ on } \Gamma_\varepsilon,\ i = 1,2,3, s = I, E, \qquad (6) \\
\text{where } C_d, C_u \text{ are positive constants.} \\
\bullet\ \text{Nonvanishing in the bulk:} \\
0 < C_l < \sum_{i=1}^{3} z_i^2 C_{i,s}^\varepsilon(t,x) \text{ in } \Omega_s^\varepsilon,\ s = I, E, \qquad (7) \\
\text{where } C_l \text{ is a positive constant.} \\
\bullet\ \text{Diffusion Constant: diffusion constants of ions are the same and denoted by } D.
\end{cases}
$$

Remark 2.2. The lower bound assumption of ion concentrations in assumption (6) is a technical one for the model wellposedness and estimates (10). In fact, according to the interface condition (2c), if the negative charge concentration on the interface, $C_{3,I}^\varepsilon$ and approaches to zero, then $\ln C_{3,I}^\varepsilon$ approaches to negative infinity, which will induce a membrane flux of the ith ion from ECS to ICS and increases its value. This is understandable as the physical law governing the transmembrane flux determines that the non physical situation as negative concentration will not occur. Same argument works for $C_{3,E}^\varepsilon$. Then by EN condition, the positive charges $C_{1,s}^\varepsilon + C_{2,s}^\varepsilon$ will not decrease to zero or become negative. The pump (5) ensure that $C_{1,E}^\varepsilon$ and $C_{2,I}^\varepsilon$ are not zero; while the logarithmic terms prevent $C_{1,I}^\varepsilon$ and $C_{2,E}^\varepsilon$ from vanishing. At the same time, the mass conservation (2a) and (2e) on the whole domain, ensure that the concentration on the interface will not go to infinity on both side if the initial values are finite.

The homogenization results (Theorem 4.2 and Theorem 4.4) show that the interfacial fluxes become source terms in the homogenized equations, and the connectivity of intracellular region will affect the homogenization results. When the intracellular region is connected, the homogenized one is a diffusion-reaction equation; when cells are isolated with each other, the homogenized equation is a reaction equation. This is consistent with relevant results in [7]. And the EN condition still holds for the homogenized equations both when intracellular region is connected and not connected.

3. **Well posedness and a priori estimate.** In order to derive the convergence results, we need a priori estimates for the solutions of (2),. In the rest of the paper, A (with or without subscript) represent a generic positive constant independent of ε (in different equations, the value of A may be different).

The weak form of (2) is: for $i = 1, 2, 3, s = I, E$, find $C^\varepsilon_{i,s} \in L^2(0, T;\ H^1(\Omega^\varepsilon_s))$, $\phi^\varepsilon_s \in L^2(0, T;\ H^1(\Omega^\varepsilon_s))$, such that

$$\int_{\Omega^\varepsilon_s} \partial_t C^\varepsilon_{i,s} v_s\ dx + \int_{\Omega^\varepsilon_s} D\nabla C^\varepsilon_{i,s} \nabla v_s\ dx + z_i \int_{\Omega^\varepsilon_s} C^\varepsilon_{i,s} D\nabla\phi^\varepsilon_s \nabla v_s\ dx$$
$$\pm\, \varepsilon \int_{\Gamma_\varepsilon} \big(\frac{G_i}{z_i}[\![\phi^\varepsilon]\!] v_s + \frac{G_i}{z_i^2}[\![\ln C^\varepsilon_i]\!] v_s + \frac{P^\varepsilon_i}{z_i} v_s + \frac{\lambda_i}{z_i} P_m \partial_t [\![\phi^\varepsilon]\!] v_s\big)\ dS = 0, \tag{8a}$$
$$\int_{\Omega^\varepsilon_s} \sigma^\varepsilon_s D\nabla\phi^\varepsilon_s \nabla\varphi_s\ dx$$
$$\pm\, \varepsilon \int_{\Gamma_\varepsilon} \big(\sum_{k=1}^3 G_k [\![\phi^\varepsilon]\!]\varphi_s + \sum_{k=1}^3 \frac{G_k}{z_k}[\![\ln C^\varepsilon_k]\!]\varphi_s + I^\varepsilon_p \varphi_s + P_m \partial_t [\![\phi^\varepsilon]\!]\varphi_s\big)\ dS = 0, \tag{8b}$$

for $\forall\ v_s \in L^2(0, T;\ H^1(\Omega^\varepsilon_s))$ and $\varphi_s \in L^2(0, T;\ H^1(\Omega^\varepsilon_s))$, where "$\pm$" takes "$+$" for $s = I$ and "$-$" for $s = E$.

Theorem 3.1. *If the assumption* $(H0)$ *holds, then the weak solutions of* (8) *exist. Moreover, if the assumption*

$$\nabla\phi^\varepsilon_s \in L^\infty((0, T) \times \Omega^\varepsilon_s),\ \ s = I, E, \tag{9}$$

holds, then the weak solutions are unique.

This theorem can be proved similarly as Theorem 6 in [23] by introducing a fixed point operator $\mathcal{F} : X \to X$, where $X = L^2(0, T;\ H^\alpha(\Omega^\varepsilon_I))^3 \times L^2(0, T;\ H^\alpha(\Omega^\varepsilon_E))^3$ with $\alpha \in (1/2, 1)$, see Appendix B for details.

Next we derive a priori estimates for $C^\varepsilon_{i,s}, \phi^\varepsilon_s,\ i = 1, 2, 3, s = I, E$.

In the rest of the paper, for a subset $\omega \in \mathbb{R}^d$, we simply denote $\|f\|_{L^2(\omega)}$ as $\|f\|_\omega$. And for a function u^ε defined both in Ω^ε_I and Ω^ε_E, denote $\int_{\Omega^\varepsilon} u^\varepsilon\ dx \triangleq \int_{\Omega^\varepsilon_I} u^\varepsilon_I\ dx + \int_{\Omega^\varepsilon_E} u^\varepsilon_E\ dx$ and $\|u^\varepsilon\|^2_{\Omega^\varepsilon} \triangleq \|u^\varepsilon_I\|^2_{\Omega^\varepsilon_I} + \|u^\varepsilon_E\|^2_{\Omega^\varepsilon_E}$. Then a priori estimates are summarized in the following theorem.

Theorem 3.2. *Let* $C^\varepsilon_{i,s}, \phi^\varepsilon_s, i = 1, 2, 3, s = I, E$ *be the solutions of* (8). *If the assumption* $(H0)$ *holds, then the following estimates are valid, for* $i = 1, 2, 3, s = I, E$,

$$\|C^\varepsilon_{i,s}\|_{L^\infty(0,T;L^2(\Omega^\varepsilon_s))} \le A, \tag{10a}$$
$$\|C^\varepsilon_{i,s}\|_{L^2(0,T;H^1(\Omega^\varepsilon_s))} \le A, \tag{10b}$$
$$\sqrt{\varepsilon}\|C^\varepsilon_{i,s}\|_{L^2(0,T;L^2(\Gamma_\varepsilon))} \le A, \tag{10c}$$
$$\|\partial_t C^\varepsilon_{i,s}\|_{L^2(0,T;H^{-1}(\Omega^\varepsilon_s))} \le A, \tag{10d}$$
$$\sqrt{\varepsilon}\|\phi^\varepsilon\|_{L^2(0,T;L^2(\Gamma_\varepsilon))} \le A, \tag{10e}$$
$$\|\phi^\varepsilon_s\|_{L^2(0,T;H^1(\Omega^\varepsilon_s))} \le A. \tag{10f}$$

Proof. If let $v_s = C^\varepsilon_{i,s},\ \varphi_s = \phi^\varepsilon_s,\ s = I, E$ in (8), we have

$$\sum_{i=1}^3 \frac{1}{2}\partial_t \|C^\varepsilon_i\|^2_{\Omega^\varepsilon} + \sum_{i=1}^3 D\|\nabla C^\varepsilon_i\|^2_{\Omega^\varepsilon} + \sum_{i=1}^3 \int_{\Omega^\varepsilon} z_i C^\varepsilon_i D\nabla\phi^\varepsilon \nabla C^\varepsilon_i\ dx + \sum_{i=1}^3 \int_{\Gamma_\varepsilon} \varepsilon \frac{P^\varepsilon_i}{z_i}[\![C^\varepsilon_i]\!]\ dS$$
$$+ \sum_{i=1}^3 \int_{\Gamma_\varepsilon} \varepsilon \frac{G_i}{z_i}[\![\phi^\varepsilon]\!][\![C^\varepsilon_i]\!]\ dS + \sum_{i=1}^3 \int_{\Gamma_\varepsilon} \varepsilon \frac{G_i}{z_i^2}[\![\ln C^\varepsilon_i]\!][\![C^\varepsilon_i]\!]\ dS$$

$$+\sum_{i=1}^{3}\int_{\Gamma_\varepsilon}\varepsilon\frac{\lambda_i}{z_i}P_m\partial_t[\![\phi^\varepsilon]\!][\![C_i^\varepsilon]\!]\;dS=0, \tag{11a}$$

$$\int_{\Omega^\varepsilon}\sigma^\varepsilon D\nabla\phi^\varepsilon\nabla\phi^\varepsilon\;dx+\sum_{i=1}^{3}\varepsilon G_i\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+\varepsilon\frac{P_m}{2}\partial_t\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2$$
$$=-\sum_{i=1}^{3}\int_{\Gamma_\varepsilon}\varepsilon\frac{G_i}{z_i}[\![\ln C_i^\varepsilon]\!][\![\phi^\varepsilon]\!]\;dS-\int_{\Gamma_\varepsilon}\varepsilon I_p^\varepsilon[\![\phi^\varepsilon]\!]\;dS. \tag{11b}$$

From assumption (6), we have

$$\begin{cases}[\![\ln C_i^\varepsilon]\!][\![C_i^\varepsilon]\!]=(\ln C_{i,I}^\varepsilon-\ln C_{i,E}^\varepsilon)(C_{i,I}^\varepsilon-C_{i,E}^\varepsilon)=\frac{1}{\xi}(C_{i,I}^\varepsilon-C_{i,E}^\varepsilon)^2\geq\frac{1}{C_u}(C_{i,I}^\varepsilon-C_{i,E}^\varepsilon)^2\\ |[\![\ln C_i^\varepsilon]\!]|=|\ln C_{i,I}^\varepsilon-\ln C_{i,E}^\varepsilon|=|\frac{1}{\xi}(C_{i,I}^\varepsilon-C_{i,E}^\varepsilon)|\leq\frac{1}{C_d}|C_{i,I}^\varepsilon-C_{i,E}^\varepsilon|,\end{cases} \tag{12}$$

where ξ is between $C_{i,I}^\varepsilon$ and $C_{i,E}^\varepsilon$. Then let $\varphi_s=\frac{\lambda_i}{z_i}C_{i,s}^\varepsilon,\;\; s=I,E$ in (8b), we have

$$\begin{aligned}&\varepsilon\int_{\Gamma_\varepsilon}\frac{\lambda_i}{z_i}P_m\partial_t[\![\phi^\varepsilon]\!][\![C_i^\varepsilon]\!]\;dS\\ =\;&-\frac{\lambda_i}{z_i}\int_{\Omega^\varepsilon}\sigma^\varepsilon D\nabla\phi^\varepsilon\nabla C_i^\varepsilon\;dx\\ &-\varepsilon\frac{\lambda_i}{z_i}\int_{\Gamma_\varepsilon}\big(\sum_{k=1}^{3}G_k[\![\phi^\varepsilon]\!][\![C_i^\varepsilon]\!]+\sum_{k=1}^{3}\frac{G_k}{z_k}[\![\ln C_k^\varepsilon]\!][\![C_i^\varepsilon]\!]+I_p^\varepsilon[\![C_i^\varepsilon]\!]\big)\;dS\end{aligned}$$

Combining the above equation, (12), (6) and (11a) yields

$$\begin{aligned}&\sum_{i=1}^{3}(\partial_t\|C_i^\varepsilon\|_{\Omega^\varepsilon}^2+\|\nabla C_i^\varepsilon\|_{\Omega^\varepsilon}^2+\varepsilon\|[\![C_i^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2)\\ &\leq A_1\left(K_1\|\nabla\phi^\varepsilon\|_{\Omega^\varepsilon}^2+\frac{1}{K_1}\sum_{i=1}^{3}\|\nabla C_i^\varepsilon\|_{\Omega^\varepsilon}^2\right)+A_2\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+A_3\varepsilon\sum_{i=1}^{3}\|[\![C_i^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+A_4.\end{aligned} \tag{13}$$

where we used the fact that I_P^ε is bounded.

From assumption (6) and (7), we can multiply (11b) with $\frac{2A_1K_1}{DC_l}$ and add it to (13) to get

$$\begin{aligned}&\sum_{i=1}^{3}(\partial_t\|C_i^\varepsilon\|_{\Omega^\varepsilon}^2+\|\nabla C_i^\varepsilon\|_{\Omega^\varepsilon}^2+\varepsilon\|[\![C_i^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2)+A_1K_1\|\nabla\phi^\varepsilon\|_{\Omega^\varepsilon}^2\\ &+A_2\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+A_3\varepsilon\partial_t\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2\\ \leq\;&\frac{A_4}{K_1}\sum_{i=1}^{3}\|\nabla C_i^\varepsilon\|_{\Omega^\varepsilon}^2+A_5\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+A_6\varepsilon\sum_{i=1}^{3}\|[\![C_i^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+A_7\\ \leq\;&\frac{A_4}{K_1}\sum_{i=1}^{3}\|\nabla C_i^\varepsilon\|_{\Omega^\varepsilon}^2+A_5\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+A_8,\end{aligned}$$

where K_1 is a positive constant. Choosing K_1 big enough, we have

$$\sum_{i=1}^{3}(\partial_t\|C_i^\varepsilon\|_{\Omega^\varepsilon}^2+\|\nabla C_i^\varepsilon\|_{\Omega^\varepsilon}^2+\varepsilon\|[\![C_i^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2)+\|\nabla\phi^\varepsilon\|_{\Omega^\varepsilon}^2+\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+\varepsilon\partial_t\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2$$

$$\leq \quad A_1\Big(\sum_{i=1}^{3}\|C_i^\varepsilon\|_{\Omega^\varepsilon}^2+\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2\Big)+A_2. \tag{14}$$

Then by using Gronwall inequality, we obtain

$$\sup_{t\in[0,T]}(\sum_{i=1}^{3}\|C_i^\varepsilon\|_{\Omega^\varepsilon}^2+\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2)+\sum_{i=1}^{3}\int_0^T\|\nabla C_i^\varepsilon\|_{\Omega^\varepsilon}^2\ dt$$
$$+\quad\int_0^T\|\nabla\phi^\varepsilon\|_{\Omega^\varepsilon}^2\ dt+\sum_{i=1}^{3}\int_0^T\varepsilon\|[\![C_i^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2\ dt+\int_0^T\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2\ dt\leq A. \tag{15}$$

This leads to (10a) and (10b).

For the L^2 estimates of ϕ^ε, by assumption (4), Lemma A.4 and (15), we obtain

$$\int_0^T\big(\|\phi_I^\varepsilon\|_{\Omega_I^\varepsilon}^2+\|\phi_E^\varepsilon\|_{\Omega_E^\varepsilon}^2\big)\ dt\leq A_1\int_0^T\big(\|\nabla\phi_I^\varepsilon\|_{\Omega_I^\varepsilon}^2+\|\nabla\phi_E^\varepsilon\|_{\Omega_E^\varepsilon}^2+\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2\big)\ dt\leq A_2,$$

(10f) is obtained by combining this with (15).

Using the following trace theorem[14, 33], (10c) follows from (10b) and (10e) follows from (10f).

$$\|v_s\|_{L^2(\Gamma^\epsilon)}\leq A\left(\delta\varepsilon^{-\frac12}\|v_s\|_{L^2(\Omega_s^\varepsilon)}+\frac{1}{\delta}\varepsilon^{\frac12}\|\nabla v_s\|_{L^2(\Omega_s^\varepsilon)}\right), \tag{16}$$

for $\forall\ v_s\in H^1(\Omega_s^\varepsilon),\ s=I,E$.

Lastly we show $\|\partial_t C_{i,s}^\varepsilon\|_{L^2(0,T;H^{-1}(\Omega_s^\varepsilon))}, i=1,2,3, s=I,E$ are bounded, we only consider $s=I$ since other cases can be discussed similarly. From (8b) we have

$$\frac{\varepsilon\lambda_i}{z_i}P_m\int_{\Gamma_\varepsilon}\partial_t[\![\phi^\varepsilon]\!]v_I\ dS$$
$$=-\frac{\lambda_i}{z_i}\int_{\Omega_I^\varepsilon}\sigma_I^\varepsilon D\nabla\phi_I^\varepsilon\nabla v_I\ dx-\frac{\varepsilon\lambda_i}{z_i}\int_{\Gamma_\varepsilon}\sum_{k=1}^{3}\left(G_k[\![\phi^\varepsilon]\!]v_I+\frac{G_k}{z_k}[\![\ln C_k^\varepsilon]\!]v_I+I_p^\varepsilon v_I\right)\ dS. \tag{17}$$

Substituting the above equation into (8a) leads to

$$\|\partial_t C_{1,I}^\varepsilon\|_{H^{-1}(\Omega_I^\varepsilon)}$$
$$\leq\quad A_1\sup_{\substack{v_1\in H^1(\Omega_I^\varepsilon),\\ \|v_1\|_{H^1(\Omega_I^\varepsilon)}\leq 1}}\Big((\|\nabla C_{1,I}^\varepsilon\|_{\Omega_I^\varepsilon}+\|\nabla\phi_I^\varepsilon\|_{\Omega_I^\varepsilon})\|\nabla v_1\|_{\Omega_I^\varepsilon}+\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}\|v_1\|_{\Gamma_\varepsilon}$$
$$+\varepsilon\sum_{i=1}^{3}\|[\![C_i^\varepsilon]\!]\|_{\Gamma_\varepsilon}\|v_1\|_{\Gamma_\varepsilon}+\sqrt{\varepsilon}\|v_1\|_{\Gamma_\varepsilon}\Big)$$
$$\leq\quad A_2\big(\|\nabla C_{1,I}^\varepsilon\|_{\Omega_I^\varepsilon}+\|\nabla\phi_I^\varepsilon\|_{\Omega_I^\varepsilon}+\sqrt{\varepsilon}\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}+\sqrt{\varepsilon}\|[\![C_1^\varepsilon]\!]\|_{\Gamma_\varepsilon}\big)+A_3,$$

where we used $\|v_1\|_{\Gamma_\varepsilon}=O(\varepsilon^{-1/2})$. Finally, combining above equation with (15) yields

$$\|\partial_t C_{1,I}^\varepsilon\|_{L^2(0,T;H^{-1}(\Omega_I^\varepsilon))}^2$$
$$\leq\quad A_1\int_0^T\left(\|\nabla C_{1,I}^\varepsilon\|_{\Omega_I^\varepsilon}^2+\|\nabla\phi_I^\varepsilon\|_{\Omega_I^\varepsilon}+\varepsilon\|[\![\phi^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2+\varepsilon\sum_{i=1}^{3}\|[\![C_i^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2\right)\ dt+A_2$$
$$\leq\quad A_3.$$

□

4. **Homogenization.** In this section, the homogenization theories for the EN model (2) are developed with different connectivity. The homogenization process for "connected-disconnected" case is shown in subsection 4.1, and then the "connected-connected" case is shown in subsection 4.2.

4.1. **"Connected-disconnected" case.** In order to use compactness results from unfolding operators and two-scale theory, we extend the functions $C^\varepsilon_{i,s}, \phi^\varepsilon_s, i = 1,2,3, s = I, E$ in a suitable way to the whole domain Ω. Since Ω^ε_E is connected and has a Lipschitz boundary, by Theorem 2.2 in [28], there exists a linear and bounded extension operator $\mathcal{L}^\varepsilon : \ L^2\left((0,T); H^1\left(\Omega^\epsilon_E\right)\right) \to L^2\left((0,T); H^1(\Omega)\right)$, we simply denote

$$\widetilde{C}^\varepsilon_{i,E} = \mathcal{L}^\varepsilon C^\varepsilon_{i,E}, \ \widetilde{\phi}^\varepsilon_E = \mathcal{L}^\varepsilon \phi^\varepsilon_E. \tag{18}$$

The a priori estimates (10a), (10b) and (10f) remain valid for the extensions $\widetilde{C}^\varepsilon_{i,E}$ and $\widetilde{\phi}^\varepsilon_E$. Such extensions can not be applied to the functions in Ω^ε_I since it is not connected[33]. Zero extensions is used instead. The zero extension of a function defined on Ω^ε_s for $s = I, E$ will be denoted by $\overline{C}^\varepsilon_{i,I}$ and $\overline{\phi}^\varepsilon_I$. It is obvious that the time derivative of $\overline{C}^\varepsilon_{i,I}$ satisfies

$$\left\langle \partial_t \overline{C}^\varepsilon_{i,s}, \psi \right\rangle_\Omega = \left\langle \partial_t C^\varepsilon_{i,s}, \psi \right\rangle_{\Omega^\epsilon_s} \text{ for all } \psi \in H^1(\Omega) \text{ and a.e. } t \in (0,T), \tag{19}$$

$$\left\| \partial_t \overline{C}^\varepsilon_{i,s} \right\|_{L^2((0,T);H^{-1}(\Omega))} \le \left\| \partial_t C^\varepsilon_{i,s} \right\|_{L^2((0,T);H^{-1}(\Omega^\epsilon_s))} \le A, \tag{20}$$

where $\langle \cdot, \cdot \rangle_G$ represent the duality paring $\langle \cdot, \cdot \rangle_{H^{-1}(G)\times H^1(G)}$ for an arbitrary measurable set G. Since unfolding operators and two-scale convergence method are used in our proof, we give some definitions and properties for them in Appendix A. First we give a lemma.

Lemma 4.1. *Suppose $a_\varepsilon, b_\varepsilon, c_\varepsilon \in L^2(\omega)$ be three series such that*

$$a_\varepsilon \to a \text{ strongly in } L^2(\omega), \ b_\varepsilon \to b \text{ strongly in } L^2(\omega), \ c_\varepsilon \rightharpoonup c \text{ weakly in } L^2(\omega),$$

and $\|a_\varepsilon\|_{L^\infty(\omega)} \le A$, $\|a\|_{L^\infty(\omega)} \le A$, $\|b_\varepsilon\|_{L^\infty(\omega)} \le A$, $\|b\|_{L^\infty(\omega)} \le A$ for some open subset $\omega \in \mathbb{R}^d$, then the following convergence result holds:

$$\int_\omega a_\varepsilon b_\varepsilon c_\varepsilon \, dx \to \int_\omega abc \, dx. \tag{21}$$

Proof. We have

$$\int_\omega a_\varepsilon b_\varepsilon c_\varepsilon \, dx = \int_\omega abc \, dx + \int_\omega ab(c_\varepsilon - c) \, dx + \int_\omega a(b_\varepsilon - b)c_\varepsilon \, dx + \int_\omega (a_\varepsilon - a) b_\varepsilon c_\varepsilon \, dx,$$

it is obvious that the limits of the last three terms on the right hand side are zero. For example, for the last term on the right hand side, we have

$$\left| \int_\omega (a_\varepsilon - a) b_\varepsilon c_\varepsilon \, dx \right| \le A \int_\omega |(a_\varepsilon - a)c_\varepsilon| \, dx \to 0,$$

the assertion is proved. □

For "connected-disconnected" case, we have the following homogenization results.

Theorem 4.2. *Suppose the intracellular region Ω^ε_I is disconnected and assumption $(H0)$ holds, let $C^\varepsilon_{i,s}, \phi^\varepsilon_s, \ i = 1,2,3, s = I, E$ be the solutions of (2), then there exist subsequences of $C^\varepsilon_{i,s}, \phi^\varepsilon_s$, still denoted as $C^\varepsilon_{i,s}, \phi^\varepsilon_s$, and $C_{i,E} \in L^2(0,T; H^1(\Omega))$, $\widehat{C}_{i,E} \in L^2((0,T) \times \Omega; H^1_{per}(Y))$, $C_{i,I} \in L^2((0,T) \times \Omega)$, $\widehat{C}_{i,I} \in L^2((0,T) \times \Omega; H^1(Y))$*

and $\phi_E \in L^2(0,T;H^1(\Omega))$, $\widehat{\phi}_E \in L^2((0,T)\times\Omega;H^1_{per}(Y))$, $\phi_I \in L^2((0,T)\times\Omega)$, $\widehat{\phi}_I \in L^2((0,T)\times\Omega;H^1(Y))$, *such that, for* $i=1,2,3$

$$\mathcal{T}^\varepsilon(\widetilde{C}^\varepsilon_{i,E}) \to C_{i,E} \text{ strongly in } L^2((0,T)\times\Omega\times Y), \tag{22a}$$

$$\mathcal{T}^\varepsilon(\nabla\widetilde{C}^\varepsilon_{i,E}) \rightharpoonup \nabla_x C_{i,E} + \nabla_y \widehat{C}_{i,E} \text{ weakly in } L^2((0,T)\times\Omega\times Y), \tag{22b}$$

$$\mathcal{T}^\varepsilon_b(\widetilde{C}^\varepsilon_{i,E}) \to C_{i,E} \text{ strongly in } L^2((0,T)\times\Omega\times\Gamma), \tag{22c}$$

$$\partial_t\overline{C}^\varepsilon_{i,E} \rightharpoonup |Y_E|\partial_t C_{i,E} \text{ weakly in } L^2(0,T;H^{-1}(\Omega)). \tag{22d}$$

$$\mathcal{T}^\varepsilon(\overline{C}^\varepsilon_{i,I}) \to \beta_I C_{i,I} \text{ strongly in } L^2((0,T)\times\Omega\times Y), \tag{23a}$$

$$\mathcal{T}^\varepsilon(\nabla\overline{C^\varepsilon_{i,I}}) \rightharpoonup \beta_I\nabla_y \widehat{C}_{i,I} \text{ weakly in } L^2((0,T)\times\Omega\times Y), \tag{23b}$$

$$\mathcal{T}^\varepsilon_b(\overline{C}^\varepsilon_{i,I}) \to C_{i,I} \text{ strongly in } L^2((0,T)\times\Omega\times\Gamma), \tag{23c}$$

$$\partial_t\overline{C}^\varepsilon_{i,I} \rightharpoonup |Y_I|\partial_t C_{i,I} \text{ weakly in } L^2(0,T;H^{-1}(\Omega)). \tag{23d}$$

$$\mathcal{T}^\varepsilon(\nabla\widetilde{\phi}^\varepsilon_E) \rightharpoonup \nabla_x\phi_E + \nabla_y\widehat{\phi}_E \text{ weakly in } L^2((0,T)\times\Omega\times Y), \tag{24a}$$

$$\mathcal{T}^\varepsilon_b(\widetilde{\phi}^\varepsilon_E) \rightharpoonup \phi_E \text{ weakly in } L^2((0,T)\times\Omega\times\Gamma), \tag{24b}$$

$$\mathcal{T}^\varepsilon(\overline{\nabla\phi^\varepsilon_I}) \rightharpoonup \beta_I\nabla_y\widehat{\phi}_I \text{ weakly in } L^2((0,T)\times\Omega\times Y), \tag{24c}$$

$$\mathcal{T}^\varepsilon_b(\phi^\varepsilon_I) \rightharpoonup \phi_I \text{ weakly in } L^2((0,T)\times\Omega\times\Gamma). \tag{24d}$$

And $C_{i,s}, \phi_s,\ i=1,2,3, s=I,E$ *are the weak solutions of the following equations*

$$\begin{cases} |Y_E|\partial_t C_{i,E} - \nabla\cdot(D^\star_E\nabla C_{i,E} + z_i C_{i,E} D^\star_E\nabla\phi_E) & \\ = |\Gamma|\Big(\frac{G_i}{z_i}(\phi_I-\phi_E) + \frac{G_i}{z_i^2}\ln\frac{C_{i,I}}{C_{i,E}} + \frac{P_i^0}{z_i} + \frac{\lambda_i}{z_i}P_m\partial_t(\phi_I-\phi_E)\Big) & \text{in } (0,T)\times\Omega, \\ -(D^\star_E\nabla C_{i,E} + z_i C_{i,E}D^\star_E\nabla\phi_E)\cdot\vec{\nu} = 0 & \text{on } (0,T)\times\partial\Omega, \\ |Y_I|\partial_t C_{i,I} & \\ = -|\Gamma|\Big(\frac{G_i}{z_i}(\phi_I-\phi_E) + \frac{G_i}{z_i^2}\ln\frac{C_{i,I}}{C_{i,E}} + \frac{P_i^0}{z_i} + \frac{\lambda_i}{z_i}P_m\partial_t(\phi_I-\phi_E)\Big) & \text{in } (0,T)\times\Omega, \\ C_{i,I}|_{t=0} = C^0_{i,I},\ C_{i,E}|_{t=0} = C^0_{i,E} & \text{in } \Omega, \end{cases} \tag{25}$$

$$\begin{cases} -\nabla\cdot(\sigma_E D^\star_E\nabla\phi_E) = 0 & \text{in } (0,T)\times\Omega, \\ -\sigma_E D^\star_E\nabla\phi_E\cdot\vec{\nu} = 0 & \text{on } (0,T)\times\partial\Omega, \\ P_m\partial_t(\phi_I-\phi_E) = -(\sum_{i=1}^3 G_i(\phi_I-\phi_E) + \sum_{i=1}^3\frac{G_i}{z_i}\ln\frac{C_{i,I}}{C_{i,E}} + I_p^0) & \text{in } (0,T)\times\Omega, \\ (\phi_I-\phi_E)|_{t=0} = \phi^0 & \text{in } \Omega, \end{cases} \tag{26}$$

where $\sigma_E = \sum_{i=1}^3 z_i^2 C_{i,E}$, $D^\star_E = \int_{Y_E} D(I_n + \nabla_y\chi_E)\,dy$ *and* $\chi_E = (\chi^1_E, \chi^2_E, \cdots, \chi^d_E)$ *is the solution of* (36), $P^0_1 = 3I^0_p, P^0_2 = -2I^0_p, P^0_3 = 0$, *and* I^0_p *has the same expression as in* (5) *but the concentrations are replaced by the corresponding limits. And* $C_{i,s}$ *are electro-neutral, i.e.* $\sum_{i=1}^3 z_i C_{i,s} = 0$ *for* $s=I,E$. *If we further assume* $\nabla\phi_s \in L^\infty((0,T)\times\Omega), s=I,E$, *then the solution for* (25) *and* (26) *is unique.*

Proof. Convergence (22), (23) and (24) are the results of a priori estimate Theorem 3.2 and relavent convergence results in [23]. Note that C_E, C_I, ϕ_E, ϕ_I are independent of y. This property will be used in the following derivation process.

First, in (8b), let

$$\varphi_I = \varepsilon u(x)v_1(x/\varepsilon)w(t), \tag{27}$$

where $u \in C_0^\infty(\Omega)$, $v_1 \in C_{per}^\infty(Y_I)$, $w \in C_0^\infty(0,T)$. Then integrating (8b) with respect to time gives

$$\begin{aligned} 0 &= 2\int_0^T \int_{\Omega_I^\varepsilon} \sigma_I^\varepsilon D\nabla\phi_I^\varepsilon(\varepsilon v_1 w\nabla u + uw\nabla_y v_1)\, dxdt + \int_0^T \int_{\Gamma_\varepsilon} \varepsilon^2 \sum_{i=1}^3 G_i [\![\phi^\varepsilon]\!] uv_1 w\, dSdt \\ &\quad + \int_0^T\int_{\Gamma_\varepsilon} \varepsilon^2 \sum_{i=1}^3 \frac{G_i}{z_i} [\![\ln C_i^\varepsilon]\!] uv_1 w\, dSdt - \int_0^T\int_{\Gamma_\varepsilon} \varepsilon^2 P_m [\![\phi^\varepsilon]\!] uv_1 \partial_t w\, dSdt \\ &\quad + \int_0^T\int_{\Gamma_\varepsilon} \varepsilon^2 I_P^\varepsilon uv_1 w\, dSdt \\ &= M_1 + M_2 + M_3 - M_4 + M_5. \end{aligned} \tag{28}$$

For M_1, using the property of unfolding operator Lemma A.2, we deduce

$$M_1 = \int_0^T \int_{\Omega\times Y_I} \mathcal{T}^\varepsilon\left(\overline{\sigma}_I^\varepsilon\right) D\, \mathcal{T}^\varepsilon\left(\overline{\nabla\phi_I^\varepsilon}\right)\left(\varepsilon v_1 w \mathcal{T}^\varepsilon\left(\nabla u\right) + \mathcal{T}^\varepsilon\left(u\right) w\nabla_y v_1\right)\, dxdydt. \tag{29}$$

By (23a) and the relation (3): $\sigma_I^\varepsilon = \sum\limits_{i=1}^3 z_i^2 C_{i,I}^\varepsilon$, it follows that

$$\mathcal{T}^\varepsilon\left(\overline{\sigma}_I^\varepsilon\right) \to \beta_I\sigma_I \text{ strongly in } L^2((0,T)\times\Omega\times Y_I), \tag{30}$$

where $\sigma_I = \sum\limits_{i=1}^3 z_i^2 C_{i,I}$. From Lemma A.3, it is obvious that, as $\varepsilon\to 0$

$$\left(\varepsilon v_1 w\mathcal{T}^\varepsilon\left(\nabla u\right) + \mathcal{T}^\varepsilon\left(u\right) w\nabla_y v_1\right) \to uw\nabla_y v_1 \text{ strongly in } L^2((0,T)\times\Omega\times Y_I). \tag{31}$$

From (31), (30), (24c), and Lemma 4.1, passing to the limit for (29) as $\varepsilon\to 0$, while noticing that $C_0^\infty((0,T)\times\Omega)\bigotimes C_{per}^\infty(Y_I)$ is dense in $L^2((0,T)\times\Omega; H^1(Y_I))$, we deduce

$$M_1 \to \int_0^T \int_{\Omega\times Y_I} \sigma_I D\nabla_y\widehat{\phi}_I\nabla_y\Phi_I\, dxdydt.$$

for $\forall\ \Phi_I \in L^2((0,T)\times\Omega; H^1(Y_I))$. For M_2, from Lemma A.2 we have

$$M_2 = \int_0^T \int_{\Omega\times\Gamma} \sum_{i=1}^3 G_i\big(\mathcal{T}_b^\varepsilon\left(\phi_I^\varepsilon\right) - \mathcal{T}_b^\varepsilon(\widetilde{\phi}_E^\varepsilon)\big)\varepsilon\mathcal{T}_b^\varepsilon\left(u\right) v_1 w\, dxdS_y dt,$$

Obviously,

$$\varepsilon\mathcal{T}_b^\varepsilon\left(u\right) v_1 w \ \to\ 0 \text{ strongly in } L^2((0,T)\times\Omega\times\Gamma),$$

by (24b) and (24d) it follows that $M_2\to 0$. For M_4, the result is similar, i.e. $M_4\to 0$.

Then, for M_3, noticing that $\mathcal{T}_b^\varepsilon(\ln C_{i,s}^\varepsilon) = \ln\mathcal{T}_b^\varepsilon(C_{i,s}^\varepsilon)$, from Lemma A.2, it follows

$$M_3 = \int_0^T \int_{\Omega\times\Gamma} \sum_{i=1}^3 (\ln\mathcal{T}_b^\varepsilon(\overline{C}_{i,I}^\varepsilon) - \ln\mathcal{T}_b^\varepsilon(\widetilde{C}_{i,E}^\varepsilon))\varepsilon\mathcal{T}_b^\varepsilon(u)v_1 w\, dxd\sigma_y dt.$$

In order to get $M_3\to 0$, we only need to show that $\ln\mathcal{T}_b^\varepsilon(C_{i,s}^\varepsilon)$ are weakly convergent in $L^2((0,T)\times\Omega\times\Gamma)$, since $\varepsilon\mathcal{T}_b^\varepsilon(u)v_1 w$ converges to zero strongly in $L^2((0,T)\times\Omega\times\Gamma)$. Due to the strong convergence result (22c) of $\mathcal{T}_b^\varepsilon(\widetilde{C}_{i,E}^\varepsilon)$ in $L^2((0,T)\times\Omega\times\Gamma)$, there exists a subsequence such that $\mathcal{T}_b^\varepsilon(\widetilde{C}_{i,E}^\varepsilon)\to C_{i,E}$ *a.e in* $(0,T)\times\Omega\times\Gamma$. The continuity of Logarithmic function yields $\ln(\mathcal{T}_b^\varepsilon(\widetilde{C}_{i,E}^\varepsilon)) \to \ln(C_{i,E})$ $a.e\ in\ (0,T)\times\Omega\times\Gamma$. And from the boundedness assumption (6) we know that $\|\ln(\mathcal{T}_b^\varepsilon(\widetilde{C}_{i,E}^\varepsilon))\|^2_{L^2((0,T)\times\Omega\times\Gamma)}$ is bounded. Finally, Theorem (13.44) in [27] states that $\ln(\mathcal{T}_b^\varepsilon(\widetilde{C}_{i,E}^\varepsilon))$ converges weakly in $L^2((0,T)\times\Omega\times\Gamma)$ to $\ln(C_{i,E})$. Same argument is valid for $\ln\mathcal{T}_b^\varepsilon(\overline{C}_{i,I}^\varepsilon)$. Then the limit of M_3 is zero as $\varepsilon\to 0$.

For the pump term M5, due to the boundness assumption in (6) and Lipschitz continuity of I_p with respect to $C_{i,s}^\epsilon$, the conditions in Corollary 15 in [23] are satisfied. Then as $\mathcal{T}_b^\epsilon(\overline{C}_{i,I}^\epsilon)\to C_{i,I}^0$, $\mathcal{T}_b^\epsilon(\widetilde{C}_{i,E}^\epsilon)\to C_{i,E}^0$ strongly in $L^2((0,T)\times\Omega\times\Gamma)$, we have $\mathcal{T}_b^\varepsilon(I_p^\varepsilon)\to I_p^0$ weakly in $L^2((0,T)\times\Omega\times\Gamma)$ and the limit of M_5 is zero as $\varepsilon\to 0$.

Summarizing the above convergence results for M_1, M_2, M_3, M_4, M_5, we deduce that the limit equation for (28) as $\varepsilon\to 0$ is

$$\int_0^T\int_{\Omega\times Y_I}\sigma_I D\nabla_y\widehat{\phi}_I\nabla_y\Phi_I\ dxdydt = 0, \tag{32}$$

for $\forall\ \Phi_I\in L^2((0,T)\times\Omega; H^1(Y_I))$. Let $\Phi_I=\widehat{\phi}_I$ and noticing $\sigma_I>0$, we obtain

$$\nabla_y\widehat{\phi}_I = 0. \tag{33}$$

Similar results were derived in, for example Proposition 11 in [23] and Theorem 3.3 in [22].

Then let $\varphi_I=\varphi_1(t,x)$ in (8b), where $\varphi_1\in C_0^\infty((0,T)\times\Omega)$. Using similar arguments as for M_1, M_2, M_3, M_4, M_5 while noticing (33), we obtain, as $\varepsilon\to 0$,

$$\int_0^T\int_{\Omega\times\Gamma}\Big[\sum_{i=1}^3 G_i(\phi_I-\phi_E)+\sum_{i=1}^3\frac{G_i}{z_i}(\ln C_{i,I}-\ln C_{i,E})+I_p^0+P_m\partial_t(\phi_I-\phi_E)\Big]\varphi_1\ dxdS_ydt = 0.$$

Since $\phi_I,\ \phi_E$ and $C_{i,I},\ C_{i,E}$ are independent of y, so

$$\sum_{i=1}^3 G_i(\phi_I-\phi_E)+\sum_{i=1}^3\frac{G_i}{z_i}(\ln C_{i,I}-\ln C_{i,E})+I_p^0+P_m\partial_t(\phi_I-\phi_E)=0. \tag{34}$$

If we let $\varphi_I=u(x)w_1(t)$ in (8b) and pass to the limit as $\varepsilon\to 0$, where $w_1\in C^\infty(0,T), w_1(T)=0$, then the initial condition for $\phi_I-\phi_E$ can be derived as

$$(\phi_I-\phi_E)|_{t=0}=\phi^0.$$

Then in (8b), let $\varphi_E=\varepsilon u(x)v_2(x/\varepsilon)w(t)$, where $v_2\in C_{per}^\infty(Y_E)$ and u,w are the same as in (27). Using similar discussion as for (28), from (24a) and (21) we have, after passing to the limit for (8b) as $\varepsilon\to 0$,

$$2\int_0^T\int_{\Omega\times Y_E}\sigma_E D(\nabla_x\phi_E+\nabla_y\widehat{\phi}_E)\nabla_y\Phi_E\ dxdydt=0, \tag{35}$$

for $\forall\ \Phi_E\in L^2((0,T)\times\Omega; H^1_{per}(Y_E))$.

The above equation yields the following representation for $\widehat{\phi}_E$

$$\widehat{\phi}_E=\nabla_x\phi_E\ \cdot\chi_E,$$

where $\chi_E=(\chi_E^1,\chi_E^2,\cdots,\chi_E^d)$, satisfying the following auxiliary problem

$$\begin{cases}-\nabla_y\cdot\big(D\nabla_y(y_j+\chi_E^j)\big)=0\ in\ Y_E,\\ -D\nabla_y(y_j+\chi_E^j)\cdot\vec{n}_1=0\ on\ \Gamma,\\ \chi_E^j\ is\ Y-periodic,\ \int_{Y_E}\chi_E^j=0.\end{cases} \tag{36}$$

If we let $\varphi_E = \varphi_1(t,x)$ in (8b), from (34) and (21), using density property, it yields the limit for (8b) as $\varepsilon \to 0$

$$2\int_0^T \int_\Omega \sigma_E D_E^\star \nabla\phi_E \nabla\Phi_1 \; dxdt = 0,$$

for $\forall\ \Phi_1 \in L^2((0,T); H^1(\Omega))$, where $D_E^\star = \int_{Y_E} D(I_n + \nabla_y \chi_E)\; dy$. The strong form of the above equation is

$$\begin{cases} -\nabla\cdot\left(\sigma_E D_E^\star \nabla\phi_E\right) = 0 & in\ (0,T)\times\Omega, \\ -\sigma_E D_E^\star \nabla\phi_E \cdot \vec{\nu} = 0 & on\ (0,T)\times\partial\Omega. \end{cases} \tag{37}$$

Now consider the equations for C_i^ε. Let $v_I = \varepsilon u(x) v_1(x/\varepsilon) w(t)$ in (8a), where u, v_1, w is the same as in (27). We deal with the interface integral similarly as for (28). From (23b), (21), (33) and density property, passing to the limit for (8a) as $\varepsilon \to 0$ leads to

$$\int_0^T \int_{\Omega\times Y_I} D\nabla_y \widehat{C}_{i,I} \nabla_y \Phi_I \; dxdydt = 0, \tag{38}$$

for $\forall\ \Phi_I \in L^2((0,T)\times\Omega; H^1(Y_I))$. Let $\Phi_I = \widehat{C}_{i,I}$ in the above equation, we have

$$\nabla_y \widehat{C}_{i,I} = 0. \tag{39}$$

If let $v_I = \varphi_1(t,x)$ in (8a), using (23d), (21), (33), (39) and passing to the limit for (8a) as $\varepsilon \to 0$ yields

$$\begin{aligned} & |Y_I| \int_0^T \int_\Omega \partial_t C_{i,I} u w_1 \; dxdt \\ = \quad & -\int_0^T \int_{\Omega\times\Gamma} \left(\frac{G_i}{z_i}(\phi_I - \phi_E) + \frac{G_i}{z_i^2}(\ln C_{i,I} - \ln C_{i,E}) + \frac{P_i^0}{z_i} + \frac{\lambda_i}{z_i} P_m \partial_t(\phi_I - \phi_E) \right) u w_1 \; dxdS_y dt. \end{aligned}$$

The integrand in the above equation is independent of y, so it is equivalent to

$$|Y_I| \partial_t C_{i,I} = -|\Gamma| \left(\frac{G_i}{z_i}(\phi_I - \phi_E) + \frac{G_i}{z_i^2}(\ln C_{i,I} - \ln C_{i,E}) + \frac{P_i^0}{z_i} + \frac{\lambda_i}{z_i} P_m \partial_t(\phi_I - \phi_E) \right). \tag{40}$$

To derive the initial conditions for $C_{i,I}$, if we let $v_I = u(x) w_1(t)$ in (8a) and pass to the limit as $\varepsilon \to 0$, it is easy to show that $C_{i,I}|_{t=0} = C_{i,I}^0$.

For $C_{i,E}^\varepsilon$, let $v_E = \varepsilon u(x) v_2(x/\varepsilon) w(t)$ in (8b). From (21), passing to the limit as $\varepsilon \to 0$ leads to

$$\int_0^T \int_{\Omega\times Y_E} \left(D(\nabla C_{i,E} + \nabla_y \widehat{C}_{i,E}) + z_i C_{i,E} D(\nabla_x \phi_E + \nabla_y \widehat{\phi}_E) \right) \nabla_y \Phi_E \; dxdydt \tag{41}$$

for $\forall\ \Phi_E \in L^2((0,T)\times\Omega; H^1_{per}(Y_E))$.

Thanks to (35), the second term on the left hand side is zero, and the following representation holds,

$$\widehat{C}_{i,E} = \nabla_x C_{i,E} \ \cdot \chi_E.$$

Lastly, if let $v_E = \varphi_1(t,x)$ in (8a) and pass to the limit as $\varepsilon \to 0$, we have by density property that

$$\begin{aligned} & \int_0^T \int_\Omega \left(|Y_E| \partial_t C_{i,E} \Phi_1 + D_E^\star \nabla C_{i,E} \nabla\Phi_1 + z_i C_{i,E} D_E^\star \nabla\phi_E \nabla\Phi_1 \right) \; dxdt \\ - \quad & \int_0^T \int_{\Omega\times\Gamma} \left(\frac{G_i}{z_i}(\phi_I - \phi_E) + \frac{G_i}{z_i^2}(\ln C_{i,I} - \ln C_{i,E}) + \frac{P_i^0}{z_i} + \frac{\lambda_i}{z_i} P_m \partial_t(\phi_I - \phi_E) \right) \Phi_1 \; dxdS_y dt = 0, \end{aligned}$$

for $\forall\ \Phi_1 \in L^2((0,T); H^1(\Omega))$.

The derivation of initial condition for $C_{i,E}$ is the same as for $C_{i,I}$, so we omit it. The strong form for the above equation is

$$\begin{cases} |Y_E|\partial_t C_{i,E} - \nabla\cdot(D_E^\star \nabla C_{i,E} + z_i C_{i,E} D_E^\star \nabla\phi_E) = \\ |\Gamma|\Big(\frac{G_i}{z_i}(\phi_I-\phi_E) + \frac{G_i}{z_i^2}\ln\frac{C_{i,I}}{C_{i,E}} + \frac{P_i^0}{z_i} + \frac{\lambda_i}{z_i}P_m\partial_t(\phi_I-\phi_E)\Big) & in\ (0,T)\times\Omega, \\ -(D_E^\star\nabla C_{i,E} + z_i C_{i,E} D_E^\star \nabla \phi_E)\cdot\vec{\nu} = 0 & on\ (0,T)\times\partial\Omega, \\ C_{i,E}|_{t=0} = C_{i,E}^0 & in\ \Omega. \end{cases} \tag{42}$$

Now we have derived all the homogenization equations, i.e. (42), (40), (34), (37), which are (25) and (26). The electro-neutrality condition for $C_{i,s}$ is obvious since the initial value of $C_{i,s}$ is electro-neutral. The uniqueness of the solutions for the macroscopic model can be proved similarly as in Theorem 3.1. The theorem is proved. □

Remark 4.3. Although $D_I^\star = 0$ in the above theorem, we could also define an auxiliary problem

$$\begin{cases} -\nabla_y\cdot\big(D\nabla_y(y_j+\chi_I^j)\big) = 0\ in\ Y_I, \\ -D\nabla_y(y_j+\chi_I^j)\cdot\vec{n}_1 = 0\ on\ \Gamma, \\ \chi_I^j\ is\ Y-periodic,\ \int_{Y_I}\chi_I^j = 0, \end{cases} \tag{43}$$

which is quite similar to (36). However, since Y_I is completely included in Y, the solution for (43) is $\chi_I^k = -y_k + c_k,\ k = 1,\cdots,n$, where c_k is a constant. And it is obvious that $D_I^\star = \int_{Y_I} D(I_n + \nabla_y\chi_I)\,dy = 0$.

4.2. **"Connected-connected" case.** Now we consider the "connected-connected" case. In this case, the status of Ω_I^ε and Ω_E^ε are "equivalent", which means the homogenized equations for both regions are in the same form. Noticing that Ω_I^ε also reaches the boundary of $\partial\Omega$, we need to add boundary conditions for C_I^ε, ϕ_I^ε on $\partial\Omega$, i.e. $J_{i,I}\cdot\vec{\nu} = 0$, and $D\sigma_I^\varepsilon\nabla\phi_I^\varepsilon\cdot\vec{\nu} = 0,\ on\ \partial\Omega$.

Since now both Ω_I^ε and Ω_E^ε are connected, by Theorem 2.2 in [28], there exist linear and bounded extension operators $\mathcal{L}_s^\varepsilon:\ L^2\left((0,T),H^1(\Omega_s^\epsilon)\right)\to L^2\left((0,T),H^1(\Omega)\right)$, $s = I,E$. Simply denote

$$\widetilde{C}_{i,s}^\varepsilon = \mathcal{L}_s^\varepsilon C_{i,s}^\varepsilon,\ \widetilde{\phi}_s^\varepsilon = \mathcal{L}_s^\varepsilon\phi_s^\varepsilon,\ s = I,E. \tag{44}$$

The priori estimates (10a), (10b) and (10f) remain valid for the extensions $\widetilde{C}_{i,s}^\varepsilon$ and $\widetilde{\phi}_s^\varepsilon$. The convergence and homogenization results for "connected-connected" case is summarized in the following theorem.

Theorem 4.4. *Suppose Ω_I^ε is connected and assumption $(H0)$ holds, let $C_{i,s}^\varepsilon,\phi_s^\varepsilon,\ i = 1,2,3, s = I,E$ be solutions of (2), then there exist subsequences of $C_{i,s}^\varepsilon,\phi_s^\varepsilon$, still denoted as $C_{i,s}^\varepsilon,\phi_s^\varepsilon$, and $C_{i,s},\phi_s\in L^2(0,T;H^1(\Omega))$, $\widehat{C}_{i,s},\widehat{\phi}_s\in L^2((0,T)\times\Omega;H^1_{per}(Y))$, such that for $i = 1,2,3, s = I,E$,*

$$\mathcal{T}^\varepsilon(\widetilde{C}_{i,s}^\varepsilon)\to C_{i,s}\ strongly\ in\ L^2((0,T)\times\Omega\times Y), \tag{45a}$$

$$\mathcal{T}^\varepsilon(\nabla\widetilde{C}_{i,s}^\varepsilon)\rightharpoonup\nabla_x C_{i,s}+\nabla_y\widehat{C}_{i,s}\ weakly\ in\ L^2((0,T)\times\Omega\times Y), \tag{45b}$$

$$\mathcal{T}_b^\varepsilon(\widetilde{C}_{i,s}^\varepsilon)\to C_{i,s}\ strongly\ in\ L^2((0,T)\times\Omega\times\Gamma), \tag{45c}$$

$$\partial_t\overline{C}_{i,s}^\varepsilon\rightharpoonup|Y_s|\partial_t C_{i,s}\ weakly\ in\ L^2(0,T;H^{-1}(\Omega)). \tag{45d}$$

$$\mathcal{T}^\varepsilon(\nabla\widetilde{\phi}_s^\varepsilon)\rightharpoonup\nabla_x\phi_s+\nabla_y\widehat{\phi}_s\ weakly\ in\ L^2((0,T)\times\Omega\times Y), \tag{46a}$$

$$\mathcal{T}_b^\varepsilon(\widetilde{\phi}_s^\varepsilon) \rightharpoonup \phi_s \text{ weakly in } L^2((0,T)\times\Omega\times\Gamma). \tag{46b}$$

$C_{i,s}, \phi_s,\ i=1,2,3, s=I,E$ are the weak solutions of the following equations

$$\begin{cases} |Y_s|\partial_t C_{i,s} - \nabla\cdot(D_s^\star\nabla C_{i,s} + z_i C_{i,s} D_s^\star \nabla\phi_s) = \\ \pm|\Gamma|\Big(\dfrac{G_i}{z_i}(\phi_I-\phi_E) + \dfrac{G_i}{z_i^2}\ln\dfrac{C_{i,I}}{C_{i,E}} + \dfrac{P_i^0}{z_i} + \dfrac{\lambda_i}{z_i}P_m\partial_t(\phi_I-\phi_E)\Big) & \text{in } (0,T)\times\Omega, \\ (D_s^\star\nabla C_{i,s} + z_i C_{i,s} D_s^\star\nabla\phi_s)\cdot\vec{\nu} = 0 & \text{on } (0,T)\times\partial\Omega, \\ C_{i,s}|_{t=0} = C_{i,s}^0 & \text{in } \Omega, \end{cases} \tag{47}$$

$$\begin{cases} -\nabla\cdot\big(\sigma_s D_s^\star\nabla\phi_s\big) = \\ \pm|\Gamma|\Big(\sum\limits_{i=1}^3 G_i(\phi_I-\phi_E) + \sum\limits_{i=1}^3 \dfrac{G_i}{z_i}\ln\dfrac{C_{i,I}}{C_{i,E}} + I_p^0 + P_m\partial_t(\phi_I-\phi_E)\Big) & \text{in } (0,T)\times\Omega, \\ \sigma_s D_s^\star\nabla\phi_s\cdot\vec{\nu} = 0 & \text{on } (0,T)\times\partial\Omega, \\ (\phi_I-\phi_E)|_{t=0} = \phi^0 & \text{in } \Omega, \end{cases} \tag{48}$$

where "$\pm$" takes "$+$" for $s=E$ and "$-$" for $s=I$. $D_s^\star = \int_{Y_s} D(I_n + \nabla_y\chi_s)\,dy$, $\sigma_s = \sum\limits_{i=1}^3 z_i^2 C_{i,s}$ and $\chi_s = (\chi_s^1, \chi_s^2, \cdots, \chi_s^d), s=I,E$ are the solutions of (53) and (50), P_i^0, I_p^0 have the same meaning as in theorem 4.2. And $C_{i,s}$ are electro-neutral, i.e. $\sum\limits_{i=1}^3 z_i C_{i,s} = 0$ for $s=I,E$. If we further assume $\nabla\phi_s\in L^\infty((0,T)\times\Omega), s=I,E$, then the solution for (47) and (48) is unique.

Proof. The proof of the convergence results (45) and (46) are the same as the proof of the convergence results for $\widetilde{C}_{i,E}^\varepsilon, \widetilde{\phi}_E^\varepsilon$ in Theorem 4.2, so we omit it. Since the status of Ω_I^ε and Ω_E^ε are "equivalent" in "connected-connected" case, we can see that the convergence results are the same for intracellular functions and extracellular functions. The homogenized equations (47) and (48) are different from the results in Theorem 4.2, but the proof are quite similar, so we only give a simplified proof and point out the differences. As the derivation of homogenized equations in Ω_I^ε and Ω_E^ε are the same, we only consider equations in Ω_I^ε.

First consider ϕ_I^ε. Let $\varphi_I = \varepsilon u(x)v_1(x/\varepsilon)w(t)$ in (8b), where $u\in C_0^\infty(\Omega)$, $v_1\in C_{per}^\infty(Y_I)$, $w\in C_0^\infty(0,T)$. By convergence result (45) and (46), we can use similar argument as for (28) to get that, for $\forall\ \Phi_I\in L^2((0,T)\times\Omega; H_{per}^1(Y_I))$,

$$\int_0^T\int_{\Omega\times Y_I}\sigma_I D(\nabla_x\phi_I + \nabla_y\widehat{\phi}_I)\nabla_y\Phi_I\,dxdydt = 0. \tag{49}$$

This result is different from (32) in last subsection, which is due to convergence result (46a) for $s=I$.

From (49) we have the following representation

$$\widehat{\phi}_I = \nabla_x\phi_I\ \cdot\chi_I,$$

where $\chi_I = (\chi_I^1, \chi_I^2, \cdots, \chi_I^d)$, satisfying

$$\begin{cases} -\nabla_y\cdot\big(D\nabla_y(y_j+\chi_I^j)\big) = 0 \text{ in } Y_I, \\ -D\nabla_y(y_j+\chi_I^j)\cdot\vec{n}_1 = 0 \text{ on } \Gamma. \\ \chi_I^j \text{ is } Y-periodic,\ \int_{Y_I}\chi_I^j = 0 \end{cases} \tag{50}$$

Then let $\varphi_I = \varphi_1(t,x)$ in (8b), where $\varphi_1\in C_0^\infty((0,T)\times\Omega)$, from convergence result (45) and (46), by density property, we can pass to the limit for (8b) as $\varepsilon\to 0$

to get

$$\int_0^T\int_\Omega \sigma_I D_I^\star \nabla\phi_I \nabla\Phi_1 \; dxdt$$
$$-\int_0^T\int_{\Omega\times\Gamma}\Big[\sum_{i=1}^3 G_i(\phi_I-\phi_E)+\sum_{i=1}^3\frac{G_i}{z_i}\ln\frac{C_{i,I}}{C_{i,E}}+I_p^0+P_m\partial_t(\phi_I-\phi_E)\Big]\Phi_1\; dxdS_ydt=0,$$

for $\forall\Phi_1\in L^2((0,T);H^1(\Omega))$, where $D_I^\star=\int_{Y_I}D(I_n+\nabla_y\chi_I)\,dy$. The corresponding strong form is

$$\begin{cases}-\nabla\cdot\big(\sigma_I D_I^\star\nabla\phi_I\big)=\\ -\sum_{i=1}^3 G_i(\phi_I-\phi_E)-\sum_{i=1}^3\dfrac{G_i}{z_i}\ln\dfrac{C_{i,I}}{C_{i,E}}-I_p^0-P_m\partial_t(\phi_I-\phi_E) & in\ (0,T)\times\Omega,\\ \sigma_I D_I^\star\nabla\phi_I\cdot\vec{\nu}=0 & on\ (0,T)\times\partial\Omega,\end{cases}\tag{51}$$

which is (48) for $s=I$.

Next we consider $C_{i,I}^\varepsilon$. Let $v_I=\varepsilon u(x)v_1(x/\varepsilon)w(t)$ in (8a), passing to the limit as $\varepsilon\to0$ leads to

$$\int_0^T\int_{\Omega\times Y_I}\Big(D(\nabla C_{i,I}+\nabla_y\widehat{C}_{i,I})+z_iC_{i,I}D(\nabla_x\phi_I+\nabla_y\widehat{\phi}_I)\Big)\nabla_y\Phi_I\; dxdydt=0,$$

for $\forall\ \Phi_I\in L^2((0,T)\times\Omega;H^1_{per}(Y_I))$. This is different from (38) in last subsection, which is due to the convergence result (46a) and (45b) for $s=I$.

According to (49), the second term on the left hand side of the above equation is zero, so we have

$$\widehat{C}_{i,I}=\nabla_x C_{i,I}\ \cdot\chi_I,$$

where χ_I is the solution of (50). Then, let $v_I=\varphi_1(t,x)$ in (8a), passing to the limit as $\varepsilon\to0$ yields

$$\int_0^T\int_\Omega\left(|Y_I|\partial_tC_{i,I}u_1w+D_I^\star\nabla C_{i,I}\nabla u_1w+z_iC_{i,I}D_I^\star\nabla\phi_I\nabla u_1w\right)\;dxdt$$
$$+\int_0^T\int_{\Omega\times\Gamma}\Big(\frac{G_i}{z_i}(\phi_I-\phi_E)+\frac{G_i}{z_i^2}\frac{\ln C_{i,I}}{\ln C_{i,E}}+\frac{P_i^0}{z_i}+\frac{\lambda_i}{z_i}P_m\partial_t(\phi_I-\phi_E)\Big)u_1w\;dxdS_ydt=0.$$

The corresponding strong form is

$$\begin{cases}|Y_I|\partial_tC_{i,I}-\nabla\cdot(D_I^\star\nabla C_{i,I}+z_iC_{i,I}D_I^\star\nabla\phi_I)=\\ -|\Gamma|\Big(\dfrac{G_i}{z_i}(\phi_I-\phi_E)+\dfrac{G_i}{z_i^2}\dfrac{\ln C_{i,I}}{\ln C_{i,E}}+\dfrac{P_i^0}{z_i}+\dfrac{\lambda_i}{z_i}P_m\partial_t(\phi_I-\phi_E)\Big) & in\ (0,T)\times\Omega,\\ -(D_I^\star\nabla C_{i,I}+z_iC_{i,I}D_I^\star\nabla\phi_I)\cdot\vec{\nu}=0 & on\ (0,T)\times\partial\Omega.\end{cases}\tag{52}$$

which is (47) for $s=I$. The initial condition for $C_{i,I}$ can be obtained by similar arguments as in the proof of Theorem 4.2. Summarizing the above results, we have (47), (48). The electro-neutrality condition for $C_{i,s}$ is a result of the electro-neutrality of $C_{i,s}^0$. Uniqueness of the solutions can be argued in the same way as in Theorem 4.2. The theorem is proved. □

Remark 4.5. The derivation of homogenized equations in Ω_E^ε in Theorem 4.4 is omitted, however, an auxiliary problem in Y_E could be given as follow:

$$\begin{cases}-\nabla_y\cdot\big(D\nabla_y(y_j+\chi_E^j)\big)=0\ in\ Y_E,\\ -D\nabla_y(y_j+\chi_E^j)\cdot\vec{n}_1=0\ on\ \Gamma,\\ \chi_E^j\ is\ Y-periodic,\ \int_{Y_E},\chi_E^j=0.\end{cases}\tag{53}$$

where the only difference from (36) is different Y_E due to $Y_I's$ connectivity.

5. **Error estimates for first order expansions.** In this section, we will present the error estimates between $C^\varepsilon_{i,s}, \phi^\varepsilon_s$ and their first order expansions,

$$C^1_{i,s} = C_{i,s} + \varepsilon\chi^k_s \frac{\partial C_{i,s}}{\partial x_k},\ \phi^1_s = \phi_s + \varepsilon\chi^k_s \frac{\partial \phi_s}{\partial x_k},\ s = I, E, \tag{54}$$

where χ_E is the solution of (36) or (53), χ_I is the solution of (43) or (50), for different cases. In (54) and formulas below, we use Einstein summation convention for indices k, p, q.

To achieve this, we need the following regularity assumption $(H1)$ on homogenization problem (47), (48) and (25), (26)

$$(H1)\ \begin{cases} \bullet \text{ concentrations} \\ C_d \le C_{i,s} \le C_u,\ C_{i,s} \in L^2(0,T;H^2(\Omega)),\ \partial_t C_{i,s} \in L^2(0,T;H^1(\Omega)), & (55) \\ \text{for } i = 1,2,3,\ s = I, E. \\ \bullet \text{ electrical potential} \\ \phi_s \in L^2(0,T;H^2(\Omega)), \partial_t\phi_s \in L^2(0,T;H^2(\Omega)), \nabla\phi_s \in L^\infty((0,T)\times\Omega), & (56) \\ \text{for } s = I, E. \end{cases}$$

Since Γ is sufficiently smooth, we have, for $s = I, E$,

$$\chi^k_s \in H^1(Y_s) \text{ and } \chi^k_s \in W^{1,\infty}(Y_s). \tag{57}$$

By Lemma 4.1 in [31], we have the following auxiliary lemma which will be used in the proof of the error estimates.

Lemma 5.1. *For given functions $f, g \in H^1(\Omega)$, which are continuous over the interface Γ_ε, it holds that*

$$\int_{\Omega^\varepsilon_s} fq\ dx - |Y_s| \int_\Omega fq\ dx \le A\varepsilon\|f\|_{H^1(\Omega)}\|g\|_{H^1(\Omega)}. \tag{58}$$

For "connected-connected" case, we have the next theorem.

Theorem 5.2. *Suppose Ω^ε_I is connected. Let $C^\varepsilon_{i,s}, \phi^\varepsilon_s,\ i = 1,2,3, s = I,E$ be solutions of (2), and $C_{i,s}, \phi_s,\ i = 1,2,3, s = I,E$ be the solutions of (47)-(48), and $C^1_{i,s},\ \phi^1_s$ are first order approximations defined in (54). If the assumption $(H1)$ holds, we have, for $i = 1,2,3,\ s = I,E$,*

$$\begin{aligned} & \|C^\varepsilon_{i,s} - C^1_{i,s}\|_{L^\infty(0,T;L^2(\Omega^\varepsilon_s))} + \|[\![\phi^\varepsilon_s - \phi^1_s]\!]\|_{L^\infty(0,T;L^2(\Gamma_\varepsilon))} \\ + \quad & \|C^\varepsilon_{i,s} - C^1_{i,s}\|_{L^2(0,T;H^1(\Omega^\varepsilon_s))} + \|\nabla(\phi^\varepsilon_s - \phi^1_s)\|_{L^2(0,T;L^2(\Omega^\varepsilon_s))} \le A\varepsilon^{\frac{1}{2}}. \end{aligned} \tag{59}$$

Proof. Multiplying (47) and (48) with v_s and $\varphi_s \in H^1(\Omega),\ s = I, E$ yields

$$\begin{aligned} & \int_\Omega |Y_s|\partial_t C_{i,s} v_s\ dx + \int_\Omega D^\star_s \nabla C_{i,s} \nabla v_s\ dx + z_i \int_\Omega C_{i,s} D^\star_s \nabla\phi_s \nabla v_s\ dx \\ & \pm |\Gamma| \int_\Omega \big(\frac{G_i}{z_i}[\![\phi]\!] v_s + \frac{G_i}{z_i^2}[\![\ln C_i]\!] v_s + \frac{P^0_i}{z_i} v_s + \frac{\lambda_i}{z_i} P_m \partial_t [\![\phi]\!] v_s\big)\ dS = 0, \end{aligned} \tag{60a}$$

$$\begin{aligned} & \int_\Omega \sigma_s D^\star_s \nabla\phi_s \nabla\varphi_s\ dx \\ & \pm |\Gamma| \int_\Omega \big(\sum_{k=1}^3 G_k [\![\phi]\!]\varphi_s + \sum_{k=1}^3 \frac{G_k}{z_k}[\![\ln C_k]\!]\varphi_s + I^0_p \varphi_s + P_m \partial_t [\![\phi]\!]\varphi_s\big)\ dS = 0. \end{aligned} \tag{60b}$$

By Lemma 2.3 in [49], $C^\varepsilon_{i,s}, \phi^\varepsilon_s$ from Ω^ε_s can be extended to Ω and satisfy

$$\|C^\varepsilon_{i,s}\|_{H^1(\Omega)} \le A\|C^\varepsilon_{i,s}\|_{H^1(\Omega^\varepsilon_s)},\ \|\phi^\varepsilon_s\|_{H^1(\Omega)} \le A\|\phi^\varepsilon_s\|_{H^1(\Omega^\varepsilon_s)}. \tag{61}$$

For simplicity, set $W^\varepsilon_{i,s} \triangleq C^\varepsilon_{i,s} - C^1_{i,s} = C^\varepsilon_{i,s} - C_{i,s} - \varepsilon\chi^k_s \frac{\partial C_{i,s}}{\partial x_k}$, $M^\varepsilon_s \triangleq \phi^\varepsilon_s - \phi^1_s = \phi^\varepsilon_s - \phi_s - \varepsilon\chi^k_s \frac{\partial \phi_s}{\partial x_k}$. Note that, (10f), (56) and (57) imply $\|M^\varepsilon_s\|_{L^2(\Omega)}$ is bounded. Let $D^\star_I(x) = (d^\star_{pq})_{n\times n}$ and

$(d_{pq})_{n\times n} = \begin{cases} DI_n, & \text{for } x \in \Omega^\varepsilon_I \\ 0, & \text{for } x \in \Omega\backslash\Omega^\varepsilon_I \end{cases}$, then we have

$$\begin{aligned}
&\int_{\Omega^\varepsilon_I} D\nabla W^\varepsilon_{i,I}\nabla W^\varepsilon_{i,I}\ dx \\
=\ & \int_{\Omega^\varepsilon_I} D\nabla\left(C^\varepsilon_{i,I} - C_{i,I} - \varepsilon\chi^k_I \frac{\partial C_{i,I}}{\partial x_k}\right)\nabla W^\varepsilon_{i,I}\ dx \\
=\ & \int_{\Omega^\varepsilon_I} D\nabla C^\varepsilon_{i,I}\nabla W^\varepsilon_{i,I}\ dx - \int_{\Omega^\varepsilon_I} D^\star_I\nabla C_{i,I}\nabla W^\varepsilon_{i,I}\ dx + \int_{\Omega^\varepsilon_I} D^\star_I\nabla C_{i,I}\nabla W^\varepsilon_{i,I}\ dx \\
& - \int_{\Omega^\varepsilon_I} D\nabla C_{i,I}\nabla W^\varepsilon_{i,I}\ dx - \int_{\Omega^\varepsilon_I} D\nabla\left(\varepsilon\chi^k_I\frac{\partial C_{i,I}}{\partial x_k}\right)\nabla W^\varepsilon_{i,I}\ dx \\
=\ & \int_{\Omega^\varepsilon_I} D\nabla C^\varepsilon_{i,I}\nabla W^\varepsilon_{i,I}\ dx - \int_{\Omega^\varepsilon_I} D^\star_I\nabla C_{i,I}\nabla W^\varepsilon_{i,I}\ dx \\
& + \int_{\Omega^\varepsilon_I} G_{pq}(x, x/\varepsilon)\frac{\partial C_{i,I}}{\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx - \int_{\Omega^\varepsilon_I} \varepsilon d_{pq}\chi^k_I\frac{\partial^2 C_{i,I}}{\partial x_k x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx,
\end{aligned} \tag{62}$$

where $G_{pq} = d^\star_{pq} - d_{pq} - d_{pk}\frac{\partial \chi^q_I}{\partial y_k}$. Since $G_{pq} = d^\star_{pq}$ in $\Omega\backslash\Omega^\varepsilon_I$, we have the following identity which plays a key role in our estimates.

$$\begin{aligned}
& -\int_{\Omega^\varepsilon_I} D^\star_I\nabla C_{i,I}\nabla W^\varepsilon_{i,I}\ dx + \int_{\Omega^\varepsilon_I} G_{pq}\frac{\partial C_{i,I}}{\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx \\
=\ & -\int_{\Omega} D^\star_I\nabla C_{i,I}\nabla W^\varepsilon_{i,I}\ dx + \int_{\Omega} G_{pq}\frac{\partial C_{i,I}}{\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx.
\end{aligned} \tag{63}$$

By Lemma 5.1, we get

$$\begin{aligned}
& \int_{\Omega^\varepsilon_I} \partial_t W^\varepsilon_{i,I}\ W^\varepsilon_{i,I}\ dx \\
=\ & \int_{\Omega^\varepsilon_I} \partial_t C^\varepsilon_{i,I} W^\varepsilon_{i,I}\ dx - \int_{\Omega^\varepsilon_I} \partial_t C_{i,I} W^\varepsilon_{i,I}\ dx - \int_{\Omega^\varepsilon_I} \varepsilon\chi^k_I\frac{\partial^2 C_{i,I}}{\partial x_k\partial t} W^\varepsilon_{i,I}\ dx \\
=\ & \int_{\Omega^\varepsilon_I} \partial_t C^\varepsilon_{i,I} W^\varepsilon_{i,I}\ dx - \int_{\Omega} |Y_I|\partial_t C_{i,I} W^\varepsilon_{i,I}\ dx + N_\varepsilon - \int_{\Omega^\varepsilon_I} \varepsilon\chi^k_I\frac{\partial^2 C_{i,I}}{\partial x_k\partial t} W^\varepsilon_{i,I}\ dx,
\end{aligned} \tag{64}$$

where $N_\varepsilon = \int_\Omega |Y_I|\partial_t C_{i,I} W^\varepsilon_{i,I}\ dx - \int_{\Omega^\varepsilon_I} \partial_t C_{i,I} W^\varepsilon_{i,I}\ dx$, and from Lemma 5.1 it yields that

$$N_\varepsilon \le A\varepsilon\|\partial_t C_{i,I}\|_{H^1(\Omega)}\|W^\varepsilon_{i,I}\|_{H^1(\Omega)}. \tag{65}$$

So, from weak forms (8a) and (60a), using (63), we have

$$\begin{aligned}
& \int_{\Omega^\varepsilon_I} \partial_t W^\varepsilon_{i,I}\ W^\varepsilon_{i,I}\ dx + \int_{\Omega^\varepsilon_I} D\nabla W^\varepsilon_{i,I}\nabla W^\varepsilon_{i,I}\ dx \\
=\ & \int_{\Omega^\varepsilon_I} \partial_t C^\varepsilon_{i,I} W^\varepsilon_{i,I}\ dx + \int_{\Omega^\varepsilon_I} D\nabla C^\varepsilon_{i,I}\nabla W^\varepsilon_{i,I}\ dx
\end{aligned}$$

$$
\begin{aligned}
&-\int_\Omega |Y_I|\partial_t C_{i,I} W^\varepsilon_{i,I}\ dx - \int_\Omega D^\star_I \nabla C_{i,I}\nabla W^\varepsilon_{i,I}\ dx + \int_\Omega G_{pq}\frac{\partial C_{i,I}}{\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx \\
&-\int_{\Omega^\varepsilon_I} \varepsilon d_{pq}\chi^k_I \frac{\partial^2 C_{i,I}}{\partial x_k x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx - \int_{\Omega^\varepsilon_I}\varepsilon\chi^k_I\frac{\partial^2 C_{i,I}}{\partial x_k\partial t}W^\varepsilon_{i,I}\ dx + N_\varepsilon \\
= \quad & -z_i\int_{\Omega^\varepsilon_I} C^\varepsilon_{i,I} D\nabla\phi^\varepsilon_I\nabla W^\varepsilon_{i,I}\ dx \\
&-\varepsilon\int_{\Gamma_\varepsilon}\left(\frac{G_i}{z_i}[\![\phi^\varepsilon]\!] + \frac{G_i}{z_i^2}[\![\ln C^\varepsilon_i]\!] + \frac{P^\varepsilon_i}{z_i} + \frac{\lambda_i}{z_i}P_m\partial_t[\![\phi^\varepsilon]\!]\right) W^\varepsilon_{i,I}\ dS \\
&+z_i\int_\Omega C_{i,I}D^\star_I\nabla\phi_I\nabla W^\varepsilon_{i,I}\ dx \\
&+|\Gamma|\int_\Omega\left(\frac{G_i}{z_i}[\![\phi]\!] + \frac{G_i}{z_i^2}[\![\ln C_i]\!] + \frac{P^0_i}{z_i} + \frac{\lambda_i}{z_i}P_m\partial_t[\![\phi]\!]\right) W^\varepsilon_{i,I}\ dx \\
&+\int_\Omega G_{pq}\frac{\partial C_{i,I}}{\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx - \int_{\Omega^\varepsilon_I}\varepsilon d_{pq}\chi^k_I\frac{\partial^2 C_{i,I}}{\partial x_k x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx \\
&-\int_{\Omega^\varepsilon_I}\varepsilon\chi^k_I\frac{\partial^2 C_{i,I}}{\partial x_k\partial t}W^\varepsilon_{i,I}\ dx + N_\varepsilon. \qquad (66)
\end{aligned}
$$

For the coupled terms, it holds that

$$
\begin{aligned}
&\int_{\Omega^\varepsilon_I} C^\varepsilon_{i,I}D\nabla\phi^\varepsilon_I\nabla W^\varepsilon_{i,I}\ dx - \int_\Omega C_{i,I}D^\star_I\nabla\phi_I\nabla W^\varepsilon_{i,I}\ dx \\
= \quad & \int_{\Omega^\varepsilon_I} C^\varepsilon_{i,I}D\nabla M^\varepsilon_I\nabla W^\varepsilon_{i,I}\ dx - \int_\Omega C_{i,I}G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx \\
&+\int_{\Omega^\varepsilon_I}(C^\varepsilon_{i,I} - C_{i,I})D^\star_I\nabla\phi_I\nabla W^\varepsilon_{i,I}\ dx - \int_{\Omega^\varepsilon_I}(C^\varepsilon_{i,I} - C_{i,I})G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx \\
&+\int_{\Omega^\varepsilon_I}\varepsilon C^\varepsilon_{i,I}d_{pq}\chi^k_I\frac{\partial^2\phi_I}{\partial x_k\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx. \qquad (67)
\end{aligned}
$$

Terms with G_{pq} in (66), (67) and in formulas below can be coped with similarly as in [49] to get, for example,

$$
\int_\Omega G_{pq}\frac{\partial C_{i,I}}{\partial x_q}\frac{\partial W^\varepsilon_{i,I}}{\partial x_p}\ dx \le A\varepsilon\left(\|C_{i,s}\|^2_{H^2(\Omega)} + \|\nabla W^\varepsilon_{i,s}\|^2_{\Omega^\varepsilon}\right). \qquad (68)
$$

By weak forms (8b) and (60b), using similar identity to (63), we have

$$
\begin{aligned}
&\int_{\Omega^\varepsilon_I}\sigma^\varepsilon_I D\nabla M^\varepsilon_I\nabla M^\varepsilon_I\ dx \\
= \quad & \int_{\Omega^\varepsilon_I}\sigma^\varepsilon_I D\nabla\phi^\varepsilon_I\nabla M^\varepsilon_I\ dx - \int_{\Omega^\varepsilon_I}\sigma^\varepsilon_I D^\star_I\nabla\phi_I\nabla M^\varepsilon_I\ dx + \int_{\Omega^\varepsilon_I}\sigma^\varepsilon_I G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial M^\varepsilon_I}{\partial x_p}\ dx \\
&-\varepsilon\int_{\Omega^\varepsilon_I}\sigma^\varepsilon_I d_{pq}\chi^k_I\frac{\partial^2\phi_I}{\partial x_k\partial x_q}\frac{\partial M^\varepsilon_I}{\partial x_k\partial x_p}\ dx \\
= \quad & \int_{\Omega^\varepsilon_I}\sigma^\varepsilon_I D\nabla\phi^\varepsilon_I\nabla M^\varepsilon_I\ dx - \int_{\Omega^\varepsilon_I}\sigma_I D^\star_I\nabla\phi_I\nabla M^\varepsilon_I\ dx + \int_{\Omega^\varepsilon_I}\sigma_I G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial M^\varepsilon_I}{\partial x_p}\ dx \\
&-\varepsilon\int_{\Omega^\varepsilon_I}\sigma^\varepsilon_I d_{pq}\chi^k_I\frac{\partial^2\phi_I}{\partial x_k\partial x_q}\frac{\partial M^\varepsilon_I}{\partial x_k\partial x_p}\ dx - \int_{\Omega^\varepsilon_I}(\sigma^\varepsilon_I - \sigma_I)D^\star_I\nabla\phi_I\nabla M^\varepsilon_I\ dx
\end{aligned}
$$

$$
\begin{aligned}
&+\int_{\Omega_I^\varepsilon}(\sigma_I^\varepsilon-\sigma_I)G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial M_I^\varepsilon}{\partial x_p}\ dx\\
=\;&\int_{\Omega_I^\varepsilon}\sigma_I^\varepsilon D\nabla\phi_I^\varepsilon\nabla M_I^\varepsilon\ dx-\int_\Omega\sigma_I D_I^\star\nabla\phi_I\nabla M_I^\varepsilon\ dx+\int_\Omega\sigma_I G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial M_I^\varepsilon}{\partial x_p}\ dx\\
&-\varepsilon\int_{\Omega_I^\varepsilon}\sigma_I^\varepsilon d_{pq}\chi_I^k\frac{\partial^2\phi_I}{\partial x_k\partial x_q}\frac{\partial M_I^\varepsilon}{\partial x_k\partial x_p}\ dx-\int_{\Omega_I^\varepsilon}(\sigma_I^\varepsilon-\sigma_I)D_I^\star\nabla\phi_I\nabla M_I^\varepsilon\ dx\\
&+\int_{\Omega_I^\varepsilon}(\sigma_I^\varepsilon-\sigma_I)G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial M_I^\varepsilon}{\partial x_p}\ dx\\
=\;&-\varepsilon\int_{\Gamma_\varepsilon}\left(\sum_{k=1}^3 G_k[\![\phi^\varepsilon]\!]+\sum_{k=1}^3\frac{G_k}{z_k}[\![\ln C_k^\varepsilon]\!]+I_p^\varepsilon+P_m\partial_t[\![\phi^\varepsilon]\!]\right)M_I^\varepsilon\ dx\\
&+|\Gamma|\int_\Omega\left(\sum_{k=1}^3 G_k[\![\phi]\!]+\sum_{k=1}^3\frac{G_k}{z_k}[\![\ln C_k]\!]+I_p^0+P_m\partial_t[\![\phi]\!]\right)M_I^\varepsilon\ dx\\
&+\int_\Omega\sigma_I G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial M_I^\varepsilon}{\partial x_p}\ dx-\varepsilon\int_{\Omega_I^\varepsilon}\sigma_I^\varepsilon d_{pq}\chi_I^k\frac{\partial^2\phi_I}{\partial x_k\partial x_q}\frac{\partial M_I^\varepsilon}{\partial x_k\partial x_p}\ dx\\
&-\int_{\Omega_I^\varepsilon}(\sigma_I^\varepsilon-\sigma_I)D_I^\star\nabla\phi_I\nabla M_I^\varepsilon\ dx+\int_{\Omega_I^\varepsilon}(\sigma_I^\varepsilon-\sigma_I)G_{pq}\frac{\partial\phi_I}{\partial x_q}\frac{\partial M_I^\varepsilon}{\partial x_p}\ dx. \qquad (69)
\end{aligned}
$$

Terms with $C_{i,I}^\varepsilon-C_{i,I}$ or $\sigma_I^\varepsilon-\sigma_I$ in (67) and (69) can be rewritten, for example, in the following way:

$$
\int_{\Omega_I^\varepsilon}(C_{i,I}^\varepsilon-C_{i,I})D_I^\star\nabla\phi_I\nabla W_{i,I}^\varepsilon\ dx=\int_{\Omega_I^\varepsilon}\left(W_{i,I}^\varepsilon+\varepsilon\chi_I^k\frac{\partial\phi_I}{\partial x_k}\right)D_I^\star\nabla\phi_I\nabla W_{i,I}^\varepsilon\ dx. \qquad (70)
$$

The above derivation process from (62) to (69) can be applied to integrals on Ω_E^ε and the same results can be derived, except that "I"s are replaced by "E"s. Combining these results and (66), (69), while noticing (67) and (70), it follows that

$$
\begin{aligned}
&\int_{\Omega^\varepsilon}\partial_t W_i^\varepsilon\ W_i^\varepsilon+\int_{\Omega^\varepsilon}D\nabla W_i^\varepsilon\nabla W_i^\varepsilon\ dx\\
=&-\int_{\Omega^\varepsilon}C_i^\varepsilon D\nabla M^\varepsilon\nabla W_i^\varepsilon\ dx+J_1^\varepsilon\\
&-\varepsilon\int_{\Gamma_\varepsilon}\left(\frac{G_i}{z_i}[\![\phi^\varepsilon]\!][\![W_i^\varepsilon]\!]+\frac{G_i}{z_i^2}[\![\ln C_i^\varepsilon]\!][\![W_i^\varepsilon]\!]+\frac{P_i^\varepsilon}{z_i}[\![W_i^\varepsilon]\!]+\frac{\lambda_i}{z_i}P_m\partial_t[\![\phi^\varepsilon]\!][\![W_i^\varepsilon]\!]\right)\ dS\\
&+|\Gamma|\int_\Omega\left(\frac{G_i}{z_i}[\![\phi]\!][\![W_i^\varepsilon]\!]+\frac{G_i}{z_i^2}[\![\ln C_i]\!][\![W_i^\varepsilon]\!]+\frac{P_i^0}{z_i}[\![W_i^\varepsilon]\!]+\frac{\lambda_i}{z_i}P_m\partial_t[\![\phi]\!][\![W_i^\varepsilon]\!]\right)\ dx, \qquad (71)
\end{aligned}
$$

and

$$
\begin{aligned}
&\int_{\Omega^\varepsilon}\sigma^\varepsilon D\nabla M^\varepsilon\nabla M^\varepsilon\ dx\\
=&-\varepsilon\int_{\Gamma_\varepsilon}\left(\sum_{k=1}^3 G_k[\![\phi^\varepsilon]\!][\![M^\varepsilon]\!]+\sum_{k=1}^3\frac{G_k}{z_k}[\![\ln C_k^\varepsilon]\!][\![M^\varepsilon]\!]+I_p^\varepsilon[\![M^\varepsilon]\!]+P_m\partial_t[\![\phi^\varepsilon]\!][\![M^\varepsilon]\!]\right)\ dS\\
&+|\Gamma|\int_\Omega\left(\sum_{k=1}^3 G_k[\![\phi]\!][\![M^\varepsilon]\!]+\sum_{k=1}^3\frac{G_k}{z_k}[\![\ln C_k]\!][\![M^\varepsilon]\!]+I_p^0[\![M^\varepsilon]\!]+P_m\partial_t[\![\phi]\!][\![M^\varepsilon]\!]\right)\ dx+J_2^\varepsilon, \qquad (72)
\end{aligned}
$$

where by assumption (55), we have

$$
\begin{aligned}
&J_1^\varepsilon + J_2^\varepsilon \\
\leq &A\varepsilon \sum_{s\in\{I,E\}} \left(\|\partial_t C_{i,s}\|^2_{H^1(\Omega)} + \|C_{i,s}\|^2_{H^2(\Omega)} + \|\phi_s\|^2_{H^2(\Omega)} + \|W^\varepsilon_{i,s}\|^2_{H^1(\Omega^\varepsilon)} + \|\nabla M^\varepsilon_s\|^2_{\Omega^\varepsilon}\right).
\end{aligned} \tag{73}
$$

Consider the interface terms in (72) , firstly rewrite

$$
\begin{aligned}
& -\varepsilon \int_{\Gamma_\varepsilon} [\![\ln C_i^\varepsilon]\!][\![M^\varepsilon]\!] \, dS + |\Gamma| \int_\Omega [\![\ln C_i]\!][\![M^\varepsilon]\!] \, dx \\
= \;& \varepsilon \int_{\Gamma_\varepsilon} \left([\![\ln C_i]\!] - [\![\ln C_i^\varepsilon]\!]\right)[\![M^\varepsilon]\!] \, dS \\
& + \left(|\Gamma| \int_\Omega [\![\ln C_i]\!][\![M^\varepsilon]\!] \, dx - \varepsilon \int_{\Gamma_\varepsilon} [\![\ln C_i]\!][\![M^\varepsilon]\!] \, dS \right) \\
\triangleq \;& I_1 + I_2.
\end{aligned} \tag{74}
$$

For I_1, we have

$$
\begin{aligned}
[\![\ln C_i^\varepsilon]\!] - [\![\ln C_i]\!] &= \xi_1 (C^\varepsilon_{i,I} - C_{i,I}) + \xi_2 (C^\varepsilon_{i,E} - C_{i,E}) \\
&= \xi_1 W^\varepsilon_{i,I} + \xi_2 W^\varepsilon_{i,E} + \varepsilon \xi_1 \chi_I^k \frac{\partial C_{i,I}}{\partial x_k} + \varepsilon \xi_2 \chi_E^k \frac{\partial C_{i,E}}{\partial x_k},
\end{aligned}
$$

so, (55), (57) and (16) implies that

$$
\begin{aligned}
I_1 &= -\varepsilon \int_{\Gamma_\varepsilon} \left(\xi_1 W^\varepsilon_{i,I} + \xi_2 W^\varepsilon_{i,E}\right)[\![M^\varepsilon]\!] \, dS - \varepsilon \int_{\Gamma_\varepsilon} \left(\varepsilon \xi_1 \chi_I^k \frac{\partial C_{i,I}}{\partial x_k} + \varepsilon \xi_2 \chi_E^k \frac{\partial C_{i,E}}{\partial x_k}\right)[\![M^\varepsilon]\!] \, dS \\
&\leq A_1 \varepsilon \sum_{s\in\{I,E\}} \left(\|W^\varepsilon_{i,s}\|^2_{\Gamma_\varepsilon} + \| + \|C_{i,s}\|^2_{H^2(\Omega)} + \|M^\varepsilon_s\|^2_{H^1(\Omega)}\right) + A_2 \varepsilon \|[\![M^\varepsilon]\!]\|^2_{\Gamma_\varepsilon} \\
&\leq A_3 \sum_{s\in\{I,E\}} \left(\delta_1 \|W^\varepsilon_{i,s}\|^2_\Omega + \frac{\varepsilon^2}{\delta_1} \|\nabla W^\varepsilon_{i,s}\|^2_\Omega\right) + A_4 \varepsilon + A_5 \varepsilon \sum_{s\in\{I,E\}} \|\nabla M^\varepsilon_s\|^2_\Omega + A_2 \varepsilon \|[\![M^\varepsilon]\!]\|^2_{\Gamma_\varepsilon}.
\end{aligned} \tag{75}
$$

For I_2, we can apply Lemma 3.4 in [49] to get

$$
\begin{aligned}
I_2 &\leq A_1 \varepsilon \left(\|C_{i,I}\|_{H^1(\Omega)} + \|C_{i,E}\|_{H^1(\Omega)}\right)\left(\|M^\varepsilon_I\|_{H^1(\Omega)} + \|M^\varepsilon_E\|_{H^1(\Omega)}\right) \\
&\leq A_2 \varepsilon + A_3 \varepsilon \left(\|\nabla M^\varepsilon_I\|^2_\Omega + \|\nabla M^\varepsilon_E\|^2_\Omega\right).
\end{aligned} \tag{76}
$$

The integral $-\varepsilon \int_{\Gamma_\varepsilon} I_p^\varepsilon [\![M^\varepsilon]\!] \, dS + |\Gamma| \int_\Omega I_p^0 [\![M^\varepsilon]\!] \, dx$ can be dealt with similarly.
Then consider

$$
\begin{aligned}
& -\varepsilon \int_{\Gamma_\varepsilon} [\![\phi^\varepsilon]\!][\![M^\varepsilon]\!] \, dS + |\Gamma| \int_\Omega [\![\phi]\!][\![M^\varepsilon]\!] \, dx \\
= \;& \varepsilon \int_{\Gamma_\varepsilon} \left([\![\phi]\!] - [\![\phi^\varepsilon]\!]\right)[\![M^\varepsilon]\!] \, dS + \left(|\Gamma| \int_\Omega [\![\phi]\!][\![M^\varepsilon]\!] \, dx - \varepsilon \int_{\Gamma_\varepsilon} [\![\phi]\!][\![M^\varepsilon]\!] \, dS\right) \\
\triangleq \;& Q_1 + Q_2.
\end{aligned} \tag{77}
$$

For Q_2, similar to I_2, we have

$$
Q_2 \leq A_1 \varepsilon + A_2 \varepsilon \left(\|\nabla M^\varepsilon_I\|^2_\Omega + \|\nabla M^\varepsilon_E\|^2_\Omega\right). \tag{78}
$$

Q_1 can be rewritten as

$$
Q_1 = -\varepsilon \int_{\Gamma_\varepsilon} [\![M^\varepsilon]\!]^2 \, dS - \varepsilon^2 \int_{\Gamma_\varepsilon} [\![\chi^k \frac{\partial \phi}{\partial x_k}]\!][\![M^\varepsilon]\!] \, dS. \tag{79}
$$

Next we consider

$$\begin{aligned}
& -\varepsilon \int_{\Gamma_\varepsilon} \partial_t [\![\phi^\varepsilon]\!][\![M^\varepsilon]\!] \; dS + |\Gamma| \int_\Omega \partial_t [\![\phi]\!][\![M^\varepsilon]\!] \; dx \\
= \; & \varepsilon \int_{\Gamma_\varepsilon} \partial_t [\![\phi - \phi^\varepsilon]\!][\![M^\varepsilon]\!] \; dS + \left(|\Gamma| \int_\Omega \partial_t [\![\phi]\!][\![M^\varepsilon]\!] \; dx - \varepsilon \int_{\Gamma_\varepsilon} \partial_t [\![\phi]\!][\![M^\varepsilon]\!] \; dS \right) \\
\triangleq \; & L_1 + L_2 \qquad (80)
\end{aligned}$$

For L_2, similar to I_2, we have

$$L_2 \leq A_1 \varepsilon + A_2 \varepsilon \left(\|\nabla M_I^\varepsilon\|_\Omega^2 + \|\nabla M_E^\varepsilon\|_\Omega^2 \right). \qquad (81)$$

For L_1, we have

$$L_1 \;=\; -\varepsilon \int_{\Gamma_\varepsilon} \partial_t [\![M^\varepsilon]\!][\![M^\varepsilon]\!] \; dS - \varepsilon^2 \int_{\Gamma_\varepsilon} \partial_t [\![\chi^k \frac{\partial \phi}{\partial x_k}]\!][\![M^\varepsilon]\!] \; dS. \qquad (82)$$

The second term on the right hand side of (79) and (82) can be estimated as follow:

$$\begin{aligned}
& -\varepsilon^2 \int_{\Gamma_\varepsilon} [\![\chi^k \frac{\partial \phi}{\partial x_k}]\!][\![M^\varepsilon]\!] \; dS - \varepsilon^2 \int_{\Gamma_\varepsilon} \partial_t [\![\chi^k \frac{\partial \phi}{\partial x_k}]\!][\![M^\varepsilon]\!] \; dS \\
\leq \; & A_1 \varepsilon \left(\|\phi_s\|_{H^2(\Omega)}^2 + \|\partial_t \phi_s\|_{H^2(\Omega)}^2 \right) + A_2 \varepsilon + A_3 \varepsilon \sum_{s \in \{I,E\}} \|\nabla M_s\|_\Omega^2. \qquad (83)
\end{aligned}$$

The interface terms in (71) can be handled similarly. And the coupled term in (71) can be estimated as follow,

$$-\int_{\Omega^\varepsilon} C_i^\varepsilon D \nabla M^\varepsilon \nabla W_i^\varepsilon \; dx \leq A \left(\delta_2 \|\nabla M^\varepsilon\|_{\Omega^\varepsilon} + \frac{1}{\delta_2} \|\nabla W_i^\varepsilon\|_{\Omega^\varepsilon} \right). \qquad (84)$$

Finally, setting δ_2 in (84) big enough and multiplying (72) with a positive constant big enough and adding it to (71), then setting δ_1 in (75) big enough, combining (71) to (84) and using assumptions (55), (56), it follows that

$$\begin{aligned}
& \sum_{i=1}^{3} \left(\partial_t \|W_i\|_{\Omega^\varepsilon}^2 + \|\nabla W_i\|_{\Omega^\varepsilon}^2 \right) + \varepsilon \partial_t \|[\![M^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2 + \|\nabla M^\varepsilon\|_{\Omega^\varepsilon}^2 \\
\leq \; & A_1 \sum_{i=1}^{3} \|W_i\|_{\Omega^\varepsilon}^2 + A_2 \varepsilon \|[\![M^\varepsilon]\!]\|_{\Gamma_\varepsilon}^2 + A_3 \varepsilon,
\end{aligned}$$

then Gronwall inequality gives (59). □

For "connected-disconnected" case, we have the following theorem.

Theorem 5.3. *Suppose Ω_I^ε is disconnected. Let $C_{i,s}^\varepsilon, \phi_s^\varepsilon,\ i = 1,2,3, s = I,E$ be solutions of (2), and $C_{i,s}, \phi_s,\ i = 1,2,3, s = I,E$ be the solutions of (25)-(26). Let $C_{i,s}^1, \phi_s^1$ be first order approximations defined in (54). If the assumption $(H1)$ holds, then we have, for $s = I,E$,*

$$\begin{aligned}
& \|C_{i,s}^\varepsilon - C_{i,s}^1\|_{L^\infty(0,T;L^2(\Omega_s^\varepsilon))} + \|[\![\phi_s^\varepsilon - \phi_s^1]\!]\|_{L^\infty(0,T;L^2(\Gamma_\varepsilon))} \\
+ \; & \|C_{i,s}^\varepsilon - C_{i,s}^1\|_{L^2(0,T;H^1(\Omega_s^\varepsilon))} + \|\nabla(\phi_s^\varepsilon - \phi_s^1)\|_{L^2(0,T;L^2(\Omega_s^\varepsilon))} \leq A \varepsilon^{\frac{1}{2}}. \qquad (85)
\end{aligned}$$

Proof of Theorem 5.3 is quite similar to the proof of Theorem 5.2, the only thing to note is that, when we consider the integrals in Ω_I^ε, $G_{pq}, D_I^\star$ are zero.

6. **Conclusion.** In this paper, we propose a micro-scale electro-neutral (EN) bidomain model to simulate ion transport in tissues. Our model takes into account the passive currents induced by ion channels, active currents induced by pumps, and currents induced by the membrane's capacitance property. We rigorously derive the homogenization theory for the nonlinear coupled system using the unfolding operator and two-scale convergence method. Different connectivity conditions for the intracellular region Ω_I^ε lead to different homogenized equations. If both the intracellular and extracellular regions are connected to form a syncytium, the obtained system is a diffusion-convection-reaction system. On the other hand, if the intracellular region is disconnected, the macroscale effective equation for the intracellular region is only a reaction equation. In this case, the intracellular region could communicate indirectly through the connected extracellular space. We carefully analyze the error between the microscale solutions and homogenized solutions. Our macroscale model can be used to study diseases induced by ion micro-circulation disorders, such as spreading depression [9] and lens problems [50].

Appendix A. **Unfolding operator.** We present in this supplementary material some homogenization theory and results about unfolding operator.

Let ω be an open set in $\mathbb{R}^d$, and $Y=(0,1)^d$.

Unfolding operator was first constructed in [4] and further studied in detail in [11, 12]. Let Γ be a (n-1)-dimensional Lipschitz manifold, compactly included in Y, and $\Gamma_\varepsilon=\bigcup_{k\in\mathbb{Z}^n}\varepsilon(\Gamma+k),\ \Gamma_\varepsilon\subset\omega$. Denote $[x]$ as the largest integer not greater than x, and let $\{x\}:=x-[x]$, then we have $[x]\in\mathbb{Z}^n,\ \{x\}\in\overline{Y}$. Let $Y^*\subset Y$ and ω_ε be the internal of $\omega\cap\bigcup_{k\in\mathbb{Z}^n}\varepsilon(k+\overline{Y^*})$.

Definition A.1. (i) Let $u_\varepsilon\in L^2((0,T)\times\omega)$, unfolding operator $\mathcal{T}^\varepsilon: L^2((0,T)\times\omega)\to L^2((0,T)\times\omega\times Y)$ is defined by

$$\left(\mathcal{T}^\varepsilon u_\varepsilon\right)(t,x,y):=u_\varepsilon\left(t,\varepsilon\left(\left[\frac{x}{\varepsilon}\right]+y\right)\right).$$

(ii) Similarly, unfolding operator in ω_ε is defined by $\mathcal{T}^\varepsilon: L^2\left((0,T)\times\omega_\varepsilon\right)\to L^2((0,T)\times\omega\times Y^*)$, and unfolding operator on Γ_ε is defined by $\mathcal{T}_b^\varepsilon: L^2((0,T)\times\Gamma_\varepsilon)\to L^2((0,T)\times\omega\times\Gamma)$ on Γ_ε.

From the above definition it is clear that $\mathcal{T}^\varepsilon$ and $\mathcal{T}_b^\varepsilon$ are bounded linear operators. Some properties of unfolding operator are given in the following lemma[11, 12, 15].

Lemma A.2. *(i) Let $u_\varepsilon,v_\varepsilon\in L^2\left((0,T)\times\omega_\varepsilon\right)$, then we have*

$$\left(\mathcal{T}^\varepsilon u_\varepsilon,\mathcal{T}^\varepsilon v_\varepsilon\right)_{L^2((0,T)\times\Omega\times Y^\star)}=\left(u_\varepsilon,v_\varepsilon\right)_{L^2((0,T)\times\omega_\varepsilon)},$$

and for $u_\varepsilon\in L^2\left((0,T),H^1\left(\omega_\varepsilon\right)\right)$ we have $\nabla_y\mathcal{T}^\varepsilon u_\varepsilon=\varepsilon\mathcal{T}^\varepsilon\left(\nabla_x u_\varepsilon\right)$.
(ii) Let $u_\varepsilon,v_\varepsilon\in L^2\left((0,T)\times\Gamma_\varepsilon\right)$, then we have

$$\left(\mathcal{T}_b^\varepsilon u_\varepsilon,\mathcal{T}_b^\varepsilon v_\varepsilon\right)_{L^2((0,T)\times\Omega\times\Gamma)}=\varepsilon\left(u_\varepsilon,v_\varepsilon\right)_{L^2((0,T)\times\Gamma_\varepsilon)},$$
$$\left\|\mathcal{T}_b^\varepsilon u_\varepsilon\right\|_{L^2((0,T)\times\Omega\times\Gamma)}=\sqrt{\varepsilon}\left\|u_\varepsilon\right\|_{L^2((0,T)\times\Gamma_\varepsilon)},$$

where $(\cdot,\cdot)_{L^2(G)}$ is the inner product of $L^2(G)$ for an arbitrary measurable set G. For the unfolding operator in ω_ε, we have the following strong convergence result[48].

Lemma A.3. *Let $\mathcal{T}^\varepsilon : L^2\left((0,T)\times\omega_\varepsilon\right) \to L^2\left((0,T)\times\omega\times Y^*\right)$ and $u \in L^2\left((0,T)\times\omega\right)$, then we have*

$$\mathcal{T}^\varepsilon(u) \to u \text{ strongly in } L^2\left((0,T)\times\omega\times Y^*\right).$$

We also state a lemma which is used in the proof of the a priori estimate (10).

Lemma A.4. *Let $\phi_s^\varepsilon, s = I, E$ be the solutions of (3.1), if $\int_{\Omega_E^\varepsilon} \phi_E^\varepsilon = 0$, then we have*

$$\int_0^T \left(\|\phi_I^\varepsilon\|^2_{\Omega_I^\varepsilon} + \|\phi_E^\varepsilon\|^2_{\Omega_E^\varepsilon}\right) dt \le A \int_0^T \left(\|\nabla\phi_I^\varepsilon\|^2_{\Omega_I^\varepsilon} + \|\nabla\phi_E^\varepsilon\|^2_{\Omega_E^\varepsilon} + \varepsilon\|[\![\phi^\varepsilon]\!]\|^2_{\Gamma^\varepsilon}\right) dt \quad (86)$$

Proof. Using poincaré inequality for functions with zero mean[39, 40], we can prove (86) along the same line as the proof of Lemma 2.8 in [33]. □

Appendix B. Proof of Theorem 3.1.

Proof. Schaefer's fixed point theorem is applied to prove the existence of weak solution. Let $X = L^2(0,T;\ H^\alpha(\Omega_I^\varepsilon))^3 \times L^2(0,T;\ H^\alpha(\Omega_E^\varepsilon))^3$ with $\alpha \in (1/2, 1)$, we introduce a fixed point operator $\mathcal{F} : X \to X$. Let $(\overline{C}_I, \overline{C}_E) \in X$ with $\overline{C}_I = (\overline{C}_{1,I}, \overline{C}_{2,I}, \overline{C}_{3,I})$, $\overline{C}_E = (\overline{C}_{1,E}, \overline{C}_{2,E}, \overline{C}_{3,E})$. Let $\overline{\phi}_s$, $C_s = (C_{1,s}, C_{2,s}, C_{3,s}), s = I, E$ be the unique solution of the following system:

$$\begin{aligned}
&\int_{\Omega_s^\varepsilon} \partial_t C_{i,s} v_s\ dx + \int_{\Omega_s^\varepsilon} D\nabla C_{i,s}\nabla v_s\ dx + z_i \int_{\Omega_s^\varepsilon} \overline{C}_{i,s} D\nabla\overline{\phi}_s \nabla v_s\ dx \\
&\pm \varepsilon \int_{\Gamma_\varepsilon} \Big(\frac{G_i}{z_i}[\![\overline{\phi}]\!] v_s + \frac{G_i}{z_i^2}[\![\ln\overline{C}_i]\!] v_s + \frac{\overline{P}_i}{z_i} v_s + \frac{\lambda_i}{z_i} P_m \partial_t [\![\overline{\phi}]\!] v_s\Big)\ dS = 0, \qquad (87a)\\
&\int_{\Omega_s^\varepsilon} \overline{\sigma}_s D\nabla\overline{\phi}_s \nabla\varphi_s\ dx \\
&\pm \varepsilon \int_{\Gamma_\varepsilon} \Big(\sum_{k=1}^3 G_k [\![\overline{\phi}]\!]\varphi_s + \sum_{k=1}^3 \frac{G_k}{z_k}[\![\ln\overline{C}_k]\!]\varphi_s + \overline{I}_p\varphi_s + P_m\partial_t[\![\overline{\phi}]\!]\varphi_s\Big)\ dS = 0, \qquad (87b)
\end{aligned}$$

where $\overline{P}_i, \overline{\sigma}_s, \overline{I}_p$ have the same form as $P_i^\varepsilon, \sigma_s^\varepsilon, I_p^\varepsilon$, except $C_{i,s}^\varepsilon$ are replaced by $\overline{C}_{i,s}$. System (87) is a linearization of system (3.1) and we can first solve (87b) to get $\overline{\phi}_s$ and then plug $\overline{\phi}_s$ in (87a) to get $\overline{C}_{i,s}$.

Define: $\mathcal{F}(\overline{C}_I, \overline{C}_E) \to (C_I, C_E)$. By similar argument as in Theorem 3.2 it can be proved that $\overline{\phi}_s \in L^2(0,T;\ H^1(\Omega_s^\varepsilon))$ and $C_{i,s} \in W$, where $W = \{(u_I, u_E) \in X :\ u_s \in L^2(0,T;H^1(\Omega_s^\varepsilon))^3, \partial_t u_s \in L^2(0,T;H^{-1}(\Omega_s^\varepsilon))^3,\ s = I, E\}$, so the set $\{u \in X : u = \lambda\mathcal{F}(u)\ for\ some\ \lambda \in [0,1]\}$ is bounded in X. Also note that the embedding $W \hookrightarrow X$ is compact, so $\mathcal{F}$ is continuous and compact. Schaefer's fixed point theorem ensures the existence of a weak solution.

For uniqueness, suppose there are two solutions: $(C_{i,s}^{(m)}, \phi_s^{(m)})$, $m = 1, 2$, with the same initial condition. The difference between the two solutions are denoted by $\widetilde{C}_{i,s} = C_{i,s}^{(1)} - C_{i,s}^{(2)}$ and $\widetilde{\phi}_s = \phi_s^{(1)} - \phi_s^{(2)}$. Plugging the two solutions in the weak form (3.1), setting test functions $v_s = \widetilde{C}_{i,s}$, $\varphi_s = \widetilde{\phi}_s$, and consider the difference between them, we have

$$\begin{aligned}
&\int_{\Omega_s^\varepsilon} \partial_t\widetilde{C}_{i,s}\widetilde{C}_{i,s}\ dx + \int_{\Omega_s^\varepsilon} D\nabla\widetilde{C}_{i,s}\nabla\widetilde{C}_{i,s}\ dx + z_i\int_{\Omega_s^\varepsilon}\Big(C_{i,s}^{(1)} D\nabla\widetilde{\phi}_s\nabla\widetilde{C}_{i,s}\ dx + \widetilde{C}_{i,s} D\nabla\phi_s^{(2)}\nabla\widetilde{C}_{i,s}\Big)\,dx \\
&\pm \varepsilon\int_{\Gamma_\varepsilon}\Big(\frac{G_i}{z_i}[\![\widetilde{\phi}]\!]\widetilde{C}_{i,s} + \frac{G_i}{z_i^2}([\![\ln C_i^{(1)}]\!] - [\![\ln C_i^{(2)}]\!])\widetilde{C}_{i,s} + \frac{P_i^{(1)} - P_i^{(2)}}{z_i}\widetilde{C}_{i,s} + \frac{\lambda_i}{z_i} P_m\partial_t[\![\widetilde{\phi}]\!]\widetilde{C}_{i,s}\Big)\ dS = 0,
\end{aligned}$$

(88a)

$$\int_{\Omega_s^\varepsilon} \sigma_s^{(1)} D\nabla\widetilde{\phi}_s\nabla\widetilde{\phi}_s \; dx + \int_{\Omega_s^\varepsilon} \widetilde{\sigma}_s D\nabla\phi_s^{(2)}\nabla\widetilde{\phi}_s \; dx$$
$$\pm\, \varepsilon \int_{\Gamma_\varepsilon} \Big(\sum_{k=1}^{3} G_k [\![\widetilde{\phi}_s]\!]\widetilde{\phi}_s + \sum_{k=1}^{3} \frac{G_k}{z_k}([\![\ln C_i^{(1)}]\!] - [\![\ln C_i^{(2)}]\!])\widetilde{\phi}_s + (I_p^{(1)} - I_p^{(2)})\widetilde{\phi}_s + P_m \partial_t [\![\widetilde{\phi}_s]\!]\widetilde{\phi}_s \Big) \; dS = 0, \tag{88b}$$

For nonlinear terms on the interface Γ_ε, we have

$$[\![\ln C_i^{(1)}]\!] - [\![\ln C_i^{(2)}]\!] = \xi_1 \widetilde{C}_{i,I} - \xi_2 \widetilde{C}_{i,E},$$

ξ_1, ξ_2 are bounded according to (2.6) And it is obvious that

$$|I_p^{(1)} - I_p^{(2)}| \le A_1 |C_{1,I}^{(1)} - C_{1,I}^{(2)}| + A_2 |C_{2,E}^{(1)} - C_{2,E}^{(2)}| = A_1 |\widetilde{C}_{1,I}| + A_2 |\widetilde{C}_{2,E}|$$

Under assumption (2.6), (2.7) and (3.2), by similar argument as in Theorem 3.2 it can be proved that

$$\sum_{i=1}^{3} \Big(\partial_t \|\widetilde{C}_i\|_{\Omega^\varepsilon}^2 + \|\nabla\widetilde{C}_i\|_{\Omega^\varepsilon}^2 \Big) + \varepsilon\partial_t \|[\![\widetilde{\phi}]\!]\|_{\Gamma^\varepsilon}^2 + \|\nabla\widetilde{\phi}\|_{\Omega^\varepsilon}^2 \le A_1 \sum_{i=1}^{3} \|\widetilde{C}_i\|_{\Omega^\varepsilon}^2 + A_2 \varepsilon \|[\![\widetilde{\phi}]\!]\|_{\Gamma^\varepsilon}^2$$

As the initial value of $\|\widetilde{C}_i\|_{\Omega^\varepsilon}^2$ and $\|[\![\widetilde{\phi}]\!]\|_{\Gamma^\varepsilon}^2$ are zero, then Gronwall inequality imply that

$$\widetilde{C}_i \equiv 0, \;\; \widetilde{\phi} \equiv 0. \tag{89}$$

The uniqueness of solution is proved. □

Acknowledgments. This work was partially supported by the National Natural Science Foundation of China (12071190, 11971342, 12231004), Science and Technology Plan Project of Jiangxi Provincial Education Department (GJJ211027), Natural Science Foundation of Guangdong Province of China (2023A1515010803), the Fundamental Research Funds for the Central Universities (2042021kf0050) and NSERC (CA) (RGPIN-2016-05306). The first author is grateful to the financial support by China Scholarship Council (CSC) during his visit to York University in Toronto, where this work is partially done.

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Received October 2022; revised March 2023; early access April 2023.