Cell Electropermeabilization Modeling via Multiple Traces Formulation and Time Semi-Implicit Coupling

Isabel A. Martínez Ávila^{*}

Carlos Jerez-Hanckes[†]

Irina Pettersson[‡]

March 29, 2024

Abstract

We simulate the electrical response of multiple disjoint biological 3D cells in the electropermeabilization process. Instead of solving the boundary value problem in the volume, we reduce it to a system of boundary integrals equations with nonlinear dynamics on the cell membranes via a coupling the local Multiple Traces Formulation with a time semi-implicit scheme. Spatially, boundary unknowns are approximated by spherical harmonics, thereby allowing for spectral convergence rates for suitable time steps. Numerical results are provided to validate our claims.

Key words: Electropermeabilization, Electroporation, Multiple Traces Formulation, Boundary integral equations, Transmembrane potential.

MSC codes: 65M38, 65R20, 65Z05

1 Introduction

Electropermeabilization designates the use of short high voltage or electric field pulses to increase the permeability of the cell membrane and its potential to allow the access of non-permeant molecules [19, 25]. This technique is used to deliver therapeutic molecules such as drugs and genes into cells to treat cancer, perform genetic engineering, screen drugs, among others applications (cf. [18]).

Theoretically, several models have been proposed to describe the reversible membrane electropermeabilization mechanism without rigorous proof. For instance, during electropermeabilization it is thought that aqueous pores are formed along the cell membrane—electroporation—thereby increasing the permeability of the membrane. Yet, this has not been experimentally observed to occur for voltages used in practice. The pores are either too small to be seen by optical microscopy and too fragile for electron imaging. Only molecular dynamics' simulations have been able to provide demonstrate pore formation (cf. [19, Section 3], [3, Section 2.1]). Moreover, the application of external electric pulses triggers other physical and chemical cell mechanisms, many of them not fully understood due to complex interactions at multiple length scales: from nanometers at the cell membrane to centimeters in tissues [19]. "Therefore, while the term electroporation is commonly

^{*}Pontificia Universidad Católica de Chile, Santiago, Chile.

[†]Facultad de Ingeniería y Ciencias, Universidad Adolfo Ibáñez, Santiago, Chile.

[‡]Chalmers University of Technology and Gothenburg University, Sweden.

used among biologists, the term electropermeabilization should be preferred in order to prevent any molecular description of the phenomenon" [25].

Still, mathematical models and numerical methods can lead to a better understanding of the different underlying phenomena. For instance, Neu and Krassowska [22] consider a pure electroporation process by modeling the nanoscale phenomena involved in the creation and resealing of the cell membrane pores, and apply homogenization theory to derive nonlinear-in-time dynamics. Well-posedness of the Neu-Krassowska model and a new one including anisotropies are derived in [2]. Alternatively, in [17] the authors propose a phenomenological model that forgoes the ab initio understanding of the mechanisms involved. A more complete phenomenological model splits in the electroporation process into two different stages: conducting and permeable [20]. This model also takes into account the diffusion and electric transport of non-permeable molecules. In [10, 21], the authors discard particle diffusion and transport in [20] to then apply the Voronoi Interface Method [9] for its numerical approximation. Specifically, they construct a Voronoi mesh of the volume coupled to a ghost fluid method to capture discontinuous boundary conditions. Further computational enhancements via parallelization are given in [21].

Instead of solving the volume boundary value problem, we recast the problem onto cell membranes via the local Multiple Traces Formulation (MTF) [13, 4, 14, 5, 16]. Originally introduced to solve acoustic wave transmission problems in heterogeneous scatterers, the local MTF considers independent trace unknowns at either side of the subdomains' boundaries to then enforce continuity conditions weakly via Calderón identities. In [12, 11] the method was successfully applied to model the electrical behavior of peripheral neurons by coupling the Laplace boundary integral operators with Hodgkin-Huxley nonlinear dynamics. The volume Laplace equations in intra- and extracellular media arises when assuming a quasi-static electromagnetic regime and one can show that for 2D and 3D the model is well posed. Numerically, the authors prove stability and convergence of time semi-implicit discretizations with low- and high (spectral) order spatial boundary unknown representations. Moreover, the numerical method proposed can be extended to model other nonlinear dynamics.

Following [12, 11], we employ the above boundary integral equations to simulate the electric potential response of multiple disjoint cells in three dimensions when subject to electric pulses. Spatially, the boundary unknowns will be approximated by spherical harmonics, thereby allowing for spectral convergence rates. The nonlinear dynamics of the cell membrane follow [17] which are solved by a semi-implicit scheme. The rest of the paper is organized as follows. In Section 2 we formulate the problem and the corresponding non-linear dynamic model, and derive MTF. In Section 3, we present a numerical scheme for spatial and time-domain discretizations, as well as discuss advantages and limitations of the proposed method. Computational results are provided in Section 4. Code validation experiments with analytic and overkill solutions confirm our theoretical results and open new avenues of research.

2 Problem Statement and Boundary Integral Formulation

2.1 Dirichlet and Neumann traces

In what follows we will need the notion of Dirichlet and Neumann traces, which we introduce below. Let $\Omega \subset \mathbb{R}^d$, d = 1, 2, 3, be an open non-empty domain with a Lipschitz boundary Γ . For



Figure 1: A system of three cells $\mathcal{N} = 3$.

 $u \in C^{\infty}(\overline{\Omega})$, Dirichlet and Neumann traces operators are defined as

$$\gamma_D u := u|_{\Gamma}, \qquad \gamma_N u := \nabla u|_{\Gamma} \cdot \widehat{\mathbf{n}}$$

where $\hat{\mathbf{n}}$ is the exterior unit normal. For a Lipschitz Γ , the Dirichlet trace has a unique extension to a linear and continuous operator $\gamma_D : H^1_{loc}(\Omega) \to L^2(\Gamma)$. The image of this operator is dense and is denoted by $H^{\frac{1}{2}}(\Gamma)$. The norm is given by $\|v\|_{H^{\frac{1}{2}}(\Gamma)} := \{\|u\|_{H^1(\Omega)} : \gamma_D u = v\}$. The space of bounded linear functionals on $H^{\frac{1}{2}}(\Gamma)$ is denoted by $H^{-\frac{1}{2}}(\Gamma)$. One can also show that the Neumann trace operator $\gamma_N : H^1_{loc}(\Delta, \Omega) \to H^{-\frac{1}{2}}(\Gamma)$ is continuous (see [26, Section 2.6 to 2.8]). $H^{\frac{1}{2}}(\Gamma)$ and $H^{-\frac{1}{2}}(\Gamma)$ are referred to as Dirichlet and Neumann trace spaces, respectively [26, Sections 2.4, 2.6 and 2.7].

2.2 Cell Electropermeabilization Model

We now present a continuous model used for the electropermeabilization process. Specifically, we assume a quasi-static electromagnetic problem in the intra- and extracellular domains coupled with non-linear dynamics at the cells' membranes. This coupling relies on enforcing adequate transmission conditions for potentials and currents across the cells. By a quasi-static regime, we imply that the frequency of the electric fields is low enough to discard any time delay in electromagnetic wave propagation [24].

We consider the electric interaction of $\mathcal{N} \in \mathbb{N}$ disjoint spherical cells located at $\mathbf{p}_{\mathbf{j}} \in \mathbb{R}^3$ with radii $R_j \in \mathbb{R}^+, j \in \{1, ..., \mathcal{N}\}$. We define the interior space of the *j*th cell by $\Omega_j := \{\mathbf{x} \in \mathbb{R}^3 : \|\mathbf{x} - \mathbf{p}_{\mathbf{j}}\|_2 < R_j\}$, with its membrane being the boundary $\Gamma_j := \partial \Omega_j = \{\mathbf{x} \in \mathbb{R}^3 : \|\mathbf{x} - \mathbf{p}_{\mathbf{j}}\|_2 = R_j\}$. The extracellular medium is defined as the complement to the intracellular domain: $\Omega_0 := \mathbb{R}^3 \setminus \bigcup_{j=1}^{\mathcal{N}} \overline{\Omega}_j$. An illustration for three cells is presented in Figure 1.

For $j \in \{0, ..., N\}$, each cell Ω_j is assumed to have constant conductivity $\sigma_j \in \mathbb{R}^+$. For $T \in \mathbb{R}^+$, let $\phi_e : [0, T] \times \Omega_0 \to \mathbb{R}$ be a given external potential. Let $u_0 : [0, T] \times \Omega_0 \to \mathbb{R}$ be the electric potential without excitation in the extracellular medium, so that total external potential is $u_0^{tot} := u_0 + \phi_e$. We denote by $u_j : [0, T] \times \Omega_j \to \mathbb{R}, \ j \in \{1, ..., \mathcal{N}\}$, the electric potential inside the *j*th cell, as in Figure 1.

On cell membranes Γ_j the potential is discontinuous, the difference $v_j := u_j - u_0$ is called the *membrane or transmembrane* potential and the flux is assumed to be continuous. Thus, our boundary value problem becomes¹

$$\begin{aligned} \operatorname{div} \left(\sigma_{j} \nabla u_{j} \right) &= 0, & (t, \mathbf{x}) \in [0, T] \times \Omega_{j}, \ j \in \{0, ..., \mathcal{N}\}, \\ -\gamma_{D}^{0j} u_{0} + \gamma_{D}^{j} u_{j} &= v_{j} + \gamma_{D}^{0j} \phi_{e}, & (t, \mathbf{x}) \in [0, T] \times \Gamma_{j}, \ j \in \{1, ..., \mathcal{N}\}, \\ \sigma_{0} \gamma_{N}^{0j} u_{0} + \sigma_{j} \gamma_{N}^{j} u_{j} &= -\sigma_{0} \gamma_{N}^{0j} \phi_{e}, & (t, \mathbf{x}) \in [0, T] \times \Gamma_{j}, \ j \in \{1, ..., \mathcal{N}\}. \end{aligned}$$

For the electro-permeabilization process, we adopt the phenomenological model presented in [17]. Specifically, at each cell $j \in \{1, ..., N\}$, one has

$$\begin{aligned} c_{m,j}\partial_{t}v_{j} + I_{j}^{ep}(v_{j}, Z_{j}) &= -\sigma_{j}\gamma_{N}^{j}u_{j} & \text{on } [0,T] \times \Gamma_{j}, \\ I_{j}^{ep}(v_{j}, Z_{j}) &= v_{j}(S_{L,j} + Z_{j}(t, v_{j}(t, \mathbf{x}))(S_{ir,j} - S_{L,j})) & \text{on } [0,T] \times \Gamma_{j}, \end{aligned}$$

with $c_{m,j}$ denoting the membrane capacitance per unit area, and I_j^{ep} being the electropermeabilization current. This last quantity depends on the transmembrane potential v_j and a C^1 -function $Z_j : [0,T] \times \Gamma_j \to [0,1]$ (cf. [17, Lemma 7]). For brevity, and slightly abusing the notations, we write $Z_j(t, \mathbf{x})$ instead of $Z_j(t, v_j(t, \mathbf{x}))$. The variable $Z_j(t, \mathbf{x})$ "measures in some way the likelihood that a given infinitesimal portion of the membrane is going to be electropermeabilized" [17, p 247]. Specifically, Z_j enforces the surface membrane conductivity to take values between two parameters: the surface conductivity $S_{L,j}$. Indeed, when $Z_j = 0$, the membrane conductivity equals the lipid conductivity, and there is no electropermeabilization; if $Z_j = 1$, the membrane conductivity ity takes the maximal value above which electropermeabilization is irreversible. Following [17], Z_j satisfies the ordinary differential equation:

$$\frac{\partial}{\partial t}Z_{j}(t,\lambda) = \max\left(\frac{\beta_{j}(\lambda) - Z_{j}(t,\lambda)}{\tau_{ep,j}}, \frac{\beta_{j}(\lambda) - Z_{j}(t,\lambda)}{\tau_{res,j}}\right)$$

Here, $\beta_j \in W^{1,\infty}(\mathbb{R};[0,1]) = \{u \in L^{\infty}(\Omega) : D^{\alpha}u \in L^{\infty}(\Omega), |\alpha| \leq 1\}$. If $\beta_j(v_j) - Z_j(t,v_j)$ is positive, the electric pulse is sufficiently intense to enlarge the electropermeabilized region with a characteristic time $\tau_{ep,j}$. Contrarily, if $\beta_j(v_j) - Z_j(t,v_j)$ is negative, the pulse is not strong enough to allow electropermeabilization and the membrane returns to its resting state, with a characteristic resealing time $\tau_{res,j}$. Experimental observations suggest that $\tau_{res,j} > \tau_{ep,j}$.

In general [17], one can use any function β_j such that $\beta_j \in W^{1,\infty}(\mathbb{R}), v\beta'_j(v) \in L^{\infty}(\mathbb{R}), \beta_j$ is non decreasing in $(0,\infty), 0 \leq \beta_j(v) \leq 1$, $\lim_{v\to\infty} \beta_j(v) = 1$. In our case, we set β_j as

$$\beta_j(v) := \frac{1 + \tanh(k_{ep,j}(|v| - V_{rev,j}))}{2},\tag{1}$$

wherein two additional parameters are introduced: the electropermeabilization switch speed $k_{ep,j}$ between $S_{ir,j}$ and $S_{L,j}$, and $V_{rev,j}$, the transmembrane potential threshold for electropermeabilization to occur. The chosen β_j (1) satisfies the above conditions. This can be checked by recalling the properties of the hyperbolic functions $\tanh : \mathbb{R} \to [-1, 1]$ and $\operatorname{sech} : \mathbb{R} \to [0, 1]$. We will assume that the threshold potential V_{rev} is constant throughout the electropermeabilization process.

In summary, the full electropermeabilization dynamic problem reads:

¹Observe that the Dirichlet and Neumann operators only act in the spatial variable **x**. For a collection of spheres, we have added super-indices to emphasize where the traces are taken from: 0j for the trace arising from Ω_0 onto Γ_j , and j for the one from Ω_j to Γ_j .

Problem 2.1. Given $T \in \mathbb{R}^+$, an external potential $\phi_e \in C([0,T], H^1_{loc}(\Omega_0))$, and the initial conditions $u_j^0 \in H^1(\Omega_j)$, and $Z_j^0 \in H^{\frac{1}{2}}(\Gamma_j)$, for $j = 1, \ldots, \mathcal{N}$, we seek $u_j \in C([0,T], H^1(\Omega_j))$, $v_j \in C([0,T], H^{\frac{1}{2}}(\Gamma_j))$, and $Z_j \in C([0,T], H^{\frac{1}{2}}(\Gamma_j))$ for $j \in \{1, \ldots, \mathcal{N}\}$ such that for $t \in [0,T]$, the following holds

$$\operatorname{div}\left(\sigma_{0}\nabla u_{0}\right) = 0 \qquad \qquad in \ \Omega_{0}, \qquad (2a)$$
$$\operatorname{div}\left(\sigma_{0}\nabla u_{0}\right) = 0 \qquad \qquad in \ \Omega_{0}, \qquad (2b)$$

$$-\gamma_{0j}^{oj}u_0 + \gamma_{j}^{o}u_i = v_i + \gamma_{0j}^{oj}\phi_c \qquad \qquad on\ \Gamma_i. \tag{2c}$$

$$c_{m,j}\partial_t v_j + I_j^{ep}(v_j, Z_j) = -\sigma_j \gamma_N^j u_j \qquad \qquad on \ \Gamma_j, \tag{2e}$$

$$u_j(0, \mathbf{x}) = u_j^0, \ Z_j(0, \mathbf{x}) = Z_j^0 \qquad \qquad in \ \Omega_j \tag{2f}$$

$$u_0(0, \mathbf{x}) = u_0^0 \qquad \qquad in \ \Omega_0, \tag{2g}$$

$$u_0 \to \mathcal{O}(\|\mathbf{x}\|_2^{-1}) \qquad \qquad as \ \|\mathbf{x}\|_2 \to \infty, \tag{2h}$$

with I_j^{ep} defined as:

$$I_j^{ep}(v_j, Z_j) := v_j \left(S_{L,j} + Z_j(t, v_j) (S_{ir,j} - S_{L,j}) \right),$$
(3)

where the $Z_j(t,\lambda)$ satisfy:

$$\frac{\partial}{\partial t}Z_j(t,\lambda) = \max\left(\frac{\beta_j(\lambda) - Z_j(t,\lambda)}{\tau_{ep,j}}, \frac{\beta_j(\lambda) - Z_j(t,\lambda)}{\tau_{res,j}}\right)$$
(4)

with β_j given by (1) and parameters $\tau_{ep,j}, \tau_{res,j}$ described above.

As above, we write $Z_j(x, \mathbf{x}) = Z_j(t, v_j(t, \mathbf{x}))$. Observe that (2h) is the standard decay condition for the Laplace problem in three dimensions that guarantees that the problem is well posed. Finally, the parameters of each cell, $c_{m,j}$, $V_{ep,j}$, $\tau_{ep,j}$ and $\tau_{res,j}$ might differ from cell to cell. In practical applications, these parameters depend on the cell type, e.g., cancer cells possess material properties different from healthy cells in the same tissue [23].

2.3 Boundary integral formulation

Due to the unboundedness of the domain as well as the constant conductivity values inside intraand extracellular domains, one can write Problem 2.1 using boundary integral operators, thereby reducing the volume problem to a boundary one as in [13, 12, 11].

2.3.1 Boundary integral potential and operators

The free space fundamental solution of the Laplace equation for a source located at \mathbf{r}' satisfying the decay condition (2h) is ([15, Section 1.7])

$$g\left(\mathbf{r},\mathbf{r}'\right) := \frac{1}{4\pi \left\|\mathbf{r}-\mathbf{r}'\right\|_{2}}, \quad \mathbf{r} \neq \mathbf{r}'.$$

We recall the standard single and double layer operators defined for smooth densities:

$$DL_{0j}(\psi)(\mathbf{r}) := \int_{\Gamma_j} \psi(\mathbf{r}') \nabla g(\mathbf{r}, \mathbf{r}') \cdot \widehat{\mathbf{n}}_{0j} \, dS', \qquad SL_{0j}(\psi)(\mathbf{r}) := \int_{\Gamma_j} \psi(\mathbf{r}') g(\mathbf{r}, \mathbf{r}') \, dS',$$
$$DL_j(\psi)(\mathbf{r}) := \int_{\Gamma_j} \psi(\mathbf{r}') \nabla g(\mathbf{r}, \mathbf{r}') \cdot \widehat{\mathbf{n}}_j \, dS', \qquad SL_j(\psi)(\mathbf{r}) := \int_{\Gamma_j} \psi(\mathbf{r}') g(\mathbf{r}, \mathbf{r}') \, dS',$$

with the gradient being taken with respect to \mathbf{r}' , $\hat{\mathbf{n}}_j$ being the exterior normal vector of Ω_j , and $\hat{\mathbf{n}}_j = -\hat{\mathbf{n}}_{0j}$. It can be shown that these operators are linear and continuous (cf. [26, Section 3.1], [11, Section 3.1]), in the following Sobolev spaces:

$$DL_{0j}: H^{\frac{1}{2}}(\Gamma_j) \to H^1_{loc}\left(\mathbb{R}^3 \setminus \bigcup_{j=1}^{\mathcal{N}} \Gamma_j\right), \qquad SL_{0j}: H^{-\frac{1}{2}}(\Gamma_j) \to H^1_{loc}\left(\mathbb{R}^3 \setminus \bigcup_{j=1}^{\mathcal{N}} \Gamma_j\right), \\ DL_j: H^{\frac{1}{2}}(\Gamma_j) \to H^1_{loc}\left(\mathbb{R}^3 \setminus \bigcup_{j=1}^{\mathcal{N}} \Gamma_j\right), \qquad SL_j: H^{-\frac{1}{2}}(\Gamma_j) \to H^1_{loc}\left(\mathbb{R}^3 \setminus \bigcup_{j=1}^{\mathcal{N}} \Gamma_j\right).$$

We will write u_j in terms of these boundary potentials, and since we aim at rendering Problem 2.1 onto the cells' boundaries, we will take traces of these potentials. This leads to boundary integral operators (BIOs), which are defined by taking the following averages [26, Section 3.1.2]:

$$V_{i,j}^{0} := \frac{1}{2} \left(\gamma_{D}^{i} SL_{0j} + \gamma_{D}^{0i} SL_{0j} \right), \qquad V_{j} := \frac{1}{2} \left(\gamma_{D}^{0j} SL_{j} + \gamma_{D}^{j} SL_{j} \right), K_{i,j}^{0} := \frac{1}{2} \left(\gamma_{D}^{i} DL_{0j} + \gamma_{D}^{0i} DL_{0j} \right), \qquad K_{j} := \frac{1}{2} \left(\gamma_{D}^{0j} DL_{j} + \gamma_{D}^{j} DL_{j} \right),$$
(5)
$$K_{i,j}^{*0} := \frac{1}{2} \left(-\gamma_{N}^{i} SL_{0j} + \gamma_{N}^{0i} SL_{0j} \right), \qquad K_{j}^{*} := \frac{1}{2} \left(-\gamma_{N}^{0j} SL_{j} + \gamma_{N}^{j} SL_{j} \right),$$
(5)
$$W_{i,j}^{0} := -\frac{1}{2} \left(-\gamma_{N}^{i} DL_{0j} + \gamma_{N}^{0i} DL_{0j} \right), \qquad W_{j} := -\frac{1}{2} \left(-\gamma_{N}^{0j} DL_{j} + \gamma_{N}^{j} DL_{j} \right).$$

One can show that these operators are linear and continuous [26, Theorem 3.1.16] in the following Sobolev spaces:

$$\begin{split} V_{i,j}^{0} &: H^{-\frac{1}{2}}(\Gamma_{j}) \to H^{\frac{1}{2}}(\Gamma_{i}), & V_{j} : H^{-\frac{1}{2}}(\Gamma_{j}) \to H^{\frac{1}{2}}(\Gamma_{j}), \\ W_{i,j}^{0} &: H^{\frac{1}{2}}(\Gamma_{j}) \to H^{-\frac{1}{2}}(\Gamma_{i}), & W_{j} : H^{\frac{1}{2}}(\Gamma_{j}) \to H^{-\frac{1}{2}}(\Gamma_{j}), \\ K_{i,j}^{0} &: H^{\frac{1}{2}}(\Gamma_{j}) \to H^{\frac{1}{2}}(\Gamma_{i}), & K_{j} : H^{\frac{1}{2}}(\Gamma_{j}) \to H^{\frac{1}{2}}(\Gamma_{j}), \\ K_{i,j}^{*0} : H^{-\frac{1}{2}}(\Gamma_{j}) \to H^{-\frac{1}{2}}(\Gamma_{i}), & K_{j}^{*} : H^{-\frac{1}{2}}(\Gamma_{j}) \to H^{-\frac{1}{2}}(\Gamma_{j}). \end{split}$$

For smooth domains, the jump relations for the potentials across a closed boundary [26, Theorem 3.3.1] yield

$$\begin{split} V_{i,j}^{0} &= \gamma_{D}^{0i}SL_{0j}, & V_{j} &= \gamma_{D}^{j}SL_{j}, \\ W_{i,j}^{0} &= -\gamma_{N}^{0i}DL_{0j}, & W_{j} &= -\gamma_{N}^{j}DL_{j}, \\ K_{i,j}^{0} &= \gamma_{D}^{0i}DL_{0j} \text{ with } i \neq j, & K_{i,j}^{*0} &= \gamma_{N}^{0i}SL_{0j} \text{ with } i \neq j, \\ K_{j,j}^{0}(\psi) &= \frac{1}{2}\psi + \gamma_{D}^{0j}DL_{0j}(\psi), & K_{j}(\psi) &= \frac{1}{2}\psi + \gamma_{D}^{j}DL_{j}(\psi), \\ K_{j,j}^{*0}(\psi) &= -\frac{1}{2}\psi + \gamma_{N}^{0j}SL_{0j}(\psi), & K_{j}^{*}(\psi) &= -\frac{1}{2}\psi + \gamma_{N}^{j}SL_{j}(\psi). \end{split}$$

In the next theorem presents the integral representation formulas for the electric potentials u_j and u_0 .

Theorem 2.2. ([26, Section 3]) The integral representation formulas for $u_j \in H^1(\Omega_j)$, $u_0 \in H^1_{loc}(\Omega_0)$ read

$$u_{0} = -\sum_{i=1}^{\mathcal{N}} DL_{0i} \left(\gamma_{D}^{0i} u_{0} \right) + \sum_{i=1}^{\mathcal{N}} SL_{0i} \left(\gamma_{N}^{0i} u_{0} \right),$$
(6a)

$$u_j = -DL_j\left(\gamma_D^j u_j\right) + SL_j\left(\gamma_N^j u_j\right), \quad \forall j \in \{1, ..., \mathcal{N}\}.$$
 (6b)

where u_i are zero-valued on the complement of Ω_i .

2.3.2 Multiple traces formulation for Problem 2.1

Using the operators introduced in above along with the integral representation formula we write the MTF of Problem 2.1 (cf. [13] and later references).

For $j \in \{1, ..., \mathcal{N}\}$, we introduce the Cartesian product of Hilbert spaces $\boldsymbol{H}_j := H^{\frac{1}{2}}(\Gamma_j) \times H^{-\frac{1}{2}}(\Gamma_j)$, with norm $\|\cdot\|_{\boldsymbol{H}_j} = \|\cdot\|_{H^{\frac{1}{2}}(\Gamma_j)} + \|\cdot\|_{H^{-\frac{1}{2}}(\Gamma_j)}$. Let be $\phi, \boldsymbol{\xi} \in \boldsymbol{H}_j$, such that $\phi = (\phi_D, \phi_N)$ and $\boldsymbol{\xi} = (\xi_D, \xi_N)$. We introduce the cross-product over Γ_j [13, Section 2.2.1] by $\langle \phi, \boldsymbol{\xi} \rangle_{\times,j} := \langle \phi_D, \xi_N \rangle_j + \langle \xi_D, \phi_N \rangle_j$, where for brevity we denote $\langle \xi_D, \phi_N \rangle_j := \langle \xi_D, \phi_N \rangle_{H^{\frac{1}{2}}(\Gamma_j) \times H^{-\frac{1}{2}}(\Gamma_j)}$.

We define also the flip-sign operator $X_j : H_j \to H_j, \gamma^{0j} : H^1_{loc}(\Delta, \Omega_0) \to H_j$ and $\gamma^j : H^1(\Delta, \Omega_j) \to H_j$ as:

$$\mathsf{X}_{j} := \begin{bmatrix} I & 0\\ 0 & -\frac{\sigma_{0}}{\sigma_{j}}I \end{bmatrix}, \quad \boldsymbol{\gamma}^{0j} := \begin{pmatrix} \gamma_{D}^{0j}\\ \gamma_{N}^{0j} \end{pmatrix} \quad \text{and} \quad \boldsymbol{\gamma}^{j} := \begin{pmatrix} \gamma_{D}^{j}\\ \gamma_{N}^{j} \end{pmatrix}, \quad j \in \{1, ..., \mathcal{N}\}, \tag{7}$$

with I being the identity operator in the corresponding functional space, and for simplicity, we adopt the same notation for I in different spaces. Then, we write Dirichlet and Neumann boundary conditions, (2c) and (2d), respectively, succinctly as

$$-\mathsf{X}_{j}\boldsymbol{\gamma}^{0j}u_{0} + \boldsymbol{\gamma}^{j}u_{j} = \mathsf{X}_{j}(v_{j}, \ 0)^{t} + \mathsf{X}_{j}\boldsymbol{\gamma}^{0j}\phi_{e},$$
(8a)

$$\boldsymbol{\gamma}^{0j} \boldsymbol{u}_0 - \boldsymbol{\mathsf{X}}_j^{-1} \boldsymbol{\gamma}^j \boldsymbol{u}_j = -(\boldsymbol{v}_j, \ 0)^t - \boldsymbol{\gamma}^{0j} \phi_e, \tag{8b}$$

where both equations are equivalent. Taking Dirichlet and Neumann traces of both (6a) and (6b), and rewriting in terms of BIOs, we obtain

$$\begin{split} \gamma_D^{0j} u_0 &= -\left(-\frac{1}{2}I\left(\gamma_D^{0j} u_0\right) + \sum_{i=1}^n K_{j,i}^0\left(\gamma_D^{0i} u_0\right)\right) + \sum_{i=1}^n V_{j,i}^0\left(\gamma_N^{0i} u_0\right),\\ \gamma_N^{0j} u_0 &= \sum_{i=1}^n W_{j,i}^0\left(\gamma_D^{0i} u_0\right) + \left(\frac{1}{2}I\left(\gamma_N^{0j} u_0\right) + \sum_{i=1}^n K_{j,i}^{*0}\left(\gamma_N^{0i} u_0\right)\right),\\ \gamma_D^j u_j &= -\left(-\frac{1}{2}I\left(\gamma_D^j u_j\right) + K_j\left(\gamma_D^j u_j\right)\right) + V_j\left(\gamma_N^j u_j\right),\\ \gamma_N^j u_j &= W_j\left(\gamma_D^j u_j\right) + \left(\frac{1}{2}I\left(\gamma_N^j u_j\right) + K_j^*\left(\gamma_N^j u_j\right)\right). \end{split}$$

After some algebra, one can write

$$\boldsymbol{\gamma}^{0j}u_0 = 2\sum_{i=1}^{\mathcal{N}} \mathsf{A}_{j,i}^0 \, \boldsymbol{\gamma}^{0i} u_0, \quad \boldsymbol{\gamma}^j u_j = 2\,\mathsf{A}_j \, \boldsymbol{\gamma}^j u_j, \quad j \in \{1, ..., \mathcal{N}\},$$

with $\mathsf{A}_{j,i}^0 := \begin{bmatrix} -K_{j,i}^0 & V_{j,i}^0 \\ W_{j,i}^0 & K_{j,i}^{*0} \end{bmatrix}$ and $\mathsf{A}_j := \begin{bmatrix} -K_j & V_j \\ W_j & K_j^* \end{bmatrix}$. By replacing $\gamma^{0j}u_0, \gamma^j u_j$ into (8b) and (8a), we obtain

$$2\sum_{i=1}^{n} \mathsf{A}_{j,i}^{0} \gamma^{0i} u_{0} - \mathsf{X}_{j}^{-1} \gamma^{j} u_{j} = -(v_{j}, \ 0)^{t} - \gamma^{0j} \phi_{e},$$
$$-\mathsf{X}_{j} \gamma^{0j} u_{0} + 2 \mathsf{A}_{j} \gamma^{j} u_{j} = \mathsf{X}_{j} (v_{j}, \ 0)^{t} + \mathsf{X}_{j} \gamma^{0j} \phi_{e} \quad \text{on } \Gamma_{j}$$

We define Cartesian product space of multiple traces:

$$\mathbb{H} := \Pi_{j=1}^{\mathcal{N}} \boldsymbol{H}_j \quad \text{and} \quad \mathbb{H}^{(2)} := \mathbb{H} \times \mathbb{H} = \Pi_{j=1}^{\mathcal{N}} \boldsymbol{H}_j \times \Pi_{j=1}^{\mathcal{N}} \boldsymbol{H}_j,$$

the multiple trace spaces reordering:

$$\mathbb{H}_D := \Pi_{j=1}^{\mathcal{N}} H^{\frac{1}{2}}(\Gamma_j), \quad \mathbb{H}_N := \Pi_{j=1}^{\mathcal{N}} H^{-\frac{1}{2}}(\Gamma_j),$$

and the cross-product:

$$\langle \boldsymbol{\phi}, \boldsymbol{\xi} \rangle_{\times} = \sum_{j=1}^{\mathcal{N}} \langle \boldsymbol{\phi}^{0j}, \boldsymbol{\xi}^{0j} \rangle_{\times,j} + \sum_{j=1}^{\mathcal{N}} \langle \boldsymbol{\phi}^{j}, \boldsymbol{\xi}^{j} \rangle_{\times,j},$$

with $\boldsymbol{\phi} = (\boldsymbol{\phi}^{01}, ..., \boldsymbol{\phi}^{0\mathcal{N}}, \boldsymbol{\phi}^{1}, ..., \boldsymbol{\phi}^{\mathcal{N}})$ and $\boldsymbol{\xi} = (\boldsymbol{\xi}^{01}, ..., \boldsymbol{\xi}^{0\mathcal{N}}, \boldsymbol{\xi}^{1}, ..., \boldsymbol{\xi}^{\mathcal{N}})$. Now, we can introduce the local Multiple Trace formulation (MTF) operator [13, Section 3.2.3], $\mathbf{M}_{\mathcal{N}} : \mathbb{H}^{(2)} \to \mathbb{H}^{(2)}$, for the geometry presented in Section 2:

$$\mathbf{M}_{\mathcal{N}} := \begin{bmatrix} 2\mathbf{A}_{0,\mathcal{N}} & -\mathbf{X}_{\mathcal{N}}^{-1} \\ -\mathbf{X}_{\mathcal{N}} & 2\mathbf{A}_{1,\mathcal{N}} \end{bmatrix}, \text{ with } \mathbf{A}_{0,\mathcal{N}} := \begin{bmatrix} \mathbf{A}_{0,1}^{0} & \mathbf{A}_{1,2}^{0} & \dots & \mathbf{A}_{1,\mathcal{N}}^{0} \\ \mathbf{A}_{2,1}^{0} & \mathbf{A}_{2,2}^{0} & \dots & \mathbf{A}_{2,\mathcal{N}}^{0} \\ \vdots & \ddots & \vdots \\ \mathbf{A}_{\mathcal{N},1}^{0} & \mathbf{A}_{\mathcal{N},2}^{0} & \dots & \mathbf{A}_{\mathcal{N},\mathcal{N}}^{0} \end{bmatrix},$$
(9)

$$\mathbf{A}_{1,\mathcal{N}} := \begin{bmatrix} \mathsf{A}_1 & 0 & \dots & 0 \\ 0 & \mathsf{A}_2 & \dots & 0 \\ \vdots & & \ddots & \vdots \\ 0 & \dots & 0 & \mathsf{A}_{\mathcal{N}} \end{bmatrix} \text{ and } \mathbf{X}_{\mathcal{N}} := \begin{bmatrix} \mathsf{X}_1 & 0 & \dots & 0 \\ 0 & \mathsf{X}_2 & \dots & 0 \\ \vdots & & \ddots & \vdots \\ 0 & \dots & 0 & \mathsf{X}_{\mathcal{N}} \end{bmatrix}$$

With the MTF operator, the interface conditions (2b), (2c) and (2d) (Problem 2.1) can be written as:

$$\mathbf{M}_{\mathcal{N}} \begin{pmatrix} \boldsymbol{\gamma}_{u}^{0} \\ \boldsymbol{\gamma}_{u} \end{pmatrix} = \begin{pmatrix} -\mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \, \mathbf{v} \\ \mathbf{X}_{\mathcal{N}} \, \mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \, \mathbf{v} \end{pmatrix} + \begin{pmatrix} -\boldsymbol{\gamma}_{\phi_{e}}^{0} \\ \mathbf{X}_{\mathcal{N}} \, \boldsymbol{\gamma}_{\phi_{e}}^{0} \end{pmatrix}, \tag{10}$$

where we use the notation:

$$\begin{split} \boldsymbol{\gamma}_{u}^{0} &:= \left(\boldsymbol{\gamma}^{01} u_{0}, \boldsymbol{\gamma}^{02} u_{0}, \dots, \boldsymbol{\gamma}^{0\mathcal{N}} u_{0}\right)^{t}, \qquad \qquad \boldsymbol{\gamma}_{u}^{u} &:= \left(\boldsymbol{\gamma}^{1} u_{1}, \boldsymbol{\gamma}^{2} u_{2}, \dots, \boldsymbol{\gamma}^{\mathcal{N}} u_{\mathcal{N}}\right)^{t}, \\ \boldsymbol{\gamma}_{\phi_{e}}^{0} &:= \left(\boldsymbol{\gamma}^{01} \phi_{e}, \boldsymbol{\gamma}^{02} \phi_{e}, \dots, \boldsymbol{\gamma}^{0\mathcal{N}} \phi_{e}\right)^{t}, \qquad \qquad \mathbf{v}^{u} &:= \left(v_{1}, v_{2}, v_{3}, \dots, v_{\mathcal{N}}\right)^{t}, \end{split}$$

with superscript t denoting the transposition, and the operator $\mathbf{I}_{2N\times N} : \mathbb{H}_D \to \mathbb{H}$ is defined as²:

$$\mathbf{I}_{2\mathcal{N}\times\mathcal{N}} := \begin{pmatrix} I & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ 0 & I & \dots & 0 \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & & \vdots \\ 0 & 0 & \dots & I \\ 0 & 0 & \dots & 0 \end{pmatrix}.$$

The following result is a consequence of [11, Proposition 3.9, Proposition 3.10] along with the Fredholm alternative.

Theorem 2.3 (Existence, uniqueness and stability). The operator M_N is a linear, injective and coercive operator in $\mathbb{H}^{(2)}$. For all $\boldsymbol{\xi} \in \mathbb{H}^{(2)}$, there exists a unique weak solution $\boldsymbol{\lambda} \in \mathbb{H}^{(2)}$ of

$$(\mathsf{M}_{\mathcal{N}}\boldsymbol{\lambda}, \boldsymbol{\phi})_{ imes} = (\boldsymbol{\xi}, \boldsymbol{\phi})_{ imes}, \quad \forall \boldsymbol{\phi} \in \mathbb{H}^{(2)},$$

that satisfies the stability estimate $\|\boldsymbol{\lambda}\|_{\mathbb{H}^{(2)}} \leq c \|\boldsymbol{\xi}\|_{\mathbb{H}^{(2)}}$, for a constant c > 0.

2.3.3 Boundary integral formulation of Problem 2.1

Until this point, we have not introduced the membrane dynamics of Problem 2.1. In the following, we will use the theory presented in [12, 11] to combine the MTF with the nonlinear dynamics. Indeed, thanks to Theorem 2.3 we can take the inverse of the MTF operator, and (10) becomes

$$\begin{pmatrix} \boldsymbol{\gamma}_u^0 \\ \boldsymbol{\gamma}_u \end{pmatrix} = \mathbf{M}_{\mathcal{N}}^{-1} \begin{pmatrix} -\mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \mathbf{v} \\ \mathbf{X}_{\mathcal{N}} \mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \mathbf{v} \end{pmatrix} + \mathbf{M}_{\mathcal{N}}^{-1} \begin{pmatrix} -\boldsymbol{\gamma}_{\phi_e}^0 \\ \mathbf{X}_{\mathcal{N}} \boldsymbol{\gamma}_{\phi_e}^0 \end{pmatrix}.$$

The even components of the vector γ_u (the interior Neumann traces), related to the nonlinear dynamics of the problem by (2e), can be retrieved as follows:

$$\begin{pmatrix} \sigma_{1}\gamma_{N}^{1}(u_{1}) \\ \sigma_{2}\gamma_{N}^{2}(u_{2}) \\ \vdots \\ \sigma_{\mathcal{N}}\gamma_{N}^{\mathcal{N}}(u_{\mathcal{N}}) \end{pmatrix} = \boldsymbol{\sigma}_{\mathcal{N}\times 4\mathcal{N}} \mathbf{M}_{\mathcal{N}}^{-1} \left(\begin{pmatrix} -\mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \mathbf{v} \\ \mathbf{X}_{\mathcal{N}} \mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \mathbf{v} \end{pmatrix} + \begin{pmatrix} -\gamma_{\phi_{e}}^{0} \\ \mathbf{X}_{\mathcal{N}} \gamma_{\phi_{e}}^{0} \end{pmatrix} \right),$$

where the dimensions of $\sigma_{N \times 4N}$ are $N \times 4N$, the first half containing only zeros:

$$\boldsymbol{\sigma}_{\mathcal{N}\times 4\mathcal{N}} := \begin{pmatrix} 0 & \dots & 0 & \sigma_1 I & 0 & 0 & \dots & 0 \\ 0 & \dots & 0 & 0 & \sigma_2 I & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \dots & 0 & 0 & 0 & 0 & \dots & \sigma_{\mathcal{N}} I \end{pmatrix}$$

²Notice that the identity operators act on the corresponding Dirichlet traces.

Now, we define the Dirichlet-to-Neumann operators $\mathcal{J}_{\mathcal{N}} : \mathbb{H}_D \to \mathbb{H}_N$, and $\Phi : H^1_{loc}(\Omega_0) \to \mathbb{H}_N$ as

$$\mathcal{J}_{\mathcal{N}}(\mathbf{v}) := \boldsymbol{\sigma}_{\mathcal{N} \times 4\mathcal{N}} \mathbf{M}_{\mathcal{N}}^{-1} \begin{pmatrix} -\mathbf{I}_{2\mathcal{N} \times \mathcal{N}} \mathbf{v} \\ \mathbf{X}_{\mathcal{N}} \mathbf{I}_{2\mathcal{N} \times \mathcal{N}} \mathbf{v} \end{pmatrix}, \text{ and } \Phi(\phi_e) := \boldsymbol{\sigma}_{\mathcal{N} \times 4\mathcal{N}} \mathbf{M}_{\mathcal{N}} \begin{pmatrix} -\boldsymbol{\gamma}_{\phi_e}^0 \\ \mathbf{X}_{\mathcal{N}} \boldsymbol{\gamma}_{\phi_e}^0 \end{pmatrix}.$$
(11)

Theorem 2.4 (Lemma 4.3 in [11]). The operator $\mathcal{J}_{\mathcal{N}} : \mathbb{H}_D \to \mathbb{H}_N$ is continuous and coercive.

Now we can finally rewrite³ Problem 2.1 as an abstract parabolic equation on Γ_i .

Problem 2.5. Given a final time $T \in \mathbb{R}^+$, $\phi_e \in C([0,T], H^1_{loc}(\Omega_0))$ an external potential, and the initial conditions $v_j(0) = v_0 \in H^{\frac{1}{2}}(\Gamma_j)$, $Z_j(0) = Z_j^0 \in H^{\frac{1}{2}}(\Gamma_j)$, for $j \in \{1, ..., \mathcal{N}\}$. We seek $\mathbf{v} = (v_1, \ldots, v_{\mathcal{N}})^t$, with $v_j \in C([0,T], H^{\frac{1}{2}}(\Gamma_j))$, and $\mathbf{Z} = (Z_1, \ldots, Z_{\mathcal{N}})^t$, $Z_j \in C([0,T], H^{\frac{1}{2}}(\Gamma_j))$, for $j \in \{1, ..., \mathcal{N}\}$, such that

$$\mathbf{C}_{\mathbf{m}}\partial_t \mathbf{v} = -\mathbf{I}^{ep}(\mathbf{v}, \mathbf{Z}) - \mathcal{J}_{\mathcal{N}}(\mathbf{v}) - \Phi(\phi_e) \ on \ [0, T] \times \Gamma_j, \tag{12}$$

where $\mathbf{C}_{\mathbf{m}}$ is a diagonal matrix diag $(c_{m,1},\ldots,c_{m,\mathcal{N}})$; the operators $\mathcal{J}_{\mathcal{N}}(\mathbf{v})$ and $\Phi(\phi_e)$ are defined in (11). The vector $\mathbf{I}^{ep}(\mathbf{v},\mathbf{Z}) = (I_1^{ep}(v_1,Z_1),\ldots,I_{\mathcal{N}}^{ep}(v_{\mathcal{N}},Z_{\mathcal{N}}))^t$ satisfy (3), (4) and (1).

3 Numerical Approximation

In this section we propose a numerical solution of Problem 2.5. We use a semi-implicit time stepping scheme, similar to one used in [12, 11] (see Section 3.1). For the space discretization, we follow an analogous approach in the two-dimensional case employed in [11], using spherical harmonics. Since we do not work with complex valued functions, we employ real spherical harmonics to approximate boundary unknowns.

3.1 Semi-implicit time stepping scheme

Let $\mathcal{T}_S := \{t_s\}_{s=0}^S$ denote the uniform partition of the time interval [0, T], with $T \in \mathbb{R}^+$, and $S \in \mathbb{N}$, where the time step is $\tau = T/S$, and $t_s = s\tau$. Write

$$t_{s+\frac{1}{2}} := t_s + \frac{\tau}{2}, \quad s \in \{0, \dots, S-1\},$$

for the midstep between t_s and t_{s+1} . For a time dependent quantity $\phi(t)$, we write $\phi^{(s)} = \phi(t_s)$, and we define the following quantities:

$$\begin{split} \phi^{(s+\frac{1}{2})} &:= \phi(t_{s+\frac{1}{2}}), \\ \hat{\phi}^{(s+\frac{1}{2})} &:= \frac{3\phi^{(s)} - \phi^{(s-1)}}{2}, \\ \bar{\phi}^{(s+\frac{1}{2})} &:= \frac{3\phi^{(s)} - \phi^{(s-1)}}{2}, \\ \bar{\partial}\phi^{(s)} &:= \frac{\phi^{(s+1)} - \phi^{(s)}}{\tau}. \end{split}$$

³The MTF (9) is similar to one in [11] and [12]. Specifically, (9) is multiplied by two, and the first row does not have a factor σ_j as in [12] and [11].

With these, we approximate in time (2.5) and (4) as follows:

$$\mathbf{C_m}\overline{\partial}\mathbf{v}^{(s)} = -\mathbf{I}^{ep}\left(\widehat{\mathbf{v}}^{(s+\frac{1}{2})}, \widehat{\mathbf{Z}}^{(s+\frac{1}{2})}\right) - \mathcal{J}_{\mathcal{N}}\left(\overline{\mathbf{v}}^{(s+\frac{1}{2})}\right) - \Phi(\phi_e^{(s+\frac{1}{2})}),$$
$$\overline{\partial}^{(s)}Z_j = \max\left(\frac{\beta_j(\widehat{v}_j^{(s+\frac{1}{2})}) - \widehat{Z_j}^{(s+\frac{1}{2})}}{\tau_{ep,j}}, \frac{\beta_j(\widehat{v}_j^{(s+\frac{1}{2})}) - \widehat{Z_j}^{(s+\frac{1}{2})}}{\tau_{res,j}}\right).$$

From these expressions, we can notice that

- (i) At each iteration, the approximation at t_{s+1} requires two previous steps, t_s and t_{s-1} , but we only have information about the time t_0 . Thus, we will estimate the values for the time t_1 with a predictor-corrector algorithm introduced later in this Section.
- (ii) Provided with values for the two previous time steps, unknowns for the next time are obtained in terms of $\overline{\partial} \mathbf{v}^{(s)}$, $\overline{\mathbf{v}}^{(s+\frac{1}{2})}$ and $\overline{\partial}^{(s)}$, which are linear. Nonlinear terms are evaluated with values already known, i.e. they are explicit terms, unlike the others. For this reason, the time scheme is called semi-implicit.
- (iii) At each time step, the discrete problem to be solved is linear. One could choose time-domain schemes with implicit non-linear parts. Consequently, more information about \mathbf{I}^{ep} may be needed. In contrast, our semi-implicit time only requires us to evaluate the function \mathbf{I}^{ep} .
- (iv) The method is not fully implicit, and the time step τ needs to be small enough for the scheme to converge.

The predictor-corrector algorithm can be found in detail in [27, Chapter 13], [12, Algorithm 1]. Set $\mathbf{w}^{(0)} = \mathbf{v}^{(0)}$ and $\mathbf{Q}^{(0)} = \mathbf{Z}(0)$. Then, proceed as follows:

(I) *Predictor*. First, construct predictions $\mathbf{w}^{(1)}$ and $\mathbf{Q}^{(1)}$ by solving:

$$\mathbf{C}_{\mathbf{m}}\overline{\partial}\mathbf{w}^{(0)} = -\mathbf{I}^{ep}\left(\mathbf{w}^{(0)}, \mathbf{Q}^{(0)}\right) - \mathcal{J}_{\mathcal{N}}\left(\overline{\mathbf{w}}^{(\frac{1}{2})}\right) - \Phi\left(\phi_{e}^{(\frac{1}{2})}\right),$$
$$\overline{\partial}Q_{j}^{(0)} = \max\left(\frac{\beta_{j}(w_{j}^{(0)}) - Q_{j}^{(0)}}{\tau_{ep,j}}, \frac{\beta_{j}(w_{j}^{(0)}) - Q_{j}^{(0)}}{\tau_{res,j}}\right) \quad \forall j \in \{1, ..., \mathcal{N}\}$$

(II) Corrector. Then, correct $\mathbf{w}^{(1)}$ and $\mathbf{Q}^{(1)}$ to obtain final values for $\mathbf{v}^{(1)}$ and $\mathbf{Z}^{(1)}$ through:

$$\mathbf{C}_{\mathbf{m}}\overline{\partial}\mathbf{v}^{(0)} = -\mathbf{I}^{ep}\left(\widehat{\mathbf{w}}^{(\frac{1}{2})}, \widehat{\mathbf{Q}}^{(\frac{1}{2})}\right) - \mathcal{J}_{\mathcal{N}}\left(\overline{\mathbf{v}}^{(\frac{1}{2})}\right) - \Phi\left(\phi_{e}^{(\frac{1}{2})}\right),$$

$$\overline{\partial}^{(0)}Z_{j} = \max\left(\frac{\beta_{j}(\widehat{w}_{j}^{(\frac{1}{2})}) - \widehat{Q_{j}}^{(\frac{1}{2})}}{\tau_{ep,j}}, \frac{\beta_{j}(\widehat{w}_{j}^{(\frac{1}{2})}) - \widehat{Q_{j}}^{(\frac{1}{2})}}{\tau_{res,j}}\right) \quad \forall j \in \{1, ..., \mathcal{N}\}.$$

From the corrector equations, $\mathbf{v}^{(1)}$ and $\mathbf{Z}^{(1)}$ are obtained implicitly. Finally, before going to the spatial discretization, we recall the following result:

Theorem 3.1. [12, Lemma 7]. Let $\phi \in C^2([0,T]; L^2(\Gamma_i)), j \in \{1,\ldots,\mathcal{N}\}$ then it holds that

$$\begin{aligned} \left\| \overline{\phi}^{(s+\frac{1}{2})} - \phi^{(s+\frac{1}{2})} \right\|_{L^{2}(\Gamma_{j})} &\leq \frac{\tau^{2}}{4} \max_{t \in [t_{s}, t_{s+1}]} \left\| \partial_{t}^{2} \phi(t) \right\|_{L^{2}(\Gamma_{j})}, \\ \left\| \widehat{\phi}^{(s+\frac{1}{2})} - \phi^{(s+\frac{1}{2})} \right\|_{L^{2}(\Gamma_{j})} &\leq \frac{5\tau^{2}}{16} \max_{t \in [t_{s-1}, t_{s+1}]} \left\| \partial_{t}^{2} \phi(t) \right\|_{L^{2}(\Gamma_{j})}. \end{aligned}$$

3.2 Spatial discretization

We now spatially discretize Problem 2.5. We start by introducing the real spherical harmonics used as spatial basis for the Dirichlet and Neumann traces (15). Then, we proceed with the BIOs discretization (see Theorem 3.3). Finally, the semi-explicit time method and the spatial discretization are combined into a fully discrete scheme (see Problem (3.7)).

3.2.1 Spherical coordinates and spherical harmonics

A vector is written as $\mathbf{r} = (r, \varphi, \theta)^t$, with $r \in [0, \infty)$, $\varphi \in [0, 2\pi)$ and $\theta \in [0, \pi]$, which in Cartesian coordinates is equivalent to $\mathbf{r} = r (\sin \theta \cos \varphi, \sin \theta \sin \varphi, \cos \theta)^t$. Spherical harmonics of degree l and order m are defined using spherical coordinates as [29, Section 2], [7, Example 4.3.33]:

$$Y_{l,m}\left(\theta,\varphi\right) := \sqrt{\left(2 - \delta_{m,0}\right) \frac{\left(2l+1\right)\left(l-m\right)!}{4\pi\left(l+m\right)!}} P_l^m\left(\cos\theta\right)\cos m\varphi, \text{ and}$$
(13a)

$$Y_{l,-m}(\theta,\varphi) := \sqrt{(2-\delta_{m,0})\frac{(2l+1)(l-m)!}{4\pi(l+m)!}} P_l^m(\cos\theta)\sin m\varphi,$$
(13b)

with $l \in \mathbb{N}_0$, $m \in \mathbb{Z}$ such that $0 \le m \le l$. If m = 0, then $\delta_{m,0} = 1$, and it is zero otherwise. P_l^m are the associated Legendre functions of degree l and order m defined as:

$$P_l^m(x) := (-1)^m \left(1 - x^2\right)^{\frac{m}{2}} \frac{d^m}{dx^m} P_l(x), \quad \text{with} \quad P_l(x) := \frac{1}{2^l l!} \frac{d^l}{dx^l} (x^2 - 1)^l.$$

Here, the term $(-1)^m$ is the Condon-Shortley phase factor. Spherical harmonics are dense in $C(\mathbb{S}^2)$, with \mathbb{S}^2 the surface of the unit sphere, and form a complete orthonormal system in $L^2(\mathbb{S}^2)$ [8, Section 7.3 and 7.5].

Let be $j \in \{1, ..., N\}$. We define the reference system j as the one centered at \mathbf{p}_j with the same orientation that the reference system centered in the origin. Furthermore, we denote by $Y_{l,m,j}$ the spherical harmonic $Y_{l,m}$ centered in the origin of the reference system j. Thus, if $(r_j, \varphi_j, \theta_j)$ are the vector spherical coordinates of \mathbf{r}_j in the reference system j, we have that $Y_{l,m,j}(\mathbf{r}_j) = Y_{l,m}(\theta_j, \varphi_j)$.

For $L \in \mathbb{N}_0$ and $j \in \{1, ..., \mathcal{N}\}$, we define subspaces

$$\mathcal{Y}_{L}\left(\Gamma_{j}\right) := \operatorname{span}\left\{Y_{l,m,j} : l \in \mathbb{N}_{0}, m \in \mathbb{Z}, l \leq L, |m| \leq l\right\},\tag{14}$$

equipped with the $L^2(\Gamma_j)$ -norm. Notice that the dimension of each subspace is $(L+1)^2$, and that the sequence of subspaces $\{\mathcal{Y}_L(\Gamma_j)\}_{L\in\mathbb{N}_0}$ is dense in $H^{\frac{1}{2}}(\Gamma_j)$ and in $H^{-\frac{1}{2}}(\Gamma_j)$. The result follows from the density of spherical harmonics in the spaces of continuous functions. This last result justifies the discretization of all boundary Dirichlet and Neumann unknowns with spherical harmonics. At a given time t, for $j \in \{1, ..., \mathcal{N}\}$, we write $u_{D,0j}^L$, $u_{D,j}^L$, $u_{N,j}^L$, v_j^L and Z_j^L in $\mathcal{Y}_L(\Gamma_j)$ for the approximations of $\gamma_D^{0j}u_0$, $\gamma_N^{0j}u_0$, $\gamma_D^ju_j$, $\gamma_N^ju_j$, v_j and Z_j , respectively. They can be written as the following series expansions:

$$u_{D,0j}^{L} = \sum_{l=0}^{L} \sum_{m=-l}^{l} u_{D,0j}^{l,m} Y_{l,m,j}, \qquad u_{N,0j}^{L} = \sum_{l=0}^{L} \sum_{m=-l}^{l} u_{N,0j}^{l,m} Y_{l,m,j}, \qquad (15a)$$

$$u_{D,j}^{L} = \sum_{l=0}^{L} \sum_{m=-l}^{l} u_{D,j}^{l,m} Y_{l,m,j}, \qquad u_{N,j}^{L} = \sum_{l=0}^{L} \sum_{m=-l}^{l} u_{N,j}^{l,m} Y_{l,m,j}, \qquad (15b)$$

$$v_j^L = \sum_{l=0}^L \sum_{m=-l}^l v_j^{l,m} Y_{l,m,j}, \qquad \qquad Z_j^L = \sum_{l=0}^L \sum_{m=-l}^l Z_j^{l,m} Y_{l,m,j}$$
(15c)

with $u_{D,0j}^{l,m}$, $u_{N,0j}^{l,m}$, $u_{D,j}^{l,m}$, $u_{N,j}^{l,m}$, $v_j^{l,m}$, and $Z_j^{l,m}$ being constants in the space but varying in time. Notice that the norm in $\mathcal{Y}_L(\Gamma_j)$ of any of these functions is the square root of the sum of squared coefficients times the radius of Γ_j , i.e.

$$\left\|v_{j}^{L}\right\|_{\mathcal{Y}_{L}(\Gamma_{j})}^{2} = R_{j} \sum_{l=0}^{L} \sum_{m=-l}^{l} (v_{j}^{l,m})^{2}.$$
(16)

Finally, let $\mathbb{Y}_L := \prod_{j=1}^{\mathcal{N}} \mathcal{Y}_{\mathcal{L}}(\Gamma_j)$, and define the following vectors in \mathbb{Y}_L :

$$\mathbf{v}^{L} := \left(v_{1}^{L}, \dots, v_{j}^{L}, \dots, v_{\mathcal{N}}^{L}\right)^{t}, \qquad \mathbf{Z}^{L} := \left(z_{1}^{L}, \dots, Z_{j}^{L}, \dots, z_{\mathcal{N}}^{L}\right)^{t}, \qquad (17a)$$

$$\mathbf{u}_{D,0}^{L} := \left(u_{D,01}^{L}, \dots, u_{D,0j}^{L}, \dots, u_{D,0N}^{L}\right)^{t}, \qquad \mathbf{u}_{D}^{L} := \left(u_{D,1}^{L}, \dots, u_{D,j}^{L}, \dots, u_{D,N}^{L}\right)^{t},$$
(17b)

$$\mathbf{u}_{N,0}^{L} := \left(u_{N,01}^{L}, \dots, u_{N,0j}^{L}, \dots, u_{N,0\mathcal{N}}^{L}\right)^{t}, \qquad \mathbf{u}_{D}^{L} := \left(u_{N,1}^{L}, \dots, u_{N,j}^{L}, \dots, u_{N,\mathcal{N}}^{L}\right)^{t}.$$
(17c)

The norm for a function in \mathbb{Y}_L , for example, \mathbf{v}^L , is $\|\mathbf{v}^L\|_{\mathbb{Y}_L}^2 = \sum_{j=1}^{\mathcal{N}} ||v_j^L||_{\mathcal{Y}_L(\Gamma_j)}^2$.

3.2.2 BIOs discretization

The fundamental solution can be expanded using spherical harmonics [7, Theorem 4.3.29, Lemma 4.4.1 and Remark 4.4.2] as the following result shows.

Theorem 3.2. Let \mathbf{r} , \mathbf{r}' be vectors, whose spherical coordinates in the reference system j are $(r_j, \theta_j, \varphi_j)$ and $(r'_i, \theta'_j, \varphi'_j)$, respectively. For $r_j > r'_j$ we have that

$$g(\mathbf{r}, \mathbf{r}') = \sum_{l=0}^{\infty} \frac{1}{2l+1} \frac{r_j^{'l}}{r_j^{l+1}} \sum_{m=-l}^{l} Y_{l,m,j}(\mathbf{r}) Y_{l,m,j}(\mathbf{r}').$$
(18)

Moreover, the series (18) and its term by term first derivatives with respect to r_j or r'_j are absolutely and uniformly convergent on compact subsets with $r_j > r'_j$ [6, Section 2.3, p.23 and p.24].

Theorem 3.3. The diagonal forms of the BIOs (5) are:

$$\begin{split} V_{j,j}^{0}\left(Y_{l,m,j}\right) &= \frac{1}{2l+1}R_{j}Y_{l,m,j}, & V_{j}\left(Y_{l,m,j}\right) &= \frac{1}{2l+1}R_{j}Y_{l,m,j}, \\ K_{j,j}^{0}\left(Y_{l,m,j}\right) &= \frac{1}{2(2l+1)}Y_{l,m,j}, & K_{j}\left(Y_{l,m,j}\right) &= -\frac{1}{2(2l+1)}Y_{l,m,j}, \\ K_{j,j}^{*0}\left(Y_{l,m,j}\right) &= \frac{1}{2l+1}Y_{l,m,j}, & K_{j}^{*}\left(Y_{l,m,j}\right) &= -\frac{1}{2(2l+1)}Y_{l,m,j}, \\ W_{j,j}^{0}\left(Y_{l,m,j}\right) &= \frac{l(l+1)}{2l+1}\frac{1}{R_{j}}Y_{l,m,j}, & W_{j}\left(Y_{l,m,j}\right) &= \frac{l(l+1)}{2l+1}\frac{1}{R_{j}}Y_{l,m,j}. \end{split}$$

Proof. The result follows from Theorem 3.2, the orthonormality of spherical harmonics, and the definitions of the BIOs presented in (5). Similar diagonal forms can also be found in [28, Section 3 and Table 2], where the result is stated for complex spherical harmonics on the unit sphere. \Box

Corollary 3.4. The following holds

$$\begin{split} \left(V_{j,j}^{0} \left(Y_{l,m,j} \right), Y_{p,q,j} \right)_{L^{2}(\Gamma_{j})} &= \left(V_{j} \left(Y_{l,m,j} \right), Y_{p,q,j} \right)_{L^{2}(\Gamma_{j})} = \frac{R_{j}^{3}}{2l+1} \delta_{l,p} \delta_{m,q}, \\ \left(K_{j,j}^{0} \left(Y_{l,m,j} \right), Y_{p,q,j} \right)_{L^{2}(\Gamma_{j})} &= - \left(K_{j} \left(Y_{l,m,j} \right), Y_{p,q,j} \right)_{L^{2}(\Gamma_{j})} = \frac{R_{j}^{2}}{2(2l+1)} \delta_{l,p} \delta_{m,q}, \\ \left(K_{j,j}^{*0} \left(Y_{l,m,j} \right), Y_{p,q,j} \right)_{L^{2}(\Gamma_{j})} &= - \left(K_{j}^{*} \left(Y_{l,m,j} \right), Y_{p,q,j} \right)_{L^{2}(\Gamma_{j})} = \frac{R_{j}^{2}}{2(2l+1)} \delta_{l,p} \delta_{m,q}, \\ \left(W_{j,j}^{0} \left(Y_{l,m,j} \right), Y_{p,q,j} \right)_{L^{2}(\Gamma_{j})} &= \left(W_{j} \left(Y_{l,m,j} \right), Y_{p,q,j} \right)_{L^{2}(\Gamma_{s})} = \frac{l(l+1)}{2l+1} R_{j} \delta_{l,p} \delta_{m,q}, \end{split}$$

with $\delta_{l,p}$, $\delta_{m,q}$ denoting the standard Kronecker deltas. Also, for the scalar identity operators presented in Section 2.3, it holds that $(I(Y_{l,m,j}), Y_{p,q,j})_{L^2(\Gamma_j)} = R_j^2 \delta_{l,p} \delta_{m,q}$.

Cross-interaction operators, e.g. $V_{i,j}^0$ for $i \neq j$, are non-singular and generally non diagonalizable. The double and single layer operators analytic expressions can be used to compute the non-singular integrals for $i \neq j$:

$$\left(V_{i,j}^{0}\left(Y_{l,m,j}\right);Y_{p,q,i}\right)_{L^{2}(\Gamma_{i})} = \int_{\Gamma_{i}} SL_{0j}(Y_{l,m,j})Y_{p,q,i} \ d\Gamma_{i},\tag{19a}$$

$$\left(K_{i,j}^{0}\left(Y_{l,m,j}\right);Y_{p,q,i}\right)_{L^{2}(\Gamma_{i})} = \int_{\Gamma_{i}} DL_{0j}(Y_{l,m,j})Y_{p,q,i} \ d\Gamma_{i},\tag{19b}$$

$$\left(K_{i,j}^{*0}(Y_{l,m,j});Y_{p,q,i}\right)_{L^{2}(\Gamma_{i})} = \int_{\Gamma_{i}} \widehat{\mathbf{n}}_{0i} \cdot \nabla SL_{0j}(Y_{l,m,j})Y_{p,q,i} \ d\Gamma_{i},$$
(19c)

$$\left(W_{i,j}^{0}\left(Y_{l,m,j}\right);Y_{p,q,i}\right)_{L^{2}(\Gamma_{i})} = -\int_{\Gamma_{i}}\widehat{\mathbf{n}}_{0i}\cdot\nabla DL_{0j}(Y_{l,m,j})Y_{p,q,i}\ d\Gamma_{i}.$$
(19d)

Approximations of the integrals (19) are provided via Gauss-Legendre quadratures. Specifically, along θ , we use the change of variable $u = \cos(\theta)$. Then, variable functions are sampled at the zeros of the Legendre Polynomial of degree $L_c + 1$, whereas the trapezoidal rule is applied to equally spaced nodes in φ , with $2L_c + 1$ points. If the function being integrated has a spherical harmonic

expansion with coefficients equal to zero for degrees higher than L_c , then the quadrature yields the exact result, assuming that there are not other sources of error [29]. Moreover, quadrature in φ can be computed using the Fast Fourier Transform.

Remark 3.5. One would expect L_c to be greater than p and l in (19). Yet, without further analysis, it is not known if a polynomial of degree L_c is a good approximation for $SL_{0j}(Y_{l,m,j})Y_{p,q,i}$, $DL_{0j}(Y_{l,m,j})Y_{p,q,i}$, $\nabla SL_{0j}(Y_{l,m,j}) \cdot \hat{\mathbf{n}}_{0i} Y_{p,q,i}$ and $\nabla SL_{0j}(Y_{l,m,j}) \cdot \hat{\mathbf{n}}_{0i} Y_{p,q,i}$, since, as the translation theorems for spherical harmonics highlight, the translation of only one spherical harmonic is expressed as another infinite series of spherical harmonics. Also, notice that (19) can also be computed using a translation theorem for real spherical harmonics as in [1]. In this case, the integral has an explicit expression and does not need to be computed numerically. Instead, the computing efforts focus on calculating the coefficients given by the translation theorem.

Corollary 3.6. The following holds

$$\begin{split} & \left(V_{i,j}^{0} \left(Y_{l,m,j} \right); Y_{p,q,i} \right)_{L^{2}(\Gamma_{i})} = \left(V_{j,i}^{0} \left(Y_{p,q,i} \right); Y_{l,m,j} \right)_{L^{2}(\Gamma_{j})}, \\ & \left(K_{i,j}^{0} \left(Y_{l,m,j} \right); Y_{p,q,i} \right)_{L^{2}(\Gamma_{i})} = -\frac{l}{R_{j}} \left(V_{i,j}^{0} \left(Y_{l,m,j} \right); Y_{p,q,i} \right)_{L^{2}(\Gamma_{i})}, \\ & \left(K_{j,i}^{*0} \left(Y_{p,q,i} \right); Y_{l,m,j} \right)_{L^{2}(\Gamma_{j})} = \left(K_{i,j}^{0} \left(Y_{l,m,j} \right); Y_{p,q,i} \right)_{L^{2}(\Gamma_{i})}, \\ & \left(W_{i,j}^{0} \left(Y_{l,m,j} \right); Y_{p,q,i} \right)_{L^{2}(\Gamma_{i})} = \frac{l}{R_{j}} \left(K_{i,j}^{*0} \left(Y_{l,m,j} \right); Y_{p,q,i} \right)_{L^{2}(\Gamma_{i})}. \end{split}$$

Proof. The result follows from Theorem 3.2, the orthonormality of spherical harmonics along with the definition of the BIOs. \Box

From this last corollary, it can be deduced that the integrals of all the cross-interactions of a couple of spheres i and j (19) can be derived having the results of the expression (19a) for all of the l, m, p and q needed, which avoids the need of computing numerically the other integral expressions.

3.3 Fully discrete scheme.

Following Section 3.1, we state the semi-implicit in time and space numerical discretization of Problem 2.5:

Problem 3.7. Let $\mathbf{v}^{L,(0)}$ and $\mathbf{Z}^{L,(0)}$ in \mathbb{Y}_L be given. Then, for $s \in \{2, ..., S-1\}$, we seek $\mathbf{v}^{L,(s)}$, $\mathbf{Z}^{L,(s)}$ in \mathbb{Y}_L solution of:

$$\left(\mathbf{C}_{\mathbf{m}}\overline{\partial}\mathbf{v}^{L,(s)} + \mathcal{J}_{\mathcal{N}}\left(\overline{\mathbf{v}}^{L,(s+\frac{1}{2})}\right) + \mathbf{I}^{ep}\left(\hat{\mathbf{v}}^{L,(s+\frac{1}{2})}, \hat{\mathbf{Z}}^{L,(s+\frac{1}{2})}\right) + \Phi\left(\phi_{e}^{(s+\frac{1}{2})}\right), \mathbf{y}\right)_{\mathbb{Y}_{L}} = 0 \qquad (20)$$

$$\overline{\partial}^{(s)} Z_j^L = \max\left(\frac{\beta_j(\widehat{v}_j^{L,(s+\frac{1}{2})}) - \widehat{Z}_j^{L,(s+\frac{1}{2})}}{\tau_{ep,j}}, \frac{\beta_j(\widehat{v}_j^{L,(s+\frac{1}{2})}) - \widehat{Z}_j^{L,(s+\frac{1}{2})}}{\tau_{res,j}}\right),$$
(21)

for all $\mathbf{y} \in \mathbb{Y}_L$. For s = 1 we use the equivalent weak formulation of the corrector-predictor algorithm presented in 3.1.

In order to solve Problem 3.7, at each time step, with the exception of the predictor-corrector algorithm, we solve the weak linear system equivalent to

$$\begin{bmatrix} 4\mathbf{A}_{0,\mathcal{N}} & -2\mathbf{X}_{\mathcal{N}}^{-1} & \mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \\ -2\mathbf{X}_{\mathcal{N}} & 4\mathbf{A}_{1,\mathcal{N}} & -\mathbf{X}_{\mathcal{N}}\mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \\ \boldsymbol{\sigma}_{\mathcal{N}\times4\mathcal{N}} & \frac{1}{\tau}\mathbf{C}_{\mathbf{m}} \end{bmatrix} \begin{pmatrix} \overline{\mathbf{u}}_{D,(s+1/2)}^{L,(s+1/2)} \\ \overline{\mathbf{u}}_{D,(s+1/2)}^{L,(s+1/2)} \\ \overline{\mathbf{u}}_{N}^{L,(s+1/2)} \\ \mathbf{v}^{L,(s+1)} \end{pmatrix} = \begin{pmatrix} -\left(2\gamma_{\phi_{e}^{L,(s+\frac{1}{2})}}^{0} + \mathbf{I}_{2\mathcal{N}\times\mathcal{N}}\mathbf{v}^{L,(s)}\right) \\ \mathbf{X}_{\mathcal{N}}\left(2\gamma_{\phi_{e}^{L,(s+\frac{1}{2})}}^{0} + \mathbf{I}_{2\mathcal{N}\times\mathcal{N}}\mathbf{v}^{L,(s)}\right) \\ \frac{1}{\tau}\mathbf{C}_{\mathbf{m}}\mathbf{v}^{L,(s)} - \mathbf{I}^{ep}\left(\hat{\mathbf{v}}^{L,(s+\frac{1}{2})}, \hat{\mathbf{Z}}^{L,(s+\frac{1}{2})}\right) \end{pmatrix}, \quad (22)$$

where the test function is in $\mathbb{Y}_L \times \mathbb{Y}_L \times \mathbb{Y}_L \times \mathbb{Y}_L \times \mathbb{Y}_L$. Notice that we obtain mid-steps (s+1/2) for traces of extra- and intracellular potentials, whereas only the transmembrane potential is obtained at time steps s.

Remark 3.8. With the exception of the scalar operators inside of $\mathbf{A}_{0,N}$ and \mathbf{I}^{ep} , which are computed numerically, all other matrices are diagonalizable and analytic for the geometry here considered (Theorem 3.4). Thus, the discrete matrix used to solve at each time step is almost entirely block diagonal. Note that if changing \mathbf{I}^{ep} without modifying the dynamics for the transmembrane potentials, leads to a modified right-hand side in the linear system of equation (22).

4 Numerical Results

In this section, we verify and test the proposed computational scheme. To this end, we first check the MTF implementation for single and multiple cells to then combine it with the semi-implicit timedomain method. Next, we perform tests for linear and non-linear dynamics. Physical parameters used thorough the Section are given in [21, Table 1] and [17, Table 1].

4.1 Hardware and Code Implementation

Numerical results were obtained in a machine with Quad Core Intel Core i7-4770 (-MT MCP-), 1498 MHz, 31982.1 MiB RAM (90% available for computations), with operating system Linux Mint 20.3 Una and Kernel: 5.4.0-131- generic x86_64. Simulation codes were programmed on Python 3.10. Its installation was via the open-source platform Anaconda⁴, Conda⁵ 4.13.0, and using the conda-forge repository.⁶ With the numpy library, we take advantage of vectorized computations. Moreover, we only use direct solvers. The code is implemented sequentially with no compression.

4.2 Code validation

In order to validate our code, we check that computed solutions satisfy to fulfill discrete Calderón identities at the boundaries as well as discrete jump conditions. Being approximations, these properties do not hold exactly, thus we define the following errors:

• Discrete Calderón exterior and interior errors respectively:

$$\frac{\left\| \left(2\mathbf{A}_{0,\mathcal{N}} - \mathbf{I} \right) \begin{pmatrix} \mathbf{u}_{D,0}^{L,(s+1)} \\ \mathbf{u}_{D,0}^{L,(s+1)} \end{pmatrix} \right\|_{\mathbb{Y}_{L} \times \mathbb{Y}_{L}}, \left\| \left(2\mathbf{A}_{1,\mathcal{N}} - \mathbf{I} \right) \begin{pmatrix} \mathbf{u}_{D}^{L,(s+1)} \\ \mathbf{u}_{N}^{L,(s+1)} \end{pmatrix} \right\|_{\mathbb{Y}_{L} \times \mathbb{Y}_{L}}.$$
(23)

⁴https://www.anaconda.com/products/distribution

⁵https://docs.conda.io/projects/conda/en/stable/

⁶The following packages were installed explicitly: pyshtools 4.10 [29], (conda install pyshtools=4.10), numpy 1.23.1, scipy 1.9.0, and matplotlib-base 3.5.2.

• Jump error:

$$\left\| \begin{pmatrix} \mathbf{u}_{D,0}^{L,(s+1)} \\ \mathbf{u}_{N,0}^{L,(s+1)} \end{pmatrix} - \mathbf{X}_{\mathcal{N}}^{-1} \begin{pmatrix} \mathbf{u}_{D}^{L,(s+1)} \\ \mathbf{u}_{N}^{L,(s+1)} \end{pmatrix} + \mathbf{I}_{2\mathcal{N}\times\mathcal{N}} \mathbf{v}^{L} + \boldsymbol{\gamma}^{0j} \phi_{e}^{L} \right\|_{\mathbb{Y}_{L}\times\mathbb{Y}_{L}} \approx 0.$$
(24)

Here the norm $\|\cdot\|_{\mathbb{Y}_L \times \mathbb{Y}_L}$ is computed as

$$\left\| \begin{pmatrix} \mathbf{u}_D^{L,(s+1)} \\ \mathbf{u}_N^{L,(s+1)} \end{pmatrix} \right\|_{\mathbb{Y}_L \times \mathbb{Y}_L}^2 = \left\| \mathbf{u}_D^{L,(s+1)} \right\|_{\mathbb{Y}_L}^2 + \left\| \mathbf{u}_N^{L,(s+1)} \right\|_{\mathbb{Y}_L}^2.$$

In what follows, we will use the following notations:

• Relative error in $L^2(\Gamma_i)$:

$$re_2(\phi_1,\phi_2)_j := \frac{\|\phi_1 - \phi_2\|_{L^2(\Gamma_j)}}{\|\phi_1\|_{L^2(\Gamma_j)}}.$$
(25)

This error is computed for spherical harmonics expansions when possible (16) or using the numerical quadrature presented at the end of Section 3.2.2.

• Relative error in $C^0((0,T), L^2(\Gamma_1))$:

$$re_{\infty,2}(\phi_1,\phi_2)_j := \frac{\max_{t_s \in T_s} \|\phi_1(t_s + \tau/2) - \phi_2(t_s + \tau/2)\|_{L^2(\Gamma_j)}}{\max_{t_s \in T_s} \|\phi_1(t_s + \tau/2)\|_{L^2(\Gamma_j)}}.$$
(26)

• Relative error in $L^2((0,T), L^2(\Gamma_1))$:

$$re_{2,2}(\phi_1,\phi_2)_j := \frac{\|\phi_1 - \phi_2\|_{L^2((0,T),L^2(\Gamma_1))}}{\|\phi_1\|_{L^2((0,T),L^2(\Gamma_1))}}.$$
(27)

The approximation of the time integral is done by a composite trapezoidal rule using the points of the computed time mid-steps.

4.2.1 MTF Validation

We verify first the MTF method without time evolution, by solving Problem 10 for four different geometrical configurations and sources. In all four experiments, we set $\mathbf{v} = \mathbf{0}$ and use the point source function $\phi_e = 1/(4\pi\sigma_0 \|\mathbf{r} - \mathbf{p}_0\|_2)$ as the external applied potential.

- Example 1: One sphere centered at the origin with intracellular conductivity σ_1 different from σ_0 .
- Example 2: Three (aligned) spheres. The first and the third one have conductivity σ_0 (phantom sphere), while the one in the middle has a different conductivity σ_1 .

The parameters used for validation for Examples 1 and 2 for a single sphere are presented in Table 1, additional parameters for Example 2 are presented in Table 3. Discrete Calderón and jump errors (23), (24) are presented in Table 2. In Example 1, the sphere has a different conductivity

Table 1: Parameters used in Section 4.2.1 for Example 1 and 2 for the MTF validation. Conductivity values are from [17, Table 1], cell radius from [21, Table 1].

Parameter	Symbol	Example 1	Unit
Intensity	a	1	μA
Source position	P0	(0, 0, 20)	$\mu \mathrm{m}$
Extracellular conductivity	σ_0	5	$\mu S/\mu m$
Intracellular conductivity	σ_1	0.455	$\mu S/\mu m$
Cell radius	R_1	10	$\mu \mathrm{m}$
Maximum degree of spherical harmonics		50	

Table 2: Discrete Calderón errors and jump errors for Examples 1 and 2 from Section 4.2.1.

Error	Example 1	Example 2
Discrete Calderón exterior	$2.61 \cdot 10^{-17}$	$2.38 \cdot 10^{-16}$
Discrete Calderón interior	$2.61 \cdot 10^{-17}$	$2.31 \cdot 10^{-16}$
Jump error	$2.61 \cdot 10^{-17}$	$2.38 \cdot 10^{-16}$

than the extracellular space, and an analytic solution can be obtained. In Figure 2 the relative errors in $L^2(\Gamma_1)$ (25) of the computed solutions for different L against the analytic solution are presented. The image shows the expected exponential convergence with respect to the maximum degree of the spectral basis L. Discrete Calderón and jump errors are given in Table 2. Example 2 involves three spheres, two of those having the same properties as the external medium, while the one in the middle is different (see Figure 3). Therefore, the traces of the latter should be equal to the ones computed without the first two, i.e. the same as in Example 1. The relative $L^2(\Gamma_1)$ error of the difference between the analytic solution for the four traces and the numerical one corresponding to the sphere with different conductivity, is $6.06 \cdot 10^{-15}$. In Figure 3, u_0^{50} is plotted where the only sphere showing a response to ϕ_e is the sphere in the middle that has different properties compared to the external medium. Discrete Calderón and jump errors are given in Table 2, with errors of order 10^{-16} .

4.2.2 Semi-implicit time approximation validation: linear case

To validate the proposed time discretization, we solve problem (20) for a linear current with only one cell $c_{m,1}\partial_t v_1 + \frac{1}{r_{m,1}}v_j = -\sigma_1\gamma_N^1 u_1$, where instead of $I_1^{ep}(v_1, Z_1)$ we use $\frac{1}{r_{m,1}}v_j$. Additionally, we assume that ϕ_e can be factorized $\phi_e(t, \mathbf{r}) = \phi_{time}(t)\phi_{space}(\mathbf{r})$. If ϕ_{space} is expanded in spherical harmonics, the coefficients for the equivalent expansion of v_1 , $v_1^{l,m}$, can be obtained by solving $\frac{\partial}{\partial_t}v_1^{l,m} + \alpha_1^{l,m} v_1^{l,m} = -\beta_1^{l,m} \phi_{time}(t)$, with

$$\alpha_1^{l,m} := \frac{1}{c_m R_m} + \frac{\sigma_0 \sigma_1 l(l+1)}{c_m R_1(\sigma_0(l+1) + \sigma_1 l)}, \ \beta_1^{l,m} := \frac{\sigma_0 \sigma_1 l(b_{d,l,m}(l+1) - b_{n,l,m} R_1)}{c_m R_1(\sigma_0(l+1) + \sigma_1 l)}$$

where $b_{d,l,m}$ and $b_{n,l,m}$ are the coefficient of degree l and order m of the Dirichlet and Neumann expansion of ϕ_{space} on the cell membrane, respectively. Then, the spherical harmonic expansion



Figure 2: Error convergence for traces in Example 1 (Section 4.2.1). The relative error $L^2(\Gamma_1)$ (25) is computed against the analytic solution with parameter values in Table 1.

Table 3: Parameters used for the MTF verification with $\phi_e = 1/(4\pi\sigma_0 \|\mathbf{r} - \mathbf{p}_0\|_2)$ in Example 2, Section 4.2.1. Conductivities are given in [17, Table 1] and radii are in [21, Table 1].

Parameter	Symbol	Value	Unit
Cell 1 intracellular conductivity	σ_1	0.455	$\mu \mathrm{S}/\mu \mathrm{m}$
Cell 2 and 3 intracellular conductivity	σ_2, σ_3	5	$\mu { m S}/\mu { m m}$
Cell 1 radius	R_1	10	$\mu { m m}$
Cell 2 radius	R_2	8	$\mu { m m}$
Cell 3 radius	R_3	9	$\mu\mathrm{m}$
Cell 1 center position	$\mathbf{p_1}$	(0, 0, 0)	$\mu { m m}$
Cell 2 center position	$\mathbf{p_2}$	(25, 0, 0)	$\mu\mathrm{m}$
Cell 3 center position	\mathbf{p}_3	(-24, 0, 0)	$\mu { m m}$
Maximum degree of spherical harmonics	L	50	
Quadrature degree	L_c	100	



Figure 3: Field u_0^{50} of Example 2, Section 4.2.1 with parameters from Table 3.

Table 4: Parameters used for the time scheme validation in Section 4.2.2 where linear dynamics are assumed. The external potential is $\phi_e = I(t)/(4\pi\sigma_0 \|\mathbf{r} - \mathbf{p_0}\|_2)$ and only one cell is considered. Conductivity values are given in [17, Table 1], the cell radius and the specific membrane capacitance are given in [21, Table 1], and the specific membrane resistance is from [12, Table 1].

Parameter	Symbol	Values	Unit
Intensity	I(t)	e^{-t} and 1	μA
Source position	\mathbf{p}_0	(0, 0, 50)	$\mu \mathrm{m}$
Extracellular conductivity	σ_0	5	$\mu S/\mu m$
Intracellular conductivity	σ_1	0.455	$\mu S/\mu m$
Specific membrane capacitance	$c_{m,1}$	$9.5\cdot10^{-3}$	$pF/(\mu m)^2 (=F/m^2)$
Specific membrane resistance	$r_{m,1}$	$1 \cdot 10^{5}$	$M\Omega(\mu m)^2$
Cell Radius	R_1	7	$\mu \mathrm{m}$
Length time step	au	0.025	μs
Final time	T	2.5	μs
Maximum degree of spherical harmonics	L	25	

coefficients of v_1 are

$$v_1^{l,m}(t) = -\beta_1^{l,m} e^{-\alpha_1^{l,m}t} \int_0^t \phi_{time}(s) e^{\alpha_1^{l,m}s} ds + v_1^{l,m}(0) e^{-\alpha_1^{l,m}t}$$

We present simulation results for the two different time parts of ϕ_e , $\phi_{time-exp} = e^{-t}$ and $\phi_{time-cte} = 1$. We use a point source function for the spatial part of ϕ_e . Parameters are presented in Table 4. In Figure 4, the absolute error of the difference between \overline{v}_1^{23} ($\tau = 0.025\mu$ s) and v_1 in space is presented for each mid-time step. We compute also $\frac{\tau^2}{4} \|\partial_t^2 v_1\|_{L^2(\Gamma_j)}$ to validate the first bound in Theorem 3.1. For $\phi_{time-exp}$, the absolute error satisfies the first bound in Theorem 3.1 everywhere except for the range between 0.4 μ s and 0.7 μ s, caused by a too large τ . For $\phi_{time-cte}$ the bound is fulfilled at all times.

Finally, Figure 5 presents the relative error in time and space for decreasing values of τ . We compute the error using two norms: an approximation of the $C^0((0,T), L^2(\Gamma_1))$ -norm taking the maximum value at each mid-step computed (26), and an approximation of the $L^2((0,T), L^2(\Gamma_1))$ -norm, using a composite trapezoidal rule with the computed mid-steps (27). We observe that the slope of the errors in the log-log plot is close to two, therefore the error decreases as τ^2 .

4.3 Numerical Results for a Single Cell with Nonlinear Dynamics

After having verified our numerical scheme for the linear dynamics, we now we study the nonlinear dynamics for a single cell (Problem 2.5). Note that in [11, Theorem 6.14] error estimates are given in 2D for the Hodgkin-Huxley model. The estimates depend on four terms: the first two are the norms of the difference between initial conditions and approximated ones used in the computations; the third is related to the spatial discretization, where a spectral basis in 2D is used, and this term is proved to decay exponentially with the total number of functions in the spatial discretization basis; the fourth one is related to the time approximation, and it decays as τ^2 . Here, we expect a similar behavior. In other words, fixing the maximum degree of spherical harmonics L used in the discretization and decreasing the length of the time step τ , we expect to see the error converging



Figure 4: Absolute error in $L^2(\Gamma_1)$ between \overline{v}_1^{25} (discrete approximation) and v_1 (analytic solution), as well as $\frac{\tau^2}{4} \|\partial_t^2 v_1(t_s)\|_{L^2(\Gamma_j)}$, plotted to verify the bound given by Theorem 3.1 for the time scheme from Section 4.2.2 where linear dynamics are assumed. The time step τ is 0.025 μ s and the rest of the parameters used are in Table 4.



Figure 5: Error convergence for diminishing time steps τ for the time scheme in Section 4.2.2 where linear dynamics are assumed. Slopes on the log-log plot show error converges as τ^2 . Relative errors $re_{\infty,2}(v_1, v_1^{25})_1$ and $re_{2,2}(v_1, v_1^{25})_1$ are given in (26) and (27), respectively. Simulation parameters can be found in Table 4.

Table 5: Parameters used for the simulation of a single cell with non-linear dynamics (2e) in Section 4.3.1 when studying the time convergence with fixed L. Parameters used are found in [17, Table 1].

Parameter	Symbol	Values	Unit
Cell Radius	R_1	10	μm
Time part of ϕ_e	ϕ_{time}	1	
Spatial part of ϕ_e	$\phi_{spatial}$	$5 \ z \cdot 10^{-2}$	V
Extracellular conductivity	σ_0	5	$\mu S/\mu m$
Intracellular conductivity	σ_1	0.455	$\mu { m S}/\mu { m m}$
Lipid surface conductivity	$S_{L,1}$	$1.9 \cdot 10^{-6}$	$\mu S/(\mu m)^2$
Irreversible surface conductivity	$S_{ir,1}$	$2.5\cdot 10^2$	$\mu S/(\mu m)^2$
Specific membrane capacitance	$c_{m,1}$	$9.5 \cdot 10^{-3}$	$\mathrm{pF}/(\mu\mathrm{m})^2$
Transmembrane potential threshold	$V_{rev,1}$	1.5	V
Electropermeabilization switch speed	$k_{ep,1}$	40	V^{-1}
Characteristic time of electropermeabilization	$\tau_{ep,1}$	1	$\mu { m s}$
Characteristic resealing time	$\tau_{res,1}$	10^{3}	$\mu { m s}$
Final time	T	26	$\mu \mathrm{s}$
Maximum degree of spherical harmonics	L	1	
Quadrature degree	L_c	2	

to a constant depending on L. Similarly, if we fix τ and increase L, we expect the error to converge to a constant depending on τ .

4.3.1 Time convergence for a fixed L

We use the parameters presented in Table 5 to solve the non-linear discrete Problem 3.7, with external applied potential $\phi_e = 5z \cdot 10^{-2}$, and initial conditions equal to zero. Since we no longer possess an analytic solution for comparison, we check for convergence as time steps become smaller. We remark that L is fixed, and we use L = 1, along with $L_c = 2$.

Table 6 displays the error norms between two successively refined solutions for different time steps. These results show a convergence rate of one as the time step decreases, and thus we do not obtain the same as in [11]. This is due to the lesser regularity in time of the functions used in the non-linear electropermeabilization model. In Figure 6, we plot the evolution of the transmembrane potential v_1^1 for three different values of τ . Though the solution shapes are similar, peaks appear at different locations and coincide as the time step decreases. Specifically, between $\tau = 2.6 \cdot 10^{-3} \mu s$ and $\tau = 2.6 \cdot 10^{-4} \mu s$, there is a delay of less than 0.16 μs , while between $\tau = 2.6 \cdot 10^{-4} \mu s$ and $\tau = 2.6 \cdot 10^{-5} \mu s$ the delay is less than 0.017 μs .

4.3.2 Spatial convergence with nonlinear dynamics

We now present numerical results for different maximum degrees of the spherical harmonics, L = 51and $L \in [1, 2, ..., 36]$, computed with $L_c = 150$. Given that we use a spectral discretization in space, we expect an exponential decrease in the error when increasing the maximum degree L—recall that the number of spatial discretization functions basis is $(L + 1)^2$ ⁷. The external applied potential is $\phi_e = 5z \cdot 10^{-2}$ until t = 5 and equal to zero thereafter. Initial conditions are set to zero, and the length of the time step used is $\tau \approx 0.0024$.

 $^{^{7}}$ The parameters used are provided in Table 7. Notice that extra- and intracellular conductivities have different values from the previous simulations, and were changed to obtain a response of the impulse sooner.

Table 6: Error convergence for the nonlinear problem with one cell from Section 4.3.1 for fixed L. Computed norms are the difference between two successive solutions. Parameters used are in Table 5.

$ au_i$	Value $[\mu s]$	$\max_{t \in [0,T]} v_1^{1,\tau_{i+1}} - v_1^{1,\tau_i} _{L^2(\Gamma_1)}$	$\max_{t \in [0,T]} Z_1^{1,\tau_{i+1}} - Z_1^{1,\tau_i} _{L^2(\Gamma_1)}$
$ au_1$	$2.6 \cdot 10^{-3}$	-	-
$ au_2$	$2.6 \cdot 10^{-4}$	8.8	$4.64 \cdot 10^{-3}$
$ au_3$	$2.6 \cdot 10^{-5}$	0.9	$3.02 \cdot 10^{-4}$
$ au_4$	$2.6 \cdot 10^{-6}$	0.097	$3.59 \cdot 10^{-5}$
$ au_5$	$2.6\cdot 10^{-7}$	0.0097	$3.15 \cdot 10^{-6}$



Figure 6: Evolution of v_1^1 at the north pole of the cell ($\theta = 0$) for different lengths of time step τ illustrating the time convergence for fixed L, Section 4.3.1. The image at the right is zoomed near to the maximum value of v_1^1 . Parameters employed are given in Table 5.

Table 7: Parameters used in the numerical simulations in Sections 4.3.2 and 4.4, with the nonlinar dynamics of the electropermeabilization model. The specific choice of extra- and intracellular conductivities, different from the previous simulations, allow us to obtain a response of the impulse sooner in time. The rest of the parameters are from [17, Table 1]. The external applied potential used is equal to zero after t = 5.

Parameter	Symbol	Values	Unit
Cell Radius	R_1	10	μm
External applied potential	ϕ_e	$5 \ z \cdot 10^{-2}$	V
Extracellular conductivity	σ_0	15	$\mu S/\mu m$
Intracellular conductivity	σ_1	1.5	$\mu S/\mu m$
Specific membrane capacitance	$c_{m,1}$	$9.5 \cdot 10^{-3}$	$pF/(\mu m)^2 (=F/m^2)$
Lipid surface conductivity	$S_{L,1}$	$1.9 \cdot 10^{-6}$	$\mu S/(\mu m)^2$
Irreversible surface conductivity	$S_{ir,1}$	$2.5 \cdot 10^{2}$	$\mu S/(\mu m)^2$
Specific membrane capacitance	$c_{m,1}$	$9.5 \cdot 10^{-3}$	$pF/(\mu m)^2$
Transmembrane potential threshold	$V_{rev,1}$	1.5	V
Electropermeabilization switch speed	$k_{ep,1}$	40	V^{-1}
Characteristic time of electropermeabilization	$ au_{ep,1}$	1	μs
Characteristic resealing time	$\tau_{res,1}$	10^{3}	μs
Final time	T	10	μs

We compute the relative errors between v_1^L and v_1^{51} , and between Z_1^L and Z_1^{51} . The results are shown in Figure 7. The plots are in a log-linear scale, and the errors tends to form a straight line with the slope of order -10^{-2} , which suggests an exponential rate of convergence. Recall, that β (1) in our case is only continuous $C^0(\mathbb{R})$ due to the discontinuity of the derivative at the origin worsening the rate of convergence. While the obtained Z_1 is an even function in space, v_1 is an odd one. Thus, the nonlinear current, is an odd function in space. The external applied potential is an odd function, so we expect that v_1 has an odd component, while Z_1 is defined by an ordinary differential equation that takes v_1 in to an even function. Finally, in Figure 8 we plot the evolution in time of v_1^{17} , v_1^{24} , v_1^{35} , and v_1^{51} at the north pole. The differences between the results are more noticeable after the peak of the potential and when the cell tries to stabilize it.

4.4 **Results with multiple cells**

In previous sections, the convergence of the numerical method was studied for a single cell. We proceed now with the case of multiple cells to perform five experiments in the nonlinear case. The examples presented highlight how the distance among cells affects the results as all cell conductivities are set to the same value σ_1 .

- Example 3: Three cells aligned along the x-axis and far from each other, with distance between cells $18R_1$.
- Example 4: Three cells aligned along the x-axis, near from each other, with distance between cells $R_1/2$.
- Example 5: Eight cells aligned in a cubic lattice, the nearest distance between two cells is $R_1/2$, the first sphere is at the origin.



Figure 7: Spatial convergence for the nonlinear dynamics of Section 4.3.2. Relative norms are computed against an overkill of L = 51. On the left, results for v_1^L , while on the right Z_1^L is displayed with time step $\tau \approx 0.0024 \ \mu$ s. The *x*-axis indicates the maximum degree used for discretization. Convergence starts from L = 11. Plots are in log-linear scale and error tends to form a straight line with slope of approximately -10^{-2} , i.e. exponential convergence. Parameters are given in Table 7.



Figure 8: Evolution of the transmembrane potentials v_1^{17} , v_1^{24} , v_1^{35} and v_1^{51} at the north pole of the cell ($\theta = 0$) obtained in Section 4.3.2 where the spatial convergence for one cell in the nonlinear case is studied. The time step used is $\tau \approx 0.0024 \ \mu$ s, with parameters given in Table 7.

Table 8: Center positions for Examples 3 and 4 from Section 4.4, where nonlinear dynamics are simulated.

Center position	Symbol	Example 3	Example 4	Unit
Cell 1	p 1	(0, 0, 0)	(0, 0, 0)	μm
Cell 2	$\mathbf{p_2}$	(200, 0, 0)	(25, 0, 0)	$\mu\mathrm{m}$
Cell 3	Pз	(-200, 0, 0)	(-25, 0, 0)	$\mu { m m}$

Table 9: Positions of cells in Example 5 from Section 4.4, where nonlinear dynamics are simulated.

Center position	Symbol	Value in μm	Center position	Symbol	Value in μm
Cell 1	P 1	(0, 0, 0)	Cell 5	P 5	(0, 0, 25)
Cell 2	$\mathbf{p_2}$	(25, 0, 0)	Cell 5	P 6	(25, 0, 25)
Cell 3	рз	(0, 25, 0)	Cell 7	P7	(0, 25, 25)
Cell 4	\mathbf{p}_4	(25, 25, 0)	Cell 8	$\mathbf{p_8}$	(25, 25, 25)



Figure 9: Illustration of cells positions for Examples 3 and 4 in Section 4.4.



Figure 10: Evolution of v_j^{35} and Z_j^{35} at the north pole of each j cell ($\theta = 0$), from Example 3 in Section 4.4. The time step is $\tau \approx 6.1 \cdot 10^{-4}$. Parameters employed are found in Tables 7 and 8.

Cell radii and physical parameters used for Examples 3–5 are presented in Table 7. Extra- and intracellular conductivity values were changed so as to obtain a response sooner. Cells centers in Examples 3 and 4 are given in Table 8 and sketched in Figure 9, while those in Example 5 are located at the corners of a cube of length 25 μ m. (cf. Table 9). Throughout initial conditions are set to zero. The external applied potential in Examples 3–5 is $\phi_e = 5z \cdot 10^{-2}$ until $t = 5 \ \mu$ s and zero thereafter.

In what follows, we present results for a time step $\tau \approx 6.1 \cdot 10^{-4}$. The maximum degree of spherical harmonics used for Examples 3 and 4 is L = 35, while for Example 5 L = 25. Quadrature degree used in all examples is $L_c = 100$. Figures 10, 11 and 12 showcase the evolution of the transmembrane potentials v_j^L and the variables Z_j^L for each cell at their north pole.

In Example 3, $\phi_e = 5z \cdot 10^{-2}$. The perceived excitation for the three cells is the same, and since they are relatively far from each other, there is almost no interaction among them, and the potentials v_j^{35} and Z_j^{35} look similar, for all j (see Figure 8). In Example 4, we take the same parameters as in Example 5, except for reducing the distance between cells, which is now $R_1/2$. Hence, the interaction between cells is stronger, and the shapes of the potentials v_j^{35} and Z_j^{35} change (see Figure 11). One should compare with the previous example in Figure 10). Due to the symmetry and the form of the external $\phi_e = 5z \cdot 10^{-2}$, cells 2 and 3 should have the same response at the north pole. However, they are slightly different, hinting at further refinement. Finally, in Example 5 eight cells close to each other are simulated. In Figure 12, the corresponding transmembrane voltage v_j^{25} and Z_j^{25} at the north pole are presented. The cells with the centers in the plane z = 0show similar response—see Table 9 for the center position of each cell—, while the cells with centers in the plane z = 25 have similar response too while differing from cells beneath them. Figure 13 shows six snapshots of the transmembrane voltages for the eight cells. The transmembrane voltage starts changing earlier on parts of the surface closest to the rest of the cells.

5 Conclusions and future work

We studied the electropermeabilization of disjoint cells following the nonlinear dynamics from [17] and recast the volume boundary value problem via a MTF to obtain a parabolic system of boundary



Figure 11: Evolution of v_j^{35} and Z_j^{35} at the north pole of each j cell ($\theta = 0$), from Example 4 from Section 4.4. Cells are near each other and the interaction among them influences the transmbembrane potential v_j^{35} and Z_j^{35} (cf. Example 5 in contrast). The only difference between Examples 5 and 6 is the distance between successive cells. The time step is $\tau \approx 6.1 \cdot 10^{-4}$, and the parameters employed are given in Tables 7 and 8.



Figure 12: Evolution of v_j^{25} and Z_j^{25} at the north pole of each cell ($\theta = 0$), from Example 5 from Section 4.4. The first four cells are in the plane z = 0, while the others are in the plane z = 25. The time step is $\tau \approx 6.1 \cdot 10^{-4} \mu$ s. The rest of parameters employed are given in Tables 7 and 8.



Figure 13: Transmembrane voltages v_j^{25} obtained in Example 9 of Section 4.4 at different times. The length of the time step is $\tau \approx 6.1 \cdot 10^{-4}$. Parameters employed are given in Tables 7 and 8.

integral equations on the cell membrane. This extends significantly the numerical method presented in [11]. Still, the semi-implicit time stepping scheme though stable requires relatively small time steps. For simplicity, we assumed spherical cells but other shapes can be easily considered.

One can easily change the dynamics' model as long as it only involves the nonlinear term and/or variables that exclude the transmembrane potential. In this case, only the right-hand side of the system to be solved (22) and the equations corresponding to the additional variables. Further improvements to the numerical method to be implemented in the future are matrix compression and parallelization techniques, along with an efficient solver for linear systems at each time step.

6 Acknowledgements

Authors I. Martinez and C. Jerez-Hanckes acknowledge the support of Agencia Nacional de Investigación y Desarrollo (ANID), respectively, through the doctoral fellowship program Conicyt-PFCHA/Doctorado Nacional/2018-21181809 and Fondecyt Regular 1231112. The work of I. Pettersson is supported by Swedish Foundation for International Cooperation in Research and Higher education (STINT), project CS2018-7908.

References

- AGANIN, A. A., AND DAVLETSHIN, A. I. Transformation of Irregular Solid Spherical Harmonics with Parallel Translation of the Coordinate System. *Lobachevskii Journal of Mathematics* 39, 3 (Apr. 2018), 433–438.
- [2] AMMARI, H., WIDLAK, T., AND ZHANG, W. Towards monitoring critical microscopic parameters for electropermeabilization. *Quarterly of Applied Mathematics* 75, 1 (July 2016), 1–17.
- [3] CHOI, S.-E., KHOO, H., AND HUR, S. C. Recent Advances in Microscale Electroporation. *Chemical Reviews* (June 2022), acs.chemrev.1c00677.
- [4] CLAEYS, X., HIPTMAIR, R., AND JEREZ-HANCKES, C. Multitrace boundary integral equations. In Direct and inverse problems in wave propagation and applications, vol. 14 of Radon Ser. Comput. Appl. Math. De Gruyter, Berlin, 2013, pp. 51–100.
- [5] CLAEYS, X., HIPTMAIR, R., JEREZ-HANCKES, C., AND PINTARELLI, S. Novel multi-trace boundary integral equations for transmission boundary value problems. In *Unified Transform* for Boundary Value Problems: Applications and Advances, A. S. Fokas and B. Pelloni, Eds. Philadelphia, SIAM, 2015, pp. 227–258.
- [6] COLTON, D., AND KRESS, R. Inverse acoustic and electromagnetic scattering theory, third ed., vol. 93. Springer Science & Business Media New York, 2013.
- [7] FREEDEN, W., AND GUTTING, M. Special Functions of Mathematical (Geo-)Physics. Springer Basel, Basel, 2013.
- [8] GALLIER, J., AND QUAINTANCE, J. Spherical harmonics and linear representations of lie groups. In *Differential Geometry and Lie Groups*. Springer, 2020, pp. 265–360.

- [9] GUITTET, A., LEPILLIEZ, M., TANGUY, S., AND GIBOU, F. Solving elliptic problems with discontinuities on irregular domains – the Voronoi Interface Method. *Journal of Computational Physics 298* (Oct. 2015), 747–765.
- [10] GUITTET, A., POIGNARD, C., AND GIBOU, F. A Voronoi Interface approach to cell aggregate electropermeabilization. *Journal of Computational Physics 332* (Mar. 2017), 143–159.
- [11] HENRÍQUEZ, F., AND JEREZ-HANCKES, C. Multiple traces formulation and semi-implicit scheme for modelling biological cells under electrical stimulation. ESAIM: Mathematical Modelling and Numerical Analysis 52, 2 (Mar. 2018), 659–703.
- [12] HENRÍQUEZ, F., JEREZ-HANCKES, C., AND ALTERMATT, F. Boundary integral formulation and semi-implicit scheme coupling for modeling cells under electrical stimulation. *Numerische Mathematik* 136, 1 (May 2017), 101–145.
- [13] HIPTMAIR, R., AND JEREZ-HANCKES, C. Multiple traces boundary integral formulation for helmholtz transmission problems. Advances in Computational Mathematics 37, 1 (2012), 39– 91.
- [14] HIPTMAIR, R., JEREZ-HANCKES, C., LEE, J.-F., AND PENG, Z. Domain decomposition for boundary integral equations via local multi-trace formulations. In *Domain Decomposition Methods in Science and Engineering XXI*. Springer International Publishing, 2014, pp. 43–57.
- [15] JACKSON, J. D. Classical Electrodynamics, 3. ed., repr. 2013, student ed ed. Wiley, Hoboken, NY, 2013.
- [16] JEREZ-HANCKES, C., PINTO, J., AND TOURNIER, S. Local multiple traces formulation for high-frequency scattering problems. J. Comput. Appl. Math. 289 (2015), 306–321.
- [17] KAVIAN, O., LEGUÈBE, M., POIGNARD, C., AND WEYNANS, L. "Classical" Electropermeabilization Modeling at the Cell Scale. *Journal of Mathematical Biology* 68, 1-2 (Jan. 2014), 235–265.
- [18] KIM, K., AND LEE, W. G. Electroporation for nanomedicine: A review. Journal of Materials Chemistry B 5, 15 (2017), 2726–2738.
- [19] KOTNIK, T., REMS, L., TAREK, M., AND MIKLAVČIČ, D. Membrane Electroporation and Electropermeabilization: Mechanisms and Models. *Annual Review of Biophysics* 48, 1 (May 2019), 63–91.
- [20] LEGUÈBE, M., SILVE, A., MIR, L. M., AND POIGNARD, C. Conducting and permeable states of cell membrane submitted to high voltage pulses: Mathematical and numerical studies validated by the experiments. *Journal of Theoretical Biology 360* (Nov. 2014), 83–94.
- [21] MISTANI, P., GUITTET, A., POIGNARD, C., AND GIBOU, F. A parallel Voronoi-based approach for mesoscale simulations of cell aggregate electropermeabilization. *Journal of Computational Physics 380* (Mar. 2019), 48–64.
- [22] NEU, J. C., AND KRASSOWSKA, W. Asymptotic model of electroporation. *Physical Review E 59*, 3 (Mar. 1999), 3471–3482.

- [23] ONEMLI, E., JOOF, S., AYDINALP, C., PASTACI ÖZSOBACI, N., ATEŞ ALKAN, F., KEPIL, N., REKIK, I., AKDUMAN, I., AND YILMAZ, T. Classification of rat mammary carcinoma with large scale in vivo microwave measurements. *Scientific Reports* 12, 1 (Dec. 2022), 349.
- [24] PLONSEY, R., AND HEPPNER, D. B. Considerations of quasi-stationarity in electrophysiological systems. The Bulletin of Mathematical Biophysics 29, 4 (Dec. 1967), 657–664.
- [25] ROLS, M.-P. Electropermeabilization, a physical method for the delivery of therapeutic molecules into cells. *Biochimica et Biophysica Acta (BBA) - Biomembranes 1758*, 3 (2006), 423–428.
- [26] SAUTER, S. A., AND SCHWAB, C. Boundary Element Methods, vol. 39 of Springer Series in Computational Mathematics. Springer Berlin Heidelberg, Berlin, Heidelberg, 2010.
- [27] THOMÉE, V. Galerkin Finite Element Methods for Parabolic Problems, 2nd ed ed. No. v. 25 in Springer Series in Computational Mathematics. Springer, Berlin; New York, 2006.
- [28] VICO, F., GREENGARD, L., AND GIMBUTAS, Z. Boundary integral equation analysis on the sphere. *Numerische Mathematik* 128, 3 (2014), 463–487.
- [29] WIECZOREK, M. A., AND MESCHEDE, M. SHTools: Tools for Working with Spherical Harmonics. Geochemistry, Geophysics, Geosystems 19, 8 (2018), 2574–2592.