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Finite volumes method for the cell electrical model

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Abstract

We present a finite volumes method to model and simulate the exposition of a biological cell to a nanosecond electric pulse in the view of electropermeabilization description. A quasi-static electric model based on the metal-dielectric equivalence is proposed for conduction modelling. A Poisson equation is solved. The method - Discrete Dual Finite Volume method (DDFV) - is shown to be efficient in taking electric jump conditions at the cell membrane. The advantages of the method are presented on axisymmetric 2D classic problems.

1 Introduction

Electroporation, or electropermeabilization, consists in applying an electrical field to modify (reversibly or irreversibly) the cell membrane permeability [1]. It allows the transfer of non-permeable molecules into the cell cytoplasm. This technique is now used in cancers therapy [2].

Nevertheless, it is necessary to precisely model the cell to adapt the field exposure. This phenomenon is well studied experimentally [3], but few predictive computational methods exist in the literature [4, 5]. This is mostly due to the difficulty of precisely taking into account the jump condition in the cell membrane and the geometry of the cell. We propose here a method to adress this issue.

Some analytical results exist for a spherical model of the cell [6]. Nevertheless models are mostly based on numerical methods [5]. The majority of these methods involve a finite elements (FE) technique [5, 7] and interpolation or refinement on the cell membrane [4].

In this article, we propose a cell model based on the metal-dielectric equivalence. It leads to a Poisson equation with jump conditions and mixed boundaries. To solve this problem we introduce and propose an adaptation of the discrete dual finite volume method (DDFV) [8, 9, 10]. We can then take into account both the discontinuity condition on the cell membrane in ε and σ. Moereover, dispersive media are introduced in recent modelisation, this will be also taken into account into the presented cell model. To the author's knowledge, the DDFV method has not been yet applied to solve this problem.

The remaining of this article is organized as follows. Section 2 describes the cell and introduces the electrical model based on the metal-dielectric equivalence. Section 3 focuses on the computational method to solve the Poisson equation with jump conditions. Section 4 finally shows numerical experiment.

2 Single cell electric model

In this section, we develop the electrical model of the cell. In this article, the cell is described by two subdomains, the membrane and the cytoplasm [11], as illustrated in Figure 1.

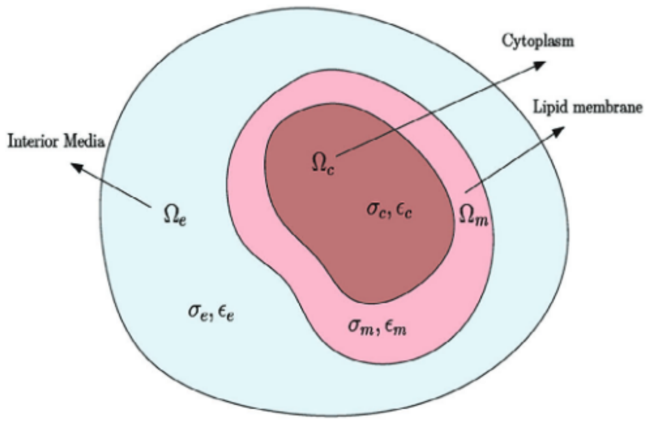

Figure 1. Cell model [7]

The cytoplasm, media Ω_c, is surrounded by the membrane, media Ω_m. There is a jump condition between both mediums. Indeed the parameters σ_c and σ_m end the permittivity ε_c and ε_m are very differents, see [12] for magnitude examples. Finally, the cell itself is surrounded by the exterior media of parameters σ_e and ε_e. We assume a uniform exterior electrical field.

In this context we can study the electro-quasi static problem [13], since the magnetic field influence is negligible. With the metal-dielectric equivalence, we have

$$\mathbf{j} = \sigma \mathbf{E} = \frac{\partial \mathbf{P_c}}{\partial t}. \tag{1}$$

The electrical induction $\mathbf{D}$ is given by

$$\mathbf{D} = \varepsilon_0 \mathbf{E} + \mathbf{P}_{\text{lin}} + \mathbf{P}_c, \tag{2}$$

with

$$\mathbf{P}_c = \int_0^t \sigma \mathbf{E} dt \text{ and } \mathbf{P}_{\text{lin}} = \varepsilon_0(\varepsilon_r - 1)\mathbf{E}, \tag{3}$$

where $\mathbf{P}_c$ and $\mathbf{P}_{\text{lin}}$ corresponds to the conductor and linear polarisations, respectively. Finally, putting these equations in the Maxwell-Gauss equation, and rewritting it for the electric potential V

$$-\nabla \cdot \left(\varepsilon_r \nabla V + \int_0^t \sigma \nabla V dt \right) = \rho. \tag{4}$$

This corresponds to a generalized Poisson equation and is equivalent to other cell models [11, 13, 4, 5].

To numerically solve this problem, a discretization along the time, step Δt, is first applied. In this case, we obtain

$$-\nabla \cdot ((\varepsilon_r + \Delta t \sigma^n) \nabla V^n) = \rho^n + \nabla \cdot \mathbf{P}_c^{n-1}, \tag{5}$$

with n the corresponding discret time, and

$$\mathbf{P}_c^{n-1} = \int_0^{t_{n-1}} \sigma \mathbf{E} dt. \tag{6}$$

To complete the model, we add the boundary relation between each subdomain :

$$\begin{aligned} (\varepsilon_m \mathbf{D}_m - \varepsilon_e \mathbf{D}_e) \cdot \hat{\mathbf{n}} &= \frac{\sigma_{s_m}}{\varepsilon_0} \\ (\varepsilon_c \mathbf{D}_c - \varepsilon_m \mathbf{D}_m) \cdot \hat{\mathbf{n}} &= \frac{\sigma_{s_c}}{\varepsilon_0}, \end{aligned} \tag{7}$$

with $\hat{\mathbf{n}}$ the normal and σ_{s_i} surface density charge on each discontinuity. Also, for dielectric model the Debye model [14] can be used as a differential equation on the polarisation $\mathbf{P}$.

Thus Poisson equation with jump conditions is solved at each time step. This is the focus of the next section.

3 Computational method for the Poisson equation

In this section, we describe how the Poisson equation (5) with jump conditions is numerically solved. For the boundary of the exterior domain, we assume mixed Neumann-Dirichlet. Therefore, at each time step, we need to solve

$$\begin{aligned} &\nabla \cdot (\varepsilon_{r_i} \nabla V) = f, \text{ sur } \Omega, \\ &\quad s.c \quad V(x) = V_b, \qquad \forall x \in \partial\Omega_D, \\ &\qquad\quad \frac{\partial V}{\partial n}(x) = 0, \qquad \forall x \in \partial\Omega_N, \end{aligned} \tag{8}$$

with the jump conditions (7). Also, $\varepsilon_{ri} = \varepsilon_r + \Delta t \sigma$ corresponds to the generalized permittivity for each media. Also, for each time step $f = \rho + \nabla \cdot \mathbf{P}_c^{n-1}$ is the source term.

To numerically solve this problem, we propose the DDFV method, which is a recent finite volumes method. This latter has been introduced in 2000 [8] and is more studied since 2005 [9, 10]. This finite volumes method is based on a dual mesh to obtain a better approximation of the gradients, with strong convergence. In our context, this method has many advantages: the matrix obtained from the system of equations is positive-definite (and symmetric without discontinuity), the jump conditions can be taken into account [15], and we can have mixed conditions on the boundaries. Furthermore, the gradient of V is obtained from one side to another of the discontinuity with at least the same accuracy as a FE method [9, 10]. In addition, the potential at the inner and outer surface is directly obtained allowing to compute precisely the trans-membrane voltage.

To solve our problem (5) under the boundary conditions (7), we modify the algorithm to take into account both the jump conditions on ε between the medium and on σ_s at the surface. Only a discontinuity in the primal mesh is taken into account, since we adapt the mesh to the physic of the problem. For the boundary of the global domain, we use a penalization method for the Dirichlet condition [16] while Neumann one are intrisic from the discrete Green relation [15, 10].

We create a conformal and structured mesh using the method described by Hyman *et al.* [17]. This allows us to manage the quandrangular mesh for the cell. Finally the system is solved using a parallelize biconjugate gradient method (in MPI environment).

4 Numerical experiments

In this section, we show the results of numerical tests on an academic case of spherical cell. Thus, we study a spherical cell of radius 0.2 μm, with a membrane of size 0.0008 μm corresponding to 0.004 the size of the cell and to experimental magnitude. To obtain a uniform field over the domain of size $D = 1$ μm in horizontal and 2 μm in vertical, two electrode of $V^+ = 1$ V and $V^- = -1$ V are placed on the left and right, respectively. This corresponds to two Dirichlet boundaries. For the top and bottom of the domain, we assume Neumann conditions. For the permittivity of the different subdomains, we use $\varepsilon_c = \varepsilon_e = 80$ and $\varepsilon_m = 2$, also corresponding to experimental magnitudes [12]. The cell is placed at the center of the domain. This setup is illustrated in Figure 2.

One can note that the problem is symetric, thus the potentiel is computed only in a subdomain containing half the cell of size $[0,1] \times [0,1]$ μm^2.

First, we plot the potential on the whole domain with the mesh in Figure 3.

As expected, the potential is decreasing from 1 to -1 V continuously far from the cell. Looking in the area of the cell, we can see that jump condition has effects on the electrical potential. Therefore, we plot an horizontal cut through the cell in Figure 4 to zoom on the effects of the

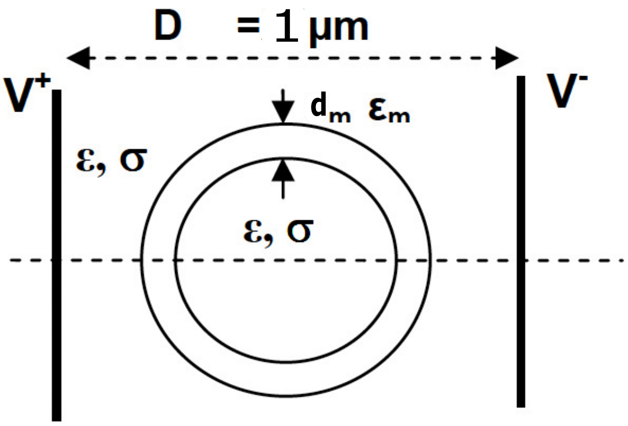

Figure 2. Numerical setup.

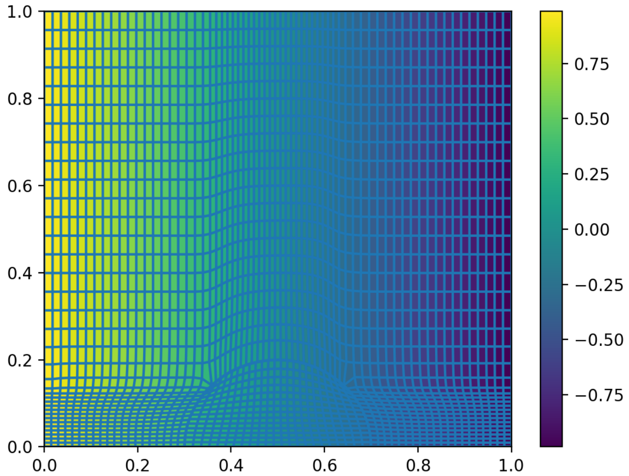

Figure 3. Electric potential (V) on the whole domain with a cell.

membrane and the discontinuity. The potentiel on the primal and dual meshes are represented. To highlight the effects of the membrane, a zoom on the discontinuity is proposed.

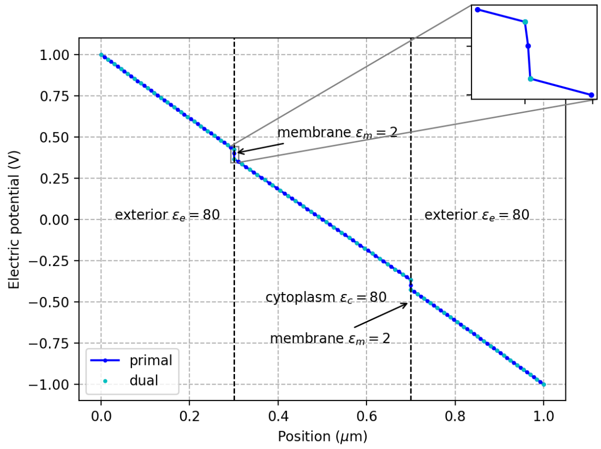

Figure 4. Electrical potential (V) on an equatorial cut along the cell on primal and dual meshes.

First, Figure 4 shows that the variation of V are the same in the cytoplasm and in the exterior media, as expected. Indeed, both medium are the same since $\varepsilon_c = \varepsilon_e$. Second, the jump condition is seen with a high decrease of the potentiel in the membrane since $\varepsilon_m \ll \varepsilon_c$. Also, the results are in line with the one described in [12] for the electric cell model.

Finally, we plot the potential in the middle of the membrane in Figure 5. Since the field is uniform in the exterior media, we expect V to decrease slowly and no discontinuity. In the context of electroporation, this figure is essential to see where electroporation occurs.

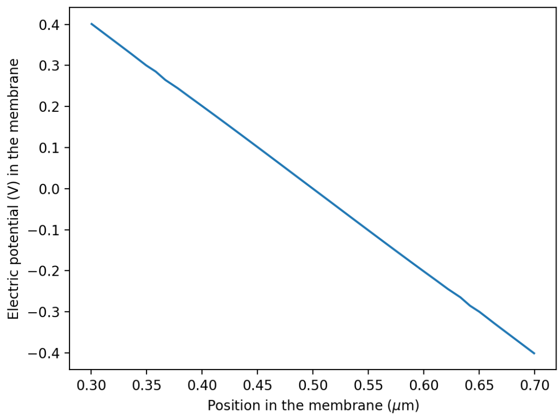

Figure 5. Electrical potential (V) in the membrane of the cell.

We can see that, as expected, the potential decrese slowly in the membrane due to the uniforme electric field and no discontinuity occurs. Therefore, the method and mesh works well to electrically model a single cell.

5 Conclusion

In this article, we develop an electric model for the cell based on the metal-dielectric equivalence. We also introduce and propose a modification of a finite volume method to numerically solve the equation associated with the model.

First, using the metal-dielectric equivalence, we have obtained an electrical model for the cell. Thus, we obtain a generalized Poisson equation with jump conditions. This latter use polarisation to describe the different medium. Indeed, the Debye model can be incorporated as an additional differential equation on the polarisation.

Second, we have introduced the discrete dual finite volume method to solve this problem. The method is relevant to our context since it can take into account both discontinuity between the medium and at the surface of each medium.

Third, a numerical experiment is proposed to show the efficiency of the method. We studied the classical test of a spherical cell in a uniform electric field. These tests show that the method works well in this context, obtaining results in line with the literature.

Further works include using the Debye model for the dispersive medium and take into account electric pulse. We also would like to compare results with experimental studies. Finally, the method can be easily generalized in 3D.

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