



**HAL**  
open science

# ”Classical” Electroporabilization Modeling at the Cell Scale

Otared Kavian, Michael Leguèbe, Clair Poignard, Lisl Weynans

► **To cite this version:**

Otared Kavian, Michael Leguèbe, Clair Poignard, Lisl Weynans. ”Classical” Electroporabilization Modeling at the Cell Scale. [Research Report] RR-8005, 2012. hal-00712683v2

**HAL Id: hal-00712683**

**<https://inria.hal.science/hal-00712683v2>**

Submitted on 9 Jul 2012 (v2), last revised 5 Dec 2012 (v3)

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



# “Classical” Electropermeabilization Modeling at the Cell Scale

O. Kavian<sup>1</sup>, M. Leguèbe<sup>2</sup>, C. Poinard<sup>2</sup>, L. Weynans<sup>2</sup>

<sup>1</sup> Département de Mathématiques, LMV CNRS UMR8100,  
Université Versailles-Saint-Quentin-en-Yvelines, France

<sup>2</sup> Team MC2, INRIA Bordeaux-Sud-Ouest & CNRS UMR 5251,  
Université de Bordeaux, France

**RESEARCH  
REPORT**

**N° 8005**

June 2012

Project-Teams MC2





## “Classical” Electroporation Modeling at the Cell Scale

O. Kavian<sup>1</sup>, M. Leguèbe<sup>2</sup>, C. Poinard<sup>2\*</sup>, L. Weynans<sup>2</sup>

<sup>1</sup> Département de Mathématiques, LMV CNRS UMR8100,  
Université Versailles-Saint-Quentin-en-Yvelines, France

<sup>2</sup>Team MC2, INRIA Bordeaux-Sud-Ouest & CNRS UMR 5251,  
Université de Bordeaux, France

Project-Teams MC2

Research Report n° 8005 — June 2012 — 28 pages

**Abstract:** In this paper, we derive two models (a static and a dynamical model) based on the description of the electric potential in a biological cell in order to model the cell electroporation. Existence and uniqueness results are provided for each model, and an accurate numerical method to compute the solution is described. We then present numerical results that corroborate the experimental results, which tends to justify the validity of our modeling. We emphasize that our new models involve very few parameters, compared with the most achieved model but they describe the same qualitative results. Moreover our numerical results are quantitatively close to the experimental data.

**Key-words:** Cell modeling, Non-linear partial differential equations, Finite differences on cartesian grids

---

\* Corresponding author: [clair.poinard@inria.fr](mailto:clair.poinard@inria.fr)

**RESEARCH CENTRE  
BORDEAUX – SUD-OUEST**

351, Cours de la Libération  
Bâtiment A 29  
33405 Talence Cedex

## Modélisation de l'électroporation cellulaire par micropulses

**Résumé :** Dans cet article, deux modèles d'électroporation cellulaire sont présentés: un modèle statique et un modèle dynamique. Ces modèles sont obtenus via une description du potentiel électrique dans une cellule. Des résultats d'existence et d'unicité sont donnés pour chaque modèle et une méthode numérique permettant de calculer précisément la solution de chacun de ces problèmes est décrite. Des simulations numériques qui corroborent les résultats expérimentaux concluent ce travail, justifiant la validité de la modélisation. Notons que ces nouveaux modèles ne comportent que peu de paramètres, comparés aux modèles existants, tout en décrivant les mêmes comportements, avec des résultats proches des résultats expérimentaux.

**Mots-clés :** Modélisation bio-cellulaire, Equations aux dérivées partielles non linéaires, Méthodes de différences finies sur grilles cartésiennes

## Contents

<b>1</b>	<b>Introduction</b>	<b>4</b>
1.1	Electric potential in a biological cell . . . . .	4
1.2	Electropermeabilization phenomenon . . . . .	5
1.3	Modeling principle . . . . .	6
<b>2</b>	<b>The static equation</b>	<b>6</b>
2.1	Existence and uniqueness of the static potential . . . . .	7
<b>3</b>	<b>The dynamical model</b>	<b>10</b>
3.1	Heuristics of the modeling . . . . .	11
3.2	Statement of the mathematical problem . . . . .	12
3.3	Properties of the function $X$ . . . . .	12
3.4	Existence and uniqueness of the dynamical potential . . . . .	14
<b>4</b>	<b>Numerical simulations</b>	<b>18</b>
4.1	Spatial discretization . . . . .	18
4.2	Accuracy of the finite difference method . . . . .	19
4.3	Computation of the non-linear static model . . . . .	20
4.3.1	Influence of the parameter $S_{\text{ir}}$ . . . . .	21
4.3.2	Comparison with the model of Ivorra, Mir and Villediejeane . . . . .	21
4.4	Computation of the dynamical problem . . . . .	22
4.4.1	Time-discretization of the model . . . . .	22
4.4.2	Main parameters influence . . . . .	22
4.4.3	Comparison with the model of Neu, Krassowska, and Debruin . . . . .	22
4.4.4	Long-time behavior of the numerical solution to the dynamical model . . . . .	25
<b>5</b>	<b>Conclusion</b>	<b>25</b>

# 1 Introduction

The distribution of the electric potential in a biological cell is important for bio-electromagnetic investigations. A sufficiently large magnitude of the difference of transmembrane potential ( $\Delta\text{TMP}$ ), which is the difference of the electric potentials between both sides of the cell membrane, leads to an increase of the membrane permeability [19, 23]. Molecules such as bleomycin can then diffuse across the plasma membrane. This phenomenon, called electropermeabilization, has already been used in oncology and holds promises in gene therapy [11, 20], motivating precise assessments of the  $\Delta\text{TMP}$ .

In this paper, we aim at studying theoretically and numerically a non-linear electrical model of biological cells. This model is inspired from the static model of Ivorra *et al.* in [10]. It describes the behavior of both electric potential and membrane conductivity when the cell is submitted to an electric pulse through few parameters that will be fitted with the experiments. We emphasize that this is a phenomenological model in the sense that the membrane conductivity is described by an *ad hoc* law, which does not come from an homogenization of the nanoscale phenomena. Before stating the model we are going to study, let us present the notation of the paper.

**Notation 1.1.** *Throughout this article, we shall use the following conventions and notation:*

- We generically denote by  $\mathbf{n}$  the normal to a closed smooth surface of  $\mathbb{R}^3$  (or a curve of  $\mathbb{R}^2$ ) outwardly directed from the inside to the outside of the domain enclosed by the surface.
- Let  $\mathcal{C}$  be a surface embedded in  $\mathbb{R}^3$ , and let  $u$  be a sufficiently smooth function (in an appropriate sense) defined in a tubular neighborhood of  $\mathcal{C}$ . We define  $u|_{\mathcal{C}\pm}$  by

$$\forall x \in \mathcal{C}, \quad u|_{\mathcal{C}\pm}(x) = \lim_{\tau \rightarrow 0^+} u(x \pm \tau \mathbf{n}(x)).$$

The notation  $\partial_{\mathbf{n}}u|_{\mathcal{C}\pm}$  and  $\partial_{\mathbf{t}}u|_{\mathcal{C}\pm}$  stands for the normal and the tangential components of  $\nabla u$ :

$$\begin{aligned} \forall x \in \mathcal{C}, \quad \partial_{\mathbf{n}}u|_{\mathcal{C}\pm}(x) &= \lim_{\tau \rightarrow 0^+} \nabla u(x \pm \tau \mathbf{n}(x)) \cdot \mathbf{n}(x), \\ \partial_{\mathbf{t}}u|_{\mathcal{C}\pm}(x) &= \nabla u(x) - \partial_{\mathbf{n}}u(x)\mathbf{n}(x), \end{aligned}$$

where the dot “ $\cdot$ ” denotes the Euclidean scalar product of  $\mathbb{R}^3$ . In the case of  $\mathbb{R}^2$ , the analogous notation is easily adapted.

- The jump  $[u]_{\mathcal{C}}$  of a function  $u$  defined in a neighborhood of the surface  $\mathcal{C}$  is defined by

$$[u]_{\mathcal{C}} = u|_{\mathcal{C}+} - u|_{\mathcal{C}-}.$$

- Observe that for a sufficiently smooth function  $v$  defined in a neighborhood of  $\Gamma$ , we have:

$$\mathbf{n}_i \cdot \nabla v|_{\Gamma^-} = \partial_{\mathbf{n}}u|_{\Gamma^-}, \quad \text{and} \quad \mathbf{n}_e \cdot \nabla v|_{\Gamma^+} = -\partial_{\mathbf{n}}u|_{\Gamma^+}.$$

## 1.1 Electric potential in a biological cell

A biological cell is a high contrast medium composed of a conducting cytoplasm  $\mathcal{O}_c$  surrounded by a thin and very insulating layer. The plasma membrane is a phospholipid bilayer, which is sprinkled over with proteins. Due to its thickness and its electrical properties, the membrane can be modeled as a surface electric material  $\Gamma$  with a capacity  $C_m$  and a surface conductivity  $S_m$ . We refer to the seminal articles of Hodgkin, Goldman, Katz, *et al.* for the electric description of

cell membranes [5, 7, 9, 8]. As described by Neu, Krassowska, and DeBruin [14, 3] the electric potential in the whole cell embedded in a bath  $\mathcal{O}_e$  is the discontinuous solution  $U$  to the following problem

$$\Delta U = 0, \quad \text{in } \mathcal{O}_e \cup \mathcal{O}_c, \quad (1a)$$

$$U(0, \cdot) = 0, \quad \text{and for all } t > 0, \quad (1b)$$

$$U(t, x) = g(t, x), \quad \text{on } \partial\Omega \quad (1c)$$

with the transmission conditions across the membrane  $\Gamma$ :

$$[\sigma \partial_{\mathbf{n}} U]_{\Gamma} = 0, \quad (1d)$$

$$C_m \partial_t [U]_{\Gamma} + S_m [U]_{\Gamma} = \sigma_c \partial_{\mathbf{n}} U|_{\Gamma^-}. \quad (1e)$$

Throughout, the paper we denote by  $\Omega$  the Lipschitz domain

$$\Omega = \mathcal{O}_e \cup \overline{\mathcal{O}_c}$$

and  $\partial\Omega$  denotes its boundary. Moreover we define  $PH^1(\Omega)$  as

$$PH^1(\Omega) = \{u \in L^2(\Omega) : u|_{\mathcal{O}_e} \in H^1(\mathcal{O}_e), u|_{\mathcal{O}_c} \in H^1(\mathcal{O}_c)\},$$

and

$$PH_0^1(\Omega) = \{u \in PH^1(\Omega) : u|_{\partial\Omega} = 0\}.$$

## 1.2 Electroporabilization phenomenon

When submitted to a high electric pulse — *i.e.* if the magnitude of the pulse  $g$  reaches a threshold value — the cell membrane permeability increases and large molecules that usually cannot diffuse through the plasma membrane (for instance, plasmids or bleomycin) enter inside the cytoplasm. This phenomenon is called *electroporation* or *electroporabilization*. For several years, different membrane models based on hydrodynamic, elasticity, hydroelasticity, viscoelasticity, or aqueous pore formation have been developed to describe the pore formation on the cell membrane (for more details, see the review of Pavlin *et al.* [17]). They all highlight a threshold value of the electric potential above which the electroporabilization phenomenon occurs. However, the critical potential value changes with the models. Theoretical biophysicists consider the aqueous pore formation model as the most convincing current explanation. Nevertheless, the predictions of the model do not coincide with experiments either quantitatively or phenomenologically since no pore has ever been observed. In addition, the models based on the paper of Neu, Krassowska, *et al.* [14, 3, 4] are too complex to be parameterized to fit the experiments. Roughly speaking, the current models provide a qualitative explanation of the electroporabilization, but the problem of the quantitative description remains open.

Actually *in vitro* and *in vivo* experiments have never proved the electropore formation, which theoretically could reach detectable size (since macropores could be created according to Smith *et al.* [21]); and it seems unclear whether electroporation results from holes punched in a lipid bilayer, as proposed in the current models (Teissié *et al.* [23, 22]). Moreover, the experimentally proved reversible process of the membrane electroporation is not clearly explained by the current models. In addition, and this is probably one of the main features of the experiments, the *vectorization* of large molecules requires both short time high-voltage pulses and long time low-voltage pulses (André *et al.* [1]). Therefore, the presence of pores is still controversial despite structural changes of the membrane. For all these reasons we prefer the term *electroporabilization* to *electroporation*.



### 1.3 Modeling principle

The probably most achieved electropermeabilization model has been proposed by Neu and Krassowska [14] and precisely described by DeBruin and Krassowska [3, 4]. It consists in adding an electroporation current  $I_{\text{ep}}$  in the right-hand side of equation (1e):

$$C_m \partial_t [U]_{\Gamma} + S_m [U]_{\Gamma} = \sigma_c \partial_{\mathbf{n}} U|_{\Gamma^-} + I_{\text{ep}}.$$

The current  $I_{\text{ep}}$  is given by a highly non-linear pore current  $i_{\text{ep}}$  multiplied by the pore density  $N_{\text{ep}}$ . The main drawback of such a model is its complexity since several parameters, such as the pore radius or the relative entrance length of the pore, which are some parameters of the model, cannot be measured. Moreover, the mathematical well-posedness of the equations cannot be clearly established. Therefore, the inverse problem, that consists in fitting the parameters for each cell species, is almost unsolvable. In addition, the ‘‘philosophy’’ of the modeling is based on the pore creation, while as hinted above the very existence of these pores is controversial. We eventually would say that the multi-pulses description is not taken into account by these models. In particular, no memory effect of the previous pulses are accounted for. For all these reasons, we choose to present here a new phenomenological model of electropermeabilization that could be fitted with the experiments. This model describes the membrane resealing and the memory of the applied pulses.

Our electropermeabilization modeling consists in describing the membrane permeabilization by choosing an appropriate function for the surface conductivity  $S_m$ , instead of adding an electroporation current based on the pore creation as Neu, Krassowska, *et al.* did (see [14, 3, 21, 15]). In addition, we propose two models: the first one is a ‘‘static’’ model that describes the electropermeabilization as being an instantaneous phenomenon for a single time-constant pulse. This can be seen as a preliminary model that describes the cell potential during the pulse. The second model is the time-dependent model of electropermeabilization. For each model, we present the theoretical results that ensure existence and uniqueness of the solution to the new problems and then we present the numerical methods that allow the computation of the equations. We conclude by comparing our model with the model of Neu, Krassowska, *et al.*

## 2 The static equation

Let  $\sigma$  be the conductivity of the medium, that is

$$\sigma = \begin{cases} \sigma_e, & \text{in the exterior domain } \mathcal{O}_e, \\ \sigma_c, & \text{inside the cell } \mathcal{O}_c. \end{cases}$$

Based on the extensive review of Ivorra *et al* [10], the surface conductivity  $S_m$  is a function of the absolute membrane voltage, which tends to the value  $S_L$  (the lipid surface conductivity) below a certain threshold  $V_{\text{rev}}$  (the reversible electropermeabilization voltage) and tends to  $S_{\text{ir}}$  (the surface conductivity of the irreversibly electropermeabilized region) above this threshold, with  $S_{\text{ir}}$  being larger than  $S_L$ . The ‘‘speed of the switch’’ between these two values is given by a parameter  $k_{\text{ep}}$ . We may choose the following sigmoid function for  $S_m$ :

$$\forall \lambda \in \mathbb{R}, \quad S_m(\lambda) = S_L + (S_{\text{ir}} - S_L)[1 + \tanh(k_{\text{ep}}(|\lambda| - V_{\text{rev}}))]/2, \quad (2)$$

however other functions with similar monotonicity properties can be considered. More precisely,

in our model the function  $S_m$  will satisfy the following condition:

$$\left. \begin{aligned} S_m &\in C(\mathbb{R}), \lambda \mapsto S_m(\lambda) \text{ is even on } \mathbb{R}, \\ 0 < S_L \leq S_m(\lambda) \leq S_{ir}, \quad S_m &\text{ is non decreasing on } [0, +\infty), \\ \lim_{\lambda \rightarrow +\infty} S_m(\lambda) &= S_{ir}. \end{aligned} \right\} \quad (3)$$

In particular, note that the mapping  $\lambda \mapsto \lambda S_m(\lambda)$  is increasing on  $\mathbb{R}$ .

Therefore, the static potential  $U$  satisfies the following problem:

$$\Delta U = 0, \quad \text{in } \mathcal{O}_e \cup \mathcal{O}_c, \quad (4a)$$

$$[\sigma \partial_{\mathbf{n}} U]_{\Gamma} = 0, \quad \text{on } \Gamma, \quad (4b)$$

$$S_m([U]_{\Gamma}) [U]_{\Gamma} = \sigma_c \partial_{\mathbf{n}} U|_{\Gamma^-}, \quad \text{on } \Gamma, \quad (4c)$$

$$U = g \quad \text{on } \partial\Omega. \quad (4d)$$

**Remark 2.1.** Model (4) can be seen as the limit of the model of Ivorra et al. [10], when the membrane thickness tends to zero (we refer to [18] for asymptotic expansion of the voltage potential in high contrast medium with resistive thin layer).

In the following subsections, we study the non-linear problem (4). In particular, we emphasize that due to the non-linearity of the membrane conductivity, increasing numerically the thickness of the membrane (as performed in [10]) leads to irrelevant results from the quantitative point of view. Therefore, we aim at providing efficient numerical methods in order to solve the above problem.

## 2.1 Existence and uniqueness of the static potential

This subsection is devoted to the proof of the following result.

**Theorem 2.2.** *Let  $g \in H^{1/2}(\partial\Omega)$ . There exists a unique  $U$  satisfying problem (4). This solution satisfies*

$$U|_{\mathcal{O}_e} \in H^1(\mathcal{O}_e), \quad U|_{\mathcal{O}_c} \in H^2(\mathcal{O}_c).$$

In order to prove this theorem, we proceed as follows. Denote by  $\Lambda_c$  and  $\Lambda_e$  the Dirichlet-to-Neumann operators on  $\Gamma$  (also called Steklov-Poincaré operators) for the Laplacian respectively in  $\mathcal{O}_c$  and in  $\mathcal{O}_e$ . More precisely, denote by  $\mathbf{n}_c$  (*resp.*  $\mathbf{n}_e$ ) the unitary outward normal to  $\Gamma$  directed from the inside to the outside of  $\mathcal{O}_c$  (*resp.*  $\mathcal{O}_e$ ). We define the operators  $\Lambda_c$  and  $\Lambda_e$  from  $H^{1/2}(\Gamma)$  to  $H^{-1/2}(\Gamma)$  as:

$$\forall f \in H^{1/2}(\Gamma), \quad \Lambda_c(f) := \mathbf{n}_c \cdot \sigma_c \nabla v_{c|_{\Gamma^-}}, \quad \text{where } \operatorname{div}(\sigma_c \nabla v) = 0 \text{ in } \mathcal{O}_c, \text{ and } v_{c|_{\Gamma}} = f, \quad (5a)$$

$$\begin{aligned} \Lambda_e(f) &:= \mathbf{n}_e \cdot \sigma_e \nabla v_{e|_{\Gamma^+}}, \quad \text{where} \\ \operatorname{div}(\sigma_e \nabla v_e) &= 0 \text{ in } \mathcal{O}_e, \quad v_{e|_{\partial\Omega}} = 0 \text{ and } v_{e|_{\Gamma}} = f. \end{aligned} \quad (5b)$$

Observe that using Wirtinger–Poincaré’s inequality in the case of  $\Lambda_c$ , or Poincaré’s inequality in the case of  $\Lambda_e$ , together with the continuity of the mapping  $u \mapsto u|_{\partial\mathcal{O}}$  from  $H^1(\mathcal{O})$  into  $H^{1/2}(\partial\mathcal{O})$ , when  $\mathcal{O}$  is sufficiently smooth, the following inequalities hold:

$$\langle \Lambda_c f, f \rangle = \int_{\mathcal{O}_c} \sigma_c(x) \nabla v(x) \cdot \nabla v(x) dx \geq C_c \|f - M(f)\|_{H^{1/2}(\Gamma)}^2, \quad (6)$$

$$\langle \Lambda_e f, f \rangle = \int_{\mathcal{O}_e} \sigma_e(x) \nabla v_e(x) \cdot \nabla v_e(x) dx \geq C_e \|f\|_{H^{1/2}(\Gamma)}^2, \quad (7)$$

where  $M(f) = |\Gamma|^{-1} \int_{\Gamma} f(\tau) d\tau$  is the mean value of  $f$  on  $\Gamma$ , and  $C_e$  and  $C_c$  are constants depending only on  $\mathcal{O}_e$  and  $\mathcal{O}_c$  respectively. Moreover, for a function  $g \in H^{1/2}(\partial\Omega)$ , we define  $\Lambda_0(g)$  by:

$$\begin{aligned} \Lambda_0(g) &:= \mathbf{n}_e \cdot \sigma_e \nabla v|_{\Gamma^+}, \quad \text{where} \\ \operatorname{div}(\sigma_e \nabla v) &= 0 \text{ in } \mathcal{O}_e, \quad v|_{\partial\Omega} = g \text{ and } v|_{\Gamma} = 0. \end{aligned} \quad (8)$$

It is useful to recall that the operator  $\Lambda_e$  is invertible, its inverse being given by another Steklov-Poincaré operator (or what is sometimes called a Neumann-to-Dirichlet operator). Namely, for any  $\psi \in H^{-1/2}(\Gamma)$  given, one has  $\Lambda_e^{-1}(\psi) = v|_{\Gamma}$  where  $v \in H^1(\mathcal{O}_e)$  satisfies the equation

$$\operatorname{div}(\sigma_e \nabla v) = 0 \text{ in } \mathcal{O}_e, \quad v|_{\partial\Omega} = 0 \text{ and } \mathbf{n}_e \cdot \sigma_e \nabla v|_{\Gamma^+} = \psi.$$

Consider the Hilbert space  $\mathbb{H}$  defined by

$$\mathbb{H} = H^{1/2}(\Gamma) \times H^{1/2}(\Gamma),$$

with the norm

$$\forall \mathbf{u} = (u_e, u_c) \in \mathbb{H}, \quad \|\mathbf{u}\|_{\mathbb{H}}^2 = \|u_e\|_{H^{1/2}(\Gamma)}^2 + \|u_c\|_{H^{1/2}(\Gamma)}^2.$$

Problem (4) can be written on the manifold  $\Gamma$  with the help of the above Steklov-Poincaré operators. More precisely, problem (4) is equivalent to finding  $(u_e, u_c) \in \mathbb{H}$  such that

$$\begin{aligned} \Lambda_e u_e + S_m(u_e - u_c)(u_e - u_c) &= -\Lambda_0(g), \\ \Lambda_c u_c - S_m(u_e - u_c)(u_e - u_c) &= 0. \end{aligned} \quad (9)$$

The proof of Theorem 2.2 is an obvious application of the following theorem.

**Theorem 2.3.** *Let  $\mathbf{G} = (G_e, G_c) \in \mathbb{H}'$ . There exists a unique  $\mathbf{u}^0 = (u_e, u_c) \in \mathbb{H}$  such that*

$$\begin{aligned} \Lambda_e u_e + S_m(u_e - u_c)(u_e - u_c) &= G_e, \\ \Lambda_c u_c - S_m(u_e - u_c)(u_e - u_c) &= G_c. \end{aligned} \quad (10)$$

*Proof.* Identifying the dual of  ${}^2(\Gamma) \times L^2(\Gamma)$  with  ${}^2(\Gamma) \times L^2(\Gamma)$ , we denote by  $\mathbb{H}'$  the dual space of  $\mathbb{H}$  and by  $\langle \cdot, \cdot \rangle$  the duality between  $\mathbb{H}$  and  $\mathbb{H}'$ . We define the operator  $\Lambda_{\sigma}$  from  $\mathbb{H}$  into  $\mathbb{H}'$  by

$$\forall \mathbf{u} \in \mathbb{H}, \quad \Lambda_{\sigma} \mathbf{u} = \begin{pmatrix} \Lambda_e u_e \\ \Lambda_c u_c \end{pmatrix} = \begin{pmatrix} \Lambda_e & 0 \\ 0 & \Lambda_c \end{pmatrix} \begin{pmatrix} u_e \\ u_c \end{pmatrix}. \quad (11)$$

Thanks to (6) and (7), we have

$$\forall \mathbf{u} \in \mathbb{H}, \quad \langle \Lambda_{\sigma} \mathbf{u}, \mathbf{u} \rangle \geq C_e \|u_e\|_{H^{1/2}(\Gamma)}^2 + C_c \|u_c - M(u_c)\|_{H^{1/2}(\Gamma)}^2. \quad (12)$$

Since the function  $S_m$  satisfies conditions (3), we introduce the function  $F$  defined by

$$\forall s \in \mathbb{R}, \quad F(s) = \int_0^s S_m(z) z dz.$$

Note that  $F$  is even, that is  $F(-s) = F(s)$ . Let  $\mathbf{J}_1$  be the function defined on  $\mathbb{H}$  by

$$\forall \mathbf{u} \in \mathbb{H}, \quad \mathbf{J}_1(\mathbf{u}) = \mathbf{J}_1(u_e, u_c) = \int_{\Gamma} F(u_e(\tau) - u_c(\tau)) d\tau.$$

One easily checks that  $\mathbf{J}_1$  is a  $C^1$  function on  $\mathbb{H}$  and

$$\mathbf{J}_1(\mathbf{u}) \geq \frac{1}{2} S_L \int_{\Gamma} |u_e(\tau) - u_c(\tau)|^2 d\tau.$$

Observe that for any  $\mathbf{u} \in \mathbb{H}$ , the linear map  $\mathbf{J}'_1(\mathbf{u})$  is defined by

$$\forall(\mathbf{u}, \mathbf{h}) \in \mathbb{H}^2, \quad \mathbf{J}'_1(\mathbf{u}) \cdot \mathbf{h} = \int_{\Gamma} S_m(u_e(\tau) - u_c(\tau))(u_e(\tau) - u_c(\tau))(h_e(\tau) - h_c(\tau)) d\tau.$$

Let  $\mathbf{J}$  be defined by

$$\forall \mathbf{u} \in \mathbb{H}, \quad \mathbf{J}(\mathbf{u}) = \frac{1}{2} \langle \Lambda_{\sigma} \mathbf{u}, \mathbf{u} \rangle + \mathbf{J}_1(\mathbf{u}) - \langle \mathbf{G}, \mathbf{u} \rangle.$$

$\mathbf{J}$  is of class  $\mathcal{C}^1$  on  $\mathbb{H}$  and  $\mathbf{J}'$  is given by

$$\forall \mathbf{u} \in \mathbb{H}, \quad \mathbf{J}'(\mathbf{u}) = \begin{pmatrix} \Lambda_e u_e + S_m(u_e - u_c)(u_e - u_c) - G_e \\ \Lambda_c u_c - S_m(u_e - u_c)(u_e - u_c) - G_c \end{pmatrix}. \quad (13)$$

In order to show that  $\mathbf{J}'$  is a monotone operator, we define the nonlinear operator  $B$  from  $\mathbb{H}^2$  into  $\mathbb{R}$  by

$$\forall(\mathbf{u}, \mathbf{v}) \in \mathbb{H}^2, \quad B(\mathbf{u}, \mathbf{v}) = S_m([\mathbf{u}])[\mathbf{u}]^2 \left(1 - \frac{[\mathbf{v}]}{[\mathbf{u}]}\right) \left(1 - \frac{S_m([\mathbf{v}])[\mathbf{v}]}{S_m([\mathbf{u}])[\mathbf{u}]}\right), \quad (14)$$

where for simplicity we denote by  $[\mathbf{u}] = u_e - u_c$  for  $\mathbf{u} = (u_e, u_c) \in \mathbb{H}$ . Taking into account the fact that  $S_m$  satisfies (3), one checks easily that  $B(\mathbf{u}, \mathbf{v}) \geq 0$ . According to (12) and (13), for  $(\mathbf{u}, \mathbf{v}) \in \mathbb{H}^2$  we have

$$\langle \mathbf{J}'(\mathbf{u}) - \mathbf{J}'(\mathbf{v}), \mathbf{u} - \mathbf{v} \rangle = \langle \Lambda_{\sigma}(\mathbf{u} - \mathbf{v}), \mathbf{u} - \mathbf{v} \rangle + \int_{\Gamma} B(\mathbf{u}(s), \mathbf{v}(s)) ds, \quad (15)$$

from which we infer that  $\mathbf{J}'$  is a monotone operator. Therefore  $\mathbf{J}$  is convex. In order to see the strict convexity of  $\mathbf{J}$ , that is the strict monotonicity of  $\mathbf{J}'$ , we have to show that if for a given  $\mathbf{u}, \mathbf{v} \in \mathbb{H}$  we have  $\langle \mathbf{J}'(\mathbf{u}) - \mathbf{J}'(\mathbf{v}), \mathbf{u} - \mathbf{v} \rangle = 0$ , then we have  $\mathbf{u} = \mathbf{v}$ . Observe first that, since  $\lambda \mapsto \lambda S_m(\lambda)$  is increasing, we have that

$$B(\mathbf{u}, \mathbf{v}) = 0 \quad \implies \quad [\mathbf{u}] = [\mathbf{v}].$$

In particular, for these  $\mathbf{u}, \mathbf{v}$ , we have  $B(\mathbf{u}, \mathbf{v}) = 0$ , which implies  $[\mathbf{u}] = [\mathbf{v}]$ , hence  $u_e - v_e = u_c - v_c$ . On the other hand, since

$$\langle \Lambda_e(u_e - v_e), u_e - v_e \rangle = \langle \Lambda_c(u_c - v_c), u_c - v_c \rangle = 0,$$

and since  $\Lambda_e$  is coercive, we conclude that  $u_e - v_e = 0$ , which in turn implies that  $u_c - v_c = 0$ . Finally, this shows that

$$\langle \mathbf{J}'(\mathbf{u}) - \mathbf{J}'(\mathbf{v}), \mathbf{u} - \mathbf{v} \rangle = 0 \quad \implies \quad \mathbf{u} = \mathbf{v}.$$

Therefore,  $\mathbf{J}'$  is strictly monotone and  $\mathbf{J}$  is strictly convex.

In order to show the coerciveness of  $\mathbf{J}$ , that is  $\mathbf{J}(\mathbf{u}) \rightarrow +\infty$  when  $\|\mathbf{u}\|_{\mathbb{H}} \rightarrow \infty$ , we proceed as follows. Observe first that

$$\begin{aligned} |\langle G_c, M(u_c) \rangle| &\leq \|G_c\|_{H^{-1/2}(\Gamma)} \|M(u_e - u_c)\|_{H^{1/2}(\Gamma)} \\ &\quad + \|G_c\|_{H^{-1/2}(\Gamma)} \|M(u_e)\|_{H^{1/2}(\Gamma)}, \\ &\leq \|G_c\|_{H^{-1/2}(\Gamma)} \|M(u_e - u_c)\|_{H^{1/2}(\Gamma)} \\ &\quad + \|G_c\|_{H^{-1/2}(\Gamma)} \|u_e\|_{H^{1/2}(\Gamma)}, \end{aligned}$$

hence

$$\begin{aligned} |\langle \mathbf{G}, \mathbf{u} \rangle| &\leq \left( \|G_e\|_{H^{-1/2}(\Gamma)} + \|G_c\|_{H^{-1/2}(\Gamma)} \right) \|u_e\|_{H^{1/2}(\Gamma)} \\ &\quad + \|G_c\|_{H^{-1/2}(\Gamma)} \|u_c - M(u_c)\|_{H^{1/2}(\Gamma)} \\ &\quad + \|G_c\|_{H^{-1/2}(\Gamma)} \|M(u_e - u_c)\|_{H^{1/2}(\Gamma)}. \end{aligned}$$

Using Young's inequality ( $ab \leq \varepsilon a^2 + C(\varepsilon)b^2$ , for  $\varepsilon > 0$  and  $C(\varepsilon) := (4\varepsilon)^{-1}$ ) we infer

$$\begin{aligned} |\langle \mathbf{G}, \mathbf{u} \rangle| &\leq \varepsilon \|u_e\|_{H^{1/2}(\Gamma)}^2 + \varepsilon \|u_c - M(u_c)\|_{H^{1/2}(\Gamma)}^2 + 2C(\varepsilon) \|\mathbf{G}\|_{\mathbb{H}}^2 \\ &\quad + \|G_c\|_{H^{-1/2}(\Gamma)} \|M(u_e - u_c)\|_{H^{1/2}(\Gamma)}. \end{aligned} \tag{16}$$

On the other hand, using the fact that  $2F(s) \geq S_L s^2$  for  $s \in \mathbb{R}$ , we deduce that

$$\begin{aligned} \mathbf{J}_1(\mathbf{u}) &\geq \frac{1}{2} S_L \int_{\Gamma} |u_e(\tau) - u_c(\tau)|^2 d\tau \\ &\geq \frac{1}{2} S_L \left( \int_{\Gamma} |(u_e - u_c) - M(u_e - u_c)|^2 d\tau + \int_{\Gamma} |M(u_e - u_c)|^2 d\tau \right). \end{aligned}$$

Using this inequality, together with (16), we obtain a lower bound for  $\mathbf{J}(\mathbf{u})$  (here  $a(\varepsilon), C(\varepsilon)$  are positive constants depending on the arbitrary  $\varepsilon > 0$ , and  $b > 0$  is a constant):

$$\begin{aligned} \mathbf{J}(\mathbf{u}) &\geq a(\varepsilon) \left( \|u_e\|_{H^{1/2}(\Gamma)}^2 + \|u_c - M(u_c)\|_{H^{1/2}(\Gamma)}^2 \right) \\ &\quad + b \int_{\Gamma} |M(u_e - u_c)|^2 d\tau - \|G_c\|_{H^{-1/2}(\Gamma)} \|M(u_e - u_c)\|_{H^{1/2}(\Gamma)} \\ &\quad - C(\varepsilon) \|\mathbf{G}\|_{\mathbb{H}}^2. \end{aligned} \tag{17}$$

Since  $M(u_e - u_c)$  is a constant, we observe that one has  $\|M(u_e - u_c)\|_{H^{1/2}(\Gamma)} = c_* \|M(u_e - u_c)\|_{L^2(\Gamma)}$  for some positive constant  $c_*$  independent of  $\mathbf{u}$ . Consequently, for any  $\varepsilon > 0$  so that  $b - \varepsilon > 0$ , there exists a constant  $c(\varepsilon)$  such that

$$\begin{aligned} b \int_{\Gamma} |M(u_e - u_c)|^2 d\tau - \|G_c\|_{H^{-1/2}(\Gamma)} \|M(u_e - u_c)\|_{H^{1/2}(\Gamma)} &\geq \\ (b - \varepsilon) \|M(u_e - u_c)\|_{H^{1/2}(\Gamma)}^2 - c(\varepsilon) \|G_c\|_{H^{-1/2}(\Gamma)}^2. \end{aligned}$$

Using this inequality in the lower bound (17), we conclude that

$$\lim_{\|\mathbf{u}\|_{\mathbb{H}} \rightarrow +\infty} \mathbf{J}(\mathbf{u}) = +\infty$$

hence  $\mathbf{J}$  achieves its minimum at a unique point  $\mathbf{u}^0 \in \mathbb{H}$ , which satisfies equation (10).  $\square$

### 3 The dynamical model

In this section, we focus on the dynamical description of the electropemabilization. Our model is based on the description of two quantities: the time-dependent electric potential and the ratio of the electropemabilized region over the total membrane area, which is also time-dependent. We present in subsection 3.1 the main considerations that lead to our model. We then study its solvability: existence and uniqueness results are presented in subsection 3.4.

### 3.1 Heuristics of the modeling

Experimental observations suggest that the permeabilization process at a certain location depends on whether the membrane conductivity is above a certain threshold or not. This leads us to define the surface membrane conductivity as an interpolation between the two values  $S_{\text{ir}}$  and  $S_{\text{L}}$ , the interpolation parameter  $\xi(t, s) \in [0, 1]$  being itself a function of time and of the point  $s$  on the membrane  $\Gamma$ . In our interpretation, the parameter  $\xi(t, s)$  measures in some way the likelihood that a given infinitesimal portion of the membrane is going to be electropermeabilized. More precisely, when  $\xi(t, s)$  equals 0 at a given point  $s \in \Gamma$ , the membrane conductivity equals the lipid conductivity at this point (thus there is no electropermeabilization), while for  $\xi(t, s) = 1$  it corresponds to the maximal value of the membrane surfacic conductivity above which electropermeabilization is irreversible. Thus we set:

$$\forall (t, s) \in (0, \infty) \times \Gamma, \quad S_{\text{m}}(t, s) = S_{\text{L}} + \xi(t, s)(S_{\text{ir}} - S_{\text{L}}). \quad (18)$$

On the other hand, the changes in the conductivity at a certain location  $s \in \Gamma$  depend on the transmembrane voltage. Denoting by  $[\mathbf{u}] := u_{\text{e}} - u_{\text{c}}$  the *jump* in the potential between the outside and the inside of the cell for  $\mathbf{u} := (u_{\text{e}}, u_{\text{c}}) \in \mathbb{H}$  (as we did in the previous sections), we therefore assume that

$$\xi(t, s) = X(t, [\mathbf{u}(t, s)]), \quad (19)$$

where the function  $(t, \lambda) \mapsto X(t, \lambda)$  will be defined below.

The main idea of the modeling consists in writing a differential equation that describes the dynamics of  $(t, \lambda) \mapsto X(t, \lambda)$  similarly to a *sliding door* model. Let  $\beta$  be a function satisfying

$$\left. \begin{aligned} &\beta \in W^{1, \infty}(\mathbb{R}), \quad \lambda \mapsto \beta(\lambda) \text{ is even on } \mathbb{R}, \\ &0 \leq \beta(\lambda) \leq 1, \quad \beta \text{ is non decreasing on } [0, +\infty), \\ &\lim_{\lambda \rightarrow +\infty} \beta(\lambda) = 1. \end{aligned} \right\} \quad (20)$$

An example of such a function would be

$$\forall \lambda \in \mathbb{R}, \quad \beta(\lambda) := (1 + \tanh(k_{\text{ep}}(|\lambda| - V_{\text{rev}})))/2.$$

For any  $\lambda_0 \in \mathbb{R}$ , which is going to denote the potential jump  $[\mathbf{u}(t_0, s)]$ , let  $X_0(\lambda_0) \in [0, 1]$  be the initial value of  $X(\cdot, \lambda_0)$  at time  $t_0$ . When a cell is at rest,  $X_0$  equals zero, but if high voltage pulses have been applied earlier than the initial time,  $X_0$  might not be equal to zero. At the time  $t_0$ , consider the jump of the potential  $\lambda_0 := [\mathbf{u}(t_0, s)]$  and set  $\beta_0 := \beta(\lambda_0)$ . There are two possibilities:

- Either  $\beta_0 - X_0$  is positive, in which case the electric pulse is sufficiently high to enlarge the electropermeabilized region, with a *characteristic time of electropermeabilization* of order  $\tau_{\text{ep}}$ .
- Or  $\beta_0 - X_0$  is negative, in which case we consider that the pulse is not high enough to increase the electropermeabilization. Therefore, the membrane *tries to reseal* with a characteristic *resealing* time of order  $\tau_{\text{res}}$ . Since experimental observations suggest that this phenomenon takes much more time than the electropermeabilization process, we assume that  $\tau_{\text{res}} > \tau_{\text{ep}}$ .

Based on these considerations,  $t \mapsto \lambda(t)$  being a given function of time (actually  $\lambda(t)$  is going to be  $[\mathbf{u}(t, s)]$ , see below for the type of regularity needed), we assume that  $X$  satisfies the following

differential equation:

$$\begin{cases} \frac{\partial X}{\partial t}(t, \lambda) = \max\left(\frac{\beta(\lambda(t)) - X(t, \lambda)}{\tau_{\text{ep}}}; \frac{\beta(\lambda(t)) - X(t, \lambda)}{\tau_{\text{res}}}\right), \\ X(0, \lambda) = X_0(\lambda(0)). \end{cases} \quad (21)$$

Observe that when  $\lambda(t) := \lambda(t, s) := [\mathbf{u}(t, s)]$ , if  $\mathbf{u}$  and  $X$  are stabilized at their respective stationary values  $\mathbf{u}^*(s)$  and  $X^*(\lambda(\cdot, s))$ , then the unique stationary solution of the above equation is given by

$$X^*(\lambda(\cdot, s)) = \beta([\mathbf{u}^*(s)]).$$

Taking definition (19) into account, equality (18) becomes

$$S_m^*(s) = S_L + (S_{\text{ir}} - S_L)\beta([\mathbf{u}^*(s)]),$$

which coincides with the definition of the static membrane conductivity (2).

As we shall see below, this interpretation of the model and the numerical simulations we present below agree with some experimental data existing in the literature.

### 3.2 Statement of the mathematical problem

We first write the problem satisfied by the potential  $U$  defined on the domain  $\mathcal{O}_e \cup \mathcal{O}_c$ . We assume that before the imposition of the electrical pulses  $g$  on the external boundary  $\partial\Omega$ , the cell potential is at rest given by  $U_0 \in H^1(\Omega)$ . This resting potential translates the ionic exchanges through the membrane. A function  $\tilde{S}_m$  is defined through equality (18) and (19) by:

$$\tilde{S}_m(t, \lambda) := S_L + (S_{\text{ir}} - S_L)X(t, \lambda). \quad (22)$$

We seek the solution  $(U, X)$  to the following system of equations:

$$\Delta U = 0, \quad \text{in } (0, T) \times (\mathcal{O}_e \cup \mathcal{O}_i), \quad (23a)$$

$$[\sigma \partial_{\mathbf{n}} U] = 0, \quad \text{on } (0, T) \times \Gamma, \quad (23b)$$

$$C_m \partial_t [U](t, \cdot) + \tilde{S}_m(t, [U])[U] = \sigma_i \partial_{\mathbf{n}} U(t, \cdot)|_{\Gamma^-}, \quad \text{on } (0, T) \times \Gamma, \quad (23c)$$

$$U(t, \cdot) = g(t, \cdot) \quad \text{on } (0, +\infty) \times \partial\Omega, \quad (23d)$$

$$U(0, \cdot) = U_0 \quad \text{in } \mathcal{O}_e \cup \mathcal{O}_c, \quad (23e)$$

where the function  $X$  appearing in (22) satisfies, for any  $t > 0$  (here we set  $\lambda(t) := \lambda(t, s) := [U(t, s)]$  for a.e.  $s \in \Gamma$ ):

$$\begin{cases} \frac{\partial X(t, \lambda)}{\partial t} = \max\left(\frac{\beta(\lambda(t)) - X(t, \cdot)}{\tau_{\text{ep}}}; \frac{\beta(\lambda(t)) - X(t, \cdot)}{\tau_{\text{res}}}\right), \\ X(0, \lambda) = 0. \end{cases} \quad (24)$$

### 3.3 Properties of the function $X$

Let us state the following lemma regarding the solution to equation (24):

**Lemma 3.1.** *Let  $T > 0$  be fixed and let  $\beta$  satisfy condition (20). For any  $\lambda \in L^p(0, T)$ , with  $1 \leq p \leq \infty$ , the following differential equation*

$$\begin{cases} \frac{\partial X(t, \lambda)}{\partial t} = \max\left(\frac{\beta(\lambda(t)) - X(t, \lambda)}{\tau_{\text{ep}}}; \frac{\beta(\lambda(t)) - X(t, \lambda)}{\tau_{\text{res}}}\right), \quad \forall t > 0, \\ X(0, \lambda) = X_0 \in [0, 1], \end{cases} \quad (25)$$

has a unique solution  $X(\cdot, \lambda) \in W^{1,p}(0, T)$ . Moreover,

$$0 \leq X(t, \lambda) \leq 1, \quad \forall t \in [0, T],$$

while

$$X(\cdot, \lambda) = X(\cdot, -\lambda) = X(\cdot, |\lambda|), \quad \forall \lambda \in \mathbb{R}.$$

Moreover, there exists a constant  $K(T) > 0$  depending on  $\|\beta'\|_\infty$  such that for any  $\lambda_1, \lambda_2 \in L^p(0, T)$  with  $1 \leq p \leq \infty$ , we have

$$\|X(\cdot, \lambda_1) - X(\cdot, \lambda_2)\|_{L^\infty(0, T)} \leq K(T) \|\lambda_1 - \lambda_2\|_{L^p(0, T)}. \quad (26)$$

More precisely, the constant  $K(T)$  is given by

$$K(T) = T^{(p-1)/p} \|\beta'\|_\infty \exp(\max(\tau_{\text{ep}}^{-1}, \tau_{\text{res}}^{-1})T).$$

*Proof.* The mapping  $X \mapsto \max([\beta(\lambda(t)) - X]/\tau_{\text{ep}}, [\beta(\lambda(t)) - X]/\tau_{\text{res}})$ , defined from  $W^{1,p}(0, T)$  into itself, is clearly Lipschitz for all fixed  $t$ , while the mapping

$$t \mapsto \max([\beta(\lambda(t)) - X]/\tau_{\text{ep}}, [\beta(\lambda(t)) - X]/\tau_{\text{res}}),$$

belongs to  $L^p(0, T)$  for all fixed  $X$ . Therefore, the differential equation (25) has a unique solution  $X \in W^{1,p}(0, T)$ , for any  $X_0 \in \mathbb{R}$ .

Assuming now that  $0 \leq X_0 \leq 1$ , multiplying the equation (25) by  $X^- := \max(-X, 0)$ , and using the fact that  $\beta \geq 0$ , one gets

$$\frac{1}{2} \partial_t |X^-|^2 \leq 0.$$

Thus  $X^-(t, \lambda) \equiv 0$  on  $[0, T]$ . Similarly, using the fact that  $\beta - 1 \leq 0$ , and multiplying the equation by  $(X - 1)^+ = \max(X - 1, 0)$ , one sees that

$$\partial_t |(X - 1)^+|^2 \leq 0,$$

and finally  $0 \leq X(t, \lambda) \leq 1$ .

In order to prove the Lipschitz continuous dependence of  $X$  on  $\lambda$ , we set

$$F(\lambda, X) := \max\left(\frac{\beta(\lambda(\cdot)) - X}{\tau_{\text{ep}}}; \frac{\beta(\lambda(\cdot)) - X}{\tau_{\text{res}}}\right), \quad (27)$$

and we denote by  $X_j := X(\cdot, \lambda_j)$  for  $j = 1, 2$ , the respective solutions to (25). We have

$$\partial_t (X_1 - X_2) = F(\lambda_1, X_1) - F(\lambda_2, X_2),$$

and thus

$$X_1(t) - X_2(t) = \int_0^t (F(\lambda_1, X_1) - F(\lambda_2, X_2))(s) ds.$$

Note that we may write

$$F(\lambda_1, X_1) - F(\lambda_2, X_2) = [F(\lambda_1, X_1) - F(\lambda_2, X_1)] + [F(\lambda_2, X_1) - F(\lambda_2, X_2)].$$

For any  $0 \leq s \leq t \leq T$  we have

$$\begin{aligned} \|F(\lambda_1, X_1) - F(\lambda_2, X_1)\|_{L^p(0, t)} &\leq \|\beta'\|_\infty \|\lambda_1 - \lambda_2\|_{L^p(0, t)}, \\ |(F(\lambda_2, X_1) - F(\lambda_2, X_2))(s)| &\leq \max(1/\tau_{\text{ep}}, 1/\tau_{\text{res}}) |X_1(s) - X_2(s)|. \end{aligned}$$



Thus, using the fact that by Hölder's inequality we have

$$\begin{aligned} \int_0^t |(F(\lambda_1, X_1) - F(\lambda_2, X_1))(s)| ds &\leq t^{(p-1)/p} \|F(\lambda_1, X_1) - F(\lambda_2, X_1)\|_{L^p(0,t)}, \\ &\leq T^{(p-1)/p} \|\beta'\|_\infty \|\lambda_1 - \lambda_2\|_{L^p(0,T)}, \end{aligned}$$

we infer that the following inequality holds for  $|X_1(t) - X_2(t)|$ :

$$\begin{aligned} |X_1(t) - X_2(t)| &\leq T^{(p-1)/p} \|\beta'\|_\infty \|\lambda_1 - \lambda_2\|_{L^p(0,T)} \\ &\quad + \max(1/\tau_{\text{ep}}, 1/\tau_{\text{res}}) \int_0^t |X_1(s) - X_2(s)| ds, \end{aligned}$$

which yields the estimate (26), thanks to Gronwall's lemma.  $\square$

**Remark 3.2.** *The results of the above lemma are still valid if one replaces  $\beta : \mathbb{R} \rightarrow \mathbb{R}$  satisfying (20) with a function  $\beta \in L^\infty((0, T) \times \mathbb{R})$  such that for almost every  $t \in (0, T)$ , the function  $\beta(t, \cdot)$  satisfies (20). Moreover, if  $\lambda \in C^0([0, T])$  then  $X \in C^1([0, T])$  and*

$$\|X(\cdot, \lambda_1) - X(\cdot, \lambda_2)\|_{C^1(0,T)} \leq \|\beta'\|_\infty \exp(\max(\tau_{\text{ep}}^{-1}, \tau_{\text{res}}^{-1})T) \|\lambda_1 - \lambda_2\|_{C^0(0,T)}.$$

### 3.4 Existence and uniqueness of the dynamical potential

Since the non-linearity of problem (23) appears in the transmission condition (23c), we are going to rewrite it on the surface  $\Gamma$  using the Steklov-Poincaré operators, in the same manner as we did in the previous section for the static model. We first prove the following property:

**Lemma 3.3.** *The operator  $\Lambda_e + \Lambda_c$  is positive, selfadjoint and invertible from  $H^{1/2}(\Gamma)$  into  $H^{-1/2}(\Gamma)$ . The operator*

$$\mathcal{B} := \text{Id} + \Lambda_e^{-1} \Lambda_c$$

*is therefore invertible, from  $H^{1/2}(\Gamma)$  into itself.*

*Moreover, define the domain  $D(\Lambda_c \mathcal{B}^{-1})$  as*

$$D(\Lambda_c \mathcal{B}^{-1}) = \left\{ \varphi \in H^{1/2}(\Gamma) : \Lambda_c \mathcal{B}^{-1} \varphi \in L^2(\Gamma) \right\}.$$

*The operator  $(\Lambda_c \mathcal{B}^{-1}, D(\Lambda_c \mathcal{B}^{-1}))$  is  $m$ -accretive (more precisely  $D(\Lambda_c \mathcal{B}^{-1}) = H^1(\Gamma)$ ).*

*Proof.* That  $\Lambda_e + \Lambda_c$  is invertible is an easy consequence of the fact that the operator  $\Lambda_e$  is a positive, selfadjoint and invertible operator while  $\Lambda_c$  is non-negative and selfadjoint. Thus,  $\Lambda_e + \Lambda_c$  is also a positive selfadjoint invertible operator.

Let  $\varphi \in D(\Lambda_c \mathcal{B}^{-1})$ . Then, by definition (and invertibility) of  $\mathcal{B}$  (i.e.  $\text{Id} = (\text{Id} + \Lambda_e^{-1} \Lambda_c) \mathcal{B}^{-1}$ ) we have

$$\begin{aligned} \langle \Lambda_c \mathcal{B}^{-1} \varphi, \varphi \rangle &= \langle \Lambda_c \mathcal{B}^{-1} \varphi, \varphi \rangle, \\ &= \langle \Lambda_c \mathcal{B}^{-1} \varphi, \mathcal{B}^{-1} \varphi \rangle + \langle \Lambda_c \mathcal{B}^{-1} \varphi, \Lambda_e^{-1} \Lambda_c \mathcal{B}^{-1} \varphi \rangle, \\ &= \langle \Lambda_c \mathcal{B}^{-1} \varphi, \mathcal{B}^{-1} \varphi \rangle + \langle \Lambda_c \Lambda_e^{-1} \Lambda_c \mathcal{B}^{-1} \varphi, \Lambda_e^{-1} \Lambda_c \mathcal{B}^{-1} \varphi \rangle \\ &\geq 0. \end{aligned}$$

$\Lambda_c \mathcal{B}^{-1}$  is therefore accretive. Let  $f \in L^2(\Gamma)$ , let  $\lambda > 0$  and let  $U$  be the unique solution in  $PH_0^1(\Omega)$  to the following problem:

$$\begin{aligned} -\Delta U &= 0, \text{ in } \mathcal{O}_e \cup \mathcal{O}_c, \quad U|_{\partial\Omega} = 0, \\ \sigma_e \partial_{\mathbf{n}} U|_{\Gamma^+} &= \sigma_c \partial_{\mathbf{n}} U|_{\Gamma^-}, \\ \lambda \sigma_c \partial_{\mathbf{n}} U|_{\Gamma^-} + U|_{\Gamma^-} - U|_{\Gamma^+} &= f. \end{aligned}$$

Therefore, setting  $v := U|_{\Gamma^-} - U|_{\Gamma^+}$ ,  $v$  satisfies

$$v + \lambda \Lambda_c \mathcal{B}^{-1} v = f.$$

In addition, since  $\Lambda_c \mathcal{B}^{-1}$  is nonnegative, we have  $\|v\|_{L^2(\Gamma)} \leq \|f\|_{L^2(\Gamma)}$ . Therefore,  $\Lambda_c \mathcal{B}^{-1}$  is  $m$ -accretive.  $\square$

**Lemma 3.4.** *Finding the solution  $U$  to problem (23), if it exists, is equivalent to finding  $(u_e, u_c)$  with  $u_e = U|_{\Gamma^+}$  and  $u_c = U|_{\Gamma^-}$  satisfying:*

$$u_e = u_c - v, \quad (28)$$

$$u_c = \mathcal{B}^{-1} (v - \Lambda_e^{-1} \Lambda_0 g), \quad (29)$$

where  $v$  is the solution to

$$\begin{aligned} C_m \partial_t v + \Lambda_c \mathcal{B}^{-1} v + \tilde{S}_m(t, v) v &= G, \\ v(0, \cdot) &= \varphi, \end{aligned} \quad (30)$$

with  $\varphi$  and  $G$  being defined as

$$\varphi = U_0|_{\Gamma^+} - U_0|_{\Gamma^-}, \quad G := \Lambda_c \mathcal{B}^{-1} \Lambda_e^{-1} \Lambda_0 g,$$

and  $X$  satisfying

$$\begin{cases} \lambda(t, \cdot) = v, \\ \partial_t X(t, \cdot) = \max \left( \frac{\beta(\lambda(t, \cdot)) - X(t, \lambda)}{\tau_{\text{ep}}}, \frac{\beta(\lambda(t, \cdot)) - X(t, \lambda)}{\tau_{\text{res}}} \right), \\ X(0, \cdot) = 0. \end{cases} \quad (31)$$

*Proof.* The lemma is a straightforward consequence of the definition of the Steklov-Poincaré operators  $\Lambda_c, \Lambda_e, \Lambda_0$ , and of the invertibility of  $\Lambda_e$ . Indeed, condition (23b), that is the continuity of the flux across  $\Gamma$ , boils down to

$$\Lambda_e u_e + \Lambda_0 g + \Lambda_c u_c = 0,$$

from which, thanks to the invertibility of  $\Lambda_e$ , we infer that

$$u_e - u_c = -(\mathcal{B} u_c + \Lambda_e^{-1} \Lambda_0 g) = -v.$$

In addition, by definition of  $v$ , we have

$$\Lambda_c u_c = \Lambda_c \mathcal{B}^{-1} v - \Lambda_c \mathcal{B}^{-1} \Lambda_e^{-1} \Lambda_0 g = \Lambda_c \mathcal{B}^{-1} v - G.$$

Then, the transmission condition (23c) (multiplied by  $(-1)$ ) reads (30), provided we recall that  $\beta$  is an even function and that  $\tilde{S}_m$  is defined by (22).  $\square$

We now show that the evolution equations appearing in lemma 3.4 have a unique solution.

**Lemma 3.5.** *Assume that  $\beta$  satisfies (20),  $G \in L^p((0, T); L^2(\Gamma))$  for some  $p > 1$ , and that  $\varphi \in L^2(\Gamma)$  is given. Then, there exists a unique function  $v \in C([0, T]; L^2(\Gamma))$ , mild solution to the system*

$$\begin{cases} C_m \partial_t v + \Lambda_c \mathcal{B}^{-1} v + \tilde{S}_m(t, v) v = G, \\ \lambda(t, \cdot) = v, \\ \partial_t X(t, \cdot) = \max \left( \frac{\beta(\lambda(t, \cdot)) - X(t, \lambda)}{\tau_{\text{ep}}}; \frac{\beta(\lambda(t, \cdot)) - X(t, \lambda)}{\tau_{\text{res}}} \right), \\ X(0, \cdot) = 0, \\ v(0) = \varphi. \end{cases} \quad (32)$$

Moreover, if  $\varphi \in H^1(\Gamma)$  and  $G \in W^{1,1}((0, T); L^2(\Gamma))$ , the above mild solution is a classical solution to (32), in the sense that

$$v \in C([0, T]; H^1(\Gamma)) \cap C^1([0, T]; L^2(\Gamma)).$$

*Proof.* To simplify the notations we denote by  $\mathcal{A}$  the operator

$$\mathcal{A} = \frac{1}{C_m} \Lambda_c \mathcal{B}^{-1}.$$

In a first step, we are going to show existence and uniqueness of a mild solution to (32) in  $C([0, T]; L^2(\Gamma))$ . For a given  $v \in C([0, T]; L^2(\Gamma))$ , thanks to lemma 3.1, we know that the solution to

$$\begin{cases} \lambda(t, \cdot) = v, \\ \partial_t X(t, \cdot) = \max \left( \frac{\beta(\lambda(t, \cdot)) - X(t, \lambda)}{\tau_{\text{ep}}}; \frac{\beta(\lambda(t, \cdot)) - X(t, \lambda)}{\tau_{\text{res}}} \right), \\ X(0, \cdot) = 0, \end{cases}$$

exists and belongs to  $W^{1,\infty}((0, T), L^2(\Gamma))$ . Moreover,  $0 \leq X \leq 1$ , and the mapping  $v \mapsto X$  is Lipschitz. Hence, for some constant  $C > 0$  and  $K(T)$  given by lemma 3.1, if  $X_j$  denotes the solution of the above equation for  $\lambda_j := v_{i,j}$  (with  $j = 1$  or  $j = 2$ ), then we have

$$\begin{aligned} \|X_1 - X_2\|_{L^\infty((0, T); L^2(\Gamma))} &\leq K(T) \|\lambda_1 - \lambda_2\|_{L^2((0, T) \times \Gamma)} \\ &\leq C K(T) \|v_{i,1} - v_{i,2}\|_{C([0, T]; L^2(\Gamma))}. \end{aligned}$$

Now, upon setting

$$\mathcal{F}(t, v) := -\tilde{S}_m(t, v) v + G,$$

solving equations (32) is equivalent to finding  $v \in C([0, T]; L^2(\Gamma))$  solution to the following equation, which is the mild version of equation (32):

$$v = e^{-t\mathcal{A}} \varphi + \frac{1}{C_m} \int_0^t \exp(-(t-\tau)\mathcal{A}) \mathcal{F}(\tau, v(\tau)) d\tau. \quad (33)$$

It is now clear that, thanks to the properties proved in lemma 3.1 for  $\lambda \mapsto X(\cdot, \lambda)$ , the mapping

$$v \mapsto \mathcal{F}(\cdot, v),$$

is Lipschitz from the space  $\mathbb{E} := C([0, T]; L^2(\Gamma))$  into itself. This means that there exists  $K_1 > 0$  such that for any  $v, w \in C([0, T]; L^2(\Gamma))$  we have

$$\|\mathcal{F}(\cdot, v) - \mathcal{F}(\cdot, w)\|_{L^\infty((0, T); L^2(\Gamma))} \leq K_1 \|v - w\|_{L^\infty((0, T); L^2(\Gamma))}.$$

We shall endow the space  $\mathbb{E}$  with the norm

$$\|\psi\|_{\mathbb{E}} := \sup_{t \in [0, T]} e^{-\alpha t} \|\psi(t, \cdot)\|_{L^2(\Gamma)},$$

for some  $\alpha > 0$ , which will be chosen below. If we set

$$\Phi(U_c)(t) := e^{-t\mathcal{A}}\varphi + \frac{1}{C_m} \int_0^t \exp(-(t-\tau)\mathcal{A}) \mathcal{F}(\tau, U_c(\tau)) d\tau,$$

then  $\Phi : \mathbb{E} \rightarrow \mathbb{E}$  is a continuous mapping. We shall check that, upon choosing  $\alpha$  appropriately, it is a strict contraction. Thus, it has a unique fixed point, providing the unique solution of (33). Indeed

$$\Phi(U_c)(t) - \Phi(V)(t) = \int_0^t \exp\left(-\frac{t-\tau}{C_m} \Lambda_c \mathcal{B}^{-1}\right) [\mathcal{F}(\tau, U_c) - \mathcal{F}(\tau, V)] d\tau.$$

Since the operator  $\Lambda_c \mathcal{B}^{-1}$  is  $m$ -accretive, the operator  $\mathcal{A}$  generates a contraction semi-group and the following estimate holds

$$\|e^{-(t-\tau)\mathcal{A}} [\mathcal{F}(\tau, U_c) - \mathcal{F}(\tau, V)]\|_{L^2(\Gamma)} \leq \|[\mathcal{F}(\tau, U_c) - \mathcal{F}(\tau, V)]\|_{L^2(\Gamma)}.$$

Therefore, we infer

$$\begin{aligned} \|\Phi(U_c)(t) - \Phi(V)(t)\|_{L^2(\Gamma)} &\leq \left\| \int_0^t \|\mathcal{F}(\tau, U_c) - \mathcal{F}(\tau, V)\|_{L^2(\Gamma)} d\tau \right\| \\ &\leq K_1 \|U_c - V\|_{\mathbb{E}} \int_0^t e^{\alpha\tau} d\tau, \\ &\leq C(p) K_1 \alpha^{-1} e^{\alpha t} \|U_c - V\|_{\mathbb{E}}, \end{aligned}$$

from which we conclude that

$$\|\Phi(U_c) - \Phi(V)\|_{\mathbb{E}} \leq \alpha^{-1} C(p) K_1 \|U_c - V\|_{\mathbb{E}}.$$

This implies that for  $\alpha$  large enough, the mapping  $\Phi$  is a strict contraction on  $\mathbb{E}$ . Equation (32) has thus a unique mild solution in  $C([0, T]; L^2(\Gamma))$ .

Suppose now that  $G$  belongs to  $W^{1,1}((0, T); L^2(\Gamma))$  and that  $\varphi \in H^1(\Gamma)$ . The mild solution given by formula (33) belongs to  $C^1([0, T]; L^2(\Gamma))$  hence we infer

$$\partial_t v + \tilde{S}_m(\cdot, v)v \in C([0, T]; L^2(\Gamma)).$$

Therefore, setting  $U_c = U|_{\mathcal{O}_c}$ , we have

$$\Delta U_c(t, \cdot) = 0, \text{ in } \mathcal{O}_c, \quad \sigma_c \partial_n U_c(t, \cdot) \in L^2(\Gamma),$$

from which we infer that  $U_c(t, \cdot) \in H^{3/2}(\mathcal{O}_c)$ . Hence we deduce that since the domains are smooth  $U_c(t, \cdot)|_{\Gamma^-}$  belongs to  $H^1(\Gamma)$ . Similar reasoning for  $U_e = U|_{\mathcal{O}_e}$  implies that  $U_e(t, \cdot)|_{\Gamma^+}$  belongs to  $H^1(\Gamma)$ , and therefore the jump  $v$  belongs to  $C([0, T]; H^1(\Gamma))$ , which ends the proof.  $\square$

## 4 Numerical simulations

In this section, we provide some numerical results that justify the consistency of our new electroporation model. In order to solve both static and dynamical problems, we first present the second-order finite-difference method on a cartesian grid adapted from the scheme of Cisternino and Weynans [2].

### 4.1 Spatial discretization

We perform the discretization on a cartesian grid covering the domain  $\Omega = \mathcal{O}_e \cup \overline{\mathcal{O}_c}$ , which is a square domain of length  $L$  ( $L$  equals  $200\mu\text{m}$  for the computations, see Table 1). The interface is described by a level-set function [16], which separates the extra- and intra-cellular domains by the use of a signed distance function  $\varphi$ . The normal to the interface  $\mathbf{n}(x)$  outwardly directed from the inner to the outer of the cell is directly obtained by computing numerically  $\nabla\varphi(x)$ .

The grid spacing is denoted by  $h$ , and  $N$  is the number of points equal to

$$N = L/h.$$

For any  $(i, j) \in N^2$  we denote by  $M_{ij}$  the grid points defined by

$$M_{i,j} = (x_i, y_j), \quad \text{where } x_i = ih_x, y_j = jh_y, \quad \forall (i, j) \in N^2.$$

The numerical approximation of the solution to the static or to the dynamical model at the point  $(x_i, y_j)$  is generically denoted by  $u_{ij}$ .

Standard approximation of the Laplacian is used in the discretized domains  $\mathcal{O}_e$  and  $\mathcal{O}_c$  far from the interface, which is the cell membrane  $\Gamma$ . However, due to the jump conditions, a special treatment of the approximation of the Laplacian and of the computation of the fluxes is needed at the points nearing the cell membrane.

If the intersection of the interface and  $[M_{ij} M_{i+1j}]$  exists, then we define the interface point  $I_{i+1/2,j} = (\tilde{x}_{i+1/2,j}, y_j)$  as this intersection. We create two additional unknowns at this interface point, called interface unknowns, and denoted by  $\tilde{u}_{i+1/2,j}^e$  and  $\tilde{u}_{i+1/2,j}^c$ . The interface point  $I_{i,j+1/2} = (x_i, \tilde{y}_{i,j+1/2})$  is similarly defined as the intersection of  $\Gamma$  and the segment  $[M_{ij} M_{ij+1}]$ .

An example of the discretization method is given by Figure 1. On regular grid points, that are not neighboring the interface, the Laplacian is discretized with a standard centered second-order finite-difference scheme. A specific five points stencil including the interface points is used for neighboring points, as shown in Figure 1(a).

Figure 1(b) provides an example of the discretization of  $\nabla U$  on both sides of the interface. The  $x$ -derivative of  $U$  can be computed with second-order accuracy using a one-sided formula involving three grid points. For example we approximate the flux on the left (for instance exterior) side of the interface with the points  $M_{i-1j}$ ,  $M_{ij}$  and  $I_{i+1/2,j}$  by:

$$\frac{\partial U}{\partial x}(\tilde{x}, y_j) \approx \frac{(u_{i-1j} - \tilde{u}_{i+1/2,j}^e)(x_i - \tilde{x})}{h_x(x_{i-1} - \tilde{x})} - \frac{(u_{ij} - \tilde{u}_{i+1/2,j}^e)(x_{i-1} - \tilde{x})}{h_x(x_i - \tilde{x})}, \quad (34)$$

where for the sake of brevity, we have replaced  $\tilde{x}_{i+1/2,j}$  by  $\tilde{x}$ . The  $y$ -derivative cannot be obtained in the same way, since there are no grid points aligned with the interface point in the  $y$ -direction. We therefore use a linear combination of  $(\partial_y u)_{ij}$  and  $(\partial_y u)_{i-1j}$ , defined respectively as second order approximations of the  $y$ -derivative on  $M_{ij}$  and  $M_{i-1j}$ . We obtain

$$\frac{\partial U}{\partial y}(\tilde{x}, y_j) \approx \frac{\tilde{x} - x_{i-1}}{h_x} (\partial_y u)_{ij} - \frac{\tilde{x} - x_i}{h_x} (\partial_y u)_{i-1j}. \quad (35)$$

The formulas for  $(\partial_y u)_{ij}$  and  $(\partial_y u)_{i-1j}$  depend on the local configuration on the interface, but they are based on the same principle as for (34). The scheme is stabilized by using a shifted  $y$ -stencil if two interface points are involved in the same flux discretization, as illustrated by Figure 1(c).

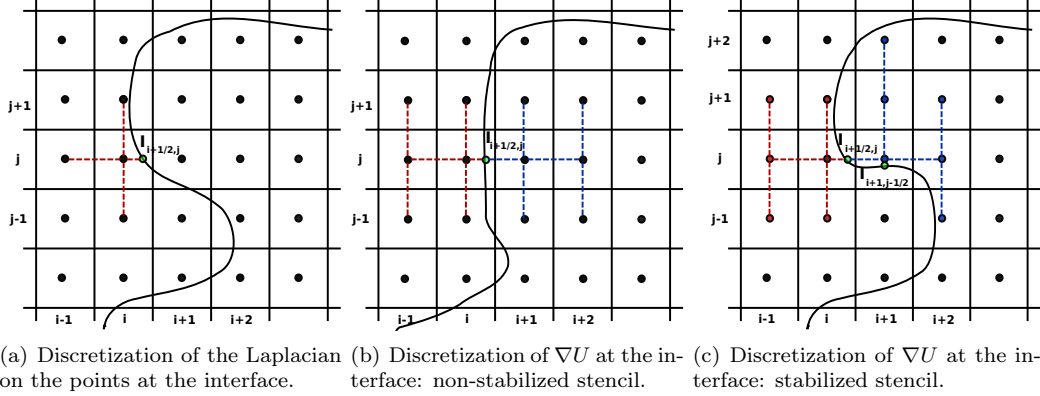


Figure 1: Discretizations of the Laplacian and of the gradient of  $U$  at the interface. The first  $y$ -derivative stencil on the right side is shifted to avoid an ill-conditioned discretization.

## 4.2 Accuracy of the finite difference method

In order to show the accuracy of the numerical method, we compare the explicit solution to the numerical solution of the linear model, *i.e.* without electroporation.

Actually, when the membrane conductivity  $\tilde{S}_m$  is fixed to the value  $S_L$ , we compute explicitly the solution  $\tilde{U}$  to the linear problem in the case of concentric circular domains. The cell is a circle of radius  $R_1$ , the domain  $\Omega$  is a circle with the same center as the cell, and whose radius is denoted by  $R_2 > R_1$ . The boundary data equals  $g = ER_2 \cos \theta$ , such that the cell is embedded in a uniform electric field of magnitude  $E$  in the  $x$ -direction. The analytic solution to the static problem has the following form:

$$\begin{aligned} \tilde{U}_e(r, \theta, t) &= (\alpha_e(t)r + \beta_e(t)r^{-1}) \cos \theta, \quad \forall (r, \theta) \in (R_1, R_2) \times [0, 2\pi], \\ \tilde{U}_c(r, \theta, t) &= \alpha_c(t)r \cos \theta, \quad \forall (r, \theta) \in (0, R_1) \times [0, 2\pi], \end{aligned} \quad (36)$$

where  $\alpha_e$ ,  $\beta_e$ , and  $\alpha_c$  are time-dependent functions with explicit expressions, which are not given here to lighten the paper. This solution is projected on the edges of our square-shaped computational domain. The error is computed using both grid and interface points:

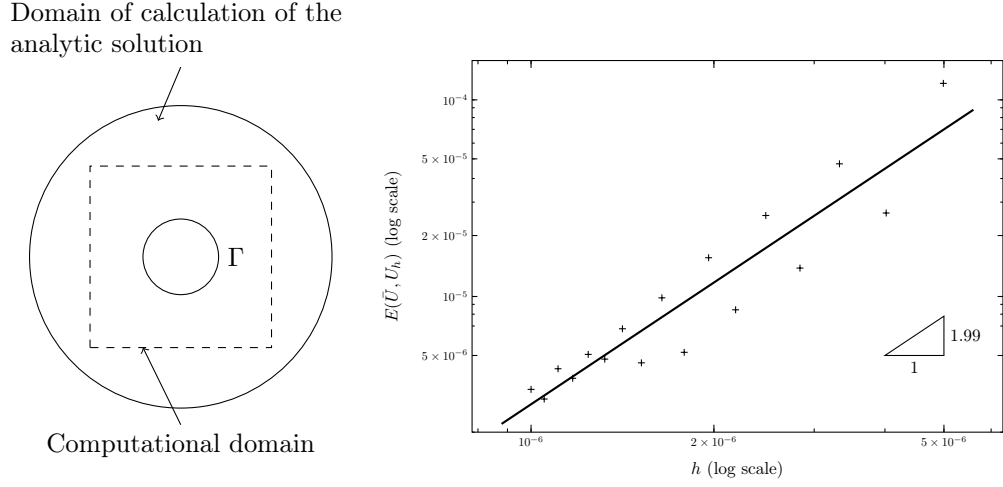
$$E(\tilde{U}, U_h) := \frac{\|U_h - \tilde{U}\|_{L^2(\Omega)} + \|U_h - \tilde{U}\|_{L^2(\Gamma)}}{\|\tilde{U}\|_{L^2(\Omega)} + \|\tilde{U}\|_{L^2(\Gamma)}}, \quad (37)$$

where  $U_h$  denotes the numerical solution on the cartesian grid of grid spacing  $h$ .

For the numerical simulations, we set the parameters equal to

$$R_2 = 150\mu\text{m}, \quad R_1 = 50\mu\text{m}, \quad E = 400 \text{ V/cm},$$

the electric parameters being given by Table 1. Figure 2 shows the comparison between this solution and our simulations, confirming that the precision of our scheme is of order  $h^2$  for the linear case.



(a) Domains of calculation of the analytic and of the numerical solutions. (b) Log-log diagram of the error  $E(\tilde{U}, U_h)$  given by (37) with respect to  $h$ .

Figure 2: Numerical estimation of the order of accuracy of the method. The analytic solution to the linear problem is calculated in concentric circular domains. The restriction of this solution to the boundary of the computational domain (dashed line) provides the Dirichlet data for the numerical solution. Relative error between the two solutions with respect to the grid spacing is plotted in Figure 2(b).

### 4.3 Computation of the non-linear static model

When solving the static equation (4), if one uses the following naive iterative method:

$$S_m([U^n])[U^{n+1}] = \sigma_c \partial_{\mathbf{n}} U_c^{n+1},$$

one finds that the iterative scheme oscillates between two values. This might be a consequence of the fact that the membrane conductivity takes its extreme values  $S_L$  and  $S_R$  instead of reaching an intermediate state. Another issue might be that the mapping  $\mathcal{L}_g$  defined by

$$\mathcal{L}_g : v \mapsto u,$$

where  $u \in PH^1(\Omega)$  is solution to

$$\begin{cases} \Delta u = 0, & \text{in } \mathcal{O}_e \cup \mathcal{O}_c, \quad u|_{\partial\Omega} = g, \\ [\sigma \partial_{\mathbf{n}} u]_{\Gamma} = 0, & S_m([v]_{\Gamma})[u]_{\Gamma} = \sigma_c \partial_{\mathbf{n}} u|_{\Gamma}, \end{cases}$$

is not a contraction, since the Lipschitz constant of  $S_m$  is of order  $k_{ep} S_m \gg 1$ .

We use a modified mapping  $\mathcal{L}_{\rho, g}$ :

$$\mathcal{L}_{\rho, g} : v \mapsto u,$$

where  $u \in PH^1(\Omega)$  is solution to

$$\begin{cases} \Delta u = 0, & \text{in } \mathcal{O}_e \cup \mathcal{O}_c, \quad u|_{\partial\Omega} = g, \\ [\sigma \partial_{\mathbf{n}} u]_{\Gamma} = 0, & [u]_{\Gamma} + \rho S_m([v]_{\Gamma})[u]_{\Gamma} - \rho \sigma_c \partial_{\mathbf{n}} u|_{\Gamma} = [v]_{\Gamma}, \end{cases}$$

where  $\rho$  is a small positive parameter chosen so as  $\mathcal{L}_{\rho,g}$  be a contractive operator. The following iteration process is used:

$$U^0 \text{ given, and for any } n \geq 0 \quad U^{n+1} = \mathcal{L}_{\rho,g}(U^n).$$

For the simulations we set the stopping criterion of the scheme at  $\gamma = 10^{-12}$ , meaning that the numerical solution is obtained when the relative error  $E(U^{n+1}, U^n)$  is smaller than  $\gamma$ .

#### 4.3.1 Influence of the parameter $S_{ir}$

The parameter  $S_{ir}$ , which is the conductivity of the fully “electroporated” membrane is hardly measurable by the experiments. It is therefore important to investigate its influence on the model. Figure 3 shows that  $S_{ir}$  has a little influence on the membrane conductivity  $S_m$ , as the value of  $X$  counter-balance the variation of  $S_{ir}$ . Therefore, the numerical criterion to define the electroporation should involve the parameter  $S_m$ .

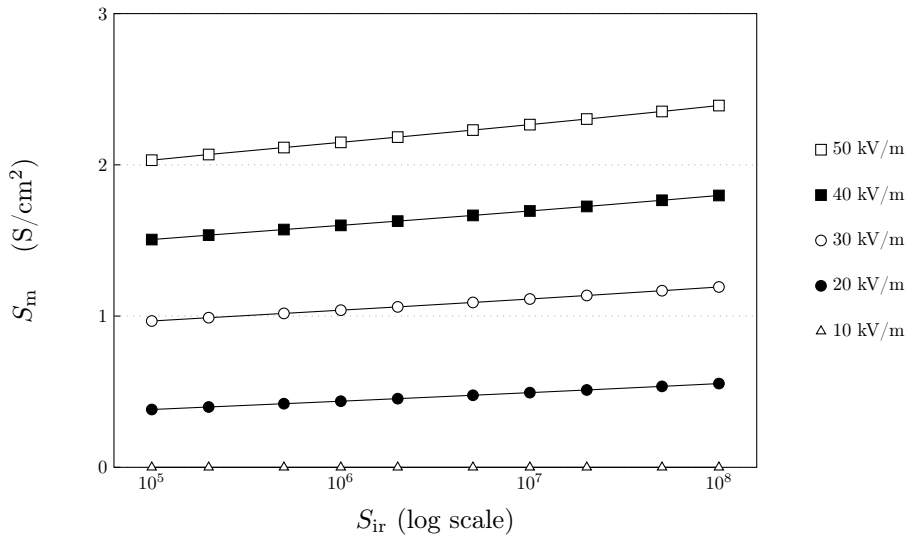


Figure 3: Membrane surfacic conductivity  $S_m$  at the pole of the cell ( $\theta = 0$ ) obtained by solving the static equation with different values of  $S_{ir}$  for pulse magnitudes from 10 to 50 kV/m (the numerical values of the other parameters are given in Table 1).

#### 4.3.2 Comparison with the model of Ivorra, Mir and Villemejeane

We compare our results with the simulations of Ivorra *et al.* by studying the influence of the extracellular medium conductivity on the membrane conductivity. In Figure 4, we show results similar to those presented in Figure 7 of [10]. Note that to perform their simulations, Ivorra *et al.* have multiplied by ten the membrane thickness. This is the reason why their permeabilizing field is of order of magnitude of 2MV/m, which is much higher than the magnitude used in the experiments, typically [12, 13, 6] to the range 20 to 30 kV/m. In contrast, our model provides more realistic conditions of electroporation.



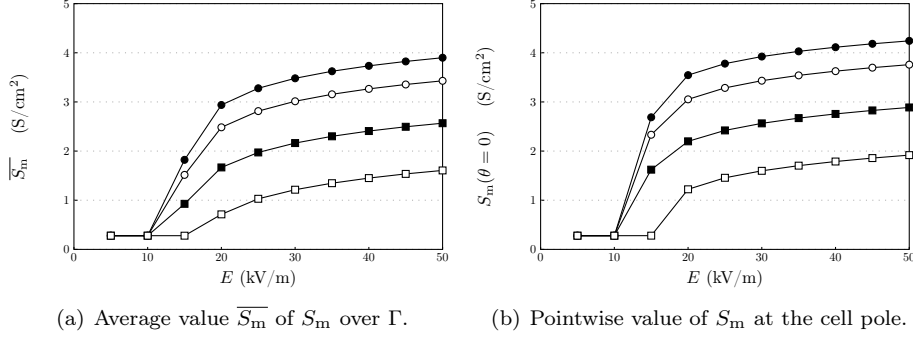


Figure 4: Non-linear membrane conductivity of the static model for 4 different extracellular conductivity:  $\sigma_e = 1$  S/m ( $\bullet$ ),  $\sigma_e = 0.1$  S/m ( $\circ$ ),  $\sigma_e = 0.01$  S/m ( $\blacksquare$ ),  $\sigma_e = 0.001$  S/m ( $\square$ ).

## 4.4 Computation of the dynamical problem

### 4.4.1 Time-discretization of the model

The time-derivative  $\partial_t[U]$  of (23) is discretized using the implicit forward Euler scheme:

$$C_m \frac{[U]^{n+1} - [U]^n}{dt} - \sigma_c \partial_n U_c^{n+1} + \tilde{S}_m([U]^n)[U]^n = 0. \quad (38)$$

The Runge-Kutta method of order 4 is used to compute the variable  $X$ .

Figure 5(a) and 5(b) show the numerical results using the parameters of Table 1. In order to visualize the membrane electropermeabilization, we depict it with boxes which colored according to the values of  $S_m$  and which is proportionally sized to the values of  $(1.5\|X\|_\infty - X)$  at each point of  $\Gamma$ . Note this is only a visualization artefact, since in our model the membrane has no thickness.

### 4.4.2 Main parameters influence

The key parameters of the model define the electropermeabilization coefficient  $\tilde{S}_m$ , that is  $k_{ep}$ ,  $V_{rev}$ ,  $S_{ir}$  and the characteristic times  $\tau_{ep}$  and  $\tau_{res}$ . A numerical sensitivity analysis was led to determine how the behavior of the solution with respect to a variation of each specific parameter, as shown on Figure 6. All the parameters defining the function  $\beta$  have a very small influence on the average  $\bar{X}$  of  $X$  over the cell membrane. Even for small values of  $k_{ep}$  the values of  $\bar{X}$  are only modified by a factor 2 (Figure 6(a)). On the other hand, the ‘‘fully electroperated’’ membrane conductivity  $S_{ir}$ , which was first taken as  $(\sigma_c + \sigma_e)/(2\delta)$ , affects greatly the order of magnitude of  $\bar{X}$ , changing from  $10^{-6}$  to  $10^{-2}$  (Figure 6(c)). Therefore, as for the static case the relevant quantity to observe the phenomenon is  $\tilde{S}_m$ .

### 4.4.3 Comparison with the model of Neu, Krassowska, and Debruin

The main difference between the model of Neu, Krassowska, *et al.* and ours resides in the addition of an electroperoration current  $I_{ep} = N_{ep}i_{ep}$ , instead of a direct description of the variations of the conductivity  $\tilde{S}_m$ .

The equation satisfied by the transmembrane voltage in the model of Neu, Krassowska, *et al.* [3] reads

$$-\sigma_c \partial_n U_c = C_m \partial_t [U] + S_L[U] + N_{ep} i_{ep}, \quad (39)$$

Table 1: Parameters set to fit to the results given by [14, 3]. (EP stands for electropermeabilization, and EPd stands for electropermeabilized).

Variable	Symbol	Value	Unit
<b><i>Biological parameters:</i></b>			
Extracellular conductivity	$\sigma_e$	5	S/m
Intracellular conductivity	$\sigma_c$	0.455	S/m
Capacitance	$C_m$	$9.5 \times 10^{-3}$	F/m <sup>2</sup>
Membrane surfacic conductivity	$S_L$	1.9	S/m <sup>2</sup>
Cell radius	$r$	50	$\mu\text{m}$
Membrane thickness	$\delta$	5	nm
<b><i>Specific parameters of the model:</i></b>			
EP threshold	$V_{\text{rev}}$	1,5	V
EP switch speed	$k_{\text{ep}}$	40	V <sup>-1</sup>
EP characteristic time	$\tau_{\text{ep}}$	$1 \times 10^{-6}$	s
Resealing characteristic time	$\tau_{\text{res}}$	$1 \times 10^{-3}$	s
EPd membrane surfacic conductivity	$S_{\text{ir}}$	$2.5 \times 10^8$	S/m <sup>2</sup>
<b><i>Numerical parameters:</i></b>			
Simulation box size		200	$\mu\text{m}$
Grid points (each side)	$N$	50	
Time step	$\Delta t$	20	ns
Pulse duration	$T_p$	100	$\mu\text{s}$
Duration of simulation	$T_f$	150	$\mu\text{s}$
Number of time steps	$N_T$	7500	

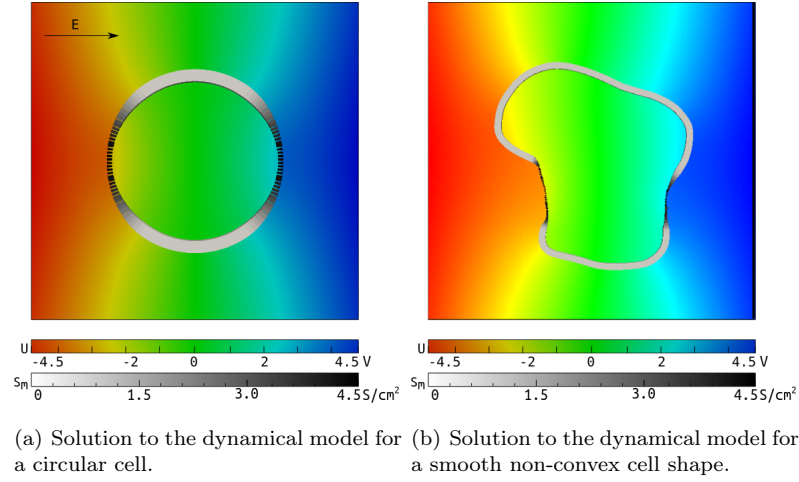


Figure 5: Solution to the dynamical problem with two different cell shapes with the parameters of Table 1 at  $T = 100\mu\text{s}$ . Fig. 5(b) shows that the electropermeabilized regions depend on the shape and orientation of  $\Gamma$ .

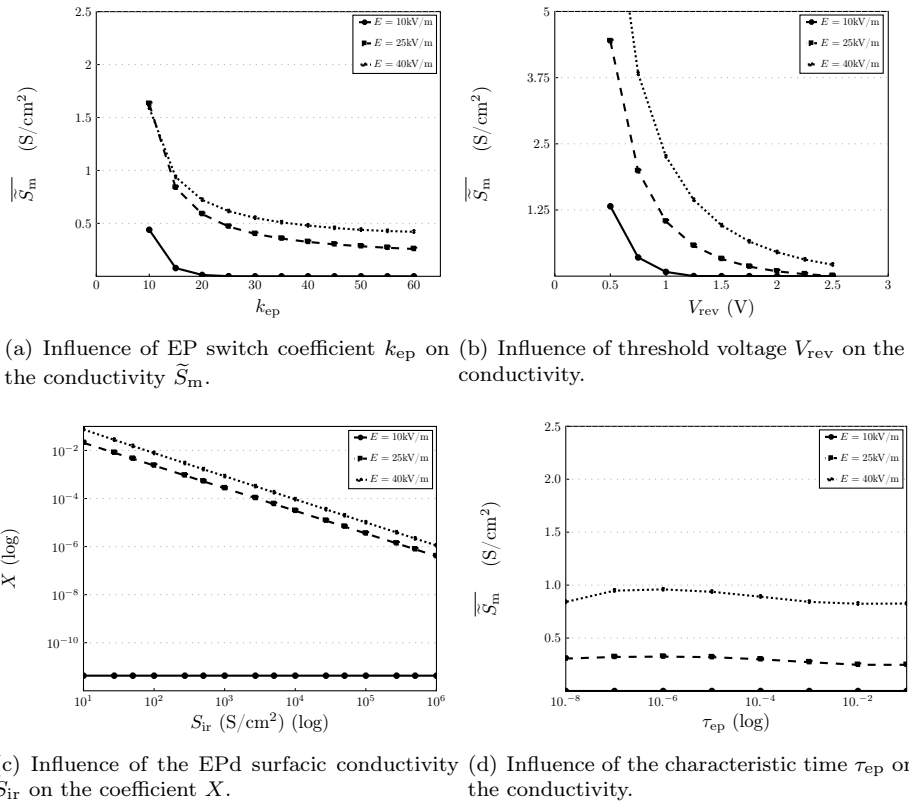


Figure 6: Influence of each parameter on the numerical solution at  $100\mu\text{s}$  after the pulse delivery. Three magnitudes of electric pulses are considered: 10, 25 and 40 kV/m.

where the ionic reversal currents have been neglected.  $N_{\text{ep}}$  is the pore density, obeying the ordinary differential equation (parameters are emphasized in **bold**):

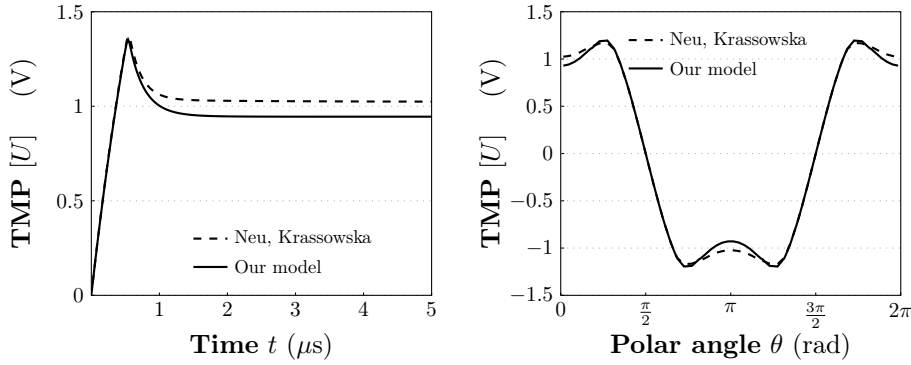
$$\frac{dN_{\text{ep}}}{dt} = \alpha e^{([U]/V_{\text{rev}})} \left( 1 - \frac{N_{\text{ep}}}{N_0} e^{-\mathbf{q}([U]/V_{\text{rev}})^2} \right), \quad (40)$$

and  $i_{\text{ep}}$  is the current flowing through a single pore:

$$i_{\text{ep}}(v_m) = \frac{\pi r_m^2 \sigma RT}{F \delta} \frac{v_m (e^{v_m} - 1)}{\frac{\mathbf{w}_0 e^{\mathbf{w}_0 - n v_m} - n v_m}{\mathbf{w}_0 - n v_m} e^{v_m} - \frac{\mathbf{w}_0 e^{\mathbf{w}_0 + n v_m} + n v_m}{\mathbf{w}_0 + n v_m}}, \quad (41)$$

with  $v_m = [U] \times F/RT$  the adimensionalized transmembrane voltage.

The numerical parameters for the model of Neu, Krassowska, *et al.* are those of Table 1 page 1215 of [3]. Our model reproduces qualitatively the behavior of  $\Delta\text{TMP}$  as shown in Figure 7. In Figure 8, we show that the variation of the membrane current density  $\tilde{S}_m[U]$  of our modeling similar to the electroporation current density  $N_{\text{ep}} i_{\text{ep}}$  of [3].



(a) Evolution of the  $\Delta\text{TMP}$  at the cell's pole. (b) Values of the  $\Delta\text{TMP}$  after  $100\mu\text{s}$  along the perimeter of the circular cell.

Figure 7: Comparison of the  $\Delta\text{TMP}$  obtained respectively with our model (solid lines) and with the model of Neu, Krassowska, *et al.* (dashed), with parameters from table 1.

#### 4.4.4 Long-time behavior of the numerical solution to the dynamical model

In this paragraph, we compare the long-time behavior of the solution  $U_{\text{dyn}}$  to the dynamic model for a constant pulse with the solution  $U_{\text{stat}}$  to the static model.

Simulations are done in order to reach the time scale of the resealing characteristic time  $\tau_{\text{res}}$  (Figure 9). A constant pulse  $g$  is applied until the steady state of the dynamical system is reached. Comparisons are made between the obtained potentials  $U_{\text{dyn}}$  and  $U_{\text{stat}}$  with the error defined in (37).

## 5 Conclusion

In this paper, we introduce two models describing the electroporation of a single cell. We first study the static model, which is inspired by Ivorra *et al.*, and we show existence and

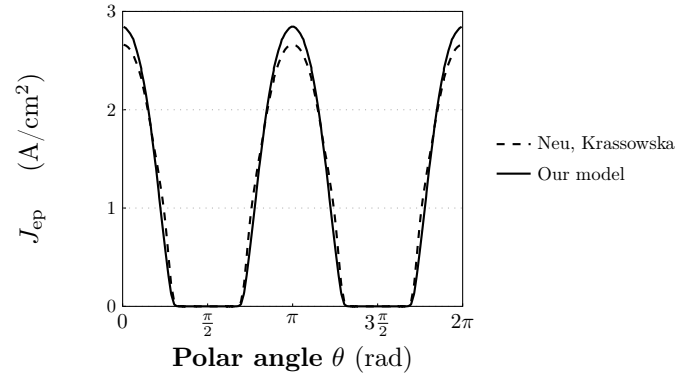


Figure 8: Current density through the membrane of the model of Neu, Krassowska, *et al.*, that is  $J_{\text{ep}} = N_{\text{ep}} i_{\text{ep}}$  (in dashed line), compared with the membrane current density of our model (in solid line),  $J_{\text{ep}} = \tilde{S}_m [U]$ , along the the cell membrane at  $100 \mu\text{s}$ .

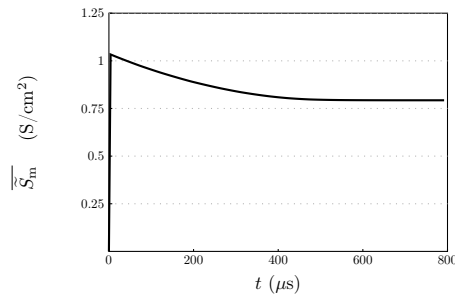


Figure 9: Averaged membrane conductivity  $\tilde{S}_m$  during long-time simulations. Steady state is reached after several hundreds of microseconds, which is larger than usual pulse duration.

uniqueness results. We then derive a new dynamic model of cell electropermeabilization, which takes the permeabilizing time into account. We studied mathematical properties of this new model. We then provided a second-order finite-difference method on cartesian grid to compute these models, and we eventually presented numerical simulations for both static and dynamic models, that corroborate the results of the most achieved model of Neu, Krassowska, *et al.*

The main feature of our models lies in the fact that without loss of accuracy it is composed by a small number of parameters (mainly 4 parameters:  $S_{ir}$ ,  $V_{rev}$ , and  $\tau_{ep}$ , and  $\tau_{res}$  for the dynamical system) compared with the sophisticated models with a tens of non measurable parameters of Neu, Krassowska, *et al.* Therefore, a forthcoming fitting of our models with the experimental data seems feasible, which is hardly the case for models with a large number of parameters.

From the biological point of view, we highlight the fact that the static model can be used for very long pulses (around 1ms) but, for short pulses around  $10\mu s$  and below, the dynamics of the phenomenon have to be considered.

## Acknowledgements

This research has been partly granted by the French national agency throughout the research projects INTCELL (2010-BLAN-916-04) and MEMOVE (2011-BS01-006-01).

## References

- [1] F.M. André and J. Gehl *et al.* Efficiency of high - and low - voltage pulse combinations for gene electrotransfert in muscle, liver tumor and skin. *Human Gene Therapy*, 19, 2008.
- [2] M. Cisternino and L. Weynans. A parallel second order cartesian method for elliptic interface problems. *Commun. Comput. Phys.*, 12, 2012.
- [3] K. DeBruin and W. Krassowska. Modelling electroporation in a single cell. I. Effects of field strength and rest potential. *Biophysical Journal*, 77:1213-1224, Sept 1999.
- [4] K. DeBruin and W. Krassowska. Modelling electroporation in a single cell. II. Effects of ionic concentrations. *Biophysical Journal*, 77:1225-1233, Sept 1999.
- [5] D.E. Goldman. Potential, impedance and rectification in membranes. *J. General Physiology*, 27:37-60, 1943.
- [6] T. R. Gowrishankar, A. T. Esser, Z. Vasilkoski, K. C. Smith, and J. C. Weaver. Microdosimetry for conventional and supra-electroporation in cells with organelles. *Biochem Biophys Res Commun*, 341(4):1266-1276, Mar 2006.
- [7] A.L Hodgkin and B. Katz. The effect of sodium ions on the electrical activity of the giant squid axon. *J. Physiology*, 108:37-77, 1949.
- [8] L. Hodgkin and P. Horowicz. The influence of potassium and chloride ions on the membrane potential of single muscle fibres. *J. Physiol.*, 148:127-160, 1959.
- [9] L. Hodgkin and A. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.*, 117:500-544, 1952.
- [10] A. Ivorra, J. Villemejeane, and L.M. Mir. Electrical modeling of the influence of medium conductivity on electroporation. *Physical Chemistry Chemical Physics*, 12(34):10055-10064, 2010.

- 
- [11] M. Marty, G. Sersa, and J.-R. Garbay *et al.* Electrochemotherapy – an easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of esope (european standard operating procedures of electrochemotherapy) study. *E.J.C Supplements*, 4:3–13, 2006.
- [12] L.M. Mir. Therapeutic perspectives of *in vivo* cell electropermeabilization. *Bioelectrochemistry*, 53:1–10, 2001.
- [13] L.M. Mir. Electroporation of cells in tissues. Methods for detecting cell electropermeabilisation *in vivo*. In *Electroporation based Technologies and Treatment: proceedings of the international scientific workshop and postgraduate course*, pages 32–35, 14-20 November 2005. Ljubljana, SLOVENIA.
- [14] J. Neu and W. Krassowska. Asymptotic model of electroporation. *Physical Review E*, 53(3):3471–3482, Mar 1999.
- [15] J. Neu and W. Krassowska. Singular perturbation analysis of the pore creation transient. *Physical Review E*, 74(031917):1–9, Sep 2006.
- [16] S. Osher and J. A. Sethian. Fronts propagating with curvature-dependent speed: Algorithms based on hamilton-jacobi formulations. *J. Comput. Phys.*, 79(12), 1988.
- [17] M. Pavlin, T. Kotnik, D. Miklavcic, P. Kramar, and A.M. Lebar. Electroporation of planar lipid bilayers and membranes. *Advanced in Planar Lipid Bilayers and Liposomes*, 6(7), 2008.
- [18] R. Perrussel and C. Poinard. Asymptotic expansion of steady-state potential in a high contrast medium with a thin resistive layer. INRIA research report RR-7163. <http://hal.inria.fr/inria-00442659/fr/>, 2011.
- [19] G. Pucihar, T. Kotnik, B. Valič, and D. Miklavčič. Numerical determination of transmembrane voltage induced on irregularly shaped cells. *Ann Biomed Eng*, 34(4):642–652, Apr 2006.
- [20] G. Serša. Application of electroporation in electrochemotherapy of tumors. In *Electroporation based Technologies and Treatment: proceedings of the international scientific workshop and postgraduate course*, pages 42–45, 14-20 November 2005. Ljubljana, SLOVENIA.
- [21] J. Smith, K. Neu and W. Krassowska. Model of creation and evolution of stable electropores for DNA delivery. *Biophys. J.*, 86:2813–2826, May 2004.
- [22] J. Teissié. *In Vitro* cell electropermeabilization. In *Electroporation based Technologies and Treatment: proceedings of the international scientific workshop and postgraduate course*, pages 29–31, 14-20 November 2005. Ljubljana, SLOVENIA.
- [23] J. Teissié, M. Golzio, and M.P. Rols. Mechanisms of cell membrane electropermeabilization: A minireview of our present (lack of?) knowledge. *Biochimica et Biophysica Acta*, 1724:270–280, 2005.



**RESEARCH CENTRE  
BORDEAUX – SUD-OUEST**

351, Cours de la Libération  
Bâtiment A 29  
33405 Talence Cedex

Publisher  
Inria  
Domaine de Voluceau - Rocquencourt  
BP 105 - 78153 Le Chesnay Cedex  
[inria.fr](http://inria.fr)

ISSN 0249-6399