

# Approximate conditions replacing thin layers

Clair Poignard, Patrick Dular, Ronan Perrussel, Laurent Krähenbühl, Laurent Nicolas, and Michelle Schatzman

*This work has been submitted to the IEEE for possible publication. Copyright may be transferred without notice, after which this version may no longer be accessible.*

**Abstract**—We provide a rigorous asymptotic method to build approximate conditions equivalent to a thin layer. With these conditions the electromagnetic field may be computed in domains such as a biological cell, without meshing the membrane. The influence of the membrane is replaced by an appropriate condition on the inner domain, while in the thin layer, the approximate field is explicitly known. We give error estimates, which validate our asymptotic method, and we present a few numerical results performed with the finite element method.

**Index Terms**—Asymptotic methods, thin layers, finite element method.

## I. INTRODUCTION

THE distribution of the electromagnetic field in a biological cell is important for bioelectromagnetic investigations. For instance, a sufficiently large amplitude of the transmembranar potential (TMP), which is the difference of the electric potentials between both sides of the cell membrane, leads to an increase of the permeability of this membrane [1], [2]. This phenomenon, called electropermeabilization, has been already used in oncology and holds promises in gene therapy [3], justifying precise assessments of the TMP. Since the experimental measurements of the TMP on living cells are limited — essentially due to the thinness of the cell membrane, which is a few nanometers thick — a numerical approach is often chosen [1], [4]. However, these computations are confronted with the heterogeneous parameters of the biological cells. Actually, in the Fear and Stuchly model [5], the cell is a medium of regular shape (without any corner) composed by a homogeneous conducting cytoplasm of diameter of a few micrometers surrounded by a very insulating membrane a few nanometers thick (see Figure 1).

To avoid difficulties, most of the numerical computations deal with unrealistic cells (spherical and ellipsoidal cells) without details about the accuracy of the numerical method used (typically the finite element method) [5]. However, biological cells have non-trivial shapes and Sebastián *et al.* have shown that the cell geometry has a significant influence on the electric field distribution. To perform computations on realistic cell

C. Poignard is with the Centre de Mathématiques Appliquées, UMR CNRS 7641, École Polytechnique, F-91128, Palaiseau, France (e-mail: poignard@cmaphx.polytechnique.fr).

P. Dular is with University of Liège, FNRS, Dept. of Electrical Engineering and Computer Science, B28, B-4000 Liège, Belgium (e-mail: Patrick.Dular@ulg.ac.be).

R. Perrussel, L. Krähenbühl and L. Nicolas are with the Laboratoire Ampère, UMR CNRS 5005, and Université de Lyon, École Centrale de Lyon, F-69134, Écully, France (e-mail: ronan.perrussel@ec-lyon.fr).

M. Schatzman is with the Institut Camille Jordan, UMR CNRS 5208, and Université de Lyon, Université Lyon 1, F-69622, Villeurbanne, France (e-mail: schatz@math.univ-lyon1.fr).

Manuscript received June 24, 2007; revised XX.

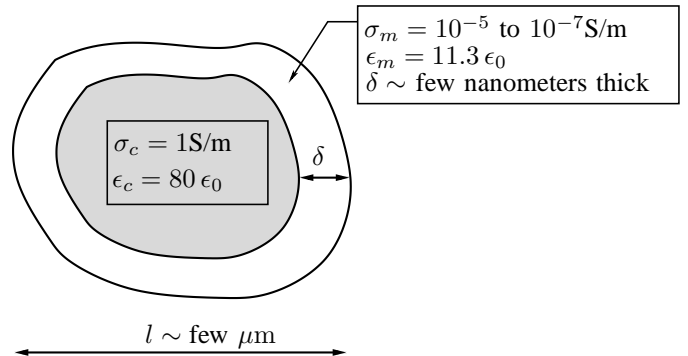


Fig. 1. The electric model of the biological cell (see Fear *et al.* [5]).

shapes by considering a conduction problem, Pucihar *et al.* [1] propose to replace the membrane by a condition on the boundary of the cytoplasm. This condition corresponds to a contact resistance model but the details for asserting the accuracy of their method are not given.

In this paper, we present a rigorous asymptotic method to compute the electromagnetic field in domains with a thin layer. Since the proofs of our results are precisely described in [6] and [7], we present the heuristics of the method and the main results, which may be useful for electromagnetic computations in biological cells and we illustrate our asymptotics with numerical simulations. For sake of simplicity, we consider a bidimensional cell, however our method might be easily extended to three-dimensional cells.

We deal with the quasistatic (also called dielectric) formulation: results for the Helmholtz equation are given in [7]. Two cases are considered:

- an electric field (*i.e.* a Neumann boundary condition) is enforced directly on the exterior boundary of the membrane; we build approximate boundary conditions asymptotically equivalent to the membrane.
- the cell is embedded in an ambient medium submitted to an electric potential; we build approximate transmission conditions.

These approximate conditions are obtained to replace the thin membrane but keeping a prescribed accuracy on the solution. To justify this accuracy, we give error estimates between the potential with the membrane and without the membrane but with the approximate conditions.

## II. APPROXIMATE BOUNDARY CONDITIONS

### A. Statement of the problem

Denote by  $\Omega$  the biological cell composed by a cytoplasm  $\mathcal{O}$  surrounded by a thin membrane  $\mathcal{O}_\delta$  with thickness  $\delta$ . Let

$\gamma_0$  be the cytoplasm complex permittivity and  $\gamma_1$  this of the membrane. Denote by  $\gamma$  the function equal to  $\gamma_0$  in  $\mathcal{O}$  and  $\gamma_1$  in  $\mathcal{O}_\delta$ . The quasistatic formulation is given by:

$$\begin{cases} \nabla \cdot (\gamma \nabla V) = 0, & \text{in } \Omega_\delta \\ \frac{\partial V}{\partial n} = \phi, & \text{on } \partial\Omega_\delta; \end{cases} \quad (1)$$

$\phi$  is the electric field imposed on the boundary of the cell. We suppose that this Neumann boundary condition is as regular as we need and it satisfies  $\int_{\partial\Omega_\delta} \phi(s) ds = 0$ . So that  $V$  is uniquely determined, we impose the gauge condition  $\int_{\partial\mathcal{O}} V(s) ds = 0$ .

Our method might be decomposed in three steps. The first step consists of a change of coordinates so that the thin parameter  $\delta$  appears explicitly in the equations. In the second step, we choose an ansatz, supposing that the potential might be written as a formal serie with respect to  $\delta$ . Then, by identifying the terms with the same power of  $\delta$ , we obtain a sequel of elementary problems. The final step is the rigorous validation of our ansatz, providing *a priori* error estimates of the method.

### B. Change of coordinates

Since the bidimensional medium  $\mathcal{O}$  is regular, we may parametrize it with the curvilinear coordinate. Suppose that the length of  $\partial\mathcal{O}$  equals 1. There exists a 1-periodic function  $\Psi$ , such that for all  $x \in \partial\mathcal{O}$ , there exists a unique  $\theta \in [0, 1]$  satisfying:

$$x = \Psi(\theta), \text{ and } \|\Psi'(\theta)\| = 1. \quad (2)$$

Denoting by  $n(\theta)$  the exterior normal to  $\partial\mathcal{O}$  at the point  $\Psi(\theta)$ , we may parametrize the thin layer  $\mathcal{O}_\delta$  as follows:

$$\mathcal{O}_\delta = \{\Phi(\eta, \theta) = \Psi(\theta) + \eta\delta n(\theta), \quad \theta \in [0, 1]\}. \quad (3)$$

The curvature  $\kappa$  of  $\partial\mathcal{O}$  is then the 1-periodic function defined by:

$$\forall \theta \in [0, 1], \quad \kappa(\theta) = \|n'(\theta)\|.$$

We denote by  $\mathfrak{K}$  the curvature of  $\mathcal{O}$  in Euclidean coordinates:

$$\mathfrak{K}(x) = \kappa \circ \Psi^{-1}(x),$$

and we define  $\varphi$  as the boundary data  $\phi$  translated on  $\mathcal{O}$ :

$$\varphi(x) = (\phi \circ \Phi|_{\eta=1}) \circ \Psi^{-1}(x).$$

The main idea of our asymptotic method is to write the Laplace operator in local coordinates so that the thin parameter  $\delta$  appears explicitly. Denote by  $\Delta_{\eta, \theta}$  the Laplace operator written in  $(\eta, \theta)$ -coordinates, then using change of coordinates (2) we have:

$$\Delta_{\eta, \theta} = \frac{1}{1 + \delta\eta\kappa} \left( \partial_\eta \left( \frac{1 + \delta\eta\kappa}{\delta} \partial_\eta \right) + \partial_\theta \left( \frac{\delta}{1 + \delta\eta\kappa} \partial_\theta \right) \right), \quad (4)$$

and the operators of normal derivative  $\partial_n$  and tangential derivative  $\partial_t$  equal

$$\partial_n = \frac{1}{\delta} \partial_\eta, \quad \partial_t = \partial_\theta. \quad (5)$$

We suppose that  $V$  may be written as follows:

$$V = V_0 + \delta V_1 + \dots.$$

We replace  $V$  by its development in (4) and we order the terms of the equations:

$$\Delta(V_0 + \delta V_1 + \dots) = 0, \text{ in } \mathcal{O}, \quad (6a)$$

$$\frac{1}{\delta} \partial_\eta^2 V_0 + \partial_\eta^2 V_1 + \kappa \partial_\eta V_0 \quad (6b)$$

$$+ \delta (\partial_\eta^2 V_2 + \kappa \partial_\eta V_1 + \partial_\theta^2 V_0) + \dots = 0, \text{ in } \mathcal{O}_\delta,$$

with transmission conditions on  $\partial\mathcal{O}$  (the subscript  $\partial\mathcal{O}^-$  indicates the cytoplasm side and  $\eta = 0^+$ , the membrane side)

$$V_0|_{\partial\mathcal{O}^-} + \delta V_1|_{\partial\mathcal{O}^-} + \dots = V_0|_{\eta=0^+} + \delta V_1|_{\eta=0^+} + \dots, \quad (6c)$$

$$\begin{aligned} \gamma_0 (\partial_n V_0|_{\partial\mathcal{O}^-} + \delta \partial_n V_1|_{\partial\mathcal{O}^-} + \dots) &= \gamma_1 \left( \frac{1}{\delta} \partial_\eta V_0|_{\eta=0^+} \right. \\ &\left. + \partial_\eta V_1|_{\eta=0^+} + \delta \partial_\eta V_2|_{\eta=0^+} + \dots \right), \end{aligned} \quad (6d)$$

and with the Neumann boundary condition on  $\partial\Omega_\delta$

$$\frac{1}{\delta} \partial_\eta V_0|_{\eta=1} + \partial_\eta V_1 + \dots = \phi \circ \Phi|_{\eta=1}. \quad (6e)$$

### C. Elementary problems and error estimates

By identifying the terms with the same power of  $\delta$  in (6) we obtain the first two terms of the asymptotic expansion of the solution  $V$  of Problem (1).

- Order 0.  $V_0$  satisfies:

$$\begin{cases} \nabla \cdot (\gamma_0 \nabla V_0) = 0, & \text{in } \mathcal{O}, \\ \partial_n V_0 = (\gamma_1/\gamma_0) \varphi & \text{on } \partial\mathcal{O}. \end{cases} \quad (7)$$

- Order 1.  $V_1$  satisfies:

$$\begin{cases} \nabla \cdot (\gamma_0 \nabla V_1) = 0, & \text{in } \mathcal{O}, \\ \partial_n V_1 = (\gamma_1/\gamma_0) (\partial_t^2 V_0^c + \mathfrak{K} \varphi) & \text{on } \partial\mathcal{O}. \end{cases} \quad (8)$$

Denote by  $V_{app} = V_0 + \delta V_1$ , we have the estimate:

$$\|V - V_{app}\|_{H^1(\mathcal{O})} \leq C \left| \frac{\gamma_1}{\gamma_0} \right| \delta^2 \|\varphi\|. \quad (9)$$

Therefore, to approximate the potential in the cytoplasm with an accuracy of order  $\delta^2$ , we have to compute problems (7)–(8) with appropriate boundary conditions for the cytoplasm.

It may be interesting to solve only one equivalent problem with a non-classical boundary condition. Observe that  $V_{app}$  satisfies

$$\begin{cases} \nabla \cdot (\gamma_0 \nabla V_{app}) = 0, \\ \partial_n V_{app} = (\gamma_1/\gamma_0) \left( (1 + \delta \mathfrak{K}) \varphi + (\delta \partial_t^2 V_{app} - \delta^2 \partial_t^2 V_1) \right). \end{cases} \quad (10)$$

Therefore, we denote by  $\tilde{V}_{app}$  the solution to

$$\begin{cases} \nabla \cdot (\gamma_0 \nabla \tilde{V}_{app}) = 0, & \text{in } \mathcal{O}, \\ \partial_n \tilde{V}_{app} - (\gamma_1/\gamma_0) \delta \partial_t^2 \tilde{V}_{app} = (\gamma_1/\gamma_0) (1 + \delta \mathfrak{K}) \varphi & \text{on } \partial\mathcal{O}. \end{cases} \quad (11)$$

Using (9) we have:

$$\|V - \tilde{V}_{app}\|_{H^1(\mathcal{O})} \leq C \left| \frac{\gamma_1}{\gamma_0} \right| \delta^2 \|\varphi\|. \quad (12)$$

In the thin layer<sup>1</sup>  $\mathcal{O}_\delta$ , we have the explicit formulae of  $V_{app}$  written in local coordinates:

$$\forall x \in \mathcal{O}_\delta, \quad V_{app}(x) = V_0(x|_{\partial\mathcal{O}}) + \delta V_1(x|_{\partial\mathcal{O}}) + \left( (x - x|_{\partial\mathcal{O}}) \cdot n(x|_{\partial\mathcal{O}}) \right) \varphi(x|_{\partial\mathcal{O}}),$$

and we have the following estimate:

$$\|V - V_{app}\|_{H^1(\mathcal{O}_\delta)} \leq C \delta^{3/2} \|\varphi\|. \quad (13)$$

The boundary condition satisfied by  $\tilde{V}_{app}$  is called approximate boundary condition. Observe that if  $\mathfrak{K}$  equals 1, *i.e.* if  $\mathcal{O}$  is a disk, approximate boundary condition (11) is exactly the same as boundary condition (10) of Krähenbühl and Müller [8]. Here, we validate the result by an error estimate. We may perform asymptotic expansion at any order  $n \geq 0$ . We emphasize that according to estimate (12), our approximate boundary condition is valid for a bounded ratio  $|\gamma_1/\gamma_0|$ , therefore it may be used to compute the electric field in a biological cell. As soon as  $|\gamma_1/\gamma_0|$  is of order  $1/\delta$  (or bigger), which means that the thin layer is very conducting, approximate boundary condition (11) is no more valid. We refer to [6] for a precise description of this case.

#### D. Numerical simulations

A geometry, where no analytic solution is known, has been studied. In order to show the error due to the asymptotic expansion, we are led to compute the solution of the problem with and without the membrane; these computations are performed using the finite element method.

A numerical validation for Estimation (13) can be difficult to obtain because the error due to the asymptotic expansion have to be greater than the discretization error. If the membrane is very thin, we have to deal with a huge number of degrees of freedom, which can prevent the use of a too thin membrane for the numerical validation. This remark fully justifies the use of the approximate conditions: by considering a thin membrane but keeping a reasonable number of degrees of freedom for the discretization, it is not possible to distinguish the solutions with and without the membrane in the inner domain.

We perform computations with GetDP [9] for an elongated cell  $\Omega$ . In Figure 2 we present the steady state potentials when the thin layer is insulating. Asymptotics (7) and (8) give the approximate potential in  $\mathcal{O}$  without meshing the membrane.

In Figure 3, we draw the error made by our asymptotics with respect to the thickness  $\delta$ . Observe for instance that if  $\delta = 5 \cdot 10^{-3}$ , the error made by our method is around 10% at the order 0 and 1% at the order 1.

<sup>1</sup>Observe that  $x \in \mathcal{O}_\delta$  equals  $x = x|_{\partial\mathcal{O}} + (x - x|_{\partial\mathcal{O}}) \cdot n(x|_{\partial\mathcal{O}})$ , with  $x|_{\partial\mathcal{O}}$  the orthogonal projection of  $x$  on  $\partial\mathcal{O}$ .

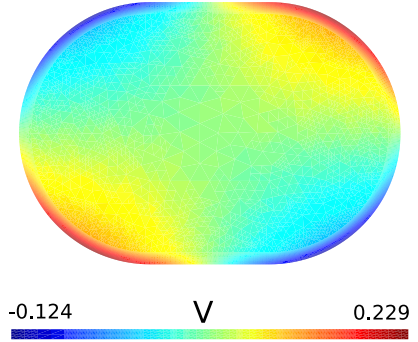


Fig. 2. Steady state potentials in an elongated cell with an insulating membrane.

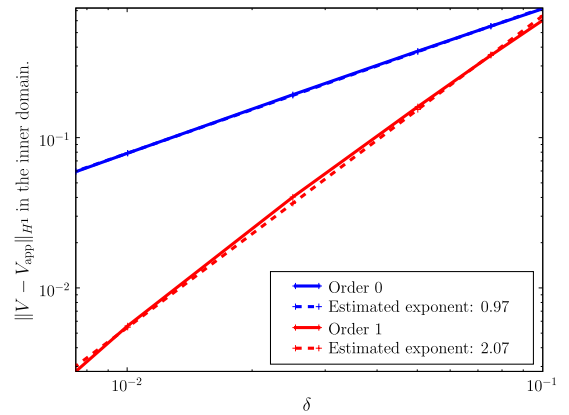


Fig. 3. Error versus the membrane thickness.  $\gamma_0 = 5$ ,  $\gamma_1 = 0.5$ . The continuous lines are the results of the numerical computations and the dotted lines used an exponent estimated for (13) using the numerical results.

### III. APPROXIMATE TRANSMISSION CONDITIONS

Suppose now that our cell  $\Omega_\delta$  is embedded in an ambient medium  $\mathcal{O}_e$ , with conductivity equal to  $\gamma_e$ . We denote by

$$\Omega = \Omega_\delta \cup \mathcal{O}_e,$$

and by  $\gamma$  the function equal to  $\gamma_0$  in  $\mathcal{O}$ ,  $\gamma_1$  in  $\mathcal{O}_\delta$  and  $\gamma_e$  in  $\mathcal{O}_e$ . Consider the steady state voltage equations:

$$\begin{cases} \nabla \cdot (\gamma \nabla V) = 0, & \text{in } \Omega \\ \frac{\partial V}{\partial n} = \phi, & \text{on } \partial\Omega; \end{cases} \quad (14)$$

with  $\phi$  as Neumann boundary condition on  $\partial\Omega$ .

We have to replace the membrane by approximate transmission conditions on the boundary of the cytoplasm. To obtain these conditions, we extend the exterior potential up to the boundary of the cytoplasm. Using the parametrization (3) of the membrane and Taylor expansions with respect to the normal variable, we then explicit the Dirichlet and Neumann values of potential on the exterior boundary of the cell in terms of  $\delta$  and of Dirichlet and Neumann traces on the boundary of the cytoplasm. More precisely, if we denote by  $V^e$  the potential in  $\mathcal{O}_e$  formally extended to  $\mathcal{O}_\delta$ , and by  $\Gamma_\delta$  the exterior

boundary of the cell, we have:

$$V^e|_{\Gamma_\delta} = V^e|_{\partial\mathcal{O}} + (x - x|_{\partial\mathcal{O}}) \cdot n(x|_{\partial\mathcal{O}}) \partial_n V^e|_{\partial\mathcal{O}} + \dots, \\ \partial_n V^e|_{\Gamma_\delta} = \partial_n V^e|_{\partial\mathcal{O}} + (x - x|_{\partial\mathcal{O}}) \cdot n(x|_{\partial\mathcal{O}}) \partial_n^2 V^e|_{\partial\mathcal{O}} + \dots.$$

We are now ready to apply the machinery of the asymptotic method presented in the previous section. We just give here the first two terms of the asymptotic expansion of  $V$  solution to (14).

- Order 0.  $V_0$  satisfies:

$$\left\{ \begin{array}{l} \nabla \cdot (\gamma_0 \nabla V_0) = 0, \text{ in } \mathcal{O}, \\ \nabla \cdot (\gamma_e \nabla V_0) = 0, \text{ in } \Omega \setminus \mathcal{O}, \\ \partial_n V_0 = \phi \text{ on } \partial\Omega \\ \text{with transmission conditions on } \partial\mathcal{O}: \\ \gamma_0 \partial_n V_0|_{\partial\mathcal{O}^-} = \gamma_e \partial_n V_0|_{\partial\mathcal{O}^+}, \\ V_0|_{\partial\mathcal{O}^-} = V_0|_{\partial\mathcal{O}^+}. \end{array} \right. \quad (15)$$

- Order 1.  $V_1$  satisfies:

$$\left\{ \begin{array}{l} \nabla \cdot (\gamma_0 \nabla V_1) = 0, \text{ in } \mathcal{O}, \\ \nabla \cdot (\gamma_e \nabla V_1) = 0, \text{ in } \Omega \setminus \mathcal{O}, \\ \partial_n V_1 = 0 \text{ on } \partial\Omega \\ \text{with transmission conditions on } \partial\mathcal{O}: \\ \gamma_0 \partial_n V_1|_{\partial\mathcal{O}^-} - \gamma_1 \partial_n V_1|_{\partial\mathcal{O}^+} = (\gamma_1 - \gamma_e) \partial_t^2 V_0|_{\partial\mathcal{O}}, \\ V_1|_{\partial\mathcal{O}^-} - V_1|_{\partial\mathcal{O}^+} = \left( \frac{\gamma_1 - \gamma_e}{\gamma_1 \gamma_e} \right) \gamma_0 \partial_n V_0|_{\partial\mathcal{O}^-}. \end{array} \right. \quad (16)$$

The approximate potential  $V_{app}$  is then the sum  $V_0 + \delta V_1$ , and there exists a constant  $C_{\gamma_0, \gamma_1, \gamma_e, \mathcal{O}}$   $\delta$ -independent such that:

$$\|V - V_{app}\|_{H^1(\mathcal{O})} \leq C_{\gamma_0, \gamma_1, \gamma_e, \mathcal{O}} \delta^2 \|\phi\|. \quad (17)$$

#### A. Numerical simulations

An elongated cell embedded in a square domain is considered as shown in Figure 4. The potential is enforced

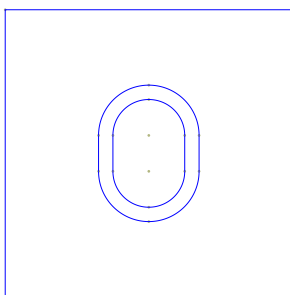


Fig. 4. The geometry considered: a cell embedded in a square domain. Representation with the thickest membrane.

Square domain:  $[-2; 2]^2$ .  
 Radius of the interior extremity from the inner domain: 0.5.  
 Length of the straight part: 0.5.  
 Thickness of the membrane: 0.2.  
 Parameters for the simulation:  $\gamma_0 = \gamma_e = 1 + 0.01j$  and  $\gamma_1 = 0.01 + 1j$ .

on the upper and lower boundaries; homogeneous Neumann conditions are considered for the lateral boundaries.

Figure 5 shows a numerical validation of the approximate transmission conditions. Let us note that the calculated order is non-optimal for the condition of order 1: an exponent of 1.7 is obtain instead of 2 as asserted in (17). As described before, it can be practically difficult to show numerically the estimate because the discretization error can be higher than what is asserted in (17).

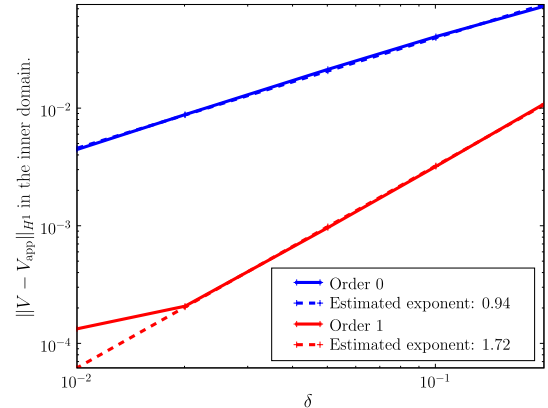


Fig. 5. Error versus the membrane thickness.  $\gamma_1 = 0.01 + 1j$ ,  $\gamma_0 = \gamma_e = 1 + 0.01j$ . The continuous lines are the results of the numerical computations and the dotted lines used an exponent estimated for (17) using the numerical results.

#### IV. CONCLUSION

We have presented how to build rigorously approximate conditions for the solution of the dielectric formulation in a domain with a thin membrane. With our method we do not have to mesh the membrane: the approximate field inside the thin layer is known explicitly, and the potential outside the membrane is the solution to the dielectric formulation with the approximate condition. We provide rigorous a priori estimates of the error. Moreover, we may build approximate boundary condition at any order, if the domain and the boundary data are enough regular (see [6], [7] for more details). This means that we may build solutions, which approach the total potential with an error in  $\delta^n$ , for  $n$  as large as desired. This method has been generalized to Helmholtz equation in [7] and it might be applied for the 3D vector wave equation.

#### REFERENCES

- [1] G. Pucihar, T. Kotnik, B. Valič, and D. Miklavčič, "Numerical determination of transmembrane voltage induced on irregularly shaped cells," *Annals of Biomedical Engineering*, vol. 34, no. 4, pp. 642–652 (electronic), 2006.
- [2] J. Teissié, N. Eynard, B. Gabriel, and M. Rols, "Electropermeabilization of cell membranes," *Adv. Drug Deliver. Rev.*, vol. 35, pp. 3–19, 1999.
- [3] M. Marty, G. Sersa, J. Garbay, J. Gehl, C. Collins, M. Snoj, V. Billard, P. Geertsen, J. Larkin, D. Miklavčič, *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," *European Journal of Cancer*, vol. Supplements n.4, pp. 3–13, 2006.
- [4] S. Muñoz, J. Sebastián, M. Sancho, and J. Miranda, "Transmembrane voltage induced on altered erythrocyte shapes exposed to RF fields," *Bioelectromagnetics*, vol. 25, no. 1, pp. 631–633 (electronic), 2004.
- [5] E. Fear and M. Stuchly, "Modeling assemblies of biological cells exposed to electric fields," *IEEE Trans. Bio. Eng.*, vol. 45, no. 1, pp. 1259–1271 (electronic), 1998.
- [6] C. Poignard, "Asymptotics for steady state voltage potentials in a bidimensional highly contrasted medium with thin layer," 2007, accepted in *Math. Meth. Appl. Sci.* [Online]. Available: <http://www.cmap.polytechnique.fr/~poignard/MMAS-31pp.html>
- [7] —, "Rigorous asymptotics for the electric field in tm mode at mid-frequency in a bidimensional medium with thin layer," 2006, 26 pages. Submitted. [Online]. Available: <http://www.cmap.polytechnique.fr/~poignard/helmholtz-27pp.html>

- [8] L. Krähenbühl and D. Müller, "Thin layers in electrical engineering. example of shell models in analysing eddy-currents by boundary and finite element methods," *IEEE Trans. Mag.*, vol. 29, no. 2, pp. 1450–1455, 1993.
- [9] P. Dular, C. Geuzaine, F. Henrotte, and W. Legros, "A general environment for the treatment of discrete problems and its application to the finite element method," *IEEE Trans. Mag.*, vol. 34, no. 5, pp. 3395–3398, sep 1998.