Stabilized variational formulation for solving cell response to applied electric field

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Abstract. In this work a stabilized variational formulation is proposed to solve the interface problem describing the electric response of cells to an applied electric field. The proposed stabilized formulation is attractive since the discrete operator resulting from finite element discretization generates a definite linear system for which efficient iterative solvers can be applied. The interface problem describing the cell response is solved with a primal variational formulation and the proposed stabilized formulation. Both methods are compared in terms of the approximation properties of the primal and the Lagrange multiplier variable. The computational performance of the methods are also compared in terms of the mean number of iterations needed to solve one time step during the polarization process of an isolated square cell. Moreover, numerical experiments are performed to validate the convergence properties of the methods.

Keywords: Cell interface problem · Primal varitional formulation · Stabilized variational formulation.

1 Introduction

The numerical study of the electrical activity of biological cells in conductive medium subject to applied electric field is of interest to the medical community [1, 2]. The development of a general tool to numerically investigate the electric field distribution in biological cells has been studied by [3–5]. In particular, employing finite element methods, numerical simulations of individual cells and cluster of cells when subjected to an applied electric field were developed by [3] using a primal hybrid variational formulation, introduced by Raviart-Thomas in [6].

Recently in [5], a framework to solve the electric field distribution at the tissue scale based in an EMI cell model has been proposed. The primal hybrid formulation with dual Lagrange multiplier was also used and a mixed formulation with $H(div)$ approximation spaces was developed with demonstrated optimal rates in convergence tests. These works use dual space as proposed in [7] to approximate the Lagrange multiplier used to enforce the interface condition associated to the primal variable. However, since the linear system resulting from the discrete

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operator of this formulation is positive indefinite, iterative methods based on Krylov subspaces usually present poor performance for large linear systems.

Another approach for the hybrid primal formulation was firstly proposed and analyzed by [8], where a stabilization term related to the Lagrange multiplier definition are included in order to circumvent the compatibility conditions between spaces necessary for stability of the Lagrange multiplier of the primal hybrid formulation. This methodology generate positive definite linear systems and consequently improves the computational solution.

In this context, this work presents a variational formulation to solve the problem of the response of a square cell to an applied electric field, using a stabilization technique based on the inclusion of terms related to Lagrange multiplier definition as proposed in [8]. This approach is interesting since when compared to the primal hybrid formulation a positive definite linear system associated to the discrete operator of finite elements is obtained. The capabilities of the proposed approach are demonstrated through numerical studies that present optimal rates of convergence for the primal variable and the Lagrange multiplier and lower computational cost when compared with primal hybrid method.

2 The model problem

Consider a square cell with conductivity given by the second order tensor $\boldsymbol{\kappa_i}$, in a bounded domain Ω_e with electrical conductivity given by the second order tensor $\boldsymbol{\kappa_e}$ subjected to an externally applied electric field $\mathbf{E}$ as depicted in Figure 1. The system of equations of electric current conservation for this system without

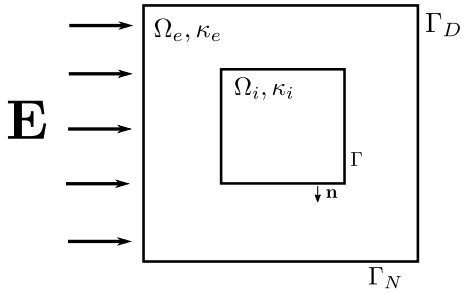

Fig. 1: A square cell in a conductive medium

source current, can be written as a function of the electric potential inside and outside the cell (u_i, u_e), as:

$$\begin{aligned} -\mathrm{div}(\boldsymbol{\kappa_e}\nabla u_e) &= 0, \quad \text{in } \Omega_e, \\ -\mathrm{div}(\boldsymbol{\kappa_i}\nabla u_i) &= 0, \quad \text{in } \Omega_i, \\ -\boldsymbol{\kappa_i}\nabla u_i \cdot \mathbf{n} = -\boldsymbol{\kappa_e}\nabla u_e \cdot \mathbf{n} &= I_m, \quad \text{on } \Gamma, \\ u_e &= \hat{u}, \quad \text{on } \Gamma_D, \\ \boldsymbol{\kappa_e}\nabla u_e \cdot \mathbf{n}_e &= 0, \quad \text{on } \Gamma_N, \end{aligned} \tag{1}$$

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Where $\hat{u}$ is the electric potential applied on Γ_D. In this system of equations, Γ denotes the cell membrane, $\mathbf{n}$ is the unitary normal vector pointing outward of Γ and I_m $[\mathrm{A} \cdot \mathrm{cm}^{-2}]$ is the transmembrane current which depends on the transmembranic potential, that is defined as $V_m = u_i - u_e$ on Γ.

The transmembrane current I_m is written as the contribution of two main currents, the capacitive and the resistive or ionic current, and is given by $I_m = C_m \frac{\partial V_m}{\partial t} + I_{ion}(V_m)$ on Γ.

2.1 Variational formulation

The variational formulation of the conservation of electric current of the unicellular system (1) is: *find* $u = (u_i, u_e) \in X$ with $X = H^1(\Omega_i) \times H^1(\Omega_e)$ *such that*

$$\begin{aligned} \int_\Omega \boldsymbol{\kappa} \nabla u \cdot \nabla v dx - \int_\Gamma \boldsymbol{\kappa} \nabla u \cdot \mathbf{n}[v] ds = 0, \quad \forall v \in X, \\ -\boldsymbol{\kappa_i} \nabla u_i \cdot \mathbf{n} = -\boldsymbol{\kappa_e} \nabla u_e \cdot \mathbf{n} = I_m, \quad \text{on } \Gamma, \\ [u] = V_m, \quad \text{on } \Gamma, \end{aligned} \tag{2}$$

where $[u] = u_i|_\Gamma - u_e|_\Gamma$ is the scalar jump of electric potential on the membrane, $\boldsymbol{\kappa} = (\boldsymbol{\kappa_i}, \boldsymbol{\kappa_e})$ denotes the electric conductivity inside and outside the cell, $H^1(\Omega_i)$ and $H^1(\Omega_e)$ are the Sobolev space of functions with first-order derivative square-integrable on the bounded domains Ω_i and Ω_e respectively and $X = H^1(\Omega_i) \times H^1(\Omega_e)$ is the product space.

Primal hybrid variational formulation An additional Hilbert space defined on Γ is included to impose the interface condition ($[u] = V_m$ on Γ) of the primal variable in a weak sense via the use of a Lagrange multiplier. Given K_i and K_e a non-overlapping domain triangulation for Ω_i and Ω_e with linear finite elements, and a polynomial base of degree at most k denoted by $P_k(K)$ defined on each triangulation, it is possible to write the discrete version of the primal variational formulation as: *find* $u_h = (u_{i_h}, u_{e_h}) \in X_h$ *and* $\lambda_h \in \mathcal{M}_h(\Gamma_{ie})$ *such that*

$$\begin{aligned} \int_\Omega \boldsymbol{\kappa} \nabla u_h \cdot \nabla v_h dx + \int_\Gamma \lambda_h [v_h] ds = 0, \quad \forall v_h \in X_h, \\ \int_\Gamma [u_h] \mu_h ds = \int_\Gamma V_m \mu_h ds, \quad \forall \mu_h \in \mathcal{M}_h(\Gamma_{ie}), \end{aligned} \tag{3}$$

with,

$$X_h = \{(v_{i_h}, v_{e_h}) \in (H^1(K_i) \times H^1(K_e)) : v_{h_i}|_{K_i} \in P_k(K_i); v_{h_e}|_{K_e} \in P_k(K_e)\}, \tag{4}$$

$$\mathcal{M}_h(\Gamma_{ie}) = \{\mu_h \in C^0(\Gamma_{ie}); \mu_h|_{\Gamma_{ie}} \in p_k(\Gamma_{ie})\}, \tag{5}$$

where Γ_{ie} denotes a domain triangulation for $\Gamma = \Omega_i \cap \Omega_e$, such that Γ_{ie} is uniquely discretized by linear finite elements of dimension $(d-1)$ with $d = 2$ inherited from K_i or K_e, and $p_k(\Gamma_{ie})$ is the space of polynomials of degree at most k on each edge Γ_{ie} on the interface Γ.

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Stabilized primal variational formulation Based on the discrete variational formulation (3), it is possible to include stabilization terms as proposed and analyzed in [8], to have the following equivalent stabilized primal variational formulation: *find* $u_h = (u_{i_h}, u_{e_h}) \in \mathcal{W}_h$ *and* $\lambda_h \in \mathcal{M}_h(\Gamma_{ie})$, *such that*

$$\int_\Omega \boldsymbol{\kappa}\nabla u_h \cdot \nabla v_h dx + \int_\Gamma \lambda_h[v_h]ds + \alpha h \int_\Gamma (\lambda_h + \boldsymbol{\kappa}\nabla u_h \cdot \mathbf{n})(\mu_h + \boldsymbol{\kappa}\nabla v_h \cdot \mathbf{n}) = 0, \tag{6}$$

$$\int_\Gamma [u_h]\mu_h ds = \int_\Gamma V_m \mu_h ds,$$

for all $v_h \in \mathcal{W}_h$ *and* $\mu_h \in \mathcal{M}_h(\Gamma_{ie})$, *with:*

$$\mathcal{W}_h = \{(v_{i_h}, v_{e_h}) \in (H^{3/2}(K_i) \times H^{3/2}(K_e)) : v_{h_i}|_{K_i} \in P_k(K_i); v_{h_e}|_{K_e} \in P_k(K_e)\}. \tag{7}$$

Here, $\alpha \in \mathbb{R}$ is an arbitrary real constant and h is the characteristic length of the finite element triangulation. Note that for $\alpha = 0$ the primal hybrid form is recovered. In order to evidence an important relation, we can rewrite equation (6) as:

$$\int_\Omega \boldsymbol{\kappa}\nabla u_h \cdot \nabla v_h dx + \int_\Gamma \lambda_h[v_h]ds + \alpha h \int_\Gamma (\lambda_h + \boldsymbol{\kappa}\nabla u_h \cdot \mathbf{n})(\boldsymbol{\kappa}\nabla v_h \cdot \mathbf{n}) = 0, \tag{8}$$

$$\int_\Gamma \big([u_h] + 2\alpha h(\lambda_h + \{\boldsymbol{\kappa}\nabla u_h \cdot \mathbf{n}\})\big)\mu_h ds = \int_\Gamma V_m \mu_h ds, \tag{9}$$

where $\{\boldsymbol{\kappa}\nabla u_h \cdot \mathbf{n}\} = \frac{\boldsymbol{\kappa_i}\nabla u_{i_h}\cdot\mathbf{n} + \boldsymbol{\kappa_e}\nabla u_{e_h}\cdot\mathbf{n}}{2}$, denotes an average quantity. Then, equation (9) can be rearranged in the following form:

$$\int_\Gamma [u_h]\mu_h ds = \int_\Gamma V_m \mu_h ds - 2\alpha h \int_\Gamma \mu_h\big(\lambda_h + \{\boldsymbol{\kappa}\nabla u_h \cdot \mathbf{n}\}\big)ds. \tag{10}$$

To show that on the approximated case by finite elements method, the interface condition over Γ of the transmembrane potential will be imposed with an error associated to the following relation: $e_{\lambda_h} = \lambda_h + \{\boldsymbol{\kappa}\nabla u_h \cdot \mathbf{n}\}$. Note that, since $\alpha \in \mathbb{R}$ the influence of the term e_{λ_h} may be reduced by choosing small values for α. Additionaly, note that from equation (10) a pair (u_h, λ_h) solving problem (8) also satisfies the following relation for the Lagrange multiplier λ_h:

$$\lambda_h = \frac{V_m - [u_h]}{2\alpha h} - \{\boldsymbol{\kappa}\nabla u_h \cdot \mathbf{n}\}, \quad \text{on } \Gamma. \tag{11}$$

3 Numerical results

In this section the spatial convergence of the stabilized hybrid and primal hybrid formulations are evaluated for an idealized problem of the polarization of a square cell. The computational perfomance of both methods, is also compared in terms of the mean number of iterations needed to solve one time step during 0.5 $[\mu s]$ of the polarization process for different iteratives methods and preconditioning techniques.

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3.1 convergence of the method

One interesting property of the proposed method is the possibility to approximate discontinuous solutions on the interface of two non-overlapping domains.

Exact solution for the model problem (1) on the unicellular cell system depicted in Figure 1 is obtained in [5] using the method of manufactured solution. The exact solution is then obtained for $f_i = -8.0\pi^2 \sin(2\pi x)\sin(2\pi y)(1 + e^{-t})$, $f_e = -8.0\pi^2 \sin(2\pi x)\sin(2\pi y)$ on the bounded domain $\Omega = \Omega_i \cup \Omega_e$ with $\Omega_i = [0.25, 0.75] \times [0.25, 0.75]$ and $\Omega_e = [0.0, 1.0] \times [0.0, 1.0] \setminus \Omega_i$.

In order to test the h-convergence of the methods an arbitrary fixed time is chosen and the forcing terms on each subdomain (f_i, f_e) are defined. The jump on the cell interface Γ is computed as $V_m = e^{-t}\sin(2\pi x)\sin(2\pi y)$. In this scenario the convergence test of the primal hybrid and the stabilized formulations are presented in Table 1 below.

Table 1: Errors and order of convergence for the approximations of u_h and λ_h obtained by the finite elements discretization of the primal hybrid variational formulation and stabilized variational formulation with $\alpha = 0.01$. The $\|\cdot\|$ norm denotes the $L^2(\Omega)$ norm used to measure the error of the primal variable, for the Lagrange multiplier $\|\cdot\|$ denotes a mesh dependant norm defined in [7].

	Primal Hybrid				Stabilized			
n	$\|u-u_h\|$	order	$\|\lambda-\lambda_h\|$	order	$\|u-u_h\|$	order	$\|\lambda-\lambda_h\|$	order
8	5.22e-2	–	6.76e-1	–	5.10e-2	–	6.31e-1	–
16	1.46e-2	1.84	1.71e-1	1.98	1.45e-2	1.56	1.61e-1	1.91
32	3.77e-3	1.90	4.26e-2	1.99	3.76e-3	1.85	4.01e-2	1.99
64	9.51e-4	1.93	1.06e-2	2.00	9.49e-4	1.96	9.96e-3	2.00
128	2.38e-4	1.95	2.63e-3	2.00	2.38e-4	1.99	2.48e-3	2.00
256	6.12e-5	1.96	6.60e-4	2.00	5.95e-5	2.00	6.22e-4	2.00

3.2 Computational aspects

In this section the mean number of iterations to solve a time step on the polarization process of an isolated square cell by an explicit time discretization with $\delta t = 0.01$ $[\mu s]$, is used to compare the performance of the primal hybrid and the stabilized formulations. To study the performance of the formulations we solve the conservation of electric current given by the system of equations (1) with $\kappa_i = 5.0$ $[\mathrm{S} \cdot \mathrm{cm}^{-1}]$, $\kappa_e = 20.0$ $[\mathrm{S} \cdot \mathrm{cm}^{-1}]$ and an applied electric potential difference between right and left of $0.1[V]$.

Since the linear system associated to the primal hybrid formulation is positive indefinite, the Minimal Residual Method (MINRES) with a Jacobi preconditioner was used and considered as a reference for further comparisons against the stabilized formulation with other solvers. For the stabilized formulation the associated linear system is definite and, therefore, the GMRES and Stabilized Biconjugate Gradient (BICGSTAB) method preconditioned by the incomplete LU factorization ILU(0) are successful in solving it in a significantly lower number of iterations. This indicates an improvement in terms of computational performance of the proposed stabilized method when compared to the primal variational form.

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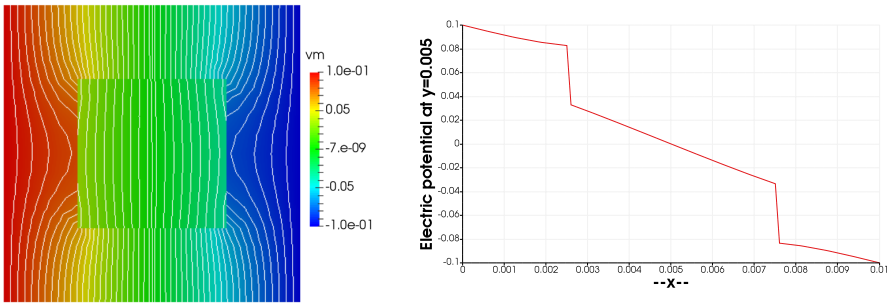

(a) (b)

Fig. 2: a) Electric potential and isocontour of an square cell in a conductive medium under an applied electric field after 0.5 [μs] of polarization; (b) electric potential magnitude at $y = 0.005$.

Table 2: Average number of iterations and standard deviation for different iterative methods to solve one time step for the distribution of electric potential on the unicellular system after 0.5 [μs] of polarization (50 time steps). The absolute tolerance for the iterative solver was set to $1e-10$. All the linear systems were solved with the high-performance scientific library PETSc [10].

Preconditioner		Jacobi	ILU(0)	ILU(0)
Iterative method		MINRES	GMRES	BICGSTAB
Primal Hybrid		928±114	-	-
Stabilized	$\alpha = 1e-5$	-	188±13	92±7

Table 2 shows the average number of iterations needed to solve 0.5 [μs] of cell polarization for both formulations using different combination of iterative solvers and preconditioners for the stabilized formulation. The empty entries in the table, correspond to cases where the preconditioner could not be constructed due to the matrix structure or the iterative solver was not able to solve the problem for the given tolerance.

4 Conclusions

In this work a stabilized formulation for an interface problem was introduced in the context of the response of a isolated square cell to an externally applied electric field. Through numerical experiments it was demonstrated that the proposed stabilized method converges with optimal convergence order for both primal and Lagrange multiplier variables.

The discrete operator from the stabilized formulation results in a definite matrix that allows the use of effective iterative solvers and preconditioning techniques that significantly improves the convergence properties of the iterative solution. Even though, the time consumed by the application phase of the

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ILU(0) preconditioner is bigger than the application phase of the jacobi preconditioner, the global perfomance of the ILU(0) preconditioned GMRES solver or the ILU(0) preconditioned BICGSTAB solver outperfom the Jacobi preconditioned MINRES solver due to the reduced number of iterations needed to achieve the demanded tolerance.

The convergence rate of the Lagrange multiplier for the presented stabilized variational formulation is optimal for straight interfaces, this meant that when solving irregular shape cells, the convergence rate of the Lagrange multiplier is degradated and the optimal convergence for the primal variable is conserved. Concerning the Krylov iterative methods, it is possible to exploit the block structure of the discrete operator in order to implement more effective preconditioning techniques, this characteristic could be explored in future works.

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