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Hamza Ammar[*1], **Moncef Mahjoub**[2], **Néjib Zemzemi**[3]

[*1,2]University of Tunis El Manar, National Engineers School of Tunis, B.P. 37, 1002 Tunis, Tunisia

[3]INRIA Bordeaux Sud-Ouest, Carmen project team. 200 Avenue de la vielle Tour 33405 Talence Cedex, France

*E-mail : hamza.ammar@enit.utm.tn

Abstract

This paper is devoted to analyze the inverse problem of determining two space dependent ionic parameters of a nonlinear reaction diffusion system described by a parabolic-elliptic one, modeling the electrical activity in the heart. We consider the classical phenomenological model in cardiac electrophysiology of FitzHugh-Nagumo to describe the ionic exchanges at the microscopic level. Our main result is the uniqueness and a Lipschitz stability estimate for two ionic parameters (k, γ) of the model using sub-boundary observations over an interval of time. The key ingredients are global Carleman-type estimates with a suitable observations acting on a part of the boundary.

Keywords

Parameter identification, Inverse problem, Reaction-diffusion equations, Carleman estimate, Uniqueness, Stability result

I INTRODUCTION

Let $\Omega \subset \mathbb{R}^3$ be a bounded connected open set whose boundary $\partial\Omega$ is regular enough and Γ_0, Γ_1 and Γ_2 are nonempty sub-boundaries of $\partial\Omega$. Given $T > 0$, in Ω we consider a modified version of the bidomain model, it decribes the electrical activity of human induced pluripotent stem cells-cardiomyocytes (hiPSC-CMs) based on multi-electrode array (MEA) experiments where the drug acts directly on the maximal conductance of the targeted ion channel:

$$
\begin{cases}
c_m(1+\sigma_e^{-1}\sigma_i)\partial_t v - \text{div}(\sigma_i \nabla v) = (1+\sigma_e^{-1}\sigma_i)(I_{stim} - I_{ion}(v,w)) & \\
-\boldsymbol{A}(x)\cdot\nabla u_e & \text{in } Q := \Omega \times (0,T), \\
-\text{div}(\sigma_e \nabla u_e) = c_m \partial_t v - I_{stim} + I_{ion}(v,w), & \text{in } Q := \Omega \times (0,T), \\
\partial_t w + f(v,w) = 0 & \text{in } Q := \Omega \times (0,T), \\
\sigma_i \nabla v.\nu + \sigma_i \nabla(u_e).\nu = 0 & \text{on } \Sigma := \partial\Omega \times (0,T), \\
u_e = 0 & \text{on } \Sigma_0 := \Gamma_0 \times (0,T), \\
\sigma_e \nabla(u_e).\nu = 0 & \text{on } \Sigma_2 := \Gamma_2 \times (0,T). \\
\boldsymbol{\sigma}_e \nabla(u_e).\nu = \displaystyle\sum_{k=1}^{9} \frac{I_{el}^k}{|e_k|}\chi_{e_k} & \text{on } \Sigma_1 := \Gamma_1 \times (0,T)\ , \\
v(.,0) = v_0,\ w(.,0) = w_0 & \text{in } \Omega \text{ a.e,}
\end{cases}
\tag{I.1}
$$

where

$$
\boldsymbol{A}(x) := -\nabla(\sigma_e^{-1}\sigma_i)\sigma_e = \sigma_e^{-1}(\sigma_i \nabla \sigma_e - \sigma_e \nabla \sigma_i). \tag{I.2}
$$

Functions u_e and v are respectively the extracellular and transmembrane potentials. The constant c_m is the transmembrane specific capacitance, $\boldsymbol{\sigma}_i$ and $\boldsymbol{\sigma}_e$ are respectively the intracellular and extracellular conductivities. $|e_k|$ denotes the surface of the electrode k, χ_{e_k} denotes its characteristic function, i.e. the function equal to one inside the electrode and zero outside and I_{el}^k is the electric current measured by the k^{th} electrode. In an isolated heart, no current flows out of the heart, as expressed by the Neumann condition on Σ_2. We use homogeneous Dirichlet boundary condition for the extracellular potential $(u_e = 0)$ on the three edges connected to the ground denoted by Γ_0 which has a "U" shape on each of our 6 wells and Γ_1 is the surface of our nine electrodes. For the remaining surface denoted by Γ_2, we use a non flux boundary condition. $\boldsymbol{\sigma}_e \nabla u_e.\nu = 0$. The transmembrane ionic current I_{ion} is provided by the FitzHugh-Nagumo phenomenological model given by

$$
I_{ion}(v,w) = -kv(v-a)(1-v) + w,\ \ f(v,w) = \gamma v + \beta w \tag{I.3}
$$

where k, a, γ, β only depend on space, belong to $L^\infty(\Omega)$ and satisfy

$$
0 \le a(x) \le 1, k(x) \ge k_0 > 0, \gamma(x) \ge 0, \beta(x) \ge 0, \forall x \in \overline{\Omega} \tag{I.4}
$$

and that there exists $M > 0$ such that

$$
\|k\|_{L^\infty(\Omega)} + \|\gamma\|_{L^\infty(\Omega)} + \|\beta\|_{L^\infty(\Omega)} \le M \tag{I.5}
$$

The variable w denotes the ionic variable. In the first and second equation of system (I.1), the current I_{stim} is an external stimulation, which can be applied at a certain location of the domain for a certain duration.

The current I_{el}^k is computed using the electric model of Figure 1, by solving the following

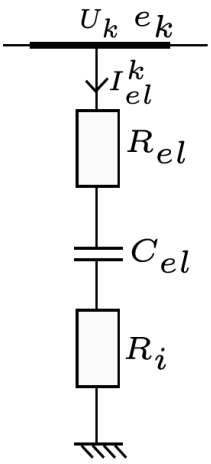

Figure 1: The electrical circuit for the electrodes description

ODE:

$$\frac{dI^k_{el}}{dt} + \frac{I^k_{el}}{\tau} = \frac{C_{el}}{\tau}\frac{dU^k}{dt} \qquad \text{With} \qquad U_k = \frac{1}{|e_k|}\int_{e_k} u_e dx \tag{I.6}$$

where $\tau = (R_i + R_{el})C_{el}$, R_i standing for the inner resistance, R_{el} and C_{el} for the resistance and the capacitance of the electrode. In Eq. (I.6) we have introduced U_k as the mean value of the extracellular potential u_e over the electrode k. We complete this model with initial data $u_e(\cdot, 0) = u_{e,0}$.

The anisotropic properties of the two media are modeled by an intracellular and extracellular conductivity tensors $\boldsymbol{\sigma}_i(x)$ and $\boldsymbol{\sigma}_e(x)$. Generally, the conductivities $\boldsymbol{\sigma}_i$ and $\boldsymbol{\sigma}_e$ are two matrices given by

$$\boldsymbol{\sigma}_j(x) = \sigma^t_j(x)\boldsymbol{I} + (\sigma^l_j(x) - \sigma^t_j(x))\boldsymbol{a}_l(x)\boldsymbol{a}^T_l(x),$$

where σ^l_j and σ^t_j, $j \in \{i, e\}$ are the intra- and extracellular conductivities along and transversal to the direction of the fiber (parallel to $\boldsymbol{a}_l(x)$), respectively. In the case of equal anisotropy, i.e the so-called anisotropy ratios $\sigma^t_i/\sigma^l_i = \sigma^t_e/\sigma^l_e = 1$, the $\boldsymbol{\sigma}_i$ and $\boldsymbol{\sigma}_e$ are simplified as $\boldsymbol{\sigma}_i(x) = \sigma_i(x)\boldsymbol{I}$ and $\boldsymbol{\sigma}_e(x) = \sigma_e(x)\boldsymbol{I}$ with $\sigma_i(x) = \sigma^t_i(x)$, $\sigma_e(x) = \sigma^t_e(x)$, which is the case we discussed.

The purpose of this work is to give an answer to the following question: Is it possible to identify simultaneously, the parameters k and γ, from observed data of the solution v, u_e, w and I_{el} on a sub-boundary of $\partial\Omega$ and some measurement at fixed times t_0 and t_1. The proof of the results relies on Carleman estimates and a certain regularity of solutions for the MAE/ hiPSC-CM assays.

II INVERSE PROBLEM: MAIN RESULTS

Let $(v^{(n)}, u^{(n)}_e, w^{(n)})$ be solutions to our problem (I.1) respectivly with initial conditions $(v^{(n)}_0, u^{(n)}_{e,0}, w^{(n)}_0)$ and ionic parameters $(k^{(n)}, \gamma^{(n)})$ for $n = 1, 2$ and they are both under hypothesis of assumptions of property (I.4)-(I.5).

Our first main result in this work gives a Carleman estimate for the Problem (I.1).
Let t_0 and t_1 two different times between 0 and T such that $t_0 < t_1$ and $t_1 - t_0 < \frac{t_0}{2}$, without loss of generality we assume that $t_0 + t_1 \leq T$ (by changing the scale of t and modifying slightly the definition of the weight functions θ_m in what follows). We put $T_0 = t_0 + t_1$, $\delta := \frac{t_1 - t_0}{4}$ and

from now on, we denote by $T := T_0$ (for notation simplicity). This estimate involves a function ψ in Ω such that

$$\psi \in \mathcal{C}^2(\overline{\Omega})\,, \quad \psi > 0 \text{ in } \Omega\,, \quad \psi = 0 \text{ on } \partial\Omega \setminus \Gamma_0\,, \quad |\nabla\psi(x)| > 0 \text{ in } \overline{\Omega}\,.$$

Then we define, for all $\lambda > 0$ and $s > 0$ the weight functions:

$$\varphi_m(x,t) = e^{\lambda\psi(x)}\theta_m(t)\,, \quad \eta_m(x,t) = (e^{2\lambda\|\psi\|_\infty} - e^{\lambda\psi(x)})\theta_m(t)\,, m = 1, 2\,,$$

the weighted integral:

$$\begin{aligned} I_\psi(\overline{v}, \overline{u_e}) = \int_Q \big\{ & s\varphi_m(|\partial_t\overline{v}|^2 + |div(\sigma_i\nabla\overline{v})|^2) + (s\varphi_m)^3\lambda^2\,|\nabla\overline{v}|^2 + (s\varphi_m)^5\lambda^4\,|\overline{v}|^2 \\ & + |div(\sigma_e\nabla\overline{u}_e)|^2 + (s\varphi_m)^2\lambda^2\,|\nabla\overline{u}_e|^2 + (s\varphi_m)^4\lambda^4\,|\overline{u}_e|^2 \big\}\, e^{-2s\eta_m}\,dx\,dt, \end{aligned}$$

and the weighted local function of observations:

$$\begin{aligned} N_{\Gamma_0,\psi}(\overline{v}, \overline{u_e}, \overline{I}_{el}) = & \int_Q (s\varphi_m)^2 \left| I_{ion}(k^{(1)}, v^{(1)}, w^{(1)}) - I_{ion}(k^{(2)}, v^{(2)}, w^{(2)}) \right|^2 e^{-2s\eta_m}\,dx\,dt \\ & + \int_{\Sigma_0} \left\{ |\partial_t\overline{v}|^2 + |\nabla\overline{v}|^2 + |\overline{v}|^2 + |\nabla\overline{u}_e|^2 \right\} dSdt + \left\| \overline{I}_{el} \right\|_{H^1(0,T)}. \end{aligned}$$

Here $\overline{v} = v^{(1)} - v^{(2)}$, $\overline{u}_e = u_e^{(1)} - u_e^{(2)}$ and $\overline{I}_{el} := (\overline{I}_{el}{}^1, \ldots, \overline{I}_{el}{}^9) = (I_{el}^{1,(1)} - I_{el}^{1,(2)}, \ldots, I_{el}^{9,(1)} - I_{el}^{9,(2)}) \in (C^1(0,T))^9$ and $\theta_0, \theta_1 \in \mathcal{C}^1(0,T)$ defined by:

$$\theta_{\mathbf{0}}(t) = \begin{cases} \frac{1}{(t(2t_0 - t))^2}, & 0 < t \le t_0 + \delta \\ \frac{t_0^2 + \delta^2 - 2(\frac{T}{2} - t)^2}{(t_0^2 - \delta^2)^3} & t_0 + \delta < t \le \frac{T}{2} \\ \theta_0(T - t), & \frac{T}{2} < t < T \end{cases} \quad \text{and} \quad \theta_{\mathbf{1}}(t) = \begin{cases} \theta_0(t), & 0 < t \le t_0 \\ \textit{constant}, & t_0 < t \le t_1 \\ \theta_0(t), & t_1 < t < T \end{cases}.$$

The Carleman inequality is then the following:

Theorem II.1:
Then there exists a number $\lambda_0 > 0$ such that for an arbitrary $\lambda \ge \lambda_0$, we can choose a constant $s_0(\lambda) \ge 1$ satisfying: there exists a constant $C = C(s_0, \lambda_0) > 0$ such that, for all $s > s_0$,

$$I_\psi(\overline{v}, \overline{u_e}) \le C N_{\Gamma_0,\psi}(\overline{v}, \overline{u_e}, \overline{I}_{el}). \tag{II.1}$$

The constant $C > 0$ depends continuously on λ_0 but it is independent of s, and λ_0 depends continuously on $\tilde{\gamma}$.

Proof The proof of Theorem II.1 is very much technical, follwing Fursikov-Immanuvilov [2] and based on integrations by parts and bounded functions. ■

The next second main result gives a positive answer to the question made above. Then, using the classical Bukhgeim-Klibanov method [1], we show Lipschitz stability inequalities on the two reaction parameters k and γ simultaneously which appears in the first three equations of (I.1).

Theorem II.2:

Let $(v^{(n)}, u_e^{(n)}, w^{(n)})$ be solutions to our problem (I.1) respectivly with initial conditions $(v_0^{(n)}, u_{e,0}^{(n)}, w_0^{(n)})$ and ionic parameters $(k^{(n)}, \gamma^{(n)})$ for $n = 1, 2$ and they are both under hypothesis of assumptions of property (I.4)-(I.5). In addition to that we assume that there exists $t_0 \in (0, T)$ such that: $\left|g(v^{(2)}(x, t_0))\right| \neq 0 \quad \forall x \in \overline{\Omega}.$, then there exists a constant $C > 0$ which depends only on Ω, T, M, $\overline{M}$, k_0,I_{stim} and initial data of solutions $(v^{(n)}, u_e^{(n)}, w^{(n)})$, $n = 1, 2$ to our problem (I.1), such that:

$$\left\|\gamma^{(1)} - \gamma^{(2)}\right\|_{L^2(\Omega)} + \left\|k^{(1)} - k^{(2)}\right\|_{L^2(\Omega)} \leq C N_{T,\Gamma_0}(\overline{v}, \overline{u_e}, \overline{w}, \overline{I}_{el}),$$

where

$$N_{T,\Gamma_0}(\overline{v}, \overline{u_e}, \overline{w}, \overline{I}_{el}) = \left\|v^{(1)} - v^{(2)}\right\|_X + \left\|u_e^{(1)} - u_e^{(2)}\right\|_X + \left\|I_{el}^{(1)} - I_{el}^{(2)}\right\|_{H^2(0,T)} + \left\|(u_e^{(1)} - u_e^{(2)})(\cdot, t_1)\right\|_{H^2(\Omega)} + \sum_{i=0}^{1} \left\|(w^{(1)} - w^{(2)})(\cdot, t_i)\right\|_{L^2(\Omega)}.$$

Here X is the vector space $H^2(0, T; H^{\frac{1}{2}}(\Gamma_0)) \cap H^1(0, T; H^{\frac{3}{2}}(\Gamma_0))$ equipped with the norm $\|u\|_X = \left(\|u\|^2_{H^2(0,T;L^2(\Gamma_0))} + \|\nabla u\|^2_{H^1(0,T;L^2(\Gamma_0))}\right)^{1/2}$ and t_1 is sufficiently close to t_0.

By Theorem II.2, we can readily derive the uniqueness in the inverse problem.

Corollary II.3:
Under the same assumptions as in Theorem II.2 and if

$$w^{(1)}(x, t_0) = w^{(2)}(x, t_0) \quad \text{for all } x \in \Omega \tag{II.2}$$

$$(u_e^{(1)}(x, t_i), w^{(1)}(x, t_i)) = (u_e^{(2)}(x, t_i), w^{(2)}(x, t_i)) \quad \text{for all } x \in \Omega, i = 0, 1 \tag{II.3}$$

$$v^{(1)} = v^{(2)}, \quad \nabla u_e^{(1)} = \nabla u_e^{(2)} \quad \text{in } \Gamma_0 \times [0, T] \tag{II.4}$$

$$I_{el}^{(1)} = I_{el}^{(2)} \quad \text{in } x \in (0, T) \tag{II.5}$$

then $\gamma^{(1)} = \gamma^{(2)}$ and $k^{(1)} = k^{(2)}$ in Ω.

III DISCUSSION AND CONCLUSION

In this work, we use a mathematical model of the field potential recorded by the MEA device which results in a system of partial differential equations with boundary conditions acting on the four edges of our multi-electrode array device. We proved that the parameter identification inverse problem is stable under certain conditions. These conditions have to be satisfied in order to proceed to the computational estimation. Our approach is based on a new Carleman inequality for the MEA/hiPSC-CM assays. We established a new global Carleman estimate for solutions to a boundary value problem of a linear parabolic equation with Robin boundary condition. This Carleman inequality is crucial for solving the parameter identification stability problem. In order to prove the stability estimate for our ionic parameters k and γ at the same time, we began by establishing the first stability estimate of parameter k only, then we used both types of weight functions $e^{-s\eta_0}$ and $e^{-s\eta_1}$ to establish the last estimate of both k and γ using that the second weight function is constant with respect to time between t_0 and t_1. This result is a very important step in order to numerically solve the parameters identification problem in cardiac electrophysiology because it provides the condition in which this problem is stable.

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