Parameters Estimation Approach for the MEA/hiPSC-CM Asaays

Julien Bouyssier[1,2,3], Nejib Zemzemi[1,2,3]

[1]Inria Bordeaux Sud-Ouest. Carmen team, Talence, France.
[2] IHU LIRYC, Electrophysiology and Heart Modeling Institute, Pessac, France.
[3]IMB UMR CNRS 5251, Talence, France.

***Abstract*— We propose a mathematical approach for the analysis of drugs effects on the electrical activity of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) based on multi-electrode array (MEA) experiments. Our goal is to produce an in silico tool able to simulate drugs action in MEA/hiPSC-CM assays and to fit the drug model parameters to the experimental data. The electrical activity of the stem cells at the ion-channel level is modeled using the *Paci et al. (2013)* transmembrane potential model. We use the bidomain model in order to describe the propagation of the electrical wave in the stem cells preparation. The field potential (FP) measured by the MEA is modeled by the extracellular potential of the bidomain equations. First, we propose a strategy allowing to generate FPs in good agreement with the experimental data. Second, we introduce a drug/ion channels interaction based on a pore block model.**

Results show that the model reflects properly the main effects of the drug on the FP. In order to estimate the parameters of the drug model, we define a cost function minimizing the gap between the model and the observed FPs. We use an optimization algorithm based on a gradient descent method where the cost function gradient is computed using an adjoint approach. We generated field potential for the five drugs with fixed gold standard IC50 and drug dose values. Then, supposing that one of the gold standard parameters is not known and adding 10% gaussian noise, the algorithm is able to estimate this parameter with more than 95% of accuracy. This approach could also be used in the future to optimize drug doses in order to achieve desired therapeutic effects.

I. Introduction

The capability of stem cells to differentiate into different tissue types have been shown in [1]. Human induced pluripotent stem cells (hiPSCs) are considered in this work. These cells are derived by reprogramming somatic cells and can be cultivated in the pluripotency state or differentiated into somatic cell types, including CMs [2]. Until now, the knowledge regarding the cardiac tissue mainly relied on animal models, like dog, rabbit or guinea pig. Today, many types of human pluripotent stem cells are investigated for their potential to produce functional CMs [3], [4]. hiPSC-CMs are valuable models because of their resemblance to adult myocytes, especially in the electrophysiological behavior [5]. Therefore, the role of hiPSC-CMs as *in vitro* models is becoming more and more important. In hiPSC-CMs preparations, a strong heterogeneity in the morphology of the action potentials is usually observed. However, the signals can be classified into three major types: nodal-like, embryonic atrial-like, and embryonic ventricular-like [3], [2].

The hiPSC-CMs have been used in different fields: toxicity testing, study of certain diseases, pharmacological response, drug design *etc.* [4], [2], [6], [7], [8], [9]. The present study is related to the problem of drug screening in safety pharmacology. Our goal is to model and simulate MEA measurements that are performed by pharmaceutical companies on hiPSC-CMs preparations. The aim of these experiments is to predict and test the main effects of a drug on the electrophysiology of cardiomyocytes. But the electrical signal collected by an MEA device, called the Field Potential (FP), is difficult to analyze, because of its variability, and because it has been much less studied than the Action Potential (AP). With this study, we want to show that mathematical modeling and numerical simulation can contribute to a better understanding of the MEA measurements. Some preliminary simulations of the FP were recently presented [10], [11], [12] and the modeling of drug effects, side effects and interactions was addressed in several works [13], [14], [15]. But to the best of our knowledge, the present article is the first *in silico* study of drug effects on the FP.

Here is a brief description of the methods adopted in this work. Our mathematical model is based on the bidomain equations, used in many works for the description of the electrical activity of the heart. In order to reproduce the electrical activity of hiPSC-CMs, a state-of-the-art ionic model describing the membrane activity of stem cells is used in Paci et al [16]. Since the experimental measurements are registered by MEA devices, a model of electrodes is introduced and coupled to the bidomain equations. The resulting equations allow us to model the field potential recorded by the MEA device. A specific device is considered (the 60-6 well MEA produced by the company Multi Channel Systems) but the methodology can be applied to other kinds of MEAs. This device is made of six independent wells. Each well contains nine electrodes. Six independent experiments can thus be done with identical surrounding conditions at once [17]. The geometry used for the computation is two-dimensional. It models one layer of cells in a well, as represented in Fig. 1(a). A special effort is dedicated to the modeling of the electrophysiological heterogeneity, which is a prominent characteristic of hiPSC-CMs preparations. This is done by introducing different phenotypes, atrial- and ventricular-like, and by varying the action potential amplitudes. Various configurations are generated following this approach. The *in silico* results corresponding to the

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different configurations are averaged and compared to *in vitro* experiments for five different drugs (mexiletine, dofetilide, bepridil, ivabradine and BayK).

Human induced pluripotent stem cell-derived cardiomyocytes are a promising tool in regenerative medicine (repair damaged areas) because of pluripotency and ability to differentiate. Computational modeling and simulation is a powerful tool to investigate [13]:

- drug effects and their side effects
- disease in cardiac electrophysiological activity.

Our goal is to perform in silico simulations (quantify and predict affinities and effects of drugs on hIPSC-CMs) to be used in early stage of the development of new compounds. Here we provide an approach allowing to fit the drug model parameters to the experimental data.

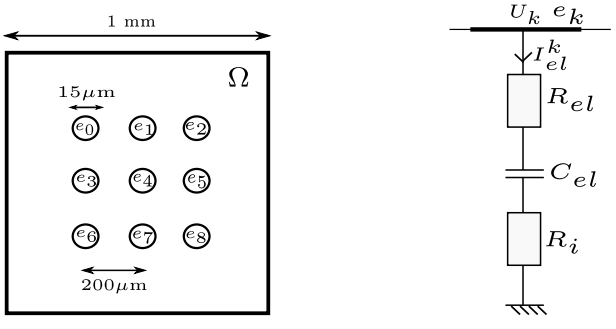
II. Methods

A. Forward problem

In order to model a layer of hIPSC-CMs, we use the bidomain model that we solve in a 2D computational domain Ω of Fig. 1(a). We compute the membrane potential V_M and the extracellular potential u_e.

$$\begin{cases} \frac{d\mathbf{w}}{dt} - \mathbf{g}\left(V_M, \mathbf{w}\right) = 0 \text{ in } \Omega \\ A_M \left(C_M \frac{\partial V_M}{\partial t} + I_{ion} \right) - \text{div}\left(\sigma_I \nabla V_M\right) - \text{div}\left(\sigma_E \nabla u_e\right) = A_M I_{stim} \text{ in } \Omega \\ -\text{div}\left((\sigma_I + \sigma_E)\nabla u_e\right) - \text{div}\left(\sigma_I \nabla V_M\right) = \frac{1}{z_{thick}} \Sigma_{e_k} \frac{I_{el}^k}{|e_k|} \chi_{e_k} \text{ in } \Omega, \end{cases} \tag{1}$$

where $|e_k|$ denotes the surface of the electrode k, and χ_{e_k} denotes its characteristic function, i.e. the function equal to one inside the electrode and zero outside. Functions V_M and u_e are respectively the transmembrane and extracellular potentials. The constant C_M is the transmembrane specific capacitance, A_M is the surface area of membrane per unit volume of tissue, σ_I and σ_E are respectively the intracellular and extracellular conductivities. The transmembrane ionic current I_{ion} is provided by the model proposed in Paci et al [16]. The electrodes are described using the circuit in



(a) Domain

(b) Electrodes circuit

Fig. 1. Schematic representation of the electrodes electrical circuit (a). 2D domain Ω with dimensions and positions of the 9 electrodes (b). Computational mesh representing a triangular discretization of the domain Ω with $h \approx 25\mu$m (c).

Fig. 1(b), by computing the measured current I_{el}^k: by solving the following ODE:

$$\frac{dI_{el}^k}{dt} + \frac{I_{el}^k}{\tau} = \frac{C_{el}}{\tau}\frac{dU^k}{dt} \qquad \text{with } U^k = \frac{1}{|e_k|}\int_{e_k} u_e \, de_k, \tag{2}$$

where $\tau = (R_i + R_{el})C_{el}$, R_i standing for the ground resistance, R_{el} and C_{el} for the resistance and the capacitance of the electrode. In Eq. (2) we have introduced U^k as the mean value of the extracellular potential u_e over the electrode k. The measured field potential is then $U_{meas}^k = R_i I_{el}^k$.

B. Model for the drug/ion channels interactions

The *in silico* approach presented in the previous sections was designed to qualitatively mimic the field potential acquired with MEA measurements, by taking into account a certain amount of variability. Our purpose is now to introduce in the model the action of compounds on ion channels. The modeling of drug-channel interactions has been the object of several studies (*see e.g.* [14], [18]). Various concepts have been introduced 1) *pore block* action: the flow of ions is inhibited by the drug binding with a continuously accessible channel receptor; 2) *modulated and guarded receptor* theories: the drug access to the binding sites is restricted due to the channel conformation during the AP cycle; 3) *allosteric effectors*: a drug binding to a protein changes its activity and also activates conformational changes in its dynamics. In the present study, the pore block model is used because it does not require too many parameters and because it proved to be able to reproduce the relevant phenomena. The pore block model is implemented with the "conductance-block" formulation [19], [20], [13], [21]. The conductance of the targeted channel is reduced by a scaling factor in the following way:

$$g_s = g_{control,s}\left[1 + \left(\frac{[D]}{IC_{50}}\right)^n\right]^{-1}, \tag{3}$$

where $g_{control,s}$ is the drug-free maximal conductance of channel s, the IC_{50} value of the drug is the drug concentration at which a 50% reduction of the specific channel peak current is observed and $[D]$ is the drug concentration. The Hill coefficient n will be assumed to be equal to 1.

C. Optimization strategy

For given synthetical field potential measurements U_{meas}^k where a drug is blocking one ionic channel, our goal is to find the dose $[D]_{opt}$ allowing to obtain these data and knowing the concerned drug and its targeted channel.
First, we define a cost function J depending on the drug dose $[D]$ minimizing the gap between the simulated and the field potential measurements:

$$J([D]) = \frac{1}{2}\Sigma_{e_k} \parallel R_i I_{el}^k([D]) - U_{meas}^k \parallel^2_{l^2([0,T])} \tag{4}$$

where $I_{el}^k([D])$ is solution of the tissue model ((1)-(2)). Our goal is to find $[D]$ minimizing (4). For this, we define an adjoint problem associated to the bidomain coupled to the

measurement system model

$$\begin{cases} \dfrac{d\mathbf{q}}{dt} + {}^t(\partial_{\mathbf{w}}\mathbf{g}(V_M,\mathbf{w},[D]))\mathbf{q} - A_M{}^t(\partial_{\mathbf{w}} I_{ion}(V_M,\mathbf{w},[D]))p_M = 0 \text{ in } \Omega, \\ A_M\left(C_M\dfrac{\partial p_M}{\partial t} - \partial_{V_M} I_{ion}(V_M,\mathbf{w},[D])\right)p_M + \text{div}\,(\sigma_I\nabla p_M) \\ \qquad +\text{div}\,(\sigma_I\nabla p_e) + {}^t\left(\partial_{V_M}\mathbf{g}\,(V_M,\mathbf{w},[D])\right)\mathbf{q} = 0 \text{ in } \Omega \\ \text{div}\,((\sigma_I+\sigma_E)\nabla p_e) + \text{div}\,(\sigma_I\nabla p_M) = \Sigma_{e_k}\dfrac{C_{el}}{\tau}\dfrac{1}{|\,e_k\,|}\dfrac{d\lambda^k}{dt}\chi_{e_k} \text{ in } \Omega, \\ \dfrac{d\lambda^k}{dt} - \dfrac{\lambda^k}{\tau} = -\dfrac{1}{z_{thick}}P_e^k - R_i(R_i I_{el}^k - U_m^k) \text{ in } e_k, \text{ for } k = 0,..,8. \end{cases} \tag{5}$$

where $\mathbf{q}$, p_M, p_e and λ^k are the adjoint states associated respectively to variables $\mathbf{w}$, V_M, u_e and I_{el}^k and solution of (5). The variable P_e^k is given by $P_e^k = \frac{1}{|e_k|}\int_{e_k} p_e\, de^k$. In order to estimate the parameters of the drug model, we use an optimization procedure based on a gradient descent method where the cost function gradient is computed using the state and adjoint state variables as follows

$$\begin{aligned} \partial_{[D]}J([D]) = &\int_0^T\int_\Omega {}^t(\partial_{[D]}\mathbf{g}\,(\mathbf{V_M},\mathbf{w},[\mathbf{D}]))\mathbf{q} \\ &- \int_0^T\int_\Omega A_M\partial_{[D]}I_{ion}(V_M,\mathbf{w},[D])p_M. \end{aligned} \tag{6}$$

Giving an initial guess $[D]_{guess}$, we solve the optimization problem using the following algorithm. Here, ϵ_{Func} and

Algorithm 1 Optimization of Drug dose

$[D] = [D]_{guess}$.
Solve state problem
Solve adjoint problem
Compute the cost function and its gradient
while $J([D]) > \epsilon_{Func}$ & $\parallel \partial_{[D]}J([D]) \parallel > \epsilon_{Grad}$ **do**
  $[D] = [D] - \alpha \times \partial_{[D]}J([D])$.
  Solve state problem
  Solve adjoint problem
  Compute the cost function and its gradient
end while
$[D]_{opt} = [D]$.

ϵ_{Grad} are positive constants defining the desired tolerance on the cost function and its gradient respectively. The coeficient α is positive and could be fixed or updated at each iteration.

III. Results

In Fig 2, we show the simulated field potential over the nine electrode in the control condition and when introducing $50\mu M$ and $100\mu M$ of mexilitine. we observe that the simulated field potential are in agreement with the experimental field potentials in terms of depolarization and repolarization times but not in terms of magnitude. More experimental data could be found in [22]. In figure 3, we show the robustness of the proposed method with respect of the initial guess $[D]_{guess}$ and also with respect to noise by adding 5% and 10% of noise on the recorded data. In the presence of noise, the cost function seems to stagnate as shown in figures 4 and so is value of [D] as shown in figure 3. But the obtained dose is 99% accurate even with 10% of noise in the recorded data. We provide a snapshot of how the adjoint state associated to the action potential looks like in figure 5. It is not easy to interpret the adjoint states as they do not represent physical quantities. The only thing that we can expect is that they converge to zero when the dose converges to the exact value.

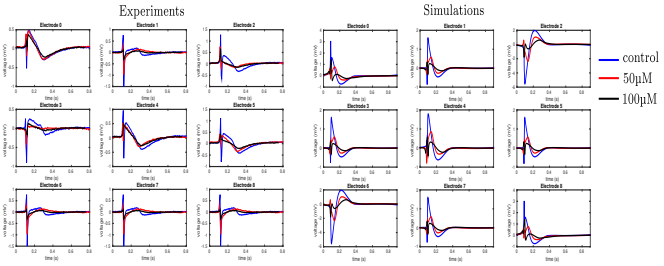


Fig. 2. Example of experimental measurement (left) and simulated (right) field potential. The nine traces are the signals recorded by the nine electrodes as shown in figure1(a)

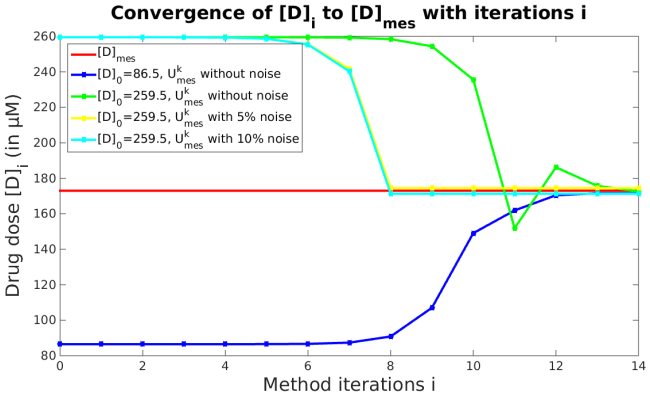


Fig. 3. INa channel block estimation. Convergence of the drug dose starting from different initial guess and with different levels of noise on the observed signals. Relative error is less than 1% for all cases.

IV. Conclusion

In this paper, we presented a proof of concept of an optimization approach able to estimate the drug dose of a compound when the characteristics of the drug are known. The robustness of the method was tested on drugs targeting INa channel using in silico experiments: with 10 % of gaussian noise on the observed field potential, the accuracy of the estimated drug dose is higher than 99%. Future developments would include estimating model parameters of drugs like Mexelitine or Dofetilide, drugs with several targeted channels and fitting of other parameters as IC_{50}, etc.

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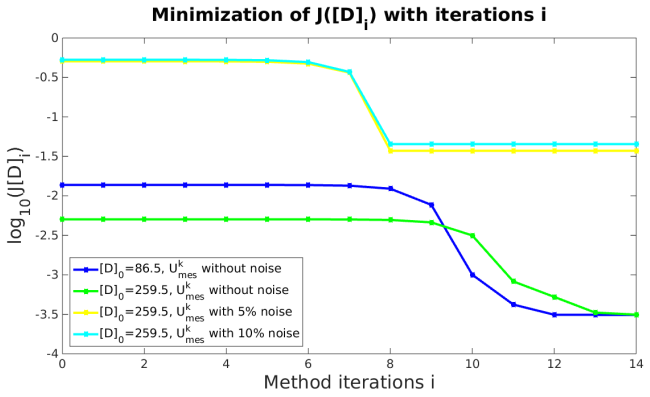

Fig. 4. Convergence of the cost function for different values of $[D]_{guess}$ and noise levels.

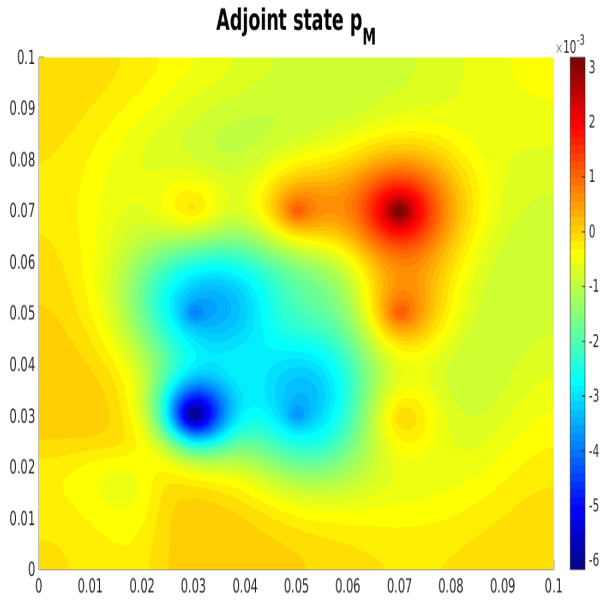

Fig. 5. Snapshot of the propagation of the adjoint state p_M used for computing the gradient of the cost function.

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Contact: Nejib Zemzemi, 200 avenue de la vieille tour 33405, Talence, France. Email: nejib.zemzemi@inria.fr

Julien Bouyssier, 200 avenue de la vieille tour 33405, Talence, France. Email: julien.bouyssier@inria.fr