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## Parameters estimation approach for the MEA/hiPSC-CM assays

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## 1) Motivation and goals

Human induced pluripotent stem cell-derived cardiomyocytes (**hiPSC-CMs**) are a promising tool in regenerative medicine (repair damaged areas) because of pluripotency and ability to differentiate [1]. Computational modeling and simulation is a powerful tool to investigate [2]:

- **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.

## 2) Tissue model

Modeling a layer of hiPSC-CMs: **bidomain model** (terms in blue) solved in the 2D computational domain  $\Omega$  of Fig. 1, to compute the membrane potential  $V_M$  and the extracellular potential  $u_e$ .

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

- Ionic current  $I_{ion}$  computed with:
  - model proposed by Paci et al. [3] in the case of *pacemaker cells*
  - modified Paci model (with adult version of  $I_{Na}$ ) in the case of *non-pacemaker cells*.
- Source term added to model a 60-6well MicroElectrode Array **MEA** (terms in red): device used to measure the *field potential* generated from multiple cells. The electrodes are described using the circuit in Fig. 1, by computing the measured current  $I_{el}^k$ :

$$\frac{dI_{el}^k}{dt} + \frac{I_{el}^k}{\tau} = \frac{C_{el}}{\tau} \frac{dU^k}{dt} \quad \text{with } U^k = \frac{1}{|e_k|} \int_{e_k} u_e, \text{ for } k = 0, \dots, 8, \quad (2)$$

where  $\tau = (R_i + R_{el})C_{el}$ ,  $R_i$  is the inner resistance,  $R_{el}$  and  $C_{el}$  are the resistance and the capacitance of the electrode. The measured **field potential** is then  $U_{mes}^k = R_i I_{el}^k$ .

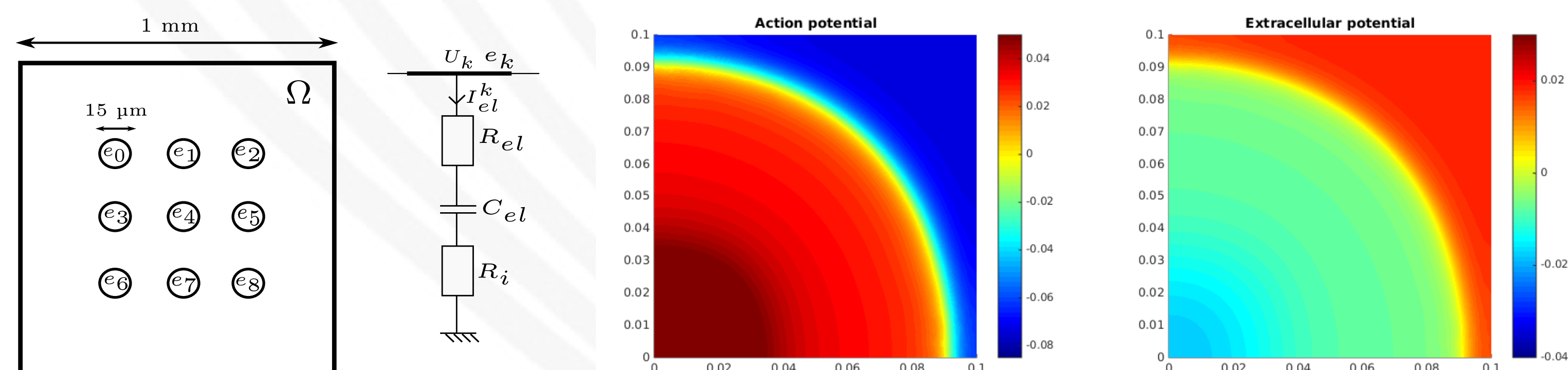


Figure 1: Left: domain  $\Omega$  for the MEA model and equivalent circuit for the electrodes. Right: propagation of the depolarization front in the case of non-pacemaker cells stimulated in the left-bottom corner.

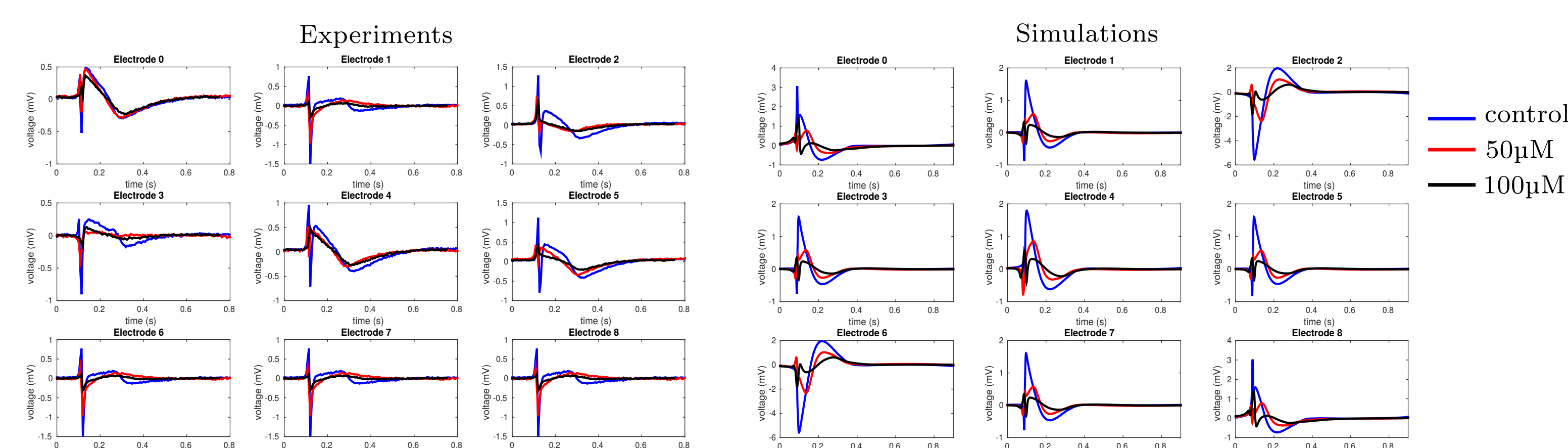
## 3) Drug action: Mexiletine example

**Pore block model:** use of a *conductance-block formulation* [2]. In the ionic model, the conductance of a targeted channel  $s$  is reduced by a scaling factor:

$$g_{blocked,s} = g_{control,s} \left[ 1 + \left( \frac{[D]}{IC_{50}} \right)^n \right]^{-1} \quad \text{with } n = 1,$$

where  $[D]$  is the drug concentration and the  $IC_{50}$  value is the dose able to block 50% of the channel activity.

- **Mexiletine:** action on  $I_{Na}$  (smaller depolarization phase)



## 4) Parameters estimation: drug dose $[D]$ example

- From given synthetical field potential measurements  $U_{mes}^k$  where a drug is blocking one ionic channel, **find the dose  $[D]_{mes}$  which allowed to obtain these data**, knowing the concerned drug and its targeted channel.
- Define a **cost function**  $J([D])$  minimizing the distance between the simulated and the synthetical field potential measurements:

$$J([D]) = \frac{1}{2} \sum_{e_k} \| R_i I_{el}^k([D]) - U_{mes}^k \|_{L^2([0,T])}^2 \quad (3)$$

where  $I_{el}^k([D])$  is solution of the tissue model ((1) + (2)). Our goal is to find  $[D]$  minimizing (3).

- For this, define an **adjoint problem** associated to the tissue model:

$$\begin{cases} \frac{d\mathbf{q}}{dt} + {}^t(\partial_{\mathbf{w}} \mathbf{g}(V_M, \mathbf{w}, [D])) \mathbf{q} - A_M {}^t(\partial_{\mathbf{w}} I_{ion}(V_M, \mathbf{w}, [D])) p_M = 0 & \text{in } \Omega \\ A_M \left( C_M \frac{\partial p_M}{\partial t} - \partial_{V_M} I_{ion}(V_M, \mathbf{w}, [D]) p_M + \text{div}(\sigma_I \nabla p_M) \right. \\ \quad \left. + \text{div}(\sigma_I \nabla p_e) + {}^t(\partial_{V_M} \mathbf{g}(V_M, \mathbf{w}, [D])) \mathbf{q} = 0 & \text{in } \Omega \\ \text{div}((\sigma_I + \sigma_E) \nabla p_e) + \text{div}(\sigma_I \nabla p_M) = \sum_{e_k} \frac{C_{el}}{\tau} \frac{1}{|e_k|} \frac{d\lambda^k}{dt} \chi_{e_k} & \text{in } \Omega \\ \frac{d\lambda^k}{dt} - \frac{\lambda^k}{\tau} = -\frac{1}{z_{thick}} p_e^k - R_i (R_i I_{el}^k - U_{mes}^k) & \text{in } e_k, \text{ for } k = 0, \dots, 8 \end{cases} \quad (4)$$

with  $p_e^k = \frac{1}{|e_k|} \int_{e_k} p_e$  and with  $\mathbf{q}$ ,  $p_M$ ,  $p_e$  and  $\lambda^k$  states adjoint associated respectively to states  $\mathbf{w}$ ,  $V_M$ ,  $u_e$  and  $I_{el}^k$  and solution of (4).

- The **cost function gradient** is given by:

$$\partial_{[D]} J([D]) = \int_{\Omega} \int_0^T {}^t(\partial_{[D]} \mathbf{g}(V_M, \mathbf{w}, [D])) \mathbf{q} - \int_{\Omega} \int_0^T A_M \partial_{[D]} I_{ion}(V_M, \mathbf{w}, [D]) p_M \quad (5)$$

- We use an optimization procedure based and gradient descent method.

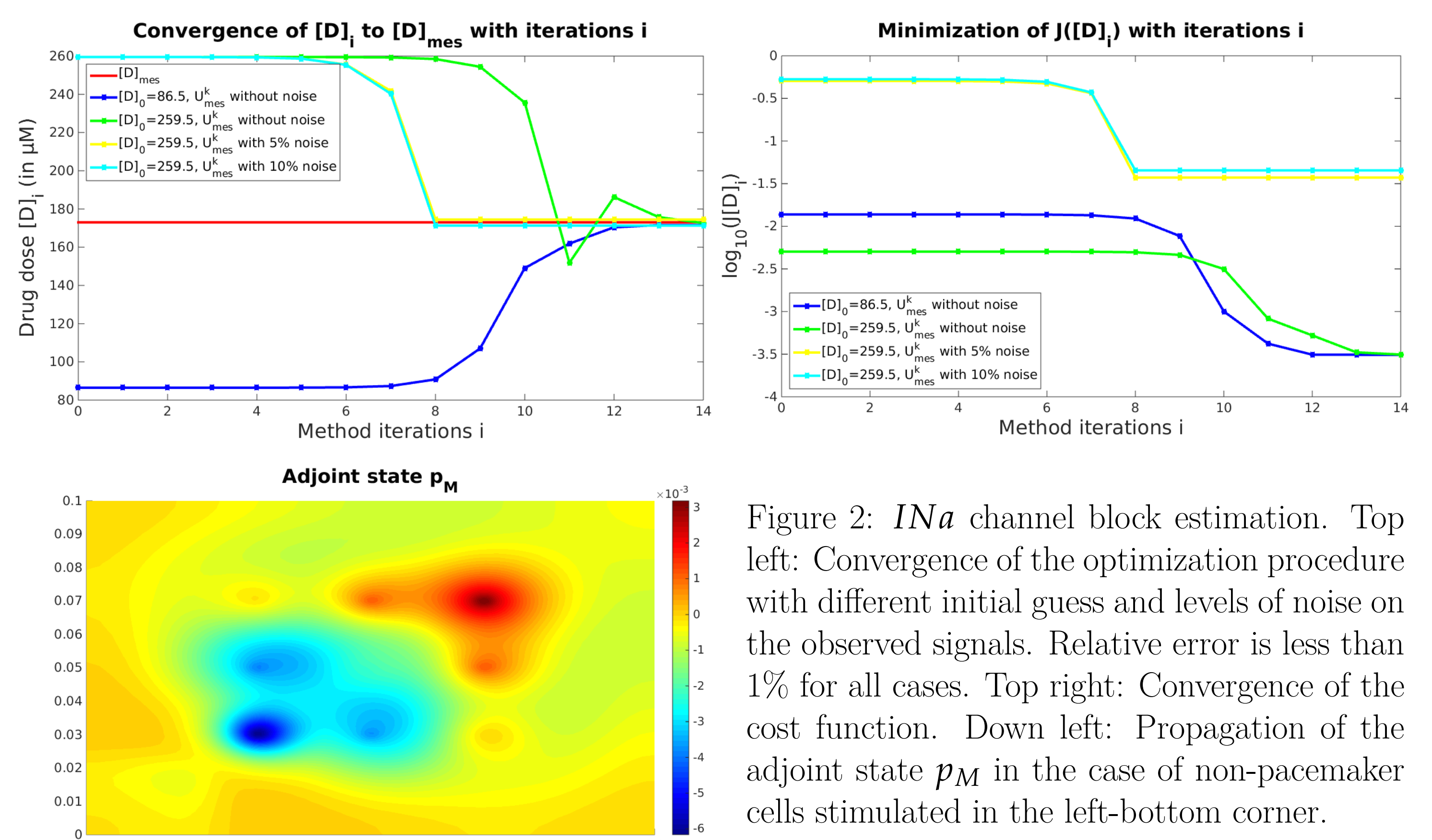


Figure 2:  $INa$  channel block estimation. Top left: Convergence of the optimization procedure with different initial guess and levels of noise on the observed signals. Relative error is less than 1% for all cases. Top right: Convergence of the cost function. Down left: Propagation of the adjoint state  $p_M$  in the case of non-pacemaker cells stimulated in the left-bottom corner.

## 5) Discussion and future work

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 Mexiletine or Dofetilide, drugs with several targeted channels and fitting of other parameters as  $IC_{50}$ , etc.

## References

- [1] K. Takahashi, S. Yamanaka. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* (2006).
- [2] N. Zemzemi, M. Bernabeu, J. Saiz, J. Cooper, P. Pathmanathan, G. Mirams, J. Pitt-Francis, B. Rodriguez. Computational assessment of drug-induced effects on the electrocardiogram: from ion channel to body surface potentials. *British journal of pharmacology* (2013).
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