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 $u_e$.

$$\begin{align*}
d\frac{dV_M}{dt} - g(V_M, w) &= 0 \quad \text{in } \Omega \\
A_M \left( \frac{\partial^2 V_M}{\partial t^2} + I_{ion} \right) - \text{div}(\sigma_I V_M) - \text{div}(\sigma_m u_e) &= A_M I_{ion,ext} \quad \text{in } \Omega \\
\text{div}((\sigma_I + \sigma_m) V_M) - \text{div}(\sigma_m u_e) &= 0 \quad \text{in } \Omega
\end{align*}$$

- Ionic current $I_{ion}$ computed with:
  - model proposed by Puci et al. [3] in the case of pacemaker cells
  - modified Puci model (with adult version of $I_{ion}$) in the case of non-pacemaker cells.
- Source term added to model a 60-fs 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 $I_{ele}$.

$$I_{ele} = \frac{U^2}{\tau}$$

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

![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.](image)

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:

$$G_{\text{pore}} = G_{\text{control}} \left( 1 + \left( \frac{[D]}{IC_{50}} \right)^n \right)^{-1}$$

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 $U_{ele,max}$ where a drug is blocking one ionic channel, find the dose $[D]_{\text{mea}}$ 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:

$$J(D) = \frac{1}{2} \sum_{k=1}^{8} \| R_{\text{ele}}(I_{V,D}(D)) - U_{ele,max} \| ^2$$

where $I_{V,D}(D)$ 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:

$$\begin{align*}
\frac{d\varphi}{dt} &= \frac{1}{\tau} \left( -I_{V,D} + \frac{\partial}{\partial V} (V_M, w, [D]) \right) \varphi - \frac{1}{\tau} \left( \frac{\partial}{\partial [D]} \varphi \right) D + \frac{1}{\tau} \left( \frac{\partial}{\partial [D]} \varphi \right) D + \frac{1}{\tau} \left( \frac{\partial}{\partial [D]} \varphi \right) D + \frac{1}{\tau} \left( \frac{\partial}{\partial [D]} \varphi \right) D + \frac{1}{\tau} \left( \frac{\partial}{\partial [D]} \varphi \right) D + \frac{1}{\tau} \left( \frac{\partial}{\partial [D]} \varphi \right) D + \frac{1}{\tau} \left( \frac{\partial}{\partial [D]} \varphi \right) D
\end{align*}$$

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