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In silico assessment of the effects of various compounds in MEA/hiPSC-CM assays: Modelling and numerical simulations

E. Abbate, M. Boulakia, Y. Coudière, J-F. Gerbeau, P. Zitoun and N. Zemzemi

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. The mathematical model takes into account the geometry of the MEA and the electrodes’ properties. The electrical activity of the stem cells at the ion-channel level is governed by a system of ordinary differential equations (ODEs). The ODEs are coupled to the bidomain equations, describing the propagation of the electrical wave in the stem cells preparation. The field potential (FP) measured by the MEA is modeled by the extra-cellular potential of the bidomain equations. First, we propose a strategy allowing us to generate a field potential in good agreement with the experimental data. We show that we are able to reproduce realistic field potentials by introducing different scenarios of heterogeneity in the action potential. This heterogeneity reflects the differentiation atria/ventricles and the age of the cells. Second, we introduce a drug/ion channels interaction based on a pore block model. We conduct different simulations for five drugs (mexiletine, dofetilide, bepridil, ivabradine and BayK). We compare the simulation results with the field potential collected from experimental measurements. Different biomarkers computed on the FP are considered, including depolarization amplitude, repolarization delay, repolarization amplitude and depolarization-repolarization segment. The simulation results show that the model reflect properly the main effects of these drugs on the FP.

Keywords: Cardiac electrophysiology, MEA, field potential, drug modelling, hIPSC-CMs.
1. Introduction

Recent studies on stem cells showed that it is possible to induce pluripotency, i.e. the capability of differentiating into all tissues of an organism [1]. Stem cell-derived cardiomyocytes (CMs) appear as a promising tool in regenerative medicine, for example to restore the cardiac function after an infarct [2, 3].

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 [4]. 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 [5, 6]. hiPSC-CMs are valuable models because of their resemblance to adult myocytes, especially in the electrophysiological behavior [7]. 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 [5, 4].

The hiPSC-CMs have been used in different fields: toxicity testing, study of certain diseases, pharmacological response, drug design etc. [6, 4, 8, 9, 10, 11]. 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 [12, 13, 14] and the modeling of drug effects, side effects and interactions was addressed in several works [15, 16, 17]. 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 [18]. 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 (Fig. 1(a)). Six independent experiments can thus be done with identical surrounding conditions at once [19].

![MEA with 6 wells](image1.png)

(a) MEA with 6 wells

![Well with 9 electrodes](image2.png)

(b) Well with 9 electrodes

Figure 1: Multichannel Systems device [19]. Panel (a): 60-6well MEA device. Panel (b): zoom on one well with the 9 electrodes (reproduced with permission).

The geometry used for the computation is two-dimensional. It models one layer of cells in a well, as represented in Fig. 1(b). 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 different configurations are averaged and compared to *in vitro* experiments for five different drugs (mexiletine, dofetilide, bepridil, ivabradine and BayK).

The paper is organized as follows. In Section 2, the mathematical models of the field potential and the drug-channel interactions are presented. In Sec-
tion, the simulation results are presented and compared with experimental measurements. Section 4 is dedicated to a discussion and some concluding remarks.

2. Materials and Methods

In this section, the methodology of the study is detailed. First, a mathematical model is presented to reproduce the experimental field potential \textit{in silico}. Then a strategy is proposed to reflect the strong variability observed in the experiments. The section ends with the approach used to model the action of compounds on the ion channels.

2.1. Electrophysiology of a monolayer of cells in a MEA

Since the culture of hiPSC-CMs is made of a monocellular layer, with a thickness $z_{thick}$ much smaller than the other dimensions, the domain occupied by the cells in a well is assumed to be two-dimensional (Fig. 1(b)). It is denoted by $\Omega$ and is schematically represented in Fig. 2(b).

The electrical activity of the tissue is described using the bidomain equations, which result from the homogenization of a microscopic model that takes into account both the intracellular and the extracellular media. For a
A detailed derivation of the bidomain model see for example [20, 21]. In the two-dimensional configuration of the MEA, these equations read:

\[
\begin{align*}
\mathcal{A}_M \left( C_M \frac{\partial V_M}{\partial t} + I_{ion} \right) - \text{div} \left( \sigma_I \nabla V_M \right) - \text{div} \left( \sigma_I \nabla u_e \right) &= \mathcal{A}_M I_{stim} \text{ in } \Omega \quad (1a) \\
- \text{div} \left( (\sigma_I + \sigma_E) \nabla u_e \right) - \text{div} \left( \sigma_I \nabla V_M \right) &= \frac{1}{z_{thick}} \sum_{e_k} \frac{I_{cl}}{|e_k|} \chi_{e_k} \text{ in } \Omega. \quad (1b) \\
\frac{d \mathbf{w}}{dt} - g(V_M, \mathbf{w}) &= 0 \quad \text{in } \Omega. \quad (1c)
\end{align*}
\]

where $|e_k|$ denotes the surface of the electrode $k$, and $\chi_{e_k}$ 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, $\sigma_I$ and $\sigma_E$ are respectively the intracellular and extracellular conductivities. The transmembrane ionic current $I_{ion}$ is provided by the model proposed in Paci et al [18]. This ionic model, based on the Hodgkin-Huxley theory [22] and represented by Equation (1c), reproduces the activity of auto-excitable hiPSC-CMs. It includes the activity of several transmembrane channels and the intracellular calcium exchanges. The state variables vector $\mathbf{w}$ consists of the concentrations of ions and the gate variables. The precise definition of function $g(V_M, \mathbf{w})$ can be found in the appendix of [18]. In Equation (1a), the current $I_{stim}$ is an external stimulation, which can be applied at a certain location of the domain for a certain duration. For the boundary conditions of the coupled problem, we impose that the flux of the intracellular potential $(V_M + u_e)$ over the boundary is equal to zero

\[
\sigma_I \nabla (V_M + u_e) \cdot \mathbf{n} = 0.
\]

For the extracellular potential, we use homogeneous Dirichlet boundary conditions ($u_e = 0$) on three edges connected to the ground, which has a "U" shape as shown in Fig1(b). For the remaining edge, we use a non flux boundary condition $\sigma_E \nabla u_e \cdot \mathbf{n} = 0$.

Let us now explain the source term added in Equation (1b) to model the presence of the electrodes. In a three-dimensional description, the following boundary condition should be introduced in the regions where the electrodes
are located \[23\]:

\[
σ_E \nabla u_e \cdot n = \frac{I_{el}^k}{|e_k|} \quad \text{on } e_k,
\]

where \( I_{el}^k \) is the electric current measured by the \( k^{th} \) electrode and computed using the electric model of Fig. 2(a) by solving the following ODE:

\[
\frac{dI_{el}^k}{dt} + \frac{I_{el}^k}{\tau} = \frac{C_{el}}{\tau} \frac{dU^k}{dt}
\]

with \( U^k = \frac{1}{|e_k|} \int_{e_k} u_e \, de_k \),

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. (3) we have introduced \( U^k \) as the mean value of the extracellular potential \( u_e \) over the electrode \( k \).

Since the thickness of the monolayer of cells \( z_{thick} \) is supposed to be very small compared to the other dimensions of the problem, we assume that all the variations along the \( z \)-direction are negligible compared to the variations along the directions \( x \) and \( y \). After some manipulations, condition (2) of the three-dimensional problem is transformed into the source term in the two-dimensional equation (1b). The field potential measured by electrode \( k \) is then computed as

\[
U_{fp}^k = R_i I_{el}^k.
\]

In Table 1 we provide the values of the macroscopic model parameters used in the simulations. For the tissue conductivity, we choose the values \( σ_i = 10 \mu \text{S cm}^{-1} \) and \( σ_e = 30 \mu \text{S cm}^{-1} \), in order to fit with the conduction velocity in the experimental data. These values are lower than conductivities in human cardiac tissue, due to the fact that in hiPSC-CMs the conduction velocity (CV) is much slower than in the human heart \[6\]. The CV obtained with the chosen conductivities is around 4cm/s. For the electrode model, we take a ground resistance \( R_i = 10^9 \Omega \) and an electrode resistance of \( R_{el} = 10^6 \Omega \). \( R_{el} \) was not introduced in the model provided in [23]. We introduce it in order to model as close to reality as possible the physical phenomena. Nevertheless, according to equation (3), the resistance \( R_{el} \) does not have any effect on the field potential since \( R_i = 10^9 \Omega >> R_{el} \). In [23], the authors prove that taking ground resistance values of \( 10^{12} \Omega \) and of \( 10^9 \Omega \) gives the same accuracy as a perfect electrode with infinite resistance. The value of \( C_{el} \) is in the range of manufacturer values provided in [23].

The system of partial differential equations is discretized in space with piecewise linear finite elements, and in time with a time stepping scheme [24].
We use a triangular mesh as shown in Figure 2(c). The full time and space numerical discretizations are given in the supplementary material, where we also provide a time convergence analysis. We have chosen the value of $\Delta t = 0.2\text{ms}$ in order to ensure a relative error lower than 1% on the action potential. The reference solution in this convergence analysis is obtained using a time step $\Delta t = 1\mu\text{s}$.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of membrane surface per volume</td>
<td>$A_M$</td>
<td>1200 cm$^{-1}$</td>
</tr>
<tr>
<td>Membrane specific capacitance</td>
<td>$C_M$</td>
<td>1 µF cm$^{-2}$</td>
</tr>
<tr>
<td>Intracellular conductivity</td>
<td>$\sigma_I$</td>
<td>10 µS cm$^{-1}$</td>
</tr>
<tr>
<td>Extracellular conductivity</td>
<td>$\sigma_E$</td>
<td>30 µS cm$^{-1}$</td>
</tr>
<tr>
<td>Electrodes capacitance</td>
<td>$C_{el}$</td>
<td>$10^{-10}$ F</td>
</tr>
<tr>
<td>Electrodes ground resistance</td>
<td>$R_i$</td>
<td>$10^9$ Ω</td>
</tr>
<tr>
<td>Electrodes internal resistance</td>
<td>$R_{el}$</td>
<td>$10^8$ Ω</td>
</tr>
<tr>
<td>$z$ thickness</td>
<td>$z_{thick}$</td>
<td>$10^{-4}$ cm</td>
</tr>
</tbody>
</table>

Table 1: Values of the parameters used in the simulations.

In Figure 3, we plot the time course of the simulated field potential for the 9 electrodes. The tissue was stimulated at the bottom-left corner with $I_{stim} = 150\text{A/cm}^2$. In this case, if we do not stimulate the tissue, all cells depolarize at the same time. The extra-cellular potential solution would then be equal to zero in the whole domain and the computed FP would also be equal to zero.

![Figure 3: Simulated field potentials over the 9 electrodes for ventricular-like hiPSC-CM without introducing any heterogeneity in the model.](image-url)
2.2. Handling the heterogeneity and the variability

2.2.1. Experimental observations and main hypotheses

The electrophysiological heterogeneity and variability are a prominent characteristic of stem cell preparations, as pointed out in different works [4, 6, 8, 26]. The heterogeneous behavior mainly comes from the intrinsic differences in the cell lines used in experiments and from the conditions under which the cells are differentiated. Patch-clamp measurements suggest a classification of the cells among three main phenotypes; atrial-, ventricular- and nodal-like. This classification is based on the comparison of their AP with adult cardiomyocytes’ AP. Distinction between atrial and ventricular-like is usually based on the following biomarker [4, 6]:

\[
RO = \frac{APD_{30-40}}{APD_{70-90}} \begin{cases} 
\leq 1.5 & \text{atrial-like} \\
> 1.5 & \text{ventricular-like}
\end{cases}
\]

where APD stands for action potential duration. This ratio measures the slope at the beginning of repolarization. A triangular shaped AP is classified as atrial-like. But still inside a phenotype, we observe large variations in the AP morphologies. For instance in [4], the variations of biomarkers such as AP amplitude, firing velocity and APD\textsubscript{90} inside each phenotype are studied and quantified. In a MEA well, the field potential signals collected by the electrodes at different locations are different in shape and behavior.
For instance, Fig. 4 shows the 9 experimental FPs in a MEA well: shape differences are striking. In Fig. 5(a), the results of a MEA experiment are presented: in the same environment conditions, the signals collected in the six wells exhibit great differences in amplitude, shape and frequency.

The in silico signals given by the model (1a)-(3) are reported in Figure 3 and are not in a good agreement with the experimental signals. Conjecturing that the discrepancy is due to the absence of heterogeneity in the in silico model, we will enrich our model with some new features detailed in the next subsections.
2.2.2. Modeling different phenotypes

In [18], the authors propose atrial- and ventricular-like ionic models: the main differences concern some channels conductances and the $I_{CaL}$ dynamics, which is the main responsible for the plateau phase. As a first attempt at modeling the electrophysiological heterogeneity, we introduce the two phenotypes in the same hiPSC-CMs preparation. The original domain is split into two different parts, as in the simple configuration of Fig. 6: $\Omega = \Omega_1 \cup \Omega_2$. Ventricular-like cells being the predominant phenotype [4], the ventricular model is solved in $\Omega_1$ and the atrial model in $\Omega_2$. As will be shown in Section 3, this strategy is not sufficient to qualitatively match the experimental signals, especially during the plateau phase. Recalling that the presence of two phenotypes mainly affect the slope at the end of the plateau and during the repolarization, we hypothesized that further heterogeneities should be included in the in silico experiments, in particular in the AP amplitude and in the plateau phase.

2.2.3. Transmembrane potential rescaling

According to the experimental measurements of Fig. 5, the interval between depolarization and repolarization is almost never flat and varies a lot among the different signals. We noticed that this behavior could be reproduced by creating a difference in the peak and in the plateau phase of the APs in different parts of the monolayer of cells. We rescale the transmembrane potential $V_M$: this way a gradient is encountered by the electrotonic current. The study by the Antzelevitch group [4] shows that the amplitude of the AP can vary from the registered mean value. The standard deviation of this variation is around 25% of the mean value of the amplitude in each
phenotype. We include this experimental evidence in the model by rescaling the transmembrane potential $V_M$ in one or more parts of the domain $\Omega$. Because of the absence of a detailed description of how the different cell phenotypes are distributed in the experiment, we try different repartitions. To understand the effect of the heterogeneities in that AP magnitude, we start with a simple splitting of the domain. As shown in Fig. 6, our goal is to simulate an action potential with a sufficiently high spatial gradient at the plateau phase, allowing to reproduce FPs with the same shape as the experimental signals. If we denote by $V_{\text{rest}}$ the resting potential of the Paci model and take $0 < c_1 < 1$ and $c_2 = (1 - c_1)V_{\text{rest}}$, by solving the following zero-D models

$$
\begin{aligned}
A_M \left( C_M \frac{d V_1}{d t} + I_{\text{ion}}(V_1, w_1, t) \right) &= 0 \\
\frac{d w_1}{d t} &= g(V_1, w_1, t),
\end{aligned}
$$

(4)

$$
\begin{aligned}
A_M \left( C_M \frac{d V_2}{d t} + c_1 I_{\text{ion}} \left( \frac{1}{c_1} (V_2 + c_2), w_2, t \right) \right) &= 0 \\
\frac{d w_2}{d t} &= g \left( \frac{1}{c_1} (V_2 + c_2), w_2, t \right).
\end{aligned}
$$

(5)

we obtain

$$
V_2 = c_1 V_1 - c_2 \quad \text{and} \quad w_1 = w_2.
$$

(6)

Since the standard deviation of the action potential magnitude variation is around 25% of the mean value of the amplitude in each phenotype [4], in what follows we will take $0.7 \leq c_1 \leq 1$. By splitting the domain $\Omega$ into two regions $\Omega_1$ and $\Omega_2$ as described in Fig. 6, we introduce the rescaling heterogeneity in the bidomain model as follows

$$
\begin{aligned}
A_M \left( C_M \frac{\partial V_M}{\partial t} + I_{\text{ion}}(V_M, w_1, t) \right) - \text{div} (\sigma I \nabla (V_M - u_e)) &= A_M I_{\text{stim}} \quad \text{in } \Omega_1 \\
\frac{d w_1}{d t} &= g(V_M, w_1, t) \quad \text{in } \Omega_1 \\
A_M \left( C_M \frac{\partial V_M}{\partial t} + c_1 I_{\text{ion}} \left( \frac{1}{c_1} (V_M + c_2), w_2, t \right) \right) - \text{div} (\sigma I \nabla (V_M - u_e)) &= A_M I_{\text{stim}} \quad \text{in } \Omega_2 \\
\frac{d w_2}{d t} &= g \left( \frac{1}{c_1} (V_M + c_2), w_2, t \right) \quad \text{in } \Omega_2.
\end{aligned}
$$

(7)
Equations (1a) and (1c) are replaced by the systems of equations (7). The electrotonic current introduced by the diffusion terms will avoid the discontinuity in the transmembrane potential at the interface between $\Omega_1$ and $\Omega_2$.

2.2.4. Arrangement in clusters

The splitting in two domains presented in Fig. 6 is clearly arbitrary. Here we consider other kinds of cell arrangements giving results which are also in good qualitative agreement with the experiments. The underlying ideas is to generate many different plausible configurations from which it will be possible to do statistics. This strategy allows us to limit the impact of arbitrary choices of cells distribution and can be a good way to circumvent the absence of information about the cell variability and heterogeneity in each well. A $10 \times 10$ grid of squares ($\omega_i$)$_{i=1,...,100}$ is introduced in $\Omega$. Let $\mathcal{I}_1$ and $\mathcal{I}_2$ be a partition of the set $\{1, \ldots, 100\}$. Each $\omega_i$ is assigned to one of the two subdomains introduced in Eq. (6): $\Omega_1 := \bigcup_{i \in \mathcal{I}_1} \omega_i$ and $\Omega_2 := \bigcup_{i \in \mathcal{I}_2} \omega_i$. Let $F$ be the fraction of domain $\Omega$ where the rescaling is employed, namely $F := |\Omega_2|/|\Omega|$ ($|\cdot|$ stands for the surface measure). We keep $F = 20\%$ and we randomly change the spatial arrangement of $\Omega_1$ and $\Omega_2$ for every simulation.

Two classes of configuration are considered: the “clustered” configurations, when $\Omega_2$ is a big connected part, and the “scattered” configurations, when $\Omega_2$ is scattered into multiple small subdomains. Examples of such configurations are given in Fig. 11.

2.2.5. Reproducing the field potential variability

Given the variability observed in the experiments (see e.g. the measurements for 6 different wells in Fig. 5(a)) and the uncertainties of the model, the exact in silico reproduction of a specific experiment would not make much sense. Instead, we propose to consider several scenarios and compute averages and standard deviations of quantities of interest. We indicate in this section how the scenarios are elaborated. In the subsections 2.2.2 and 2.2.3, two ways of reproducing the shape heterogeneity of the signals measured from hiPSC-CMs preparations have been investigated: the introduction of two phenotypes (atrial and ventricular types) and the introduction of a rescaling in the AP amplitude. We will use these two tools to generate various configurations. To do so, the domain is split as $\Omega = \Omega_1 \cup \Omega_2$ and we consider in $\Omega_1$ a ventricular model with a rescaling while in $\Omega_2$ we consider an atrial model. The splitting is performed by favoring clustered configura-
tions. The ventricular-like transmembrane potential is rescaled because the AP amplitude of ventricular cells is lower, in average, than the one of atrial cells [4]. Following the experimental results in [4] and taking to account the maturity and phenotype heterogeneities, we set the parameters $c_1$ and $c_2$ in order to reduce the magnitude of the AP by about 30% in $\Omega_2$.

### 2.3. 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 (see Fig. 13), 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. [16, 27]). 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 [28, 29, 15, 30]. The conductance of the targeted channel is reduced by a scaling factor in the following way:

$$g_s = g_{\text{control},s} \left[1 + \left(\frac{[D]}{IC_{50}}\right)^n\right]^{-1}, \quad (8)$$

where $g_{\text{control},s}$ 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.

### 3. Results

In this section, we first present the MEA signals given by our simulation and the impact of the modeling choices presented in subsection 2.2 to handle heterogeneity and variability. Next, in the second part of this section, we investigate the influence of drugs on numerical MEA signals and compare
them to experimental data. All *in silico* and *in vitro* signals that will be presented below are obtained without introducing any stimulation current. The firing occurs because of the pacemaker behavior of the cells, *in vitro* and *in silico*.

3.1. MEA signals simulation

![Figure 7: Field potentials measured by the 9 electrodes: comparison between experimental and simulation signals, obtained with the phenotype heterogeneity model.](image)

To start with, we consider an heterogeneous media with two different phenotypes as explained in Section 2.2.2. In Fig. 7, the results provided by our model (red lines) can be compared with experimental signals (blue lines). We observe that the depolarization is sharper in the simulations than in the experiments and that the shapes of the FP during the plateau phase exhibit significant differences. This motivates the use of the rescaling strategy, presented in Section 2.2.3. The results obtained with the rescaling are compared with the experimental measurements in Fig. 8. The simulation results (red lines) are now closer to the measured signals (blue lines). Even if polarity differences remain for some electrodes, the agreement is very good for electrodes 1, 2, 3 and 5. Globally, a comparison with Fig. 7 shows that the experimental measurements are better reproduced in the present case, especially in the depolarization and in the plateau phases.
Figure 8: Field potentials measured by the 9 electrodes: comparison between experimental and simulation signals, obtained with the transmembrane rescaling model (all cells are ventricular-like).

In Fig. 9(b) we present the simulated FP signals obtained with the rescaling procedure, which can be compared to those obtained without the rescaling procedure (Fig. 3). In Fig. 9(a), we show the corresponding action potential (AP) traces averaged over the electrodes. One could see that the magnitude of the transmembrane potential in the plateau phase is gradually rescaled from the left bottom to the right top corner. This gradation is due to the electrotonic effect. In Fig. 9(d) (respectively, Fig. 9(c)), we present the simulated FPs (respectively, APs) obtained when introducing only a phenotype heterogeneity. The repartition of cells phenotypes follows the example in Fig. 6, where in $\Omega_1$ we use ventricular model and in the domain $\Omega_2$, we use atrial cells model. One could see in Fig. 9(c) a gradation in the AP duration from the top right representing atrial phenotype to the bottom left corners representing ventricular phenotype. Also this result can be explained by the electrotonic effect. We observe that the rescaling allows to have numerical results closer to the experimental curves presented in Fig. 4. The level of heterogeneity is then quantified in the box plots presented of Fig. 10: the magnitudes of the repolarization peak (Fig. 10(a)) and of the depolarization-repolarization interval (Fig. 10(b)) show a significantly higher standard deviation when the rescaling strategy is introduced in the model.
In the absence of rescaling (Fig. 3) the tissue is stimulated at the bottom-left corner with $I_{\text{stim}} = 150 \ \mu\text{A cm}^{-2}$ for 1 ms to trigger the propagation. In all these simulation, we have considered a clustered configuration (as introduced in Section 2.2.4). Let us now compare the results obtained with the clustered and scattered repartitions of cells. In Fig. 11 and Fig. 12 a comparison of the results obtained with these two arrangements is shown: the clustered configuration produces a higher level of variability of the FP shapes and of the repolarization magnitude than the scattered one. This last configuration tends to flatten the effects of heterogeneity. These results are in agreement with experimental observations, since the differentiation between cells is distributed in a sort of clustered manner and also neighbour-
Figure 10: Effect of the rescaling heterogeneity on the plateau and repolarisation peak amplitudes of the field potential: Experimental data (first box), simulation with heterogeneity (second box) and simulation without heterogeneity (third box). Y-axis refers to voltage, values are in mV.

In all the simulations where heterogeneities are introduced (by phenotype or by AP rescaling), we did not introduce any stimulation.

3.2. Assessment of the hiPSC-CMs/MEA/Drug model

In this section, results for different compounds are presented, commented and compared with experimental observations. The experiments are performed with a 6-well MEA, all data are provided by Janssen Pharmaceuticals, Inc., and post-processed by Notocord®. A set of 54 in silico signals is generated as explained right above in order to compute some statistics and to assess that the general effects of the specific drug are well reproduced by the model. In the experimental data, we select from the 54 experimental...
Figure 11: Field potential shapes obtained with $F = 20\%$, with two different spatial arrangements (the black part is $\Omega_2$): on the left results for a “clustered configuration”, on the right results for a “scattered configuration”.

Figure 12: Repolarization magnitudes of the field potential collected by a single electrode for 10 clustered simulations (left) and 10 scattered simulations (right). All results obtained with $F = 20\%$.

signals those which are clean enough for extracting the different biomarkers. For the sake of clarity, the measurements and the simulations are presented for only one electrode. Figures containing the traces of the field potential for the 9 electrodes with multiple heart beats for both in vitro and in silico experiments are provided in the supplementary material.

3.2.1. Mexiletine

The effects of mexiletine on hiPSC-CMs are the blocks of the sodium and of the L-type calcium currents with $IC_{50,I_{Na}} = 106.25\mu M$ and $IC_{50,I_{CaL}} = 75\mu M$ [31]. Therefore this compound has an impact mainly on the depolarizing phase of cells, as can be observed in the measurements of Fig. 14(a). The same dose-dependent effects are observed in both experiments and sim-
Figure 13: Field potentials obtained with the phenotype heterogeneity model together with the rescaling of the ventricular-like $V_M$. 6 heterogeneity cases: change of the domain splitting and of the rescaling parameters $c_1$ and $c_2$ inside the physiological range.

Simulations (see the comparison of one beat in Fig. 14) blue lines correspond to control conditions, red lines to 50µM and black lines to 100µM. The reduction of the depolarization amplitude is well reproduced. The results obtained with a simulation of 4s are shown in Fig. 15. These curves correspond to one electrode and one configuration of cells. The frequency of firing is consistently reduced in presence of mexiletine. The same effect was observed in all the other studied configurations. In the paper by Harris et al. [9], it is observed that the beating is stopped in 3 out of 5 plates, with 30µM of mexiletine. Nevertheless, the present experimental data do not show this behavior. In order to get a more general assessment, we have reported in Table 2(a)-(b) the mean and standard deviation of the effect on the depolarization for six simulated wells (54 signals) and for the six experimental wells.
Figure 14: Comparison of the field potential between control conditions and 50µM and 100µM of mexiletine for one beat: experimental measurements (a) and simulations results (b).

Figure 15: Comparison of the field potential between control conditions and 50µM and 100µM of mexiletine for 4 seconds simulation.

For the experimental signals, a few electrodes with a too low signal to noise ratio were removed. The amplitude of the depolarization wave is computed as the absolute difference between the maximum and the minimum of the FP during depolarization. The relative depolarization amplitude (amplitude of the signal with the drug relative to the amplitude in control conditions) is computed as

\[ \text{RelAmpl}_{i,j} = \frac{Amp_{i,j}^{\text{dose}}}{Amp_{i,j}^{\text{control}}} \quad \text{for } i = i^{th} \text{ well, } j = j^{th} \text{ electrode}. \]  

(9)

This is a quantification of which fraction of the “control amplitude” is obtained with a certain dose. The mean values of our simulations confirm that the general effect of mexiletine is well reproduced: the higher the drug
concentration the smaller the absolute and relative amplitudes. The statis-

tics results on simulations and on experiments are comparable, especially the relative ones. The difference in control conditions between simulations (8.6241 ± 2.0071) and experiments (1.7425 ± 0.6374) might be due to an imperfect modeling of the electrodes. But rather that an absolute value, the important information is that the general trend is well captured by the model. In Table 2(c)-(d), we compare the statistics on the repolarization peak amplitude of experimental and simulated signals: a reduction is observed in both in vitro and in silico, but more pronounced in the latter. Regarding the repolarization time, we report in Table 3.2.1(a)-(b) statistics on the repolarization time (RT) with and without rate correction. Corrections follow Bazett’s formula. We observe that, without rate correction RT intervals are increase when introducing each drug dose. But in experiment, this effect is more pronounced with 50µM than with 100µM, which is not the case in the in silico simulations. When looking at the rate corrected repolarization times, we observe the same effect as without rate correction in the experimental data. But in the in silico results, we observe that the rate corrected RTs decrease with respect to the drug dose.

<table>
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<th>Std dev</th>
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Table 2: Statistics computed on simulated and experimental signals to assess the effect of mexiletine. Absolute values of mean and standard deviation of the depolarization amplitude and repolarization peak amplitude in control conditions and with 50µM and 100µM.
Table 3: Statistics computed on simulated and experimental signals to assess the effect of mexiletine. Repolarization time with and without rate correction in control conditions and for 50µM and 100µM drug doses.

3.2.2. Dofetilide

Dofetilide is known to block the $I_{Kr}$ channel with $IC_{50,I_{Kr}} = 5$ nM \[29\]. This induces a delay and a reduction of the peak amplitude in the repolarization phase. In Fig. 16, blue lines correspond to control conditions, red lines to 10nM and black lines to 50nM. In both experimental and simulation curves, we can notice the same dose-dependent delay of the repolarization wave and also a (slight) reduction of the peak amplitude of the repolarization.

In Table 4(c)-(d), we show the effect on the FP repolarization for different heterogeneity configurations. The reduction of the repolarization maximal amplitude (absolute values and values relative to control conditions) shows very high standard deviations. It is therefore difficult to draw a conclusion on this aspect. The delay of repolarization for a given dose is quantified as the difference between the instant of the repolarization peak in presence and absence of dofetilide:

$$TDelay_{i,j} = time_{repol,dose}^{i,j} - time_{repol,control}^{i,j} \quad \text{for } i = i^{th} \text{ well, } j = j^{th} \text{ electrode.}$$

We compute the rate correction of the time delay $TDelay^c$ using Bazett’s formula as follows

$$TDelay_{i,j}^c = \frac{time_{repol,dose}^{i,j} - time_{repol,control}^{i,j}}{\sqrt{RR_{dose}^{i,j}}} - \frac{time_{repol,control}^{i,j}}{\sqrt{RR_{control}^{i,j}}} \quad \text{for } i = i^{th} \text{ well, } j = j^{th} \text{ electrode.}$$

This delay, causing an increase of the signal duration, is well reproduced in all our simulations, as confirmed by the computed statistics in Table 4(e). Repolarization delay statistics in the experimental data are reported in Table...
Figure 16: Comparison between control conditions and 10nM and 50nM of dofetilide for one beat: experimental measurements (a) and simulations results (b).

We observe that the delay periods with and without rate correction are less pronounced in the experimental data than they are in the in silico results.

In Figure 16(c) and 16(d) we show multiple beats: one could see that dofetilide reduces the spike amplitude. This effect is clearly seen in in vitro experiments, as shown also by Table 4(a). The same effect is present also in silico, but it is less pronounced. As a consequence, we also see that dofetilide reduces beating rate of the stem cells. In fact, the cycle length in the simulated results is $0.903 \pm 0.028$ s (respectively, $1.114 \pm 0.043$ s, $1.349 \pm 0.037$ s) for the control (respectively, 10nM, 50nM) case. These unexpected effects have been reported in the case of in vitro experiments in the work by Qu and Vargas (2015) \([32]\). More figures on the effect of dofetilide on the nine electrodes extracted from one well are provided in the supplementary material.

3.2.3. BayK
Bay K8644 is an $I_{Ca,L}$ agonist, namely a drug that activates the L-type calcium channels by increasing the current in a dose-dependent manner. This
Table 4: Comparison of the effect of dofetilide on the field potential for both in silico and in vitro experiments. The comparison is evaluated on repolarization peak amplitude, depolarization amplitude and repolarization wave delay for doses 10 nM and 50 nM.

action evidently cannot be modeled with the conductance block formulation, because the conductance needs to be increased. The following relation models the effect of an agonist on a generic channel $s$ [33]:

$$g^A_s = g_s \left(1 + \frac{\alpha D^n}{K^n_A + D^n}\right).$$  \hspace{1cm} (12)

g^A_s$ is the conductance modified with the agonist, depending on the conductance in control conditions $g_s$, on the drug dose $D$, on the Hill coefficient $n$, on $\alpha$ (the maximal relative increase of the channel current induced by the agonist) and on the dissociation constant $K_A$. In Fig. [17] both the experimental and the simulation signals clearly show the expected prolongation of the plateau when BayK is added. The two doses of 1µM and 5µM produce almost the same effect (signals almost superposed), because they are close to the threshold of concentration after which the effect is at its maximum. This behavior is present in both experiments and simulations. The general effect
is always reproduced, as observed when running simulations for six different configurations. The plateau duration can be quantified as

$$P_{duration}^{i,j} = t_S^{i,j} - t_{repol}^{i,j} \quad \text{for } i = i^{th} \text{ well, } j = j^{th} \text{ electrode}, \quad (13)$$

$t_S^{i,j}$ being the time of the end of the depolarization and $t_{repol}$ the peak of the repolarization time. Table 5(a) (respectively, (b)) shows the mean values and the standard deviations of the plateau duration for the in silico (respectively, in vitro) signals for each drug dose. We observe that when adding BayK, the mean value increases dose-dependently. For the two doses, the mean values are very close for the reason explained above when commenting the superposed curved of Fig. 17. In Table 5(c)-(d) the effect of BayK on the T-peak magnitude is presented. We observe that this biomarker is decreased in the experimental data, whereas it is increased in simulation: for a dose of 5µM, the mean of the relative magnitude of the T-peak is 0.76 in experiments and 1.34 in simulations.

3.2.4. Ivabradine

Ivabradine is a compound which blocks the funny current $I_f$ with $IC_{50} = 2.1\mu M$ [34]. $I_f$ is only present in pacemaker cells and is able to give rise to instability during the resting potential phase. Therefore, the general effect of ivabradine is a decrease of the beating frequency, which can be observed on the measurements plotted in Fig. 18(a). In Fig. 18(b), the simulations results obtained with a specific configuration on one electrode are shown. In both experimental and computed signals, the frequency is slowed down as the concentration of ivabradine is increased. The drug does not alter the general

![Figure 17: Comparison between control conditions and 1µM and 5µM of BayK for one beat: experimental measurements and simulations results.](image-url)
Table 5: Comparison of the effect of BayK on the field potential for both in silico and in vitro experiments. The comparison is evaluated on repolarization peak amplitude and on the plateau duration for doses 1µM and 5µM.

<table>
<thead>
<tr>
<th>Plateau duration</th>
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<th>Mean (rate corrected)</th>
<th>SD (rate corrected)</th>
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<td>0.1240</td>
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<td>1µM BayK</td>
<td>0.1770</td>
<td>0.0609</td>
<td>0.1844</td>
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<td>5µM BayK</td>
<td>0.1802</td>
<td>0.0609</td>
<td>0.1858</td>
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</table>

<table>
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<th>Plateau duration</th>
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<th>Mean (rate corrected)</th>
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<td>0.0152</td>
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</tr>
<tr>
<td>1µM BayK</td>
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<td>0.0264</td>
<td>0.2419</td>
</tr>
<tr>
<td>5µM BayK</td>
<td>0.1855</td>
<td>0.0146</td>
<td>0.2616</td>
</tr>
</tbody>
</table>

3.2.5. Bepridil

As a last example, we reproduce the effects of bepridil, a compound that blocks multiple channels. The main action is on $I_{Kr}$, but for high doses it also affects the sodium channel $I_{Na}$ and the L-type calcium current $I_{CaL}$; the $IC_{50}$ values for the three channels are respectively 33nM, 3.7µM and 211nM [29]. In Fig. [20(b)], the doses of 1µM and 5µM are analyzed: at these concentrations, all the three channels are affected and the whole signal is dose-dependently changing. In our results in Fig. [20(b)], the repolarization wave almost disappears, the depolarization is enlarged and its amplitude decreases with the drug dose. The duration is slightly increased due to the fact that bepridil affects more $I_{Kr}$ than $I_{CaL}$. The same effects are also present in the experimental signals of Fig. [20(a)] but less pronounced: the
amplitude of the depolarization is reduced but the wave is not enlarged and
the peak of the repolarization is delayed but does not disappear. This can
be explained by the fact that the $IC_{50}$ values that we are using are not fitted
on the case of hiPSC-CMs but on guinea pig CMs. In the case of stem cells,
for bepridil, we expect that higher $IC_{50}$ values would better reproduce the
experimental signals. In Table 6, we quantify the action of bepridil on the

depolarization wave for the six simulations cases and the six wells, as done
for the case of mexiletine. The mean values confirm that the reduction of the
depolarization amplitude is reproduced by the simulations. Regarding the
experimental measurements, the standard deviations are very high, because
this set of data are noisy. As observed above, the computation results show
a more pronounced effect of the compound than the experiments.
Figure 19: Effect of Ivabradine on the activation rate: Comparison between control conditions and 5µM and 10µM, experimental measurements (left) and simulations results (right).

4. Discussion and conclusion

The main objective of the study was to introduce a mathematical model of MEA measurements on hiPSC-CMs. After its mathematical derivation, the model has been tested with several simulations and compared with experimental measurements. Many modelling hypotheses were justified by literature studies and experimental observations. Based on the works [6, 9, 11, 5], two different phenotypes have been introduced in the model and a variability in the action potential amplitudes has been taken into account. We do not have any information on how the cells are seeded in the monolayer preparation. According to the collected signals and to the simulation obtained with the mathematical model that we use, our hypothesis is that phenotypes are organized in a clustered manner.

Obtaining in silico signals that exactly match a specific experiment is very difficult and not necessarily desirable. The difficulty comes from various experimental uncertainties. However, the model was able to qualitatively reproduce the main features observed in the experiments. This proved to be sufficient to detect the effect of drugs, which were studied with the pore block model. MEA pharmaceutical experiments were simulated for five different compounds. Again, the assessment was not done by a point to point comparison, which would not make sense given the variability of the experiments.
Instead, it was performed by considering average trends of biomarkers. For Mexiletine, our study shows a good agreement in terms of depolarization and repolarization peak amplitudes between in vitro and in silico results. On the contrary, the comparison on the repolarization times shows that the effect of Mexiletine of the RT without rate correction is not monotonous with the value of the drug dose in the in vitro measurements, whereas it is in the in silico data. However, when introducing rate correction we obtain this non-monotonicity for both in silico in vitro signals, but still more pronounced in experiments than it is in simulations. For dobutilide, both in silico and in vitro models show a repolarization delay and a reduction of the repolarization peak amplitude with the drug doses. However, the effect of dobutilide on the depolarization amplitude was very small in simulation compared to what it is in experiments. A high effect of dobutilide on the depolarization is not expected because it is not supposed to affect the sodium current. This unexpected effect has been reported in the experimental study by Qu and Vargas (2015) [32] where for high doses of dobutilide early after depolarization waves appear and may consequently alter the sodium current in the depolarization. This could explain the reduction of the depolarization wave magnitude. More investigations on both in vitro and in silico experiments are needed in order to clarify this issue. For BayK, we obtained a good agreement between simulation and experiment in terms of repolarization delay due to an increase of the plateau duration. However, both models provide do not agree on the effect of BayK on the depolarization magnitude. While in experiments we observe a decrease of this biomarker, in the simulation we observe a pronounced increase of the depolarization magnitude with the drug dose. The reason of
this contradictory effect is not clear, it could be related to the formulation of the calcium current in the Paci et al [18] model. Again more investigations are needed in order to elucidate this question. For bepridil, both models are in agreement in the effect of the drug on the reduction of depolarization amplitude which is more pronounced in the in silico model. For Ivabradine both models are also in agreement its effect on prolonging cycle length with a higher effect in the in vitro model. Even if for some compounds the effect was more pronounced in the simulations than in the experiments, the in silico model generally gave results in good agreement with the experiments. Many aspects of the modelling approach could be improved.

- Some parameters used for the bidomain equations such as the intracellular and extra-cellular conductivities are not based on experimental values. Their values are less than the conductivities in the cardiac tissue. This is in agreement with the findings of Blazeski et al [6], where it has been shown that for hIPSC-CM the conduction velocity (CV) is much slower than in a normal human heart. However, this could be related to other factors that are not taken into account in our model, such as gap junctions. The values that we introduced have been chosen to fit the CV in the in vitro experiment.

- The heterogeneity of the hiPSC-CMs preparations has been modeled in a somehow arbitrary way, with mainly qualitative arguments. Even if an averaging procedure allows to limit the consequences of this arbitrariness, it would be more satisfactory to rely on a better experimental characterization of the phenotypes repartition in the monolayer model.

- The ionic model is not necessarily well adapted to the hiPSC-CMs used in the experiments, even if it was designed for stem cells. For instance, there is no description of late sodium current in the Paci model and this limitation moderates the results obtained on the effect of mexiletine on the field potential.

- When computing the different biomarkers quantities on the QRS and the repolarization wave, we only perform rate variability corrections when computing time intervals or delays. For the magnitude related biomarkers, the only correction that we introduce is to compute relative quantities with respect to the control case.
• The parameters used for the drug model, like the IC\textsubscript{50} values, do not necessarily correspond to the parameters of hiPSC-CMs.

In spite of all these limitations, this multiscale approach, which combines physiologically detailed ionic models with the bidomain equations and a model of a MEA device, is able to reproduce the correct trends of the effect of drugs. It might therefore be a valuable tool to analyze the signals acquired by MEAs: given a series of measurements corresponding to different doses of a compound, parameter identification algorithms could be used to automatically identify which channels were affected. This is the object of an ongoing work.

5. Acknowledgments

This work was partially supported by the French National Agency of Research through the grant ANR-13-LAB1-0007 (LabCom “CardioXcomp”). We would like to thank Janssen Pharmaceutica NV for providing us with the raw data, and David Labarre, Fabien Raphel and Christophe Bleunven for many fruitful discussions and for their assistance to deal with the experimental data.

6. References


[34] A. Bucchi, M. Baruscotti, M. Nardini, A. Barbuti, S. Micheloni, M. Bolognesi, D. DiFrancesco, Identification of the molecular site of ivabradine binding to hcn4 channels, PloS one 8 (1) (2013) e53132.