From Field Potential Waves to Ionic Current Knowledge by Leveraging Mathematical Modeling

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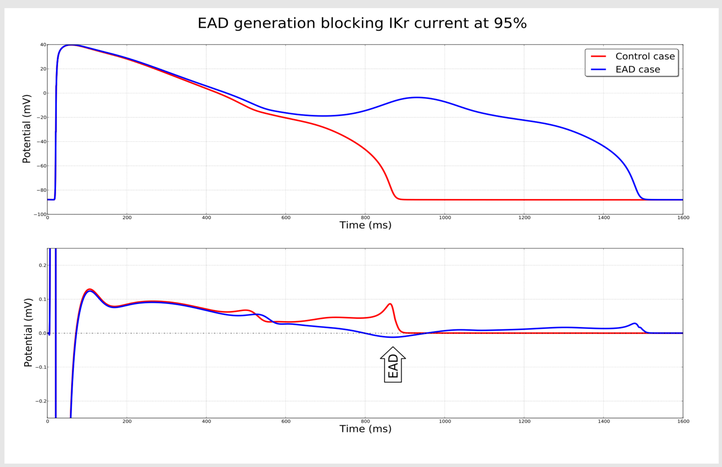
Objectives

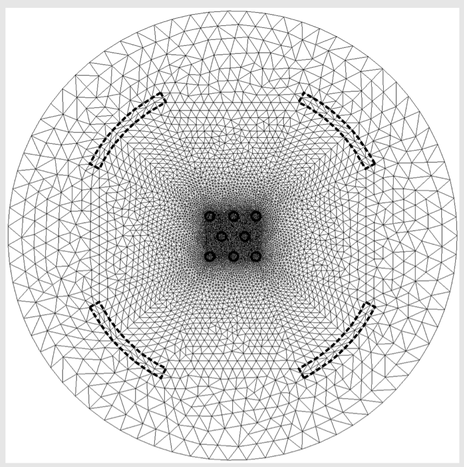
- The combined use of :
  - microelectrode arrays (MEAs).
  - induced pluripotent stem cells cardiomyocytes (hiPSC-CMs) allows high-throughput screening on human-derived cells.
- But the field potential (FP) signals acquired by MEAs are difficult to analyze.
- Objectives:
  - **Direct problem**: propose a mathematical model of MEA signals.
  - **Inverse problem**: use this model to identify channel activities.
  - **Classification**: use a hybrid modeling/machine learning approach to classify compounds.

Direct problem: concept

- Bidomain equations: electrophysiological model to get both transmembrane potential and extracellular potential.
- Ionic models: phenomenological (Minimal Ventricular,...) or physiological (Paci, O'Hara-Rudy,...).
- Electrode model: for the culture-electrode contact.
- Devices: well modeling.

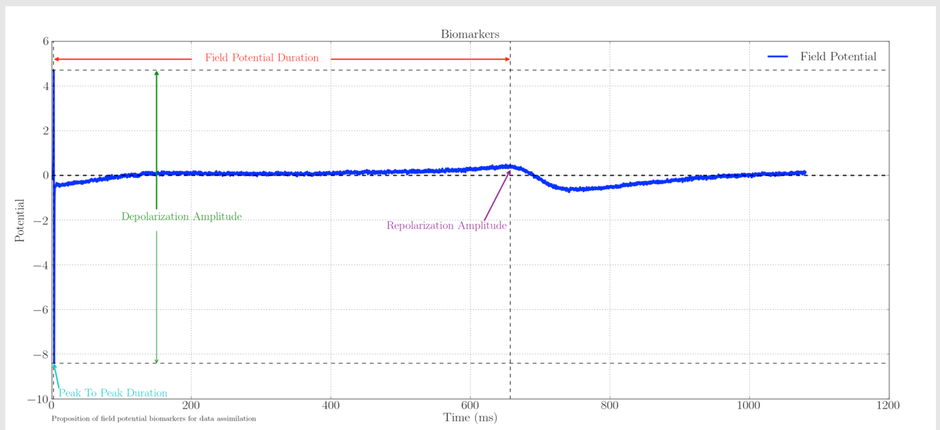
Example : an Early After Depolarization simulation, O'Hara-Rudy model (O'Hara *et al.*, PLOS Comp Biol 2011), 96-well of 8 electrodes device (Axion)





Inverse problem: method

- Extraction of 3 biomarkers from **real signals** with NOTOCORD-fps: depolarization amplitude (DA), repolarization amplitude (RA) and field potential duration (FPD).



- Identification of channel conductance by minimizing the cost function:

$$J(\theta) = \sum_{k=1}^{N_{elec}} \left(\frac{DA^k_{meas}}{DA^k_{c,meas}} - \frac{DA^k(\theta)}{DA^k_c} \right)^2 + \left(\frac{RA^k_{meas}}{RA^k_{c,meas}} - \frac{RA^k(\theta)}{RA^k_c} \right)^2 + \left(\frac{FPD^k_{meas}}{FPD^k_{c,meas}} - \frac{FPD^k(\theta)}{FPD^k_c} \right)^2$$

X^k_{meas}: experimental biomarker at electrode k (with compound)

$X^k(\theta)$: *in silico* biomarker at electrode k with channel conductances θ

$X^k_{c,meas}$: control experimental biomarker at electrode k (without compound)

X^k_c: control *in silico* biomarker at electrode k

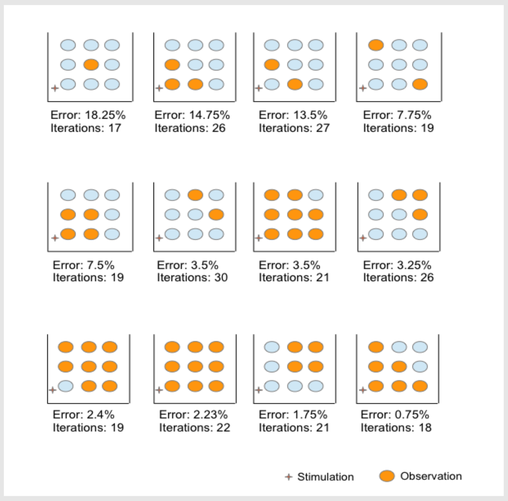
with $X = DA, RA$ or FPD

Inverse problem: number of electrodes for the observation

- Model: MV.
- Device: 6-well of 9 electrodes (MCS).
- Data: synthetic.
- Identification of the conductance of the fast inward currents.
- By observing 1, 2, 3, 4, 6, 8 or 9 electrodes.

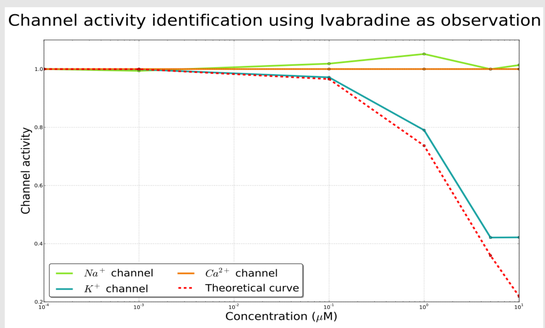
➔ the error on the identification of the conductance depends on the relative positions of the electrodes and of the initial activation.

➔ it is worth keeping all the electrodes.



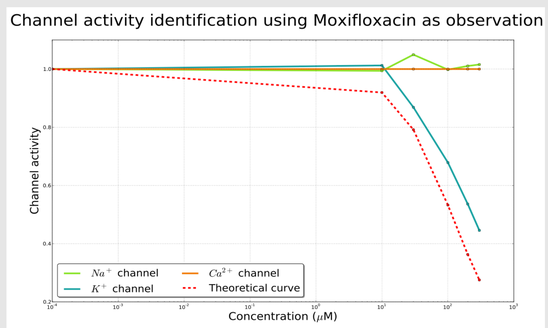
Inverse problem: channel activity identification

- **IC50 estimation of real data with the inverse problem approach**
  - Model: MV.
  - Data: real experiments (CDI) processed with NOTOCORD-fps.
  - Identification of 3 channel conductances: fast inward, slow inward and outward currents (denoted "Na+", "Ca2+", "K+" for simplicity).
  - Theoretical curves obtained with the published IC50 and the function: $f(c) = \left(1 + \frac{c}{IC_{50}}\right)^{-1}$



Ivabradine

IC_{50} identified *in silico* $\approx 3.7\mu M$
Theoretical curve with $IC_{50}(I_{Kf}) = 2.8\mu M$
(Shattock et al.- British J Cardiology, 2006)

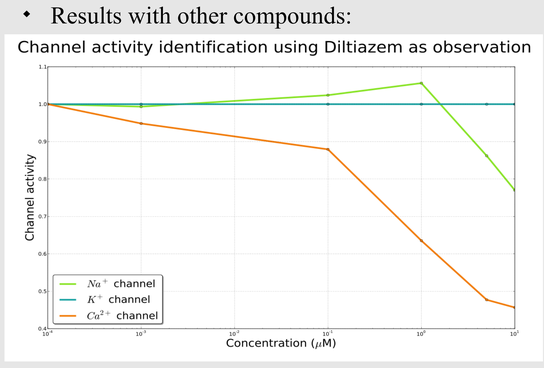


Moxifloxacin

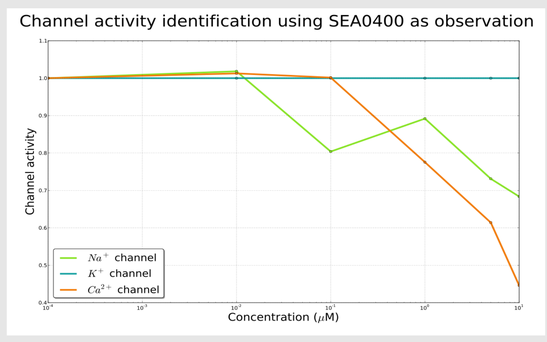
IC_{50} identified *in silico* $\approx 220\mu M$
Theoretical curve with $IC_{50}(I_{Kr}) = 114\mu M$
(Alexandrou et al., British J Pharmacol. 2006)

➔ realistic values of IC50 found by the inverse problem approach.

- Results with other compounds:



Diltiazem



SEA0400

Classification

- **Training with real experimental data**

Classification probabilities obtained with SVM using experimental data* for training

Means (8 electrodes tested per drug)

	Ivabradine	Mexiletine	Moxifloxacin	Diltiazem	JNJ303	Dofetilide	BayK**	SEA0400	Ranolazine	Nimodipine
Na antagonist	0.0	**0.98**	0.04	**0.48**	0.16	0.0	0.0	0.04	**0.38**	0.03
K antagonist	**1.0**	0.0	0.0	0.0	0.0	**1.0**	0.0	0.0	0.0	0.0
Ca antagonist	0.0	0.01	**0.66**	0.43	0.41	0.0	0.1	**0.86**	0.33	**0.92**
Ca agonist	0.0	0.01	0.3	0.08	**0.43**	0.0	**0.9**	0.1	0.29	0.05

*Ivabradine, Mexiletine, BayK and SEA0400 (as a Calcium blocker). **4 electrodes tested for the prediction.

Best probability / Expected solution

➔ Moxifloxacin, Diltiazem, JNJ303 are not correctly classified.

- **Training with 4096 in silico experiments (results of simulation of a simplified model)**

Classification probabilities obtained with SVM using MV model (4K samples) for training

Means (8 electrodes tested per drug)

	Ivabradine	Mexiletine	Moxifloxacin	Diltiazem	JNJ303	Dofetilide	BayK*	SEA0400	Ranolazine	Nimodipine
Na antagonist	0.0	**0.99**	0.0	0.01	0.22	0.0	0.1	0.0	0.39	0.0
Na agonist	0.05	0.0	0.14	0.0	0.0	0.0	0.12	0.0	0.0	0.01
K antagonist	0.0	0.0	**0.8**	0.0	**0.77**	0.0	0.0	0.0	**0.61**	0.0
K agonist	0.0	0.0	0.0	0.22	0.0	0.0	**0.39**	0.42	0.0	**0.68**
Ca antagonist	0.0	0.0	0.01	**0.77**	0.0	0.0	0.0	**0.58**	0.0	0.31
Ca agonist	**0.95**	0.0	0.05	0.0	0.01	**1.0**	**0.39**	0.0	0.0	0.0

*4 electrodes tested for the prediction.

Best probability / Expected solution

➔ Ivabradine, Dofetilide, Ranolazine, Nimodipine are not correctly classified.

- **Training with the real experimental data and the 4096 in silico experiments**

Classification probabilities obtained with SVM using MV model (4K samples) and experimental data* for training

Means (8 electrodes tested per drug)

	Ivabradine	Mexiletine	Moxifloxacin	Diltiazem	JNJ303	Dofetilide	BayK**	SEA0400	Ranolazine	Nimodipine
Na antagonist	0.0	**0.96**	0.0	0.0	0.19	0.0	0.01	0.0	**0.51**	0.01
Na agonist	0.0	0.0	0.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0
K antagonist	**0.83**	0.0	**0.6**	0.0	**0.73**	**0.98**	0.0	0.0	0.48	0.0
K agonist	0.0	0.0	0.0	0.12	0.0	0.0	0.0	0.45	0.0	0.48
Ca antagonist	0.0	0.03	0.05	**0.87**	0.01	0.01	0.0	**0.54**	0.01	**0.51**
Ca agonist	0.17	0.0	0.19	0.0	0.06	0.01	**0.99**	0.0	0.0	0.0

*Ivabradine, BayK and SEA0400 (as a Calcium blocker). **4 electrodes tested for the prediction.

Best probability / Expected solution

➔ By mixing real and *in silico* data for the training, all the compounds are correctly classified.

Conclusion

- We proposed a mathematical model of MEA (direct and inverse problems) and we trained a machine learning algorithm with real and in silico signals.
- Direct problem: allow to reproduce *in silico* observed phenomena and better understand some features of the signals (EAD, …).
- Inverse problem: identify the channel activity from synthetic and real signals, determine IC50.
- Limitations and future work:
  - The cell model used for the inverse problem should be replaced by a more comprehensive one.
  - To improve inverse problems and classification, additional biomarkers should be identified on the FP.
  - Machine learning algorithm has to be trained with more experimental and synthetic signals.
  - The overall methodology has to be tested with more compounds.