Coupled impedance & field potential data analysis of in vitro cardiomyocyte assays

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Coupled Impedance & Field Potential Data Analysis of in vitro Cardiomyocyte Assays

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Background. One goal of the Comprehensive in vitro ProArrhythmia Assay initiative is to predict more accurately potentially torsadogenic compounds in an earlier stage of drug development. To that aim one of the CiPA component is to assess capabilities of label-free in vitro assays (impedance and extracellular field potential signals) applied to human stem cell-derived cardiomyocytes.

Objectives

Impedance and extracellular field potential signals belong to the class of **high-content data** for which the most challenging issue to be addressed is to identify **predictive biomarkers of cardiotoxicity** in a large amount of data. To that aim, **new statistical signal-processing methods** are needed and the objective of this study is to develop a non-supervized technique able to rank the contractility and electrophysiological effects of tested compounds.

Methods

The CardioExcyte 96 (Nanion Technologies Gmbh) is used to measure both **impedance** and **extracellular field potential** signals on two **CiPA** compounds applied to cardiomyocytes. The developed method for data processing firstly computes nine numerical indicators. They characterize the time variations of frequency, amplitude, shape and irregularity of cell impedance and field potential signals. The ninth parameter is the cardiomyocyte viability index. In a second phase, statistical tests are applied on each characteristics to evaluate the concentration effect of the tested compounds. Finally, results of the previous statistical results are aggregated in a **cardio-effect score**, graduated from 0 (no influence) to 18 (highly disturbed beating). This innovative approach was tested using in vitro data obtained from two molecules (1 cardiotoxic and 1 non-cardiotoxic compounds).

Results

Results have emphasized some **correlations** but also some **differences** between the cardio-effects detected between the two types of signals. For the first tested compound, the absence of effects is detected by the two measurements. For the second compound, effects are detected but the modified characteristics are different in impedance and field potential signals.

Conclusion

The proposed computation method automates the combined analysis of impedance and extracellular field potential measurements on cardiomyocytes. Complementary effects have been **detected** by the data analysis for the impedance and field potential signals. This comparative study will be soon extended to a larger batch of molecules for **validation**

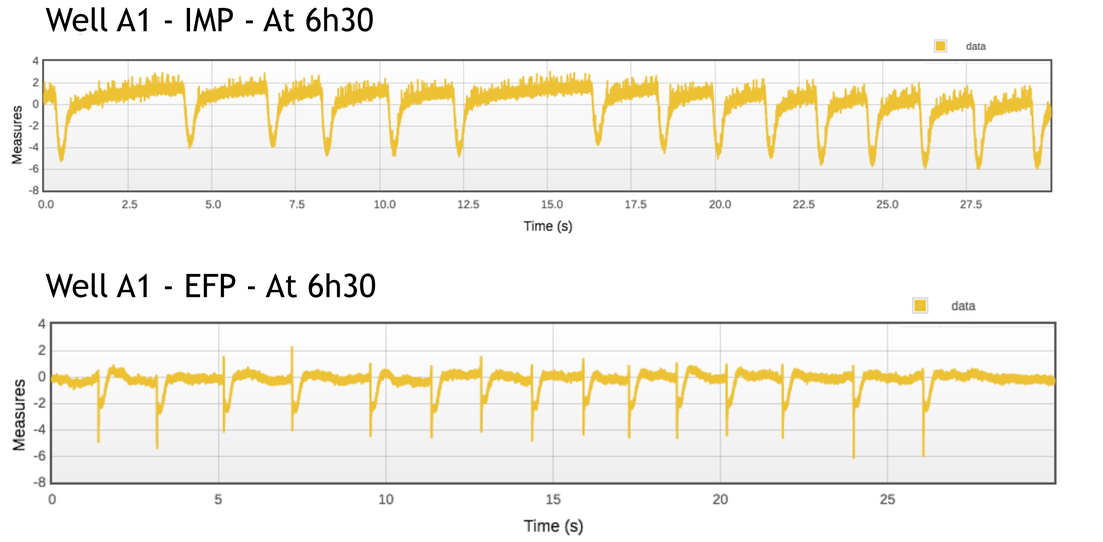
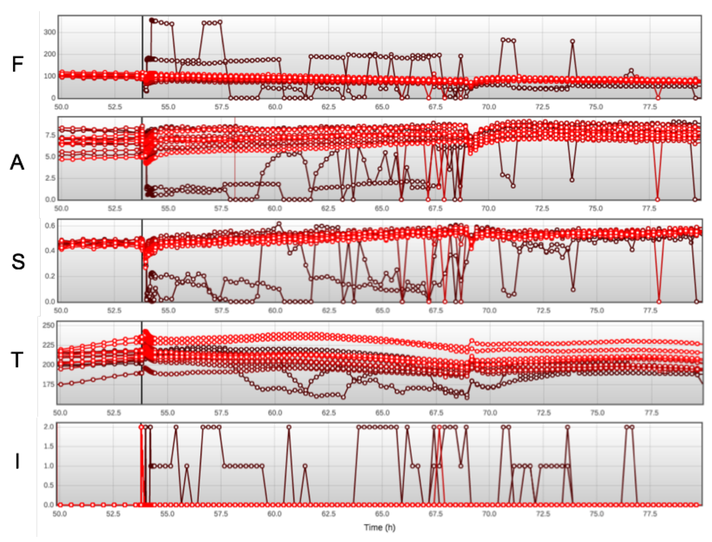


Fig.1: Two types of signals
Top : Impedance (IMP). Bottom: Extracellular field potential (EFP)



F: Frequency (bpm)

A: Peak-to-Peak Amplitude

S: Beating Shape

T: Cell Impedance Trend

I: Beating Irregularity

Fig.2: Characterization of each sweep with 5 indicators (IMP) among the time (4 indicators for EFP)

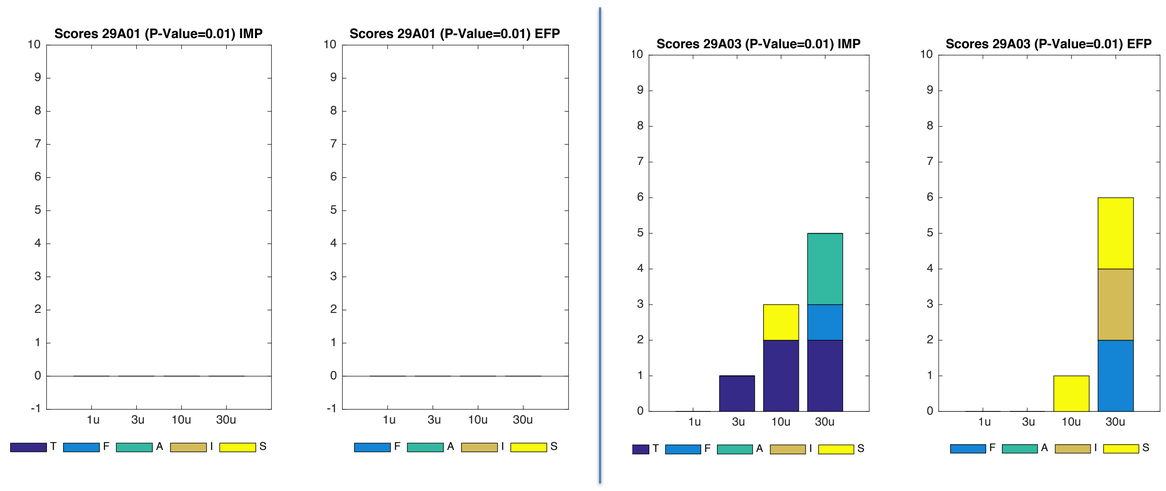


Fig.3: Scores calculated on all indicators. Left: No statistically significant effect. Right: A dose-response information appears but on different indicators between IMP and EFP

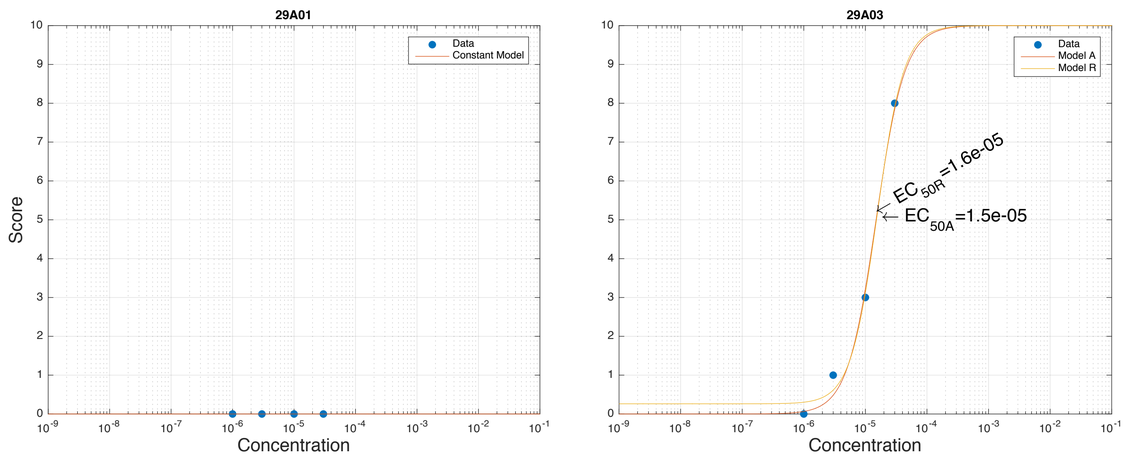


Fig.4: Estimation of the EC50 profiles. Left: Flat model meaning no effect. Right: EC50 values estimation based on the Hill's model

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