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Customer App Note

MEA Based Cardiac-Electronic Interface: A Novel Resource for AP Measurements

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Since the early 1970s, micro-electrode array (MEA) systems have been used to study the bioelectric properties of excitable cells[1-4]. Joshi-Mukherjee and colleagues[5] recently discovered a novel application of MEA technology for high-throughput action potential (AP) measurements. Multiwell PEDOT MEAs (24W300/30G-288) from Multi Channel Systems (MCS) were employed to generate AP waveforms simultaneously recorded from several independent hiPSC-cardiomyocyte (hiPSC-CM) constructs. In addition, multiple AP recordings from the same cell site across several days allowed long-term electrophysiological study of the same preparation, without any detrimental effect, thus validating the approach for longitudinal studies. The current gold standard techniques of patch-clamp and optical mapping require specialized training to conduct experiments whereas, MEA-based AP studies are simple to setup and the methodology is straightforward.

Employing low voltage pulses (for parameters see reference 5), we gain access to the inside of the cells within seconds and record APs from the same cell site, over days, showing no detrimental effect on the electrogenic properties of the cellular network (Figure 1A). We also show that one can easily record high quality AP signals in milli-volt ranges, requiring minimal filtering from the same cell site multiple times (Figure 1B).

In order to confirm AP amplitude dependence on the sodium current (I_{Na}), voltage gated sodium channels were blocked with tetrodotoxin (TTX). Indeed, we observed a dose dependent attenuation of the AP amplitude and excitability (Figure 1C). Recently, a few studies have reported the ability of MEA systems to record APs but they did not conduct an in-depth AP study to demonstrate the reliability of their devices[6-12].

Unlike conventional MEAs, our cardiac PEDOT MEA model (1) allows for non-invasive electrophysiological studies from multiple independent monolayer constructs; (2) it is a powerful, high-fidelity tool for observing the long-term effect of ion channels, signaling molecules, and gene expression on the AP; (3) it overcomes the limitation of single use, one at a time monolayer studies that could yield misleading results due to short-term electrophysiological effects; and (4) it permits simultaneous measurement of field potential and action potential (FP/AP) thereby generating libraries of extracellular and intracellular potential data, from the same cell site.

A MATLAB workflow, designed in the lab, was used to automate extraction and analysis of large volumes of experimental data, illustrating the reliability of this high-throughput model for AP studies.

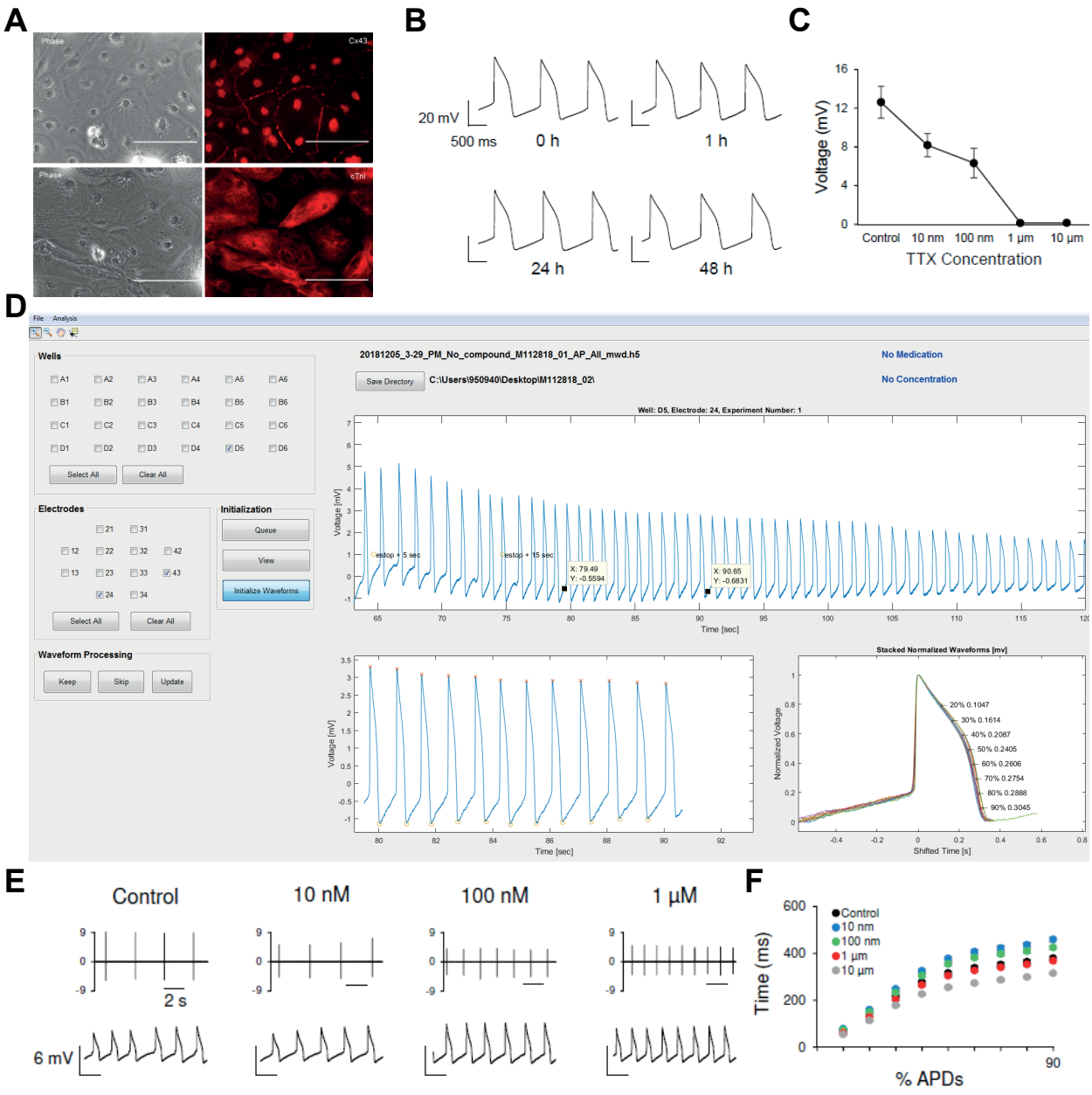

Figure 1:

Human iPSC-derived cardiomyocyte network on multiwell PEDOT MEA expressing cardiac markers (Cx43 (top right panel) and troponin I (bottom right panel)) showing no detrimental effect of electroporation on cellular network (A). Multiple electroporation allow action potential (AP) recordings from the same cell site across several days (B). Tetrodotoxin (TTX) dose dependent attenuation of the AP amplitude and excitability confirms dependency of sodium current (INa) (C). A custom Matlab graphical user interface (GUI) and code was combined with Matlab Signal Processing and Statistics and Machine Learning Toolboxes to produce a signal extraction, quality assurance, and segmentation workflow (D). Pharmacological responsiveness to catecholamine with dose-dependent increase in heart rate to norepinephrine (E) and shortening of repolarization (AP duration) (F)

Additionally, the cardiac PEDOT MEA model recapitulated cardiac physiological responses thus extending its application for the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative for drug screening for arrhythmia (Figure 1E and F).
Overall, MEA systems can be employed for recording APs from cardiomyocytes of various origins.

Biological Applications

This novel MEA based approach for AP measurements holds the potential to transform many areas of basic and clinical research. It will be of interest not only to electrophysiologists but also to cell biologists and in-silico modelers to simplify the study of cellular electrophysiology.
FDA has proposed the use of Mutliwell MEA and hiPSC-CMs for drug screening and arrhythmia studies. Thus, availability of FP/AP data libraries from the same cell site on hiPSC-CMs, along with other cellular and molecular data, will offer novel insights to membrane electrophysiology for drug development and in the understanding of disease.
Additionally, it will enable researchers to quickly generate large electrobiomic data libraries from a wide array of excitable cellular networks. These bioelectric resource libraries will be of great value to the scientific community for future drug discoveries and therapeutic approaches.
The advantages of this approach are several but further advancements in MEA system design are needed to overcome the limitations of rate-dependent AP measurement and the upstroke of the APs remains to be calibrated.

Conclusion

The cardiac PEDOT MEA model presents a unique cardio-electronic interface that allows high-fidelity measurements of APs for cardiomyocyte development and maturation studies. It is a high-throughput platform for screening novel cardio-factors. The effect of diseases or mutations on cardiac development and maturation could easily be studied on the same cells for an extended period of time.
Furthermore, membrane rupture and repair are of clinical significance in age-associated cardiomyopathies and thus subtle changes in APs over a period of time might have implications on cardiomyocyte pathophysiology.
Overall, continous / non-terminal, high-throughput, long-term AP measurements and modulations will advance our understanding of cardiac biology and arrhythmia. By making these high-quality Multiwell PEDOT MEA interface systems more broadly accessible to the scientific community, MCS is helping these technologies reach their full potential to transform the scientific and clinical research realms.

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