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Other Conference Item

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Publication date:
2018-07

Permanent link:
https://doi.org/10.3929/ethz-b-000322045

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Originally published in:

Funding acknowledgement:
694829 - Microtechnology and integrated microsystems to investigate neuronal networks across scales (EC)
Title
Comparison of axonal-conduction velocity in developing primary cells and human iPSC-derived neurons

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Abstract
Neurons communicate through action potentials propagating along axons. In developing cell cultures, axonal arbor outgrowth indicates the formation of synaptic connections between neurons, which form networks. As axons regulate the transfer of information, we hypothesize that axonal conduction characteristics, e.g., axonal action potential amplitude and propagation velocity, may be indicative of the maturation state of cells and the strength of interneuronal connections.

Here, we investigated the axonal-conduction characteristics of individual neurons, which have been tracked across multiple days. Using a high-density microelectrode array (HD-MEA, MaxOne, MaxWell Biosystems), we performed electrical imaging of 2-dimensional cell culture samples and identified single neurons. The HD-MEAs were used to detect extracellular action potentials (EAPs) at sub-cellular resolution and to extract the shapes of axonal arbors by means of spike-triggered averaging (Bakkum et al., Nature Communications, 2013). We plated the following cell types on the HD-MEA dishes: (1) primary cortical cells and (2) hippocampal cells from Wistar rats (embryonic day 18); human-induced-pluripotential-stem-cell (h-iPSC)-derived dopaminergic neurons (iCell DopaNeurons, Cellular Dynamics International or CDI, USA) in (3) monoculture and (4) in co-culture with h-iPSC-derived astrocytes (iCell Astrocytes, CDI, USA); (5) h-iPSC-derived dopaminergic neurons modeling Parkinson’s disease (myCell A53T DopaNeurons, CDI, USA) in monoculture and (6) in co-culture with h-iPSC-derived astrocytes.

Upon extraction of axonal morphologies through spike-triggered averaging, we computed the propagation velocity of the axonal action potentials per neuron. We observed that across multiple days, both, the spike amplitude and propagation velocity increased during development of healthy cells in culture. We compared axonal conduction features between primary cells and h-iPSC derived neurons in healthy and diseased state and found significant differences. In summary, HD-MEAs with sufficient SNRs provided a reliable platform for label-free and long-term investigation of axonal functions in h-iPSC neuronal cultures. Our results indicated that axonal conduction velocity may be a valuable functional parameter for disease modeling, drug discovery, and safety pharmacology.

Acknowledgements
Financial support through the H2020 ERC Advanced Grant 2015 - 694829 “neuroXscales” (Microtechnology and integrated microsystems to investigate neuronal networks across scales) and Project CTI-No. 25933.2 PFLS-LS (Multi-well electrophysiology platform for high-throughput cell-based assays) are acknowledged.

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