A robust, high-throughput electrophysiology platform for drug screening in a peripheral Nerve-on-a-Chip microphysiological system

Corey Rountree[1], Monica Metea[2], Michael J. Moore[1,3], J. Lowry Curley[1]

[1]AxoSim Inc, New Orleans, LA; [2]Preclinical Electrophysiology Consulting LLC, Boston, MA; [3]Dept. of Biomedical Engineering, Tulane University, New Orleans, LA

Correspondence: lowry.curley@axosim.com

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Abstract 31

Overview

Microphysiological systems (MPS) have the potential to better inform preclinical stages of drug development by enabling toxicity screening with systems that mimic in vivo physiology. These systems are attracting attention from the pharmaceutical industry in the hope they will curb attrition rates, lower costs, and reduce reliance on animal models. AxoSim has developed an innovative MPS, the NerveSim® platform, for screening neurotoxic compounds using an embedded electrode array (EEA) to record compound action potentials (CAPs) from peripheral nerve cultures. The efficacy of this system was demonstrated by recording from cultured rat sensory dorsal root ganglia (DRG) exposed to Paclitaxel (PTX), a chemotherapeutic known to cause peripheral neuropathy.

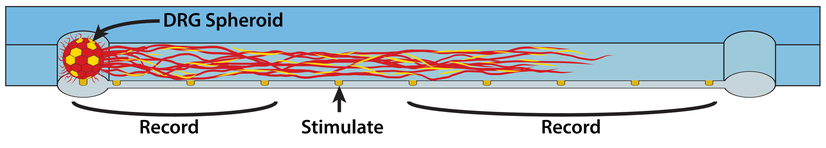
Embedded Electrode Arrays

Design: Custom 24-well tissue culture plate with 10 microelectrodes per well that can be used for recording or stimulation.

Microphysiological system: Guide axonal growth of dissociated rat DRG spheroids along electrode array to mimic nerve fiber tract.

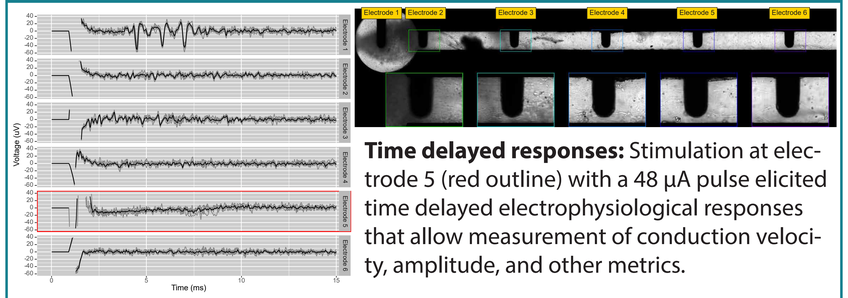
Study Design

Neurotoxic Compounds Dosing: Paclitaxel (PTX) was applied at 200 nM and 500 nM levels, as well as a vehicle control, to NerveSim® cultures for 7 days before measuring electrophysiology.



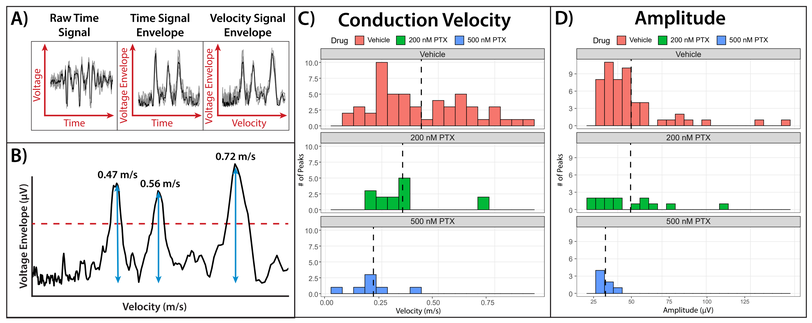
Electrophysiology: NerveSim® EEA cultures were stimulated in parallel at multiple distal sites at DIV35 with a stimulation current ramp (1 to 71 µA) while recording CAPs at the DRG body and axons.

Microelectrode Electrophysiology



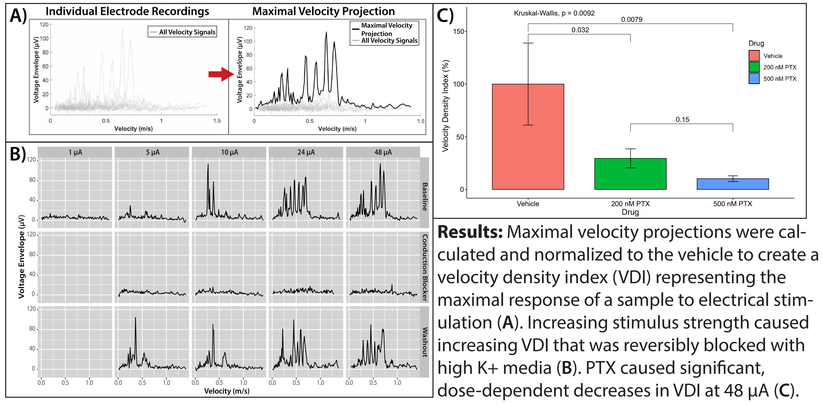
Time delayed responses: Stimulation at electrode 5 (red outline) with a 48 µA pulse elicited time delayed electrophysiological responses that allow measurement of conduction velocity, amplitude, and other metrics.

Compound Action Potentials



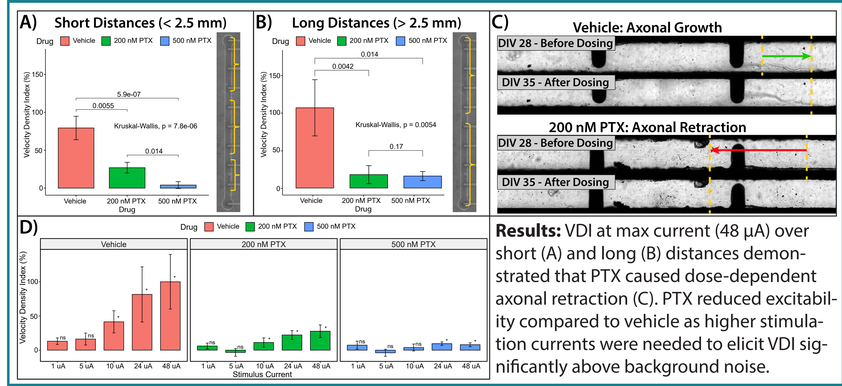
Peak Detection: Raw signals were processed (A) and significant peaks were detected (B) for each electrode recording. The distributions of conduction velocity (C) and amplitude (D) exhibited a dose-dependent decrease caused by PTX.

Maximal Velocity Projection



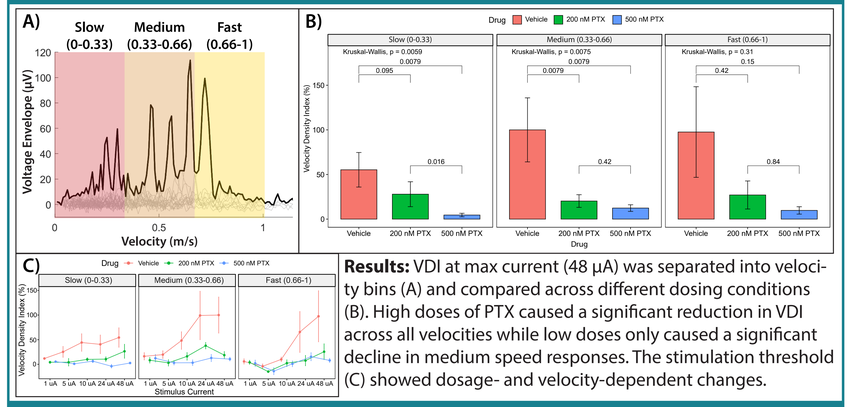
Results: Maximal velocity projections were calculated and normalized to the vehicle to create a velocity density index (VDI) representing the maximal response of a sample to electrical stimulation (**A**). Increasing stimulus strength caused increasing VDI that was reversibly blocked with high K+ media (**B**). PTX caused significant, dose-dependent decreases in VDI at 48 µA (**C**).

Functional Electrophysiology Metrics



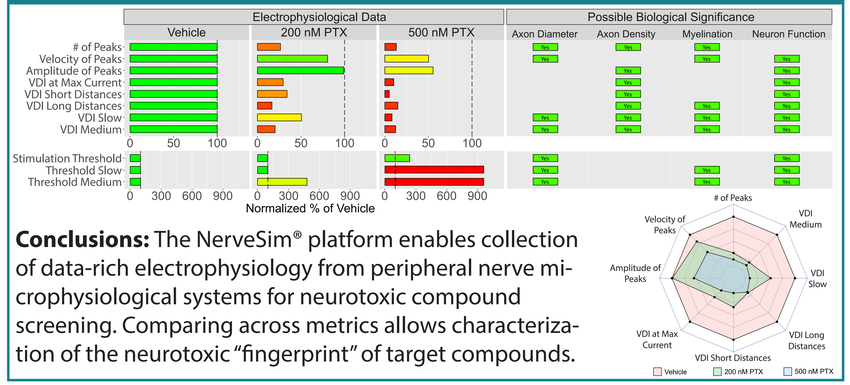
Results: VDI at max current (48 µA) over short (A) and long (B) distances demonstrated that PTX caused dose-dependent axonal retraction (C). PTX reduced excitability compared to vehicle as higher stimulation currents were needed to elicit VDI significantly above background noise.

Neurotoxic Effects on Conduction Velocity



Results: VDI at max current (48 µA) was separated into velocity bins (A) and compared across different dosing conditions (B). High doses of PTX caused a significant reduction in VDI across all velocities while low doses only caused a significant decline in medium speed responses. The stimulation threshold (C) showed dosage- and velocity-dependent changes.

Conclusions



Conclusions: The NerveSim® platform enables collection of data-rich electrophysiology from peripheral nerve microphysiological systems for neurotoxic compound screening. Comparing across metrics allows characterization of the neurotoxic "fingerprint" of target compounds.