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Single-neuron sub-cellular-resolution electrical stimulation with high-density microelectrode arrays

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Abstract

Non-invasive electrical stimulation is a consolidated technique to study and control neural activity in the brain and peripheral nervous system. It is used, e.g., for controlling Parkinson's disease or to induce sensation in paralyzed patients (Armenta Salas et al., 2018), as well as for attempts to restore vision (Fan et al., n.d.; Grosberg et al., 2017) and hearing (Wilson & Dorman, 2008). A common requirement in electrical stimulation is the precise and controlled stimulation of individual targeted neurons. For achieving this purpose, it is necessary that electrodes can stimulate and record extracellular signals at sub-cellular resolution. Furthermore, it is important to design efficient stimulation pulses to be delivered to the neurons. In the present work we used an CMOS-based high-density microelectrode array (HD-MEA) (Ballini et al., 2014), featuring 26'400 bidirectional electrodes with a pitch of 17.5 µm, which was designed for in-vitro applications. This high-resolution was used to test electrical stimulation parameters in vitro, which then could potentially be adapted to elicit single-cell action potentials *in vivo*. In this work we used different stimulation parameters, such as waveforms, amplitudes and durations (Grosberg et al., 2017; Wagenaar, Pine, & Potter, 2004), using 5x9 µm² electrodes to target sub-cellular structures in single neurons. E-18 Wistar rat cortical neurons were stimulated at days-in-vitro 10, 15, 20 and 25 using randomized voltage and current stimulation modalities. Axon initial segments of individual neurons (Radivojevic et al., 2016) were targeted for stimulation, enabled by the HD-MEA device. We found that voltage biphasic anodic-cathodic waveforms were less efficient than biphasic cathodic-anodic waveforms in eliciting action potentials in a single neuron. Moreover, it was possible to detect action potentials directly at the cell soma, which ensured a reliable confirmation of successful neuron stimulation. Finally, HD-MEA technology enabled to elicit action potentials in single-neurons embedded in high-density cell cultures. The obtained results can be used to optimize *in vivo* single-cell targeting for stimulation and read-out.

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