Soo Jin Choi
schoi84@jh.edu
Graduate Student, Johns Hopkins University
Advisor: Deok-Ho Kim, David H. Gracias

All Abstract Authors and Affiliations:
Soo Jin Choi1, Zhaoyu Liu2, Feiyu Yang2, Hanwen Wang2, Derosh George1, David H. Gracias1,3-8*, Deok-Ho Kim2,3,4*

1Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA., 2Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA. 3Department of Materials Science and Engineering, Johns Hopkins University, Baltimore, MD, USA. 4Department of Chemistry, Johns Hopkins University, Baltimore, MD, USA.
5Laboratory for Computational Sensing and Robotics (LCSR), Johns Hopkins University, Baltimore, MD, USA. 6Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA. 7Center for Micro Physiological Systems, Johns Hopkins School of Medicine, Baltimore, MD, USA. 8Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Spatiotemporal activation mapping and detection of conduction blocks in cardiac organoids via 3D shell microelectrode arrays (MEAs)

Stem cell-derived cardiac organoids offer the unique advantage of recapitulating the native structure of the human heart via multicellular self-assembly, eliminating the need for external scaffolds or additional processing. Recent advances have highlighted the ability of human induced pluripotent stem cells (hiPSCs) to replicate the structural complexity of the heart, including the formation of distinct atrial and ventricular regions through electrical conditioning1; multi-chambered architectures via co-developing progenitor subsets2; and hypoxic gradients to model myocardial infarction3. The three-dimensional (3D) architecture of cardiac organoids is ideal for modeling tissue-scale phenomena, such as arrhythmic events, conduction blocks, and interstitial fibrosis within a spatially organized tissue context. However, the development of high-throughput analytical tools for detecting region-specific and comprehensive electrical signals across 3D organoids with high spatiotemporal resolution remains a significant bottleneck, particularly for modeling conduction disorders that can lead to arrhythmias.

By engineering microelectrode arrays (MEAs) using thin, flexible materials that can autonomously shape-change to conform to the curvilinear surfaces of organoids, we mapped the 3D activation of cardiac organoids for the first time. We tuned the folding angle of the MEAs to encapsulate 0.5- to 1.5-millimeter diameter organoids, ensuring close

contact with electrodes for high signal-to-noise ratio while preserving their natural self-organized structure. We showed the propagation of spontaneous cardiac organoid beating by detecting the local activation timepoint of each electrode and creating a 3D isochrone map with conduction velocity vectors. We validated the propagation pattern by generating a 2D perspective of the isochrone map and comparing it with calcium imaging data. Additionally, we assessed the MEA system on cardiac organoids treated with cardioactive drugs, including isoproterenol, E-4031, and solatol, and observed region-specific electrophysiological responses. We also subjected the cardiac organoid to specific areas of conduction block via precise UV laser ablation and captured changes in signal trajectory following ablation. This cardiac organoid mapping platform shows considerable potential for long-term monitoring of tissue-scale arrhythmic events in organoids, modeling disease conditions, and advancing 3D compartmentalize

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