

Graph Deviation Networks for Schizophrenia Signatures Detection in Brain Organoids' MEA Signals

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Summary:

We present a Graph Deviation Network (GDN) framework to detect early alterations in the neuronal network of human Forebrain Organoids (hFOs) associated with schizophrenia risk. MEA-recorded signals from PCCB-knockdown hFOs are preprocessed into amplitude-modulated spike arrays and represented as time-varying graphs. Topological descriptors extracted from these graphs feed a linear discriminant analysis classifier, achieving 91% accuracy in distinguishing PCCB-knockdown from control hFOs at early time sessions. This approach provides a powerful tool for identifying disease-relevant electrophysiological signatures in neuronal organoid models.

Keywords: brain organoids, graph deviation network, schizophrenia, multi-electrode arrays, deep learning.

Background, Motivation and Objective

Human Forebrain Organoids (hFOs) are self-organized 3D cell aggregates that faithfully recapitulate the cellular architecture of the human brain, representing a powerful in vitro platform for studying brain development and neurological disorders. Their functional characterization is greatly facilitated by multi-electrode arrays (MEAs), which enable non-invasive, long-term acquisition of electrical signals directly correlated with organoid activity, capturing the spike and burst dynamics of developing neuronal networks. Among the disorders that can be investigated through this approach, schizophrenia (SCZ) stands out as a severe psychiatric condition with complex environmental and genetic etiology. Notably, hFOs have been used to demonstrate the involvement of Propionyl-CoA Carboxylase Subunit Beta (PCCB), a nuclear-encoded gene, in SCZ risk [1]: PCCB knockdown induces mitochondrial dysfunction that disrupts GABA production, leading to measurable alterations in hFO electrical activity. However, MEA-recorded signals are commonly reduced to temporal averages such as mean firing rate or burst rate, thereby discarding the most informative

spatiotemporal patterns for identifying disease-relevant signatures. To overcome this limitation, we introduce a Graph Deviation Network (GDN) [2], a deep learning framework based on graph theory, to detect early network alterations in hFO activity associated with SCZ risk, enabling anomaly identification from only a few milliseconds of electrical signal [3].

Description of the New Method or System

Neural activity from PCCB-knockdown hFOs and controls was recorded across multiple time sessions using 16-electrode MEA platforms (see Fig. 1a). Prior to GDN processing, raw recordings undergo a preprocessing step that extracts amplitude-modulated (AM) signals centered around each detected spike event (see Fig. 1b), preserving the informative content surrounding neuronal firing [3]. The resulting AM-spike arrays (see Fig. 2a) constitute the input to the GDN, a deep learning framework that models MEA dynamics as time-varying graphs: each node represents an electrode, and directed edges encode asymmetric, potentially causal interactions among them (see Fig. 2b). The GDN operates by predicting future signal samples from learned

past values. To this end, signals are first projected into low-dimensional space through embedding vectors; a directed graph is then derived from their pairwise similarities, capturing the evolving relational structure of the network. From each graph instance, topological descriptors are extracted to quantify network dynamics over time [3]. These descriptors feed a linear discriminant analysis (LDA) classifier, trained to distinguish PCCB-knockdown from control conditions across recording wells.

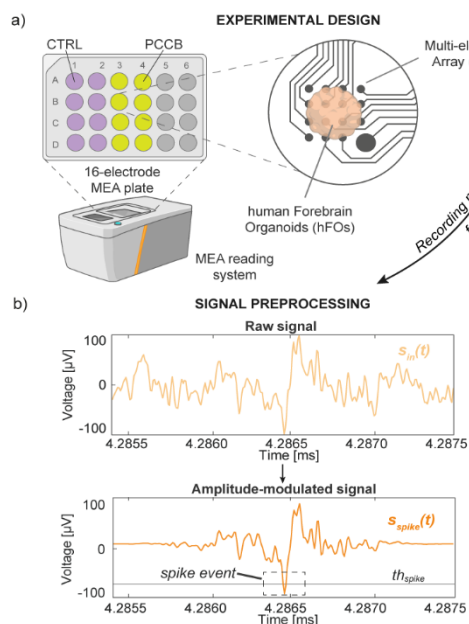


Fig. 1. a) Experimental design showing the MEA reading system, the 16-electrode MEA platform in which hFOs are cultured, and a detailed view of the MEA electrodes-coupled hFOs. b) MEA-acquired data undergo preprocessing, resulting in amplitude-modulated (AM) signals where spike events are detected.

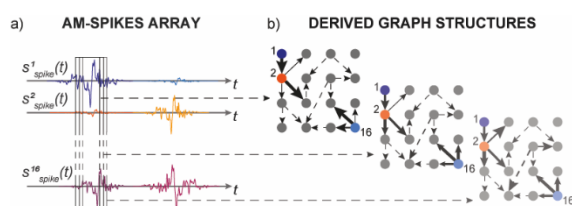


Fig. 2. a) AM-spike signals coming from one electrode are concatenated along the time axis, and vertically with the other MEA data, resulting in an AM-spikes array. b) AM-spikes arrays are encoded as graph structures from which topological features are extracted.

Results

The proposed pipeline was evaluated across five recording sessions spanning approximately 80 hours of organoid development (11h, 27h, 46h, 57h, 80h). The LDA classifier, trained on topological descriptors extracted from GDN-derived graph representations, consistently distinguished PCCB-knockdown hFOs from controls across the entire observation window (see Table 1). At the earliest time point (11h), the model

achieved its highest classification accuracy of 91%, confirming that the GDN framework can detect disease-relevant electrophysiological signatures from very early stages of network activity. At this stage, organoid maturation is still limited, and PCCB-mediated mitochondrial dysfunction leaves a clearly measurable imprint on network topology, making the two conditions well separable in the topological feature space. As recording sessions progressed, a gradual yet consistent decline in classification accuracy was observed, dropping from 86% at 27h to 76% at 80h. Inspection of the confusion matrices (see Fig. 3) revealed that this trend is primarily driven by an increasing number of misclassified samples over time. This pattern is consistent with the progressive maturation of the organoids. Actually, as neuronal connectivity consolidates and network dynamics become more complex, maturation-driven signals increasingly dominate electrophysiological activity, gradually masking condition-specific alterations induced by PCCB knockdown and reducing inter-class separability.

Tab. 1: Classification accuracy achieved for each time session applying an LDA model.

Time session	11h	27h	46h	57h	80h
Accuracy	91%	86%	83%	78%	76%

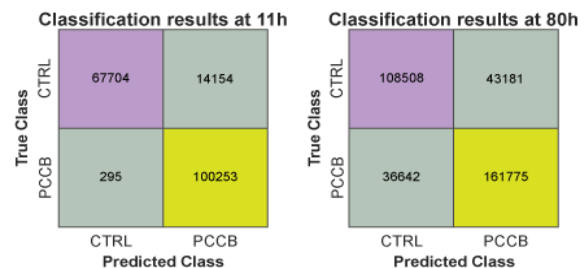


Fig. 3. Classification results for the first and last time sessions, showing how the LDA model tends to misclassify samples of the two classes.

References

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