# High Entropy Deep Brain Stimulation for Treatment Resistant Depression

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## Abstract

**A key challenge for reliably treating psychiatric disorders such as depression through deep brain stimulation (DBS) is characterizing the individual brain responses to electrical stimulation over the target stimulation space. Here, we propose the high-entropy stimulation paradigm that can sample from a wide array of spatiotemporal patterns, and explore a much larger and more natural portion of the stimulation space than conventional piecewise constant pulse trains. We used the high entropy stimulation paradigm to stimulate a patient with treatment-resistant depression who had implanted DBS electrodes, using a custom-built GUI, and the patient's ongoing brain activity was recorded using intracranial stereo encephalogram (sEEG). We show that the stimulation modulates the responses along a low-dimensional manifold spanned by the evoked responses in pre-frontal brain regions. Overall, by generating richer and more natural patterns of electrical stimulation, the proposed high entropy stimuli are useful to efficiently probe the influence of external stimulation on brain states.**



**Keywords:** High entropy stimulation, Cox process, Deep brain stimulation, Treatment-resistant depression


## Introduction

Deep brain stimulation (DBS) is increasingly being used to treat mood disorders such as Treatment Resistant Depression (TRD) and Obsessive Compulsive Disorder (OCD) (Sheth & Mayberg, 2023). It involves stimulating implanted electrodes in the brain, connected to a surgically-implanted, battery powered pulse generator. In the clinical setting, the DBS parameters – amplitude, pulse width, frequency, and contact configuration – are empirically adjusted. However, the number of possible parameter combinations grows exponentially making the exploration of this high-dimensional space intractable.

In this work, we propose a high-entropy electrical stimulation paradigm that can sample from a wide array of spatiotemporal patterns, and explore a much larger and more natural portion of the stimulation space than conventional piecewise constant pulse trains. We created stimulation sequences with flexible spatio-temporal correlations across DBS channels, allowing the contact configuration to change over time (see example in Figure 1a). We generalized the approach in (Krumin & Shoham, 2009) to draw samples from a generalized Cox process that results in continuous time-varying pulse rates and a continuous spectrum of interval distributions from periodic to Poisson to bursty. In the following, we demonstrate the efficacy of the proposed stimulation paradigm in characterizing the stimulation-driven responses.

## Methods

We used high entropy electrical stimulation in a patient with treatment-resistant depression (age 32 yrs, non-hispanic white female) who had implanted current-steerable DBS electrodes (4 leads, 8 contacts per lead) in subcallosal cingulate (SCC) and the ventral capsule/ventral striatum (VCVS) regions of the brain, known targets for regulating mood (Sheth et al., 2022). The patient was recruited for a clinical trial for individualized DBS, guided by intracranial recordings. We delivered stimulation through Cerestim, Blackrock Microsystems, using a custom-built GUI, for 3 hours, and the patient's

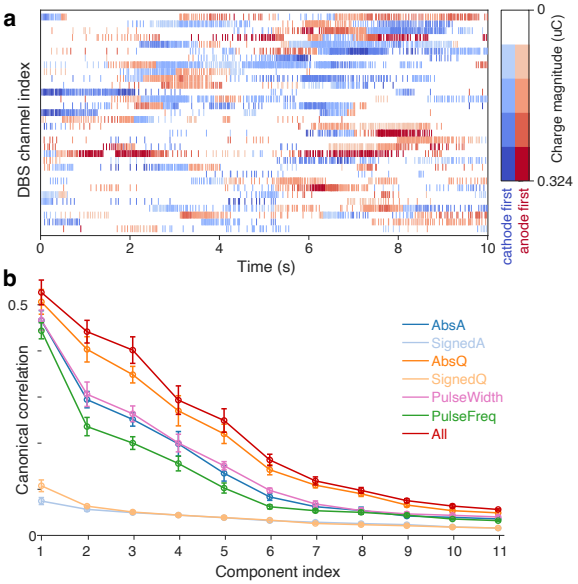
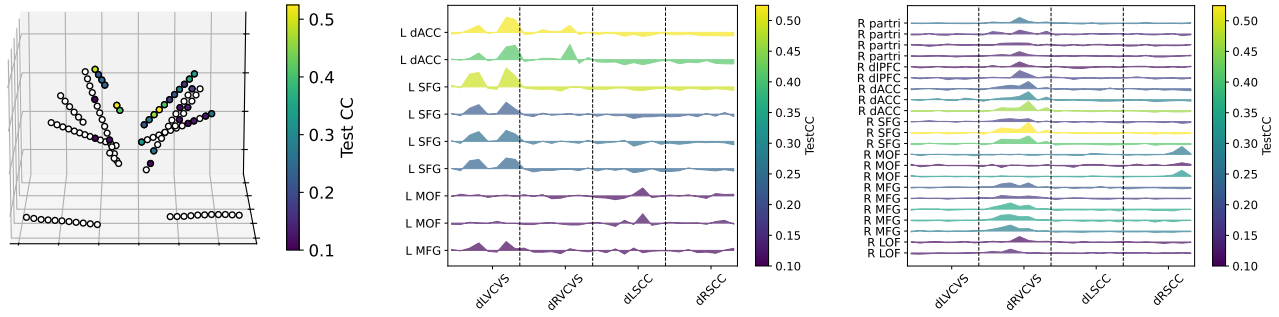



Figure 1: (**a**) Example high entropy stimulation sequence. Each vertical bar pulse represents a charge-balanced electrical pulse with cathode/anode first leading phase (blue/red). Bars are shaded by the charge delivered per phase. (**b**) Canonical correlations using CCA between sEEG responses (concatenated across frequency bands) and various stimulation features.

ongoing brain activity was recorded using intracranial stereoencephalogram (sEEG), acquired at a sampling frequency of 30KHz. Due to device constraints, the amplitude and pulse-width parameters were limited to discrete values. We mapped each pulse to one of 14 biphasic charge-balanced waveforms, each with unique parameters within safety limits (Amplitude: 50 $\mu$A-1.8 mA per phase, Pulse Width: 50-180 $\mu$s, Polarity: anode/cathode first, Phase-ratio: 1), with smoothly varying stimulation frequency between 0 and 200 Hz.

To remove the stimulation-induced artifacts, the sEEG signals were bipolar re-referenced and blanked adaptively around stimulation onset. Blanked signals were then interpolated using a moving-mean approach, low-pass filtered, and downsampled to 1 KHz. We excluded channels with residual stimulation artifacts from the analyses, resulting in 108 sEEG channels. The time-varying power was computed using band-pass filtering and the Hilbert envelope with a sliding window (1s duration, 50% overlap) in five frequency bands: Delta-Theta (1-8 Hz), Alpha (8-12 Hz), Beta (12-20 Hz), low Gamma (20-35 Hz), and high Gamma (35-55 Hz) for each sEEG contact. Stimulation features (Amplitude, Pulse Width, Charge, Frequency) were also computed for each DBS contact (32 contacts) with a sliding window.

We used Canonical Correlation Analysis (CCA) to quantify the linear associations between the individual stimulation features ($d = 32$) and sEEG features (concatenated across the five frequency bands, $d = 540$). Further, we used ridge regression to predict the sEEG responses (spectral power in




(a) Prediction performance

(b) Regression coefficients: left hemi

(c) Regression coefficients: right hemi

Figure 2: Ridge regression: predicting power in low Gamma band using charge features (**a**) prediction performance across sEEG contacts (shaded if test CC exceeds 0.1, white otherwise) (**b**) regression coefficients for the sEEG contacts in the left hemisphere indicated in 2a grouped by region, and colored by the prediction performance (**c**) same as (b) for contacts in the right hemisphere

each frequency band, $d = 108$) from the stimulation inputs ($d = 32$). We report the mean correlation coefficient (CC) between the true and predicted responses in the test data. All analyses were performed session-wise, with 6-fold cross-validation.

## Results

Canonical correlation analysis between stim features and sEEG responses (log power in canonical frequency bands) revealed that the stimulation modulates neural responses along a low-dimensional subspace spanning 4–8 dimensions (see Figure 1b). These canonical correlation were found to be significant ($p < 0.01$, using permutation testing). The response is sensitive to all considered stimulation parameters. For charge and amplitude features, the magnitude of the features (AbsQ and AbsA) showed a higher canonical correlation than when polarity was considered (SignedQ and SignedA). This can be attributed to the known non-linear dependence of the responses on pulse polarity. Of the features considered, the charge features have the highest canonical correlation.

We used ridge regression to quantify the extent to which the stimulation alone can predict the sEEG responses. The prediction performance was highest in the higher frequency bands (Beta, low Gamma, and high Gamma). Figure 2a shows the cross-validated prediction performance when charge features (total charge delivered per phase within the time window) are used to predict the spectral power in the low Gamma band. The most predictable sEEG contacts are in the pre-frontal cortex (L/R anterior cingulate, L/R superior frontal gyri, L/R medial orbitofrontal cortex, and L/R middle frontal gyri), consistent with earlier studies reporting pre-frontal network engagement during DBS in TRD patients (Allawala et al., 2024). For each sEEG contact, the regression coefficients show the spatial configuration of the DBS contacts that optimally predicts the stimulation-driven responses (see Figures 2b and 2c). Within the stimulation-driven response subspace, VCVS stimulation has a dominant effect across the various pre-frontal contacts in the ipsilateral hemisphere compared to more localized effects of SCC stimulation in the medial orbitofrontal cortex. Further, using reduced rank regression reveals that a low-rank approximation of the regression coefficients matrix yields comparable performance to the full ridge regression model (results not shown). This finding is consistent with our observation of a low-dimensional stimulation subspace using CCA.

## Conclusion

We showed that the high-entropy stimulation paradigm can be used to efficiently probe the effect of external stimulation on the brain states. In particular, the stimulation modulates the pre-frontal network responses along a low-dimensional manifold. Our results highlighted the sensitivity of the responses to the spatial configuration of the stimulation, both within and across DBS leads. Further analyses are needed to understand the effects of the temporal complexity of the stimulation, and evaluate across-subject consistency of results. One potential application of the proposed stimulation paradigm is in closed-loop stimulation, to adaptively determine optimal stimulation patterns associated with desired brain states (reflecting 'low depression severity').

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